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# The Flavonoids

## ADVANCES in RESEARCH

edited by  
J. B. Harborne and T.J. Mabry

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*The Flavonoids:  
Advances in Research*

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Edited by

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The Flavonoids: advances in research

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I. Harborne, J. B.    II. Mabry, T. J.

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## Preface

The flavonoid pigments, one of the most numerous and widespread groups of natural constituents, are of importance and interest to a wide variety of physical and biological scientists and work on their chemistry, occurrence, natural distribution and biological function continues unabated. In 1975, a monograph covering their chemistry and biochemistry was published by Chapman and Hall under our editorship entitled *The Flavonoids*. The considerable success of this publication indicated that it filled an important place in the scientific literature with its comprehensive coverage of these fascinating and versatile plant substances.

The present volume is intended to update that earlier work and provide a detailed review of progress in the flavonoid field during the years 1975 to 1980. Although cross references are made to *The Flavonoids*, this supplement is entirely self-contained and where necessary, tabular data from the earlier volume are included and expanded here.

The choice of topics in *Recent Advances* has been dictated by the developments that have occurred in flavonoid research since 1975, so that not all subjects covered in *The Flavonoids* are reviewed again here. A major advance in flavonoid separation has been the application of high performance liquid chromatography (HPLC) and this is reviewed *inter alia* in the opening chapter on separation techniques. An equally important development in the spectral analysis of flavonoids has been the measurement of carbon-13 NMR spectra and this subject is authoritatively discussed in Chapter 2 and is also illustrated with the spectra of 125 representative flavonoids.

With the continuing emphasis on the isolation and characterization of flavonoid structures from novel plant sources, a most important prerequisite for all flavonoid workers is to have listings of known substances and the plants from which they have been obtained. Very remarkably, the number of known structures among some classes of flavonoid has more than doubled during the six years under review. In this respect, the burden of the reviewer covering new isoflavonoids has been particularly onerous. The central section of this book, therefore, is given over to a series of chapters covering in detail all the major classes of flavonoid, with extensive tabulation and description of new substances. A novel feature introduced into all these chapters is the provision of check lists of all known compounds. This allows the reader to see at a glance which new

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structures have been described since 1975 and which compounds are recorded in the earlier literature.

One further chapter in *Recent Advances* covers flavonoid biosynthesis. The major development here has been the isolation and description of the enzymes of biosynthesis. The final chapter on the mammalian metabolism of flavonoids covers an important area of research which was only briefly referred to in *The Flavonoids*. Here it receives a proper, extensive and up-to-date treatment.

As editors, we are particularly grateful to our contributors who have met all our deadlines and allowed us to produce this supplement on schedule. The literature coverage is comprehensive to the end of 1980 and there are also some 1981 papers included. To our readers, we ask for comments, criticisms and suggestions, since we hope to produce a second supplement within the next five years. One of us (T.J.M.) would like to thank Dr Lin Yong-long, Mr Richard Pfeil and Mr Dan Leisure for editorial and technical assistance. We are both grateful to our publishers for their continued support and interest in this endeavour.

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## CHAPTER ONE

# *Isolation Techniques for Flavonoids*

KURT HOSTETTMANN and MARYSE HOSTETTMANN

### 1.1 INTRODUCTION

Within the last five years, numerous new chromatographic techniques have become available for the flavonoid chemist. They not only reduce the separation time, but simplify the isolation of previously unknown or unstable constituents from crude plant extracts or other complex biological sources. High-performance liquid chromatography (HPLC) and droplet counter-current chromatography (DCCC) are major innovations and are complementary to each other. Whereas HPLC has been extensively used for analytical separations, DCCC is an ideal method for the isolation of flavonoids on a preparative scale. Centrifugal thin-layer chromatography and rotation locular counter-current chromatography are other new promising techniques, but at this date, little is known about their application in the field of flavonoids. However, there is no single method of separation capable of solving all isolation problems. Classical techniques such as column chromatography and thin-layer chromatography are still very useful.

In the present chapter, emphasis is given to recently developed separation techniques. It is not an exhaustive survey of the literature, but illustrations are given of the large variety of separations already achieved.

### 1.2 THIN-LAYER CHROMATOGRAPHY (TLC)

Thin-layer chromatography (TLC) remains an important method for the detection and separation of flavonoids in crude plant extracts. Since the spray reagents for the detection of flavonoids were reviewed by Markham (1975), some new chromogenic reagents have been reported. Saleh (1976) observed that sodium ethoxide (0.05 M in ethanol) can be employed for differentiating between the isomeric 3'- and 4'-methyl ethers of quercetin, isorhamnetin and tamarixetin. Alkaline chloramine- $\tau$  reagent has been recommended as an ideal reagent for the detection of different phenolic compounds on thin-layer plates (Bajaj and Arora, 1980). The detection of flavanones and 3-hydroxyflavanones on TLC plates has been discussed by Schmidtlein and Herrmann (1976), who used diazobenzene sulphonic acid reagent or sodium borohydride-aluminium chloride reagent.

## 2 The Flavonoids

Suitable adsorbents and solvent systems for the TLC of flavonoids were mentioned in the review of Markham (1975). Some systems devised more recently are presented here. Flavone aglycones have been separated on silica gel with benzene–pyridine–ammonia (80:20:1 drop) by Voirin and Jay (1977) and with benzene–pyridine–formic acid (72:18:10) by Adzet and Martinez-Verges (1980), whereas benzene–acetic acid (45:4) or methylene chloride–acetic acid–water (2:1:1) was found to be ideal for flavanone aglycones (Schmidtlein and Herrmann, 1976). Flavone *O*-glycosides, flavone *C*-glycosides and flavonol *O*-glycosides have been separated recently on silica gel with the following solvent systems: butan-1-ol–acetic acid–water (3:1:1) (Kery *et al.*, 1977), formic acid–ethyl acetate–water (9:1:1) (Kwasniewski, 1978), chloroform–ethyl acetate–acetone (5:1:4) (Chopin *et al.*, 1978), ethyl acetate–pyridine–water–methanol (16:4:2:1) (Markham and Porter, 1979), ethanol–pyridine–water–methanol (80:12:10:5) (Bouillant *et al.*, 1979) and chloroform–methanol–water (65:45:12) (Tschesche *et al.*, 1980). For the separation of various flavanone *O*-glycosides, Ghosal *et al.* (1978) employed chloroform–acetic acid (100:4), benzene–acetic acid (100:4) or chloroform–acetic acid–methanol (90:5:5).

Solvent systems suitable for the separation of flavonoid aglycones on polyamide are the following: benzene–methyl ethyl ketone–methanol (4:3:3), (Ulubelen *et al.*, 1980), benzene–petrol–methyl ethyl ketone–methanol (60:26:7:7) (Mues *et al.*, 1979) or (30:60:5:5) (Jay *et al.*, 1979). Glycosides have been separated with water–ethanol–methyl ethyl ketone–acetyl acetone (65:15:15:5) (Teuber and Herrmann, 1978), water–butan-1-ol–acetone–acetic acid (16:2:2:1) (Parker *et al.*, 1979), nitromethane–methanol (3:4) (Geiger and de Groot-Pfleiderer, 1979), methanol–water–acetic acid (90:5:5) (Hostettmann-Kaldas and Jacot-Guillarmod, 1978) and water–methyl ethyl ketone–methanol–2,4-pentanedione (13:3:3:1) (Theodor *et al.*, 1980).

For TLC on cellulose, the classical solvent systems 5–40 % acetic acid, butan-1-ol–acetic acid–water (4:1:5) or 2-methylpropan-2-ol–acetic acid–water (3:1:1) are still often used. For flavone aglycones, benzene–acetic acid–water (125:72:3) or chloroform–acetic acid–water (10:9:1) is recommended (Markham and Wallace, 1980; Markham and Porter, 1979).

### 1.3 HIGH-PERFORMANCE THIN-LAYER CHROMATOGRAPHY (HPTLC)

Recent research has shown that high-performance thin-layer chromatography (HPTLC) can provide much better separations than TLC of complex flavonoid mixtures (Zlatkis and Kaiser, 1977). HPTLC is a development of TLC carried out using small particles, usually about 5  $\mu\text{m}$  in diameter, all of a closely similar size. However, Guiochon *et al.* (1978) have shown that the use of very fine particles is not necessarily the best method, since the mobile phase flows slowly and diffusion becomes an important factor. Rapid separations can be achieved horizontally by linear, circular and anti-circular developments (Jänchen and Schmutz, 1979;

Kadar-Pauncz, 1979; Kaiser, 1978). Thus, HPTLC can be of interest for chemotaxonomic studies of flavonoids as it requires very small samples (nanogram amounts). An application has been reported by Hiermann and Kartnig (1977) who separated numerous flavonoids on HPTLC silica gel plates, followed by quantitative determination *in situ*. The solvent system for the aglycones was benzene–ethyl acetate–formic acid (40:10:5), whereas acetone–methyl ethyl ketone–formic acid (50:35:5) was used for the glycosides. The latter solvent system was also used for the identification of three flavone glycosides in the leaves of *Digitalis lanata* (Hiermann, 1978).

Chemically bonded silica gel, which is a common packing material for HPLC columns (see Section 1.6.2), has not yet been extensively employed in HPTLC, but it appears that the material of widest application is the octadecyl bonded reverse-phase silica gel or RP-18. In certain cases, RP-2 and RP-8 materials have also been applied to the separation of flavonoids (Becker *et al.*, 1979; Vanhaelen and Vanhaelen-Fastré, 1980).

Methanol–water mixtures are indicated for flavonoid aglycones but require the addition of an acid (formic acid or acetic acid) in order to avoid tailing. Lipophilic stationary phases are not suitable for the separation of highly polar glycosides since they require a high percentage of water in the mobile phase which causes difficulties in development (Hiermann, 1979).

**Table 1.1** Solvent systems for reverse-phase HPTLC of flavonoid aglycones

| <i>Solvent system</i>                | <i>Reference</i>                      |
|--------------------------------------|---------------------------------------|
| Methanol–water–formic acid (28:10:5) | Hiermann (1979)                       |
| Methanol–water–formic acid (28:4:5)  | Hiermann (1979)                       |
| Methanol–water–acetic acid (70:28:2) | Becker <i>et al.</i> (1979)           |
| Ethanol–water (55:44)                | Vanhaelen and Vanhaelen-Fastré (1980) |

Reverse-phase HPTLC is indicated for the analysis of crude plant extracts since the lipophilic plant constituents remain at the application point, whereas the more polar compounds such as flavonoid aglycones are mobile (Becker *et al.*, 1979).

#### 1.4. CENTRIFUGAL THIN-LAYER CHROMATOGRAPHY

Among the commonly used preparative-scale separation techniques, centrifugal chromatography has so far played only a minor role. Numerous attempts have been made to increase the speed of separation by acceleration of the flow rate of the mobile phase using centrifugal force (Deyl *et al.*, 1964; Heftmann *et al.*, 1972). Recently, commercially available equipment has been applied to the separation of several classes of phenolic compounds. In one of these methods, the TLC plate

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(rotor) is not horizontal but inclined, and this allows the more efficient collection of the eluate. Its principle of operation is simple. The mixture to be separated is applied as a solution near the centre of a rotor, which is coated with a thin layer of adsorbent (layer thickness 1–4 mm). Elution with a solvent produces concentric rings of the components, which are spun off in turn from the edge of the rotor, together with solvent. A collection system brings each eluate to a single output tube. UV-absorbing compounds can be observed directly through a quartz lid during the separation.

The efficiency of this method was demonstrated by Derguini *et al.* (1979), who separated 100 mg amounts of *cis/trans* isomeric esters on silica with *n*-hexane–ether (99:1). The recovery of pure esters was 90% whereas it was only 80% in preparative liquid chromatography. Recently, Hostettmann *et al.* (1980) and Hostettmann-Kaldas *et al.* (1981) applied centrifugal TLC to the isolation of xanthone aglycones from *Gentiana* species. From a crude chloroform extract (400 mg) of *Gentiana detonsa* (Gentianaceae) 7 mg of 1-hydroxy-3,7,8-trimethoxyxanthone and 12 mg of 1,7-dihydroxy-3,8-dimethoxyxanthone were isolated within 30 min. As flavones are structurally related to xanthenes and possess a similar chromatographic behaviour, preparative centrifugal TLC should be an ideal method for their isolation. This very rapid technique can handle up to 1 g of sample and can replace preparative TLC (where bands have to be scraped off in order to recover the sample), and, in some instances, column chromatography. However, its application is limited by the relatively low resolution and the restriction in the choice of stationary phases. The procedure described by Gilpin and Sisco (1976) for converting silica gel layers into octadecyl reverse-phase layers may greatly increase the versatility of centrifugal TLC and make it more suitable for the separation of glycosides.

### 1.5. COLUMN CHROMATOGRAPHY

Column chromatography remains a very useful technique for preliminary purification or for preparative scale separation of large quantities of flavonoids from crude plant extracts. It has been discussed in depth by Markham (1975). Polyamide is the most widely used packing material. Aglycones have been separated with chloroform–methanol–methyl ethyl ketone–acetone (40:20:5:1) (Ulubelen *et al.*, 1980) or with benzene–petrol–methyl ethyl ketone–methanol (60:26:3.5:3.5) Mues *et al.*, 1979). Numerous glycosides have been isolated from crude extracts with methanol–water mixtures (Parker *et al.*, 1979; Ulubelen *et al.*, 1980; Marston *et al.*, 1976; Bouillant *et al.*, 1979; Geiger and de Groot-Pfleiderer, 1979). Flavonol glycosides have been resolved by Geiger *et al.* (1978) using water with increasing amounts of acetone.

On silica gel, flavone aglycones have been separated with chloroform–methanol mixtures (Karl *et al.*, 1977), whereas for glycosides, it is necessary to add water to such systems. Good separations were obtained with chloro-

form-methanol-water in the proportions (80:20:1) (Higuchi and Donnelly, 1978) or in the proportions (65:20:2) and (80:18:2) (Tschesche *et al.*, 1980). The last authors also employed ethyl acetate-acetone-water (25:5:1). Homoisoflavonoids have been separated on silicic acid with chloroform-acetone mixtures by Tada *et al.* (1980). The solvent systems used for cellulose TLC (see Section 1.2) are suitable for column chromatography on the same adsorbent.

Sephadex gel is an excellent stationary phase and its advantages in the isolation of flavonoids have already been discussed (Markham, 1975). Table 1.2 summarizes some of the gel types and the corresponding solvent systems which are most widely used.

**Table 1.2** Column chromatography of flavonoids on Sephadex

| Type  | Solvent system                  | Flavonoids           | Reference                             |
|-------|---------------------------------|----------------------|---------------------------------------|
| G-10  | Water                           | Flavonols            | Cabrera and Juliani (1979)            |
| G-10  | Water → water-methanol (6:4)    | 6-Hydroxyflavones    | Ulubelen <i>et al.</i> (1980)         |
| G-25  | Water-acetone (8:2 → 6:4)       | Flavonoid glycosides | Parker <i>et al.</i> (1979)           |
| LH-20 | Methanol-water (3:7)            |                      |                                       |
|       | Methanol → methanol-water (8:2) |                      | Mues <i>et al.</i> (1979)             |
|       |                                 |                      | Higuchi and Donnelly (1978)           |
|       | Chloroform-methanol (9:1)       |                      | Karl <i>et al.</i> (1977)             |
|       | Methanol-water (3:1)            |                      | Geiger and de Groot-Pfleiderer (1979) |
|       | Acetone-methanol-water (2:1:1)  |                      | Geiger <i>et al.</i> (1978)           |
|       | Methanol, ethanol               | Homoisoflavonoids    | Tada <i>et al.</i> (1980)             |
|       |                                 | Flavone C-glycosides | Kaldas <i>et al.</i> (1975)           |

## 1.6. HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC)

High-performance liquid chromatography (HPLC) has proven to be one of the most useful techniques available today for separating complex mixtures of organic substances. The range of compounds that have been successfully separated by HPLC continues to expand at a very rapid rate. Within the last five years, HPLC has been applied to highly complex separations in the field of natural products chemistry. There has also been a dramatic increase in the scope and versatility of this technique, due mainly to the availability of the necessary instrumentation and to improvements in the efficiency and nature of column packing materials. An excellent and very useful recent review is that of Kingston (1979). Some selected examples of HPLC separations have been presented by Adams and Nakanishi (1979), while Van Sumere *et al.* (1979) have reviewed the application of HPLC to the separation of plant phenolics. Useful information on the theory and on the relationship of theory to practice in HPLC has been published (Snyder and Kirkland, 1974; Engelhardt, 1979) and will not be discussed here.

## 6 The Flavonoids

It is noteworthy that in the flavonoid field HPLC has been mainly used as an analytical technique, e.g. for quantitative determination of plant constituents, for checking the purity of natural samples, and for chemotaxonomic comparisons. For the isolation of flavonoids on a preparative scale, the full potential of HPLC has not yet been exploited. Without doubt, by using larger reverse-phase columns with high efficiencies, HPLC will become a method of choice for the isolation of previously unknown flavonoid structures.

### 1.6.1 Separations on silica gel columns

This column packing material has not been used often, but can be recommended for the separation of non-polar or weakly polar flavonoid aglycones. HPLC using LiChrosorb Si 60 as adsorbent and a mixture of heptane–propan-2-ol (60:40) as eluent was found to be a very efficient method for the separation of the major polymethoxylated flavones present in citrus fruits (Bianchini and Gaydou, 1980). Tangeretin, tetra-*O*-methylscutellarein, nobiletin and sinensetin have been separated and identified in crude extracts of tangerine and orange peels within 25 min. Complex mixtures of isoflavone aglycones have been resolved on a  $\mu$ Porasil column using different gradient systems (Carlson and Dolphin, 1980). On the other hand, isocratic chromatography of a *Glycine max* hydrolysate with [dichloromethane–ethanol–acetic acid (97:3:0.2)]–hexane (8:2) resulted in a rapid separation of the two isoflavones present, daidzein and genistein. The isocratic run does not require solvent re-equilibration for each sample and thus increases the rate of analysis. Silica gel has also been used by Ward and Pelter (1974) for the separation of isoflavones with hexane–tetrahydrofuran (2:1) and biflavonoids with isopropyl ether containing 8% methanol. Recently, a range of flavonoid acetates has been separated and determined on 5- $\mu$ m LiChrosorb Si 60, using four solvent systems by Galensa and Herrmann (1980) (see Table 1.3). Benzene–acetonitrile was the most suitable mobile phase, especially at 45°C. With this solvent system, the flavonoids were readily detected by absorption measurements at 285 nm, and flavanones could therefore also be determined. Benzene–acetonitrile (85:40) separated the flavone glycosides very well, whereas flavonol and flavanone glycosides showed very short retention times with this solvent mixture. In this work, flavonoid glycosides were acetylated prior to HPLC separation and an excellent resolution was obtained. By using reverse-phase column packing materials (see below), however derivatization can be avoided.

### 1.6.2 Separations on reverse-phase columns

Soon after the introduction of HPLC, numerous new types of stationary phases appeared on the market. The most important of these are the so-called chemically bonded stationary phases which are prepared by bonding various organosilane molecules (e.g. octadecyltrichlorosilane, octyltrichlorosilane or phenyltrichloro-

silane) to the hydroxyl groups of a silica type surface. One of the most important factors affecting the performance of bonded-phase columns is the amount of organic material deposited on the silica surface (Snyder and Kirkland, 1974). Since the trichlorosilanes polymerize readily in the presence of moisture, the amount of material bonded to the surface may vary unless the amount of water present is standardized. In practice, numerous types of packed columns possessing a high degree of reproducibility are commercially available. But simple procedures for preparing octadecylsilyl bonded stationary phase have been described (Kingston and Gerhart, 1976; Gilpin *et al.*, 1975) and may be needed, for example, when packing a wide column for preparative-scale separations. Wehrli *et al.* (1978) estimated that 80% of current separations are done on octadecylsilyl bonded phase columns, commonly called C<sub>18</sub> columns (see Table 1.3).

When using the above column material, the stationary phase is less polar than the mobile phase and the procedure is called reverse-phase chromatography. Thus, highly polar solutes possess shorter retention times than less polar solutes. This is of prime importance in the separation of complex mixtures of flavonoids: glycosides will be eluted first, followed by the aglycones, generally in order of decreasing polarities. For aglycones possessing only a few free hydroxyl groups or fully methoxylated aglycones, it is obvious that reverse-phase chromatography is not necessarily indicated, since this class of flavonoid can easily be separated by adsorption chromatography on silica gel (Bianchini and Gaydou, 1980; Carlson and Dolphin, 1980). Nevertheless, several authors have obtained excellent separations of non-polar aglycones on octadecylsilyl or octylsilyl bonded columns (Rouseff and Ting, 1979; Ting *et al.*, 1979). A practical application of the reverse-phase separation technique can be seen in an analysis of isoflavone aglycones in soybeans (West *et al.*, 1978). In this case, the positional isomers 5,7,4'-trihydroxyisoflavone, genistein, and 6,7,4'-trihydroxyisoflavone were separated with water–acetonitrile (4:1) on a Partisil-10-ODS column.

Acetonitrile–water mixtures or methanol–water containing small amounts of acetic acid are commonly used solvent systems for flavonoid glycosides. These mobile phases are suitable for use with UV detection and can easily be employed in gradient systems for complex separations (Niemann and Koerselmann-Kooy, 1977; Strack and Krause, 1978; Quercia *et al.*, 1978). In many cases, the acetic acid in the mobile phase has been replaced by very small amounts of phosphoric acid (Williams *et al.*, 1978; Court, 1977; Niemann, 1977; Niemann and Van Brederode, 1978; Seitz and Wingard, 1978). Depending on the compounds to be separated, it may be advantageous to replace C<sub>18</sub>-chemically bonded phases by C<sub>8</sub> reverse-phase material. For example, isovitexin arabinoside and vitexin rhamnoside were poorly resolved on a LiChrosorb RP-18 column, whereas these two C-glycosides were clearly separated on a RP-8 column with a methanol–acetic acid–water solvent system (Strack *et al.*, 1979). This system has been applied to the analysis of flavone glycosides in crude extracts of *Avena sativa* leaves. Strack and Krause (1978) compared the selectivities of RP-8 and RP-18 columns and obtained, in

Table 1.3 HPLC of flavonoids

| <i>Separated flavonoids</i>     | <i>Column</i>                   | <i>Mobile phase</i>                                              | <i>Reference</i>                      |
|---------------------------------|---------------------------------|------------------------------------------------------------------|---------------------------------------|
| <i>Anthocyanidins</i>           | $\mu$ -Bondapak C <sub>18</sub> | Methanol-acetic acid-water (20:5:75)                             | Adamovics and Stermitz (1976)         |
| <i>Anthocyanidin glycosides</i> | $\mu$ -Bondapak C <sub>18</sub> | Methanol-acetic acid-water (19:10:71)                            | Wilkinson <i>et al.</i> (1977)        |
| 3-Glucosides                    | $\mu$ -Bondapak C <sub>18</sub> | Acetic acid-water (15:85)                                        | Williams <i>et al.</i> (1978)         |
| 3,5-Diglucosides                |                                 | 0.1% H <sub>3</sub> PO <sub>4</sub> in acetic acid-water (10:90) |                                       |
| <i>p</i> -Coumarylglucosides    |                                 | Methanol-acetic acid-water (20:15:65)                            |                                       |
| <i>Anthocyanins</i>             | Pellidon                        | Chloroform-methanol (87:13)                                      | Manley and Shubiak (1975)             |
| <i>Methoxylated flavones</i>    | Zorbax C <sub>8</sub>           | Tetrahydrofuran-acetonitrile-water (22:6:72)                     | Rouseff and Ting (1979)               |
|                                 | Micropak C <sub>18</sub>        | Acetonitrile-water (40:60)                                       | Ting <i>et al.</i> (1979)             |
|                                 | Zorbax C <sub>8</sub>           | Tetrahydrofuran-water (25:75)                                    |                                       |
|                                 | Lichrosorb Si 60                | Heptane-ethanol (75:25)                                          | Bianchini and Gaydou (1980)           |
| <i>Flavones and flavonols</i>   |                                 |                                                                  |                                       |
| Aglycones                       | $\mu$ -Bondapak alkylphenyl     | Ethanol-acetic acid-water (47.5:5:47.5)                          | Vanhaelen and Vanhaelen-Fastré (1980) |
|                                 | $\mu$ -Bondapak C <sub>18</sub> | Methanol-acetic acid-water (30:5:60)                             | Wulf and Nagel (1976)                 |
|                                 | $\mu$ -Bondapak C <sub>18</sub> | 40% methanol in phosphate buffer                                 | Court (1977)                          |
|                                 | Zipax HCP (hydrocarbon polymer) | Phosphate buffer-ethanol-ethyl acetate (100:1:0.1)               | Okuda <i>et al.</i> (1979)            |
| <i>Flavones and flavonols</i>   |                                 |                                                                  |                                       |
| Glycosides                      | Zorbax ODS                      | 45% → 100% methanol containing 0.1% acetic acid                  | Niemann and Koerselmann-Kooy (1977)   |
|                                 | Vydac ODS                       | Methanol-phosphoric acid-water (15:0.5:85)                       |                                       |
|                                 | Lichrosorb RP8                  | Acetonitrile-water (1:9 → 9:1)                                   |                                       |
|                                 | $\mu$ -Bondapak C <sub>18</sub> | Methanol-acetic acid-water (30:5:60)                             | Wulf and Nagel (1976)                 |
|                                 | $\mu$ -Bondapak C <sub>18</sub> | Methanol-acetic acid-water (30:5:70)                             | Adamovics and Stermitz (1976)         |
|                                 | $\mu$ -Bondapak C <sub>18</sub> | 40% methanol in phosphate buffer                                 | Court (1977)                          |
|                                 | Zorbax ODS                      | 20% → 100% ethanol containing 0.1% phosphoric acid               | Niemann (1977)                        |
|                                 | Zypax HCP (hydrocarbon polymer) | Phosphate buffer-ethanol-ethyl acetate (100:1:0.1)               | Okuda <i>et al.</i> (1979)            |



|                                                       |                                                                                                                                                                                           |                                                                                                                                                                                                                        |                                                                                                                                        |
|-------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| <i>Flavone C-glycosides</i>                           | Lichrosorb RP-8<br>Lichrosorb RP-18                                                                                                                                                       | (A) Methanol-acetic acid-water (5:5:90)<br>(B) Methanol-acetic acid-water (90:5:5)<br>Linear gradient from 0 → 35% B<br>Linear gradient from 0 → 50% B<br>Concave gradient of methanol in water:<br>15% → 95% methanol | Strack <i>et al.</i> (1979)<br><br>Strack <i>et al.</i> (1979)<br>Quercia <i>et al.</i> (1978)                                         |
| <i>O-Glycosides of glycoflavones</i>                  | Lichrosorb NH <sub>2</sub><br>Zorbax ODS                                                                                                                                                  | acetonitrile-water (1:9 → 9:1)<br>Ethanol-water with 0.1M-H <sub>3</sub> PO <sub>4</sub> 20% → 100%                                                                                                                    | Becker <i>et al.</i> (1977)<br>Niemann and van Brederode (1978)                                                                        |
| <i>Flavanone aglycones</i>                            | $\mu$ -Bondapak C <sub>18</sub><br>$\mu$ -Bondapak C <sub>18</sub>                                                                                                                        | Butanol-acetic acid-methanol-water (5:2:25:6)<br>10% → 100% methanol in phosphate buffer                                                                                                                               | Hardin and Stutte (1980)<br>Seitz and Wingard (1978)                                                                                   |
| <i>Flavanone glycosides</i>                           | $\mu$ -Bondapak C <sub>18</sub><br>$\mu$ -Bondapak C <sub>18</sub><br>$\mu$ -Bondapak C <sub>18</sub><br>$\mu$ -Bondapak C <sub>18</sub><br>$\mu$ -Bondapak C <sub>18</sub><br>Zorbax ODS | Methanol-acetic acid-water (30:5:60)<br>Acetonitrile-water (80:20)<br>Acetonitrile-water (80:20)<br>10% → 100% methanol in phosphate buffer<br>45% → 100% methanol containing 0.1% acetic acid                         | Wulf and Nagel (1976)<br>Fisher and Wheaton (1976)<br>Fisher (1978)<br>Seitz and Wingard (1978)<br>Niemann and Koerselmann-Kooy (1977) |
| <i>Isoflavone aglycones</i>                           | Partisil-10-ODS<br>$\mu$ -Porasil                                                                                                                                                         | Water-acetonitrile (4:1)<br>Dichloromethane-ethanol-acetic acid<br>(97:3:0.2)-hexanes (12:88) or (8:2)<br>32% → 90% methanol                                                                                           | West <i>et al.</i> (1978)<br>Carlson and Dolphin (1980)                                                                                |
| <i>Isoflavone glycosides</i>                          | $\mu$ -Bondapak C <sub>18</sub>                                                                                                                                                           | Benzene-acetonitrile (85:20)                                                                                                                                                                                           | Ohta <i>et al.</i> (1980)                                                                                                              |
| <i>Flavonoid acetates</i>                             | Lichrosorb Si60                                                                                                                                                                           | Benzene-acetone (90:15)<br>Benzene-ethanol (80:0.8)                                                                                                                                                                    | Galensa and Herrmann (1980)                                                                                                            |
| Flavone, flavonol, flavanone aglycones and glycosides |                                                                                                                                                                                           | Iso-octane-ethanol-acetonitrile (70:16:5.5)                                                                                                                                                                            |                                                                                                                                        |
| <i>Flavonolignans</i>                                 | $\mu$ -Bondapak C <sub>18</sub>                                                                                                                                                           | Methanol-acetic acid-water (40:5:60)                                                                                                                                                                                   | Tittel and Wagner (1977)                                                                                                               |
|                                                       | Lichrosorb RP-18                                                                                                                                                                          | Methanol-acetic acid-water (40:5:60)                                                                                                                                                                                   | Tittel and Wagner (1978)                                                                                                               |
| <i>Biflavonoids</i>                                   | Merckosorb S-160                                                                                                                                                                          | Isopropyl ether containing 8% methanol                                                                                                                                                                                 | Ward and Pelter (1974)                                                                                                                 |

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general, better resolutions of flavone C-glycosides on RP-8 reverse-phase material.

A hydrocarbon polymer column (Zipax HCP) coupled with a phosphate buffer-ethanol-ethyl acetate solvent system was used for the analysis of hydrolysable tannins and related polyphenols in *Geranium thunbergii* (Okuda *et al.*, 1979). Becker *et al.* (1977) employed an amino-chemically bonded silica gel column (LiChrosorb NH<sub>2</sub>) eluted with acetonitrile-water for the separation of isomeric O-glycosides of glycoflavones. An amino-chemically bonded phase gave excellent separations of xanthenes with three and four hydroxyl groups (Hostettmann and McNair, 1976). The same authors separated less polar xanthenes (i.e. those with a single hydroxyl or those lacking free hydroxyl groups) on a more polar nitrile-chemically bonded phase (Micropak CN) with *n*-hexane-chloroform. Xanthone glycosides have been separated isocratically in the reverse-phase mode on C<sub>18</sub>-chemically bonded silica gel with methanol-water mixtures (Pettei and Hostettmann, 1978). This system allowed the separation of isomeric diglycosides and monoglycosides as well as of polar xanthone aglycones. As flavones are structurally closely related to xanthenes and show a similar chromatographic behaviour, the HPLC methods discussed above are suited for flavonoid separations. Although reverse-phase HPLC is extensively used in many areas of natural products chemistry and biochemistry (Montgomery *et al.*, 1977), excellent results can often be obtained by combining its use with other procedures (Nelson, 1977).

HPLC has proven to be one of the most powerful methods for the analysis of flavonoids. It is especially indicated for the quantitative determination of plant phenolics and will in the future certainly become more popular as a method for their isolation on a semi-preparative or preparative scale.

### 1.7 DROPLET COUNTER-CURRENT CHROMATOGRAPHY (DCCC)

A simple and very efficient all-liquid separation technique called droplet counter-current chromatography (DCCC) has been developed by Tanimura *et al.* (1970). DCCC is less cumbersome than counter-current distribution and has a higher resolving power. It is carried out by passing droplets of a mobile phase through columns of surrounding stationary liquid phase. The mobile phase may be either heavier or lighter than the stationary phase; when lighter, the mobile phase is delivered at the bottom of the columns (ascending mode) and, when heavier, through the top (descending mode). Recently, apparatus for DCCC has become commercially available and the method has already been applied to the isolation of many natural products. It is particularly indicated for the preparative-scale separation of polar compounds, such as glycosides (Hostettmann *et al.*, 1979a). A general account of DCCC has been given by Hostettmann (1980) who discussed the advantages and limitations of the method.

The absence of a solid support in DCCC is the main advantage of the technique

and is of great interest in flavonoid separation. The acidic hydroxyl groups in polyphenols often cause irreversible adsorption of the solute on to the solid stationary phase during column chromatographic procedures. This can be partially avoided by adding an acid to the mobile phase and is useful for analytical work. However, when developing a preparative-scale separation, the use of acid as one of the components of the mobile phase is to be avoided. The risk of sample deterioration, i.e. by hydrolysis of glucosidic links, is increased during the long operation and the recovery of the sample from the relatively large volume of eluate. Acid is not necessary for DCCC separation. Best results have been obtained with chloroform–methanol–water mixtures in different proportions and with chloroform–methanol–propanol–water or chloroform–methanol–butanol–water mixtures. The selected solvent system must, of course, form two layers. For flavonoids and related compounds bearing few hydroxyl groups and one sugar moiety or aglycones possessing several free hydroxyl groups, the separation can be achieved by using the less polar layer as mobile phase, whereas the more polar layer is suited for more polar monoglycosides or diglycosides. For example, from a crude fraction of *Tecoma stans* (Bignoniaceae), Hostettmann *et al.* (1979a) isolated within 6 hours a pure glycoside identified as quercetin-3-*O*-glucoside using the upper layer of chloroform–methanol–water (7:13:8) as mobile phase. The same solvent system has been used by Takeda *et al.* (1977) for the isolation of rutin and various isoflavone glycosides from *Sophora japonica* (Leguminosae). In this case, the glycosides were eluted in order of decreasing polarity: rutin, biochanin A 7-*O*-gentiobioside, biochanin A 7-*O*-xylosylglucoside, biochanin A 7-*O*-glucoside and irisolidone 7-*O*-glucoside.

Flavonoid separations carried out by DCCC are summarized in Table 1.4. It is noteworthy that the technique is ideal for the isolation of various glycosides, including *C*-glycosylflavonoids. A remarkable separation of two closely related flavonol monoacetylrahnosides has been reported by Tanaka *et al.* (1978). These authors isolated 3''-*O*-acetylquercitrin and 4''-*O*-acetylquercitrin from the aerial parts of *Pteris grandifolia* (Pteridaceae) using chloroform–methanol–water (4:4:3) in the ascending mode (mobile phase: upper layer). A base-line separation of both isomers was obtained. Separations of isomeric acylated flavonoid glycosides are usually very difficult to achieve, by any other means. Thus, DCCC opens new possibilities and will be of great help in the future for difficult glycosidic isolations. Although, DCCC is more suited for glycoside separations, some examples of aglycone isolations have been reported (Hostettmann *et al.*, 1979b; Tanaka *et al.*, 1978).

Although DCCC is an excellent and highly promising technique for the preparative-scale separation of flavonoids, it possesses limitations arising from the fact that the efficiency of the method depends entirely upon droplet formation. By using columns with 2 mm internal diameter, the choice of solvent systems is limited since the droplets formed must have a smaller size than the internal diameter of the column. In most of the DCCC separations achieved up to now, chloroform–methanol–water or chloroform–methanol–propanol–

Table 1.4 Flavonoids isolated by DCCC

| Flavonoids                                | Solvent system                                    | Plant source                 | Reference                                                  |
|-------------------------------------------|---------------------------------------------------|------------------------------|------------------------------------------------------------|
| <i>C-glycosylflavonoids</i>               |                                                   |                              |                                                            |
| Iso-orientin                              | Chloroform-methanol-propanol-water<br>(5:6:1:4)   | <i>Gentiana strictiflora</i> | Hostettmann-Kaldas <i>et al.</i> (1981)                    |
| Iso-orientin                              | Chloroform-methanol-<br>butanol-water (10:10:1:6) | <i>Lespedeza cuneata</i>     | Numata <i>et al.</i> (1980)<br>Numata <i>et al.</i> (1979) |
| Isovitexin                                |                                                   |                              |                                                            |
| Lucenin-2                                 |                                                   |                              |                                                            |
| Vicenin-2                                 |                                                   |                              |                                                            |
| Swertisin                                 |                                                   |                              |                                                            |
| Vitexin                                   |                                                   |                              |                                                            |
| <i>Flavonol aglycones and glycosides</i>  |                                                   |                              |                                                            |
| Quercetin 3- <i>O</i> -glucoside          | Chloroform-methanol-water (7:13:8)                | <i>Zizyphus jujuba</i>       | Tanimura <i>et al.</i> (1975)                              |
| Quercetin 3- <i>O</i> -rutinoside         | Chloroform-methanol-water (5:6:4)                 | <i>Lindsaea ensifolia</i>    | Satake <i>et al.</i> (1978)                                |
| 3'- <i>O</i> -acetylquercitrin            | Chloroform-methanol-water (7:13:8)                | <i>Tecoma stans</i>          | Hostettmann <i>et al.</i> (1979a)                          |
| 4"- <i>O</i> -acetylquercitrin            | Chloroform-methanol-water (7:13:8)                | <i>Sophora japonica</i>      | Takeda <i>et al.</i> (1977)                                |
| Quercetin 3- <i>O</i> -glucoside          | Chloroform-methanol-water (4:4:3)                 | <i>Pteris grandifolia</i>    | Tanaka <i>et al.</i> (1978)                                |
|                                           | Chloroform-methanol-butanol-water<br>(10:10:1:6)  | <i>Polygonum nodosum</i>     | Isobe <i>et al.</i> (1980)                                 |
| <i>Isoflavone glycosides</i>              |                                                   |                              |                                                            |
| Biochanin A 7- <i>O</i> -glucoside        | Chloroform-methanol-water (7:13:8)                | <i>Sophora japonica</i>      | Takeda <i>et al.</i> (1977)                                |
| Biochanin A 7- <i>O</i> -gentiobioside    |                                                   |                              |                                                            |
| Biochanin A 7- <i>O</i> -xylosylglucoside |                                                   |                              |                                                            |
| Irisolidone 7- <i>O</i> -glucoside        |                                                   |                              |                                                            |

water mixtures were used as solvent systems (Hostettmann, 1980). Recently, 40 cm columns with 3.4 mm internal diameters have become commercially available. It is likely that they will allow the use of many other solvent systems, e.g. butanol–pyridine–water, ethyl acetate–ethanol–water, etc. This naturally will greatly increase the versatility of the technique and make it suitable for the isolation of highly polar flavonoids, such as tri- or tetra-glycosides. However, an increase in the internal diameter of the columns reduces the resolving power. However, in the case of difficult separations, up to 1000 columns can be interconnected.

### 1.8 GAS-LIQUID CHROMATOGRAPHY (GLC)

Direct GLC analysis is restricted to the few thermally stable naturally occurring aglycones which are sufficiently volatile, e.g. the polymethoxylated flavones in the fruit peel of *Citrus reticulata* (Iinuma *et al.* (1980)) in such a GLC analysis found a correlation between flavone structure and the relative retention time. Retention times of flavones having one methoxyl in ring B were shorter than those of flavones with two methoxyls. The retention time did not change with the introduction of a methoxyl into the 8-position. When the mode of substitution in ring B was the same, the retention times of 5,6,7-trisubstituted flavones were shorter than those of 5,7,8-trisubstituted flavones. The stationary phase used was 1% OV-17 and the separations were monitored with a flame ionization detector (FID).

Derivatization of flavonoids prior to GLC analysis is usually needed in order to increase their volatility. Different silylation procedures have been reviewed by Vande Castele *et al.* (1976). These authors reported an excellent separation of naturally occurring benzoic acid, cinnamic acid, coumarin, flavone and iso-flavone derivatives. By using *NN*-bis-(trimethylsilyl) trifluoroacetamide (BSTFA) as a silylating agent, a glass column packed with Chromosorb WAW DMCS coated with 1.5% SE-30 + 1.5% SE-52 and a temperature program from 80 to 300°C, about 36 of the above mentioned substances were separated in a single run. In this study, preparative GLC was also used. After hydrolysis of the collected trimethylsilyl (TMS) derivatives, it was established by TLC that the substances could be recovered unchanged in yields between 81 and 85%.

GLC of plant glycosides as the TMS derivatives should ideally be combined with mass spectrometry (Martinelli, 1980). Three flavone glycosides (luteolin 4'-*O*-glucoside, luteolin 7-*O*-glucoside and luteolin 7-*O*-rhamnoglucoside) have been identified in artichoke extracts (*Cynara scolymus*) by Bombardelli *et al.* (1977a). The column used was filled with 0.5% OV-101 liquid phase loaded on silanized Chromosorb WHP. The same stationary phase was employed in a gas–liquid chromatography–mass spectrometry (GLC–MS) investigation of numerous anthocyanidins (Bombardelli *et al.*, 1976) and anthocyanins (Bombardelli *et al.*, 1977b). Treatment of anthocyanins with trimethylchlorosilane (TMCS) and

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hexamethyldisilazane (HMDS) yielded nitrogen-containing derivatives which, after injection into the gas chromatograph, produced quinoline-like compounds. The latter were easily separated and showed fragmentation patterns which were useful for identification purposes. Attempts are currently being made to employ capillary GLC columns for the analysis of highly complex mixtures of anthocyanins. GLC-MS has also been applied to the determination of new flavonoid triglycosides from the leaves of *Cerbera manghas* (Sakushima *et al.*, 1980). Nine flavonoid aglycones (as silylated derivatives) have been separated on a column packed with OV-17 by Vanhaelen and Vanhaelen-Fastré (1980). These authors reported that the temperature and gas flow rate required to elute flavonoids are inconsistent with the use of capillary columns.

Although interesting results have been obtained by GLC, this technique is not commonly used for the separation of flavonoids because of the disadvantages associated with the need to derivatize the sample. The application of GLC to the separation of plant phenolics in general has been reviewed by Van Sumere *et al.* (1979).

### 1.9 MISCELLANEOUS TECHNIQUES

#### 1.9.1 Paper electrophoresis

This technique has only limited application in the field of flavonoid isolation and separation (Markham, 1975). It is, however, important for the separation of flavonoids, when they occur in conjugation with inorganic salts as sulphates (Harborne, 1977). Measurement of electrophoretic mobility is an important criterion in the structural identification of such flavonoid conjugates. Disulphates are very clearly separated from monosulphates by this means. Harborne (1977) reported that at pH 2.2 flavonol sulphates generally move further than flavone sulphates, and that flavonoid sulphates containing sugar residues are usually more mobile on electrophoretograms than the corresponding conjugates lacking sugar substitution. The presence of a sulphate group in 6-methoxyflavonoids from *Brickellia californica* has been confirmed by high-voltage electrophoresis (1.5 kV) on paper for 1.5 h at pH 1.9 (Mues *et al.*, 1979). The same conditions were used by Ulubelen *et al.* (1980) for the isolation and identification of quercetagenin 3-methyl ether 7-sulphate from the leaves of *Neurolaena oaxacana*.

Cabrera and Juliani (1976, 1977, 1979) isolated various flavonols with a high degree of sulphation from the genus *Flaveria* by paper electrophoresis at pH 2.2. The electrophoretic mobilities of some of these sulphates are given in Table 1.5.

#### 1.9.2 Paper chromatography

Most separations are achieved with acetic acid at different concentrations, with butan-1-ol-acetic acid-water or with 2-methylpropan-2-ol-acetic acid-water.

**Table 1.5** Electrophoretic mobilities of some flavonol sulphates (Cabrera and Juliani, 1979)

| <i>Flavonol sulphate</i>               | <i>Mobility*</i> |
|----------------------------------------|------------------|
| Isorhamnetin 3-sulphate                | 1.17             |
| Quercetin 3-sulphate                   | 1.00             |
| Quercetin 4'-sulphate                  | 0.39             |
| Quercetin 3,4'-disulphate              | 4.80             |
| Quercetin 3,7,4'-trisulphate           | 7.0              |
| Quercetin 3-acetyl-7,3',4'-trisulphate | 7.1              |
| Quercetin 3,7,3',4'-tetrasulphate      | 8.2              |

\* Relative to quercetin 3-sulphate, run at pH 2.2 (formate-acetate buffer) for 5 h at 10 V/cm.

Some other solvents have been used by Saito (1976), namely butan-1-ol-ethanol-water (5:1:4), butan-1-ol-pyridine-water (30:20:15), propan-2-ol-water (6:4), ethyl acetate-pyridine-water (2:1:2) or phenol saturated with water. These systems are also indicated for preparative paper chromatography. Harborne (1977) has described the separation of the recently discovered flavonoid sulphates on paper. Some flavonoid sulphates can be separated on paper with water as solvent (Cabrera and Juliani, 1979).

### 1.9.3 Counter-current distribution

This liquid-liquid partition technique, invented by Craig (1944), has rarely been used for flavonoid separations. Since it can handle large sample size, it is of interest in the preliminary separation of crude extracts. Nine kaempferol glycosides have been isolated from *Equisetum telmateja* by Craig counter-current distribution with a methyl ethyl ketone-water solvent system (Geiger *et al.*, 1978). However, pure compounds could only be obtained by combining the Craig distribution technique with column chromatography on Sephadex LH-20.

### 1.9.4 Rotation locular counter-current chromatography

A highly interesting partition technique called rotation locular counter-current chromatography (RLCC) has been invented by Ito and Bowman (1970). This method employs a column prepared by placing multiple centrally perforated partitions across the diameter of a tubular column which divide the space into multiple cells called locules. In each locule, the liquids form an interface while the solute partitioning is promoted by stirring of each phase induced by either rotation or gyration of the column. The column itself, inclined at an angle of 30° from the horizontal, is filled with the lower phase. The upper phase (mobile phase) is continuously introduced through the bottom of the column and then displaces the lower phase in each locule down to the level of the hole which leads

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to the next locule, the process being continued throughout the column. Consequently, solute introduced into the column is subjected to a multistep partition process, promoted by the rotation of the column and collected at the outlet of the system. In practice, a modified system is used in which multiple column units, interconnected by fine Teflon tubes, are mounted lengthwise on a rotating shaft to produce a similar effect (Ito and Bowman, 1971). Depending on the compounds to be separated, the mobile phase may be either the upper or the lower layer.

Recently, an RLCC instrument became commercially available. Preliminary assays have shown that this new technique is suitable for flavonoid separations (Hostettmann, 1981). It is a complementary partition technique to droplet counter-current chromatography (no limitation in the choice of solvent system) and to counter-current distribution (less cumbersome and higher resolution). It will certainly gain more importance in the near future for the preparative-scale separation of polar natural products.

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## CHAPTER TWO

# *Carbon-13 NMR Spectroscopy of Flavonoids*

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(with TOM J. MABRY, Section 2.5)

## 2.1 INTRODUCTION

Carbon-13 with a natural abundance of only 1.1% and a smaller magnetic moment than  $^1\text{H}$  (and hence a weaker NMR signal) was for many years a nucleus relatively inaccessible to NMR spectroscopists. However, with the advent in recent years of pulsed NMR and Fourier Transform (FT) analysis,  $^{13}\text{C}$ -NMR spectroscopy has become more readily available. As a result the past five years have seen a dramatic increase in the number of publications on, or involving,  $^{13}\text{C}$ -NMR spectroscopy of flavonoids. For example major compilations include those of Ternai and Markham (1976), Markham and Ternai (1976), Markham *et al.* (1978), Wagner *et al.* (1976), Chari *et al.* (1977a), Pelter *et al.* (1976) and Wenkert and Gottlieb (1977). The increasing availability and sensitivity of modern FT-NMR spectrometers is assurance that this powerful technique will become a major tool for the structure elucidation of flavonoids and their glycosides.

It should be stressed, however, that  $^{13}\text{C}$ -NMR is in no sense superseding  $^1\text{H}$ -NMR, but is complementary to it. Information gained relates to the carbon 'backbone' of the molecule while  $^1\text{H}$ -NMR gives information about the structural environment of each proton. Further, it is possible to obtain a good  $^1\text{H}$ -NMR spectrum on a sample that is much too small for carbon-13 analysis. Modern FT-NMR techniques now permit measurement of proton spectra on samples down to a few micrograms whereas  $^{13}\text{C}$  spectra still require in excess of 5 mg of sample if they are to be measured without excessive expenditure of instrument time.

It is not the intention in this chapter to discuss instrumental or theoretical aspects of this technique. For this type of information the reader is referred to Breitmaier *et al.* (1971) and to the now standard texts of Levy and Nelson (1972) and Stothers (1972). The present chapter will be devoted largely to comment on the interpretation of spectra and to a discussion of the general usefulness of the technique in solving flavonoid structural problems. Illustrations of spectra have been avoided, since Section 2.5 is devoted entirely to their pictorial display.

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### 2.1.1 Sample size and solvents

As mentioned above, sample size can be reduced to a few milligrams with modern FT-NMR techniques. However, the smaller the sample, the more instrument time is required to produce a spectrum of reasonable intensity. Thus in practice sample sizes in the range 10–50 mg (ca. 1/10 mmol) are preferred.

The two key factors in solvent selection are, as in  $^1\text{H}$ -NMR, sample solubility and the position of solvent (carbon) resonances. Solvents commonly found suitable include deuteriochloroform ( $\text{CDCl}_3$ ), dioxan, hexadeuteroacetone [ $(\text{CD}_3)_2\text{CO}$ ], hexadeuterodimethylsulphoxide ( $\text{DMSO-d}_6$ ), deuterium oxide ( $\text{D}_2\text{O}$ ) and combinations of these. A deuterium lock for the instrument is, in most of these, provided by the solvent. Resonances are normally expressed in parts per million (p.p.m.) downfield from tetramethylsilane (TMS) which may or may not be added as reference since solvent carbon signals usually suffice for this purpose. As a guide to solvent selection, chemical shifts reported in the literature for some common solvents (relative to TMS) are listed below:

|                            |                             |
|----------------------------|-----------------------------|
| Cyclohexane                | 27.7 p.p.m.                 |
| $(\text{CD}_3)_2\text{CO}$ | 29.2 p.p.m. (middle signal) |
| $\text{DMSO-d}_6$          | 39.5 p.p.m. (middle signal) |
| Dioxan                     | 66.5 p.p.m.                 |
| $\text{CDCl}_3$            | 77.2 p.p.m. (middle signal) |
| Benzene                    | 128.7 p.p.m.                |
| Pyridine- $\text{d}_5$     | 123.4, 135.3, 149.8 p.p.m.  |
| $\text{CS}_2$              | 192.8 p.p.m.                |

In mixed solvents these values may be altered slightly owing to solvent effects. Varying the solvent may also have important effects on  $^{13}\text{C}$  chemical shifts. Thus Pelter *et al.* (1976) report solvent shifts of up to 0.5 p.p.m. (in flavonoid spectra) for individual carbon resonances when the solvent is changed from  $\text{CDCl}_3$  to  $\text{DMSO-d}_6$ . Again, pyridine, owing to its basicity and polarity, is known to shift signals of phenolic carbons as well as those of nearby carbons. As early as 1964 Maciel and James (1964) noted significant variation of the chemical shifts in phenolic carbon resonances with changing solvent and examples are presented in Table 2.1. Even the detection of certain coupling constants may be affected by small changes in solvent composition, e.g. by the presence of  $\text{H}_2\text{O}$  in  $\text{DMSO-d}_6$  (Chang, 1978).

### 2.1.2 The spectrum

Carbon-13 resonances (for flavonoids) occur over a range of 0–200 p.p.m. downfield from TMS compared with a range of only 0–10 p.p.m. for  $^1\text{H}$  resonances. For this reason  $^{13}\text{C}$ -NMR spectra are much more highly resolved than are  $^1\text{H}$ -NMR spectra. In proton-decoupled spectra (see later) each carbon atom is represented by one line and its chemical shift is determined primarily by the electron density at that carbon atom (for flavonoids see e.g. Kalabin *et al.*, 1977). Thus the carbon resonances at lowest field are generally those of carbonyl

**Table 2.1** Carbon-13 chemical shifts of phenol in different solvents\*

| <i>Solvent</i> | <i>Phenolic carbon</i> | <i>Ortho-carbon</i> | <i>Meta-carbon</i> | <i>Para-carbon</i> |
|----------------|------------------------|---------------------|--------------------|--------------------|
| Cyclohexane    | 155.6                  | 116.1               | 130.5              | 120.8              |
| Benzene        | 156.6                  |                     |                    |                    |
| Dioxan         | 157.6                  | 115.6               | 129.8              | 119.3              |
| Acetone        | 157.9                  | 116.0               | 130.5              | 120.5              |
| DMSO           | 158.5                  | 115.5               | 130.2              | 119.8              |

\* The original spectra measured by Maciel and James (1964) relative to benzene have been converted to the TMS standard by using 128.7 p.p.m. as the chemical shift of benzene relative to TMS.

carbons and oxygenated aromatic carbons, whereas those at highest field will represent non-oxygenated aliphatic carbons. As a general guide approximate chemical shift ranges for carbon types encountered in flavonoids are outlined in Table 2.2. For more detailed data see the appropriate section later in this chapter.

**Table 2.2** Carbon-13 chemical-shift ranges for various carbon types encountered in flavonoids

| <i>Carbon type</i>                             | <i>Approximate chemical-shift range<br/>(p.p.m. from TMS)</i>                                        |
|------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Carbonyl (4-keto, acyl)                        | 210–170                                                                                              |
| Aromatic and olefinic:                         |                                                                                                      |
| (a) Oxygenated                                 | 165–155 (no <i>o/p</i> -oxygenation);<br>150–130 (with <i>o/p</i> -oxygenation); ca. 135<br>(C-3-OH) |
| (b) Non-oxygenated                             | 135–125 (no <i>o/p</i> -oxygenation);<br>125–90 (with <i>o/p</i> -oxygenation);<br>102–110 (C-3).    |
| Aliphatic:                                     |                                                                                                      |
| (a) Oxygenated (sugars)                        | 105–55                                                                                               |
| (b) Non-oxygenated (C-2, 3 flavanones)         | 80–40 (epicatechin C-4, 28 p.p.m.)                                                                   |
| Methylenedioxy                                 | ca. 100                                                                                              |
| Aromatic –OCH <sub>3</sub>                     | 55–60 (59–64 for <i>ortho</i> -disubstituted)                                                        |
| Aromatic C-CH <sub>3</sub> , COCH <sub>3</sub> | ca. 20                                                                                               |
| Aliphatic C-CH <sub>3</sub>                    | ca. 17                                                                                               |

### 2.1.13 $^{13}\text{C}-^1\text{H}$ and $^{13}\text{C}-^{13}\text{C}$ coupling and the nuclear Overhauser effect

In principle  $^{13}\text{C}$  resonances couple with both  $^1\text{H}$  and other  $^{13}\text{C}$  nuclei in the molecule. But in practice  $^{13}\text{C}-^{13}\text{C}$  coupling is not normally observed, since the natural abundance of carbon-13 at 1.1 % is so low that the chances of two  $^{13}\text{C}$  atoms being adjacent to one another in the same molecule are remote (1 in 10 000).  $^{13}\text{C}-^1\text{H}$  coupling, however, is observed and can be most useful in signal assignment problems. With complex molecules, however, the  $^{13}\text{C}-^1\text{H}$  coupling

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complicates the spectrum considerably by producing multiple signals for most carbons. Thus, '<sup>1</sup>H-decoupled' or 'noise-decoupled' spectra are favoured for initial analysis. For such spectra, irradiation of the sample at all <sup>1</sup>H frequencies simultaneously (= radiofrequency noise) during the measurement of the spectrum is carried out. This results in a spectrum in which each carbon is represented by one resonance signal. An added advantage of this decoupling is the signal enhancement achieved (of up to 3 times) due to the nuclear Overhauser effect (n.O.e). This enhancement is due to the fact that the irradiated protons relax the <sup>13</sup>C nuclei more efficiently, thereby favourably perturbing the population ratio of <sup>13</sup>C nuclei in the excited and ground states. The enhancement may be retained in <sup>1</sup>H-coupled spectra by use of techniques such as 'gated' decoupling and 'off-resonance' decoupling.

### 2.1.4 Integration

In contrast to the value of integration in <sup>1</sup>H-NMR spectroscopy, integration of <sup>13</sup>C-NMR spectra is largely uninformative unless special precautions are taken. As a result, integrations are rarely reported. The Fourier Transform operation utilizes an average carbon relaxation time ( $T_1$ ), but in fact  $T_1$  values for individual carbon atoms differ widely, depending on the environment of the carbon, and this results in non-quantitative representation of resonance lines. For example, in the spectrum of rutin (Section 2.5) it can be seen that the one-carbon signal at 104.2 p.p.m. (C-10) is markedly less intense than the one-carbon signal at 115.3 p.p.m. (C-2'). This is due to the longer relaxation time of the quaternary carbon.

### 2.1.5 Substituent effects – general

The introduction of a new substituent into a molecule will normally cause changes in the chemical shifts of nearby <sup>13</sup>C atoms. Such changes are referred to as 'substituent effects' and a knowledge of the extent of these effects is of immense predictive value. In particular, from reference spectra of flavonoids of known structure, e.g. apigenin, it is possible to predict with some accuracy the spectrum of an unavailable flavonoid, e.g. 6-carboxyapigenin, by application of the appropriate substituent effects. Substituent effects on the carbon resonances in substituted benzenes are obviously of prime importance for the interpretation of flavonoid spectra and a number of compilations of these data derived from studies of simple aromatics have appeared in the literature. Table 2.3 represents a selection of substituent effects from the compilations of Stothers (1972) and Levy and Nelson (1972) which are most relevant to the flavonoid field.

The effects listed in Table 2.3 are to a large extent additive and so more than one substituent can be taken into consideration in any calculation. However, the inaccuracies inherent in data obtained from simple molecules and applied to complex molecules are also additive, and the more substituents allowed for, the

**Table 2.3** Substituent effects on the carbon-13 chemical shifts of benzene\*

| <i>Substituent</i>   | <i>C-1</i> | <i>Ortho</i> | <i>Meta</i> | <i>Para</i> |
|----------------------|------------|--------------|-------------|-------------|
| OH                   | + 26.9     | − 12.7       | + 1.4       | − 7.3       |
| OCH <sub>3</sub>     | + 31.4     | − 14.4       | + 1.0       | − 7.7       |
| O <sup>−</sup> †     | + 39.6     | − 8.2        | + 1.9       | − 13.6      |
| OCOCH <sub>3</sub> † | + 23.0     | − 6.4        | + 1.3       | − 2.3       |
| O-phenyl†            | + 29.2     | − 9.4        | + 1.6       | − 5.1       |
| F                    | + 34.8     | − 12.9       | + 1.4       | − 4.5       |
| Cl                   | + 6.2      | + 0.4        | + 1.3       | − 1.9       |
| Br                   | − 5.5      | + 3.4        | + 1.7       | − 1.6       |
| Phenyl               | + 13.1     | − 1.1        | + 0.4       | − 1.2       |
| CH <sub>3</sub>      | + 8.9      | + 0.7        | − 0.1       | − 2.9       |
| CH <sub>2</sub> OH†  | + 12.3     | − 1.4        | − 1.4       | − 1.4       |
| CH=CH <sub>2</sub> † | + 9.5      | − 2.0        | + 2.0       | − 0.5       |
| CO <sub>2</sub> H    | + 2.1      | + 1.5        | 0.0         | + 5.1       |
| COCH <sub>3</sub>    | + 9.1      | + 0.1        | 0.0         | + 4.2       |

\* Shifts in Hertz units. Positive shifts are downfield.

† Data from Stothers (1972), other data from Levy and Nelson (1972).

greater the overall errors will be. In general terms the additivity principles established for simple aromatic systems have been found to be a reliable guide to the interpretation of flavonoid spectra; see e.g. Markham and Ternai (1976), Wagner *et al.* (1976), Kingsbury and Looker (1975), Pelter *et al.* (1976) and Chari *et al.* (1977a). The main exceptions noted have been in rings A and C in situations where the new substituent might be expected to have a modified influence: e.g. the introduction of hydroxyls at C-3 and C-5 (where they would be hydrogen-bonded to the 4-keto function) and the introduction of a methoxyl *ortho* to an existing methoxyl (where steric interaction would be expected). In the case of the introduction of a 3-hydroxyl, C-3 was found to shift downfield (i.e. deshielded by a larger than expected 33 p.p.m.) and the '*ortho*'-effect on C-2 was also large at − 17 p.p.m. The introduction of a 5-hydroxyl causes a downfield shift of about 31 p.p.m. in the C-5 signal and the '*meta*'-related C-4 resonance is deshielded by about 6 p.p.m. The *para*-related C-8 shifts upfield by an unexpectedly large 11 p.p.m. (Ternai and Markham, 1976). In one further example of non-adherence to established substitution effects, Pelter *et al.* (1976) noted that the shifts induced by the introduction of a methoxyl group into the A ring did not correlate well, although B-ring substitution gave good agreement except when *ortho*-substituents were involved.

### 2.1.6 Substituent effects of acetylation and methylation

Acetylation of free phenolic hydroxyl groups produces marked changes in the <sup>13</sup>C-NMR of flavonoids (Pelter *et al.*, 1976) and can be used to detect the location

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of hydroxyl groups on the aromatic rings. On acetylation, the signal of the hydroxylated carbon moves upfield by 6.6–15.6 p.p.m., the *ortho*- and *para*-carbon signals are moved downfield by 4.1–12.1 and 2–7.9 p.p.m. respectively, and the *meta*-carbon signals are only slightly affected (+0.9 to –4.3 p.p.m.).

Methylation of free phenolic hydroxyl groups generally produces smaller, opposite and rather variable effects (Markham *et al.*, 1978; Chari *et al.*, 1977a). The signal of the hydroxylated carbon shifts downfield by 1.0–4.7 p.p.m. and the signal of the *ortho*-related carbon, upfield by 0.8–3.6 p.p.m. Methylation of the 5-hydroxyl in apigenin, however, produces an upfield shift of 1.6 p.p.m. in C-5 and shifts of –3.7, +4.3 and –6.1 p.p.m. in the resonances of C-2, -3 and -4 respectively (Wagner *et al.*, 1976), the anomalous behaviour presumably being due to the disruption of H-bonding with the 4-keto function [cf. 2-hydroxyacetophenone which is also anomalous (Kobayashi *et al.*, 1976)].

### 2.2 FLAVONOID AGLYCONES

#### 2.2.1 General

Although  $^{13}\text{C}$ -NMR is not normally the method of choice for distinguishing this class of a flavonoid, it may be of use in special situations. The different types of aglycone are not distinguishable on the basis of the aromatic carbon resonances alone, but chemical shifts for the central three-carbon unit are often quite distinctive. This is exemplified by the data in Table 2.4, most of which have been taken from Pelter *et al.* (1976).

**Table 2.4** Carbon-13 resonances for ring C in flavonoids\*

|             | C-2                 | C-3                   | >C=O†                 |
|-------------|---------------------|-----------------------|-----------------------|
| Chalcones   | 136.9–145.4(d)‡     | 116.6–128.1(d)‡       | 188.6–194.6(s)        |
| Flavanones  | 75.0– 80.3(d)       | 42.8– 44.6(t)         | 189.5–195.5(s)        |
| Flavones    | 160.5–165(s)        | 103–111.8(d)          | 176.3–184(s)          |
| Flavonols   | 145–150             | 136–139               | 172–177               |
| Isoflavones | 149.8–155.4(d)      | 122.3–125.9(s)        | 174.5–181(s)          |
| Aurones     | 146.1–147.7(s)      | 111.6–111.9(d) (=CH–) | 182.5–182.7(s)        |
| Pterocarpan | 66.4– 66.5(t) (C–6) | 39.5– 40.2(d) (C–6a)  | 78.4– 78.5(d) (C–11a) |

\* Data for  $\text{CDCl}_3$  or  $\text{CDCl}_3/\text{DMSO-d}_6$  solutions according to Pelter *et al.* (1976) except for flavonols,  $\text{DMSO-d}_6$  (Markham *et al.*, 1978; Ternai and Markham, 1976).

† Shifts affected by presence or absence of H-bonded hydroxyls. Data for flavones and isoflavones have been altered to include 5-OH derivatives not studied by Pelter *et al.* (1976). 4-OH aurones have not been studied.

‡ For chalcones, C-2 and C-3 represent the C- $\beta$  and C- $\alpha$ , respectively.

(s) = singlet, (d) = doublet, (t) = triplet



### 2.2.2 $^{13}\text{C}$ - $^1\text{H}$ coupling and signal assignments

The earliest report of a  $^{13}\text{C}$ -NMR study of a flavonoid aglycone appears to be that of Joseph-Nathan *et al.* (1974) in which a complete assignment of the spectrum of flavone itself was made. These assignments were based on a study of the proton noise-decoupled spectra of 5,6,7,8-tetradeuteroflavone, 2',3',4',5',6'-pentadeuteroflavone and 4'-bromoflavone and provided a sound base for the later interpretation of more complex spectra via substituent effect and  $^{13}\text{C}$ - $^1\text{H}$  coupling data. At about the same time, Kingsbury and Looker (1975) published a study of simple methoxylated flavones and made most of their assignments using the known substituent effect of a methoxyl group and observed  $^{13}\text{C}$ - $^1\text{H}$  coupling. These methods of signal assignment have proven generally reliable with flavonoids and have been used extensively in all recent compilations of flavonoid  $^{13}\text{C}$ -NMR spectra.

$^{13}\text{C}$ - $^1\text{H}$  coupling data are especially valuable for confirmation of tentative assignments based on standard substituent effect shift calculations (see Introduction). For example, the presence of a directly attached proton will give rise to a coupling of 155–170 Hz while a *meta*-related proton will produce a highly diagnostic coupling of 4.5–9 Hz. *Ortho*- and *para*- related protons are generally recognized by a 1–4 Hz coupling, although this coupling is unreliable and is not always observed.

Examples of commonly encountered  $^{13}\text{C}$ - $^1\text{H}$  couplings in oxygenated flavonoid nuclei are listed in Table 2.5 and are derived largely from the data of Chang (1978), Ternai and Markham (1976) and Markham and Ternai (1976). The figures quoted are based on a limited number of samples and as such must be considered only as guides to expected coupling constants. For a more detailed study of flavonoid  $^{13}\text{C}$ - $^1\text{H}$  coupling constants (especially long-range), the reader is referred to the work of Chang (1978). Many of the interactions referred to in Table 2.5 are exemplified in the  $^1\text{H}$ -coupled  $^{13}\text{C}$ -NMR spectrum of luteolin (Fig. 2.1).

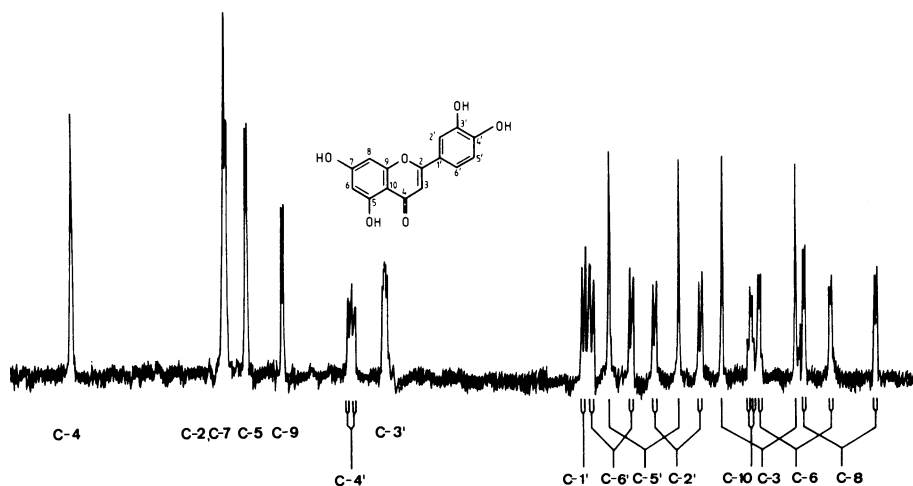
Coupling data have been used to good effect in the distinction of C-6 from C-8 signals, and C-5 from C-9 signals, in the spectra of 5,7-dihydroxy-flavones, -flavonols, -isoflavones and -flavanones (Wehrli, 1975; Chang, 1976, 1978; Wagner *et al.*, 1976; Lallemand and Duteil, 1977). In particular, coupling between the 5-hydroxyl proton and each of the above carbons can be observed for certain compounds in *dry* DMSO solutions. The degree of coupling identifies each carbon and demonstrates that C-5 resonates downfield from C-9 and that C-6 resonates downfield from C-8 (the reverse of the order for H-6 and H-8 resonances in the  $^1\text{H}$ -NMR; see Mabry *et al.*, 1970).

Assignments for C-6 and C-8 in flavones and flavonols have also been made on the basis of heteronuclear decoupling experiments. Thus the selective decoupling of H-6 and H-8 led to the unambiguous assignment of the respective carbon resonances (Wagner *et al.*, 1976). Similarly, low-power irradiation of H-6 and H-8 have also led to definite assignments for C-9 and C-5, in the two compound types,

**Table 2.5**  $^{13}\text{C}$ - $^1\text{H}$  coupling in oxygenated flavonoid nuclei

| <i>Coupled atoms*</i>            | <i>Type location</i>                                         | <i>Coupling constant (J) (Hz)</i> |
|----------------------------------|--------------------------------------------------------------|-----------------------------------|
| <u>CH</u> -aromatic              | A and B ring                                                 | 155–170                           |
| <u>H-ortho</u> /C-aromatic       | A and B ring                                                 | 1.5–4                             |
| <u>H-meta</u> /C-aromatic        | A and B ring                                                 | 4.5–9                             |
| <u>H-para</u> /C-aromatic        | A and B ring                                                 | 1–3                               |
| H-3/C-3                          | Flavones                                                     | 155–170                           |
| H-3/C-2                          | Flavones                                                     | ca. 5                             |
| H-2'/C-2                         | Flavones, Flavonols<br>Flavanones, Isoflavones<br>(C-3/H-2') | ca. 3–4.5                         |
| H-2/C-2                          | Isoflavones                                                  | ca. 200                           |
| H-3/C-3                          | Flavanones                                                   | ca. 130                           |
| H-2/C-2                          | Flavanones                                                   | ca. 150                           |
| 5-OH/C-6                         | Flavanones, Isoflavones<br>(dry DMSO) Flavanone              | ca. 7.0 (anti)                    |
| 5-OH/C-10                        | (dry DMSO)                                                   | ca. 4.7 (syn)                     |
| 5-OH/C-7                         |                                                              | ca. 1.5                           |
| <u>OCH</u> <sub>2</sub> <u>O</u> | Methylenedioxy                                               | ca. 175                           |
| <u>OCH</u> <sub>3</sub>          | Methoxyl                                                     | ca. 145                           |

\* Underlining is used where necessary to indicate atoms involved.

**Fig. 2.1**  $^1\text{H}$ -coupled  $^{13}\text{C}$ -NMR spectrum of luteolin.

taking into consideration their respective  $^2J_{\text{CH}}$  interactions (Chari *et al.*, 1977a). Thus, not only were early tentative assignments based on 'substituent effects' reversed, but a valuable method was established for the distinction of 6- from 8-C-alkylated flavonoids.

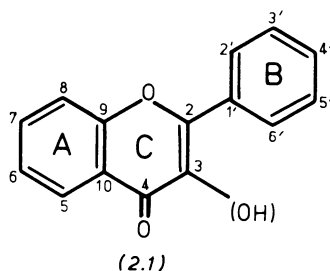
### 2.2.3 The effect of 6- and 8-substitution

From the data presented in Table 2.6, it is evident that substitution of C-6 or C-8, in 5,7-dihydroxyflavonoids, does not markedly alter the chemical shift of the unsubstituted aromatic methine carbon atom. The resonances for C-6 and C-8 in such compounds are distinct and, as their shift ranges do not overlap, can be unambiguously identified. Substitution at C-6 or C-8 can thus readily be determined (Chari *et al.*, 1978a). This also enables differentiation of 5,6,7- and 5,7,8-trioxygenation patterns and of 6-C- and 8-C-glycoflavones (see Section 2.4).

**Table 2.6** Chemical shifts of C-6 and C-8 in some 5,7-dihydroxyflavonoids in DMSO- $d_6$

| <i>Compound</i>                               | <i>C-6</i> | <i>C-8</i> | <i>Reference</i>                |
|-----------------------------------------------|------------|------------|---------------------------------|
| 1. 5,7-Dihydroxyflavanone                     | 96.1       | 95.1       | Wagner <i>et al.</i> (1976)     |
| 2. 6-C-Methyl-5,7-dihydroxyflavanone          | 102.1      | 94.7       | } Chari <i>et al.</i> (1977a)   |
| 3. 8-C-Methyl-5,7-dihydroxyflavanone          | 95.7       | 101.9      |                                 |
| 4. 6-C-Prenyl-5,7,3',4'-tetrahydroxyflavanone | 108.6      | 95.0       | Yakushijin <i>et al.</i> (1980) |
| 5. 5,7,4'-Trihydroxyflavone                   | 98.8       | 94.0       | Wagner <i>et al.</i> (1976)     |
|                                               |            |            | Markham and Ternai (1976)       |
| 6. 5,6,7,3',4'-Pentahydroxyflavone            | 140.4      | 93.6       | Chari <i>et al.</i> (1977a)     |
| 7. 6-C-Glucosyl-5,7,4'-trihydroxyflavone      | 108.8      | 94.2       | } Chari <i>et al.</i> (1978b)   |
| 8. 8-C-Glucosyl-5,7,4'-trihydroxyflavone      | 98.9       | 104.2      |                                 |

### 2.2.4 Flavones and flavonols



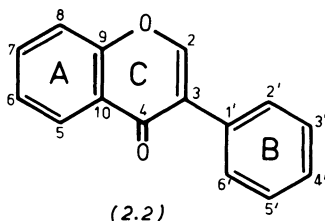
Numerous workers have published compilations of flavone and flavonol aglycone spectra and these include: Kingsbury and Looker (1975), Ternai and Markham (1976), Wagner *et al.* (1976), Pelter *et al.* (1976), Kalabin *et al.* (1977), Wenkert and Gottlieb (1977), Calvert *et al.* (1979) and Iinuma *et al.* (1980). In

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addition, prenylated flavones have been studied by Wenkert and Gottlieb (1977), Chari *et al.* (1978b) and Waterman and Khalid (1980), and several 6-oxygenated flavones by Panichpol and Waterman (1978) and Iinuma *et al.* (1980). A selection of spectra from the work of Wagner *et al.* (1976), Ternai and Markham (1976), and Markham *et al.* (1978) is presented in Table 2.7 to highlight the effects of differing hydroxylation and methoxylation patterns on the spectra. Not evident from these data is the effect of 2'-oxygenation on the chemical shift of C-3 in flavones. In compounds such as wightin, echiodin and echiodinin which all possess 2'-oxygenation, C-3 appears at ca. 109–110 p.p.m., considerably downfield from its position in other flavones. Also not evident is the observation (Iinuma *et al.*, 1980) that the presence of 6-oxygenation reverses the relative positions of the C-5 and C-9 signals as defined for 5,7-dihydroxyflavones (above).

Apart from effects due to changes in the oxygenation pattern, the most notable differences evident between spectra listed in Table 2.7 are those observed in the C-ring resonances. The carbonyl carbon, C-4, for example resonates at around 175–178 p.p.m. when the carbonyl is not hydrogen-bonded, but in the presence of hydrogen-bonding to a 5-hydroxyl group it moves downfield to about 182 p.p.m. When a 3-hydroxyl is present as well as a 5-hydroxyl the resonance returns to about 176 p.p.m., but with the 3-hydroxyl alone the resonance appears at about 171–173 p.p.m. The marked effects brought about by the presence of 5- and 3-hydroxyl groups on both A- and C-ring carbon resonances were discussed earlier in Section 2.1.5.

### 2.2.5 Isoflavones



Reports on the  $^{13}\text{C}$ -NMR spectra of isoflavones include those of Pelter *et al.* (1976), Pelter *et al.* (1978), Wenkert and Gottlieb (1977) and Jha *et al.* (1980). Crombie *et al.* (1975) have reported studies on a range of natural rotenoids. A selection of isoflavone spectra is presented in Table 2.8, and it is evident that only in the C-ring signals are there major differences from the spectra of flavones and flavonols. As a consequence of the different B-ring linkage site, C-2 in isoflavones resonates at higher field than in flavones and C-3 at lower field. Additionally, the C-2 signal is readily identified by its large  $^{13}\text{C}$ - $^1\text{H}$  coupling constant of about 200 Hz. A further feature of the coupled spectrum which is distinctive for isoflavones is the appearance of C-4 as a doublet ( $J = 6.5$  Hz) due to a  $^3J_{\text{CH}}$  interaction with H-2.

Table 2.7 A selection of flavone and flavonol <sup>13</sup>C-NMR spectra (solvent, DMSO-d<sub>6</sub>)

| Flavones             | C-2 | C-3    | C-4   | C-5   | C-6    | C-7   | C-8    | C-9   | C-10   | C-1'  | C-2'  | C-3'  | C-4'  | C-5'  | C-6'    |
|----------------------|-----|--------|-------|-------|--------|-------|--------|-------|--------|-------|-------|-------|-------|-------|---------|
| Flavone              | **  | 162.1  | 106.7 | 176.7 | 125.1  | 124.5 | 133.8  | 118.2 | 155.3  | 123.1 | 130.8 | 126.0 | 131.4 | 128.7 | 126.0   |
| 5-OH flavone         | *   | 164.1  | 105.6 | 182.9 | 159.8  | 110.8 | 135.6  | 107.2 | 155.9  | 110.1 | 130.5 | 126.4 | 132.0 | 128.9 | 126.4   |
| 5,4'-OH flavone      | *   | 165.5  | 103.9 | 183.5 | 160.0  | 111.4 | 136.2  | 108.0 | 156.4  | 110.5 | 121.9 | 129.2 | 161.7 | 116.7 | 129.2   |
| 5,7-OH flavone       |     | 163.0  | 105.0 | 181.6 | 161.5  | 98.9  | 164.3  | 94.0  | 157.3  | 103.9 | 131.7 | 126.0 | 130.6 | 128.0 | 126.0   |
| Apigenin             |     | 164.1  | 102.8 | 181.8 | 161.5  | 98.8  | 163.7  | 94.0  | 157.3  | 103.7 | 121.3 | 128.4 | 161.1 | 116.0 | 128.4   |
| Acacetin             |     | 163.9  | 103.9 | 182.3 | 162.2  | 99.4  | 164.8  | 94.3  | 157.9  | 104.4 | 123.5 | 128.4 | 162.8 | 114.8 | 128.4   |
| 5-Me apigenin        |     | 160.4† | 107.1 | 175.7 | 159.9† | 96.4  | 162.4  | 95.2  | 159.0† | 106.0 | 121.5 | 127.7 | 160.6 | 115.8 | 127.7   |
| 7-Me apigenin        |     | 164.6  | 103.4 | 182.3 | 161.8  | 98.2  | 165.6  | 92.9  | 157.7  | 105.0 | 121.6 | 128.8 | 161.8 | 116.3 | 128.8   |
| Luteolin             |     | 164.5† | 103.3 | 182.2 | 162.1  | 99.2  | 164.7† | 94.2  | 157.9  | 104.2 | 122.1 | 113.8 | 146.2 | 150.1 | 119.3†† |
| Chrysoeriol          |     | 163.7† | 103.8 | 181.8 | 161.6  | 98.8  | 164.2† | 94.0  | 157.4  | 103.3 | 121.7 | 110.2 | 148.0 | 115.8 | 120.4†† |
| Diosmetin            |     | 163.6  | 104.0 | 181.8 | 161.7  | 99.0  | 164.4  | 94.0  | 157.5  | 103.7 | 123.3 | 113.1 | 146.9 | 151.2 | 118.7†† |
| Tricetin             | *   | 164.2  | 103.2 | 181.6 | 161.6  | 99.0  | 164.2  | 93.9  | 157.5  | 104.0 | 120.9 | 106.0 | 146.5 | 137.9 | 106.0   |
| Flavonols            |     |        |       |       |        |       |        |       |        |       |       |       |       |       |         |
| Kaempferol           |     | 146.8  | 135.6 | 175.9 | 160.7  | 98.2  | 163.9  | 93.5  | 156.2  | 103.1 | 121.7 | 129.5 | 115.4 | 159.2 | 129.5   |
| Quercetin            |     | 146.9  | 135.8 | 175.9 | 160.8  | 98.3  | 164.0  | 93.5  | 156.2  | 103.1 | 122.1 | 115.2 | 145.1 | 147.7 | 120.1   |
| 5-Me quercetin       |     | 142.0  | 137.1 | 171.1 | 160.6  | 96.0  | 162.6  | 94.8  | 158.1  | 105.2 | 122.4 | 114.6 | 145.1 | 147.1 | 119.3   |
| 7-Me quercetin       |     | 147.3  | 136.0 | 175.9 | 160.4  | 97.4  | 164.9  | 91.9  | 156.0  | 103.7 | 121.9 | 115.2 | 145.0 | 147.8 | 120.1   |
| 4',7-Me quercetin    |     | 146.7  | 136.4 | 176.0 | 160.4  | 97.4  | 164.9  | 91.8  | 156.0  | 104.0 | 123.4 | 114.8 | 146.2 | 149.4 | 119.8   |
| Morin                | *   | 149.6  | 136.5 | 176.7 | 161.3  | 99.6  | 164.1  | 95.0  | 156.9  | 105.0 | 111.2 | 158.1 | 105.0 | 161.0 | 132.3   |
| Myricetin (3-O-glyc) | *   | —      | —     | —     | 161.2  | 98.6  | 164.0  | 93.3  | 156.2  | 104.0 | 120.0 | 108.8 | 145.3 | 136.6 | 108.8   |

† Assignments may be reversed.

†† Assignments for C-1' and C-6' reversed according to Iinuma *et al.* (1980).\* Spectra from Ternai and Markham (1976) or Markham *et al.* (1978). All others from Wagner *et al.* (1976).

\*\* Spectrum from Wenkert and Gottlieb (1977).

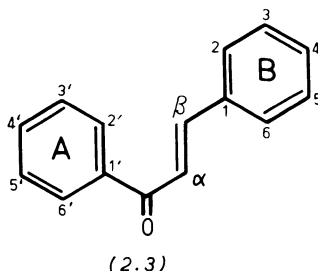
Table 2.8 A selection of isoflavone  $^{13}\text{C}$ -NMR spectra

| <i>Isoflavones</i>                | * | C-2   | C-3    | C-4   | C-5   | C-6   | C-7   | C-8   | C-9   | C-10  | C-1'   | C-2'  | C-3'   | C-4'   | C-5'  | C-6'  |
|-----------------------------------|---|-------|--------|-------|-------|-------|-------|-------|-------|-------|--------|-------|--------|--------|-------|-------|
| 7-OMe                             | P | 152.4 | 125.1  | 175.3 | 127.6 | 114.4 | 163.8 | 100.0 | 157.7 | 118.3 | 127.9  | 128.3 | 128.8  | 131.8  | 128.8 | 128.3 |
| 2',7'-OMe                         | P | 155.8 | 122.7  | 175.5 | 127.9 | 114.4 | 164.0 | 100.3 | 158.1 | 118.6 | 121.1  | 157.7 | 111.4  | 131.8  | 120.6 | 129.7 |
| 4'-OH, 7-OMe                      | P | 151.8 | 124.4  | 175.2 | 127.0 | 114.3 | 163.5 | 100.0 | 157.2 | 117.9 | 122.4  | 129.8 | 115.2  | 157.5  | 115.2 | 129.8 |
| 7,3',4'-OMe                       | W | 151.8 | 124.3† | 175.3 | 127.2 | 114.2 | 163.5 | 99.8  | 157.4 | 118.0 | 124.4† | 112.3 | 148.4‡ | 148.7‡ | 110.9 | 120.6 |
| 6,7,4'-OMe                        | W | 151.5 | 124.2† | 175.2 | 104.7 | 147.4 | 154.1 | 99.3  | 151.9 | 117.6 | 124.1† | 129.8 | 113.7  | 159.2  | 113.7 | 129.8 |
| 5,7,4'-OH                         | C | 153.6 | 121.4† | 180.2 | 157.6 | 98.6  | 164.3 | 93.7  | 157.6 | 104.6 | 122.4† | 130.0 | 115.2  | 162.1  | 115.2 | 130.0 |
| 5-OH,3',4'-(O-CH <sub>2</sub> -O) | M | 153.7 | 123.4† | 174.5 | 126.9 | 115.6 | 161.4 | 103.9 | 156.9 | 118.7 | 125.6† | 109.3 | 147.0  | 147.0  | 107.9 | 122.2 |
| 5,7-OH, 6,2',3',4'-OMe            | W | 154.5 | 119.3  | 180.6 | 152.6 | 130.9 | 156.3 | 93.6  | 153.0 | 105.5 | 110.4  | 151.6 | 97.8   | 149.6  | 142.4 | 115.0 |

\* Source of spectrum: P = Pelter *et al.* (1976), Solvent  $\text{CDCl}_3$  and  $\text{CDCl}_3/\text{DMSO-d}_6$  for 4'-OH,7-OMe.W = Wenkert and Gottlieb (1977); Solvent  $\text{CDCl}_3$  and  $\text{CDCl}_3/\text{MeOH}$  for 5,7-OH, 6,2',3',4'-OMe.C = Chari *et al.* (1977), Solvent  $\text{DMSO-d}_6$ .M = Markham and Ternai (1976), Solvent  $\text{DMSO-d}_6$ .

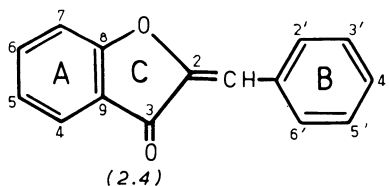
† or ‡ Assignments may be reversed.

## 2.2.6 Chalcones



The  $^{13}\text{C}$ -NMR spectrum of chalcone itself was originally assigned by Radeaglia *et al.* (1976) and since that time the spectra of a number of oxygenated (Pelter *et al.*, 1976; Markham and Ternai, 1976; Solaniova *et al.*, 1976) and other (Solaniova *et al.*, 1976) derivatives have appeared in the literature. Some of the former are presented in Table 2.9. Of interest primarily are the chemical shifts of the  $\alpha$ ,  $\beta$  and carbonyl carbons. The carbonyl carbon at 188–195 p.p.m. is, as expected, shifted downfield by the presence of a 2'-hydroxyl due to hydrogen-bonding. C- $\alpha$  and C- $\beta$  give rise to signals in the ranges 116–128 and 136–146 p.p.m. respectively, and according to Pelter *et al.* (1976) can be identified by their characteristic appearance as a six-line multiplet in the off-resonance-decoupled spectrum. Both are affected by changes in the B-ring substitution and C- $\alpha$  also by the presence or absence of a 2'-hydroxyl group.

## 2.2.7. Aurones



Very little has been published on the  $^{13}\text{C}$ -NMR of aurones, the major contributions known to the authors being those of Pelter *et al.* (1976, 1979). The aurones studied are all synthetic and several of the reported spectra are presented in Table 2.9. The data in the table refer to the (natural product type) *Z*-isomers which were shown by Pelter *et al.* (1979) to be readily distinguishable from the equivalent *E*-isomers by the chemical shift of the exocyclic olefinic carbon. In *E*-isomers this resonance occurs at about 10 p.p.m. downfield from its position in *Z*-isomers. The carbonyl carbon resonates in the range 181–186 p.p.m. in the aurones studied, but all of these lack the hydrogen-bonding 4-hydroxyl.

Table 2.9 A selection of chalcone and aurone  $^{13}\text{C}$ -NMR spectra

| Chalcones           | * | C-1   | C-2   | C-3   | C-4   | C-5   | C-6   | C- $\beta$ | C- $\alpha$ | C=O   | C-1'  | C-2'  | C-3'  | C-4'  | C-5'  | C-6'  |
|---------------------|---|-------|-------|-------|-------|-------|-------|------------|-------------|-------|-------|-------|-------|-------|-------|-------|
| Chalcone            | R | 134.7 | 128.3 | 128.3 | 130.3 | 128.3 | 128.3 | 144.4      | 121.7       | 189.8 | 138.0 | 128.3 | 128.7 | 132.6 | 128.7 | 128.3 |
| 2'-OH               | P | 134.5 | 128.9 | 128.6 | 130.8 | 128.6 | 128.9 | 145.3      | 118.5       | 193.6 | 119.9 | 163.6 | 118.8 | 136.3 | 119.9 | 129.6 |
| 2'-OH, 4'-OMe       | P | 134.6 | 128.8 | 128.4 | 130.5 | 128.4 | 128.8 | 144.2      | 120.2       | 191.6 | 113.9 | 166.5 | 101.0 | 166.0 | 107.6 | 131.1 |
| 2'-OH 4-OMe         | P | 127.4 | 130.6 | 114.6 | 162.1 | 114.6 | 130.6 | 145.4      | 118.6       | 193.7 | 120.2 | 163.6 | 118.8 | 136.2 | 117.7 | 129.6 |
| 2, 2'-OH 4'-OMe     | P | 122.0 | 157.7 | 116.7 | 131.8 | 120.4 | 130.0 | 141.1      | 119.8       | 192.8 | 114.4 | 166.5 | 101.1 | 166.1 | 107.4 | 131.5 |
| 2, 2', 3'-OH 4'-OMe | P | 135.8 | 115.1 | 157.7 | 118.2 | 129.8 | 120.0 | 144.5      | 119.8       | 191.7 | 113.9 | 166.3 | 101.0 | 165.9 | 107.3 | 131.3 |
| 3-OH 2',4'-OMe      | P | 127.8 | 114.9 | 146.9 | 150.5 | 111.7 | 122.2 | 144.7      | 118.1       | 191.8 | 114.0 | 166.1 | 101.0 | 165.8 | 107.2 | 131.0 |
| Aurones             |   | C-1'  | C-2'  | C-3'  | C-4'  | C-5'  | C-6'  | =CH-       | C-2         | C-3   | C-4   | C-5   | C-6   | C-7   | C-8   | C-9   |
| 4'-OMe              | P | 125.0 | 133.4 | 114.4 | 161.0 | 114.4 | 133.4 | 112.8      | 145.8       | 184.3 | 124.4 | 123.2 | 136.4 | 113.3 | 165.7 | 121.9 |
| 6-OMe               | P | 132.3 | 131.1 | 128.7 | 129.4 | 128.7 | 131.1 | 111.6      | 147.7       | 182.7 | 125.6 | 112.0 | 167.2 | 96.5  | 168.3 | 114.7 |
| 4'-OH, 6-OMe        | P | 123.4 | 133.2 | 116.1 | 159.3 | 116.1 | 133.2 | 111.9      | 146.1       | 182.5 | 125.3 | 112.8 | 166.9 | 96.5  | 167.8 | 114.9 |
| 2'-OH, 6-OMe        | P | 119.0 | 157.2 | 115.6 | 131.1 | 119.3 | 130.9 | 105.9      | 146.8       | 181.8 | 125.0 | 112.0 | 164.9 | 96.6  | 167.7 | 114.4 |

\* Source of spectrum: R = Radeigia *et al.* (1976), Solvent  $\text{CDCl}_3$ .P = Pelter *et al.* (1976) – chalcones; (1979) – aurones. Solvent  $\text{CDCl}_3$ , except for 2',4'-OH,4'-OMe chalcone, 4'-OH,6-OMe and 2'-OH,6-OMe aurones,  $\text{CDCl}_3/\text{DMSO}-d_6$ .



## 2.2.8. Biflavonoids

Among the naturally occurring biflavonoids, those possessing a C–C linkage to at least one of the A rings (C-6 or C-8) predominate. Distinguishing the C-6 from the C-8 signal is thus of considerable significance in structure studies. The chemical shift difference between C-6 and C-8 in 5,7-dihydroxyflavonoids is small in flavanones and 3-hydroxyflavanones (ca. 1 p.p.m.) and larger in flavones, isoflavones and flavonols (ca. 4.8 p.p.m.). However, they may be distinguished unambiguously by selective heteronuclear decoupling (Wagner *et al.*, 1976) and on the basis of proton-coupled spectra (Wehrli, 1975; Markham and Ternai, 1976).

Examples of the range of C–C linkage types studied by  $^{13}\text{C}$ -NMR and involving apigenin and/or naringenin are presented in Table 2.10. Interflavonoid linkages between rings A and A, A and B, and A and C are exemplified.

**Table 2.10** Comparison of chemical shifts in the region 90–110 p.p.m. in the  $^{13}\text{C}$ -NMR spectra of C–C-linked biflavonoids involving ring A

| Carbon atom                         |    | C-3   | C-6   | C-8   | C-10  |
|-------------------------------------|----|-------|-------|-------|-------|
| Apigenin                            |    | 102.8 | 98.8  | 94.0  | 103.7 |
| Cupressuflavone                     | I  | 102.8 | 99.0  | 98.7  | 104.3 |
| [(I-8, II-8) biapigenin]            | II | 102.8 | 99.0  | 98.7  | 104.3 |
| Agathisflavone                      | I  | 103.1 | 103.6 | 93.7  | 103.8 |
| [(I-6, II-8) biapigenin]            | II | 102.8 | 98.9  | 98.7  | 104.0 |
| Robustaflavone                      | I  | 102.9 | 99.0  | 94.0  | 103.9 |
| [(I-3', II-6) biapigenin]           | II | 102.9 | 103.5 | 93.9  | 103.9 |
| Amentoflavone                       | I  | 103.2 | 98.9  | 94.2  | 104.0 |
| [(I-3', II-8) biapigenin]           | II | 102.8 | 99.1  | 104.1 | 104.0 |
| Naringenin                          |    | 42.0  | 95.9  | 95.0  | 101.8 |
| Succedaneaflavone                   | I  | 42.2  | 101.1 | 94.7  | 101.9 |
| [(I-6, II-6) binaringenin]          | II | 42.2  | 101.1 | 94.7  | 101.9 |
| Volkensiflavone                     | I  | 48.2  | 96.4  | 95.3  | 101.7 |
| [Naringeninyl (I-3, II-8) apigenin] | II | 102.8 | 98.5  | 100.6 | 103.6 |

These data were taken from Chari *et al.* (1977c). The spectra were run in DMSO- $d_6$  at 80°C.

In the spectrum of cupressuflavone, apigeninyl (I-8, II-8)\* apigenin, the quaternary C-8 resonance appears at 98.7 p.p.m. whereas the chemical shift of C-6 is at 99.0 p.p.m. The only other resonances, each for two carbons, in the region 93.0–104.0 p.p.m. are those at 102.8 p.p.m. (I-3, II-3) and 104.3 p.p.m. (I-10, II-10). From a comparison with the chemical shifts of the corresponding carbon atoms in apigenin, it is evident that the C-8 signal experiences a downfield shift of 4.7 p.p.m. and that the others are largely unaffected. The spectrum of agathisflavone [apigeninyl(I-8, II-6) apigenin] shows eight distinct resonances in this region but only the signals for I-8 and II-6 are shifted downfield relative to the

\* For nomenclature see Locksley (1973).

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signals of C-8 and C-6 in the spectrum of apigenin. The spectrum of the naturally occurring (II-8, I-5') biluteolin (Osterdahl, 1979) is characterized by the appearance of two C-6 signals (I-6, II-6) at 99.3 and 99.2 p.p.m. as well as that of I-8 at 94.3 p.p.m. In addition, the signal for the quaternary I-5' appears at 120.6 p.p.m. and is 4.5 p.p.m. downfield relative to that of II-5'. Another example, 5-methoxybilobetin [apigeninyl(I-8, II-5')-3',4'-di-*O*-methyl-luteolin] has also recently been studied (Joly *et al.*, 1980). The only example of linkage involving the rings A and C is that of I-8, II-3, e.g. volkensiflavone. Owing to the restricted rotation about the C–C interflavonoid linkage, the  $^{13}\text{C}$ -NMR spectrum of volkensiflavone at room temperature shows multiple resonances as well as considerable broadening of signals. Other (I-3, II-8)-linked biflavonoids that have been investigated by  $^{13}\text{C}$ -NMR spectroscopy are GB-1 (naringeninyl-naringenin), morelloflavone [naringeninyl(I-3, II-8) luteolin; Duddeck *et al.*, 1978], kolaflavanone [naringeninyl(I-3, II-8) taxifolin 4'-*O*-methyl ether; Cotterill *et al.*, 1978] and manniflavanone [eriodictyolyl (I-3, II-8) taxifolin; Crichton and Waterman, 1979].

The evidence above suggests that an inspection of the chemical shift values of the signals in the region 90.0–105 p.p.m. can give a good indication of the position of the linkage in a C–C-linked biflavonoid provided that the component monoflavonoids are known. Additional confirmation can be gained by running the off-resonance and proton-coupled spectra.

### 2.2.9 Flavanones (2,3-dihydroflavones)

Published  $^{13}\text{C}$  chemical-shift data for flavanones include those of Wehrli (1975), Wagner *et al.* (1976), Markham and Ternai (1976), Panichpol and Waterman (1978) and Wenkert and Gottlieb (1977). Prenylated flavanones have been studied by Komatsu *et al.* (1978), van Zyl *et al.* (1979) and Yakushijin *et al.* (1980).  $^{13}\text{C}$ -NMR spectral investigations on naturally occurring C-benzylated flavanones have been reported by Hufford and Lasswell (1978) and on their methyl ethers by El-Sohly *et al.* (1979).

Increased polarization of the carbonyl group in flavanones as compared with that in flavones, results in a ca. 14 p.p.m. downfield shift of the C-4 resonance of the former relative to the latter. The carbonyl resonance in 5-hydroxylated flavanones occurs in the region  $195 \pm 2$  p.p.m. The C-3 methylene carbon signal is characteristic and is at  $42 \pm 0.5$  p.p.m. whereas the C-2 oxymethine carbon resonates at  $78 \pm 0.3$  p.p.m. for such compounds. Further consequences of the reduction of the 2,3 double bond in flavones, as exemplified by naringenin, are downfield shifts of the C-5 (2 p.p.m.), C-7 (3 p.p.m.) and C-9 (5.5 p.p.m.) resonances as compared with the corresponding carbon signals in apigenin. The C-6 signal, however, shifts upfield by about 2 p.p.m. possibly owing to increased electron donation to this carbon by the C-9 ring oxygen. Loss of conjugation between the rings B and C results in a downfield shift of the C-1' resonance by 8.6 p.p.m. with an upfield shift of 3.3 p.p.m. for C-4' as compared with apigenin.

The chemical-shift data for the carbon atoms in some representative flavanones are presented in Table 2.11.

### 2.2.10 2,3-Dihydroflavonols

Hydroxyl substitution of C-3 in flavanones leads to 30.5 and 4.8 p.p.m. downfield shifts of the signals for the carbon atoms C-3 and C-2 respectively as exemplified by taxifolin (Table 2.11; Markham and Ternai, 1976). In contrast, the C-4 resonance is only slightly influenced (+ 0.9 p.p.m.). In the case of dihydromorin (Table 2.11) the C-2 signal shifts upfield by 4.8 p.p.m. relative to C-2 in taxifolin, presumably owing to a  $\gamma$ -type of interaction between H-2 and the 2'-OH (Wenkert and Gottlieb, 1977). There has been a report that *O*-glucosidation of the 3-OH in (2*R*, 3*R*)-taxifolin leads to a 7.8 p.p.m. upfield shift of the C-4 resonance (Sakurai and Okumura, 1978).

### 2.2.11 Isoflavanones (2,3-dihydroisoflavones)

The  $^{13}\text{C}$ -NMR spectra of two (methoxylated) isoflavanones have been reported by Wenkert and Gottlieb (1977). They are characterized by C-2 oxymethylene resonances at 71.7 p.p.m. and 71.5 p.p.m. and C-3 methine carbon signals at 50.9 p.p.m. and 51.5 p.p.m., so affording a clear differentiation from the isomeric flavanones. Other examples of oxygenated isoflavanones investigated are the mono- and di-isoprenylated 5,7,4'-trihydroxy-2'-methoxyisoflavanones (Komatsu *et al.*, 1978). In both cases, however, interaction of the C-2' substituent with H-3 shifts the C-3 resonances upfield to 44.6 p.p.m. and 44.7 p.p.m. respectively (cf. dihydromorin). Selected examples are presented in Table 2.11.

### 2.2.12 Miscellaneous flavonoid conjugates

$^{13}\text{C}$ -NMR spectroscopy has been used in the structure elucidation of several flavonoid conjugates. Reports in the literature on the various types are listed briefly in this section.

Empirical use of chemical-shift data and model compounds has enabled the structure elucidation of a  $\text{C}_{30}$  proanthocyanidin (Jacques *et al.*, 1974; Schilling *et al.*, 1973). Schilling (1975) elegantly demonstrated by  $^{13}\text{C}$ -NMR spectroscopy that there exists an isomer of the above mentioned compound in which the position of the interflavonoid linkage was different. The two structure types were characterized by deuteration studies on model compounds.  $^{13}\text{C}$ -NMR spectroscopy was used by Fletcher *et al.* (1977) to establish the absolute stereochemistry of 2,3-*cis*-procyanidins at C-4. Additionally characteristic spectral differences were noted between the configurational isomers of procyanidin dimers and their derivatives. By a combination of  $^{13}\text{C}$ -NMR, chiroptical and chemical degradative evidence it has been demonstrated that polymeric proanthocyanidins consist exclusively of repeating flavan-3-ol units with C-4-C-6 or C-4-C-8 interflavonoid

Table 2.11 A selection of  $^{13}\text{C}$ -NMR spectra of dihydroflavonoids

| Flavonoid                                                                      | Carbon number |      |       |       |       |       |       |       |       |       |       |       |       |       |       | †  |
|--------------------------------------------------------------------------------|---------------|------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|----|
|                                                                                | C-2           | C-3  | C-4   | C-5   | C-6   | C-7   | C-8   | C-9   | C-10  | C-1'  | C-2'  | C-3'  | C-4'  | C-5'  | C-6'  |    |
| Flavanone                                                                      | 78.7          | 43.5 | 191.1 | 128.3 | 121.2 | 136.0 | 117.8 | 160.8 | 120.5 | 138.7 | 126.3 | 128.3 | 126.1 | 128.3 | 126.3 | W  |
|                                                                                | 78.4          | 42.2 | 195.8 | 163.6 | 96.1  | 166.6 | 95.1  | 162.7 | 101.9 | 138.0 | 126.5 | 128.5 | 128.5 | 128.5 | 126.5 | Wa |
| 5,7-Dihydroxyflavanone<br>(Pinocembrin)                                        |               |      |       |       |       |       |       |       |       |       |       |       |       |       |       |    |
| 5,7,4'-Trihydroxyflavanone<br>(Naringenin)                                     | 78.4          | 42.0 | 196.2 | 163.6 | 95.9  | 166.7 | 95.0  | 162.9 | 101.8 | 128.9 | 128.2 | 115.2 | 157.8 | 115.2 | 128.2 | Wa |
| 5,7,3',4'-Tetrahydroxy-<br>flavanone (Eriodictyol)                             | 78.3          | 42.2 | 196.2 | 163.4 | 95.7  | 166.6 | 94.8  | 162.8 | 101.7 | 129.4 | 114.2 | 145.1 | 145.6 | 115.3 | 117.8 | Wa |
| 5,7,3'-Trihydroxy-4'-<br>methoxyflavanone.<br>(Hesperetin)                     | 78.5          | 42.1 | 196.2 | 163.8 | 96.2  | 166.9 | 95.4  | 163.0 | 102.1 | 131.4 | 114.3 | 146.7 | 148.1 | 112.1 | 118.0 | Wa |
| 5,7,4'-Trihydroxy-6-<br>prenylflavanone<br>(Sophoraflavanone B)                | 78.3          | 42.0 | 197.1 | 161.6 | 107.1 | 164.7 | 95.4  | 160.1 | *     | 129.5 | 128.3 | 115.4 | 157.9 | 115.4 | 128.3 | K  |
| 5,7,8-Trimethoxyflavanone                                                      | 79.0          | 45.6 | 189.2 | 156.2 | 89.5  | 158.7 | 131.0 | 157.8 | 106.3 | 138.9 | 125.9 | 128.7 | 128.4 | 128.7 | 125.9 | P  |
| 3,5,7,3',4'-Pentahydroxy-<br>flavanone(Taxifolin)                              | 83.1          | 71.7 | 197.1 | 163.3 | 96.1  | 166.8 | 95.1  | 162.5 | 100.6 | 128.1 | 115.3 | 144.9 | 145.7 | 115.3 | 119.2 | M  |
| 3,5,7,2',4'-Pentahydroxy-<br>flavanone(Dihydromorin)                           | 78.3          | 70.9 | 198.4 | 163.7 | 96.5  | 167.1 | 95.5  | 163.1 | 100.9 | 114.2 | 159.0 | 103.0 | 157.5 | 107.1 | 130.3 | M  |
| 7,4'-Dimethoxyiso-<br>flavanone                                                | 71.7          | 50.9 | 190.6 | 129.1 | 109.8 | 165.6 | 100.4 | 163.1 | 114.6 | 127.1 | 129.3 | 114.0 | 158.7 | 114.0 | 129.3 | M  |
| 7,3',4'-Trimethoxyiso-<br>flavanone                                            | 71.5          | 51.5 | 190.4 | 129.0 | 109.7 | 165.6 | 100.3 | 163.0 | 114.4 | 127.5 | 111.6 | 148.2 | 148.7 | 111.2 | 120.2 | M  |
| 5,7,4'-Trihydroxy-2'-methoxy-<br>3-prenyl isoflavanone<br>(Sophoraflavanone A) | 70.7          | 44.6 | 198.0 | 164.2 | 96.1  | 167.0 | 95.0  | 163.5 | 102.4 | 121.3 | 156.3 | 118.9 | 157.9 | 111.4 | 127.3 | K  |

\* Signal not observed

† Source of spectrum:

W = Wenkert and Gottlieb (1977), DMSO-d<sub>6</sub>, CDCl<sub>3</sub>.Wa = Wagner *et al.* (1976), DMSO-d<sub>6</sub>.K = Komatsu *et al.* (1978), DMSO-d<sub>6</sub>.P = Panichpol and Waterman (1978), CDCl<sub>3</sub>.M = Markham and Ternai (1976), DMSO-d<sub>6</sub>.

linkages (Czochanska *et al.*, 1979, 1980). Likewise some natural trimeric proanthocyanidins have recently been shown to possess mixed C-4-C-6 and C-4-C-8 interflavonoid linkages (Hemmingway *et al.*, 1981). Chemical-shift data on six rotenoids, which are essentially prenylated isoflavonoids with an oxymethylene bridge between C-2' and C-2 have been published by Crombie *et al.* (1975). Chalmers *et al.* (1977) have reported on the  $^{13}\text{C}$ -NMR spectral data of pterocarpanes.  $^{13}\text{C}$ -NMR spectroscopy has played a key role in the structure elucidation of silychristin, a flavonolignan, for which two alternative formulations were advanced (Chari *et al.*, 1977a; Wagner *et al.*, 1978). Further reports on the carbon chemical-shift data for flavonolignans are those of Parthasarathy *et al.* (1979), Cooper *et al.* (1977) and Merlini *et al.* (1980). A number of reports on the  $^{13}\text{C}$ -NMR of prenylated and chromeno-flavonoids have appeared in the literature. They include Wenkert and Gottlieb (1977), Chari *et al.* (1978a), Nomura *et al.* (1978), Nomura and Fukai (1978, 1979, 1980), Komatsu *et al.* (1978), Van Zyl *et al.* (1979), Yakushijin *et al.* (1980) and Oshima *et al.* (1980a,b).

### 2.3 FLAVONOID O-GLYCOSIDES

Because sugar carbon resonances occur largely well clear of the resonances of the flavonoid nucleus carbons,  $^{13}\text{C}$ -NMR offers a convenient non-destructive method of studying the sugar moieties of flavonoid glycosides. O-Glycoside spectra are often best measured at higher than ambient temperature as this not only sharpens the sugar signals but also eliminates conformational equilibria (through hindered rotation in branched oligosaccharides).

#### 2.3.1 Monosaccharides

The sugars commonly occurring in glycosidic form are all readily distinguishable from one another by  $^{13}\text{C}$ -NMR spectroscopy. This is clearly seen from the selection of spectra presented in Table 2.12. These data were obtained by Gorin and Mazurek (1975) using  $\text{D}_2\text{O}$  solutions of the sugars. Solvent effects with different solvents, however, may alter the chemical shifts markedly, and this is well exemplified by the spectra reported by Tori *et al.* (1978) for  $\text{C}_5\text{D}_5\text{N}$  solutions which differ significantly from those listed in Table 2.12. Different levels of water in  $\text{DMSO-d}_6$  solutions are also known to affect the chemical shifts of sugar carbons. It is evident from the data in Table 2.12 that pyranoses having the same hydroxyl configurations (i.e. homomorphous pyranoses) show similar patterns of carbon resonances. Thus, C-1,-2,-3 and -4 of xylose exhibit chemical shifts close to those of C-1,-2,-3 and -4 of glucose, and similarly, the arabinose spectra are related to those of galactose. Also evident from the table is the potential usefulness of  $^{13}\text{C}$ -NMR spectra for the identification of the C-1 configuration in sugars (and glycosides).

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**Table 2.12**  $^{13}\text{C}$ -NMR spectra\* of selected monosaccharides in  $\text{D}_2\text{O}$  solvent

| <i>Sugar</i>              |          | <i>C-1</i> | <i>C-2</i> | <i>C-3</i> | <i>C-4</i> | <i>C-5</i> | <i>C-6</i> |
|---------------------------|----------|------------|------------|------------|------------|------------|------------|
| D-Glucopyranose           | $\alpha$ | 92.7       | 72.1       | 73.4       | 70.4       | 72.1       | 61.3       |
|                           | $\beta$  | 96.5       | 74.8       | 76.4       | 70.3       | 76.6       | 61.5       |
| D-Galactopyranose         | $\alpha$ | 93.6       | 69.8       | 70.6       | 70.6       | 71.7       | 62.5       |
|                           | $\beta$  | 97.7       | 73.3       | 74.2       | 70.1       | 76.3       | 62.3       |
| D-Mannopyranose           | $\alpha$ | 95.0       | 71.7       | 71.3       | 68.0       | 73.4       | 62.1       |
|                           | $\beta$  | 94.6       | 72.3       | 74.1       | 67.8       | 77.2       | 62.1       |
| D-Xylopyranose            | $\alpha$ | 93.3       | 72.5       | 73.9       | 70.4       | 62.1       | —          |
|                           | $\beta$  | 97.6       | 75.1       | 76.9       | 70.3       | 66.3       | —          |
| L- (or D) Arabinopyranose | $\alpha$ | 97.8       | 73.0       | 73.5       | 69.6       | 67.5       | —          |
|                           | $\beta$  | 93.7       | 69.6       | 69.8       | 69.8       | 63.6       | —          |
| L-Rhamnopyranose          | $\alpha$ | 95.0       | 71.9       | 71.1       | 73.3       | 69.4       | 18.0       |
|                           | $\beta$  | 94.6       | 72.4       | 73.8       | 72.9       | 73.1       | 18.0       |

\* Chemical shifts expressed in p.p.m. from TMS.

Furanose sugars are readily distinguished from their pyranose isomers as is demonstrated by the comparative data on methyl glucopyranosides and methyl glycofuranosides presented in Table 2.13. The data are selected from the published work of Gorin and Mazurek (1975) and (for glycofuranosides) from Ritchie *et al.* (1975).

**Table 2.13**  $^{13}\text{C}$ -NMR spectra\* of selected methyl glucopyranoside/furanoside pairs in  $\text{D}_2\text{O}$  solvent

| <i>Methyl glycoside</i>       | <i>C-1</i> | <i>C-2</i> | <i>C-3</i> | <i>C-4</i> | <i>C-5</i> | <i>C-6</i> |
|-------------------------------|------------|------------|------------|------------|------------|------------|
| $\beta$ -D-Glucopyranoside    | 104.3      | 74.2       | 76.9       | 70.8       | 76.9       | 61.9       |
| $\beta$ -D-Glucofuranoside    | 110.0      | 80.6       | 75.8       | 82.3       | 70.7       | 64.7       |
| $\beta$ -D-Galactopyranoside  | 104.9      | 71.8       | 73.9       | 69.8       | 76.2       | 62.1       |
| $\beta$ -D-Galactofuranoside  | 109.9      | 81.3       | 78.4       | 84.7       | 71.7       | 63.6       |
| $\beta$ -D-Xylopyranoside     | 105.1      | 74.0       | 76.9       | 70.4       | 66.3       | —          |
| $\beta$ -D-Xylofuranoside     | 109.7      | 81.0       | 76.0       | 83.6       | 62.2       | —          |
| $\alpha$ -L-Arabinopyranoside | 105.1      | 71.8       | 73.4       | 69.4       | 67.3       | —          |
| $\alpha$ -L-Arabinofuranoside | 109.2      | 81.8       | 77.5       | 84.9       | 62.4       | —          |

\* Chemical shifts expressed in p.p.m. from TMS.

### 2.3.2 Mono-O-glycosides

In O-glycosides carbon-1 of the monosaccharide is linked via a hemiacetal bond to the aglycone moiety. This produces a shift in the C-1 resonance to lower field. In methyl glycosides this shift is of the order of 7–8 p.p.m. (cf. data in Tables 2.12 and 2.13), and apart from a much smaller shift of the C-2 resonance the rest of the spectrum is largely unaffected. In flavonoid glycosides the extent of the downfield shift of the C-1 signal depends very much on the environment of the phenolic

hydroxyl group (Markham *et al.*, 1978), and, although it is generally 4–6 p.p.m., the precise variation appears to be of some diagnostic value (see Table 2.14). The presence of oxygen substituents in both *ortho* positions appears to shift the C-1 sugar signal downfield to about 107 p.p.m. (Osazawa and Takino, 1979) and this also could be of diagnostic value.

**Table 2.14** Chemical shifts (p.p.m.) of sugar C-1 resonances in the  $^{13}\text{C}$ -NMR spectra of flavone and flavonol glycosides

| <i>Glucosides</i> *     | <i>Shift</i> | <i>Rhamnosides</i> *    | <i>Shift</i> |
|-------------------------|--------------|-------------------------|--------------|
| (Glucose) <sup>†</sup>  | 96.5         | (Rhamnose) <sup>†</sup> | 95.0         |
| 7- <i>O</i> -Glucoside  | 100.4        | 7- <i>O</i> -Rhamnoside | 98.9         |
| 2'- <i>O</i> -Glucoside | 100.5        |                         |              |
| 3- <i>O</i> -Glucoside  | 101.4        | 3- <i>O</i> -Rhamnoside | 101.9        |
| 4'- <i>O</i> -Glucoside | 102.2        |                         |              |
| 3'- <i>O</i> -Glucoside | 102.4        |                         |              |
| 5- <i>O</i> -Glucoside  | 104.3        |                         |              |

\* Solvent: DMSO- $\text{d}_6$ .

† Solvent:  $\text{D}_2\text{O}$ .

Other sugar carbon resonances are little affected by glycosylation (see Table 2.15), and so in principle the  $^{13}\text{C}$ -NMR spectrum of a flavonoid monoglycoside can be used to identify both the sugar and the configuration of its linkage from data such as those listed in Tables 2.12 and 2.13 (provided that the same solvent is used for sugar and glycoside).

More diagnostic than the glycosylation effect on the sugar carbon signals is the effect on the signals of the flavonoid nucleus itself. In general terms the carbon at the site of glycosylation is shifted to a higher field following glycosylation, whereas the *ortho*- and *para*-related carbons shift downfield. Thus, the effect of glycosylation of the 7-hydroxyl on the C-7 signal (see Table 2.15) is a 1.4 ppm upfield shift and this is accompanied by downfield shifts of about 1 p.p.m. in the *ortho*-related C-6 and C-8 signals and 1.7 p.p.m. in the *para*-related C-10 signal (Markham *et al.*, 1978). Shifts qualitatively similar but quantitatively different have been observed for glycosylation at sites such as 3' and 4' in flavones and flavonols (Markham *et al.*, 1978; Österdahl, 1979). Significantly, the most reliable indicator of glycosylation appears to be the downfield shift of the *para*-related carbon signal which is invariably larger than the other shifts and generally in the range 1.7–4 p.p.m. There is some evidence that glycosylation with rhamnose produces shifts of a different magnitude from those above (Markham *et al.*, 1978), but this has yet to be confirmed with a significant number of reference compounds.

Glycosylation of the 3- and 5-hydroxyls (Markham *et al.*, 1978; Chari *et al.*, 1977a), as expected, produces unusual effects (see Table 2.15). With the

Table 2.15 Sugar carbon resonances\* in the  $^{13}\text{C}$ -NMR spectra of a selection of flavonoid-O-glycosides

| Glycoside†                  | ‡   | C-1                | C-2               | C-3               | C-4               | C-5               | C-6               | Reference                                   |
|-----------------------------|-----|--------------------|-------------------|-------------------|-------------------|-------------------|-------------------|---------------------------------------------|
| A-7-O-glc                   | 7   | 100.2              | 73.3              | 76.6 <sup>a</sup> | 69.8              | 77.4 <sup>a</sup> | 60.9              | Chari <i>et al.</i> (1977c)                 |
| A-7-O-glc(2-1)apiose        | 7   | 99.7               | 76.8              | 76.6 <sup>a</sup> | 70.2              | 77.2 <sup>a</sup> | 60.9              | Markham <i>et al.</i> (1978)                |
|                             | 2'' | 109.0              | 76.5 <sup>a</sup> | 79.1              | 74.0              | 64.4              | —                 |                                             |
| Ac-7-O-glc(6-1)rha          | 7   | 101.3              | 73.7              | 77.0 <sup>a</sup> | 70.4              | 76.4 <sup>a</sup> | 66.7              | Chari <i>et al.</i> (1977c)                 |
|                             | 6'' | 100.3              | 71.5              | 71.0              | 73.0              | 69.0              | 17.8              |                                             |
| Ac-7-O-glc(6-1)rha(2''-OMB) | 6'' | 97.8               | 73.4 <sup>a</sup> | 68.4              | 72.8 <sup>a</sup> | 69.0              | 17.8              |                                             |
| Ac-7-O-glc(6-1)rha(3''-OMB) | 6'' | 100.3              | 69.2 <sup>a</sup> | 72.3              | 69.5              | 69.0 <sup>a</sup> | 17.8              | Chari <i>et al.</i> (1981)                  |
| Is-4'-OMe-7-O-glc(2-1)      | 7   | 102.5              | 82.5              | 75.5              | 69.2              | 77.2              | 60.6              |                                             |
| -allose(6''-OAc)            | 2'' | 100.0              | 70.7              | 71.5              | 66.9              | 71.5              | 63.6              | Garcia-Granados and Saenz de Buruaga (1980) |
| G-5-O-glc(6-1)xyl           | 5   | 104.3 <sup>a</sup> | 74.0 <sup>b</sup> | 76.5 <sup>c</sup> | 70.8              | 76.4              | 69.1              |                                             |
|                             | 6'' | 104.4 <sup>a</sup> | 73.7 <sup>b</sup> | 76.8 <sup>c</sup> | 70.1              | 65.8              | 61.0              | Markham <i>et al.</i> (1978)                |
| K-3-O-glc                   | 3   | 101.4              | 74.2              | 76.5 <sup>a</sup> | 70.1              | 77.2 <sup>a</sup> | 61.0 <sup>c</sup> |                                             |
| K-3-O-glc(2-1)glc           | 3   | 98.6               | 82.0              | 76.6 <sup>a</sup> | 70.0 <sup>b</sup> | 76.6 <sup>a</sup> | 61.0 <sup>c</sup> |                                             |
|                             | 2'' | 103.6              | 74.3              | 76.7 <sup>a</sup> | 70.5 <sup>b</sup> | 76.7 <sup>a</sup> | 61.4 <sup>c</sup> |                                             |
| K-3-O-glc(6-1)rha           | 3   | 101.5              | 74.2              | 76.5 <sup>a</sup> | 70.1              | 75.8 <sup>a</sup> | 66.9              |                                             |
|                             | 6'' | 100.6              | 70.3 <sup>b</sup> | 70.7 <sup>b</sup> | 72.0              | 68.1              | 17.4              | Markham <i>et al.</i> (1978)                |
| K-7-O-glc-3-O-glc           | 7   | 100.3              | 73.3              | 76.6 <sup>a</sup> | 70.0 <sup>b</sup> | 77.3 <sup>a</sup> | 61.0              |                                             |
|                             | 3   | 101.3              | 74.4              | 76.6 <sup>a</sup> | 70.2 <sup>b</sup> | 77.4 <sup>a</sup> | 61.0              |                                             |
| K-7-O-glc-3-O-glc(6''-OAc)  | 7   | 100.3              | 73.2              | 76.5 <sup>a</sup> | 70.0              | 77.1 <sup>a</sup> | 60.9              |                                             |
|                             | 3   | 101.3              | 74.1              | 76.4              | 70.0              | 74.1              | 62.8              |                                             |
| K-7-O-glc-3-O-glc(2-1)      | 7   | 100.4              | 73.2              | 76.7 <sup>a</sup> | 70.0 <sup>b</sup> | 77.0 <sup>a</sup> | 61.2 <sup>c</sup> | Markham <i>et al.</i> (1978)                |
| -glc(2''-O-sinapoyl)        | 3   | 97.7               | 80.0              | 76.7 <sup>a</sup> | 70.4 <sup>b</sup> | 77.0 <sup>a</sup> | 61.0 <sup>c</sup> |                                             |
|                             | 2'' | 99.1               | 74.6 <sup>d</sup> | 74.1 <sup>d</sup> | 70.7 <sup>b</sup> | 76.1 <sup>a</sup> | 61.0 <sup>c</sup> |                                             |



|                                     |      |       |                   |                   |      |                   |      |                                 |
|-------------------------------------|------|-------|-------------------|-------------------|------|-------------------|------|---------------------------------|
| K-3-O-gal(6-1)rha(4''-OAc)-(3-1)glc | 3    | 102.3 | 71.1              | 72.0              | 68.0 | 73.3              | 66.5 | Guinaudeau <i>et al.</i> (1981) |
|                                     | 6''  | 100.5 | 69.7              | 77.2              | 73.3 | 66.0              | 17.3 |                                 |
|                                     | 3''' | 103.9 | 73.0              | 76.7              | 69.6 | 76.3              | 60.7 |                                 |
| K-3-O-allopyranoside                | 3    | 99.9  | 71.6              | 71.6              | 67.2 | 75.1              | 61.3 | Okuyama <i>et al.</i> (1978)    |
| Q-3-O-gal                           | 3    | 102.3 | 71.3              | 73.4              | 68.0 | 75.8              | 60.8 |                                 |
| Q-3-O-gal(6''-O-galloyl)            | 3    | 102.4 | 71.2              | 73.1              | 68.0 | 72.7              | 62.3 |                                 |
| Q-3-O-rha                           | 3    | 101.9 | 70.4 <sup>a</sup> | 70.6 <sup>a</sup> | 71.5 | 70.1 <sup>a</sup> | 17.3 | Markham <i>et al.</i> (1978)    |
| Q-3-O-ara(pyranose)                 | 3    | 101.8 | 71.7              | 70.8              | 65.9 | 64.1              | —    |                                 |
| Q-3-O-ara(furanose)                 | 3    | 108.1 | 82.1              | 77.2              | 86.2 | 61.0              | —    |                                 |

\* In p.p.m. from TMS, DMSO-d<sub>6</sub> solvent.

† Abbreviations: A, apigenin; Ac, acacetin; K, kaempferol; Q, quercetin; G, genkwanin; Is, isoscutellarein; OAc, acetyl; MB, 2-methylbutyryl, glc, glucose; rha, rhamnose; xyl, xylose; ara, arabinose.

‡ Glycosylation site.

a, b, c, d Assignments bearing the same superscript in any one spectrum may be reversed.

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3-hydroxyl, although the upfield shift of the C-3 signal is of the expected order (ca. 2 p.p.m.), the downfield shift of the 'ortho-related' C-2 signal at 9.2 p.p.m. is especially pronounced. Glycosylation of the 5-hydroxyl in luteolin has a marked effect on the resonances of all A- and C-ring carbons (see Fig. 2.2), presumably owing to the disruption of 5-hydroxy-4-keto hydrogen-bonding.

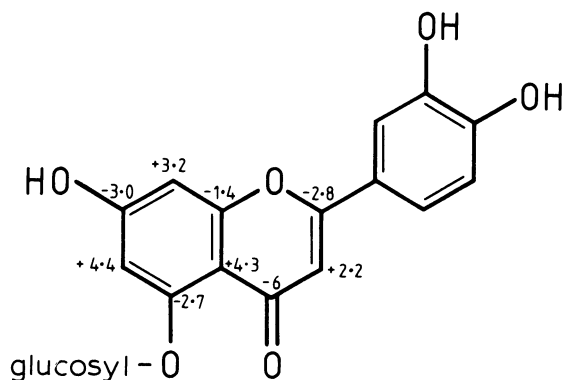


**Fig. 2.2** Signal shifts observed on glycosylation of the 5-hydroxyl of luteolin (Markham *et al.*, 1978).

### 2.3.3 O-Diglycosides

The site at which a second sugar is attached to the sugar of a flavonoid mono-*O*-glycoside is readily determined by  $^{13}\text{C}$ -NMR spectroscopy, and this is perhaps the most significant information contained in the spectrum, as it is difficult to obtain it by other methods (see Chapter 5, Section 5.3). It has been established that glycosylation of sugar hydroxyls produces a sizeable downfield shift in the resonance of the hydroxylated carbon and upfield shifts in the resonances of adjacent carbons (Yamoaka *et al.*, 1971; Colson *et al.*, 1974). Likewise, this has been observed in studies of flavonoid *O*-diglycosides (e.g. Markham *et al.*, 1978; Österdahl, 1979a).

#### Rhamnosylglucosides

A well-studied example of the usefulness of  $^{13}\text{C}$ -NMR spectroscopy in this field is the distinction of flavonoid neohesperidosides [rhamnosyl(1–2)glucosides], rutinosides [rhamnosyl(1–6)glucosides] and rhamnosyl(1–4)glucosides, all of which occur naturally and are otherwise difficult to distinguish. Reports by Österdahl (1978a) and Markham *et al.* (1978) indicate that rutinosides show a 4.5–6.0 p.p.m. downfield shift of the C-6 signal, rhamnosyl(1–4)glucosides a similar downfield shift of the C-4 and neohesperidosides a 3–4 p.p.m. downfield

shift of the C-2. The upfield shifts of adjacent carbons seem to be less consistent. It is of interest that substitution of a glucoside with apiose at the 2-position has been shown to have an effect similar to that of rhamnose (see Table 2.15).

### Glucosylglucosides

Shifts qualitatively similar to those reported for rhamnosylation of glucosides have been reported for glucosylation of glucosides (Markham *et al.*, 1978; Österdahl, 1979a), although as yet only flavonoid sophorosides, gluco(1–2) glucosides, appear to have been studied. In sophorosides a much larger downfield shift (8 p.p.m.) of the glycosylated carbon is observed than in neohesperidosides. This is accompanied by a 2.9 p.p.m. upfield shift of the C-1 signal and is in accord with data previously reported for disaccharides of this type (Yamoaka *et al.*, 1971; Colson *et al.*, 1974). It is to be expected that other linkage types, too, would parallel the equivalent disaccharides in terms of carbon-13 shifts.

### Others

For apiosylglucosides, xylosylglucosides and allosylglucosides see Table 2.15.

### 2.3.4 Polyglycosides

Data such as the above have also been used with some success in defining the glycoside structures of flavonoid tri- (Markham *et al.*, 1978; Österdahl, 1979a; Guinaudeau *et al.*, 1981) and tetra-glycosides (Österdahl, 1978a, 1979a,b) involving mainly glucose and rhamnose. Assignments for polyglycosides are generally achieved by the 'best fit' method, but the reader is referred to the original work for further details.

### Sugar sequencing

The use of  $T_1$  data for sugar sequencing has recently been reported by Guinaudeau *et al.* (1981). The principle of the technique, as reported earlier in connection with studies of the linear oligosaccharide chain of a cardiac glycoside (Bock and Pederson, 1974), is that the average  $NT_1$  values for sugar carbons increase with increasing distance from the aglycone moiety. Thus in the compound studied, faralatoside {kaempferol-3-*O*-[ $\beta$ -D-glucopyranosyl-(1–3)-4'''-*O*-acetyl- $\alpha$ -L-rhamnopyranosyl-(1–6)- $\beta$ -D-galactopyranoside]} the glucose was demonstrated to be terminal by the relatively larger  $NT_1$  values of its carbon resonances, and in particular C-3 and C-5 (see Table 2.16), for which assignments were unambiguous.

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**Table 2.16** Relaxation times of the saccharide carbon atoms in faralatoside

| Carbon | Relaxation time (chemical shift*, p.p.m.) |         |          |         |         |         |
|--------|-------------------------------------------|---------|----------|---------|---------|---------|
|        | Galactose                                 |         | Rhamnose |         | Glucose |         |
| C-1    | 0.21                                      | (103.7) | 0.25     | (100.7) | 0.32    | (104.3) |
| C-2    | 0.21                                      | (71.7)  | 0.25     | (70.4)  | 0.34    | (73.4)  |
| C-3    | 0.22                                      | (72.4†) | 0.24     | (78.2)  | 0.35    | (76.5†) |
| C-4    | 0.18                                      | (68.6)  | 0.23     | (73.7)  | 0.36    | (70.0)  |
| C-5    | 0.21                                      | (73.9†) | 0.25     | (66.4)  | 0.34    | (76.3†) |
| C-6    | 0.12                                      | (67.3)  | 0.59     | (16.7)  | 0.15    | (61.2)  |

\* Solvent: C<sub>5</sub>D<sub>5</sub>N.

† Assignments in any one sugar are reversible.

The chemical shifts of the sugar anomeric carbons may also be of use in sugar sequencing since the downfield shift experienced by C-1 on glycosylation of a phenol (4–6 p.p.m.) is consistently less than the 7–8 p.p.m. associated with glycosylation of a sugar (see Table 2.15). Thus in a flavonoid-*O*-diglucoside, C-1 of the first glucose will normally resonate in the range 100–102.5 p.p.m. whereas C-1 of the terminal glucose will resonate at about 104 p.p.m. Likewise with rhamnose, the C-1 resonance occurs at about 98.8 p.p.m. in 7-*O*-rhamnosides but in rutinoides and neohesperidosides it occurs at about 100.6 p.p.m.

### 2.3.5 Acylated glycosides

The site of acylation in the sugar moiety of flavonoid glycosides is readily determined from the <sup>13</sup>C-NMR spectrum and is evidenced by a downfield shift of the acylated carbon and upfield shifts of the adjacent carbons. It has been shown (Vignon and Vottero, 1976) that as the electron-withdrawing power of the acylating function increases, so also does the extent of the downfield shift of the acylated carbon. This principle also applies to the spectra of flavonoid glycosides and accordingly different acyl functions will exert quantitatively different effects.

Acetates have been studied by a number of workers (e.g. Markham *et al.*, 1978; Guinaudeau *et al.*, 1981; Chari *et al.*, 1980; Markham and Wallace, 1980; Redaelli *et al.*, 1980), and it has been established that acetylation at C-6 of a sugar is evidenced by a downfield shift of 1.8–3 p.p.m. in the C-6 signal and an upfield shift of about 3.4 p.p.m. in the C-5 signal (see Table 2.15). The acetate carbons resonate at about 21 p.p.m. ( $\text{CH}_3\text{CO}$ ) and 171 p.p.m. ( $\text{CH}_3\text{C=O}$ ).

Acylation with 2-methylbutyric acid at sugar C-2 and C-3 sites has been shown (Chari *et al.*, 1977b) to result in similar downfield shifts to acetylation (Table 2.15), and adjacent carbons exhibit 1.2–2.6 p.p.m. upfield shifts in their resonances. Visible portions of the 2-methylbutyryl spectrum included C-3, C-4, C-5 and the carbonyl, at 26.5, 11.4, 16.4 and 175.5 p.p.m. respectively.

Glycoside benzoates studied by  $^{13}\text{C}$ -NMR include gallates (Markham *et al.*, 1978; Isobe *et al.*, 1979) and benzoates themselves (Markham and Wallace, 1980). Here, downfield shifts of the acylated carbon are variable in the range 0–3 p.p.m. More reliable indicators of the acylation site appear to be the upfield shifts of adjacent carbons by about 3 p.p.m. The galloyl carbons resonate at 165 ( $\text{C}_\text{O}_2$ ), 145.4 (C-3,5), 138.4 (C-4), 119.5 (C-1) and 108.8 (C-2, 6) p.p.m.

With sinapates and *p*-coumarates (Rahman *et al.*, 1978; Chari *et al.*, 1978a,b; Markham *et al.*, 1978; Ansari *et al.*, 1979) the downfield shift of the acylated carbon is in the range 2–3 p.p.m. if acylation is at C-6, but is often not observed when acylation is at C-2 (see also Table 2.15). However, the concomitant 2–4 p.p.m. upfield shifts of the adjacent carbons do seem to be reliable. *p*-Coumaroyl carbons resonate at 166.4 ( $\text{C}_\text{O}_2$ ), 144.9 (C- $\beta$ ), 130.3 (C-2,6), 125 (C-1), 115.7 (C-3,5) and 113.9 (C- $\alpha$ ) p.p.m., and sinapoyl carbons at 165.4 ( $\text{C}_\text{O}_2$ ), 145.4 (C-3,5), 138.4 (C-4), 119.5 (C-1) and 108.8 (C-2,6) p.p.m.

## 2.4 FLAVONOID C-GLYCOSIDES

Flavonoid-C-glycosides, in which the sugar residue is a hexosyl or pentosyl moiety, may be considered as 1-arylated-1, 5-anhydro-hexitols or- pentitols. In contrast to *O*-glycosides, the signal for C-1 in C-glycosides appears in the same region as do the other oxymethine carbon resonances, owing to the presence of only one oxygen substituent on this carbon. Thus with the exception of the 6-desoxy derivatives, e.g. rhamnosyl, all carbons of the glycosyl moiety resonate between 60.0 and 82.0 p.p.m.

### 2.4.1 Model compounds: 1-arylated-1,5-anhydroalditols

Table 2.17 lists the chemical shifts for the carbon atoms of the sugar residue of some synthetic 1-arylated-1,5-anhydroalditols (Chari *et al.*, 1981). The assignments were made on the basis of chemical-shift data for the 1,5-anhydroalditols themselves (Que and Gray, 1974) as well as by selective decoupling and off-resonance experiments. In the spectrum of 1-phenyl-1,5-anhydroglucitol, the C-1 resonance is easily identified by selective decoupling of the H-1 and appears at 77.1 p.p.m. This ca. 30 p.p.m. upfield shift of the signal for C-1 as compared with the chemical shift of the anomeric carbon in alkyl and phenolic glycosides is due to the lack of the oxygen substituent on that carbon atom. The shifts induced by the phenyl substituent at C-1, as compared with 1,5-anhydroglucitol itself, are + 7.4 p.p.m. for C-1 and + 3.8 p.p.m. for C-2. Values for the other carbon atoms remain essentially unchanged. When the aryl substituent is 2',4',6'-trimethoxyphenyl the C-1 resonance appears at 73.3 p.p.m. and that of C-2 at 71.0 p.p.m. This 3.8 p.p.m. upfield shift of the C-1 signal from its position in the 1-phenyl analogue can be rationalized as being due to the  $\gamma$ -effect of the 2'-methoxyl substituent. Steric interaction of the same group with the axial H-2 results in a

**Table 2.17** Chemical shifts of sugar carbons in 1-aryl-1, 5-anhydroalditols\*

| <i>Model Compound</i>                                           | <i>C-1</i> | <i>C-2</i> | <i>C-3</i> | <i>C-4</i> | <i>C-5</i> | <i>C-6</i> | <i>References</i>           |
|-----------------------------------------------------------------|------------|------------|------------|------------|------------|------------|-----------------------------|
| 1,5-Anhydroglucitol*                                            | 69.7       | 70.2       | 78.3       | 70.6       | 81.2       | 61.4       | Que and Gray (1974)         |
| 1-Phenyl-1,5-anhydroglucitol                                    | 77.1       | 74.0       | 79.7       | 69.7       | 81.6       | 60.9       | Chari <i>et al.</i> (1981)  |
| 1-(2',4',6'-Trimethoxyphenyl)- $\beta$ -D-1,5-anhydroglucitol   | 73.3       | 71.0       | 79.2       | 70.7       | 80.9       | 61.9       | Chari <i>et al.</i> (1981). |
| 1,5-Anhydrogalactitol*                                          | 70.0       | 67.3       | 75.0       | 70.0       | 80.3       | 62.2       | Que and Gray (1974)         |
| 1-(2',4',6'-Trimethoxyphenyl)- $\beta$ -D-1,5-anhydrogalactitol | 74.0       | 68.6       | 76.2       | 69.5       | 79.3       | 61.0       | Chari <i>et al.</i> (1981)  |
| 1-(2',4',6'-Trimethoxyphenyl)- $\beta$ -D-1,5-anhydroxylitol    | 74.3       | 70.7       | 79.6       | 70.2       | 70.2       | —          | Chari <i>et al.</i> (1981)  |
| 1-(2',4',6'-Trimethoxyphenyl)- $\beta$ -D-1,5-anhydroarabitol   | 73.2       | 67.1       | 74.4       | 68.2       | 69.0       | —          | Chari <i>et al.</i> (1981)  |

\* Solvent: DMSO-d<sub>6</sub>. Ref. DMSO-d<sub>6</sub> 39.6 p.p.m. at 80°C.† These values were taken from Que and Gray (1974) and converted using  $\delta_{CS_2} - \delta_{TMS} = 193.5$  p.p.m. The chemical shifts were determined in D<sub>2</sub>O solution.

– 3.1 p.p.m. shift of the C-2 signal. The same considerations also apply to the galactitol analogue. The assignments for C-1, and C-2 for the xylitol and arabitol analogues (homomorphous with glucitol and galactitol), were made by selective proton decoupling, whereas the C-5 of the arabinose compound was confirmed by an off-resonance experiment. In all cases, the  $^1J_{CH}$  values for the oxymethine carbons were of similar magnitude being  $143 \pm 3.0$  Hz. Hence an assignment of the C-1 signal on the basis of the  $^1J_{CH}$  value alone, which can be done with *O*-glycosides, is not possible for *C*-glycosides. The only significant effect of the sugar moiety on the chemical shifts of the phenolic residue was a 16.0 p.p.m. downfield shift of the resonance of the glycosylated carbon.

### 2.4.2 Flavonoid mono- and di-*C*-glycosides

The data in Table 2.17 serve as a basis for the signal assignments for the sugar carbons in the  $^{13}\text{C}$ -NMR spectra of 6-*C* and 8-*C* as well as 6,8-di-*C*-glycosides of 5,7-dihydroxyflavonoids and their derivatives. The assignments for iso-orientin were determined by selective decoupling experiments at highfield (270 MHz  $^1\text{H}$  and 67.88 MHz for  $^{13}\text{C}$ ), (Chari *et al.*, 1978a) and necessitated revision of previous assignments (Österdahl, 1978b; Hostettmann and Guillardmod, 1976; Miura *et al.*, 1979). From the data in Table 2.18 it is evident that the position of linkage of the *C*-glycosyl unit to the 5,7-dihydroxyflavonoid aglycone does not affect the sugar carbon resonances (cf. the pairs, vitexin and isovitexin; orientin and iso-orientin). The position of linkage can, however, be inferred from the chemical shift of the remaining aromatic methine of ring A, since the only significant effect of *C*-glucosylation on the aglycone spectrum is a downfield shift of ca. 9.8 p.p.m. of the signal for the glycosylated carbon atom. Small upfield shifts of the *ortho* and *para* carbon resonances are also observed but the *meta* carbon resonance is unaffected.

Substitution of the 7-OH of the aglycone by methylation or glycosylation introduces restriction of rotation on the *C*-glucosyl moiety leading to the presence of conformers in solution at room temperature. This can be of use in structure elucidation. Such behaviour is exhibited, for example, by 7,3',4'-tri-*O*-methyl-iso-orientin and saponarin as well as their derivatives. Multiple signals as well as peak broadening can be observed in their spectra at ambient temperature (Chari *et al.*, 1981).

Assignments analogous to those for *C*-glucosides have also been made for 8-galactosylapigenin (Chari *et al.*, 1980). In this case the C-5 assignment was facilitated by comparison of the shift values with those of the naturally occurring 6''-*O*-acetyl derivative.

When both C-6 and C-8 are glycosylated with the same sugar, either both sets of sugar carbon signals are observed in the region 60.0 p.p.m. to 82.0 p.p.m., or coincidence of some signals may occur. Thus the spectrum of 6,8-di-*C*-glucosylchrysoeriol exhibits 11 signals for the two hexosyl units, (Table 2.18) while the spectra of apigenin and tricetin 6,8-di-*C*- $\beta$ -D-glucopyranosides

Table 2.18 Chemical shifts of sugar carbons in flavonoid C- and C-O-glycosides and derivatives\*

| Compound                                                                  | Sugar linkage        | Carbon chemical shifts |      |      |      |      |      | Reference                   |
|---------------------------------------------------------------------------|----------------------|------------------------|------|------|------|------|------|-----------------------------|
|                                                                           |                      | C-1                    | C-2  | C-3  | C-4  | C-5  | C-6  |                             |
| Vitexin (8-C-glucosylapigenin)                                            | 8-C-glc              | 73.9                   | 71.4 | 78.8 | 70.8 | 81.4 | 61.5 |                             |
| Isovitexin (6-C-glucosylapigenin)                                         | 6-C-glc              | 73.4                   | 70.7 | 79.0 | 70.7 | 81.3 | 61.6 |                             |
| Orientin (8-C-glucosyl-luteolin)                                          | 8-C-glc              | 74.6                   | 75.0 | 79.5 | 71.0 | 81.4 | 60.2 |                             |
| Isoorientin (6-C-glucosyl-luteolin)                                       | 6-C-glc              | 72.9                   | 70.4 | 78.8 | 70.1 | 81.3 | 61.3 |                             |
| 7,3',4'-Tri-O-methylisoorientin                                           | 6-C-glc              | 72.6                   | 70.8 | 78.9 | 70.0 | 81.0 | 61.7 | Chari <i>et al.</i> (1980)  |
| 8-C-Galactosylapigenin                                                    | 8-C-gal              | 73.9                   | 68.5 | 75.4 | 69.1 | 80.5 | 61.3 | Chari <i>et al.</i> (1980)  |
| 8-C-(6''-O-acetyl)galactosylapigenin                                      | 8-C-gal              | 73.8                   | 68.2 | 75.0 | 69.4 | 76.7 | 64.8 | Chari <i>et al.</i> (1980)  |
| Molludistin (7-O-methyl-8-C-arabinosyl-apigenin)                          | 8-C-ara              | 74.1                   | 67.8 | 74.9 | 68.9 | 71.0 | —    | Besson <i>et al.</i> (1979) |
| Saponarin (7-O- $\beta$ -glucosylisovitexin)                              | 6-C-glc              | 73.0                   | 70.5 | 79.2 | 70.1 | 81.0 | 61.1 | Wagner <i>et al.</i> (1979) |
|                                                                           | 7-O-glc              | 101.7                  | 73.8 | 76.2 | 71.0 | 77.3 | 61.1 |                             |
| Schaftoside (6-C-glucosyl-8-C-arabinosylapigenin)                         | 6-C-glc              | 73.7                   | 71.1 | 78.7 | 70.2 | 81.5 | 61.0 | Chari, unpublished          |
| 6-C-Arabinosyl-8-C-galactosylapigenin                                     | 8-C-ara              | 74.6                   | 68.9 | 75.1 | 69.2 | 71.1 | —    |                             |
|                                                                           | 6-C-ara              | 74.4                   | 69.1 | 74.4 | 69.1 | 70.3 | —    | Chari, unpublished          |
| 6-C-Galactosyl-8-C-arabinosylapigenin                                     | 8-C-gal              | 74.4                   | 69.1 | 75.4 | 69.1 | 80.1 | 61.3 |                             |
|                                                                           | 6-C-gal              | 73.5                   | 69.4 | 74.8 | 68.3 | 79.0 | 60.7 | Chari, unpublished          |
|                                                                           | 8-C-ara              | 74.4                   | 68.2 | 74.5 | 68.9 | 71.0 | —    |                             |
| 6,8-Di-C-glucosylchrysoeriol                                              | 6-C-glc              | 73.4                   | 70.8 | 78.1 | 69.6 | 80.8 | 60.5 | Mues <i>et al.</i> (1980)   |
|                                                                           | 8-C-glc              | 74.0                   | 71.1 | 78.3 | 69.8 | 81.1 | 60.5 |                             |
| Vicenin-1 (6-C-xylosyl-8-C-glucosylapigenin)                              | 6-C-xyl              | 74.6                   | 70.3 | 78.5 | 70.0 | 70.0 | —    | Chopin, unpublished         |
| Violanthin (6-C-glucosyl-8-C-rhamnosylapigenin)                           | 8-C-glc              | 72.1                   | 70.3 | 78.6 | 70.0 | 81.6 | 61.2 |                             |
| Linocide B (2''-O- $\alpha$ -L-rhamnosyl-7,3',4'-tri-O-methylisoorientin) | 6-C-glc              | 73.5                   | 70.6 | 79.2 | 70.2 | 81.4 | 61.6 | Chari, unpublished          |
| Linocide A (6''-O-acetyl-linocide B)                                      | 8-C- $\alpha$ -rha   | 77.3                   | 75.0 | 75.0 | 72.2 | 72.2 | 18.1 |                             |
|                                                                           | 6-C-glc              | 71.6                   | 75.4 | 79.4 | 70.2 | 80.5 | 61.5 | Chari, unpublished          |
|                                                                           | 2''-O- $\alpha$ -rha | 101.1                  | 70.2 | 70.7 | 70.7 | 67.6 | 17.0 |                             |
|                                                                           | 6-C-glc              | 71.6                   | 75.5 | 79.3 | 70.3 | 77.5 | 63.8 | Chari, unpublished          |
|                                                                           | 2''-O- $\alpha$ -rha | 100.3                  | 70.3 | 70.8 | 70.3 | 67.8 | 17.2 |                             |
|                                                                           | 8-C-glc              | 71.4                   | 75.0 | 79.8 | 70.3 | 81.7 | 61.0 | Chari, unpublished          |
| 2''-O- $\alpha$ -L-rhamnosylvitexin                                       | 2''-O- $\alpha$ -rha | 100.2                  | 70.3 | 71.4 | 70.3 | 68.1 | 17.6 |                             |



|                                                               |                     |       |      |      |      |      |      |                                      |
|---------------------------------------------------------------|---------------------|-------|------|------|------|------|------|--------------------------------------|
| 4'''-O-acetyl-2''-O- $\alpha$ -L-rhamnosylvitexin             | 8-C-glc             | 71.6  | 74.0 | 79.8 | 70.1 | 81.8 | 61.0 | Chari, unpublished                   |
| Adonivernith (2''-O- $\beta$ -D-xylosylvitexin)               | 2'-O- $\alpha$ -rha | 99.2  | 70.5 | 67.6 | 73.5 | 65.3 | 17.0 | Chari, unpublished                   |
|                                                               | 8-C-glc             | 71.6  | 80.8 | 78.5 | 70.5 | 82.0 | 61.4 |                                      |
| Spinosin (2''-O- $\beta$ -D-glucosyl-7-O-methylisovitexin)    | 2'-O- $\beta$ -xyl  | 102.4 | 73.7 | 75.9 | 69.4 | 65.5 | —    | Woo <i>et al.</i> (1979)             |
|                                                               | 6-C-glu             | 70.7  | 80.3 | 78.2 | 70.3 | 81.0 | 61.3 |                                      |
|                                                               | 2'-O- $\beta$ -glc  | 104.6 | 74.3 | 75.9 | 69.6 | 76.1 | 60.5 | Woo <i>et al.</i> (1980)             |
|                                                               | 6-C-glc             | 71.2  | 81.4 | 78.8 | 70.7 | 81.4 | 61.9 |                                      |
| 6'''-O-Feruloylspinosin                                       | 2'-O- $\beta$ -glc  | 105.1 | 74.6 | 76.5 | 69.4 | 73.6 | 62.6 | Hostettmann and<br>Guillarmod (1976) |
|                                                               | 6-C-glc             | 72.4  | 70.6 | 78.7 | 70.3 | 79.7 | 68.7 |                                      |
|                                                               | 6'-O-ara            | 103.7 | 70.3 | 73.1 | 67.2 | 64.7 | —    | Wagner <i>et al.</i> (1979)          |
| 2''-O- $\beta$ -glucosyl-7-O- $\beta$ -galactosylisovitexin   | 6-C-glc             | 71.4  | 81.0 | 78.4 | 70.3 | 81.0 | 60.9 | Wagner <i>et al.</i> (1979)          |
|                                                               | 2'-O- $\beta$ -glc  | 104.8 | 74.8 | 76.1 | 70.3 | 76.6 | 60.9 |                                      |
|                                                               | 7-O- $\beta$ -gal   | 102.0 | 71.4 | 73.2 | 68.5 | 76.0 | 61.3 |                                      |
| 2''-O- $\alpha$ -rhamnosyl-7-O- $\beta$ -galactosylisovitexin | 6-C-glc             | 71.9  | 79.7 | 78.8 | 70.5 | 80.8 | 60.4 | Wagner <i>et al.</i> (1979)          |
|                                                               | 2'-O- $\alpha$ -rha | 100.3 | 70.5 | 70.8 | 71.9 | 68.1 | 17.3 |                                      |
|                                                               | 7-O- $\beta$ -gal   | 102.6 | 71.4 | 72.9 | 68.1 | 75.9 | 60.4 |                                      |

\* Solvent: DMSO-d<sub>6</sub>.

The assignments in this table represent those determined by Chari, unpublished. Previous assignments were either not made or were incorrect.

## 50 The Flavonoids

(Österdahl, 1978b; Theodor *et al.*, 1980) exhibit 12. When the two glycosyl moieties are different as in schaftoside (6-*C*-glucosyl-8-*C*-arabinosylapigenin) it is not possible by  $^{13}\text{C}$ -NMR to determine the position of linkage of each sugar residue. However, this can often be done by mass spectrometry of the permethyl ether derivative (see Chapter 8).

### 2.4.3 *O*-Glycosides of *C*-glycosylflavonoids

Glycosylation of the existing *C*-glycosyl moiety in naturally occurring flavonoid *C*-glycosides has been reported so far only at the C-2 and C-6 positions (see Table 2.18). The resulting downfield shift of the C-2 resonance is ca. 10 p.p.m. where the second sugar is  $\beta$ -glucose (e.g. spinosin) or  $\beta$ -xylose (e.g. adonivernith), and the corresponding shift for  $\alpha$ -rhamnosylation is ca. 5.0 p.p.m. (e.g. linoside A and B). However, in the presence of additional 7-*O*-glycosylation, the rhamnosylation shift is about 9 p.p.m. (see Table 2.18; Wagner *et al.*, 1979). Glycosylation at C-2 also results in an upfield shift of ca. 2.0 p.p.m. in the C-1 resonance of the *C*-glycosyl moiety. This parallels the effects observed with the corresponding flavonoid (2-*O*-glycosyl-*O*-glycosides) (see Section 2.3.3). Interestingly the spectrum of 2''-*O*- $\beta$ -xylosylvitexin shows the presence of more than one conformer in solution at room temperature but that of 2''-*O*- $\alpha$ -rhamnosylvitexin does not.

Arabinosylation of the primary hydroxyl at C-6 results in a 7.5 p.p.m. downfield shift of the signal of the glycosylated carbon (Table 2.18) and it is probable that the effects of glycosylation at C-6 by other sugars would parallel those observed with *O*-glycosides (see Section 2.3.3). The identity of the C-6 signal can be readily established by its distinctive proton-coupling.

Similar solvent effects are encountered with *C*-glycosides as for *O*-glycosides. Examination of the chemical shift values in Table 2.18 reveals variations ( $\pm 0.8$  p.p.m.) in chemical shifts for corresponding carbon atoms in the same glycosyl moieties in different compounds. This is presumably due to the varying moisture content of the sample or the DMSO- $\text{d}_6$  solvents used by different workers.

### 2.4.4 Acylated *C*-glycosides

$^{13}\text{C}$ -NMR spectroscopy is the easiest and only general method for the location of an acyl group when it is linked to the *C*-glycosyl moiety. The effects observed are very similar to those previously discussed for acylated *O*-glycosides. For example, in the case of linoside A (6''-*O*-acetyl-2''-*O*- $\alpha$ -L-rhamnosyl-7,3',4'-tri-*O*-methyliso-orientin; see Table 2.18) the C-5'' signal of the *C*-glucosyl unit is shifted upfield by 3.0 p.p.m. to 77.5 p.p.m. compared with the C-5'' resonance in linoside B, the deacetylated product (Chari *et al.*, 1981). This established that

C-6'' bears the acetyl group in linoside A. Analogously, the position of the acetyl group in 6''-O-acetyl-8- $\beta$ -D-galactosylapigenin has been established by  $^{13}\text{C}$ -NMR spectroscopy (Chari *et al.*, 1980). The location of the feruloyl group on the C-6''' of the O-glucosyl (rather than the C-glucosyl) moiety in 6'''-O-feruloylspinosin is clearly demonstrated by the appearance of the C-5'' resonance of the C-glucose moiety at 81.4 p.p.m., which is very similar to that of C-5'' in spinosin itself (Woo *et al.*, 1979, 1980).

### 2.5 C-13 NMR SPECTRA OF FLAVONOIDS

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Spectra 1–125 follow the index of oxidation patterns commencing on the next page.

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| Spec-<br>trum<br>no. | Flavonoid                                                                                                         | Oxidation pattern |   |   |     |        |                                        |           |    |     |     |   |    |
|----------------------|-------------------------------------------------------------------------------------------------------------------|-------------------|---|---|-----|--------|----------------------------------------|-----------|----|-----|-----|---|----|
|                      |                                                                                                                   | 2                 | 3 | 4 | 5   | 6      | 7                                      | 8         | 2' | 3'  | 4'  | 5 | 6  |
| Flavones             |                                                                                                                   |                   |   |   |     |        |                                        |           |    |     |     |   |    |
| 1                    | 5-Hydroxyflavone                                                                                                  |                   |   |   | OH  |        |                                        |           |    |     |     |   |    |
| 2                    | Chrysin                                                                                                           |                   |   |   | OH  |        | OH                                     |           |    |     |     |   |    |
| 3                    | $\gamma,\gamma$ -Dimethyl-5-hydroxychromenoflavone                                                                |                   |   |   | OH  | prenyl | OR                                     |           |    |     |     |   |    |
| 4                    | 5,4'-Dihydroxyflavone                                                                                             |                   |   |   | OH  |        |                                        |           |    |     |     |   |    |
| 5                    | 3',4'-Dihydroxyflavone                                                                                            |                   |   |   |     |        |                                        |           |    | OH  | OH  |   |    |
| 6                    | 3',4'-Dimethoxyflavone                                                                                            |                   |   |   |     |        |                                        |           |    | OMe | OMe |   |    |
| 7                    | 5-Hydroxy-3',4'-dimethoxyflavone                                                                                  |                   |   |   |     |        |                                        |           |    | OMe | OMe |   |    |
| 8                    | Apigenin                                                                                                          |                   |   |   | OH  |        | OH                                     |           |    |     | OH  |   |    |
| 9                    | Apigenin 7-O- $\beta$ -D-glucoside                                                                                |                   |   |   | OH  |        | O-Glc                                  |           |    |     | OH  |   |    |
| 10                   | Apigenin 7-O-neohesperidoside                                                                                     |                   |   |   | OH  |        | O-Neohesp                              |           |    |     | OH  |   |    |
| 11                   | Apigenin 7-O-apiosylglucoside                                                                                     |                   |   |   | OH  |        | O-Api-Glc                              |           |    |     | OH  |   |    |
| 12                   | Vitexin                                                                                                           |                   |   |   | OH  |        | OH                                     | C-Glc     |    |     | OH  |   |    |
| 13                   | 2'-O-Rhamnosylvitexin                                                                                             |                   |   |   | OH  |        | OH                                     | C-Neohesp |    |     | OH  |   |    |
| 14                   | Saponarin                                                                                                         |                   |   |   | OH  |        | O-Glc                                  |           |    |     | OH  |   |    |
| 15                   | Schaftoside                                                                                                       |                   |   |   | OH  | C-Glc  | OH                                     | C-Ara     |    |     | OH  |   |    |
| 16                   | Violanthin                                                                                                        |                   |   |   | OH  | C-Glc  | OH                                     | C-Rha     |    |     | OH  |   |    |
| 17                   | Thevetiaflavone                                                                                                   |                   |   |   | OMe |        | OH                                     |           |    |     | OH  |   |    |
| 18                   | Genkwanin                                                                                                         |                   |   |   | OH  |        | OMe                                    |           |    |     | OH  |   |    |
| 19                   | Spinosin                                                                                                          |                   |   |   | OH  | C-Soph | OMe                                    |           |    |     | OH  |   |    |
| 20                   | Acacetin                                                                                                          |                   |   |   | OH  |        | OH                                     |           |    |     | OMe |   |    |
| 21                   | Apigenin trimethyl ether                                                                                          |                   |   |   | OMe |        | OMe                                    |           |    |     | OMe |   |    |
| 22                   | Scutellarein 7-O-glucoside                                                                                        |                   |   |   | OH  | OH     | O-Glc                                  |           |    |     | OH  |   |    |
| 23                   | Pectolinarigenin                                                                                                  |                   |   |   | OH  | OMe    | OH                                     |           |    |     | OMe |   |    |
| 24                   | Salvigenin                                                                                                        |                   |   |   | OH  | OMe    | OMe                                    |           |    |     | OMe |   |    |
| 25                   | Isoscutellarein 4'-methyl ether<br>7-O-[2'-O-(6''-acetyl)- $\beta$ -<br>allopyranosyl]-<br>$\beta$ -glucuronanose |                   |   |   | OH  |        | O-(6''-acetyl)-<br>OH Allo<br>(1-2)Glc |           |    |     | OMe |   |    |
| 26                   | Luteolin                                                                                                          |                   |   |   | OH  |        | OH                                     |           |    | OH  |     |   | OH |

|    |                                                                                  |                                 |                |  |               |        |     |
|----|----------------------------------------------------------------------------------|---------------------------------|----------------|--|---------------|--------|-----|
| 27 | Luteolin 5- <i>O</i> -glucoside                                                  | O-Glc                           | OH             |  |               | OH     |     |
| 28 | Luteolin 7- <i>O</i> -glucoside                                                  | OH                              | O-Glc          |  |               | OH     |     |
| 29 | Luteolin 3'- <i>O</i> -glucoside                                                 | OH                              | OH             |  |               | O-Glc  |     |
| 30 | Isoorientin                                                                      | OH                              | C-Glc          |  |               | OH     |     |
| 31 | Adonivermith                                                                     | OH                              | OH             |  |               | OH     |     |
|    |                                                                                  |                                 |                |  | C-Xyl(1-2)Glc |        |     |
| 32 | Diosmetin                                                                        | OH                              | OH             |  |               | OH     |     |
| 33 | Chrysoeriol                                                                      | OH                              | OH             |  |               | OMe    |     |
| 34 | Chrysoeriol 7- <i>O</i> -(2''- $\beta$ -allopyranosyl)- $\beta$ -glucopyranoside | OH                              | O-Allo(1-2)Glc |  |               | OMe    |     |
| 35 | Hydnocarpin                                                                      | OH                              | OH             |  |               | OR     |     |
| 36 | 6-Hydroxyluteolin                                                                | OH                              | OMe            |  |               | OMe    |     |
| 37 | 6-Hydroxyluteolin pentamethyl ether                                              | OMe                             | OMe            |  |               | OMe    |     |
| 38 | Tricetin                                                                         | OH                              | OMe            |  |               | OMe    |     |
| 39 | Isoaifnetin                                                                      | OH                              | C-Glc          |  |               | OH     | OH  |
| 40 | Tricetin 3',4',5'-trimethyl ether                                                | OH                              | OH             |  |               | OH     | OMe |
| 41 | Wightin                                                                          | OH                              | OMe            |  |               | OMe OH |     |
|    | <i>Flavonols</i>                                                                 |                                 |                |  |               |        |     |
| 42 | Galangin                                                                         | OH                              | OH             |  |               | OH     |     |
| 43 | 3'-4'-Dihydroxyflavonol                                                          | OH                              |                |  |               | OMe    |     |
| 44 | 3',4'-Dimethoxyflavonol                                                          | OH                              | OH             |  |               | OH     |     |
| 45 | Kaempferol                                                                       | OH                              | OH             |  |               | OH     |     |
| 46 | Kaempferol 3- <i>O</i> -glucoside                                                | O-Glc                           | OH             |  |               | OH     |     |
| 47 | Tiliroside                                                                       | O-(6''- <i>p</i> -coumaroyl)Glc | OH             |  |               | OH     |     |
| 48 | Kaempferol 3- <i>O</i> -sophoroside                                              | O-Soph                          | OH             |  |               | OH     |     |
| 49 | Kaempferol 3- <i>O</i> -rutinoside                                               | O-Rut                           | OH             |  |               | OH     |     |
| 50 | Kaempferol 7- <i>O</i> -glucoside                                                | OH                              | O-Glc          |  |               | OH     |     |
| 51 | Kaempferol 7- <i>O</i> -neohesperidoside                                         | OH                              | OH             |  |               | OH     |     |
| 52 | Kaempferol 3,7-di- <i>O</i> -glucoside                                           | O-Glc                           | O-Neohesp      |  |               | OH     |     |
| 53 | Kaempferol 3- <i>O</i> -(6''-acetyl)glucoside                                    | O-(6''-acetyl)Glc               | O-Glc          |  |               | OH     |     |
|    | 7- <i>O</i> -glucoside                                                           | OH                              | O-Glc          |  |               | OH     |     |

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| Spec-<br>trum<br>no. | Flavonoid                                   | Oxidation pattern |                    |   |     |   |       |   |    |     |       |   |   |
|----------------------|---------------------------------------------|-------------------|--------------------|---|-----|---|-------|---|----|-----|-------|---|---|
|                      |                                             | 2                 | 3                  | 4 | 5   | 6 | 7     | 8 | 2' | 3'  | 4'    | 5 | 6 |
| 54                   | Kaempferol 3-O-sophoroside                  |                   |                    |   |     |   |       |   |    |     |       |   |   |
|                      | 7-O-glucoside                               |                   | O-Soph             |   | OH  |   | O-Glc |   |    |     | OH    |   |   |
| 55                   | Kaempferol 3-O-(2''-sinapyl)<br>sophoroside |                   | 2''-sinapylsoph    |   | OH  |   | O-Glc |   |    |     | OH    |   |   |
| 56                   | Kaempferol 3-O-glucoside                    |                   |                    |   |     |   |       |   |    |     |       |   |   |
|                      | 7-O-rhamnoside                              |                   | O-Glc              |   | OH  |   | O-Rha |   |    |     | OH    |   |   |
| 57                   | Kaempferol 3-O-(6''-acetyl)<br>glucoside    |                   |                    |   |     |   |       |   |    |     |       |   |   |
|                      | 7-O-rhamnoside                              |                   | O-(6''-acetyl)Glc  |   | OH  |   | O-Rha |   |    |     | OH    |   |   |
| 58                   | Kaempferol 3-O-rutinoside                   |                   |                    |   |     |   |       |   |    |     |       |   |   |
|                      | 7-O-rhamnoside                              |                   | O-Rut              |   | OH  |   | O-Rha |   |    |     | OH    |   |   |
| 59                   | Kaempferol 4'-methyl ether                  |                   |                    |   | OH  |   | OH    |   |    |     | OMe   |   |   |
| 60                   | Quercetin                                   |                   |                    |   | OH  |   | OH    |   |    | OH  | OH    |   |   |
| 61                   | Quercetin 3-O-glucoside                     |                   |                    |   | OH  |   | OH    |   |    | OH  | OH    |   |   |
| 62                   | Quercetin 3-O-rutinoside                    |                   | O-Glc              |   | OH  |   | OH    |   |    | OH  | OH    |   |   |
| 63                   | Quercetin 3-O-galactoside                   |                   |                    |   | OH  |   | OH    |   |    | OH  | OH    |   |   |
| 64                   | Quercetin 3-O-(6''-galloyl)<br>galactoside  |                   |                    |   | OH  |   | OH    |   |    | OH  | OH    |   |   |
|                      |                                             |                   | O-(6''-galloyl)Glc |   |     |   |       |   |    |     |       |   |   |
| 65                   | Quercetin 3-O-rhamnoside                    |                   | O-Rha              |   | OH  |   | OH    |   |    | OH  | OH    |   |   |
| 66                   | Quercetin 3-O-arabinopyranoside             |                   | O-Ara              |   | OH  |   | OH    |   |    | OH  | OH    |   |   |
| 67                   | Quercetin 3-O-arabinofuranoside             |                   | O-Ara              |   | OH  |   | OH    |   |    | OH  | OH    |   |   |
| 68                   | Quercetin 7-O-glucoside                     |                   | OH                 |   | OH  |   | O-Glc |   |    | OH  | OH    |   |   |
| 69                   | Quercetin 4'-O-glucoside                    |                   | OH                 |   | OH  |   | OH    |   |    | OH  | O-Glc |   |   |
| 70                   | Azaleatin                                   |                   | OH                 |   | OMe |   | OH    |   |    | OH  | OH    |   |   |
| 71                   | Rhamnetin                                   |                   | OH                 |   | OH  |   | OMe   |   |    | OH  | OH    |   |   |
| 72                   | Isorhamnetin                                |                   | OH                 |   | OH  |   | OH    |   |    | OMe | OH    |   |   |
| 73                   | Isorhamnetin 3-O-rutinoside                 |                   | O-Rut              |   | OH  |   | OH    |   |    | OMe | OH    |   |   |
| 74                   | Tamarixetin 7-O-rutinoside                  |                   | OH                 |   | OH  |   | O-Rut |   |    | OH  | OMe   |   |   |
| 75                   | Quercetin 3,4'-dimethyl ether               |                   | OMe                |   | OH  |   | OH    |   |    | OH  | OMe   |   |   |
| 76                   | Quercetin 7,4'-dimethyl ether               |                   | OH                 |   | OH  |   | OMe   |   |    | OH  | OMe   |   |   |
| 77                   | 7,8,3,4'-Tetrahydroxyflavonol               |                   | OH                 |   |     |   | OH    |   |    | OH  | OH    |   |   |



Index of  $^{13}\text{C}$ -NMR spectra of flavonoids (Contd.)

| Spec-<br>trum<br>no. | Flavonoid                                            | Oxidation pattern |                   |                      |                    |        |                    |                      |     |                   |                    |
|----------------------|------------------------------------------------------|-------------------|-------------------|----------------------|--------------------|--------|--------------------|----------------------|-----|-------------------|--------------------|
|                      |                                                      | 2                 | 3                 | 4                    | 5                  | 6      | 7                  | 8                    | 2'  | 3'                | 4'                 |
| 107                  | Hesperetin 7-O-rutinoside<br>(Hesperidin)            |                   |                   |                      | OH                 |        | O-Rut              |                      |     | OMe               | OH                 |
|                      | <i>Dihydroflavonols</i>                              |                   |                   |                      |                    |        |                    |                      |     |                   |                    |
| 108                  | (+)-Dihydroquercetin (Taxifolin)                     |                   | OH                |                      | OH                 |        | OH                 |                      |     | OH                | OH                 |
| 109                  | (+)-Dihydroquercetin 5,7,3',4'-<br>tetramethyl ether |                   | OH                |                      | OMe                |        | OMe                |                      |     | OMe               | OMe                |
|                      | <i>Dihydroisoflavone</i>                             |                   |                   |                      |                    |        |                    |                      |     |                   |                    |
| 110                  | Sophoraisoflavanone A                                |                   |                   |                      | OH                 |        | OH                 |                      | OMe | prenyl            | OH                 |
|                      | <i>Biflavones</i>                                    |                   |                   |                      |                    |        |                    |                      |     |                   |                    |
| 111                  | Robustaflavone                                       |                   |                   |                      | (OH) <sub>2</sub>  | (6→3') | (OH) <sub>2</sub>  |                      |     | (3'→6)            | (OH) <sub>2</sub>  |
| 112                  | Cupressuflavone                                      |                   |                   |                      | (OH) <sub>2</sub>  |        | (OH) <sub>2</sub>  | (8→8)                |     |                   | (OH) <sub>2</sub>  |
| 113                  | Cupressuflavone hexamethyl ether                     |                   |                   |                      | (OMe) <sub>2</sub> |        | (OMe) <sub>2</sub> | (8→8)                |     |                   | (OMe) <sub>2</sub> |
| 114                  | Volkensiflavone                                      |                   | (3→8)             |                      | (OH) <sub>2</sub>  |        | (OH) <sub>2</sub>  | (8→3)                |     |                   | (OH) <sub>2</sub>  |
|                      | <i>Biflavonones</i>                                  |                   |                   |                      |                    |        |                    |                      |     |                   |                    |
| 115                  | Succedaneaflavanone                                  |                   |                   |                      | (OH) <sub>2</sub>  | (6→6)  | (OH) <sub>2</sub>  |                      |     |                   | (OH) <sub>2</sub>  |
|                      | <i>Catechin/tannins</i>                              |                   |                   |                      |                    |        |                    |                      |     |                   |                    |
| 116                  | (-)-Epicatechin                                      |                   |                   |                      | OH                 |        | OH                 |                      |     | OH                | OH                 |
| 117                  | Procyanidin B5                                       |                   | (OH) <sub>2</sub> | (4→6)                | (OH) <sub>2</sub>  | (6→4)  | (OH) <sub>2</sub>  |                      |     | (OH) <sub>2</sub> | (OH) <sub>2</sub>  |
| 118                  | Procyanidin B2                                       |                   | (OH) <sub>2</sub> | (4→8)                | (OH) <sub>2</sub>  |        | (OH) <sub>2</sub>  | (8→4)                |     | (OH) <sub>2</sub> | (OH) <sub>2</sub>  |
| 119                  | Procyanidin trimer                                   |                   | (OH) <sub>3</sub> | (4→8) <sub>2</sub>   | (OH) <sub>3</sub>  |        | (OH) <sub>3</sub>  | (8→4) <sub>2</sub>   |     | (OH) <sub>3</sub> | (OH) <sub>3</sub>  |
| 120                  | Procyanidin polymer                                  |                   | (OH) <sub>n</sub> | (4→8) <sub>n-1</sub> | (OH) <sub>n</sub>  |        | (OH) <sub>n</sub>  | (8→4) <sub>n-1</sub> |     | (OH) <sub>n</sub> | (OH) <sub>n</sub>  |
|                      | <i>Miscellaneous</i>                                 |                   |                   |                      |                    |        |                    |                      |     |                   |                    |
| 121                  | Protogekwanin 4'-O-glucoside*                        |                   |                   |                      |                    |        |                    |                      |     |                   |                    |
| 122                  | Cassiachromone*                                      |                   |                   |                      |                    |        |                    |                      |     |                   |                    |
| 123                  | Aloesin*                                             |                   |                   |                      |                    |        |                    |                      |     |                   |                    |
| 124                  | Silydianin*                                          |                   |                   |                      |                    |        |                    |                      |     |                   |                    |
| 125                  | Silymonin (3-Deoxysilydianin)*                       |                   |                   |                      |                    |        |                    |                      |     |                   |                    |

\* See spectra pages for formulae.

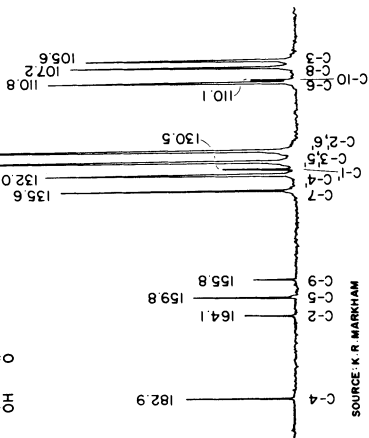
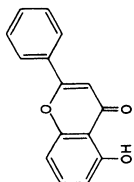


1

5-HYDROXYFLAVONE

DMSO-d<sub>6</sub> (95°C)

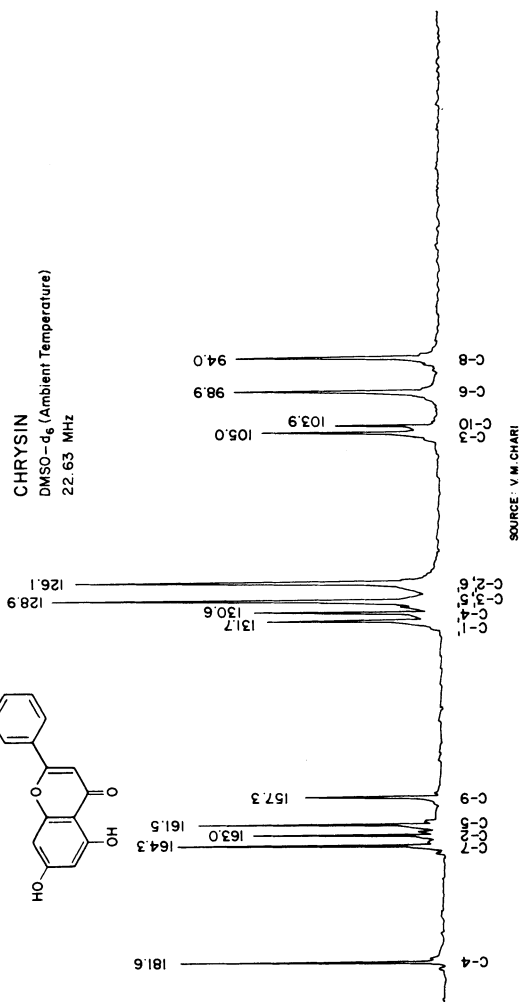
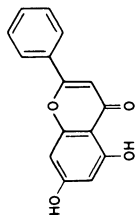
25.15 MHz



SOURCE: K. R. MARKHAM

2

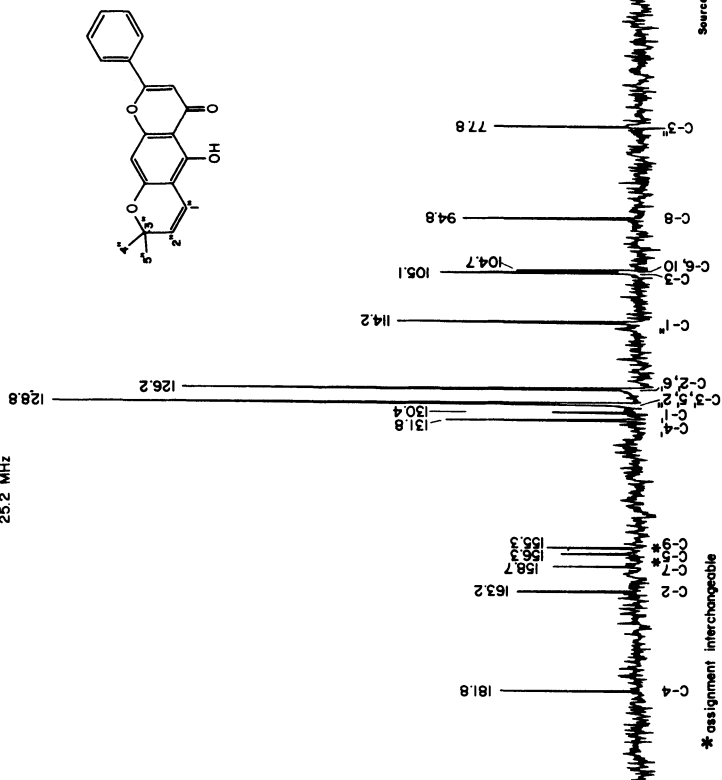
CHRYSIN  
DMSO-d<sub>6</sub> (Ambient Temperature)  
22.63 MHz



SOURCE: V. M. CHARI

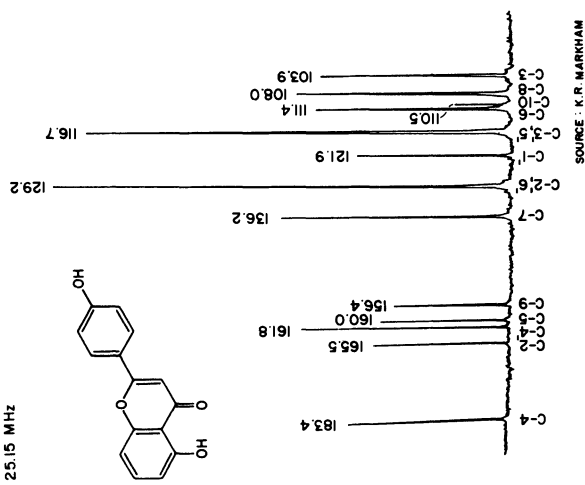
3

## 7,7-DIMETHYL-5-HYDROXY-CHROMENOFLAVONE

DMSO- $d_6$   
25.2 MHz

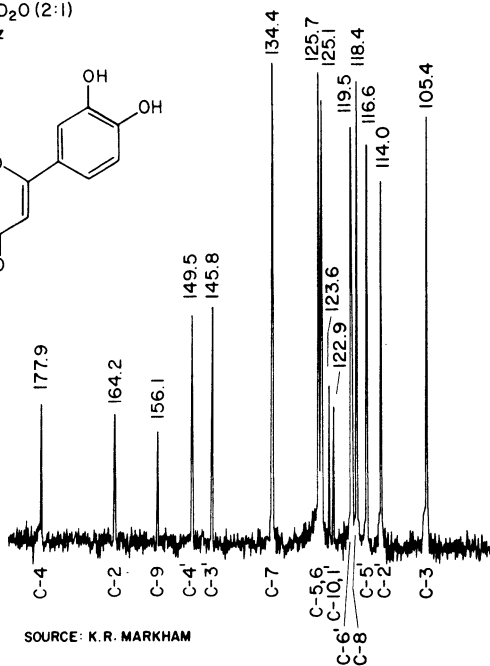
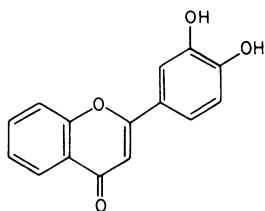
4

## 5,4'-DIHYDROXYFLAVONE

DMSO- $d_6$ , D $_2$ O (2:1)  
25.15 MHz

# 5 3',4'-DIHYDROXYFLAVONE

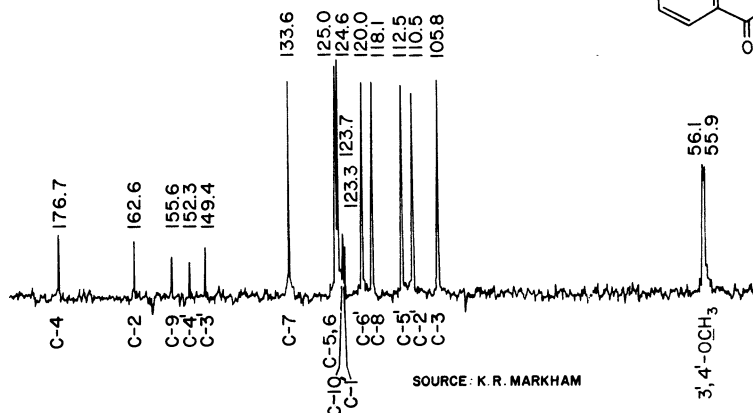
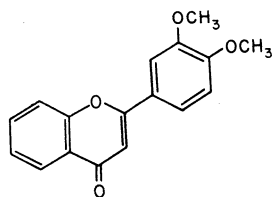
DMSO-d<sub>6</sub>:D<sub>2</sub>O (2:1)  
25.15 MHz



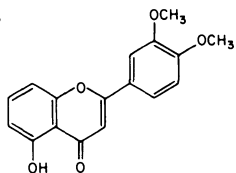
# 6

## 3',4'-DIMETHOXYFLAVONE

DMSO - d<sub>6</sub> (95°C)  
25.15 MHz



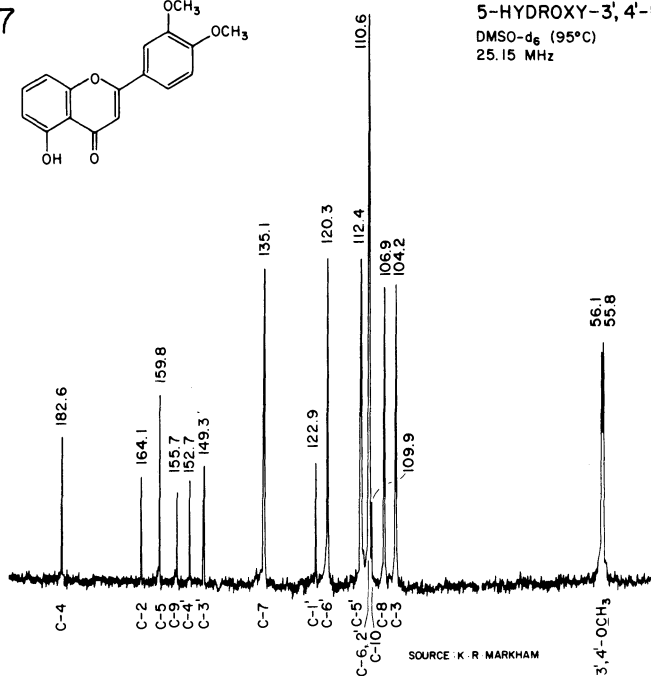
7



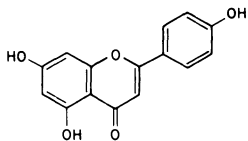
## 5-HYDROXY-3',4'-DIMETHOXYFLAVONE

DMSO-d<sub>6</sub> (95°C)

25.15 MHz



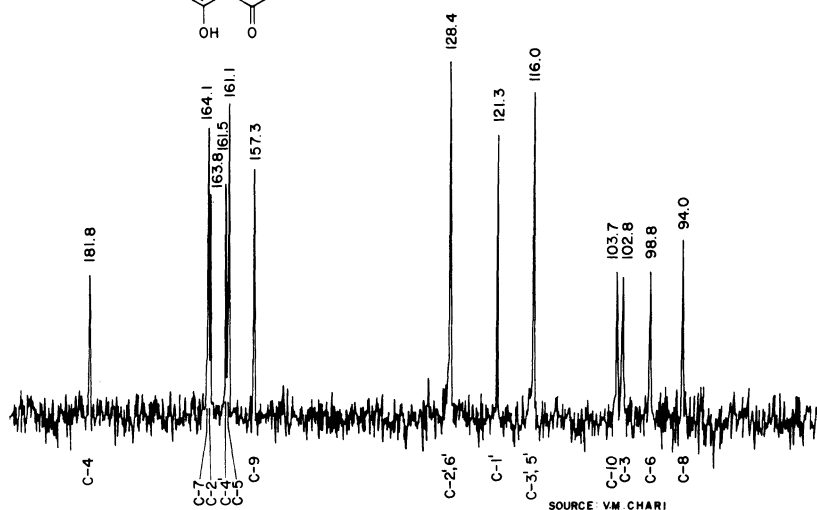
8



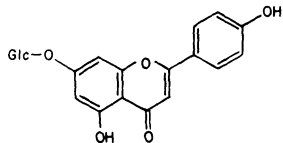
## APIGENIN

DMSO-d<sub>6</sub> (Ambient Temperature)

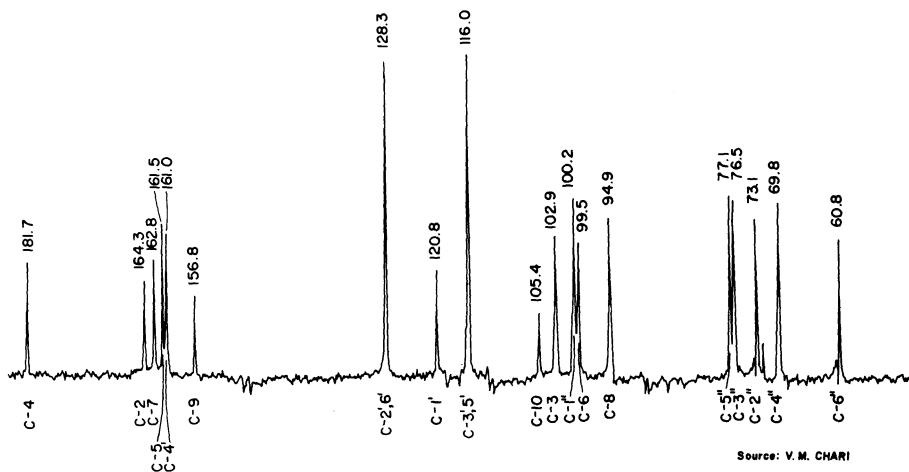
22.63 MHz



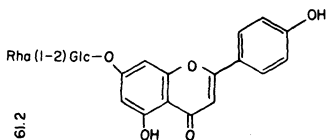
9



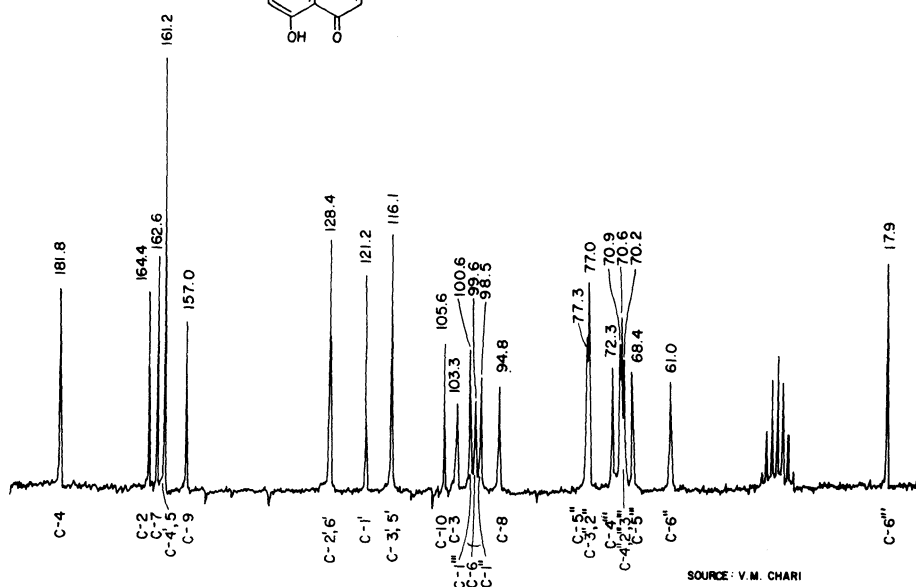
APIGENIN 7-O- $\beta$ -D-GLUCOSIDE  
DMSO- $d_6$  (80°C)  
20.15 MHz



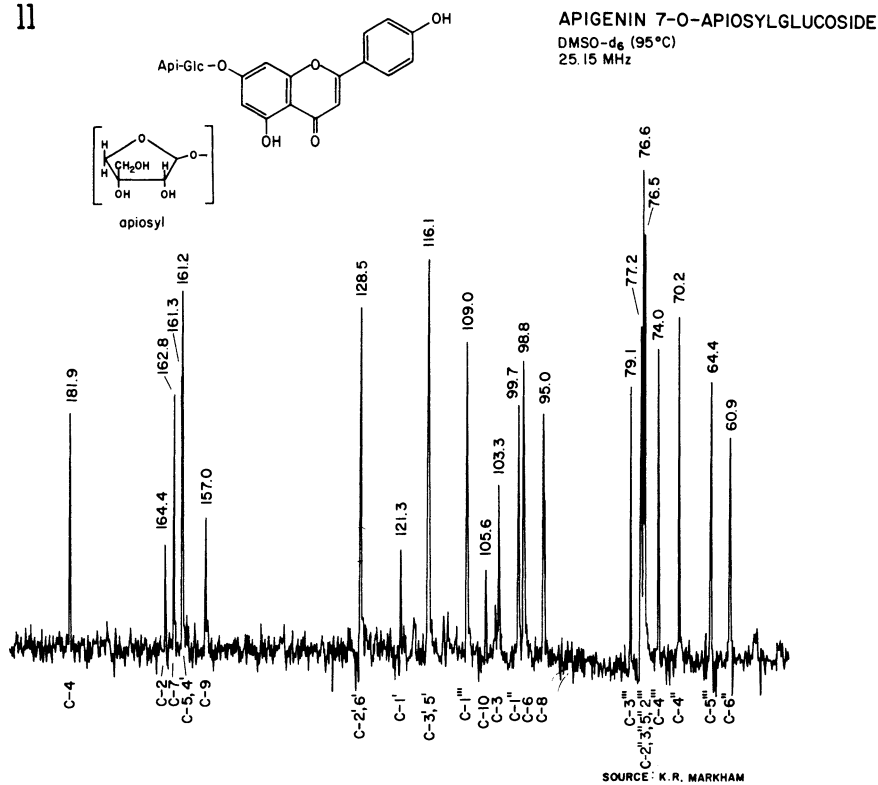
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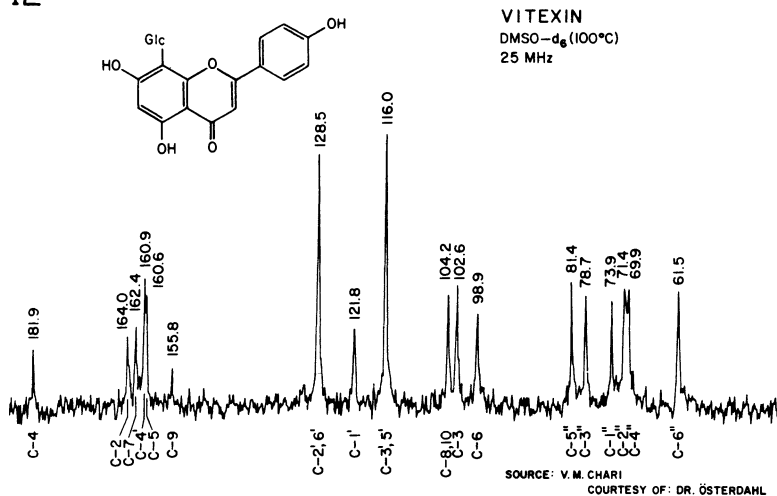
APIGENIN 7-O-NEOHESPERIDOSIDE  
DMSO- $d_6$  (80°C)  
20.15 MHz



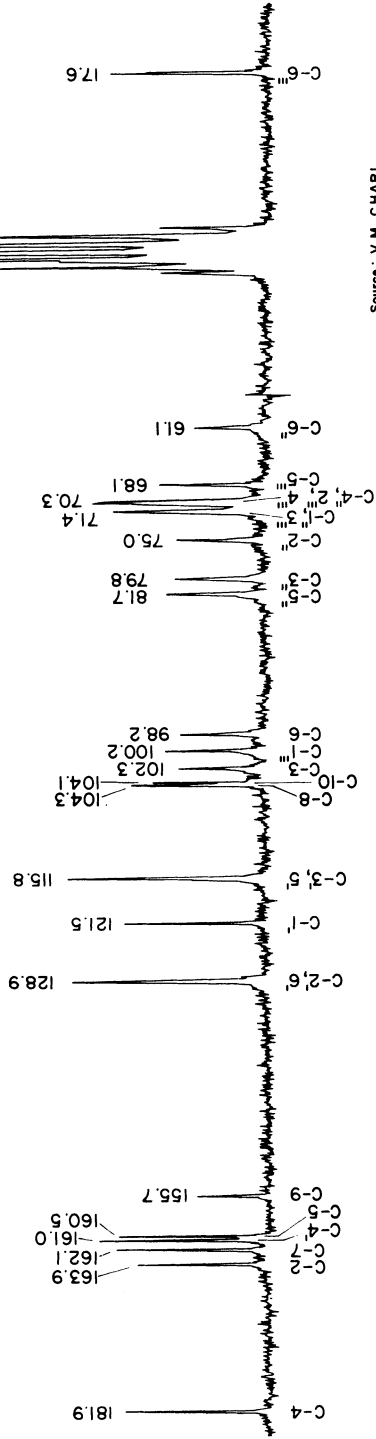
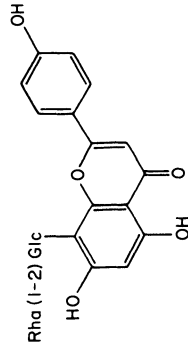
11



12

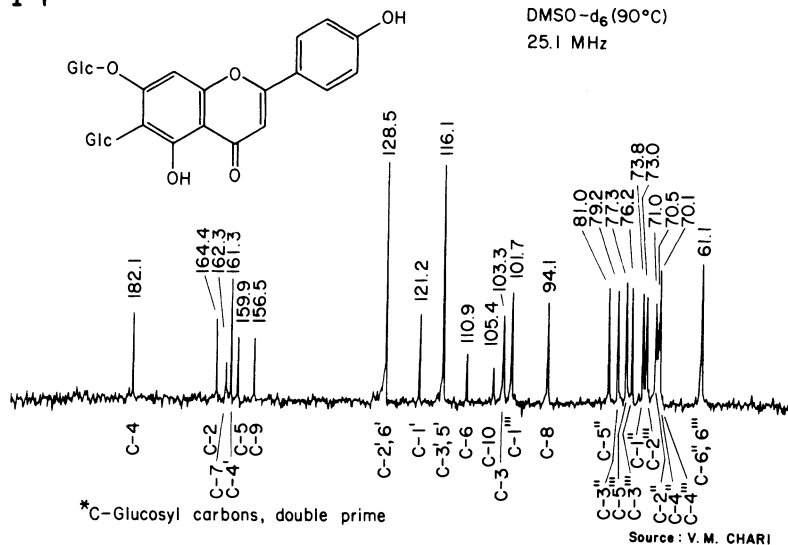


2"-O-RHAMNOSYLVITEXIN  
DMSO-d<sub>6</sub> (Ambient Temperature)  
22.6 MHz

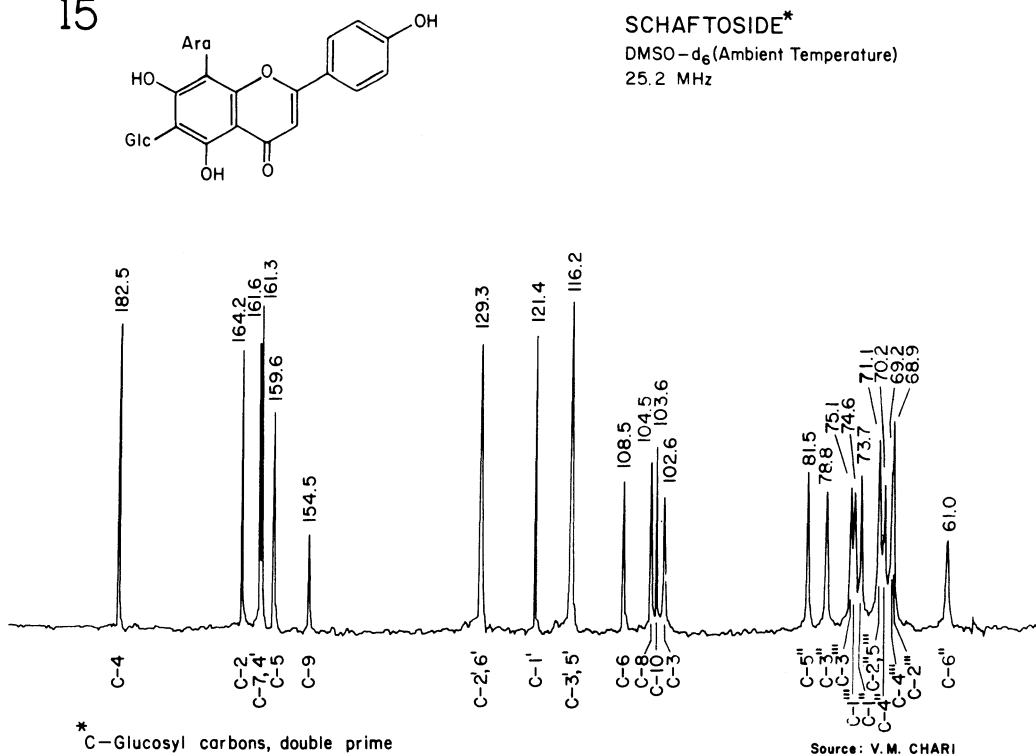


Source : V. M. CHARI

14



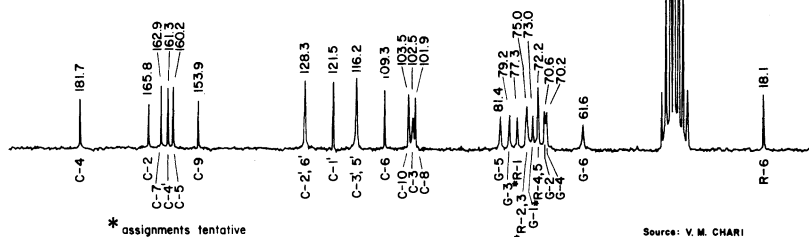
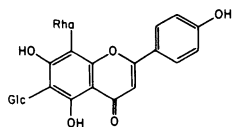
15





16

**VIOLANTHIN**  
DMSO- $d_6$  (Ambient Temperature)  
20.1 MHz

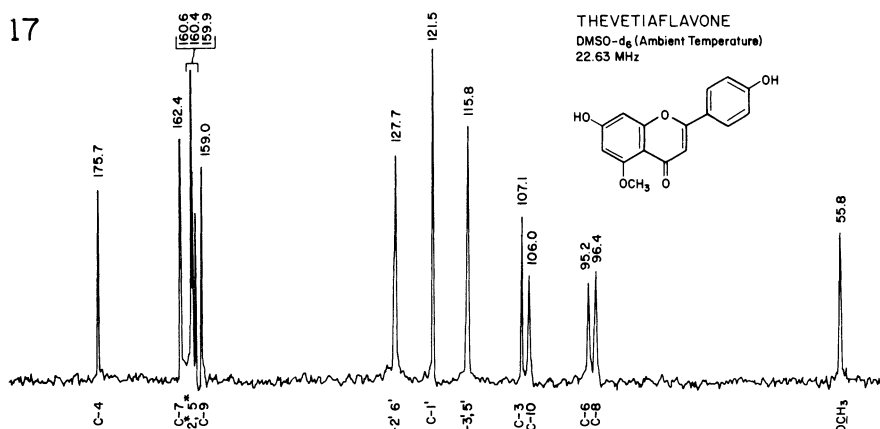
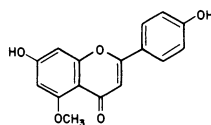


\* assignments tentative

Source: V. M. CHARI

17

**THEVETIAFLAVONE**  
DMSO- $d_6$  (Ambient Temperature)  
22.63 MHz

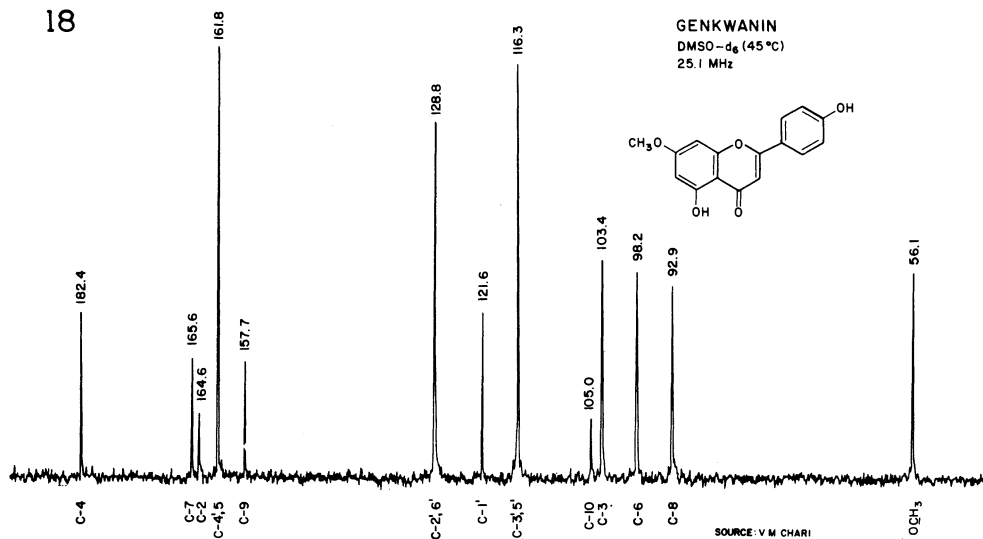
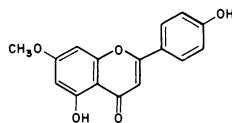


\*assignment interchangeable

SOURCE: V. M. CHARI

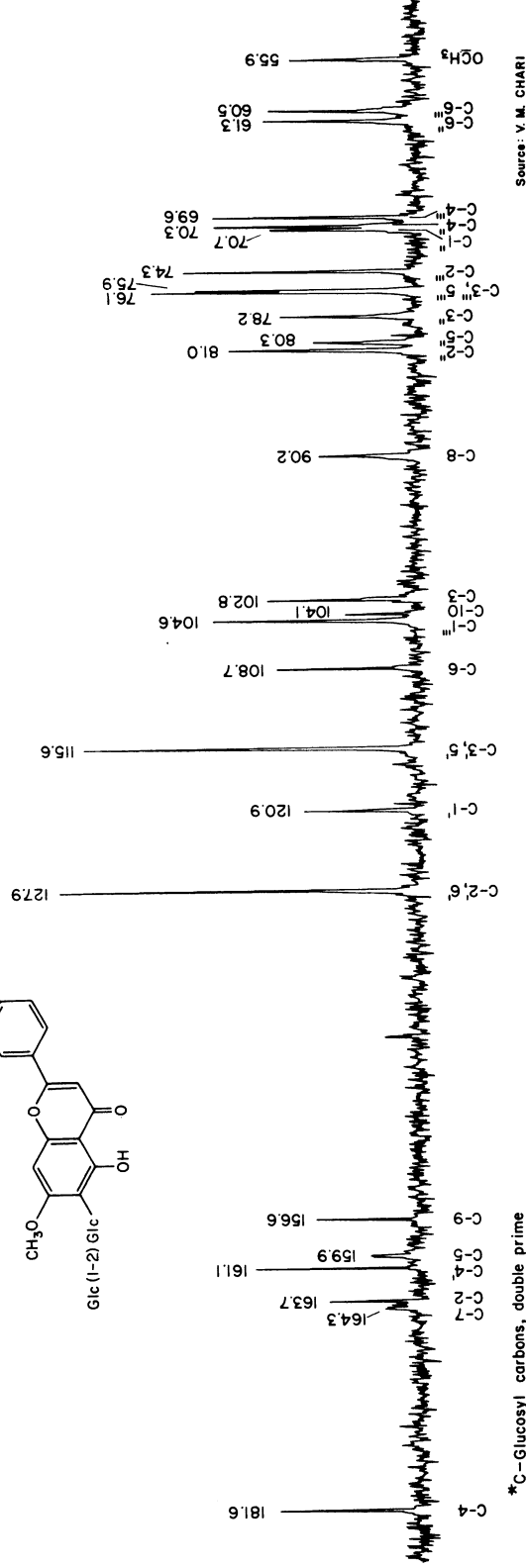
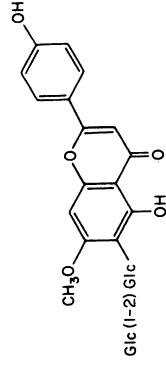
18

**GENKWANIN**  
DMSO- $d_6$  (45 °C)  
25.1 MHz



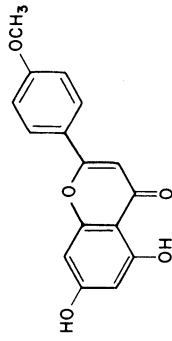
SOURCE: V. M. CHARI

SPINOSIN\*  
DMSO- $d_6$  (90°C)  
22.6 MHz

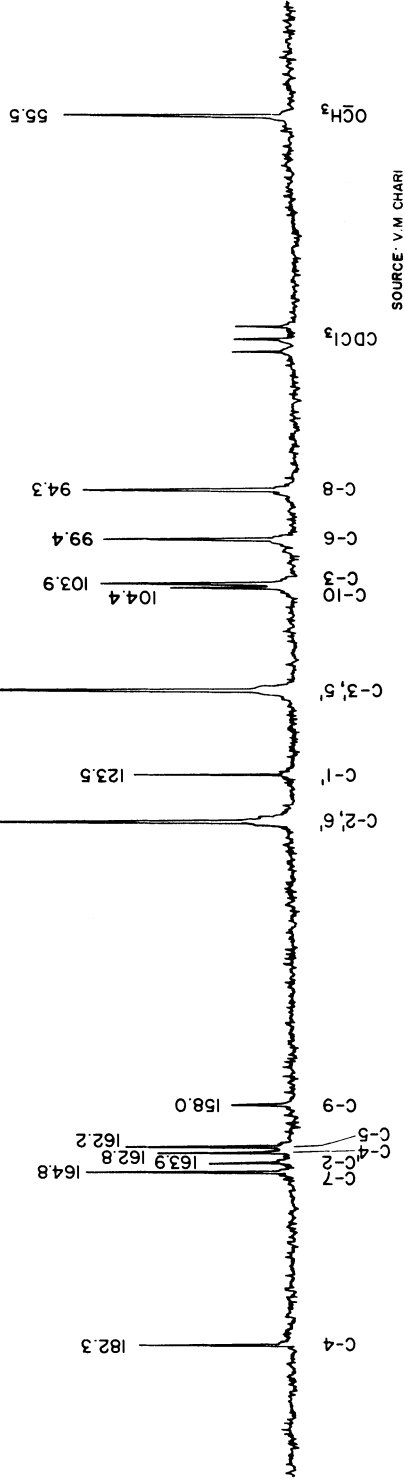


Source: V. M. CHARI

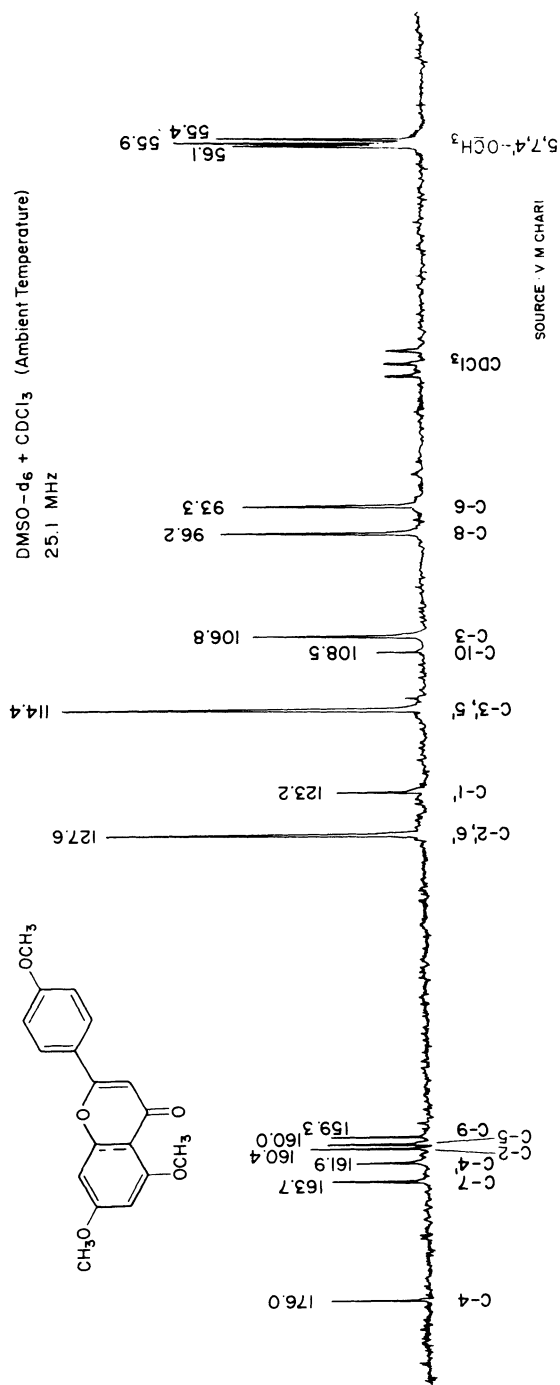
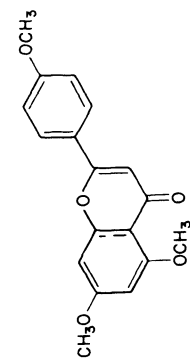
\*C-Glucosyl carbons, double prime



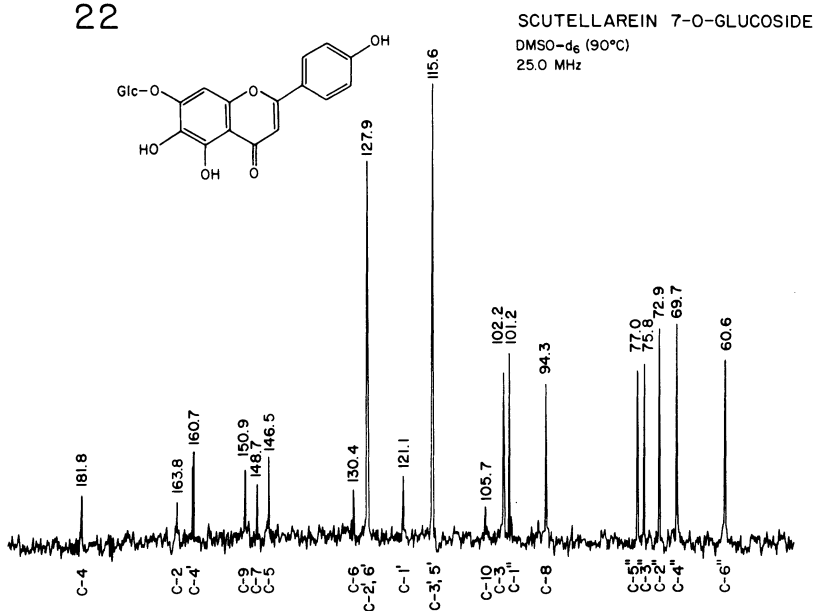
ACACETIN  
DMSO-d<sub>6</sub> + CDCl<sub>3</sub> (Ambient Temperature)  
25.2 MHz



APIGENIN TRIMETHYL ETHER  
DMSO- $d_6$  +  $CDCl_3$  (Ambient Temperature)  
25.1 MHz

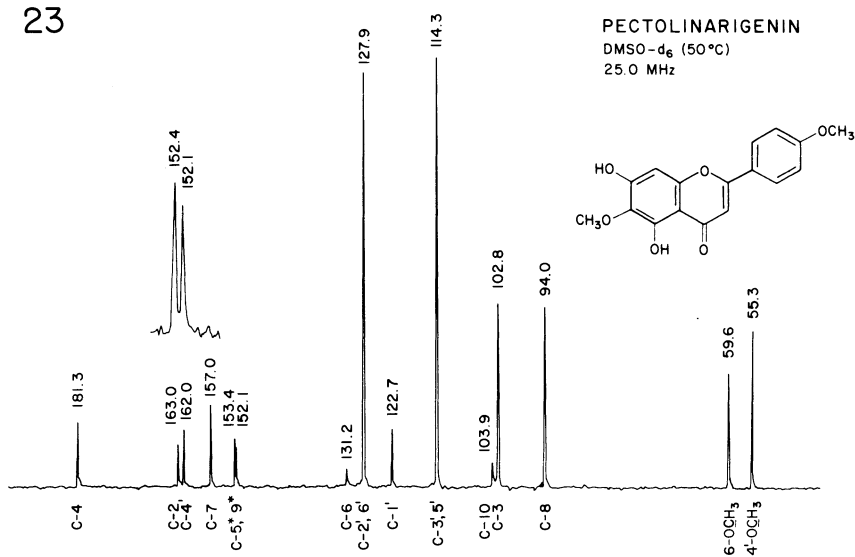


22



SOURCE: V.M. CHARI  
COURTESY OF: DR. ÖSTERDAHL

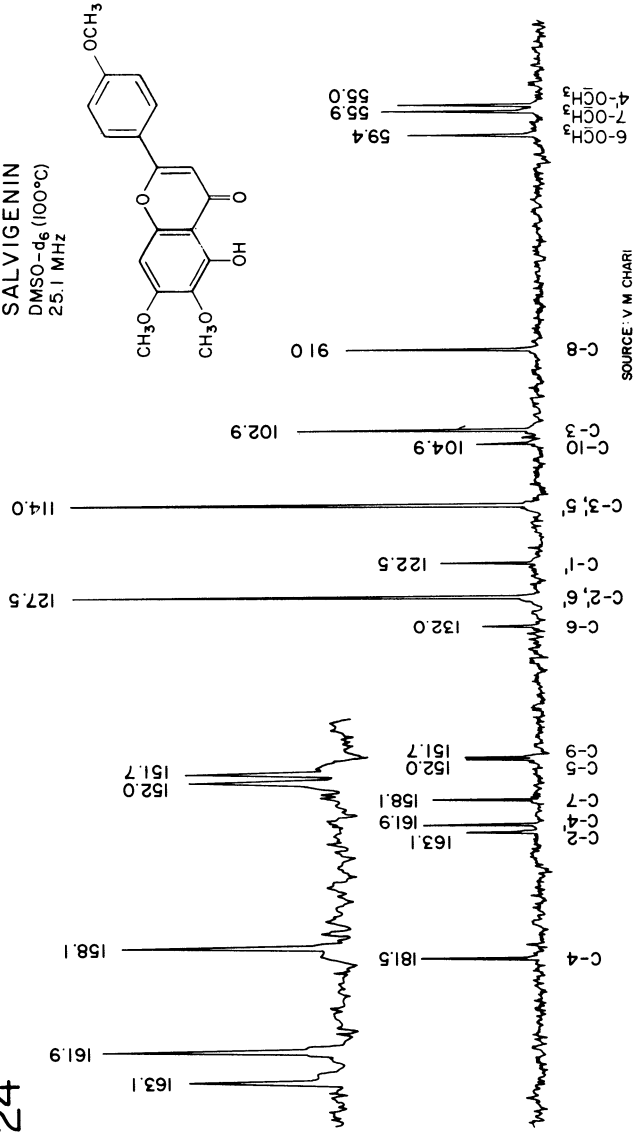
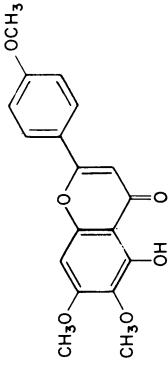
23



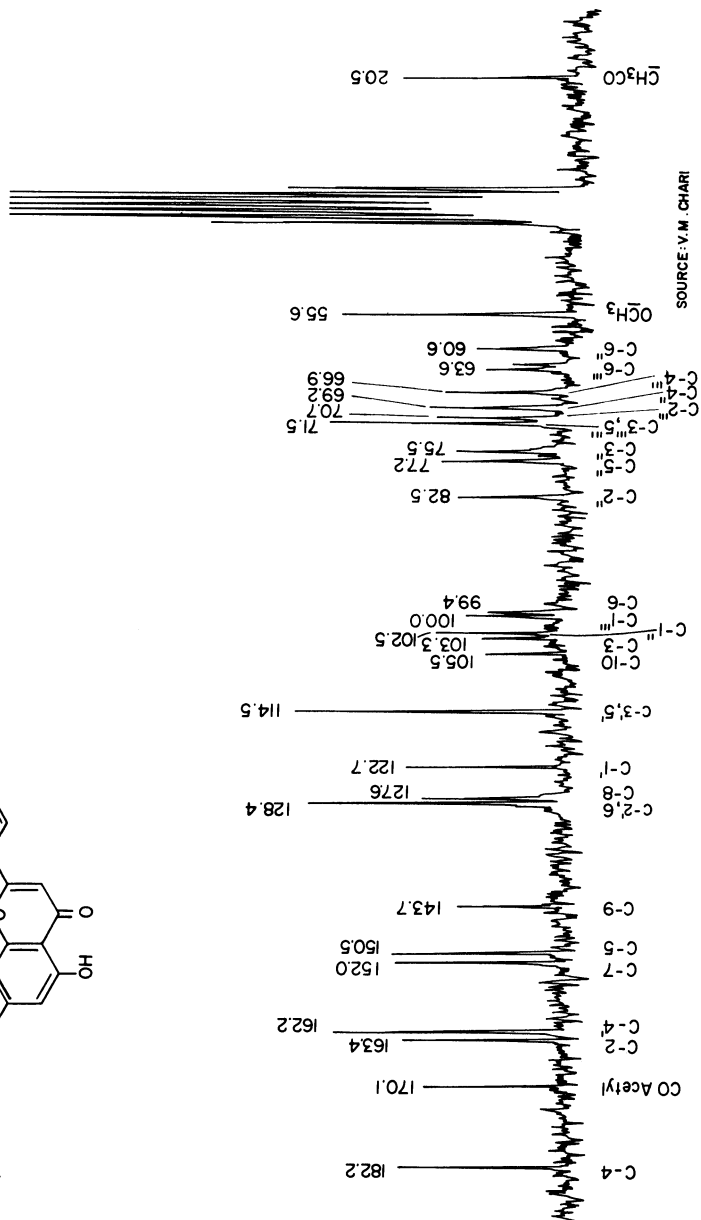
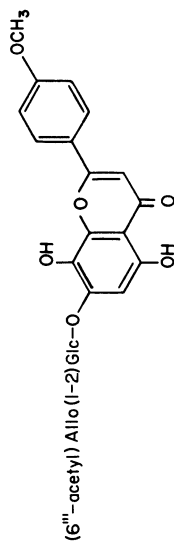
\*assignment interchangeable

SOURCE: V.M. CHARI

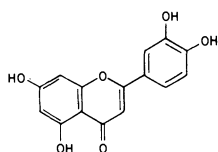
SALVIGENIN  
DMSO-d<sub>6</sub> (100°C)  
25.1 MHz



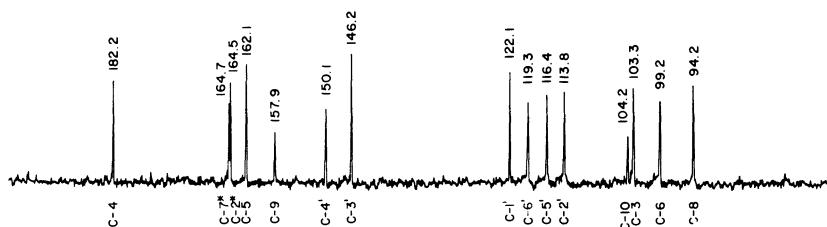
## ISOSCUTELLAREIN 4'-METHYL ETHER

7-O-[2''-O-(6'''-ACETYL)- $\beta$ -D-ALLOPYRANOSYL]- $\beta$ -D-GLUCOPYRANOSIDEDMSO- $d_6$  (Ambient Temperature)  
25 MHz

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LUTEOLIN  
DMSO- $d_6$  (Ambient Temperature)  
25.2 MHz

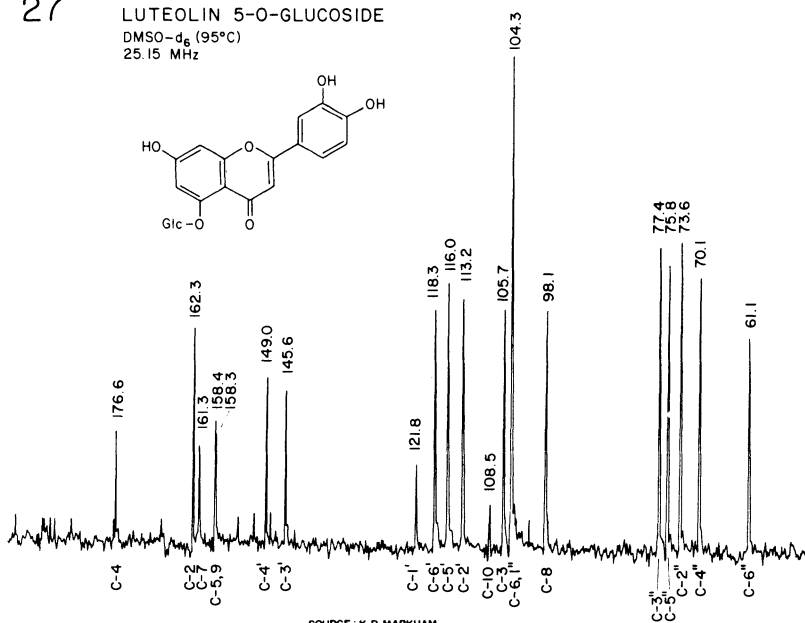
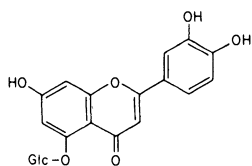


\* assignment interchangeable

SOURCE: V. M. CHARI

27

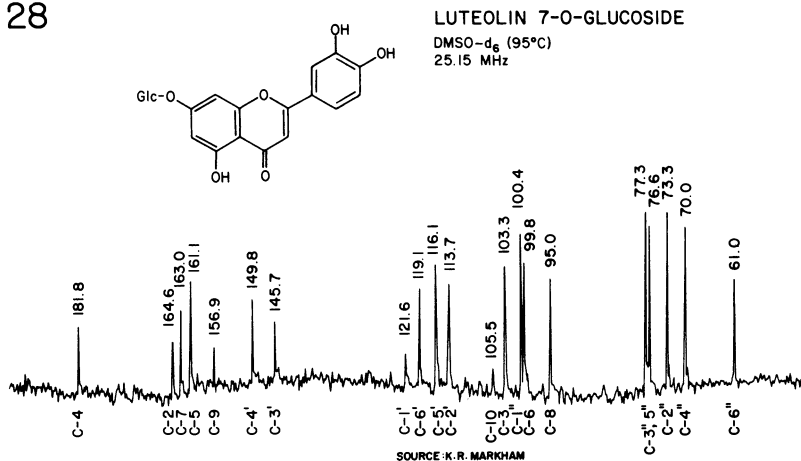
LUTEOLIN 5-O-GLUCOSIDE  
DMSO- $d_6$  (95°C)  
25.15 MHz



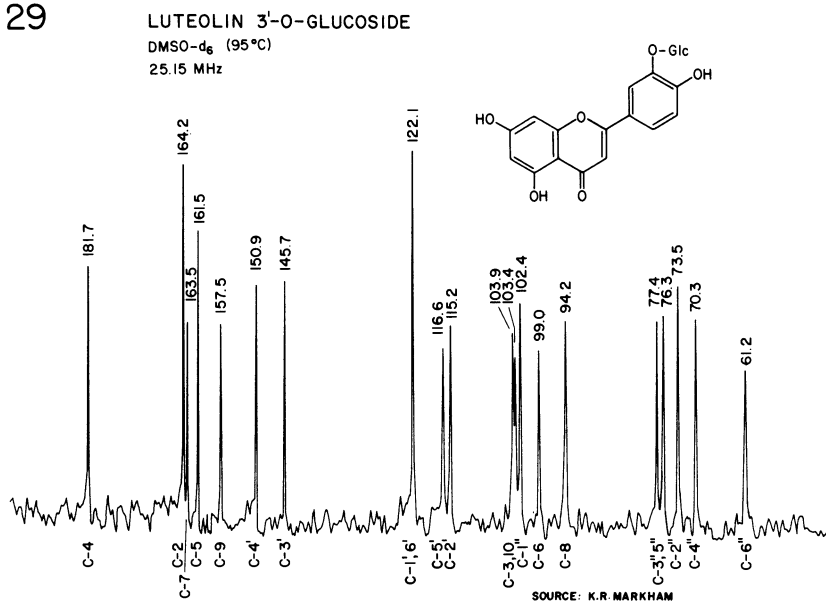
SOURCE: K. R. MARKHAM

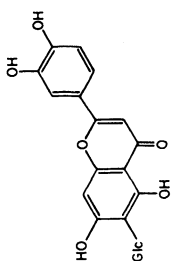


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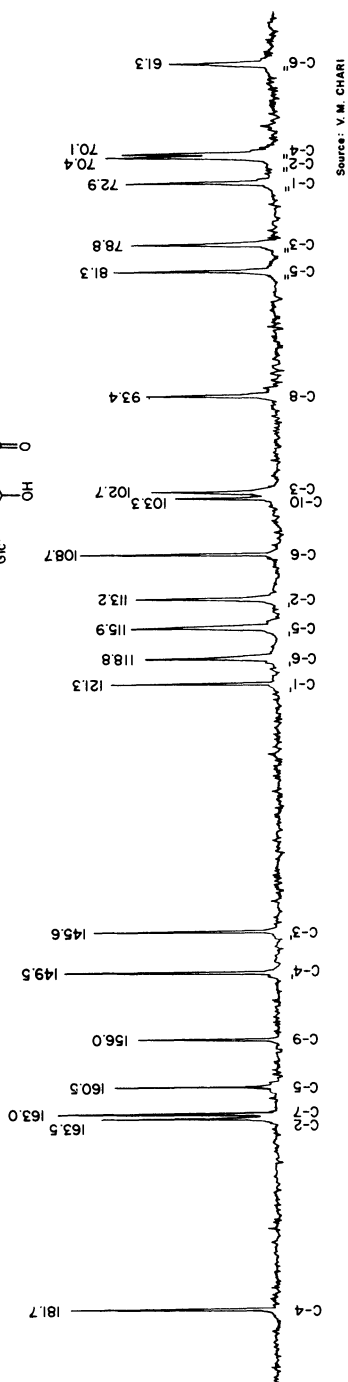


29





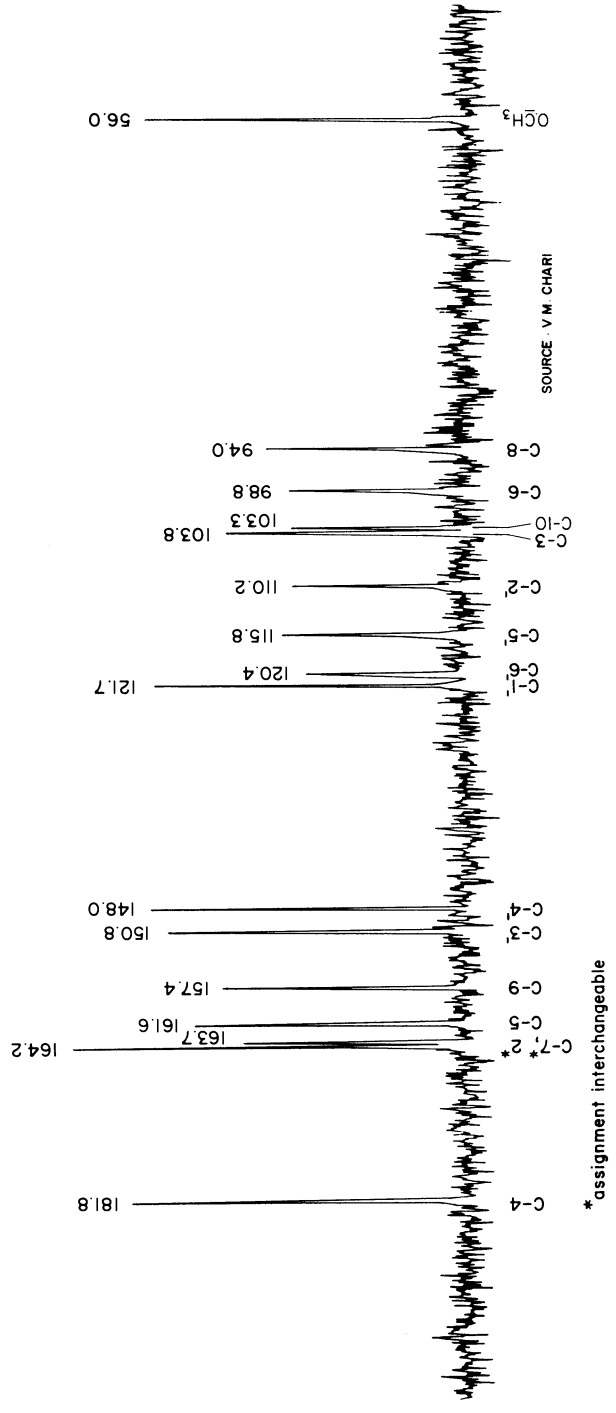
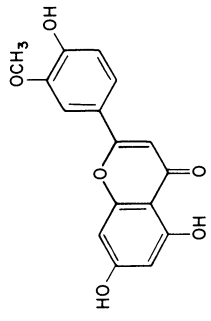
ISOORIENTIN  
DMSO- $d_6$  (Ambient Temperature)  
22.6 MHz



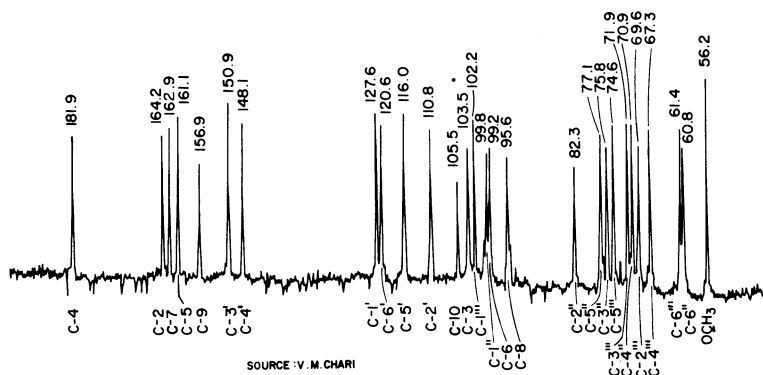
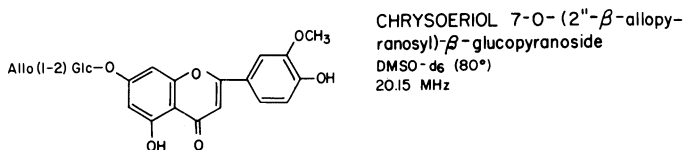
Source: V. M. CHARI



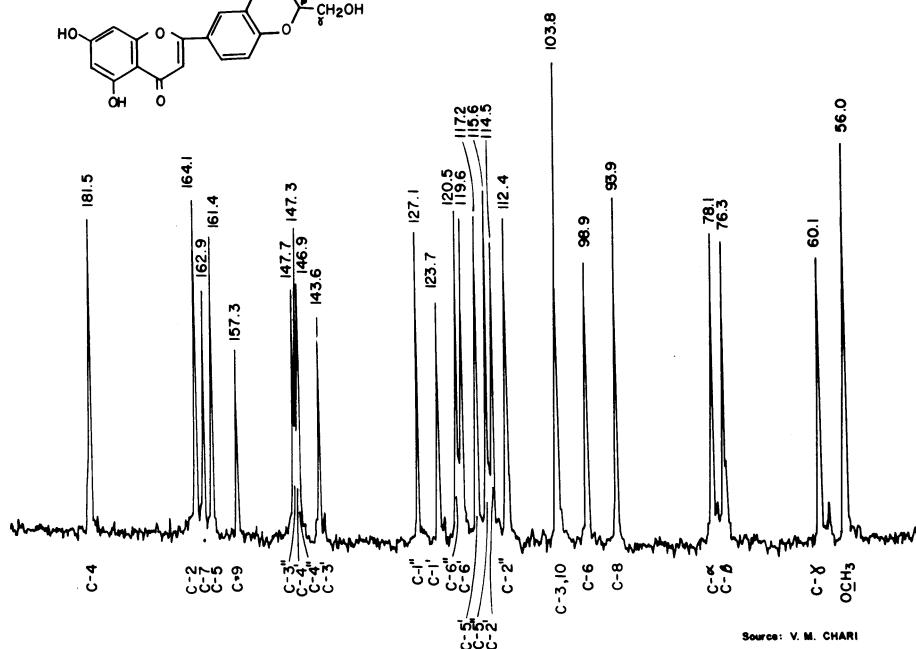
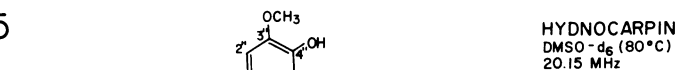
CHRYSOERIOL  
DMSO-d<sub>6</sub> (Ambient Temperature)  
22.63 MHz



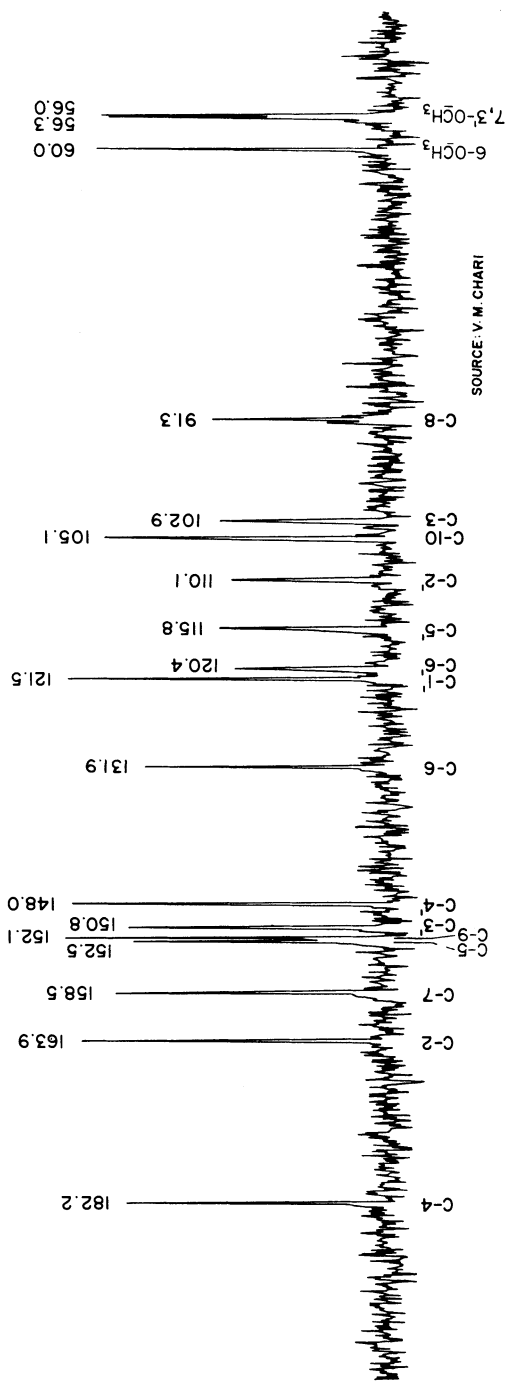
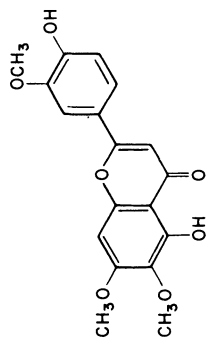
34



35

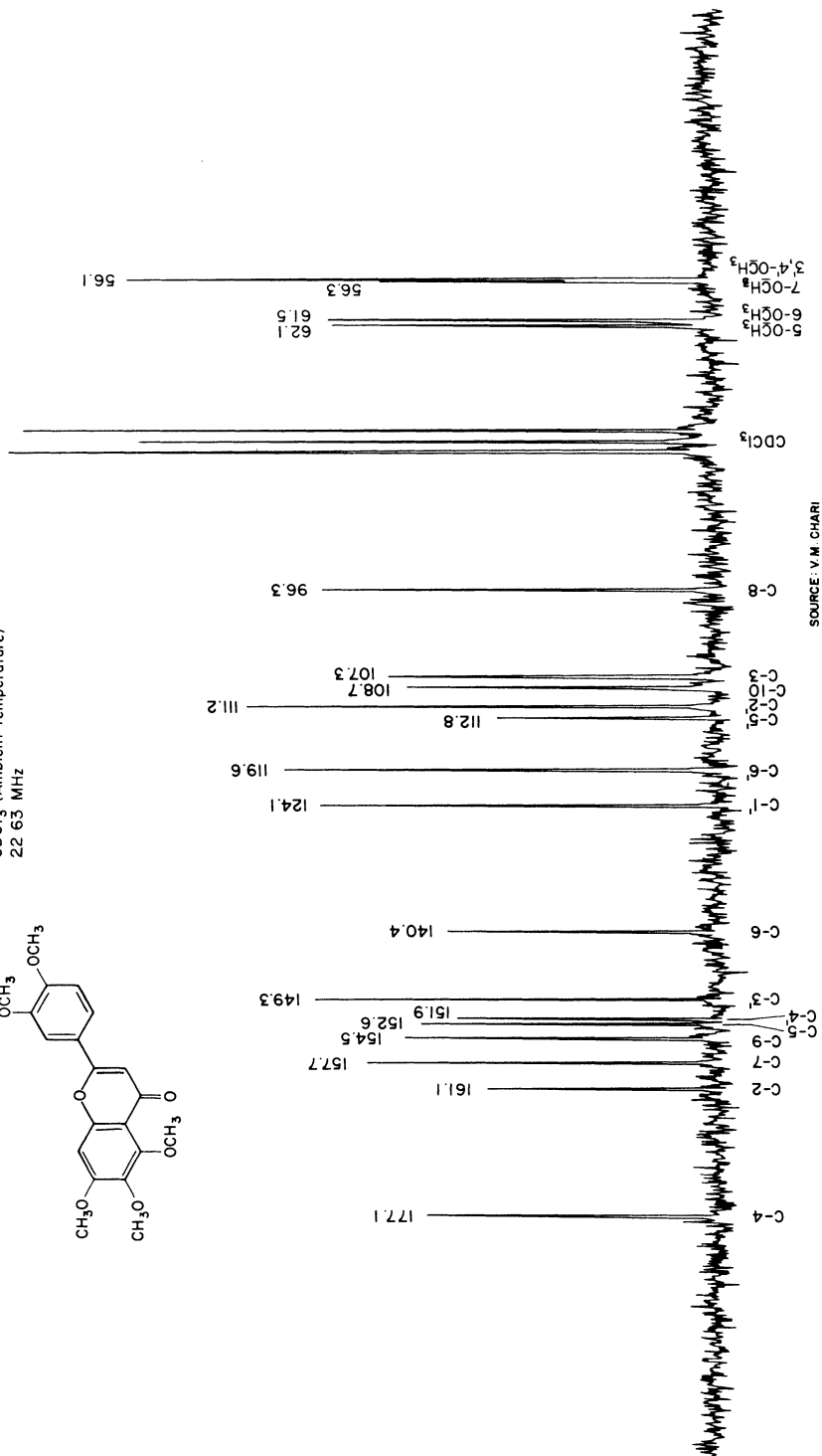
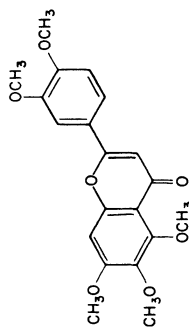


6-HYDROXYLUTEOLIN 6,7,3'-TRIMETHYL ETHER  
 DMSO-d<sub>6</sub> (Ambient Temperature)  
 22.63 MHz



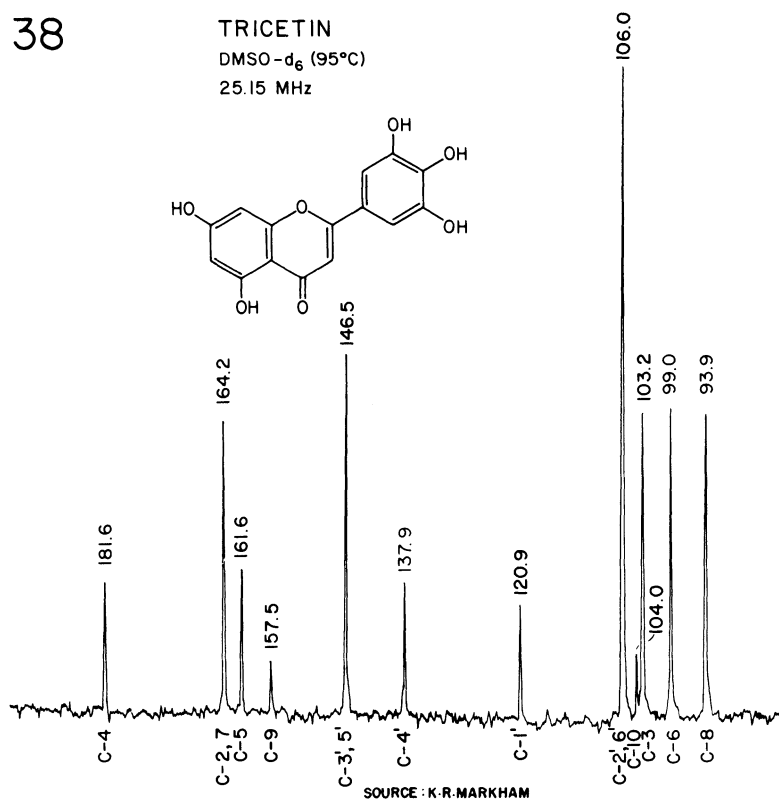
## 6-HYDROXYLUTEOLIN PENTAMETHYL ETHER

CDCl<sub>3</sub> (Ambient Temperature)  
22.63 MHz



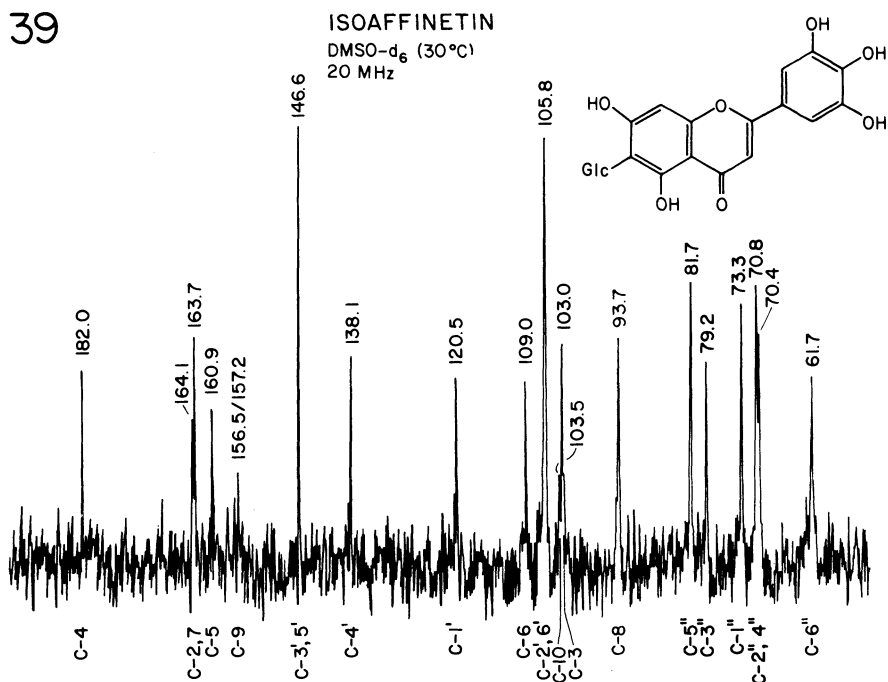
38

TRICETIN  
DMSO- $d_6$  (95°C)  
25.15 MHz



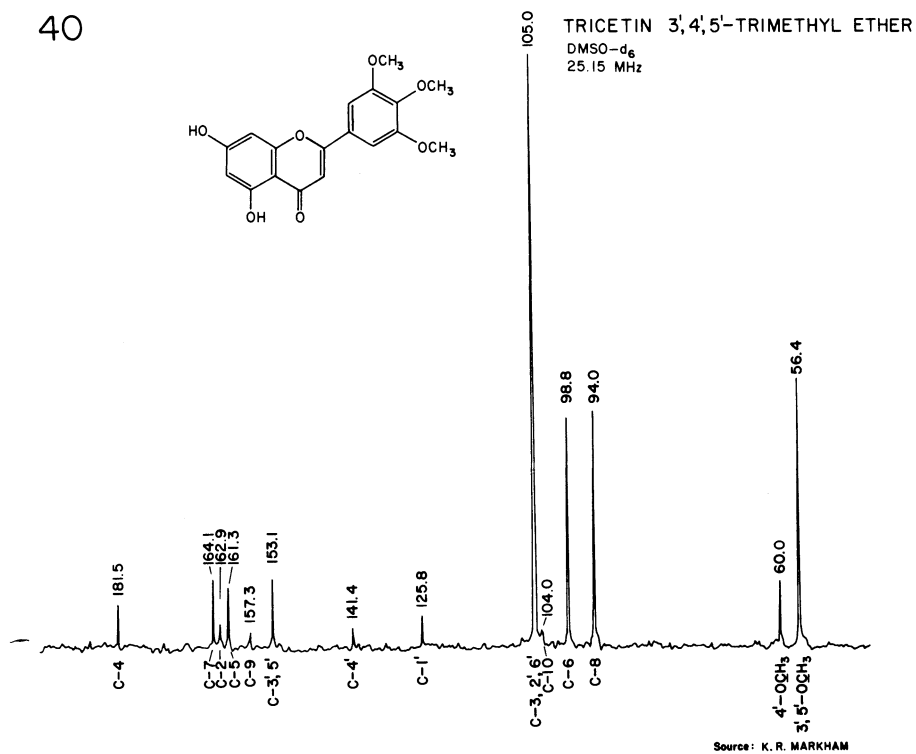
39

ISOAFFINETIN  
DMSO- $d_6$  (30°C)  
20 MHz

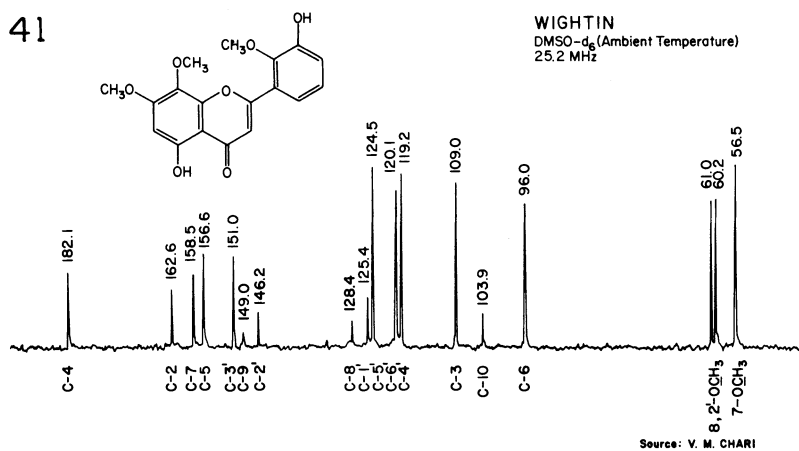




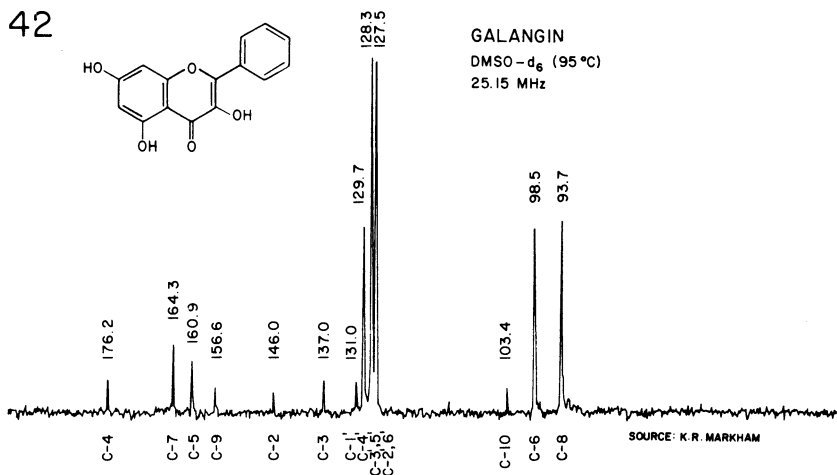
40



41

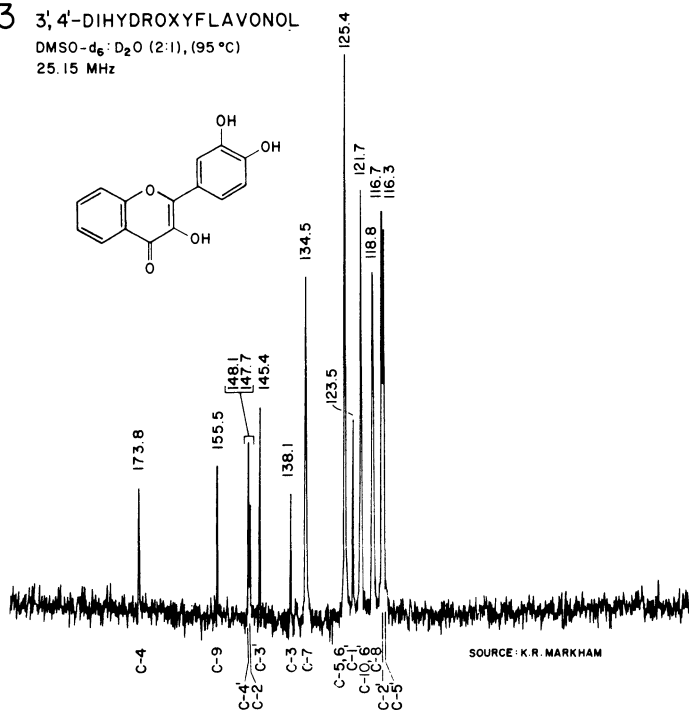


42

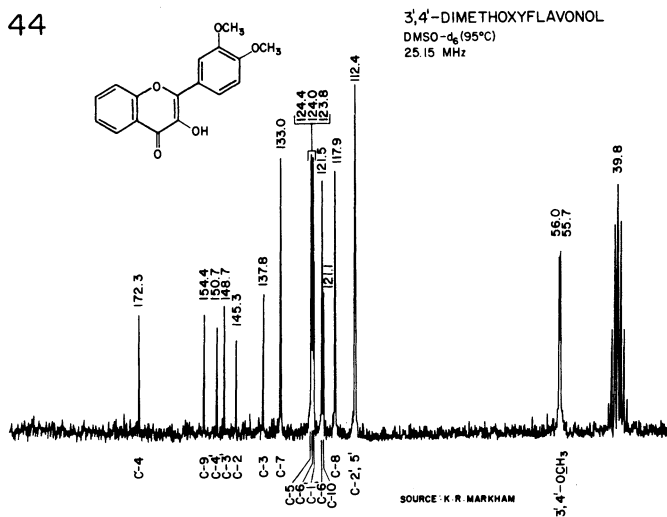


43

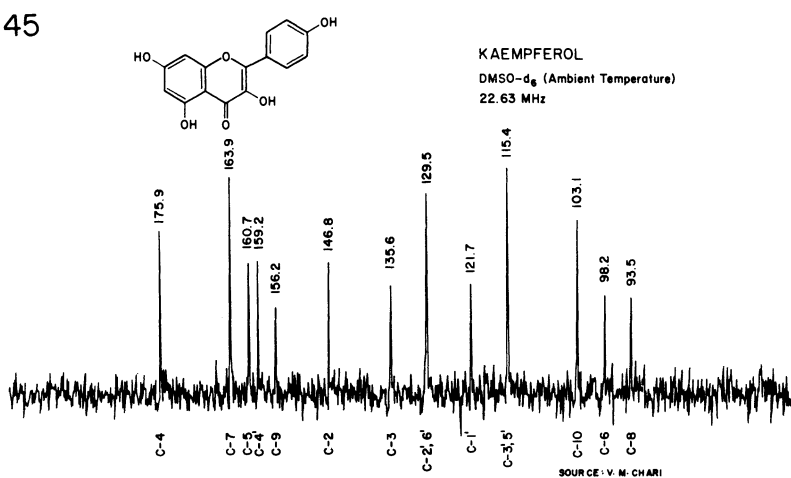
**3', 4'-DIHYDROXYFLAVONOL**  
DMSO- $d_6$ :D $_2$ O (2:1), (95 °C)  
25.15 MHz



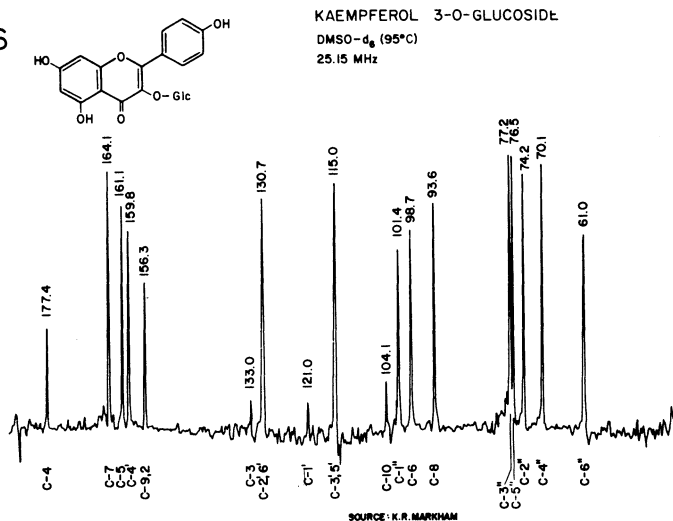
44



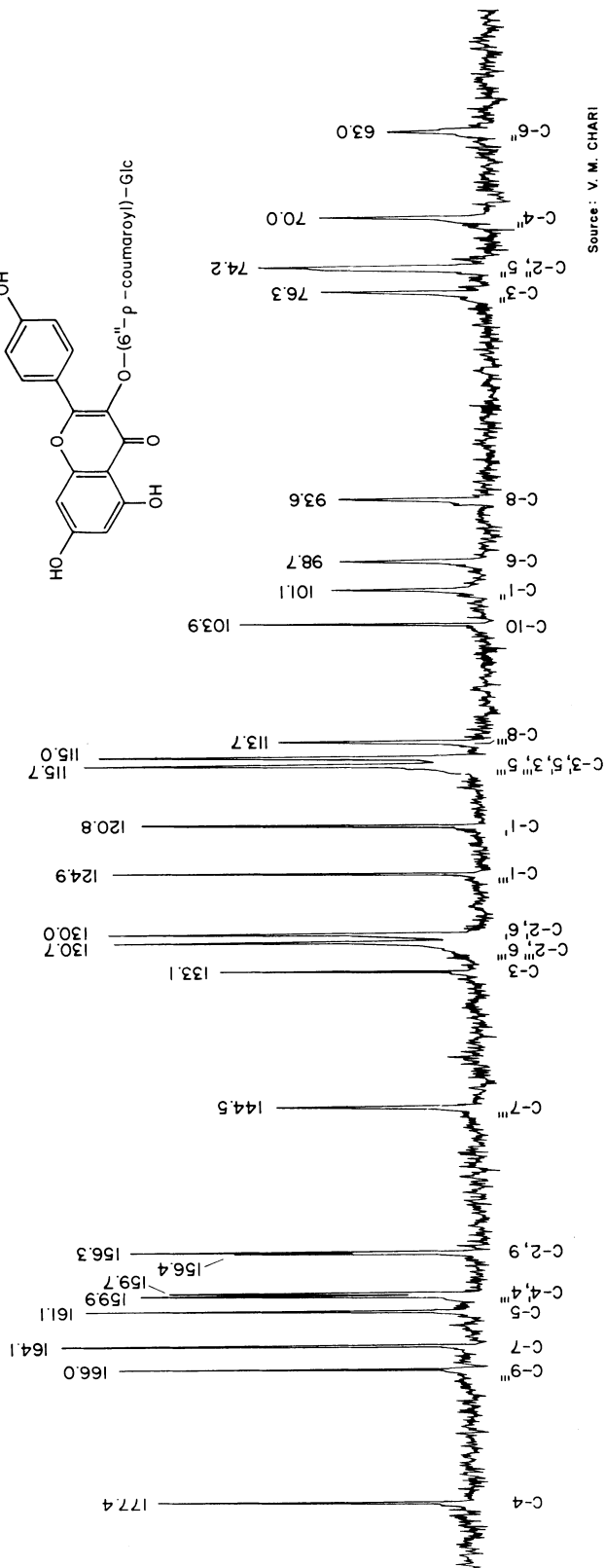
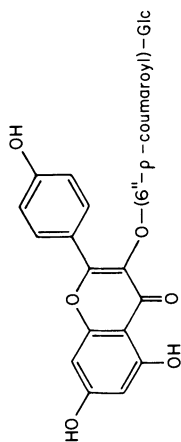
45



46



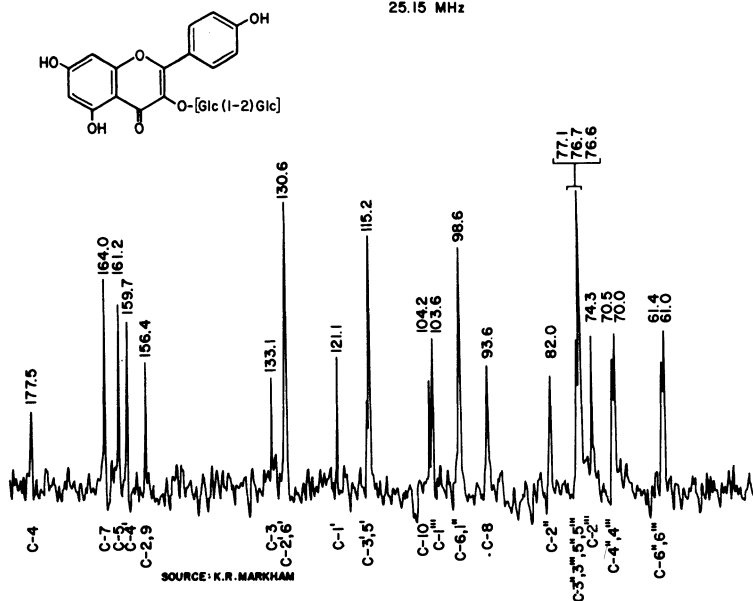
**TILIROSIDE**  
DMSO- $d_6$  (40°C)  
22.6 MHz



