Tetrahedron, 1958, Vol. 4, pp. 256–270. Pergamon Press Ltd., London

A STUDY OF THE ORIGIN AND MODIFICATIONS OF THE C_5 UNIT IN PLANT PRODUCTS—NEW SYNTHESIS OF ANGELICIN AND PSORALEN

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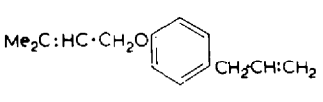
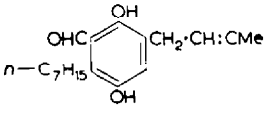
Abstract—A large number of natural essentially non-terpenoid compounds contain isoprene units. The C_5 units may have their origin based on senecioic acid, or mevalonic acid, but the fundamental stage seems to be an α-hydroxy-γ,γ-dimethylallyl system, which can undergo a number of modifications giving rise to types of compounds listed below under (A) to (F) in increasing order of complexity. The simpler furan derivatives are also now considered to be derived from C_5 units by the loss of three carbon atoms by oxidation. This is based not only on co-occurrence of types but also on the experimental feasibility of converting the dimethylallyl (C_5) and allyl groups into furans. In this connection, syntheses of angelicin and psoralen are described. Further the furan rings of furanoquinolines should be considered to have a similar origin.

AMONG natural products, a number of compounds are essentially non-terpenoid but have isoprene units present in them. Such compounds belong to diverse molecular types. The majority are components of higher plants, a few, however, are mould metabolic products. Their wide distribution has been noticed earlier.[1,2] Most of them are derivatives of benzopyrones though there are a number of examples which are derivatives of benzene, naphthalene and also of quinoline (see Tables 1 and 2).

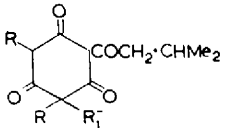
TABLE 1



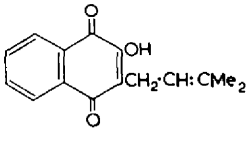
Foeniculin[51]



Flavoglaucin[52]



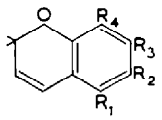
Lupulone[53], R=R_1
Humulone[53], R_1=OH
R=CH_2—CH:CMe_2



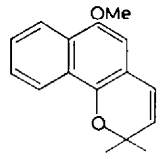
Lapachol[54]

[1] See T. A. Geissman and E. Hinreiner, *Bot. Rev.* **18**, 77–244 (1952).
[2] See R. Robinson, *The Structural Relations of Natural Products*. Clarendon Press, Oxford, (1955).
[51] See T. A. Geissman and E. Hinreiner, *Bot. Rev.* **18**, 82 (1952).
[52] A. Quilico and C. Cardani, *Gazz. Chim. Ital.* **83**, 1088 (1953).
[53] See T. J. Halsall, *Ann.* Reports. **49**, 190 (1952).
[54] S. C. Hooker, *J. Chem. Soc.* 1356 (1896); *J. Amer. Chem. Soc.* **58**, 1181 (1936).

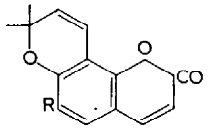
TABLE 2



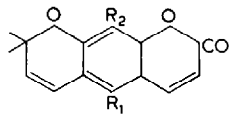
Evodione[55]; R_1=R_2=R_4=OMe, R_3=Acetyl
*allo*Evodione[57]; R_1=R_2=R_3=OMe, R_4=Acetyl
Evodionol[56]; R_1=OMe,R_2=Acetyl, R_3=OH, R_4=H.
*allo*Evodionol[57]; R_1=OMe, R_2=H, R_3=OH, R_4=Acetyl.
*allo*Evodionol methyl ether[56]; R_1=R_3=OMe, R_2=H, R_4=Acetyl



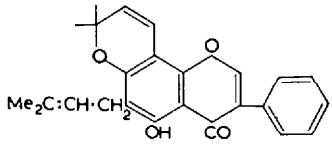
Lapachenol[58]



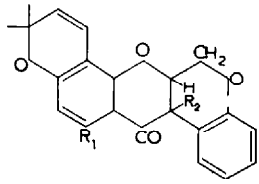
Seselin[59] (L); R=H
Braylin[20] (LI); R=OMe.



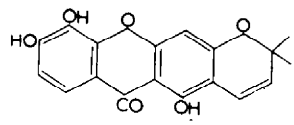
Xantylethin[60] (LII); R_1=R_2=H
Xanthoxyletin[61] (LIII); R_1=OMe, R_2=H
Luvangetin[62] (LIV); R_1=H, R_2=OMe



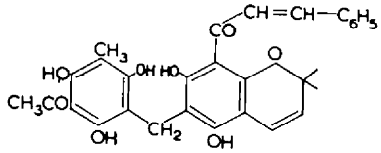
Osajin[63]; R=H
Pomiferin[63]; R=OH



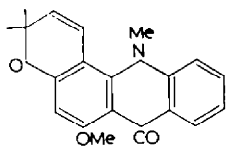
Deguelin[64] (LV); R_1=R_2=H
Toxicarol[64]; R_1=OH, R_2=H
Tephrosin[64]; R_1=R_2=OH.



