Syntheses and Structural Elucidation

of Natural Coumarins.

THESIS

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Summary

A short review of natural coumarins is given which incorporates some of the structural features and biosynthetic aspects of those coumarins unsubstituted at positions 3 and 4. All of the 5,7-dioxygenated simple coumarins, known to occur naturally, have been tabulated.

Part I The 'Claisen Rearrangement' has been investigated as a method of synthesising ortho-(1,1-dimethylallyl)hydroxy-coumarins.   Thus, pyrolysis of 7-O-(3,3-dimethylallyl)scopoletin(61) yielded obliquetin(62) and the corresponding cyclic ether, nieshoutin(63).   A third product of this pyrolysis was 3-(1,1-dimethylallyl)scopoletin(76), the result of a triple 'Claisen Rearrangement'.

In a similar manner, 7-O-(3,3-dimethylallyl)-5-methoxy-coumarin(120) was converted to a phenol which was trapped as the butyrate.   Hydrolysis and methylation yielded the coumarin pinnarin(122).

A general study of the 'Claisen Rearrangement' products of the 7-O-(3,3-dimethylallyl) ethers of the following coumarins was made, namely aesculetin(19), 4-methylscopoletin(101), umbelliferone(4) and 4-methylumbelliferone(115).

Part II A new method of introducing a 3,3-dimethylallyl unit ortho to a phenol has been developed.   The 1,1-dimethylpropargyl

ethers of umbelliferone(4) and 7-hydroxy-5-methoxycoumarin were prepared and then selectively reduced to the corresponding 1,1-dimethylallyloxycoumarins.   Pyrolyses of the latter ethers enabled the natural coumarins, osthenol(21), 7-demethylsuberosin (22), osthol(146), suberosin(147) and coumurrayin(131) to be prepared.

Part III   The structure of nieshoutol(160), the only trioxygen- ated coumarin isolated from the heartwood of Ptaeroxylon obliquum, was deduced from chemical and spectroscopic evidence. The ortho relationship of the phenolic hydroxyl to the oxygen of the 2,3,3-trimethyldihydrofuran ring was determined by n.m.r. shielding effects.   Demethylation, ester interchange and cyclic ketal formation showed that the methoxyl of nieshoutol is ortho to the phenolic hydroxyl.   Structure 160 was confirmed when a nuclear Overhauser effect was observed between the methoxyl and the C-4 proton.

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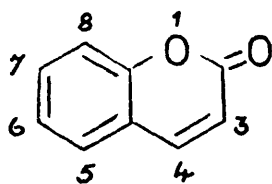P.H. McCabe, A. Martin, and K.P. Mathai is
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Martin, Mrs. M. Kirkland, Mr. J.M.L. Cameron,B.Sc.,
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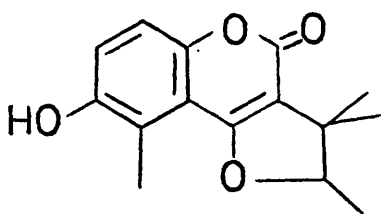I am, also, indebted to the Science Research
Council for a maintenance award.

<u>Syntheses and Structural Elucidation of Natural Coumarins.</u>
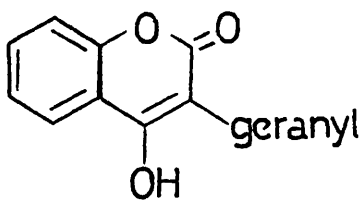
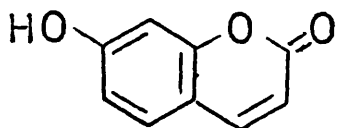A Short Review of Natural Coumarins.

(1)

(2)

geranyl

OH

(3)

(4)

The history of the benzo-α-pyrones can be traced back to 1820 when Vogel isolated the simplest member of this class of oxygen heterocycles, coumarin(1)[1,2] from Coumarouna clorata Willd. (Tonka beans). Since then, coumarin derivatives have been found to be widely distributed[2-6] throughout the plant kingdom (Table 1). Only a few have been isolated from animals[7] or micro-organisms[8]. In 1964, there were about one hundred naturally occurring coumarins[4,6]. After only six years, this number has more than doubled and is still increasing rapidly. There have, of course, been improvements made to the isolation techniques[4,9] but recent years have seen a large increase in the number of publications from the U.S.S.R. The intense interest in the coumarin field from this quarter is indicated by the number of short reviews[10] which appear periodically.

Coumarin(1), itself, is atypical in that there is no oxygen at C-7. There are only a few others, e.g. glaupalol(2)[11] and ferulenol(3)[12], with this distinction. Therefore, 7-hydroxy-coumarin(umbelliferone)(4) is often regarded as the parent of the coumarins in general.

Oxygenation is known to occur at any of the six available positions on the coumarin nucleus. These oxygen atoms can be present as phenols, methyl ethers or glycosidic ethers. In common with many natural phenolic compounds[4-6,13], coumarins are frequently found with isoprenoid chains of one, two or three units. These can be attached to the nucleus, to nuclear

Table 1.

Plant orders and related species frequently associated with coumarins.

Order.	Species.
Umbelliferae	Agasyllis, Ammi, Angelica, Archangelica, Cnidium, Ferula, Heracleum, Nicotiana, Pastinaca, Peucedanum, Pimpinella, Prangos.
Rutaceae	Aegle, Citrus, Fagara, Flindersia, Ptelea, Ruta, Skimmia.
Compositae	Artemesia.
Labiatae	Lavandula.
Leguminosae	Coronilla, Dalbergia, Derris, Melilotus.
Oleaceae	Fraxinus.
Orchidaceae	Dendrobium.
Rosaceae	Prunus.
Saxifragaceae	Hydrangea.
Solanaceae	Brunfelsia, Scopolia, Solanum.
Thymelaeaceae	Daphne.

Scheme 1.
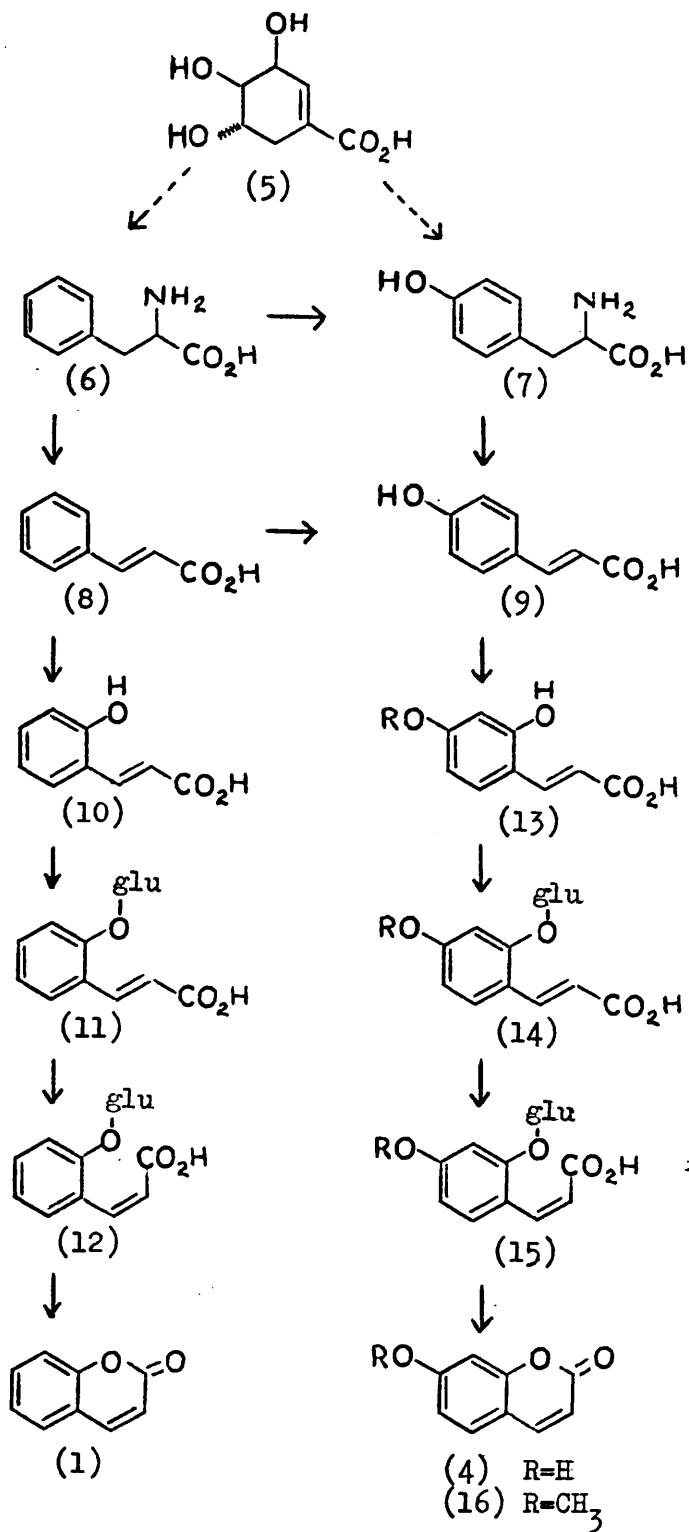
glu = glucose residue

oxygen or to both in the form of a cyclic ether. The natural
coumarins can be loosely divided into several categories.
Although these divisions are made on the basis of the substitution
pattern, they can, to some extent, be justified on biosynthetic
grounds.

§ 1. C-3,C-4: Hydrogen.

This is, by far, the largest category. They are frequently
called the 'simple coumarins' and can be subdivided into mono-,
di- and tri-oxygenated systems. None, as yet, have been
positively assigned to the tetra-oxygenated[14] class. By the
very nature of the natural coumarins, the mono-oxygenated group
will be umbelliferone(4) derivatives in almost every case and at
least one oxygen will be at C-7 in each of the other systems.
There is no biosynthetic justification on which to subdivide on
the basis of oxygenation pattern (vide infra) but it has often
been found convenient to designate a natural coumarin, e.g. an
umbelliferone derivative. The mono-oxygenated group is the
most extensive, there being almost thirty natural ethers of
umbelliferone(4) alone.

The biosynthetic pathways[15-21] relating to coumarin(1) and
a few of the 'simple coumarins' have received considerable
attention. Brown has shown[18,19] that coumarin(1), umbelliferone(4)
and herniarin(16) arise by way of shikimic acid(5) (Scheme 1).
In lavender (Lavandula officinalis), trans-cinnamic acid(8) was
found[18] to be a good precursor of both coumarin(1) and herniarin(16).

Scheme 2.
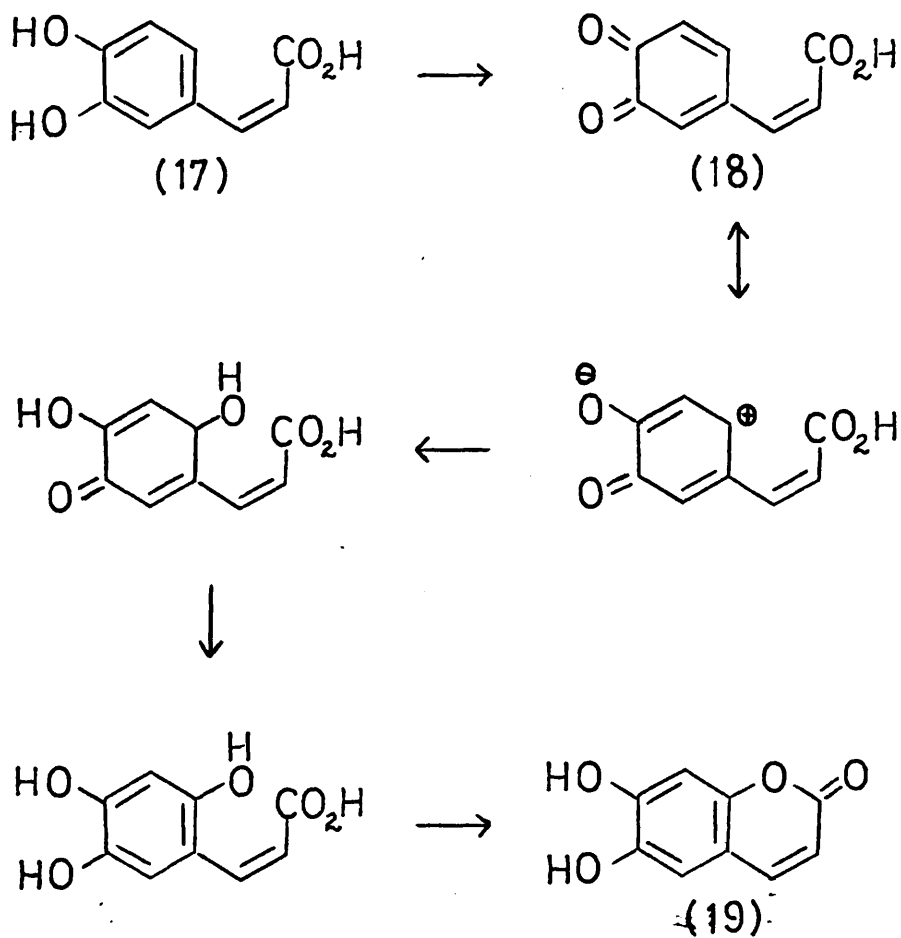
It would appear, however, that whereas ortho-hydroxylation of 8
leads to coumarin, para-hydroxylation followed by ortho-hydroxyl-
ation leads to herniarin.   In Hydrangea macrophylla, although
both para- and ortho-coumaric acids, (9) and (10), were converted[19]
successfully into umbelliferone(4), Brown proposes that the plant
itself cannot synthesise ortho-coumaric acid.   The route to
umbelliferone would, therefore, differ little from that of its
methyl ether, herniarin.   For all three, (1), (4) and (16), it
has been proposed that ortho-hydroxylation occurs prior to the
isomerisation of the trans side chain double bond.   There is,
however, some doubt as to whether the isomerisation is enzymat-
ically controlled or is a photochemical process[20].

Prior to 1966, the biosynthetic pathways leading to more
highly oxygenated coumarins had received little attention and
it had been assumed that they would arise by a pathway analogous
to that of the mono-oxygenated coumarins.   It was shown[21],
however, that cis-caffeic acid(17) can be transformed to
aesculetin(19) under photolytic conditions in an oxygen atmosphere.
Both the isomerisation of trans-caffeic acid to 17 and the
cyclisation to aesculetin are, apparently, photochemically
controlled under these conditions.   The work by Sato, using a
homogenate of Saxifraga stolonifera has confirmed[22] that aesculetin
(19) is derived from cis-caffeic acid(17) and it appears that the
first step, after the isomerisation of the double bond, is the
transformation of 17 into the ortho-quinone(18).   Scheme 2 has,

Scheme 3.

$$HO \quad \underset{5}{\overset{CO_2H}{\diagup}} \quad \underset{4}{\diagdown} OH$$

(20)

$$\underset{5}{\diagup} OPP$$
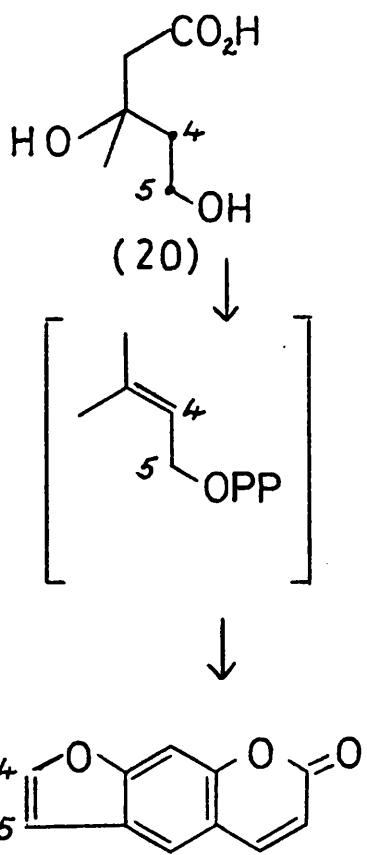
PP = pyrophosphate

therefore, been proposed[22] as a possible biosynthetic route to
aesculetin(19).

