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THE BIOSYNTHESIS OF AROMATIC HEMITERPENES

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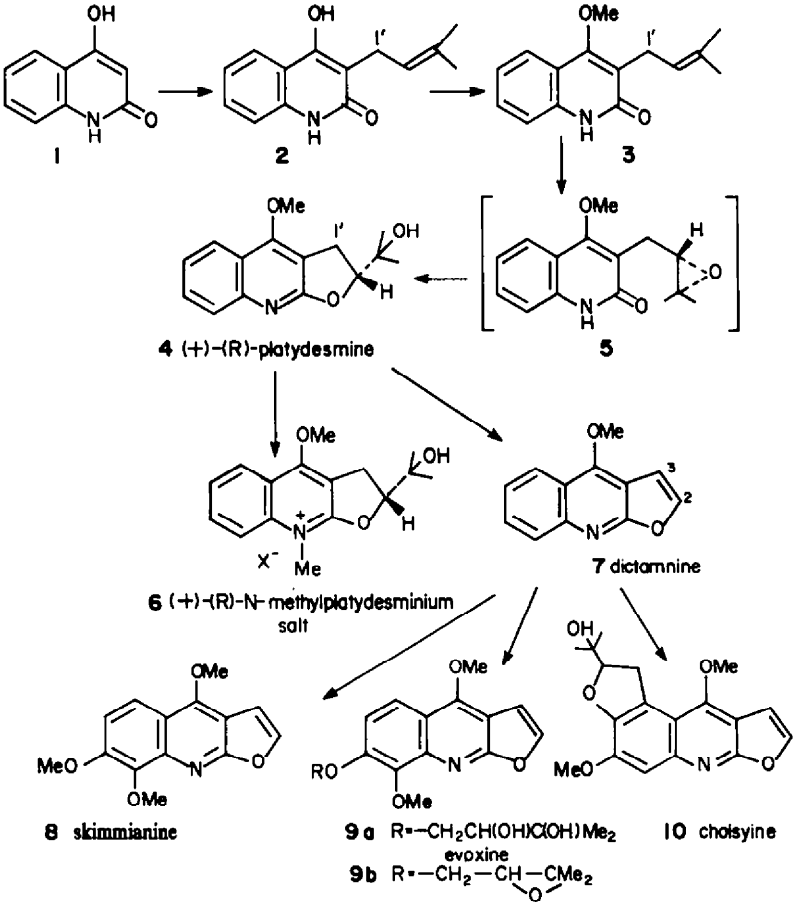
INTRODUCTION

In the context of this review, the term aromatic hemiterpenes is meant to cover compounds of natural origin in which an isoprenyl group is attached through a C–C bond to an aromatic or heterocyclic system. The greatest number and variety of such hemiterpenes are found amongst coumarins, chromones, quinones, and indole and quinoline alkaloids. Compartmentation is a problem not only for biosynthetic research but also for a reviewer, and many accounts of recent results in this area have been confined to particular chemical groups.[1] Two valuable articles[2] that appeared in 1961 used a different approach and included discussion of the structures, synthesis and biosynthesis of aromatic hemiterpenes as a composite group; at that time, however, few experimental biosynthetic results were available and it is one of the purposes of this account to up-date the 1961 reviews by evaluating critically the biosynthetic work of the last decade. A comprehensive treatment has not been attempted; the choice of topics primarily reflects the author's current interests and some subjects have been omitted because excellent recent reviews are available, for example on the biosynthesis of ergot alkaloids.[3]

OXIDATIVE CYCLISATION OF PRENYL GROUPS

Hydroxyisopropyldihydrofurans. Numerous compounds containing a hydroxyisopropyl dihydrofuran group attached to an aromatic or heterocyclic ring have been isolated, particularly in the quinoline, coumarin and chromone series, for example, N-methylplatydesminium salt **6**, balfourodine **25**, marmesin **16** and visamminol **22**. For many years it has been assumed that the furan ring is derived *in vivo* by oxidative cyclisation of a prenyl group adjacent to a hydroxyl function, but experimental



Scheme 1.

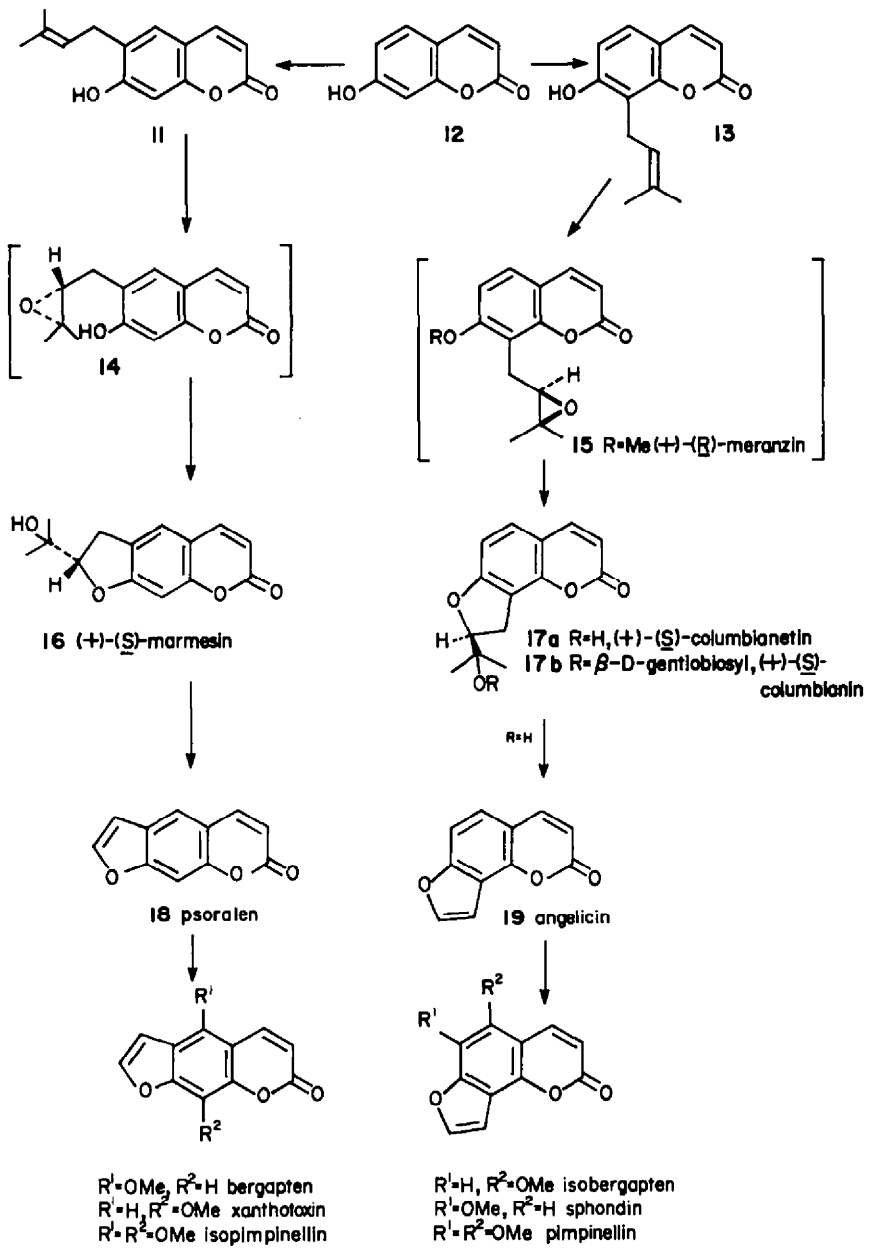
evidence was not available until 1969, when the alkaloids of the rutaceous shrub, *Skimmia japonica* were studied.[4]

The 3-prenylquinolones **2** and **3**, labelled at C-1′ with ^{14}C were good precursors of the alkaloid N-methylplatydesminium salt **6** in *S. japonica* and specific incorporation was established by degradation. The tertiary base, platydesmine **4**, is also a specific precursor of the quaternary salt **6** in *S. japonica*. Thus, the most probable biosynthetic sequence was considered to be **1**→**2**→**3**→**5**→**4**→**6** (Scheme 1).

Analogously, [2-^{14}C] - 7 - Hydroxy - 6 - prenylcoumarin **11** was an effective precursor of the dihydrofurocoumarin marmesin **16** in *Ruta graveolens*.[5] Although the prenyl derivative **11** was not detected in the plant, it was shown to be a biosynthetic intermediate by trapping experiments using labelled umbelliferone **12** and the cold prenyl compound.

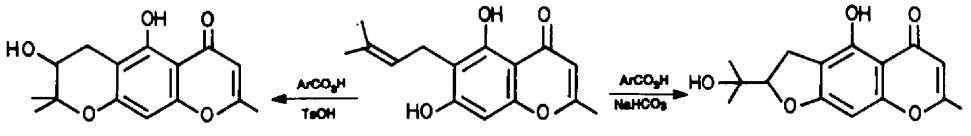
Hydroxydimethyldihydropyrans and the role of epoxides. Aromatic dihydropyrano derivatives, isomeric with the furo compounds just discussed occur in *Balfourodendron, Lunasia* and *Ptelea* species (Rutaceae) and in various members of the Umbelliferae. No direct biosynthetic work appears to have been carried out on these pyrano compounds, but the co-occurrence of the furo- and pyrano-isomers, for example, (+)-balfourodine **25** and (+)-isobalfourodine **31** in *Balfourodendron riedelianum*, the enantiomeric pair (−)-hydroxylunacrine (see **25**) and (−)-lunacrinol **30** in *Lunasia amara*, and (+)-columbianin **17b** and (+)-lomatin **32** in *Lomatium nuttalii* strongly suggested at least before the absolute configurations were known, that isomers are derived by oxidative cyclisation of a common precursor, a prenylquinoline **3** or a prenylcoumarin **11**.

The proposal that epoxidation of a prenyl group was



Scheme 2.

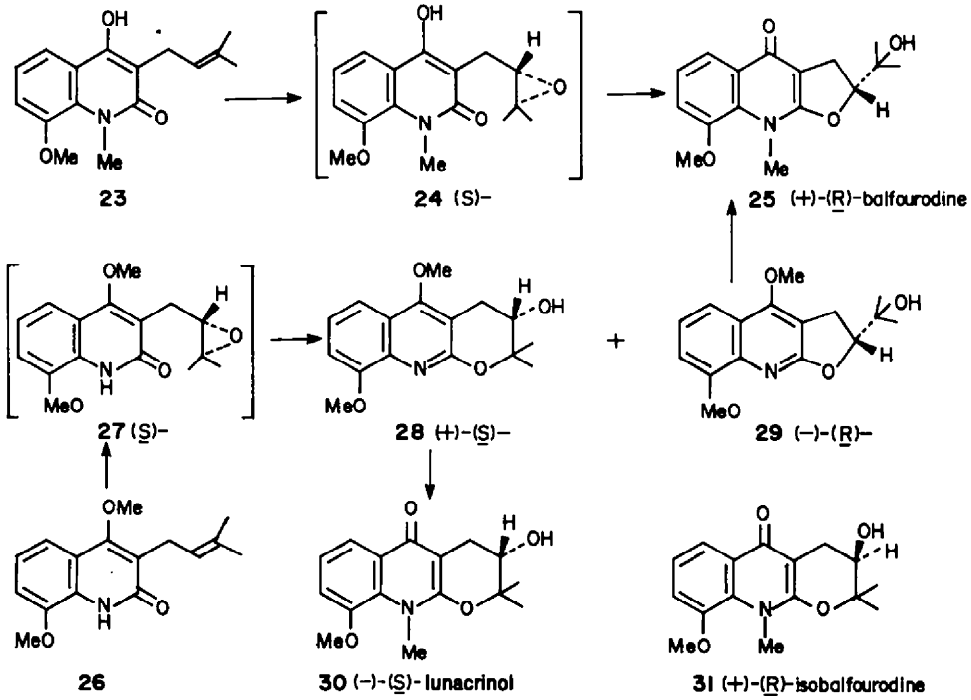
involved in the biosynthetic cyclisation[2a] was based originally on *in vitro* evidence. The prenylchromone, peucenin **21**, for instance, yields hamaudol **20** exclusively when treated with a peracid containing *p*-toluene sulphonic acid,[7] the strong acid directing the reaction to the pyrano-derivative through a tertiary carbonium ion; epoxidation of peucenin in the presence of bicarbonate, however, gives only the dihydrofuran, visamminol **22**.[8] The occurrence of prenyl epoxides in which spontaneous cyclisation is impossible, for example the coumarin **15** and the quinoline alkaloid **9b**, provides further support for the epoxide route to dihydrofuro- and dihydropyrano-derivatives.