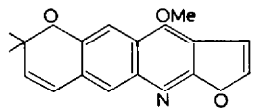
Jacareubin[65]



Rottlerin[68]



Acronycin[66]



Medicosmine[67]

[55] S. E. Wright, *J. Chem. Soc.* 2005 (1948).
[56] L. H. Briggs and R. H. Locker, *J. Chem. Soc.* 2376 (1950).
[57] K. D. Kirby and M. D. Sutherland, *Aust. J. Chem.* **9**, 411 (1956).
[58] R. Livingstone and M. C. Whiting, *J. Chem. Soc.* 3631, (1955).
[59] P. K. Bose, N. C. Guha, J. Matzke and E. Späth, *Ber. Dtsch. Chem. Ges.* **72**, 821 (1939).
[60] J. C. Bell and A. Robertson, *J. Chem. Soc.* 1828 (1936); J. C. Bell, A. Robertson and T. S. Subramaniam, *J. Chem. Soc.* 286 (1937).
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[64] See H. Haller, L. D. Goodhue and H. A. Jones, *Chem. Rev.* **30**, 33 (1942).
[65] F. E. King, T. J. King and L. C. Manning, *J. Chem. Soc.* 563 (1957).
[66] L. J. Drummond and F. N. Lahey, *Aust. J. Sci. Res.* **A2**, 630 (1949).
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[68] A. McGookin, A. B. Percival and A. Robertson, *J. Chem. Soc.* 309 (1938); H. H. Brockmann and K. Maier, *Ann.* 535, 149 (1938); T. Backhouse, A. MacGookin, J. Machet, A. Robertson and E. Tittensor, *J. Chem. Soc.* 113 (1948).

More than one C_5 unit is often present in a molecule. It may be linked to an oxygen atom forming an ether or to a nuclear carbon atom of the main skeleton. The unit has been encountered in several modifications differing in state of oxidation and also involved in ring formation by combination with an adjacent hydroxyl. Representative examples are given in the tables and also in the sequel, wherein a discussion of the evolution of various types is presented. Multiples of the C_5 unit, such as the geranyl group (C_{10}) and the farnesyl group (C_{15}), are also found. There seems to be adequate justification to consider that these C_5 units are introduced into the benzopyrone or other types at more or less the last stage. This is supported by the positions they occupy and the fact that frequently the unsubstituted nuclei occur along with the C_5-substituted compounds. In this respect there is considerable analogy with methylation including nuclear methylation.[3]

Origin

Various views have been expressed in the past regarding the origin of the C_5 unit, either present in larger terpene molecules or attached to aromatic nuclei. Geissman and Hinreiner[4] have adopted the earlier ideas that the C_5 is the result of condensation of C_2 and C_3. Recently, Robinson[5] has suggested senecioic acid (β,β-dimethylacrylic acid) (I) as the terpene precursor. Support for this scheme is provided by the experiments on the stimulation of rubber formation with senecioic acid in the guayule plant,[6] and *en bloc* incorporation of it into cholesterol[7] in rats, and pulegone[8] in *Mentha*. Robinson[5] considered the carboxyl of senecioic acid as the spearhead attacking aromatic nuclei.

More recent work has emphasised the importance of mevalonic acid (β-hydroxy-β-methyl-δ-valerolactone)[9] (II) as a very likely intermediate in the biosynthesis of C_5 units in steroids,[10,11,12] carotenoids[13] and other terpenoid compounds.[14,15] The formation of C_5 isoprenoid units from this C_6 acid involves loss of a carbon atom by decarboxylation.[10] The dihydroxy acid from (II) may be considered to undergo initial oxidation of the primary alcoholic group to aldehyde and dehydration to produce a double bond, giving rise to (III).[15] Reaction of the aldehyde spearhead of (III) with an activated nuclear position of a phenolic compound (e.g. phloroglucinol) and decarboxylation would lead to the formation of (IV) which could be regarded as the primary stage, and from it various modified forms could be derived. An aldehyde grouping has been found to be an active spearhead, and further, recently aldehydes derived from the C_5 unit have been found to occur in nature.[16] It may be mentioned that in the study of nuclear methylation[3] in plant products, formaldehyde or its equivalent has been considered to be an active reagent.

[3] A. C. Jain and T. R. Seshadri, *Quart. Rev.* **10,** 169 (1956).
[4] T. A. Geissman and E. Hinreiner, *Bot. Rev.* **18,** 229 (1952).
[5] R. Robinson, *The Structural Relations of Natural Products* p. 14. Clarendon Press, Oxford (1955).
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[7] K. Bloch, L. C. Clarke and I. Harry, *J. Amer. Chem. Soc.* **76,** 3859 (1954).
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[10] P. A. Tavormina, M. H. Gibbs and J. H. Huff, *J. Amer. Chem. Soc.* **78,** 4498 (1956).
[11] F. Dituri, S. Gurin and J. L. Rabinowitz, *J. Amer. Chem. Soc.* **79,** 2650 (1957).
[12] O. Isler, R. Ruegg, J. Wursch, K. F. Gey and A. Pletscher, *Helv. Chim. Acta* **40,** 2369 (1957).
[13] G. D. Braithwaite and T. W. Goodwin, *Biochem. J.* **67,** 13P (1957).
[14] J. W. Cornforth, R. M. Cornforth, G. Popjak and I. Youhotsky-Gore, *Biochem. J.* **66,** 10P (1957).
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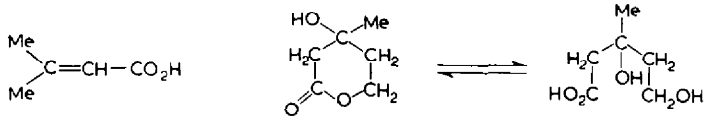
[16] G. W. K. Cavill, D. L. Ford, H. Hinterberger and D. H. Solomon, *Chem. & Ind.* 292 (1958).