Source: V. M. CHARL

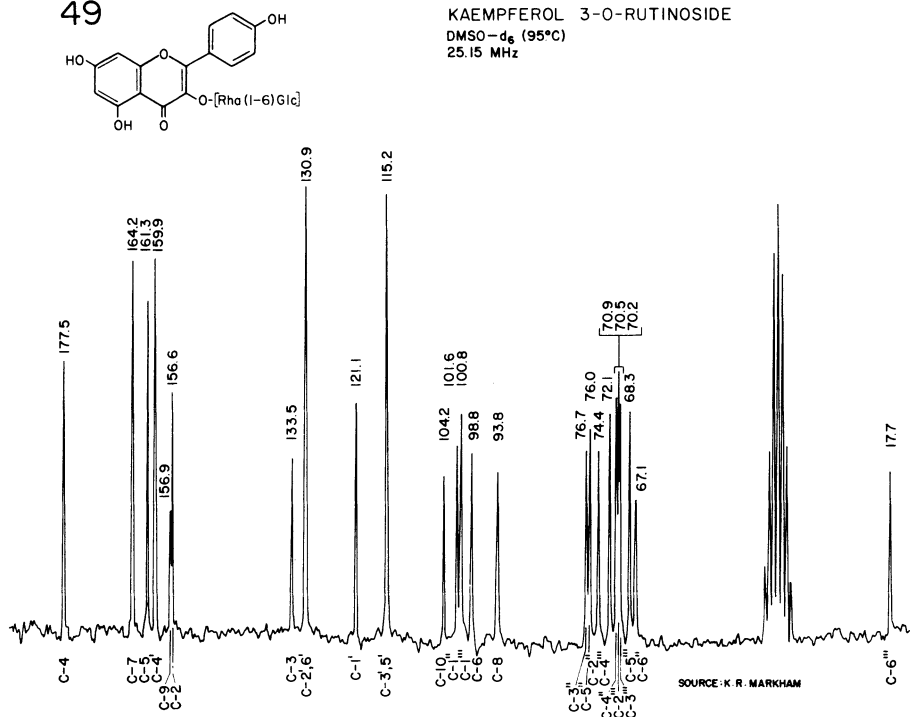
48

## KAEMPFEROL 3-O-SOPHOROSIDE

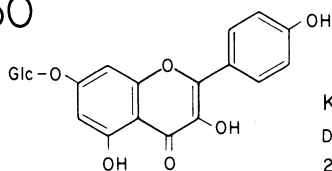
DMSO-d<sub>6</sub> (95°C)  
25.15 MHz

49

## KAEMPFEROL 3-O-RUTINOSIDE

DMSO-d<sub>6</sub> (95°C)  
25.15 MHz

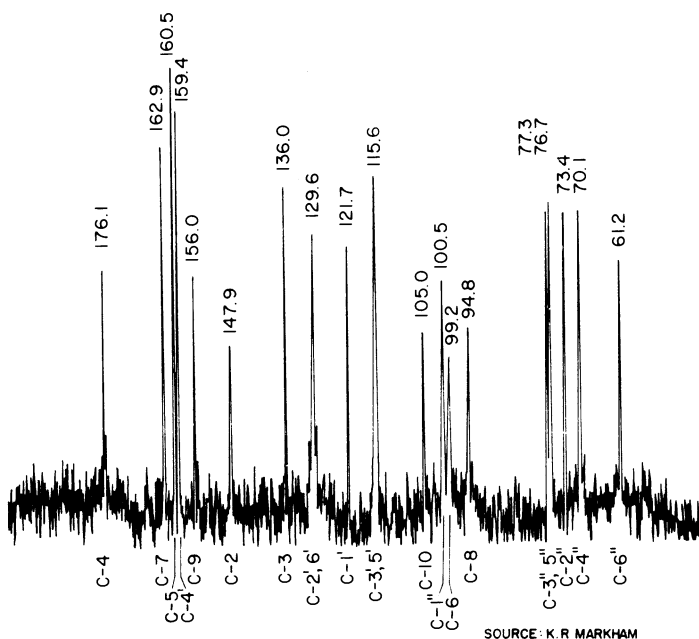
50



KAEMPFEROL 7-O-GLUCOSIDE

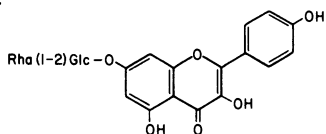
DMSO- $d_6$  (95°C)

25.15 MHz



SOURCE: K. R. MARKHAM

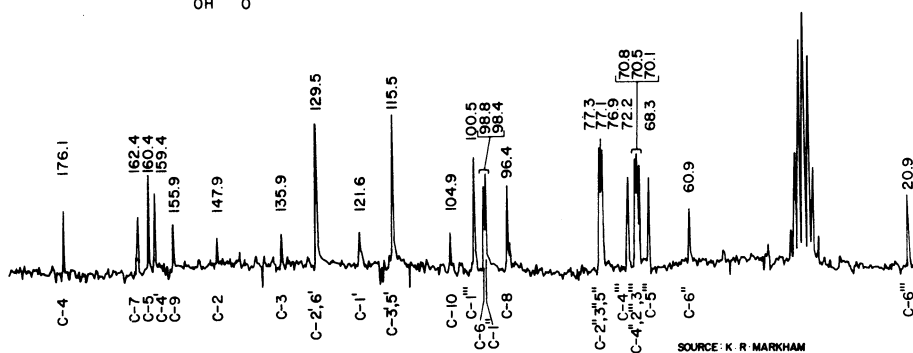
51



KAEMPFEROL 7-O-NEOHESPERIDOSIDE

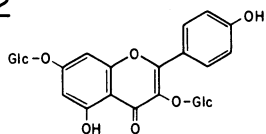
DMSO- $d_6$  (95°C)

25.15 MHz



SOURCE: K. R. MARKHAM

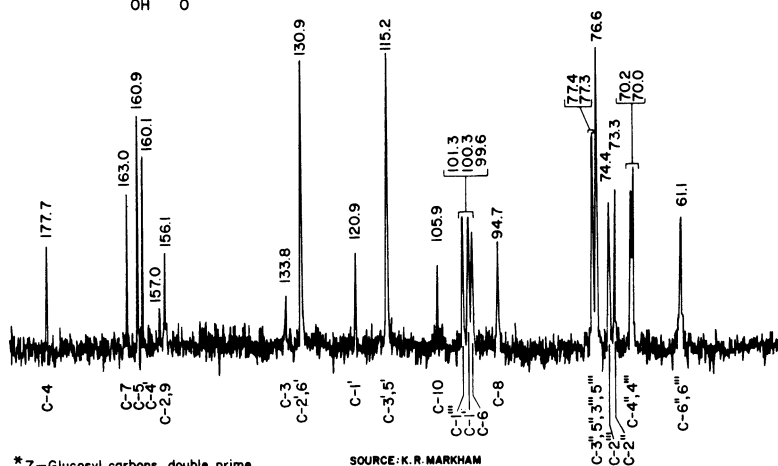
52



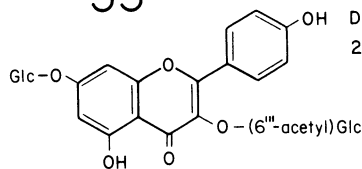
KAEMPFEROL 3,7-DI-O-GLUCOSIDE\*

DMSO- $d_6$  (95°C)

25.15 MHz



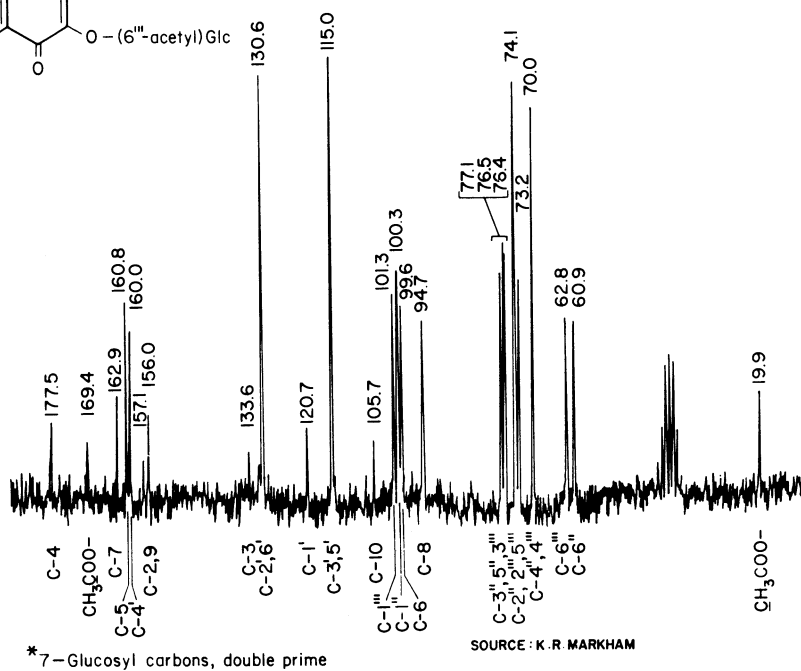
53



KAEMPFEROL 3-O-(6'''-ACETYL)-GLUCOSIDE 7-O-GLUCOSIDE\*

DMSO- $d_6$  (95°C)

25.15 MHz



25.15 MHz

Oc1cc(OC(=O)C2=CC=CC=C2)c3cc(OC(=O)C4=CC=CC=C4)cc(O)c3o1

[Glc(1-2)Glc]

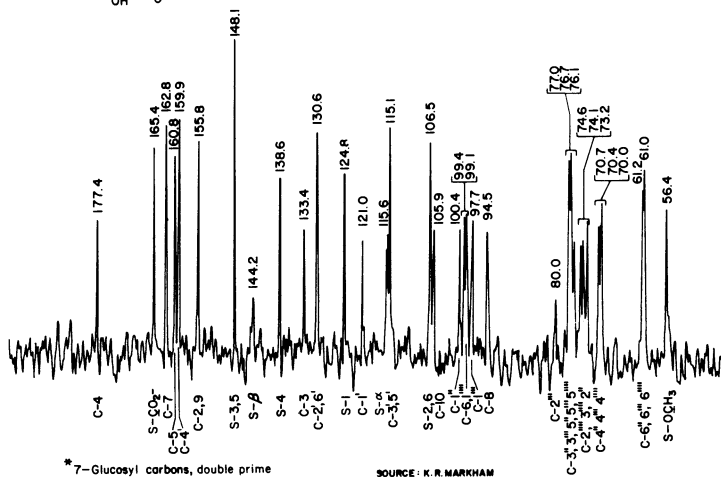
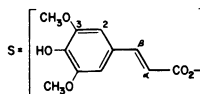
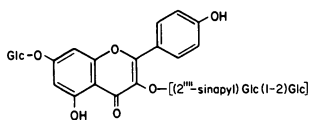
177.5, 162.8, 160.9, 159.9, 155.9, 133.3, 130.7, 120.8, 115.2, 105.8, 103.6, 100.3, 99.4, 98.4, 94.6, 82.1, 76.6, 77.2, 76.4, 74.3, 73.2, 70.3, 69.9, 61.3, 61.0, 60.9

C-4, C-7, C-8', C-2,9, C-3', C-2',6', C-1', C-3',5', C-10<sup>'''</sup>, C-1<sup>'''</sup>, C-6<sup>'''</sup>, C-8, C-2<sup>'''</sup>, C-3',5',8',10<sup>'''</sup>, C-4',2', C-4',6',8', C-6',6<sup>'''</sup>,6<sup>'''</sup>

\*7-Glucosyl carbons, double prime

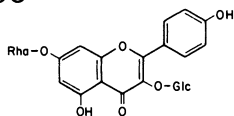
SOURCE: K R MARRHAM

KAEMPFEROL 3-O-(2<sup>HH</sup>-SINAPYL)-SOPHOROSIDE 7-O-GLUCOSIDE \*

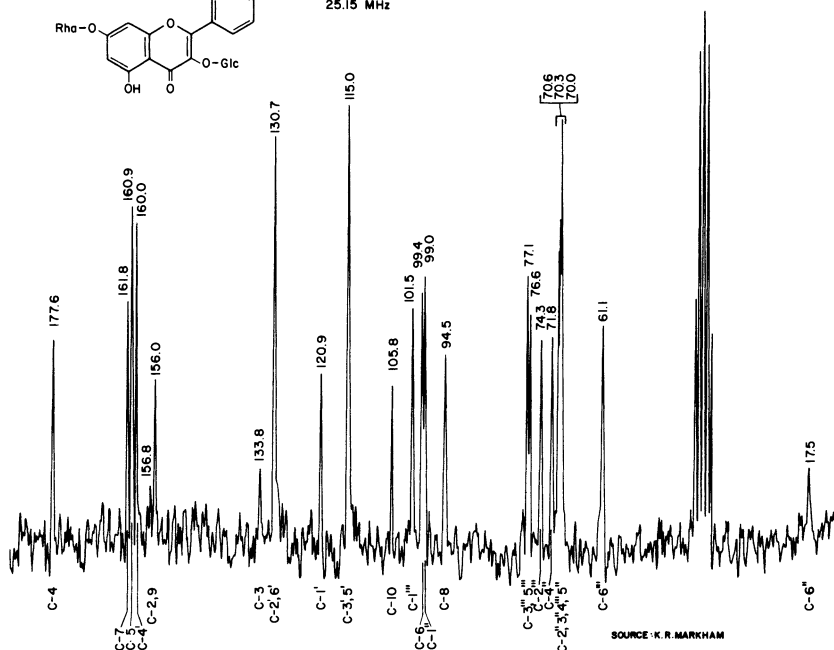




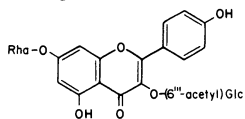
56



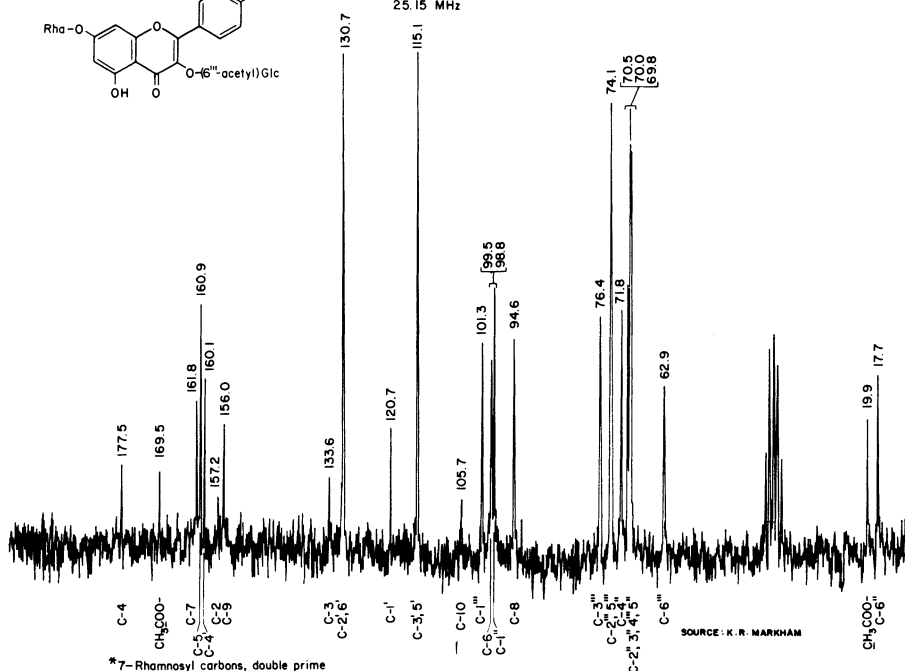
KAEMPFEROL 3-O-GLUCOSIDE 7-O-RHAMNOSIDE  
DMSO- $d_6$  (95°C)  
25.15 MHz



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KAEMPFEROL 3-O-(6''-ACETYL)-GLUCOSIDE 7-O-RHAMNOSIDE\*  
DMSO- $d_6$  (95°C)  
25.15 MHz

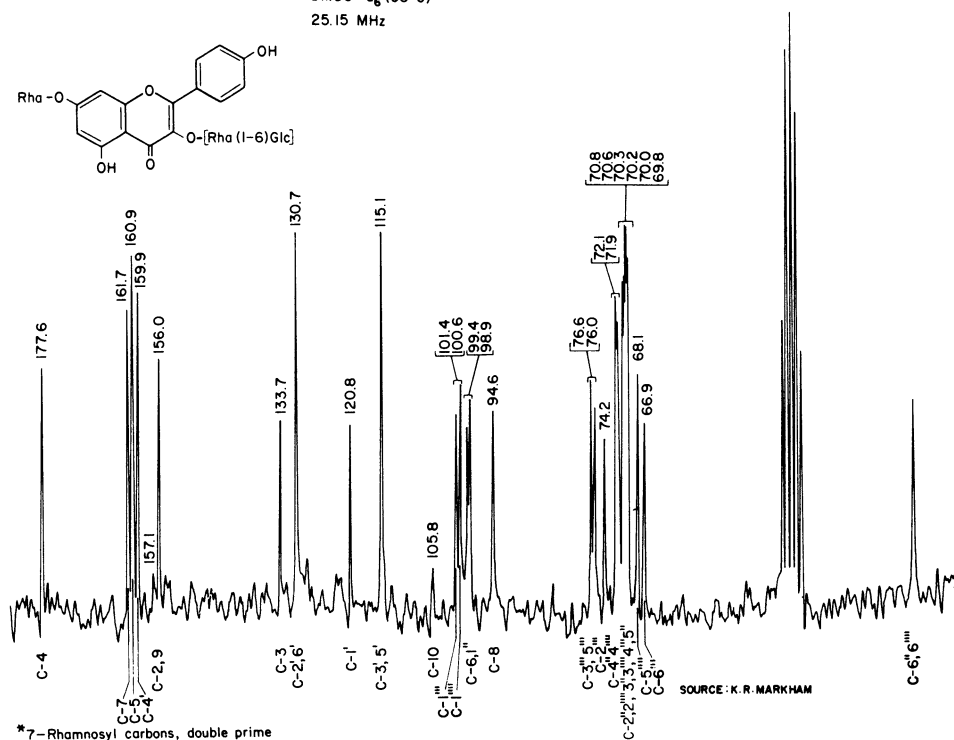
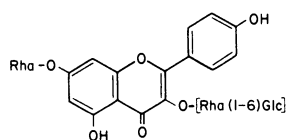


\*7-Rhamnosyl carbons, double prime

## KAEMPFEROL 3-O-RUTINOSIDE 7-O-RHAMNOSIDE\*

DMSO-d<sub>6</sub> (95°C)

25.15 MHz

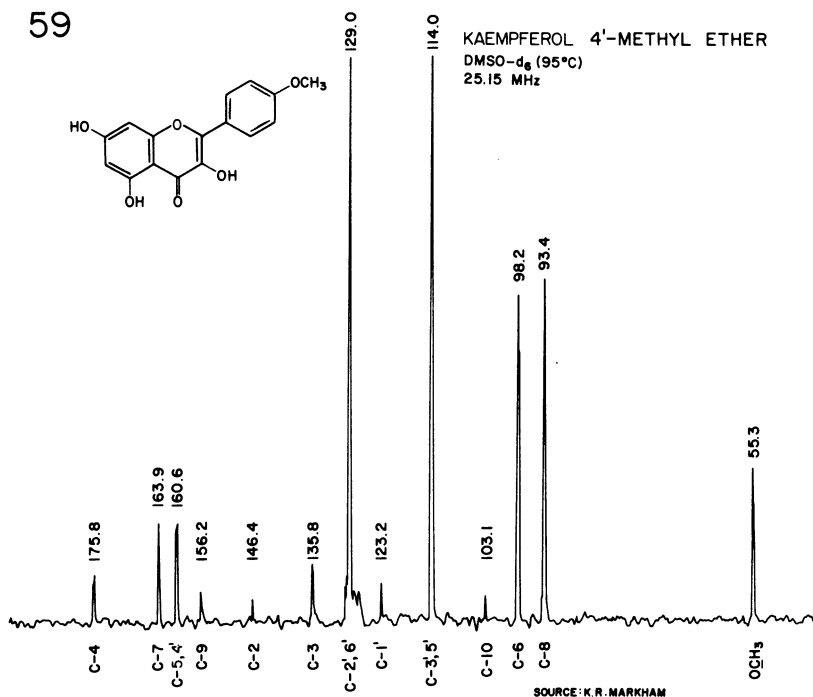
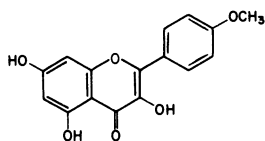


\*7-Rhamnosyl carbons, double prime

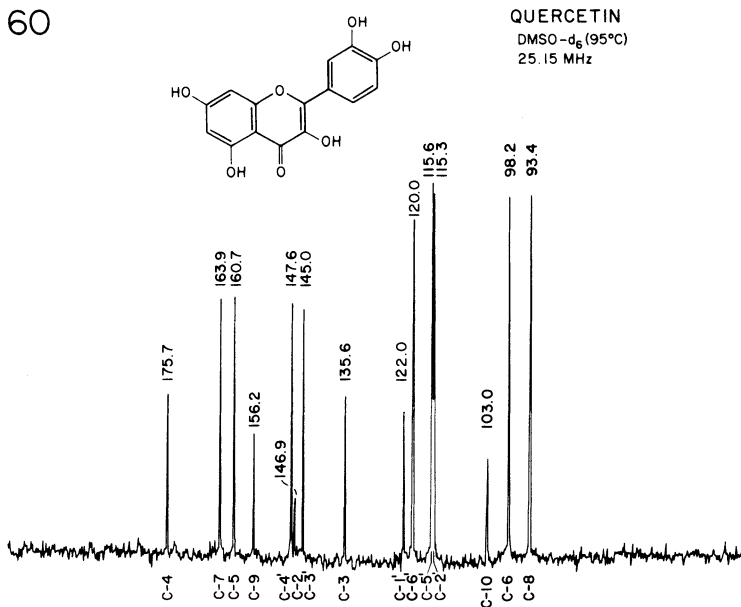
## KAEMPFEROL 4'-METHYL ETHER

DMSO-d<sub>6</sub> (95°C)

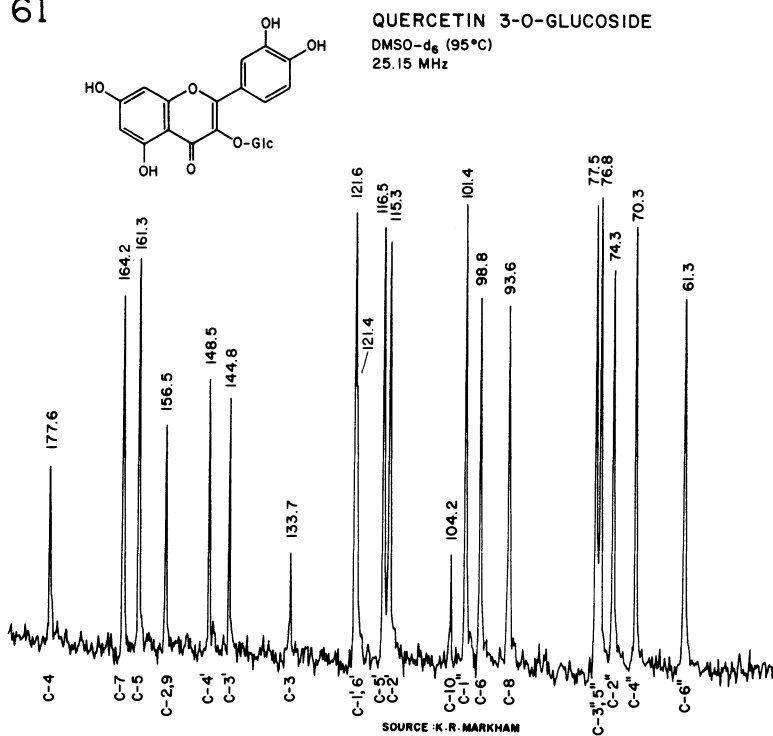
25.15 MHz



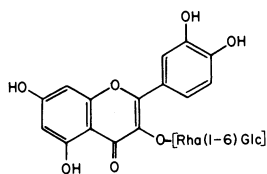
60



61

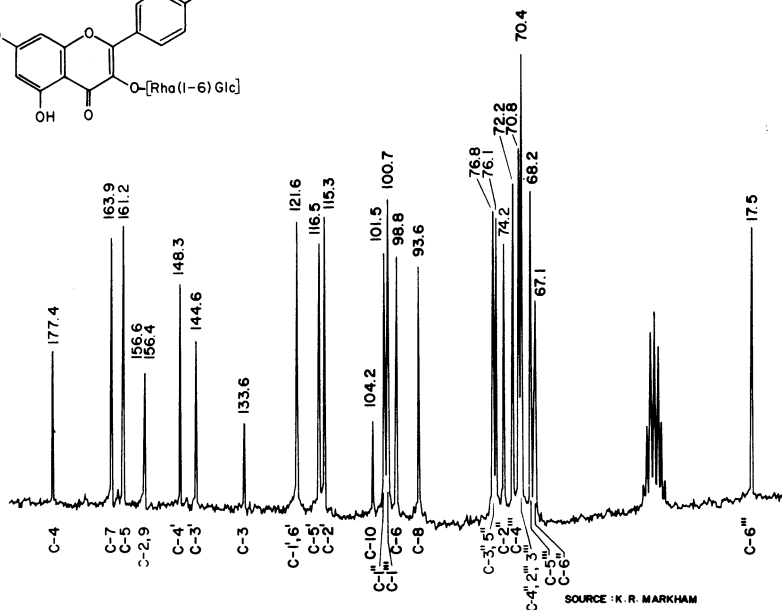


62

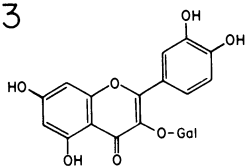


## QUERCETIN 3-O-RUTINOSIDE

DMSO- $d_6$  (95°C)  
25.15 MHz

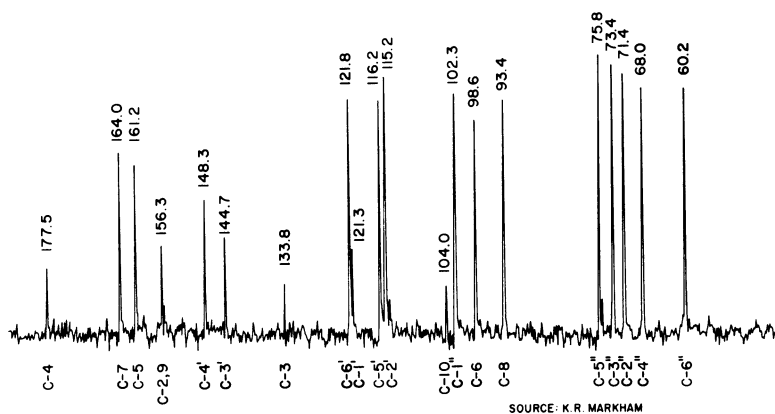


63

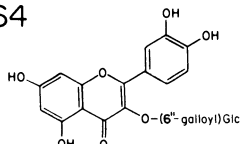


## QUERCETIN 3-O-GALACTOSIDE

DMSO- $d_6$  (95°C)  
25.15 MHz



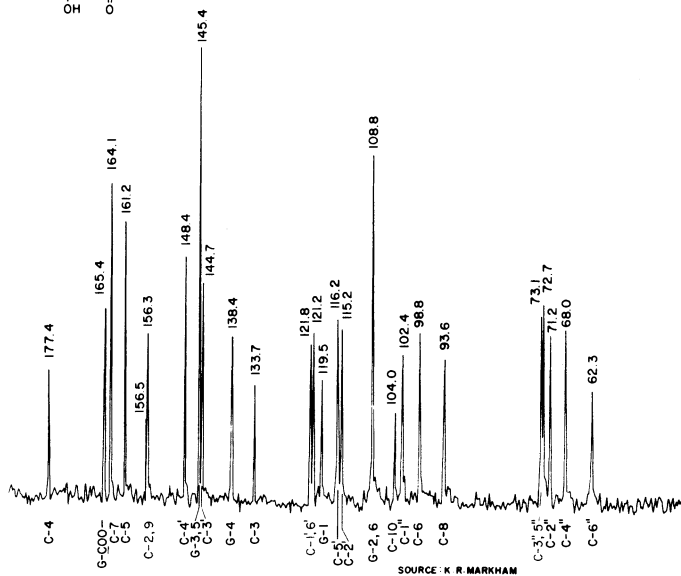
64



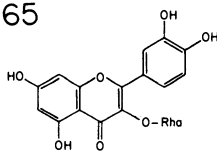
QUERCETIN 3-O-(6''-GALLOYL)-GALACTOSIDE

DMSO- $d_6$  (95°C)

25.15 MHz



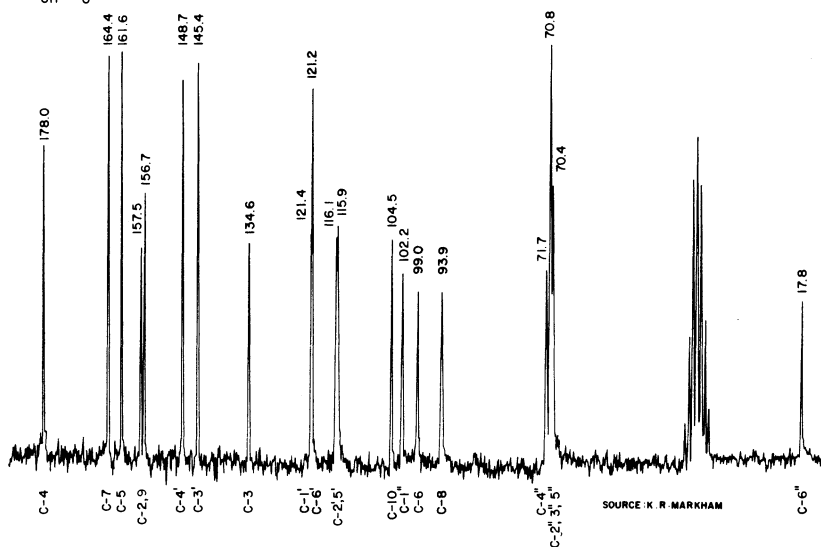
65



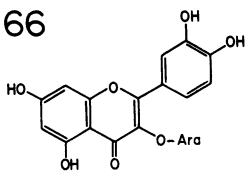
QUERCETIN 3-O-RHAMNOSIDE

DMSO- $d_6$  (95°C)

25.15 MHz



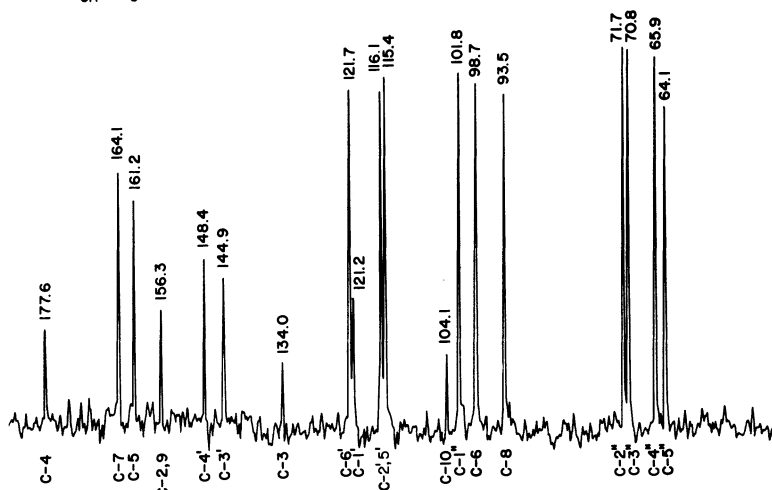
66



## QUERCETIN 3-O-ARABINOPYRANOSIDE

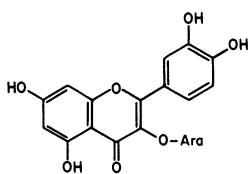
DMSO- $d_6$  (95 °C)

25.15 MHz



SOURCE : K. R. MARKHAM

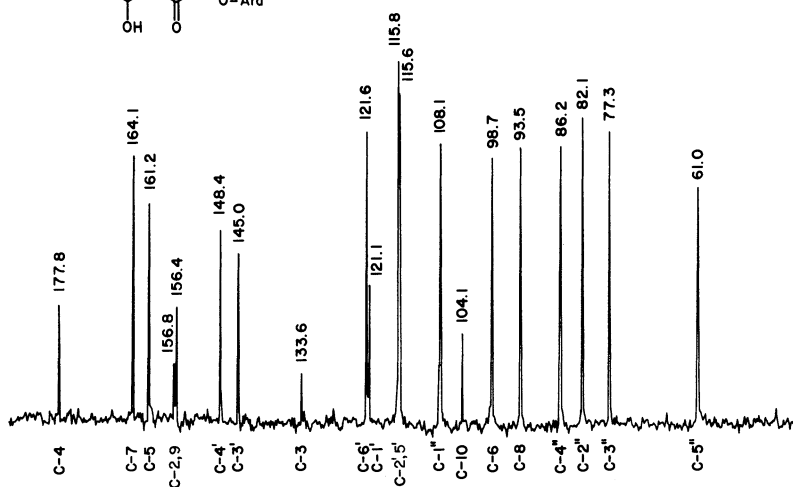
67



## QUERCETIN 3-O-ARABINOFURANOSIDE

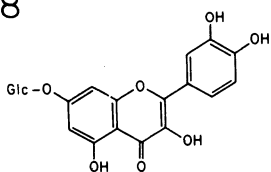
DMSO- $d_6$  (95 °C)

25.15 MHz

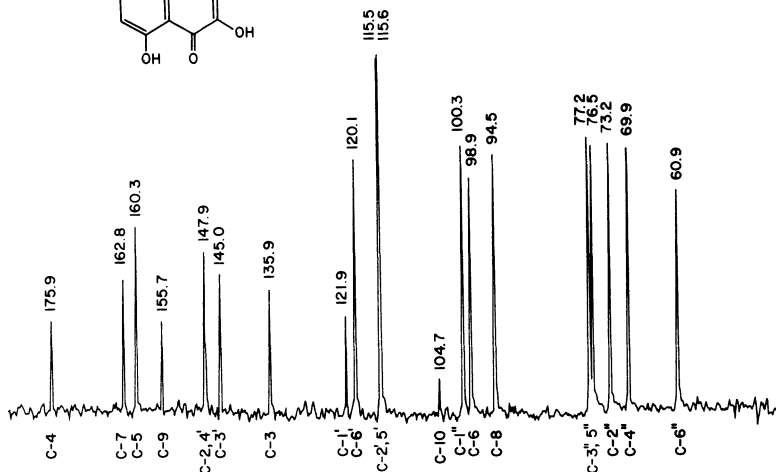


SOURCE : K. R. MARKHAM

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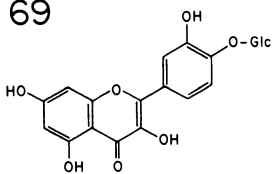


QUERCETIN 7-O-GLUCOSIDE  
DMSO- $d_6$  (95°C)  
25.15 MHz

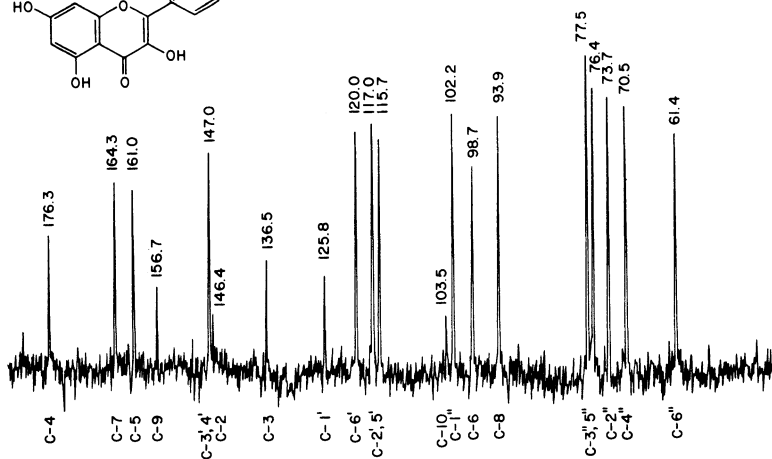


SOURCE : K. R. MARKHAM

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QUERCETIN 4'-O-GLUCOSIDE  
DMSO- $d_6$  (95°C)  
25.15 MHz

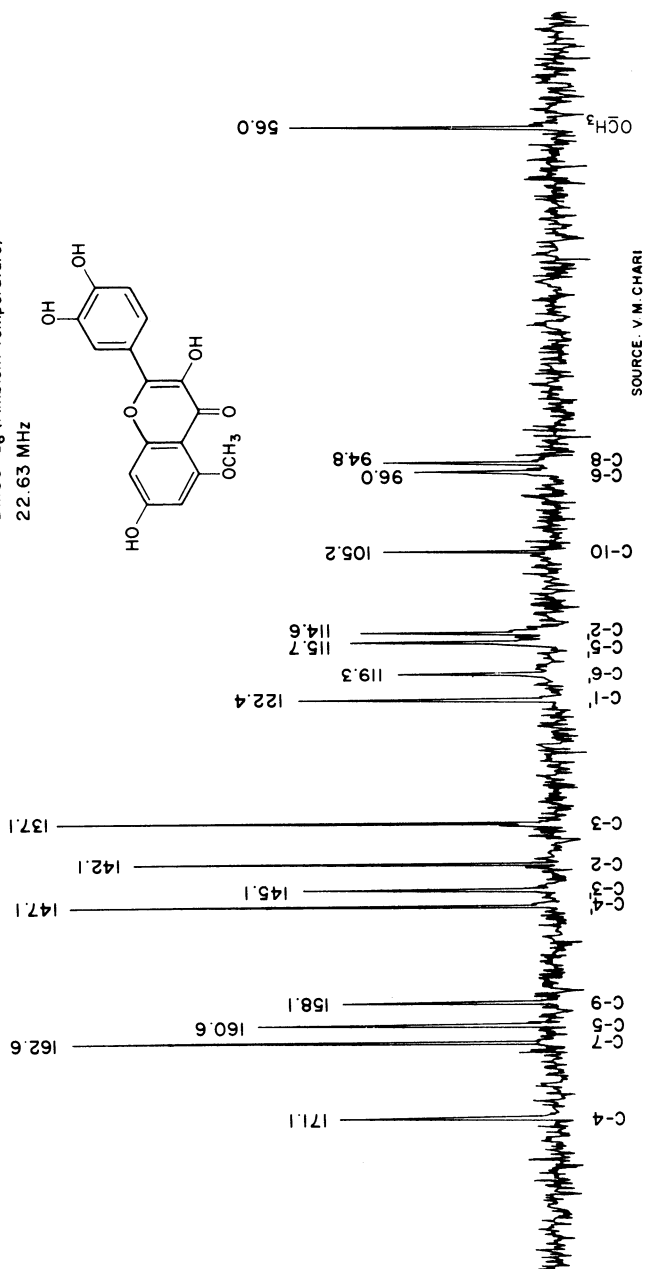
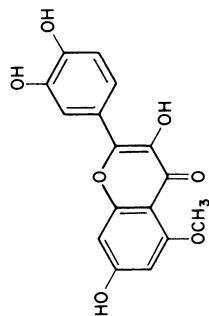


SOURCE : K. R. MARKHAM

## AZALEATIN

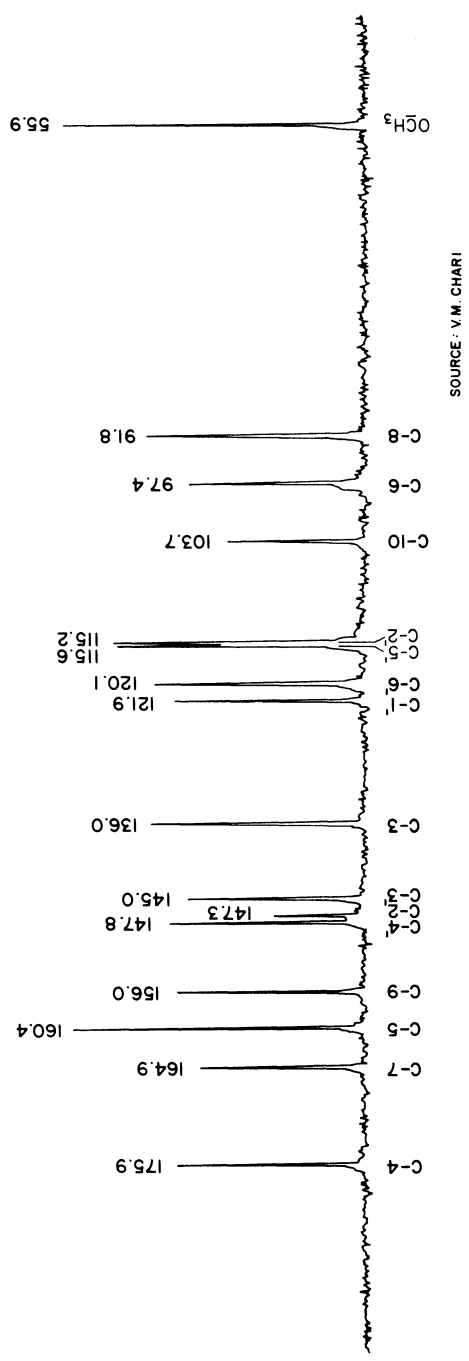
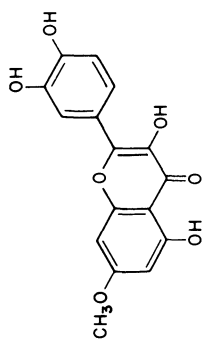
DMSO- $d_6$  (Ambient Temperature)

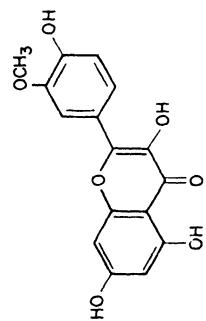
22.63 MHz



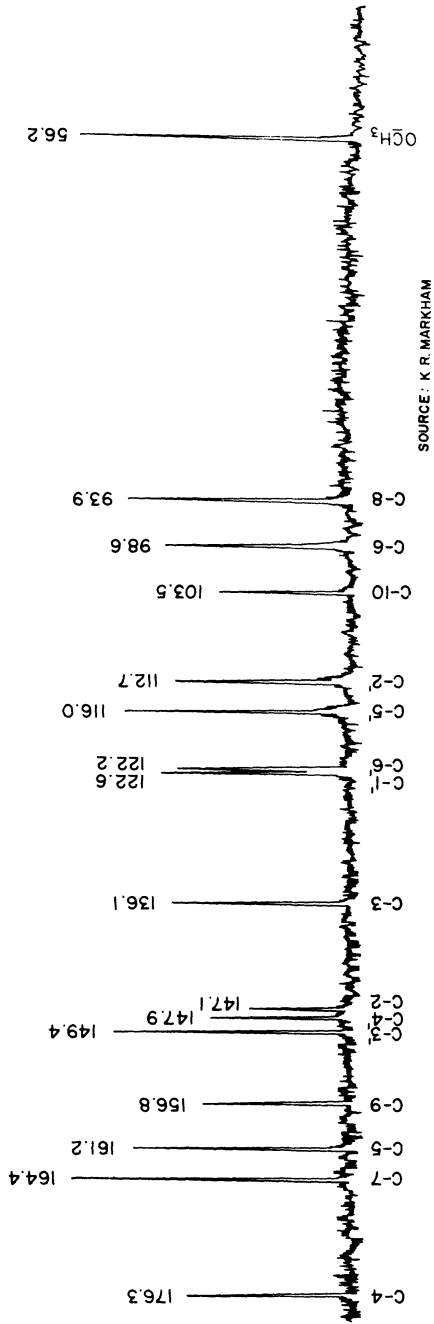


RHAMNETIN  
DMSO-d<sub>6</sub> (Ambient Temperature)  
22.63 MHz





ISORHAMNETIN  
DMSO-d<sub>6</sub> (70°C)  
25.2 MHz

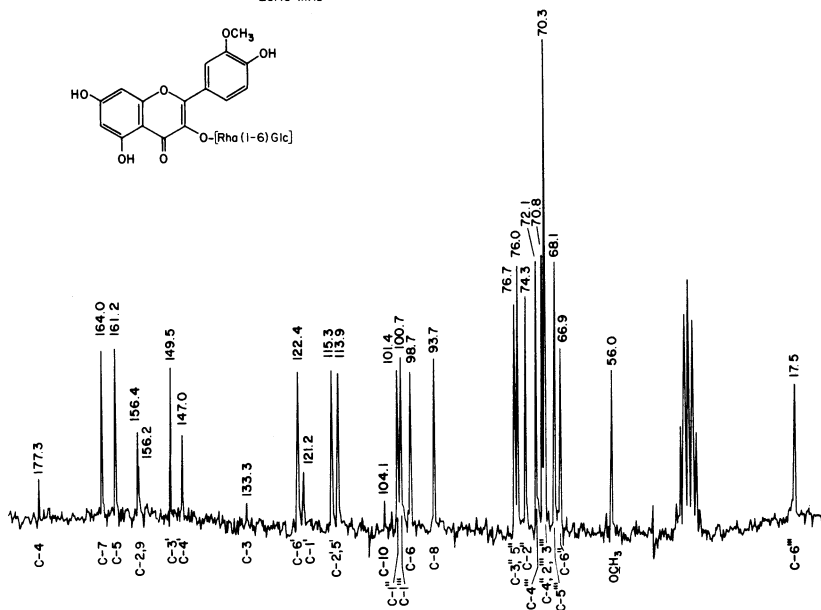
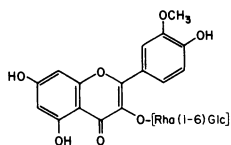


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## ISORHAMNETIN 3-O-RUTINOSIDE

DMSO- $d_6$  (95°C)

25.15 MHz



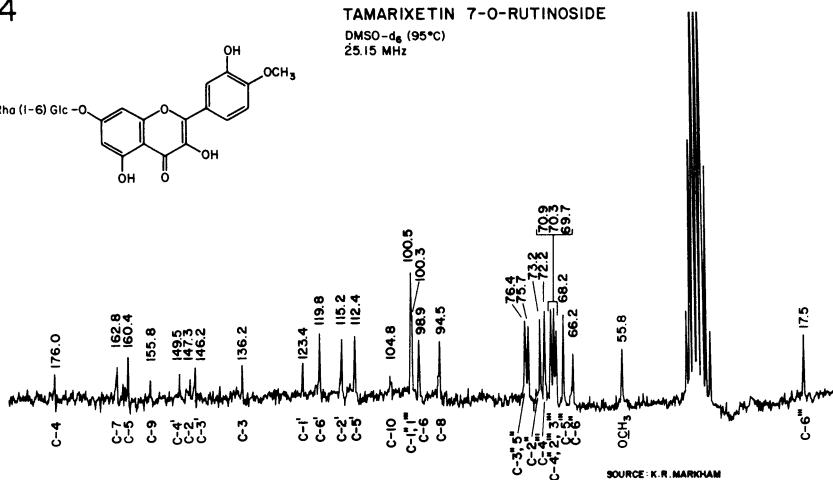
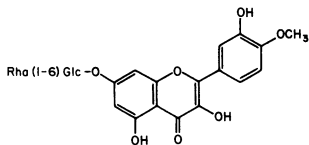
SOURCE: K. R. MARKHAM

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## TAMARIXETIN 7-O-RUTINOSIDE

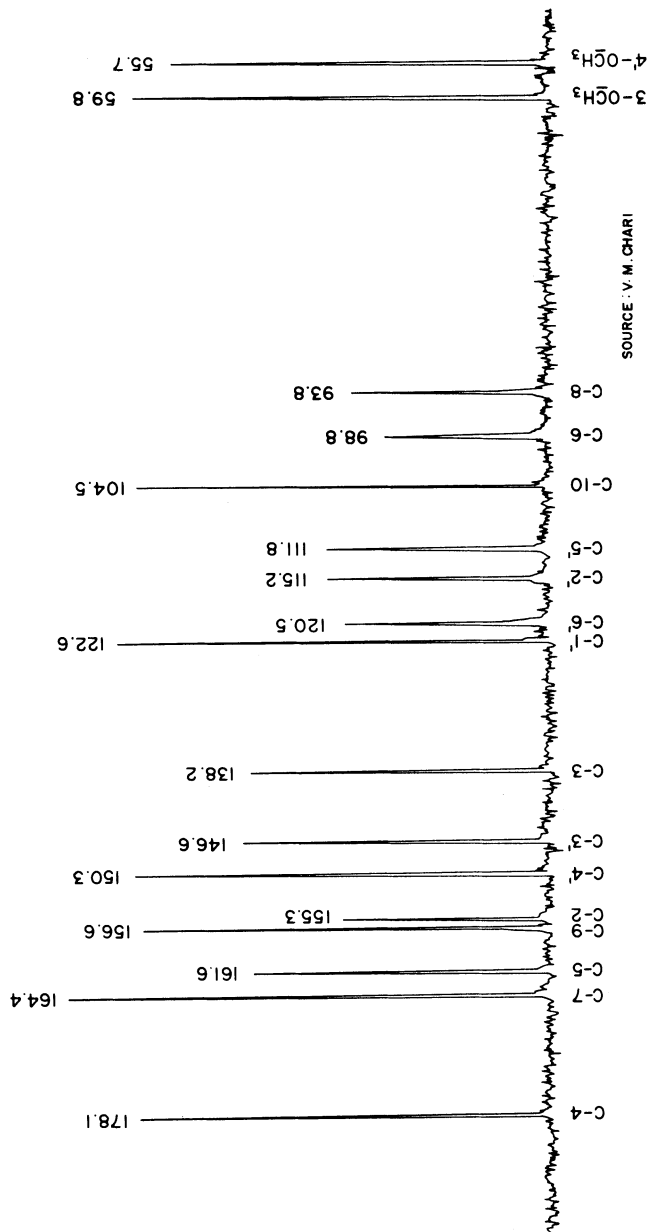
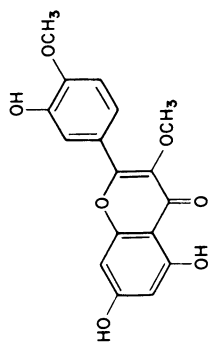
DMSO- $d_6$  (95°C)

25.15 MHz



SOURCE: K. R. MARKHAM

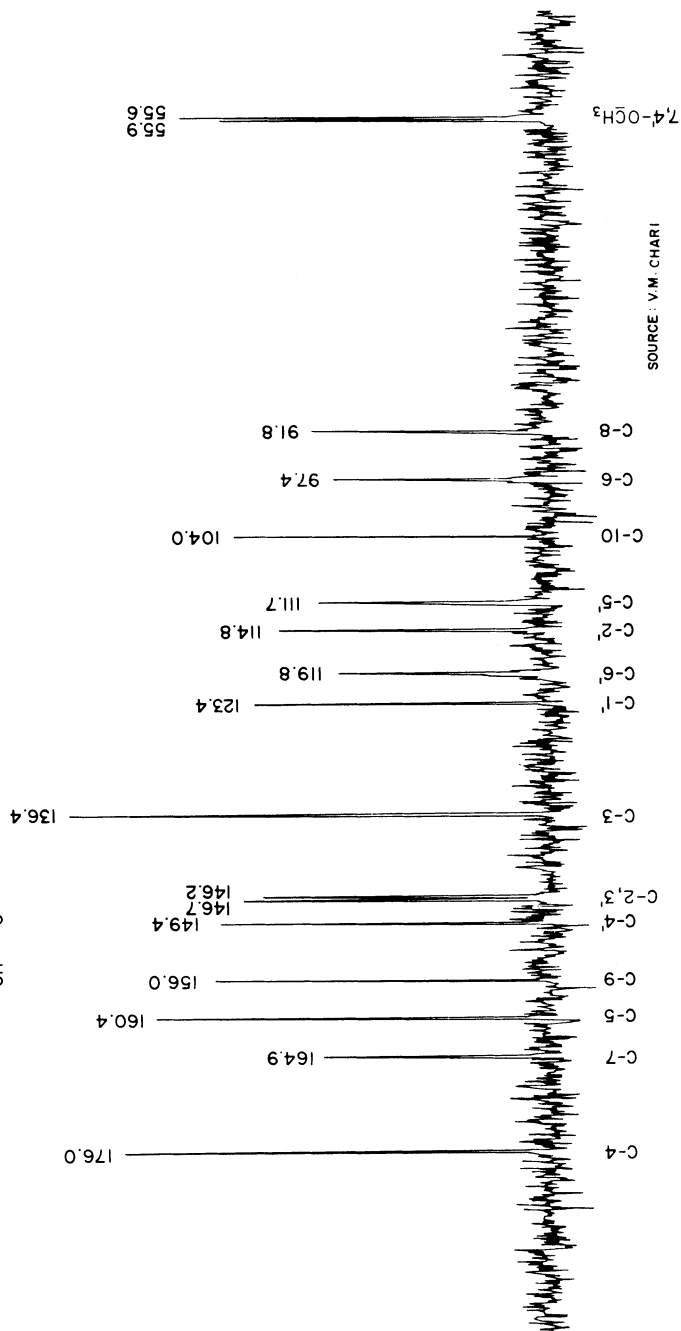
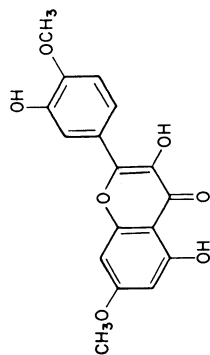
QUERCETIN 3,4'-DIMETHYL ETHER  
 DMSO- $d_6$  (Ambient Temperature)  
 22.63 MHz



## QUERCETIN 7, 4'-DIMETHYL ETHER

DMSO- $d_6$  (Ambient Temperature)

22.63 MHz

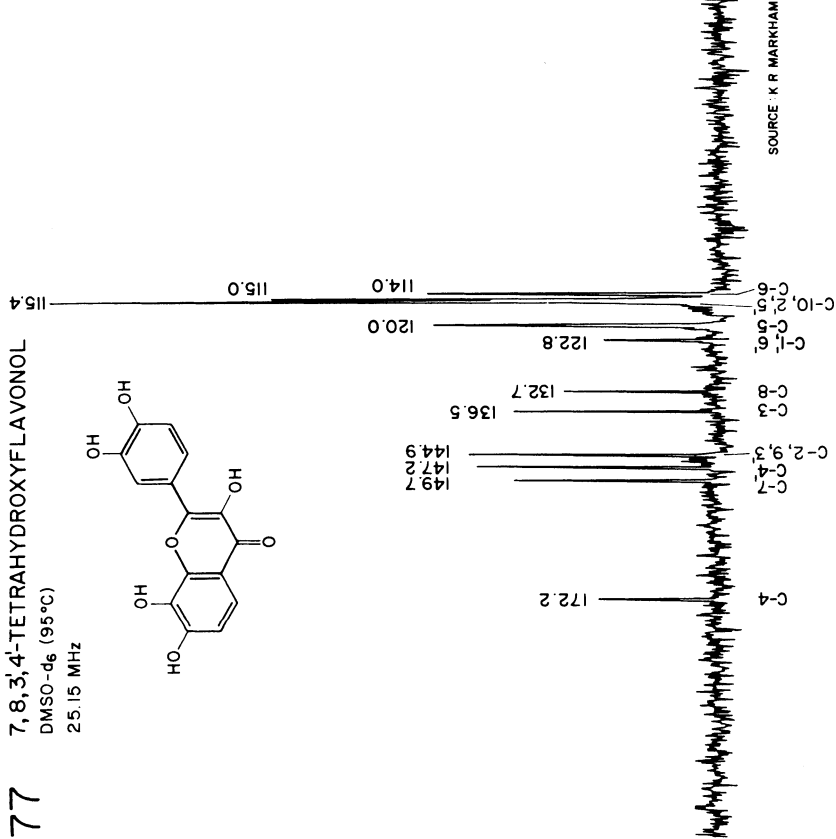
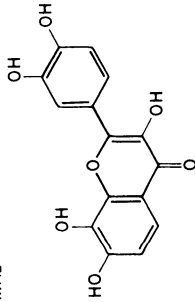


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## 7,8,3',4'-TETRAHYDROXYFLAVONOL

DMSO-d<sub>6</sub> (95°C)

25.15 MHz

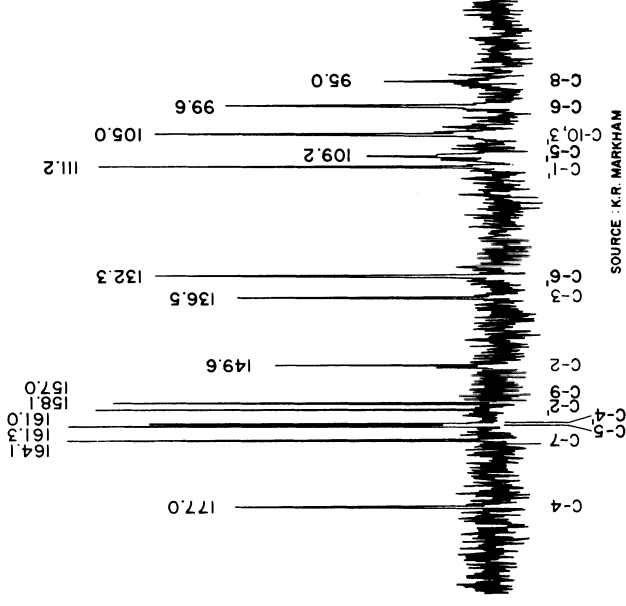
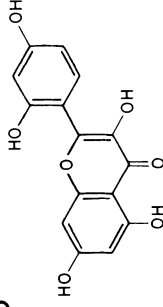


78

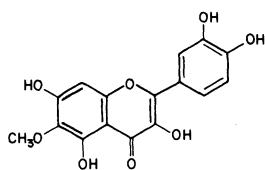
## MORIN

DMSO-d<sub>6</sub>: D<sub>2</sub>O (2:1), 95°C

25.15 MHz



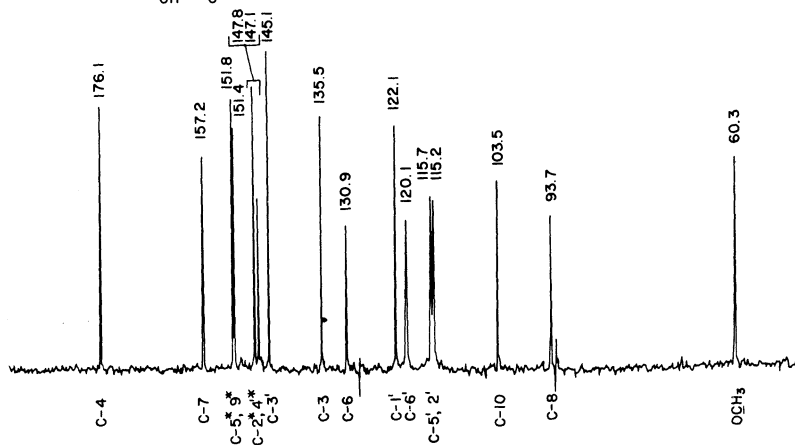
79



## PATULETIN

DMSO- $d_6$  (Ambient Temperature)

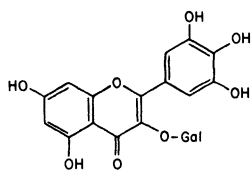
20 MHz



\* assignment interchangeable

SOURCE: V.M.CHARI

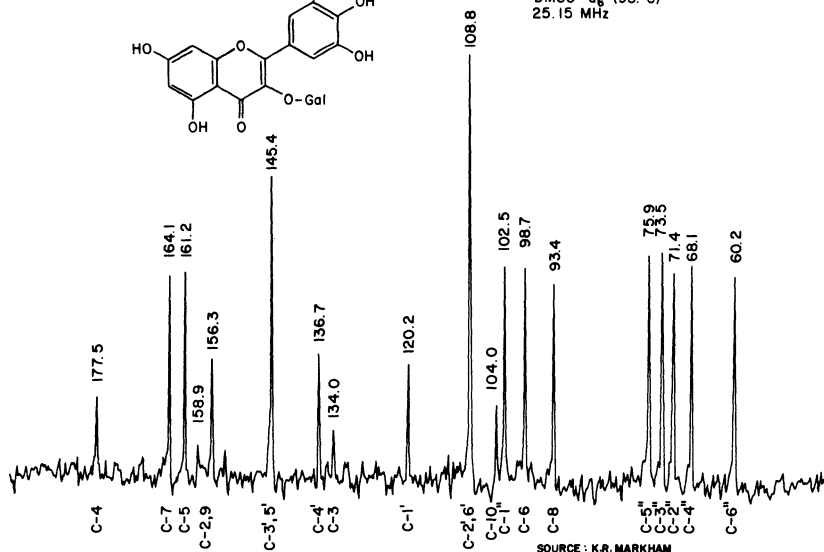
80



## MYRICETIN 3-O-GALACTOSIDE

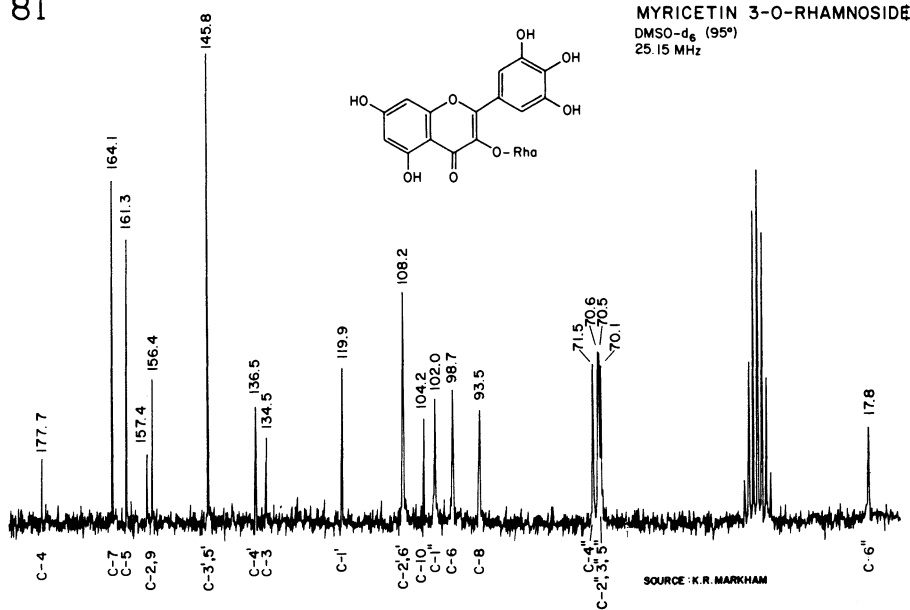
DMSO- $d_6$  (95.°C)

25.15 MHz

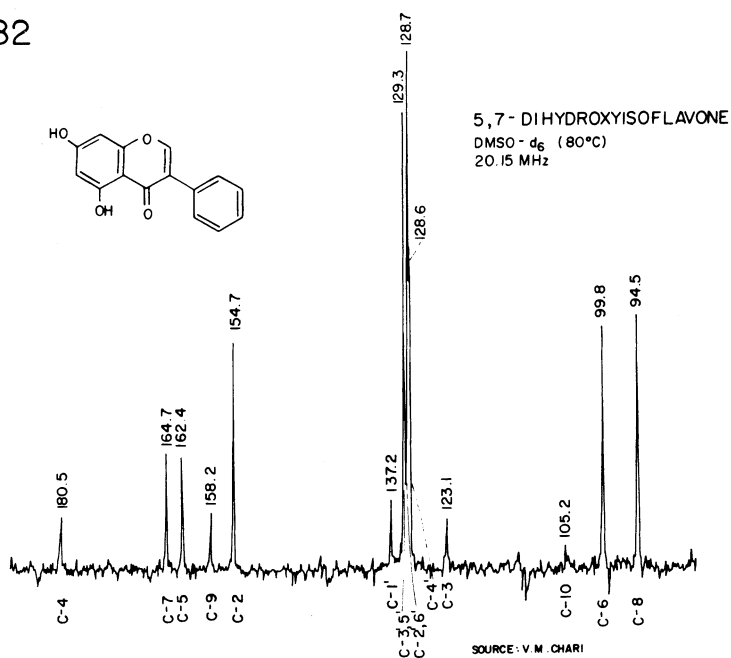


SOURCE: K.R. MARKHAM

81

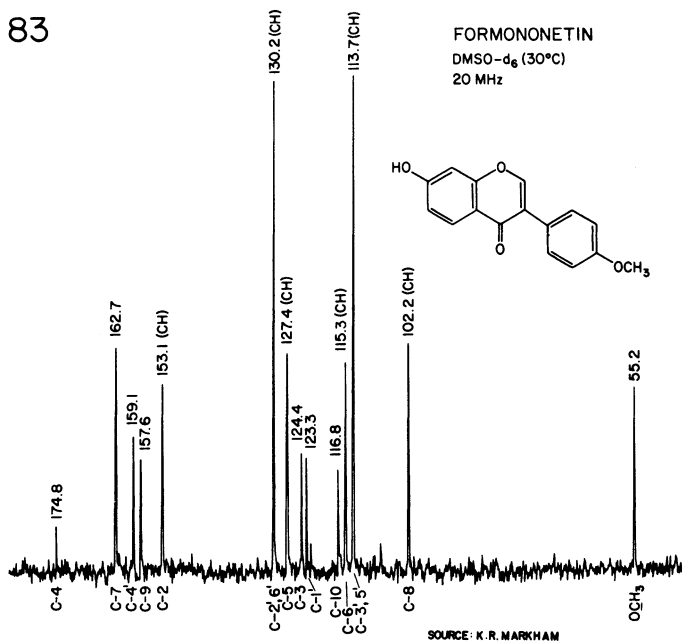


82

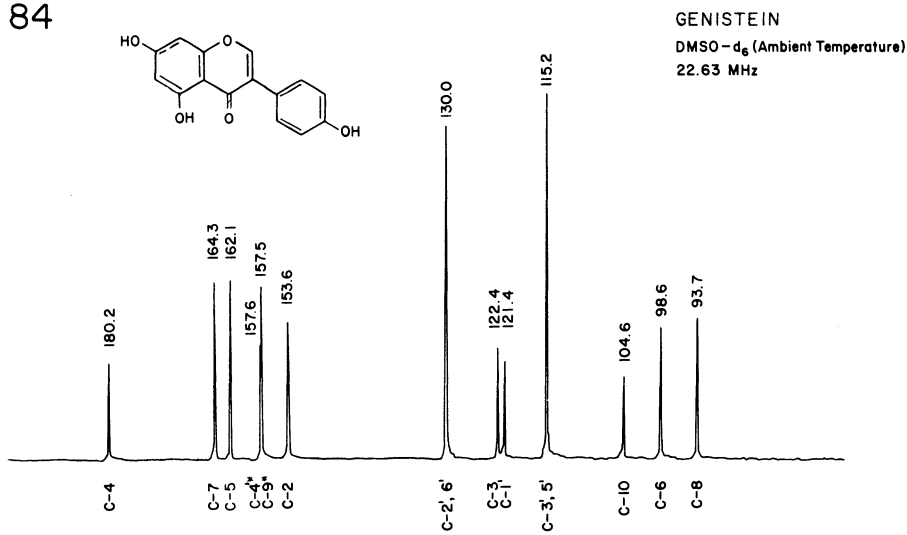




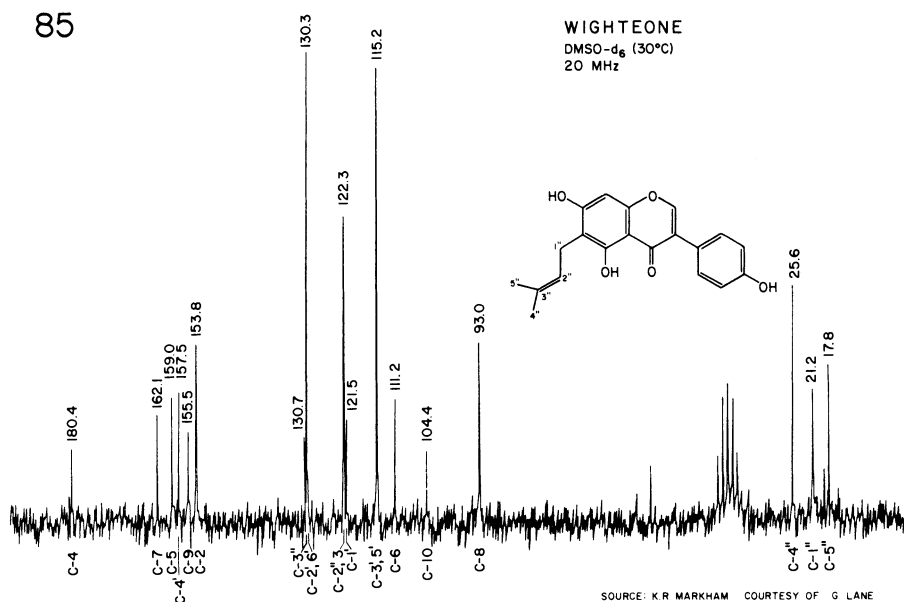
83



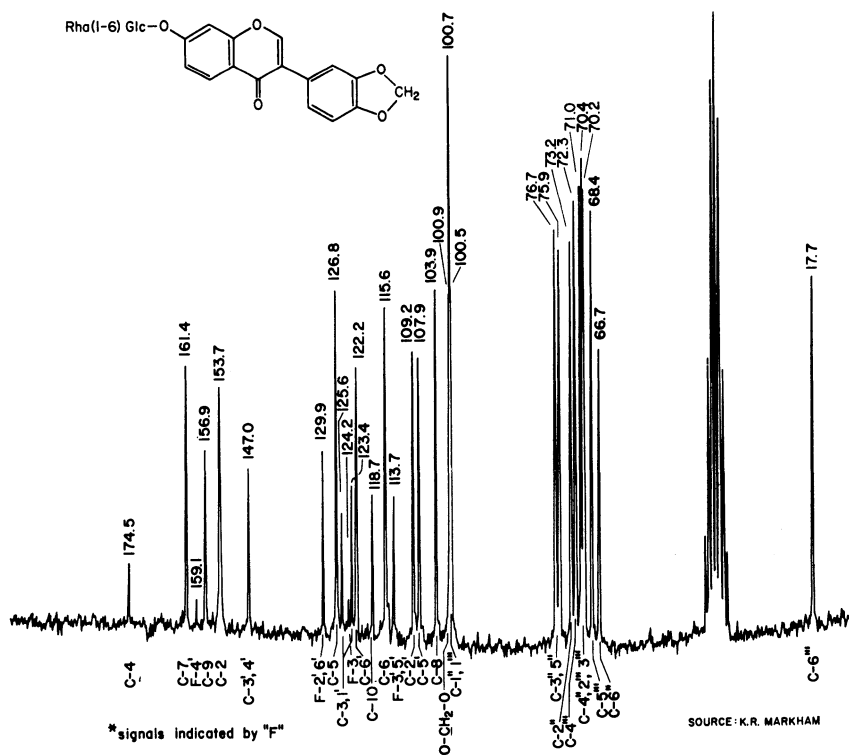
84



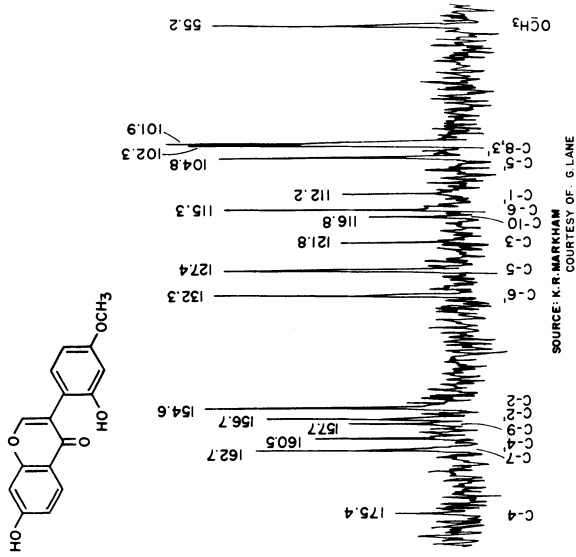
85



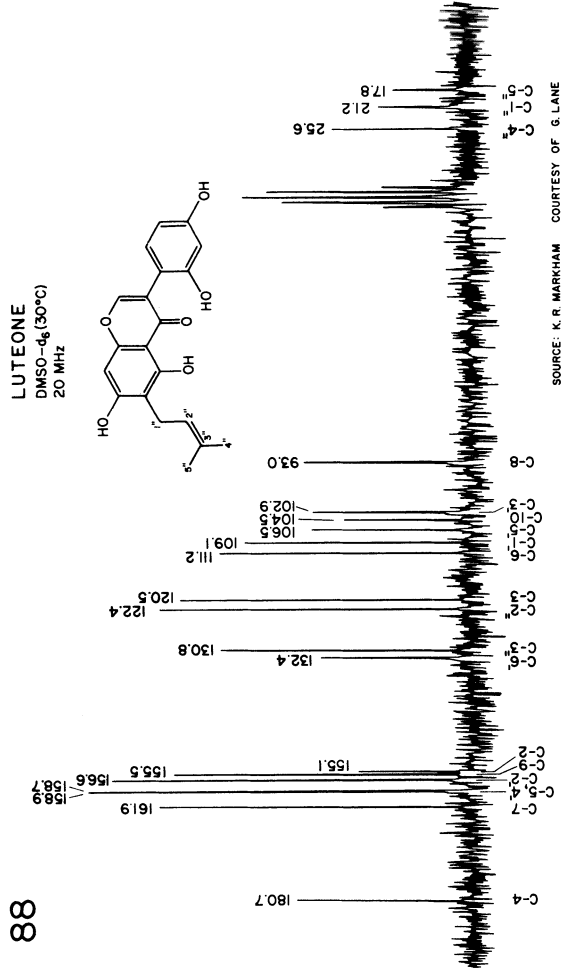
86

**PSEUDOBAPTISIN (FORMONONETIN 7-O-RUTINOSIDE Impurity\*)**DMSO-d<sub>6</sub> (95°C)  
25.15 MHz

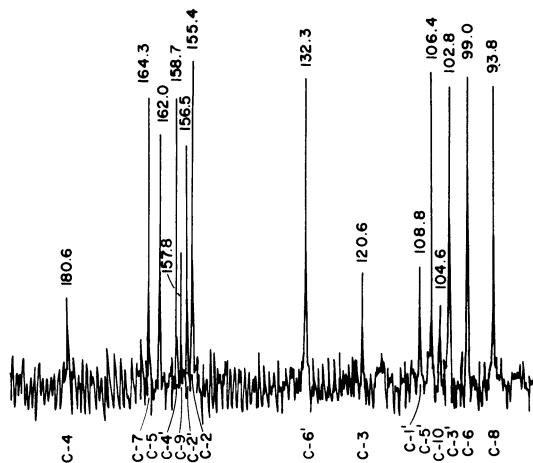
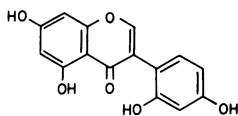
87 2'-HYDROXYFORMONONETIN  
DMSO - d<sub>6</sub> (30°C)  
20 MHz



88



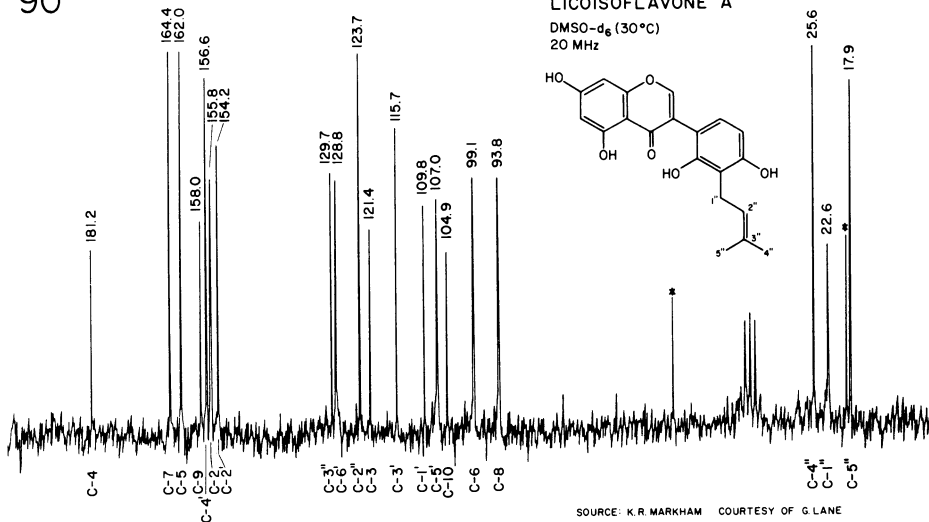
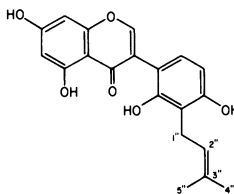
89 2'-HYDROXYGENISTEIN  
DMSO-d<sub>6</sub> (30°C)  
20 MHz



SOURCE: K. R. MARKHAM  
COURTESY OF G. LANE

90

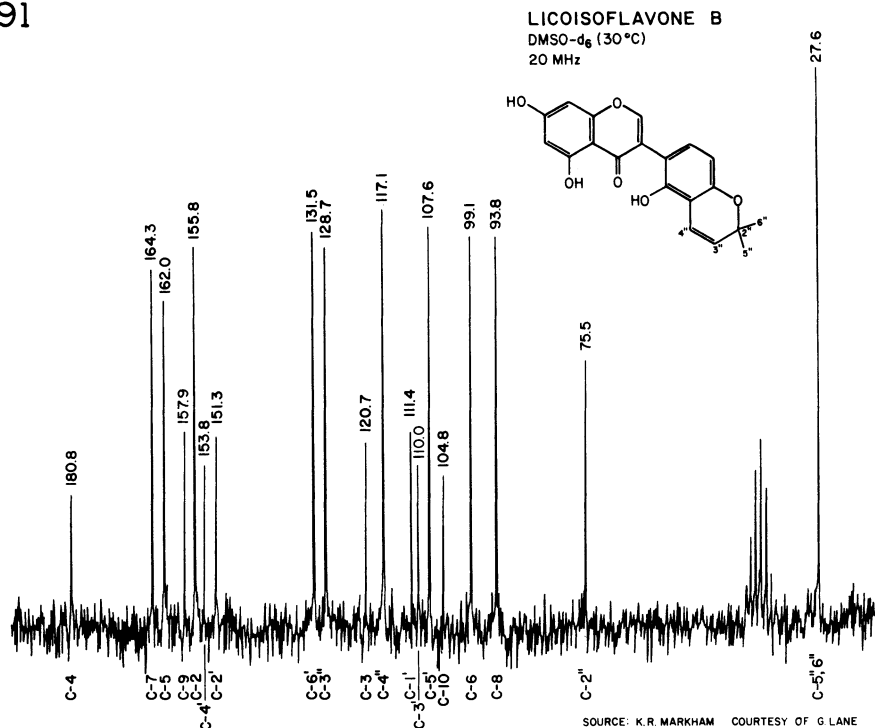
LICOISOFLAVONE A  
DMSO-d<sub>6</sub> (30°C)  
20 MHz



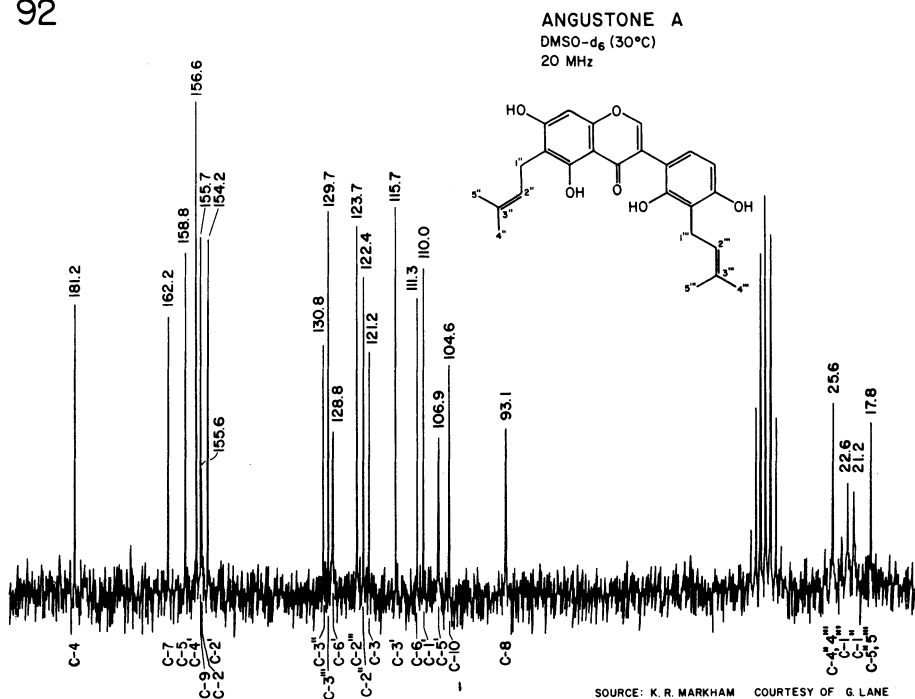
SOURCE: K. R. MARKHAM COURTESY OF G. LANE

\* Ethanol Peaks

91

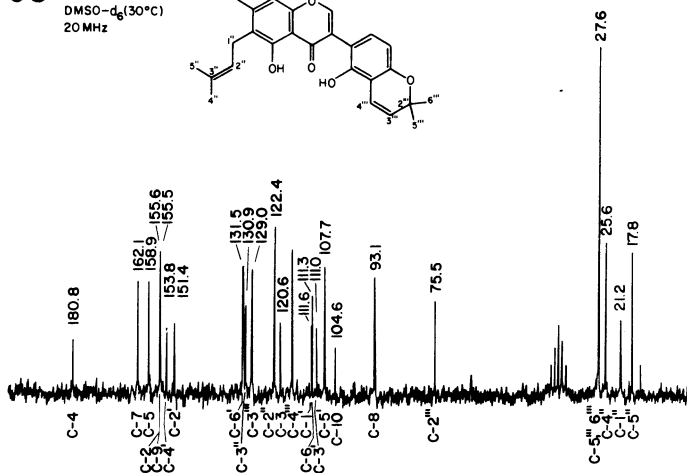
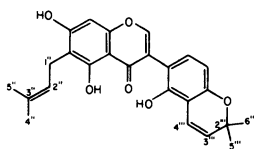


92



93

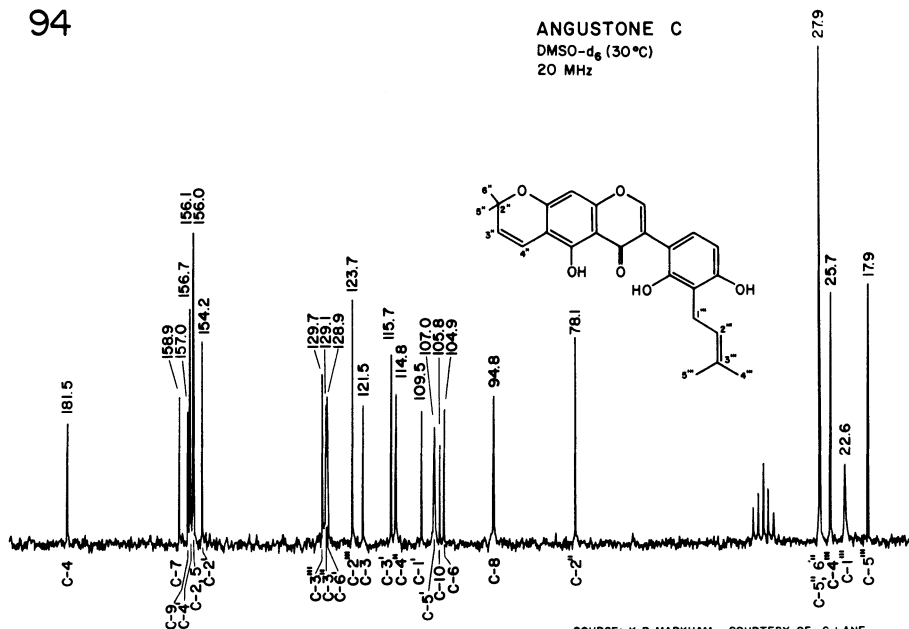
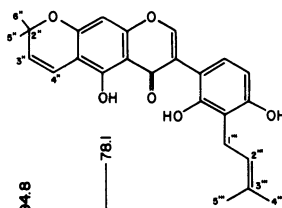
ANGUSTONE B  
DMSO- $d_6$  (30°C)  
20 MHz



SOURCE: K. R. MARKHAM COURTESY OF G. LANE

94

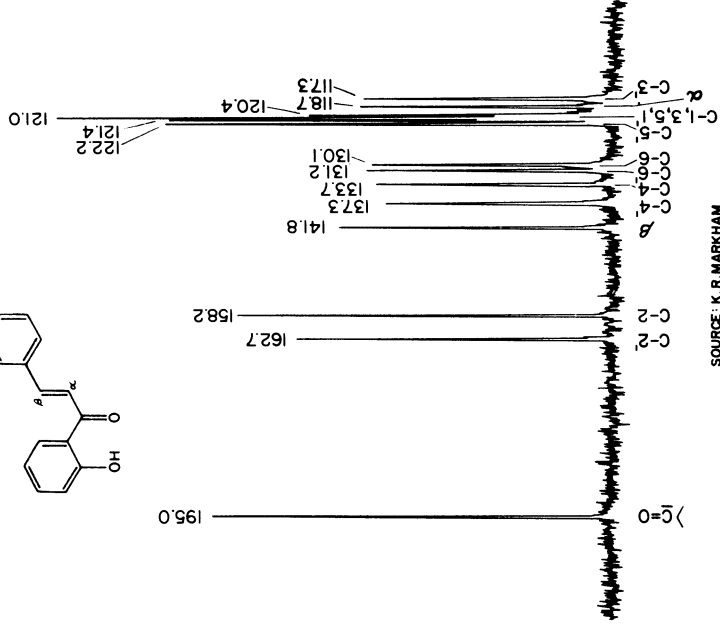
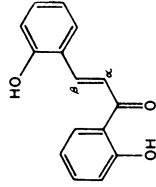
ANGUSTONE C  
DMSO- $d_6$  (30°C)  
20 MHz



SOURCE: K. R. MARKHAM COURTESY OF G. LANE

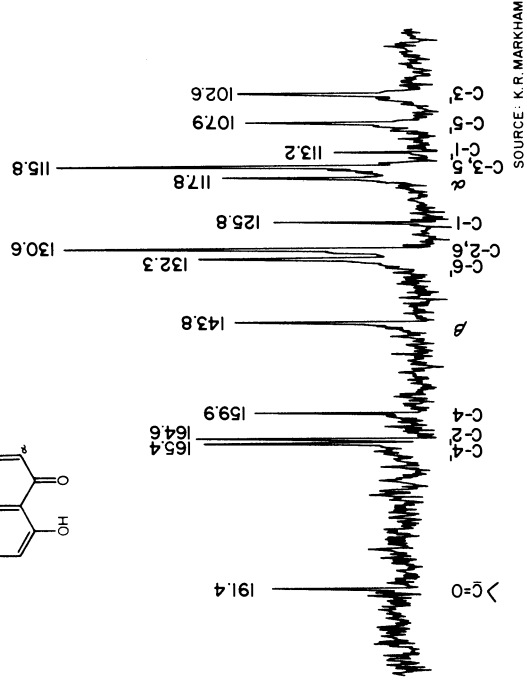
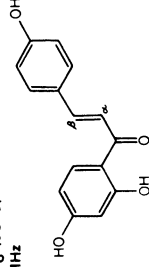
95

2,2'-DIHYDROXYCHALCONE  
DMSO-d<sub>6</sub> D<sub>2</sub>O (7:2) (95°C)  
25.15 MHz



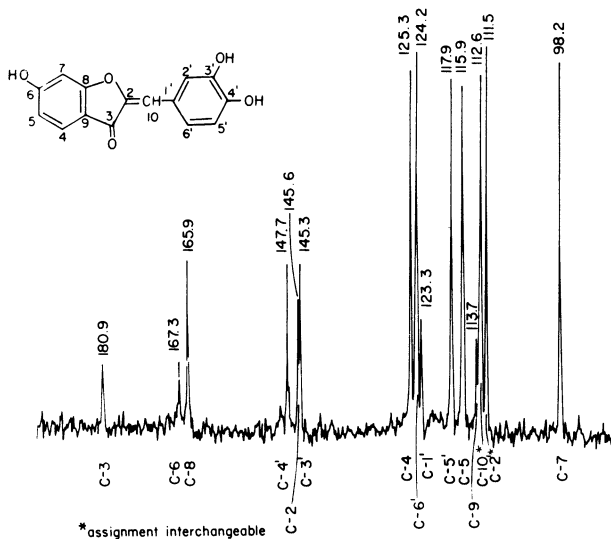
96

ISOLIQURITIGENIN  
DMSO-d<sub>6</sub> (95°C)  
25.15 MHz



97

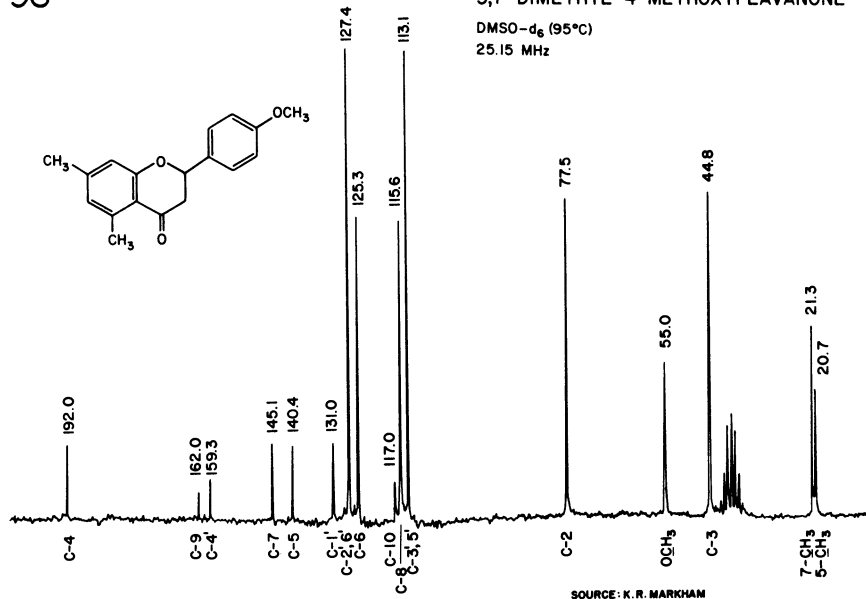
SULFURETIN  
DMSO-d<sub>6</sub> (60°C)  
20.15 MHz



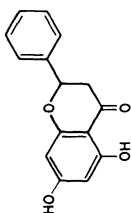
SOURCE: V. M. CHARI

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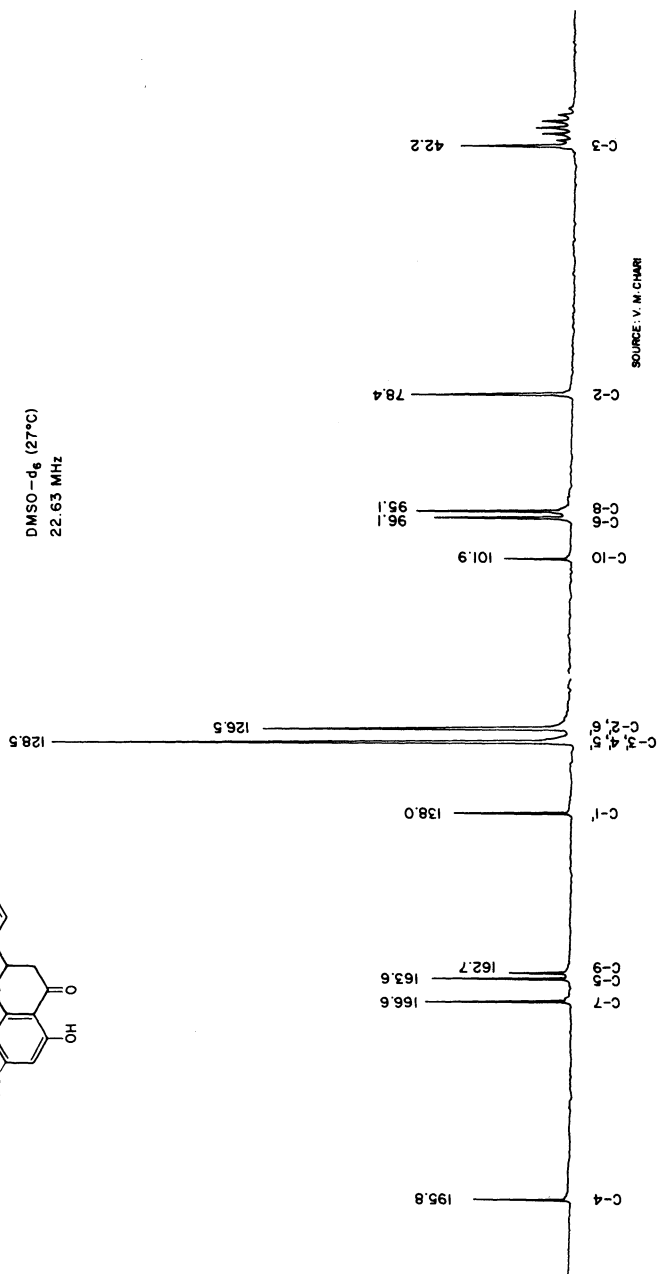
5,7-DIMETHYL 4'-METHOXYFLAVANONE  
DMSO-d<sub>6</sub> (95°C)  
25.15 MHz



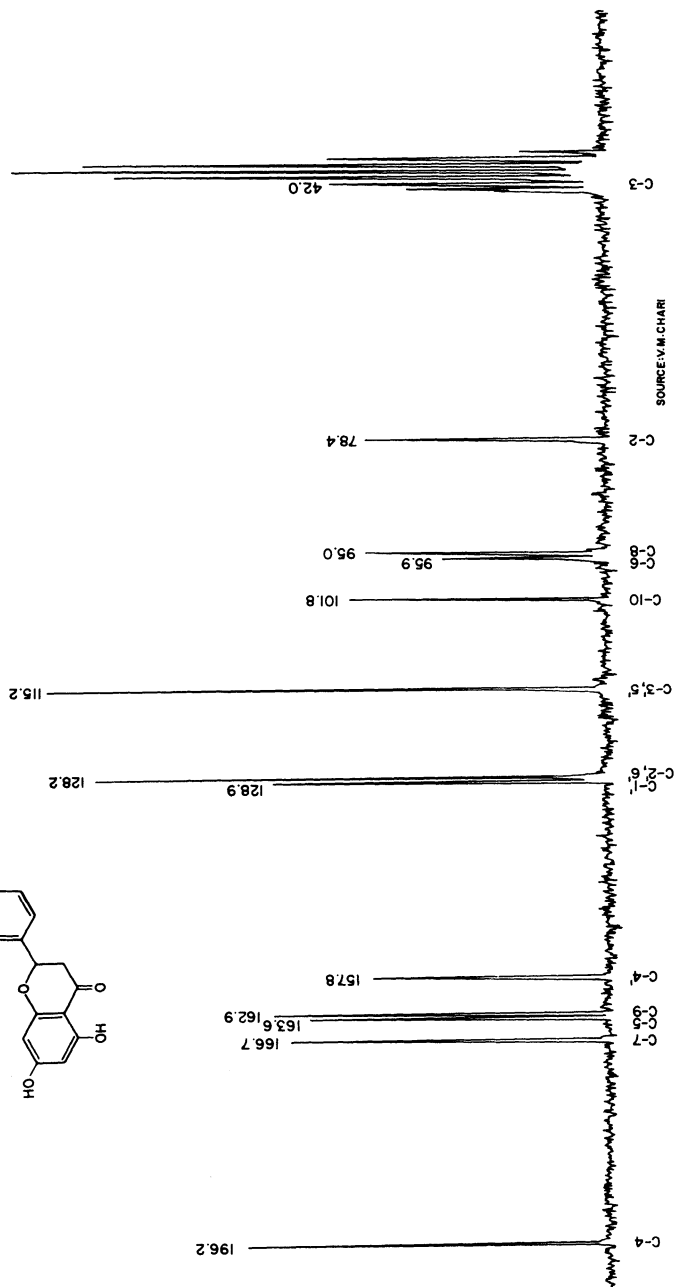
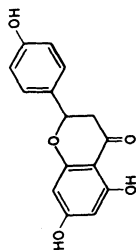




PINOCEMBRIN  
DMSO- $d_6$  (27°C)  
22.63 MHz



NARINGENIN  
DMSO- $d_6$  (Ambient Temperature)  
22.63 MHz

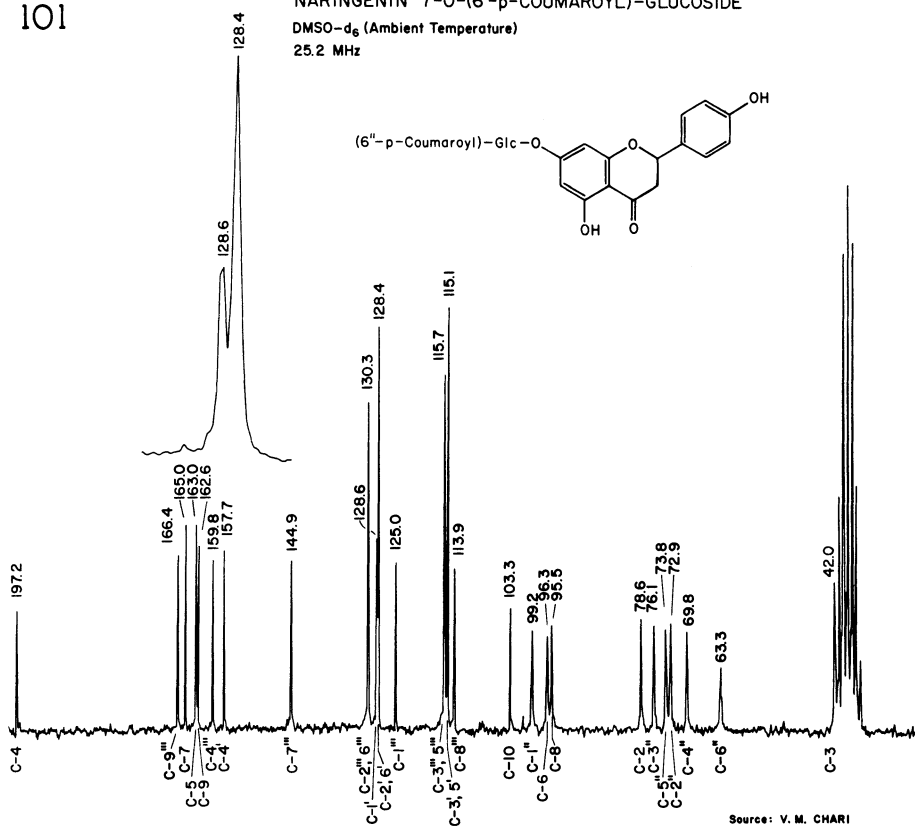


101

## NARINGENIN 7-O-(6''-p-COUMAROYL)-GLUCOSIDE

DMSO-d<sub>6</sub> (Ambient Temperature)

25.2 MHz



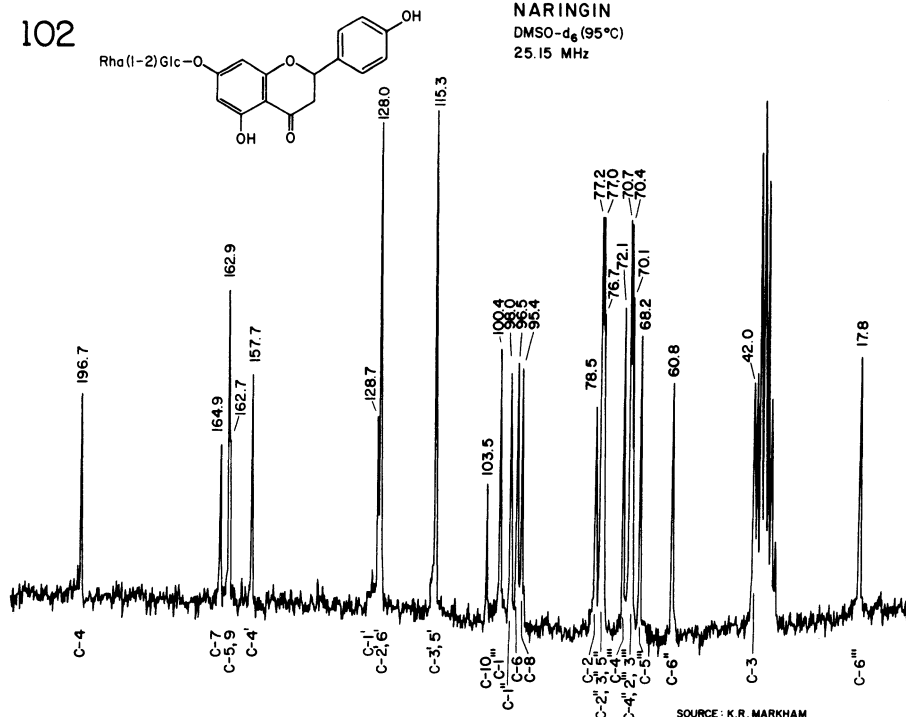
Source: V. M. CHARI

102

## NARINGIN

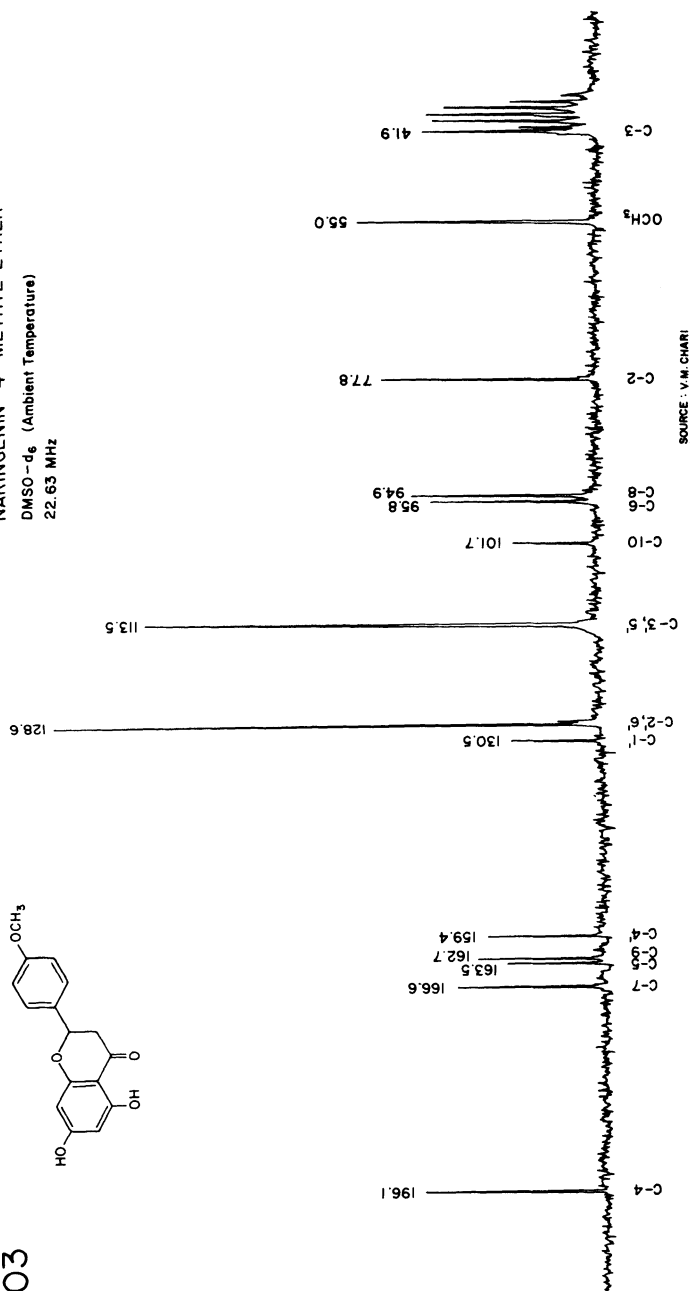
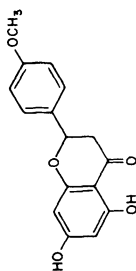
DMSO-d<sub>6</sub> (95°C)

25.15 MHz

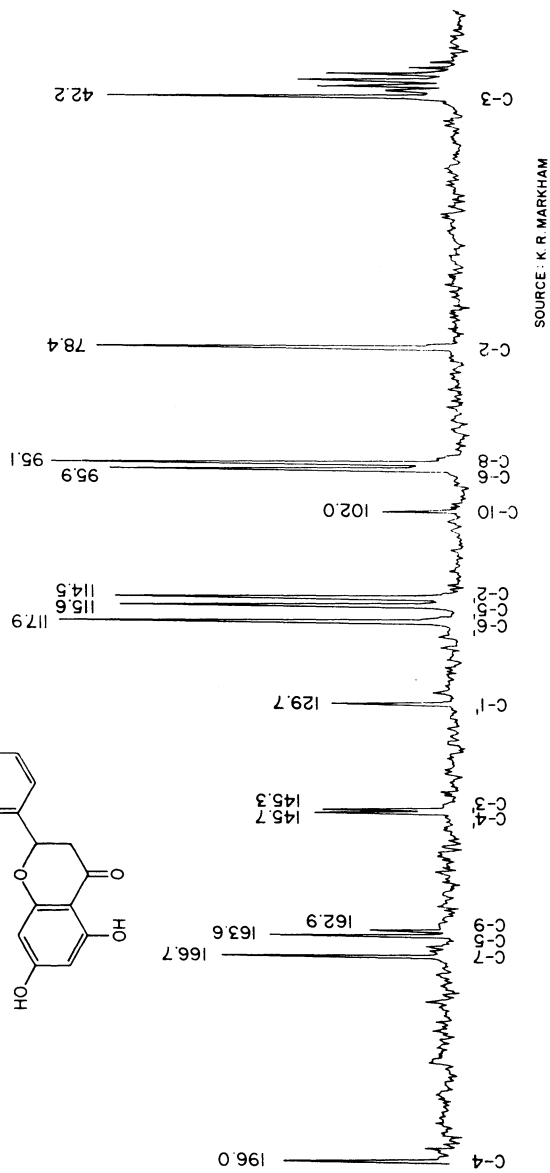
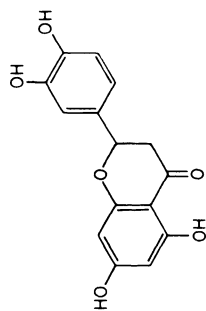


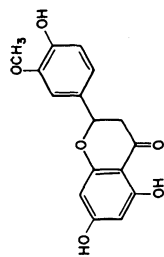
SOURCE: K. R. MARKHAM

NARINGENIN 4'-METHYL ETHER  
DMSO-d<sub>6</sub> (Ambient Temperature)  
22.63 MHz

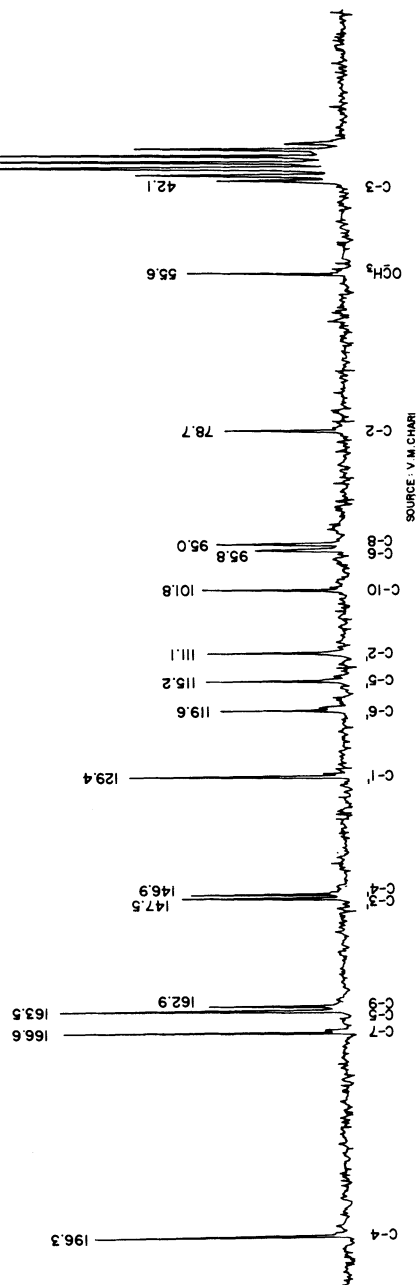


ERIODICTYOL  
DMSO-d<sub>6</sub> (95 °C)  
25.15 MHz

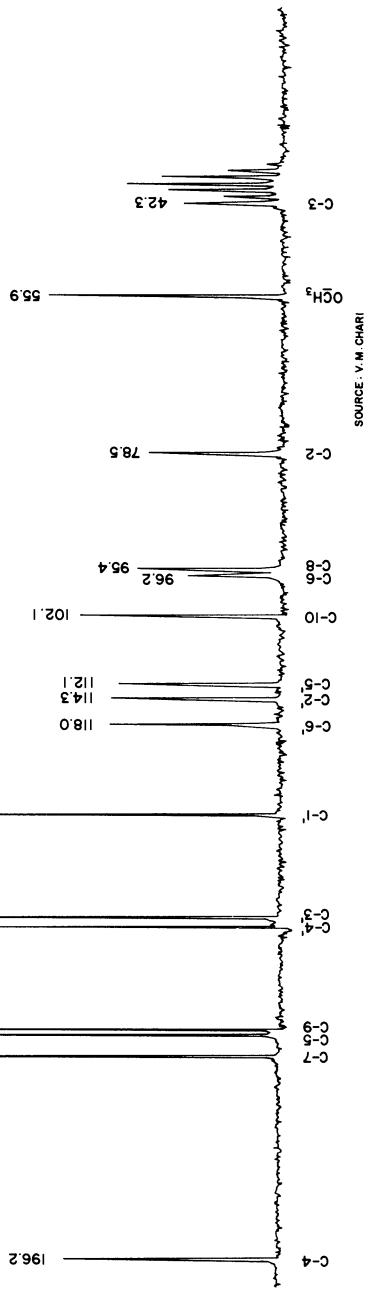
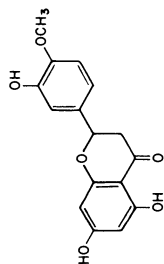




HOMOERIODICTYOL  
DMSO- $d_6$  (Ambient Temperature)  
22.63 MHz

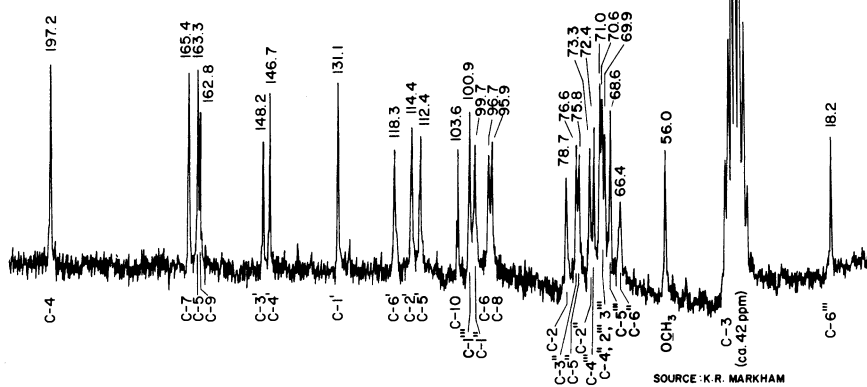
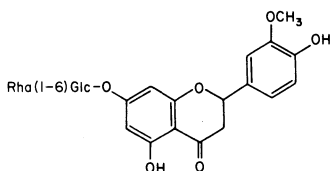


HESPERETIN  
DMSO- $d_6$  (Ambient Temperature)  
22.63 MHz



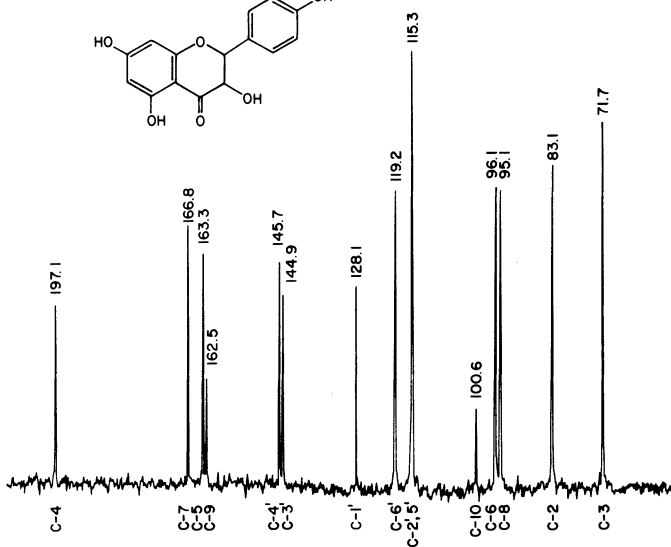
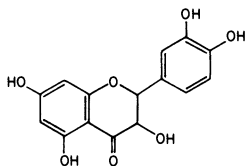
107

## HESPERETIN 7-O-RUTINOSIDE (HESPERIDIN)

DMSO- $d_6$  (20°C)  
25.15 MHz

108

## (+)-DIHYDROQUERCETIN (TAXIFOLIN)

DMSO- $d_6$  (95°C)  
25.15 MHz

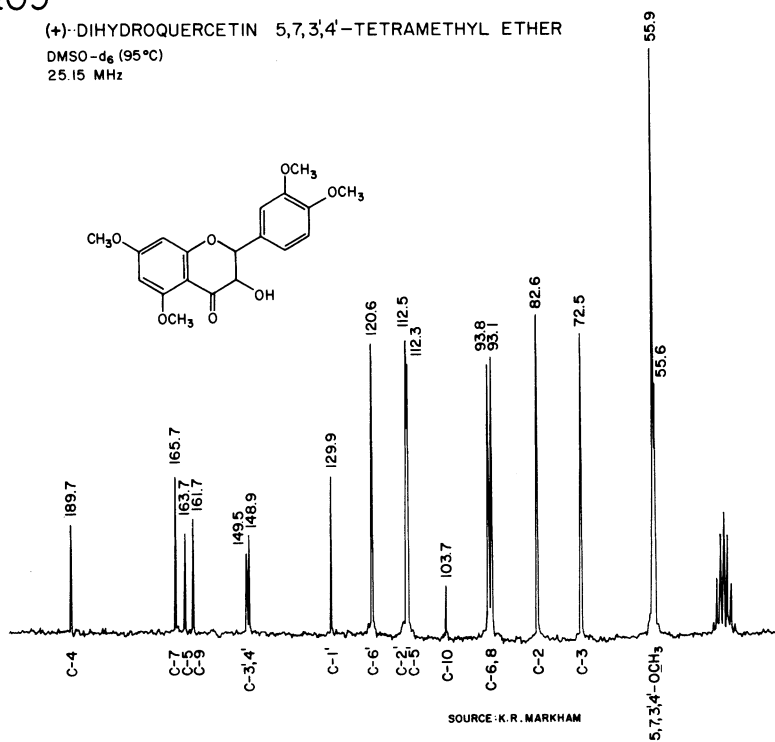


109

(+)·DIHYDROQUERCETIN 5,7,3',4'-TETRAMETHYL ETHER

DMSO-d<sub>6</sub> (95°C)

25.15 MHz

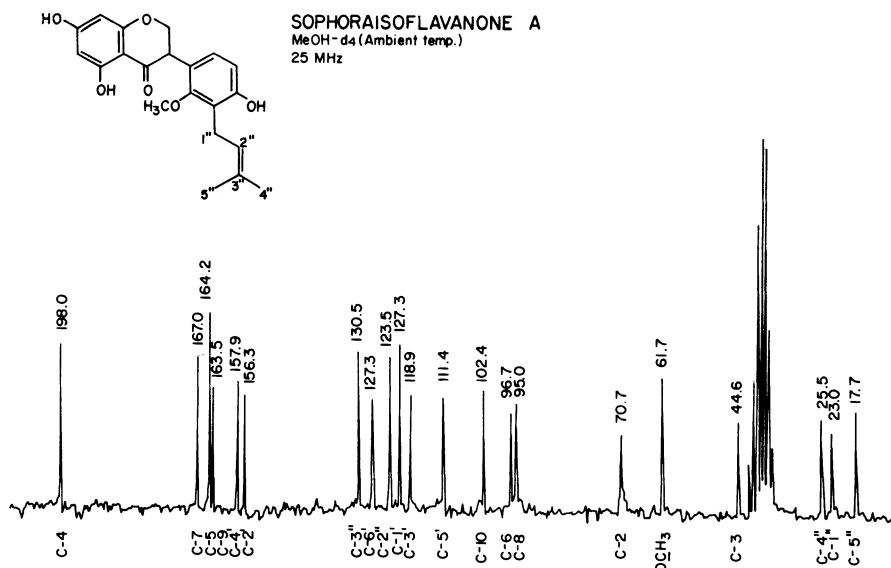


110

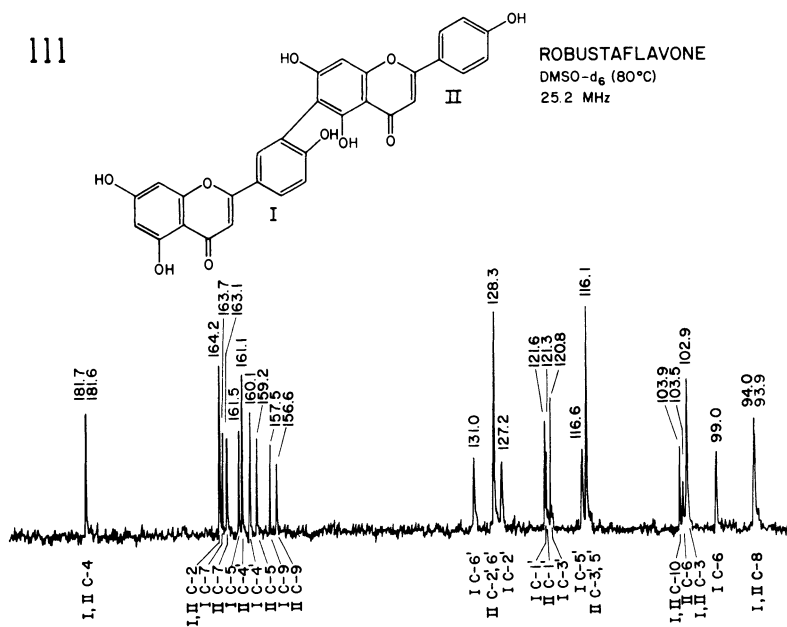
SOPHORAISOFLAVANONE A

MeOH-d<sub>4</sub> (Ambient temp.)

25 MHz

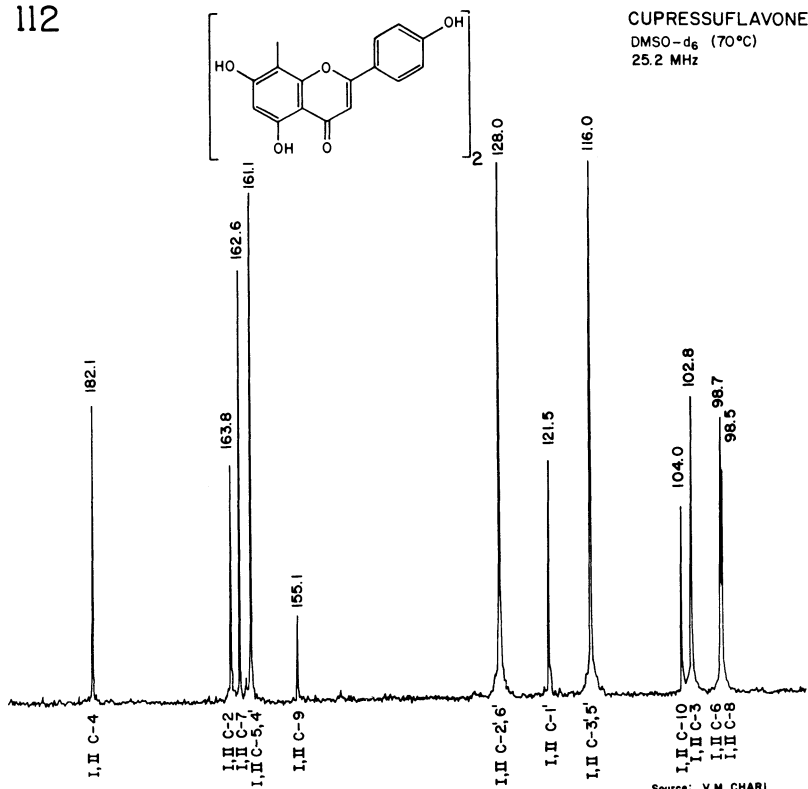


111



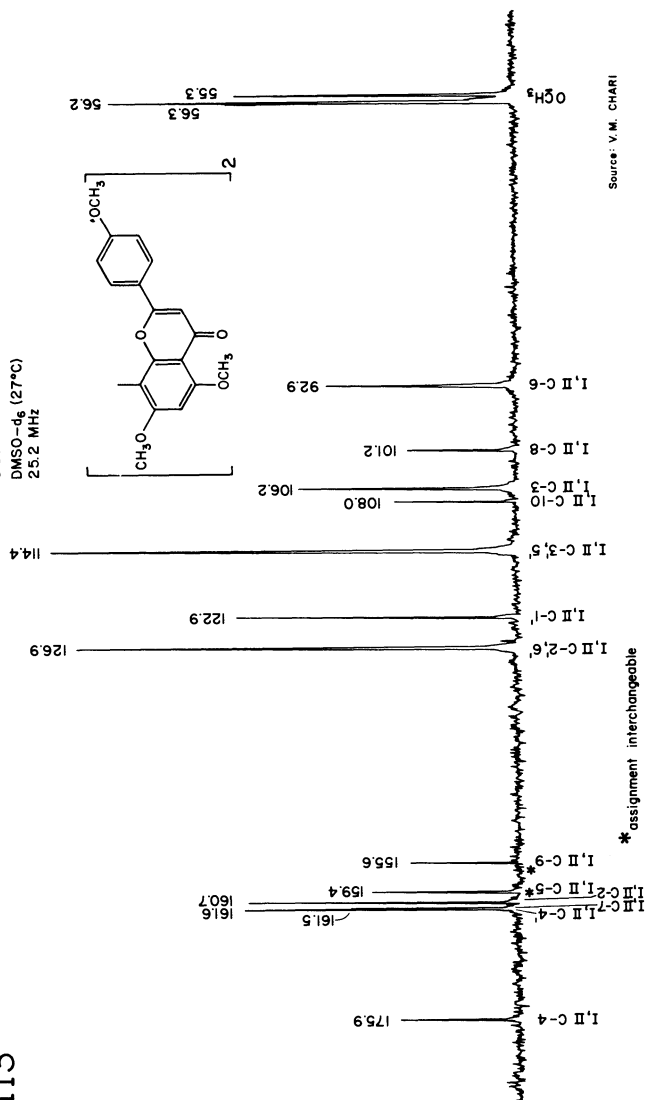
Source: V. M. CHARI

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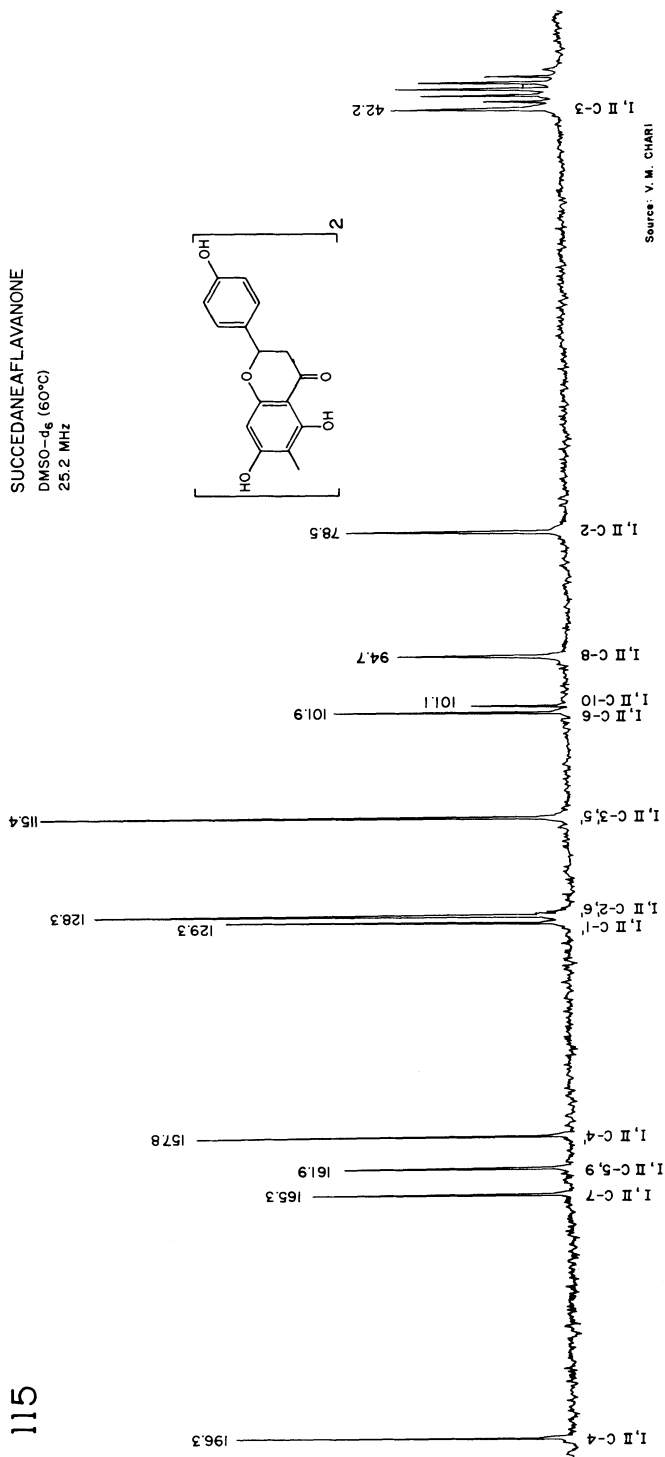
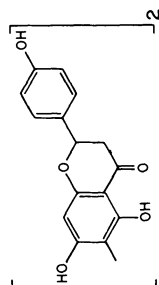
Source: V. M. CHARI

CUPRESSUFLAVONE HEXAMETHYL ETHER  
DMSO- $d_6$  (27°C)  
25.2 MHz



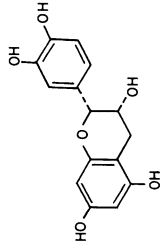


SUCCEDANEAFLAVANONE  
 DMSO- $d_6$  (60°C)  
 25.2 MHz

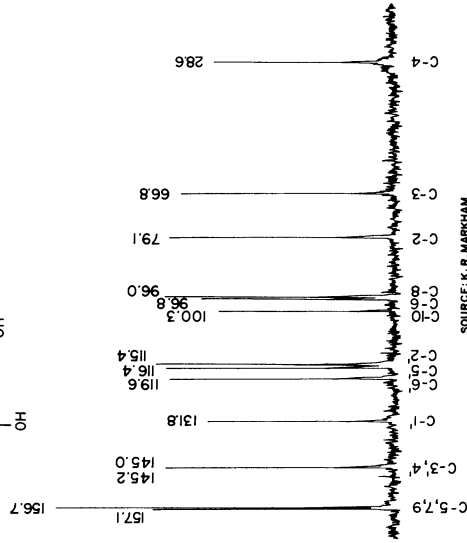


Source: V. M. CHARL

116

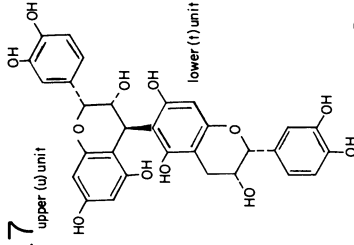


(-)-EPICATECHIN  
ACETONE- $d_6$ :H $_2$ O (1:1) (30°C)  
20 MHz

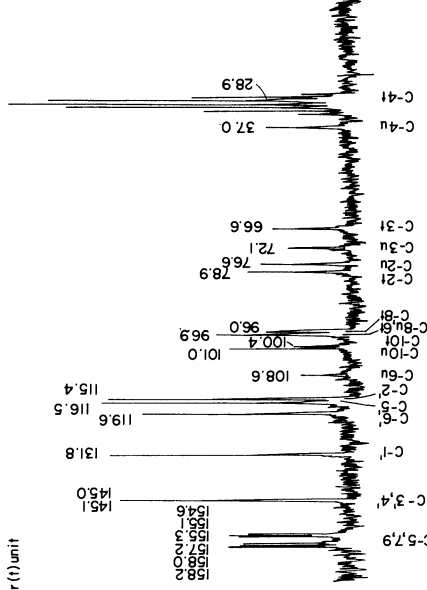


SOURCE: K. R. MARKHAM  
COURTESY OF L. J. PORTER

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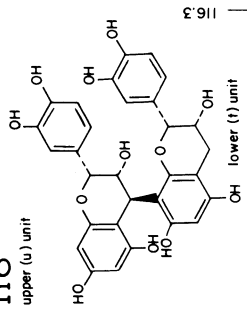
PROCYANADIN B5  
ACETONE- $d_6$ :H $_2$ O (1:1) (30°C)  
20 MHz



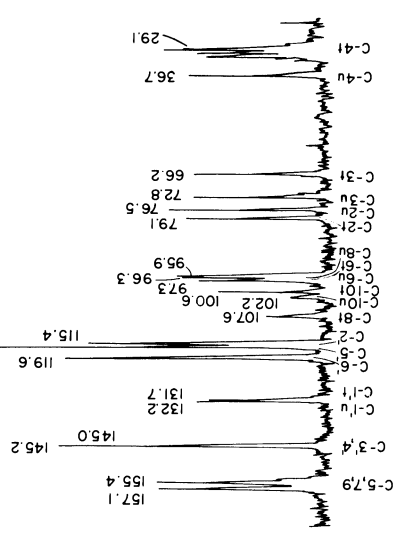
SOURCE: K. R. MARKHAM  
COURTESY OF L. J. PORTER

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upper (u) unit

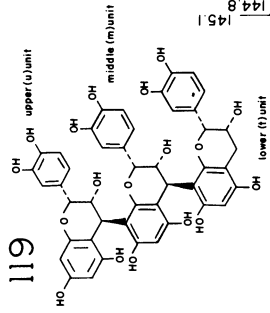


PROCYANIDIN B2  
ACETONE- $d_6$  :  $H_2O$  (1:1) (30°)  
20 MHz

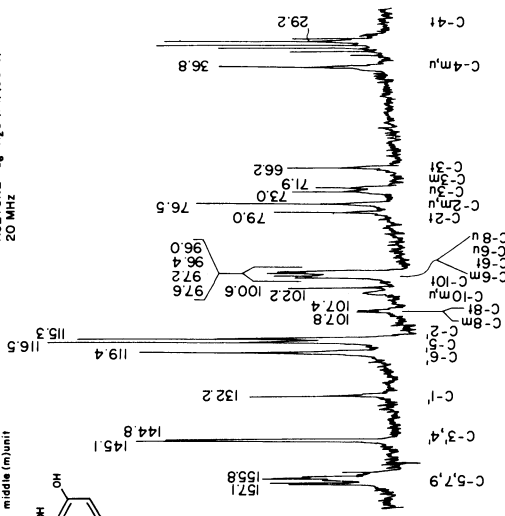


SOURCE: K. R. MARKHAM, COURTESY OF L. J. PORTER

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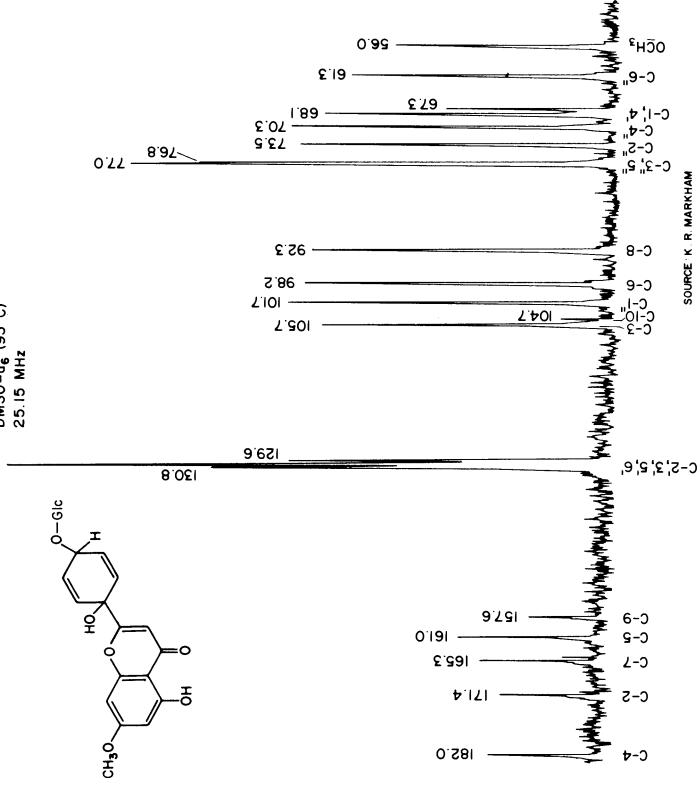


PROCYANIDIN TRIMER  
(All units C(4) - C(8) lined)  
ACETONE- $d_6$  :  $H_2O$  (1:1) (30°)  
20 MHz



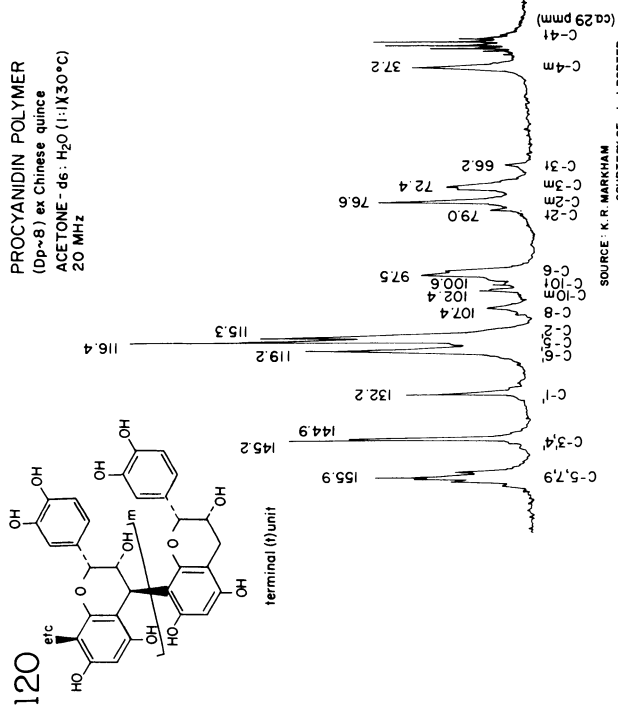
SOURCE: K. R. MARKHAM, COURTESY OF L. J. PORTER

PROTOGENKWANIN 4'-O-GLUCOSIDE  
DMSO-d<sub>6</sub> (95°C)  
25.15 MHz

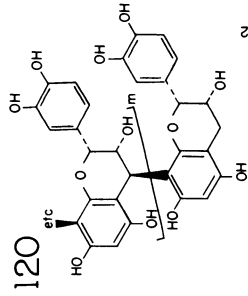


SOURCE: K. R. MARKHAM

PROCYANIDIN POLYMER  
(Dp~8) ex Chinese quince  
ACETONE-d<sub>6</sub> : H<sub>2</sub>O (1:1) (30°C)  
20 MHz

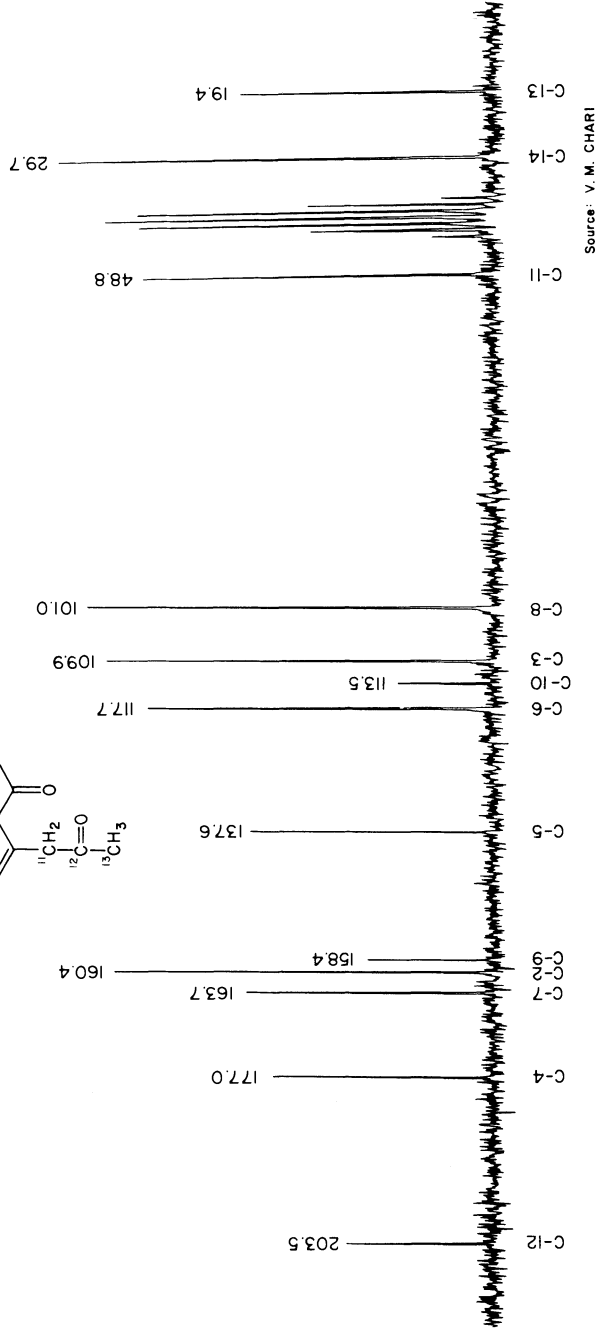
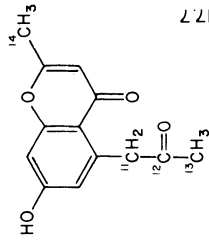


SOURCE: K. R. MARKHAM  
COURTESY OF L.J. PORTER

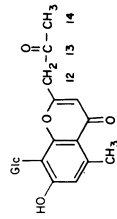




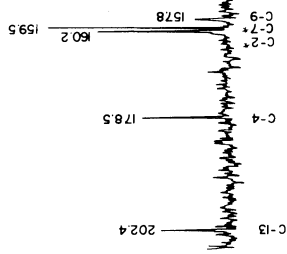
CASSIACHROMONE  
DMSO-d<sub>6</sub> (Ambient Temperature)  
20.0 MHz



123

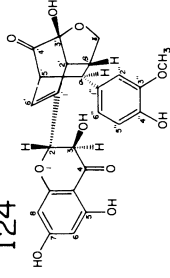


ALOESIN  
DMSO- $d_6$  (Ambient temp.)  
25.1 MHz

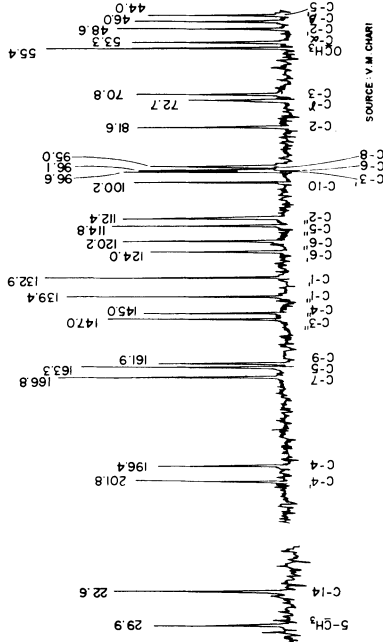


\* assignment interchangeable

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SILYDIANIN  
DMSO- $d_6$  (Ambient temp.)  
25 MHz

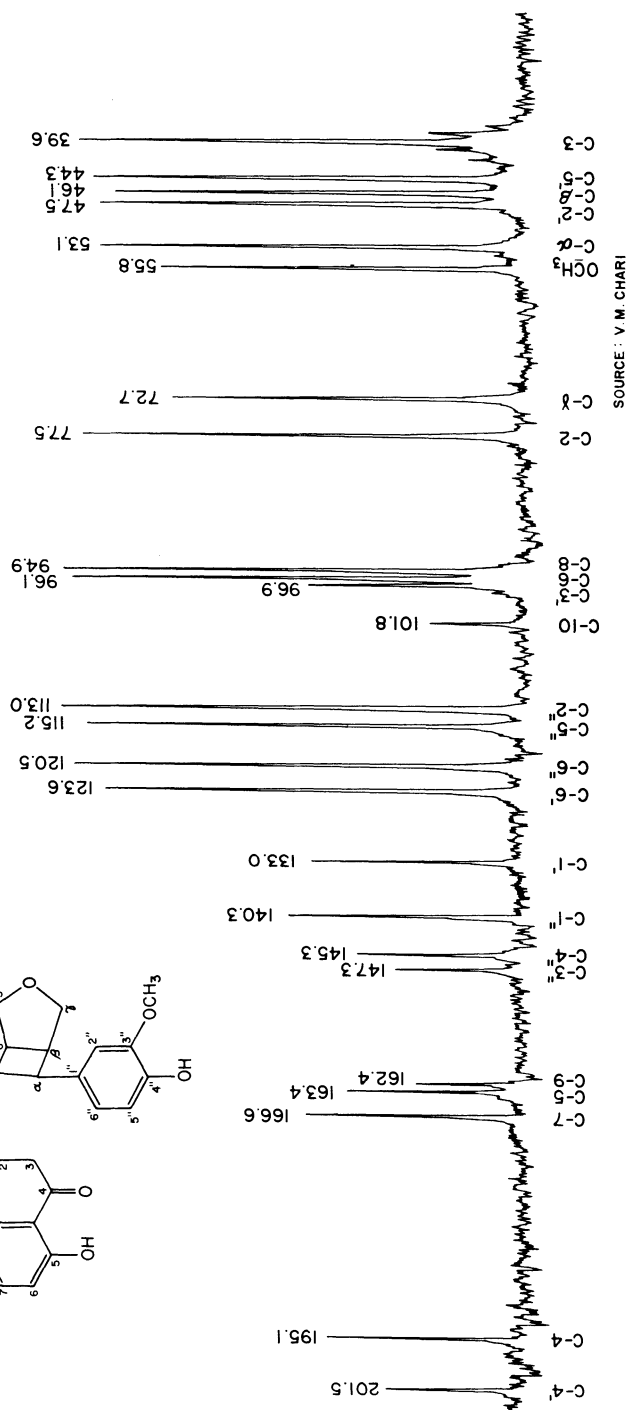
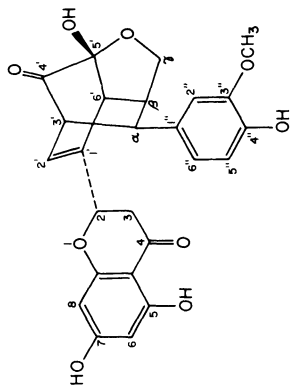


SOURCE V M CHART

## SILYMONIN (3-DEOXSILYDIANIN)

DMSO- $d_6$  (80°C)

20.15 MHz



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## CHAPTER THREE

# *Anthocyanins*

GEZA HRAZDINA

### 3.1 INTRODUCTION

Anthocyanin research in the past 5 years has remained dynamic. Progress in the field can best be summarized under twelve headings. These are (1) Further investigations into the occurrence of anthocyanins in plants; (2) Taxonomic role of anthocyanins; (3) Anthocyanins as genetic markers; (4) Anthocyanins as stress markers; (5) Food-related aspects of anthocyanins; (6) Progress in analytical techniques; (7) Progress in chemistry; (8) Subcellular status of anthocyanins; (9) Photocontrol of anthocyanin biosynthesis; (10) Enzymology of anthocyanin biosynthesis; (11) Effect of physiologically active chemicals on anthocyanin biosynthesis; (12) Physiological role of anthocyanins. This chapter has been divided along these lines in the present review of the past 5 years' progress.

All reports on anthocyanins which have appeared in Biological Abstracts and Chemical Abstracts between 1974 and 1980 are considered here.

### 3.2. OCCURRENCE OF ANTHOCYANINS

Investigations on the occurrence of anthocyanins in the past 5 years included hitherto unreported families, and detailed studies on previously reported genera. Major reviews appeared on the anthocyanin profiles of the Compositae (Harborne, 1977), Polemoniaceae (Harborne and Smith, 1978) and Orchidaceae (Arditti and Fisch, 1977); therefore these are not treated here. The results of surveying various monocotyledonous families for their anthocyanin patterns are summarized in Stirton and Harborne (1980). Other reports on occurrence of anthocyanins in plants are collected together in Table 3.1. Anthocyanins are not commonly found in marine organisms; the report of pelargonidin 3-glucoside and cyanidin 3-glucoside, their *p*-coumaryl derivatives and cyanidin 3,5-diglucoside (Garcia-Jalon *et al.*, 1974) in *Urginea maritima* is therefore of special note.

While the majority of the plants investigated contained anthocyanins previously identified in other species, a number of new anthocyanins were reported. These are cyanidin 3-xylosylglucosylgalactoside and its ferulyl derivative

identified in the black carrot (Harborne, 1976b), and a malonyl derivative of cyanidin 3-sophoroside-5-glucoside in *Brassica* (Hrazdina *et al.*, 1977) and of cyanidin 3-glucoside in *Spirodela* (Krause and Strack, 1979). The latter two pigments are especially interesting because they indicate that in addition to the hydroxycinnamic acid derivatives (the precursors of flavonoid and lignin biosynthesis) malonate, a precursor of both flavonoid and fatty acid biosynthesis, can also be utilized as an acylating agent. It is possible that the acylating reactions have controlling or regulating effects in the biosynthetic processes in the cell. Hitherto unreported anthocyanins are also pelargonidin 3-di (*p*-hydroxybenzoyl) rutinoside-7-glucoside in *Campanula* flowers (Asen *et al.*, 1979) and caffeoylferuloyl-*p*-coumaryldelphinidin 3-rutinoside-5,3',5'-triglucoside isolated from *Lobelia erinus* (Yoshitama, 1977). The latter compound is unique among the flavonoids because of its exceptional glycosylation pattern, particularly the presence of sugars attached to the B-ring hydroxyls.

### 3.3 TAXONOMIC ROLE OF ANTHOCYANINS

The evolution of anthocyanins in plants has been well studied in the past. From these studies it appears that pelargonidin- and delphinidin-type pigments occur more frequently in advanced plants, replacing cyanidin which is considered to be the simplest and most primitive pigment (Harborne, 1976a). Since biosynthetically pelargonidin is a simpler pigment than cyanidin (see Chapter 11), its production in replacement of cyanidin in the flowers of certain highly advanced plant families (e.g. Polemoniaceae; Harborne and Smith, 1978) must be by loss mutation. Correlations between the flower anthocyanins and pollination ecology is further discussed by these authors.

Against the background, anthocyanins have been used successfully by a number of authors to characterize families, genera, species or cultivars. Giannasi's work (1975) on the chemotaxonomy of 21 taxa of *Dahlia* indigenous to Mexico, Central America and Northern South America showed that this genus is made up of two major chemical lines, one with sections *Dahlia* and *Pseudodendron*, the other representing section *Entomophyllon*. These chemotaxonomic findings confirm earlier classifications based on morphological and taxonomic studies. A study by Monties *et al.* (1976) underlines the importance of quantitative studies in plant taxonomic investigations. Quantitative varietal differences were found in maize in the overall content and relative proportions of anthocyanins in the sheath of the first leaf of 10-day-old plants. Similar differences exist in the amounts of anthocyanins and other flavonoids in the petals of red or white carnations. Anthocyanins have also been used as chemotaxonomic markers in the analysis of synthetic hybrids and backcrosses of *Camelia japonica* and *C. saluenensis* (Parks and Kondo, 1974) and in investigations on species belonging to the Saxifragaceae, Rosaceae and Caprifoliaceae (Sobolevskaya and Demina, 1971, Publ. 1973).



**Table 3.1** Occurrence of anthocyanins in plant orders, families, genera and species

| <i>Orders, family, genus, species</i> | <i>Organ examined</i> | <i>Pigments present</i>                                      | <i>Reference</i>               |
|---------------------------------------|-----------------------|--------------------------------------------------------------|--------------------------------|
| <b>PTEROPHYTA</b>                     |                       |                                                              |                                |
| <b>SALVINIACEAE</b>                   |                       |                                                              |                                |
| <i>Azolla mexicana</i>                | Fronds                | Lu 5-glucoside                                               | Holst (1977)                   |
| <i>A. filiculoides</i>                |                       |                                                              | Pieterse <i>et al.</i> (1977)  |
| <i>A. caroliniana</i>                 |                       |                                                              |                                |
| <b>ANGIOSPERMAE</b>                   |                       |                                                              |                                |
| <b>MONOCOTYLEDONEAE</b>               |                       |                                                              |                                |
| <b>AMARYLLIDACEAE</b>                 |                       |                                                              |                                |
| <i>Allium cepa</i>                    | Bulb                  | Cy 3-glucoside Cy, 3-laminaribioside                         | Du <i>et al.</i> (1974a)       |
| <i>Clivia nobilis</i>                 | Fruit                 | Pg 3-rutinoside; Pg glucoside; Cy 3-rutinoside, Cy glucoside | Ishikura and Sugahara (1979)   |
| <b>ARACEAE</b>                        |                       |                                                              |                                |
| <i>Anthurium andreaeanum</i>          | Flower                | Pg, Cy 3-rhamnosylglucosides                                 | Iwata <i>et al.</i> (1979)     |
| <b>DIOSCOREACEAE</b>                  |                       |                                                              |                                |
| <i>Dioscorea tryphida</i>             | Tuber                 | Pn, Mv 3,5-diglucoside, Mv 3,5-diglucosideferulate           | Carreno-Diaz and Grau (1977)   |
| <b>GRAMINEAE</b>                      |                       |                                                              |                                |
| <i>Saccharum officinarum</i>          | Epidermis             | Pn 3-galactoside                                             | Misra and Dubey (1974)         |
| <i>Zea mays</i>                       | Seed                  | Cy 3-glucoside                                               | Nakatani <i>et al.</i> (1979)  |
| <b>HYDROCHARITACEAE</b>               |                       |                                                              |                                |
| <i>Egeria densa</i>                   | Leaves                | 5-O-Me-Cy 3-glucoside                                        | Momose <i>et al.</i> (1977)    |
| <b>IRIDACEAE</b>                      |                       |                                                              |                                |
| <i>Iris ensata</i>                    | Flowers               | Dp, Pt, Mv glucosides                                        | } Ishikura and Yamamoto (1978) |
| <i>I. spontanea</i>                   | Flower                | Dp, Pt, Mv glucosides                                        |                                |
| <b>LILIACEAE</b>                      |                       |                                                              |                                |
| <i>Disporum sessile</i>               | Fruit                 | Cy 3-glucoside, Cy glycoside                                 | } Ishikura and Sugahara (1979) |
| <i>Liriope platyphylla</i>            | Fruit                 | Dp 3-glucoside, Dp, Pt 3-rutinosides                         |                                |
| <i>Majanthemum bifolium</i>           | Fruit                 | Cy 3-glucoside, 3-rhamnoglucoside                            |                                |
| <b>MARANTACEAE</b>                    |                       |                                                              |                                |
| <i>Thaumatococcus danielli</i>        | Flower                | Pg glucoside, Cy, Dp 3-rutinoside                            | Adesina and Harborne (1978).   |
| <i>Ophiopogon japonicus</i>           | Fruit                 | Dp 3-rutinoside, Pt glycoside                                | Ishikura and Sugahara (1979)   |
| <i>Smilacina japonica</i>             | Fruit                 | Cy 3-rutinoside, Pn glycoside                                | Ishikura and Sugahara (1979)   |

Table 3.1 (Contd.)

| Orders, family, genus, species                  | Organ examined | Pigments present                                            | Reference                                             |
|-------------------------------------------------|----------------|-------------------------------------------------------------|-------------------------------------------------------|
| <i>Smilax china</i>                             | Fruit          | Cy 3-glucoside, 3-rhamnoglucoside                           | Ishikura (1975c)                                      |
| <i>S. riparie</i>                               | Fruit          | Cy 3-glucoside, 3-rutinoside                                | Ishikura and Sugahara (1979)                          |
| <i>Spirodela polyrrhiza</i>                     |                | Cy 3-malonylglucoside                                       | Krause and Strack (1979)                              |
| <i>Urginea maritima</i>                         | Whole plant    | Pg, Cy 3-glucosides, Pg, Cy 3- <i>p</i> -coumarylglucosides | Garcia-Jalon <i>et al.</i> (1974)                     |
| ORCHIDACEAE                                     |                |                                                             |                                                       |
| <i>Cymbidium</i> sp.                            | Petal          | Cy 3-glucoside, 3-diglucoside                               | Sugiyama <i>et al.</i> (1977)                         |
| <i>Orchis</i> sp.                               | Petal          | Cy 3-glucoside, 3-diglucoside, 3,5-diglucoside              | Uphoff (1979)                                         |
| ZINGIBERACEAE                                   |                |                                                             |                                                       |
| <i>Renanthera reginelliana</i>                  | Fruit          | Pt 3-glucoside, Dp, Pt, Mv 3,5-diglucosides                 | Gibaja-Oviedo (1978)                                  |
| DICOTYLEDONEAE                                  |                |                                                             |                                                       |
| ACANTHACEAE                                     |                |                                                             |                                                       |
| <i>Justicia procumbense</i>                     | Flower         | Pn 3-glucoside                                              | Tiwari <i>et al.</i> (1978)                           |
| <i>Peristrophe bicalyculata</i>                 | Flower         | Pt 3-rhamnoglucoside                                        | Tiwari <i>et al.</i> (1978)                           |
| <i>Ruellia</i> sp.                              | Flower         | Pg, Mv 3,5-diglucosides                                     | Bloom (1976)                                          |
| ANACARDIACEAE                                   |                |                                                             |                                                       |
| <i>Schinus molle</i>                            | Fruit          | Cy 3-galactoside, 3-rutinoside, Pn 3-glucoside              | Aziz-Ur-Rahman <i>et al.</i> (1974)                   |
| APOCYNACEAE                                     |                |                                                             |                                                       |
| <i>Catharanthus roseus</i>                      | Tissue culture | Hirs, Pt, Mv glucosides                                     | Krueger and Carew (1975);<br>Carew and Krueger (1976) |
| AQUIFOLIACEAE                                   |                |                                                             |                                                       |
| <i>Ilex buergeri</i>                            | Fruit          | Pg, Cy 3-xylosylglucoside                                   | Ishikura (1975a)                                      |
| <i>I. crenata</i> cv. Fukasawa                  | Fruit          | Cy, 3-glucoside, 3-sambubioside                             |                                                       |
| <i>I. geniculata</i>                            | Fruit          | Pg, Cy 3-xylosylglucosides                                  | Ishikura and Sugahara (1979)                          |
| <i>I. geniculata</i> cv. <i>glabra</i>          | Fruit          | Pg, Cy 3-xylosylglucosides                                  |                                                       |
| Ossuyama                                        |                |                                                             |                                                       |
| <i>I. kiusiana</i>                              | Fruit          | Cy 3-glucoside, Pg, Cy 3-xylosylglucosides                  | Ishikura (1975a)                                      |
| <i>I. macrostoma</i>                            | Fruit          | Cy 3-xylosylglucoside                                       |                                                       |
| <i>I. micrococca</i>                            | Fruit          | Cy 3-glucoside                                              | Ishikura (1975a)                                      |
| <i>I. nipponica</i>                             | Fruit          | Pg, Cy 3-xylosylglucosides                                  |                                                       |
| <i>I. sagerokii</i> cv. <i>brevipedunculata</i> | Fruit          | Cy 3-glucoside, 3-xylosylglucoside                          |                                                       |

|                                                                                                                                                                                                                                                                                                                                                       |        |                                                                           |                                            |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|---------------------------------------------------------------------------|--------------------------------------------|
| ARALIACEAE<br><i>Acanthopanax divaricatus</i><br><i>Aralia elata</i><br><i>A. canescens</i><br><i>Dendropanax trifidus</i><br>ASCLEPIADACEAE<br><i>Calatropis procera</i><br><i>Periploca gracea</i><br>BALSAMINACEAE<br><i>Impatiens</i> spp.<br>BEGONIACEAE<br><i>Begonia</i> sp.                                                                   | Fruit  | Dp 3-xylosylgalactoside                                                   | Ishikura (1975b)                           |
|                                                                                                                                                                                                                                                                                                                                                       | Fruit  | Cy 3-xylosylgalactoside                                                   |                                            |
|                                                                                                                                                                                                                                                                                                                                                       | Fruit  | Cy 3-xylosylgalactoside                                                   |                                            |
|                                                                                                                                                                                                                                                                                                                                                       | Flower | Cy 3-rhamnoglucoside                                                      | Tiwari <i>et al.</i> (1978)<br>Mein (1975) |
|                                                                                                                                                                                                                                                                                                                                                       | Stem   | Cy, Pn glucosides                                                         |                                            |
|                                                                                                                                                                                                                                                                                                                                                       | root   | Cy 3-glycosides                                                           | Thakur and Nozzolillo (1978)               |
|                                                                                                                                                                                                                                                                                                                                                       | Flower | Cy 3-(2 <sup>G</sup> -xylosylrutinoside)                                  | Langhammer and<br>Grandet (1974)           |
|                                                                                                                                                                                                                                                                                                                                                       | Leaves | Cy, Pn, Dp 3-glucosides                                                   | Semkina (1975)                             |
|                                                                                                                                                                                                                                                                                                                                                       | Fruit  | Cy, Dp, Pt, Mv 3-glucosides, Pn-glucoside, Cy, Dp<br>Pt, Mv 3-rutinosides | Ishikura and Sugahara (1979)               |
|                                                                                                                                                                                                                                                                                                                                                       | Flower | Cy, Dp-glycosides                                                         | Delorme <i>et al.</i> (1977)               |
| BORAGINACEAE<br><i>Anchusa italica</i><br><i>A. officinalis</i><br><i>Borago officinalis</i><br><i>Cerithe minor</i><br><i>Cynoglossum amabile</i><br><i>C. cheirifolium</i><br><i>Echium amoneum</i><br><i>E. vulgare</i><br><i>Heliotropium peruvianum</i><br><i>Lithospermum purpureo-</i><br><i>Lycopsis arensis</i><br><i>Myosotis alpestris</i> | Flower | Cy, Dp-glycosides                                                         |                                            |
|                                                                                                                                                                                                                                                                                                                                                       | Flower | Cy, Dp-glycosides                                                         | Ishikura (1974)                            |
|                                                                                                                                                                                                                                                                                                                                                       | Flower | Cy, Dp-glycosides                                                         |                                            |
|                                                                                                                                                                                                                                                                                                                                                       | Flower | Dp glycosides                                                             | Delorme <i>et al.</i> (1977)               |
|                                                                                                                                                                                                                                                                                                                                                       | Flower | Dp 3,5-diglucoside                                                        |                                            |
|                                                                                                                                                                                                                                                                                                                                                       | Flower | Dp glycosides                                                             | Delorme <i>et al.</i> (1977)               |
|                                                                                                                                                                                                                                                                                                                                                       | Flower | Cy, Dp-glycosides                                                         |                                            |
|                                                                                                                                                                                                                                                                                                                                                       | Flower | Dp-glycosides                                                             | Ishikura (1974)                            |
|                                                                                                                                                                                                                                                                                                                                                       | Flower | Cy, Dp-glycosides                                                         |                                            |
|                                                                                                                                                                                                                                                                                                                                                       | Flower | Cy, Dp-glycosides                                                         | Delorme <i>et al.</i> (1977)               |
| M. silvatica<br>M. versicolor<br>Pulmonaria officinalis                                                                                                                                                                                                                                                                                               | Flower | Cy, Dp, Mv glucosides                                                     |                                            |
|                                                                                                                                                                                                                                                                                                                                                       | Flower | Cy, Dp, Mv glucosides                                                     |                                            |
|                                                                                                                                                                                                                                                                                                                                                       | Flower | Cy, Dp, Mv glucosides                                                     | Ishikura (1974)                            |
|                                                                                                                                                                                                                                                                                                                                                       | Flower | Cy, Dp-glycosides                                                         |                                            |

Table 3.1 (Contd.)

| Orders, family, genus, species   | Organ examined | Pigments present                                                        | Reference                         |
|----------------------------------|----------------|-------------------------------------------------------------------------|-----------------------------------|
| <i>P. visianii</i>               | Flower         | Dp, Pt, Mv glycosides                                                   | Coassini-Lokar and Poldini (1978) |
| <i>Symphytum asperum</i>         | Flower         | Dp, Mv 3,5-diglucosides                                                 | Ishikura (1974)                   |
| <i>S. officinale</i>             | Flower         | Cy, Dp, Mv glycosides                                                   | } Delorme <i>et al.</i> (1977)    |
| <i>Tournefortia heliotropium</i> | Flower         | Cy, Mv glycosides                                                       |                                   |
| <i>Trigonotis peduncularis</i>   | Flower         | Dp 3,5-diglucoside                                                      | Ishikura (1974)                   |
| BUXACEAE                         |                |                                                                         |                                   |
| <i>Buxus microphylla</i>         | Fruit          | Cy 3-glucoside, 3-rhamnoglucoside                                       | Ishikura (1975c)                  |
| CAMPANULACEAE                    |                |                                                                         |                                   |
| <i>Campanula</i> sp. cv. Rose    | Flower         | Pg 3-di ( <i>p</i> -hydroxybenzoyl)-rutinoside-7-glucoside              | Asen <i>et al.</i> (1979)         |
| <i>Lobelia erinus</i>            | Flower         | Caffeyl-ferulyl- <i>p</i> -coumaryl-Dp-3-rutinoside-5,3',5'triglucoside | Yoshitama (1977)                  |
| CAPRIFOLIACEAE                   |                |                                                                         |                                   |
| <i>Lonicera hypoglauca</i>       | Fruit          | Cy 3-glucoside, 3,5-diglucoside                                         | Ishikura and Sugahara (1979)      |
| <i>L. japonica</i>               | Fruit          | Cy, Pn 3,5-diglucoside                                                  |                                   |
| <i>Sambucus ebulus</i>           | Fruit          | Cy 3-sambubioside, 3-sambubioside-5-glucoside                           | Chiarlo <i>et al.</i> (1978)      |
| <i>S. nigra</i>                  | Fruit          | Cy 3 (2-1-xylosylglucoside) Sambicyanin                                 | Reichel and Reichwald (1977)      |
| <i>Viburnum awabuki</i>          | Fruit          | Cy-3-xylosylglucoside                                                   | } Ishikura (1975c)                |
| <i>V. dilatatum</i>              | Fruit          | Cy 3-xylosylglucoside                                                   |                                   |
| <i>V. erosum</i>                 | Fruit          | Cy 3-xylosylglucoside                                                   |                                   |
| <i>V. furcatum</i>               | Fruit          | Cy 3-xylosylglucoside                                                   |                                   |
| <i>V. japonicum</i>              | Fruit          | Cy-3-xylosylglucoside                                                   |                                   |
| <i>V. lautata</i>                | Fruit          | Cy 3-glucoside                                                          | Ishikura (1975c)                  |
| <i>V. phlebotrichum</i>          | Fruit          | Cy 3-xylosylglucoside                                                   | Guichard <i>et al.</i> (1976)     |
| <i>V. sargentii</i>              | Fruit          | Cy 3-xylosylglucoside                                                   | } Ishikura (1975c)                |
| <i>V. tinus</i>                  | Fruit          | Cy 3-glucoside, 3-sambubioside                                          |                                   |
| <i>V. urceolatum</i>             | Fruit          | Cy 3-glucoside                                                          | Godeau <i>et al.</i> (1979)       |
| <i>V. wrightii</i>               | Fruit          | Cy 3-xylosylglucoside                                                   | } Ishikura (1975b)                |
|                                  |                |                                                                         |                                   |

CARYOPHYLLACEAE

*Silene dioica*

Flower Pg, Cy 3-glucosides, 3,5-diglucosides, 3-rutinosides  
3 rutinoside-5-glucosides, Pg 3(4-*O*-*p*-coumaryl-  
rhamnoglucoside), Cy 3-(6-*O*-caffeoylglucoside) Kamsteeg *et al.* (1978)

CELASTRACEAE

*Eumyrmus fortunei*

*E. oxyphyllus*

*E. sieboldianus*

Fruit Cy 3-glucoside  
Fruit Cy 3-glucoside  
Fruit Cy 3-glucoside } Ishikura (1975a)

COMBRETACEAE

*Lumnitzera littorea*

*Quisqualis indica*

*Terminalia catappa*

Flower Pg, Cy, Pn 3-glucosides, Pg, Pn 3,5-diglucosides  
Flower Cy 3-glucoside  
Fruit Cy 3-glucoside } Lowry (1976b)

COMPOSITAE

*Callistephus chinensis*

Flower Pg, Cy, Dp 3-glucosides, 3-acylglucosides, Pg,  
Cy, Dp 3,5-diglucosides, acylated 3,5-diglucosides Pg,  
Cy, Dp 3-glucosides, 3,5-diglucoside, Pg, Cy,  
3-galactosides, Pg, Cy-3-rhamnoglucosides,  
5-glucosides, 2*G*-glucosylrutinosides  
Flower Cy-3-glucoside, 3,5-diglucoside  
Flower Cy-3-glucoside, 3,5-diglucoside  
Flower Cy 3-glucoside; caffeoylglucoside; 3-diglucoside;  
3-caffeoyldiglucoside } Kamanzi and Raynaud (1977)  
Sugiyama and Takano  
(1974a,b)

*Cosmos caudatus*

*C. sulphureus*

*Cynara scolymus*

*Senecio cruentus*

CORNACEAE

*Cornus alba*

Flower Cy 3-glucoside, 3-rhamnoglucoside  
Flower Cy 3-glucoside, 3-rhamnoglucoside  
Flower Cy glycoside  
Whole plant Dp 3,7,3'-dicafeoyltriglucoside  
 } Samata *et al.* (1977)  
Foury and Aubert (1977)  
Yoshitama *et al.* (1975)

*C. alternifolia*

Du *et al.* (1975b)

*C. brachypoda*

*C. canadensis*

Ishikura and Sugahara (1979)

*C. controversa*

Du *et al.* (1974b)

Ishikura and Sugahara (1979)

Table 3.1 (Contd.)

| Orders, family, genus, species          | Organ examined       | Pigments present                                                                                                                                                                                                                                                  | Reference                     |
|-----------------------------------------|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| <i>C. florida</i>                       | Fruit                | Cy 3-glucoside                                                                                                                                                                                                                                                    | Ishikura (1975c)              |
| <i>C. kousa</i>                         | Fruit                | Cy 3-glucoside                                                                                                                                                                                                                                                    |                               |
| CRUCIFERAE                              |                      |                                                                                                                                                                                                                                                                   |                               |
| <i>Brassica juncea</i>                  | Leaves               | Pn, 3-glucoside, 3-galactoside                                                                                                                                                                                                                                    | Park (1979a,b)                |
| <i>Brassica oleracea</i> cv. Red Danish | Seedlings            | Cy 3-malonylsophorose-5-glucoside, 3- <i>p</i> -coumarylsophorose-5-glucoside, 3-di- <i>p</i> -coumarylsophorose-5-glucoside, 3-ferulylsophorose-5-glucoside, 3-di-ferulylsophorose-5-glucoside, 3-sinapylsophorose-5-glucoside, 3-disinapylsophorose-5-glucoside |                               |
| EPACRIDACEAE                            |                      |                                                                                                                                                                                                                                                                   | Hrazdina <i>et al.</i> (1977) |
| <i>Acroticha serrulata</i>              | Flower, bark         | Cy 3-arabinoside, 3-galactoside, Dp 3-arabinoside                                                                                                                                                                                                                 | Jarman and Crowden (1974)     |
| <i>Archeria comberi</i>                 | Petals, leaves, bark | Cy 3-arabinoside, 3-galactoside                                                                                                                                                                                                                                   |                               |
| <i>A. eriocarpa</i>                     |                      |                                                                                                                                                                                                                                                                   |                               |
| <i>A. hirtella</i>                      |                      |                                                                                                                                                                                                                                                                   |                               |
| <i>A. serpyllifolia</i>                 |                      |                                                                                                                                                                                                                                                                   |                               |
| <i>Astroloma humifusum</i>              | Leaves               | Cy 3-arabinoside, 3-galactoside                                                                                                                                                                                                                                   |                               |
| <i>Brachyoloma daphnoides</i>           | Leaves               | Cy 3-arabinoside, 3-galactoside                                                                                                                                                                                                                                   |                               |
| <i>Cyathodes</i> spp.                   | Leaves, flowers      | Cy 3-arabinoside, 3-galactoside, 3-rhamnogalactoside                                                                                                                                                                                                              |                               |
|                                         | Fruit, bark, stem    | Dp 3-galactoside                                                                                                                                                                                                                                                  |                               |
| <i>Dracophyllum</i> spp.                | Leaf, flower         | Cy 3-arabinoside, 3-galactoside                                                                                                                                                                                                                                   |                               |
| <i>Epacris</i> spp.                     | Leaves, flowers      | Cy 3-arabinoside, 3-galactoside                                                                                                                                                                                                                                   |                               |
| <i>Leucopogon</i> spp.                  | Flower               | Cy 3-arabinoside, 3-galactoside, 3-rhamnogalactoside                                                                                                                                                                                                              |                               |
| <i>Lissantha</i> spp.                   | Leaf, flower         | Cy 3-arabinoside, 3-galactoside                                                                                                                                                                                                                                   |                               |
|                                         | fruit                |                                                                                                                                                                                                                                                                   |                               |
| <i>Monotoca</i> spp.                    | Leaf, flower         | Cy 3-arabinoside, 3-galactoside, 3-rhamnogalactoside                                                                                                                                                                                                              |                               |
| <i>Pentachondra</i> spp.                | Leaf, flower         | Cy, Dp 3-arabinosides, 3-galactosides, Cy-3-rhamnogalactosides                                                                                                                                                                                                    |                               |
| <i>Richea</i> spp.                      | Leaves               | Cy 3-arabinoside, 3-galactoside                                                                                                                                                                                                                                   |                               |
| <i>Sprengelia incarnata</i>             | Leaf, flower         | Cy 3-arabinoside, 3-galactoside                                                                                                                                                                                                                                   |                               |
| <i>Styphelia</i> spp.                   |                      | Cy 3-arabinoside, 3-galactoside                                                                                                                                                                                                                                   |                               |

|                                  |               |                                                                                                                                                        |                                   |
|----------------------------------|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| <i>Trochocarpa</i> spp.          |               | Cy, Dp 3-arabinosides, 3-galactosides, 3-glucosides, 3-rhamnogalactosides                                                                              | Jarman and Crowden (1974)         |
| <i>Woolstia pangens</i>          | Flower        | Cy 3-arabinoside, 3-galactoside                                                                                                                        |                                   |
| ERICACEAE                        |               |                                                                                                                                                        |                                   |
| <i>Andromeda polyfolia</i>       | Leaves        | Cy, Mv glucosides                                                                                                                                      | Tamas <i>et al.</i> (1975)        |
| <i>Cyanococcus</i> sp.           | Fruit         | Cy, Pn, Dp, Pt, Mv galactosides and arabinosides<br>Cy, Pn, glycosides; Cy-3-xylosylglucoside;<br>Dp 3-glycoside; Dp 5-glycoside, Dp 3-rhamnoglycoside | Ballinger <i>et al.</i> (1979)    |
| <i>Erica</i> , 39 sp             | Flower        | Pg, Cy, Pn, Dp, Pt, Mv glucosides, arabinosides and biosides                                                                                           | Crowden and Jarman (1976)         |
| <i>Rhododendron simsii</i>       | Flower        | Cy, Pn, Mv glycosides                                                                                                                                  | DeLoose (1974)                    |
| <i>Vaccinium bracteatum</i>      | Fruit         | Cy, Dp, Pt glycosides                                                                                                                                  | Ishikura and Sugahara (1979)      |
| <i>V. corymbosum</i>             | Leaf          | Cy, Dp, Pt, Mv 3-glucosides                                                                                                                            | Pourrat <i>et al.</i> (1978)      |
| <i>V. floribundum</i>            | Fruit         | Cy-glycosides                                                                                                                                          | Martinod <i>et al.</i> (1975)     |
| <i>V. myrtilis</i>               | Fruit         | Cy 3-xylosylglucoside                                                                                                                                  | Ballinger <i>et al.</i> (1979)    |
| <i>V. smailii</i>                | Fruit         | Dp, Pt, Mv glycosides                                                                                                                                  | Ishikura and Sugahara (1979)      |
| <i>Vaccinium stamineum</i>       | Fruit         | Cy, Pn glycosides                                                                                                                                      | Ballinger <i>et al.</i> (1979)    |
| <i>V. vitis-idae</i>             |               | Dp 3-glucoside, Dp 5-glucoside, 3-rhamnoglucoside                                                                                                      |                                   |
| <i>Vaccinium</i> sp.             | Fruit         | Cy 3-glucoside, 3-rhamnoglucoside, 3-rhamnoglucosyl-glucoside                                                                                          | Fikiin and Chau (1977)            |
| FOUQUIERACEAE                    |               |                                                                                                                                                        |                                   |
| <i>Fouquieria</i> sp.            | Flowers, stem | Pg, Cy, Pn, Dp, Pt, 3-glucosides                                                                                                                       | Scogin, (1977)                    |
| FRANKENIACEAE                    |               |                                                                                                                                                        |                                   |
| <i>Frankenia grandiflora</i>     | Flower        | Dp 3-glucoside, Dp 3-galactoside, Pn 3-galactoside                                                                                                     | Scogin (1979)                     |
| FUMARIACEAE                      |               |                                                                                                                                                        |                                   |
| <i>Corydalis cava</i>            | Flower        | Cy, Pn-glucosides                                                                                                                                      | Coassini-Lokar and Poldini (1978) |
| <i>C. solida</i>                 | Flower        | Cy, Pn-glucosides                                                                                                                                      |                                   |
| GENTIANACEAE                     |               |                                                                                                                                                        |                                   |
| <i>Tripterospermum japonicum</i> | Fruit         | Cy 3-rutinoside, Cy glycoside                                                                                                                          | Ishikura and Sugahara (1979)      |
| GERANIACEAE                      |               |                                                                                                                                                        |                                   |
| <i>Erodium cicutarium</i>        | Flower        | Cy, Pn, Mv 3-glucosides, Cy 5-glucoside, Cy 3-rutinoside;<br>Mv 3,5-diglucoside                                                                        | Medrano <i>et al.</i> (1978)      |
| <i>E. malacoides</i>             | Flower        | Mv 3-glucoside, 3,5-diglucoside                                                                                                                        |                                   |

Table 3.1 (Contd.)

| Orders, family, genus, species   | Organ examined | Pigments present                                                                                    | Reference                                                                                             |
|----------------------------------|----------------|-----------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| <b>HYDROPHYLLACEAE</b>           |                |                                                                                                     |                                                                                                       |
| <i>Hydrophyllum macrophyllum</i> | Flower         | Cy 3,5-diglucoside                                                                                  | Beckmann (1979)                                                                                       |
| <i>H. occidentale</i>            | Flower         | Cy 3,5-diglucoside                                                                                  |                                                                                                       |
| <i>H. tenupes</i>                | Flower         | Cy 3,5-diglucoside                                                                                  |                                                                                                       |
| <i>H. virginianum</i>            | Flower         | Cy 3,5-diglucoside                                                                                  |                                                                                                       |
| <b>LARDIZABALACEAE</b>           |                |                                                                                                     |                                                                                                       |
| <i>Akebia quinata</i>            | Flower         | Cy 3-coumarylglucoside, 3- <i>p</i> -coumarylxylosylglucoside<br>3-xylosylglucoside                 | Ishikura (1975c)<br>Ishikura and Nagamizo (1976)                                                      |
| <i>A. trifoliata</i>             |                |                                                                                                     |                                                                                                       |
| <i>Stauntonia hexaphylla</i>     | Flower         | Cy 3- <i>p</i> -coumarylglucoside, 3- <i>p</i> -coumarylxylosyl-<br>glucoside Cy 3-xylosylglucoside | Ishikura (1975c)                                                                                      |
| <b>LAURACEAE</b>                 |                |                                                                                                     |                                                                                                       |
| <i>Cinnamomum camphora</i>       |                |                                                                                                     |                                                                                                       |
| <i>C. japonicum</i>              | Fruit          | Cy 3-rhamnoglucoside; Cy 3-glucoside                                                                | Ishikura (1975c)                                                                                      |
| <i>Lindera glauca</i>            | Fruit          |                                                                                                     | Ishikura and Sugahara (1979)<br>Ishikura (1975c)<br>Ishikura and Sugahara, (1979)<br>Ishikura (1975c) |
| <i>Litsea japonica</i>           | Fruit          | Cy 3-glucoside, 3-rutinoside                                                                        |                                                                                                       |
| <i>Machilus thumbergii</i>       | Fruit          | Cy 3-glucoside, 3-glucosylrutinoside                                                                |                                                                                                       |
| <i>Neolitsea sericeae</i>        | Fruit          | Cy, Pn 3-glucosides, 3-rutinosides                                                                  |                                                                                                       |
| <b>LECYTHIDACEAE</b>             |                |                                                                                                     |                                                                                                       |
| <i>Couropita quinensis</i>       |                |                                                                                                     |                                                                                                       |
| <b>LEGUMINOSAE</b>               |                |                                                                                                     |                                                                                                       |
| <i>Albizia julibrissin</i>       | Flower         | Cy, Dp 3-glucosides                                                                                 | Lowry, (1976a)                                                                                        |
| <i>Anthyllis alpestris</i>       | Flower         |                                                                                                     | Ishikura <i>et al.</i> (1978)                                                                         |
| <i>A. iberica</i>                | Flower         | Cy 3-glucoside<br>Cy, Pn glycosides                                                                 |                                                                                                       |
| <i>A. maura</i>                  | Flower         | Cy, Dp glycosides                                                                                   |                                                                                                       |
| <i>A. montana</i> ssp.           | Flower         | Cy, Pn, Dp-glycosides                                                                               |                                                                                                       |
| <i>A. praepropera</i>            | Flower         | Cy, Pn, Dp, Mv-glycosides                                                                           |                                                                                                       |
| <i>A. pyrenaica</i>              | Flower         | Cy, Dp glycosides                                                                                   |                                                                                                       |
|                                  | Leaf           | Cy, Pn, Dp glycosides                                                                               |                                                                                                       |
| <i>Anthyllis vulneraria</i>      | Flower         | Cy, 3-galactoside, Pn, Dp 3-galactosides<br>Cy, Pn, Dp glycosides                                   |                                                                                                       |
|                                  |                |                                                                                                     | Sterk <i>et al.</i> (1977)                                                                            |



|                                    |        |                                                                                  |                                 |
|------------------------------------|--------|----------------------------------------------------------------------------------|---------------------------------|
| <i>Astragalus sinicus</i>          | Flower | Cy 3-xylosylglucoside, Dp diglucoside                                            | Ishikura <i>et al.</i> (1978)   |
| <i>Bauhinia purpurea</i>           | Flower | Pg 3-glucoside, 3-triglucoside                                                   | Tiwari <i>et al.</i> (1978)     |
| <i>Canavalia gladiata</i>          | Flower | Pt 3,5-diglucoside, Mv 3-glucoside; Mv 3,5-diglucoside                           | Ishikura <i>et al.</i> (1978)   |
| <i>C. lineata</i>                  | Flower | Pt 3,5-diglucoside, Mv 3-glucoside; Mv 3,5-diglucoside                           | Singh <i>et al.</i> (1979)      |
| <i>Cassia javanica</i>             | Flower | Pn 3-rhamnoside                                                                  | Ishikura (1978)                 |
| <i>Cercis chinensis</i>            | Flower | Pt 3-glucoside; Mv 3-glucoside, Mv 3-diglucoside; Mv 3,5-diglucoside             | Srivastava and Pande (1977)     |
| <i>Clitoria ternata</i>            | Flower | Dp, Pt, Mv 3-glucoside                                                           | Martinod <i>et al.</i> (1978)   |
| <i>Desmodium adhesivum</i>         | Leaves | Cy 3-glucoside, 3,5-diglucoside                                                  | Ishikura and Sugahara (1979)    |
| <i>Dumosa truncata</i>             | Fruit  | Cy 3-glucoside, Mv 3,5-diglucoside, 3-rutinoside-5-glucoside, Mv glycoside       | Verna <i>et al.</i> (1977)      |
| <i>Erythrina suberosa</i>          | Flower | Pg, Cy Dp 3,5-diglucosides                                                       | Ishikura <i>et al.</i> (1978)   |
| <i>Indigofera pseudotinctorium</i> | Flower | Pt, 3-glucoside, Mv 3,5-diglucoside                                              | Sarkar and Banerjee (1977)      |
| <i>Lathyrus sativus</i>            | ?      | Pg, Cy 3,5-diglucosides                                                          | } Ishikura <i>et al.</i> (1978) |
| <i>Lespedeza bicolor</i>           | Flower | Mv 3-glucoside, 3,5-diglucoside                                                  |                                 |
| <i>L. homoloba</i>                 | Flower | Mv 3-glucoside, 3,5-diglucoside                                                  | Nozzolillo (1978)               |
| <i>L. penduliflora</i>             | Flower | Pt, Mv 3-glucosides, Mv 3,5-diglucoside                                          | Yokoyama (1976)                 |
| <i>Mucuna macrocarpa</i>           | Flower | Dp, Pt, Mv 3-glucoside                                                           | Ishikura and Sugahara (1979)    |
| <i>Pisum sativum</i>               | Stem   | Pg, Cy, Dp 3-glucosides, 3-oligosides                                            | Lakshmi and Chauhan (1976)      |
| <i>Pueraria lobata</i>             | Flower | Dp 3-glucoside, 3-diglucoside, Mv 3,5-diglucoside                                | } Ishikura <i>et al.</i> (1978) |
| <i>Rhynchosia acuminatifolia</i>   | Fruit  | Cy 3-glucoside                                                                   |                                 |
| <i>Saraca indica</i>               | Flower | Pg, Cy 3,5-diglucosides                                                          | } Ishikura <i>et al.</i> (1978) |
| <i>Trifolium pratense</i>          | Flower | Pn 3-glucoside, 3-diglucoside, 3-xylosylglucoside, Dp, Pt, Mv 3-rhamnoglucosides |                                 |
| <i>Vicia angustifolia</i>          | Flower | Pt, Mv 3-glucosides, Mv 3,5-diglucoside                                          | } Ishikura (1978)               |
| <i>V. cracca</i>                   | Flower | Pt, Mv 3,5-diglucosides, 3-rhamnosylglucosides                                   |                                 |
| <i>V. deflexa</i>                  | Flower | Dp, Pt 3-rhamnoside-5-glucoside, Mv 3,5-diglucoside 3-rhamnoside-5-glucoside     | } Ishikura (1978)               |
| <i>V. pseudo-orobus</i>            | Flower | Dp diglucoside, 3-rhamnoside-5-glucoside, Pt, Mv 3-rhamnoside-5-glucoside        |                                 |
| <i>V. unijuga</i>                  | Flower | Dp, Pt, Mv 3,5-diglucoside, 3-rhamnoside-5-glucoside Dp 3-triglucoside           | } Ishikura (1978)               |
| <i>Wisteria brachybotrys</i>       | Flower | Dp, 3,5-diglucoside; Pt 3-rhamnoside-5-glucosides                                |                                 |
| <i>W. floribunda</i>               | Flower | Dp, 3,5-diglucoside; Pt 3,5-diglucoside Mv 3,5-diglucoside                       |                                 |

Table 3.1 (Contd.)

| Orders, family, genus, species | Organ examined | Pigments present                                                                    | Reference                         |
|--------------------------------|----------------|-------------------------------------------------------------------------------------|-----------------------------------|
| <b>LINACEAE</b>                |                |                                                                                     |                                   |
| <i>Linum usitatissimum</i>     | Flower         | Pg, Cy, Dp 3-glucosylrutinosides, Cy, Dp 3-trigluco-<br>sides                       | Dubois and Harborne (1975)        |
| <b>LYTHRACEAE</b>              |                |                                                                                     |                                   |
| <i>Lagerstromia indica</i>     | Flower         | Dp, Pt, Mv 3-glucosides                                                             | Egolf and Santamour (1975)        |
| <i>L. speciosa</i>             | Flower         | Pn, Mv 3,5-diglucosides                                                             | Lowry, (1976a)                    |
| <i>Woodfordia fruticosa</i>    | Flower         | Pg, 3,5-diglucoside                                                                 | Nair <i>et al.</i> (1976)         |
| <b>MAGNOLIACEAE</b>            |                |                                                                                     |                                   |
| <i>Michelia compressa</i>      | Fruit          | Cy 3-glucoside, 3-rutinoside                                                        | Ishikura and Sugahara (1979)      |
| <b>MALVACEAE</b>               |                |                                                                                     |                                   |
| <i>Abelmoschus</i> spp.        | Flower         | Cy 3-glucoside, 3-rutinoside, 3-sambubioside, 3-sopho-<br>roside, Dp 3-sambubioside | Lowry (1976b)                     |
| <i>Hibiscus syriacus</i>       | Flower         | Dp, Pt, Mv 3-glucosides                                                             | Egolf and Santamour (1975)        |
| <i>Hibiscus</i> spp.           | Flower         | Cy, 3-glucoside, 3-rutinoside, 3-sophoroside,<br>3-sambubioside Dp 3-sambubioside   | Lowry (1976b)                     |
| <i>Malva silvestris</i>        | Flower         | Dp, Mv 3-glucosides, Mv 3,5-diglucoside                                             | Rakhimkhanov <i>et al.</i> (1975) |
| <i>Thespesia</i> spp.          | Flower         | Cy 3-glucoside, 3-rutinoside, 3-sophoroside, Cy, Dp,<br>3-sambubioside              | Scogin (1979)                     |
| <b>MARTYNIACEAE</b>            |                |                                                                                     |                                   |
| <i>Martynia annua</i>          | Flower         | Cy 3-galactoside, Pg 3,5-diglucoside                                                | Tiwari <i>et al.</i> (1978)       |
| <b>MELASTOMATACEAE</b>         |                |                                                                                     |                                   |
| <i>Clidemia hirta</i>          | Fruit          | Acylated Dp 3,5-diglucoside                                                         | Lowry (1976a)                     |
| <i>Dissochaeta bractata</i>    | Fruit          | Dp 3-( <i>p</i> -coumarylglucoside)-5-glucoside                                     |                                   |
| <i>D. celebica</i>             | Fruit          | Dp, Mv 3-acetylglucoside-5-glucoside                                                |                                   |
| <i>Dissotis rotundifolia</i>   | Flower         | Mv 3,5-diglucoside                                                                  |                                   |
| <i>Driessenia glandulifera</i> | Flower         | Cy diglucoside acylated                                                             |                                   |
| <i>Marumia nemorosa</i>        | Flower         | Mv 3-acetylglucoside-5-glucoside                                                    |                                   |
| <i>M. reticulata</i>           | Flower         | Mv 3-acetylglucoside-5-glucoside                                                    |                                   |
| <i>Medinilla hasseltii</i>     | Fruit          | Pg 3-acetylglucoside-5-glucoside                                                    |                                   |
| <i>M. heteroanthera</i>        | Flower         | Pg 3-acetylglucoside-5-glucoside                                                    |                                   |
| <i>M. schortechinii</i>        | Flower         | Pg 3- <i>p</i> -coumarylglucoside-5-glucoside                                       |                                   |

|                                  |                 |                                                                          |                                                    |                   |
|----------------------------------|-----------------|--------------------------------------------------------------------------|----------------------------------------------------|-------------------|
| <i>Melastoma malabathricum</i>   | Flower          | Mv 3,5-diglucoside                                                       | } Lowry (1976a)                                    | } Ishikura (1975) |
| <i>M. sanguineum</i>             | Flower          | Cy, Mv 3,5-diglucosides                                                  |                                                    |                   |
| <i>Memecylon amplexicaule</i>    | Fruit           | Cy 3,5-diglucoside                                                       |                                                    |                   |
| <i>M. caeruleum</i>              | Fruit           | Mv 3,5-diglucoside                                                       |                                                    |                   |
| <i>Oritrephes grandiflora</i>    | Flower          | Cy 3-glucoside                                                           |                                                    |                   |
| <i>Osbeckia perakensis</i>       | Flower          | Mv 3-(acetylglucoside)-5-glucoside                                       |                                                    |                   |
| <i>Oxyspora hispida</i>          | Inflorescence   | Mv 3-( <i>p</i> -coumarylrutinoside)-5-glucoside                         |                                                    |                   |
| <i>Phyllagathis elliptica</i>    | Flower          | Acylated Mv glucoside                                                    |                                                    |                   |
| <i>P. rotundifolia</i>           | Flower          | Mv 3-acetylglucoside-5-glucoside                                         |                                                    |                   |
| <i>P. scortechinii</i>           | Flower          | Acylated Pn glucoside                                                    |                                                    |                   |
| <i>P. tuberculata</i>            | Flower          | Mv 3- <i>p</i> -coumarylglucoside-5-glucoside                            |                                                    |                   |
| <i>Pternandra coerulescens</i>   | Fruit           | Acylated Mv glycoside                                                    |                                                    |                   |
| <i>Sarcopyramus nepalensis</i>   | Flower          | Mv 3,5-diglucoside, acylated glycoside                                   |                                                    |                   |
| <i>Sonerila argentata</i>        | Flower          | Acylated Mv diglycoside                                                  |                                                    |                   |
| <i>S. erecta</i>                 | Flower          | Acylated Pn, Mv glycosides                                               |                                                    |                   |
| <i>S. heterostemon</i>           | Flower          | Acylated Mv glycosides                                                   |                                                    |                   |
| <i>S. rudis</i>                  | Flower          | Acylated Mv glycosides                                                   |                                                    |                   |
| <i>S. prostrata</i>              | Flower          | Acylated Mv glycosides                                                   |                                                    |                   |
| <i>Tibouchina semidecandra</i>   | Flower          | Mv 3-( <i>p</i> -coumarylglucoside)-5-glucoside                          |                                                    |                   |
| <b>MENISPERMACEAE</b>            |                 |                                                                          |                                                    |                   |
| <i>Cocculus trilobus</i>         | Fruit           | Cy 3-glucoside                                                           | Ishikura (1975)                                    |                   |
| <b>MORACEAE</b>                  |                 |                                                                          |                                                    |                   |
| <i>Ficus carica</i>              | Fruit epidermis | Pg 3-rhamnoglucoside, Cy 3-glucoside, 3-rhamnoglucoside; 3,5-diglucoside | Puech <i>et al.</i> (1975)                         |                   |
| <i>F. erecta</i>                 | Fruit           | Cy 3-glucoside 3-rhamnoglucoside                                         | } Ishikura (1975c)<br>Ishikura and Sugahara (1979) |                   |
| <i>F. nipponica</i>              | Fruit           | Cy 3-glucoside, 3-rutinoside, 3,5-diglucoside                            |                                                    |                   |
| <i>F. pumila</i>                 | Fruit           | Cy 3-glucoside                                                           |                                                    |                   |
| <i>F. wrightiana</i>             | Fruit           | Cy 3-glucoside, 3-rhamnoglucoside                                        | Ishikura (1975)                                    |                   |
| <i>Morus alba</i>                | Fruit           | Cy 3-glucoside, 3-rhamnoglucoside                                        | Ishikura (1975)                                    |                   |
| <b>MYRICACEAE</b>                |                 |                                                                          |                                                    |                   |
| <i>Myrica rubra</i>              | Fruit           | Cy 3-glucoside                                                           | Ishikura and Sugahara (1979)                       |                   |
| <b>MYRTACEAE</b>                 |                 |                                                                          |                                                    |                   |
| <i>Barringtonia macrostachya</i> | Flower          | Cy, Dp 3-sambubioside                                                    | } Lowry (1976a)                                    |                   |
| <i>B. racemosa</i>               |                 |                                                                          |                                                    |                   |

Table 3.1 (Contd.)

| Orders, family, genus, species  | Organ examined | Pigments present                                             | Reference                 |
|---------------------------------|----------------|--------------------------------------------------------------|---------------------------|
| <i>Beaufortia squarrosa</i>     | Flower         | Pg, Pn 3,5-diglucosides                                      | Lowry (1976a)             |
| <i>Callistemon lanceolatus</i>  | Flower         | Cy 3-glucoside                                               |                           |
| <i>C. phoeniceus</i>            | Flower         | Cy 3-glucoside                                               |                           |
| <i>Calothamnus gilesii</i>      | Flower         | Cy 3,5-diglucoside                                           |                           |
| <i>C. oldfieldii</i>            |                | Pn, Cy 3-glucosides; Cy-3,5-diglucoside                      |                           |
| <i>C. quadrifidus</i>           |                | Cy 3-glucoside                                               |                           |
| <i>C. torulosa</i>              |                | Cy 3-glucoside                                               |                           |
| <i>Chamelaiucium uncinatum</i>  | Flower         | Dp 3-glucoside; Dp glucosides                                |                           |
| <i>Darwinia citriodora</i>      | Flower         | Pg, Cy 3,5-diglucosides                                      |                           |
| <i>D. oldfieldii</i>            | Flower         | Cy, 3,5-diglucosides                                         |                           |
| <i>Eucalyptus caesia</i>        | Flower         | Cy 3-glucoside                                               | Sharma and Crowden (1974) |
| <i>E. macrocarpa</i>            | Flower         | Cy glucoside                                                 |                           |
| <i>Eucalyptus</i> sp.           | Leaves, bark   | Cy 3-glucoside, 3,5-diglucoside, Dp glycosides, galactosides |                           |
| <i>Eugenia aquea</i>            | Fruit          | Cy 3-glucoside                                               |                           |
| <i>E. jambolana</i>             | Fruit          | Dp, Pt 3-gentiobioside, Mv 3-laminaribioside                 | Lowry, (1976a)            |
| <i>E. malaccensis</i>           | Flower         | Mv 3,5-diglucoside                                           | Jain and Seshadri (1975)  |
| <i>Feijoa sellowiana</i>        | Flower         | Cy 3-glucoside                                               |                           |
| <i>Hypocalymma robustum</i>     | Flower         | Mv, 3,5-diglucoside                                          | Lowry (1976a)             |
| <i>Kunzea baxterii</i>          | Flower         | Cy, Dp 3-glucosides                                          |                           |
| <i>K. juncunda</i>              | Flower         | Mv 3,5-diglucoside                                           |                           |
| <i>Leptospermum erubescence</i> | Flower         | Mv 3,5-diglucoside                                           |                           |
| <i>L. flavescens</i>            | Flower         | Cy 3-glucoside                                               |                           |
| <i>L. scoparium</i>             | Flower         | Cy, Pn 3-glucosides                                          |                           |
| <i>L. seriaceum</i>             | Flower         | Mv 3,5-diglucoside                                           |                           |
| <i>Lophomyrtus bullata</i>      | Fruit          | Cy 3-glucoside                                               |                           |
| <i>L. obcordata</i>             | Fruit          | Cy 3-glucoside                                               |                           |
| <i>Melaleuca nesophila</i>      | Flower         | Mv 3,5-diglucoside                                           |                           |
| <i>M. steedmani</i>             | Flower         | Cy 3,5-diglucoside                                           |                           |
| <i>Meterosideros excelsa</i>    | Flower         | Cy, Pn, Mv 3-glucosides                                      |                           |

|                                 |         |                                                                              |                                                                      |
|---------------------------------|---------|------------------------------------------------------------------------------|----------------------------------------------------------------------|
| <i>M. fulgens</i>               | Flower  | Cy, Dp 3-glucosides                                                          | Lowry (1976a)                                                        |
| <i>M. kermadecensis</i>         | Flower  | Pn(?) Cy, Pn 3-glucosides, Pn, Mv 3,5-diglucosides                           |                                                                      |
| <i>Neomyrtus pedunculata</i>    | Fruit   | Cy 3-glucoside                                                               |                                                                      |
| <i>Pileanthus pendunculatus</i> | Flower  | Dp 3-glucoside, Dp-rhamnoside                                                |                                                                      |
| <i>Psidium guajavica</i>        | Fruit   | Cy 3-glucoside                                                               |                                                                      |
| <i>Rhodomyrtus tomentosa</i>    | Flower  | Mv 3-glucoside                                                               |                                                                      |
| <i>Scholtzia capitata</i>       | Flower  | Cy 3-glucoside, 3,5-diglucoside                                              |                                                                      |
| <i>S. parvifolia</i>            | Flower  | Cy 3-glucoside, 3,5-diglucoside                                              |                                                                      |
| <i>Thryptomene denticulata</i>  | Flower  | Cy 3-glucoside, Dp 3-rhamnoside                                              |                                                                      |
| <i>T. maisonervii</i>           | Flower  | Cy, Dp, 3,5-diglucoside                                                      |                                                                      |
| <i>Verticordia monadelphica</i> | Flower  | Cy, 3,5-diglucoside, Cy glycoside                                            |                                                                      |
| OLEACEAE                        |         |                                                                              | Medrano <i>et al.</i> (1977)                                         |
| <i>Ligustrum amurense</i>       | Fruit   | Cy 3-glucoside, 3-rutinoside, Mv 3-rutinoside-5-glucoside                    |                                                                      |
| <i>L. lucidum</i>               | Fruit   | Cy 3-glucoside, 3-rutinoside, Mv 3-rutinoside-5-glucoside                    |                                                                      |
| <i>L. sinense</i>               | Fruit   | Cy 3-glucoside, 3-rutinoside, Mv 3-rutinoside-5-glucoside                    |                                                                      |
| <i>L. vulgare</i>               | Fruit   | Cy 3-glucoside, 3-rutinoside, Mv 3-rutinoside-5-glucoside                    |                                                                      |
| <i>L. ibota</i>                 | Fruit   | Cy glycosides                                                                |                                                                      |
| <i>L. ovalifolium</i>           | Fruit   | Cy 3-caFFEylglucoside, 3-caFFEylrutinoside                                   |                                                                      |
| <i>L. obtusifolium</i>          | Fruit   | Cy 3-caFFEylglucoside, 3-caFFEylrutinoside                                   |                                                                      |
| <i>Olea europaea</i>            | Fruit   | Cy 3-glucoside                                                               |                                                                      |
| <i>Osmanthus fragrans</i>       | Fruit   | Cy 3-rhamnoglucoside                                                         |                                                                      |
| <i>O. ilicifolius</i>           | Fruit   | Cy 3-glucosylrhamnoside                                                      |                                                                      |
| ONAGRACEAE                      |         |                                                                              | Ishikura and Sugahara (1979)<br>Vazquez-Roncero <i>et al.</i> (1974) |
| <i>Fuchsia</i> spp.             | Flowers | Pg, Cy, Pn, Dp, Pt, Mv 3-glucosides, 3,5-diglucosides                        |                                                                      |
| PAPAVERACEAE                    |         |                                                                              | Ishikura (1975c)                                                     |
| <i>Papaver bracteatum</i>       | Flower  | Pg, Cy 3-glucosides, Cy 3-sophoroside                                        |                                                                      |
| PASSIFLORACEAE                  |         |                                                                              | Crowden <i>et al.</i> (1977)                                         |
| <i>Passiflora edulis</i>        | Fruit   | Cy 3-glucoside                                                               |                                                                      |
| <i>P. quadrangularis</i>        | Flower  | Dp, Pt, Mv 3-glucosides, 3,5-diglucosides                                    | Yaklich and Gentner (1974)                                           |
| POLYGONACEAE                    |         |                                                                              |                                                                      |
| <i>Polygonum japonica</i>       | Leaf    | Cy, Dp, Mv glycosides, Cy 3,5-caFFEylglucosylarabinoside, Cy 3,5-diglucoside | Ishikura and Sugahara (1979)<br>Billot (1974)                        |
| <i>P. pentjuncti</i>            | Leaf    | Cy, Dp, Mv glycosides, Cy 3,5-caFFEylglucosylarabinoside, Cy 3,5-diglucoside |                                                                      |
|                                 |         |                                                                              | Kuznetsova (1979)                                                    |

Table 3.1 (Contd.)

| Orders, family, genus, species  | Organ examined  | Pigments present                                                                       | Reference                                                                       |
|---------------------------------|-----------------|----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| <i>P. perfoliatum</i>           | Fruit           | Mv 3,5-diglucoside                                                                     | Ishikura and Sugahara (1979)                                                    |
| <i>P. sadralinense</i>          | Leaf            | Cy, Dp, Mv glycosides, Cy 3,5-caFFEylglucosylarabinoside<br>Cy 3,5-diglucoside         | Kuznetsova (1979)                                                               |
| <i>P. tomentosum</i>            | Flower          | Pg 3-glucoside                                                                         | Tiwari <i>et al.</i> (1978)                                                     |
| <i>P. weyridzii</i>             | Leaf            | Cy, Dp, Mv glycosides, Cy 3,5-caFFEylglucosylarabinoside<br>Cy 3,5-diglucoside         | Kuznetsova (1979)                                                               |
| <b>PUNICACEAE</b>               |                 |                                                                                        |                                                                                 |
| <i>Punica granatum</i>          | Fruit           | Cy, Dp, Pt 3-glucoside, 3,5-diglucosides, Cy, Dp<br>Mv glucosides, Pg 3,5-diglucosides | Du <i>et al.</i> (1975b)<br>Abdurazakova and Gabrazova<br>(1972); Lowry (1976a) |
| <b>RANUNCULACEAE</b>            |                 |                                                                                        |                                                                                 |
| <i>Clematis terniflora</i>      | Fruit           | Cy 3-glucoside                                                                         | Ishikura (1975c)                                                                |
| <i>Paeonia japonica</i>         | Fruit           | Pn 3-glucoside 3,5-diglucoside                                                         | Ishikura and Sugahara (1979)                                                    |
| <b>RHIZOPHORACEAE</b>           |                 |                                                                                        |                                                                                 |
| <i>Gynotroches axillaris</i>    | Fruit           | Cy 3-glucoside                                                                         | Lowry (1976a)                                                                   |
| <b>ROSACEAE</b>                 |                 |                                                                                        |                                                                                 |
| <i>Cotoneaster melanocarpus</i> | Fruit           | Cy 3-glucoside                                                                         | Demina (1974)                                                                   |
| <i>C. uniflora</i>              | Fruit           | Cy 3-glucoside                                                                         |                                                                                 |
| <i>Duchesnea chrysantha</i>     | Fruit           | Cy, Pn 3-glucosides, Pn 3-rutinoside                                                   | Ishikura and Sugahara (1979)                                                    |
| <i>Fragaria ananassa</i>        | Fruit           | Pg, Cy 3-glucosides                                                                    | Ishikura (1975c)                                                                |
| <i>F. vesca</i>                 | Fruit           | Pg, Cy 3-glucosides                                                                    | Fikini and Chau (1977)                                                          |
| <i>Laurocerasus officinalis</i> | Fruit           | Cy, Pn 3-arabinosides                                                                  | Tsiklauri (1975)                                                                |
| <i>Malus</i> sp.                | Fruit epidermis | Cy 3-arabinoside, 3-galactoside, 3-arabinoside                                         | Posokhlyarova (1975)                                                            |
| <i>Photini glabra</i>           | Fruit           | Cy 3-glucoside, 3-rhamnoglucoside                                                      | Ishikura (1975c)                                                                |
| <i>Pourthaea villosa</i>        | Fruit           | Cy 3-glucoside                                                                         | Posello and Bonzini (1977b)                                                     |
| <i>Prunus cerasus</i>           | Fruit           | Cy 3-glucoside, Cy, Pn 3-rhamnoglucosides                                              | Rahman <i>et al.</i> (1975)<br>Takeda and Sano (1978)                           |
| <i>P. jamasakura</i>            | Fruit           | Cy, 3-glucoside, 3-rhamnoglucoside                                                     | Ishikura (1975c)                                                                |
| <i>P. mume</i>                  | Fruit           | Cy 3-glucoside, 3-rhamnoglucoside                                                      |                                                                                 |
| <i>P. persica</i>               | Fruit           | Cy 3-glucoside, 3-rhamnoglucoside                                                      |                                                                                 |
| <i>P. salicina</i>              | Fruit           | Cy 3-glucoside, 3-rhamnoglucoside                                                      |                                                                                 |

|                              |        |                                                                    |                                                                                                                                                                                                                                                                                                                         |
|------------------------------|--------|--------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>P. sargentii</i>          | Fruit  | Pg, Cy 3-glucosides, 3-rutinosides, Cy 3-diglucoside               | <div> <div>Du <i>et al.</i> (1975)</div> <div>Ishikura (1975c)</div> <div>Tiwari <i>et al.</i> (1978)</div> <div>Chumbalov <i>et al.</i> (1976)</div> <div>Plekhanova <i>et al.</i> (1978)</div> <div>Torre and Barritt (1977)</div> <div>Ishikura and Sugahara (1979)</div> <div>Barritt and Torre (1975)</div> </div> |
| <i>P. tomentosa</i>          | Fruit  | Pg, Cy 3-rhamnoglucosides                                          |                                                                                                                                                                                                                                                                                                                         |
| <i>P. yedoensis</i>          | Fruit  | Cy 3-glucoside, 3-rhamnoglucoside                                  |                                                                                                                                                                                                                                                                                                                         |
| <i>Raphiolepis umbellata</i> | Fruit  | Cy 3-glucoside                                                     |                                                                                                                                                                                                                                                                                                                         |
| <i>Rasselia multiflora</i>   | Flower | Pn 3-glucoside                                                     |                                                                                                                                                                                                                                                                                                                         |
| <i>Rosa plathyacantha</i>    | Flower | Cy 3-glucoside, 3,5-diglucoside                                    |                                                                                                                                                                                                                                                                                                                         |
| <i>R. spinosissima</i>       | Fruit  | Cy, Dp glucosides                                                  |                                                                                                                                                                                                                                                                                                                         |
| <i>Rubus crataegifolius</i>  | Fruit  | Pg glucosides                                                      |                                                                                                                                                                                                                                                                                                                         |
| <i>R. hirsutus</i>           | Fruit  | Pelargonidin-3-glucoside                                           |                                                                                                                                                                                                                                                                                                                         |
| <i>R. idaeus</i>             | Fruit  | Cy 3-glucosides, Cy 3-sophorosides, Cy 3-rutinoside                |                                                                                                                                                                                                                                                                                                                         |
|                              |        | Cy 3-glucosylrutinoside, Cy 3-sambubioside,                        |                                                                                                                                                                                                                                                                                                                         |
|                              |        | Cy 3-xylosylrutinoside                                             |                                                                                                                                                                                                                                                                                                                         |
| <i>R. illecebrosus</i>       | Fruit  | Pg glucosides                                                      | <div> <div>Torre and Barritt (1977)</div> </div>                                                                                                                                                                                                                                                                        |
| <i>R. morifolius</i>         | Fruit  | Pg glucosides                                                      |                                                                                                                                                                                                                                                                                                                         |
| <i>R. parviflorus</i>        | Fruit  | Pg glucosides                                                      | <div> <div>Ishikura (1975c)</div> </div>                                                                                                                                                                                                                                                                                |
| <i>Sorbus commixta</i>       | Flower | Cy 3-glucoside                                                     |                                                                                                                                                                                                                                                                                                                         |
| <i>Spiraea cantoniensis</i>  | Fruit  | Cy 3-glucoside                                                     |                                                                                                                                                                                                                                                                                                                         |
| <b>RUBIACEAE</b>             |        |                                                                    |                                                                                                                                                                                                                                                                                                                         |
| <i>Cinchona ledgerana</i>    | Leaves | Cy 3-arabinoside, galactoside, 7-arabinoside                       | Paris and Jacquemin (1975)                                                                                                                                                                                                                                                                                              |
| <i>C. succirubra</i>         | Leaves |                                                                    | Posokhyarova (1975)                                                                                                                                                                                                                                                                                                     |
| <i>Damnacanthus indicus</i>  | Fruit  | Pg 3-glycoside                                                     | <div> <div>Ishikura and Sugahara (1979)</div> </div>                                                                                                                                                                                                                                                                    |
| <i>D. macrophyllus</i>       | Fruit  | Pg 3-glycoside, 3-rutinoside                                       |                                                                                                                                                                                                                                                                                                                         |
| <i>Lasianthus japonicus</i>  | Flower | Pg 3-rutinoside, Pg-glycosides                                     |                                                                                                                                                                                                                                                                                                                         |
| <i>Mitchella undulata</i>    | Fruit  | Pg 3-rutinoside, Pg-glycosides                                     |                                                                                                                                                                                                                                                                                                                         |
| <i>Rubia akane</i>           | Fruit  | Cy 3-rutinoside                                                    |                                                                                                                                                                                                                                                                                                                         |
| <b>RUTACEAE</b>              |        |                                                                    |                                                                                                                                                                                                                                                                                                                         |
| <i>Skimmia japonica</i>      | Fruit  | Pg 3-glucoside, 3-rhamnoglucoside                                  | <div> <div>Ishikura (1975c)</div> </div>                                                                                                                                                                                                                                                                                |
| <i>Zanthoxylum piperitum</i> | Fruit  | Cy 3-rhamnoglucoside                                               |                                                                                                                                                                                                                                                                                                                         |
| <b>SABIACEAE</b>             |        |                                                                    |                                                                                                                                                                                                                                                                                                                         |
| <i>Meliosma tenuis</i>       | Fruit  | Cy, Dp 3-rutinosides, Dp 3-glucoside                               | Ishikura and Sugahara (1979)                                                                                                                                                                                                                                                                                            |
| <b>SAPINDACEAE</b>           |        |                                                                    |                                                                                                                                                                                                                                                                                                                         |
| <i>Litchi chinensis</i>      | Fruit  | Pg, Cy 3-glucosides, Pg 3,5-diglucoside, Cy 3-galactoside          | Prasad and Jha (1978)                                                                                                                                                                                                                                                                                                   |
| <b>SAXIFRAGACEAE</b>         |        |                                                                    |                                                                                                                                                                                                                                                                                                                         |
| <i>Ribes nigrum</i>          | Fruit  | Cy, Dp 3-glucosides, 3-rutinosides, 3-sophoroside, Pg 3-rutinoside | Lous <i>et al.</i> (1975)                                                                                                                                                                                                                                                                                               |

Table 3.1 (Contd.)

| Orders, family, genus, species          | Organ examined | Pigments present                                                      | Reference                       |
|-----------------------------------------|----------------|-----------------------------------------------------------------------|---------------------------------|
| <i>Ribes</i> spp.                       | Fruit          | Cy 3-sophorose, 3-(2 <sup>G</sup> -glucosyl)-rutinose, 3-sambubioside | Oydivin (1975)                  |
| <i>Ribes</i> spp.                       | Fruit          | Cy 3-glucoside, 3-glucosylrhamnose, 3-glucosylxyloside, 3-diglucoside | Nilsson and Trajkovski (1977)   |
| <b>SCROPHULARIACEAE</b>                 |                |                                                                       |                                 |
| <i>Penstemon centranthifolius</i>       | Flower         | Pg 3,5-diglucoside                                                    | Harborne and Smith (1978)       |
| <i>P. grinnellii</i>                    | Flower         | Cy, Dp 3,5-diglucosides                                               |                                 |
| <i>P. spectabilis</i>                   | Flower         | Cy, Dp 3,5-diglucosides                                               |                                 |
| <b>SOLANACEAE:</b>                      |                |                                                                       |                                 |
| <i>Cyphomandra betacea</i>              | Fruit          | Pg, Cy, Dp 3-glucosides; Pg, Cy, Dp 3-rutinosides                     | Wrolstad and Heatherbell (1974) |
| <b>STERCULIACEAE</b>                    |                |                                                                       |                                 |
| <i>Brachychiton acerifolia</i>          | Flower         | Cy 3-glucoside, Dp 3-glucoside, Pg 3-glucoside                        | Scogin (1979)                   |
| <i>B. discolor</i>                      | Flower         | Cy 3-glucoside, Cy 3-arabinoside                                      |                                 |
| <i>B. populneum</i>                     | Flower         | Cy 3-glucoside, Cy 3-arabinoside                                      |                                 |
| <i>Cheirostemon platinoideis</i>        | Flower         | Cy 3-glucoside                                                        |                                 |
| <i>Dombeya burgessia</i>                | Flower         | Cy 3-glucoside                                                        |                                 |
| <i>D. cayeuxii</i>                      | Flower         | Cy 3-glucoside                                                        |                                 |
| <i>D. burgessia</i> cv. <i>Seminole</i> | Flower         | Cy 3-glucoside                                                        |                                 |
| <i>Firmiana plataniifolia</i>           | Flower         | Cy 3-glucoside                                                        |                                 |
| <i>Fremontia californica</i>            | Flower         | Cy 3-glucoside, Dp 3-glucoside                                        |                                 |
| <i>F. mexicana</i>                      | Flower         | Cy 3-glucoside, Dp 3-glucoside                                        |                                 |
| <i>F. californica</i> hybrid            | Flower         | Cy 3-glucoside, Dp 3-glucoside                                        |                                 |
| <i>Guichenotia sarotes</i>              | Flower         | Cy 3-glucoside, Dp 3-glucoside                                        | Ishikura (1975c)                |
| <i>Theobroma cacao</i>                  | Flower         | Cy 3-galactoside, Cy 3-arabinoside                                    |                                 |
| <b>SYMPLOCACEAE</b>                     |                |                                                                       |                                 |
| <i>Symplocos chinensis</i>              | Fruit          | Dp 3-xylosylglucoside                                                 | Ishikura and Sugahara (1979)    |
| <i>S. coreana</i>                       | Fruit          | Dp 3-xylosylglucoside, 3-diglucoside-5-glucoside                      |                                 |
| <i>S. lucida</i>                        | Fruit          | Dp 3-glucoside, 3-sambubioside                                        |                                 |
| <i>S. myrtacea</i>                      | Fruit          | Dp 3-xylosylglucoside                                                 |                                 |



|                                        |        |                                                                                                                                                           |                                                                                                                                                                                   |  |
|----------------------------------------|--------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| <b>TAMARICACEAE</b>                    |        |                                                                                                                                                           |                                                                                                                                                                                   |  |
| <i>Tamarix tetrandra</i>               | Flower | Cy 3-glucoside, Cy 3,5-diglucoside                                                                                                                        | Scogin (1977)                                                                                                                                                                     |  |
| <b>THEACEAE:</b>                       |        |                                                                                                                                                           |                                                                                                                                                                                   |  |
| <i>Camellia japonica</i>               | Fruit  | Cy 3-glucoside                                                                                                                                            | Ishikura and Sugahara (1979)                                                                                                                                                      |  |
| <i>Cleyera japonica</i>                | Fruit  | Cy 3-glucoside; Cy 3-rhamnoglucoside                                                                                                                      | Ishikura (1975c)                                                                                                                                                                  |  |
| <i>Eurya emarginata</i>                | Fruit  | Cy 3-glucoside; 3-rutinoside, Cy glucosides                                                                                                               | Ishikura and Sugahara (1979)                                                                                                                                                      |  |
| <i>Ternstroemia japonica</i>           | Fruit  | Cy 3-glucoside                                                                                                                                            | Ishikura (1975c)                                                                                                                                                                  |  |
| <b>THYMELAEACEAE</b>                   |        |                                                                                                                                                           |                                                                                                                                                                                   |  |
| <i>Daphne kiusiana</i>                 | Fruit  | Cy 3-glucoside                                                                                                                                            | Ishikura (1975c)                                                                                                                                                                  |  |
| <b>UMBELLIFERAE</b>                    |        |                                                                                                                                                           |                                                                                                                                                                                   |  |
| <i>Angelica decursiva</i>              | Fruit  | Cy 3-sambubioside, 3-rutinoside                                                                                                                           | Ishikura and Sugahara (1979)                                                                                                                                                      |  |
| <i>Conium maculatum</i>                | Stems  | Cy 3-ferulylglucosylgalactoside                                                                                                                           |                                                                                                                                                                                   |  |
| <i>Daucus carota</i> ssp <i>sativa</i> | Root   | Cy 3-lathyroside, 3-xylosylglucosylgalactoside                                                                                                            |                                                                                                                                                                                   |  |
| <i>D. carota</i> ssp <i>maritimum</i>  | Stem   | 3-ferulxylosylglucosylgalactoside                                                                                                                         |                                                                                                                                                                                   |  |
| <i>Foeniculum vulgare</i>              | Stem   | Cy 3-glucosylgalactoside                                                                                                                                  |                                                                                                                                                                                   |  |
| <b>VERBENACEAE</b>                     |        |                                                                                                                                                           | Harborne (1976b)                                                                                                                                                                  |  |
| <i>Callicarpa</i> spp.                 | Fruit  | Cy 3-sinapylglucosylgalactoside                                                                                                                           | Ishikura (1975c)                                                                                                                                                                  |  |
| <b>VITACEAE</b>                        |        |                                                                                                                                                           |                                                                                                                                                                                   |  |
| <i>Parthenocissus tricuspidatum</i>    | Fruit  | Cy glucoside, Pn glycoside                                                                                                                                |                                                                                                                                                                                   |  |
| <i>Vitis amurensis</i>                 | Fruit  | Cy, Pn, Dp, Pt, Mv 3-glucosides, Cy, Mv 3-rutinosides                                                                                                     |                                                                                                                                                                                   |  |
|                                        | Fruit  | 3-rutinosides-5-glucosides, Cy glycosides                                                                                                                 |                                                                                                                                                                                   |  |
|                                        |        | Pn, Dp, Pt, Mv 3,5-diglucosides, Dp, Mv 3- <i>p</i> -coumaroylglucosides                                                                                  | Ishikura and Sugahara (1979)                                                                                                                                                      |  |
|                                        |        | Ph, Dp, 3- <i>p</i> -coumarylglucoside-5-glucoside                                                                                                        | Akuta <i>et al.</i> (1977a,b)                                                                                                                                                     |  |
| <i>V. flexuosa</i>                     | Fruit  | Dp, Pt, Mv 3-glucosides, Mv 3,5-diglucoside, 3-sophoroside-5-glucoside, Mv acylglucoside                                                                  | Ishikura and Ito (1976)                                                                                                                                                           |  |
| <i>V. vinifera</i> cvs                 | Fruit  | Cy, Pn, Dp, Pt, Mv 3-glucosides, 3- <i>p</i> -coumarylglucosides, 3,5 diglucosides, 3- <i>p</i> -coumarylglucoside-5-glucosides, Mv 3,5-acetyldiglucoside | Diaz <i>et al.</i> (1975a,b); Fong <i>et al.</i> (1974); Hrazdina (1975); Hrazdina and Franzesa (1974); Malikov (1971); Matsudomi <i>et al.</i> (1977); Ohta <i>et al.</i> (1978) |  |

One group of plants, the order Centrospermae, are unique among the angiosperms in not synthesizing anthocyanins but producing the alkaloid-like betalains. However, there are two families within this order, the Caryophyllaceae and Molluginaceae, which have retained the ability to produce anthocyanins (Mabry, 1976). It is the classification and evolutionary status of these two families that causes considerable controversy among both chemists and taxonomists (Harborne, 1976a). Other families thought to be somewhat related morphologically to the Centrospermae, namely the Plumbaginaceae, Polygonaceae, Primulaceae (Nowicke, 1975; Nowicke and Skvarla, 1977) and Vivianiaceae (Behnke and Mabry, 1977) have recently been excluded from this order because of their ability to synthesize anthocyanins.

While most chemotaxonomic investigations of anthocyanins are based on paper chromatography, a recent development has been the use of high-pressure liquid chromatography (see Section 6). For example, Asen (1979) obtained a rapid and accurate separation of cyanidin 3-galactoside, the 3-glucosides and rutinoides of pelargonidin and cyanidin present in poinsettia cultivars. Because of the accuracy and reproducibility of such separations, the method can be adapted for resolving difficulties in the description of new cultivars protected by plant patent law.

### 3.4. ANTHOCYANINS AS GENETIC MARKERS

Flower anthocyanins have been consciously used as genetic markers since Mendel's 'Experiments on hybridization of plants' using pea plants appeared in 1855. While other members of the Leguminosae have been used since for genetic investigations (Arkotov *et al.* 1976; Picard, 1976; Nozzolillo, 1978, 1979), experiments with plant species from other families have provided most information on genetic control of anthocyanin production.

Certain subspecies of the genus *Rosa* have been found to be new genetic sources of peonin and provide a new combination of anthocyanins (Marshall, 1975). *Petunia hybrida* has a special place among flowers for plant biochemists, since the development of Hess's 'cinnamic acid starter hypothesis' (Hess, 1968) was based on work with this plant. Genetic experiments designed to clarify whether the substitution pattern in anthocyanin is established at the C<sub>9</sub> or at the C<sub>15</sub> level suggest the involvement of two polymeric genes with independent inheritance (Wiering and DeVlaming, 1977). The action of these genes results in the conversion of petunidin glycosides into malvidin glycosides, suggesting that modification in the B ring of anthocyanins (and possibly flavonoids in general) takes place at the C<sub>15</sub> level. Similar data have accrued for the 28-chromosome 'Siberian Iris', which is able to convert delphinidin into malvidin (Vaughn and Lyster, 1978). Genetic manipulations have also revealed the presence of unstable systems affecting anthocyanin production in *Petunia* flowers. The cause of these unstable systems is at the *an2-1* allele, having a regulatory effect on anthocyanin

biosynthesis (Cornu, 1977; Farcy and Cornu, 1979). Genetic manipulations affecting anthocyanin production were also carried out on bluebells (Stickland and Harrison, 1977), on *Centaurea phrygia* (Szweykowski and Bobowicz, 1976), on rhododendrons (Heursel and Horn, 1977) and on *Antirrhinum majus* (Gilbert and Richards, 1976; Sastry, 1976; Linnert, 1978).

Among crop plants, members of the Gramineae have received the closest attention. Barley was investigated for mutations affecting anthocyanin and flavonoid synthesis (Babayan *et al.*, 1977; Jende-Strid, 1978; Von Wettstein *et al.*, 1978) and for the nature of the linkage controlling anthocyanin pigmentation (Hayashi *et al.*, 1977). In rye, anthocyanin synthesis, waxy covering, ligula and spike development were shown to be under independent gene action (Surikov and Romanova, 1978). This plant was also shown to have three pairs of dominant gene suppressors involved in its anthocyanin-synthesizing mechanism (Ruebenbauer and Ruebenbauer, 1978). While genetic manipulation can provide unstable anthocyanin-producing systems, anthocyanin inheritance is nevertheless relatively constant in most tetraploid and hexaploid wheats (Raut *et al.*, 1978).

Investigations in maize on the location of *Dotted* (a gene controlling anthocyanin development in the stalks, leaves and endosperm), usually located in the terminal knob of chromosome 9, showed that the location of this gene is not permanent, but it can change position with chromosomal complements (Doerschug, 1976). Similar investigations by Dooner and Kermicle (1976) and Chen and Coe (1977) established the presence of the anthocyanin-pigmenting factor on a chromosomal segment identical with the standard duplicated sequence. Instability of the colour-producing system was found to be caused by segment duplication in a displaced position on the chromosome. This extra segment can easily be lost, resulting in diminished colour-producing ability of the plant (Gavazzi *et al.*, 1977). In addition to the position affecting phenomena for induced pigmentation, the size of the incorporated genetic material can also play a role, as has been shown for bacterial insertion sequences (Gonella and Peterson, 1978). While test crosses of maize often provide unstable systems, several stable germinal derivatives with varied phenotype expressions were also obtained (Reddy and Peterson, 1976). Controlling elements of anthocyanin synthesis in maize must act early in the flavonoid biosynthetic path, since not only the production of anthocyanins, but also that of quercetin was inhibited (Reddy and Peterson, 1977, 1978) in colourless tissues.

There is insufficient information available presently even to guess the number of genes involved in the control of anthocyanin biosynthesis in maize, or any other plant. The number of controlling genes is almost certainly greater than the number of enzymes involved, since it has been shown (Dooner and Nelson, 1977a,b, 1979) that three or more genes are involved in the control of production and activity of UDPG: flavonol-3-*O*-glucosyltransferase, an enzyme involved in the later stages of anthocyanin (and other flavonoid) biosynthesis.

Genetic experiments on crop plants involving anthocyanins are designed

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mainly to improve the quality or marketability of the produce. Major efforts in this direction have been undertaken with Brussels sprouts (Ockendon, 1977), on intergeneric hybrids of *Raphanus sativus* × *Brassica oleracea*, *Raphanus sativus* × *Brassica caulorapa* (Bubarova, 1974), in turnips (Hoshi, 1975), green cabbage (Bagett, 1978), grapes (Golodriga and Dubovenko, 1977), globe artichoke, *Cynara scolymus* (Foury and Aubert, 1977), *Capsicum* cultivars (Daskalov, 1973; Pochard, 1977), pears (Tuz, 1978), *Nicotiana* cultivars (Sand, 1976), sweet potato (Ayyangar and Sampathkumar, 1978), *Solanum* species (Rao, 1978), red clover (Broda, 1979), *Medicago* hybrids (Lesins *et al.*, 1976), cotton (Konoplya *et al.*, 1978) and apples (Williams *et al.*, 1979). While all the above experiments were carried out with whole plants, anthocyanins have also been used in cytological identifications of colony formation in intergenic somatic hybrid cells (Gosch and Reinert, 1978).

### 3.5 ANTHOCYANINS AS STRESS MARKERS

Some plant species, acyanic when grown under normal conditions, produce anthocyanins in the presence of high amounts of sugars, or when deficient in certain metals. The appearance of autumn coloration (e.g. reddening of leaves) is thought to be caused by high sugar production during the photosynthetic period and lower metabolic rates and/or reduced transport during the cool nights, resulting in a steady increase in the concentration of sugars in the photosynthetic tissues. Some plants develop red spots around the infection site after attack by pathogens. Since these phenomena do not occur during the normal development of the plants, such discoloration is obviously a sign of stress.

Irradiation of plants by UV light apparently affects anthocyanin production. While tissue cultures of *Haplopappus gracilis* grown in the dark can be induced to form anthocyanins by UV radiation (Wellmann *et al.*, 1976), detached leaves of *Zebrina pendula*, when irradiated on their lower surface with UV light and placed in the dark become water-logged and necrotic within 5 days, losing anthocyanins in their lower epidermis (Witztum, 1978a, b). While the combined effect of light and low quanta of ionizing radiation seems to enhance anthocyanin production in seedlings of *Lactuca sativa*, *Brassica oleracea*, *Secale cereale* and *Raphanus raphanistrum* (Kuzin and Vagabova, 1978), plants developed from haploid protoplasts of *Datura innoxia* after treatment with ionizing radiation lose their ability to synthesize anthocyanins (Schieder, 1976). In 4-day-old seedlings of buckwheat, *Fagopyrum esculentum*, raised within the first year after irradiation of the seeds with  $\gamma$ -rays (3,6 and 12 R total dose), slight but significant increase in the content of rutin and leucoanthocyanidins (but not anthocyanins and flavone glycosides) were found in the cotyledons (Margna and Vainjarv, 1976). During this time hypocotyls accumulated mainly anthocyanins and leucoanthocyanidins.

The effect of water stress on plants is also significant and results in changes in

the formation of flavonoid compounds. *Quercus* species, when exposed to water stress, show higher amounts of anthocyanins than plants grown under normal conditions (Spyropoulos and Mavrommatis, 1978). Exposure to higher temperature during a period of water stress further increases the anthocyanin concentration in these plants (Spyropoulos and Lambiris, 1979). In desert plants the appearance of anthocyanins during the dehydration process has been correlated with survivability in some species (Gaff, 1977).

The simultaneous effect of mechanical damage, thermal shock and deprivation of water seems to be rather complex. One hour after slightly bruising the leaf blades of *Coleus blumei*, levels of flavonoid and phenolic compounds containing an *o*-dihydroxy phenylpropanoid moiety decreased in the entire leaf blade, while the level of flavonoid containing only a monohydroxyl in the B ring increased. After 5 h exposure to 35°C, a slight reduction in the anthocyanin content was observed with a simultaneous increase in caffeic acid derivatives (Tronchet, 1975). Exposure to low temperatures (0–5°C) resulted in an increase in anthocyanin content and a decrease in the content of cinnamic acids. Water deprivation caused a decrease of apigenin glycoside content in the leaves. Roses reacted similarly (Plant *et al.*, 1979).

Deficiency of important minerals, such as phosphorus, also results in an increase in anthocyanin content in plants. Thus phosphorus-deficient maize plants accumulate larger quantities of cyanidin 3-rhamnoside (Bhatla and Plant, 1977). Infection of tomato plants with *Mycoplasma* reportedly results in phosphorus-deficient plants containing anthocyanins, while healthy plants do not accumulate these pigments (Rodeia and Borges, 1974). Administration of nitrogen to plants seems to have the reverse effect on anthocyanin production. Isolated buckwheat cotyledons and hypocotyls produce lower amounts of anthocyanins and flavonol glycosides (Margna *et al.*, 1974a) when incubated in a 1%  $\text{NH}_4\text{NO}_3$  solution. The effect on intact seedlings is much less pronounced.

Exposure to ozone of leaves of *Brassica pekinensis*, *Zelkova serrata* and *Prunus yedoensis* resulted in an increased formation of anthocyanins (Nouchi and Oodaira, 1974), while fumigation of *Coleus blumei* leaves with HF destroyed their anthocyanin pigments (Lamprecht and Powell, 1977). The latter is not surprising since HF is among the strongest known acids.

Some plants respond with anthocyanin and general phenolic compound production when invaded by pathogenic organisms. Resistant and hypersensitive varieties of corn plants respond more rapidly to infection by *Colletotrichum graminicola* with accumulations of anthocyanins than susceptible varieties (Hammerschmidt and Nicholson, 1977). 'Scar skin' and 'dapple apple', diseases whose cause has not been satisfactorily identified, result in a decreased anthocyanin production in both Red Delicious and Hyslop Crab apples (Huang and Agrios, 1979). Infection of cowberry plants by *Marsonina potentillae fragariae* and *Exobasidium vaccinii* also causes the production of less anthocyanin in the leaves (Radaitiene, 1977). By contrast, anthocyanin-containing

cultivars of rice plants respond by producing higher amounts of anthocyanins when infected with rice tungro virus (Rao *et al.*, 1979).

Embryos of *Ilex aquifolium*, when excised and cultured on a medium lacking hormones and 'optional' constituents, produce anthocyanins and fail to develop to mature plants upon illumination (Hu *et al.*, 1978). Similar anthocyanin accumulation was observed in emasculated *Cymbidium* flowers (Van Staden, 1979), pointing to metabolic disturbances in the plants following this manipulation.

### 3.6. FOOD-RELATED ASPECTS OF ANTHOCYANINS

Because of recent restrictions in the use of possibly harmful synthetic colourants in foods, anthocyanins as safe natural pigments have considerable potential in the food industry. There have been many reports in this area. Patents concerning anthocyanins describe basically minor modifications in their synthesis from precursors (Wakihira *et al.*, 1976) or their isolation from raw materials (Mitsuoka and Nishi, 1974; Nakamura *et al.*, 1975; Finedoc-Sica, 1976; Urushido, 1977; Abutalybov *et al.*, 1977; Kikuchi *et al.*, 1977; Minoda *et al.*, 1978; Asen *et al.*, 1978; VanPraag and Duijf, 1978; Wallin, 1979; Josse and Klæui, 1979) and their recovery from industrial by-products (Inagami and Koga, 1975; Philip, 1976; Okajima *et al.*, 1976; Mirabel and Meiller, 1978). Large efforts spent on finding plant-material sources for anthocyanin isolation are summarized in reviews (Lowry and Chew, 1974; Francis, 1975, 1977; Shrikhande, 1976; Lancrenon, 1978a,b). The plants investigated include red cabbage (Shewfelt and Ahmed, 1977), roselle (Du and Francis, 1974), miracle fruit (Buckmire and Francis, 1976, 1978), garlic (Du and Francis, 1976), apple skins (Posokhlyarova, 1975), leaves of *Acalypha* (Billot, 1975), sour cherries (Shrikhande and Francis, 1974a,b) and olives (Maestro-Duran and Vazquez-Roncero, 1976; Fantozzi and Montedoro, 1978). Work has also continued on the characterization of anthocyanins in economically important plants. Thus the anthocyanin composition of currants (Dankanits, 1976), eggplant (Dikii *et al.*, 1978), taro (Chen *et al.*, 1977), strawberries (Selvaraj *et al.*, 1976), plums (Astegiano and Ciolfi, 1974), Ukrainian garlic (Borukh and Demkevich, 1976), whortleberries and bilberries (Borukh, 1974), cowberries (Bandzaitiene and Butkus, 1975) and cranberries (Schmid, 1977) was investigated.

Because anthocyanins appear in fruits near maturity, they have been used in monitoring maturation (Christensen and Graslund, 1979; Gasanov, 1975; Bisson and Ribereau-Gayon, 1978; Carbonneau *et al.*, 1978). Owing to the direct relationship between anthocyanin content and maturity in certain fruits, anthocyanin content is often used as a criterion for quality (Cantarelli, 1975; Kushman and Ballinger, 1975a,b; Mosorinski, 1975a,b; Andreotti *et al.*, 1976; Deubert, 1978; Bourzeix *et al.*, 1977).

Unlike the synthetic red pigments used previously by the food industry, anthocyanins are not stable and readily undergo changes during storage and processing of the raw material. These changes result in loss of colour, browning of the product and formation of precipitates in liquids. Because all these changes affect quality, investigations on pigment changes during storage (Posello and Bonzini, 1977a, b) and processing (Do *et al.*, 1976) were undertaken in order to obtain a better understanding of the events taking place. Methods were devised and suggested to enable simple quality control (Watade and Abbott, 1975; Johnson *et al.*, 1976; Little, 1977), and attempts undertaken to improve simple chromatographic separation of the pigments (Tanner and Zuerrer, 1976). Investigations on the degradation of anthocyanins in model systems (Tanchev and Ioncheva, 1974, 1975, 1976; Shrikhande and Francis, 1974a, b) and in food products (Fang-Yung and Kuznetsova, 1974; Markakis, 1974; Sistrunk and Cash, 1974; Skalski and Sistrunk, 1974; Sakanishi and Fukuzumi, 1975; Mosorinski, 1975a, b; Bourzeix and Heredia, 1976; Du *et al.*, 1975a, b, c; Fang-Yung and Kuznetsova, 1976; Flora, 1976, 1978; Sistrunk, 1976; Calvi and Francis, 1978; Tanchev, 1978; Abers and Wrolstad, 1979; Kim *et al.*, 1979; Manabe *et al.*, 1979; Yoon and Lee, 1979), while giving some hints on the general nature of the reactions, failed to provide the answers sought because of the complexity of the systems. The reactions of anthocyanins in food products have been reviewed (Hrazdina, 1974).

The basic problem with the use of anthocyanins in food products is their colour sensitivity towards changes in pH. While at low pH values (pH=2) the pigments are present as the red-coloured flavylum salts, at higher pH their colour fades or changes to purple/blue. This colour change is caused by structural transformations as has already been described (Timberlake and Bridle, 1975). Therefore anthocyanins can presently be used only in those food products where the pH is relatively low. Even here a relatively large amount of pigment has to be added to compensate for the pH-dependent colour loss. To improve the colour stability of anthocyanin preparations in foods, it is possible to add di- and tri-valent cations (Starr and Francis, 1974; Gabor, 1977; Kuusi *et al.*, 1977); this, however, also changes the colour towards blue and has limited applications at best.

Problems associated with the pigments were reviewed by Lancrenon (1978a, b). A recently reported condensation product of anthocyanins with catechins in the presence of acetaldehyde has potential value as a food colouring agent, because its colour is resistant to pH-variation (Timberlake and Bridle, 1977). The colour of the condensation product is ca. 30–40 nm towards the blue but when mixed with anthocyanin, it could provide the major characteristics required by the industry. There seem to be current limitations concerning the use of this preparation, since only ca. 10% of the available anthocyanin reacts with catechin and acetaldehyde. Investigation of the reaction products showed the presence of at least six compounds with similar spectral and chromatographic

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behaviour, the exact structures of which have not yet been determined (L. J. Chen, unpublished data).

Notwithstanding the above limitations of anthocyanin preparations as food colourants, a number of investigators are promoting their use in certain food products (Clydesdale *et al.*, 1978; Kolesnik *et al.*, 1978; Main *et al.*, 1978; Shewfelt and Ahmed, 1978; Yoon *et al.*, 1978; Clydesdale *et al.*, 1979a,b,c; Ferenczi and Kerenyi, 1979). An anthocyanin preparation isolated from cherries has also been used to produce maraschino-type cherries (McClellan and Cash, 1979). While the presence of anthocyanins is desired in most cases to add colour to the food products, in others their presence can cause problems during processing (Darmaniyan and Dudkin, 1976; Moy *et al.*, 1977).

Another related area where anthocyanins play an important role is the production of red wines. Investigations have covered the anthocyanin composition of grapes (Ballinger *et al.*, 1974; Bourzeix *et al.*, 1974, 1975; Philip, 1974a,b; Sakellarides and Luh, 1974; Kantarev, 1975; Diaz *et al.*, 1976; Cash *et al.*, 1976; Bourzeix, 1978; Ohta and Osajima, 1978a,b; Symonds and Cantagrel, 1978; Ohta *et al.*, 1979a), correlation between quality and pigment parameters (Somers and Evans, 1974, 1977; Jackson *et al.*, 1978; Timberlake *et al.*, 1978), and changes of colour and anthocyanins during the vinification process (Erdoss and Fodor, 1976; Gadzhiev and Vlasova, 1976; Getov *et al.*, 1976; Glories and Augustin, 1976; Kapustina, 1976; Samvelyan, 1976; Tikhonova and Lebedeva, 1976; Timberlake and Bridle, 1976a,b; Dancic, 1977; Glories, 1978a,b,c; Margheri, 1978; Morgan and Mitjavila, 1978; Maksimova, 1979; Mandzhukov, 1979; Odarchenko, 1979; Somers and Evans, 1979).

During the vinification process a relatively large amount of pomace is produced in a winery. To reduce the cost of its disposal and eliminate possible water pollution problems, investigations were carried out on the extraction of anthocyanins from the pomace (Philip, 1974a,b; Saquet, 1974; Champemont *et al.*, 1975; Bernou *et al.*, 1976; Peri and Bonini, 1976; Bakos *et al.*, 1977; Mandzhukov, 1977). If the pomace contains sufficient quantities of anthocyanins, this process could prove to be an economic way to produce anthocyanin preparations for the food industry.

### 3.7 PROGRESS IN THE ANALYTICAL TECHNIQUES OF ANTHOCYANINS

Paper and thin-layer chromatography are still the traditional tools of investigators working with anthocyanins. In addition, some more elaborate techniques using conventional column chromatography are being adopted by an increasing number of investigators. Recent developments in column support materials for high-pressure liquid chromatography make this technique the most powerful in the analysis of natural products. Some of the above techniques have been reviewed recently (Glories, 1976; Saquet, 1976; Hrazdina, 1979).



### 3.7.1 Paper and thin-layer chromatography

Progress using these traditional techniques has consisted mainly in developing new solvent systems for sharper separations (Krishnamurty and Krishnaswami, 1975; Gombkoto, 1977; Vacarri and Pifferi, 1978) and adaptation of the existing system for semiquantitative determination of anthocyanins (Ohta *et al.*, 1979b). Both of these methods, in spite of their general use, have drawbacks. Paper chromatography is cumbersome and time consuming when analysing large numbers of samples. Thin-layer chromatography is not as reproducible as paper chromatography and requires the use of reference compounds in most cases.

### 3.7.2 Column chromatography

Development of column chromatographic methods for the separation of anthocyanins was necessitated by the need for pure compounds in large amounts for chemical and biochemical investigations or as reference substances for qualitative or quantitative analysis. Polyamide powders show good retention of anthocyanins when aqueous plant extracts are percolated through the columns, and permit the removal of sugars, organic acids, soluble polysaccharides, proteins and cations by simply washing with water. While certain anthocyanin classes can be resolved on polyamide columns (Strack and Mansell, 1975), in most cases the resolution is mediocre and one must turn to thin-layer or paper chromatography for further separations and purification. Insoluble polyvinylpyrrolidone (PVP, Polyclar AT) can separate the individual anthocyanins within specific groups, e.g. 3-monosides, 3-biosides, 3,5-diglucosides and their acyl derivatives (Hrazdina, 1970). While single columns of either polyamide or polyvinylpyrrolidone do not give complete separation of anthocyanins, a combination of both is usually sufficient to resolve up to 20 different pigments (Hrazdina and Franzese, 1974a, b; Hrazdina, 1975). These methods are being increasingly adapted for anthocyanin isolation (Brouillard and Delaporte, 1978; Ohta *et al.*, 1979a), or in a combination of silica gel, ion exchange, molecular sieve chromatography, ultrafiltration and electrophoretic separations (Lin and Hilton, 1980). While the combination of polyamide–polyvinylpyrrolidone columns works well in general, certain plant species can contain pigment mixtures where purification of the individual anthocyanin requires further separation on paper chromatograms (Hrazdina *et al.*, 1977). Ion-exchange chromatography usually does not separate individual anthocyanins; it, however, can be used for preliminary separation of the pigments from sugars, polysaccharides and proteins, and to remove trace amounts of metals from anthocyanin preparations (Pifferi and Vaccari, 1980). Satisfactory separations of anthocyanins and other phenolic compounds have also been achieved by chromatography on a poly (ethylene glycol) dimethacrylate gel column (Goldstein, 1976).

### 3.7.3 Gas chromatography

Anthocyanin chemistry has benefited little from developments of gas chromatographic techniques because of their non-volatility and general instability. It is the structure and properties of anthocyanins that makes their separation difficult. Derivatization of anthocyanins for gas chromatographic (GC) or gas chromatographic-mass spectrometric (GC-MS) analysis is strongly hampered by the structural transformations which these pigments undergo. At pH of 0.5–1.0 only the red-coloured flavylium salt is present, but this pH range is unfortunately not suitable for derivatization. As the pH is raised, the flavylium salt undergoes structural transformations (see following section), where the colourless carbinol base and the purple-coloured anhydrobases are formed. At pHs above 7 the anthocyanins also undergo ring fission to produce chalcones. Therefore, under the conditions best suited for derivatization (e.g. alkaline), at least four different structural transformation forms of these pigments are present. This is the reason why it is practically impossible to obtain homogeneous derivatives of anthocyanins. In spite of these serious limitations, some reports have appeared on the GC and GC-MS analysis of anthocyanins (Bombardelli *et al.*, 1977; Drawert and Leupold, 1976a,b; Lanzarini *et al.*, 1977).

### 3.7.4 High-pressure liquid chromatography (HPLC)

Recent developments in both instrumentation and column support material such as Lichrosorb, Zorbax, Bondapack and  $\mu$ -Bondapack treated with octadecyltrichlorosilane have opened up new possibilities for the separation of plant products using this technique. The adoption of variable-wavelength spectrophotometers as detectors for HPLC made possible the monitoring of each group of compounds at their specific absorption maxima. With these techniques, anthocyanins can be selectively monitored at their visible maxima without interference from other materials.

The first HPLC separation of anthocyanins was reported by Manley and Shubiak (1975), who used Pellidone as column support material. This technique, which resolved mixtures of the 3-glucosides of peonidin, petunidin and malvidin, did not prove readily useful, because the pigments had to be separated first from sugars and organic acids and required prior concentration on polyvinylpyrrolidone. A report by Wulf and Nagel (1976) on the successful separation of phenolic acids and flavonoids on a reverse-phase column support material soon led to methods for separating anthocyanidins (Adamovics and Stermitz, 1976; Wilkinson *et al.*, 1977). These methods permitted the identification of anthocyanidins in plant extract hydrolysates, but did not permit the analysis of anthocyanin composition.

An almost simultaneous development in this methodology using reverse-phase Lichrosorb (Wulf and Nagel, 1978) and  $\mu$ -Bondapack column support materials (Williams *et al.*, 1978) enabled the separation of complex anthocyanin mixtures.

Since anthocyanins can be detected selectively in the 520 nm region, where few other compounds absorb, these methods do not require preliminary treatment of the samples. Centrifuged or ultrafiltered samples free from any particulate material can be directly injected on to the columns and separation of 20 or more anthocyanins accomplished in 90–120 min.

These methods have been successfully used in the identification of plant cultivars (Stewart *et al.*, 1979) and food-research-related work (Camire and Clydesdale, 1979). The methods were originally developed for qualitative analysis of plant extracts. However, simple modification by using standard curves obtained with pure compounds enables their use for quantitative determination of the individual anthocyanins and other flavonoids in complex mixtures (Nagel and Wulf, 1979; Moskowitz and Hrazdina, 1980). The technique is very sensitive. Using the above method (Williams *et al.*, 1978), the qualitative and quantitative composition of anthocyanins, flavonoid glycosides and hydroxycinnamic acid esters could be determined in vacuoles isolated from grape berry subepidermal tissues (Moskowitz and Hrazdina, 1980).

### 3.8 PROGRESS IN THE CHEMISTRY OF ANTHOCYANINS

Because of the complexity of reactions and the large number of steps involved in the direct synthesis of anthocyanins, it is often more convenient to obtain them by conversion of more readily available flavonoids. In this manner a number of 3-deoxyanthocyanidins were produced by benzoquinone oxidation of the corresponding flavan-4-ol derivatives (Sweeny and Iacobucci, 1977a,b). Flavan-4-ols are rather conveniently prepared by  $\text{NaBH}_4$  reduction of flavones. Treatment of the flavan-4-ol with benzoquinone results in the formation of flav-3-ene intermediates of which further abstraction of the  $\text{C}_2$  allylic hydrogen produces the 3-deoxyanthocyanidin derivatives. However, not all compounds behave in a similar manner. Flavan-3,4-diols, prepared by  $\text{NaBH}_4$  reduction of tetramethyldihydroquercetin, showed no improved yield under conditions when the amount of the benzoquinone was varied or chloranil was used. A reason for this may be the known tendency of flavan-3,4-diols to undergo condensation and polymerization reactions in the presence of strong acids. Using a modification of the above method, apigeninidin and 4'-*O*-methyl-luteolinidin were synthesized from naringenin and hesperetin respectively (Sweeny and Iacobucci, 1977a,b).

The main reason why the chemical properties of anthocyanins have been little investigated is the difficulty encountered in their isolation, and their general instability, especially in aqueous solution. From earlier work (see Timberlake and Bridle, 1975) with synthetic flavylum salts, some natural anthocyanidins and anthocyanins, it was established that these reactions in solution involve the formation of anhydrobases (3.2), carbinol base (3.3) and chalcone (3.4) in acidic media with the former, and anhydrobases and carbinol base with the latter two compounds in addition to the flavylum salt (3.1). The decolourization of an

anthocyanin solution in the pH region 4–5 is thought to occur via the anhydrobase (3.2) by hydration. Investigations by Abe *et al.* (1977) suggest that there are differences even among the anthocyanidin 3,5-diglucosides in the formation of their anhydrobases. Anhydrobases of pelargonidin, cyanidin and peonidin 3,5-diglucosides reportedly have the 7-keto structure, while that of malvidin 3,5-diglucoside is present in the 4'-keto structure.

Recent investigations by Brouillard (Brouillard and Dubois, 1977; Brouillard and Delaporte, 1977; Brouillard *et al.*, 1978, 1979; Brouillard and El Hage Chanine, 1980) suggest that structural transformations do not proceed on the above paths. On the basis of kinetic and thermodynamic experiments these authors suggest, that in aqueous acidic solutions there is an acid–base equilibrium between flavylum salt (3.1) and the anhydrobase (3.2), and that the formation of the colourless carbinol base (3.3) is due solely to the hydroxylation of the flavylum salt (3.1). The carbinol base (3.3) forms a tautomeric equilibrium with the chalcone (3.4) (Fig. 3.1). The majority of investigations have been carried out with commercial anthocyanin preparations under the assumption that there is only one anhydrobase structure of the anthocyanins, which is blue, and that the colourless, chalcone absorbs in the 340 nm region of the spectrum. Spectroscopic evidence, however, shows that in a mildly acidic medium there are two purple anhydrobase species absorbing at 534 nm and 556 nm respectively, and these ionize in the pH region of 6–6.5, producing the blue-coloured ionized anhydrobase, which absorbs at 610 nm (L. J. Chen, unpublished data). The chalcone form of anthocyanins absorbs at 396 nm, and this absorption band does not appear below pH 6. Both the purple and blue colours fade and turn colourless or yellowish (from the ionized anhydrobase) producing the carbinol base or ionized carbinol base upon storage, and the latter undergoes ring fission to the chalcone (L. J. Chen, unpublished).

From the above data and observations, the following transformation mechanism can be suggested: in aqueous acidic media there is an acid–base equilibrium between the flavylum salt (3.1) and the quinoidal anhydrobases (3.2), with increasing stability of the flavylum salt under pH 4–4.5 as the pH decreases. The stability of the anhydrobases increases with increasing pH up to 6–6.5. Nucleophilic attack of water on the flavylum salt (3.1) produces the carbinol base (3.3), which can also be produced by hydration of the anhydrobases (3.2). The chalcone form appears above pH 6 and is produced from the carbinol base, or ionized carbinol base under these conditions.

These structural transformation reactions are mainly responsible for the fact that NMR and MS spectral methods are of limited value in the structural investigations on anthocyanins. Similar transformations also occur during oxidation. Thus under strongly acidic conditions (pH 1–4) anthocyanidin 3,5-diglucosides and their *p*-coumaryl derivatives, when oxidized with H<sub>2</sub>O<sub>2</sub>, undergo a Bayer–Villiger reaction to produce malvone-type compounds. However, when the same reaction is carried out under low acidity to neutral conditions (e.g. with anhydrobases), the B ring of the pigments becomes lost and

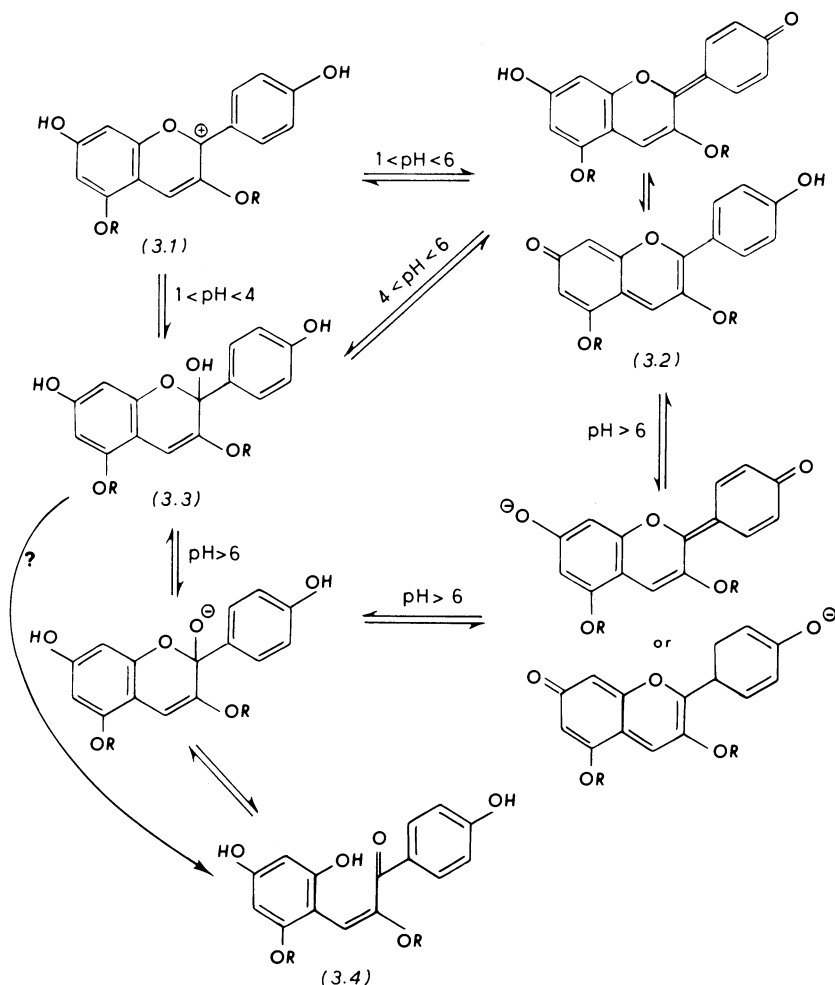


Fig. 3.1 Structural transformation reactions of anthocyanins.

the end products of the reaction are coumarin derivatives (Hrazdina and Franzese, 1974a,b). The yield on these unique oxidation products is rather low and changes significantly when the pH is varied. However, reaction products in higher yields could possibly be produced at other pH values also, since it has been reported that high concentrations of neutral salts have a stabilizing effect on both flavylium salts and anhydrobases (Goto *et al.*, 1976).

Another interesting reaction of anthocyanins is their condensation with catechins and catechin-type compounds in the absence and presence of acetaldehyde (Timberlake and Bridle, 1976a,b). While in the absence of acetaldehyde the condensation reaction is very slow, and xanthylum salts seem

to be the end products, in the presence of acetaldehyde a number of intensely coloured compounds are produced. Owing to limitations in available analytical methods, the exact structure of the condensation products have not been determined.

Photochemical investigations on an anthocyanin mixture indicate stability of compounds in the pH 2–4 range (Riva *et al.*, 1974). Investigations on the stability of anthocyanin in wines show that the compounds undergo continuous changes, but the intermediates formed are not known (Nagel and Wulf, 1979). The chemical problems related to structure identification of anthocyanins were reviewed by Ueno and Saito (1976), those pertinent to food production by Hrazdina (1974).

### 3.9 SUBCELLULAR STATUS OF ANTHOCYANINS

Anthocyanins accumulate in the vacuoles of epidermal or subepidermal tissues in plants, and thus are responsible for the pink, red, purple and blue colours present in flowers and fruits. This is true of all angiosperm families, except for members of the Centrospermae (see Section 3.3). Several different factors are involved in plant colour expression, the most important being the pH of the cell sap (vacuole), the nature of the aglycone, the extent of glycosylation, the concentration of anthocyanin(s) and other flavonoids in the vacuole, and metal-complexing (Timberlake and Bridle, 1975).

The role of metals in the colour expression in some plants was further confirmed by Takeda (1977), and by Takeda and Hayashi (1977), who found that commelinin, the pigment of *Commelina communis*, consists of awobanin, flavocommelin and magnesium in the ratio 2 : 2 : 1. Manganese, cobalt, nickel, zinc and cadmium can replace magnesium in the complex without significant colour changes. Iron can also form complexes with the anhydrobases of anthocyanins (Kim and Ahn, 1978); its role in colour expression, however, seems to be limited at best because of the scarcity of iron-accumulating flowering plants. The role of pH in colour expression has been further confirmed by measurements in the vacuolar sap (Stewart *et al.*, 1975). These showed that the pH value of the vacuolar environment can vary widely from 2.5 in *Begonia* species to 7.5, as in the Morning Glory cv. Heavenly Blue. In these two extreme examples the formation of the coloured species is due to the flavylum salt (red) at 2.3 and the ionized anhydrobase (blue) at 7.5. Anhydrobases of anthocyanins start to ionize around pH 6. In most plants, however, the pH of the vacuolar environment is in the range of 4–5, where anthocyanins are expected to be present in the colourless carbinol base form. The intense red–purple colouration in the epidermal tissue of flowers where the vacuolar pH is in this region is an unmistakable sign of another structural factor, the existence of pigment–co-pigment complexing.

Recent work (Sugiyama and Takano, 1974a,b; Asen, 1975, 1976; Asen *et al.*,

1975, 1977; Ishikura and Shimizu, 1975; Saleh and Ishak, 1976; Yazaki, 1976; Maekawa and Nakamura, 1977; DeLoose, 1978; Yoshitama, 1978) has confirmed that anthocyanins in most flowers are present as anhydrobase complexes with other flavonoids. While acylated anthocyanins in general show a much lower response to co-pigmentation reactions than do the 3,5-diglucosides (Scheffeldt and Hrazdina, 1978; Williams and Hrazdina, 1979), in one instance it was reported (Hoshino *et al.*, 1980) that acyl groups have a stabilizing effect on complexes formed between acylated anthocyanins and flavone *C*-glycosides. The complex between anthocyanin and flavone (or flavonol) is a rather loose association and is pH-dependent, therefore hydrogen-bond formation was originally suggested as the mechanism (Asen *et al.*, 1972; Scheffeldt and Hrazdina, 1978; Williams and Hrazdina, 1979). Systematic investigations with a large number of differently substituted flavonoids suggest that *in addition* to hydrogen-bond formation between the carbonyl group of the anthocyanin anhydrobases and aromatic hydroxyl groups of the complexing flavonoids, other factors are also important. These are unsaturation at C<sub>2</sub>–C<sub>3</sub> in the flavonoid co-pigment, electrostatic forces and configurational or steric effects between the two molecules (Chen and Hrazdina, 1981). In addition to flavonoids, pectin or protopectin has also been reported to form complexes with anthocyanins (Yasuda, 1976). How this association can take place in the living tissue is not quite clear, since anthocyanins are accumulated in the vacuole, and pectin or protopectin is a component of the middle lamella.

While it is generally true that anthocyanins are present as complexes with other flavonoids in the epidermal tissues of flowers, this may not necessarily be the case in other plant tissues. In vacuoles isolated from grape berry subepidermal tissues, anthocyanins were found to be present as the flavylium salts, not associated with flavonoids or other compounds (Moskowitz and Hrazdina, 1980). Eggplant epidermal tissue, on the other hand, seems to contain the stabilized anhydrobase form of these compounds (Nothmann *et al.*, 1976).

Anthocyanins and flavonoid glycosides are known to accumulate in the vacuole of plant cells since this has been shown with isolated vacuole preparations (Wagner and Siegelman, 1975; Hrazdina *et al.*, 1978; Wagner, 1979). Therefore a report on their presence in chloroplasts (Saunders and McClure, 1976) requires further confirmation.

### 3.10 PHOTOCONTROL OF ANTHOCYANIN BIOSYNTHESIS

The synthesis of anthocyanins is, as are most processes in plants, light-dependent. The light promotion of anthocyanin biosynthesis is mediated by at least two photoreactions: 1, a low-energy, red/far-red (R/FR) reversible, phytochrome-controlled reaction, and 2, a 'high-energy' reaction, referred to as high irradiance response (HIR), most effective in the blue and far-red spectral regions. Recent experiments have been designed to prove directly or indirectly

these reactions in carnations (Maekawa, 1975), apples (Bishop and Klein, 1975), grapes (Kliewer, 1977), tea plants (Koretskaya and Zaprometov, 1976), water-pepper (Asahira and Masuda, 1977) and/or to establish the quantitative light requirements (Dzhaparidze, 1974; Axelsson *et al.*, 1979). Detailed investigations on the effect of light on anthocyanin synthesis and of some enzymes involved in mustard seedlings (Blaauw-Jansen, 1974; Mohr *et al.*, 1974, 1979; Drumm and Mohr, 1974; Drumm *et al.*, 1975; Steinitz *et al.*, 1976, 1979; Steinitz and Bergfeld, 1977; Buehler *et al.*, 1978; Kinnersley and Davies, 1976, 1977), red cabbage (Peckel and Hathout-Bassim, 1974 a,b; Mancinelli and Rabino, 1975; Mancinelli *et al.*, 1975; Rabino *et al.*, 1977; Mancinelli and Walsh, 1979), buckwheat (Tokhver, 1976; Tokhver and Margna, 1978; Kefeli and Amrhein, 1977a,b) and *Spirodela* (Mancinelli, 1977) showed or reconfirmed the involvement of phytochrome in the above reactions.

Similar investigations with sorghum (Drumm and Mohr, 1978) and maize seedlings (Duke and Naylor, 1974, 1976a,b; Duke *et al.*, 1976; Styles and Ceska, 1977; McCormic, 1978; Tselas *et al.*, 1979) indicated that a HIR system is responsible for anthocyanin production in these plants. Thus HIR of anthocyanin accumulation has been usually interpreted either in terms of phytochrome, or of another, as yet unknown, photoreceptor. The above investigations now suggest the presence and function of phytochrome in these two plants and seem to rule out the controversial contribution of photosynthesis to the HIR anthocyanin accumulation.

There is, however, a serious flaw in attempting to correlate the activity of PAL (phenylalanine-ammonia-lyase) directly to the synthesis of anthocyanins. While PAL is an important enzyme in anthocyanin biosynthesis, its reaction product, cinnamic acid, and its hydroxylated and activated form (see Chapter 11) do not enter the flavonoid path exclusively. The activated hydroxycinnamic acids also enter in transformations leading to the biosynthesis of lignin and to glucose, quinic and tartaric acid derivatives, and are also the major acylating components of complex flavonoids and anthocyanins. Therefore only a fraction of the enzymic transformation products of phenylalanine is converted directly into anthocyanins. This is why investigations on the activity of this enzyme do not permit a direct correlation with anthocyanin production. To establish the true effect of phytochrome on the biosynthesis of anthocyanins, an enzyme, such as a specific UDP-glucose: anthocyanidin 3-*O*-glucosyltransferase, or other enzymes located toward the end of the biosynthetic path (see Chapter 11), should be investigated. An observation in the maize system (Duke and Naylor, 1976) that  $P_{fr}$  controls an enzymic reaction other than PAL supports this proposition.

