Tetrahedron, 1959, Vol. 6, pp. 169 to 200. Pergamon Press Ltd. Printed in Northern Ireland

RECENT DEVELOPMENTS IN THE CHEMISTRY OF FLAVONOIDS

T. R. SESHADRI
Department of Chemistry, University of Delhi, Delhi

(*Received* 30 *October* 1958)

Physiological importance

IN recent years, there has been considerable development in the study of vitamin P action and other therapeutic properties of flavonoids.[1,2] Rutin and quercetin have now an established place in therapeutics and are being produced in large quantities. A study of the subject has revealed many possibilities of application. Flavonoids occur in a variety of plants and their extensive use provides opportunity for a new industry based on agriculture.

In food industries such as those of fruit products and beverages, the presence of flavonoids and the various changes they undergo are of importance in regard to taste, flavour, stability and physiological properties. It has been reported by El-Rafey[3] that quercetin enhances the nutritive value of butter.

Flavonoids as antioxidants

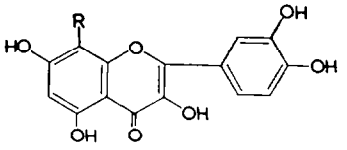
Another direction in which interest has been created is the use of flavonoids as antioxidants. Though reports were made, more than twenty years ago, that quercetin (I) acts an an antioxidant for fats, only recently this subject received attention. Heimann *et al.*[4] suggested that the α:β-unsaturated ketonic structure of the pyrone ring, a free hydroxyl group in the 3-position and free *ortho*-dihydroxy (3′:4′-) grouping in the side phenyl nucleus contribute to the antioxidant activity of quercetin. These structural requirements are similar to those needed for vitamin P properties as recorded earlier.[5]

More recently[6,7] the antioxidant properties of a large number of flavones and flavonols using methyl linoleate have been studied. About the same time a comprehensive study of the antioxidant properties was carried out[8] employing natural fats. There is general agreement between our results and those of other workers.

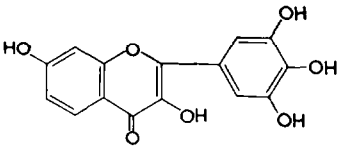
Flavonols are much superior to the other groups of flavonoids and *ortho* and *para* dihydroxy groupings enhance the antioxidant activity; in certain cases the 7:8-dihydroxy system is very favourable. Among the large number of compounds examined, gossypetin (II) and robinetin (III) are compounds of great potency. They are better than quercetin though the latter has the advantage of large availability

[1] J. Q. Griffith, Jr., C. F. Krewson and J. Naghski, *Rutin and related flavonoids'—Chemistry, Pharmacology and Clinical Applications* pp. 1–275. Mack Publishing, Pennsylvania (1955).
[2] G. J. Martin and A. Szent-Györgyi, *Ann. N. Y. Acad. Sci.* **61**, 1–100 (1956).
[3] M. S. El-Rafey, *Wisc. Agri. Exptl. Sta. Bull.* **465**, 33 (1944).
[4] W. Heimann, A. Heimann, M. Gremminger and H. Holland, *Fette u. Seif.* **55**, 394 (1953).
[5] W. G. Clark and T. A. Geissman, *J. Pharm. Exp. Ther.* **95**, 362 (1949).
[6] T. H. Simpson and N. Uri, *Chem. & Ind.* 956 (1956).
[7] C. H. Lea and P. A. T. Swoboda, *Chem. & Ind.* 1426 (1956).
[8] A. C. Mehta and T. R. Seshadri, *J. Sci. Industr. Res. India* In press (1959).

from a number of plant sources. As the result of studies on nuclear oxidation, the conversion of quercetin into gossypetin[9] is easy and good yields are obtained; hence large scale preparation of gossypetin may not offer any difficulty. Robinetin, though not occurring widely in the plant kingdom, can be synthesised by the well known Allan–Robinson condensation. The flavonols should further be considered because of their vitamin P properties.



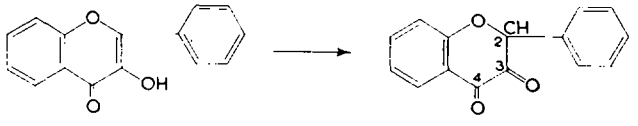
I, R=H
II, R=OH



III

From the above results relating to antioxidant properties, the occurrence of flavonoids in the heartwoods of plants has considerable significance in connection with their stability to atmospheric oxidation. The toxic properties of these compounds towards fish have already been discussed[10] and they seem to be able to confer resistance to attack by micro-organisms and insects.

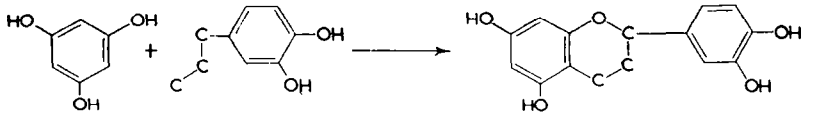
It is significant that flavonols are markedly better antioxidants compared with other types. Particular mention may be made that quercetin is much better than taxifolin (dihydroquercetin) though the latter is known to undergo ready oxidation. Based on the free radical theory of autoxidation, the capacity of flavonols (IV) to isomerize into the diketone form (V) seems to provide a possible explanation. The carbon atom in the 2-position will be capable of developing the free electron centre for immobilising free radicals. Catechol and quinol systems in the benzene rings may reinforce the above centre and may also play independent parts as antioxidant groups.



IV V

Biogenesis of flavonoids

This has been a subject of great interest and the main contributions to our know ledge were made earlier by Robinson[11] who considered the flavonoid (C_{15}) skeleton (VI) to be composed of two parts viz. C_6 and C_9 (VII & VIII).

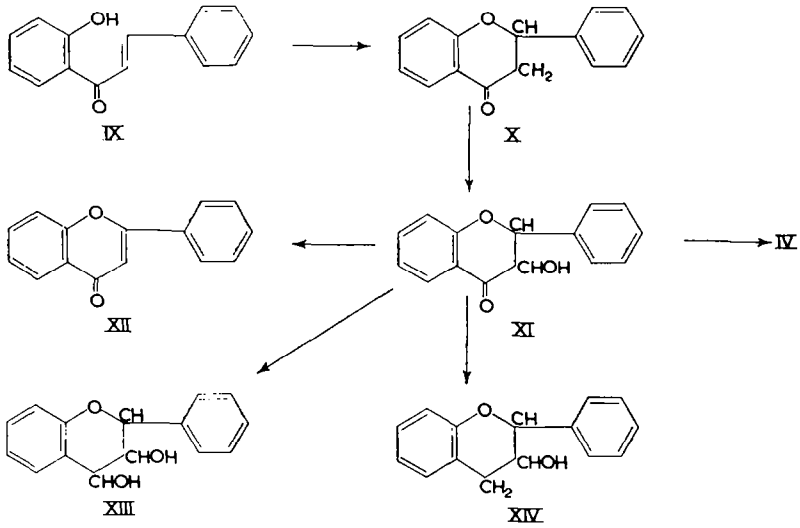


VII VIII VI

Attempts have recently been made to gain information on the origin of the different parts by employing the tracer technique. The compounds whose syntheses have been

[9] K. V. Rao and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 25**, 417 (1947).
[10] T. R. Seshadri, *Ann. Rev. Biochem.* **20**, 490 (1951).
[11] R. Robinson, *Nature, Lond.* **137**, 172 (1936).

studied are quercetin and cyanidin. Underhill *et al.*,[12] followed by others,[13,14] have reported their observations on the biosynthesis of quercetin using buckwheat (*Fagopyrum tataricus*) which produces rutin (quercetin-3-rhamnoglucoside). A number of isotopically labelled (C^{14}) compounds were supplied and the quercetin produced by the plant was decomposed by standard methods. The general indications are that the C_9 and C_6 units have different origins. The latter seem to be produced from acetate units whereas the former seem to arise either from shikimic acid, phenylalanine or cinnamic acid derivatives. The biosynthesis of cyanidin in red cabbage has also been studied[15,16] and the results support the origin of phloroglucinol from acetate units.



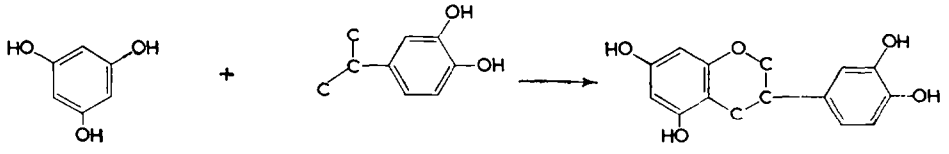
Whatever may be the origin of the C_6 and C_9 units, these seem to be definitely involved in the structure of the flavonoid skeleton.[11] More information has been available in recent years on the inter-relationship between various groups of flavonoids and the possibility of one undergoing change into another. The earliest of the series would appear to be chalkones (IX) and the related flavanones (X). These occur invariably together[17] so long as a phloroglucinol unit with free hydroxyl groups is not present. The flavanone becomes the only stable entity if a 5-hydroxyl group is present in it and this has been attributed to the existence of chelation between this hydroxyl and the neighbouring keto group. A study of the co-occurrence of various groups of flavonoids has revealed important results.[18] The data led to the conclusion that a flavanone (X) can undergo hydroxylation in the 3-position to give rise to a 3-hydroxyflavanone (XI). This reaction has been carried out in a number of ways; the most satisfactory and significant is Fenton's method of oxidation.[19] The hydroxyl

[12] E. W. Underhill, J. E. Watkins and A. C. Neish, *Canad. J. Biochem. Physiol.* **35**, 219, 229 (1957).
[13] T. A. Geissman and T. Swain, *Chem. & Ind.* 984 (1957).
[14] S. Shibata and M. Yamazaki, *Pharm. Bull.* **6**, 42 (1958).
[15] F. Weygand, W. Bruckers, H. Grisebach and E. Schulze, *Z. Naturf.* **B 12**, 222 (1957).
[16] H. Grisebach, *Z. Naturf.* **B 12**, 227 (1957); **B 13**, 335 (1958).
[17] T. R. Seshadri, *Sci. Proc. Roy. Dublin Soc.* **27**, 77 (1956).
[18] T. R. Seshadri, *Les Heterocycles Oxygenes* p. 71. Colloques Internationaux du Centre National la Recherche Scientifique (1955).
[19] V. B. Mahesh and T. R. Seshadri, *J. Chem. Soc.* 2503 (1955).

thus introduced seems to be in the correct conformation for the elimination of water (i.e. *cis* hydrogens) to give a flavone (XII). This conformation is, however, unstable and can undergo change into the more stable *trans*-form which is common in Nature. The stable type undergoes facile dehydrogenation to give rise to flavonols (IV). Thus 3-hydroxyflavanones would appear to hold a key position in the biogenesis of flavonoids. Further, they can be reduced conveniently to yield *leuco*anthocyanidins (XIII),[20,21] which are widely distributed, and also form the catechins (XIV).[22]

3-Phenyl- and 4-phenylchroman derivatives

*iso*Flavones were originally few and considered to be derived from normal flavonoids by a process involving migration of the phenyl group.[23,24] A number of them have later been discovered. Further, we have the same skeleton in pterocarpin and *homo*-pterocarpin[25] and also in angolensin.[26,27] A more recent discovery is that of wedelolactone[28] which is a 3-phenylcoumarin derivative, closely related to the compounds mentioned above. It has, therefore, been suggested[29] that the C_9 forked unit (XV) which is present in all these compounds should be considered as being directly involved in the biogenesis of 3-phenylchroman derivatives (XVI).



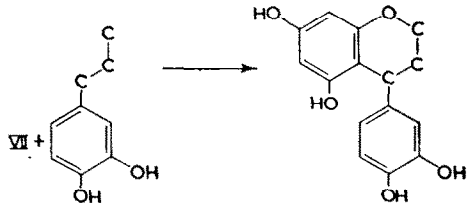
VII XV XVI

Only two compounds were known having a 4-phenylchroman system, namely brazilin and haematoxylin, and Robinson[30,31] originally indicated that they were derived from butein by incorporating a single carbon unit; and the skeleton could be built up on this basis in the laboratory. There has also been the suggestion[32] that their origin involves double migration of phenyl groups starting with the normal 2-phenylchroman structure.