Many of the 'simple coumarins' contain an unsubstituted
furan ring fused to the benzenoid nucleus.   This is a feature
common to many natural phenolic compounds.   It has been shown
that the coumarin nucleus of a few of these furocoumarins is
derived[23-27] from cinnamic acid and that the two carbons required
to form the furan ring are obtained[23] from mevalonic acid(20)
in a specific manner (Scheme 3).   These factors will, undoubtedly,
hold for all the furocoumarins.   Although many coumarins contain
an oxygenated isoprene side chain, it is generally accepted that
the first unit to be inserted into the coumarin-type nucleus is
an isoprene one and that oxygenation of the side chain takes place
at a later stage.   A discussion of the modifications made to a
3,3-dimethylallyl side chain will be incorporated later.
However, in the context of the furocoumarins, nuclear isoprenylation
of an umbelliferone-type precursor could give rise to osthenol(21)[4]
or 7-demethylsuberosin(22)[4].   The derived epoxides and glycols,
(23) to (26), have not been isolated.   The methyl ethers of 23
and 25 have, however, been encountered[4,28].   A simple cyclisation
would then yield the isopropyldihydrofurans 27 and 28 (Scheme 4).
The dextrarotatory form of 27, columbianetin,and both optical
isomers of 28, marmesin and nodakenetin, occur[4] naturally,as well
as numerous esterified forms.   On this basis, with some chemical
evidence, Birch has proposed[29] that similar isopropyldihydrofurans

Scheme 4.
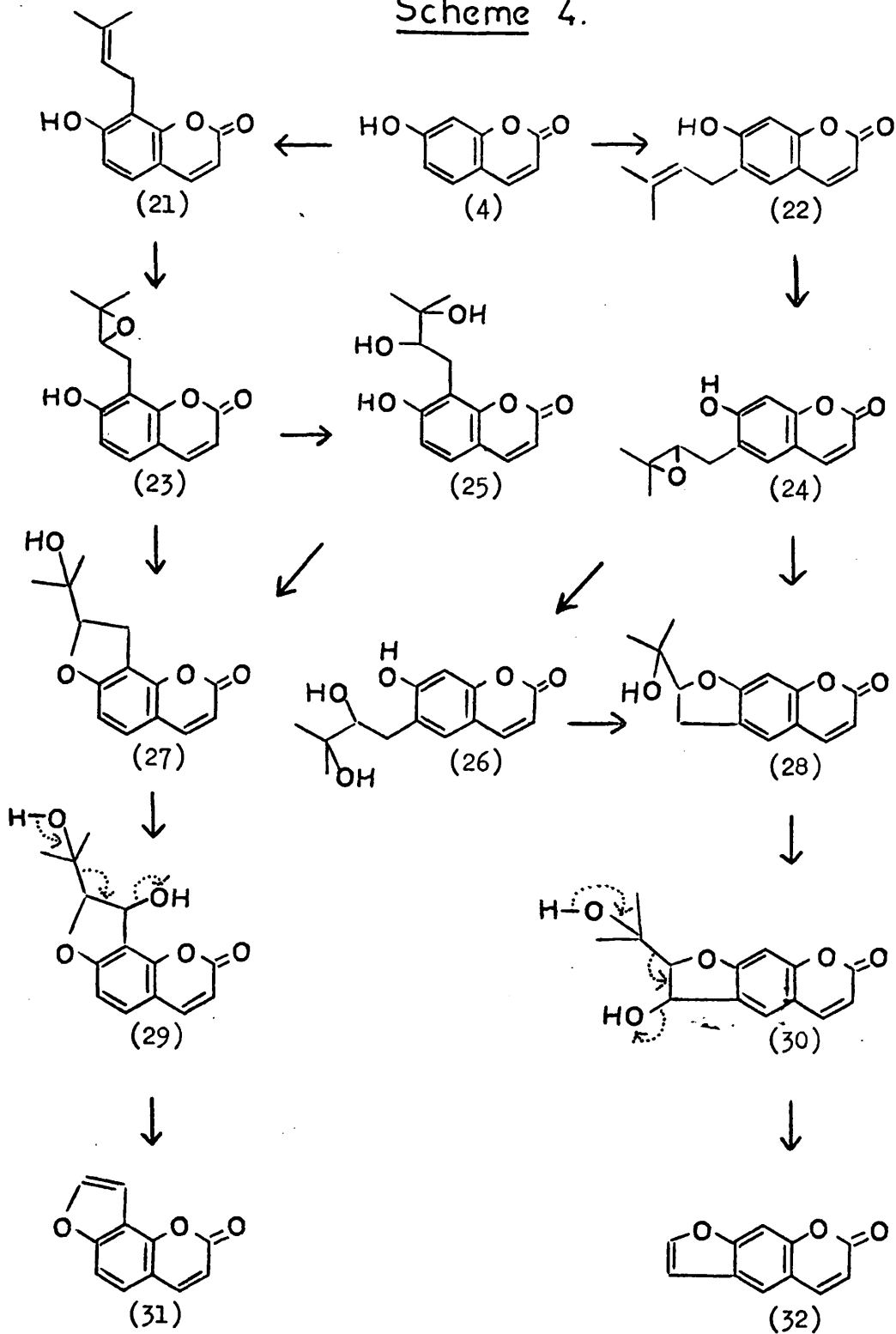
might well be the precursors[23] of the benzofurans in general.
Benzylic oxidation of 27 and 28 would then give intermediates
such as 29 and 30. Several di-esters of 29 have been isolated
from natural sources[4,30,31]. Cleavage of the three carbon
unit (Scheme 4) would then give rise to angelicin(31) and
psoralen(32). This hypothetical route to the furocoumarins
is supported by the fact that hydrolysis of libanotin(33)[32] or
vaginidin(34), di-esters of 29, yields[31] angelicin(31). The
fact that very few of the proposed intermediates on the
psoralen(32) pathway have been isolated might imply that e.g.
the cyclic ether 30, or an esterified form, is more readily
converted to the furocoumarin 32, than the isolatable C-8
isomers to angelicin(31). Psoralen(32) is, also, more
frequently encountered in nature than the angular analogue 31.
Further evidence of the validity of Birch's proposals[29] has
come recently from the work of Brown and Steck. In addition
to confirming that columbianetin(27) and marmesin(28) have
umbelliferone-type precursors, they have also shown[27] that 27
and 28 are highly incorporated into the corresponding furo-
coumarins, (31) and (32).

Seshadri has put forward an alternative pathway to the
furocoumarins, in which he postulates[33] that cleavage of the
isopropyl grouping occurs prior to the formation of the furan
ring. Calcicolin, which has been assigned[34] structure 35,
has been put forward[35] in support of his hypothesis.

(33) R_1 = COC(CH$_3$):CH(CH$_3$)
R_2 = COCH$_3$

(34) R_1 = COCH$_2$CH(CH$_3$)$_2$
R_2 = H

(35)

OCH$_3$
(36)
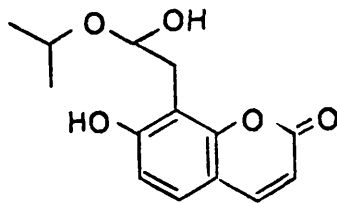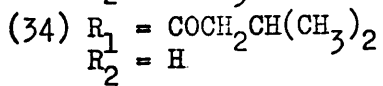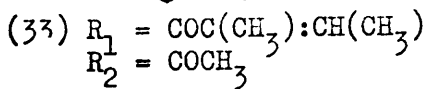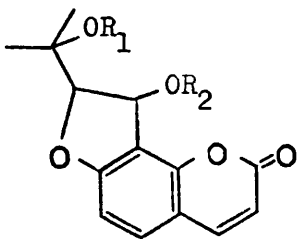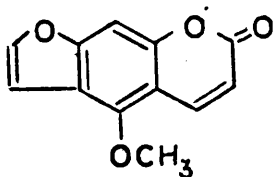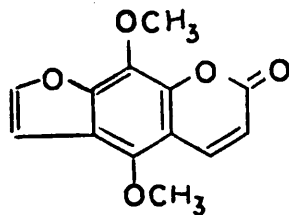
OCH$_3$
(37)
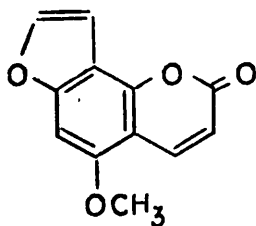
(38)
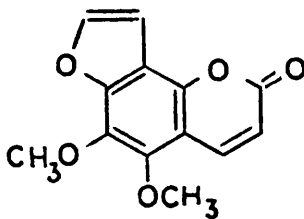
(39)
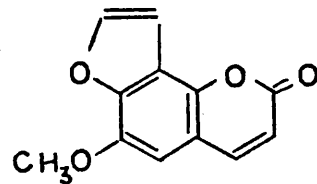
(40)
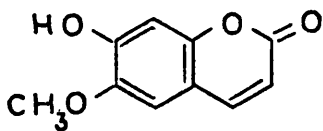
(41)
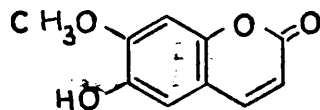
(42)

Since this structure contains an unusual and presumably unstable hemi-acetal grouping, Birch has proposed[29] that, on the basis of the published data, calcicolin could alternatively be assigned structure 29.   If this were correct, it would fall in line with Birch's hypothesis since calcicolin can readily be converted[34] to angelicin(31).

In di- and tri-oxygenated 'simple coumarins', the intriguing question arises as to whether the isoprene unit is inserted into the nucleus after the oxygen pattern has been completed or whether it is inserted into an umbelliferone-type precursor with further nuclear oxygenation occurring at a later stage.

Floss has investigated Pimpinella magna which, in addition to two linear furocoumarins, bergapten(36) and isopimpinellin(37), produces three angular ones, isobergapten(38), pimpinellin(39) and sphondin(40).   After feeding experiments with labelled cinnamic and mevalonic acids, Floss speculated[23] that, on the basis of the specific activities of the furocoumarins isolated, isoprenylation occurs after oxygenation of the nucleus is completed.   Working on this premise, he expected that scopoletin (41) would prove to be an efficient precursor of sphondin(40) and perhaps of 39.   Unfortunately, no preferential labelling of the furocoumarins was observed[24]. Scopoletin(41) was only incorporated to a slight extent.   Even this slight uniform incorporation was suspect since the isomer 42 was also incorporated to the same extent.   These results do not substantiate his earlier

hypothesis and, in view of the predominance of 6,7- and 7,8-furocoumarins in nature, Floss now speculates[24] that isoprenylation occurs at a much earlier stage than he had previously envisaged. Thus, this aspect of coumarin biosynthesis is at an unsatisfactory stage but, undoubtedly, future research will yield many interesting results.

A small group of coumarins have recently been discovered, which have a 1,1-dimethylallyl unit at C-3. These would obviously not fulfil the 'C-3, C-4: Hydrogen' requirements of the 'simple coumarins', but, since there is a good possibility that a close precursor might, it will be convenient for the moment to include them in this category. This group and their biosynthesis[36] will be discussed more fully in Part I.

The remaining coumarins, i.e. those substituted at C-3 (with the above exceptions), at C-4 or at both of these positions, contain, of course, many facinating aspects. A detailed discussion is outwith the scope of this review since in most cases the biosynthetic pathways differ so much from those of the 'simple coumarins' that they cannot truly be regarded as 'coumarin' derivatives. However, each of the main categories will be indicated and a few examples given to illustrate the type of 'coumarin' involved. These examples will also serve to indicate many features which are atypical of the coumarins in general.
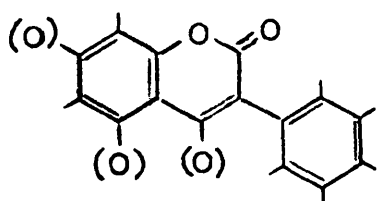
(43)
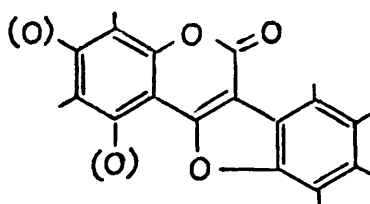
(44)
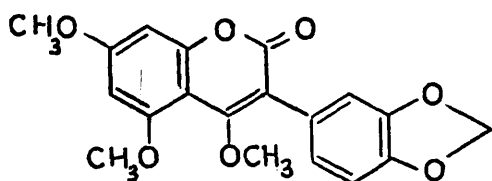
(45)
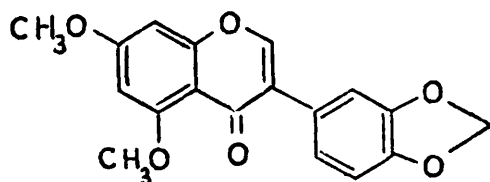
(46)
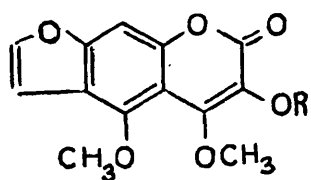
(47) R = CH$_3$

(48) R = C(CH$_3$)$_2$CH:CH$_2$

(49)

noviosyl-O

(50)

CH₃O

(51)

(52)

CH₃O

HO

OH

(53)

HO

OH

OH

(54)
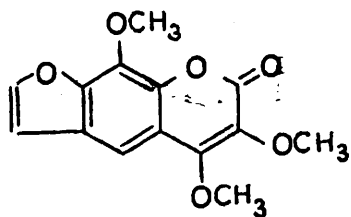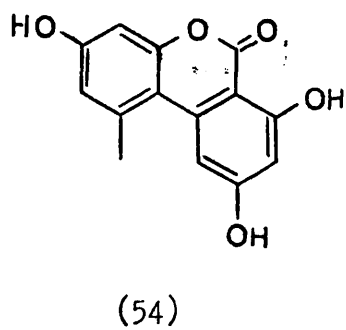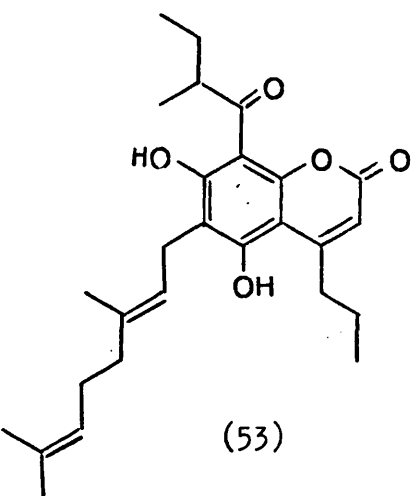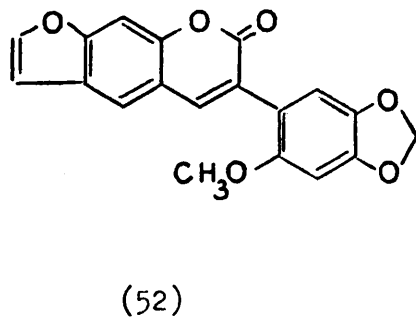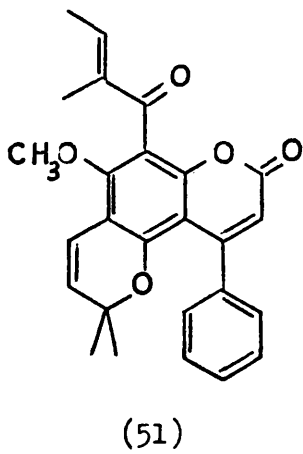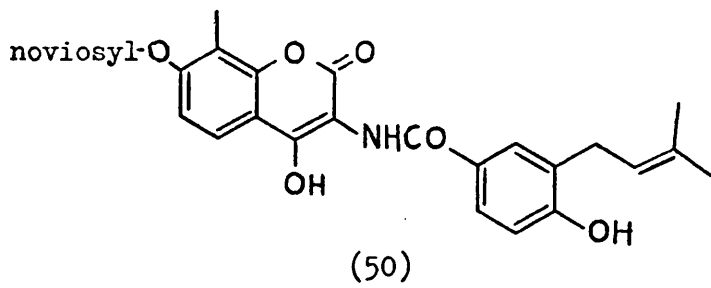
§ 2. C-4: Oxygen.

From a chemical, biosynthetic or physiological[4] point of view, these form a distinguished category.   The largest groups are the Derris coumarins[2,37], so called from the original discovery in the Derris species, and the closely related coumestans[2,37]. The former have partial structure 43 and the latter 44.   In common with the frequently co-occurring isoflavanoids, these compounds often contain a di-oxy-methylene residue as found e.g. in derrusnin(45)[37].   This unit is seldom encountered in the coumarins but since compounds such as 45 are thought[37] to arise from the isoflavanoids e.g. derrustone(46)[37], they cannot be regarded as true representatives of the coumarin class.

Three furocoumarins[38], (47), (48) and (49) which have oxygen at both C-3 and C-4, have been isolated from Halfordia scleroxyla.   Halfordinin(48) is unique amongst the coumarins in that it is a 1,1-dimethylallyl ether.

Novobiocin(50)[4,6,39] which has nitrogen at C-3, appears to have undergone C-methylation.   Despite the fact that O-methylation occurs frequently, C-methylation is rarely encountered[4,6,11,40] in the coumarins.

§ 3. C-4: Aryl (The neoflavanoids[41]);   e.g. calophyllolide(51)[4,41].

§ 4. C-3: Aryl; e.g. pachyrrhizin(52)[4].

§ 5. C-4: Alkyl;e.g. surangin A(53)[42].

§ 6. C-3, C-4: Benzo (The coumarin analogues of the xanthones);
    e.g. alternariol(54)[4].

Scheme 5.