Reports on the direct effect of UV light on anthocyanin formation (Balazs and Toth, 1974; Wellmann, 1975; Wellman *et al.*, 1976; Lindoo and Caldwell, 1978) are suggestive of a specific UV photoreceptor system in some plants. While such a system cannot be excluded presently, it is also possible that anthocyanin production upon UV irradiation is a photo-independent stress response.



Similarly, the effect of 'penetrant carriers' in relation to photocontrol (Dumortier and Vendrig, 1978) could also be due to the chemical stress caused by the compounds used.

### 3.11 BIOSYNTHESIS OF ANTHOCYANINS

Since the biosynthesis of all flavonoids is covered in detail in Chapter 11, only certain aspects of anthocyanin biosynthesis are described here. Phenylalanine ammonia lyase (PAL), the first enzyme on the phenylpropanoid path, has been further investigated (Duke and Naylor, 1976; Melin *et al.*, 1977; Faragher and Chalmers, 1977; Heinzmann and Seitz, 1977; Tan, 1979, 1980) in relationship to anthocyanin production. As mentioned in the previous section (3.10) it is difficult to correlate PAL activity directly with anthocyanin production because of the involvement of its product(s) in other pathways. In rye and radish seedlings, no direct relationship between the above-discussed parameters could be established (Margna *et al.*, 1974b,c). Feeding experiments with phenylalanine indicate that exogenous material does not equilibrate with the endogenous pool of this precursor. It also appears that enzymic complexes responsible for the synthesis of different flavonoids are not in an equal position regarding their capability of consuming common precursors (Margna and Margna, 1978). A closer relationship between phenylpropanoid accumulation and anthocyanin biosynthesis (Braun and Seitz, 1975) may exist in tissue cultures, where lignification reactions play only a minor role. The solubility of precursors used in feeding experiments may also play an important role. Solubility properties of phenylalanine and cinnamic acid may explain the preferential uptake of the former and its incorporation into anthocyanins in *Petunia* (Steiner, 1975, 1977).

Investigations on genetically blocked mutants of *Callistephus* (Kuhn *et al.*, 1978), *Petunia* (Forkmann and Kuhn, 1979) and in tapetum sections of *Tulipa* (Suetfeld and Wiermann, 1980) indicated that chalcones are the first  $C_{15}$  intermediates in the pathway. Isolation of a chalcone synthase from *Tulipa* anther tapetum sections, producing naringenin chalcone at the interphase of an acidic biphasic system, seems to confirm this. This would also explain the necessity of the chalcone flavanone isomerase in the biosynthetic path. The presence of  $\beta$ -mercaptoethanol in the incubation assay, which is known to cause the premature release of 'short chain release products' (Hrazdina *et al.*, 1976), and the strong acidity of the medium (pH 4–4.8) cannot presently exclude the possibility that the chalcone is prematurely released owing to the stress effect of  $\beta$ -mercaptoethanol or the low pH on the 'flavanone synthase'. Previous investigations with *Haplopappus gracilis* tissue culture (Wellman *et al.*, 1976), petals of *Hippeastrum* and *Tulipa* (Hrazdina *et al.*, 1978) red cabbage seedlings (Hrazdina and Creasy, 1979) and *Pisum*, *Phaseolus*, *Brassica* and *Spinacia* seedlings (Hrazdina *et al.*, 1980) indicated 'flavanone synthase' as the enzyme responsible for the establishment of the  $C_{15}$  flavonoid skeleton. Further

transformation of the naringenin so produced to eriodictyol by a microsomal preparation and of dihydrokaempferol to dihydroquercetin from *Haplopappus gracilis* cultures (Fritsch, 1974; Fritsch and Grisebach, 1975) suggest that in some plants the establishment of the hydroxylations (or generally substitution) pattern of the B ring in flavonoids occurs *after* establishment of the C<sub>15</sub> skeleton. Supporting this view are sequential and genetically controlled investigations on anthocyanin biosynthesis in *Antirrhinum majus* (Harrison and Stickland, 1974, 1978; Stickland and Harrison, 1974), *Petunia* (Kho, 1978; Tabak *et al.*, 1978), *Matthiola* (Forkmann, 1977a,b), *Pisum* (Statham and Crowden, 1974) and *Silene dioica* (Kamsteeg *et al.*, 1976), and the substrate-specificity experiments of hydroxycinnamate:CoA-ligase from anthocyanin-containing and anthocyanin-free carrot cell cultures (Heinzmann *et al.*, 1977). Contrary to these data are the results of Endress (1974a,b), whose chalcone-feeding experiments indicate preferential incorporation of hydroxylated and methoxylated chalcone glucosides into corresponding anthocyanins.

The major difference between the biosynthetic path of anthocyanins and that of flavone and flavonol glycosides is the reduction of the 4-carbonyl in the former, followed by water abstraction. The only information available on these parts of the biosynthetic path is indirect, obtained from feeding experiments with dihydroquercetin and/or its glycoside (Kho *et al.*, 1975, 1977; Kho, 1979; Stickland and Harrison, 1977). These experiments uniformly show the incorporation of this compound into cyanidin and delphinidin. Naringenin, naringin, kaempferol and quercetin were not converted. From these data the anthocyanin path *via* dihydroflavanol  $\rightarrow$  flavan-3, 4-diol  $\rightarrow$  flav-3-ene  $\rightarrow$  anthocyanidin (anhydrobase) seems to emerge as the mechanism in plants. The exact biosynthetic mechanisms can however only be established by isolation and identification of every enzyme in the pathway.

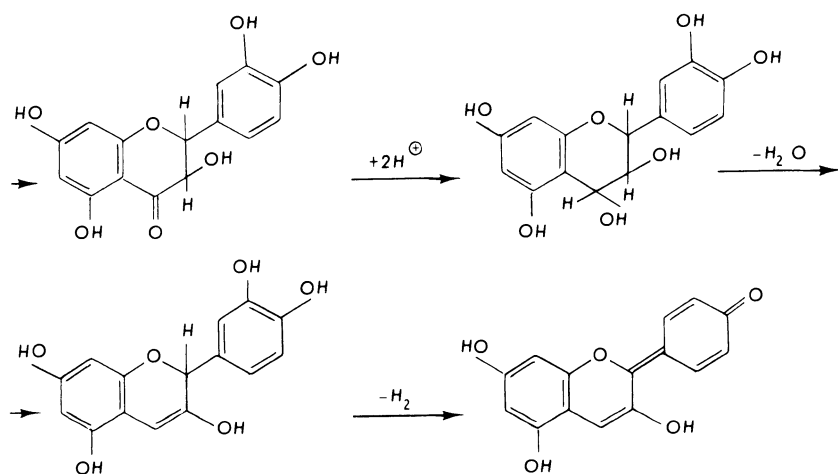


Fig. 3.2 Schematic biosynthetic paths of anthocyanidin from naringenin.

Direct methylation experiments with anthocyanins have not been carried out yet. Data concerning this are available from a genetically designed experiment indicating the conversion of petunidin glycosides into malvidin glycosides (Wiering and DeVlaming, 1977), suggesting that methylation here, similarly to other flavonoid compounds, is among the last steps in biosynthesis. Glycosylation and acylation are the last steps in flavonoid, hence also anthocyanin, biosynthesis. Experiments with *Silene dioica* (Kamsteeg *et al.*, 1979), maize (Dooner and Nelson, 1977a,b) and *Impatiens* (Strack and Mansell, 1979) confirm this (see Chapter 11) and also the *de novo* synthesis of some of the enzymes involved. In tissue cultures of *Daucus carota* the size of the cell aggregates seems to be one of the determining factors for an increased activation of anthocyanin biosynthesis (Seitz, 1976; Kinnersley and Dougall, 1980). In intact plants the accumulation of sugars seems to coincide with the activation of this pathway (Creasy, 1974; Ishikura, 1977; Maekawa and Nakamura, 1978).

Recently, there has been speculation about the localization of enzymic activities; it has been suggested (Fritsch and Grisebach, 1975), that some of the enzymic activities associated with anthocyanin (flavonoid) biosynthesis may occur on or in the tonoplast, or in the vacuolar sap. There were also suggestions that anthocyanins (and other flavonoids) can be produced in chloroplasts (Ranjeva *et al.*, 1977; McClure, 1975; Banerji and Sharma, 1979). Experiments with protoplasts, vacuoles and tonoplasts isolated from *Hippeastrum* and *Tulipa* (Hrazdina *et al.*, 1978) and with intact chloroplast preparations obtained from *Pisum*, *Phaseolus*, *Brassica* and *Spinacia* cultivars (Hrazdina *et al.*, 1980) showed that none of the above subcellular sites is the location of the anthocyanin (and flavonoid) biosynthesis. It is thought presently that the overall conversion of phenylalanine and malonyl-CoA to anthocyanins and other flavonoids occurs near the endoplasmic reticulum (ER) by cytoplasmic and ER-bound enzymes acting in close proximity to each other. The anthocyanins and other flavonoids produced are then transported by an unknown transport mechanism to the central vacuole of the cells, where they accumulate.

### 3.12 EFFECT OF PHYSIOLOGICALLY ACTIVE CHEMICALS ON THE BIOSYNTHESIS OF ANTHOCYANINS

The use of synthetic growth regulators, herbicides and other physiologically active compounds in agriculturally important plants, or in tissue cultures, can either stimulate (Table 3.2), or inhibit (Table 3.3) anthocyanin synthesis in the plants. While it is not possible at present to generalize about the chemicals which produce these effects, it seems that kinetin-type compounds seem to promote and auxin analogues inhibit anthocyanin synthesis.

The biochemical action of these compounds is not clear, with two exceptions. These exceptions are the direct action of  $\alpha$ -amino-oxy- $\beta$ -phenylpropionic acid and glyphosate (*N*-phosphomethylglycine). The action of  $\alpha$ -amino-oxy- $\beta$ -

Table 3.2 Chemicals promoting anthocyanin synthesis

| Compound                                                                      | Plant                        | Reference                           |
|-------------------------------------------------------------------------------|------------------------------|-------------------------------------|
| 6-Benzylaminopurine                                                           | <i>Saintpaulia ionantha</i>  | Jungnickel (1976)                   |
| Benzyladenine                                                                 | <i>Helianthus</i> sp.        | Servettaz <i>et al.</i> (1975a,b)   |
| CGA-15281 (?) R-27969 (?)                                                     | <i>Vaccinium macrocarpon</i> | Devlin and Demoranville (1978)      |
| 2-Chloroethyltrimethyl ammonium chloride                                      | <i>Primula obconica</i>      | Abou-Zied and Bakry (1978)          |
| PRB-8 [ $\alpha$ -chloro- $\beta$ -(3-chloro- <i>O</i> -tolyl) propionitrile] | <i>Malus pumila</i>          | Clijsters (1974)                    |
| <i>NN</i> -Dimethylformamide                                                  | <i>Phaseolus aureus</i>      | Dumortier and Vendrig (1978)        |
| Dimethyl sulphoxide                                                           |                              |                                     |
| 2,2-Dimethylhydrazide                                                         | <i>Primula obconica</i>      | Abou-Zied and Bakry (1978)          |
| Di-1- <i>p</i> -menthene (Wilt-pruf)                                          | <i>Malus</i> sp.             | Creasy (1976)                       |
| Cytokinin                                                                     | <i>Olea europaea</i>         | Shulman and Lavee (1976)            |
| EDTA                                                                          | <i>Brassica oleracea</i>     | Hathout-Bassim and Pecket (1975)    |
|                                                                               | <i>Spirodela oligorhiza</i>  | Elliott (1977)                      |
| Ethylene                                                                      | <i>Sinapis alba</i>          | Buehler <i>et al.</i> (1978)        |
|                                                                               | <i>Sorghum vulgare</i>       | Craker (1975)                       |
| Ethephon (2-chloroethylphosphonic acid)                                       | <i>Ficus carica</i>          | Puech <i>et al.</i> (1976)          |
|                                                                               | <i>Vitis vinifera</i>        | Steenkamp <i>et al.</i> (1977)      |
| Kinetin                                                                       | <i>Vaccinium</i> sp.         | Shawa (1979)                        |
| $\alpha$ -Naphthaleneacetic acid                                              | <i>Brassica oleracea</i>     | Pecket and Hathout-Bassim (1974a,b) |
|                                                                               | <i>Saintpaulia ionantha</i>  | Jungnickel (1976)                   |

**Table 3.3** Chemicals inhibiting anthocyanin synthesis

| Compound                                               | Plant                                                                     | Reference                         |
|--------------------------------------------------------|---------------------------------------------------------------------------|-----------------------------------|
| Abscic acid                                            | <i>Zea mays</i>                                                           | Pilet and Takahashi (1979)        |
| Actinomycin D                                          | <i>Raphanus sativus</i>                                                   | Guruprasad and Laloraya (1980)    |
| Amino-oxyacetate                                       | <i>Helianthus annuus</i> , <i>Sinapis alba</i>                            | Gerhardt (1974)                   |
| N-(phosphomethyl)glycine (Glyphosate)                  | <i>Fagopyrum esculentum</i>                                               | Amrhein (1979)                    |
|                                                        | <i>Glycine max</i>                                                        | Hoagland <i>et al.</i> (1979)     |
|                                                        | <i>Zea mays</i>                                                           | Duke and Hoagland (1978)          |
| $\alpha$ -Amino-oxy- $\beta$ -phenylpropionic acid     | <i>Fagopyrum esculentum</i>                                               | Amrhein <i>et al.</i> (1980)      |
|                                                        | <i>Ipomea tricolor</i> , <i>Catharanthus roseus</i> , <i>Brassica</i> sp. | Amrhein and Hollaender (1979)     |
| Cycloheximide                                          | <i>Elodea densa</i>                                                       | Witztum (1978a,b)                 |
| Ethylene                                               | <i>Solanum tuberosum</i>                                                  | Mingo-Castel <i>et al.</i> (1976) |
| Ethylenediamine-di-O-hydroxyphenyl acetic acid (EDDHA) | <i>Spirodela punctata</i>                                                 | Scharfetter <i>et al.</i> (1978)  |
| Ethyl methanesulphonate                                |                                                                           |                                   |
| Gibberellic acid                                       | <i>Amaranthus tricolor</i>                                                | Behera and Patnaik (1975)         |
|                                                        | <i>Lycopersicon</i> sp.                                                   | Aung and Bryan (1974)             |
|                                                        | <i>Daucus carota</i>                                                      | Seitz and Heinzmann (1975)        |
|                                                        | <i>Fagopyrum esculentum</i>                                               | Margna <i>et al.</i> (1978)       |
|                                                        | <i>Fagopyrum esculentum</i>                                               | Amrhein <i>et al.</i> (1976)      |
|                                                        | <i>Phaseolus vulgaris</i>                                                 | Curtis and John (1975)            |
|                                                        | <i>Phaseolus aureus</i>                                                   | Geuns (1977)                      |
|                                                        | <i>Glycine max</i>                                                        | Hoagland (1980)                   |
| Hydroxylamine                                          |                                                                           |                                   |
| Indoleacetic acid, auxin analogues                     |                                                                           |                                   |
| Malformin                                              |                                                                           |                                   |
| Metryapone                                             |                                                                           |                                   |
| Paraquat (1,1'-dimethyl-4,4'-bipyridinium ion)         |                                                                           |                                   |

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phenylpropionic acid has been shown to be competitive inhibition of phenylalanine ammonia-lyase (Amrhein and Hollaender, 1979). It is presently not known if the inhibition is based purely on lack of substrate for further enzymic transformation, or if it is caused by the absence of induction or activation of further enzymes in the path.

Feeding experiments with glyphosate in soybean seedlings suggested that the inhibition of anthocyanin synthesis is caused by the inhibitory effect of the substance at some point on aromatic amino acid biosynthesis (Duke *et al.*, 1979) and a concomitant increase in PAL activity that resulted in a depletion of the phenylalanine pool (Duke *et al.*, 1980). Recent investigations on the effect of this compound in buckwheat show that its direct action is the inhibition of shikimate conversion to chorismate (Amrhein *et al.*, 1980). A diminished production of phenylalanine, and thus depletion of substrate for the phenylpropanoid and flavonoid pathways results. Since phenylalanine is also an essential substrate for protein biosynthesis, it would be interesting to learn if the decreased production of this amino acid affects only the secondary metabolic path, or if it also interferes with the synthesis of protein in these plants.

### 3.13 PHYSIOLOGICAL ROLE OF ANTHOCYANINS

Physiological properties have been attributed to anthocyanins in both plants and animals. In plants the presence of these compounds is associated with resistance to pathogens in species of *Brassica* (Weisaeth, 1976), sunflower (Burlov and Kostyuk, 1976), pea seedlings (Kraft, 1977; Muehlbauer and Kraft, 1978), maize (Hammerschmidt and Nicholson, 1977) and roots of avocado trees (VanLelyveld and Bester, 1978). Anthocyanins have also been implicated in effecting the growth of *Diplodia maydis* in liquid cultures (Larson and Bussard, 1979), as rhizobium specific markers in lupin nodules (Caradus and Silvester, 1979); as enhancers of photosynthesis in leaves of tropical rain-forest plants (Lee *et al.*, 1979); or regulators of photosynthesis in some woody plant species grown in the Far East (Chernyshev, 1975). In some palm species they are thought to provide protection against herbivores by causing the leaves to appear brown (thus seemingly dry) in combination with chlorophyll (Stone, 1979). Their presence in the seeds or seed coats of some desert plants is thought to prevent germination (Makhamadzhinov, 1975).

All the evidence presented above is circumstantial at best, and no direct role of anthocyanins has been shown. Our present knowledge on their physiological properties does not permit firm conclusions. The protective effect of anthocyanins in plants against herbivores seems to lack support, since the compounds do not have any pronounced taste even at high concentrations. The physiological effect of anthocyanins in mammals, if any, seems to be related to the prevention of capillary fragility. This phenomenon was recently reviewed by Pourrat (1977) and Proserpio (1977). In addition to investigations on their stability in

pharmaceutical preparations (Bonati and Crippa, 1978), their effect in rats (Lietti and Forni, 1975, 1976) and mechanism of action has been studied (Mian *et al.*, 1977; Robert *et al.*, 1977; Lagrue *et al.*, 1979; Detre and Jellinek, 1979). It has also been suggested that anthocyanins provide protection against UV radiation (Kano and Miyakoshi, 1975, 1976).

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### CHECK LIST OF ALL KNOWN ANTHOCYANIDINS AND ANTHOCYANINS

- |                                                  |                                                      |
|--------------------------------------------------|------------------------------------------------------|
| 1 Apigeninidin (5,7,4'-tri-OH flavylum)          | 24 3-sophoroside                                     |
| 2 5-glucoside (gesnerin)                         | 25 3-glucosylxyloside                                |
| 3 Adientum 1 [apigeninidin (?) glycoside]        | 26 3-rhamnosylgalactoside                            |
| 4 Dryopteris 1 [apigeninidin (?) glycoside]      | 27 3-rhamnoside-5-glucoside                          |
| 5 Luteolinidin (5,7,3',4'-tetra-OH flavylum)     | 28 3-robinobioside*                                  |
| 6 5-glucoside                                    | 29 3-rutinoside                                      |
| 7 5-diglucoside                                  | 30 3-gentiotrioside                                  |
| 8 Adientum 2 [luteolinidin (?) glycoside]        | 31 3-(2 <sup>G</sup> -glucosylrutinoside)            |
| 9 Dryopteris 2 [luteolinidin (?) glucoside]      | 32 3-galactoside-5-glucoside                         |
| 10 Pteris 1 [luteolinidin (?) glycoside]         | 33 3,5-diglucoside                                   |
| 11 Pteris 2 [luteolinidin (?) glycoside]         | 34 3,7-diglucoside                                   |
| 12 Tricetinidin (5,7,3',4',5'-penta-OH flavylum) | 35 3-rutinoside-5-glucoside                          |
| 13 5-(?) glucoside                               | 36 3-sambubioside-5-glucoside                        |
| 14 3,5-diglucoside                               | 37 3-sophoroside-5-glucoside                         |
| 15 Pelargonidin (3,5,7,4'-tetra-OH flavylum)     | 38 3-sophoroside-7-glucoside                         |
| 16 3-galactoside                                 | 39 3-(4'''-p-coumarylrhamnoglucoside)*               |
| 17 3-glucoside                                   | 40 3,5-diglucoside malonyl ester                     |
| 18 3-rhamnoside                                  | 41 3,5-diglucoside-p-coumaric acid ester (monardein) |
| 19 5-glucoside                                   | 42 3,5-diglucoside-caffeic acid ester (salvianin)    |
| 20 7-glucoside                                   | 43 3-(p-coumarylglucoside)-5-glucoside               |
| 21 3-gentiobioside                               | 44 3-(caFFEylglucoside)-5-glucoside                  |
| 22 3-lathyroside                                 | 45 3-(p-coumarylrutinoside)-5-glucoside              |
| 23 3-sambubioside                                | 46 3-(p-coumarylsophoroside)-5-glucoside             |
|                                                  | 47 3-(dicaffeYldiglucoside)-5-glucoside              |
|                                                  | 48 3-(ferulylsophoroside)-5-glucoside                |

- 49 3-(*p*-coumarylcaFFEYldiglucoside)-5-glucoside
- 50 3-(*p*-coumarylferulylsambubioside)-5-glucoside
- 51 3-(dicaffeYldiglucoside)-5-glucoside
- 52 3-(*p*-coumaryldicaffeYldiglucoside)-5-glucoside
- 53 3-(di-*p*-hydroxybenzoylrutinoside)-7-glucoside\*
- 54 3-diglucoside-5-glucoside-*p*-coumaric acid ester (raphanusin A)
- 55 3-diglucoside-5-glucoside-ferulic acid ester (raphanusin B)
- 56 3-rhamnoglucoside-5-glucoside-*p*-coumaric acid ester (pelanin)
- 57 3-xylosylglucoside-5-glucoside-*p*-coumaric-ferulic acid ester (matthiolanin)
- 58 Cyanidin (3,5,7,3',4'-penta-OH flavylium)
- 59 3-arabinoside
- 60 3-galactoside
- 61 3-glucoside
- 62 3-rhamnoside
- 63 5-glucoside
- 64 4'-glucoside
- 65 3-arabinosylgalactoside
- 66 3-arabinosylglucoside
- 67 3-gentiobioside
- 68 3-lathyroside
- 69 3-robinobioside\*
- 70 3-rutinoside
- 71 3-sambubioside
- 72 3-sophoroside
- 73 3-xylosylarabinoside
- 74 3-gentiotrioside
- 75 3-(2<sup>G</sup>-glucosylrutinoside)
- 76 3-rhamnosyldiglucoside
- 77 3-xylosylglucosylgalactoside\*
- 78 3-(2<sup>G</sup>-xylosylrutinoside)
- 79 3-arabinoside-5-glucoside
- 80 3-galactoside-5-glucoside
- 81 3-rhamnoside-5-glucoside
- 82 3,5-diglucoside
- 83 3,7-diglucoside
- 84 3-glucoside-7-rhamnoside
- 85 3,4'-diglucoside
- 86 3-rutinoside-5-glucoside
- 87 3-sambubioside-5-glucoside
- 88 3-sophoroside-5-glucoside
- 89 3-rhamnosylglucoside-7-xyloside
- 90 3-acetylglucoside
- 91 3-*p*-coumarylglucoside (hyacinthin)
- 92 3-caFFEYlglucoside
- 93 3-*p*-coumarylgentiobioside
- 94 3-caFFEYlgentiobioside
- 95 3-*p*-coumarylxylosylglucoside\*
- 96 3-caFFEYlglucosylarabinoside\*
- 97 3-ferulylglucosylgalactoside\*
- 98 3-sinapylglucosylgalactoside\*
- 99 3-caFFEYlrhamnosylglucoside
- 100 3-caFFEYlrhamnosyldiglucoside
- 101 3-ferulylxylosylglucosylgalactoside\*
- 102 3,5-diglucoside malonyl ester
- 103 3,5-diglucoside-*p*-coumaric acid ester (perillanin)
- 104 3-(6-*p*-coumarylglucoside)-5-glucoside
- 105 3-(*p*-coumarylrutinoside)-5-glucoside (cyananin)
- 106 3-caFFEYlglucoside-5-glucoside
- 107 3-(*p*-coumarylsophoroside)-5-glucoside
- 108 3-malonylsophoroside-5-glucoside
- 109 3-caFFEYlsophoroside-5-glucoside
- 110 3-ferulylsophoroside-5-glucoside
- 111 3-sinapylsophoroside-5-glucoside
- 112 3-(di-*p*-coumaryl)sophoroside-5-glucoside
- 113 3-(di-ferulyl)sophoroside-5-glucoside
- 114 3-(di-sinapyl)sophoroside-5-glucoside
- 115 3-(*p*-coumarylcaFFEYl)-sophoroside-5-glucoside
- 116 Peonidin (3,5,7,4'-tetra-OH, 3'OMe flavylium)
- 117 3-arabinoside
- 118 3-galactoside
- 119 3-glucoside
- 120 3-rhamnoside
- 121 5-glucoside
- 122 3-gentiobioside
- 123 3-lathyroside
- 124 3-rutinoside
- 125 3-galactoside-5-glucoside
- 126 3,5-diglucoside
- 127 3-rhamnoside-5-glucoside
- 128 3-rutinoside-5-glucoside
- 129 3-gentiotrioside
- 130 3-glucosylrhamnosylglucoside (?)
- 131 3-acetylglucoside
- 132 3-*p*-coumarylglucoside
- 133 3-caFFEYlglucoside
- 134 3-*p*-coumarylgentiobioside
- 135 3-caFFEYlgentiobioside
- 136 3-(*p*-coumarylglucoside)-5-glucoside
- 137 3-(*p*-coumarylrutinoside)-5-glucoside (peonanin)

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- 138 3-(*p*-coumarylsophoroside)-5-glucoside
- 139 3-(di-*p*-coumaryl)glucoside
- 140 3-(di-caFFEylsophoroside)-5-glucoside
- 141 3-(*p*-coumarylcaFFEylsophoroside)-5-glucoside
- 142 Delphinidin(3,5,7,3',4',5'-hexa-OH flavylium)
- 143 3-arabinoside
- 144 3-galactoside
- 145 3-glucoside
- 146 3-rhamnoside
- 147 3-rutinoside
- 148 3-sambubioside
- 149 7-galactoside
- 150 7-glucoside
- 151 3-glucosylglucoside
- 152 3-lathyroside
- 153 3-rhamnosylgalactoside
- 154 3,5-diglucoside
- 155 3-rhamnoside-5-glucoside
- 156 3-rutinoside-5-glucoside
- 157 3-acetylglucoside
- 158 3-*p*-coumarylglucoside
- 159 3-caFFEylglucoside
- 160 3-(di-*p*-coumaryl)glucoside
- 161 3,5-diglucoside malonyl ester
- 162 3-(*p*-coumarylglucoside)-5-glucoside (awobanin)
- 163 3-(*p*-coumarylrutinoside)-5-glucoside (delphanin)
- 164 3-(*p*-coumarylsophoroside)-5-glucoside
- 165 3-caFFEylglucoside-5-glucoside
- 166 3-(di-caFFEylrutinoside)-5-glucoside
- 167 3-rutinoside-5,3',5'-triglucoside-caFFEylferulyl-*p*-coumaryl ester\*
- 168 Petunidin(3,5,7,3',4'-penta-OH-5'-OMe flavylium)
- 169 3-arabinoside
- 170 3-galactoside
- 171 3-glucoside
- 172 3-rhamnoside
- 173 3-rutinoside
- 174 5-glucoside
- 175 3-gentiobioside
- 176 3-sophoroside
- 177 3,5-diglucoside
- 178 3-rhamnoside-5-glucoside
- 179 3-rutinoside-5-glucoside
- 180 3-gentiotrioside
- 181 3-acetylglucoside
- 182 3-(*p*-coumarylglucoside)
- 183 3-caFFEylglucoside
- 184 3-(dicaffeyl)-glucoside
- 185 3-(*p*-coumarylglucoside)-5-glucoside
- 186 3-(*p*-coumarylrutinoside)-5-glucoside (petanin)
- 187 3-(di-*p*-coumaryl)rutinoside (guineesin)
- 188 Malvidin(3,5,7,4'-tetra-OH. 3',5'-diOMe flavylium)
- 189 3-arabinoside
- 190 3-galactoside
- 191 3-glucoside
- 192 3-rhamnoside
- 193 5-glucoside
- 194 3-gentiobioside
- 195 3-laminaribioside\*
- 196 3-rutinoside
- 197 3,5-diglucoside
- 198 3-rhamnoside-5-glucoside
- 199 3-rutinoside-5-glucoside
- 200 3-gentiotrioside
- 201 3-arabinosylglucoside-5-glucoside
- 202 3-sophoroside-5-glucoside\*
- 203 3-acetylglucoside
- 204 3-(*p*-coumarylglucoside)
- 205 3-caFFEylglucoside
- 206 3-(di-*p*-coumaryl)-glucoside
- 207 3,5-diglucoside acetyl ester
- 208 3,5-diglucoside-*p*-coumaric acid ester (tibouchinin)
- 209 3-(*p*-coumarylglucoside)-5-glucoside
- 210 3-caFFEylglucoside-5-glucoside
- 211 3-(*p*-coumarylrutinoside)-5-glucoside (negretein)
- 212 Aurantinidin(3,5,6,7,4'-penta-OH flavylium)
- 213 3-sophoroside
- 214 3,5-diglucoside
- 215 Rosinidin(3,5,4'-tri-OH-7,3'-di-OMe flavylium)
- 216 3,5-diglucoside
- 217 Pulchellidin(3,7,3',4',5'-penta-OH-5-OMe flavylium)
- 218 3-glucoside
- 219 Europinidin(3,7,4',5'-tetra-OH-5,3'-di-OMe flavylium)
- 220 3-glucoside
- 221 3-galactoside
- 222 Capensinidin(3,7,4'-tri-OH-5,3',5'-tri-OMe flavylium)
- 223 3-rhamnoside
- 224 Hirsutidin(3,5,4'-tri-OH-7,3',5'-tri-OMe flavylium)
- 225 3,5-diglucoside

\* Newly reported during 1975–1980.

## CHAPTER FOUR

# *Flavones and Flavonols*

ECKHARD WOLLENWEBER

### 4.1 FLAVONOIDS WITH HYDROXY AND/OR METHOXY SUBSTITUTION

Most reports on the identification of known flavonoids in new plant sources as well as those on novel flavonoids naturally deal with the two most abundant classes, the flavones and flavonols. For this chapter we have listed all references to the occurrence of flavone and flavonol aglycones which have appeared from 1975 to 1980, and also include such earlier references as were overlooked in the relevant chapters of 'The Flavonoids' (1975). Emphasis is given to the natural distribution of these compounds. The data are collected in Tables 4.1 and 4.2 which cite substances, plant sources and references. Since 1974, some 50 flavones and 60 flavonols with common substitution patterns have been described as novel compounds. Many are simply new methyl ethers of known compounds. The structures are arranged throughout the Tables by number and arrangement of substituents in ring A, followed by ring B. Wherever possible, the plant organs from which the compounds have been isolated are cited. In cases where authors have extracted the 'whole plant' or 'aerial parts', it does not necessarily follow that the compound is present in all parts, since these substances are often specifically located in certain organs only. In all cases where free aglycones are encountered, especially highly methylated flavonoids, it is likely that they occur externally, or are associated with secretory structures and are correlated with the production of other lipophilic secondary compounds, mainly of terpenoid origin. The occurrence and distribution of free flavonoid aglycones in nature has recently been reviewed (Wollenweber and Dietz, 1981).

Except for very common compounds, we have attempted to cite all plants from which flavonoids have been reported. In order to avoid excessive references, in some cases only the most recent literature is quoted and original reports are omitted. Plant sources of such widespread compounds as apigenin, luteolin or kaempferol, are given only in those cases where it is obvious that they occur externally. Those compounds which have as yet only been found in glycosidic combinations are also included in order to provide a complete list of all known flavones and flavonols. However, references are given only for those which have been reported for the first time since 1975. The natural occurrence of flavones and flavonols in bound form is covered separately in Chapter 5.

Table 4.1 List of flavones reported between 1975 and 1980 and their plant sources

| Substitution     | Trivial name          | Plant source                                            | References                               |
|------------------|-----------------------|---------------------------------------------------------|------------------------------------------|
| 5-OH             | Flavone               |                                                         | Synthesis: Kasahara <i>et al.</i> (1974) |
| 2'-OH            | Primuletin            |                                                         | Synthesis: Ashihara <i>et al.</i> (1977) |
| (5,6-di-OH)      |                       |                                                         |                                          |
| 6-Me             |                       |                                                         |                                          |
| 5,6-di-Me        |                       |                                                         |                                          |
| 5,7-di-OH (G)    | Chrysin               | <i>Oroxylum indicum</i> (Bign.) stem bark               | Subramanian and Nair (1972a)             |
|                  |                       | <i>Escallonia</i> , 3 spp. (Sax.), leaf                 | Wollenweber (1981a)                      |
|                  |                       | <i>Flourensia resinosa</i> (Ast.), leaf                 | Wollenweber (unpublished)                |
|                  |                       | <i>Andrographis serpyllifolia</i> , (Acanth.), leaf     | Govindachari <i>et al.</i> (1968)        |
|                  |                       | <i>Flourensia resinosa</i> (Ast.), leaf                 | Wollenweber (unpublished)                |
| 7-Me             | Tectochrysin          | <i>Helichrysium herbaceum</i> (Ast.), aerial parts      | Bohlmann <i>et al.</i> (1979)            |
| 5,7-di-Me*       | Primetin              |                                                         |                                          |
| 5,8-di-OH        |                       |                                                         |                                          |
| 5,2'-di-OH       |                       |                                                         |                                          |
| 7,4'-di-OH (G)   |                       |                                                         |                                          |
| 3',4'-di-OH (G)  |                       |                                                         |                                          |
| 5,6,7-tri-OH (G) |                       |                                                         |                                          |
| 6-Me (G)         | Baicalin              | <i>Primula</i> spp. (Prim.), farinose exudate           | Wollenweber (1974b)                      |
| 7-Me (G only)    | Oroxylon (oroxylon A) |                                                         |                                          |
| 6,7-di-Me*       | Negletein             |                                                         |                                          |
| 5,6,7-tri-Me     |                       | <i>Popowia cauliflora</i> (Annon.), stem                | Panichpol and Waterman (1978)            |
|                  |                       | <i>Callicarpa japonica</i> (Verb.)                      | Hosozawa <i>et al.</i> (1972)            |
|                  |                       | <i>Kickxia lanigera</i> (Scroph.), whole plant          | Pinar (1973)                             |
|                  |                       | <i>Colebrookia oppositifolia</i> , leaf                 | Ahmad <i>et al.</i> (1974)               |
|                  |                       | <i>Popowia cauliflora</i> (Annon.), stem                | Panichpol and Waterman (1978)            |
|                  |                       | synthesis:                                              | Matsuura <i>et al.</i> (1978)            |
| 5,7,8-tri-OH (G) | Norwogonin            |                                                         |                                          |
| 8-Me             | Wogonin               | <i>Scutellaria rivularis</i> (Scroph.), root            | Chou (1978)                              |
| 7,8-di-Me*       |                       | <i>Scutellaria rivularis</i> (Scroph.), root            | Chou (1978)                              |
|                  |                       | <i>Gnaphalium pellitum</i> (Ast.), inflorescence        | Escarria <i>et al.</i> (1977)            |
|                  |                       | <i>Andrographis paniculata</i> (Acanth), tissue culture | Jalal <i>et al.</i> (1979)               |

|                                                                                                                 |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-----------------------------------------------------------------------------------------------------------------|------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5,7,8-tri-Me*                                                                                                   |                              | <i>Helichrysium mundii</i> (Ast.), aerial parts<br><i>Actinodaphne madraspatana</i> (Laurac.), heartwood                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Bohlmann <i>et al.</i> (1978)<br>Adinarayana and Gunasekar (1979)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| (5,6,2'-tri-OH) 5,6,2'-tri-Me<br>(5,6,3'-tri-OH) 5,6,3'-tri-Me<br>(5,7,2'-tri-OH) 7-Me (G)<br>5,7,4'-tri-OH (G) | Echioidimin<br>Apigenin      | ° <i>Sabia glutinosa</i> (Lab.), aerial parts<br><i>Larrea divaricata</i> , <i>L. tridentata</i> (Zyg.), leaf-resin<br><i>Cheilanthes</i> spp., <i>Notholaena</i> spp. (Polypod.), farinose exudate on fronds<br><i>Saccharum officinarum</i> (Poac.), flower<br>° <i>Sabia glutinosa</i> (Lab.), aerial parts<br><i>Alnus</i> , <i>Betula</i> , <i>Ostrya</i> (Bet.), bud excretions<br><i>Artemisia capillaris</i> (Ast.), aerial parts<br><i>Larrea divaricata</i> , <i>L. tridentata</i> (Zyg.), leaf-resin<br><i>Cheilanthes</i> spp., <i>Notholaena</i> spp.<br><i>Pityrogramma</i> spp. (Polypod.) farinose exudate<br><i>Alnus</i> and <i>Betula</i> spp.<br><i>Ostrya japonica</i> (Bet.) bud excretions<br><i>Eupatorium tinifolium</i> (Ast.) aerial parts<br><i>Notholaena</i> spp. (Polypod.), farinose exudate on fronds<br><i>Cheilanthes</i> spp.<br>(see sect. 4.5)<br>° <i>Beyeria</i> spp. (Euphorb.), leaf, terminal branches<br>° <i>Acacia ixiohylla</i> (Leg.), leaf<br>° <i>Piper peepuloides</i> (Piper.), fruit<br><i>Alnus japonica</i> , <i>Betula</i> spp. (Bet.), bud excretions<br><i>Cheilanthes</i> spp., <i>Notholaena</i> spp., (Polypod.), farinose exudate on fronds<br><i>Baccharis crispa</i> (Ast.), aerial parts | Wollenweber (1974a)<br>Sakakibara <i>et al.</i> (1976)<br>Wollenweber (1976c)<br><br>Misra and Mishra (1979)<br>Wollenweber (1974a)<br>Wollenweber (1975b)<br>Komiya <i>et al.</i> (1976)<br>Sakakibara <i>et al.</i> (1976)<br>Wollenweber (1976b)<br>Wollenweber and Dietz (1980)<br>Wollenweber (1975b)<br><br>Moreno <i>et al.</i> (1980)<br>Wollenweber (1981b)<br>Wollenweber (unpublished)<br><br>Dawson <i>et al.</i> (1965)<br>Clark-Lewis and Daimis (1968)<br>Dhar <i>et al.</i> (1970)<br>Wollenweber (1975b)<br>Wollenweber (1976b)<br><br>Bandoni <i>et al.</i> (1978) |
| 5-Me(G)<br>7-Me (G)                                                                                             | Thevetiaflavone<br>Genkwanin |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 4'-Me (G)                                                                                                       | Acacetin                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 5,7-di-Me (G only)*<br>7,4'-di-Me (G)                                                                           |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

Table 4.1 (Contd.)

| Substitution          | Trivial name        | Plant source                                                                                        | References                                  |
|-----------------------|---------------------|-----------------------------------------------------------------------------------------------------|---------------------------------------------|
| 5,7,4'-tri-Me*        |                     | <i>Sideritis gomeræ</i> (Lam.), aerial parts                                                        | González <i>et al.</i> (1978)               |
| 5,8,2'-tri-OH         |                     | <i>Eupatorium tinifolium</i> (Ast.) aerial parts                                                    | Moreno <i>et al.</i> (1980)                 |
| 7,3',4'-tri-OH (G)    |                     | <i>Elaeagia utilis</i> (Rub.), bud excretion                                                        | Biftu and Stevenson (1978)                  |
|                       |                     | <i>Pityrogramma tartarea</i> (Polypod.),<br>farinose exudate on fronds                              | Wollenweber and Dietz (1980)                |
|                       |                     | <i>Citrus reticulata</i> (Rut.), fruit peel                                                         | Iinuma <i>et al.</i> (1980)                 |
|                       |                     |                                                                                                     | synthesis:<br>Matsuura <i>et al.</i> (1978) |
|                       |                     | <i>Juncus trifidus</i> , <i>Luzula</i>                                                              | Williams and Harborne (1975)                |
|                       |                     | <i>purpurea</i> (Juncac.), stem, leaf                                                               |                                             |
|                       |                     | <i>Salvertia convallarioides</i> ,                                                                  | Lopes <i>et al.</i> (1979)                  |
|                       |                     | <i>Vochysia cinnamomea</i> , <i>V. tucanorum</i> (Vochys.), leaf                                    |                                             |
| 3'-Me (G)             | Geraldone           | <i>Salvertia convallarioides</i>                                                                    | Lopes <i>et al.</i> (1979)                  |
|                       |                     | <i>Vochysia cinnamomea</i> (Vochys.), leaf                                                          |                                             |
| 7,4'-di-Me            | Tithonine           |                                                                                                     |                                             |
| (5,6,7,8-tetra-OH)    |                     |                                                                                                     |                                             |
| 6,7-di-Me*            |                     | <i>Helichrysum herbaceum</i> (Ast.), aerial parts                                                   | Bohlmann <i>et al.</i> (1979)               |
| 6,8-di-Me*            |                     | <i>Pityrogramma triangularis</i> var. <i>triangularis</i><br>(Polypod.), farinose exudate on fronds | Dietz <i>et al.</i> (1981)                  |
|                       |                     | <i>Helichrysum herbaceum</i> (Ast.), aerial parts                                                   | Bohlmann <i>et al.</i> (1979)               |
| 5,6,7-tri-Me*         | Alnetin             |                                                                                                     |                                             |
| 6,7,8-tri-Me          |                     | <i>Helichrysum herbaceum</i> (Ast.), aerial parts                                                   | Bohlmann <i>et al.</i> (1979)               |
| 5,6,7,8-tetra-Me      | Scutellarein        | <i>Oroxylum indicum</i> (Bign.), leaf                                                               | Subramanian and Nair (1972a)                |
| 5,6,7,4'-tetra-OH (G) |                     | <i>Clerodendron phlomidis</i> , <i>Durante repens</i> (Verb.), leaf                                 | Subramanian and Nair (1972b)                |
|                       |                     | <i>Scoparia dulcis</i> (Scroph.), leaf                                                              | Ramesh <i>et al.</i> (1979)                 |
|                       |                     | <sup>a</sup> <i>Iva nevadensis</i> (Ast.), whole plant                                              | Farkas <i>et al.</i> (1966)                 |
|                       |                     | <sup>a</sup> <i>Iva hayesiana</i> (Ast.), aerial parts                                              | Herz and Sudarsanam (1970)                  |
|                       |                     | <sup>a</sup> <i>Salvia officinalis</i> (Lam.), leaf                                                 | Brieskorn and Biechele (1971)               |
|                       |                     | <sup>a</sup> <i>Gaillardia</i> spp., <i>Helenium</i> spp.                                           | Carman <i>et al.</i> (1972)                 |
|                       |                     | <i>Hymenoxis</i> spp.                                                                               |                                             |
| 6-Me (G)              | Hispidulin, Dinatin |                                                                                                     |                                             |



|                |                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|----------------|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 7-Me (G)       |                               | <i>Plummera ambigens P. floribunda, Ratibida columnaris</i> (Ast.), leaf                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                | Sorbifolin                    | ° <i>Digitalis ferruginea</i> (Scroph.), leaf<br><i>Digitalis schischkini</i> (Scroph.), leaf<br><i>Betula verrucosa</i> (Bet.), bud excretion<br><i>Santolina chamaecyparissus</i> (Ast.), aerial parts<br>synthesis:<br><i>Pleocarpus revolutus</i> (Ast.), leaf, stem<br><i>Adenocalymma alliaceum</i> (Bign.) flower<br><i>Anvillea garcini</i> (Ast.), leaf<br><i>Scoparia dulcis</i> (Scroph.), leaf<br><i>Clerodendron inerme</i> (Verb.), leaf<br>° <i>Helichrysum viscosum</i> var. <i>bracteatum</i> (Ast.), whole plant | Imre <i>et al.</i> (1973)<br>Imre <i>et al.</i> (1977)<br>Popravko <i>et al.</i> (1979)<br>Becchi and Carrier (1980)<br>Ahluwalia <i>et al.</i> (1976)<br>Silva <i>et al.</i> (1977)<br>Rao and Rao (1980)<br>Ulubelen <i>et al.</i> (1979a)<br>Ramesh <i>et al.</i> (1979)<br>Vandantham <i>et al.</i> (1977)<br>Geissman <i>et al.</i> (1967)                                                                                                                                                                                                                                                                       |
|                | Cirsimaritin<br>(scrophulein) | ° <i>Teucrium pelium</i> (Lam.), aerial parts<br>° <i>Flourensia cernua</i> (Ast.), plant heads<br>° <i>Salvia officinalis</i> (Lam.), leaf<br><i>Salvia tomentosa</i> (Lam.), leaf<br>° <i>Helenium</i> spp. (Ast.)<br><i>Coleus aromaticus</i> (Lam.), leaf<br><i>Coleus amboinicus</i> (Lam.), leaf<br><i>Artemisia capillaris</i> (Ast.), aerial parts<br><i>Sideritis dasygnaphala</i> (Lam.), aerial parts<br><i>Brickellia californica</i> (Ast.), leaf<br><i>Digitalis thapsi</i> (Scroph.), leaf                          | Brieskorn and Biechele (1969)<br>Rao <i>et al.</i> (1970)<br>Brieskorn and Biechele (1971)<br>Ulubelen <i>et al.</i> (1979b)<br>Bierner (1973)<br>Misra <i>et al.</i> (1976)<br>Brieskorn and Riedel (1977)<br>Komiya <i>et al.</i> (1976)<br>González <i>et al.</i> (1978)<br>Mues <i>et al.</i> (1979)<br>Pascual Teresa <i>et al.</i> (1980)<br>Ahluwalia <i>et al.</i> (1976)<br>Herz <i>et al.</i> (1970)<br>Subramanian and Nair (1972b)<br>Vandantham <i>et al.</i> (1977)<br>Wollenweber (1975b)<br>Tiware and Bajpai (1977)<br>Imre <i>et al.</i> (1977)<br>González <i>et al.</i> (1978)<br>Bierner, (1978) |
| 6,4'-di-Me (G) | Pectolinarigenin              | ° <i>Hymenoxis rusbyi</i> (Ast.), aerial parts<br>° <i>Clerodendron phlomidis, Durante repens</i> (Verb.), leaf<br><i>Clerodendron inerme</i> , (Verb.), leaf<br><i>Alnus</i> spp., <i>Betula</i> spp. (Bet.), bud excretions<br><i>Cassia reniger</i> (Leg.), stem, bark<br><i>Digitalis schischkini</i> (Scroph.), leaf<br><i>Sideritis dasygnaphala</i> (Lam.), aerial parts<br><i>Plummera ambigua, P. floribunda</i> (Ast.), aerial parts                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

Table 4.1 (Contd.)

| Substitution                        | Trivial name | Plant source                                                   | References                            |
|-------------------------------------|--------------|----------------------------------------------------------------|---------------------------------------|
| 7,4'-di-Me (G)<br>6,7,4'-tri-Me (G) | Salvigenin   | <i>Brickellia californica</i> (Ast.), leaf                     | Mues <i>et al.</i> (1979)             |
|                                     |              | <i>Brickellia dentata</i> (Ast.), leaf                         | Ulubelen <i>et al.</i> (1980a)        |
|                                     |              | <i>Santolina chamaecyparissus</i> (Ast.), aerial parts         | Becchi and Carrier (1980)             |
|                                     |              | <i>Milletia pachycarpa</i> (Leg.), aerial parts                | Singhal <i>et al.</i> (1980)          |
|                                     |              | ° <i>Ageratine gilbertii</i> (Ast.) aerial parts               | Herz and Gibaja (1972)                |
|                                     |              | ° <i>Psathyrothes annua</i> (Ast.), leaf                       | Finnegan <i>et al.</i> (1972)         |
|                                     |              | ° <i>Eupatorium odoratum</i> (Ast.), whole plant               | Talapatra <i>et al.</i> (1974)        |
|                                     |              | <i>Alnus</i> spp., <i>Betula nigra</i> bud excretions          | Wollenweber (1975b)                   |
|                                     |              | <i>Salvia aethiopis</i> (Lam.), whole plant                    | Ulubelen and Uygur (1976)             |
|                                     |              | <i>Coleus amboinicus</i> (Lam.), leaf                          | Brieskorn and Riedel (1977)           |
|                                     |              | <i>Phyllanthron madagascariensis</i> (Bignon.), leaf           | Tillequin <i>et al.</i> (1977)        |
|                                     |              | <i>Sideritis dasygnaphala</i> (Lam.), aerial parts             | Gonzalez <i>et al.</i> (1978)         |
|                                     |              | <i>Brickellia dentata</i> (Ast.), leaf                         | Ulubelen <i>et al.</i> (1980a)        |
|                                     |              | <i>Ocimum canum</i> (Lam.), leaf and flower                    | Xaasan <i>et al.</i> (1980)           |
| 5,6,7,4'-tetra-Me                   |              | <i>Milletia pachycarpa</i> (Leg.), aerial parts                | Singhal <i>et al.</i> (1980)          |
|                                     |              | <i>Kickxia spuria</i> (Scroph.), aerial parts                  | Tóth <i>et al.</i> (1980)             |
|                                     |              | ° <i>Callicarpa japonica</i> (Verb.)                           | Hosozawa <i>et al.</i> (1972)         |
|                                     |              | ° <i>Kickxia lanigera</i> (Scroph.), whole plant               | Pinar (1973)                          |
|                                     |              | ° <i>Colebrookia oppositifolia</i> (Verb.), leaf               | Ahmad <i>et al.</i> (1974)            |
|                                     |              | <i>Chromolaena odorata</i> (Ast.), (= Eupat. od.) aerial parts | Barua <i>et al.</i> (1978)            |
|                                     |              | <i>Citrus</i> cult. 'calamondin' (Rut.), fruit peel            | Tatum and Berry (1978)                |
|                                     |              | <i>Kickxia spuria</i> (Scroph.), aerial parts                  | Tóth <i>et al.</i> (1980)             |
|                                     |              | synthesis:                                                     | Matsuura <i>et al.</i> (1978)         |
|                                     |              | Skulcapflavone I<br>(see Section 4.5)                          | <i>Scutellaria baicalensis</i> (Lam.) |
| 5,7,8,2'-tetra-OH (G)<br>7,8-di-Me* |              | <i>Andrographis paniculata</i> (Acanth.), tissue culture       | Jalal <i>et al.</i> (1979)            |
|                                     |              | synthesis:                                                     | Iinuma and Matsuura (1979)            |

|                        |                 |                                                                      |                                                    |
|------------------------|-----------------|----------------------------------------------------------------------|----------------------------------------------------|
| 7,8,2'-tri-Me*         | Isoscutellarein | <i>Andrographis paniculata</i> (Acan.), tissue culture synthesis:    | Jalal <i>et al.</i> (1979)                         |
| 5,7,8,4'-tetra-OH (G)  | Salvitin        | <i>Salvia plebeja</i> (Lam.), flower                                 | Farkas <i>et al.</i> (1974)                        |
| 7-Me*                  |                 |                                                                      | H. C. Gupta <i>et al.</i> (1975) (incl. synthesis) |
| 8-Me*                  | Takakin         | <i>Gardenia gummifera</i> , <i>G. lucida</i> (Rut.), dikamali gum    | S. R. Gupta <i>et al.</i> (1975)                   |
| 4-Me                   |                 | <i>Takakia ceratophylla</i> , <i>T. lepidozoioides</i> (Hepat.)      | Markham and Porter (1979)                          |
| 7,8-di-Me*             |                 | <i>Citrus reticulatum</i> (Rut.), fruit peel                         | Linuma <i>et al.</i> (1980)                        |
| 8,4'-di-Me*            | Cirsitakaogenin | <i>Cirsium japonicum</i> var. <i>takoense</i> (Ast.), leaf           | Lin <i>et al.</i> (1978)                           |
| 7,8,4'-tri-Me*         |                 | <i>Citrus reticulata</i> (Rut.), fruit peel                          | Linuma <i>et al.</i> (1980)                        |
| 5,7,8,4'-tetra-Me      |                 | <i>Citrus</i> cult. 'calamondin' (Rut.), fruit peel                  | Tatum and Berry (1978)                             |
|                        |                 | <i>Citrus reticulata</i> (Rut.)                                      | Linuma <i>et al.</i> (1980)                        |
| (5,6,2',6'-tetra-OH)   | Zapotin         |                                                                      |                                                    |
| 6,2',6'-tri-Me         | Zapotin         |                                                                      |                                                    |
| 5,6,2',6'-tetra-Me     |                 |                                                                      |                                                    |
| (5,6,3',5'-tetra-OH)   | Cerosillin      |                                                                      |                                                    |
| 5,6,3',5'-tetra-Me     | Norartocarpetin |                                                                      |                                                    |
| 5,7,2',4'-tetra-OH     | Artocarpetin    |                                                                      |                                                    |
| 7-Me                   |                 |                                                                      |                                                    |
| 5,7,2',4'-tetra-Me*    |                 | <i>Terminalia arjuna</i> (Combret.), fruit                           | Nagar <i>et al.</i> (1979)                         |
| 5,7,3',4'-tetra-OH (G) | Luteolin        | <i>Vernonia pectoralis</i> (Ast.), aerial parts                      | Bézanger-Beauquesne <i>et al.</i> (1975)           |
|                        |                 | <i>Ceratodon purpureus</i> (Ditrich.), sporophyt                     | Vandekerckhove (1978)                              |
|                        |                 | <i>Notholaena californica</i> (Polypod.), farinose exudate on fronds | Wollenweber (1977b)                                |
|                        |                 | <i>Juncus</i> spp., <i>Luzula</i> spp. (Juncac.), leaf, stem         | Williams and Harborne (1975)                       |
| 5-Me (G)*              |                 | <i>Notholaena californica</i> (Polypod.), farinose exudate           | Wollenweber (1977b)                                |
| 7-Me (G)               |                 | <i>Coleus amboinicus</i> (Lam.), leaf                                | Brieskorn and Riedel (1977)                        |
| 3-Me (G)               | Chrysoeriol     | <i>Notholaena californica</i> (Polypod.), farinose exudate on fronds | Wollenweber (1981b)                                |
|                        |                 | <i>Brickellia laciniata</i> (Ast.), leaf                             | Timmermann <i>et al.</i> (1979a)                   |
| 4-Me (G)               | Diosmetin       | <i>Stemodia viscosa</i> (Scroph.), leaf                              | Ramesh <i>et al.</i> (1979)                        |
|                        |                 | <i>Medicago x varia</i> (Leg.), seed                                 | Gehring and Geiger (1980)                          |
| 5,3'-di-Me*            |                 | <i>Vernonia flexuosa</i> (Ast.), aerial parts                        | Kiesel (1975)                                      |
| 7,3'-di-Me (G) velutin |                 | <i>Larrea divaricata</i> , <i>L. tridentata</i> (Zyg.), leaf resin   | Sakakibara <i>et al.</i> (1976)                    |
|                        |                 | <i>Notholaena californica</i> (Polypod.), farinose exudate on fronds | Wollenweber (1981b)                                |

Table 4.1 (Contd.)

| Substitution                                                                                           | Trivial name                                                                                                           | Plant source                                                                                                                                                                                                                                                                                                                                                                                                                                                   | References                                                                                                                                                                                                                                                                                                   |
|--------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 7,4'-di-Me (G) pilloin                                                                                 |                                                                                                                        | <i>Baccharis crispa</i> (Ast.), aerial parts<br><i>Lychnohora affinis</i> (Ast.), leaf, stem<br><i>Notholaena californica</i> (Polypod.), farinose exudate<br>synthesis:<br><i>Rhynchosia beddomei</i> (Leg.), leaf<br><i>Betula nigra</i> (Bet.), bud excretion<br><i>Salvia aethiopis</i> (Lam.), whole plant<br><i>Turnera diffusa</i> (Turner.), aerial parts<br><i>Lychnohora affinis</i> (Ast.), leaf, stem<br>° <i>Merillia caloxylon</i> (Rut.), fruit | Bandoni <i>et al.</i> (1978)<br>Le Quesne <i>et al.</i> (1976)<br>Wollenweber (1981b)<br>Jain and Sharma (1973)<br>Adinarayana <i>et al.</i> (1980a)<br>Wollenweber (unpublished)<br>Ulubelen and Uygun (1976)<br>Dominguez and Hinojosa (1976)<br>Le Quesne <i>et al.</i> (1976)<br>Fraser and Lewis (1974) |
| 3',4'-di-Me (G only)*<br>7,3',4'-tri-Me                                                                |                                                                                                                        | <i>Abrus precatorius</i> (Leg.), seed kernel<br>° <i>Hymenoxis scaposa</i> (Ast.), leaf                                                                                                                                                                                                                                                                                                                                                                        | Bhardwaj <i>et al.</i> (1980a)<br>Thomas and Mabry (1968)                                                                                                                                                                                                                                                    |
| 5,7,3',4'-tetra-Me*<br>(6,7,3',4'-OH)<br>6,4'-di-Me<br>(5,6,7,8,4'-penta-OH)<br>6,8-di-Me              | Abrectorin<br>Desmethoxy-<br>sudachitin                                                                                | <i>Gardenia gummifera</i> , <i>G. lucida</i> (Rub.), 'dikamali gum'<br><i>Sideritis dasygnaphala</i> (Lam.), aerial parts<br>° <i>Gardenia gummifera</i> , <i>G. lucida</i> (Rub.), 'dikamali gum'<br><i>Helianthus pumilus</i> (Ast.), whole plant<br><i>Ocimum canum</i> (Lab.), leaf and flower<br><i>Helichrysum herbaceum</i> (Ast.), aerial parts<br><i>Brickellia squarrosa</i> (Ast.),<br>synthesis:                                                   | S. R. Gupta <i>et al.</i> (1975)<br>González <i>et al.</i> (1978)<br>Krishnamurti <i>et al.</i> (1972)<br>Herz and de Groote (1977)<br>Xaasan <i>et al.</i> (1980)<br>Bohlmann <i>et al.</i> (1979)<br>Rodriguez <i>et al.</i> (1974)<br>Matsuura <i>et al.</i> (1978)                                       |
| 5,6,7,8,4'-penta-Me<br>(5,7,8,2',6'-penta-OH)<br>7,8,6'-tri-Me<br>5,6,7,3',4'-penta-OH (G)<br>6-Me (G) | Gardenin B,<br>desmethyltangeretin<br>Tangeretin (ponkanetin)<br>Rivularin<br>6-Hydroxyluteolin<br>Nepetin (eupafolin) | <i>Scutellaria rivularis</i> (Scroph.), root<br>° <i>Eupatorium cuneifolium</i> (Ast.), leaf<br>° <i>Eupatorium subhastatum</i> (Ast.), leaf<br>° <i>Salvia officinalis</i> (Lam.), leaf                                                                                                                                                                                                                                                                       | Chou (1978)<br>Kupchan <i>et al.</i> (1969)<br>Ferraro and Coussio (1973)<br>Brieskorn and Biechele (1971)                                                                                                                                                                                                   |

|                                                         |                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                        |
|---------------------------------------------------------|-----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 7-Me (G)                                                | Pedaltin                                | ° <i>Helenium</i> spp. (Ast.)<br><i>Artemisia tridentata</i> spp. <i>roseyana</i> (Ast.)<br><i>Digitalis schischkinii</i> (Scroph.), leaf<br><i>Brickellia californica</i> (Ast.), leaf<br><i>Anvillea garcini</i> (Ast.), leaf<br><i>Brickellia dentata</i> (Ast.), leaf<br><i>Santolina chamaecyparissus</i> (Ast.), aerial parts<br>synthesis:<br><i>Eupatorium inulaefolium</i> var.<br><i>suaveolens</i> (Ast.), aerial parts<br><i>Neurolaena oaxacana</i> (Ast.), aerial parts | Bierner (1973)<br>Brown <i>et al.</i> (1975)<br>Imre <i>et al.</i> (1977)<br>Mues <i>et al.</i> (1979)<br>Ulubelen <i>et al.</i> (1979a)<br>Ulubelen <i>et al.</i> (1980a,b)<br>Becchi and Carrier (1980)<br>Midge and Rama Rao (1975)<br>Ferraro <i>et al.</i> (1977) |
| 3'-Me (G)                                               | Nodifloretin<br>(batatifolin)           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Ulubelen <i>et al.</i> (1980b)                                                                                                                                                                                                                                         |
| 6,7-di-Me (G)                                           | Cirsiliol                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Mues <i>et al.</i> (1979)<br>Ulubelen <i>et al.</i> (1980a)<br>Geissman <i>et al.</i> (1967)<br>Herz <i>et al.</i> (1968)<br>Herz <i>et al.</i> (1970)<br>Bierner (1978)<br>Ulubelen <i>et al.</i> (1979b)<br>Becchi and Carrier (1980)                                |
| 6,3'-di-Me                                              | Jaceosidin                              | <i>Brickellia californica</i> (Ast.), leaf<br><i>Brickellia dentata</i> (Ast.), leaf<br>° <i>Helichrysum viscosum</i> var. <i>bracteatum</i> (Ast.), aerial parts<br>° <i>Helenium alternifolium</i> (Ast.), aerial parts<br>° <i>Artemisia dracunculoides</i> (Ast.), aerial parts<br><i>Plumiera ambigua</i> <i>P. floribunda</i> (Ast.)<br><i>Salvia tomentosa</i> (Lam.)<br><i>Santolina chamaecyparissus</i> (Ast.), aerial parts                                                |                                                                                                                                                                                                                                                                        |
| 6,4'-di-Me (G)                                          | Desmethoxy-<br>centaureidin             | <i>Brickellia californica</i> (Ast.), leaf<br><i>Brickellia laciniata</i> (Ast.), leaf<br><i>Citharexylum subserratum</i> (Verb.), leaf<br><i>Eupatorium inulaefolium</i> var. <i>suaveolens</i> (Ast.), aerial parts<br><i>Ajania fastigiata</i> (Ast.)                                                                                                                                                                                                                              | Mues <i>et al.</i> (1979)<br>Timmermann <i>et al.</i> (1979a)<br>Mathuram <i>et al.</i> (1976)<br>Ferraro <i>et al.</i> (1977)<br>Chumbalov <i>et al.</i> (1974)                                                                                                       |
| 7,3'-di-Me (G only)*<br>7,4'-di-Me<br>6,7,3'-tri-Me (G) | Cirsilineol<br>(fastigenin, anisomelin) | <i>Artemisia capillaris</i> (Ast.)<br><i>Artemisia monosperma</i> (Ast.)<br><i>Sideritis mugronensis</i> (Lam.), aerial parts<br><i>Anisomela malabarica</i> (Lam.), aerial parts<br><i>Salvia tomentosa</i> (Lam.), aerial parts<br>° <i>Orthosiphon stamineus</i> (Lam.), aerial parts<br>° <i>Salvia lavanduloides</i> (Lam.)                                                                                                                                                      | Komiya <i>et al.</i> (1976)<br>Khafagy <i>et al.</i> (1979)<br>B. Rodriguez (1977)<br>Devi <i>et al.</i> (1979b)<br>Ulubelen <i>et al.</i> (1979b)<br>Matsuura <i>et al.</i> (1973)<br>J. Rodriguez <i>et al.</i> (1974)                                               |
| 6,7,4'-tri-Me                                           | Eupatorin                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                        |

Table 4.1 (Contd.)

| Substitution             | Trivial name | Plant source                                                         | References                        |
|--------------------------|--------------|----------------------------------------------------------------------|-----------------------------------|
|                          |              | <i>Centaurea pseudomaculosa</i> (Ast.), aerial parts                 | Zapochnayaya <i>et al.</i> (1977) |
|                          |              | <i>Eupatorium altissimum</i> (Ast.), aerial parts                    | Dobberstein <i>et al.</i> (1977)  |
|                          |              | <i>Otostegia limbata</i> (Lam.), stem                                | Ikram <i>et al.</i> (1979)        |
|                          |              | <i>Brickellia dentata</i> , <i>B. laciniata</i> (Ast.), leaf         | Timmermann <i>et al.</i> (1979a)  |
| 6,3',4'-tri-Me           | Eupalitin    | <i>Sideritis gomera</i> aerial parts                                 | Wagner <i>et al.</i> (1974)       |
|                          |              |                                                                      | González <i>et al.</i> (1978)     |
|                          |              |                                                                      | Gupta <i>et al.</i> (1979)        |
| 5,6,7,4'-tetra-Me        |              | ° <i>Orthosiphon stamineus</i> (Lam.)                                | Matsuura <i>et al.</i> (1973)     |
| 6,7,3',4'-tetra-Me       |              | ° <i>Merillia caloxylon</i> (Rut.), root                             | Fraser and Lewis (1974)           |
|                          |              | ° <i>Salvia lavanduloides</i> (Lam.), whole plant                    | Rodriguez <i>et al.</i> (1974)    |
|                          |              | <i>Salvia tomentosa</i> (Lam.), leaf                                 | Ulubelen <i>et al.</i> (1979b)    |
|                          |              | <i>Sideritis mugronensis</i> (Lam.), aerial parts                    | B. Rodriguez (1977)               |
|                          |              | <i>Sideritis gomerae</i> (Lam.)                                      | González <i>et al.</i> (1978)     |
|                          |              | <i>Otostegia limbata</i> (Ast.)                                      | Ikram <i>et al.</i> (1979)        |
|                          |              | <i>Eupatorium altissimum</i> (Ast.), whole plant                     | Dobberstein <i>et al.</i> (1977)  |
|                          |              | <i>Citrus reticulata</i> (Rut.), fruit peel                          | Iinuma <i>et al.</i> (1980)       |
| 5,6,7,3',4'-penta-Me     | Sinensetin   | ° <i>Orthosiphon stamineus</i> (Lam.)                                | Komiya <i>et al.</i> (1976)       |
|                          |              | <i>Chromolaena odorata</i> (Ast.)                                    | Matsuura <i>et al.</i> (1973)     |
|                          |              | (= <i>Eupatorium od.</i> ), aerial parts                             | Barua <i>et al.</i> (1978)        |
|                          |              | <i>Kickxia spuria</i> (Scroph.), aerial parts                        | Tóth <i>et al.</i> (1980)         |
|                          |              | <i>Citrus cult.</i> 'calamondin' (Rut.), fruit peel                  | Tatum and Berry (1978)            |
|                          |              | <i>Citrus reticulata</i> (Rut.), fruit peel                          | Iinuma <i>et al.</i> (1980)       |
| (5,7,8,2',3'-penta-OH)   | Norwightin   |                                                                      | Matsuura <i>et al.</i> (1978)     |
| 7,8,2'-tri'-Me           | Wightin      |                                                                      |                                   |
| 7,8,2',3'-tetra-Me       |              |                                                                      |                                   |
| 5,7,8,3',4'-penta-OH (G) | Hypolaetin   |                                                                      |                                   |
| 8-Me                     | Onopordin    | <i>Gardenia gummiifera</i> , <i>G. lucida</i> (Rub.), 'dikamali gum' | Chhabra <i>et al.</i> (1976a)     |
|                          |              |                                                                      | Chhabra <i>et al.</i> (1978)      |



Table 4.1 (Contd.)

| Substitution                                      | Trivial name          | Plant source                                                               | References                        |
|---------------------------------------------------|-----------------------|----------------------------------------------------------------------------|-----------------------------------|
| 6,8,4'-tri-Me (G)                                 | Acerosin              | <i>Gardenia gummifera</i> , <i>G. lucida</i> (Rub.), 'dikamali gum'        | S. R. Gupta <i>et al.</i> (1975)  |
| 6,7,8,3'-tetra-Me*                                |                       | <i>Sideritis mugronensis</i> (Lam.), aerial parts                          | B. Rodriguez (1977)               |
|                                                   |                       | <i>Sideritis leucantha</i> (Lam.), whole plant                             | Tomas <i>et al.</i> (1979)        |
| 6,7,8,4'-tetra-Me*                                | Gardenin D            | <i>Sideritis flavovirens</i> (Lam.), aerial parts                          | Escamilla and Rodriguez (1980)    |
| 6,8,3',4'-tetra-Me                                | Hymenoxin             | <i>Sideritis mugronensis</i> (Lam.), aerial parts                          | B. Rodriguez (1977)               |
|                                                   |                       | ° <i>Hymenoxis linearifolia</i> (Ast.), aerial parts                       | Herz <i>et al.</i> (1970)         |
|                                                   |                       | ° <i>Helianthus angustifolium</i> (Ast.), aerial parts                     | Waddell (1973)                    |
| 5,6,7,8,3'-penta-Me*                              |                       | <i>Citrus reticulata</i> (Rut.), fruit peel                                | Linuma <i>et al.</i> (1980)       |
| 6,7,8,3',4'-penta-Me                              | 5-Desmethoxynobiletin | ° <i>Citrus</i> cult. 'tangerine' (Rut.), fruit peel                       | Tatum and Berry (1972)            |
|                                                   |                       | <i>Sideritis mugronensis</i> (Lam.)                                        | B. Rodriguez (1977)               |
| 5,6,7,8,3',4'-hexa-Me<br>(5,6,7,2',4',5'-hexa-OH) | Nobiletin             | <i>Citrus</i> cult. 'calamondin' (Rut.), fruit peel                        | Tatum and Berry (1978)            |
| 6,2',4',5'-tetra-Me*                              |                       |                                                                            |                                   |
| 5,6,7,3',4',5'-hexa-OH                            | Tabularin             | <i>Chukrasia tabularis</i> (Meliac.), leaf                                 | Purushotaman <i>et al.</i> (1977) |
| 6,3',5'-tri-Me*                                   |                       |                                                                            |                                   |
| 6,4',5'-tri-Me*                                   |                       |                                                                            | Herz <i>et al.</i> (1980)         |
| 6,7,3',4',5'-penta-Me*                            |                       | <i>Conoclinium coelestinum</i> (Ast.), herbac. parts                       | Liu and Mabry (1980)              |
| (5,7,8,2',3',4'-hexa-OH)                          |                       | <i>Artemisia frigida</i> (Ast.), leaf and stem                             | Liu and Mabry (1981)              |
| 7,8,2',3',4'-penta-Me                             |                       | ° <i>Merillia caloxylon</i> (Rut.), fruit                                  | Fraser and Lewis (1974)           |
| (5,7,8,3',4',5'-hexa-OH)                          |                       |                                                                            |                                   |
| 8-Me*                                             | Serpyllin             | <i>Gardenia gummifera</i> , <i>G. lucida</i> (Rut.), 'dikamali' synthesis: | Chhabra <i>et al.</i> (1976a)     |
| 8,4'-di-Me*                                       |                       | <i>Gardenia gummifera</i> , <i>G. lucida</i> (Rut.), 'dikamali gum'        | Chhabra <i>et al.</i> (1978)      |
| 8,3',4'-tri-Me*                                   |                       | <i>Gardenia gummifera</i> <i>G. lucida</i> (Rut.)                          | Chhabra <i>et al.</i> (1977a)     |
| 7,8,4',5'-tetra-Me*                               |                       | <i>Lychnophora affinis</i> (Ast.), leaf, stem                              | Gupta <i>et al.</i> (1975)        |
| 8,3',4',5'-tetra-Me*                              |                       | <i>Gardenia gummifera</i> , <i>Gardenia lucida</i> (Rut.) 'dikamali gum'   | Le Quesne <i>et al.</i> (1976)    |
|                                                   |                       |                                                                            | Gupta <i>et al.</i> (1975)        |



|                                                   |                   |                                                                         |                                  |
|---------------------------------------------------|-------------------|-------------------------------------------------------------------------|----------------------------------|
| (5,6,7,8,2',4',5'-hepta-OH)<br>6,7,8,5'-tetra-Me* | Agecorynin-D      | <i>Ageratum corymbosum</i> (Ast.), aerial parts                         | Quijano <i>et al.</i> (1980)     |
| 5,6,7,8,2',4',5'-hepta-Me*                        | Agecorynin-C      | <i>Ageratum corymbosum</i> (Ast.), aerial parts                         | Quijano <i>et al.</i> (1980)     |
| (5,6,7,8,3',4',5'-hepta-OH)<br>6,7,8,4'-tetra-Me  | Gardenin E        | <i>Gardenia gummiifera</i> , <i>G. lucida</i><br>(Rut.), 'dikamali gum' | S. R. Gupta <i>et al.</i> (1975) |
| 6,8,3',4'-tetra-Me                                | Scaposin          |                                                                         |                                  |
| 8,3',4',5'-tetra-Me*(G)                           | Trimethoxywogonin | <i>Gardenia gummiifera</i> , <i>G. lucida</i> (Rut.), 'dikamali gum'    | S. R. Gupta <i>et al.</i> (1975) |
|                                                   |                   | <i>Vitex negundo</i> (Verb.), stem bark                                 | Subramanian and Misra (1979)     |
| 6,7,8,4',5'-penta-Me                              | Gardenin C        | <i>Gardenia gummiifera</i> , <i>G. lucida</i> (Rut.), 'dikamali gum'    | S. R. Gupta <i>et al.</i> (1975) |
| 6,7,8,3',4',5'-hexa-Me                            | Gardenin A        | <i>Eupatorium coelestinum</i> (Ast.), aerial parts                      | Le-Van and Pham (1979)           |
| 5,6,7,8,3',4',5'-hepta-Me*                        |                   | <i>Ageratum conyzoides</i> (Ast.), aerial parts                         | Adesogan and Okunade (1979)      |
|                                                   |                   | <i>Ageratum corymbosum</i> (Ast.) aerial parts                          | Quijano <i>et al.</i> (1980)     |

Key: G = occurs in glycosidic combination; \* = compound newly reported during 1975–1980; ° = earlier report, not included in 'The Flavonoids'.

**Table 4.2** List of flavonols reported between 1975 and 1980 and their plant sources

| Substitution                                 | Trivial name                             | Plant source                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | References                                                                                                                                                                                                                                                                                                                                                               |
|----------------------------------------------|------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 3,5,7-tri-OH (G)                             | Galangin                                 | <ul style="list-style-type: none"> <li>°<i>Helichrysum arenarium</i> (Ast.), seeds</li> <li>°<i>Alnus pendula</i> (Bet.), male flowers</li> <li><i>Alnus viridis</i> (Bet.), bud excretion</li> <li>°<i>Comptonia peregrina</i> (Myr.), leaf</li> <li><i>Populus</i> spp. (Salic.), bud excretion</li> <li><i>Escallonia</i>, 4 spp. (Sax.), on leaf</li> <li><i>Adiantum sulphureum</i>, <i>Cheilanthes kauffussii</i>, <i>Pellaea longimucronata</i> (Polypod.), farinose exudate on fronds</li> <li><i>Pityrogramma chrysoconia</i>, <i>Pityrogramma triangularis</i> var. <i>maxonii</i> (Polypod.), farinose exudate on fronds</li> </ul>                                                | <ul style="list-style-type: none"> <li>Vrkoč <i>et al.</i> (1973)</li> <li>Suga <i>et al.</i> (1972)</li> <li>Wollenweber (1975b)</li> <li>Lau-Cam and Chan (1973)</li> <li>Wollenweber (1975a)</li> <li>Wollenweber (1981a)</li> <li>Wollenweber (1979)</li> <li>Wollenweber and Dietz (1980)</li> </ul>                                                                |
| 3-Me (G)                                     |                                          | <ul style="list-style-type: none"> <li><i>Ericameria diffusa</i> (Ast.)</li> <li><i>Populus</i> spp. (Salic.), bud excretion</li> <li><i>Escallonia</i>, 3 spp. (Sax.), on leaf</li> <li><i>Cheilanthes kauffussii</i>, <i>Notholaena</i> spp. (Polypod.), farinose exudate on fronds</li> <li><i>Populus</i> spp. (Salic.), bud excretion</li> <li><i>Aniba riparia</i> (Laurac.), trunk wood</li> <li><i>Escallonia</i>, 3 spp. (Sax.), leaf</li> <li><i>Adiantum sulphureum</i> (Polypod.), farinose exudate on frond</li> <li><i>Pityrogramma chrysoconia</i> (Polypod.), farinose exudate on frond</li> <li><i>Notholaena sulphurea</i> (Polypod.), farinose exudate on frond</li> </ul> | <ul style="list-style-type: none"> <li>Urbatsch <i>et al.</i> (1976)</li> <li>Wollenweber (1975a)</li> <li>Wollenweber (1981a)</li> <li>Wollenweber (1979)</li> <li>Wollenweber, (1975a)</li> <li>Fernandes <i>et al.</i> (1978)</li> <li>Wollenweber (1981a)</li> <li>Wollenweber (1976b)</li> <li>Wollenweber and Dietz (1980)</li> <li>Wollenweber (1981b)</li> </ul> |
| 7-Me (G)                                     | Izalpinin                                | <ul style="list-style-type: none"> <li><i>Escallonia langlayensis</i>, <i>E. illit.</i> × <i>illit.</i> (Sax.), on leaf</li> <li><i>Cheilanthes kauffussii</i>, <i>Notholaena</i> spp. (Polypod.)</li> <li><i>Aniba riparia</i> (Laurac.), wood</li> <li><i>Gomphrena martiana</i> (Amar.), whole plant</li> <li>Leguminosae, tribe Loteae</li> </ul>                                                                                                                                                                                                                                                                                                                                         | <ul style="list-style-type: none"> <li>Wollenweber (1981a)</li> <li>Wollenweber (1979)</li> <li>Franca <i>et al.</i> (1976)</li> <li>Buschi <i>et al.</i> (1980)</li> <li>Jay <i>et al.</i> (1980)</li> </ul>                                                                                                                                                            |
| 3,7-di-Me*                                   |                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                          |
| 3,5,7-tri-Me*                                |                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                          |
| 3,7,4'-tri-OH (G only)<br>(3,5,6,7-tetra-OH) | 5-Deoxykaempferol<br>(6-Hydroxygalangin) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                          |
| 6-Me                                         | Alnusin                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                          |
|                                              |                                          | synthesis:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Goudard and Chopin (1976)                                                                                                                                                                                                                                                                                                                                                |

|                                         |                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                               |
|-----------------------------------------|---------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 3,6-di-Me*                              |                     | <i>Helichrysium chrysargyrum</i> ,<br><i>H. heterolasium</i> (Ast.), aerial parts<br><i>Helichrysium chrysargyrum</i> (Ast.)<br><i>Gnaphalium wrightii</i> (Ast.)                                                                                                                                                                                                                                                                                                                                                                                                                                       | Bohlmann and Abraham (1979)                                                                                                                                   |
| 3,7-di-Me*                              |                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Bohlmann <i>et al.</i> (1979)<br>Bohlmann (personal communication)<br>Buschi <i>et al.</i> (1980)<br>Goudard and Chopin (1976)<br>Buschi <i>et al.</i> (1980) |
| 5,7-di-Me*                              | Alnustin            | <i>Gomphrena martiana</i> (Amar.), whole plant<br>synthesis:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Wollenweber <i>et al.</i> (1978)                                                                                                                              |
| 3,6,7-tri-Me                            | (8-Hydroxygalangin) | <i>Gomphrena martiana</i> (Amar.), whole plant                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                               |
| 3,5,6,7-tetra-Me*<br>(3,5,7,8-tetra-OH) |                     | <i>Notholaena galapagensis</i> , <i>N. neglecta</i><br>(Polypod.), (as ester with acetic and with<br>butyric acid), farinose exudate on fronds                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                               |
| 7-Me*                                   |                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                               |
| 3,7-di-Me                               | Isognaphalin        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                               |
| 3,8-di-Me                               | Gnaphalin           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                               |
| 7,8-di-Me*                              |                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                               |
| 3,7,8-tri-Me                            | Methylgnaphalin     | <i>Gnaphalium obtusifolium</i><br>(Ast.), aerial parts<br><i>Gnaphalium obtusifolium</i> (Ast.), aerial parts                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Goudard and Chopin (1976)<br>Gupta <i>et al.</i> (1979)<br>Bohlmann (personal communication)<br>Bohlmann (personal communication)                             |
| 3,5,7,2'-tetra-OH (G)                   | Datiscetin          | (see Section 4.5)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                               |
| 2'-Me                                   | Ptaeroxylol         | ° <i>Datisca cannabina</i> (Datisc.)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                               |
| 7-Me                                    | Datin               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                               |
| 3,5,7,4'-tetra-OH (G)                   | Kaempferol          | <i>Larrea tridentata</i> (Zyg.) leaf<br><i>Larrea nitida</i> (Zyg.) leaf<br><i>Aesculus</i> spp. (Hipp.), <i>Betula</i> spp. (Bet.),<br><i>Populus</i> spp. (Salic.), bud excretion<br><i>Cheilanthes</i> spp., <i>Notholaena</i> spp., <i>Pityrogramma</i> spp.<br>(Polypod.), farinose exudate on fronds<br><i>Chrysothamnus niscidiflorus</i> (Ast.), leaf<br><i>Ericameria diffusa</i> (Ast.), leaf<br><i>Flourensia ilicifolia</i> (Ast.), leaf<br><i>Didiera madagascariensis</i> , <i>D. troltii</i> (Didier.), aerial parts<br><i>Tetragonotheca ludoviciana</i> , <i>T. texana</i> (Ast.) leaf | Pangaroa and<br>Zapsochnaya (1974)<br>Sakakibara <i>et al.</i> (1975)<br>Timmermann <i>et al.</i> (1979b)<br>Wollenweber (1981a)<br>Wollenweber (1978)        |
| 3-Me (G)                                | Isokaempferide      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Urbatsch <i>et al.</i> (1975)<br>Urbatsch <i>et al.</i> (1976)<br>Dillon and Mabry (1977)<br>Rabesa and Lebreton (1977)<br>Bacon <i>et al.</i> (1978)         |

Table 4.2 (Contd.)

| Substitution         | Trivial name           | Plant source                                                                                                                                                                                                                                                                                    | References                                                                                                                                                   |
|----------------------|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5-Me (G)<br>7-Me (G) | Rhamnocitrin           | <i>Prosopis</i> spp. (Leg.), leaf                                                                                                                                                                                                                                                               | Bragg <i>et al.</i> (1978)                                                                                                                                   |
|                      |                        | <i>Eupatorium tinifolium</i> (Ast.), aerial parts                                                                                                                                                                                                                                               | Moreno <i>et al.</i> (1980)                                                                                                                                  |
|                      |                        | <i>Parthenium</i> spp. (Ast.), leaf                                                                                                                                                                                                                                                             | Mears (1980)                                                                                                                                                 |
|                      |                        | <i>Betula nigra</i> (Bet.), <i>Aesculus</i> spp., (Hipp.), <i>Populus</i> spp. (Salic.), bud excretion                                                                                                                                                                                          | Wollenweber (1981a)                                                                                                                                          |
| 4'-Me (G)            | Kaempferide            | <i>Cheilanthes</i> spp., <i>Notholaena</i> spp. (Polypod.), farinose exudate on frond                                                                                                                                                                                                           | Wollenweber (1976c)                                                                                                                                          |
|                      |                        | <i>Pityrogramma triangularis</i> var. <i>triangularis</i>                                                                                                                                                                                                                                       | Smith (1980)                                                                                                                                                 |
|                      |                        | <i>Larrea tridentata</i> (Zyg.), leaf                                                                                                                                                                                                                                                           | Sakakibara <i>et al.</i> (1976)                                                                                                                              |
|                      |                        | <i>Larrea nitida</i> (Zyg.), leaf                                                                                                                                                                                                                                                               | Timmermann <i>et al.</i> (1979b)                                                                                                                             |
| 3,7-di-Me            | Kumatakenin<br>Jaranol | <i>Alnus</i> spp., <i>Betula</i> spp., <i>Ostrya</i> spp. (Bet.), <i>Aesculus</i> . 4 spp. (Hipp.), <i>Populus</i> spp. (Salic.), bud excretion                                                                                                                                                 | Wollenweber (1981a)                                                                                                                                          |
|                      |                        | <i>Parthenium</i> spp. (Ast.), leaf                                                                                                                                                                                                                                                             | Mears (1980)                                                                                                                                                 |
|                      |                        | <i>Cheilanthes</i> spp., <i>Notholaena</i> spp. (Polypod.) farinose exudate on frond                                                                                                                                                                                                            | Wollenweber (1976c)                                                                                                                                          |
|                      |                        | <i>Dillenia indica</i> (Dillen.), fruit, pericarp                                                                                                                                                                                                                                               | Pavanasivam and Sultanbawa (1975)                                                                                                                            |
| 3,7-di-Me            | Kumatakenin<br>Jaranol | <i>Alnus</i> spp., <i>Betula</i> spp. <i>Ostrya</i> spp. (Bet.), <i>Populus</i> spp. <i>Pityrogramma triangularis</i> (Polypod.), farinose exudate on frond                                                                                                                                     | Wollenweber (1981a)<br>Star <i>et al.</i> (1975)                                                                                                             |
|                      |                        | <i>Notholaena</i> spp. (Polypod.), farinose exudate on frond                                                                                                                                                                                                                                    | Wollenweber (1981b)                                                                                                                                          |
|                      |                        | <i>Cheilanthes</i> spp. (Polypod.), farinose exudate on frond                                                                                                                                                                                                                                   | Wollenweber (unpublished)                                                                                                                                    |
|                      |                        | ° <i>Ambrosia eriocentra</i> (Ast.), aerial parts<br>° <i>Salvia glutinosa</i> (Lam.), aerial parts<br><i>Ericameria diffusa</i> (Ast.), leaf<br><i>Flourensia cernua</i> , <i>F. retinophylla</i> (Ast.), leaf<br><i>Larrea nitida</i> (Zyg.), leaf<br><i>Digitalis thapsi</i> (Scroph.), leaf | Herz <i>et al.</i> (1973)<br>Wollenweber (1974a)<br>Urbatsch <i>et al.</i> (1976)<br>Timmermann <i>et al.</i> (1979b)<br>Pascual Teresa <i>et al.</i> (1980) |



Table 4.2 (Contd.)

| Substitution                               | Trivial name        | Plant source                                                                                                                                                                                                                                                   | References                                                                                                                                                                                               |
|--------------------------------------------|---------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 4'-Me                                      |                     |                                                                                                                                                                                                                                                                |                                                                                                                                                                                                          |
| 3,7,3',4'-tetra-Me<br>(3,5,6,7,8-penta-OH) |                     |                                                                                                                                                                                                                                                                |                                                                                                                                                                                                          |
| 6,8 di-Me                                  |                     |                                                                                                                                                                                                                                                                |                                                                                                                                                                                                          |
| 3,6,8-tri-Me*                              | Araneol             | <i>Anaphalis araneosa</i> (Ast.), flowering part<br><i>Gnaphalium elegans</i> (Ast.), flower<br>° <i>Helichrysum graveolens</i> (Ast.), aerial parts<br><i>Artemisia ludoviciana</i> (Ast.), stem<br>(see Section 4.5)                                         | Ali <i>et al.</i> (1979)<br>Torrenegra <i>et al.</i> (1980)<br>Hänsel and Cubukcu (1972)<br>Dominguez and Cardenas (1975)                                                                                |
| 6,7,8-tri-Me                               |                     |                                                                                                                                                                                                                                                                |                                                                                                                                                                                                          |
| 3,5,6,7,4'-penta-OH (G only)               | 'Galeitin' (?)      | <i>Tetragonotheca texana</i> (Ast.),<br><i>Neurolaena oaxacana</i> (Ast.), leaf<br><i>Neurolaena lobata</i> (Ast.)                                                                                                                                             | Bacon <i>et al.</i> (1978)<br>Ulubelen <i>et al.</i> (1980b)<br>Ulubelen (personal communication)                                                                                                        |
| 3-Me (G)                                   | Vogeleitin          |                                                                                                                                                                                                                                                                |                                                                                                                                                                                                          |
| 5-Me (G)                                   |                     |                                                                                                                                                                                                                                                                |                                                                                                                                                                                                          |
| 6-Me (G)                                   | 6-Methoxykaempferol | ° <i>Artemisia arbuscula</i> (Ast.), whole plant<br><i>Flourensia illicifolia</i> (Ast.), leaf<br><i>Ostrya japonica</i> (Bet.), bud excretion                                                                                                                 | E. Rodriguez <i>et al.</i> (1972b)<br>Dillon and Mabry (1977)<br>Wollenweber (1975c)                                                                                                                     |
| 4'-Me (G)                                  |                     | <i>Alnus</i> , 3 spp., <i>Ostrya carpinifolia</i> (Bet.), bud excretion<br><i>Acanthospermum glabratum</i> (Ast.), whole plant<br><i>Flourensia illicifolia</i> (Ast.), leaf<br><i>Parthenium</i> spp. (Ast.), leaf                                            | Wollenweber (1975b)<br>Saleh <i>et al.</i> (1976)<br>Dillon and Mabry (1977)<br>Mears (1980)                                                                                                             |
| 3,6-di-Me (G)                              |                     | <i>Didiera trolitii</i> (Didier.), aerial parts<br><i>Prunus cerasus</i> (Ros.), bud excretion<br><i>Inula grandis</i> (Ast.), leaf<br><i>Parthenium</i> spp. (Ast.), leaf<br><i>Neurolaena oaxacana</i> (Ast.), leaf<br><i>Neurolaena lobata</i> (Ast.), leaf | Rabesa and Lebreton (1977)<br>Wollenweber (unpublished)<br>Nikinova and Nikonov (1975)<br>Shen <i>et al.</i> (1976); Mears (1980)<br>Ulubelen <i>et al.</i> (1980b)<br>Ulubelen (personal communication) |
| 3,7-di-Me*                                 |                     |                                                                                                                                                                                                                                                                |                                                                                                                                                                                                          |
| 6,7-di-Me (G)                              | Eupalitin           | <i>Ostrya japonica</i> (Bet.), bud excretion<br><i>Matricaria chamomilla</i> , flowers<br><i>Cheilanthes argentea</i> (Polypod.), farinose exudate on frond                                                                                                    | Wagner <i>et al.</i> (1977a)<br>Wollenweber (1975b)<br>Exner <i>et al.</i> (1981)<br>Wollenweber (unpublished)                                                                                           |

|                                                 |                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------------------------------------|--------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 6,4'-di-Me                                      | Betuletol                      | <i>Alnus</i> spp., <i>Betula</i> spp. (Bet.), bud excretion<br><i>Alluaudia ascendens</i> , <i>A. procera</i> ,<br><i>Decarya madagascariensis</i> (Didier.), aerial parts<br>synthesis:<br><br>° <i>Artemisia</i> , 3 spp. (Ast.), whole plant<br><i>Parthenium</i> spp. (Ast.), leaf<br><i>Digitalis thapsi</i> (Scroph.), leaf<br><i>Betula nigra</i> (Bet.), <i>Prunus avium</i> (Ros.), bud excretion<br><i>Gardenia fosbergii</i> (Rub.), bud exudate<br>° <i>Chrysanthemum parthenium</i> (Ast.), leaf<br><i>Alnus</i> spp., <i>Betula</i> spp. (Bet.), bud excretion<br><i>Alluaudia ascendens</i> , <i>A. procera</i> , <i>Decarya</i><br><i>madagascariensis</i> (Didier.), aerial parts<br>evtl. in Betulaceae, bud excretion<br><i>Achillea millefolium</i> (Ast.), flower<br><i>Sideritis gomerae</i> (Lam.), aerial parts<br><br><i>Notholaena standleyi</i> (Polypod.), farinose<br>exudate on frond<br><i>N. aschenborniana</i> (Polypod.), (as ester with acetic<br>and butyric acid), farinose exudate on frond<br><br><i>Larrea divaricata</i> , <i>L. tridentata</i> (Zyg.), leaf resin<br>synthesis:<br><br><i>Rudbeckia bicolor</i> (Ast.), whole plant<br><i>Notholaena standleyi</i> (Polypod.), farinose<br>exudate on frond<br><i>Notholaena affinis</i> (Pol.), (as ester with acetic<br>and butyric acid), farinose exudate on frond<br>synthesis:<br><br>Prudomestin | Wollenweber (1975b)<br>Rabesa (1980)<br>Rabesa (1980)<br>Wagner <i>et al.</i> (1976, 1977a);<br>Goudard and Chopin (1976)<br>E. Rodriguez <i>et al.</i> (1972b)<br>Shen <i>et al.</i> (1976); Mears (1980)<br>Pascual Teresa <i>et al.</i> (1980)<br>Wollenweber (unpublished)<br>Gunatilaka <i>et al.</i> (1979)<br>J. Rodriguez <i>et al.</i> (1974)<br>Wollenweber (1975b)<br>Rabesa (1980)<br><br>Wollenweber (unpublished)<br>Falk <i>et al.</i> (1975)<br>Gonzalez <i>et al.</i> (1978)<br><br>Wollenweber and Rehse<br>(unpublished)<br>Wollenweber <i>et al.</i> (1978)<br><br>Sakakibara <i>et al.</i> (1975)<br>Wagner <i>et al.</i> (1976)<br><br>Jauhari <i>et al.</i> (1979)<br>Wollenweber and Rehse<br>(unpublished)<br>Wollenweber <i>et al.</i> (1978)<br><br>Goudard and Chopin (1976) |
| 3,6,7-tri-Me                                    | Penduletin                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 3,6,4'-tri-Me                                   | Santin, 3-Methyl-<br>betuletol |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 6,7,4'-tri-Me (G)<br>3,6,7,4'-tetra-Me          | Mikanin                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 3,5,7,8,4'-penta-OH (G only)<br>7-Me            | Herbacetin<br>Pollenitin       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 8-Me (G only)<br>3,7-di-Me                      | Sexangularetin                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 3,8-di-Me<br>7,8-di-Me (G only)*<br>7,4'-di-Me* |                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 8,4'-di-Me<br>3,7,8-tri-Me                      |                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

Table 4.2 (Contd.)

| Substitution             | Trivial name | Plant source                                                                     | References                              |
|--------------------------|--------------|----------------------------------------------------------------------------------|-----------------------------------------|
| 3,8,3'-tri-Me            | Tambulin     | ° <i>Cyanostegia angustifolia</i> (Verb.)                                        | Ghisalberti <i>et al.</i> (1967)        |
| 3,8,4'-tri-Me            |              | <i>Conyza stricta</i> (Ast.), whole plant                                        | Tandon and Rastogi (1977)               |
| 7,8,4'-tri-Me            | Flindulatin  | (see Section 4.5)                                                                |                                         |
| 3,7,8,4'-tetra-Me        | Auranetin    | <i>Inula cappa</i> (Ast.), aerial parts<br>widespread                            | Baruah <i>et al.</i> (1979)             |
| 3,6,7,8,4'-penta-OH      |              |                                                                                  |                                         |
| 3,6,7,8,4'-penta-Me      | Morin        | ° <i>Alpinia officinalis</i> (Zingib.), rhizome                                  | Bleier and Chirikdjian (1972)           |
| 3,5,7,2',4'-penta-OH (G) |              | ° <i>Larrea tridentata</i> (Zyg.), leaf resin                                    | Chirikdjian (1973)                      |
| (3,5,7,2',5'-penta-OH)   | Quercetin    | <i>Larrea nitida</i> (Zyg.), leaf resin                                          | Timmermann <i>et al.</i> (1979b)        |
| 3,5,2'-tri-Me*           |              | <i>Haplopappus beilahnii</i> (Ast.), aerial parts                                | Hörhammer <i>et al.</i> (1973)          |
| 3,5,7,3',4'-penta-OH     |              | <i>Chrysothamnus viscidiflorus</i> (Ast.)                                        | Urbatsch <i>et al.</i> (1975)           |
| 3-Me                     |              | <i>Vernonia pectoralis</i> (Ast.), aerial parts                                  | Bézanger-Bauquesne <i>et al.</i> (1975) |
|                          |              | <i>Ericameria diffusa</i> (Ast.), leaf                                           | Urbatsch <i>et al.</i> (1976)           |
|                          |              | <i>Inula viscosa</i> (Ast.), flower                                              | Öksüz (1977)                            |
|                          |              | <i>Betula nigra</i> (Bet.), bud excretion                                        | Wollenweber (1977a)                     |
|                          |              | <i>Prosopis</i> spp. (Leg.), leaf                                                | Bragg <i>et al.</i> (1978)              |
|                          |              | <i>Didiera madagascariensis</i> , <i>D. trollii</i><br>(Didier), bark and spines | Rabesa (1980)                           |
|                          |              | <i>Neurolaena oaxacana</i> (Ast.), leaf                                          | Ulbelen <i>et al.</i> (1980a,b)         |
|                          |              | <i>Notholaena californica</i> (Polypod.),<br>farinose exudate on frond           | Wollenweber (1981b)                     |
| 5-Me (G)                 | Azaleatin    | <i>Alnus maritima</i> , <i>Betula</i> spp. (Bet.), bud excretion                 | Wollenweber (1975b)                     |
| 7-Me (G)                 | Rhamnetin    | <i>Populus</i> spp. (Salic.), bud excretion                                      | Wollenweber (1975a)                     |
|                          |              | <i>Cheilanthes</i> spp. (Polypod.) farinose exudate on frond                     | Wollenweber (unpublished)               |



|                                                 |                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------------------------------------------------|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 3'-Me (G)                                       | Isorhamnetin            | <i>Dillenia indica</i> , bark<br><i>Ericameria diffusa</i> (Ast.), leaf<br><i>Larrea divaricata</i> , <i>L. tridentata</i> (Zyg.), leaf resin<br><i>Alnus</i> spp., <i>Betula</i> spp., (Bet.), <i>Aesculus</i> spp. (Hipp.), bud excretion<br><i>Cheilanthes</i> spp. (Polypod.), farinose exudate on frond                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Pavanasivam and Sultanbawa (1975)<br>Urbatsch <i>et al.</i> (1976)<br>Sakakibara <i>et al.</i> (1976)<br>Wollenweber (1981a)<br><br>Wollenweber (unpublished)                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 4'-Me (G)<br>3,5-di-Me (G)<br>3,7-di-Me         | Tamarixetin<br>Caryatin | <i>Ericameria diffusa</i> (Ast.), leaf<br><i>Larrea divaricata</i> , <i>L. tridentata</i> , (Zyg.), leaf resin<br><i>Angelonia grandiflora</i> (Scroph.), leaf<br><i>Alnus</i> spp., <i>Betula</i> spp. (Bet.)<br><i>Populus</i> spp. (Salic.), bud excretion<br>° <i>Melicope perspicuineria</i> (Rut.), leaf<br><i>Chrysothamnus viscidiflorus</i> (Ast.), leaf<br><i>Populus</i> spp., (Salic.), bud excretion<br><i>Larrea divaricata</i> , <i>L. tridentata</i> (Zyg.), leaf resin<br><i>Larrea nitida</i> (Zyg.), leaf resin<br><i>Betula nigra</i> (Bet.), bud excretion<br><i>Didiera madagascariensis</i> (Didier.), aerial parts<br><i>Parthenium rollinsianum</i> (Ast.), aerial parts<br><i>Escallonia</i> , 3 spp. (Sax.), on leaf<br><i>Ericameria diffusa</i> (Ast.), leaf<br><i>Angelonia grandiflora</i> (Scroph.), leaf<br><i>Medicago</i> × <i>varia</i> (Leg.), seed<br>° <i>Artemisia pygmaea</i> (Ast.), aerial parts<br><i>Larrea divaricata</i> , <i>L. tridentata</i> (Zyg.), leaf resin<br><i>Alnus</i> spp., <i>Betula</i> spp. (Bet.), <i>Aesculus</i> , 4 spp. (Hipp.), <i>Populus</i> spp. (Salic.), bud excretion<br><i>Cheilanthes</i> spp., <i>Notholaena</i> spp. (Polypod.), farinose exudate on frond | Urbatsch <i>et al.</i> (1976)<br>Sakakibara <i>et al.</i> (1976)<br>Nair <i>et al.</i> (1978)<br>Wollenweber (1981a)<br><br>Murphy <i>et al.</i> (1974)<br>Urbatsch <i>et al.</i> (1975)<br>Wollenweber (1975a)<br>Sakakibara <i>et al.</i> (1976)<br>Timmermann <i>et al.</i> (1979b)<br>Wollenweber (1977a)<br>Rabesa and Lebreton (1977)<br>E. Rodriguez (1977)<br>Wollenweber (1981a)<br>Urbatsch <i>et al.</i> (1976)<br>Nair <i>et al.</i> (1978)<br>Gehring and Geiger (1980)<br>E. Rodriguez <i>et al.</i> (1972b)<br>Sakakibara <i>et al.</i> (1976)<br>Wollenweber (1981a)<br><br>Wollenweber (unpublished) |
| 3,4'-di-Me<br><br>5,3'-di-Me*<br>7,3'-di-Me (G) | Rhamnazin               | <i>Ostrya japonica</i> (Bet.), bud excretion<br><i>Cassia laevigata</i> (Leg.), leaf<br><i>Angelonia grandiflora</i> (Scroph.), leaf                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Wollenweber (1975b)<br>Singh and Tiwari (1979)<br>Nair <i>et al.</i> (1978)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 7,4'-di-Me (G)                                  | Ombuin                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

Table 4.2 (Contd.)

| Substitution       | Trivial name | Plant source                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | References                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|--------------------|--------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 3',4'-di-Me (G)    | Dillenetin   | <i>Dillenia indica</i> (Dill.), fruit, pericarp                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Pavanasasivam and Sultanbawa (1975)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 3,7,3'-tri-Me (G)  | Pachypodol   | ° <i>Pachypodanthium confine</i> (Annon.), root<br>° <i>Larrea tridentata</i> (Zyg.), leaf resin<br><i>Betula nigra</i> (Bet.), bud excretion<br><i>Larrea divaricata</i> (Zyg.), leaf resin<br><i>Digitalis thapsi</i> (Scroph.)<br>° <i>Apuleia leiocarpa</i> (Leg.), wood<br>° <i>Salvia glutinosa</i> (Lam.), aerial parts<br><i>Alnus</i> spp., <i>Betula</i> spp., <i>Ostrya</i> spp. (Bet.), bud excretion<br><i>Ericameria diffusa</i> (Ast.), leaf<br><i>Physalis angulata</i> (Sol.), whole plant<br><i>Distemonanthus benthamianus</i> (Leg.), heartwood<br><i>Escallonia</i> , 3 spp. (Sax.)<br><i>Notholaena</i> spp. (Polypod.), farinose exudate on frond<br><i>Cheilanthes</i> spp. (Polypod.), farinose exudate on frond<br><i>Ericameria diffusa</i> (Ast.), leaf<br><i>Betula nigra</i> (Bet.), bud excretion<br><i>Diospyros melanoxylon</i> (Ebenac.), leaf<br><i>Larrea divaricata</i> , <i>L. tridentata</i> (Zyg.), leaf resin<br><i>Larrea nitida</i> (Zyg.)<br><i>Alnus</i> spp., <i>Betula</i> spp., <i>Ostrya</i> spp. (Bet.),<br><i>Aesculus</i> spp. (Hipp.), bud excretion | Cavé <i>et al.</i> (1973)<br>Chirikjian (1974)<br>Wollenweber (1975b)<br>Sakakibara <i>et al.</i> (1976)<br>Pascual Teresa <i>et al.</i> (1980)<br>Braz Filho and Gottlieb (1971)<br>Wollenweber (1974a)<br>Wollenweber (1975b)<br>Urbatsch <i>et al.</i> (1976)<br>Lopez <i>et al.</i> (1976)<br>Malan and Roux (1979)<br>Wollenweber (1981a)<br>Wollenweber (1981b)<br>Wollenweber (unpublished)<br>Urbatsch <i>et al.</i> (1976)<br>Wollenweber (1977a)<br>Desai <i>et al.</i> (1976)<br>Sakakibara <i>et al.</i> (1976)<br>Timmermann <i>et al.</i> (1979b)<br>Wollenweber (1981a) |
| 3,3',4'-tri-Me*    |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 7,3',4'-tri-Me (G) |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 3,5,7,4'-tetra-Me  |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 3,5,3',4'-tetra-Me |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 3,7,3',4'-tetra-Me | Retusin      | ° <i>Geranium macrorrhizum</i> (Geran.)<br>° <i>Salvia glutinosa</i> (Lam.), aerial parts<br><i>Betula nigra</i> (Bet.), bud excretion<br><i>Larrea divaricata</i> , <i>L. tridentata</i> (Zyg.), leaf resin<br><i>Distemonanthus benthamianus</i> (Leg.), heartwood<br><i>Parthenium</i> spp., (Ast.) leaf<br><i>Notholaena</i> spp. (Polypod.), farinose exudate on frond                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | °Nakashima <i>et al.</i> (1973)<br>Wollenweber (1974a)<br>Wollenweber (1975b)<br>Sakakibara <i>et al.</i> (1976)<br>Malan and Roux (1979)<br>Mears (1980)<br>Wollenweber (unpublished)                                                                                                                                                                                                                                                                                                                                                                                                 |

|                                        |               |                                                                                  |                                     |  |
|----------------------------------------|---------------|----------------------------------------------------------------------------------|-------------------------------------|--|
| 3,5,8,3',4'-penta-OH ( <i>G only</i> ) |               | (see Section 4.5)                                                                |                                     |  |
| 3,6,7,3',4'-penta-OH*                  | Rhynchostin   | <i>Rhynchostia beddomei</i> (Leg.), leaf                                         | Adinarayana <i>et al.</i> (1980b)   |  |
| 3,7,8,3',4'-penta-OH                   | Melanoxetin   | <i>Albizia adianthifolia</i> (Leg.), wood                                        | Candy <i>et al.</i> (1978)          |  |
| 3,7,3',4',5'-penta-OH                  | Robinetin     |                                                                                  |                                     |  |
| (3,5,6,7,8,3'-hexa-OH)                 |               |                                                                                  |                                     |  |
| 3,6,7,8,3'-penta-Me*                   | Emmaosunin    | ° <i>Gymnosperma glutinosa</i> (Ast.), aerial parts                              | Dominguez & Torre (1974)            |  |
| (3,5,6,7,8,4'-hexa-OH)                 |               |                                                                                  |                                     |  |
| 3,6,7,8-tetra-Me                       | Calicopterin  | <i>Gardenia fosbergii</i> (Rub.) bud exudate                                     | Gunatilaka <i>et al.</i> (1980)     |  |
| 5,6,7,4'-tetra-Me                      | Eriostemin    |                                                                                  |                                     |  |
| 3,6,8,4'-tetra-Me                      | Araneosol     | <i>Anaphalis araneosa</i> (Ast.), flowering plant                                | Ali <i>et al.</i> (1979)            |  |
| 3,6,7,8,4'-penta-Me*                   |               | ° <i>Calycopteris floribunda</i> (Combr.), leaf                                  | Gupta <i>et al.</i> (1973)          |  |
| (3,5,6,7,2',4'-hexa-OH)                |               |                                                                                  |                                     |  |
| 3,6,7,2'-tetra-Me                      | Chrysosplenin | <i>Chrysosplenium tetrandrum</i> (Sax.), aerial parts                            | Bohm <i>et al.</i> (1977)           |  |
| 3,5,6,7,3',4'-hexa-OH ( <i>G</i> )     | Quercetagetin | <i>Neurolaena oaxacana</i> (Ast.), leaf                                          | Ulubelen <i>et al.</i> (1980b)      |  |
| 3-Me( <i>G only</i> )*                 |               | <i>Tagetes patula</i> (Ast.), petals                                             | Bhardwaj <i>et al.</i> (1980c)      |  |
|                                        |               | <i>Tetragonotheca</i> , 3 spp. (Ast.), leaf                                      | Bacon <i>et al.</i> (1978)          |  |
|                                        |               | <i>Brickellia laciniata</i> (Ast.), leaf                                         | Timmermann <i>et al.</i> (1979a)    |  |
|                                        |               | <i>Brickellia chlorolepis</i> (Ast.), leaf                                       | Ulubelen <i>et al.</i> (1980a)      |  |
|                                        |               | <i>Brickellia cylindracea</i> (Ast.), leaf                                       | Timmermann (personal communication) |  |
| 5-Me*                                  | Patuletin     | <i>Matricaria chamomilla</i> (Ast.), flowers                                     | Exner <i>et al.</i> (1981)          |  |
| 6-Me ( <i>G</i> )                      |               | synthesis:                                                                       | Bhardwaj <i>et al.</i> (1978b)      |  |
|                                        |               |                                                                                  |                                     |  |
| 3'-Me ( <i>G only</i> )                |               | ° <i>Artemisia</i> spp. (Ast.), leaf                                             | E. Rodriguez <i>et al.</i> (1972b)  |  |
| 3,6-di-Me                              | Axillarin     | <i>Chrysanthamnus viscidiflorus</i> (Ast.), leaf                                 | Urbatsch <i>et al.</i> (1975)       |  |
|                                        |               | <i>Flourensia ilicifolia</i> (Ast.), aerial parts                                | Dillon and Mabry (1977)             |  |
|                                        |               | <i>Didiera madagascariensis</i> (Didier.), aerial parts                          | Rabesa and Lebreton (1977)          |  |
|                                        |               | <i>Tetragonotheca helianthoides</i> (Ast.), leaf                                 | Bacon <i>et al.</i> (1978)          |  |
|                                        |               | <i>Didiera trollii</i> , <i>Decarya madagascariensis</i> (Didier.), aerial parts | Rabesa (1980)                       |  |
|                                        |               | <i>Neurolaena oaxacana</i> (Ast.), leaf                                          | Ulubelen <i>et al.</i> (1980b)      |  |
|                                        |               | <i>Matricaria chamomilla</i> (Ast.), flower                                      | Exner <i>et al.</i> (1981)          |  |
|                                        |               | <i>Parthenium</i> spp. (Ast.) leaf                                               | Mears (1980)                        |  |

Table 4.2 (Contd.)

| Substitution                | Trivial name                  | Plant source                                                                                                                                                                                                                                                                             | References                                                                                                                                                                                                                           |
|-----------------------------|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 3,7-di-Me (G)               | Tomentin                      | <i>Parthenium</i> spp. (Ast.), leaf<br><i>Neurolaena oaxacana</i> (Ast.) leaf                                                                                                                                                                                                            | Shen <i>et al.</i> (1976); Mears (1980)<br>Ulubelen <i>et al.</i> (1980b)                                                                                                                                                            |
| 6,7-di-Me (G)               | Eupatolitin                   | <i>Brickellia laciniata</i> (Ast.), leaf<br><i>Brickellia dentata</i> (Ast.), leaf<br><i>Brickellia veronicaefolia</i> (Ast.), leaf<br><i>Matricaria chamomilla</i> (Ast.), flower                                                                                                       | Wagner <i>et al.</i> (1976, 1977b)<br>Timmermann <i>et al.</i> (1979a)<br>Ulubelen <i>et al.</i> (1980a)<br>Roberts <i>et al.</i> (1980)<br>Exner <i>et al.</i> (1981)                                                               |
| 6,3'-di-Me (G)              | Spinacetin                    | <i>Chrysothamnus viscidiflorus</i> (Ast.), leaf<br><i>Brickellia californica</i> (Ast.), leaf<br><i>Brickellia laciniata</i> (Ast.), leaf<br><i>Brickellia laciniata</i> (Ast.), leaf<br>° <i>Artemisia</i> , 3 spp. (Ast.), aerial parts<br><i>Parthenium rollinsianum</i> (Ast.), leaf | Wagner <i>et al.</i> (1974)<br>Urbatsch <i>et al.</i> (1975)<br>Mues <i>et al.</i> (1979)<br>Timmermann <i>et al.</i> (1979a)<br>Timmermann <i>et al.</i> (1979a)<br>E. Rodriguez <i>et al.</i> (1972b)<br>Shen <i>et al.</i> (1976) |
| 6,4'-di-Me*<br>3,6,7-tri-Me | Laciniatin<br>Chrysosplenol-D | <i>Blumea lacera</i> (Ast.), leaf<br><i>Brickellia veronicaefolia</i> (Ast.), aerial parts<br><i>Matricaria chamomilla</i> (Ast.), flower                                                                                                                                                | Rao <i>et al.</i> (1977)<br>Roberts <i>et al.</i> (1980)<br>Exner <i>et al.</i> (1981)                                                                                                                                               |
| 3,6,3'-di-Me (G)            | Jaceidin                      | <i>Chrysothamnus viscidiflorus</i> (Ast.), leaf<br><i>Centaurea salicifolia</i> (Ast.), aerial parts<br><i>Flourensia illicifolia</i> (Ast.), aerial parts<br><i>Didiera madagascariensis</i> , <i>D. trollii</i> (Didier.), aerial parts                                                | Urbatsch <i>et al.</i> (1975)<br>Zapsochnaya <i>et al.</i> (1977)<br>Dillon and Mabry (1977)<br>Rabesa (1980)                                                                                                                        |
| 3,6,4'-tri-Me               | Centaureidin                  | <i>Matricaria chamomilla</i> (Ast.), flower<br><i>Prunus cerasus</i> (Ros.), bud excretion<br><i>Alnus</i> , 4 spp. (Bet.), bud excretion<br><i>Tetragonotheca repanda</i> (Ast.), leaf<br><i>Brickellia laciniata</i> (Ast.), leaf<br><i>Brickellia cylindracea</i> (Ast.), leaf        | Exner <i>et al.</i> (1981)<br>Wollenweber (unpublished)<br>Wollenweber (1975b)<br>Bacon <i>et al.</i> (1978)<br>Timmermann <i>et al.</i> (1979a)<br>Timmermann (personal communication)                                              |

|                         |                 |                                                                                     |                                     |
|-------------------------|-----------------|-------------------------------------------------------------------------------------|-------------------------------------|
| 3,7,3'-tri-Me           | Chrysosplenol-C | <i>Parthenium bipinnatifidum</i> , <i>P. glomeratum</i> (Ast.), aerial parts        | E. Rodriguez (1977)                 |
|                         |                 | <i>Chrysosplenium alternifolium</i> , <i>C. oppositifolium</i> (Sax.), aerial parts | Jay and Voirin (1976)               |
| 3,7,4'-tri-Me           | Oxyyanin-B      | <i>Disemonanthus benthamianus</i> (Leg.), heartwood                                 | Malan and Roux (1979)               |
| 6,7,3'-tri-Me (G only)* | Veronicafolin   | <i>Brickellia veronicaefolia</i> (Ast.), leaf                                       | Roberts <i>et al.</i> (1980)        |
|                         |                 | <i>Brickellia chlorolepis</i> (Ast.), leaf                                          | Ulubelen <i>et al.</i> (1980a)      |
| 6,7,4'-tri-Me           | Eupatin         | <i>Brickellia californica</i> (Ast.), leaf                                          | Mues <i>et al.</i> (1979)           |
|                         |                 | <i>Brickellia lacinata</i> (Ast.), leaf                                             | Timmermann <i>et al.</i> (1979a)    |
|                         |                 | <i>Brickellia dentata</i> (Ast.), leaf                                              | Ulubelen <i>et al.</i> (1980a)      |
|                         |                 | <i>Brickellia veronicaefolia</i> (Ast.), leaf                                       | Roberts <i>et al.</i> (1980)        |
| 3,5,6,3'-tetra-Me*      |                 | <i>Chrysorhannus visidiflorus</i> (Ast.), leaf                                      | Urbatsch <i>et al.</i> (1975)       |
| 3,6,7,3'-tetra-Me (G)   | Chrysosplenetin | ° <i>Lepidophyllum quadrangulare</i> (Ast.), leaf                                   | Marini-Bettolo <i>et al.</i> (1957) |
|                         |                 | <i>Parthenium</i> , 3 spp. (Ast.), leaf                                             | E. Rodriguez (1977)                 |
|                         |                 | <i>Digitalis thapsi</i> (Scroph.), leaf                                             | Pascual Teresa <i>et al.</i> (1980) |
| 3,6,7,4'-tetra-Me       | Casticin        | <i>Achillea millefolium</i> (Ast.), flowerhead                                      | Falk <i>et al.</i> (1975)           |
|                         |                 | <i>Parthenium</i> , 3 spp. (Ast.), leaf                                             | E. Rodriguez (1977)                 |
|                         |                 | <i>Brickellia chorolepis</i> (Ast.), leaf                                           | Timmermann <i>et al.</i> (1979a)    |
|                         |                 | <i>Brickellia lacinata</i> (Ast.), leaf                                             | Ulubelen <i>et al.</i> (1980a)      |
|                         |                 | <i>Brickellia veronicaefolia</i> (Ast.), leaf                                       | Roberts <i>et al.</i> (1980)        |
| 5,6,7,4'-tetra-Me       | Eupatoretin     | <i>Vitex trifoliata</i> (Verb.), (whole plant)                                      | Nair and Subramanian (1975)         |
| 3,6,3',4'-tetra-Me      | Bonanzin        | <i>Parthenium ligulatum</i> (Ast.), leaf                                            | Rodriguez (1977)                    |
| 3,7,3',4'-tetra-Me*     |                 | <i>Disemonanthus benthamianus</i> (Leg.), heartwood                                 | Malan and Roux (1979)               |
| 3,6,7,3',4'-penta-Me    | Artemetin       | <i>Achillea millefolium</i> (Ast.), flowerhead                                      | Falk <i>et al.</i> (1975)           |
|                         |                 | <i>Vitex trifoliata</i> (Verb.), leaf                                               | Nair and Subramanian (1975)         |
|                         |                 | <i>Parthenium rollinsianum</i> (Ast.), leaf                                         | E. Rodriguez (1977)                 |
|                         |                 | <i>Blumea lacera</i> (Ast.), leaf                                                   | Rao <i>et al.</i> (1977)            |
|                         |                 | <i>Sideritis gomerae</i> (Lam.), aerial parts                                       | González <i>et al.</i> (1978)       |
|                         |                 | <i>Brickellia cylindracea</i> , <i>B. veronicaefolia</i> (Ast.), leaf               | Roberts <i>et al.</i> (1980)        |
|                         |                 | <i>Brickellia chlorolepis</i> (Ast.), leaf                                          | Ulubelen <i>et al.</i> (1980a)      |
| 3,5,6,7,3',4'-hexa-Me   |                 |                                                                                     |                                     |
| (3,5,7,8,2',4'-hexa-OH) |                 |                                                                                     |                                     |
| 3,7,8,2'-tetra-Me*      |                 |                                                                                     | Jay <i>et al.</i> (1979b)           |
| 3,7,8,2',4'-penta-Me*   |                 |                                                                                     | Jav <i>et al.</i> (1979b)           |

Table 4.2 (Contd.)

| Substitution                                                                                                                                                                                                                                                                                    | Trivial name              | Plant source                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | References                                                                                                                                                                                                                                                                                                                   |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 3,5,7,8,3',4'-hexa-OH (G)<br>7-Me (G only)                                                                                                                                                                                                                                                      | Gossypetin<br>Ranupenin   | (see Section 4.5)<br><i>Atraphaxis purpurea</i> (Polygon.), leaf<br><i>Eriogonum nudum</i> (Polygon), flower<br><i>Leptocarpus similis</i> , <i>Staberoha cernus</i> (Rest.), aerial parts<br>synthesis:<br><i>Lotus corniculatus</i> (Leg.), leaf<br><i>Eriogonum nudum</i> (Polygon.),<br><i>Geraea canescens</i> (Ast.), flower<br>synthesis:<br><i>Coronilla valentina</i> (Leg.), flower<br><i>Larrea divaricata</i> , <i>L. tridentata</i> (Zyg.), leaf resin<br>synthesis:<br><i>Notholaena affinis</i> (Polypod.), (as ester with butyric<br>and acetic acid) farinose exudate on frond | Chumalov (1976)<br>Harborne <i>et al.</i> (1978)<br>Harborne (1979)<br>Wagner <i>et al.</i> (1977c)<br>Jay <i>et al.</i> (1978a)<br>Harborne <i>et al.</i> (1978)<br>Wagner <i>et al.</i> (1977c)<br>Harborne, (1981)<br>Sakakibara <i>et al.</i> (1976)<br>Wagner <i>et al.</i> (1977b)<br>Wollenweber <i>et al.</i> (1978) |
| 8-Me (G only)                                                                                                                                                                                                                                                                                   | Corniculatusin            | <i>Heteromma simplicifolia</i> (Ast.), aerial parts                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Bohlmann and Fritz (1979)                                                                                                                                                                                                                                                                                                    |
| 3'-Me (G only)<br>3,7-di-Me<br>3,8-di-Me<br>7,4'-di-Me (G)                                                                                                                                                                                                                                      | Limocitrin                | <i>Cyanostegia angustifolia</i> , (Verb.), leaf<br><i>Larrea tridentata</i> (Zyg.), leaf resin<br><i>Heteromma simplicifolia</i> (Ast.), aerial parts                                                                                                                                                                                                                                                                                                                                                                                                                                           | Ghisalberti <i>et al.</i> (1967)<br>Sakakibara <i>et al.</i> (1976)<br>Bohlmann and Fritz (1979)                                                                                                                                                                                                                             |
| 8,3'-di-Me (G)<br>8,4'-di-Me (G only)<br>3,7,8-tri-Me<br>3,7,3'-tri Me*<br>3,8,3'-tri-Me<br>7,8,3'-tri-Me*<br>3,7,8,3'-tetra-Me<br>3,7,8,4'-tetra-Me<br>3,7,3',4'-tetra-Me<br>3,8,3',4'-tetra-Me*<br>3,7,8,3',4'-penta-Me<br>3,5,7,8,3',4'-hexa-Me<br>(3,5,7,2',3',4'-hexa-OH)<br>3,7,4'-tri-Me | Ternatin<br><br>Apuleidin | <i>Heteromma simplicifolia</i> (Ast.), aerial parts<br>synthesis:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Kalra <i>et al.</i> (1975)                                                                                                                                                                                                                                                                                                   |

|                            |                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                   |
|----------------------------|---------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 3,5,7,2',4',5'-hexa-OH     | 5'-OH-morin         | <i>Geranium macrorrhizum</i> (Geran.), aerial parts<br><i>Distemonanthus benthamianus</i> (Leg.), heartwood                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Ognyanov and Ivantcheva (1972)<br>Malan and Roux (1979)                                                                                                                                                                                           |
| 3,7,4'-tri-Me              | Oxyanin-A           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                   |
| 3,5,7,4'-tetra-Me          |                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                   |
| 3,7,4',5'-tetra-Me         |                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                   |
| 3,7,2',4',5'-penta-Me*     |                     | <i>Distemonanthus benthamianus</i> (Leg.), heartwood                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Malan and Roux (1979)                                                                                                                                                                                                                             |
| 3,5,7,4',5'-penta-Me*      |                     | <i>Distemonanthus benthamianus</i> (Leg.), heartwood                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Malan and Roux (1979)                                                                                                                                                                                                                             |
| 3,5,7,2',4',5'-hexa-Me*    |                     | <i>Distemonanthus benthamianus</i> (Leg.), heartwood                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Malan and Roux (1979)                                                                                                                                                                                                                             |
| (3,6,7,2',4',5'-hexa-OH)   |                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                   |
| 3,6,7,4'-tetra-Me          | 5-O-Demethylapulein |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                   |
| 3,5,7,3',4',5'-hexa-OH (G) | Myricetin           | <i>Soymidia febrifuga</i> (Mel.), heartwood                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Rao <i>et al.</i> (1979)                                                                                                                                                                                                                          |
| 3-Me (G only)              | Annulatin           | synthesis:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Chhabra <i>et al.</i> (1976b)                                                                                                                                                                                                                     |
| 5-Me (G only)              | Europetin           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                   |
| 7-Me (G only)              | Laricitrin          | <i>Larix sibirica</i> (Pin.)<br><i>Cedrus atlantica</i> (Pin.)<br><i>Tetragonolobus siliquosus</i> (Leg.)<br><i>Elegia galpinii</i> , <i>E. parviflora</i> (Rest.), stem<br><i>Ginkgo biloba</i> (Gink.), leaf<br><i>Liatris pauciflora</i> (Ast.), aerial parts<br><i>Elaeocarpus lanceifolius</i> (Elaeoc.), leaf<br><i>Elaeocarpus floribundus</i> (Elaeoc.), leaf<br><i>Alluaudia</i> , 6 spp., <i>Decarya madagascariensis</i> (Didier.), stem bark<br><i>Alluaudia ascendens</i> <i>A. procera</i> , <i>Decarya madagascariensis</i> (Didier.), stem bark<br><i>Artemisia monosperma</i> (Ast.), flowerhead<br><i>Heuchera micrantha</i> var. <i>diversifolia</i> (Sax.), aerial parts<br><i>Elegia</i> spp. (Rest.) stem | Tyukavkina <i>et al.</i> (1974)<br>Niemann (1977)<br>Jay <i>et al.</i> (1978b)<br>Harborne (1979)<br>Geiger (1979)<br>Iyengar <i>et al.</i> (1976)<br>Ray <i>et al.</i> (1976)<br>Dasgupta <i>et al.</i> (1977)<br>Rabesa (1980)<br>Rabesa (1980) |
| 4'-Me (G)                  | Mearnsetin          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                   |
| 3,4'-di-Me*                |                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                   |
| 3,5'-di-Me*                |                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                   |
| 3,5'-di-Me (G)             | Syringetin          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Khafagy <i>et al.</i> (1979)<br>Wilkins and Bohm (1976)<br>Harborne (1979)                                                                                                                                                                        |
| 3,7,4'-tri-Me              |                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                   |
| 7,3',4'-tri-Me             |                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                   |
| 3,7,3',4'-tetra-Me         |                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Kumari <i>et al.</i> (1979)<br>Gurni (1979)                                                                                                                                                                                                       |

Table 4.2 (Contd.)

| Substitution                                       | Trivial name     | Plant source                                                                                                                        | References                                 |
|----------------------------------------------------|------------------|-------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| 3,7,3',4',5'-penta-Me                              | Combretol        | <i>Betula nigra</i> (Bet.), bud excretion<br><i>Notholaena candida</i> var. <i>candida</i> (Polypod.),<br>farinose exudate on frond | Wollenweber (1976a)<br>Wollenweber (1976b) |
| (3,5,6,7,8,2',4'-hepta-OH)<br>3,6,7,8-tetra-Me*    |                  | <i>Notholaena affinis</i> (Polypod.), farinose exudate on frond                                                                     | Jay <i>et al.</i> (1979a)                  |
| 3,6,7,8,2'-penta-Me*                               |                  | <i>Notholaena affinis</i> (Polypod.), farinose exudate on frond                                                                     | Jay <i>et al.</i> (1979a)                  |
| 3,6,7,8,4'-penta-Me*                               |                  | <i>Notholaena affinis</i> (Polypod.), farinose exudate on frond                                                                     | Jay <i>et al.</i> (1979a)                  |
| 3,6,7,8,2',4'-hexa-Me*                             |                  | <i>Notholaena affinis</i> (Polypod.), farinose exudate on frond                                                                     | Jay <i>et al.</i> (1979a)                  |
| (3,5,6,7,8,3',4'-hepta-OH)<br>3,6,8-tri-Me         |                  | <i>Pluchea sagittalis</i> (Ast.)                                                                                                    | Martino <i>et al.</i> (1976)               |
| 6,8,3'-tri-Me                                      | Limocitrol       |                                                                                                                                     |                                            |
| 6,8,4'-tri-Me                                      | Isolimocitrol    |                                                                                                                                     |                                            |
| 3,6,8,3'-tetra-Me*                                 |                  | <i>Chrysothamnus viscidiflorus</i> (Ast.), leaf                                                                                     | Urbatsch <i>et al.</i> (1975)              |
| 3,6,7,8,3'-penta-Me*                               |                  | <i>Calycopteris floribundus</i> (Combr.), leaf                                                                                      | Rama Rao and Varadan, (1973)               |
|                                                    |                  | <i>Digitalis thapsi</i> (Scroph.), leaf                                                                                             | Pascual Teresa <i>et al.</i> (1980)        |
| 3,6,7,8,3',4'-hexa-Me                              |                  |                                                                                                                                     |                                            |
| 5,6,7,8,3',4'-hexa-Me                              | Natsudadain      | <i>Citrus</i> cult. (Rut.), fruit peel                                                                                              | Tatum and Berry (1978)                     |
| 3,5,6,7,8,3',4'-hepta-Me                           |                  |                                                                                                                                     |                                            |
| (3,5,6,7,2',3',4'-hepta-OH)<br>3,7,4'-tri-Me       | Apuleisin        | <i>Distemonanthus benthamianus</i> (Leg.), heartwood                                                                                | Malan and Roux (1979)                      |
| 3,5,6,7,2',3',4'-hepta-Me*                         |                  |                                                                                                                                     |                                            |
| (3,5,6,7,2',4',5'-hepta-OH)<br>3,5,6,7,4'-penta-Me | Apulein          | <i>Distemonanthus benthamianus</i> (Leg.), heartwood                                                                                | Malan and Roux (1979)                      |
| 3,5,7,4',5'-penta-Me*                              |                  | <i>Distemonanthus benthamianus</i> (Leg.), heartwood                                                                                | Malan and Naidoo (1980)                    |
| 3,7,2',4',5'-penta-Me*                             |                  | <i>Distemonanthus benthamianus</i> (Leg.), heartwood                                                                                | Malan and Naidoo (1980)                    |
| 3,5,6,7,2',4',5'-hepta-Me*                         |                  |                                                                                                                                     |                                            |
| (3,5,6,7,3',4',5'-hepta-OH)<br>3,6-di-Me*          | (6-OH-myricetin) | <i>Alluaudia ascendens</i> (Didier.), stem bark                                                                                     | Rabesa and Voirin (1979d)                  |
| 3,4'-di-Me*                                        |                  | <i>Alluaudia ascendens</i> (Didier.), stem bark                                                                                     | Rabesa and Voirin (1979d)                  |



|                                             |                                                                                                          |                                 |
|---------------------------------------------|----------------------------------------------------------------------------------------------------------|---------------------------------|
| 3,6,3'-tri-Me*                              | <i>Alluaudia ascendens</i> , <i>A. procera</i> , <i>Decarya madagascariensis</i> (Didier.), aerial parts | Rabesa (1980)                   |
| 3,6,4'-tri-Me*                              | <i>Alluaudia ascendens</i> , <i>A. procera</i> , <i>Decarya madagascariensis</i> (Didier.), aerial parts | Rabesa (1980)                   |
| 6,3',4'-tri-Me ( <i>G only</i> )*           | <i>Tillandsia usneoides</i> (Brom.)                                                                      | Williams (1978)                 |
| 3,3',5'-tri-Me                              | <i>Gardensia fosbergii</i> (Rub.) bud exudate                                                            | Gunatilaka <i>et al.</i> (1979) |
| 3,5,6,5'-tetra-Me                           |                                                                                                          |                                 |
| 3,6,7,4'-tetra-Me                           |                                                                                                          |                                 |
| 3,6,3',4'-tetra-Me*                         |                                                                                                          |                                 |
| 3,6,3',5'-tetra-Me*                         |                                                                                                          |                                 |
| 5,6,3',5'-tetra-Me                          |                                                                                                          |                                 |
| 3,7,3',4'-tetra-Me                          |                                                                                                          |                                 |
| 3,7,7,4'-tetra-Me                           |                                                                                                          |                                 |
| 3,5,7,3',4'-penta-Me                        |                                                                                                          |                                 |
| 3,6,7,3',4'-penta-Me                        |                                                                                                          |                                 |
| 3,6,7,3',5'-penta-Me*                       |                                                                                                          |                                 |
| 6,7,3',4',5'-penta-Me                       |                                                                                                          |                                 |
| 3,5,6,7,3',5'-hexa-Me                       |                                                                                                          |                                 |
| 3,5,6,7,3',4',5'-hepta-Me                   |                                                                                                          |                                 |
| 3,5,7,8,3',4',5'-hepta-OH ( <i>G only</i> ) |                                                                                                          |                                 |
| 3,7,4'-tri-Me*                              |                                                                                                          |                                 |
| 3,7,8,4'-tetra-Me*                          |                                                                                                          |                                 |
| 3,8,4',5'-tetra-Me                          |                                                                                                          |                                 |
| 3,8,3',4',5'-penta-Me*                      |                                                                                                          |                                 |
| 7,8,3',4',5'-penta-Me*                      |                                                                                                          |                                 |
| 3,5,7,8,3',4',5'-hepta-Me                   |                                                                                                          |                                 |
| (3,5,6,7,8,3',4',5'-octa-OH)                |                                                                                                          |                                 |
| 3,6,7,8,4',5'-hexa-Me                       |                                                                                                          |                                 |
| 3,5,6,7,3',4',5'-hepta-Me                   |                                                                                                          |                                 |
| 3,5,6,7,8,3',4',5'-octa-Me                  |                                                                                                          |                                 |
| Apuleitrin                                  | <i>Gardensia fosbergii</i> (Rub.) bud exudate                                                            | Kalra <i>et al.</i> (1977)      |
| Apuleirin                                   | <i>Gardensia fosbergii</i> (Rub.) bud exudate                                                            | Gunatilaka <i>et al.</i> (1979) |
| Murrayanol                                  | <i>Murraya omphalocarpa</i> (Rut.), fruit                                                                | Kalra <i>et al.</i> (1977)      |
|                                             | <i>Gardenia fosbergii</i> (Rub.) bud exudate                                                             | Gunatilaka <i>et al.</i> (1979) |
|                                             | <i>Murraya paniculata</i> (Rut.), leaf                                                                   | Wu <i>et al.</i> (1980)         |
|                                             | <i>Murraya omphalocarpa</i> (Rut.), fruit                                                                | Gunatilaka <i>et al.</i> (1979) |
|                                             |                                                                                                          | De Silva <i>et al.</i> (1980)   |
|                                             |                                                                                                          | Wu <i>et al.</i> (1980)         |
| Hibiscetin                                  | <i>Solanum</i> spp. (Solan.)                                                                             | Whalen and Mabry (1979)         |
|                                             | <i>Solanum</i> spp. (Solan.)                                                                             | Whalen and Mabry (1979)         |
| Conyzatin                                   | <i>Conyza stricta</i> (Ast.), whole plant                                                                | Tandon and Rastogi (1977)       |
|                                             | <i>Heteromma simplicifolia</i> (Ast.), aerial parts                                                      | Bohlmann and Fritz (1979)       |
| Digitratin                                  |                                                                                                          |                                 |
| Exoticin                                    |                                                                                                          |                                 |

Key: G = occurs in glycosidic combination; \* = compound newly reported during 1975-1980; ° = earlier report, not included in 'The flavonoids'.

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General observations on the frequencies of different substitution patterns in the flavonoid skeleton have been made by Harborne (1967) and Gottlieb (1975) and are still valid. The distribution and accumulation of free aglycones in certain families and their correlation with other structural features have been reviewed elsewhere (Wollenweber and Dietz, 1981). Although a general discussion of flavones and flavonols with 'normal' substitution patterns is not therefore needed, brief comments on flavonoids with more unusual patterns (e.g. isoprenoid constituents, additional ring systems) are necessary. To our knowledge no report of important new routes for chemical synthesis of flavones and flavonols has appeared. References to the synthesis of certain individual compounds, however, are interesting enough to be included.

### 4.2 C-METHYLFLAVONOIDS

#### 4.2.1 Flavones

The first natural C-methylated flavonoid to be reported was the flavanone matteucinol (6,8-di-C-methylnaringenin). Today C-methylated compounds are known among every class of flavonoid, but they are still most abundant among the flavanones (Wollenweber and Dietz, 1981). In every known case C-methylation takes place at C-6 and/or C-8. In 'The Flavonoids' only four C-methylflavones were cited, and this number has not been augmented since. However, reports of eucalyptin from the leaf wax of two *Angophora* species as well as from the leaf of *Eugenia biflora* and *Myrcia citrifolia* deserve mention. Except for the presence of strobachrysin in *Pinus* species, C-methylated flavones are restricted in their occurrence to plants of the Myrtaceae.

#### 4.2.2 Flavonols

In the flavonol series, only two compounds (6-C-methylquercetin and 6-C-methylmyricetin) were known previously (Gottlieb, 1975) and these were reported from *Pinus ponderosa*. Meanwhile one new flavonol (sylpin) has been reported from *Pinus silvestris*, and two from the Californian goldenback fern. In addition, ten C-methylflavonols have been found in aglycone form in bark and spines of Didieraceae. This family, comprising only 11 species in four genera endemic to Madagascar, appears to produce C-methylflavonols as an extreme specialization. The compounds present are methyl derivatives of kaempferol and myricetin. Three further compounds, methyl derivatives of quercetin, also appear to occur in these plants (Rabesa, 1980). C-Methylation is regarded as a primitive character (Harborne, 1967). Taking into account that within the flavonols, it is always accompanied by O-methylation (except for pinoquercetin and 6-C-methylmyricetin) at C-3 and/or C-4' (except pityrogrammin), Rabesa (1980) assumed that O-methylation at these positions also might be regarded as a

primitive character, such methylation occurring at an early stage in the formation of the  $C_{15}$  skeleton.

#### 4.2.3 Formylflavones

A special type of *C*-methylflavone is represented by three flavones from *Unonawillii* (Table 4.3), the only formylflavones known as yet. [Two *C*-formylated chalcones have been found in *Psoralea corylifolia* (see B. K. Gupta *et al.*, 1980)]. Finally, it should be mentioned that one additional *C*-methylflavone (desmodol) is found among the pyranoflavones (Table 4.6).

### 4.3 METHYLENEDIOXYFLAVONOIDS

Methylenedioxyflavonoids were not treated as a separate group in 'The Flavonoids'. In the present chapter they have been listed separately to allow easier access. Completeness, however, cannot be guaranteed. Plant sources are cited for those compounds known before 1975. To our knowledge, since then six new flavones and five new flavonols with methylenedioxy groups have been reported. However, this type of substitution is more abundant among flavonols than among flavones. Only positions 6/7 and 3'/4' are concerned; in one compound (meliternatin), all four positions are so substituted. In general, methylenedioxy substitution is a rare feature among flavones and flavonols but is more abundant with the isoflavonoids (see Chapter 10). An earlier preliminary report of a methylenedioxyflavonol from chloroplasts of spinach (Oettmeier and Heupel, 1972) has still not been confirmed by more detailed studies.

### 4.4 FLAVONOIDS WITH OTHER SUBSTITUENTS

#### 4.4.1 Flavones and flavonols with isoprene substitution

Most of the compounds dealt with in this section are found in *Artocarpus*, *Morus* and *Tephrosia*, except for the flavonols with  $C_5$  and  $C_{10}$  side chains. Venkataraman's treatment (1975) of the flavones found in these genera was appropriate. However, the more formal setting out of these substances in tabular form should allow easier access to the relevant information. For this reason plant sources are given in Table 4.5 for those compounds already covered in 'The Flavonoids'. Only for the special flavonoids of *Tephrosia* and *Pityrogramma* separate treatment is still deemed to be justified.

The majority of the flavonoids listed in Tables 4.5–4.7 bear isoprenoid substituents. Simple  $C_5$  and  $C_{10}$  side chains occur as well as additional pyran and furan (or dihydrofuran) rings. The pyran ring is indicated in Table 4.6 by the abbreviation ODmp for the dimethylallyl unit ( $Me_2C-CH=CH-$ ) linked via

Table 4.3 C-Methylated flavonoids

| Substitution                            | Trivial name                   | Plant source                                                                                                                                                                                                                                                        | References                     |
|-----------------------------------------|--------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| <b>C-METHYLFLAVONES</b>                 |                                |                                                                                                                                                                                                                                                                     |                                |
| 5,7-di-OH, 6-Me                         | 6-Methylchrysin<br>Sideroxylin | ° <i>Eugenia biflora</i> , <i>Myrcia citrifolia</i> , (Myrtac.), leaf<br>° <i>Angophora lanceolata</i> , <i>A. subvelutina</i> , (Myrtac.), leaf wax<br><i>Unona lawii</i> (Anonac), stem<br><i>Unona lawii</i> (Anonac), stem<br><i>Unona lawii</i> (Anonac), stem | Gottlieb and Da Rocha (1972)   |
| 5,4'-di-OH, 7-OMe, 6,8-di-Me            |                                |                                                                                                                                                                                                                                                                     | Lamberton (1964)               |
| 5-OH, 7,4'-di-OMe, 6-Me                 |                                |                                                                                                                                                                                                                                                                     | Joshi and Gawad (1976)         |
| 5-OH, 7,4'-di-OMe, 6,8-di-Me            |                                |                                                                                                                                                                                                                                                                     | Joshi and Gawad (1976)         |
| 5,7-di-OH, 8-Me, 6-CHO                  | Eucalyptin                     |                                                                                                                                                                                                                                                                     |                                |
| 5,7-di-OH, 6-Me, 8-CHO                  | Unonal                         |                                                                                                                                                                                                                                                                     |                                |
| 5-OH, 7-OMe, 8-Me, 6-CHO                | Isounonal                      |                                                                                                                                                                                                                                                                     |                                |
|                                         | Unonal 7-Methyl ether          |                                                                                                                                                                                                                                                                     |                                |
| <b>C-METHYLFLAVONOLS</b>                |                                |                                                                                                                                                                                                                                                                     |                                |
| 5,7-di-OH, 3-OMe, 6,8-di-Me             |                                | <i>Pityrogramma triangularis</i> var. <i>triangularis</i> , (Polypod.),<br>farinose exudate on fronds                                                                                                                                                               | Dietz <i>et al.</i> (1981)     |
| 3,5,7-tri-OH, 8-OMe, 6-Me               | Pityrogrammin                  | <i>Pityrogramma triangularis</i> var. <i>triangularis</i> , (Polypod.),<br>farinose exudate on fronds                                                                                                                                                               | Star <i>et al.</i> (1975)      |
| 5,6,4'-tri-OH, 3-OMe, 8-Me              | Sylpin                         | <i>Pinus silbestris</i> , (Pin.)                                                                                                                                                                                                                                    | Medvedeva <i>et al.</i> (1977) |
| 5,7,4'-tri-OH, 3-OMe, 6-Me              |                                | <i>Alluaudia dumosa</i> (Didier.), aerial parts                                                                                                                                                                                                                     | Rabesa and Voirin (1978)       |
| 5,7,4'-tri-OH, 3-OMe, 6,8-di-Me         | Pinoqueretin                   | <i>Alluaudia dumosa</i> , <i>A. humbertii</i> (Didier.), aerial parts                                                                                                                                                                                               | Rabesa (1980)                  |
| 3,5,7,3',4'-penta-OH, 6-Me              |                                |                                                                                                                                                                                                                                                                     |                                |
| 3,5,7,3',4'-penta-OH, 6,8-di-Me         |                                | <i>Alluaudia humbertii</i> (Didier.), aerial parts                                                                                                                                                                                                                  | Rabesa (1980)                  |
| 5,7,4'-tri-OH, 3,3'-di-OMe, 6-Me        |                                | <i>Alluaudia humbertii</i> (Didier.), aerial parts                                                                                                                                                                                                                  | Rabesa (1980)                  |
| 3,5,7,3',4',5'-hexa-OH, 6-Me            | Alluaudiol                     | <i>Alluaudia humbertii</i> (Didier.), aerial parts                                                                                                                                                                                                                  | Rabesa (1980)                  |
| 5,7,3',4',5'-penta-OH, 3-OMe, 6-Me      |                                | <i>Alluaudia dumosa</i> (Didier.), bark                                                                                                                                                                                                                             | Rabesa and Voirin (1979a)      |
| 5,7,3',4',5'-penta-OH, 3-OMe, 6,8-di-Me |                                | <i>Alluaudia humbertii</i> (Didier.), bark                                                                                                                                                                                                                          | Rabesa (1980)                  |
| 3,5,7,3',5'-penta-OH, 4'-OMe, 6-Me      |                                | <i>Alluaudia humbertii</i> (Didier.), aerial parts                                                                                                                                                                                                                  | Rabesa (1980)                  |
|                                         | Dumosol                        | <i>Alluaudia dumosa</i> (Didier.),<br>aerial parts                                                                                                                                                                                                                  | Rabesa and Voirin (1979b)      |

|                                               |                                                                          |                                                        |
|-----------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------|
| 3,5,7,3',5'-penta-OH, 4'-OMe<br>6,8-di-Me     | <i>Alluaudia humbertii</i> (Didier.),<br>aerial parts                    | Rabesa and Voirin (1979c)                              |
| 5,7,3',5'-tetra-OH,<br>3,4'-di-OMe, 6-Me      | <i>Alluaudia dumosa</i> ,<br><i>A. humbertii</i> (Didier.), aerial parts | Rabesa and Voirin (1979b)<br>Rabesa and Voirin (1979c) |
| 5,7,3',5'-tetra-OH,<br>3,4'-di-OMe, 6,8-di-Me | <i>Alluaudia dumosa</i> ,<br><i>A. humbertii</i> (Didier.) aerial parts  | Rabesa and Voirin (1979b)                              |

Key: \* Compound newly reported during 1975-1980; ° = earlier report, not included in *The Flavonoids*.

Table 4.4 Methylendioxyflavonoids

| Substitution                                                 | Trivial name       | Plant source                                                                                    | References                       |
|--------------------------------------------------------------|--------------------|-------------------------------------------------------------------------------------------------|----------------------------------|
| <b>FLAVONES</b>                                              |                    |                                                                                                 |                                  |
| 5-OMe, 7,8-O <sub>2</sub> CH <sub>2</sub> *                  |                    | <i>Helichrysium mundii</i> (Ast.), root and aerial parts                                        | Bohlmann <i>et al.</i> (1978)    |
| 5,6-di-OMe, 3',4'-O <sub>2</sub> CH <sub>2</sub> *           |                    | <i>Milletia ovalifolia</i> (Leg.), leaf                                                         | Khan and Zaman (1974)            |
| 7-OH, 6-OMe, 3',4'-O <sub>2</sub> CH <sub>2</sub> *          | Prosogerin-A       | <i>Prosopis spiciqera</i> (Leg.), flower                                                        | Bhardwaj <i>et al.</i> (1979)    |
| 5,4'-di-OH, 6,7-O <sub>2</sub> CH <sub>2</sub> *             | Kanzakiflavone-2   | <i>Iris unguicularis</i> (Ir.), rhizome synthesis:                                              | Arisawa <i>et al.</i> (1976)     |
| 5,8-di-OH, 4'-OMe, 6,7-O <sub>2</sub> CH <sub>2</sub> *      | Kanzakiflavone-1   | <i>Iris unguicularis</i> (Ir.), rhizome                                                         | Bhardwaj <i>et al.</i> (1978b)   |
| 5,7-di-OH, 8-di-OMe, 3',4'-O <sub>2</sub> CH <sub>2</sub>    | Linderoflavone A   | synthesis:                                                                                      | Bhardwaj <i>et al.</i> (1978b)   |
| 5,6,7,8-tetra-OMe, 3',4'-O <sub>2</sub> CH <sub>2</sub>      | Linderoflavone B   | <i>Lindera lucida</i> (Laur.), root                                                             |                                  |
| 5,6,7,8,5'-penta-OMe, 3',4'-O <sub>2</sub> CH <sub>2</sub> * | Eupalestin         | <i>Lindera lucida</i> (Laur.), root                                                             | Le-Van and Pham (1979)           |
|                                                              |                    | <i>Eupatorium coelestinum</i> (syn. <i>Conoclinium coel.</i> )(Ast.), aerial (herbaceous) parts | Herz <i>et al.</i> (1980)        |
|                                                              |                    | <i>Ageratum corymbosum</i> (Ast.), aerial parts                                                 | Quijano <i>et al.</i> (1980)     |
| <b>FLAVONOLS</b>                                             |                    |                                                                                                 |                                  |
| 3,5-di-OMe, 6,7-O <sub>2</sub> CH <sub>2</sub> *             |                    | <i>Gomphrena martiana</i> (Amarant.), whole plant                                               | Buschi <i>et al.</i> (1979)      |
| 3,5-di-OMe, 6,7-O <sub>2</sub> CH <sub>2</sub>               | Meliteratin        | <i>Melicope</i> , 3 spp. (Rut.), wood                                                           |                                  |
| 3',4'-O <sub>2</sub> CH <sub>2</sub>                         |                    |                                                                                                 |                                  |
| 3,7-di-OMe, 3',4'-O <sub>2</sub> CH <sub>2</sub>             | Demethoxykanunigin | <i>Pongamia glabra</i> (Leg.), root and stem bark; heartwood                                    |                                  |
| 3,5,4'-tri-OH, 6,7-O <sub>2</sub> CH <sub>2</sub> *          | Gomphrenol         | <i>Gomphrena globosa</i> (Amar.), leaf                                                          | Bouillant <i>et al.</i> (1978)   |
| 3,7,3'-tri-OMe, 4',5'-O <sub>2</sub> CH <sub>2</sub>         | Kanugin            | <i>Pongamia glabra</i> (Leg.), root and stem bark; heartwood                                    | Subramanyan <i>et al.</i> (1977) |
| 5-OH, 3,6,7-tri-OMe, 3',4'-O <sub>2</sub> CH <sub>2</sub>    | Melisimplin        | <i>Melicope simplex</i> (Rut.), wood                                                            |                                  |
| 3,5,6,7-tetra-OMe, 3',4'-O <sub>2</sub> CH <sub>2</sub>      | Melisimplexin      | <i>Melicope simplex</i> <i>M. broadbentiana</i> (Rut.), wood                                    |                                  |

|                                                                  |            |                                                   |                             |
|------------------------------------------------------------------|------------|---------------------------------------------------|-----------------------------|
| 5-OH, 3,7,8-tri-OMe, 3',4'-O <sub>2</sub> CH <sub>2</sub> *      |            | <i>Pelea barbigera</i> (Rut.)<br>aerial parts?    | Higa and Scheuer (1974)     |
| 3,5,7,8-tetra-OMe, 3',4'-O <sub>2</sub> CH <sub>2</sub>          | Meliternin | <i>Melicope ternata</i><br>(Rut.), wood           |                             |
| 5,3',4'-tri-OH, 3-OMe, 6,7-O <sub>2</sub> CH <sub>2</sub>        |            | <i>Spinacia oleracea</i> (Chen.),<br>chloroplasts | (see text, Section 4.3)     |
| 5,3',4'-tri-OH, 3-OMe, 7,8-O <sub>2</sub> CH <sub>2</sub>        | Wharangin  | <i>Melicope ternata</i> (Rut.),<br>bark           |                             |
| 3,5,7-tri-OH, 6,8-di-OMe, 3',4'-O <sub>2</sub> CH <sub>2</sub> * | Melinervin | <i>Melicope perspicuinervia</i> (Rut.),<br>leaf   | Murphy <i>et al.</i> (1974) |
| 5-OH, 3,6,7,8-tetra-OMe, 3',4'-O <sub>2</sub> CH <sub>2</sub> *  |            | <i>Pelea barbigera</i> (Rut.),<br>aerial parts?   | Higa and Scheuer (1974)     |
| 3,5,6,7,8-penta-OMe, 3',4'-O <sub>2</sub> CH <sub>2</sub>        | Melibentin | <i>Melicope broadbentiana</i> (Rut.),<br>wood     |                             |

Key: \*Compound newly reported during 1975–1980.

Table 4.5 Flavones and flavonols with C<sub>5</sub>, C<sub>5</sub>-OH and C<sub>10</sub> side chains†

| Substitution                                             | Trivial name                            | Plant source                                                                              | References                                                                              |
|----------------------------------------------------------|-----------------------------------------|-------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| <b>FLAVONES</b>                                          |                                         |                                                                                           |                                                                                         |
| 7-OMe, 8-C <sub>5</sub> -OH*                             | <i>trans</i> -Lanceolatin               | <i>Tephrosia lanceolata</i> ,<br><i>T. purpurea</i> , roots<br><i>T. apollinea</i> (Leg.) | Ayengar <i>et al.</i> (1973)<br>Rao and Ranga Raju (1979)<br>Waterman and Khalid (1980) |
| 5,7-di-OMe, 8-C <sub>5</sub> -OH*                        | <i>cis</i> -Tephrostachin               | <i>Tephrosia polystachyoides</i> (Leg.)                                                   | Vleggar <i>et al.</i> (1973)                                                            |
| 5,7-di-OMe,<br>8-CH = CH-C(Me) = CH <sub>2</sub>         | <i>trans</i> -Tephrostachin             | <i>Tephrosia bracteolata</i> (Leg.), seed                                                 | Khalid and Waterman (1981)                                                              |
| 5,7,2',4'-tetra-OH, 6-C <sub>5</sub>                     | <i>trans</i> -Anhydro-<br>tephrostachin | <i>Tephrosia bracteolata</i><br>(Leg.), seed                                              | Khalid and Waterman (1981)                                                              |
| 5,7,2',4'-tetra-OH, 6-C <sub>5</sub> -OH                 | Artocarpesin                            | <i>Artocarpus</i> (Morac.)                                                                |                                                                                         |
| 5,7,2',4'-tetra-OH, 3,6-di-C <sub>5</sub>                | Oxidihydroartocarpesin                  | <i>Artocarpus</i> (Morac.)                                                                |                                                                                         |
| 5,7,2',4'-tetra-OH, 3,6-di-C <sub>5</sub>                | Norartocarpin                           | <i>Artocarpus</i>                                                                         |                                                                                         |
| 5,7,2',4'-tetra-OH, 3,6-di-C <sub>5</sub>                | Mulberrin                               | <i>Morus</i>                                                                              |                                                                                         |
| 5,2',4'-tri-OH, 7-OMe, 3-C <sub>5</sub> *                | Integrin                                | <i>Artocarpus integer</i> (Mor.)                                                          | Pendse <i>et al.</i> (1976)                                                             |
| 5,2',4'-tri-OH, 7-OMe, 3,6-di-C <sub>5</sub>             | Artocarpin                              | synthesis of trimethyl-ether                                                              | Midge <i>et al.</i> (1977)                                                              |
| 5,7,2',4'-tetra-OH, 3,8-di-C <sub>5</sub> *              | Kuwanone C                              | <i>Artocarpus</i>                                                                         |                                                                                         |
| 5,7,3',4'-tetra-OH, 8-C <sub>5</sub>                     |                                         | <i>Morus alba</i> (Mor.),<br>root bark                                                    | Nomura <i>et al.</i> (1977)                                                             |
| 7,4',6'-tri-OH, 3-C <sub>10</sub>                        | Rubraflavone A                          | <i>Xanthium</i> (Ast.)                                                                    | Nomura <i>et al.</i> (1978b)                                                            |
| 7,4',6'-tri-OH, 3-C <sub>10</sub> , 8-C <sub>5</sub>     | Rubraflavone B                          | <i>Morus</i>                                                                              |                                                                                         |
| 5,7,4',6'-tetra-OH, 3-C <sub>10</sub> , 6-C <sub>5</sub> | Rubraflavone C                          | <i>Morus</i>                                                                              |                                                                                         |
| <b>FLAVONOLS</b>                                         |                                         |                                                                                           |                                                                                         |
| 3,7,4'-tri-OH, 8-C <sub>5</sub> -OH                      |                                         | <i>Phellodendron</i> (Rut.)                                                               |                                                                                         |
| 3,5,7,8-tetra-OH, 6-C <sub>5</sub> *                     |                                         | <i>Platanus acerifolia</i> (Plat.),<br>bud excretion                                      | Egger <i>et al.</i> (1972)                                                              |
| 3,5,7,4'-tetra-OH, 8-C <sub>5</sub>                      | Noranhydrocaritin                       | <i>Sophora</i> (Leg.)                                                                     |                                                                                         |
| 3,5,7,4'-tetra-OH, 8-C <sub>5</sub> -OH                  | Noricaritin                             | <i>Epimedium</i> (Berb.)<br><i>Epimedium</i> (Berb.)                                      |                                                                                         |



|                                                     |                   |                             |                         |
|-----------------------------------------------------|-------------------|-----------------------------|-------------------------|
| 3,5,4'-tri-OH, 7-OMe, 8-C <sub>5</sub>              | Isoanhydrocaritin | <i>Sophora</i> (Leg.)       | Fraser and Lewis (1973) |
| 3,5,7-tri-OH, 4'-OMe, 8-C <sub>5</sub> -OH          | Icaritin          | <i>Epimedium</i> (Berb.)    |                         |
| 3,5,7,3',4'-penta-OH, 6-C <sub>5</sub> -OH (G only) |                   |                             |                         |
| 5,4'-di-OH, 3,3'-di-OMe, 7-O-C <sub>5</sub> * ‡     |                   | <i>Euodia glabra</i> (Rub.) |                         |
| 5,4'-di-OH, 3,7,3'-tri-OMe, 8-C <sub>5</sub>        |                   | <i>Phebalium</i> (Rut.)     |                         |

Key: \* = Compound newly reported during 1975–1980; G = Occurs in glycosidic combination.

† C<sub>5</sub> = Me<sub>2</sub>CH-CH=CH<sub>2</sub> or Me<sub>2</sub>C=CH-CH<sub>2</sub>; C<sub>5</sub>-OH = Me<sub>2</sub>C(OH)CH<sub>2</sub>CH<sub>2</sub>; C<sub>10</sub> = (Me<sub>2</sub>C = CH-CH<sub>2</sub>)<sub>2</sub>.

‡ Note O-prenylation!

Table 4.6 Pyranoflavones and pyranoflavonols

| Substitution <sup>†</sup>                             | Trivial name         | Plant source                                   | References                                                  |
|-------------------------------------------------------|----------------------|------------------------------------------------|-------------------------------------------------------------|
| PYRANOFILAVONES                                       |                      |                                                |                                                             |
| 5-OH,7,8-ODmp*                                        | Isopongaflavone      | <i>Derris obtusa</i> (Leg.)                    | do Nascimento <i>et al.</i> (1976)                          |
| 5-OMe, 7,8-ODmp*                                      |                      | <i>Pongamia glabra</i> (Leg.), seed            | Roy <i>et al.</i> (1977)<br>(includes synthesis)            |
|                                                       |                      | <i>Tephrosia bracteolata</i> (Leg.), seed      | Khalid and Waterman (1981)                                  |
| 5-OMe, 7,6-ODmp*                                      | Praeansone B         | <i>Tephrosia praecana</i> (Leg.), seed         | Camele <i>et al.</i> (1980)                                 |
| 5,4'-di-OH, 7,6-ODmp*                                 |                      | <i>Pamburus missionis</i> (Rut.)               | Dreyer and Park (1975)                                      |
| 5,4'-di-OH, 7,6-ODmp, 6',3-ODmp                       | Cyclomulberochromene | <i>Morus</i>                                   |                                                             |
| 5,4'-di-OH, 7,8-ODmp, 6',3-ODmp*                      |                      | <i>Morus alba</i> (Mor.) root bark             | Nomura <i>et al.</i> (1976)<br>Nomura <i>et al.</i> (1978a) |
| 5,2',4'-tri-OH,7,6-ODmp                               | Cycloartocarpesin    | <i>Artocarpus</i>                              |                                                             |
| 5,2',4'-tri-OH,3-C <sub>5</sub> ,7,6-ODmp             |                      | <i>Morus</i> (Mor.)                            |                                                             |
| 5,7,2'-tri-OH,3-C <sub>5</sub> ,3',4'-ODmp*           | Mulberochromene      | <i>Morus alba</i> (Mor.), root bark            | Nomura <i>et al.</i> (1977)<br>Nomura <i>et al.</i> (1978b) |
|                                                       |                      | <i>Morus alba</i> (Mor.), root bark            | Nomura <i>et al.</i> (1977b)                                |
| 5,2',4'-tri-OH,3-C <sub>5</sub> -OH, 7,8-ODmp*        | Oxydihydromorusin    | <i>Morus alba</i> (Mor.), root bark            | Nomura <i>et al.</i> (1976)<br>Nomura <i>et al.</i> (1977)  |
| 5,2',4'-tri-OH,3-C <sub>5</sub> , 7,8-ODmp*           |                      | <i>Morus alba</i> root bark                    | Nomura <i>et al.</i> (1978a)                                |
| 5,7,4'-tri-OH,3-C <sub>5</sub> , 2',3'-ODmp*          | Morusin              | <i>Morus alba</i> root bark                    | Nomura <i>et al.</i> (1977b)                                |
|                                                       |                      | <i>Morus alba</i> root bark                    | Nomura <i>et al.</i> (1977)                                 |
| 5,2',4'-tri-OH,3-C <sub>10</sub> , 7,6-ODmp           | Rubraflavone D       | <i>Morus</i>                                   |                                                             |
| 5,7,4'-tri-OH,6-C <sub>5</sub> , 6',3-ODmp            |                      | <i>Morus</i>                                   |                                                             |
| 5,4'-di-OH,7-OMe, 6-C <sub>5</sub> , 6',3-ODmp        | Cycloartocarpin      | <i>Artocarpus</i>                              |                                                             |
| 5,3',4'-tri-OH,6-CH <sub>3</sub> , 7,8-ODmp*          |                      | <i>Desmodium caudatum</i> (Leg.) root and stem | Ueno <i>et al.</i> (1978)                                   |
| 5,3',4'-tri-OH,8-C <sub>5</sub> , 7,6-ODmp, 6',3-ODmp | Cycloheterophyllin   | <i>Artocarpus</i>                              |                                                             |
| 5,3',4',6'-tetra-OH,5'-C <sub>5</sub> , 7,6-ODmp*     |                      | <i>Artocarpus nobilis</i> (Mor.), bark         | Kumar <i>et al.</i> (1977)                                  |

|                                                              |                 |                                         |                                    |
|--------------------------------------------------------------|-----------------|-----------------------------------------|------------------------------------|
| PYRANOFLAVONOLS                                              |                 |                                         |                                    |
| 3-OMe, 7,8-ODmp*                                             | Karanjachromene | <i>Pongamia glabra</i> (Leg.), seed oil | Satam and Bringi (1973)            |
| 3,5-di-OMe, 3',4'-O <sub>2</sub> CH <sub>3</sub> , 7,8-ODmp* | Pongafflavone   | <i>Pongamia glabra</i> (Leg.), stem     | Lakshmi <i>et al.</i> (1974)       |
| 3,6-di-OMe, 7,8-ODmp*                                        | Pongachromene   | <i>Pongamia glabra</i> (Leg.) stem bark | Subramanyam <i>et al.</i> (1977)   |
| 3,5-di-OH, 8-C <sub>3</sub> , 7,6-ODmp                       | Sericetin       | <i>Derris obtusa</i> (Leg.), root bark  | do Nascimento <i>et al.</i> (1976) |
| 3,5,4'-tri-OH, 7,8-ODmp                                      | Phellamuretin   | <i>Mundulea</i> (Leg.)                  | Grimshaw and Lamer-                |
|                                                              |                 | <i>Phellodendron japonicum</i> (Rut.)   | Zarawska (1972)                    |
| 3,5,3',4'-tetra-OH, 7,8-ODmp*                                |                 | <i>Asclepias syriaca</i> (Asclep.)      | Gonnet <i>et al.</i> (1973)        |

† For structures, see Fig. 4.1

Table 4.7 Furano-flavones and flavonols

| Substitution <sup>†</sup>                                    | Trivial name                                                    | Plant source                             | References                       |
|--------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------------|----------------------------------|
| <b>FURANOFLAVONES</b>                                        |                                                                 |                                          |                                  |
| 7,8-fur                                                      | Lanceolatin B                                                   | <i>Tephrosia, T. falsiformis</i> (Leg.)  | Ghanim and Jayaraman (1979)      |
| 3',4'-O <sub>2</sub> CH <sub>2</sub> , 7,8-fur*              | Pongaglabrone                                                   | <i>Pongamia glabra</i> (Leg.), heartwood | Subramanyam <i>et al.</i> (1977) |
| 5-OH, 7,8-fur*                                               | Pongaglabol                                                     | <i>Pongamia glabra</i> (Leg.), flower    | Talapatra <i>et al.</i> (1980)   |
| 5-OMe, 7,8-fur                                               | Pinnatin                                                        | <i>Pongamia</i>                          |                                  |
| 5-OMe, 3',4'-O <sub>2</sub> CH <sub>2</sub> , 7,8-fur        | Gamatrin                                                        | <i>Pongamia</i>                          |                                  |
| 6-OMe, 7,8-fur*                                              |                                                                 | <i>Pongamia glabra</i> (Leg.), leaf      | Malik <i>et al.</i> (1977)       |
| 8-OMe, 7,6-fur*                                              |                                                                 | <i>Pongamia glabra</i> (Leg.), leaf      | Malik <i>et al.</i> (1977)       |
| 3'-OH, 7,8-fur*                                              |                                                                 | <i>Pongamia glabra</i> (Leg.), seed      | Roy and Khanna (1979)            |
| 5,3',6'-tri-OH, 4',5'-fur-ODmp                               | Dihydrofurano-artiblichromene b <sub>1</sub> and b <sub>2</sub> | <i>Artocarpus nobilis</i> (Mor.), bark   | Kumar <i>et al.</i> (1977)       |
| 5,3',4'-tri-OH,6',5'-fur-ODmp                                | Dihydrofurano-artiblichromene a                                 | <i>Artocarpus nobilis</i> (Mor.), bark   | Kumar <i>et al.</i> (1977)       |
| 5,4',6'-tri-OH, 3-C <sub>5</sub> , 7,6-fur-ODmp-OH*          | Mulberranol                                                     | <i>Morus alba</i> (Mor.), bark           | Deshpande <i>et al.</i> (1976)   |
| <b>FURANOFLAVONOLS</b>                                       |                                                                 |                                          |                                  |
| 3-OMe, 7,8-fur                                               | Karanjin                                                        | <i>Pongamia</i> (Leg.)                   |                                  |
| 3-OMe, 3',4'-O <sub>2</sub> CH <sub>2</sub> ,7,8-fur         | Pongapin                                                        | <i>Pongamia</i>                          |                                  |
| 3,3'-di-OMe, 4',5'-O <sub>2</sub> CH <sub>2</sub> , 7,8-fur* | 3'-Methoxypongapin                                              | <i>Pongamia glabra</i> (Leg.), leaf      | Malik <i>et al.</i> (1977)       |

<sup>†</sup> For structures see Fig. 4.1

oxygen, the first cipher always indicating the position of the O. In Table 4.7 isoprenylfuran rings are indicated by 'fur-ODmp', while the simple furan ring is marked as 'fur' only. The latter compounds again are included here for the sake of completeness.

The terms pyranoflavonoid and furanoflavonoid have come into use in recent years. If the pyran or furan ring jointly with the aromatic ring to which they are linked form a benzochromene or a furanochromene system, these flavonoids can also be called chromenoflavonoids. This term cannot be used for those in which annulation takes place from C-6' to C-3.

Tables 4.6 and 4.7 listing these compounds may not be absolutely complete but it is hoped they will be useful as a basic entry into this group of substances. Structures of some typical furano- and pyrano-flavones and -flavonols are given in Fig. 4.1.

The occurrence of flavones with  $C_5$ ,  $OH-C_5$  and  $C_{10}$  side chains (12 compounds) is still almost completely restricted to the Moraceae. However, in addition to the one solitary earlier example of 8-prenyl-luteolin from *Xanthium* (Asteraceae), two more 8-prenylated flavones have now been found in *Tephrosia* (Leguminosae). Flavonols with these substituents (nine compounds) occur in members of the Berberidaceae, Leguminosae, Platanaceae, Rubiaceae and Rutaceae. Two of these compounds were accidentally overlooked in Gottlieb (1975). Isoprene substitution of this type is more abundant in the flavanone series and is also encountered among chalcones and isoflavonoids. The simple 8-prenyl compounds are common in several genera of the Leguminosae.

Among the pyranoflavones and pyranoflavonols, a considerable number of new reports have appeared recently; 11 of the 18 flavones and five of the seven flavonols are new. Except for the presence of three of these compounds in the Leguminosae, all flavones are found in Moraceae. Five pyranoflavonols are from the Leguminosae, one from the Asclepiadaceae and one from the Rutaceae.

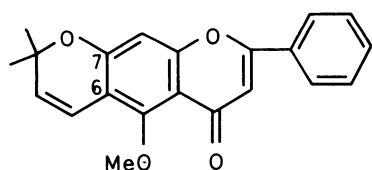
Eight of the 13 furanoflavones and furanoflavonols listed in Table 4.7 are new compounds. They are almost completely restricted to the genera *Pongamia* (Leguminosae) and *Artocarpus* (Moraceae), with one compound each from *Tephrosia* (Leguminosae) and from *Morus* (Moraceae) as exceptions.

The number of flavones with a 7-membered oxepine ring have increased from two or four. Cyclointegrin (see Fig. 4.1) is the first natural flavone with an oxocin ring system.

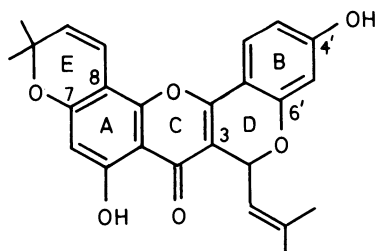
#### 4.4.2 *Tephrosia* flavonoids

The genus *Tephrosia* (Leguminosae, Papilionoideae) is distinguished by the production of a special group of flavonoids: 7-oxygenated or 5/7-oxygenated compounds with unsubstituted B ring and extra substituents at C-8, derived from a prenyl unit. Most are flavones, three are flavanones and one is a chalcone. Waterman and Khalid (1980) recently surveyed all such flavonoids; one new one can be added to their list, the flavanone, 2,3-dihydrosemiglabrin, or purpurin

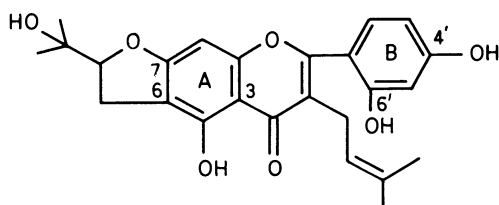
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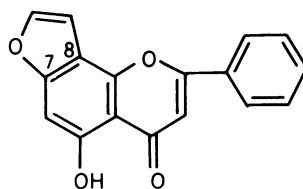
Praecansone B  
(5-OMe, 7,6-ODmp)  
(linear linkage)



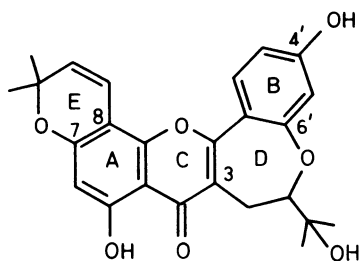
Cyclomorusin  
(5,4'-OH, 7,8-ODmp, 6,3'-ODmp)  
(angular linkage for AE)



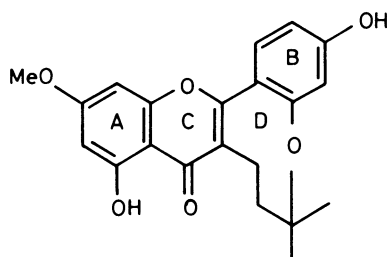
Mulberranol  
(5,4',6'-tri-OH, 3-C<sub>5</sub>, 7,6-fur-ODmp-OH)



Pongaglabrol  
(5-OH, 7,8-fur)



'Compound A'  
(5,4'-di-OH, 7,8-ODmp, 6,3'-ox-OH)



Cyclointegrin  
(5,4'-OH, 7-OMe, 6',3-oxecin)

Fig. 4.1 Structures of selected furano- and pyrano-flavones.

(R. K. Gupta *et al.*, 1980). The first reported representatives, tachrosin, stachyoidin, and tephrocin, were obtained from *Tephrosia polystachyoides*. Their structures were confirmed by synthesis (Antus *et al.*, 1977). In the

**Table 4.8** Flavones with oxepine and oxocin rings

| Substitution†                                           | Trivial name          | Plant sources                                  | Reference                                                        |
|---------------------------------------------------------|-----------------------|------------------------------------------------|------------------------------------------------------------------|
| 5,4'-di-OH, 7,8-ODmp,<br>6',3-ox-OH*                    | 'Compound A'          | <i>Morus alba</i> (Mor.)<br>root bark          | Nomura <i>et al.</i><br>1976)<br>Nomura <i>et al.</i><br>(1978a) |
| 5,4'-di-OH, 7-OMe,<br>6',3-ox.-OH                       | Oxyisocyclointegrin   | <i>Artocarpus integer</i><br>(Mor.), heartwood | Pendse <i>et al.</i><br>(1976)                                   |
| 5,4'-di-OH, 7-OMe, 6-C <sub>5</sub> ,<br>6',3-ox.-OH    | Chaplashin            | <i>Artocarpus</i>                              |                                                                  |
| 5,3',4'-tri-OH, 6-C <sub>5</sub> ,<br>7,8-ODmp 6',3-ox. | Isocycloheterophyllin | <i>Artocarpus</i>                              |                                                                  |
| 5,4'-di-OH, 7-OMe,<br>6',3-oxocin*                      | Cyclointegrin         | <i>Artocarpus integer</i><br>(Mor.), heartwood | Pendse <i>et al.</i><br>(1976)                                   |

† for structures see Fig. 4.1

meantime, these unusual flavonoids were also found in *T. apollinea* (apollinine, glabratephrine, pseudosemiglabrin, semiglabrin), *T. bracteolata* (the flavanone, obovatin-5-Me ether), *T. candida* (obovatin-5-Me ether), *T. multijuga* (multijugin, multijuginol), *T. obovata* (flavanones, obovatin and its 5-Me ether; the chalcone, obovatachalcone), *T. praecana* (obovatin-Me ether), *T. purpurea* (flavanone, purpurin) and *T. semiglabra* (glabratephrin, semiglabrin, semiglabrinol) (simple C-5 derivatives not cited here). From *T. polystachyoides* in addition polystachin has been reported (for references, see Waterman and Khalid, 1980). A total of 15 flavones of this type (including stereoisomers) are now known. Jain and Gupta (1978) suggest that these flavones are formed biogenetically from chrysin by prenylation at C-8, followed in many cases by a complex process of further substitution and cyclization. It may be mentioned in this context that two flavanones, lupinifolin and lupinifolinol, from *T. lupinifolia* (Smalberger *et al.*, 1974) are known which bear a  $\gamma$   $\gamma'$ -dimethylallyl unit at C-8 (and an additional pyran ring), and tephrostachin and lanceolatin-A bear, respectively, *cis*- and *trans*-3-hydroxy-3-methyl-but-1-ene side chains (of prenyl origin) at C-8.

In Fig. 4.2, one complete structural formula is given at the top as an example; details of the stereochemistry are omitted. The rest of the substituents are presented in Fig. 4.2 according to Waterman and Khalid (1980).

#### 4.4.3 *Pityrogramma* flavonoids

During extensive studies on the composition of frond exudates on gymnogram-moid ferns by Wollenweber and co-workers, several new constituents were isolated from the farinose indument of some *Pityrogramma* species. These constituents represent a novel structural type among complex flavonoids, in which a flavonoid moiety is linked with a dihydrophenylcoumarin (or

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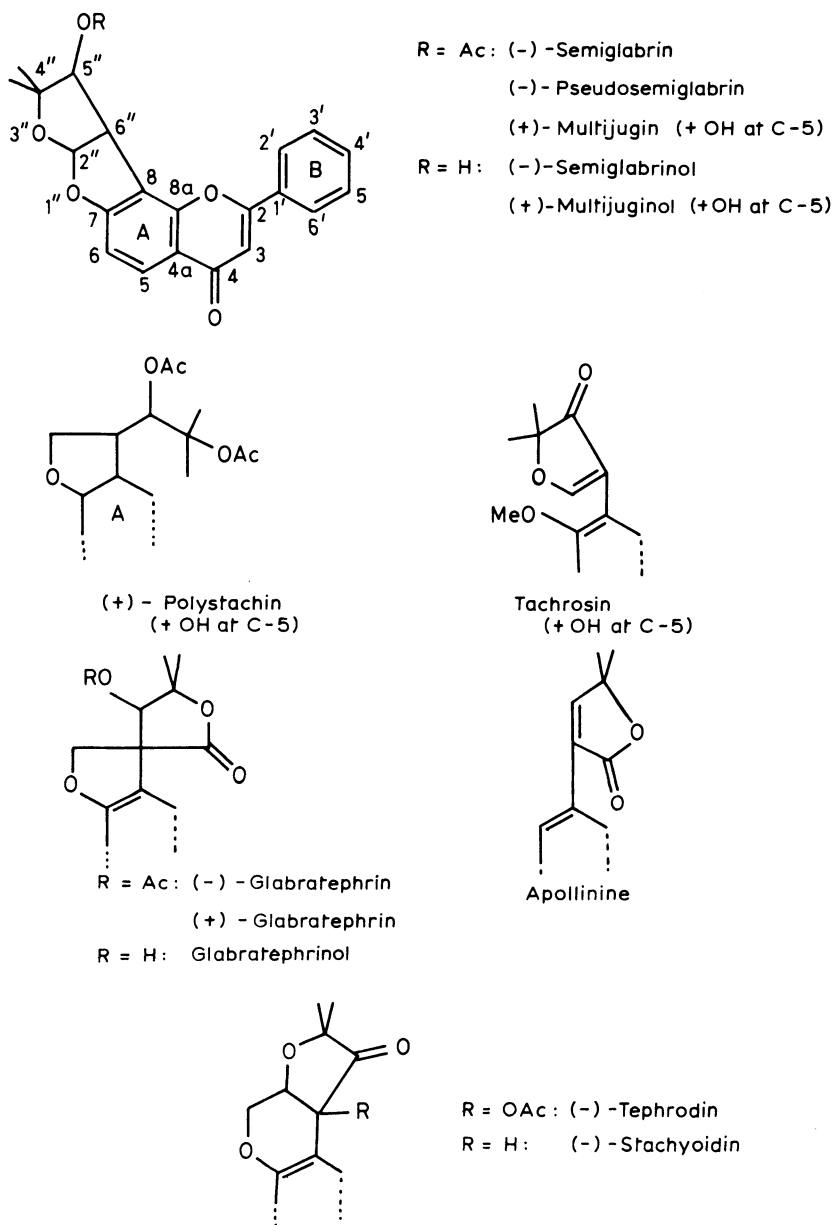


**Fig. 4.2** Structures of *Tephrosia* flavonoids.

dihydroneoflavonoid) moiety via a common phloroglucinol ring. So far a dihydrochalcone (Wagner *et al.*, 1979) and three chalcones (Dietz *et al.*, 1980) have been reported as well as a flavone and a flavonol (Wagner *et al.*, 1979). The latter two compounds (Fig. 4.3) have the same substitution pattern and are



inseparable in any known chromatographic system. That they are both present is apparent from the spectral data. These compounds D-1 and D-2 contribute to the quasi genus-specific flavonoid pattern in *Pityrogramma* (Wollenweber and Dietz, 1980); they have also been labelled A and B<sub>1</sub>/B<sub>2</sub>, respectively, by Wagner *et al.* (1979). Closely related are two further flavones, in which no additional  $\gamma$ -pyrone ring is present; they bear dihydrocinnamoyl substituents. They were reported by Favre-Bonvin *et al.* (1980) as X-1 and X-2 (Fig. 4.3) and are found in some individual plants of *P. calomelanos* var. *aureoflava* only.

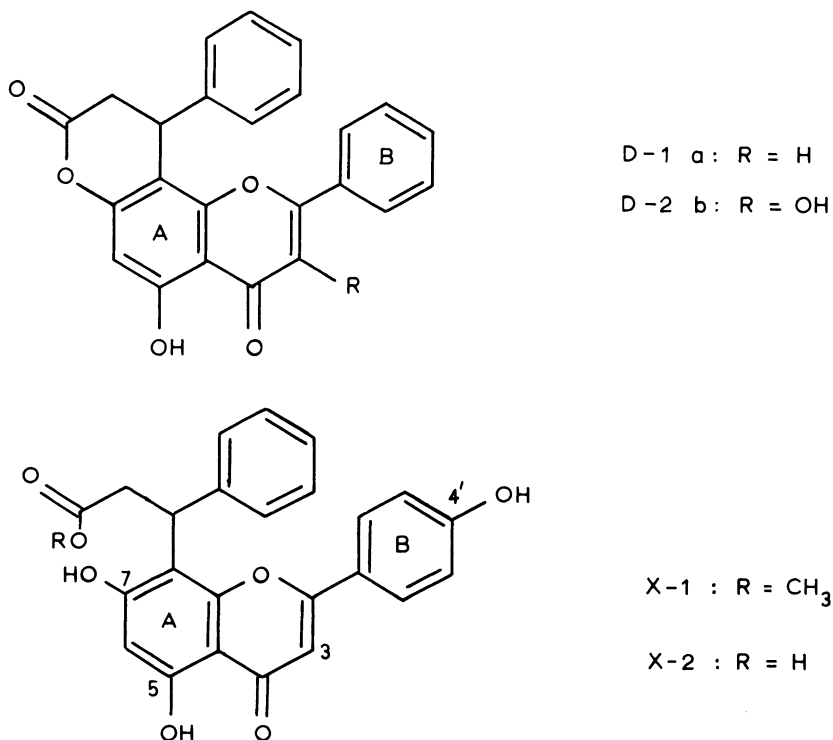


Fig. 4.3 Structures of *Pityrogramma* flavonoids.

#### 4.5 REVISIONS AND PROBLEMATICAL STRUCTURES

Gottlieb (1975) included a section on revisions and problems. Some of the problems discussed there have been resolved in recent years; others still await solution. A few new topics can now be added to the list.

##### *Uncertain structures*

A variety of compounds have yet to be fully characterized. These include wharangin (Geissman, 1962, p. 430), a flavone from *Colutea arborescens*

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(Geissman, 1962, p. 422), a flavone from *Acacia cavenia* (Geissman, 1962, p. 422), polycladin, atanasin (Flores and Herran, 1960), Primula F3A (possibly a gossypetin dimethyl ether), ptaeroxylol (3,5,7-trihydroxy-2'-methoxyflavone ?) and pratoletin from *Trifolium pratense*. Two unidentified flavones reported earlier from *Larrea* (Geissman, 1962, pp. 427 and 430) are probably, according to more recent papers, methyl ethers of quercetin (see Table 4.2). With regard to the structures of gardenins A to C, it is clear from more recent results that all substances from *Gardenia* have 7-*O*-methyl substitution and are flavones (see Table 4.1). The structure of sericetin from *Mundulea sericea* is still uncertain, in that both a linear or angular structure are possible (see Gottlieb, 1975). The earlier identification of galangin from *Citrus sinensis* also needs confirmation. More detailed reports on other structural problems follow.

### *Gossypium flavonol.*

Struck and Kirk (1970), in their paper on flavonoids from *Gossypium hirsutum* flower petals, reported  $R_F$  values on polyamide for a Substance III. It has the same  $R_F$  as ombuin and rhamnazin in two solvents, and the small difference in the third is negligible. Quercetin-3',4'-dimethyl ether in  $\text{CHCl}_3/\text{EtOH}/\text{MEK}$  would appear between rhamnetin and rhamnazin; hence in our opinion this possibility can be excluded. The substance must therefore be quercetin-7,4'-dimethyl ether. We do not know if this substance has been reinvestigated in the meantime.

### *6-Hydroxykaempferol*

Harborne (1967, p. 164) failed to find a flavonoid with the expected chromatographic properties from *Galega officinalis* flowers, although Maksyutina and Litvinenko (1964) assumed its presence in this plant. Wollenweber (1974, unpublished) compared the hydrolysed extract with an authentic sample of 6-hydroxykaempferol (from demethylation of betuletol) and also could not detect it, but found only kaempferol, quercetin and isorhamnetin. 6-Hydroxykaempferol therefore appears to be absent from *Galega*. Hence the trivial name 'galetin' should not be used for this flavonol. Unfortunately, its use has already become established, see e.g. Dillon and Mabry (1977). In fact, 6-hydroxykaempferol has now been found once in nature, as a 7-*O*-glucoside in *Tetragonothea texana* (Bacon *et al.*, 1978).

### *Tambulin*

Chatterjee *et al.* (1976) confirmed this compound as being herbacetin-7,8,4'-trimethyl ether as originally proposed by Bose and Bose (1939), on grounds of spectroscopic investigations, chemical reactions and synthesis.

*3,5,8,3',4'-Pentahydroxyflavone*

Wollenweber (1974, unpublished) in a search for galetin in *Galega* did not detect a compound which might be this flavone as had been earlier suggested by Lapinina (1965).

*Apigenin 5,7-dimethyl ether*

The assumed presence of this flavone as a 4'-glucoside in *Saccharum officinarum* (Dubey and Misra, 1974) still needs to be confirmed.

*Ladanetin*

Ladanetin and ladanein were reported as constituents of *Galeopsis ladanum* (Gritsenko and Litvinenko, 1969) and ascribed the structures: scutellarein 7-methyl ether and scutellarein 7, 4'-dimethyl ether. By synthesis of the 7-methyl ether (sorbifolin), Farkas *et al.* (1971) showed that ladanetin was not identical with this product. Although Venkataraman (1975) drew attention to this fact, ladanetin and ladanein to our knowledge still await proper identification.

*Skullcapflavone I*

Takido *et al.* (1975) isolated two flavones, skullcapflavone I and II, from roots of *Scutellaria baicalensis*. The structures 5,2'-dihydroxy-6,8-dimethoxyflavone and 5,2'-dihydroxy-6,7,8,6'-tetramethoxyflavone were ascribed to these compounds. Later Takido *et al.* (1979) revised the first structure because of spectral data and colour reactions and proposed that skullcapflavone I was 5,2'-dihydroxy-7,8-dimethoxyflavone. This was confirmed by synthesis of 5,2'-dihydroxy-6,8-dimethoxyflavone, 5,2'-dihydroxy-7,8-dimethoxyflavone and 5,2'-dihydroxy-6,7-dimethoxyflavone (Iinuma and Matsuura, 1979). For skullcapflavone II the earlier proposed structure has now been confirmed by synthesis (Iinuma and Matsuura, 1979).

*Alnus flavone*

Another flavone has been described on the basis of the UV spectra to have 'in all likelihood' the 5,6,8-trioxygenation pattern, which is rather unlikely biosynthetically. The structure proposed was 5,4'-dihydroxy-6,8-dimethoxyflavone, from *Alnus glutinosa* fruits (Karczewska and Krolikowska, 1974). After synthesis of the above structure, Iinuma and Matsuura (1980) found that this cannot be correct for the *Alnus* flavone. By comparison of melting points, they suggested that the natural product could be 5,4'-dihydroxy-6,7-dimethoxyflavone (cirsimaritin). Wollenweber *et al.* (1971) reported the isomeric 6,4'-dimethyl ether of scutellarein (pectolinarigenin) as a constituent of the lipophilic material on buds, male flowers (catkins) and fruits of black alder. A reinvestig-

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ation (involving a direct comparison of freshly prepared extracts with scutellarein 6,7- and 6,4'-dimethyl ethers and a synthetic sample of 5,4'-dihydroxy-6,8-dimethoxyflavone) showed that the only flavone of this type present is pectolinarigenin. No trace of 5,4'-dihydroxy-6,8-dimethoxyflavone could be detected (Wollenweber unpublished).

### *5,4'-Dihydroxy-7,8,3'-trimethoxyflavone*

Le Quesne *et al.* (1976) identified five methylated flavones in *Lychnophora affinis*, two of which were new compounds. One of these, namely the 7,8,3'-trimethyl ether of hypolaetin, was synthesized later by Bhardwaj *et al.* (1978c). However, the properties of the synthetic product were different from the natural sample. Hence the structure of the natural flavone clearly needs revision.

### *Luiselozindin*

A flavone called luiselozindin, isolated from the essential oil of *Gymnosperma glutinosa*, was ascribed the structure of 5,7-dihydroxy-6,8,3',4',6'-penta-methoxyflavone (Dominguez and Torre, 1974). Chhabra *et al.* (1977b) synthesized this compound and found it to be different from the natural product. Hence the constitution of luiselozindin still needs revision.

### *Mikanin*

In 'The Flavonoids' the name mikanin has erroneously been used for the scutellarein trimethyl ether, salvigenin (p. 272).

### *Tomentin*

Rodriguez *et al.* (1972a) ascribed the structure of quercetagetin 3,3'-dimethyl ether to a substance 'tomentin', isolated from *Parthenium tomentosum*. Shen *et al.* (1976) then reported that the earlier statement was incorrect in that tomentin was in fact quercetagetin 3,7-dimethyl ether. This was confirmed by direct comparison with the synthetic product (Wagner *et al.*, 1976, 1977b). Unfortunately, in a review by Rodriguez (1977) on *Parthenium* constituents substance no. 38 is described as the 3,3'-dimethyl ether in the Figure of structural formulae, but as the 3,7-dimethyl ether in the Table of distribution. The latter is, clearly, the correct structure and there is no evidence now (Mabry, 1981) that the 3, 3'-dimethyl ether occurs in *Parthenium*.

### *Artemisia compound*

The structure of quercetagetin 6,7,3',4'-tetramethyl ether has been ascribed to a flavonol isolated from *Artemisia annua* by Djermanovic *et al.* (1975). Bhardwaj

*et al.* (1977), however, demonstrated that a synthetic sample of this compound had a melting point and spectral data markedly different from those reported for the natural product. The *Artemisia* compound must, therefore, have a different structure; it may be an isomeric tetramethyl ether of quercetagenin, or perhaps of gossypetin.

### *Ranupenin*

Urschler (1968) reported a monomethyl ether of gossypetin, called ranupenin, as a glycoside in flowers of *Ranunculus repens* and ascribed it the structure of gossypetin 8-methyl ether. Wagner *et al.* (1977c) after synthesis of three monomethyl ethers of gossypetin were able to show that ranupenin is in fact gossypetin 7-methyl ether. Unfortunately later authors (Harborne *et al.*, 1978) caused trouble again by confusing these two flavonols. The plant sources of the two isomeric 7- and 8-methyl ethers of gossypetin are shown correctly in Table 4.2.

### *Unonia formylflavonoids*

Three formylflavonoids, isolated from *Unonia lawii*, have been ascribed the structures of 5,7-dihydroxy-6-methyl-8-aldehydoflavone (unonal), 5,7-dihydroxy-8-methyl-6-aldehydoflavone (isounonal), and 5-hydroxy-7-methoxy-6-methyl-8-aldehydoflavone (unonal 7-methyl ether) by Joshi and Gawad (1976). According to B. S. Joshi (1980) they now have been revised, i.e. the positions of methyl and aldehyde groups must be exchanged. This follows from a comparison with the C-methylfavanones strobopinin and cryptostrobin, the structures of which have been determined by  $^{13}\text{C}$ -NMR spectroscopy and X-ray crystal analysis of bromocryptostrobin (Joshi and Cannon, unpublished).

## 4.6 METHODS FOR SEPARATION AND IDENTIFICATION

### 4.6.1 Chromatography on polyamide

Recent advances in chromatographic techniques for flavonoids (including HPLC) are generally discussed in Chapter 1. Only certain aspects of particular importance in separating flavones and flavonols will be treated here. TLC on polyamide, for example, is especially valuable for distinguishing the many and various methyl ethers of both flavones and flavonols. In his chapter on isolation techniques in 'The Flavonoids', Markham (1975) referred to Egger's publications on polyamide TLC, especially his contribution to Stahl's textbook on TLC (Egger, 1967). Solvents for TLC of the aglycones first were based on chloroform and are cited in the literature sometimes as 'Egger's solvents'. Chloroform has been successively replaced by benzene (Wollenweber, 1970) and then by toluene, which is somewhat less toxic than benzene, since in contrast to

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benzene, it can be metabolized. The 'standard solvents' currently in use are listed in Table 4.9 in order of increasing polarity. Solvents I and II (Table 4.9) are used for non-polar flavonoids, especially for highly methylated compounds (and will separate, for example, galangin 3,7-dimethyl ether from kaempferol 3,7,4'-trimethyl ether). They also are used for a first run of extracts containing much lipid material, which impedes or even prevents development with the other solvents. Solvent III is the one most often used for routine work. It is applicable to a wide range of aglycones, from chrysin 7-methyl ether to apigenin, from kaempferol 3,7,4'-trimethyl ether to kaempferol itself. It therefore is always used on unknown extracts containing lipophilic flavonoids. More polar compounds should be chromatographed in solvents IV to VI. Solvent V is used for the most common flavonols. Very polar compounds, penta- and hexa-hydroxyflavones and their monomethyl ethers are better separated in VI. VII is a useful second solvent for two-dimensional TLC. It can be helpful in the rare cases when other solvents give little or no separation, e.g. for the 3'- and 4'-methyl ethers of quercetin.

**Table 4.9** Solvents for polyamide TLC

| <i>Solvents</i>                                   | <i>Composition</i>         |
|---------------------------------------------------|----------------------------|
| (I) Toluene/petrol (b.p. 100–140°C)/MeCOEt/MeOH   | 30:90: 2:1.5               |
| (II) Toluene/petrol (b.p. 100–140°C)/MeCOEt/MeOH  | 30:60: 5:5                 |
| (III) Toluene/petrol (b.p. 100–140°C)/MeCOEt/MeOH | 60:30:10:5<br>(60:26: 7:7) |
| (IV) Toluene/dioxan/MeOH                          | 80:10:10                   |
| (V) Toluene/MeCOEt/MeOH                           | 60:25:15<br>(60:26:14)     |
| (VI) Toluene/MeOH/MeCOEt/Acetylacetone            | 40:30:20:10                |
| (benzene/MeCOEt/MeOH)                             | (40:30:30)                 |
| (VII) HOAc/dioxan/DMF/H <sub>2</sub> O            | 10:30:15:15                |

Previous composition with benzene is given in parentheses where the quantities have been altered.

Some of these solvents have been adopted by other laboratories (e.g. Charrière and Tissut, 1973: IV, V; Mues *et al.*, 1979: III, VI; Reichling *et al.*, 1979: III, V), sometimes with slight variations, or with benzene instead of toluene. Similar solvents have been used as eluents in column chromatography on polyamide (e.g. Sakakibara *et al.*, 1975). Usually the separations are clear, even when spots overlap. Nearly all the methyl derivatives of quercetin (except those with 5-*O*-methylation) can be distinguished on two one-dimensional chromatograms in solvents III and V (see Jay *et al.*, 1975; Wollenweber, 1975c).

For detection of flavonoids, colours in UV<sub>366</sub> are much more valuable on polyamide than on paper and allow conclusions as to the substitution at C-3, C-5, presence of additional substituents at C-6 and C-8. Also the various colours produced after spraying with 'Naturstoffreagenz A' are more easily dis-

criminated on polyamide. This reagent, introduced by Neu (1956), because of its sensitivity and the variety of colours developed (see also Somaroo *et al.*, 1973) is still unsurpassed for the detection of flavonoids. Additional information comes from UV-induced changes in visual colours in the case of methyl derivatives of apigenin, luteolin, and several other compounds. The TLC plates should therefore be re-examined in daylight some hours after spraying with 'Naturstoffreagenz A' and evaluation in UV<sub>366</sub>.

TLC plates are prepared by spreading a slurry of powdered polyamide (Polyamid DC-11, polyaminoundecanic acid; Macherey-Nagel, Düren) with 15% cellulose powder in MeOH on thoroughly cleaned glass plates (Egger, 1967). Thickness of the layer is 0.2 or 0.3 mm (85 g of polyamide with 15 g of cellulose yield ca. 14 plates 20 cm × 20 cm). Such 'home-made' plates give much better separations and show better UV colours than the pre-coated plates or sheets available commercially. 'Naturstoffreagenz A' ( $\beta$ -aminodiethyl ester of diphenylboric acid) is used in 0.5% solution in MeOH.

Preparative separations of flavones and flavonols can readily be achieved on thicker layers (0.5 mm) of polyamide, using the solvents listed in Table 4.10. Markham (1975) has noted that removal of compounds from polyamide may on occasions be difficult. In our experience, it is difficult to get rid of low-molecular-weight polyamide during elution of flavone adsorbents. This is a nuisance especially when MS and NMR studies are to follow (see next sections). To overcome this problem, plates should be run in MeOH prior to use, in order to bring most of the soluble material to the front. Then, the eluate should be thoroughly dried in a small conical bulb; the flavonoid is then taken up in benzene (or methyl ethyl ketone (MEK), but not MeOH) and pipetted off, leaving the polyamide sticking to the glass wall. If these steps are not successful, the sample should undergo a final purification on silica (TLC) or on Sephadex LH-20 (see p. 243).

Finally, some hints on the use of polyamide for column chromatographic separations may be appropriate. One of the commercially available products is Polyamid SC-6 ( $\epsilon$ -aminopolycaprolactam; particle size 0.05–0.16 mm; Macherey-Nagel). Small particles (and especially soluble low-molecular-weight fractions) are removed by washing with MeOH. The material is stirred with excess MeOH. After standing, the supernatant is sucked off and the material dried at 50–60°C and then kept ready for use in toluene (Jay, 1978). Elution of columns is either with solvent mixtures similar to those recommended for TLC (Sakikabara *et al.*, 1975; Mues *et al.*, 1979) or with toluene (benzene) and increasing quantities of MEK and MeOH (Egger *et al.*, 1970). Polyamide can be used many times! The dried powder is suspended in water and a few ml of NH<sub>4</sub>OH (30%) and H<sub>2</sub>O<sub>2</sub> (30%) are added. After standing overnight the water is renewed several times until the supernatant remains colourless. Then the polyamide is sucked dry, washed with acetone, and ether, and after evaporation of the latter dried at 50–60°C. No loss of capacity has ever been observed (Egger, 1968; Dietz, 1980).

**Table 4.10** UV spectral characteristics of flavones and flavonols

| <i>Reagent</i>                   | <i>Substitution pattern</i> | <i>Shift of Band I (nm)</i> | <i>Remarks</i>                                                               |
|----------------------------------|-----------------------------|-----------------------------|------------------------------------------------------------------------------|
| MeOH                             | 6-OH                        | -8-12                       | Flavonols incl. 3-OMe-flavonols                                              |
|                                  | 6-OMe                       | -9                          | Flavones                                                                     |
|                                  | 8-OH                        | -                           |                                                                              |
|                                  |                             | +13-16                      | Flavonols; + peak at $\pm 330$ nm                                            |
|                                  |                             | -7                          | Flavones                                                                     |
| + AlCl <sub>3</sub>              | 3-OH                        | +60                         | Complex stable with H <sup>+</sup>                                           |
|                                  | 5-OH                        | +35-55                      | Complex stable with H <sup>+</sup>                                           |
|                                  | 3,5-di-OH                   | +50-60                      | Complex stable with H <sup>+</sup>                                           |
|                                  | 5,6-di-OH                   | +20                         |                                                                              |
|                                  | 5-OH, 3,6-di-OMe            | +20                         |                                                                              |
| + AlCl <sub>3</sub>              |                             |                             |                                                                              |
| + HCl                            | o-di-OH at ring B           | -30-40                      | Relative to spectrum with AlCl <sub>3</sub>                                  |
|                                  | tri-OH at ring B            | -20                         | Relative to spectrum with AlCl <sub>3</sub>                                  |
|                                  | 5-OH, 6-OH                  | +25-30                      | Relative to MeOH-spectrum; for flavones and 3-O-subst. flavonols.            |
|                                  | 5-OH, 6-OMe                 | +20                         |                                                                              |
|                                  | 5-OH, 8-OMe                 | +55-57                      |                                                                              |
| + NaOMe (NaOH)                   | 4'-OH                       | +40-60                      | Increase of intensity (or at least no decrease)                              |
|                                  | 3-OH                        | +50-60                      | Decrease of intensity                                                        |
|                                  | 3,4'-di-OH                  |                             | Slow degeneration                                                            |
|                                  | 3,3',4'-tri-OH              |                             | } Rapid degeneration                                                         |
|                                  | 3,3',4',5'-tetra-OH         |                             |                                                                              |
|                                  | 7-OH                        |                             | Small additional peak or shoulder at $\pm 330$ nm                            |
| + NaOAc                          | 7-OH                        | +5-20*                      | Minor or no shift when CH <sub>3</sub> or OCH <sub>3</sub> at C-6 and/or C-8 |
|                                  | 5,6,7-tri-OH                |                             | } Compound alkali-sensitive                                                  |
|                                  | 5,7,8-tri-OH                |                             |                                                                              |
|                                  | 3,3',4'-tri-OH              |                             | } Rapid decomposition                                                        |
|                                  | 3,4'-OH, 3'-OMe             |                             |                                                                              |
| + NaOAc                          |                             |                             |                                                                              |
| + H <sub>3</sub> BO <sub>3</sub> | o-di-OH                     | +12-30                      | at ring B                                                                    |
|                                  |                             | +5-10                       | at 6.7 or 7.8                                                                |

\* This is a shift in band II, not band I.

#### 4.6.2 Spectroscopic methods

##### (a) UV spectroscopy

##### *Spectra in methanol*

In general, flavones exhibit Band I between 304 and 350 nm, flavonols absorb between 352 and 385 nm. For flavonols with *O*-substitution at C-3 the general shapes of the curve as well as the ranges of Band I (328–357 nm) approach those of flavones. This is as well known as the observation that increasing oxygenation



of ring B results in a bathochromic shift of Band I. Band II appears as one peak (at about 270 nm) in compounds with monosubstituted B ring, but as two peaks or one peak (at about 258 nm) plus a shoulder (at about 272 nm) when a di- or tri-*O*-substituted B ring is present (Mabry *et al.*, 1970; Gottlieb, 1975; Hasan, 1976). The flavonoids thus have been grouped according to their B-ring substitution and UV spectra into kaempferol-types, quercetin-types etc. (Jay *et al.*, 1975). The latter authors present UV data for 23 flavones and 32 flavonols not given in Mabry *et al.* (1970). Averett (1977) has presented a table of absorption maxima for 252 flavonoids of different classes, mostly glycosides, but also a number of *O*-methylated aglycones. To this basic knowledge about the range of maxima and shape of UV curves, some additional findings may be added.

#### *6-O-substitution*

Introduction of an OH group at C-6 produces a hypsochromic shift on Band I of 8 nm in flavonols and up to 12 nm in 3-*O*-methylflavonols, but there is no effect in the flavone series. Methylation of the OH at C-6 cancels this effect in flavonols, except if there is methylation at C-3. In such 3-methyl ethers, methylation at C-6 causes a hypsochromic effect of 9 nm on Band I. Thus 3-*O*-methylated flavonols with *O*-substitution at C-6 do not follow the usual spectral rules (Hasan, 1976).

#### *8-O-substitution*

Introduction of a OH group at C-8 in flavonols produces a bathochromic shift of 13–16 nm on Band I and an additional peak at 330 nm (Hasan, 1976). The absorption curves of these compounds thus are quite characteristic (cf. Wollenweber *et al.*, 1978; Wollenweber and Wiermann, 1979). The relatively high wavelength of the absorption maxima also means that these compounds are yellow in colour (Harborne, 1969; Wollenweber and Wiermann, 1979). In flavones, on the other hand, a hypsochromic effect of 7 nm is observed in some cases on insertion of an 8-OH (Combier *et al.*, 1975). Methylation of the OH at C-8 causes minor shifts in the same direction.

#### *Aluminium chloride/hydrochloric acid*

Mears and Mabry in 1972 reported a procedure for the UV detection of OH- and -OMe groups at C-6 in flavones and 3-*O*-substituted flavonols. They emphasized that in such compounds the bathochromic shift of Band I produced by addition of AlCl<sub>3</sub>/HCl relative to the MeOH spectrum is only about 20 nm, whereas otherwise the shift is about 45 nm (or up to 57–62 nm; Hasan, 1976). This allows the discrimination of 6-*O*-substituted from 8-*O*-substituted compounds. Similarly C-methylation at C-6 may cause a weak AlCl<sub>3</sub> reaction of the 5-OH due to steric hindrance (Wollenweber *et al.*, 1980; Dietz *et al.*, 1981). Later, Sakakibara and Mabry (1977) after studying more compounds than Mears and

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Mabry (1972) showed that the  $\text{AlCl}_3/\text{HCl}$  shift on Band I of +25–30 nm, relative to the MeOH spectrum, is indicative for 5-OH flavones and 3-*O*-substituted flavonols with free OH at C-6, whereas the earlier observed shift of 20 nm is only valid for compounds *O*-methylated at C-6. The same authors (Sakakibara and Mabry, 1978) found that  $\text{AlCl}_3/\text{HCl}$  produced a large shift of 55–75 nm of Band I (relative to MeOH spectrum) for flavones and 3-*O*-substituted flavonols with free OH at C-8. It may be mentioned that recent results of B. Voirin (unpublished, cited by Rabesa, 1980) will possibly require some minor corrections of these rules. Rabesa (1980) recommends that the  $\text{AlCl}_3$  solution should be prepared fresh at least every month.

### *Sodium methoxide*

Degeneration of the UV absorption peaks of flavonols on addition of NaOMe does not necessarily indicate a 3,4'-di-OH system. It can also be due to 3',4',5'-tri-OH substitution, e.g. in tricetin derivatives (Mues, 1975). In the flavone series, this is the only relatively reliable evidence that a 3',4',5'-tri-OH system is present. Occurrence of a small peak or a shoulder at +330 nm on addition of NaOMe is indicative for a free OH at C-7, or at least supports the relevant evidence from the NaOAc reaction (see below). The French workers use NaOH (1M) instead of NaOMe (Rabesa, 1980).

### *Sodium Acetate*

This reagent for detection of 7-OH groups usually produces bathochromic shifts of band II of 8–20 nm (Mabry *et al.*, 1970). Rabesa (1980) points out that in flavones with OMe- or  $\text{CH}_3$ - groups at C-6 and/or C-8 the effect can be less than 5 nm and even zero. This has been observed also by Dietz *et al.* (1981). The adjacent substituents may reduce or even prevent the acidity of the 7-OH. Rabesa (1980) emphasizes that fused NaOAc, kept permanently in a drying oven at 120°C, should always be used.

On the basis of the publications cited above, Dietz (1980) has compiled a table of UV characteristics which is reproduced here (Table 4.10) in a slightly altered version. It should be stressed that the observations discussed above as well as those summarized in this Table must not be regarded as strict rules. They should be considered as useful hints for structural assignments, which should then be confirmed by other procedures.

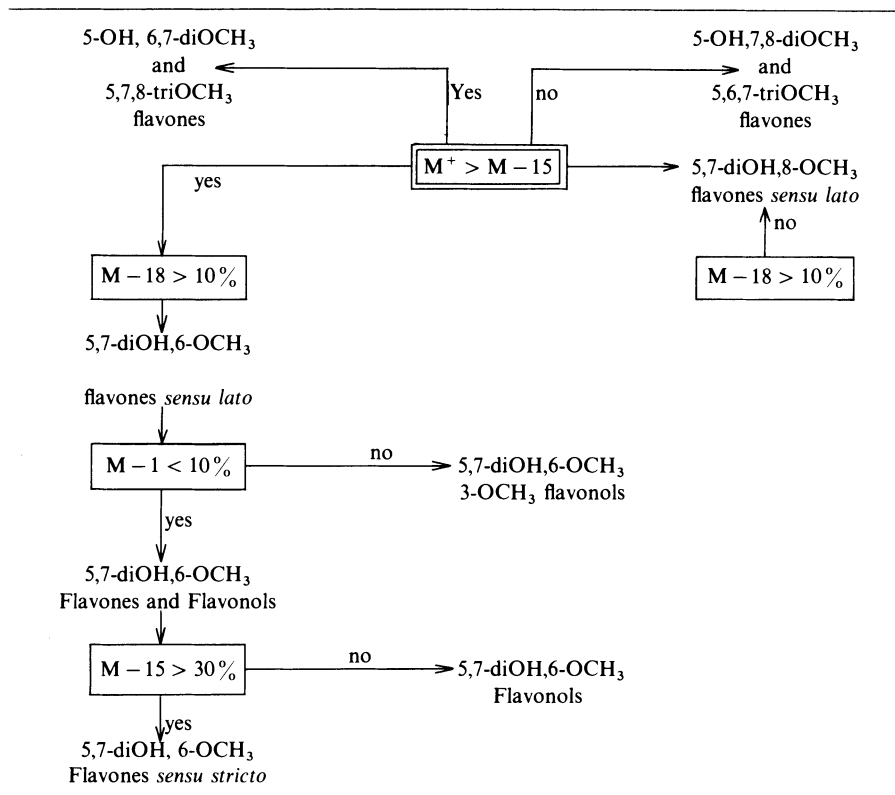
### **(b) Mass spectroscopy**

Mass spectroscopy was treated *in extenso* by Mabry and Markham (1975). The general rules for fragmentation have been confirmed repeatedly in more recent measurements. It may be mentioned that some authors still prefer the abbreviations for the fragments as introduced by Audier (1966) and adapted by Kingston (1971) to those used by Mabry and Markham. The problems of

eliminating impurities in samples before mass spectral analysis are legion. In the case of flavones and flavonols, the polyamide dissolved from the adsorbent when performing preparative TLC can cause very annoying artefact peaks. It can be eliminated by a further preparative-scale TLC on silica, preferably with a concentration zone (Wollenweber and Wiermann, 1979; Wollenweber *et al.*, 1980). A passage of the sample to be analysed via a small column of Sephadex LH-20 (eluted with MeOH) or Polyamide SC.6 (0.5 cm  $\times$  5 cm, elution with toluene, then increasing quantities of MeOH) can also be recommended (Rabesa, 1980).

Wollenweber and Dietz (1979) have prepared a valuable time-saving Table of MS parent ions. This table can be used either to find out at a glance if the molecular ion ( $M^+$ ) of a substance to which one ascribed a certain structure by other methods fits the molecular formula, or it can help to determine the number of hydroxyl and/or methoxyl groups present in a flavonoid of known molecular weight. It must be kept in mind that the much less frequent *C*-methyl substitution may cause errors (one OH and one  $\text{CH}_3=\text{OCH}_3$ ). Differentiation between flavonoids of the same molecular ion but belonging to different classes is possible by evaluation of TLC behaviour and UV spectra and by determining the number of hydroxyl groups originally present after mass spectroscopy of the acetate (or TMS derivative).

As in UV spectroscopy, discrimination between substitution at C-6 and C-8 is a special problem which has received special attention. Kingston (1971) earlier found intense  $(M - \text{CH}_3)^+$  and  $(M - \text{CH}_3\text{CO})^+$  fragments to be significant for 6- and 8-methoxyflavonoids. Nielsen and Møller (1970) also had indicated that in 6-methoxyquercetin,  $M^+$  appears as base peak, whereas in 8-methoxyquercetin the base peak is at  $M - 15$ . By contrast, it may be noted that in case of PM (permethyl) and PDM (perdentromethyl) derivatives of 6-methoxyflavones and 6-methoxyflavonols, the  $M - 15$  peak is the base peak (Mues *et al.*, 1979). More recently Goudard *et al.* (1978) have confirmed that, in underivatized 5,7-dihydroxyflavones with methoxyl at C-6, in general  $M^+$  is more important than  $M - 15$  and mostly produces the base peak, whereas in those with methoxyl at C-8 the base peak is due to  $M - 15$ . In addition, in 6-methoxy compounds the relative intensity of  $M - 18$  is greater than 10%, whilst in 8-methoxy compounds it is lower. 3-*O*-Methylflavonols with methoxyl at C-6 differ from the corresponding flavonols with a free 3-hydroxyl by the relative intensity of  $M - 1$  being greater than 10%. According to Mues (1975) the limit is not 10% but 30%. 6-*O*-Methylflavonols exhibit a less important peak at  $M - 15$  than the corresponding flavonols (Goudard *et al.*, 1978).  $M - 13$  signals of less than 30% intensity might be indicative of underivatized 8-methoxy and/or 3-methoxyflavonols, whereas  $M - 43$  signals of more than 30% are indicative for underivatized 6-methoxyflavones or 6-methoxyflavonols which have a free 3-hydroxyl. These relationships are collected together in Table 4.11, from Goudard *et al.* (1978), modified by Dietz (1980). Goudard and co-workers (1979) have also reported that in underivatized 5-hydroxy-6,7-dimethoxyflavones the relative intensity of  $M^+$  is higher (usually the base peak) than  $M - 15$ , whereas

**Table 4.11** Mass spectral-fragmentation of flavones and flavonols

the latter fragment occurs as the base peak in 5-hydroxy-7,8-dimethoxyflavones (flavonols). For 5,6,7-trimethoxy and for 5,7,8-trimethoxy derivatives, however, the intensity relationships are reversed. It may be mentioned finally that Rama Rao *et al.* (1972) have published a paper dealing with mass spectroscopy of flavones with *C*-isoprenyl substituents, and draw attention to the significant structural information obtainable by this method.

### (c) $^1\text{H}$ -NMR spectroscopy

$^1\text{H}$  nuclear magnetic resonance (NMR) spectroscopy of flavones and flavonols has been treated in detail by Markham and Mabry (1975), and Chapter 2 in this book is dedicated to  $^{13}\text{C}$ -NMR. To my knowledge, no important new results on  $^1\text{H}$ -NMR spectroscopy have been published since 'The Flavonoids' appeared. Therefore I only want to mention one practical hint. Recovering the sample after measurement is often important, since a considerable amount of pure substance is then available for other purposes. Although  $\text{DMSO}-d_6$  is the most generally useful solvent for underivatized flavonoids, it is a difficult solvent to get rid of

(Markham and Mabry, 1975). Column chromatography on polyamide, preparative TLC on silica, and preparative PC have been used for this purpose (Exner, 1978). The most convenient method for recovering aglycones, however, is passage of the sample solution over a small column (e.g. 15 cm × 3 cm; Dietz, 1980) of Sephadex LH-20. On elution with MeOH the DMSO will leave the column with the first portion (Hiemann *et al.*, 1978).

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## CHECK LIST OF FLAVONES AND FLAVONOLS

### I Hydroxyflavones and their methyl ethers

- |                                 |                               |
|---------------------------------|-------------------------------|
| 1 Flavone                       | 10 5,2'-Dihydroxyflavone      |
| 2 Primuletin (5-OH)             | 11 7,4'-Dihydroxyflavone      |
| 3 2'-Hydroxyflavone             | 12 3',4'-Dihydroxyflavone     |
| 4 5-Hydroxy-6-methoxyflavone    | 13 Baicalein (5,6,7-tri-OH)   |
| 5 5,6-Dimethoxyflavone          | 14 6-Methyl ether (oroxylin)  |
| 6 Chrysin (5,7-di-OH)           | 15 7-Methyl ether (negletein) |
| 7 7-Methyl ether (tectochrysin) | 16 6,7-Dimethyl ether*        |
| 8 5,7-Dimethyl ether            | 17 5,6,7-Trimethyl ether      |
| 9 Primetin (5,8-di-OH)          | 18 Norwogonin (5,7,8-tri-OH)  |

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- 19 8-Methyl ether (wogonin)
- 20 7,8-Dimethyl ether\*
- 21 5,7,8-Trimethyl ether\*
- 22 5,6,2'-Trimethoxyflavone
- 23 5,6,3'-Trimethoxyflavone
- 24 5,2'-Dihydroxy-7-methoxyflavone (echiodinin)
- 25 Apigenin (5,7,4'-tri-OH)
- 26 5-Methyl ether (thevetiaflavone)
- 27 7-Methyl ether (genkwanin)
- 28 4'-Methyl ether (acacetin)
- 29 5,7-Dimethyl ether\*
- 30 7,4'-Dimethyl ether
- 31 5,7,4'-Trimethyl ether\*
- 32 5,8,2'-Trihydroxyflavone
- 33 7,3',4'-Trihydroxyflavone
- 34 3'-Methyl ether (geraldone)
- 35 7,4'-Dimethyl ether (tithonine)
- 36 5,8-Dihydroxy-6,7-dimethoxyflavone
- 37 5,7-Dihydroxy-6,8-dimethoxyflavone
- 38 8-Hydroxy-5,6,7-trimethoxyflavone
- 39 Alnetin (5-OH,6,7,8-tri-OMe)
- 40 5,6,7,8-Tetramethoxyflavone
- 41 Scutellarein (5,6,7,4'-tetra-OH)
- 42 6-Methyl ether (hispidulin)
- 43 7-Methyl ether (sorbifolin)
- 44 4'-Methyl ether
- 45 6,7-Dimethyl ether (cirsimaritin)
- 46 6,4'-Dimethyl ether (pectolinarigenin)
- 47 7,4'-Dimethyl ether
- 48 6,7,4'-Trimethyl ether (salvigenin)
- 49 5,6,7,4'-Tetramethyl ether
- 50 5,7,8,2'-Tetrahydroxyflavone
- 51 7,8-Dimethyl ether (skullcapflavone I)\*
- 52 7,8,2'-Trimethyl ether\*
- 53 Isoscutellarein (5,7,8,4'-tetra-OH)
- 54 7-Methyl ether (salvitin)\*
- 55 8-Methyl ether\*
- 56 4'-Methyl ether (takakin)
- 56 7,8-Dimethyl ether\*
- 57 8,4'-Dimethyl ether\* (cirsitakaogenin)
- 58 7,8,4'-Trimethyl ether\*
- 59 5,7,8,4'-Tetramethyl ether
- 60 Zapotinin (5-OH, 6,2',6'-tri-OMe)
- 61 Zapotin (5,6,2',6'-tetra-OMe)
- 62 Cerosillin (5,6,3',5'-tetra-OMe)
- 63 Norartocarpetin (5,7,2',4'-tetra-OH)
- 64 7-Methyl ether (artocarpetin)
- 65 5,7,2',4'-Tetramethyl ether\*
- 66 Luteolin (5,7,3',4'-tetra-OH)
- 67 5-Methyl ether\*
- 68 7-Methyl ether
- 69 3'-Methyl ether (chrysoeriol)
- 70 4'-Methyl ether (diosmetin)
- 71 5,3'-Dimethyl ether\*
- 72 7,3'-Dimethyl ether (velutin)
- 73 7,4'-Dimethyl ether (pilloin)
- 74 3',4'-Dimethyl ether\*
- 75 7,3',4'-Trimethyl ether
- 76 5,7,3',4'-Tetramethyl ether\*
- 77 Abrectorin (7,3'-di-OH, 6,4'-di-OMe)
- 78 Desmethoxysudachitin (5,7,4'-tri-OH, 6,8-di-OMe)
- 79 Xanthomicrol (5,4'-di-OH, 6,7,8-tri-OMe)
- 80 Nevadensin (5,7-di-OH, 6,8,4'-tri-OMe)
- 81 7-Hydroxy-5,6,8,4'-tetramethoxy\*
- 82 Gardenin B (5-OH, 6,7,8,4'-tetra-OMe)
- 83 Tangeretin (5,6,7,8,4'-penta-OMe)
- 84 Rivularin (5,2'-di-OH, 7,8,6'-tri-OMe)
- 85 6-Hydroxyluteolin
- 86 6-Methyl ether (nepetin)
- 87 7-Methyl ether (pedalitin)
- 88 3'-Methyl ether (nodifloretin)
- 89 6,7-Dimethyl ether (cirsiliol)
- 90 6,3'-Dimethyl ether (jaceosidin)
- 91 6,4'-Dimethyl ether
- 92 7,3'-Dimethyl ether\*
- 93 7,4'-Dimethyl ether
- 94 6,7,3'-Trimethyl ether (cirsileneol)
- 95 6,7,4'-Trimethyl ether (eupatorin)
- 96 6,3',4'-Trimethyl ether (eupalitin)
- 97 5,6,7,4'-Tetramethyl ether
- 98 6,7,3',4'-Tetramethyl ether
- 99 5,6,7,3',4'-Pentamethyl ether (sinensetin)
- 100 Norwightin (5,7,8,2',3'-penta-OH)
- 101 7,8,2'-Trimethyl ether (wightin)
- 102 7,8,2',3'-Tetramethyl ether
- 103 Hypolaetin (5,7,8,3',4'-penta-OH)
- 104 8-Methyl ether (onopordin)
- 105 3'-Methyl ether\*
- 106 7,3'-Dimethyl ether\*
- 107 8,3'-Dimethyl ether
- 108 7,8,3',4'-Tetramethyl ether
- 109 5,7,8,3',4'-Pentamethyl ether (isosinensetin)
- 110 Isoetin (5,7,2',4',5'-penta-OH)\* (= hieracin)
- 111 Tricetin (5,7,3',4',5'-penta-OH)
- 112 5'-Methyl ether (selgin)\*
- 113 3',5'-Dimethyl ether (tricin)
- 114 3',4',5'-Trimethyl ether\*
- 115 7,3',4',5'-Tetramethyl ether (corymbosin)
- 116 5,7,3',4',5'-Pentamethyl ether

- 117 Prosogerin D (7-OH, 6,3',4',5'-tetra-OMe)
- 118 Prosogerin C (6,7,3',4',5'-penta-OMe)
- 119 Skullcapflavone II (5,2'-di-OH, 6,7,8,6'-tetra-OMe)\*
- 120 5,7,3',4'-Tetrahydroxy-6,8-dimethoxyflavone\*
- 121 5,6,7,8'-Tetrahydroxy-3',4'-dimethoxyflavone
- 122 5,3',4'-Trihydroxy-6,7,8-trimethoxyflavone\*
- 123 Sudachitin (5,7,4'-tri-OH, 6,8,3'-tri-OMe)
- 124 Acerosin (5,7,3'-tri-OH, 6,8,4'-tri-OMe)
- 125 5,4'-Dihydroxy-6,7,8,3'-tetramethoxyflavone\*
- 126 Gardenin D (5,3'-di-OH, 6,7,8,4'-tetra-OMe)\*
- 127 Hymenoxin (5,7-di-OH, 6,8,3',4'-tetra-OMe)
- 128 4'-Hydroxy-5,6,7,8,3'-pentamethoxyflavone\*
- 129 5-Desmethoxynobiletin (6,7,8,3',4'-penta-OMe)
- 130 Nobiletin (5,6,7,8,3',4'-hexa-OMe)
- 131 Tabularin (5,7-di-OH, 6,2',4',5'-tetra-OMe)\*
- 132 5,7,4'-Trihydroxy-6,3',5'-trimethoxyflavone\*
- 133 5,7,3'-Trihydroxy-6,4',5'-trimethoxyflavone\*
- 134 5-Hydroxy-6,7,3',4',5'-pentamethoxyflavone\*
- 135 5-Hydroxy-7,8,2',3',4'-pentamethoxyflavone
- 136 5,7,3',4',5'-Pentahydroxy-8-methoxyflavone\*
- 137 5,7,3',5'-Tetrahydroxy-8,4'-dimethoxyflavone\*
- 138 5,7,5'-Trihydroxy-8,3',4'-trimethoxyflavone\*
- 139 5,3'-Dihydroxy-7,8,4',5'-tetramethoxyflavone\*
- 140 5,7-Dihydroxy-8,3',4',5'-tetramethoxyflavone\*
- 141 5,2',4'-Trihydroxy-6,7,8,5'-tetramethoxyflavone\*
- 142 5,6,7,8,2',4',5'-Heptamethoxyflavone\*
- 143 Gardenin E (5,3',5'-tri-OH, 6,7,8,4'-tetra-OMe)
- 144 6,7,8,5'-Tetramethyl ether (agecorynin-O)

- 145 5,6,7,8,2',4',5'-Heptamethyl ether (agecorynin-O)
- 146 Scaposin (5,7,5'-tri-OH, 6,8,3',4'-tetra-OMe)
- 147 5,6,7-Trihydroxy-8,3',4',5'-tetramethoxyflavone\*
- 148 Gardenin C (5,3'-di-OH, 6,7,8,4',5'-penta-OMe)
- 149 Gardenin A (5-OH, 6,7,8,3',4',5'-hexa-OMe)
- 150 5,6,7,8,3',4',5'-Heptamethoxyflavone\*

## II Hydroxyflavonols and their methyl ethers

- 1 Galangin (3,5,7-tri-OH)
- 2 3-Methyl ether
- 3 7-Methyl ether (izalpinin)
- 4 3,7-Dimethyl ether\*
- 5 3,5,7-Trimethyl ether\*
- 6 5-Deoxykaempferol (3,7,4'-tri-OH)
- 7 Alnus (3,5,7-tri-OH, 6-OMe)
- 8 5,7-Dihydroxy-3,6-dimethoxyflavone\*
- 9 5,6-Dihydroxy-3,7-dimethoxyflavone\*
- 10 3,6-Dihydroxy-5,7-dimethoxyflavone\*
- 11 Alnustin (5-OH, 3,6,7-tri-OMe)
- 12 3,5,6,7-Tetramethoxyflavone\*
- 13 3,5,8-Trihydroxy-7-methoxyflavone\*
- 14 Isognaphalin (5,8-di-OH, 3,7-di-OMe)
- 15 Gnaphalin (5,7-di-OH, 3,8-di-OMe)
- 16 3,5-Dihydroxy-7,8-dimethoxyflavone\*
- 17 Methylgnaphalin (5-OH, 3,7,8-tri-OMe)
- 18 Datisetin (3,5,7,2'-tetra-OH)
- 19 7-Methyl ether (datin)
- 20 Kaempferol (3,5,7,4'-tetra-OH)
- 21 3-Methyl ether (isokaempferide)
- 22 5-Methyl ether
- 23 7-Methyl ether (rhamnocitrin)
- 24 4'-Methyl ether (kaempferide)
- 25 3,7-Dimethyl ether (kumatakenin)
- 26 3,4'-Dimethyl ether (ermanin)
- 27 7,4'-Dimethyl ether
- 28 3,5,7-Trimethyl ether\*
- 29 3,7,4'-Trimethyl ether
- 30 Pratoletin (3,5,8,4'-tetra-OH)
- 31 3,7,8,4'-Tetrahydroxyflavone
- 32 3-Methyl ether
- 33 Fisetin (3,7,3',4'-tetra-OH)
- 34 3-Methyl ether
- 35 3'-Methyl ether (geraldol)
- 36 4'-Methyl ether
- 37 3,7,3',4'-Tetramethyl ether
- 38 3,5,7-Trihydroxy-6,8-dimethoxyflavone
- 39 Araneol (5,7-di-OH, 3,6,8-tri-OMe)

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- 40 3,5-Dihydroxy-6,7,8-trimethoxyflavone\*
- 41 6-Hydroxykaempferol (3,5,6,7,4'-penta-OH)
- 42 3-Methyl ether
- 43 5-Methyl ether (vogeleitin)
- 44 6-Methyl ether
- 45 4'-Methyl ether
- 46 3,6-Dimethyl ether
- 47 3,7-Dimethyl ether\*
- 48 6,7-Dimethyl ether (eupalitin)
- 49 6,4'-Dimethyl ether (betuletol)
- 50 3,6,7-trimethyl ether (penduletin)
- 51 3,6,4'-Trimethyl ether (santin)
- 52 6,7,4'-Trimethyl ether (mikanin)
- 53 3,6,7,4'-Tetramethyl ether
- 54 Herbacetin (3,5,7,8,4'-penta-OH)
- 55 7-Methyl ether (pollenitin)
- 56 8-Methyl ether (sexangularetin)
- 57 3,7-Dimethyl ether
- 58 3,8-Dimethyl ether
- 59 7,8-Dimethyl ether\*
- 60 7,4'-Dimethyl ether\*
- 61 8,4'-Dimethyl ether (prudomestin)
- 62 3,7,8-Trimethyl ether
- 63 3,8,3'-Trimethyl ether
- 64 3,8,4'-Trimethyl ether
- 65 7,8,4'-Trimethyl ether (tambulin)
- 66 3,7,8,4'-Tetramethyl ether (flindulatin)
- 67 Auranetin (3,6,7,8,4'-penta-OMe)
- 68 Morin (3,5,7,2',4'-penta-OH)
- 69 7,5'-Dihydroxy-3,5,2'-trimethoxyflavone\*
- 70 Quercetin (3,5,7,3',4'-penta-OH)
- 71 3-Methyl ether
- 72 5-Methyl ether (azaleatin)
- 73 7-Methyl ether (rhamnetin)
- 74 3'-Methyl ether (isorhamnetin)
- 75 4'-Methyl ether (tamarixetin)
- 76 3,5-Dimethyl ether (caryatin)
- 77 3,7-Dimethyl ether
- 78 3,3'-Dimethyl ether
- 79 3,4'-Dimethyl ether
- 80 5,3'-Dimethyl ether\*
- 81 7,3'-Dimethyl ether (rhamnazin)
- 82 7,4'-Dimethyl ether (ombuin)
- 83 3',4'-Dimethyl ether (dillenetin)
- 84 3,7,3'-Trimethyl ether (pachypodol)
- 85 3,7,4'-Trimethyl ether (ayanin)
- 86 3,3',4'-Trimethyl ether\*
- 87 7,3',4'-Trimethyl ether
- 88 3,5,7,4'-Tetramethyl ether
- 89 3,5,3',4'-Tetramethyl ether
- 90 3,7,3',4'-Tetramethyl ether (retusin)
- 91 3,5,8,3',4'-Pentahydroxyflavone
- 92 Rhynchosin (3,6,7,3',4'-penta-OH)
- 93 Melanoxetin (3,7,8,3',4'-penta-OH)
- 94 Robinetin (3,7,3',4',5'-penta-OH)
- 95 Emmaosunin (5-OH,3,6,7,8,3'-penta-OMe)\*
- 96 Calicopterin (5,4'-di-OH, 3,6,7,8-tetra-OMe)
- 97 Eriostemon (3,8'-di-OH, 5,6,7,4'-tetra-OMe)
- 98 Araneosol (5,7-di-OH, 3,6,8,4'-tetra-OMe)
- 99 5-Hydroxy-3,6,7,8,4'-pentamethoxyflavone\*
- 100 Chrysosplenin (5,4'-di-OH, 3,6,7,2'-tetra-OMe)
- 101 Quercetagetin (3,5,6,7,3',4'-hexa-OH)
- 102 3-Methyl ether\*
- 103 5-Methyl ether\*
- 104 6-Methyl ether (patuletin)
- 105 3'-Methyl ether
- 106 3,6-Dimethyl ether (axillarin)
- 107 3,7-Dimethyl ether (tomentin)
- 108 6,7-Dimethyl ether (eupatolitin)
- 109 6,3'-Dimethyl ether (spinacetin)
- 110 6,4'-Dimethyl ether (laciniatin)
- 111 3,6,7-Trimethyl ether (chrysosplenol-D)
- 112 3,6,3'-Trimethyl ether (jaceidin)
- 113 3,6,4'-Trimethyl ether (centaureidin)
- 114 3,7,3'-Trimethyl ether (chrysosplenol-C)
- 115 3,7,4'-Trimethyl ether (oxyyanin-B)
- 116 6,7,3'-Trimethyl ether (veronicafolin)
- 117 6,7,4'-Trimethyl ether (eupatin)
- 118 7,3',4'-Trimethyl ether
- 119 3,5,6,3'-Tetramethyl ether\*
- 120 3,6,7,3'-Tetramethyl ether (chrysosplenetin)
- 121 3,6,7,4'-Tetramethyl ether (casticin)
- 122 5,6,7,4'-Tetramethyl ether (eupatoretin)
- 123 3,6,3',4'-Tetramethyl ether (bonanzin)
- 124 3,7,3',4'-Tetramethyl ether\*
- 125 3,6,7,3',4'-Pentamethyl ether (artemetin)
- 126 3,5,6,7,3',4'-Hexamethyl ether
- 127 5,4'-Dihydroxy-3,7,8,2'-tetramethoxyflavone\*
- 128 5-Hydroxy-3,7,8,2',4'-pentamethoxyflavone\*
- 129 Gossypetin (3,5,7,8,3', 4'-hexa-OH)
- 130 7-Methyl ether
- 131 8-Methyl ether (corniculatusin)
- 132 3'-Methyl ether
- 133 3,7-Dimethyl ether
- 134 3,8,-Dimethyl ether
- 135 7,4'-Dimethyl ether
- 136 8,3'-Dimethyl ether (limocitrin)



- 137 8,4'-Dimethyl ether
- 138 3,7,8-Trimethyl ether
- 139 3,7,3'-Trimethyl ether\*
- 140 3,8,3'-Trimethyl ether
- 141 7,8,3'-Trimethyl ether\*
- 142 3,7,8,3'-Tetramethyl ether (ternatin)
- 143 3,7,8,4'-Tetramethyl ether
- 144 3,7,3',4'-Tetramethyl ether
- 145 3,8,3',4'-Tetramethyl ether\*
- 146 3,7,8,3',4'-Pentamethyl ether
- 147 3,5,7,8,3',4'-Hexamethyl ether
- 148 Apuleidin (5,2',3'-tri-OH, 3,7,4'-tri-OMe)
- 149 5'-Hydroxymorin (3,5,7,2',4',5'-hexa-OH)
- 150 3,7,4'-Trimethyl ether (oxyanin-A)
- 151 3,5,7,4'-Tetramethyl ether
- 152 3,7,4',5'-Tetramethyl ether
- 153 3,7,2',4',5'-Pentamethyl ether\*
- 154 3,5,7,4',5'-Pentamethyl ether\*
- 155 3,5,7,2',4',5'-Hexamethyl ether\*
- 156 5-Demethylapulein (2',5'-di-OH, 3,6,7,4'-tetra-OMe)
- 157 Myricetin (3,5,7,3',4',5'-hexa-OH)
- 158 3-Methyl ether (annulatin)
- 159 5-Methyl ether
- 160 7-Methyl ether (europetin)
- 161 3'-Methyl ether (laricitrin)\*
- 162 4'-Methyl ether (mearnsetin)
- 163 3,4'-Dimethyl ether\*
- 164 3,5'-Dimethyl ether\*
- 165 3',5'-Dimethyl ether (syngnetin)
- 166 3,7,4'-Trimethyl ether
- 167 3,3',4'-Trimethyl ether\*
- 168 7,3',4'-Trimethyl ether
- 169 3,7,3',4'-Tetramethyl ether
- 170 3,7,3',4',5'-Pentamethyl ether (combretol)
- 171 5,2',4'-Trihydroxy-3,6,7,8-tetramethoxyflavone\*
- 172 5,4'-Dihydroxy-3,6,7,8,2'-penta-methoxyflavone\*
- 173 5,2'-Dihydroxy-3,6,7,8,4'-penta-methoxyflavone\*
- 174 5-Hydroxy-3,6,7,8,2',4'-hexa-methoxyflavone\*
- 175 5,7,3',4'-Tetrahydroxy-3,6,8-trimethoxyflavone
- 176 Limocitrol (3,5,7,4'-tetra-OH,6,8,3'-tri-OMe)
- 177 Isolimocitrol (3,5,7,3'-tetra-OH,6,8,4'-tri-OMe)
- 178 5,7,4'-Trihydroxy-3,6,8,3'-tetramethoxyflavone\*
- 179 5,4'-Dihydroxy-3,6,7,8,3'-penta-methoxyflavone\*
- 180 5-Hydroxy-3,6,7,8,3',4'-hexa-methoxyflavone
- 181 3-Hydroxy-5,6,7,8,3',4'-hexa-methoxyflavone
- 182 3,5,6,7,8,3',4'-Heptamethoxyflavone
- 183 Apuleisin (5,6,2',3'-tetra-OH,3,7,4'-tri-OMe)
- 184 3,5,6,7,2',3',4'-Heptamethoxyflavone
- 185 Apulein (2',5'-di-OH, 3,5,6,7,4'-penta-OMe)
- 186 6,2'-Dihydroxy-3,5,7,4',5'-penta-methoxyflavone\*
- 187 5,6-Dihydroxy-3,7,2',4',5'-penta-methoxyflavone\*
- 188 3,5,6,7,2',4',5',-Heptamethoxyflavone\*
- 189 6-Hydroxymyricetin 3,6-dimethyl ether\*
- 190 3,4'-Dimethyl ether\*
- 191 3,6,3'-Trimethyl ether\*
- 192 3,6,4'-Trimethyl ether\*
- 193 6,3',4'-Trimethyl ether\*
- 194 3,5,6,5'-Tetramethyl ether
- 195 3,6,7,4'-Tetramethyl ether
- 196 3,6,3',4'-Tetramethyl ether\*
- 197 3,6,3',5',-Tetramethyl ether\*
- 198 5,6,3',5',-Tetramethyl ether
- 199 3,7,3',4'-Tetramethyl ether (apuleitrin)
- 200 3,5,7,3',4'-Pentamethyl ether (apuleirin)
- 201 3,6,7,3',5'-Pentamethyl ether (murrayanol)\*
- 202 3,5,6,7,3',5'-Hexamethyl ether
- 203 3,5,6,7,3',4',5'-Heptamethyl ether
- 204 Hibiscetin (3,5,7,8,3',4',5'-hepta-OH)
- 205 3,7,4'-Trimethyl ether\*
- 206 3,7,8,4'-Tetramethyl ether\*
- 207 3,8,4',5'-Tetramethyl ether
- 208 3,8,3',4',5'-Pentamethyl ether (conyzatin)\*
- 209 7,8,3',4',5'-Pentamethyl ether\*
- 210 3,5,7,8,3',4',5'-Heptamethyl ether
- 211 Digicitrin (5,3'-di-OH, 3,6,7,8,4',5'-hexa-OMe)
- 212 8-Hydroxy-3,5,6,7,3',4',5'-Heptamethoxyflavone
- 213 Exoticin (3,5,6,7,8,3',5'-octa-OMe)

### III C-Methyl flavones and C-methyl flavonols

- 1 6-Methyl chrysin (5,7-di-OH, 6-Me)
- 2 Sideroxylin (5,4'-di-OH, 7-OMe, 6,8-di-Me)
- 3 5-Hydroxy-7,4'-dimethoxy-6-methylflavone
- 4 Eucalyptin (5-OH, 7,4'-di-OMe, 6,8-di-Me)

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- 5 Unonal (5,7-di-OH, 8-Me, 6-CHO)\*
- 6 Isounonal (5,7-di-OH, 6-Me, 8-CHO)\*
- 7 Unonal 7-methyl ether (5-OH, 7-OMe, 8-Me, 6-CHO)\*
- 8 5,7-Dihydroxy-3-methoxy-6,8-dimethylflavone\*
- 9 Pityrogrammin (3,5,7-tri-OH, 8-OMe, 6-Me)\*
- 10 Sylpin (5,6,4'-tri-OH, 3-OMe, 8-Me)\*
- 11 5,7,4'-Trihydroxy-3-methoxy-6-methylflavone\*
- 12 5,7,4'-Trihydroxy-3-methoxy-6,8-dimethylflavone\*
- 13 Pinoquercetin (6-Me quercetin)
- 14 6,8-Dimethyl quercetin\*
- 15 Pinoquercetin 3,3'-dimethyl ether\*
- 16 6-Methylmyricetin
- 17 6-Methylmyricetin 3-methyl ether (alluaudiol)\*
- 18 6,8-Dimethylmyricetin 3-methyl ether\*
- 19 6-Methylmyricetin 4'-methyl ether (dumosol)\*
- 20 6,8-Dimethylmyricetin 4'-methyl ether\*
- 21 6-Methylmyricetin 3,4'-dimethyl ether\*
- 22 6,8-Dimethylmyricetin 3,4'-dimethyl ether\*

### IV Methyleneedioxyflavones and methylenedioxyflavonols

- 1 5-Hydroxy-7,8-methylenedioxyflavone\*
- 2 5,6-Dimethoxy-3',4'-methylene-dioxyflavone\*
- 3 Prosogerin-A (7-OH, 6-OMe, 3',4'-O<sub>2</sub>CH<sub>2</sub>)\*
- 4 Kanzakiflavone-2 (5,4'-di-OH, 6,7-O<sub>2</sub>CH<sub>2</sub>)\*
- 5 Kanzakiflavone-1 (5,8-di-OH, 4'-OMe, 6,7-O<sub>2</sub>CH<sub>2</sub>)\*
- 6 Linderoflavone A (5,7-di-OH, 6,8-di-OMe, 3',4'-O<sub>2</sub>CH<sub>2</sub>)
- 7 Linderoflavone B (5,6,7,8-tetra-OMe, 3',4'-O<sub>2</sub>CH<sub>2</sub>)
- 8 Eupalestin (5,6,7,8,5'-penta-OMe, 3',4'-O<sub>2</sub>CH<sub>2</sub>)\*
- 9 3,5-Dimethoxy-6,7-methylenedioxyflavone\*
- 10 Meliternatin (3,5-di-OMe, 6,7-O<sub>2</sub>CH<sub>2</sub>, 3',4'-O<sub>2</sub>CH<sub>2</sub>)
- 11 Demethoxykanungin (3,7-di-OMe, 3',4'-O<sub>2</sub>CH<sub>2</sub>)
- 12 Gomphrenol (3,5,4'-tri-OH, 6,7-O<sub>2</sub>CH<sub>2</sub>)\*
- 13 Kanugin (3,7,3'-tri-OMe, 4',5'-O<sub>2</sub>CH<sub>2</sub>)
- 14 Melisimplin (5-OH, 3,6,7-tri-OMe, 3',4'-O<sub>2</sub>CH<sub>2</sub>)

- 15 Melisimplexin (3,5,6,7-tetra-OMe, 3',4'-O<sub>2</sub>CH<sub>2</sub>)
- 16 5-Hydroxy-3,7,8-trimethoxy-3',4'-methylenedioxyflavone\*
- 17 Meliternin (3,5,7,8-tetra-OMe, 3',4'-O<sub>2</sub>CH<sub>2</sub>)
- 18 5,3',4'-Trihydroxy-3-methoxy-6,7-methylenedioxyflavone
- 19 Wharangin (5,3',4'-tri-OH, 3-OMe, 7,8-O<sub>2</sub>CH<sub>2</sub>)
- 20 Melinervin (3,6,7-tri-OH, 6,8-di-OMe, 3',4'-O<sub>2</sub>CH<sub>2</sub>)\*
- 21 5-Hydroxy-3,6,7,8-tetramethoxy-3',4'-methylenedioxyflavone\*
- 22 Melibentin (3,5,6,7,8-penta-OMe, 3',4'-O<sub>2</sub>CH<sub>2</sub>)

### V Isoprene-substituted flavones and flavonols

- 1 *Trans*-lanceolatin\*
- 2 *Cis*-tephrostachin\*
- 3 *Trans*-tephrostachin
- 4 *Trans*-anhydrotephrostachin
- 5 Artocarpesin
- 6 Oxodihydroartocarpesin
- 7 Norartocarpin
- 8 Mulberrin
- 9 Integrin\*
- 10 Artocarpin
- 11 Kuwanone C\*
- 12 8-Prenyl-luteolin
- 13 Rubraflavone A
- 14 Rubraflavone B
- 15 Rubraflavone C
- 16 8-Hydroxyprenyl-5-deoxykaempferol
- 17 6-Prenyl-3,5,7,8-tetrahydroxyflavone\*
- 18 Noranhydroicaritin
- 19 Noricaritin
- 20 Isoanhydroicaritin
- 21 Icaritin
- 22 6-Hydroxyprenylquercetin
- 23 7-O-Prenylquercetin 3,3'-dimethyl ether\*
- 24 8-Prenylquercetin 3,7,3'-trimethyl ether
- 25 7,8-Dimethylallyloxy-5-hydroxyflavone\*
- 26 Isopongaflavone
- 27 Praecansone B
- 28 7,6-Dimethylallyloxy-5,4'-dihydroxyflavone\*
- 29 Cyclomulberrochromene
- 30 Cyclomorusin\*
- 31 Cycloartocarpesin
- 32 Mulberrochromene

- |                                                            |                                     |
|------------------------------------------------------------|-------------------------------------|
| 33 Kuwanone B*                                             | 50 Lanceolatin B                    |
| 34 Hydroxydihydromorusin*                                  | 51 Pongaglabrone*                   |
| 35 Morusin*                                                | 52 Pongaglabol*                     |
| 36 Kuwanone A*                                             | 53 Pinnatin                         |
| 37 Rubraflavone D                                          | 54 Gamatin                          |
| 38 Cyclomulberrin                                          | 55 6-Methoxy-7,8-furanoflavone*     |
| 39 Cycloartocarpin                                         | 56 8-Methoxy-7,8-furanoflavone*     |
| 40 Desmodol*                                               | 57 3'-Hydroxy-7,8-furanoflavone*    |
| 41 Cycloheterophyllin                                      | 58 Dihydrofuranoartobilichromene b* |
| 42 Artobilichromene*                                       | 59 Dihydrofuranoartobilichromene a* |
| 43 Karanjachromene                                         | 60 Mulberranol                      |
| 44 Pongaflavone                                            | 61 Karanjin                         |
| 45 Pongachromene*                                          | 62 Pongapin                         |
| 46 7,8-Dimethylallyloxy-<br>3,6-dimethoxyflavone*          | 63 3'-Methoxypongapin               |
| 47 Sericetin                                               | 64 <i>Morus alba</i> compound A     |
| 48 Phellamuretin                                           | 65 Oxyisocyclointegrin              |
| 49 7,8-Dimethylallyloxy-3,5,3',<br>4'-tetrahydroxyflavone* | 66 Chaplashin                       |
|                                                            | 67 Isocycloheterophyllin            |
|                                                            | 68 <i>Artocarpus</i> oxocin flavone |

\* Structures newly reported 1975–1980

The details of isoprene substituted flavones and flavonols can be found in Tables 4.5–4.8 and Figs. 4.1–4.3; the total number of these structures may be slightly greater than 68 since the list here may not be completely exhaustive.

## CHAPTER FIVE

# *Flavone and Flavonol Glycosides*

JEFFREY B. HARBORNE and CHRISTINE A. WILLIAMS

### 5.1 INTRODUCTION

In 1975, some 360 flavone and flavonol glycosides were known to occur in plants (Harborne and Williams, 1975). In the intervening five years, a similar number of new compounds have been recorded, bringing the total to about 720 structures (see the check list at the end of the chapter). This is, in fact, a conservative estimate, since a variety of partly characterized glycosides, probably differing in structure from those reported in the Tables in this chapter, have been omitted from this check list. In the present chapter, therefore, we provide an account of the new substances discovered during the period 1975–1980. References to the earlier literature will be included from time to time, since a number of structural reassignments have also taken place. The term ‘conjugate’ might be more apt than ‘glycoside’, since here, as in our previous account, we are including flavones and flavonols with acyl and sulphate substituents; these usually, but not invariably, have glycosidic attachments as well.

Many of the new compounds reported have the expected structures and simply fill in gaps among known derivatives. For example, the 3-xyloside of quercetin was first described from the leaves of *Reynoutria japonica* (Polygonaceae) by Nakaoki and Morita (1956), and has been found in a number of other plants since (see Harborne, 1967). The related kaempferol and myricetin derivatives have now been discovered: kaempferol 3-xyloside occurs in *Euonymus* leaf (Celastraceae) (Ishikura and Sato, 1977); and myricetin 3-xyloside is one of a number of glycosides present in *Leptarrhena pyrolifolia* (Saxifragaceae), reported by Miller and Bohm (1979).

An increasing number of other new glycosides reported contain acyl substituents (e.g. acetyl, galloyl, *p*-coumaroyl etc.) attached to sugar hydroxyls, and a powerful tool for the location of these substituents is <sup>13</sup>C-NMR spectroscopy (see Chapter 2). The application of this technique to flavonoids has also led to the discovery of a new rare hexose, allose, in glycosidic combination. Allose occurs as such in kaempferol 3-alloside and in certain flavones in combination with glucose as a disaccharide (see Section 5.4). Allose was only recognized as a plant sugar as recently as 1973 by Perold *et al.*, who isolated some allose derivatives from the leaves of *Protea rubropilosa*; it has since also been found in glycosidic combination with iridoids (Jensen *et al.*, 1981).

A variety of new oligosaccharides has also been reported, particularly in association with kaempferol and quercetin. A notable series of four branched trisaccharides occur attached to flavonols in soya bean leaves: 2<sup>G</sup>-rhamnosyl- and 2<sup>G</sup>-glucosyl-rutinosyl, 2<sup>G</sup>-rhamnosyl- and 2<sup>G</sup>-glucosyl-gentiobiosyl (Buttery and Buzzell, 1975). Several new linear trisaccharides have also been described, e.g. rhamnosyl(1→2)rutinosyl. Only one tetrasaccharide (an acetylated rhamnosylsophorotriose) has yet been fully characterized as a flavonoid sugar. Since penta- and even hexa-saccharides are known to occur in glycosidic combination with triterpenoids (Chandel and Rastogi, 1980), their discovery in association with flavonoids cannot be far off.

In recent years attention has been given to the importance of glycosylation in relation to the function of flavones and flavonols in plants (Harborne, 1979a). A significant number of these compounds has been detected in plants occurring in the free state without sugar attachment (Wollenweber and Dietz, 1981). These tend to be those which have one or more *O*-methyl groups; furthermore, their occurrence is often associated with other lipophilic constituents and may be restricted to certain parts of the plant, e.g. the waxy coatings of the leaves. Free flavones and flavonols are potentially toxic to living cells and inhibit many enzymic activities (Harborne, 1979a), so that glycosylation must be an essential protective device to prevent cytoplasmic damage and to locate the flavonoids safely in the cell vacuole. While glycosylation is most frequent with the fully hydroxylated compounds such as kaempferol and quercetin, it also occurs with many of their methyl ethers. Indeed, an increasing number of novel *O*-methylated flavonols, especially those in the quercetagenin and gossypetin series, have been discovered recently. Significantly, most of these are found with at least one or two sugar residues and many of the new flavonol glycosides recorded here (see Section 5.6) are of this type.

## 5.2 SEPARATION AND PURIFICATION

Standard procedures based on thin-layer, paper and column chromatography are still most widely used for the separation and purification of flavone and flavonol glycosides. These techniques provide most compounds in sufficient quantity for routine structural determination. If larger amounts are desired, then other techniques may be needed (see below). It is perhaps worth emphasizing the importance of checking homogeneity of isolated compounds in as many chromatographic systems as possible. It is certainly advisable to test for purity using thin-layer chromatography on microcrystalline cellulose, polyamide and silica gel, employing several solvent systems in each case. Even so, there may be pairs of glycosides which are unresolvable in any known system. The 3-arabinosylglucoside and 3-xylosylglucoside of isorhamnetin present in *Festuca* leaf extracts are apparently inseparable, as are the related quercetin derivatives (Wong, 1980).

A number of new chromatographic techniques has been developed recently (see Chapter 1) for flavonoids and some of these will be of importance for separating glycoside mixtures. In particular, droplet counter-current (DCC) chromatography appears to offer an efficient and rapid method for separating glycosides on a preparative scale. In one trial run, a crude 130 mg fraction from the plant *Tecoma stans* (Bignoniaceae) was subjected to DCC separation using the upper phase of chloroform–methanol–water (7:13:8) to yield 27 mg of pure quercetin 3-glucoside within about 6 h (Hostettmann *et al.*, 1979).

High-performance liquid chromatography (HPLC) can also be applied on the preparative scale but up to the present it has mainly been used analytically. Its value in quantitative analysis of glycosides is nicely illustrated by recent determinations of amounts of flavonol glycosides in sepals of *Poinsettia* (Stewart *et al.*, 1980). By using two solvent systems, it was possible to measure individual amounts of the ten glycosides present, namely the 3-rutinosides, 3-rhamnosylgalactosides, 3-rhamnosides, 3-glucosides and 3-galactosides of kaempferol and quercetin. Difficulties were experienced in distinguishing the 3-glucoside and 3-galactoside of quercetin, but these are two glycosides which run close together in every chromatographic system. HPLC is obviously a technique that will be used more and more in the determination of the complex glycosidic patterns that are present in many angiosperm plants.

### 5.3 IDENTIFICATION

The most important recent development in the structural identification of flavonoids is the application of  $^{13}\text{C}$ -NMR spectroscopy. It has been used successfully with flavone and flavonol glycosides (see Chapter 2, Section 2.3) to provide information on the nature and position of glycosidic attachment(s). The only limitation is that of sample size. It is necessary to have about 10 mg of material, preferably more, for spectral analysis. Its especial value is in revealing the sequence and mode of interglycosidic linkages of complex glycosides and in locating and identifying acyl substitution.  $^{13}\text{C}$ -NMR spectroscopy, for example, has been used to identify the acylated trisaccharide present in two flavonols of *Colubrina faralaotra* (Rhamnaceae) as glucosyl(1→3)-4'''-acetylramnosyl(1→6)galactose. This sequence of the three sugars attached linearly to the 3-hydroxyl position of kaempferol and quercetin followed from relaxation time measurements (Guinaudeau *et al.*, 1981).

Even with simple flavone or flavonol monoglycosides,  $^{13}\text{C}$ -NMR data may be of value in establishing the position of sugar attachment, the nature of the linkage and the configuration and conformation of the sugar. While all these can be determined by other methods (e.g. enzymically), the procedure has importance where controversy exists. Application of this technique should, for example, reveal finally whether any flavones or flavonols occur naturally with glucose, rhamnose or xylose attached to them, in the furanose form (see Section 5.4). It is

significant that all measurements made to date on a variety of such *O*-glycosides (see Table 2.15, Chapter 2) have shown that these three sugars always exist in the expected pyranose form.

Mass spectroscopy still has a place in the structural analysis of glycosides, since it can be applied to smaller samples (1 mg or less) than are required for NMR measurements. It is possible to detect weak molecular ion signals on permethylated or perdeuteriomethylated derivatives and thus establish the molecular weight. The fragmentation may also be quite characteristic of the glycosidic pattern present (see Harborne and Williams, 1975). According to Schels *et al.* (1977, 1978) there are advantages in making these measurements on the silyl ethers. The advantage over permethylation is that silylation occurs rapidly and there is no need to purify before analysis, as with the permethyl ethers. The molecular mass of the silylated glycoside is apparent from a weak  $M^+$  ion (2–4% intensity of parent ion) and a stronger  $M^+ - 15$  ion. In the case of silylated flavonol 3-biosides, it is possible to deduce the sugar sequence because the terminal sugar produces a very intense fragment (relative intensity > 30%) accompanied by two other related ions. Again, with flavonol 3,7-diglycosides, it is possible to deduce the positions of attachment, since the 3-*O*-sugar gives more intense signals than that in the 7-position.

The position of sugar attachment can often be determined more simply from colour reactions and UV spectral measurements. Homberg and Geiger (1980) have now shown that it can also be deduced from the fluorescence spectra. These have been determined for a representative number of flavone and flavonol glycosides adsorbed on cellulose, either alone or in the presence of various shift reagents.

Enzymic procedures for the structural determination of glycosides are very simple but are often neglected. Until recently, it has not been clear that specific enzymes can be employed for the removal of the terminal sugar or for the stepwise removal of all the sugars in complex glycosides. Buttery and Buzzell (1975), however, have shown that  $\beta$ -glucosidase will specifically remove terminal glucose units from flavonol triglycosides to give diglycosides in good yield. Thus kaempferol 3-(2<sup>G</sup>-glucosylgentiobioside) by cleavage of the  $\beta 1 \rightarrow 6$  linkage gives kaempferol 3-sophoroside whereas kaempferol 3-(2<sup>G</sup>-glucosylrutinoside) by cleavage of the  $\beta 1 \rightarrow 2$  linkage gives kaempferol 3-rutinoside. It is interesting that given the choice of a  $\beta 1 \rightarrow 2$ - and  $\beta 1 \rightarrow 6$ -linked glucose in the first triglycoside,  $\beta$ -glucosidase only hydrolyses the latter; the preference of the enzyme for a  $\beta 1 \rightarrow 6$  over a  $\beta 1 \rightarrow 2$  linkage is, however, expected from earlier studies (Harborne, 1965). These enzymic results, together with those from partial acidic hydrolysis, were helpful in characterizing the above kaempferol triglycoside as a new glycosidic type.

The stepwise removal of sugars from complex glycosides has also been successfully used to determine the structure of new compounds. For example, *Primula officinalis* leaves (Primulaceae) contain a quercetin 3-rhamnosyl-robinobioside (Karl *et al.*, 1981). The terminal position of the second rhamnose

was established when soyaremanase, an enzyme preparation from soya beans, selectively removed it to give quercetin 3-robinobioside. These authors were also able to recover the robinobiose [rhamnosyl( $\alpha$ 1 $\rightarrow$ 6)galactose] intact from this intermediate following enzymic hydrolysis with rhamnodistase, a disaccharidase from *Rhamnus cathartica* seed.

Similarly, a kaempferol 3-(caffeoyl-laminaribioside)-7-rhamnoside from *Phyllitis scolopendrium* lost its 7-rhamnose sugar with  $\alpha$ -rhamnosidase to give kaempferol 3-(caffeoyl-laminaribioside). This compound, on cellulase hydrolysis, lost a glucose unit to yield kaempferol 3-(caffeoylglucoside), an experiment which proved that the caffeoyl residue must be located on the sugar nearest to the aglycone moiety (Karl *et al.*, 1980). Clearly, such procedures deserve to be more widely known, since they may often simplify structural determinations. It is to be hoped that some of the more specific enzyme preparations needed will eventually become available commercially.

## 5.4 SUGARS OF FLAVONE AND FLAVONOL GLYCOSIDES

### 5.4.1 Monosaccharides

The ten monosaccharides known to occur in association with flavones and flavonols are shown in Table 5.1. Most occur both in monosaccharide combination and as components of di- and tri-saccharides attached to these substances (see Sections 5.4.2 and 5.4.3). Three of the sugars deserve further comment: allose, apiose and galacturonic acid. The hexose allose is the only new sugar reported in the last five years. It was discovered attached to kaempferol in the 3-position in the glycoside, asiaticalin, from the fern *Osmunda asiatica* (Okuyama *et al.*, 1978). It has also been found in disaccharide combination with glucose, as 2-allosylglucose, in two flavones based on chrysoeriol and isoscutellarein from *Sideritis* and *Veronica* species respectively (Chari *et al.*, 1981).

**Table 5.1** Monosaccharides of flavone and flavonol glycosides

| Pentoses     | Hexoses     | Uronic acids         |
|--------------|-------------|----------------------|
| D-Apiose     | D-Allose    | D-Galacturonic acid† |
| L-Arabinose* | D-Galactose | D-Glucuronic acid†   |
| L-Rhamnose   | D-Glucose   |                      |
| D-Xylose     | D-Mannose   |                      |

\* Definitely known to occur in both pyranose and furanose forms; all other sugars (except apiose) are normally (always) in the pyranose form.

† Also reported to occur as the methyl ester.

Apiose, an unusual branched pentose, is well known to occur as a disaccharide with glucose. Indeed apigenin 7-apiosylglucoside, called apiin, from seeds of *Apium graveolens* (Umbelliferae) was one of the very first flavone glycosides to be



isolated in crystalline condition (Lindenborn, 1869). Its discovery as a monoglycoside is, however, quite novel. The 7-apioside of 6-hydroxyluteolin has just been reported in *Lepidagathis cristata* (Acanthaceae) by Ranganathan *et al.* (1980).

Until recently, galacturonic acid has only appeared quite rarely as a flavonoid sugar. However, a remarkable range of such derivatives has been uncovered in liverworts and extend the number of uronic acid derivatives considerably. Quercetin 3-galacturonide has been found for the first time, for example, in *Corsinia coriandrina* (Markham, 1980). A variety of luteolin derivatives present in *Marchantia berteroana* also deserve mention, namely the 7-galacturonide, the 3'-galacturonide, the 7,3'-digalacturonide and the 3',4'-digalacturonide (Markham and Porter, 1975).

One other sugar, besides the ten listed in Table 5.1, may be associated with flavonoids, namely the keto sugar fructose, although the evidence for its occurrence is still not fully authenticated. The description of its presence in leaves of the tea plant *Camellia sinensis* in association with quercetin and glucose is limited by the fact that it could only be detected in processed leaves and thus might be of artifactual origin (Imperato, 1976). Fructose has also been reported in disaccharide combination with glucose attached to the flavone tricetin in *Hyacinthus orientalis* (Liliaceae) (Williams, 1975) but the nature of its linkage in this glycoside is still obscure.

Of the ten sugars listed in Table 5.1, only arabinose is definitely known to occur in both the furano and pyrano forms. There have, in addition, been reports of rhamnose, glucose, galactose and xylose also occurring in furanose form when attached to flavones and flavonols, but these are exclusively from the Russian literature. Furthermore, the evidence for the presence of these furano forms is far from unequivocal and was based largely on IR-spectral and hydrolytic data. A careful examination in our laboratory of a reputed quercetin 3- $\alpha$ -rhamnopyranoside from horse chestnut showed that it was indistinguishable in all respects from the well known and well characterized 3- $\alpha$ -rhamnopyranoside (quercitrin). The same question has now been taken up by Farkas *et al.* (1976a) regarding furanose-containing forms of the glycoside robinin with similar negative conclusions.

