position des consommateurs que si on les remplaçait par des bovins domestiques. Cela permettra sans doute de sauver la grande faune d'Afrique, mieux que le maintien problématique des parcs nationaux de ce continent, dans leur forme actuelle, de la part des dirigeants des nouveaux états africains. L'utilisation du sol – le «land use» des Américains – dans les conditions optimales exige dans bien des cas la conservation des habitats originaux.

Là encore l'écologiste a un rôle prépondérant dans la détermination des conditions les plus favorables et du contigent d'animaux à abattre ou de plantes à exploiter pour assurer le meilleur rapport de ces aires protégées de tout changement essentiel.

La conservation des réserves naturelles pour la faune et la flore sauvages, de même que l'utilisation des ressources qu'elles représentent exigent donc maintenant des bases scientifiques sérieuses. C'est en cela que l'esprit positiviste du scientifique vient au secours du protecteur de la nature auquel une sorte de «paternalisme» et de romantisme désuet, masque parfois les vrais problèmes. La nature ne sera sauvée que par l'association du scientifique et de l'économiste.

Summary. The concept of nature conservation has greatly varied in recent years. Instead of forbidding any human interference with nature the modern conservationnists think that man must control the natural balance in the protected areas through appropriate measures.

This action must be under the permanent control of ecologists, who have the task of determining, among many other data, the carrying capacity of the area, the evolution of habitats under physical and biological influences, the structure of animal populations and the rate of reproduction.

In the case of large animals, this new concept leads to substituting game management for static protection. Thus conservation of natural resources will need more and more cooperation from scientists, especially in the field of ecology and population studies.

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Biogenetic Relationships between Coumarins, Flavonoids, Isoflavonoids, and Rotenoids*

By H. GRISEBACH** and W. D. OLLIS***

Two biosynthetic routes have been established as those usually responsible for the formation of the aromatic rings in natural products which may be regarded as phenolic, enolic, or oxygen heterocyclic. These two routes involve either a) a poly-β-keto-acid intermediate produced by head-to-tail condensation of acetate units[1–4], whose importance has been emphasised by BIRCH, or b) the intervention of C_9-intermediates associated with the shikimic-prephenic acid pathway as elucidated by DAVIS[5–7]. Considerable progress has been made in the study of the biosynthesis of the flavonoids: this work has been reviewed[8–10] and is summarised below. The purpose of this communication is to comment on recent corresponding studies of isoflavone biosynthesis, and to indicate a possible relationship to the biosynthesis of other isoflavanoids and the rotenoids.

* We should like to thank Professor L. RUZICKA for his advice and detailed criticism of this manuscript.

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*** University of Bristol (England).

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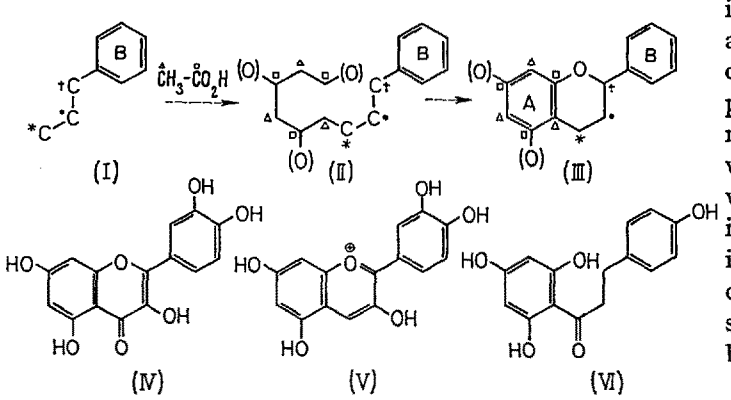
Biosynthesis of Flavonoids. Various classes of natural products belong to the flavonoid group; they all contain a 1,3-diarylpropane-(C_6-C_3-C_6)-unit which is usually accommodated in a 2-phenylchroman structure (III). By feeding certain labelled compounds to plants, it has been demonstrated that the formation of quercetin (IV)[11–13], cyanidin (V)[14, 15], and phloretin (VI)[16] conforms to one biosynthetic pattern. These flavonoids were usually isolated from the plants as the glycosides rutin, rubrobrassicin, and phloridzin respectively, but these studies were concerned with the biosynthetic origin of the aglycones (IV, V, and VI) only.



Acetate has been shown to be a very effective source of the C_6-unit comprising ring-A in flavonoids (III)[11, 13, 14, 16], but a variety of compounds may act as precursors of the remaining C_9-part of the molecule which contains ring-B and the C_3-interaryl-unit. These compounds are of varying effectiveness. Good precursors include shikimic acid (C_7)[11] and various C_9-compounds[11–16] such as phenylalanine, and the cinnamic acids, such as caffeic and cinnamic acid itself. It is suggested that shikimic acid and these C_9-compounds become incorporated into the C_9-metabolic pool which is associated with the shikimic-prephenic pathway, and that it is this pool which provides the C_9-precursor (I) of the flavonoids (III)[11, 17]. The incorporation of the carbon atoms of phenylalanine may, therefore, be regarded as a pointer indicating the participation of the shikimic-prephenic pathway and specifically labelled phenylalanine is incorporated into quercetin without appreciable randomisation, which indicates that it is probably acting as a direct precursor.

In some cases it is probable that there is a transformation of one flavonoid into another in the plant. SESHADRI[18] has emphasised the feasibility of this process particularly with regard to the introduction of hydroxyl groups oxidatively. It is probable that the recently discovered biflavonyls arise by dehydrogenative coupling of flavonoid precursors[19]. The alternative situation in which the biosynthesis of structurally related natural products proceeds fairly independently in the same plant occurs in the formation of the glycosides of quercetin (IV) and cyanidin (V) in *Fagopyrum esculentum*[15]. There is apparently no interconversion of the flavonol and the anthocyanidin as might have been expected from their closely similar structures. They both arise independently from similar or related precursors.