(a) (b) (c) (d) (e) (f) (g) (h) (i) (j) (k) (l) (m) (n) (o) (p) (q) (r) (s) (t) (u) (v) (w) (x)
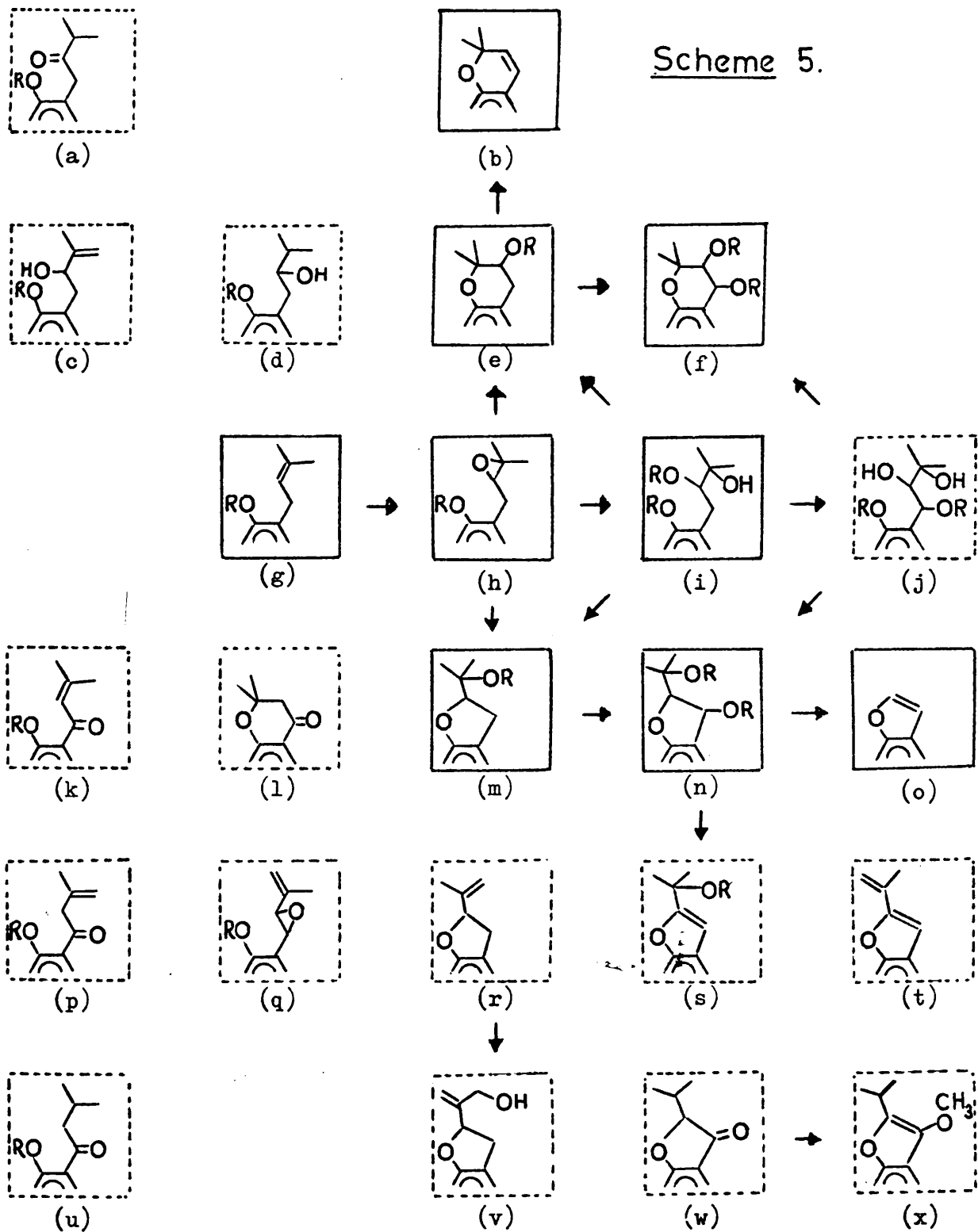
☐ frequently encountered

R = H or CH₃ etc.

The feature common to almost all of the coumarins is the presence of an isoprenoid side chain or the residue of one (vide supra). The 3,3-dimethylallyl unit is frequently found attached to the benzenoid ring and is thought[23] to arise by direct C-alkylation of a phenolic precursor by a moiety such as 3,3-dimethylallyl pyrophosphate. Subsequent modifications can then give rise to a variety of C_5 side chains. A similar biosynthesis, however, seems unlikely for a 1,1-dimethylallyl unit. This group has been encountered more frequently in recent years but, as yet, no simple variations, such as oxygenation, have been found in the coumarins. There are a few 'natural', optically inactive coumarins[11,43-45] which could have arisen by cyclisation of the corresponding ortho-(1,1-dimethylallyl)phenols during isolation. It is noted that when this inverted isoprene unit is attached to the benzenoid nucleus of a coumarin, it has been located only at C-8 in di-oxygenated 'simple coumarins'. No mono-oxygenated analogues have been isolated.

Most of the modifications of a nuclear 3,3-dimethylallyl unit which have been found to occur naturally, are illustrated in Scheme 5. When there is an asymmetric carbon atom, the compound is generally optically active and frequently both antipodes have been isolated from different sources. The arrows in Scheme 5 do not represent proven biosynthetic pathways but are only meant to indicate the close structural relationships

Scheme 6.

CH$_3$O ... OCH$_3$ **1.**	CH$_3$O ... O geranyl **2.**	CH$_3$O ... O **3.**	O ... OCH$_3$ **4.**
CH$_3$O ... OCH$_3$ **5.**	C-6 isomer of 5. **6.**	CH$_3$O ... OCH$_3$ **7.**	C-6 isomer of 7. **8.**
OH OH CH$_3$O ... OCH$_3$ **9.**	C-6 isomer of 9. **10.**	CH$_3$O ... OCH$_3$ **11.**	C-6 isomer of 11. **12.**
CH$_3$O ... OCH$_3$ **13.**	CH$_3$O ... OCH$_3$ **14.**	... OCH$_3$ **15.**	CH$_3$O ... **16.**
... OH **17.**	... OCH$_3$ **18.**	CH$_3$O ... **19.**	HO ... **2o.**

Scheme 6.

21.

22.

23.

24.

25.

26.

27.

28.

29. R = H

30. ester of 29. R =

31. ester of 29. R =

32.

33.

34. OCH₃

35. OCH₃

36.

37.

38.
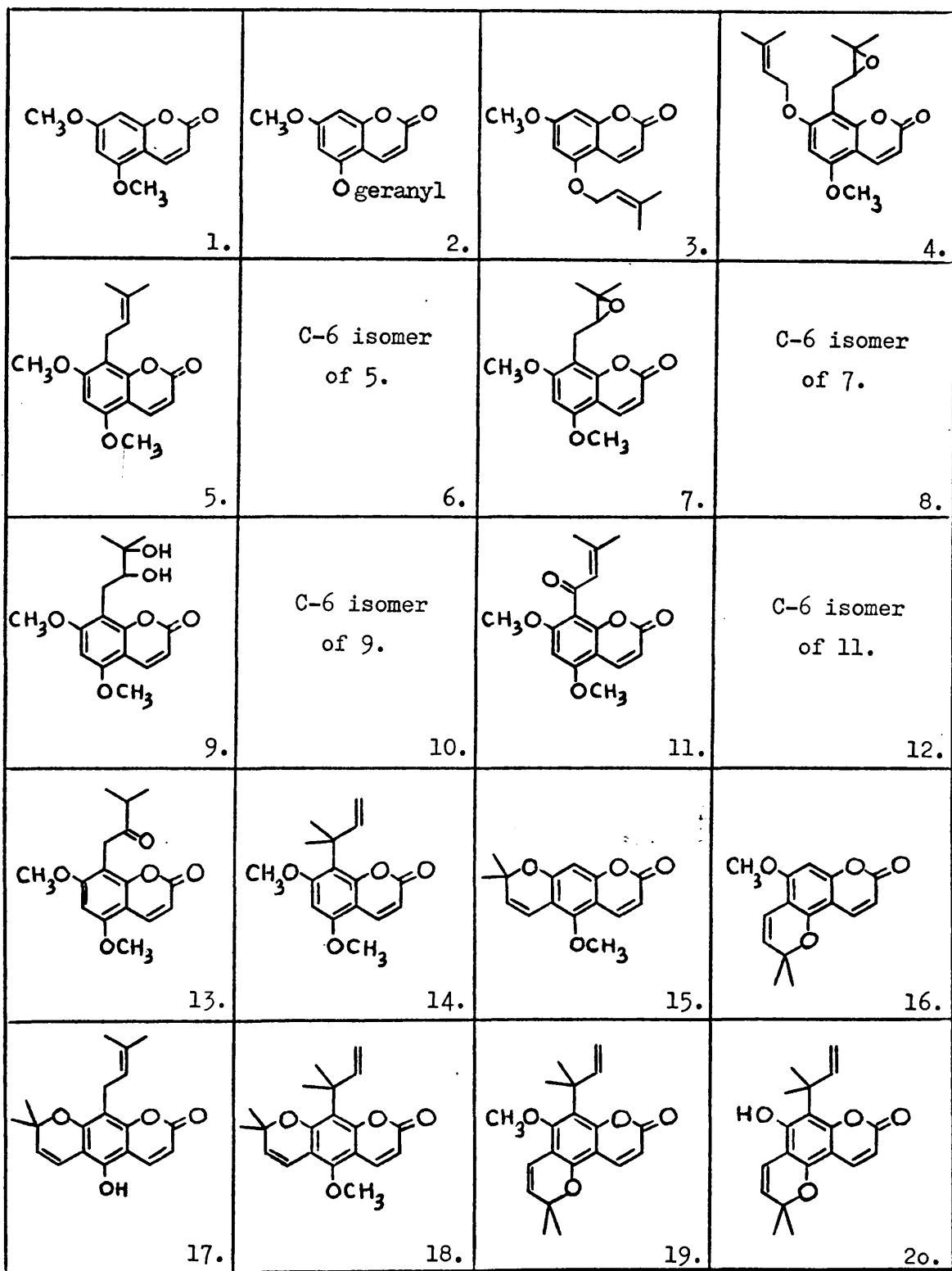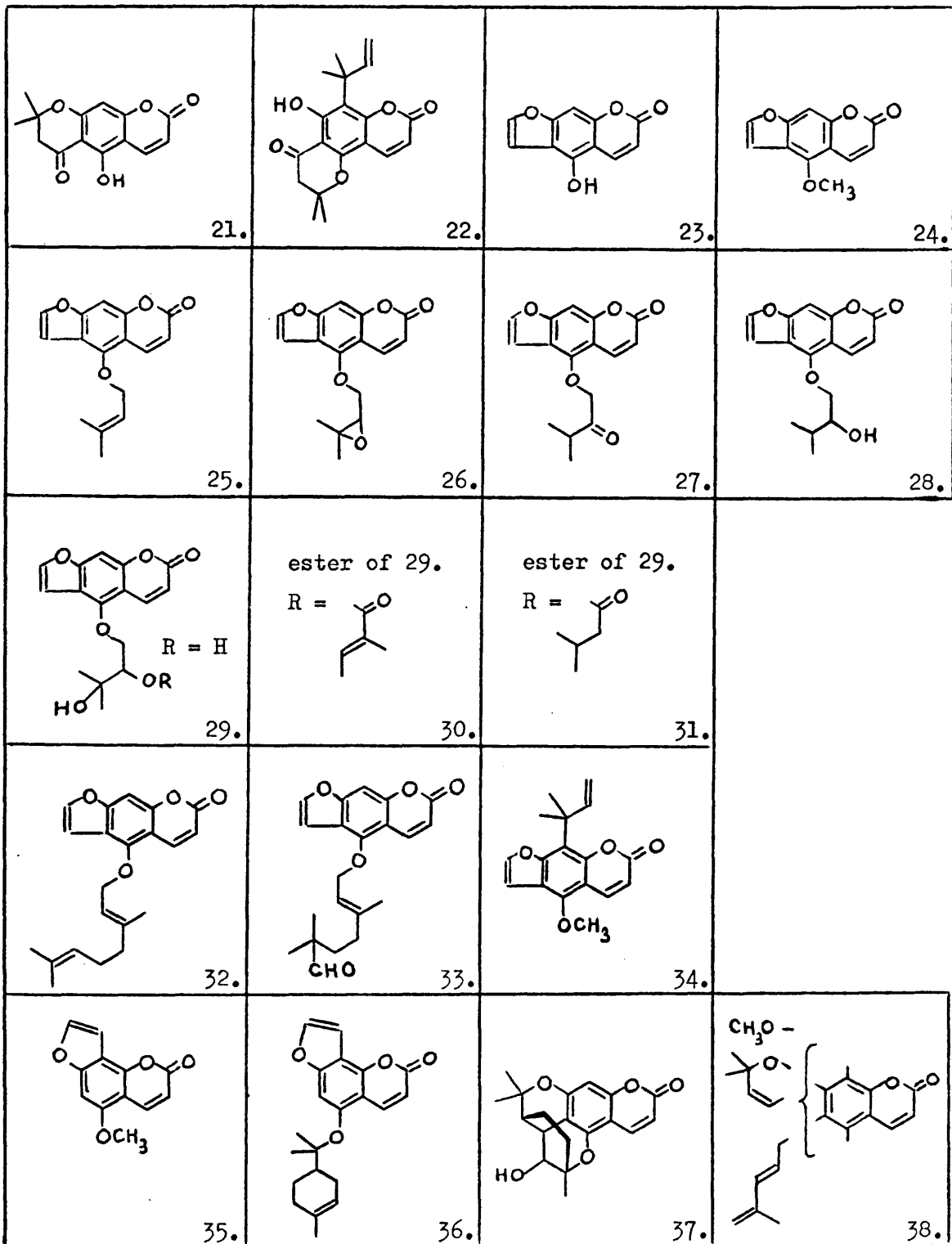
Index to Scheme 6.

The numbering system refers only to Scheme 6 and not to that of the text. If more than one name is given opposite a number, these names refer to optical isomers or to alternative trivial names.

existing between the different C_5 units. No plant has been found, of course, which possesses many coumarins which are very closely related in this manner. It is more usual to isolate e.g. types (m) and ($\overset{O}{x}$) in the same skeletal environment from a natural source. The intermediate type (n) might have been found in a different plant or it might not (vide supra). This point is further illustrated in Scheme 6 which contains all of the known 5,7-dioxygenated 'simple coumarins'. Types (m) and (n), (Scheme 5), do not occur in Scheme 6 whereas furan (o) rings appear frequently. Of course, in these cases, unlike that of psoralen(32) discussed earlier, if the C-5 oxygen were inserted after the isoprene unit, the appearance of types (m) and (n) would depend upon the stage at which the oxygen were inserted. This explanation cannot hold, however, for all of the dimethylchromenes (b) in the 5,7-dioxygenated coumarins. In these cases, the C_5 unit has as yet only been located at C-6 and the C-5 oxygen is frequently involved in the ring formation. Scheme 6 also illustrates the fact that, just as in the umbelliferone series, both the C-6 and the C-8 isomers of many of the side chains are known. It is noticeable that, in the 5,7-dioxygenated coumarins several types of C_5 units have been located only at C-6 (Scheme 6).

There are a few coumarins with isoprenoid side chains which deserve special mention. Alloimperatorin(55)[6] is unusual in that there is no oxygen ortho to the C-5 unit. This is, in fact,
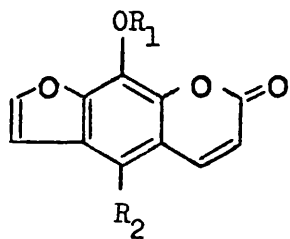
(55) $R_1 = H$, $R_2 = CH_2CH:C(CH_3)_2$

(56) $R_1 = CH_2CH:C(CH_3)_2$, $R_2 = H$

(57)

(58)

(59) R = H

(60) R = OH

(19)
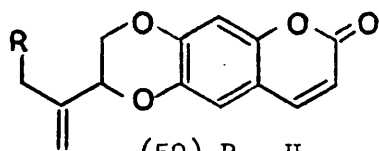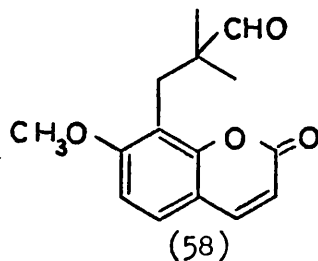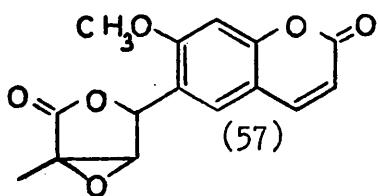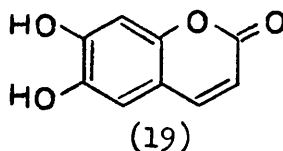
Scheme 7.
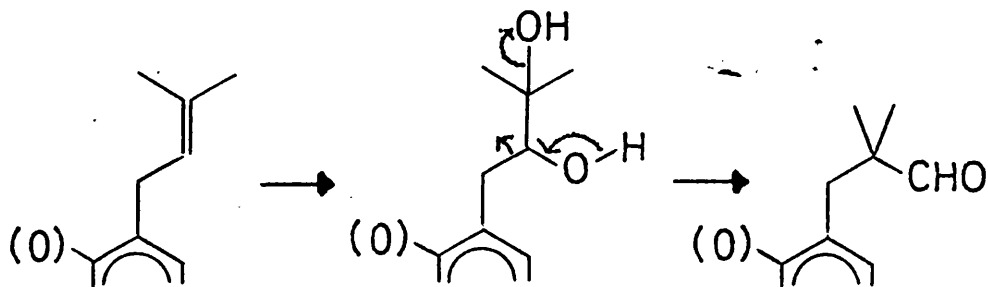
one of the few coumarins isolated with an isoprene unit

at C-5.   The co-occurring coumarin imperatorin(56)[4,6], however,

readily rearranges to 55.   Thus, alloimperatorin could be an

artefact and perhaps for this reason it has been omitted from

Soine's list[4] of the natural coumarins.   Micromelumin(57)[46] has

a very interesting side chain.   It is highly oxygenated but is

presumably derived from a simple dimethylallyl unit.   The origin

of the side chain of 58 is not quite so obvious.   Its structure

has been deduced[47] mainly from the n.m.r. evidence but there can

be little doubt that it is correct.   On the assumption that it

·also has been derived from a dimethylallyl precursor, Scheme 7

represents a possible biosynthetic pathway[69].