More compounds of this type have recently been found in plants: (i) dalbergin and methyldalbergin in the heartwood of *Dalbergia sissoo*[33] and (ii) calophyllolide in the fruits of *Calophyllum inophyllum*.[34] There seems to be justification for considering that these compounds have an origin independent of the normal flavonoids. Obviously, the linking of C_6 and C_9 (VII & VIII) units can take place in an alternative way to yield 4-phenylchroman derivatives (XVII). The reaction seems to be feasible since,

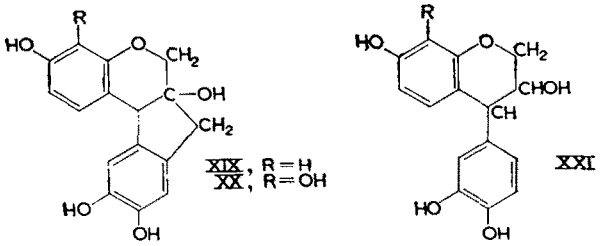
[20] T. Swain, *Chem. & Ind.* 1144 (1954).
[21] A. K. Ganguly and T. R. Seshadri, *Tetrahedron* **6**, 21 (1959).
[22] J. W. Clark-Lewis and W. Korytnyk, *J. Chem. Soc.* 2367 (1958).
[23] T. A. Geissman and E. Hinreiner, *Bot. Rev.* **18**, 165 (1952).
[24] R. Robinson, *The Structural Relations of Natural Products* p. 41. The Clarendon Press, Oxford (1955).
[25] A. McGookin, A. Robertson and W. B. Whalley, *J. Chem. Soc.* 787 (1940).
[26] F. E. King, T. J. King and A. J. Warwick, *J. Chem. Soc.* 1920 (1952).
[27] V. N. Gupta and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 15**, 146 (1956).
[28] T. R. Govindachari, K. Nagarajan and B. R. Pai, *J. Chem. Soc.* 629 (1956).
[29] T. R. Seshadri, *Curr. Sci.* **26**, 239 (1957).
[30] H. G. Crabtree and R. Robinson, *J. Chem. Soc.* **113**, 859 (1918).
[31] R. Robinson, *The Structural Relations of Natural Products* p. 43. The Clarendon Press, Oxford (1955).
[32] W. B. Whalley, *Chem. & Ind.* 1049 (1956).
[33] V. K. Ahluwalia and T. R. Seshadri, *J. Chem. Soc.* 970 (1957).
[34] J. Polonsky, *C. R. Acad. Sci., Paris* **242**, 2961 (1956).

for example, resorcinol reacts with cinnamic acid to yield 7-hydroxy-4-phenyldihydrocoumarin.[35]



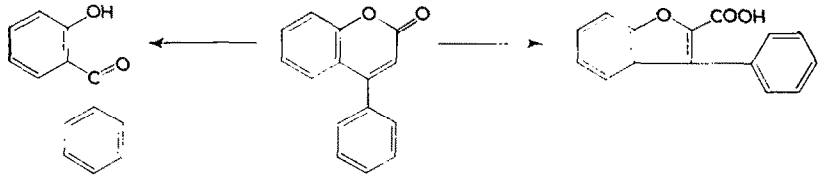
VII + VIII → XVII

Since the 4-phenylcoumarins can undergo ready oxidation to benzophenones (XVIII), they are probably intermediates in the formation of the latter. A more satisfactory scheme for the evolution of brazilin (XIX) and haematoxylin (XX) may, therefore, be the incorporation of a single carbon atom into the 4-phenylchroman structure (XXI).[29,32]



XIX, R = H; XX, R = OH

XXI



XVIII XXII XXIII

An interesting and significant property of the 4-phenylcoumarins (XXII) is the colour reaction they give with magnesium and alcoholic hydrochloric acid. Initially an emerald green colour is produced and this changes to a permanent red. The colour seems to be due to the formation of 4-phenylpyrylium salts similar to the flavylium salts. Further, these 4-phenylcoumarins (XXII) exhibit a marked tendency to undergo oxidation with mercuric oxide in alkaline solutions to yield the corresponding coumarilic acids (XXIII).[36]

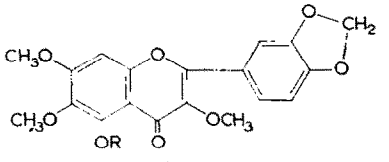
Nuclear oxidation and reduction

Earlier studies of the occurrence of a large number of flavonoids and of their association in plant sources has conclusively established the incidence of nuclear

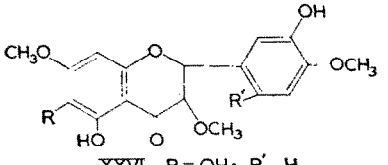
[35] J. D. Simpson and H. Stephen, *J. Chem. Soc.* 1382 (1956).
[36] V. K. Ahluwalia, A. C. Mehta and T. R. Seshadri, *Tetrahedron* 4, 271 (1958).

oxidation (hydroxylation) in the development of more complex compounds from simpler ones. But no experimental proof was provided about the feasibility of this process and particularly about the reactivity of the molecules in support of this biosynthesis. Many earlier experiments were not successful, but by adopting mild methods and special conditions, Seshadri and co-workers have successfully carried out the nuclear oxidation of a large number of flavonoids. A very important example is the hydroxylation of quercetin to gossypetin[9] on one hand and to myricetin[37] on the other. They have shown that the *para* oxidation is most conveniently effected by alkaline persulphate and the *ortho* oxidation by a two stage process involving aldehyde synthesis and Dakin oxidation. This has led to the convenient preparation, from simpler compounds, of (i) the gossypetin, quercetagetin and calycopterin series of flavonols, (ii) the wogonin, baicalein and nobiletin series of flavones, (iii) chalkones of the pedicin group, (iv) *iso*flavones and (v) anhydro-colour bases like carajurin, and also of many partial methyl ethers occurring in Nature. Reference compounds, needed in the structural studies of naturally occurring anthoxanthin glycosides and partial methyl ethers, can be readily made by the application of these methods. The work has already been reviewed.[38–40]

A more recent extension of this method is the synthesis of the quercetagetin group of flavonols[41] and analogous *iso*flavones.[42] This is particularly useful for the synthesis of certain naturally occurring partial methyl ethers which are difficult to obtain by other methods. Starting from the appropriate 6-hydroxy compounds and introducing a 5-hydroxyl group by the two-stage oxidation, melisimplin (XXIV),[41] melisimplexin (XXV)[41] and oxyayanin-B (XXVI)[43] have been obtained. By applying *para* oxidation in the side phenyl nucleus, oxyayanin-A (XXVII) has been prepared.[44]



XXIV, R = H
XXV, R = CH_3



XXVI, R = OH; R' = H
XXVII, R = H; R' = OH

The possibility of nuclear reduction involving the removal of a phenolic hydroxyl group was also indicated by the survey of anthocyanins and anthoxanthins and the study of their association in Nature. Adequate laboratory analogies, at first sight, seemed to be lacking and hence this process had not been generally recognised as a feasible one. Numerous examples have been recorded in which laboratory reactions involve the loss of a nuclear hydroxyl group.[45]

The following additional cases may be mentioned; boiling hydriodic acid and

[37] K. V. Rao and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 28,** 210 (1948).
[38] T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 28,** 1 (1948); **A 30,** 333 (1949).
[39] T. R. Seshadri, *Rev. Pure Appl. Chem. Aust.* **1,** 186 (1951).
[40] T. R. Seshadri, *Experientia Suppl.* II, 258 (1955).
[41] A. C. Jain, T. R. Seshadri and K. R. Sreenivasan, *J. Chem. Soc.* 3908 (1955).
[42] K. Aghoramurthy, T. R. Seshadri and G. B. V. Subramanian, *J. Sci. Industr. Res. India* **B 15,** 11 (1956).
[43] R. N. Goel, A. C. Jain and T. R. Seshadri, *J. Chem. Soc.* 1369 (1956).
[44] N. K. Anand, S. R. Gupta, K. S. Pankajamani and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 15,** 263 (1956).
[45] T. R. Seshadri, *XIV Int. Congress Pure App. Chem. Zurich. Experientia Suppl.* II, 270 (1955).

red phosphorus convert asperthecin[46] into *frangula*-emodin anthranol, and tocopherols[47] lose one nuclear hydroxyl by this treatment. Examples have been recorded among simpler benzene derivatives also. Reduction of 1:2:3:5-tetrahydroxybenzene, its monomethyl ether (iretol) and hexahydroxybenzene with sodium amalgam yields phloroglucinol, and hydroxyquinol gives dihydroresorcinol.[48]

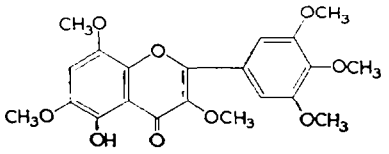
A number of types of compounds have been employed and various reducing agents such as stannous chloride, sodium dithionite, zinc and acetic acid, hydriodic acid and red phosphorus, and sodium amalgam have been used for the direct removal of a hydroxyl group usually from a quinol or a catechol system. A different method, used by Kenner and Murray,[49] involves catalytic reduction (hydrogenolysis) of a tosyl ester using Raney nickel and has been found subsequently to be capable of wide application. Conversion of salicylic acid into benzoic acid,[49] phloroglucinol carboxylic acid into γ-resorcylic acid[50] and orsellinic acid into 6-methylsalicylic acid[51] are typical examples.

The reduction of chrysin to 5-hydroxyflavone and of 3-O-methylgalangin into 5-hydroxy-3-methoxyflavone was carried out almost simultaneously by Ramanathan and Venkataraman;[52] and Jain and Seshadri.[53] This involves the removal of the 7-hydroxyl group. Nuclear reduction in the 5-position giving rise to 7-hydroxy compounds has been reported[54] using as examples, chrysin, apigenin, galangin and quercetin. The hydroxyl groups in the side phenyl nucleus can also be removed[55] i.e. a quercetin derivative is converted into kaempferol and a kaempferol derivative into galangin. Complete removal of hydroxyl groups from the condensed benzene ring as well as the side phenyl nucleus is possible if it is a flavonol derivative, e.g. 3-methoxyflavone can be obtained from 7-hydroxy-3-methoxyflavone; but if there is no substituent in the pyrone ring, further reduction takes place affecting this ring also. 7-Hydroxy- and 5-hydroxy-flavones yield 4-hydroxyflavan.[56,57] Hydroxyxanthones undergo similar nuclear reduction.[58,59] Thus a hydroxyl group in 1- or 3-position can be removed in the case of 1:3-dihydroxyxanthone, yielding 3-hydroxy- and 1-hydroxyxanthone respectively. The successful laboratory preparation of the natural euxanthone (1:7-dihydroxyxanthone) and *allo*euxanthone (3:7-dihydroxyxanthone) from the naturally occurring compound, gentisein (1:3:7-trihydroxyxanthone), further supports the feasibility of nuclear reduction process in Nature. It is also of interest to note that 1-hydroxyxanthone on reduction gives xanthone and not a further reduction product as is obtained in the case of 7- and 5-hydroxyflavones.

The utility of these methods of oxidation and reduction in the synthesis of

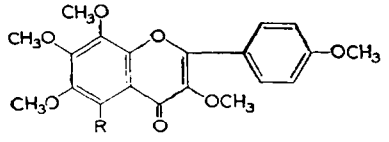
[46] B. H. Howard and H. Raistrick, *Biochem. J.* **59**, 475 (1955).
[47] W. John, E. Dietzel and P. Gunther, *Z. Physiol. Chem.* **252**, 208 (1938).
[48] T. Posternak, *Helv. Chim. Acta* **19**, 1336 (1936).
[49] G. W. Kenner and M. A. Murray, *J. Chem. Soc.* **S**, 178 (1949).
[50] V. Ramanathan and K. Venkataraman, *Curr. Sci.* **21**, 283 (1952).
[51] K. Aghoramurthy, M. K. Ramanathan and T. R. Seshadri, *Chem. & Ind.* 1327 (1954).
[52] V. Ramanathan and K. Venkataraman, *Proc. Indian Acad. Sci.* **A 38**, 40 (1953).
[53] A. C. Jain and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 12**, 503 (1953).
[54] A. C. Jain and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 38**, 294 (1953).
[55] A. C. Jain and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 38**, 467 (1953).
[56] V. N. Gupta, A. C. Jain and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 38**, 470 (1953).
[57] J. E. Gowan, S. P. MacGiolla, G. T. MacMohan, S. O'Cleirigh, E. M. Philbin and T. S. Wheeler, *Terathedron* **2**, 120 (1958).
[58] A. C. Jain, O. P. Mittal and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 12**, 647 (1953).
[59] O. P. Mittal and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 14**, 76 (1955).

gardenin (XXVIII), a compound which is otherwise difficult to build up, has already been reviewed.[60]



XXVIII

More recently, a detailed analysis of the peel of a sweet variety of *Citrus aurantium* has revealed the occurrence of auranetin (3:6:7:8:4′-pentamethoxyflavone) (XXIX) and 5-hydroxyauranetin (XXX) together.[61] This may be of significance in biogenesis; the removal of the free hydroxyl of 5-hydroxyauranetin can be smoothly effected by the above method of tosylation and hydrogenation giving rise to auranetin.