Regarding the biosynthetic route (I → II → III), very little can be said about the nature of the intermediates which are formally represented by structure (II). These intermediates could be regarded as arising either directly or indirectly from one cinnamic acid and three acetate residues. In this connection the important observation has been made by GAMBORG and NEISH[20] that the transformation phenylalanine → cinnamic acid is irreversible in wheat and buckwheat plants. The incorporation of cinnamic acid into flavonoids is therefore strong evidence that condensation with acetate occurs either with cinnamic acid itself or with a closely related derivative. This view certainly indicates a probable importance for the cinnamic acids in flavonoid biosynthesis[11, 12, 21–24] and the chalkones[25] could well be important intermediates along the biosynthetic pathways which connect them. These possibilities are examined in more detail in the next section.

Biosynthesis of Cinnamic Acids and Coumarins. Recently there has been considerable interest in the occurrence and possible function of cinnamic acids in plants[20, 21, 23, 24, 26, 27]. These acids include, for example,

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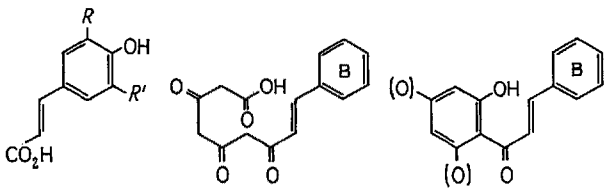
p-coumaric (VIIa), caffeic (VIIb), and sinapic (VIIc) acids and their sites of nuclear oxidation suggest that they are related biogenetically to the C_6 (B) -C_3 part of the flavonoid structure (III). The frequent co-occurrence of flavonoids and cinnamic acids is well known[21,23,24] and furthermore when 2-^{14}C-labelled phenylalanine is fed to *Fagopyrum esculentum* it is transformed into quercetin (IV) and caffeic acid (VIIb), which are correspondingly labelled in their C_3-units[12]. Thus it would appear that C_9-compounds of the type (I) are precursors of cinnamic acids and flavonoids. This is supported by the formation of labelled tricin (3',5'-dimethoxy-4',5,7-trihydroxylflavone) from labelled ferulic acid[22].

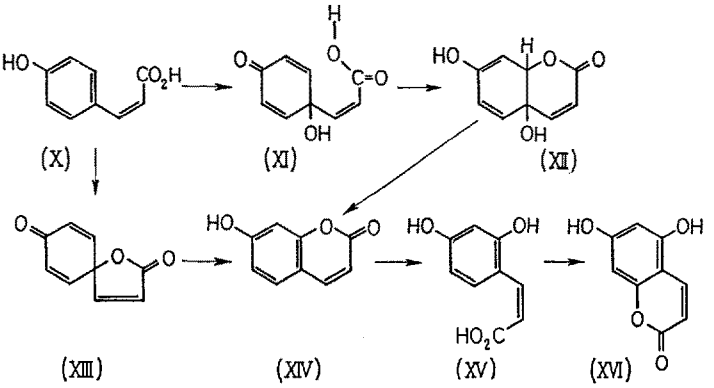


(VIIa) (*R* = *R'* = H)
(VIIb) (*R* = OH; *R'* = H) (VIII) (IX)
(VIIc) (*R* = *R'* = OMe)

If cinnamic acids are directly involved in flavonoid biosynthesis then condensation with three acetate units would give an intermediate (VIII; cf. II) equivalent to the chalkone (IX). There are excellent chemical analogies for the suggestion that epoxides derived from such chalkones (IX) could act as progenitors of the various flavonoids which occur naturally[28]. The possibility that chalkone-epoxides are precursors of some of the flavonoids has not yet been subjected to experimental scrutiny, but we already have evidence (*vide infra*) of their possible participation in isoflavone biosynthesis.

Just as the cinnamic acids are involved in flavonoid biosynthesis so it is likely that they are also concerned as precursors of coumarins. The natural coumarins almost invariably have an oxygen atom located at position-7[4, 29] and this led HAWORTH[30] many years ago to make the interesting suggestion, which is supported by BIRCH[3], that 7-hydroxy coumarins (e.g. XIV) may be formed oxidatively from 4-hydroxycinnamic acids (e.g. X). There are many mechanistic precedents for this proposal; it is supported by the easy transformation of cinnamic acids into coumarins[31], their frequent co-occurrence[32], and the results of recent tracer studies. REID[33] has shown that labelled caffeic acid (VIIb) and labelled scopoletin (7-hydroxy-6-methoxycoumarin) are both formed when labelled phenylalanine is fed to *Nicotiana tabacum*. The detailed study of the biosynthesis of coumarin[34–36] has shown that phenylalanine, cinnamic acid, and shikimic acid are all effectively incorporated, whereas acetic acid is not. It follows, therefore, that the biosynthesis of many of the coumarins almost certainly follows the shikimic-prephenic acid pathway. Support for the proposed oxidative cyclisation of cinnamic acids to coumarins is provided by the formation of labelled scopolin (scopoletin-D-glucoside) from labelled ferulic acid by *Helianthus annuus*, *Triticum vulgare*, and *Zea mays*[22].