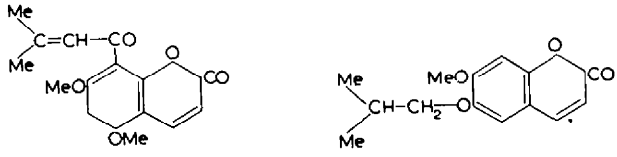
I II

III IV

Other methods of deriving (IV) are possible, e.g. the senecioic acid hypothesis[5] will yield a ketone which could be considered to suffer selective reduction, but the aldehyde-acid (III) appears more convenient, particularly for building up multiple C_5 units. As a characteristic feature of (IV) may be mentioned its great capacity to undergo a number of changes. These points will be explained in the discussion of the typical examples given below.

Types

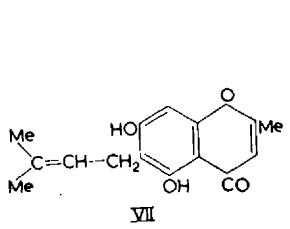
(A) *β,β-Dimethylacryl derivatives.* Probably the simplest modification of (IV) is represented by the β,β-dimethylacryl derivatives of coumarins, one example being glabra lactone[17] (V). Its formation requires a single step of oxidation of the secondary alcohol (IV) to the ketone(V). Closely related to this are the dihydro-compounds in which the *exo*cyclic double bond has undergone reduction, e.g. geigerin[18] (VI).



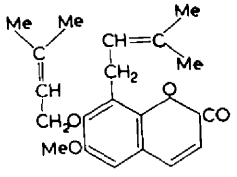
V VI

(B) *γγ-Dimethylallyl group and its modifications.* In this type, the intermediate (IV) has undergone reduction, the —CHOH being converted into $—CH_2$, which seems to be fairly common and has been suggested as a biosynthetic step.[15] Peucenin[19] (VII) and brayleyanin[20] (VIII) are among the many known examples of this type. The double bond in the dimethylallyl group frequently gets oxidised forming either an epoxide as in auropten[21] (IX, R=CH_3), or a glycol, as in toddalolactone[22] (X, R=Me). These transformations have established laboratory analogies. It is interesting to record the simultaneous occurrence of both the oxidised (glabra lactone; V) and reduced (osthol; XI) forms of the precursor (IV) in *Angelica glabra* Makino.[17] Further, the dimethylallyl, the epoxide and the glycol types occur together linked to oxygen atoms of identical furanocoumarin structures (see Table IV).

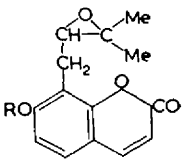
[17] K. Hata and A. Nita, *J. Pharm. Soc. Japan.* **77**, 941 (1957)
[18] F. N. Lahey and D. J. Wluka, *Aust. J. Chem.* **8**, 125 (1955).
[19] E. Späth and K. Eiter, *Ber. Dtsch. Chem. Ges.* **74**, 1851 (1941).
[20] F. A. L. Anet, G. K. Hughes and E. Ritchie, *Aust. J. Sci. Res.* A **2**, 608 (1949).
[21] H. Bohme and E. Schneider, *Ber. Dtsch. Chem. Ges.* **72**, 780 (1939).
[22] E. Späth, B. B. Dey and E. Tyray, *Ber. Dtsch. Chem. Ges.* **72**, 53 (1939).



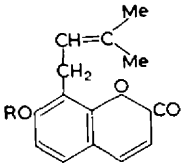
VII



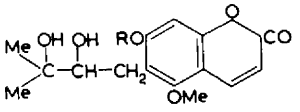
VIII



IX

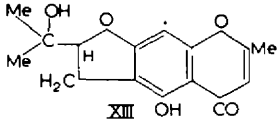


XI; R = OMe
XII; R = H

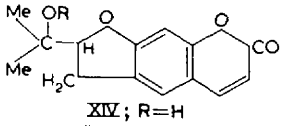


X

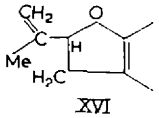
(C) *α-(β'-hydroxypyropyl)-dihydrofurans and α-isopropenyl-dihydrofurans.* Cyclisation of the epoxide (type IX, R=H) or the glycol (type X, R=H) with an adjacent phenolic hydroxyl can give rise to the dihydrofuran structure found in visamminol[23] (XIII) and marmesin[24] (XIV). Nodakenin[25] is a glucoside of the structure (XV) and on hydrolysis gives nodakenetin, a stereoisomer of (XIV). Loss of water leads to the modified structure, *iso*propenyl dihydrofuran (XVI), which is characteristic of rotenone[26] (XVII). These changes can be effected in the laboratory, e.g. 7-demethyl suberosin (XVIII) undergoes epoxidation and cyclisation to yield ± (XIV)[27]. The final dehydration, however, yields an isomeric *iso*propylfuran (XX) owing to the instability of the *iso*propenyl compounds in the presence of acids (compare isomerisation of rotenone into *iso*rotenone[28]).