20 hamaudol **21** peucenin **22** visamminol

The stereochemical consequences of the cyclisation of prenyl epoxides have been discussed in relation to biosynthesis[9,10] and in the light of the determination of the absolute configuration of a number of dihydrofuro- and dihydropyrano-coumarin[11a] and quinoline[10,11b] derivatives. Reactions of (+)-(*S*)-peroxycamphoric acid with monosubstituted olefins were known to furnish epoxides containing a preponderance of the (*S*)-enantiomers,[12] and application of the reaction to trisubstituted prenyl olefins produced a similar result[9,10] (Scheme 3). Thus, reaction of the *N*-methyl prenylquinolone **23** with a range of (*S*)-peroxyacids furnished balfourodine **25** containing an excess of the (+)-(*R*)-enantiomer; this arises apparently through an intermediate (*S*)-epoxide **24** undergoing spontaneous cyclisation with stereochemical inversion at the chiral centre. A preponderance of the opposite enantiomer, (−)-(*S*)-balfourodine was obtained by the use of (*R*)-peroxyacids. Applying the reaction to the 4-methoxyquinolone **26** gave a mixture of dihydrofuroquinoline **29** and its pyrano-isomer **28** converted by reaction not affecting the chiral centres into (+)-(*R*)-balfourodine **25** and (−)-(*S*)-lunacrinol **30**, respectively; this is the expected stereochemical result, the pyrano-compound **28** being formed from (*S*)-epoxide **27** by attack at the tertiary carbon without disturbing the chiral centre. If these asymmetric syntheses serve as models for the biosynthetic routes we would expect isomeric pairs of dihydrofuro- and dihydropyrano-isomers occurring together in a single species to have 'opposite' absolute configurations (see Scheme 4).[13] This is indeed the case for known pairs of coumarin derivatives; for example, the presence of (+)-(*S*)-columbianin **17b** and (+)-(*R*)-lomatin **32** in *L. nuttalii* is consistent with a biosynthetic route through a common (*R*)-epoxide intermediate.

The stereochemistry of the dihydrofuro- and dihydropyrano-quinolines in contrast to the corresponding coumarin derivatives, is inconsistent with Scheme 4.[10] Thus, balfourodine **25** and isobalfourodine **31** from *B. riedelianum* have (*R*)-configurations, and their respective (*S*)-enantiomers are constituents of *L. amara*; this indicates that the isomers present in one plant do not both originate directly from a single epoxide. Since an *in vitro* rearrangement of balfourodine and isobalfourodine occurs mainly with retention of configuration, it was suggested that the biosynthetic pathway to isobalfourodine involves a similar rearrangement. The 6-hydroxyquinol-

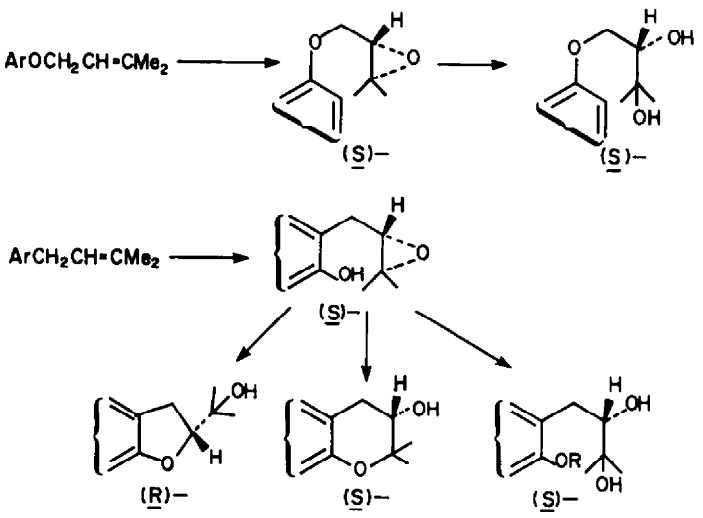


23 **24** (S)- **25** (+)-(R)-balfourodine

27 (S)- **28** (+)-(S)- **29** (−)-(R)-

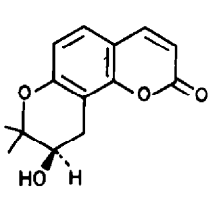
26 **30** (−)-(S)-lunacrinol **31** (+)-(R)-isobalfourodine

Scheme 3.

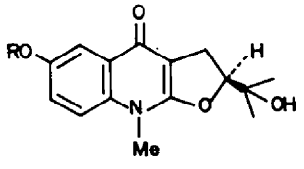


Scheme 4.

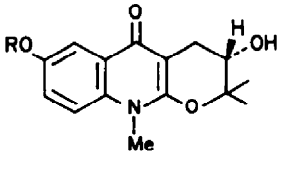
ines, (+)-ribaline **33a** and (−)-ribalinidine **34a**, isolated from *B. riedelianum* growing in Argentina, are another pair of furo-pyrano isomers. (+)-*O*-Methylribaline **33b** and hence (+)-ribaline **33a** was shown to have the (*S*)-configuration.[14] Since rearrangement of (+)-methylribaline furnished (−)-methylribalinidine **34b** and this reaction in the 8-methoxyquinoline series is now known to involve retention of configuration,[10] (−)-ribalinidine appears to have the (*S*)-configuration also. This example, then, is analogous to the balfourodine-isobalfourodine case. It is curious that balfourodine and isobalfourodine with (*R*)-configurations occur in Brazilian *B. riedelianum* whereas (*S*)-ribaline and (*S*)-ribalinidine are found in *B. riedelianum* of Argentine origin, and raises the possibility that two species of *Balfourodendron* are involved. *Ptelea trifoliata* contains another pair of dihydrofuro- and dihydropyrano-quinolines[15] but in this case the configuration of the pyrano-isomer has not yet been established.



32 (+)-(R)-lomatin



33 a R=H (+)-(S)-ribaline
33 b R=Me (+)-(S)-methylribaline



34 a R=H (−)-(S)-ribalinidine
34 b R=Me (−)-(S)-methylribalinidine

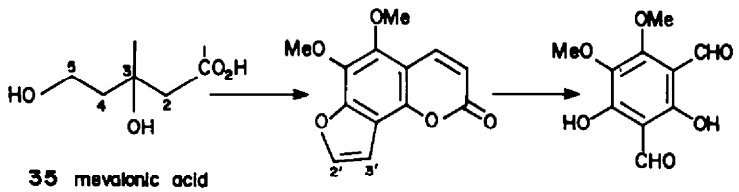
The stereochemical relationships discussed above give useful insight into biosynthetic pathways but are no substitute for direct experiment; for dihydropyrano derivatives tracer feeding work is now overdue and for quinoline alkaloids should include an exploration of a hydroxyisopropyldihydrofuroquinoline as a precursor of its dihydropyrano isomer.

Other stereochemical relations. With a view to extending biosynthetic-stereochemical correlations, a chemotaxonomic survey was carried out of coumarins and quinolines containing oxygenated prenyl groups of established stereochemistry.[13] The configurations suggested that *C*-isoprenoids in a particular plant species are derived by stereospecific oxidation via epoxidation by means of a single mono-oxygenase, irrespective of the nature of the aryl group. A similar correlation applies to O-prenyl derivatives that occur together. The proposal for (*S*)-epoxides is summarised in Scheme 4. There is, however, no general stereochemical consistency between O-prenyl and C-prenyl derivatives that co-occur. It seems that stereospecific oxidation of the C- and O-isoprenyl types may be controlled by distinct mono-oxygenases, perhaps as a result of different stereoelectronic requirements of groups $ArCH_2CH{=}CMe_2$ and $ArOCH_2CH{=}CMe_2$. The conclusions can be only tentative since data was available for only fifteen plant species, but it was hoped that the survey would stimulate further work on the stereochemistry and biosynthesis of oxygenated aryl hemiterpenes.

BENZOFURANS AND RELATED COMPOUNDS

Benzofurans and compounds in which a furan ring is part of a fused heterocyclic system occur widely in species of the Umbelliferae and Rutaceae. The best known derivatives are benzofurans of the furocoumarin group, e.g. angelicin **19**, isopimpinellin **42** and furoquinoline alkaloids, e.g. skimmianine **8**. The biosynthetic origin of the furan ring has been discussed for many years, but experimental evidence has been available only during the last decade. The present state of knowledge is summarised in Schemes 1, 2, 5 and 6.

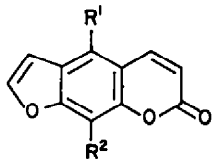
The role of mevalonate. The first clear indication that the two furan carbon atoms are the residue of a degraded isoprene substituent was obtained from feeding experiments with *Pimpinella magna*; [4-^{14}C]-Mevalonate (see **35**) was incorporated to the extent of 0.5% into the total furocoumarins; since ozonolysis of one constituent, pimpinellin **36**, gave the dialdehyde **37** containing only 11% of the radioactivity of the coumarin, it was concluded that the tracer carbon of the precursor was centred at C-2′ and that the furan ring was isoprenoid derived.[16] Thereafter the role of mevalonate in the



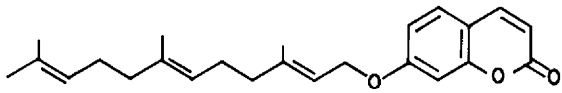
35 mevalonic acid

36 pimpinellin

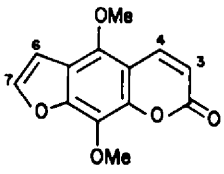
37



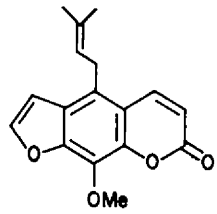
38 R^1=H, R^2=OMe xanthotoxin
39 R^1=OMe, R^2=H bergapten
40 R^1=H, R^2=$OCH_2CH=CMe_2$ imperatorin



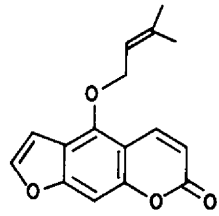
41 umbelliprenin



42 isopimpinellin



43 alloimperatorin methyl ether



44 isoimperatorin

biosynthesis of furo derivatives became confused and controversial. Mevalonate did not appear to be a significant precursor of dictamine **7** in *Dictamnus albus*[17] or in *Skimmia japonica*,[18] although in the latter case good incorporation into the associated triterpene, friedooleanen-14-en-3β-ol, was observed. Labelled mevalonate was only poorly incorporated into the furocoumarins, xanthotoxin **38**, bergapten **39**, imperatorin **40**, and isopimpinellin **42** of *Pastinaca sativa*[19] and into psoralen **18**, xanthotoxin **38**, bergapten **39** and isopimpinellin **42** in cell cultures of *Ruta graveolens*.[6] The *P. sativa* study showed that 2-^{14}C-mevalonate, which was not expected to introduce radioactivity into furan rings, was as good a precursor as the 5-^{14}C-derivatives and that ^{14}C-acetate was more efficient; as a result, the whole theory of the isoprenoid origin of furo rings was regarded as questionable. Much of the otherwise excellent work on the biosynthesis of furoquinolines is marred by the failure to degrade the products or to use double-labelling techniques thereby establishing the extent of randomisation of the label; this important principle which has been emphasised by others[20,21] will be referred to again in this review. A detailed and exemplary study of coumarins umbelliprenin **41**, isopimpinellin **42**, alloimperatorin methyl ether **43** and isoimperatorin **44** in *Thamnosa montana* was concerned with the role of mevalonate.[21] There was negligible incorporation of [2-^{14}C]-mevalonate into the coumarins except umbelliprenin in *T. montana* plants but [4-^{3}H]-mevalonate was shown to be a specific precursor of the furan ring of isopimpinellin (0.0003%) incorporation. Plant tissue cultures proved to be more satisfactory, [4-$^{3}H_3$]- and [5-$^{3}H_3$]-mevalonate being incorporated into coumarins **42–44** to the extent of *ca.* 0.002%. The fate of the label was established by degradation. In the [5-$^{3}H_3$]-mevalonate experiments, e.g. 56% of the label was present in C-6 of isopimpinellin **42** and, unexpectedly, the rest in the methoxyl groups, whereas in coumarin **43** 30–32% was at C-6 and the remaining activity in the prenyl side-chain. [2-^{14}C]-Acetate was fed to *T. montana* plants and radioactive isopimpinellin **42** (*ca.* 0.002%) was isolated; degradation indicated that *ca.* 10% of the label was at C-7, 0–3% at C-6 and the remainder in methoxyl groups. This work confirmed that furan carbon atoms of furocoumarins are derived from mevalonate and indicated that earlier doubts arose from undetected randomisation of the labelled precursors. [4-^{14}C]- and [5-^{14}C]-Mevalonate were also shown to be specific precursors of the furan ring of the furoquinoline alkaline, skimmianine **8** in *Fagara coco*.[22]