The complete structure of robinin as kaempferol 3-*O*-(6-*O*- $\alpha$ -L-rhamnopyranosyl- $\beta$ -D-galactopyranoside)-7-*O*- $\alpha$ -L-rhamnopyranoside was established by Zemlén and Bognár (1941) and confirmed by Shimokoriyama (1949). In spite of this, Maksyutina *et al.* (1965) later claimed robinin to be a mixture of four isomeric glycosides in which the 7-rhamnose moiety existed in the  $\alpha$ - and  $\beta$ -furanose as well as the  $\alpha$ - and  $\beta$ -pyranose forms; in all these forms, the two sugars attached in the 3-position were reported to be furanose. Farkas *et al.* (1976a), in a detailed rebuttal of these allegations, reconfirmed that all the sugars in robinin are in fact pyranose. Thus the kaempferol 7-rhamnoside, obtained by partial hydrolysis of robinin, was fully methylated and after hydrolysis, reduction and acetylation yielded 2,3,4-trimethylrhamnitol diacetate. The  $\alpha$ -configuration and anomeric homogeneity of the kaempferol 7-rhamnoside was

further established by synthesis. Finally, a total synthesis of robinin itself once more confirmed the absence of furanose rings from any of its sugars.

We can only conclude from these results that all reports of furanose-containing glycosides (other than arabinosides) must be treated with caution and cannot be regarded as correct, unless supported by more conclusive evidence. We are therefore excluding these reports from our lists, although many of them were mentioned in our earlier survey (Harborne and Williams, 1975).

One final point regarding the monosaccharides needs emphasizing: the nature of the linkage to the phenolic hydroxyl. This is usually assumed to be  $\beta$ - for glucosides, galactosides, glucuronides and xylosides and  $\alpha$ - for arabinosides and rhamnosides. A  $\beta$ -linked 3-arabinoside of quercetin is, however, well-known (Geissman, 1962) and other  $\beta$ -linked arabinosides may be present in plants. On the other hand,  $\alpha$ -linked glucosides and galactosides are also possible and need to be distinguished from the much more common  $\beta$ -derivatives (see Harborne and Williams, 1975). Studies with appropriate hydrolytic enzymes are thus desirable in all cases when new compounds are found.

#### 5.4.2 Disaccharides

Ten disaccharides were listed by Harborne and Williams (1975) as being fully characterized as components of flavone or flavonol glycosides. A further 11 disaccharides have now been described since 1975 and all 21 are collected together in Table 5.2. Considerable progress has thus been made in the characterization of disaccharide moieties. Nevertheless, as will be clear in later sections of this chapter, there are still many diglycosides reported in plants which probably have new disaccharides but which have not been fully characterized. Eventually, some of the gaps in Table 5.2 will be filled from further studies on such compounds.

Of the new disaccharides, the discovery of lactose in association with isorhamnetin in seeds of *Cassia multijuga* (Leguminosae) (Dubey and Gupta, 1980) is unexpected, since this disaccharide otherwise occurs in the free state in human milk. Most of the others are related to earlier reported disaccharides. Thus, the arabinosyl( $\alpha 1 \rightarrow 6$ )galactose, present attached to quercetin in *Hydrocotyle vulgaris* leaf (Umbelliferae) (Hiller *et al.*, 1979), is related to vicianose except that galactose replaces glucose. Again, the rhamnosyl( $\alpha 1 \rightarrow 2$ )galactose, in a kaempferol 3-glycoside from *Chenopodium fremontii* leaf (Chenopodiaceae) (Crawford and Mabry, 1978), is an isomer of the well-known robinobiose, which has the same two sugars in an  $\alpha 1 \rightarrow 6$  linkage.

The first disaccharides based on glucose and galactose have been characterized, i.e. Glc( $\beta 1 \rightarrow 6$ )Gal and Gal( $\beta 1 \rightarrow 4$ )Glc, as have two disaccharides based on glucose and mannose (Table 5.2). The first digalactose to be fully characterized is also reported Gal( $\beta 1 \rightarrow 4$ )Gal, which is attached to a myricetin derivative from *Vitex negundo* (Verbenaceae) (Misra and Subramanian, 1980). Finally, one of the most distinctive of the new disaccharides must be Gal( $\alpha 1 \rightarrow 4$ )Rha where the

**Table 5.2** Disaccharides of flavone and flavonol glycosides

| Structure                                         | Trivial name   |
|---------------------------------------------------|----------------|
| <i>Pentose–pentose</i>                            |                |
| 4- <i>O</i> - $\alpha$ -L-Rhamnosyl-D-xylose*     |                |
| <i>Pentose–hexose</i>                             |                |
| 2- <i>O</i> - $\alpha$ -L-Rhamnosyl-D-glucose     | Neohesperidose |
| 3- <i>O</i> - $\alpha$ -L-Rhamnosyl-D-glucose     | Rungiose       |
| 6- <i>O</i> - $\alpha$ -L-Rhamnosyl-D-glucose     | Rutinose       |
| 2- <i>O</i> - $\beta$ -D-Xylosyl-D-glucose        | Sambubiose     |
| 6- <i>O</i> - $\alpha$ -L-Arabinosyl-D-glucose    | Vicianose      |
| 2- <i>O</i> - $\alpha$ -L-Rhamnosyl-D-galactose*  |                |
| 6- <i>O</i> - $\alpha$ -L-Rhamnosyl-D-galactose   | Robinobiose    |
| 2- <i>O</i> - $\beta$ -D-Xylosyl-D-galactose      | Lathyrose      |
| 6- <i>O</i> - $\alpha$ -L-Arabinosyl-D-galactose* | —              |
| <i>Hexose–pentose</i>                             |                |
| 4- <i>O</i> - $\beta$ -D-Glucosyl-L-rhamnose*     | —              |
| 4- <i>O</i> - $\beta$ -D-Galactosyl-L-rhamnose*   | —              |
| <i>Hexose–hexose</i>                              |                |
| 2- <i>O</i> - $\beta$ -D-Glucosyl-D-glucose       | Sophorose      |
| 3- <i>O</i> - $\beta$ -D-Glucosyl-D-glucose       | Laminaribiose  |
| 6- <i>O</i> - $\beta$ -D-Glucosyl-D-glucose       | Gentiobiose    |
| 2- <i>O</i> - $\beta$ -D-Mannosyl-D-glucose*      | —              |
| 4- <i>O</i> - $\beta$ -D-Glucosyl-D-mannose*      | —              |
| 2- <i>O</i> - $\beta$ -D-Allosyl-D-glucose*       | —              |
| 4- <i>O</i> - $\beta$ -D-Galactosyl-D-glucose*    | Lactose        |
| 6- <i>O</i> - $\beta$ -D-Glucosyl-D-galactose*    |                |
| 4- <i>O</i> - $\beta$ -D-Galactosyl-D-galactose*  | —              |

\* Newly discovered in diglycosidic combination, in the period 1975–1980.

normal order pentose–hexose is reversed and the rhamnose is directly attached to the aglycone with the galactose as the terminal sugar. This disaccharide occurs linked to the 3-hydroxyl of galangin in *Artocarpus lakoocha* rootbark (Moraceae) (Chauhan *et al.*, 1979a).

### 5.4.3 Trisaccharides

The rapid progress that has been made in the study of flavonol 3-triglycosides is apparent from the fact that seven trisaccharides (five linear, two branched) were reported as fully characterized in 1975, while a further ten (three linear, seven branched) have been described since then. All these structures are shown in Table 5.3. In all cases, the trisaccharide is attached to the 3-hydroxyl of a flavonol, either kaempferol and/or quercetin or a simple methyl ether of these two aglycones.

One reassignment of structure has occurred. This is of a triglucose attached to kaempferol and quercetin and reported in *Primula sinensis* and other *Primula*

**Table 5.3** Trisaccharides of flavonol glycosides

| Structure                                                                                                           | Trivial name                            |
|---------------------------------------------------------------------------------------------------------------------|-----------------------------------------|
| <i>Linear</i>                                                                                                       |                                         |
| <i>O</i> - $\alpha$ -Rhamnosyl-(1 $\rightarrow$ 2)- <i>O</i> - $\alpha$ -rhamnosyl-(1 $\rightarrow$ 6)-glucose*     | 2'-Rhamnosylrutinose                    |
| <i>O</i> - $\beta$ -Glucosyl-(1 $\rightarrow$ 2)- <i>O</i> - $\beta$ -glucosyl-(1 $\rightarrow$ 6)-glucose*         | 2'-Glucosylgentiobiose                  |
| <i>O</i> - $\beta$ -Glucosyl-(1 $\rightarrow$ 2)- <i>O</i> - $\beta$ -glucosyl-(1 $\rightarrow$ 2)-glucose          | Sophorotriose                           |
| <i>O</i> - $\beta$ -Glucosyl-(1 $\rightarrow$ 6)- <i>O</i> - $\beta$ -glucosyl-(1 $\rightarrow$ 4)-glucose          | Sorborose                               |
| <i>O</i> - $\alpha$ -Rhamnosyl-(1 $\rightarrow$ 4)- <i>O</i> - $\alpha$ -rhamnosyl-(1 $\rightarrow$ 6)-galactose    | Rhamninose                              |
| <i>O</i> - $\alpha$ -Rhamnosyl-(1 $\rightarrow$ 3)- <i>O</i> - $\alpha$ -rhamnosyl-(1 $\rightarrow$ 6)-galactose    | Sugar of alaternin                      |
| <i>O</i> - $\beta$ -Glucosyl-(1 $\rightarrow$ 3)- <i>O</i> - $\alpha$ -rhamnosyl-(1 $\rightarrow$ 6)-galactose*     | Sugar of faraltrosid†                   |
| <i>O</i> - $\beta$ -Glucosyl-(1 $\rightarrow$ 6)- <i>O</i> - $\beta$ -glucosyl-(1 $\rightarrow$ 4)-rhamnose*        | —                                       |
| <i>Branched</i>                                                                                                     |                                         |
| <i>O</i> - $\beta$ -Apiosyl-(1 $\rightarrow$ 2)- <i>O</i> -[ $\alpha$ -rhamnosyl-(1 $\rightarrow$ 6)-glucose]*      | 2 <sup>G</sup> -Apiosylrutinose         |
| <i>O</i> - $\alpha$ -Rhamnosyl-(1 $\rightarrow$ 2)- <i>O</i> -[ $\alpha$ -rhamnosyl-(1 $\rightarrow$ 6)-glucose]*   | 2 <sup>G</sup> -Rhamnosylrutinose       |
| <i>O</i> - $\beta$ -Glucosyl-(1 $\rightarrow$ 2)- <i>O</i> -[ $\alpha$ -rhamnosyl-(1 $\rightarrow$ 6)-glucose]      | 2 <sup>G</sup> -Glucosylrutinose        |
| <i>O</i> - $\beta$ -Glucosyl-(1 $\rightarrow$ 3)- <i>O</i> -[ $\alpha$ -rhamnosyl-(1 $\rightarrow$ 2)-glucose]      | 3 <sup>G</sup> -Glucosylneohesperidose  |
| <i>O</i> - $\alpha$ -Rhamnosyl-(1 $\rightarrow$ 2)- <i>O</i> -[ $\beta$ -glucosyl-(1 $\rightarrow$ 6)-glucose]*     | 2 <sup>G</sup> -Rhamnosylgentiobiose    |
| <i>O</i> - $\beta$ -Glucosyl-(1 $\rightarrow$ 2)- <i>O</i> -[ $\beta$ -glucosyl-(1 $\rightarrow$ 6)-glucose]*       | 2 <sup>G</sup> -Glucosylgentiobiose     |
| <i>O</i> - $\alpha$ -Rhamnosyl-(1 $\rightarrow$ 4)- <i>O</i> -[ $\alpha$ -rhamnosyl-(1 $\rightarrow$ 2)-glucose]*   | 4 <sup>G</sup> -Rhamnosylneohesperidose |
| <i>O</i> - $\alpha$ -Rhamnosyl-(1 $\rightarrow$ 2)- <i>O</i> -[ $\alpha$ -rhamnosyl-(1 $\rightarrow$ 6)-galactose]* | 2 <sup>Gal</sup> -Rhamnosylrobinobiose  |
| <i>O</i> - $\alpha$ -Rhamnosyl-(1 $\rightarrow$ 4)- <i>O</i> -[ $\alpha$ -rhamnosyl-(1 $\rightarrow$ 6)-galactose]* | 4 <sup>Gal</sup> -Rhamnosylrobinobiose  |

\* Newly reported 1975–1980.

† Only present with an acetyl group at the 4-hydroxyl of rhamnose.

species (Harborne and Sherratt, 1961). Since this sugar gave only gentiobiose on hydrolysis and  $R_M$  values indicated two  $\beta 1 \rightarrow 6$  linkages, it was suggested that it might be gentiotriose (Harborne, 1968). More recently, both kaempferol and quercetin 3-gentiotriosides were synthesized by standard procedures (Farkas *et al.*, 1976b) and comparison with the natural kaempferol 3-triglucoside showed that the two compounds were different. Subsequently, the quercetin 3-triglucoside in *Primula officinalis* has been re-examined and the trisaccharide identified as one with both  $\beta 1 \rightarrow 2$  and  $\beta 1 \rightarrow 6$  links, i.e. as 2'-glucosylgentiobiose (Karl *et al.*, 1981). Since the pattern of flavonol glycosylation is probably the same throughout the genus, it is reasonable to assume that the *P. sinensis* derivatives also contain the same sugar.

Among the new trisaccharides reported (Table 5.3) are a remarkable number of branched sugars. A very rich source of kaempferol and quercetin 3-triglycosides is the soya-bean *Glycine max* (Leguminosae). From the leaf, Buttery and Buzzell (1975) have characterized four such trisaccharides in flavonol combination: 2<sup>G</sup>-glucosylrutinose, 2<sup>G</sup>-rhamnosylrutinose, 2<sup>G</sup>-glucosylgentiobiose and 2<sup>G</sup>-rhamnosylgentiobiose—the latter three are all new compounds. The genetic control of the synthesis of these branched triglycosides has also been examined, and their production occurs whenever plants have the ability to synthesize related pairs of diglycosides, i.e. 3-sophorosides and 3-rutinosides, 3-gentiobiosides and 3-rutinosides etc. Interestingly, the two

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flavonol 3-(2<sup>G</sup>-rhamnosylrutinosides) of soya bean also occur in hops, *Humulus lupulus*, but here they are accompanied by the related linear triglycosides, the 3-(2'-rhamnosylrutinosides) (Vancraenenbraeck *et al.*, 1969).

Finally, it must be pointed out that other trisaccharides occur associated with flavonols and with flavones, which await full characterization. Many of these are indicated in later Tables in this chapter.

### 5.4.4 Acylated derivatives

Some 60 new acyl derivatives have been reported in the period 1975–1980. The increasing frequency of these reports reflects to some extent the introduction of <sup>13</sup>C-NMR spectroscopy for flavonoid analysis; some acyl substituents, such as acetyl, are not readily detectable by any other means. The report of 2-methylbutyric acid attached to the rhamnose moiety of acacetin 7-rutinoside in *Valeriana wallichii* represents one of the first examples of the utility of <sup>13</sup>C-NMR spectroscopy for pinpointing the nature and location of an acyl substitution (Chari *et al.*, 1977).

*In toto*, some seven aliphatic and eight aromatic acids have been identified as acyl substituents in flavones and flavonols (Table 5.4). The usual linkage is through one of the sugar hydroxyls and any one of the three or four free hydroxyls may be involved. The direct linkage of acyl group to a phenolic hydroxyl also occasionally occurs. Recent examples of this are the 8-*O*-acetates and 8-*O*-butyrates of several flavonols found in frond exudates of the fern genus *Notholaena* by Wollenweber *et al.* (1978a,b,c).

The most common acyl groups appear to be acetic, gallic, *p*-coumaric and ferulic acids. Monoacylation is usual, but substances with two acyl groups have been reported. Thus apigenin 4'-glucoside occurs with *p*-coumaroyl residues at the 2'' and 6''-positions of the glucose moiety, in *Lycopodium clavatum* leaf (Ansari *et al.*, 1979). Furthermore, the acyl groups may be different. Thus, kaempferol 3-glucoside has been reported as the 3''-*p*-coumarate-6''-ferulate ester in *Picea obovata* needles (Zapesochnaya *et al.*, 1978).

Several pairs of isomeric acyl derivatives are known. These may occur together in the same plant. While acyl migration might possibly occur during isolation and handling, there is no suggestion as yet that one or other of a given pair are of artifactual origin. One example is apigenin 7-glucoside, which occurs in *Matricaria chamomilla* flowers as a mixture of the 2''- and 6''-acetates (Redaelli *et al.*, 1980). Another is quercetin 3-galactoside which is present in *Tellima grandiflora* as a mixture of 2''- and 6''-gallates (Collins *et al.*, 1975).

In some cases, the number of known isomers has not yet been clarified. This is true of the mono-*p*-coumaroyl esters of kaempferol 3-glucoside. Two are of certain structure: the 6''-ester, tiliroside from *Tilea argentea* petals and recently described from *Anaphalis contorta* (Compositae) (Lin *et al.*, 1975) and from *Pinus contorta* needles (Higuchi and Donnelly, 1978); and the 3''-ester, found in needles of *Picea obovata* by Zapesochnaya *et al.* (1978). An ester (of undefined

Table 5.4 Acylating acids found in flavone and flavonol derivatives

| Organic acid           | Example of occurrence                              | Reference                          |
|------------------------|----------------------------------------------------|------------------------------------|
| <i>Aliphatic acids</i> |                                                    |                                    |
| Acetic                 | Apigenin 7-(2"-acetyl)glucoside                    | Redaelli <i>et al.</i> (1980)      |
| Malonic                | Quercetin 3-(malonyl)glucoside*                    | Woeldecke and Herrmann (1974)      |
| Succinic               | Kaempferol 7-(6"-succinyl)glucoside                | Hiraoka and Maeda (1979)           |
| Butyric                | Herbacetin 8-butyrate                              | Wollenweber <i>et al.</i> (1978a)  |
| 2-Methylbutyric        | Acacetin 7-[2'''-(2 methylbutyryl)rutinoside]      | Chari <i>et al.</i> (1977)         |
| Tiglic                 | Quercetin 7-(6"-tiglyl)glucoside                   | Ogawa and Ogiwara (1975)           |
| <i>Aromatic acids</i>  |                                                    |                                    |
| Benzoic                | Kaempferol 3-(benzoyl)glucoside)*                  | } Schonsiegel <i>et al.</i> (1969) |
| p-Hydroxybenzoic       | Kaempferol 3( <i>p</i> -hydroxybenzoyl)glucoside)* |                                    |
| Galic                  | Quercetin 3-(6"-galloyl)glucoside                  | Collins <i>et al.</i> (1975)       |
| p-Coumaric             | Apigenin 7-(4"- <i>p</i> -coumaroyl)glucoside      | Karl <i>et al.</i> (1976)          |
| Caffeic                | Apigenin 7-glucoside-4'-caffeate                   | Gella <i>et al.</i> (1967)         |
| Ferulic                | Luteolin 7-glucuronide-3'-feruloylglucoside*       | Markham <i>et al.</i> (1978a)      |
| Isoferulic             | Quercetin 3-(isoferuloyl)glucuronide*              | El Ansari <i>et al.</i> (1976)     |
| Sinapic                | Kaempferol 3-(sinapoylsphoroside)-7-glucoside*     | Stengel and Geiger (1976)          |

\* In these examples, the position of attachment of acyl group to sugar has not been established.

linkage) is reported to be present in leaves of *Larix* and other Pinaceae by Niemann (1979), but it is not clear whether this refers to the 3''- or 6''-ester, or both. Yet another ester that has been described is tribuloside, which occurs in *Tribulus terrestris* and is known to be different from tiliroside. It cannot be the 6''-ester as originally proposed (Bhutani *et al.*, 1969) since this is the now proven structure of tiliroside, based on  $^{13}\text{C}$  NMR studies (Pijewska and Kamecki, 1977; Chari *et al.*, 1978). The most recent work on the structure of tribuloside suggests it is, in fact, a mixture of tiliroside with the related isorhamnetin derivative (Saleh, N. A. M., private communication).

The most complex acyl derivative to date is probably an acacetin derivative from *Coptis japonica* leaves, which not only has three acetyl residues attached variously to two different monosaccharide units, but also contains the only known tetrasaccharide, namely 6<sup>G</sup>-rhamnosylsophorotriose (Fujiwara *et al.*, 1976). The sugar moiety is thus glucosyl (1→2)glucosyl(1→2) [2,4-diacetyl-rhamnosyl(1→6)]-3-acetylglucose.

#### 5.4.5 Sulphate conjugates

In 1975, only a relatively few sulphate conjugates had been characterized. A range of new structures has been described between 1975 and 1980 and the total number of conjugates is now 54 (Table 5.5). In both the flavone and flavonol series, the most common type is the 7- and 3-sulphate respectively. Sulphation at other hydroxyl groups is also possible and flavones with sulphation at the B-ring hydroxyls have been described from *Daucus carota* (Harborne and King, 1976), *Lachenalia unifolia* (Williams *et al.*, 1976) and *Zostera marina* (Harborne and Williams, 1976). The first known disulphated flavone, luteolin 7,3'-disulphate, was also obtained from the latter plant. While a polysulphated quercetin salt was reported earlier from *Flaveria bidentis* (Pereyra de Santiago and Juliani, 1972), several new forms, including the 3,4'-disulphate and 3,7,4'-trisulphate, have been subsequently detected in the same species (Cabrera and Juliani, 1979). Such polysulphation, however, is still rare and the normal rule is to find monosulphates only.

A significant number of glycosidesulphates has been described (Table 5.5). In some of these, the sugar and sulphate residues occupy different phenolic hydroxyls of the flavone or flavonol, but in others the sulphate is attached through one of the sugar hydroxyls. In two pigments of the latter type, the position of the sulphate has been shown to be on the 6-hydroxyl. Thus, in the kaempferol 3- $\alpha$ -glucosidesulphate of the fern *Asplenium filix-foemina*, 6-*O*-sulphation was established by methylation and hydrolysis to give 2,3,4-tri-*O*-methylglucose (Imperato, 1979b). Similarly, in the kaempferol 3-gentiobioside sulphate present in *Asplenium fontanum*, the sulphate was located by similar methods as being at the 6-position of the terminal glucose (Imperato, 1980).

One other variation in sulphate conjugation has been detected recently, in the nature of the associated cation. While potassium is usual, a eupatin 3-sulphate

**Table 5.5** Sulphate conjugates of flavones and flavonols

| Type of conjugate                 | Known aglycones                                                                                                                                                       |
|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Flavones</i>                   |                                                                                                                                                                       |
| 7-Sulphate                        | Apigenin, luteolin, chrysoeriol, diosmetin                                                                                                                            |
| 8-Sulphate                        | Hypolaetin                                                                                                                                                            |
| 3'-Sulphate                       | Luteolin, diosmetin, tricetin                                                                                                                                         |
| 4'-Sulphate                       | Luteolin                                                                                                                                                              |
| 7, 3'-Disulphate                  | Luteolin, diosmetin, tricetin                                                                                                                                         |
| 7-Glucosidesulphate               | Apigenin, luteolin, chrysoeriol, tricin                                                                                                                               |
| 7-Rutinosidesulphate              | Luteolin                                                                                                                                                              |
| 8-Glucoside-3'-sulphate           | Hypolaetin                                                                                                                                                            |
| 7-Sulphate-3'-glucoside           | Luteolin                                                                                                                                                              |
| 7-Sulphate-3'-rutinoid            | Luteolin                                                                                                                                                              |
| <i>Flavonols</i>                  |                                                                                                                                                                       |
| 3-Sulphate                        | Rhamnocitrin, kaempferol 7, 4'-dimethyl ether, quercetin, isorhamnetin, tamarixetin, rhamnetin, rhamnazin, gossypetin, patuletin, eupatoletin, eupatin, veronicafolin |
| 7-Sulphate                        | Kaempferol, isorhamnetin, patuletin, quercetagenin 3-methyl ether                                                                                                     |
| 3,7-Disulphate                    | Kaempferol, isorhamnetin                                                                                                                                              |
| 3,4'-Disulphate                   | Quercetin                                                                                                                                                             |
| 3,5,4'-Trisulphate                | Rhamnetin                                                                                                                                                             |
| 3,7,4'-Trisulphate                | Quercetin                                                                                                                                                             |
| 3,7,3',4'-Tetrasulphate           | Quercetin                                                                                                                                                             |
| 3-Glucosidesulphate               | Kaempferol                                                                                                                                                            |
| 3-Rhamnosidesulphate              | Kaempferol, quercetin, myricetin                                                                                                                                      |
| 3-Rutinosidesulphate              | Quercetin, isorhamnetin                                                                                                                                               |
| 3-Gentiobiosidesulphate           | Kaempferol                                                                                                                                                            |
| 3-Glucoside-7-sulphate            | Patuletin                                                                                                                                                             |
| 3-Glucuronide-7-sulphate          | Kaempferol, quercetin, isorhamnetin                                                                                                                                   |
| 3'-Glucuronide-3,5,4'-trisulphate | Rhamnetin                                                                                                                                                             |

present in *Brickellia californica* and *B. laciniata* has been discovered as the half calcium salt (Mues *et al.*, 1979). Interestingly, other sulphates in *Brickellia*, e.g. of patuletin, are present as the potassium salts, so that variation can clearly occur within the same plant.

## 5.5 NEW REPORTS OF FLAVONE GLYCOSIDES

About 130 new flavone glycosides have been reported in the period 1975–1980. These are shown in Table 5.6, together with plant source and reference. A complete check list of all known flavone glycosides appears at the end of this chapter. About twice as many compounds are now known as compared to 1975. The number of apigenin glycosides has increased from 22 to 40, luteolin from 18



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**Table 5.6** New flavone glycosides

| Glycoside                                           | Source                                                 | Reference                                 |
|-----------------------------------------------------|--------------------------------------------------------|-------------------------------------------|
| <i>5,7-Dihydroxyflavone</i> (Chrysin)               |                                                        |                                           |
| 7-Galactoside                                       | <i>Aerva persica</i> roots;<br>Amaranthaceae           | Garg <i>et al.</i> (1979)                 |
| <i>3', 4'-Dihydroxyflavone</i>                      |                                                        |                                           |
| 4'-Glucoside                                        | <i>Rhus</i> spp. heartwood;<br>Anacardiaceae           | Young (1979)                              |
| <i>5,7-Dihydroxy-8-methoxyflavone</i> (Wogonin)     |                                                        |                                           |
| 7-Glucuronide                                       | <i>Scutellaria galericulata</i> ;<br>Labiatae          | Popova <i>et al.</i> (1976)               |
| <i>Apigenin</i>                                     |                                                        |                                           |
| 7-Arabinoside                                       | <i>Hieracium umbellatum</i> whole<br>plant; Compositae | Guppy and Bohm (1976)                     |
| 7-Xyloside                                          | <i>Muscari armeniacum</i> ;<br>Liliaceae               | Ellnain-Wojtaszek <i>et al.</i><br>(1978) |
| 7-Galacturonide                                     | <i>Marchantia berteroa</i><br>thallus; Hepaticae       | Markham and Porter (1975)                 |
| 4'-Glucuronide                                      | <i>Chrysanthemum cinerariifolium</i> ;<br>Compositae   | Rao <i>et al.</i> (1973)                  |
| 7-Arabinosylglucoside                               | <i>Hieracium umbellatum</i><br>whole plant; Compositae | Guppy and Bohm (1976)                     |
| 7-Sophoroside                                       | <i>Glandularia bipinnatifida</i> ;<br>Verbenaceae      | Umber (1980)                              |
| 7-Rhamnosylglucuronide                              | <i>Marchantia foliacea</i><br>thallus; Hepaticae       | Markham and Porter<br>(1973)              |
| 7-Diglucuronide                                     | <i>Adenocalymma alliaceum</i><br>flowers; Bignoniaceae | Rao and Rao (1980)                        |
| 7-Glucuronide-4'-rhamnoside                         | <i>Conocephalum conicum</i><br>whole plant; Hepaticae  | Markham <i>et al.</i> (1976)              |
| 7-Rutinoside-4'-glucoside                           | <i>Galium mollugo</i> ;<br>Rubiaceae                   | Borisov (1974)                            |
| 7-Neohesperidoside-4'-glucoside                     | <i>Hedwigia ciliata</i> ;<br>Bryophyta                 | Österdahl (1979)                          |
| 7-Diglucuronide-4'-glucuronide                      | <i>Conocephalum conicum</i><br>whole plant; Hepaticae  | Markham <i>et al.</i> (1976)              |
| 7-Neohesperidoside-4'-sophoroside                   | <i>Hedwigia ciliata</i> ;<br>Bryophyta                 | Österdahl (1979)                          |
| 7-(4''- <i>p</i> -Coumaroyl)glucoside               | <i>Salix alba</i> leaf;<br>Salicaceae                  | Karl <i>et al.</i> (1976)                 |
| 7-(2''-Acetyl)glucoside                             | <i>Matricaria chamomilla</i><br>flowers; Compositae    | Redaelli <i>et al.</i> (1980)             |
| 7-(6''-Acetyl)glucoside                             | <i>Matricaria chamomilla</i><br>flowers; Compositae    | Kunde and Issac (1979)                    |
| 4'-(2'', 6''-Di- <i>p</i> -coumaroyl)-<br>glucoside | <i>Lycopodium clavatum</i><br>leaf; Lycopodiaceae      | Ansari <i>et al.</i> (1979)               |
| 7-Glucosidesulphate                                 | <i>Phoenix canariensis</i><br>flowers; Palmae          | Harborne <i>et al.</i> (1974)             |

| Glycoside                                                                               | Source                                                         | Reference                         |
|-----------------------------------------------------------------------------------------|----------------------------------------------------------------|-----------------------------------|
| 7-Sulphate                                                                              | <i>Bixa orellana</i><br>leaf; Bixaceae                         | Harborne (1975)                   |
| <i>Apigenin 4'-methyl ether</i> (Acacetin)                                              |                                                                |                                   |
| 7-(6''-Acetyl)glucoside                                                                 | <i>Agastache rugosa</i> ;<br>Labiatae                          | Zakharova <i>et al.</i> (1979)    |
| 7-(4'''-Acetyl)rutinoside                                                               | <i>Thalictrum aquilegifolium</i><br>whole plant; Ranunculaceae | Ina and Iida (1981)               |
| 7-[2'''-(2-Methyl)butyryl]rutinoside                                                    | <i>Valeriana wallichii</i>                                     | Chari <i>et al.</i> (1977)        |
| 7-[3'''-(2-Methyl)butyryl]rutinoside                                                    | rhizome; Valerianaceae                                         | Fujiwara <i>et al.</i> (1976)     |
| 7-Glucosyl(1 → 2)glucosyl(1 → 2)<br>[2, 4-diacetylramnosyl](1 → 6)<br>3-acetylglucoside | <i>Coptis japonica</i> ;<br>Ranunculaceae                      |                                   |
| <i>Apigenin 5, 7-dimethyl ether</i>                                                     |                                                                |                                   |
| 4'-Galactoside                                                                          | <i>Morinda citrifolia</i><br>flower; Rubiaceae                 | Singh and Tiwari (1976)           |
| 6-Hydroxyapigenin (Scutellarein)                                                        |                                                                |                                   |
| 6-Xyloside                                                                              | <i>Juniperus communis</i><br>fruit; Cupressaceae               | Lamer-Zarawska (1980)             |
| 6-Glucuronide                                                                           | <i>Sterculia foetida</i><br>leaf; Sterculiaceae                | Nair <i>et al.</i> (1977b)        |
| <i>Scutellarein 6-methyl ether</i>                                                      |                                                                |                                   |
| 7-Rutinoside                                                                            | <i>Oncidium excavatum</i><br>leaf; Orchidaceae                 | Williams (1979)                   |
| <i>Scutellarein 7-methyl ether</i>                                                      |                                                                |                                   |
| 6-Rhamnosyl (1 → 4)xyloside                                                             | <i>Sorbaria sorbifolia</i><br>flowers and leaves; Rosaceae     | Zaitsev <i>et al.</i> (1974)      |
| <i>Scutellarein 4'-methyl ether</i>                                                     |                                                                |                                   |
| 6-Glucoside                                                                             | <i>Catalpa ovata</i> ;<br>Bignoniaceae                         | Okuda <i>et al.</i> (1975)        |
| 7-Glucuronide                                                                           | <i>Clerodendron trichotomum</i> ;<br>Verbenaceae               | Morita <i>et al.</i> (1977)       |
| 6-Sophoroside                                                                           | <i>Catalpa ovata</i> ;<br>Bignoniaceae                         | Okuda <i>et al.</i> (1975)        |
| <i>Scutellarein 6, 4'-dimethyl ether</i> (Pectolinarigenin)                             |                                                                |                                   |
| 7-Glucoside                                                                             | <i>Oncidium excavatum</i><br>leaf; Orchidaceae                 | Williams (1979)                   |
| 7-Glucuronide                                                                           | <i>Comanthosphace japonica</i><br>leaf; Labiatae               | Arisawa <i>et al.</i> (1979)      |
| 7-Glucuronide methyl ester                                                              |                                                                |                                   |
| 7-(4'''-Acetyl)rutinoside                                                               | <i>Linaria japonica</i><br>leaf; Scrophulariaceae              | Morita <i>et al.</i> (1974)       |
| <i>Scutellarein 6, 7, 4'-trimethyl ether</i>                                            |                                                                |                                   |
| 5-Glucoside                                                                             | <i>Salvia virgata</i> ;<br>Labiatae                            | Ulubelen and Ayanoglu<br>(1975)   |
| 8-Hydroxyapigenin<br>(Isoscutellarein)                                                  |                                                                |                                   |
| 8-Glucuronide                                                                           | <i>Marchantia berteroana</i><br>whole plant; Hepaticae         | Markham and Porter (1975)         |
| 4'-Mannosyl(1 → 2)-glucoside                                                            | <i>Stachys inflata</i><br>aerial parts; Labiatae               | Komissarenko <i>et al.</i> (1978) |

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**Table 5.6** (Contd.)

| <i>Glycoside</i>                               | <i>Source</i>                                                  | <i>Reference</i>                 |
|------------------------------------------------|----------------------------------------------------------------|----------------------------------|
| 7-(Acetyl)sophoroside                          | <i>Stachys palustris</i> ;<br>Labiatae                         | Bishara <i>et al.</i> (1976)     |
| 8-Hydroxyapigenin 4'-methyl ether<br>(Takakin) |                                                                |                                  |
| 8-Glucuronide }<br>8-Xylosylglucoside }        | <i>Takakia lepidozoides</i><br>whole plant; Hepaticae          | Markham and Porter (1979)        |
| 7-(6'''-Acetylallosyl)-<br>(1→2)glucoside      | <i>Veronica filiformis</i><br>whole plant;<br>Scrophulariaceae | Chari <i>et al.</i> (1981)       |
| <i>Luteolin</i>                                |                                                                |                                  |
| 5-Galactoside                                  | <i>Dracocephalum nutans</i> ;<br>Labiatae                      | Shamyrina <i>et al.</i> (1977)   |
| 7-Galacturonide                                | <i>Marchantia berteroana</i><br>thallus; Hepaticae             | Markham and Porter (1975)        |
| 3'-Glucuronide                                 | <i>Lunularia cruciata</i><br>thallus; Hepaticae                | Markham and Porter<br>(1974a)    |
| 3'-Galacturonide                               | <i>Marchantia berteroana</i><br>thallus; Hepaticae             | Markham and Porter (1975)        |
| 4'-Arabinoside                                 | <i>Hieracium umbellatum</i><br>whole plant; Compositae         | Guppy and Bohm (1976)            |
| 4'-Glucuronide                                 | <i>Riccia fluitans</i><br>thallus; Hepaticae                   | Markham <i>et al.</i> (1978a)    |
| 7-Arabinosylglucoside                          | <i>Vernonia</i> spp.; Compositae                               | Mabry <i>et al.</i> (1975)       |
| 7-Gentiobioside                                | <i>Campanula rotundifolia</i> ;<br>Campanulaceae               | Teslov (1980)                    |
| 7-Sophoroside                                  | <i>Glandularia bipinnatifida</i> ;<br>Verbenaceae              | Umber (1980)                     |
| 7-Digalactoside                                | <i>Cephalaria procera</i> ;<br>Dipsacaceae                     | Ulubelen <i>et al.</i> (1978)    |
| 7-Galactosylglucoside                          | <i>Vernonia</i> spp.; Compositae                               | Mabry <i>et al.</i> (1975)       |
| 7-Glucuronide-3'-glucoside                     | <i>Riccia fluitans</i><br>thallus; Hepaticae                   | Markham <i>et al.</i><br>(1978a) |
| 7,3'-Diglucuronide                             | <i>Marchantia polymorpha</i><br>thallus; Hepaticae             | Markham and Porter<br>(1974b)    |
| 7,3'-Digalacturonide                           | <i>Marchantia berteroana</i><br>thallus; Hepaticae             | Markham and Porter<br>(1975)     |
| 7-Galactoside-4'-glucoside                     | <i>Vernonia</i> spp.; Compositae                               | Mabry <i>et al.</i> (1975)       |
| 7-Glucuronide-3'-rhamnoside                    | <i>Riccia fluitans</i> ; Hepaticae                             | Vandekerckhove (1978)            |
| 7-Glucuronide-4'-rhamnoside                    | <i>Conocephalum conicum</i><br>thallus; Hepaticae              | Markham <i>et al.</i><br>(1976)  |
| 7,4'-Diglucuronide                             | <i>Marchantia polymorpha</i><br>thallus; Hepaticae             | Markham and Porter<br>(1974b)    |
| 3',4'-Diglucoside                              | <i>Listera ovata</i><br>leaf; Orchidaceae                      | Williams (1979)                  |
| 3',4'-Diglucuronide                            | <i>Lunularia cruciata</i><br>thallus; Hepaticae                | Markham and Porter<br>(1974a)    |
| 3',4'-Digalacturonide                          | <i>Marchantia berteroana</i><br>thallus; Hepaticae             | Markham and Porter<br>(1975)     |

| <i>Glycoside</i>                                          | <i>Source</i>                                           | <i>Reference</i>                   |
|-----------------------------------------------------------|---------------------------------------------------------|------------------------------------|
| 7-Glucosylarabinoside-4'-glucoside                        | <i>Galium mollugo</i> ; Rubiaceae                       | Borisov (1974)                     |
| 7-Neohesperidoside-4'-glucoside                           | <i>Hedwigia ciliata</i> ;                               | Österdahl (1979)                   |
| 7-Glucoside-4'-neohesperidoside                           | Bryophyta                                               |                                    |
| 7-Glucuronide-3',4'-dirhamnoside                          | <i>Conocephalum conicum</i> thallus; Hepaticae          | Markham <i>et al.</i> (1976)       |
| 7,4'-Diglucuronide-3'-glucoside                           | <i>Riccia fluitans</i> thallus; Hepaticae               | Markham <i>et al.</i> (1978c)      |
| 7,3',4'-Triglucuronide                                    | <i>Marchantia polymorpha</i> thallus; Hepaticae         | Markham and Porter (1974b)         |
| 7-Neohesperidoside-4'-sophoroside                         | <i>Hedwigia ciliata</i> ;                               | Österdahl and Lindberg (1977)      |
| 7-Glucuronide-3'-feruloylglucoside                        | Bryophyta                                               |                                    |
| 7,4'-Diglucuronide-3'-feruloylglucoside                   | <i>Riccia fluitans</i> thallus; Hepaticae               | Markham <i>et al.</i> (1978c)      |
| 7-Glucosidesulphate                                       | <i>Phoenix roebelenii</i> leaf; Palmae                  | Williams <i>et al.</i> (1973)      |
| 7-Rutinosidesulphate                                      | <i>Washingtonia robusta</i> leaf; Palmae                | Williams <i>et al.</i> (1973)      |
| 7-Sulphate-3'-rutinose                                    | <i>Opsandra maya</i> leaf; Palmae                       | Williams <i>et al.</i> (1973)      |
| 7-Sulphate                                                | <i>Bixa orellana</i> leaf; Bixaceae                     | Harborne (1975)                    |
| 3'-Sulphate                                               | <i>Lachenalia unifolia</i> leaf; Liliaceae              | Williams <i>et al.</i> (1976)      |
| 4'-Sulphate                                               | <i>Daucus carota</i> leaf; Umbelliferae                 | Harborne and King (1976)           |
| 7,3'-Disulphate                                           | <i>Zostera marina</i> leaf; Zosteraceae                 | Harborne and Williams (1976)       |
| <i>Luteolin 5-methyl ether</i> 7-Glucoside                | <i>Juncus</i> spp. leaf; Juncaceae                      | Williams and Harborne (1975)       |
| <i>Luteolin 3'-methyl ether</i> (Chrysoeriol) 5-Glucoside | <i>Lycopodium scariosum</i> aerial parts; Lycopodiaceae | Markham and Moore (1980)           |
| 7-Xyloside                                                | <i>Salvia seravschanica</i> ; Labiatae                  | Smirnova <i>et al.</i> (1974)      |
| 7-Rhamnoside                                              | <i>Sedum formosanum</i> whole plant; Crassulaceae       | Chou <i>et al.</i> (1976)          |
| 4'-Glucoside                                              | <i>Dianthus deltoides</i> aerial parts; Caryophyllaceae | Boguslavskaya <i>et al.</i> (1976) |
| 5-Diglucoside                                             | <i>Lycopodium scariosum</i> aerial parts; Lycopodiaceae | Markham and Moore (1980)           |

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**Table 5.6** (Contd.)

| <i>Glycoside</i>                                   | <i>Source</i>                                               | <i>Reference</i>                    |
|----------------------------------------------------|-------------------------------------------------------------|-------------------------------------|
| 7-Rhamnosylglucuronide                             | <i>Marchantia foliacea</i><br>thallus; Hepaticae            | Markham and Porter<br>(1973)        |
| 7-Allosyl(1→2)glucoside                            | <i>Sideritis grandiflora</i><br>whole plant; Labiatae       | Rabanal <i>et al.</i> (1982)        |
| 5,4'-Diglucoside }<br>7,4'-Diglucoside }           | <i>Lycopodium scariosum</i><br>aerial parts; Lycopodiaceae  | Markham and Moore<br>(1980)         |
| 7-Glucuronide-4'-rhamnoside                        | <i>Conocephalum conicum</i><br>thallus; Hepaticae           | Markham <i>et al.</i> (1976)        |
| 7-Sophorotrioside                                  | <i>Sideritis romana</i><br>aerial parts; Labiatae           | Venturella <i>et al.</i> (1977)     |
| 7-Glucosidesulphate                                | <i>Juncus effusus</i><br>leaf; Juncaceae                    | Williams and Harborne<br>(1975)     |
| 7-Sulphate                                         | <i>Zostera marina</i><br>leaf; Zosteraceae                  | Harborne and Williams<br>(1976)     |
| <i>Luteolin 4'-methyl ether</i><br>(Diosmetin)     |                                                             |                                     |
| 7-Xylosylglucoside                                 | <i>Anacyclus</i> spp.<br>leaf; Compositae                   | Greger (1978)                       |
| 7-Sophoroside                                      | <i>Glandularia</i><br><i>bipinnatifida</i> ;<br>Verbenaceae | Umber (1980)                        |
| 7-(4 <sup>G</sup> -Rhamnosyl-<br>neohesperidoside) | <i>Dicranum scoparium</i> ;<br>Dicranaceae                  | Österdahl (1978)                    |
| 7-Sulphate                                         | <i>Zostera marina</i><br>leaf; Zosteraceae                  | Harborne and Williams,<br>(1976)    |
| 3'-Sulphate }<br>7,3'-Disulphate }                 | <i>Lachenalia unifolia</i><br>leaf; Liliaceae               | Williams <i>et al.</i> (1976)       |
| <i>Luteolin 3',4'-dimethyl ether</i>               |                                                             |                                     |
| 7-Rhamnoside                                       | <i>Linum maritimum</i> ;<br>Linaceae                        | Volk and Sinn (1968)                |
| 7-Glucuronide                                      | <i>Rhynchosia beddomei</i><br>leaf; Leguminosae             | Adinarayana <i>et al.</i><br>(1980) |
| <i>6-Hydroxyluteolin</i>                           |                                                             |                                     |
| 6-Xyloside                                         | <i>Juniperus communis</i><br>fruit; Cupressaceae            | Lamer-Zarawska (1980)               |
| 6-Glucoside                                        | <i>Stereospermum suaveolens</i> ;<br>Bignoniaceae           | Nair (1979)                         |
| 6-Glucuronide                                      | <i>Sterculia colorata</i> ;<br>Sterculiaceae                | Nair <i>et al.</i> (1976)           |
| 7-Arabinoside                                      | <i>Lippia nodiflora</i> ;<br>Verbenaceae                    | Nair <i>et al.</i> (1973)           |
| 7-Xyloside                                         | <i>Parahebe</i> spp. leaf;<br>Scrophulariaceae              | Grayer-Barkmeijer<br>(1978)         |
| 7-Apioside                                         | <i>Lepidagathis cristata</i> ;<br>Acanthaceae               | Ranganathan <i>et al.</i><br>(1980) |
| 7-Rhamnosyl(1→4)xyloside                           | <i>Pityrodia coerulea</i><br>leaf; Verbenaceae              | Harborne and Stacey<br>(1978)       |

| Glycoside                                             | Source                                                  | Reference                                 |
|-------------------------------------------------------|---------------------------------------------------------|-------------------------------------------|
| 7-Arabinoside-4'-rhamnoside                           | <i>Lippia nodiflora</i> ;<br>Verbenaceae                | Nair <i>et al.</i> (1973)                 |
| 6-Hydroxyluteolin 7-methyl ether<br>(Pedalitin)       |                                                         |                                           |
| 6-Galactoside }<br>6-Galactosylglucoside }            | <i>Sullivantia</i> spp.;<br>Saxifragaceae               | Soltis (1980)                             |
| 6-Hydroxyluteolin 3'-methyl ether                     |                                                         |                                           |
| 7-Diglucoside                                         | <i>Sideritis leucantha</i> ; Labiatae                   | Tomas (1979)                              |
| 6-Hydroxyluteolin 6,3'-dimethyl ether                 |                                                         |                                           |
| 7-Rhamnoside                                          | <i>Cassia occidentalis</i><br>leaf; Leguminosae         | Tiwari and Singh<br>(1977)                |
| 7-(6''-Caffeoyl)glucoside                             | <i>Gnaphalium uliginosum</i><br>whole plant; Compositae | Konopleva <i>et al.</i><br>(1979)         |
| 6-Hydroxyluteolin 7,3'-dimethyl ether                 |                                                         |                                           |
| 6-Glucoside                                           | <i>Citharexylum subserratum</i><br>leaf; Verbenaceae    | Mathuram <i>et al.</i><br>(1976)          |
| 8-Hydroxyluteolin<br>(Hypolaetin)                     |                                                         |                                           |
| 8-Glucuronide }<br>8,4'-Diglucuronide }               | <i>Marchantia berteroana</i><br>thallus; Hepaticae      | Markham and Porter<br>(1975)              |
| 8-Glucoside-3'-sulphate                               | <i>Malva sylvestris</i><br>leaf; Malvaceae              | Nawwar <i>et al.</i> (1977a)              |
| 8-Sulphate                                            | <i>Bixa orellana</i><br>leaf; Bixaceae                  | Harborne (1975)                           |
| 8-Hydroxyluteolin 3'-methyl ether                     |                                                         |                                           |
| 7-Glucoside                                           | <i>Solanum grayi</i><br>leaf; Solanaceae                | Whalen and Mabry<br>(1979)                |
| 7-Mannosyl(1→2)glucoside                              | <i>Stachys spectabilis</i> ;<br>Labiatae                | Derkach <i>et al.</i> (1980)              |
| 5,7,3',4'-Tetrahydroxy-6,8-dimethoxyflavone           |                                                         |                                           |
| 7-Glucoside                                           | <i>Sideritis leucantha</i><br>whole plant; Labiatae     | Tomas and Ferreres<br>(1980)              |
| 5,7,3'-Trihydroxy-6,8,4'-trimethoxyflavone (Acerosin) |                                                         |                                           |
| 5-(6''-Acetyl)glucoside                               | <i>Vitex negundo</i> stem bark;<br>Verbenaceae          | Subramanian and Misra<br>(1979)           |
| 5,7,4'-Trihydroxy-6,8,3'-trimethoxyflavone            |                                                         |                                           |
| 7-Glucoside                                           | <i>Sideritis leucantha</i><br>whole plant; Labiatae     | Tomas and Ferreres<br>(1980)              |
| Tricetin                                              |                                                         |                                           |
| 3'-Sulphate }<br>7,3'-Disulphate }                    | <i>Lachenalia unifolia</i><br>leaf; Liliaceae           | Williams <i>et al.</i> (1976)             |
| Tricetin 3'-methyl ether                              |                                                         |                                           |
| 7-Glucoside                                           | <i>Taxodium distichum</i><br>short shoots; Taxodiaceae  | Geiger and de Groot-<br>Pfleiderer (1979) |

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**Table 5.6** (Contd.)

| Glycoside                                                             | Source                                                               | Reference                     |
|-----------------------------------------------------------------------|----------------------------------------------------------------------|-------------------------------|
| <i>Tricetin 3',5'-dimethyl ether</i> (Tricin)                         |                                                                      |                               |
| 4'-Glucoside }<br>5,7-Diglucoside }                                   | <i>Lycopodium</i><br><i>scariosum</i> aerial<br>parts; Lycopodiaceae | Markham and Moore<br>(1980)   |
| 7-Fructosylglucoside                                                  | <i>Hyacinthus orientalis</i><br>leaf; Liliaceae                      | Williams (1975)               |
| 7-Neohesperidoside }<br>7-Diglucoside }                               | <i>Saccharum officinarum</i><br>leaf; Gramineae                      | Williams <i>et al.</i> (1974) |
| 7-Rhamnosylglucuronide                                                | <i>Marchantia foliacea</i><br>thallus; Hepaticae                     | Markham and Porter<br>(1973)  |
| 7-Rutinoside-4'-glucoside                                             | <i>Hyacinthus orientalis</i><br>leaf; Liliaceae                      | Williams (1975)               |
| 7-Glucosidesulphate                                                   | <i>Saccharum officinarum</i><br>leaf; Gramineae                      | Williams <i>et al.</i> (1974) |
| <i>5,7,2',4',5'-Pentahydroxyflavone</i> (Isoetin)                     |                                                                      |                               |
| 7-Glucoside                                                           | <i>Hispidella hispanica</i><br>leaf; Compositae                      | Harborne (1978)               |
| 2'-Arabinoside }<br>2'-Glucoside }<br>2'-Xylosylarabinosylglucoside } | <i>Heywoodiella</i><br><i>oligocephala</i><br>leaf; Compositae       | Harborne (1978)               |
| 4'- or 5'-Glucoside                                                   | <i>Isoetes delilei</i> ; Isoetales                                   | Voirin <i>et al.</i> (1975)   |

to 53, chrysoeriol from 9 to 21 and tricetin from 8 to 14. One or two reports refer to the pre-1975 literature, e.g. of luteolin 3',4'-dimethyl ether 7-rhamnoside (Volk and Sinn, 1968), where compounds have been accidentally overlooked in our earlier listing (Harborne and Williams, 1975). Some reports represent confirmation of earlier provisional identifications. For example, the 4'-glucoside of 3',4'-dihydroxyflavone was provisionally identified in *Primula* leaves (Harborne, 1968), but its full characterization has only recently been accomplished following its isolation from another source, in *Rhus* heartwood (Young, 1979).

Some of the more complex and unusual new glycosides reported have been isolated from lower plants. A notable example is the first apigenin derivative with two disaccharide moieties, namely the 7-neohesperidoside-4'-sophoroside from the moss *Hedwigia ciliata* (Österdahl, 1979). Among several new flavones highly substituted with glucuronic acid are apigenin 7-diglucuronide-4'-monoglucuronide from the liverwort *Conocephalum conicum* (Markham *et al.*, 1976) and luteolin 7,3',4'-triglucuronide in *Marchantia polymorpha* (Markham and Porter, 1974b).

A number of incompletely characterized di- and tri-glycosides has been included in Table 5.6, where the structures are clearly new, but further analyses to determine interglycosidic linkages are needed in many cases. For example, a tricetin 5-diglucoside was reported in *Triticum dicoccum* by Harborne and Hall (1964) and more recently in *Lycopodium scariosum* (Markham and Moore, 1980). It is

not known whether they are the same, with the same disaccharide unit, or whether they are different.

Several flavone triglycosides have been reported, but few have been fully described. Indeed, one of the few which seems to have been completely identified is chrysoeriol 7-sophorotrioside in *Sideritis romana* (Labiatae) (Venturella *et al.*, 1977). Another, diosmetin 7-(4<sup>G</sup>-rhamnosylneohesperidoside) from the moss *Dicranum scoparium*, is unusual in having a unique branched trisaccharide as the sugar moiety (Österdahl, 1978). One other interesting one, awaiting complete analysis, is an isoetin 2'-triglycoside with the sugars xylose, arabinose and glucose reported in *Heywoodiella* (Harborne, 1978).

## 5.6 NEW REPORTS OF FLAVONOL GLYCOSIDES

The new flavonol glycosides reported in plants in the period 1975–1980 are shown in Table 5.7. The rate of discovery of new glycosides is apparent from the increase in the number of known kaempferol derivatives from 50 to 104, of quercetin derivatives from 62 to 112, and of myricetin derivatives from 12 to 25.

**Table 5.7** New flavonol glycosides

| Glycoside                                                 | Source                                                   | Reference                         |
|-----------------------------------------------------------|----------------------------------------------------------|-----------------------------------|
| <i>3,5-Dihydroxy-6-methoxyflavone</i><br>3-Rutinoside     | <i>Datisca cannabina</i><br>root cortex; Datisceae       | Zapesochneya (1969)               |
| <i>3,5,7-Trihydroxyflavone</i> (Galangin)<br>3-Rhamnoside | <i>Artocarpus lakoocha</i><br>root bark; Moraceae        | Chauhan and Kumari (1979)         |
| 3-Glucoside }<br>7-Glucoside }                            | <i>Cephalaria procera</i> ;<br>Dipsacaceae               | Ulubelen <i>et al.</i> (1978)     |
| 3-Galactosyl(1→4)rhamnoside                               | <i>Artocarpus lakoocha</i><br>root bark; Moraceae        | Chauhan <i>et al.</i> (1979a)     |
| <i>Galangin 3-methyl ether</i><br>7-Glucoside             | <i>Calluna vulgaris</i><br>flowers; Ericaceae            | Stepien <i>et al.</i> (1978)      |
| <i>8-Hydroxygalangin</i><br>7-methyl ether                |                                                          |                                   |
| 8-Acetate }<br>8-Butyrate }                               | <i>Notholaena</i> spp.<br>farinose exudate;<br>Filicales | Wollenweber <i>et al.</i> (1978b) |
| <i>Kaempferol</i><br>3-Xyloside                           | <i>Euonymus ciliatus</i><br>leaf; Celastraceae           | Ishikura and Sato (1977)          |
| 3-Alloside                                                | <i>Osmunda asiatica</i><br>trophophyll; Osmundaceae      | Okuyama <i>et al.</i> (1978)      |



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**Table 5.7** (Contd.)

| <i>Glycoside</i>                                             | <i>Source</i>                                                                                       | <i>Reference</i>                                  |
|--------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|---------------------------------------------------|
| 7-Arabinoside }<br>7-Xyloside }<br>7-Galactoside             | <i>Dryopteris</i> spp. frond;<br>Dryopteridaceae<br><i>Tithymalus densus</i><br>leaf; Euphorbiaceae | Hiraoka (1978)<br>Litvinenko <i>et al.</i> (1973) |
| 4'-Rhamnoside                                                | <i>Phyllanthus niruri</i><br>roots; Euphorbiaceae                                                   | Chauhan <i>et al.</i> (1977)                      |
| 4'-Glucoside                                                 | <i>Ophiopogon jaburan</i><br>seed coat; Liliaceae                                                   | Ishikura and<br>Hayashida (1979)                  |
| 3-Arabinosyl(1→6)galactoside                                 | <i>Lysichiton camtschaticense</i><br>leaf; Araceae                                                  | Williams <i>et al.</i> (1981)                     |
| 3-Xylosylrhamnoside                                          | <i>Woodsia polystichoides</i><br>frond; Athyriaceae                                                 | Hiraoka (1978)                                    |
| 3-Rhamnosylxyloside                                          | <i>Euonymus alatus</i><br>leaf; Celastraceae                                                        | Ishikura <i>et al.</i> (1976)                     |
| 3-Xylosylgalactoside                                         | <i>Lysichiton camtschaticense</i><br>leaf; Araceae                                                  | Williams <i>et al.</i> (1981)                     |
| 3-Glucosyl(1→4)rhamnoside                                    | <i>Rosa multiflora</i><br>fruit; Rosaceae                                                           | Takagi <i>et al.</i> (1976b)                      |
| 3-Neohesperidoside                                           | <i>Humulus lupulus</i><br>cones; Cannabidaceae                                                      | Vancraenenbroeck <i>et al.</i><br>(1969)          |
| 3-Rhamnosyl(1→2)galactoside                                  | <i>Chenopodium fremontii</i><br>leaf; Chenopodiaceae                                                | Crawford and Mabry<br>(1978)                      |
| 3-Glucosyl(1→6)galactoside                                   | <i>Eryngium planum</i> ;<br>Umbelliferae                                                            | Hiller <i>et al.</i> (1980)                       |
| 3-Galactosylglucoside                                        | <i>Heuchera</i> spp., whole<br>plant; Saxifragaceae                                                 | Wells and Bohm (1980)                             |
| 3-Arabinoside-7-rhamnoside }<br>3-Rhamnoside-7-arabinoside } | <i>Asplenium trichomanes</i> ;<br>Aspleniaceae                                                      | Imperato (1979a)                                  |
| 3-Glucoside-7-arabinoside                                    | <i>Loxsona cunninghamii</i><br>leaf; Filicales                                                      | Markham and Given<br>(1979)                       |
| 3-Glucoside-7-xyloside                                       | <i>Takakia lepidozoides</i><br>whole plant; Hepaticae                                               | Markham and Porter<br>(1979)                      |
| 3,7-Digalactoside                                            | <i>Pachyphragma<br/>macrophyllum</i><br>flowers; Cruciferae                                         | Zentsova and<br>Dzhumyrko (1974)                  |
| 3,4'-Diglucoside                                             | <i>Ophiopogon jaburan</i><br>seed coat; Liliaceae                                                   | Ishikura and<br>Hayashida (1979)                  |
| 3-Glucosylxylosylarabinoside                                 | <i>Antitoxicum sibiricum</i> ;<br>Asclepiadaceae                                                    | Shatokhina <i>et al.</i> (1974)                   |
| 3-Rhamnosyl(1→2)<br>rhamnosyl(1→6)glucoside                  | <i>Humulus lupulus</i><br>cones; Cannabidaceae                                                      | Vancraenenbroeck<br><i>et al.</i> (1969)          |
| 3-(2 <sup>G</sup> -Rhamnosylrutinoside)                      | <i>Glycine max</i>                                                                                  | Buttery and Buzzell                               |
| 3-(2 <sup>G</sup> -Rhamnosylgentiobioside)                   | leaf; Leguminosae                                                                                   | (1975)                                            |
| 3-(2 <sup>G</sup> -Glucosylgentiobioside)                    |                                                                                                     |                                                   |
| 3-Rhamnosylglucosylgalactoside                               | <i>Peltophorum africanum</i> ;<br>Leguminosae                                                       | El Sherbeiny <i>et al.</i> (1977)                 |
| 3-Rhamnosylxyloside-7-glucoside                              | <i>Euonymus ciliatus</i><br>leaf; Celastraceae                                                      | Ishikura and Sato (1977)                          |

| Glycoside                                                    | Source                                                          | Reference                                                      |
|--------------------------------------------------------------|-----------------------------------------------------------------|----------------------------------------------------------------|
| 3-Glucosylxyloside-7-xyloside                                | <i>Heuchera micrantha</i><br>whole plant; Saxifragaceae         | Wilkins and Bohm (1976)                                        |
| 3-Glucosylrhamnoside-7-rhamnoside                            | <i>Oxytropis komarovii</i><br>aerial parts; Leguminosae         | Baimukhambetov (1975)                                          |
| 3-Rutinoside-7-rhamnoside                                    | <i>Equisetum silvaticum</i><br>green parts; Equisetaceae        | Aly <i>et al.</i> (1975)                                       |
| 3-Rhamnosylgalactoside-7-arabinoside                         | <i>Dryopteris</i> spp. frond;<br>Dryopteridaceae                | Hiraoka (1978)                                                 |
| 3-Glucoside-7-gentiobioside                                  | <i>Nerisyrenia</i> spp.<br>leaf; Cruciferae                     | Bacon and Mabry (1976)                                         |
| 3-Rutinoside-4'-diglucoside                                  | <i>Prunus</i> spp.<br>leaf; Rosaceae                            | Henning and Herrmann<br>(1980)                                 |
| 3-(2''- <i>p</i> -Coumaroyl)<br>arabinofuranoside            | <i>Picea koraiensis</i><br>needles; Pinaceae                    | Ivanova <i>et al.</i> , (1978)                                 |
| 3-(3''- <i>p</i> -Coumaroyl)glucoside                        | <i>Picea obvata</i><br>needles; Pinaceae                        | Zapesochnaya <i>et al.</i> (1980)                              |
| 3-(Feruloyl)glucoside                                        | <i>Pseudolarix amabilis</i><br>leaf; Pinaceae                   | Niemann (1975)                                                 |
| 3-(Di- <i>p</i> -coumaroyl)glucoside                         | <i>Pinus contorta</i><br>needles; Pinaceae                      | Higuchi and Donnelly<br>(1978)                                 |
| 3-(3''- <i>p</i> -Coumaroyl-6''-feruloyl)<br>glucoside       | <i>Picea obvata</i><br>needles; Pinaceae                        | Zapesochnaya <i>et al.</i> (1978)                              |
| 3-(6''- <i>p</i> -Coumaroyl)acetylglucoside                  | <i>Anaphalis contorta</i> ;<br>Compositae                       | Lin <i>et al.</i> (1976)                                       |
| 3-(6''-Galloyl)glucoside                                     | <i>Heuchera</i> spp. whole<br>plant; Saxifragaceae              | Wells and Bohm (1980)                                          |
| 3-(2''-Galloyl)glucoside                                     | <i>Polygonum nodosum</i><br>aerial parts; Polygonaceae          | Isobe <i>et al.</i> (1980)                                     |
| 7-(6''-Succinyl)glucoside                                    | <i>Cyathea contaminans</i><br>frond; Cyatheaceae,<br>Pterophyta | Hiraoka and Maeda<br>(1979)                                    |
| 3-(6'''-Acetyl)glucosyl-<br>(1→4)rhamnoside                  | <i>Rosa multiflora</i><br>fruit; Rosaceae                       | Takagi <i>et al.</i> (1976b);<br>Yamasaki <i>et al.</i> (1977) |
| 3-(6''-Acetyl)glucoside-7-<br>rhamnoside                     | <i>Equisetum telmateja</i> ;<br>Equisetaceae                    | Geiger <i>et al.</i> (1978)                                    |
| 3-(6''-Acetyl)glucoside-7-<br>glucoside                      |                                                                 |                                                                |
| 3-(2'''-Sinapoyl)sophoroside-7-<br>glucoside                 | <i>Brassica napus</i><br>seed; Cruciferae                       | Stengel and Geiger, (1976);<br>Markham <i>et al.</i> (1978b)   |
| 3-[Glucosyl-(1→3)-4''-acetyl-<br>rhamnosyl-(1→6)galactoside] | <i>Colubrina faralaostra</i><br>leaf; Rhamnaceae                | Guinaudeau <i>et al.</i> (1981)                                |
| 3-(4''-Caffeoyl)laminaribioside-<br>7-rhamnoside             | <i>Phyllitis scolopendrium</i><br>aerial parts; Aspleniaceae    | Karl <i>et al.</i> (1980)                                      |
| 3- $\alpha$ -(6''-Sulphate)glucoside                         | <i>Asplenium filix-foemina</i><br>frond; Aspleniaceae           | Imperato (1979b)                                               |
| 3-Rhamnosylsulphate                                          | <i>Davidsonia pruriens</i><br>leaf; Davidsoniaceae              | Wilkins and Bohm (1977)                                        |
| 3-Glucuronide-7-sulphate                                     | <i>Frankenia pulverulenta</i><br>leaf; Frankeniaceae            | Harborne (1975)                                                |

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**Table 5.7** (Contd.)

| <i>Glycoside</i>                                            | <i>Source</i>                                                                                                     | <i>Reference</i>                                             |
|-------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| 3-(6''-Sulphate)gentiobioside                               | <i>Asplenium fontanum</i> ,<br>Aspleniaceae                                                                       | Imperato (1980)                                              |
| 7-Sulphate                                                  | <i>Frankenia pulverulenta</i><br>leaf; Frankeniaceae                                                              | Harborne (1975)                                              |
| 3,7-Disulphate                                              | <i>Reaumuria mucronata</i><br>leaf; Tamaricaceae                                                                  | Nawwar <i>et al.</i> (1977b)                                 |
| <i>Kaempferol 7-methyl ether</i> (Rhamnocitrin)             |                                                                                                                   |                                                              |
| 3-Glucoside }<br>7-Rutinoside }<br>3-Sulphate }             | <i>Pityrogramma</i><br><i>triangularis</i><br>frond; Polypodiaceae<br><i>Ammi visnaga</i><br>flower; Umbelliferae | Star <i>et al.</i> (1975)<br><br>Harborne and King<br>(1976) |
| <i>Kaempferol 4'-methyl ether</i> (Kaempferide)             |                                                                                                                   |                                                              |
| 3-Glucuronide                                               | <i>Cleome viscosa</i><br>root; Capparidaceae                                                                      | Chauhan <i>et al.</i> (1979b)                                |
| <i>Kaempferol 7,4'-dimethyl ether</i>                       |                                                                                                                   |                                                              |
| 3-sulphate                                                  | <i>Tamarix aphylla</i><br>flowers; Tamaricaceae                                                                   | El Ansari <i>et al.</i> (1976)                               |
| <i>6-C-Methylkaempferol</i>                                 |                                                                                                                   |                                                              |
| 3-Glucoside                                                 | <i>Pinus contorta</i><br>needles; Pinaceae                                                                        | Higuchi and Donnelly<br>(1978)                               |
| <i>6-Hydroxykaempferol</i>                                  |                                                                                                                   |                                                              |
| 7-Glucoside                                                 | <i>Tetragonotheca</i> spp.<br>leaf; Compositae                                                                    | Bacon <i>et al.</i> (1978)                                   |
| <i>6-Hydroxykaempferol 3-methyl ether</i>                   |                                                                                                                   |                                                              |
| 6-Glucoside }<br>7-Glucoside }                              | <i>Neurolaena oaxacana</i><br>leaf; Compositae                                                                    | Ulubelen <i>et al.</i> (1980b)                               |
| <i>6-Hydroxykaempferol 6-methyl ether</i> (Eupafolin)       |                                                                                                                   |                                                              |
| 3-Glucoside                                                 | <i>Flaveria brownii</i> leaf<br>and stem; Compositae                                                              | Al-Khubaizi <i>et al.</i> (1977)                             |
| 3-Galactoside                                               | <i>Anvillea garcini</i><br>leaf; Compositae                                                                       | Ulubelen <i>et al.</i> (1979)                                |
| 7-Glucoside                                                 | <i>Tetragonotheca</i> spp.<br>leaf; Compositae                                                                    | Bacon <i>et al.</i> (1978)                                   |
| 3-Rutinoside                                                | <i>Anvillea garcini</i><br>leaf; Compositae                                                                       | Ulubelen <i>et al.</i> (1979)                                |
| <i>6-Hydroxykaempferol 4'-methyl ether</i>                  |                                                                                                                   |                                                              |
| 3,7-Dirhamnoside                                            | <i>Tephrosia candida</i> aerial<br>parts; Leguminosae                                                             | Sarin <i>et al.</i> (1976)                                   |
| <i>6-Hydroxykaempferol 6,7,4'-trimethyl ether</i> (Mikanin) |                                                                                                                   |                                                              |
| 3-Galactoside                                               | <i>Anvillea garcini</i><br>leaf; Compositae                                                                       | Ulubelen <i>et al.</i> (1979)                                |
| <i>8-Hydroxykaempferol</i> (Herbacetin)                     |                                                                                                                   |                                                              |
| 7-Arabinoside                                               | <i>Rhodiola gelida</i><br>rhizomes; Crassulaceae                                                                  | Krasnov and<br>Alekseyuk (1979)                              |

| <i>Glycoside</i>                                      | <i>Source</i>                                              | <i>Reference</i>                            |
|-------------------------------------------------------|------------------------------------------------------------|---------------------------------------------|
| 8-Xyloside                                            | <i>Rhodiola algida</i> ;<br>Crassulaceae                   | Zapesochnaya (1978)                         |
| 8-Rhamnoside                                          | <i>Rhodiola litvinovii</i><br>rhizome; Crassulaceae        | Krasnov (1979)                              |
| 8-Glucuronide                                         | <i>Melochia corychorifolia</i> ;<br>Sterculiaceae          | Nair <i>et al.</i> (1977a)                  |
| 4'-Arabinoside                                        | <i>Rhodiola algida</i><br>roots; Crassulaceae              | Pangarova and<br>Zapesochnoya (1974)        |
| 4'-Glucoside                                          | <i>Rhodiola gelida</i> rhizomes<br>and roots; Crassulaceae | Krasnov and<br>Aleksyuk (1979)              |
| 4'-Glucuronide                                        | <i>Rhodiola algida</i><br>roots; Crassulaceae              | Pangarova and<br>Zapesochnoya (1974)        |
| 8-Rutinoside                                          | <i>Fagonia arabica</i> whole<br>plant; Zygophyllaceae      | Saleh and El-Hadidi<br>(1977)               |
| 8-Gentiobioside                                       | <i>Calluna vulgaris</i><br>flowers; Ericaceae              | Olechnowicz-Stepien<br><i>et al.</i> (1978) |
| 8-Arabinoside-4'-xyloside                             | <i>Rhodiola algida</i> ;<br>Crassulaceae                   | Krasnov and<br>Demidenko (1979)             |
| 8-(3''-Acetyl)xyloside                                | <i>Rhodiola algida</i> ;<br>Crassulaceae                   | Zapesochnaya (1978)                         |
| 4'-(Acetyl)arabinoside                                | <i>Rhodiola algida</i><br>roots; Crassulaceae              | Pangarova and<br>Zapesochnoya (1974)        |
| 8-(Di-acetyl)glucoside                                | <i>Rhodiola algida</i> ;<br>Crassulaceae                   | Krasnov and<br>Demidenko (1979)             |
| 4'-(Di-acetyl)xyloside }<br>4'-(Tri-acetyl)xyloside } | <i>Rhodiola algida</i><br>roots; Crassulaceae              | Pangarova and<br>Zapesochnoya (1974)        |
| 8-Acetate }<br>8-Butyrate }                           | <i>Notholaena</i> spp.<br>farinose exudates; Filicales     | Wollenweber <i>et al.</i><br>(1978a)        |
| <i>Herbacetin 7-methyl ether</i>                      |                                                            |                                             |
| 8-Acetate }<br>8-Butyrate }                           | <i>Notholaena</i> spp.<br>farinose exudates; Filicales     | Wollenweber <i>et al.</i><br>(1978b)        |
| <i>Herbacetin 8-methyl ether</i>                      |                                                            |                                             |
| 3-Glucoside                                           | <i>Sorbus aucuparia</i><br>inflorescence; Rosaceae         | Jerzmanowska and<br>Kamecki (1973)          |
| 3-Rutinoside                                          | <i>Fagonia arabica</i> whole<br>plant; Zygophyllaceae      | Saleh and El-Hadidi<br>(1977)               |
| <i>Herbacetin 7,8-dimethyl ether</i>                  |                                                            |                                             |
| 3-Rhamnoside                                          | <i>Rudbeckia bicolor</i><br>whole plant; Compositae        | Jauhari <i>et al.</i> (1979)                |
| <i>Herbacetin 7,4'-dimethyl ether</i>                 |                                                            |                                             |
| 8-Acetate                                             | <i>Notholaena</i> spp. farinose<br>exudates; Filicales     | Wollenweber <i>et al.</i><br>(1978a)        |
| 8-Butyrate                                            | <i>Notholaena</i> spp. farinose<br>exudates; Filicales     | Wollenweber <i>et al.</i><br>(1978c)        |
| <i>Quercetin</i>                                      |                                                            |                                             |
| 3- $\alpha$ -Galactoside                              | <i>Rhododendron dauricum</i> ;<br>Ericaceae                | Liu <i>et al.</i> (1976)                    |

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**Table 5.7** (Contd.)

| <i>Glycoside</i>                                                    | <i>Source</i>                                            | <i>Reference</i>                      |
|---------------------------------------------------------------------|----------------------------------------------------------|---------------------------------------|
| 3-Galacturonide                                                     | <i>Corsinia coriandrina</i> thallus; Marchantia          | Markham (1980)                        |
| 7-Arabinoside                                                       | <i>Conyza dioscoridis</i> leaf; Compositae               | Ismail <i>et al.</i> (1979)           |
| 7- $\beta$ -Galactoside                                             | <i>Coptis japonica</i> ; Ranunculaceae                   | Fujiwara <i>et al.</i> (1976)         |
| 3'-Xyloside                                                         | <i>Euphorbia paralias</i> ; Euphorbiaceae                | Rizk <i>et al.</i> (1976)             |
| 3-Arabinosyl(1 $\rightarrow$ 6)galactoside                          | <i>Hydrocotyle vulgaris</i> leaf; Umbelliferae           | Hiller <i>et al.</i> (1979)           |
| 3-Dixyloside }<br>3-Xylosylglucoside }                              | <i>Heuchera micrantha</i> whole plant; Saxifragaceae     | Wilkins and Bohm (1976)               |
| 3-Glucosyl(1 $\rightarrow$ 4)ramnoside                              | <i>Rosa multiflora</i> fruit; Rosaceae                   | Takagi <i>et al.</i> (1976a)          |
| 3-Robnobioside                                                      | <i>Crataegus pinnatifida</i> flowers; Rosaceae           | Bykov and Glyzin (1977)               |
| 3-Galactosylglucoside                                               | <i>Lasthenia</i> spp. whole plant; Compositae            | Ornduff <i>et al.</i> (1973)          |
| 3-Glucosylmannoside                                                 | <i>Solanum xanthocarpum</i> flowers; Solanaceae          | Dubey and Gupta (1978)                |
| 3-Galactosylglucuronide                                             | <i>Sullivantia</i> spp. Saxifragaceae                    | Soltis (1980)                         |
| 3-Glucoside-7-arabinoside                                           | <i>Loxsona cunninghamii</i> leaf; Filicales              | Markham and Given (1979)              |
| 3-Galactoside-7-glucoside                                           | <i>Verbesina encelioides</i> leaf and flower; Compositae | Glennie and Jain (1980)               |
| 3-(2 <sup>G</sup> -Rhamnosylrutinoside)                             | <i>Glycine max</i> leaf; Leguminosae                     | Buttery and Buzzell (1975)            |
| 3-Rhamnosyl(1 $\rightarrow$ 2)rutinoside                            | <i>Humulus lupulus</i> cones; Cannabidaceae              | Vancraenenbroeck <i>et al.</i> (1969) |
| 3-Rhamnosylrobinobioside                                            | <i>Primula officinalis</i> flowers; Primulaceae          | Karl <i>et al.</i> (1981)             |
| 3-Glucosyl(1 $\rightarrow$ 6)glucosyl(1 $\rightarrow$ 4) rhamnoside | <i>Rosa multiflora</i> fruit; Rosaceae                   | Takagi <i>et al.</i> (1976a)          |
| 3-(2 <sup>G</sup> -Rhamnosylgentiobioside)                          | <i>Glycine max</i> leaf; Leguminosae                     | Buttery and Buzzell, (1975)           |
| 3-(2 <sup>G</sup> -Apiosylrutinoside)                               | <i>Solanum glaucophyllum</i> leaf; Solanaceae            | Rappaportt <i>et al.</i> (1977)       |
| 3-Glucosyl(1 $\rightarrow$ 2)gentiobioside                          | <i>Primula officinalis</i> flowers; Primulaceae          | Karl <i>et al.</i> (1981)             |
| 3-(2 <sup>G</sup> -Glucosylgentiobioside)                           | <i>Glycine max</i> leaf; Leguminosae                     | Buttery and Buzzell (1975)            |
| 7-Triglucoside                                                      | <i>Inula helenium</i> inflorescence; Compositae          | Kowalewska and Lutomski (1978)        |
| 3-Dixyloside-7-glucoside                                            | <i>Heuchera micrantha</i> whole plant; Saxifragaceae     | Wilkins and Bohm (1976)               |
| 3-Gentiobioside-7-glucoside                                         | <i>Tribulus</i> spp. whole plant; Zygophyllaceae         | Saleh and El-Hadidi (1977)            |

| Glycoside                                                                                                    | Source                                                                             | Reference                                                             |
|--------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-----------------------------------------------------------------------|
| 3-(2 <sup>G</sup> -Rhamnosylrutinoside-7-glucoside)                                                          | <i>Cerbera manghas</i><br>leaf; Apocynaceae                                        | Sakushima <i>et al.</i> (1980)                                        |
| 3-Rhamnosyldiglucoside-7-glucoside                                                                           | <i>Coprosma repens</i><br>leaf; Rubiaceae                                          | Wilson (1979)                                                         |
| 3-Rutinoside-7,3'-bisglucoside }<br>3-Rutinoside-4'-diglucoside }<br>3-(6''- <i>p</i> -Coumaroyl)glucoside } | <i>Prunus</i> spp.<br>leaf; Rosaceae<br><i>Helichrysum krausii</i> ;<br>Compositae | Henning and Herrmann<br>(1980)<br>Candy <i>et al.</i> (1975)          |
| 3-(3''- <i>p</i> -Coumaroyl)glucoside                                                                        | <i>Pinus</i> sp. needles; Pinaceae                                                 | Ivanova (1978)                                                        |
| 3-Isoferuloylgucuronide                                                                                      | <i>Tamarix aphylla</i><br>flower; Tamaricaceae                                     | El Ansari <i>et al.</i> (1976)                                        |
| 3-(3''-Acetyl)- $\alpha$ -L-arabinofuranoside                                                                | <i>Boehmeria tricuspidis</i><br>root; Urticaceae                                   | Takemoto and Miyase<br>(1974)                                         |
| 3-(3''-Acetyl)rhamnoside                                                                                     | <i>Pteris grandiflora</i><br>aerial parts; Pteridaceae                             | Tanaka <i>et al.</i> (1978)                                           |
| 3-(4''-Acetyl)rhamnoside                                                                                     | <i>Pinus</i> sp. needles;<br>Pinaceae                                              | Ivanova (1978)                                                        |
| 3-(6''-Acetyl)glucoside                                                                                      | <i>Polygonum nodosum</i> ;<br>Polygonaceae                                         | Isobe <i>et al.</i> (1979)                                            |
| 3-(2''-Galloyl)glucoside                                                                                     | <i>Tellima grandiflora</i><br>leaf; Saxifragaceae                                  | Collins <i>et al.</i> (1975)                                          |
| 3-(2''-Galloyl)galactoside                                                                                   | <i>Euphorbia seguieriana</i> ;<br>Euphorbiaceae                                    | Nahrstedt <i>et al.</i> (1974)                                        |
| 3-(Malonylglucoside)                                                                                         | <i>Lactuca sativa</i><br>leaf; Compositae                                          | Kreuzaler and<br>Hahlbrock (1973)<br>Woeldecke and Hermann<br>(1974). |
| 3-(3'',6''-Di- <i>p</i> -coumaroyl)glucoside                                                                 | <i>Pinus sylvestris</i><br>needles; Pinaceae                                       | Ivanova <i>et al.</i> (1980)                                          |
| 3- <i>p</i> -Coumaroylsophoroside-7-rhamnoside }<br>3-Acetylsophoroside-7-rhamnoside }                       | <i>Oxytropis myriophylla</i> ;<br>Leguminosae                                      | Blinova and Thuan (1977)                                              |
| 3-[Glucosyl-(1 $\rightarrow$ 3)-4''-acetyl-rhamnosyl-(1 $\rightarrow$ 6)galactoside]                         | <i>Colubrina faralaoatra</i><br>leaf; Rhamnaceae                                   | Guinaudeau <i>et al.</i> (1981)                                       |
| 7-(6''-Tiglyl)glucoside                                                                                      | <i>Enkianthus nudipes</i><br>stem; Ericaceae                                       | Ogawa and Ogihara<br>(1975)                                           |
| 3-Rhamnosidesulphate                                                                                         | <i>Davidsonia pruriens</i><br>leaf; Davidsoniaceae                                 | Wilkins and Bohm (1977)                                               |
| 3-Glucuronide-7-sulphate                                                                                     | <i>Frankenia pulverulenta</i><br>leaf; Frankeniaceae                               | Harborne (1975)                                                       |
| 3-Rutinosidesulphate                                                                                         | <i>Arecastrum roman-zoffianum</i> $\times$ <i>Butia capitata</i><br>leaf; Palmae   | Williams <i>et al.</i> (1973)                                         |
| 3-Acetyl-7,3',4'-trisulphate                                                                                 | <i>Flaveria bidentis</i> ;<br>Compositae                                           | Cabrera and Juliani (1976)                                            |
| 3-Sulphate                                                                                                   | <i>Ammi visnaga</i><br>leaf; Umbelliferae                                          | Harborne and King (1976)                                              |

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**Table 5.7** (Contd.)

| <i>Glycoside</i>                                                                            | <i>Source</i>                                            | <i>Reference</i>                          |
|---------------------------------------------------------------------------------------------|----------------------------------------------------------|-------------------------------------------|
| 3,4'-Disulphate }<br>3,7,4'-Trisulphate }<br><i>Quercetin 5-methyl ether</i><br>(Azaleatin) | <i>Flaveria bidentis</i><br>leaf; Compositae             | Cabrera and Juliani (1979)                |
| 3-Arabinoside                                                                               | <i>Carya pecan</i> branches;<br>Juglandaceae             | El Ansari <i>et al.</i> (1977)            |
| 5-Glucoside                                                                                 | <i>Stizolophus</i><br><i>coronopifolius</i> ; Compositae | Oganesyan and<br>Dzhumyrko (1974)         |
| 3-Xylosylarabinoside }<br>3-Rhamnosylarabinoside }                                          | <i>Erysimum perofskianum</i><br>Cruciferae               | Matlawska and Kowalew<br>(1976)           |
| 3-Rutinoside                                                                                | <i>Carya pecan</i> branches;<br>Juglandaceae             | El Ansari <i>et al.</i> (1977)            |
| <i>Quercetin 7-methyl ether</i> (Rhamnetin)                                                 |                                                          |                                           |
| 3-Glucoside                                                                                 | <i>Thalictrum foetidum</i> ;<br>Ranunculaceae            | Nuralieva <i>et al.</i> (1969)            |
| 3'-Glucuronide                                                                              | <i>Tamarix aphylla</i> ;<br>Tamaricaceae                 | Saleh <i>et al.</i> (1975)                |
| 3-Rutinoside                                                                                | <i>Suriana maritima</i><br>whole plant;<br>Simaroubaceae | Mitchell and Geissman<br>(1971)           |
| 3-2Gal-Rhamnosylrobinobioside                                                               | <i>Rhamnus petiolaris</i><br>fruit; Rhamnaceae           | Wagner <i>et al.</i> (1974)               |
| 3-Sulphate                                                                                  | <i>Ammi visnaga</i><br>flower; Umbelliferae              | Harborne and King (1976)                  |
| 3,5,4'-Trisulphate                                                                          | <i>Tamarix aphylla</i> ;<br>Tamaricaceae                 | Saleh <i>et al.</i> (1975)                |
| <i>Quercetin 3'-methyl ether</i> (Isorhamnetin)                                             |                                                          |                                           |
| 3- $\alpha$ -L-Arabinofuranoside                                                            | <i>Taxodium distichum</i><br>short shoot; Taxodiaceae    | Geiger and de Groot-<br>Pfleiderer (1979) |
| 3-Xyloside                                                                                  | <i>Leptarrhena pyrolifolia</i><br>leaf; Saxifragaceae    | Miller and Bohm (1979)                    |
| 3-Arabinosyl(1 $\rightarrow$ 6)glucoside                                                    | <i>Papaver orientale</i><br>leaf; Papaveraceae           | Sakar <i>et al.</i> (1980)                |
| 3-Xylosylglucoside                                                                          | <i>Festuca arundinacea</i> ;<br>Gramineae                | Wong (1980)                               |
| 3-Sophoroside                                                                               | <i>Hippophae rhamnoides</i> ;<br>Elaeagnaceae            | Mukamedyarova and<br>Chumbalov (1979)     |
| 3-Lactoside                                                                                 | <i>Cassia multijuga</i><br>seed; Leguminosae             | Dubey and Gupta (1980)                    |
| 3-Glucoside-7-xyloside                                                                      | <i>Heuchera micrantha</i><br>whole plant; Saxifragaceae  | Wilkins and Bohm (1976)                   |
| 3-Xylosylrhamnosylgalactoside                                                               | <i>Nitraria retusa</i> whole<br>plant; Zygophyllaceae    | Saleh and El-Hadidi (1977)                |
| 3-Rhamnosylrutinoside                                                                       | <i>Limnanthes douglassi</i><br>leaf; Limnanthaceae       | Parker and Bohm (1975)                    |
| 3-Galactosylrhamnosylgalactoside                                                            | <i>Nitraria retusa</i><br>whole plant;<br>Zygophyllaceae | Saleh and El-Hadidi (1977)                |

| Glycoside                                           | Source                                                                         | Reference                          |
|-----------------------------------------------------|--------------------------------------------------------------------------------|------------------------------------|
| 3-Arabinoside-7-rhamnoside                          | <i>Cheiranthus cheiri</i><br>flower; Cruciferae                                | Kowalewski <i>et al.</i> (1979)    |
| 3-Rutinoside-7-glucoside                            | <i>Limnanthes douglassi</i><br>leaf; Limnanthaceae                             | Parker and Bohm (1975)             |
| 3-Glucoside-7-gentiobioside                         | <i>Nerisyrenia</i> spp.<br>leaf; Cruciferae                                    | Bacon and Mabry (1976)             |
| 3-Galactoside-4'-glucoside                          | <i>Senecio subdentatus</i> ;<br>Compositae                                     | Fadeeva and<br>Nikishchenko (1979) |
| 3-(6''-Acetyl)glucoside                             | <i>Salix viminalis</i><br>leaf; Salicaceae                                     | Karl <i>et al.</i> (1977)          |
| 3-(6''-Acetyl)galactoside                           | <i>Pinus</i> sp. needles; Pinaceae                                             | Ivanova (1978)                     |
| 3-Rutinosidesulphate                                | <i>Arecastrum roman-<br/>zoffianum</i> × <i>Butia capitata</i><br>leaf; Palmae | Williams <i>et al.</i> (1973)      |
| 3-Glucuronide-7-sulphate }<br>7-Sulphate }          | <i>Frankenia pulverulenta</i><br>leaf; Frankeniaceae                           | Harborne (1975)                    |
| 3,7-Disulphate                                      | <i>Flaveria bidentis</i><br>flower; Compositae                                 | Cabrera and Juliani<br>(1977)      |
| <i>Quercetin 4'-methyl ether</i> (Tamarixetin)      |                                                                                |                                    |
| 3-Rutinoside                                        | <i>Albizia amara</i> ;<br>Leguminosae                                          | Sastry <i>et al.</i> (1967)        |
| <i>Quercetin 3,5-dimethyl ether</i> (Caryatin)      |                                                                                |                                    |
| 3'-(or 4'-)Glucoside                                | <i>Carya pecan</i><br>branches; Juglandaceae                                   | El Ansari <i>et al.</i> (1977)     |
| <i>Quercetin 5,3'-dimethyl ether</i>                |                                                                                |                                    |
| 3-Glucoside                                         | <i>Medicago</i> × <i>varia</i><br>seed; Leguminosae                            | Gehring and Geiger<br>(1980)       |
| <i>Quercetin 7,3'-dimethyl ether</i><br>(Rhamnazin) |                                                                                |                                    |
| 3-(4 <sup>Gal</sup> -Rhamnosylrobinobioside)        | <i>Rhamnus petiolaris</i><br>Fruit; Rhamnaceae                                 | Wagner <i>et al.</i> (1974)        |
| <i>Quercetin 7,4'-dimethyl ether</i> (Ombuin)       |                                                                                |                                    |
| 3-Galactoside                                       | <i>Cassia laevigata</i><br>pods; Leguminosae                                   | Tiwari and Singh (1978)            |
| 3-Neohesperidoside                                  | <i>Cassia laevigata</i><br>leaf; Leguminosae                                   | Singh and Tiwari (1979)            |
| <i>Quercetin 3',4'-dimethyl ether</i>               |                                                                                |                                    |
| 3-Rutinoside                                        | <i>Anvillea garcini</i><br>leaf; Compositae                                    | Ulubelen <i>et al.</i> (1979)      |
| <i>Quercetin 7,3',4'-trimethyl ether</i>            |                                                                                |                                    |
| 3-Digalactoside                                     | <i>Cassia laevigata</i><br>pods; Leguminosae                                   | Tiwari and Singh (1978)            |
| <i>6-Hydroxyquercetin</i><br>(Quercetagenin)        |                                                                                |                                    |
| 3-Rhamnoside                                        | <i>Juniperus macropoda</i><br>leaf; Cupressaceae                               | Ilyas <i>et al.</i> (1977)         |
| 3,7-Diglucoside                                     | <i>Parthenium rollinsianum</i><br>whole plant; Compositae                      | Rodriguez (1977)                   |



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**Table 5.7** (Contd.)

| <i>Glycoside</i>                                      | <i>Source</i>                                                   | <i>Reference</i>                 |
|-------------------------------------------------------|-----------------------------------------------------------------|----------------------------------|
| <i>Quercetagenin 3-methyl ether</i>                   |                                                                 |                                  |
| 7-Glucoside }<br>7-Sulphate }                         | <i>Neurolaena oaxacana</i><br>leaf; Compositae                  | Ulubelen <i>et al.</i> (1980b)   |
| <i>Quercetagenin 6-methyl ether (Patuletin)</i>       |                                                                 |                                  |
| 3-Xyloside                                            | <i>Lasthenia</i> spp. whole<br>plant; Compositae                | Ornduff <i>et al.</i> (1973)     |
| 3-Rhamnoside                                          | <i>Lepidophorum repandum</i><br>leaf; Compositae                | Harborne <i>et al.</i> (1976)    |
| 3,7-Dirhamnoside                                      | <i>Kalanchoe spathulata</i> ;<br>Crassulaceae                   | Gaind <i>et al.</i> (1981)       |
| 3-Acetylglucoside                                     | <i>Lagascea mollis</i> aerial<br>parts; Compositae              | El-Naggar and Doskotch<br>(1979) |
| 3-Sulphate                                            | <i>Brickellia californica</i><br>leaf; Compositae               | Mues <i>et al.</i> (1979)        |
| <i>Quercetagenin 7-methyl ether</i>                   |                                                                 |                                  |
| 3-Glucoside                                           | <i>Parthenium rollinsianum</i><br>whole plant; Compositae       | Rodriguez (1977)                 |
| <i>Quercetagenin 3,6-dimethyl ether</i>               |                                                                 |                                  |
| 7-Glucoside                                           | <i>Artemisia taurica</i><br>flower; Compositae                  | Oganesyan <i>et al.</i> (1976)   |
| <i>Quercetagenin 3,7-dimethyl ether</i>               |                                                                 |                                  |
| 6-Glucoside                                           | <i>Chrysosplenium</i><br><i>glechomaefolium</i> ;<br>Compositae | Bohm and Collins (1979)          |
| 6-Galactoside                                         | <i>Neurolaena oaxacana</i><br>leaf; Compositae                  | Ulubelen <i>et al.</i> (1980b)   |
| 4'-Glucoside                                          | <i>Chrysosplenium</i><br><i>glechomaefolium</i> ;<br>Compositae | Bohm and Collins (1979)          |
| <i>Quercetagenin 6,7-dimethyl ether (Eupatolitin)</i> |                                                                 |                                  |
| 3-Sulphate                                            | <i>Brickellia veronicaefolia</i><br>leaf; Compositae            | Roberts <i>et al.</i> (1980)     |
| <i>Quercetagenin 6,3'-dimethyl ether (Spinacetin)</i> |                                                                 |                                  |
| 7-Glucoside                                           | <i>Lepidophorum repandum</i><br>flower; Compositae              | Harborne <i>et al.</i> (1976)    |
| 3-Rutinoside                                          | <i>Anvillea garcini</i><br>leaf; Compositae                     | Ulubelen <i>et al.</i> (1979)    |
| <i>Quercetagenin 3,6,7-trimethyl ether</i>            |                                                                 |                                  |
| 4'-Glucoside                                          | <i>Chrysosplenium</i><br><i>glechomaefolium</i> ;<br>Compositae | Bohm and Collins (1979)          |
| <i>Quercetagenin 3,7,4'-trimethyl ether</i>           |                                                                 |                                  |
| 6-Glucoside                                           | <i>Chrysosplenium echinus</i> ;<br>Compositae                   | Bohm and Collins (1979)          |
| 3'-Glucoside                                          | <i>Chrysosplenium</i><br><i>americanum</i> ; Compositae         | Bohm and Collins (1979)          |

| Glycoside                                                                                   | Source                                                                                                    | Reference                                         |
|---------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| <i>Quercetagenin</i> 6,7,3'-trimethyl ether (Veronicafolin)                                 |                                                                                                           |                                                   |
| 3-Rutinoside                                                                                | <i>Brickellia chlorolepis</i><br>leaf; Compositae                                                         | Ulubelen <i>et al.</i> (1980a)                    |
| 3-Digalactoside }<br>3-Sulphate }                                                           | <i>Brickellia veronicaefolia</i><br>leaf; Compositae                                                      | Roberts <i>et al.</i> (1980)                      |
| <i>Quercetagenin</i> 6,7,4'-trimethyl ether (Eupatin)                                       |                                                                                                           |                                                   |
| 3-Sulphate                                                                                  | <i>Brickellia californica</i><br>leaf; Compositae                                                         | Mues <i>et al.</i> (1979)                         |
| <i>Quercetagenin</i> 3,6,7,3',4'-pentamethyl ether (Artemetin)                              |                                                                                                           |                                                   |
| 5-Glucosylrhamnoside                                                                        | <i>Vitex negundo</i> stem<br>bark; Verbenaceae                                                            | Misra and<br>Subramanian (1980)                   |
| 8-Hydroxyquercetin (Gossypetin)                                                             |                                                                                                           |                                                   |
| 3-Sulphate                                                                                  | <i>Malva sylvestris</i><br>leaf; Malvaceae                                                                | Nawwar <i>et al.</i> (1977a)                      |
| <i>Gossypetin</i> 7-methyl ether                                                            |                                                                                                           |                                                   |
| 3-Arabinoside                                                                               | <i>Eriogonum nudum</i><br>flowers; Polygonaceae                                                           | Harborne <i>et al.</i> (1978)                     |
| 3-Rhamnoside                                                                                | <i>Atraphaxis purpurea</i><br>leaf; Polygonaceae                                                          | Chumbalov (1976)                                  |
| 3-Galactoside }<br>8-Glucoside }<br>3-Galactoside-8-glucoside }<br>3-Rhamnoside-8-acetate } | <i>Eriogonum nudum</i><br>flowers; Polygonaceae<br><i>Atraphaxis purifolia</i><br>leaf; Polygonaceae      | Harborne <i>et al.</i> (1978)<br>Chumbalov (1976) |
| <i>Gossypetin</i> 8-methyl ether                                                            |                                                                                                           |                                                   |
| 3-Galactoside                                                                               | <i>Geraea canescens</i><br>flowers; Compositae                                                            | Harborne <i>et al.</i> (1978)                     |
| <i>Gossypetin</i> 3'-methyl ether                                                           |                                                                                                           |                                                   |
| 3-Rutinoside                                                                                | <i>Coronilla valentina</i><br>petals; Leguminosae                                                         | Harborne (1981)                                   |
| 7-(6''-Acetyl)glucoside                                                                     | <i>Haplophyllum perforatum</i> ;<br>Rutaceae                                                              | Batirov and Malikov (1980)                        |
| <i>Gossypetin</i> 7,4'-dimethyl ether                                                       |                                                                                                           |                                                   |
| 8-Acetate                                                                                   | <i>Notholaena</i> spp.<br>farinose exudate; Filicales                                                     | Wollenweber <i>et al.</i> (1978a)                 |
| 8-Butyrate                                                                                  | <i>Notholaena</i> spp.<br>farinose exudate; Filicales                                                     | Wollenweber <i>et al.</i> (1978b)                 |
| <i>Gossypetin</i> 8,3'-dimethyl ether                                                       |                                                                                                           |                                                   |
| 3-Rutinoside                                                                                | <i>Coronilla valentina</i><br>petals; Leguminosae                                                         | Harborne (1981)                                   |
| <i>Myricetin</i>                                                                            |                                                                                                           |                                                   |
| 3-Xyloside                                                                                  | <i>Leptarrhena pyrolifolia</i><br>leaf; Saxifragaceae                                                     | Miller and Bohm (1979)                            |
| 3-Dixyloside }<br>3-Xylosylglucoside }<br>3-Xylosylgalactoside }                            | <i>Heuchera</i> spp. whole<br>plant; Saxifragaceae<br><i>Saxifraga</i> spp. whole<br>plant; Saxifragaceae | Wells and Bohm (1980)<br>Miller and Bohm (1980)   |

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**Table 5.7** (Contd.)

| <i>Glycoside</i>                                                                                                                                 | <i>Source</i>                                                                                                                                                 | <i>Reference</i>                                                        |
|--------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| 3-Diglucoside                                                                                                                                    | <i>Heuchera</i> spp. whole plant; Saxifragaceae                                                                                                               | Wells and Bohm (1980)                                                   |
| 3-Galactosylglucoside                                                                                                                            | <i>Heuchera</i> spp. whole plant; Saxifragaceae                                                                                                               | Wells and Bohm (1980)                                                   |
| 3-Rhamnosylrutinoside }<br>3-Rutinoside-7-glucoside }<br>3-Triglucoside                                                                          | <i>Limnanthes douglasii</i> leaf; Limnanthaceae<br><i>Heuchera cylindrica</i> whole plant; Saxifragaceae                                                      | Parker and Bohm (1975)<br>Bohm and Wilkins (1978)                       |
| 3-(6''-Galloyl)glucoside }<br>3-(6''-Galloyl)galactoside }<br>3-(2''-Acetyl)rhamnoside                                                           | <i>Sedum kamtschaticum</i> ; Crassulaceae<br><i>Sedum solskianum</i> aerial parts; Crassulaceae                                                               | Zapesochneya and Shnyakina (1978)<br>Zapesochneya and Shnyakina, (1975) |
| 3-Rhamnosidesulphate                                                                                                                             | <i>Davidsonia pruriens</i> leaf; Davidsoniaceae                                                                                                               | Wilkins and Bohm (1977)                                                 |
| <i>Myricetin 3'-methyl ether</i> (Laricitrin)                                                                                                    |                                                                                                                                                               |                                                                         |
| 3-Rhamnoside                                                                                                                                     | <i>Abies amabilis</i> needles; Pinaceae                                                                                                                       | Parker <i>et al.</i> (1979)                                             |
| 3-Glucoside                                                                                                                                      | <i>Larix sibirica</i> needles; Pinaceae                                                                                                                       | Tyukavkina <i>et al.</i> (1974)                                         |
| 3-Galactoside                                                                                                                                    | <i>Chondropetalum hookerianum</i> stem; Restionaceae                                                                                                          | Harborne (1979b)                                                        |
| 3-Rutinoside }<br>3-Rhamnosylrutinoside }<br>3-Rutinoside-7-glucoside }<br>3- <i>p</i> -Coumaroylglucoside                                       | <i>Limnanthes douglasii</i> leaf and petal; Limnanthaceae<br><i>Larix gmelinii</i> needles; Pinaceae                                                          | Parker and Bohm (1975)<br>Niemann (1980)                                |
| <i>Myricetin 4'-methyl ether</i>                                                                                                                 |                                                                                                                                                               |                                                                         |
| 3-Galactosyl(1→4)galactoside                                                                                                                     | <i>Vitex negundo</i> Stem bark; Verbenaceae                                                                                                                   | Misra and Subramanian (1980)                                            |
| <i>Myricetin 3',5'-dimethyl ether</i> (Syringetin)                                                                                               |                                                                                                                                                               |                                                                         |
| 3-Rhamnoside                                                                                                                                     | <i>Hedychium stenopetalum</i> leaf; Zingiberaceae                                                                                                             | Williams and Harborne (1977)                                            |
| 3-Galactoside }<br>3-Glucuronide }<br>3-Rutinoside }<br>3-Rhamnosylrutinoside }<br>3-Rutinoside-7-glucoside }<br>3- <i>p</i> -Coumaroylglucoside | <i>Philydrum lanuginosum</i> whole plant; Philydraceae<br><i>Limnanthes douglasii</i> leaf and petal; Limnanthaceae<br><i>Larix gmelini</i> needles; Pinaceae | Bohm and Collins (1975)<br>Parker and Bohm (1975)<br>Niemann (1980)     |
| <i>6-Hydroxymyricetin 6,3',5'-trimethyl ether</i>                                                                                                |                                                                                                                                                               |                                                                         |
| 3-Glucoside                                                                                                                                      | <i>Tillandsia usneoides</i> leaf and stem; Bromeliaceae                                                                                                       | Williams (1978)                                                         |
| <i>6-Hydroxymyricetin 4,6,3',5'-tetramethyl ether</i>                                                                                            |                                                                                                                                                               |                                                                         |
| 7-Glucoside                                                                                                                                      | <i>Tillandsia usneoides</i> leaf and stem; Bromeliaceae                                                                                                       | Williams (1978)                                                         |

| Glycoside                                   | Source                                             | Reference               |
|---------------------------------------------|----------------------------------------------------|-------------------------|
| 8-Hydroxymyricetin (Hibiscetin)             |                                                    |                         |
| 8-Glucosylxyloside                          | <i>Solanum citrullifolium</i><br>leaf; Solanaceae  | Whalen and Mabry (1979) |
| 2'-Hydroxyflavonols                         |                                                    |                         |
| 5,2'-Dihydroxy-3,7,4'-trimethoxyflavone     |                                                    |                         |
| 2'-Glucoside                                | <i>Chrysosplenium americanum</i> ; Compositae      | Bohm and Collins (1979) |
| 5,2',5'-Trihydroxy-3,7,4'-trimethoxyflavone |                                                    |                         |
| 2'-Glucoside                                | <i>Chrysosplenium glechomaefolium</i> ; Compositae | Bohm and Collins (1979) |

A general problem in drawing up Table 5.7 has been the difficulty of relating 3-diglycosides of known structure with similar compounds in which the interglycosidic links have not been determined. In general, the assumption has been made of identity, although confirmation is desirable in all cases. For example, the kaempferol 3-glucosylgalactoside (called panasenoside) reported in *Panax ginseng* (Araliaceae) by Komatsu *et al.* (1969) may or may not be the same as the 3-glucosyl(1 → 6)galactoside recently fully characterized in *Eryngium planum* (Umbelliferae) by Hiller *et al.* (1980). The presumption that they are the same is strengthened by the facts that the two plants concerned are from closely related families and that the anthocyanin patterns in the two families are also closely similar (see Harborne, 1976).

Other examples of presumed identity are of a kaempferol 3-xylosylgalactoside in *Lysichiton camtschatcense* (Araceae) (Table 5.7) and the 3-xylosyl(1 → 6)galactoside, reported in *Laurocerasus officinale* (Rosaceae) as having the xylose moiety in the unlikely furanose form (Tsiklauri *et al.*, 1979). Again, the 3-rhamnosylglucoside-7-rhamnoside of kaempferol in *Hesperis matronalis* (Cruciferae) (Ellnain-Wojtaszek and Kowalewski, 1971) could be identical with the 3-rutinoside-7-rhamnoside reported in *Equisetum* (see Table 5.7). Also, the quercetin 3-rhamnosylgalactoside of *Lasthenia* species (Compositae) (Ornduff *et al.*, 1973) could be the same as the 3-robinobioside reported in *Crateagus* by Bykov and Glyzin (1977) (see Table 5.7). There are also problems with partly characterized flavonol triglycosides. Thus, the 3-rhamnosylrutinosides of kaempferol and quercetin reported in *Limnanthes douglasii* (Parker and Bohm, 1975) and the 3-rhamnosyldiglucoide of quercetin in *Camellia sinensis* (Roberts, 1962) may well be identical separately with various triglycosides more recently described from *Glycine* or *Humulus* (see Table 5.7).

The possibilities of isomerism among flavonol 3-diglycosides are lessened by the fact that certain glycosidic patterns are very common in plants. For example, flavonol 3-diglycosides containing rhamnose and glucose nearly always have the sugars joined in an  $\alpha 1 \rightarrow 6$  linkage, as in rutinose. Thus, quercetin 3-rutinoside or

rutin is probably the most widespread of all known flavonol glycosides. The related 3-neohesperidoside, with an  $\alpha 1 \rightarrow 2$  linkage, has been described but it is definitely rare in occurrence. It is interesting that a third isomer has very recently been reported in the flowers of *Crataegus pinnatifida* (Rosaceae) by Bykov and Glyzin (1977), but it is not yet clear whether the two sugars in this compound are  $\alpha 1 \rightarrow 3$ - or  $\alpha 1 \rightarrow 4$ -linked.

Several examples of isomeric flavonol 3-diglycosides occurring in the same plant have been reported, e.g. of isomeric quercetin 3-xylosylglucosides in *Heuchera micrantha* (Wilkins and Bohm, 1976), but until the nature of the isomerism is clear, it is not appropriate to include such variation in Table 5.7.

It is worth remembering here that the presence of impurities in glycoside samples can interfere both with the measurement of  $R_F$  values and also with sugar analyses. It is also important that sugar:aglycone ratios be determined wherever possible. This was not done on what appeared to be kaempferol 7,4'-diglucoside, isolated earlier from an acylated complex present in *Asplenium* (Harborne *et al.*, 1973) because of shortage of material. A recent reinterpretation of the UV spectrum and shifts (J. B. Harborne, unpublished results) now indicates that this compound must also have a glucose residue in the 3-position and is the so far undescribed 3,7,4'-triglucoside of kaempferol. A related trisubstituted kaempferol derivative containing glucose and rhamnose and with the same spectral properties has also been isolated from *Coronilla* leaves, and trisubstitution was confirmed in this case by methylation and hydrolysis to yield kaempferol 5-methyl ether. These two substances represent the first known examples of kaempferol glycosides with sugars present at three different hydroxyl groups in the flavonoid moiety; full details of their structural analyses will be published later.

One simplification to the earlier 1975 review of flavonol glycosides can now be made: the removal of foeniculin from the list. At that time, four quercetin 3-L-arabinosides were mentioned: two of known structure, the  $\alpha$ -arabofuranoside avicularin and the  $\alpha$ -arabopyranoside, guajaverin; and two of incompletely determined structure, the  $\beta$ -arabinoside polystachoside from *Polygonum polystachyum* and the arabinoside, foeniculin, from fennel *Foeniculum vulgare* (Umbelliferae). Recent studies by Jarman and Crowden (1977) of foeniculin, which occurs widely in plants of the Epacridaceae, have confirmed on the basis of enzymic and  $R_F$  data that it is different from both avicularin and polystachoside. Nevertheless, its m.p. is close to that of guajaverin and indeed, a direct  $R_F$  comparison in many solvent systems (J. B. Harborne, unpublished data) with an authentic sample of guajaverin, kindly supplied by H. Geiger, showed foeniculin to be identical with it. One final question remains to be answered with these compounds; is the sugar moiety of polystachoside in the furano- or pyrano- form?

## 5.7. DISTRIBUTION PATTERNS IN PLANTS

Most of the work recorded in this chapter refers to the isolation and identification of individual glycosides from single plant taxa. In addition to these detailed investigations, the flavone and flavonol glycosides present in a much wider range of plants have been surveyed over the past five years. New glycosides are often first detected during such surveys. In addition much new information on distribution patterns of known derivatives has accumulated. In most recent chemotaxonomic investigations of flavonoids, glycosidic patterns have been determined and, in many cases, significant correlations with morphological groupings have become apparent.

The discovery in liverworts of a range of interesting and unusual flavone glycosides has already been mentioned (Section 5.5). Distribution patterns of these compounds in Bryophyta have been reviewed by Markham and Porter (1978). Chemotaxonomic aspects of flavone and flavonol glycosides in ferns have also been the subject of a recent review (Cooper-Driver, 1980). Although flavones and flavonols are widespread in gymnosperms, their glycosides have not been extensively studied except in a few genera such as *Pinus* and *Larix*; recent work is summarized by Niemann (1979).

In the case of the angiosperms, so many papers have appeared on distribution patterns that only a small selection can be referred to here. At the species level, the detailed investigation of 35 flavonol glycosides variously present in 26 populations of *Anthyllis vulneraria* deserves mention (Gonnet, 1978). At the generic level, extensive surveys have been carried out in the following genera, among others: *Anacyclus* (Greger, 1978), *Hazardia* (Clark and Mabry, 1978), *Solanum* (Wietschel, 1978), *Sorbus* (Challice and Kovanda, 1978) and *Veronica* (Grayer-Barkmeijer, 1978). At the family level, reviews of known glycosides have appeared for the Celastraceae (Brüning and Wagner, 1978), Compositae (Harborne, 1977), Oleaceae (Harborne and Green, 1980) and Solanaceae (Harborne and Swain, 1979). With regard to monocotyledonous families, glycosidic patterns have been reported in a number of families, including Bromeliaceae, Cyperaceae, Gramineae and Orchidaceae; for references, see the latest paper on Araceae (Williams *et al.*, 1981).

In spite of all these investigations, our knowledge of the glycosidic complexity of flavones and flavonols is still remarkably fragmentary, and further studies cannot but uncover a yet wider range of these conjugates among vascular plants.

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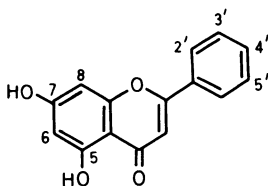
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### CHECK LIST OF KNOWN FLAVONE GLYCOSIDES



#### 5,7-Dihydroxyflavone (*Chrysin*)

- 1 5-Glucoside (toringin)
- 2 7-Glucoside (aequinetin)
- 3 7-Galactoside\*
- 4 7-Glucuronide
- 5 7-Rutinoside

#### 7,4'-Dihydroxyflavone

- 6 7-Glucoside
- 7 7-Rutinoside

#### 3',4'-Dihydroxyflavone

- 8 4'-Glucoside\*

#### 5,6,7-Trihydroxyflavone (*Baicalein*)

- 9 6-Glucoside
- 10 6-Glucuronide
- 11 7-Rhamnoside
- 12 7-Glucuronide

#### *Baicalein 6-methyl ether*

- 13 7-Glucoside
- 14 7-Glucuronide

#### *Baicalein 7-methyl ether*

- 15 5-Glucuronide
- 16 5-Glucuronosylglucoside

#### 5,7-Dihydroxy-8-methoxyflavone (*Wogonin*)

- 17 7-Glucuronide\*

#### 7,3',4'-Trihydroxyflavone

- 18 7-Glucoside
- 19 7-Rutinoside

#### 7,4'-Dihydroxy-3'-methoxyflavone

- 20 7-Glucoside

#### 5,2'-Dihydroxy-7-methoxyflavone

- 21 2'-Glucoside (echioidin)

#### 5,7,4'-Trihydroxyflavone (*Apigenin*)

- 22 5-Glucoside
- 23 7-Arabinoside\*
- 24 7-Xyloside\*
- 25 7-Rhamnoside
- 26 7-Glucoside (cosmosiin)

- 27 7-Galactoside
- 28 7-Glucuronide
- 29 7-Galacturonide\*
- 30 7-Methylgalacturonide
- 31 4'-Glucoside
- 32 4'-Glucuronide\*
- 33 7-Arabinosylglucoside\*
- 34 7-Xylosyl (1→2) glucoside
- 35 7-Rutinoside
- 36 7-Neohesperidoside
- 37 7-Rhamnosylglucuronide
- 38 7-Sophoroside
- 39 7-Apiosylglucoside (apiin)
- 40 7-Xylosylglucuronide
- 41 7-Rhamnosylglucuronide\*
- 42 7-Diglucuronide\*
- 43 7,4'-Diglucoside
- 44 7,4'-Diglucuronide
- 45 7-Glucuronide-4'-rhamnoside\*
- 46 4'-Diglucoside
- 47 7-Rutinoside-4'-glucoside\*
- 48 7-Neohesperidoside-4'-glucoside\*
- 49 7-Diglucuronide-4'-glucuronide\*
- 50 7-Neophesperidoside-4'-sophoroside\*
- 51 7-(4''-p-Coumaroyl)glucoside\*
- 52 7-(2''-Acetyl)glucoside\*
- 53 7-(6''-Acetyl)glucoside\*
- 54 7-(Malonyl)glucoside
- 55 7-Glucoside-4'-p-coumarate
- 56 7-Glucoside-4'-caffeate
- 57 4'-(2'',6''-Di-p-coumaroyl)glucoside\*
- 58 7-(Malonyl)apiosylglucoside
- 59 7-Rutinoside-4'-caffeate
- 60 7-Glucosidesulphate\*
- 61 7-sulphate\*

#### *Apigenin 7-methyl ether (Genkwanin)*

- 62 5-Glucoside
- 63 4'-Glucoside
- 64 5-Xylosylglucoside

#### *Apigenin 4'-methyl ether (Acacetin)*

- 65 7-Glucoside (tilianine)
- 66 7-Glucuronide
- 67 7-Rutinoside (linarin)
- 68 7-Neohesperidoside (fortunellin)
- 69 7-Diglucoside
- 70 7-Rhamnosylgalacturonide
- 71 7-Glucuronosyl(1→2)glucuronide
- 72 7-(6''-Acetyl)glucoside\*
- 73 7-(4'''-Acetyl)rutinoside\*

- 74 7-[2''-(2-Methyl)butyryl]rutinoside\*
- 75 7-[3''-(2-Methyl)butyryl]rutinoside\*
- 76 7-Glucosyl(1→2)glucosyl(1→2)  
[2,4-diacetylramnosyl](1→6)-3-acetyl-  
glucoside\*
- Apigenin 5,7-dimethyl ether*
  - 77 4'-Galactoside\*
- Apigenin 7,4'-dimethyl ether*
  - 78 5-Xylosylglucoside
- 6-Hydroxyapigenin*
  - 79 5-Glucuronide
  - 80 6-Xyloside\*
  - 81 6-Glucuronide\*
  - 82 7-Rhamnoside
  - 83 7-Glucuronide
  - 84 4'-Arabinoside
  - 85 7-Xylosyl(1→4)rhamnoside
  - 86 7-Rutinoside
  - 87 7-Diglucoside
  - 88 7,4'-Dirhamnoside
  - 89 7-(Sinapoyl)glucuronide
- Scutellarein 6-methyl ether (Hispidulin)*
  - 90 7-Glucoside (homoplantagin)
  - 91 7-Glucuronide
  - 92 7-Rutinoside\*
- Scutellarein 7-methyl ether*
  - 93 6-Rhamnosyl(1→4)xyloside\*
- Scutellarein 4'-methyl ether*
  - 94 6-Glucoside\*
  - 95 7-Glucuronide\*
  - 96 6-Sophoroside\*
  - 97 7-[p-Coumaroyl]glucosyl  
(1→2)mannoside]
- Scutellarein 6,7-dimethyl ether*
  - 98 4'-Glucoside
  - 99 4'-Rutinoside
- Scutellarein 6,4'-dimethyl ether  
(Pectolarigenin)*
  - 100 7-Glucoside\*
  - 101 7-Glucuronide\*
  - 102 7-Glucuronic acid methyl ester\*
  - 103 7-Rutinoside
  - 104 7-(4''-Acetyl)rutinoside)\*
  - 105 7-Acetylrutinoside
- Scutellarein 7,4'-dimethyl ether*
  - 106 6-Glucoside
- Scutellarein 6,7,4'-trimethyl ether*
  - 107 5-Glucoside\*
- 8-Hydroxyapigenin (Isoscutellarein)*
  - 108 8-Glucuronide\*
  - 109 4'-Mannosyl(1→2)glucoside\*
  - 110 7-(Acetyl)sophoroside\*
- 8-Hydroxyapigenin 4'-methyl ether*
  - 111 8-Glucuronide\*
  - 112 8-Xylosylglucoside\*
  - 113 7-(6'''-Acetyl)allosyl(1→2)glucoside\*
- 5,7,3',4'-Tetrahydroxyflavone (Luteolin)*
  - 114 5-Glucoside (Galuteolin)
  - 115 5-Galactoside\*
  - 116 7-Glucoside
  - 117 7-Galactoside
  - 118 7-Glucuronide
  - 119 7-Galacturonide\*
  - 120 3'-Glucoside
  - 121 3'-Glucuronide\*
  - 122 3'-Galacturonide\*
  - 123 4'-Arabinoside\*
  - 124 4'-Glucoside
  - 125 4'-Glucuronide\*
  - 126 7-Arabinosylglucoside\*
  - 127 7-Xylosylglucoside
  - 128 7-Glucosylarabinoside
  - 129 7-Rutinoside
  - 130 7-Neohesperidoside (veronicastroside)
  - 131 7-Gentiobioside\*
  - 132 7-Sophoroside\*
  - 133 7-Laminaribioside
  - 134 7-Digalactoside\*
  - 135 7-Glucosylgalactoside
  - 136 7-Galactosylglucoside\*
  - 137 7-Glucosylglucuronide
  - 138 7-Apiosylglucoside
  - 139 7,3'-Diglucoside
  - 140 7-Glucuronide-3'-rhamnoside\*
  - 141 7-Glucuronide-4'-rhamnoside\*
  - 142 7-Glucuronide-3'-glucoside\*
  - 143 7,3'-Diglucuronide\*
  - 144 7,3'-Digalacturonide\*
  - 145 7-Galactoside-4'-glucoside\*
  - 146 7,4'-Diglucuronide\*
  - 147 3',4'-Diglucoside\*
  - 148 3',4'-Diglucuronide\*
  - 149 3',4'-Digalacturonide\*
  - 150 7-Glucosylarabinoside-4'-glucoside\*
  - 151 7-Rutinoside-4'-glucoside
  - 152 7-Neohesperidoside-4'-glucoside\*
  - 153 7-Glucoside-4'-neohesperidoside\*
  - 154 7-Glucuronide-3',4'-dirhamnoside\*
  - 155 7,4'-Diglucuronide-3'-glucoside\*
  - 156 7,3',4'-Triglucuronide\*

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- 157 7-Neohesperidoside-4'-sophoroside\*
- 158 7-*p*-Coumaroylglucoside
- 159 7-Glucuronide-3'-feruloylglucoside\*
- 160 7,4'-Diglucuronide-3'-feruloylglucoside\*
- 161 7-Glucosidesulphate\*
- 162 7-Sulphate-3'-glucoside
- 163 7-Rutinosidesulphate\*
- 164 7-Sulphate-3'-rutinoside\*
- 165 7-Sulphate\*
- 166 3'-Sulphate\*
- 167 4'-Sulphate\*
- 168 7,3'-Disulphate\*

### *Luteolin 5-methyl ether*

- 169 7-Glucoside\*

### *Luteolin 7-methyl ether*

- 170 4'-Rhamnoside
- 171 4'-Gentiobioside
- 172 5-Xylosylglucoside

### *Luteolin 3'-methyl ether (Chrysoeriol)*

- 173 5-Glucoside\*
- 174 7-Xyloside\*
- 175 7-Rhamnoside\*
- 176 7-Glucoside
- 177 7-Glucuronide
- 178 4'-Glucoside\*
- 179 5-Diglucoside\*
- 180 7-Arabinofuranosyl(1→2)galactoside
- 181 7-Rutinoside
- 182 7-Rhamnosylglucuronide\*
- 183 7-Digalactoside
- 184 7-Apiosylglucoside
- 185 7-Allosyl(1→2)glucoside\*
- 186 5,4'-Diglucoside\*
- 187 7,4'-Diglucoside\*
- 188 7-Glucuronide-4'-rhamnoside\*
- 189 7-Sophorotrioside\*
- 190 7-(Malonyl)glucoside
- 191 7-*p*-Coumaroylglucosylglucuronide
- 192 7-(6'''-Acetyl)glucosyl(1→2)mannoside
- 193 7-Glucosidesulphate\*
- 194 7-Sulphate\*

### *Luteolin 4'-methyl ether (Diosmetin)*

- 195 7-Glucoside
- 196 7-Glucuronide
- 197 7- $\alpha$ -[Glucosyl(1→6)arabinoside]
- 198 7- $\beta$ -[Glucosyl(1→6)arabinoside]
- 199 7-Xylosylglucoside\*
- 200 7-Rutinoside(diosmin)
- 201 7-Sophoroside\*
- 202 7-(4<sup>G</sup>-Rhamnosylneohesperidoside)\*
- 203 7-Sulphate\*

- 204 3'-Sulphate\*

- 205 7,3'-Disulphate\*

### *Luteolin 7,3'-dimethyl ether*

- 206 4'-Glucoside
- 207 4'-Apiosylglucoside

### *Luteolin 7,4'-dimethyl ether*

- 208 5-Xylosylglucoside

### *Luteolin 3',4'-dimethyl ether*

- 209 7-Rhamnoside\*
- 210 7-Glucuronide\*

### *Luteolin 7,3',4'-trimethyl ether*

- 211 5-Glucoside

### *6-Hydroxyluteolin*

- 212 6-Xyloside\*
- 213 6-Glucoside\*
- 214 6-Glucuronide\*
- 215 7-Arabinoside\*
- 216 7-Xyloside\*
- 217 7-Glucoside
- 218 7-Galactoside
- 219 7-Glucuronide
- 220 7-Apioside\*
- 221 7-Rhamnosyl(1→4)xyloside\*
- 222 7-Diglucoside
- 223 7-Arabinoside-4'-rhamnoside\*

### *6-Methoxyluteolin*

- 224 7-Glucoside
- 225 7-Rutinoside

### *6-Hydroxyluteolin 7-methyl ether*

- 226 6-Glucoside (pedaliin)
- 227 6-Galactoside\*
- 228 6-Galactosylglucoside\*

### *6-Hydroxyluteolin 3'-methyl ether*

- 229 7-Diglucoside\*

### *6-Hydroxyluteolin 6,7-dimethyl ether (Cirsiliol)*

- 230 4'-Glucoside

### *6-Hydroxyluteolin 6,3'-dimethyl ether*

- 231 7-Rhamnoside\*
- 232 7-Glucoside
- 233 7-(6''-Caffeoyl)glucoside

### *6-Hydroxyluteolin 6,4'-dimethyl ether*

- 234 7-Glucoside
- 235 7-Rutinoside

### *6-Hydroxyluteolin 7,3'-dimethyl ether*

- 236 6-Glucoside\*

### *6-Hydroxyluteolin 6,7,3'-trimethyl ether (Cirsilineol)*

- 237 4'-Glucoside

*8-Hydroxyluteolin (Hypolaetin)*

- 238 7-Glucoside
- 239 8-Glucuronide\*
- 240 8,4'-Diglucuronide\*
- 241 8-Glucoside-3'-sulphate\*
- 242 8-Sulphate\*

*Hypolaetin 3'-methyl ether*

- 243 7-Glucoside\*
- 244 7-Mannosyl(1→2)glucoside\*

*5,7,3',4'-Tetrahydroxy-6,8-dimethoxyflavone*

- 245 7-Glucoside\*

*5,7,3'-Trihydroxy-6,8,4'-trimethoxyflavone (Acerosin)*

- 246 5-(6''-Acetyl)glucoside\*

*5,7,4'-Trihydroxy-6,8,3'-trimethoxyflavone*

- 247 7-Glucoside\*

*5,7,3',4',5'-Pentahydroxyflavone (tricetin)*

- 248 7-Glucoside
- 249 3'-Glucoside
- 250 3'-Sulphate\*
- 251 3'-Disulphate\*

*Tricetin 3'-methyl ether*

- 252 7-Glucoside\*
- Tricetin 3',5'-dimethyl ether (Tricin)*

- 253 5-Glucoside
- 254 5-Diglucoside
- 255 7-Glucoside
- 256 7-Glucuronide
- 257 4'-Glucoside\*
- 258 7-Rutinoside
- 259 7-Neohesperidoside\*
- 260 7-Diglucoside\*
- 261 7-Fructosylglucoside\*
- 262 7-Rhamnosylglucuronide\*
- 263 7-Diglucuronide
- 264 5,7-Diglucoside\*
- 265 7-Rutinoside-4'-glucoside\*
- 266 7-Glucosidesulphate\*

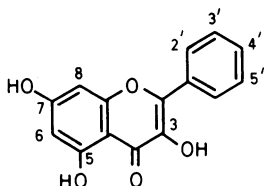
*5,7,2,4',5'-Pentahydroxyflavone (Isoetin)*

- 267 7-Glucoside\*
- 268 2'-Arabinoside\*
- 269 2'-Glucoside\*
- 270 2'-Xylosylarabinosylglucoside\*
- 271 4'-or 5'-Glucoside\*

**Key to check list**

In all cases except where otherwise indicated, all sugars can be assumed to be in the pyranose form and have the appropriate linkage to aglycone or between sugars ( $\beta$ - for glucosides, galactosides, glucuronides, xylosides, etc.;  $\alpha$ - for rhamnosides, arabinosides). With arabinosides,  $\beta$ - linkages are not uncommon and are so indicated where they are known. The glycosides of a given flavone aglycone are listed in sequence: monoglycosides, diglycosides, triglycosides, tetraglycosides, acylated glycosides, sulphated derivatives. Where the di- or tri-saccharide is well known, the trivial name is used: sophorose, Glc $\beta$ 1 → 2Glc; laminaribiose, Glc $\beta$ 1 → 3Glc; gentiobiose, Glc $\beta$ 1 → 6Glc; maltose, Glc $\alpha$ 1 → 4Glc; rutinose, Rha $\alpha$ 1 → 6Glc; neohesperiodose, Rha $\alpha$ 1 → 2Glc; robinobiose, Rha $\alpha$ 1 → 6Gal; sambubiose, Xyl $\beta$ 1 → 2Glc; vicianose, Ara $\alpha$ 1 → 6Glc. An asterisk indicates that the compound is newly reported during the period 1975–1980.

**CHECK LIST OF KNOWN FLAVONOL GLYCOSIDES**



*3,5-Dihydroxy-6-methoxyflavone*

- 1 3-Rutinoside\*

*3,5,7-Trihydroxyflavone (Galangin)*

- 2 3-Rhamnoside\*

- 3 3-Glucoside\*

- 4 7-Glucoside\*

- 5 3-Rutinoside

- 6 3-Galactosyl (1→4) rhamnoside\*

*3-Methylgalangin*

- 7 7-Glucoside\*

*3,7,4'-Trihydroxyflavone*

- 8 3-Glucoside

- 9 7-Glucoside

- 10 4'-Glucoside

- 11 7-Rutinoside



## 306 The Flavonoids

### 8-Hydroxygalangin 7-methyl ether

- 12 8-Acetate\*
- 13 8-Butyrate\*

### 3,7,3',4'-Tetrahydroxyflavone (Fisetin)

- 14 3-Glucoside
- 15 7-Glucoside
- 16 7-Rutinoside

### 3,7,4'-Trihydroxy-3'-methoxyflavone (Geraldol)

- 17 4'-Glucoside

### 3,5,7,4'-Tetrahydroxyflavone (Kaempferol)

- 18 3-Arabinofuranoside (juglanin)
- 19 3-Xyloside\*
- 20 3-Rhamnoside (afzelin)
- 21 3-Glucoside (astragalin)
- 22 3-Galactoside (trifolin)
- 23 3-Glucuronide
- 24 3-Alloside\* (asiaticalin)
- 25 5-Glucoside
- 26 7-Arabinoside\*
- 27 7-Xyloside\*
- 28 7-Rhamnoside
- 29 7-Glucoside (populnin)
- 30 7-Galactoside\*
- 31 4'-Rhamnoside\*
- 32 4'-Glucoside\*
- 33 3-Xylosylrhamnoside\*
- 34 3-Rhamnosylxyloside\*
- 35 3-Arabinosyl (1→6) galactoside\*
- 36 3-Xylosylgalactoside\*
- 37 3-Rutinoside
- 38 3-Neohesperidoside\*
- 39 3-Rhamnosyl (1→3) glucoside (rungsioside)
- 40 3-Glucosyl (1→4) rhamnoside\*
- 41 3-Sambubioside
- 42 3-Xylosylglucoside
- 43 3-Gentiobioside
- 44 3-Sophoroside
- 45 3-Robinobioside
- 46 3-Rhamnosyl (1→2) galactoside\*
- 47 3-Glucosyl (1→6) galactoside\*
- 48 3-Galactosylglucoside\*
- 49 3-Apiosylglucoside
- 50 3-Digalactoside
- 51 3-Arabinoside-7-rhamnoside\*
- 52 3-Rhamnoside-7-arabinoside\*
- 53 3-Glucoside-7-arabinoside\*
- 54 3-Xyloside-7-rhamnoside
- 55 3-Glucoside-7-xyloside\*
- 56 3,7-Dirhamnoside
- 57 3,7-Diglucoside

### 58 3,7-Digalactoside

- 59 3-Glucoside-7-rhamnoside
- 60 3-Rhamnoside-4'-arabinoside
- 61 3,4'-Diglucoside\*
- 62 3-Glucosyl- $\beta$ -(1→4) arabinofuranosyl- $\alpha$ -(1→2) arabinopyranoside (primflasin)
- 63 3-Glucosylxylosylarabinoside\*
- 64 3-Rhamnosyl (1→2) rhamnosyl (1→6) glucoside\*
- 65 (2<sup>G</sup>-Rhamnosylrutinoside)\*
- 66 3-(2<sup>G</sup>-Rhamnosylgentiobioside)\*
- 67 3-(2<sup>G</sup>-Glucosylrutinoside)
- 68 3-(2<sup>G</sup>-Glucosylgentiobioside)\*
- 69 3-Glucosyl (1→2) gentiobioside\*
- 70 3-Sophorotrioside
- 71 3- $\beta$ -Maltosyl (1→6) glucoside
- 72 3-Rhamnosylglucosylgalactoside\*
- 73 3-(2'-Rhamnosyllaminaribioside)
- 74 3-Rhamnosylarabinoside-7-rhamnoside
- 75 3-Glucosylxyloside-7-xyloside\*
- 76 3-Rhamnosylxyloside-7-glucoside\*
- 77 3-Glucosylrhamnoside-7-rhamnoside\*
- 78 3-Rutinoside-7-rhamnoside\*
- 79 3-Rhamnosylgalactoside-7-arabinoside\*
- 80 3-Robinobioside-7-rhamnoside (robinin)
- 81 3-Robinobioside-7-glucoside
- 82 3-Lathyroside-7-rhamnoside
- 83 3-Rutinoside-7-glucoside
- 84 3-Rutinoside-7-galactoside
- 85 3-Rutinoside-7-glucuronide
- 86 3-Sophoroside-7-rhamnoside
- 87 3-Sophoroside-7-glucoside
- 88 3-Glucoside-7-gentiobioside\*
- 89 3-Sambubioside-7-glucoside
- 90 3-Rutinoside-4'-diglucoside\*
- 91 3-Sophorotrioside-7-rhamnoside
- 92 3,7,4'-Triglucoside
- 93 3-(2''-p-Coumaroyl) arabinoside\*
- 94 3-(3''-p-Coumaroyl) glucoside\*
- 95 3-(6''-p-Coumaroyl) glucoside (tiliroside)
- 96 3-(6''-Feruloyl) glucoside\*
- 97 3-Benzoylglucoside
- 98 3-p-Hydroxybenzoylglucoside
- 99 3-(2''-Galloyl) glucoside\*
- 100 3-(6''-Galloyl) glucoside\*
- 101 7-(6''-Succinyl) glucoside\*
- 102 3-(Di-p-coumaroyl) glucoside\*
- 103 3-(6''-p-Coumaroyl) acetylglucoside\*
- 104 3-(3''-p-Coumaroyl-6''-feruloyl) glucoside\*
- 105 3-(4''-Caffeoyl) laminaribioside-7-rhamnoside\*
- 106 3-(Feruloylsophoroside) (petunoside)
- 107 3-Benzoylglucoside-7-glucoside

- 108 3-(*p*-Hydroxybenzoylglucoside)-7-glucoside
- 109 3-(6''-Acetyl) glucosyl (1→4) rhamnoside
- 110 3-(6''-Acetyl) glucoside-7-rhamnoside\*
- 111 3-(6''-Acetyl) glucoside-7-glucoside\*
- 112 3-(*p*-Coumaroylsophorotrioside)
- 113 3-Glucosyl (1→3) (4''-acetyl) rhamnosyl (1→6) galactoside
- 114 3-(Feruloylsophorotrioside)
- 115 3-(2''-Sinapoyl) sophoroside-7-glucoside\*
- 116 3- $\alpha$ -(6''-Sulphate) glucoside\*
- 117 3-Rhamnosylsulphate\*
- 118 3-Glucuronide-7-sulphate\*
- 119 3-(6''-Sulphate) gentiobioside\*
- 120 7-Sulphate\*
- 121 3,7-Disulphate\*

*Kaempferol 3-methyl ether*  
122 7-Rutinoside

*Kaempferol 5-methyl ether*  
123 3-Galactoside

*Kaempferol 7-methyl ether (Rhamnocitrin)*  
124 3-Glucoside\*  
125 3-Glucuronide  
126 3-Rutinoside\*  
127 3-Rhamnosyl (1→3) rhamnosyl (1→6) galactoside (alaternin)  
128 4'-Rhamnosyl (1→4) rhamnosyl (1→6) galactoside (catharticin)  
129 3-Sulphate\*

*Kaempferol 4'-methyl ether (Kaempferide)*  
130 3-Glucuronide\*  
131 3-Diglucoside

*Kaempferol 3,4'-dimethyl ether*  
132 7-Glucoside

*Kaempferol 7,4'-dimethyl ether*  
133 3-Sulphate

*6-C-Methylkaempferol*  
134 3-Glucoside\*

*6-Hydroxykaempferol*  
135 7-Glucoside\*

*6-Hydroxykaempferol 3-methyl ether*  
136 6-Glucoside\*  
137 7-Glucoside\*

*6-Hydroxykaempferol 5-methyl ether*  
138 4'-Rhamnoside  
139 3-Arabinosylrhamnoside

*6-Hydroxykaempferol 6-methyl ether (Eupafolin)*  
140 3-Glucoside\*

- 141 3-Galactoside\*
- 142 7-Glucoside\*
- 143 3-Rutinoside\*

*6-Hydroxykaempferol 7-methyl ether*  
144 6-Rhamnosyl (1→4) xyloside\*

*6-Hydroxykaempferol 4'-methyl ether*  
145 3,7-Dirhamnoside\*

*6-Hydroxykaempferol 3,6-dimethyl ether*  
146 7-Glucoside

*6-Hydroxykaempferol 6,7-dimethyl ether (Eupalitin)*

- 147 3-Rhamnoside (eupalin)
- 148 3-Galactoside
- 149 3-Diglucoside

*6-Hydroxykaempferol 3,6,7-trimethyl ether*  
150 4'-Glucoside

*6-Hydroxykaempferol 6,7,4'-trimethyl ether (Mikanin)*  
151 3-Galactoside\*

*8-Hydroxykaempferol (Herbacetin)*

- 152 3-Glucoside
- 153 7-Arabinoside\*
- 154 7-Glucoside
- 155 8-Xyloside\*
- 156 8-Rhamnoside\*
- 157 8-Glucoside
- 158 8-Glucuronide\*
- 159 4'-Arabinoside\*
- 160 4'-Glucoside\*
- 161 4'-Glucuronide\*
- 162 8-Rutinoside\*
- 163 8-Gentiobioside\*
- 164 8-Arabinoside-4'-xyloside\*
- 165 8-(3''-Acetyl) xyloside\*
- 166 4'-(Acetyl) arabinoside
- 167 8-(Diacetyl) glucoside\*
- 168 8-Acetate\*
- 169 8-Butyrate\*
- 170 4'-(Diacetyl) xyloside\*
- 171 4'-(Triacetyl) xyloside\*

*Herbacetin 7-methyl ether*  
172 8-Acetate\*  
173 8-Butyrate\*

*Herbacetin 8-methyl ether*

- 174 3-Glucoside\*
- 175 3-Rutinoside\*
- 176 3-Rhamnosylglucoside-7-rhamnoside

*Herbacetin 7,8-dimethyl ether*  
177 3-Rhamnoside\*

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### *Herbacetin 7,4'-dimethyl ether*

178 8-Acetate\*

179 8-Butyrate\*

### *Quercetin*

180 3- $\alpha$ -L-Arabinofuranoside (avicularin)

181 3- $\alpha$ -L-Arabinopyranoside (guajaverin)

182 3- $\beta$ -L-Arabinoside (polystachoside)

183 3-Xyloside (reynoutrin)

184 3-Rhamnoside (quercitrin)

185 3-Glucoside (isoquercitrin)

186 3- $\beta$ -Galactoside (hyperin)

187 3- $\alpha$ -Galactoside\*

188 3-Glucuronide (miquelianin)

189 3-Galacturonide\*

190 5-Glucoside

191 7-Arabinoside\*

192 7-Rhamnoside

193 7-Glucoside (quercimeritrin)

194 7- $\alpha$ -Galactoside

195 7- $\beta$ -Galactoside\*

196 3'-Xyloside\*

197 3'-Glucoside

198 4'-Glucoside (spiraeoside)

199 3-Diarabinoside

200 3-Rhamnosylarabinoside

201 3-Vicianoside

202 3-Arabinosyl (1 $\rightarrow$ 6) galactoside\*

203 3-Galactosylarabinoside

204 3-Dixyloside\*

205 3-Rhamnosylxyloside

206 3-Xylosylglucoside\*

207 3-Xylosylgalactoside

208 3-Rutinoside (rutin)

209 3-Neohesperidoside

210 3-Glucosyl (1 $\rightarrow$ 4) rhamnoside\*

211 3-Robnobioside\*

212 3-Gentiobioside

213 3-Sophoroside

214 3-Galactosylglucoside\*

215 3-Glucosylmannoside\*

216 3-Glucosylglucuronide

217 3-Digalactoside

218 3-Galactosylglucuronide\*

219 7-Rutinoside

220 3,5-Digalactoside

221 3-Arabinoside-7-glucoside

222 3-Glucoside-7-arabinoside\*

223 3-Xyloside-7-glucoside

224 3-Galactoside-7-xyloside

225 3,7-Dirhamnoside

226 3-Rhamnoside-7-glucoside

227 3-Glucoside-7-rhamnoside

228 3-Galactoside-7-rhamnoside

229 3,7-Diglucoside

230 3-Galactoside-7-glucoside\*

231 3,7-Diglucuronide

232 3,3'-Diglucoside

233 3,4'-Diglucoside

234 7,4'-Diglucoside

235 3-Rhamnosyl (1 $\rightarrow$ 2) rutinoside\*

236 3-(2<sup>G</sup>-Rhamnosylrutinoside)\*

237 3-Rhamnosylrobinobioside\*

238 3-(2<sup>G</sup>-Glucosylrutinoside)

239 3-(2<sup>G</sup>-Rhamnosylgentiobioside)\*

240 3-Glucosyl (1 $\rightarrow$ 6) glucosyl (1 $\rightarrow$ 4) rhamnoside\*

241 3-(2<sup>G</sup>-Apiosylrutinoside)\*

242 3-Sophorotrioside

243 3-Glucosyl (1 $\rightarrow$ 2) gentiobioside\*

244 3-(2<sup>G</sup>-Glucosylgentiobioside)

245 3-Dixyloside-7-glucoside\*

246 3-Xylosylglucoside-7-glucoside

247 3-Rutinoside-7-glucoside

248 3-Glucoside-7-rutinoside

249 3-Rutinoside-7-galactoside

250 3-Robnobioside-7-rhamnoside

251 3-Robnobioside-7-glucoside

252 3-Rutinoside-7-glucuronide

253 3-Gentiobioside-7-glucoside\*

254 3-Sophoroside-7-glucoside

255 3-Sambubioside-7-glucoside

256 3-Sambubioside-3'-glucoside

257 3-(2<sup>G</sup>-Rhamnosylrutinoside)-7-glucoside\*

258 3-Rhamnosyldigluco-7-glucoside\*

259 3-Rutinoside-7,3'-bisglucoside\*

260 3-Rutinoside-4'-diglucoside\*

261 7-Triglucoside\*

262 3-(6''-p-Coumaroyl) glucoside\* (helichrysoside)

263 3-(3''-p-Coumaroyl) glucoside\*

264 3-Isoferuloylglucuronide\*

265 3-(3''-Acetyl)- $\alpha$ -arabinofuranoside\*

266 3-(3''-Acetyl) rhamnoside\*

267 3-(4''-Acetyl) rhamnoside\*

268 3-(6''-Acetyl) glucoside\*

269 3-(2''-Galloyl) glucoside\*

270 3-(6''-Galloyl) glucoside\*

271 3-(2''-Galloyl) galactoside\*

272 3-(6''-Galloyl) galactoside

273 3-Malonylglucoside

274 3-(3'',6''-Di-p-coumaroyl) glucoside\*

275 3-Glucosyl (1 $\rightarrow$ 3)-4'''-acetylramnosyl (1 $\rightarrow$ 6) galactoside\*

276 3-p-Coumaroylsophoroside-7-rhamnoside\*

- 277 3-Caffeoylsophoroside-7-glucoside  
 278 3-Acetylsophoroside-7-rhamnoside\*  
 279 3-(*p*-Coumaroylsophorotrioside)  
 280 3-(Feruloylsophorotrioside)  
 281 3-Rhamnoside-7-glucoside-4'-(caffeoylgalactoside)  
 282 7-Acetyl-3'-glucoside  
 283 7-(6''-Tiglyl) glucoside\*  
 284 3-Rhamnosidesulphate\*  
 285 3-Glucuronide-7-sulphate\*  
 286 3-Rutinosidesulphate\*  
 287 3-Acetyl-7,3',4'-trisulphate\*  
 288 3-Sulphate  
 289 3,4'-Disulphate\*  
 290 3,7,4'-Trisulphate\*  
 291 3,7,3',4'-Tetrasulphate  
  
*Quercetin 3-methyl ether*  
 292 5-Glucoside\*  
 293 7-Glucoside  
 294 7-Diglucoside-4'-glucoside  
  
*Quercetin 5-methyl ether (Azaleatin)*  
 295 3-Arabinoside\*  
 296 3-Rhamnoside (azalein)  
 297 3-Galactoside  
 298 3-Glucuronide  
 299 3-Xylosylarabinoside\*  
 300 3-Rhamnosylarabinoside\*  
 301 3-Arabinosylgalactoside  
 302 3-Rutinoside\*  
 303 3-Diglucoside  
  
*Quercetin 7-methyl ether (Rhamnetin)*  
 304 3- $\alpha$ -L-Arabinofuranoside  
 305 3- $\alpha$ -L-Arabinopyranoside  
 306 3-Glucoside\*  
 307 3-Galactoside  
 308 3'-Glucuronide\*  
 309 3- $\alpha$ -Diarabinoside  
 310 3- $\beta$ -Diarabinoside  
 311 3-Rutinoside\*  
 312 3-Rhamninoside  
 313 3-Rhamnosyl (1 $\rightarrow$ 2) rhamnosyl (1 $\rightarrow$ 6) galactoside\*  
 314 3-Sulphate\*  
 315 3'-Glucuronide-3,5,4'-trisulphate\*  
  
*Quercetin 3'-methyl ether (Isorhamnetin)*  
 316 3- $\alpha$ -L-Arabinopyranoside (distichin)  
 317 3- $\alpha$ -L-Arabinofuranoside\*  
 318 3-Xyloside\*  
 319 3-Glucoside  
 320 3-Galactoside  
 321 3-Glucuronide  
 322 5-Glucoside  
 323 3-Arabinosyl (1 $\rightarrow$ 2) rhamnoside  
 324 3-Arabinosyl (1 $\rightarrow$ 6) glucoside\*  
 325 3-Xylosylglucoside\*  
 326 3-Dirhamnoside  
 327 3-Rutinoside (narcissin)  
 328 3-Rhamnosylgalactoside  
 329 3-Sophoroside\*  
 330 3-Gentiobioside  
 331 3-Lactoside\*  
 332 3-Arabinoside-7-glucoside  
 333 3-Glucoside-7-arabinoside  
 334 3-Glucoside-7-xyloside\*  
 335 3-Glucoside-7-rhamnoside  
 336 3,7-Diglucoside  
 337 3-Galactoside-7-glucoside  
 338 3-Glucoside-4'-rhamnoside  
 339 3,4'-Diglucoside (dactylin)  
 340 3-Xylosylrutinoside  
 341 3-Xylosylrhamnosylgalactoside\*  
 342 3-Rhamnosylrutinoside\*  
 343 3-Rutinosylglucoside  
 344 3-Glucosylrhamnosylgalactoside  
 345 3-Galactosylrhamnosylgalactoside\*  
 346 3-Arabinoside-7-rhamnoside\*  
 347 3-Rutinoside-7-glucoside\*  
 348 3-Sophoroside-7-rhamnoside  
 349 3-Sophoroside-7-glucoside  
 350 3-Glucoside-7-gentiobioside\*  
 351 3-Galactoside-4'-glucoside\*  
 352 3-(6''-Acetyl) glucoside\*  
 353 3-(6''-Acetyl) galactoside\*  
 354 3-Rutinosidesulphate\*  
 355 3-Glucuronide-7-sulphate\*  
 356 3-Sulphate\*  
 357 7-Sulphate  
 358 3,7-Disulphate\*  
  
*Quercetin 4'-methyl ether (Tamarixetin)*  
 359 3-Glucoside (tamarixin)  
 360 3-Rutinoside  
 361 3-Sulphate  
  
*Quercetin 3,5-dimethyl ether (Caryatin)*  
 362 3'-(or 4'-) Glucoside\*  
  
*Quercetin 5,3'-dimethyl ether*  
 363 3-Glucoside\*  
  
*Quercetin 7,3'-dimethyl ether (Rhamnazin)*  
 364 3-Glucoside  
 365 3-Rhamnoside  
 366 3-Rhamnosyl (1 $\rightarrow$ 4) rhamnosyl (1 $\rightarrow$ 6) galactoside\*  
 367 3-Sulphate

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### *Quercetin 7,4'-dimethyl ether (Ombuin)*

- 368 3-Galactoside\*
- 369 3-Rutinoside (ombuoside)
- 370 3-Neohesperidoside\*
- 371 3,5-Diglucoside

### *Quercetin 3',4'-Dimethyl ether*

- 372 3-Rutinoside\*

### *Quercetin 7,3',4'-Trimethyl ether*

- 373 3-Digalactoside\*

### *6-Hydroxyquercetin (Quercetagetin)*

- 374 3-Rhamnoside\*
- 375 3-Glucoside (tagetiin)
- 376 7-Glucoside
- 377 3,7-Diglucoside\*

### *Quercetagetin 3-methyl ether*

- 378 7-Glucoside\*
- 379 7-Sulphate\*

### *Quercetagetin 6-methyl ether (Patuletin)*

- 380 3-Xyloside\*
- 381 3-Rhamnoside\*
- 382 3-Glucoside
- 383 3-Galactoside
- 384 3-Glucuronide
- 385 7-Glucoside
- 386 3-Rutinoside
- 387 3-Diglucoside
- 388 3,7-Dirhamnoside\*
- 389 3-Acetylglucoside\*
- 390 3-Glucoside-7-sulphate
- 391 3-Sulphate\*
- 392 7-Sulphate

### *Quercetagetin 7-methyl ether*

- 393 3-Glucoside\*

### *Quercetagetin 3'-methyl ether*

- 394 7-Glucoside

### *Quercetagetin 3,6-dimethyl ether*

- 395 7-Glucoside\* (axillaroside)

### *Quercetagetin 3,7-dimethyl ether*

- 396 6-Glucoside\*
- 397 6-Galactoside\*
- 398 4'-Glucoside\*

### *Quercetagetin 6,7-dimethyl ether (Eupatolitin)*

- 399 3-Rhamnoside (eupatolin)
- 400 3-Glucoside
- 401 3-Galactoside
- 402 3-Sulphate\*

### *Quercetagetin 6,3'-dimethyl ether*

- 403 7-Glucoside\*
- 404 3-Rutinoside\*

### *Quercetagetin 3,6,7-trimethyl ether*

- 405 4'-Glucoside\*

### *Quercetagetin 3,6,3'-trimethyl ether*

- 406 7-Glucoside (jacein)

### *Quercetagetin 3,7,4'-trimethyl ether*

- 407 6-Glucoside\*
- 408 3'-Glucoside\*

### *Quercetagetin 6,7,3'-trimethyl ether*

(*Veronicafolin*)

- 409 3-Rutinoside\*
- 410 3-Digalactoside\*
- 411 3-Sulphate\*

### *Quercetagetin 6,7,4'-trimethyl ether (Eupatin)*

- 412 3-Sulphate\*

### *Quercetagetin 7,3',4'-trimethyl ether*

- 413 3-Rhamnoside

### *Quercetagetin 3,6,7,3'-tetramethyl ether*

- 414 4'-Glucoside (chrysosplenin)

### *Quercetagetin 3,6,7,3',4'-pentamethyl ether*

(*Artemetin*)

- 415 5-Glucosylrhamnoside\*

### *8-Hydroxyquercetin (Gossypetin)*

- 416 3-Glucoside
- 417 3-Galactoside
- 418 3-Glucuronide
- 419 7-Glucoside
- 420 8-Glucoside
- 421 3-Sulphate\*
- 422 3-Gentiotrioside

### *Gossypetin 7-methyl ether*

- 423 3-Arabinoside\*
- 424 3-Rhamnoside\*
- 425 3-Galactoside\*
- 426 8-Glucoside\*
- 427 3-Galactoside-8-glucoside\*
- 428 3-Rhamnoside-8-acetate\*

### *Gossypetin 8-methyl ether*

- 429 3-Galactoside

### *Gossypetin 3'-methyl ether*

- 430 3-Rutinoside\*
- 431 7-(6''-Acetyl) glucoside\*

### *Gossypetin 7,4'-dimethyl ether*

- 432 8-Glucoside
- 433 8-Acetate\*
- 434 8-Butyrate\*

### *Gossypetin 8,3'-dimethyl ether*

- 435 3-Rutinoside\*

*Myricetin*

- 436 3-Arabinoside
- 437 3-Xyloside\*
- 438 3-Rhamnoside (myricitrin)
- 439 3-Glucoside
- 440 3-Galactoside
- 441 7-Glucoside
- 442 3'-Arabinoside
- 443 3'-Glucoside (cannabiscitrin)
- 444 3-Dixyloside\*
- 445 3-Xylosylglucoside\*
- 446 3-Xylosylgalactoside\*
- 447 3-Rutinoside
- 448 3-Diglucoside\*
- 449 3-Galactosylglucoside\*
- 450 3-Digalactoside
- 451 3,3'-Digalactoside
- 452 3-Rhamnosylrutinoside\*
- 453 3-Rutinoside-7-rhamnoside
- 454 3-Rutinoside-7-glucoside\*
- 455 3-Robinoside-7-rhamnoside
- 456 3-Triglucoside\*
- 457 3-(2''-Acetyl) rhamnoside\*
- 458 3-(6''-Galloyl) glucoside\*
- 459 3-(6''-Galloyl) galactoside\*
- 460 3-Rhamnosidesulphate\*

*Myricetin 3-methyl ether*

- 461 3'-Glucoside

*Myricetin 5-methyl ether*

- 462 3-Rhamnoside
- 463 3-Galactoside

*Myricetin 7-methyl ether (Europetin)*

- 464 3-Rhamnoside

*Myricetin 3'-methyl ether (Laricitrin)*

- 465 3-Rhamnoside\*
- 466 3-Glucoside\*
- 467 3-Galactoside\*
- 468 3-Rutinoside\*
- 469 3-Rhamnosylrutinoside\*
- 470 3-Rutinoside-7-glucoside\*
- 471 3-*p*-Coumaroylglucoside\*

*Myricetin 4'-methyl ether*

- 472 3-Rhamnoside (mearnsitrin)
- 473 3-Galactosyl (1→4) galactoside

*Myricetin 3',5'-dimethyl ether (Syringetin)*

- 474 3-Rhamnoside\*
- 475 3-Glucoside
- 476 3-Galactoside\*
- 477 3-Glucuronide\*
- 478 3-Rutinoside\*
- 479 3-Rhamnosylrutinoside\*
- 480 3-Rutinoside-7-glucoside\*
- 481 3-*p*-Coumaroylglucoside\*

*6-Hydroxymyricetin 6,3',5'-trimethyl ether*

- 482 3-Glucoside\*

*6-Hydroxymyricetin 4,6,3',5'-tetramethyl ether*

- 483 7-Glucoside\*

*8-Hydroxymyricetin (Hibiscetin)*

- 484 3-Glucoside
- 485 8-Glucosylxyloside\*

*3,5,7,2'-Tetrahydroxyflavone (Datiscetin)*

- 486 3-Rutinoside

## CHAPTER SIX

# *The Minor Flavonoids*

BRUCE A. BOHM

### 6.1 GENERAL INTRODUCTION

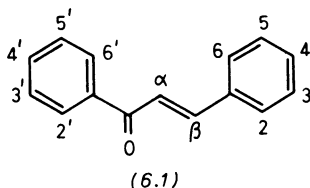
As defined for the present treatment the minor flavonoids consist of chalcones, aurones (including auronols), dihydrochalcones (including  $\beta$ -oxygenated derivatives), flavanones and dihydroflavonols. The first three types were covered in Chapter 9 of 'The Flavonoids' while the latter two were discussed in Chapter 11. The approach adopted for the present review is essentially the same as for the above two chapters. The compounds in each class are presented and discussed in order of increasing hydroxylation of the B ring, i.e. none, one, two or three hydroxyl groups. Within each subgroup the compounds are covered roughly in order of increasing complexity of A-ring substitution. In this way readers may follow the material in this review in parallel with corresponding structural types in the earlier chapters.

Sections 6.2–6.6 of this review focus on structures but also make many references to distribution. However, in the case of compounds enjoying wide distribution only new or unusual reports are mentioned in the text. New records for families are indicated and family names are shown parenthetically following the appearance of each genus for the first time. All occurrences of flavonoids of the five classes which I have found in the literature since appearance of *The Flavonoids* are presented in tabulated form. Some references overlooked during preparation of the earlier work have also been included.

### 6.2 CHALCONES

#### 6.2.1 Introduction

It may be useful to remind the reader that chalcone numbering is different from the system used for flavonoid types that possess heterocyclic rings. In chalcones the A ring, always written to the left, is given the primed numbers, while the B-ring carbons are given the unprimed numbers. The positions are shown numbered in structure (6.1). Bridge carbons are marked relative to the carbonyl function.

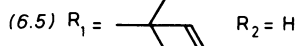
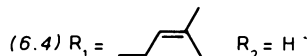
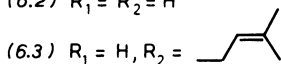
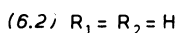
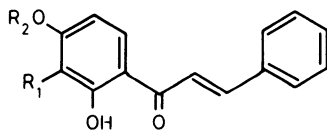


### 6.2.2 Structures of naturally occurring chalcones

Structures of naturally occurring chalcones are summarized in Tables 6.1 and 6.2. A summary of natural sources appears in Table 6.10.

#### (a) Chalcones lacking B-ring hydroxyls

The simplest member of this subgroup is 2',4'-dihydroxychalcone (6.2) whose discovery in *Flourensia heterolepis* (Compositae) was reported by Bohlmann and Jakupovic (1979). Compounds based upon either *O*- or *C*-prenylation of the parent compound are known. The 4'-prenyl ether (6.3), known as 'derricidin' or 'cordoin', has been found in *Derris floribunda* (Braz Filho *et al.*, 1975b) and in *Lonchocarpus* species (De Lima *et al.*, 1973; Delle Monache *et al.*, 1978)



(both Leguminosae). 2',4'-Dihydroxy-3'-prenylchalcone (4), whose trivial names are 'isocordoin' and 'flemistricin-A', is also known from *Derris* (Braz Filho *et al.*, 1975b), *Lonchocarpus* (De Lima *et al.*, 1973) and *Flemingia* (Rao *et al.*, 1976). A compound isomeric to structure (6.4) has also been isolated from *Lonchocarpus* by Delle Monache *et al.* (1974, 1978). Called ' $\psi$ -isocordoin' by those authors, the compound is the 2',4'-dihydroxy-3'-*C*-( $-\alpha,\alpha$ -dimethylallyl) chalcone shown as structure (6.5).

Ring closure of the alkyl side chain of isocordoin (6.4) with the 4'-hydroxyl group affords the dimethylchromenochalcone 'lonchocarpin' (6.6) known from *Derris* (Braz Filho *et al.*, 1975b), *Pongamia glabra* (Leguminosae) (Subramanyam *et al.*, 1977) and *Lonchocarpus* (Delle Monache *et al.*, 1978). Several closely related compounds have been isolated from species of *Flemingia* (Leguminosae). Rao and co-workers (1976) isolated 'flemistricin-C' (6.7) and 'flemistricin-B' (6.8) from *F. stricta* while compound (6.9), 'flemichapparin-A', was described by Adityachaudhury and co-workers (1973) as a constituent of



Table 6.1 Structures of naturally occurring chalcones

| OH       | OCH <sub>3</sub> | Substituents                                    | Other       | No. in text | Trivial name         | Source*                         | References                            |
|----------|------------------|-------------------------------------------------|-------------|-------------|----------------------|---------------------------------|---------------------------------------|
| 2',4'    |                  |                                                 |             | (6.2)       |                      | <i>Flourensia heterolepis</i>   | Bohlmann and Jakupovic (1979)         |
| 2',4'    |                  |                                                 | 4'-O-Prenyl | (6.3)       | Derricidin           | <i>Derris floribunda</i>        | Braz Filho <i>et al.</i> (1975b)      |
|          |                  |                                                 |             |             | Cordoin              | <i>Lonchocarpus</i> sp.         | De Lima <i>et al.</i> (1972, 1973)    |
| 2',4'    |                  |                                                 | 3'-C-Prenyl | (6.4)       | Isocordoin           | <i>Lonchocarpus</i> sp.         | De Lima <i>et al.</i> (1973)          |
|          |                  |                                                 |             |             | Flemi-<br>strictin-A | <i>Flemingia stricta</i>        | Rao <i>et al.</i> (1975a, 1976)       |
|          |                  |                                                 |             |             | ψ-Isocordoin         | <i>Derris floribunda</i>        | Braz Filho <i>et al.</i> (1975b)      |
| 2',4'    |                  | 3'-(α-Dimethyl-allyl)                           |             | (6.5)       |                      | <i>Lonchocarpus</i> sp.         | Delle Monache <i>et al.</i> (1974)    |
|          | 2'               | Furano-<br>(2'',3'',4',3')                      |             | (6.10)      | Ovalitenin-A         | <i>Milletia ovalifolia</i>      | Gupta and Krishnamurti (1977b)        |
| 2'       |                  | 6'',6''-Dimethyl-<br>pyrano-<br>(2'',3'',4',3') |             | (6.6)       | Lonchocarpin         | <i>Derris floribunda</i>        | Braz Filho <i>et al.</i> (1975b)      |
|          |                  |                                                 |             |             |                      |                                 |                                       |
| 2',4'    | 3'               |                                                 |             | (6.11)      |                      | <i>Pongamia glabra</i>          | Subramanyam <i>et al.</i> (1977)      |
| 2',4',6' |                  |                                                 |             | (6.12)      |                      | <i>Zuccagnia punctata</i>       | Pederiva <i>et al.</i> (1975)         |
|          |                  |                                                 |             |             |                      | <i>Helichrysum acutatum</i>     | Bohlmann and Abraham (1979c)          |
|          |                  |                                                 |             |             |                      | <i>H. polycladum</i>            | Bohlmann <i>et al.</i> (1980c)        |
|          |                  |                                                 |             |             |                      | <i>Populus</i> spp.             | Wollenweber and Weber (1973)          |
|          |                  |                                                 |             |             |                      | <i>Adiantum sulphureum</i>      | Wollenweber (1979)                    |
| 2',4'    | 6'               |                                                 |             | (6.13)      |                      | <i>Alnus</i> spp.               | Wollenweber <i>et al.</i> (1974)      |
|          |                  |                                                 |             |             |                      | <i>Betula</i> spp.              | Wollenweber <i>et al.</i> (1974)      |
| 2',6'    | 4'               |                                                 |             | (6.14)      |                      | <i>Populus</i> spp.             | Wollenweber <i>et al.</i> (1974)      |
|          |                  |                                                 |             |             |                      | <i>Adiantum sulphureum</i>      | Wollenweber (1979)                    |
|          |                  |                                                 |             |             |                      | <i>Pityrogramma chrysoconia</i> | Wollenweber (1979)                    |
|          |                  |                                                 |             |             |                      | <i>Onychium auratum</i>         | Ramakrishnan <i>et al.</i> (1974)     |
|          |                  |                                                 |             |             |                      | <i>Notholaena</i> spp.          | Wollenweber (1977a)                   |
|          |                  |                                                 |             |             |                      | <i>Cheilanthes</i> spp.         | Wollenweber (1977a)                   |
|          |                  |                                                 |             |             |                      | <i>Helichrysum</i> spp.         | Bohlmann <i>et al.</i> (1979c, 1980c) |

Table 6.1 (Contd.)

| OH       | OCH <sub>3</sub> | Substituents                                    | No. in text | Trivial name                           | Source*                                                                         |            | References                                                                                              |
|----------|------------------|-------------------------------------------------|-------------|----------------------------------------|---------------------------------------------------------------------------------|------------|---------------------------------------------------------------------------------------------------------|
| 2'       | 4',6'            |                                                 | (6.15)      | Flavokawin-B                           | <i>Aniba riparia</i><br><i>Pityrogramma triangularis</i><br>var. <i>pallida</i> | Lau<br>Fil | Fernandes <i>et al.</i> (1978)<br>Wollenweber <i>et al.</i> (1980b)<br>Wollenweber <i>et al.</i> (1980) |
| 2',4',6' |                  | 3'-C-Prenyl                                     | (6.16)      |                                        | <i>Didymocarpus corchorifolia</i>                                               | Ges        | Bohlmann <i>et al.</i> (1979c, 1980c)                                                                   |
| 2',6'    | 4'               | 3'-C-Prenyl                                     | (6.17)      |                                        | <i>Helichrysum</i> spp.                                                         | Com        | Bohlmann <i>et al.</i> (1979c)                                                                          |
| 2'       | 4',6'            | 3'-C-Prenyl                                     | (6.18)      |                                        | <i>H. cymosum</i> ssp. <i>calvum</i>                                            | Com        | Gupta and Krishnamurti (1977a)                                                                          |
| 2',5'    |                  | 6'',6''-Dimethyl-<br>pyrano-<br>(2'',3'',4',3') | (6.9)       | Ovalichalkone<br>Flemi-<br>chapparin-A | <i>Milletia ovalifolia</i><br><i>Flemingia chappari</i>                         | Leg<br>Leg | Adityachaudhury <i>et al.</i> (1973)                                                                    |
| 2'       | 6'               | 6'',6''-Dimethyl-<br>pyrano-<br>(2'',3'',4',3') | (6.20)      | Ponga-<br>chalcone-I                   | <i>Pongamia glabra</i>                                                          | Leg        | Subramanyam <i>et al.</i> (1977)                                                                        |
|          | 2',6',β          | 6'',6''-Dimethyl-<br>pyrano-<br>(2'',3'',4',3') | (6.21)      | Praecano-<br>sone-A                    | <i>Tephrosia praecans</i>                                                       | Leg        | Camele <i>et al.</i> (1980)                                                                             |
| β        | 2',6'            | 6'',6''-Dimethyl-<br>pyrano-<br>(2'',3'',4',3') | (6.22)      | Praecano-<br>sone-B                    | <i>Tephrosia praecans</i>                                                       | Leg        | Camele <i>et al.</i> (1980)                                                                             |
| 2',4',6' |                  | 3'-C-Geranyl                                    | (6.24)      | Cannabigerol                           | <i>Helichrysum</i><br><i>umbraculigerum</i><br><i>H. sutherlandii</i>           | Com<br>Com | Bohlmann and Hoffmann (1979)<br>Bohlmann <i>et al.</i> (1978)                                           |
| 2'       | 2',6'            | 3',4'-Methylene-<br>dioxy                       | (6.34)      |                                        | <i>H. sutherlandii</i>                                                          | Com        | Bohlmann <i>et al.</i> (1978)                                                                           |
| 2',6'    | 4',5',6'         | 3'-C-Methyl                                     | (6.29)      | Triangularin                           | <i>Pityrogramma triangularis</i>                                                | Fil        | Star <i>et al.</i> (1978)                                                                               |
| 2'       | 3',4',6'         |                                                 | (6.36)      |                                        | <i>Popowia cauliflora</i>                                                       | Ano        | Panichpol and Waterman (1978)                                                                           |
|          | 2',3',4',6'      |                                                 | (6.37)      |                                        | <i>Popowia cauliflora</i>                                                       | Ano        | Panichpol and Waterman (1978)                                                                           |
| 2'       | 4',6'            | 3'-C-Methyl                                     | (6.30)      | Aurentiacin                            | <i>Didymocarpus aurentiaca</i><br><i>Pityrogramma</i> spp.                      | Ges<br>Fil | Adityachaudhury <i>et al.</i> (1976)<br>Wollenweber <i>et al.</i> (1980b)                               |

|          |             |                                        |         |                         |                                 |     |                                       |
|----------|-------------|----------------------------------------|---------|-------------------------|---------------------------------|-----|---------------------------------------|
| 2',4'    | 6'          | 5'-C-Methyl                            | (6.30a) | Aurentiacin-A           | <i>Didymocarpus aurentiacum</i> | Ges | Adityachaudhury and Daskanungo (1975) |
| 2',4'    | 3',6'       |                                        | (6.33)  |                         | <i>Dalea</i> spp.               | Leg | Dominguez <i>et al.</i> (1980)        |
| 2',6'    | 3',4'       |                                        | (6.38)  | Pashanone               | <i>Polygonatum senegalense</i>  | Lil | Maradufu and Ouma (1978)              |
|          |             |                                        |         |                         | <i>Didymocarpus pedicellata</i> | Ges | Agarwal <i>et al.</i> (1973)          |
| 2',4'    | 3',5',6'    |                                        | (6.39)  | Isodidymocarpin         | <i>Onychium auratum</i>         | Fil | Ramakrishnan <i>et al.</i> (1974)     |
|          |             |                                        |         |                         | <i>Didymocarpus pedicellata</i> | Ges | Bhattacharyya <i>et al.</i> (1979)    |
| 2'       | 3',4',5',6' |                                        | (6.40)  | Kanakugiol              | <i>Popowia cauliflora</i>       | Ano | Waterman and Pootakahn (1979)         |
| 2',4'    | 6'          | 3',5'-di-C-Methyl                      | (6.31)  |                         | <i>Myrica gale</i>              | Myr | Malterud <i>et al.</i> (1977)         |
| 2',4',4' |             |                                        | (6.41)  | Isoliquiritigenin       | <i>Sophora tomentosa</i>        | Leg | Komatsu <i>et al.</i> (1978)          |
|          |             |                                        |         |                         | <i>Dalbergia ecastophyllum</i>  | Leg | Matos <i>et al.</i> (1975)            |
|          |             |                                        |         |                         | <i>D. retusa</i>                | Leg | Manners <i>et al.</i> (1974)          |
|          |             |                                        |         |                         | <i>D. sericea</i>               | Leg | Parthasarathy <i>et al.</i> (1976)    |
|          |             |                                        |         |                         | <i>Onobrychis viciifolia</i>    | Leg | Ingham (1978)                         |
|          |             |                                        |         |                         | <i>Medicago</i> spp.            | Leg | Ingham (1979)                         |
|          |             |                                        |         |                         | <i>Machaerium mucronulatum</i>  | Leg | Kurosawa <i>et al.</i> (1978)         |
|          |             |                                        |         |                         | <i>Lespedeza cyrtobotrya</i>    | Leg | Miyase <i>et al.</i> (1980)           |
| 2',4',4' | 4'          | 3'-C-Glucose                           | (6.49)  |                         | <i>Dahlia tenuicaulis</i>       | Com | Lam and Wrang (1975)                  |
| 2',4'    |             | 5'-Formyl                              | (6.48)  | Neobavachalcone         | <i>Cladrastis platycarpa</i>    | Leg | Ohashi <i>et al.</i> (1977)           |
|          |             |                                        |         |                         | <i>Psoralea corylifolia</i>     | Leg | Gupta <i>et al.</i> (1975b, 1977)     |
| 4',4'    | 2'          | 5'-Formyl                              |         | Isonobavachalcone       | <i>Psoralea corylifolia</i>     | Leg | B. K. Gupta <i>et al.</i> (1980)      |
| 2',4',4' |             | 3'-C-Prenyl                            | (6.42)  | 4-Hydroxyisocordoin     | <i>Lonchocarpus</i> sp.         | Leg | Delle Monache <i>et al.</i> (1974)    |
| 2',4'    | 4'          | 3'-C-Prenyl                            | (6.43)  | 4-Hydroxyderricin       | <i>Lonchocarpus</i> sp.         | Leg | Delle Monache <i>et al.</i> (1974)    |
| 2',4'    |             | 6'',6''-Dimethylpyrano-(2'',3'',4',5') | (6.45)  | 4-Hydroxy-loncho-carpin | <i>Angelica keiskei</i>         | Umb | Kozawa <i>et al.</i> (1977)           |
|          |             | 3'-C-Geranyl                           | (6.44)  | Xanthoangelol           | <i>Derris floribunda</i>        | Leg | Braz Filho <i>et al.</i> (1975b)      |
| 2',4',4' |             |                                        |         |                         | <i>Angelica keiskei</i>         | Umb | Kozawa <i>et al.</i> (1977)           |
|          |             |                                        |         |                         | <i>Lespedeza cyrtobotrya</i>    | Leg | Miyase <i>et al.</i> (1980)           |

Table 6.1 (Contd.)

| OH                            | Substituents<br>OCH <sub>3</sub> | Other                                          | No. in<br>text   | Trivial<br>name                     | Source*                                                                                    | References                                                                                               |
|-------------------------------|----------------------------------|------------------------------------------------|------------------|-------------------------------------|--------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| 2',4',6',4                    |                                  |                                                | (6.50)           | Isosalipurpol                       | <i>Petunia hybrida</i>                                                                     | de Vlaming and Kho (1976)                                                                                |
|                               | 4-O-Glucose                      |                                                | (6.52)           |                                     | <i>Nothofagus antartica</i>                                                                | Wollenweber and Wiermann (1979)                                                                          |
|                               | 2'-O-Glucose                     |                                                | (6.51)           | Isosali-<br>purposide               | <i>Acacia cyanophylla</i><br><i>Salix rubra</i>                                            | Imperato (1978)<br>Vinokurov (1979)                                                                      |
|                               |                                  |                                                |                  |                                     | <i>Oenothera hookeri</i><br>ssp. <i>venusta</i>                                            |                                                                                                          |
| 2',4',4                       | 6'                               |                                                | (6.54)           |                                     | <i>Ruellia</i> spp.                                                                        | Dement and Raven (1974)                                                                                  |
|                               |                                  |                                                | (6.55)           | Gnaphalin                           | <i>Helichrysium heterolasium</i><br><i>Gnaphalium multiceps</i>                            | Bloom (1976)<br>Bohlmann and Abraham (1979b)<br>Maruyama <i>et al.</i> (1974); Ahluwalia and Rami (1976) |
| 2',4                          | 4'-O-Glucose                     |                                                | (6.56)           |                                     | <i>G. affine</i>                                                                           | Aritomi and Kawasaki (1974)                                                                              |
| 2',6'                         |                                  |                                                | (6.57)           |                                     | <i>Viscum album</i>                                                                        | Becker <i>et al.</i> (1978)                                                                              |
| 2'                            | 4',6',4                          |                                                | (6.59)           |                                     | <i>Pterozonium brevifrons</i>                                                              | Wollenweber (1979)                                                                                       |
| 2',4                          | 4',5',6'                         |                                                | (6.60)           |                                     | <i>Dahlia tenuicaulis</i>                                                                  | Lam and Wrang (1975)                                                                                     |
| 2',4                          | 4',5',6',4                       |                                                | (6.58)           |                                     | <i>Chromolaena odorata</i><br><i>Chromolaena odorata</i><br><i>Helichrysium glomeratum</i> | Barua <i>et al.</i> (1978)<br>Barua <i>et al.</i> (1978)<br>Bohlmann and Suwita (1979c)                  |
| 4',4                          | 2                                |                                                | (6.62)           | Echinatin                           | <i>Glycyrrhiza echinata</i>                                                                | Saitoh <i>et al.</i> (1975)                                                                              |
| 4',4                          | 2                                | 5-C-( $\alpha$ -Dimethyl)-<br>allyl            | (6.63)           | Licochal-<br>cone-A                 | <i>G. glabra</i>                                                                           | Saitoh and Shibata (1975)                                                                                |
| 4',3,4                        | 2                                |                                                | (6.64)           | Licochal-<br>cone-B                 | <i>G. glabra</i>                                                                           | Saitoh and Shibata (1975)                                                                                |
| 2',4',3,4, $\alpha$<br>2',3,4 |                                  | 6'',6''-Dimethyl<br>pyrano(2'',3'',4',3')      | (6.78)<br>(6.73) | 3,4-Dihydro-<br>xylon-<br>chocarpin | <i>Peltogyne</i> spp.<br><i>Derris floribunda</i>                                          | Malan and Roux (1974)<br>Braz Filho <i>et al.</i> (1975b)                                                |
| 2',4                          | 3                                | 6'',6''-Dimethyl-<br>pyrano<br>(2'',3'',4',3') | (6.74)           | Ponga-<br>chalkone-II               | <i>Pongamia glabra</i>                                                                     | Sharma <i>et al.</i> (1973); Subramanyam <i>et al.</i> (1977)                                            |

|              |                                                                                    |        |                        |                                                                                                                                                           |                                        |                                                                                                                                      |
|--------------|------------------------------------------------------------------------------------|--------|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| 2'           | 6'',6''-Dimethyl-<br>pyrano<br>(2'',3'',4',3')-<br>and 3,4-Methyl-<br>enedioxy     | (6.75) | Glabra-<br>chromene-II | <i>Pongamia glabra</i>                                                                                                                                    | Leg                                    | Sharma <i>et al.</i> (1973);<br>Subramanyam <i>et al.</i> (1977)                                                                     |
| 2'           | 6' 6'',6''-Dimethyl-<br>pyrano-<br>(2'',3'',4',3')-<br>and 3,4-Methyl-<br>enedioxy | (6.76) | Glabra-<br>chromene    | <i>Pongamia glabra</i>                                                                                                                                    | Leg                                    | Subramanyam <i>et al.</i> (1977)                                                                                                     |
| 2'           | Furano(2'',3'',-<br>4',3')-and 3,4-<br>methylene-<br>dioxy                         | (6.77) | Ovalitenin-C           | <i>Milletia ovalifolia</i>                                                                                                                                | Leg                                    | Islam <i>et al.</i> (1980)                                                                                                           |
| 2',4',3,4    |                                                                                    | (6.65) | Butein                 | <i>Machaerium mucronulatum</i><br><i>Bidens laevis</i>                                                                                                    | Ana<br>Com                             | Kurosawa <i>et al.</i> (1978)<br>Scogin and Zakar (1976)                                                                             |
|              | 4'-O-Glucose                                                                       | (6.66) | Coreopsisin            | <i>Pyrrhopappus</i> spp.<br><i>Helianthus</i> spp.<br><i>Viguiera laciniata</i><br><i>Bidens</i> spp.<br><i>Coreopsis bigelovii</i><br><i>Bidens</i> spp. | Com<br>Com<br>Com<br>Com<br>Com<br>Com | Harborne (1977a)<br>Harborne and Smith (1978)<br>Harborne and Smith (1978)<br>Hart (1979)<br>Nicholls and Bohm (1979)<br>Hart (1979) |
|              | 4'-O-Glucosyl-<br>glucose                                                          | (6.67) |                        |                                                                                                                                                           |                                        |                                                                                                                                      |
|              | 2',3-di-O-Glucose                                                                  | (6.68) |                        | <i>Coreopsis bigelovii</i><br><i>Rhus</i> spp.<br><i>Amphiterygium adstrigens</i>                                                                         | Com<br>Ana<br>Ana                      | Nicholls and Bohm (1979)<br>Young (1979)<br>Young (1976)                                                                             |
| 2',4',3      | 4'-O-Arabinosyl-<br>galactose                                                      | (6.69) |                        | <i>Bauhinia purpurea</i>                                                                                                                                  | Leg                                    | Bhartiya <i>et al.</i> (1979)                                                                                                        |
| 2',4',4      |                                                                                    | (6.70) |                        | <i>Dahlia tenuicaulis</i>                                                                                                                                 | Com                                    | Lam and Wrang (1975)                                                                                                                 |
| 2',4'        |                                                                                    | (6.71) |                        | <i>Iryanthera polyneura</i>                                                                                                                               | Myt                                    | de Almeida <i>et al.</i> (1979)                                                                                                      |
| 2',3',4',3,4 |                                                                                    | (6.72) |                        | <i>Iryanthera polyneura</i>                                                                                                                               | Myt                                    | de Almeida <i>et al.</i> (1979)                                                                                                      |
|              |                                                                                    | (6.80) | Okandin                | <i>Albizia adianthifolia</i>                                                                                                                              | Leg                                    | Candy <i>et al.</i> (1978)                                                                                                           |
|              | 4'-O-Glucose                                                                       | (6.81) | Marein                 | <i>Coreopsis bigelovii</i>                                                                                                                                | Com                                    | Nicholls and Bohm (1979)                                                                                                             |

Table 6.1 (Contd.)

| OH           | OCH <sub>3</sub> | Substituents<br>Other                       | No. in<br>text | Trivial<br>name                | Source*                                                                                                                                                                                                                | References                                                                                                                                                                                                         |
|--------------|------------------|---------------------------------------------|----------------|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2',4',3,4    | 3'               | 4'-O-Glucose                                | (6.82)         | Lanceoletin<br>Lanceolin       | <i>C. nucensis</i><br><i>C. grandiflora</i><br><i>Bidens</i> spp.<br><i>B. laevis</i><br><i>Coreopsis bigelovii</i><br><i>C. bigelovii</i><br><i>C. nucensis</i><br><i>C. grandiflora</i><br><i>Bidens pilosa</i> s.l. | Harborne (1977a)<br>Crawford and Smith (1980)<br>Hart (1979)<br>Scogin and Zakar (1976)<br>Nicholls and Bohm (1979)<br>Nicholls and Bohm (1979)<br>Harborne (1977a)<br>Crawford and Smith (1980)<br>Ballard (1975) |
| 2',3',4',4   | 3                |                                             | (6.82a)        | 3-O-Methyl-<br>okanin          | <i>Bidens pilosa</i> s.l.                                                                                                                                                                                              | Com                                                                                                                                                                                                                |
| 2',3',4'     | 3,4              |                                             | (6.82b)        | 3,4-Di-O-<br>methyl-<br>okanin | <i>B. pilosa</i> s.l.                                                                                                                                                                                                  | Com                                                                                                                                                                                                                |
| 2',4',5',3,4 | 5'               | 4'-O-Glucose                                | (6.83)         | Stillopsin                     | <i>Coreopsis bigelovii</i>                                                                                                                                                                                             | Com                                                                                                                                                                                                                |
| 2',4'        |                  | 3,4-Methylene-<br>dioxy                     | (6.84)         | Prosogerin-B                   | <i>Prosopis spicigera</i>                                                                                                                                                                                              | Leg                                                                                                                                                                                                                |
| 2',3         | 4',6',4          |                                             | (6.85)         |                                | <i>Merillia caloxylon</i>                                                                                                                                                                                              | Rut                                                                                                                                                                                                                |
| 2'           | 4',6',3,4        |                                             | (6.86)         |                                | <i>M. caloxylon</i>                                                                                                                                                                                                    | Rut                                                                                                                                                                                                                |
| 2'           | 4',6'            | 3'-C-Prenyl and-<br>3,4-methyl-<br>enedioxy | (6.87)         | Ovali-<br>chalkone-A           | <i>Milletia ovalifolia</i>                                                                                                                                                                                             | Leg                                                                                                                                                                                                                |
| 2',4'        | 6',2,4           |                                             | (6.88)         | Cerasin                        | <i>Prunus cerasus</i>                                                                                                                                                                                                  | Ros                                                                                                                                                                                                                |
| 2'           | 4',6',2,4        |                                             | (6.89)         | Cerasidin                      | <i>P. cerasus</i><br><i>Terminalia arjuna</i><br><i>Chromolaena odorata</i><br><i>Merrillea caloxylon</i><br><i>Derris robusta</i>                                                                                     | Ros<br>Cmb<br>Com<br>Rut<br>Leg                                                                                                                                                                                    |
| 2'           | 4',5',6',3,4     |                                             | (6.90)         |                                |                                                                                                                                                                                                                        |                                                                                                                                                                                                                    |
| 2',3         | 4',6',4,5        |                                             | (6.91)         |                                |                                                                                                                                                                                                                        |                                                                                                                                                                                                                    |
| 2'           | 4',6',2,4,5      |                                             | (6.92)         | Rubone                         |                                                                                                                                                                                                                        |                                                                                                                                                                                                                    |

\* Key: Aca = Acanthaceae, Ana = Anacardiaceae, Ano = Anonaceae, Bet = Betulaceae, Cmb = Combretaceae, Com = Compositae, Fag = Fagaceae, Fil = Filicinae, Ges = Gesneriaceae, Lau = Lauraceae, Leg = Leguminosae, Lil = Liliaceae, Lor = Loranthaceae, Myr = Myrtaceae, Myt = Myristicaceae, Ona = Onagraceae, Ros = Rosaceae, Rut = Rutaceae, Sal = Salicaceae, Sol = Solanaceae, Umb = Umbelliferae.

Table 6.2 Structures of chalcones having complex substituents

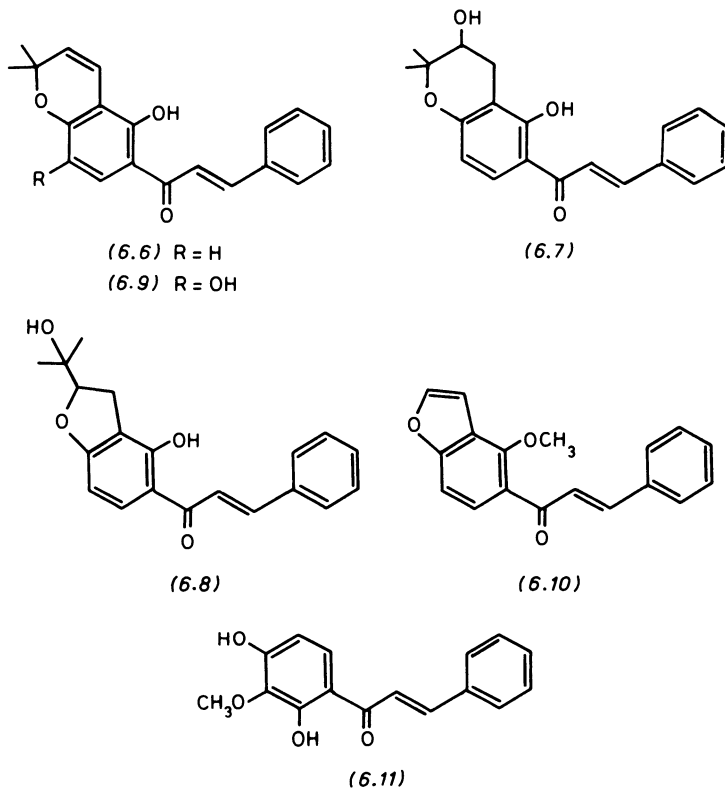
| Name                                                       | No.                | Source*                                       | References                       |
|------------------------------------------------------------|--------------------|-----------------------------------------------|----------------------------------|
| Flemistricitin-B                                           | (6.8)              | <i>Flemingia stricta</i>                      | Rao <i>et al.</i> (1976)         |
| Flemistricitin-C                                           | (6.7)              | <i>F. stricta</i>                             | Rao <i>et al.</i> (1976)         |
| 4'-O-Methyl-4-deoxybavachromanol                           | (6.19)             | <i>Helichrysum cymosum</i> spp. <i>calvum</i> | Bohlmann <i>et al.</i> (1979c)   |
| (-)-Rubranine                                              | (6.23)             | <i>Aniba rosaeodora</i>                       | de Alleluia <i>et al.</i> (1978) |
| 5,7-Dihydroxy-8-cinnamoyl-4-phenyl-2H-1-benzopyran-2-ones† | (6.26, 6.27, 6.28) | <i>Pityrogramma trifoliata</i>                | Dietz <i>et al.</i> (1980)       |
| Ceroptin                                                   | (6.32)             | <i>P. triangularis</i>                        | Star <i>et al.</i> (1975a, b)    |
| Bavachromanol                                              | (6.46)             | <i>Psoralea corylifolia</i>                   | Suri <i>et al.</i> (1980)        |
| Lespeol                                                    | (6.47)             | <i>Lespedeza cyrtobotrya</i>                  | Miyase <i>et al.</i> (1980)      |

\* Key: Com = Compositae, Fil = Filicinae, Lau = Lauraceae, Leg = Leguminosae.

† Trivial names for these have not been put forward.

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*F. chappar*. Compound (6.7) is a hydration product of lonchocarpin, compound (6.8) would arise by ring closure at carbon-3'' of the isopentenyl side chain (instead of at carbon-4''), and compound (6.9) is the result of extra hydroxylation of lonchocarpin at position 5'.

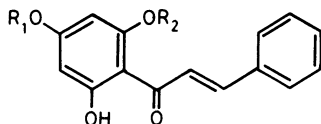


The furano derivative (6.8) represents a rare structure, at least amongst the minor flavonoids. Somewhat more common are furanochalcones such as 'ovalitenin-A' (6.10) which occurs in *Milletia ovalifolia* (Leguminosae) seeds along with other flavonoids having the same A-ring substitution, namely compounds 'ovalitenin-B' (6.156), 'ovalitenin-C' (6.77) and 'ovalitenone' (6.148) (Gupta and Krishnamurti, 1977b). Compound (6.11) is a simple extra-hydroxylated chalcone isolated from *Zuccagnia punctata* (Leguminosae) by Pederiva *et al.* (1975).

The next group of compounds is based upon a phloroglucinol-type A ring. The parent compound (6.12) occurs in *Helichrysum* (Bohlmann and Abraham, 1979c; Bohlmann *et al.*, 1980c), in the exudate of *Adiantum sulphureum* (Pteridaceae) (Wollenweber, 1979), and in the lipid fraction of *Populus* buds (Wollenweber and Weber, 1973) where it occurs with its 6'-methyl ether (6.13) (Wollenweber *et al.*, 1974). The 4'-methyl ether (6.14) occurs in *Helichrysum* (Bohlmann *et al.*, 1979c, 1980c), the oil of *Populus* buds (Wollenweber and Weber, 1973), and a variety of



ferns (Ramakrishnan *et al.*, 1974; Wollenweber 1977a, 1979; Wollenweber and Weber, 1973). 'Flavokawin-B' (6.15) has been found in *Helichrysum* (Bohlmann *et al.*, 1980c), *Aniba* (Lauraceae) (Fernandes *et al.*, 1978), *Didymocarpus* (Gesneriaceae) and *Pityrogramma* species (Wollenweber, unpublished).



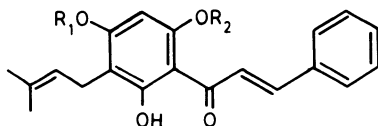
(6.12)  $R_1 = R_2 = H$

(6.13)  $R_1 = H, R_2 = CH_3$

(6.14)  $R_1 = CH_3, R_2 = H$

(6.15)  $R_1 = R_2 = CH_3$

C-Prenylation and O-methylation of the parent molecule yield the 3'-prenyl- and 3'-prenyl-4'-O-methylchalcones, (6.16) and (6.17), that Bohlmann and co-workers (1979c, 1980c) isolated from species of *Helichrysum*. Gupta and Krishnamurti (1977a) isolated 'ovalichalkone' from *Milletia ovalifolia* and showed it to be 2'-hydroxy-3'-prenyl-4',6'-dimethoxychalcone (6.18).

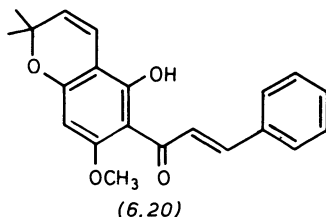
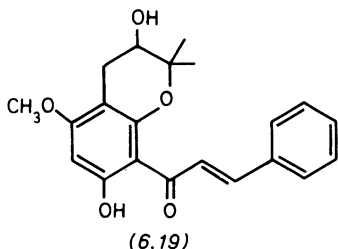


(6.16)  $R_1 = R_2 = H$

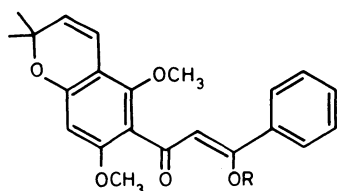
(6.17)  $R_1 = CH_3, R_2 = H$

(6.18)  $R_1 = R_2 = CH_3$

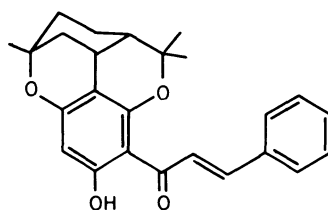
Ring closure reactions in this series occur to yield such compounds as chalcone (6.19), isolated by Bohlmann *et al.* (1979c) from *Helichrysum cymosum* ssp. *calvum*, and 'pongachalcone-I' (6.20) from the heartwood of *Pongamia glabra* (Subramanyam *et al.*, 1977).



Recently, Camele and co-workers (1980) described two  $\beta$ -oxygenated chalcones from *Tephrosia praecans* (Leguminosae). 'Praecanosone-B' (6.21) could also be written in the tautomeric  $\beta$ -diketo form but 'praecanosone-A' (6.22) is locked into the chalcone structure by virtue of the  $\beta$ -methoxy group.



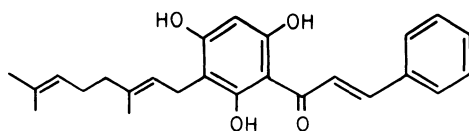
(6.21) R = H

(6.22) R = CH<sub>3</sub>

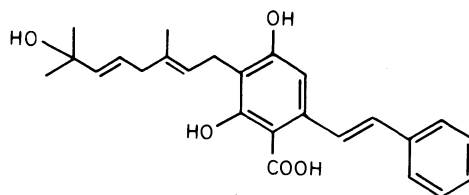
(6.23)

The structure of 'rubranine' (6.23) was originally proposed by Combes *et al.* (1970) for a compound that they isolated from *Aniba rosaeodora*. The existence of rubranine as a natural product was questioned by Montero and Winternitz (1973) who succeeded in synthesizing it through reaction of pinocembrin (5,7-dihydroxyflavanone) with citral in the presence of anibine, a known alkaloidal constituent of *A. rosaeodora*. The argument was joined more recently by de Alleluia and co-workers (1978), who demonstrated conclusively that (–)-rubranine is a natural product and not an artifact of isolation. Their conclusion was based upon two observations: (a) (–)-rubranine ( $[\alpha]_D^{25} = -32.7^\circ$ ) could be extracted from *A. rosaeodora* wood by very brief washing with hexane, conditions which minimize the opportunity for chemical transformations of the sort suggested by Montero and Winternitz (1973); and (b) citral does not accompany linalol and geraniol in *A. rosaeodora*.

Another example of the rich treasure of natural products elaborated by members of the genus *Helichrysum* is the chalcone (6.24) described by Bohlmann and Hoffmann (1979). It is interesting to note the co-occurrence of compound (6.25), a stilbene which would result from the alternative cyclization of the protoflavonoid precursor and by eventual modification of the terminal portion of the C-10 side chain.



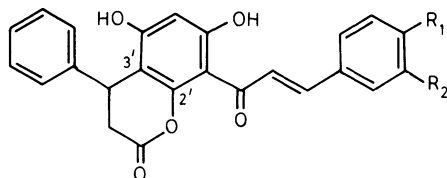
(6.24)



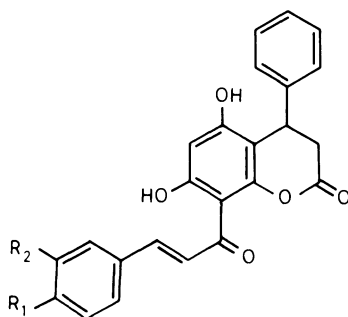
(6.25)

One of the most interesting sets of new chalcone derivatives was discovered by Dietz and co-workers (1980) in the exudate of *Pityrogramma trifoliata*. The three compounds, (6.26), (6.27) and (6.28), can be thought of as chalcones to which a

phenylpropanoid moiety is attached through esterification at the 2'-OH group and by carbon-carbon bond coupling at C-3'. Alternatively, as these authors state, these compounds may be considered 4-phenyldihydrocoumarins, structures of which are easier to visualize if they are rewritten as (6.26a), (6.27a) and (6.28a). Confirmation of these structures by synthesis is clearly needed. A dihydrochalcone corresponding to compound (6.26) has been reported from this plant as well (Wagner *et al.*, 1979; Dietz *et al.*, 1980) and a similar compound



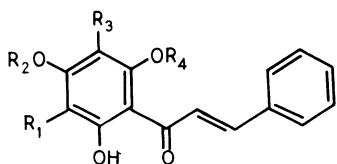
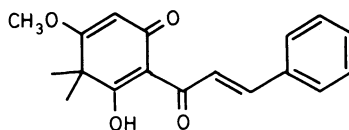
(6.26)  $R_1 = R_2 = H$  (6.27)  $R_1 = OH, R_2 = H$  (6.28)  $R_1 = R_2 = OH$



(6.26a)  $R_1 = R_2 = H$  (6.27a)  $R_1 = OH, R_2 = H$  (6.28a)  $R_1 = R_2 = OH$

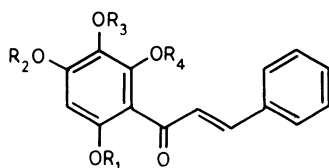
related to chalcone (6.27) is also indicated. Structural confirmation through unequivocal synthesis would be in order, as would biosynthetic studies, for this family of compounds.

Several C-methylated chalcones having the phloroglucinol A-ring pattern are also known. 'Triangularin' (6.29) occurs in the leaf exudate of *Pityrogramma triangularis* (Star *et al.*, 1978) while 'aurentiacin' (6.30) occurs in *Pityrogramma* exudates (Wollenweber *et al.*, 1980b) as well as in *Didymocarpus* (Adityachaudhury *et al.*, 1973). 'Aurentiacin-A' (6.30a) also occurs in *Didymocarpus* (Adityachaudhury and Daskanungo, 1975) and in *Dalea* (Leguminosae) (Dominguez *et al.*, 1980). The di-C-methylchalcone (6.31) occurs in leaves of *Myrica gale* (Myricaceae) (Malterud *et al.*, 1977). Further studies of the distribution of the known 'ceroptin' (6.32) in chemotypes of *Pityrogramma triangularis* have been described by Star and co-workers (1975a,b).

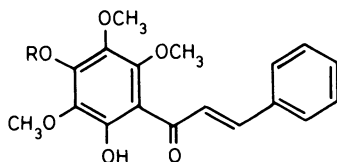
(6.29)  $R_1 = R_2 = \text{CH}_3$ ,  $R_3 = R_4 = \text{H}$ (6.30)  $R_1 = R_2 = R_4 = \text{CH}_3$ ,  $R_3 = \text{H}$ (6.30a)  $R_1 = R_2 = \text{H}$ ,  $R_3 = R_4 = \text{CH}_3$ (6.31)  $R_1 = R_3 = \text{CH}_3$ ,  $R_2 = R_4 = \text{H}$ 

(6.32)

Chalcones having four A-ring hydroxylations occur widely. Structures and source genera are as follows: (6.33), *Polygonatum* (Liliaceae) (Maradufu and Ouma, 1978); (6.34) and (6.35), *Helichrysum* (Bohlmann *et al.*, 1978); (6.36) and (6.37), *Popowia* (Panichpol and Waterman, 1978); and compound (6.38) from both *Didymocarpus* (Agarwal *et al.*, 1973) and *Onychium auratum* (Gymnogrammataceae) (Ramakrishnan *et al.*, 1974).

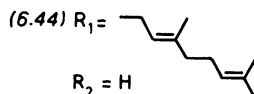
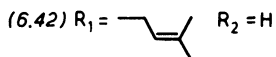
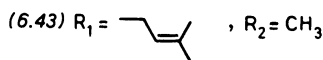
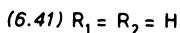
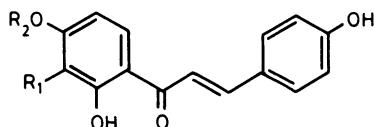
(6.33)  $R_1 = R_3 = \text{CH}_3$ ,  $R_2 = R_4 = \text{H}$ (6.34)  $R_1 = R_4 = \text{CH}_3$ ,  $R_2$  and  $R_3 = -\text{O}-\text{CH}_2-\text{O}-$ (6.35)  $R_1 = \text{H}$ ,  $R_2 = R_3 = R_4 = \text{CH}_3$ (6.36)  $R_1 = R_2 = R_3 = \text{CH}_3$ ,  $R_4 = \text{H}$ (6.37)  $R_1 = R_2 = R_3 = R_4 = \text{CH}_3$ (6.38)  $R_1 = R_4 = \text{H}$ ,  $R_2 = R_3 = \text{CH}_3$ 

Only two chalcones are known in this subgroup in which the A rings are completely oxygenated. Compound (6.39) was found in *Didymocarpus* by Bhattacharyya and co-workers (1979), and 'kanakugiol' (6.40) was isolated from fruit of *Popowia cauliflora* by Waterman and Pootakahm (1979).

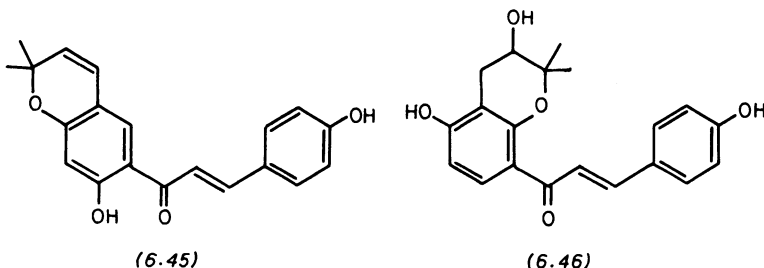
(6.39)  $R = \text{H}$ (6.40)  $R = \text{CH}_3$

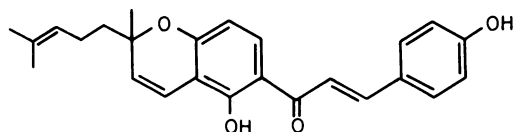
**(b) Chalcones having one B-ring hydroxyl**

'Isoliquiritigenin' (6.41), the simplest chalcone encountered in this subgroup, occurs in *Dahlia* species (Lam and Wrang, 1975; see Bohm, 1975, Table 9.1) and from *Xanthorrhoea* (Xanthorrhaceae, *loc. cit.*, Table 9.1), but is most often encountered in members of Leguminosae. Recent work describes its occurrence in *Sophora* (Komatsu *et al.*, 1978) for the first time, and in *Dalbergia* (Matos *et al.*, 1975). Members of Leguminosae also synthesize C-prenylchalcones based upon isoliquiritigenin. Variations on this structural theme are seen in '4-hydroxyisocordoin' (6.42) and '4-hydroxyderricin' (6.43) which occur in *Lonchocarpus* (Delle Monache *et al.*, 1974). The chalcone (6.43), isolated from *Angelica keiskei* by Kozawa and co-workers (1977), accompanies the newly discovered 'xanthoangelol' (6.44). This represents the first report of chalcones from Umbelliferae.



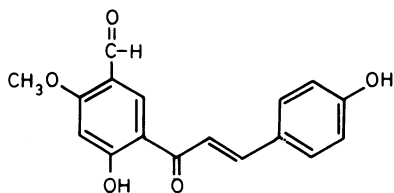
Cyclization of the prenyl group of compound (6.42) to the 4'-phenolic function would yield '4-hydroxylonchocarpin' (6.45), known as a constituent of *Derris floribunda* (Braz Filho *et al.*, 1975b), while closure at the 2'-hydroxyl function could give, after hydration, 'bavachromenol' (6.46) which Suri and co-workers (1980) recently isolated from seeds of *Psoralea corylifolia*. The novel compound xanthoangelol (6.44) also occurs in *Lespedeza cyrtobotrya* (Leguminosae) where it occurs with, and presumably could act as precursor to, another newly found chalcone, 'lespeol' (6.47) (Miyase *et al.*, 1980).



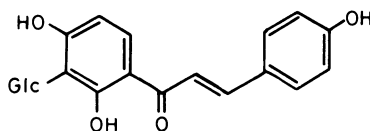


(6.47)

The last two compounds in this subsection contain unique structural features among naturally occurring chalcones. Compound (6.48), 'neobavachalcone', 2',4-dihydroxy-4'-methoxy-5'-formylchalcone, isolated from *Psoralea corylifolia* (Leguminosae) and subsequently synthesized by Gupta *et al.* (1975b, 1977) is distinctive in its aldehydo substitution. 3'-C-( $\beta$ -D-Glucopyranosyl) isoliquiritigenin (6.49) was isolated from the wood of *Cladrastis platycarpa* (Leguminosae) by Ohashi and co-workers (1977) and represents the first report of a naturally occurring C-glycosylchalcone.

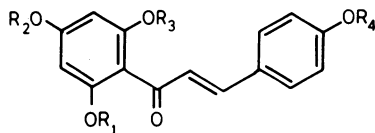


(6.48)



(6.49)

The only reports of 'isosalipurpol' (6.50) as the free phenol involve, interestingly, its occurrence in the pollen of two unrelated families, namely, *Petunia hybrida* (Solanaceae) (de Vlaming and Kho, 1976), and *Nothofagus antartica* (Fagaceae) (Wollenweber and Wiermann, 1979). Glycosides of isosalipurpol are much more common in nature and a variety of O-methylated derivatives is known. Glycosides include 'isosalipurposide', the 2'-O-glucoside (6.51) which occurs in *Ruellia* species (Acanthaceae) (Bloom, 1976), *Acacia*



(6.50)  $R_1 = R_2 = R_3 = R_4 = H$

(6.51)  $R_1 = \text{Glucose}, R_2 = R_3 = R_4 = H$

(6.52)  $R_1 = R_2 = R_3 = H, R_4 = \text{Glucose}$

(6.53)  $R_1 = R_2 = R_3 = H, R_4 = \text{Glucose-X}''(\text{p-coumaroyl})$

(6.54)  $R_1 = R_2 = R_4 = H, R_3 = CH_3$

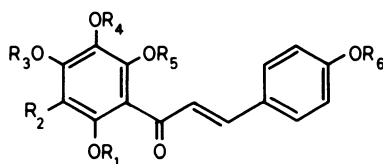
(6.55)  $R_1 = CH_3, R_2 = \text{Glucose}, R_3 = R_4 = H$

(6.56)  $R_1 = R_2 = CH_3, R_3 = H, R_4 = \text{Glucose}$

(6.57)  $R_1 = R_2 = R_4 = CH_3, R_3 = H$

*cyanophylla*, where it accompanies the newly discovered 4-*O*-glucoside (6.52) (Imperato, 1978) and in *Salix rubra*, where it is also found as a *p*-coumaroyl derivative (6.53) (Vinokurov, 1979). Isosalipurpol 6'-methyl ether (6.54) is known as a constituent of *Helichrysum heterolasium* (Bohlmann and Abraham, 1979b), while its 4'-*O*-glucoside (6.55) has been found in species of *Gnaphalium* (Compositae) by Aritomi and Kawasaki (1974) and Maruyama *et al.* (1974) and synthesized by Ahluwalia and Rami (1976). The di-*O*-methylchalcone, as its glucoside (6.56), occurs in *Viscum album*, the European mistletoe (Becker *et al.*, 1978), and the trimethyl ether (6.57) is one of several flavonoids isolated from *Dahlia tenuicaulis* by Lam and Wrang (1975).

Extra hydroxylation of salipurpol followed by greater or lesser degrees of *O*-methylation would yield the following chalcones, all of which occur in the free state: (6.58) occurs in *Helichrysum glomeratum* (Bohlmann and Suwita, 1979c); (6.59) and (6.60) were found in *Chromolaena odorata* (Compositae) (Barua *et al.*, 1978); (6.61) occurs with other *O*-methylated flavonoids in *Popowia cauliflora* (Panichpol and Waterman, 1978); and (6.61a) plus an unidentified chalcone were found in roots of *Flemingia strobilifera* by Bhatt (1975).



(6.58)  $R_1 = \text{CH}_3$ ,  $R_2 = R_5 = R_6 = \text{H}$ ,  $R_3$  and  $R_4 = -\text{O}-\text{CH}_2-\text{O}-$

(6.59)  $R_1 = R_2 = R_6 = \text{H}$ ,  $R_3 = R_4 = R_5 = \text{CH}_3$

(6.60)  $R_1 = R_2 = \text{H}$ ,  $R_3 = R_4 = R_5 = R_6 = \text{CH}_3$

(6.61)  $R_1 = R_3 = R_4 = \text{CH}_3$ ,  $R_2 = R_5 = R_6 = \text{H}$

(6.61a)  $R_1 = R_4 = \text{H}$ ,  $R_2 = \text{OCH}_3$ ,  $R_3 = R_5 = R_6 = \text{CH}_3$

### (c) Chalcones having two B-ring hydroxyls

Chemically, as opposed to biosynthetically, compounds (6.62) and (6.63) are the simplest members of this subgroup by virtue of their single A-ring hydroxyl group. [The closely related trihydroxy B-ring compound (6.64) will also be treated here, owing to its biosynthetic similarity to the other two compounds.] 'Echinatin' (6.62) occurs in cultures of *Glycyrrhiza echinata* (Saitoh *et al.*, 1975) while 'licochalcone-A' (6.63) and 'licochalcone-B' (6.64) occur in root tissue of *G. glabra* (Saitoh and Shibata, 1975). The unusual hydroxylation pattern of these compounds, with a single hydroxyl group at position-4' and an apparent polyacetate-derived substitution pattern on ring B, prompted the name 'retro-flavonoids' for this small group. The biosynthesis of these compounds was studied by Saitoh *et al.* (1975), whose results show that the singly hydroxylated

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ring in these compounds is derived from the ring of a phenylpropanoid precursor while the right-hand ring is derived from malonyl-CoA. A shift of bridge oxygen position must have occurred during their formation. The pathway suggested by Saitoh *et al.* (1975) is summarized in Fig. 6.1.

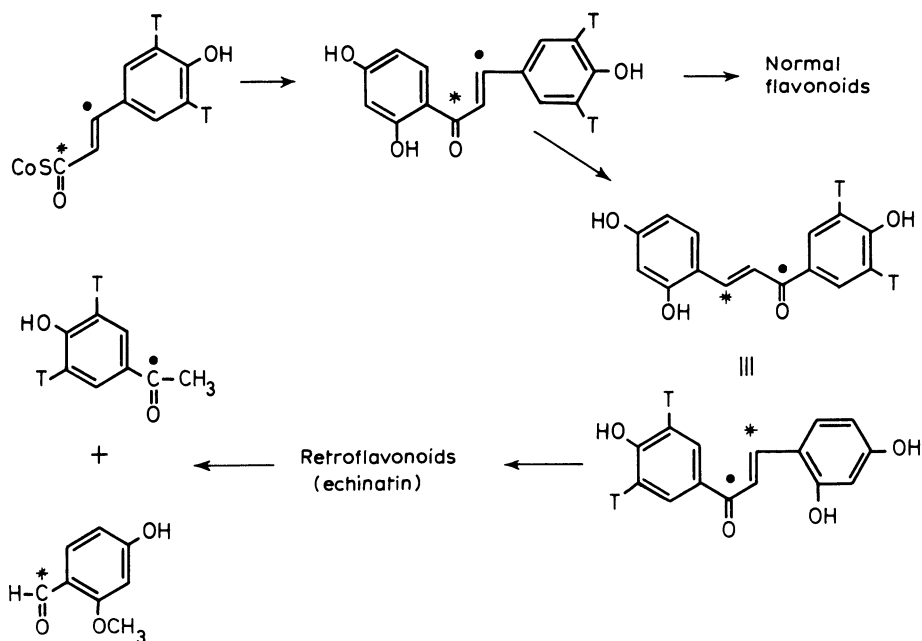
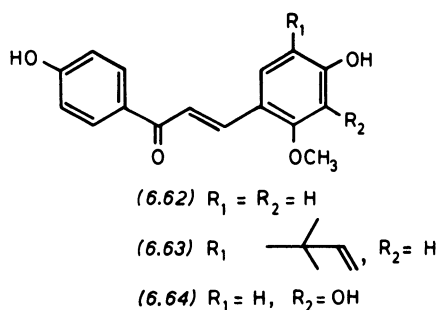


Fig. 6.1 Biosynthetic route to retroflavonoids (after Saitoh *et al.*, 1975).

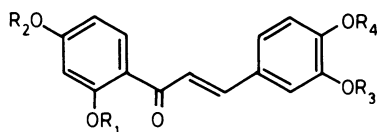


The majority of compounds in this hydroxylation subgroup are based upon a resorcinol-type A ring, seen in the parent compound butein (6.65). Butein itself occurs in trunkwood of *Machaerium mucronulatum* (Anacardiaceae) (Kurosawa *et al.*, 1978) and in the ligules of *Bidens laevis* (Compositae) (Scogin and Zakar, 1976). Glycosidic forms include the well-known 4'-O-glucoside (6.66) coreopsin known from several genera of Compositae, the 4'-O-diglucoside (6.67) from



*Bidens* (Hart, 1979) and *Coreopsis bigelovii* (Nicholls and Bohm, 1979), the 2',3-di-*O*-glucoside (6.68) from species of *Rhus* (Young, 1979) and *Amphipterigium adstrigens* (Young, 1976) (both Anacardiaceae), and a novel 4'-*O*-arabinosylgalactoside (6.69) from *Bauhinia purpurea* (Leguminosae) (Bhartiya *et al.*, 1979).

Simple *O*-methyl derivatives of butein include the 4-*O*-methyl ether (6.70) from *Dahlia* (Giannasi, 1975; Lam and Wrang, 1975) and *Megalodonta* (Roberts, 1980) and the 3-*O*-methyl- (6.71) and 3,4-di-*O*-methyl (6.72) derivatives from *Iryanthera polyneura* (Myristicaceae) (de Almeida *et al.*, 1979).



(6.65)  $R_1 = R_2 = R_3 = R_4 = H$

(6.66)  $R_1 = R_3 = R_4 = H, R_2 = \text{Glc}$

(6.67)  $R_1 = R_3 = R_4 = H, R_2 = \text{Glc-O-Glc}$

(6.68)  $R_1 = R_3 = \text{Glc}, R_2 = R_4 = H$

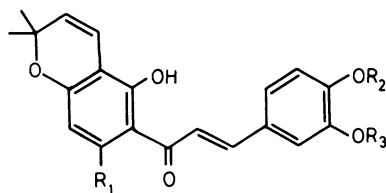
(6.69)  $R_1 = R_3 = R_4 = H, R_2 = -\text{Gla-O-Ara}$

(6.70)  $R_1 = R_2 = R_3 = H, R_4 = \text{CH}_3$

(6.71)  $R_1 = R_2 = R_4 = H, R_3 = \text{CH}_3$

(6.72)  $R_1 = R_2 = H, R_3 = R_4 = \text{CH}_3$

The following set of compounds share a structural feature commonly seen in flavonoids from Leguminosae, the presence of the dimethylchromeno A-ring structure. 3,4-Dihydroxylonchocarpin (6.73), from *Derris floribunda* (Braz Filho *et al.*, 1975b) is the simplest of these. The *O*-methylated derivatives (6.74) and (6.75) occur in *Pongamia glabra* (Sharma *et al.*, 1973; Subramanyam *et al.*, 1977). The related compound (6.76) also occurs in *P. glabra* (Subramanyam *et al.*, 1977) along with chalcones (6.6) and (6.20) treated earlier in this chapter. 'Ovalitenin-C' (6.77) was isolated from *Milletia ovalifolia* (Islam *et al.*, 1980), and is a member of a series of closely related compounds having the furano A ring.

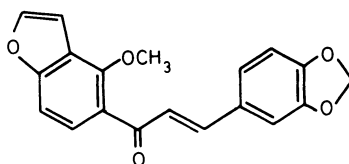


(6.73)  $R_1 = R_2 = R_3 = H$

(6.74)  $R_1 = R_2 = H, R_3 = \text{CH}_3$

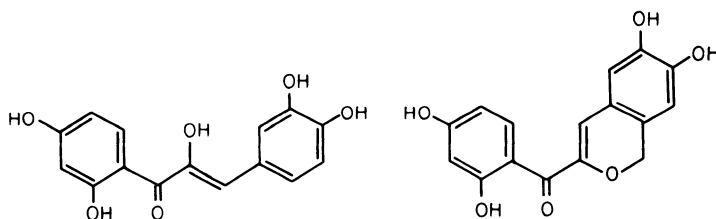
(6.75)  $R_1 = H, R_2 \text{ and } R_3 = -\text{O-CH}_2\text{-O-}$

(6.76)  $R_1 = \text{OCH}_3, R_2 \text{ and } R_3 = -\text{O-CH}_2\text{-O-}$



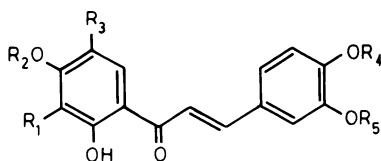
(6.77)

Extra hydroxylation of the butein skeleton at the  $\alpha$ -carbon would yield  $\alpha,2',4',3,4$ -pentahydroxychalcone (6.78) which has been isolated from *Peltogyne* species by Malan and Roux (1974). The occurrence of a chalcone hydroxylated at that position suggests a possible biosynthetic relationship with such compounds as the peltogynoid flavonoids represented below by peltochalcone (6.79). Extra hydroxylation of butein at position 3' yields okanin (6.80) which is known to occur as the free phenol in wood of *Albizia adianthifolia* (Leguminosae) (Candy *et al.*, 1978) and as the 4'-*O*-glucoside, marein (6.81), in many species of *Bidens* and *Coreopsis* (see Table 6.1 for references). *O*-Methylation of marein at position 3' affords lanceolin (6.82), also known from *Coreopsis* species. 3-*O*-Methyl- (6.82a) and 3,4-*O*-methylokanin (6.82b) glucosides occur in several members of the *Bidens pilosa* group of species (Ballard, 1975). 'Stillopsidin',



(6.78)

(6.79)



(6.80)  $R_1 = \text{OH}, R_2 = R_3 = R_4 = R_5 = \text{H}$

(6.81)  $R_1 = \text{OH}, R_2 = \text{Glc}, R_3 = R_4 = R_5 = \text{H}$

(6.82)  $R_1 = \text{OCH}_3, R_2 = \text{Glc}, R_3 = R_4 = R_5 = \text{H}$

(6.82a)  $R_1 = \text{OH}, R_2 = R_3 = R_4 = \text{H}, R_5 = \text{CH}_3$

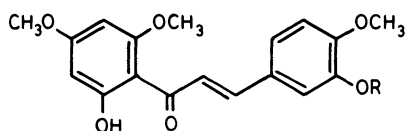
(6.82b)  $R_1 = \text{OH}, R_2 = R_3 = \text{H}, R_4 = R_5 = \text{CH}_3$

(6.83)  $R_1 = R_4 = R_5 = \text{H}, R_2 = \text{Glc}, R_3 = \text{OH}$

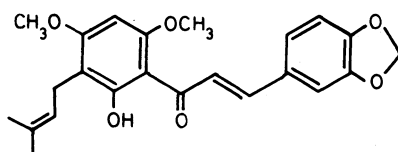
(6.84)  $R_1 = R_2 = \text{H}, R_3 = \text{OCH}_3, R_4 \text{ and } R_5 = -\text{O}-\text{CH}_2-\text{O}-$

which is 5'-hydroxybutein, occurs as the 4'-*O*-glucoside (6.83) in *Coreopsis bigelovii* (Nicholls and Bohm, 1979). The 5'-hydroxybutein pattern also occurs in 'prosogerin-B' (6.84), a constituent of flowers of *Prosopis spicigera* (Leguminosae) (Bhardwaj *et al.*, 1979).

Only a few pentahydroxychalcones having the phloroglucinol A-ring pattern have been reported during the past few years. Two of these, (6.85) and (6.86), were isolated from *Merrillia caloxylon* (Rutaceae) by Fraser and Lewis (1974). Structure (6.87) was established for 'ovalichalkone-A' by Gupta and Krishnamurti (1979) who isolated it from the seeds of *Milletia ovalifolia*.

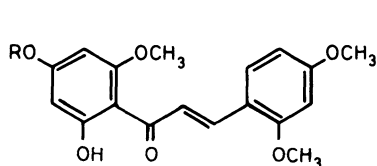


(6.85) R = H

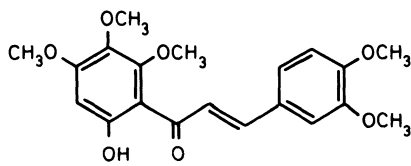
(6.86) R = CH<sub>3</sub>

(6.87)

Compounds (6.88) and (6.89) exhibit the comparatively uncommon 2,4-dihydroxy B-ring substitution pattern. Both compounds occur in the heartwood of *Prunus cerasus* (Rosaceae) (Nagarajan and Parmar, 1977a,c) while (6.89) also occurs in *Terminalia arjuna* (Combretaceae) (Nagar *et al.*, 1979).



(6.88) R = H

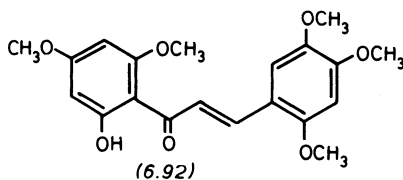
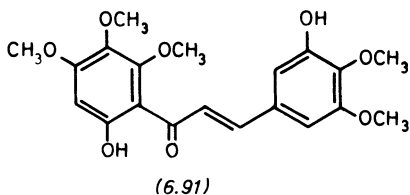
(6.89) R = CH<sub>3</sub>

(6.90)

The pentamethoxychalcone (6.90) has been found in *Chromolaena odorata* (Compositae) by Barua *et al.* (1978) where it occurs with several other highly *O*-methylated flavonoids.

#### (d) Chalcones having three B-ring hydroxyls

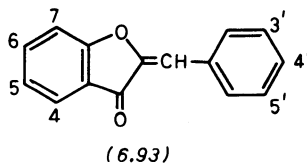
Two new members of this group of chalcones have been discovered. Chalcone (6.91) was isolated from *Merrillia caloxylon* by Fraser and Lewis (1974) where it occurs with the related *O*-methyl derivatives (6.85) and (6.86). Compound (6.92), isolated from *Derris robusta* by Chibber *et al.* (1979), exhibits the unusual 2,4,5-trihydroxy B-ring substitution pattern.



### 6.3 AURONES

#### 6.3.1 Introduction

Aurones are hydroxylated 2-benzylidenecoumaranones, the parent compound being (6.93). The 'normal' numbering system applies to this group of compounds: positions on the A ring are identified by unprimed numbers and the B-ring positions by primed numbers. Note that in aurones position 4 corresponds biosynthetically to position 5 of other heterocyclic flavonoids. Included in this section are two 'auronol' derivatives, distinguished by the presence of a methoxy group in place of the carbonyl function at position 3.



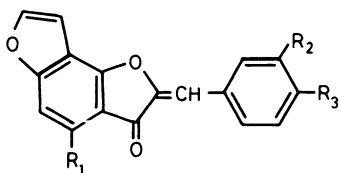
#### 6.3.2 Structures of naturally occurring aurones

Structures of naturally occurring aurones and auronols appear in Table 6.3

##### (a) Aurones lacking B-ring hydroxyls

The first naturally occurring aurones lacking B-ring substitution were isolated from *Derris obtusa* by do Nascimento *et al.* (1976). The three compounds, (6.94), (6.95) and (6.96), were accompanied by a methylenedioxy derivative (6.96a), and by two auronol derivatives (6.97) and (6.98). The first suggestion of the existence of an auronol was made by Hänsel and co-workers based on a compound from *Helichrysum arenarium* (Hänsel *et al.*, 1965). Soon thereafter, however, these authors (Hänsel *et al.*, 1967) withdrew their proposal having correctly identified the compound as a flavonol. In the case of the 3-*O*-methylauronols from *Derris* do Nascimento and co-workers presented convincing evidence for their existence. In the first place, both isomeric flavonols are known and were observed to differ in all physical respects from derriobtusone-A (6.97) and derriobtusone-B

(6.98). Secondly, both flavonols were resistant to dilute refluxing HCl while the 3-*O*-methylauronols were readily demethylated under these conditions. Longer acid treatment resulted in the production of the furanocoumaranone from both compounds and benzoic acid from (6.97) and piperonylic acid (3,4-methylenedioxybenzoic acid) from (6.98).

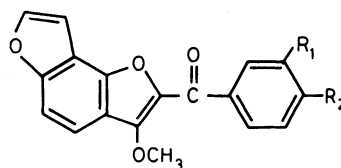


(6.94)  $R_1 = R_2 = R_3 = H$

(6.95)  $R_1 = OH, R_2 = R_3 = H$

(6.96)  $R_1 = OCH_3, R_2 = R_3 = H$

(6.96a)  $R_1 = H, R_2 \text{ and } R_3 = -O-CH_2-O-$

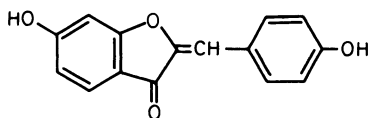


(6.97)  $R_1 = R_2 = H$

(6.98)  $R_1 \text{ and } R_2 = -O-CH_2-O-$

### (b) Aurones having one B-ring hydroxyl

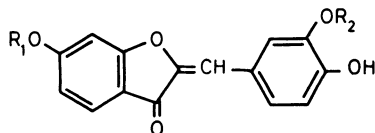
Only one member of this subgroup has been reported since the 1975 review. E1 Sherbeiny and co-workers (1978) reported the presence of the known aurone hispidol (6.99) and its 6-*O*-glucoside in seeds of *Lygos raetam* (Leguminosae)



(6.99)

### (c) Aurones having two B-ring hydroxyls

Sulfuretin (6.100), one of the most common aurones, has recently been reported to occur as the free phenol and as the 6,3'-di-*O*-glucoside (6.101) in *Rhus* species (Young, 1979) and in *Amphipterygium adstrigens* (Young, 1976), as a series of 6-mono- and di-glycosides in several *Bidens* species (Hart, 1979; Scogin and Zakar, 1976), and as the 6-*O*-glucoside (102) in several *Helianthus* species (Harborne and Smith, 1978), *Coreopsis bigelovii* (Nicholls and Bohm, 1979) and *Viguiera laciniata* (Harborne and Smith, 1978).



(6.100)  $R_1 = R_2 = H$

(6.101)  $R_1 = R_2 = \text{Glc}$

(6.102)  $R_1 = \text{Glc}, R_2 = H$

Table 6.3 Structures of naturally occurring aurones (including auronols)

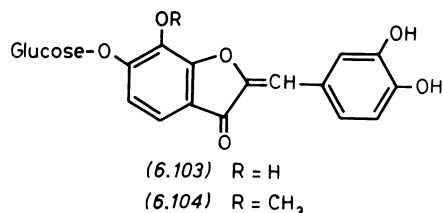
| OH        | OCH <sub>3</sub> | Substituents                                               | No. in text | Trivial name                           | Source* | References                         |
|-----------|------------------|------------------------------------------------------------|-------------|----------------------------------------|---------|------------------------------------|
| 4         |                  | Furano(2'',3'',6,7)                                        | (6.94)      | <i>Derris obtusa</i>                   | Leg     | do Nascimento <i>et al.</i> (1976) |
|           |                  | Furano(2'',3'',6,7)                                        | (6.95)      | <i>D. obtusa</i>                       | Leg     | do Nascimento <i>et al.</i> (1976) |
| 4         |                  | Furano(2'',3'',6,7)                                        | (6.96)      | <i>D. obtusa</i>                       | Leg     | do Nascimento <i>et al.</i> (1976) |
| 3         |                  | Furano(2'',3'',6,7); $\beta$ -carbonyl                     | (6.97)      | Derriobtusone-A                        | Leg     | do Nascimento <i>et al.</i> (1976) |
| 6,4'      |                  |                                                            | (6.99)      | Hispidol                               | Leg     | El Sherbeiny <i>et al.</i> (1978)  |
|           |                  |                                                            |             | Hispidol glucoside                     | Leg     | El Sherbeiny <i>et al.</i> (1978)  |
| 6,3',4'   |                  | 6-O-Glucose                                                | (6.100)     | Sulfuretin                             | Ana     | Young (1979)                       |
|           |                  |                                                            |             | <i>Amphiterygium adstrigens</i>        | Ana     | Young (1976)                       |
|           |                  | 6-O-Glucose                                                | (6.102)     | Sulfurein                              | Com     | Harborne and Smith (1978)          |
|           |                  |                                                            |             | <i>Helianthus</i> spp.                 | Com     | Harborne and Smith (1978)          |
|           |                  |                                                            |             | <i>Viguiera lacinata</i>               | Com     | Hart (1979)                        |
|           |                  |                                                            |             | <i>Bidens</i> spp.                     | Com     | Nicholls and Bohm (1979)           |
|           |                  |                                                            |             | <i>Coreopsis bigelovii</i>             | Com     | Scogin and Zakar (1976)            |
|           |                  |                                                            |             | <i>Bidens laevis</i>                   | Com     | Hart (1979)                        |
|           |                  | 6-O-Glucosylglucose                                        | (6.101)     | <i>Bidens</i> spp.                     | Com     | Hart (1979)                        |
|           |                  | 6,3'-di-O-Glucose                                          |             | <i>Rhus</i> spp.                       | Ana     | Young (1979)                       |
|           |                  |                                                            |             | <i>Amphiterygium adstrigens</i>        | Ana     | Young (1976)                       |
| 6,7,3',4' |                  | 6-O-Glucose                                                | (6.103)     | Maritimein                             | Com     | Nicholls and Bohm (1979)           |
| 6,3',4'   |                  | 6-O-Glucose                                                | (6.104)     | Leptosin                               | Com     | Crawford and Smith (1980)          |
|           |                  | Furano(2'',3'',6,7); 3,4-methylenedioxy                    | (6.96a)     | <i>Coreopsis grandiflora</i>           | Leg     | do Nascimento <i>et al.</i> (1976) |
| 3         |                  | Furano(2'',3'',6,7); 3,4-methylenedioxy; $\beta$ -carbonyl | (6.98)      | <i>Derris obtusa</i>                   | Leg     | do Nascimento <i>et al.</i> (1976) |
| 4,6,3',4' |                  | 6-O-Glucose                                                | (6.105)     | Derriobtusone-B                        | Leg     | do Nascimento <i>et al.</i> (1976) |
|           |                  | 6-O-Glucuronic acid                                        | (6.107)     | Aureusidin                             | Ana     | Ogiyama <i>et al.</i> (1976)       |
|           |                  |                                                            | (6.108)     | Aureusin                               | Ser     | Gilbert (1975)                     |
|           |                  |                                                            |             | <i>Antirrhinum orontium</i>            | Hep     | Markham and Porter (1978)          |
|           |                  |                                                            |             | <i>Marchantia berteriana</i>           | Hep     | Markham and Porter (1978)          |
|           |                  |                                                            |             | <i>M. polymorpha</i>                   | Hep     | Markham and Porter (1978)          |
|           |                  |                                                            |             | <i>Conocephalum supra-decompositum</i> | Hep     | Markham (1980)                     |
|           |                  |                                                            |             | <i>Carrpos sphaerocarpos</i>           | Hep     | Markham (1980)                     |

|              |                      |         |            |                                                |     |                              |
|--------------|----------------------|---------|------------|------------------------------------------------|-----|------------------------------|
| 6,3',4'      | 4                    | (6.106) | Rengasin   | <i>Melanorrhoea aptera</i><br><i>Rhus</i> spp. | Ana | Ogiyama <i>et al.</i> (1976) |
| 4,6,3',4',5' |                      | (6.109) | Bracteatin | <i>Amphipterygium adstrigens</i>               | Ana | Young (1979)                 |
|              | 6-O-Glucose          | (6.110) |            | <i>Funaria hygrometrica</i>                    | Ana | Young (1976)                 |
| 6,3',4',5'   | 4                    | (6.111) | Subulin    | <i>Antirrhinum orontium</i>                    | Mus | Weitz and Ikan (1977)        |
|              | 6-O-Rhamnosylglucose |         |            | <i>Anomum subulatum</i>                        | Scr | Gilbert (1975)               |
|              |                      |         |            |                                                | Zin | Lakshmi and Chauhan (1977)   |

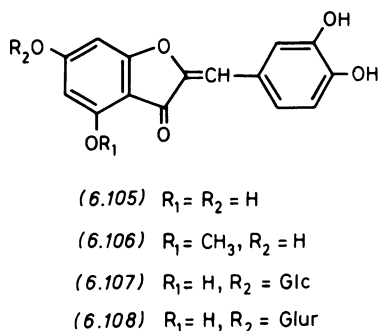
\* Key: Ana = Anacardiaceae, Com = Compositae, Hep = Hepaticae, Leg = Leguminosae, Mus = Musci, Scr = Scrophulariaceae, Zin = Zingiberaceae.

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Extra hydroxylation at position 7 of sulfuretin yields maritimetin, which exists as maritimetin (6.103) in *Coreopsis bigelovii* (Nicholls and Bohm, 1979), and in *C. grandiflora*, where it occurs with its 7-methyl ether, leptosin (6.104) (Crawford and Smith, 1980).



Aureusidin, 4,6,3',4'-tetrahydroxyaurone (6.105), occurs as the free phenol in heartwood of *Melanorrhoea aptera* (Anacardiaceae) along with its 4-methyl ether, rengasin (6.106) (Ogiyama *et al.*, 1976). Aureusin (6.107), the 6-*O*-glucoside of aureusidin, was found with bracteatin 6-*O*-glucoside (6.110) in *Antirrhinum orontium* (Scrophulariaceae) by Gilbert (1975), who discussed the observation in terms of the sectional disposition of this species. Aureusidin 6-*O*-glucuronide (6.108) has been found by Markham and Porter (1978) as a constituent of the antheridiophores of three liverworts: *Marchantia berteroana*, *M. polymorpha* and *Conocephalum supradecompositum*. The compound was not found in associated thallus tissue or in female plants and was detectable for only 4–8 weeks, which corresponds to the lifespan of the reproductive structures. Aureusidin 6-*O*-glucuronide has been found in another liverwort, *Carrposphaerocarpus* (Markham, 1980), as well.

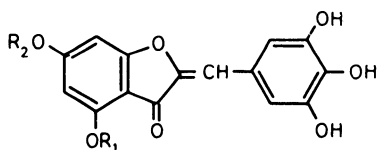


### (d) Aurones having three B-ring hydroxyls

Only two aurones having this pattern have been found in nature. Bracteatin (6.109) occurs as the free phenol in the sporophytes, but not in the leaves, of the moss *Funaria hygrometrica* (Weitz and Ikan, 1977) and as the 6-*O*-glucoside (6.110) in *Antirrhinum orontium* (Gilbert, 1975). 'Subulin', recently isolated from seeds of *Amomum subulatum* (Zingiberaceae) by Lakshmi and Chauhan (1977),



was shown to be the novel 6,3',4',5'-tetrahydroxy-4-methoxyaurone 6-*O*- $\alpha$ -L-rhamnopyranosyl-(1 $\rightarrow$ 4)- $\beta$ -D-glucopyranoside (6.111).



(6.109)  $R_1 = R_2 = H$

(6.110)  $R_1 = H, R_2 = Glc$

(6.111)  $R_1 = CH_3, R_2 = -Glc-O-Rha$

## 6.4 DIHYDROCHALCONES

### 6.4.1 Introduction

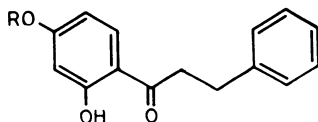
For the identification of positions in the dihydrochalcone molecule, the numbering system is the same as that for chalcones [see structure (6.1)]. Included here is a group of compounds that bear oxygenation on the  $\beta$ -carbon and are referred to often as dibenzoylmethane derivatives in the literature.

### 6.4.2 Structures of naturally occurring dihydrochalcones

The structures of dihydrochalcones reported since 1974, including dibenzoylmethane derivatives, are given in Tables 6.4 and 6.5.

#### (a) Dihydrochalcones lacking B-ring hydroxyls

In the 1975 review only one dihydrochalcone belonging to this hydroxylation subgroup had been reported in nature, except for the existence of dihydrochalcone itself. The situation has changed markedly since that time. The simplest dihydrochalcone, in terms of hydroxylation pattern, is 2',4'-dihydroxydihydrochalcone (6.112) which occurs as the 4'-( $\gamma\gamma$ -dimethyl)allyl ether (6.113) in *Lonchocarpus* species (Delle Monache *et al.*, 1974). A similar compound based



(6.112)  $R = H$

(6.113)  $R = \text{---CH}_2\text{---CH=C(CH}_3\text{)}_2$

Table 6.4 Structures of naturally occurring dihydrochalcones

| OH       | OCH <sub>3</sub> | Substituents                                                             | No. in text                                                    | Trivial name                               | Source*                                                                                                                                                                                      | References                                                                                                                                                                                                                    |
|----------|------------------|--------------------------------------------------------------------------|----------------------------------------------------------------|--------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2'       |                  | 4'-O-Prenyl<br>Furano(2'',3'',4',3')<br>Furano(2'',3'',4',3');<br>β-keto | (6.113)<br>(6.156)<br>(6.149)                                  | Dihydrocordoin<br>Ovalitenin-B<br>Pongamol | <i>Lonchocarpus</i> sp.<br><i>Milletia ovalifolia</i><br><i>Pongamia glabra</i>                                                                                                              | Delle Monache <i>et al.</i> (1974)<br>Gupta and Krishnamurti (1977b)<br>Talapatra <i>et al.</i> (1980)                                                                                                                        |
| 2',4',6' |                  | 2'-O-Glucose<br>4'-O-Glucose<br>4'-O-Prenyl<br>2'-O-Glucose; β-keto      | (6.114)<br>(6.116)<br>(6.117)<br>(6.115)<br>(6.145)<br>(6.118) |                                            | <i>Tephrosia purpurea</i><br><i>Helichrysum tenuifolium</i><br><i>Malus fusca</i><br><i>Malus cultivar</i><br><i>Helichrysum polycladum</i><br><i>Malus</i> spp.<br><i>Pityrogramma</i> spp. | Gupta <i>et al.</i> (1980)<br>Bohlmann and Abraham (1979a)<br>A. H. Williams (1979)<br>A. H. Williams (1979)<br>Bohlmann <i>et al.</i> (1980c)<br>A. H. Williams (1979)<br>Wollenweber (1977b);<br>Dietz <i>et al.</i> (1980) |
| 2',4'    | 6'               |                                                                          |                                                                |                                            | <i>P. chrysoconia</i>                                                                                                                                                                        | Wollenweber (1977b, 1979)                                                                                                                                                                                                     |
| 2'       | 4',6'            |                                                                          |                                                                |                                            | <i>Notholaena</i> spp.                                                                                                                                                                       | Wollenweber (1977a)                                                                                                                                                                                                           |
| 2',6'    | 4'               |                                                                          |                                                                | Uvangoletin                                | <i>Adiantum sulphureum</i>                                                                                                                                                                   | Wollenweber (1979)                                                                                                                                                                                                            |
|          |                  | 3'-C-Methyl<br>3',5'-Di-O-methyl                                         | (6.119)<br>(6.120)                                             |                                            | <i>Uvaria angolensis</i><br><i>Myrica gale</i><br><i>M. gale</i>                                                                                                                             | Hufford and Oguntimein (1980)<br>Malterud <i>et al.</i> (1977)<br>Anthonen <i>et al.</i> (1971);<br>Uyar <i>et al.</i> (1978)                                                                                                 |
| 2',4'    | 6'               | 3',5'-Di-O-methyl                                                        |                                                                | Angoletin                                  | <i>Uvaria angolensis</i>                                                                                                                                                                     | Hufford and Oguntimein (1980)                                                                                                                                                                                                 |
| 2',6',β  | 2',6',β          | 3',4'-Methylenedioxy                                                     | (6.157)                                                        |                                            | <i>Helichrysum mundii</i>                                                                                                                                                                    | Bohlmann <i>et al.</i> (1978)                                                                                                                                                                                                 |
| β        | 2',6'            | 3',4'-Methylenedioxy;<br>carbonyl reduced<br>to OH                       | (6.158,<br>6.159)                                              |                                            | <i>Helichrysum mundii</i>                                                                                                                                                                    | Bohlmann <i>et al.</i> (1978)                                                                                                                                                                                                 |
| 2',4',6' |                  | 3'-C-Methyl;<br>5'-formyl; β-keto                                        | (6.152)                                                        |                                            | <i>Unona lawii</i>                                                                                                                                                                           | Joshi and Gawad (1976)                                                                                                                                                                                                        |
| 2',6'    | 4'               | 3'-C-Methyl;<br>5'-formyl; β-keto                                        | (6.153)                                                        |                                            | <i>Unona lawii</i>                                                                                                                                                                           | Joshi and Gawad (1976)                                                                                                                                                                                                        |
| 2',4'    | 6'               | 3'-C-(2-Hydroxybenzyl)                                                   | (6.131)                                                        | Uvaretin                                   | <i>U. angolensis</i><br><i>Uvaria acuminata</i><br><i>U. kiskii</i>                                                                                                                          | Hufford and Oguntimein (1980)<br>Cole <i>et al.</i> (1976)<br>Tammami <i>et al.</i> (1977)                                                                                                                                    |

|                    |      |                                                                |                             |                                            |     |                                                                                                  |
|--------------------|------|----------------------------------------------------------------|-----------------------------|--------------------------------------------|-----|--------------------------------------------------------------------------------------------------|
| 2',4'              | 6'   | 5'-C-(2-Hydroxybenzyl)                                         | Isouaretin or<br>chaumuarin | <i>U. chamae</i>                           | Ano | Okorie (1977)                                                                                    |
| 2',4',6'           | 3'   | 5'-C-Prenyl                                                    | (6.127)                     | <i>U. angolensis</i>                       | Ano | Hufford and Oguntimein (1980)                                                                    |
| 2',4',6'           |      | 3',5'-di-C-Prenyl                                              | (6.128)                     | <i>Helichrysum polycladum</i>              | Com | Bohlmann <i>et al.</i> (1980c)                                                                   |
| 4',6'              |      | 3',3',5'-tri-C-Prenyl;                                         | (6.129)                     | <i>H. polycladum</i>                       | Com | Bohlmann <i>et al.</i> (1980c)                                                                   |
|                    |      | 2'-keto                                                        |                             | <i>H. polycladum</i>                       | Com | Bohlmann <i>et al.</i> (1980c)                                                                   |
| 4',6'              | 3'   | 3',5'-di-C-Prenyl;                                             | (6.130)                     | <i>H. polycladum</i>                       | Com | Bohlmann <i>et al.</i> (1980c)                                                                   |
|                    |      | 2'-keto                                                        |                             |                                            |     |                                                                                                  |
| 2',4',4            |      | 2'-O-Glucose                                                   | Davidogenin<br>(6.133)      | <i>H. cymosum</i> ssp. <i>calbum</i>       | Com | Bohlmann <i>et al.</i> (1979c)                                                                   |
| 2',4               | 4'   |                                                                | (6.134) 4'-O-Methyl-        | <i>Viburnum davidii</i>                    | Cpr | Jensen <i>et al.</i> (1977)                                                                      |
|                    |      |                                                                | davidigenin                 | <i>Viburnum</i> spp.                       | Cpr | Jensen <i>et al.</i> (1977)                                                                      |
| 2',4',4            |      | $\beta$ -Keto                                                  | (6.147) Licodione           | <i>Glycyrrhiza echinata</i>                | Leg | Furuya <i>et al.</i> (1976)                                                                      |
| 2',4',6',4         |      |                                                                | (6.135)                     | <i>Helichrysum splendidum</i>              | Com | Bohlmann and Suwita (1979b)                                                                      |
| 2',4',4            | 4'   | 2'-O-Glucose                                                   | (6.136) Phlorthizin         | <i>Malus</i> spp.                          | Ros | A. H. Williams (1979)                                                                            |
|                    |      |                                                                |                             | <i>Rhododendron</i> spp.                   | Eri | Mabry <i>et al.</i> (1975); King (1977a,b)                                                       |
| 2',4'              | 6',4 | 2'-O-Glucose                                                   | (6.137) Asebotin            | <i>Rhododendron</i> spp.                   | Eri | Mabry <i>et al.</i> (1975); King (1977a,b)                                                       |
| 2',6'              | 4',4 |                                                                | (6.138)                     | <i>Iryanthera laevis</i>                   | Myt | Mabry <i>et al.</i> (1975); King (1977a,b)                                                       |
| 2',6',4            | 4'   | 3'-C-Methyl                                                    | (6.139)                     | <i>Iryanthera laevis</i>                   | Fil | Braz Filho <i>et al.</i> (1980)                                                                  |
|                    |      |                                                                | (6.140)                     | <i>Notholaena sulphurea</i>                | Fil | Wollenweber (1977a)                                                                              |
|                    |      |                                                                |                             | <i>Pityrogramma</i>                        | Fil | Wollenweber <i>et al.</i> (1979b)                                                                |
|                    |      |                                                                |                             | <i>triangularis</i> var.<br><i>viscosa</i> |     |                                                                                                  |
| 2',3',4',6',4      |      | 5'-C-Geranyl                                                   | (6.141)                     | <i>Helichrysum monticola</i>               | Com | Bohlmann and Zdero (1980)                                                                        |
| 2',3',4',6',4      |      | 5'-C-Neryl                                                     | (6.142)                     | <i>H. monticola</i>                        | Com | Bohlmann and Zdero (1980)                                                                        |
| 2',4',4            | 3'   |                                                                | (6.143)                     | <i>Iryanthera polyneura</i>                | Myt | de Almeida <i>et al.</i> (1979)                                                                  |
| 2',4',6',3,4       |      |                                                                | (6.144)                     | <i>Balanophora tobricola</i>               | Bal | Ito <i>et al.</i> (1980)                                                                         |
|                    |      | 4'-O-Glucose                                                   |                             | <i>B. tobricola</i>                        | Bal | Ito <i>et al.</i> (1980)                                                                         |
| 2'                 |      | Furano(2'',3'',4',3');<br>3,4-methylenedioxy;<br>$\beta$ -keto | (6.148) Ovalitenone         | <i>Pongamia glabra</i>                     | Leg | Garg <i>et al.</i> (1978); Sharma and<br>Parthasarathy<br>(1977); Talapatra <i>et al.</i> (1980) |
| 2',4',3,5, $\beta$ | 4    |                                                                | (6.160)                     | <i>Milletia ovalifolia</i>                 | Leg | Gupta and Krishnamurti (1977b)                                                                   |
|                    |      |                                                                |                             | <i>Gliricidia sepium</i>                   | Leg | Manners and Jurd (1979)                                                                          |

\* Key: Ano = Anonaceae, Bal = Balanophoraceae, Com = Compositae, Cpr = Caprifoliaceae, Eri = Ericaceae, Fil = Filicinae, Leg = Leguminosae, Myr = Myricaceae, Myt = Myristicaceae, Ros = Rosaceae.

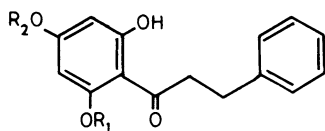
Table 6.5 Structures of dihydrochalcones having complex substituents

| <i>Names*</i>                                                 | <i>No. in text</i> | <i>Source†</i>           | <i>References</i>                                              |
|---------------------------------------------------------------|--------------------|--------------------------|----------------------------------------------------------------|
| 2',4',4'-Tri-C-methylcyclopentenenedione-A-ring               | (6.122)            | <i>Myrica gale</i>       | Myr    Anthonen <i>et al.</i> (1971)                           |
| 3',5',5'-Tri-C-methylcyclohexanetrione-A-ring                 | (6.121)            | <i>M. gale</i>           | Myr    Uyar <i>et al.</i> (1978)                               |
| Cyclic 7-ring dihydrochalcone                                 | (6.123)            | <i>Radula variabilis</i> | Hep    Asakawa <i>et al.</i> (1978)                            |
| Chamuvaritin                                                  | (6.132)            | <i>Uvaria chamae</i>     | Ano    Okorie (1977)                                           |
| 5,7-Dihydroxy-8-(3-phenylpropionyl)-4-phenyl-dihydrocoumarins |                    | <i>Pityrogramma</i> spp. | Fil    Wagner <i>et al.</i> (1979); Dietz <i>et al.</i> (1980) |

\* Trivial names have not been proposed for entries other than chamuvaritin.

† Key: Ano = Anonaceae, Fil = Filicinae, Hep = Hepaticae, Myr = Myricaceae.

upon a phloroglucinol A ring (6.115) has been found in *Helichrysum polycladum* (Bohlmann *et al.*, 1980c) where it occurs with other prenylated flavonoids. 2',4',6'-Trihydroxydihydrochalcone (6.114), itself, occurs in *H. tenuifolium* (Bohlmann and Abraham, 1979a), while its 2'-O- and 4'-O-glucosides, (6.116) and (6.117) respectively have been reported in several taxa of *Malus* (C. A. Williams, 1979). 2',6'-Dihydroxy-4'-methoxydihydrochalcone (6.118) has



(6.114)  $R_1 = R_2 = H$

(6.115)  $R_1 = H, R_2 = \text{---CH=CH-CH}_3$

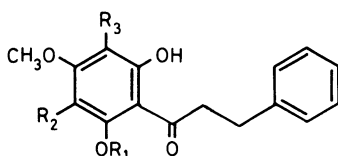
(6.116)  $R_1 = \text{Glc}, R_2 = H$

(6.117)  $R_1 = H, R_2 = \text{Glc}$

(6.118)  $R_1 = H, R_2 = \text{CH}_3$

been found as a constituent of the exudate of white farinose forms of members of the following genera of ferns: *Pityrogramma* (Wollenweber, 1977b, 1979; Dietz *et al.*, 1980), *Notholaena* (Wollenweber, 1977a) and *Adiantum* (Wollenweber, 1979).

Higher levels of methylation, including C-methylation, are seen in several of the compounds isolated from *Myrica gale* (Myricaceae). Relatively simple members of this group include 2',4'-dimethoxy-5'-methyl-6'-hydroxydihydrochalcone (6.119) (Malterud *et al.*, 1977) and 2',6'-dihydroxy-3', 5'-di-C-methyl-4'-methoxydihydrochalcone (6.120) (Anthonsen *et al.*, 1971; Uyar *et al.*, 1978).



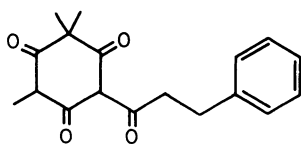
(6.119)  $R_1 = R_3 = \text{CH}_3, R_2 = H$

(6.120)  $R_1 = H, R_2 = R_3 = \text{CH}_3$

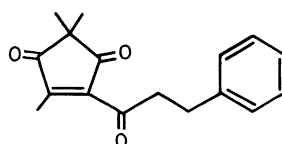
Two C-methylations at position 3' make aromatization impossible and lead to the triketo 'dihydrochalcone' (6.121) discovered by Uyar and co-workers (1978). A most unusual dihydrochalcone is shown as structure (6.122). This compound, also from *M. gale* (Anthonsen *et al.*, 1971), is reminiscent of the contracted A-ring chalcones linderone and methyl-linderone isolated by Kiang and co-workers from *Lindera pipericarpa* (see Bohm, 1975, p. 454). In the case of the compounds from *Myrica* it would be of interest to see if the five-membered ring of (6.122) arises through loss of carbon-6' from (6.121). There seems to be no information

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available concerning the formation of contracted ring flavonoids, although the number is admittedly very small.



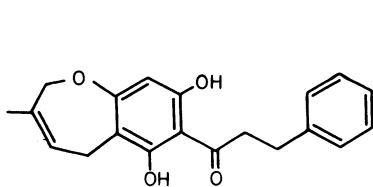
(6.121)



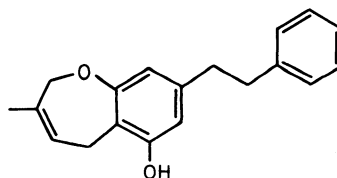
(6.122)

At the time at which the earlier review was prepared *C*-alkylated dihydrochalcones were limited to a small number of *C*-glycosyl derivatives. More recently several *C*-prenylated dihydrochalcones have been isolated from sources as varied as the liverwort *Radula variabilis* to species of *Helichrysum*. The *C*-alkylated compound from *Radula* is shown as structure (6.123). Asakawa and his co-workers (1978) also isolated a series of bibenzyls from *Radula*, the structures of which are shown as (6.124), (6.125) and (6.126) for comparison. The seven-membered ring closure is unusual and has not been reported before in any flavonoid type covered in this chapter and may be unique amongst flavonoids in general.

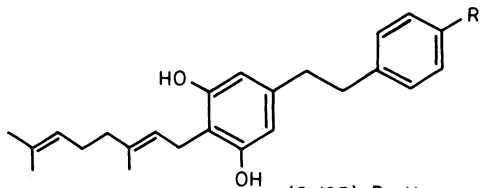
Recent work by Bohlmann and colleagues (1979c, 1980c) has shown a high level of *C*-alkylation in species of *Helichrysum*. Compound (6.127) results from



(6.123)



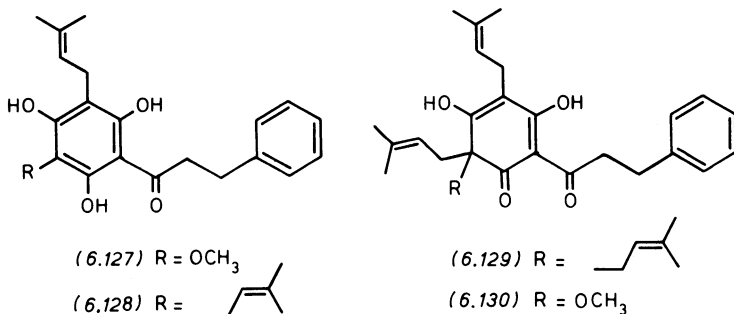
(6.124)



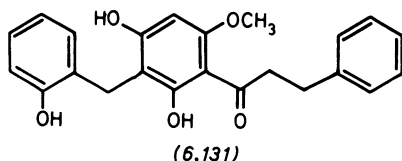
(6.125) R = H

(6.126) R = OH

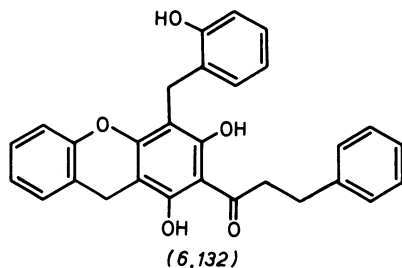
*C*-prenylation, extra hydroxylation and *O*-methylation (not necessarily in that order) while (6.128) would result simply from two *C*-prenylations. Compound (6.129) is unique in having three prenyl substitutions on the A ring, two of which at position 3' prevent formation of the aromatic ring. In compound (6.130) a prenyl group and a methoxy function occupy position 3' which also prevents aromatization.



Studies of the flavonoids of *Uvaria* (Anonaceae) have shown the presence of novel C-benzyl dihydrochalcones in several species. Cole and co-workers (1976) established the structure of 'uvaretin', isolated from *U. acuminata*, as 2',4'-dihydroxy-3'-(2-hydroxybenzyl)-6'-methoxydihydrochalcone (6.131).

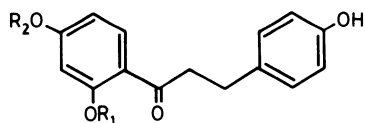


Uvaretin showed inhibitory activity against the P-388(3PS) lymphocytic leukaemia test system. Tammami and co-workers (1977) found uvaretin in *U. kiskii*, while Okorie (1977) isolated the 5'-(2-hydroxybenzyl) isomer of (6.131) from *U. chamae* and called it 'chamuvarin.' Okorie (1977) also found the 3',5'-dibenzyl derivative 'chamuvaretin' (6.132) in *U. chamae*. In (6.132) ring closure has occurred involving the phenolic groups at the 4' position of the flavonoid and on the 2-hydroxybenzyl substituent.



#### (b) Dihydrochalcones having one B-ring hydroxyl

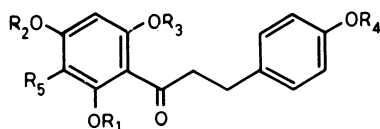
Jensen and colleagues (1977) have confirmed the existence of 'davidoside' (6.133) in *Viburnum davidii* (Caprifoliaceae), reported its presence in *V. lantanoides*, and demonstrated that 4'-O-methyldavidogenin (6.134) is also a constituent of both species.



(6.133)  $R_1 = \text{Glc}$ ,  $R_2 = \text{H}$

(6.134)  $R_1 = \text{H}$ ,  $R_2 = \text{CH}_3$

4,2',4',6'-Tetrahydroxydihydrochalcone (6.135) occurs as the free phenol in *Helichrysum splendidum* (Bohlmann and Suwita, 1979b) and in the form of the well-known 2'-O-glucoside, 'phlorrhizin (phloridzin)' (6.136), in *Malus* species (A. H. Williams, 1979). Phlorrhizin 4'-methyl ether (6.137), commonly called 'asebotin', occurs in several species of *Rhododendron* (King, 1977a,b; Mabry *et al.*, 1975b). The 4,6'-dimethyl ether (6.138) occurs as a trunk-wood constituent of *Iryanthera laevis* (Myristicaceae) (Braz Filho *et al.*, 1980), while the 4,4'-dimethyl ether (6.139) occurs in the farina of the white form of *Notholaena sulphurea* (Wollenweber, 1977a). 4,2',6'-Trihydroxy-3'-methyl-4'-methoxydihydrochalcone (6.140) also occurs as a constituent of the exudate of *Pityrogramma triangularis* var. *viscosa* (Wollenweber *et al.*, 1979b).



(6.135)  $R_1 = R_2 = R_3 = R_4 = R_5 = \text{H}$

(6.136)  $R_1 = \text{Glc}$ ,  $R_2 = R_3 = R_4 = R_5 = \text{H}$

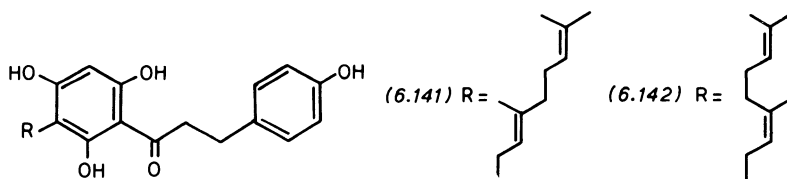
(6.137)  $R_1 = \text{Glc}$ ,  $R_3 = R_4 = R_5 = \text{H}$ ,  $R_2 = \text{CH}_3$

(6.138)  $R_1 = R_2 = R_5 = \text{H}$ ,  $R_3 = R_4 = \text{CH}_3$

(6.139)  $R_1 = R_3 = R_5 = \text{H}$ ,  $R_2 = R_4 = \text{CH}_3$

(6.140)  $R_1 = R_3 = R_4 = \text{H}$ ,  $R_2 = R_5 = \text{CH}_3$

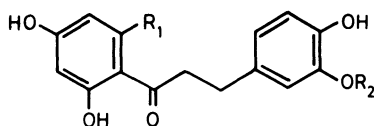
Bohlmann and Zdero (1980) isolated the following pair of isomeric dihydrochalcones from *Helichrysum monticola*: compound (6.141) is the C-geranyl and compound (6.142) is the C-neryl derivative of the parent dihydrochalcone of this subgroup.





**(c) Dihydrochalcones having two B-ring hydroxyls**

Only two representatives of this subgroup have been reported since the 1975 review. 2',4',4'-Trihydroxy-3-methoxydihydrochalcone (6.143) is known to occur in *Iryanthera polyneura* (de Almeida *et al.*, 1979) along with other flavonoids and diarylpropanoids having the same or related substitution patterns. The other member of this subgroup is the unsubstituted pentahydroxydihydrochalcone (6.144) which is found in *Balanophora tobiracola* (Balanophoraceae) along with its 4'-*O*-glucoside (Ito *et al.*, 1980). This represents the first report of a dihydrochalcone from Balanophoraceae.

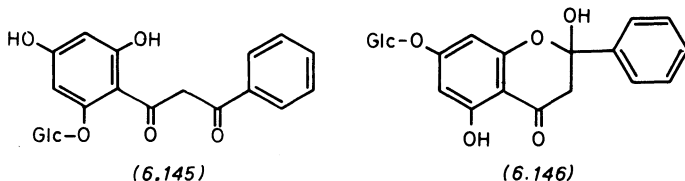


(6.143)  $R_1 = H, R_2 = CH_3$

(6.144)  $R_1 = OH, R_2 = H$

### 6.4.3 Structures of naturally occurring dihydrochalcones having $\beta$ -oxygenation

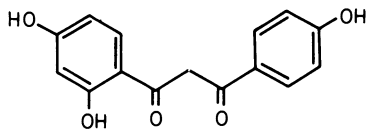
In 1967 A. H. Williams proposed the structure (6.145), 2,4,6-trihydroxydibenzoylmethane 4-glucoside, for a compound that he isolated from *Malus*. In 1972 Chadenson and co-workers suggested that the compound should in fact be written in the form of a 2-hydroxyflavanone (6.146). A similar structure having a 7-methoxyl function was also proposed by Chandenson *et al.* (1972) for a substance isolated from *Populus niger*. Since the time of those reports, several other groups have described the isolation of dibenzoylmethane derivatives from natural sources. In a continuation of his study of phenolic compounds in *Malus*



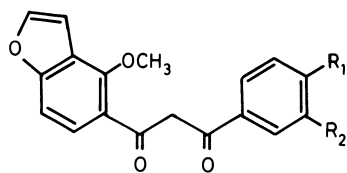
A. H. Williams (1979) reported the occurrence of (6.145) from six species. 'Licodione', isolated from the roots and from cultured cells of *Glycyrrhiza echinata* by Furuya *et al.* (1976), is 2,4,4'-trihydroxybenzoylmethane (6.147). 'Ovalitenone' (6.148) is known from both *Milletia ovalifolia* (Gupta and Krishnamurti, 1977b) and *Pongamia glabra* (Talapatra *et al.*, 1980; Garg *et al.*, 1978; Sharma and Parthasarthy, 1977) where it occurs with 'pongamol' (6.149) (Talapatra *et al.*, 1980). Traub and Geiger (1975) reported the existence of 2,5,7,3',4'-pentahydroxyflavanone 5-*O*-glucoside in seeds of *Galega officinalis*

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(Leguminosae), but represented it as being in equilibrium with the corresponding dibenzoylmethane glucoside (6.151).