XXIX, R=H
XXX, R=OH

Nuclear methylation[62]

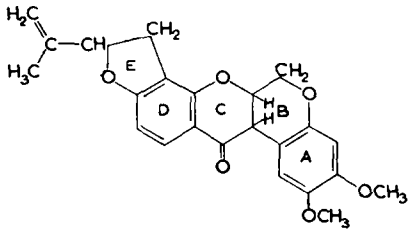
During the ordinary methylation of flavonoids, certain complications arise owing to C-methylation which was noted towards the end of the last century. Based on analogies, the position involved in C-methylation was considered by Baker and Robinson[63] to be 6. The subject has been studied in detail in recent years and the various groups of flavonoids have been examined. It is now established that methylation with methyl iodide and alcoholic potash or better sodium methoxide uniformly gives 6-methyl derivatives. The 8-methyl compounds could be obtained by an alternative method of synthesis using hexamine or similar reagents. The mechanism of these reactions has also been considered; in the first case a β-diketo form of the 5:7-dihydroxyflavonoid seems to be involved and in the second case it is a reaction at an anionoid nuclear position. In Nature one or both of these positions (6 and 8) are found to undergo nuclear methylation and a large number of such compounds have been discovered in recent years. Based on analogy with laboratory experience, it has been suggested that formaldehyde equivalents as well as transmethylating agents can be involved in the process. In the place of methylation, substitution involving dimethylallyl groups is also common and seems to be more facile.

Furan derivatives of flavonoids

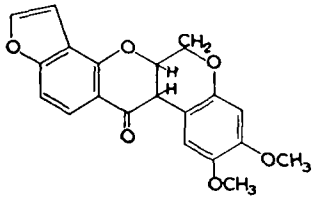
Rotenone and related compounds have been known for a long time. Their valuable selective insecticidal action has made them important. Rotenone (XXXI)

[60] T. R. Seshadri, *Experientia Suppl.* II, 271 (1955).
[61] P. S. Sarin and T. R. Seshadri, *Tetrahedron* To be published.
[62] A. C. Jain and T. R. Seshadri, *Quart. Rev.* **10**, 169 (1956).
[63] W. Baker and R. Robinson, *J. Chem. Soc.* 2713 (1926).

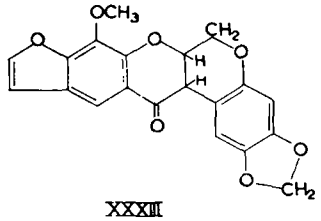
itself has a reduced furan ring with an *iso*propenyl substituent in the α-position. Occurring along with it are other rotenoids which have an unsubstituted furan ring, e.g. elliptone (XXXII)[64] from *Derris elliptica*. In these compounds the fusion of the furan ring to the main skeleton is of the angular type. The alternative fusion of the linear type is also possible as indicated by the isolation of pachyrrhizon[65] (XXXIII) from *Pachyrrhizus erosus*. Harper[66] has recorded that simpler furano-*iso*flavones, in which the oxide ring B was absent, also occurred with rotenoids. Robinson[67] compared rotenone with berberine, brazilin and haematoxylin and made the suggestion that its structure could be derived from the branch chain C_6-C_3-C_6-*iso*flavone skeleton by the addition of one carbon bridge.



XXXI



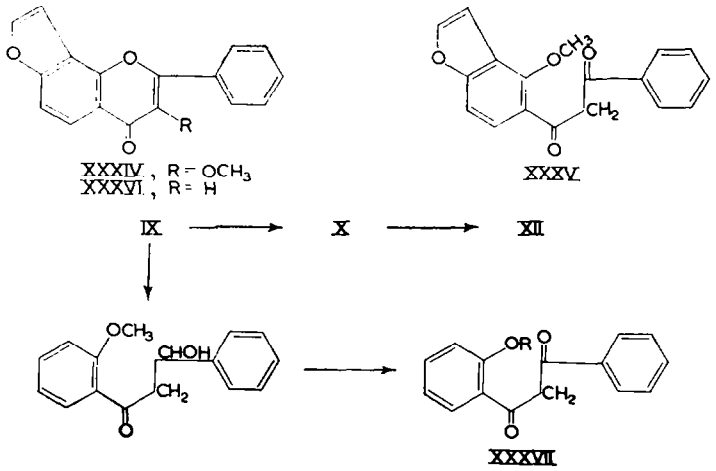
XXXII



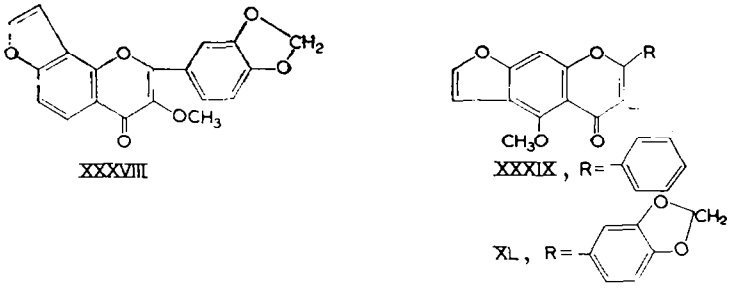
XXXIII

Somewhat later than the rotenoids, flavone derivatives with a fused furan ring were discovered. Karanjin (XXXIV) was the first member to be isolated, studied and synthesised.[68,69] In the seeds of *Pongamia glabra*, pongamol (XXXV) was subsequently found along with karanjin.[70] It is the diketonic analogue[71] of the simplest furanoflavone of the angular type (XXXVI) and its occurrence indicates that the diketone may be a stage in the biosynthesis of flavones. But such combinations are rare and the formation of the diketone seems to be dependent on the *ortho* hydroxyl group being protected by methylation. A more satisfactory explanation of their occurrence would be to consider that both flavones (XII) and diketones (XXXVII) are the result of parallel evolution from chalkones (IX) as shown below.

[64] S. H. Harper, *J. Chem. Soc.* 1099 (1939).
[65] H. Bickel and H. Schmid, *Helv. Chim. Acta* **36**, 664 (1953).
[66] S. H. Harper, *J. Chem. Soc.* 1118 (1940).
[67] R. Robinson, *The molecular architecture of some plant products* p. 11. IX Int. Congress Pure Appl. Chem. Madrid (1934).
[68] D. B. Limaye, *Rasayanam* 1 (1936); 119 (1937).
[69] T. R. Seshadri and V. Venkateswarlu, *Proc. Indian Acad. Sci.* A **9**, 259 (1939).
[70] S. Rangaswami and T. R. Seshadri, *Curr. Sci.* **9**, 179 (1940).
[71] S. Narayanaswami, S. Rangaswami and T. R. Seshadri, *J. Chem. Soc.* 1871 (1954).



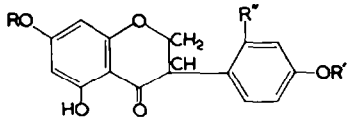
Pongapin (XXXVIII) is another important member of this group and it occurs along with karanjin (XXXIV) in the Australian plant, *Pongamia pinnata*.[72] Present in the same source are gammatin (XXXIX) and pinnatin (XL) which are linear furanoflavones[73] isomeric respectively with karanjin and pongapin.



Pongamol (XXXV) has also been found in the root bark of *Tephrosia lanceolata*[74] (originally called lanceolatin C) along with the simplest furanoflavone (XXXVI) named as lanceolatin B. This discovery is interesting since other *Tephrosia* species are known to contain rotenoids (complex *iso*flavonofuran derivatives). In a related species, *Tephrosia maxima isoflavones* having isoprene units attached have been discovered.[75] These significant observations would suggest that there are common features, particularly as regards the origin of the furan unit.

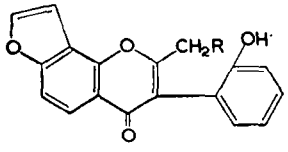
The suggestion[76] seems to be justified that in rotenoids, the *iso*flavone or *iso*flavanone structure constitutes the core of the molecule and the other parts have been built at later stages, and in this connexion may be mentioned the recent isolation of the *iso*flavanones, padmakastein (XLI) (bark of *Prunus puddum*),[77] ferreirin (XLII) and *homo*ferreirin (XLIII) (from the heartwood of *Ferreirea spectabilis*).[78] The oxygen ring in them is of the reduced type, as found in rotenoids (ring C).

[72] L. R. Row, *Aust. J. Sci. Res.* A **5**, 754 (1952).
[73] S. K. Pavanaram and L. R. Row, *Aust. J. Chem.* **9**, 132 (1956).
[74] S. Rangaswami and B. V. R. Sastry, *Curr. Sci.* **24**, 13 (1955).
[75] S. Rangaswami and B. V. R. Sastry, *Curr. Sci.* **23**, 397 (1954); **24**, 337 (1955).
[76] T. R. Seshadri and S. Varadarajan, *Proc. Indian Acad. Sci.* A **37**, 784 (1953).
[77] N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **35**, 202 (1952).
[78] F. E. King, M. F. Grundon and K. G. Neill, *J. Chem. Soc.* 4580 (1952).

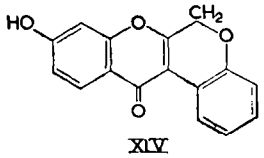


XLI, R = CH_3; R′ = R″ = H
XLII, R = H; R′ = CH_3; R″ = OH
XLIII, R = H; R′ = CH_3; R″ = OCH_3

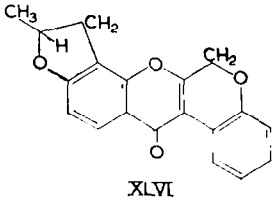
Based on the above-mentioned considerations, simplified methods of synthesis have been developed for building up the 5 ring system of rotenoids. Starting with an *iso*flavone, the intermediate stage would be a 4 ring system, either a furano*iso*-flavone (XLIV)[79] or a chromenochromone (XLV)[76,80] to which the fifth ring could be finally added. A simpler compound having the 5 ring system (XLVI) has been synthesised[81] by the second procedure.



R = OH or halogen XLIV



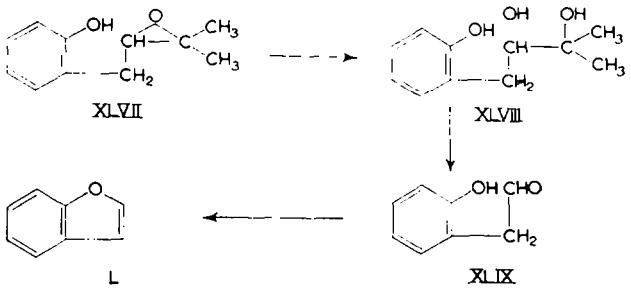
XLV



XLVI

There has been considerable difficulty in the application of the available methods for the construction of a furan ring on to the flavonoid structure. A satisfactory method for this purpose has been recently developed[82] and it is based on considerations of biosynthesis.[83] A careful study of the relationships of furan and other extra skeletal structures present in a variety of naturally occurring substances had led to the conclusion that the C_5 *iso*pentene unit is fundamental and can undergo various modifications. One of these is the capacity to undergo oxidation through the epoxide (XLVII) and glycol (XLVIII) stages, leading to an *o*-hydroxyphenylacetaldehyde system (XLIX); this undergoes ready *cyclo*dehydration to form an unsubstituted furan (L). For laboratory syntheses, such aldehydes are conveniently obtained by ozonolysis or similar treatment of the simpler allyl unit. A study of typical examples (karanjin,[82] pongapin,[82] angelicin,[83] psoralene,[83] visnagin[84] and kellin[85]) has established the full value of this method of approach; good yields of the furano compounds are obtained by the minimum number of steps.

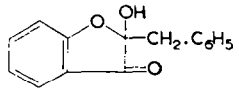
[79] L. R. Row and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **34**, 187 (1951).
[80] A. C. Mehta and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **42**, 192 (1955).
[81] P. S. Sarin, J. M. Sehgal and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **47**, 292 (1958).
[82] R. Aneja, S. K. Mukerjee and T. R. Seshadri, *Tetrahedron* **2**, 203 (1958).
[83] R. Aneja, S. K. Mukerjee and T. R. Seshadri, *Tetrahedron.*
[84] R. Aneja, S. K. Mukerjee and T. R. Seshadri, *Tetrahedron.*
[85] R. Aneja, S. K. Mukerjee and T. R. Seshadri, *J. Sci. Industr. Res. India* B **17**, 382 (1958).



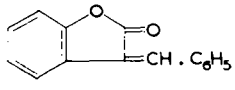
XLVII XLVIII L XLIX

3-Hydroxyflavanones

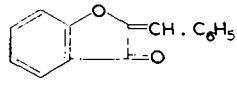
As one of the important lines of recent advances should be mentioned 3-hydroxyflavanones (XI).[86] More than a dozen of these compounds are now known and their constitution established. The main sources are heartwoods and barks of trees. Their isolation and purification are based on their appreciable solubility in water and in ether[87,88] and also on their capacity to form somewhat sparingly soluble salts.[89] They can undergo both dehydration and dehydrogenation giving rise to flavones and flavonols respectively. They are unstable particularly in the presence of alkali and undergo isomeric change into the related 2-hydroxy-2-benzylcoumaran-3-ones (LI).[90] Further change is also possible (involving benzil-benzilic acid change) giving rise to the anhydro-lactones (3-benzalcoumaran-2-ones, LII).[91–93]



LI



LII



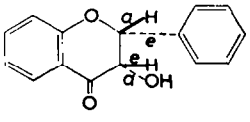
LIII

Methylation of 3-hydroxyflavanones has been reported to yield a variety of products.[94,95] Under mild conditions avoiding aqueous medium, it is possible to prepare partial methyl ethers with most or all of the phenolic hydroxyl groups methylated and the alcoholic hydroxyl group free. By prolonged treatment, dehydrogenation and subsequent methylation of the 3-hydroxyl group take place giving rise to the corresponding flavonol methyl ethers. But strong alkaline conditions cause opening of the flavanone ring, leading eventually to the production of methyl ethers of (LI) or (LIII).