Prenyl-coumarins and 3-prenyl-2-quinolones as biosynthetic intermediates. Concurrently with the mevalonate studies, 7-hydroxycoumarin (umbelliferone) was identified as a general precursor of furocoumarins[5,6,19,23–25] and 4-hydroxy-2-quinolone **1** as the corresponding intermediate for furoquinoline alkaloids.[4,26,27] These results led to an investigation of 3 - prenyl - 2 - quinolones as intermediates in the biosynthesis of furoquinoline alkaloids.

In 1969 [1-^{14}C] - 4 - hydroxy - 3 - prenyl - 2 - quinolone **2** and the corresponding 4-methoxy compound **3** (4.7–4.8% incorporation) were shown to be equally good precursors of dictamnine **7**; degradation indicated that randomisation of the label had not occurred.[4] The doubly-labelled [1'-$^{3}H_2$, 1'-^{14}C] - 4 - methoxyderivative **3** was incorporated into skimmianine **8** (6.0–6.4%) and less well (0.20–0.34%) into evoxine **9a** and choisyine **10** in *Choisya ternata*[28] in accord with Scheme 1. The 3-prenylquinolone **3** has been isolated from other members of the Rutaceae, but not from *S. japonica* or *C. ternata*, and to complete the biosynthetic study it would be desirable to carry out trapping experiments to ensure

that the intermediates **2** and **3** are synthesised by these species. Correspondingly, [1'-^{14}C] - 6 - prenyl - 7 - hydroxycoumarin (demethylsuberosin, DMS) **11** was shown to be a good specific precursor of the linear furocoumarin, bergapten **39**, in *Angelica archangelica*.[29] ^{14}C-labelled DMS was incorporated into psoralen **18** in *Conium maculatum* and *Ruta graveolens* but not in *Coronilla glauca*;[5] although it was not isolated from these plants, DMS was clearly an intermediate in furocoumarin biosynthesis since a trapping experiment with [2-^{14}C]-umbelliferone **12** in the presence of cold DMS gave DMS with a specific activity higher than that of psolalen. [2-^{14}C]-Osthenol **13** was shown similarly to be a good precursor of the angular furocoumarin, angelicin **19**, in *Heracleum lanatum*.[5] Psoralen and angelicin were not degraded to show that specific labelling had occurred. The prenylcoumarin **11** was utilised by cell cultures of *R. graveolens* in the biosynthesis of furocoumarins; labelled 7-prenyloxycoumarin was also incorporated although less efficiency and in order to account for this unexpected observation *in vivo* cleavage to umbelliferone was proposed.[6] Umbelliferone dimethylallyltransferase, has now been obtained from *R. graveolens*.[30] Incubation of the enzyme with labelled umbelliferone, dimethylallylphosphate and Mn^{2+} resulted in the formation of DMS containing more than 90% of the label but not the 8-prenylisomer, osthenol. This work convincingly establishes the nature of the first stage of the biosynthetic route from umbelliferone to linear furocoumarins (Scheme 2).

Hydroxyisopropyldihydrofurans as precursors. Two principal theories have been suggested for the biosynthetic origin of the furan ring in benzofurans, one involving the oxidation of a prenyl substituent to an aldehyde which subsequently cyclises, the other postulating loss of a three-carbon fragment from a hydroxyisopropyldihydrofuran.[31,32] Experimental evidence supports the latter proposal.[4] Thus, (±)-[1'-^{14}C]-platydesmine, (see **4**) was fed to shoots of *S. japonica* and [3-^{14}C]-dictamnine **7** was isolated with minimal randomisation of the label. The incorporation into dictamnine was 18.8% or twice this figure if it is assumed that only one enantiomer present in racemic platydesmine is utilised. Platydesmine is a constituent of several rutaceous plants but was not detected in *S. japonica*; it was shown to be a biosynthetic intermediate, however, by feeding a mixture of [1'-^{14}C] - 3 - prenylquinolines **3** and unlabelled (±)-platydesmine and after a short period isolating radioactive platydesmine of higher activity than dictamnine. [1'-^{14}C] - 3 - prenylquinoline **3** and unlabelled (±)-(*R*) - *N* - methylplatydesminium salt **6** in *S. japonica* it seems that it is the (+) - (*R*) - enantiomer of platydesmine **4** that is biologically active. Studies of the biosynthesis of furocoumarins using precursors generally labelled with tritium showed that marmesin **16** was converted into linear furocoumarins in *R. graveolens*[23] and columbianetin **17a** into angular furocoumarins in *H. lanatum* and in *A. archangelica*;[24] the appropriate trapping experiments were carried out. Marmesin **16** is a constituent of *R. graveolens* but insufficient of the compound was isolated to determine the sign of rotation. Feeding experiments using enantiomers specifically-labelled with ^{14}C, however, demonstrated that it was (+)-(*S*)-marmesin **16** and not the (−)-(*R*)-enantiomer (nodakenetin) that was a precursor of furocoumarins, e.g. psoralen **18**, found in the plant.[33] (+)-Marmesin was isolated from cell cultures of *R. graveolens*.[6]

Dehydrogenation of a dihydrofuro derivative was suggested as an alternative route to furocoumarins following the observation that dihydropsoralen **45** was a precursor of psoralen **18** in *Ficus carica*.[34] On the other hand, an attempt to trap dihydropsoralen by feeding [2-^{14}C]-umbelliferone and the inactive dihydroderivative to *R. graveolens* gave a negative result.[35] Similarly in the furoquinoline group labelled dihydrodictamnine **46** was not incorporated significantly into dictamnine in *S. japonica*.[4] It seems that a pathway to benzofurans through their dihydroderivatives is not an important one; the earlier result was obtained with dihydropsoralen generally labelled with tritium and possibly arose through randomisation of the label.

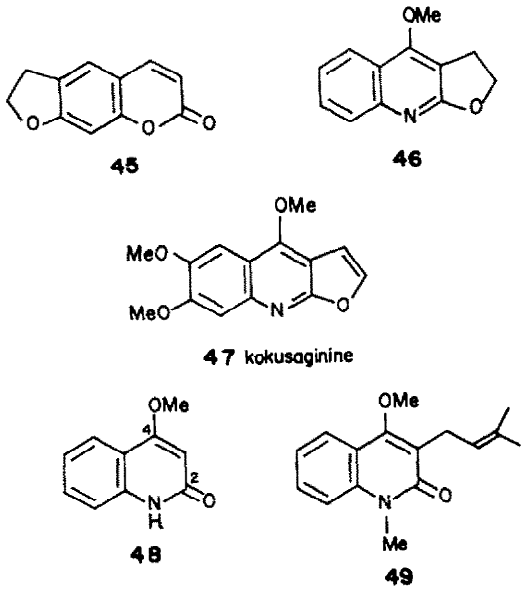
The balance of experimental evidence obtained with over twelve plant species and more than fifteen furocoumarins and furoquinolines indicates that the biosynthesis of these two groups follow parallel pathways and provides support for Schemes 1 and 2. The interpretation of results, however, is dependent to some extent on knowledge of the sequence of aromatic hydroxylation and, particularly in the quinoline series, of methylation of oxygen and nitrogen functions, and these topics merit some discussion here.

Aromatic hydroxylation. The fact that 4 - hydroxy - 2 - quinolone and 7-hydroxycoumarin are precursors of oxygenated furoquinolines, e.g. skimmianine **8** and furocoumarins, e.g. bergapten **39**, respectively, as well as the parent compounds dictamnine and psoralen suggests that hydroxylation occurs later in the pathway. The situation is not entirely clear however since degradation of labelled products was not usually carried out. In one study where this was done,[26] 4 - hydroxy - 2 - quinolone was a specific precursor of skimmianine whereas incorporation into kokusaginise **47** involved randomisation of the label.

The pathway to skimmianine has been defined more clearly than that of other furan derivatives. Feeding experiments with double-labelled precursors and identification of ^{14}C-labelled carbon atoms in the product have shown that the 4 - methoxy - 3 - prenylquinolone **3**[28] and dictamnine **7**[36] are excellent specific precursors of skimmianine **8** in *C. ternata* and in a *Skimmia* species (1.3–6.4% incorporation). Thus, a principal route to skimmianine involves hydroxylation of the homocyclic ring after formation of the furoquinoline ring system. A corresponding sequence appears to apply to furocoumarins since studies with *A. archangelica* and with *H. lanatum* shows that labelled angelicin **19** is incorporated into several hydroxylated angular furocoumarins[24] and in cell cultures of *R. graveolens* psoralen was a good precursor of the linear furocoumarins xanthotoxin, bergapten and isopimpinellin (Scheme 2); specific incorporation of the precursors was not established.

It is tempting to assume that all furocoumarins and furoquinolines originate from psoralen, angelicin or dictamnine but this generalisation is not yet justifiable. For example, the dioxygenated dictamnine derivatives evoxine **9a** and choisyine **10** are present with skimmianine **8** in *C. ternata*; although dictamnine **7** is a specific precursor of all three alkaloids, the low incorporation (0.1%) into evoxine and choisyine compared to skimmianine (2.1%) in the same experiments suggests that hydroxylation of dictamnine is not the only route to these alkaloids.