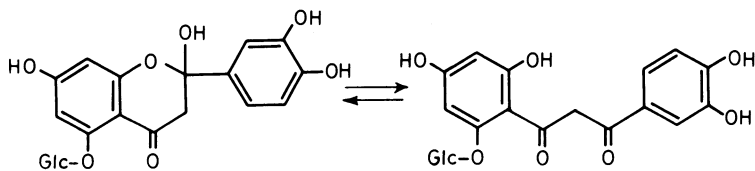


(6.147)

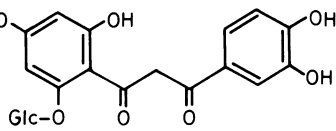


(6.148)  $R_1$  and  $R_2 = -O-CH_2-O-$

(6.149)  $R_1 = R_2 = H$



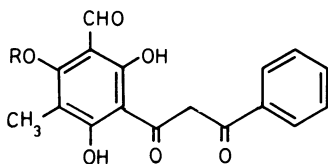
(6.150)



(6.151)

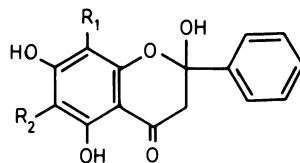
Compounds (6.152) and (6.153) were reported as constituents of *Unona lawii* (Anonaceae) by Joshi and Gawad (1976). A reinvestigation of these structures by Chopin and Hauteville in collaboration with Joshi and Gawad (Chopin *et al.*, 1978) showed that when the 4 position is occupied by a methoxyl function (6.153) the natural product exists in the dibenzoylmethane form, while the presence of the unsubstituted phenolic function at that position is correlated with the existence of the compound as a mixture of the two cyclic hemiketals (= 2-hydroxyflavanones) (6.154) and 6.155).

The explanation for the existence of these compounds in the 2-hydroxyflavanone form would seem to be more complex than whether position 4 has a free phenolic group or whether it is substituted. While the 4-substituted compound (6.153) occurs in the dibenzoylmethane form, the compound from



(6.152)  $R = H$

(6.153)  $R = CH_3$



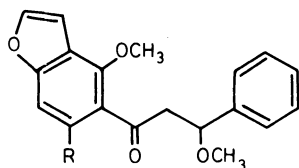
(6.154)  $R_1 = CHO, R_2 = CH_3$

(6.155)  $R_1 = CH_3, R_2 = CHO$

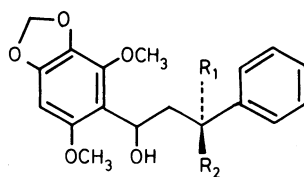
*Malus*, with 4-*O*-glucose, and the compound from *Populus*, with 4-*O*-methyl, appear to exist in the 2-hydroxyflavanone form. Studies with model compounds could be instructive in resolving this problem.

Three dihydrochalcones having  $\beta$ -hydroxyl functions have been described in the recent literature. 'Ovalitenin-B' (6.156) occurs in *Milletia ovalifolia* (Gupta

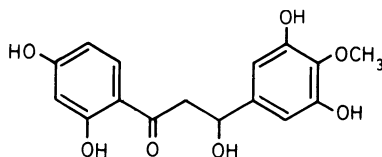
and Krishnamurti, 1977b) along with several other flavonoids having similar substitution patterns. It seems reasonable to suggest biosynthesis from a B-ring unsubstituted precursor which resembles pongamol (6.149) through reduction of the  $\beta$ -keto function followed by *O*-methylation. The structurally very similar (6.157) is known from *Helichrysum mundii* (Bohlmann *et al.*, 1978) where it occurs with the dihydroxy compounds (6.158) and (6.159). These compounds are not, strictly speaking, flavonoids, but they are sufficiently similar structurally to suggest close biosynthetic ties.



(6.156) R = H

(6.157) R = OCH<sub>3</sub>(6.158) R<sub>1</sub> = H, R<sub>2</sub> = OH(6.159) R<sub>1</sub> = OH, R<sub>2</sub> = H

Finally, the  $\beta$ -hydroxy compound (6.160) has been reported by Manners and Jurd (1979) to occur in *Gliricidia sepium* along with the dihydroflavonol 'sepinol', described below, which is characterized by the same, rare *O*-methylation pattern, viz. 3',5'-dihydroxy-4'-methoxy B ring.



(6.160)

## 6.5 FLAVANONES

### 6.5.1 Introduction

The numbering system for flavanones uses primed numbers for the A ring and unprimed numbers for the B ring. Since carbon-2 of the flavanone molecule is a centre of asymmetry, two isomeric forms of each structure are possible. Evidence leading to the establishment of the (2*S*) configuration for the naturally occurring flavanones was presented in the earlier review (Bohm, 1975, pp. 594–595). Not all investigators cited in the present work determined the optical properties of flavanones with which they were working so configurations are not known for some compounds. In many cases newly discovered glycosides or methyl ethers are derived from flavanones of known configuration. In these cases I have taken the liberty of assigning these compounds the configuration of the parent compound. In other cases the (2*S*) configuration has been assigned on the basis of

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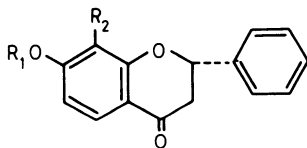
reported laevorotation. An asterisk above a bond (e.g. 6.165) means that no stereochemical assignment is possible based upon the available data. Obviously, more detailed study is required for these compounds. Optical properties of flavanones for which data are available are summarized in Table 6.8.

### 6.5.2 Structures of naturally occurring flavanones

Structures of flavanones reported since 1974 are summarized in Tables 6.6 and 6.7.

#### (a) Flavanones lacking B-ring hydroxyls

The simplest naturally occurring flavanone is compound (6.161) known previously only from members of Leguminosae. A report has now been published describing its occurrence in *Flourensia heterolepis* (Compositae) where it occurs with its methyl ether (6.162) (Bohlmann and Jakupovic, 1979). Hydroxylation at position 8 followed by *O*-methylation affords compound (6.163) isolated from *Zuccagnia punctata* (Leguminosae) by Pederiva *et al.* (1975) while the dimethyl ether (6.164) was isolated from the leaves of *Tetragonia expansa* (Aizoaceae) (Kemp *et al.*, 1979).



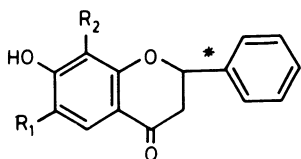
(6.161)  $R_1 = R_2 = H$

(6.162)  $R_1 = CH_3, R_2 = H$

(6.163)  $R_1 = H, R_2 = OCH_3$

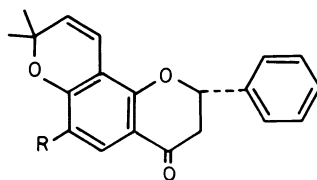
(6.164)  $R_1 = CH_3, R_2 = OCH_3$

Prenylation of the parent compound at position 8 affords flavanone (6.165) while prenylation at both positions 6 and 8 gives (6.166); both compounds occur in *Milletia ovalifolia* where they occur with the dimethylchromenoflavanone (6.167) (Gupta and Krishnamurti, 1976a). 'Isolonchocarpin' (6.168) is the product of cyclization of the prenylated flavanone (6.165) and has been found in



(6.165)  $R_1 = H, R_2 =$

(6.166)  $R_1 = R_2 =$



(6.167)  $R = OCH_3$

(6.168)  $R = H$

Table 6.6 Structures of naturally occurring flavanones

| OH  | OCH <sub>3</sub> | Substituents                         | No. in text | Trivial name           | Source*                                      | References                                                  |
|-----|------------------|--------------------------------------|-------------|------------------------|----------------------------------------------|-------------------------------------------------------------|
| 7   |                  |                                      | (6.161)     |                        | <i>Flourensia heterolepis</i>                | Com Bohlmann and Jakupovic (1979)                           |
|     | 7                |                                      | (6.162)     |                        | <i>F. heterolepis</i>                        | Com Bohlmann and Jakupovic (1979)                           |
| 7   | 8                |                                      | (6.163)     |                        | <i>Zuccagnia punctata</i>                    | Leg Pederiva <i>et al.</i> (1975)                           |
|     | 7,8              |                                      | (6.164)     |                        | <i>Tetragonia expansa</i>                    | Aiz Kemp <i>et al.</i> (1979)                               |
|     |                  | 6'',6''-Dimethyl-pyrano(2'',3'',7,8) | (6.168)     | (-)-Isoloboncho-carpin | <i>Tephrosia purpurea</i>                    | Leg R. K. Gupta <i>et al.</i> (1980); Rao and Raju (1979)   |
|     |                  |                                      |             |                        | <i>Pongamia glabra</i>                       | Leg Satam and Brinji (1973); Talapatra <i>et al.</i> (1980) |
|     | 6                | 6'',6''-Dimethyl-pyrano(2'',3'',7,8) | (6.167)     | Ovali-chromene         | <i>Milletia ovalifolia</i>                   | Leg Gupta and Krishnamurti (1976b)                          |
| 7   |                  | 6,8-di-C-Prenyl                      | (6.166)     |                        | <i>M. ovalifolia</i>                         | Leg Gupta and Krishnamurti (1976a)                          |
| 7   |                  | 8-C-Prenyl                           | (6.165)     |                        | <i>M. ovalifolia</i>                         | Leg Gupta and Krishnamurti (1976a)                          |
| 5,7 |                  |                                      | (6.170)     | Pino-cembrin           | <i>Chrysothamnus nauseus</i>                 | Com Bohlmann <i>et al.</i> (1979a)                          |
|     |                  |                                      |             |                        | <i>Glycyrrhiza glabra</i>                    | Leg Kaltaev and Nikonov (1974)                              |
|     |                  |                                      |             |                        | <i>Helichrysum calliconum</i>                | Com Bohlmann and Abraham (1979b)                            |
|     |                  |                                      |             |                        | <i>H. oreophyllum</i>                        | Com Bohlmann <i>et al.</i> (1980c)                          |
|     |                  |                                      |             |                        | <i>H. tenuifolium</i>                        | Com Bohlmann and Abraham (1979a)                            |
|     |                  |                                      |             |                        | <i>Iryanthera polyneura</i>                  | Myt de Almeida <i>et al.</i> (1979)                         |
|     |                  |                                      |             |                        | <i>Larix dahurica</i>                        | Cnf Lapteva <i>et al.</i> (1974)                            |
|     |                  |                                      |             |                        | <i>Prunus domestica</i>                      | Ros Nagarajan and Parmar (1977b)                            |
|     |                  |                                      |             |                        | <i>Tarchonanthus trilobus</i>                | Com Bohlmann and Suwita (1979a)                             |
|     |                  |                                      |             |                        | <i>Polystichum lepidocaulon</i>              | Fil Hiraoka (1978)                                          |
|     |                  |                                      |             |                        | <i>Nierembergia hippomanica</i>              | Sol Pomilio and Gros (1979)                                 |
|     |                  | 7-O-Rhamnose                         |             |                        | <i>Chrysothamnus nauseus</i>                 | Com Bohlmann <i>et al.</i> (1979a)                          |
|     |                  | 7-O-Neohesperidose                   | (6.171)     | Alpinetin              | <i>Helichrysum herbaceum</i>                 | Com Bohlmann <i>et al.</i> (1979e)                          |
| 7   | 5                |                                      |             |                        | <i>Dalea scandens</i> var. <i>paucifolia</i> | Leg Dominguez <i>et al.</i> (1980)                          |

Table 6.6 (Contd.)

| OH    | OCH <sub>3</sub> | Substituents                                             | Other | No. in text | Trivial name               | Source*                         | References                                                     |
|-------|------------------|----------------------------------------------------------|-------|-------------|----------------------------|---------------------------------|----------------------------------------------------------------|
| 5     | 7                |                                                          |       | (6.172)     | Pino-strobin               | <i>Aniba riparia</i>            | Lau Fernandes <i>et al.</i> (1978)                             |
|       |                  |                                                          |       |             |                            | <i>Helichrysum polycladum</i>   | Com Bohlmann <i>et al.</i> (1980c)                             |
|       |                  |                                                          |       |             |                            | <i>Larix dahurica</i>           | Cnf Lapteva <i>et al.</i> (1974)                               |
|       |                  |                                                          |       |             |                            | <i>Prunus cerasus</i>           | Ros Nagarajan and Parmar (1977c)                               |
|       | 5,7              |                                                          |       | (6.173)     | Dimethyl-pinoembrin        | <i>Agonis spathulata</i>        | Myr Cannon and Martin (1977)                                   |
|       |                  |                                                          |       |             |                            | <i>Aniba riparia</i>            | Lau Fernandes <i>et al.</i> (1978)                             |
| 5     | 6,7              |                                                          |       | (6.174)     |                            | <i>Chrysothamnus nauseosus</i>  | Com Bohlmann <i>et al.</i> (1979a)                             |
| 5,7   | 8                |                                                          |       | (6.175)     | Dihydro-wogonin            | <i>Prunus cerasus</i>           | Ros Nagarajan and Parmar (1977c)                               |
|       | 5,7,8            |                                                          |       | (6.176)     |                            | <i>Popowia cauliflora</i>       | Ano Panichpol and Waterman (1978)                              |
| 7     | 5,6,8            |                                                          |       | (6.178)     | 'Didymocarpin'             | <i>Didymocarpus pedicellata</i> | Ges Bose and Adityachaudhury (1978); Garg <i>et al.</i> (1979) |
|       | 5,6,7,8          |                                                          |       | (6.177)     | Kanakugin                  | <i>Popowia cauliflora</i>       | Ano Waterman and Pootakahn (1979)                              |
| 5,7   |                  | 6-C-Methyl                                               |       | (6.179)     | Strobopinin                | <i>Pityrogramma pallida</i>     | Fil Wollenweber <i>et al.</i> (1979a)                          |
| 5     | 7                | 6-C-Methyl                                               |       | (6.182)     | 7-Methyl-strobopinin       | <i>P. triangularis</i>          | Fil Star <i>et al.</i> (1978)                                  |
| 5,7   |                  | 8-C-Methyl                                               |       | (6.180)     | (-)-Cryptostrobin          | <i>Agonis spathulata</i>        | Myr Cannon and Martin (1977)                                   |
| 5,7   |                  | 6,8-Di-C-methyl                                          |       | (6.181)     | (-)-Desmethoxy-matteucinol | <i>Agonis spathulata</i>        | Myr Cannon and Martin (1977)                                   |
|       |                  |                                                          |       |             |                            | <i>Dalea polyadenia</i>         | Leg Dreyer <i>et al.</i> (1975)                                |
|       |                  |                                                          |       |             |                            | <i>Pityrogramma pallida</i>     | Fil Wollenweber <i>et al.</i> (1979a)                          |
|       |                  |                                                          |       |             |                            | <i>Unona lawii</i>              | Ano Joshi and Gawad (1974)                                     |
|       |                  |                                                          |       |             |                            | <i>Matteucia</i> spp.           | Fil Hiraoka (1978)                                             |
| 5     | 7                | 7-O-Glucose                                              |       | (6.183)     |                            | <i>Unona lawii</i>              | Ano Joshi and Gawad (1974)                                     |
| 5,7,2 |                  | 6,8-Di-C-methyl<br>6-(or 8)-C-Methyl;<br>8-(or 6) formyl |       |             |                            | <i>Unona lawii</i>              | Ano Chopin <i>et al.</i> (1978)                                |

|        |                                                              |         |                        |                                  |      |                                                                                                                          |
|--------|--------------------------------------------------------------|---------|------------------------|----------------------------------|------|--------------------------------------------------------------------------------------------------------------------------|
| 5,7    | 6-Formyl; 8-C-Methyl                                         | (6.184) | Lawinal                | <i>Unona lawii</i>               | Ano  | Joshi and Gawad (1974)                                                                                                   |
| 5,7    | 6-C-Prenyl                                                   | (6.185) |                        | <i>Chlorophora tinctoria</i>     | Mor  | Gottlieb <i>et al.</i> (1975)                                                                                            |
|        |                                                              |         |                        | <i>Helichrysium polycladum</i>   | Com  | Bohlmann <i>et al.</i> (1980c)                                                                                           |
|        |                                                              |         |                        | <i>Derris floribunda</i>         | Leg  | Braz Filho <i>et al.</i> (1975b)                                                                                         |
|        |                                                              |         |                        | <i>D. rariflora</i>              | Leg  | Braz Filho <i>et al.</i> (1975a)                                                                                         |
| 5      | 6-C-Prenyl                                                   | (6.186) |                        | <i>D. rariflora</i>              | Leg  | Braz Filho <i>et al.</i> (1975a)                                                                                         |
|        | 6'',6''-Dimethyl-<br>pyrano(2'',3'',7,8)                     | (6.192) |                        | <i>Tephrosia praecans</i>        | Leg  | Camele <i>et al.</i> (1980)                                                                                              |
| 5,7    | 8-C-Prenyl                                                   | (6.187) | Glabranin              | <i>Helichrysium hypocephalum</i> | Com  | Bohlmann and Abraham (1979d)                                                                                             |
|        |                                                              |         |                        | <i>Platentia absinthifolia</i>   | ?    | Ubaev <i>et al.</i> (1974)                                                                                               |
| 5,7    | 8-C-( $\beta$ -Methyl- $\beta$ -<br>hydroxy-<br>methylallyl) | (6.188) |                        | <i>Helichrysium hypocephalum</i> | Com  | Bohlmann and Abraham (1979d)                                                                                             |
|        | 8-C-( $\beta$ -Methyl-<br>$\beta$ -formylallyl)              |         |                        |                                  |      |                                                                                                                          |
| 5,7    | 8-C-Geranyl                                                  | (6.189) |                        | <i>H. hypocephalum</i>           | Com  | Bohlmann and Abraham (1979d)                                                                                             |
| 5      | 8-C-Prenyl                                                   | (6.190) |                        | <i>H. hypocephalum</i>           | Com  | Bohlmann and Abraham (1979d)                                                                                             |
|        |                                                              | (6.191) | 7-Methyl-<br>glabranin | <i>Tephrosia villosa</i>         | Leg  | Jayaraman <i>et al.</i> (1980)                                                                                           |
| 5,7    | 8-C-(2-Hydroxybenzyl)                                        | (6.194) |                        | <i>Uvaria chamae</i>             | Ano  | Hufford and Laswell (1976)                                                                                               |
| 5,7    | 6-C-(2-Hydroxybenzyl)                                        | (6.195) |                        | <i>Uvaria chamae</i>             | Ano  | Hufford and Laswell (1976)                                                                                               |
| 6,8    | 7-C-(5-Hydroxy-<br>geranyl)                                  | (6.197) | Flemi-<br>flavanone-B  | <i>Flemingia stricta</i>         | Leg  | Sivarambabu <i>et al.</i> (1979a)                                                                                        |
|        |                                                              |         |                        |                                  |      |                                                                                                                          |
| 7,4'   |                                                              | (6.202) | Liquiri-<br>tigenin    | <i>Dalbergia</i> spp.            | Leg. | Matos <i>et al.</i> (1975); Manners <i>et al.</i> (1974); Parthasarathy <i>et al.</i> (1976); Letcher and Shirley (1976) |
|        |                                                              |         |                        | <i>Medicago</i> spp.             | Leg  | Ingham (1979)                                                                                                            |
|        |                                                              |         |                        | <i>Myroxylon balsamum</i>        | Leg  | de Oliveira <i>et al.</i> (1978)                                                                                         |
|        |                                                              |         |                        | <i>Onobrychis viciifolia</i>     | Leg  | Ingham (1978)                                                                                                            |
|        |                                                              |         |                        | <i>Peltogyne</i> spp.            | Leg  | Malan and Roux (1974)                                                                                                    |
|        |                                                              |         |                        | <i>Aerva persica</i>             | Amr  | Garg <i>et al.</i> (1980)                                                                                                |
| 7,4'   | 8-C-Galactose                                                | (6.203) | Aervanone              | <i>Sophora subprostrata</i>      | Leg  | Jain and Gupta (1978)                                                                                                    |
| 7,4'   | 6,8-Di-C-prenyl                                              | (6.204) |                        | <i>Baccharis alaternoides</i>    | Leg  | Bohlmann <i>et al.</i> (1979b)                                                                                           |
| 5,7,4' |                                                              | (6.205) | Naringenin             | <i>Cochlospermum gillivraei</i>  | Com  | Bohlmann <i>et al.</i> (1979b)                                                                                           |
|        |                                                              |         |                        | <i>Cochlospermum gillivraei</i>  | Coc  | Cook and Knox (1975)                                                                                                     |
|        |                                                              |         |                        | <i>Dillenia indica</i>           | Dil  | Pavanasivan and Sultanbawa (1975)                                                                                        |

Table 6.6 (Contd.)

| OH | OCH <sub>3</sub> | Substituents                  | Other | No. in text | Trivial name | Source*                         | References                              |
|----|------------------|-------------------------------|-------|-------------|--------------|---------------------------------|-----------------------------------------|
|    |                  |                               |       |             |              | <i>Equisetum arvense</i>        | Equ Syrchina <i>et al.</i> (1975, 1978) |
|    |                  |                               |       |             |              | <i>Larix dahurica</i>           | Cnf Lapteva <i>et al.</i> (1974)        |
|    |                  |                               |       |             |              | <i>Lygos raetan</i>             | Leg El Sherbeiny <i>et al.</i> (1978)   |
|    |                  |                               |       |             |              | <i>Matthiola incana</i>         | Cru Forkmann (1979)                     |
|    |                  |                               |       |             |              | <i>Nothofagus antarctica</i>    | Fag Wollenweber and Wiermann (1979)     |
|    |                  |                               |       |             |              | <i>Othonna euphorboides</i>     | Com Bohlmann and Knoll (1978)           |
|    |                  |                               |       |             |              | <i>Persica vulgaris</i>         | Ros Sadykov and Sadykov (1979)          |
|    |                  |                               |       |             |              | <i>Picea ajanensis</i>          | Cnf Ivanova <i>et al.</i> (1975)        |
|    |                  |                               |       |             |              | <i>Polymnia fruticosa</i>       | Com Bohlmann and Zdero (1977)           |
|    |                  |                               |       |             |              | <i>Prunus domestica</i>         | Ros Nagarajan and Parmar (1977b)        |
|    |                  |                               |       |             |              | <i>Rhynchosia beddomei</i>      | Leg Adinarayana <i>et al.</i> (1980b)   |
|    |                  |                               |       |             |              | <i>Senecio longilinguae</i>     | Com Bohlmann and Zdero (1979)           |
|    |                  |                               |       |             |              | <i>Soymida febrifuga</i>        | Mel Rao <i>et al.</i> (1979)            |
|    |                  |                               |       |             |              | <i>Steiractinia mollis</i>      | Com Bohlmann <i>et al.</i> (1980b)      |
|    |                  | 5-O-Glucose                   |       |             |              | <i>Persica vulgaris</i>         | Ros Sadykov and Sadykov (1979)          |
|    |                  |                               |       |             |              | <i>Salix elbursensis</i>        | Sal Kompantsev and Shinkarenko (1975)   |
|    |                  | 7-O-Glucose                   |       |             |              | <i>Dryopteris</i> spp.          | Fil Hiraoka (1978)                      |
|    |                  |                               |       |             |              | <i>Matthiola incana</i>         | Cru Forkmann (1979)                     |
|    |                  |                               |       |             |              | <i>Coriaria</i> spp.            | Cor Bohm and Ornduff (1981)             |
|    |                  |                               |       |             |              | <i>Cochlospermum gillivraei</i> | Coc Cook and Knox (1975)                |
|    |                  | 7-O-Glucose-6''-galloyl       |       |             |              | <i>Acacia farnesiana</i>        | Leg El Sissi <i>et al.</i> (1974)       |
|    |                  | 7-O-Glucose-6''-O-p-coumaroyl |       |             |              | <i>Anacardium occidentale</i>   | Ana Rahman <i>et al.</i> (1978)         |
|    |                  | 7-O-Rhamnose                  |       |             |              | <i>Litsea glutinosa</i>         | Lau Mohan <i>et al.</i> (1978)          |
|    |                  | ?-O-Fructose                  |       |             |              | <i>Camellia sinensis</i>        | The Imperato (1976)                     |
|    |                  | 4'-O-Galactose                |       |             |              | <i>Cleome viscosa</i>           | Cpr Chauhan <i>et al.</i> (1979b)       |
|    |                  | 4'-O-Xylosylglucose           |       |             |              | <i>C. viscosa</i>               | Cpr Srivastava <i>et al.</i> (1979)     |
|    |                  | 4'-O-Rutinose                 |       |             |              | <i>Bauhinia variegata</i>       | Leg Gupta <i>et al.</i> (1979)          |
|    |                  | 7-O-Rutinose                  |       |             |              | <i>Citrus hybrids</i>           | Rut Kamiya <i>et al.</i> (1979)         |
|    |                  |                               |       |             | Narirutin    |                                 |                                         |



|                               |                    |                                                  |     |                                       |
|-------------------------------|--------------------|--------------------------------------------------|-----|---------------------------------------|
| 7-O-Neohesperidose            | Naringin           | <i>Adiantum</i> spp.                             | Fil | Cooper-Driver and Swain (1977)        |
|                               |                    | <i>Citrus</i> hybrids                            | Rut | Kamiya <i>et al.</i> (1979)           |
|                               |                    | <i>Clymenia polyandra</i>                        | Rut | Grieve and Scora (1980)               |
|                               |                    | <i>Fortunella japonica</i>                       | Rut | Grieve and Scora (1980)               |
| 6-C-Glucose                   | (6.213)            | <i>F. margarita</i>                              | Rut | Grieve and Scora (1980)               |
|                               |                    | <i>Microcitrus inodora</i>                       | Rut | Grieve and Scora (1980)               |
|                               |                    | <i>Tulipa gesneriana</i>                         | Lil | Budzianowski and Skrzypczakowa (1978) |
|                               |                    | <i>Baccharis trinervis</i> var. <i>rhexoides</i> | Com | Bohlmann <i>et al.</i> (1979b)        |
| 7                             | Sakuranetin        | <i>Betula</i> spp.                               | Bet | Wollenweber (1975)                    |
|                               |                    | <i>Gymnopentzia bifurcata</i>                    | Com | Bohlmann and Zdero (1978)             |
|                               |                    | <i>Notholaena fendleri</i>                       | Fil | Wollenweber <i>et al.</i> (1980a)     |
|                               |                    | <i>Polymnia fruticosa</i>                        | Com | Bohlmann and Zdero (1977)             |
| 5,7                           | (6.207)            | <i>Prunus cerasus</i>                            | Ros | Nagarajan and Parmar (1977c)          |
|                               |                    | <i>Baccharis alaternoides</i>                    | Com | Bohlmann <i>et al.</i> (1979b)        |
|                               |                    | <i>Betula</i> spp.                               | Bet | Wollenweber (1975)                    |
|                               |                    | <i>Gymnopentzia bifurcata</i>                    | Com | Bohlmann and Zdero (1978)             |
| 5-O-Glucose<br>7-O-Rutinoside | Didymin            | <i>Notholaena fendleri</i>                       | Fil | Wollenweber <i>et al.</i> (1980)      |
|                               |                    | <i>Prunus domestica</i>                          | Ros | Nagarajan and Parmar (1977b)          |
|                               |                    | <i>Hopaea dichotoma</i>                          | Gen | Ghosal <i>et al.</i> (1978)           |
|                               |                    | 'Satsuma orange'                                 | Rut | Bandyukova and Fishman (1979)         |
| 7-O-Neo-hesperidose           | Poncirin           | <i>Citrus</i> hybrids                            | Rut | Kamiya <i>et al.</i> (1979)           |
|                               |                    | <i>Citrus</i> hybrids                            | Rut | Kamiya <i>et al.</i> (1979)           |
|                               |                    | <i>Eremocitrus glauca</i>                        | Rut | Grieve and Scora (1980)               |
|                               |                    | <i>Microcitrus australasica</i>                  | Rut | Grieve and Scora (1980)               |
| 5<br>7,4'                     | (6.208)<br>(6.210) | <i>M. inodora</i>                                | Rut | Grieve and Scora (1980)               |
|                               |                    | <i>Gnaphalium multiceps</i>                      | Com | Maruyama <i>et al.</i> (1974)         |
|                               |                    | <i>Betula</i> spp.                               | Bet | Wollenweber (1975)                    |
|                               |                    | <i>Dahlia tenuicaulis</i>                        | Com | Lam and Wrag (1975)                   |
| 5,7                           | (6.207)            | <i>Eupatorium odoratum</i>                       | Com | Arene <i>et al.</i> (1978)            |

Table 6.6 (Contd.)

| OH             | OCH <sub>3</sub> | Substituents                                                                                             | Other | No. in text                   | Trivial name            | Source*                                                                                                                                                                | References                                                                                                                                             |
|----------------|------------------|----------------------------------------------------------------------------------------------------------|-------|-------------------------------|-------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| 4'             | 5,7              | 4'-O-Xylosyl-arabinose<br>4'-O-Rhamnosyl-glucose                                                         |       | (6.209)                       |                         | <i>Baccharis alaternoides</i><br><i>Hibiscus mutabilis</i><br><i>Bauhinia variegata</i>                                                                                | Com Bohlmann <i>et al.</i> (1979b)<br>Mal Chauhan <i>et al.</i> (1979c)<br>Leg Gupta <i>et al.</i> (1980)                                              |
| 5,2'<br>5,7,4' | 5,7,4'<br>7      | 2'-O-Glucose<br>6,8-Di-C-methyl<br>5,7-Di-O-glucose<br>7-O-Glucose                                       |       | (6.211)<br>(6.212)<br>(6.214) | Haplanthin<br>Farrerol  | <i>Dahlia tenuicaulis</i><br><i>Haplanthus tentaculatus</i><br><i>Rhododendron</i> spp.<br><i>Rhododendron</i> spp.<br><i>Cyrtomium</i> spp.<br><i>Matteuccia</i> spp. | Com Lam and Wrang (1975)<br>Aca Viswanathan and Sidhaye (1976)<br>Eri King (1977a,b)<br>Eri King (1977a,b)<br>Fil Hiraoka (1978)<br>Fil Hiraoka (1978) |
| 5,7            | 4'               | 6,8-Di-C-methyl;<br>7-O-glucose                                                                          |       | (6.215)                       | Matteucinol-7-glucoside |                                                                                                                                                                        | Fil Hiraoka (1978)                                                                                                                                     |
| 5,7,4'<br>5,4' |                  | 8-C-Prenyl<br>6-C-Prenyl; 6'',6''-dimethylpyrano-(2'',3'',7,8)<br>6- or 8-C-Prenyl;<br>4',7-Di-O-glucose |       | (6.216)<br>(6.217)            | Cajafuranone            | <i>Marshallia grandiflora</i><br><i>Cajanus cajan</i>                                                                                                                  | Com Bohlmann <i>et al.</i> (1979d)<br>Leg Bhanumati <i>et al.</i> (1978)                                                                               |
| 5,7,4'         |                  |                                                                                                          |       |                               |                         | <i>Eioda rutaecarpa</i>                                                                                                                                                | Rut Grimshaw and Lamer-Zarawska (1975)                                                                                                                 |
| 5,4'           | 6,7              |                                                                                                          |       | (6.218)                       |                         | <i>Cheilanthes argentea</i>                                                                                                                                            | Fil Wollenweber <i>et al.</i> (1980a)                                                                                                                  |
| 5              | 6,7,4'           |                                                                                                          |       | (6.219)                       |                         | <i>C. argentea</i>                                                                                                                                                     | Fil Wollenweber <i>et al.</i> (1980a)                                                                                                                  |
| 5,4'           | 7,8              |                                                                                                          |       | (6.220)                       |                         | <i>C. argentea</i>                                                                                                                                                     | Fil Wollenweber <i>et al.</i> (1980a)                                                                                                                  |
| 5              | 7,8,4'           |                                                                                                          |       | (6.221)                       |                         | <i>C. argentea</i>                                                                                                                                                     | Fil Wollenweber <i>et al.</i> (1980a)                                                                                                                  |
| 5,6            | 7,8,4'           |                                                                                                          |       | (6.222)                       |                         | <i>C. argentea</i>                                                                                                                                                     | Fil Wollenweber <i>et al.</i> (1980a)                                                                                                                  |
| 5,4'           | 6,7,8            |                                                                                                          |       | (6.223)                       |                         | <i>C. argentea</i>                                                                                                                                                     | Fil Wollenweber <i>et al.</i> (1980a)                                                                                                                  |
| 5              | 6,7,8,4'         |                                                                                                          |       | (6.224)                       |                         | <i>C. argentea</i>                                                                                                                                                     | Fil Wollenweber <i>et al.</i> (1980a)                                                                                                                  |
| 4'             | 5,6,7            |                                                                                                          |       | (6.225)                       |                         | <i>Chromolaena odorata</i>                                                                                                                                             | Com Barua <i>et al.</i> (1978)                                                                                                                         |
| 7,3',4'        |                  |                                                                                                          |       | (6.226)                       |                         | <i>Gliricidia sepium</i><br><i>Acacia saxatilis</i><br><i>Peltogyne</i> spp.<br><i>Acacia</i> spp.                                                                     | Leg Jurd and Manners (1977)<br>Leg Fourie <i>et al.</i> (1974)<br>Leg Malan and Roux (1974)<br>Leg Tindale and Roux (1974)                             |

|           |                                       |         |                             |                            |     |                                                            |
|-----------|---------------------------------------|---------|-----------------------------|----------------------------|-----|------------------------------------------------------------|
| 7,8,3',4' | 7-O-Glucose                           | (6.227) | (2R)-Iso-okanin-7-glucoside | <i>Bidens tripartita</i>   | Com | Serbin <i>et al.</i> (1975)                                |
|           |                                       | (6.228) | (2S)-Iso-okanin-7-glucoside |                            |     |                                                            |
| 7         | 8-C-Prenyl; 3',4'-methylenedioxy      | (6.231) | Ovaliflavone-C              | <i>Bidens</i> spp.         | Com | Hart (1979)                                                |
|           |                                       | (6.232) | Ovaliflavone-D              | <i>Milletia ovalifolia</i> | Leg | Islam <i>et al.</i> (1980)                                 |
| 7         | 6,8-Di-C-prenyl; 3',4'-methylenedioxy | (6.230) | Ovaliflavone-B              | <i>M. ovalifolia</i>       | Leg | Islam <i>et al.</i> (1980)                                 |
|           |                                       | (6.229) | Ovaliflavone-A              | <i>M. ovalifolia</i>       | Leg | Islam <i>et al.</i> (1980)                                 |
| 5,7,3',4' |                                       | (6.233) | Eriodictyol                 | <i>Coleus amboinicus</i>   | Lab | Brieskorn and Riedel (1977)                                |
|           |                                       |         |                             | <i>Garcinia conrauaana</i> | Clu | Waterman and Crichton (1980)                               |
|           |                                       |         |                             | <i>Lasianthus japonica</i> | Rub | Ishikura <i>et al.</i> (1979)                              |
|           | 5-O-Rhamnose                          |         |                             | <i>Cleome viscosa</i>      | Cpr | Srivastava and Srivastava (1979a)                          |
|           | 7-O-Rhamnose                          |         |                             | <i>Phyllanthus niruri</i>  | Eup | Chauhan <i>et al.</i> (1977)                               |
|           | 7-O-Glucose                           |         |                             | <i>Lasianthus japonica</i> | Rub | Ishikura <i>et al.</i> (1979)                              |
|           |                                       |         |                             | <i>Dryopteris</i> spp.     | Fil | Hiraoka (1978)                                             |
|           | 7-O-Rhamnosylglucose                  |         |                             | <i>Mentha longifolia</i>   | Lab | Bourweig and Pohl (1973)                                   |
|           |                                       |         |                             | <i>Dryopteris</i> spp.     | Fil | Hiraoka (1978)                                             |
|           |                                       |         |                             | <i>Rhododendron</i> spp.   | Eri | King (1977a,b)                                             |
|           | Unidentified-glycoside                |         |                             | <i>Citrus</i> hybrids      | Rut | Kamiya <i>et al.</i> (1979)                                |
|           | 7-O-Rutinose                          |         | Eriocitrin                  | <i>Citrus</i> hybrids      | Rut | Kamiya <i>et al.</i> (1979)                                |
|           | 7-O-Neohesperidose                    | (6.234) | Neocitricitrin              | <i>Persica vulgaris</i>    | Ros | Sadykov and Sadykov (1979)                                 |
| 5,7,3'    |                                       |         | Hesperetin                  | <i>P. vulgaris</i>         | Ros | Sadykov and Sadykov (1979)                                 |
|           | 5-O-Glucose                           |         |                             | <i>Cordia obliqua</i>      | Bor | Chauhan <i>et al.</i> (1978); Tiwari and Srivastava (1979) |
|           | 7-O-Rhamnose                          |         |                             |                            |     |                                                            |

Table 6.6 (Contd.)

| OH           | OCH <sub>3</sub> | Substituents                                     | Other | No. in text | Trivial name   | Source*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Lab                                                                                                                                                           | References                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|--------------|------------------|--------------------------------------------------|-------|-------------|----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|              |                  | 7-O-Rutinose                                     |       |             | Hesperidin     | <i>Mentha longifolia</i><br><i>Vernonia brevifolia</i><br><i>Zanthoxylum avicennae</i><br><i>Z. dipetalum</i><br><i>Citrus</i> hybrids<br><i>Eremocitrus glauca</i><br><i>Fortunella margarita</i><br><i>Pleiospermium sumatranum</i><br><i>Poncirus trifoliata</i><br><i>Citrus</i> hybrids<br><i>Eupatorium odoratum</i><br><i>Notholaena</i> spp.<br><i>Persica vulgaris</i><br><i>P. vulgaris</i><br><i>Hoppea dichotoma</i><br><i>Notholaena</i> spp.<br><i>Cyrtomium</i> spp.<br><i>Galega officinalis</i><br><i>Inula cappa</i><br><i>Terminalia arjuna</i><br><i>Prunus cerasus</i><br><i>Flourensia heterolepis</i><br><i>Flemingia stricta</i><br><i>F. wallichii</i> | Com<br>Rut<br>Rut<br>Rut<br>Rut<br>Rut<br>Rut<br>Rut<br>Rut<br>Com<br>Fil<br>Ros<br>Ros<br>Gen<br>Fil<br>Fil<br>Leg<br>Com<br>Cmb<br>Ros<br>Com<br>Leg<br>Leg | Bourweig and Pohl (1973)<br>Mabry <i>et al.</i> (1975)<br>Fish <i>et al.</i> (1975a)<br>Fish <i>et al.</i> (1975b)<br>Kamiya <i>et al.</i> (1979)<br>Grieve and Scora (1980)<br>Grieve and Scora (1980)<br>Grieve and Scora (1980)<br>Grieve and Scora (1980)<br>Kamiya <i>et al.</i> (1979)<br>Arene <i>et al.</i> (1978)<br>Wollenweber <i>et al.</i> (1980a)<br>Sadykov and Sadykov (1979)<br>Sadykov and Sadykov (1979)<br>Ghosal <i>et al.</i> (1978)<br>Wollenweber <i>et al.</i> (1980a)<br>Hiraoka (1978)<br>Traub and Geiger (1975)<br>Baruah <i>et al.</i> (1979)<br>Nagar <i>et al.</i> (1979)<br>Nagarajan and Parmar (1977a)<br>Bohlmann and Jakupovic (1979)<br>Sivarambabu <i>et al.</i> (1979a)<br>Rao <i>et al.</i> (1975b) |
| 5,4'         | 7,3'             | 7-O-Neohesperidose                               |       | (6.235)     | Neohesperidin  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 5,3'         | 7,4'             |                                                  |       | (6.236)     | Persicogenin   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 5,7          | 3',4'            | 5-O-Glucose                                      |       | (6.237)     |                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 5            | 7,3',4'          | 5-O-Glucose                                      |       | (6.238)     |                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 5,7,3',4'    |                  | 6,8-Di-C-methyl                                  |       | (6.239)     | Cyrtominetin   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 5,7,2',3',4' |                  | 5-O-Glucose                                      |       | (6.241)     |                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 5,7,2',5'    |                  |                                                  |       | (6.243)     | Arjunone       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 7            | 5,7,2',4'        |                                                  |       | (6.242)     |                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 5,3',4'      | 7                | 8-C-Prenyl                                       |       | (6.240)     |                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 5,7,2'       | 4'               | 6,8-Di-C-methyl                                  |       | (6.244)     | Flemiflavone-A |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 5,2',4'      |                  | 6'',6''-Dimethyl-pyrano(2'',3'',7,6); 8-C-prenyl |       | (6.245)     | Flemichin-D    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| S | 7,3',4',5'   | (enantiomer of<br>flemichin-D) | Flemiflavone-C<br>(6.248) | <i>F. stricta</i><br><i>Notholaena lemmonii</i><br><i>Cassia renigera</i> | Leg | Sivarambabu <i>et al.</i> (1979a) |
|---|--------------|--------------------------------|---------------------------|---------------------------------------------------------------------------|-----|-----------------------------------|
|   |              |                                |                           |                                                                           |     |                                   |
| S | 6,7,3',4',5' | 5-O-Rhamnose                   | (6.249)                   |                                                                           | Leg | Wollenweber <i>et al.</i> (1980a) |

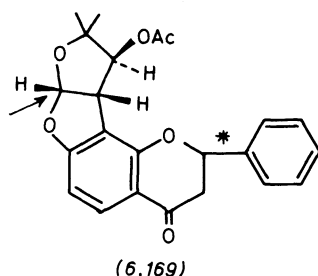
\* Key: Aca = Acanthaceae, Aiz = Aizoaceae, Amr = Amaranthaceae, Ano = Anonaceae, Bet = Betulaceae, Bor = Boraginaceae, Cpr = Capparaceae, Clu = Clusiaceae, Cnf = Coniferae, Coc = Cochlospermaceae, Cmb = Combretaceae, Com = Compositae, Cor = Coriariaceae, Cru = Cruciferae, Dil = Dilleniaceae, Equ = Equisetaceae, Eri = Ericaceae, Eup = Euphorbiaceae, Fag = Fagaceae, Fil = Filicinae, Gen = Gentianaceae, Ges = Gesneriaceae, Lab = Labiatae, Lau = Lauraceae, Leg = Leguminosae, Lil = Liliaceae, Mal = Malvaceae, Mel = Meliaceae, Mor = Moraceae, Myr = Myrtaceae, Myt = Myristicaceae, Ros = Rosaceae, Rub = Rubiaceae, Rut = Rutaceae, Sal = Salicaceae, Sol = Solanaceae, The = Theaceae.

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**Table 6.7** Structures of flavanones having complex substituents

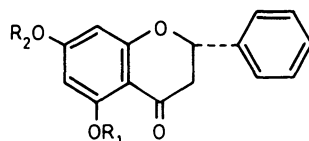
| Name             | No. in text | Source*                        | References                            |
|------------------|-------------|--------------------------------|---------------------------------------|
| Purpurin         | (6.169)     | <i>Tephrosia purpurea</i>      | Leg R. K. Gupta <i>et al.</i> (1980)  |
| Uvarinol         | (6.196)     | <i>Uvaria chamae</i>           | Ano Hufford <i>et al.</i> (1979)      |
| Louisfieserone-A | (6.200)     | <i>Dalea</i> spp.              | Leg Dominguez <i>et al.</i> (1980)    |
|                  |             | <i>Indigofera suffruticosa</i> | Leg Dominguez <i>et al.</i> (1978a,b) |
| Louisfieserone-B | (6.201)     | <i>Dalea</i> spp.              | Leg Dominguez <i>et al.</i> (1980)    |
| Flemichin-E      | (6.246)     | <i>Flemingia wallachii</i>     | Leg Sivarambabu <i>et al.</i> (1979b) |
| Flemichin-A      | (6.247)     | <i>Flemingia wallachii</i>     | Leg Rao <i>et al.</i> (1974)          |

\* Key: Ano = Anonaceae, Leg = Leguminosae.



a number of leguminous genera: *Tephrosia* (Rao and Raju, 1979; Gupta *et al.*, 1980), *Pongamia* (Talapatra *et al.*, 1980; Satam and Bringi, 1973) and *Lonchocarpus* (Delle Monache *et al.*, 1978). Accompanying isolonchocarpin in *Tephrosia purpurea* is the highly unusual alkylated flavanone, 'purpurin' (6.169). The biosynthetic origin of purpurin could be viewed as an interaction between a normal prenyl function at C-8 and an *O*-methyl (or biochemical equivalent) at position 7 (marked with an arrow). Hydration and acetylation would complete the process.

The simplest flavanone that bears the phloroglucinol hydroxylation pattern on the A ring is pinocembrin (6.170). Distribution of pinocembrin and its glycosidic derivatives is summarized in Table 6.6. Pinocembrin has been reported for the first time from the following flowering plant families: Compositae, Leguminosae,



(6.171)  $R_1 = CH_3$ ,  $R_2 = H$

(6.172)  $R_1 = H$ ,  $R_2 = CH_3$

(6.173)  $R_1 = R_2 = CH_3$

Table 6.8 Optical properties of some flavanones

| Name                                          | No. in text | Rotation* | Sources†                          | References                            |
|-----------------------------------------------|-------------|-----------|-----------------------------------|---------------------------------------|
| Purpurin                                      | (6.169)     | —         | 25 <i>Tephrosia purpurea</i>      | Leg R. K. Gupta <i>et al.</i> (1980)  |
| Cajafavanone                                  | (6.217)     | 1.05      | 25 <i>Cajanus cajan</i>           | Leg Bhanumati <i>et al.</i> (1978)    |
| Didymocarpin‡                                 | —           | 0.7       | — <i>Didymocarpus pedicellata</i> | Ges Bose and Adityachaudhury (1978)   |
| Eriodictyol 3',4-dimethyl ether               | —           | —         | —                                 | —                                     |
| 5-O-glucoside                                 | (6.237)     | 0.5       | 28 <i>Hoppea dichotoma</i>        | Gen Ghosal <i>et al.</i> (1978)       |
| Isopentenylnaringenin                         | —           | 0.7       | — <i>Evodia rutaecarpa</i>        | Rut Grimshaw and Lamer-               |
| 7,4'-diglucoside†                             | —           | —         | —                                 | Zarawska (1975)                       |
| Ovalichromene                                 | (6.167)     | —         | 20 <i>Milletia ovalifolia</i>     | Leg Gupta and Krishnamurti (1976b)    |
| Ovalichromene-A                               | (6.229)     | —         | 25 <i>M. ovalifolia</i>           | Leg Gupta and Krishnamurti (1976c)    |
| Ovalichromene-B                               | (6.230)     | —         | 25 <i>M. ovalifolia</i>           | Leg Gupta and Krishnamurti (1976c)    |
| (-)-Salipurposide (naringenin-5-O-glucoside)§ | —           | 0.78      | 20 <i>Salix elbursensis</i>       | Sal Kompantsev and Shinkarenko (1975) |
| Flemichin-A                                   | (6.247)     | 0.135     | 25 <i>Flemingia wallichii</i>     | Leg Rao <i>et al.</i> (1974)          |
| Flemichin-D                                   | (6.245)     | 0.10      | — <i>F. wallichii</i>             | Leg Rao <i>et al.</i> (1975b)         |
| Isolouchocarpin                               | (6.168)     | —         | 28 <i>Tephrosia purpurea</i>      | Leg Rao and Raju (1979)               |
| Isolouchocarpin                               | —           | 0.065     | 28 <i>Pongamia glabra</i>         | Leg Talapatra <i>et al.</i> (1980)    |
| Flemifavanone-A                               | (6.244)     | 0.034     | 25 <i>Flemingia stricta</i>       | Leg Sivarambabu <i>et al.</i> (1979a) |
| Flemifavanone-B                               | (6.197)     | 0.045     | 25 <i>Flemingia stricta</i>       | Leg Sivarambabu <i>et al.</i> (1979a) |
| Flemifavanone-C                               | (6.245)     | 0.026     | 25 <i>F. stricta</i>              | Leg Sivarambabu <i>et al.</i> (1979a) |
| Flemichin-E                                   | (6.246)     | 0.29      | — <i>F. wallichii</i>             | Leg Sivarambabu <i>et al.</i> (1979b) |
| Kanakugin                                     | (6.177)     | 0.00      | 24 <i>Popowia cauliflora</i>      | Ano Waterman and Pootakham (1979)     |

\* Rotation data: rotation in degrees using sodium D-line, concentration, solvent, temperature. "—" means datum not provided by authors.

† Key: Ano = Anonaceae, Gen = Gentianaceae, Ges = Gesneriaceae, Leg = Leguminosae, Sal = Salicaceae, Rut = Rutaceae.

‡ Structure of this compound has been challenged, see text.

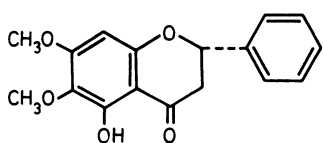
§ Structures of these compounds were not drawn in text.

|| Flemifavanone-C is thought to be an enantiomer of Flemichin-D.

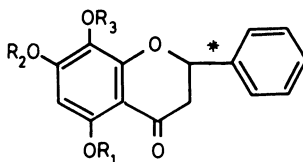
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Myristicaceae and Solanaceae. Pinocembrin, as the 7-rhamnoside, has also been detected in several members of Athyriaceae and Dryopteridaceae (Hiroaka, 1978). Pinocembrin 5-methyl ether, 'alpinetin' (6.171), has been reported from Compositae (Bohlmann *et al.*, 1979a,e) and *Dalea scandens* (Leguminosae) (Dominguez *et al.*, 1980), both of which constitute new familial records. Pinostrobin (6.172) and dimethylpinostrobin (6.173) occur in *Aniba riparia* (Lauraceae) (Fernandes *et al.*, 1978).

The dimethyl ether (6.174), not previously known as a natural product, has been found by Bohlmann *et al.* (1979a) in *Chrysothamnus nauseosus* (Compositae) where it occurs with alpinetin and pinocembrin. 5,7-Dihydroxy-8-methoxyflavanone (6.175), commonly called dihydrowogonin, occurs in *Prunus cerasus* and has been synthesized by Nagarajan and Parmar (1977c). The fully *O*-methylated flavanone (6.176) occurs in *Popowia cauliflora* (Panichpol and Waterman, 1978). Other constituents of *P. cauliflora* include 'kanakugin' (6.177) and the corresponding chalcone kanakugiol (6.40). In 1978 Bose and Adityachaudhury reported structure (6.178) for a flavanone 'didymocarpin'

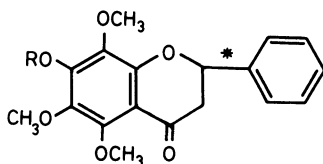


(6.174)



(6.175)  $R_1 = R_2 = H, R_3 = CH_3$

(6.176)  $R_1 = R_2 = R_3 = CH_3$



(6.177)  $R = CH_3$

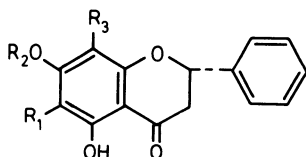
(6.178)  $R = H$

which they isolated from *Didymocarpus pedicellata*. Garg and co-workers (1979) synthesized 7-hydroxy-5,6,8-trimethoxyflavanone but found that melting point and spectral data did not agree with those reported for didymocarpin; therefore the structure of the flavanone from *D. pedicellata* remains in question.

Several *C*-methyl derivatives of pinocembrin have also been reported from nature. Wollenweber and co-workers (1979a) found both strobopinin (6.179) and cryptostrobin (6.180) in the farina of *Pityrogramma pallida* along with the dimethylated compound desmethoxymatteucinol (6.181). Star and co-workers (1978) reported a trace of strobopinin 7-methyl ether (6.182) along with larger quantities of the corresponding chalcone (6.29) in the exudate of *P. triangularis*.



Desmethoxymatteucinol (6.181) has been reported from *Agonis spathulata* (Cannon and Martin, 1977), *Dalea polyadenia* (Dreyer *et al.*, 1975) and *Unonia lawii* (Joshi and Gawad, 1974). *Unonia lawii* also contains desmethoxy-matteucinol 7-methyl ether (6.183) and 'lawinal', 6-formyl-8-methylpinocembrin (6.184). A discussion of the naturally occurring forms of a pair of 2-hydroxyflavanones from *U. lawii* appears on page 348 (see structures 6.152–6.155).



(6.179)  $R_1 = \text{CH}_3$ ,  $R_2 = R_3 = \text{H}$

(6.180)  $R_1 = R_2 = \text{H}$ ,  $R_3 = \text{CH}_3$

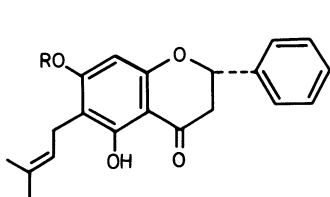
(6.181)  $R_1 = R_3 = \text{CH}_3$ ,  $R_2 = \text{H}$

(6.182)  $R_1 = R_2 = \text{CH}_3$ ,  $R_3 = \text{H}$

(6.183)  $R_1 = R_2 = R_3 = \text{CH}_3$

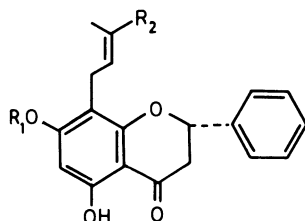
(6.184)  $R_1 = \text{CHO}$ ,  $R_2 = \text{H}$ ,  $R_3 = \text{CH}_3$

6-Prenylpinocembrin (6.185) occurs in *Helichrysum polycladum* (Bohlmann *et al.*, 1980c), *Chlorophora tinctoria* (Moraceae) (Gottlieb *et al.*, 1975), *Derris floribunda* (Braz Filho *et al.*, 1975b), and in *D. rariflora* where it occurs with its 7-methyl ether (6.186). A series of 8-prenylpinocembrin derivatives, (6.187), (6.188) and (6.189) and 8-geranylpinocembrin (6.190) occur in *Helichrysum hypocephalum* (Bohlmann and Abraham, 1979d). Compound (6.187), known commonly as 'glabranin', is also known from *Platitenia absinthifolia* (Fam. ?) (Ubaev *et al.*, 1974). 7-Methylglabranin (6.191) occurs in *Tephrosia villosa* (Jayaraman *et al.*, 1980). The dimethylchromenoflavanone (6.192) has been described from *T. praecans* by Camele *et al.* (1980). The structure of (6.193),



(6.185)  $R = \text{H}$

(6.186)  $R = \text{CH}_3$

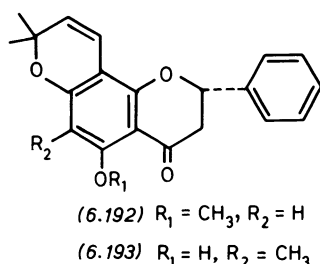
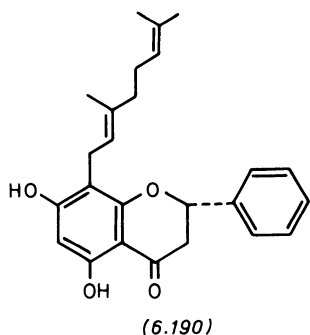


(6.187)  $R_1 = \text{H}$ ,  $R_2 = \text{CH}_3$

(6.188)  $R_1 = \text{H}$ ,  $R_2 = \text{CH}_2\text{OH}$

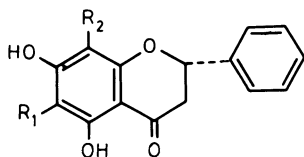
(6.189)  $R_1 = \text{H}$ ,  $R_2 = \text{CHO}$

(6.191)  $R_1 = R_2 = \text{CH}_3$



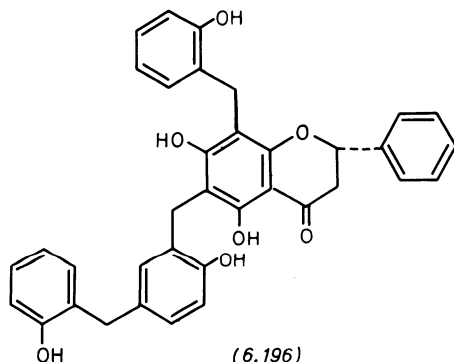
originally isolated from *Mallotus philippinensis* (see Bohm, 1975, p. 569), has been confirmed by synthesis (Manchanda and Khanna, 1977).

In a series of detailed studies by Hufford and co-workers (1976, 1978a, 1978b, 1979), several cytotoxic flavanones were isolated from *Uvaria chamae* and examined for their biological activity. 'Uvaretin' (6.194) or (6.195) and 'isouvaretin' (6.194 or 6.195) are the 6- and 8-alkyl derivatives of pinocembrin. The alkyl group is 2-hydroxybenzyl. The relationship between the two flavanones was established through hydrogenation which yielded a single dihydrochalcone. The most complex member of the group is the tribenzylated flavanone 'uvarinol' (6.196). Bark extracts of the plant were active *in vivo* against P-388 lymphocytic leukaemia and *in vitro* against cells from human carcinoma of the nasopharynx. In addition the extracts showed significant activity against *Staphylococcus aureus*, *Bacillus subtilis* and *Mycobacterium smegmatis* (Hufford and Laswell, 1978b).

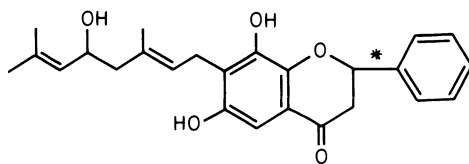


(6.194)  $R_1 = \text{H}, R_2 = 2\text{-hydroxybenzyl}$

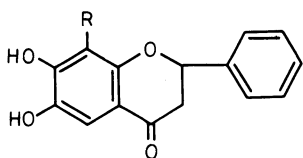
(6.195)  $R_1 = 2\text{-hydroxybenzyl}, R_2 = \text{H}$



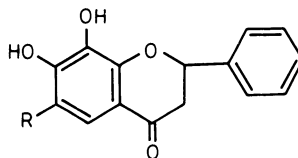
In 1979 Sivarambabu and co-workers described several new flavanones from *Flemingia stricta*, three of which will appear later. The structure that concerns us here is (6.197) proposed for 'flemiflavanone-B.' The authors considered two structures, (6.197) and (6.198), which could account for the spectral data obtained. Both of these are consistent with the presence of a single A-ring proton and the absence of a chelated hydroxyl signal in the  $^1\text{H-NMR}$  spectrum. Structure (6.197) was chosen on the basis that the unknown compound gave a positive Gibbs test (2,6-dichlorobenzoquinone-4-chloroimide in borate buffer) to detect *para*-unsubstituted phenols. Structure (6.197) has such a position; structure (6.198) does not. Structure (6.197), however, poses several problems



(6.197)

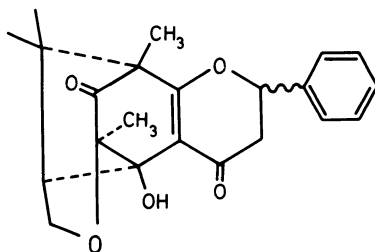


(6.198)



(6.199)

when viewed biosynthetically. In order to arrive at this structure following the normal pathway there would have to have been loss of hydroxyl groups from positions 5 and 7, oxygenation at positions 6 and 8, and alkylation at position 7. This is a tortuous pathway, although loss of oxygen from carbon-5 is a common occurrence in leguminous plants. Structure (6.199) is an alternative possibility which would require postulation of a less complicated pathway and would be consistent with the observed  $^1\text{H-NMR}$  data and would be expected to give a positive Gibbs test. This possible structure was apparently not considered by Sivarambabu and co-workers (1979a,b).

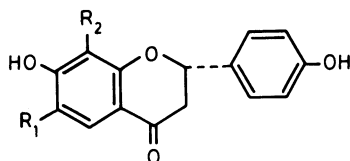
(6.200)  $\alpha$ -phenyl (2s)(6.201)  $\beta$ -phenyl (2R)

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Two of the most complex A-ring alkylated flavanones to have been found in nature are compounds (6.200) and (6.201), 'louisfieserone' and 'isolouisfieserone' respectively. Both isomers have been found to occur in *Dalea* species (Dominguez *et al.*, 1980) while flavanone (6.200) is also known from *Indigofera suffruticosa* (Dominguez *et al.*, 1978a, 1978b).

### (b) Flavanones having one B-ring hydroxyl

With the exception of an early report of liquiritigenin glycosides in *Dahlia* (Compositae) this simple flavanone (6.202) is otherwise known only from Leguminosae. New generic records from that family include *Onobrychis* (Ingham, 1978), *Medicago* (Ingham, 1979), *Myroxylon* (De Oliveira *et al.*, 1978) and *Peltogyne* (Malan and Roux, 1974). The finding of 8-C- $\beta$ -galactosyl-liquiritigenin (6.203) Garg *et al.*, 1980) in *Aerva persica* represents a first report of this compound in nature and the first report of a flavanone from the Amaranthaceae. Compound (6.204), however, is yet another C-prenylated derivative of liquiritigenin from the genus *Sophora* (Jain and Gupta, 1978; see Bohm, 1975, pp. 572–573).

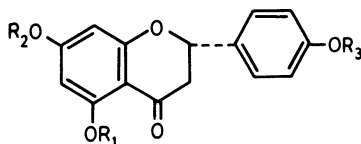


(6.202) R<sub>1</sub> = R<sub>2</sub> = H

(6.203) R<sub>1</sub> = H, R<sub>2</sub> = Gal

(6.204) R<sub>1</sub> = R<sub>2</sub> = 

The most widely occurring of all flavanones is naringenin (6.205), represented in Table 6.6 by reports from 26 genera, although some of the genera had been listed in the earlier survey. New family records include: Anacardiaceae, Athyriaceae, Capparaceae, Cochlospermaceae, Coriariaceae, Dilleniaceae, Dryopteridaceae, Equisetaceae, Lauraceae, Meliaceae, Pinaceae and Theaceae (see Table 6.6 for references). Naringenin occurs as the free phenol in many



(6.205) R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = H

(6.209) R<sub>1</sub> = R<sub>2</sub> = CH<sub>3</sub>, R<sub>3</sub> = H

(6.206) R<sub>1</sub> = R<sub>3</sub> = H, R<sub>2</sub> = CH<sub>3</sub>

(6.210) R<sub>1</sub> = H, R<sub>2</sub> = R<sub>3</sub> = CH<sub>3</sub>

(6.207) R<sub>1</sub> = R<sub>2</sub> = H, R<sub>3</sub> = CH<sub>3</sub>

(6.211) R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = CH<sub>3</sub>

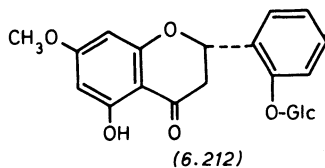
(6.208) R<sub>1</sub> = CH<sub>3</sub>, R<sub>2</sub> = R<sub>3</sub> = H

species and as a variety of glycosides in several of the others, the most noteworthy of which is the fructoside (position of attachment not determined) which Imperato (1976) discovered in leaves of *Camellia sinensis* (Theaceae).

All three mono-*O*-methyl derivatives of naringenin are known to occur naturally. Sakuranetin, the 7-methyl ether (6.206), and isosakuranetin, the 4'-methyl ether (6.207), are well-known compounds occurring either as free phenols or glycosides (Table 6.6). The remaining member of this group is 5-*O*-methyl naringenin (6.208) which was reported as a natural product for the first time by Maruyama *et al.* (1974), who obtained it from flowers of *Gnaphalium multiceps* (Compositae).

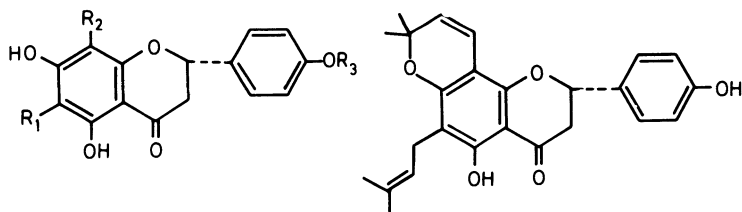
Naringenin-5,7-dimethyl ether (6.209) was first reported from nature by Bohlmann and co-workers (1979) who isolated the free phenol from *Baccharis alternoides* (Compositae). Very soon thereafter, two reports of glycosidic derivatives of this flavanone appeared. Chauhan *et al.* (1979c) obtained the 4'- $\beta$ -D-xylopyranosyl- $\beta$ -D-arabinopyranoside from stem tissues of *Hibiscus mutabilis* (Malvaceae). A. K. Gupta and co-workers (1980) reported the 4'- $\alpha$ -L-rhamnopyranosyl- $\beta$ -D-glucopyranoside from stems of *Bauhinia variegata* (Leguminosae). Naringenin-7,4'-dimethyl ether (6.210), a well known constituent of *Betula*, has been reported as a constituent of the bud excretions of several additional *Betula* species by Wollenweber (1975), as well as from two new sources: *Eupatorium odoratum* (Compositae) (Arene *et al.*, 1978) and *Dahlia tenuicaulis* (Lam and Wrang, 1975). These last mentioned workers also reported naringenin trimethyl ether (6.211) from *D. tenuicaulis*, the only genus from which this flavanone has been isolated.

The flavanone (6.212) is a new member of the rare flavonoid group having only 2'-hydroxylation on the B ring. This member is known as 'haplanthin' and was isolated from a variety of *Haplanthus tentaculatus* (Acanthaceae) by Viswanathan and Sidhaye (1976), who also confirmed the structure by synthesis.



C-Alkylation of the naringenin ring occurs in several plants to provide a variety of derivatives. The simple 6-*C*- $\beta$ -D-glucopyranosyl derivative (6.213), reported from *Tulipa gesneriana* by Budzianowski and Skrzypczakowa (1978), is the first flavanone reported from the Liliaceae. The *C*-methylflavanone farrerol (6.214) and its 5,7-diglucoside occur in *Rhododendron* species belonging to subgenus *Pentanthera* (King, 1977a,b). Farrerol 7-*O*-glucoside and the closely related compound matteucinol (6.215) are thought to occur in several members of the Athyriaceae and Dryopteridaceae (Hiraoka, 1978), although confirmation of farrerol glucoside was lacking. 8-*C*-Prenylnaringenin (6.216) occurs in the

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(6.213)  $R_1 = \text{Glc}, R_2 = R_3 = \text{H}$

(6.217)

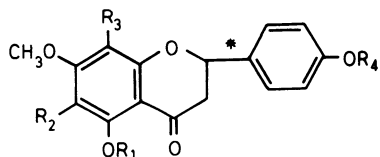
(6.214)  $R_1 = R_2 = \text{CH}_3, R_3 = \text{H}$

(6.215)  $R_1 = R_2 = R_3 = \text{CH}_3$

(6.216)  $R_1 = R_3 = \text{H}, R_2 = \text{---CH}_2\text{CH}=\text{CHCH}_3$

roots of *Marshallia grandiflora* (Compositae) (Bohlmann *et al.*, 1979d). An isopentenylnaringenin-7,4'-diglucoside has been discovered in *Evodia rutaecarpa* (Rutaceae) by Grimshaw and Lamer-Zarawska (1975), who were unable to place the alkyl group with certainty at either position 6 or 8. 'Cajaf flavanone' (6.217) consists of naringenin having two prenyl functions one of which has been cyclized with the 7-hydroxyl group to afford the dimethylchromeno ring system. The compound was described as a natural product for the first time by Bhanumati *et al.* (1978), who isolated it from *Cajanus cajan* (Leguminosae).

Seven poly-*O*-methylated flavanones having 6-, 8- or 6,8-hydroxylation were isolated from the exudate of the fern *Cheilanthes argenta* by Wollenweber and co-workers (1980a). The compounds are shown as structures (6.218–6.224). If it



(6.218)  $R_1 = R_3 = R_4 = \text{H}, R_2 = \text{OCH}_3$

(6.219)  $R_1 = R_3 = \text{H}, R_2 = \text{OCH}_3, R_4 = \text{CH}_3$

(6.220)  $R_1 = R_2 = R_4 = \text{H}, R_3 = \text{OCH}_3$

(6.221)  $R_1 = R_2 = \text{H}, R_3 = \text{OCH}_3, R_4 = \text{CH}_3$

(6.222)  $R_1 = \text{H}, R_2 = \text{OH}, R_3 = \text{OCH}_3, R_4 = \text{CH}_3$

(6.223)  $R_1 = \text{H}, R_2 = R_3 = \text{OCH}_3, R_4 = \text{H}$

(6.224)  $R_1 = \text{H}, R_2 = R_3 = \text{OCH}_3, R_4 = \text{CH}_3$

(6.225)  $R_1 = \text{CH}_3, R_2 = \text{OCH}_3, R_3 = R_4 = \text{H}$

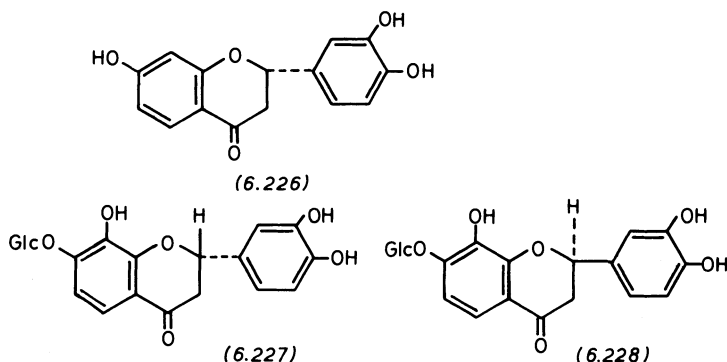
were possible to get the biosynthetically active tissue of this plant into a manageable form this system would offer an interesting opportunity to examine the specificities of hydroxylation and *O*-methylation reactions.

Compound (6.225), isolated from *Chromolaena odorata* (Compositae) by

Barua *et al.* (1978), may have been an artifact of isolation since it was obtained in optically inactive form. The corresponding 4,2'-dihydroxy-4',5',6'-trimethoxy-chalcone (6.59) was also isolated from the plant (Barua *et al.*, *loc. cit.*).

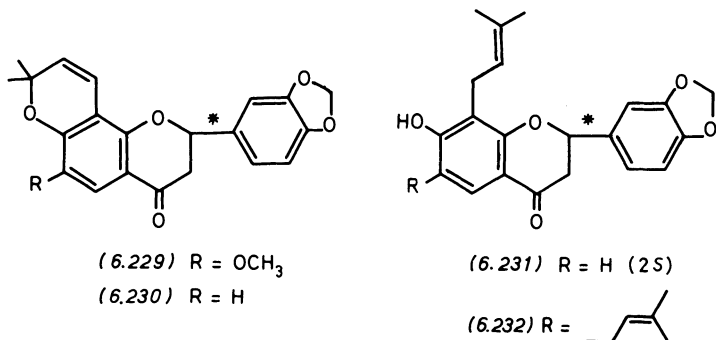
### (c) Flavanones having two B-ring hydroxyls

The simplest flavanone of this series is (6.226) recorded as a constituent of *Acacia saxatilis* (Fourie *et al.*, 1974), *Peltogyne* species (Malan and Roux, 1974) and *Gliricidia sepium* (Jurd and Manners, 1977). Isoökanin is a well-known flavanone



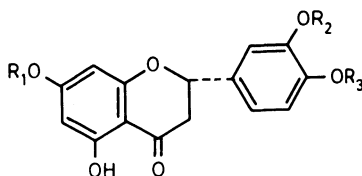
which was isolated as its 7-*O*- $\beta$ -D-glucoside from several members of the *Bidens ferulaefolia* complex by Hart (1979). The majority of flavanones studied to date exhibit the (2*S*) configuration as written for compound (6.227). It is of interest, then, that compound (6.228) has also been isolated from a *Bidens* species, *B. tripartita*, by Serbin *et al.* (1975). Analysis showed that the compound has the (2*R*) configuration. Further detailed examination of flavanone stereochemistry of *Bidens* would be in order.

A complex series of *C*-alkylated flavanones, all possessing the 3',4'-methylenedioxy function, has been studied by Gupta and his colleagues (Gupta and Krishnamurti, 1976b; Islam *et al.*, 1980). The compounds are from *Milletia ovalifolia* and are 'ovalichromene-A' (6.229), 'ovalichromene-B' (6.230), 'ovaliflavanone-C' (6.231) and 'ovaliflavanone-D' (6.232).



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Eriodictyol (6.233) occurs widely in flowering plants (Table 6.6) and has recently been reported from members of the Athyriaceae and Dryopteridaceae (Hiraoka, 1978). New familial records for the compound, or its glycosidic forms, include: Capparaceae, Clusiaceae, Ericaceae, Euphorbiaceae, Labiatae and Rubiaceae (see Table 6.6 for references). Eriodictyol 4'-methyl ether, hesperitin (6.234), also enjoys a modest distribution with new reports from the Boraginaceae, Compositae and Labiatae (see Table 6, for references). Flavanone (6.235), formerly known only from *Melicope* in the Rutaceae, has recently been found in *Eupatorium odoratum* by Arene and co-workers (1978). The isomeric 7,4'-dimethyl ether (6.236), known as 'persicogenin', occurs as such and as the 5-glucoside in *Persica vulgaris* (Rosaceae) (Sadykov and Sadykov, 1979), and as



(6.233)  $R_1 = R_2 = R_3 = H$

(6.234)  $R_1 = R_2 = H, R_3 = CH_3$

(6.235)  $R_1 = R_2 = CH_3, R_3 = H$

(6.236)  $R_1 = R_3 = CH_3, R_2 = H$

(6.237)  $R_1 = H, R_2 = R_3 = CH_3$

(6.238)  $R_1 = R_2 = R_3 = CH_3$

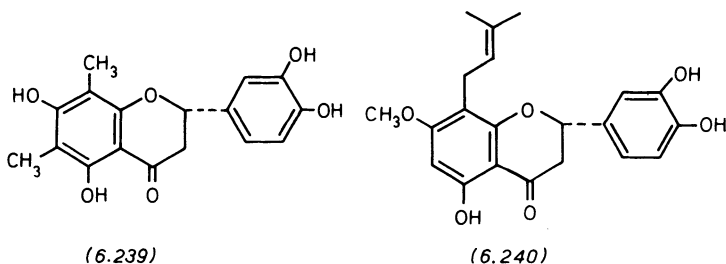
the aglycone in leaf exudates of the ferns *Notholaena limitanea* var. *mexicana* and *N. fendleri* (Wollenweber *et al.*, 1980a). A third dimethyl ether was reported by Ghosal *et al.* (1978): eriodictyol 3',4'-dimethyl ether occurs as the 5-*O*- $\beta$ -glucoside (6.237) in *Hoppea dichotoma*, which represents a first report for this flavanone (aglycone and glycoside) and the first record for a flavanone from Gentianaceae. Eriodictyol 7,3',4'-trimethyl ether (6.238) was also one of the exudate constituents found on leaves of *Notholaena* species by Wollenweber and his colleagues (1980a).

Sastry and Row (1961a,b) reported the presence of two highly *O*-methylated flavanones from the peel of *Citrus mitis*: 5,6,7,8,3',4'-hexamethoxy- and 5-hydroxy-6,7,8,3',4'-pentamethoxy-flavanone. Recently, Tatum and Berry (1978) examined the flavonoids of the *Citrus* cultivar 'Calamondin' and concluded that the two 'flavanones' were identical with the flavones nobiletin and 5-*O*-desmethylnobiletin.

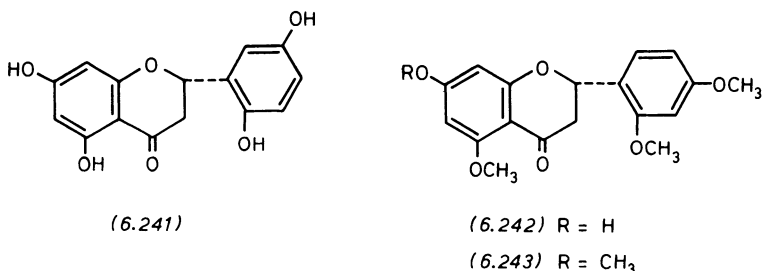
Cyrtometin, the 6,8-di-*C*-methyl derivative of eriodictyol (6.239), was detected in several species of fern (Athyriaceae and Dryopteridaceae) by Hiraoka (1978), although structural confirmation was not obtained. To date, this compound has only been reported from ferns (see Bohm, 1975, Table 11.1). An



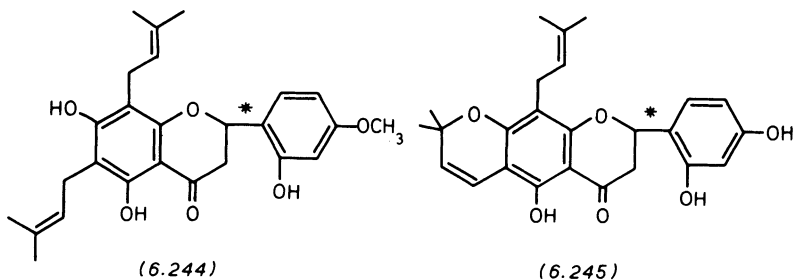
8-prenyl derivative of eriodictyol (6.240) was isolated from *Flourensia heterolepis* by Bohlmann and Jakupovic (1979), and a 2-hydroxyeriodictyol derivative (6.150) occurs in *Galega officinalis* (Traub and Geiger, 1975).

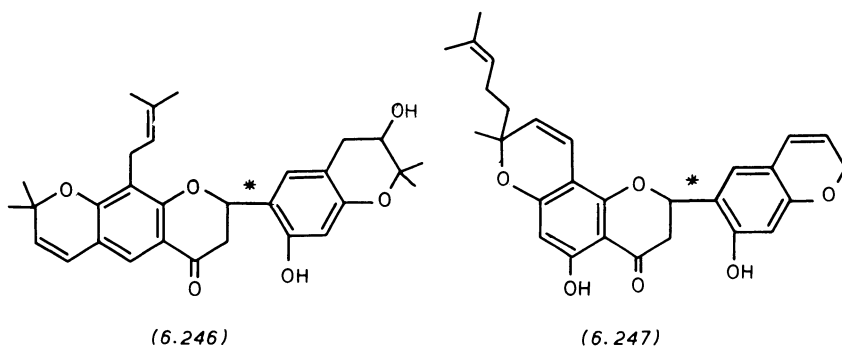


The last group of flavanones having two B-ring hydroxyls exhibit either the 2',5'- or the 2',4'- pattern. Only one member of the former type has been found recently. Compound (6.241) occurs in *Inula cappa* (Compositae) along with a dihydroflavonol (6.269) with the same hydroxylation pattern (Baruah *et al.*, 1979). Compound (6.242) was isolated from *Prunus cerasus* and its structure determined and confirmed by synthesis by Nagarajan and Parmar (1977a, 1978).



The completely *O*-methylated compound (6.243), 'arjunone', has been isolated from *Terminalia arjuna* (Combretaceae) (Nagar *et al.*, 1979), where it occurs with the corresponding chalcone cerasidin (6.89). Five additional compounds are known that are based on the 2',4'- pattern; all exhibit extensive *C*-alkylation and all have been found in the genus *Flemingia*. The simplest of these is 'flemiflavanone-A' (6.244) isolated from *F. stricta* by Sivarambabu *et al.* (1979a). 'Flemichin-D' (6.245), 'flemichin-E' (6.246) and 'flemichin-A' (6.247) occur

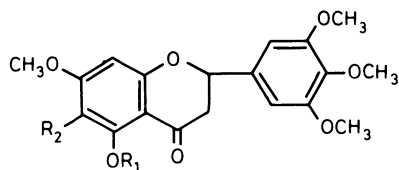




in *F. wallichii* (Sivarambabu *et al.*, 1979b; Rao *et al.* 1974, 1975b). 'Flemiflavanone-C' has been isolated from *F. stricta* by Sivarambabu *et al.* (1979a), who concluded on the basis of its optical rotation that it is an enantiomer of flemichind (6.245).

#### (d) Flavanones having three B-ring hydroxyls

Only two such compounds are known if one excludes the benzoquinone-type B-ring compounds isolated from Cyperaceae (see Bohm, 1975, p. 582). Compound (6.248) occurs in the leaf exudates of *Notholaena lemmonii* var. *lemmonii* (Wollenweber *et al.*, 1980a) while compound (6.249) was found by Tiwari and Bajpai (1977) in the stem bark of *Cassia renigera* (Leguminosae).



(6.248)  $R_1 = R_2 = H$  (stereochemistry not determined)

(6.249)  $R_1 = Rha$ ,  $R_2 = OCH_3$ , (2*S*) stereochemistry

## 6.6 DIHYDROFLAVONOLS

### 6.6.1. Introduction

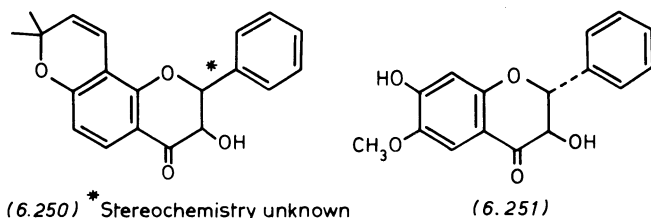
Dihydroflavonols, or 3-hydroxyflavanones, are numbered in the same fashion as flavanones. Carbons-2 and -3 are asymmetric in dihydroflavonols, so four isomers are possible for each compound. The majority of naturally occurring dihydroflavonols exist in the (2*R*:3*R*) configuration, but a few compounds are known with (2*S*:3*S*) stereochemistry (see Bohm, 1975, p. 597 and examples below).

### 6.6.2 Structures of naturally occurring dihydroflavonols

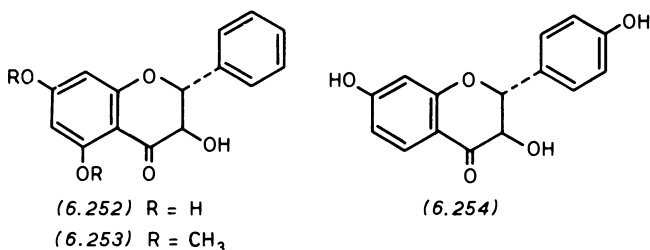
The structures of naturally occurring dihydroflavonols are summarized in Table 6.9.

#### (a) Dihydroflavonols lacking B-ring hydroxyls

Compounds based upon the resorcinol A-ring pattern include 3-hydroxy-isolonchocarpin (6.250) from *Lonchocarpus eriocaulinalis* (Delle Monache *et al.*, 1978) and (6.251) from *Dalbergia ecastophyllum*. Structure (6.251) was originally suggested for the compound by Matos and co-workers some years ago, and has now been confirmed by synthesis (Matos *et al.*, 1975). The simplest dihydroflavonol exhibiting the phloroglucinol A-ring substitution pattern is pinobanksin (6.252) which is widely distributed in *Pinus*. Recent reports have described



pinobanksin in aerial parts of *Helichrysum tenuifolium* (Bohlmann and Abraham, 1979a) and in the heartwood of *Larix dahurica* (Lapteva *et al.*, 1974). Pinobanksin dimethyl ether (6.253), a new naturally occurring dihydroflavonol, was isolated from *Aniba riparia* by Fernandes and co-workers (1978).



#### (b) Dihydroflavonols having one B-ring hydroxyl

7,4'-Dihydroxydihydroflavonol (6.254), garbanzol, has been found as a constituent of several species of *Rhus* as part of a biosystematic study of that genus by Young (1979). This represents the first report of this compound from Anacardiaceae.

The most widely occurring member of this subgroup is dihydrokaempferol, or aromadendrin (6.255). Recent reports of its natural occurrence are summarized in Table 6.9. Families from which aromadendrin has been obtained for the first

Table 6.9. Structures of naturally occurring dihydroflavonols

| OH     | Substituents                     | No. in text | Trivial name                 | Source*                                 | References                              |
|--------|----------------------------------|-------------|------------------------------|-----------------------------------------|-----------------------------------------|
|        | OCH <sub>3</sub>                 |             |                              |                                         |                                         |
| 7      |                                  | (6.251)     | Pinobanksin                  | <i>Dalbergia ecastophyllum</i>          | Leg Matos <i>et al.</i> (1975)          |
| 5,7    |                                  | (6.252)     |                              | <i>Helichrysum tenuifolium</i>          | Com Bohlmann and Abraham (1979a)        |
|        |                                  | (6.253)     |                              | <i>Larix dahurica</i>                   | Cnf Lapteva <i>et al.</i> (1974)        |
|        |                                  | (6.250)     |                              | <i>Aniba riparia</i>                    | Lau Fernandes <i>et al.</i> (1978)      |
|        | 6"-Dimethylpyrano<br>(2",3",7,8) |             | 3-Hydroxyisolon<br>chocarpin | <i>Lonchocarpus<br/>eritocaulinalis</i> | Leg Delle Monache <i>et al.</i> (1978)  |
| 7,4'   |                                  | (6.254)     | Garbanzol                    | <i>Rhus</i> spp.                        | Ana Young (1979)                        |
| 5,7,4' |                                  | (6.255)     | Aromadendrin                 | <i>Cavendishia</i> spp.                 | Eri Luteyn <i>et al.</i> (1980)         |
|        |                                  |             |                              | <i>Cudrania javanensis</i>              | Mor S. R. Gupta <i>et al.</i> (1975a)   |
|        |                                  |             |                              | <i>Dillenia retusa</i>                  | Dil Pavanavasivan and Sultanbawa (1975) |
|        |                                  |             |                              | <i>Equisetum arvense</i>                | Equ Syrchina <i>et al.</i> (1975, 1978) |
|        |                                  |             |                              | <i>Eucryphia cordifolia</i>             | Euc Tschesche <i>et al.</i> (1979)      |
|        |                                  |             |                              | <i>Matthiola incana</i>                 | Cru Forkmann (1979)                     |
|        |                                  |             |                              | <i>Morus</i> spp.                       | Mor Deshpande <i>et al.</i> (1975)      |
|        |                                  |             |                              | <i>Othonna euphorboides</i>             | Com Bohlmann and Knoll (1978)           |
|        |                                  |             |                              | <i>Persica vulgaris</i>                 | Ros Sadykov and Sadykov (1979)          |
|        |                                  |             |                              | <i>Picea ajanensis</i>                  | Cnf Ivanova <i>et al.</i> (1975)        |
|        |                                  |             |                              | <i>Prunus</i> spp.                      | Ros Nagarajan and Parmar (1977b,c)      |
|        |                                  |             |                              | <i>Wormia triquetra</i>                 | Dil Pavanavasivan and Sultanbawa (1975) |
|        | 3-O-Rhamnose                     |             | Engelitin                    | <i>Eucryphia cordifolia</i>             | Euc Tschesche <i>et al.</i> (1979)      |
|        | 3-O-Glucose                      |             |                              | <i>Dalbergia sericea</i>                | Leg Dayal and Parthasarathy (1977)      |
|        | 4'-O-Xylose                      |             |                              | <i>Cleome viscosa</i>                   | Cpr Chauhan <i>et al.</i> (1979b)       |
|        | 7-O-Glucose                      |             |                              | <i>Matthiola incana</i>                 | Cru Forkmann (1979)                     |
|        |                                  |             |                              | <i>Cudrania javanensis</i>              | Mor Gupta <i>et al.</i> (1975a)         |
| 5,7    |                                  | (6.256)     |                              | <i>Prunus domestica</i>                 | Ros Nagarajan and Parmar (1977b)        |
| 5      |                                  | (6.257)     |                              | <i>Podocarpus nerifolius</i>            | Cnf Rizvi and Rahman (1974)             |
|        | 5-O-Glucose                      |             |                              | <i>P. nerifolius</i>                    | Cnf Rizvi and Rahman (1974)             |

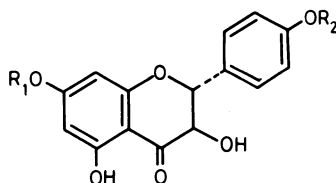
|           |     |                           |          |                                   |      |                                                      |
|-----------|-----|---------------------------|----------|-----------------------------------|------|------------------------------------------------------|
| 5,4'      | 6,7 | 8-C-Prenyl                | (6.258)  | <i>Saxifraga caespitosa</i>       | Sax  | Miller and Bohm (1979)                               |
| 5,7,4'    |     | 6'',6''-Dimethylpyrano    | (6.259)  | <i>Marshallia obovata</i>         | Com  | Bohlmann <i>et al.</i> (1980a)                       |
| 5,4'      |     | (2'',3'',7,8)             | (6.260)  | <i>Milletia pachycarpa</i>        | Leg  | Singhal <i>et al.</i> (1980)                         |
| 5,7,4'    |     | 6'',6''-Dimethylpyrano    |          | <i>Phellodendron</i> spp.         | Rut. | Oryashenkova <i>et al.</i> (1977)                    |
| 7,3',4'   |     | (2'',3'',7,6); 8-C-prenyl |          | <i>Rhus</i> spp.                  | Ana  | Young (1979)                                         |
|           |     | butyl); 7-O-glucose       | (6.261)  | <i>Amphipterygium adstringens</i> | Ana  | Young (1976)                                         |
|           |     |                           |          | <i>Acacia</i> spp.                | Leg  | Fourie <i>et al.</i> (1974); Tindale and Roux (1974) |
|           | 3   |                           | (6.262b) | <i>Peltogyne</i> spp.             | Leg  | Malan and Roux (1974)                                |
|           |     |                           |          | <i>Georgia pellucida</i>          | Mus  | Vandekerkhove (1977)                                 |
|           | 3   | 3,7-Di-O-glucose          | (6.262a) | <i>Peltogyne</i> spp.             | Leg  | Malan and Roux (1974)                                |
|           |     |                           |          | <i>Acacia</i> spp.                | Leg  | Tindale and Roux (1974)                              |
| 7,8,3',4' |     |                           | (6.263)  | <i>Albizia adianthifolia</i>      | Leg  | Candy <i>et al.</i> (1978)                           |
|           |     |                           | (6.264)  | <i>Acacia saxatilis</i>           | Leg  | Fourie <i>et al.</i> (1974)                          |
| 5,7,3',4' |     |                           |          | <i>Acacia</i> spp.                | Leg  | Tindale and Roux (1974)                              |
|           |     |                           |          | <i>Cavendishia</i> spp.           | Eri  | Luteyn <i>et al.</i> (1980)                          |
|           |     |                           |          | <i>Coleus amboinicus</i>          | Lab  | Brieskorn and Riedel (1977)                          |
|           |     |                           |          | <i>Cudrania javanensis</i>        | Mor  | Gupta <i>et al.</i> (1975a)                          |
|           |     |                           |          | <i>Dillenia retusa</i>            | Dil  | Pavanasavan and Sultanbawa (1975)                    |
|           |     |                           |          | <i>Eucryphia cordifolia</i>       | Euc  | Tschesche <i>et al.</i> (1979)                       |
|           |     |                           |          | <i>Abies amabilis</i>             | Cnf  | Parker <i>et al.</i> (1979)                          |
|           |     |                           |          | <i>Cedrus deodara</i>             | Cnf  | Agrawal <i>et al.</i> (1980a,b)                      |
|           |     |                           |          | <i>Larix leptolepis</i>           | Cnf  | Niemann (1974)                                       |
|           |     | 3-O-Glucose               |          | <i>Aerides fieldingii</i>         | Orc  | C. A. Williams (1979)                                |
|           |     |                           |          | <i>Zizyphus nummularia</i>        | Rhm  | Srivastava and Chauhan (1977)                        |
|           |     | 3'-O-Glucose              |          | <i>Cedrus deodara</i>             | Cnf  | Agrawal <i>et al.</i> (1980b)                        |

Table 6.9 (Contd.)

| OH           | OCH <sub>3</sub> | Substituents                           | No. in text | Trivial name | Source*                        | References                             |
|--------------|------------------|----------------------------------------|-------------|--------------|--------------------------------|----------------------------------------|
|              |                  | 3-O-Galactose                          |             |              | <i>Rhododendron</i> spp.       | Eri King (1977a,b)                     |
|              |                  | 7-O-Galactose                          |             |              | <i>Rhododendron</i> spp.       | Eri King (1977a,b)                     |
|              |                  | 3-O-Rhamnose                           |             | Astilbin     | <i>Eucryphia cordifolia</i>    | Euc Tschesche <i>et al.</i> (1979)     |
| 5,7,3',4'    | 3                | 3,5-Di-O-rhamnose                      | (6.265)     |              | <i>Cordia obliqua</i>          | Bor Srivastava and Srivastava (1979b)  |
|              |                  |                                        |             |              | <i>Dillenia indica</i>         | Dil Pavanasivan and Sultanbawa (1975)  |
| 5,7,3',4'    |                  | 6-C-Methyl                             | (6.266)     | Cedeolarin   | <i>Cedrus deodara</i>          | Cnf Agrawal <i>et al.</i> (1980a)      |
| 5,3'         | 7,4'             | 8-C-Prenyl                             | (6.267)     | Tirumalin    | <i>Rhynchosia cyanosperma</i>  | Leg Adinarayana <i>et al.</i> (1980a)  |
| 5,7,2'       | 5'               |                                        | (6.269)     |              | <i>Inula cappa</i>             | Com Baruah <i>et al.</i> (1979)        |
| 5,7,2',4'    |                  |                                        |             | Dihydromorin | <i>Morus</i> spp.              | Mor Deshpande <i>et al.</i> (1975)     |
| 5,7          | 2'               | 6'',6''-Dimethyl-pyrano(2'',3'',4',3') | (6.268)     | Sophoronol   | <i>Sophora tomentosa</i>       | Leg Delle Monache <i>et al.</i> (1976) |
| 7,3',5'      | 4'               |                                        | (6.273)     | Sepinol      | <i>Gliricidia sepium</i>       | Leg Manners and Jurd (1979)            |
| 5,7,3',4',5' |                  |                                        | (6.274)     | Ampelopsin   | <i>Soymida febrifuga</i>       | Mel Rao <i>et al.</i> (1979)           |
|              |                  |                                        |             |              | <i>Leptarrhena pyrolifolia</i> | Sax Miller and Bohm (1979)             |
|              |                  |                                        |             |              | <i>Heuchera villosa</i>        | Sax Wells and Bohm (1980)              |
|              |                  |                                        |             |              | <i>Cedrus deodara</i>          | Cnf Agrawal <i>et al.</i> (1980a)      |
| 5,7,3',4',5' |                  | 6-C-Methyl                             | (6.275)     | Cedrin       | <i>Cedrus deodara</i>          | Cnf Agrawal <i>et al.</i> (1980a)      |
|              |                  | 3'-O-Glucose                           |             | Cedrinoside  | <i>C. deodara</i>              | Cnf Agrawal <i>et al.</i> (1980a)      |
| 5,7,3',4'    | 5'               | 4'-O-Rhamnose                          | (6.276)     |              | <i>Diospyros peregrina</i>     | Ebn Chauhan <i>et al.</i> (1979a)      |

\* Key: Ana = Anacardiaceae, Bor = Boraginaceae, Cpr = Capparaceae, Cnf = Coniferae, Com = Compositae, Cru = Cruciferae, Dil = Dilleniaceae, Equ = Equisetaceae, Eri = Ericaceae, Ebn = Ebenaceae, Euc = Eucryphiaceae, Lab = Labiatae, Lau = Lauraceae, Leg = Leguminosae, Mel = Meliaceae, Mor = Moraceae, Mus = Musci, Orc = Orchidaceae, Rhm = Rhamnaceae, Ros = Rosaceae, Rut = Rutaceae, Sax = Saxifragaceae.

time are: Capparaceae, Compositae, Cruciferae, Dilleniaceae, Equisetaceae and Eucryphiaceae (see Table 6.9 for references). Aromadendrin 4'-methyl ether



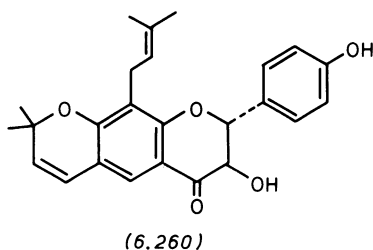
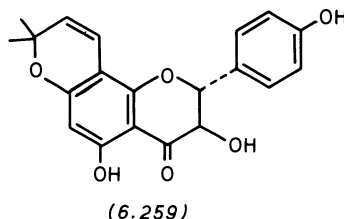
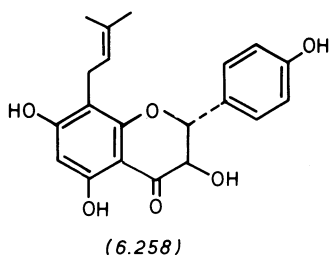
(6.255)  $R_1 = R_2 = H$

(6.256)  $R_1 = H, R_2 = CH_3$

(6.257)  $R_1 = R_2 = CH_3$

(6.256) has been reported from *Prunus domestica* (Nagarajan and Parmar, 1977b) which is a confirmation of earlier work by Nagarajan and Seshadri (see Bohm, 1975, Table 11.8). Aromadendrin 7,4'-dimethyl ether (6.257) was reported to occur in *Podocarpus neriifolius* (Podocarpaceae) as the 5-*O*-glucoside (Rizvi and Rahman, 1974).

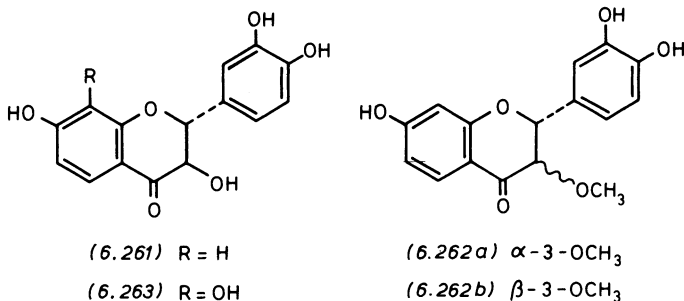
Three *C*-prenylated aromadendrin derivatives have been described in the recent literature. Bohlmann and co-workers (1980a) isolated compounds (6.258) and (6.259) from *Marshallia obovata* along with a series of flavans with identical or very similar substitution patterns. Compound (6.259) is clearly an intramolecular cyclization product derived from (6.258). A diprenylated dihydroflavonol (6.260) has been reported from *Millettia pachycarpa* by Singhal and co-



workers (1980), where it occurs with a group of similarly substituted isoflavones. These are the first reports of these dihydroflavonols as naturally occurring compounds.

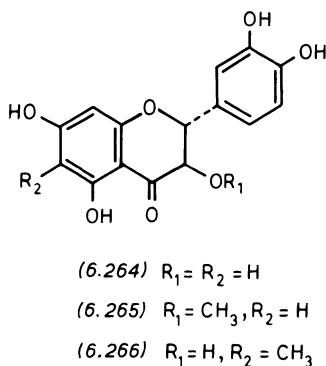
**(c) Dihydroflavonols having two B-ring hydroxyls**

Several 5-deoxydihydroflavonols having 3',4'-dihydroxylation have been isolated in recent years. The simplest one of these is 'fustin' (6.261) which has long been known as a constituent of the Anacardiaceae. Further reports of its occurrence in *Rhus* were published recently by Young (1979). A '5-deoxydihydroflavonol glycoside with B-ring *ortho*-hydroxyl groups' similar to fustin 3,7-diglycoside was reported by Vandekerkhove (1977) as a constituent of the moss *Georgia pellucida*.



In a detailed study of the polyphenols of *Peltogyne* Malan and Roux (1974) reported finding ( $\pm$ )-3-*O*-methyl-2,3-*cis*-fustin (6.262a) and ( $\pm$ )-3-*O*-methyl-2,3-*trans*-fustin (6.262b) in both *P. pubescens* and *P. venosa*. Fourie and co-workers (1974) reported fustin (6.261) and 8-hydroxyfustin (6.263) from *Acacia saxatilis*. The latter compound has also been found to occur in *Albizia adianthifolia* (Leguminosae) wood (Candy *et al.*, 1978).

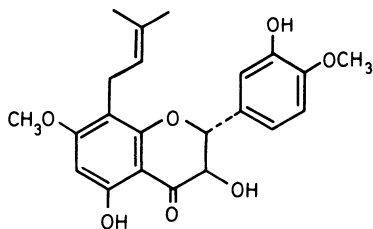
The most commonly encountered member of this subgroup, however, is dihydroquercetin or taxifolin (6.264). New records of taxifolin and its glycosidic derivatives are summarized in Table 6.9. Of note are several new family records: Boraginaceae, Dilleniaceae, Equisetaceae, Eucryphiaceae, Labiatae, Orchidaceae and Rhamnaceae (see Table 6.9 for references).



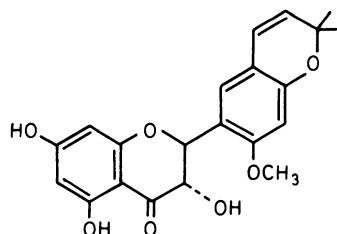
Naturally occurring derivatives of taxifolin include 3-*O*-methyltaxifolin (6.265) from *Dillenia indica* (Pavanasasivan and Sultanbawa, 1975), 6-*C*-methyl



taxifolin (6.266), called 'cedeodarin', from *Cedrus deodara* (Agrawal *et al.*, 1980a) and (+)-(2*R*:3*R*)-8-*C*-prenyltaxifolin 7,4'-dimethyl ether (6.267) from *Rhynchosia cyanosperma* (Leguminosae) (Adinaryana *et al.*, 1980a).

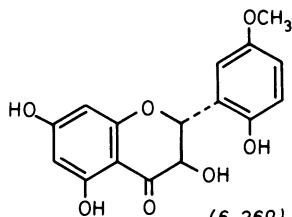


(6.267)



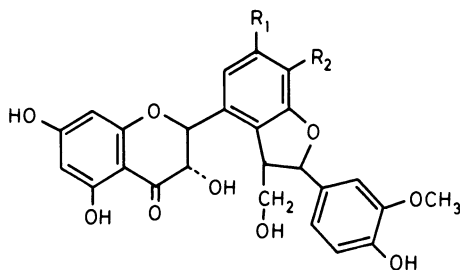
(6.268)

A prenylated dihydroflavonol having two unusual features was isolated from *Sophora tomentosa* by Delle Monache and co-workers (1976). 'Sophoronol' (6.268) possesses the uncommon 2',4'-dihydroxylation of ring B and it exists in the rare (2*S*:3*S*) configuration. Also exhibiting an odd B-ring hydroxylation pattern is the compound whose structure is shown as (6.269). This compound accompanied a flavanone (6.241) with the same substitution pattern in *Inula cappa* (Baruah *et al.*, 1979).



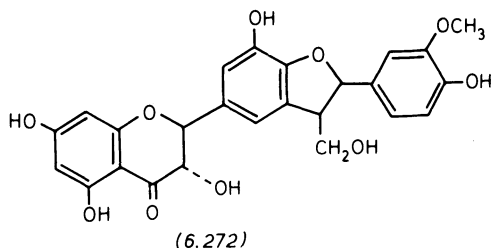
(6.269)

The structures of three antihepatotoxic flavonolignans isolated from *Silybum marianum* (Compositae) were discussed in the 1975 review (p. 593). Some question existed concerning the structure of one of these, however. The original structure proposed for 'silychristin' by Wagner *et al.* (1971) is shown as (6.270). An alternative structure (6.271) was proposed by Hänsel and co-workers (1976).

(6.270)  $R_1 = H, R_2 = OH$ (6.271)  $R_1 = OH, R_2 = H$

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More recent work by Pelter and co-workers (1977) and by Wagner and co-workers (1978), using  $^{13}\text{C}$  NMR of silychristin and model compounds, unequivocally support yet another structure (6.272) for the naturally occurring compound.

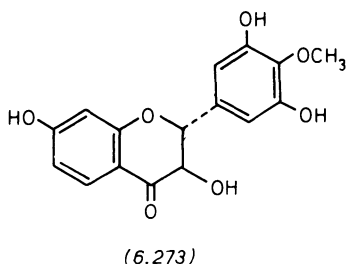


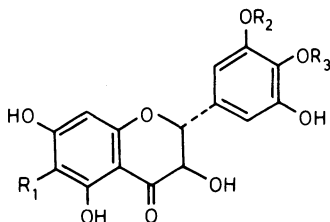
The correct stereochemistry of the known flavonolignans involves the (2*S*:3*S*) configuration, as shown in (6.272); the stereochemistry of silychristin presented in the 1978 paper by Wagner and his colleagues was in error (Wagner, 1980).

Two recent papers treat physiological activities of the *Silybum* flavonolignans. All three were shown to inhibit indoleacetic acid oxidase activity (Greimel and Koch, 1977; Becker and Schrall, 1977). Silybin, silydianin and taxifolin stimulated growth of cell cultures of *Silybum* while silychristin had no effect. All were toxic when applied to the cultures at concentrations of  $10^{-2}$  mol. litre $^{-1}$  (Becker and Schrall, 1977).

### (d) Dihydroflavonols having three B-ring hydroxyls

'Sepinol', recently described by Manners and Jurd (1979) from *Gliricidia sepium*, is the 4'-methyl ether of dihydrorobinetin (= fustin-4'-methyl ether) (6.273). Dihydromyricetin (6.274), commonly known as ampelopsin, has been isolated from *Soymida febrifuga* (Rao *et al.*, 1979) which represents a first report for Meliaceae, and from *Cedrus deodara* (Agrawal *et al.*, 1980a) 6-C-Methyl-dihydromyricetin (6.275) and its 3'-*O*- $\beta$ -D-glucopyranoside also occur in *C. deodara* (Agrawal *et al.*, 1980a). It is of interest to note that this plant also accumulates taxifolin (6.264) and its 6-C-methyl derivative (6.266). Chauhan and co-workers (1979a) have identified dihydromyricetin 3'-methyl ether (6.276) as the 4'-*O*- $\alpha$ -L-rhamnopyranoside from *Diospyros peregrina* (Ebenaceae).





(6.274)  $R_1 = R_2 = R_3 = H$

(6.275)  $R_1 = CH_3, R_2 = R_3 = H$

(6.276)  $R_1 = R_3 = H, R_2 = CH_3$

## 6.7 TAXONOMIC IMPLICATIONS OF THE DISTRIBUTION OF THE MINOR FLAVONOIDS

### 6.7.1 Introduction

The occurrence of the five classes of minor flavonoids are summarized in Tables 6.10 (chalcones), 6.11 (aurones), 6.12 (dihydrochalcones) 6.13 (flavanones) and 6.14 (dihydroflavonols). A few general comments on flavonoid distribution would seem in order before considering specific taxonomic problems. We are frequently required to make comparisons of flavonoid patterns when only limited data are available. For example, it is difficult to assess the significance of the paucity of minor flavonoids in the Monocotyledonae. The apparent rarity of these types may reflect a real chemical difference between the Monocotyledonae and Dicotyledonae, or there may simply be insufficient information on the monocots to justify extensive comparisons. Similarly, the amount of information available on the distribution of flavonoids (of all types) in mosses and liverworts is limited. It is important to appreciate, however, that the occurrence of flavonoids in these organisms does not simply represent a chemical novelty. Rather, it would seem that we are witnessing the early stages of accumulation of what is likely to become a taxonomically significant body of knowledge. Application of these data at higher taxonomic levels is simply not feasible yet. On the other side of the coin is the situation exemplified by the Leguminosae and Compositae with regard to minor flavonoids. These families have attracted a great deal of attention because of their size, ready availability, and, no doubt, their economic importance. The result is a very large body of information. In many cases, then, comparisons between families, one of which has been well studied and the other(s) much less so, lead only to very speculative and tentative conclusions. The discussions of the taxonomic implications of minor flavonoid distribution which follow will focus on problems at lower taxonomic levels where reasonable amounts of data are available.

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**Table 6.10** Summary of natural sources of chalcones by genus

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|                                   |                                                                                                                                                                                 |
|-----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>FILICINAE</b>                  |                                                                                                                                                                                 |
| <i>Adiantum</i>                   | Wollenweber (1979)                                                                                                                                                              |
| <i>Cheilanthes</i>                | Wollenweber (1977a)                                                                                                                                                             |
| <i>Notholaena</i>                 | Wollenweber (1977a)                                                                                                                                                             |
| <i>Onychium</i>                   | Ramakrishnan <i>et al.</i> (1974)                                                                                                                                               |
| <i>Pityrogramma</i>               | Wollenweber (1977b, 1979); Wollenweber <i>et al.</i> (1980); Dietz <i>et al.</i> (1980); Star <i>et al.</i> (1975a,b, 1978)                                                     |
| <i>Pterozonium</i>                | Wollenweber (1979)                                                                                                                                                              |
| <b>ANGIOSPERMAE–DICOTYLEDONAE</b> |                                                                                                                                                                                 |
| <b>Acanthaceae</b>                |                                                                                                                                                                                 |
| <i>Ruellia</i>                    | Bloom (1976)                                                                                                                                                                    |
| <b>Anacardiaceae</b>              |                                                                                                                                                                                 |
| <i>Amphipterygium</i>             | Young (1976)                                                                                                                                                                    |
| <i>Machaerium</i>                 | Kurosawa <i>et al.</i> (1978)                                                                                                                                                   |
| <i>Rhus</i>                       | Young (1979)                                                                                                                                                                    |
| <b>Anonaceae</b>                  |                                                                                                                                                                                 |
| <i>Popowia</i>                    | Panichpol and Waterman (1978)                                                                                                                                                   |
| <b>Betulaceae</b>                 |                                                                                                                                                                                 |
| <i>Alnus</i>                      | Wollenweber <i>et al.</i> (1974)                                                                                                                                                |
| <i>Betula</i>                     | Wollenweber <i>et al.</i> (1974)                                                                                                                                                |
| <b>Combretaceae</b>               |                                                                                                                                                                                 |
| <i>Terminalia</i>                 | Najar <i>et al.</i> (1979)                                                                                                                                                      |
| <b>Compositae</b>                 |                                                                                                                                                                                 |
| <i>Bidens</i>                     | Ballard (1975); Hart (1979); Scogin and Zakar (1976)                                                                                                                            |
| <i>Coreopsidineae</i>             | Crawford and Stuessy (1981), see Table 6.19                                                                                                                                     |
| <i>Coreopsis</i>                  | Nicholls and Bohm (1979); Harborne (1977); Crawford and Smith (1980)                                                                                                            |
| <i>Chromolaena</i>                | Barua <i>et al.</i> (1978)                                                                                                                                                      |
| <i>Dahlia</i>                     | Giannasi (1975); Lam and Wrang (1975)                                                                                                                                           |
| <i>Flourensia</i>                 | Bohlmann and Jakupovic (1979)                                                                                                                                                   |
| <i>Gnaphalium</i>                 | Maruyama <i>et al.</i> (1974); Ahluwalia and Rami (1976); Aritomi and Kawasaki (1974)                                                                                           |
| <i>Helianthus</i>                 | Harborne and Smith (1978)                                                                                                                                                       |
| <i>Helichrysum</i>                | Bohlmann and Suwita (1979c); Bohlmann and Abraham (1979b,c); Bohlmann <i>et al.</i> (1979c, 1980c, 1978); Bohlmann and Hoffmann (1979)                                          |
| <i>Pyrrhopappus</i>               | Harborne (1977)                                                                                                                                                                 |
| <i>Simsia</i>                     | Crawford and Stuessy (1981)                                                                                                                                                     |
| <i>Viguiera</i>                   | Harborne and Smith (1978)                                                                                                                                                       |
| <b>Fagaceae</b>                   |                                                                                                                                                                                 |
| <i>Nothofagus</i>                 | Wollenweber and Wiermann (1979)                                                                                                                                                 |
| <b>Gesneriaceae</b>               |                                                                                                                                                                                 |
| <i>Didymocarpus</i>               | Adityachaudhury <i>et al.</i> (1976); Adityachaudhury and Dasskanugo (1975); Agarwal <i>et al.</i> (1973); Bhattacharyya <i>et al.</i> (1979); Wollenweber <i>et al.</i> (1980) |
| <b>Lauraceae</b>                  |                                                                                                                                                                                 |
| <i>Aniba</i>                      | Fernandes <i>et al.</i> (1978); de Alleluia <i>et al.</i> (1978)                                                                                                                |

## Leguminosae

- Acacia*  
*Albizia*  
*Bauhinia*  
*Cladrastis*  
*Dalbergia*  
*Dalea*  
*Derris*  
*Flemingia*  
  
*Glycyrrhiza*  
*Lepedeza*  
*Lonchocarpus*  
*Machaerium*  
*Medicago*  
*Milletia*  
*Onobrychis*  
*Peltogyne*  
*Pongamia*  
*Prosopis*  
*Psoralea*  
*Sophora*  
*Tephrosia*  
*Zuccagnia*
- Imperato (1978); Tindale and Roux (1974)  
Candy *et al.* (1978)  
Bhartiya *et al.* (1979)  
Ohashi *et al.* (1977)  
Matos *et al.* (1975); Manners *et al.* (1974)  
Dominguez *et al.* (1980)  
Chibber *et al.* (1979); Braz Filho *et al.* (1975a,b)  
Adithyachaudhury *et al.* (1973); Rao *et al.* (1974, 1975a,b,c, 1976);  
Bhatt (1975)  
Saitoh *et al.* (1975); Saitoh and Shibata (1975)  
Miyase *et al.* (1980)  
Delle Monache *et al.* (1974); De Lima *et al.* (1973)  
Kurosawa *et al.* (1978)  
Ingham (1979)  
Islam *et al.* (1980); Gupta and Krishnamurti (1977a, 1979)  
Ingham (1978)  
Malan and Roux (1974)  
Sharma *et al.* (1973); Subramanyam *et al.* (1977)  
Bhardwaj *et al.* (1979)  
Gupta (1975b, 1977); Suri *et al.* (1980); B. K. Gupta *et al.* (1980)  
Komatsu *et al.* (1978)  
Camele *et al.* (1980)  
Pederiva *et al.* (1975)

## Loranthaceae

- Viscum*  
Becker *et al.* (1978)

## Myricaceae

- Myrica*  
Malterud *et al.* (1977)

## Myristicaceae

- Iryanthera*  
de Almeida *et al.* (1979)

## Onagraceae

- Oenothera*  
Dement and Raven (1974)

## Rosaceae

- Prunus*  
Nagarajan and Parmar (1977a,b,c)

## Rutaceae

- Merrillea*  
Fraser and Lewis (1974)

## Salicaceae

- Populus*  
Wollenweber *et al.* (1974); Wollenweber and Weber (1973);  
*Salix*  
Vinokurov (1979)

## Solanaceae

- Petunia*  
de Vlaming and Kho (1976)

## Umbelliferae

- Angelica*  
Kozawa *et al.* (1977)

## MONOCOTYLEDONAE

## Liliaceae

- Polygonatum*  
Maradufu and Ouma (1978)

**Table 6.11** Summary of natural sources of aurones by genus**BRYOPHYTA-HEPATICAE**

|                     |                           |
|---------------------|---------------------------|
| <i>Carrpos</i>      | Markham (1980)            |
| <i>Conocephalum</i> | Markham and Porter (1978) |
| <i>Marchantia</i>   | Markham and Porter (1978) |

**BRYOPHYTA-MUSCI**

|                |                       |
|----------------|-----------------------|
| <i>Funaria</i> | Weita and Ikan (1977) |
|----------------|-----------------------|

**ANGIOSPERMAE-DICOTYLEDONAE****Anacardiaceae**

|                       |                              |
|-----------------------|------------------------------|
| <i>Amphipterygium</i> | Young (1976)                 |
| <i>Melanorrhoea</i>   | Ogiyama <i>et al.</i> (1976) |
| <i>Rhus</i>           | Young (1979)                 |

**Compositae**

|                   |                                                     |
|-------------------|-----------------------------------------------------|
| <i>Bidens</i>     | Hart (1979); Scogin and Zakar (1976)                |
| Coreopsidinae     | Crawford and Stuessy (1981)                         |
| <i>Coreopsis</i>  | Nicholls and Bohm (1979); Crawford and Smith (1980) |
| <i>Helianthus</i> | Harborne and Smith (1978)                           |
| <i>Viguiera</i>   | Harborne and Smith (1978)                           |

**Leguminosae**

|               |                                    |
|---------------|------------------------------------|
| <i>Derris</i> | do Nascimento <i>et al.</i> (1976) |
| <i>Lygos</i>  | El Sherbeiny <i>et al.</i> (1978)  |

**Scrophulariaceae**

|                    |                |
|--------------------|----------------|
| <i>Antirrhinum</i> | Gilbert (1975) |
|--------------------|----------------|

**MONOCOTYLEDONAE****Zingiberaceae**

|               |                            |
|---------------|----------------------------|
| <i>Amomum</i> | Lakshmi and Chauhan (1977) |
|---------------|----------------------------|

**6.7.2 Filicineae****(a) Introduction**

The flavonoid chemistry of this ancient and widespread group of plants has received comparatively little systematic study despite its size (Mabry, 1973). The last few years, however, have witnessed a growing interest in chemosystematic studies of ferns (Cooper-Driver, 1980). Several compounds belonging to the structural types treated in this chapter have been isolated from fern species. Some of the occurrences, such as the presence of naringin in six *Adiantum* species (of 58 tested) (Cooper-Driver and Swain, 1977), have little systematic value and will not be dwelt upon. Other situations, such as the flavanone distributions described by Hiraoka (1978) and the exudate chemistry of *Pityrogramma* (Wollenweber, 1978; Wollenweber and Dietz, 1980) are discussed in some detail below.

The part played by flavonoids, and a few related phenolic compounds, in fern systematics has been reviewed recently by Cooper-Driver (1980) to which the reader is referred for details. Included in that treatment is a tabulation of the distribution of flavonoid types in fern families. Flavanones and/or chalcones were reported absent from 17 families and present in only three: Pteridaceae, Dennstaedtiaceae and Dryopteridaceae (includes Athyriaceae in this treatment).

**Table 6.12** Summary of natural sources of dihydrochalcones by genus**BRYOPHYTA-HEPATICAE**

*Radula* Asakawa *et al.* (1978)

**FILICINAE**

*Adiantum* Wollenweber (1979)

*Notholaena* Wollenweber (1977a)

*Pityrogramma* Wollenweber (1977b, 1979); Dietz *et al.* (1980); Wagner *et al.* (1979);  
Wollenweber *et al.* (1979b)

**ANGIOSPERMAE-DICOTYLEDONAE****Anonaceae**

*Uvaria* Hufford and Oguntimein (1980); Cole *et al.* (1976); Tammami *et al.* (1977); Okorie (1977)

*Unona* Joshi and Gawad (1976)

**Balanophoraceae**

*Balanophora* Ito *et al.* (1980)

**Compositae**

*Helichrysum* Bohlmann and Abraham (1979a); Bohlmann and Suwita (1979b);  
Bohlmann and Zdero (1980); Bohlmann *et al.* (1978, 1979c, 1980c)

**Caprifoliaceae**

*Viburnum* Jensen *et al.* (1977)

**Ericaceae**

*Rhododendron* King (1977); Mabry *et al.* (1975)

**Leguminosae**

*Gliricidia* Manners and Jurd (1979)

*Glycyrrhiza* Furuya *et al.* (1976)

*Lonchocarpus* Delle Monache *et al.* (1974)

*Milletia* Gupta and Krishnamurti (1976a,b,c, 1977a,b, 1979)

*Pongamia* Talapatra *et al.* (1980); Garg *et al.* (1978); Sharma and Parthasarathy (1977)

*Tephrosia* R. K. Gupta *et al.* (1980)

**Myricaceae**

*Myrica* Malterud *et al.* (1977); Anthonsen *et al.* (1971); Uyar *et al.* (1978)

**Myristicaceae**

*Iryanthera* Braz Filho *et al.* (1980); de Almeida *et al.* (1979)

**Rosaceae**

*Malus* A. H. Williams (1979)

The phylogenetic significance of flavonoid distribution was commented upon by Cooper-Driver (1980), who pointed out that more advanced families of ferns accumulate flavone-*C*-glycosides, flavanones, chalcones and xanthones, whereas the most ancient families accumulate only proanthocyanidins and flavonols. Some specific studies are summarized below.

**(b) Athyriaceae**

Hiraoka (1978) studied the flavonoid composition of 21 species representing six genera in the Athyriaceae. The flavonoids of the onocleoid ferns (*Matteuccia*, *Onoclea*, *Onocleopsis*) differ from those present in the athyreoid ferns (*Athyrium*,

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**Table 6.13** Summary of natural sources of flavanones by genus

### FILICINAE (Includes *Equisetum*)

|                     |                                                              |
|---------------------|--------------------------------------------------------------|
| <i>Adiantum</i>     | Cooper-Driver and Swain (1977)                               |
| <i>Cheilanthes</i>  | Wollenweber <i>et al.</i> (1980a)                            |
| <i>Cyrtomium</i>    | Hiraoka (1978)                                               |
| <i>Dryopteris</i>   | Hiraoka (1978)                                               |
| <i>Matteuccia</i>   | Hiraoka (1978)                                               |
| <i>Notholaena</i>   | Wollenweber <i>et al.</i> (1980a)                            |
| <i>Pityrogramma</i> | Wollenweber <i>et al.</i> (1979a); Star <i>et al.</i> (1978) |
| <i>Polystichum</i>  | Hiraoka (1978)                                               |
| <i>Equisetum</i>    | Syrchina <i>et al.</i> (1975, 1978)                          |

### CONIFERAE

|              |                              |
|--------------|------------------------------|
| <i>Larix</i> | Lapteva <i>et al.</i> (1974) |
| <i>Picea</i> | Ivanova <i>et al.</i> (1975) |

### ANGIOSPERMAE-DICOTYLEDONAE

#### Acanthaceae

|                   |                                |
|-------------------|--------------------------------|
| <i>Haplanthus</i> | Viswanathan and Sidhaye (1976) |
|-------------------|--------------------------------|

#### Aizoaceae

|                   |                           |
|-------------------|---------------------------|
| <i>Tetragonia</i> | Kemp <i>et al.</i> (1979) |
|-------------------|---------------------------|

#### Amaranthaceae

|              |                           |
|--------------|---------------------------|
| <i>Aerva</i> | Garg <i>et al.</i> (1980) |
|--------------|---------------------------|

#### Anacardiaceae

|                   |                             |
|-------------------|-----------------------------|
| <i>Anacardium</i> | Rahman <i>et al.</i> (1978) |
|-------------------|-----------------------------|

#### Anonaceae

|                |                                                              |
|----------------|--------------------------------------------------------------|
| <i>Unona</i>   | Joshi and Gawad (1974); Chopin <i>et al.</i> (1978)          |
| <i>Uvaria</i>  | Hufford and Laswell (1976); Hufford <i>et al.</i> (1979)     |
| <i>Popowia</i> | Panichpol and Waterman (1978); Waterman and Pootakahm (1979) |

#### Betulaceae

|               |                    |
|---------------|--------------------|
| <i>Betula</i> | Wollenweber (1975) |
|---------------|--------------------|

#### Boraginaceae

|               |                                                            |
|---------------|------------------------------------------------------------|
| <i>Cordia</i> | Chauhan <i>et al.</i> (1978); Tiwari and Srivastava (1979) |
|---------------|------------------------------------------------------------|

#### Capparidaceae

|               |                                                                                                  |
|---------------|--------------------------------------------------------------------------------------------------|
| <i>Cleome</i> | Chauhan <i>et al.</i> (1979b); Srivastava <i>et al.</i> (1979) Srivastava and Srivastava (1979a) |
|---------------|--------------------------------------------------------------------------------------------------|

#### Clusiaceae

|                 |                              |
|-----------------|------------------------------|
| <i>Garcinia</i> | Waterman and Crichton (1980) |
|-----------------|------------------------------|

#### Cochlospermaceae

|                      |                      |
|----------------------|----------------------|
| <i>Cochlospermum</i> | Cook and Knox (1975) |
|----------------------|----------------------|

#### Combretaceae

|                   |                            |
|-------------------|----------------------------|
| <i>Terminalia</i> | Nagar <i>et al.</i> (1979) |
|-------------------|----------------------------|

#### Compositae

|                       |                                          |
|-----------------------|------------------------------------------|
| <i>Baccharis</i>      | Bohlmann <i>et al.</i> (1979b)           |
| <i>Bidens</i>         | Hart (1979); Serbin <i>et al.</i> (1975) |
| <i>Chromolaena</i>    | Barua <i>et al.</i> (1978)               |
| <i>Chrysanthamnus</i> | Bohlmann <i>et al.</i> (1979a)           |
| <i>Dahlia</i>         | Lam and Wrang (1975)                     |
| <i>Eupatorium</i>     | Arene <i>et al.</i> (1978)               |
| <i>Flourensia</i>     | Bohlmann and Jakupovic (1979)            |
| <i>Gnaphalium</i>     | Maruyama <i>et al.</i> (1974)            |
| <i>Gymnopentzia</i>   | Bohlmann and Zdero (1978)                |



|                       |                                                                               |
|-----------------------|-------------------------------------------------------------------------------|
| <i>Helichrysum</i>    | Bohlmann and Abraham (1979a,b,d); Bohlmann <i>et al.</i> (1978, 1979e, 1980c) |
| <i>Inula</i>          | Baruah <i>et al.</i> (1979)                                                   |
| <i>Marshallia</i>     | Bohlmann <i>et al.</i> (1979d)                                                |
| <i>Othonna</i>        | Bohlmann and Knoll (1978)                                                     |
| <i>Polymnia</i>       | Bohlmann and Zdero (1977)                                                     |
| <i>Senecio</i>        | Bohlmann and Zdero (1979)                                                     |
| <i>Steiractinia</i>   | Bohlmann <i>et al.</i> (1980b)                                                |
| <i>Tarchonanthus</i>  | Bohlmann and Suwita (1979a)                                                   |
| Coriariaceae          |                                                                               |
| <i>Coriaria</i>       | Bohm and Ornduff (1981)                                                       |
| Cruciferae            |                                                                               |
| <i>Matthiola</i>      | Forkmann (1979)                                                               |
| Dilleniaceae          |                                                                               |
| <i>Dillenia</i>       | Pavanasasivan and Sultanbawa (1975)                                           |
| Ericaceae             |                                                                               |
| <i>Rhododendron</i>   | King (1977a,b)                                                                |
| Euphorbiaceae         |                                                                               |
| <i>Phyllanthus</i>    | Chauhan <i>et al.</i> (1977)                                                  |
| Fagaceae              |                                                                               |
| <i>Nothofagus</i>     | Wollenweber and Wiermann (1979)                                               |
| Gentianaceae          |                                                                               |
| <i>Hoppea</i>         | Ghosal <i>et al.</i> (1978)                                                   |
| Gesneriaceae          |                                                                               |
| <i>Didymocarpus</i>   | Bose and Adithyachaudhury (1978); Garg <i>et al.</i> (1979)                   |
| Labiatae              |                                                                               |
| <i>Coleus</i>         | Brieskorn and Riedel (1977)                                                   |
| <i>Mentha</i>         | Bourweig and Pohl (1973)                                                      |
| Lauraceae             |                                                                               |
| <i>Aniba</i>          | Fernandes <i>et al.</i> (1978)                                                |
| <i>Litsea</i>         | Mohan <i>et al.</i> (1978)                                                    |
| Malvaceae             |                                                                               |
| <i>Hibiscus</i>       | Chauhan <i>et al.</i> (1979c)                                                 |
| Meliaceae             |                                                                               |
| <i>Soymida</i>        | Rao <i>et al.</i> (1979)                                                      |
| Moraceae              |                                                                               |
| <i>Chlorophora</i>    | Gottlieb <i>et al.</i> (1975)                                                 |
| Myrtaceae             |                                                                               |
| <i>Agonis</i>         | Cannon and Martin (1977)                                                      |
| Myristicaceae         |                                                                               |
| <i>Iryanthera</i>     | de Almeida <i>et al.</i> (1979)                                               |
| Rosaceae              |                                                                               |
| <i>Persica</i>        | Sadykov and Sadykov (1979)                                                    |
| <i>Prunus</i>         | Nagarajan and Parmar (1977a,b,c)                                              |
| Rubiaceae             |                                                                               |
| <i>Lasianthus</i>     | Ishikura <i>et al.</i> (1979)                                                 |
| Rutaceae              |                                                                               |
| <i>Citrus</i> hybrids | Kamiya <i>et al.</i> (1979)                                                   |
| <i>Clymenia</i>       | Grieve and Scora (1980)                                                       |
| <i>Eremocitrus</i>    | Grieve and Scora (1980)                                                       |
| <i>Fortunella</i>     | Grieve and Scora (1980)                                                       |
| <i>Microcitrus</i>    | Grieve and Scora (1980)                                                       |
| <i>Pleiiospermium</i> | Grieve and Scora (1980)                                                       |

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**Table 6.13** (Contd.)

|                     |                                                                                                                          |
|---------------------|--------------------------------------------------------------------------------------------------------------------------|
| <i>Poncirus</i>     | Grieve and Scora (1980)                                                                                                  |
| <i>Zanthoxylum</i>  | Fish <i>et al.</i> (1975a,b)                                                                                             |
| <i>Evoda</i>        | Grimshaw and Lamer-Zarawska (1975)                                                                                       |
| Leguminosae         |                                                                                                                          |
| <i>Acacia</i>       | Fourie <i>et al.</i> (1974); El Sissi <i>et al.</i> (1974); Gupta <i>et al.</i> (1980); Rao and Raju (1979)              |
| <i>Bauhinia</i>     | A. K. Gupta <i>et al.</i> (1979, 1980)                                                                                   |
| <i>Cajanus</i>      | Bhanumati <i>et al.</i> (1978)                                                                                           |
| <i>Cassia</i>       | Tiwari and Geiger (1975)                                                                                                 |
| <i>Dalbergia</i>    | Matos <i>et al.</i> (1975); Manners <i>et al.</i> (1974); Parthasarathy <i>et al.</i> (1976); Letcher and Shirley (1976) |
| <i>Dalea</i>        | Dreyer <i>et al.</i> (1975); Dominguez <i>et al.</i> (1980)                                                              |
| <i>Derris</i>       | Braz Filho <i>et al.</i> (1975)                                                                                          |
| <i>Flemingia</i>    | Sivarambabu <i>et al.</i> (1979a,b); Rao <i>et al.</i> (1974, 1975b)                                                     |
| <i>Galega</i>       | Traub and Geiger (1975)                                                                                                  |
| <i>Gliricidia</i>   | Jurd and Manners (1977)                                                                                                  |
| <i>Glycyrrhiza</i>  | Kaltaev and Nikonov (1974)                                                                                               |
| <i>Indigofera</i>   | Dominguez <i>et al.</i> (1978a,b)                                                                                        |
| <i>Lygos</i>        | El Sherbeiny <i>et al.</i> (1978)                                                                                        |
| <i>Medicago</i>     | Ingham (1979)                                                                                                            |
| <i>Milletia</i>     | Islam <i>et al.</i> (1980); Gupta and Krishnamurti, (1976a,b)                                                            |
| <i>Myroxylon</i>    | de Oliveira <i>et al.</i> (1978)                                                                                         |
| <i>Onobrychis</i>   | Ingham (1978)                                                                                                            |
| <i>Peltogyne</i>    | Malan and Roux (1974)                                                                                                    |
| <i>Pongamia</i>     | Satam and Brinji (1973); Talapatra <i>et al.</i> (1980)                                                                  |
| <i>Rhynchosia</i>   | Adinarayana <i>et al.</i> (1980a,b)                                                                                      |
| <i>Sophora</i>      | Jain and Gupta (1978)                                                                                                    |
| <i>Tephrosia</i>    | Jayaraman <i>et al.</i> (1980); Camele <i>et al.</i> (1980)                                                              |
| <i>Zuccagnia</i>    | Pederiva <i>et al.</i> (1975)                                                                                            |
| Salicaceae          |                                                                                                                          |
| <i>Salix</i>        | Kompantsev and Shinkarenko (1975)                                                                                        |
| Solanaceae          |                                                                                                                          |
| <i>Nierembergia</i> | Pomilio and Gros (1979)                                                                                                  |
| Theaceae            |                                                                                                                          |
| <i>Camellia</i>     | Imperato (1976)                                                                                                          |
| MONOCOTYLEDONAE     |                                                                                                                          |
| Liliaceae           |                                                                                                                          |
| <i>Tulipa</i>       | Budzianowski and Skrzypczakowa (1978)                                                                                    |

**Table 6.14** Summary of natural sources of dihydroflavonols by genus

### BRYOPHYTA-MUSCI

|                   |                                              |
|-------------------|----------------------------------------------|
| <i>Georgia</i>    | Vandekerkhove (1977)                         |
| CONIFERAE         |                                              |
| <i>Abies</i>      | Parker <i>et al.</i> (1979)                  |
| <i>Cedrus</i>     | Agrawal <i>et al.</i> (1980a,b)              |
| <i>Larix</i>      | Niemann (1974); Lapteva <i>et al.</i> (1974) |
| <i>Picea</i>      | Ivanova <i>et al.</i> (1975)                 |
| <i>Podocarpus</i> | Rizvi and Rahman (1974)                      |

## ANGIOSPERMAE-DICOTYLEDONAE

- Anacardiaceae  
*Amphipterygium* Young (1976)  
*Rhus* Young (1979)
- Boraginaceae  
*Cordia* Srivastava and Srivastava (1979)
- Capparidaceae  
*Cleome* Chauhan *et al.* (1979b)
- Compositae  
*Helichrysum* Bohlmann and Abraham (1979a)  
*Inula* Barauh *et al.* (1979)  
*Marshallia* Bohlmann *et al.* (1980a)  
*Othonna* Bohlmann and Knoll (1978)
- Cruciferae  
*Matthiola* Forkmann (1979)
- Dilleniaceae  
*Dillenia* Pavanadasivan and Sultanbawa (1975)  
*Wormia* Pavanadasivan and Sultanbawa (1975)
- Ebenaceae  
*Diospyros* Chauhan *et al.* (1979a)
- Ericaceae  
*Cavendishia* Luteyn *et al.* (1980)  
*Rhododendron* King (1977a,b)
- Eucryphiaceae  
*Euchryphia* Tschesche *et al.* (1979)
- Labiatae  
*Coleus* Brieskorn and Riedl (1977)
- Lauraceae  
*Aniba* Fernandes *et al.* (1978)
- Leguminosae  
*Acacia* Fourie *et al.* (1974)  
*Albizia* Candy *et al.* (1978)  
*Dalbergia* Matos *et al.* (1975, 1976); Dayal and Parthasarathy (1977)  
*Gliricidia* Manners and Jurd (1979)  
*Lonchocarpus* Delle Monache *et al.* (1978)  
*Milletia* Singhal *et al.* (1980)  
*Peltogyne* Malan and Roux (1974)  
*Rhynchosia* Adinarayana *et al.* (1980a)  
*Sophora* Delle Monache *et al.* (1976)
- Meliaceae  
*Soyimida* Rao *et al.* (1979)
- Moraceae  
*Cudrania* Gupta *et al.* (1975a)
- Rhamnaceae  
*Zizyphus* Srivastava and Chauhan (1977)
- Rosaceae  
*Persica* Sadykov and Sadykov (1979)  
*Prunus* Nagarajan and Parmar (1977b,c)
- Rutaceae  
*Phellodendron* Otryashenkova *et al.* (1977)
- Saxifragaceae  
*Heuchera* Wells and Bohm (1980)

**Table 6.14** (Contd.)

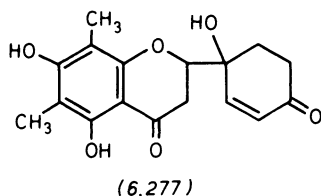
|                    |                        |
|--------------------|------------------------|
| <i>Leptarrhena</i> | Miller and Bohm (1979) |
| <i>Saxifraga</i>   | Miller and Bohm (1980) |
| MONOCOTYLEDONAE    |                        |
| Orchidaceae        |                        |
| <i>Aerides</i>     | C. A. Williams (1979)  |

*Diplazium*, *Lunathyrium*), a difference which parallels morphological differences between the two groups. The onocleoid ferns show a much more complex pattern of flavonol glycosides, and *Matteuccia* is further distinguished through the presence of the flavanones matteucinol 7-glucoside and desmethoxymatteucinol 7-glucoside (tentative identification).

### (c) Dryopteridaceae

In the same paper Hiraoka (1978) also determined the flavonoids of 30 species from five genera of Dryopteridaceae. Flavanones figure significantly in discussions of inter- as well as infra-generic distinctions. *Cyrtomium* is clearly distinguished from other members of the family owing to the presence of the flavanones cyrtominetin and farrerol (tentative identifications). Cyrtominetin has been found only in this genus to date (see Bohm, 1975, Table 11.1, p. 568) while farrerol, also known from *Cyrtomium*, occurs in flowering plants as well (ibid., p. 568).

In support of the recognition of *Arachniodes* and *Leptorumohra* as separate genera, Hiraoka (1978) pointed out that species of the former make only flavones while the latter makes only flavonols. He did not mention that a further distinguishing compound marks separate generic status: *L. miqueliana* has been shown to possess the odd, reduced B-ring flavanone 'protofarrerol' (6.277) (Noro *et al.*, 1969).



Differences between *Polysticum* and *Dryopteris* exist in the array of flavonols and flavones elaborated by each. There are differences in flavanone structure and distribution as well, but these differences are much less clear cut.

Flavonoids allow clear distinctions to be drawn between groups of species within *Dryopteris* section *Erythro-variae*, however. The first group, comprising *D. bissetiana*, *D. sordidipes*, *D. pacifica* and *D. sacrosancta*, exhibits a complex pattern of both flavones and flavonol glycosides and has naringenin 7-O-glucoside. The second group of species, *D. erythrosera*, *D. nipponensis*,

*D. championii*, *D. hondoensis*, *D. gymnosora* and *D. gymnophylla*, has the simpler array of flavones and flavonols and has eriodictyol 7-*O*-rhamnoglucoside. All members of both groups possess eriodictyol 7-*O*-glucoside. Hiraoka (1978) pointed out that the Japanese members of this section fall into two groups on the basis of morphological characters which parallel the flavonoid variation.

*Dryopteris watanabei* has been shown by cytological analysis to be a natural hybrid between *D. crassirhizoma* and *D. uniformis*. *Dryopteris uniformis* accumulates an array of flavonoids consisting of six flavonol glycosides while *D. crassirhizoma* was shown to have three flavones, two flavonol glycosides and eriodictyol 7-*O*-glucoside. The pattern of *D. watanabei* shows total additivity of the parental flavonoid phenotypes.

#### (d) Pteridaceae

Much intensive work on the chemistry of *Pityrogramma* has been published during the past few years. Members of this genus are commonly referred to as silver-back or gold-back ferns owing to the frequently copious production of semi-crystalline material by leaf glands. Chalcones and dihydrochalcones are major constituents of the exudates of most species while in others they occur along with a variety of methylated flavone and flavonol aglycones. Several reviews of the subject have appeared recently (Wollenweber, 1978; Star, 1980; Wollenweber and Dietz, 1980). Table 6.15 summarizes the distribution of the most commonly met chalcones and dihydrochalcones and attempts to point out some of the variation seen. A detailed discussion of the variation patterns observed is beyond the scope of this chapter and should be sought in the article by Wollenweber and Dietz (1980).

*Pityrogramma triangularis* is distinguished from other members of the genus studied to date by virtue of the replacement of the chalcones and dihydrochalcones seen in all other species by several flavonoids including the unusual A-ring chalcone ceroptin. The occurrence of these other flavonoids is not general throughout the species but closely follows varietal lines. These data are presented in Table 6.16. Further flavonoid variation in *P. triangularis* var. *triangularis* was found and discussed by Star and co-workers (1975a,b), who pointed out the usefulness of the vacuolar flavonoids in distinguishing ploidy levels in the chemotypes.

Although there are some exceptions, notably in *Cheilanthes* and *Notholaena*, the four main compounds whose distribution is summarized in Table 6.15, serve well as generic markers, setting *Pityrogramma* off from other *Gymnogrammoid* ferns (Wollenweber and Dietz, 1980). These authors point out that *P. triangularis* does not fit the pattern, but offer no suggestion as to why this taxon, with its four chemically different varieties, should be expected to be so different.

In 1852 Fée removed *P. trifoliata* from *Pityrogramma* on the basis of differences in frond morphology and placed it as the sole member of *Trismeria*. Tryon (1962) disagreed with this view and returned the taxon to *Pityrogramma*,

Table 6.15 Summary of the distribution of chalcones and dihydrochalcones in *Pityrogramma*\*†

| Species                                   | 2',6'-Dihydroxy-4'-methoxychalcone-4-R |                      | 2',6'-Dihydroxy-4'-methoxydihydrochalcone-4-R |                      | Comments                                                                                                                                                                                                                                                                                                                                                                 |
|-------------------------------------------|----------------------------------------|----------------------|-----------------------------------------------|----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                           | R = H                                  | R = OCH <sub>3</sub> | R = H                                         | R = OCH <sub>3</sub> |                                                                                                                                                                                                                                                                                                                                                                          |
| <i>P. argentea</i>                        | + (9/9) <sup>  </sup>                  | —                    | + (4/4)                                       | —                    | Extensive intra- and inter-variatal variation*<br>var. <i>marginata</i> has 2',4-dihydroxy-4',6'-dimethoxydihydrochalcone†                                                                                                                                                                                                                                               |
| <i>P. aurentiaca</i>                      | + (4/4)                                | —                    | —                                             | —                    |                                                                                                                                                                                                                                                                                                                                                                          |
| <i>P. calomelanos</i>                     | +                                      | +                    | +                                             | +                    |                                                                                                                                                                                                                                                                                                                                                                          |
| <i>P. chrysoconia</i>                     | + (1/7)                                | —                    | + (5/7)                                       | —                    |                                                                                                                                                                                                                                                                                                                                                                          |
| <i>P. chrysophylla</i>                    | + (8/10)                               | + (6/10)             | + (3/10)                                      | + (3/10)             | Only one sample tested<br>Only one sample tested<br>Only one sample tested<br>No variation data available<br>Has cinnamoyldihydrocoumarin ('T-1')§<br>Extensive variation; has 2',6',4-trihydroxy-4'-methoxychalcone<br>Extensive variation, see Table 6.16 for details<br>Has cinnamoyldihydrocoumarins ('T-1', 'T-2', 'T-3')§<br>Has cinnamoyldihydrocoumarin ('T-1')§ |
| <i>P. dealbata</i>                        | + (1/9)                                | —                    | + (8/9)                                       | + (2/9)              |                                                                                                                                                                                                                                                                                                                                                                          |
| <i>P. dukei</i>                           | —                                      | + (1/1)              | —                                             | —                    |                                                                                                                                                                                                                                                                                                                                                                          |
| <i>P. lehmannii</i>                       | —                                      | —                    | —                                             | + (1/1)              |                                                                                                                                                                                                                                                                                                                                                                          |
| <i>P. pulchella</i>                       | —                                      | —                    | — (1/1)                                       | —                    | Only one sample tested<br>Only one sample tested<br>No variation data available<br>Has cinnamoyldihydrocoumarin ('T-1')§<br>Extensive variation; has 2',6',4-trihydroxy-4'-methoxychalcone<br>Extensive variation, see Table 6.16 for details<br>Has cinnamoyldihydrocoumarins ('T-1', 'T-2', 'T-3')§<br>Has cinnamoyldihydrocoumarin ('T-1')§                           |
| <i>P. schizophylla</i> †                  | —                                      | +                    | —                                             | +                    |                                                                                                                                                                                                                                                                                                                                                                          |
| <i>P. sulphurea</i>                       | + (7/7)                                | +†                   | —                                             | —                    |                                                                                                                                                                                                                                                                                                                                                                          |
| <i>P. tartarea</i>                        | +                                      | +                    | +                                             | +                    |                                                                                                                                                                                                                                                                                                                                                                          |
| <i>P. triangularis</i>                    | —                                      | —                    | —                                             | —                    | Only one sample tested<br>Only one sample tested<br>No variation data available<br>Has cinnamoyldihydrocoumarin ('T-1')§<br>Extensive variation; has 2',6',4-trihydroxy-4'-methoxychalcone<br>Extensive variation, see Table 6.16 for details<br>Has cinnamoyldihydrocoumarins ('T-1', 'T-2', 'T-3')§<br>Has cinnamoyldihydrocoumarin ('T-1')§                           |
| <i>P. trifoliata</i>                      | + (1/27)                               | + (1/27)             | + (27/27)                                     | + (15/27)            |                                                                                                                                                                                                                                                                                                                                                                          |
| <i>P. williamsii</i>                      | + (2/3)                                | —                    | —                                             | —                    |                                                                                                                                                                                                                                                                                                                                                                          |
| <i>P. trifoliata</i> × <i>calomelanos</i> | —                                      | —                    | + (5/5)                                       | + (4/5)              |                                                                                                                                                                                                                                                                                                                                                                          |

\* Data for this Table comes from Wollenweber and Dietz (1980) with additions from other sources as indicated below.

† From Star (1980).

‡ Nilsson (1961).

§ Dietz *et al.* (1980).

|| Number of samples positive for the compound/number of samples tested.

**Table 6.16** Flavonoid variation in *Pityrogramma triangularis*

| Varieties of<br><i>P. triangularis</i> | Constituents (No.)*                                                  | References                                                   |
|----------------------------------------|----------------------------------------------------------------------|--------------------------------------------------------------|
| var. <i>triangularis</i>               | Ceroptin (6.32)<br>Galangin and kaempferol methyl<br>ethers†         | Star <i>et al.</i> (1975a,b)<br>Star <i>et al.</i> (1975a,b) |
| var. <i>maxonii</i>                    | Triangularin (6.29)‡                                                 | Star <i>et al.</i> (1978)                                    |
| var. <i>pallida</i> ‡                  | Galangin                                                             | Wollenweber and Dietz (1980)                                 |
|                                        | Cryptostrobin (6.180)                                                | Wollenweber <i>et al.</i> (1979a)                            |
|                                        | Strobopinin (6.179)                                                  | Wollenweber <i>et al.</i> (1979a)                            |
|                                        | Desmethoxymatteucinol (6.181)                                        | Wollenweber <i>et al.</i> (1979a)                            |
|                                        | Pinocembrin (6.170)                                                  | Wollenweber <i>et al.</i> (1979a)                            |
|                                        | Aurentiacin (6.30)                                                   | Wollenweber <i>et al.</i> (1980b)                            |
|                                        | Flavokawin-B (6.15)                                                  | Wollenweber <i>et al.</i> (1980b)                            |
| var. <i>viscosa</i>                    | 2',6',4-Trihydroxy-4'-methoxy-5-C-<br>methyl dihydrochalcone (6.140) | Wollenweber <i>et al.</i> (1979b)                            |

\* Refer to text for structures, the numbers of which are shown.

† Flavonol derivatives.

‡ A trace of the corresponding flavanone, 7-methylstrobopinin (6.182), was also detected.

§ Also seen as *Pityrogramma pallida* in text and Table 6.6.

a move which is supported by the farina chemistry. *Pityrogramma trifoliata* exhibits the characteristic dihydrochalcones seen in the genus. It also can make the cinnamoyl dihydrocoumarin derivatives (T-1, T-2 and T-3 of Dietz *et al.*, 1980) in common with *P. sulphurea* and *P. williamsii*.

### 6.7.3 Anacardiaceae

#### (a) *Rhus*

Young (1979) examined the heartwood flavonoids of 23 taxa of *Rhus* as part of an investigation of infrageneric relationships. The aglycones identified were the aurones rengasin and sulfuretin, 7,4' dihydroxydihydroflavonol, 7,3',4'-trihydroxydihydroflavonol, 7,3',4'-trihydroxyflavonol (fisetin) and 3',4'-dihydroxyflavone. These compounds plus a glucoside of sulfuretin were found in all 23 taxa. Variation was seen in the distribution of glucosides of butein, fisetin and 3',4'-dihydroxyflavone. It is this variation that sheds light on subgeneric relationships. *Rhus* subgenus *Rhus* lacks all three glucosides, *Rhus* subgenus *Lobadium* section *Terebinthifolia* has fisetin glucoside but lacks the other two compounds, section *Lobadium* has fisetin glucoside and dihydroxyflavone glucoside, while section *Styphonia*, with significant exceptions, has all three glucosides. Section *Styphonia* is subdivided into three subsections on the basis of leaf morphology. Subsections *Intermediae* and *Styphoniae* are identical in their possession of all three glucosides while some species of subsection *Compositae* lack the capacity to make the 3',4'-dihydroxyflavone glucoside. It is of interest

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that the species lacking the compound are among the more primitive members of the group. Young (1979) pointed out that the major evolutionary trend seemed to be toward accumulation of glycosides of the heartwood flavonoids. The data are summarized in Table 6.17.

**Table 6.17** Distribution of selected flavonoid glycosides in *Rhus*\*

|                                 | Glycosides of |       |     |
|---------------------------------|---------------|-------|-----|
|                                 | FIS           | DHF   | BUT |
| <i>Rhus</i> subgen. <i>Rhus</i> | —             | —     | —   |
| subgen. <i>Lobadium</i>         |               |       |     |
| sect. <i>Terebinthifolia</i>    | +             | —     | —   |
| sect. <i>Lobadium</i>           | +             | +     | —   |
| sect. <i>Stylonia</i>           |               |       |     |
| subsect. <i>Compositae</i>      | +             | — / + | +   |
| subsect. <i>Intermediae</i>     | +             | +     | +   |
| subsect. <i>Styphoniae</i>      | +             | +     | +   |

\* After Young (1979). Key: FIS = fisetin, DHF = 3',4'-dihydroxy-flavone, BUT = butein.

### (b) *Amphipterygium*

In an earlier paper Young (1976) also used flavonoid chemistry to assess the relationships of the Julianaceae, a family whose position in or near the Anacardiaceae has been the subject of some discussion. Sixteen compounds were isolated from *Amphipterygium adstrigens*: seven 5-deoxyflavonoids plus rengasin from the roots, and nine 5-hydroxyflavonoids, including rengasin, and sulfuretin from the leaves. The flavonoid pattern of *Amphipterygium* is very similar to that of the Anacardiaceae, particularly to that of the tribe Rhoeae. Young concluded, on the basis of the flavonoid data as well as anatomical and morphological similarities, that the genus, and thus *Orthopterygium* by association, belonged in the Rhoeae. Differences in fruit structure and some floral characteristics, however, were taken as support for placing these genera in the subtribe Julianiinae within Rhoeae.

## 6.7.4 Compositae

### (a) *Bidens*

*Bidens pilosa* L. was considered by Sherff (1937) to be a single species having widely variant morphological characters throughout its very extensive range. Detailed field studies coupled with an experimental breeding programme and cytological and flavonoid studies led Ballard (1975) to recognize the existence of four species (eight taxa in all). A significant contribution to Ballard's data was the taxon-specific distribution of okanin derivatives, namely, 4'-glycosides, 3',4'-



diglycosides, 3-*O*-methyl-4'-glycosides and 3,4-di-*O*-methyl-4'-glycosides. The absence of flavonols from leaves of *B. clavatus*, along with its self-incompatibility, also helps to distinguish it from *B. odorata*, since these two species are the only diploids ( $n = 12$ ) in the group. Ballard's data are summarized in Table 6.18. The Table includes information about *B. bigelovii* to which the *B. pilosa* complex was compared.

**Table 6.18** Summary of *Bidens pilosa* complex data\*

| Taxon                           | n  | Breed <sup>†</sup><br>biol. | Okanin derivatives <sup>‡</sup> |      |     |      | Flav |
|---------------------------------|----|-----------------------------|---------------------------------|------|-----|------|------|
|                                 |    |                             | 4'G                             | 3'4G | 3OM | 34OM |      |
| <i>B. odorata</i>               |    |                             |                                 |      |     |      |      |
| var. <i>odorata</i>             | 12 | comp                        |                                 |      | +   |      | +    |
| var. <i>calicicola</i>          | 12 | comp                        | +                               |      |     |      | +    |
| var. <i>oaxacensis</i>          | 12 | comp                        |                                 | +    |     |      | +    |
| var. <i>chilpancingensis</i>    | 12 | comp                        |                                 |      |     | +    | +    |
| <i>B. clavatus</i>              | 12 | incomp                      |                                 |      | +   |      | —    |
| <i>B. alba</i> var. <i>alba</i> | 24 | incomp                      |                                 |      | +   |      | +    |
| var. <i>radiata</i>             | 24 | incomp                      |                                 |      | +   | +    | +    |
| <i>B. pilosa</i>                | 36 | comp                        | +                               |      |     |      | +    |
| <i>B. bigelovii</i>             |    |                             |                                 |      |     |      |      |
| var. <i>bigelovii</i>           | 24 | comp                        | +                               |      |     |      | +    |
| var. <i>angustiloba</i>         | 24 | comp                        | +                               |      |     |      | +    |

\* From Ballard (1975).

<sup>†</sup> Breeding biology: comp = self-compatible, incomp = self-incompatible.

<sup>‡</sup> 4'G = 4'-*O*-glucoside, 3'4G = 3',4'-di-*O*-glucoside, 3OM = 3-*O*-methyl, 34OM = 3,4-di-*O*-methyl, Flav = flavonols.

### (b) *Megalodonta*

*Megalodonta* is a specialized aquatic genus closely related to *Bidens*. In a recent paper Roberts (1980) described the flavonoid chemistry of *M. beckii*, the sole member of the genus, as part of a study of the relationship between the two genera. *Megalodonta* accumulates a number of chalcones and aurones including the comparatively rare 2',4',3-trihydroxy-3'-methoxychalcone 4'-*O*-glucoside. This chalcone, as the free phenol, occurs in *Dahlia* (Giannasi, 1975) and in members of two sections of *Bidens*: *Platycarpaea* and *Heterodonta* (Roberts, 1980). The systematic significance of this distribution remains to be determined following wider sampling within *Bidens*, but a close association between the two genera is clearly supported by these phytochemical observations.

### (c) *Dahlia*

In a detailed study of *Dahlia*, Giannasi (1975) reported the distribution of 64 glycosides and 15 aglycones in 21 taxa obtained from Mexico, Central America and northern South America. The flavonoids represented five classes of

compounds: flavones, flavonols, chalcones, aurones and anthocyanins. The chemical data are useful at several taxonomic levels. Several glycosides appear to characterize the genus: diosmetin (= luteolin 4'-O-methyl ether) glucosides, butein galactoside, butein-4,4'-tri- and tetra-glucosides and butein arabinosylgalactosides. At the sectional level the presence of 6-methoxyflavones clearly separates section *Entemophyllum* from sections *Dahlia* and *Pseudodendron* wherein flavonols were found. At the interspecific level individual species exhibited specific combinations of pigments, although in several cases in sections *Dahlia* and *Pseudodendron* greater use of tissue specific profiles was necessary, since total flavonoid complements were often identical.

Some distinctions at the intergeneric level can be made on the basis of localization of anthochlors. In *Dahlia*, flavones, flavonols and anthochlors occur in both leaf and floral tissue, whereas in *Cosmos*, leaves possess flavones and flavonols while anthochlors are restricted to floral tissue. It is tempting to speculate that this situation reflects specialization in the case of *Cosmos* where anthochlors are responsible for the flavonoid contribution to flower colour, whereas the even distribution of anthochlor and non-anthochlor pigments throughout aerial parts of *Dahlia* species represents the non-specialized situation. A detailed comparative study of the reproductive biology of these two genera might afford useful insight into the selective pressures associated with tissue specific distribution of anthochlors and of flavonoids in general.

#### (d) Coreopsidinae

*Coreopsis* has figured significantly in the study of the structure and distribution of anthochlor pigments. Beginning with the research of Gertz (1938) the subject has proceeded from surveys using simple colour tests to the present position where anthochlor pigments, along with a host of other characters, play an important part in helping to define the limits of the subtribe Coreopsidinae (Heliantheae) (Crawford and Stuessy, 1981). In that paper, Crawford and Stuessy reported the presence of anthochlors in 15 genera of Coreopsidinae not studied to date [their count of 16 included *Megalodonta*, work on which has now been published by Roberts (1980)]. Table 6.19 lists the genera studied and the types of compounds found.

With publication of these data 30 of 32 genera in Coreopsidinae have been tested for anthochlors (*Cyathomone* and *Sphagneticola* were not available). Of the 30 genera tested only two lacked anthochlors: *Guardiola* Cerv. ex H. and B (five species of 13 known) and *Venegasia* DC. (monotypic, four collections tested). The authors state that, although exact affinities within the tribe are difficult to establish, a number of characters clearly place *Guardiola* in the subtribe. They suggest that absence of anthochlors represents an evolutionary loss. The absence of anthochlors from *Venegasia* was similarly explained since the genus is closely related to *Jaumea*; both have  $n = 19$ , an unusual number within the subtribe. The authors suggest that loss of anthochlors could be explained through 'addition of

**Table 6.19** New generic records of anthochlors in the Coreopsidinae\*

| <i>Genus</i>          | <i>Taxa tested</i> <sup>†</sup> | <i>Anthochlors found</i>                                            |
|-----------------------|---------------------------------|---------------------------------------------------------------------|
| <i>Coreocarpus</i>    | 3/3/10                          | Butein and sulfuretin glucosides                                    |
| <i>Dicranocarpus</i>  | 1/1/1                           | Not identified                                                      |
| <i>Ericentrodea</i>   | 2/2/3                           | Butein and sulfuretin glucosides                                    |
| <i>Eringiophyllum</i> | 1/1/1                           | Butein and sulfuretin glucosides, okanin and maritimetin glucosides |
| <i>Glossocardia</i>   | 1/1/2                           | Not identified                                                      |
| <i>Goldmanella</i>    | 1/1/1                           | Butein and sulfuretin glucosides, okan and maritimetin glucosides   |
| <i>Guerreroia</i>     | 1/1/1                           | Not identified                                                      |
| <i>Henricksonia</i>   | 1/1/1                           | Not identified                                                      |
| <i>Jaumea</i>         | 3/3/20                          | Butein and sulfuretin glucosides                                    |
| <i>Moonia</i>         | 1/1/1                           | Not identified                                                      |
| <i>Narvalina</i>      | 1/1/4                           | Butein and sulfuretin glucosides, okanin and maritimetin glucosides |
| <i>Oparanthus</i>     | 1/1/2                           | Not identified                                                      |
| <i>Petrobium</i>      | 1/1/1                           | Not identified                                                      |
| <i>Selleophytum</i>   | 1/1/1                           | Butein and sulfuretin glucosides                                    |
| <i>Staurochlamys</i>  | 1/1/1                           | Not identified                                                      |

\* After Crawford and Stuessy (1981).

<sup>†</sup>  $m/n/p$  where  $m$  = number of species positive for anthochlors,  $n$  = number of species tested,  $p$  = number of species recognized in genus.

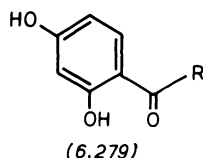
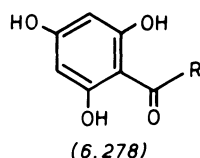
a few enzymes to the basic flavonoid biosynthetic pathway.' It is not clear to me how this could happen. Since formation of aurones appears to require an oxidase, absence of aurones would imply loss or suppression of such an enzyme. Also, since chalcones are generally considered to be obligate intermediates in flavonoid biosynthesis the absence of chalcones may only indicate that the rate of chalcone consumption exceeds the rate of formation, the result being manifested in the lack of *accumulation* of chalcone derivatives.

Crawford and Stuessy also extended the list of genera of the Heliantheae in which anthochlors do *not* occur. Also of interest is their report of two genera in Heliantheae wherein anthochlors have been found for the first time; butein and sulfuretin glycosides in *Simsia* Pers. (one species of three tested; 35 species known) and *Tithonia* Desf. (five species of 11 tested, 11 species known) (unpublished data of J. La Duke). These observations increase to four the number of genera in tribe Heliantheae subtribe Helianthinae known to accumulate anthochlors [the others being *Helianthus* L. and *Viguiera* H. B. K. (Harborne and Smith, 1978)]. The close morphological similarities of these four genera have been recognized for many years (Stuessy, 1977).

The synthesis and accumulation of anthochlors can clearly be taken as a characteristic of Coreopsidinae. Occurrence of anthochlors in other members of the Compositae, however, is not at all easily explained in evolutionary terms.

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Anthochlors are known from Cardueae, Eupatorieae, Inuleae, Helenieae, Lactuceae and, as described above, Heliantheae. [The Helenieae is now considered defunct with its constituent genera dispersed to several tribes (Turner and Powell, 1977)]. It is of interest to note that the compounds from the Cardueae, Eupatorieae and Inuleae are based upon the phloroglucinol A-ring pattern (6.278) while those from Heliantheae and Lactuceae are based upon the resorcinol pattern (6.279). Crawford and Stuessy point out that distribution of



these structural types does not correlate well with subfamilial treatments of the Compositae (see their paper for extensive references). Parallel evolution of the two types in the subfamilies may have occurred. Until more is learned about the biosynthesis and biological function(s) of these types of compounds in their respective organisms little more can be said at this time.

In addition to work aimed at establishing relationships at generic and higher taxonomic levels studies at infrageneric levels also continue. The distribution of okanin and maritimetin proved useful in a study of *Coreopsis* section *Pseudo-agarista* in Mexico (Crawford, 1976). Chalcone–aurone glycoside pairs coupled with chromosome counts allowed a clear distinction to be drawn between section *Pseudo-agarista* and sections *Electra* and *Anathysana*. Other discussions of the significance of anthochlor distribution at the sectional level within *Coreopsis* have appeared (Crawford, 1978; Nicholls and Bohm, 1979), and Crawford and Smith (1980) showed that the anthochlors of the four varieties of *C. grandiflora* are identical despite widely different geographic ranges and chromosome numbers.

### 6.7.5 Ericaceae

#### (a) *Rhododendron* subgen. *Pentanthera*

The flavonoid complement of *Rhododendron* subgen. *Pentanthera* was shown by King (1980, and references cited therein) to include a variety of structural types: flavonols (including 5-*O*-methylflavonols), a dihydroflavonol, flavanones, dihydrochalcones and chalcones, although not all compounds were fully characterized. Despite populational variation it was possible for King to describe species-specific groups of compounds and to show that the flavonoids were useful in arranging the species into five ‘alliances.’ King found that the *R. canescens*–*R. nudiflorum*–*R. roseum* group (alliance-A) is characterized by the presence of the dihydrochalcone asebotin and the flavanone eriodictyol. The alliance comprising *R. speciosum*–*R. prunifolium*–*R. calendulaceum*–*R. bakeri* (alliance-B) can be distinguished by the presence of the flavanone farrerol and its

5,7-diglucoside. The presence of asebotin in *R. calendulaceum* suggests a possible link with alliance-A. A further link between these two alliances involves the presence of two (unidentified) chalcones in *R. prunifolium* and *R. bakeri* (alliance-B) and in three collections of *R. canescens* (alliance-A). Alliance-C, consisting of *R. alabamense* and *R. arborescens*, and alliance-D comprising *R. atlanticum*, *R. viscosum*, *R. coryi*, *R. serrulatum* and *R. oblongifolium*, are closely related and both lack the flavones and dihydrochalcones characteristic of the other alliances. Alliance-E consists of *R. austrinum* of southeastern North America, *R. occidentale* of western North America and *R. luteum* of Europe. In spite of the highly disjunct nature of this alliance the group is unique in *Pentanthera* in possessing 5-O-methylflavonols as major constituents.

### 6.7.6 Leguminosae

In the 1975 treatment of legume flavonoids it was stated (Bohm, 1975, p. 490) that, with only one exception, the anthochlors of this family were based upon the resorcinol A ring and that such 5-deoxyflavonoids (6'-deoxychalcones, 4-deoxyaurones) might be considered to characterize the Leguminosae. Since that time a good deal of work has been published concerning the flavonoid chemistry of the family with the result being that a reconsideration of that generalization is in order. In fact, shortly after the appearance of 'The Flavonoids' a paper appeared by do Nascimento and co-workers (1976) that described a number of flavonoids from *Derris obtusa* many of which had the phloroglucinol A ring (aurones, auronols, flavones and flavonols). It was pointed out by those authors that my generalization was no longer valid. A tabulation of data from the present survey shows that members of five genera make chalcones having phloroglucinol-type A rings: *Dalea*, *Derris*, *Milletia*, *Pongamia* and *Tephrosia*. Phloroglucinol-type A-ring aurones and auronols are found in *Derris* as mentioned above. Two genera, *Rhynchosia* and *Sophora*, make 6-oxygenated dihydroflavonols, and no less than 13 genera of legumes make 6-oxygenated flavanones: *Acacia*, *Bauhinia*, *Cajanus*, *Cassia*, *Dalea*, *Derris*, *Flemingia*, *Galega*, *Glycyrrhiza*, *Indigofera*, *Lygos*, *Rhynchosia* and *Tephrosia*.

### 6.7.7 Rutaceae

#### (a) *Citrus* hybrids

In a recent paper, Kamiya and co-workers (1979) studied the flavanone glycoside complement of a large number of artificial *Citrus* hybrids, in order to determine whether the product of a hybridization experiment is a true genetic hybrid or the product of nucellar embryony which is of regular occurrence in many *Citrus* species. Since nucellar embryony yields an offspring arising solely from maternal tissue the flavonoid patterns of the adult plant and the offspring would be identical. An altered pattern would indicate contribution from another

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source, that is, from the male or pollen parent. In all, 94 hybrids were examined of which 53 had patterns which were different from those of the maternal plant.

### (b) Aurantioideae

In another recent paper Grieve and Scora (1980) concluded that morphological specialization in subfamily Aurantioideae has been paralleled by an increase in the complexity of the flavonoid complement. Their study described the distribution of *C*- and *O*-glycosylflavones, flavonols and flavanones in members of subtribes Clauseninae and Merrillinae of tribe Clauseneae and subtribes Triphasiinae, Citrinae and Balsamocitrinae of tribe Citrae (all *sensu* Swingle). Flavanones (naringin, poncirin, hesperidin and two unidentified compounds) were found only in Citrinae and within this subtribe they were largely restricted to members considered as true citrus trees: *Citrus*, *Clymenia*, *Eremocitrus*, *Fortunella*, *Microcitrus* and *Poncirus*. The only exceptional report involved the occurrence of hesperidin in *Pleiospermium sumatranum*, which, though still a member of the subtribe, belongs to a group of more primitive citrus trees.

## 6.8 NATURAL FUNCTIONS OF ANTHOCHLORS

### 6.8.1 Ultraviolet patterning

Significant evidence for the operation of certain flavonoid types as nectar-guide components in flowers of various plants has accumulated. The flavonoids involved in nectar-guide chemistry include 'yellow flavonols' (Harborne, 1977b, p. 369 ff.), 2'-hydroxyflavones (Harborne and Smith, 1978) and anthochlors (*vide infra*). All of these compounds exert their effect by absorbing ultraviolet light and thus appearing dark or 'bee-purple' (Proctor and Yeo, 1973, p. 168 ff.) to the eye of the pollinators. Nectar-guide compounds often occur in association with carotenoids which, in reflecting UV and yellow wavelengths, act to provide a background against which the nectar-guide is visible.

In a study of *Oenothera hookeri* ssp. *venusta* Dement and Raven (1974) observed that only carotenoids occurred in the distal portion of petals while the basal portion had carotenoids plus the chalcone isosalipurposide. The chalcone absorbs UV light and appears bee-purple to insect visitors or simply dark to the human eye. Seven other species of *Oenothera* having the chalcone in their flowers were also listed.

Scogin and Zakar (1976) observed that the uniformly golden-yellow ray florets of *Bidens laevis*, when exposed to ammonia vapours, displayed a colour change to bright orange involving the involucre, the entire disc, the basal 50–66% of the ligule, and the veins running the length of the ligule. The UV absorbance pattern, and thus the pattern which would appear bee-purple to a pollinator, was exactly

congruent with the zone of colour change caused by the ammonia. These workers went on to survey a number of *Bidens* species for pigment floral patterns. Anthochlor distribution fell into three categories: (a) uniform distribution throughout the ligule, (b) distribution restricted to basal portion of the ligule (ranging from 25 to 80 % of the ligules in the samples tested) and (c) pigment absent except for some in the veins of the ligule. The distribution patterns in 36 species correlated reasonably well with sectional taxonomy of the genus. The compounds determined in *B. laevis* were marein, sulfurein, coreopsin, butein and sulfuretin. Very similar results were obtained by Scogin and his co-workers (Scogin, 1976; Scogin *et al.*, 1977) in a study of anthochlor distribution in flowers of 34 species of *Coreopsis*.

Details of pigment localization in ligules of *Coreopsis bigelovii* were reported by Harborne and Smith (1978), who found that the entire lower surface of ray florets gave a positive anthochlor test and absorbed ultraviolet light, while on the upper surface only the basal two-thirds gave a positive test. Closer examination using microtome sections showed that the upper surfaces were papillate while epidermal cells on the undersides were only slightly convex. The anthochlor test was observed to occur in papillate cells. These observations are in complete accord with the report of anthochlor-bearing papillate cells on the upper epidermis of ligules of *Lasthenia chrysostoma* (Brehm and Krell, 1975). Further discussion of ligule microstructure including reference to UV-absorption patterns can be found in a review by Baagøe (1977).

Harborne and Smith (1978) also identified anthochlors from ligules of *Viguiera laciniata* and three species of *Helianthus*, and detected anthochlors by means of their colour reaction with base, in an additional 28 species of *Helianthus* (37 tested). Nectar guides occur in some of these taxa but not in all, i.e. *Viguiera*, where the entire ligule is pigmented. In a recent study of *Megalodonta* Roberts (1980) showed that a UV-absorbing pattern does not exist in contrast to the patterns seen in *Bidens* the genus most closely related to *Megalodonta*. According to Roberts (1980) the uniformly absorbing capitulum of *Megalodonta* may be an adaptation to the aquatic habitat that has the effect of maximizing the 'target area' of the head against the reflective water surface.

### 6.8.2 Larval-growth inhibition

Five flavanone derivatives and two dihydroflavonol derivatives were tested, along with several other flavonoids, for their activity against the growth of larva of *Heliothis zea* (Elliger *et al.*, 1980). Eriodictyol, dihydroquercetin and dihydroquercetin 3-*O*-rhamnoside were active but naringenin, naringin, hesperetin and neohesperidin were inactive. The results were discussed in terms of the number and disposition of phenolic groups in the active molecules. The presence of *ortho*-dihydroxylation seems to be important. The oxidation level of the C ring appears not to be an important factor, nor does glycosylation appear to play a major part. No mechanism of action was postulated.

### 6.8.3 Allelopathy

Star (1980) tested the effects of 2',6'-dihydroxy-4'-methoxydihydrochalcone, 2',6'-dihydroxy-4'-methoxychalcone and 5-hydroxy-7-methoxyflavonol (izalpinin) on the germination of spores of *Pityrogramma calomelanos*. The dihydrochalcone was the most effective causing inhibition of germination at concentrations of  $5 \times 10^{-5}$  M and higher. The chalcone was inhibitory at  $5 \times 10^{-4}$  M and  $5 \times 10^{-6}$  M but stimulatory at  $5 \times 10^{-7}$  M and  $5 \times 10^{-9}$  M. Izalpinin was stimulatory at  $5 \times 10^{-4}$  and  $5 \times 10^{-3}$  M.

The author (Star, 1980) went on to describe observations of dispersal patterns of *P. calomelanos* plants at three sites in the Hawaiian Islands. Two features of these patterns were described in terms of the amounts of exudate substances in the soil. Distances from the parent plants to their nearest neighbours were greater than the distances between the smaller neighbours suggesting that higher concentrations of exudate near the parent plant had inhibited spore germination. At greater distances from the parent, however, amount of exudate would be lower, hence stimulation of germination could be expected. Despite the correlation between the laboratory and field observations one would like to see studies undertaken to determine actual concentrations of the putatively active compounds in the soil. Such an attempt to link cause and effect under natural conditions would be very welcome.

### 6.8.4 Flavonoids and disease resistance in plants

#### (a) *Malus*

The relationship between dihydrochalcones and the resistance of apples to attack by scab (*Venturia inaequalis* Cke. Wint) has been investigated by Hunter (1975). Neither trilobatin (2',4',6',4-tetrahydroxydihydrochalcone 4'-O-glucoside) nor sieboldin (2',4',6',3,4-pentahydroxydihydrochalcone 4'-O-glucoside) conferred resistance to infection on seedlings of *Malus* crosses. He also reported a natural infection of *M. astrosanguinea* by scab despite the presence of both phlorrhizin (2',4',6',4-tetrahydroxydihydrochalcone 2'-O-glucoside) and sieboldin. Cultures of the pathogen could use phloretin, phlorrhizin, trilobatin, sieboldin or 3-hydroxyphlorrhizin as carbon source.

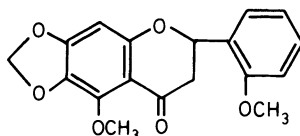
#### (b) *Medicago*

Ingham (1979) tested the ability of leaves of 25 species of *Medicago* to produce phytoalexins following inoculation by *Helminthosporium carbonum*. Pterocarpan and isoflavans were detected in most species. However, diffusates of *M. sativa* cv. Du Puits and *M. lupulina* yielded the chalcone-flavanone pair isoliquiritigenin and liquiritigenin. Control leaves (uninfected) of *M. lupulina* did not appear to contain either of these compounds. Bioassays using *Cladosporium herbarum* showed minor inhibition of growth with the chalcone-flavanone mixture.



## (c) Beta

Evidence has also appeared suggesting that the flavanone 'betagarin', 5,2'-dimethoxy-6,7-methylenedioxyflavanone (6.280), acts as a phytoalexin in sugar beet (*B. vulgaris*) infected with leaf-spot fungus *Cercospora beticola* (Johnson *et al.*, 1976; Martin, 1977).



(6.280)

## ACKNOWLEDGEMENTS

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### CHECK LIST OF CHALCONES

- 1 4'-Methoxychalcone
- 2 2',4'-Dihydroxychalcone
- 3 2'-Hydroxy-4'-prenyloxychalcone
- 4 2',4'-Dihydroxy-3'-C-prenylchalcone\*
- 5 2'-Hydroxy-3'-C-prenyl-4'-methoxychalcone\*
- 6 2',4'-Dihydroxy-3'- ( $\alpha$ -dimethylallyl)chalcone\*
- 7 2'-Methoxyfurano(2'',3'',4',3')chalcone\*
- 8 2'-Hydroxy-6'',6''-dimethylpyrano(2'',3'',4',3')chalcone
- 9 2',4'-Dihydroxy-3'-methoxychalcone\*
- 10 2',4'-Dihydroxy-5'-methoxychalcone
- 11 2',4',6'-Trihydroxychalcone\*
- 12 2',4'-Dihydroxy-6-methoxychalcone
- 13 2',6'-Dihydroxy-4'-methoxychalcone
- 14 2'-Hydroxy-4',6'-dimethoxychalcone
- 15 2',4',6'-Trihydroxy-3'-C-prenylchalcone\*
- 16 2',6'-Dihydroxy-4'-methoxy-3'-C-prenylchalcone\*
- 17 2'-Hydroxy-3'-C-prenyl-4',6'-dimethoxychalcone\*
- 18 2',5'-Dihydroxy-6'',6''-dimethylpyrano(2'',3'',4',3')chalcone
- 19 2',4'-Dihydroxy-3'-C-methyl-6'',6''-dimethylpyrano(2'',3'',6',5') chalcone
- 20 2'-Hydroxy-6'-methoxy-6'',6''-dimethylpyrano(2'',3'',4',3') chalcone\*
- 21 2',6', $\beta$ -Trimethoxy-6'',6''-dimethylpyrano(2'',3'',4',3') chalcone\*
- 22  $\beta$ -Hydroxy-2',6'-dimethoxy-6'',6''-dimethylpyrano(2'',3'',4',3') chalcone\*
- 23 2',4',6'-Trihydroxy-3'-C-geranylchalcone\*
- 24 2',6'-Dimethoxy-3',4'-methylenedioxychalcone\*
- 25 2'-Hydroxy-4',5',6'-trimethoxychalcone\*
- 26 2',3',4',5',6'-Pentamethoxychalcone
- 27 2'-Hydroxy-3',6'-diketo-4',5'-dimethoxychalcone
- 28 2',5'-Dihydroxy-3',6'-diketo-4'-methoxychalcone
- 29 2',5'-Dihydroxy-3',4',6'-trimethoxychalcone
- 30 2',4'-Dihydroxy-5'-C-methyl-6'-methoxychalcone
- 31 2',6'-Dihydroxy-3'-C-methyl-4'-methoxychalcone\*
- 32 2'-Hydroxy-3'-C-methyl-4',6'-dimethoxychalcone\*
- 33 2',4'-Dihydroxy-3',5'-di-C-methyl-6'-methoxychalcone\*
- 34 2'-Hydroxy-3',4',6'-trimethoxychalcone\*
- 35 2',3',4',6'-Tetrahydroxychalcone\*
- 36 2',4'-Dihydroxy-3',6'-dimethoxychalcone\*
- 37 2',6'-Dihydroxy-3',4'-dimethoxychalcone\*
- 38 2',4'-Dihydroxy-3',5',6'-trimethoxychalcone\*
- 39 2'-Hydroxy-3',4',5',6'-tetramethoxychalcone\*
- 40 2',4',4-Trihydroxychalcone
- 41 4'-O-Glucoside
- 42 4'-O-Glucosylglucoside
- 43 4',4-Di-O-glucoside
- 44 4'-O-Glucosylglucoside-4-O-glucoside
- 45 4-O-Glucoside
- 46 4-O-Apiosylglucoside
- 47 4-O-Rhamnosylglucoside
- 48 2',4',4-Trihydroxy-3'-C-glucosylchalcone
- 49 2',4-Dihydroxy-4'-methoxychalcone
- 50 2',4-Dihydroxy-4'-methoxy-5'-formylchalcone
- 51 2'-Methoxy-4',4-dihydroxy-5'-formylchalcone\*
- 52 2',4',4-Trihydroxy-3'-C-prenylchalcone\*
- 53 2',4-Dihydroxy-3'-C-prenyl-4'-methoxychalcone\*
- 54 2',4-Dihydroxy-4'-methoxy-5'-C-prenylchalcone
- 55 2',4',4-Trihydroxy-3'-C-geranylchalcone\*
- 56 2',4',4-Trihydroxy-3,3',5-tri-C-prenylchalcone
- 57 2',4-Dihydroxy-6'',6''-dimethylpyrano(2'',3'',4',5')chalcone\*
- 58 2',4',6',4-Tetrahydroxychalcone\*
- 59 4-O-Glucoside\*



- 60 2'-*O*-Glucoside
- 61 2',4',4-Trihydroxy-3'-*C*-prenyl-6'-methoxychalcone\*
- 62 2',4',4-Trihydroxy-6'-methoxychalcone\*
- 63 4'-*O*-Glucoside\*
- 64 6',2,4-Trihydroxy-4'-methoxychalcone 2'-*O*-glucoside
- 65 2',4-Dihydroxy-4',6'-dimethoxychalcone 4'-*O*-glucoside\*
- 66 2',6'-Dihydroxy-4',4-dimethoxychalcone
- 67 2'-Hydroxy-4',6',4-trimethoxychalcone\*
- 68 2',4-Dihydroxy-4',5',6'-trimethoxychalcone\*
- 69 2'-Hydroxy-4',5',6',4-tetramethoxychalcone\*
- 70 2',4-Dihydroxy-3',4'-methylenedioxy-6'-methoxychalcone\*
- 71 4',4-Dihydroxy-2-methoxychalcone\*
- 72 4',3,4-Trihydroxy-2-methoxychalcone\*
- 73 4',4-Dihydroxy-2-methoxy-5-( $\alpha$ , $\alpha$ -dimethylallyl)chalcone\*
- 74 2',4',3,4, $\alpha$ -Pentahydroxychalcone\*
- 75 2',3',4',4-Tetrahydroxychalcone
- 76 2',3',4',6',4-Pentahydroxychalcone 6'-*O*-glucoside
- 77 2',4',4-Trihydroxy-3',6'-diketochalcone 2'-*O*-glucoside
- 78 2',5'-Dihydroxy-3',4,4',6'-tetramethoxychalcone
- 79 2',3,4-Trihydroxy-6'',6''-dimethylpyrano(2'',3'',4',3')chalcone\*
- 80 2',4-Dihydroxy-3-methoxy-6'',6''-dimethylpyrano(2'',3'',4',3') chalcone\*
- 81 2'-Hydroxy-3,4-methylenedioxy-6'',6''-dimethylpyrano(2'',3'',4',3') chalcone\*
- 82 2'-Hydroxy-3,4-methylenedioxy-6'-methoxy-6'',6''-dimethylpyrano(2'',3'',4',3')chalcone\*
- 83 2'-Methoxy-3,4-methylene-dioxyfurano(2'',3'',4',3') chalcone\*
- 84 2',4',3,4-Tetrahydroxychalcone
- 85 3-*O*-Glucoside
- 86 4'-*O*-Glucoside
- 87 3,4'-*Di-O*-glucoside
- 88 2',3-*Di-O*-glucoside
- 89 4'-*O*-Glucosylglucoside
- 90 4'-*O*-Arabinosylgalactoside
- 91 2',4',3-Trihydroxy-4-methoxychalcone\*
- 92 2',4',4-Trihydroxy-3-methoxychalcone
- 93 4-*O*-Glucoside
- 94 2',4'-Dihydroxy-3,4-dimethoxychalcone\*
- 95 2',3',4',3,4-Pentahydroxychalcone
- 96 4'-*O*-Glucoside
- 97 2',4',3,4, $\alpha$ -Pentahydroxychalcone
- 98 2',4',3,4-Tetrahydroxy-3'-methoxychalcone 4'-*O*-Glucoside
- 99 2',4',5',3,4-Pentahydroxychalcone
- 100 4'-*O*-Glucoside
- 101 2',3',4',4-Tetrahydroxy-3-methoxychalcone\*
- 102 2',3',4'-Trihydroxy-3,4-dimethoxychalcone\*
- 103 2',4'-Dihydroxy-3,4-methylenedioxy-5'-methoxychalcone\*
- 104 2',4',6',3,4-Pentahydroxychalcone
- 105 2'-*O*-Glucoside
- 106 2',3-Dihydroxy-4',6',4-trimethoxychalcone
- 107 2'-Hydroxy-4',6',3,4-tetramethoxychalcone
- 108 2'-Hydroxy-3,4-methylenedioxy-3'-*C*-prenyl-4',6'-tetramethoxychalcone\*
- 109 2',4'-Dihydroxy-6',2,4-trimethoxychalcone\*
- 110 2'-Hydroxy-4',6',2,4-tetramethoxychalcone\*
- 111 2'-Hydroxy-4',5',6',3,4-pentamethoxychalcone\*
- 112 2',4',4,2-Tetrahydroxy-3'-(2-isopropylidene-5-methylhex-4-enyl)-5'-methoxychalcone
- 113 2',4',2-Trihydroxy-3'-geranyl-5'-methoxychalcone
- 114 2',4',2,5-Tetrahydroxy-3'-geranyl-5'-methoxychalcone
- 115 2',4',3,4,5-Pentahydroxychalcone
- 116 2',4',6',3,4,5-Hexahydroxychalcone 2'-*O*-glucoside
- 117 2',3',4',5',3,4, $\alpha$ -Heptahydroxychalcone 2'-*O*-glucoside
- 118 2',3-Dihydroxy-4',6',4,5-tetramethoxychalcone\*
- 119 2'-Hydroxy-4',6',3,4,5-pentamethoxychalcone
- 120 2'-Hydroxy-4',6',2,4,5-pentamethoxychalcone\*
- 121 5,7-Dihydroxy-8-cinnamoyl-4-phenyl-2H-1-benzopyran-2-one\*
- 122 5,7-Dihydroxy-8-(4-hydroxycinnamoyl)-4-phenyl-2H-1-benzopyran-2-one\*
- 123 5,7-Dihydroxy-8-(3,4-dihydroxycinnamoyl)-4-phenyl-2H-1-benzopyran-2-one\*
- 124 2-Cinnamoyl-3-hydroxy-4,4-dimethyl-5-methoxycyclohexadienone (= ceroptin)
- 125 2',4'-Dihydroxy-3'-*C*-(2,4,6-trihydroxy-3-acetyl-5-methylbenzyl)-6'',6''-di-

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- |     |                                                                                                                                                           |                                                |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|
|     | methylpyrano(2'',3'',4',5')chalcone<br>(= rottlerin)                                                                                                      | 129 Cryptocaryone (I 8)†                       |
| 126 | 2',4',4-Trihydroxy-3'-C-(2,4,6,-trihydroxy-<br>3-acetyl-5-methylbenzyl)-6'',6''-<br>dimethylpyrano(2'',3'',4',5')chalcone<br>(= 4-hydroxyrottlerin)       | 130 Fleming-in-A (I 69)†                       |
| 127 | 4',2,3,4-Tetrahydroxy-3'-C-(2,4,6-<br>trihydroxy-3-acetyl-5-methylbenzyl)-<br>6'',6''-dimethylpyrano(2'',3'',4',5')<br>chalcone(= 3,4-dihydroxyrottlerin) | 131 Fleming-in-B (I 70)†                       |
| 128 | 2',4'-Dihydroxy-3',3-di-C-prenyl-<br>6'',6''-dimethylpyrano(2'',3'',4,5)<br>chalcone                                                                      | 132 Fleming-in-C (I 71)†                       |
|     |                                                                                                                                                           | 133 Peltogynoid chalcone (I 64)†               |
|     |                                                                                                                                                           | 134 (-)-Rubranine (23)‡                        |
|     |                                                                                                                                                           | 135 Bavachromanol (46)*‡                       |
|     |                                                                                                                                                           | 136 4'-O-Methyl-4-deoxybavachromanol<br>(19)*‡ |
|     |                                                                                                                                                           | 137 Flemistricin-B (8)*‡                       |
|     |                                                                                                                                                           | 138 Flemistricin-C (7)*‡                       |
|     |                                                                                                                                                           | 139 Lespeol (47)*‡                             |

\* New structures reported during 1975–1980.

† Refers to structure number in Bohm (1975) Chapter 9.

‡ Refers to structure number in present chapter.

### CHECK LIST OF AURONES

- |    |                                       |    |                                                                    |
|----|---------------------------------------|----|--------------------------------------------------------------------|
| 1  | Furano(2'',3'',6,7)aurone*            | 14 | 6-O-Glucoside                                                      |
| 2  | 4'-Hydroxyfurano(2'',3'',6,7)aurone*  | 15 | 4,3-Methylenedioxyfurano<br>(2'',3'',6,7)aurone*                   |
| 3  | 4'-Methoxyfurano(2'',3'',6,7)aurone*  | 16 | 4,3',4',6'-Tetrahydroxyaurone                                      |
| 4  | 6,4'-Dihydroxyaurone*                 | 17 | 6-O-Glucoside                                                      |
| 5  | 6-O-Glucoside                         | 18 | 6-O-Glucuronide*                                                   |
| 6  | 4,6,4'-Trihydroxyaurone 4-O-glucoside | 19 | 6,3',4'-Trihydroxy-4-methoxyaurone                                 |
| 7  | 6,3',4'-Trihydroxyaurone              | 20 | 4,6,3',4',5'-Pentahydroxyaurone*                                   |
| 8  | 6-O-Glucoside                         | 21 | 4-O-Glucoside                                                      |
| 9  | 6,3'-Di-O-glucoside                   | 22 | 6-O-Glucoside                                                      |
| 10 | 6-O-Glucosylglucoside                 | 23 | 6,3',4',5'-Tetrahydroxy-4-methoxyaurone<br>6-O-rhamnosylglucoside* |
| 11 | 6,7,3',4'-Tetrahydroxyaurone          | 24 | Derriobutone (6.97)*†                                              |
| 12 | 6-O-Glucoside                         |    |                                                                    |
| 13 | 6,3',4'-Trihydroxy-7-methoxyaurone    |    |                                                                    |

\* New structures reported during 1975–1980.

† Refers to structure in current chapter.

### CHECK LIST OF DIHYDROCHALCONES

- |   |                                                            |    |                                                                  |
|---|------------------------------------------------------------|----|------------------------------------------------------------------|
| 1 | Dihydrochalcone                                            | 9  | 2',4',6'-Trihydroxy-β-ketodihydrochalcone<br>2'-O-glucoside*     |
| 2 | 2'-Hydroxy-4'-prenyloxydihydrochalcone*                    | 10 | 2',6'-Dihydroxy-4'-methoxy-<br>dihydrochalcone                   |
| 3 | 2',β-Dimethoxyfurano<br>(2'',3'',4',3')dihydrochalcone*    | 11 | 2',4'-Dihydroxy-6'-methoxy-<br>dihydrochalcone*                  |
| 4 | 2'-Methoxyfurano(2'',3'',4',3')-β-<br>ketodihydrochalcone* | 12 | 2'-Hydroxy-3'-C-methyl-4',6'-<br>dimethoxydihydrochalcone*       |
| 5 | 2',4',6'-Trihydroxydihydrochalcone*                        | 13 | 2',6'-Dihydroxy-3',5'-di-C-methyl-4'-<br>methoxydihydrochalcone* |
| 6 | 2'-O-Glucoside*                                            | 14 | 2',4'-Dihydroxy-3',5'-di-C-methyl-6'-                            |
| 7 | 4'-O-Glucoside*                                            |    |                                                                  |
| 8 | 2',6'-Dihydroxy-4'-<br>prenyloxydihydrochalcone*           |    |                                                                  |

- methoxydihydrochalcone\*
- 15 2',6', $\beta$ -Trimethoxy-3',4'-methylene-dioxydihydrochalcone\*
  - 16 1-Phenyl-3-(2,6-dimethoxy-3,4-methylenedioxyphenyl)-propan-1,3-diol\*
  - 17 2',4',6'-Trihydroxy-3'-C-methyl-5'-formyl- $\beta$ -ketodihydrochalcone\*
  - 18 2',6'-Dihydroxy-3'-C-methyl-4'-methoxy-5'-formyl- $\beta$ -ketodihydrochalcone\*
  - 19 2',4'-Dihydroxy-3'-C-(2-hydroxybenzyl)-6'-methoxydihydrochalcone\*
  - 20 2',4'-Dihydroxy-5'-C-(2-hydroxybenzyl)-6'-methoxydihydrochalcone\*
  - 21 2',4',6'-Trihydroxy-3'-methoxy-5'-C-prenyldihydrochalcone\*
  - 22 2',4',6'-Trihydroxy-3',5'-di-C-prenyldihydrochalcone\*
  - 23 4',6'-Dihydroxy-3',3',5'-tri-C-prenyl- $\beta$ -ketodihydrochalcone\*
  - 24 4',6'-Dihydroxy-3'-methoxy-3',5'-di-C-prenyl- $\beta$ -ketodihydrochalcone\*
  - 25 2',4',4'-Trihydroxydihydrochalcone\*
  - 26 2'-O-Glucoside
  - 27 2',4-Dihydroxy-4'-methoxy-dihydrochalcone\*
  - 28 2',4',4'-Trihydroxy- $\beta$ -ketodihydrochalcone\*
  - 29 2',4',6',4-Tetrahydroxydihydrochalcone\*
  - 30 2'-O-Glucoside
  - 31 2'-O-Rhamnoside
  - 32 4'-O-Glucoside
  - 33 2'-O-Xylosylglucoside
  - 34 2',6',4-Trihydroxy-4'-methoxydihydrochalcone 2'-O-glucoside
  - 35 2',6'-Dihydroxy-4,4'-dimethoxy-dihydrochalcone
  - 36 2',4'-Dihydroxy-4,6'-dimethoxy-dihydrochalcone\*
  - 37 2',6',4-Trihydroxy-3'-C-methyl-4'-methoxydihydrochalcone\*
  - 38 2',4',6',4-Tetrahydroxy-3'-C-glycosyldihydrochalcone
  - 39 2',3',4',6',4-Pentahydroxy-5'-geranyldihydrochalcone\*
  - 40 2',3',4',6',4-Pentahydroxy-5'-neryldihydrochalcone\*
  - 41 2',4',4-Trihydroxy-3'-methoxy-dihydrochalcone\*
  - 42 2',4',6',3,4-Pentahydroxydihydrochalcone\*
  - 43 4'-O-Glucoside
  - 44 2'-Methoxy-3,4-methylene-dioxyfurano(2'',3'',4',3')- $\beta$ -ketodihydrochalcone\*
  - 45 2',4',6',3,4-Pentahydroxy-3'-C-glucosyldihydrochalcone
  - 46 2',4',3,5, $\beta$ -Pentahydroxy-4-methoxydihydrochalcone\*

\* New structures reported during 1975–1980.

## CHECK LIST OF FLAVANONES

- 1 7-Hydroxyflavanone
- 2 7-Methoxyflavanone\*
- 3 7-Hydroxy-8-methoxyflavanone\*
- 4 7,8-Dimethoxyflavanone\*
- 5 7-Prenyloxyflavanone
- 6 6'',6''-Dimethylpyrano(2'',3'',7,8)flavanone
- 7 6-Methoxy-6'',6''-dimethylpyrano(2'',3'',7,8)flavanone\*
- 8 7-Hydroxy-6,8-di-C-prenylflavanone\*
- 9 7-Hydroxy-8-C-prenylflavanone\*
- 10 5,7-Dihydroxyflavanone\*
- 11 5-O-Glucoside
- 12 7-O-Rhamnoside
- 13 7-O-Neohesperidoside\*
- 14 5-Methoxy-7-hydroxyflavanone
- 15 5-Hydroxy-7-methoxyflavanone
- 16 5,7-Dimethoxyflavanone
- 17 5,7-Dihydroxy-6-methoxyflavanone
- 18 5-Hydroxy-6,7-dimethoxyflavanone\*
- 19 5,7-Dihydroxy-8-methoxyflavanone
- 20 7-O-Glucoside
- 21 5,7,8-Trimethoxyflavanone\*
- 22 7-Hydroxy-5,6,8-trimethoxyflavanone\*  
(structure has been challenged)
- 23 6-Hydroxy-5,7,8-trimethoxyflavanone\*
- 24 5,6,7,8-Tetramethoxyflavanone\*
- 25 5,7-Dihydroxy-6-C-methylflavanone
- 26 5-Hydroxy-6-C-methyl-7-methoxy-flavanone\*
- 27 5,7-Dihydroxy-8-C-methylflavanone
- 28 5,7-Dihydroxy-6,8-di-C-methylflavanone
- 29 7-O-Glucoside\*

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- 30 5-Hydroxy-6,8-di-*C*-methyl-7-methoxy-flavanone\*
- 31 2,5,7-Trihydroxy-6-(or 8)-*C*-methyl-8-(or 6)-formylflavanone\*
- 32 5,7-Dihydroxy-6-formyl-8-*C*-methylflavanone\*
- 33 5,7-Dihydroxy-6-*C*-prenylflavanone\*
- 34 5,7-Dihydroxy-8-*C*-prenylflavanone
- 35 5-Hydroxy-6-*C*-prenyl-7-methoxyflavanone\*
- 36 5-Methoxy-6'',6''-dimethylpyrano(2'',3'',7,8)flavanone\*
- 37 5,7-Dihydroxy-8-*C*-( $\beta$ -methyl- $\beta$ -hydroxy-methylallyl)flavanone\*
- 38 5,7-Dihydroxy-8-*C*-( $\beta$ -methyl- $\beta$ -formylallyl)flavanone\*
- 39 5,7-Dihydroxy-8-*C*-geranylflavanone\*
- 40 5-Hydroxy-7-methoxy-8-*C*-prenylflavanone\*
- 41 5,7-Dihydroxy-6-*C*-(2-hydroxybenzyl)flavanone\*
- 42 5,7-Dihydroxy-8-*C*-(2-hydroxybenzyl)flavanone
- 43 6,8-Dihydroxy-7-*C*-(5-hydroxygeranyl)flavanone\* (structure has been challenged)
- 44 7,8,4'-Trihydroxyflavanone
- 45 7,4'-Dihydroxyflavanone
- 46 4'-*O*-Glucoside
- 47 7-*O*-Glucoside
- 48 4'-*O*-Rhamnosylglucoside
- 49 7-*O*-Glucosylglucoside
- 50 7,4'-Dihydroxy-8-*C*-galactosylflavanone\*
- 51 7,4'-Dihydroxy-6,8-*C*-prenylflavanone\*
- 52 5,7,4'-Trihydroxyflavanone
- 53 5-*O*-Glucoside
- 54 7-*O*-Glucoside
- 55 7-*O*-Rhamnoside\*
- 56 4'-*O*-Glucoside
- 57 4'-*O*-Galactoside
- 58 ?-*O*-Fructoside
- 59 7-*O*-Glucoside-6''-*O*-galloyl\*
- 60 7-*O*-Glucoside-6''-*p*-coumaroyl\*
- 61 5,7-Di-*O*-glucoside
- 62 5-*O*-Glucosylglucoside
- 63 7-*O*-Rutinoside
- 64 7-*O*-Neohesperidoside
- 65 4'-*O*-Rutinoside
- 66 4'-*O*-Xylosylglucoside\*
- 67 5,7,4'-Trihydroxy-6-*C*-glucosylflavanone\*
- 68 5,4'-Dihydroxy-7-methoxyflavanone
- 69 5-*O*-Glucoside
- 70 5,7-Dihydroxy-4'-methoxyflavanone
- 71 5-*O*-Glucoside\*
- 72 7-*O*-Glucoside
- 73 7-*O*-Rutinoside
- 74 7-*O*-Neohesperidoside
- 75 7-*O*-4'-(Rhamnosyl)glucoside
- 76 5-Methoxy-7,4'-dihydroxyflavanone\*
- 77 5-Hydroxy-7,4'-dimethoxyflavanone
- 78 4'-Hydroxy-5,7-dimethoxyflavanone\*
- 79 4'-*O*-Xylosylarabinoside\*
- 80 4'-*O*-Rhamnosylglucoside\*
- 81 5,7,4'-Trimethoxyflavanone
- 82 5,6,7,4'-Tetrahydroxyflavanone 5-*O*-glucoside
- 83 4'-Prenyloxy-5,7-dihydroxyflavanone
- 84 5,7,4'-Trihydroxy-6-*C*-glucosylflavanone
- 85 5,7,4'-Trihydroxy-8-*C*-glucosylflavanone
- 86 5,2'-Dihydroxy-7-methoxyflavanone 2'-*O*-glucoside\*
- 87 5,7,4'-Trihydroxy-6-*C*-methylflavanone
- 88 7-*O*-Glucoside
- 89 5,7,4'-Trihydroxy-6,8-di-*C*-methylflavanone
- 90 7-*O*-Glucoside
- 91 5,7-Di-*O*-glucoside
- 92 5,4'-Dihydroxy-6,8-di-*C*-methyl-7-methoxyflavanone
- 93 4'-Methoxy-5,7-dihydroxy-6,8-di-*C*-methylflavanone
- 94 7-*O*-Glucoside\*
- 95 7-*O*-Glucosylglucoside
- 96 5,7,4'-Trihydroxy-8-*C*-prenylflavanone\*
- 97 7,4'-Dihydroxy-5-methoxy-8-*C*-prenylflavanone
- 98 7,4'-Dihydroxy-8-*C*-prenylflavanone
- 99 7,4'-Dihydroxy-6-*C*-prenylflavanone
- 100 4'-Hydroxy-6-*C*-prenyl-7-methoxyflavanone
- 101 5,4'-Dihydroxy-6-*C*-prenyl-6'',6''-dimethylpyrano(2'',3'',7,8)flavanone\*
- 102 5,7,4'-Trihydroxy-6-(or 8)-*C*-prenylflavanone 7,4'-di-*O*-glucoside\*
- 103 7,4'-Dihydroxy-8,3',5'-tri-*C*-prenylflavanone
- 104 7-Hydroxy-8,5'-di-*C*-prenyl-6'',6''-dimethylpyrano(2'',3'',4',3')flavanone
- 105 5,4'-Dihydroxy-6,7-dimethoxyflavanone\*
- 106 5-Hydroxy-6,7,4'-trimethoxyflavanone\*
- 107 5,4'-Dihydroxy-7,8-dimethoxyflavanone\*
- 108 5-Hydroxy-7,8,4'-trimethoxyflavanone\*
- 109 5,6-Dihydroxy-7,8,4'-trimethoxyflavanone\*
- 110 5,4'-Dihydroxy-6,7,8-trihydroxyflavanone\*

- 111 5-Hydroxy-6,7,8,4'-tetramethoxyflavanone\*
- 112 4'-Hydroxy-5,6,7-trimethoxyflavanone\*
- 113 5,4'-Dimethoxy-6,7-methylenedioxy-flavanone\*
- 114 7,3',4'-Trihydroxyflavanone
- 115 3'-O-Glucoside
- 116 7-O-Glucoside
- 117 7,3'-Di-O-glucoside
- 118 6,7,3',4'-Tetrahydroxyflavanone
- 119 7,8,3',4'-Tetrahydroxyflavanone
- 120 7-O-Glucoside
- 121 7,3',4'-Trihydroxy-8-methoxyflavanone
- 122 3',4'-Methylenedioxy-7-hydroxy-8-C-prenylflavanone\*
- 123 3',4'-Methylenedioxy-6,8-di-C-prenyl-7-hydroxyflavanone\*
- 124 3',4'-Methylenedioxy-6'',6''-dimethylpyrano(2'',3'',7,8)flavanone\*
- 125 3',4'-Methylenedioxy-6-methoxy-6'',6''-dimethylpyrano(2'',3'',7,8)flavanone\*
- 126 5,7,3',4'-Tetrahydroxyflavanone
- 127 5-O-Rhamnoside\*
- 128 7-O-Glucoside
- 129 7-O-Rhamnoside
- 130 5,3'-Di-O-glucoside
- 131 7-O-Rhamnosylglucoside
- 132 7-O-Rutinoside
- 133 7-O-Neohesperidoside
- 134 5,7,4'-Trihydroxy-3'-methoxyflavanone
- 135 5,7,3'-Trihydroxy-4'-methoxyflavanone
- 136 5-O-Glucoside
- 137 7-O-Rhamnoside\*
- 138 7-O-Rutinoside
- 139 7-O-Neohesperidoside
- 140 5,4'-Dihydroxy-7,3'-dimethoxyflavanone
- 141 5,3'-Dihydroxy-7,4'-dimethoxyflavanone
- 142 5-O-Glucoside
- 143 5,7-Dihydroxy-3',4'-methylenedioxy-flavanone 5-O-glucoside\*
- 144 5-Hydroxy-7,3',4'-trimethoxyflavanone\*
- 145 5-Hydroxy-7,3'-dimethoxy-4'-prenyloxy-flavanone
- 146 5,7,3',4'-Tetrahydroxy-6-C-methylflavanone 7-O-glucoside
- 147 5,7,3',4'-Tetrahydroxy-6,8-di-C-methylflavanone
- 148 2,5,7,3',4'-Pentahydroxyflavanone 5-O-glucoside\*
- 149 5,7,2',5'-Tetrahydroxyflavanone\*
- 150 7-Hydroxy-5,2',4'-trimethoxyflavanone\*
- 151 5,7,2',4'-Tetramethoxyflavanone\*
- 152 5,3',4'-Trihydroxy-7-methoxy-8-C-prenylflavanone\*
- 153 5,7,2'-Trihydroxy-4'-methoxy-6,8-di-C-methylflavanone\*
- 154 5,2',4'-Trihydroxy-8-C-prenyl-6'',6''-dimethylpyrano(2'',3'',7,6)flavanone\*
- 155 5-Hydroxy-6,7,8,3',4'-pentamethoxy-flavanone
- 156 5,6,7,8,3',4'-Hexamethoxyflavanone
- 157 5-Hydroxy-7,3',4',5'-tetramethoxy-flavanone\*
- 158 5-Hydroxy-6,7,3',4',5'-pentamethoxy-flavanone 5-O-rhamnoside\*
- 159 Artocarpinone (I 78)†
- 160 Breverin, 6- or 8- (I 78b)†
- 161 Kurarinone (I 77)†
- 162 Nor-kurarinone (I 78)†
- 163 Remerin (I 78a)†
- 164 Scaberin (I 78c)†
- 165 Steppogenin (I 75)†
- 166 Stepposide (I 76)†
- 167 Flemichin-A (6.247)†\*
- 168 Flemichin-E (6.246)†\*
- 169 Louisfieserone-A (6.200)‡\*
- 170 Louisfieserone-B (6.201)‡\*
- 171 Purpurin (169)‡\*
- 172 Uvarinol (196)‡\*

\* New structures reported during 1975–1980.

† Refers to structures in Bohm (1975) Chapter 11.

‡ Refers to structures in current chapter.

## CHECK LIST OF DIHYDROFLAVONOLS

- |                                      |                                               |
|--------------------------------------|-----------------------------------------------|
| 1 7-Hydroxydihydroflavonol           | 4 5-Hydroxy-7-methoxydihydroflavonol          |
| 2 6-Methoxy-7-hydroxydihydroflavonol | 5 3-Acetyl-5-hydroxy-7-methoxydihydroflavonol |
| 3 5,7-Dihydroxydihydroflavonol       |                                               |

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- 6 5,7-Dimethoxydihydroflavonol\*
- 7 5,7-Dihydroxy-6-methoxydihydroflavonol
- 8 5,7-Dihydroxy-6-C-methyldihydroflavonol
- 9 6'',6''-Dimethylpyrano(2'',3'',7,8)dihydroflavonol\*
- 10 7,4'-Dihydroxydihydroflavonol
- 11 3-O-Glucoside
- 12 7,8,4'-Trihydroxydihydroflavonol
- 13 5,7,4'-Trihydroxydihydroflavonol
- 14 3-O-Glucoside
- 15 3-O-Rhamnoside
- 16 4'-O-Xyloside
- 17 7-O-Glucoside
- 18 4'-Hydroxy-7-methoxydihydroflavonol (*cis* and *trans* isomers)
- 19 5,7-Dihydroxy-4'-methoxydihydroflavonol
- 20 4'-Hydroxy-5,7-dimethoxydihydroflavonol
- 21 5-Hydroxy-4',7-dimethoxydihydroflavonol
- 22 5-O-Glucoside
- 23 5,4'-Dihydroxy-6,7-dimethoxydihydroflavonol
- 24 5,7-Dihydroxy-8,4'-dimethoxydihydroflavonol 7-O-glucoside
- 25 5,4'-Dihydroxy-6-C-glucosyl-7-methoxydihydroflavonol
- 26 5,7,4'-Trihydroxy-6-(3-hydroxy-3-methylbutyl)dihydroflavonol 7-O-glucoside
- 27 5,7,4'-Trihydroxy-8-(3-hydroxy-3-methylbutyl)dihydroflavonol 7-O-glucoside
- 28 5,7,4'-Trihydroxy-8-(3-glucosyloxy-3-methylbutyl)dihydroflavonol 7-O-glucoside
- 29 5,7,4'-Trihydroxy-8-C-prenyldihydroflavonol\*
- 30 5,4'-Dihydroxy-6'',6''-dimethylpyrano(2'',3'',7,8)dihydroflavonol\*
- 31 5,4'-Dihydroxy-8-C-prenyl-6'',6''-dimethylpyrano(2'',3'',7,6)dihydroflavonol\*
- 32 7,3',4'-Trihydroxydihydroflavonol
- 33 3-O-Glucoside
- 34 3,7-Di-O-glucoside\*
- 35 7,3',4'-Trihydroxy-3-O-methyldihydroflavonol (*cis* and *trans* isomers)\*
- 36 7,8,3',4'-Tetrahydroxydihydroflavonol\*
- 37 5,7,3',4'-Tetrahydroxydihydroflavonol
- 38 3-O-Glucoside\*
- 39 3-O-Galactoside\*
- 40 3-O-Rhamnoside
- 41 3-O-Xyloside
- 42 4'-O-Glucoside
- 43 7-O-Galactoside\*
- 44 3,5-Di-O-rhamnoside\*
- 45 5,7,3',4'-Tetrahydroxy-3-O-methyldihydroflavonol\*
- 46 5,3',4'-Trihydroxy-7-methoxydihydroflavonol
- 47 3-O-Glucoside
- 48 5,4'-(or 3')-Dihydroxy-7,3'-(or 4')-dimethoxydihydroflavonol
- 49 5,7,3',4'-Tetrahydroxy-6-C-methyldihydroflavonol
- 50 5,6,3',4'-Tetrahydroxy-8-C-methyldihydroflavonol (?)
- 51 5,3'-Dihydroxy-7,4'-dimethoxy-8-C-prenyldihydroflavonol\*
- 52 5,7,2'-Trihydroxy-5'-methoxydihydroflavonol\*
- 53 5,7,2',4'-Tetrahydroxydihydroflavonol
- 54 5,7-Dihydroxy-2'-methoxy-6'',6''-dimethylpyrano(2'',3'',4',3')dihydroflavonol
- 55 7,3',4',5'-Tetrahydroxydihydroflavonol
- 56 7,3',5'-Trihydroxy-4'-methoxydihydroflavonol\*
- 57 5,7,3',4',5'-Pentahydroxydihydroflavonol
- 58 5,7,3',4',5'-Pentahydroxy-6-C-methyldihydroflavonol\*
- 59 3'-O-Glucoside\*
- 60 5,7,3',4'-Tetrahydroxy-5'-methoxydihydroflavonol 4'-O-rhamnoside\*
- 61 5,7,4'-Trihydroxy-3',5'-dimethoxydihydroflavonol

\* New structures reported during 1975-1980. To this list may be added three peltogynoids [compounds 108, 109 and 110 in Bohm (1975)] and three flavonolignans (compounds 111, 113 and 114).

## CHAPTER SEVEN

# *Proanthocyanidins*

EDWIN HASLAM

### 7.1 INTRODUCTION

Rapid advances in our knowledge of the proanthocyanidins were made during the last decade, and although this review necessarily concentrates upon recent aspects, this is also an appropriate moment to look at the subject in a broader context. With this viewpoint in mind facets of earlier work which are of importance – such as the solvolytic reactions of flavan-3,4-diols – and related areas of research into natural phenolic compounds are discussed.

One of the pioneers of research into the proanthocyanidins and to whom much of our present knowledge of their biochemistry is due is Dr E. C. Bate-Smith. His name will always be inextricably linked with the 'LA's' and it is a pleasure to dedicate this chapter to him on the occasion of his 80th birthday.

#### 7.1.1 Leucoanthocyanins, leucoanthocyanidins and proanthocyanidins

*What's in a name? that which we call a rose  
By any other name would smell as sweet.  
Shakespeare*

The subtleties and puritanical rigours of chemical nomenclature should never be permitted to stand in the way of good chemistry. However, the field of proanthocyanidin chemistry has been bedevilled by the changes in nomenclature which have paralleled advances in knowledge. Confusion still arises from the use by latterday Capulets of older forms of nomenclature and in particular the word *leucoanthocyanin*. A full historical analysis of the way in which the nomenclature was derived was given in an earlier review (Haslam, 1975) and it is perhaps useful to reiterate the nomenclature introduced by Freudenberg and Weinges (1960). These workers collectively designated all the colourless substances isolated from plants which when heated with acid form anthocyanidins as *proanthocyanidins*. This is a chemical term and does not imply any biogenetic relationship. The terminology of *leucoanthocyanidin* was reserved (Weinges *et al.*, 1969) for the monomeric proanthocyanidins such as the phenolic flavan-3,4-diols and the name condensed proanthocyanidin for the various flavan-3-ol dimers and higher oligomers which, on the basis of present evidence, constitute the

overwhelming majority of proanthocyanidins found in plants. This is the nomenclature used in this review and except where it is important to develop points from a historical viewpoint the description *leucoanthocyanin* is one which should no longer be used.

### 7.1.2 Proanthocyanidins and vegetable tannins

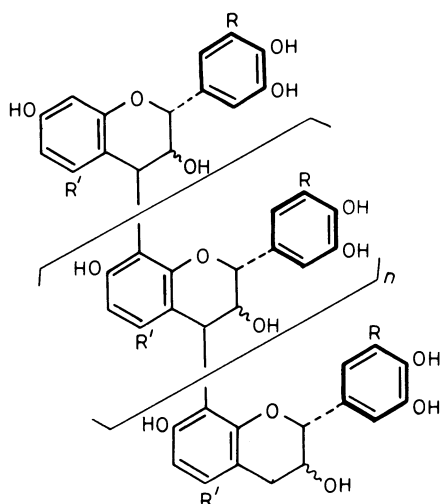
Bate-Smith (1962) in a classical study of phenolic metabolism demonstrated that three classes of phenol predominate in the leaves of vascular plants. These are the esters, amides and glycosides of the various hydroxycinnamic acids and hexahydroxydiphenic acid, the glycosylated flavonols (derivatives of kaempferol, quercetin and myricetin) and the proanthocyanidins (7.1) in particular those which gave cyanidin or delphinidin with acid. Bate-Smith used the pattern of distribution of these three classes of phenolic constituent as a taxonomic guide for the classification of plants and in particular he noted the correlation between the presence of leucoanthocyanins (as proanthocyanidins were known at that point in time!) and a woody habit of growth in the plant. Bate-Smith and Swain (1953) had earlier also noted the close similarity in systematic distribution between leucoanthocyanins and many members of that class of substance rather indefinitely defined in the botanical literature as 'tannins', and they were led to suggest that leucoanthocyanins were most commonly responsible for the broad range of reactions – such as the precipitation of proteins, polysaccharides, alkaloids; the impaired nutritional characteristics of some foodstuffs and their astringent taste – which have generally been attributed to the presence in plants of 'tannins'.

A curious but significant observation also made by Bate-Smith was the complete absence of 3,4,5-trihydroxycinnamic acid from plant tissues. In situations where the acid might have been predicted to occur he found hexahydroxydiphenic acid (7.2) and Bate-Smith suggested that this was the taxonomic equivalent of the missing acid. Later work (E. Haslam and R. K. Gupta, unpublished observations) has demonstrated the widespread occurrence in plants of (7.2) as esters with D-glucose and the putative biogenetic precursors of these esters the galloyl-D-glucoses. In contrast to the natural phenolic esters of the hydroxycinnamic acids, which are invariably found as mono- and bis- esters with polyols, and the esters of *p*-hydroxybenzoic and protocatechuic acid which are extremely rare, gallic and hexahydroxydiphenic acid (7.2) occur in a range of forms esterified to D-glucose and with molecular weights spanning the range 500 to at least 2000. A typical example is the ester (7.3)\* found widely in the Hamamelidaceae, Paeonaceae, Aceraceae and Anacardiaceae and sporadically in the Ericaceae.

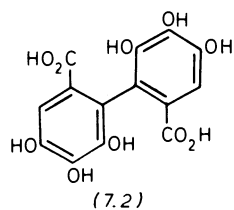
Whilst the biosynthetic implications of these observations remain to be resolved the metabolism of these esters and the various proanthocyanidins by a whole range of plants is worthy of comment and consideration. These compounds are unique to the plant kingdom and because of their polyphenolic

\* Recent work has led to a revision of this structure (E. Haslam and R. K. Gupta).

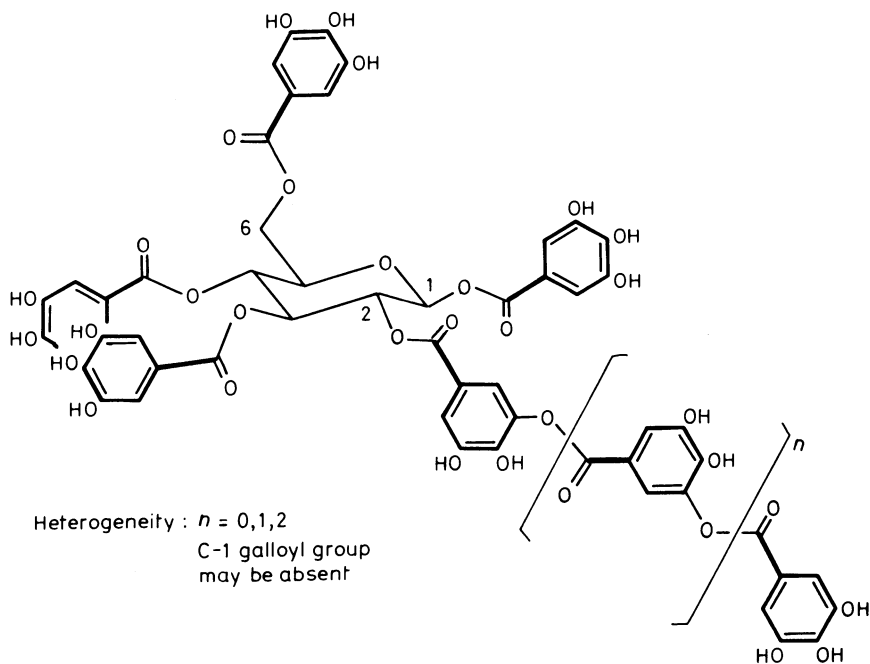




(R = R' = H.... Profisetinidin)  
 (R = H ; R' = OH.... Procyanidin)  
 (R = R' = OH.... Prodelphinidin)  
 (7.1)



(7.2)



(7.3) Tannic acid - Chinese gallotannin

character they possess the distinctive properties referred to above – such as that of precipitating proteins. The overwhelming circumstantial evidence points unmistakably to the fact that these properties derive from the accumulation, within a molecule of moderate molecular size, of a substantial number of unconjugated phenolic groups with an *ortho*-dihydroxy (catechol) or *ortho*-trihydroxy orientation within a phenyl ring. Recent experimental support for this suggestion has come from quantitative studies on the interaction of phenols with proteins (J. McManus, unpublished observations), using equilibrium dialysis and microcalorimetry. The affinity of resorcinol for proteins is weak but with catechol, pyrogallol and methyl gallate the binding to protein was considerably enhanced, both in its strength and in the number of primary and secondary sites on the protein molecule which are available for complexation. These observations give quantitative support to earlier proposals (Haslam, 1974a) that the *ortho*-dihydroxyphenolic groups in natural polyphenols are the primary points for association with protein and that isolated phenolic groups do not participate to any significant extent. A further interesting feature of the observations is that the affinity for protein of the isolated catechol group and the simple esters of gallic acid are broadly comparable. The two functionalities are found respectively as the pendant aromatic nuclei of the procyanidins (7.1) ( $R' = OH, R = H$ ) and of the natural galloyl esters (7.3) which constitute the most widely distributed polyphenols of the vegetable tannin group found in plants.

Despite their apparently disparate modes of construction these two classes of natural polyphenols display many similarities in shape and disposition of phenolic groups and coupled with their similar physical properties it is tempting to suggest that they have similar roles in plant metabolism. A word of caution is, however, appropriate. The elaboration during biosynthesis of the proanthocyanidins of the difficultly soluble and the insoluble polymeric forms (*vide infra*) does raise the question whether these metabolites have a function which is principally structural in character. Bate-Smith has repeatedly drawn attention to the empirical relationship which exists between the presence of proanthocyanidins in plants and the 'woodiness' of a particular family or species. From the phylogenetic point of view proanthocyanidins first appeared as plants developed a vascular character – in ferns, for example, proanthocyanidins are frequently found in polymeric forms. Although Bate-Smith generally discounted a connection with lignification, an examination of the proanthocyanidins to ascertain if they have a structural role would be very valuable.

In a recent series of papers Bate-Smith has amplified and collated earlier data of a semiquantitative nature and has commented on the various classes of complex polyphenol as markers of evolutionary trends in plants (Bate-Smith, 1972, 1973, 1975, 1977). Proanthocyanidins are present in the most primitive of vascular plants such as ferns and gymnosperms, but the galloyl and hexahydroxydiphenoyl esters are not. These latter two groups appear for the first time in dicotyledons and Bate-Smith was led to propose a phylogenetic order – proanthocyanidins – hexahydroxydiphenoyl esters – galloyl esters – which,

incidentally parallels their order of increasing efficiency as precipitants for proteins (Bate-Smith, 1972). Further facets of polyphenol metabolism have been revealed by other studies which are worthy of brief mention. Several plant families (e.g. Aceraceae, Ericaceae, Fagaceae and Rosaceae) retain the capacity to biosynthesize different types of complex polyphenol but one particular species may specialize in just one particular form. Thus in the Ericaceae, species of the three genera *Calluna*, *Erica* and *Rhododendron* are all rich sources of proanthocyanidins but *Arctostaphylos uva ursi* has only a minimal capacity for proanthocyanidin synthesis and combines with this a very high level of gallic acid metabolism (principally as 7.3). This distinctive feature has been noted on several occasions.

## 7.2 NATURAL LEUCOANTHOCYANIDINS (FLAVAN-3,4-DIOLS)

### 7.2.1 Occurrence, distribution and structure

The principal flavan-3,4-diols of natural origin whose structure and stereochemistry have been fully characterized are shown in Table 7.1. The majority, it may be noted, have been isolated from the wood or bark of *Acacia* species. Extensive compilations of chemical and spectroscopic data for these flavan-3,4-diols are contained in a review by Weinges and his collaborators (Weinges *et al.*, 1969).

The question of the natural occurrence of other flavan-3,4-diols – particularly those of the leucopelargonidin, leucocyanidin and leucodelphinidin classes – remains essentially unresolved. Definitive stereochemical work has not been completed for any member of these last three groups of leucoanthocyanidins, and in most cases indeed the evidence for the actual flavan-3,4-diol structure is not wholly adequate.

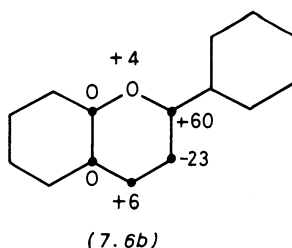
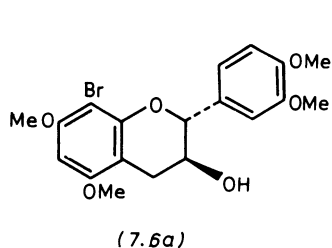
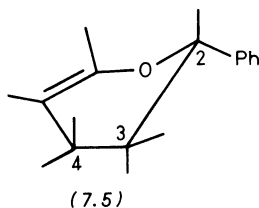
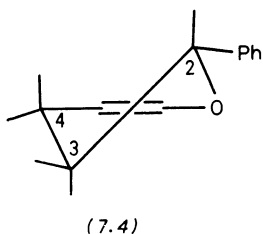
The various physical and chemical methods used for the determination of structure and stereochemistry of leucoanthocyanidins have been fully described in a number of earlier publications (Weinges *et al.*, 1969; Clark-Lewis, 1968; Clark-Lewis *et al.*, 1969; Drewes, 1968). An observation of particular value for stereochemical assignments in six-membered ring systems is the upfield shift for the resonance of a carbon atom which is gauche to another carbon or heteroatom at the  $\gamma$ -position (Roberts *et al.*, 1970). Similar results obtain in the flavan ring and the C-2 resonance in the  $^{13}\text{C}$  resonance spectrum of flavan 3,4-diols occurs at higher field when a quasi-axial hydroxy or acetoxy group is placed at the C-4 position. This  $\gamma$ -effect (4.1–4.6 p.p.m.) has been observed by several workers (Weinges *et al.*, 1973; Haslam *et al.*, 1977a) and is useful for the assignment of relative configurations in flavan-3,4-diols. The phenomenon is discussed in more detail in the assignment of relative configuration to procyanidins (*vide infra*).

The preferred conformation of the heterocyclic ring of flavan derivatives has been discussed by Whalley (1962) and by Clark-Lewis (1968), and two conformations (7.4 and 7.5) in which the aromatic ring attached to position 2 is in

Table 7.1 Natural leucoanthocyanidins – occurrence, structure and stereochemistry

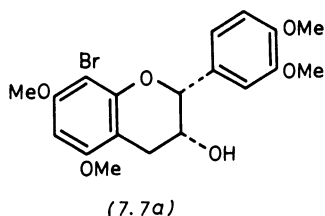
| Trivial name                                                  | Hydroxylation pattern | Absolute configuration | Source                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|---------------------------------------------------------------|-----------------------|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (+)-Guibourtacacidin                                          | 7,4'                  | 2R:3S:4S               | <i>Guibourtia colesperma</i> (Saayman and Roux, 1965)<br><i>Acacia cultriformis</i> (du Preez and Roux, 1970)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| (+) Mollisacacidin                                            | 7,4'                  | 2R:3S:4R               | <i>Acacia cultriformis</i> (du Preez and Roux, 1970)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                               | 7,3',4'               | 2R:3S:4R               | <i>Acacia mearnsii</i> (Keppler, 1957)<br><i>Acacia saxatilis</i> (Fourie <i>et al.</i> , 1974)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| (+) Gleditsin                                                 |                       |                        | <i>Gleditsia japonica</i> (Mitsuno and Yoshizaki, 1958; Clark-Lewis and Mitsuno, 1958)<br><i>Acacia cultriformis</i> (du Preez and Roux, 1970)<br><i>Acacia cultriformis</i> (du Preez and Roux, 1970)<br><i>Acacia saxatilis</i> (Fourie <i>et al.</i> , 1974)<br><i>Neuratanenia amboensis</i> (Oberholzer <i>et al.</i> , 1980)<br><i>Neuratanenia amboensis</i> (Oberholzer <i>et al.</i> , 1980)<br><i>Neuratanenia amboensis</i> (Oberholzer <i>et al.</i> , 1980)<br><i>Schinopsis lorentzii</i> (Drewes and Roux, 1964)<br><i>Acacia orites</i> (Clark-Lewis <i>et al.</i> , 1961)<br><i>Acacia sparsiflora</i> ,<br><i>Acacia obtusifolia</i> (Clark-Lewis and Dainis, 1964, 1967)<br><i>Acacia maidenii</i> (Clark-Lewis and Porter, 1972)<br><i>Acacia auriculiformis</i> (Drewes and Roux, 1966)<br><i>Acacia cultriformis</i> (du Preez and Roux 1970)<br><i>Acacia melanoxylon</i> (King and Bottomley, 1954)<br><i>Acacia saxatilis</i> (Fourie <i>et al.</i> , 1974)<br><i>Acacia harpophylla</i> (Clark-Lewis and Mortimer, 1960)<br><i>Acacia excelsa</i> ,<br><i>Acacia cultriformis</i> (du Preez and Roux, 1970)<br><i>Acacia saxatilis</i> (Fourie <i>et al.</i> , 1974)<br><i>Robinia pseudacacia</i> (Weinges, 1958) |
| (–)-Leucofisetinidin<br>(–)-Teracacidin<br>(–)-Isoteracacidin | 7,3',4'-tri-OMe       |                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                               | 3,4,7,3',4'-penta-OMe |                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                               | 7,3',4'               | 2S:3R:4S               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                               | 7,8,4'                | 2R:3R:4R               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| (–)-Melacacidin                                               | 7,8,4'                | 2R:3R:4S               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                               | 7,8,4'-tri-OMe        |                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                               | 7,8,3',4'             | 2R:3S:4R               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| (–)-Isomelacacidin                                            | 7,3',4',3,8-di-OMe    | 2R:3R:4R               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                               | 7,8,3',4'             | 2R:3R:4S               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| (+) Leucorobinetinidin                                        | 7,8,3',4'-tetra-OMe   | 2R:3S:4S               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|                                                               | 7,3',4',5'            | 2R:3S:4R               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

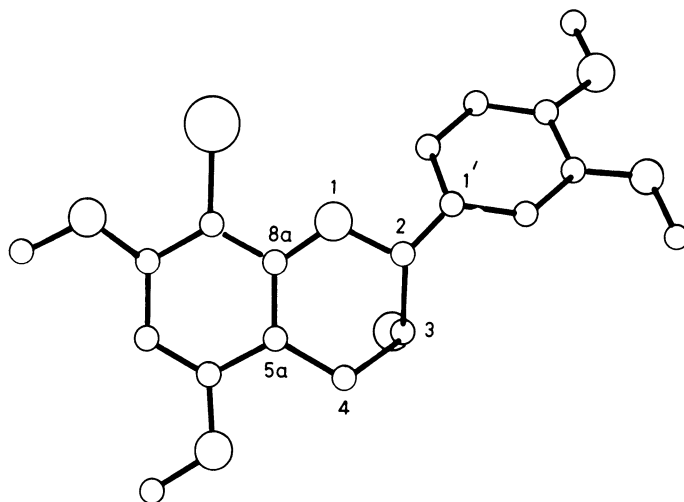
the quasi-equatorial position have received particular attention. Definitive evidence of the shape of the flavan-3-ol ring system has come from X-ray analysis of 8-bromotetramethyl-(+)-catechin (7.6a) (Roux *et al.*, 1978a), and this shows the conformation of the puckered heterocyclic ring is in fact somewhere between the 'half-chair' and 'sofa' (7.4 and 7.5). Structure (7.6b) shows the distances out of the mean plane of the adjacent benzene ring in pm for the atoms of the heterocyclic ring of the bromo-(+)-catechin derivative. Structure (7.7b) shows a stereo drawing of the corresponding 8-bromo-tetramethyl-(−)-epicatechin (7.7a) derived from X-ray data (M. J. Begley, D. A. Whiting and E. Haslam, unpublished observations). In this instance the atoms O(1), C(8a), C(5a) and C-4 lie virtually co-planar, C-2 lies 0.004 nm, C-3 lies 0.07 nm and C-1' lies 0.07 nm below that plane. The shape of the heterocyclic ring is in this case best described as an envelope and it is clearly much flatter than that in the (+)-catechin derivative. These X-ray structures define the shape of the flavan ring in the crystal structure of (7.6a and 7.7a) and in solution conformational equilibria and solvation may well modify these shapes.



## Dihedral angles

|            |      |
|------------|------|
| C-8a-O     | 24°  |
| O — C-2    | -57° |
| C-2 — C-3  | 68°  |
| C-3 — C-4  | -45° |
| C-4 — C-5a | 13°  |



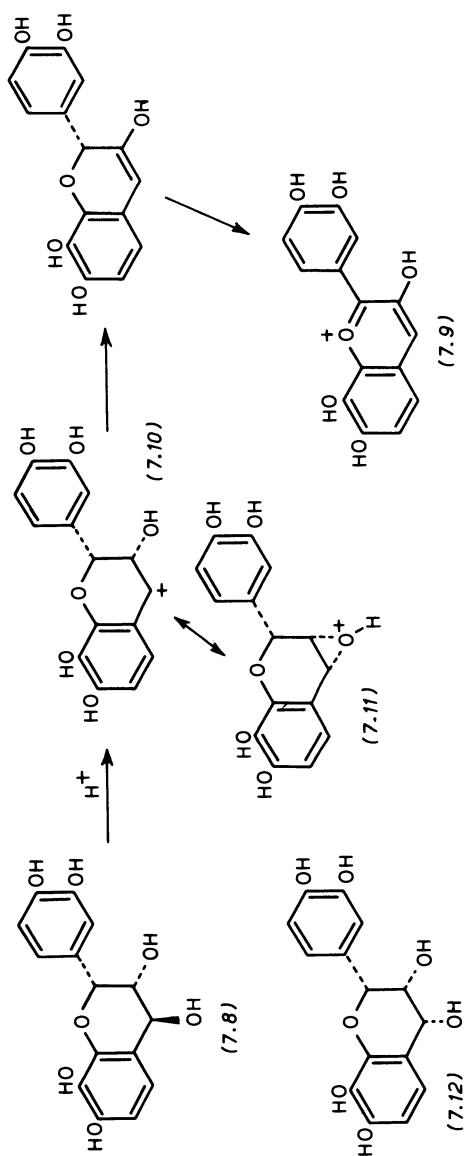


(7.7b)

### 7.2.2 Solvolysis of leucoanthocyanidins

The hallmark of phenolic flavan-3,4-diols is their partial (up to 50 %) conversion with hot mineral acid to the corresponding anthocyanidin (Robertson, 1959; Creasey and Swain, 1965). The reaction is believed to proceed by an initial dehydration to the flav-3-en-3-ol followed by aerial oxidation to yield the anthocyanidin (7.9). The environment of the 4-hydroxyl group in the naturally occurring phenolic flavan-3,4-diols is such that in acidic media it is readily solvolysed to give the corresponding resonance-stabilized benzyl carbocation (7.10), and this property is the essence of much of the chemistry of these compounds. These solvolytic reactions were discussed at length in an earlier review (Haslam, 1975), but some of the salient features are summarized here as they are relevant to the more recent chemistry of the condensed proanthocyanidins.

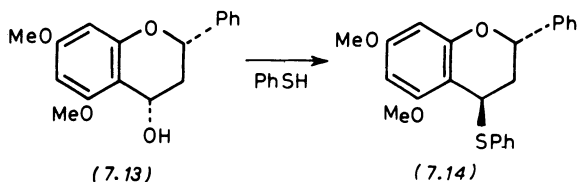
The ease of ionization at the 4 position is influenced by the stereochemistry at both the 4 and 3 positions. Clark-Lewis and Mortimer (1960) first noted that isomelacacidin (7.8) was more readily solvolysed than its epimer at the 4 position, melacacidin (7.12). This was rationalized on stereochemical grounds. Thus (7.8) has a quasi-axial hydroxyl group at C-4 and a small deformation of the geometry of the heterocyclic ring brings the C-4 hydroxyl group into a truly axial position and this facilitates overlap of the aromatic  $\pi$  orbitals to assist in the development of the C-4 carbocation. In addition, the neighbouring *trans*-oriented C-3 hydroxyl group is also favourably disposed to assist in this solvolysis at the benzylic positions and probably leads to a protonated epoxide intermediate (7.11).



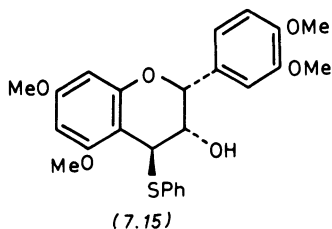
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The carbocation, once formed, may be captured by other nucleophiles such as water, alcohols, nucleophilic phenols, such as resorcinol and phloroglucinol which result in the formation of new C–C bonds, and a variety of sulphur nucleophiles. The products which result from these reactions are often determined by the acidity of the reaction conditions. Thus if the acidity of the reaction is such that the product is not transformed back once again to the carbocation, then that product which is formed fastest will predominate. The reaction is said to be under *kinetic* control and factors which influence the approach of the external nucleophile to the carbocation will dominate the energy profile of the reaction (steric approach control). If, however, the reaction is under *thermodynamic* control, then the products which are most stable will be formed. Under these conditions the capture of the carbocation by the external nucleophile is reversible under the acidity of the reaction. These are the principal features which dominate the factors controlling the range of products formed in the solvolysis of phenolic flavan-3,4-diols.

Brown and Shaw (1974) have recently extended their observations on the solvolysis of a range of flavan-4-ols and 4-arylflavans in the presence of external sulphur nucleophiles. They showed that the carbocation formed from these substrates in acidic media may be captured by both benzene thiol and benzene sulphinic acid and interestingly showed that 5,7-dimethoxyflavan-4 $\beta$ -ol (7.13) reacts with benzene thiol – in the absence of acid – to give the thioether (7.14) in 88 % yield. A study of the stability of the 4-thioether derivatives of flavans lent strong support to the suggestion that the 4- $\alpha$ -thioether derivatives are formed under kinetically rather than thermodynamically controlled S<sub>N</sub>1 reactions.



Brown and Shaw further suggested that this different lability of groups attached to the 4 position of phenolic flavans towards different sulphur nucleophiles, with and without acid, might be used as a structural probe. Thus a reaction in which the 'condensed tannin' from *Calluna vulgaris* was refluxed in aqueous ethanol with benzene thiol yielded, after methylation, the thioether (7.15). This result they





interpreted as showing the presence in the tannin of interflavan bonds comprising C–O linkages at the 4 position.

### 7.3 CONDENSED PROANTHOCYANIDINS

#### 7.3.1 Procyanidins

Oligomeric\* condensed procyanidins are most commonly responsible for the distinctive reactions associated with many plants which have been attributed by biochemists and botanists alike to '*condensed tannins*'. Studies of these compounds – the procyanidins – has shed considerable light on their chemistry and biochemistry. As such it forms a significant contribution to an understanding of the class of '*condensed tannins*' as a whole and hence to a solution to one of the classical unsolved problems of natural product chemistry.

Fruit-bearing plants have proved to be particularly rich sources of oligomeric condensed procyanidins, and studies have concentrated upon the four major naturally occurring dimeric\* procyanidins (B-1, B-2, B-3 and B-4) which have been isolated from the fruit, fruit pods, seeds and seed shells of a diverse range of plants. The procyanidins occur free and unglycosylated and almost invariably are found with one or both of the flavan-3-ols, (+)-catechin or (–)-epicatechin (Fig. 7.1). These patterns of occurrence of the procyanidins are most effectively revealed by two-dimensional paper chromatography as a distinctive 'fingerprint' which may be used as a taxonomic guide (Fig. 7.2).

Although many plants contain mixtures of the procyanidins B-1, B-2, B-3 and B-4 and (+)-catechin and (–)-epicatechin, several simpler and highly characteristic 'fingerprints' have been discerned. Probably the most commonly encountered is that found, for example, in hawthorn (*Crataegus monogyna*). Co-occurring with (–)-epicatechin is one major procyanidin dimer [B-2, formally two (–)-epicatechin units C-4 to C-8-linked], a minor procyanidin dimer [B-5, two (–)-epicatechin units C-4 to C-6-linked], a major trimer C-1 and various higher oligomers (Fig. 7.2). Much less widely found is a second 'fingerprint' (present for example in the catkins of the male Sallow, *Salix caprea*) where (+)-catechin, a major procyanidin dimer [B-3, two (+)-catechin units C-4 to C-8-linked], a minor procyanidin dimer [B-6, two (+)-catechin units C-4 to C-6-linked], a trimer C-2 and various higher oligomers occur together (Fig. 7.2). Two further categories, which are the most significant from a biosynthetic point of view, are again not widely found. Thus in various *Rubus* sp. (–)-epicatechin, procyanidin B-4 and associated oligomers are found, and in the cereal sorghum (*Sorghum vulgare*) the seed coat contains (+)-catechin, procyanidin B-1 and various higher oligomers. The two flavan-3-ol units which formally compose the structures of procyanidins B-1 and B-4 are of opposite absolute stereochemistry

\* This is the most convenient terminology to employ in this field, since the procyanidins are formally built up of numbers of flavan-3-ol units.

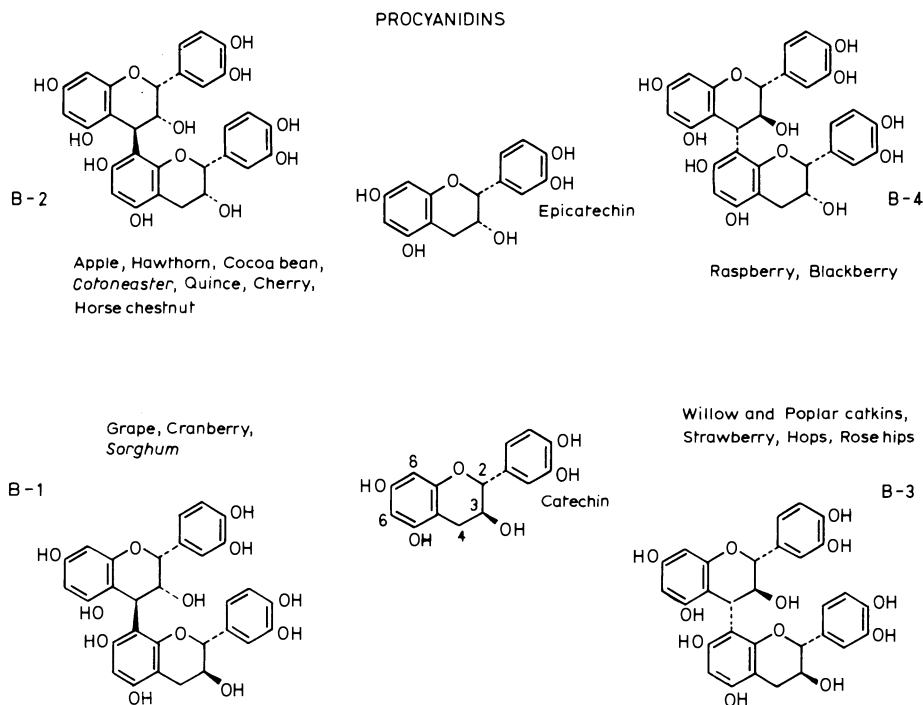


**Fig. 7.1** The principal naturally occurring procyanidin dimers: plant sources (Weinges *et al.*, 1968a,b; Thompson *et al.*, 1972).

at C-3, but in the plants noted they co-occur with only *one* of the two possible flavan-3-ols (Haslam, 1977).

The procyanidins may be isolated as their deca-acetates (Weinges *et al.*, 1968a) or in their free phenolic forms by chromatography on Sephadex LH-20 (Thompson *et al.*, 1972). The yields in some cases may be quite impressive. Thus 1 kg of fresh horse chestnut shells (*Aesculus hippocastanum* or *A. carnea*) yields upwards of 1 g of procyanidin B-2. Weinges and his colleagues (Weinges *et al.*, 1968a) successfully assigned the structures and some of the stereochemical details of the four procyanidins (B-1, B-2, B-3 and B-4) on the basis principally of an examination of the  $^1\text{H-NMR}$  spectra of the deca-acetates. Analysis of the  $^1\text{H-NMR}$  evidence coupled with the presumption that the two 'halves' of the procyanidin dimers were related in absolute stereochemistry at C-2, 2' and C-3,3' to the natural flavan-3-ols [(+)-catechin and (–)-epicatechin] permitted Weinges to define the absolute stereochemistry at C-4 as 4 *S* in procyanidins B-3 and B-4. The 'lower' flavan-3-ol unit in these two dimeric procyanidins thus occupies a quasi-equatorial position at C-4 on the heterocyclic ring of the upper (+)-catechin unit.

Later work illustrated some of the important facets of the chemistry of the procyanidins. Most distinctive are the reactions based upon the acid-catalysed

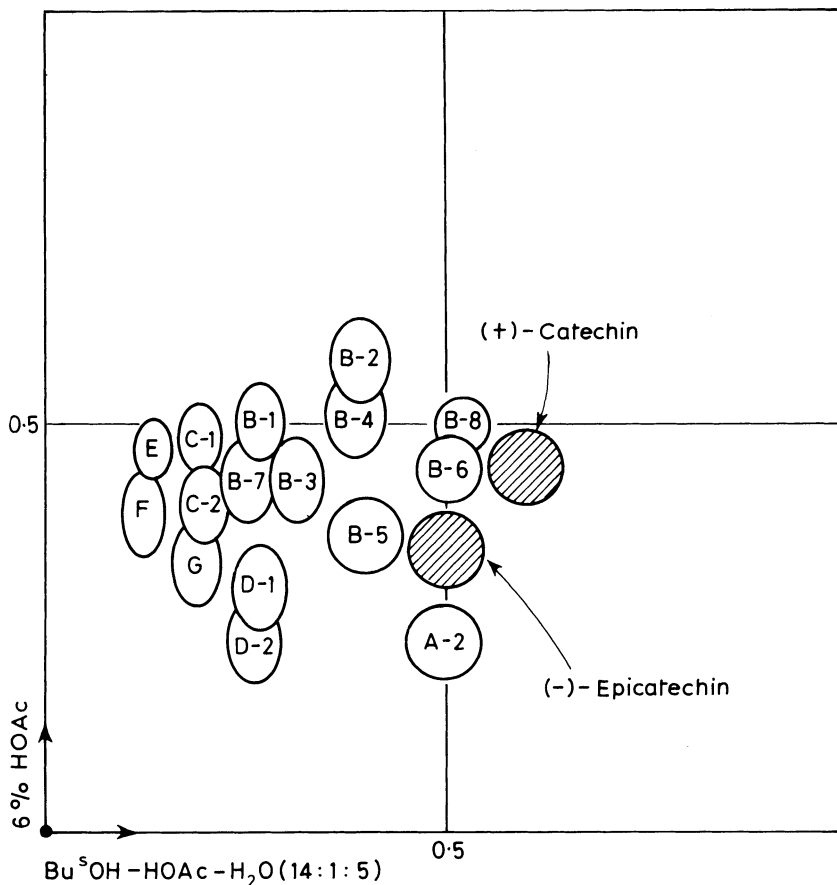


Fig. 7.2 Paper chromatography of the plant procyanidins (Thompson *et al.*, 1972).

solvolysis of the C—C interflavan bond (Fig. 7.3). Thus the procyanidin dimers are degraded by acid to give initially the familiar benzylic carbocation from the 'upper half' of the molecule and the appropriate flavan-3-ol, (+)-catechin or (–) epicatechin from the 'lower half' of the dimer. The carbocation, as is the case with the leucoanthocyanidins, is normally rapidly converted by proton loss and oxidation to give cyanidin, but, under appropriate conditions, it may be intercepted by various nucleophiles. Thus in the presence of toluene- $\alpha$ -thiol the flavanyl-4-thioether (7.16) is formed and with phloroglucinol the product is the 4-arylflavan (7.17). The thioether-forming reaction occurs in the presence of acetic acid and is a kinetically controlled reaction. It has proved of particular value for structural identification purposes. Capture of the flavan-4-yl carbocation (7.18) with 2,3-*cis* [(–)-epicatechin] stereochemistry, (from procyanidins B-1 and B-2) gives almost exclusively one thioether (7.16) with 3,4-*trans* stereochemistry. On the other hand, the alternative flavanyl carbocation with 2,3-*trans* [(+)-catechin] stereochemistry derived from procyanidins B-3 and B-4

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gives a mixture of the two diastereoisomeric thioethers with 3,4-*cis* and 3,4-*trans* stereochemistry.

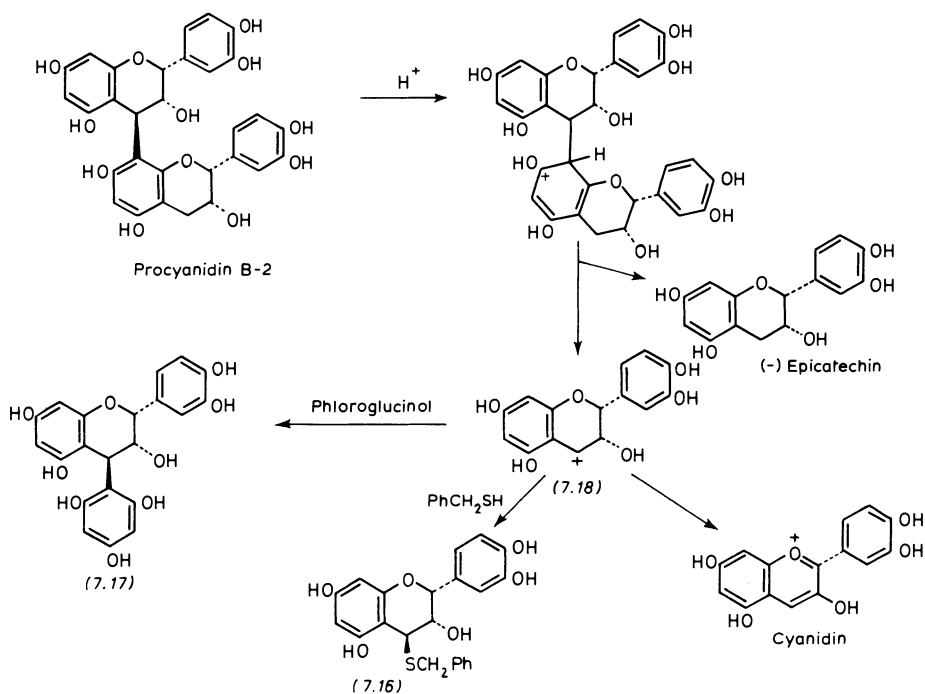


**Fig. 7.3** Solvolytic reaction of plant procyanidins: reactions of procyanidin B-2 (Thompson *et al.*, 1972; Haslam *et al.*, 1977a).

The absolute stereochemistry in procyanidins B-1 and B-2 was determined as 4*R* in later work by the Sheffield group (Haslam *et al.*, 1977a) using  $^{13}C$ -NMR. The C–C interflavan bond in procyanidins B-1 and B-2 thus occupies a quasi-axial position at C-4 on the ‘upper’ flavan-3-ol heterocyclic ring. These observations were based on the ‘ $\gamma$  effect’ in the  $^{13}C$ -NMR spectra of the carbon atoms of the heterocyclic ring of the flavan-3-ol system. When an aryl group is substituted at C-4 in flavan its effect on the  $^{13}C$  chemical shift at C-2 is dependent on its orientation (Fig. 7.4). Thus in 2,4-*cis*-4-phenylflavan (7.19) (4-phenyl group quasi-equatorial) the effect of the substitution of the phenyl group at C-4 on the resonance at C-2 is minimal (+0.4 p.p.m.); however, in 2,4-*trans*-4-phenylflavan (7.20), (4-phenyl group quasi-axial) a characteristic upfield shift ( $\gamma$  effect, –4.5 p.p.m.) was observed on the  $^{13}C$  chemical shift of C-2. Similar  $\gamma$ -effects were observed in the resonances at C-2 in the ‘upper’ flavan-3-ol unit of procyanidin B-1 and of procyanidin B-2 (7.22) when compared to the C-2 resonance of the parent flavan-3-ol (–)-epicatechin (7.21). These observations demonstrated that the configuration at C-4 in the ‘upper’ flavan-3-ol unit of these

procyanidin dimers is *4R* and this places the 'lower' flavan-3-ol unit in a quasi-axial position at C-4. In contrast no  $\gamma$ -effects were seen in the  $^{13}\text{C}$ -NMR spectra of the procyanidin dimers B-3 (7.24) and B-4 when compared to the parent flavan-3-ol (+)-catechin (7.23). It is thus noteworthy that the major natural procyanidin dimers (B-1, B-2, B-3 and B-4) all possess a *trans* orientation of the hydroxyl group at C-3 and the flavan substituent at C-4 in the 'upper' flavan-3-ol unit.

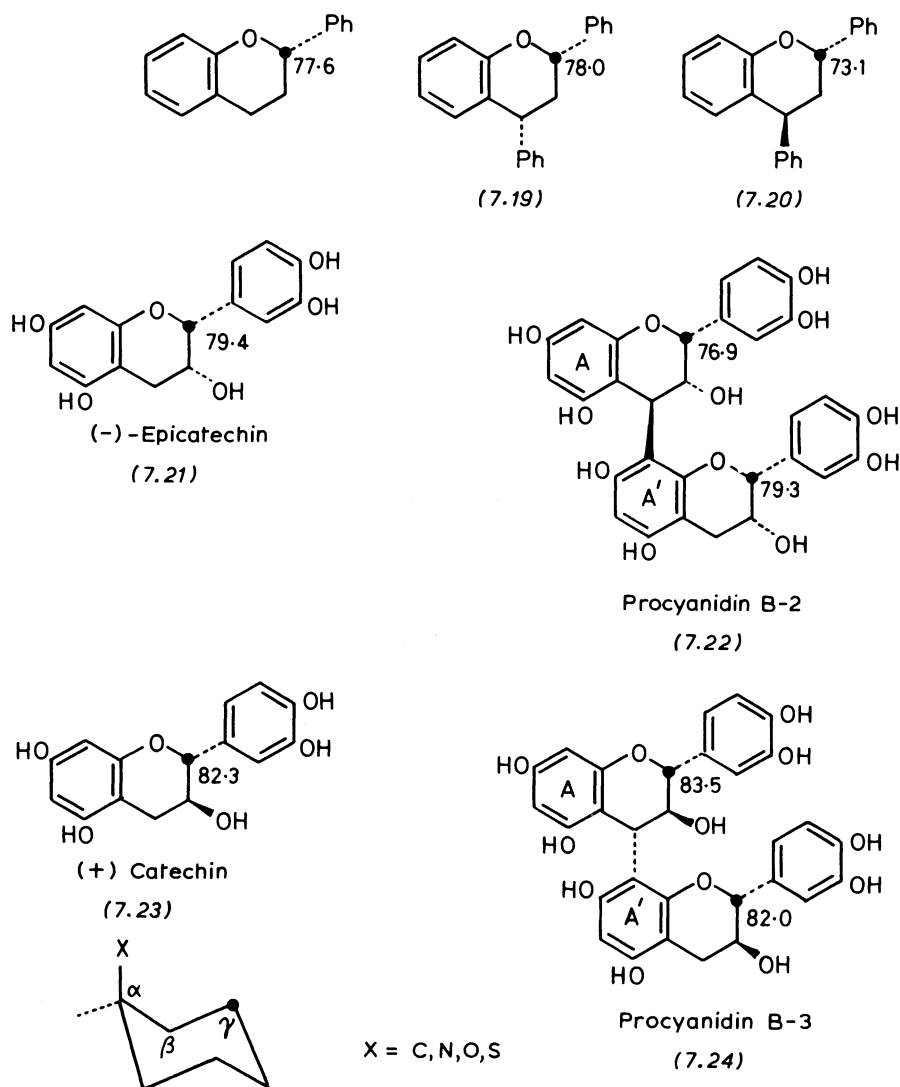


Fig. 7.4.  $^{13}\text{C}$ -NMR analysis of procyanidin stereochemistry: the  $\gamma$ -effect in flavan derivatives and some procyanidins (Haslam *et al.*, 1977a).  $^{13}\text{C}$ - $\delta$  values (p.p.m. from TMS).

These stereochemical features of the natural procyanidins were confirmed by circular dichroism (CD) measurements (Scopes *et al.*, 1979). The principal feature of the CD spectra is a very large positive or negative couplet at short wavelength (200–220 nm), and this possibly originates from the two aryl chromophores linked by a benzylic carbon atom (i.e. rings A and A' in procyanidin B-2). Procyanidins B-1 and B-2 with 4*R* stereochemistry and related models all show a strong positive couplet whilst procyanidins B-3 and B-4 and models with 4*S* stereochemistry exhibit a negative couplet. A further notable feature of the CD spectra of the procyanidins is that as the degree of polymerization increases (with the formation of trimers, tetramers etc.) then the distinctive CD couplet increases in amplitude.

Despite the successful application of NMR methods to the structure determination of the various dimeric procyanidins, anomalous features of the spectra (Thompson *et al.*, 1972) led to speculation by several workers (Weinges *et al.*, 1970; Jurd and Lundin, 1968; du Preez *et al.*, 1971; Thompson *et al.*, 1972) that restricted rotation about the interflavan bond existed in this group of natural products. A detailed study (Haslam *et al.*, 1977a) has revealed the correctness of this hypothesis and has defined two different forms of hindered rotation about the interflavan bond which may be associated with the two groups of procyanidin dimers [B-1 and B-2, 4*R* absolute configuration, (–)-epicatechin 'upper' flavan-3-ol unit] and [B-3 and B-4, 4*S* absolute configuration, (+)-catechin 'upper' flavan-3-ol unit] (Fig. 7.5). For the dimers B-1 and B-2 the observations have been interpreted (Fig. 7.5 – procyanidin B-2) in terms of restricted rotation caused primarily by steric interactions between the proton at C-2 and the aromatic  $\pi$  system of ring A of the 'upper' flavan unit, and the substituents *ortho* to the inter-flavan linkage on the phloroglucinol ring of the 'lower' flavan unit. Alternatively for the procyanidin dimers B-3 and B-4 with the 4*S* configuration the restricted rotation around the interflavan bond has several analogies, and molecular models show that the oxygen substituents at C-3 and C-5 in the 'upper' flavan unit and those in the *ortho* position to the interflavan bond on the phloroglucinol ring in the 'lower' flavan unit are primarily responsible for the steric interference (Fig. 7.5 – procyanidin B-3). Typical values for the  $\Delta G_{\text{rot}}^{\ddagger}$  (free energy of activation for the rotational process) for the procyanidins B-2 and B-3 and their derivatives are shown in Fig. 7.5.

The results of this work thus imply that, although dimers of the B group and their derivatives exhibit atropisomerism under the conditions of the  $^1\text{H}$ -NMR experiment, the energy barriers observed are too small to permit the isolation of the different conformational forms of the procyanidins or their derivatives. From the practical point of view, however, these observations indicate clearly that first-order spectra of the procyanidins and their derivatives can only be observed at elevated temperatures – for the acetate and methyl ether derivatives at 180° in pentadeuterionitrobenzene and for the free phenols at 60–90° in hexadeuteriodimethylsulphoxide.

Although the  $^1\text{H}$  NMR experiments show that for each procyanidin a number

of conformations about the interflavan bond are accessible, examination of molecular models suggests that one preferred conformation probably exists for each of the free phenolic forms of the procyanidins. These are shown in Fig. 7.5 for procyanidin B-2 and procyanidin B-3. An interesting feature of these two conformations is that inspected from different view points (as indicated by the arrows) they bear an almost object-to-mirror-image relationship; the structures are quasi-enantiomeric.

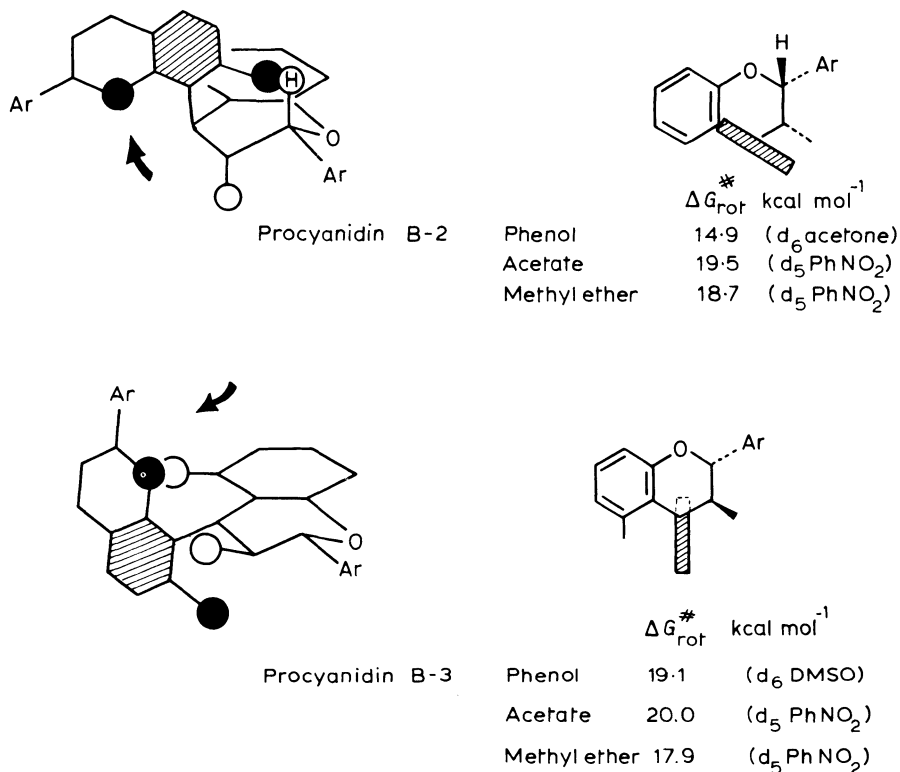


Fig. 7.5 Restricted rotation in procyanidin dimers; preferred conformations of procyanidins (Haslam *et al.*, 1977a). Rotational barriers in procyanidin dimers.

Elaboration of the oligomeric forms of procyanidins by the addition of further flavan-3-ol units [(–)-epicatechin to B-1 and B-2 and (+)-catechin to B-3 and B-4], bearing in mind the type of conformational restraint about the interflavan bond which has been demonstrated, leads to two helical structures. The central core of these linear polymers is composed of rings A and C of the flavan repeat unit and ring B – the *ortho* dihydroxyphenyl ring – projects laterally from this core. Significantly perhaps those formed from units related to (–)-epicatechin (e.g. the extension of the procyanidin B-1 or B-2) are *left-hand* helices, whilst those of the type related to procyanidin B-3 or B-4 formed by the addition of

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(+)-catechin units are *right-hand* helices. Although the biological significance of these observations is not clear, they are a further interesting example of the economy of nature. Thus different plants have evolved the means of synthesis of isomeric oligomers and polymers with opposite helicities by the simple expedient of a change in stereochemistry of the hydroxyl group at C-3 in the carbocation precursor (*vide infra*).