The oxidative cyclisation of cinnamic acids (e.g.) X to coumarins (e.g. XIV) could involve either a quinol intermediate (XI) as is well known for other phenol oxidation processes[37], or a spirohexadienone intermediate (XIII)[38] which by rearrangement could yield a 7-hydroxycoumarin (XIV). In connection with this postulated rearrangement (XIII → XIV), it may be mentioned that migration of the carbon-substituent rather than the oxygen-substituent might be expected to be more likely[39], but related examples of O-migration rather than C-migration are known[38]. If spirohexadienones (e.g. XIII) were biosynthetic intermediates then C-migration could lead to 6-hydroxycoumarins. An interesting alternative to these processes is provided by the observation[40] that oxidative cyclisation of diphenyl-2-carboxylic acid to 3,4-benzocoumarin may be achieved. Thus the direct oxidative transformation of cinnamic acids to coumarins is possible*.



* Added in proof: Powerful support for this biosynthetic process has been provided by a recent study of the biosynthesis of novobiocin (K. CHAMBERS, G. W. KENNER, M. J. TEMPLE ROBINSON, and B. R. WEBSTER, Proc. Chem. Soc. *1960*, 291).

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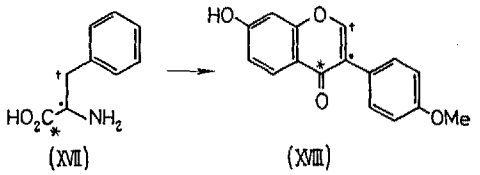
The biosynthesis of the 5,7-dioxygenated coumarins which, however, occur less frequently possibly involves the acetate route. Alternatively they might be formed by two successive oxidative couplings (X → XIV → XV → XVI) which would permit them also to arise from the shikimic-prephenic pathway. The experimental evidence regarding the origin of these unusual coumarins is not yet available.

It follows therefore, as far as the origin of the C_9-unit in their structure is concerned, that there is a close inter-relationship between the biosynthesis of cinnamic acids, coumarins, and flavonoids. This view may be extended to include the lignins since it has been shown that their polymeric structure also originates from similar C_9-units[41–43].

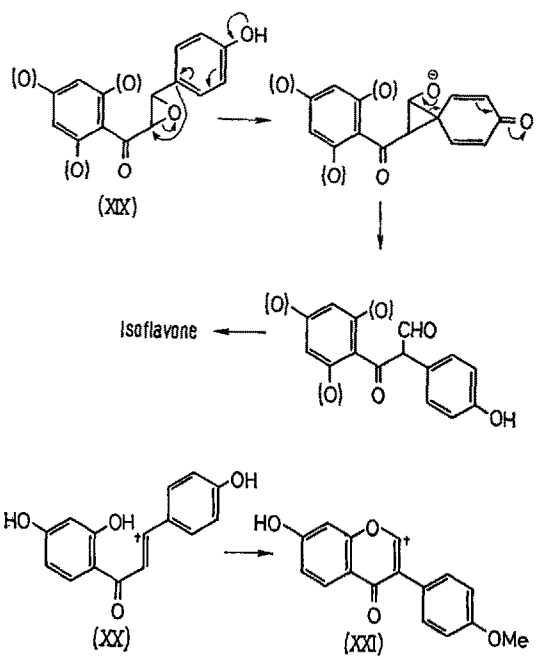
Biosynthesis of Isoflavones. GRISEBACH[44] has shown that an aryl-migration is certainly involved in the production of formononetin (XVIII) by *Trifolium pratense* from specifically labelled phenylalanine.



The route (XVII → XVIII) to isoflavones presumably involves the participation of the intermediate formally represented by the structure (II, cf. VIII) which is also believed to be typical of flavonoid biosynthesis. The further transformation of such an intermediate into an isoflavone requires an aryl-migration and chemical analogies for this type of rearrangement are available[45]. The details for the transformation (XVII → XVIII) are not yet known, but it is conceivable that a chalkone-epoxide might be involved here; the rearrangement of chalkone-epoxides to isoflavones was investigated many years ago by BAKER and ROBINSON[48]. The mechanistic basis for this proposal rests upon the detailed study of the rearrangement of $\alpha\beta$-epoxidoketones which has been made by HOUSE[49]. In the case of a suitably hydroxylated chalkone-epoxide (e.g. XIX) one can visualise that its transformation into an isoflavone could take place very easily either by the mechanism elucidated by HOUSE or by the one shown below[50]. The suggestion that chalkone-epoxides are involved in this way has received support from the observation that the labelled chalkone (XX) when fed to *Trifolium pratense* does in fact yield formonetin labelled as expected (see XXI)[52].

These considerations may be summarised as in Figure 1, from which it is clear that the biosynthesis of flavonoids and certain isoflavonoids involves the same or closely related precursors and intermediates.

However, in their investigation of the biosynthesis of biochanin-A (XXII) by *Cicer arietinum*, GEISSMAN et al.[53] have found that the isotope distribution after incorporation of phenylalanine-2-^{14}C and-3-^{14}C into the



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[42] K. KRATZL and G. BILLEK, Holzforsch. *10*, 161 (1956).
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[45] Related reactions include the lead tetracetate oxidation of flavanones to isoflavones[46], the dehydration of catechin tetramethyl ether to isoflavenes[47], and the rearrangement reactions of chalkone-epoxides[48].
[46] G. W. K. CAVILL, F. M. DEAN, A. McGOOKIN, B. M. MARSHALL, and A. ROBERTSON, J. chem. Soc. *1954*, 4573.
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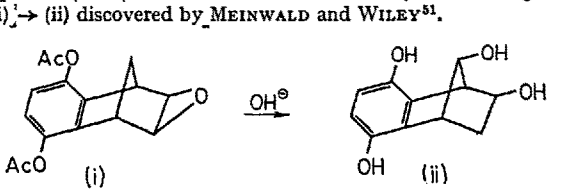
[50] The mechanism depicted for the rearrangement of a chalkone-epoxide (XIX) is related to the base catalysed rearrangement (i) → (ii) discovered by MEINWALD and WILEY[51].