O-Methylation in furoquinolines. A reasonable biosynthetic pathway to skimmianine is the sequence 4 - hydroxy - 2 - quinolone **1**→ the 4-hydroxyprenylquinolone **2**→ the 4-methoxyprenylquinolone **3**→

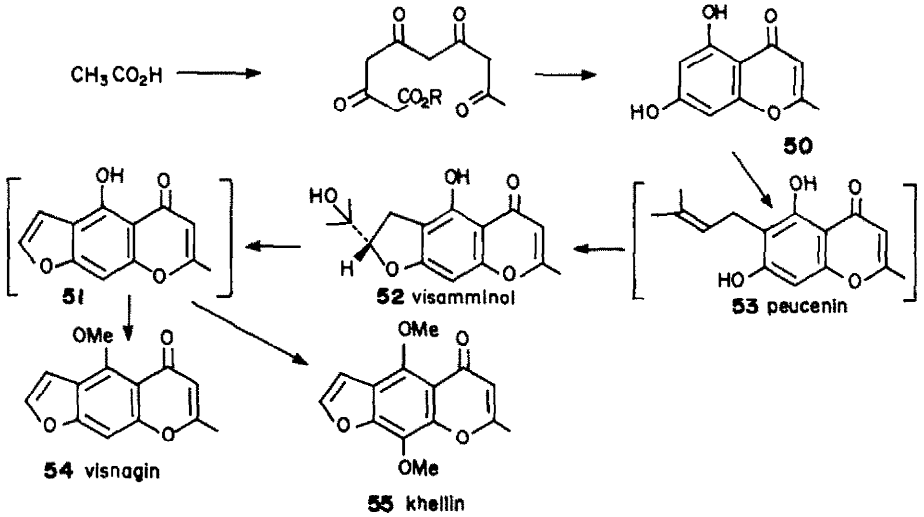


4→7→8 (Scheme 1), and indeed the first four compounds are effective precursors of dictamnine **7** in *S. japonica*. Further support is provided by the observation that the 4-methoxyprenylquinoline **3** labelled on the O-methyl group is an excellent specific precursor of skimmianine in *C. ternata*, indicating that a principal pathway involves retention of the 4-methoxy group in the intermediates platydesmine **4** and dictamnine **7**.[28]

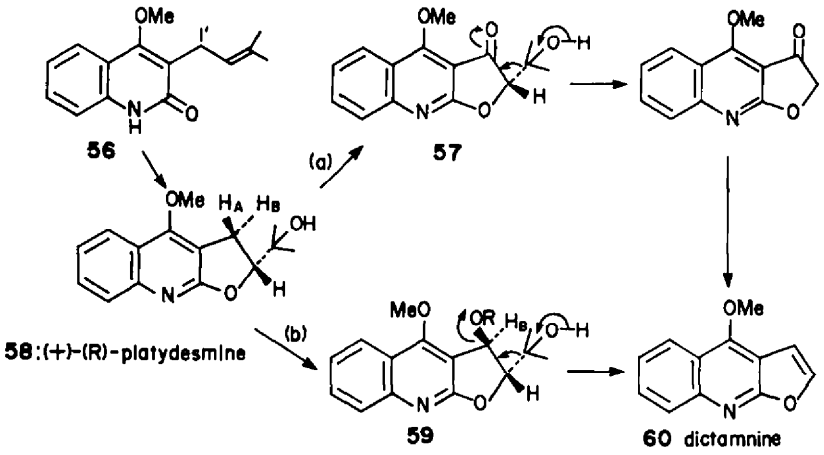
4 - Methoxy - [2,4-$^{14}C_2$] - 2 - quinolone **48** was incorporated (1.5%) into dictamnine[4], suggesting either that there is more than one route to platydesmine **4** or that enzymatic O-demethylation occurs; the latter proposition has now been supported by the observation that 4 - methoxy - 2 - quinolone labelled on the methoxy group is not incorporated into skimmianine in *C. ternata*.[37] 4 - Methoxy - *N* - methyl - 3 - prenyl - 2 - quinoline **49** also is a precursor of dictamnine (2.0% incorporation) in *S. japonica*, indicating that enzymatic loss of an N-methyl group takes place.[38] The most likely explanation of these results is that 4 - methoxy - 2 - quinolone and the N - methyl - 2 - quinolone **49** are unnatural precursors of the furoquinolones, but clarification is certainly required.

Furochromones. It is not surprising that the overall biosynthetic pathways to the furan rings in furocoumarins and furoquinolines appear to be entirely analogous since there is less opportunity to introduce prenyl groups before the formation of the requisite heterocyclic systems than, for example, with aromatic compounds derived from polyketides. In this connection the study of the biosynthesis of the chromones in *Ammi visnaga* is particularly relevant.[7] The plant contains the hydroxyisopropyl dihydrofurochromone, visamminol **52**, and the furochromones, visnagin **54** and khellin **55**; trapping experiments showed that 5,7 - dihydroxy - 2 - methyl - chromone **50** was also a constituent. Labelled acetate was incorporated into the chromone **50** as well as into the prenyl derivatives, indicating in confirmation of earlier results that the chromone system was of polyketide origin. The [2-^{14}C]-chromone **50** proved to be a precursor of visamminol **52**, visnagin **54** and khellin **55**; specific labelling of the two furochromones appeared to have occurred since loss of the C-2 carbons and their attached methyl groups gave inactive aromatic derivatives. The proposed pathway (Scheme 5) has not been fully established, but the role of the polyketide derived chromone **50** clearly is analogous to that of 7-hydroxycoumarin and 4 - hydroxy - 2 - quinolone in the biosynthesis of furocoumarins and furoquinolines, respectively.

Biomechanism of the formation of furan rings. The final stages in the biosynthesis of benzofurans have provoked considerable discussion and mechanisms have been suggested for the loss of the 3-carbon fragment from hydroxyisopropyldihydrofuran derivatives; they are depicted in Scheme 6 for the conversion of (+)-(*R*)-platydesmine into dictamnine, but are also applicable to benzofurans. One proposal (a)[32] involves oxidation to ketone **57**, loss of acetone by a retro-aldol reaction and formation of dictamnine by reduction and then elimination. Alternatively, (b),[39,40] oxidation at the methylene group adjacent to the heterocyclic ring could lead to an alcohol derivative **59** or to an electron deficient species and thence by a fragmentation reaction directly to a furan ring. Chemotaxanomic evidence has been advanced in support of these schemes. For example, the dihydroxydihydrofuran derivative, vaginidin **61**, co-occurs in *Peucedanum oreoselinium* with angelicin and is converted into the angular furocoumarin by treatment with base.[41,42] In the

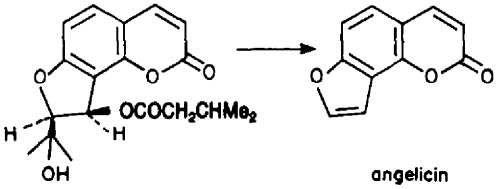


Scheme 5.



Scheme 6.

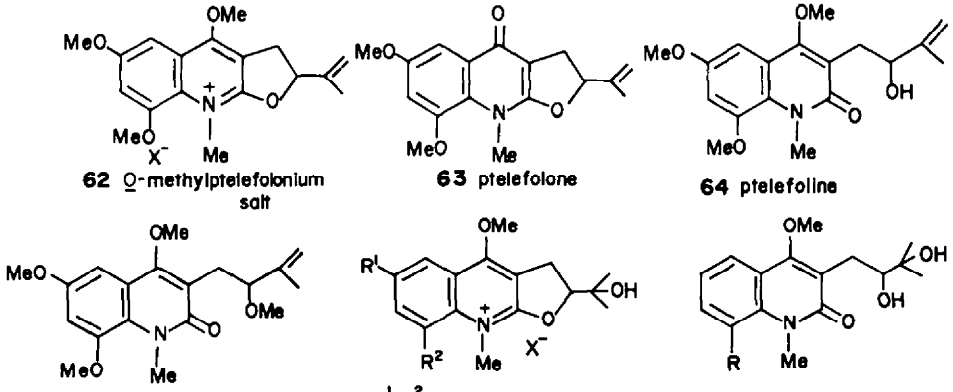
quinoline series the oxidative fragmentation reaction has been achieved by irradiating platydesmine **4** in the presence of lead tetra-acetate and iodine; dictamnine was obtained in 34% yield.[39]



The biomechanism of the platydesmine-dictamnine transformation is being studied, and some progress has been made already.[28] Thus, the [1'-$^3H_2$, 1'-^{14}C] - 4 - methoxy - 3 - prenylquinoline **56** in which both benzylic H atoms were labelled with tritium was fed to *C. ternata* and skimmianine, evoxine and choisyine were isolated; dictamnine is a known precursor of these three alkaloids (Scheme 1). The double-labelled products had ^3H:^{14}C ratios indicating that approximately half the tritium label had been retained. Degradation showed that skimmianine **8** was labelled with ^{14}C specifically at C-3, as predicted. The position of the tritium label has not yet been established, but the validity of the result is supported by a study of the stability of [2,3-$^2H_2$]-dictamnine that showed, for example, that no exchange occurred with dilute acid. The feeding experiments eliminate the possibility that the furan rings of dictamnine and skimmianine are formed from platydesmine via a ketone **57**. The most likely route involves stereospecific oxidation of platydesmine to an alcohol derivative **59** with loss of H_A *trans* to the hydroxyisopropyl group [Scheme 6(b)], but on the other hand it should be noted that vaginidin **61** with a *cis*-arrangement of corresponding substituents is converted into a furocoumarin (see before). Current work is concerned with stereospecific labelling of platydesmine to determine the configuration of the benzylic proton lost during formation of a furan ring, and with an investigation of the biosynthetic roles of alcohol derivatives **59**. As pointed our earlier, a benzylic hydrogen may be lost without formation of a carbon–oxygen bond and the results obtained so far are equally consistent with this possibility.

HEMITERPENES WITH TERMINAL DOUBLE BONDS AND RELATED COMPOUNDS

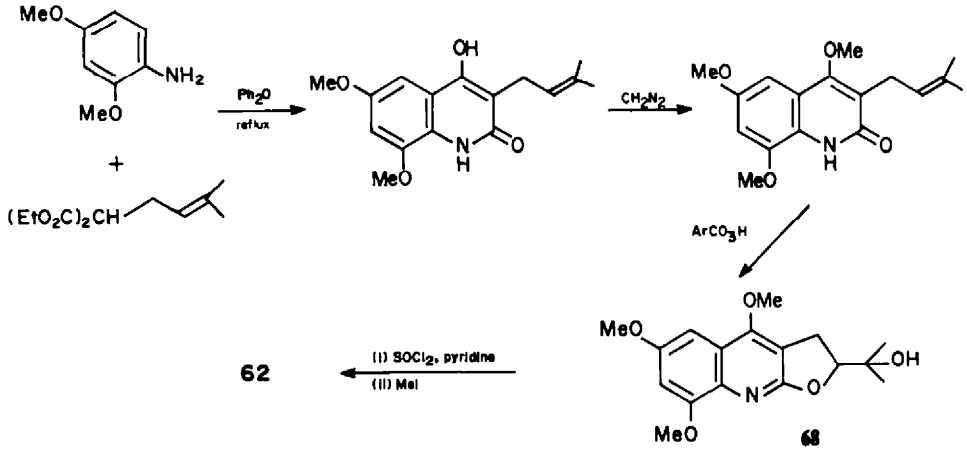
Isopropenyldihydrobenzofurans, for example, rotenone **73**, have been traditionally regarded as dehydration products of hydroxyisopropyldihydrobenzofurans. This may indeed represent a biosynthetic pathway, but no experimental evidence is apparently yet available. Current interest in this topic has been stimulated by the isolation of new groups of aromatic hemiterpenes containing terminal double bonds and of their oxidation and cyclisation products.



Quinoline alkaloids of Ptelea trifoliata. An intensive study of the constituents of *Ptelea trifoliata* led to the isolation of eight quinoline alkaloids with terminal double bonds in the prenyl side-chain.[43,44] Four structural types are represented by O-methylptelefolonium salt **62**, ptelefolone **63**, ptelefoline **64** and ptelofoline methyl ether **65**, other compounds of the group differing in the O-alkyl substituents present in the homocyclic ring. O-Methylptelefolonium salt **62** and ptelefolone **63** are optically-active and the obvious biosynthetic routes involve dehydration of the respective hydroxyisopropyldihydrofuro-derivatives (see **66a**), a process which would not be expected to affect the chiral centres. The isolation of pteleatinium salt[44] **66c** and of balfourodine[45] **25** from *P. trifoliata* provides chemotaxonomic support for this proposal. The four secondary alcohols (see **64**), were obtained as racemates; related compounds, balfourolone **67a** and edulinine **67b** isolated from *Balfourodendron riedelianum*[46] and from *Pelea barbigera*,[47] respectively, were shown to be artefacts of the isolation procedures, apparently derived from quaternary salts (see **66**) by mild base treatment; alkaloids of type **64** may also be artefacts obtained from the corresponding salts (see **62**), but this does not explain the lack of optical activity since base cleavage of O-methyl balfourodinium salt and similar compounds does not affect the chiral centre. The structures of the *Ptelea* alkaloids were determined by spectroscopy; the chemistry of the group was not explored but is now being examined with synthetic compounds.[48] A biomimetic synthesis (Scheme 7) followed the procedure established previously for analogous compounds as far as the furo-derivative **68**. Preliminary results indicate that treatment with thionyl chloride in pyridine followed by reaction with methyl iodide furnishes the quaternary salt **62**.