Ideas on the biosynthesis of the plant proanthocyanidins and associated flavan-3-ols are based upon a range of structural and chemical observations (Weinges *et al.*, 1968a,b; Thompson *et al.*, 1972; Geissman and Yoshimura, 1966) and upon various biosynthetic experiments (Opie *et al.*, 1977; Haslam *et al.*, 1977b). The results of these experiments, in which variously labelled ( $^{14}\text{C}$  and  $^3\text{H}$ ) cinnamic acid precursors were administered to procyanidin-metabolizing plants [*A. hippocastanum*, *A. carnea* – (–)-epicatechin, procyanidin B-2, proanthocyanidin A-2; *Rubus fruticosus*, *R. idaeus* – (–)-epicatechin, procyanidin B-4; *Salix caprea*, *S. inorata*, *Chamaecyparis lawsoniana* – (+)-catechin, procyanidin B-3] are summarized in Fig. 7.6. The most significant of the results – which are in general accord with ideas on the biosynthesis of flavonoids outlined by earlier workers (Grisebach, 1968) – are:

- The retention in both flavan units in the dimers of the proton  $\text{H}_a$  at C-2, C-2'.
- The loss of the proton  $\text{H}_c$  from the cinnamic acid precursor.
- The NIH shift which accompanies the hydroxylation of ring B of the flavan-3-ol nucleus (40–50% loss of  $\text{H}_b$ ).
- The differential extent of labelling obtained in the 'upper' and 'lower' flavan-3-ol units of the procyanidin dimers (dependent on the individual experiment but generally a ratio of 1:2 to 5).

The most straightforward interpretation of this last result (d) is that the two 'halves' of the procyanidin dimers are derived from different metabolic sources.

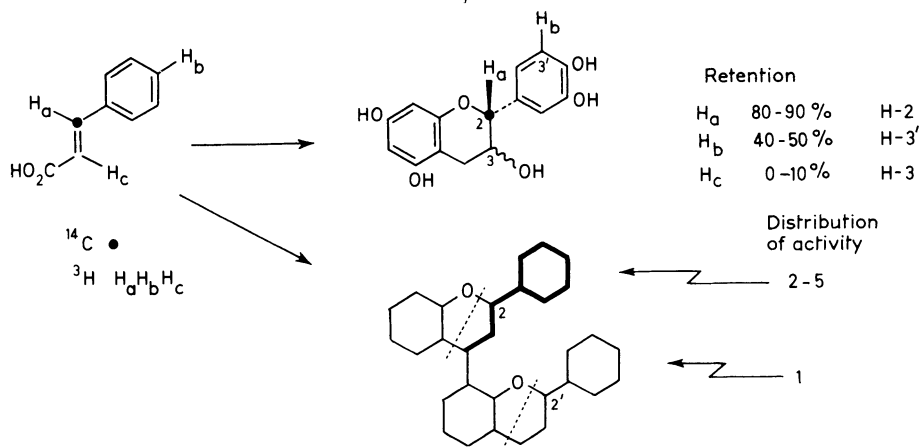


Fig. 7.6 Biosynthesis of flavan-3-ols and procyanidins: the fate of isotopically labelled cinnamic acids (Haslam *et al.*, 1977b).



The other results have been incorporated along with (d) in a general scheme of procyanidin and flavan-3-ol biosynthesis which is illustrated in Fig 7.7 (Haslam *et al.*, 1977b). The biosynthesis of the  $C_6.C_3.C_6$  carbon skeleton of the flavonoids is thought to involve the chalcone as the first formed intermediate (Fig. 7.7). However, the sequence of chemical changes (e.g. oxidation, reduction etc.) in the C-3 fragment which lead to the production of the individual flavonoids nevertheless remains poorly defined. Assuming the chalcone–dihydroflavone pair to be key intermediates on the biosynthetic pathway, several mechanistically plausible schemes can lead to the flavan-3-ols. Fig. 7.7, route A shows one such pathway and route B is a possible alternative scheme of biogenesis in which the  $C_6.C_3$  precursor is the  $\alpha$ -keto acid, phenylpyruvic acid. A key intermediate in both schemes is the flav-3-en-3-ol and it is postulated that a two-stage stereospecific reduction of this compound (proton transfer, followed by hydride addition) might lead to the two stereoisomeric flavan-3-ols (+)-catechin and (–)-epicatechin. It has been argued that this reaction also provides a basis for the biogenesis of the procyanidins. If the supply of biological reductant (say NADPH) is rate-limiting, the intermediate C-4 carbocations (3*S* or 3*R* absolute stereochemistry) might then escape from the active site of the enzyme and react with the reduced product [the flavan-3-ol, (+)-catechin or (–)-epicatechin] to produce dimers, trimers, tetramers and higher oligomers (Haslam *et al.*, 1977b; Haslam, 1977). The hypothesis has been elaborated in greater detail (Haslam, 1977) to account for the four major procyanidin ‘fingerprints’ (*vide supra*) and in particular to account for the derivation of procyanidin dimers, such as B-1 and B-4, in which the component ‘halves’ have opposite absolute stereochemistry at C-3.

The various distinctive patterns of procyanidins found in plants are therefore thought to be derived directly by reaction of one or both of the parent flavan-3-ols [(+)-catechin, (–)-epicatechin] utilizing their nucleophilic character at C-8 or C-6 with one or both of the carbocations (related in stereochemistry at C-2 and C-3). Support for this theory has been obtained from experiments *in vitro* in which the postulated carbocation intermediate(s) are released in solution in the presence of the appropriate flavan-3-ol metabolite (Haslam, 1974b). The simplest procedure is to use a procyanidin dimer as a source of the appropriate carbocation. Thus procyanidin B-2 in acidic media releases (Fig. 7.3) the carbocation related in absolute stereochemistry at C-3 to (–)-epicatechin, and similarly procyanidin B-3 gives the analogous carbocation to the 2,3-*trans* stereochemistry of (+)-catechin. Correct adjustment of the acidity enables a biomimetic synthesis to be set up. Each of the four possible reactions can be reproduced in the laboratory and the products, both qualitatively and quantitatively, match those found in particular plants (Fig. 7.1). The biomimetic syntheses closely resemble some of the solvolytic reactions discussed earlier for phenolic flavan-3,4-diols (Section 7.2.2). The experiments *in vitro* are clearly under thermodynamic control and a point therefore of some interest is that in each “biomimetic situation” the major dimer which is produced is that in which the carbocation at C-4 captures the flavan-3-ol with the formation of a new C–C bond *trans* to the C-3 hydroxyl group of the carbocation.

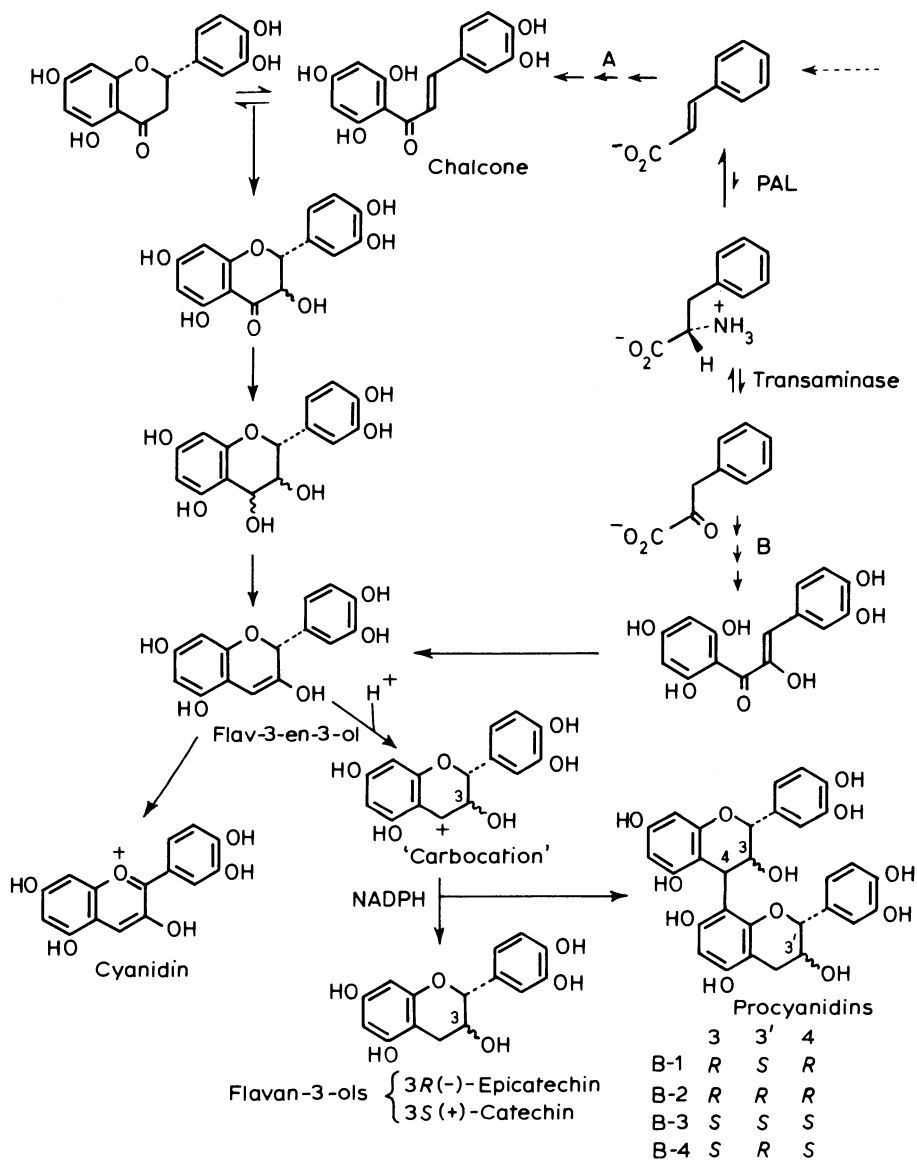
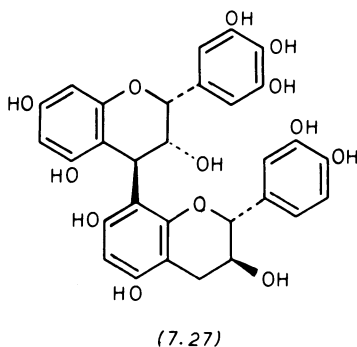
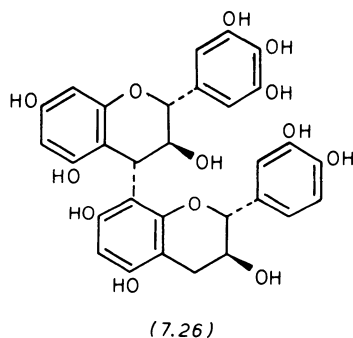
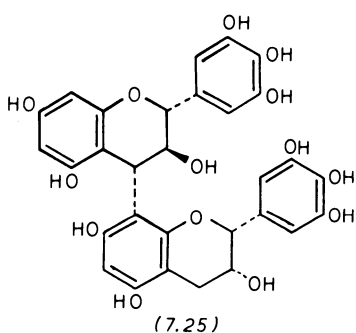


**Fig. 7.7** Biosynthesis of flavan-3-ols and procyanidins: a hypothesis (Haslam *et al.*, 1977b; Haslam, 1977).

The status of the flavan-3,4-diols in procyanidin biosynthesis remains something of an enigma, since to date *no* flavan-3,4-diol with the, 5,7,3',4'-tetrahydroxy pattern of phenolic hydroxyl groups has been found in the vegetative tissues of a procyanidin-metabolizing plant, and attempts to obtain experimental evidence to support their suggested role have so far proved negative (Haslam *et al.*, 1977b).

## 7.3.2 Prodelphinidins

In contrast to the ubiquitous procyanidins, little is yet known in detail of the chemistry of the prodelphinidins, although Bate-Smith in his earlier surveys (Bate-Smith, 1962) showed that a wide range of 'woody' plants yield delphinidin (usually with cyanidin) when fruit or leaf extracts are heated with butanol and hydrochloric acid. The limited amount of work reported on these substances does, however, suggest a very similar chemistry to the procyanidins and an occurrence which follows the pattern of occurrence of (+)-gallocatechin and (–)-epigallocatechin in plants. Thus Porter and Foo (1978) have isolated a prodelphinidin (7.25), (–)-epigallocatechin and (+)-gallocatechin as their polyacetates from the leaves of *Ribes sanguineum* and a further prodelphinidin (7.26), with a mixed B-ring oxidation pattern from *Salix caprea*. Likewise E. Haslam and R. K. Gupta (unpublished observations) have obtained (+)-catechin, (+)-gallocatechin and the prodelphinidin (7.27) from *Pinus sylvestris*. The structures of these prodelphinidins were established by methods analogous to those outlined above for the procyanidins (NMR, degradation in acid in the presence of a thiol or phloroglucinol). These limited observations support the suggestion of a relationship between prodelphinidin metabolism and that of the gallocatechins. However, the occurrence of the dimers (7.26) and (7.27) is noteworthy and has important biosynthetic implications.



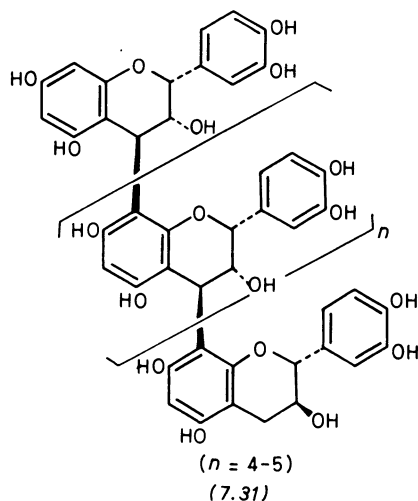
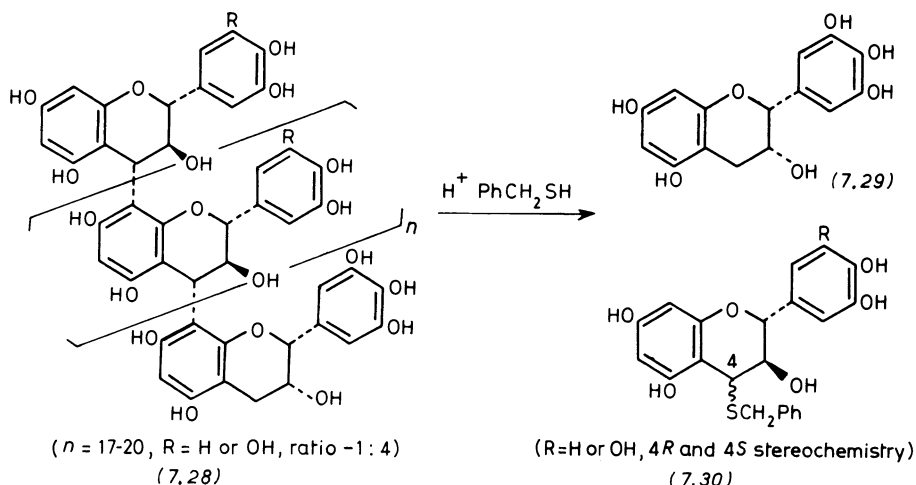
### 7.3.3 Polymeric procyanidins and prodelphinidins

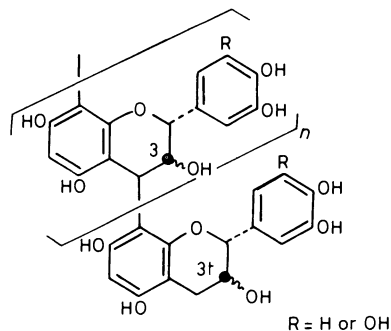
In any plant tissue where proanthocyanidin synthesis occurs there is invariably found a range of proanthocyanidins – from the monomeric flavan-3-ols (catechins and gallocatechins) to the polymers (7.1). For each tissue the balance between these molecular forms is probably determined by the corresponding balance between the metabolic flux to the flav-3-en-3-ol (Fig. 7.7) and the rate of supply of the biological reductant NADPH. Tissues in which the flux is low and the NADPH supply is high will contain a range of proanthocyanidins of varying molecular size but those tissues in which the flux is high and the supply of NADPH is low will conversely contain predominantly the higher oligomeric forms – for example the seed coat of the cereal sorghum (Gupta and Haslam, 1978). This facet of proanthocyanidin metabolism was noted very early by Sir Robert and Lady Robinson (Robinson and Robinson, 1935) who recognized the presence in plants of leucoanthocyanins (proanthocyanidins!) of quite different solubilities. With increasing degrees of polymerization the proanthocyanidins become more difficult to solubilize in aqueous and alcoholic media, and it has been suggested (Porter *et al.*, 1979) that those which can be coaxed into solution may have molecular weights up to 7000 – corresponding to the accumulation of up to 20 flavan-3-ol units ( $1, n = 18$ ) in the polymer chain. Currently available techniques enable such polymers to be isolated and purified in an undegraded form (Jones *et al.*, 1976), and very recent work has concentrated upon structural examinations of these polymers.

Chemical degradation of the polymers occurs by solvolysis in acidic media and results in the familiar fission of the interflavan C–C bonds (Fig. 7.3). The chain-extension units of the polymer are released as the corresponding flavan-4-yl carbocation which may be trapped with phloroglucinol or toluene  $\alpha$ -thiol (Fig. 7.3), and the terminal unit is released as the corresponding flavan-3-ol. Porter and Foo (1978) thus showed that the predominantly prodelphinidin polymers from *Ribes sanguineum* consisted largely of chain-extension units corresponding to the (+)-gallocatechin structure linked to a (–)-epigallocatechin terminal group (7.28). The polymer was quantitatively degraded in the presence of toluene  $\alpha$ -thiol (Porter *et al.*, 1979) and the products (7.29 and 7.30) were separated and analysed by GLC as their trimethylsilyl ethers. In this way the ratio of chain extension to terminal units in the polymer structure was estimated as 21:1, implying a molecular weight of  $\sim 6600$  and an average structure (7.28). Gupta and Haslam (1978) used a similar approach for the determination of the average structure of the procyanidin polymer from the seed coat of sorghum as (7.31) and a molecular weight of 1700–2000.

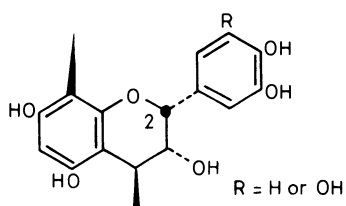
Porter and his colleagues (Porter *et al.*, 1979) have described a novel spectroscopic method for the estimation of proanthocyanidin polymer compositions and molecular weights. The method uses  $^{13}\text{C}$ -NMR as the analytical probe and makes use of the different signals observed for carbon atoms in the heterocyclic rings of procyanidin dimers (Haslam *et al.*, 1977a). Thus the  $^{13}\text{C}$  signal for C-3 of the terminal flavan-3-ol unit of a proanthocyanidin oligomer

usually occurs at 65–66 p.p.m., quite separate from the C-3 signal of flavan-3-ol chain-extension units which occur at 72–73 p.p.m. (7.32). The mean molecular weight of the *Ribes* polymer was calculated from the ratio of the areas of these two signals and gave a chain extension:chain terminal unit ratio of 18:1 (i.e. a mean molecular weight of 5900). Estimation of molecular weight by  $^{13}\text{C}$ -NMR spectroscopy is controlled by the observable limit of the C-3 signal from the terminal unit and this was suggested to mean a limit of about 8000 to the molecular weight of the polymer under examination. The ratio of procyanidin to prodelphinidin chain-extension units in the polymer from *R. sanguineum* was similarly determined by an examination of the aryl C atom region of the  $^{13}\text{C}$ -NMR spectrum (145–150 p.p.m) and a value of  $\sim 1:4$  was obtained, in good agreement with other measurements of this ratio.

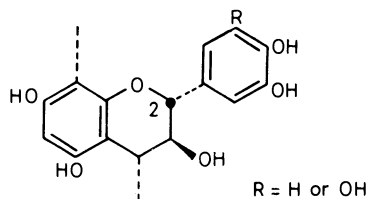




( $^{13}\text{C}$ -NMR  $\delta$  values: C-3f...65-66 p.p.m., C-3... 72-73 p.p.m.)  
(7.32)



( $^{13}\text{C}$ -NMR  $\delta$  value: C-2...~77 p.p.m.)  
(7.33)



( $^{13}\text{C}$ -NMR  $\delta$  value: C-2...~83 p.p.m.)  
(7.34)

Porter and his collaborators have also outlined the application of  $^{13}\text{C}$  and optical rotary dispersion (ORD) measurements for the determination of polymer structures containing chain-extension units of mixed stereochemistry, i.e. those with 2,3-*cis* [(−)-epicatechin or (−)-epigallocatechin] stereochemistry and 2,3-*trans* [(+)-catechin or (+)-gallocatechin] stereochemistry (Porter *et al.*, 1979, 1980). Earlier surveys of plants (Thompson *et al.*, 1972) suggest that these types of proanthocyanidin polymers are widely distributed in the plant kingdom. The  $^{13}\text{C}$ -NMR method again makes use of the  $\gamma$ -effect (*vide supra*: Sections 7.2.1 and 7.3.1) in the  $^{13}\text{C}$ -NMR spectra of certain flavan derivatives. The interflavan bonds between flavan-3-ol chain-extension units with 2,3-*cis* stereochemistry occupy quasi-axial positions at C-4 in these units and this substitution leads to a  $\gamma$ -effect on the C-2 signal in such units (7.33, C-2 signal ~ 77 p.p.m.). This effect is not present in units with 2,3-*trans*-stereochemistry and the corresponding signal is now quite distinct (7.34) (C-2 signal ~ 83 p.p.m.). Estimation of the ratio of the areas under each signal thus yields the ratio of chain-extension units in the polymer with 2,3-*cis* as opposed to 2,3-*trans* stereochemistry. Table 7.2 gives a summary and comparison of results for various proanthocyanidin polymers determined by Porter and his colleagues (Porter *et al.*, 1979; Porter and Foo, 1980) by the methods outlined.

**Table 7.2** Composition of proanthocyanidin polymers (taken from Porter *et al.*, 1979).

| Proanthocyanidin | [ $\alpha$ ] <sub>578</sub> | Mole fraction of<br>2,3-cis-isomer |                             | Ratio, prodelphinidin:procyanidin |                      | Mean Mol.           |                            |
|------------------|-----------------------------|------------------------------------|-----------------------------|-----------------------------------|----------------------|---------------------|----------------------------|
|                  |                             | From<br>rotation                   | From<br><sup>13</sup> C-NMR | Acid<br>degradation               | Thiol<br>degradation | <sup>13</sup> C-NMR | wt.<br><sup>13</sup> C-NMR |
| Sainfoin*†       | + 345°                      | 0.91                               | 0.87                        | 81:19                             | 83:17                | 81:19               |                            |
| Lotus*†          | + 255°                      | 0.83                               | 0.75                        | 77:23                             | 80:20                | 82:18               |                            |
| Ribes*†          | − 692°                      | 0                                  | 0                           | 87:13                             | 93:7                 | 91:9                | 5900                       |
| Siebel*‡         | + 436°                      | 0.99                               | 1.0                         | 20:80                             | 22:78                | 10:90               |                            |
| Beaujolais*‡     | + 390°                      | 0.95                               | 0.91                        | 20:80                             | 18:82                | 13:87               | 4900                       |
| Cyathea*†        | + 455°                      | 1.00                               | 1.0                         | 41:59                             | 38:62                | 40:60               |                            |
| Dicksonia*†      | + 425°                      | 0.98                               | 1.0                         | 18:82                             | 5:95                 | 13:87               | 2900                       |
| Pinus radiata*§  | + 217°                      | 0.80                               | 0.76                        | 50:50                             | 49:51                | 48:52               | 1800                       |
| Rose hips*‡      | + 111°                      | 0.70                               | 0.72                        | 10:90                             | 13:87                | 13:87               | 6400                       |

\* Polymer. † Isolated from leaves. ‡ Isolated from unripe fruit.

§ Isolated from phloem. || C<sub>3</sub>(t) Signal not observed.

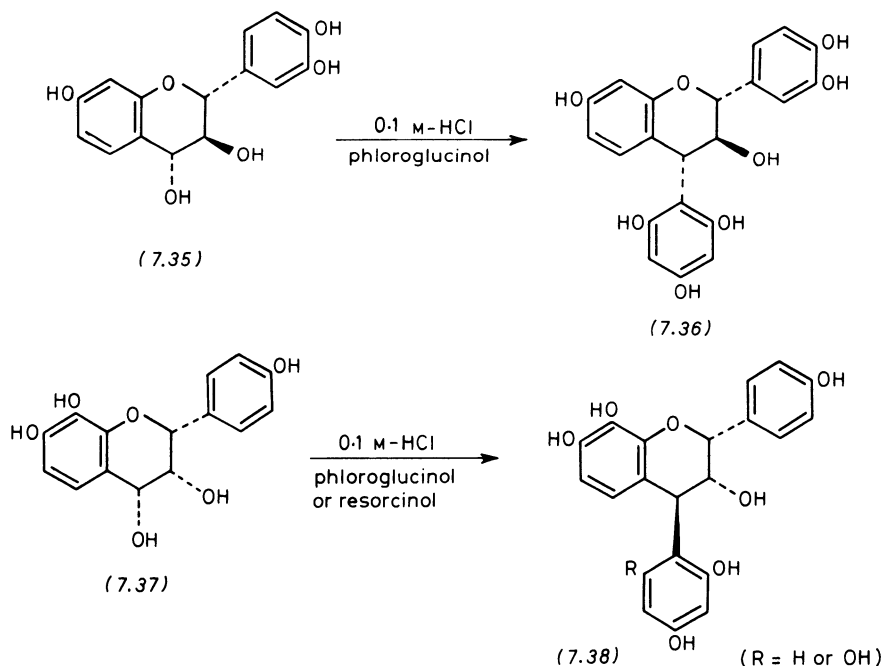
Electrophilic substitution reactions of the (+)-catechin and (−)-epicatechin nucleus occur much more readily at the C-8 than the C-6 position, and all the proanthocyanidin biosynthetic (and hence structural) arguments are based on this assumption – namely that the proanthocyanidin C–C-bond-forming reaction occurs predominantly *via* C-4 of one flavan unit (the carbocation) and C-8 of the next unit. On this basis the proanthocyanidin polymers probably have essentially linear structures with C-4 to C-8 interflavan bonds. However, simply on a statistical basis the formation of some C-4 to C-6 linkages might be expected to be present in the polymers and hence that they may well possess a degree of branching within them. Roux and his collaborators (Roux and Hundt, 1978), on the basis of model experiments, have suggested degradative bromination and <sup>1</sup>H-NMR as methods to determine the position (C-6 or C-8) of the interflavan linkage. The <sup>1</sup>H-NMR method utilizes the position of the chemical shift of the singlet proton (C-6 or C-8)- in the (C-8 or C-6)-substituted flavan-3-ol nucleus. A number of C-8- and C-6-substituted derivatives of (−)-epicatechin and (+)-catechin tetramethyl ethers were prepared by unequivocal methods. It was observed that in these derivatives the residual A-ring proton absorbs in one of two narrow ranges dependent on its location at C-6 or C-8 –  $\delta$  (8H) falls in the range 6.32–6.47 and  $\delta$  (6H) at 6.10–6.22. There are some problems applying this method to natural procyanidins and prodelphinidins because of the hindered rotation about the C–C interflavan bond at ambient temperatures (*vide supra*, Section 7.3.1, Fig. 7.5). However, the chemical shift of the singlet A-ring proton in procyanidin B-2 octamethyl ether at 170° in d<sub>5</sub> nitrobenzene is at  $\delta$  6.08, and if the extrapolation can be made, this confirms the assignment of the C-8 to C-4 linkage in this dimer (Haslam, 1977; Haslam *et al.*, 1977a).

### 7.3.4 Miscellaneous proanthocyanidins

The heartwood and bark of trees are often rich sources of proanthocyanidins, often of an unusual type, and Roux and his collaborators have continued their

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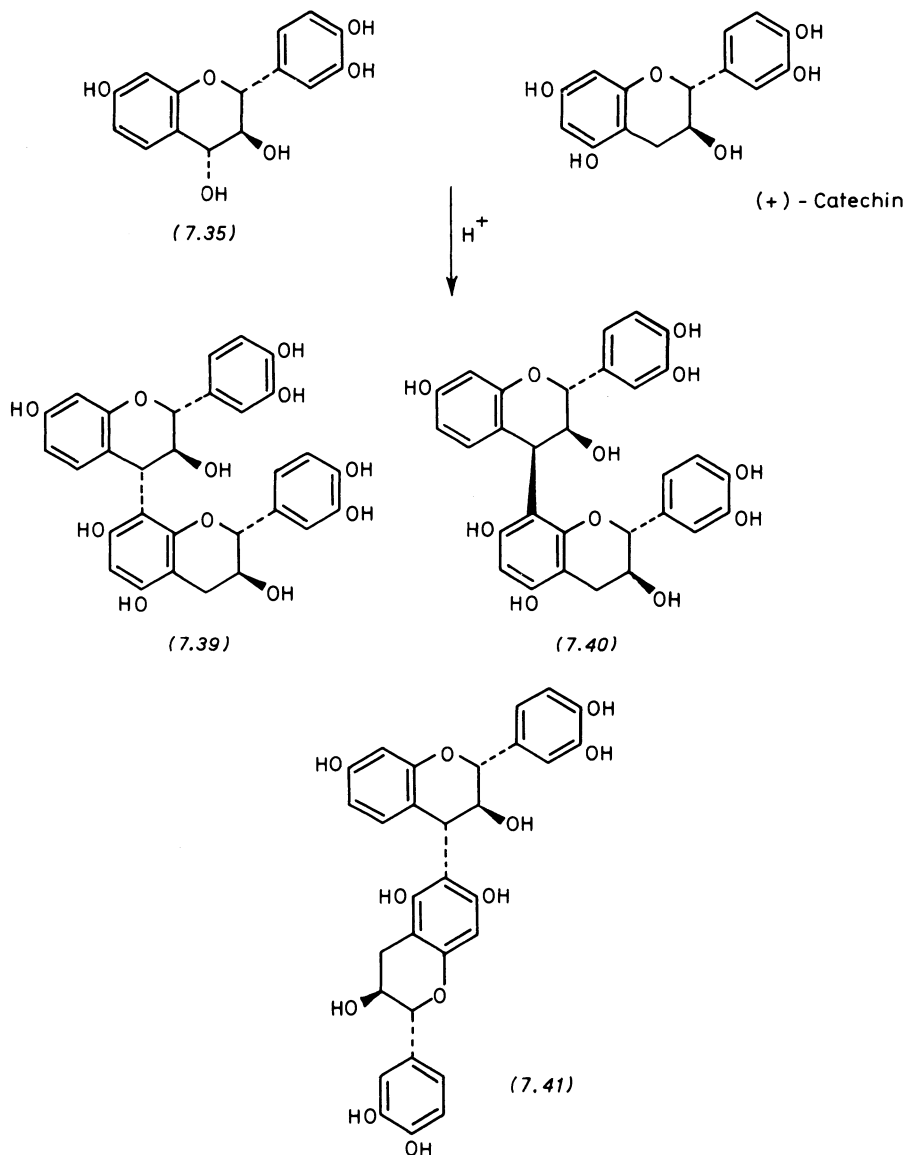
notable researches into the profisetinidins, prorobinetinidins and proguibourtinidins which they have found principally in trees of the *Acacia* family (Roux, 1972). They have favoured a scheme of biosynthesis for many of these proanthocyanidins which is based on the derivation of the appropriate phenolic flavan-4-yl carbocation from the associated flavan-3,4-diol which is frequently found alongside the proanthocyanidins in the wood. In recent work they have optimized the conditions for biomimetic synthesis of proanthocyanidins derived from (+)-mollisacacidin (7.35) in black wattle (*Acacia mearnsii*). The flavan-3,4-diol was thus condensed at ambient temperatures (20°C) in 0.1 M-HCl with appropriate nucleophilic substrates. Phloroglucinol was thus stereoselectively captured to give (7.36) whilst with resorcinol both the 3,4-*cis* and 3,4-*trans* products were obtained (Roux *et al.*, 1978b). Under similar conditions (–)-teracacidin (7.37) gave with both phloroglucinol and resorcinol a product with the same (4*R*) absolute stereochemistry at C-4 (7.38). Roux and his colleagues attributed these differences to varying degrees of steric-approach control in the C–C-bond-forming reaction and in particular to the influence of the orientation of the C-3 hydroxyl group. The differences in absolute stereochemistry at C-4 in these 4-arylflavans were assigned with the aid of CD spectra and the strong bands in the 220–240 nm region and <sup>1</sup>H-NMR.



Using similar reaction conditions Roux *et al.* (1978c) condensed (+)-mollisacacidin (7.35) and (+)-catechin to give good yields of the two C-4 to C-8-linked and one of the C-4 to C-6-linked proanthocyanidins (7.39, 7.40, 7.41).



Structures and stereochemistry were assigned using  $^1\text{H-NMR}$  and CD spectra and both of the C-4 to C-8-linked profisetinidins (7.39, 7.40) were identified with compounds isolated from black wattle or 'Mimosa' extract. These observations support the long-held view (Geissman and Yoshimura, 1966; Creasey and Swain, 1965) that flavan-3,4-diols *via* the reaction of their derived 4-carbocations and nucleophilic phenolic flavan-3-ols represents the mode of biogenesis of the proanthocyanidins found in the woods and bark of many trees (Drewes *et al.*, 1967).



## APPENDIX: PROANTHOCYANIDIN NOMENCLATURE

Procyanidins are currently named according to a trivial system introduced by Weinges (Weinges *et al.*, 1968) and later perpetuated and extended by Haslam and his collaborators (Thompson *et al.*, 1972). However, as investigations of the chemistry and biochemistry of the proanthocyanidins have developed over the past decade the isolation of further proanthocyanidin oligomers (some with mixed oxidation patterns in the flavan-3-ol B ring) and of proanthocyanidin polymers has underlined the growing need for an acceptable and usable form of nomenclature in this field. The IUPAC system which uses flavan as the fundamental ring system and the *R* and *S* symbols to signify absolute stereochemistry is fully descriptive but exceedingly cumbersome to use. To the uninitiated it may also be misleading in its description of related centres in a molecule with the same relative configuration at C-4 of the flavan units.

Very recently Porter and his colleagues (Porter *et al.*, 1982) have proposed a form of nomenclature which appears neat and exceedingly attractive. It offers a precise alternative to the fully systematic and more rigorous IUPAC method. Proanthocyanidins are named in an analogous manner to oligo- and polysaccharides, and in the Porter system C-4 of the flavan-3-ol building unit of proanthocyanidins is (in the nomenclature sense) equivalent to the anomeric centre C-1 of the sugar unit in oligosaccharides. The interflavonoid bond is indicated in the same way as the linkage between sugars in oligosaccharides; the bond and its direction are contained in brackets (4 → ).

The system then uses commonly accepted and modified trivial names for the building units of the proanthocyanidins and the  $\alpha\beta$  system to denote the configuration of the interflavonoid bond at C-4. These conventions are outlined as follows:

- (a) The fundamental flavan structural units of proanthocyanidin oligomers are defined in terms of the familiar monomeric flavan-3-ols. The names catechin, epicatechin, gallocatechin, epigallocatechin, afzelechin, epiafzelechin, fisetinidol, robinetinidol etc., are thus reserved for units with the most commonly encountered 2*R* absolute configuration. Flavan-3-ol units with the 2*S* configuration, whose occurrence in Nature is sporadic, are distinguished by the *enantio* prefix. Thus (+)-epicatechin becomes *ent* epicatechin. The absolute configuration at C-3 for each flavan-3-ol unit is thus automatically defined.
- (b) Flavan-3-ol structures are drawn and numbered according to present conventions. The configuration of the interflavonoid bond at C-4 is indicated by the appropriate  $\alpha\beta$  nomenclature (IUPAC rules).

The major dimeric procyanidins (Fig. 7.1) thus become:

procyanidin B1: epicatechin-(4 $\beta$  → 8)-catechin

procyanidin B2: epicatechin-(4 $\beta$  → 8)-epicatechin

procyanidin B3: catechin-(4 $\alpha$  → 8)-catechin

procyanidin B4: catechin-(4 $\alpha$   $\rightarrow$  8)-epicatechin

Structures (7.25) and (7.26) now are named respectively as:

(7.25): gallocatechin-(4 $\alpha$   $\rightarrow$  8)-epigallocatechin

(7.26): gallocatechin-(4 $\alpha$   $\rightarrow$  8)-catechin

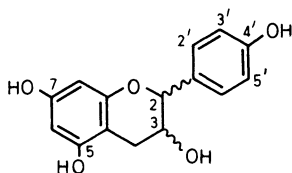
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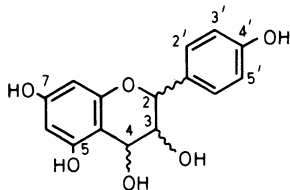
## CHECK LIST OF FLAVAN-3-OLS, FLAVAN 3,4-DIOLS AND PROANTHOCYANIDINS

*Flavan-3-ols*

- (+)-Afzelechin (2*R*:3*S*, 3,5,7,4'-tetra-OH)  
 (-)-Afzelechin (2*R*:3*R*, 3,5,7,4'-tetra-OH)  
 (+)-Epiafzelechin (2*S*:3*S*, 3,5,7,4'-tetra-OH)

- (-)-Fisetinidol (2*R*:3*S*, 3,7,3',4'-tetra-OH)  
 (-)-Robinetinidol (2*R*:3*S*, 3,7,3',4',5'-penta-OH)  
 (+)-Catechin (2*R*:3*S*, 3,5,7,3',4'-penta-OH)  
 (-)-Epicatechin (2*R*:3*R*, 3,5,7,3',4'-penta-OH)  
 Symplocoside (epicatechin 3'-methyl ether 7-*O*-glucoside)  
 (+)-Epicatechin (2*S*:3*S*, 3,5,7,3',4'-penta-OH)  
 (+)-Gallocatechin (2*R*:3*S*, 3,5,7,3',4',5'-hexa-OH)  
 (-)-Epigallocatechin (2*R*:3*R*), 3, 5, 7, 3',4',5'-hexa-OH)  
 (-)-Epigallocatechin 4'-methyl ether

(References to flavan-3-ols, see Haslam, 1975; for symplocoside, see Tschesche *et al.*, 1980).

*Flavan-3,4-diols*

- (+)-Guibourtacacidin (2*R*:3*S*:4*S*, 3,4,7,4'-tetra-OH)  
 isomer (2*R*:3*S*:4*R*)  
 (+)-Mollisacacidin (2*R*:3*S*:4*R*, 3,4,7,3',4'-penta-OH)  
 (+)-Gleditsin (2*R*:3*S*:4*S*, 3,4,7,3',4'-penta-OH)  
 7,3,4'-Trimethyl ether  
 3,4,7,3',4'-Pentamethyl ether  
 (-)-Leucofisetinidin (2*S*:3*R*:4*S*, 3,4,7,3',4'-penta-OH)

- (-)-Teracacidin (2*R*:3*R*:4*R*, 3,4,7,8,4'-penta-OH)  
 (-)-Isoteracacidin (2*R*:3*R*:4*S*, 3,4,7,8,4'-penta-OH)  
 7,8,4'-Trimethoxyflavan-3,4-diol (2*R*:3*S*:4*R*)  
 (-)-Melacacidin (2*R*:3*R*:4*R*, 3,4,7,8,3',4'-hexa-OH)  
 3,8-Dimethyl ether  
 (-)-Isomelacacidin (2*R*:3*R*:4*S*, 3,4,7,8,3',4'-hexa-OH)  
 7,8,3',4'-Tetramethoxyflavan-3,4-diol (2*R*:3*S*:4*S*)  
 (+)-Leucorobinetinidin (2*R*:3*S*:4*R*, 3,4,7,3',4',5'-hexa-OH)

*Proanthocyanidins*

- Procyanidins B-1, B-2, B-3, B-4 (dimers)  
 Prodelphinidin dimers  
 Procyanidin, prodelphinidin polymers  
 Profisetinidins  
 Prorobinetinidins  
 Proguibourtinidins

## CHAPTER EIGHT

# *C-Glycosylflavonoids*

J. CHOPIN, M. L. BOUILLANT and E. BESSON

### 8.1 INTRODUCTION

In line with the general rapid expansion of phytochemistry, the field of *C*-glycosylflavonoids has grown rapidly over the last five years. Naturally occurring *C*-arabinosyl-, *C*-galactosyl- and *C*-rhamnosyl-flavonoids have been added to the already known *C*-glucosyl- and *C*-xylosyl-flavonoids, and a large number of *O*-glycosides derived from these *C*-glycosides have been found. Moreover an unusual carbon-linked sugar residue (6-deoxy-xylo-hexos-4-ulosyl) has been identified in *C*-glycosylflavones of *Zea mays*, which inhibit insect development in this plant (Elliger *et al.*, 1980). The natural occurrence of several new types of *C*-glycosylflavonoids (*C*-glycosylchalcones, *C*-glycosylflavanonols, *C*-glycosylisoflavanones) and of tricin-derived *C*-glycosylflavones has been fully established during the period under review.

Besides the well-known Wessely–Moser acid isomerization of 5-hydroxy-*C*-glycosylflavones, which involves hydrolytic opening of the flavone heterocycle and cyclodehydration of the intermediary  $\beta$ -diketone, a further acid isomerization of the sugar heterocycle leading to a mixture of anomeric *C*-pyranosyl- and *C*-furanosyl-flavones has now been definitely proved to occur in *C*-arabinosylflavones (Besson and Chopin, 1980). This explains why the symmetrical 6,8-di-*C*-arabinopyranosyl-5,7-dihydroxyflavones unexpectedly undergo isomerization on acid treatment.

The natural sources of *C*-glycosylflavonoids reported in the last six years are listed in Table 8.1. The number of species are given for each genus, except in the case of the large family surveys that have been carried out in the Cyperaceae, Gramineae, Orchidaceae and Palmae (Harborne, Williams and co-workers). Liverworts have been mainly studied by Markham and Zinsmeister's groups, mosses by Österdahl, pteridophytes by Hiraoka and Wallace, gymnosperms by the Lebreton, Niemann and Wallace groups, monocotyledons by Harborne and Williams, Caryophyllales by Richardson, Labiatae by Weightman, and Polemoniaceae by Smith and co-workers. Some genera have been intensively studied, e.g. *Achillea* (Valant), *Carlina* (Raynaud and co-workers), *Gentiana* (Jacot-Guillarmod, Hostettmann and co-workers), *Larix* (Niemann and co-workers) and *Silene* (Zemtsova, Darmograi). The same is true for some species, e.g. *Avena sativa* (Weissenböck and co-workers), *Crataegus monogyna*

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**Table 8.1** Natural sources of C-glycosylflavonoids

### BRYOPHYTA

- Apometzgeria* (3) Theodor *et al.* (1980, 1981a,b)
- Conocephalum* (1) Markham *et al.* (1976a)
- Hedwigia* (1) Österdahl (1978, 1979a,b)
- Hymenophyllum* (1) Markham and Wallace (1980)
- Hymenophyton* (2) Markham *et al.* (1976b)
- Mnium* (1) Vandekerckhove (1978); Österdahl (1979a,c)
- Plagiochila* (1) Mues and Zinsmeister (1975, 1976)
- Takakia* (2) Markham and Porter (1979)
- Trichomanes* (2) Markham and Wallace (1980)

### PTERIDOPHYTA

- Angiopteridaceae
  - Angiopteris* (4) Wallace and Story (1978); Wallace *et al.* (1979, 1981)
- Athyriaceae
  - Lunathrium* (7) Hiraoka (1978)
  - Matteucia* (2) Hiraoka (1978)
  - Onoclea* (1) Hiraoka (1978)
  - Woodsia* (2) Hiraoka (1978)
- Dryopteridaceae
  - Arachnoides* (4) Hiraoka (1978)
  - Cyrtomium* (3) Hiraoka (1978)
  - Dryopteris* (13) Hiraoka (1978)
  - Polystichum* (5) Hiraoka (1978)
- Lycopodiaceae
  - Lycopodium* (1) Markham and Moore (1980)
- Psilotaceae
  - Psilotum* (1) Wallace and Markham (1978a,b)
- Tmesipteridaceae
  - Tmesipteris* (2) Wallace and Markham (1978a,b)

### SPERMATOPHYTES

#### GYMNOSPERMAE

- Cycadaceae
  - Cycas* (3) Lebreton (1980); Niemann and Miller (1975)
- Ephedraceae
  - Ephedra* (4) Castledine and Harborne (1976); Wallace (1978, 1979); Thivend *et al.* (1979); Niemann and Miller (1975)
- Gnetaceae
  - Gnetum* (3) Wallace (1978); Wallace and Morris (1978); Thivend *et al.* (1979)
- Pinaceae
  - Abies* (11) Lebreton *et al.* (1978); Parker *et al.* (1979)
  - Keteleeria* (1) Lebreton *et al.* (1978)
  - Larix* (8) Niemann (1973, 1974, 1975a,b 1979, 1980a,b); Niemann and Miller (1975); Niemann and Baas (1978); Medvedeva *et al.* (1973, 1974); Tjukavkina *et al.* (1975)
  - Pseudotsuga* (1) Niemann and Van Genderen (1980)
  - Tsuga* (4) Lebreton *et al.* (1978)
- Podocarpaceae
  - Podocarpus* (2) Lebreton *et al.* (1978); Niemann and Miller (1975)
- Stangeriaceae
  - Stangeria* (1) Lebreton (1980)

## Taxodiaceae

*Sequoia* (1) Lebreton *et al.* (1978); Niemann and Miller (1975)

## Welwitschiaceae

*Welwitschia* (1) Wallace (1978); Thivend *et al.* (1979)

## ANGIOSPERMAE

## MONOCOTYLEDONEAE

## Araceae

*Acorus* (1) El'Yashevich *et al.* (1974a,b)

*Asterostigma* (1) Markham and Williams (1980)

## Bromeliaceae

*Pitcairnia* (1) Williams (1978)

*Tillandsia* (5) Williams (1978)

## Cyperaceae Williams and Harborne (1977a)

## Gramineae

(93% of 274 species from 121 genera) Harborne and Williams (1976); Murray and Williams (1976); (18 sp.) Kaneta and Sugiyama (1973)

*Avena sativa* Chopin *et al.* (1977a); Effertz and Weissenböck (1980); Nabeta *et al.* (1977); Plessner and Weissenböck (1977); Popovici and Weissenböck (1977); Popovici *et al.* (1977); Weissenböck and Schneider (1974); Weissenböck and Effertz (1974); Weissenböck *et al.* (1976); Weissenböck and Sachs (1977); Weissenböck *et al.* (1978)

*Briza (media)* Casteldine and Harborne (1976); Chari *et al.* (1980)

*Eleusine* (9) Hilu *et al.* (1978)

*Hordeum vulgare* Blume and McClure (1978); Carlin and McClure (1973); Saunders and McClure (1976)

*Phragmites* (1) Nawwar *et al.* (1980); Jay and Viricel (1980)

*Saccharum* (120) Williams *et al.* (1974)

*Zea mays* Saunders and McClure (1976); Elliger *et al.* (1980)

## Iridaceae

*Crocus* (1) Sergeeva (1977)

*Fosteria* (1) Ballard and Cruden (1978)

*Iris* (2) Arisawa *et al.* (1973); Blinova *et al.* (1977)

*Rigidella* (4) Ballard and Cruden (1978)

*Sessilanthura* (3) Ballard and Cruden (1978)

## Juncaceae

*Prionium* (1) Williams and Harborne (1975)

## Lemnaceae

*Spirodela* (2) Wallace (1975); Saunders and McClure (1976)

## Liliaceae

*Asphodelus* (1) Abdel-Gawad and Raynaud (1974)

*Nartheceum* (1) Williams (1975)

*Paradisica* (1) Williams (1975)

*Polygonatum* (2) Chopin *et al.* (1977b); Najjar *et al.* (1978); Morita *et al.* (1976)

*Ruscus* (1) El Alfy and Paris (1975)

*Tulipa* (1) Budzianowski and Skrzypczakowa (1978)

*Urginea* (1) Fernandez *et al.* (1975); Vega (1976); Williams (1975)

## Marantaceae

*Calathea* (1) Williams and Harborne (1977b)

*Ctenanthe* (2) Williams and Harborne (1977b)

*Monotagma* (1) Williams and Harborne (1977b)

*Sarcophrynium* (1) Williams and Harborne (1977b)

*Stromanthe* (1) Williams and Harborne (1977b)

## Orchidaceae (52 genera) Williams (1979)

Palmae Harborne *et al.* (1974)



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**Table 8.1** (*Contd.*)

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### Piperaceae

*Piper* (1) Tillequin *et al.* (1978)

### Xyridaceae

*Xyris* (1) Linard *et al.* (1976)

### Zingiberaceae

*Costus* (7) Williams and Harborne (1977b)

### DICOTYLEDONEAE

#### Acanthaceae

*Ecbolium* (1) Nair *et al.* (1975a)

#### Amaranthaceae

*Achyranthes* (1) Burret (1980)

*Aerva* (1) Garg *et al.* (1980)

*Alternanthera* (1) Richardson (1978)

*Amaranthus* (2) Richardson (1978)

*Deeringia* (1) Richardson (1978)

#### Asclepiadaceae

*Hoya* (4) Niemann *et al.* (1979); Niemann (1980a,b)

#### Basellaceae

*Basella* (2) Richardson (1978); Burret (1980)

*Boussingaultia* (1) Burret (1980)

#### Cannabinaceae

*Cannabis* (1) Paris and Paris (1973); Paris *et al.* (1976); Segelman *et al.* (1978)

#### Caprifoliaceae

*Viburnum* (1) Saunders and McClure (1976)

#### Caryophyllaceae

*Arenaria* (6) Darmograi (1979)

*Cerastium* (12) Richardson (1978); Darmograi (1979); Dubois (1980); Dubois *et al.* (1980)

*Coronaria* (1) Darmograi (1976)

*Dianthus* (3) Boguslavskaya and Beletskii (1978); Seraya *et al.* (1978); Richardson (1978)

*Lychnis* (5) Richardson (1978); Darmograi (1976)

*Melandrium album* Brederode and Nigtevecht (1972a,b, 1973, 1974a,b,c)

= *Silene alba*, *Silene dioica* Zykova and Pivnenko (1975); Zykova *et al.* (1976); Kamsteeg *et al.* (1976); Besson *et al.* (1979a); Wagner *et al.* (1979); Heinsbroek *et al.* (1979, 1980); Brederode *et al.* (1979, 1980)

*Silene* spp. (47) Richardson (1978); Zemtsova *et al.* (1975); Zemtsova and Dzhumyrko (1976); Darmograi (1976, 1977); Chopin *et al.* (1974); Galle (1974)

*Stellaria* (3) Richardson (1978); Zoll and Nouvel (1974); Ferreres de Arce (1977)

*Spergularia* (1) Richardson (1978); Bouillant *et al.* (1979)

*Vaccaria* (1) Baeva *et al.* (1974)

other genera (10) Richardson (1978)

#### Chenopodiaceae

*Beta* (2) Richardson (1978); Burret (1980)

*Chenopodium* (2) Richardson (1978)

#### Commelinaceae

*Gibasis schiedeana* (2) Del Pero de Martinez and Swain (1976, 1977)

#### Compositae

*Achillea* (38) Valant (1978); Valant *et al.* (1978, 1980)

*Ajania* sp. Chumbalov and Zhubaeva (1976)

*Atractylis* (1) Raynaud and Dombris (1978)

- Carlina* (4) Raynaud and Rasolojaona (1976, 1978, 1979); Dombriš and Raynaud (1977); Besson *et al.* (1979b); Rasolojaona and Raynaud (1979)
- Catananche* (1) Proliac and Raynaud (1977)
- Centaurea* (1) Kamanzi and Raynaud (1976)
- Flourensia* (1) Dillon *et al.* (1976)
- Hazardia* (12) Clark and Mabry (1978)
- Helenium* sp. Bierner (1973)
- Liatris* (5) Wagner *et al.* (1973)
- Otospermum* sp. Greger (1977)
- Coridaceae
- Coris* (1) Frezet *et al.* (1975)
- Cucurbitaceae
- Cucumis* (1) Monties *et al.* (1976)
- Cucurbita* (1) Saunders and McClure (1976)
- Didiereaceae
- Alluaudia* (4) Richardson (1978); Rabesa (1980)
- Didierea* (2) Rabesa (1980)
- Dipsacaceae
- Cephalaria* (1) Galle (1974)
- Knautia* (1) Zemtsova and Bandyukova (1974)
- Gentianaceae
- Gentiana* (31) Lebreton and Dangy-Caye (1973); Bellmann and Jacot-Guillarmod (1973); Hostettmann *et al.* (1973, 1975); Kaldas *et al.* (1974); Hostettmann and Jacot-Guillarmod (1974a,b, 1975, 1977); Kaldas *et al.* (1975); Jacot-Guillarmod *et al.* (1975); Luong Minh Duc *et al.* (1976, 1980); Marston *et al.* (1976); Goetz *et al.* (1976a,b); Luong Minh Duc and Jacot-Guillarmod (1977); Goetz and Jacot-Guillarmod (1977a,b, 1978); Chulia and Debelmas (1977); Hostettmann-Kaldas and Jacot-Guillarmod (1978); Chulia *et al.* (1978); Burret *et al.* (1978, 1979); Zoring *et al.* (1980)
- Hoppea* (1) Ghosal *et al.* (1978)
- Swertia* (2) Miana (1973); Hostettmann and Jacot-Guillarmod (1976)
- Geraniaceae
- Geranium* (2) Boutard and Lebreton (1975); Gonnet (1980) (*G. sylvaticum*)
- Labiatae (28 genera) Weightman (1979)
- Ajuga* (4) Salehian *et al.* (1973); Weightman (1979)
- Phlomis* (1) Vavilova and Gella (1973a,b)
- Teucrium* (1) Raynaud and Chouikha (1976)
- Leguminosae
- Acacia* Thieme and Khogali (1974, 1975)
- Cladrastis* (2) Ohashi *et al.* (1976, 1977a, 1980)
- Dalbergia* (2) Chawla *et al.* (1974, 1975, 1976); Parthasarathy *et al.* (1974, 1976)
- Desmodium* (1) Chernobrovaya (1973)
- Eysenhardtia* (1) Vita-Finzi *et al.* (1980)
- Lespedeza* (2) Linard *et al.* (1978); Numata *et al.* (1979, 1980)
- Lupinus* (2) Laman and Volynets (1974); Nicholls and Bohm (1979); Zapesochneya and Laman (1977)
- Melilotus* (1) Specht *et al.* (1976)
- Onobrychis* Moniava and Kemertelidze (1976)
- Pterocarpus* (1) Gupta *et al.* (1981)
- Pueraria* (1) Inoue and Fujita (1974, 1977)
- Rynchosia* (2) Besson *et al.* (1977); Adinarayana *et al.* (1980)
- Sarothamnus* (1) Brum-Bousquet *et al.* (1977)
- Securigera* (1) Coronilla (1) Jay *et al.* (1980)
- Trigonella* (1) Sood *et al.* (1976)

**Table 8.1** (Contd.)

## Molluginaceae

*Mollugo* (3) Chopin *et al.* (1978, 1979); Richardson (1978)

## Nyctaginaceae

*Mirabilis* (3) Richardson (1978)

## Ochnaceae

*Brackenridgea* (1) Bombardelli *et al.* (1974)*Ochna* (1) Nair *et al.* (1975b)

## Onagraceae

*Circaea* (3) Boufford *et al.* (1978)

## Oxalidaceae

*Oxalis* (1) Tschesche and Struckmeyer (1976)

## Passifloraceae

*Passiflora* Loehdefink (1976); Quercia *et al.* (1978); Ulubelen and Mabry (1980)

## Phytolaccaceae

*Trichostigma* (1) Richardson (1978)

## Plumbaginaceae

*Limonium* Asen *et al.* (1973)

## Polemoniaceae

*Cantua* (1) Smith *et al.* (1977)*Gilia* (3) Smith *et al.* (1977)*Langloisia* (1) Smith *et al.* (1977)*Leptodactylon* (3) Smith *et al.* (1977)*Linanthus* (16) Smith *et al.* (1977)*Loselia* (3) Smith *et al.* (1977)*Microsteris* (1) Smith *et al.* (1977)*Phlox* (19) Levy and Levin (1974); Levy (1976); Smith *et al.* (1977); Levy and Fujii (1978)

## Polygonaceae

*Fagopyrum* (1) Saunders and McClure (1976)*Polygonum* (2) Krause (1976a,b); Gonnet (1980) (*P. bistorta*)

## Portulacaceae

*Calandrinia* (2) Richardson (1978)*Montia* (1) Richardson (1978)

## Ranunculaceae

*Adonis* (4) Komissarenko *et al.* (1973a,b); Ponomarenko *et al.* (1974); Galle (1974); Wagner *et al.* (1975)*Clematis* (6) Dennis and Bierner (1980)

## Rhamnaceae

*Zizyphus* (1) Woo *et al.* (1979)

## Rosaceae

*Crataegus* (2) Nikolov and Litvinenko (1973); Nikolov (1973, 1974, 1975); Nikolov *et al.* (1973, 1976); Nikolov and Vodenicharov (1975)

## Rubiaceae

*Canephora* (1) Paris and Debray (1973)

## Rutaceae

*Almeidea* (1) Jay *et al.* (1979)*Citrus* (2) Montoro *et al.* (1974); Tomas *et al.* (1975)*Fortunella* (1) Horowitz *et al.* (1974)

## Sterculiaceae

*Sterculia* (1) Nair *et al.* (1976)*Theobroma* (1) Jalal and Collin (1977)

## Thymelaeaceae

*Thymelaea* (1) Nawwar *et al.* (1977)

## Ulmaceae

*Zelkova* (1) Hayashi (1980)

## Umbelliferae

*Astrantia* (1) Hiller *et al.* (1975)*Chaerophyllum aureum* Gonnet (1980)*Myrris odorata* Gonnet (1980)

## Verbenaceae

*Vitex* (1) Subramanian and Misra (1979)

## Zygophyllaceae

*Larrea* (1) Sakakibara *et al.* (1977)

(Nikolov), *Melandrium album* (= *Silene alba*) (Brederode and Nigtevecht), for physiological, pharmacological and genetical purposes respectively. The occurrence of C-glycosylflavonoids in chloroplasts of various plants has been unambiguously demonstrated by Monties (1969), Weissenböck and Schneider (1974) and Saunders and McClure (1976). The evolutionary significance of distribution patterns of C-glycosylflavones in the angiosperms has been discussed by Harborne (1977).

Major advances in the most difficult problem in C-glycosylflavonoid chemistry, i.e. identification of the glycosyl residue, have involved the use of permethyl ethers of synthetic C-glycosylflavonoids in mass spectrometry (Bouillant *et al.*, 1975, 1978) and the application of  $^{13}\text{C}$ -NMR spectrometry to natural C-glycosylflavonoids of known structure (Chari *et al.*, 1978). Because it can be used with very small amounts of substance, mass spectrometry of permethyl ethers is the method of choice in the study of the nature (hexose, pentose or deoxyhexose) of the C-linked sugars in C-glycosylflavones which remain by far the most widespread group of C-glycosylflavonoids. It is the only method which identifies the nature of the 6-C-linked sugar in 6,8-di-C-glycosylflavones, owing to the striking fragmentation pattern difference between permethylated 6-C-glycosylflavones and 8-C-glycosylflavones and to the fact that the  $^{13}\text{C}$ -NMR signals of a carbon-linked sugar residue are not significantly affected by the 6 or 8 position of the latter in C-glycosylflavones. Its systematic use has disclosed that difficultly separated mixtures of di-C-hexosyl- and C-hexosyl-C-pentosylflavones often co-occur in plant extracts. In such cases the characteristic  $R_F$  differences observed on TLC between isomeric permethylated C-glucosyl- and C-galactosyl-flavones on the one hand, permethylated C-xylosyl- and C-arabinosyl-flavones on the other, has often provided useful separations on the micro-scale.

Moreover, the mass spectrometry of permethyl ethers has solved the difficult problem of locating the position of the O-linked sugar in natural 6-C-glucosylflavone x''-O-glycosides (Bouillant *et al.*, 1979a), following the synthesis of such compounds by C-substitution of acacetin with the acetobromo derivatives of neohesperidose, runggiose, cellobiose and rutinose (Besset, 1977;

Bouillant *et al.*, 1980). However,  $^{13}\text{C}$ -NMR spectrometry is of more general applicability, since the same problem can be solved in 8- as well as in 6-*C*-glycosylflavone  $x''$ -*O*-glycosides. Acyl groups are generally lost during permethylation and their presence must be detected beforehand by alkaline hydrolysis of the natural product under study. Again, with  $^{13}\text{C}$ -NMR spectrometry it is possible to identify the acyl groups and their position in the intact molecule. The differentiation by circular dichroism between 6- and 8-*C*-glycosylflavones has been extended to *C*-arabinosyl-, *C*-xylosyl- and *C*-galactosylflavones, whereas *C*-rhamnosylflavones show a different behaviour (Gaffield *et al.*, 1978).

The introduction of the *C*-glucosyl group at the chalcone stage in the biosynthesis of the *C*-glycosylisoflavone puerarin in *Pueraria* roots was suggested by Inoue and Fujita (1974, 1977). The same authors have shown that *C*-glucosylflavones are biosynthesized in *Swertia japonica* via *C*-glucosylflavanones, and that 3'-hydroxylation occurs prior to *C*-glycosylation (Fujita and Inoue, 1979).

Total syntheses of 7,4'-di-*O*-methylbayin (1975), 7,4'-di-*O*-methylpuerarin (1978) and 5,7,4'-tri-*O*-methylvitexin (1979) have been described by Eade and co-workers. The high-yield *C*-glucosylation of 1,3,5-trimethoxybenzene opens the way to the synthesis of almost all types of 8-*C*-glycosyl-5,7-di-*O*-methylflavonoids. The low-yield *C*-glycosylation of 5,7-dihydroxyflavones has still been used in the authors' laboratory for specific purposes (*C*-arabinofuranosylation and *C*-diglycosylation of acacetin, di-*C*-glycosylation of apigenin). HPLC has been recently applied to *C*-glycosylflavonoid analysis (Niemann and Brederode, 1978; Strack *et al.*, 1979). Flavonoid *O*- and *C*-glycosides have been reviewed by Wagner (1974, 1977).

## 8.2 NATURALLY OCCURRING C-GLYCOSYLFLAVONOIDS

Natural *C*-glycosylflavonoids can be divided in two groups: the unhydrolysable 'aglycones' (mono- and di-*C*-glycosylflavonoids) and their hydrolysable derivatives (*O*-glycosides and *O*-acyl derivatives). Mono-*C*-glycosylflavonoids are listed in Table 8.2, di-*C*-glycosylflavonoids in Table 8.3, *C*-glycosylflavonoid *O*-glycosides in Table 8.4 and *O*-acyl-*C*-glycosylflavonoids in Table 8.5. New structures are indicated with an asterisk.

### 8.2.1 Mono-*C*-glycosylflavonoids

Eight types of mono-*C*-glycosylflavonoids are now well defined: *C*-glycosylflavones, *C*-glycosylflavanols, *C*-glycosylflavanones, *C*-glycosylflavanonols, *C*-glycosylchalcones, *C*-glycosyldihydrochalcones, *C*-glycosylisoflavones and *C*-glycosylisoflavanones. *C*-Glycosylflavones remain by far the most important group. All these flavonoids have a phloroglucinol A ring with the following exceptions: bayin (a flavone); aervanone and palodulcin B (two flavanones);

Table 8.2 Naturally occurring mono-C-glycosylflavonoids

| Compounds                                                                       | Sources                                                 | References                                 |
|---------------------------------------------------------------------------------|---------------------------------------------------------|--------------------------------------------|
| <b>C-GLYCOSYLFLAVONES</b>                                                       |                                                         |                                            |
| Bayin<br>(7,4'-di-OH 8-Glc)                                                     | <i>Cladrastis platycarpa</i> (Leguminosae)              | Ohashi <i>et al.</i> (1976)                |
| Isovitexin (saponaretin)<br>(5,7,4'-tri-OH 6-Glc)                               | Many sources                                            | Horowitz and Gentili (1964) (structure)    |
| Vitexin<br>(5,7,4'-tri-OH 8-Glc)                                                | Many sources                                            | Horowitz and Gentili (1964) (structure)    |
| *8-C- $\beta$ -D-Galactopyranosylapigenin                                       | <i>Briza media</i> (Gramineae)                          | Castledine and Harborne (1976)             |
| (5,7,4'-tri-OH 8-Gal)                                                           | <i>Polygonatum multiflorum</i> (Liliaceae)              | Chopin <i>et al.</i> (1977b)               |
| 6-C- $\beta$ -D-Xylopyranosylapigenin<br>(5,7,4'-tri-OH 6-Xyl) (Ceratvensin)    | <i>Cerastium arvense</i> (Caryophyllaceae)              | Dubois (1980); Dubois <i>et al.</i> (1980) |
| *Isomollupentin<br>(5,7,4'-tri-OH 6-Ara)                                        | <i>Spergularia rubra</i> (Caryophyllaceae)              | Bouillant <i>et al.</i> (1979b)            |
| *Mollupentin<br>(5,7,4'-tri-OH 8-Ara)                                           | <i>Mollugo pentaphylla</i> (Molluginaceae)              | Chopin <i>et al.</i> (1979)                |
| *3'-Deoxyderhamnosylmaysin<br>[5,7,4'-tri-OH 6-(6-deoxy-xyl)-lo-hexos-4-ulose]] | <i>Zea mays</i> (Gramineae)                             | Elliger <i>et al.</i> (1980)               |
| Swertisin<br>(5,4'-di-OH 7-OMe 6-Glc)                                           | Many sources                                            | Komatsu and Tomimori (1966) (structure)    |
| Isoswertisin<br>(5,4'-di-OH 7-OMe 8-Glc)                                        | <i>Mollugo distica</i> (Molluginaceae)                  | Chopin <i>et al.</i> (1978)                |
| *Isomolludistin<br>(5,4'-di-OH 7-OMe 6-Ara)                                     | <i>Gnetum gnemon</i> (Gnetales)                         | Wallace and Morris (1978d)                 |
| *Molludistin<br>(5,4'-di-OH 7-OMe 8-Ara)                                        | <i>Rigidella, Sessilanthera, Fosteria</i> (Iridaceae)   | Ballard and Cruden (1978)                  |
| *Isocytiside<br>(5,7-di-OH 4'-OMe 6-Glc)                                        | <i>Asterostigma reidelianum</i> (Araceae) (as 2"-O-Glc) | Markham and Williams (1980)                |
|                                                                                 | <i>Mollugo distica</i> (Molluginaceae)                  | Chopin <i>et al.</i> (1978)                |
|                                                                                 | <i>Fortunella margarita</i> (Rutaceae) (as 2"-O-Rha)    | Horowitz <i>et al.</i> (1974)              |
|                                                                                 | <i>Gentiana pyrenaica</i> (Gentianaceae) (as 7-O-Glc)   | Marston <i>et al.</i> (1976)               |
|                                                                                 | <i>Securigera coronilla</i> (Leguminosae) (as 2"-O-Glc) | Jay <i>et al.</i> (1980)                   |

Table 8.2 (Contd.)

| Compounds                                                                                 | Sources                                                  | References                               |
|-------------------------------------------------------------------------------------------|----------------------------------------------------------|------------------------------------------|
| Cytisoidide<br>(5,7-di-OH 4'-OMe 8-Glc)                                                   | <i>Lupinus arboreus</i> (Leguminosae)                    | Nicholls and Bohm (1979)                 |
| Embigenin<br>(5-OH 7,4'-di-OMe 6-Glc)                                                     | <i>Iris japonica</i> (Iridaceae) (as 2"-O-Rha)           | Arisawa <i>et al.</i> (1973)             |
| *7,4'-di-O-methylisomollupentin<br>(5-OH 7,4'-di-OMe 6-Ara)                               | <i>Asterostigma reidelianum</i> (Araceae)                | Markham and Williams (1980)              |
| Iso-orientin<br>(5,7,3',4'-tetra-OH 6-Glc)                                                | Many sources                                             | Koeppen (1964) (structure)               |
| Orientin<br>(5,7,3',4'-tetra-OH 8-Glc)                                                    | Many sources                                             | Koeppen (1964) (structure)               |
| 6-C- $\beta$ -D-Xylopyranosyl-luteolin<br>(5,7,3',4'-tetra-OH 6-Xyl)                      | <i>Phlox drummondii</i> (Polemoniaceae)<br>(as 2"-O-Rha) | Mabry <i>et al.</i> (1971)               |
| *Derhamnosylmaysin<br>[5,7,3',4'-tetra-OH 6-(6-deoxy-xyllo-hexos-4-ulosyl)]               | <i>Zea mays</i> (Gramineae) (as 2"-O-Rha)                | Elliger <i>et al.</i> (1980)             |
| *Isoswertiajaponin<br>(5,3',4'-tri-OH 7-OMe 8-Glc)                                        | <i>Gnetum gnemon</i> (Gnetaceae)                         | Wallace and Morris (1978)                |
| Swertiajaponin<br>(5,3',4'-tri-OH 7-OMe 6-Glc)                                            | <i>Phragmites australis</i> (Gramineae)                  | Nawwar <i>et al.</i> (1980)              |
| Isoscoparin<br>(5,7,4'-tri-OH 3'-OMe 6-Glc)                                               | Many sources                                             | Komatsu <i>et al.</i> (1967) (structure) |
| Scoparin<br>(5,7,4'-tri-OH 3'-OMe 8-Glc)                                                  | Many sources                                             | Chopin <i>et al.</i> (1968) (structure)  |
| *3'-O-Methyl-derhamnosylmaysin<br>[5,7,4'-tri-OH 3'-OMe 6-(6-deoxy-xyllo-hexos-4-ulosyl)] | <i>Zea mays</i> (Gramineae) (as 2"-O-Rha)                | Chopin <i>et al.</i> (1968) (structure)  |
| 6-C- $\beta$ -D-Glucopyranosyldiosmetin<br>(5,7,3'-tri-OH 4'-OMe 6-Glc)                   | <i>Citrus limon</i> (Rutaceae)                           | Elliger <i>et al.</i> (1980)             |
| 8-C- $\beta$ -D-Glucopyranosyldiosmetin<br>(5,7,3'-tri-OH 4'-OMe 8-Glc)                   | <i>Lupinus arboreus</i> (Leguminosae)                    | Gentili and Horowitz (1968)              |
| *7,3'-di-O-Methyliso-orientin                                                             | <i>Achillea cretica</i> (Compositae)                     | Nicholls and Bohm (1979)                 |
|                                                                                           |                                                          | Valant <i>et al.</i> (1980)              |

|                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                   |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (5,4'-di-OH 7,3'-di-OMe 6-Glc)<br>7,3',4'-Tri- <i>O</i> -methylo-orientin<br>(5-OH 7,3',4'-tri-OMe 6-Glc)<br>*Isoaaffnetin<br>(5,7,3',4',5'-penta-OH 6-Glc)<br>*Affnetin<br>(5,7,3',4',5'-penta-OH 8-Glc)<br>*Isopyrenin<br>(5,7,4'-tri-OH 3',5'-di-OMe 6-Glc)<br>*6- <i>C</i> -Glucosyl-5,7-dihydroxy-8,3',4',5'-<br>tetramethoxyflavone | <i>Phragmites australis</i> (Gramineae)<br><i>Linum maritimum</i> (Linaceae) (as 2'- <i>O</i> -Rha)<br><br><i>Polygonum affine</i> (Polygonaceae)<br><i>Trichomanes venosum</i> (Hymenophyllaceae)<br><i>Trichomanes venosum</i> (Hymenophyllaceae)<br><br><i>Gentiana pyrenaica</i> (Gentianaceae)<br><br><i>Vitex negundo</i> (Verbenaceae) (as 5- <i>O</i> -Rha) | Jay and Viricel (1980)<br>Wagner <i>et al.</i> (1972)<br><br>Krause (1976a,b)<br>Markham and Wallace (1980)<br>Markham and Wallace (1980)<br><br>Marston <i>et al.</i> (1976)<br><br>Subramanian and Misra (1979) |
| C-GLYCOSYLFLAVONOLS<br>*6- <i>C</i> -Glucosylkaempferol<br>(3,5,7,4'-tetra-OH 6-Glc)<br>Keyakinin<br>(3,5,4'-tri-OH 7-OMe 6-Glc)<br>*6- <i>C</i> -Glucosylquercetin<br>(3,5,7,3',4'-penta-OH 6-Glc)<br>Keyakinin B<br>(3,5,3',4'-tetra-OH 7-OMe 6-Glc)                                                                                    | <i>Zelkova serrata</i> (Ulmaceae)<br><br><i>Zelkova serrata</i> (Ulmaceae)<br><br><i>Zelkova serrata</i> (Ulmaceae)<br><br><i>Zelkova serrata</i> (Ulmaceae)                                                                                                                                                                                                        | Hayashi (1980)<br><br>Funaoka (1956)<br><br>Hayashi (1980)<br><br>Hillis and Horn (1966)                                                                                                                          |
| C-GLYCOSYLFLAVANONES<br>*Aervanone<br>(7,4'-di-OH 8-Gal)<br>*Palodulcine B<br>(7,3',4'-tri-OH 8-Gal)<br>Hemiphloin<br>(5,7,4'-tri-OH 6-Glc)<br>Isohemiphloin<br>(5,7,4'-tri-OH 8-Glc)                                                                                                                                                     | <i>Aerva persica</i> (Amaranthaceae)<br><i>Eysenhardtia polystachya</i> (Leguminosae)<br><i>Eysenhardtia polystachya</i> (Leguminosae)<br><br><i>Tulipa gesneriana</i> (Liliaceae)<br><br><i>Eucalyptus hemiphloia</i> (Myrtaceae)                                                                                                                                  | Garg <i>et al.</i> (1980)<br>Vita-Finzi <i>et al.</i> (1980)<br>Vita-Finzi <i>et al.</i> (1980)<br><br>Budzianowski and Skrzypczakowa (1978)<br><br>Hillis and Horn (1965) (structure)                            |
| C-GLYCOSYLFLAVANONOLS<br>*6- <i>C</i> -Glucosyldihydrokaempferol<br>(3,5,7,4'-tetra-OH 6-Glc)                                                                                                                                                                                                                                             | <i>Zelkova serrata</i> (Ulmaceae)                                                                                                                                                                                                                                                                                                                                   | Hayashi (1980)                                                                                                                                                                                                    |



Table 8.2 (Contd.)

| Compounds                                                            | Sources                                                        | References                                |
|----------------------------------------------------------------------|----------------------------------------------------------------|-------------------------------------------|
| <b>Keyakinol</b><br>(3,5,4'-tri-OH 7-OMe 6-Glc)                      | <i>Zelkova serrata</i> (Ulmaceae)                              | Funaoka (1956)                            |
| <b>*6-C-Glucosyldihydroquercetin</b><br>(3,5,7,3',4'-penta-OH 6-Glc) | <i>Zelkova serrata</i> (Ulmaceae)                              | Hayashi (1980)                            |
| <b>C-GLYCOSYLCHALCONES</b>                                           |                                                                |                                           |
| <b>*3'-C-Glucosylisoliquiritigenin</b><br>(2',4',4-tri-OH 3'-Glc)    | <i>Cladrastis platycarpa</i> (Leguminosae)                     | Ohashi <i>et al.</i> (1977a)              |
| <b>C-GLYCOSYLDIHYDROCHALCONES</b>                                    |                                                                |                                           |
| <b>Nothofagin</b><br>(2',4',6',4-tetra-OH C-Gly)                     | <i>Nothofagus fusca</i> (Fagaceae)                             | Hillis and Inoue (1967)                   |
| <b>Konnarin</b><br>(2',4',6',3,4-penta-OH C-Gly)                     | <i>Nothofagus fusca</i> (Fagaceae)                             | Hillis and Inoue (1967)                   |
| <b>Aspalathin</b><br>(2',4',6',3,4-penta-OH 3'-Glc)                  | <i>Aspalathus linearis</i> ( <i>acuminatus</i> ) (Leguminosae) | Koeppen and Roux (1965)                   |
| <b>C-GLYCOSYLISOFLAVONES</b>                                         |                                                                |                                           |
| <b>Puerarin</b><br>(7,4'-di-OH 8-Glc)                                | <i>Pueraria</i> sp. (Leguminosae)                              | Murakami <i>et al.</i> (1960) (structure) |
| <b>*8-C-Glucosylgenistein</b><br>(5,7,4'-tri-OH 8-Glc)               | <i>Lupinus luteus</i> (Leguminosae)                            | Zapesochnya and Laman (1977)              |
| <b>*8-C-Glucosylprunetin</b><br>(5,4'-di-OH 7-OMe 8-Glc)             | <i>Dalbergia paniculata</i> (Leguminosae)                      | Parthasarathy <i>et al.</i> (1974, 1976)  |
| <b>*Volubiline</b><br>(5-OH 7,4'-di-OMe 8-Rha)                       | <i>Dalbergia volubilis</i> (Leguminosae)                       | Chawla <i>et al.</i> (1974)               |
| <b>*Isovolubiline</b><br>(5-OH 7,4'-di-OMe 6-Rha)                    | <i>Dalbergia volubilis</i> (Leguminosae)                       | Chawla <i>et al.</i> (1975)               |
| <b>*8-C-Glucosylorobol</b><br>(5,7,3',4'-tetra-OH 8-Glc)             | <i>Lupinus luteus</i> (Leguminosae)                            | Zapesochnya and Laman (1977)              |
| <b>*Volubiline</b><br>(5,7-di-OH 6,4'-di-OMe 8-Glc)                  | <i>Dalbergia volubilis</i> (Leguminosae)                       | Chawla <i>et al.</i> (1976)               |

Dalpanitin  
(5,7,4'-tri-OH 3'-OMe 8-Glc)  
C-GLYCOSYLISOFLAVANONES

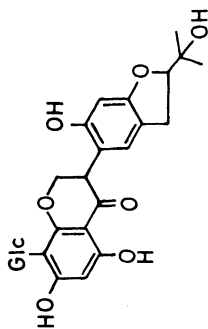
*Dalbergia paniculata* (Leguminosae)

Adinarayana and Rao (1972)

Adinarayana and Rao (1975)

*Dalbergia paniculata* (Leguminosae)

\*Dalpanin



\*6-C-Glucosyldalbergiodin  
(5,7,2',4'-tetra-OH 6-Glc)

*Pterocarpus macrocarpus* (Leguminosae)

Gupta (1981)

\* Indicates their discovery as new compounds during the period 1975-1980.

Table 8.3 Naturally occurring di-C-glycosylflavonoids

| Compounds                                                                     | Sources                                                                                                                                                             | References                                                                                                                |
|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| <b>DI-C-GLYCOSYLFLAVONES</b>                                                  |                                                                                                                                                                     |                                                                                                                           |
| Vicenin-2<br>(5,7,4'-tri-OH 6,8-di Glc)                                       | Many sources                                                                                                                                                        | Chopin <i>et al.</i> (1969) (structure)                                                                                   |
| 6,8-Di-C-hexosylapigenin<br>(5,7,4'-tri-OH 6,8-di-Hex)                        | <i>Plagiochila asplenoides</i> (Hepaticae)<br><i>Hedwigia ciliata</i> (Bryophyta)                                                                                   | Mues and Zinsmeister (1976)<br>Österdahl (1979a,b)                                                                        |
| Vicenin-3<br>(5,7,4'-tri-OH 6-Glc-8-Xyl)                                      | Many sources                                                                                                                                                        | Bouillant and Chopin (1971) (structure)                                                                                   |
| Vicenin-1<br>(5,7,4'-tri-OH 6-Xyl-8-Glc)                                      | <i>Cladrastis platycarpa</i> (Leguminosae)                                                                                                                          | Ohashi <i>et al.</i> (1977) (NMR)                                                                                         |
| Violanthin<br>5,7,4'-tri-OH 6-Glc-8-Rha                                       | Gramineae spp.<br><i>Eleusine</i> sp. (Gramineae)<br><i>Angiopteris evecta</i> (Marattiales)<br><i>Angiopteris evecta</i> (Marattiales)                             | Kaneta and Sugiyama (1973)<br>Hilu <i>et al.</i> (1978)<br>Wallace <i>et al.</i> (1979b)<br>Wallace <i>et al.</i> (1979b) |
| *Isoviolanthin<br>(5,7,4'-tri-OH 6-Rha-8-Glc)                                 | <i>Silene schafta</i> (Caryophyllaceae)                                                                                                                             | Biol and Chopin (1972) (structure)                                                                                        |
| *Schaftoside<br>(5,7,4'-tri-OH 6-Glc-8-Ara)                                   | Many sources                                                                                                                                                        | Chopin <i>et al.</i> (1974) (structure)                                                                                   |
| *Isoschaftoside<br>(5,7,4'-tri-OH 6-Ara-8-Glc)                                | Many sources                                                                                                                                                        | Dillon <i>et al.</i> (1976)                                                                                               |
| *Neoschaftoside<br>(5,7,4'-tri-OH 6-Glc-8-Ara)                                | <i>Flourensia cernua</i> (Compositae)<br><i>Catananche cerulea</i> (Compositae)                                                                                     | Proliac <i>et al.</i> (1973)                                                                                              |
| *Neoisoschaftoside<br>(5,7,4'-tri-OH 6-Ara-8-Glc)                             | Many sources                                                                                                                                                        | Österdahl (1979a,c)                                                                                                       |
| *Isocorymboside (compound S)<br>(5,7,4'-tri-OH 6-Gal-8-Ara)                   | <i>Mnium undulatum</i> (Bryophyta)                                                                                                                                  | Chopin <i>et al.</i> (1977b)                                                                                              |
| *Corymboside<br>(5,7,4'-tri-OH 6-Ara-8-Gal)                                   | <i>Polygonatum multiflorum</i> (Liliaceae)                                                                                                                          | Besson <i>et al.</i> (1979b)                                                                                              |
| *6,8-Di-C- $\alpha$ -L-arabinopyranosylapigenin<br>(5,7,4'-tri-OH 6,8-di-Ara) | <i>Carlina corymbosa</i> (Compositae)<br><i>Melilotus alba</i> (Leguminosae)<br><i>Hymenophyton leptopodium</i> (Hepaticae)<br><i>Angiopteris</i> sp. (Marattiales) | Specht <i>et al.</i> (1976)<br>Markham <i>et al.</i> (1976b)<br>Wallace <i>et al.</i> (1981)                              |

- \*6-C-Arabinosyl-8-C-pentosylapigenins  
(5,7,4'-tri-OH 6-Ara-8-Pen)
- \*Almeidein  
(5,4'-di-OH 7-OMe 6,8-di-Ara)
- \*6-C-Pentosyl-8-C-hexosylacetin  
(5,7-di-OH 4'-OMe 6-Pen-8-Hex)
- \*7,4'-Di-*O*-methyl-6,8-di-C- $\alpha$ -L-arabinopyranosylapigenin  
(5-OH 7,4'-di-OMe 6,8-di-Ara)
- Lucenin-2  
(5,7,3',4'-tetra-OH 6,8-di Glc)
- Lucenin-3  
(5,7,3',4'-tetra-OH 6-Glc-8-Xyl)
- Lucenin-1  
(5,7,3',4'-tetra-OH 6-Xyl-8-Glc)
- \*Carlinoside  
(5,7,3',4'-tetra-OH 6-Glc-8-Ara)
- \*Neocarlinoside  
(5,7,3',4'-tetra-OH 6-Glc-8-Ara)
- \*6-C-Arabinosyl-8-C-pentosyl-luteolin  
(5,7,3',4'-tetra-OH 6-Ara-8-Pen)
- \*6,8-Di-C- $\beta$ -D-glucopyranosylchrysoeriol  
(5,7,4'-tri-OH 3'-OMe 6,8-di-Glc)
- \*6-C-Arabinosyl-8-C-hexosylchrysoeriol  
(5,7,4'-tri-OH 3'-OMe 6-Ara-8-Hex)
- Hymenophyton leptopodum* (Hepaticae)
- Takakia lepidiozoides* (Hepaticae)
- Mollugo pentaphylla* (Molluginaceae)
- Lespedeza cuneata* (Leguminosae)
- Apometzgeria pubescens* (Hepaticae)
- Almeidea guyanensis* (Rutaceae)
- Trigonella corniculata* (Leguminosae)
- Asterostigma reidelianum* (Araceae)
- Hedwigia ciliata* (Bryophyta)
- Spergularia rubra* (Caryophyllaceae)
- Many sources
- Many sources
- Many sources
- Carlina vulgaris* (Compositae)
- Catananche cerulea* (Compositae)
- Takakia lepidiozoides* (Hepaticae)
- Gibasis schiedeana* (Commelinaceae)
- Oryza sativa* (Gramineae)
- Oryza sativa* (Gramineae)
- Takakia lepidiozoides* (Hepaticae)
- Stellaria holostea* (Caryophyllaceae)
- Larrea tridentata* (Zygophyllaceae)
- Spergularia rubra* (Caryophyllaceae)
- Mnium undulatum* (Bryophyta)
- Markham *et al.* (1976b)
- Markham and Porter (1979)
- Chopin *et al.* (1979)
- Numata *et al.* (1979)
- Theodor *et al.* (1980)
- Jay *et al.* (1979)
- Bouillant *et al.* (1975) (MS)
- Markham and Williams (1980)
- Österdahl (1978) (structure)
- Bouillant *et al.* (1979) (structure)
- Bouillant and Chopin (1972) (structure)
- Bouillant and Chopin (1972) (structure)
- Raynaud and Rasolojaona (1976)
- Proliac *et al.* (1973, 1977)
- Markham and Porter (1979)
- Del Pero de Martinez and Swain (1976, 1977)
- Besson and Fukami (unpublished)
- Besson and Fukami (unpublished)
- Markham and Porter (1979)
- Zoll and Nouvel (1974)
- Sakakibara *et al.* (1977)
- Bouillant *et al.* (1979)
- Österdahl (1979a,c)

Table 8.3 (Contd.)

| Compounds                                    | Sources                                    | References                          |
|----------------------------------------------|--------------------------------------------|-------------------------------------|
| 6,8-Di-C-glycosyldiosmetin                   | <i>Citrus limon</i> (Rutaceae)             | Chopin <i>et al.</i> (1964)         |
| (5,7,3'-tri-OH 4'-OMe 6,8-di-Gly)            |                                            | Gentili and Horowitz (1968)         |
| *6,8-Di-C- $\beta$ -D-glucopyranosyltricitin | <i>Plagiochila asplenoides</i> (Hepaticae) | Mues and Zinsmeister (1976)         |
| (5,7,3',4',5'-penta-OH 6,8-di-Glc)           | <i>Apometzgeria pubescens</i> (Hepaticae)  | Theodor <i>et al.</i> (1980)        |
| *6,8-Di-C-hexopyranosyltricitin              | <i>Plagiochila asplenoides</i> (Hepaticae) | Mues and Zinsmeister (1976)         |
| (compound 4)                                 |                                            |                                     |
| *6-C-Hexopyranosyl-8-C-pentopyranosyl        | <i>Plagiochila asplenoides</i> (Hepaticae) | Mues and Zinsmeister (1976)         |
| tricitins (compounds 2 and 3)                | <i>Takakia lepidiozoides</i> (Hepaticae)   | Markham and Porter (1979)           |
| *6-C-Arabinopyranosyl-8-C-glucopyranosyl     | <i>Apometzgeria pubescens</i> (Hepaticae)  | Theodor <i>et al.</i> (1980, 1981a) |
| tricitin                                     |                                            |                                     |
| (5,7,3',4',5'-penta-OH 6-Ara 8-Glc)          |                                            |                                     |
| *6,8-Di-C-pentoseyltricitin                  | <i>Takakia lepidiozoides</i> (Hepaticae)   | Markham and Porter (1979)           |
| (5,7,3',4',5'-penta-OH 6,8-di-Pen)           |                                            |                                     |
| *6-C-Hexopyranosyl-8-C-pentopyranosyl        | <i>Plagiochila asplenoides</i> (Hepaticae) | Mues and Zinsmeister (1976)         |
| 3'-O-methyltricitin (compound 7)             |                                            |                                     |
| (5,7,4',5'-tetra-OH 3'-OMe 6-Hex 8-Pen)      |                                            |                                     |
| *6,8-Di-C-glucopyranosyltricitin             | <i>Apometzgeria pubescens</i> (Hepaticae)  | Theodor <i>et al.</i> (1980, 1981a) |
| (5,7,4'-tri-OH 3',5'-di-OMe 6,8-di-Glc)      |                                            |                                     |
| *6-C-glucopyranosyl 8-C-arabinopyranosyl     | <i>Apometzgeria pubescens</i> (Hepaticae)  | Theodor <i>et al.</i> (1980, 1981a) |
| tricin                                       |                                            |                                     |
| (5,7,4'-tri-OH 3',5'-di-OMe 6-Glc 8-Ara)     |                                            |                                     |
| *6-C-arabinopyranosyl-8-C-glucopyrano        | <i>Apometzgeria pubescens</i> (Hepaticae)  | Theodor <i>et al.</i> (1980, 1981a) |
| sylicitrin                                   |                                            |                                     |
| (5,7,4'-tri-OH 3',5'-di-OMe 6-Ara 8-Glc)     |                                            |                                     |
| *6-C-Xylosyl-8-C-hexosyltricin               | <i>Metzgeria leptoneura</i> (Hepaticae)    | Theodor <i>et al.</i> (1981b)       |
| (5,7,4'-tri-OH 3',5'-di-OMe 6-Xyl 8-Hex)     |                                            |                                     |
| *6,8-Di-C-arabinopyranosyltricin             | <i>Apometzgeria pubescens</i> (Hepaticae)  | Theodor <i>et al.</i> (1980, 1981a) |
| (5,7,4'-tri-OH 3',5'-di-OMe 6,8-di-Ara)      |                                            |                                     |
| *6-C-Hexosyl-8-C-pentosylapometzgerin        | <i>Apometzgeria pubescens</i> (Hepaticae)  | Theodor <i>et al.</i> (1980, 1981a) |
| (5,7,5'-tri-OH 3',4'-di-OMe 6-Hex-8-Pen)     |                                            |                                     |

|                                                                                  |                                            |                                     |
|----------------------------------------------------------------------------------|--------------------------------------------|-------------------------------------|
| *6,8-Di-C-arabinopyranosylapometzgerin<br>(5,7,5'-tri-OH 3',4'-diOMe 6,8-di-Ara) | <i>Apometzgeria pubescens</i> (Hepaticae)  | Theodor <i>et al.</i> (1980, 1981a) |
| DI-C-GLYCOSYLDIHYDROCHALCONES                                                    |                                            |                                     |
| *3',5'-Di-C-glycosylphloretin<br>(2,4',6',4-tetra-OH 3',5'-di-Gly)               | <i>Hymenophyton leptopodum</i> (Hepaticae) | Markham <i>et al.</i> (1976b)       |
| DI-C-GLYCOSYLISOFLAVONES                                                         |                                            |                                     |
| Paniculatin<br>(5,7,4'-tri-OH 6,8-di-Glc)                                        | <i>Dalbergia paniculata</i> (Leguminosae)  | Narayanan and Seshadri (1971)       |

\* Indicates their discovery as new compounds during the period 1975-1980.

Table 8.4 Naturally occurring C-glycosylflavonoid O-glycosides

| Compounds                        | Sources                                         | References                                                |
|----------------------------------|-------------------------------------------------|-----------------------------------------------------------|
| <b>ISOVITEXIN</b>                |                                                 |                                                           |
| 7-O-Glucoside (saponarin)        | Many sources                                    | Wagner <i>et al.</i> (1979)                               |
| *7-O-Galactoside (neosaponarin)  | <i>Melandrium album</i> (Caryophyllaceae)       | Brederode and Nigtevecht (1972a)                          |
| *7-O-Xyloside                    | <i>Melandrium album</i> (Caryophyllaceae)       | Hostettmann <i>et al.</i> (1975b)                         |
| 4'-O-Glucoside (isosaponarin)    | <i>Gentiana</i> sp. (Gentianaceae)              | Tschesche and Struckmeyer (1976)                          |
| *2"-O-Glucoside                  | <i>Oxalis acetosella</i> (Oxalidaceae)          | Goetz <i>et al.</i> (1976a)                               |
|                                  | <i>Gentiana asclepiadea</i> (Gentianaceae)      | Monties <i>et al.</i> (1976)                              |
|                                  | <i>Cucumis melo</i> (Cucurbitaceae)             | Besson <i>et al.</i> (1979a)                              |
|                                  | <i>Melandrium album</i> (Caryophyllaceae)       | Chernobrovaya (1973)                                      |
| *2"-O-Xyloside                   | <i>Desmodium canadense</i> (Leguminosae)        | Ulubelen and Mabry (1980)                                 |
|                                  | <i>Passiflora serratifolia</i> (Passifloraceae) | Chopin <i>et al.</i> (1977a) (structure)                  |
| *2"-O-Arabinoside                | <i>Avena sativa</i> (Gramineae)                 | Besson <i>et al.</i> (1979a)                              |
|                                  | <i>Melandrium album</i> (Caryophyllaceae)       | Nikolov <i>et al.</i> (1976)                              |
| *2"-O-Rhamnoside                 | <i>Crataegus monogyna</i> (Rosaceae)            | Besson <i>et al.</i> (1979a); Wagner <i>et al.</i> (1979) |
|                                  | <i>Melandrium album</i> (Caryophyllaceae)       | Jay <i>et al.</i> (1980)                                  |
| *6"-O-Arabinoside                | <i>Securigera coronilla</i> (Leguminosae)       | Hostettmann and Jacot-Guillarmod (1976)                   |
| *7,2"-Di-O-glucoside             | <i>Swertia perennis</i> (Gentianaceae)          | Brederode and Nigtevecht (1974b)                          |
|                                  | <i>Melandrium album</i> (Caryophyllaceae)       | Dubois (1980); Dubois <i>et al.</i> (1980)                |
| *7-O-Glucoside 2"-O-arabinoside  | <i>Cerastium arvense</i> (Caryophyllaceae)      | Brederode and Nigtevecht (1972a)                          |
| *7-O-Glucoside 2"-O-rhamnoside   | <i>Melandrium album</i> (Caryophyllaceae)       | Nigtevecht and Brederode (1972)                           |
| *7-O-Galactoside 2"-O-glucoside  | <i>Melandrium album</i> (Caryophyllaceae)       | Wagner <i>et al.</i> (1979)                               |
| *7-O-Galactoside 2"-O-rhamnoside | <i>Melandrium album</i> (Caryophyllaceae)       | Wagner <i>et al.</i> (1979)                               |
| *7-O-Xyloside 2"-O-glucoside     | <i>Melandrium album</i> (Caryophyllaceae)       | Brederode and Nigtevecht (1974b)                          |
| *7-O-Xyloside 2"-O-arabinoside   | <i>Melandrium album</i> (Caryophyllaceae)       | Brederode and Nigtevecht (1972a)                          |
| *7-O-Xyloside 2"-O-rhamnoside    | <i>Melandrium album</i> (Caryophyllaceae)       | Brederode and Nigtevecht (1972a)                          |
| *4',2"-Di-O-glucoside            | <i>Gentiana asclepiadea</i> (Gentianaceae)      | Goetz and Jacot-Guillarmod (1977a)                        |
| *4'-O-Glucoside 2"-O-arabinoside | <i>Vaccaria segetalis</i> (Caryophyllaceae)     | Baeva <i>et al.</i> (1974)                                |

|                                         |                                                |                                             |
|-----------------------------------------|------------------------------------------------|---------------------------------------------|
| VITEXIN                                 |                                                |                                             |
| 7-O-Glucoside                           | <i>Achillea fragrantissima</i> (Compositae)    | Shalaby <i>et al.</i> (1965)                |
|                                         | <i>Cymbidium</i> sp. (Orchidaceae)             | Williams (1979)                             |
| 4'-O-Glucoside                          | <i>Briza media</i> (Gramineae)                 | Williams and Murray (1972)                  |
| *2"-O-Glucoside                         | <i>Polygonatum odoratum</i> (Liliaceae)        | Morita <i>et al.</i> (1976)                 |
|                                         | <i>Cannabis sativa</i> (Cannabaceae)           | Segelman <i>et al.</i> (1978)               |
| 2"-O-Xyloside                           | <i>Citrus limonum</i> (Rutaceae)               | Tomas <i>et al.</i> (1975)                  |
| 6"-O-Xyloside                           | <i>Gypsophila paniculata</i> (Caryophyllaceae) | Darmograi <i>et al.</i> (1968)              |
| *X"-O-Arabinoside                       | <i>Trichomanes venosum</i> (Hymenophyllaceae)  | Markham and Wallace (1980)                  |
| *2"-O-Rhamnoside                        | <i>Crataegus oxyacantha</i> (Rosaceae)         | Chopin <i>et al.</i> (1977a) (structure)    |
|                                         | <i>Crataegus monogyna</i> (Rosaceae)           | Nikolov <i>et al.</i> (1976)                |
| *6"-O-Rhamnoside                        | <i>Avena sativa</i> (Gramineae)                | Chopin <i>et al.</i> (1977a) (structure)    |
| *7-O-Rutinoside                         | <i>Larix sibirica</i> (Pinaceae)               | Medvedeva <i>et al.</i> (1974)              |
| *2"-O-Sophoroside                       | <i>Phoenix</i> sp. (Palmae)                    | Williams <i>et al.</i> (1973)               |
| *6"-O-Gentiobioside (marginatoside)     | <i>Polygonatum odoratum</i> (Liliaceae)        | Morita <i>et al.</i> (1976)                 |
| 6-C-XYLOSYLAPIGENIN (cerarvensin)       | <i>Piper marginatum</i> (Piperaceae)           | Tillequin <i>et al.</i> (1978)              |
| *7-O-Glucoside                          | <i>Cerastium arvense</i> (Caryophyllaceae)     | Dubois, (1980); Dubois <i>et al.</i> (1980) |
| 2"-O-Rhamnoside                         | <i>Phlox drummondii</i> (Polemoniaceae)        | Bouillant <i>et al.</i> (1978) (structure)  |
| 6-C-ARABINOSYLAPIGENIN (isomollupentin) | <i>Spergularia rubra</i> (Caryophyllaceae)     | Bouillant <i>et al.</i> (1979b)             |
| *7,2"-Di-O-glucoside                    | <i>Zea mays</i> (Gramineae)                    | Elliger <i>et al.</i> (1980)                |
| 3'-DEOXYDERHAMNOSYLMAYSIN               |                                                |                                             |
| *2"-O-Rhamnoside (3'-deoxymaysin)       |                                                |                                             |
| SWERTISIN                               |                                                |                                             |
| 4'-O-Glucoside                          | <i>Commelina</i> sp. (Commelinaceae)           | Komatsu <i>et al.</i> (1968)                |
| *2"-O-Glucoside (spinosin)              | <i>Zizyphus vulgaris</i> (Rhamnaceae)          | Woo <i>et al.</i> (1979)                    |
| X"-O-Xyloside                           | <i>Iris tingitana</i> (Iridaceae)              | Asen <i>et al.</i> (1970)                   |
| ISOSWERTISIN                            |                                                |                                             |
| 4'-O-Glucoside                          | <i>Triticum aestivum</i> (Gramineae)           | Julian <i>et al.</i> (1971)                 |
| *2"-O-Rhamnoside                        | <i>Avena sativa</i> (Gramineae)                | Chopin <i>et al.</i> (1977a) (structure)    |
|                                         | <i>Mollugo distica</i> (Molluginaceae)         | Chopin <i>et al.</i> (1978)                 |
| MOLLUDISTIN                             |                                                |                                             |
| *2"-O-Glucoside                         | <i>Almeidea guyanensis</i> (Rutaceae)          | Jay <i>et al.</i> (1979)                    |
| *2"-O-Rhamnoside                        | <i>Mollugo distica</i> (Molluginaceae)         | Chopin <i>et al.</i> (1978)                 |



Table 8.4 (Contd.)

| Compounds                                    | Sources                                       | References                               |
|----------------------------------------------|-----------------------------------------------|------------------------------------------|
| <b>ISOCYTIOSIDE</b>                          |                                               |                                          |
| *7- <i>O</i> -Glucoside                      | <i>Gentiana pyrenaica</i> (Gentianaceae)      | Marston <i>et al.</i> (1976)             |
| *2"- <i>O</i> -Glucoside                     | <i>Securigera coronilla</i> (Leguminosae)     | Jay <i>et al.</i> (1980)                 |
| *2"- <i>O</i> -Rhamnoside (isomargariten)    | <i>Fortunella margarita</i> (Rutaceae)        | Horowitz <i>et al.</i> (1974)            |
| <b>CYTISOSIDE</b>                            |                                               |                                          |
| 7- <i>O</i> -Glucoside                       | <i>Trema aspera</i> (Ulmaceae)                | Oelrichs <i>et al.</i> (1968)            |
| *2"- <i>O</i> -Rhamnoside (margariten)       | <i>Fortunella margarita</i> (Rutaceae)        | Horowitz <i>et al.</i> (1974)            |
| <b>EMBIGENIN</b>                             |                                               |                                          |
| 2"- <i>O</i> -Rhamnoside (embinin)           | <i>Iris japonica</i> (Iridaceae)              | Arisawa <i>et al.</i> (1973)             |
| <b>7,4'-Di-<i>O</i>-METHYLISOMOLLUPENTIN</b> |                                               |                                          |
| *2"- <i>O</i> -Glucoside                     | <i>Asterostigma reidelianum</i> (Araceae)     | Markham and Williams (1980)              |
| <b>ISO-ORIENTIN</b>                          |                                               |                                          |
| 7- <i>O</i> -Glucoside (lutronarin)          | Many sources                                  |                                          |
| *3'- <i>O</i> -Glucoside                     | <i>Gentiana nivalis</i> (Gentianaceae)        | Hostettmann and Jacot-Guillarmod (1974a) |
| *3'- <i>O</i> -Glucuronide                   | <i>Rhynchospora eximia</i> (Cyperaceae)       | Williams and Harborne (1977a)            |
| 4'- <i>O</i> -Glucoside                      | <i>Gentiana</i> sp. (Gentianaceae)            | Hostettmann <i>et al.</i> (1975b)        |
| *2"- <i>O</i> -Glucoside                     | <i>Gentiana verna</i> (Gentianaceae)          | Hostettmann and Jacot-Guillarmod (1975)  |
|                                              | <i>Cucumis melo</i> (Cucurbitaceae)           | Monties <i>et al.</i> (1976)             |
|                                              | <i>Desmodium canadense</i> (Leguminosae)      | Chernobrovaya (1973)                     |
| *2"- <i>O</i> -Xyloside                      | <i>Avena sativa</i> (Gramineae)               | Chopin <i>et al.</i> (1977a) (structure) |
| *2"- <i>O</i> -Arabinoside                   | <i>Trichomanes venosum</i> (Hymenophyllaceae) | Markham and Wallace (1980)               |
| *2"- <i>O</i> - $\beta$ -L-Arabinofuranoside | <i>Crataegus monogyna</i> (Rosaceae)          | Nikolov <i>et al.</i> (1976)             |
| *2"- <i>O</i> -Rhamnoside                    | <i>Securigera coronilla</i> (Leguminosae)     | Jay <i>et al.</i> (1980)                 |
|                                              | <i>Swerteria peremisi</i> (Gentianaceae)      | Hostettmann and Jacot-Guillarmod (1976)  |
|                                              | <i>Gentiana asclepiadea</i> (Gentianaceae)    | Goetz and Jacot-Guillarmod (1977a)       |
| <b>7-<i>O</i>-Rutinoside</b>                 | <i>Triticum aestivum</i> (Gramineae)          | Julian <i>et al.</i> (1971)              |
| <b>ORIENTIN</b>                              |                                               |                                          |
| *7- <i>O</i> -Glucoside bisulphate           | <i>Phoenix canariensis</i> (Palmae)           | Harborne <i>et al.</i> (1974)            |

|                                                           |                                               |                                            |
|-----------------------------------------------------------|-----------------------------------------------|--------------------------------------------|
| 4'-O-Glucoside                                            | <i>Briza media</i> (Gramineae)                | Williams and Murray (1972)                 |
| *2"-O-Glucoside                                           | <i>Cannabis sativa</i> (Cannabaceae)          | Segelman <i>et al.</i> (1978)              |
| 2"-O-Xyloside (adonivernith)                              | <i>Adonis vernalis</i> (Ranunculaceae)        | Wagner <i>et al.</i> (1975) (structure)    |
| *2"-O- $\beta$ -L-Arabinofuranoside                       | <i>Trichomanes venosum</i> (Hymenophyllaceae) | Markham and Wallace (1980)                 |
| *2"-O-Rhamnoside                                          | <i>Crataegus monogyna</i> (Rosaceae)          | Nikolov <i>et al.</i> (1976)               |
| 7-O-Rhamnoside                                            | <i>Linum usitatissimum</i> (Linaceae)         | Ibrahim and Shaw (1970)                    |
| 6-C-XYLOSYL-LUTEOLIN                                      |                                               |                                            |
| 2"-O-Rhamnoside                                           | <i>Phlox drummondii</i> (Polemoniaceae)       | Bouillant <i>et al.</i> (1978) (structure) |
| SWERTIAJAPONIN                                            |                                               |                                            |
| *3'-O-Glucoside                                           | <i>Phragmites australis</i> (Gramineae)       | Nawwar <i>et al.</i> (1980)                |
| *2"-O-Rhamnoside                                          | <i>Securigera coronilla</i> (Leguminosae)     | Jay <i>et al.</i> (1980)                   |
| *3'-O-Gentiobioside                                       | <i>Phragmites australis</i> (Gramineae)       | Nawwar <i>et al.</i> (1980)                |
| ISOCOPARIN                                                |                                               |                                            |
| 7-O-Glucoside                                             | <i>Gentiana pyrenaica</i> (Gentianaceae)      | Marston <i>et al.</i> (1976)               |
| SCOPARIN                                                  |                                               |                                            |
| *X"-O-Rhamnosylglucoside                                  | <i>Crocus reticulatus</i> (Iridaceae)         | Sergeyeva (1977)                           |
| *Episcoparin-7-O-glucoside (Knautinoside)                 | <i>Knautia montana</i> (Dipsacaceae)          | Zemitsova and Bandyukova (1974)            |
| 7,3',4'-Tri-O-METHYLISO-ORIENTIN                          |                                               |                                            |
| 2"-O-Rhamnoside (linoside B)                              | <i>Linum maritimum</i> (Linaceae)             | Chari <i>et al.</i> (1978)                 |
| ISOPYRENIN                                                |                                               |                                            |
| *7-O-Glucoside                                            | <i>Gentiana pyrenaica</i> (Gentianaceae)      | Marston <i>et al.</i> (1976)               |
| 6-C-GLUCOSYL-5,7-DIHYDROXY-8,3',4',5'-TETRAMETHOXYFLAVONE |                                               |                                            |
| 5-O-Rhamnoside                                            | <i>Vitex negundo</i> (Verbenaceae)            | Subramanian and Misra (1979)               |
| PUERARIN                                                  |                                               |                                            |
| O-Xyloside                                                | <i>Pueraria thunbergiana</i> (Leguminosae)    | Murakami <i>et al.</i> (1960)              |

\* Indicates their discovery as new compounds during the period 1975-1980.

Table 8.5 Naturally occurring acyl-C-glycosylflavonoids

| Compounds                                                      | Sources                                        | References                                                   |
|----------------------------------------------------------------|------------------------------------------------|--------------------------------------------------------------|
| ISOVITEXIN                                                     |                                                |                                                              |
| *2"- <i>O</i> - <i>trans</i> -Feruloyl                         |                                                |                                                              |
| *2"- <i>O</i> - <i>trans</i> -Feruloyl 4'- <i>O</i> -glucoside | <i>Gentiana punctata</i> (Gentianaceae)        | Luong and Jacot-Guillarmod (1977)                            |
| *X"- <i>O</i> - <i>trans</i> -Caffeoyl 2"- <i>O</i> -glucoside | <i>Cucumis melo</i> (Cucurbitaceae)            | Monies <i>et al.</i> (1976)                                  |
| *7-Bisulphate                                                  | Palmae                                         | Williams <i>et al.</i> (1973); Harborne <i>et al.</i> (1974) |
| VITEXIN                                                        |                                                |                                                              |
| 2"- <i>O</i> - <i>p</i> -Hydroxybenzoyl                        | <i>Vitex lucens</i> (Verbenaceae)              | Horowitz and Gentili (1966)                                  |
| *2"- <i>O</i> - <i>p</i> -Coumaroyl                            | <i>Trigonella foenum-graecum</i> (Leguminosae) | Sood <i>et al.</i> (1976)                                    |
| *4"- <i>O</i> -acetyl 2"- <i>O</i> -rhamnoside                 | <i>Crataegus monogyna</i> (Rosaceae)           | Nikolov <i>et al.</i> (1976)                                 |
| *7-Bisulphate                                                  | Palmae                                         | Williams <i>et al.</i> (1973); Harborne <i>et al.</i> (1974) |
| *7- <i>O</i> -Rutinoside bisulphate                            |                                                |                                                              |
| 8-C-GALACTOSYLAPIGENIN                                         |                                                |                                                              |
| *6"- <i>O</i> -Acetyl                                          | <i>Briza media</i> (Gramineae)                 | Chari <i>et al.</i> (1980) (structure)                       |
| VICENIN-2                                                      |                                                |                                                              |
| *Feruloyl 6"- <i>O</i> -glucoside                              | <i>Stellaria holostea</i> (Caryophyllaceae)    | Ferreres de Arce (1977)                                      |
| *X"- <i>O</i> -Diferuloylhexaside                              | <i>Spergularia rubra</i> (Caryophyllaceae)     | Ferreres de Arce (1977)                                      |
| VICENIN-1                                                      |                                                |                                                              |
| *Sinapoyl                                                      | <i>Triticum</i> (wheat germ) (Gramineae)       | Galle (1974)                                                 |
| ISOSCHAFTOSIDE                                                 |                                                |                                                              |
| *Sinapoyl                                                      | <i>Triticum</i> (wheat germ) (Gramineae)       | Galle (1974)                                                 |
| *Feruloyl                                                      | <i>Apometzgeria pubescens</i> (Hepaticae)      | Theodor <i>et al.</i> (1980)                                 |
| SCHAFTOSIDE                                                    |                                                |                                                              |
| *Feruloyl 6"- <i>O</i> -glucoside                              | <i>Stellaria holostea</i> (Caryophyllaceae)    | Ferreres de Arce (1977)                                      |
| ISOSWERTISIN                                                   |                                                |                                                              |
| *2"- <i>O</i> -Acetyl                                          | <i>Brackenridgea zanguebarica</i> (Ochnaceae)  | Bombardelli <i>et al.</i> (1974)                             |
| CYTISOSIDE                                                     |                                                |                                                              |
| <i>O</i> -Acetyl 7-glucoside                                   | <i>Trema aspera</i> (Ulmaceae)                 | Oelrichs <i>et al.</i> (1968)                                |
| 7,4'-DI- <i>O</i> -METHYLISOMOLLUPENTIN                        |                                                |                                                              |
| *2"- <i>O</i> -Caffeoylglicoside                               | <i>Asterostigma reidelianum</i> (Araceae)      | Markham and Williams (1980)                                  |

|                                                 |                                            |                                                              |  |
|-------------------------------------------------|--------------------------------------------|--------------------------------------------------------------|--|
| ISO-ORIENTIN                                    |                                            |                                                              |  |
| X"-O-Acetyl                                     | <i>Crataegus monogyna</i> (Rosaceae)       | Nikolov <i>et al.</i> (1976)                                 |  |
| *2"-O-p-Hydroxybenzoyl                          | <i>Gentiana asclepiadea</i> (Gentianaceae) | Goetz and Jacot-Guillarmod (1978)                            |  |
| *2"-O-trans-p-Coumaroyl                         | <i>Gentiana X marcaillhouana</i>           | Luong <i>et al.</i> (1980)                                   |  |
| *2"-O-trans-Caffeoyl                            | <i>Gentiana burseri</i>                    | Jacot-Guillarmod <i>et al.</i> (1975)                        |  |
|                                                 | <i>Gentiana punctata</i>                   | Luong and Jacot-Guillarmod (1977)                            |  |
|                                                 | <i>Gentiana cruciata</i>                   | Goetz <i>et al.</i> (1976)                                   |  |
|                                                 | <i>Gentiana X marcaillhouana</i>           | Luong <i>et al.</i> (1980)                                   |  |
| *2"-O-trans-Feruloyl                            | <i>Gentiana burseri</i>                    | Jacot-Guillarmod <i>et al.</i> (1975)                        |  |
|                                                 | <i>Gentiana punctata</i>                   | Luong and Jacot-Guillarmod (1977)                            |  |
|                                                 | <i>Gentiana X marcaillhouana</i>           | Luong <i>et al.</i> (1980)                                   |  |
| *2"-O-p-Hydroxybenzoyl 4'-O-glucoside           | <i>Gentiana asclepiadea</i>                | Goetz and Jacot-Guillarmod (1978)                            |  |
| *2"-O-trans-Caffeoyl 4'-O-glucoside             | <i>Gentiana punctata</i>                   | Luong and Jacot-Guillarmod (1977)                            |  |
| *2"-(p-O-Glucosyl)trans-caffeoyl 4'-O-Glucoside | <i>Gentiana burseri</i>                    | Jacot-Guillarmod <i>et al.</i> (1975)                        |  |
| *2"-trans-Feruloyl 4'-O-glucoside               | <i>Gentiana burseri</i>                    | Jacot-Guillarmod <i>et al.</i> (1975)                        |  |
|                                                 | <i>Gentiana punctata</i>                   | Luong and Jacot-Guillarmod (1977)                            |  |
| *2"-O-trans-Caffeoylglucoside                   | <i>Cucumis melo</i> (Cucurbitaceae)        | Monties <i>et al.</i> (1976)                                 |  |
| *7-Bisulphate                                   | Palmae                                     | Williams <i>et al.</i> (1973); Harborne <i>et al.</i> (1974) |  |
| ORIENTIN                                        |                                            |                                                              |  |
| *7-Bisulphate                                   | Palmae                                     | Williams <i>et al.</i> (1973); Harborne <i>et al.</i> (1974) |  |
| *7-O-Glucoside bisulphate                       |                                            |                                                              |  |
| SCOPARIN                                        | <i>Sarothamnus scoparius</i> (Leguminosae) | Brum-Bousquet <i>et al.</i> (1977)                           |  |
| *6"-O-Acetyl                                    |                                            |                                                              |  |
| 7,3',4'-TRI-O-METHYLISO-ORIENTIN                |                                            |                                                              |  |
| 6"-O-Acetyl 2"-O-rhamnoside (linoside A)        | <i>Linum maritimum</i> (Linaceae)          | Chari <i>et al.</i> (1978) (structure)                       |  |
| PUERARIN                                        |                                            |                                                              |  |
| 4',6"-di-O-Acetyl                               | <i>Pueraria tuberosa</i> (Leguminosae)     | Bhutani <i>et al.</i> (1969)                                 |  |

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3'-C-glycosylisoliquiritigenin (a chalcone) and puerarin (an isoflavone) in which the A ring derives from resorcinol; 6-C-glucosyl-5,7-dihydroxy-8,3',4',5'-tetramethoxyflavanone and volubilinine (an isoflavone) in which the A ring derives from iretol (methoxyphloroglucinol). Most are C- $\beta$ -D-glucopyranosylflavonoids, but C- $\beta$ -D-xylopyranosyl, C- $\beta$ -D-galactopyranosyl, C- $\alpha$ -L-arabinopyranosyl, C- $\alpha$ -L-rhamnopyranosyl and even C-6-deoxy-xylo-hexos-4-ulosylflavonoids are also known. These sugar residues are illustrated in Fig. 8.1

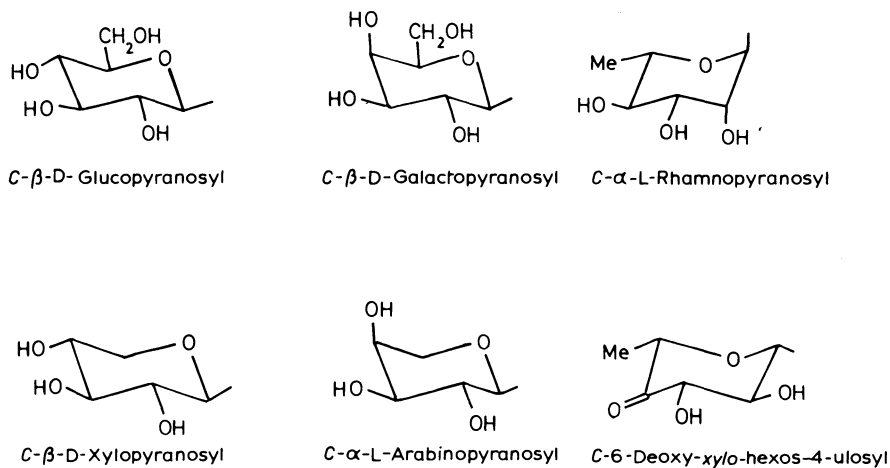


Fig. 8.1 C-Glycosyl residues in natural C-glycosylflavonoids.

### (a) Mono-C-glycosylflavones

Some Wessely-Moser isomers of already known natural C-glucosylflavones have now been found in plant extracts: isocytiside (as O-glycosides), isoswertiajaponin, as well as a new di-O-methyl ether of iso-orientin, but the major advances in the last five years have been in the identification of new C-glycosyl residues and of new substitution types. New natural C-glycosyl residues have been found in 8-C- $\beta$ -D-galactopyranosylapigenin from *Briza media* by Castledine and Harborne (1976), in 8-C- $\alpha$ -L-arabinopyranosylgenkwanin (molludistine) from *Mollugo distica* by Chopin *et al.* (1978) and in derhamnosylmaysin from *Zea mays* by Elliger *et al.* (1980). The structure of the sugar residue was assigned on the basis of <sup>1</sup>H-NMR spectra in the latter case, but on the basis of comparison with synthetic compounds in the former cases. New substitution types in the flavone moiety that have been reported are: 6-C-glucosyltricin (isopyrenin) from *Gentiana pyrenaica* by Marston *et al.* (1976), 6-C-glycosyltricetin (isoaffnetin) from *Polygonum affine* by Krause (1976a,b), and 8-C-glucosyltricetin (affnetin) from *Trichomanes venosum* by Markham and Wallace (1980). In addition 6-C-glucosyl-5,7-dihydroxy-8,3',4',5'-tetramethoxyflavone has been reported from *Vitex negundo* by Subramanian and Misra (1979), but in this case confirmation of the latter unusual structure by physical methods is still awaited.

Epiorientin and parkinsonins A and B have not been listed in Table 8.2 since a reinvestigation of *Parkinsonia aculeata* failed to reveal any such substances: instead orientin, vitexin, iso-orientin and isovitexin were isolated (Besson *et al.*, 1980). 6-C-Xylosylapigenin, already known as the O-rhamnoside, has been found in the free state in *Cerastium arvense* and named cerarvensin by Dubois (1980). C-Arabinosylflavones appear more widespread than C-xylosylflavones, since five examples of the former have already been found against two already known of the latter.

#### (b) Mono-C-glycosylflavonols and flavanonols

Reinvestigation of the extracts from *Zelkova serrata* led Hayashi (1980) to isolate, beside the already known keyakinin and keyakinol, four new compounds which are considered to be 6-C-glucosylkaempferol, 6-C-glucosylquercetin, 6-C-glucosyldihydrokaempferol and 6-C-glucosyldihydroquercetin from their UV and <sup>1</sup>H-NMR spectra.

#### (c) Mono-C-glycosylflavanones

Two new compounds of this type have recently been identified, both with a resorcinol-derived A ring and with the C-galactosyl residue, in *Eysenhardtia polystachya* by Vita-Finzi *et al.* (1980) and named palodulcins A and B. Indeed the structure assigned to palodulcin A has also been published by Garg *et al.* (1980) for aervanone, isolated from *Aerva persica*.

#### (d) Mono-C-glycosylchalcones and dihydrochalcones

The first example of mono-C-glycosylchalcone, again with a resorcinol-derived A ring, was isolated by Ohashi *et al.* (1977a) from *Cladrastis platycarpa* where it co-occurs with the corresponding C-glucosylflavone bayin and the apigenin-derived di-C-glycosylflavone vicenin-1.

#### (e) Mono-C-glycosylisoflavones and isoflavanones

Six new C-glycosylisoflavones have been identified. Two of them, volubiline and isovolubiline from *Dalbergia volubilis* (Chawla *et al.*, 1974, 1975, 1976), are the first examples of mono-C-rhamnosylflavonoids. They co-occur with volubilinine, a C-glucosylisoflavone in which the A ring is derived from iretol. The three others are 8-C-glucosylisoflavones with a phloroglucinol-derived A ring, isolated from *Dalbergia paniculata* (Parthasarathy *et al.*, 1974, 1976) and *Lupinus luteus* (Zapesochneya and Laman, 1977). Two C-glucosylisoflavanones have been described: dalpanin, an 8-C-glucoside isolated from *Dalbergia paniculata* by Adinarayana and Rao (1975) and 6-C-glucosyldalbergioidin isolated from *Pterocarpus macrocarpus* by Gupta *et al.* (1981), both with a phloroglucinol-derived A ring and a 2',4'-di-O-substitution.

### 8.2.2 Di-C-glycosylflavonoids

Except for one di-C-glucosylisoflavone and one poorly characterized di-C-glycosyldihydrochalcone, all members of this group are di-C-glycosylflavones and the most impressive advances in the last five years have been in their recognition and identification. This has been mainly due to the development of mass spectrometry and TLC of permethyl ethers by Bouillant *et al.* (1975), as already mentioned. By such procedures, it has been shown that mixtures of di-C-glucosyl, C-xylosyl-C-glucosyl and C-arabinosyl-C-glucosylapigenins are very commonly encountered in plant extracts.

The four isomeric C-arabinosyl-C-glucosylapigenins which are produced from schaftoside by acid isomerization have all been isolated as natural products. Schaftoside, isolated from *Silene schafta*, was shown to be 6-C-glucopyranosyl-8-C-arabinopyranosylapigenin by Chopin and Wagner's groups (Chopin *et al.*, 1974) and its acid isomerization product, isoschaftoside, to be identical with 6-C- $\alpha$ -L-arabinopyranosyl-8-C- $\beta$ -D-glucopyranosylapigenin synthesized by C-arabinopyranosylation of natural vitexin (Biol *et al.*, 1974). Isoschaftoside was later isolated from *Flourensia cernua* by Dillon *et al.* (1976). Another isomer, co-occurring with schaftoside in *Catananche cerulea* had previously been named isoschaftoside (Proliac *et al.*, 1973) but was renamed neoschaftoside after mass spectrometry of the permethyl ether showed it to be a 6-C-hexosyl-8-C-pentosylapigenin (Bouillant *et al.*, 1975). Its structure as 6-C- $\beta$ -D-glucopyranosyl-8-C- $\beta$ -L-arabinopyranosylapigenin was deduced from the study of synthetic 6-C- $\alpha$  and  $\beta$ -L-arabinopyranosyl and furanosylacetins (Besson, unpublished). Neoisoschaftoside has recently been isolated from *Mnium undulatum* by Österdahl (1979c) and considered to be the Wessely-Moser isomer of neoschaftoside.

Compound S, isolated from *Polygonatum multiflorum*, was shown to be 6-C- $\beta$ -D-galactopyranosyl-8-C- $\alpha$ -L-arabinopyranosylapigenin by Chopin *et al.* (1977b) and renamed isocorymboside after identification of corymboside, from *Carlina corymbosa*, as the Wessely-Moser isomer of compound S (Besson *et al.*, 1979b). Isoviolanthin, the Wessely-Moser isomer of natural violanthin, has been recently identified in *Angiopteris evecta* by Wallace *et al.* (1979). A new type of 6,8-di-C-hexosylapigenin different from vicianin-2 has been found in *Plagiochila asplenioides* and *Hedwigia ciliata*, but the sugar residues could not be identified. Synthetic 6,8-di-C- $\alpha$ -L-arabinopyranosylapigenin has been identified with natural products from several sources. The 7-O-methyl ether (almeidein) and the 7,4'-di-O-methyl ether were also found as natural compounds and their structure proved by permethylation.

One of the 6-C-arabinosyl-8-C-pentosylapigenins isolated from *Mollugo pentaphylla* (Chopin *et al.*, 1979), identical with the 6,8-di-C-pentosylapigenin from *Lespedeza cuneata* (Numata *et al.*, 1979), is likely 6-C- $\alpha$ -L-arabinopyranosyl-8-C- $\beta$ -D-xylopyranosylapigenin (Besson, unpublished). The compound isolated from *Trigonella corniculata* and considered to be 6,8-di-C-

glucosylacetin by Seshadri *et al.* (1972) has been shown to be a 6-*C*-pentosyl-8-*C*-hexosylacetin by Bouillant *et al.* (1975).

6,8-Di-*C*- $\beta$ -D-glucopyranosylluteolin (lucenin-2) has been unambiguously characterized in *Hedwigia ciliata* (Österdahl, 1978) and in *Spergularia rubra* (Bouillant *et al.*, 1979b), but lucenins have been found in many plants. Carlinoside, isolated from *Carlina vulgaris*, has been considered as 6-*C*- $\beta$ -D-glucopyranosyl-8-*C*- $\alpha$ -L-arabinopyranosylluteolin by Raynaud and Rasolojaona (1976) mainly from the MS of its permethyl ether. This was indirectly confirmed by the co-occurrence of carlinoside and neocarlinoside in *Oryza sativa*, the sugar part of the  $^1\text{H-NMR}$  spectrum of perdeuteriomethylneocarlinoside being identical with that of perdeuteriomethylneoschaftoside (Besson and Fukami, unpublished). One di-*C*-pentosylluteolin co-occurs with the corresponding di-*C*-pentosylapigenin and di-*C*-pentosyltricetin in *Takakia lepidozoides* (Markham and Porter, 1979). 6,8-Di-*C*- $\beta$ -D-glucopyranosylchrysoeriol synthesized by *C*-glycosylation of natural scoparin (Bouillant, 1976) has been identified in several sources and a 6-*C*-arabinosyl-8-*C*-hexosylchrysoeriol found in *Mnium undulatum* (Österdahl, 1979c). The Hepaticae have been shown by Markham and Zinsmeister's groups to be a very rich source of di-*C*-glycosyltricetin derivatives, since not less than 14 compounds of this type were isolated from *Plagiochila asplenioides*, *Takakia lepidozoides*, *Apometzgeria pubescens*, *Metzgeria conjugata* and *Metzgeria leptoneura*. The flavone moieties were tricetin, 3'-*O*-methyltricetin, tricin and 3',4'-di-*O*-methyltricetin (apometzgerin) and the identified sugar moieties glucose, arabinose and xylose.

### 8.2.3 C-Glycosylflavonoid O-glycosides

*C*-Glycosylflavones are often found in nature as *O*-glycosides in which the sugar is linked either to a phenolic hydroxyl group (*X* or *X'*-*O*-glycosides) or to an hydroxyl group of the glycosyl side chain (*X''*-*O*-glycosides or *C*-diglycosylflavones), but natural compounds are now known in which both linkages co-occur. Glycosylation of a phenolic hydroxyl group is usually detected and located by changes in UV spectral shifts after hydrolysis. No change occurs with *X''*-*O*-glycosides which show the same UV spectrum as the corresponding *C*-glycosylflavone, and identification of the glycosidic linkage raises difficult problems which have not found any general solution before the advent of  $^{13}\text{C-NMR}$  spectroscopy (see Chapter 2), because mass spectrometry of permethyl ethers only solves the problem as far as 6-*C*-glycosylflavones are concerned (Bouillant *et al.*, 1979a). Moreover, it has been observed that the presence of a highfield acetyl signal in the  $^1\text{H-NMR}$  spectrum of acetylated 6-*C*-glucosylflavone *X''*-*O*-glycosides is not diagnostic for the presence of a 2''-*O*-acetyl group (Woo *et al.*, 1979).

Except for the previously reported puerarin *O*-xyloside, all compounds listed in Table 8.4 are *C*-glycosylflavone *O*-glycosides, mainly derived from isovitexin,



vitexin, iso-orientin and orientin. Most of the X''-O-glycosides are 2''- and only a few are 6''-O-glycosides. No natural 3''- or 4''-O-glycoside has yet been described.

Establishment of the structure of vitexin O-rhamnoside isolated from various *Crataegus* species has been solved in different ways. The vitexin 2''-O-rhamnoside structure was independently determined by mass spectrometry of the permethyl ether (Chopin *et al.*, 1977a), by  $^1\text{H-NMR}$  (Nikolov *et al.*, 1976) and  $^{13}\text{C-NMR}$  (Weinges, 1977). Various isovitexin 7,2''-di-O-glycosides have been found in *Melandrium album* (= *Silene alba*) by van Brederode and van Nigtevecht who showed the glycosylation of isovitexin to be governed by a series of distinctive enzymes. Two of them respectively transfer glucose and xylose to the 7-hydroxyl group, three others transfer arabinose, rhamnose and glucose to the 2''-hydroxyl group of isovitexin. That galactose also can be transferred to the 7-hydroxyl group was shown later by Wagner *et al.* (1979). 4',2''-Di-O-glucosides of isovitexin and iso-orientin have been isolated from *Gentiana asclepiadea* (Goetz and Jacot-Guillarmod, 1977a).

Two 8-C-triglycosylapigenins are known: polygonatiine (vitexin 2''-O-sophoroside) from *Polygonatum odoratum* (Morita *et al.*, 1976) and marginatoside (vitexin 6''-O-gentiobioside) from *Piper marginatum* (Tillequin *et al.*, 1978). The presence of 2''-O- $\beta$ -L-arabinofuranosides of iso-orientin and orientin in *Trichomanes venosum* has been suggested by Markham and Wallace (1980) on the basis of  $^{13}\text{C-NMR}$  data.

#### 8.2.4 Acyl C-glycosylflavonoids

Many new O-acylated derivatives of mono- and di-C-glycosylflavones, C-glycosylflavone O-glycosides and C-diglycosylflavones have been reported during the last five years. O-Acetyl, O-*p*-hydroxybenzoyl, O-*p*-coumaroyl, O-feruloyl, O-caffeoyl, O-sinapoyl and bisulphate groups are linked either to phenolic hydroxyl groups or to sugar hydroxyl groups. In the latter case, location of the acyl group raises the same problem as that of glycosyl groups, and  $^{13}\text{C-NMR}$  spectroscopy again affords a general solution which is only just beginning to be used in this field. In most of the compounds listed in Table 8.5, the highfield shift of 2''-O-acetyl in 6- and 8-C-glucosylflavones and of 6''-O-acetyl in 8-C-glucosylflavones was used to locate the acyl group in the 2'' or 6'' position. In some cases, the nature of acyl groups can be deduced from the molecular ion and fragmentation pattern when the acyl group survives permethylation, and the presence of a free hydroxyl group deduced from the molecular ion observed can give information about the position of the lost acyl group from the fragmentation pattern when saponification only occurs after permethylation. In 4'''-O-acetylvitexin 2''-O-rhamnoside isolated from various *Crataegus* species, the acetyl group is linked to the rhamnose as shown by  $^1\text{H-NMR}$  (Nikolov *et al.*, 1976) and  $^{13}\text{C-NMR}$  (Weinges, 1977). However, in linoside A, the acetyl group is linked to the C-glucosyl moiety as shown by  $^{13}\text{C-NMR}$  (Chari *et al.*, 1978). Various 2''-O-acyl iso-orientins and their 4'-O-glucosides have been identified in *Gentiana* by Jacot-Guillarmod and co-

workers. The acyl group of feruloylisoschaftoside from *Apometzgeria pubescens* was first shown to be linked to the 8-C-glucosyl residue by mass spectrometry of the permethyl ether and later located at the 2"-position by  $^{13}\text{C}$ -NMR (Theodor *et al.*, 1980, 1981b). The existence of feruloyl di-C-glycosylflavone O-glycosides has been demonstrated in *Stellaria holostea* and *Spergularia rubra* by mass spectrometry of permethyl ethers (Ferrerres de Arce, 1977).

### 8.3 SYNTHESIS OF C-GLYCOSYLFLAVONIDS

Following their successful total synthesis of 7,4'-di-O-methylbayin (8-C- $\beta$ -D-glucopyranosyl-7,4'-dimethoxyflavone) (Eade *et al.*, 1975), Eade *et al.* (1978) used the intermediate 3'- $\beta$ -D-glucopyranosyl-2'-hydroxy-4,4'-dimethoxychalcone for the first synthesis of a C-glucosylisoflavone: 7,4'-di-O-methylpuerarin (8-C- $\beta$ -D-glucopyranosyl-7,4'-dimethoxyisoflavone). The product of the reaction of 2'-acetoxy-4,4'-dimethoxy-3'-(tetra-acetyl- $\beta$ -D-glucopyranosyl)chalcone (7) with thallium(III) nitrate in methanol/trimethyl orthoformate solution gave, after acid hydrolysis, a high yield of 7,4'-di-O-methylpuerarin (10). From the reaction of the latter chalcone with thallium(III) nitrate in methanol, following the method of Farkas *et al.* (1974), the intermediates dimethyl acetal (8) and enol ether (9) have been isolated (Fig. 8.2).

A more general synthesis of C-glycosylflavonoids, exemplified by the synthesis of 5,7,4'-tri-O-methylvitexin (8-C- $\beta$ -D-glucopyranosyl-5,7,4'-trimethoxyflavone) has been later provided by Eade and Pham (1979) (Fig. 8.2). The reaction between 1,3,5-trimethoxybenzene (1) and tetra-acetyl- $\alpha$ -D-glucosyl bromide (2) in the presence of zinc oxide gave  $\beta$ -D-glucopyranosyl-2,4,6-trimethoxybenzene tetra-acetate (3) in 70% yield. This tetra-acetate was converted by acetic anhydride and anhydrous aluminium chloride into 3- $\beta$ -D-glucopyranosyl-2-hydroxy-4,6-dimethoxyacetophenone tetra-acetate (4). Condensation of the latter with 4-methoxybenzaldehyde in the presence of sodium hydroxide gave 3'- $\beta$ -D-glucopyranosyl-2'-hydroxy-4,4',6'-trimethoxychalcone (5) from which reaction with selenium dioxide gave 5,7,4'-tri-O-methylvitexin (6). A new era is thus opened up, since, from now on, synthesis in good yield of almost every type of 8-C-glycosylflavonoid methyl ether may be expected from the C-glycosylacetophenones derived from the corresponding glycosyl-2,4,6-trimethoxybenzenes.

In spite of the low yields of 6-C-glycosylflavones obtained in the reaction of acetobromosugars with 5,7-dihydroxyflavones, this method has been used in the authors' laboratory to prepare some standard compounds for mass spectral studies or to solve some specific problems. For example, 6-C- $\alpha$ -L-arabinopyranosylacetin and 6-C- $\alpha$ -L-arabinofuranosylacetin were prepared from acetin and the corresponding acetobromo-L-arabinoses in order to study their acid isomerization products and to compare their chromatographic and spectral properties with the possibly naturally occurring C-arabinofuranosylflavones

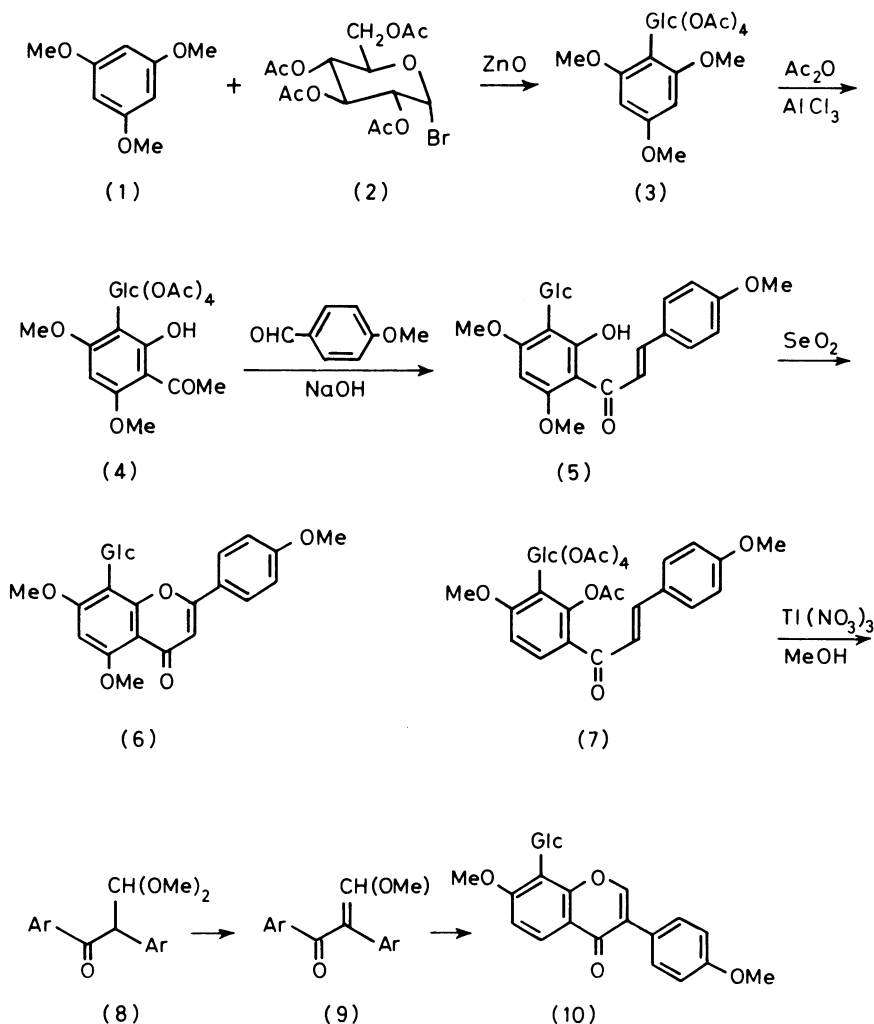


Fig. 8.2 Synthesis of 5,7,4'-tri-O-methylvitexin and 7,4'-di-O-methylpuerarin.

(Besson, 1977). *C*-Glycosylation of 5,7-dihydroxy-3',4',5'-trimethoxyflavone has been achieved with acetobromoglucose and acetobromoarabinose following the discovery of natural *C*-glycosyltricetins and *C*-glycosyltricinins, and 6,8-di-*C*-glycosylation was observed in both cases (Lardy, 1981). Similarly 6,8-di-*C*- $\alpha$ -L-arabinopyranosylacetin was obtained as a byproduct in the previously mentioned *C*-arabinosylation of acetin, 6,8-di-*C*- $\beta$ -D-xylopyranosylacetin and 6,8-di-*C*- $\beta$ -D-xylopyranosylapigenin in the *C*-xylosylation of acetin and

apigenin respectively, 6,8-di-C- $\alpha$ -L-rhamnopyranosylapigenin in the C-rhamnosylation of apigenin (Bouillant, 1976; Besson, 1977). 6,8-Di-C- $\beta$ -D-glucopyranosylchrysoeriol was prepared by reaction of acetobromoglucose with natural scoparin (8-C- $\beta$ -D-glucopyranosylchrysoeriol) for comparison with the natural compound (Bouillant, 1976).

Following the isolation of 7-O-, 6-C- and 8-C- $\beta$ -neohesperidosylacetins from *Fortunella margarita* (Horowitz *et al.*, 1974), C-neohesperidosylation of acacetin was successfully accomplished with the acetobromo derivative of  $\beta$ -neohesperidose ( $\alpha$ -L-rhamnopyranosyl-1  $\rightarrow$  2- $\beta$ -D-glucopyranose) which provided confirmation of the proposed structure (Chopin *et al.*, 1977c; Besset, 1977). Then, because of the difficulty of locating the position of the O-linked sugar in 6-C-glycosylflavone X"-O-glycosides and with the hope of solving this problem by mass spectrometry of permethyl ethers, synthesis of 3"-, 4"- and 6"-O-glycosides was undertaken. Reaction of acacetin with the acetobromo derivatives of rungirose ( $\alpha$ -L-rhamnopyranosyl-1  $\rightarrow$  3-D-glucopyranose), cellobiose ( $\beta$ -D-glucopyranosyl-1  $\rightarrow$  4-D-glucopyranose) and rutinose ( $\alpha$ -L-rhamnopyranosyl-1  $\rightarrow$  6-D-glucopyranose) respectively led to the corresponding 6-C-diglycosylacetins, i.e. the 3"-O-rhamnoside, 4"-O-glucoside and 6"-O-rhamnoside of isocytiside (6-C-glucosylacetin) (Besset, 1977; Bouillant *et al.*, 1980). 6-C-Cellobiosyl 3',4'-di-O-methyl-luteolin was synthesized in the same way (Besset, 1977). These new compounds are listed in Table 8.6.

**Table 8.6** New synthetic C-glycosylflavones from flavone C-glycosylation

|                                                          |                                               |
|----------------------------------------------------------|-----------------------------------------------|
| <i>6-C-Glycosylflavones</i>                              |                                               |
| 6-C- $\alpha$ -L-Arabinopyranosylacetin                  | Besson (1977)                                 |
| 6-C- $\alpha$ -L-Arabinofuranosylacetin                  | Besson (1977)                                 |
| 6-C- $\beta$ -D-Glucopyranosyl-4'-O-methyltricin         | Lardy (1981)                                  |
| 6-C- $\alpha$ -L-Arabinopyranosyl-4'-O-methyltricin      | Lardy (1981)                                  |
| <i>6,8-Di-C-glycosylflavones</i>                         |                                               |
| 6,8-Di-C- $\beta$ -D-glucopyranosylchrysoeriol           | Bouillant (1976)                              |
| 6,8-Di-C- $\alpha$ -L-arabinopyranosylacetin             | Besson (1977)                                 |
| 6,8-Di-C- $\beta$ -D-xylopyranosylapigenin               | Bouillant (1976)                              |
| 6,8-Di-C- $\beta$ -D-xylopyranosylacetin                 | Besson (1977)                                 |
| 6,8-Di-C- $\alpha$ -L-rhamnopyranosylapigenin            | Bouillant (1976)                              |
| 6,8-Di-C- $\beta$ -D-glucopyranosyl-4'-O-methyltricin    | Lardy (1981)                                  |
| 6,8-Di-C- $\alpha$ -L-arabinopyranosyl-4'-O-methyltricin | Lardy (1981)                                  |
| <i>6-C-Diglycosylflavones</i>                            |                                               |
| 6-C-Neohesperidosylacetin                                | Besset (1977); Chopin <i>et al.</i> (1977c)   |
| 6-C-Rungiosylacetin                                      | Bouillant <i>et al.</i> (1980)                |
| 6-C-Cellobiosylacetin                                    | Besset (1977); Bouillant <i>et al.</i> (1980) |
| 6-C-Rutinosylacetin                                      | Besset (1977); Bouillant <i>et al.</i> (1980) |
| 6-C-Cellobiosyl-3',4'-di-O-methyl-luteolin               | Besset (1977)                                 |

## 8.4 IDENTIFICATION OF C-GLYCOSYLFLAVONOIDS

## 8.4.1 Chemical methods

Acid treatment of C-glycosylflavonoids is always used for their characterization. Isomerization cannot be used unequivocally for distinguishing asymmetrical from symmetrical (no isomerization) 6,8-di-C-glycosylflavones, since 6,8-di-C- $\alpha$ -L-arabinopyranosylapigenin gives rise to several isomers under these conditions. Sugar ring isomerization in C-arabinosylflavones has been demonstrated by Besson and Chopin (1980) with synthetic 6-C- $\alpha$ -L-arabinopyranosyl- and 6-C- $\alpha$ -L-arabinofuranosyl-acacetins and with natural 8-C- $\alpha$ -L-arabinopyranosylgenkwanin (molludistine). Sugar ring isomerization of the C-arabinosyl moiety is faster than Wessely-Moser isomerization of the flavone moiety when O-methyl groups are present in the 7 or 4' positions. All four 6-C- $\alpha$ - and  $\beta$ -L-arabinopyranosyl and furanosylacacetins can be isolated from the acid isomerization of 6-C- $\alpha$ -L-arabinopyranosylacacetin, whereas 8-C- $\alpha$ -L-arabinopyranosylgenkwanin mainly gives a mixture of the two 8-C- $\alpha$  isomers under similar conditions. Even after methylation of the phenolic hydroxyl groups, periodate oxidation of spinosin (swertisin 2''-O-glucoside) led to abnormal results, 1.9 mol of periodate being consumed and di-O-methylswertisin being identified after hydrolysis of the oxidation product erroneously suggesting 3''-O-glycosylation (Woo *et al.*, 1979). Ferric chloride oxidation of about 25 mg of C-glycosylflavonoid is still widely used to identify the carbon-linked sugar residue, e.g. rhamnose in volubilin and isovolubilin (Chawla *et al.*, 1974, 1975). However, glucose and arabinose, but no trace of xylose were formed from the FeCl<sub>3</sub> oxidation of vicenin-1 (6-C-xylosyl-8-C-glucosylapigenin) by Ohashi *et al.* (1977b). In parallel experiments, glucose and arabinose were obtained from schaftoside (6-C-glucosyl-8-C-arabinosylapigenin), but no sugar could be detected from compound S (6-C-galactosyl-8-C-arabinosylapigenin) by Chopin *et al.* (1977b). However, FeCl<sub>3</sub> oxidation of 3 g of aervanone (8-C-galactosyl 7,4'-dihydroxyflavanone) led Garg *et al.* (1980) to 7,8,4'-trihydroxyflavanone in good yield and PC-detectable amounts of galactose and lyxose. This destructive method is now obsolete, since the same amount of sample can be more profitably employed for non-destructive <sup>13</sup>C-NMR spectroscopy. Isopropylidenation of C-glycosylflavone O-glycosides was used by Wagner's group for structural studies. Refluxing with acetone in the presence of dry CuSO<sub>4</sub> afforded mono- and diisopropylidene derivatives from spinosin (a 6-C-glucosylflavone 2''-O-glucoside) (Woo *et al.*, 1979). Isopropylidenation of glucose residues was similarly observed on prolonged stirring of 2''-O-glucosylisovitexin-7-O-galactoside with acetone at room temperature in the presence of *p*-toluene sulphonic acid (TsOH) (Wagner *et al.*, 1979). However, isopropylidenation with 2,2-dimethoxypropane and 6M-HCl-dioxan in anhydrous dimethylformamide (DMF) according to Jarman and Ross (1969) was found to be specific for C-galactopyranosyl and C-arabinopyranosyl residues in mono- and di-C-glycosylflavones (Besson, 1977; Chopin *et al.*, 1977b).

### 8.4.2 Physical methods

#### (a) $^1\text{H}$ -NMR spectrometry

Proton-NMR spectrometry has been widely used to assign the 6 or 8 position to the glycosyl residue in mono-C-glycosylflavonoids, from the chemical shift difference exhibited either by H-6 and H-8 protons in 5,7-dihydroxyflavones or by the 2''-acetyl protons in 6- and 8-C-glucosylflavone acetates (Gentili and Horowitz, 1968). Absence of a highfield acetyl signal ( $\delta \leq 1.83$ ) in the spectrum of the acetylation products of natural acyl C-glycosylflavonoids and O-glycosides was for a long time the only available test for 2''-substitution. However, the presence of such a signal cannot be used as diagnostic for a 2''-O-acetyl, since it was observed in the spectrum of peracetyl 6-C-glucosylflavone 2''-O-glycosides. In such cases, 2''-O-glycosylation was established by mass spectrometry of permethyl ethers or by permethylation followed by hydrolysis and acetylation of the resulting monohydroxypermethyl 6-C-glucosylflavone; in the  $^1\text{H}$ -NMR spectrum of the latter, the acetyl signal was found at high field and shown to be 2''-acetyl by spin decoupling (Tschesche and Struckmeyer, 1976; Woo *et al.*, 1979).

The C-1'' configuration of the glycosyl residue was usually deduced from the coupling constant of H-1'' in the NMR spectra of trimethylsilyl or acetyl derivatives. In the authors' laboratory, perdeuteriomethyl ethers have been used for this purpose, anomeric protons being well separated from other sugar protons, so that one could observe the splitting of the anomeric protons in perdeuteriomethyl (PDM) 6,8-di-C-glycosylflavones (Besson *et al.*, 1979b). The structure and configuration of the unusual C-glycosyl residue of maysin could be deduced from  $^1\text{H}$ -NMR spectra of derhamnosylmaysin (Elliger *et al.*, 1980).

#### (b) $^{13}\text{C}$ -NMR spectrometry

The first published application of  $^{13}\text{C}$ -NMR spectrometry in the field of C-glycosylflavonoids was the determination of the position of arabinose in iso-orientin 6''-O-arabinoside isolated from *Swertia perennis* (Hostettmann and Jacot-Guillarmod, 1976), but the correct assignments for the C-glucosyl moiety were given by Chari *et al.* (1978) and used for the structure determination of linosides A and B, spinosin and *Melandrium album* glycosides, all of which are 6-C-glucosylflavone 2''-O-glycosides. It soon became evident from the comparison of  $^{13}\text{C}$ -NMR spectra of natural 6- and 8-C-glucosylflavones that the glucose signals remained the same in all cases. This was used by Chopin *et al.* (1977b) to confirm the 6-C-galactosyl-8-C-arabinosylapigenin structure of compound S isolated from *Polygonatum multiflorum*, by comparing the sugar signals of schaftoside (6-C-glucosyl-8-C-arabinosylapigenin), iso-orientin (6-C-glucosyl-luteolin), molludistin (8-C-arabinosylgenkwanin) and 8-C-galactosylapigenin with those of compound S, without any assignment of the individual signals. The same technique was used in the structure determination of corymboside (6-C-arabinosyl-8-C-galactosylapigenin) by Besson *et al.* (1979b).  $^{13}\text{C}$ -NMR was also used by

Österdahl (1978) to identify vicenin-2 and lucenin-2 in *Hedwigia ciliata* by comparison of their spectra with those of vitexin, isovitexin, saponarin, iso-orientin and apigenin. The signals of the C-galactosyl residue have been obtained from 6''-O-acetyl-8-C- $\beta$ -D-galactopyranosylapigenin isolated from *Briza media* (Chari *et al.*, 1980), those of the C-xylosyl residue from vicenin-1 (6-C-xylosyl-8-C-glucosylapigenin) isolated from *Cladrastis platycarpa* (Chopin, unpublished) and those of the C-rhamnosyl residue from violanthin (6-C-glucosyl-8-C-rhamnosylapigenin) isolated from *Viola tricolor* (Chari, 1980). Each C-glycosyl residue shows a characteristic spectrum, so that their identification in any given C-glycosylflavonoid is now very easy (see Chapter 2).

### (c) Mass spectrometry

The main advance in this field has been the use of permethyl (PM) or perdeuteriomethyl (PDM) ethers which provide: (1) molecular peaks from mono- and di-C-glycosylflavones and their mono- and di-O-glycosides; (2) an unambiguous distinction between 6- and 8-C-glycosylflavones from the striking difference in their fragmentation patterns; (3) identification of the 6-C-glycosyl residue in asymmetrical 6,8-di-C-glycosylflavones resulting from the preferential fragmentation of the 6-residue; (4) determination of the position of O-glycosidic bonds in 6-C-glycosylflavone O-glycosides; and (5) characterization of 6-C-glycosylflavone 7,2''-di-O-glycosides as shown by Bouillant *et al.* (1975, 1978, 1979a,b). Permethylation is carried out on less than 1 mg of C-glycosylflavone using MeI and NaH in DMF under anhydrous conditions in a N<sub>2</sub> atmosphere and the crude product purified by TLC on silica gel in CHCl<sub>3</sub>—EtOAc—Me<sub>2</sub>CO (5:4:1) or (5:1:4). In this way, an excellent reproducibility of mass spectra (MS) can be obtained and conclusions can safely be drawn from the relative intensities of ions. Finally the fragmentation pattern (Fig. 8.3) of PM 6-C-glycosylflavones can be deduced from the MS of PM derivatives mono-O-deuteriomethylated in the 2'', 3'', 4''- or 6''- positions (Bouillant *et al.*, 1980), prepared from the corresponding synthetic O''-glycosyl-6-C-glucosylflavones (Besset, 1977). Application of MS of the PM ethers to the structural study of C-glycosylflavones is described below for each type of compound. Main fragments in MS of PM C-glycosylflavones are listed in Table 8.7.

#### (i) PM mono-C-glycosylflavones

**PM 8-C-glycosylflavones** At  $m/z$  values higher than 150, the MS of PM 5,7-dihydroxy-8-C-glycosylflavones, as shown by the spectrum of PM vitexin (Fig. 8.4), is dominated by two major peaks: the molecular ion and the ion *i* in which only a CHOMe group remains of the C-glycosyl moiety, with transfer of a sugar methoxyl group to C-1''. The nature of the sugar moiety can be deduced from the difference between the  $m/z$  values of *M* and *i* (hexose: 175, deoxyhexose: 145, pentose: 131) and the nature of the flavone moiety from *i* itself (apigenin: 355,

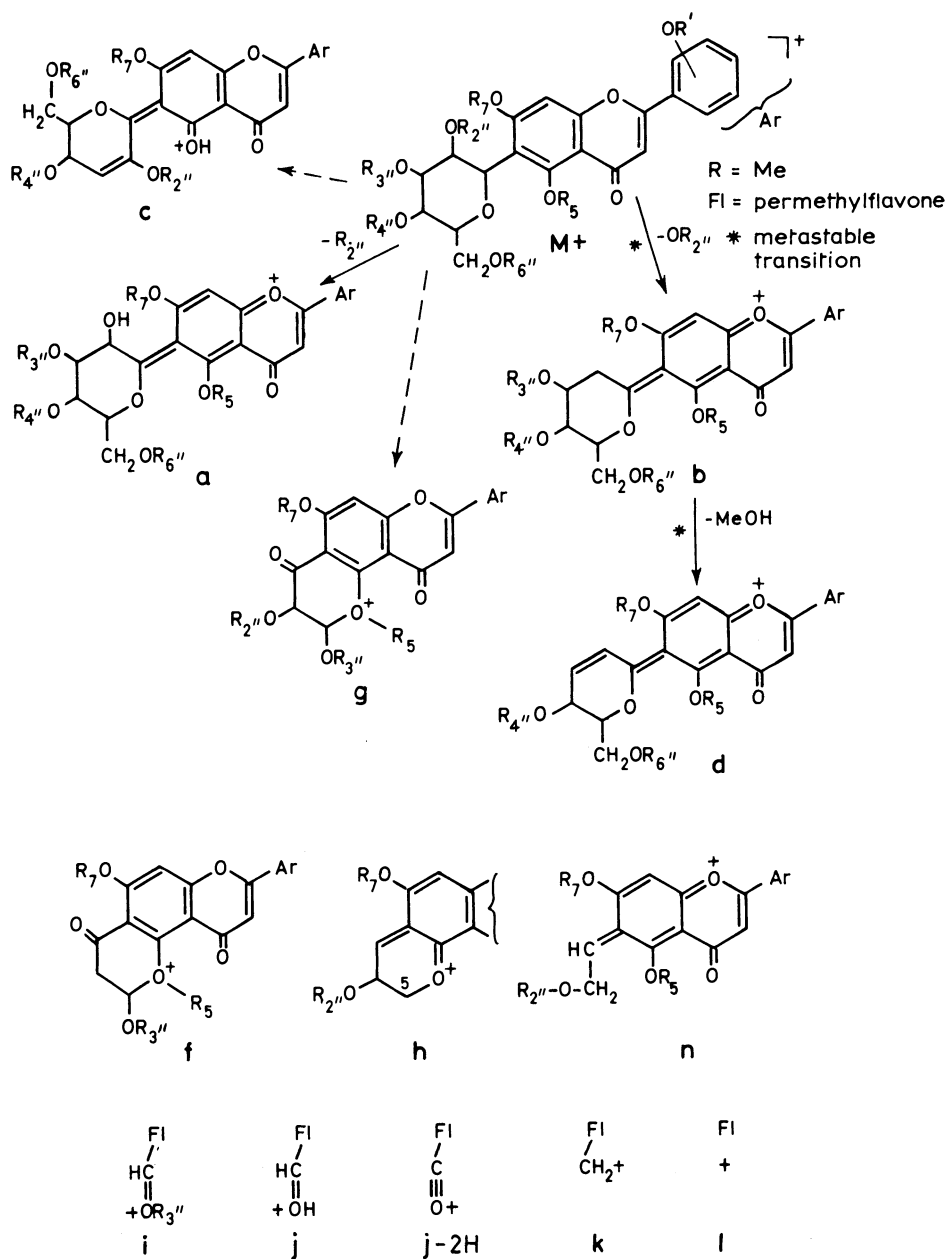


Fig. 8.3 Fragmentation pattern of 6-C-glycosylflavones.



**Table 8.7** Main fragments in MS of permethyl C-glycosylflavones

| Common fragments:         | $a(M-15)$ |         | $b(M-31)$ |         | $c(M-47)$ |         | $d(M-63)$ |         |
|---------------------------|-----------|---------|-----------|---------|-----------|---------|-----------|---------|
| Sugar specific fragments: | $f$       | $g$     | $h$       | $i$     | $j$       | $k$     | $l$       | $n$     |
| Hexose                    | $M-133$   | $M-103$ | $M-163$   | $M-175$ | $M-189$   | $M-205$ | $M-219$   | $M-161$ |
| Deoxyhexose               | $M-103$   | $M-73$  | $M-133$   | $M-145$ | $M-159$   | $M-175$ | $M-189$   | $M-131$ |
| Pentose                   | $M-89$    | $M-59$  | $M-119$   | $M-131$ | $M-145$   | $M-161$ | $M-175$   | $M-117$ |

luteolin: 385, tricetin: 415). The other characteristic peaks are  $M-14$  and  $M-29$  (very weak),  $n$ ,  $j$ ,  $k$  and  $l$  (Fig. 8.3). Retro-Diels-Alder (RDA) fragments are very weak. The transition  $M \rightarrow i$  is indicated by a metastable ion. The influence of the 5-hydroxyl group is shown by the MS of PM bayin (PM 5-deoxyvitexin) in which the importance of  $i$ ,  $j$ ,  $k$ ,  $l$ ,  $n$  remains the same, whereas the molecular peak is considerably lowered and new peaks ( $M-74$ ,  $M-130$ ,  $M-145$ ) appear between  $M$  and  $i$ ,  $M-15$  replacing  $M-14$  and  $M-29$ .

**PM 6-C-glycosylflavones** Again at  $m/z$  values higher than 150, the MS of PM 5,7-dihydroxy-6-C-glycosylflavones, as shown by the spectrum of PM isovitexin (Fig. 8.4), is clearly different from the preceding ones. The ion  $i$  remains a major peak, but the molecular ion is weaker (20–40%) and is followed by important new peaks:  $a(M-15)$ ,  $b(M-31)$ ,  $c(M-47)$  independent of the sugar moiety and  $g$ ,  $f$ ,  $h$  characteristic of the sugar moiety. The relative importance of  $i$ ,  $j$ ,  $k$ ,  $l$  and  $n$  remains the same as in 8-C-isomers. The transitions  $M \rightarrow b$  and  $b \rightarrow b\text{-MeOH}$  are indicated by metastable ions.  $b$  is usually lower than  $i$ , except for 6-C-xylosylflavones. Another difference between C-xylosyl- and C-arabinosylflavones is that the permethylation of 6-C-arabinosylflavones gives, as a byproduct, a compound of which the molecular peak appears at 28 m.u. above that of the PM flavone (6-formyl PM flavone?).

The same fragmentation pattern has been observed in the MS of PM 6-C- $\alpha$  and  $\beta$ -L-arabinopyranosyl- and furanosyl-acacetins (Besson, 1977). Some peaks ( $M$ ,  $M-47$ ,  $M-79$ ,  $M-117$ ,  $M-119$ ) are much higher in the furanosyl isomers and a characteristic difference was found in the metastable ions which showed the transitions  $M \rightarrow M-15 \rightarrow M-47 \rightarrow M-79$  in the furanosyl isomers instead of  $M \rightarrow M-31 \rightarrow M-63$  in the pyranosyl isomers.

#### (ii) PM 6,8-di-C-glycosylflavones

**Symmetrical 6,8-di-C-glycosylflavones** The MS of PM 5,7-dihydroxy-6,8-di-C-glycosylflavones bearing the same sugar in positions 6 and 8 is closely similar to that of the corresponding PM 5,7-dihydroxy-6-C-glycosylflavones, as shown by the spectrum of PM 6,8-di-C-glucosylapigenin (Fig. 8.4). The important molecular ion is followed by all 6-C-glycosylflavone peaks and only relative intensities

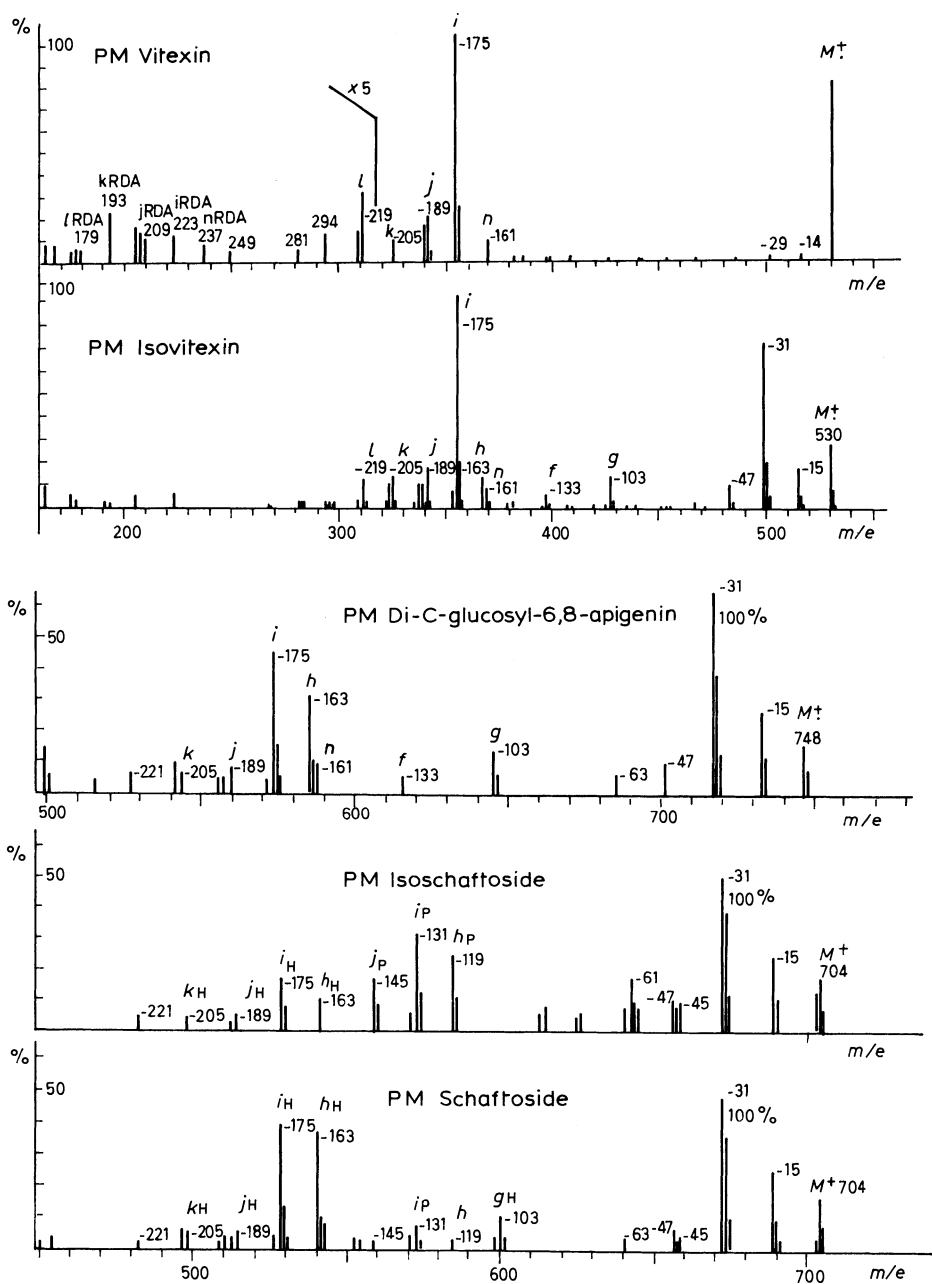


**Fig. 8.4** MS of permethyl mono- and di-C-glycosylflavones.

are modified,  $b$  [ $(M - 31)$ , now the major peak] and  $h$  being increased and  $i$  decreased. This implies the same fragmentation of the 6-sugar giving ions in which the 8-sugar remains intact. Corresponding RDA fragments are very weak. Interesting differences were found between 6,8-di-*C*-arabinopyranosyl- and 6,8-di-*C*-xylopyranosyl-apigenins. Permethylaton of the former led to a byproduct, the MS of which corresponded to a PM 6-formyl-8-*C*-pentosylapigenin. Furthermore the relative intensities of the ions  $h$ ,  $i$  and  $j$  are in the order  $h > i > j$  in the MS of PM 6,8-di-*C*-xylosylapigenin and  $i > h > j$  in the MS of PM 6,8-di-*C*-arabinosylapigenin. The nature of the sugar moiety is given by the difference between the  $m/z$  values of  $M$  and  $i$  (hexose: 175, deoxyhexose: 145, pentose: 131) and the nature of the flavone moiety by the difference  $M - 2i$  (apigenin: 398, luteolin: 428, tricetin: 458).

*Asymmetrical 6,8-di-C-glycosylflavones* From the MS of PM 5,7-dihydroxy-6,8-di-*C*-glycosylflavones bearing different sugars in positions 6 and 8 can be deduced the nature and the position of each sugar, as shown by the spectra of PM schaftoside (PM 6-*C*-glucosyl-8-*C*-arabinosylapigenin) and PM isoschaftoside (PM 6-*C*-arabinosyl-8-*C*-glucosylapigenin). As expected from the preferential fragmentation of the 6-sugar observed above, the MS of PM schaftoside shows the fragmentation pattern of PM 6,8-di-*C*-glucosylapigenin to which are added the peaks  $h_p$ ,  $i_p$ ,  $j_p$  corresponding to the fragmentation of the 8-sugar, but the latter peaks are lower than the peaks  $h_H$ ,  $i_H$ ,  $j_H$  corresponding to the fragmentation of the 6-sugar. Similarly, the MS of PM isoschaftoside shows the fragmentation pattern of PM 6,8-di-*C*-arabinosylapigenin to which are added the peaks  $h_H$ ,  $i_H$ ,  $j_H$  corresponding to the fragmentation of the 8-sugar, but the latter peaks are lower than the peaks  $h_p$ ,  $i_p$ ,  $j_p$  corresponding to the fragmentation of the 6-sugar.

In the MS of PM vicenin-1 (PM 6-*C*-xylosyl-8-*C*-glucosylapigenin),  $h_p$ ,  $i_p$ ,  $j_p$  are again higher than  $h_H$ ,  $i_H$ ,  $j_H$ , the reverse being observed in the MS of PM vicenin-3 (PM 6-*C*-glucosyl-8-*C*-xylosylapigenin). The same differences as above were found between 6-*C*-arabinosyl- and 6-*C*-xylosyl-8-*C*-hexosylflavones. In the MS of PM vicenin-1,  $h_p > i_p > j_p$ , whereas  $i_p > h_p > j_p$  in the MS of PM isoschaftoside. Again, permethylation of the latter led to a byproduct, the MS of which corresponded to a PM 6-formyl-8-*C*-hexosylapigenin.

In the MS of PM violanthin (PM 6-*C*-glucosyl-8-*C*-rhamnosylapigenin)  $h_H$ ,  $i_H$ ,  $j_H$  are higher than  $h_D$ ,  $i_D$ ,  $j_D$  corresponding to the fragmentation of rhamnose (deoxyhexose), the reverse being observed in the MS of PM isoviolanthin (PM 6-*C*-rhamnosyl-8-*C*-glucosylapigenin). The nature of the 6-sugar is thus given by the difference between the  $m/z$  values of  $M$  and higher  $i$ , that of the 8-sugar by the difference between  $M$  and lower  $i$  (hexose: 175, deoxyhexose: 145, pentose: 131) and the nature of the flavone moiety by  $M - (\text{higher } i + \text{lower } i)$  (apigenin: 398, luteolin: 428, tricetin: 458).

Identification of the molecular ion in the MS of di-*C*-glycosylflavones is made easier by the importance of  $b$  ( $M - 31$ ) which always is the major peak at  $m/z$  values higher than 150 and by the characteristic peak system  $M$ ,  $M - 15$ ,  $M - 31$ ,  $M - 47$ .

## (iii) PM isopropylidene C-glycosylflavones

When isopropylidenation was carried out using the conditions described by Jarman and Ross (1969), only C-arabinopyranosyl- and C-galactopyranosylflavones led to isopropylidene derivatives (Besson, 1977; Chopin *et al.*, 1977b). The reaction being usually incomplete, partial isopropylidenation may take place. For example, isopropylidenation of a natural 6-C-galactopyranosyl-8-C-arabinopyranosylflavone followed by permethylation of the reaction mixture led to four products separated by silica-gel TLC, which could be identified by their MS as the PM derivatives of the starting compound, two monoisopropylidene and one di-isopropylidene derivative. All of them showed the  $M - 15$  and  $M - 31$  peaks originating from the 2-methoxyl group of the permethyl 6-C-glycosyl residue and the fragmentation pattern, governed by the 6-C-glycosyl residue, remained the same as that of the PM starting compound when the isopropylidene group was attached to the 8-C-glycosyl residue only.

## (iv) PM 6-C-glycosylflavone O-glycosides

**PM 5,7-dihydroxy-6-C-diglycosylflavones** As shown by the spectrum of PM 6-C-neohesperidosylacacetin (Fig. 8.5) the characteristic feature of the MS of PM 2''-O-glycosyl-6-C-glycosylflavones compared with those of the corresponding PM

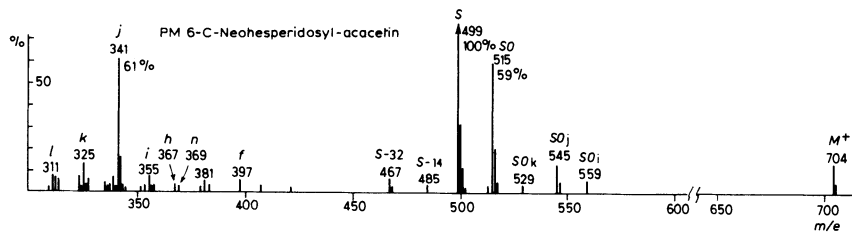


Fig. 8.5 MS of PM 2''-O-glycosyl-6-C-glycosylflavones.

6-C-glycosylflavones is the absence of the  $M - 15$  and  $M - 31$  peaks, which are replaced by the ions  $SO$  (40–60%) and  $S$  (100%) (Fig. 8.6), derived from the elimination of the permethylated 2''-O-glycosyl residue without and with the oxygen atom of the glycosidic bond respectively. Between the rather weak molecular peak (5–15%) and the ion  $SO$  are found some ions  $SO_i$ ,  $SO_j$ ,  $SO_k$  (Fig. 8.6) in which fragments of the O-glycosyl residue (similar to the fragments  $i$ ,  $j$ ,  $k$  of PM 6-C-glycosylflavones) remain bound to  $SO$ . At lower  $m/z$  values, the most important peak is the ion  $j$  of the corresponding PM 6-C-glycosylflavone. The nature of the flavone moiety is thus given by the  $m/z$  value of  $j$  (apigenin: 341, luteolin: 371, tricetin: 401), that of the 6-C-glycosyl residue by  $S - j$  (hexose: 158, deoxyhexose: 128, pentose: 114) and that of the 2''-O-glycosyl residue by  $M - S$  (hexose: 235, deoxyhexose: 205, pentose: 191).

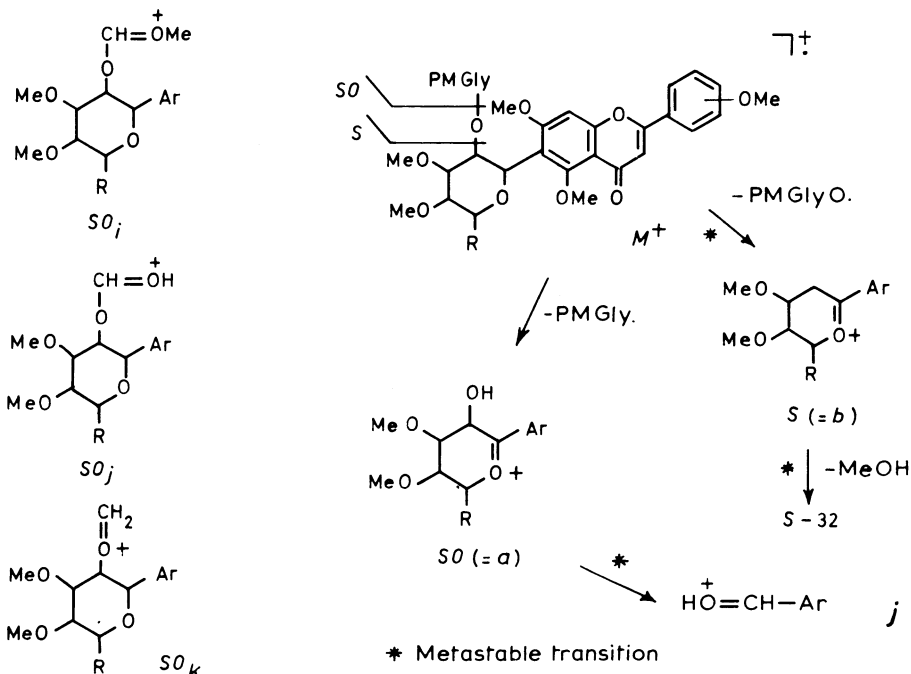


**Fig. 8.6** Fragmentation pattern of PM 2''-O-glycosyl-6-C-glycosylflavones.

As expected from the MS of PM 8-*C*-glycosylflavones, the *M* – 15 and *M* – 31 peaks are also absent from the MS of PM 2''-*O*-glycosyl-8-*C*-glycosylflavones but the ion *S* becomes very weak and the molecular peak stronger, allowing a clear distinction from the 6-isomers (Bouillant *et al.*, 1978).

In the MS of PM 3"-, 4"- or 6"-O-glycosyl-6-C-glycosylflavones, the presence of *M* - 15 and *M* - 31 peaks proves their derivation from the 2"-methyl and methoxyl groups respectively. The ions *SO* and *S* are much lower than in the MS of PM 2"-O-glycosides. The base peak is the ion *j* in 3"-O-glycosides and the ion *i* in 4"- or 6"-O-glycosides (Besson *et al.*, 1979a). The presence of a peak *S* - 14 > *S* in the MS of 6"-O-glycosides may be ascribed to the elimination of the C-5" PM glycosyloxymethyl side chain. Mass spectrometry of the hydrolysis products of PM X"-O-glycosyl-6-C-glucosylflavones has been shown to provide the complete determination of the position of the O"-glycosyl group, characteristic differences being observed in the relative intensities of *M*, *M* - 31, *M* - 89, *M* - 103, *M* - 161 and *M* - 175 peaks of the four possible monohydroxy PM 6-C-glucosylflavones (Bouillant *et al.*, 1979a).

*PM 5,7-dihydroxy-6-C-glycosylflavones 7-O-glycosides* As shown by the spectrum of PM saponarin (Fig. 8.7), the characteristic features of their MS are the importance of the ion *A* and the presence of two homologous series of peaks, both

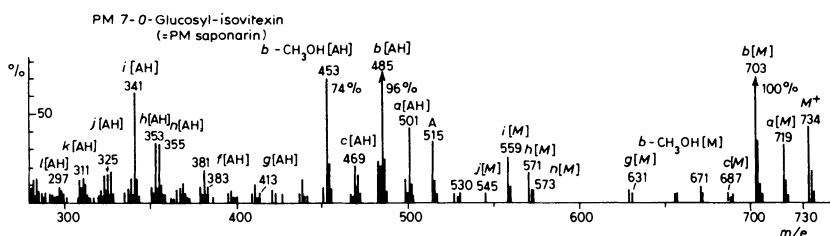


Fig. 8.7 MS of PM 7-*O*-glucosyl-6-*C*-glycosylflavones.

corresponding to the fragmentation of PM 6-*C*-glycosylflavones, the first series related to the molecular peak, the second to the aglycone peak AH (Fig. 8.8). However, the AH – 47 and AH – 63 peaks exhibit a much higher intensity than the corresponding *c* and *b*-MeOH peaks in the MS of PM 6-*C*-glycosylflavones. The nature of the 7-*O*-bound sugar is thus given by the difference  $M - A$  (hexose: 219, deoxyhexose: 189, pentose: 175), the nature of the C-bound sugar by the difference  $AH - i(AH)$  (hexose: 175, deoxyhexose: 145, pentose: 131) and the nature of the flavone moiety by *i*(AH) itself (apigenin: 341, luteolin: 371, tricetin: 401).

The transfer of one hydrogen atom from the *O*-glycosyl residue to the oxygen atom on rupture of the *O*-glycosidic bond is always observed with PM flavone *O*-glycosides, giving rise to a strong aglycone peak AH. This indeed is the case with PM *C*-glycosylflavone *O*-glycosides when the *O*-bound sugar is linked to the B ring, the ion *A* being absent or very weak. The unusual importance of the ion *A* in the MS of 7-*O*-glycosides may be ascribed to the possible hydrogen transfer from the vicinal *C*-glycosyl instead of the *O*-glycosyl residue.

**PM 5,7-dihydroxy-6-*C*-glycosylflavone 7,2''-di-*O*-glycosides** Owing to the different stability of the 7- and 2''-*O*-glycosidic bonds, the MS of these compounds show the characteristic features observed above in 2''-*O*-glycosides and 7-*O*-glycosides (Fig. 8.9). The molecular peak is easily detected and the absence of  $M - 15$  and  $M - 31$  peaks replaced by *SO* and *S* shows the loss of the PM 2''-*O*-glycosyl group as a first step in the fragmentation. Then each of the *SO* and *S* peaks loses in a second step the PM 7-*O*-glycosyl group with hydrogen transfer, giving the homologous peaks *SO* (AH) and *S* (AH). Finally *SO* (AH) leads to *j* (AH), the most important peak at lower  $m/z$  values, which indicates the nature of the flavone moiety (apigenin: 327, luteolin: 357, tricetin: 387), that of the 6-*C*-glycosyl residue being given by  $S(AH) - j(AH)$  (hexose: 158, deoxyhexose: 128, pentose: 114), that of the 7-*O*-glycosyl residue by  $S - S(AH)$  (hexose: 218, deoxyhexose: 188, pentose: 174) and that of the 2''-*O*-glycosyl residue by  $M - S$  (hexose: 235, deoxyhexose: 205, pentose: 191).

Confirmation of the 7,2''-*O*-glycosylation can be found in the MS of the hydrolysis product of the PM derivative showing a characteristic fragmentation pattern initiated by the loss of one molecule of water from the 7- and 2''-hydroxyl

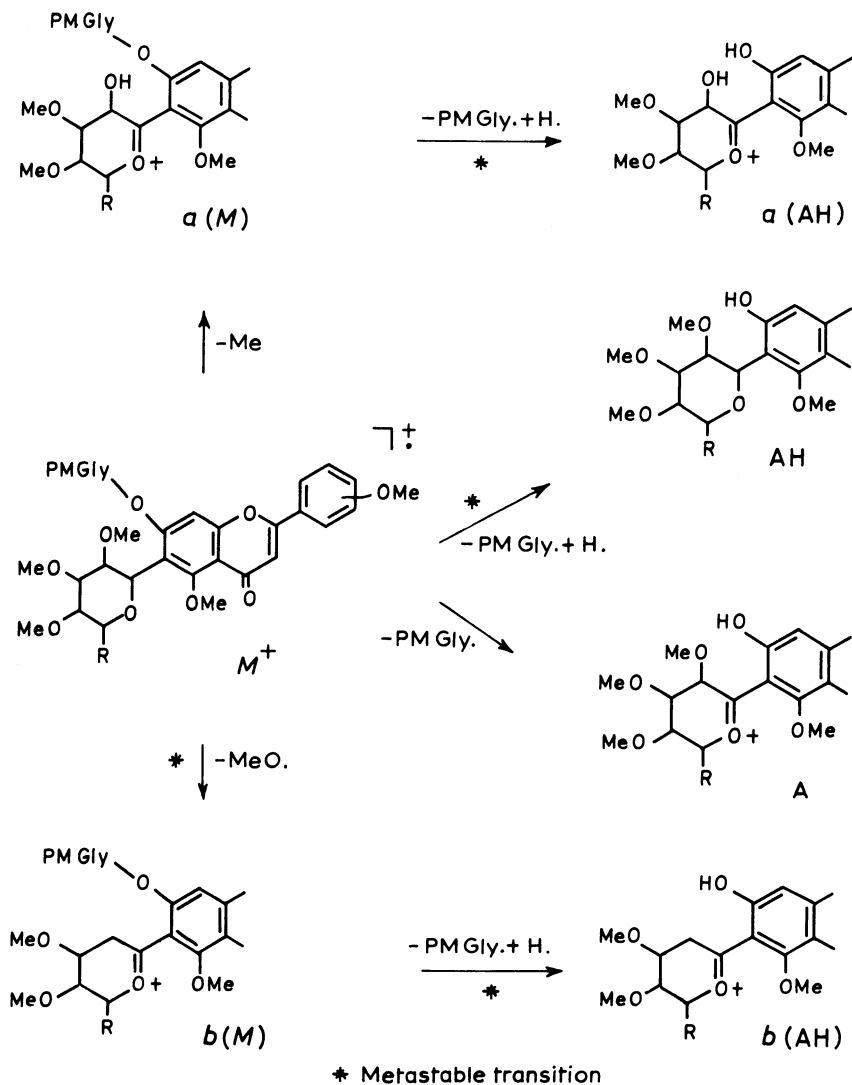


Fig. 8.8 Fragmentation pattern of PM 7-O-glycosyl-6-C-glycosylflavones.

groups. Moreover selective methylation with diazomethane of the phenolic hydroxyl group of this hydrolysis product affords a 2''-monohydroxy derivative showing a characteristic MS (Bouillant *et al.*, 1979b).

#### (d) Circular dichroism

The chiroptical differentiation of 6- and 8-C-glycosylflavones deduced from circular dichroism (CD) studies which had shown that a positive Cotton effect at

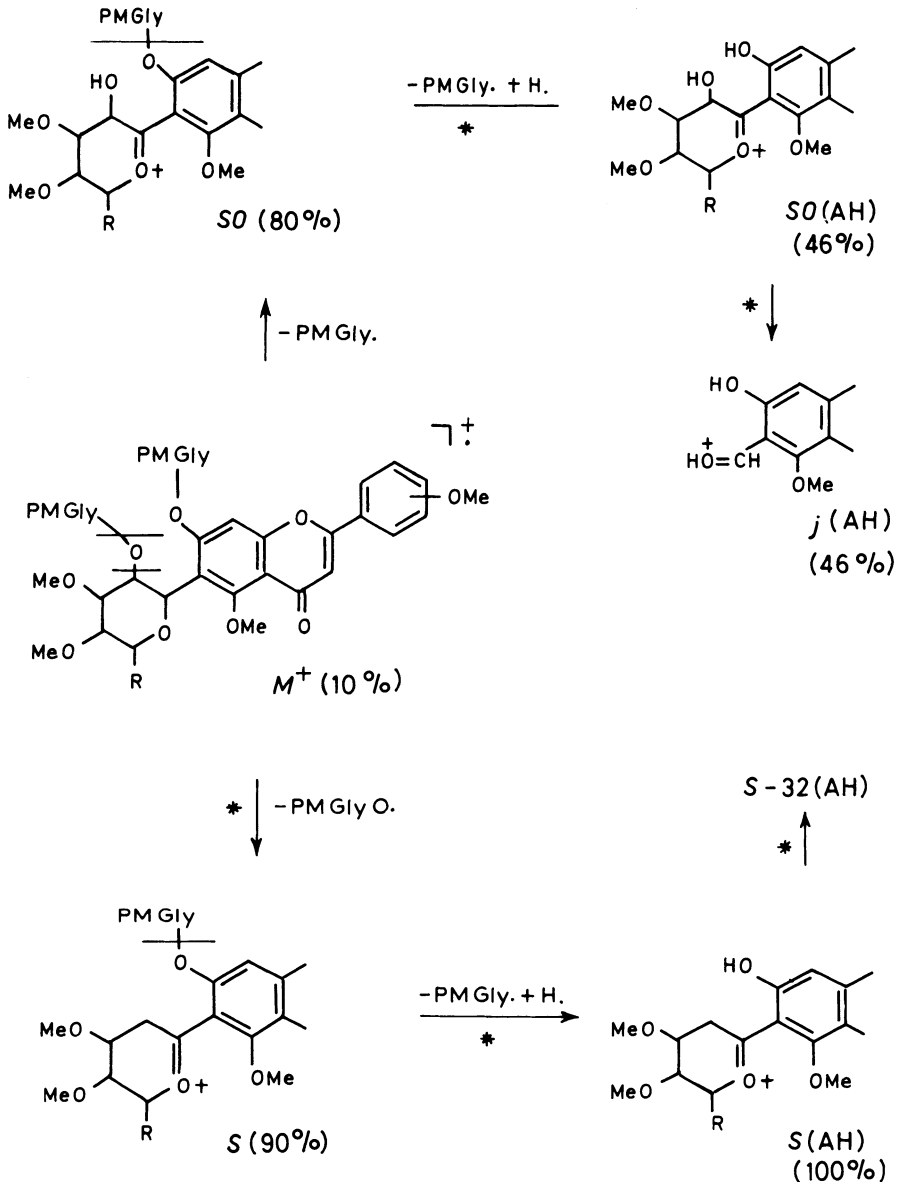


Fig. 8.9 Fragmentation pattern of PM 7,2''-di-O-glycosyl-6-C-glycosylflavones.

250–275 nm indicates a 6-C-linkage whereas a negative one indicates a 8-C-linkage has now been extended to C- $\beta$ -D-galactopyranosyl-, C- $\beta$ -D-xylopyranosyl- and C- $\alpha$ -L-arabinopyranosyl-flavones, and a quadrant rule has been suggested to explain these chiroptical properties. Both 6-C- and



8-*C*- $\alpha$ -L-rhamnopyranosylflavones show a negative CD band at 250–275 nm (Gaffield *et al.*, 1978).

### 8.4.3 Chromatographic methods

Permethylation of synthetic *C*-glycosylflavones for mass spectrometry disclosed interesting differences in the behaviour of PM ethers on silica-gel TLC (Table 8.8). In  $\text{CHCl}_3$ –EtOAc– $\text{Me}_2\text{CO}$  (5:4:1) PM 8-*C*-glycosylapigenins show a lower migration than PM 6-*C*-glycosylapigenins, and a large difference was observed between isomeric PM 6-*C*-glycosylapigenins, PM 6-*C*-glucosylapigenin being well separated from PM 6-*C*-galactosylapigenin and PM 6-*C*-xylosylapigenin being well separated from PM 6-*C*-arabinosylapigenin, whereas PM 6-*C*-glucosyl- and 6-*C*-xylosyl-apigenin on the one hand and PM 6-*C*-galactosyl- and 6-*C*-arabinosyl-apigenin on the other show similar migrations. With PM 6,8-di-*C*-glycosylapigenins, interesting differences were found between PM vicenins-1,-2, and -3, which show similar migrations, and PM neoschaftoside, PM schaftoside and PM isoschaftoside, which migrate well below. Owing to the frequent co-occurrence of these di-*C*-glycosylapigenins in many plant extracts, these differences are extremely useful in analysing such mixtures by mass spectrometry of PM ethers. When the glucose of schaftoside and isoschaftoside is replaced by galactose, the corresponding PM compounds respectively migrate slower than PM schaftoside and PM isoschaftoside. Likewise PM 6,8-di-*C*-arabinosylapigenin migrates much slower than PM 6,8-di-*C*-xylosylapigenin.

**Table 8.8** TLC of permethyl *C*-glycosylflavones

| <i>R<sub>F</sub></i> value on silica gel in $\text{CHCl}_3$ –EtOAc–MeOH (5:4:1) |                      |                        |                      |
|---------------------------------------------------------------------------------|----------------------|------------------------|----------------------|
| PM Mono- <i>C</i> -glycosylflavones                                             |                      |                        |                      |
| Compound                                                                        | <i>R<sub>F</sub></i> | Compound               | <i>R<sub>F</sub></i> |
| PM 6-Glc-apigenin                                                               | 0.36                 | PM 8-Glc-apigenin      | 0.16                 |
| PM 6-Gal-apigenin                                                               | 0.24                 | PM 8-Xyl-apigenin      | 0.14                 |
| PM 6-Xyl-apigenin                                                               | 0.38                 | PM 8-Rha-apigenin      | 0.13                 |
| PM 6-Ara-apigenin                                                               | 0.20                 | PM 8-Glc-luteolin      | 0.11                 |
| PM 6-Rha-apigenin                                                               | 0.17                 | PM 8-Xyl-luteolin      | 0.07                 |
| PM 6-Glc-luteolin                                                               | 0.31                 |                        |                      |
| PM 6-Xyl-luteolin                                                               | 0.30                 |                        |                      |
| PM Di- <i>C</i> -glycosylflavones                                               |                      |                        |                      |
| Compound                                                                        | <i>R<sub>F</sub></i> | Compound               | <i>R<sub>F</sub></i> |
| PM vicenin 1                                                                    | 0.43                 | PM 6,8-di-Xyl-apigenin | 0.40                 |
| PM vicenin 2                                                                    | 0.40                 | PM 6,8-di-Rha-apigenin | 0.25                 |
| PM vicenin 3                                                                    | 0.38                 | PM 6,8-di-Ara-apigenin | 0.15                 |
| PM neoschaftoside                                                               | 0.32                 | PM lucenin 1           | 0.35                 |
| PM schaftoside                                                                  | 0.28                 | PM lucenin 2           | 0.32                 |
| PM isoschaftoside                                                               | 0.23                 | PM lucenin 3           | 0.24                 |

Under UV light, PM 6-C-glycosylapigenins give blue spots, turning to turquoise on spraying with 50%  $\text{H}_2\text{SO}_4$ , whereas PM 8-C-glycosylapigenins give pale-blue spots, turning to yellow-green with  $\text{H}_2\text{SO}_4$ ; PM 6-C- and 8-C-glycosyl-luteolins give pale-blue spots turning to yellow with  $\text{H}_2\text{SO}_4$ ; PM 6,8-di-C-glycosylapigenins give blue spots turning to yellow-green with  $\text{H}_2\text{SO}_4$  and PM 6,8-di-C-glycosyl-luteolins give pale-blue spots turning to orange-yellow with  $\text{H}_2\text{SO}_4$ .

PM 6-C- $\alpha$ -L-arabinopyranosyl ( $R_f$  0.20) and furanosyl ( $R_f$  0.39) acacetins are well separated, whereas the free compounds cannot be separated on PC in 15% HOAc or n-butanol-acetic acid-water (BAW) (4:1:5) and on silica-gel TLC in ethyl acetate-pyridine-water-methanol (80:12:10:5) (APWM). This means that C-arabinofuranosylflavones cannot be easily distinguished from their pyranosyl isomers when the usual solvent systems are used. A good separation can be obtained on silica-gel TLC in  $\text{CHCl}_3$ -MeOH (5:1) (Besson, 1977).

The efficiency of chromatographic methods in the separation of C-glycosylflavones from complex mixtures has been recently demonstrated by the isolation and identification of 11 di-C-glycosides of apigenin, tricetin, tricetin and tricetin 3',4'-dimethyl ether from 80 g of *Apometzgeria pubescens* (Theodor *et al.*, 1980). HPLC has been recently applied to C-glycosylflavonoid analysis by Niemann and Brederode (1978) and by Strack *et al.* (1979) (see also Chapter 1).

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### CHECK LIST OF C-GLYCOSYLFLAVONIDS

#### *Mono-C-glycosylflavones*

- |                                        |                                                            |
|----------------------------------------|------------------------------------------------------------|
| 1 Bayin (7,4'-di-OH 8-Glc)             | 24 X"-O-trans-Caffeoyl 2"-O-glucoside*                     |
| 2 Isovitetexin (5,7,4'-tri-OH 6-Glc)   | 25 7-Bisulphate*                                           |
| 3 7-O-Glucoside                        | 26 Vitexin (5,7,4'-tri-OH 8-Glc)                           |
| 4 7-O-Galactoside*                     | 27 7-O-Glucoside                                           |
| 5 7-O-Xyloside*                        | 28 4'-O-Glucoside                                          |
| 6 4'-O-Glucoside                       | 29 2"-O-Glucoside*                                         |
| 7 2"-O-Glucoside*                      | 30 2"-O-Xyloside                                           |
| 8 2"-O-Xyloside*                       | 31 6"-O-Xyloside                                           |
| 9 2"-O-Arabinoside*                    | 32 X"-O-Arabinoside*                                       |
| 10 2"-O-Rhamnoside*                    | 33 2"-O-Rhamnoside*                                        |
| 11 6"-O-Arabinoside*                   | 34 6"-O-Rhamnoside*                                        |
| 12 7,2"-Di-O-glucoside*                | 35 7-O-Rutinoside*                                         |
| 13 7-O-Glucoside 2"-O-arabinoside*     | 36 2"-O-Sophoroside*                                       |
| 14 7-O-Glucoside 2"-O-rhamnoside*      | 37 6"-O-Gentiobioside (marginatoside)*                     |
| 15 7-O-Galactoside 2"-O-glucoside*     | 38 2"-O-p-Hydroxybenzoyl                                   |
| 16 7-O-Galactoside 2"-O-rhamnoside*    | 39 2"-O-p-Coumaroyl*                                       |
| 17 7-O-Xyloside 2"-O-glucoside*        | 40 4"-O-Acetyl 2"-O-rhamnoside*                            |
| 18 7-O-Xyloside 2"-O-arabinoside*      | 41 7-Bisulphate*                                           |
| 19 7-O-Xyloside 2"-O-rhamnoside*       | 42 7-O-Rutinoside bisulphate*                              |
| 20 4',2"-Di-O-glucoside*               | 43 8-C-β-D-Galactopyranosylapigenin (5,7,4'-tri-OH 8-Gal)* |
| 21 4'-O-Glucoside 2"-O-arabinoside     | 44 6"-O-Acetyl*                                            |
| 22 2"-O-trans-Feruloyl*                | 45 6-C-β-D-Xylopyranosylapigenin (5,7,4'-tri-OH 6-Xyl)     |
| 23 2"-O-trans-Feruloyl 4'-O-glucoside* |                                                            |

- 46 7-*O*-Glucoside\*
- 47 2''-*O*-Rhamnoside
- 48 Isomollupentin (5,7,4'-tri-OH 6-Ara)\*
- 49 7,2''-Di-*O*-glucoside\*
- 50 Mollupentin (5,7,4'-tri-OH 8-Ara)\*
- 51 3'-Deoxyderhamnosylmaysin [5,7,4'-tri-OH 6-(6-deoxyxylohexos-4-ulosyl)]\*
- 52 2''-*O*-Rhamnoside (3'-deoxymaysin)\*
- 53 Swertisin (5,4'-di-OH 7-OMe 6-Glc)
- 54 4'-*O*-Glucoside
- 55 2''-*O*-Glucoside (spinosin)\*
- 56 X''-*O*-Xyloside
- 57 Isoswertisin (5,4'-di-OH 7-OMe 8-Glc)
- 58 4'-*O*-Glucoside
- 59 2''-*O*-Rhamnoside\*
- 60 2''-*O*-Acetyl\*
- 61 Isomolludistin (5,4'-di-OH 7-OMe 6-Ara)\*
- 62 2''-*O*-Glucoside\*
- 63 Molludistin (5,4'-di-OH 7-OMe 8-Ara)\*
- 64 2''-*O*-Glucoside\*
- 65 2''-*O*-Rhamnoside\*
- 66 Isocytiside (5,7-di-OH 4'-OMe 6-Glc)\*
- 67 7-*O*-Glucoside\*
- 68 2''-*O*-Glucoside\*
- 69 2''-*O*-Rhamnoside (isomargariten)\*
- 70 Cytiside (5,7-di-OH 4'-OMe 8-Glc)
- 71 7-*O*-Glucoside
- 72 2''-*O*-Rhamnoside (margariten)\*
- 73 *O*-Acetyl 7-*O*-glucoside
- 74 Embigenin (5-OH 7,4'-di-OMe 6-Glc)
- 75 2''-*O*-Rhamnoside (embinin)
- 76 7,4'-Di-*O*-methylisomollupentin (5-OH 7,4'-di-OMe 6-Ara)\*
- 77 2''-*O*-Glucoside\*
- 78 2''-*O*-Caffeoylglucoside\*
- 79 Iso-orientin (5,7,3',4'-tetra-OH 6-Glc)
- 80 7-*O*-Glucoside
- 81 3'-*O*-glucoside\*
- 82 3'-*O*-Glucuronide\*
- 83 4'-*O*-Glucoside
- 84 2''-*O*-Glucoside\*
- 85 2''-*O*-Xyloside\*
- 86 2''-*O*-Arabinoside\*
- 87 2''-*O*-β-L-Arabinofuranoside\*
- 88 2''-*O*-Rhamnoside\*
- 89 6''-*O*-Arabinoside\*
- 90 4',2''-Di-*O*-glucoside\*
- 91 7-*O*-Rutinoside
- 92 X''-*O*-Acetyl
- 93 2''-*O*-*p*-Hydroxybenzoyl\*
- 94 2''-*O*-*trans*-*p*-Coumaroyl\*
- 95 2''-*O*-*trans*-Caffeoyl\*
- 96 2''-*O*-*trans*-Feruloyl\*
- 97 2''-*O*-*p*-Hydroxybenzoyl
- 98 4'-*O*-Glucoside\*
- 99 2''-*O*-*trans*-Caffeoyl 4'-*O*-Glucoside\*
- 100 2''-(*p*-*O*-Glucosyl)*trans*-caffeoyl 4'-*O*-glucoside\*
- 101 2''-*O*-*trans*-Caffeoylglucoside\*
- 102 7-Bisulphate\*
- 103 Orientin (5,7,3',4'-tetra-OH 8-Glc)
- 104 7-*O*-Glucoside bisulphate\*
- 105 4'-*O*-Glucoside
- 106 2''-*O*-Glucoside\*
- 107 2''-*O*-Xyloside (adonivernith)
- 108 2''-*O*-β-L-Arabinofuranoside\*
- 109 2''-*O*-Rhamnoside\*
- 110 7-*O*-Rhamnoside
- 111 7-Bisulphate\*
- 112 7-*O*-Glucoside bisulphate\*
- 113 6-*C*-β-D-Xylopyranosyl-luteolin (5,7,3',4'-tetra-OH 6-Xyl)
- 114 2''-*O*-Rhamnoside
- 115 Derhamnosylmaysin [5,7,3',4'-tetra-OH 6-(6-deoxyxylohexos-4-ulosyl)]\*
- 116 2''-*O*-Rhamnoside (maysin)\*
- 117 Swertiajaponin (5,3',4'-tri-OH 7-OMe 6-Glc)
- 118 3'-*O*-Glucoside\*
- 119 2''-*O*-Rhamnoside\*
- 120 3'-*O*-Gentiobioside\*
- 121 Isoswertiajaponin (5,3',4'-tri-OH 7-OMe 8-Glc)\*
- 122 Isoscoparin (5,7,4'-tri-OH 3'-OMe 6-Glc)
- 123 7-*O*-Glucoside\*
- 124 Scoparin (5,7,4'-tri-OH 3'-OMe 8-Glc)
- 125 X''-*O*-Rhamnosylglucoside\*
- 126 epi-7-*O*-Glucoside (knautinoside)\*
- 127 3'-*O*-Methyllderhamnosylmaysin [5,7,4'-tri-OH 3'-OMe 6-(6-deoxyxylohexos-4-ulosyl)]\*
- 128 2''-*O*-Rhamnoside (3'-*O*-methylmaysin)\*
- 129 6-*C*-Glucosyldiosmetin (5,7,3'-tri-OH 4'-OMe 6-Glc)
- 130 8-*C*-Glucosyldiosmetin (5,7,3'-tri-OH 4'-OMe 8-Glc)
- 131 7,3'-Di-*O*-methyliso-orientin (5,4'-di-OH 7,3'-di-OMe 6-Glc)\*
- 132 7,3',4'-Tri-*O*-methyliso-orientin (5-OH 7,3',4'-tri-OMe 6-Glc)
- 133 2''-*O*-Rhamnoside (linoside B)
- 134 6''-*O*-Acetyl 2''-*O*-rhamnoside (linoside A)
- 135 Isoaffinetin (5,7,3',4',5'-penta-OH 6-Glc)\*

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- 136 Affinetin (5,7,3',4',5'-penta-OH 8-Glc)\*
- 137 Isopyrenin (5,7,4'-tri-OH 3',5'-di-OMe 6-Glc)\*
- 138 7-O-Glucoside\*
- 139 6-C-Glucosyl-5,7-dihydroxy-8,3',4',5'-tetramethoxyflavone\*
- 140 5-O-Rhamnoside\*

### *Di-C-glycosylflavones*

- 141 Vicenin-2 (5,7,4'-tri-OH 6,8-di-Glc)
- 142 Feruloyl 6''-O-glucoside\*
- 143 X'''-O-Diferuloylhexoside\*
- 144 6,8-Di-C-hexosylapigenin (5,7,4'-tri-OH 6,8-di-Hex)\*
- 145 Vicenin-3 (5,7,4'-tri-OH 6-Glc-8-Xyl)
- 146 Vicenin-1 (5,7,4'-tri-OH 6-Xyl-8-Glc)
- 147 Sinapoyl\*
- 148 Violanthin (5,7,4'-tri-OH 6-Glc-8-Rha)
- 149 Isoviolanthin (5,7,4'-tri-OH 6-Rha-8-Glc)\*
- 150 Schaftoside (5,7,4'-tri-OH 6-Glc-8-Ara)\*
- 151 Feruloyl 6''-O-glucoside\*
- 152 Isoschaftoside (5,7,4'-tri-OH 6-Ara-8-Glc)\*
- 153 Sinapoyl\*
- 154 Feruloyl\*
- 155 Neoschaftoside (5,7,4'-tri-OH 6-Glc-8-Ara)\*
- 156 Neoisoschaftoside (5,7,4'-tri-OH 6-Ara-8-Glc)\*
- 157 Isocorymboside (5,7,4'-tri-OH 6-Gal-8-Ara)\*
- 158 Corymboside (5,7,4'-tri-OH 6-Ara-8-Gal)\*
- 159 6,8-Di-C- $\alpha$ -L-arabinopyranosylapigenin (5,7,4'-tri-OH 6,8-di-Ara)\*
- 160 6-C-Arabinosyl-8-C-pentosylapigenins (5,7,4'-tri-OH 6-Ara-8-Pen)\*
- 161 Almeidain (5,4'-di-OH 7-OMe 6,8-di-Ara)\*
- 162 6-C-Pentosyl-8-C-hexosylacetin (5,7-di-OH 4'-OMe 6-Pen-8-Hex)\*
- 163 7,4'-Di-O-methyl 6,8-di-C- $\alpha$ -L-arabinopyranosylapigenin (5-OH 7, 4'-di-OMe 6,8-di-Ara)
- 164 Lucenin-2 (5,7,3',4'-tetra-OH 6,8-di-Glc)
- 165 Lucenin-3 (5,7,3',4'-tetra-OH 6-Glc-8-Xyl)
- 166 Lucenin-1 (5,7,3',4'-tetra-OH 6-Xyl-8-Glc)
- 167 Carlinoside (5,7,3',4'-tetra-OH 6-Glc-8-Ara)\*
- 168 Neocarlinoside (5,7,3',4'-tetra-OH 6-Glc-8-Ara)\*
- 169 6-C-Arabinosyl-8-C-pentosyl-luteolin (5,7,3',4'-tetra-OH 6-Ara-8-Pen)\*

- 170 6,8-Di-C-glucosylchrysoeriol (5,7,4'-tri-OH 3'-OMe 6,8-di-Glc)\*
- 171 6-C-Arabinosyl-8-C-hexosylchrysoeriol (5,7,4'-tri-OH 3'-OMe 6-Ara-8-Hex)\*
- 172 6,8-Di-C-glycosyldiosmetin (5,7,3'-tri-OH 4'-OMe 6,8-di-Gly)
- 173 6,8-Di-C-glucosyltricin (5,7,3',4',5'-penta-OH 6,8-di-Glc)\*
- 174 6,8-Di-C-hexosyltricin\*
- 175 6-C-Hexosyl-8-C-pentosyltricitins\*
- 176 6-C-Arabinosyl-8-C-glucosyltricin\*
- 177 6,8-Di-C-pentosyltricin\*
- 178 6-C-Hexosyl-8-C-pentosyl 3'-O-methyltricin\*
- 179 6,8-Di-C-glucopyranosyltricin (5,7,4'-tri-OH 3',5'-di-OMe 6,8-di-Glc)\*
- 180 6-C-Glucosyl-8-C-arabinosyltricin\*
- 181 6-C-Arabinosyl-8-C-glucosyltricin\*
- 182 6-C-Xylosyl-8-C-hexosyltricin\*
- 183 6,8-Di-C-arabinosyltricin\*
- 184 6-C-Hexosyl-8-C-pentosylapometzgerin (5,7,5'-tri-OH 3',4'-di-OMe 6-Hex-8-Pen)\*
- 185 6,8-Di-C-arabinosylapometzgerin\*

### *C-Glycosylflavonols*

- 186 6-C-Glucosylkaempferol (3,5,7,4'-tetra-OH 6-Glc)\*
- 187 Keyakinin (3,5,4'-tri-OH 7-OMe 6-Glc)
- 188 6-C-Glucosylquercetin (3,5,7,3',4'-penta-OH 6-Glc)\*
- 189 Keyakinin B (3,5,3',4'-tetra-OH 7-OMe 6-Glc)

### *C-Glycosylflavanones*

- 190 Aervanone (7,4'-di-OH 8-Gal)\*
- 191 Palodulcine B (7,3',4'-tri-OH 8-Gal)\*
- 192 Hemiphloin (5,7,4'-tri-OH 6-Glc)
- 193 Isohemiphloin (5,7,4'-tri-OH 8-Glc)

### *C-Glycosylflavanonols*

- 194 6-C-Glucosyldihydrokaempferol (3,5,7, 4'-tetra-OH 6-Glc)\*
- 195 Keyakanol (3,5,4'-tri-OH 7-OMe 6-Glc)
- 196 6-C-Glucosyldihydroquercetin (3,5,7,3',4'-penta-OH 6-Glc)\*

### *C-Glycosylchalcone*

- 197 3'-C-Glucosylisoliquiritigenin (2',4',4'-tri-OH 3'-Glc)\*

### *C-Glycosyldihydrochalcones*

- 198 Nothofagin (2',4',6',4'-tetra-OH C-Gly)
- 199 Konnanin (2',4',6',3,4'-penta-OH C-Gly)
- 200 Aspalathin (2',4',6',3,4'-penta-OH 3'-Glc)

*Di-C-Glycosyldihydrochalcone*

- 201 3',5'-Di-C-glycosylphloretin (2',4',6',  
4-tetra-OH 3',5'-di-Gly)\*

*C-Glycosylisoflavones*

- 202 Puerarin (7,4'-di-OH 8-Glc)  
203 O-Xyloside  
204 4',6''-Di-O-acetyl  
205 8-C-Glucosylgenistein (5,7,4'-tri-OH  
8-Glc)\*  
206 8-C-Glucosylprunetin (5,4'-di-OH 7-OMe  
8-Glc)\*  
207 Volubilin (5-OH 7,4'-di-OMe 8-Rha)\*

- 208 Isovolubilin (5-OH 7,4'-di-OMe 6-Rha)\*

- 209 8-C-Glucosylorobol (5,7,3',4'-tetra-OH  
8-Glc)\*

- 210 Volubilin (5,7-di-OH 6,4'-di-OMe  
8-Glc)\*

- 211 Dalpanitin (5,7,4'-tri-OH 3'-OMe 8-Glc)

*Di-C-Glycosylisoflavone*

- 212 Paniculatin (5,7,4'-tri-OH 6,8-di-Glc)

*C-Glycosylisoflavanones*

- 213 Dalpanin (cf. Table 8.2)\*  
214 6-C-Glucosyldalbergoidin (5,7,2',4'-tetra-  
OH 6-Glc)\*

This list includes all known naturally occurring C-glycosylflavonoids. Compounds reported as new during the period 1975 to 1980 are asterisked.

## CHAPTER NINE

# *Biflavonoids*

HANS GEIGER and CHRISTOPHER QUINN

### 9.1 COMPLETE LIST OF KNOWN BIFLAVONOIDS

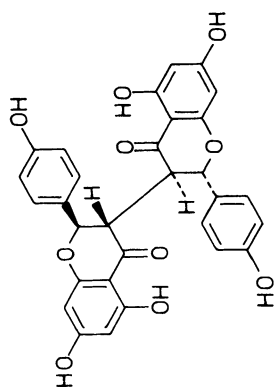
It is only five years since the present authors reviewed the biflavonoids (Geiger and Quinn, 1975). The number of new compounds found during the period 1975 to 1980 is of course limited, but nevertheless there are some very interesting new types, indicating that many more biflavonoids are likely to be uncovered in plants in the future. Three new types of interflavonoid link – 3,3''(1), 3,3'''(3), and 6,6''(4) – have been found (see Table 9.1); the formation of all three types can be explained by the mechanism of phenol oxidation discussed earlier (Geiger and Quinn, 1975). Two compounds with a new substitution pattern have been reported (8A.19), which contains both an apigenin and a luteolin moiety, and (8A.21), a C-methylated biflavonoid. Until recently glycosides had been found only among the group of *Garcinia* biflavonoids; the recent detection of amentoflavone glycosides (8A.2) in the Psilotales demonstrates that glycosylation is by no means restricted to the former group.

In the list of known biflavonoids (Table 9.1), all new compounds are marked by an asterisk; those which are known only synthetically, but, by analogy, might occur naturally, are given in parentheses. The numbering system of the compounds in this list is as follows: the first numeral refers to the type of interflavonyl link; the letter refers to the type of flavonoid moieties present – A = biflavones, B = flavanone–flavone, C = biflavanones and D = others; and the last numeral refers to the individual compound in each group. The names of the compounds are again those given to them by the authors, since no generally accepted system for naming biflavonoids yet exists, and the full systematic names as used in Chemical Abstracts are too tongue-twisting for practical use.

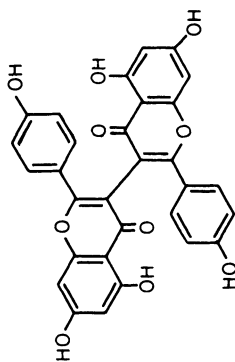
### 9.2 ISOLATION, IDENTIFICATION AND STRUCTURE DETERMINATION

No basically new methods of separation and isolation of biflavonoids have been reported during the past five years. For identification purposes, lists of  $R_F$  values (Lin and Chen, 1974a, 1975; Dossaji *et al.*, 1975b) and of UV-visible spectra using the standard shift reagents (Dossaji *et al.*, 1975b) have been reported.

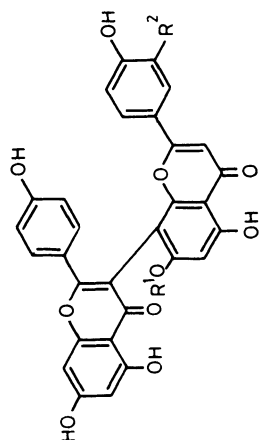
**Table 9.1** Complete list of known biflavonoids



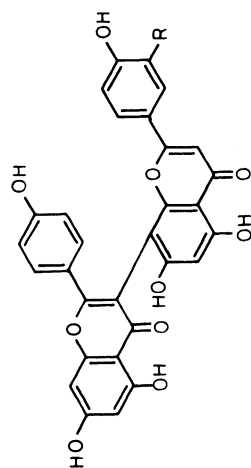
**\*1C.1 Chamaejasmin**  
Hwang and Chang (1979)



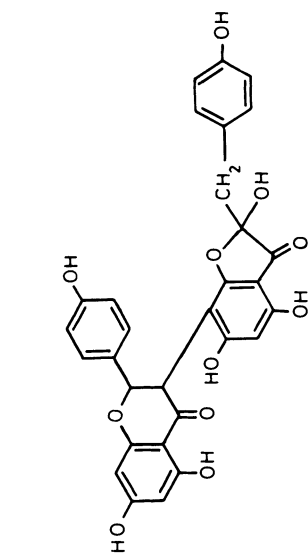
**(1A.1 3,3''-Biapigenin)**  
Geiger and Quinn (1975)



**2B**



**2A**



2D

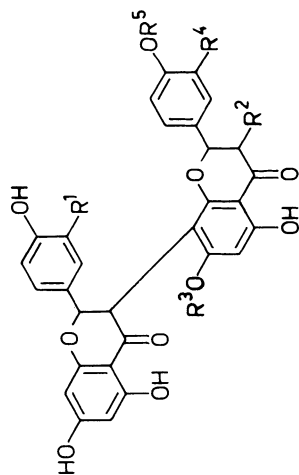
Leading references

Geiger and Quinn (1975)

Geiger and Quinn (1975)

Geiger and Quinn (1975)  
Chen *et al.* (1975c)

Geiger and Quinn (1975)



\*2C

R

H  
OH

R<sup>1</sup> R<sup>2</sup>

H H  
Glc H  
H OH  
H OMe  
Glc OH

R<sup>1</sup> R<sup>2</sup> R<sup>3</sup> R<sup>4</sup> R<sup>5</sup>

H H  
H H  
H OH  
H H  
H OH  
H OH

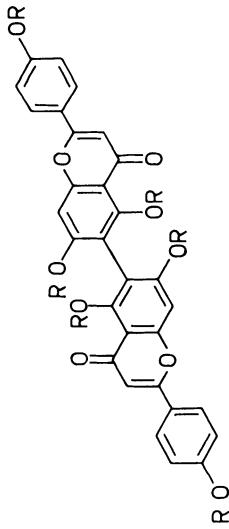
2A.1 Bisdehydro-GB1a  
2A.2 Sahrflavone

2B.1 Volkensiflavone (= BGH-III = talbotiflavone)  
2B.2 Spicatiside  
2B.3 Fukugetin (= BGH-II = morelloflavone)  
2B.4 3-O-Methylfukugetin  
2B.5 Fukugetin

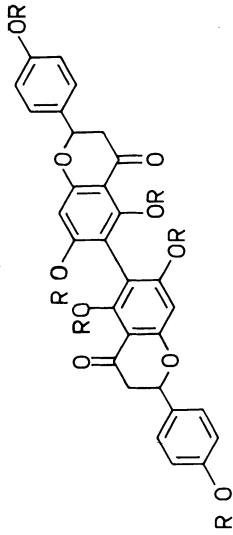
2C.1 GB1a  
\*2C.2 GB1a-7''-O-glucoside  
2C.3 GB1  
2C.4 GB2a  
2C.5 GB2





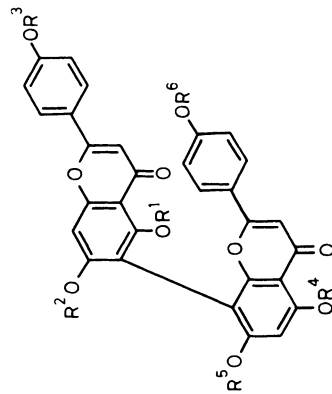


4A

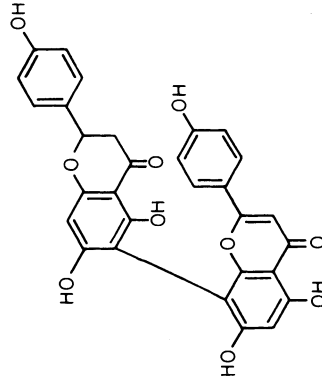


\*4C

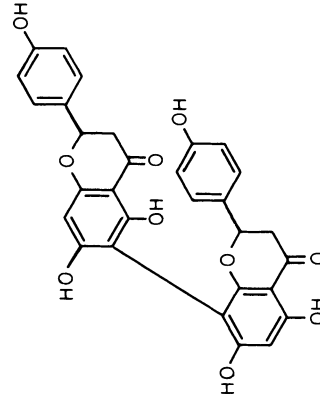
|                                                    | Leading references |                               |
|----------------------------------------------------|--------------------|-------------------------------|
|                                                    | <i>R</i>           |                               |
| (4A.1) Didehydrosuccedaneoflavone                  | H                  | Lin and Chen (1974b)          |
| (4A.2) Didehydrosuccedaneoflavone hexamethyl ether | Me                 | Chen <i>et al.</i> (1975d, e) |
| *4C.1 Succedaneoflavone                            | H                  | Chen and Lin (1975)           |
| (4C.2) Succedaneoflavone hexamethyl ether          | Me                 | Chen <i>et al.</i> (1975d, e) |



5A



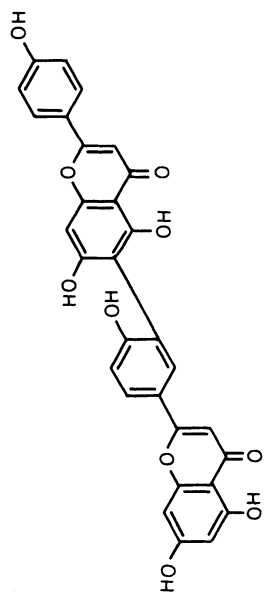
5B



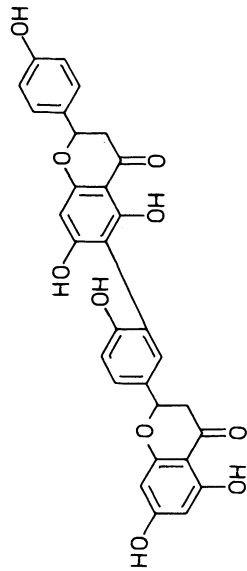
5C



|                                                      |    |    |    |    |    |                                                                              |
|------------------------------------------------------|----|----|----|----|----|------------------------------------------------------------------------------|
| *6A.3 4'-O-Methylcupressuflavone                     | H  | H  | H  | H  | H  | Taufeeq <i>et al.</i> (1978)                                                 |
| 6A.4 7,7''-Di-O-methylcupressuflavone                | H  | Me | H  | H  | Me | Geiger and Quinn (1975); Ahmad and Razaq (1976)                              |
| *6A.5 7,4' or 4'''-Di-O-methyl cupressuflavone       | H  | Me | Me | H  | H  | Ilyas <i>et al.</i> (1978)                                                   |
|                                                      | H  | Me | or | H  | Me |                                                                              |
| 6A.6 7,4',7''-Cupressuflavone trimethyl ether        | H  | Me | H  | H  | Me | Geiger and Quinn (1975)                                                      |
| 6A.7 Cupressuflavone tetramethyl ether (= WB1 = AC3) | H  | Me | Me | H  | Me | Geiger and Quinn (1975); Ilyas <i>et al.</i> (1977b); Ahmad and Razaq (1976) |
| (6A.8 Cupressuflavone pentamethyl ether)             | H  | Me | Me | Me | Me | Geiger and Quinn (1975)                                                      |
| (6A.9 Cupressuflavone hexamethyl ether)              | Me | Me | Me | Me | Me | Geiger and Quinn (1975); Moriyama <i>et al.</i> (1974)                       |
| *6B.1 Mesuaferone B                                  | H  | H  | H  | H  | H  | Raju <i>et al.</i> (1976)                                                    |
| (6B.2 Mesuaferone B hexamethyl ether)                | Me | Me | Me | Me | Me |                                                                              |
| *6C.1 Neorhusflavanone                               | H  | H  | H  | H  | H  | Chen <i>et al.</i> (1975a); Chen <i>et al.</i> (1978)                        |
| (6C.2 Neorhusflavanone hexamethyl ether)             | Me | Me | Me | Me | Me |                                                                              |



7A.1  
Robustaflavone Geiger and Quinn (1975); Lin and Chen (1974d) (isoln. and ppn. of hexamethyl ether).



\*7C.1  
Tetrahydrorobustaflavone Ishratullah *et al.* (1977) (isoln. and ppn. of several methyl ethers)

**Table 9.1** (Contd.)

|                                               |  |  |
|-----------------------------------------------|--|--|
| <p style="text-align: center;"><b>*8A</b></p> |  |  |
| <p style="text-align: center;"><b>*8B</b></p> |  |  |
| <p style="text-align: center;"><b>*8C</b></p> |  |  |

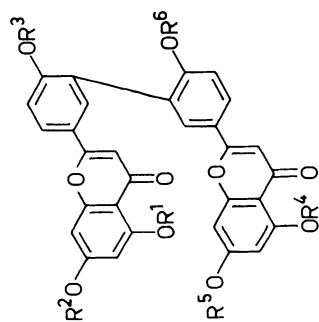
8A.1 Amentoflavone  
 \*8A.2 Amentoflavone glucosides

*Leading references*

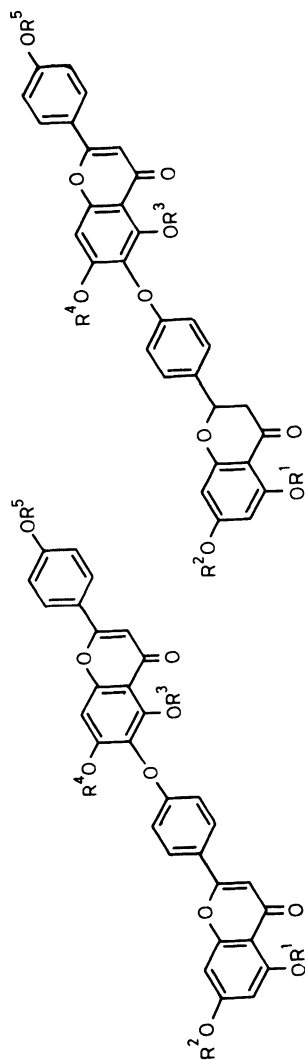
Geiger and Quinn (1975)  
 Wallace and Markham (1978)  
 (detectn. of several  
 glucosides)

|                                                                  |    |    |    |    |    |    |     |    |     |                                                                                                   |
|------------------------------------------------------------------|----|----|----|----|----|----|-----|----|-----|---------------------------------------------------------------------------------------------------|
| 8A.3 Sequoiaflavone                                              | H  | Me | H  | H  | H  | H  | H   | H  | H   | Geiger and Quinn (1975)                                                                           |
| 8A.4 Bilobetin                                                   | H  | H  | Me | H  | H  | H  | H   | H  | H   |                                                                                                   |
| 8A.5 Sotetsuflavone                                              | H  | H  | H  | H  | Me | H  | H   | H  | H   |                                                                                                   |
| 8A.6 Podocarpusflavone A                                         | H  | H  | H  | H  | H  | Me | H   | H  | H   | Geiger and Quinn (1975);<br>Ilyas <i>et al.</i> (1978)                                            |
| 8A.7 Ginkgetin                                                   | H  | Me | Me | H  | H  | H  | H   | H  | H   |                                                                                                   |
| 8A.8 7,7''-Di- <i>O</i> -methylamentoflavone                     | H  | Me | H  | H  | Me | H  | H   | H  | H   |                                                                                                   |
| 8A.9 Podocarpusflavone B (= putraflavone)                        | H  | Me | H  | H  | H  | Me | H   | H  | H   | Geiger and Quinn (1975)                                                                           |
| 8A.10 Amentoflavone 4',7''-dimethyl ether                        | H  | H  | Me | H  | Me | H  | H   | H  | H   |                                                                                                   |
| 8A.11 Isoginkgetin                                               | H  | H  | Me | H  | H  | Me | H   | H  | H   |                                                                                                   |
| 8A.12 Amentoflavone 7'',4''-dimethyl ether                       | H  | H  | H  | H  | Me | Me | H   | H  | H   | Ilyas <i>et al.</i> (1978)                                                                        |
| *8A.13 7,4',7''-Tri- <i>O</i> -methylamentoflavone               | H  | Me | Me | H  | Me | H  | H   | H  | H   |                                                                                                   |
| 8A.14 Sciadopitysin                                              | H  | Me | Me | H  | H  | Me | H   | H  | H   |                                                                                                   |
| 8A.15 Heveaflavone                                               | H  | Me | H  | H  | Me | Me | H   | H  | H   | Geiger and Quinn (1975)                                                                           |
| 8A.16 Kayaflavone                                                | H  | H  | Me | H  | Me | Me | H   | H  | H   |                                                                                                   |
| 8A.17 Amentoflavone 7,7'',4',4'''-tetra-<br>methyl ether (= W13) | H  | Me | Me | H  | Me | Me | H   | H  | H   |                                                                                                   |
| 8A.18 Amentoflavone hexamethyl ether<br>(= Dioonflavone)         | Me | Me | Me | Me | Me | Me | H   | H  | H   | Joly <i>et al.</i> (1980b)                                                                        |
| *8A.19 5'-Methoxybilobetin                                       | H  | H  | Me | H  | H  | H  | OMe | H  | OMe |                                                                                                   |
| 8A.20 5',8''-Bilutocolin                                         | H  | H  | H  | H  | H  | H  | OH  | OH | OH  |                                                                                                   |
| *8A.21 7- <i>O</i> -Methyl-6-methylamentoflavone                 | H  | Me | H  | H  | H  | H  | Me  | H  | H   | Geiger and Quinn (1975)                                                                           |
| 8B.1 2,3-Dihydroamentoflavone                                    | H  | H  | H  | H  | H  | H  | H   | H  | H   |                                                                                                   |
| 8B.2 2,3-Dihydroamentoflavone 7'',4''-dimethyl ether             | H  | H  | H  | H  | Me | Me | H   | H  | H   |                                                                                                   |
| 8B.3 2,3-Dihydrosciadopitysin                                    | H  | Me | Me | H  | H  | Me | H   | H  | H   | Geiger and Quinn (1975)                                                                           |
| (8B.4 2,3-Dihydroamentoflavonehexamethyl ether)                  | Me | Me | Me | Me | Me | Me | H   | H  | H   |                                                                                                   |
| 8C.1 Tetrahydroamentoflavone                                     | H  | H  | H  | H  | H  | H  | H   | H  | H   |                                                                                                   |
|                                                                  |    |    |    |    |    |    |     |    |     | Ishtatullah <i>et al.</i> (1977);<br>El-Sohly <i>et al.</i> (1978);<br>Ahmad <i>et al.</i> (1981) |

Table 9.1 (Contd.)



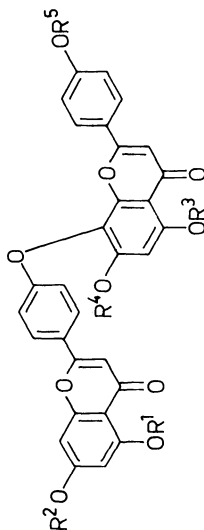
[9A.1(R¹ = R² = R³ = R⁴ = R⁵ = R⁶ = Me)3',3'''-biapigenin-5,5'',7'',4',4'''-hexamethyl ether] Geiger and Quinn (1975)



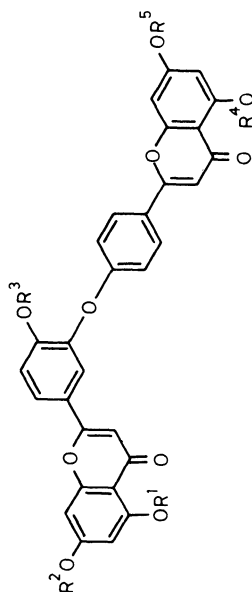
10A

10B

|                                                   | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Leading references      |
|---------------------------------------------------|-------|-------|-------|-------|-------|-------------------------|
| 10A.1 Hinokiflavone                               | H     | H     | H     | H     | H     | Geiger and Quinn (1975) |
| 10A.2 Neocryptomerin                              | H     | Me    | H     | H     | H     |                         |
| 10A.3 Isocryptomerin                              | H     | H     | H     | H     | H     |                         |
| 10A.4 Cryptomerin A                               | H     | H     | H     | Me    | H     |                         |
| 10A.5 Chamaecyparin                               | H     | H     | H     | H     | Me    |                         |
| 10A.6 Hinokiflavone 7,4'''-dimethyl ether         | H     | Me    | H     | Me    | H     |                         |
| 10A.7 Cryptomerin B                               | H     | Me    | H     | H     | Me    |                         |
| 10A.8 Hinokiflavone 7,7'',4'''-trimethyl ether    | H     | H     | H     | Me    | Me    |                         |
| (10A.9 Hinokiflavone pentamethyl ether)           | Me    | Me    | Me    | Me    | Me    |                         |
| 10B.1 2,3-Dihydrohinokiflavone                    | H     | H     | H     | H     | H     | Geiger and Quinn (1975) |
| (10B.2 2,3-Dihydrohinokiflavonepentamethyl ether) | Me    | Me    | Me    | Me    | Me    |                         |



[11A.1( $R^1 = R^2 = R^3 = R^4 = R^5 = \text{Me}$ )4'',5',7'',7'''-pentamethoxy-4',8'-biflavonyl ether] Geiger and Quinn (1975)



12A

Table 9.1 (Contd.)

|                                                       | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Leading references                                       |
|-------------------------------------------------------|-------|-------|-------|-------|-------|----------------------------------------------------------|
| 12A.1 Ochnaflavone(=OSI)                              | H     | H     | H     | H     | H     | Geiger and Quinn (1975);<br>Okigawa <i>et al.</i> (1976) |
| 12A.2 Ochnaflavone 4'-methyl ether (=OSII)            | H     | Me    | H     | H     | H     |                                                          |
| 12A.3 Ochnaflavone 7,4'-dimethyl ether(=OSII)         | H     | Me    | Me    | H     | H     |                                                          |
| (12A.4 Ochnaflavone 4',7,7''-trimethyl ether [=OSIV]) | H     | Me    | Me    | H     | Me    |                                                          |
| 12A.5 Ochnaflavone pentamethyl ether                  | Me    | Me    | Me    | Me    | Me    |                                                          |



For the determination of biflavonoid structure,  $^{13}\text{C}$ -NMR spectroscopy is a new and useful method (Chari *et al.*, 1977) and is described in more detail in Chapter 2. With  $^1\text{H}$ -NMR spectroscopy, the shift reagent  $\text{Eu}(\text{fod})_3$  has been used successfully to establish the location of substituents at the 6 and 8 positions of the A rings (Okigawa *et al.*, 1975).

A new mass spectrometric technique is field desorption (FD), which yields only molecular ions, and sometimes doubly charged ions, but no fragments (Geiger, unpublished); it is therefore the best method for determining the molecular weight unequivocally. Its accuracy is, however, unfortunately not sufficient for providing exact elemental composition data.

### 9.3 SYNTHESIS AND TRANSFORMATIONS

In certain cases (e.g. the partial methyl ethers of agathisflavone or cupressuflavone) synthesis is still the best method to prove the structure. The earlier synthetic work has been reviewed quite comprehensively by Locksley (1973). Recent synthetic work falls into two categories. Some authors are concerned with the synthesis of naturally occurring biflavonoids and their methyl ethers (Ahmad and Razag, 1972, 1976; Chen *et al.*, 1975a,d, 1976a,b, 1978; Gandhi and Tiwari, 1975; Khan *et al.*, 1978; Lindberg *et al.*, 1974; Nakazawa and Wada, 1974; Okigawa *et al.*, 1976). Other authors are carrying out 'pure synthetic work', since the biflavonoids which they are preparing, have not yet been found to be naturally occurring. When new biflavonoids are found or when new syntheses are planned, it would be worthwhile consulting these papers (Berge *et al.*, 1979; Gandhi, 1976, 1977, 1978; Gandhi and Tiwari, 1975, 1976, 1977, 1978; Mathai *et al.*, 1967; Saharia and Tiwari, 1976).

The work on transformation of biflavonoids has been mainly concerned with the dehydrogenation of flavanone to flavone moieties. Lin and Chen (1974b) and Chen and Lin (1976) reported that dehydrogenation with iodine/potassium acetate might lead to isomeric flavone moieties, due to the formation of chalcone intermediates and they demonstrated that dehydrogenation with *N*-bromosuccinimide proceeds without rearrangement. A new reagent for the same reaction – iodine–dimethyl sulphoxide–sulphuric acid – has been described by Fatma *et al.* (1979a).

### 9.4 PHARMACOLOGY

Since several biflavone-containing plants (e.g. *Viburnum prunifolium* L., *Juniperus communis* L. and *Ginkgo biloba* L.) are used medicinally, some pharmacological and biochemical tests have been carried out on a few biflavonoids. These tests have included spasmolysis (Hörhammer *et al.*, 1967), peripheral vasodilatation, antibradykinin activity and antispasmodic action against prostaglandin  $\text{PGE}_1$  (Natarajan *et al.*, 1970), inhibition of cyclic GMP

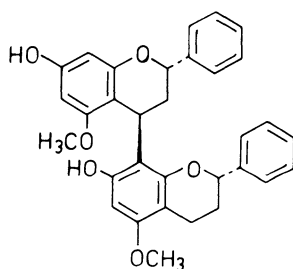
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and cyclic AMP phosphodiesterase (Ruckstuhl *et al.*, 1979; Beretz *et al.*, 1979) and inhibition of hepatoma cells (Joly *et al.*, 1980a). In most tests, biflavonoids proved to be more active than their monomeric counterparts.

### 9.5 SOME UNRELATED BI- AND TRI-FLAVONOID STRUCTURES

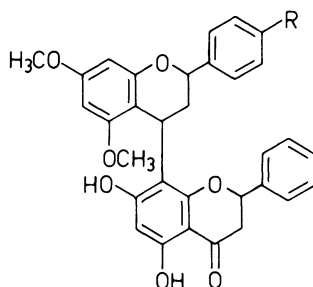
The compounds treated in this section are biogenetically unrelated to the other biflavonoids discussed in this chapter. Most of them (13–17; Table 9.2) are indeed closer related to the proanthocyanidins (see Chapter 8) because the 4 position is involved in the interflavonyl link, but they are not proanthocyanidins in the strict sense, since they do not yield anthocyanidins upon acid treatment. Since their occurrence is to our present knowledge quite erratic, they are not dealt with in the next section of this chapter, so that plant sources are mentioned along with their structures (Table 9.2).

**Table 9.2** List of miscellaneous di- and trimeric flavonoids



#### 13.1 'Biflavon 12'; Camarda *et al.* (1981)

occurrence: Dragon's blood [resin of *Daemonorops draco* (Palmae)]

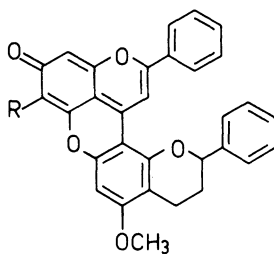


#### 14.1 Xanthorrone

#### 14.2 Hydroxyxanthorrone

occurrence: resin of *Xanthorrhoea* sp. (Liliaceae).

} Birch *et al.* (1967) and (1969);  
} Birch and Dahl (1974)



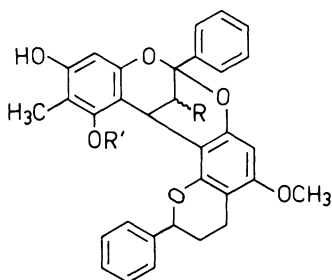
15.1 Nor-dracorubin (R = H);

Cardillo *et al.* (1971)

15.2 Dracorubin (R = CH<sub>3</sub>);

Robertson *et al.* (1950) and references quoted therein.

occurrence: Dragon's blood [resin of *Daemonorops draco* (Palmae)]



16.1 'Prodeoxyanthocyanidin 13'

R

OH

16.2 'Prodeoxyanthocyanidin 14'

H

16.3 'Prodeoxyanthocyanidin 15'

H

16.4 'Trimeric compound 31'

R'

CH<sub>3</sub>

CH<sub>3</sub>

H

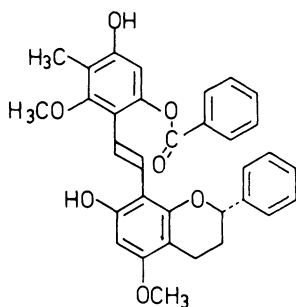
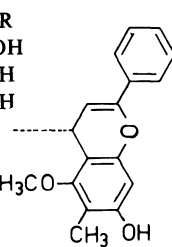
CH<sub>3</sub>

Camarda

*et al.* (1981)

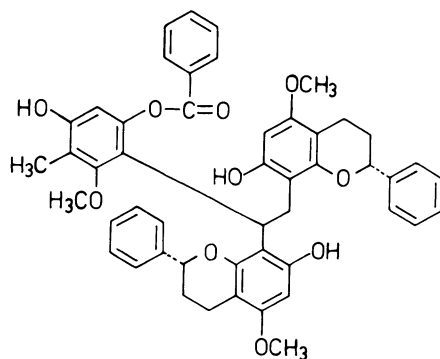
occurrence of 16.1-4: Dragon's blood

[resin of *Daemonorops draco* (Palmae)]



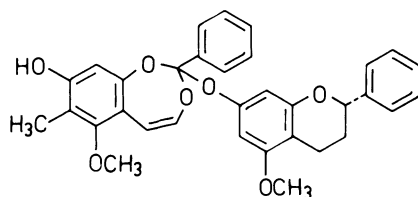
17.1 (2,*S*)-8-*trans*-[2-(6-Benzoyloxy-4-hydroxy-2-methoxy-3-methylphenyl) ethenyl]-5-methoxyflavon-7-ol; Merlini and Nasini (1976).

occurrence: Dragon's blood [resin of *Daemonorops draco* (Palmae)]



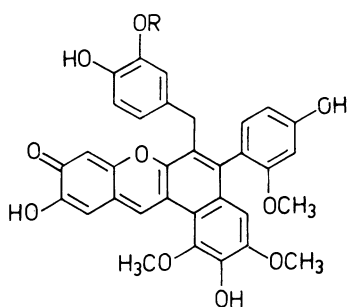
18.1 'Trimeric compound 29'; Camarda *et al.* (1981).

occurrence: Dragons blood [resin of *Daemonorops draco* (Palmae)]



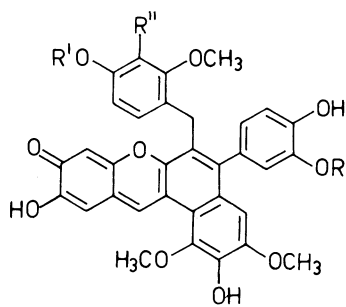
19.1 'Benzodioxepin 21'; Camarda *et al.* (1981)

occurrence: Dragon's blood [resin of *Daemonorops draco* (Palmae)]



20.1 Santalin A (R = H)

20.2 Santalin B (R = CH<sub>3</sub>)



21.1 Santarubin A (R = R'' = H; R' = CH<sub>3</sub>)

21.2 Santarubin B (R = R' = CH<sub>3</sub>; R'' = H)

21.3 Santarubin C (R = R' = H; R'' = OH)

Arnone *et al.* (1975, 1977a, b, 1981).

occurrence: Red Woods from several *Pterocarpus* spp. and *Baphia nitida* (all Fabaceae).

## 9.6 NATURAL OCCURRENCE

The natural occurrence of biflavonoids is presented in Table 9.3 and 9.4. For reasons of brevity all compounds isolated from any member of a genus are listed under that genus. Intrageneric variations should be sought in Geiger and Quinn (1975; Tables 13.2–13.5) and in the more recent references listed at the right of the Tables. The number of species listed for each genus is the number reported to contain biflavonoids. The classification of angiosperm taxa is according to Dahlgren (1980).

Biflavonoids are now known to occur in a wide range of vascular plants, but for non-vascular plants there is still only the single record of a rather unusual substance (*viz.*, 5',8''-biluteolin – 8A.20) in the moss *Dicranum scoparium* Hedw. (Lindberg *et al.*, 1974). A detailed discussion of the range and distribution of biflavonoids may be found in Geiger and Quinn (1975, p. 727 *et seq.*). Although the general picture has changed only slightly since the publication of that account, there have been some significant advances in our knowledge in particular groups, and these will be dealt with here.

### 9.6.1 Psilotales

Amentoflavone has now been reported in three species of *Psilotum* and two species of *Tmesipteris* (Table 9.3), and so appears to be a characteristic constituent of this very primitive order of living vascular plants. Wallace and Markham (1978) also reported the presence of amentoflavone glycosides in *Psilotum nudum* (L.) Beauv. and *Tmesipteris tannensis* (Spreng.) Bernh.; these are the first reports of a biflavone glycoside in nature. An earlier report that hinokiflavone (in the free state) occurs in *Psilotum* has not been borne out (Wallace & Markham, 1978).

### 9.6.2 Cycadales

The initial work by Dossaji *et al.* (1973) and others reported in Geiger and Quinn (1975, p. 728) has been extended to a systematic survey of the order encompassing 82 species drawn from all but one of the known genera (Dossaji *et al.*, 1975a). Their work showed a high degree of uniformity in biflavonoid pattern between species of the same genus, but showed significant differences between genera (Table 9.3), so providing support for the existing generic boundaries. In addition, the three families recognized by Johnson (1959) to comprise this order may be characterized by their biflavonoid profiles. Thus, all genera in the Zamiaceae contain amentoflavone and its methyl ethers only, while the monogeneric Cycadaceae possesses both amentoflavone and hinokiflavone derivatives, including 2,3-dihydro derivatives of both (8B and 10B); by contrast, the monotypic Stangeriaceae is devoid of biflavonoids.

Table 9.3 Natural occurrence of biflavonoids in non-flowering plants

|                      | No.<br>species | Biflavonoid series |                  |     |            | References<br>not in Geiger and Quinn (1975)                            |
|----------------------|----------------|--------------------|------------------|-----|------------|-------------------------------------------------------------------------|
|                      |                | 6A                 | 8A               | 10A | Other      |                                                                         |
| BRYALES              |                |                    |                  |     |            |                                                                         |
| <i>Dicranum</i>      | 1              |                    | 20               |     |            | Lindberg <i>et al.</i> (1974)                                           |
| PSILOTALES           |                |                    |                  |     |            |                                                                         |
| <i>Psilotum</i>      | 3              |                    | 1,2              |     |            | Cooper-Driver (1977); Wallace and Markham (1978)                        |
| <i>Tmesipteris</i>   | 2              |                    | 1,2              |     |            | Cooper-Driver (1977); Wallace and Markham (1978); Voirin and Jay (1977) |
| SELAGINELLALES       |                |                    |                  |     |            |                                                                         |
| <i>Selaginella</i>   | 19             |                    | 1                | 1,3 |            | Voirin (1972)                                                           |
| CYCADALES            |                |                    |                  |     |            |                                                                         |
| Cycadaceae           |                |                    |                  |     |            |                                                                         |
| <i>Cycas</i>         | 9              |                    | 1,5,7            | 1   | 8B.1 10B.1 | Dossaji <i>et al.</i> (1975a)                                           |
| Zamiaceae            |                |                    |                  |     |            |                                                                         |
| <i>Lepidozamia</i>   | 2              |                    | 1,6,7,11,14,17   |     |            |                                                                         |
| <i>Macrozamia</i>    | 14             |                    | 1,4,7,14         |     |            |                                                                         |
| <i>Encephalartos</i> | 28             |                    | 1,4,7,11,14,17   |     |            |                                                                         |
| <i>Dioon</i>         | 6              |                    | 1,3,4,7,14,17,18 |     |            |                                                                         |
| <i>Ceratozamia</i>   | 5              |                    | 1,7,14           |     |            |                                                                         |
| <i>Zamia</i>         | 14             |                    | 1,3,4,7,14,17    |     |            |                                                                         |
| <i>Bowenia</i>       | 2              |                    | 1,4,7,11,14,17   |     |            |                                                                         |
| <i>Microcycas</i>    | 1              |                    | 1,4,5,7          |     |            |                                                                         |
| Stangeriaceae        |                |                    |                  |     |            |                                                                         |
| <i>Stangeria</i>     | 1              |                    | —                | —   | —          |                                                                         |
| GINKGOALES           |                |                    |                  |     |            |                                                                         |
| <i>Ginkgo</i>        | 1              |                    | 4,7,11,14,19     |     |            | Joly <i>et al.</i> (1980b)                                              |
| TAXALES              |                |                    |                  |     |            |                                                                         |
| <i>Amentotaxus</i>   | 1              |                    | 1                |     |            | Khan <i>et al.</i> (1976)                                               |
| <i>Taxus</i>         | 3              |                    | 3,5,7,14         |     |            |                                                                         |
| <i>Torreya</i>       | 1              |                    | 16               |     |            |                                                                         |



Table 9.3 (Contd.)

|                       | No.<br>species | Biflavonoid series |             |         |        | References<br><i>not in Geiger and Quinn (1975)</i> |
|-----------------------|----------------|--------------------|-------------|---------|--------|-----------------------------------------------------|
|                       |                | 6A                 | 8A          | 10A     | Other  |                                                     |
| Taxodiaceae           |                |                    |             |         |        |                                                     |
| <i>Cryptomerid</i>    | 1              |                    |             | 1,4,7   |        |                                                     |
| <i>Cunninghamia</i>   | 2              |                    | 3,5,16      | 1       |        |                                                     |
| <i>Glyptostrobus</i>  | 1              |                    |             | 1,3,4   |        |                                                     |
| <i>Metasequoia</i>    | 1              |                    | 1,12,14     | 1,3     | 8B,2,3 |                                                     |
| <i>Sequoia</i>        | 1              |                    | 3,16        | 1       |        |                                                     |
| <i>Sequoiadendron</i> | 1              |                    | 1,6         | 1       |        |                                                     |
| <i>Sciadopitys</i>    | 1              |                    | 14          |         |        |                                                     |
| <i>Taiwania</i>       | 1              |                    | 1,3,8       | 1,3     | 3A,1-3 | Kamil <i>et al.</i> (1977), Kawano (1980)           |
| <i>Taxodium</i>       | 2              |                    | 1,4,6,12,14 | 1,3,4,7 |        | Ishratullah <i>et al.</i> (1978)                    |

\* Indicates the presence of incompletely identified derivatives.



When Johnson (1959) removed *Stangeria eriopus* (Kunze) Nash from the Zamiaceae to a family of its own, he did so on the basis of its frond morphology. While recognizing that there was 'no apparent character in the reproductive structures inconsistent with its inclusion in the Zamiaceae', he concluded that the profound difference between the systems of growth processes involved in the development of the pinnately veined leaflets of *Stangeria* and the longitudinally veined leaflets found elsewhere in the order, neither of which was easily derivable from the other, indicated an early separation in the evolution of the two lines from an ancient procycadalean ancestor with a more generalized vascularization of the frond. The chemical discontinuity between these two morphological types provides strong independent evidence to support the isolated taxonomic position assigned to *Stangeria eriopus* by Johnson.

There is a striking resemblance in the morphology of the frond of *Stangeria* to those of the eusporangiate ferns belonging to the family Marattiaceae, and the absence of biflavonoids from *Stangeria*, as well as from all the ferns (Cooper-Driver, 1977), might be seen as evidence that this genus is one of the more primitive and fern-like cycads. However, as pointed out by Dossaji *et al.* (1975a), this absence may not be a primitive condition, but might have been derived by the secondary loss of the ability to form biflavonoids during the evolution of this line of cycads. Indeed there is a large weight of evidence from internal anatomy and reproductive structures to show that *Stangeria* is a natural member of the Cycadales, and that the morphological resemblance to marattialean ferns has resulted from convergence in one set of characters by members of two quite distant groups. Further, the occurrence of the same type of biflavonoid (*viz.*, amentoflavones) in three other orders of the gymnosperms (Ginkgoales, Coniferales and Taxales) as well as in two groups of non-seed plants (psilophytes and lycopods) is evidence that the ability to form these biflavones was probably evolved early in the development of vascular plants (Geiger and Quinn, 1975; pp. 735–736), and so is almost certainly primitive in the gymnosperms as a whole. Thus it seems most likely that Johnson's common procycadalean ancestor already had the ability to form these biflavones, and that while this has been retained and even elaborated in the rest of the living members of the order, it has been lost in *Stangeria*, just as has been postulated for the conifer family Pinaceae (Geiger and Quinn, 1975; p. 735).

### 9.6.3 Coniferales

Continuing investigations in the Araucariaceae (e.g. Ilyas *et al.*, 1977b) have confirmed the distinctive complexity of the biflavonoid pattern in this family (Geiger and Quinn, 1975), and have added yet another series of biflavones (*viz.*, robustaflavone – 7A.1), to the four series previously recorded (5A, 6A, 8A and 10A).

Quinn and Gadek (1981) have recently completed an extensive survey of the biflavones of the genus *Dacrydium sensu lato* (family Podocarpaceae). For the

most part, the species were found to contain a complex mixture of amentoflavone derivatives\*, together with trace amounts of hinokiflavone, in line with what has been reported elsewhere in the family (Table 9.3). Three species, however, were found to contain cupressuflavone derivatives as their major biflavonoid constituents and only minor amounts of amentoflavones and hinokiflavone. This striking biochemical discontinuity was used, along with other available data, to remove these three species to a new genus, *Lepidothamnus* Phil. (Quinn, 1982), which is considered to have no close affinity with any of the other species in *Dacrydium*. Even within the remainder of the genus, discontinuities were evident in the distribution of various partial methyl ethers of amentoflavone, which supported the previously expressed views of several workers that the whole concept of the genus *Dacrydium* was artificial. Thus these biochemical data were applied, with all other taxonomic evidence, to the task of redefining the generic boundaries, which has led to the recognition of another two new genera, *Halocarpus* Quinn and *Lagarostrobos* Quinn, in addition to a smaller and more appropriately circumscribed *Dacrydium* Sol. ex Lamb. emend. Quinn (Quinn, 1982).

The presence of these biflavonoids in *Lepidothamnus* is only the second record of cupressuflavone derivatives outside the Cupressaceae and Araucariaceae, the other being from a single species of *Casuarina* (Natarajan *et al.*, 1971). There is good evidence from reproductive morphology, karyotype and embryogeny to suggest that the genus *Lepidothamnus* is a natural member of the Podocarpaceae with no special relationship with either of the other two families. Thus it would seem that this is yet another example of the independent evolution of the ability to form cupressuflavone (Geiger and Quinn, 1975; p. 737).

Within the Taxodiaceae, two recent reports are worth noting. First, Ishratullah *et al.* (1978) have isolated several partial methyl ethers of both amentoflavone and hinokiflavone (8A.6,14; 10A.1,3,4,7) from the leaves of *Taxodium mucronatum* Tenore, which were previously reported to contain hinokiflavone alone (Pelter *et al.*, 1969). These results bring this species into line with the biflavonoid pattern found elsewhere in that genus and the family (Geiger and de Groot-Pfleiderer, 1973). Secondly, Kamil *et al.* (1977) report a similar mixture of amentoflavones and hinokiflavones (8A.1,3,8; 10A.1,3) from the monotypic genus *Taiwania*, but also isolated derivatives of the 3,3'-biapigenin, taiwaniaflavone (3A.1,2,3), previously known only as a synthetic compound.

Although there have been several important contributions to our knowledge of the biflavonoids of subfamily Cupressoideae of the Cupressaceae, this subfamily still presents a complex picture. Taufeeq *et al.* (1978) have recorded amentoflavones (8A.1,6), cupressuflavones (6A.1,3) and a monomethyl ether of hinokiflavone from *Cupressus lusitanica* var. *benthami* Carr., in line with earlier reports of members of all three series of biflavones in most members of this

\* Subsequent work has identified band 2B as sequoiaflavone, 3C as podocarpusflavone A and 4A as sotetsuflavone.

genus (Geiger and Quinn, 1975; Table 13.3). Recent investigations on a wide range of *Juniperus* species indicate that a similar pattern based on the same three series of biflavones is widespread. Such a pattern may be shown to be a characteristic feature of both genera, although preliminary work by one of us (C.J.Q.) on cultivated material obtained from the Royal Botanic Gardens, Sydney, bears out the absence of cupressuflavone derivatives from the leaves of both *J. chinensis* L. and *J. conferta* Parl. as reported by Pelter *et al.* (1971). The occurrence of cupressuflavone derivatives in at least the majority of species of both *Cupressus* and *Juniperus*, and their absence from *Chamaecyparis* (Table 9.3), calls into question the present taxonomy which separates *Juniperus* and *Cupressus* into different tribes, but considers the latter to be very closely related to *Chamaecyparis*. An extensive chemotaxonomic survey should produce data that would be very valuable in reassessing affinities within the subfamily Cupressoideae.

The only recent report for a member of the subfamily Callitroideae is of amentoflavone in the leaves of *Callitris rhomboidea* R.Br. ex A. and L.C. Rich. (Prasad and Krishnamurty, 1977). Preliminary results of a survey of several species of *Callitris* now underway (C. J. Quinn, unpublished results) indicate the biflavonoid pattern in this genus is both highly uniform and relatively simple, including amentoflavone and its mono- and di-methyl ethers only. This contrasts with the early record of hinokiflavone in one species of *Callitris* by Sawada (1958), and the apparent universal occurrence of hinokiflavone in members of the subfamily Cupressoideae, and appears to support the present arrangement of subfamilies, although investigations of other genera in both subfamilies are obviously needed to confirm any such conclusion.

#### 9.6.4 Angiospermae

The discovery of the occurrence of biflavonoids in the angiosperms has now been extended to a total of 11 families, with the report of amentoflavone in the leaves of *Garuga pinnata* Roxb. (Burseraceae; Ansari *et al.*, 1978) and *Nandina domestica* Thunb. (Nandinaceae; Morita *et al.*, 1974), a 3,8-linked biflavanone (2C.1) from the stem of *Lophiola americana* Wood (Amaryllidaceae; Xue and Edwards, 1980) and chamaejasmine (1C.1) in *Stellera chamaejasmine* L. (Thymeliaceae; Hwang and Chang, 1979). This includes the first report of a biflavonoid in a monocotyledon. Biflavonoids of the 2B and 2C series have now been isolated from the leaves, fruits, bark, wood or roots of 16 species of *Garcinia*, as well as *Allanblackia floribunda* Oliv. and *Pentaphalangium solomonse* Warb., and it would seem that these substances may well be a characteristic feature of the Clusiaceae (Guttiferae). In addition, amentoflavone and its derivatives have been isolated from the leaves of *Calophyllum inophyllum* L. and two species of *Garcinia*, and mesuaferrone A and B (6C.1; 6B.1) from the stamens of *Mesua ferrea* L. (Raju *et al.*, 1976, 1978). Amentoflavone derivatives (8A.1, 6) have also been recorded from a third member of the Euphorbiaceae, *viz.*, *Manihot utilissima* Pohl, by Kamil *et al.* (1974).

Table 9.4 Natural occurrence of biflavonoids in the angiosperms

| MAGNOLIIDAE (DICOTYLEDONAE) | Biflavonoid series |     |       |       |             | References                                                                                                                                                              |
|-----------------------------|--------------------|-----|-------|-------|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                             | No.                |     |       |       |             |                                                                                                                                                                         |
|                             | species            | 2B  | 2C    | 8A    | Other       |                                                                                                                                                                         |
| RANUNCULIFLORAE             |                    |     |       |       |             |                                                                                                                                                                         |
| Nandinaeae                  |                    |     |       |       |             |                                                                                                                                                                         |
| <i>Nandina</i>              | 1                  |     |       | 1     |             | Morita <i>et al.</i> (1974)                                                                                                                                             |
| MALVIFLORAE                 |                    |     |       |       |             |                                                                                                                                                                         |
| Rhamnaceae                  |                    |     |       |       |             |                                                                                                                                                                         |
| <i>Phyllogeiton</i>         | 1                  |     |       |       | 2D.1        |                                                                                                                                                                         |
| Euphorbiaceae               |                    |     |       |       |             |                                                                                                                                                                         |
| <i>Hevea</i>                | 1                  |     |       | 15    |             |                                                                                                                                                                         |
| <i>Manihot</i>              | 1                  |     |       | 1,6   |             |                                                                                                                                                                         |
| <i>Putranjiva</i>           | 1                  |     |       | 1,6,9 |             | Kamil <i>et al.</i> (1974)                                                                                                                                              |
| Thymeliaceae                |                    |     |       |       |             |                                                                                                                                                                         |
| <i>Stellera</i>             | 1                  |     |       |       | 1C.1        | Hwang and Chang (1979)                                                                                                                                                  |
| THEIFLORAE                  |                    |     |       |       |             |                                                                                                                                                                         |
| Ochnaceae                   |                    |     |       |       |             |                                                                                                                                                                         |
| <i>Ochna</i>                | 1                  |     |       |       | 12A.1,2,3   | Okigawa <i>et al.</i> (1976)                                                                                                                                            |
| Clusiaceae (Guttiferae)     |                    |     |       |       |             |                                                                                                                                                                         |
| <i>Allanblackia</i>         | 1                  | 1,3 |       |       |             | { Ansari <i>et al.</i> (1976); Bandaranayake <i>et al.</i> (1975);<br>Chen <i>et al.</i> (1975b, c); Crichton and Waterman (1979); Cotterill <i>et al.</i> (1977, 1978) |
| <i>Calophyllum</i>          | 1                  |     |       | 1     |             |                                                                                                                                                                         |
| <i>Garcinia</i>             | 16                 | 1-5 | 1,3-8 | 1,6   |             |                                                                                                                                                                         |
|                             |                    |     |       |       |             |                                                                                                                                                                         |
| <i>Mesua</i>                | 1                  |     |       |       | 6B.1; 6C.1  | Raju <i>et al.</i> (1976, 1978)                                                                                                                                         |
| <i>Pentaphalangium</i>      | 1                  |     | 1     |       |             | Owen and Scheinmann (1974)                                                                                                                                              |
| ROSIFLORAE                  |                    |     |       |       |             |                                                                                                                                                                         |
| Casuarinaceae               |                    |     |       |       |             |                                                                                                                                                                         |
| <i>Casuarina</i>            | 4                  |     |       |       | 6A.1; 10A.1 |                                                                                                                                                                         |

|                            |   |   |                                                 |                                                                               |
|----------------------------|---|---|-------------------------------------------------|-------------------------------------------------------------------------------|
| RUTIFLORAE                 |   |   |                                                 |                                                                               |
| Anacardiaceae              |   |   |                                                 |                                                                               |
| <i>Rhus</i>                | 1 | 1 | 4C.1; 5A.1; 5B.1;<br>5C.1; 6C.1; 7A.1;<br>10A.1 | Lin and Chen (1974c, d); Chen and Lin (1975, 1976); Chen <i>et al.</i> (1978) |
| <i>Semecarpus</i>          | 2 | 1 | 7C.1; 8C.1                                      | Ahmad <i>et al.</i> (1981); Ishratullah <i>et al.</i> (1977)                  |
| <i>Toxicodendron</i>       | 1 | 1 | 8C.1                                            | El Sohly <i>et al.</i> (1978)                                                 |
| Burseraceae                |   |   |                                                 |                                                                               |
| <i>Garuga</i>              | 1 | 1 |                                                 | Ansari <i>et al.</i> (1978)                                                   |
| CORNIFLORAE                |   |   |                                                 |                                                                               |
| Caprifoliaceae             |   |   |                                                 |                                                                               |
| <i>Viburnum</i>            | 1 | 1 |                                                 |                                                                               |
| LILIIDAE (MONOCOTYLEDONAE) |   |   |                                                 |                                                                               |
| LILIIFLORAE                |   |   |                                                 |                                                                               |
| Amaryllidaceae             | 1 | 1 |                                                 | Xue and Edwards (1980)                                                        |
| <i>Lophiola</i>            |   |   |                                                 |                                                                               |

## 9.7 EVOLUTIONARY ASPECTS

The extent of the natural occurrence of biflavonoids in angiosperm taxa is still very imperfectly known, so any conclusions on the taxonomic implications or evolutionary status of these biochemical markers must be speculative. There is evidence, however, that while biflavonoids may prove to be a characteristic feature of some families (e.g. the Clusiaceae) or groups of families, in other cases their distribution is isolated or sporadic (e.g. the isolation of amentoflavone from only one of 22 species of *Viburnum* examined by Hörhammer *et al.*, 1966). Further, these occurrences are mainly in families that are regarded neither as being relatively primitive nor as showing any close affinity with one another. Thus, according to a recently published classification of the angiosperms (Dahlgren, 1980), the ten dicotyledonous families with biflavonoids are assigned to six different superorders as set out in Table 9.4. Of these, only the Ranunculiflorae can be said to be relatively primitive among the angiosperms, and the single occurrence of amentoflavone is recorded in one of the more specialized members of the superorder (see Metcalfe and Chalk, 1957, p. 62). A survey of the more primitive angiosperms is obviously needed, but the apparent absence of these dimers from the Magnolialean and most Ranalean families, and their sporadic occurrence in more specialized families including one monocotyledonous family, does not appear to support the view that the latter have simply retained a primitive pre-angiosperm set of metabolic pathways that have been lost in the majority of angiosperms. It seems more likely that the ability to form biflavonoids was lost early in the evolution of the angiosperms, but that it has arisen again as a more recent specialization in several families quite independently.