Two closely related coumarins, (59) and (60), have been

isolated[45] by Dean.   His elegant synthesis[48] of obliquin(59)

confirmed the assigned structure.   Using more of a biosynthetic

approach, Birch reacted[29] aesculetin(19) with isoprene dibromide.

He obtained, in low yield, a compound which was probably obliquin

(59) but unfortunately an authentic sample was not available for

comparison.   These two coumarins, (59) and (60),represent the

first examples of a dehydrodioxan system in the coumarins.

Only about twenty coumarins[4,43-45,49-59] are known which

contain an isoprenoid unit attached to nuclear oxygen.   Although

few in number, many of these coumarins are frequently encountered

especially in the _Angelica_ species.   The modifications of this

ether unit are similar to the initial variations of the nuclear

3,3-dimethylallyl unit. However, unlike the nuclear analogues, it is common to find the 3,3-dimethylallyl ether of a particular coumarin, its epoxide and glycol, all co-occurring[60] in the same plant. Examples of all the known modifications of the 3,3-dimethylallyl ether in the coumarins have been found in the 5,7-dioxygenated series (Scheme 6).

This review has been concerned primarily with the structural variations found within the 'simple coumarins'. However, it is felt that since the physiological properties of the coumarins, in general, cover such a wide and varied field, a short mention would be justified. A review on this subject by Soine[4] makes excellent reading and leads to a greater understanding of the intense interest invested in both natural and synthetic coumarins. Although most of these properties are associated with other than the 'simple coumarins', the furocoumarins, famous for their blistering effect on the skin, are widely used in the treatment of leucoderma[4] and now appear to have potential as general contraceptives[61]. The physiological and pharmaceutical properties of the coumarins have, therefore, undoubtedly stimulated a great deal of the basic research carried out in this field of oxygen heterocycles.

Introduction.

(61)

(62)

(63)

$$HO-$$
$$CH_3O-$$
$$O-$$
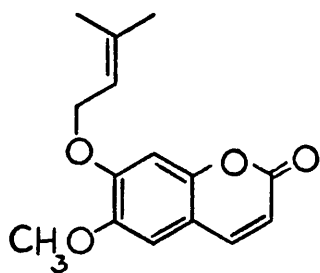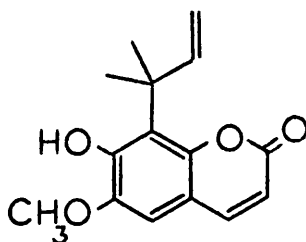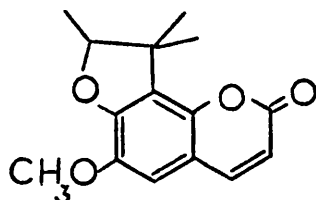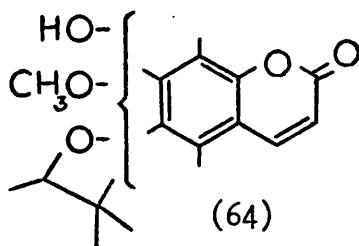
(64)
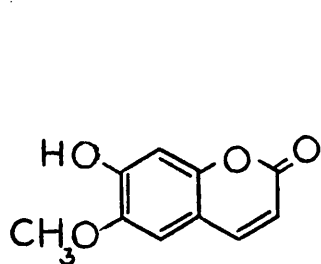
(41)
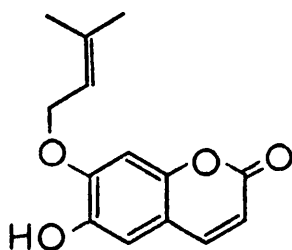
(65)
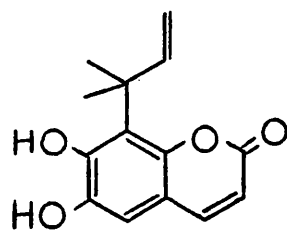
(66)
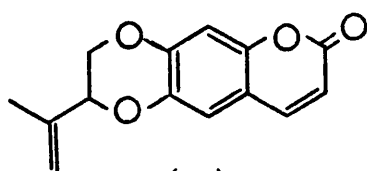
(59)
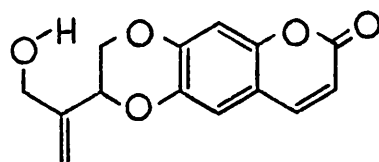
(60)

There has been considerable controversy[62] as to whether the genus <u>Ptaeroxylon</u> belongs to the Meliaceous order of plants or to the Rutaceous order.   With a view to clarifying this situation, several chemical investigations were undertaken[43,63]. These could have been of some taxonomical value, since, for example, the presence of degraded triterpenes is often taken as being indicative of the Meliaceae[64].   The heartwood of <u>Ptaeroxylon obliquum</u> (trivial names: sneezewood, nieshout or umTati) does not appear to possess this characteristic and although the taxonomy has not yet been decided, <u>P.obliquum</u> has proved to be a rich source of chromones[43,63] and coumarins[43,45,48].

Following a preliminary investigation of this heartwood, in this department, McCabe, McCrindle and Murray isolated[43,62] four new coumarins, namely 7-O-(3,3-dimethylallyl)scopoletin(61), 8-(1,1-dimethylallyl)scopoletin(62), nieshoutin(63) and nieshoutol (64).

Concurrently, Dean and Taylor, using samples of <u>P.obliquum</u> from Lushoto (Tanganyika) and Kokstadt (South Africa), isolated[45] scopoletin(41), prenyletin(65), obliquetol(66), obliquin(59) and obliquol(60).   They also obtained 62 and 63 which they named obliquetin and cyclo-obliquetin respectively.   The sample from Lushoto contained all seven of their coumarins but that from Kokstadt lacked 41, 62 and 63.

When it was realised by the Glasgow group, that the taxonomical study by Dean and Taylor was well in progress, no

further examination of their extract was made. However, although the structures of 62 and 63 were firmly based[45,62] on spectroscopic evidence, it was decided to undertake their syntheses. Parts I and II of this thesis are primarily concerned with this aspect and with the work which ensued from it. The names obliquetin and nieshoutin have been adopted for 62 and 63 respectively.

It is interesting to note that nieshoutol(64), isolated[43] by McCabe, McCrindle and Murray, is the only coumarin obtained from P.obliquum, which is not an aesculetin(6,7-dihydroxycoumarin) derivative. The elucidation of its structure is contained within Part III.

PART I

Pyrolyses of 3,3-Dimethylallyloxycoumarins.

a) 6,7-Dioxygenated Series.
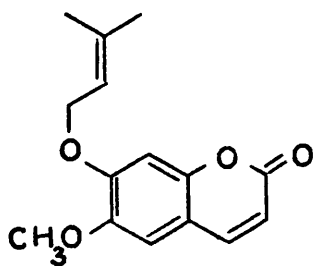
(61)
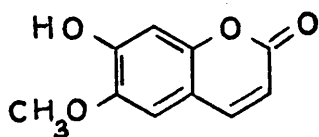
(41)
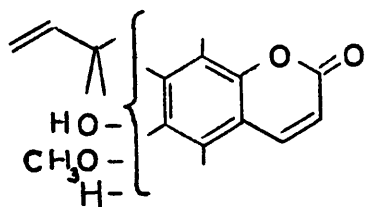
(67)
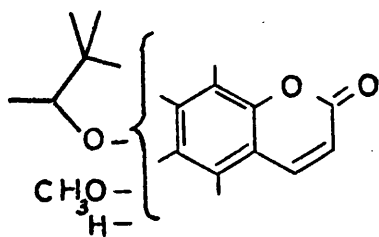
(68)

From the ethyl acetate extract of <u>Ptaeroxylon</u> <u>obliquum</u>
heartwood, McCabe, McCrindle and Murray isolated[43] three new
isomeric coumarins, $C_{15}H_{16}O_4$. One of these hydrolysed, under
acidic conditions, to the known coumarin scopoletin(41). This
degradation, when taken in conjunction with spectroscopic evidence,
enabled structure 61 to be assigned[43] to this new coumarin.
Confirmation of this structure was provided by the synthesis[62]
(<u>vide</u> <u>infra</u>) of 61 from synthetic scopoletin.

For convenience the names obliquetin and nieshoutin have
been adopted for the two other new coumarins (Introduction).
The n.m.r. spectra of these compounds enabled partial structures
67 and 68 to be assigned[62] to obliquetin and nieshoutin
respectively. At the time of this work (1966), the 1,1-dimethyl-
allyl type of side chain had only rarely been encountered in
natural coumarins. It was noted[62] that a close similarity
existed between the u.v. spectra of 67 and 68 and those of
scopoletin(41) and 7-0-(3,3-dimethylallyl)scopoletin(61) (Table 1.1).
From this it was deduced that the former must also be 6,7-dioxygen-
ated coumarins. The effect of an oxygen at C-6 of the coumarin
nucleus on the u.v. spectra of such compounds is so marked that a
6,7-dioxygenated coumarin can easily be distinguished from 5,7-
or 7,8-dioxygenated systems (Appendix). Table 1.1 also contains
several simple coumarin derivatives which have since been synth-
esised and which further illustrate the validity of this argument.

Table 1.1

U.v. spectra (nm.) in ethanol.

	λ max (log ε)				
scopoletin(41)	230 (4.12)	254 (3.68)	260 (3.63)	299 (3.69)	346 (4.06)
7-O-(3,3-dimethyl-allyl)scopoletin(61) [**]	231 (4.25)	252 (3.76)	260 (3.69)	296 (3.75)	346 (4.09)
obliquetin [**]	230 (4.08)	254 (3.60)	262 (3.56)	308[*] (3.74)	346 (3.99)
nieshoutin [**]	232 (4.19)	254 (3.50)	262 (3.46)	309[*] (3.74)	346 (4.11)
6,7-dimethoxycoumarin	229 (4.23)	251 (2.76)	257 (3.69)	293 (3.73)	344 (4.02)
5,7-dimethoxycoumarin	218[*] (4.04)	245 (3.75)	254 (3.75)	325 (4.15)	
5,7-dimethoxy-4-methylcoumarin	218[*] (4.17)	243 (3.71)	253 (3.75)	319 (4.13)	
7,8-dimethoxy-4-methylcoumarin	215[*] (4.23)	247 (3.71)	255 (3.74)	315 (4.14)	

* shoulder.

** natural samples.

An additional piece of information was obtained from the u.v. spectrum of obliquetin. The addition of a small amount of base to the ethanol solution of a hydroxy-coumarin changes the spectrum from one of a phenol to that of a phenoxide anion. The effect of this transformation on the u.v. spectrum obtained, will be discussed in greater detail in the appendix. At the moment it is sufficient to say that, under these conditions, obliquetin behaves as a 7-hydroxycoumarin. The most plausible structures for obliquetin and nieshoutin, from a biosynthetic point of view, would, therefore, be 62 and 63 respectively.

Concurrently, Dean and Taylor also isolated[45] from P.obliquum heartwood two coumarins to which they also assigned structures 62 and 63 using similar arguments. In addition, they showed[45] that acid treatment of 62 yielded 63. The latter, which they call cyclo-obliquetin, was subsequently shown by m.m.p., t.l.c., and spectral comparison to be identical to nieshoutin. There can, therefore, be little doubt that the assignments made[62] by McCabe, McCrindle and Murray were indeed correct.

Both groups of workers have pointed out that, although nieshoutin(63) possesses an asymmetric centre, the 'natural' coumarin is optically inactive and might have arisen by cyclisation of obliquetin(62) during the isolation procedure. This proposal has not so far been investigated.

The synthesis of obliquetin(62) presented an interesting
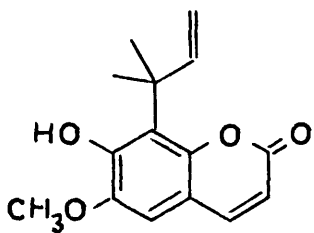
(62)

obliquetin
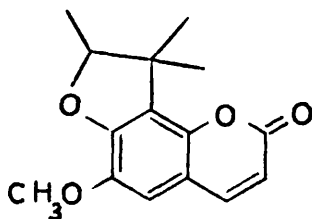
(63)

nieshoutin

cyclo-obliquetin

Scheme 1.1

(61)
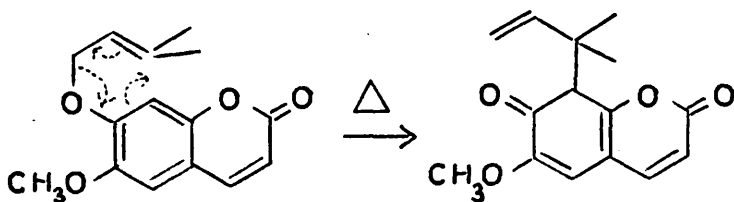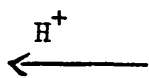
(63) $\xleftarrow{\text{H}^+}$ (62)

problem.   The co-occurrence of 61 and 62 immediately suggested
that they could be related, if not in vivo then in vitro, by a
'Claisen Rearrangement' (Scheme 1.1).   In such a way, it might
be possible to synthesise obliquetin(62), and subsequently
nieshoutin(63), from 7-O-(3,3-dimethylallyl)scopoletin(61).   A
short discussion of the Claisen and the problems involved in
effecting a 3,3-dimethylallyl ether rearrangement now follows.
Many of the points raised have a direct bearing not only on the
synthesis of obliquetin but also on the subsequent rearrangements
which were undertaken.

The 'Claisen Rearrangement'[80-82] has a long and distinguished
history.   It was first discovered by Claisen in 1912 and has
since proved to be a useful and versatile reaction, which converts
a vinyl allyl ether into a γ, δ -unsaturated carbonyl compound
(Scheme 1.2).   A fundamental property which has been especially
useful is that no matter what the stereochemistry is at position 1'
(Scheme 1.2), these rearrangements give predominantly trans-
substituted olefins [80-82].   The transition state is thought[82]
to resemble the chair conformation of cyclohexane and there is a
close agreement[83] between the observed cis/trans ratio of the
olefins and the observed axial/equatorial ratios in cyclohexane.
In recent years the sulphur[84] and the nitrogen[85] analogues of the
'Claisen Rearrangement' have grown in prominence.

Scheme 1.2
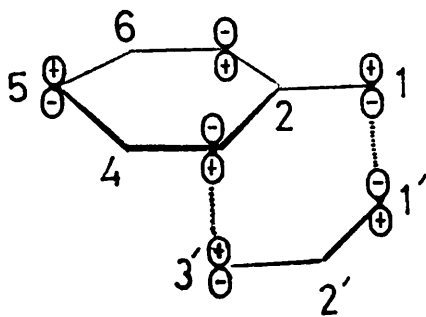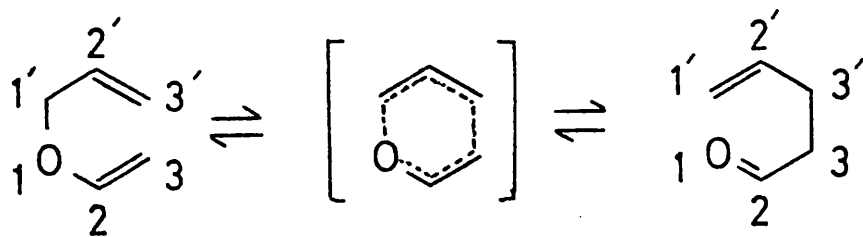
(69)

One of the most intensively investigated types of Claisen is the rearrangement of aryl allyl ethers, in which the initial rearrangement is generally followed[80] by enolisation of the resulting dienone into the corresponding phenol. The method which is usually employed to convert an aryl allyl ether into an ortho-allylphenol is to heat the ether either by itself or in a suitable solvent at approximately 200°.

The 'Claisen Rearrangement' and the all carbon analogue, the 'Cope Rearrangement', can be classified[86] as [3,3] sigmatropic rearrangements. It can be seen from Scheme 1.2 that the σ-bond, designated 1-1′, has apparently moved to position 3-3′ during the rearrangement.

A greater understanding of the 'Claisen Rearrangement' can be acquired by regarding it from the simple molecular orbital point of view developed by Woodward and Hoffmann[86] and recently utilised by Jefferson and Scheinmann in their excellent review[80] of the Claisen.