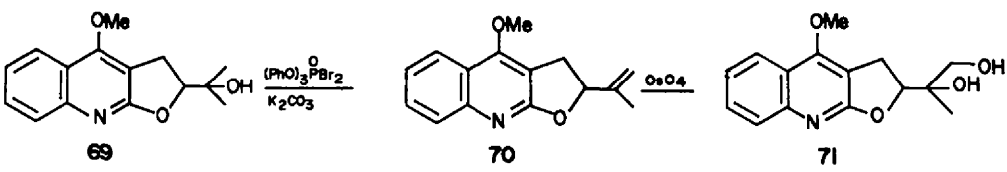
amorphigenol **74**, and can be extended to allylic alcohols, e.g. amorphigenin **72** by postulating allylic oxidation of a terminal olefin (Scheme 8);[50] further hydroxylation could then furnish triols, exemplified by the alkaloid, gravacridontriol **75b**. More than one sequence can be envisaged, however, and experimental evidence is lacking, but the co-occurrence of the rotenoids and the isolation of acridones **75a** and **75b** from the same plant[51] lends general chemotaxonomic support.

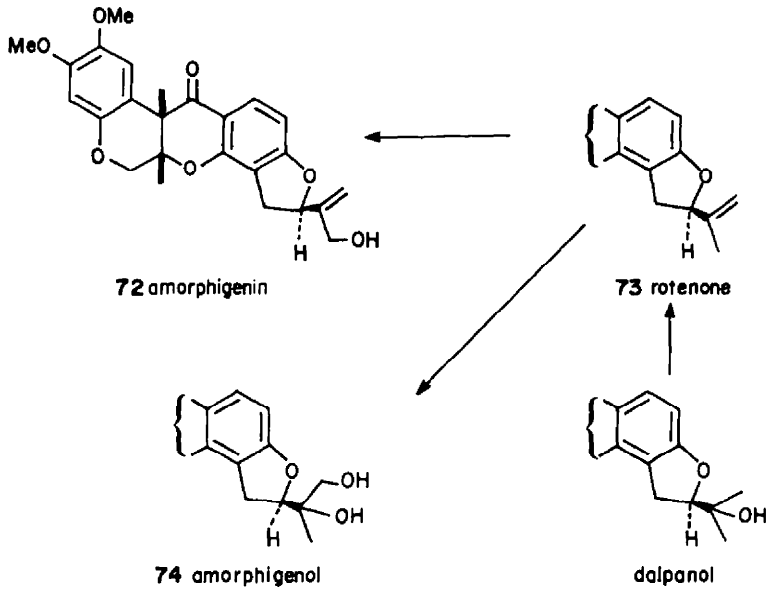
Acetophenone derivatives. A large group of hemiterpenoid acetophenones was isolated from *Helianthella uniflora*, including the terminal olefins **80a** and **81a**.[52] Biosynthetic proposals involved dehydration of a hydroxyisopropyldihydrofuran **77**→**80** or oxidation followed by loss of water **77**→**78**→**81** (Scheme 9). The biosynthesis of the analogous compound dehydrotremetone **81b** in *Eupatorium rugosum* was studied by tracer feeding methods.[53] The specific incorporation of acetate showed that the acetophenone portion of the molecule was of polyketide origin. The furan ring was formed apparently from a prenyl group, since feeding [2-^{14}C]-mevalonate gave radioactive dehydrotremetone shown by degradation to contain over 90% of the activity at C-2. Tremetone **80b** was efficiently incorporated (0.11%) into dehydrotremetone, indicating either that both are formed from a common intermediate or that tremetone is a direct precursor of its dehydro-derivative; the latter process could occur by allylic oxidation followed by dehydration, **80b**→**78**→**81b**. Surprisingly, the expected precursors of tremetone, 4-hydroxyacetophenone and 4 - hydroxy - 3 - prenylacetophenone **76** were not detected in *E. rugosum* and were poorly incorporated (0.04 and 0.004%, respectively). Isopentenylpyrophosphate was a better precursor of dehydrotremetone than dimethylallylpyrophosphate in a cell free



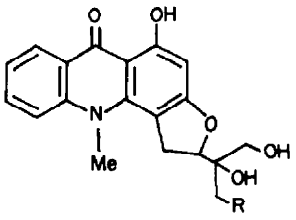
Scheme 7.

Terminal alcohols. Dehydration of platydesmine **69** with triphenylphosphite dibromide furnished the terminal alcohol **70** and thence by hydroxylation the alkaloid, dubinidine **71**.[49] This is a plausible biosynthetic route to diols of the dubinidine type, for example, the rotenoid, homogenate of *E. rugosum*, and from this system a new compound was isolated and proved to be an efficient precursor of dehydrotremetone. The new compound has not been identified but is likely to be the terminal olefin **83** or a related compound. This work, although not





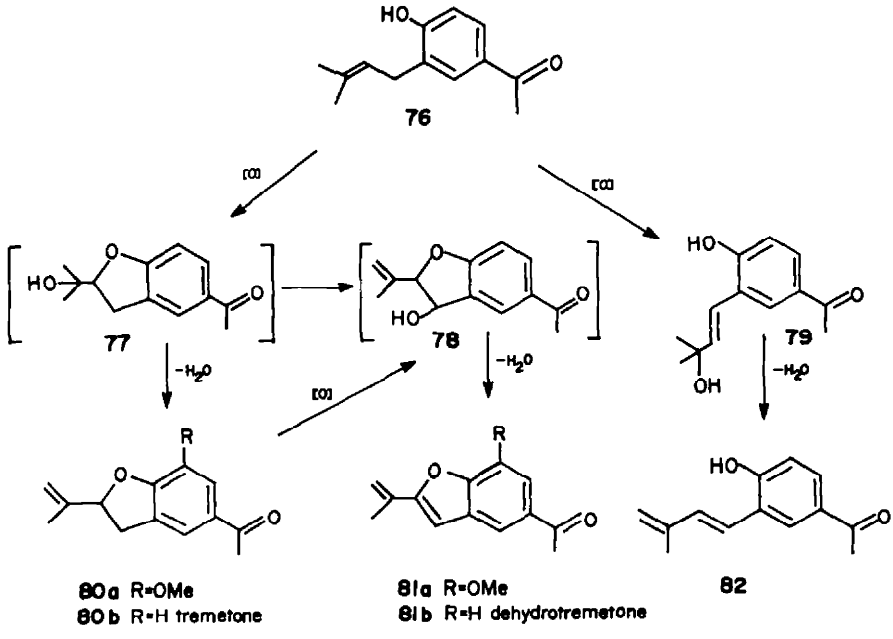
Scheme 8.



75a R=H gravacridondiol
75b R=OH gravacridontriol

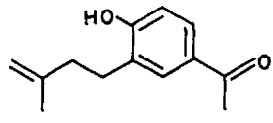
phenone into dehydrotremetone supports the former proposition.

The prenyl derivatives **79** and **82** were also obtained from *H. uniflora*.[52] The ene-ol **79** was regarded as an oxidation product of the 3,3-dimethylallyl compound **76** and indeed compounds of this type are known to be rearrangement products of prenyl epoxides.[54] It was suggested that the butadiene derivative **82** originated by



Scheme 9.

complete, raises the interesting possibility that isopentenylpyrophosphate is a general precursor of aromatic hemiterpenes with terminal double bonds. In compounds derived from a polyketide the prenyl group could be introduced before or after cyclisation to an aromatic ring; the poor incorporation of 4 - hydroxy - aceto-



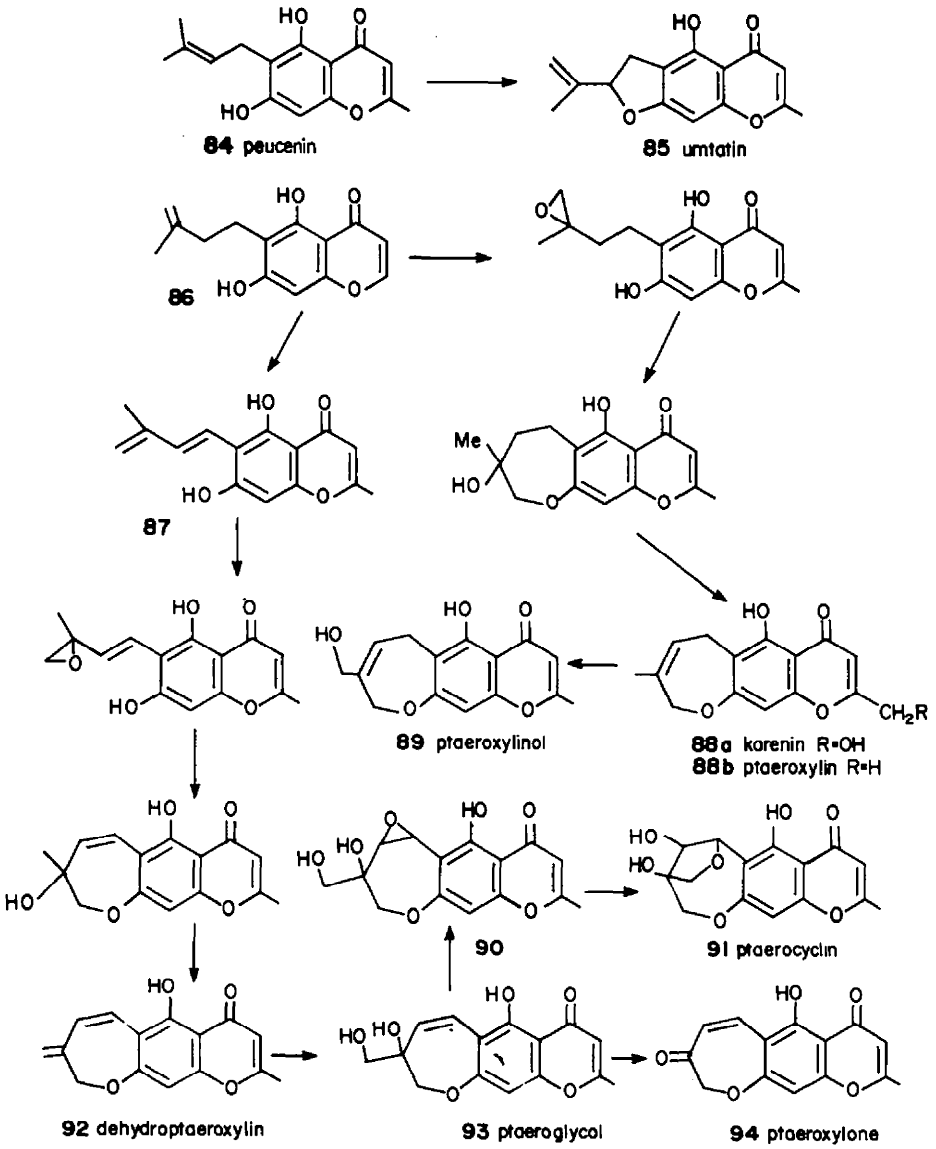
83

dehydration of the ene-ol **79**, but a reasonable alternative pathway involves allylic oxidation of a terminal olefin **83**. Whatever the precise biosynthetic route to these compounds, their identification is consistent with the role of terminal olefins or prenyldienes as biosynthetic intermediates.