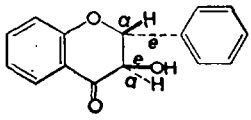
[86] J. E. Gowan, E. M. Philbin and T. S. Wheeler, *The Chemistry of Vegetable Tannins* p. 133. Society of Leather Trades' Chemists, Croydon (1956).
[87] J. C. Pew, *J. Amer. Chem. Soc.* **70**, 3031 (1948).
[88] W. R. Carruthers, R. H. Farmer and R. A. Laidlow, *J. Chem. Soc.* 4440 (1957).
[89] E. F. Kurth, H. L. Hergert and J. D. Ross, *J. Amer. Chem. Soc.* **77**, 1621 (1955).
[90] J. Gripenberg, *Acta Chem. Scand.* **7**, 1323 (1953).
[91] T. Oyemada, *Liebigs Ann.* **538**, 44 (1939).
[92] M. Chadenson, L. Molho-Lacroix, D. Molho and C. Mentzer, *C. R. Acad. Sci., Paris* **249**, 1362 (1955).
[93] J. Gripenberg and B. Jesulius, *Acta Chem. Scand.* **8**, 734 (1954).
[94] W. E. Hillis, *Aust. J. Sci. Res.* **A 5**, 379 (1952).
[95] O. P. Goel, N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 39**, 254 (1954).

The stereochemistry[96] of 3-hydroxyflavanones involves the configuration of the carbon atoms 2 and 3. As a consequence, four optically active and two racemic forms are possible. The natural compounds seem to belong to the *trans* variety and undergo ready dehydrogenation in the presence of alkali or acid and air yielding the corresponding flavonols. This conclusion is supported by the hydrogenation of a (+) taxifolin derivative in the presence of Adams catalyst whereby a (+) catechin derivative is obtained.[22]

A number of methods have been developed for the synthesis of 3-hydroxyflavanones, but the most convenient seems to be the direct hydroxylation of flavanones in the 3-position, either by means of iodine and silver acetate[95,97] or by Fenton's reagent.[19] The synthetic compounds differ markedly from the natural ones in undergoing ready dehydration instead of dehydrogenation. This could be explained as due to the difference in the stereochemistry of the 2- and 3-positions. The synthetic compounds seem to have *cis* hydrogens and the 3-hydroxyl is in the axial conformation (LIV) favourable for the elimination of water. This is also the conformation that could be expected from the substitution reaction employed for the preparation. The *cis*-form is, however, unstable and on treatment with sodium acetate gets converted into the more stable *trans*-form (LV) which is the one occurring in Nature.[96]



LIV



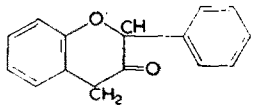
LV

As already mentioned earlier, these compounds are of biogenetic interest since they seem to constitute an essential common step for other groups of flavonoids.

Leuco*anthocyanidins*

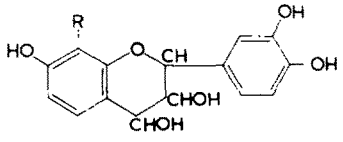
In view of the recent review on this subject,[98] only important points and more recent developments are mentioned here. Rosenheim[99] discovered the existence of *leuco*anthocyanins in the course of his study of the grape vine and the skin of white grapes. He considered them to have the structure of *pseudo*-bases corresponding to the anthocyanins. Robinson[100] made a comprehensive survey of plant materials and found that *leuco*anthocyanidins were widely distributed, either occurring in combination with sugars or free. *Leuco*cyanidins were the most common. He showed that these are not really *pseudo*-bases, and based on their characteristic properties, he suggested that they may have either a flavan-diol (XIII) or the related ketoflavan (LVI) structure. Bate-Smith[101] considered that many plant sources, reported to contain phlobatannins, really contained *leuco*anthocyanidins having probably the flavan-diol structure.

[96] V. B. Mahesh and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 41**, 210 (1955).
[97] R. N. Goel, V. B. Mahesh and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 47**, 184 (1958).
[98] T. Swain and E. C. Bate-Smith, *The Chemistry of Vegetable Tannins* p. 109. Society of Leather Trades' Chemists, Croydon (1956).
[99] O. Rosenheim, *Biochem. J.* **14**, 178 (1920).
[100] G. M. Robinson and R. Robinson, *Biochem. J.* **27**, 206 (1933).
[101] E. C. Bate-Smith, *Biochem. J.* **58**, 122 (1954).



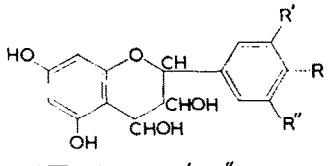
LVI

The first crystalline *leuco*anthocyanidins to be studied were cyanomaclurin and peltogynol, but they had special complexity. King and Bottomley[102] isolated melacacidin from the wood of *Acacia melanoxylon*, prepared a number of derivatives and established its constitution as 7:8:3′:4′-tetrahydroxyflavan-3:4-diol (LVII). This was supported by the synthesis of its tetramethyl ether from 3-hydroxy-7:8:3′:4′-tetramethoxyflavone by hydrogenation using Raney nickel catalyst.[103] Keppler[104] isolated another member of this group, mollisacacidin, from *A. mollissima*. It was shown to have the structure of 7:3′:4′-trihydroxyflavan-3:4-diol (LVIII) and was prepared from fustin by catalytic hydrogenation. But the more widely occurring group of *leuco*anthocyanidins resisted isolation and characterisation. Many of them have now been prepared using certain plant drugs and tanning materials as the most satisfactory sources. The *leuco*anthocyanidins could be obtained in an almost colourless crystalline condition; their partial methyl ethers and acetates are more definitely crystalline and more suitable for physical and chemical studies.



LVII, R=OH LVIII, R=H

(−) *Leuco*pelargonidin (LIX)[105] has now been obtained from *Eucalyptus calophylla* gum (Australian kino). *Butea* gum, another drug, has yielded a (+) *leuco*cyanidin (LX)[21] and tamarind seed testa, a large by-product of industry, another dextrorotatory isomer of the same.[106] Karada bark, a well known tanning material, yields a (−) *leuco*delphinidin (LXI);[107] the gum of *Eucalyptus pilularis* (Nilgiris kino) and the bark of *Phyllanthus emblica* contain a (+) *leuco*delphinidin,[107,108] and a third isomeric (+) *leuco*delphinidin[109] has been obtained from the bark of *Myrica nagi*. All these belong to the flavan-diol type. The results so far obtained show that each *leuco*anthocyanidin can occur in more than one form in Nature.



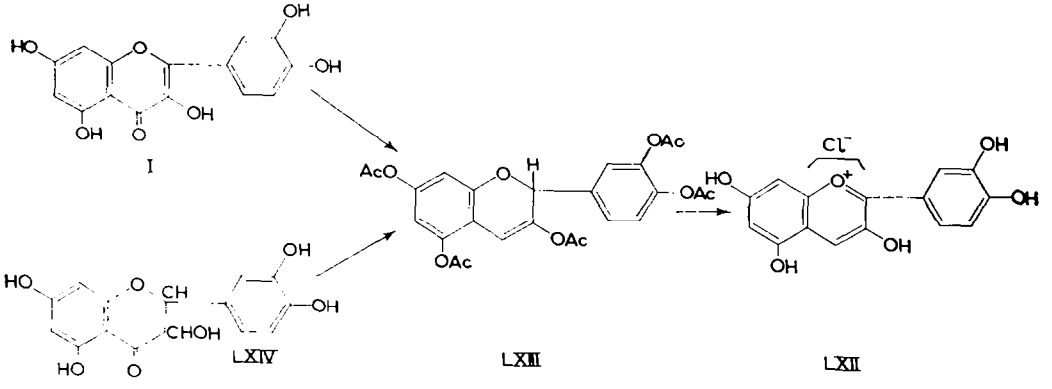
LIX, R=OH; R′=R″=H
LX, R=R′=OH; R″=H
LXI, R=R′=R″=OH

[102] F. E. King and W. Bottomley, *J. Chem. Soc.* 1399 (1954).
[103] F. E. King and J. W. Clark-Lewis, *J. Chem. Soc.* 3384 (1955).
[104] H. H. Keppler, *J. Chem. Soc.* 2721 (1957).
[105] A. K. Ganguly and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 17**, 168 (1958).
[106] K. R. Laumas and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 17**, 44 (1958).
[107] A. K. Ganguly and T. R. Seshadri, *Tetrahedron* **6**, 21 (1959)
[108] K. R. Laumas and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 17**, 167 (1958).
[109] K. R. Laumas and T. R. Seshadri, Unpublished work.

The methods of synthesis of *leuco*anthocyanidins could be considered under two categories: (i) reduction of flavonols and (ii) reduction of dihydroflavonols. The successful synthesis of a *leuco*anthocyanidin by method (i) was made by King and Clark-Lewis[103] who obtained melacacidin tetramethyl ether by the hydrogenation of 3-hydroxy-7:8:3′:4′-tetramethoxyflavone in the presence of Raney nickel. (ii) In the reduction of aromadendrin acetate using lithium aluminium hydride, Bauer, *et al.*[110] isolated a colourless gum which was converted by hot acid in propanol into pelargonidin. Following on this work, Swain[20] reported that the reduction of taxifolin with sodium borohydride gave a non-crystalline *leuco*cyanidin which yielded a hexa-acetate and a tetramethyl ether. The borohydride method has been used as the most convenient, and taxifolin and its methyl ether have been reduced.[21] They yield mixtures of racemates which could be separated by fractional crystallisation. One of these isomers is found to agree with the derivative of the naturally occurring *leuco*cyanidin. Similar reduction of aromadendrin and its methyl ether[111] also gives *leuco*pelargonidin derivatives. Keppler[104] prepared mollisaccacidin by catalytic reduction (Pt catalyst) of the dihydroflavonol, fustin. Freudenberg has used this method for the reduction of a number of dihydroflavonols. An ingenious modification is the use of tetrabenzoyldihydroquercetin to obtain *leuco*cyanidin.[112] In this reaction the benzoyl groups are reduced to benzyl and eventually removed.

In the acetylation of the *leuco*anthocyanidins certain stereoisomers suffered dehydration even in the cold and yielded the corresponding flaven-3-ol acetates.[113] Other stereoisomers did so when the reaction was carried out by heating. These enol acetates have the special characteristic of forming high yields of the corresponding anthocyanidins.

The enol acetate seems to be capable of being formed easily in an unexpected way by the reduction of flavonols. King and White[114] recently carried out the reductive acetylation of flavonols by boiling with zinc dust, acetic anhydride and sodium acetate and thought that the reaction affected only the carbonyl group. From quercetin (I), they obtained an amorphous product to which they gave a constitution which did not agree with the analytical results, but it gave a good yield of cyanidin



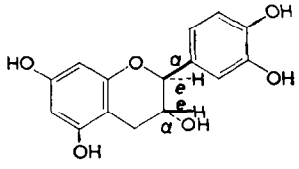
[110] L. Bauer, A. J. Birch and W. E. Hillis, *Chem. & Ind.* 433 (1954).
[111] A. K. Ganguly and T. R. Seshadri, Unpublished work.
[112] K. Freudenberg and K. Weinges, *Angew. Chem.* **70**, 51 (1958).
[113] K. R. Laumas and T. R. Seshadri, *Proc. Indian Acad. Sci.* (1959) under publication.
[114] H. G. C. King and T. White, *J. Chem. Soc.* 3901 (1957).

chloride (LXII) with alcoholic hydrochloric acid. In this respect and in most properties, the reductive acetylation product is found to resemble the flaven-3-ol acetate (LXIII).[113] Obviously the reaction involves reduction of both the ethylene and carbonyl groups followed by the elimination of the elements of water. The same product could be obtained by the reductive acetylation of the dihydroflavonol, taxifolin (LXIV). Quercetin pentamethyl ether also undergoes this reaction. The important point is that these enol derivatives undergo conversion into anthocyanidins in good yields and thus provide better routes for the preparation of anthocyanidins not only from flavonols but also from natural *leuco*anthocyanidins which are known to give very poor yields by direct heating with alcoholic hydrochloric acid.

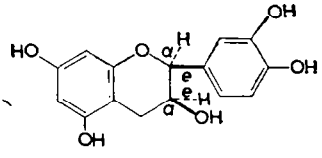
The *leuco*anthocyanidins seem to be capable of ready polymerisation and also of reacting with aldehydic substances to form plastics.[106] In view of their very wide distribution, they could be considered as one of Nature's plastic materials like catechins and lignins. They are definitely capable of combining with proteins.

Catechins

Considerable interest has been shown in the stereochemistry of catechins and the most important of these are (+) catechin (LXV), present in *Gambier catechu*, and (—) *epi*catechin (LXVI) in *Acacia catechu*. Their constitutions are very similar and they have been shown to be stereoisomers of 3:5:7:3′:4′-pentahydroxyflavan. The most significant proofs were provided by the reduction of cyanidin chloride to *epi*catechin (LXVI) and of quercetin pentamethyl ether to *epi*catechin pentamethyl ether and also by the conversion of the catechin into cyanidin chloride (LXII).