Members of one of the two series of biflavonoids most common in non-flowering plants (8A or 10A) have been found in some members of all six dicotyledonous superorders, and amentoflavone or its partial methyl ethers have been found in all but one (the Rosiflorae). This homology of biflavones with the non-flowering plants is difficult to reconcile with the conclusion reached above of their independent evolution. In fact, it would appear that amentoflavones are the generalized and therefore primitive form of biflavonoid in the angiosperms as well as in the vascular plants as a whole (see Geiger and Quinn, 1975; p. 736). In order to reconcile these two lines of evidence, it is suggested that, although the ability to form biflavonoids was lost early in the evolution of the angiosperms, much of the genetic information may have been retained, so that only a few reverse mutations were required to restore full function to the pathway. This hypothesis of parallel evolution from a common gene pool would explain the curious distribution of compounds of the same series in so few extremely diverse angiosperm taxa. Subsequent evolution could easily have modified the pathway in order to form the various specialized biflavonoid series (e.g., 2B, 2C and 6B) found in particular families. Hence, while the presence of biflavonoids appears to be primitive in the non-flowering plants, and the angiosperms must have had

their origin amongst them, within the angiosperms these substances would be seen as a secondary specialization that has arisen independently in several families by parallel evolution.

## 9.8 CONCLUSION

The problems of applying chemical data accumulated piecemeal by many different workers have been discussed by Geiger and Quinn (1975; p. 726), and these problems are still evident in the recent data. For example, although cupressuflavone had already been reported in two species of *Juniperus* by Hameed *et al.* (1973), Ilyas *et al.* (1977a) reported only amentoflavone and hinokiflavone and its monomethyl ether in *J. macropoda* Boiss. Fatma *et al.* (1979b) re-examined the same species and reported, in addition to the above, podocarpusflavone A (8A.6) and cupressuflavone. The problem would be eased if authors made it clear whether they were reporting only some or perhaps only the major biflavonoid fractions present in the species. The presence of further unidentified fractions should always be indicated.

Techniques for the isolation and identification of biflavonoids, as well as the range of commonly occurring structures, are now well established, so that the stage is set for more wide-ranging surveys employing strictly comparable techniques. The studies of Dossaji *et al.* (1975a) and Quinn and Gadek (1981) referred to above are examples of what can be achieved. Such studies, with a stronger taxonomic flavour, as distinct from the strictly chemical approach that has been most common to date, are likely to produce data that will make significant contributions to our understanding of the affinities within several areas of the plant kingdom. In particular, it is desirable that the distribution of biflavonoids among the angiosperms should be investigated, starting with those families where these compounds have already been reported or with families that are closely allied to them. Biflavonoids appear to have come of age as chemotaxonomic characters.

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### CHECK LIST OF ALL KNOWN BIFLAVONOIDS

- |                                      |                                                 |
|--------------------------------------|-------------------------------------------------|
| 1 3,3''-Biapigenin                   | 42 Amentoflavone                                |
| 2 Chamaejasmin*                      | 43 Glucoside*                                   |
| 3 Bisdehydro Garcinia biflavonoid Ia | 44 7-Methyl ether (sequoiflavone)               |
| 4 Sahranflavone                      | 45 4'-Methyl ether (bilobetin)                  |
| 5 Volkensiflavone                    | 46 7''-Methyl ether (sotetsuflavone)            |
| 6 Spicatoside                        | 47 4'''-Methyl ether (podocarpus flavone A)     |
| 7 Fukugetin                          | 48 7,4'-Dimethyl ether (gingketin)              |
| 8 3-Methyl ether                     | 49 7,7''-Dimethyl ether                         |
| 9 Fukugiside                         | 50 7,4'''-Dimethyl ether (podocarpus flavone B) |
| 10 Garcinia biflavonoid Ia           | 51 4', 7''-Dimethyl ether                       |
| 11 7''-Glucoside*                    | 52 4',4'''-Dimethyl ether (isoginkgetin)        |
| 12 Garcinia biflavonoid 1            | 53 7'',4'''-Dimethyl ether                      |
| 13 Garcinia biflavonoid 2a           | 54 7,4',7''-Trimethyl ether                     |
| 14 Garcinia biflavonoid 2            | 55 7,4',4'''-Trimethyl ether (sciadopitysin)    |
| 15 Kolaflavanone*                    | 56 7,7'',4'''-Trimethyl ether (heveaflavone)    |
| 16 Xanthochymusside                  | 57 4',7'',4'''-Trimethyl ether (kayaflavone)    |
| 17 Manniflavanone*                   | 58 7,7'',4',4'''-Tetramethyl ether              |
| 18 Zeyherin                          | 59 Hexamethyl ether (dioonflavone)              |
| 19 Taiwaniaflavone*                  | 60 5'-Methoxybilobetin*                         |
| 20 7''-Methyl ether*                 | 61 5',8''-Biluteolin                            |
| 21 4',7''-Dimethyl ether*            | 62 6-Methylamentoflavone 7-methyl ether*        |
| 22 Succedaneaflavone*                | 63 2,3-Dihydroamentoflavone                     |
| 23 Agathisflavone                    | 64 7'',4'''-Dimethyl ether                      |
| 24 7-Methyl ether                    | 65 2,3-Dihydrosciadopitysin                     |
| 25 7,7''-Dimethyl ether              | 66 Tetrahydroamentoflavone                      |
| 26 7,4'''-Dimethyl ether             | 67 Hinokiflavone                                |
| 27 7,7'',4'''-Trimethyl ether*       | 68 7-Methyl ether (neocryptomerin)              |
| 28 Tetramethyl ether                 | 69 7''-Methyl ether (isocryptomerin)            |
| 29 Rhusflavone                       | 70 4'''-Methyl ether (cryptomerin A)            |
| 30 Rhusflavanone                     | 71 7,7''-Dimethyl ether (chamaecyparin)         |
| 31 Cupressuflavone                   | 72 7,4'''-Dimethyl ether                        |
| 32 7-Methyl ether                    | 73 7'',4'''-Dimethyl ether (cryptomerin B.)     |
| 33 4'-Methyl ether*                  | 74 7,7'',4'''-Trimethyl ether                   |
| 34 7,7''-Dimethyl ether              | 75 2,3-Dihydrohinokiflavone                     |
| 35 7,4'-(or 7,4'')-Dimethyl ether*   | 76 Ochnaflavone                                 |
| 36 7,4',7''-Trimethyl ether          | 77 4'-Methyl ether                              |
| 37 Tetramethyl ether                 | 78 7,4'-Dimethyl ether                          |
| 38 Mesuaferone B*                    | 79 Pentamethyl ether                            |
| 39 Neorhusflavanone*                 |                                                 |
| 40 Robustaflavone                    |                                                 |
| 41 Tetrahydrorobustaflavone*         |                                                 |

\* Newly reported during 1975—1980.

## CHAPTER TEN

# *Isoflavonoids*

P. M. DEWICK

### 10.1 INTRODUCTION

The isoflavonoids are biogenetically related to the flavonoids but constitute a distinctly separate class in that they contain a rearranged  $C_{15}$  skeleton and may be regarded as derivatives of 3-phenylchroman. The enzyme(s) responsible for this biochemical rearrangement would appear to be rather specialized, since isoflavonoids have a very limited distribution, being confined essentially to the subfamily Papilionoideae (Lotoideae) of the Leguminosae. There are, however, occasional examples of their occurrence in the subfamily Caesalpinioideae, and in other families (Rosaceae, Moraceae, Amaranthaceae, Podocarpaceae, Chenopodiaceae, Cupressaceae, Iridaceae, Myristicaceae, Stemonaceae) together with recent reports of their isolation from microbial sources. Unless otherwise stated, all plants mentioned in this chapter are members of the Leguminosae.

Structurally, the isoflavonoids may be subdivided into several classes according to oxidation levels in the skeleton, and the complexity of the skeleton, for instance, formation of further heterocyclic rings. The structural variety encountered is surprisingly large, and several new classes have been identified during the period of review.

This chapter covers the important developments in isoflavonoid chemistry and biochemistry since the previous review of Wong (1975) and includes the data reported briefly in the addendum to that chapter. The last few years have seen considerable activity in the isoflavonoid field, and the number of known naturally occurring isoflavonoid aglycones has more than doubled during this period. Reviews covering the occurrence of isoflavonoids (Bandyukova and Kazakov, 1978; Torck, 1976), and the chemistry of coumestans (Darbarwar *et al.*, 1976), pterocarpanoids (pterocarpanes, pterocarpenes, coumestans) (Jain and Tuli, 1978) and rotenoids (Jain *et al.*, 1978b) have been published.

### 10.2 SPECTROSCOPY

Although the established spectral techniques (UV, IR,  $^1\text{H}$ -NMR, MS etc.) are still essential for structure determination of isoflavonoids,  $^{13}\text{C}$ -NMR is a potentially useful tool yet to be generally applied in this area. A number of papers

containing  $^{13}\text{C}$ -NMR spectral data for isoflavonoids have been published and are covered in detail in Chapter 2. MS and NMR data, where relevant, will be included in the appropriate class section. One important advance in identification techniques for isoflavonoids is in the use of combined GLC–MS with selected ion monitoring (Woodward, 1980b). Each compound in a mixture is monitored by means of two or three prominent ions chosen because of high relative intensities and because they were not present in the mass spectrum of other compounds of the mixture. It was possible by this technique to detect and measure a wide range of isoflavonoids produced in inoculation droplets from *Monilinia fructicola*–infected *Phaseolus vulgaris*. Detection limits were of the order of 0.1–3 pmol.

As in other flavonoid classes, UV spectroscopy is of prime importance in structure determination, particularly when only small amounts of sample are available. UV spectral data for isoflavones are well documented (Mabry *et al.*, 1970), but no such comprehensive information and diagrams are available for the other classes of isoflavonoids. Because the presence of UV absorbances at particular wavelengths together with the shape of the UV spectrum is so characteristic for some of the isoflavonoid classes, some typical neutral UV spectra (EtOH) are illustrated in Fig. 10.1. The precise absorption wavelength observed will naturally depend on the substitution pattern of the compound, and in some cases, this may result in the presence of an additional band, cf. maackiain and medicarpin.

The use of shift reagents is of less value than in the UV spectroscopy of flavonoids because of the lack of conjugation between the two aromatic nuclei in many classes of isoflavonoids. Most investigators record only shifts with NaOH to establish the presence/absence of phenolic groupings.

*Isoflavones* exhibit an intense absorption at  $\sim 245$ – $275$  nm and generally a less intense band or inflection at  $\sim 300$ – $340$  nm.

*Isoflavanones* show absorption at  $\sim 270$  nm and  $\sim 310$  nm, and the spectrum shape resembles that of a simple aryl aldehyde or ketone.

*Isoflavans* and *Pterocarpan*s, lacking any additional conjugation with the aromatic rings, typically absorb at  $\sim 281$  and  $287$  nm, but the two peaks may not always be resolved. With 8,9-disubstituted pterocarpanes, an intense band at  $300$ – $310$  nm is also observed – this is more marked with methylenedioxy rather than dimethoxy substituents and does not occur with 9,10-disubstituted pterocarpanes (Ingham and Dewick, 1980b). This extra band also occurs in the corresponding isoflavan spectra ( $\sim 300$  nm), but overlaps the other bands.

*6a-Hydroxypterocarpan*s exhibit spectra identical with the corresponding pterocarpanes, but may easily be differentiated since the compounds readily dehydrate in acid solution to yield pterocarpenes. After the addition of one or two drops of

HCl to the cuvette, the characteristic stilbene-like spectrum of the *pterocarpene* rapidly appears. This shows twin peaks at  $\sim 335$  nm and 353 nm.

*Coumestans* show intense absorption at about 340–350 nm, dependent on substitution pattern, together with a sharp, low intensity band at 300–310 nm. Their intense blue to violet fluorescence under UV light is, however, their most characteristic property.

*Rotenoids* usually show absorption in the region 280–300 nm with often a shoulder at  $\sim 315$  nm, and spectra of *12a-hydroxy-* and *12a-methoxy-rotenoids* are virtually identical.

*Dehydrorotenoids* typically exhibit two bands at 275–280 nm and 300–320 nm, and further hydroxyl substitution at C-6 has little effect on the spectrum. *6-Oxodehydrorotenoids* absorb similarly, but at the slightly lower wavelengths 260–270 nm and 290–300 nm, and the increased conjugation may result in a low intensity band at higher wavelength, typically 320–350 nm.

*Isoflav-3-enes* show a broad band at  $\sim 320$ –325 nm in the UV spectrum, and *3-arylcoumarins* a similarly shaped spectrum with absorption in the region 340–360 nm. *3-Aryl-4-hydroxycoumarin* spectra are essentially the same.

*2-Arylbenzofuran* spectra are stilbene-like and resemble those of pterocarpenes, although usually at rather lower wavelengths, with the twin peaks at  $\sim 320$  nm and  $\sim 335$  nm.

*Isoflavanquinones* exhibit a strong absorption at 265–270 nm, with a weaker band at 360–400 nm, depending on substitution patterns.

Other classes of isoflavonoid are relatively rare, and it is not possible to generalize about typical spectra.

### 10.3 ISOFLAVONES

Isoflavones (*10.1*) continue to be the most abundant of the natural isoflavonoid derivatives, and over 160 isoflavone aglycones are now recognized. Table 10.1 lists the structures and sources of new isoflavones, and also newer sources of known compounds. The four simple isoflavones daidzein, formononetin, genistein and biochanin A are extremely common, and mention of new sources in the Table is restricted to genus only.

In the last review, only two isoflavones, tlatlancuayin and podospicatin, lacking 4'-oxygenation were known. Two compounds with no B-ring substitution at all have now been isolated, 5-hydroxy-7-methoxyisoflavone from

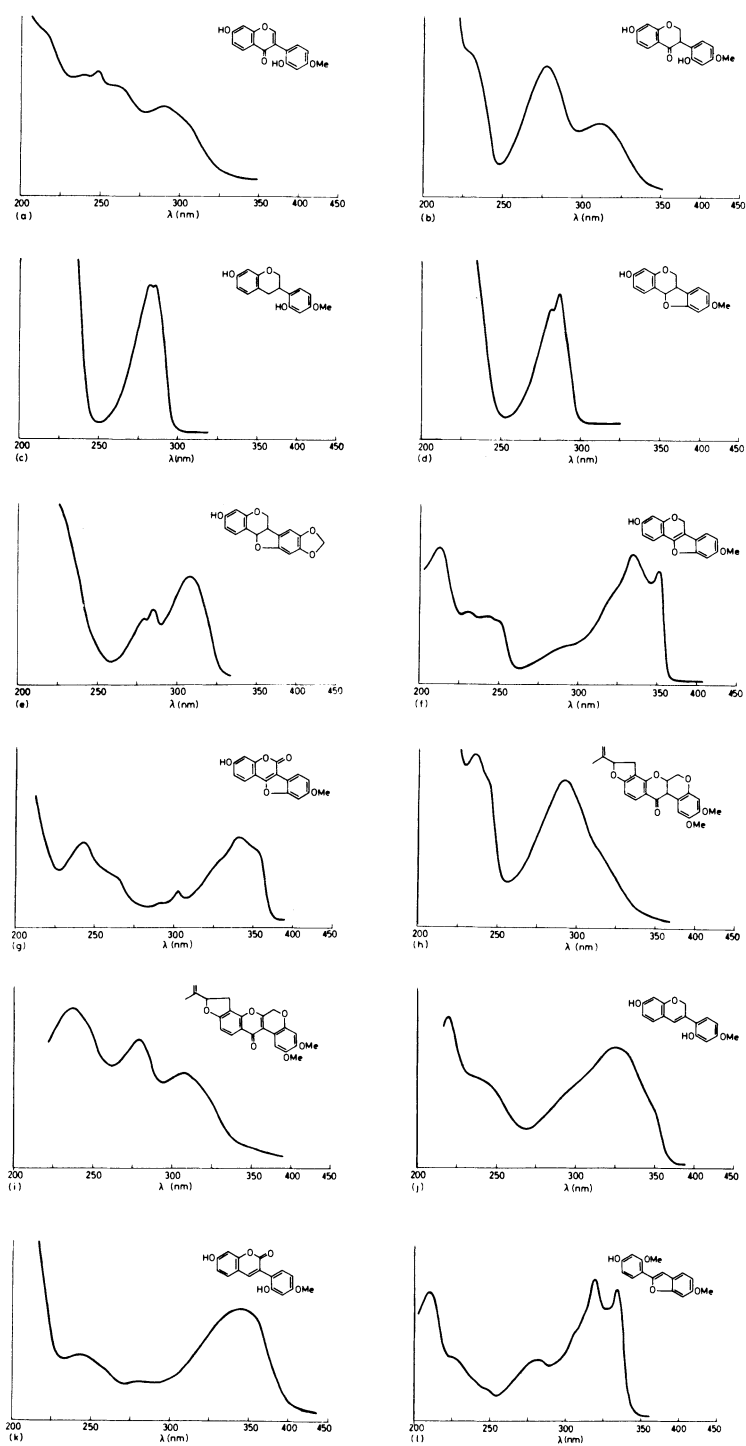
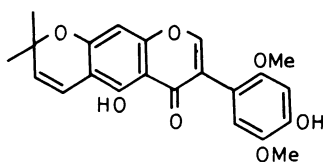
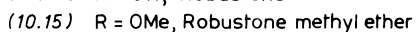
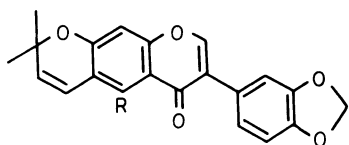
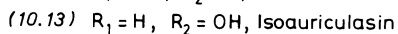
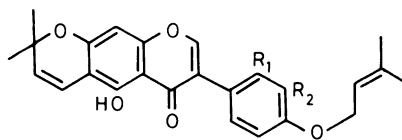
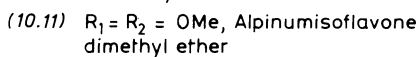
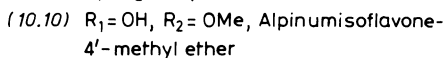
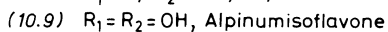
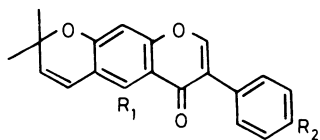
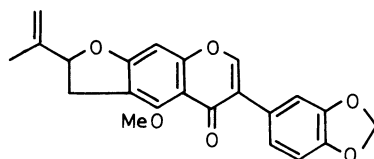
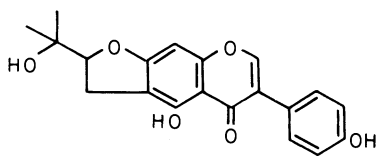
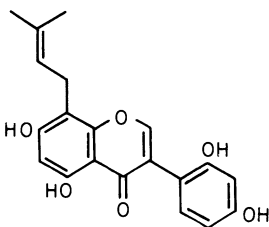
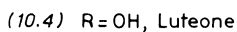
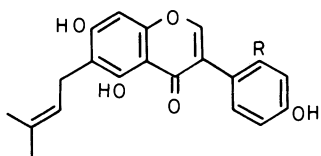
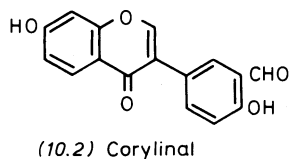
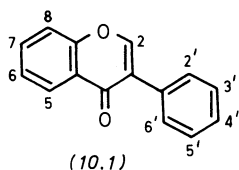
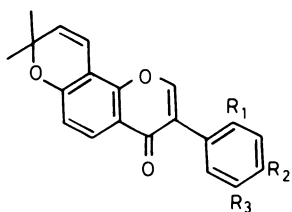


**Fig. 10.1** UV spectra (EtOH) of isoflavonoids.

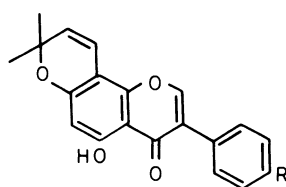




(10.17)  $R_1 = R_3 = \text{H}$ ,  $R_2 = \text{OMe}$ ,  
Calopogonium isoflavone A

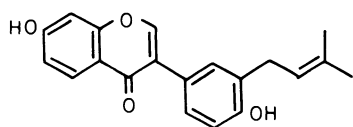
(10.18)  $R_1 = \text{H}$ ,  $R_2 R_3 = \text{OCH}_2\text{O}$ ,  
Calopogonium isoflavone B

(10.19)  $R_1 = R_2 = R_3 = \text{OMe}$ , Barbigerone

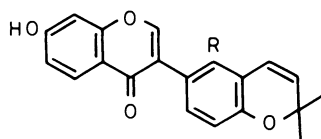


(10.20)  $R = \text{OH}$ , Derrone

(10.21)  $R = \text{OMe}$ , Derrone-4'-methyl ether

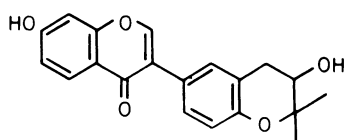


(10.22) Neobavaisoflavone

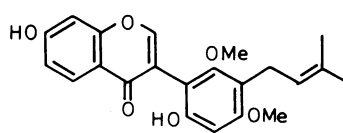


(10.23)  $R = \text{H}$ , Corylin

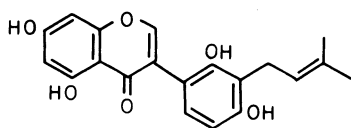
(10.25)  $R = \text{OH}$ , Glabrone



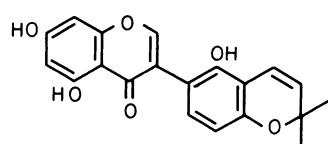
(10.24) Psoralenol



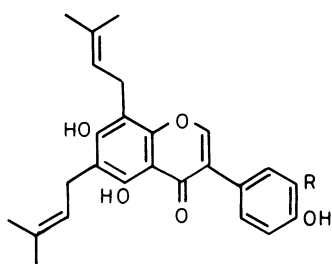
(10.26) Licoricone



(10.27) Licoisoflavone A

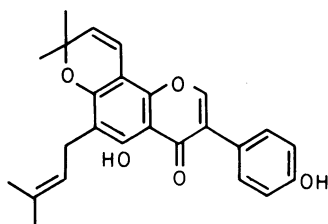


(10.28) Licoisoflavone B



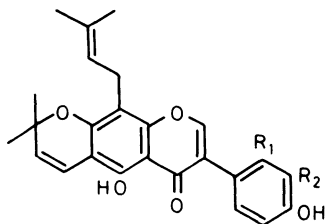
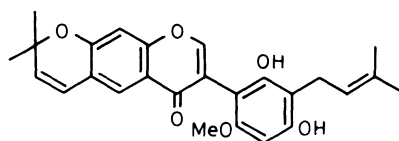
(10.29)  $R = \text{H}$ , 6,8-Di-(dimethylallyl)-  
genistein

(10.30)  $R = \text{OH}$ , 6,8-Di-(dimethylallyl)-  
orobol



(10.31) Osajin

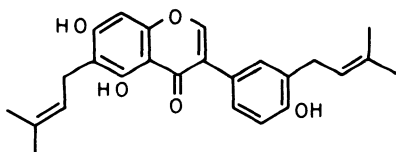


(10.32)  $R_1 = \text{OH}$ ,  $R_2 = \text{H}$ , Auriculatin(10.33)  $R_1 = \text{H}$ ,  $R_2 = \text{OH}$ , Auriculasin

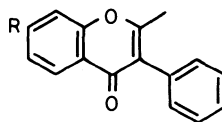
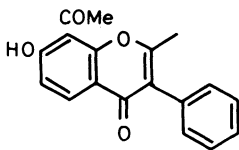
(10.34) Cajaisoflavone

*Derris robusta* seed (Chibber and Sharma, 1979b), and 5,7-dimethoxyisoflavone from immature fruit of groundnut (*Arachis hypogaea*) infected with *Aspergillus flavus* (Turner *et al.*, 1975). These compounds are remarkable because current theories for the aryl migration during the biosynthesis of isoflavones (see Section 10.18) require the presence of a 4'-(or 2'-) oxygen function. Both tlatlancuayin and podospicatin contain 2'-oxygen functions. Two other isoflavones, 5,7,2'-trihydroxyisoflavone (as its 7-glucoside) from *Cajanus cajan* (Bhanumati *et al.*, 1979b) and betavulgarin (2'-hydroxy-5-methoxy-6,7-methylenedioxyisoflavone or 2'-demethyltlatlancuayin), a phytoalexin from the *Cercospora beticola*-infected leaves of *Beta vulgaris* (Chenopodiaceae) (Geigert *et al.*, 1973) are further examples of 4'-deoxyisoflavones.

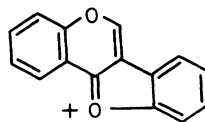
Some novel 2-methylisoflavones, also lacking any B-ring substitution, have been isolated from *Glycyrrhiza glabra* root (Bhardwaj *et al.*, 1976, 1977). These are 7-hydroxy-2-methylisoflavone (10.36) and its 7-acetyl (10.38), 7-methyl (10.37) and 8-acetyl (glyzarin) (10.39) derivatives. The structures have been



(10.35) 6,3'-Di-(dimethylallyl)-genistein

(10.36)  $R = \text{OH}$ , 7-Hydroxy-2-methylisoflavone(10.37)  $R = \text{OMe}$ , 7-Methoxy-2-methylisoflavone(10.38)  $R = \text{OCOMe}$ , 7-Acetoxy-2-methylisoflavone

(10.39) Glyzarin



(10.42)

confirmed by Perkin condensation of a deoxybenzoin with acetic anhydride-sodium acetate. Whether or not these compounds are true isoflavonoids, i.e.

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Table 10.1 Isoflavones

| Isoflavone                                     | Substituents |   |           |   |          |                           |           |     |    |  |
|------------------------------------------------|--------------|---|-----------|---|----------|---------------------------|-----------|-----|----|--|
|                                                | 5            | 6 | 7         | 8 | 2'       | 3'                        | 4'        | 5'  | 6' |  |
| Daidzein                                       |              |   | OH        |   |          |                           | OH        |     |    |  |
| Formononetin                                   |              |   | OH        |   |          |                           | OMe       |     |    |  |
| Isoformononetin                                |              |   | OMe       |   |          |                           | OH        |     |    |  |
| Dimethyldaidzein                               |              |   | OMe       |   |          |                           | OMe       |     |    |  |
| 7,2',4'-Trihydroxy-<br>2'-Hydroxyformononetin  |              |   | OH<br>OH  |   | OH<br>OH |                           | OH<br>OMe |     |    |  |
| Theralin                                       |              |   | OH        |   | OMe      |                           | OH        |     |    |  |
| 3'-Hydroxydaidzein                             |              |   | OH        |   |          | OH                        | OH        |     |    |  |
| 3'-Hydroxyformononetin<br>(Calycosin)          |              |   | OH        |   |          | OH                        | OMe       |     |    |  |
| Syanedin                                       |              |   | OMe       |   |          | OMe                       | OH        |     |    |  |
| Cabreuvin                                      |              |   | OMe       |   |          | OMe                       | OMe       |     |    |  |
| Pseudobaptigenin ( $\psi$ -Baptigenin)         |              |   | OH        |   |          | OCH <sub>2</sub> O        |           |     |    |  |
| 7-Methoxy-3',4'-methylenedioxy-<br>Koparin     |              |   | OMe<br>OH |   |          | OCH <sub>2</sub> O<br>OH  | OMe       |     |    |  |
| 2'-Hydroxy-7,3',4'-trimethoxy-<br>Glyzaglabrin |              |   | OMe<br>OH |   | OH<br>OH | OMe<br>OCH <sub>2</sub> O | OMe       |     |    |  |
| 7,2',4',5'-Tetramethoxy-                       |              |   | OMe       |   | OMe      |                           | OMe       | OMe |    |  |
| 7,2'-Dimethoxy-4',5'-<br>methylenedioxy-       |              |   | OMe       |   | OMe      | OCH <sub>2</sub> O        |           |     |    |  |
| Gliricidin                                     |              |   | OH        |   |          | OH                        | OMe       | OH  |    |  |
| 5-Hydroxy-7-methoxy-                           | OH           |   | OMe       |   |          |                           |           |     |    |  |
| 5,7-Dimethoxy-                                 | OMe          |   | OMe       |   |          |                           |           |     |    |  |
| 5,7,2'-Trihydroxy-(as glucoside)               | OH           |   | OH        |   | OH       |                           |           |     |    |  |

## Plant sources

## References

- Albizia*, *Dalbergia*, *Echinopartum*, *Glycine*,  
*Lespedeza*, *Machaerium*, *Phaseolus*,  
*Piptanthus*, *Pterodon*, *Pueraria*,  
*Aspergillus niger*  
*Streptomyces xanthophaeus*  
*Albizia*, *Amorpha*, *Cajanus*, *Cicer*, *Cladrastis*,  
*Dalbergia*, *Echinopartum*, *Ferreira*,  
*Glycyrrhiza*, *Machaerium*, *Myroxylon*,  
*Onobrychis*, *Ononis*, *Pericopsis*, *Piptanthus*,  
*Pueraria*, *Sophora*, *Spartium*, *Trifolium*,  
*Vatairea*, *Viola* (Myristicaceae), *Wistaria*.  
*Machaerium villosum*  
*Dalbergia miscolobium*  
*Pterodon apparicioi*  
*Phaseolus vulgaris*  
*Viola caducifolia* (Myristicaceae) *V. multinervia*  
*Thermopsis alterniflora*  
*Machaerium villosum*  
*Bowdichia nitida*  
*Cyclobium clausenii*  
*Machaerium mucronulatum*, *M. villosum*  
*Myroxylon balsamum*  
*M. peruiiferum*  
*Sophora secundiflora*  
*Trifolium pratense*  
*Pisum sativum*  
*Calopogonium mucunoides*  
*Myroxylon peruiiferum*  
*Cladrastis platycarpa*  
*Dalbergia assamica*  
*D. sericea*  
*D. spruceana*  
*D. stevensonii*  
*Trifolium pratense*  
*Calopogonium mucunoides*  
*Castanospermum australe*  
*Myroxylon peruiiferum*  
*Glycyrrhiza glabra*  
*Amorpha fruticosa*  
*Calopogonium mucunoides*  
*Pterodon apparicioi*  
  
*Gliricidia sepium*  
*Derris robusta*  
*Arachis hypogaea*  
*Cajanus cajan*
- Umezawa *et al.* (1975)  
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 Berry *et al.* (1977)  
 Maranduba *et al.* (1979)  
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 Ognyanov and Somleva (1980)  
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 Galina and Gottlieb (1974)  
  
 Manners and Jurd (1979)  
 Chibber and Sharma (1979b)  
 Turner *et al.* (1975)  
 Bhanumati *et al.* (1979b)

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Table 10.1 (Contd.)

| Isoflavone                                | Substituents |     |     |   |     |                    |     |     |    |  |
|-------------------------------------------|--------------|-----|-----|---|-----|--------------------|-----|-----|----|--|
|                                           | 5            | 6   | 7   | 8 | 2'  | 3'                 | 4'  | 5'  | 6' |  |
| Genistein                                 | OH           |     | OH  |   |     |                    | OH  |     |    |  |
| Biochanin A                               | OH           |     | OH  |   |     |                    | OMe |     |    |  |
| 5-Methylgenistein                         | OMe          |     | OH  |   |     |                    | OH  |     |    |  |
| Prunetin                                  | OH           |     | OMe |   |     |                    | OH  |     |    |  |
| 5-Methylbiochanin A                       | OMe          |     | OH  |   |     |                    | OMe |     |    |  |
| 7-Methylbiochanin A<br>(as C-rhamnosides) | OH           |     | OMe |   |     |                    | OMe |     |    |  |
| 2'-Hydroxygenistein                       | OH           |     | OH  |   | OH  |                    | OH  |     |    |  |
| 2'-Hydroxybiochanin A                     | OH           |     | OH  |   | OH  |                    | OMe |     |    |  |
| Cajanin                                   | OH           |     | OMe |   | OH  |                    | OH  |     |    |  |
| 5,2'-Dihydroxy-7,4'-dimethoxy-            | OH           |     | OMe |   | OH  |                    | OMe |     |    |  |
| 2'-Methoxybiochanin A                     | OH           |     | OH  |   | OMe |                    | OMe |     |    |  |
| Orobol                                    | OH           |     | OH  |   |     | OH                 | OH  |     |    |  |
| 3'-Methylorobol                           | OH           |     | OH  |   |     | OMe                | OH  |     |    |  |
| Glabrescione B                            | OMe          |     | OMe |   |     | OR                 | OR* |     |    |  |
| 5,7-Dihydroxy-3',4'-<br>methylenedioxy-   | OH           |     | OH  |   |     | OCH <sub>2</sub> O |     |     |    |  |
| Derrugenin                                | OH           |     | OMe |   | OMe |                    | OH  | OMe |    |  |
| Robustigenin                              | OH           |     | OMe |   | OMe |                    | OMe | OMe |    |  |
| 5,7,3',5'-Tetrahydroxy-4'-<br>methoxy-    | OH           |     | OH  |   |     | OH                 | OMe | OH  |    |  |
| Texasin                                   |              | OH  | OH  |   |     |                    | OMe |     |    |  |
| Glycitein                                 |              | OMe | OH  |   |     |                    | OH  |     |    |  |
| Kakkatin                                  |              | OH  | OMe |   |     |                    | OH  |     |    |  |
| Afrormosin                                |              | OMe | OH  |   |     |                    | OMe |     |    |  |

Plant sources

References

- Albizia*, *Bowdichia*, *Cajanus*, *Echinospartum*,  
*Glycine*, *Lespedeza*, *Pericopsis*, *Phaseolus*,  
*Piptanthus*, *Pueraria*, *Spartium*, *Trifolium*,  
*Streptomyces griseus*  
*S. xanthophaeus*  
*Albizia*, *Cicer*, *Cotoneaster* (Rosaceae),  
*Dalbergia*, *Echinospartum*, *Myroxylon*,  
*Pericopsis*, *Pueraria*, *Sophora*, *Trifolium*,  
*Viola* (Myristicaceae)  
*Echinospartum horridum*  
*Spartium junceum*  
*Dalbergia miscolobium*  
*Genista carinalis*  
*Echinospartum horridum*  
*Dalbergia volubilis*
- Cajanus cajan*  
*Glycine wightii*  
*Lablab niger*  
*Moghania macrophylla*  
*Phaseolus vulgaris*  
*Spartium junceum*  
*Viola caducifolia* (Myristicaceae)  
*V. multinervia*  
*Cajanus cajan*  
*Cajanus cajan*  
*Viola caducifolia* (Myristicaceae)  
*V. multinervia*  
*Aspergillus niger*, *Stemphylium* spp.  
*Streptomyces neyagawaensis* var. *orobolere*  
*Dalbergia inundata*  
*Derris glabrescens*  
*Lupinus luteus*  
*Sophora japonica*  
*Derris robusta*\*\*  
*Derris robusta*  
*Juniperus macropoda* (Cupressaceae)
- Myroxylon peruiferum*  
*Mildbraedeodendron excelsa*  
*Pueraria* spp.  
*Cladrastis platycarpa*  
*Myroxylon peruiferum*  
*Onobrychis viciifolia*  
*Onobrychis* spp.  
*Pericopsis elata*  
*P. mooniana*
- Konig *et al.* (1977)  
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- Maranduba *et al.* (1979)  
Meegan and Donnelly (1975)  
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Imamura *et al.* (1974)  
Maranduba *et al.* (1979)
- Ingham (1978b)
- Fitzgerald *et al.* (1976)

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Table 10.1 (Contd.)

| Isoflavone                                                                                                      | Substituents |                    |     |     |     |                    |                    |     |    |
|-----------------------------------------------------------------------------------------------------------------|--------------|--------------------|-----|-----|-----|--------------------|--------------------|-----|----|
|                                                                                                                 | 5            | 6                  | 7   | 8   | 2'  | 3'                 | 4'                 | 5'  | 6' |
| Odoratin                                                                                                        |              | OMe                | OH  |     |     | OH                 | OMe                |     |    |
| Cladrastin                                                                                                      |              | OMe                | OH  |     |     | OMe                | OMe                |     |    |
| 6,7,3',4'-Tetramethoxy-<br>Fujikinetin                                                                          |              | OMe                | OMe |     |     | OMe                | OMe                |     |    |
|                                                                                                                 |              | OMe                | OH  |     |     | OCH <sub>2</sub> O |                    |     |    |
| 3',4'-Dimethoxy-6,7-<br>methylenedioxy-<br>7-Hydroxy-6,2',4',5'-<br>tetramethoxy-<br>6,7,2',4',5'-Pentamethoxy- |              | OCH <sub>2</sub> O |     |     |     | OMe                | OMe                |     |    |
|                                                                                                                 |              | OMe                | OH  |     | OMe |                    | OMe                | OMe |    |
|                                                                                                                 |              | OMe                | OMe |     | OMe |                    | OMe                | OMe |    |
| Dalpatein                                                                                                       |              | OMe                | OH  |     | OMe |                    | OCH <sub>2</sub> O |     |    |
| 6-Hydroxy-7,2'-dimethoxy-4',5'-<br>methylenedioxy-                                                              |              | OH                 | OMe |     | OMe |                    | OCH <sub>2</sub> O |     |    |
| Milldurone                                                                                                      |              | OMe                | OMe |     | OMe |                    | OCH <sub>2</sub> O |     |    |
| 6,7,3',4',5'-Pentamethoxy-<br>6,7,3'-Trimethoxy-4',5'-<br>methylenedioxy-                                       |              | OMe                | OMe |     |     | OMe                | OMe                | OMe |    |
|                                                                                                                 |              | OMe                | OMe |     |     | OMe                | OCH <sub>2</sub> O |     |    |
| Retusin                                                                                                         |              |                    | OH  | OH  |     |                    | OMe                |     |    |
| 8-Methylretusin                                                                                                 |              |                    | OH  | OMe |     |                    | OMe                |     |    |
| 8-Methyl-3'-hydroxyretusin                                                                                      |              |                    | OH  | OMe |     | OH                 | OMe                |     |    |
| 7-Hydroxy-8,3',4'-trimethoxy-<br>7,8,2'-Trimethoxy-4',5'-<br>methylenedioxy-                                    |              |                    | OH  | OMe |     | OMe                | OMe                |     |    |
|                                                                                                                 |              |                    | OMe | OMe | OMe |                    | OCH <sub>2</sub> O |     |    |
| Betavulgarin                                                                                                    | OMe          | OCH <sub>2</sub> O |     |     | OH  |                    |                    |     |    |
| Tectorigenin                                                                                                    | OH           | OMe                | OH  |     |     |                    | OH                 |     |    |
| 7-Methyltectorigenin                                                                                            | OH           | OMe                | OMe |     |     |                    | OH                 |     |    |
| Irisolidone                                                                                                     | OH           | OMe                | OH  |     |     |                    | OMe                |     |    |

| <i>Plant sources</i>                  | <i>References</i>                   |
|---------------------------------------|-------------------------------------|
| <i>Pterodon apparicioi</i>            | Galina and Gottlieb (1974)          |
| <i>Wistaria floribunda</i>            | Ohashi <i>et al.</i> (1979)         |
| <i>Dipteryx odorata</i>               | Hayashi and Thomson (1974)          |
| <i>Pterodon apparicioi</i>            | Galina and Gottlieb (1974)          |
| <i>Cladrastis platycarpa</i>          | Imamura <i>et al.</i> (1974)        |
| <i>Pterodon apparicioi</i>            | Almeida and Gottlieb (1975)         |
| <i>Cladrastis platycarpa</i>          | Imamura <i>et al.</i> (1974)        |
| <i>Dalbergia sericea</i>              | Parthasarathy <i>et al.</i> (1976a) |
| <i>Pterodon apparicioi</i>            | Galina and Gottlieb (1974)          |
| <i>Xanthocercis zambesiaca</i>        | Harper <i>et al.</i> (1976)         |
| <i>Pterodon apparicioi</i>            | Galina and Gottlieb (1974)          |
| <i>Mildbraedeodendron excelsa</i>     | Meegan and Donnelly (1975)          |
| <i>Pterodon apparicioi</i>            | Galina and Gottlieb (1974)          |
| <i>Dalbergia paniculata</i>           | Radhakrishniah (1973)               |
| <i>Corydala africana</i>              | Campbell and Tannock (1973)         |
| <i>Dalbergia assamica</i>             | Chibber and Sharma (1978)           |
| <i>Mildbraedeodendron excelsa</i>     | Meegan and Donnelly (1975)          |
| <i>Dalbergia paniculata</i>           | Adinarayana and Rao (1975b)         |
| <i>Mildbraedeodendron excelsa</i>     | Meegan and Donnelly (1975)          |
| <i>Pterodon apparicioi</i>            | Galina and Gottlieb (1974)          |
| <i>Pterodon apparicioi</i>            | Galina and Gottlieb (1974)          |
| <i>Mildbraedeodendron excelsa</i>     | Meegan and Donnelly (1975)          |
| <i>Dipteryx odorata</i>               | Hayashi and Thomson (1974)          |
| <i>Dalbergia retusa</i>               | Gregson <i>et al.</i> (1978a)       |
| <i>D. variabilis</i>                  | Kurosawa <i>et al.</i> (1978d)      |
| <i>Dipteryx odorata</i>               | Hayashi and Thomson (1974)          |
| <i>Pericopsis schliebenii</i>         | Fitzgerald <i>et al.</i> (1976)     |
| <i>Xanthocercis zambesiaca</i>        | Harper <i>et al.</i> (1976)         |
| <i>Dipteryx odorata</i>               | Hayashi and Thomson (1974)          |
| <i>Myroxylon balsamum</i>             | Oliveira <i>et al.</i> (1978)       |
| <i>Xanthocercis zambesiaca</i>        | Harper <i>et al.</i> (1976)         |
| <i>Xanthocercis zambesiaca</i>        | Harper <i>et al.</i> (1976)         |
| <i>Pterodon apparicioi</i>            | Galina and Gottlieb (1974)          |
| <i>Beta vulgaris</i> (Chenopodiaceae) | Geigert <i>et al.</i> (1973)        |
| <i>Dalbergia sissoo</i>               | Sharma <i>et al.</i> (1979b)        |
| <i>D. stevensonii</i>                 | Donnelly <i>et al.</i> (1973b)      |
| <i>D. volubilis</i>                   | Chawla and Chibber (1977)           |
| <i>Iris germanica</i> (Iridaceae)     | Pailer and Franke (1973)            |
| <i>Dalbergia volubilis</i>            | Khera and Chibber (1978a)           |
| <i>Iris germanica</i> (Iridaceae)     | Pailer and Franke (1973)            |
| <i>I. kashmiriana</i>                 | Dhar and Kalla (1975)               |
| <i>I. tingitana</i>                   | El-Emary <i>et al.</i> (1980)       |
| <i>Pericopsis mooniana</i>            | Fitzgerald <i>et al.</i> (1976)     |

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**Table 10.1** (*Contd.*)

| <i>Isoflavone</i>                                   | <i>Substituents</i> |                    |     |     |     |                    |     |     |    |
|-----------------------------------------------------|---------------------|--------------------|-----|-----|-----|--------------------|-----|-----|----|
|                                                     | 5                   | 6                  | 7   | 8   | 2'  | 3'                 | 4'  | 5'  | 6' |
| 5-Methoxyafrormosin                                 | OMe                 | OMe                | OH  |     |     |                    | OMe |     |    |
| Irilone                                             | OH                  | OCH <sub>2</sub> O |     |     |     |                    | OH  |     |    |
| Irisolone                                           | OMe                 | OCH <sub>2</sub> O |     |     |     |                    | OH  |     |    |
| Irisolone methyl ether                              | OMe                 | OCH <sub>2</sub> O |     |     |     |                    | OMe |     |    |
| Iristectorigenin A                                  | OH                  | OMe                | OH  |     |     | OH                 | OMe |     |    |
| Iristectorigenin B                                  | OH                  | OMe                | OH  |     |     | OMe                | OH  |     |    |
| 7-Hydroxy-5,6-dimethoxy-<br>3',4'-methylenedioxy-   | OMe                 | OMe                | OH  |     |     | OCH <sub>2</sub> O |     |     |    |
| [Name dipteryxine pre-empted]                       |                     |                    |     |     |     |                    |     |     |    |
| 5,6,7-Trimethoxy-3',4'-<br>methylenedioxy-          | OMe                 | OMe                | OMe |     |     | OCH <sub>2</sub> O |     |     |    |
| [Name odoratine pre-empted]                         |                     |                    |     |     |     |                    |     |     |    |
| Iriflogenin (as irifloside)                         | OH                  | OCH <sub>2</sub> O |     |     |     | OMe                | OH  |     |    |
| Iriskumaonin                                        | OMe                 | OCH <sub>2</sub> O |     |     |     | OH                 | OMe |     |    |
| 5,3',4'-Trimethoxy-6,7-<br>methylenedioxy-          | OMe                 | OCH <sub>2</sub> O |     |     |     | OMe                | OMe |     |    |
| Caviunin                                            | OH                  | OMe                | OH  |     | OMe |                    | OMe | OMe |    |
| Irigenin                                            | OH                  | OMe                | OH  |     |     | OMe                | OMe | OH  |    |
| Irisflorentin                                       | OMe                 | OCH <sub>2</sub> O |     |     |     | OMe                | OMe | OMe |    |
| 8-Hydroxygenistein                                  | OH                  |                    | OH  | OH  |     |                    | OH  |     |    |
| Isotectorigenin<br>(pseudotectorigenin)             | OH                  |                    | OH  | OMe |     |                    | OH  |     |    |
| Aurmillone                                          | OH                  |                    | OH  | OMe |     |                    | OR* |     |    |
| 5,7,3',4'-Tetrahydroxy-8-<br>methoxy-               | OH                  |                    | OH  | OMe |     | OH                 | OH  |     |    |
| 5,7,3'-Trihydroxy-8,4'-<br>dimethoxy-               | OH                  |                    | OH  | OMe |     | OH                 | OMe |     |    |
| 5,7,4'-Trihydroxy-8,3'-<br>dimethoxy-(as glycoside) | OH                  |                    | OH  | OMe |     | OMe                | OH  |     |    |



| <i>Plant sources</i>                      | <i>References</i>               |
|-------------------------------------------|---------------------------------|
| <i>Pueraria thunbergiana</i>              | Kurihari and Kikuchi (1973)     |
| <i>Sophora japonica</i>                   | Komatsu <i>et al.</i> (1976b)   |
| <i>Cladrastis platycarpa</i>              | Imamura <i>et al.</i> (1974)    |
| <i>Wistaria floribunda</i>                | Ohashi <i>et al.</i> (1979)     |
| <i>Iris germanica</i> (Iridaceae)         | Dhar and Kalla (1973)           |
|                                           | Pailer and Franke (1973)        |
| <i>Trifolium pratense</i>                 | Fraishtat <i>et al.</i> (1979a) |
| <i>Iris florentina</i> (Iridaceae)        | Morita <i>et al.</i> (1973)     |
| <i>I. germanica</i>                       | Pailer and Franke (1973)        |
| <i>Iris tingitana</i> (Iridaceae)         | El-Emary <i>et al.</i> (1980)   |
| <i>Iris germanica</i> (Iridaceae)         | Pailer and Franke (1973)        |
| <i>I. unguicularis</i>                    | Arisawa and Morita (1976)       |
| <i>Streptomyces roseolus</i> †            | Chimura <i>et al.</i> (1975)    |
| <i>Iris florentina</i> (Iridaceae)        | Morita <i>et al.</i> (1973)     |
| <i>I. germanica</i>                       | Pailer and Franke (1973)        |
| <i>Dipteryx odorata</i>                   | Nakano <i>et al.</i> (1979)     |
| <br>                                      |                                 |
| <i>Corydala africana</i>                  | Campbell and Tannock (1973)     |
| <i>Dipteryx odorata</i> ‡                 | Nakano <i>et al.</i> (1979)     |
| <br>                                      |                                 |
| <i>Iris florentina</i> (Iridaceae)        | Arisawa <i>et al.</i> (1973)    |
| <i>Iris kumaonensis</i> (Iridaceae)       | Kalla <i>et al.</i> (1978)      |
| <i>I. tingitana</i>                       | El-Emary <i>et al.</i> (1980)   |
| <i>Iris germanica</i> (Iridaceae)         | Pailer and Franke (1973)        |
| <i>I. tingitana</i>                       | El-Emary <i>et al.</i> (1980)   |
| <br>                                      |                                 |
| <i>Dalbergia inundata</i>                 | Almeida and Gottlieb (1974)     |
| <i>D. paniculata</i>                      | Radhakrishniah (1973)           |
| <i>D. spruceana</i>                       | Cook <i>et al.</i> (1978)       |
| <i>Iris florentina</i> (Iridaceae)        | Morita <i>et al.</i> (1973)     |
| <i>I. germanica</i>                       | Pailer and Franke (1973)        |
| <i>I. tingitana</i>                       | El-Emary <i>et al.</i> (1980)   |
| <i>I. unguicularis</i>                    | Arisawa and Morita (1976)       |
| <i>Juniperus macropoda</i> (Cupressaceae) | Sethi <i>et al.</i> (1980)      |
| <i>Iris florentina</i> (Iridaceae)        | Morita <i>et al.</i> (1973)     |
| <i>I. germanica</i>                       | Pailer and Franke (1973)        |
| <i>I. tingitana</i>                       | El-Emary <i>et al.</i> (1980)   |
| <i>Aspergillus niger</i>                  | Umezawa <i>et al.</i> (1975)    |
| <i>Dalbergia sissoo</i>                   | Dhingra <i>et al.</i> (1974)    |
| <i>Aspergillus niger</i>                  | Umezawa <i>et al.</i> (1975)    |
| <i>Milletia auriculata</i>                | Raju and Srimannarayana (1978)  |
| <i>Aspergillus niger</i>                  | Umezawa <i>et al.</i> (1975)    |
| <br>                                      |                                 |
| <i>Streptomyces roseolus</i>              | Chimura <i>et al.</i> (1975)    |
| <br>                                      |                                 |
| <i>Iris germanica</i> (Iridaceae)         | Kawase <i>et al.</i> (1973)     |

**Table 10.1 (Contd.)**[illegible]

| <i>Plant sources</i>           | <i>References</i>                   |
|--------------------------------|-------------------------------------|
| <i>Cladrastis platycarpa</i> § | Imamura <i>et al.</i> (1974)        |
| <i>Dalbergia sissoo</i>        | Sharma <i>et al.</i> (1979b)        |
| <i>Dipteryx odorata</i>        | Hayashi and Thomson (1974)          |
| <i>Streptomyces roseolus</i>   | Chimura <i>et al.</i> (1975)        |
| <i>Petalostemon candidum</i>   | Torrance <i>et al.</i> (1979)       |
| <i>Xanthocercis zambesiaca</i> | Harper <i>et al.</i> (1976)         |
| <i>Corydala africana</i>       | Campbell and Tannock (1973)         |
| <i>Streptomyces griseus</i>    | Konig <i>et al.</i> (1977)          |
| <i>Streptomyces griseus</i>    | Konig <i>et al.</i> (1977)          |
| <i>Psoralea corylifolia</i>    | Gupta <i>et al.</i> (1978)          |
| <i>Erythrina variegata</i>     | Deshpande <i>et al.</i> (1977)      |
| <i>Glycine wightii</i>         |                                     |
| <i>Lupinus albus</i>           | Ingham <i>et al.</i> (1977)         |
| <i>Lupinus luteus</i>          | Fukui <i>et al.</i> (1973)          |
| <i>L. spp.</i>                 | Harborne <i>et al.</i> (1976)       |
| <i>Phaseolus vulgaris</i>      | Woodward (1979b)                    |
| <i>Erythrina variegata</i>     | Deshpande <i>et al.</i> (1977)      |
| <i>Derris glabrescens</i>      | Delle Monache <i>et al.</i> (1977b) |
| <i>Erythrina variegata</i>     | Deshpande <i>et al.</i> (1977)      |
| <i>Calopogonium mucunoides</i> | Vilain and Jadot (1976)             |
| <i>Erythrina variegata</i>     | Deshpande <i>et al.</i> (1977)      |
| <i>Calopogonium mucunoides</i> | Vilain and Jadot (1975)             |
| <i>Derris robusta</i>          | Chibber and Sharma (1979a)          |
| <i>Millettia auriculata</i>    | Minhaj <i>et al.</i> (1976a)        |
| <i>Millettia auriculata</i>    | Minhaj <i>et al.</i> (1976a)        |
| <i>Derris robusta</i>          | Chibber and Sharma (1979a)          |
| <i>Derris robusta</i>          | Chibber and Sharma (1979a)          |
| <i>Tephrosia elongata</i>      | Smalberger <i>et al.</i> (1975)     |
| <i>Calopogonium mucunoides</i> | Vilain and Jadot (1975)             |
| <i>Calopogonium mucunoides</i> | Vilain and Jadot (1976)             |
| <i>Tephrosia barbigera</i>     | Vilain (1980)                       |
| <i>Derris robusta</i>          | Chibber and Sharma (1980)           |
| <i>Calopogonium mucunoides</i> | Vilain and Jadot (1975)             |
| <i>Psoralea corylifolia</i>    | Bajwa <i>et al.</i> (1974)          |
| <i>Psoralea corylifolia</i>    | Jain <i>et al.</i> (1974)           |
| <i>Psoralea corylifolia</i>    | Suri <i>et al.</i> (1978)           |
| <i>Glycyrrhiza glabra</i>      | Kinoshita <i>et al.</i> (1976)      |
| <i>Glycyrrhiza uralensis</i>   | Kaneda <i>et al.</i> (1973)         |

Table 10.1 (Contd.)

| Isoflavone                              | Substituents |   |   |   |    |    |    |    |    |
|-----------------------------------------|--------------|---|---|---|----|----|----|----|----|
|                                         | 5            | 6 | 7 | 8 | 2' | 3' | 4' | 5' | 6' |
| Licoisoflavone A (10.27)                |              |   |   |   |    |    |    |    |    |
| [Name phaseoluteone pre-empted]         |              |   |   |   |    |    |    |    |    |
| Licoisoflavone B (10.28)                |              |   |   |   |    |    |    |    |    |
| 6,8-Di(dimethylallyl)genistein (10.29)  |              |   |   |   |    |    |    |    |    |
| 6,8-Di(dimethylallyl)orobol (10.30)     |              |   |   |   |    |    |    |    |    |
| Osajin (10.31)                          |              |   |   |   |    |    |    |    |    |
| Auriculatin (10.32)                     |              |   |   |   |    |    |    |    |    |
| Auriculasin (10.33)                     |              |   |   |   |    |    |    |    |    |
| Cajaisoflavone (10.34)                  |              |   |   |   |    |    |    |    |    |
| 6,3'-Di(dimethylallyl)genistein (10.35) |              |   |   |   |    |    |    |    |    |
| 7-Hydroxy-2-methyl- (10.36)             |              |   |   |   |    |    |    |    |    |
| 7-Methoxy-2-methyl- (10.37)             |              |   |   |   |    |    |    |    |    |
| 7-Acetoxy-2-methyl- (10.38)             |              |   |   |   |    |    |    |    |    |
| Glyzarin (10.39)                        |              |   |   |   |    |    |    |    |    |

\* R =  $-\text{CH}_2\text{CH}=\text{CMe}_2$ .

† The *Streptomyces* metabolite is reported to be different from that from *Iris* spp.

‡ The *Dipteryx* and *Corydalis* metabolites are not identical.

§ This structure for platycarpanetin has been disputed.

\*\* The structure was revised after synthetic studies.

derived from chalcone–flavanone precursors and involving an aryl migration, remains to be established.

Corylin (10.2) is a rather unusual isoflavone from seed of *Psoralea corylifolia* and has been identified as 3'-formylaidzein (Gupta *et al.*, 1978). It co-occurs with neobavaisoflavone (10.22), and may thus arise by oxidation of the dimethylallyl substituent.

Synthesis of natural isoflavones remains an important adjunct to structural elucidation, and the long-established methods of ring closure of a C<sub>1</sub> unit on to an appropriate deoxybenzoin are still widely employed. The use of ethoxalyl chloride, triethyl orthoformate, dimethylformamide–phosphorus oxychloride and ethyl formate as C<sub>1</sub> sources continues (Wagner and Farkas, 1975). Improved yields in the Baker synthesis (ethoxalyl chloride) can be obtained by pyridine hydrochloride decarboxylation (Szabo *et al.*, 1975a), but aromatic methoxyls may also be demethylated, and in the Claisen condensation (ethyl formate), sodium *t*-butoxide is found to be a better and safer alternative to sodium (Szabo *et al.*, 1975b). Newer routes employing deoxybenzoins have also been reported. Thus Bass (1976) has utilized methanesulphonyl chloride with boron trifluoride–etherate in dimethylformamide as the C<sub>1</sub> unit, and excellent yields of isoflavones

| <i>Plant sources</i>        | <i>References</i>               |
|-----------------------------|---------------------------------|
| <i>Glycyrrhiza</i> spp.     | Kinoshita <i>et al.</i> (1978b) |
| <i>Phaseolus vulgaris</i>   | Woodward (1979a)                |
| <i>Glycyrrhiza</i> spp.     | Saitoh <i>et al.</i> (1978)     |
| <i>Millettia pachycarpa</i> | Singhal <i>et al.</i> (1980)    |
| <i>Millettia pachycarpa</i> | Singhal <i>et al.</i> (1980)    |
| <i>Erythrina variegata</i>  | Deshpande <i>et al.</i> (1977)  |
| <i>Millettia auriculata</i> | Raju and Srimannarayana (1978)  |
| <i>Millettia auriculata</i> | Minhaj <i>et al.</i> (1976a)    |
| <i>Cajanus cajan</i>        | Bhanumati <i>et al.</i> (1979a) |
| <i>Millettia pachycarpa</i> | Singhal <i>et al.</i> (1980)    |
| <i>Glycyrrhiza glabra</i>   | Bhardwaj <i>et al.</i> (1976)   |
| <i>Glycyrrhiza glabra</i>   | Bhardwaj <i>et al.</i> (1976)   |
| <i>Glycyrrhiza glabra</i>   | Bhardwaj <i>et al.</i> (1976)   |
| <i>Glycyrrhiza glabra</i>   | Bhardwaj <i>et al.</i> (1977)   |

(or other chromones) may be obtained. Pelter and Foot (1976) report dimethylformamide dimethylacetal in benzene to be another source of the one-carbon unit with good yields of isoflavones, except for 5,7-dihydroxyisoflavones where protection of these two hydroxyl functions is necessary. By the addition of  $\text{BF}_3\text{-Et}_2\text{O}$  as in Bass's method, such protection is no longer essential (Pelter *et al.*, 1978). A further source of the additional carbon atom is provided by *N*-formylimidazole, generated by reaction of formic acid with *NN*-carbonyldiimidazole (Krishnamurthy and Prasad, 1977). Excellent yields of isoflavone are also reported.

Whilst addition of a one-carbon unit on to a deoxybenzoin can be accomplished efficiently, synthesis of the deoxybenzoin itself may proceed in rather poor yields, and starting materials are usually not readily available. Much more appropriate to isoflavonoid syntheses are routes utilizing chalcones obtained by condensation of the more readily available aromatic acetophenones and aldehydes. The boron trifluoride-catalysed rearrangement of chalcone epoxides still finds occasional use, but yields are never good. However, the thallium nitrate oxidation of 2'-hydroxychalcones (Farkas *et al.*, 1974) has become established as the most popular route to isoflavones. The intermediate acetal is usually

transformed to the isoflavone by treatment with acid, but base-catalysed cyclization is also effective, and thus isoflavones containing acid-labile groupings such as dimethylchromene rings can be synthesized by this route. In such cases, the highly acid-sensitive methoxymethyl groups may be used to protect hydroxyls from oxidation, and the synthesis of isoflavone (10.40) (Antus *et al.*, 1976) exemplifies the procedure (Fig. 10.2). Unfortunately, dimethylchromene rings may be oxidized by thallium nitrate to give ring-contracted furano derivatives, and such compounds may be formed as unwanted byproducts, as in the synthesis of corylin methyl ether (10.41) (Antus *et al.*, 1979b) (Fig. 10.3). Whilst the thallium nitrate oxidative rearrangement of chalcones seems to be of general application, it has been criticized because nitric acid released during the reaction may lead to the production of nitroisoflavones (Oliveira *et al.*, 1979). Under standardized conditions, however, no nitration is observed (Antus *et al.*, 1979a). The method has also been used to synthesize *O*- and *C*-glycosides (Antus and Nogradi, 1979a,b; Eade *et al.*, 1978). The structure of 7-methoxy-2-methylisoflavone (10.37) has also been confirmed by its synthesis from  $\alpha$ -methyl-2'-hydroxy-4'-methoxychalcone using the thallium nitrate oxidation reaction (Jain *et al.*, 1978a).

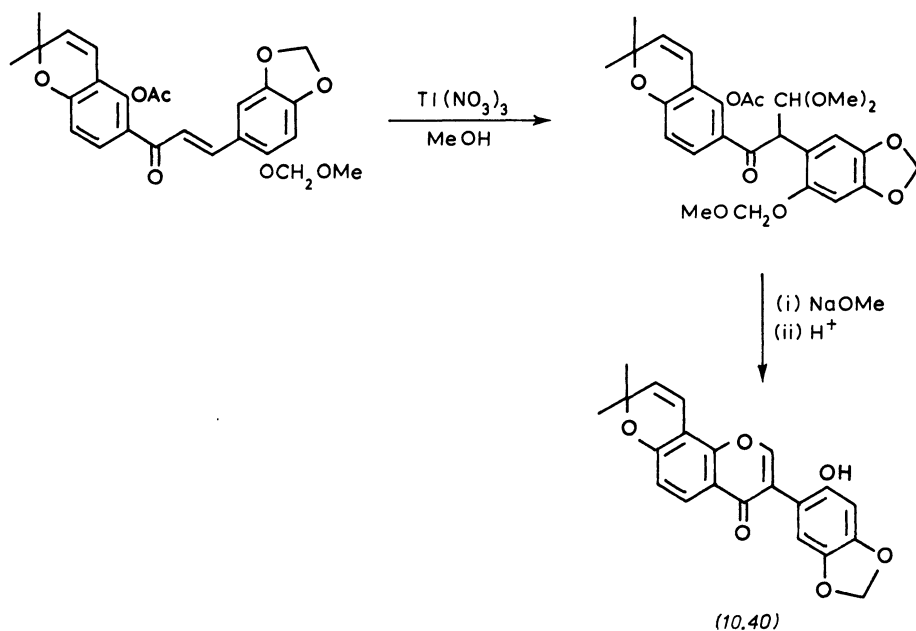


Fig. 10.2

A further route to isoflavones, though of less general synthetic value, is via the rearrangement of 3-bromoflavanones by treating with  $\text{AgSbF}_6$  in dichloromethane (Pelter *et al.*, 1976).

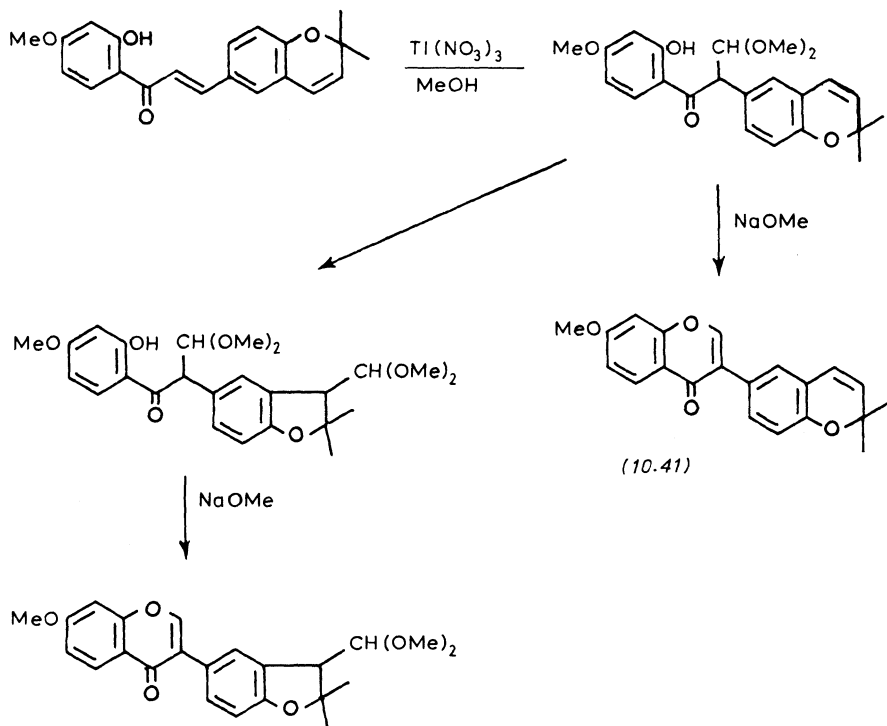


Fig. 10.3

The presence of a 2'-substituent in isoflavones can be determined by MS analysis: elimination of a 2'-hydrogen or 2'-substituent gives rise to a resonance-stabilized oxonium ion (10.42) (Eguchi *et al.*, 1977). Thus, 2'-unsubstituted isoflavones show a base peak at  $M - 1$ , 2'-methoxyisoflavones a base peak at  $M - 31$  (cf. Campbell *et al.*, 1969), and 2'-hydroxyisoflavones a prominent  $M - 17$  peak (cf. Ingham, 1976c). To aid identification of the hydroxylation pattern of isoflavones, Harper *et al.* (1976) have hydrolysed them in base- $\text{D}_2\text{O}$ , thus producing deuteriated deoxybenzoins. Under these conditions, deuteriation occurs at the methylene and also at positions in the aromatic rings *ortho* or *para* to a free hydroxyl, including that produced by hydrolysis of the pyrone ring. MS analysis of the deoxybenzoin indicates how many deuterium atoms have been incorporated. This method thus differentiates between, say, a 3'-hydroxy-4'-methoxyisoflavone and a 4'-hydroxy-3'-methoxyisoflavone.

A number of isoflavones and glycosides have been isolated from microbial cultures (Chimura *et al.*, 1975; Hazato *et al.*, 1979; König *et al.*, 1977; Umezawa *et al.*, 1975), and the question of whether isoflavonoids are restricted to the higher plants is again raised. In all of the above cases, the cultures were grown on a soybean meal medium, and it is quite likely that these isoflavonoids are either soybean-derived or microbial metabolites of soybean isoflavones.

Table 10.2 Isoflavone glycosides

| <i>Isoflavone glycoside</i>              | <i>Plant sources</i>                   | <i>References</i>                   |
|------------------------------------------|----------------------------------------|-------------------------------------|
| Daidzein 7-glucoside (daidzin)           | <i>Glycine max</i>                     | Naim <i>et al.</i> (1974)           |
| Daidzin-6''-acetate                      | <i>Glycine max</i>                     | Ohta <i>et al.</i> (1979)           |
| Daidzein 7-rhamnoside                    | <i>Streptomyces xanthophaeus</i>       | Hazato <i>et al.</i> (1979)         |
| Daidzein 7, 4'-dirhamnoside              | <i>Streptomyces xanthophaeus</i>       | Hazato <i>et al.</i> (1979)         |
| Formononetin 7-glucoside (ononin)        | <i>Amorpha fruticosa</i>               | Shibata and Shimizu (1978)          |
|                                          | <i>Cladrastis platycarpa</i>           | Imamura <i>et al.</i> (1974)        |
|                                          | <i>Dalbergia paniculata</i>            | Parthasarathy <i>et al.</i> (1974)  |
|                                          | <i>Ononis spinosa</i>                  | Haznag <i>et al.</i> (1978)         |
|                                          | <i>Spartium junceum</i>                | Ozimina <i>et al.</i> (1979)        |
|                                          | <i>Trifolium</i> spp.                  | Kazakov <i>et al.</i> (1972)        |
|                                          | <i>Wistaria floribunda</i>             | Ohashi <i>et al.</i> (1979)         |
| Formononetin 7-glucosylglucoside         | <i>Cladrastis platycarpa</i>           | Imamura <i>et al.</i> (1974)        |
| Formononetin 7-rutinoside                | <i>Dalbergia paniculata</i>            | Parthasarathy <i>et al.</i> (1976b) |
| Pseudobaptigenin 7-glucoside (rothindin) | <i>Lupinus luteus</i>                  | Laman (1974)                        |
|                                          | <i>Ononis spinosa</i>                  | Haznag <i>et al.</i> (1978)         |
|                                          | <i>Rothia indica</i>                   | Nair and Subramanian (1976)         |
|                                          | <i>Cajanus cajan</i>                   | Bhanumati <i>et al.</i> (1979b)     |
| 5,7,2'-Trihydroxyisoflavone 7-glucoside  | <i>Glycine max</i>                     | Naim <i>et al.</i> (1974)           |
| Genistein 7-glucoside (genistin)         | <i>Lupinus luteus</i>                  | Laman (1974)                        |
|                                          | <i>Spartium junceum</i>                | Ozimina <i>et al.</i> (1979)        |
|                                          | <i>Thermopsis alterniflora</i>         | Kattaev and Nikonov (1972)          |
|                                          | <i>Glycine max</i>                     | Ohta <i>et al.</i> (1980)           |
|                                          | <i>Lupinus luteus</i>                  | Laman and Volynets (1974)           |
|                                          | <i>Streptomyces xanthophaeus</i>       | Hazato <i>et al.</i> (1979)         |
|                                          | <i>Streptomyces xanthophaeus</i>       | Hazato <i>et al.</i> (1979)         |
| Biochanin A 7-glucoside (sissotrin)      | <i>Cotoneaster serotina</i> (Rosaceae) |                                     |
|                                          | <i>C. pinnosa</i>                      | Cooke and Fletcher (1974)           |
|                                          | <i>Dalbergia paniculata</i>            | Parthasarathy <i>et al.</i> (1974)  |
|                                          | <i>Dalbergia paniculata</i>            | Parthasarathy <i>et al.</i> (1976b) |
|                                          | <i>Sophora japonica</i>                | Takeda <i>et al.</i> (1977)         |
| Biochanin A 7-rutinoside                 |                                        |                                     |
| Biochanin A 7-gentiobioside              |                                        |                                     |



- Biochanin A 7-xylosylglucoside  
 Prunetin 4'-glucoside (trifoside)
- Prunetin 8-C-glucoside  
 7-Methylbiochanin A 8-C-rhamnoside (volubilin)  
 7-Methylbiochanin A 6-C-rhamnoside (isovolubilin)  
 5,7-Dihydroxy-3',4'-methylenedioxyisoflavone 7-glucoside  
 5,7-Dihydroxy-3',4'-methylenedioxyisoflavone 7-glucosylglucoside  
 Glycitein 7-glucoside  
 Afformosin 7-glucoside (wistin)
- Cladrastin 7-glucoside  
 Fujikinetin 7-glucoside (fujikinin)
- 8-Methylretusin 7-glucoside  
 8-Methylretusin 7-glucosylglucoside  
 Tectorigenin 7-glucoside (tectordin)
- Tectorigenin 7-gentiobioside  
 Isoloidone 7-glucoside  
 Isoloidone 8-C-glucoside (volubilin)  
 Isoloidone 7-xylosylglucoside (kakkalide)  
 Cavinunin 7-glucoside
- Cavinunin 7-rhamnosylglucoside  
 Cavinunin 7-gentiobioside  
 Irigenin 7-glucoside (iridin)
- Sophora japonica*  
*Genista carinalis*  
*Trifolium pratense*  
*Dalbergia paniculata*  
*Dalbergia volubilis*  
*Dalbergia volubilis*  
*Lupinus luteus*  
*Lupinus luteus*  
*Glycine max*  
*Amorpha fruticosa*  
*Cladrastis platycarpa*  
*Wistaria floribunda*  
*Cladrastis platycarpa*  
*Cladrastis platycarpa*  
*Wistaria floribunda*  
*Cladrastis platycarpa*  
*Dalbergia sissoo*  
*D. volubilis*  
*Iris germanica* (Iridaceae)  
*Pueraria montana*  
*Dalbergia volubilis*  
*Pueraria lobata*  
*Dalbergia volubilis*  
*Pueraria thunbergiana*  
*Dalbergia sissoo*  
*D. paniculata*  
*Dalbergia paniculata*  
*Dalbergia sissoo*  
*Iris florentina* (Iridaceae)  
*I. kumaonensis*  
*I. unguicularis*  
*Juniperus macrospora* (Cupressaceae)
- Takeda *et al.* (1977)  
 Nakov *et al.* (1978)  
 Kattaev *et al.* (1972)  
 Parthasarathy *et al.* (1976b)  
 Chawla *et al.* (1974)  
 Chawla *et al.* (1975)  
 Laman and Volynets (1974)  
 Laman and Volynets (1974)  
 Naim *et al.* (1974)  
 Shibata and Shimizu (1978)  
 Imamura *et al.* (1974)  
 Ohashi *et al.* (1979)  
 Ohashi *et al.* (1976)  
 Imamura *et al.* (1974)  
 Ohashi *et al.* (1976)  
 Ohashi *et al.* (1979)  
 Imamura *et al.* (1974)  
 Sharma *et al.* (1980b)  
 Khara and Chibber (1978a)  
 Kawase *et al.* (1973)  
 Kubo *et al.* (1973)  
 Khara and Chibber (1978c)  
 Kubo *et al.* (1973)  
 Chawla *et al.* (1976)  
 Kurihari and Kikuchi (1975)  
 Sharma *et al.* (1980b)  
 Radhakrishniah (1979)  
 Rajulu and Rao (1980)  
 Sharma *et al.* (1979a)  
 Arisawa *et al.* (1973)  
 Kalla *et al.* (1978)  
 Arisawa *et al.* (1976)  
 Sethi *et al.* (1980)

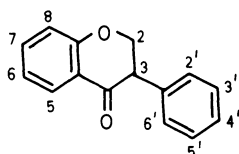
Table 10.2 (Contd.)

| <i>Isoflavone glycoside</i>                                                | <i>Plant sources</i>               | <i>References</i>                  |
|----------------------------------------------------------------------------|------------------------------------|------------------------------------|
| 7-Methyltectorigenin 4'-glucoside                                          | <i>Dalbergia volubilis</i>         | Khera and Chibber (1978b)          |
| 7-Methyltectorigenin 4'-gentiobioside                                      | <i>Dalbergia volubilis</i>         | Khera and Chibber (1978b)          |
| Irilone 4'-glucoside                                                       | <i>Iris florentina</i> (Iridaceae) | Tsukida <i>et al.</i> (1973)       |
|                                                                            | <i>Trifolium pratense</i>          | Fraistat <i>et al.</i> (1979a)     |
| Irisolone 4'-bioside                                                       | <i>Iris florentina</i> (Iridaceae) | Tsukida <i>et al.</i> (1973)       |
| Iristectorigenin A 7-glucoside                                             | <i>Iris tectorum</i> (Iridaceae)   | Morita <i>et al.</i> (1972)        |
| Iriflogenin 3'-glucoside (irifloside)                                      | <i>Iris florentina</i> (Iridaceae) | Arisawa <i>et al.</i> (1973)       |
| 5,7,4'-Trihydroxy-8,3'-dimethoxyisoflavone 7-glucoside<br>(homotectoridin) | <i>Iris germanica</i> (Iridaceae)  | Kawase <i>et al.</i> (1973)        |
| Isocaviunin 7-glucoside<br>(isocaviudin)                                   | <i>Dalbergia sissoo</i>            | Sharma <i>et al.</i> (1980b)       |
| Isocaviunin 7-gentiobioside                                                | <i>D. paniculata</i>               | Parthasarathy <i>et al.</i> (1980) |
| Platycarpanetin 7-glucoside                                                | <i>Dalbergia sissoo</i>            | Sharma <i>et al.</i> (1980a)       |
|                                                                            | <i>Cladrastis platycarpa</i>       | Imamura <i>et al.</i> (1974)       |
|                                                                            |                                    | Ohashi <i>et al.</i> (1976)        |

Isoflavone glycosides (Table 10.2) are isolated much less frequently than aglycones, but a considerable number have now been described. The previously unreported isoflavone 7-methylbiochanin A is known only as its 8- and 6-*C*-rhamnosides volubilin and isovolubilin in *Dalbergia volubilis* (Chawla *et al.*, 1974, 1975). Similarly, 5,7,2'-trihydroxyisoflavone (Bhanumati *et al.*, 1979b), iriflogenin (Arisawa *et al.*, 1973) and 5,7,4'-trihydroxy-8,3'-dimethoxyisoflavone (Kawase *et al.*, 1973) have been isolated only as *O*-glycosides.

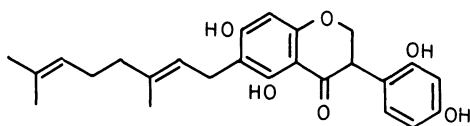
#### 10.4 ISOFLAVANONES

Isoflavanones (10.43) are much rarer than isoflavones, though the number of known naturally occurring examples continues to grow (Table 10.3). Two



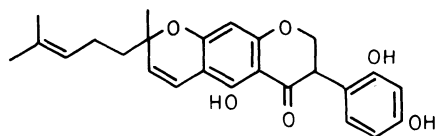
(10.43)

unusual ones isolated from *Lespedeza homoloba* (Ueno *et al.*, 1973a,c) contain geranyl substituents. Lespedeol A (10.44) is 6-geranyldalbergioidin and



(10.44) Lespedeol A

lespedeol B (10.45) is the cyclized chromeno analogue, which may also be obtained by dichlorodicyanobenzoquinone (DDQ) treatment of lespedeol A.



(10.45) Lespedeol B

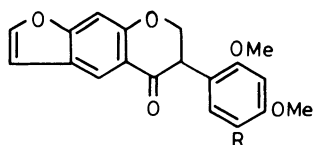
For many years, the only natural optically active isoflavanone known was 3*R*-sophorol. Since racemization may occur under relatively mild conditions, it was assumed that extraction and purification techniques were responsible for the observed isolation of optically inactive forms. Recently, 3*S*-7,4'-di-

Table 10.3 Isoflavanones

| Isoflavanone                                                                                                                                                                                               | Substituents |     |     |     |     |     |     |     |                    |  | Plant sources                                                                                                                                                                                                                                    | Chirality<br>Optical<br>activity | References                                                                                                                                                                                                                |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|-----|-----|-----|-----|-----|-----|-----|--------------------|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                            | 5            | 6   | 7   | 8   | 2   | 3   | 4'  | 5'  | 6'                 |  |                                                                                                                                                                                                                                                  |                                  |                                                                                                                                                                                                                           |
| 7,4'-Dihydroxy-<br>7-Hydroxy-4'-methoxy-<br>2,3-Dihydroononin<br>7,2,4'-Trihydroxy-<br>Vesitane<br>Sativanone                                                                                              | OH           |     | OH  |     |     |     | OH  | OH  |                    |  | <i>Pericopsis mooniana</i><br><i>Myroxylon balsamum</i><br><i>Ononis spinosa</i><br><i>Phaseolus vulgaris</i><br><i>Onobrychis viciifolia</i><br><i>Dalbergia stevensonii</i><br><i>Medicago sativa</i>                                          | S*<br>±<br>±<br>±<br>±<br>±      | Fitzgerald <i>et al.</i> (1976)<br>Oliveira <i>et al.</i> (1978)<br>Hahnagy <i>et al.</i> (1978)<br>Woodward (1980a)<br>Ingham (1978b)<br>Donnelly <i>et al.</i> (1973b)<br>Ingham (1979a)                                |
| 7,3'-Dihydroxy-4'-methoxy-<br>Violanone<br>3'-Methylviolanone<br>2'-Hydroxy-7,3',4'-trimethoxy-<br>Onogenin                                                                                                | OH           |     | OH  |     | OMe | OH  | OMe | OMe |                    |  | <i>Myroxylon balsamum</i><br><i>Dalbergia oliveri</i><br><i>Dalbergia cearensis</i><br><i>Myroxylon peruiferum</i><br><i>Dalbergia stevensonii</i><br><i>Ononis amensis</i>                                                                      | ±<br>±<br>±<br>±<br>±            | Oliveira <i>et al.</i> (1978)<br>Donnelly and Kavanagh (1974)<br>Guimaraes <i>et al.</i> (1975)<br>Maranduba <i>et al.</i> (1979)<br>Donnelly <i>et al.</i> (1973b)<br>Kovalev <i>et al.</i> (1975)                       |
| Dalbergioidin                                                                                                                                                                                              | OH           |     | OH  |     | OH  |     | OH  | OH  |                    |  | <i>Lablab niger</i><br><i>Lespedeza cyrtobotrya</i><br><i>Phaseolus vulgaris</i><br><i>Cajanus cajan</i>                                                                                                                                         |                                  | Ingham (1977b)<br>Miyase <i>et al.</i> (1980)<br>Woodward (1979a)<br>Ingham (1979b)                                                                                                                                       |
| Cajanol<br>6,7-Dimethoxy-3',4'-methylenedioxy-<br>Lespedeol A (10.44)<br>Lespedeol B (10.45)<br>Neoraunone (10.46)<br>Ambonone (10.47)<br>Erosenone (10.48)<br>5-Deoxykivitone (10.49)<br>Kivitone (10.50) | OH           | OMe | OMe | OMe | OMe | OMe | OH  | OH  | OCH <sub>2</sub> O |  | <i>Milbraedendendron excelsa</i><br><i>Lespedeza homoloba</i><br><i>Lespedeza homoloba</i><br><i>Neorautanenia amboensis</i><br><i>Neorautanenia amboensis</i><br><i>Pachyrrhizus erosus</i><br><i>Phaseolus vulgaris</i><br><i>Lablab niger</i> | ±<br>±<br>±<br>±<br>±<br>±<br>±  | Meegan and Donnelly (1975)<br>Ueno <i>et al.</i> (1973c)<br>Ueno <i>et al.</i> (1973a).<br>Breytenbach and Rall (1980)<br>Breytenbach and Rall (1980)<br>Kalra <i>et al.</i> (1977)<br>Woodward (1979b)<br>Ingham (1977b) |
| 1'',2''-Dehydrocycloketivone (10.51)<br>Sophoraiflavanone A (10.52)<br>Licoisoflavanone (10.53)<br>Isosophoronol (10.54)                                                                                   |              |     |     |     |     |     |     |     |                    |  | <i>Phaseolus vulgaris</i><br><i>Sophora tomentosa</i><br><i>Glycyrrhiza</i> , spp.<br><i>Sophora tomentosa</i>                                                                                                                                   | -<br>±<br>±<br>±                 | Woodward (1979b)<br>Komatsu <i>et al.</i> (1978b)<br>Saitoh <i>et al.</i> (1978)<br>Delle Monache <i>et al.</i> (1977a)                                                                                                   |

|                            |   |  |                                     |
|----------------------------|---|--|-------------------------------------|
| Isosophoranone (10.55)     |   |  |                                     |
| Cajanone (10.56)           |   |  | Delle Monache <i>et al.</i> (1977a) |
| 2'-Methylecajanone (10.57) |   |  | Preston (1977a)                     |
| Dalpanin (10.58)           | ± |  | Bhanumati <i>et al.</i> (1979c)     |
| Secondifloran (10.59)      | ± |  | Adinarayana and Rao (1975a)         |
|                            |   |  | Minhaj <i>et al.</i> (1977)         |

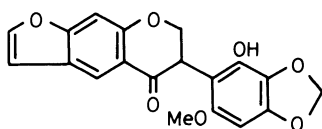
\* The chirality was wrongly assigned in this publication.



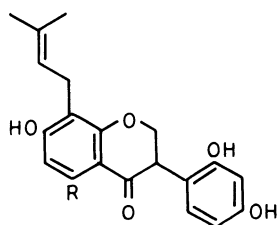
(10.46) R = H, Neoraunone

(10.47) R = OMe, Ambonone

hydroxyisoflavanone  $\{[\alpha]_D$  as acetate  $-20.7^\circ$  ( $\text{CHCl}_3$ ) $\}$  from *Pericopsis mooniana* (Fitzgerald *et al.*, 1976), sophoraisoflavanone A (10.52)  $\{[\alpha]_D -17.3^\circ$  (EtOH) $\}$  (Komatsu *et al.*, 1978b) and isosophoranone (10.55)  $\{[\alpha]_D -26^\circ$  ( $\text{CHCl}_3$ ) $\}$  (Delle Monache *et al.*, 1977a; Komatsu *et al.*, 1978b) from *Sophora tomentosa* have been isolated in optically active forms. Erosenone  $\{[\alpha]_D -37.7^\circ$  ( $\text{CHCl}_3$ ) $\}$  from *Pachyrrhizus erosus* is also an optically active isoflavanone and has been assigned the tentative structure (10.48) (Kalra *et al.*, 1977). As with isoflavans,

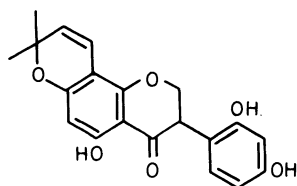


(10.48) Erosenone

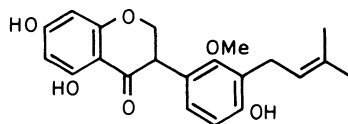


(10.49) R = H, 5-Deoxykievitone

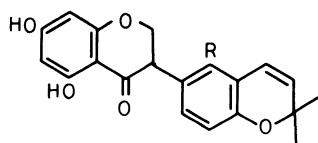
(10.50) R = OH, Kievitone



(10.51) 1'', 2''-Dehydrocyclokievitone

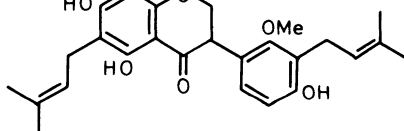


(10.52) Sophoraisoflavanone A

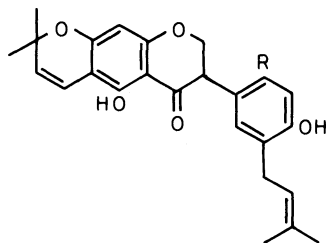


(10.53) R = OH, Licoisoflavanone

(10.54) R = OMe, Isosophoronol

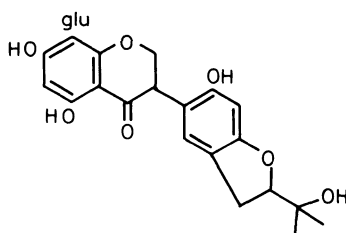


(10.55) Isosophoranone



(10.56) R = OH, Cajanone

(10.57) R = OMe, 2'-Methylcajanone



(10.58) Dalpanin

the sign of the rotation is not indicative of the chirality at C-3, but in the ORD curves, 3*S*-isoflavanones show intense negative Cotton effects in the 330–350 nm range (Kurosawa *et al.*, 1978b). Thus, (+)-7,2',4'-trimethoxyisoflavanone derived from (+)-homopterocarpin via hydrogenolysis to the isoflavan, methylation and  $\text{KMnO}_4$  oxidation has the same chirality 3*S* as (–)-7,4-diacetoxyisoflavanone (Kurosawa *et al.*, 1978b; Fitzgerald *et al.*, 1976).

In the MS of a number of 2'-hydroxy- and 2'-methoxyisoflavanones, the intensity of the ring A fragment formed from retro-Diels-Alder (RDA) fragmentation with hydrogen transfer appears to be influenced by the 2'-substituent. Thus with 2'-methoxyisoflavanones, a major ring A fragment is either not observed or is of very low intensity, whereas this fragment is of very high intensity or even base peak with 2'-hydroxyisoflavanones (Ingham, 1976c). However, this cannot be regarded as completely general, since the structure of cajanol was revised after degradative studies (Ingham, 1979b).

Synthetic routes to isoflavanones are in general not efficient, and new approaches are thus welcome. Palladium-catalysed Heck arylation of chroman-4-one enol esters gives very satisfactory yields of isoflavanones (Saito *et al.*, 1973), and uses as starting materials chroman-4-ones and aryl mercuric halides (Fig. 10.4). Isoflavanones may also be obtained from 3-arylcoumarins or 3-aryl-4-hydroxycoumarins via hydroboration followed by chromic acid oxidation (Kirkiacharian, 1975), but this method can result in production of the isoflavan as well as, or instead of the required isoflavanone (Kirkiacharian and Chidiac, 1975; Kirkiacharian and Ravise, 1976) and is thus less attractive.

Although catalytic hydrogenation of isoflavanones normally gives isoflavans, in basic medium ring opening can occur to yield  $\alpha$ -methyldeoxybenzoins and the corresponding alcohols (Szabo and Antal, 1976). Similar ring-opening reactions may occur when 2'-methoxyisoflavanones are treated with aluminium chloride in acetonitrile, rather than selective demethylation as occurs with 2'-methoxyisoflavones. Thus, 7,2',4'-trimethoxyisoflavanone yields an  $\alpha$ -methylenedeoxybenzoin (Malik and Grover, 1978), but the reaction is by no means general. 5-Methoxyisoflavanones are demethylated at position 5, even if a 2'-methoxy substituent is present.

A novel 3-hydroxyisoflavanone, secondifloran (10.59), has been isolated from *Sophora secundiflora* (Minhaj *et al.*, 1977), and although such isoflavonoid

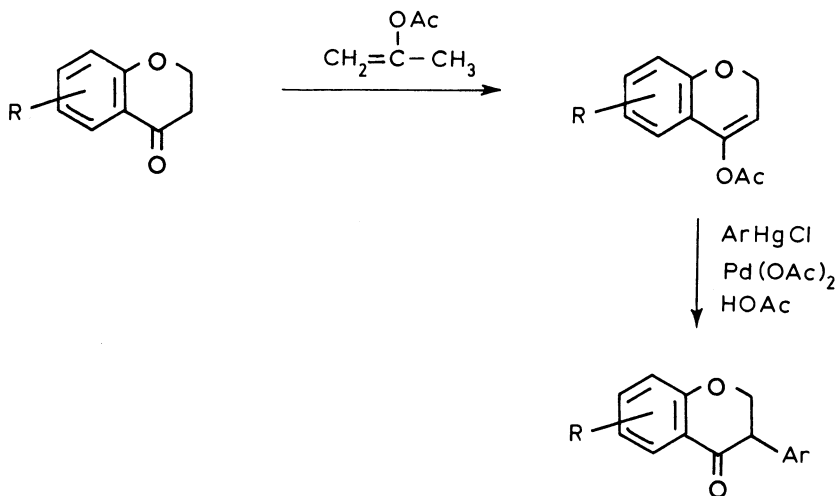
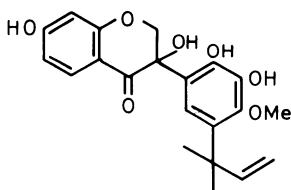


Fig. 10.4

derivatives are known chemically, this is the only example reported in nature. Since the corresponding isoflavanone trimethyl ether is resistant to aerial oxidation, secondifloran is not considered to be an artefact. Secondifloran also contains the uncommon 1,1-dimethylallyl substituent (see Section 10.7).



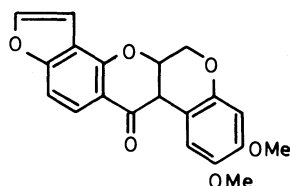
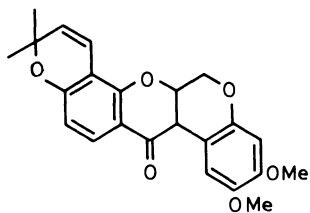
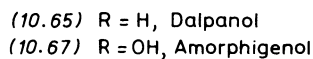
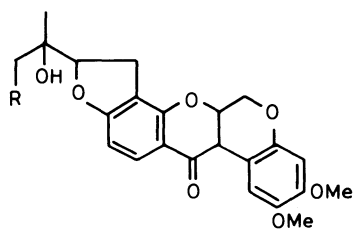
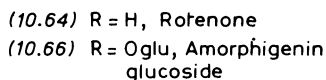
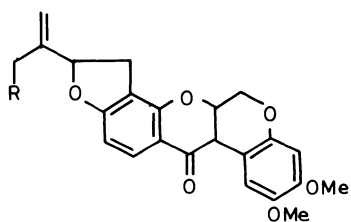
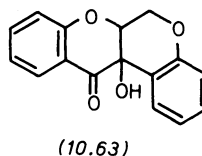
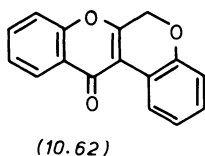
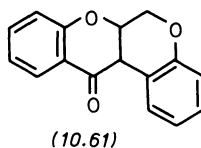
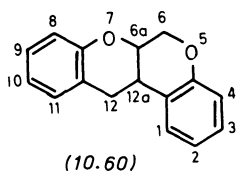
(10.59) Secondifloran

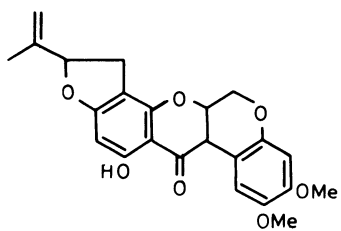
## 10.5 ROTENOIDS

Rotenoid is a general name for a class of isoflavonoid compound containing an extra carbon atom in an additional heterocyclic ring (10.60). A considerable amount of variation in the oxidation levels of this ring system is encountered in nature, and it now becomes necessary to subdivide the natural rotenoids to aid classification. Systematic nomenclature of the rotenoids based on the parent structure rotoxin has never been generally adopted, and a more recent suggestion is that new names based on derran, the reduced structure (10.60) should be employed (Jain *et al.*, 1978b). This has merits in that the scheme is analogous to flavan/isoflavan nomenclature, and simple rotenoids would become derranones, dehydrorotenoids derrones etc. However, since most

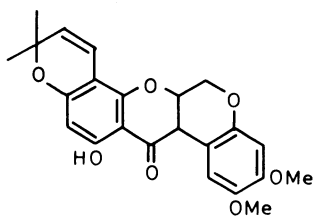


rotenoids are currently known by trivial names, and these names form the basis for indicating different oxidation levels, it is unlikely that this nomenclature will be widely used. In this review, the group of compounds will be treated in three subdivisions: rotenoids (10.61), dehydrorotenoids (10.62) and 12a-hydroxy-rotenoids (10.63), thus continuing nomenclature already established and in current use. Other variations in oxidation level will be regarded as derivatives of one of these subdivisions.

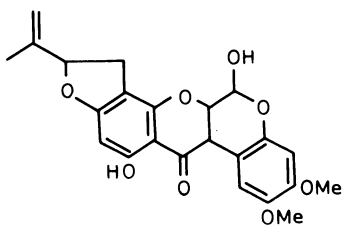




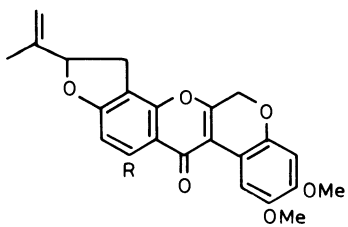
(10.70) Sumatrol



(10.71) Toxicarol

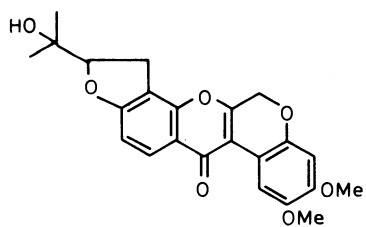


(10.72) Villosin

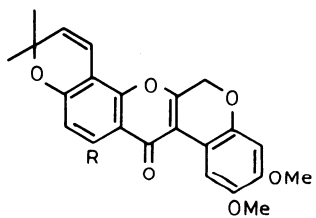


(10.73) R = H, Dehydrorotenone

(10.77) R = OH, Villosol

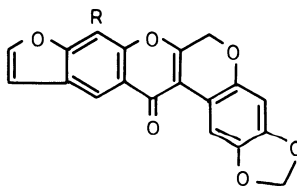


(10.74) Dehydrodalpanol



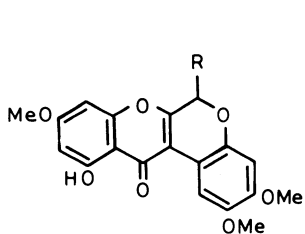
(10.75) R = H, Dehydrodeguelin

(10.78) R = OH, Dehydrotoxicarol



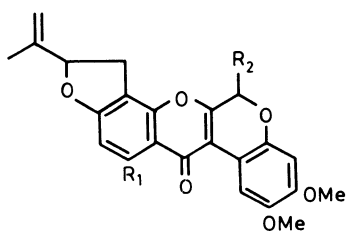
(10.76) R = H, Dehydrodolineone

(10.79) R = OMe, Dehydropachyrrhizone



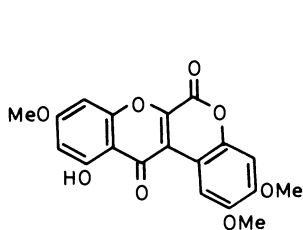
(10.80) R = OH, Stemonal

(10.81) R = OEt, Stemonacetal

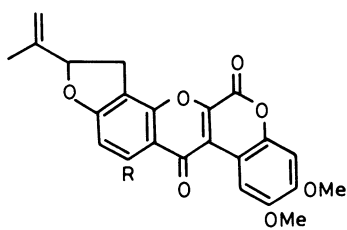


(10.82) R<sub>1</sub> = H, R<sub>2</sub> = OH, Amorpholone

(10.83) R<sub>1</sub> = OH, R<sub>2</sub> = OMe, Villinol

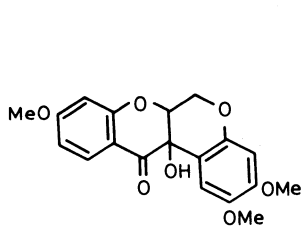


(10.84) Stemonone

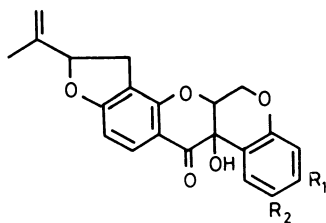


(10.85) R = H, Rotenone

(10.86) R = OH, Villosone

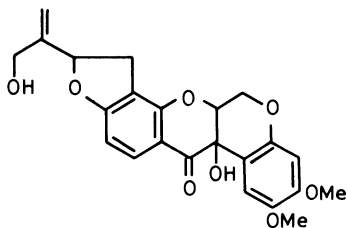


(10.87) 12α-Hydroxymunduserone

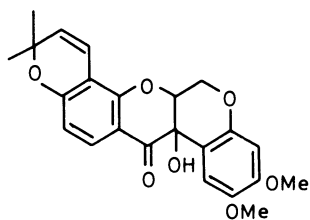


(10.88) R<sub>1</sub> = R<sub>2</sub> = OMe, 12α-Hydroxyrotenone

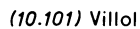
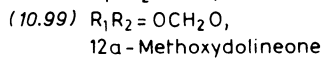
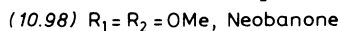
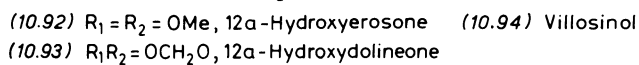
(10.89) R<sub>1</sub> R<sub>2</sub> = OCH<sub>2</sub>O, 12α-Hydroxyisomilleton



(10.90) Dalbinol



(10.91) Tephrosin



### 10.5.1 Rotenoids

Surprisingly, the number of known simple rotenoids has not increased during the review period, although new sources have been reported and a number of glycosides have been isolated (Table 10.4). The presence of rotenoids (and 12a-hydroxyrotenoids) in tissue cultures of *Tephrosia* spp. (Sharma and Khanna, 1975) and *Crotalaria burhia* (Uddin and Khanna, 1979) is worthy of note. Villosin (10.72) is 6-hydroxysumatrol isolated from *Tephrosia villosa* pods (Krupadanam *et al.*, 1977) along with other derivatives of rotenone and sumatrol.

The absolute configuration of (–)-rotenone has been established as 6a*S*, 12a*S*, 5'*R* by X-ray analysis of the 8'-bromo derivative (Begley *et al.*, 1975), thus confirming earlier chemical and spectroscopic studies. Rotenone reacts with one molecular equivalent of boron tribromide at low temperature to give the bromide of rotenonic acid (10.102) (Carson *et al.*, 1975b) in a reappraisal of earlier results (Unai and Yamamoto, 1973) (Fig. 10.5). The bromide (10.102) on treatment with sodium cyanoborohydride in hexamethylphosphorotriamide (HMPT) yields rotenonic acid (10.103) and offers a route for the synthesis of specifically labelled derivatives (Carson *et al.*, 1975b). The same overall transformation can be achieved by hydrogenolysis using Pd–BaSO<sub>4</sub> in pyridine with substantial, though not complete, stereoselectivity for introduction of hydrogen (Crombie *et al.*, 1979a). The former route proceeds in quite high yields and has been included in the chemical transformation of rotenone to deguelin (10.68) (Fig. 10.5) (Anzeveno, 1979a). Rotenonic acid is also a key intermediate in the conversion of rotenone into elliptone (10.69) (Fig. 10.5) (Anzeveno, 1979b). These side-chain modifications could find application in the other classes of isoflavonoids.

A number of new rotenoid syntheses have been published. As in many earlier routes, Carson *et al.* (1975a) have exploited the addition of a C<sub>2</sub>-unit on to a deoxybenzoin, but using allyl bromide as the source of this unit, cleaving off one carbon via OsO<sub>4</sub>-KIO<sub>4</sub> prior to cyclization (Fig. 10.6). This route circumvents dehydrorotenoids as intermediates, but requires protection of the deoxybenzoin from *C*-allylation via an isoflavone structure, and the synthesis of (±)-isorotenone is described. The carbon skeleton of rotenoids can be provided by reacting an aryloxyacetylide with an aromatic aldehyde to give an acetylenic intermediate (Omokawa and Yamashita, 1973). The alcohol produced, after MnO<sub>2</sub> oxidation to the ketone, is thermally cyclized then treated with mild base to yield the rotenoid (Fig. 10.7). This method has been applied in the synthesis of (+)-munduserone (Omokawa and Yamashita, 1973), (±)-9-demethylmunduserone (Omokawa *et al.*, 1975), (±)-deguelin (Omokawa and Yamashita, 1974) and (–)-rotenone (Sasaki and Yamashita, 1979). In the last synthesis, (–)-tuba-aldehyde was used as starting material, and with correct choice of the mild base (pyridine-ethanol), cyclization occurred to yield (–)-rotenone, with no trace of *epi*-isomer.

Table 10.4 Rotenoids

| Rotenoid                            | Plant sources                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | References                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (i) <i>Rotenoids</i>                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Rotenone (10.64)                    | <i>Crotalaria burhia</i><br><i>C. medicaginea</i><br><i>Derris negensis</i><br><i>D. urucu</i><br><i>Tephrosia falciformis</i><br><i>T. purpurea</i><br><i>T. vogelii</i><br><i>Neorautanenia amboensis</i><br><i>Dalbergia paniculata</i><br><i>Dalbergia paniculata</i><br><i>Amorpha</i> spp.<br><i>Amorpha fruticosa</i><br><i>Amorpha</i> spp.<br><i>Crotalaria burhia</i><br><i>Lonchocarpus unifoliatius</i><br><i>Tephrosia falciformis</i><br><i>T. purpurea</i><br><i>T. vogelii</i><br><i>Crotalaria burhia</i><br><i>C. medicaginea</i><br><i>Tephrosia falciformis</i><br><i>T. purpurea</i><br><i>T. vogelii</i> | Uddin and Khanna (1979)<br>Jain (1979)<br>Vasconcelos and Maia (1976)<br>Braz Filho <i>et al.</i> (1975)<br>Kamal and Jain (1978)<br><br>Sharma and Khanna (1975)<br>Oberholzer <i>et al.</i> (1974)<br>Radhakrishniah (1973)<br>Radhakrishniah (1973)<br>Kasymov <i>et al.</i> (1968)<br>Kasymov <i>et al.</i> (1970)<br>Kasymov <i>et al.</i> (1974)<br>Uddin and Khanna (1979)<br>Delle Monache <i>et al.</i> (1978)<br>Kamal and Jain (1978)<br><br>Sharma and Khanna (1975)<br>Uddin and Khanna (1979)<br>Jain (1979)<br>Kamal and Jain (1978)<br><br>Sharma and Khanna (1975)<br>Uddin and Khanna (1979)<br>Raju and Srinannarayana (1978)<br>Uddin and Khanna (1979)<br>Krupadanam <i>et al.</i> (1977) |
| Dalpanol (10.65)                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Dalpanol glucoside                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Amorphigenin glucoside (10.66)      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Amorphigenol (10.67) (as glucoside) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| (as bioside-Amorphol)               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Deguelin (10.68)                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Elliptone (10.69)                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Sumatrol (10.70)                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Toxicarol (10.71)                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Villosin (10.72)                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

- (ii) *Dehydrorotenoids*  
 Dehydrorotenone (10.73)
- Dehydrodialpanol (10.74)  
 Dehydrodeguelin (10.75)  
 Dehydrodolineone (10.76)  
 Villosol (10.77) (dehydrosumatrol)  
 Dehydrotoxicarol (10.78)  
 Dehydropachyrhizone (10.79)  
 Stemonal (10.80)  
 Stemonacetal (10.81)
- Amorpholone (10.82)  
 Villinol (10.83)  
 Stemonone (10.84)  
 Rotenonone (10.85)  
 Villosone (10.86)
- (iii) *12a-Hydroxyrotenoids*  
 12a-Hydroxymunduserone (10.87)  
 12a-Hydroxyrotenone (10.88)
- 12a-Hydroxyisomilletone (10.89)  
 Dalbinol (10.90) (12a-hydroxyamorphigenin)
- Dalbin (dalbinol glucoside)  
 Tephrosin (10.91)
- Derris negrensis*  
*D. uliginosa*  
*D. urucu*  
*Neorautanenia amboensis*  
*Tephrosia falciformis*  
*Dalbergia paniculata*  
*Amorpha fruticosa*  
*Neorautanenia amboensis*  
*Tephrosia villosa*  
*Amorpha fruticosa*  
*Pachyrhizus erosus*  
*Stemona collinsae* (Stemonaceae)  
*Clitoria macrophylla*  
*Stemona collinsae* (Stemonaceae)  
*Amorpha canescens*  
*Tephrosia villosa*  
*Stemona collinsae* (Stemonaceae)  
*Neorautanenia amboensis*  
*Tephrosia villosa*
- Pachyrhizus erosus*  
*Derris urucu*  
*Neorautanenia amboensis*  
*Pachyrhizus erosus*  
*Tephrosia praecans*  
*Neorautanenia amboensis*  
*Dalbergia assamica*  
*D. latifolia*  
*Dalbergia assamica*  
*D. latifolia*  
*Crotalaria burhia*  
*C. medicaginea*  
*Derris urucu*
- Vasconcelos and Maia (1976)  
 Bose *et al.* (1976)  
 Braz Filho *et al.* (1975)  
 Oberholzer *et al.* (1974)  
 Ghanim and Jayaraman (1979)  
 Adinarayana and Rao (1975b)  
 Ognyanov and Somleva (1980)  
 Oberholzer *et al.* (1974)  
 Sarma *et al.* (1976)  
 Reisch *et al.* (1976)  
 Krishnamurti *et al.* (1970)  
 Shienghong *et al.* (1974)  
 Taguchi *et al.* (1977)  
 Shienghong *et al.* (1974)  
 Piatak *et al.* (1975)  
 Krupadanam *et al.* (1977)  
 Shienghong *et al.* (1974)  
 Oberholzer *et al.* (1976)  
 Krupadanam *et al.* (1977)
- Kalra *et al.* (1977)  
 Braz Filho *et al.* (1975)  
 Oberholzer *et al.* (1974)  
 Kalra *et al.* (1977)  
 Camele *et al.* (1980)  
 Oberholzer *et al.* (1976)  
 Chibber and Sharma (1978)  
 Chibber and Khara (1978)  
 Chibber and Sharma (1978)  
 Chibber and Khara (1979)  
 Uddin and Khanna (1979)  
 Jain (1979)  
 Braz Filho *et al.* (1975)

Table 10.4 (Contd.)

| Rotenoid                                 | Plant sources                                                                                                                  | References                                                                                       |
|------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
|                                          | <i>Lonchocarpus unifolius</i><br><i>Tephrosia falciformis</i><br><i>T. praecans</i><br><i>T. purpurea</i><br><i>T. vogelii</i> | Delle Monache <i>et al.</i> (1978)<br>Kamal and Jain (1978)<br>Camele <i>et al.</i> (1980)       |
| 12a-Hydroxyerosone (10.92)               | <i>Neorautanenia amboensis</i><br><i>Pachyrrhizus erosus</i>                                                                   | Sharma and Khanna (1975)<br>Breytenbach and Rall (1980)                                          |
| 12a-Hydroxydolineone (10.93)             | <i>Neorautanenia amboensis</i><br><i>Pachyrrhizus erosus</i>                                                                   | Kalra <i>et al.</i> (1977)<br>Oberholzer <i>et al.</i> (1974)                                    |
| Villosinol (10.94) (12a-hydroxysumatrol) | <i>Neorautanenia amboensis</i><br><i>Pachyrrhizus erosus</i><br><i>Tephrosia villosa</i>                                       | Krishnamurti <i>et al.</i> (1970)<br>Sarma <i>et al.</i> (1976)<br>Mitscher <i>et al.</i> (1979) |
| 11-Hydroxytephrosin (10.95)              | <i>Amorpha fruticosa</i>                                                                                                       | Krishnamurti <i>et al.</i> (1970)                                                                |
| 12a-Hydroxypachyrrhizone (10.96)         | <i>Pachyrrhizus erosus</i>                                                                                                     | Oberholzer <i>et al.</i> (1974)                                                                  |
| 12a-Methoxyrotenone (10.97)              | <i>Neorautanenia amboensis</i>                                                                                                 | Oberholzer <i>et al.</i> (1976)                                                                  |
| Neobanone (10.98)                        | <i>Neorautanenia amboensis</i>                                                                                                 | Oberholzer <i>et al.</i> (1974)                                                                  |
| 12a-Methoxydolineone (10.99)             | <i>Neorautanenia amboensis</i>                                                                                                 | Taguchi <i>et al.</i> (1977)                                                                     |
| Clitoriactal (10.100)                    | <i>Clitoria macrophylla</i>                                                                                                    | Krupadanam <i>et al.</i> (1977)                                                                  |
| Villol (10.101)                          | <i>Tephrosia villosa</i>                                                                                                       |                                                                                                  |



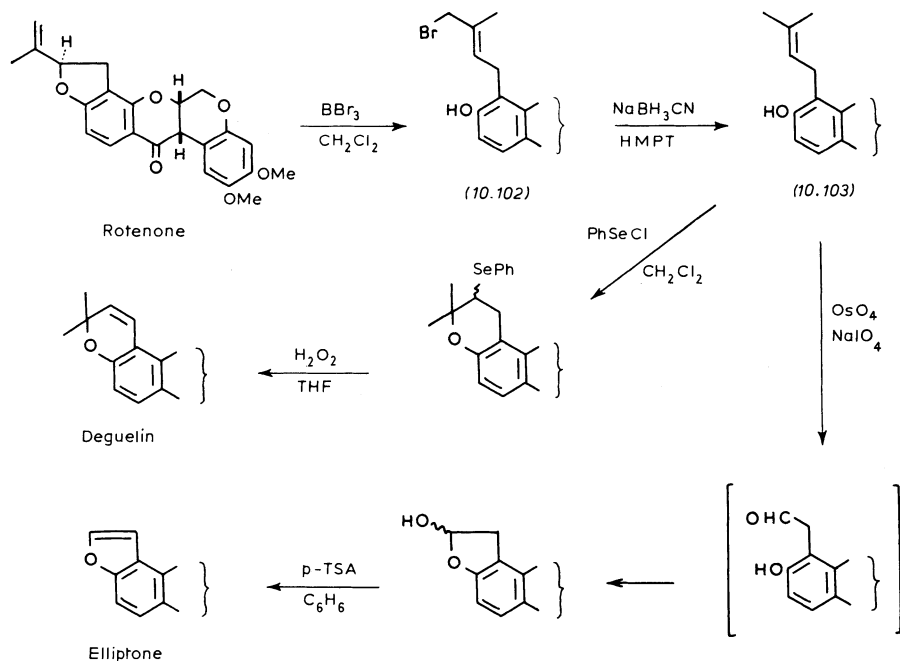


Fig. 10.5

In a further new route to rotenoids via dehydrorotenoids (Fig. 10.8), the  $\beta$ -keto ester (10.104) reacts thermally with the appropriate phenol, and rotenoids can be obtained by hydrogenation (Verhe and Schamp, 1975). Because the A ring of natural rotenoids contains, without exception, 2,3-dimethoxy or 2,3-methylenedioxy substituents, this route may prove more useful than the unusual starting materials might indicate.

### 10.5.2 Dehydrorotenoids

Because 6a,12a-dehydrorotenoids may be formed by the ready dehydration of 12a-hydroxyrotenoids, themselves formed by aeration of rotenoid solutions, the natural occurrence of both of these classes has been disputed in the past. It is now accepted that dehydrorotenoids are plant products and not artefacts, and dehydro derivatives of eight rotenoids are recognized. Those recently reported are listed in Table 10.4.

6-Oxy derivatives of dehydrorotenoids have also been isolated. Stemonal (10.80) from roots of the Thai medicinal plant *Stemona collinsae* (Stemonaceae) (Shiengthong *et al.*, 1974) and stemonacetal (10.81) from *S. collinsae* and also *Clitoria macrophylla* (Taguchi *et al.*, 1977) are 6-hydroxy and 6-ethoxy derivatives respectively of dehydrosermundone, amorpholone (10.82) from root

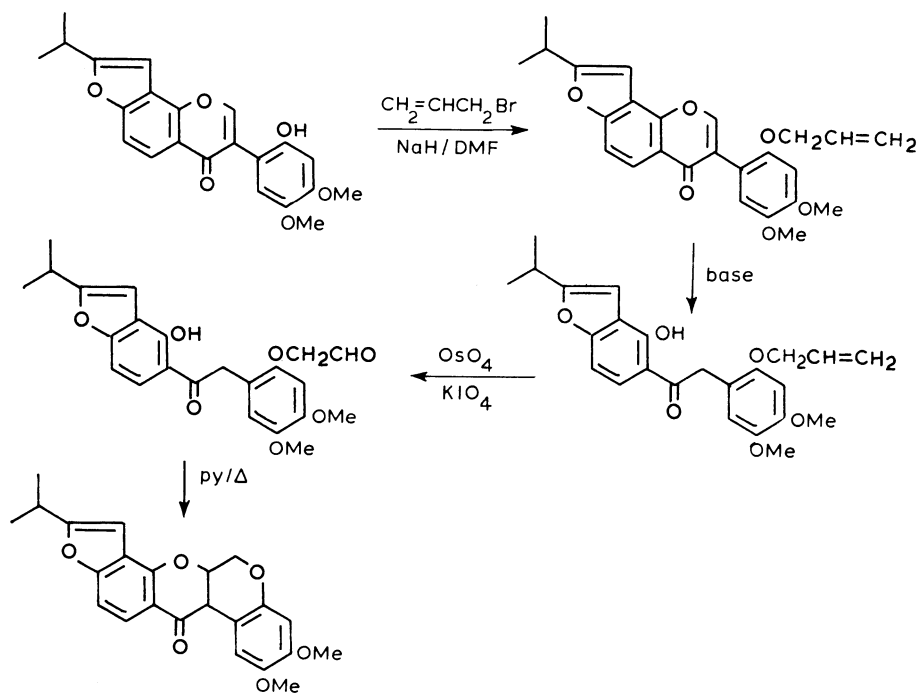


Fig. 10.6

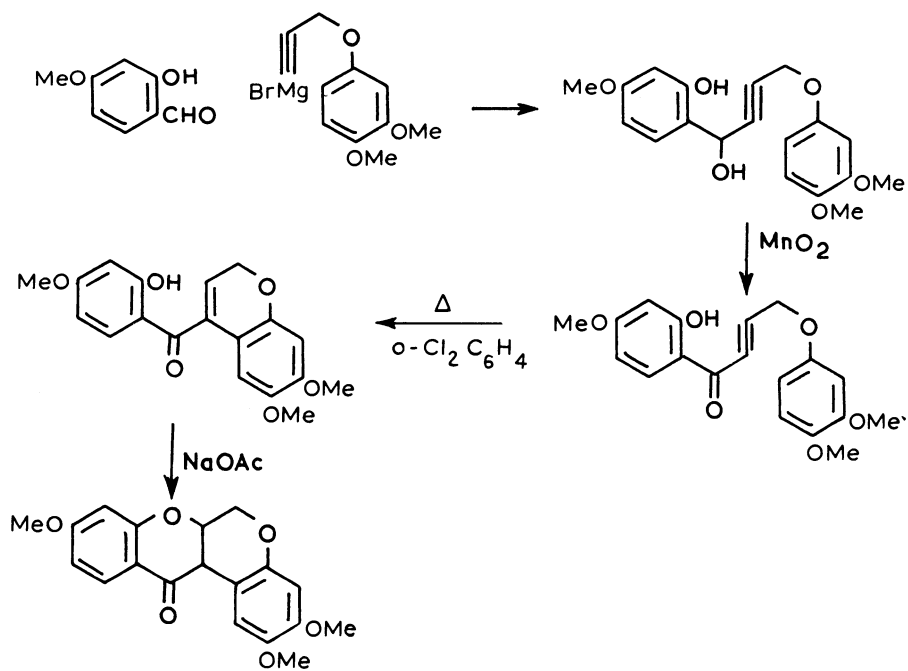


Fig. 10.7

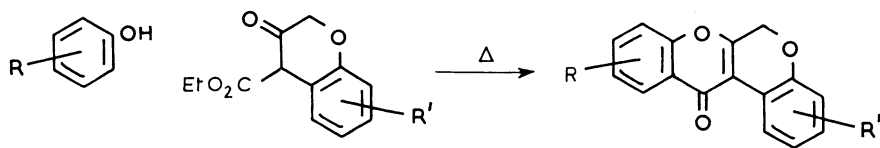


Fig. 10.8

of *Amorpha canescens* (Piatak *et al.*, 1975) is 6-hydroxydehydrorotenone, and villinol (10.83) from *Tephrosia villosa* pods (Krupadanam *et al.*, 1977) is 6-methoxydehydrosumatrol. Stemonone (10.84) and villosone (10.86) are 6-keto dehydrorotenoids co-occurring with stemonal and villinol respectively, and rotenonone (10.85) has been isolated from *Neorautanenia amboensis* (Oberholzer *et al.*, 1976).

As with the dehydrorotenoids, it is important to establish that 6-oxygenated compounds do not arise as artefacts, since photochemical studies (Chubachi and Hamada, 1974; Krupadanam *et al.*, 1978) have shown that these types of compounds can be produced by UV irradiation of rotenoid and dehydro-rotenoid solutions. The conversion into 6-oxorotenoids can be almost total in the case of some 6a,12a-dehydrorotenoids (Krupadanam *et al.*, 1978).

### 10.5.3 12a-Hydroxyrotenoids

( $\pm$ )-Tephrosin (10.91) has been known for many years but was often regarded as an artefact of deguelin via aerial oxidation (Wong, 1975). With the isolation of optically active tephrosin and millettosin, these compounds were accepted to be natural products. 12a-Hydroxy derivatives of most of the known rotenoids have now been reported (Table 10.4), and many of these have also been isolated in optically active forms. Where absolute configurations have been reported, these compounds have the 6aS, 12aS configuration, as do the natural rotenoids. Further evidence that these materials must be regarded as natural products has been obtained during biosynthetic studies in *Amorpha fruticosa* seedlings (Crombie *et al.*, 1979b). 12a-Hydroxyamorphigenin (10.90) with a specific activity some six times greater than that of the co-occurring amorphigenin was isolated, and it could thus not have arisen as an artefact of isolation.

Optically active 12a-methoxy derivatives of rotenone, erosone (neobanone) and dolineone have also been reported in *Neorautanenia amboensis* (Oberholzer *et al.*, 1974, 1976). The structure of neobanone has been confirmed by total synthesis, via the rotenoid erosone, aerial oxidation to 12a-hydroxyerosone, then methylation (Oberholzer *et al.*, 1977a).

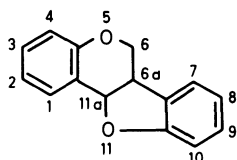
6,12a-Dihydroxyrotenoids are a further variation in rotenoid structure, and two examples of these have been isolated from plants, namely clitoriactal (10.100) which co-occurs with the 6-ethoxydehydrorotenoid stemonacetal in

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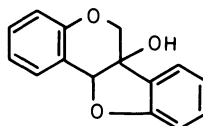
*Clitoria macrophylla* (Taguchi *et al.*, 1977) and villol (10.101) from *Tephrosia villosa* pods (Krupadanam *et al.*, 1977). This last plant produces an interesting array of rotenoid variants, namely 6-hydroxyrotenoid, dehydrorotenoid, 6-methoxy- and 6-keto-dehydrorotenoid, 12a-hydroxyrotenoid and 6,12a-dihydroxyrotenoid derivatives.

### 10.6 PTEROCARPANS

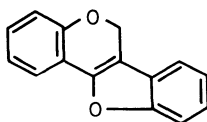
Pterocarpan (10.105) are widely distributed in leguminous plants both as heartwood and bark constituents, and also in young tissue challenged by micro-organisms, since many function as phytoalexins (see Section 10.20). It is convenient to subdivide the group into pterocarpan, 6a-hydroxypterocarpan (10.106) and pterocarpenes (10.107), in general reserving the nomenclature pterocarpan for the fully reduced ring system (10.105).



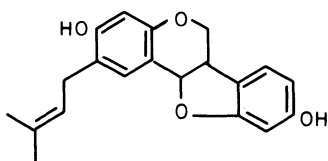
(10.105)



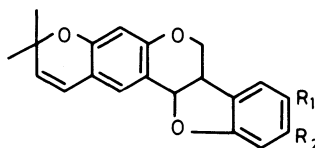
(10.106)



(10.107)

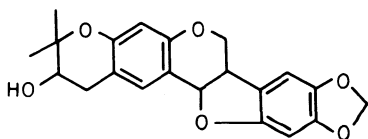


(10.108) Homoedudiol

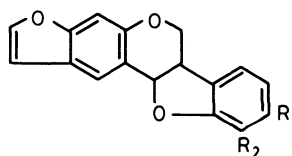


(10.109)  $R_1 = H$ ,  $R_2 = OH$ , Neorautenol

(10.110)  $R_1 R_2 = OCH_2O$ , Neorautenane

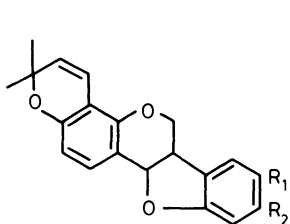


(10.111) Neorautanol



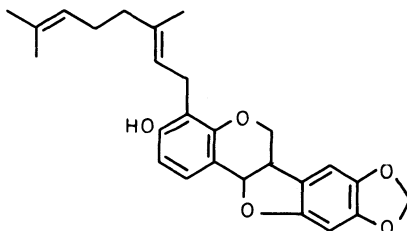
(10.112)  $R_1 = OH$ ,  $R_2 = H$ , Neodunol

(10.113)  $R_1 = R_2 = OMe$ , Ambonane

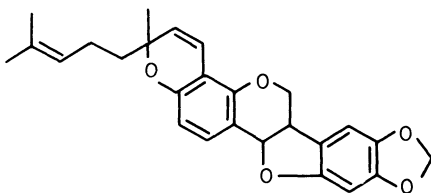


(10.114)  $R_1 = H$ ,  $R_2 = OMe$ , Hemileiocarpin

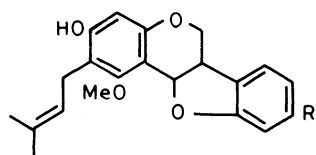
(10.115)  $R_1 R_2 = OCH_2O$ , Leiocarpin



(10.116) Nitiducol

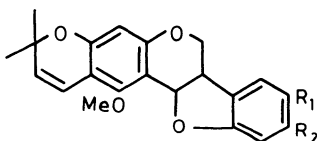


(10.117) Nitiducarpin



(10.118)  $R = OH$ , Edudiol

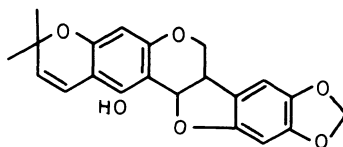
(10.119)  $R = OMe$ , Edulenol



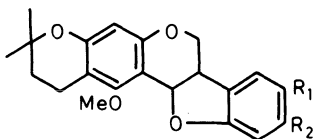
(10.120)  $R_1 = H$ ,  $R_2 = OH$ , Edulenanol

(10.121)  $R_1 = H$ ,  $R_2 = OMe$ , Edulenane

(10.122)  $R_1 = OMe$ ,  $R_2 = OH$ , Desmodin

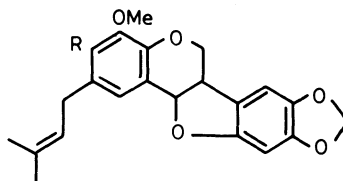


(10.123) Neorautenanol



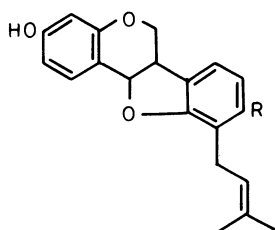
(10.124)  $R_1 = H$ ,  $R_2 = OMe$ , Edulane

(10.125)  $R_1 R_2 = OCH_2O$ , Neorautanin



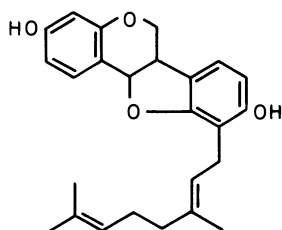
(10.126)  $R = OH$ , Neoraucarpanol

(10.127)  $R = OMe$ , Neoraucarpan

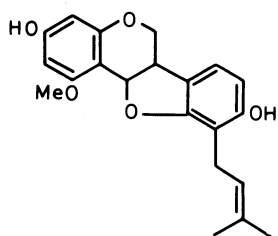


(10.128) R=OH, Phaseollidin

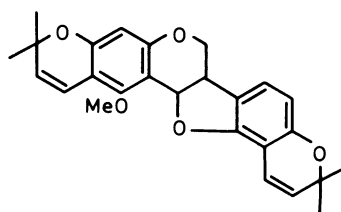
(10.129) R=OMe, Sandwicensin



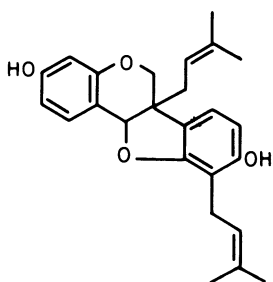
(10.130) Lespedezin



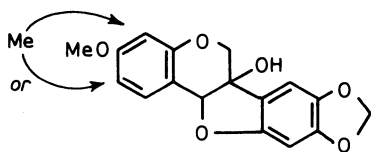
(10.131) 1-Methoxyphaseollidin



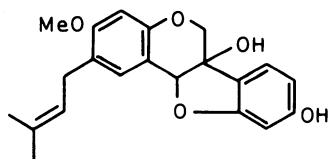
(10.132) Gangetinin



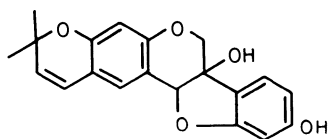
(10.133) Lespein



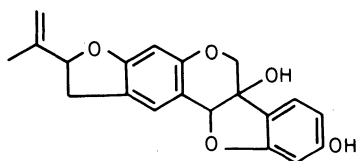
(10.134) Acanthocarpan



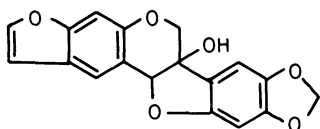
(10.135) Glyceollin IV



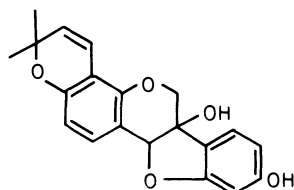
(10.136) Glyceollin II



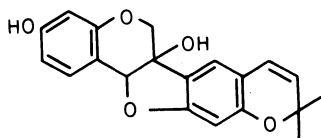
(10.137) Glyceollin III



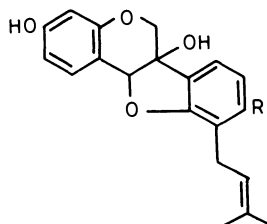
(10.138) Neobanol



(10.139) Glyceollin III

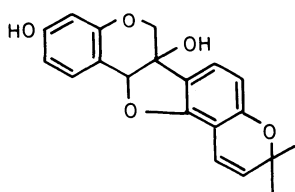


(10.140) Tuberosin

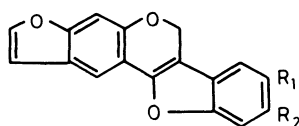


(10.141) R = OH, Sandwicarpin

(10.142) R = OMe, Cristacarpin

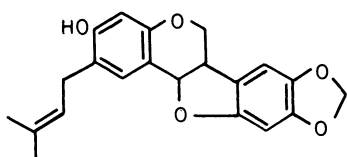


(10.143) 6a-Hydroxyphaseollin

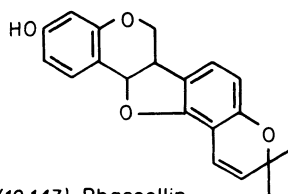


(10.144) R<sub>1</sub> = H, R<sub>2</sub> = OH, Neorauteen

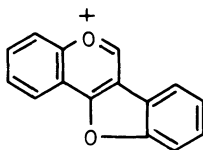
(10.145) R<sub>1</sub>R<sub>2</sub> = OCH<sub>2</sub>O, Neoduleen



(10.146) Edunol



(10.147) Phaseollin



(10.148)

### 10.6.1 Pterocarpan

New pterocarpan and further sources of known structures are presented in Table 10.5. It is interesting to note that medicarpin (previously known as demethylhomopterocarpin, but this name is too cumbersome for general usage) is now undoubtedly the most common of natural pterocarpan since it functions as a phytoalexin in tissues of many legumes. A wide variety of substitution patterns is encountered, but 3,9- and 3,8,9-oxygenation patterns predominate, and 1-oxygenated compounds (corresponding to position 5 in isoflavones) are relatively uncommon. Unusual geranyl substituents have been found in nitiducol (10.116) and nitiducarpin (10.117) from *Dalbergia nitidula* bark (Van Heerden *et al.*, 1978) and in lespedezin (10.130) from *Lespedeza homoloba* bark (Ueno *et al.*, 1973b). Lespein (10.133), also isolated from the latter plant is 6a-dimethylallylphaseollidin and represents the first example of a 6a-alkylated pterocarpin.

Pterocarpan are easily recognized from their characteristic UV and NMR spectra, but assignment of substitution may be complicated, since MS fragmentation may give peaks which could arise from either ring (Wong, 1975). Hydrogenolysis to 2'-hydroxyisoflavans is the usual means of overcoming this difficulty. The reverse reaction can be brought about by treatment with DDQ (provided that there is a hydroxyl or methoxyl at position 7 of the isoflavan) (Cornia and Merlini, 1975; Gunning *et al.*, 1977), and this synthetic route to pterocarpan may often proceed more smoothly (Ingham and Dewick, 1979) than the established method via borohydride reduction of 2'-hydroxyisoflavones (Wagner and Farkas, 1975). Excess reagent must be avoided, since DDQ also converts the pterocarpin into a coumestan in excellent yield (Ferreira *et al.*, 1974; Gunning *et al.*, 1977). A further new approach to pterocarpan is by the  $\text{Li}_2\text{PdCl}_4$ -catalysed Heck arylation of chromenes (Fig. 10.9), and this has been used to synthesize the natural pterocarpan pterocarpin (Horino and Inoue, 1976), neorautenane (10.110) and neorautanol (10.111) (via maackiain) (Breytenbach and Rall, 1980). Although pterocarpan are produced in excellent yields, the route is somewhat limited by difficulties in preparing the chromene starting materials (Breytenbach and Rall, 1980).

Pterocarpan undergo photolytic cleavage in methanol or acetic acid solution to give 3,4-*trans*-2'-hydroxy-4-methoxy (or acetoxyl)-isoflavans (Fig. 10.10). The



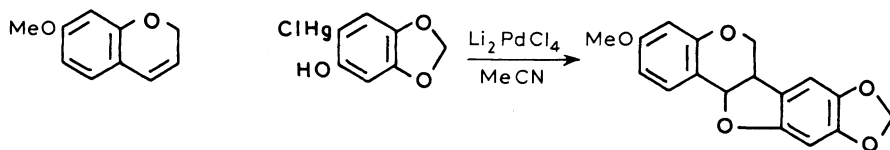


Fig. 10.9

methoxy compounds slowly revert to pterocarpan, rapidly on treatment with dilute HCl, similar results being obtained after hydrolysis of the acetoxy compounds. Cyclization is dependent on an effective leaving group at C-4, and the evidence favours a carbonium ion mechanism (Van der Meerwe *et al.*, 1978).

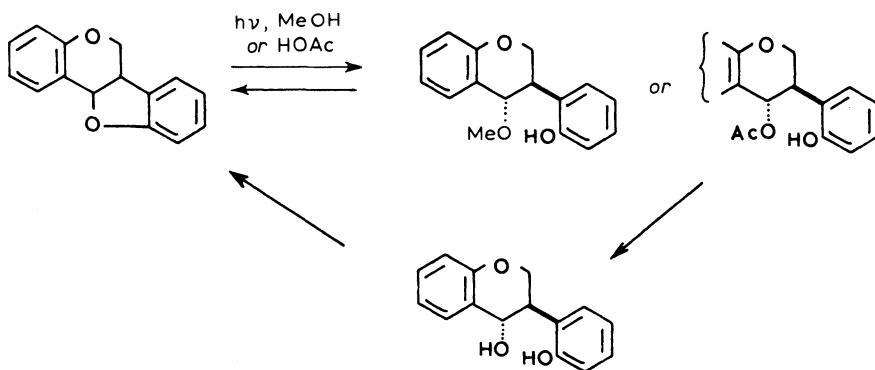


Fig. 10.10

The reactions of pterocarpan and their interrelationship with other classes of isoflavonoid have been summarized in flow-chart form (Gunning *et al.*, 1977).

Few pterocarpan glycosides have been reported in nature, but these derivatives do offer a means of resolving synthetic pterocarpan racemates, and the 3-glucoside has been used to resolve ( $\pm$ )-medicarpin (Antus and Nogradi, 1979a). Though pterocarpan contains two chiral centres, only *R,R* and *S,S* configurations are stereochemically possible. Laevorotatory, dextrorotatory and racemic forms are known in nature, and as a result of chemical degradation, NMR and ORD studies, it has been generally accepted that all laevorotatory pterocarpan have the 6a*R*, 11a*R* absolute configuration, and dextrorotatory ones the 6a*S*, 11a*S* configuration (Wong, 1975). Pterocarpan displays multiple Cotton effects in the 250–350 nm region of their ORD spectra, and these may also be used to aid chirality assignments (Cook *et al.*, 1978). X-ray crystallographic study of (+)-edunol (10.146) as its 4-bromo-3-methyl derivative confirmed this (Leipoldt *et al.*, 1977), though in a recent communication (Breytenbach and Rall, 1980), the dextrorotatory nature of the pterocarpan has been admitted to be erroneous, and



|                      |  |      |                    |                                                 |                                 |   |
|----------------------|--|------|--------------------|-------------------------------------------------|---------------------------------|---|
| Medicarpin glucoside |  | Oglu | OMe                | <i>Onobrychis</i> spp.                          | Ingham (1978b)                  | ± |
|                      |  |      |                    | <i>Osteophleum platyspermum</i> (Myristicaceae) | Braz Filho <i>et al.</i> (1977) |   |
|                      |  |      |                    | <i>Parochetus communis</i>                      | Ingham (1979c)                  |   |
|                      |  |      |                    | <i>Pericopsis schliebenii</i>                   | Fitzgerald <i>et al.</i> (1976) | - |
|                      |  |      |                    | <i>Platymiscium trinitatis</i>                  | Craveiro and Gottlieb (1974)    | + |
|                      |  |      |                    | <i>Trifolium arvense</i>                        | Ingham and Dewick (1977)        |   |
|                      |  |      |                    | <i>T. hybridum</i>                              | Ingham (1976b)                  |   |
|                      |  |      |                    | <i>T. spp.</i>                                  | Ingham (1978c)                  |   |
|                      |  |      |                    | <i>Trigonella</i> spp.                          | Ingham and Harborne (1976)      |   |
|                      |  |      |                    | <i>Vicia faba</i>                               | Hargreaves <i>et al.</i> (1976) |   |
| Isomedicarpin        |  | Oglu | OMe                | <i>Vigna unguiculata</i>                        | Lampard (1974)                  | - |
|                      |  |      |                    | <i>Medicago sativa</i>                          | Sakagami <i>et al.</i> (1974)   | - |
|                      |  |      |                    | <i>Ononis spinosa</i>                           | Haznag <i>et al.</i> (1978)     |   |
|                      |  |      |                    | <i>Psophocarpus tetragonolobus</i>              | Preston (1977b)                 | - |
|                      |  |      |                    | <i>Bowdichia nitida</i>                         | Brown <i>et al.</i> (1974)      |   |
|                      |  |      |                    | <i>Machaerium villosum</i>                      | Kurosawa <i>et al.</i> (1978c)  | + |
|                      |  |      |                    | <i>Pericopsis angolensis</i>                    | Fitzgerald <i>et al.</i> (1976) | - |
|                      |  |      |                    | <i>P. schliebenii</i>                           | Fitzgerald <i>et al.</i> (1976) | - |
|                      |  |      |                    | <i>Caragana</i> spp.                            | Ingham (1979d)                  |   |
|                      |  |      |                    | <i>Cicer arietinum</i>                          | Ingham (1976d)                  |   |
| Homopterocarpin      |  | OH   | OCH <sub>3</sub> O | <i>Dalbergia oliveri</i>                        | Donnelly and Kavanagh (1974)    | + |
|                      |  |      |                    | <i>D. sericea</i>                               | Ingham (1979f)                  |   |
|                      |  |      |                    | <i>D. spruceana</i>                             | Cook <i>et al.</i> (1978)       |   |
|                      |  |      |                    | <i>D. stevensonii</i>                           | Donnelly <i>et al.</i> (1973b)  | ± |
|                      |  |      |                    | <i>Osteophleum platyspermum</i> (Myristicaceae) | Braz Filho <i>et al.</i> (1977) | ± |
|                      |  |      |                    | <i>Pericopsis schliebenii</i>                   | Fitzgerald <i>et al.</i> (1976) | - |
|                      |  |      |                    | <i>Pisum sativum</i>                            | Ingham (1979e)                  |   |
|                      |  |      |                    | <i>Sophora japonica</i>                         | Komatsu <i>et al.</i> (1976b)   | + |
|                      |  |      |                    | <i>S. microphylla</i>                           | Briggs <i>et al.</i> (1975)     |   |
|                      |  |      |                    | <i>S. subprostrata</i>                          | Komatsu <i>et al.</i> (1976a)   | - |
| Maackiain            |  | OH   | OCH <sub>3</sub> O | <i>S. tetraptera</i>                            | Briggs <i>et al.</i> (1975)     |   |
|                      |  |      |                    | <i>S. tomentosa</i>                             | Komatsu <i>et al.</i> (1978a)   | - |
|                      |  |      |                    | <i>Trifolium arvense</i>                        | Ingham and Dewick (1977)        |   |
|                      |  |      |                    | <i>T. hybridum</i>                              | Ingham (1976b)                  |   |
|                      |  |      |                    | <i>T. spp.</i>                                  | Ingham (1978c)                  |   |
|                      |  |      |                    | <i>Trigonella</i> spp.                          | Ingham and Harborne (1976)      |   |

Table 10.5 (Contd.)

| Pterocarpan                               | Substituents |     |      |     |   |                    |     |     |     |  | Plant sources                  | Optical activity | References                      |
|-------------------------------------------|--------------|-----|------|-----|---|--------------------|-----|-----|-----|--|--------------------------------|------------------|---------------------------------|
|                                           | 1            | 2   | 3    | 4   | 7 | 8                  | 9   | 10  |     |  |                                |                  |                                 |
| Trifolirhizin<br>[(-)-Maackian glucoside] |              |     | Oglu |     |   | OCH <sub>2</sub> O |     |     |     |  | <i>Ononis arvensis</i>         | -                | Kovalev <i>et al.</i> (1976)    |
|                                           |              |     |      |     |   |                    |     |     |     |  | <i>O. spinosa</i>              | -                | Haznagý <i>et al.</i> (1978)    |
| Trifolirhizin-6'-monoacetate              |              |     |      |     |   |                    |     |     |     |  | <i>Sophora subprostrata</i>    | -                | Komatsu <i>et al.</i> (1976a)   |
| Pterocarpin                               |              |     | OMe  |     |   | OCH <sub>2</sub> O |     |     |     |  | <i>Sophora subprostrata</i>    | -                | Komatsu <i>et al.</i> (1976a)   |
| Vesticarpan                               |              |     | OH   |     |   |                    | OMe | OH  |     |  | <i>Sophora subprostrata</i>    | -                | Komatsu <i>et al.</i> (1976a)   |
|                                           |              |     |      |     |   |                    |     |     |     |  | <i>Machaerium vestitum</i>     | +                | Kurosawa <i>et al.</i> (1978a)  |
|                                           |              |     |      |     |   |                    |     |     |     |  | <i>Platymiscium trinitatis</i> | +                | Craveiro and Gottlieb (1974)    |
| Nissolin                                  |              |     | OH   |     |   |                    | OH  | OMe |     |  | <i>Lathyrus nissolia</i>       |                  | Robeson and Ingham (1979)       |
| Methylnissolin                            |              |     | OH   |     |   |                    | OMe | OMe |     |  | <i>Lathyrus nissolia</i>       |                  | Robeson and Ingham (1979)       |
| 3-Hydroxy-2,9-dimethoxy-                  |              | OMe | OH   |     |   |                    | OMe |     |     |  | <i>Pisum sativum</i>           | -                | Pueppke and Van Eiten (1975)    |
| Sparticarpin                              |              | OMe | OMe  |     |   |                    | OH  |     |     |  | <i>Spartium junceum</i>        | -                | Ingham and Dewick (1980a)       |
| 2,3,9-Trimethoxy-                         |              | OMe | OMe  |     |   |                    | OMe |     |     |  | <i>Pisum sativum</i>           | -                | Pueppke and Van Eiten (1975)    |
| 2,8-Dihydroxy-3,9-dimethoxy-              |              | OH  | OMe  |     |   | OH                 |     | OMe |     |  | <i>Swartzia laevicarpa</i>     | -                | Braz Filho <i>et al.</i> (1980) |
| Mucronucarpan                             |              | OH  | OMe  |     |   |                    | OMe | OH  |     |  | <i>Machaerium mucronulatum</i> | +                | Kurosawa <i>et al.</i> (1978c)  |
| 2,8-Dihydroxy-3,9,10-trimethoxy-          |              | OH  | OMe  |     |   | OH                 | OMe | OMe |     |  | <i>Swartzia laevicarpa</i>     | -                | Braz Filho <i>et al.</i> (1980) |
| 3,4,9-Trihydroxy-                         |              |     | OH   | OH  |   |                    | OH  | OH  |     |  | <i>Melilotus alba</i>          | -                | Ingham (1976a)                  |
| 3,4-Dihydroxy-9-methoxy-                  |              |     | OH   | OH  |   |                    | OMe | OMe |     |  | <i>Melilotus alba</i>          | -                | Ingham (1976a)                  |
| 4-Hydroxy-3,9-dimethoxy-                  |              |     | OMe  | OH  |   |                    | OMe | OMe |     |  | <i>Melilotus alba</i>          | -                | Ingham (1976a)                  |
| 3,4,9-Trimethoxy                          |              |     | OMe  | OMe |   |                    | OMe | OMe |     |  | <i>Myroxylon peruiferum</i>    | -                | Maranduba <i>et al.</i> (1979)  |
| 3,4-Dihydroxy-8,9-methylene-dioxy-        |              |     | OH   | OH  |   | OCH <sub>2</sub> O |     | OMe |     |  | <i>Dalbergia spruceana</i>     | -                | Cook <i>et al.</i> (1978)       |
| 3-Hydroxy-4-methoxy-8,9-methylenedioxy-   |              |     | OH   | OMe |   | OCH <sub>2</sub> O |     |     |     |  | <i>Dalbergia spruceana</i>     | -                | Cook <i>et al.</i> (1978)       |
| 4-Hydroxy-3-methoxy-8,9-methylenedioxy-   |              |     | OMe  | OH  |   | OCH <sub>2</sub> O |     |     |     |  | <i>Trifolium hybridum</i>      | -                | Ingham (1976b)                  |
| 8-Hydroxy-3,4,9,10-tetramethoxy-          |              |     | OMe  | OMe |   | OH                 | OMe | OMe |     |  | <i>Dalbergia spruceana</i>     | -                | Cook <i>et al.</i> (1978)       |
| Trifolian                                 | OH           | OMe | OH   |     |   | OCH <sub>2</sub> O |     | OMe | OMe |  | <i>Swartzia laevicarpa</i>     | -                | Braz Filho <i>et al.</i> (1980) |
| 4-Hydroxy-2,3,9-trimethoxy-               |              | OMe | OMe  | OH  |   |                    | OMe |     |     |  | <i>Trifolium pratense</i>      | -                | Fraishat <i>et al.</i> (1979b)  |
|                                           |              |     |      |     |   |                    |     | OMe | OMe |  | <i>Pisum sativum</i>           | -                | Pueppke and Van Eiten (1975)    |



Table 10.5 (Contd.)

| Pterocarpan                                     | Substituents |   |     |   |    |   |   |    |                                          |     | Plant sources                      | Optical activity | References                         |
|-------------------------------------------------|--------------|---|-----|---|----|---|---|----|------------------------------------------|-----|------------------------------------|------------------|------------------------------------|
|                                                 | 1            | 2 | 3   | 4 | 7  | 8 | 9 | 10 |                                          |     |                                    |                  |                                    |
| Sandwicensin (10.129)                           |              |   |     |   |    |   |   |    |                                          |     | <i>Erythrina sandwicensis</i>      | -                | Ingham (1980)                      |
| Lespedezin (10.130)                             |              |   |     |   |    |   |   |    |                                          |     | <i>Lespedeza homoloba</i>          | ±                | Ueno <i>et al.</i> (1973b)         |
| 1-Methoxyphascolidin (10.131)                   |              |   |     |   |    |   |   |    |                                          |     | <i>Psophocarpus tetragonolobus</i> | -                | Preston (1977b)                    |
| Gangetinin (10.132)                             |              |   |     |   |    |   |   |    |                                          |     | <i>Desmodium gangeticum</i>        | -                | Puroshothaman <i>et al.</i> (1975) |
| Lespein (10.133)                                |              |   |     |   |    |   |   |    |                                          |     | <i>Lespedeza homoloba</i>          | -                | Ueno <i>et al.</i> (1973b)         |
| (ii) 6a-Hydroxypterocarpan                      |              |   |     |   |    |   |   |    |                                          |     |                                    |                  |                                    |
| 3,6a,9-Trihydroxypterocarpan                    |              |   | OH  |   |    |   |   |    |                                          | OH  | <i>Erythrina sandwicensis</i>      | -                | Ingham (1980)                      |
| 6a-Hydroxymedicarpin                            |              |   | OH  |   |    |   |   |    |                                          | OMe | <i>Glycine max</i>                 | -                | Lyne and Mulheim (1978)            |
|                                                 |              |   | OH  |   |    |   |   |    |                                          | OMe | <i>Melilotus alba</i>              | -                | Ingham (1976a)                     |
| 6a-Hydroxyisomedicarpin                         |              |   | OMe |   |    |   |   |    |                                          | OH  | <i>Trifolium pratense</i>          | -                | Bilton <i>et al.</i> (1976)        |
| Variabilin (homopisatin)                        |              |   | OMe |   |    |   |   |    |                                          | OMe | <i>Melilotus alba</i>              | -                | Ingham (1976a)                     |
|                                                 |              |   |     |   |    |   |   |    |                                          |     | <i>Caragana</i> spp.               | -                | Ingham (1979d)                     |
|                                                 |              |   |     |   |    |   |   |    |                                          |     | <i>Dalbergia variabilis</i>        | +                | Kurosawa <i>et al.</i> (1978d)     |
|                                                 |              |   |     |   |    |   |   |    |                                          |     | <i>Lathyrus odoratus</i>           | -                | Robeson <i>et al.</i> (1980)       |
|                                                 |              |   |     |   |    |   |   |    |                                          |     | <i>Lens culinaris</i>              | -                | Robeson (1978)                     |
| 6a-Hydroxymaackiain                             |              |   | OH  |   |    |   |   |    |                                          |     | <i>Trifolium pratense</i>          | -                | Bilton <i>et al.</i> (1976)        |
| Pisatin                                         |              |   | OMe |   |    |   |   |    | OCH <sub>2</sub> O<br>OCH <sub>2</sub> O |     | <i>Trifolium pratense</i>          | -                | Bilton <i>et al.</i> (1976)        |
|                                                 |              |   |     |   |    |   |   |    |                                          |     | <i>Caragana</i> spp.               | -                | Ingham (1979d)                     |
|                                                 |              |   |     |   |    |   |   |    |                                          |     | <i>Lathyrus odoratus</i>           | -                | Robeson <i>et al.</i> (1980)       |
|                                                 |              |   |     |   |    |   |   |    |                                          |     | <i>L. spp.</i>                     | -                | Robeson and Harborne (1977)        |
| 3,6a,7-Trihydroxy-9-methoxy-pterocarpan         |              |   | OH  |   | OH |   |   |    |                                          | OMe | <i>Trifolium pratense</i>          | -                | Bilton <i>et al.</i> (1976)        |
|                                                 |              |   | OH  |   | OH |   |   |    |                                          |     | <i>Trifolium pratense</i>          | -                | Ingham (1976a)                     |
| 3,6a,7-Trihydroxy-8,9-methylenedioxypterocarpan |              |   | OH  |   | OH |   |   |    | OCH <sub>2</sub> O                       |     | <i>Trifolium pratense</i>          | -                | Ingham (1976a)                     |
| Acanthocarpan (10.134)                          |              |   |     |   |    |   |   |    |                                          |     | <i>Trifolium pratense</i>          | -                | Ingham (1976a)                     |
| Glyceollin IV (10.135)                          |              |   |     |   |    |   |   |    |                                          |     | <i>Caragana acanthophyllum</i>     | -                | Ingham (1979d)                     |
| Glyceollin II (10.136)                          |              |   |     |   |    |   |   |    |                                          |     | <i>Glycine max</i>                 | -                | Lyne and Mulheim (1978)            |
| Glyceollin III (10.137)                         |              |   |     |   |    |   |   |    |                                          |     | <i>Glycine max</i>                 | -                | Lyne <i>et al.</i> (1976)          |



the absolute configuration has been reversed. The same conclusion was reached in an X-ray crystallographic study of (–)-phaseollin (10.147) (DeMartinis *et al.*, 1978), but this structure was assigned without the aid of a heavy atom, and these authors have given no indication why the *S,S* configuration should be preferred over *R,R*. At this moment, the picture is very confusing, and definitive conclusions about absolute configurations are awaited. Thus, in Table 10.5, optical rotations rather than absolute configurations are expressed.

### 10.6.2 6a-Hydroxypterocarpan

Pisatin (6a-hydroxypterocarpin), a phytoalexin produced by *Pisum* spp. on fungal infection, was the only member of this class to be recognized for some years. A related phytoalexin from soya bean (*Glycine max*) was erroneously assigned the structure 6a-hydroxyphaseollin (10.143) (Sims *et al.*, 1972), but since 6a-hydroxyphaseollin was subsequently known as a fungal metabolite of phaseollin (Burden *et al.*, 1974), the soya phytoalexin structure was reassigned as (10.139) (Burden and Bailey, 1975). The material isolated, however, after HPLC purification, separated into three 6a-hydroxypterocarpan components which are now named glyceollins I (10.139), II (10.136) and III (10.137) (Lyne *et al.*, 1976). Further minor 6a-hydroxypterocarpan phytoalexins of *Glycine max* have since been identified (Lyne and Mulheirn, 1978). These and other 6a-hydroxypterocarpan are listed in Table 10.5.

Acanthocarpan (10.134), a phytoalexin from the *Helminthosporium carbonum*-infected leaflets of *Caragana acanthophylla*, has been characterized as a *C*-methyl derivative of pisatin (Ingham, 1979d), although the position of substitution (2 or 4) could not be established with certainty from MS data, and insufficient material was available for a NMR spectrum. The only other natural *C*-methylated isoflavonoid known is the isoflavanone ougenin.

Chirality assignments in 6a-hydroxypterocarpan are perhaps more confused now than with pterocarpan. It has generally been assumed that replacement of a hydrogen at 6a with a hydroxyl will have no effect on optical rotation, and thus (–)-6a-hydroxypterocarpan should have the same absolute configuration as (–)-pterocarpan. A number of researchers have, however, misinterpreted the rules for *R,S* nomenclature and assigned the wrong chirality. Thus, although substitution of the 6a-hydrogen with a hydroxyl in a 6a*R*,11a*R*-pterocarpan does not change the absolute configuration, it does affect the nomenclature, and the product is now 6a*S*,11a*S* (Fig. 10.11). Literature reports include several errors, and it has been necessary for this discrepancy to be brought to the general attention of other workers (Sicherer and Sicherer-Roetman, 1980; Ingham and Markham, 1980).

6a-Hydroxypterocarpan are characterized by their rapid dehydration to pterocarpenes in the presence of acids, and this is conveniently noted by UV spectroscopy (see Section 10.2). A similar process is encountered on MS analysis, and *M* – 18 is a major fragment. Unless the compound contains isopentenyl or



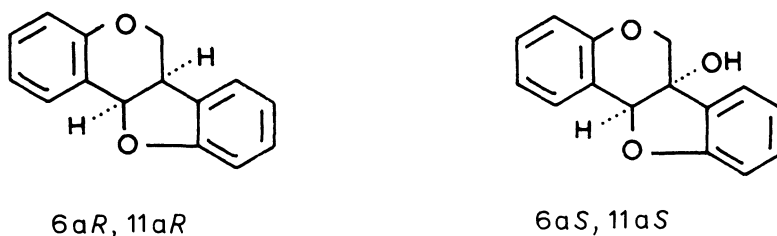


Fig. 10.11

chromene ring substituents for example, further fragmentation may be limited to loss of hydrogen from this intermediate pterocarpene (see Section 10.6.3). NMR spectra are much simpler than with pterocarpans, and in some cases the two C-6 protons are magnetically equivalent, thus showing a singlet instead of the usual double doublet (Ingham and Markham, 1980). This equivalence is presumably accidental and cannot be predicted.

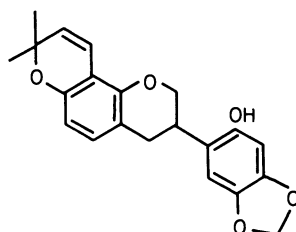
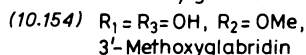
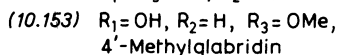
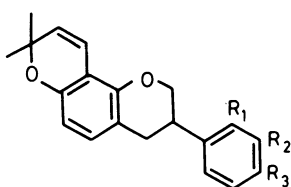
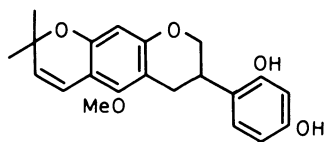
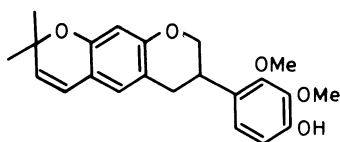
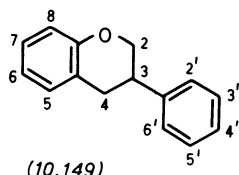
### 10.6.3 Pterocarpenes

Pterocarpenes could, in some cases, arise as artefacts of 6a-hydroxypterocarpans, but there is now a considerable selection of naturally occurring examples (Table 10.5). The heartwood of *Brya ebenus* has proved a very rich source, five bryacarpenes having been isolated from this material (Ferreira *et al.*, 1974). As mentioned above, MS fragmentation of pterocarpenes is frequently limited to loss of hydrogen to yield the very stable ion (10.148, cf. 10.42). By adjusting the spectrometer settings, it is possible to produce doubly charged ion mass spectra, and under such conditions, more meaningful fragmentation results (Eguchi *et al.*, 1976).

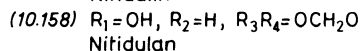
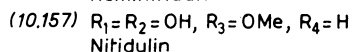
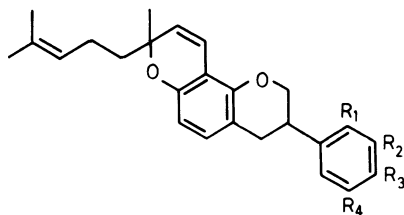
Generally, pterocarpenes are synthesized by acid-catalysed cyclization of 2'-hydroxyisoflavanones (Farkas *et al.*, 1974). They are somewhat labile in solution, and are readily oxidized to coumestans, even by atmospheric oxygen. This conversion may be brought about particularly efficiently by treatment with DDQ (Ferreira *et al.*, 1974).

## 10.7 ISOFLAVANS

The simplest example of the isoflavans (10.149) is 7,4'-dihydroxyisoflavan (equol), an animal metabolite undoubtedly produced by degradation of simple isoflavones such as formononetin and daidzein obtained in the diet (Wong, 1975). Every plant-derived isoflavan, however, contains a 2'-oxygen substituent, as well as 7,4'-oxygenation. This feature has been associated with possible biosynthetic derivation by reduction of pterocarpans (Wong, 1975), and



isoflavan biosynthesis is indeed closely related to that of pterocarpan, but not necessarily in this manner (see Section 10.18). Isoflavans often function as phytoalexins, and many of the new structures reported (Table 10.6) have been isolated during antifungal screens. Typically, the isoflavan phytoalexins are simple hydroxy/methoxy-substituted structures. 5-Oxygenation is a rare feature in isoflavan structures (cf. Section 10.6). Complex geranyl-substituted isoflavans, namely heminitidulan (10.156), nitidulin (10.157) and nitidulan (10.158)



have been isolated from the bark of *Dalbergia nitidula* along with pterocarpans analogues (Van Heerden *et al.*, 1978). Although 3,3-dimethylallyl substituents



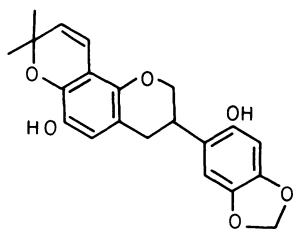


| Astracercan                                       | OH  | OMe | OCH <sub>3</sub> O |  |  |
|---------------------------------------------------|-----|-----|--------------------|--|--|
| 5-Methoxyvestitol                                 | OMe |     |                    |  |  |
| Bryaflavan                                        | OH  | OH  | OMe                |  |  |
| 8-Demethylduartin                                 | OH  | OMe | OMe                |  |  |
| Duartin                                           | OH  | OMe | OMe                |  |  |
| Spherosinin (10.150)                              |     |     |                    |  |  |
| Neoraufavane (10.151)                             |     |     |                    |  |  |
| Glabridin (10.152)                                |     |     |                    |  |  |
| 4-Methylglabridin (10.153)                        |     |     |                    |  |  |
| 3-Methoxyglabridin (10.154)                       |     |     |                    |  |  |
| Leiocin (10.155)                                  |     |     |                    |  |  |
| Heminitidulan (10.156)                            |     |     |                    |  |  |
| Nitidulin (10.157)                                |     |     |                    |  |  |
| Nitidulan (10.158)                                |     |     |                    |  |  |
| Leiocinol (10.159)                                |     |     |                    |  |  |
| 2-Methylphaseollidin-isoflavan (10.160)           |     |     |                    |  |  |
| Phaseollinisoflavan (10.161)                      |     |     |                    |  |  |
| 2-Methylphaseollin-isoflavan (10.162)             |     |     |                    |  |  |
| $\alpha,\alpha$ -Dimethylallylcyclolobin (10.163) |     |     |                    |  |  |
| Unanisoiflavan (10.164)                           |     |     |                    |  |  |
| Hispaglabridin A (10.165)                         |     |     |                    |  |  |
| Hispaglabridin B (10.166)                         |     |     |                    |  |  |

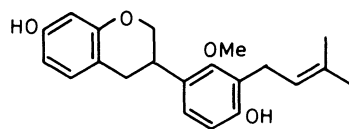
|                                |  |  |  |   |                                  |
|--------------------------------|--|--|--|---|----------------------------------|
| <i>Astragalus cicer</i>        |  |  |  |   | Ingham and Dewick (1980b)        |
| <i>A. pyrenaicus</i>           |  |  |  |   | Ingham and Dewick (1979)         |
| <i>Lotus hispidus</i>          |  |  |  |   | Ferreira <i>et al.</i> (1974)    |
| <i>Brya ebenus</i>             |  |  |  | S | Donnelly <i>et al.</i> (1973a)   |
| <i>Dalbergia ecastophyllum</i> |  |  |  | R | Kurosawa <i>et al.</i> (1978c)   |
| <i>Machaerium mucronulatum</i> |  |  |  | S | Ollis <i>et al.</i> (1978c)      |
| <i>M. opacum</i>               |  |  |  | S | Kurosawa <i>et al.</i> (1978c)   |
| <i>M. villosum</i>             |  |  |  | + | Kattaev <i>et al.</i> (1975)     |
| <i>Sphaerophysa salsula</i>    |  |  |  | — | Brink <i>et al.</i> (1974a)      |
| <i>Neorautanenia edulis</i>    |  |  |  | R | Saitoh <i>et al.</i> (1976)      |
| <i>Glycyrrhiza glabra</i>      |  |  |  | R | Mitscher <i>et al.</i> (1980)    |
| <i>Glycyrrhiza glabra</i>      |  |  |  | R | Mitscher <i>et al.</i> (1980)    |
| <i>Glycyrrhiza glabra</i>      |  |  |  | S | Van Heerden <i>et al.</i> (1978) |
| <i>Dalbergia nitidula</i>      |  |  |  | S | Van Heerden <i>et al.</i> (1978) |
| <i>Dalbergia nitidula</i>      |  |  |  | S | Van Heerden <i>et al.</i> (1978) |
| <i>Dalbergia nitidula</i>      |  |  |  | S | Van Heerden <i>et al.</i> (1978) |
| <i>Dalbergia nitidula</i>      |  |  |  | S | Van Heerden <i>et al.</i> (1978) |
| <i>Vigna unguiculata</i>       |  |  |  | R | Preston (1975)                   |
| <i>Glycyrrhiza glabra</i>      |  |  |  | + | Mitscher <i>et al.</i> (1980)    |
| <i>Phaseolus vulgaris</i>      |  |  |  | R | Gottlieb <i>et al.</i> (1975)    |
| <i>Cyclobium clauseni</i>      |  |  |  | — | Minhaj <i>et al.</i> (1976b)     |
| <i>Sophora secundiflora</i>    |  |  |  | R | Mitscher <i>et al.</i> (1980)    |
| <i>Glycyrrhiza glabra</i>      |  |  |  | R | Mitscher <i>et al.</i> (1980)    |
| <i>Glycyrrhiza glabra</i>      |  |  |  | R | Mitscher <i>et al.</i> (1980)    |

## 594 The Flavonoids

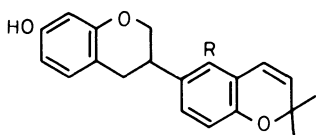
are common in isoflavonoid structures, related 1,1-dimethylallyl substituents are rare. Two isoflavans with this unusual grouping, probably formed by Claisen-type rearrangement of an *O*-3,3-dimethylallyl grouping, have been reported,  $\alpha,\alpha$ -dimethylallylcyclolobin (10.163) from *Cyclobium claussemi* (Gottlieb *et al.*, 1975) and its 4'-methyl ether unanisoiflavan (10.164) from *Sophora secundiflora*



(10.159) Leiocinol

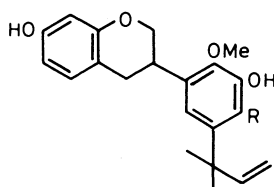


(10.160) 2'-Methylphaseollidinisoiflavan



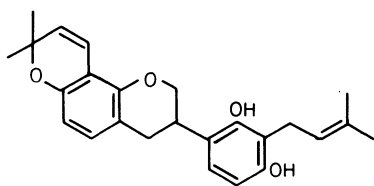
(10.161) R = OH, Phaseollinisoflavan

(10.162) R = OMe, 2'-Methylphaseollinisoiflavan

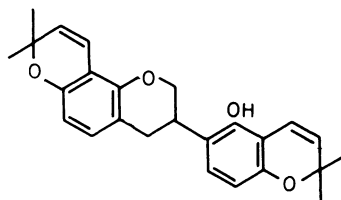


(10.163) R = OH,  $\alpha,\alpha$ -Dimethylallylcyclolobin

(10.164) R = OMe, Unanisoiflavan

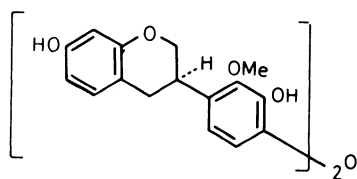


(10.165) Hispaglabridin A



(10.166) Hispaglabridin B

(Minhaj *et al.*, 1976b). Unanisoiflavan could not be found in a second sample of *S. secundiflora*, but the related 3-hydroxyisoflavanone secundifloran was isolated (Minhaj *et al.*, 1977). *Cyclobium claussemi* also yielded a material biscyclolobin, formulated as a dehydrative dimer based on cyclolobin, and a tentative structure such as (10.167) is suggested (Gottlieb *et al.*, 1975).



(10.167) Biscyclolobin

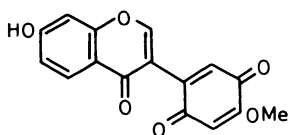
The absolute configuration of isoflavans cannot be assigned merely by optical rotation measurements, but 3*S*-isoflavans exhibit a negative Cotton effect in the 260–300 nm region of their ORD curves (Kurosawa *et al.*, 1978b). Thus, (+)-vestitol, (–)-mucronulatol and (–)-duartin all have the 3*S*-configuration. This assignment is, however, based partly on knowledge of the absolute configuration of pterocarpan, and any reappraisal there could naturally change current assignments. It is important to realize that both ORD and NMR characteristics are markedly influenced by the preferred conformation of the molecule in solution, and it is essential not to restrict ORD measurements to long-wavelength regions (Kurosawa *et al.*, 1978b).

Isoflavans are usually synthesized by catalytic hydrogenation of isoflavones (Wagner and Farkas, 1975). The particular condition of the catalyst is an important consideration, and to avoid hydrogenation of aromatic rings, and to optimize isoflavan yield, pretreatment of Pd–C catalysts in acetic acid with oxygen is regarded as desirable (Lamberton *et al.*, 1978).

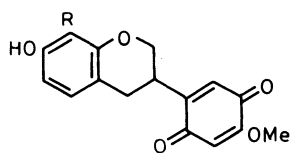
## 10.8 QUINONE DERIVATIVES

### 10.8.1 Isoflavonequinone

Bowdichione (10.168) is the only example of this class, and was isolated from the heartwood of *Bowdichia nitida* (Brown *et al.*, 1974), along with 3'-hydroxyformononetin, genistein and homopterocarpin. This coloured compound displays both isoflavone and quinone characteristics in its MS fragmentation, showing RDA fragmentation in the isoflavone portion and loss of CO + Me in the quinone. Its constitution was confirmed by oxidation of 3'-hydroxyformononetin with Fremy's salt.

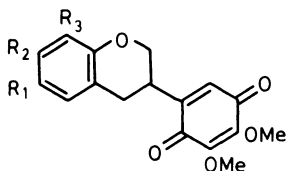


(10.168) Bowdichione



(10.169) R = OH, Claussequinone

(10.171) R = OMe, Mucroquinone

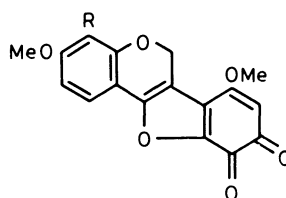


(10.170) R<sub>1</sub>=R<sub>2</sub>=OMe, R<sub>3</sub>=H, Abruquinone A

(10.172) R<sub>1</sub>=H, R<sub>2</sub>=OH, R<sub>3</sub>=OMe, Amorphaquinone

(10.173) R<sub>1</sub>=OH, R<sub>2</sub>=R<sub>3</sub>=OMe, Abruquinone C

(10.174) R<sub>1</sub>=R<sub>2</sub>=R<sub>3</sub>=OMe, Abruquinone B



(10.175) R = H, 4-Deoxybryaquinone

(10.176) R = OH, Bryaquinone

### 10.8.2 Isoflavanquinones

Three isoflavanquinones abruquinones-A -B and -C (10.170, 10.174, 10.173) from *Abrus precatorius* root (Lupi *et al.*, 1979) and amorphaquinone (10.172) from *Amorpha fruticosa* root (Shibata and Shimizu, 1978) are recently reported examples of this isoflavonoid class, to be added to the previously known claussequinone and mucroquinone (Table 10.7). Mucroquinone (10.171) is known in both enantiomeric forms. Absolute configurations have been assigned by ORD in essentially the same manner as with isoflavans, 3*S*-isoflavanquinones exhibiting negative Cotton effects in the 260–300 nm region, although materials with the same absolute configuration can produce ORD curves almost enantiomeric in the 400–500 nm region (Kurosawa *et al.*, 1978b). Confirmation has been achieved by the oxidation of isoflavans of known configuration. As with isoflavans, NMR characteristics are influenced by preferred conformations in solution. Isoflavanquinones are readily reduced to the corresponding quinol, but these derivatives are unstable and reoxidize in the presence of atmospheric oxygen. RDA fragmentation with hydrogen transfer to ring A predominates in the MS.

**Table 10.7** Isoflavanquinones

| <i>Isoflavanquinone</i> | <i>Plant sources</i>           | <i>Chirality</i> | <i>References</i>              |
|-------------------------|--------------------------------|------------------|--------------------------------|
| Claussequinone (10.169) | <i>Cyclobium claussemi</i>     | <i>R</i>         |                                |
|                         | <i>C. vecchi</i>               | <i>R</i>         | Gottlieb <i>et al.</i> (1975)  |
| Abruquinone A (10.170)  | <i>Abrus precatorius</i>       | <i>S</i>         | Lupi <i>et al.</i> (1979)      |
| Mucroquinone (10.171)   | <i>Cyclobium claussemi</i>     | <i>R</i>         | Gottlieb <i>et al.</i> (1975)  |
|                         | <i>Machaerium mucronulatum</i> | <i>S</i>         | Kurosawa <i>et al.</i> (1978c) |
| Amorphaquinone (10.172) | <i>Amorpha fruticosa</i>       |                  | Shibata and Shimizu (1978)     |
| Abruquinone C (10.173)  | <i>Abrus precatorius</i>       | <i>S</i>         | Lupi <i>et al.</i> (1979)      |
| Abruquinone B (10.174)  | <i>Abrus precatorius</i>       | <i>S</i>         | Lupi <i>et al.</i> (1979)      |

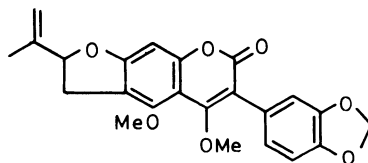
### 10.8.3 Pterocarpenequinones

Two purple pterocarpenequinones, bryaquinone (10.176) and 4-deoxy-bryaquinone (10.175) have been isolated in small amounts from the heartwood of *Brya ebenus* (Ferreira *et al.*, 1975) along with a number of pterocarpenes. Confirmation of structure was made with the aid of reductive acetylation (Zn–Ac<sub>2</sub>O–NaOAc) to the pterocarpene acetate, then hydrogenolysis to the isoflavan derivative. Whether or not these compounds are artefacts remains to be established.

## 10.9 3-ARYL-4-HYDROXYCOUMARINS

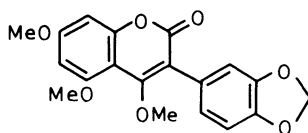
One new example of this class, glabrescin (10.177) from the seed of *Derris glabrescens* (Delle Monache *et al.*, 1977b) has been reported. This is a 4-methoxy





(10.177) Glabrescin

derivative, and co-occurs in this plant with a further example derrusnin (10.178). So far, these isoflavonoids have not been found outside the genus *Derris* and all compounds known have 5-methoxy substituents thus favouring the coumarin



(10.178) Derrusnin

tautomer rather than the 2-hydroxyisoflavone form (Wong, 1975). A new approach to the synthesis of 3-aryl-4-hydroxycoumarins via Meerwein arylation of 4-hydroxycoumarins with diazonium salts in the presence of a cupric catalyst has been described (Sawhney and Mathur, 1976). A useful conversion of isoflavones into 3-aryl-4-hydroxycoumarins may be achieved by treatment of the isoflavone with aqueous hydroxylamine to yield an intermediate oxime and isoxazole (Fig. 10.12). The isoxazole under basic conditions gives the coumarin imine from which the arylhydroxycoumarin may be obtained by hydrolysis (Szabo *et al.*, 1980).

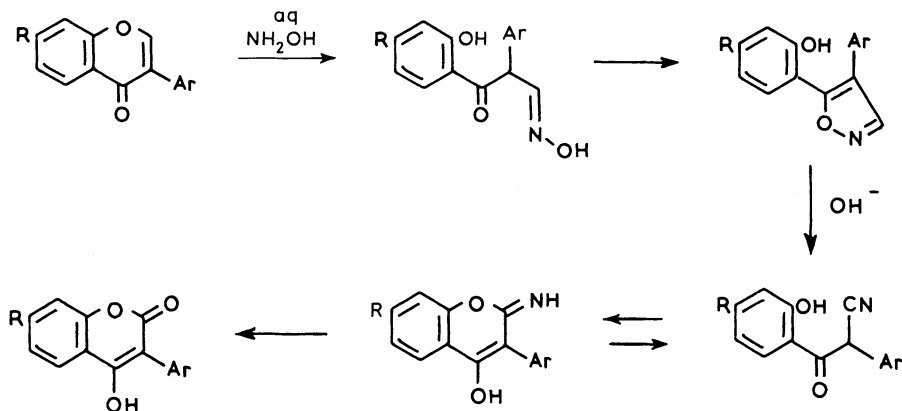
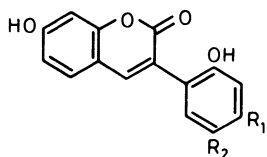
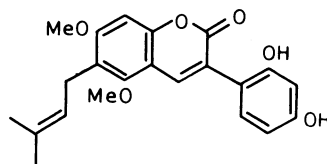


Fig. 10.12

## 10.10 3-ARYLCOUMARINS

For many years, only two naturally occurring examples of this class of isoflavonoids have been recognized, namely pachyrrhizin and neofolin. Two further compounds (10.179) and (10.180) have been isolated from the heartwood of *Dalbergia oliveri*, along with pterocarpans and coumestan analogues (Donnelly and Kavanagh, 1974). A fifth example, glycyrin (10.181) is reported in the root of *Glycyrrhiza* spp. (Kinoshita *et al.*, 1978a). These compounds characteristically show a low-field ethylenic singlet for H-4 in their NMR spectra, and in their MS behave as typical coumarins losing 28 m.u. ( $-\text{CO}$ ).

(10.179)  $\text{R}_1 = \text{OMe}$ ,  $\text{R}_2 = \text{H}$ (10.180)  $\text{R}_1, \text{R}_2 = \text{OCH}_2\text{O}$ 

(10.181) Glycyrin

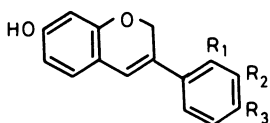
Synthesis of 3-aryl coumarins may be effected in several ways. Perkin condensation of the appropriate phenylacetic acid and aldehyde in acetic anhydride is the standard preparation (Donnelly and Kavanagh, 1974; Jurd and Manners, 1977), but other classes of isoflavonoid may be modified, e.g. oxidation of isoflav-3-enes with  $\text{CrO}_3$  (Jurd and Manners, 1977), oxidation of isoflavans (not 2'-hydroxy) with DDQ (Ferreira *et al.*, 1974) and reduction of 3-aryl-4-hydroxycoumarin tosylates with  $\text{Zn}-\text{HCl}$  (Ahluwalia and Mehta, 1978).

## 10.11 ISOFLAV-3-ENES

Isoflav-3-enes have been known chemically for many years, being synthesized by dehydration of isoflavanols or by controlled acid treatment of pterocarpans. They are, however, very reactive, especially in solution, and this is presumably why their existence as natural products has not been established until recently. Neorauflavene (10.186) from *Neorautanenia edulis* (Brink *et al.*, 1974a) was the first example reported, followed by sepiol (10.183) and 2'-methylsepiol (10.185) from *Gliricidia sepium* (Jurd, 1976; Jurd and Manners, 1977) and glabrene (10.187) from *Glycyrrhiza glabra* root (Kinoshita *et al.*, 1976). Two further examples, haginins A and B (10.184, 10.182) have recently been isolated from heartwood of *Lespedeza cyrtobotrya* (Miyase *et al.*, 1980) (Table 10.8). Isoflav-3-enes show typical allylic coupling in their NMR spectrum, and in the MS of sepiol and 2'-methylsepiol, very prominent ions at  $M-1$  were observed due to ready formation of the isoflavylium ion. Characterization is aided by conversion into the isoflavan by hydrogenation, or by  $\text{CrO}_3$  oxidation to the corresponding 3-aryl coumarin.

**Table 10.8** Isoflav-3-enes

| <i>Isoflav-3-ene</i>     | <i>Plant sources</i>         | <i>References</i>              |
|--------------------------|------------------------------|--------------------------------|
| Haginin B (10.182)       | <i>Lespedeza cyrtobotrya</i> | Miyase <i>et al.</i> (1980)    |
| Sepiol (10.183)          | <i>Gliricidia sepium</i>     | Jurd and Manners (1977)        |
| Haginin A (10.184)       | <i>Lespedeza cyrtobotrya</i> | Miyase <i>et al.</i> (1980)    |
| 2'-Methylsepiol (10.185) | <i>Gliricidia sepium</i>     | Jurd and Manners (1977)        |
| Neorauflavene (10.186)   | <i>Neorautanenia edulis</i>  | Brink <i>et al.</i> (1974a)    |
| Glabrene (10.187)        | <i>Glycyrrhiza glabra</i>    | Kinoshita <i>et al.</i> (1976) |

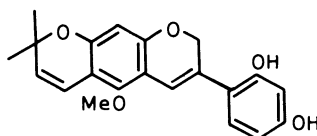


(10.182)  $R_1 = \text{OMe}$ ,  $R_2 = \text{H}$ ,  $R_3 = \text{OH}$ , Haginin B

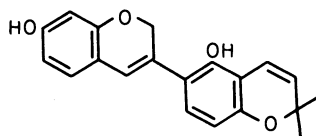
(10.183)  $R_1 = R_2 = \text{OH}$ ,  $R_3 = \text{OMe}$ , Sepiol

(10.184)  $R_1 = R_2 = \text{OMe}$ ,  $R_3 = \text{OH}$ , Haginin A

(10.185)  $R_1 = R_3 = \text{OMe}$ ,  $R_2 = \text{OH}$ , 2'-Methylsepiol



(10.186) Neorauflavene

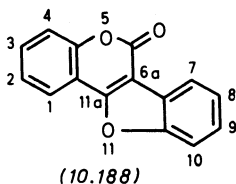


(10.187) Glabrene

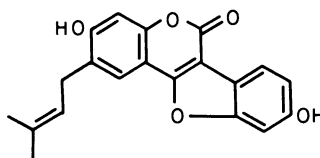
These compounds appear to play an important role in the biosynthesis of coumestans (see Section 10.18), and it is anticipated that further naturally occurring examples will be reported in due course.

## 10.12 COUMESTANS

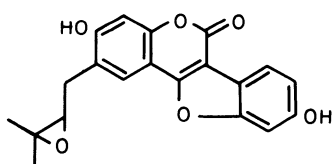
Coumestans (10.188) are widely distributed and are easily recognized in solution or on chromatograms from their intense bright-blue or violet fluorescence under UV light. Only three new coumestans have been reported during the period of review, tephrosol from *Tephrosia villosa* (Rao and Srimannarayana, 1980), and corylidin (10.191) (Gupta *et al.*, 1977) and psoralidin oxide (10.190) (Gupta *et al.*,



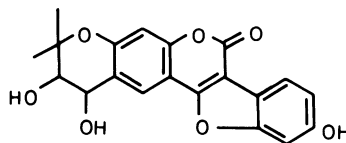
(10.188)



(10.189) Psoralidin



(10.190) Psoralidin oxide



(10.191) Corylidin

1980) from *Psoralea corylifolia* (Table 10.9). Several numbering systems have been employed in the past for coumestan nomenclature (Wong, 1975) and despite the occasional appearance of the old ones, most authors have adopted the systematic numbering also applied to pterocarpanes.

A number of new synthetic routes to coumestans have been published. The use of DDQ under mild conditions to oxidize pterocarpanes and pterocarpenes results in excellent yields of coumestans (Ferreira *et al.*, 1974), and this reagent has also been employed to convert 2'-hydroxyisoflav-3-enes and 2'-hydroxy-3-arylcoumarins into coumestans, by analogy with the biosynthetic process (Martin and Dewick, 1978). DDQ oxidation of 2'-hydroxy-3-arylcoumarins is a much less efficient route than the others mentioned, and although lead tetraacetate is an alternative oxidizing agent (Kurosawa and Nogami, 1976), yields are still relatively low. However, these methods do allow isoflavones to be modified into coumestans. 3-Aryl-4-hydroxycoumarins may also be oxidatively cyclized to coumestans by refluxing in diphenyl ether in the presence of Pd-C catalyst (Kappe and Schmidt, 1972), and the syntheses of coumestrol and dimethylcoumestrol have been achieved by this method (Kappe and Brandner, 1974). The electrochemical synthesis of coumestans (Grujic *et al.*, 1976) from a 4-hydroxycoumarin and a catechol is reminiscent of the Wanzlick synthesis (Wagner and Farkas, 1975).

### 10.13 $\alpha$ -METHYLDEOXYBENZOINS

Angolensin remained the sole example of this class of natural product for a quarter of a century, but the 2-*O*-methyl derivative (10.192) has since been extracted from heartwood of *Pericopsis elata*, where it co-occurs with angolensin (Fitzgerald *et al.*, 1976). Although both compounds isolated from this source have been assigned the *R*-configuration, they exhibit different specific rotations, angolensin being laevorotatory  $\{[\alpha]_D - 114^\circ (\text{CHCl}_3)\}$  and 2-methylangolensin dextrorotatory  $\{[\alpha]_D + 5.3^\circ (\text{CHCl}_3)\}$ . Biochanin A and afrormosin were also

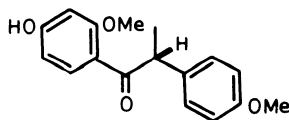
(10.192) *R*-2-Methylangolensin

Table 10.9 Coumestans

| Coumestan                         | Substituents |     |    |   |   |                    |     |    |                                                           |                                                              | References |
|-----------------------------------|--------------|-----|----|---|---|--------------------|-----|----|-----------------------------------------------------------|--------------------------------------------------------------|------------|
|                                   | 1            | 2   | 3  | 4 | 7 | 8                  | 9   | 10 | Plant sources                                             |                                                              |            |
| Coumestrol                        |              |     | OH |   |   |                    | OH  |    | <i>Phaseolus lunatus</i><br><i>P. vulgaris</i>            | Rich <i>et al.</i> (1977)<br>Gnanamanickan and Patil (1977)  |            |
| 9-Methylcoumestrol                |              |     | OH |   |   |                    | OMe |    | <i>Trifolium alexandrinum</i><br><i>Dalbergia oliveri</i> | Shemesh <i>et al.</i> (1976)<br>Donnelly and Kavanagh (1974) |            |
|                                   |              |     |    |   |   |                    |     |    | <i>D. stevensonii</i>                                     | Donnelly <i>et al.</i> (1973b)                               |            |
|                                   |              |     |    |   |   |                    |     |    | <i>Myroxylon balsamum</i>                                 | Oliveira <i>et al.</i> (1978)                                |            |
|                                   |              |     |    |   |   |                    |     |    | <i>Trifolium pratense</i>                                 | Dewick (1977)                                                |            |
|                                   |              |     |    |   |   |                    |     |    | <i>Myroxylon balsamum</i>                                 | Oliveria <i>et al.</i> (1978)                                |            |
| 3-Hydroxy-8,9-dimethoxy-Medicagol |              |     | OH |   |   | OMe                | OMe |    | <i>Dalbergia oliveri</i>                                  | Donnelly and Kavanagh (1974)                                 |            |
|                                   |              |     | OH |   |   | OCH <sub>2</sub> O |     |    | <i>D. stevensonii</i>                                     | Donnelly <i>et al.</i> (1973b)                               |            |
|                                   |              |     |    |   |   |                    |     |    | <i>Sophora tomentosa</i>                                  | Komatsu <i>et al.</i> (1978a)                                |            |
|                                   |              |     |    |   |   |                    |     |    | <i>Trifolium pratense</i>                                 | Dewick (1977)                                                |            |
| Tephrosol                         |              |     |    |   |   |                    |     |    | <i>Tephrosia villosa</i>                                  | Rao and Srimannarayana (1980)                                |            |
| Psoralidin (10.189)               |              | OMe | OH |   |   | OCH <sub>2</sub> O |     |    | <i>Phaseolus lunatus</i>                                  | Rich <i>et al.</i> (1977)                                    |            |
| Psoralidin oxide (10.190)         |              |     |    |   |   |                    |     |    | <i>Psoralea corylifolia</i>                               | Gupta <i>et al.</i> (1980)                                   |            |
| Corylidin (10.191)                |              |     |    |   |   |                    |     |    | <i>Psoralea corylifolia</i>                               | Gupta <i>et al.</i> (1977)                                   |            |

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isolated from *P. elata*, and it is generally assumed that  $\alpha$ -methyldeoxybenzoin also share an isoflavonoid origin. It is thus interesting to note that catalytic hydrogenation of isoflavanone in basic media can lead to 2-hydroxy- $\alpha$ -methyldeoxybenzoin and the corresponding alcohol (Szabo and Antal, 1976),

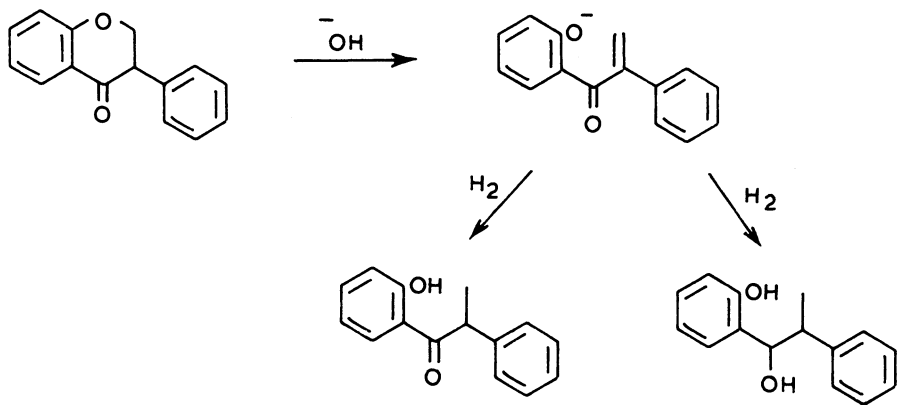
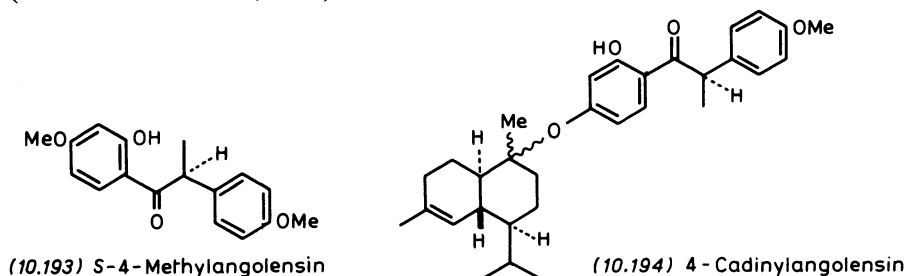


Fig. 10.13

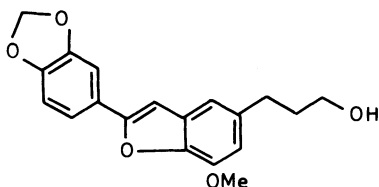
derived presumably via the ring-opened  $\alpha$ -methylene derivative (Fig. 10.13). Isoflavones may also be converted into  $\alpha$ -methyldeoxybenzoin by Birch reduction using lithium in liquid ammonia (Major *et al.*, 1980). A re-examination of *Pterocarpus angolensis* heartwood has led to the isolation of *S*-4-methylangolensin (10.193), together with *R*-angolensin and an unusual pair of epimeric sesquiterpene derivatives, cadinyl ethers of *R*-angolensin (10.194) (Bezuidenhoudt *et al.*, 1980).



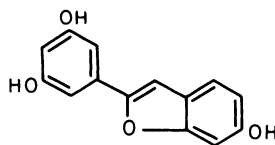
### 10.14 2-ARYLBENZOFURANS

The variety of structures encountered in the known naturally occurring 2-arylbenzofurans suggests that several different biosynthetic origins are involved. Thus, egonol (10.195) appears to be of lignan/neolignan origin and may

be derived by loss of one carbon atom from a bisarylpropanoid. Benzofuran (10.196) co-occurs with oxyresveratrol and probably arises by oxidative cyclization of this stilbene in a process analogous to laboratory conversions.

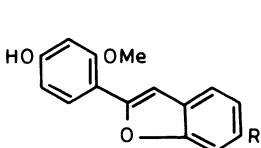


(10.195) Egonol



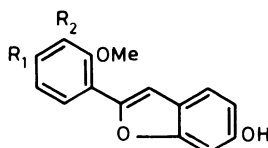
(10.196)

However, a third group of 2-arylbenzofurans (Table 10.10) co-occur in leguminous plants with isoflavonoids having related substitution patterns, and a biosynthetic origin by loss of one carbon from an isoflavonoid is likely. Pterofuran (10.199) from *Pterocarpus indicus* was first to be isolated in 1964 and was found to co-occur with formononetin, pterocarpin and angolensin (Cooke and Rae, 1964). A biosynthetic sequence involving loss of C-6 from a coumestan, by analogy with alkaline degradation of coumestans (Wong, 1975), is generally

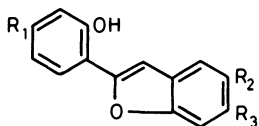
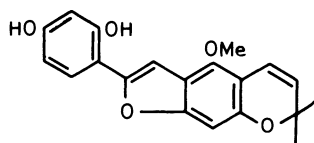


(10.197) R = OH, 6-Demethylvignafuran

(10.198) R = OMe, Vignafuran

(10.199) R<sub>1</sub> = OMe, R<sub>2</sub> = OH, Pterofuran(10.200) R<sub>1</sub> = OH, R<sub>2</sub> = OMe, Isopterofuran

postulated. The co-occurrence of (10.201) with 3-hydroxy-8,9-dimethoxycoumestan in *Myroxylon balsamum* (Oliveira *et al.*, 1978) and (10.202) and (10.203) with medicagol in *Sophora tomentosa* (Komatsu *et al.*, 1978a) lend support for this view. Neoraufurane (10.204), though, co-occurs with similarly substituted pterocarpin, isoflav-3-ene and isoflavan derivatives, e.g. edudiol, neorauflavene and neorauflavane respectively (Brink *et al.*, 1974a, 1977), and in this case, the benzofuran moiety is presumably related to the acetate-derived ring of the isoflavonoid, not the shikimate-derived ring as above. This latter relationship may well operate in the case of vignafuran, a phytoalexin from

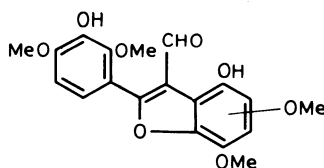
(10.201) R<sub>1</sub> = OH, R<sub>2</sub> = R<sub>3</sub> = OMe(10.202) R<sub>1</sub> = OH, R<sub>2</sub> R<sub>3</sub> = OCH<sub>2</sub>O(10.203) R<sub>1</sub> = OMe, R<sub>2</sub> R<sub>3</sub> = OCH<sub>2</sub>O

(10.204) Neoraufurane

**Table 10.10** 2-Arylbenzofurans

| 2-Arylbenzofuran                                                  | Plant sources                   | References                    |
|-------------------------------------------------------------------|---------------------------------|-------------------------------|
| 6-Demethylvignafuran (10.197)                                     | <i>Coronilla emerus</i>         | Dewick and Ingham (1980)      |
| Vignafuran (10.198)                                               | <i>Tetragonolobus maritimus</i> | Ingham and Dewick (1978)      |
|                                                                   | <i>Lablab niger</i>             | Ingham (1977b)                |
|                                                                   | <i>Vigna unguiculata</i>        | Preston <i>et al.</i> (1975)  |
|                                                                   | <i>Coronilla emerus</i>         | Dewick and Ingham (1980)      |
| Isopterofuran (10.200)                                            |                                 |                               |
| (2,4-Dihydroxyphenyl)-5,6-dimethoxybenzofuran (10.201)            | <i>Myroxylon balsamum</i>       | Oliveira <i>et al.</i> (1978) |
| (2,4-Dihydroxyphenyl)-5,6-methylenedioxybenzofuran (10.202)       | <i>Sophora tomentosa</i>        | Komatsu <i>et al.</i> (1978a) |
| (2-Hydroxy-4-methoxyphenyl)-5,6-methylenedioxybenzofuran (10.203) | <i>Sophora tomentosa</i>        | Komatsu <i>et al.</i> (1978a) |
| Neoraufurane (10.204)                                             | <i>Neorautanenia edulis</i>     | Brink <i>et al.</i> (1974a)   |

*Colletotrichum lindemuthianum*-infected cowpea (*Vigna unguiculata*) (Preston *et al.*, 1975), as demonstrated by feeding experiments with labelled phenylalanine precursors (Martin and Dewick, 1979; see Section 10.18). Demethylvignafuran (10.197) and isopterofuran (10.200) have also been found to function as phytoalexins (Ingham and Dewick, 1978; Dewick and Ingham, 1980).



(10.205) Bryebinal

The UV spectra of 2-arylbenzofurans are stilbene-like and closely resemble those of pterocarpenes. Little structural information is usually obtained from the MS where the only major fragments result from loss of methyls and CO. Several synthetic approaches have been employed to confirm structures. Hoesch synthesis from a phenylacetonitrile and a phenol is limited because the position of coupling cannot be predicted and a mixture of 2-arylbenzofurans results (Preston *et al.*, 1975). A route exploiting the similarity of 2-arylbenzofurans to the isoflavonoids involves as key step the formation of deoxybenzoins by base hydrolysis of 2'-benzyloxyisoflavones. Debenzylation and acid-catalysed ring closure produced 2-arylbenzofurans in reasonable yields (Ingham and Dewick, 1978; Dewick and Ingham, 1980). Essentially the same transformation, but in a different sequence, was achieved by debenzylation, hydrolysis, then HBr–Ac<sub>2</sub>O cyclization of the acetal derived by thallium nitrate oxidation of



2-benzyloxychalcones (Meyer-Dayana *et al.*, 1978). Vignafuran and pterofuran have also been synthesized by reaction of a copper(I) arylacetylide with an *o*-halogenophenol (Duffley and Stevenson, 1977), a method which has wide applicability to all types of 2-arylbenzofuran derivatives.

A further route by treatment of isoflavylum perchlorates with  $\text{H}_2\text{O}_2$  in acidified propan-2-ol gives good yields of 2-arylbenzofurans, and is of particular interest in that it mimics the possible biosynthetic process because the 2-aryl substituent is provided by the B ring of the isoflavonoid (Deschamps-Vallet *et al.*, 1979) (Fig. 10.14). This biogenetic analogy is also exemplified in two other conversions, though of less synthetic value (Fig. 10.14). Treatment of a chalcone with excess thallium acetate gave a coumaranone instead of the required isoflavone, and the coumaranone, after reduction with sodium borohydride, eliminated formic acid to give a 2-arylbenzofuran (Ollis *et al.*, 1970). A similar ring-contraction process leading to a coumaranone has been observed on treatment of the isoflavone elongatin with alkaline  $\text{H}_2\text{O}_2$  (Smalberger *et al.*, 1975). The second example involves reduction of a 3-arylcoumarin with  $\text{AlH}_3$  to the corresponding alcohol which yields a 2-arylbenzofuran on treatment with DDQ (Kinoshita *et al.*, 1978a).

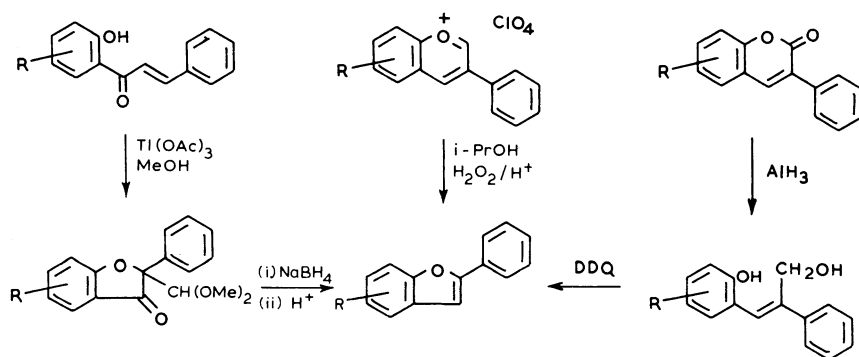
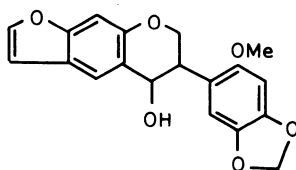


Fig. 10.14

Bryebinal, a minor yellow pigment from *Brya ebenus*, has been identified as a 3-formyl-2-arylbenzofuran, and has been assigned the tentative structure (10.205) (Ferreira *et al.*, 1975). Since it co-occurs with a number of pterocarpenes, bryebinal could represent an intermediate between these compounds and 2-arylbenzofurans if such a relationship exists.

### 10.15 ISOFLAVANOL

(+)-Ambanol (10.206) is the only known naturally occurring isoflavanol and was isolated from the root of *Neorautanenia amboensis* (Oberholzer *et al.*,

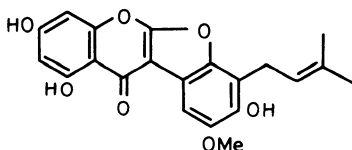


(10.206) Ambanol

1977b). On treatment with acid, it readily eliminates water to yield the corresponding isoflav-3-ene. Synthesis of ( $\pm$ )-ambanol was achieved by potassium borohydride reduction of the isoflavone dehydroneotoneone. 2'-Hydroxyisoflavanols are regarded as important intermediates in the biosynthesis of pterocarpan, isoflavans and other classes of isoflavonoid (see Section 10.18), but it is unlikely that such isoflavanols will ever be isolated because of their ready cyclization to pterocarpan. Such cyclization is prevented by the 2'-methoxy group in ambanol.

#### 10.16 COUMARONOCHROMONE

Lisetin (10.207) remains the only natural example of this class of isoflavonoid, and so far, this has been isolated from only one source *Piscidia erythrina*.



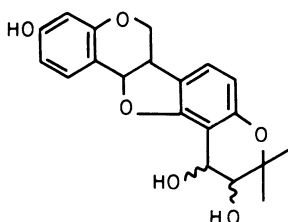
(10.207) Lisetin

Synthesis of coumaronochromones has been achieved by  $K_3Fe(CN)_6$  oxidation of 2'-hydroxyisoflavones (Falshaw *et al.*, 1966; Tsukayama *et al.*, 1979), but recent studies have shown that other oxidizing agents may be employed.  $Ag_2CO_3$  in quinoline (Antus and Nogradi, 1979b), and Pb(IV) or Mn(III) acetates (Kurosawa and Araki, 1979) are all suitable reagents.

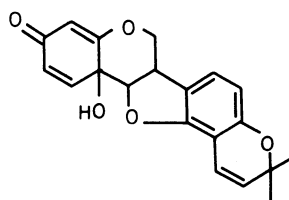
#### 10.17 MICROBIAL METABOLITES OF ISOFLAVONOIDS

A number of modified isoflavonoid structures have been identified when specific isoflavonoids have been introduced into microbial cultures. These probably represent intermediates in the metabolic pathway employed by the microorganism to detoxify the isoflavonoid. Because these intermediates are not yet recognized as normal plant products, it is appropriate to consider them separately. It may be, though, that some of the isoflavonoids already dealt with in

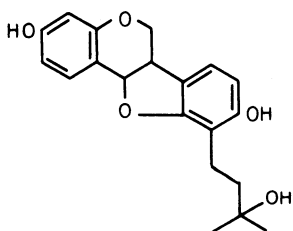
the other sections are in fact microbial metabolites themselves, since it is not usual for researchers to employ aseptically grown plants. Particularly in the case of phytoalexin studies, it is almost impossible in microbially infected tissues to differentiate between plant and microbial metabolism, and a multiple phytoalexin response could well be a mixture of induced plant products and their microbial metabolites. Rapid detoxification of phytoalexins to reduce their antifungal properties may be an essential step for fungi to become pathogenic in a particular plant; in most cases investigated, the metabolites identified tend to be less fungitoxic than the substrate. The data in Table 10.11 have been subdivided according to the mechanism of initial metabolism, i.e. hydrogenolysis-type reactions, hydroxylation, demethylation and others.



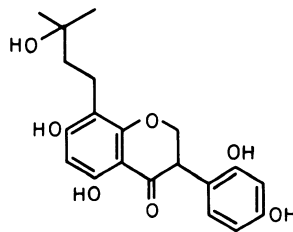
(10.208)



(10.209) 1a-Hydroxyphaseollone



(10.210) Phaseollidin hydrate



(10.211) Kievitone hydrate

The ability of fungi to convert pterocarpan into 2'-hydroxyisoflavans, a reaction analogous to hydrogenolysis, has been recognized for some time. *Stemphylium botryosum* converts several pterocarpan phytoalexins in this manner. Consequently, the common co-occurrence of isoflavans with pterocarpan in phytoalexin samples may be the result of fungal metabolism, although some isoflavan phytoalexins can be induced by abiotic treatments (Dewick and Martin, 1979), and isoflavans in many cases are more fungitoxic than the corresponding pterocarpan (Harborne and Ingham, 1978). 3-Hydroxy-2,9-dimethoxypterocarpan is similarly degraded by *Fusarium solani* f.sp. *pisi* cultures to 7,2'-dihydroxy-6,4'-dimethoxyisoflavan (Pueppke and Van Etten, 1976). The pterocarpan, isolated from *F. solani* f.sp. *pisi*-infected pea (*Pisum sativum*) is itself believed to be a fungal metabolite of a pea isoflavonoid, since its synthesis could not be induced abiotically.

Table 10.11 Microbial metabolites of isoflavonoids

| Substrate                            | Organism                                 | Product(s)                                                       | Reference                          |
|--------------------------------------|------------------------------------------|------------------------------------------------------------------|------------------------------------|
| (i) <i>Hydrogenolysis reactions</i>  |                                          |                                                                  |                                    |
| Medicarpin                           | <i>Stemphylium botryosum</i>             | Vestitol                                                         | Steiner and Millar (1974)          |
| Maackian                             | <i>Stemphylium botryosum</i>             | 7,2'-Dihydroxy-4,5'-methylene-dioxyisoflavan (Maackianisoflavan) | Higgins (1975)                     |
| Phaseollin                           | <i>Stemphylium botryosum</i>             | Phaseollinisoflavan                                              | Higgins <i>et al.</i> (1974)       |
| 3-Hydroxy-2,9-dimethoxy-pterocarpan  | <i>Fusarium solani</i> f.sp. <i>pisi</i> | 7,2'-Dihydroxy-6,4'-dimethoxyisoflavan                           | Pueppke and Van Etten (1976)       |
| (ii) <i>Hydroxylation reactions</i>  |                                          |                                                                  |                                    |
| Medicarpin                           | <i>Botrytis cinerea</i>                  | 6a-Hydroxymedicarpin                                             | Ingham (1976a)                     |
| Medicarpin                           | <i>Sclerotinia trifoliorum</i>           | 6a-Hydroxymedicarpin                                             | Bilton <i>et al.</i> (1976)        |
| Maackian                             | <i>Sclerotinia trifoliorum</i>           | 6a-Hydroxymaackian                                               | Bilton <i>et al.</i> (1976)        |
| Phaseollin                           | <i>Botrytis cinerea</i>                  | 6a-Hydroxyphaseollin                                             | Van den Heuvel and Glazener (1975) |
| Phaseollin                           | <i>Colletotrichum lindemuthianum</i>     | 6a-Hydroxyphaseollin                                             | Burden <i>et al.</i> (1974)        |
|                                      |                                          | 6a,7-Dihydroxyphaseollin                                         |                                    |
| (iii) <i>Demethylation reactions</i> |                                          |                                                                  |                                    |
| Pisatin                              | <i>Ascochyta pisi</i>                    | 6a-Hydroxymaackian                                               | Van't Land <i>et al.</i> (1975)    |
|                                      | <i>Nectria haematococca</i>              | 6a-Hydroxymaackian                                               | Van Etten <i>et al.</i> (1980)     |
|                                      | <i>Fusarium solani</i> f.sp. <i>pisi</i> | 6a-Hydroxymaackian                                               | Van Etten <i>et al.</i> (1975)     |
|                                      | <i>F. anguioides</i>                     | 6a-Hydroxymaackian                                               | Lappe and Barz (1978)              |
|                                      | <i>F. avenaceum</i>                      | 6a-Hydroxymaackian                                               | Lappe and Barz (1978)              |
|                                      | <i>F. oxysporum</i> f. sp. <i>pisi</i>   | 6a-Hydroxymaackian                                               | Fuchs <i>et al.</i> (1980)         |
| Medicarpin                           | <i>Fusarium proliferatum</i>             | 3-Hydroxymaackianisoflavan                                       | Weltring and Barz (1980)           |
|                                      |                                          | Demethylmedicarpin                                               |                                    |
| Homopterocarpin                      | <i>Fusarium proliferatum</i>             | 7,2,4'-Trihydroxyisoflavan                                       | Weltring and Barz (1980)           |
|                                      |                                          | Isomedicarpin                                                    |                                    |
|                                      |                                          | Demethylmedicarpin                                               |                                    |
|                                      |                                          | 7,2,4'-Trihydroxyisoflavan                                       |                                    |

|                             |                                                                                                         |                                                                                                                                                         |                                                                                                             |
|-----------------------------|---------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| 5,7,4'-Trimethoxyisoflavone | <i>Fusarium</i> spp.                                                                                    | 5-Methylbiochanin A<br>Biochanin A<br>Genistein<br>Orobol                                                                                               | Barz <i>et al.</i> (1976)                                                                                   |
| (iv) <i>Other reactions</i> |                                                                                                         |                                                                                                                                                         |                                                                                                             |
| Phaseollin                  | <i>Septoria nodorum</i><br><i>Fusarium solani</i> f.sp. <i>phaseoli</i><br><i>Cladosporium herbarum</i> | <i>cis</i> - and <i>trans</i> -3',4'-Dihydroxy-<br>3',4'-dihydrophaseollin (10.208)<br>1a-Hydroxyphaseollone (10.209)<br>1a-Hydroxyphaseollone (10.209) | Bailey <i>et al.</i> (1977)<br>Van den Heuvel <i>et al.</i> (1974)<br>Van den Heuvel and Glazener<br>(1975) |
| Phaseollidin<br>Kievitone   | <i>Fusarium solani</i> f.sp. <i>phaseoli</i><br><i>Fusarium solani</i> f.sp. <i>phaseoli</i>            | Phaseollidin hydrate (10.210)<br>Kievitone hydrate (10.211)                                                                                             | Smith <i>et al.</i> (1980)<br>Kuhn <i>et al.</i> (1977)                                                     |

6a-Hydroxylation of pterocarpan is also a common fungal modification. Thus, cultures of *Sclerotinia trifoliorum* modify medicarpin and maackiain into their 6a-hydroxy derivatives (Bilton *et al.*, 1976). In the presence of plant tissue, methylation at the 7-hydroxyl may also occur and variabilin and pisatin have been isolated from *S. trifoliorum* - or *Botrytis cinerea*-infected *Trifolium pratense* (Bilton *et al.*, 1976). Phaseollin may be 6a-hydroxylated also, and in *Colletotrichum lindemuthianum*, further aromatic hydroxylation takes place, since 6a,7-dihydroxyphaseollin has been identified as a second metabolite (Burden *et al.*, 1974). Similar 6a,7-dihydroxy derivatives of medicarpin and maackiain have been isolated from the *Trifolium pratense*-*Colletotrichum coffeanum* combination (Ingham, 1976a).

The 6a-hydroxypterocarpan pisatin is typically metabolized by demethylation at position 3 yielding 6a-hydroxymaackiain, and this transformation has been observed in cultures of several organisms. In *Fusarium oxysporum* f.sp. *pisi*, further metabolism occurs and a hydrogenolysis-type reaction yields 3-hydroxymaackiainisoflavan (Fuchs *et al.*, 1980). The metabolism of medicarpin and homopterocarpin by *Fusarium proliferatum* proceeds via demethylmedicarpin and hydrogenolysis to 7,2',4'-trihydroxyisoflavan (Weltring and Barz, 1980). However, homopterocarpin is demethylated initially at position 9, and the metabolic pathway proceeds through isomedicarpin rather than medicarpin. A sequence of demethylations followed by aromatic hydroxylation, then ring cleavage is believed to operate in the metabolism of isoflavones by a number of *Fusarium* species (Barz *et al.*, 1976). Incubation of 5,7,4'-trimethoxyisoflavone resulted in the production of 5-methylbiochanin A, biochanin A, genistein and orobol.

A combination of plant and fungal metabolism is probably responsible for the production of 4-hydroxy derivatives of medicarpin, demethylmedicarpin and homopterocarpin in *Botrytis cinerea*-infected *Melilotus alba* (Ingham, 1976a), along with vestitol, demethylmedicarpin, 6a-hydroxymedicarpin and 6a-hydroxyisomedicarpin. All are regarded as metabolites of medicarpin and are illustrative of the processes described above.

The metabolic pathway employed to detoxify an isoflavonoid is markedly dependent on the organism concerned. Thus, phaseollin, in addition to the routes already outlined, has been observed to be converted into two other metabolites. *Septoria nodorum* attacks the dimethylchromene system and *cis*- and *trans*-diols result (Bailey *et al.*, 1977), whereas *Fusarium solani* f.sp. *phaseoli* produces the metabolite 1a-hydroxyphaseollone (Van den Heuvel *et al.*, 1974). When phaseollidin is the substrate, however, this latter organism hydrates the dimethylallyl substituent producing phaseollidin hydrate (Smith *et al.*, 1980), an analogous modification of the isoflavanone kievitone yielding kievitone hydrate (Kuhn *et al.*, 1977). An enzymic system from *F. solani* f.sp. *phaseoli* catalyses the same conversions (Kuhn and Smith, 1979).

## 10.18 BIOSYNTHESIS OF ISOFLAVONOIDS

The isoflavonoids share a common biosynthetic pathway with the flavonoids as far as chalcone intermediates, but then a 1,2-aryl migration occurs to give the characteristic rearranged skeleton. The mechanism of this rearrangement step is still completely unknown despite the amount of biosynthetic research undertaken, but from the information available, it is possible that only two chalcones, 2',4',4-trihydroxychalcone and 2',4',6',4-tetrahydroxychalcone, normally act as substrates for aryl migration (Dewick, 1978). An oxidative reaction is undoubtedly involved and the site of oxidation would appear to be the 4-hydroxyl, since 4-methoxychalcones are accepted for isoflavonoid biosynthesis only after demethylation (Hahlbrock and Grisebach, 1975). Of the several hundred known naturally occurring isoflavonoids, very few indeed lack the corresponding 4'-oxygen substituent. An attractive mechanism is the hypothesis of Pelter *et al.* (1971) in which phenolic oxidation of the chalcone leads to a spirodienone intermediate (10.212) (Fig. 10.15). Decomposition of this intermediate via a proton would give daidzein or genistein, and if methylation via *S*-adenosylmethionine is associated with the aryl migration, formononetin or biochanin A would be formed. These four isoflavones could then, by further substitution, act as precursors of virtually all other natural isoflavonoids. (Similar oxidation of 2-hydroxychalcones could lead to 2'-hydroxy/methoxyisoflavones and would account for a number of the known 4'-deoxyisoflavonoids.)

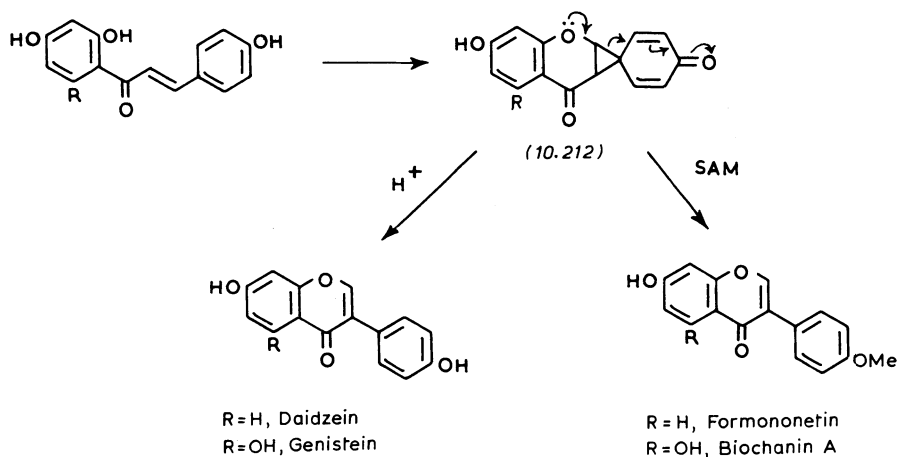


Fig. 10.15

The study of isoflavonoid biosynthesis has been aided considerably by the knowledge that many isoflavonoids act as phytoalexins, and that their synthesis can be induced by treatment of the appropriate plant with fungi, or, more

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appropriate to biosynthetic experiments, by UV light or heavy-metal salts. Thus in feeding experiments, the precursor can be added at precisely the time of maximum synthesis of the isoflavonoid, and extremely high incorporations of precursor (e.g. 1–10 %) are achieved.

In  $\text{CuCl}_2$ -treated seedlings of red clover (*Trifolium pratense*), labelled 2',4',4'-trihydroxychalcone and formononetin were good precursors of the pterocarpan phytoalexins (–)-medicarpin and (–)-maackiain, whereas 2',4'-dihydroxy-4-methoxychalcone and daidzein were poor precursors (Dewick, 1975a), illustrating that methylation is probably associated with the aryl-migration step. Such results do not contradict the findings of Wengenmayer *et al.* (1974), who have isolated an enzyme preparation catalysing the 4'-methylation of daidzein, since a small, but significant incorporation of daidzein into formononetin was also observed. However, a further, major route from 2',4',4'-trihydroxychalcone to formononetin, not via daidzein is implicated by the incorporation data.

The pathway from formononetin to medicarpin probably proceeds via 2'-hydroxylation to (10.213), reduction to the isoflavanol (10.214), then further reduction to the isoflavanone (10.215) followed by cyclization via the carbonium ion (10.216) (Fig. 10.16). The conversion of (10.213) into medicarpin is thus analogous to the borohydride reduction sequence used for chemical synthesis of

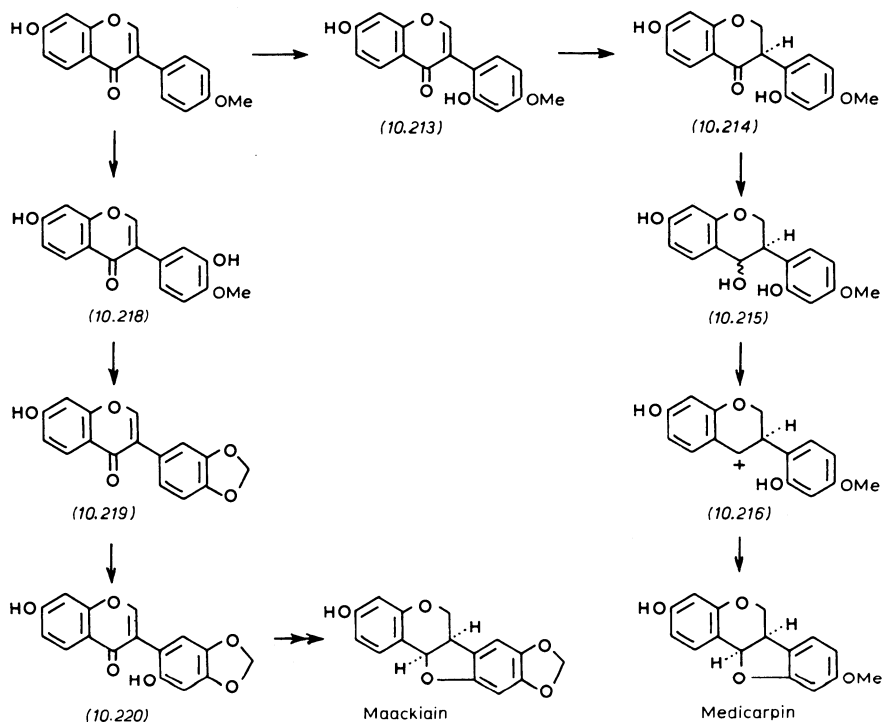
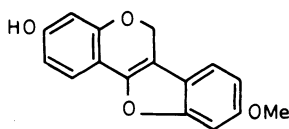


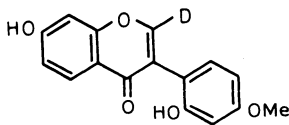
Fig. 10.16



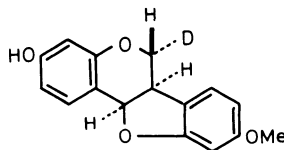
pterocarpan. Isoflavone (10.213) and ( $\pm$ )-isoflavanone (10.214) were extremely good precursors of medicarpin, but not maackiain in  $\text{CuCl}_2$ -treated red clover, and the pathway to maackiain presumably branches at formononetin (Dewick, 1977). Pterocarpene (10.217) was a rather poor precursor of medicarpin, and ( $\pm$ )-medicarpin was not incorporated into maackiain. In further experiments (Dewick and Ward, 1978), the isoflavones formononetin, calycosin (10.218), pseudobaptigenin (10.219) and 7,2'-dihydroxy-4',5'-methylenedioxyisoflavone (10.220) were all excellent precursors of maackiain, and form a logical sequence for elaboration of the substitution pattern of this pterocarpin (Fig. 10.16). The reduction sequence from isoflavone (10.213) to (–)-medicarpin is undoubtedly completely stereospecific, and this was demonstrated in UV- and  $\text{CuCl}_2$ -treated fenugreek (*Trigonella foenum-graecum*) seedlings where [2D]-isoflavone (10.221) gave rise to (–)-medicarpin with deuterium located exclusively in the 6-pro-*R* position (10.222), and thus indicated an overall *trans* addition of hydrogen to the double bond (Dewick and Ward, 1977). Location of the label was accomplished by the use of deuterium NMR.



(10.217)



(10.221)



(10.222)

Lucerne (*Medicago sativa*) seedlings on treatment with  $\text{CuCl}_2$  synthesize (–)-6a*R*, 11a*R*-medicarpin together with the isoflavans 3*R*-vestitol and 3*R*-sativan as phytoalexins (Fig. 10.17). Isoflavone (10.213) and ( $\pm$ )-isoflavanone (10.214) proved excellent precursors of all three compounds in feeding experiments (Dewick and Martin, 1979a), but 7-hydroxy-2',4'-dimethoxyisoflavone was not incorporated, even into sativan, ruling out a direct reductive sequence to this isoflavan. To ascertain whether isoflavans are biosynthesized via pterocarpan (cf. hydrogenolysis reactions) or whether the reverse sequence occurs (cf. DDQ oxidations), labelled ( $\pm$ )-medicarpin and ( $\pm$ )-vestitol were tested as precursors. Medicarpin was incorporated into vestitol and sativan, and vestitol into medicarpin and sativan, thus demonstrating the interconversion of these two compounds. However, incorporation data, and the results of kinetic feeding experiments with phenylalanine suggested that medicarpin and vestitol were

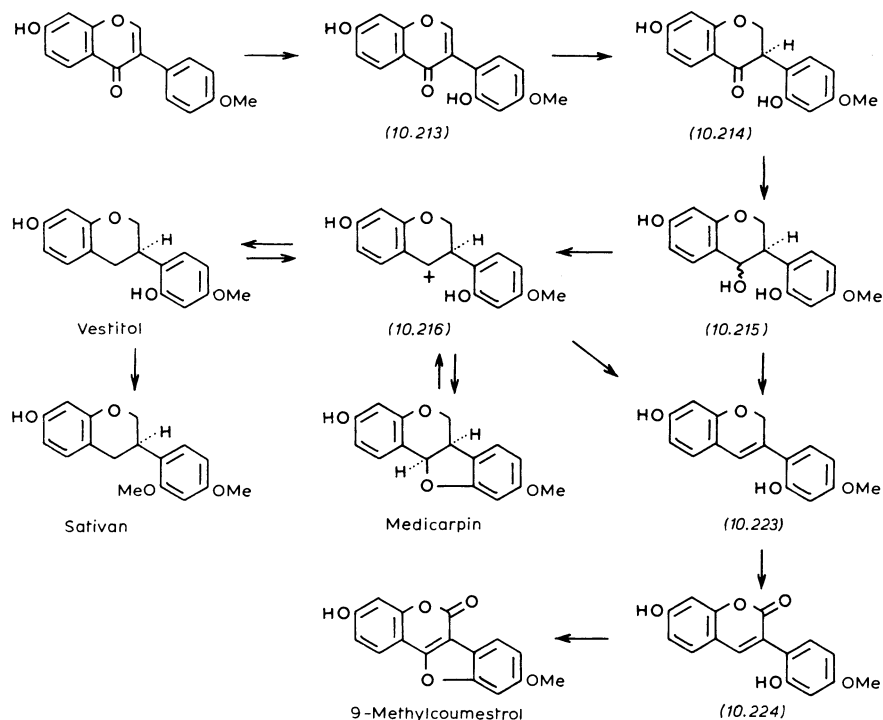


Fig. 10.17

synthesized simultaneously from a common intermediate, probably the carbonium ion (10.216). Sativan was synthesized later than the other two phytoalexins and is most likely derived by methylation of vestitol. Red clover seedlings also had the ability to transform vestitol into medicarpin, but isoflavonone (10.214) was a much better precursor.

In a further series of feeding experiments in lucerne seedlings, 2',4',4'-trihydroxychalcone and formononetin proved good precursors of medicarpin, vestitol, sativan and the coumestan 9-methylcoumestrol, but 2',4'-dihydroxy-4-methoxychalcone and daidzein were poorly incorporated (Dewick and Martin, 1979b). These results were also interpreted in terms of methylation occurring during the aryl migration, and further evidence was obtained by also studying incorporations into coumestrol. Thus daidzein was a precursor of coumestrol but not of 9-methylcoumestrol, despite the fact that synthesis of the latter compound is greatly stimulated by the induction process. Since the isoflavones formononetin and (10.213), and the corresponding isoflavanones were all good precursors of the phytoalexins and 9-methylcoumestrol, a metabolic grid may be involved in their biosynthetic origin, although the major route appeared to be via isoflavone (10.213).

The interconversion of medicarpin and vestitol via a carbonium ion is a chemically viable process (Van der Meerwe *et al.*, 1978), but in nature would probably require suitable stabilization of such an intermediate. When  $(\pm)$ -[6a- $^3\text{H}$ ,9-*O*-Me- $^{14}\text{C}$ ]medicarpin and  $(\pm)$ -[3- $^3\text{H}$ ,4'-*O*-Me- $^{14}\text{C}$ ]vestitol were fed to induced lucerne seedlings (Martin and Dewick, 1978), they were both incorporated into the other phytoalexins with no change in  $^3\text{H}$ : $^{14}\text{C}$  ratio, thus excluding the involvement of an alternative  $\Delta^3$  intermediate such as an isoflav-3-ene. The isoflav-3-ene (10.223) was not incorporated into the phytoalexins, but it did prove to be a most efficient precursor of the coumestan, as was the arylcoumarin (10.224). The biosynthesis of coumestans had been considered to proceed via allylic oxidation of pterocarpenes, derived by cyclization of 2'-hydroxyisoflavanones (Hahlbrock and Grisebach, 1975), but this had never been proven in feeding experiments because of the ready aerial oxidation of pterocarpenes to coumestans. These more recent results suggest that a different route operates, namely allylic oxidation of a 2'-hydroxyisoflav-3-ene to a 2'-hydroxy-3-arylcoumarin, followed by cyclization and further oxidation to the coumestan. Isoflav-3-ene (10.223) may be produced by dehydration of isoflavanol (10.215), or by loss of a proton from carbonium ion (10.216), the latter route explaining the observed significant incorporation of medicarpin into 9-methylcoumestrol (Martin and Dewick, 1978) (Fig. 10.17).

These phytoalexin studies have indicated that the B-ring oxygenation pattern appears to be built up, generally at the isoflavone level, by the sequences 4'→2',4' and 4'→4',5' ( $\equiv$  3',4')→2',4',5'. The A-ring pattern of 7 or 5,7 is determined at the chalcone level, but this can be modified further (i.e. 7→6,7) at the isoflavone level, as is demonstrated by the incorporation of formononetin (Dewick, 1978) and texasin (6,7-dihydroxy-4'-methoxyisoflavone) (Al-Ani and Dewick, 1980) into afrormosin (7-hydroxy-6,4'-dimethoxyisoflavone) in sainfoin (*Onobrychis viciifolia*) seedlings. Once again, 4'-methylation appears to be effected during aryl migration. The origin of the acetate-derived ring of the 6a-hydroxypterocarpan phytoalexin pisatin has been studied by feeding sodium [1,2- $^{13}\text{C}_2$ ]acetate to  $\text{CuCl}_2$ -treated pea (*Pisum sativum*) pods (Stoessl and Stothers, 1979). By analysing  $^{13}\text{C}$ - $^{13}\text{C}$  coupling in the  $^{13}\text{C}$ -NMR spectrum of the pisatin produced, it was possible to show that carbons 1 and 1a, 2 and 3, and 4 and 4a had been incorporated as intact  $\text{C}_2$  units, that cyclization of the polyketide must have occurred as in *a* rather than *c*, and that reduction of the 'lost' oxygen function must have occurred before cyclization (Fig. 10.18). By contrast, a similar experiment in parsley cell suspension cultures produced the flavonoids apigenin and kaempferol in which randomization of label occurred, demonstrating that free rotation of the acetate-derived ring had occurred and thus proving the intermediacy of 2',4',6',4-tetrahydroxychalcone (Light and Hahlbrock, 1980). It is remarkable that this amount of information can be inferred from a single feeding experiment and illustrates the potential of  $^{13}\text{C}$ -NMR studies in biosynthesis. More conventional precursor studies in  $\text{CuCl}_2$ -treated pea pods and seedlings (Dewick and Banks, 1980) have shown that formononetin,

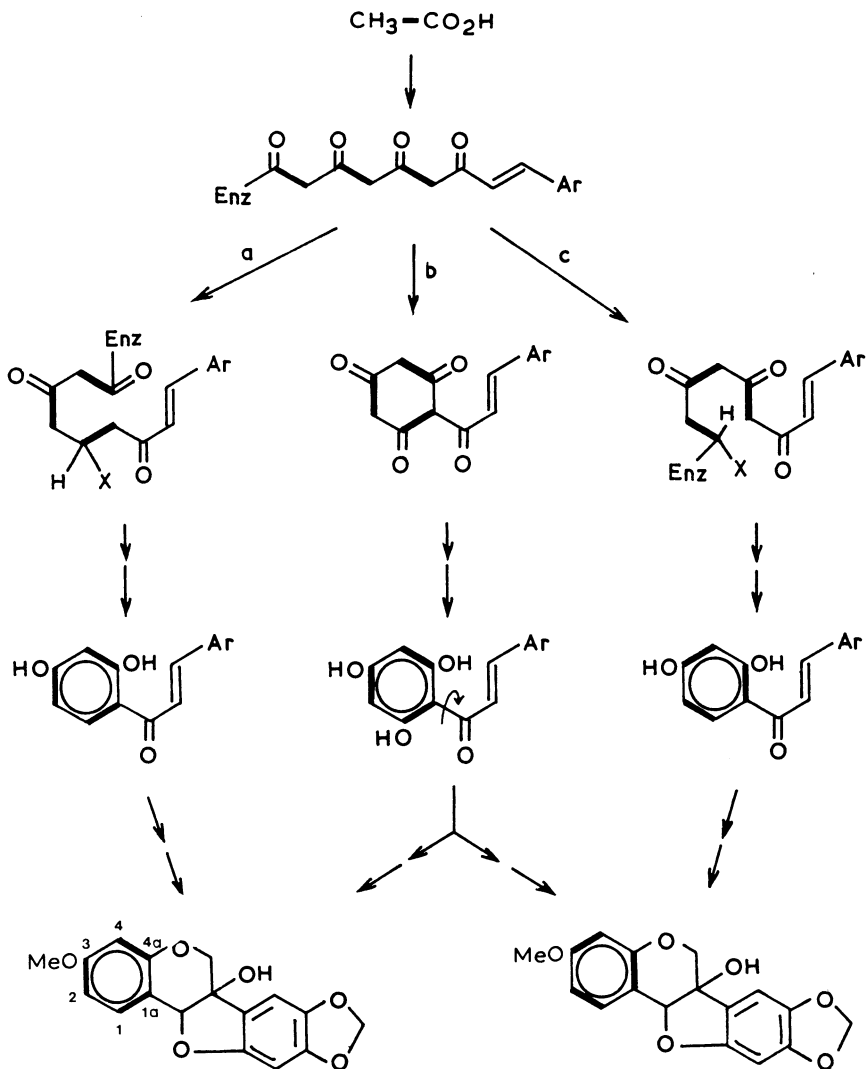


Fig. 10.18

calycosin, pseudobaptigenin, 7,2'-dihydroxy-4',5'-methylenedioxyisoflavone, maackiain and 6a-hydroxymaackiain all function as efficient precursors of pisatin, and these represent a logical sequence for the biosynthetic pathway. Some incorporations of the pterocarpene anhydropisatin were also recorded and the precise role, if any, of this compound awaits clarification. This 6a-hydroxylation of pterocarpanes is paralleled by fungal modification of some phytoalexins (see Section 10.17).

On the basis of feeding experiments with labelled chalcones, isoflavones and rotenoids (Crombie *et al.*, 1973), a tentative pathway to the rotenoid amorphigenin (10.230) via 9-demethylmunduserone (10.225), rotenonic acid (10.226) and rotenone (10.229) had been established. A route involving the epoxide of rotenonic acid (10.227), cyclization to dalpanol (10.228), then dehydration to rotenone (10.229) and finally hydroxylation was postulated (Fig. 10.19). In further feeding experiments in seedlings of *Amorpha fruticosa* (Crombie *et al.*, 1979b), the presence of rotenone, dalpanol and rot-2'-enonic acid (10.226) has been established by isotope dilution, although labelled rotenonic acid could be isolated only after short feeding times, in keeping with its role as a biosynthetic intermediate. Rot-3'-enonic acid was not incorporated into amorphigenin, although it had earlier been established that isopentenyl alcohol was a better precursor than dimethylallyl alcohol (Crombie *et al.*, 1979a). Rot-2'-enonic acid, labelled mainly in the 4' position, was a good precursor of amorphigenin, dalpanol and 12a-hydroxyamorphigenin, the specific activities of the latter two compounds being some six times higher than that of amorphigenin. This fits with the involvement of dalpanol as a biosynthetic intermediate, and also establishes that the 12a-hydroxyrotenoid is not an artefact, but a true natural product. Degradation of labelled rotenone from a further experiment indicated that, after correction for the labelling pattern of the precursor, cyclization of the dimethylallyl side chain was accomplished with virtually complete stereoselectivity. From this, the configuration of the postulated epoxide intermediate can be assigned as in (10.227). Neither of the 6'-epimers of amorphigenol was

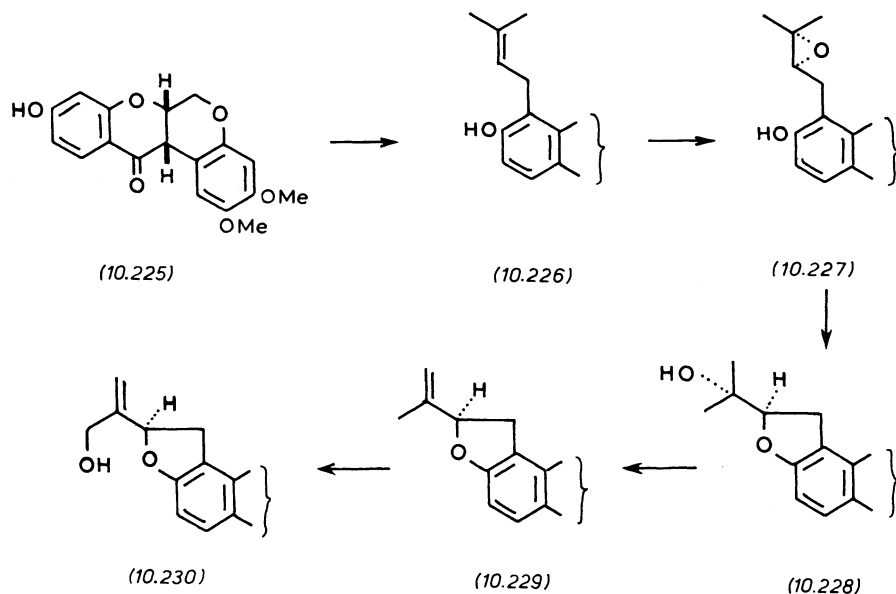


Fig. 10.19

incorporated into amorphigenin, and thus allylic hydroxylation of rotenone must be involved rather than hydroxylation of dalpanol followed by dehydration (Crombie *et al.*, 1979c). Of interest is that the label from [7'-<sup>14</sup>C]rotenone becomes distributed equally between 7' and 8' of amorphigenin, but the reason is unknown.

The glucosylation of daidzein to the 7-*O*-glucoside daidzin and the 8-*C*-glucoside puerarin has been investigated in *Pueraria lobata* root (Inoue and Fujita, 1977). By a series of competition feeding experiments with 2',4',4'-trihydroxychalcone and 7,4'-dihydroxyflavanone mixtures, it was demonstrated that the chalcone was the more immediate precursor of both glucosides. Daidzin was a poor precursor of puerarin, and although daidzein was well incorporated into daidzin, it proved a poor precursor of puerarin. Thus, since 2',4',4'-trihydroxychalcone was well incorporated into both glycosides, it was suggested that daidzin was formed by glucosylation of daidzein, but puerarin was perhaps produced via the chalcone-*C*-glucoside. This conclusion has not been confirmed by testing the appropriate chalcone-*C*-glucoside as a precursor.

The isoflavonoid nature of the 2-arylbenzofuran phytoalexin viginafuran has been demonstrated in UV-induced cowpea (*Vigna unguiculata*) seedlings using [U-<sup>14</sup>C]-, [1-<sup>14</sup>C]- and [2-<sup>14</sup>C]-phenylalanine precursors (Martin and Dewick, 1979). During the biosynthetic process, C-3 of phenylalanine appears to be lost, and the resulting labelling pattern shows that the phenylalanine-derived aromatic ring becomes the 2-aryl substituent, and not part of the benzofuran system (Fig. 10.20). Thus, a pathway to 2-arylbenzofurans by loss of C-6 from a coumestan is excluded. Chemical analogies for possible alternative routes are noted in Section 10.14. Incorporation levels were very small, most of the administered label being found in kievitone, an isoflavanone phytoalexin of *V. unguiculata*. The low rate of biosynthesis was probably responsible for the observed lack of incorporation of labelled chalcone and isoflavone compounds administered which may nevertheless be precursors.

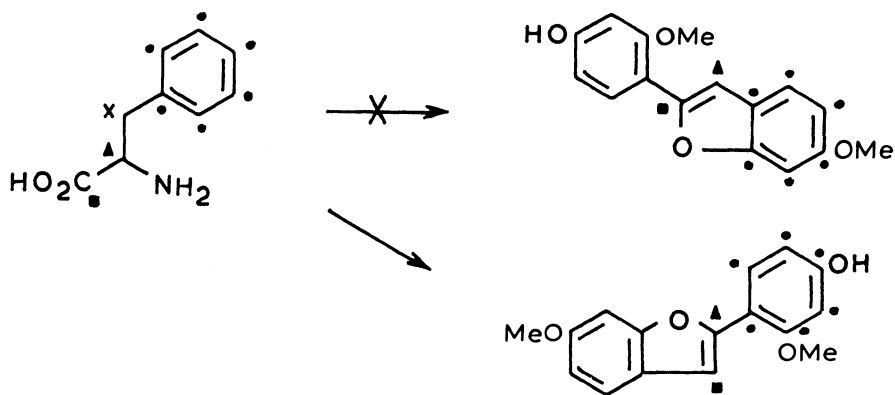


Fig. 10.20

Biosynthetic experiments have established that the homoisoflavonoid eucomin is formed in bulbs of *Eucomis bicolor* (Liliaceae) by addition of a carbon atom from methionine on to a  $C_{15}$  chalcone-type skeleton (Dewick, 1975b), and 2'-methoxychalcones appear to be biosynthetic precursors (Fig. 10.21). Thus the homoisoflavonoids are formed by a pathway not involving the 1,2-aryl migration step characteristic of isoflavonoids and it is now inappropriate to consider these compounds along with the isoflavonoids. The 'homoisoflavonoids' merely represent a further modification of the unrearranged flavonoid-type skeleton.

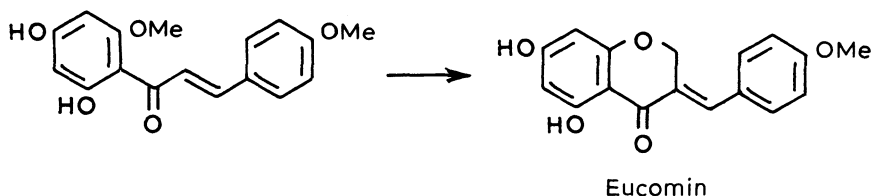


Fig. 10.21

Enzymic studies of isoflavonoid biosynthesis are much less advanced than those on flavonoids, but several enzyme preparations have been purified and investigated. An *S*-adenosylmethionine:isoflavone-4'-*O*-methyltransferase from cell suspension cultures of *Cicer arietinum* catalyses the 4'-methylation of daidzein and genistein (Wengenmayer *et al.*, 1974), and a dimethylallylpyrophosphate:trihydroxypterocarpan dimethylallyltransferase has been reported in a fraction from elicitor-induced soybean (*Glycine max*) cotyledons (Zähringer *et al.*, 1979). The latter enzyme catalyses the dimethylallylation of 3,6a,9-trihydroxypterocarpan and is probably a key enzyme in the biosynthesis of the glyceollins, the soybean phytoalexins. Another prenyltransferase from *Lupinus albus* catalyses the 6-dimethylallylation of the isoflavones genistein and 2'-hydroxygenistein to give the antifungal isoflavones wighteone and luteone respectively (Schröder *et al.*, 1979). Detailed discussion of these enzymes is included in Chapter 11.

#### 10.19 BIOGENETIC RELATIONSHIPS AMONG THE ISOFLAVONOIDS

Because of the lack of experimental data, discussions of biogenetic relationships (e.g. Wong, 1975) have had to rely heavily on chemical interconversions of various isoflavonoid classes and information about the natural co-occurrence of various compounds. Metabolic schemes presented previously have thus been largely speculative. As biosynthetic evidence increases, it is now possible to

interrelate a large number of isoflavonoid classes, and to produce a scheme based entirely on direct experimental data (Fig. 10.22). This scheme is, of course, far from complete, but differs considerably from earlier ones, since chemically based hypotheses have not always been proved correct. In particular, no central role is ascribed to pterocarpenes. The inclusion of other classes of isoflavonoids must await further experimentation.

Knowledge of the co-occurrence of various isoflavonoids is nevertheless an essential foundation for biosynthetic research. The studies of Woodward (1979a,b,1980a) on *Monilinia fruticola*-infected *Phaseolus vulgaris* illustrate the value of such work. From drop diffusates, a whole range of 5-oxy- and 5-deoxy-isoflavonoids was isolated, and these compounds represent a nearly complete biosynthetic sequence from the simple isoflavones daidzein and genistein to phytoalexins phaseollin and kievitone.

#### 10.20 BIOLOGICAL PROPERTIES OF ISOFLAVONOIDS

The oestrogenic activity of simple isoflavones and coumestans, and the insecticidal properties of rotenoids have been extensively discussed earlier (Wong, 1975; McClure, 1975). At that time, the antifungal properties of isoflavonoids and their function as phytoalexins were only just being recognized. Phytoalexins are antifungal compounds induced by a plant in response to infection or attempted invasion by fungi or other micro-organisms, but may also be induced by treatment with abiotic agents such as toxic chemicals or UV light (Harborne and Ingham, 1978). During the period of review, a considerable amount of data about new isoflavonoid phytoalexin structures and the mode of action of these materials has been published, and a number of important reviews have appeared (e.g. Van Etten and Pueppke, 1976; Gross, 1977; Grisebach and Ebel, 1978; Harborne and Ingham, 1978; Mahadevan, 1979).

Pterocarpan and isoflavans account for the bulk of isoflavonoid phytoalexins, although 6a-hydroxypterocarpan, isoflavanones, isoflavones and 2-arylbenzofurans may also function in this role. Medicarpin is by far the most common of pterocarpan phytoalexins and is sometimes accompanied by the methylenedioxy analogue maackiain. Vestitol and sativan are the most commonly encountered isoflavans. In the Phaseoleae and related tribes, more complex prenylated isoflavonoid derivatives, e.g. phaseollin and phaseollidin, are produced (Ingham and Markham, 1980). *Vicia faba* (broad bean) and *Lens esculenta* (lentil) are atypical amongst the Leguminosae in producing mainly furanoacetylene structures, e.g. wyerone rather than isoflavonoids, although traces of medicarpin in *V. faba* (Hargreaves *et al.*, 1976) and variabilin in *L. esculenta* (Robeson, 1978) have been isolated. Stilbene structures rather than isoflavonoids have been reported in *Arachis hypogaea* (Ingham, 1976c; Keen and Ingham, 1976) and *Trifolium dubium* and *T. campestre* (Ingham, 1978c), and *Lathyrus odoratus* produces unusual chromone derivatives as well as



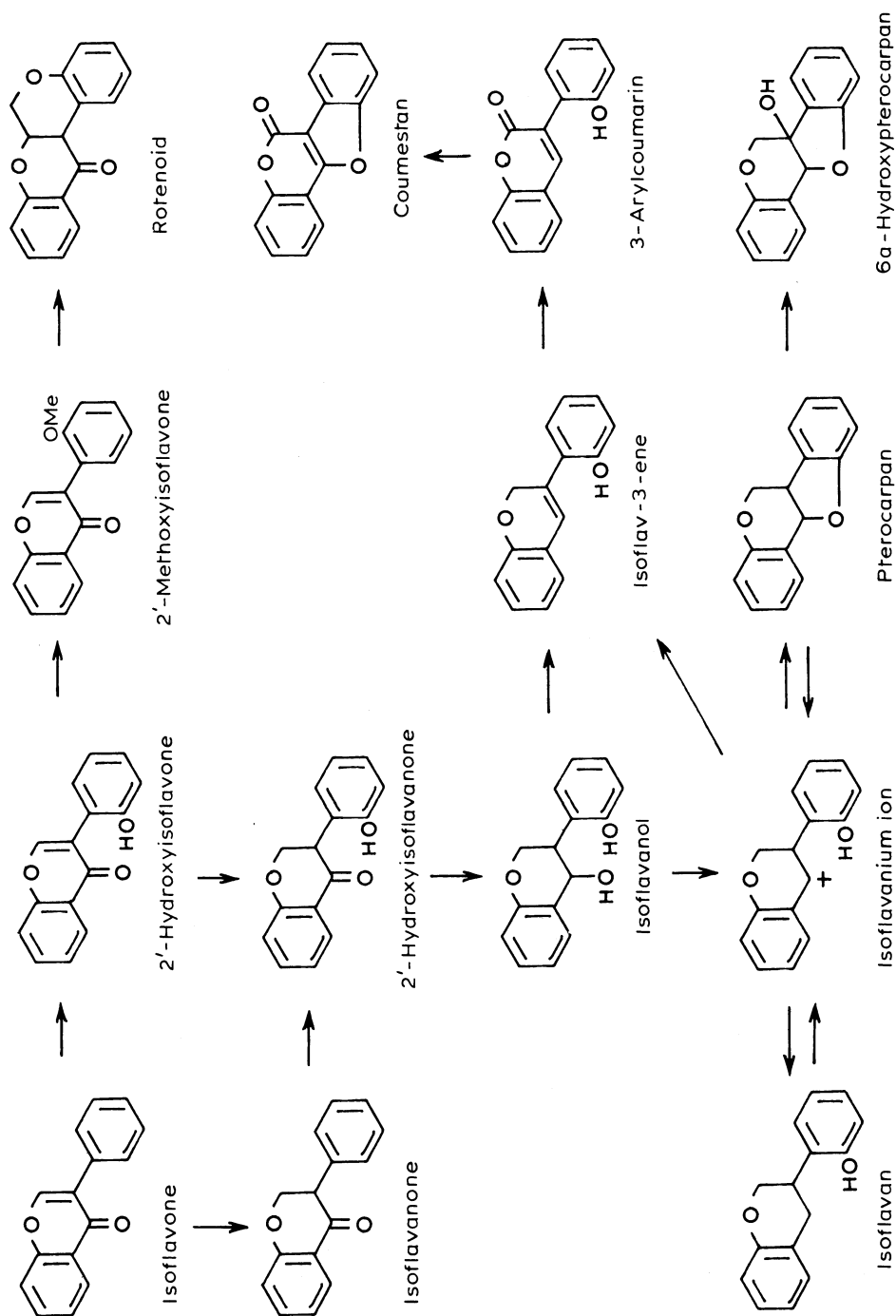


Fig. 10.22

6a-hydroxypterocarpan (Robeson *et al.*, 1980). The pattern of phytoalexins formed by a particular plant appears to be a useful taxonomic marker, not only for tribe (Harborne and Ingham, 1978), but also at species level (e.g. Ingham and Harborne, 1976).

The antifungal activity of pterocarpan has been correlated with their non-planar molecular shape (Perrin and Cruickshank, 1969), since planar derivatives such as pterocarpenes and coumestans lacked activity. A more recent study of selected pterocarpan and other isoflavonoids has suggested that a non-planar molecular shape is not the major criterion for antifungal activity (Van Etten, 1976). Thus, three planar pterocarpenes were significantly fungitoxic to *Aphanomyces euteiches* and *Fusarium solani* f.sp. *cucurbitae*, and in one case, the pterocarpene was much more active than the corresponding non-planar 6a-hydroxypterocarpan. Some physicochemical property other than three-dimensional shape, e.g. lipophilic character, is implicated. The isolation of strongly antifungal isoflavones luteone (Fukui *et al.*, 1973; Harborne *et al.*, 1976) and wightone (Ingham *et al.*, 1977) from healthy *Lupinus* tissues further indicates that three-dimensional molecular shape is not a prerequisite.

Phytoalexins have generally been isolated after fungal infection of suitable plant tissue, in most cases, by employing the drop-diffusate technique (Harborne and Ingham, 1978), in which phytoalexins diffuse from fungus-infected cells into the applied spore suspension. Antifungal compounds can then be identified by a bioassay technique. The antifungal activity of phytoalexins is not restricted to plant pathogens, however, and a significant level of activity has been observed with some phytoalexins, especially phaseollinisoflavan, against a range of zoopathogens (Gordon *et al.*, 1980). Antibacterial activity has also been noted (Gnanamanickam and Patil, 1977; Wyman and Van Etten, 1978), kievitone being the most effective of those tested against a range of *Pseudomonas*, *Xanthomonas* and *Achromobacter* species (Wyman and Van Etten, 1978). It has also been demonstrated that phytoalexins exhibit insect-feeding-deterrent activity against root-feeding larvae of scarabs (*Costelytra zealandica*, *Heteronychus arator*) at levels of the same order of magnitude as those at which fungal growth is reduced (Sutherland *et al.*, 1980). Phaseollin was the most active of those tested, and it is suggested that phytoalexins may also play a role in defence against insect predators. Many legumes known to produce phytoalexins (e.g. *Medicago sativa*) are resistant to attack by these larvae. Activity against the root-knot nematode *Meloidogyne incognita* has been observed in the case of glyceollin, this phytoalexin being induced when roots of soya bean (*Glycine max*) are challenged with the nematode (Kaplan *et al.*, 1980a,b). Similarly, a hypersensitive response to the nematode *Pratylenchus scribneri* resulted in the production of active coumestans by *Phaseolus lunatus* (Rich *et al.*, 1977), although no antifungal phytoalexins were detected.

Screening programmes to detect antimicrobial activity in plant extracts have led to the isolation of several antimicrobial isoflavonoids from *Glycyrrhiza glabra* (Mitscher *et al.*, 1980). Significant *in vitro* activity against *Haptylococcus*

*aureus* and *Mycobacterium swegmatis* were observed for the isoflavans hispaglabridin-A and -B, glabridin and 4'-methylglabridin, and two flavanones. In contrast to phytoalexins, these are not induced metabolites, though are closely related structurally to phytoalexins such as phaseollinisoflavan, which was also identified in the extract. A similar screening of *Amorpha fruticosa* demonstrated that the rotenoid 11-hydroxytephrosin possessed antimicrobial activity (Mitscher *et al.*, 1979), and suggests that a systematic study of isoflavonoids as potential antimicrobial agents may well be worth while.

Several simple isoflavonoids, pseudobaptigenin, calycosin, maackiain and irilone, present in red clover (*Trifolium pratense*) root suppress the growth of wheat coleoptiles *in vitro* (Popravko *et al.*, 1979), and glycosides of genistein and pseudobaptigenin from *Lupinus luteus* have similar properties (Laman, 1974). Though not confirmed, these compounds could act as endogenous growth regulators. The isoflavonoid content of red clover decreased during the autumn following hardening and vernalization.

The isolation of a number of isoflavones and their glycosides from microbial sources has been commented upon in Section 10.3. Whether or not these are true microbial metabolites remains to be established, but they were found to inhibit specific enzyme systems, including  $\beta$ -galactosidase (Hazato *et al.*, 1979), catechol-*O*-methyltransferase (Chimura *et al.*, 1975) and dopa decarboxylase (Umezawa *et al.*, 1975).

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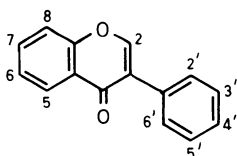
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### CHECK LIST OF KNOWN NATURAL ISOFLAVONOID AGLYCONES

#### Isoflavones



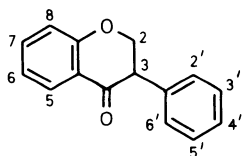
- 1 Daidzein, 7,4'-(OH)<sub>2</sub>
- 2 Formononetin, 7-OH,4'-OMe
- 3 Isoformononetin, 4'-OH, 7-OMe
- 4 Dimethyldaidzein, 7,4'-(OMe)<sub>2</sub>
- 5 Durretone, 7-OMe,4'-OCH<sub>2</sub>  
CH = CMe<sub>2</sub>
- \*6 7,2',4'-(OH)<sub>3</sub>
- \*7 2'-Hydroxyformononetin, 7,2'-(OH)<sub>2</sub>,  
4'-OMe
- \*8 Theralin, 7,4'-(OH)<sub>2</sub>,2'-OMe
- 9 3'-Hydroxydaidzein, 7,3',4'-(OH)<sub>3</sub>
- 10 7,4'-(OH)<sub>2</sub>,3'-OMe
- 11 3'-Hydroxyformononetin, calycosin,  
7,3'-(OH)<sub>2</sub>,4'-OMe
- 12 Sayanedin, 4'-OH,7,3'-(OMe)<sub>2</sub>
- 13 Cladrin, 7-OH,3',4'-(OMe)<sub>2</sub>
- 14 Cabreuvin, 7,3',4'-(OMe)<sub>3</sub>
- 15 Pseudobaptigenin, 7-OH,3',4'-  
OCH<sub>2</sub>O-
- \*16 7-OMe, 3',4'-OCH<sub>2</sub>O-
- 17 Maximaisoflavone B, 7-OCH<sub>2</sub>  
CH = CMe<sub>2</sub>, 3',4'-OCH<sub>2</sub>O-
- \*18 Koparin, 7,2',3'-(OH)<sub>3</sub>, 4'-OMe
- \*19 2'-OH, 7,3',4'-(OMe)<sub>3</sub>
- \*20 Glyzaglabrin, 7,2'-(OH)<sub>2</sub>, 3',4'-  
OCH<sub>2</sub>O-
- 21 Maximaisoflavone C, 7-OCH<sub>2</sub>  
CH = CMe<sub>2</sub>, 2'-OMe, 4',5'-OCH<sub>2</sub>O-
- \*22 7,2',4',5'-(OMe)<sub>4</sub>
- \*23 7,2'-(OMe)<sub>2</sub>, 4',5'-OCH<sub>2</sub>O-
- 24 Baptigenin, 7,3',4',5'-(OH)<sub>4</sub>
- \*25 Gliricidin, 7,3',5'-(OH)<sub>3</sub>, 4'-OMe
- \*26 5-OH,7-OMe
- \*27 5,7-(OMe)<sub>2</sub>
- \*28 5,7,2'-(OH)<sub>3</sub>
- 29 Genistein, 5,7,4'-(OH)<sub>3</sub>
- 30 Biochanin A, 5,7-(OH)<sub>2</sub>, 4'-OMe
- 31 5-Methylgenistein, 7,4'-(OH)<sub>2</sub>, 5-OMe
- 32 Prunetin, 5,4'-(OH)<sub>2</sub>, 7-OMe
- \*33 5-Methylbiochanin A, 7-OH, 5,4'-  
(OMe)<sub>2</sub>
- \*34 7-Methylbiochanin A, 5-OH, 7,4'-  
(OMe)<sub>2</sub>
- \*35 2'-Hydroxygenistein, 5,7,2',4'-(OH)<sub>4</sub>
- \*36 2'-Hydroxybiochanin A, 5,7,2'-(OH)<sub>3</sub>, 4'-  
OMe
- \*37 Cajanin, 5,2',4'-(OH)<sub>3</sub>, 7-OMe
- \*38 5,2'-(OH)<sub>2</sub>, 7,4'-(OMe)<sub>2</sub>(?)