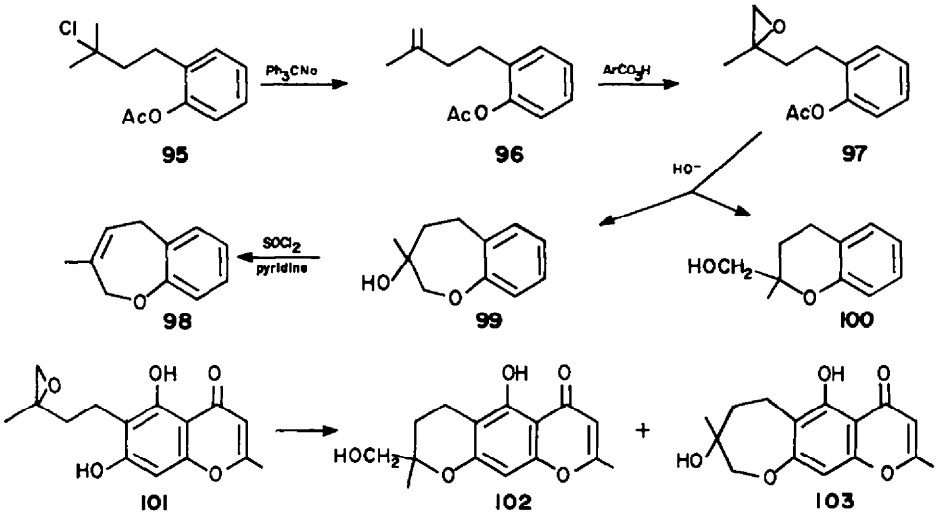
Chromoxepins. An interesting group of chromonoxepins has been isolated from *Ptaeroxylon obliquum*; the compounds were shown to have structures **88a**, **88b**, **89**, **91**, **92**, **93** and **94**, although the structure of ptaerocyclin **91** is not yet secure.[55,56] The presence in the same plant of peucenin **84** and umtatin **85** emphasises the hemiterpenoid nature of the oxepins. A biosynthetic pathway can be formulated from the terminal olefin **86** and the prenyl diene **87** involving formation of oxepin rings by attack of an adjacent hydroxyl group on the less substituted carbon atom of a terminal epoxide (Scheme 10). The tricyclic compound **91** can be accommodated in the Scheme by postulating epoxidation of a prenyl 1,2-double bond **93**→**90**→**91**. Biosynthetic studies on the chromonoxepins have not been reported and present work is confined to exploring relevant *in vitro* reactions (Scheme 11). For example, reaction of the tertiary chloride **95** with sodium triphenylmethyl potassium gave a quantitative yield of the simple isoprenoid terminal olefin **96** which was converted into the corresponding epoxide **97**; reaction with base then resulted in hydrolysis of the acetate function and cyclisation to a mixture of isomeric alcohols **99** and **100** in an approximate ratio of 1:1. Dehydration of **99** then furnished as principal product the 3 - methyl - 2,5 - dihydrooxepin derivative **98**, an analogue of ptaeroxylin **88b**.[57] Application of the reaction to the chromone epoxide **101** gave the pyran derivative **102**,[8] but the isomeric oxepin **103** has been detected in the reaction mixture[57] and may lead to a synthesis of ptaeroxylin and other constituents of *P. obliquum*.

1,1- AND 1,2-DIMETHYLALLYL DERIVATIVES

Aromatic hemiterpenes discussed so far are apparently derived ultimately from 3,3-dimethylallyl derivatives but in recent years an increasing number of plant and fungal



Scheme 10.

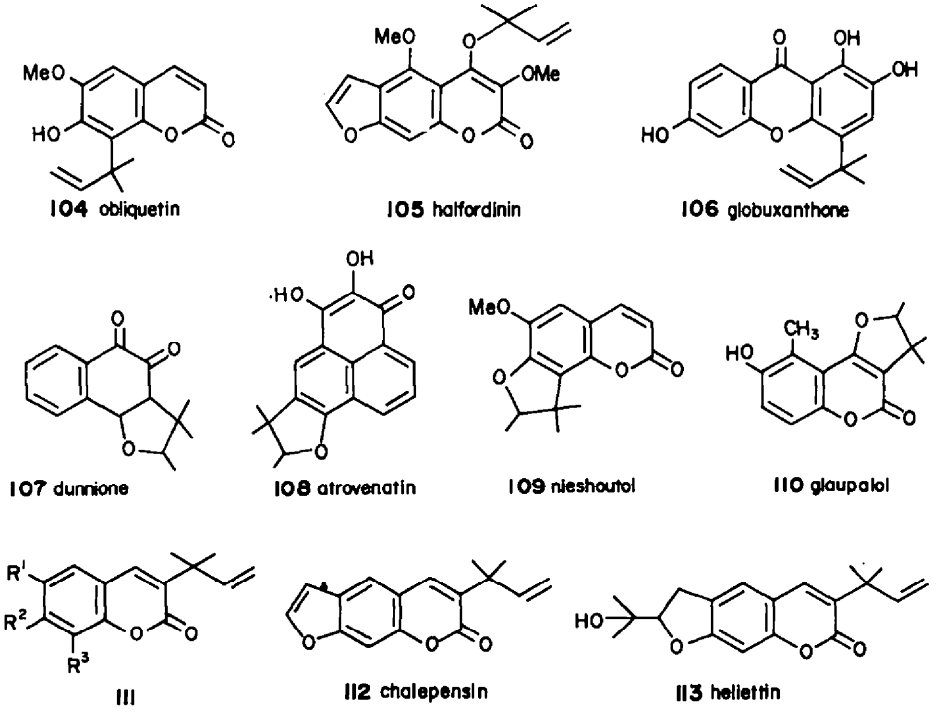


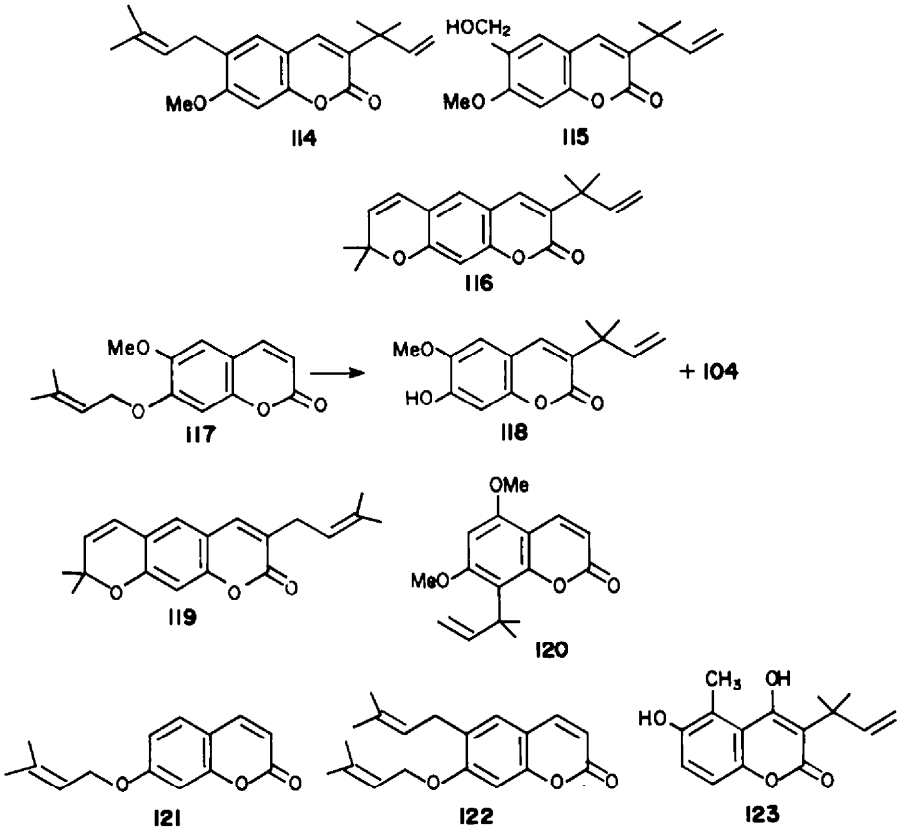
Scheme 11.

products have been isolated containing a C- or O-1,1-dimethylallyl substituent. Examples include the coumarins obliquetin **104**,[55] halfordinin **105**[58] and rutamarin **126**,[59] the xanthone, globuxanthone **106**,[60] and the indole alkaloid, echinulin **145**.[61] The presence of a phenolic hydroxy group adjacent to a 1,1-dimethylallyl function provides the opportunity for cyclisation to a dihydrobenzofuran and compounds of this type are well-known, for instance, dunnione **107**,[62] atrovenatin **108**[63] and ifflaiamine **130**;[64,65] these substances are optically-active and their biosynthesis probably involves enzyme-controlled cyclisation of a 1,1-dimethylallyl group. On the other hand, the coumarins nieshoutol **109**[66] and glaupalol **110**[67] were obtained as racemates, suggesting that the requisite *C*-1,1-dimethylallyl derivatives are the genuine metabolites and that formation of the dihydrofuran rings occurs during isolation.

1,1-Dimethylallyl ethers are derived presumably by reaction of the phenolic oxygen at the tertiary carbon of dimethylallylpyrophosphate. The most obvious biosynthetic route to C-1,1-dimethylallyl compounds is by direct substitution but appropriate rearrangement of an O-3,3-dimethylallyl derivative is a possible alternative and chemotaxonomic and *in vitro* evidence for the proposal has been advanced.[68]

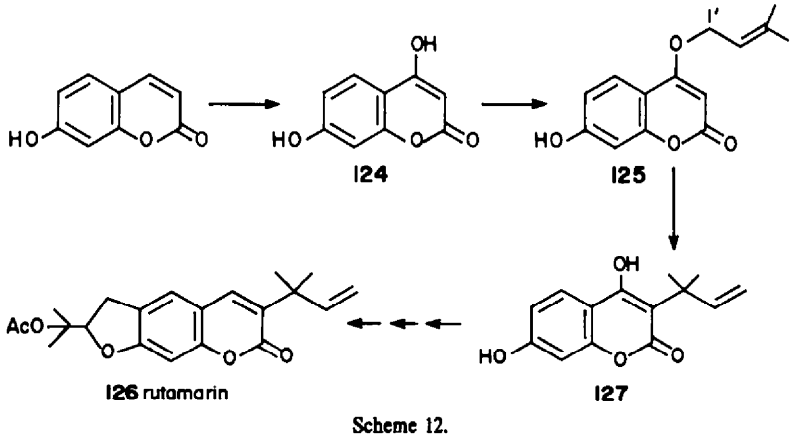
3-(1,1-*Dimethylallyl*) *coumarins*. A large group of 7-oxygenated coumarins substituted at position 3 by a 1,1-dimethylallyl group were isolated, principally from *Ruta* species.[69] *Ruta graveolens* was shown to contain seven compounds of type **111** (R^1, R^2, R^3 = H, OH or OMe), chalepensin **112**, heliettin **113**, rutamarin **126** and the coumarin **114**, while the related compounds, **115** and **116** were obtained from *R. pinnata* and from *Boeninghausenia albiflora*, respectively. At about the same





time that most of these compounds were identified, the pyrolysis of the 3,3-dimethylallyl ether **117** was shown to yield a mixture of the expected products **109** and **104** and the 3-(1,1-dimethylallyl) derivative **118** (14%);[70] the latter apparently is formed by Claisen rearrangement to a 6 - methoxy - 6 - prenyl derivative and then successive Cope rearrangements. It was suggested that the biosynthesis of 3 - (1,1 - dimethylallyl) - coumarins occurs by a similar rearrangement;[68] the co-occurrence in *Ruta* species of the predicted rearrangement products (**111**) and (**120**) of a 7 - (3,3 - dimethylallyloxy) coumarin provided supporting evidence for this proposal. Direct substitution of an allyl group appeared to be less likely for stereoelectronic reasons and in any case the alternative substitution products containing 3,3-dimethylallyl groups at the 3 position had not been observed. Although the latter argument has recently been weakened by the recognition that coumarin **119** is a constituent of *Amyris simplicifolia*,[71] the remarkable number of 3 - (1,1 - dimethylallyl) coumarins present in one species prompted a study of the biosynthesis of these compounds in *R. graveolens* by tracer feeding methods. Rutamarin **126** is the member of the group most readily isolated and experimental work has been confined to this compound. (+) - Marmesin **16** was not incorporated into rutamarin,[33] so it appears that the 1,1-dimethylallyl substituent is introduced before formation of the dihydrofuran ring. 7-Hydroxycoumarin is a precursor of rutamarin (0.37% incorporation) but not 7 - (3,3 - dimethylallyloxy) coumarin **121** or the 6-prenyl derivative **122**.[72] Although negative results should be interpreted with caution, there is certainly no support for a biosynthetic pathway to rutamarin involving an across-ring rearrangement.