The transition state of the rearrangement of phenyl allyl ether can be regarded as consisting of two radical species held together probably in a quasi-chair conformation. This arrangement and the highest occupied molecular orbitals of each radical species are represented by diagram 69. Thus, it can be seen that the 1-1′ bond can be broken and a new bond formed at 3-3′ by a suprafacial movement, i.e. bonds are broken and formed on

the same side.   The resulting intermediate could either return
to the starting ether by the reverse procedure, enolise if there
is an available hydrogen or undergo a further suprafacial
migration (i.e. a 'Cope Rearrangement') with the new bond being
formed between carbons 5 and 1′.   Migration to carbon 5 would
constitute what is known as a 'para-Claisen Rearrangement'.
However, in the case of phenyl allyl ether itself there is no
driving force, such as hindered enolisation, to produce such a
para product.   Diagram 69 also illustrates the fact that a
concerted ortho-ortho migration would require to be antarafacial
i.e. the new bond is formed on the opposite side to the one
being broken.   Since this is not feasible, such a migration
is said[86] to be 'forbidden'.   Many of these points will be
discussed in greater detail at relevant places in the text.

The proposed synthesis of obliquetin(62) involves the
rearrangement of a 3,3-dimethylallyl ether into the ortho
position.   This type of Claisen is very unpredictable and is
often accompanied by side reactions which are generally
undesirable.   One of the problems is that the starting ether
frequently dissociates into isoprene and the parent phenol
(Scheme 1.3).   This occurrence was well illustrated by
Chaudhury, Saha and Chatterjee who showed that the pyrolysis
of 3,3-dimethylallyl ethers of 5-, 6-, 7- and 8-hydroxycoumarin
gave[87] either recovered starting material or, at higher
temperatures, the parent phenol and isoprene (Scheme 1.3).

Scheme 1.3

$175-185°$

Scheme 1.4

(70)

[3,3]
sigmatropic
rearrangement

(71)

$200-225°$

[1,5]
sigmatropic
rearrangement

(73)

(72)

OR_1

R_2

(55) $R_1 = H$, $R_2 = CH_2CH:C(CH_3)_2$
(56) $R_1 = CH_2CH:C(CH_3)_2$, $R_2 = H$
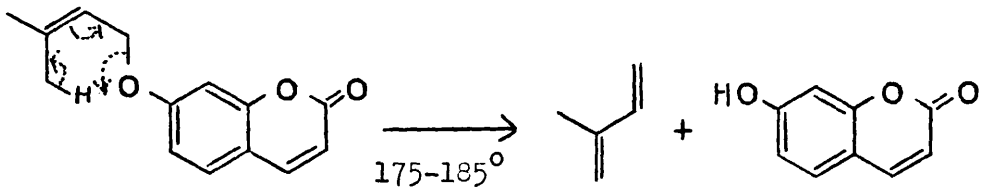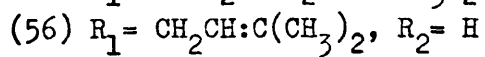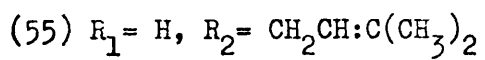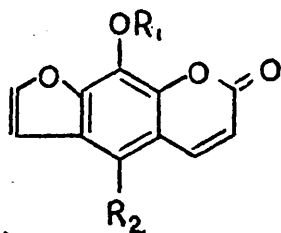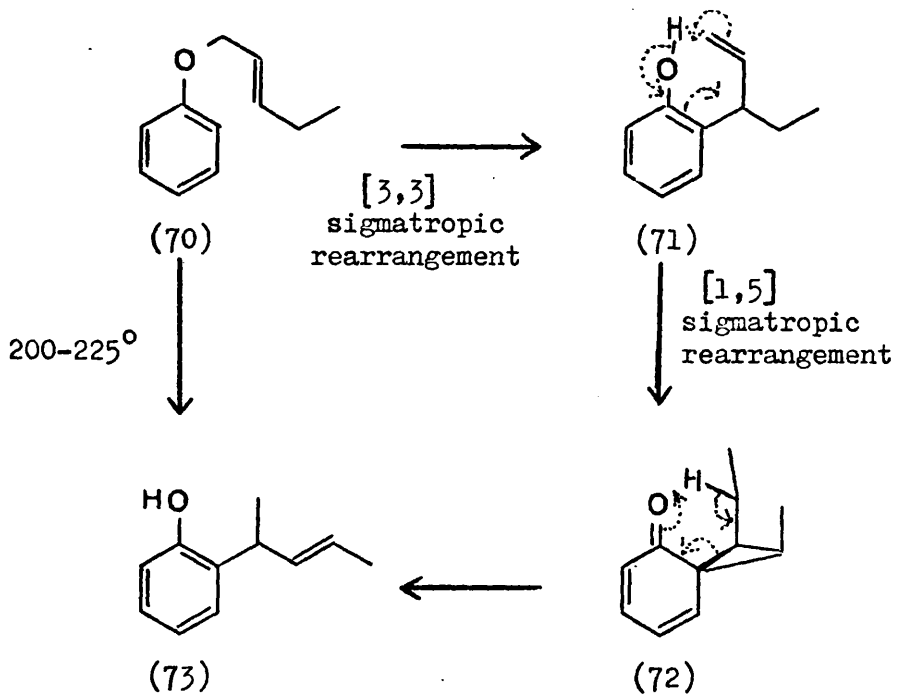
The ethers in question showed no tendency to undergo the 'Claisen Rearrangement'.

A second problem can be that, if the required rearrangement takes place, the resulting <u>ortho</u>-(1,1-dimethylallyl)phenol can cyclise to the corresponding 2,3,3-trimethyldihydro-furan (or -coumaran) system. Even heating simple allyl aryl ethers without solvent, can result[88] in the production of 2-methyldihydro-furans in fairly high yields. Cyclisation can be eliminated, in these cases, to a great extent by using N,N-diethylaniline as solvent. Fortunately in the case of obliquetin(62) such a cyclisation should result in nieshoutin(63).

The major drawback to the proposed synthesis of obliquetin(62), was the strong possibility that an 'abnormal Claisen Rearrangement'[80,89] might occur. This is really a misnomer since it implies that the 'abnormal' competes with the 'normal' and this is not the case. An 'abnormal' rearrangement is one in which the first formed 'normal' product undergoes a [1,5] sigmatropic rearrangement. Scheme 1.4 has been proposed[90] as the mechanism of the 'abnormal Claisen Rearrangement' and labelling experiments have provided[91] strong evidence to support the proposed spiro-dienone intermediate 72. From a synthetic point of view, products arising from the 'abnormal' reaction must be anticipated whenever the allyl moiety has a γ-alkyl substituent. It is fortunate, therefore, that this subsequent rearrangement is generally slower than the normal

Scheme 1.5
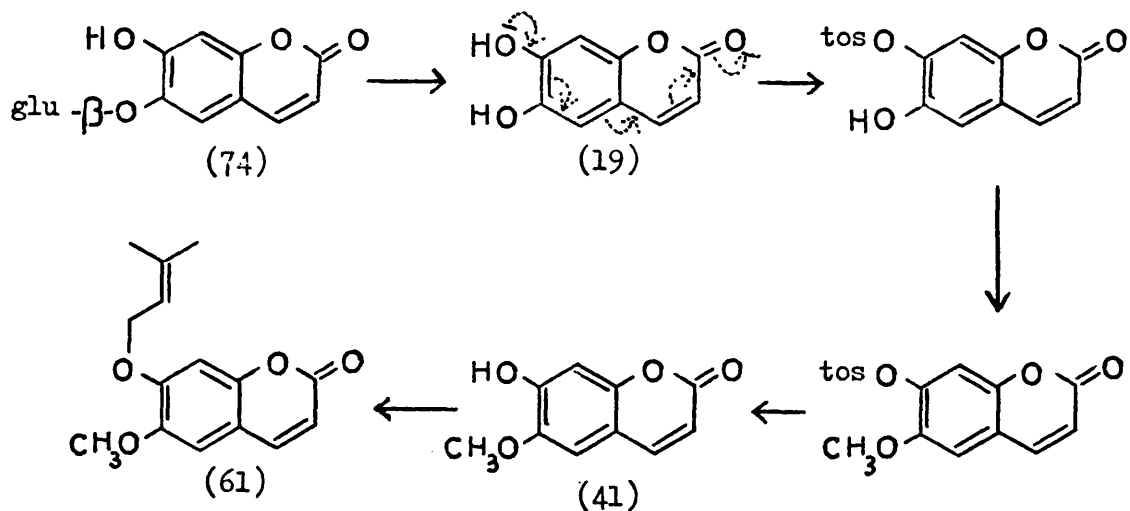
glu = glucose residue

tos = tosyl

Scheme 1.6
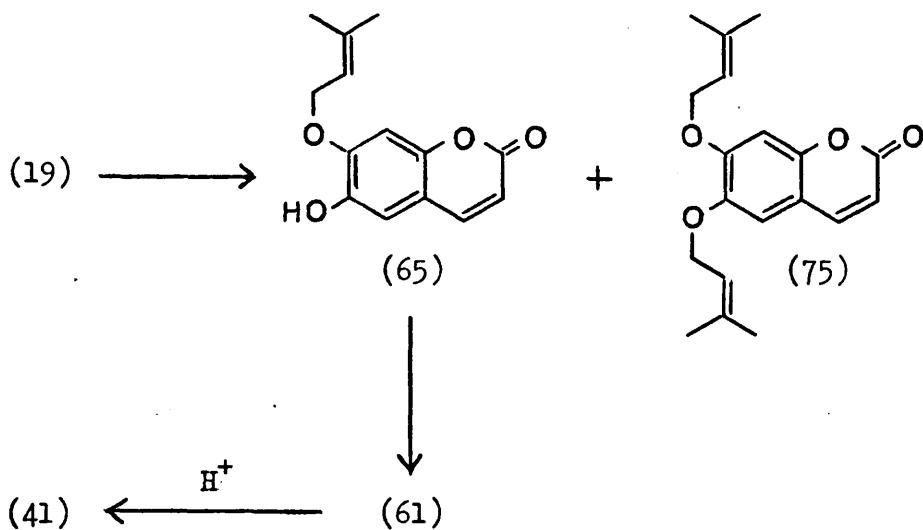
Claisen with the result that e.g. the phenol(71) can be isolated[90] if a lower temperature is used.

There is, however, one promising aspect of the pyrolysis of 3,3-dimethylallyloxycoumarins. The natural compound, imperatorin(56) has been shown[92] by Spath to rearrange very readily to allo-imperatorin(55) in 90% yield. This constitutes a facile 'para-Claisen Rearrangement'.

It appeared, therefore, that the scheme (1.1) proposed for the synthesis of obliquetin(62) had a fair chance of success and for this purpose a convenient synthesis of 7-O-(3,3-dimethyl-allyl)scopoletin(61) was sought.

This compound had already been synthesised[43,62] by Murray et al following the method[93] of Desai and Desai as outlined in Scheme 1.5. This involved hydrolysis of the commercially available aesculin(74) followed by protection of the more acidic C-7 hydroxyl of aesculetin(19). However, the overall yield of 61 was only 19% from 19.

It was known that a preferential O-alkylation of aesculetin had been effected[94] by Seshadri and Sood. They obtained 7-O-(allyl)aesculetin in 41% yield on reacting aesculetin(19) with allyl bromide and sodium bicarbonate in ethanolic acetone.

Using this approach, aesculetin was treated with a slight excess of 3,3-dimethylallyl bromide in the presence of potassium carbonate. Analytical t.l.c. was used as a monitor and the

reaction terminated when almost all of the starting material
had been converted.   The mixture obtained was separated on the
basis of solubility in very dilute aqueous sodium hydroxide
($\sim$0.5% w./v.).   The base insoluble fraction yielded the
bis-ether(75) (23%), the n.m.r. spectrum of which indicated the
presence of two 3,3-dimethylallyloxy units.   The base soluble
fraction gave one mono-ether (63%).   The n.m.r. spectrum of the
latter compound contains three broad signals which can be
attributed to the 3,3-dimethylallyl ether grouping, namely a six
proton singlet at τ 8.23, a two proton doublet (J 7 Hz.) at
τ 5.35 and a one proton triplet (J 7 Hz.) at τ 4.52.   The
phenolic nature of this compound was deduced from the following
evidence;   the one proton singlet at τ 4.30 in the n.m.r. spectrum,
which disappears on addition of deuterium oxide to the solution;
the band at 3556 cm.$^{-1}$ in the i.r. spectrum(CCl_4), which can be
attributed to an intramolecularly hydrogen bonded hydroxyl;   and the
bathochromic shift which the u.v. spectrum exhibits on addition of
base to the ethanol solution.   Since the decrease in absorption
accompanying this, is not that of a 7-hydroxycoumarin (Appendix), the
mono-ether isolated must be the required derivative (65).

The most convenient method of preparing aesculetin for the
above reaction was found to be by refluxing a solution of aesculin
(74) in methanol and conc. hydrochloric acid until hydrolysis was
complete.   An alternative method[62], which involves bubbling
hydrogen chloride into an aqueous methanol solution of aesculin

and leaving the resulting solution at room temperature, can be considerably hampered by the precipitation of aesculin from solution.

It was also noted that if much stronger solutions of aqueous sodium hydroxide was used to effect the separation of 65 and 75, the yield of 65 was considerably lowered (63% → 45-50%).

A similar procedure for the synthesis of 7-0-(3,3-dimethyl-allyl)aesculetin(65) has been employed [48] by Dean and Taylor who isolated this coumarin from P.obliquum and named it prenyletin[45,95]. Using dimethylsulphoxide as solvent instead of acetone, they obtained the bis-ether(75) (1%), prenyletin(65) (47%), the isomeric mono-ether (1.2%) and a compound (< 0.1%) to which they tentatively assigned the structure 8-(3,3-dimethylallyl)aesculetin. The last coumarin is presumably the result of a small amount of C-alkylation.

7-0-(3,3-Dimethylallyl)aesculetin(65) was converted to the required methyl ether(61) in high yield by treatment with methyl iodide in the presence of potassium carbonate. Thus, 61 has been synthesised in a 57% overall yield from aesculetin. This not only provided the coumarin required for the proposed synthesis of obliquetin but incidentally provided a useful route to scopoletin(41) since the ether 61 can be readily hydrolysed to 41 in 88% yield.

The effect of heating 7-0-(3,3-dimethylallyl)scopoletin(61)

without solvent was now investigated. This was accomplished
by having the ether in a sublimation tube which was then
partially evacuated and inserted into a sublimation block
preheated to the required temperature. The partial vacuum
appeared to reduce the tendency to char over a period of time
at higher temperatures ($\sim 200^{\circ}$). However, initially the
material tended to sublime and when this happened, the tube
was merely pushed further into the block to resubmit the
sublimate to the block temperature. Although, for 61, this
was generally sufficient, at very low pressures (~ 0.005 mm.)
it was more convenient not to have the vacuum pump constantly
evacuating the system.

After 2 hr. at 150°, there was a considerable amount of
starting ether(61) left (as estimated by analytical t.l.c. and
n.m.r spectrum of the mixture). A reasonable temperature/time
balance was obtained when the ether was pyrolysed at 195° for
2 hr. Careful separation by preparative t.l.c. yielded, apart
from recovered starting material (4%), the cleavage product
scopoletin (30%). This side reaction had been anticipated (vide
supra) but fortunately the loss by this route was not as great
as it might have been. The required ortho-(1,1-dimethylallyl)-
phenol, obliquetin(62), was also obtained but only in 9% yield.
This was quite sufficient, however, to confirm the structural
assignment made to the natural coumarin.

Figure 1.1

N.m.r. spectrum of a 1,1-dimethylallyl unit attached

to a benzenoid ring. (J Hz).
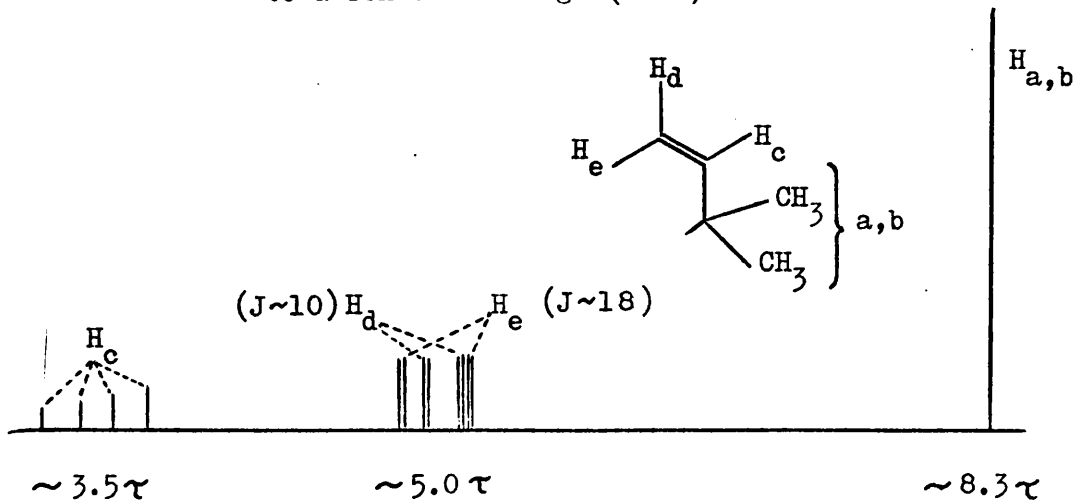
The chemical shift of H_e can be higher than that of H_d and, in that case, the downfield signals of the two doublets generally coalesce.