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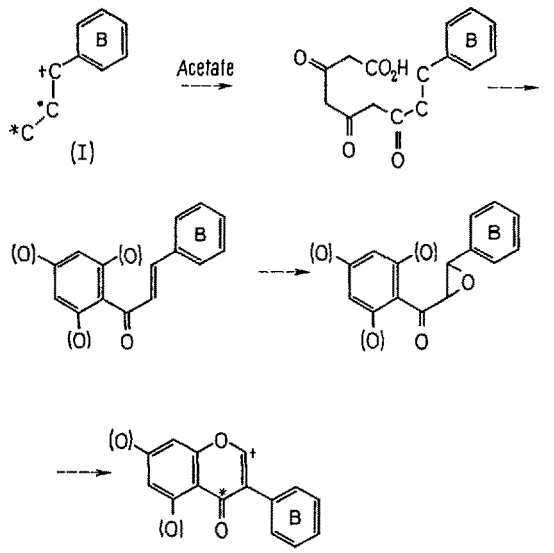
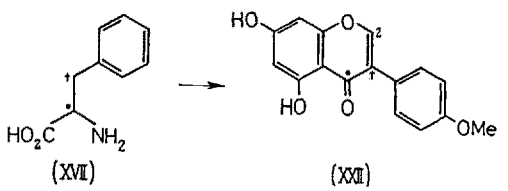


Fig. 1. Representation of isoflavone biosynthesis (GRISEBACH[44])

isoflavone is not consistent with an aryl-migration, but requires the incorporation of a C_6–C_2 unit formed by the loss of the carboxyl group of phenylalanine (XVII → XXII).



The studies by GEISSMAN et al. did not reveal the origin of the carbon atom in position-2 of the isoflavone (XXII) and their route (see Fig. 2) requires the introduction of this carbon atom from a one-carbon precursor. The conversion of a C_9-precursor to a C_8-intermediate has many biochemical analogies. It is presumably involved in many alkaloid biosyntheses[54] which require the aromatic-α-amino-acid → β-arylethylamine change[55] and the biosynthesis of hordenine[56], N-methyltyramine[56], ephedrine[57], nor-ψ-ephedrine[58], pungenin[59], and tropic acid[60] have been shown to involve a C_9 to C_8 transformation in which the C_6–C–C unit remains intact.

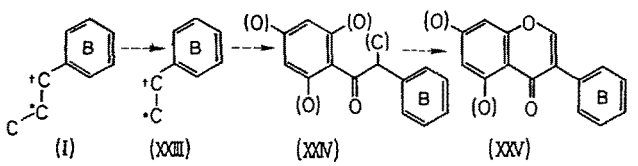
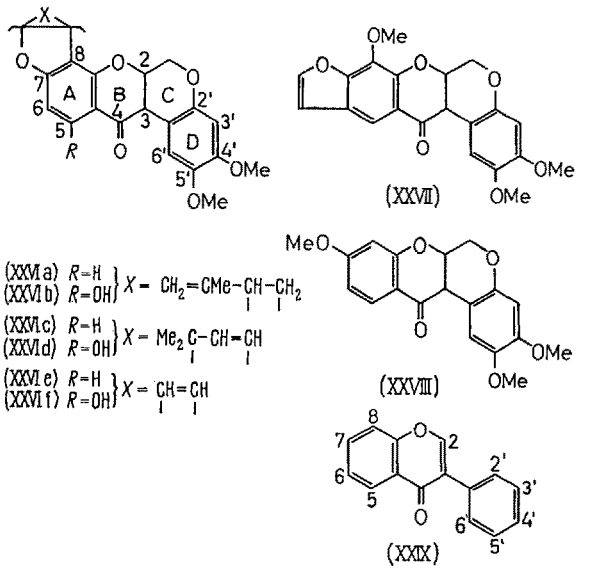


Fig. 2. Representation of isoflavone biosynthesis (GEISSMAN[53])

Further experiments by GRISEBACH and BRANDNER[61] have yielded results which are compatible only with the scheme of Figure 1: they are not compatible with the scheme of Figure 2. Cinnamic acid-3-^{14}C was fed to *Cicer arietinum* and both the isoflavones formononetin (XXI) and biochanin-A (XXII) were isolated. It was shown that C-2 of each isoflavone was derived from the benzylic carbon atom of a phenylpropane precursor. This is in agreement with the earlier results[44] with isoflavone biosynthesis by red clover (*Trifolium pratense*) which also required an aryl-migration*.

Structural relationships between isoflavonoids and rotenoids. The rotenoids[62,63] constitute a class of natural products which includes rotenone (XXVIa), sumatrol (XXVIb), deguelin (XXVIc), toxicarol (XXVId), elliptone (XXVIe), malaccol (XXVIf), pachyrrhizone (XXVII)[64], and munduserone (XXVIII)[65,66].



* Added in proof: Prof. GEISSMAN has kindly informed that us further work has established that his earlier proposal (see Fig. 2) is not correct and that his later results agree with the biosynthetic scheme given in Figure 1.

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[64] H. BICKEL and H. SCHMID, Helv. chim. Acta *36*, 664 (1953).
[65] N. FINCH and W. D. OLLIS, Proc. chem. Soc. *1960*, 176.

[66] The structures given for sumatrol and malaccol are probably correct although they have not been completely established.