- \*39 2'-Methoxybiochanin A, 5,7-(OH)<sub>2</sub>, 2',4'-(OMe)<sub>2</sub>  
 40 Orobol, 5,7,3',4'-(OH)<sub>4</sub>  
 41 3'-Methylorobol, 5,7,4'-(OH)<sub>3</sub>, 3'-OMe  
 42 Pratensein, 5,7,3'-(OH)<sub>3</sub>, 4'-OMe  
 43 Santal, 5,3',4'-(OH)<sub>3</sub>, 7-OMe  
 \*44 Glabrescione B, 5,7-(OMe)<sub>2</sub>, 3',4'-(OCH<sub>2</sub>CH = CMe<sub>2</sub>)<sub>2</sub>  
 \*45 5,7-(OH)<sub>2</sub>, 3',4'-OCH<sub>2</sub>O-  
 46 Derrustone, 5,7-(OMe)<sub>2</sub>, 3',4'-OCH<sub>2</sub>O-  
 \*47 Derrugenin, 5,4'-(OH)<sub>2</sub>, 7,2',5'-(OMe)<sub>3</sub>  
 \*48 Robustigenin, 5-OH, 7,2',4',5'-(OMe)<sub>4</sub>  
 \*49 5,7,3',5'-(OH)<sub>4</sub>, 4'-OMe  
 50 6,7,4'-(OH)<sub>3</sub>  
 51 Texasin, 6,7-(OH)<sub>2</sub>, 4'-OMe  
 52 Glycitein, 7,4'-(OH)<sub>2</sub>, 6-OMe  
 \*53 Kakkatin, 6,4'-(OH)<sub>2</sub>, 7-OMe  
 54 Afrormosin, 7-OH, 6,4'-(OMe)<sub>2</sub>  
 \*55 Odoratin, 7,3'-(OH)<sub>2</sub>, 6,4'-(OMe)<sub>2</sub>  
 56 Cladrastin, 7-OH, 6,3',4'-(OMe)<sub>3</sub>  
 57 6,7,3',4'-(OMe)<sub>4</sub>  
 58 Fujikinetin, 7-OH, 6-OMe, 3',4'-OCH<sub>2</sub>O-  
 59 6,7-(OMe)<sub>2</sub>, 3',4'-OCH<sub>2</sub>O-  
 \*60 6,7-OCH<sub>2</sub>O-, 3',4'-(OMe)<sub>2</sub>  
 61 6,7,2',3',4'-(OMe)<sub>5</sub>  
 \*62 7-OH, 6,2',4',5'-(OMe)<sub>4</sub>  
 63 6,7,2',4',5'-(OMe)<sub>5</sub>  
 64 Dalpatein, 7-OH, 6,2'-(OMe)<sub>2</sub>, 4',5'-OCH<sub>2</sub>O-  
 65 6-OH, 7,2'-(OMe)<sub>2</sub>, 4',5'-OCH<sub>2</sub>O-  
 66 Milldurone, 6,7,2'-(OMe)<sub>3</sub>, 4',5'-OCH<sub>2</sub>O-  
 \*67 6,7,3',4',5'-(OMe)<sub>5</sub>  
 68 6,7,3'-(OMe)<sub>3</sub>, 4',5'-OCH<sub>2</sub>O-  
 69 Retusin, 7,8-(OH)<sub>2</sub>, 4'-OMe  
 70 8-Methylretusin, 7-OH, 8,4'-(OMe)<sub>2</sub>  
 \*71 8-Methyl-3'-hydroxyretusin, 7,3'-(OH)<sub>2</sub>, 8,4'-(OMe)<sub>2</sub>  
 \*72 7-OH, 8,3',4'-(OMe)<sub>3</sub>  
 73 Maximaisoflavone A, 7,8; 3',4'-(OCH<sub>2</sub>O)<sub>2</sub>  
 \*74 7,8,2'-(OMe)<sub>3</sub>, 4',5'-OCH<sub>2</sub>O-  
 75 Betavulgarin, 2'-OH, 5-OMe, 6,7-OCH<sub>2</sub>O-  
 76 Tlatlancuayin, 5,2'-(OMe)<sub>2</sub>, 6,7-OCH<sub>2</sub>O-  
 77 6-Hydroxygenistein, 5,6,7,4'-(OH)<sub>4</sub>  
 78 Tectorigenin, 5,7,4'-(OH)<sub>3</sub>, 6-OMe  
 79 7-Methyltectorigenin, 5,4'-(OH)<sub>2</sub>, 6,7-(OMe)<sub>2</sub>  
 80 Muningin, 6,4'-(OH)<sub>2</sub>, 5,7-(OMe)<sub>2</sub>  
 81 Irisolidone, 5,7-(OH)<sub>2</sub>, 6,4'-(OMe)<sub>2</sub>  
 \*82 5-Methoxyafrormosin, 7-OH, 5,6,4'-(OMe)<sub>3</sub>  
 83 7,4'-Dimethyltectorigenin, 5-OH, 6,7,4'-(OMe)<sub>3</sub>  
 84 Irilone, 5,4'-(OH)<sub>2</sub>, 6,7-OCH<sub>2</sub>O-  
 85 Irisolone, 4'-OH, 5-OMe, 6,7-OCH<sub>2</sub>O-  
 \*86 Irisolone methyl ether, 5,4'-(OMe)<sub>2</sub>, 6,7-OCH<sub>2</sub>O-  
 87 Podospicatin, 5,7,2'-(OH)<sub>3</sub>, 6,5'-(OMe)<sub>2</sub>  
 88 Iristectorigenin A, 5,7,3'-(OH)<sub>3</sub>, 6,4'-(OMe)<sub>2</sub>  
 \*89 Iristectorigenin B, 5,7,4'-(OH)<sub>3</sub>, 6,3'-(OMe)<sub>2</sub>  
 \*90 7-OH, 5,6-(OMe)<sub>2</sub>, 3',4'-OCH<sub>2</sub>O-  
 91 5,6,7-(OMe)<sub>3</sub>, 3',4'-OCH<sub>2</sub>O-  
 92 Iriflogenin, 5,4'-(OH)<sub>2</sub>, 3'-OMe, 6,7-OCH<sub>2</sub>O-  
 \*93 Iriskumaonin, 3'-OH, 5,4'-(OMe)<sub>2</sub>, 6,7-OCH<sub>2</sub>O-  
 94 5,3',4'-(OMe)<sub>3</sub>, 6,7-OCH<sub>2</sub>O-  
 95 Caviunin, 5,7-(OH)<sub>2</sub>, 6,2',4',5'-(OMe)<sub>4</sub>  
 96 Iriginin, 5,7,5'-(OH)<sub>3</sub>, 6,3',4'-(OMe)<sub>3</sub>  
 97 Irisflorentin, 5,3',4',5'-(OMe)<sub>4</sub>, 6,7-OCH<sub>2</sub>O-  
 \*98 8-Hydroxygenistein, 5,7,8,4'-(OH)<sub>4</sub>  
 \*99 Isotectorigenin, pseudotectorigenin, 5,7,4'-(OH)<sub>3</sub>, 8-OMe  
 \*100 Aurmillone, 5,7-(OH)<sub>2</sub>, 8-OMe, 4'-OCH<sub>2</sub>CH = CMe<sub>2</sub>  
 \*101 5,7,3',4'-(OH)<sub>4</sub>, 8-OMe  
 \*102 5,7,3'-(OH)<sub>3</sub>, 8,4'-(OMe)<sub>2</sub>  
 \*103 5,7,4'-(OH)<sub>3</sub>, 8,3'-(OMe)<sub>2</sub>  
 \*104 Platycarpanetin, 7-OH, 5,8-(OMe)<sub>2</sub>, 3',4'-OCH<sub>2</sub>O-(?)  
 \*105 Isocaviunin, 5,7-(OH)<sub>2</sub>, 8,2',4',5'-(OMe)<sub>4</sub>  
 \*106 Dipteryxin, 7,8-(OH)<sub>2</sub>, 6,4'-(OMe)<sub>2</sub>  
 \*107 8,3'-(OH)<sub>2</sub>, 6,7,4'-(OMe)<sub>3</sub>  
 \*108 Petalostetin, 6,7,8-(OMe)<sub>3</sub>, 3',4'-OCH<sub>2</sub>O-  
 \*109 8,3',4'-(OMe)<sub>3</sub>, 6,7-OCH<sub>2</sub>O-  
 110 5,6,7,8-(OMe)<sub>4</sub>, 3',4'-OCH<sub>2</sub>O-  
 \*111 6-Chlorogenistein, 5,7,4'-(OH)<sub>3</sub>, 6-Cl  
 \*112 6,3'-Dichlorogenistein, 5,7,4'-(OH)<sub>3</sub>, 6,3'-Cl<sub>2</sub>  
 \*113 Corylinal, 7,4'-(OH)<sub>2</sub>, 3'-CHO  
 \*114 Wighteone, erythrinin B, 5,7,4'-(OH)<sub>3</sub>, 6-CH<sub>2</sub>CH = CMe<sub>2</sub>  
 \*115 Luteone, 5,7,2',4'-(OH)<sub>4</sub>, 6-CH<sub>2</sub>CH = CMe<sub>2</sub>  
 116 Derrubone, 5,7-(OH)<sub>2</sub>, 3',4'-OCH<sub>2</sub>O-, 6-CH<sub>2</sub>CH = CMe<sub>2</sub>  
 \*117 2,3-Dehydrokievitone, 5,7,2',4'-(OH)<sub>4</sub>, 8-CH<sub>2</sub>CH = CMe<sub>2</sub>

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- \*118 Erythrinin C, 5,4'-(OH)<sub>2</sub>, 6,7-CH<sub>2</sub>CH(COHMe<sub>2</sub>)O-
- \*119 Glabrescione A, 5-OMe, 3',4'-OCH<sub>2</sub>O-, 6,7-CH<sub>2</sub>CH(CMe = CH<sub>2</sub>)O-
- 120 Dehydroneoteneone, 2'-OMe, 4',5'-OCH<sub>2</sub>O-, 6,7-CH = CH-O-
- \*121 Erythrinin A, 4'-OH, 6,7-CH = CH-CMe<sub>2</sub>O-
- 122 Alpinumisoflavone, 5,4'-(OH)<sub>2</sub>, 6,7-CH = CHCMe<sub>2</sub>O-
- \*123 Alpinumisoflavone-4'-methyl ether, 5-OH, 4'-OMe, 6,7-CH = CHCMe<sub>2</sub>O-
- \*124 Alpinumisoflavone dimethyl ether, 5,4'-(OMe)<sub>2</sub>, 6,7-CH = CHCMe<sub>2</sub>O-
- 125 Parvisoflavone B, 5,2',4'-(OH)<sub>3</sub>, 6,7-CH = CHCMe<sub>2</sub>O-
- 126 Isoauriculatin, 5,2'-(OH)<sub>2</sub>, 4'-OCH<sub>2</sub>CH = CMe<sub>2</sub>, 6,7-CH = CHCMe<sub>2</sub>O-
- \*127 Isoauriculasin, 5,3'-(OH)<sub>2</sub>, 4'-OCH<sub>2</sub>CH = CMe<sub>2</sub>, 6,7-CH = CHCMe<sub>2</sub>O-
- 128 Robustone, 5-OH, 3',4'-OCH<sub>2</sub>O-, 6,7-CH = CHCMe<sub>2</sub>O-
- 129 Robustone methyl ether, 5-OMe, 3',4'-OCH<sub>2</sub>O-, 6,7-CH = CHCMe<sub>2</sub>O-
- \*130 Elongatin, 5,4'-(OH)<sub>2</sub>, 2',5'-(OMe)<sub>2</sub>, 6,7-CH = CHCMe<sub>2</sub>O-
- \*131 Calopogonium isoflavone A, 4'-OMe, 7,8-OCMe<sub>2</sub>CH = CH-
- \*132 Calopogonium isoflavone B, 3',4'-OCH<sub>2</sub>O-, 7,8-OCMe<sub>2</sub>CH = CH-
- \*133 Barbigerone, 2',4',5'-(OMe)<sub>3</sub>, 7,8-OCMe<sub>2</sub>CH = CH-
- 134 Jamaicin, 2'-OMe, 4',5'-OCH<sub>2</sub>O-, 7,8-OCMe<sub>2</sub>CH = CH-
- 135 Ferrugone, 2',5'-(OMe)<sub>2</sub>, 3',4'-OCH<sub>2</sub>O-, 7,8-OCMe<sub>2</sub>CH = CH-
- \*136 Derrone, 5,4'-(OH)<sub>2</sub>, 7,8-OCMe<sub>2</sub>CH = CH-
- \*137 Derrone-4'-methyl ether, 5-OH, 4'-OMe, 7,8-OCMe<sub>2</sub>CH = CH-
- 138 Parvisoflavone A, 5,2',4'-(OH)<sub>3</sub>, 7,8-OCMe<sub>2</sub>CH = CH-
- 139 Toxicarol isoflavone, 5-OH, 2',4',5'-(OMe)<sub>3</sub>, 7,8-OCMe<sub>2</sub>CH = CH-
- 140 Durmillone, 6-OMe, 3',4'-OCH<sub>2</sub>O-, 7,8-OCMe<sub>2</sub>CH = CH-
- 141 Ichthyne, 6,2'-(OMe)<sub>2</sub>, 4',5'-OCH<sub>2</sub>O-, 7,8-OCMe<sub>2</sub>CH = CH-
- 142 Neobavaisoflavone, 7,4'-(OH)<sub>2</sub>, 3'-CH<sub>2</sub>CH = CMe<sub>2</sub>
- \*143 Corylin, 7-OH, 3',4'-CH = CHCMe<sub>2</sub>O-
- \*144 Psoralenol, 7-OH, 3',4'-CH<sub>2</sub>CHOHCMe<sub>2</sub>O-
- \*145 Glabrone, 7,2'-(OH)<sub>2</sub>, 3',4'-CH = CHCMe<sub>2</sub>O-
- 146 Licoricone, 7,6'-(OH)<sub>2</sub>, 2',4'-(OMe)<sub>2</sub>, 3'-CH<sub>2</sub>CH = CMe<sub>2</sub>
- \*147 Licoisoflavone A, 5,7,2',4'-(OH)<sub>4</sub>, 3'-CH<sub>2</sub>CH = CMe<sub>2</sub>
- \*148 Licoisoflavone B, 5,7,2'-(OH)<sub>3</sub>, 3',4'-CH = CHCMe<sub>2</sub>O-
- 149 Piscerythrone, 5,7,2',4'-(OH)<sub>4</sub>, 5'-OMe, 3'-CH<sub>2</sub>CH = CMe<sub>2</sub>
- 150 Piscidone, 5,7,3',4'-(OH)<sub>4</sub>, 6'-OMe, 2'-CH<sub>2</sub>CH = CMe<sub>2</sub> or 5,7,3',6'-(OH)<sub>4</sub>, 4'-OMe, 2'CH<sub>2</sub>CH = CMe<sub>2</sub>(?)
- \*151 6,8-Di(dimethylallyl)genistein, 5,7,4'-(OH)<sub>3</sub>, 6,8-(CH<sub>2</sub>CH = CMe<sub>2</sub>)<sub>2</sub>
- \*152 6,8-Di(dimethylallyl)orobol, 5,7,3',4'-(OH)<sub>4</sub>, 6,8-(CH<sub>2</sub>CH = CMe<sub>2</sub>)<sub>2</sub>
- 153 Osajin, 5,4'-(OH)<sub>2</sub>, 6-CH<sub>2</sub>CH = CMe<sub>2</sub>, 7,8-OCMe<sub>2</sub>CH = CH-
- 154 Scandione, nallanin, 4'-OH, 5-OMe, 6-CH<sub>2</sub>CH = CMe<sub>2</sub>, 7,8-OCMe<sub>2</sub>CH = CH-
- 155 Pomiferin, 5,3',4'-(OH)<sub>3</sub>, 6-CH<sub>2</sub>CH = CMe<sub>2</sub>, 7,8-OCMe<sub>2</sub>CH = CH-
- 156 Auriculin, 5,2'-(OH)<sub>2</sub>, 4'-OMe, 8-CH<sub>2</sub>CH = CMe<sub>2</sub>, 6,7-CH = CHCMe<sub>2</sub>O-
- 157 Scandenone, warangalone, 5,4'-(OH)<sub>2</sub>, 8-CH<sub>2</sub>CH = CMe<sub>2</sub>, 6,7-CH = CHCMe<sub>2</sub>O-
- 158 Auriculatin, 5,2',4'-(OH)<sub>3</sub>, 8-CH<sub>2</sub>CH = CMe<sub>2</sub>, 6,7-CH = CHCMe<sub>2</sub>O-
- \*159 Auriculasin, 5,3',4'-(OH)<sub>3</sub>, 8-CH<sub>2</sub>CH = CMe<sub>2</sub>, 6,7-CH = CHCMe<sub>2</sub>O-
- \*160 Cajaisoflavone, 2',4'-(OH)<sub>2</sub>, 6'-OMe, 3'-CH<sub>2</sub>CH = CMe<sub>2</sub>, 6,7-CH = CHCMe<sub>2</sub>O-
- 161 Munetone, 2'-OMe, 6,7; 3',4'-(CH = CHCMe<sub>2</sub>O-) <sub>2</sub>
- 162 Mundulone, 2'-OMe, 6,7-CH<sub>2</sub>-CHOHCMe<sub>2</sub>O-, 3',4'-CH = CHCMe<sub>2</sub>O-
- \*163 6,3'-Di(dimethylallyl)genistein, 5,7,4'-(OH)<sub>3</sub>, 6,3'-(CH<sub>2</sub>CH = CMe<sub>2</sub>)<sub>2</sub>
- 164 Chandalone, 5,4'-(OH)<sub>2</sub>, 3'-CH<sub>2</sub>-CH = CMe<sub>2</sub>, 6,7-CH = CHCMe<sub>2</sub>O-
- \*165 7-OH, 2-Me
- \*166 7-OMe, 2-Me
- \*167 7-OCMe, 2-Me
- \*168 Glyzarin, 7-OH, 8-COMe, 2-Me

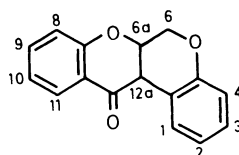
## Isoflavanones



- \*1 7,4'-(OH)<sub>2</sub>
- \*2 7-OH,4'-OMe
- \*3 7,2',4'-(OH)<sub>3</sub>
- \*4 Vestitone, 7,2'-(OH)<sub>2</sub>, 4'-OMe
- 5 Sativanone, 7-OH, 2',4'-(OMe)<sub>2</sub>
- \*6 7,3'-(OH)<sub>2</sub>, 4'-OMe
- 7 Violanone, 7,3'-(OH)<sub>2</sub>, 2',4'-(OMe)<sub>2</sub>
- \*8 3'-Methylviolanone, 7-OH, 2',3',4'-(OMe)<sub>3</sub>
- \*9 2'-OH, 7,3',4'-(OMe)<sub>3</sub>
- 10 Sophorol, 7,2'-(OH)<sub>2</sub>, 4',5'-OCH<sub>2</sub>O-
- 11 Onogenin, 7-OH, 2'-OMe, 4',5'-OCH<sub>2</sub>O-
- 12 5,7-(OH)<sub>2</sub>, 4'-OMe
- 13 Padmakastein, 5,4'-(OH)<sub>2</sub>, 7-OMe
- 14 Dalbergioidin, 5,7,2',4'-(OH)<sub>4</sub>
- 15 Ferreirin, 5,7,2'-(OH)<sub>3</sub>, 4'-OMe
- 16 Homoferreirin, 5,7-(OH)<sub>2</sub>, 2',4'-(OMe)<sub>2</sub>
- \*17 Cajanol, 5,4'-(OH)<sub>2</sub>, 7,2'-(OMe)<sub>2</sub>
- 18 Parvisoflavanone, 5,7,4'-(OH)<sub>3</sub>,2',3'-(OMe)<sub>2</sub>
- 19 6,7-(OMe)<sub>2</sub>, 3',4'-OCH<sub>2</sub>O-
- 20 Ougenin, 5,2',4'-(OH)<sub>3</sub>, 7,3'-(OMe)<sub>2</sub>, 6-Me
- \*21 Lespedeol A, 5,7,2',4'-(OH)<sub>4</sub>, 6-CH<sub>2</sub>CH=CMech<sub>2</sub>CH<sub>2</sub>CH=CMe<sub>2</sub>
- \*22 Lespedeol B, 5,2',4'-(OH)<sub>3</sub>, 6,7-CH=CHCMe(CH<sub>2</sub>CH<sub>2</sub>CH=CMe<sub>2</sub>)O-
- \*23 Neoraunone, 2',4'-(OMe)<sub>2</sub>, 6,7-CH=CHO-
- 24 Nepseudin, 2',3',4'-(OMe)<sub>3</sub>, 6,7-CH=CHO-
- \*25 Ambonone, 2',4',5'-(OMe)<sub>3</sub>, 6,7-CH=CHO-
- 26 Neotenone, 2'-OMe, 4',5'-OCH<sub>2</sub>O-, 6,7-CH=CHO-
- \*27 Erosenone, 2'-OH, 6'-OMe, 3',4'-OCH<sub>2</sub>O-, 6,7-CH=CHO-(?)
- \*28 5-Deoxykievitone, 7,2',4'-(OH)<sub>3</sub>, 8-CH<sub>2</sub>CH=CMe<sub>2</sub>
- 29 Kievitone, 5,7,2',4'-(OH)<sub>4</sub>, 8-CH<sub>2</sub>CH=CMe<sub>2</sub>
- \*30 Kievitone hydrate, 5,7,2',4'-(OH)<sub>4</sub>, 8-CH<sub>2</sub>CH<sub>2</sub>CMe<sub>2</sub>OH (Metabolite)
- \*31 1'',2''-Dehydrocyclokievitone, 5,2',4'-(OH)<sub>3</sub>, 7,8-OCMe<sub>2</sub>CH=CH-

- \*32 Sophoraisoflavanone A, 5,7,4'-(OH)<sub>3</sub>, 2'-OMe, 3'-CH<sub>2</sub>CH=CMe<sub>2</sub>
- \*33 Licoisoflavanone, 5,7,2'-(OH)<sub>3</sub>, 3',4'-CH=CHCMe<sub>2</sub>O-
- \*34 Isosophoronol, 5,7-(OH)<sub>2</sub>, 2'-OMe, 3',4'-CH=CHCMe<sub>2</sub>O-
- 35 5,7,2'-(OH)<sub>3</sub>, 4',5'-OCH(CMe<sub>2</sub>OH)CH<sub>2</sub>-
- \*36 Isosophoranone, 5,7,4'-(OH)<sub>3</sub>, 2'OMe, 6,3'-(CH<sub>2</sub>CH=CMe<sub>2</sub>)<sub>2</sub>
- \*37 Cajanone, 5,2',4'-(OH)<sub>3</sub>, 5'-CH<sub>2</sub>CH=CMe<sub>2</sub>, 6,7-CH=CHCMe<sub>2</sub>O-
- \*38 2'-Methylcajanone, 5,4'-(OH)<sub>2</sub>, 2'-OMe, 5'-CH<sub>2</sub>CH=CMe<sub>2</sub>, 6,7-CH=CHCMe<sub>2</sub>O-
- \*39 Secondifloran, 7,3,2',3'-(OH)<sub>4</sub>, 4'-OMe, 5'-CMe<sub>2</sub>CH=CH<sub>2</sub>

## Rotenoids



## (i) Rotenoids

- 1 Munduserone, 2,3,9-(OMe)<sub>3</sub>
- 2 Sermundone, 11-OH, 2,3,9-(OMe)<sub>3</sub>
- 3 Rotenone, 2,3-(OMe)<sub>2</sub>, 8,9-CH<sub>2</sub>CH(CMe=CH<sub>2</sub>)O-
- 4 Isomillettone, 2,3-OCH<sub>2</sub>O-, 8,9-CH<sub>2</sub>CH(CMe=CH<sub>2</sub>)O-
- 5 Dalpanol, 2,3-(OMe)<sub>2</sub>, 8,9-CH<sub>2</sub>CH(CMe<sub>2</sub>OH)O-
- 6 Amorphigenin, 2,3-(OMe)<sub>2</sub>, 8,9-CH<sub>2</sub>CH[C(CH<sub>2</sub>OH)=CH<sub>2</sub>]O-
- 7 Dihydroamorphigenin, 2,3-(OMe)<sub>2</sub>, 8,9-CH<sub>2</sub>CH(CMeCH<sub>2</sub>OH)O-
- 8 Amorphigenol, 2,3-(OMe)<sub>2</sub>, 8,9-CH<sub>2</sub>CH[CMe(OH)CH<sub>2</sub>OH]O-
- 9 Deguelin, 2,3-(OMe)<sub>2</sub>, 8,9-CH=CHCMe<sub>2</sub>O-
- 10 Millettone, 2,3-OCH<sub>2</sub>O-, 8,9-CH=CHCMe<sub>2</sub>O-
- 11 Myricanol, 9-OH, 2,3-(OMe)<sub>2</sub>, 10-CH=CHCH<sub>2</sub>CH=CH<sub>2</sub>(?)
- 12 Elliptone, 2,3-(OMe)<sub>2</sub>, 8,9-CH=CHO-
- 13 Erosone, 2,3-(OMe)<sub>2</sub>, 9,10-OCH=CH-
- 14 Dolineone, 2,3-OCH<sub>2</sub>O, 9,10-OCH=CH-
- 15 Sumatrol, 11-OH, 2,3-(OMe)<sub>2</sub>, 8,9-CH<sub>2</sub>CH(CMe=CH<sub>2</sub>)O-

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- 16 Toxicarol, 11-OH, 2,3-(OMe)<sub>2</sub>, 8,9-CH = CHCMe<sub>2</sub>O-
- 17 Malaccol, 11-OH, 2,3-(OMe)<sub>2</sub>, 8,9-CH = CHO-
- 18 Pachyrrhizone, 8-OMe, 2,3-OCH<sub>2</sub>O-, 9,10-OCH = CH-
- 19 Villosin, 11,6-(OH)<sub>2</sub>, 2,3-(OMe)<sub>2</sub>, 8,9-CH<sub>2</sub>CH(CMe = CH<sub>2</sub>)O-

### (ii) Dehydrorotenoids

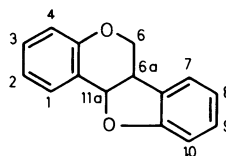
- 1 Dehydrorotenone, 6a,12a-dehydro, 2,3-(OMe)<sub>2</sub>, 8,9-CH<sub>2</sub>CH(CMe = CH<sub>2</sub>)O-
- \*2 Dehydrodalpanol, 6a,12a-dehydro, 2,3-(OMe)<sub>2</sub>, 8,9-CH<sub>2</sub>CH(CMe<sub>2</sub>OH)O-
- 3 Dehydrodeguelin, 6a,12a-dehydro, 2,3-(OMe)<sub>2</sub>, 8,9-CH = CHCMe<sub>2</sub>O-
- 4 Dehydromillettone, 6a,12a-dehydro, 2,3-OCH<sub>2</sub>O-, 8,9-CH = CHCMe<sub>2</sub>O-
- 5 Dehydrodolineone, 6a,12a-dehydro, 2,3-OCH<sub>2</sub>O-, 9,10-OCH = CH-
- \*6 Villosol, dehydrosumatrol, 6a,12a-dehydro, 11-OH, 2,3-(OMe)<sub>2</sub>, 8,9-CH<sub>2</sub>CH(CMe = CH<sub>2</sub>)O-
- \*7 Dehydrotoxicarol, 6a,12a-dehydro, 11-OH, 2,3-(OMe)<sub>2</sub>, 8,9-CH = CHCMe<sub>2</sub>O-
- \*8 Dehydropachyrrhizone, 6a,12a-dehydro, 8-OMe, 2,3-OCH<sub>2</sub>O-, 9,10-OCH = CH-
- 9 Stemonal, 6a,12a-dehydro, 11,6-(OH)<sub>2</sub>, 2,3,9-(OMe)<sub>3</sub>
- 10 Stemonacetal, 6a,12a-dehydro, 11-OH, 2,3,9-(OMe)<sub>3</sub>, 6-OEt
- \*11 Amorpholone, 6a,12a-dehydro, 6-OH, 2,3-(OMe)<sub>2</sub>, 8,9-CH<sub>2</sub>CH(CMe = CH<sub>2</sub>)O-
- \*12 Villinol, 6a,12a-dehydro, 11-OH, 2,3,6-(OMe)<sub>3</sub>, 8,9-CH<sub>2</sub>CH(CMe = CH<sub>2</sub>)O-
- 13 Stemonone, 6a,12a-dehydro, 6-oxo, 11-OH, 2,3,9-(OMe)<sub>3</sub>
- \*14 Rotenonone, 6a,12a-dehydro, 6-oxo, 2,3-(OMe)<sub>2</sub>, 8,9-CH<sub>2</sub>CH(CMe = CH<sub>2</sub>)O-
- \*15 Villosone, 6a,12a-dehydro, 6-oxo, 11-OH, 2,3-(OMe)<sub>2</sub>, 8,9-CH<sub>2</sub>CH(CMe = CH<sub>2</sub>)O-

### (iii) 12a-Hydroxyrotenoids

- \*1 12a-Hydroxymunduserone, 12a-OH, 2,3,9-(OMe)<sub>3</sub>
- 2 12a-Hydroxyrotenone, 12a-OH, 2,3-(OMe)<sub>2</sub>, 8,9-CH<sub>2</sub>CH(CMe = CH<sub>2</sub>)O-
- \*3 12a-Hydroxyisomillettone, 12a-OH, 2,3-OCH<sub>2</sub>O-, 8,9-CH<sub>2</sub>CH(CMe = CH<sub>2</sub>)O-
- \*4 Dalbinol, 12a-hydroxyamorphigenin, 12a-OH, 2,3-(OMe)<sub>2</sub>, 8,9-

- CH<sub>2</sub>CH[C(CH<sub>2</sub>OH) = CH<sub>2</sub>]O-
- 5 Tephrosin, 12a-OH, 2,3-(OMe)<sub>2</sub>, 8,9-CH = CHCMe<sub>2</sub>O-
- 6 Millettosin, 12a-OH, 2,3-OCH<sub>2</sub>O-, 8,9-CH = CHCMe<sub>2</sub>O-
- \*7 12a-Hydroxyerosone, 12a-OH, 2,3-(OMe)<sub>2</sub>, 9,10-OCH = CH-
- \*8 12a-Hydroxydolineone, 12a-OH, 2,3-OCH<sub>2</sub>O-, 9,10-OCH = CH-
- \*9 Villosinol, 12a-hydroxysumatrol, 11,12a-(OH)<sub>2</sub>, 2,3-(OMe)<sub>2</sub>, 8,9-CH<sub>2</sub>CH(CMe = CH<sub>2</sub>)O-
- \*10 11-Hydroxytephrosin, 11,12a-(OH)<sub>2</sub>, 2,3-(OMe)<sub>2</sub>, 8,9-CH = CHCMe<sub>2</sub>O-
- \*11 12a-Hydroxypachyrrhizone, 12a-OH, 8-OMe, 2,3-OCH<sub>2</sub>O-, 9,10-OCH = CH-
- 12 12a-Methoxyrotenone, 2,3,12a-(OMe)<sub>3</sub>, 8,9-CH<sub>2</sub>CH(CMe = CH<sub>2</sub>)O-
- \*13 Neobanone, 2,3,12a-(OMe)<sub>3</sub>, 9,10-OCH = CH-
- 14 12a-Methoxydolineone, 12a-OMe, 2,3-OCH<sub>2</sub>O-, 9,10-OCH = CH-
- \*15 Clitoriactal, 6,11,12a-(OH)<sub>3</sub>, 2,3,9-(OMe)<sub>3</sub>
- \*16 Villol, 6,11,12a-(OH)<sub>3</sub>, 2,3-(OMe)<sub>2</sub>, 8,9-CH<sub>2</sub>CH(CMe = CH<sub>2</sub>)O-

### Pterocarpan

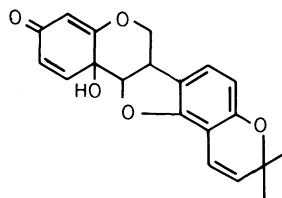


### (i) Pterocarpan

- \*1 Demethylmedicarpin, 3,9-(OH)<sub>2</sub>
- 2 Medicarpin, demethylhomopterocarpin, 3-OH, 9-OMe
- \*3 Isomedicarpin, 9-OH, 3-OMe
- 4 Homopterocarpin, 3,9-(OMe)<sub>2</sub>
- 5 Maackiain, 3-OH, 8,9-OCH<sub>2</sub>O-
- 6 Pterocarpin, 3-OMe, 8,9-OCH<sub>2</sub>O-
- \*7 Vesticarpin, 3,10-(OH)<sub>2</sub>, 9-OMe
- \*8 Nissolin, 3,9-(OH)<sub>2</sub>, 10-OMe
- \*9 Methylnissolin, 3-OH, 9,10-(OMe)<sub>2</sub>
- 10 Philenopteran, 3,9-(OH)<sub>2</sub>, 7,10-(OMe)<sub>2</sub>
- 11 9-Methylphilenopteran, 3-OH, 7,9,10-(OMe)<sub>3</sub>
- \*12 3-OH, 2,9-(OMe)<sub>2</sub>
- \*13 Sparticarpin, 9-OH, 2,3-(OMe)<sub>2</sub>
- \*14 2,3,9-(OMe)<sub>3</sub>
- \*15 2,8-(OH)<sub>2</sub>, 3,9-(OMe)<sub>2</sub>



- 16 2-Hydroxypterocarpin, 2-OH, 3-OMe, 8,9-OCH<sub>2</sub>O-
- 17 2-Methoxypterocarpin, 2,3-(OMe)<sub>2</sub>, 8,9-OCH<sub>2</sub>O-
- \*18 Mucronucarpin, 2,10-(OH)<sub>2</sub>, 3,9-(OMe)<sub>2</sub>
- \*19 2,8-(OH)<sub>2</sub>, 3,9,10-(OMe)<sub>3</sub>
- \*20 3,4,9-(OH)<sub>3</sub>
- \*21 3,4-(OH)<sub>2</sub>, 9-OMe
- \*22 4-OH, 3,9-(OMe)<sub>2</sub>
- 23 3-OH, 4,9-(OMe)<sub>2</sub>
- 24 3,4,9-(OMe)<sub>3</sub>
- 25 3,4-(OH)<sub>2</sub>, 8,9-OCH<sub>2</sub>O-
- 26 3-OH, 4-OMe, 8,9-OCH<sub>2</sub>O-
- 27 4-OH, 3-OMe, 8,9-OCH<sub>2</sub>O-
- 28 3,4-(OMe)<sub>2</sub>, 8,9-OCH<sub>2</sub>O-
- \*29 8-OH, 3,4,9,10-(OMe)<sub>4</sub>
- \*30 Trifolian, 1,3-(OH)<sub>2</sub>, 2-OMe, 8,9-OCH<sub>2</sub>O-
- \*31 4-OH, 2,3,9-(OMe)<sub>3</sub>
- \*32 2,8-(OH)<sub>2</sub>, 3,4,9,10-(OMe)<sub>4</sub>
- \*33 Homoedudiol, 3,9-(OH)<sub>2</sub>, 2-CH<sub>2</sub>CH = CMe<sub>2</sub>
- 34 Edunol, 3-OH, 8,9-OCH<sub>2</sub>O-, 2-CH<sub>2</sub>CH = CMe<sub>2</sub>
- \*35 Neorautenol, 9-OH, 2,3-CH = CHCMe<sub>2</sub>O-
- \*36 Neorautenane, 8,9-OCH<sub>2</sub>O-, 2,3-CH = CHCMe<sub>2</sub>O
- 37 Neorautane, 8,9-OCH<sub>2</sub>O-, 2,3-CH<sub>2</sub>CH<sub>2</sub>CMe<sub>2</sub>O-
- \*38 Neorautanol, 8,9-OCH<sub>2</sub>O-, 2,3-CH<sub>2</sub>CHOHCMe<sub>2</sub>O-
- \*39 Neodunol, 9-OH, 2,3-CH = CHO-
- 40 Neodulin, 8,9-OCH<sub>2</sub>O, 2,3-CH = CHO-
- \*41 Ambonane, 9,10-(OMe)<sub>2</sub>, 2,3-CH = CHO-
- \*42 Hemileiocarpin, 9-OMe, 3,4-OCMe<sub>2</sub>CH = CH-
- 43 Leiocarpin, 8,9-OCH<sub>2</sub>O, 3,4-OCMe<sub>2</sub>CH = CH-
- \*44 Nitiducol, 3-OH, 8,9-OCH<sub>2</sub>O-, 4-CH<sub>2</sub>CH = CMeCH<sub>2</sub>CH<sub>2</sub>CH = CMe<sub>2</sub>
- \*45 Nitiducarpin, 8,9-OCH<sub>2</sub>O-, 3,4-OCMe(CH<sub>2</sub>CH<sub>2</sub>CH = CMe<sub>2</sub>)CH = CH-
- \*46 Edudiol, 3,9-(OH)<sub>2</sub>, 1-OMe, 2-CH<sub>2</sub>CH = CMe<sub>2</sub>
- 47 Edulenol, 3-OH, 1,9-(OMe)<sub>2</sub>, 2-CH<sub>2</sub>CH = CMe<sub>2</sub>
- \*48 Edulenanol, 9-OH, 1-OMe, 2,3-CH = CHCMe<sub>2</sub>O-
- \*49 Eduleneane, 1,9-(OMe)<sub>2</sub>, 2,3-CH = CHCMe<sub>2</sub>O-
- \*50 Desmodin, 9-OH, 1,8-(OMe)<sub>2</sub>, 2,3-CH = CHCMe<sub>2</sub>O-
- \*51 Neorautenanol, 1-OH, 8,9-OCH<sub>2</sub>O-, 2,3-CH = CHCMe<sub>2</sub>O-
- \*52 Edulane, 1,9-(OMe)<sub>2</sub>, 2,3-CH<sub>2</sub>CH<sub>2</sub>CMe<sub>2</sub>O-
- \*53 Neorautanin, 1-OMe, 8,9-OCH<sub>2</sub>O-, 2,3-CH<sub>2</sub>CH<sub>2</sub>CMe<sub>2</sub>O-
- \*54 Neoraucarpanol, 3-OH, 4-OMe, 8,9-OCH<sub>2</sub>O-, 2-CH<sub>2</sub>CH = CMe<sub>2</sub>
- \*55 Neoraucarpan, 3,4-(OMe)<sub>2</sub>, 8,9-OCH<sub>2</sub>O-, 2-CH<sub>2</sub>CH = CMe<sub>2</sub>
- 56 Ficinin, 4-OMe, 8,9-OCH<sub>2</sub>O-, 2,3-CH = CHO-
- 57 Phaseollidin, 3,9-(OH)<sub>2</sub>, 10-CH<sub>2</sub>CH = CMe<sub>2</sub>
- \*58 Sandwicensin, 9-methylphaseollidin, 3-OH, 9-OMe, 10-CH<sub>2</sub>CH = CMe<sub>2</sub>
- \*59 Phaseollidin hydrate, 3,9-(OH)<sub>2</sub>, 10-CH<sub>2</sub>CH<sub>2</sub>CMe<sub>2</sub>OH (Metabolite)
- 60 Phaseollin, 3-OH, 9,10-OCMe<sub>2</sub>CH = CH-
- \*61 3-OH, 9,10-OCMe<sub>2</sub>CHOH CHOH- (Metabolite)
- \*62 Lespedezin, 3,9-(OH)<sub>2</sub>, 10-CH<sub>2</sub>CH = CMeCH<sub>2</sub>CH<sub>2</sub>CH = CMe<sub>2</sub>
- \*63 1-Methoxyphaseollidin, 3,9-(OH)<sub>2</sub>, 1-OMe, 10-CH<sub>2</sub>CH = CMe<sub>2</sub>
- 64 Ficifolinol, 3,9-(OH)<sub>2</sub>, 2,8-(CH<sub>2</sub>CH = CMe<sub>2</sub>)<sub>2</sub>
- 65 Folitenol, 3-OH, 2-CH<sub>2</sub>CH = CMe<sub>2</sub>, 9,10-OCMe<sub>2</sub>CH = CH-
- 66 Folinin, 2,3-CH<sub>2</sub>CH<sub>2</sub>CMe<sub>2</sub>O-, 9,10-OCMe<sub>2</sub>CH = CH-
- 67 Gangetin, 9-OH, 1-OMe, 10-CH<sub>2</sub>CH = CMe<sub>2</sub>, 2,3-CH = CHCMe<sub>2</sub>O-
- \*68 Gangetinin, 1-OMe, 2,3; 10,9-(CH = CHCMe<sub>2</sub>O-)<sub>2</sub>
- \*69 Lespein, 3,9-(OH)<sub>2</sub>, 6a, 10-(CH<sub>2</sub>CH = CMe<sub>2</sub>)<sub>2</sub>
- \*70 la-Hydroxyphaseollone (Metabolite)



(ii) 6a-Hydroxypterocarpan

- \*1 3,9,6a-(OH)<sub>3</sub>
- \*2 6a-Hydroxypticarpan, 3,6a-(OH)<sub>2</sub>, 9-OMe

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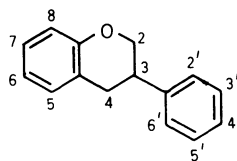
- \*3 6a-Hydroxyisomedicarpin, 9,6a-(OH)<sub>2</sub>, 3-Ome
- 4 Variabilin, homopisatin, 6a-OH, 3,9-(OMe)<sub>2</sub>
- \*5 6a-Hydroxymaackiain, 3,6a-(OH)<sub>2</sub>, 8,9-OCH<sub>2</sub>O-
- 6 Pisatin, 6a-OH, 3-OMe, 8,9-OCH<sub>2</sub>O-
- \*7 3,7,6a-(OH)<sub>3</sub>, 9-OMe
- \*8 3,7,6a-(OH)<sub>3</sub>, 8,9-OCH<sub>2</sub>O-
- \*9 Acanthocarpin, 6a-OH, 3-OMe, 8,9-OCH<sub>2</sub>O-, 2 or 4-Me(?)
- \*10 Glyceollin IV, 9,6a-(OH)<sub>2</sub>, 3-OMe, 2-CH<sub>2</sub>CH = CMe<sub>2</sub>
- \*11 Glyceollin II, 9,6a-(OH)<sub>2</sub>, 2,3-CH = CHCMe<sub>2</sub>O-
- \*12 Glyceollin III, 9,6a-(OH)<sub>2</sub>, 2,3-CH<sub>2</sub>CH(CMe = CH<sub>2</sub>)O-
- \*13 Neobanol, 6a-OH, 8,9-OCH<sub>2</sub>O-, 2,3-CH = CHO-
- \*14 Glyceollin I, 9,6a-(OH)<sub>2</sub>, 3,4-OCMe<sub>2</sub>CH = CH-
- 15 Tuberosin, 3,6a-(OH)<sub>2</sub>, 8,9-CH = CHCMe<sub>2</sub>O-
- \*16 Sandwicarpin, 6a-hydroxyphaseollidin, 3,9,6a-(OH)<sub>3</sub>, 10-CH<sub>2</sub>CH = CMe<sub>2</sub>
- \*17 Cristacarpin, 3,6a-(OH)<sub>2</sub>, 9-OMe, 10-CH<sub>2</sub>CH = CMe<sub>2</sub>
- \*18 6a-Hydroxyphaseollin, 3,6a-(OH)<sub>2</sub>, 9,10-OCMe<sub>2</sub>CH = CH-
- \*19 3,7,6a-(OH)<sub>3</sub>, 9,10-OCMe<sub>2</sub>CH = CH-(Metabolite)

### (iii) Pterocarpenes

- \*1 6a, 11a-dehydro, 3,9-(OH)<sub>2</sub>
- 2 6a, 11a-dehydro, 3,9-(OMe)<sub>2</sub>
- 3 Flemichapparin B, anhydropisatin, 6a,11a-dehydro, 3-OMe,8,9-OCH<sub>2</sub>O-
- \*4 Bryacarpene-5, 6a,11a-dehydro, 3,9,10-(OMe)<sub>3</sub>
- \*5 Bryacarpene-2, 6a,11a-dehydro, 10-OH, 3,8,9-(OMe)<sub>3</sub>
- \*6 Bryacarpene-3, 6a,11a-dehydro, 3,8,9,10-(OMe)<sub>4</sub>
- \*7 6a,11a-dehydro, 3-OH, 4-OMe, 8,9-OCH<sub>2</sub>O-
- \*8 Bryacarpene-4, 6a,11a-dehydro, 4-OH, 3,9,10-(OMe)<sub>3</sub>
- \*9 Bryacarpene-1, 6a,11a-dehydro,4,10-(OH)<sub>2</sub>, 3,8,9-(OMe)<sub>3</sub>
- 10 Leiocalycin, 6a,11a-dehydro, 2-OH, 1,3-(OMe)<sub>2</sub>, 8,9-OCH<sub>2</sub>O-
- \*11 Neorauteen, 6a,11a-dehydro, 9-OH, 2,3-CH = CHO-

- \*12 Neoduleen, 6a, 11a-dehydro, 8,9-OCH<sub>2</sub>O-, 2,3-CH = CHO-

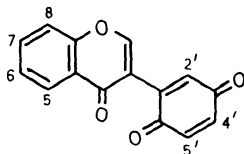
### Isoflavans



- 1 Equol, 7,4'-(OH)<sub>2</sub> (Metabolite)
- \*2 Demethylvestitol, 7,2',4'-(OH)<sub>3</sub>
- 3 Vestitol, 7,2'-(OH)<sub>2</sub>, 4'-OMe
- \*4 Isovestitol, 7,4'-(OH)<sub>2</sub>, 2'-OMe
- \*5 Neovestitol, 2',4'-(OH)<sub>2</sub>, 7-OMe
- 6 Sativan, 7-OH, 2',4'-(OMe)<sub>2</sub>
- 7 Isosativan, 2'-OH, 7,4'-(OMe)<sub>2</sub>
- \*8 Arvensan, 4'-OH, 7,2'-(OMe)<sub>2</sub>
- 9 Laxifloran, sphaerosin, 7,4'-(OH)<sub>2</sub>, 2',3'-(OMe)<sub>2</sub>
- 10 Mucronulatol, 7,3'-(OH)<sub>2</sub>, 2',4'-(OMe)<sub>2</sub>
- \*11 Isomucronulatol, 7,2'-(OH)<sub>2</sub>, 3',4'-(OMe)<sub>2</sub>
- \*12 Maackiainisoflavan, 7,2'-(OH)<sub>2</sub>, 4',5'-OCH<sub>2</sub>O-(Metabolite)
- \*13 Astraciceran, 7-OH, 2'-OMe, 4',5'-OCH<sub>2</sub>O-
- 14 Lonchocarpin, 7,4'-(OH)<sub>2</sub>, 2',3',6'-(OMe)<sub>2</sub>
- \*15 5-Methoxyvestitol, 7,2'-(OH)<sub>2</sub>, 5,4'-(OMe)<sub>2</sub>
- \*16 7,2'-(OH)<sub>2</sub>, 6,4'-(OMe)<sub>2</sub> (Metabolite)
- \*17 Bryaflavan, 6,7,3'-(OH)<sub>3</sub>, 2',4'-(OMe)<sub>2</sub>
- 18 8-Demethylduartin, 7,8,3'-(OH)<sub>3</sub>, 2',4'-(OMe)<sub>2</sub>
- 19 Duartin, 7,3'-(OH)<sub>2</sub>, 8,2',4'-(OMe)<sub>3</sub>
- \*20 Sphaerosinin, 4'-OH, 2',3'-(OMe)<sub>2</sub>, 6,7-CH = CHCMe<sub>2</sub>O-
- 21 Neorauflavane, 2',4'-(OH)<sub>2</sub>, 5-OMe, 6,7-CH = CHCMe<sub>2</sub>O-
- \*22 Glabridin, 2',4'-(OH)<sub>2</sub>, 7,8-OCMe<sub>2</sub>CH = CH-
- \*23 4'-Methylglabridin, 2'-OH, 4'-OMe, 7,8-OCMe<sub>2</sub>CH = CH-
- \*24 3'-Methoxyglabridin, 2',4'-(OH)<sub>2</sub>, 3'-OMe, 7,8-OCMe<sub>2</sub>CH = CH-
- \*25 Leiocin, 2'-OH, 4',5'-OCH<sub>2</sub>O-, 7,8-OCMe<sub>2</sub>CH = CH-
- \*26 Heminitidulan, 2'-OH, 4'-OMe, 7,8-OCMe(CH<sub>2</sub>CH<sub>2</sub>CH = CMe<sub>2</sub>)CH = CH-
- \*27 Nitidulin, 2',3'-(OH)<sub>2</sub>, 4'-OMe, 7,8-OCMe(CH<sub>2</sub>CH<sub>2</sub>CH = CMe<sub>2</sub>) CH = CH-

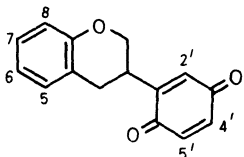
- \*28 Nitidulan, 2'-OH, 4',5'-OCH<sub>2</sub>O-, 7,8-OCMe(CH<sub>2</sub>CH<sub>2</sub>CH = CMe<sub>2</sub>) CH = CH-
- \*29 Leiocinol, 6,2'-(OH)<sub>2</sub>, 4',5'-OCH<sub>2</sub>O-, 7,8-OCMe<sub>2</sub>CH = CH-
- \*30 2'-Methylphaseollidiniso flavan, 7,4'-(OH)<sub>2</sub>, 2'-OMe, 3'-CH<sub>2</sub>CH = CMe<sub>2</sub>
- 31 Phaseollinisoflavan, 7,2'-(OH)<sub>2</sub>, 3',4'-CH = CHCMe<sub>2</sub>O-
- 32 2'-Methylphaseollinisoflavan, 7-OH, 2'-OMe, 3',4'-CH = CHCMe<sub>2</sub>O-
- \*33 α,α-Dimethylallylcyclolobin, 7,3',4'-(OH)<sub>3</sub>, 2'-OMe, 5'-CMe<sub>2</sub>CH = CH<sub>2</sub>
- \*34 Unaniso flavan, 7,3'-(OH)<sub>2</sub>, 2',4'-(OMe)<sub>2</sub>, 5'-CMe<sub>2</sub>CH = CH<sub>2</sub>
- \*35 Hispaglabridin A, 2',4'-(OH)<sub>2</sub>, 3'-CH<sub>2</sub>CH = CMe<sub>2</sub>, 7,8-OCMe<sub>2</sub>CH = CH-
- \*36 Hispaglabridin B, 2'-OH, 7,8; 4',3'-(OCMe<sub>2</sub>CH = CH-)<sub>2</sub>
- 37 Licoricidin, 5,2',4'-(OH)<sub>3</sub>, 6,3'-(CH<sub>2</sub>CH = CMe<sub>2</sub>)<sub>2</sub>
- \*38 3-Hydroxymaackiainiso flavan, 7,3,2'-(OH)<sub>3</sub>, 4',5'-OCH<sub>2</sub>O- (Metabolite)
- \*39 Biscyclolobin, (7,3'-(OH)<sub>2</sub>, 2'-OMe, 4'-)<sub>2</sub>O (?)

#### Isoflavonequinone



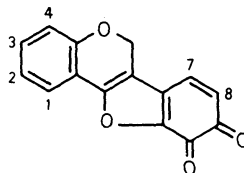
- \*1 Bowdichione, 7-OH, 4'-OMe

#### Isoflavanquinones



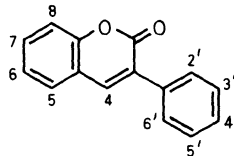
- 1 Claussequinone, 7-OH, 4'-OMe
- \*2 Abruquinone A, 6,7,4',5'-(OMe)<sub>4</sub>
- 3 Mucroquinone, 7-OH, 8,4'-(OMe)<sub>2</sub>
- \*4 Amorphiquinone, 7-OH, 8,4',5'-(OMe)<sub>3</sub>
- \*5 Abruquinone C, 6-OH, 7,8,4',5'-(OMe)<sub>4</sub>
- \*6 Abruquinone B, 6,7,8,4',5'-(OMe)<sub>5</sub>

#### Pterocarpenequinones



- \*1 4-Deoxybryaquinone, 3,7-(OMe)<sub>2</sub>
- \*2 Bryaquinone, 4-OH, 3,7-(OMe)<sub>2</sub>

#### 3-Arylcoumarins

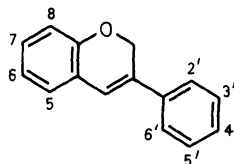


- \*1 7,2'-(OH)<sub>2</sub>, 4'-OMe
- \*2 7,2'-(OH)<sub>2</sub>, 4',5'-OCH<sub>2</sub>O-
- 3 Pachyrrhizin, 2'-OMe, 4',5'-OCH<sub>2</sub>O-, 6,7-CH = CHO-
- \*4 Glycyrrin, 2',4'-(OH)<sub>2</sub>, 5,7-(OMe)<sub>2</sub>, 6-CH<sub>2</sub>CH = CMe<sub>2</sub>
- 5 Neofolin, 8,2'-(OMe)<sub>2</sub>, 4',5'-OCH<sub>2</sub>O-, 6,7-CH = CHO-

#### 3-Aryl-4-hydroxycoumarins

- 1 Derrusin, 4,5,7-(OMe)<sub>3</sub>, 3',4'-OCH<sub>2</sub>O-
- 2 Robustic acid, 4-OH, 5,4'-(OMe)<sub>2</sub>, 6,7-CH = CHCMe<sub>2</sub>O-
- 3 Robustic acid methyl ether, 4,5,4'-(OMe)<sub>3</sub>, 6,7-CH = CHCMe<sub>2</sub>O-
- 4 Robustin, 4-OH, 5-OMe, 3',4'-OCH<sub>2</sub>O-, 6,7-CH = CHCMe<sub>2</sub>O-
- 5 Robustin methyl ether, 4,5-(OMe)<sub>2</sub>, 3',4'-OCH<sub>2</sub>O-, 6,7-CH = CHCMe<sub>2</sub>O-
- \*6 Glabrescin, 4,5-(OMe)<sub>2</sub>, 3',4'-OCH<sub>2</sub>O-, 6,7-CH<sub>2</sub>CH(CMe = CH<sub>2</sub>)O-
- 7 Scandenin, 4,4'-(OH)<sub>2</sub>, 5-OMe, 6-CH<sub>2</sub>CH = CMe<sub>2</sub>, 7,8-OCMe<sub>2</sub>CH = CH-
- 8 Lonchocarpic acid, 4,4'-(OH)<sub>2</sub>, 5-OMe, 8-CH<sub>2</sub>CH = CMe<sub>2</sub>, 6,7-CH = CHCMe<sub>2</sub>O-
- 9 Lonchocarpin, 4-OH, 5,4'-(OMe)<sub>2</sub>, 8-CH<sub>2</sub>CH = CMe<sub>2</sub>, 6,7-CH = CHCMe<sub>2</sub>O-

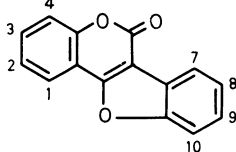
#### Isoflav-3-enes



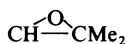
## 640 The Flavonoids

- \*1 Haginin B, 7,4'-(OH)<sub>2</sub>, 2'-OMe
- \*2 Sepiol, 7,2',3'-(OH)<sub>3</sub>, 4'-OMe
- \*3 Haginin A, 7,4'-(OH)<sub>2</sub>, 2',3'-(OMe)<sub>2</sub>
- \*4 2'-Methylsepiol, 7,3'-(OH)<sub>2</sub>, 2',4'-(OMe)<sub>2</sub>
- 5 Neorauflavene, 2',4'-(OH)<sub>2</sub>, 5-OMe, 6,7-CH = CHCMe<sub>2</sub>O-
- \*6 Glabrene, 7,2'-(OH)<sub>2</sub>, 3',4'-CH = CHCMe<sub>2</sub>O-

### Coumestans

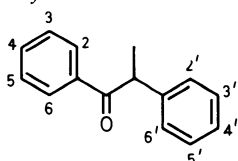


- 1 Coumestrol, 3,9-(OH)<sub>2</sub>
- 2 9-Methylcoumestrol, 3-OH, 9-OMe
- 3 Dimethylcoumestrol, 3,9-(OMe)<sub>2</sub>
- 4 3,9-(OH)<sub>2</sub>, 8-OMe
- 5 3-OH, 8,9-(OMe)<sub>2</sub>
- 6 Medicagol, 3-OH, 8,9-OCH<sub>2</sub>O-
- 7 Flemichapparin C, 3-OMe, 8,9-OCH<sub>2</sub>O-
- 8 Repensol, 3,7,9-(OH)<sub>3</sub>
- 9 Trifoliol, 3,7-(OH)<sub>2</sub>, 9-OMe
- 10 Demethylwedelolactone, 1,3,8,9-(OH)<sub>4</sub>
- 11 Wedelolactone, 1,8,9-(OH)<sub>3</sub>, 3-OMe
- 12 Lucernol, 2,3,9-(OH)<sub>3</sub>
- \*13 Tephrosol, 3-OH, 2-OMe, 8,9-OCH<sub>2</sub>O-
- 14 2-OH, 3-OMe, 8,9-OCH<sub>2</sub>O-
- 15 Sativol, 4,9-(OH)<sub>2</sub>, 3-OMe
- 16 2-OH, 1,3-(OMe)<sub>2</sub>, 8,9-OCH<sub>2</sub>O-
- 17 Psoralidin, 3,9-(OH)<sub>2</sub>, 2-CH<sub>2</sub>CH = CMe<sub>2</sub>
- \*18 Psoralidin oxide, 3,9-(OH)<sub>2</sub>, 2-CH<sub>2</sub>



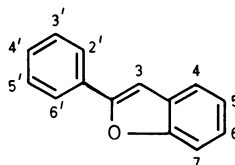
- \*19 Corylidin, 9-OH, 2,3-CHOHCHOHCMe<sub>2</sub>O-
- 20 Erosnin, 8,9-OCH<sub>2</sub>O-, 2,3-CH = CHO-
- 21 Glycyrol, 1,9-(OH)<sub>2</sub>, 3-OMe, 2-CH<sub>2</sub>CH = CMe<sub>2</sub>
- 22 1-Methylglycyrol, 9-OH, 1,3-(OMe)<sub>2</sub>, 2-CH<sub>2</sub>CH = CMe<sub>2</sub>
- 23 Isoglycyrol, 9-OH, 3-OMe, 1,2-OCMe<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-
- 24 Sojagol, 3-OH, 9,10-OCMe<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-

### α-Methyldeoxybenzoins



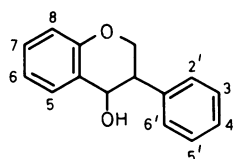
- 1 Angolensin, 2,4-(OH)<sub>2</sub>, 4'-OMe
- \*2 2-Methylangolensin, 4-OH, 2,4'-(OMe)<sub>2</sub>
- \*3 4-Methylangolensin, 2-OH, 4,4'-(OMe)<sub>2</sub>
- \*4 4-Cadinylangolensin, 2-OH, 4'-OMe, 4-O-C<sub>15</sub>H<sub>25</sub>

### 2-Arylbenzofurans



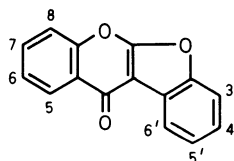
- \*1 6-Demethylvignafuran, 4',6-(OH)<sub>2</sub>, 2'-OMe
- \*2 Vignafuran, 4'-OH, 2',6-(OMe)<sub>2</sub>
- 3 Pterofuran, 3',6-(OH)<sub>2</sub>, 2',4'-(OMe)<sub>2</sub>
- \*4 Isopterofuran, 4',6-(OH)<sub>2</sub>, 2',3'-(OMe)<sub>2</sub>
- \*5 2',4'-(OH)<sub>2</sub>, 5,6-(OMe)<sub>2</sub>
- \*6 2',4'-(OH)<sub>2</sub>, 5,6-OCH<sub>2</sub>O-
- \*7 2'-OH, 4'-OMe, 5,6-OCH<sub>2</sub>O-
- \*8 Neoraufurane, 2',4'-(OH)<sub>2</sub>, 4-OMe, 5,6-CH = CHCMe<sub>2</sub>O-
- \*9 Bryebinal, 3',4'(OH)<sub>2</sub>, 2',4',7,5 or 6-(OMe)<sub>4</sub>, 3-CHO(?)

### Isoflavanol



- \*1 Ambanol, 2'-OMe, 4',5'-OCH<sub>2</sub>O-, 6,7-CH = CHO-

### Coumaronochromone



- 1. Lisetin, 5,7,4'-(OH)<sub>3</sub>, 5'-OMe, 3'-CH<sub>2</sub>CH = CMe<sub>2</sub>

## CHAPTER ELEVEN

# *Biosynthesis*

J. EBEL and K. HAHLBROCK

### 11.1 INTRODUCTION

Our present knowledge in the field of flavonoid biosynthesis is based on a combination of earlier results from radioactive tracer studies *in vivo* and more recent data obtained at the enzyme level *in vitro*. In the past few years, the enzymology of flavonoid biosynthesis has made particularly rapid progress. It became firmly established that all classes of flavonoids derive their carbon skeleton from compounds of intermediary cell metabolism through the action of two consecutive (general phenylpropanoid and flavonoid glycoside) pathways. Although the first (general phenylpropanoid) pathway is shared with some other biosynthetic routes, it is discussed in some detail in the first part of this chapter, because it may in some cases determine the substitution pattern of the flavonoid end products through structural modifications introduced at the level of the substrates supplied for their synthesis. The second, major part then deals with the reactions of the various flavonoid pathways proper.

### 11.2 GENERAL PHENYLPROPANOID METABOLISM

Phenylpropanoid units derived from the shikimate pathway are common structural elements of all flavonoid compounds and of various other classes of phenylpropanoids, such as lignin, stilbenes and cinnamate esters. The sequence of reactions converting phenylalanine into the CoA ester derivatives of substituted cinnamic acids was therefore termed 'general phenylpropanoid metabolism' (Ebel *et al.*, 1974). The enzymes catalysing the individual steps are phenylalanine ammonia-lyase, cinnamate 4-hydroxylase and 4-coumarate:CoA ligase (Fig. 11.1, Table 11.1). A close metabolic relationship between these three enzymes is apparent from their interdependent regulation in a number of plant tissues either during developmental changes or in response to changes in the environmental conditions.

Phenylalanine ammonia-lyase catalyses the *anti* elimination of ammonia and the (*pro-3S*)-proton from L-phenylalanine to yield *trans*-cinnamic acid. The enzymes from many plants also convert L-tyrosine into *trans*-4-coumarate, albeit with much lower efficiency. There is much evidence that both substrates are of

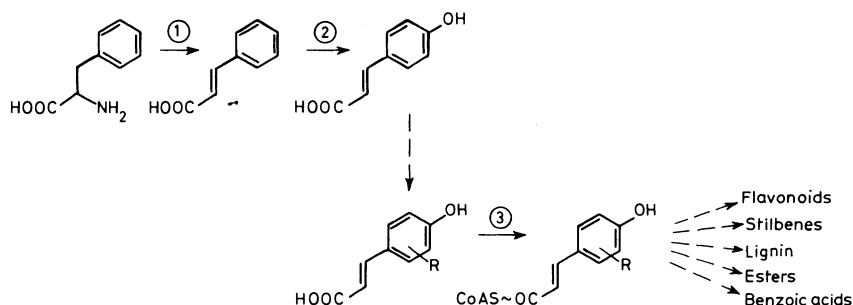


**Fig. 11.1** Scheme illustrating the reactions of general phenylpropanoid metabolism. The enzymes marked by numbers are listed in Table 11.1. The CoA esters of 4-coumarate and other substituted cinnamic acids are central intermediates at the branch point between the general metabolism and the various subsequent, specific pathways. The dashed arrow indicates (a) hypothetical 3- and 5-hydroxylase(s) as well as a methyltransferase which is not a typical enzyme of this sequence. R = H, OH, or OCH<sub>3</sub>.

physiological importance. Various properties of phenylalanine ammonia-lyases from a large number of sources have been studied, including their widely differing reactivities towards tyrosine. No tyrosine ammonia-lyase has so far

**Table 11.1** List of enzymes mentioned in Figures

| Enzyme                                                        | EC number  | Key to Figure     |
|---------------------------------------------------------------|------------|-------------------|
| <i>General phenylpropanoid metabolism</i>                     |            |                   |
| Phenylalanine ammonia-lyase                                   | 4.3.1.5    | Fig. 11.1, No. 1  |
| Cinnamate 4-hydroxylase                                       | 1.14.13.11 | Fig. 11.1, No. 2  |
| 4-Coumarate:CoA ligase                                        | 6.2.1.12   | Fig. 11.1, No. 3  |
| <i>Additional reaction preceding the CoA ligase step</i>      |            |                   |
| S-Adenosyl-L-methionine:<br>caffeate 3-O-methyltransferase    | 2.1.1.-    | Fig. 11.1         |
| <i>Flavone and flavonol glycoside pathways</i>                |            |                   |
| Acetyl-CoA carboxylase                                        | 6.4.1.2    | Fig. 11.3, No. 1  |
| Chalcone synthase                                             | —          | Fig. 11.3, No. 2  |
| Chalcone isomerase                                            | 5.5.1.6    | Fig. 11.3, No. 3  |
| 'Flavonoid 3-hydroxylase'                                     | —          | Fig. 11.3, No. 4  |
| 'Flavonoid oxidase'                                           | —          | Fig. 11.3, No. 5  |
| 'Flavonoid 3'-hydroxylase'                                    | —          | Fig. 11.3, No. 6  |
| S-Adenosyl-L-methionine:flavonoid 3'-O-<br>methyltransferase  | 2.1.1.42   | Fig. 11.3, No. 7  |
| UDP-Glucose:flavonoid 7-O-glucosyltransferase                 | 2.4.1.81   | Fig. 11.3, No. 8  |
| UDP-Glucose:flavonol 3-O-glucosyltransferase                  | 2.4.1.-    | Fig. 11.3, No. 9  |
| UDP-Apiose/UDP-xylose synthase                                | —          | Fig. 11.3, No. 10 |
| UDP-Apiose:flavone 7-O-glucoside 2''-O-<br>apiosyltransferase | 2.4.2.25   | Fig. 11.3, No. 11 |
| Malonyl-CoA:flavonoid 7-O-glycoside<br>malonyltransferase     | 2.3.1.-    | Fig. 11.3, No. 12 |
| Malonyl-CoA:flavonol 3-O-glucoside<br>malonyltransferase      | 2.3.1.-    | Fig. 11.3, No. 13 |

been found which does not possess phenylalanine ammonia-lyase activity. Most of this work has been reviewed by Hanson and Havir (1972a,b) and Camm and Towers (1973).

Phenylalanine ammonia-lyase has attracted considerable attention because it provides the link between primary metabolism and the phenylpropanoid pathways (Fig. 11.1). Regulation of phenylalanine ammonia-lyase activity *in vivo* may be exerted through both allosteric effects and modulation of the enzyme level by various stimuli. A strong correlation between flavonoid production and the expression of phenylalanine ammonia-lyase activity in developing plant tissues or after treatment of plant tissues or plant cell cultures with light, micro-organisms, microbial products (elicitors) or hormones and other chemicals has been observed (see Section 11.4.10). It should be noted, however, that phenylalanine ammonia-lyase cannot be regarded as the 'key enzyme' of flavonoid biosynthesis, because of its involvement in other phenylpropanoid pathways.

The second enzyme of general phenylpropanoid metabolism, cinnamate 4-hydroxylase (*trans*-cinnamate 4-mono-oxygenase), catalyses the 4-hydroxylation of cinnamate to yield 4-coumarate. The enzyme has been isolated from a variety of plants and its properties have been studied.

Cinnamate 4-hydroxylase was first detected in microsomal membranes of pea seedlings by Russell and Conn (1967). Microsomal systems have since provided convenient sources of the enzyme (Russell, 1971; Potts *et al.*, 1974; Tanaka *et al.*, 1974; Tanaka and Uritani, 1974; Young and Beevers, 1976; Rich and Lamb, 1977; Pfändler *et al.*, 1977). Tanaka *et al.* (1974) concluded from their studies of microsomal fractions of *Brassica* that cinnamate 4-hydroxylase activity is not associated with the endoplasmic reticulum (ER). By contrast, later studies by others have convincingly demonstrated that the enzyme is associated with the ER in *Ricinus* endosperm tissues (Young and Beevers, 1976), Jerusalem artichoke (*Helianthus tuberosus*) tuber (Benveniste *et al.*, 1977) and *Sorghum* seedlings (Saunders *et al.*, 1977).

Cinnamate 4-hydroxylase is a mono-oxygenase which catalyses the NADPH- and O<sub>2</sub>-dependent hydroxylation of *trans*-cinnamate to give *trans*-4-coumarate (Russell, 1971; Potts *et al.*, 1974; Pfändler *et al.*, 1977). The enzyme is highly substrate-specific and is inhibited by *cis*-cinnamate and by the reaction product, *trans*-4-coumarate (Russell, 1971; Pfändler *et al.*, 1977). Further investigations have demonstrated the involvement of cytochrome P-450 in the enzyme-mediated reaction (Potts *et al.*, 1974; Rich and Lamb, 1977).

The involvement of cytochrome P-450, the occurrence of a 'NIH-shift' during the hydroxylation reaction (Reed *et al.*, 1973) and the requirement of a lipid component for enzyme activity (Büche and Sandermann, 1973) provide some evidence for a basic similarity between plant and animal microsomal hydroxylation. Differences appear to exist, however, with regard to the mechanism of induction of these hydroxylases and their substrate specificities (Büche and Sandermann, 1973; Pfändler *et al.*, 1977).

The CoA esters of 4-coumarate and of other substituted cinnamic acids play a central role as intermediates at the branch point between general phenylpropanoid metabolism and the various subsequent specific pathways (Fig. 11.1). The function of CoA esters of substituted cinnamic acids as substrates in the biosynthesis of flavonoids (Hahlbrock, 1977, 1981; Hahlbrock and Grisebach, 1979), lignin (Hahlbrock, 1977; Gross, 1977; Hahlbrock and Grisebach, 1979), stilbenes (Rupprich and Kindl, 1978; Schöppner and Kindl, 1979; Rupprich *et al.*, 1980; Fritzemeier and Kindl, 1981) and cinnamate esters (Rhodes and Woollorton, 1976; Ulbrich *et al.*, 1976; Ulbrich and Zenk, 1980) has been demonstrated in recent years.

The enzyme responsible for CoA ester synthesis from various cinnamic acids is 4-coumarate:CoA ligase\* (Fig. 11.1, Table 11.1). A cinnamate-activating activity was first reported for extracts from leaves of spinach beet (*Beta vulgaris*) (Walton and Butt, 1970, 1971). 4-Coumarate:CoA ligases were isolated from various plant tissues and partially purified (Gross and Zenk, 1974; Knobloch and Hahlbrock, 1975, 1977; Ranjeva *et al.*, 1975 a,b, 1976; Wallis and Rhodes, 1977). The existence of isoenzymes has been demonstrated in soybean (*Glycine max*) cell cultures, pea (*Pisum sativum*) shoots and *Petunia hybrida* leaves (Table 11.2).

The basic properties of 4-coumarate:CoA ligase from various sources are fairly uniform. A molecular weight of 55 000 has been reported for both isoenzymes from soybean (Lindl *et al.*, 1973; Knobloch and Hahlbrock, 1975) and for the *Forsythia* enzyme (Gross and Zenk, 1974). A similar molecular weight (approximately 60 000) has been estimated for the parsley enzyme (Knobloch and Hahlbrock, 1977; Ragg *et al.*, 1981). 4-Coumarate:CoA ligase is specific for the activation of substituted cinnamic acids in the presence of ATP,  $Mg^{2+}$  and CoASH, with the respective cinnamoyl-AMP being an intermediate in this reaction (Rhodes and Woollorton, 1973; Gross and Zenk, 1974; Knobloch and Hahlbrock, 1975, 1977). The substrate specificities of the ligases from several plants have been studied (Table 11.2). No significant activation of 4-hydroxybenzoate, differently substituted phenylacetic acids, phenylalanine, tyrosine and of several aliphatic mono- and di-carboxylic acids was observed with the enzymes from *Forsythia*, *Glycine max* and *Petroselinum hortense* (Gross and Zenk, 1974; Knobloch and Hahlbrock, 1975, 1977). The enzyme acts only on the *trans* form of 4-coumarate (Knobloch and Hahlbrock, 1975, 1977).

Much interest has been focused on the question as to whether the activities of distinct 4-coumarate:CoA ligases are related to specific phenylpropanoid pathways. Most of the enzymes studied exhibit a preference for only a few substituted cinnamic acids, such as 4-coumarate, caffeate and ferulate, and do

\* Some authors have designated the ligase as 'hydroxycinnamate:CoA ligase'. Because 4-coumarate was one of the most efficient substrates for nearly all ligases reported so far to be involved in phenylpropanoid metabolism (Gross, 1977; Knobloch and Hahlbrock, 1977), and the EC number was assigned to 4-coumarate:CoA ligase, this latter term is used here throughout.



not activate sinapate or other highly methoxylated cinnamic acids (Table 11.2). For example, 4-coumarate:CoA ligase from irradiated parsley cells, which is thought to be involved in the biosynthesis of both flavonoids (Knobloch and Hahlbrock, 1977) and cinnamate esters (Kühnl, unpublished results), shows relatively low  $K_m$  values and high rates of conversion for 4-coumarate, caffeate and ferulate. Their substitution patterns correspond to those of the flavones and flavonols identified as aglycones in parsley cells (Kreuzaler and Hahlbrock, 1973). However, a comparatively narrow substrate specificity of the chalcone synthase from these cells, which utilizes only 4-coumaroyl-CoA with high efficiency (Section 11.4.2) and the occurrence of a flavonoid-specific methyl-transferase (Section 11.4.6) leave some doubt as to whether caffeoyl-CoA and feruloyl-CoA are natural substrates of the flavonoid glycoside pathway in parsley. Ligases with substrate specificities similar to that of the parsley enzyme have been isolated from various sources (Table 11.2). Their possible functions in flavonoid, lignin and cinnamate ester biosynthesis have been discussed by several authors (Gross *et al.*, 1975; Rhodes and Woollorton, 1973, 1975a,b, 1976; Rhodes *et al.*, 1976; Gross, 1977).

An important contribution to the elucidation of the metabolic function of 4-coumarate:CoA ligase was the discovery of isoenzymes (Table 11.2). The two isoenzymes of soybean (*Glycine max*) cell cultures differ markedly in their substrate specificities and other characteristic properties (Knobloch and Hahlbrock, 1975). Isoenzyme 1 shows relatively low  $K_m$  values and high rates of conversion for the three typical substrates of the lignin pathway, 4-coumarate, ferulate and sinapate, indicating that these acids are substrates of the enzyme *in vivo*. Isoenzyme 2 has relatively high affinities for 4-coumarate and caffeate, but does not activate sinapate. Therefore the assignment of a function in lignin biosynthesis to isoenzyme 1 is obvious from its substrate specificity. A similar clear-cut relation between isoenzyme 2 and a specific phenylpropanoid pathway cannot be deduced with certainty merely from its substrate specificity. Both isoenzymes could provide the substrate(s) for the flavonoid pathway, 4-coumaroyl-CoA and perhaps caffeoyl-CoA (Hrazdina *et al.*, 1976; Saleh *et al.*, 1978), with similar efficiency (Knobloch and Hahlbrock, 1975). However, the involvement of isoenzyme 2 in the flavonoid pathway was indirectly concluded from the great similarity of its substrate specificity with that of 4-coumarate:CoA ligase from parsley cells (Knobloch and Hahlbrock, 1977), whose involvement in flavonoid biosynthesis seems obvious. It cannot be excluded, however, that isoenzyme 2 is also involved in lignin biosynthesis in soybean cells (Hahlbrock and Grisebach, 1979).

Two ligase isoenzymes from extracts of pea (*Pisum sativum*) shoots with possible metabolic functions similar to those of the soybean isoenzymes have been separated (Wallis and Rhodes, 1977; Butt and Wilkinson, 1979). The two enzymes not only showed different substrate specificities (Table 11.2) but also responded differently to illumination of etiolated pea shoots (Butt and Wilkinson, 1979). Both forms were present in buds and stems, but while the

**Table 11.2** 4-Coumarate:CoA ligases from various sources

| Source of enzyme               | Number of ligases reported | Basis for distinction of isoenzymes                     | Type of assay* | Substrate specificity:<br>Relative rate of conversion (4-coumarate = 100 %) and $K_m$ value (in parenthesis, $\times 10^5$ mol/l) |          |          |          |
|--------------------------------|----------------------------|---------------------------------------------------------|----------------|-----------------------------------------------------------------------------------------------------------------------------------|----------|----------|----------|
|                                |                            |                                                         |                | 4-Coumarate                                                                                                                       | Caffeate | Ferulate | Sinapate |
| <i>Acer saccharinum</i>        | †                          |                                                         | A              | 100                                                                                                                               | 59       | 50       | 0        |
| <i>Brassica napo-brassica</i>  | 1                          |                                                         | A              | 100(1.4)                                                                                                                          | 68       | 73(3.1)  | 2        |
| <i>Forsythia suspensa</i>      | 1                          |                                                         | A              | 100(2.5)                                                                                                                          | 62(1.9)  | 96(2.0)  | 0        |
| <i>Glycine max</i>             | 2                          | DEAE-cellulose chromatography, disc-gel electrophoresis |                |                                                                                                                                   |          |          |          |
| Isoenzyme 1                    |                            |                                                         | B              | 100(3.2)                                                                                                                          | 56(4.0)  | 56(0.9)  | 46(1.1)  |
| Isoenzyme 2                    |                            |                                                         | B              | 100(1.7)                                                                                                                          | 87(1.4)  | 96(13)   | 0        |
| <i>Lycopersicon esculentum</i> | 1                          |                                                         | A              | 100(0.14)                                                                                                                         | 77(0.89) | 89       | 0        |
| <i>Petroselinum hortense</i>   | 1                          |                                                         | B              | 100(1.4)                                                                                                                          | 85(2.0)  | 90(3.0)  | 0        |
| <i>Petunia hybrida</i>         | 3                          | DEAE-cellulose and hydroxyapatite chromatography        | A              |                                                                                                                                   |          |          |          |
| Isoenzyme 1a                   |                            |                                                         |                | 100(6)                                                                                                                            | 300(10)  | 0        | 0        |
| Isoenzyme 1b                   |                            |                                                         |                | 100(10)                                                                                                                           | 0        | 0        | 80(17)   |
| Isoenzyme 2                    |                            |                                                         |                | 100(5)                                                                                                                            | 0.2(480) | 162(7)   | 0        |
| <i>Pisum sativum</i>           | 2                          | DEAE-cellulose chromatography                           |                |                                                                                                                                   |          |          |          |
| 'Peak' 1                       |                            |                                                         |                | 100                                                                                                                               | 38       | 78       | 56       |
| 'Peak' 2                       |                            |                                                         |                | 100                                                                                                                               | 27       | 63       | 2        |
| <i>Solanum tuberosum</i>       | †                          |                                                         | A              | 100(0.62)                                                                                                                         | 51(1.6)  | 77(1.4)  | 0        |
| <i>Taxus baccata</i>           | †                          |                                                         | A              | 100                                                                                                                               | 80       | 92       | ‡        |

\* Data were determined either (A) with substrate concentrations of the order of 0.2–0.7 mmol/l or (B) as relative  $V$  values.

† Not determined.

‡ Not reported.

activities of both forms increased in stems upon illumination, only ligase 2 activity increased in buds. Butt and Wilkinson (1979) concluded that ligase 1 is involved in lignin synthesis in stems and ligase 2 may be involved in both lignin and flavonoid biosynthesis in stems and leaves.

An even more complex system is present in *Petunia hybrida* leaves which produce flavonoids, cinnamate esters (caffeoyl- and feruloylquinic acids) and lignin (Ranjeva *et al.*, 1975a, 1976). After chromatography of cell free extracts from *Petunia* leaves on DEAE-cellulose and hydroxyapatite, three forms of

| <i>Remarks</i>                                                                                                           | <i>Reference</i>                                                                             |
|--------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
|                                                                                                                          | Gross <i>et al.</i> (1975)                                                                   |
| Isolated from roots,<br>activity increased by aging<br>or ethylene treatment                                             | Rhodes and Wooltorton (1973)<br>Rhodes and Wooltorton (1975a)<br>Rhodes <i>et al.</i> (1976) |
| Isolated from young xylem                                                                                                | Gross <i>et al.</i> (1973)<br>Gross <i>et al.</i> (1974)<br>Gross <i>et al.</i> (1975)       |
| Isolated from cell suspension cultures,<br>activity dependent on growth stage of<br>culture                              | Knobloch and Hahlbrock (1975)                                                                |
| Isolated from fruits                                                                                                     | Rhodes and Wooltorton (1976)                                                                 |
| Isolated from cell suspension cultures, activity<br>increased by irradiation, dilution, elicitor treat-<br>ment of cells | Knobloch and Hahlbrock (1977)                                                                |
| Isolated from leaves                                                                                                     | Ranjeva <i>et al.</i> (1975a)<br>Ranjeva <i>et al.</i> (1976)                                |
| Isolated from shoots                                                                                                     | Wallis and Rhodes (1977)<br>Butt and Wilkinson (1979)                                        |
| Isolated from tubers, activity increased upon<br>aging of potato tuber disks in the light                                | Rhodes and Wooltorton (1975b)                                                                |
|                                                                                                                          | Gross <i>et al.</i> (1975)                                                                   |

4-coumarate:CoA ligase were isolated (Table 11.2). All three isoenzymes activated 4-coumarate but differed significantly with respect to their specificities for caffeate, ferulate and sinapate. The involvement of the three ligases in the formation of flavonoids, cinnamate esters and lignin respectively was concluded from their differential sensitivity to feedback inhibition by naringenin and cinnamate esters (Ranjeva *et al.*, 1976, 1979).

Other interesting properties of 4-coumarate:CoA ligases from parsley and soybean are their inhibition by the substrates, 4-coumarate and CoA, and the

product, AMP (Knobloch and Hahlbrock, 1975, 1977). Thus, a combination of pronounced substrate specificities, the occurrence of isoenzymes and complex regulatory effects of various metabolites indicate an important role of this enzyme in controlling the distribution of cinnamoyl-CoA esters among different pathways of phenylpropanoid metabolism (Hahlbrock and Grisebach, 1979).

Some of the specific pathways into which general phenylpropanoid metabolism branches require, in addition to 4-hydroxylation, further substitution of the aromatic ring. The most prominent additional reactions are hydroxylation and subsequent methylation in the 3 and 5 positions. Of the enzymes involved, only methyltransferases have so far been characterized to any considerable extent (Poulton, 1981). Some of these transferases have been assigned to lignin biosynthesis. Since flavonoid-specific methyltransferases have been found in various plants, too, it appears unlikely that general phenylpropanoid metabolism includes a 'general' methyltransferase (Hahlbrock and Grisebach, 1979). Phenolases catalyse the hydroxylation of 4-coumarate to caffeate. However, the significance of these enzymes in general phenylpropanoid metabolism and flavonoid biosynthesis is not established (Hahlbrock and Grisebach, 1975). The results of genetic and biochemical investigations with *Silene dioica* petals were interpreted as indicating that in this plant the 3'-hydroxylation pattern of the B ring of anthocyanidins is determined at the 4-coumaroyl-CoA stage (Kamsteeg *et al.*, 1980d, 1981).

The question of whether the activated products of 4-coumarate substitution, caffeoyl-CoA and feruloyl-CoA, are intermediates in flavonoid biosynthesis is discussed below in connection with the substrate specificity of chalcone synthase (Section 11.4.2).

### 11.3 INDIVIDUAL PATHWAYS OF FLAVONOID BIOSYNTHESIS

All classes of flavonoids are biosynthetically closely related, with a chalcone being the first common intermediate. Earlier feeding experiments with radioactively labelled precursors have established that the carbon skeleton is derived from acetate and phenylalanine; ring A is formed by a head-to-tail condensation of three acetate units and ring B as well as carbon atoms 2,3 and 4 of the heterocyclic ring C arise from phenylalanine. Most of the results of this work have been reviewed previously by Hahlbrock and Grisebach (1975). The biosynthetic relationships of the flavonoids as concluded mainly from labelling experiments *in vivo* are illustrated in Fig. 11.2. More recent investigations at the enzymic level have largely confirmed the hypothetic steps which had been deduced from incorporation experiments. In particular, detailed knowledge of the central reaction of flavonoid biosynthesis, the condensation of the acyl residues from one molecule of 4-coumaroyl-CoA and three molecules of malonyl-CoA (Fig. 11.3), was obtained by several authors (see below). Extensive studies of the enzymology and regulation of flavone and flavonol glycoside

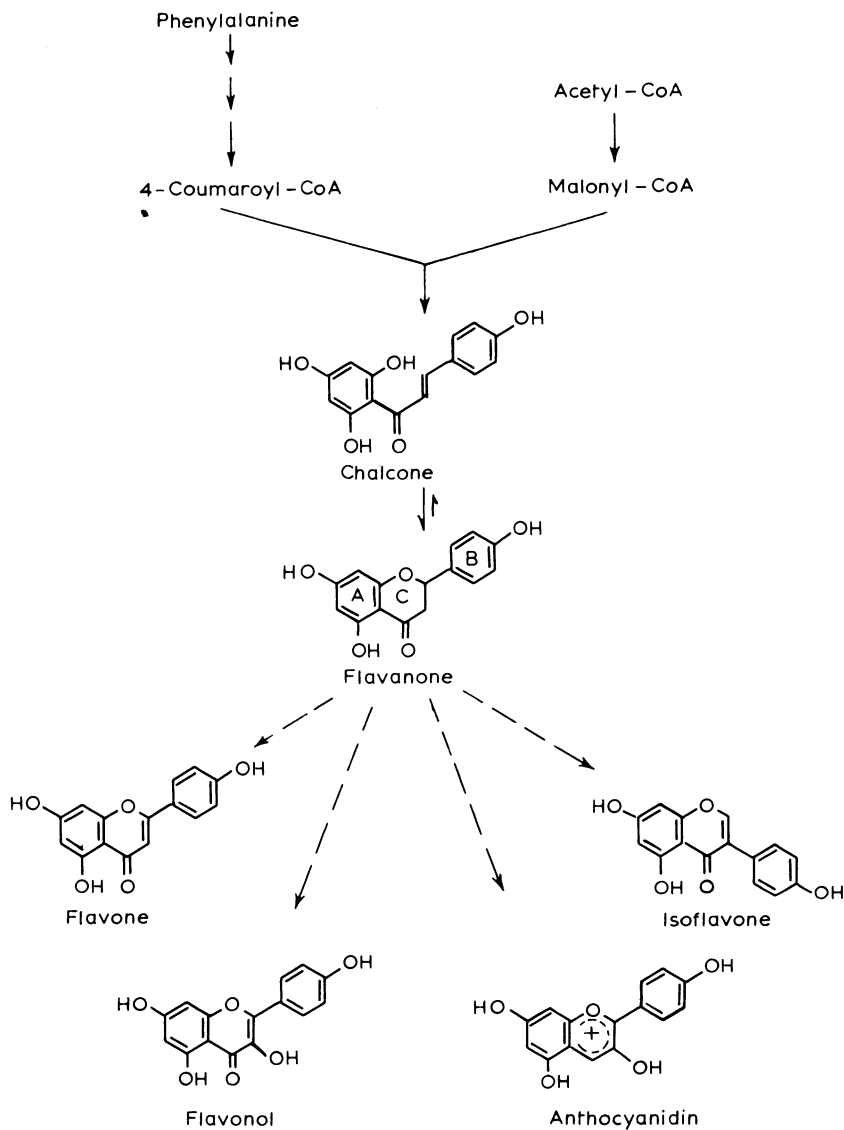


**Fig. 11.2** Scheme illustrating the position of the chalcone as the first common intermediate in the biosynthesis of all classes of flavonoid.

biosynthesis revealed many details of the reactions involved in the formation of these two important classes of flavonoid (Section 11.4). On the other hand, relatively little beyond the results of tracer studies is known about the synthesis of anthocyanins (Section 11.5), isoflavonoids (Section 11.6) and other flavonoids (Section 11.7).

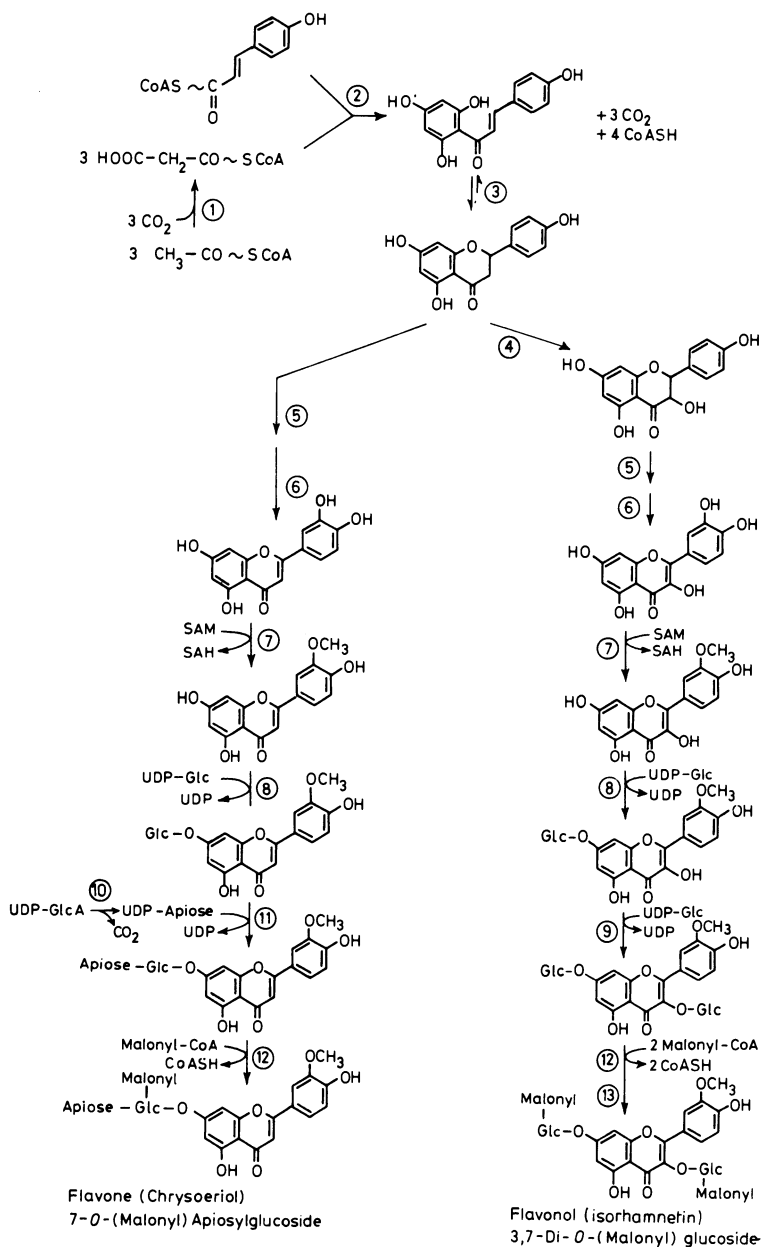


**Fig. 11.3** Scheme illustrating the sequence of reactions of the flavone and flavonol glycoside pathways. The enzymes marked by numbers are listed in Table 11.1. SAM, *S*-adenosyl-L-methionine; SAH, *S*-adenosyl-L-homocysteine.

## 11.4 CHALCONES, FLAVANONES, FLAVONES AND FLAVONOLS

The chalcone/flavanone isomers are the central intermediates in the synthesis of all flavonoids (Hahlbrock and Grisebach, 1975; Hahlbrock, 1981). Compelling evidence has now been presented that the chalcone is the immediate product of the synthase reaction (see below). In a second step, chalcone isomerase catalyses the stereospecific formation of the (–)(2*S*)-flavanone from the corresponding chalcone.

The frequent co-occurrence of chalcones, flavanones, flavones and flavonols suggests that their biosynthetic pathways are closely related. *In vivo*, chalcones with a phloroglucinol-type substitution in ring A are exclusive intermediates in the formation of 5, 7-dihydroxyflavonoids, while chalcones with a resorcinol-type substitution in ring A are selectively converted into 7-hydroxyflavonoids (cf. Hahlbrock and Grisebach, 1975). However, an enzyme catalysing the synthesis of a chalcone with a resorcinol structure in ring A has not been reported. Further, the actual mechanisms through which flavanones are converted into flavones, flavonols and other flavonoids are in most cases not well understood. Only a few studies with cell-free extracts have demonstrated the oxidation of flavanones to the corresponding flavones and the hydroxylation of flavanones in the 3 position to yield the corresponding dihydroflavonols. Several properties of the enzymes catalysing flavanone oxidation and 3-hydroxylation indicate that they are not peroxidases (Section 11.4.4). This is in contrast to earlier reports which demonstrated the conversion of 4,2',4'-trihydroxychalcone to the corresponding dihydroflavonol, flavonol and aurone either by plant extracts or by horseradish peroxidase (Wong, 1965; Wong and Wilson, 1972; Rathmell and Bendall, 1972).

The most frequently occurring substitution patterns of the aromatic ring B require further hydroxylation and methylation reactions at positions 3' and 5'. The existence of flavonoid-specific 3'-hydroxylases and 3'-*O*- and 4'-*O*-methyltransferases in several plants suggests that at least in some tissues the introduction of 3'-hydroxyl and 3'-*O*- and 4'-*O*-methyl groups into these compounds takes place after formation of the flavonoid ring structure (Sections 11.4.5 and 11.4.6).

The biosynthesis of flavones and flavonols has been studied most extensively in cultured parsley (*Petroselinum hortense*) cells. Leaves and seeds from parsley plants contain large amounts of flavone and flavonol glycosides with a phloroglucinol-type substitution in ring A. A high concentration of these compounds occurs also in irradiated suspension cultures of parsley cells derived from leaf petioles. More than 20 different flavonoid glycosides were found. These are derived from only three flavone and three flavonol aglycones, all of which have very similar substitution patterns (Kreuzaler and Hahlbrock, 1973). The chemical structures of the aglycones and their proposed biosynthetic relations are shown in Fig. 11.4. Except for the characteristic 3-hydroxyl group of the flavonols, the six aglycones differ only with respect to their substitution patterns in the 3' position.

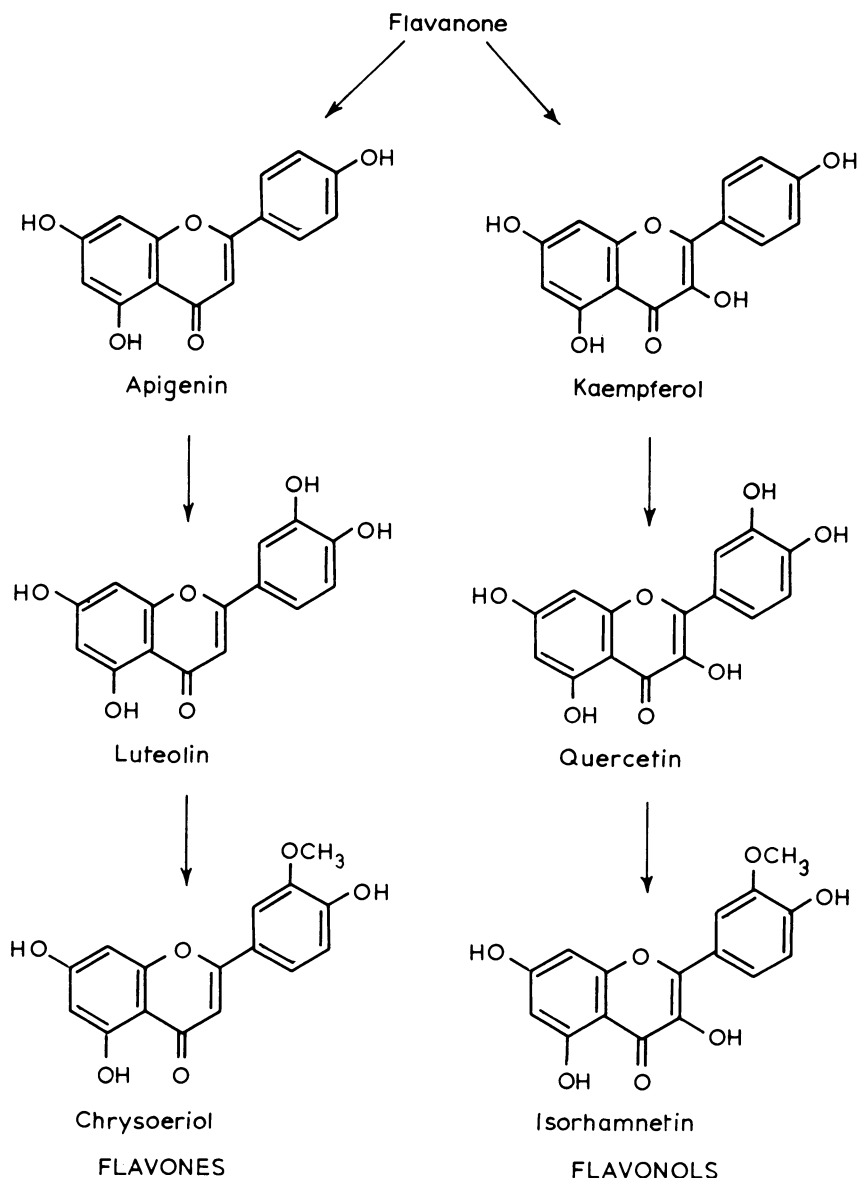


**Fig. 11.4** Proposed biosynthetic relations of flavones and flavonols isolated from parsley (*Petroselinum hortense*).

The flavonoid glycosides from parsley were isolated either as malonylated or as non-acylated flavone and flavonol 7-*O*-glucosides, flavone 7-*O*-apiosyl (1→2)-glucosides and flavonol 3,7-*O*-diglucosides (Kreuzaler and Hahlbrock, 1973). Examples are given in Fig. 11.3. The site of malonylation of flavone and flavonol glycosides is not known with certainty, but is deduced from indirect

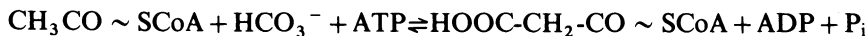


evidence to be the 6-*O*- position of the glucose moiety (Hahlbrock, 1972). Many tissues possess high esterase activity which might impair the isolation of acylated compounds. It is therefore possible that flavonoid glycosides occur more frequently in the acylated form than normally found in plant extracts.

The flavonoid glycoside pathway in parsley consists of about 13 enzymes which catalyse several consecutive steps of flavone and flavonol biosynthesis (Fig. 11.3). The first step is the conversion of acetyl-CoA to malonyl-CoA, which serves as substrate for three enzymes, chalcone synthase and two malonyltransferases. In the second step, the chalcone is formed from 4-coumaroyl-CoA (and possibly from other substituted cinnamoyl-CoA esters) and malonyl-CoA. The chalcone is isomerized to the corresponding flavanone, which is further converted into the basic flavone and flavonol structures. The subsequent steps are substitutions of ring B of the aglycones by hydroxylation and *O*-methylation. The final steps are glycosylation of the aglycones and acylation of the resulting glycosides. The enzymes involved in the individual steps, as elucidated with parsley cells, are listed in Table 11.1.

#### 11.4.1 Formation of malonyl-CoA

In parsley, malonyl-CoA is required for two types of reaction in flavonoid biosynthesis, the formation of the aromatic ring A and the malonylation of flavone and flavonol glycosides. Malonyl-CoA can be supplied in higher plants by the ATP-dependent carboxylation of acetyl-CoA catalysed by acetyl-CoA carboxylase:



Plant acetyl-CoA carboxylase has been studied in different tissues and is usually regarded as an enzyme of fatty acid biosynthesis (Heinstein and Stumpf, 1969; Kannangara and Stumpf, 1972; Brock and Kannangara, 1976; Nielsen *et al.*, 1979; Mohan and Kekwick, 1980; Stumpf, 1980). However, it was deduced from the regulation of acetyl-CoA carboxylase activity in irradiated parsley cells (Section 11.4.10) that this enzyme is also an integral member of the flavonoid glycoside pathway (Ebel and Hahlbrock, 1977).

The acetyl-CoA carboxylase which is involved in flavonoid biosynthesis in parsley has been purified from irradiated cells and characterized to some extent (Egin-Bühler *et al.*, 1980). The biotin-containing enzyme has a molecular weight of about 840 000 and is probably composed of four subunits of  $M_r = 210\,000$  each. Similar structural properties have been found in comparative studies for the enzyme of wheat germ (Egin-Bühler *et al.*, 1980). These results suggest that the three catalytic subsites of the two carboxylases from these phylogenetically divergent plants, the biotin-carboxylation site, the transcarboxylation site and the biotin-carrying site reside in the same enzyme subunit. This type of structural organization has been found also for animal acetyl-CoA carboxylases (Tanabe *et al.*, 1975; Mackall and Lane, 1977; Ahmad *et al.*, 1978) which catalyse the first

committed step in fatty acid biosynthesis. Parsley acetyl-CoA carboxylase catalyses the carboxylation of the CoA esters of acetate, propionate and butyrate at decreasing rates in this order and does not accept hexanoyl-CoA and methylcrotonoyl-CoA as substrates (Egin-Bühler and Ebel, unpublished). The apparent  $K_m$  values for the substrates of the carboxylation reaction are: acetyl-CoA, 0.15 mmol/l;  $\text{HCO}_3^-$ , 1.0 mmol/l;  $\text{MgATP}^{2-}$ , 0.07 mmol/l. Recent successful application of the affinity adsorbent avidin-monomer Sepharose 4B to the isolation of the parsley carboxylase substantially improves and simplifies the purification of this enzyme (Egin-Bühler and Ebel, unpublished).

#### 11.4.2 Formation of chalcone

The formation of a chalcone is the exceptional step in flavonoid biosynthesis which is both specific for this pathway and common to all flavonoids. The enzyme catalysing this step, chalcone synthase, can therefore be regarded as the key enzyme of flavonoid biosynthesis. The product of general phenylpropanoid metabolism, 4-coumaroyl-CoA, serves as one of two substrates for the synthase reaction. The overall reaction consists of three successive condensation steps with 'acetate units' derived from malonyl-CoA. The result is the elongation of the aliphatic side chain of 4-coumarate by six carbon atoms which then cyclize to give the aromatic ring A (Fig. 11.3). The putative formation of a poly- $\beta$ -ketoacyl intermediate according to the 'acetate rule' (Birch and Donovan, 1953; Lynen and Tada, 1961) was initially postulated on the basis of tracer experiments *in vivo* (Grisebach, 1959).

Chalcone synthesis *in vitro* was first demonstrated with a crude extract from irradiated parsley cells which contained all enzymes of the flavonoid glycoside pathway (Kreuzaler and Hahlbrock, 1972). Owing to the presence of chalcone isomerase in the extract, the synthase reaction led to the formation of the flavanone, naringenin. More recently, however, it was shown that the immediate product is the corresponding chalcone and not the flavanone (Heller and Hahlbrock, 1980; Light and Hahlbrock, 1980). Essentially the same result was obtained by Sütfield and Wiermann (1980a, 1981) working with anthers from tulip (*Tulipa* cv. 'Apeldoorn') and petals from *Cosmos sulphureus*. Further support for the notion that the enzyme is a chalcone synthase – and not a flavanone synthase, as presumed earlier (Kreuzaler and Hahlbrock, 1975a) – comes from genetic studies on the control of chalcone isomerase activity (see below).

Chalcone synthase has been purified from cell cultures of parsley (Kreuzaler and Hahlbrock, 1975a; Kreuzaler *et al.*, 1979) and *Haplopappus gracilis* (Saleh *et al.*, 1978) and from parts of tulip and *Cosmos* plants (Sütfield and Wiermann, 1981). The enzymes from parsley and tulip have apparent molecular weights in the range from 55 000 to 80 000 (Kreuzaler *et al.*, 1979; Sütfield *et al.*, 1978). Chalcone synthase has no cofactor requirements. Substrates are malonyl-CoA and the CoA ester of a substituted cinnamic acid. 4-Coumaroyl-CoA is in all

known cases more efficient than caffeoyl-CoA and feruloyl-CoA. In tulip anthers, caffeoyl-CoA and feruloyl-CoA, in addition to 4-coumaroyl-CoA, were proposed to function as substrates of chalcone synthase *in vivo* (Sütfeld *et al.*, 1978). The substitution pattern of the starter molecule(s) for chalcone synthesis in parsley is not known for certain, but the possible occurrence of a flavonoid-specific 3'-hydroxylase and the unequivocal demonstration of a 3'-O-methyltransferase might rule out caffeoyl-CoA and feruloyl-CoA.

The sequence of reactions shown in Fig. 11.5 was deduced from the occurrence of several side products of the chalcone synthase reaction with the partially purified enzymes from parsley and *Haplopappus* (Kreuzaler and Hahlbrock, 1975b; Hrazdina *et al.*, 1976; Saleh *et al.*, 1978). Under certain assay conditions, chalcone synthase catalyses only one or two (instead of three) condensation steps. This leads to the formation of short-chain release products containing either one 'acetate unit' (benzalacetones or dihydropyrone) or two 'acetate units' (styrylpyrones). The respective release products were formed with all three substrates tested *in vitro*, 4-coumaroyl-CoA, caffeoyl-CoA and feruloyl-CoA with both the parsley and *Haplopappus* enzymes (Hrazdina *et al.*, 1976; Saleh *et al.*, 1978). The formation of release products can be greatly reduced by using proper assay conditions (Schröder *et al.*, 1979a). No such products were observed with the enzyme from tulip anthers (Sütfeld *et al.*, 1978).

Other artificial side reactions in the chalcone synthase assay, which have been very useful for the elucidation of the reaction mechanism, are CO<sub>2</sub> exchange and decarboxylation of malonyl-CoA (Kreuzaler *et al.*, 1978). Their occurrence can be explained by assuming the intermediate formation of an acetyl-CoA carbanion from malonyl-CoA during the condensation reaction (Fig. 11.6). Both these side reactions are unlikely to occur *in vivo*. The apparent  $K_m$  values for malonyl-CoA in the side reactions are two to three orders of magnitude higher, and the pH optimum is much lower, than the respective values for malonyl-CoA in the complete chalcone synthase reaction (Heller *et al.*, 1980). With chalcone synthase preparations from parsley and tulip, apparent  $K_m$  values for all possible substrates leading to chalcone formation at appreciable rates *in vitro* were around 2  $\mu\text{mol/l}$  (Hrazdina *et al.*, 1976; Sütfeld *et al.*, 1978), or somewhat higher (18  $\mu\text{mol/l}$ ) in the case of malonyl-CoA with the parsley enzyme (Heller *et al.*, 1980), indicating a high affinity of these enzymes for their substrates in the complete synthase reaction. Both enzymes are strongly inhibited by the reaction products, chalcone (or flavanone) and coenzyme A.

The activity of chalcone synthase has been related to the biosynthesis of all major classes of flavonoids in a variety of plants: flavones and flavonols in parsley (Hahlbrock *et al.*, 1976), chalcones and flavonols in tulip (Herdt *et al.*, 1978; Sütfeld *et al.*, 1978), anthocyanins in *Haplopappus gracilis* (Saleh *et al.*, 1978), in *Hippeastrum* (Hrazdina *et al.*, 1978) and in red cabbage (*Brassica oleracea*) (Hrazdina and Creasy, 1979), isoflavonoids in soybean (*Glycine max*) (Zähringer *et al.*, 1978) and C-glycosylflavones in oat (*Avena sativa*) (Fuisting and Weissenböck, 1980).

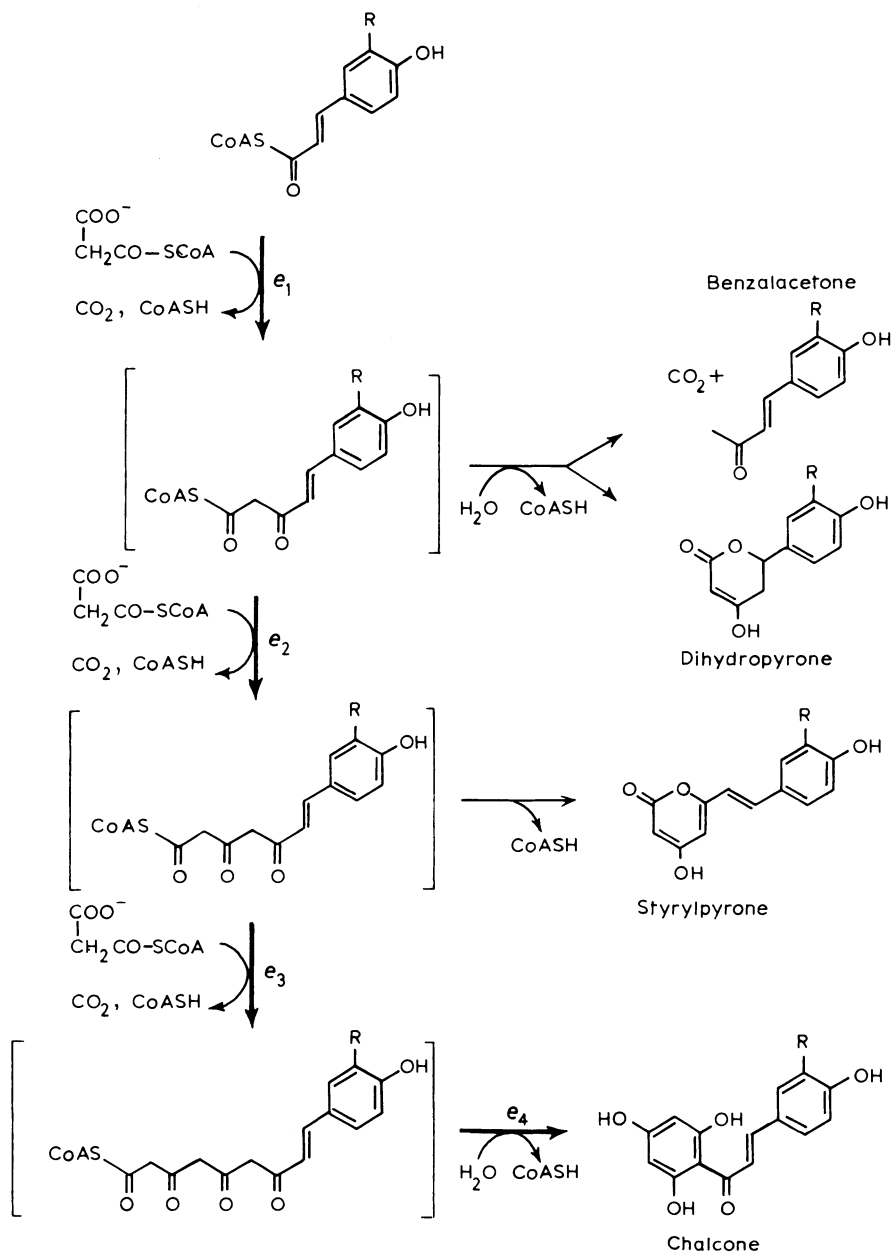


**Fig. 11.5** Scheme illustrating the proposed mechanism of action of chalcone synthase from parsley. Broad arrows (reactions  $e_1$ – $e_4$ ): major reactions *in vivo*, other arrows: side reactions *in vitro*. R = H or OH (after Hahlbrock, 1981).

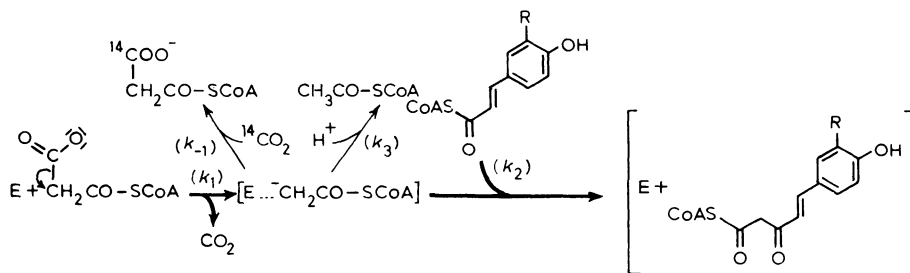


**Fig. 11.6** Proposed mechanism of reaction  $e_1$  (Fig. 11.5) of chalcone synthase from parsley. Broad arrows (rate constants  $k_1$  and  $k_2$ ): putative reactions *in vivo*, other arrows (rate constants  $k_{-1}$  and  $k_3$ ): side reactions *in vitro*. R = H or OH, E = chalcone synthase (after Hahlbrock, 1981).

### 11.4.3 Isomerization of chalcone

From the results described above it is clear that the product of the chalcone synthase reaction is the chalcone and not the isomeric flavanone. Thus, the function of chalcone isomerase appears to be the provision of the flavanone as the substrate for conversion into other flavonoids (Fig. 11.2).

Chalcone isomerase was the first isolated enzyme of flavonoid metabolism (Moustafa and Wong, 1967). The enzyme has been partially purified from a variety of flavonoid-producing plants and plant tissues and extensively studied (cf. Hahlbrock and Grisebach, 1975). In summary, the enzyme shows the following characteristics. It catalyses the formation of the 6-membered heterocyclic ring C of flavanones from the corresponding chalcones and has no cofactor requirements. The kinetics of isomerization of 2',4,4'-trihydroxychalcone (isoliquiritigenin) to 7,4'-dihydroxyflavanone (liquiritigenin) by the soybean (*Glycine max*) enzyme have been examined and have indicated that at pH 7.6 the reaction was reversible with an equilibrium constant of 37 in favour of the flavanone (Boland and Wong, 1975). The product was shown to have the (-) (2S) configuration (Moustafa and Wong, 1967). The stereochemistry of the isomerase reaction at position C-3 was elucidated by NMR studies with deuterated flavanones (Hahlbrock *et al.*, 1970a). When [3-<sup>2</sup>H]isoliquiritigenin was used as substrate for either one of two chalcone isomerase isoenzymes from mung bean (*Phaseolus aureus*) seedlings, deuterium was located preferentially in the equatorial position at C-3 of liquiritigenin. Conversely, when the enzymic cyclization was carried out in deuterium oxide with unlabelled chalcone, deuterium was preferentially introduced in the axial position at C-3 of the flavanone.

Chalcone isomerases from seedlings or leaves of mung bean, chick pea (*Cicer arietinum*), parsley or *Datisca cannabina* have been separated by polyacrylamide gel electrophoresis into a number of activities as measured by the disappearance of the chalcone in a spectrophotometric assay (Hahlbrock *et al.*, 1970b;

Grambow and Grisebach, 1971). Since KCN was not added to avoid possible interference of peroxidase with the assay (Boland and Wong, 1975) and the reaction products were not unequivocally identified, it is not known whether all of these different enzyme activities are true isoenzymes of chalcone isomerase. In general, the substitution patterns of the preferred substrates correspond to those of the flavonoids found in the plant tissue from which the enzyme was isolated. For example, chalcone isomerase from parsley is specific for 4,2',4'6'-tetrahydroxychalcone as substrate, in agreement with the exclusive occurrence of 5,7-dihydroxyflavonoids in this plant (Hahlbrock *et al.*, 1970b). Chalcone glucosides will not serve as substrates of isomerases, in all cases so far studied.

A molecular weight of 15 600 has been determined for the enzyme from soybean seeds (Boland and Wong, 1975). Effects of iodoacetamide and sodium tetrathionate on the soybean enzyme, and a strong dependence of the activity on pH, were interpreted as indicating that a sulfhydryl group is not involved in the reaction mechanism and that the catalytic site is probably an imidazole group which assists in ring closure at C-2 of the chalcone (Boland and Wong, 1975, 1979).

Kuhn *et al.* (1978) investigated the genetic control of chalcone isomerase activity in 18 lines of *Callistephus chinensis*. The absence of the enzyme from four mutants (recessive genotypes) was correlated with an abnormally high level of chalcone glucoside accumulation. In genotypes with the wild-type allele, anthocyanin glycosides were formed without intermediate chalcone accumulation. Similar results have been found in studies with different genotypes of *Dianthus caryophyllus* (Forkmann and Dangelmayr, 1980) and *Petunia hybrida* (Forkmann and Kuhn, 1979). The importance of chalcone isomerase in the formation of various basic flavonoid structures is also strongly indicated by the regulatory behaviour of chalcone isomerase activity during the light-induced flavonoid glycoside formation in parsley cells (Section 11.4.10) and during developmentally regulated phenylpropanoid metabolism in *Tulipa* anthers (Wiermann, 1972, 1979). When chalcone isomerase activity was measured at different stages of pollen development in *Tulipa* anthers, highest enzyme activity occurred at a period when the concentration of chalcones in the tissue decreased rapidly and that of flavonols increased.

#### 11.4.4 Modifications at ring C

The flavanone, naringenin, is the putative substrate for flavone and dihydroflavonol formation in flavone and flavonol glycoside biosynthesis (Fig. 11.3). Studies by Sutter *et al.* (1975) with protein extracts from primary leaves of parsley which catalysed the oxidation of naringenin to the corresponding flavone, apigenin, in the presence of  $\text{Fe}^{2+}$  ions and (an) other heat-stable non-proteinaceous cofactor(s) have now been extended to parsley cell cultures as source of the enzyme. Britsch *et al.* (1981) demonstrated that the enzyme from parsley cells required 2-oxoglutarate,  $\text{Fe}^{2+}$  and possibly ascorbate as cofactors.

The same protein extract, in the presence of these cofactors, also catalysed the 3-hydroxylation of naringenin to the dihydroflavonol, dihydrokaempferol and the oxidation of dihydrokaempferol to kaempferol. The proposed sequence of reactions which would be in agreement with the experimental data thus far obtained is shown in Fig. 11.7. The number of enzymes involved in the formation of apigenin and kaempferol and further details of these complex reactions are under investigation. According to the cofactor requirement, the soluble enzyme(s) belong(s) to the class of 2-oxoglutarate-dependent dioxygenases (Abbott and Udenfriend, 1974).

In contrast to the studies with the enzyme from parsley cells, oxidation of flavanones to flavones in flower extracts from *Antirrhinum majus* was catalysed by an enzyme activity in the microsomal fraction which required NADPH as co-substrate (Stotz and Forkmann, 1981).

3-Hydroxylation of the flavanone intermediate is also an obligatory step in anthocyanin biosynthesis (Grisebach, 1979). Formation of dihydrokaempferol from naringenin was found with dimethyl sulphoxide (DMSO)-permeabilized cells of *Haplopappus gracilis* cell cultures which produced cyanidin 3-*O*-glucoside in response to irradiation with UV light (Fritsch and Grisebach, 1975). Recent results have proved that flowers of *Matthiola incana* and *Antirrhinum majus* are valuable systems for studies of 3-hydroxylation in relation to anthocyanin biosynthesis (Forkmann *et al.*, 1980; Forkmann and Stotz, 1981). Enzyme preparations from flowers of defined genotypes of both plants contain 3-hydroxylase activity which catalyses the formation of dihydrokaempferol and dihydroquercetin from naringenin and eriodictyol respectively. Again, 2-oxoglutarate,  $\text{Fe}^{2+}$  and ascorbate are required as cofactors. The gene controlling 3-hydroxylation in *M. incana* is not yet known, but in *Antirrhinum majus* the gene *inc* seems to control the conversion of flavanones into dihydroflavonols (Harrison and Stickland, 1974). Investigations of different genotypes of *A. majus* demonstrate a correlation between a block of the anthocyanin pathway by recessive alleles of the gene *inc* and the absence of 3-hydroxylase activity (Forkmann and Stotz, 1981).

#### 11.4.5 Hydroxylation of ring B

The most frequently occurring structural modifications of flavonoid aglycones are hydroxylation and subsequent methylation in the 3' and 5' positions of ring B. The synthesis of 3'-hydroxynaringenin (eriodictyol) from caffeoyl-CoA can be catalysed under certain assay conditions *in vitro* by chalcone synthase. If this compound were synthesized in sufficient amounts *in vivo* and accepted as substrate for flavone and flavonol formation, the 3'-hydroxyl group would not need to be introduced at a later stage. However, investigations with cell-free extracts from cell cultures of *H. gracilis* and parsley and flowers of *M. incana* and *A. majus* demonstrated the presence of a 3'-hydroxylase in microsomal fractions which required NADPH as a cofactor (Fritsch and Grisebach, 1975; Forkmann

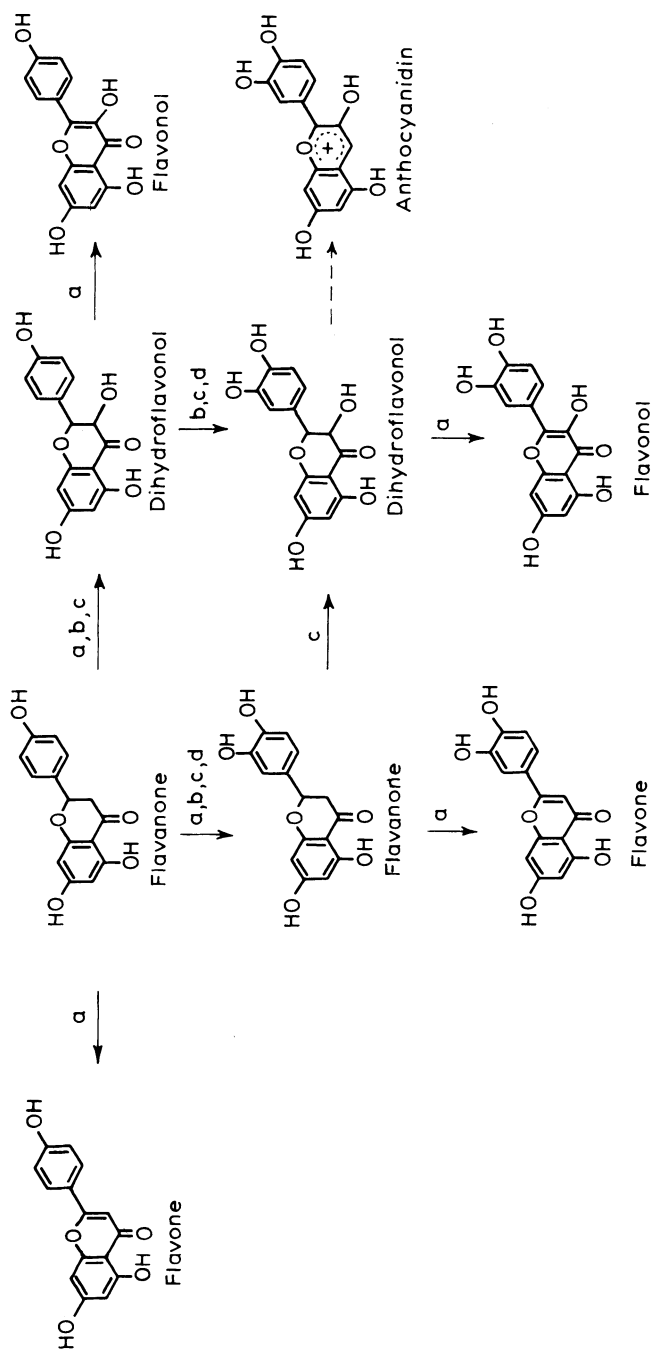


**Fig. 11.7** Conversion by 3-hydroxylation and oxidation of naringenin to various substituted flavones, dihydroflavonols, flavonols and anthocyanidins by cell-free extracts from *Petroselinum hortense* cell cultures (a), *Haploappus gracilis* cell cultures (b), flowers of *Matthiola incana* (c) and flowers of *Antirrhinum majus* (d).



*et al.*, 1980; Forkmann and Stotz, 1981; Britsch *et al.*, 1981). It can be assumed that these enzymes are haem-containing mono-oxygenases (Ullrich and Duppel, 1975), like cinnamate 4-hydroxylase (Section 11.2). In extracts from *H. gracilis* and *M. incana*, 3'-hydroxylation yielded eriodictyol and dihydroquercetin from naringenin and dihydrokaempferol respectively (Fig. 11.7). A strict correlation between 3'-hydroxylase activity of *M. incana* and the wild-type allele  $b^+$  controlling 3'-hydroxylation in this plant was found. Basically similar results were obtained from experiments with flower extracts of *A. majus*. Chemogenetic and enzymic studies on different genotypes suggest that the 3'-hydroxyl group of flavonoids in *A. majus* is introduced at the stage of a  $C_{15}$  intermediate. 3'-Hydroxylation in microsomal fractions from *A. majus* was readily demonstrated with naringenin as substrate, but the formation of dihydroquercetin from dihydrokaempferol could not be shown.

#### 11.4.6 Methylation

Methylation of 3',4'-dihydroxy-substituted flavonoids has been extensively studied in a number of plants (Poulton, 1981). Methylation in the 3' position of luteolin and quercetin is catalysed by a specific *S*-adenosyl-L-methionine: flavonoid 3'-*O*-methyltransferase from parsley cell cultures (Ebel *et al.*, 1972; Ebel and Hahlbrock, 1977). Luteolin and its 7-*O*-glucoside served as substrates with the lowest  $K_m$  and highest  $V/K_m$  values (Table 11.3). The enzyme methylated eriodictyol at a low rate and showed no activity towards mono-phenols such as 4-coumarate or apigenin. Under appropriate conditions (e.g. pH 9.3), the enzyme also methylated caffeate, albeit with a  $K_m$  which was about 35-fold higher and a  $V/K_m$  which was about 20-fold lower than the respective values for luteolin. This low specificity of the methyltransferase for caffeate, together

**Table 11.3** Substrate specificities of parsley (*Petroselinum hortense*) and soybean (*Glycine max*) flavonoid *O*-methyltransferases

| Source of enzyme                   | <i>Petroselinum hortense</i> *  |                       |                           | <i>Glycine max</i> †            |                       |                           |
|------------------------------------|---------------------------------|-----------------------|---------------------------|---------------------------------|-----------------------|---------------------------|
|                                    | $K_m$<br>( $\times 10^6$ mol/l) | Relative<br>$V_{max}$ | Relative<br>$V_{max}/K_m$ | $K_m$<br>( $\times 10^6$ mol/l) | Relative<br>$V_{max}$ | Relative<br>$V_{max}/K_m$ |
| Eriodictyol                        | 1200                            | 17                    | 0.01                      | 75                              | 35                    | 0.47                      |
| Luteolin                           | 46                              | 100                   | 2.2                       | 16<br>(16.7)                    | 100<br>(138)          | 6.2<br>(8.3)              |
| Luteolin<br>7- <i>O</i> -glucoside | 31                              | 114                   | 3.7                       | 28                              | 40                    | 1.4                       |
| Quercetin                          | —‡                              | —‡                    | —‡                        | 35                              | 210                   | 6.0                       |
| Caffeate                           | 1600                            | 168                   | 0.11                      | (770)                           | (92)                  | (0.12)                    |

\* Rates measured at pH 9.3 (Ebel *et al.*, 1972).

† Rates measured at pH 7.8 or pH 8.7 (in parenthesis) (Poulton *et al.*, 1977).

‡ Not measured.

with the fact that 3-methylcaffeoyl-CoA (feruloyl-CoA) is a poor substrate of chalcone synthase from parsley (Section 11.4.2), indicates that methylation of flavonoids in this plant occurs predominantly or exclusively after completion of the C<sub>15</sub> skeleton. In parsley, the same methyltransferase is probably associated with both the flavone and flavonol glycoside pathways (Ebel and Hahlbrock, 1977). In general, flavonoid *O*-methyltransferases differ considerably from caffeate *O*-methyltransferases with respect to both substrate specificity and various other properties (Table 11.4). A flavonoid *O*-methyltransferase which was remarkably similar to the enzyme from parsley has been isolated from soybean (*Glycine max*) cell cultures and separated from caffeate *O*-methyltransferase (Poulton *et al.*, 1976, 1977). The flavonoid-specific enzyme closely resembled parsley flavonoid *O*-methyltransferase in several respects. *Ortho*-dihydroxy-substituted phenols were methylated specifically at the *meta* position. A pronounced preference was shown towards flavonoid substrates, as demonstrated by their low  $K_m$  and high  $V/K_m$  values (Table 11.3). Flavones and flavonols were methylated more efficiently than flavanones and dihydroflavonols. The substrate specificities indicate that in soybean, as in parsley, methyl groups are introduced into flavonoid compounds after formation of the flavonoid ring structure.

The question of whether methylation precedes glucosylation in the biosynthesis of methylated flavonoid glycosides cannot be answered unambiguously. As with the parsley 3'-*O*-methyltransferase, both luteolin and its 7-*O*-glucoside were efficient substrates of the soybean 3'-*O*-methyl transferase. On the other hand, quercetin 3-*O*-glucoside and 3-*O*-rutinoside (rutin) were methylated at lower rates than quercetin. These results suggest that, at least in the biosynthesis of methylated flavonol 3-*O*-glucosides, methylation precedes glucosylation (Poulton *et al.*, 1977). Some other properties of flavonoid *O*-methyltransferases are listed in Table 11.4.

During pollen development in *Tulipa* anthers, these organs successively accumulate simple cinnamic acid derivatives, chalcones, flavonols and finally anthocyanins (Wiermann, 1970; Quast and Wiermann, 1973). Methylated derivatives, such as ferulate and 3'-*O*-methylquercetin (isorhamnetin), constitute a considerable portion of the phenylpropanoids produced. Two distinct *S*-adenosyl-L-methionine:*ortho*-dihydroxyphenol *meta*-*O*-methyltransferases were detected in protein extracts of tulip anthers and could be partially separated upon protein fractionation (Sütfeld and Wiermann, 1978). The properties of the two enzymes correlated closely with those of caffeate and flavonoid *O*-methyltransferases from soybean cell cultures. Analysis of the distribution of these enzymes between the pollen and tapetum fractions of the anthers revealed that both methyltransferases were predominantly present in the tapetum fraction (Herdt *et al.*, 1978). However, the activity changes of the two enzymes during various stages of pollen development were remarkably different (Sütfeld and Wiermann, 1980b). While a close correlation between high activity of caffeate *O*-methyltransferase and the accumulation of large amounts of ferulic acid

derivatives was observed, no such relationship between the level of flavonoid *O*-methyltransferase activity and the formation of methylated flavonol glycosides was found. Since chalcone synthase from tulip anthers possesses a relatively broad substrate specificity *in vitro*, utilizing 4-coumaroyl-CoA, caffeoyl-CoA and feruloyl-CoA with similar efficiencies (see above), it seems possible that in tulip anthers methylation occurs, at least in part, at the C<sub>9</sub> stage (Sütfeld and Wiermann, 1980b).

Three distinct *ortho*-dihydroxyphenol *O*-methyltransferases were identified in leaves of *Nicotiana tabacum* var. Samsun NN (Legrand *et al.*, 1976a,b, 1978). They could be separated by ion-exchange chromatography on DEAE-cellulose and distinguished both by differences in specificity towards a variety of *ortho*-diphenolic substrates and by the degree of enhancement of their activities upon virus infection of tobacco leaves. Caffeate was most efficiently methylated by transferase I, and quercetin, the major *ortho*-dihydroxyphenol of tobacco leaves, by transferases II and III. Rutin (quercetin 3-*O*-rutinoside) was not a substrate for either one of the enzymes, again suggesting that methylation precedes glycosylation.

Although flavonoids *O*-methylated in ring A frequently occur in nature (Harborne *et al.*, 1975), *in vitro* *O*-methylation of ring A is not well documented. Citrus tissues, especially the fruit flavedo, produce a complement of polymethylated flavones characteristic of the genus (Swift, 1967; Kefford and Chandler, 1970). Recently, investigations of a stepwise methylation of quercetin and other flavonoids by cell-free extracts of peel, root, or callus tissues of calamondin (*Citrus mitis*) have been reported (Brunet *et al.*, 1978; Brunet and Ibrahim, 1980). Product identification by thin-layer chromatography indicated that methylation occurred at almost all hydroxyl groups of the various substrates tested. The authors concluded that citrus tissues contain several transferases methylating hydroxyl groups at different positions of the A, B and C ring of the flavonoid skeleton.

Texasin (6,7-dihydroxy-4'-methoxyisoflavone) was efficiently methylated by the flavonoid *O*-methyltransferase from soybean cell cultures, but the exact position of methylation remains unknown (Poulton *et al.*, 1977). Methylation of quercetin and luteolin at both 7 and 3' positions has been observed with a partially purified methyltransferase of tobacco (*Nicotiana tabacum*) cell cultures (Tsang and Ibrahim, 1979a,b). Two forms of the enzyme were resolved by DEAE-cellulose chromatography. One enzyme catalysed the methylation of quercetin almost exclusively at the 7 position to yield rhamnetin, whereas the other methylated caffeate predominantly at the 3 position to give ferulate. It has not been reported whether one of the transferases isolated from tobacco leaves (Legrand *et al.*, 1978) is also capable of methylating quercetin or luteolin in the 7 position. One important aspect of further investigations should concern the question of whether A-ring methylation is catalysed by transferase activities with broad substrate specificity or by distinct enzymes with high preference for specific hydroxyl groups.

Table 11.4 Methyltransferases from various sources

| Source of enzyme                           | Number of transferases reported | Basis for distinction between enzymes                 | Substrate specificity: compounds converted and position of methylation (in parenthesis)                                                                              | pH optimum  | Effects of $Mg^{2+}$ ions and EDTA            | Remarks                                                                      | Reference                           |
|--------------------------------------------|---------------------------------|-------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|-----------------------------------------------|------------------------------------------------------------------------------|-------------------------------------|
| <i>Cicer arietinum</i> cell cultures       | 1                               |                                                       | Daidzein and genistein (4' position)                                                                                                                                 | 9.0         | None                                          | Inhibition by SAH*                                                           | Wengenmayer <i>et al.</i> (1974)    |
| <i>Glycine max</i> cell cultures           | 2                               | Sephadex G-200 chromatography, stability upon storage |                                                                                                                                                                      |             |                                               |                                                                              |                                     |
| 1. Caffeate 3-O-methyltransferase          |                                 |                                                       | 1. Caffeate, 5-hydroxyferulate, 3,4,5-trihydroxycinnamate (3 position)                                                                                               | 6.5-7.0     | None                                          | Inhibition by SAH, luteolin, and quercetin                                   | Poulton <i>et al.</i> (1976)        |
| 2. Flavonoid 3'-O-methyltransferase        |                                 |                                                       | 2. Caffeate, 5-hydroxyferulate (3 position), luteolin and 7-O-glucoside, eriodictiol, quercetin (3' position)                                                        | 8.6-8.9     | Stimulation by $Mg^{2+}$ , inhibition by EDTA | Inhibition by SAH                                                            | Poulton <i>et al.</i> (1977)        |
| <i>Nicotiana tabacum</i> leaves            | 3                               | DEAE-cellulose chromatography                         | Caffeate, 5-hydroxyferulate (3 position), protocatechuic acid (3 and 4 positions), esculetin (6,7-dihydroxycoumarin, 6 and 7 positions), quercetin (3' position)     | 7.4         | ?                                             | Different specificities of the three transferases toward phenolic substrates | Legrand <i>et al.</i> (1976b, 1978) |
| cell cultures                              | 2                               | DEAE-cellulose chromatography                         | Caffeate, 5-hydroxyferulate, 3,4,5-trihydroxycinnamate (3 and 4 positions), daphnetin and esculetin (6 and 7 positions), luteolin and quercetin (7 and 3' positions) | 7.3 and 8.3 | None                                          |                                                                              | Tsang and Ibrahim (1979a,b)         |
| <i>Petroselinum hortense</i> cell cultures | 1                               |                                                       | Caffeate (3 position) luteolin and 7-O-glucoside, eriodictiol, quercetin (3' position)                                                                               | 9.7         | Stimulation by $Mg^{2+}$ , inhibition by EDTA |                                                                              | Ebel <i>et al.</i> (1972)           |

| <i>Tulipa</i><br>anthers                         | 2 | Sephadex G-200<br>chromatography,<br>isoelectric focusing,<br>disc-gel electro-<br>phoresis |                                                 | Sütfeld and Wiermann<br>(1978)                                      |
|--------------------------------------------------|---|---------------------------------------------------------------------------------------------|-------------------------------------------------|---------------------------------------------------------------------|
| 1. Caffeate 3- <i>O</i> -<br>methyltransferase   |   |                                                                                             | 1. Caffeate, 5-hydroxyferulate<br>(3' position) | None<br>Inhibition by SAH                                           |
| 2. Flavonoid 3'- <i>O</i> -<br>methyltransferase |   |                                                                                             | 2. Luteolin, quercetin<br>(3' position)         | Mg <sup>2+</sup> required<br>for full activity<br>Inhibition by SAH |

\* *S*-Adenosyl-L-homocysteine.  
† Data not reported.

#### 11.4.7 Glycosylation

It is most likely that glycosylation occurs subsequent to all other substitutions and modifications of the flavonoid ring structure (Hahlbrock and Grisebach, 1975). The various 7-*O*-glycosides and 3,7-di-*O*-glycosides in parsley are formed by sequential glycosylation steps as indicated in Fig. 11.3. The first reaction of this sequence (No. 8) is identical for flavones and flavonols and is catalysed by UDP-glucose:flavone/flavonol 7-*O*-glucosyltransferase (Table 11.5). The enzyme has a broad specificity for several flavone, flavonol and flavanone aglycones, but does not glucosylate various other phenolic compounds, including isoflavones and cyanidin (Sutter *et al.*, 1972). Quercetin 3-*O*-glucoside is not further glucosylated in the 7-*O*-position (Sutter and Grisebach, 1973). This suggests that the reaction sequence for the 7-*O*- and 3-*O*-glucosylation of flavonols in parsley is as indicated in Fig. 11.3. UDP-glucose or TDP-glucose can serve as glucosyl donors *in vitro*.

The second glucosylation of flavonols is catalysed by UDP-glucose:flavonol 3-*O*-glucosyltransferase (Fig. 11.3, No. 9) which was completely separated from 7-*O*-glucosyltransferase on the basis of different net charges of the two enzymes (Sutter and Grisebach, 1973). Flavonol 3-*O*-glucosyltransferase exhibits a strict positional specificity and catalyses the 3-*O*-glucosylation of a number of flavonols, including quercetin 7-*O*-glucoside, *in vitro* (Table 11.5). It is not known whether both aglycones and 7-*O*-glucosides are substrates *in vivo*, but this is likely because, at least in parsley, 3-*O*-glucosides do not serve as substrates for 7-*O*-glucosylation (see above). Glucosyl transfer from UDP-glucose to the 3-*O* position of kaempferol or quercetin was freely reversible in the presence of 3-*O*-glucosyltransferase (Sutter and Grisebach, 1975). It is not known at present whether or not this interesting feature is of significance *in vivo*.

Further glycosylation of the sugar moiety of flavonoid glucosides occurs in the biosynthesis of apiosylglucosides (Fig. 11.3). The branched-chain sugar, apiose, is found in parsley only in flavone glycosides and not in other glycosides (Sandermann, 1969). The synthesis of the sugar nucleotide, UDP-apiose (reaction No. 10), and the apiosyltransfer from UDP-apiose (No. 11) are therefore specifically related to flavonoid biosynthesis in this plant. UDP-apiose synthase (complete name: UDP-D-apiose/UDP-D-xylose synthase) catalyses the NAD<sup>+</sup>-dependent conversion of UDP-D-glucuronate to give two products *in vitro*, UDP-apiose and UDP-xylose. The significance of UDP-xylose synthesis is not known, but might be an artificial side reaction occurring only under the assay conditions *in vitro*. The ratio of UDP-apiose/UDP-xylose formation remained constant during a 1400-fold purification of the synthase from irradiated parsley cells (Matern and Grisebach, 1977). Gel electrophoresis under denaturing conditions and sedimentation-equilibrium measurements showed that the highly purified enzyme was composed of two proteins with molecular weights of about 65 000 and 86 000 which were present in approximately equimolar amounts. Each protein contained two apparently identical subunits. Only the larger protein showed synthase activity. Studies on the reaction mechanism indicated

that an *L-threo*-4-pentosulose was an intermediate in the synthesis of both sugar nucleotides. The reaction appears not to involve an intermediate bound to the enzyme as a Schiff base (Baron and Grisebach, 1973; Matern and Grisebach, 1977) in contrast to the conversion of fructose 1,6-bisphosphate by class I aldolase (Horecker *et al.*, 1972).

Transfer of the apiosyl residue from UDP-apiose to flavone 7-*O*-glucosides is catalysed in parsley by UDP-D-apiose:flavone 7-*O*-glucoside 2''-*O*-apiosyltransferase (Fig. 11.3, No. 11). The reaction products are flavone 7-*O*-[ $\beta$ -D] apiofuranosyl(1 $\rightarrow$ 2)[ $\beta$ -D]glucosides, such as apiin (apigenin 7-*O*-apiosylglucoside) or graveobioside B (chrysoeriol 7-*O*-apiosylglucoside) (Ortmann *et al.*, 1972). The enzyme is specific for UDP-apiose as glycosyl donor and acts on 7-*O*-glucosides of a variety of flavones, flavanones and isoflavones (Table 11.5), but does not accept flavonol 7-*O*- or 3-*O*-glucosides, flavonoid aglycones or free glucose as substrates. The substrate specificity of apiosyltransferase *in vitro* is compatible with the observation that only flavone, but no flavonol apiosylglucosides, occur in parsley.

Several enzymic reactions in crude extracts catalysing the formation of flavonol glycosides from the corresponding aglycones and sugar nucleoside diphosphates have been reported (for an earlier review, see Hahlbrock and Grisebach, 1975). Here, only the more recent work will be discussed. UDP-glucose:flavonol and/or UDP-glucose:anthocyanidin 3-*O*-glucosyltransferases have been demonstrated in protein extracts from various sources (Table 11.5). In those cases where flavonols and anthocyanidins were tested, most of the 3-*O*-glucosyltransferase activities glucosylated both types of substrate, albeit with different efficiencies. The 3-*O*-glucosyltransferases had a pronounced positional specificity. In the cases investigated, glucosylation could not be detected at the 5 position (Kamsteeg *et al.*, 1978a) or 7 position (Saleh *et al.*, 1976a,b). Anthocyanidin 3-*O*-glucosyltransferase from *Silene dioica* specifically glucosylated anthocyanidins, but did not convert flavonols into the respective 3-*O*-glucosides (Kamsteeg *et al.*, 1978a). It is not known whether 3-*O*-glucosylation of both flavonols and anthocyanidins by other enzyme preparations reflects a broader substrate specificity or the presence of more than one enzyme exhibiting different specificities. All 3-*O*-glucosyltransferases used UDP-glucose as glucosyl donor. Optimal activities between pH 7.5 and pH 8.5 have been reported for the various 3-*O*-glucosyltransferase reactions.

One important aspect of research concerning flavonol/anthocyanidin 3-*O*-glucosyltransferase is the use of genetically defined mutants. In maize (*Zea mays*) the amount of 3-*O*-glucosyltransferase activity in different plant tissues and the dosage of the wild-type *Bz* allele are directly correlated (Larson and Coe, 1977). Dooner and Nelson (1977a, 1979a) reported a more complex control of this enzyme by the action of four genes in maize endosperm. *Bz* appeared to be the structural gene, whereas the nature of the genes *C*, *R* and *Vp* is not known and their effect seemed to be indirect. The *Bz* locus in maize is one of many loci at which controlling element-induced phenotypic changes are known (Dooner and Nelson, 1977b, 1979b).

Table 11.5 Glycosyltransferases from various sources

| Source of enzyme                              | Flavonoid compounds tested as possible substrates                                                 | Position of glycosylation | Glycosyl donor           | pH Optimum | Reference                                                 |
|-----------------------------------------------|---------------------------------------------------------------------------------------------------|---------------------------|--------------------------|------------|-----------------------------------------------------------|
| <i>Brassica oleracea</i> seedlings            | Various anthocyanidins, flavonols, flavones, dihydroquercetin, naringenin                         | 3                         | UDP-glucose              | 8          | Saleh <i>et al.</i> (1976b)                               |
| <i>Glycine max</i> cell cultures              | Malvidin                                                                                          | 3                         | UDP-glucose              | 8.5        | Hrazdina <i>et al.</i> (1980)<br>Poulton and Kauer (1977) |
|                                               | Various flavonols, cyanidin, apigenin, luteolin                                                   | 3                         | UDP-glucose              |            |                                                           |
| <i>Haplopappus gracilis</i> cell cultures     | Various anthocyanidins, flavonols, flavones, dihydroquercetin, naringenin                         | 3                         | UDP-glucose              | 8          | Saleh <i>et al.</i> (1976a)                               |
| <i>Hippeastrum</i> petals                     | Malvidin                                                                                          | 3                         | UDP-glucose              |            | Hrazdina <i>et al.</i> (1978)                             |
| <i>Petroselinum hortense</i> cell cultures    |                                                                                                   |                           |                          |            |                                                           |
| 1. Flavone/flavonol 7-O-glucosyl-transferase  | Various flavones, flavonols, flavanones, quercetin 3-O-glucoside, cyanidin, daidzein, biochanin A | 7                         | UDP-glucose, TDP-glucose | 7.5        | Sutter <i>et al.</i> (1972)                               |
| 2. Flavonoid 7-O-glucoside apiosyltransferase | 7-Glucosides of various flavones, flavanones, isoflavones, flavonol 7-O-glucosides                | 2"                        | UDP-apiose               | 7.0        | Ortmann <i>et al.</i> (1972)                              |
| 3. Flavonol 3-O-glucosyl-transferase          | Various flavonols, quercetin 7-O-glucoside, dihydroquercetin                                      | 3                         | UDP-glucose              | 8.0        | Sutter and Grisebach (1973, 1975)                         |



|                                                                                        |                                                                                                                                       |    |              |                                                                              |                                                                  |
|----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|----|--------------|------------------------------------------------------------------------------|------------------------------------------------------------------|
| <i>Petunia hybrida</i><br>corollas                                                     | Cyanidin, delphinidin                                                                                                                 | 3  | UDP-glucose  | 7.5-8.0                                                                      | Kho <i>et al.</i> (1978)                                         |
| <i>Phaseolus vulgaris</i><br>seedlings                                                 | Malvidin                                                                                                                              | 3  | UDP-glucose  |                                                                              | Hrazdina <i>et al.</i> (1980)                                    |
| <i>Pisum sativum</i><br>seedlings                                                      | Malvidin                                                                                                                              | 3  | UDP-glucose  |                                                                              | Hrazdina <i>et al.</i> (1980)                                    |
| <i>Silene alba</i><br>petals, green parts                                              | Isovitexin, iso-orientin<br>vitexin                                                                                                   | 2" | UDP-glucose  | 8.5 (isovitexin)<br>7.5 (iso-orientin)                                       | van Brederode <i>et al.</i> (1979)                               |
| <i>Silene dioica</i><br>petals                                                         | Several anthocyanidins,<br>cyanidin 3- <i>O</i> -glucoside<br>cyanidin 3- <i>O</i> -rhamnosyl-<br>glucoside, kaempferol,<br>quercetin | 3  | UDP-glucose  | 7.5                                                                          | Kamsteeg <i>et al.</i> (1978a)                                   |
| 1. Anthocyanidin<br>3- <i>O</i> -glucosyl-<br>transferase                              | 3- <i>O</i> -Glucosides of cyanidin,<br>pelargonidin, delphinidin                                                                     | 6" | UDP-rhamnose | 8.1                                                                          | Kamsteeg <i>et al.</i> (1980a)                                   |
| 2. Anthocyanidin<br>3- <i>O</i> -glucoside<br>rhamnosyltrans-<br>ferase                |                                                                                                                                       |    |              |                                                                              |                                                                  |
| 3. Anthocyanidin<br>3-rhamnosyl-<br>glucoside<br>5- <i>O</i> -glucosyl-<br>transferase | Anthocyanidin 3- <i>O</i> -glucosides,<br>anthocyanidin 3- <i>O</i> -rhamnosyl-<br>glucosides                                         | 5  | UDP-glucose  | 6.5 (3- <i>O</i> -glucosides)<br>7.4 (3- <i>O</i> -rhamnosyl-<br>glucosides) | Kamsteeg <i>et al.</i> (1978b)<br>Kamsteeg <i>et al.</i> (1980b) |
| <i>Spinacea oleracea</i><br>seedlings                                                  | Malvidin                                                                                                                              | 3  |              |                                                                              | Hrazdina <i>et al.</i> (1980)                                    |
| <i>Tulipa</i><br>leaves, petals, pollen                                                | Quercetin, malvidin                                                                                                                   | 3  | UDP-glucose  |                                                                              | Hrazdina <i>et al.</i> (1978)<br>Wiermann and Buth-Weber (1980)  |
| <i>Zea mays</i><br>seeds, seedlings, pollen                                            | Quercetin anthocyanidins                                                                                                              | 3  | UDP-glucose  | 8.2                                                                          | Larson (1971)<br>Larson and Lonergan (1973)                      |

Other glucosyltransferases (Table 11.5) whose activities have been related specifically to anthocyanin biosynthesis are discussed in Section 11.5.

#### 11.4.8 Acylation

Malonylation (Fig. 11.3, Nos. 12 and 13) of the sugar moieties is the last step in the biosynthesis of flavonoid glycosides in cultured parsley cells (Hahlbrock, 1972; Ebel and Hahlbrock, 1977). Several malonylated flavone and flavonol glycosides have been isolated from irradiated cell suspension cultures of parsley (Kreuzaler and Hahlbrock, 1973), and it is possible that the corresponding non-malonylated compounds were formed artificially by deacylation during the isolation procedure (Matern *et al.*, 1981). Two malonyltransferases have been isolated from irradiated parsley cells and extensively purified (Matern *et al.*, 1981). Both transferases have an apparent molecular weight of approximately 50 000 and are probably glycoproteins. One enzyme (Fig. 11.3, No. 12) is most active with flavone and flavonol 7-*O*-glycosides as substrates, such as apigenin 7-*O*-glucoside and the 7-*O*-apiosylglucosides of apigenin and chrysoeriol. The other enzyme (Fig. 11.3, No. 13) preferentially malonylates the 3-*O*-glucosides of kaempferol, quercetin and isorhamnetin. All flavone and flavanone 7-*O*-glucosides tested were relatively poor substrates of the second enzyme. The substrate specificities of the two enzymes *in vitro* are in good agreement with the pattern of malonylated flavonoid glycosides occurring in the cell cultures *in vivo*. Further acylations will be discussed below in Section 11.5.

#### 11.4.9 Proposed sequence of reactions

Our present knowledge of the biosynthetic pathways of flavone and flavonol glycosides is illustrated in Fig. 11.3. The sequence of the individual reactions has been derived mainly from enzyme studies in parsley but is likely to be the same in other plants. The scheme indicates that some of the reactions of both flavone and flavonol glycoside formation (e.g. reactions 7, 8 and 12) are probably catalysed by the same enzyme. Other reactions (e.g. 9, 10, 11 and 13) are specific for either flavone or flavonol glycoside formation. As discussed above, little is known at present about reactions 4–6, and their exact sequence is unknown. Some of the early steps in flavone and flavonol glycoside synthesis are probably common to the formation of most, or all, flavonoid classes, including anthocyanins and isoflavonoids.

#### 11.4.10 Regulation of enzyme activities

Regulation of flavonoid biosynthesis is closely correlated with differentiation and development in the plant tissue producing the pigments. Various types of endogenous and exogenous stimuli, including hormones, nutrients, light and temperature, are known to exert regulatory influences on the enzymes of

flavonoid biosynthesis. Even a brief summary of this complex subject would be far beyond the scope of this chapter. For recent reviews, the reader is referred to articles by Hahlbrock and Grisebach (1979) and Wiermann (1981). To give here only one illustrative example, Fig. 11.8 shows the time courses of large light-

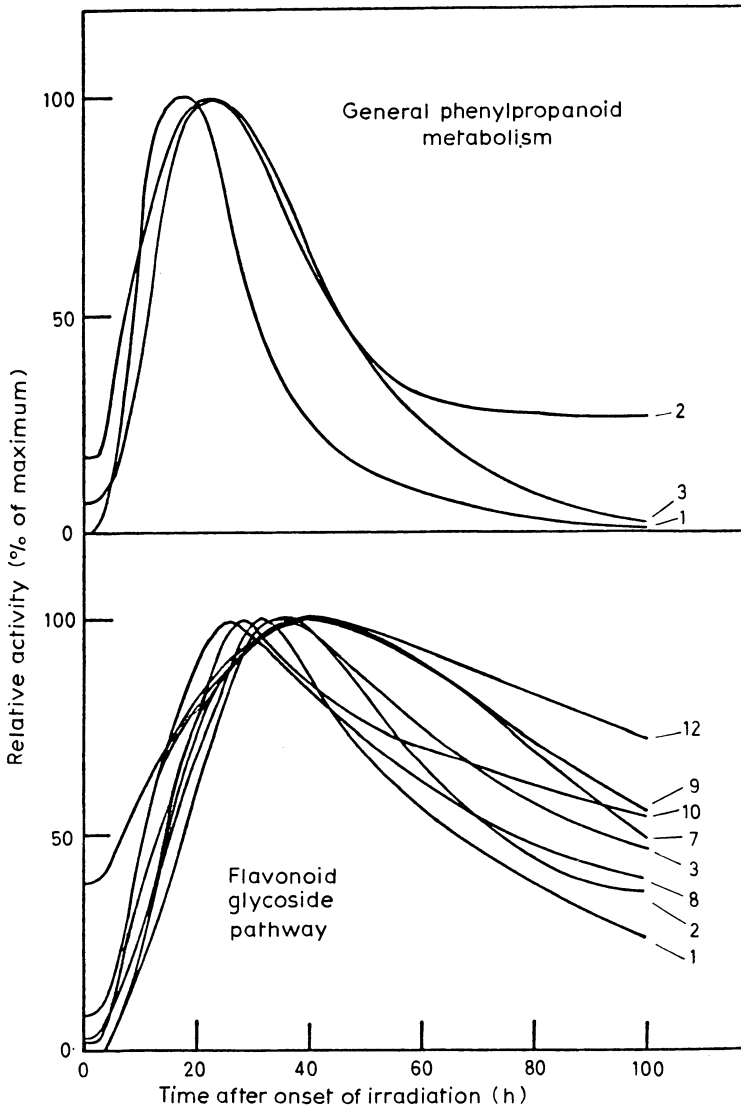


**Fig. 11.8** Activity changes for the three enzymes of general phenylpropanoid metabolism and for eight enzymes of the flavonoid glycoside pathway during continuous irradiation of a previously dark-grown parsley cell culture. The numbering of enzymes is the same as in Table 11.1 (after Hahlbrock *et al.*, 1976; Ebel and Hahlbrock, 1977; Heller and Hahlbrock, 1980).

induced changes in the activities of the enzymes related to flavone and flavonol glycoside biosynthesis in cultured parsley cells. In this particular case, the changes in enzyme activities were shown to be caused by corresponding changes in the activities of the respective mRNAs (Schröder *et al.*, 1979b; Gardiner *et al.*, 1980). The relationships between flavonoid glycoside accumulation rates and enzyme as well as mRNA activities can be expressed by simple mathematical equations (cf. Hahlbrock and Grisebach, 1979). Under certain conditions, phenylalanine ammonia-lyase seems to be the rate-limiting enzyme of flavonoid biosynthesis in parsley cells (Hahlbrock *et al.*, 1976). It should be noted, however, that our limited knowledge of other systems in this respect does not allow us to draw conclusions yet as to whether this is the exception or rather the rule.

### 11.5 ANTHOCYANINS

Tracer studies with  $^3\text{H}$ - and  $^{14}\text{C}$ -labelled precursors have confirmed the general rule that anthocyanins, like other flavonoids, are synthesized from acetate and phenylalanine. These experiments also established that chalcones and dihydroflavonols are intermediates in anthocyanin biosynthesis (cf. Hahlbrock and Grisebach, 1975; Grisebach, 1981; see also Sections 11.3 and 11.4.4). Further strong support for the role of chalcones, flavanones and dihydroflavonols as intermediates has been derived from studies with genetically defined lines of *Antirrhinum majus* (Harrison and Stickland, 1974; Stickland and Harrison, 1974), *Petunia hybrida* (Kho *et al.*, 1975, 1977), *Matthiola incana* (Forkmann, 1977, 1980) and *Zea mays* (McCormick, 1978). The general approach in these studies with defined genotypes has been to supplement putative biosynthetic intermediates subsequent to the genetic block. For example, mutants of *M. incana*, which were assumed to be blocked in chalcone synthesis, accumulated cyanidin glycosides upon feeding of the appropriate chalcone, flavanone or dihydroflavonol, whereas substituted cinnamic acids were ineffective. Mutants of *P. hybrida* thought to be blocked in dihydroflavonol formation produced cyanidin and delphinidin glycosides when dihydroflavonols were supplied as precursors. Additional evidence for the function of dihydroflavonols as intermediates in anthocyanin biosynthesis was obtained from studies with plant tissues which had been exposed to potent inhibitors of phenylalanine ammonia-lyase, such as amino-oxyacetate or  $\alpha$ -amino-oxy- $\beta$ -phenylpropionate (Amrhein *et al.*, 1976; Amrhein and Gödeke, 1977). For example, the inhibition by amino-oxyacetate of the light-induced formation of cyanidin glycosides in buckwheat (*Fagopyrum esculentum*) hypocotyls was completely or partially reversed in the presence of dihydrokaempferol or dihydroquercetin (Amrhein, 1979).

The co-occurrence of anthocyanins and flavonols in a large variety of plants suggests that anthocyanin biosynthesis may be closely related to flavonol biosynthesis (Fig. 11.3 and Fig. 11.7). In agreement with this assumption, the

enzymes chalcone synthase, chalcone isomerase and flavanone 3-hydroxylase have been demonstrated in a number of anthocyanidin-forming plants and plant tissues. In suspension-cultured cells of *Haplopappus gracilis*, irradiation with UV light greatly stimulated the activities of phenylalanine ammonia-lyase, chalcone synthase and chalcone isomerase concomitant with cyanidin glycoside accumulation (Wellmann *et al.*, 1976). Flavanone 3-hydroxylase activity was demonstrated in cell-free extracts from flowers of *Matthiola incana* and *Antirrhinum majus* which synthesize large amounts of anthocyanins (Forkmann *et al.*, 1980; Forkmann and Stotz, 1981). The important function of chalcone synthase, chalcone isomerase and flavanone 3-hydroxylase in anthocyanin biosynthesis has also been documented by studies with defined genotypes of several plants in which certain genetic blocks in the anthocyanin pathway were correlated with the absence of the respective enzyme activity (Kuhn *et al.*, 1978; Forkmann and Kuhn, 1979; Forkmann and Dangelmayr, 1980; Forkmann and Stotz, 1981; Spribille and Forkmann, 1981, see also above). The conversion of dihydroflavonols into anthocyanidins has yet to be demonstrated in cell-free extracts.

As in the cases of flavones and flavonols (Sections 11.4.7 and 11.4.8), glycosylation and acylation are probably the last steps in anthocyanin biosynthesis. It can be assumed that the first glycosylation occurs at the 3-*O*-position of the anthocyanidin. Because of the instability of the flavylium cation, 3-*O*-glycosylation is very likely a prerequisite for anthocyanin accumulation *in vivo*. Further glycosyl moieties may then be transferred to the 3-*O*-glycosyl residue and/or to the 5 position of anthocyanidin 3-*O*-glycosides. Several 3-*O*-glucosyltransferases from various sources are listed in Table 11.5; some of their properties have been discussed in Section 11.4.7. Most of these enzymes efficiently glucosylate both anthocyanidins and flavonols, whereas a 3-*O*-glucosyltransferase from *Silene dioica* was reported to be specific for anthocyanidins (Kamsteeg *et al.*, 1978a).

In petals of *S. dioica*, additional glycosylations occur in the biosynthesis of anthocyanidin 3,5-di-*O*-glycosides. According to Kamsteeg *et al.* (1980a), glycosylation of 3-*O*-glucosides is catalysed by UDP-rhamnose:anthocyanidin 3-*O*-glucoside 6''-*O*-rhamnosyltransferase which transfers the rhamnosyl moiety to the 6-hydroxyl group of the 3-*O*-linked glucose. The 3-*O*-glucosides of pelargonidin, cyanidin and delphinidin are more efficient substrates for rhamnosylation than the 3,5-di-*O*-glucosides. A third transferase from *S. dioica* catalyses the transfer of glucose from UDP-glucose to the 5-hydroxyl group of anthocyanins (Kamsteeg *et al.*, 1978b). The substrate specificity of the 5-*O*-glucosyltransferase was reported to be pH-dependent (Kamsteeg *et al.*, 1980b).

The anthocyanidin glycosides from petals of *S. dioica* occur mostly in the acylated form, with 4-coumarate or caffeate being the acyl residue. An enzyme catalysing the transfer of the 4-coumaroyl or caffeoyl moiety from the corresponding CoA ester to the 4-hydroxyl group of the rhamnosyl moiety of anthocyanidin 3-*O*-rhamnosylglucosides or 3-*O*-rhamnosylglucoside-5-*O*-glucosides has been demonstrated in this plant tissue (Kamsteeg *et al.*, 1980c).

## 11.6 ISOFLAVONOIDS

As in the case of anthocyanins, most of our knowledge about the biosynthesis of isoflavonoids originates from studies with radioactive isotopes. Again, it was established that acetate gives rise to ring A and that phenylalanine or cinnamate (or ring-substituted cinnamic acids) are incorporated into ring B and carbon atoms 2,3 and 4 of the heterocyclic ring C (cf. Hahlbrock and Grisebach, 1975). The mode of incorporation of phenylpropanoid compounds into isoflavonoids is depicted in Fig. 11.9. The central reaction where the isoflavonoid pathway branches off from the common biosynthetic pathway of all flavonoids is a 1→2 aryl migration. Since chalcones and flavanones are efficient precursors of isoflavonoids, the migration of ring B from the former  $\beta$  to the former  $\alpha$  carbon atom of the phenylpropanoid precursor must take place after formation of the basic  $C_{15}$  skeleton. However, the actual mechanism of aryl migration is not known (see Chapter 10). The chemical structures of isoflavonoids exhibit a wide range of modifications. The conversion of basic into structurally modified isoflavonoids is well documented (Chapter 10).

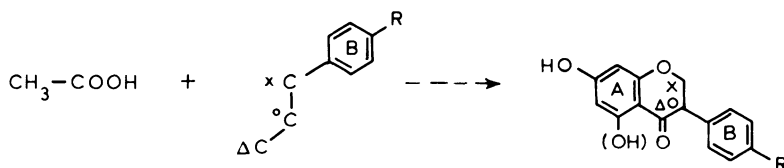


Fig. 11.9 Mode of incorporation of phenylpropanoid compounds into isoflavonoids.

Recent studies on the induced synthesis of isoflavonoid phytoalexins in legumes have contributed to some extent to the still limited knowledge about the enzymology of isoflavonoid biosynthesis. Phytoalexins constitute a chemically heterogeneous class of naturally occurring antimicrobial agents, including isoflavonoid as well as non-flavonoid compounds. They are produced in various plants in response to microbial attack (Grisebach and Ebel, 1978). For example, various tissues of soybean (*Glycine max*) respond to the fungal pathogen *Phytophthora megasperma* f. sp. *glycinea* and to an elicitor isolated from this fungus by synthesizing large amounts of glyceollin, which was identified as a mixture of structurally related pterocarpanoid, i.e. isoflavonoid, compounds (Burden and Bailey, 1975; Lyne *et al.*, 1976; Lyne and Mulheirn, 1978; Grisebach and Ebel, 1978). The accumulation of glyceollin in challenged cotyledons and cell cultures of soybean coincides with large increases in the activities of several enzymes of both general phenylpropanoid metabolism (phenylalanine ammonia-lyase, cinnamate 4-hydroxylase and 4-coumarate:CoA ligase) and flavonoid biosynthesis (chalcone synthase and chalcone isomerase) (Ebel *et al.*, 1976; Zähringer *et al.*, 1978; Ebel, 1979; Hille *et al.*, 1982). This coincidence confirms the conclusions drawn from tracer studies that the same

enzymes are involved in the initial steps of isoflavonoid biosynthesis as in other flavonoid pathways. Further investigations demonstrated a dimethylallyl pyrophosphate:3,6a,9-trihydroxypterocarpan dimethylallyltransferase in a particulate fraction from elicitor-treated cotyledons and cell suspension cultures of soybean (Zähringer *et al.*, 1979, 1981). The major product of dimethylallyl transfer *in vitro* was 2-dimethylallyl-trihydroxypterocarpan. A minor product was the 4-substituted pterocarpan (Zähringer *et al.*, 1979, 1981). Both products are likely intermediates in the biosynthesis of the various structurally related soybean phytoalexins. Introduction of a prenyl substituent into genistein (5,7,4'-trihydroxyisoflavone) and 2'-hydroxygenistein is catalysed by a particulate fraction from white lupin (*Lupinus albus*) (Schröder *et al.*, 1979c). Another isoflavonoid phytoalexin, phaseollin, accumulates in cell suspension cultures of french bean (*Phaseolus vulgaris*) in response to treatment with an elicitor from the bean pathogen, *Colletotrichum lindemuthianum*, or with an artificial elicitor, autoclaved ribonuclease A. This accumulation is accompanied by large increases in the activities of enzymes of both general phenylpropanoid metabolism and flavonoid biosynthesis (Dixon and Bendall, 1978a,b; Dixon and Lamb, 1979).

4'-O-Methylation of ring B of isoflavonoids is catalysed by a 4'-O-methyltransferase from seedlings or cell suspension cultures of chick pea (*Cicer arietinum*) (Wengenmayer *et al.*, 1974). The enzyme is specific for 4'-hydroxyisoflavones, such as daidzein (7,4'-dihydroxyisoflavone) or genistein, and does not methylate 4-coumarate, naringenin, apigenin nor luteolin (Table 11.4). The high specificity of this transferase for isoflavones suggests that 4'-O-methylation of isoflavonoids takes place after aryl migration.

## 11.7 OTHER FLAVONOIDS

Minor groups of flavonoids are the biflavonoids, proanthocyanidins, C-glycosylflavonoids and neoflavonoids. Feeding experiments with radioactively labelled precursors have demonstrated that they are synthesized according to the general scheme for flavonoid formation (Fig. 11.2), but as yet no enzymic studies have been reported with these compounds. For the chemistry, biochemistry and taxonomic distribution of these compounds see Chapters 7, 8 and 9.

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## CHAPTER TWELVE

# *Mammalian Metabolism of Flavonoids*

LESLIE A. GRIFFITHS

### 12.1 INTRODUCTION

Although earlier investigations of the mammalian metabolism of flavonoid compounds were largely concerned with the identification of their urinary metabolites (cf. De Eds, 1968), more recent studies have centred on the role of the intestinal microflora in the catabolism of flavonoid molecules, on the significance of the biliary-enteric route of excretion and on the disposition of flavonoids in mammalian tissues following oral and parenteral administration. Additionally the introduction of chemically modified flavonoids and of synthetic phenylchromones as therapeutic agents has promoted metabolic and pharmacokinetic investigations on compounds showing close structural relationships with the naturally occurring flavonoids.

The reported biological activity of certain flavonoids in specific mammalian systems has also resulted in the initiation of studies on their interaction with isolated enzymes, cell constituents and membranes, which may be of importance in the mediation of pharmacological effects. Interest in the metabolism of other flavonoids has been stimulated by the finding that the aglycones of certain naturally occurring flavonol glycosides are mutagenic (Bjeldanes and Chang, 1977; Sugimura *et al.*, 1977; MacGregor and Jurd, 1978) and that the aglycone quercetin may, following oral ingestion, give rise to neoplasms of the gastrointestinal tract (Pamukcu *et al.*, 1980a,b) (see Sections 12.2.5 and 12.2.11).

Shorter specialized reviews of mammalian flavonoid biochemistry in relation to (a) nutrition (Kühnau, 1976), (b) the intestinal microflora (Griffiths, 1975), (c) biotransformation (Wurm, 1975; Scheline, 1978), (d) biliary excretion (Griffiths and Hackett, 1977) and (e) pharmacological activity (Gabor, 1975) have been published over the period 1975–1980. Since the last comprehensive review of mammalian flavonoid metabolism was that of De Eds (1968), an attempt has been made in the current review to provide coverage from 1968 to 1980.

### 12.2 BIOTRANSFORMATION

#### 12.2.1 Ring fission

Three main types of ring scission have been postulated for the cleavage of flavonoid molecules *in vivo* (Fig. 12.1).

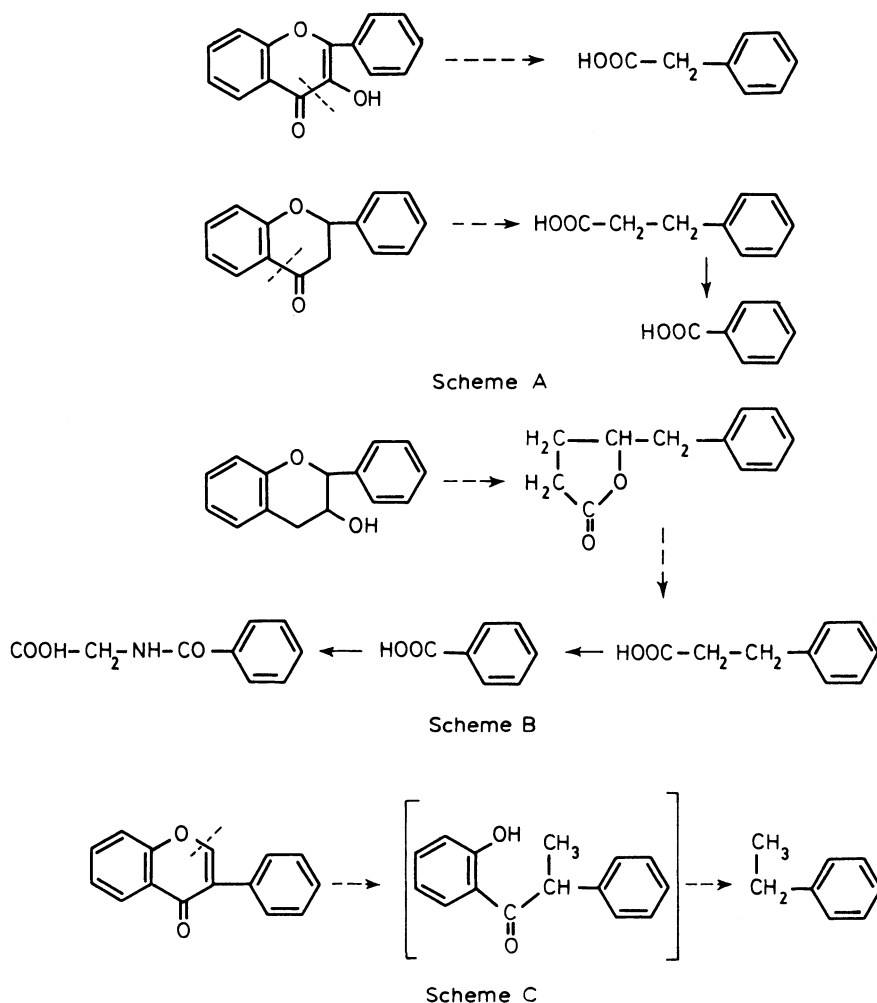


Fig. 12.1 Postulated scission of flavonoid molecules *in vivo*.

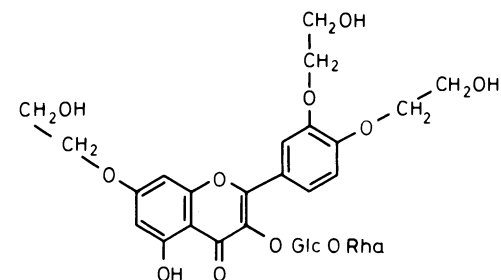
Scheme A scission was originally advanced by Booth *et al.* (1956) based on their investigations on the metabolism of the flavonols rutin and quercetin in which the formation of phenolic acids of the  $C_6-C_2$  type were observed. A modified form of scheme A, where cleavage occurs between  $C_4$  and  $C_5$ , was later advanced by Booth *et al.* (1958a,b) to account for the observed formation of  $C_6-C_3$  phenolic acids from the flavanones, naringenin, hesperetin and eriodictyol.

Scheme B scission was proposed by Oshima and Watanabe (1958) and extended by Griffiths (1964) and Das and Griffiths (1969) for the catabolism of (+)-catechin and related flavanols via the obligate intermediates  $\delta$ -phenyl- $\gamma$ -valerolactones.

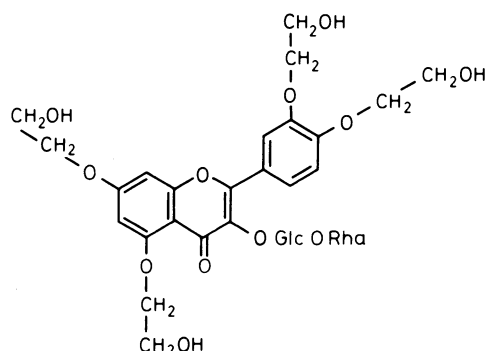
Scheme C for isoflavones is suggested by the findings of Batterham *et al.* (1965) and Griffiths and Smith (1972a), who reported the formation of *p*-ethylphenol from genistein by sheep and rat microflora respectively and by the experiments of Shutt and Braden (1968) and Batterham *et al.* (1971), who identified a phenyl- $\alpha$ -methylbenzyl ketone intermediate, namely 2,4-dihydroxyphenyl- $\alpha$ -4-hydroxyphenylethyl ketone (*O*-desmethylangolensin) as a urinary metabolite of formononetin in sheep. Formation of *p*-ethylphenol was not observed, however, following the administration of formononetin, indicating that the absence of the 5-hydroxyl group from the isoflavone molecule restricts cleavage beyond the phenyl- $\alpha$ -methylbenzyl ketone intermediate.

Other classes of flavonoid may also undergo ring fission. The anthocyanidin, delphinidin and the anthocyanins, malvin and pelargonin, were shown by Griffiths and Smith (1972a,b) to be degraded *in vivo* and *in vitro* to phenolic metabolites which were, however, dissimilar to those reported to be formed from the corresponding flavanols and flavonols, indicating a different pathway of degradation for compounds possessing a flavylum structure. Studies on the proanthocyanidin, leucocyanidin by Masquelier *et al.* (1965) and Claveau and Masquelier (1966) have shown that this compound undergoes ring fission in the rat to phenolic metabolites, including homovanillic acid and *m*-hydroxyphenylacetic acid. Although the dihydrochalcones, phlorrhizin (phloridzin) and phloretin are known to undergo ring fission following oral administration to the rat (Booth *et al.*, 1958a,b; Griffiths and Smith, 1972a), the naturally occurring chalcones, butein and isoliquiritigenin do not give rise to detectable urinary ring fission products (Brown and Griffiths, unpublished observation). This may be attributable to the A ring of these chalcones showing resorcinol-type substitution as opposed to the phloroglucinol substitution of flavonoids known to undergo ring fission (see below).

The early studies on the metabolism of flavonols, flavones and flavanones by Booth and his associates (Booth *et al.*, 1956, 1958a,b) which led to recognition that ring fission to phenolic acids was a major route of degradation of flavonoid molecules have been confirmed and extended by a number of subsequent investigations. Two groups of flavonoid the former showing 4'-monohydroxylation (Griffiths and Smith, 1972a) and the latter 3',4',5'-trihydroxylation (Griffiths and Smith, 1972b) were the subject of comparative studies. It was shown that only those flavonoids, which possessed free 5,7-dihydroxylation in the A ring underwent cleavage to ring fission products analogous to those reported by Booth and his associates. The absence of either 5- or 7-hydroxylation or the presence of *O*-methyl substitution in those positions reduced susceptibility to cleavage. Additionally it has been shown that hydroxyethylation on the free ring hydroxyls of rutin to give the pharmacologically active hydroxyethylrutosides (Courbat *et al.*, 1966a,b) results in compounds [*viz.* 7,3',4'-trihydroxyethylrutoside (12.1) and 5,7,3',4'-tetrahydroxyethylrutoside (12.2)] which are resistant to ring scission, when administered orally or parenterally to the rat (Barrow and Griffiths, 1972, 1974a,b). The highly methoxylated flavonols nobiletin and

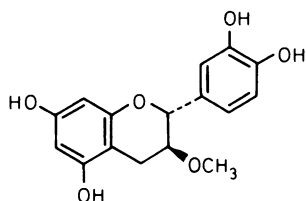


(12.1) 7, 3', 4'- Tri-O-( $\beta$ -hydroxyethyl)rutoside  
(rutoside  $\equiv$  rutin)



(12.2) 5, 7, 3', 4'- Tetra-O-( $\beta$ -hydroxyethyl)rutoside

tangeretin have also been reported to be resistant to ring scission and likewise the 5- and 7-O-methylquercetins (De Eds, 1968). Methylation of the 3-hydroxyl group of (+)-catechin also results in a derivative [3-O-methyl-(+)-catechin (12.3)] which is resistant to ring scission in the rat and mouse (Griffiths and Hackett, 1978). Oral administration of the non-hydroxylated compounds flavone and flavanone resulted in no significant ring cleavage of the administered compounds (Das and Griffiths, 1966; Das *et al.*, 1973; Buset and Scheline, 1980; Svoldal *et al.*, 1980).



(12.3) 3-O-Methyl-(+)-catechin

### 12.2.2 Site of ring fission

The early demonstration that excretion of the urinary ring fission products of (+)-catechin (Griffiths, 1964) and of quercetin (Nakagawa *et al.*, 1965) was

markedly reduced by co-administration of oral antibiotics suggested that certain flavonoids were significantly metabolized by the intestinal microflora. Subsequently, investigations on a range of flavonoids, including apigenin, apiin, kaempferol, robinin, myricetin, myricitrin and tricetin (Griffiths and Smith, 1972a,b), provided evidence not only that the metabolism of these compounds was dependent *in vivo* upon the participation of the intestinal flora but also showed that many were degraded by intestinal micro-organisms *in vitro* during anaerobic incubation to metabolites identical with those isolated from the urine of dosed animals. The degradation of other flavonoids by intestinal micro-organisms under conditions of anaerobic incubation *in vitro* has been reported by Scheline (1968b), Das (1969), Simpson *et al.* (1969), Krishnamurty *et al.* (1970), Honohan *et al.* (1976) and Harmand and Blanquet (1978).

Although these observations indicated that the intestinal microflora was capable of effecting degradation of these flavonoids to the ring fission products detected in mammalian urine, it remained to be determined whether the ring fission was wholly mediated by intestinal bacteria or whether additionally, mammalian tissue enzymes also participated in cleavage of these molecules. Investigations employing germ-free animals maintained in a sterile Trexler isolator showed, however, that such animals were wholly unable to effect ring fission of a group of orally administered flavonoids, which included (+)-catechin, rutin, apigenin, myricetin, hesperidin and naringin (Griffiths and Barrow, 1972). Conventionalization (i.e. deliberate reinfection of the gastrointestinal tract with the microflora derived from normal animals) conferred on the ex-germ-free animals the ability to effect ring fission to the urinary metabolites normally found. Accordingly it was concluded that ring cleavage of flavonoid compounds is normally wholly mediated by the gastrointestinal microflora and not by enzyme systems present in mammalian tissues.

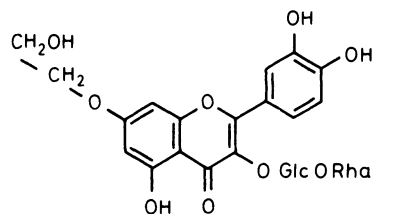
As several authors have suggested that ring fission of flavonoid molecules may occur in the liver (Takacs and Gabor, 1975; Förster, 1975; Harmand and Blanquet, 1978), the ability of rat liver to degrade (+)-[U-<sup>14</sup>C]catechin was recently investigated using the liver perfusion technique of Hems *et al.* (1966). Although large amounts of labelled flavanol conjugates were detected in both the perfusate and the formed bile, no labelled phenolic acids or phenyl- $\gamma$ -valerolactones known to be formed *in vivo* from (+)-catechin by rats with a viable microflora were detected (Griffiths *et al.*, 1980). The possibility that some flavonoids may undergo ring cleavage in liver is, however, suggested by the liver perfusion experiments of Takacs and Gabor (1975), who reported that the flavanol glycoside, rutin, underwent ring fission during perfusion of the rat liver to give 3,4-dihydroxyphenyl- $\gamma$ -valerolactone and several phenolic acids. Although 3,4-dihydroxyphenyl- $\gamma$ -valerolactone is well established as a metabolite of (+)-catechin (Oshima and Watanabe, 1958; Das and Griffiths, 1968, 1969), it has, however, not previously been reported as metabolite of a flavanol. Since a non-labelled rutin was used in these studies, the possibility that the



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phenolic metabolites detected may have arisen from dietary precursors or endogenous liver metabolism cannot be excluded.

Although Förster (1975, 1978) has also claimed that ring fission of a flavonoid, namely 7-mono-*O*-( $\beta$ -hydroxyethyl)rutoside (12.4), was observed in the course of his liver perfusion experiments in the rat, the only evidence advanced was the apparent disappearance of the perfused fluorescent flavonoid from the perfusate as no ring fission products were identified.



### 12.2.3 Intermediates in flavonoid ring fission

Although investigation has revealed the identity of the phenolic metabolites derived from the B ring of many flavonoids (cf. De Eds, 1968), limited information is available concerning both the early intermediates of ring scission in the mammalian intestine and the subsequent fate of the A ring fragment. Metabolites derived from the A ring have seldom been detected as urinary metabolites in the rat, but evidence has been presented that phloroglucinol intermediates may occur in the course of degradation of flavonoids possessing 5,7-dihydroxylation. An early report by Kallianos *et al.* (1959) claimed that phloroglucinol and phloroglucinolcarboxylic acid were detectable in the gastrointestinal tract of the rat following quercetin administration and it has been reported that excretion of phloroglucinol glucuronides occur following the administration of leucocyanidin to the rat (Masquelier *et al.*, 1965; Claveau and Masquelier, 1966). Since, however, acid treatment at elevated temperatures was used by both groups of workers to recover phloroglucinol from complex mixtures of metabolites, the possibility of direct chemical degradation cannot be excluded, especially as Masri *et al.* (1959) have demonstrated that quercetin is degraded to phloroglucinol and other products under similar conditions of acid treatment.

Investigations on flavonoid catabolism by rat microflora *in vitro* have likewise failed to provide definitive information on the fate of the A ring (Scheline, 1968a; Griffiths and Smith, 1972a,b). The detection of phloroglucinol as an intermediate in the microfloral degradation of the dihydrochalcone, phlorrhizin (Griffiths and Smith, 1972a) is of limited importance, as it appears probable that the absence of an oxygen bridge from compounds of this type may result in different cleavage reactions from those found in *O*-heterocycles.

Studies by Simpson *et al.* (1969) and Cheng *et al.* (1971) using isolated rumen micro-organisms under conditions of anaerobic incubation have, however, demonstrated that phloroglucinol is, under these conditions, a metabolite of rutin, quercetin, naringin and naringenin. The phloroglucinol detected was, however, further metabolized on extended incubation. The ability to degrade flavonoids via phloroglucinol was shown to be effected by the rumen micro-organism, *Butyrivibrio* sp. (Cheng *et al.*, 1971) which is probably absent from the gastrointestinal tracts of non-ruminant species.

De Eds (1968) has also made reference to unpublished experiments in which phloroglucinol was detected as a transient intermediate of quercetin following incubation with rat faeces for shorter periods of time but no quantitative data were reported. The available evidence that phloroglucinol intermediates are obligate intermediates in non-ruminant species is therefore very slender and clearly requires re-examination by modern techniques.

Although phloroglucinol has been postulated as an intermediate in the degradation of flavones, flavonols and flavanones (cf. De Eds, 1968), studies have established that the flavanols including (+)-catechin (Oshima and Watanabe, 1958; Griffiths, 1964; Das and Griffiths, 1969; Das, 1971, 1974), (–)-epicatechin (Oshima *et al.*, 1960) and epi-afzelechin (Griffiths and Smith, 1972a) are degraded via phenyl- $\gamma$ -valerolactones which are derived from both A and B ring carbon atoms (Fig. 12.1, Scheme B).

Furthermore, evidence has been presented based on experiments using a (+)-[ $^{14}\text{C}$ ]catechin preparation, predominantly labelled in the A ring, that the carbons of this ring are largely metabolized *in vivo* to  $^{14}\text{CO}_2$ , although radioactivity was also associated with the phenyl- $\gamma$ -valerolactones excreted (Das and Griffiths, 1969) which, as noted above, contain carbon atoms derived from the A ring. [ $^{14}\text{C}$ ]Quercetin has also been shown to give rise to respired  $^{14}\text{CO}_2$  (15% of dose) on administration to the rat (Kallianos *et al.*, 1959), but as this early study employed a randomly labelled quercetin, the carbon atom precursors of the  $^{14}\text{CO}_2$  could not be identified.

The possibility that aliphatic intermediates might be formed in the course of metabolism of the A ring carbons to  $^{14}\text{CO}_2$  was suggested on the basis of data obtained in an investigation *in vivo* of (+)-[ $^{14}\text{C}$ ]catechin metabolism in the rat (Das and Griffiths, 1969), but it was not until 1972 that evidence of the identity of such an aliphatic intermediate was obtained. Using cell-free extracts of a *Pseudomonas* sp. isolated from rat faeces, Jeffrey *et al.* (1972b) obtained evidence for the metabolism of the A ring of dihydrogossypetin via the four-carbon intermediate, oxaloacetic acid. Since it had previously been reported that dihydrogossypetin and taxifolin were intermediates in the metabolism of (+)-catechin (Fig. 12.2) by this pseudomonad (Jeffrey *et al.*, 1969, 1972a), these findings may also be of considerable significance in relation to flavanol metabolism. It is, however, important to note that to date *none* of the intermediates formed by the cell-free pseudomonad extracts have been reported as *in vivo* metabolites of (+)-catechin in the rat and secondly that formation of

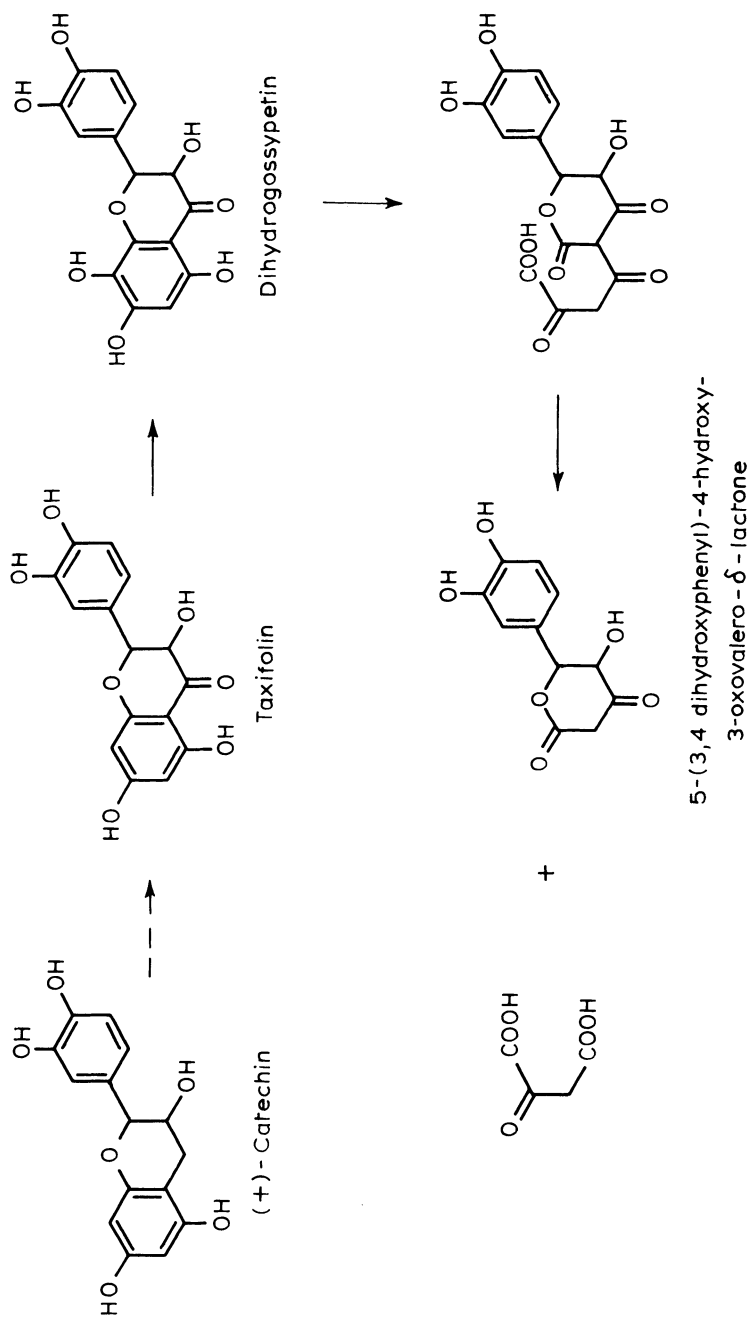


Fig. 12.2 Metabolism of (+)-catechin by a pseudomonad from rat faeces (Jeffrey *et al.*, 1972a,b).

the early intermediates, taxifolin and dihydrogossypetin, required highly aerobic conditions which would not normally obtain in the mammalian intestine which favours the activities of anaerobic or micro-aerophilic organisms.

A soil pseudomonad, *P. putida*, has also been isolated by elective culture on quercetin by Schultz *et al.* (1974), which has been shown to possess enzymes able to effect 8-hydroxylation of certain flavones and flavanones followed by ring fission to give a pyrone intermediate and ultimately oxaloacetic acid, and in the case of quercetin, protocathechuic acid (Fig. 12.3). Since quercetin degradation *in vivo* results largely in the urinary excretion of phenylacetic acid derivatives (Booth *et al.*, 1956), the products of the pseudomonad pathway are again seen to be dissimilar to those observed in mammalian studies. Although there is therefore no reason to suppose that the isolated pseudomonads are responsible for flavonoid degradation in the mammalian intestine, the metabolic data reported in these studies indicate new mechanisms of ring fission, which in a modified form may be of significance in intestinal metabolism.

It is of interest to note that the structural requirements for flavonoid ring fission *in vivo*, namely the possession of free hydroxyls at C-5 and C-7, are also important for ring cleavage by the pseudomonad pathway of Schultz *et al.* (1974), suggesting dependence upon similar enzymic mechanisms. However, additional structural requirements were noted by Schultz *et al.* for cleavage by the pseudomonad pathway, indicating greater specificity of the oxygenases involved. It was noted that the second dioxygenase (Fig. 12.3) required a hydroxyl at C-3 which must be at an unsaturated site. In consequence, taxifolin did not serve as a substrate despite the fact that it has been found to be a substrate for the pseudomonad isolated by Jeffrey *et al.* (1972). Conversely, quercetin which is readily degraded by preparations of the pseudomonad of Schultz *et al.* was not metabolized by the pseudomonad employed by Jeffrey *et al.* These apparent anomalies may be attributable to the fact that the enzyme preparations were initially obtained by induction with different substrates, namely quercetin and (+)-catechin. The wider specificity observed in relation to degradation of flavonoids by the intestinal microflora may point to participation of a number of induced enzymes. Evidence has been presented that the administration of certain flavonoids, namely robinin and 7-*O*-hydroxyethylrutin, over an extended period of time may result in elevated excretion of the microfloral ring-fission products (Griffiths and Smith, 1972; Barrow and Griffiths, 1974b).

#### 12.2.4 Species variation in flavonoid metabolism

Since many of the earlier investigations on flavonoid metabolism were carried out using a limited number of animal species, relatively few differences in the metabolic fate of flavonoids were noted, although Booth *et al.* (1958) reported that whilst hesperetin and hesperidin gave rise to large amounts of *m*-hydroxyphenylpropionic acid in rat urine, the major metabolite in man was 3-hydroxy-4-methoxyphenylhydracrylic acid.

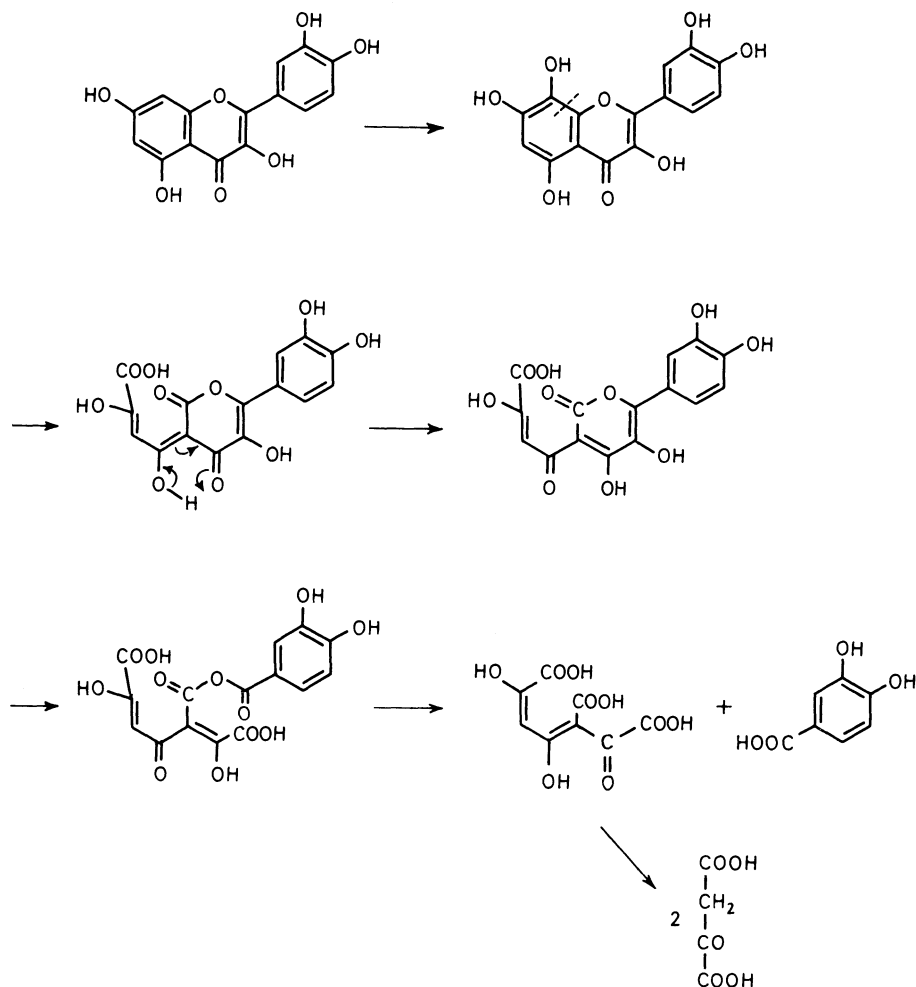


Fig. 12.3 Metabolism of quercetin by a soil pseudomonad (Schultz *et al.*, 1974).

More recent investigations on the metabolism of the flavonol, (+)-catechin in a wide range of mammalian species has shown considerable species variation in relation to the urinary ring fission products. Whereas the early study of Oshima *et al.* (1958) indicated that in the rabbit, the major phenolic acid metabolites were vanillic acid, protocatechuic acid and *m*-hydroxybenzoic acid, the studies of Griffiths (1962, 1964) and Das and Griffiths (1969) on the rat indicated that *m*-hydroxyphenylpropionic acid and *m*-hydroxyhippuric acid were the major metabolites in this species. In the guinea pig, however, it was found that *m*-hydroxybenzoic acid was the major metabolite and that *m*-hydroxyphenylpropionic acid was present in trace amounts only (Das and Griffiths,



1968). Investigations in primate species indicated that in man the metabolic pattern resembled that of the rat in that *m*-hydroxyphenylpropionic acid was the major metabolite (Das, 1971), but that in monkey (*Macaca iris* sp.) the major metabolite was *m*-hydroxyphenylhydracrylic acid (Das, 1974). In all species investigated, the formation of phenylvalerolactones was reported and it appears probable that these are important obligatory intermediates in the degradation of (+)-catechin to phenolic acids, as was demonstrated in the rat employing *m*-[<sup>14</sup>C]hydroxyphenylvalerolactone which was shown to be metabolized to *m*-[<sup>14</sup>C]hydroxyphenylpropionic acid (Das and Griffiths, 1969). These interrelationships are shown in Fig. 12.4. Since evidence has been presented earlier (see Section 12.2.2) that the catabolism of flavonoids, including (+)-catechin, is largely attributable to the intestinal microflora, it appears probable that the divergent pathways shown in Fig. 12.4 are due to differences in the microflora present in the gastrointestinal tracts of different species. This is in accord with the observation that a suspension of micro-organisms from the *rabbit* gastrointestinal tract is able to metabolize (+)-catechin to 5-(3,4-dihydroxyphenyl)valeric acid and 5-(3-hydroxyphenyl)valeric acid (Scheline, 1970), whereas incubation of (+)-catechin with micro-organisms from the *rat* intestine yielded mainly *m*-hydroxyphenylpropionic acid, whilst phenylvaleric acids were either not detected (Das, 1969) or were detected only in trace amounts (Scheline, 1970).

Not only is species variation seen in relation to degradative pathways of flavonoid metabolism but also in relation to conjugation reactions. Recently 3,3' (or 4')-*O*-dimethyl-(+)-catechin glucuronide has been observed to be the major urinary metabolite of 3-*O*-[<sup>14</sup>C]methyl-(+)-catechin in the rat where it amounts to 64–92 % of the total radioactivity. In the mouse and marmoset monkey, however, this conjugate was found to be a minor metabolite and the major metabolite was the free aglycone 3,3'-*O*-dimethyl-(+)-catechin, which accounted for 68 % of the total activity in mouse urine and 78 % in marmoset urine (Hackett and Griffiths, 1981).

#### 12.2.5 Metabolic hydrolysis of flavonoid glycosides

The ability of mammals to hydrolyse the linkages of orally administered flavonoid glycosides is widely reported (cf. De Eds, 1968) and since the resultant aglycones are in part excreted in faeces (Griffiths and Smith, 1972a,b), it appeared probable that hydrolysis occurred in the gastrointestinal tract. Anaerobic incubation of flavonoid glycosides with the intestinal microflora has also resulted in the detection of aglycone intermediates. Scheline (1968b) demonstrated the release of quercetin and hesperetin when their respective glycosides rutin and hesperidin were incubated with rat microflora. Similarly, release of the aglycones of myricitrin (Fig. 12.5), apiin, robinin, naringin and phlorrhizin has been demonstrated under similar conditions (Griffiths and Smith, 1972a,b). Interest in flavonoid glycosidases has recently been stimulated by the finding that microbial glycosidases of the rat and human intestine are able

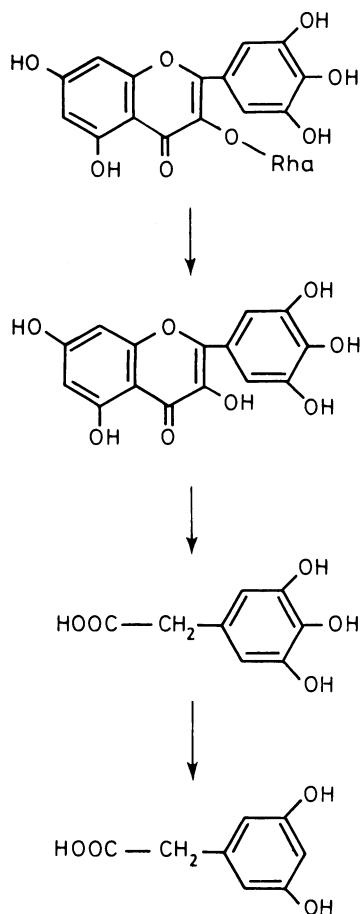


**Fig. 12.5** Degradation of myricitrin by the intestinal microflora of the rat (Griffiths and Smith, 1972b).

to release mutagenic aglycones from certain flavonoid glycosides, which are known to be of widespread occurrence in vegetable food stuffs (Brown and Dietrich, 1979; Tamura *et al.*, 1980). Since, moreover, parenteral administration of the flavonoid glycosides naringin and hesperidin to biliary cannulated rats, in which contact between the administered flavonoid and the gut microflora is precluded, resulted in the excretion of conjugates of the intact glycosides but not of the corresponding aglycones (Hackett *et al.*, 1979), it appears probable that glycosidases able to hydrolyse these compounds are absent from mammalian tissues. This conclusion is supported by earlier observations on the metabolism of the flavonoid glycosides rutin, naringin and hesperidin in germ-free rats, when the unchanged glycosides but not the free aglycones were detected on examination of the faeces (Griffiths and Barrow, 1972).

Limited information is available on the fate of the flavonoid conjugates which are known to be extensively excreted in bile (see Section 12.3.3). It appears



probable, however, that the flavonoid glucuronides undergo metabolic hydrolysis in the lumen of the intestine, as it is known that large amounts of  $\beta$ -glucuronidase of microfloral origin are present in the intestinal contents (Marsh *et al.*, 1952; Hawksworth *et al.*, 1971) and that the aglycones of certain flavonoid conjugates, known to be excreted in bile, can be recovered from the faeces. Administration of 7,3',4'-trihydroxyethylrutoside and 7-monohydroxyethylrutoside has been shown to result in extensive excretion of their glucuronide conjugates in the bile of bile-duct-cannulated rats, but examination of the faeces of non-cannulated rats following dosage revealed that the major faecal metabolites were the aglycones, 7,3',4'-trihydroxyethylquercetin and 7-monohydroxyethylquercetin respectively, which indicates that hydrolysis of both sugar and glucuronide linkages occurs in the intestine of the normal animal (Barrow and Griffiths, 1974a,b).

It is also of interest here to note that, although flavanol glucuronides can be recovered from the faeces of germ-free rats following the administration (+)-catechin, these conjugates are not detectable in the faeces of normal rats (Griffiths and Barrow, 1972), again indicating that these biliary conjugates are under normal conditions degraded by the intestinal microflora.

### 12.2.6 Hydroxylation

A number of flavonoids have been reported to undergo hydroxylation *in vivo*. Both chrysin and tectochrysin were reported to undergo 4'-hydroxylation following oral administration to the rat (Griffiths and Smith, 1972a). Following administration of flavone to the guinea pig, several hydroxylation products were detected in urine including 4'-hydroxyflavone and 3',4'-dihydroxyflavone (Das and Griffiths, 1966). Recently Buset and Scheline (1979) have reported hydroxylation of flavanone following oral administration to the rat. Urinary metabolites isolated and identified by GC-MS included 6-hydroxyflavanone, 6-hydroxyflavan-4- $\beta$ -ol and *trans*-3-hydroxyflavan-4- $\beta$ -ol (Fig. 12.6). Little hydroxylation was reported in ring B.

In a parallel investigation on the biliary and urinary metabolites of a group of naturally occurring polyhydroxylated flavanones following parenteral and oral administration to the rat, metabolic hydroxylation was detected only as a minor pathway of a single flavanone, *viz.* naringenin which gave rise to trace amounts of eriodictyol (Hackett *et al.*, 1979). Evidence has been presented by Jeffrey *et al.* (1972) that the dihydroflavonol, taxifolin, was hydroxylated to dihydrogossypetin by a pseudomonad present in rat faeces, but no evidence is available whether this reaction occurs *in vivo* in the rat intestine.

### 12.2.7 Reductive reactions

Although the excretion of *m*-hydroxyphenacyl derivatives following the administration of 3',4'-dihydroxylated flavonoids is widely reported the available

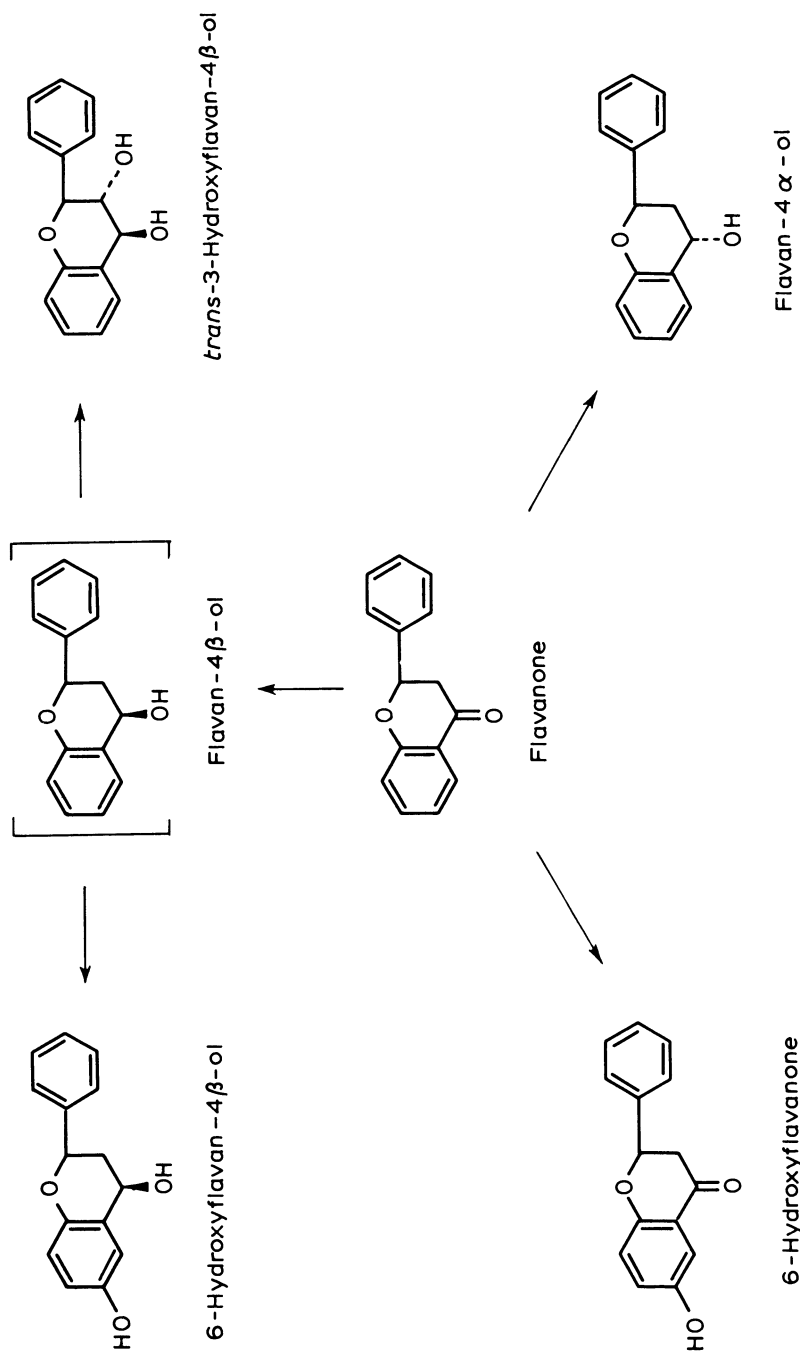


**Fig. 12.6** Major metabolites of flavanone (Buset and Scheline, 1979).

evidence indicates that dehydroxylation occurs *following* ring fission to *o*-dihydric phenacyl products, which are then dehydroxylated by the intestinal microflora (cf. De Eds, 1968). No evidence has to date been presented to indicate that direct reductive dehydroxylation of *intact* flavonoids occurs in the mammal.

An interesting reductive reaction has recently been reported by Buset and Scheline (1979) in their investigations on the metabolism of flavanone in the rat. Examination of the urinary metabolites using a GC-MS technique has revealed that the carbonyl group of flavanone is reduced to give a number of carbinol metabolites, which included flavan-4- $\alpha$ -ol, *trans*-3-hydroxyflavan-4- $\beta$ -ol and 6-hydroxyflavan-4- $\beta$ -ol (Fig. 12.6). Another recent study on a group of naturally occurring plant flavanones has, however, shown that their major metabolites in bile and urine are the glucuronide conjugates of the aglycone or glycoside administered (Hackett *et al.*, 1979), indicating that carbinol formation is probably restricted to non-hydroxylated compounds.

### 12.2.8 Conjugation

Although early investigations on flavonoid metabolism were largely concerned with the ring fission products which were excreted in urine (cf. De Eds, 1968), more recent investigations have focused upon the nature of the flavonoid conjugates excreted predominantly in bile but also in urine after both oral and parenteral administration, which it has recently been shown (see also Section 12.3.3) may represent a very high proportion of the dose (Table 12.1).

Whilst administration of flavonoid *glycosides* may result in biliary excretion of the *unchanged* compound as reported for naringin (Hackett *et al.*, 1979) and 5,7,3',4'-tetrahydroxyethylrutin (Barrow and Griffiths, 1972), more usually excretion of conjugates of the administered flavonoid is observed. Thus glucuronides of the flavanones, hesperetin and naringenin, are excreted in bile after both oral or parenteral administration and likewise the glucuronides of naringin and hesperidin (Hackett *et al.*, 1979).

It is important to note that whilst flavonoid *glycosides* may be excreted unchanged in bile, flavonoid *aglycones* are not excreted in bile to a significant extent without prior conjugation. The flavanols, (+)-catechin and 3-*O*-methyl-(+)-catechin, have been shown to be excreted in rat bile as glucuronide conjugates (Das and Sothy, 1971; Barrow and Griffiths, 1971; Griffiths and Hackett, 1978; Hackett and Griffiths, 1981), the flavanones, naringenin and hesperetin, are similarly excreted (Honohan *et al.*, 1976; Hackett *et al.*, 1979), but the chalcones, butein and 2',4',4'-trihydroxychalcone, have recently been shown to be excreted in bile mainly as sulphate conjugates (Griffiths *et al.*, 1980; Brown and Griffiths, unpublished). Silybin (12.5) is reported to be excreted in bile as both glucuronide and sulphate (Bülles *et al.*, 1975). It will be noted that conjugation with glucuronic acid or with sulphate not only elevates the molecular weight of the administered flavonoid but also confers considerable polarity upon the molecule and in consequence favours elimination via the biliary route (see Section 12.3.3).

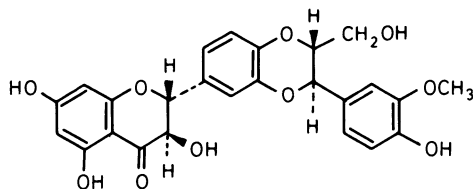
Table 12.1 Excretion of flavonoids and their conjugates in bile and urine of the rat

| Compound                                         | Route | Dose        | Excretion in bile (% of dose) | Excretion in urine (% of dose) | Period of collection (h) | References                    |
|--------------------------------------------------|-------|-------------|-------------------------------|--------------------------------|--------------------------|-------------------------------|
| (+)-Catechin                                     | i.v.  | 25 mg*      | 42.7                          | 32.6                           | 24                       | Das and Sothy (1971)          |
|                                                  | oral  | 10 mg*      | 34.0                          | 19.6                           | 24                       | Shaw and Griffiths (1980)     |
| 3-O-Methyl-(+)-catechin                          | i.v.  | 25 mg/kg    | 57.4                          | 17.5                           | 24                       | Hackett and Griffiths (1980)  |
|                                                  | oral  | 25-30 mg/kg | 48.3                          | 16.4                           | 48                       |                               |
| Hesperetin                                       | i.p.  | 0.15 mg*    | 100.7                         | ND                             | 24                       | Honohan <i>et al.</i> (1976)  |
|                                                  | oral  | 0.29 mg*    | 56.5                          | ND                             | 24                       |                               |
| Naringin                                         | i.p.  | 5 mg*       | 89.7                          | 0                              |                          | Hackett <i>et al.</i> (1979)  |
|                                                  | oral  | 50 mg*      | 11.4                          | 2.3                            | 48                       |                               |
| 7-Monohydroxyethylrutoside†                      | i.v.  | 5 mg/kg     | 78.1                          | 18.4                           | 24                       | Barrow and Griffiths (1974a)  |
|                                                  | oral  | 7.4 mg/kg   | 22.6                          | 4.0                            | 72                       | Barrow and Griffiths (1974b)  |
| 7,3',4'-Tri-O-( $\beta$ -hydroxy-ethyl) rutoside | i.v.  | 1.1 mg/kg   | 65.3                          | 14.3                           | 24                       | Barrow and Griffiths (1974a)  |
|                                                  | oral  | 1.4 mg/kg   | 13.2                          | 1.3                            | 72                       | Barrow and Griffiths (1974b)  |
| Silybin                                          | i.v.  | 20 mg/kg    | 76.0                          | 8.0                            | 48                       | Bulles <i>et al.</i> (1975)   |
|                                                  | oral  | 2-20 mg/kg  | 20.0                          | ND                             | 48                       |                               |
| Flavoxate                                        | i.v.  | 5 mg/kg     | 22.1                          | 17.6                           | 24                       | Setnikar <i>et al.</i> (1975) |
|                                                  | oral  | 30 mg/kg    | 58.2                          | 20.0                           | 24                       |                               |

ND Not determined.

\* Dose per rat.

† Rutoside  $\equiv$  rutin.



(12.5) Silybin

### 12.2.9 Site(s) of formation of flavonoid conjugates

Although studies on flavonoid metabolism *in vivo* are numerous, a very limited amount of research upon the metabolism of flavonoids *in vitro* by mammalian tissues has been reported and information on the site(s) of formation of flavonoid glucuronides is sparse. Evidence has been presented, however, that rabbit liver microsomal fractions are able to effect the transfer of glucuronic acid from UDP-glucuronic acid to the isoflavones, biochanin A, formononetin, daidzein, genistein and equol to give the corresponding monoglucuronides (Labow and Layne, 1972). Using a rat liver perfusion technique, Förster *et al.* (1972) demonstrated the formation of a blue fluorescent metabolite from perfused 7,3',4'-trihydroxyethylrutoside which was subsequently identified as a glucuronide (Förster, 1977) and which appears to be identical with 7,3',4'-trihydroxyethylrutoside 5-glucuronide detected earlier in the bile and urine of the intact rat (Barrow and Griffiths, 1974a). The formation of flavanol glucuronides in the perfused liver has also been demonstrated using [U-<sup>14</sup>C] (+)-catechin. Labelled flavanol glucuronides were detected in both the perfusate and in the formed bile (Griffiths *et al.*, 1980).

The limited information available on the origin of flavonoid glucuronides in the mammal thus clearly indicates that the liver is able to form conjugates of this type. However, the relative importance of this organ in relation to other possible sites, such as the intestinal mucosa which has been implicated as an important site of phenol conjugation by Powell *et al.* (1974), remains to be evaluated by further research.

### 12.2.10 Methylation

Although many reports have been published indicating that methoxylated phenolic acids are excreted by the mammal following the administration of certain flavonoids especially those possessing 3',4'-dihydroxylation of the B ring, the view has usually been taken that these metabolites arise largely if not wholly by methylation of phenolic acid intermediates formed as the direct products of ring fission (cf. De Eds, 1968). Such a view is supported by evidence that *o*-dihydric C<sub>6</sub>—C<sub>1</sub>, C<sub>6</sub>—C<sub>2</sub> and C<sub>6</sub>—C<sub>3</sub> acids readily undergo methylation *in vivo* (Booth *et al.*, 1955, 1957) and *in vitro* (Masri *et al.*, 1962) and by failure in earlier

investigations to detect intact methylated flavonoids among the products of excretion.

Recently, however, evidence has been obtained that the methyl ethers of certain administered flavonoids are excreted as their glucuronide and sulphate conjugates in the bile of rats (Griffiths and Hackett, 1978; Griffiths *et al.*, 1980; Shaw and Griffiths, 1980). Studies on the flavanol, (+)-catechin indicated that following both oral (Barrow and Griffiths, 1971) and parenteral administration (Das and Sothy, 1971) flavanol conjugates were excreted in bile. The major biliary metabolite was not identified in the earlier studies, but it has now been identified by mass spectrometry and other techniques as 3'-*O*-methyl-(+)-catechin glucuronide (Griffiths *et al.*, 1980). The metabolite was shown, following oral administration of [U-<sup>14</sup>C] (+)-catechin to the rat, to account for approx. 50 % of the total biliary radioactivity which corresponded to 34 % of the administered dose. Perfusion of rat liver with [U-<sup>14</sup>C](+)-catechin was also shown to result in rapid transformation of the flavanol to the methylcatechin glucuronide.

Incubation of non-labelled (+)-catechin with a homogenate of rat liver containing added *S*-[methyl-<sup>14</sup>C] adenosylmethionine resulted in the formation of a radioactive product which was shown by HPLC and paper chromatography to be identical with the aglycone of the biliary metabolite (Shaw and Griffiths, 1980).

The synthetic derivative, 3-*O*-methyl-(+)-catechin has also been reported to undergo methylation in the rat giving rise to large amounts of 3,3'(or 4')-*O*-dimethyl-(+)-catechin glucuronide which was excreted in bile and urine. Mass spectrometric examination of the aglycone obtained by  $\beta$ -glucuronidase hydrolysis of the major biliary metabolite indicated that the second methyl substituent had been introduced into a hydroxyl of ring B (Griffiths and Hackett, 1978; Hackett and Griffiths, 1981). The free aglycone was also detected in rat urine as a minor metabolite.

Comparative studies in the mouse and marmoset showed that methylation of 3-*O*-methyl-(+)-catechin occurred to a similar extent as in the rat but that the major urinary metabolite in both species was the free aglycone, 3,3'(or 4')-*O*-dimethyl-(+)-catechin whilst the corresponding glucuronide was a minor metabolite (Hackett and Griffiths, 1981).

The chalcone, butein (2',4',3,4-tetrahydroxychalcone), has also been shown to undergo methylation *in vivo* in the rat. Following parenteral administration, the major biliary metabolite of butein was shown to be a sulphate conjugate. The aglycone, released by treatment with arylsulphatase, was shown by mass spectrometry to be a methylbutein, which possessed UV absorption characteristics and fluorescence identical with 3-*O*-methylbutein (Griffiths *et al.*, 1980). Similarly 2',3,4-trihydroxychalcone has been shown to undergo 3-*O*-methylation and conjugation with sulphate in the rat. Parenteral administration of the flavonol glycoside, rutin, resulted in the biliary excretion of small amounts of glucuronide conjugates, the aglycone of which was shown by UV spectral

analysis to be the 3'-methyl ether of quercetin, namely isorhamnetin (Brown and Griffiths, unpublished observations). Trace amounts of isorhamnetin have previously been detected in rat urine following the administration of quercetin (Peter *et al.*, 1966). It is important to note that methyl ethers have been detected only in respect of flavonoids possessing *o*-dihydric substitution in ring B of the molecule.

The subsequent metabolic fate of methylated flavonoids secreted in bile is determined by their susceptibility to ring fission in the intestine. An intact aglycone of the metabolite 3-*O*-methylbutein sulphate was, after metabolic hydrolytic cleavage, detectable in rat faeces (Brown and Griffiths, unpublished observation). The aglycone of the biliary metabolite 3'-*O*-methyl-(+)-catechin glucuronide was not, however, detectable in faeces of the rat, indicating that the 3'-*O*-methyl-(+)-catechin, like (+)-catechin, is readily degraded by the intestinal microflora (Shaw and Griffiths, unpublished observations). It appears possible therefore that the earlier reported urinary metabolites of (+)-catechin, 3-methoxy-4-hydroxyphenyl- $\gamma$ -valerolactone (Oshima and Watanabe, 1958; Das and Griffiths, 1969) and vanillic acid (Oshima *et al.*, 1958) may in part be derived from the methylated biliary metabolite. Since it is also well established that methoxylated aromatic acids are readily demethylated by gut micro-organisms (Scheline, 1966, 1968a; Griffiths, 1970), a significant proportion of the phenolic acids detected in urine after the administration of (+)-catechin and other flavonoids may be derived from methylated intermediates.

The possibility that methylated flavonoids secreted in bile may undergo *direct* dealkylation also requires consideration in view of the reports, that the isoflavones, biochanin A (4'-*O*-methylgenistein) and formononetin (4'-*O*-methyldaidzein), are demethylated to genistein and daidzein respectively when incubated with rumen fluid (Nilsson *et al.*, 1967) and that small amounts of apigenin are detectable in urine following the administration of acacetin (4'-methylapigenin) to the rat (Griffiths and Smith, 1972a).

#### 12.2.11 Interactions of flavonoids with enzymes and other cell constituents

A number of flavonoids have been reported to have specific effects upon the activity of enzyme systems of mammalian cells, and certain of these may be of importance in mediating pharmacological action. Schwabe and Flohe (1972) reported inhibition of rat liver catechol-*O*-methyltransferase by certain flavonoids and have shown that the structural requirements for inhibitory activity are a flavonol ring system, a keto group at C-4 and hydroxylation at C-5. Gugler and Dengler (1973) have also demonstrated inhibition of *human* liver catechol-*O*-methyltransferase by flavonoids. They noted that flavonoid glycosides were less active than the corresponding aglycones and that reduction of the double bond between C-2 and C-3 diminished the inhibitory effect. Both groups reported that the presence of a keto group at C-4 and *o*-dihydroxylation in the B ring enhanced inhibition, and Schwabe and Flohe noted that compounds

possessing *o*-dihydric substitution could themselves serve as substrates for methylation *in vitro*. Recent investigations (Griffiths *et al.*, 1980) have shown that this reaction may be of major importance in the metabolism of flavonoids *in vivo*.

Certain flavones and flavonols have been reported to inhibit bovine pancreatic ribonuclease at concentrations of  $10^{-3}$ – $10^{-4}$  M. The effect is dependent on the presence of a keto group at C-4 and of certain hydroxyl groups. Flavanones and flavanonols lacked activity as did all flavonoid glycosides examined (Mori and Noguchi, 1970). The ability to inhibit lens aldose reductase is shown by a large number of flavonoids (Varma *et al.*, 1975; Varma and Kinoshita, 1976). At concentrations of  $10^{-5}$  M, rutin and quercitrin showed inhibition of 95%.

The flavanol (+)-catechin has been shown to produce a half-maximal inhibition of the prostaglandin synthetase of the renal medulla at a concentration of  $5 \times 10^{-5}$  M (Baumann and von Bruchhausen, 1979). (+)-Catechin has also recently been shown to be among a group of flavonoids able to inhibit cyclic GMP phosphodiesterase selectively (Ruckstuhl *et al.*, 1979). Certain ATPases were at an earlier date shown to be inhibited by the flavonol quercetin (Carpenedo *et al.*, 1969), and the significance for membrane-linked activity was discussed.

Certain flavones including 5,6- and 7,8-benzoflavones have been shown to exert an inhibitory effect on mono-oxygenases *in vitro* (Diamond and Gelboin, 1969; Wiebel and Gelboin, 1975) but to induce microsomal mono-oxygenase activity *in vivo* (Boobis *et al.*, 1977; Fang and Strobel, 1978; Wattenberg *et al.*, 1968). The latter authors also studied the structural requirements for induction and noted that increasing hydroxylation in the flavone series reduced inducing capacity but that the corresponding methoxy compounds were active. Active compounds included the naturally occurring flavones tangeretin and nobiletin. Several flavones have recently been shown to stimulate mammalian epoxide hydrase activity (Alworth *et al.*, 1980).

Since both arylhydrocarbon mono-oxygenase and epoxide hydrase are known to be important in the formation of carcinogenic metabolites, these findings are of considerable medical interest and further research on the ability of naturally occurring flavonoids to induce the formation of these enzymes *in vivo* appears to be an area of priority.

The interaction of flavonoids with the genetic material of the cell is indicated by numerous reports that certain flavonoids display mutagenicity in the Ames test (cf. Brown, 1980). Several studies have been carried out to determine the structural features necessary for mutagenic activity (McGregor and Jurd, 1978; Hardigree and Epler, 1978) and McGregor and Jurd concluded that for mutagenic activity in *Salmonella typhimurium* strain TA 98, a flavonoid should possess a free 3-hydroxyl substituent, a double bond in the 2,3 position, a keto group at the 4 position and a structure which permits the proton of the 3-hydroxyl group to tautomerize to a 3-keto compound. A high level of mutagenic activity was shown by quercetin, and Bjeldanes and Chang (1977) have shown that the mutagenic activity of quercetin is tripled by incubation with



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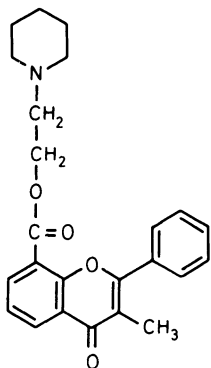
the microsomal fraction of liver. Although several reported metabolites of quercetin (*viz.* phenolic acids arising by ring fission) were examined for activity, all were found to be non-mutagenic and it was concluded that the proximate carcinogen was an unidentified metabolite.

Quercetin has been shown to be carcinogenic also in the rat following oral dosage, as neoplasms were subsequently observed in the gastrointestinal tract and bladder (Pamukcu *et al.*, 1980a,b). As quercetin is poorly absorbed (less than 1 % of dose) from the gastrointestinal tract (Gugler *et al.*, 1975), the development of neoplasms in the bladder epithelium appears somewhat surprising, but it is perhaps important to bear in mind that activation of the small amounts of absorbed quercetin may occur during transit through the liver as the microsomes of rat liver have been shown at least *in vitro* to increase the mutagenicity of quercetin (Bjeldanes and Chang, 1977).

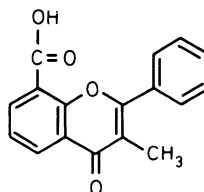
### 12.2.12 Metabolism of synthetic and chemically modified flavonoids

In addition to the investigations reported on the metabolism of naturally occurring flavonoids which are reviewed in preceding sections, the introduction of a number of chemically modified and synthetic compounds as pharmacological agents or food additives has resulted in metabolic study of compounds showing structural features absent from the natural plant flavonoids.

The synthetic flavone, flavoxate, (12.6), an antispasmodic drug was, following oral and intravenous administration to the rat, reported to be metabolized to a conjugate of 3-methylflavone-8-carboxylic acid (12.7) which was excreted in bile



(12.6) Flavoxate



(12.7) 3-Methylflavone-8-carboxylic acid

and urine. Up to 58 % of the dose was recovered from the bile of orally dosed biliary-cannulated animals within 24 h of administration. Total recovery from bile and urine under these conditions was 78 % (Setnikar *et al.*, 1975). Although the authors suggest the remainder of the dose is probably metabolized by ring

fission, the pattern of substitution of the molecule, especially the absence of A-ring hydroxylation, makes this improbable (see Section 12.2.1).

Metabolic study of the vaso-active hydroxyethylrutosides obtained by the hydroxyethylation of rutin has shown that the hydroxyethyl groups are not only resistant to metabolic change but confer greater metabolic stability upon the O-heterocyclic ring system, which as a consequence of hydroxyethylation becomes resistant to microfloral ring fission (Barrow and Griffiths, 1972, 1974a,b), whereas rutin is readily degraded to phenolic acids and CO<sub>2</sub> following oral administration to the rat (Booth *et al.*, 1956; Petrakis *et al.*, 1959). 7,4-[<sup>14</sup>C] Di-O-(β-hydroxyethyl)rutoside, 7,3',4' [<sup>14</sup>C]-tri-O-(β-hydroxyethyl)rutoside (Fig. 12.7) and 5,7,3',4' [<sup>14</sup>C]-tetra-O-(β-hydroxyethyl)rutoside are degraded *in vivo* only to the aglycone level, as the corresponding [<sup>14</sup>C]hydroxyethylquercetins can be recovered from the faeces (Barrow and Griffiths, 1972, 1974a,b). No <sup>14</sup>C labelled ring-fission products were detected in urine which contained small amounts of unchanged hydroxyethylrutosides and their glucuronide conjugates. Large amounts of the unchanged hydroxyethylrutosides and their glucuronides have been recovered from bile (see Section 12.3.3). No <sup>14</sup>CO<sub>2</sub> was detected in the respired air.

A new therapeutic agent, 3-O-methyl-(+)-catechin, has also been shown to be resistant to microfloral ring fission (Griffiths and Hackett, 1978), unlike the parent compound, (+)-catechin, which readily undergoes ring fission in the rat (Griffiths, 1964). The major metabolite of 3-O-methyl-(+)-catechin was shown to be 3,3'(or 4')-dimethyl-O-(+)-catechin glucuronide which was secreted in both bile and urine in the rat, whereas in the mouse and marmoset, the aglycone was the major urinary metabolite (Hackett and Griffiths, 1981). Metabolic studies utilizing 3-O-[methyl-<sup>14</sup>C] methyl-(+)-catechin showed that the 3-O-methyl substituent was resistant to metabolic attack and no <sup>14</sup>CO<sub>2</sub> was detected in respired air following oral administration to the rat (Hackett and Griffiths, 1981).

Although the possible use of chemically modified flavonoid derivatives, especially substituted dihydrochalcones as sweetening agents, has been explored in a number of laboratories, only limited data have been published on the metabolism of these compounds. Recently, however, investigations have been reported upon the fate of a group of sulphopropylated [<sup>14</sup>C]hesperetin derivatives (Brown *et al.*, 1978). Although [<sup>14</sup>C]hesperetin is known to be well absorbed (84% of dose) in the bile-duct-ligated rat (Honohan *et al.*, 1976), absorption of orally administered 7-O-[<sup>14</sup>C]sulphopropylhesperetin, 4-O-[<sup>14</sup>C] sulphopropylhesperetin dihydrochalcone and 2,4-[<sup>14</sup>C]di-O-sulphopropylhesperetin dihydrochalcone by these rats was found to decrease sharply with both sulphopropylation and reductive opening of the dihydropyrone ring. The sulphopropyl derivatives were also reported to be largely resistant to microfloral degradation.

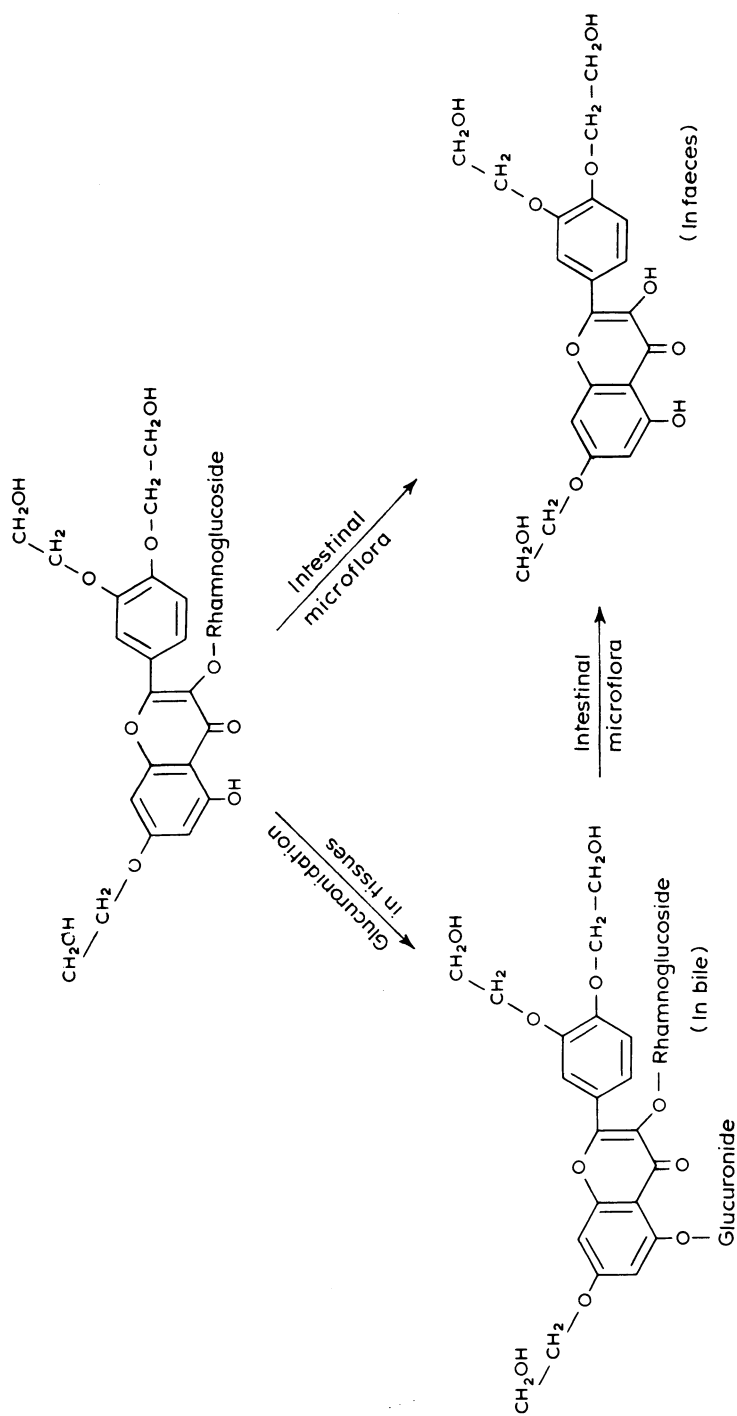


Fig. 12.7 Mammalian metabolism of 7,3',4'-tri-O-(β-hydroxyethyl)rutoside.

## 12.3 METABOLIC DISPOSITION

Studies on the distribution of radiochemically labelled compounds and their metabolites in the organs and tissues of animals can provide useful information, not only on the fate of the compound, but also on their sites of metabolism, the routes of excretion and the sequence of metabolite formation.

## 12.3.1 Distribution in organs, tissues and biological fluids

The earliest detailed study of the metabolic disposition of a flavonoid was that of Petrakis *et al.* (1959), who orally administered randomly labelled [ $^{14}\text{C}$ ]quercetin to the rat and reported on the distribution of radioactivity in a range of organs, tissues and biological fluids. They showed that 12 h after administration, radioactivity was largely associated with gastrointestinal contents (44.2%), although significant levels were present in lungs (11.5%), respired  $\text{CO}_2$  (15%), kidney (0.3%), urine (3.9%) and blood (0.2%). Rather surprisingly, no significant radioactivity was detected in liver. The urinary metabolites detected included the  $\text{C}_6\text{--C}_2$  phenolic acids reported by Booth *et al.* (1956). Following intraperitoneal administration of [ $^{14}\text{C}$ ]quercetin the formation of  $^{14}\text{C}$ -labelled  $\text{C}_6\text{--C}_2$  phenolic acids was reduced but [ $^{14}\text{C}$ ]vanillic acid was detected in urine. No  $^{14}\text{CO}_2$  was respired. This indicates not only that the metabolism of quercetin is determined by the route of administration but also suggests that the  $^{14}\text{CO}_2$  production observed after oral administration was dependent upon contact with the intestinal microflora, which is largely diminished by the *intraperitoneal* administration of quercetin. It is of interest here to note that Pfeifer *et al.* (1970) have shown that parenteral administration of rutin (quercetin rhamnoglucoside) results in deposition of the compound at the injection site and in the bile ducts, and in consequence effective biliary excretion is minimal (Barrow and Griffiths, 1971, 1974a).

Following the oral administration of [ $^3\text{H}$ ] rutin to rats, Tamemasa *et al.* (1976) showed that trace amounts of radioactivity only were detectable in bile, whereas 66% of the administered radioactivity was excreted in urine. The labelled metabolites of rat urine were not identified but their chromatographic properties suggest that they are largely ring fission products. The levels of radioactivity in a wide range of tissues was reported.

Early investigation of the disposition of flavanols showed that following oral administration of a [ $^{14}\text{C}$ ]catechin preparation containing non-labelled ascorbic acid, radioactivity was detectable in the muscles, liver, spleen, adrenals and kidneys of scorbutic guinea pigs (Shamrai and Zaprometov, 1964). The [ $^{14}\text{C}$ ]catechin preparation used was stated to contain a mixture of labelled catechins including (–)-epigallocatechin gallate, epicatechin gallate, (–)-epigallocatechin and (–)-epicatechin. The authors noted that the highest levels of radioactivity were observed in the adrenals. This was confirmed in a later publication (Shamrai and Fedurov, 1967), when additional data were presented

which indicated that 30 % of the administered  $^{14}\text{C}$  was eliminated as  $^{14}\text{CO}_2$ , 30 % in the faeces and 10 % in the urine.

The distribution of the leucoanthocyanidin, 5,7,3',4'-[ $^{14}\text{C}$ ]tetrahydroxyflavan-3,4-diol, in the tissues of the mouse has been studied by Laparra and Michaud (1973) using a radioautographic technique. Following intravenous administration, radioactivity disappeared rapidly from the systemic circulation, accumulating initially in liver and kidney and subsequently in skin, the periosteum of bone and in cartilaginous structures. Later, large amounts of radioactivity were observed in the gastrointestinal tract. Although low levels of activity were detected in the heart, high activity was found to be associated with aorta. Later, high activity was also observed in the intervertebral cartilages of the spinal column. The authors suggest that localization of the radioactive tetrahydroxyflavandiol in these cartilaginous structures may be attributable to the availability of reactive anionic sites in the mucopolysaccharides.

Recently Harmand and Blanquet (1977) have investigated the distribution of radioactivity in the rat following the intravenous administration of a mixed [ $^{14}\text{C}$ ]flavanol preparation containing (+)-catechin, (–)-epicatechin and several proanthocyanidin dimers. Radioactivity in blood was reported to reach a maximum value at 9 h, whilst radioactivity in connective tissues including cartilage, trachea, aorta and skin peaked at 15 h. The data obtained showed a specific accumulation of radioactivity in the latter tissues, resembling the pattern of distribution of [ $^{14}\text{C}$ ]tetrahydroxyflavandiol reported by Laparra and Michaud (1973). A specific accumulation was also shown in respect of the thyroid, pituitary and adrenal glands. Radioactivity in liver was also shown to attain maximal values at 15 h. Subsequently, radioactivity equivalent to 49 % of the intravenous dose was excreted in urine, 3 % in faeces and 1 % in expired air within 24 h.

The disposition of the chemically modified flavonoids, 7,3',4'-tri-*O*-( $\beta$ -hydroxyethyl)rutoside and 7-mono-*O*-( $\beta$ -hydroxyethyl)rutoside, has recently been investigated following intravenous administration to the mouse (Hackett and Griffiths, 1977). Blood concentrations of both compounds fell rapidly, whilst accumulation of radioactivity in the liver and kidneys was observed. The period of greatest decline in liver  $^{14}\text{C}$  (0–4 h) corresponded to the period of maximal biliary excretion.  $^{14}\text{C}$  was also readily detected in the more vascularized tissues, namely spleen and lung. In none of the experiments was radioactivity detected in brain, indicating that neither the administered compounds nor their metabolites were able to cross the blood–brain barrier. At no stage was  $^{14}\text{C}$  detected in peritoneal fat or in bone samples. The  $^{14}\text{C}$  in carcasses of animals killed between 3 and 72 h after intravenous dosage was associated mainly with gastrointestinal contents, indicating the importance of the biliary route of excretion.

Employing radioautography, the disposition of an intravenous dose of [ $^{14}\text{C}$ ]trihydroxyethylrutoside was investigated in mice sacrificed at 15 min, 30 min and 4 h after administration (Fig. 12.8; Hackett and Griffiths, unpublished observation). Following initial concentration in the liver (I), radio-

activity was transferred via the gall bladder (gb) and bile duct to the upper and lower intestine (ui, li). Radioactivity was also observed by this technique in kidney (k) and in the urinary bladder (ub). The major metabolites present in mouse faeces have been shown to be the corresponding aglycones of the rutosides administered (Hackett and Griffiths, 1977).

Radioautographic examination of [ $^{14}\text{C}$ ]hydroxyethylrutoside-dosed mice did not reveal localization of label in the connective tissue sites, including cartilage of the intervertebral discs, trachea and aorta, which were identified by Laparra and Michaud (1973) and Harmand and Blanquet (1977) as specific sites of accumulation of radioactivity following [ $^{14}\text{C}$ ]flavan-3,4-diol and/or [ $^{14}\text{C}$ ]flavan-3-ol administration.

Following the injection of [ $^{14}\text{C}$ ]trihydroxyethylrutoside and [ $^{14}\text{C}$ ]mono-hydroxyethylrutoside into the tail vein of pregnant mice on the 18th day of pregnancy, it was shown that 5 min after injection, the time corresponding to peak tissue levels in male mice,  $^{14}\text{C}$  in all foetuses was less than 0.1 % of the administered dose. Foetuses from mice killed 3 h after injection of either compound contained no detectable  $^{14}\text{C}$  (Hackett and Griffiths, 1977a,b).

### 12.3.2 Blood levels

Although the plasma levels attained in several mammalian species following the administration of certain flavonoids employed in clinical practice has been reported, blood pharmacokinetic data are available for relatively few flavonoids.

Plasma levels of the flavonol, quercetin, following intravenous administration to man were monitored by Gugler *et al.* (1975) using a specific and highly sensitive assay method. Disappearance of quercetin from plasma after a single dose was apparently bi-exponential with a mean terminal half life of 2.4 h. The decline of the plasma level curve after the distribution phase was attributed by the authors mainly to metabolism of the drug. Following oral administration, however, no measurable plasma concentration was observed and the authors concluded that unchanged quercetin did not reach the systemic circulation.

Following the oral administration of a [ $^{14}\text{C}$ ]hydroxyethylrutoside preparation to a group of human volunteers, peak plasma levels were observed from 2 to 9 h (Fig. 12.9). These levels then showed a progressive decline until at 40 h, a low  $^{14}\text{C}$  level was established which then declined slowly over the following 120 h when the experiment was terminated (Hackett *et al.*, 1976). The maximal plasma levels observed were approx. 0.3  $\mu\text{g}/\text{ml}$ . Insufficient  $^{14}\text{C}$ -labelled metabolite(s) were present in the blood plasma to permit identification, but since the hydroxyethylrutosides present in this preparation are known to be resistant to ring fission (Barrow and Griffiths, 1972, 1974a,b), it is probable that the radioactivity detected in plasma was associated with unchanged hydroxyethylrutosides or their glucuronide conjugates.

Similar quantitative data have subsequently been presented by Förster (1977) following oral administration of labelled hydroxyethyl rutosides to human

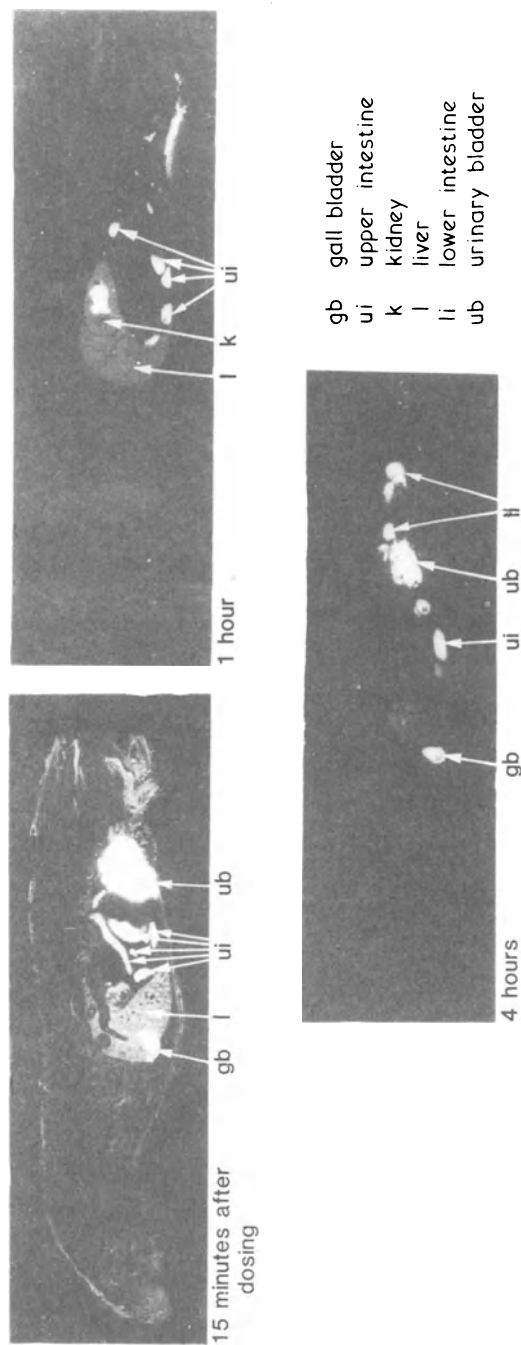


**Fig. 12.8** Distribution of  $^{14}\text{C}$  in the mouse following intravenous administration of 7,3',4',-[ $^{14}\text{C}$ ] tri-*O*-( $\beta$ -hydroxyethyl) rutoside.

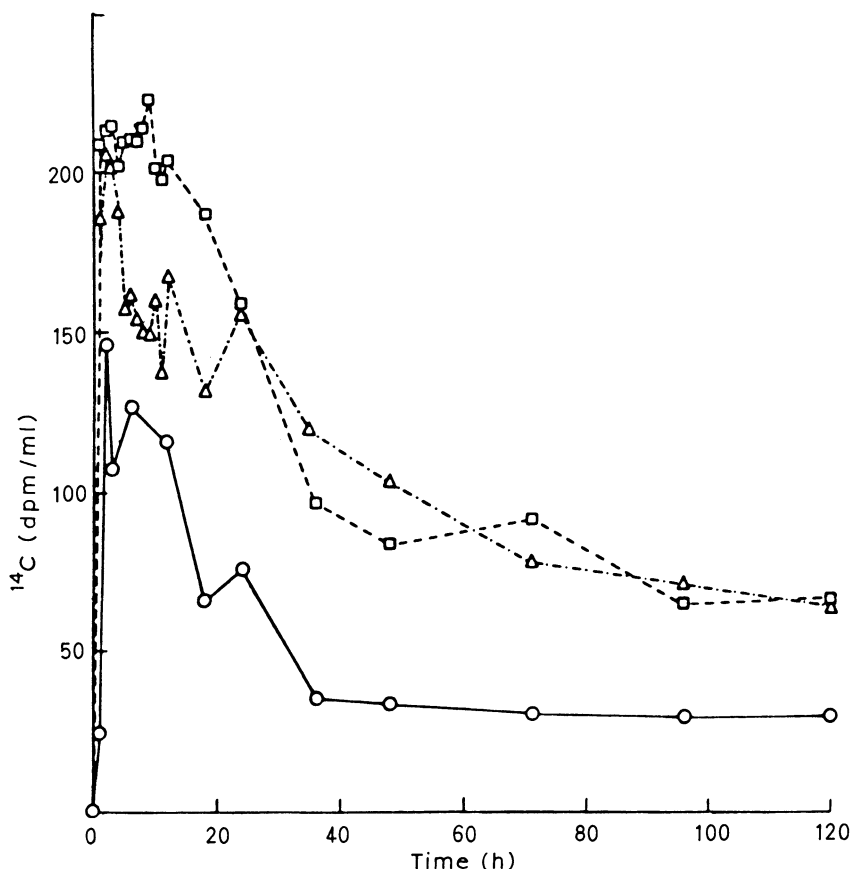


Fig. 12.9  $^{14}\text{C}$  levels in the plasma of three human subjects following a single oral dose of  $[\text{}^{14}\text{C}]$ hydroxyethylrutinosides.

volunteers. Additionally, data obtained by intravenous infusion were reported which showed that the hydroxyethylrutinosides are under these conditions rapidly removed from the systemic circulation.

The plasma levels of hydroxyethylrutinoside in man have also been determined by circular dichroism measurements (Jung *et al.*, 1977), following the administration of a non-labelled hydroxyethylrutinoside preparation. After intravenous administration, it was observed that the major part of the hydroxyethylrutinosides disappeared from the blood within 1–2 h. Following oral administration maximal concentrations were found over the 6–10 h period.

Investigation on plasma levels of dogs following the oral administration of a  $^{14}\text{C}$ -labelled mixed hydroxyethylrutinoside preparation showed that peak levels were attained between 5 and 6 h (Mirkovitch *et al.*, 1973). Studies employing 7- $[\text{}^{14}\text{C}]$ mono-*O*-( $\beta$ -hydroxyethyl)rutinoside also showed that  $^{14}\text{C}$  peak levels were



attained within 6 h of oral dosage after which a slow decline to 72 h was observed. Chromatographic examination of plasma samples revealed the presence of a single radioactive metabolite, which was shown to be 7-mono-*O*-( $\beta$ -hydroxyethyl)rutoside glucuronide (Hackett and Griffiths, 1979).

A pharmacokinetic investigation of (+)-catechin in man showed that peak plasma levels of metabolites of this flavanol determined by a colorimetric technique occurred within 1–2 h after oral administration when up to 17  $\mu$ g of metabolites/ml serum were observed. These peak blood levels corresponded to 2.5–3 % of the ingested dose (Giles and Gumma, 1973). Subsequently, however, Balant *et al.* (1979) using a highly specific HPLC technique concluded that at the maximum serum concentrations, 10 % of serum metabolites represented unchanged (+)-catechin, 40 % corresponded to metabolites possessing an intact phloroglucinol ring, whilst 50 % represented other unidentified metabolites of (+)-catechin. The apparent half life of unchanged (+)-catechin was estimated from sera data to be 1–1.3 h.

It may be concluded that high serum levels of administered flavonoids are not readily sustained, whether single doses of the compounds are administered orally or parenterally. The data available do not, however, indicate whether this is attributable wholly to the efficient hepatic extraction observed in biliary cannulated animals and to renal excretion or whether rapid uptake by other tissues plays a significant part.

### 12.3.3 Routes of excretion

Earlier studies on the metabolism and excretion of flavonoids were largely restricted to metabolites eliminated in urine which were mainly compounds of small molecular weight, subsequently shown to be products of ring fission (see Section 12.2.1). These metabolites were sometimes observed to be accompanied by small or trace amounts of the flavonoid administered or its glucuronide conjugates. In 1971, evidence was presented that the biliary-enteric route was of major importance for the excretion of intact flavonoid molecules and their conjugates (Barrow and Griffiths, 1971; Das and Sothy, 1971).

#### (a) Biliary excretion

Following parenteral administration of [ $^{14}$ C](+)-catechin to the bile-duct-cannulated rat, Das and Sothy showed that 33–44 % of the administered radioactivity was excreted in bile largely as flavanol conjugates. Parallel investigations showed that following *oral* as well as parenteral administration, conjugates of (+)-catechin, naringin and 7,3',4'-tri-*O*-( $\beta$ -hydroxyethyl)rutoside were excreted in rat bile (Barrow and Griffiths, 1971). Following intraperitoneal administration of the latter hydroxyethylrutoside to intact rats, large amounts of the aglycone were detected in faeces. The corresponding aglycones of naringin, naringenin and (+)-catechin were not detected under similar experimental

conditions in faeces, but this can be attributed to the known susceptibility of the latter to degradation by the intestinal microflora (Griffiths and Smith, 1972a; Griffiths, 1964; Das, 1969).

Further investigations have established that biliary excretion is an important factor in the metabolism and pharmacokinetics of many flavonoid compounds (Table 12.1). Flavonoids now known to be excreted in bile include: flavanols (Barrow and Griffiths, 1971; Das and Sothy, 1971; Griffiths and Hackett, 1978; Hackett and Griffiths, 1980; Harmand *et al.*, 1978; Shaw and Griffiths, 1980), flavanones (Honohan *et al.*, 1976; Hackett *et al.*, 1979; Buset and Scheline, 1980), flavolignans (Bülles *et al.*, 1975; Mennicke *et al.*, 1979), anthocyanins (Lietti *et al.*, 1976), flavones (Oustrin *et al.*, 1977; Setnikar *et al.*, 1975; Svardal *et al.*, 1980), flavonols (Barrow and Griffiths, 1971, 1972, 1974a,b), chalcones (Griffiths *et al.*, 1980), dihydrochalcones (Barrow and Griffiths, 1971) and the C-glycosylflavone, orientin (luteolin-8-C-glucopyranoside) (Paris and Delaveau, 1977).

The major factors leading to the excretion of organic compounds in significant quantity in rat bile have been identified by Smith (1973) as (a) a molecular weight exceeding 325 ( $\pm 50$ ) and (b) the degree of polarity of the compound excreted. Since most *non-glycosidic* flavonoids show low polarity and possess a molecular weight below the described threshold, they would not be expected to be readily excreted in bile. However, recent studies have shown that the major products of hepatic metabolism of many flavonoids are the corresponding glucuronides (Barrow and Griffiths, 1974a,b; Bülles *et al.*, 1975; Hackett and Griffiths, 1979; Griffiths *et al.*, 1980; Shaw and Griffiths, 1980), which not only possess considerable polarity but also show molecular weights in excess of the 325 threshold.

Flavonoid glycosides, although of low polarity, do possess molecular weights above this described threshold and in consequence may be excreted to an appreciable extent in bile without glucuronidation. This has been noted in relation to 5,7,3',4'-tetra-O-( $\beta$ -hydroxyethyl)rutoside (Barrow and Griffiths, 1972) and naringin (Hackett *et al.*, 1979).

The substitution of certain flavonoids has been shown to be an important factor in determining the extent of biliary excretion. In studies on the hydroxyethylrutoside series (Barrow and Griffiths, 1972, 1974a,b), it was shown that progressive hydroxyethylation of the parent rutin molecule resulted in a reduction in the proportion of the dose excreted in bile. The highest levels of biliary excretion were observed in respect of the mono- and di-hydroxyethylrutosides and the lowest shown by the fully hydroxyethylated 5,7,3',4'-O-( $\beta$ -tetrahydroxyethyl)rutoside. The latter rutoside alone was excreted in larger amounts in urine than in bile. Progressive hydroxyethylation not only diminished biliary excretion but also reduced the percentage of the flavonoid excreted as glucuronide, which accords well with the view that glucuronide formation facilitates excretion of flavonoids by the biliary route.

Dosage levels may also be an important factor in determining the extent of biliary excretion. Hackett *et al.* (1979) have shown that progressive reduction of

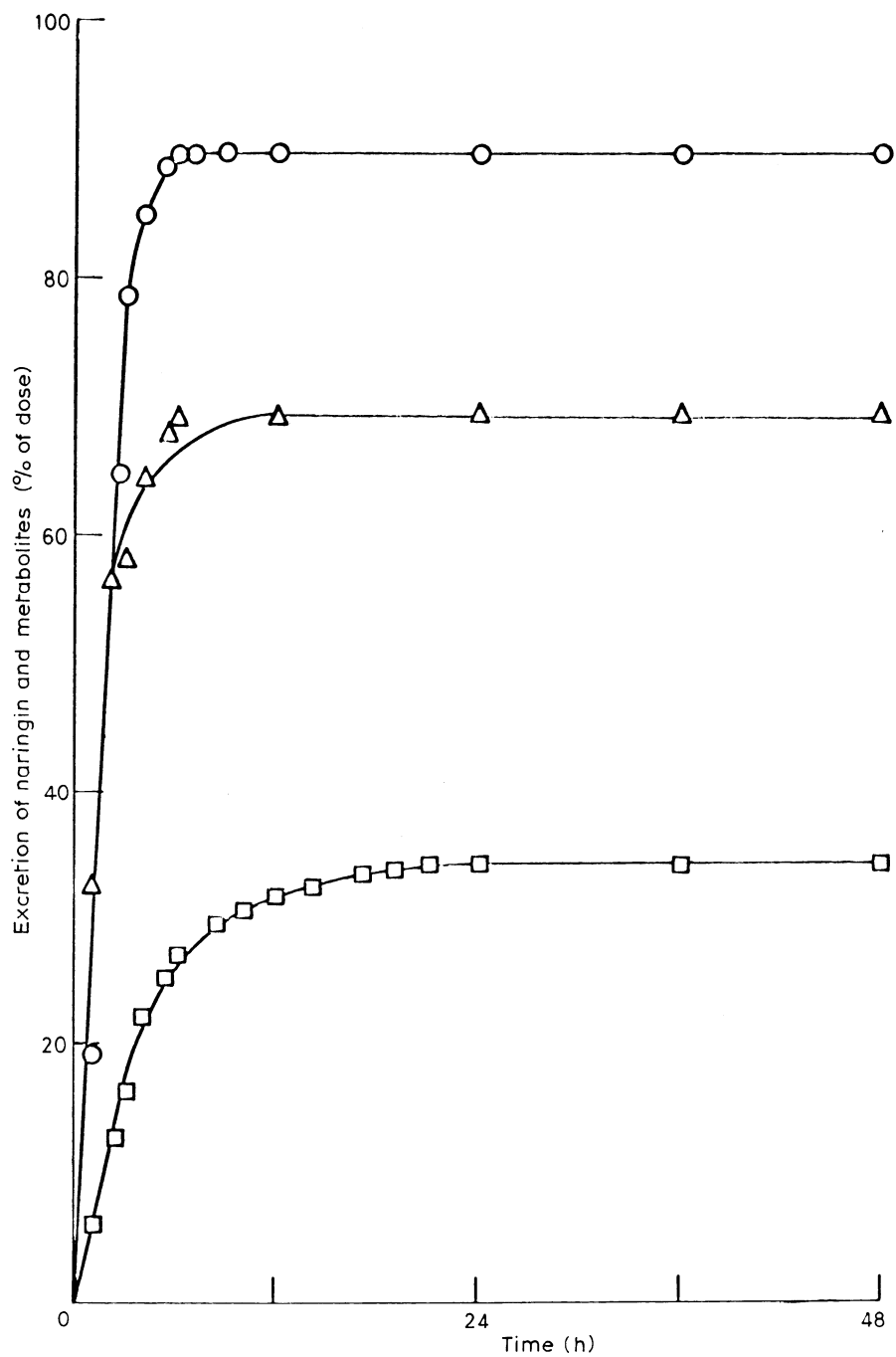


**Fig. 12.10** The excretion of naringin and its metabolites in bile as a percentage of dose following intraperitoneal administration to the rat. Dosage levels per rat: 5 mg: ○ 10 mg: △ 50 mg: □

the intraperitoneal dose of certain flavanones results in elevation of the percentage of the dose excreted in bile. The inverse relationship between dose and the magnitude of biliary excretion in respect of naringin is shown in Fig. 12.10.

Although the extent of biliary excretion of flavonoid is usually greater after parenteral administration than after oral administration, this is usually seen to be a consequence of slow absorption from the gastrointestinal tract rather than attributable to any change in the partitioning of metabolites between the biliary and the renal route, as the total excretion by both these routes is usually significantly less after oral administration (Table 12.1)

### **(b) Enterohepatic cycling**

Although biliary excretion has been established as a major route of excretion of many flavonoids limited information is available concerning the subsequent fate of the conjugates entering the intestine. The presence of large amounts of  $\beta$ -glucuronidase in intestinal contents (Marsh *et al.*, 1952; Hawkesworth *et al.*, 1971) and of micro-organisms able to effect ring scission of the released aglycones (see Section 12.2.2) provides the means by which the biliary metabolites of many naturally occurring flavonoids may be degraded to compounds of low molecular weight. Additionally, however, the possibility of reabsorption of the biliary metabolites with the establishment of an enterohepatic cycle requires consideration. Evidence that the hydroxyethylrutosides undergo enterohepatic cycling in the rat has recently been presented (Hackett and Griffiths, 1977b). Using intercannulated rat preparations, the biliary metabolites, formed following the parenteral dosage of [ $^{14}\text{C}$ ]monohydroxyethylrutoside and [ $^{14}\text{C}$ ]trihydroxyethylrutoside to the first animal of each pair, were transferred by a bile-duct cannula into the gut lumen of a second animal and the levels of radioactivity determined subsequently in the bile and urine of the second animal. The results obtained showed that a significant uptake of the biliary metabolites from the gut of the second animal had occurred. The radioactive constituents of the bile and urine were shown to consist largely of the glucuronide conjugates of the administered hydroxyethylrutoside. The evidence obtained does not, however, reveal whether deconjugation of the biliary metabolites precedes absorption followed by resynthesis, but this appears probable in view of the known polarity of the glucuronide conjugates. Since enterohepatic cycling extends the period during which pharmacologically active compounds persist in the systemic circulation, these findings may be of significance in relation to the maintenance of therapeutic levels in man but the possibility of species differences should not be excluded.

### **(a) Urinary excretion**

Although as noted above, the flavonoid metabolites excreted in urine are largely ring fission products of low molecular weight, small amounts of flavonoids and

their conjugates have not been infrequently observed. Following the oral administration of naturally occurring flavonols, urinary excretion of flavonols and their conjugates is minimal. In a definitive study on the disposition of quercetin in man, Gugler *et al.* (1975) reported that following oral administration to man, neither quercetin nor quercetin conjugates were detectable in urine at any time following ingestion. Following the oral administration of rutin to the rat, Barrow and Griffiths (1974a) were likewise unable to detect the administered compound or its conjugates in urine. Although an early investigation failed to detect the excretion of the rutin derivative, 7,3',4'-tri-*O*-( $\beta$ -hydroxyethyl)rutoside in human urine following the oral administration of the unlabelled compound (Wienert and Gahlen, 1970), subsequent investigation revealed that following oral administration to the rat low but significant urinary excretion (1.7–2.5%) of the administered compound and of its glucuronide(s) occurred (Barrow and Griffiths, 1974b). In man following the oral administration of  $^{14}\text{C}$ -labelled hydroxyethylrutosides, 1.6–2% of the administered radioactivity was excreted in urine as unchanged hydroxyethylrutoside. Total urinary radioactivity corresponding to 3.05–5.97% of the dose was observed (Hackett *et al.*, 1976). Subsequent investigations on the fate of orally administered [ $^{14}\text{C}$ ]7,3',4'-tri-*O*-( $\beta$ -hydroxyethyl)rutoside in man (Tan *et al.*, 1978) showed that following  $\beta$ -glucuronidase treatment of the urine 5.3% of the administered  $^{14}\text{C}$  could be recovered from the urine.

In a recent pharmacokinetic study on the absorption and elimination of the flavone, [ $^3\text{H}$ ]diosmin, it has been claimed that 25% of the dose is eliminated in urine (Oustrin *et al.*, 1977). Much of this radioactivity may, however, be associated with ring fission products, earlier reported in rat urine after diosmin administration (Booth *et al.*, 1958).

Following the oral administration of [ $\text{U-}^{14}\text{C}$ ] (+)-catechin to the rat, it was shown that 50–63% of the administered radioactivity was excreted in urine but only 0.12% was attributable to unchanged (+)-catechin (Das and Griffiths, 1969). In man, Balant *et al.* (1979) have shown by means of an HPLC technique that only 0.5% of an oral dose of (+)-catechin appears in human urine as unchanged (+)-catechin. Although unchanged (+)-catechin is thus a minor urinary metabolite, recent investigation has shown that following the oral dosage of [ $^{14}\text{C}$ ] (+)-catechin to the rat, a high proportion of the urinary radioactivity (approx. 30%) is associated with the flavonoid conjugate, 3'-*O*-methyl-(+)-catechin glucuronide (Shaw and Griffiths, unpublished observation) which is also known to be the major biliary metabolite of (+)-catechin in the rat (Griffiths *et al.*, 1980).

The large amounts of radioactivity (*ca.* 50% of dose) excreted in the urine of the rat following oral dosage with the related flavanol, 3-*O*-methyl-(+)-catechin have been shown to be largely associated with the metabolite, 3,3' (or 4')-dimethyl-(+)-catechin glucuronide which accounts for approx. 80% of the urinary radioactivity in this species (Hackett and Griffiths, 1981). In the mouse and marmoset, however, the major urinary metabolite is the free aglycone,

3,3'-dimethyl-(+)-catechin. The high level of urinary excretion of metabolites containing an intact flavonoid ring system is probably attributable to high absorption of orally administered 3-O-methyl-(+)-catechin associated with resistance of the molecule to microfloral ring fission.

Although the extent of urinary excretion of orally administered flavonoids has been employed by a number of investigators as a measure of absorption, it is evident that any assessment of flavonoid absorption based on urinary excretion data alone may lead to erroneous conclusions on two counts. Firstly, it has been shown that many flavonoids are excreted to a significant extent in bile; indeed this may represent the major proportion of the absorbed dose. Secondly, many flavonoids undergo degradation in the intestine to compounds of low molecular weight which are readily absorbed and subsequently excreted in urine. Much of the urinary radioactivity measured, following the administration of a labelled flavonoid, may be attributable to intestinal metabolic products of this type.

It is, therefore, important that in assessing flavonoid absorption by excretion data that both biliary and urinary metabolites should be fully characterized and a measure of absorption obtained by summation of recoveries of intact flavonoids and flavonoid conjugates from both bile and urine. Although the excretion of ring fission products provides no evidence of absorption of the parent flavonoid molecules, it is, however, important to give consideration in specific cases to the possibility that the fission products may be derived from biliary metabolites rather than from the unabsorbed flavonoid.

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