The n.m.r. signals of a 1,1-dimethylallyl unit are easily recognisable (Figure 1.1) and in the spectrum of obliquetin the six proton singlet at τ 8.29 can be attributed to the geminal methyls attached to a carbon which is both benzylic and allylic. The ABX system of the three olefinic protons gives rise to a one proton doublet (J_{AX} 18 Hz.; i.e. <u>trans</u> coupling) at τ 5.02 (H_A), a one proton doublet (J_{BX} 11 Hz.; i.e. <u>cis</u> coupling) at τ 5.00 (H_B) and a one proton double doublet (J_{AX} 18 Hz.; J_{BX} 11 Hz.) at τ 3.62 (H_X). In this type of system there is usually evidence of a J_{AB} in the region of 1 Hz.

The cyclic ether, nieshoutin(63) (21%), was, as had been anticipated, isolated from the pyrolysis. This synthetic coumarin was shown to be identical to the 'natural' compound isolated[43] by McCabe, McCrindle and Murray and hence to that isolated[45] by Dean and Taylor. The cyclisation of obliquetin during the pyrolysis was probably a consequence of the phenolic nature of several of the products.

The C_5 side chain of nieshoutin is, therefore, as had been deduced[43,45], in the form of a 2′,3′,3′-trimethyldihydrofuran system fused $\left[5′,4′:7,8\right]$ to the coumarin nucleus. The n.m.r. signals of this furan system in nieshoutin consist of two three proton singlets at τ 8.71 and 8.44, a three proton doublet (J 6.5 Hz.) at τ 8.57 and a one proton quartet (J 6.5 Hz.) at τ 5.45. The chemical shift of the methine proton is consistent
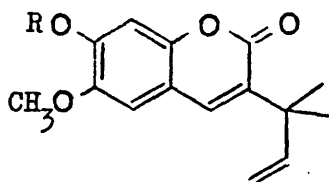
(76) R = H

(77) R = CH$_3$

Table 1.2

	Ce^{4+}
(61)	pale pink
(62)	bright purple
(63)	yellow
(76)	lilac
(77)	pale lilac
(41)	bright purple with green centre

with the presence of a secondary methyl system on a carbon bearing

oxygen.   The tertiary methyl signal at high field may be the one

cis to the secondary methyl[96].

A fourth product was isolated from the pyrolysis in 14% yield.

It is isomeric with obliquetin and nieshoutin and is undoubtedly

the most interesting.   That it was a 7-hydroxycoumarin was

deduced from the band at 3515 cm.$^{-1}$ in the i.r. spectrum $(CHCl_3)$

and from the bathochromic shift of u.v. spectrum observed on

addition of base.   However, unlike obliquetin, the n.m.r.

spectrum of this compound had two one proton singlets at τ 3.18

and 3.14 which indicates the presence of two para aromatic protons.

The usual AB system of the α -pyrone double bond has been replaced

by a one proton singlet at τ 2.51, implying that substitution

has occurred at C-3.   The remainder of the spectrum is easily

recognisable as that of a 1,1-dimethylallyl unit $\left[(\tau \text{ 8.55; 6H; s),} \right.$

$(\tau$ 4.96; 1H; d; J 18 Hz.), $(\tau$ 4.93; 1H; d; J 10 Hz.), $(\tau$ 3.82; 1H;

d/d; J 18 & 10 Hz.)$\left. \right]$ which on the above evidence can be placed at

C-3.   Structure 76 is therefore assigned to this pyrolysis product.

Methylation of 76 (methyl iodide and potassium carbonate) readily

afforded the methyl ether(77).

Before discussing this interesting pyrolysis product further,

the use of analytical t.l.c. as a pre-spectroscopic tool must be

noted.   Table 1.2 indicates how it is possible to identify many

of these coumarins by simply spraying a chromatoplate with a cold

Scheme 1.7

(41)

(78)

(61)

(79)

(80)

(62)

(81)

(76)
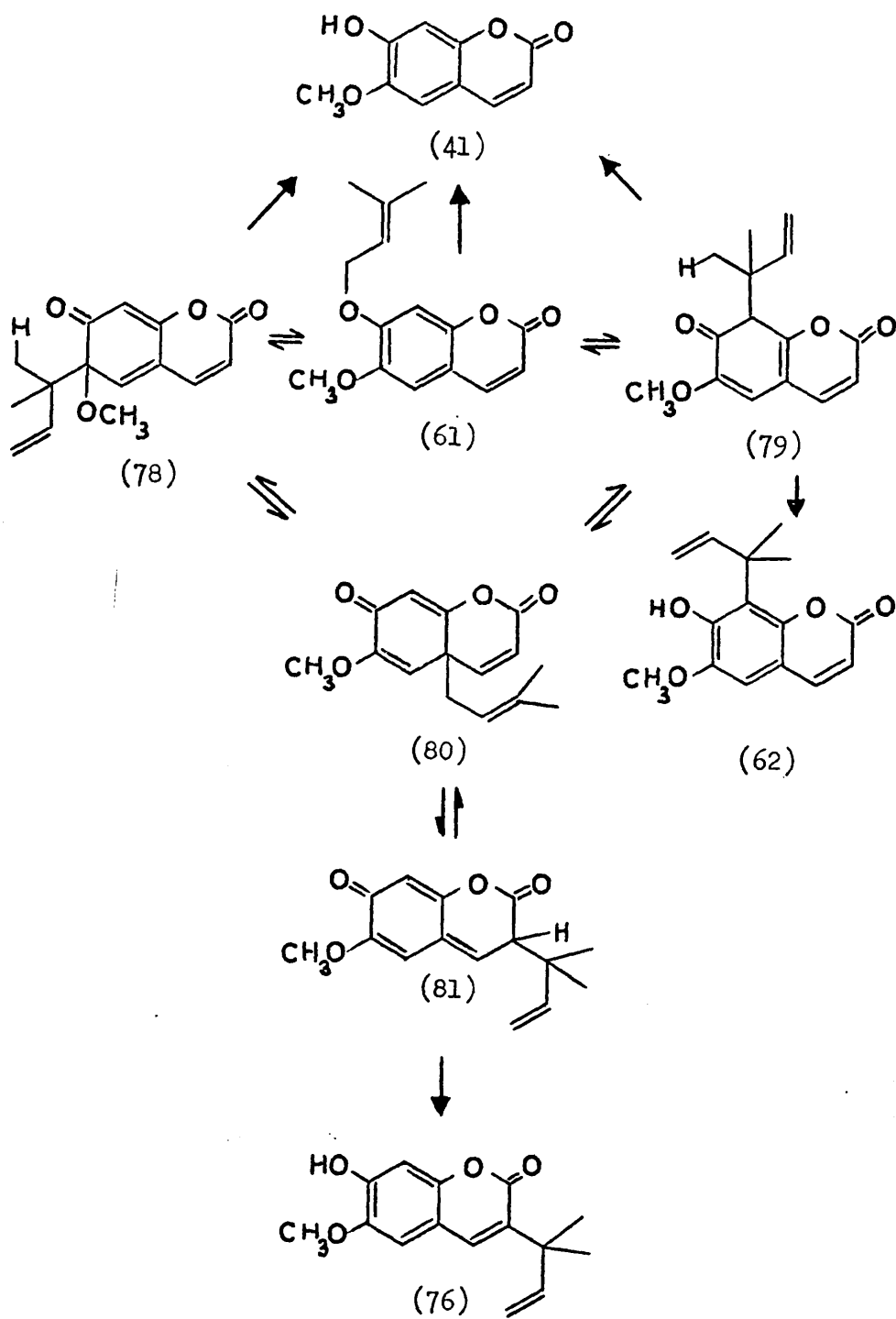
solution of acidic ceric ammonium sulphate (for preparation see General Experimental). The different intensities of colouring mean that this is of little use as a semi-quantitative method. However, it enables a fairly good estimation to be made as to which coumarins might be present in a mixture of compounds with similar polarities. This property, common to most of the coumarins encountered in the course of this research, has proved to be exceptionally useful.

In retrospect, the 'out-of-ring' compound(76) might have been expected from the pyrolysis of 7-O-(3,3-dimethylallyl)-scopoletin. Assuming that rearrangement of the dimethylallyl ether can take place to both <u>ortho</u> positions, two pathways, outlined in Scheme 1.7, can be envisaged which would give rise to the 'out-of-ring' compound. Both require intermediate 80, the result of a '<u>para</u>-Claisen Rearrangement'.

Rearrangement of the dimethylallyl unit to the free <u>ortho</u> position (C-8) would give 79. If the side chain in 79 takes up a pseudo-equatorial conformation (diagram 82), 79 could enolise to give obliquetin(62), rearrange back to the starting ether(61) or dissociate to scopoletin(41) and isoprene. However, in this conformation there could be an interaction[80] between the 'equatorial' side chain and the substituents <u>ortho</u> to it. This might be sufficient to enable the side chain to adopt a pseudo-axial conformation (diagram 83). A 'Cope Rearrangement' would
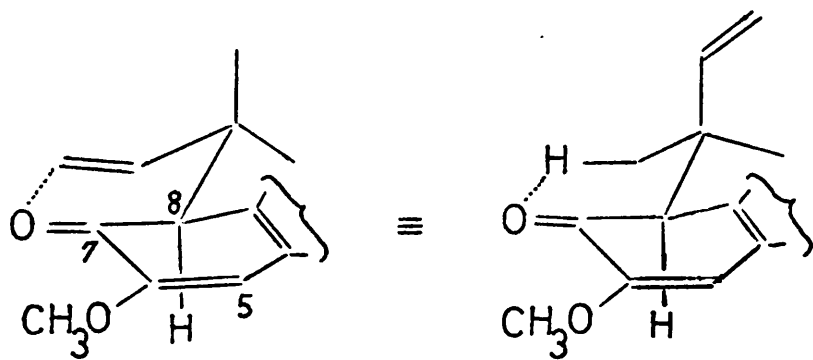
(82)
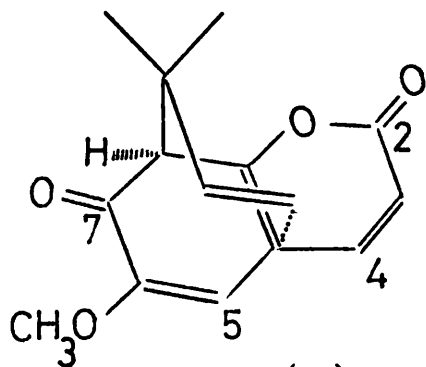
(83)
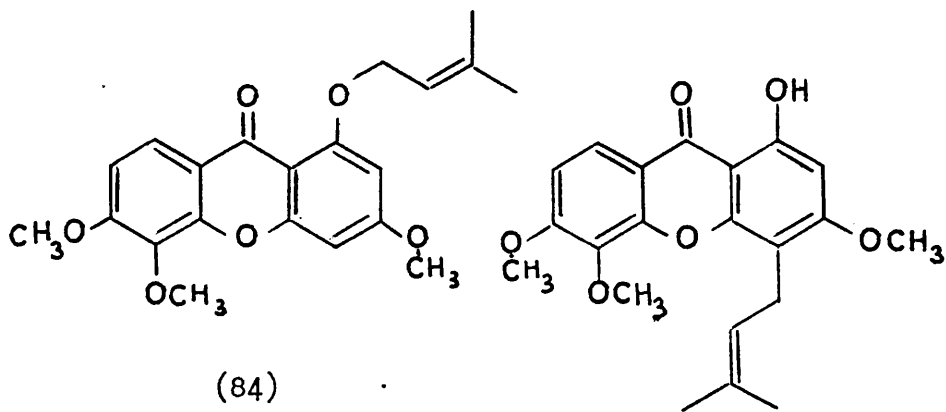
(84)

(85)

then give intermediate 80 (Scheme 1.7).

Similar arguments can be applied if it is assumed that
rearrangement of the dimethylallyl unit of 61 also takes place
to the blocked ortho position (C-6). From a study of models
there seems less chance of the side chain of 78 adopting the
pseudo-axial conformation required for rearrangement to 80.
However, until there is more concrete evidence, it must be
assumed that either or both of these pathways could be the
route to the observed 'out-of-ring' rearrangement.

In the case of the xanthone 84, it has been postulated[97]
that the para product 85 is the result of rearrangement via
the free ortho position since the corresponding allyl ether
gives only the ortho product. It might be possible, however,
that 85 could arise via both ortho positions since 3,3-dimethyl-
allyl ethers can rearrange to the para position when all ortho
and meta positions are blocked[92].

With regard to the 'out-of-ring' compound 76, the migration
of an allyl grouping into a benzenoid ring and then out of it,
is not unusual and has been observed[80] several times. The
exception appears to be when the acceptor double bond for the
'out-of-ring' rearrangement is part of a benzene ring.

The synthesis of 3-(1,1-dimethylallyl)scopoletin(76) takes
on added interest when it is known that several 3-(1,1-dimethyl-
allyl)coumarins[98,99] have been isolated from natural sources.

Scheme 1.8

(86)

(87)ᵃ

(88)ᵇ

(89)ᵇ

(90)ᵇ
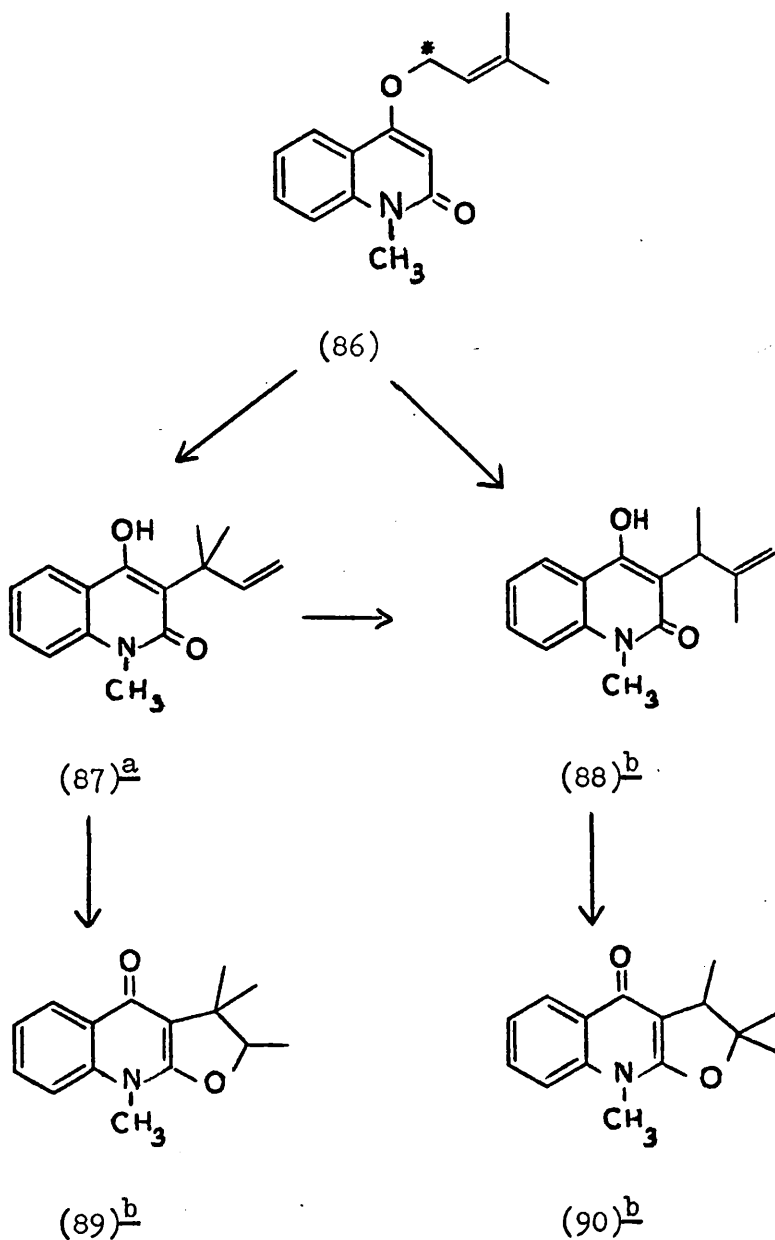
a has not been isolated from a natural source.
b optically active natural alkaloids.
* position of C^{13} in the labelling experiment.
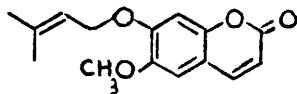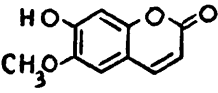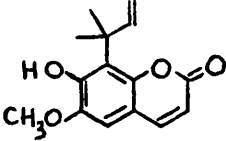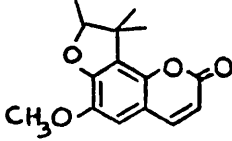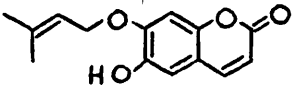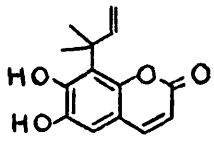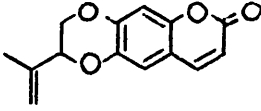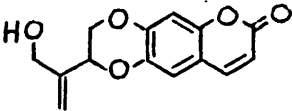
Those, in the literature, are all umbelliferone derivatives, the simplest being 3-(1,1-dimethylallyl)herniarin[99]. It seems unlikely that the biosynthesis of such compounds involves a reaction with dimethylallylpyrophosphate at its tertiary centre, similar to that suggested to account for the natural occurrence of ortho-(1,1-dimethylallyl)phenols. However, several authors have proposed[36,62,100] that these 'inverted isoprene' units could arise by an in vivo Claisen Rearrangement. This proposal is strengthened by the above in vitro synthesis of a 3-(1,1-dimethylallyl)coumarin.