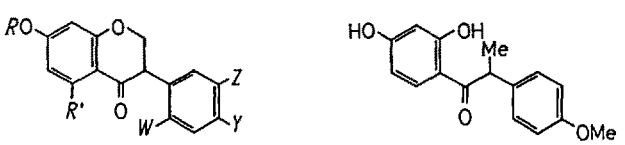
The rotenoids show a remarkable uniformity in their structure and the major problem which is raised when their biosynthesis is considered, is how the tetracyclic C_{16}-nucleus comprising rings A, B, C, and D (see XXVI) is formed. The development of the various structures of the rotenoids from such a C_{16}-precursor then involves subsidiary processes such as O-methylation and the introduction of C_2- and C_5-units. The addition of C_5-units[67] almost certainly involves isopentenyl pyrophosphate or $\gamma\gamma$-dimethylallyl pyrophosphate generated by the mevalonate route[68]. BIRCH[3] and SESHADRI[67] have suggested that the C_2 residues in elliptone, malaccol, and pachyrrhizone are produced by modification of C_5-groupings. The structure of munduserone (XXVIII) is of particular interest regarding this speculation because in its biosynthesis it may be presumed that O-methylation has occurred rather than the introduction of a C_5-unit.

The rotenoids (XXVI, XXVII, and XXVIII) bear an obvious structural relationship[69] to the isoflavones derivable from the structure (XXIX). This is emphasised by a comparison of the frequency of location of oxygen for the corresponding positions of the twenty-five known isoflavones and the eight known rotenoids. These figures are recorded as percentage frequencies in Table I, which also includes the corresponding figures for the eleven isoflavanoids whose structures are given below.

Tab. I. Percentage frequency of sites bearing oxygen atoms

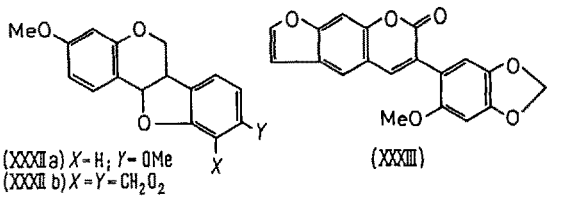
Position	5	6	7	8	2′	3′	4′	5′	6′
Isoflavones	56	32	100	0	32	4	88	56	0
Rotenoids	37	0	100	13	100	0	100	100	0
Isoflavanoids	36	0	100	0	81	9	100	36	0

The eleven isoflavanoids considered in Table I include the isoflavanones, padmakastein (XXXa)[70] ferreirin (XXXb)[71] homoferreirin (XXXc)[71] and sophorol (XXXd)[72] the deoxybenzoin, angolensin (XXXI)[73], the coumarano-chromans, homopterocarpin (XXXIIa)[74] and pterocarpin (XXXIIb)[74], the 3-arylcoumarin, pachyrrhizin (XXXIII)[75], and the coumarano-coumarins, coumestrol (XXXIVa)[76], wedelolactone (XXXIVb)[77] and erosnin (XXXV)[78].



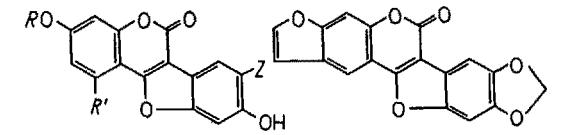
(XXXa) R=Me; R'=OH; W=H; Y=OH; Z=H
(XXXb) R=H; R'=OH; W=OH; Y=OMe; Z=H
(XXXc) R=H; R'=OH; W=OMe; Y=OMe; Z=H
(XXXd) R=H; R'=OH; W=OH; Y-Z=CH_2O_2

(XXXI)



(XXXIIa) X=H; Y=OMe
(XXXIIb) X=Y=CH_2O_2

(XXXIII)



(XXXIVa) R=H; R'=H; Z=H
(XXXIVb) R=Me; R'=OH; Z=OH

(XXXV)

In spite of the variety of structure shown by the isoflavones, isoflavonoids, and rotenoids, there is nevertheless an underlying uniformity. One obvious difference that separates them from the flavonoids is the comparatively frequent occurrence of 2′-oxygenation (see Tab. I); this occurs very rarely among flavanoids although a much larger number of them is known. This is strongly indicative of a close biogenetic relationship between isoflavones and rotenoids and is supported by their frequent co-occurrence in the same plant (see Tab. II). It may be noted that natural products of these types usually exist in plants of one family – the *Leguminosae*. When plants contain both flavonoids and isoflavonoids, there is often a correspondence in positions bearing oxygen containing substituents[79]. This suggests that flavonoid and isoflavonoid biosyntheses are developing either from similar precursors or along parallel courses. This situation is exemplified by the constituents of *Prunus puddum* which belong to five different structural types. As shown in the Table II, similar phytochemical relationships also exist among the natural products of these types isolated from other plants.

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[68] A. J. BIRCH, J. SCHOFIELD, and H. SMITH, Chem. & Ind. *1958*, 1321. – F. LYNEN, B. W. AGRANOFF, H. EGGERER, U. HENNING, and E. W. MÖSLEIN, Angew. Chem. *71*, 657 (1959). – J. W. CORNFORTH and G. POPJÁK, Tetrahedron Letters *No. 19*, 29 (1959).
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Biosynthesis of the rotenoids. This raises two problems: a) the origin of the ether-oxygen in ring C and the possible significance of its relationship to the 2'-oxygen function in isoflavones, and b) the origin of the $> CH_2$ group in ring C. Regarding a), a relationship between 2'-oxygenated isoflavones and rotenoids can be detected if it is recognised that an oxygen in such a position could indicate the participation of an *o*-coumaric acid intermediate (XXXVIII). Such an intermediate, derivable from a coumarin (XXXVII), could provide an intermediate hydroxychalkone (XXXIX) which can be transformed to a 2'-oxygenated isoflavonoid *via* the route to isoflavones already discussed (see Fig. 1). This scheme is represented diagrammatically in Figure 3. The alternative possibility that the 2-hydroxyl group in the chalkone (XXXIX) is introduced after chalkone formation is not, of course, excluded (see Fig. 4).