LXV



LXVI

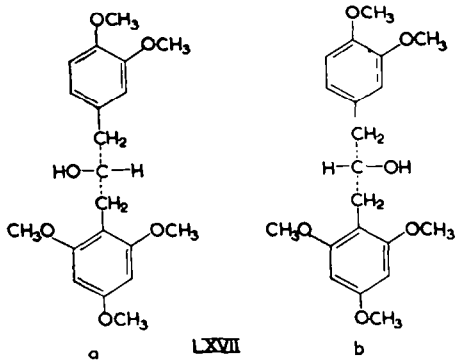
The stereoisomerism involved has been difficult to unravel in all its detail. All the four possible optically active isomers and two racemic compounds are known. The epimerisation from the catechin series to the *epi*catechin series and vice-versa is comparatively easy to carry out. The original suggestion of Freudenberg[115] that this involves change in the 2-position has been unequivocally established.[116] (+) Catechin tetramethyl ether and (—) *epi*catechin tetramethyl ether were subjected to sodium ammonia reduction and by subsequent methylation enantiomorphous pentamethoxy-1:3-diarylpropan-2-ols (LXVIIa & b) were obtained.

This could only be explained if the 3-carbon atoms in (+) catechin tetramethyl ether and (—) *epi*catechin tetramethyl ether have opposite configurations. From this it would follow that (+) catechin and (+) *epi*catechin will have the same configuration at position 3 and the epimerisation takes place by inversion at the 2-position.

The easy formation of a flavene from *epi*catechin was considered to indicate that the hydrogen at C_2 and hydroxyl at C_3 were *trans* to each other favouring smooth

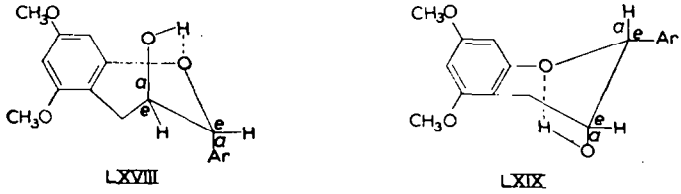
[115] K. Freudenberg, H. Fikentscher and M. Harder, *Liebigs Ann.* **441**, 157 (1925).
[116] A. J. Birch, J. W. Clark-Lewis and A. V. Robertson, *J. Chem. Soc.* 3586 (1957).

elimination of water or in other words the hydrogen atoms in the C_2 and C_3 positions were *cis* to each other (LXVI). Catechin which does not undergo a similar



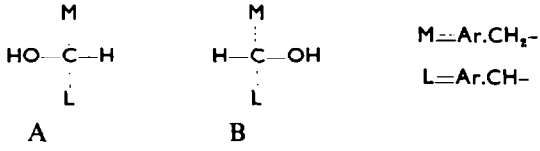
a LXVII b

change has been assigned the *trans* structure (LXV). In both of them the alcoholic hydroxyl groups are involved in hydrogen bond formation with the ring oxygen and hence are in the axial conformation. The conformation in position 2 then follows as indicated in the formulae (LXVIII and LXIX). It will be noticed that the general expectation that heavier groups would occupy the equatorial positions is not satisfied in these structures. The deviation seems to be due to the hydrogen bond formation leading to the axial disposition of the hydroxyl in the 3-position. Regarding the phenyl group in the 2-position though the two possibilities are found, viz. axial and equatorial, the more widely occurring (−) *epi*catechin has an equatorial phenyl ring. This agrees with the earlier observation that the reduction of cyanidin which has a definitely planar structure gives rise to *epi*catechin.



LXVIII LXIX

The absolute configuration of the alcohols has recently been determined.[116a] In the case of the *cis* compound, (−) epicatechin, the arrangement at the carbon atom 3 was shown to be represented by A and consequently B will represent the arrangement in (+) catechin.

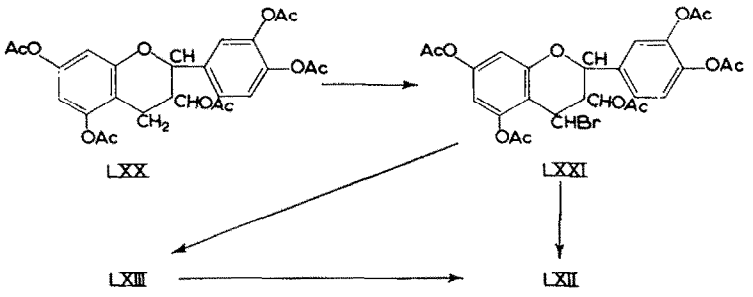


A B

Appel and Robinson[117] effected the conversion of catechin into cyanidin by the action of bromine on the tetramethyl ether in technical dioxan medium. The immediate product was considered to be 8-bromocyanidin bromide tetramethyl ether. A more convenient method of conversion is to brominate the penta-acetates

[116a] E. Hardegger, H. Gempeler and A. Züst, *Helv. Chim. Acta* **40**, 1819 (1957).
[117] H. Appel and R. Robinson, *J. Chem. Soc.* 426 (1935).

(LXX) of (+) catechin and (−) *epi*catechin with NBS; the resulting bromo compound (LXXI) undergoes conversion into cyanidin chloride (LXII) in good yield.[118] With silver acetate, the bromo compound is found to eliminate a molecule of hydrobromic acid and yield *leuco*cyanidin acetate whose analysis and infra-red spectrum suggest a flaven-3-ol formula (LXIII). It gives a good yield of cyanidin chloride (LXII) when boiled with alcoholic hydrochloric acid. Thus the oxidation of catechin has been carried out in stages.



Quinonoid anhydro-bases

Quinonoid anhydro-bases[119] occur widely in the plant kingdom. It was observed by Willstätter and co-workers that anthocyanins change into colour-bases under mild basic conditions (pyridine, aqueous sodium acetate). The colours of these anhydro-bases can vary considerably and depend on the structure of the compounds. The stabler naturally occurring colour-bases are 7-keto derivatives related to flavones and are deep red. The absence of a substituent in the 3-position facilitates the formation of a stable colour-base.

The first known natural compound of this group was carajurin which was isolated by Perkin[120] and which occurs along with another minor component, carajurone, in the rare cosmetic pigment 'Carajura' prepared from the leaves of *Bignonia chica*. The constitution of carajurin ($C_{17}H_{14}O_5$; $2OCH_3$) was established by Chapman, *et al.*[121] Its reactions indicated that it was an anhydro colour-base without a hydroxyl group in the 3-position. Demethylation experiments yielded scutellereinidin chloride (5:6:7:4′-tetrahydroxyflavylium chloride) and boiling with aqueous alkali gave *p*-methoxyacetophenone. These results gave the main skeleton and the position of one of the methoxyl groups. The position of the second methoxyl group was fixed as 5 by eliminating other possibilities and the formula (LXXII) was given to carajurin.

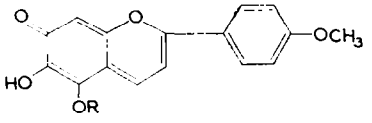
An important point that had not been settled was the possibility of isomeric change during demethylation. It was found[122] that 6:7-dihydroxy-4′-methoxyflavylium chloride was markedly different from 7:8-dihydroxy-4′-methoxyflavylium chloride in the ferric reaction and in the colour and staining capacity of the colour-base. 6:7-Dihydroxy-4′-methoxy-5-methylflavylium chloride resembled the above 6:7-dihydroxy compound as well as carajurin very closely. These results were in agreement

[118] A. K. Ganguly, T. R. Seshadri and P. Subramanian, *Proc. Indian Acad. Sci.* A **46**, 25 (1957).
[119] T. R. Seshadri, *Naturally Occurring Quinonoid Anhydro-bases*. Festschrift Arthur Stoll. *Experientia* 318 (1956).
[120] A. G. Perkin, *Proc. Chem. Soc.* **30**, 212 (1914).
[121] E. Chapman, A. G. Perkin and R. Robinson, *J. Chem. Soc.* 3015 (1927).
[122] L. Ponniah and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **37**, 544 (1953).

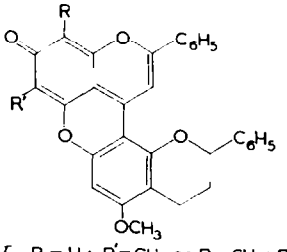
with the constitution of carajurin given above. 7-Hydroxy-5:8:4′-trimethoxyflavylium chloride when subjected to demethylation did not undergo isomeric change under ordinary conditions[123] and the product was different from carajuretin chloride (scutellereinidin chloride).

The synthesis of carajurin has also been achieved[124] by employing an unambiguous series of steps. The important intermediate is 2:4:5-trihydroxy-6-methoxybenzaldehyde which was prepared conveniently by employing the method of nuclear oxidation.

Carajurone, the minor component of Carajura, had one methoxyl group less in its molecule but otherwise resembled carajurin closely. Though no detailed study of the substance could be made, Chapman, *et al.*[121] suggested the possible structure as shown in LXXIII. Its synthesis also offered some difficulty since the isomeric compound with the 5:7:8-arrangement of hydroxyl groups tended to be formed. Finally by employing 2:6-dibenzyloxyquinol and condensing it with anisoylacetaldehyde, carajurone could be synthesised in good yield.[125]



LXXII, R = CH_3
LXXIII, R = H



LXXIV, R = H; R′ = CH_3 or R = CH_3; R′ = H

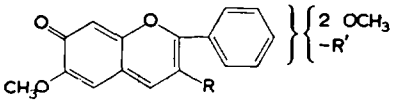
Dragon's blood resin is another source of natural anhydro-bases. This resin is obtained from trees belonging to the genera, *Dracaena* and *Daemonorops* and it contains two substances viz. dracorubin (major component) and dracorhodin (minor component). The latter has a simpler structure; it was shown to be the colour-base of 7-hydroxy-5-methoxy-6-methylflavylium chloride and this constitution was confirmed by synthesis using 2:4-dihydroxy-6-methoxy-5-methylbenzaldehyde and acetophenone.[126,127]

Dracorubin has a more complex structure which has been studied by Brockmann as well as by Robertson *et al.*[128,129] and the latter have given it the formula (LXXIV).

The group of insoluble red woods belonging to the genus *Pterocarpus* provides some of the most valued and durable timbers of the tropical areas. They contain a number of colourless crystalline components belonging to the flavone, *iso*flavone and stilbene groups of compounds. The red colouring matter of these woods has long been an interesting subject of study. Two pigments, santalin (major component) and santarubin (minor component), have been isolated from red woods and tentative structures LXXV and LXXVI respectively for these have been proposed.[130] They

[123] L. Ponniah and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **38**, 288 (1953).
[124] L. Ponniah and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **38**, 77 (1953).
[125] L. Ponniah and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **39**, 45 (1954).
[126] H. Brockmann and H. Junge, *Ber. Dtsch. Chem. Ges.* **76**, 751 (1943).
[127] A. Robertson and W. B. Whalley, *J. Chem. Soc.* 1882 (1950).
[128] H. Brockmann, R. Haase and E. Freienschner, *Ber. Dtsch. Chem. Ges.* **77**, 279 (1944).
[129] A. Robertson, W. B. Whalley and J. Yates, *J. Chem. Soc.* 3117 (1950).
[130] A. Robertson and W. B. Whalley, *J. Chem. Soc.* 2794 (1954).

are also quinonoid anhydro-bases and the flavonoid, *iso*flavonoid and stilbene structures seem to be incorporated in them.

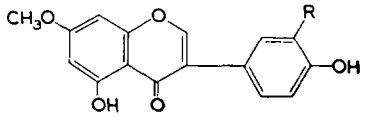


LXXV, R = 3:4-Dimethoxyphenyl; R' = 2:4-dimethoxyphenyl.
LXXVI, R = 2:4-Dimethoxyphenyl; R' = 3:4-dimethoxyphenyl.

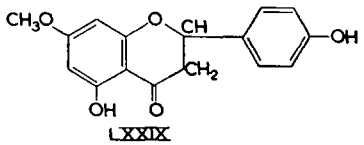
Regarding the relationship between constitution and colour it is significant that the 7-position of the C_{15} unit is involved in the quinonoid structure. This seems to contribute to the stability and the deep red colour of the natural anhydro-bases. Substitution in the 5- and 6-positions with a hydroxyl, methoxyl or methyl group is favourable whereas hydroxy substitution in the 8-position seems to be unfavourable.[131]

Partial methylation and demethylation

In a flavonoid structure, practically all the free positions can contain hydroxyl groups though the 2'- and 6'-positions are rarely occupied in natural compounds. Methylation of these groups seems to be capable of taking place without marked restriction. The more intriguing aspect is the partial methylation of the hydroxyl groups in certain positions leaving the others free. This reaction seems to depend on two important factors: (i) superior reactivity of certain hydroxyl groups and (ii) partial protection of some of them by glycosidation, chelation or complex formation and subsequent methylation. Originally it was considered[132,133] that only in flavanones and *iso*flavones, the hydroxyl group in the 7-position is the most predominantly active and the partial methylation in this position was successfully used for the laboratory synthesis of prunetin (LXXVII),[132] santal (LXXVIII)[134,135] and sakuranetin (LXXIX).[132] This difference seems to exist, though to a lesser extent, in other groups of compounds also. Recently, it has been shown[136] that the partial methylation of the 7-hydroxyl group is possible in certain flavones.