Grundon and his collaborators have investigated[36] the biosynthesis of the 'inverted isoprene' unit in the alkaloid field. Alkaloids 89 and 90 have been isolated[36,101] from Flindersia ifflaiana F. Meull and 86 and 88 from[102] Ravenia spectabilis Engl. Scheme 1.8 has therefore been proposed[36] as a possible biosynthetic route to these alkaloids. Grundon has shown[36] that after feeding labelled ravenine(86) to R.spectabilis, radioactive ravenoline(88) was isolated and that this result was not a consequence of rearrangement of labelled 86 during isolation.

It is perhaps significant that 88, the product of an 'abnormal Claisen Rearrangement' is a natural alkaloid and is also the product isolated[103] on pyrolysis of the ether 86 unless the first formed phenol 87 is trapped as an ester.

Table 1.3

	1.	2.	3.
(structure)	+		
(structure)			+
(structure)	+		+
(structure)	+		+
(structure)		+	+
(structure)		+	+
(structure)		+	+
(structure)		+	+

1. Murray et al : P.obliquum : source ; unknown[43].

2. Dean et al : " : " ; Kokstadt[45].

3. Dean et al : " : " ; Lushoto[45].

+ present in sample

There is no parallel for the optically active side chains found in the alkaloids 88, 89 or 90 in the coumarin field.

The theory that the natural coumarins having a 1,1-dimethylallyl unit at C-3 could arise by an _in vivo_ 'Claisen Rearrangement' of the corresponding 7-(3,3-dimethylallyloxy)coumarin, or a closely related precursor, is further strengthened by the recent discovery[104] by Steck and his co-workers of rutacultin in _Ruta graveolens_ cell cultures. This coumarin has been shown to be identical to the methyl ether of 3-(1,1-dimethylallyl)scopoletin(76) which was synthesised above.

Although a preliminary investigation of the crude extract of _P.obliquum_ by analytical t.l.c. has not revealed the presence of coumarin 76, a fuller investigation is required before any definite conclusions can be reached. It is possible that, just as in _in vitro_ systems the _ortho_ product can be enhanced by a solvent which favours enolisation, the system operating in _P.obliquum_ might exclude the formation of the 'out-of-ring'.

One interesting feature which emerges on surveying the 6,7-dioxygenated coumarins which have been isolated from three samples (Table 1.3) of _P.obliquum_, is that the sample from Lushoto appears to combine the coumarin characteristics of the other two.
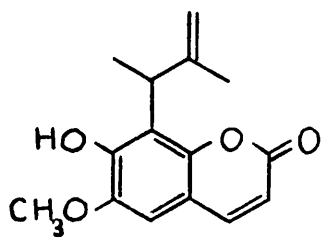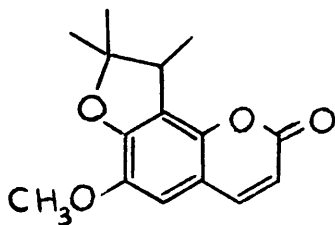
(91)   (92)

Scheme 1.9
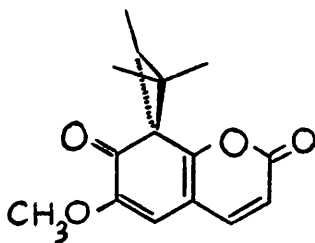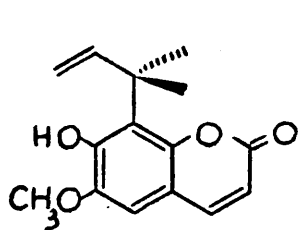
There are a few results from the pyrolyses of 7-0-(3,3-dimethylallyl)scopoletin(61) which have not yet been satisfactorily explained. One pyrolysis which was performed under conditions almost identical to those employed for that whose results have been quoted, gave somewhat anomalous results. To aid separation the mixture obtained from the pyrolysis was separated into a base insoluble fraction and a base soluble. The former gave approximately 26% yield of a mixture of nieshoutin(63) (major component) and the starting ether(61) and the latter gave scopoletin(41) (26%), the 'out-of-ring' compound (76) (13%) and a new phenolic compound (7.5%). This new coumarin had the same t.l.c. characteristics as obliquetin but its n.m.r. spectrum possesses a three proton doublet (J 7 Hz.) at τ 8.49, a three proton singlet at τ 8.30, a one proton quartet (J 7 Hz.) at τ 5.78 and a two proton broad singlet at τ 5.03. This n.m.r spectrum is consistent with structure 91, the product of an 'abnormal Claisen Rearrangement'. This was confirmed by the acid catalysed cyclisation of 91 to the cyclic ether 92. The n.m.r. spectrum of the latter compound possesses a benzylic secondary methyl system (τ 8.66; 3H; d. and τ 6.59; 1H; q; J 7 Hz.) and two tertiary methyls (τ 8.54; s) which can be attributed to the gem-dimethyl group on a carbon bearing oxygen.

It had already been demonstrated several times that under these conditions, the normal product was formed. At first,

it was thought that the base separation had merely catalysed
the rearrangement of the normal to the abnormal product.
This subsequent rearrangement would tend to relieve the steric
interaction between the gem-dimethyls and the adjacent
substituents (Scheme 1.9).   However, base catalysation of
this rearrangement is unknown.

When the pyrolysis was performed for a longer period of
time (195°/4 hr.), the isomer 91 was isolated with no base
treatment.   The fact that this isomer does not cyclise readily
under the thermal conditions being used, explains why nieshoutin
(63) was isolated from each pyrolysis and not a mixture of 63
and the isomeric cyclic ether.

The abnormal Claisen is generally a slower reaction which
is promoted[90] by an increase in temperature or time.   However,
the question as to whether the base separation, discussed above,
did in fact promote the production of the abnormal, has not yet
been answered, although it is suspected that this was not the
cause.   The efforts which were made to answer this question are
discussed at the end of Part Ic.
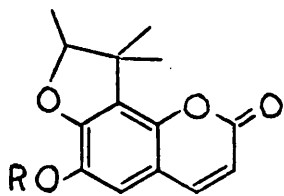
(62) R = CH₃
(93) R = H
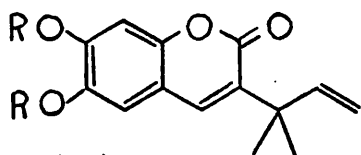
(94) R = H
(77) R = CH₃
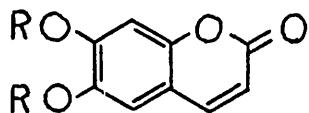
(19) R = H
(95) R = CH₃
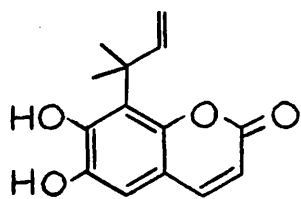
(66)
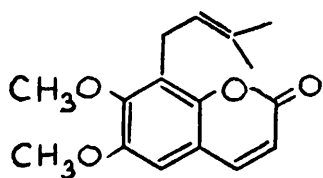
(96)

At the time, the 'out-of-ring' compound was considered to
be of more interest than the ortho products.   Since 7-0-(3,3-
dimethylallyl)aesculetin(65) was readily available, an
investigation into the pyrolysis of 65 was undertaken to
determine the difference, if any, on the amount of 'out-of-ring'
obtained.   The same method was employed as for the previous
pyrolyses.   After 15 min., the oil solidified and after a
further 25 min., the pale yellow solid began to char.   From
analytical t.l.c., there appeared to be more compounds than had
been expected and the polar nature of some of the products made
recovery difficult from preparative chromatoplates. Nevertheless,
pyrolysis at 198° for 40 min., yielded in addition to an
undetermined amount of starting material, the cleavage product
aesculetin(19) (19%) and 6-demethylnieshoutin(93) (10%).
Both of these percentages are probably slightly lower than they
should be, the former due to low recovery from chromatoplates
and the latter due to the fact that it was not totally isolated
from the mixture.   The spectroscopic data obtained for 93 is
in complete accord with the structure proposed.   This compound
was later synthesised by treatment of nieshoutin with hydrogen
bromide in glacial acetic acid (Part III).   A third product
of the above pyrolysis was identified as 3-(1,1-dimethylallyl)-
aesculetin(94) (10%).   The n.m.r. spectrum of this compound
in deutero-dimethylsulphoxide indicates the presence of a

1,1-dimethylallyl unit at C-3, a proton at C-4 and two para

aromatic protons at C-5 and C-8.

Although the method employed for the pyrolysis was unsatis-

factory from the point of view of charring and insolubility of

the products, it did show that the replacement of a C-6 methoxyl

for a C-6 hydroxyl had little effect on the production of the

'out-of-ring' type compound.   An added incentive to investigate

this pyrolysis had been that the natural coumarin, obliquetol

(66), isolated[45] by Dean and Taylor, should be the ortho product

of this rearrangement.   Unfortunately, although this compound

might have been present it was not isolated.   An alternative

method would be required to further investigate the rearrange-

ment of 65.

The migration of the dimethylallyl unit to C-3 was confirmed

by heating 7-O-(3,3-dimethylallyl)aesculetin(65) at 170° for

60 min. and methylating the mixture obtained with methyl iodide

and potassium carbonate.   This afforded several compounds of

very similar polarity, but by careful preparative t.l.c. a few

were isolated and identified;   namely, scoparin(95) (29%),

3-(1,1-dimethylallyl)scoparin(77) (11%) and a third coumarin

(~ 2%) isomeric with 77.   The first two had been synthesised

earlier and were easily identified.   However, the type of n.m.r.

spectrum exhibited by the third had not been encountered previously.

The signals are reminiscent of the familiar 3,3-dimethylallyloxy

grouping but with the broad doublet at τ 6.42 instead of τ 5.5. It was deduced that the observed signals represented a 3,3-dimethylallyl unit attached to the benzenoid ring. Since it was difficult to envisage how this isoprene unit could have become attached to C-5, it is proposed that the structure of this minor component is 8-(3,3-dimethylallyl)-scoparin(96). The occurrence of this compound can be explained in two ways. It could have been the result of a small amount of impurity in the starting material, C-alkylation of aesculetin(19) giving rise to 8-(3,3-dimethylallyl)aesculetin, but since this would require at least 3-5% of C-alkylation, the following explanation is preferred. This involves an ortho-ortho type of rearrangement which, as was mentioned earlier, is 'forbidden' by the Woodward-Hoffmann rules, assuming that the highest occupied orbital involved in the coumarin 'radical' is analogous to the phenoxyl one discussed earlier. A compound was subsequently isolated which could not be due to a C-alkylation impurity. Therefore, a discussion of these pseudo-ortho-ortho rearrangements will be deferred until then.

The 'out-of-ring' Claisen is now known to occur in both the aesculetin and scopoletin series. The effect of a C-4 methyl was therefore investigated. 4-Methylaesculetin(97) was readily prepared[105] from quinone and by a similar method to that employed for the synthesis of 7-0-(3,3-dimethylallyl)aesculetin(65), 97 was

(97) $R_1 = R_2 = H$

(98) $R_1 = CH_2CH:C(CH_3)_2$ $R_2 = H$

(99) $R_1 = CH_2CH:C(CH_3)_2$ $R_2 = CH_3$
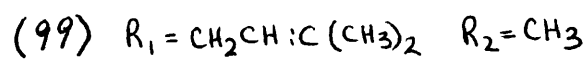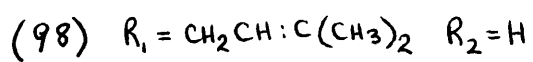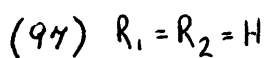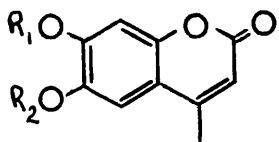
converted into 7-0-(3,3-dimethylallyl)-4-methylaesculetin(98).

The n.m.r. spectrum of 98 is very similar to that of 65, except

that the α-pyrone AB system has been replaced by a broad one

proton singlet at τ 3.87 and a three proton singlet, τ 7.67.

The bathochromic shift of the u.v. spectrum observed on adding

base to an ethanol solution of 98 confirmed that the required

isomer had been isolated. Methylation of 98 using methyl iodide

and potassium carbonate yielded 7-0-(3,3-dimethylallyl)-4-methyl-

scopoletin(99).

Numerous pyrolyses of 99 were performed under similar

conditions (150-220°/partial pressure) to those used previously.

No evidence for an 'out-of-ring' rearrangement was obtained.

Since the chromatographic behaviour of the 4-methylscopoletin

derivatives is comparable with that of the scopoletin counter-

parts, special care was taken to investigate the polarity region

in which such an 'out-of-ring' compound might be found. There

were at least two minor products in this region but 100 MHz. n.m.r.

spectra of the mixture ($<$1% of recovered pyrolysis material)

never revealed any trace of a 1,1-dimethylallyl grouping. The

C-4 methyl substituent would, therefore, appear to eliminate the

tendency of the isoprene unit to migrate out to C-3. No matter

whether the C_5 side chain of intermediate 100 adopts a pseudo-

axial or pseudo-equatorial conformation with respect to the dienone

ring, it is possible to envisage (diagram 100) the chair type of

(100)
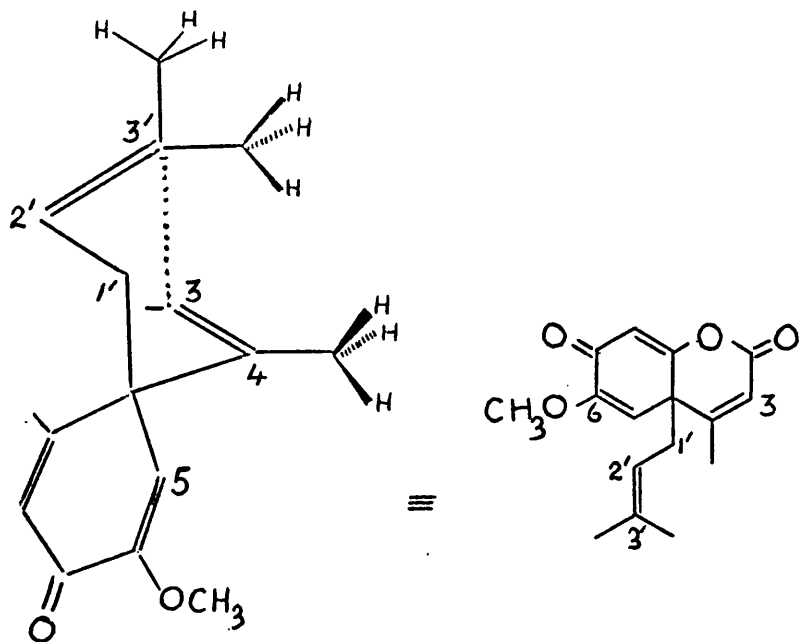
n.m.r. signals (τ); coupling constants in Hz.

5.08   5.07

(J 10) H   H (J 18)

3.63
(J 18   H
& 10)   } 8.28

HO

CH$_3$O

6.03

H
3.17

(103)
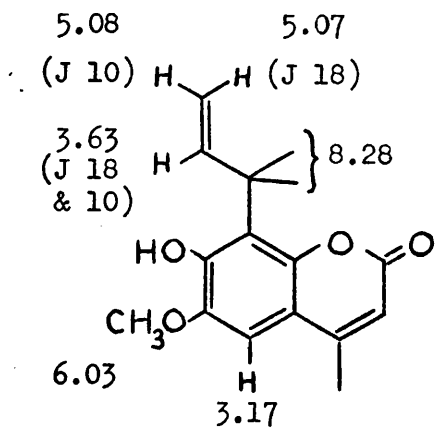
transition state which would give rise to the 'out-of-ring'.
However, the 1,3-diaxial type interaction must be great enough
to prohibit the formation of such a transition state and thus
the 'out-of-ring' rearrangement.