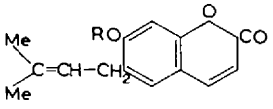
XIII



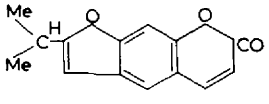
XIV; R=H
XV; R=Gl



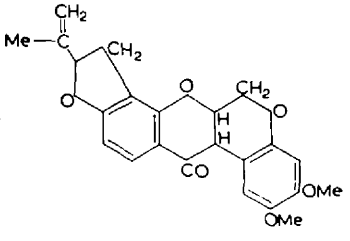
XVI



XVIII; R = H
XIX; R = Me



XX



XVII

[23] W. Bencze, J. Eisenbeiss and H. Schmid, *Helv. Chem. Acta* **39**, 923 (1956).
[24] A. Chatterjee and S. S. Mitra, *J. Amer. Chem. Soc.* **71**, 606 (1949).
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[26] F. B. LaForge, H. L. Haller and L. E. Smith, *Chem. Rev.* **12**, 181 (1933).
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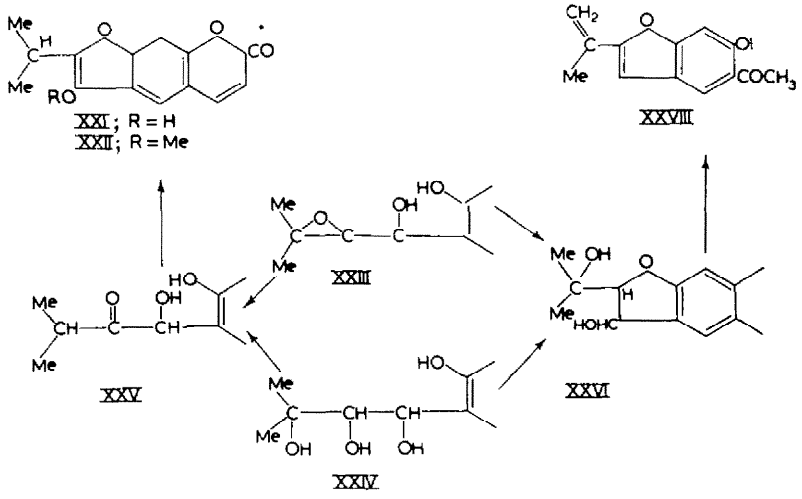
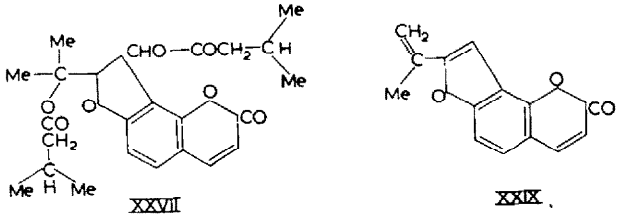
(D) α-iso*propyl-β-hydroxy-furans and relations.* As similar to type (C) but derived directly from the common precursor (IV) may be mentioned oreoselone[29] (XXI) and its methyl ether, peucedanin (XXII).[29] For their formation, it is suggested that (IV) is oxidised to the epoxide (XXIII) or the triol (XXIV). Rearrangement of the epoxide or dehydration of the triol yields a ketone (XXV) which is capable of cyclisation to (XXI). On the other hand, the epoxide (XXIII) or the triol (XXIV) can cyclise to form the dihydroxy-dihydrofuran derivative (XXVI) which is found in athamantin[30,31] (XXVII) as the di-ester of *iso*valeric acid. The dihydroxy structure (XXVI) can dehydrate to yield the type represented by euparin[32] (XXVIII). When athamantin is subjected to acid hydrolysis, it undergoes dehydration also to form oroselone[30,31,33] (XXIX).



(E) 3-*Hydroxy*-iso*pentanyl derivatives.* This type involves a reduced form of an isomer (XXX), which is produced by the oxotropic rearrangement of the precursor (IV). Such an oxotropic change of 1-phenylallyl alcohols into cinnamyl alcohols[37] is well known. The simplest example is found in the flavonol glycoside icariin[34,35] (XXXI) which on hydrolysis yields the aglycone icaritin (XXXII). The ten-carbon fragment in the coumarin marmin[36] (XXXIII) is also based on the same pattern.



[29] E. Späth, K. Klager and C. Schlösser, *Ber. Dtsch. Chem. Ges.* **64**, 2203 (1931).
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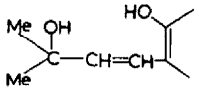
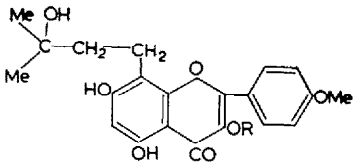
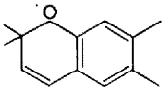
(F) 2:2-*Dimethyl chromenes* (XXXIV) are very common and widely distributed. Many examples are available in different groups including benzene, naphthalene and benzopyrone derivatives (see Table 2). We consider that the oxotropic rearrangement of (IV), mentioned under (E), followed by ring closure with elimination of water, gives rise to 2:2-dimethyl chromenes. There seems to be no strict laboratory analogy for the ring closure but the structure of the tertiary alcohol (XXX) which is also allylic would be conducive to formation of the chromene ring.