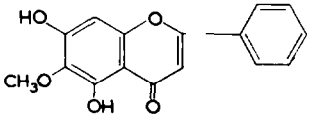
LXXVII, R = H
LXXVIII, R = OH



LXXIX

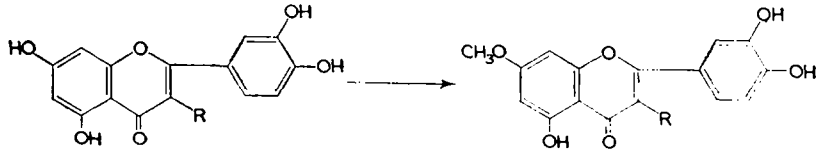
Protection of a reactive hydroxyl by a sugar group, followed by methylation and glycoside hydrolysis was suggested[137] as the possible mechanism for the evolution of oroxylin-A (LXXX) (a 6-methyl ether) and similar compounds in Nature. In these cases, the glycosidic group seems to have been present in the most reactive 7-position.

[131] T. R. Seshadri, *Naturally Occurring Quinonoid Anhydro-bases*. Festschrift Arthur Stoll. *Experientia* 328 (1956).
[132] N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **32**, 256 (1950).
[133] T. R. Seshadri, *Ann. Rev. Biochem.* **20**, 507 (1951).
[134] N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **32**, 342 (1950).
[135] N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **37**, 531 (1953).
[136] T. H. Simpson and J. L. Beton, *J. Chem. Soc.* 4065 (1954).
[137] A. C. Jain, K. S. Pankajamani and T. R. Seshadri, *J. Sci. Industr. Res. India* B **12**, 127 (1953).



LXXX

The 5-hydroxyl group of most flavonoids is protected by chelation involving the carbonyl group of the pyrone ring. Partial protection of hydroxyl groups in other positions seems to be also possible by complex formation. As an example the borate complexes of hydroxyflavonoids[137,138] may be mentioned. These involve both the chelate structure of the 5-hydroxyl group and the catechol units present in various parts of the molecule. Using this feature, it is possible to prepare partial methyl ethers. Typical examples are rhamnetin[137] (LXXXI) from rutin (LXXXII) or quercetin (I) and 7-O-methylluteolin[139] (LXXXIII) from luteolin (LXXXIV).



I, R = OH
LXXXII, R = O—Rutinosyl
LXXXIV, R = H

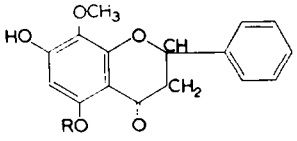
LXXXI, R = OH
LXXXIII, R = H

The naturally occurring partial methyl ethers azaleatin[140] (quercetin-5-methyl ether) and muningin[141] (6:4′-dihydroxy-5:7-dimethoxy*iso*flavone) are extraordinary in that the resistant 5-hydroxyl group is methylated and at the same time more reactive hydroxyl groups are left free. In the flavones, nobiletin and tangeretin, this 5-hydroxyl group is also methylated, but there is otherwise complete methylation. Cases of partial glycosidation of hydroxyl groups in the 5-position are more common (e.g. salipurposide, sakuranin, galuteolin and apigenin-5-glucoside). The explanation offered earlier[142,143] for the evolution of such glycosides is also applicable for the partial methylation as found in azaleatin and muningin. It has been suggested[144] that methylation of the hydroxyl group concerned takes place before pyrone ring closure.

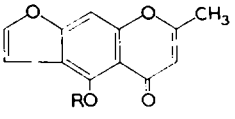
Partial methylation and partial demethylation of flavonoids seem to be related processes and in many cases, the methoxyl groups which arise by methylation of the more acidic hydroxyl groups are those that are less easily demethylated by ordinary methods and vice-versa. A number of reagents have been used by different workers for the partial demethylation of flavonoid methyl ethers. The positions of the methoxyl groups that undergo demethylation depend on the nature of the reagent, the solvent medium and the temperature of the reaction. Methods are available for the selective demethylation of the 5-methoxyl group alone or 3- and 5-methoxyls or 5- and 8-methoxyls or all the methoxyl except that in the 7-position. Typical examples are given below.

[138] M. Shimizu, G. Ohta and T. Yoshikawa, *J. Pharm. Soc. Japan* **71**, 1488 (1951).
[139] K. S. Pankajamani and T. R. Seshadri, *J. Indian Chem. Soc.* **31**, 565 (1954).
[140] E. Wada, *J. Amer. Chem. Soc.* **78**, 4725 (1956).
[141] F. E. King, T. J. King and A. J Warwick, *J. Chem. Soc.* 96 (1952).
[142] T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 32**, 372 (1950).
[143] T. R. Seshadri, *Ann. Rev. Biochem.* **20**, 508 (1951).
[144] M. Krishnamurti and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 13**, 474 (1954).

The most convenient reagent which can bring about preferential demethylation of the 5-methoxyl group is anhydrous aluminium chloride in ether solution. This reagent has found wide application in different groups of flavonoids. As an example may be mentioned the recent synthesis of dihydrowogonin (LXXXV)[145] in which 7-hydroxy-5:8-dimethoxy-flavanone (LXXXVI) is subjected to partial demethylation with this reagent in dry ether solution. This provides the most convenient method of synthesis of this naturally occurring flavanone. However, if this reagent is used in nitrobenzene solution, the 3-methoxyl group of flavonols is also demethylated in addition to that in the 5-position.[146] Another demethylating agent of this type is concentrated hydrochloric acid. It has been used in the synthesis of *nor*visnagin (LXXXVII) from visnagin (LXXXVIII)[147] and in the preparation of partial methyl ethers of *iso*flavones.[148] Care has to be taken when hydrobromic acid is used for this selective demethylation because heating at 100° affects the 3-methoxyl group also.[149]

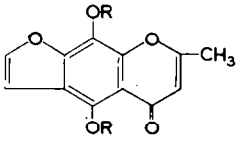


LXXXV, R = H
LXXXVI, R = CH_3



LXXXVII, R = H
LXXXVIII, R = CH_3

In certain cases, where demethylation in both 5- and 8-positions is involved, nitric acid can be used. It forms a 5:8-quinone which can be reduced to the corresponding quinol. The preparation of *nor*kellin (LXXXIX) from kellin (XC)[150] is based on this principle.

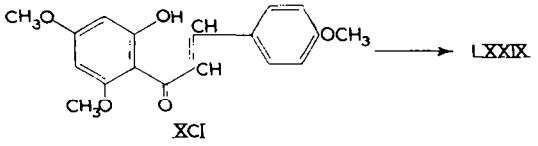


LXXXIX, R = H
XC, R = CH_3

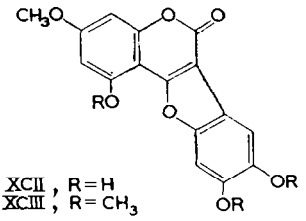
Hydrobromic acid has been found to be a convenient reagent for the demethylation of all the methoxyl groups except the one in the 7-position of flavanones and *iso*flavones. For example, sakuranetin (LXXIX) can be prepared from 2-hydroxy-4:6:4′-trimethoxychalkone (XCI).[151] A more satisfactory reagent for the *iso*flavones is hydriodic acid which is employed under controlled conditions. By this means, the naturally occurring *iso*flavones, prunetin (LXXVII)[152] and santal (LXXVIII),[134,135] have been synthesised. A recent example of the utilisation of this method of partial demethylation is the preparation of wedelolactone (XCII) from its full methyl ether

[145] S. N. Aiyar, I. Dass and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **46**, 238 (1954).
[146] K. V. Rao and T. R. Seshadri, *J. Chem. Soc.* 771 (1946); 122 (1947).
[147] A. Schönberg and N. Badran, *J. Amer. Chem. Soc.* **73**, 2960 (1951).
[148] M. L. Dhar, N. Narasimhachari and T. R. Seshadri, *J. Sci. Industr. Res. India* B **14**, 73 (1955).
[149] R. C. Shah, V. V. Virkar and K. Venkataraman, *J. Indian Chem. Soc.* **19**, 135 (1942).
[150] V. V. S. Murty and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **30**, 107 (1949).
[151] N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **29**, 265 (1949).
[152] N. Narasimhachari, T. R. Seshadri and S. Sethuraman, *Proc. Indian Acad. Sci.* A **36**, 194 (1952).

(XCIII).[153] Other methods of synthesis involving protection of hydroxyl groups by other means are far more difficult.



XCI → LXXIX



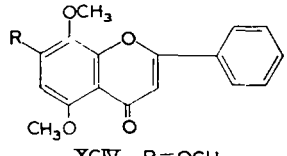
XCII, R=H
XCIII, R=CH3

Ring isomeric change in flavonoids

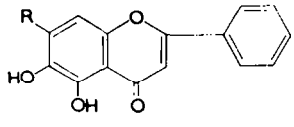
In a number of cases of flavonoids, two isomers can arise as the result of the pyrone ring closing in two different ways. Both isomers occur in a few natural sources, but this is not general. The question then arises as to whether both are produced from a common precursor by ring closure in two ways or a factor of special stability plays a part favouring one structure. The alternative would be the process of direct substitution of a precursor in two different ways. Hence the study of isomeric change under laboratory conditions may be of value.

Mukerjee and Seshadri[154] reviewed this subject in detail. It was emphasised that the pyrone ring can open even in hot acid solutions and can thus provide conditions suitable for isomeric change. The earlier work of Wessely and Moser[155] and many others[156–158] related to the conversion of 5:7:8-methoxyflavones (XCIV) into the 5:6:7-hydroxy compounds (XCV) during demethylation with hydriodic acid. This was of importance from the point of view of the determination of structure. Rao, *et al.*[159] utilised this reaction for synthetic purposes. A similar position existed also with 5:8-dimethoxy compounds (XCVI) undergoing change into the 5:6-dihydroxy compounds (XCVII).[160,161]

In chromones and flavones the above isomeric change took place with considerable



XCIV, R=OCH3
XCVI, R=H



XCV, R=OH
XCVII, R=H

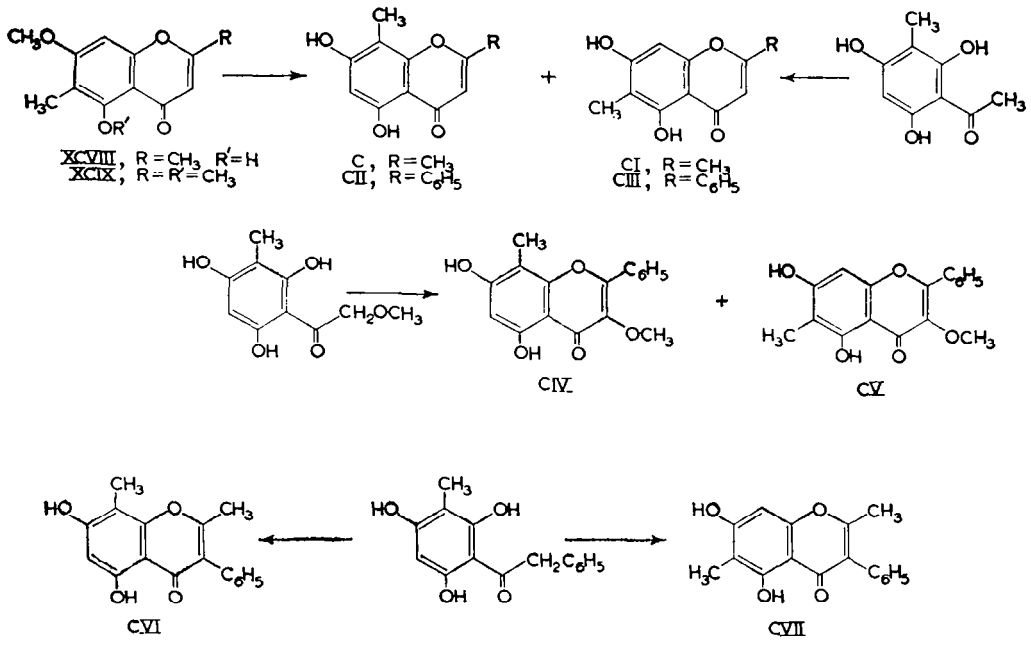
[153] N. R. Krishnaswamy and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 16**, 268 (1957).
[154] S. K. Mukerjee and T. R. Seshadri, *Chem. & Ind.* 271 (1955).
[155] F. Wessely and G. H. Moser, *Monatsh.* **56**, 97 (1930).
[156] F. Wessely and F. Kallab, *Monatsh.* **60**, 26 (1932).
[157] R. C. Shah, C. R. Mehta and T. S. Wheeler, *J. Chem. Soc.* 1555 (1938).
[158] V. D. N. Sastri and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 24**, 245 (1946).
[159] K. V. Rao, T. R. Seshadri and N. Viswanadham, *Proc. Indian Acad. Sci.* **A 29**, 72 (1949).
[160] W. Baker, N. C. Brown and J. A. Scott, *J. Chem. Soc.* 1922 (1939).
[161] A. Ballio and F. Pocchiari, *Ric. Sci.* **20**, 1301 (1950).

facility. The reverse change was not found to happen. Using select examples, Seshadri and co-workers[162–164] showed further that substitution in the 3-position is of importance, a methoxy, hydroxy or phenyl substituent prevents this isomeric change under ordinary conditions of demethylation while a methyl group does not. This was explained as due to their influence on the reactivity of the 2-position. The work of Wheeler and co-workers[165] and of Baker *et al.*[166] showed that even this effect can be overcome by employing drastic conditions, i.e. high temperature in a sealed tube. The preferential formation of the 5:6:7-arrangement of hydroxyl groups during demethylation was attributed to the greater stability of this arrangement[167] and this was also supported by similar preferential formation of flavones and flavonols of this type when the method of synthesis (e.g. Allan–Robinson method) can lead to the production of both isomers.