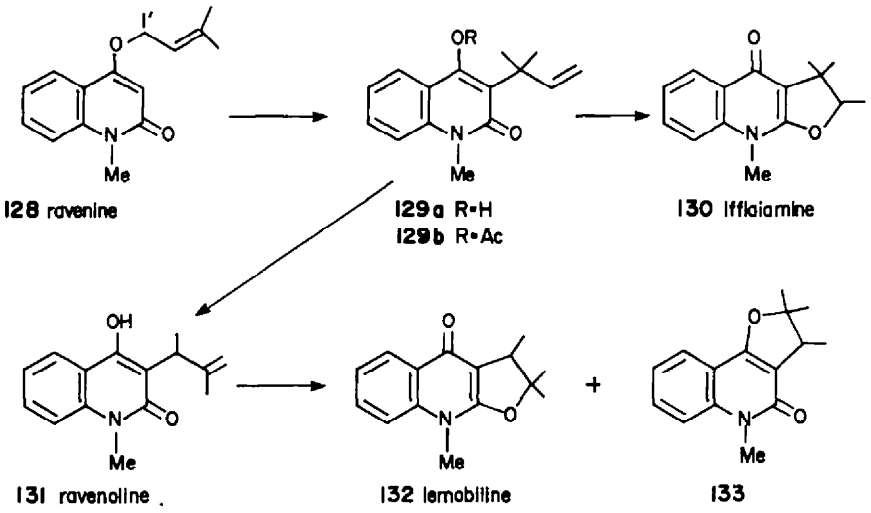
The identification of glaupalol **110** and the probability



Scheme 12.

as expressed earlier that the actual metabolite is the 3(1,1-dimethylallyl) coumarin **123** suggested an alternative biosynthetic route to rutamarin and similar compounds involving formation and Claisen rearrangement of a 4-prenyloxycoumarin (Scheme 12). This proposal is also being tested by tracer feeding experiments with *R. graveolens*.[72] The labelled compounds [3-^{14}C] - 4,7 - dihydroxycoumarin and [1'-$^{3}H_2$] - 4 - (3,3 - dimethylallyoxy) - 7 - hydroxy coumarin were incorporated into rutamarin to the extent of 0.26 and 0.03%, respectively. Degradation of rutamarin from experiments with the prenyloxy precursor indicated that the label was essentially confined to the terminal methylene group. Further work is required to confirm that randomisation of the label in 4,7-dihydroxycoumarin does not occur and that the prenyl group of compound **125** remains intact in its conversion into rutamarin. The preliminary results however clearly support the pathway shown in Scheme 12, although the disappointing level of incorporation may mean that there is more than one biosynthetic route to rutamarin. The loss of the 4-hydroxy group must occur at some later stage, perhaps by reduction of the potential cyclic β-keto-ester **127** followed by the elimination of water.

isolation from a natural source. The presence of "abnormal" Claisen products and their possible precursor in one plant, the presence of "abnormal" and "normal" Claisen products in another, and the formation of all the compounds in the synthetic sequence strongly suggested that these rearrangements featured in the biosynthetic pathways. This possibility was investigated by conducting tracer feeding experiments with *R. spectabilis*.[68] The 4-prenyloxyquinolone, ravenine **138**, specifically labelled at C-1' with ^{14}C was incorporated into ravenoline to the extent of 0.75%. The product was not formed in these experiments by rearrangement of ether **128** during isolation, since inactive ravenoline was recovered after a mixture containing labelled ether **128** had been submitted to the isolation and purification procedure. Thus, ravenine is a precursor of ravenoline in *R. spectabilis* in accord with the biosynthetic pathway **128** → **129a** → **131**. Confirmation of this result for example by establishing the labelling pattern in ravenoline is clearly desirable, but the continuation of the work has been subject to frustrating delay because of the difficulty in obtaining fresh plant material. Ravenoline and ifflaiamine are optically-active and therefore are not artefacts derived from the prenyl ether **128** during isolation. Although it is optically-active,

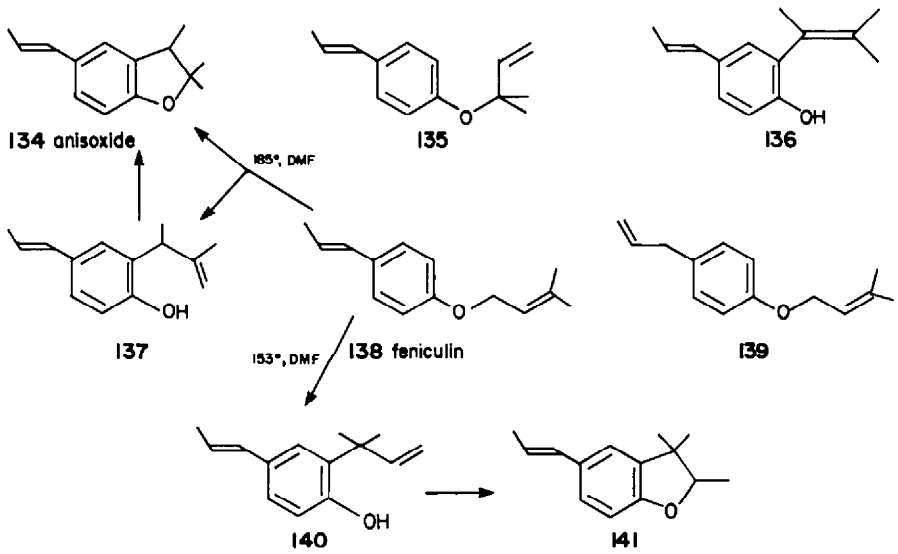


Scheme 13.

Quinoline alkaloids containing 1,2-dimethylallyl groups. An interest in biological rearrangements of quinoline alkaloids arose from a study of *in vitro* synthesis of the 1,1-dimethylallylquinoline derivative, ifflaiamine **130**.[65] The prenylether **128** rearranged readily but the "normal" Claisen product **129a** was not obtained; the products of the reaction **131**, **132** and **133** were 1,2-dimethylallyl derivatives formed aparently by "abnormal" rearrangement of olefin **129a** to quinolone **131** which then underwent cyclisation to dihydrofurans through participation of the 2- and 4-oxygen substituents (Scheme 13). The normal Claisen product was trapped as its acetate **129b** which through standard procedures was converted into ifflaiamine **130**. An enantiomer of the 3-(1,2-dimethylallyl)-quinolone **131** (ravenoline) was shown subsequently to co-occur with ifflaiamine in *Flindersia ifflaiana*[65,68] and to be a constituent of *Ravenia spectabilis*.[73] The 4-prenyloxyquinolone (**128**) (ravenine)[73] and the dihydrofuran (**132**) (lemobiline)[74] were also obtained from *R. spectabilis*. Remarkably, the three *Ravenia* alkaloids were synthesised before their lemobiline could be formed from ravenoline as a result of acid treatment of the plant extract, since cyclisation does not affect the chiral centre; the fact that this reaction *in vitro* requires an elevated temperature suggests, however, that lemobiline is produced in the two rutaceous plants by enzymatically-controlled cyclisation of ravenoline. If the results obtained with *R. spectabilis* are applicable to the alkaloids of *F. ifflaiana* then lemobiline (**132**) and ifflaiamine (**130**) that co-occur in the latter species apparently are derived from a common precursor **129a** (Scheme 13); hence the biosynthesis of the 1,1-dimethylallyl derivative, ifflaiamine, as well as that of the coumarin, rutamarin **126**, probably proceeds by rearrangement of a 3,3-dimethylallyl ether.

Anisoxide. Anisoxide **134** was isolated from star anise oil in 1937 and its structure was elucidated by degradation and synthesis in 1958[28b]; it is a well-known example of an aromatic hemiterpene containing the elements of a 1,2-dimethylallyl group and thereby analogous to ravenoline and lemobiline. As a result of an interest in such compounds, we intended to study the

biosynthesis of anisoxide. Anisoxide was reported to be optically-inactive in spite of the presence of a chiral centre and it was suggested that during work-up racemisation might have been effected or that cyclisation of an olefinic precursor **135** or **136** might have occurred. In the light of recent work on the abnormal Claisen rearrangement, the 1,2-dimethylallyl derivative **137** is a more plausible precursor of anisoxide. It was necessary to clarify the origin of anisoxide before embarking on a biosynthetic study.



Scheme 14.

The major component, anethole, was removed from commercial anise oil, obtained from the seeds of *Illicium verum*, and the other constituents were analysed by glc. The 3,3-dimethylallyl ether, feniculin **138**, and the hitherto unknown isomer **139** were identified, but anisoxide was not present.[75] In fact, anisoxide does not appear to be a constituent of *I. verum* or of another species *Foeniculum vulgare*, reported to contain the compound, since it was not detected in the oils obtained from the seeds of these plants.

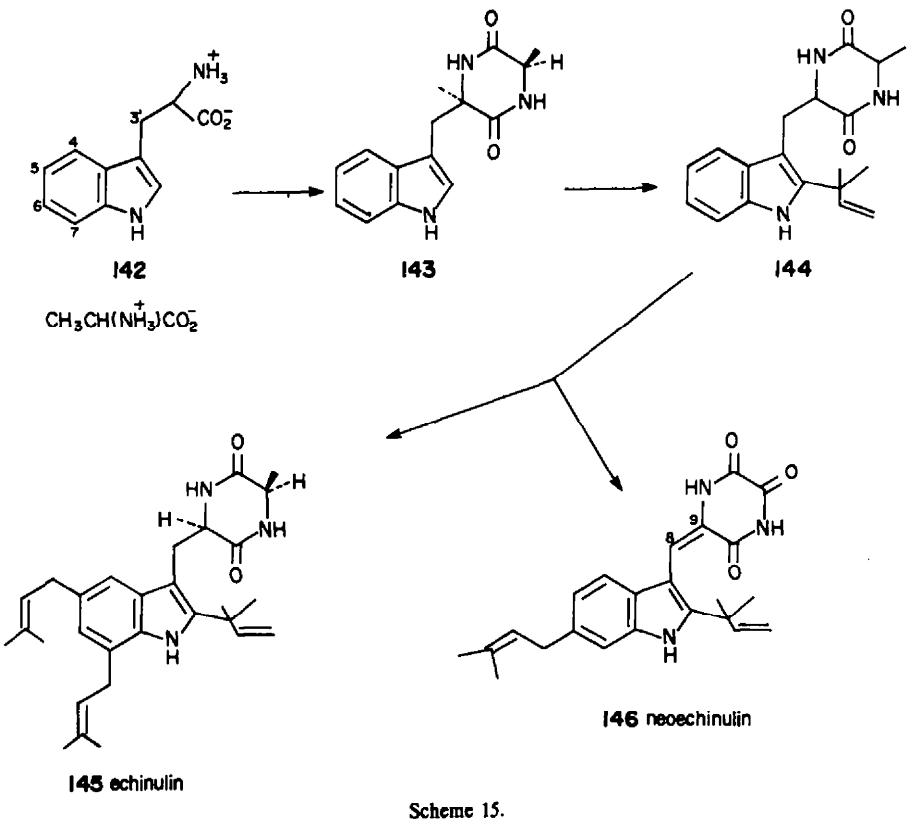
The rearrangement of the anise oil constituent, feniculin **138**, was then studied[75] (Scheme 14). The ether in dimethylformamide at 185° furnished a mixture of anisoxide **134** and the product of abnormal Claisen rearrangement, the olefin **137**; the latter compound was readily converted into anisoxide by treatment with hydrogen bromide in acetic acid. Rearrangement of the ether **138**, at a lower temperature gave as principal product the 1,1-dimethylallyl derivative **140** which was cyclised with acid to the dihydrofuran **141**. After star anise oil enriched with feniculin **138** had been heated at 180°, anisoxide was obtained, and it was concluded that the original isolation of the substance was due to the prolonged distillation procedure employed, resulting in rearrangement of feniculin present in the oil; plans to investigate the biosynthesis of anisoxide therefore were abandoned.