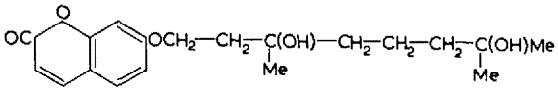
XXX



XXXI; R=Rhamno - glucose
XXXII; R=H



XXXIV



XXXIII

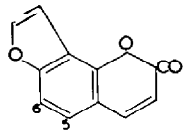
(G) *Simple furans:* In the types (A) to (F) above, the structural relations are fairly obvious, since all of them contain the C_5 unit. The biogenesis of unsubstituted furan structure (XXXV) has been far more difficult to understand. It is encountered mainly in the benzopyrone group and the furanocoumarins are the most numerous and the earliest known. However furano-derivatives of 2-methyl chromones and flavones are also well represented. In the furanoquinoline alkaloids the furan ring is found fused to the heterocyclic ring. The known examples are listed in Table 3. The furan ring present in all these groups seems to have similar biogenetic history.

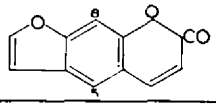
In his review of naturally occurring coumarins, Späth[38] enumerated compounds having the C_5 units and the furanocoumarins. He considered that the four carbon atoms of the furan ring along with one carbon atom of the central benzene ring could constitute an *iso*pentane unit as shown in (XXXVI). However, this is not consistent with his view of the origin of the benzene ring in simple coumarins and those carrying discreet *iso*pentane substituents; in these cases he preferred a carbohydrate origin for the benzene ring. In reviewing the same subject, Haworth[39] suggested that the unsubstituted furan rings of these natural coumarins were theoretically derivable by elimination of propane from a hypothetical α-*iso*propyl-dihydrofuran structure (XXXVII). Geissmann and Hinreiner[4] also examined the question. A two carbon phosphorylated keto alcohol moiety (XXXVIII) was suggested as the precursor and this was considered to cyclise to a furan-3-one (XXXIX) which subsequently yielded a furan ring by reduction and dehydration. It may be mentioned that this intermediate

[38] E. Späth, *Ber. Dtsch. Chem. Ges.* **70**, A83 (1937).
[39] R. D. Haworth, *Ann. Rep.* 344 (1937).

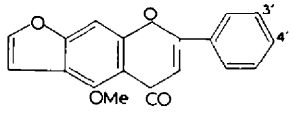
TABLE 3

Furanocoumarins

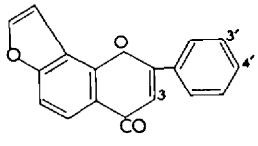


Name of compound	Substituents
Angelicin[44] (XLIII)	—
Sphondin[69]	6-OMe
*iso*Bergapten[70]	5-OMe
Pimpinellin[71]	5:6-$(OMe)_2$
Psoralene[46] (XLV)	—
Bergaptol[72]	5-OH
Bergapten[73] (LVI)	5-OMe
Xanthotoxol[74]	8-OH
Xanthotoxin[75] (LVII)	8-OMe
*iso*Pimpinellin[76] (LVIII)	5:8-$(OMe)_2$
8-Hydroxy bergapten[77] (LIX)	5-OMe-8-OH.
Prangenin[78]	8-O-Butyl
*iso*Imperatorin[79] (LX)	5-OCH_2—CH=CMe_2
Oxypeucedanin[80](LXI)	
Ostruthol[81] (LXII)	5-OCH_2—CH—$C(OH)Me_2$ | OCO—C(Me)=CHMe
Imperatorin[82] (LXIII)	8-OCH_2—CH=CMe_2
Phellopterin[83]	5-OMe-8-OCH_2—CH=CMe_2
Byakangelicol[84]	
Byakangelicin[84]	5-OMe-8-OCH_2—CH—CMe_2 | | OH OH
Bergamotin[85]	5-O-Geranyl
8-Geranyloxypsoralene[86]	8-O-Geranyl 

Furanoflavones



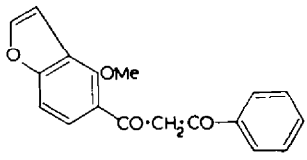
Name of compound	Substituents
Pinnatin[87]	—
Gamatin[87]	3′-4′-methylenedioxy



References for Table 3 on page 265

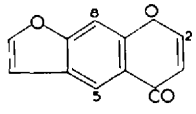
TABLE 3—*contd.*

Name of compound	Substituents
Lanceolatin[88] B	—
Karanjin[89]	3-OMe
Pongapin[90]	3-OMe-3′:4′-methylenedioxy.