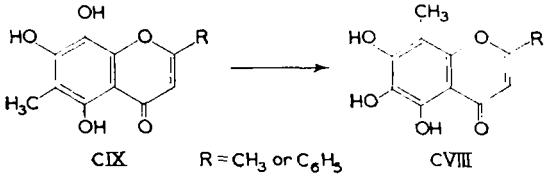
The position is rather more complex when C-methylchromone and flavone derivatives are employed. Schmid[168] first noticed that the 6-methylchromone derivatives, eugenitin (XCVIII) and its methyl ether (XCIX) underwent isomeric change into the 8-methyl derivative (C) by demethylation with hydriodic acid. But in the Kostanecki–Robinson condensation, the 6-methyl compound (CI) was reported to be obtained exclusively.[167,168] Later work by Mukerjee and Seshadri[169] showed that mixtures were obtained in both reactions, but in the former, the 8-methyl compound (C) was the most predominant and in the latter, the 6-methyl compound (CI). In the case of the corresponding flavones, both demethylation and Allan–Robinson condensation led to almost equal quantities of the mixture (CII & CIII).[170,171] On the other hand with C-methylflavonols, though the synthesis gives mixtures containing almost equal amounts of the isomers (CIV & CV), demethylation with hydriodic acid under ordinary conditions brings about no isomeric change[172] owing to the stabilising effect of the 3-hydroxyl group. In the synthesis of *iso*flavones, the 8-methyl compounds (CVI) are generally formed if the temperature of the reaction is high[173] (boiling acetic anhydride) whereas if the reaction is conducted at 0°, the 6-methyl compounds (CVII) result.[174] The position is slightly different in the case of 6- or 8-methoxy*iso*flavones. Ordinary methods seem to favour the formation of the 8-methoxy compounds[166] whereas under special conditions the 6-methoxy isomers are obtained.[175]

Recently, experiments have been conducted in order to follow up the isomeric change when all the four positions of the condensed benzene ring are substituted and there is one methyl or hydroxyl group in the 6- and 8-positions.[176,177] It was

[162] T. R. Seshadri, S. Varadarajan and V. Venkateswarlu, *Proc. Indian Acad. Sci.* **A 32,** 250 (1950).
[163] N. Narasimhachari, L. R. Row and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 35,** 46 (1952).
[164] S. K. Mukerjee, T. R. Seshadri and S. Varadarajan, *Proc. Indian Acad. Sci.* **A 35,** 82 (1952).
[165] D. M. X. Donnelly, E. M. Philbin and T. S. Wheeler, *Chem. & Ind.* 163 (1954).
[166] W. Baker, I. Dunstan, J. B. Harborne, W. D. Ollis and R. Winter, *Chem. & Ind.* 277 (1953).
[167] S. K. Mukerjee, T. R. Seshadri and S. Varadarajan, *Proc. Indian Acad. Sci.* **A 37,** 127 (1953).
[168] H. Schmid, *Helv. Chim. Acta* **32,** 813 (1949).
[169] S. K. Mukerjee and T. R. Seshadri, *Chem. & Ind.* 1009 (1955).
[170] S. K. Mukerjee and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 38,** 207 (1953).
[171] N. R. Bannerjee and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 13,** 598 (1954).
[172] A. C. Jain and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 12,** 564 (1953).
[173] R. Iengar, A. C. Mehta, T. R. Seshadri and S. Varadarajan, *J. Sci. Industr. Res. India* **B 13,** 166 (1954).
[174] A. C. Mehta and T. R. Seshadri, *J. Chem. Soc.* 3823 (1954).
[175] S. A. Kagal, S. S. Karmarkar and K. Venkataraman, *Proc. Indian Acad. Sci.* **A 44,** 36 (1956).
[176] S. K. Mukerjee, T. R. Rajagopalan and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 16,** 58 (1957).
[177] V. V. S. Murty, T. R. Seshadri, V. Sundaresan and B. Venkataramani, *Proc. Indian Acad. Sci.* **A 46,** 265 (1957).



observed that the 5:6:7-trihydroxy-8-methyl compound (CVIII) was the stable form and the 6-methyl compound (CIX) underwent isomeric change on treatment with hot hydriodic acid. A hydroxyl in the 6- and a methyl group in the 8-position seem to provide the more stable structure.

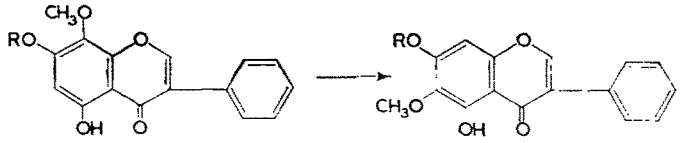


Flavylium salts have not been fully investigated but the results obtained so far suggest that contrary to expectation, based on the analogy of the flavones, the 5:7:8-arrangement of hydroxyl groups is more favoured during the synthesis, and subsequent demethylation does not bring about any change under ordinary conditions.[123] Recently Wheeler *et al.*[178] have reported the isomeric change of 5:7:8-substituted flavylium salts into 5:6:7-substituted ones under drastic conditions.

In the case of chromones and flavones, the isomeric change was studied only in boiling acid solutions since under mild alkaline treatment they do not undergo change and on boiling in alkaline solutions they undergo fission. With *iso*flavones, the position is different. Under mild alkaline conditions, the *iso*flavone system undergoes isomeric change. The first example to be studied was the conversion of 5-hydroxy-7:8-dimethoxy*iso*flavone (CX).[179] Subsequently, modifications[180,181] have been

[178] D. M. X. Donnelly, P. B. Green, E. M. Philbin, F. T. B. Smyth and T. S. Wheeler, *Chem. & Ind.* 892 (1958).
[179] V. B. Mahesh, N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 39, 165 (1954).**
[180] M. L. Dhar and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 14,** 422 (1955).
[181] V. B. Mahesh and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 14,** 671 (1955).

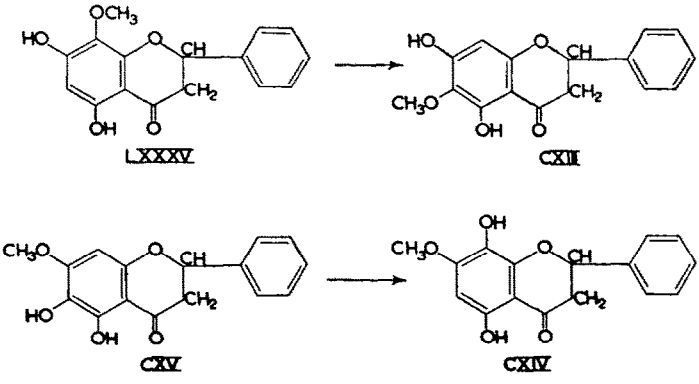
employed and it has been found possible to isomerise satisfactorily 5:7-dihydroxy-8-methoxy*iso*flavone (CXI) into the more difficultly available 6-methoxy compound (CXII).[182] This method is capable of useful application.



CX, R=CH_3
CXI, R=H

CXII, R=H

The flavanone ring structure is susceptible to opening in mild acid as well as alkaline conditions and hence isomeric change takes place readily. The earliest example was the conversion of carthamidin into *iso*carthamidin when heated with water.[183] With flavanones having fewer number of hydroxyl groups, mild alkali in the cold can be used. This treatment was employed by Narasimhachari and Seshadri[184] to test the stability of the 5-hydroxyflavanone derivatives. More recently, Chopin *et al.*[185] have used it for converting 5:7:8-substituted flavanones into 5:6:7-substituted flavanones. For example, dihydrowogonin (LXXXV) was changed into dihydro-oroxylin (CXIII) when dissolved in alkali and subsequently acidified. But a new observation was made by them that in the case of 5:8-dihydroxy-7-methoxy-flavanone (CXIV) there is no isomeric change in acid or alkaline medium; in fact, the isomeric 5:6-dihydroxy-7-methoxyflavanone (CXV) is more unstable and undergoes change into the 5:8-dihydroxy isomer (CXIV). This was attributed to chelation between the 8-hydroxyl and the pyrone oxygen stabilising this isomeric form. The 7-methoxyl group is considered to be essential for this stability of the quinol as otherwise the 7-hydroxy compound behaves in the normal way and undergoes isomeric change.



LXXXV

CXIII

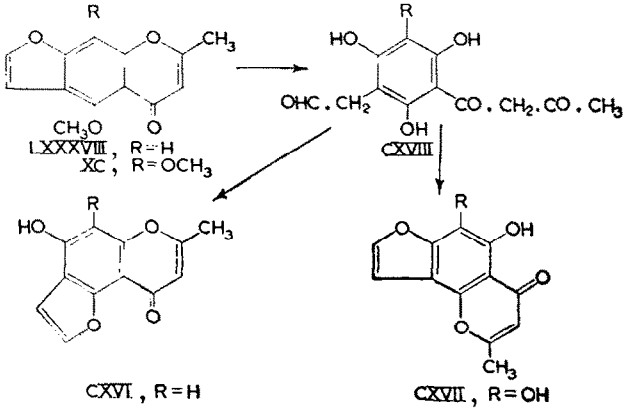
CXV

CXIV

The unexpected difference in the behaviour of the closely related furanopyrones, visnagin (LXXXVIII) and kellin (XC), when subjected to demethylation, has already been mentioned.[154] It is now definite that the formation of *noriso*visnagin (CXVI)[186]

[182] M. L. Dhar and T. R. Seshadri, Unpublished work.
[183] C. Kuroda, *J. Chem. Soc.* 752 (1930).
[184] N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **28**, 223 (1948).
[185] J. Chopin, D. Molho, H. Pachéco and C. Mentzer, *C. R. Acad. Sci., Paris* **243**, 712 (1956).
[186] J. R. Clarke, G. Glaser and A. Robertson, *J, Chem. Soc.* 2260 (1948).

involves the rearrangement of the furan ring whereas the formation of *noriso*kellin (CXVII)[187] involves the rearrangement of the pyrone ring. More recent studies[84] on the synthesis of furanopyrones lead to the conclusion that both the rings open in acid medium (CXVIII) and rearrangement takes place involving one or the other ring depending on structural factors.



It should be emphasised that the methods of demethylation and methylation can influence structure. As indicated above, demethylation with hydriodic acid can bring about isomeric change in a large number of cases; to avoid this, anhydrous aluminium chloride is the reagent of choice. It seems to be clear that in the more stable structures (flavones, chromones and *iso*flavones) methylation does not produce any isomeric change but with flavanones, the position is different. Aqueous alkali and dimethyl sulphate are unsuitable because of ring opening. There are indications that even methylation with dimethyl sulphate, acetone and potassium carbonate can produce isomeric change.[188]

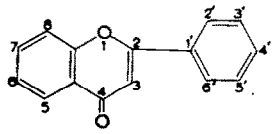
Though in general we could anticipate the manner in which isomeric change would take place in the many systems investigated, the position is not definite and predictable. Hence, adequate caution has to be exercised in drawing conclusions based on the experimental results.

New discoveries

In an earlier review,[189] a list of naturally occurring flavonoids was presented and they were arranged according to the well known groups. During the intervening period, there has been a large number of new discoveries and a few cases of correction of the old constitutions. Hence, the additional matter in this regard is provided in the following tables with the recent references from which the earlier references could be traced.

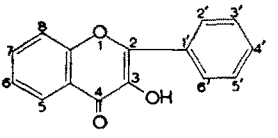
[187] S. K. Mukerjee and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 13**, 400 (1954).
[188] H. G. Krishnamurti and T. R. Seshadri, Unpublished work.
[189] T. R. Seshadri, *Ann. Rev. Biochem.* **20**, 491 (1951).