Indole alkaloids with 1,1-dimethylallyl groups. A 1,1-dimethylallyl substituent is also a feature of the structures of a rapidly expanding group of indole alkaloids obtained from fungi; examples are echinulin **145** and neoechinulin **146** from *Aspergillus amstelodami* austamide **147** from *A. austus* and lanosulin **148** from *Penicillium lanosum*. These compounds, which were reviewed briefly in a recent *Tetrahedron Report*,[3] are essentially cyclic dipeptides involving tryptophan and alanine or proline and incorporating prenyl groups in the indole portion of the molecules. This discussion will be centred on the biosynthetic origin of the prenyl substituents.

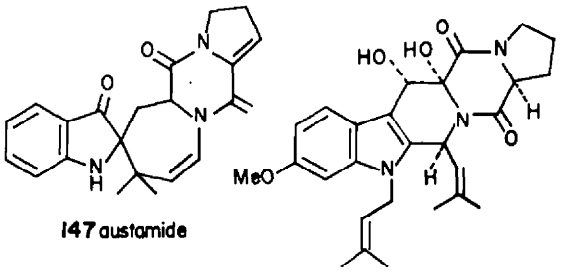
Echinulin **145** has received most attention and by tracer feeding experiments tryptophan, alanine and the diketopiperazine **143** were shown to be good specific precursors.[76] Hence, the prenyl groups are introduced later in the biosynthetic pathway. The same conclusion applies to brevianamide A **165**, since the corresponding diketopiperazine **156** derived from proline is not only a constituent of *Penicillium brevicompactum*[77] but was shown by double-labelling experiments to be incorporated intact into the alkaloid.[78] *Cyclo* - L - alanyl - L - tryptophan **143** is also introduced as a unit into neoechinulins **146**.[79] A structural feature of the neo- and cryto-echinulins is the presence of a dehydrotrytophan unit; the homocyclic rings are either unsubstituted or contain a prenyl group at the 6-position and it was suggested that the site of prenylation (which contrasts with the 5,7-substitution pattern in echinulin **145**) may be controlled by the unsaturation at C-8, C-9.

The mode of introduction of the homocyclic prenyl groups into echinulin and neoechinulin was studied by feeding [5,7-$^3H_2$; 3^1-^{14}C]-tryptophan **142** to *A. amstelodamii*;[80] tritium was lost in the formation of the 5,7-diprenyl derivative **145** and retained in the 6-prenylindole **146**. In complementary fashion, addition of [4,6-$^3H_2$; 3^1-^{14}C]-tryptophan to the culture medium resulted in isolation of echinulin with essentially 100% retention of the ^{3}H-label and neoechinulin with approximately 50% loss of tritium. It appears therefore that hydroxylation of the indole nucleus is not a prerequisite for allylation and that introduction of the prenyl groups occurs by removal of hydrogen at positions undergoing allylation.

Information about the sequence of allylation in the biosynthesis of echinulin has been obtained by working with a partially purified enzyme isolated from *A. amstelodamii*.[81] The enzyme catalysed the reaction of diketopiperazine **143** with dimethylallylpyrophosphate to

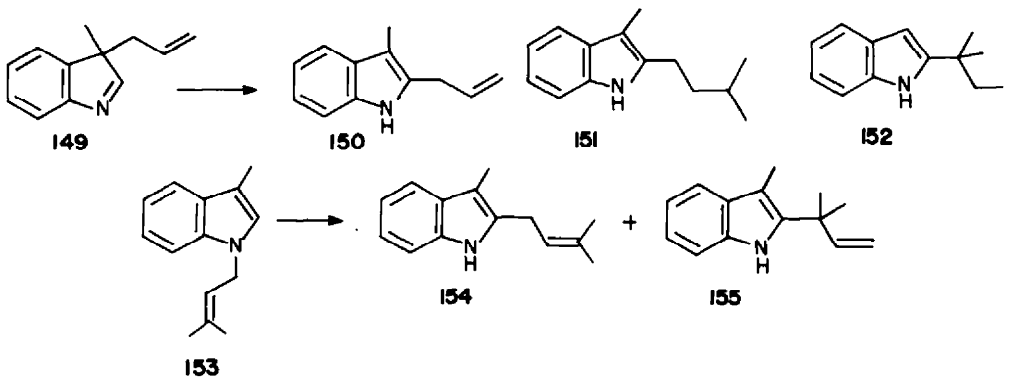


Scheme 15.



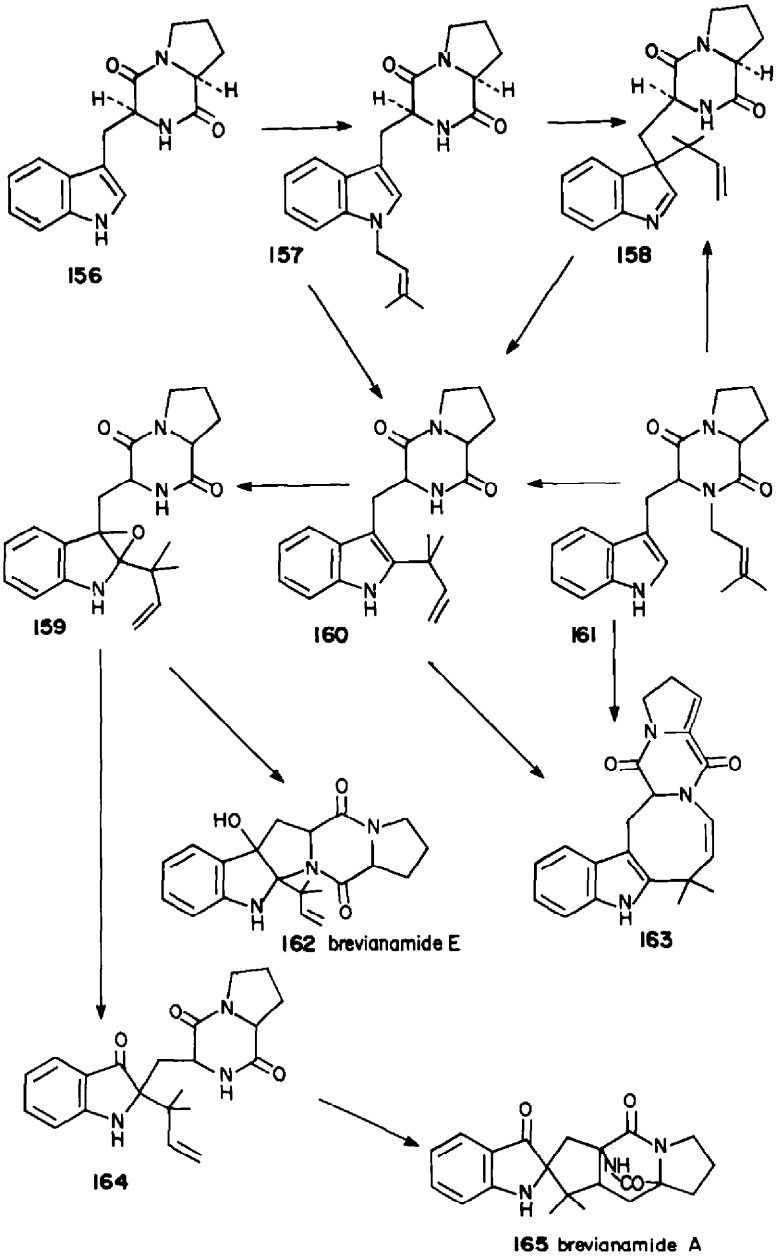
give a monoprenylated derivative. The latter was not characterised fully but comparison with a synthetic sample indicated that the 2-(1,1-dimethylallyl) indole structure **144** was the most likely for the product. In any case, the metabolite was shown to be a specific precursor of echinulin. The probability that 1,1-dimethylallyl derivatives **144** and **160** are intermediates in the biosynthesis of echinulin and related compounds (Schemes 15 and 16) was further supported by the isolation of the proline derivative **160** from *A. ustus*[82] and from *P. italicum*.[86] Feeding experiments with labelled prenyl compound **144** of established constitution and with **160** have not yet been reported.

The means whereby a reversed prenyl group is introduced at the 2-position of the indole group perhaps is the most interesting feature of the biosynthesis of echinulin, the brevianamides, austamide and related compounds. The suggestion that the 1,1-dimethylallyl group originates by rearrangement of a 3 - (3,3 - dimethylallyl) indolenine was supported by *in vitro* experiments.[83] Thus, the 3-allyl derivative **149** readily rearranged under acid conditions into 2 - allyl - 3 - methylindole **150**; reaction of 3-methylindole with 3,3 - dimethylallyl - bromide and catalytic hydrogenation of the products furnished a mixture of indoles **151** and **152**, apparently via the corresponding 2-prenylindoles. Rear-



rangement of a 3 - (1,1 - dimethylallyl) - indolenine (see **158**), is another biosynthetic possibility. An alternative route involves rearrangement of a 3,3-dimethylallyl group attached to the indolic nitrogen (see **157**) or to the side-chain nitrogen atom of tryptophan incorporated into a diketopiperazine ring system (see **161**); either possibility is apparent from the structure of lanosulin (fumitremorgin B) **148**.[84] The co-occurrence of the oxindole, austamide **147**, the related indole **163** and the 2 - (1,1 - dimethylallyl) indole **160**[82] is in accord with a pathway involving transfer of a prenyl group from diketopiperazine nitrogen (see **161**), but formation of a 7- or 8-membered ring by cyclisation of a 1,1-dimethylallyl derivative (see **160**) clearly is not excluded; the former process which may occur through transfer initially to the 3-position, (see **158**) perhaps is more attractive mechanically, and has been discussed.[79] Rearrangement of 1-allylindoles has been explored with model compounds. Although 1 - allyl - 3 - methylindole was reported to resist rearrangement under thermal or acidic conditions,[83] trifluoroacetic acid and Lewis acids were later found to be effective, the 1-prenylindole **153**, for example, giving a mixture of compounds **154** and **155**,[85] and 1 - (3 - methylallyl) - indole furnishing 3 - (1 - methylallyl) indole. The charge induced rearrangement of **153** into **155** is believed to occur via a 3-substituted derivative (see **158**).[87,88]

The 2 - (1,1 - dimethylallyl) indole **160** may be a direct precursor of brevianamide E **162**, a plausible route involving attack of a diketopiperazine N atom on an indole epoxide **159**. Rearrangement of indole epoxides of this type could lead to indoxyl derivatives such as austamide **147** and brevianamide A **165**. The latter alkaloid can also be regarded as a derivative of 2 - (1,1 - dimethylallyl) indole and its biosynthesis, **164** → **165**, may involve 1,4-addition of the olefinic bond to an appropriate con-



Scheme 16.

jugated system present in the diketopiperazine portion of the molecule.

The various biosynthetic proposals discussed above are summarised in Scheme 16. Further progress in elucidating the later stages in the biosynthesis of this group of indole alkaloids is unlikely to be made until the role of 2-(1,1-dimethylallyl) indoles is fully explored and until 1- and 3-prenylindoles and N-prenyldiketopiperazines are tested as biosynthetic precursors.

CONCLUSIONS

During the last 7 years, a great deal of progress has been made in elucidating biosynthetic pathways to aromatic hemiterpenes, but much remains to be done, including especially the determination of routes to pyrano-derivatives, to hemiterpenes containing terminal double bonds and other structural variants arising from oxidative reactions and to 1,1-dimethylallyl compounds. In the latter connection, a start has been made in exploring the biological role of rearrangement reactions of O- and N-prenyl derivatives, but the generality of this type of process has yet to be established. In any case, the biosynthesis of many more aromatic hemiterpenes must be studied before we can conclude that results obtained for one metabolite are applicable to other compounds with the same structural feature.

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