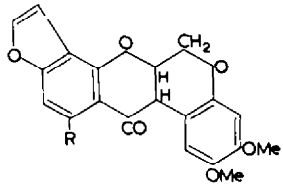


Pongamol[91]

Furanochromones

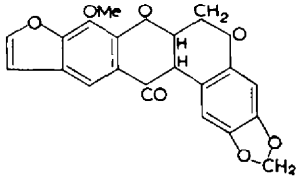


Name of compound	Substituents
Visnagin[92] (LXIV)	2-Me-5-OMe
Khellin[93] (LXV)	2-Me-5:8-$(OMe)_2$
Khellinol[21] (LXVI)	2-Me-5-OH-8-OMe
Khellol glucoside[94] (LXVII)	2-CH_2O-Gl-5-OMe
Ammiol[95] (LXVIII)	2-CH_2OH-5:8-$(OMe)_2$



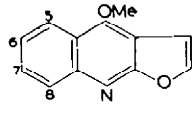
Rotenoids

Name of compound	Substituents
Elliptone[84] (LXIX)	R=H
Malaccol[84] (LXX)	R=OH



Pachyrrhizon[96] (LXXI)

Furanoquinolines



References for Table 3 on page 265

TABLE 3—*contd.*

Name of compound	Substituents
Dictamnine[97] (LXXII)	—
γ-Fagarine[98] LXXIII)	8-OMe
Evolitrine[99]	6-OMe
Skimmianine[100] (LXXIV)	7:8-$(OMe)_2$
Kokusaginine[101,102]	6:7-$(OMe)_2$
Maculosidine[50] (XLVII)	6:8-$(OMe)_2$
Acronycidine[103]	5:7:8-$(OMe)_3$
Maculin[50]	?-methylenedioxy.
Kakusagin[104]	?-methylenedioxy
Flindersiamine[105]	8-OMe-6:7-methylenedioxy
Evoxine[48] (LXII)	8-OMe-7-OCH_2—CH(OH)—CMe_2(OH)
Evolatine[106]	6-OMe-7-OCH_2—CH(OH)—CMe_2(OH)

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[104] M. Terasaka, T. Ohta and K. Narahasi, *Pharm. Bull. (Japan)* **2**, 159 (1954).
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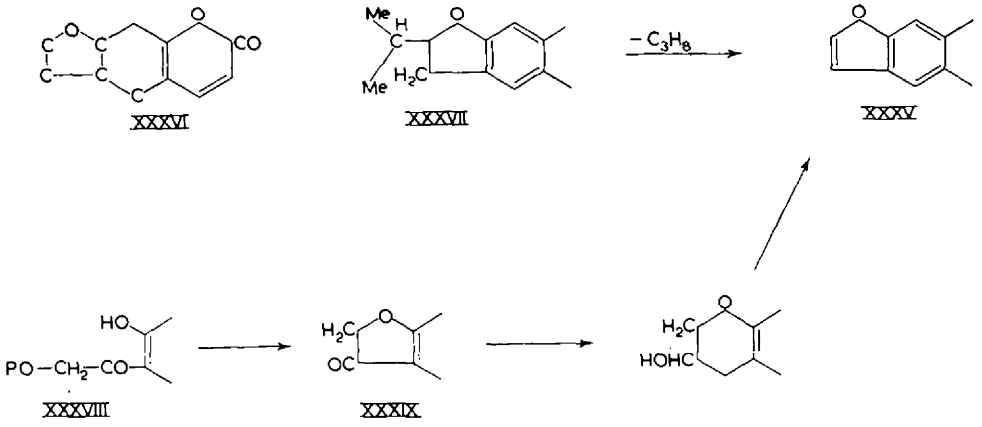
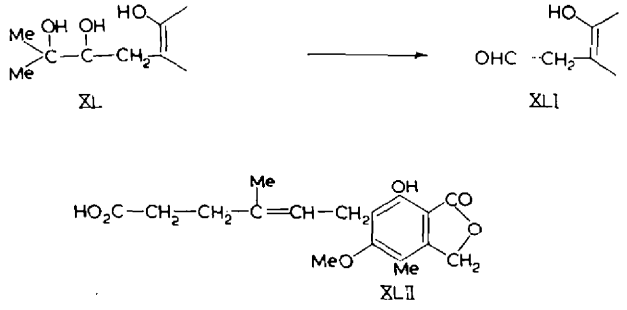
(XXXVIII) was considered to be capable of condensation with acetone or its equivalent to form the *iso*pentane skeletal unit. Recently, Robinson[40] has indicated a few possibilities for the origin of the furan ring in furanoquinolines but has emphasised the uncertainty of these routes in the absence of any good clues.



A review of natural products reveals the striking association of compounds having unsubstituted furan rings with those having obviously noticeable *iso*pentane units. A number of examples of their co-occurrence are available (see Table 4). A more important feature is that, frequently, definite *iso*pentane units and unsubstituted furan rings are found incorporated together in one compound. Based on this intimate association, it is now suggested that the structure (IV) from which all known types of *iso*pentane structures can be derived, is also the precursor of simple furan rings. The transformation of structure (IV) into the glycol (XL) was discussed earlier under type (B). Oxidative cleavage of the glycol would result in the loss of three carbon atoms leaving a residue of two as an acetaldehyde (XLI), cyclodehydration of which would form unsubstituted furans.

The uncyclised two carbon system like (XLI) has not so far been encountered among natural products, but the *iso*prenoid substituent in the mould metabolite mycophenolic acid[41] (XLII) provides an instance where one of the two double bonds in a ten-carbon geranyl side chain has been cleaved in the above fashion leaving a chain of seven. Oxidation of the terminal aldehyde has yielded the carboxylic acid.