FLAVONES



Name	Position of hydroxyl groups	Position of methoxyl and other groups	Source
(1) Tectochrysin[190]	5	7	*Pinus and Populus* species
(2) 5:6-Dimethoxyflavone[191]	–	5,6	*Casimiroa edulis*
(3) Tangeretin[192] (Ponkanetin[193,194])	–	5,6,7,8,4′	*Citrus poonensis*
(4) 5-O-Desmethylnobiletin[61]	5	6,7,8,3′,4′	*Citrus aurantium*
(5) Strobochrysin[170]	5,7	(6-methyl)	*Pinus strobus*

FLAVONOLS

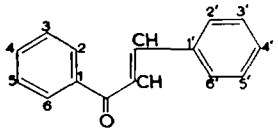


(1) Rhamnocitrin[146]	3,5,4′	7	*Rhamnus catharticus*
(2) Tamarixetin[195]	3,5,7,3′	4′	*Tamarix troupii*
(3) Azaleatin[140]	3,7,3′,4′	5	*Rhododendron mucronatum*
(4) Ombuin[44]	3,5,3′	7,4′	*Phytolacca dioica*
(5) Ayanin[196]	5,3′	3,7,4′	*Distemonanthus benthamianus.*
(6) Flindulatin[197]	5	3,7,8,4′	*Flindersia maculosa.*
(7) Penduletin[198]	5,4′	3,6,7,	*Brickelia pendula.*
(8) Limocitrin[199]	3,5,7,4′	8,3′	*Citrus limon.*
(9) Ternatin[200]	5,4′	3,7,8,3′	*Melicope ternata.*
(10) Oxyayanin-B[43]	5,6,3′	3,7,4′	*Distemonanthus benthamianus.*
(11) Chrysosplenetin[201]	3,5,4′	6,7,3′	*Chrysosplenium japonicum.*
(12) Polycladin[202]	5,4′	3,6,7,3′	*Policlados abietinus.*
(13) Artemisetin[203]	5	3,6,7,3′,4′	*Artemisia* species.
(14) Oxyayanin-A[44]	5,2′,5′	3,7,4′	*Distemonanthus benthamianus.*
(15) 5-Hydroxyauranetin[61]	5	3,6,7,8,4′	*Citrus aurantium.*

[190] V. B. Mahesh and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 13**, 835 (1954).
[191] J. Iriarte, F. A. Kincl, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.* 4170 (1956).
[192] L. J. Goldsworthy and R. Robinson, *Chem. & Ind.* 47 (1957).
[193] J. M. Sehgal, T. R. Seshadri and K. L. Vadhera, *Proc. Indian Acad. Sci.* **A 42**, 252 (1955).
[194] S. Matsuura, *J. Pharm. Soc. Japan* **77**, 328 (1957).
[195] R. N. Goel and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 47**, 191 (1958).
[196] F. E. King, T. J. King and K. Sellars, *J. Chem. Soc.* 92 (1952).
[197] R. F. C. Brown, P. T. Gilham, G. K. Hughes and E. Ritchie, *Aust. J. Chem.* **7**, 181 (1954).
[198] S. E. Flores and J. Herran, *Tetrahedron* **2**, 308 (1958).
[199] R. M. Horowitz, *J. Amer. Chem. Soc.* **79**, 6561 (1957).
[200] L. H. Briggs and R. H. Locker, *J. Chem. Soc.* 864 (1950).
[201] T. Nakaoki and N. Morita, *J. Pharm. Soc. Japan* **76**, 320 (1956).
[202] G. B. Marini-Bettolo and St. Chiavarelli, Abstracts of papers presented at the XVI Int. Congress Pure Appl. Chem. Paris, p. 212 (1957).
[203] L. Y. Mazur and A. Meisels, *Bull. Res. Council Israel* **A 5**, 67 (1955).

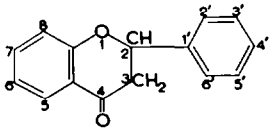
Name	Position of hydroxyl groups	Position of methoxyl and other groups	Source
(16) Desmethoxykanugin[204]	–	3,7(3′:4′-methylene-dioxy)	*Pongamia glabra.*
(17) Melisimplin[41]	5	3,6,7(3′:4′-methyl-enedioxy)	*Melicope simplex.*
(18) Melisimplexin[41]	–	3,5,6,7(3′:4′-methyl-enedioxy)	*Melicope simplex.*
(19) Meliternatin[205]	–	3,5(6:7:3′:4′-bis-methylenedioxy)	*Melicope ternata.*
(20) Pinoquercetin[206]	3,5,7,3′,4′	(6-methyl)	*Ponderosa* pine bark.
(21) Pinomyricetin[206]	3,5,7,3′,4′,5′	(6-methyl)	*Ponderosa* pine bark.
(22) Persicarin[207]	5,7,3′,4′	(3-potassium sulphate)	*Polygonum hydropiper.*
(23) Persicarin-7-methyl ether[208]	5,3′,4′	7(3-potassium sulphate)	*Eonanthe stolonifera.*
(24) Distemonanthin[209]	5,7,4′	6(6′-3-lactone)	*Distemonanthus benthamianus.*

CHALKONES



(1) *iso*Liquiritigenin[17]	2,4,4′	–	Liquorice roots, *Dahlia* spp.
(2) *iso*Liquiritigenin-4-methyl ether[210]	2,4′	4	*Xanthorrhoea* resins.
(3) Excelsin[190]	2	4,6	*Pinus excelsa.*
(4) Stillopsidin[211] (*neo*plathymenin)	2,4,5,3′,4′	–	*Plathymenia reticulata, Coreopsis stillmanii.*
(5) Okanin (*trans*) & *iso*-okanin[212] (*cis*)	2,3,4,3′,4′	–	*Cyclicodiscus gabrinensis.*
(6) Lanceoletin[213]	2,4,3′,4′	3	*Coreopsis* species.

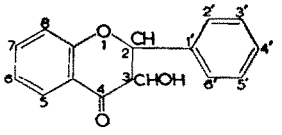
FLAVANONES



[204] O. P. Mittal and T. R. Seshadri, *J. Chem. Soc.* 2176 (1956).
[205] L. H. Briggs and R. H. Locker, *J. Chem. Soc.* 3131 (1951).
[206] R. Mani, V. Ramanathan and K. Venkataraman, *J. Sci. Industr. Res. India* **B 15**, 490 (1956).
[207] H. Tatsuta and Y. Cochii, *J. Chem. Soc. Japan* **75**, 941 (1954).
[208] H. Tatsuta, *J. Chem. Soc. Japan* **75**, 939 (1954).
[209] F. E. King, T. J. King and P. J. Stokes, *J. Chem. Soc.* 4594 (1954).
[210] H. Duewell, *J. Chem. Soc.* 2562 (1954).
[211] K. R. Laumas, S. Neelakantan and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 46**, 343 (1957).
[212] F. E. King and T. J. King, *J. Chem. Soc.* 569 (1951).
[213] M. Shimokoriyama and S. Hattori, *J. Amer. Chem. Soc.* **75**, 1900 (1953).

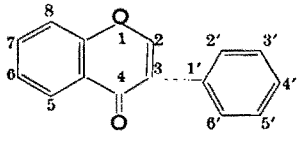
Name	Position of hydroxyl groups	Position of methoxyl and other groups	Source
(1) Pinocembrin[190]	5,7	–	*Pinus* species.
(2) Alpinetin[214]	7	5	*Alpinia chinensis.*
(3) Pinostrobin[190]	5	7	*Pinus* strobus.
(4) 5:4′-Dihydroxy-7:3′-dimethoxy flavanone[215]	5,4′	7,3′	*Melicope sarcococca.*
(5) 5-Hydroxy-7:3′-dimethoxy-4′-prenyloxyflavanone[215]	5	7,3′(4′-prenyloxy)	*Melicope sarcococca.*
(6) Dihydrowogonin[145]	5,7	8	*Prunus avium.*
(7) Plathymenin[216]	6,7,3′,4′	–	*Plathymenia reticulata.*
(8) 8-Methoxybutin[213]	7,3′,4′	8	*Coreopsis grandiflora.*
(9) Strobopinin[217]	5,7	(6-methyl)	*Pinus strobus.*
(10) Cryptostrobin[217]	5,7	(8-methyl)	*Pinus strobus.*
(11) Ferrerol[218]	5,7,4′	(6,8-dimethyl)	*Rhododendron farrerae.*
(12) Cyrtominetin[219]	5,7,3′,4′	(6,8-dimethyl)	*Cyrtomium* species.

3-HYDROXYFLAVANONES

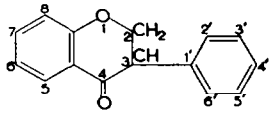
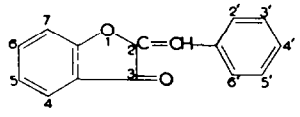
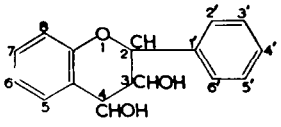


(1) Pinobanksin[190]	3,5,7	–	*Pinus strobus.*
(2) Pinobanksin-7-methyl ether[195] (alpinone)	3,5	7	*Pinus excelsa, Alpinia japonica.*
(3) Aromadendrin 7-methyl ether[220]	3,5,4′	7	*Eucalyptus maculata* kino.
(4) Dihydrorobinetin[86]	3,7,3′,4′,5′	–	*Robinia pseudacacia.*
(5) Dihydrorhamnetin[221]	3,5,3′,4′	7	*Prunus puddum.*
(6) Dihydroquercetin-3′-methyl ether[86]	3,5,7,4′	3′	*Abies concolor.*
(7) Dihydromorin[88]	3,5,7,2′,4′	–	*Morus lactea.*
(8) Dihydroherbacetin-8:4′-dimethyl ether[222]	3,5,7	8,4′	*Prunus mume.*
(9) Strobobanksin[86]	3,5	7(6-methyl)	*Pinus strobus.*

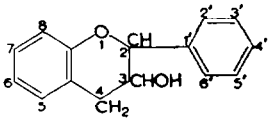
*iso*FLAVONES



[214] V. B. Mahesh, S. Neelakantan and T. R. Seshadri, *J. Sci. Industr. Res. India* **B 15**, 287 (1956).
[215] T. A. Geissman, *Aust. J. Chem.* **11**, 376 (1958).
[216] F. E. King, T. J. King and K. G. Neill, *J. Chem. Soc.* 1055 (1953).
[217] R. N. Goel and T. R. Seshadri, Unpublished work.
[218] R. H. Arthur, *J. Chem. Soc.* 3909 (1955).
[219] Y. Kishimoto, *Pharm. Bull.* **4**, 24 (1956).
[220] R. J. Gell, J. T. Pinley and E. Ritchie, *Aust. J. Chem.* **11**, 372 (1958).
[221] R. N. Goel and T. R. Seshadri, *Tetrahedron* In press.
[222] M. Hasegawa, Private communication.

Name	Position of hydroxyl groups	Position of methoxyl and other groups	Source
(1) Muningin[223]	6,4′	5,7	*Pterocarpus angolensis.*
DIHYDRO*iso*FLAVONES			
(1) Padmakastein[224]	5,4′	7	*Prunus puddum.*
(2) Ferreirin[78]	5,7,2′	4′	*Ferreirea spectabilis.*
(3) *Homo*ferreirin[78]	5,7	2′,4′	*Ferreirea spectabilis.*
AURONES			
(1) Palasetin[17]	6,3′,4′	–	*Butea frondosa, Cosmos sulphureus. Dahlia variabilis.*
(2) Leptosidin[225]	6,3′,4′	7	*Coreopsis* species.
(3) Aureusidin[226]	4,6,3′,4′	–	*Oxalis cernua, Antirrhenium majus.*
*leuco*ANTHOCYANIDINS (flavan diols)			
(1) Mollisacacidin[104] (Gleditsin[227])	7,3′,4′	–	*Acacia mollisima. Gleditsia japonica.*
(2) Melacacidin[102]	7,8,3′,4′	–	*Acacia melanoxylon.*
(3) *leuco*Pelargonidin[105]	5,7,4′	–	*Eucalyptus calophylla* gum.
(4) *leuco*Cyanidin[21]	5,7,3′,4′	–	*Butea* gum, Tamarind seed testa.

[223] M. L. Dhar and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 43,** 79 (1956).
[224] S. Ramanujam and T. R. Seshadri, *Proc. Indian Acad. Sci.* **A 47,** 175 (1958).
[225] T. A. Geissman and W. Moje, *J. Amer. Chem. Soc.* **73,** 5765 (1951).
[226] T. A. Geissman and J. B. Harborne, *J. Amer. Chem. Soc.* **77,** 4622 (1955).
[227] J. W. Clark-Lewis and M. Mitsuno, *J. Chem. Soc.* 1724 (1958).

Name	Position of hydroxyl groups	Position of methoxyl and other groups	Source
(5) *leuco*Delphinibin[107]	5,7,3′,4′,5′	–	Karada bark, *Eucalyptus pilularis* gum.
CATECHINS			
(1) (—) *epi*Afzelechin[228]	5,7,4′	–	*Afzelia* species.

[228] F. E. King, J. W. Clark-Lewis and W. F. Forbes, *J. Chem. Soc.* 2948 (1955).