Tab. II

Plant	Flavonoid	Isoflavonoid	Rotenoid
Ferreirea spectabilis[71, 80]	Naringenin	Biochanin-A (XIX) Ferreirin (XXXb) Homoferreirin (XXXc)	— — —
Prunus puddum[70, 81]	Sakuranin Sakuranetin Genkwanin Taxifolin	Prunetin Padmakastin Padmakastein (XXXa)	— — — —
Mundulea sericea[65, 82, 83, 84]	Sericetin	Mundulone Munetone	Munduserone (XXVIII) —
Pachyrrhizus erosus[64, 75, 78, 85]	—	Pachyrrhizin (XXXIII) Erosnin (XXXV)	Rotenone (XXVIa) Pachyrrhizone (XXVII)
Pterocarpus angolensis[73, 86]	—	Muningin Angolensin (XXXI)	— —
Derris malaccensis[69]	—	Toxicarol isoflavone	Rotenone (XXVIa) Sumatrol (XXVIb) Deguelin (XXVIc) Toxicarol (XXVId) Elliptone (XXVIe) Malaccol (XXVIf)

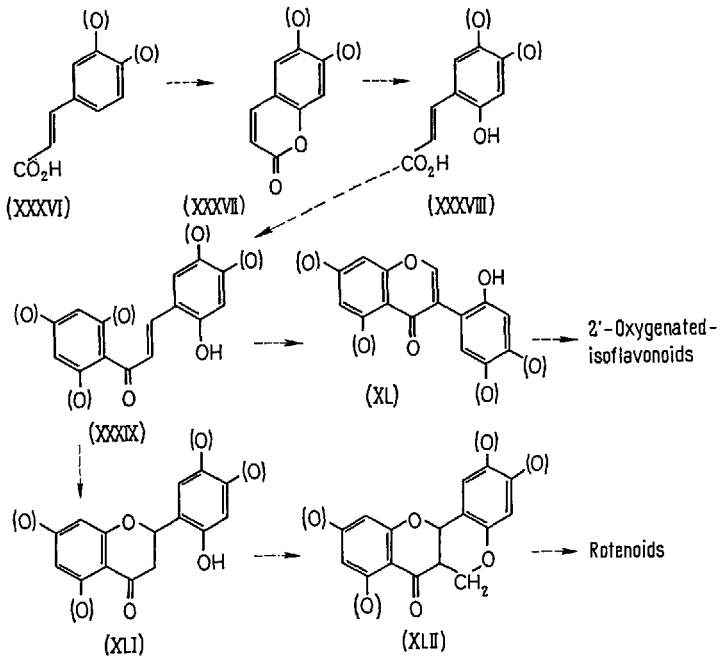
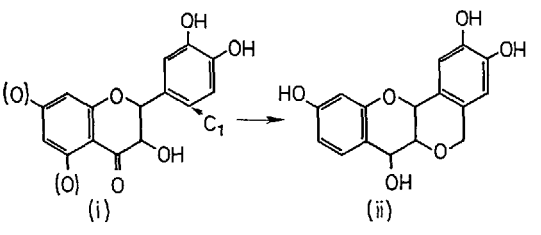


Fig. 3. Tentative correlation of the biosynthesis of rotenoids and 2'-oxygenated isoflavanoids

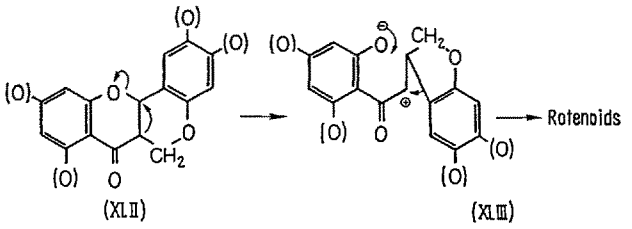
[80] F. E. KING, M. F. GRUNDON, and K. G. NEILL, J. chem. Soc. *1952*, 4580.
[81] N. NARASIMHACHARI and T. R. SESHADRI, Proc. Indian Acad. Sci. [A], 271 (1949).
[82] B. F. BURROWS, N. FINCH, W. D. OLLIS, and I. O. SUTHERLAND, Proc. chem. Soc. *1959*, 150.
[83] B. F. BURROWS, W. D. OLLIS, and L. M. JACKMAN, Proc. chem. Soc. *1960*, 177.
[84] N. L. DUTTA, J. Indian chem. Soc. *33*, 716 (1956); *36*, 165 (1959).
[85] L. B. NORTON and R. HANSBERRY, J. Amer. chem. Soc. *67*, 1609 (1945).
[86] F. E. KING, T. J. KING, and A. J. WARWICK, J. chem. Soc. *1952*, 96.
[87] A closely related biosynthesis (i) is, as recognised by HASSALL et al.[88] presumably involved in the formation of peltogynol (ii).



[88] W. R. CHAN, W. G. C. FORSYTH, and C. H. HASSALL, J. chem. Soc. *1958*, 3174.