[40] R. Robinson, *The Structural Relations of Natural Products* p. 94. Clarendon Press, Oxford (1955).
[41] J. H. Birkinshaw, H. Raistrick and D. J. Ross, *Biochem. J.* **50**, 630 (1952).

TABLE 4

Source	Constituents	Type
Angelica archangelica[107]	Umbelliprenin (LXXV)	C_{15}
	Osthol (XI)	C_5
	Angelicin (XLIII)	C_2
	Xanthotoxin (LVII)	C_2
	Imperatorin (LXIII)	C_2–C_5
Imperatoria Ostruthium[108]	Ostruthin (LXXVII)	C_{10}
	Osthol (XI)	C_5
	Imperatorin (LXIII)	C_2–C_5
	*iso*Imperatorin (LX)	C_2–C_5
	Oxypeucedanin (LXI)	C_2–C_5
	Ostruthol (LXII)	C_2–C_5–C_5
Luvanga scandens[109]	7-Methoxy-5-geranyloxy coumarin (LXXVI)	C_{10}
	Xanthyletin (LII)	C_5
	Luvangetin (LIV)	C_5
	Xanthotoxin (LVII)	C_2
	*iso*Pimpinellin (LVIII)	C_2
Zanthoxylum flavum[27]	Suberosin (XIX)	C_5
	Psoralene (XLV)	C_2
	Xanthotoxin (LVII)	C_2
Ammi visnaga	Visamminol[23] (XIII)	C_5
	Visnidin[110] (LXXVIII)	C_5
	Samidin[110] (LXXIX)	C_5
	Dihydrosamidin[110] (LXXX)	C_5
	Visnagin[92] (LXIV)	C_2
	Khellin[93] (LXV)	C_2
	Khellinol[31] (LXVI)	C_2
	Khellol glucoside[94] (LXVII)	C_2
	Ammiol[95] (LXVIII)	C_2
Derris elliptica[84]	Rotenone (XVII)	C_5
	Deguelin (LV)	C_5
	Elliptone (LXIX)	C_2
Pachyrrhizus erosus[96]	Rotenone (XVII)	C_5
	Pachyrrhizon (LXXI)	C_2
Zanthoxylum rhetsa[111]	Suberosin (XIX)	C_5
	Skimmianine (LXXIV)	C_2
Skimmia japonica[112]	Seselin (L)	C_5
	Skimmianine (LXXIV)	C_2

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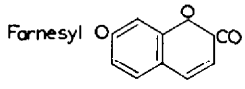
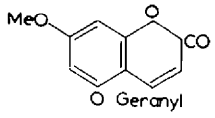
TABLE 4 (*contd.*)

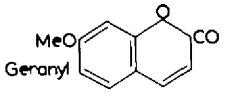
Source	Constituent	Types
Aegle marmelose[113]	Marmin[86] (XXXIII)	C_{10}
	Marmesin[86] (XIV)	C_5
	Imperatorin (LXIII)	C_2–C_5
	γ-Fagarine[114] (LXXIII)	C_2
Casimiroa edulis[77,115]	Bergapten (LVI)	C_1
	*iso*Pimpinellin (LVIII)	C_2
	8-Hydroxy bergapten (LIX)	C_1
	Dictamnine (LXXII)	C_1
	γ-Fargarine (LXXIII)	C_2
	Skimmianine (LXXIV)	C_1



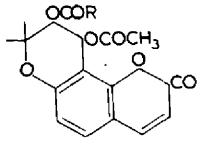
Umbelliprenin (LXXV)



7-Methoxy-5-geranyloxy coumarin (LXXVI)



Ostruthin (LXXVII)



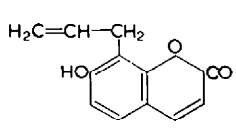
Visnidin[110] (LXXVIII); R=CH(Me)C_2H_5
Samidin[110] (LXXIX); R=CH:CMe_2
Dihydrosamidin[110] (LXXX); R=CH_2.$CHMe_2$

Support for the postulated biosynthetic route is provided by our recent work[42,43] on the synthesis of benzofuran derivatives, which has been based on these ideas. A facile laboratory synthesis for this group of natural products has been developed starting with *o*-hydroxy-allyl compounds. Cleavage of the allyl double bond has been effected by hydroxylation and subsequent fission of the glycol, or more directly by ozonolysis. The resulting acetaldehydes undergo ready *cyclo*dehydration to furans. For convenience, the work has been carried out with simple allyl derivatives instead of the γ,γ-dimethylallyl type, and the method has been shown to be workable for derivatives of benzene[42] chromone[42,43] and flavone.[42] Its successful extension to coumarins is reported in this paper; a new synthesis of angelicin[44] (XLIII) starting with 7-hydroxy-8-allyl coumarin[45] (XLIV) has been carried out.