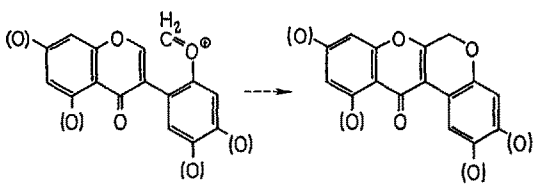
This hydroxy-chalkone (XXXIX) could also be regarded as a reasonable progenitor of the rotenoids. Thus, it is equivalent to the flavanone (XLI) and this with formaldehyde[87] or its equivalent could give rise to a tetracyclic intermediate (XLII) which could rearrange to the rotenoid skeleton by various mechanisms; one is indicated below[89].

The rearrangement (XLII → rotenoids) bears some relationship to the rearrangement studied by ISOE and NAKAZAKI[91].



(XLII) (XLIII)

There are other biogenetic routes to the rotenoid structure which should be considered. These include the possibility that the interpolation of the methylene group in ring C involves a process (e.g. XLIV → XLV) which is related to O-methylation, but this is open to objections on mechanistic grounds. Alternatively it can be envisaged that just as the formation of isoflavones by the GEISSMAN route (see Fig. 2) requires the introduction of a C_1 unit, so the introduction of a C_2 unit (acetate?) leading to a rotenoid skeleton might be possible. However, both these processes would probably lead to a 2,3-dehydrorotenoid (XLV) and the suggestion that such compounds are intermediates is rendered unlikely since the isolation of 2,3-dihydrorotenoids is very rare. In those few cases where they have been isolated, the procedures used suggest that they could well be artefacts.



(XLIV) (XLV)

An interesting suggestion regarding the biosynthesis of the rotenoids has been made by SCHMID et al.[92] in which it is proposed that an intermediate isoflav-2-ene could undergo a Prins type of reaction with formaldehyde. Although this could lead to the tetracyclic rotenoid nucleus, its oxidation state would be that of the 2,3-dehydrorotenoids, so this proposal may also be questioned on this account.

It is possible that some of the questions which have been raised by this consideration of rotenoid biosynthesis may be answered by experiments which we are currently undertaking, using labelled substances as possible precursors. It would appear, however, that the biosynthesis of rotenoids is closely related to the biosynthesis of flavonoids and isoflavonoids and a summary of tentative correlations is given in Figure 4. Rotenoid biosynthesis is also apparently quite a stereoselective process since it has recently been shown that six natural rotenoids (see XXVI) have the same absolute stereochemistry at positions 2 and 3[93]. In this connection it is of considerable interest to note that a further

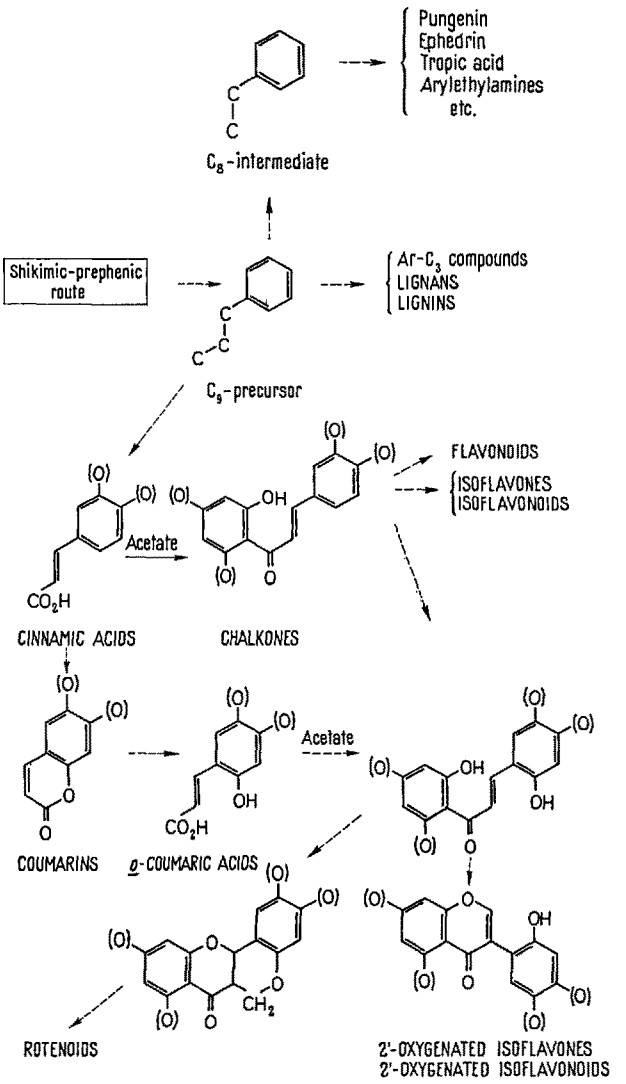


Fig. 4. Possible biosynthetic relationships between flavonoids, isoflavonoids, and rotenoids

[89] The postulated carbonium ion intermediate (XLIII) may cause concern since it bears a positive charge located α to a carbonyl group. However, this has precedent[49], and appreciable stabilisation may be provided by phenonium and oxonium contributing structures. It may be noted that the acid catalysed acylation of the tertiary hydroxyl group of certain hindered acyloins is remarkably facile[37,38,90].

[90] HUANG-MINLON, E. WILSON, N. L. WENDLER, and M. TISHLER, J. Amer. chem. Soc. *74*, 5396 (1952). – R. B. TURNER, J. Amer. chem. Soc. *75*, 3488 (1953).

[91] S. ISOE and M. NAKAZAKI, Chem. & Ind. *1959*, 1574.