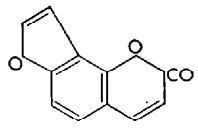
The use of simple allyl derivatives in these model experiments does not in any way detract from the argument in favour of biogenesis based on γ,γ-dimethylallyl

[42] R. Aneja, S. K. Mukerjee and T. R. Seshadri, *Tetrahedron* **2**, 203 (1958).
[43] R. Aneja, S. K. Mukerjee and T. R. Seshadri, *Tetrahedron* **2**, 203 (1958)
[45] B. Krishnaswamy and T. R. Seshadri, *Proc. Indian Acad. Sci.* A **13**, 43 (1941).
[113] A Chatterjee, *Curr. Sci.* **12**, 209 (1943).
[114] K. K. Chakravarty, *J. Indian Chem. Soc.* **21**, 401 (1944).
[115] J. Iriarte, F. A. Kincl, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.* 4170 (1956).

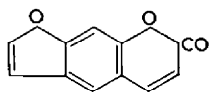
substituents. However, as a more appropriate example, the conversion of 7-hydroxy-6-dimethylallyl coumarin[27] (ex. Chloroxylon swietenia) (XVIII) into the furanocoumarin, psoralene[46] (XLV), is also described in the present communication. This is effected by ozonolysis and subsequent cyclisation of the product with phosphoric acid.



XLIV



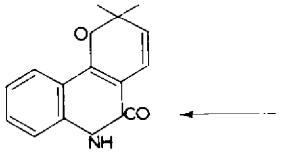
XLIII



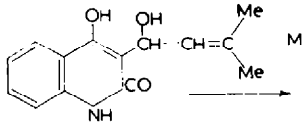
XLV

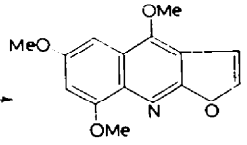
Furanoquinolines.

Since the furanoquinolines frequently occur along with the type of compounds discussed above, (see Table 4), there seems to be little doubt that the furan groups have, in this type also, the same origin. Further support is provided by the occurrence of flindersine[47] (XLVI) a pyranoquinoline and a number of furanoquinolines like maculosidine[48] (XLVII) in closely related *Flindersia* species. Another significant feature is the occurrence of furanoquinolines having *iso*pentane substituents in the same molecule, for example acronidine[49] (XLVIII) and evoxine[50] (XLIX). Hence the evolution of pyranoquinoline (XLVI) and furanoquinolines from a common precursor can be represented as given below.

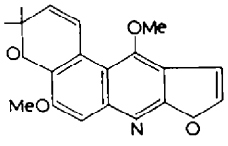


XLVI

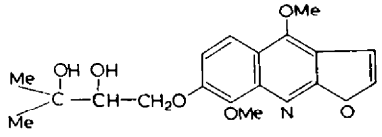




XLVII



XLVIII



XLIX

EXPERIMENTAL

7-Hydroxy coumarin-8-acetaldehyde. A stream of 2% ozonised oxygen (50 ml/min) was passed for 25 min through a cold solution (—5°) of 7-hydroxy-8-allyl coumarin[46] (XLIV) (200 mg) in dry ethyl acetate (30 ml). The solution was hydrogenated in the presence of 1% palladised charcoal (500 mg) till the rapid absorption of hydrogen ceased. The catalyst was then filtered and the filtrate evaporated to dryness. The residue was crystallised from ethyl acetate-hexane when the acetaldehyde (170 mg) was obtained as colourless short prisms, m.p. 140–41° (Found: C, 64·4; H 3·9; Calc. for $C_{11}H_8O_4$ C, 64·7; H, 3·9%). Its 2:4-dinitrophenylhydrazone crystallised from chloroform-methanol as light orange prisms m.p. 238–239°.

[47] R. F. C. Brown, J. J. Hobbs, G. K. Hughes and E. Ritchie, *Aust. J. Chem.* **7**, 348 (1954).
[48] R. F. C. Brown, P. T. Gilham, G. K. Hughes and E. Ritchie, *Aust. J. Chem.* **7**, 181 (1954).
[49] J. A. Lamberton and J. R. Price, *Aust. J. Chem.* **6**, 66 (1953).
[50] F. W. Eastwood, G. K. Hughes and E. Ritchie, *Aust. J. Chem.* **7**, 87 (1954).

Angelicin (XLIII). The acetaldehyde obtained above (100 mg) was dissolved in *ortho*-phosphoric acid (2 ml) and heated at 100° for 10 min. The solution was poured into water and the product extracted with benzene. The dried benzene solution was allowed to percolate through a short column of activated alumina and eluted with hexane. The eluate on evaporation yielded angelicin (90 mg). It crystallised from benzene–petroleum ether as colourless needles m.p. and mixed m.p. with an authentic sample, isolated from *Psoralea corylifolia*, 141–42°.

Conversion of 6-dimethylallyl-7-hydroxy-coumarin[27] (XVIII) *into psoralene*[46] (XLV). Ozonolysis of demethyl suberosin[27] (XVIII) (50 mg) was carried out as described in the above experiment, ozonised oxygen being passed for 7 min. After hydrogenation, the crude acetaldehydo-coumarin was cyclised by heating to 80° for 2 min with *ortho*-phosphoric acid (1 ml). The mixture was diluted with water and extracted with benzene. The dried benzene solution was allowed to percolate through a short column of activated alumina. The eluate on evaporation yielded psoralene (40 mg) crystallising as colourless needles from methanol, m.p. and mixed m.p. with an authentic sample isolated from *Psoralea corylifolia*, 161–62°.

Acknowledgement—Our grateful thanks are due to Prof. F. E. King for a gift of 7-demethyl suberosin.