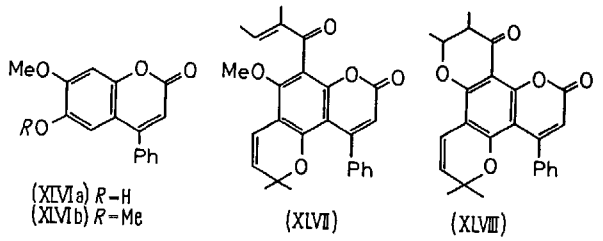
[92] O. A. STAMM, H. SCHMID, and J. BÖCHI, Helv. chim. Acta *41*, 2006 (1958).

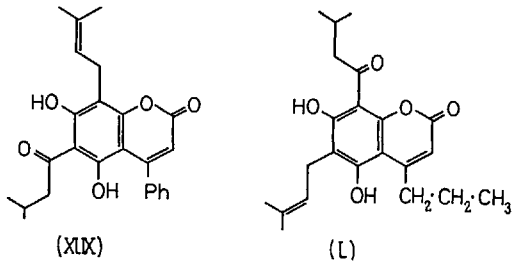
[93] C. DJERASSI, W. D. OLLIS, and R. C. RUSSELL, J. chem. Soc., in press.

relationship between flavonoids and rotenoids may well exist since the dihydroflavonols, leucoanthocyanidins, and catechins which have been examined all have the same R-configuration at the 2-position[94].

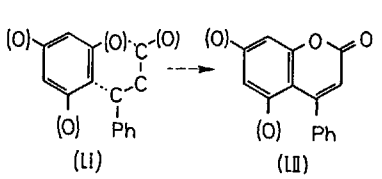
The inter-relationships given in Figure 4 are not meant to be detailed representations, but merely to indicate feasible relationships between the various types of natural products which have been considered. It should be emphasised that although only one route to 2'-oxygenated isoflavones is indicated, this does not imply that such compounds can be formed solely by this route. Their origin *via* this route may, however, be more likely.

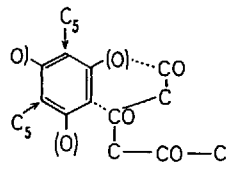
4-Aryl chromans. Recently several members of this class of compounds have been detected naturally including dalbergin (XLVIa) and methyl-dalbergin (XLVIb) from *Dalbergia sissoo*[95], calophyllolide (XLVII) and inophyllolide (XLVIII) from *Calophyllum inophyllum*[96], and the compound (XLIX) from *Mammea americana*[97].

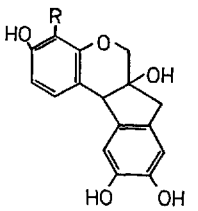




The five compounds (XLVIa), (XLVIb), (XLVII), (XLVIII), and (XLIX) are all derivatives of 4-phenylcoumarin and it is conceivable that they might arise biosynthetically from flavonoids *via* isoflavonoids by two 1,2-aryl shifts[44]. This has already been considered in the case of brazilin (*vide infra*), but in the case of the 4-aryl coumarins a more likely route has been suggested by SESHADRI[98] which involves interaction of phloroglucinol or its equivalent with a C_9-compound (LI → LII). This is obviously supported by the structure of mammein (L)[99], a congener of the compound (XLIX), whose formation requires a similar biosynthetic reaction involving acetate (see LIII).







It is interesting to note that the similarity of the structures of these 4-phenylcoumarins is phytochemically acceptable. The *Calophyllum* and *Mammea* genera belong to the same family (*Guttiferae*).

Brazilin (LIVa) and haematoxylin (LIVb) present certain difficulties when their biogenesis is considered[100]. It has been suggested that their 4-aryl-chroman skeletons could arise from an isoflavanoid precursor by a 3–4 shift of an aryl group[92,101]. This is one of several biogenetic routes which may be postulated and clearly the elucidation of the biosynthesis of brazilin and haematoxylin is of special interest[102].

Zusammenfassung. Einleitend wird auf die bisherigen Ergebnisse über die Biogenese der Flavonoide, der Zimtsäurederivate und der Cumarine eingegangen. Für die Herkunft der C_9-Einheit in diesen Verbindungen ergeben sich enge biogenetische Zusammenhänge. Die unter Phenylwanderung verlaufende Biogenese der Isoflavone wird eingehend diskutiert. Die Bildung der Isoflavone und der Flavonoide verläuft sehr wahrscheinlich über eng verwandte Vorstufen. Es wird dann ausführlich auf die strukturellen Beziehungen zwischen Isoflavonen und Rotenoiden eingegangen und ein Biosyntheseweg für die Rotenoide vorgeschlagen, welcher zu der richtigen Oxydationsstufe des Heterocyclus führt. Als zentrale Zwischenstufe für die Biogenese der Flavonoide, der Isoflavone und der Rotenoide kann ein Chalkon angesehen werden. Abschliessend werden die biogenetischen Beziehungen zu den 4-Arylchromanen behandelt.

[94] J.W. CLARK-LEWIS, in A. ALBERT, G. M. BADGER, and C. W. SHOPPEE, *Current Trends in Heterocyclic Chemistry* (Butterworths Scientific Publications, 1958).

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[97] R. A. FINNEGAN and C. DJERASSI, Tetrahedron Letters *No. 13*, 11 (1959).

[98] T. R. SESHADRI, Curr. Sci. *26*, 239 (1957).

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[100] Ref. [54], p. 42.

[101] W. B. WHALLEY, Chem. & Ind. *1956*, 1049; *Chemistry of Vegetable Tannins Symposium*, Society of Leather Trades' Chemists, 151–160 (London 1956).

[102] H. GRISEBACH, *The Biosynthesis of Isoflavones* in *Recent Developments in the Chemisty of Natural Phenolic Compounds* (ed. W. OLLIS, Pergamon Press) in the press.