These pyrolyses did, however, produce some interesting
results with respect to <u>ortho</u> substitution. After heating
7-0-(3,3-dimethylallyl)-4-methylscopoletin(99) at 200° for 1 hr.
under partial pressure,the following results were obtained.
In addition to the cleavage product, 4-methylscopoletin(101)
(29%), the cyclised <u>ortho</u> product, 4-methylnieshoutin(102) (15%)
was obtained. The n.m.r. spectrum of the latter compound is
so similar to those of nieshoutin(62) and 6-demethylnieshoutin
(93) to be unmistakable. The remainder of the material from
the above pyrolysis consisted mainly of two compounds which
were barely separable on analytical t.l.c. The n.m.r. spectrum
of the mixture indicated that the major component was the
starting ether 99 (~38%). The signals (given on structure
103 opposite),discernible from those of 99,are sufficient to
identify the minor component as 4-methylobliquetin(103) (~7%).
The u.v. spectra of this mixture indicates the prescence of some
phenolic material, which is consistent with the above assignments.

Thus, although no 'out-of-ring' compound was obtained,
7-0-(3,3-dimethylallyl)-4-methylscopoletin(99) does rearrange
to the normal <u>ortho</u> product with subsequent cyclisation.

(104)

5.04 5.76
H
[8.33] 8.49
3.57 HO O O
[6.07]CH$_3$O H[3.88]
3.15 H
[7.62]

(105)

8.17, [8.33]
6.46 H 4.75
3.74 HO O O
[6.07]CH$_3$O H[3.88]
3.21 H [7.62]

(91)

5.03 5.78
H
8.30 8.49
3.60 HO O O
6.09 CH$_3$O H 3.75
3.24 H 2.42 H

(106)

8.16, 8.32
6.43 H 4.72
3.77 HO O O
6.07 CH$_3$O H 3.79
3.29 H 2.46 H

(96)

8.17, 8.29
6.42 H 4.92
6.20 { CH$_3$O O O
6.07 { CH$_3$O H 3.73
3.25 H 2.23 H
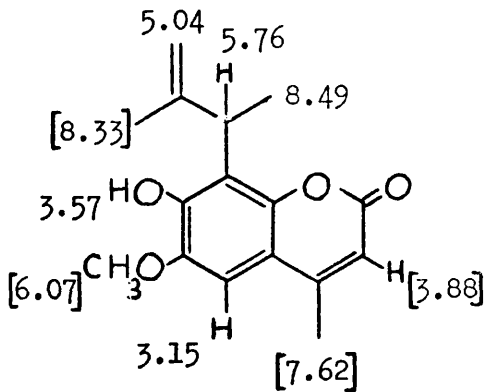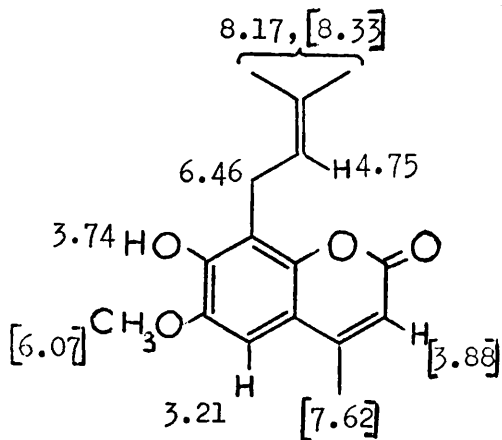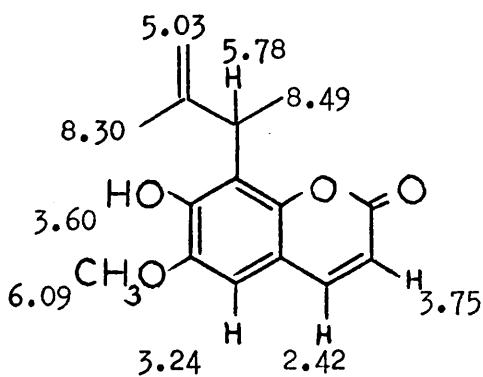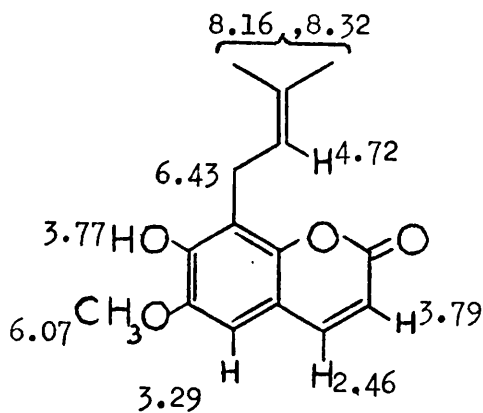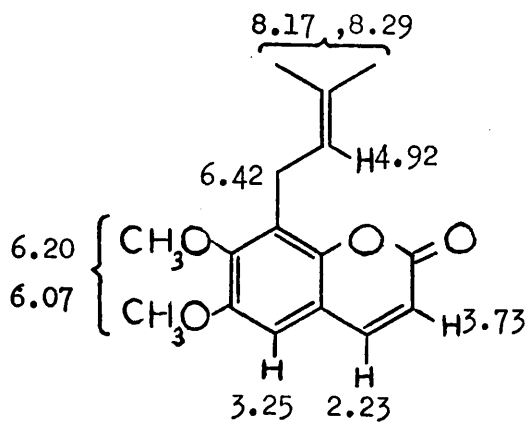
The percentage cleavage, relevant to the amount of starting

material consumed, is somewhat higher than in the scopoletin

series.

In an attempt to decrease the amount of starting material

and thus facilitate the separation of 4-methylobliquetin(103),

the above pyrolysis was repeated, the temperature being maintained

at 200° for 3 hr. instead of 1 hr.   After this time no starting

material could be detected by analytical t.l.c., but there were

still four compounds in the mixture obtained.   Two of these

were 4-methylscopoletin(101) (38%) and 4-methylnieshoutin(102)

(28%).   The remaining two could not be separated by preparative

t.l.c.   The n.m.r. spectrum (100 MHz.) of this mixture indicates

the presence of a 1,2-dimethylallyl side chain, i.e. the product

of an abnormal Claisen, and of a 3,3-dimethylallyl side chain, i.e.

the product of an 'ortho-ortho' rearrangement.   Since these

two units were present in the mixture in a ratio of approximately

2:1 (as estimated from the integration of the spectrum), it is

possible to some extent to allocate associated signals.   It is

estimated that 8-(1,2-dimethylallyl)-4-methylscopoletin(104) and

8-(3,3-dimethylallyl)-4-methylscopoletin(105) were present in

approximately 6% and 3% respectively.   The n.m.r. signals (τ)

indicated opposite, are those assigned to 104 and 105 from the

spectrum of the mixture.   The values in brackets represent

those which are either common to both or are too close to be

Scheme 1.10

(99) → (107) → [bridged intermediate] → (104) ← [enone intermediate]

Scheme 1.11

(108) → (109) → (110) → (111) → (112)

distinguished. A comparison of the n.m.r. signals assigned to these two coumarins with those of 8-(1,2-dimethylallyl)scopoletin(91) (vide supra), 8-(3,3-dimethylallyl)scopoletin(106) (Part II) and 8-(3,3-dimethylallyl)scoparin(96) (vide supra) indicates the validity of the above structural assignments. The u.v. spectra of the mixture of 104 and 105 confirms that it is phenolic and that probably both components are 7-hydroxycoumarins (Appendix). In addition, the mass spectrum contains only a parent ion at m/e 274. There is no sign of m/e (274+14) or (274-14) which would have indicated a C_5 side chain on a scoparin or an aesculetin nucleus. It would appear, therefore, that both of these compounds are genuine pyrolysis products.

The isolation of 8-(1,2-dimethylallyl)-4-methylscopoletin(104) can be rationalised on the basis of an 'abnormal Claisen Rearrangement'. It is quite feasible that the normal product would be detected after a 1 hr. pyrolysis at 200° and the abnormal after 3 hr. The isolation of 8-(3,3-dimethylallyl)-4-methylscopoletin (105), however, albeit in only 3% yield, is not quite so easily rationalised. Two mechanisms have been proposed to account for such 'ortho-ortho' rearrangements. The first, suggested by Schmid[82], involves an internal Diels Alder and is illustrated in Scheme 1.10. The second (Scheme 1.11) has been proposed by Waight[106] to accommodate the fact that pyrolysis of a β-naphthol ether 108 yields a dihydrochroman(112). He has shown that the

first formed phenol is the normal Claisen product 109, so therefore Schmid's pathway cannot hold in this case. Since the same results were obtained in the presence of radical scavengers, it seems unlikely that 112 arises by a radical mechanism as do the products of some thio-Claisen Rearrangements[107]. Waight has, therefore, proposed[106] the spirocyclobutane intermediate 110 which, although not stated, presumably isomerises by a [1,5] sigmatropic rearrangement to 111. Both of these mechanisms could account for many unexplained ortho-ortho rearrangements[80,108].

In the case of the coumarin (104), it seems reasonable that should intermediate 107 be formed and take up a pseudo-axial conformation, the internal Diels Alder outlined in Scheme 1.10 would provide an alternative to migration to C-3. It must be noted, however, that a similar 'ortho-ortho' rearrangement product was isolated from the pyrolysis of 7-O-(3,3-dimethyl-allyl)aesculetin and in this case 'out-of-ring' migration takes place. The normal Claisen product, 4-methylobliquetin, is known to be present at some time during the pyrolysis. It is, therefore, conceivable that the spirocyclopropane which leads to the abnormal product has competition from the spirocyclobutane[106] intermediate.·

Part of this work has been summarised in a short communication[44].

b) <u>7-Mono-oxygenated Series.</u>

R_2O —[structure: 7-substituted coumarin ring system with O and O at top, R_1 at bottom]

(4) $R_1 = R_2 = H$

(16) $R_1 = H$, $R_2 = CH_3$

(113) $R_1 = H$, $R_2 = CH_2CH:C(CH_3)_2$

(114) $R_1 = H$, $R_2 = CH_2CH:CH_2$

(115) $R_1 = CH_3$, $R_2 = H$

(116) $R_1 = CH_3$, $R_2 = CH_2CH:C(CH_3)_2$
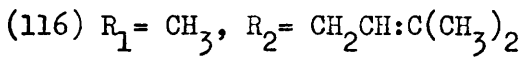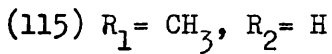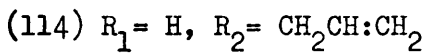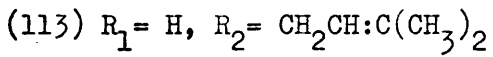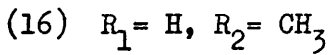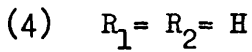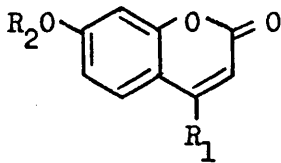
Now that it was known that the 6,7-dioxygenated coumarins,
described previously, all showed some tendency to undergo the
'Claisen Rearrangement', it was surprising that no such tendency
had been observed by Chaudhury, Saha and Chatterjee[87] for the
3,3-dimethylallyl ethers of the mono-oxygenated coumarins.
Since coumarins such as 7-0-allyl-umbelliferone(114) readily
rearrange[109], it may be that loss of isoprene in the cases
described by Chaudhury et al is such that the 'Claisen Rearrange-
ment' is not a competing reaction.   It was decided to re-examine
the pyrolysis of 7-0-(3,3-dimethylallyl)umbelliferone(113) and
since the 4-methyl analogue could be readily synthesised, this
ether 116 was also investigated.

Umbelliferone(4)[110] and 4-methylumbelliferone(115)[111] were
prepared from resorcinol.   They were then converted in the
usual way (3,3-dimethylallyl bromide and potassium carbonate)
to the corresponding 3,3-dimethylallyl ethers, 113 and 116
respectively.   The n.m.r. spectra of these two ethers and that
of herniarin(16), prepared by methylation of 4, indicate that
the C-8 proton signal is normally at only slightly higher field
than the C-6 and that the C-5 proton signal is approximately
0.5 ppm lower than the other two.

Numerous pyrolyses of 7-0-(3,3-dimethylallyl)umbelliferone(113)
were performed over a temperature range 185-235°, without solvent.
The results obtained confirmed the report by the Indian workers[87]
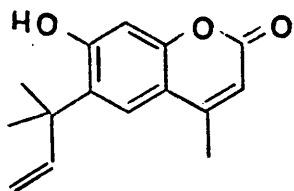
(117)
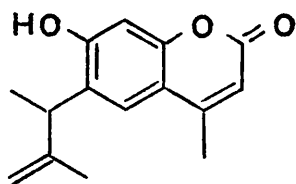
(118)
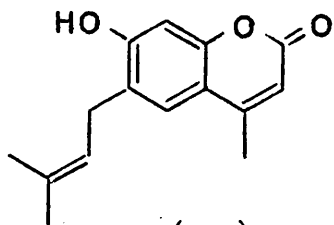
(119)

that only cleavage to umbelliferone(4) occurs.   In the present

study, several minor products could be observed when analytical

t.l.c. plates were viewed under an ultra-violet lamp, but they

could not be isolated in sufficient quantity to enable identification.

   The second ether, 7-O-(3,3-dimethylallyl)-4-methylumbelliferone

(116), gave more promising results.   Using the same method as was

employed for the 6,7-dioxygenated coumarins, this ether was heated

at 196° for 2 hr. under partial pressure.   Although analytical

t.l.c. and n.m.r. indicated that some starting material remained,

it was not possible to estimate accurately how much of 116 was

contained in the mixture of compounds (of similar polarity) which

was obtained from preparative t.l.c.   The cleavage product,

4-methylumbelliferone(115), was isolated, however, in 22% yield.

Three other phenolic compounds were isolated.   The n.m.r. spectrum

of one of these clearly indicates a phenolic hydroxyl (confirmed

by i.r. and u.v. spectra), a 1,1-dimethylallyl unit and two para

aromatic protons.   The chemical shift values (Υ 3.13 and 2.55)

of these aromatic protons are consistent with the values associated

with the C-8 and the C-5 protons of a 4-methylumbelliferone nucleus.

This coumarin, isolated in 15% yield from the pyrolysis, is there-

fore allocated structure 117, i.e. the product of a normal 'Claisen

Rearrangement' into position C-6.   The two other products isolated,

in approximately 2% and 1.4% yield, possess n.m.r. spectra very

similar to that of 117 except that signals for a 1,1-dimethylallyl

unit had been replaced by those of a 1,2-dimethylallyl unit in one compound, and by those of a 3,3-dimethylallyl unit in the other. Structures 118 and 119 are therefore assigned to these minor products. The former is the product of an 'abnormal Claisen Rearrangement' and the latter of an 'ortho-ortho' rearrangement.

Although it was gratifying to isolate rearrangement products, it was disturbing to discover that substitution had occurred at C-6 in those isolated. It is known that simple 7-allyloxy-coumarins rearrange[94,109,112,113] exclusively into C-8 unless this position is blocked. Competition for the two positions might occur in the case of a 3,3-dimethylallyl ether but it had been expected that rearrangement would still occur predominantly into C-8. Nevertheless, since the C-8 isomers might be among the unidentified components, no conclusions as to the distribution between the two ortho positions can be reached.

It was now quite apparent that the advantages of having no solvent, can be outweighed by the complex mixture of products which are possible as a result of using this method of pyrolysis. Part Ic, which follows, indicates how the information which has been gained was utilised in the efficient synthesis of a new natural coumarin.

c) 5,7-Dioxygenated Series.

RO
O
O

OCH₃

CH₃O
O
O

OCH₃
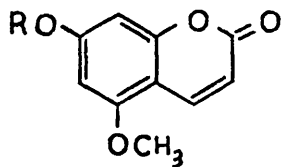
(120) R = CH₂CH:C(CH₃)₂
(121) R = CH₃

(122)

Scheme 1.12

O

O

O
O

OCH₃

O

(124)

→

O

O

O
O

OCH₃

(125)

+

CH₃O
O
O

OCH₃

(126)

HO
O
O

OCH₃
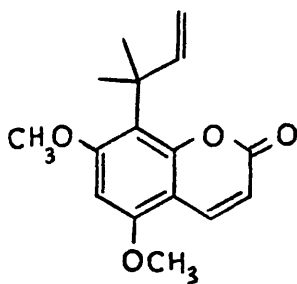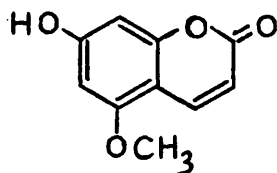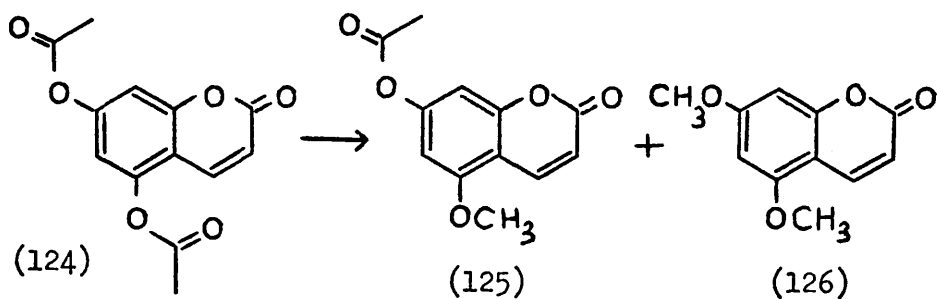
(127)

An investigation of the 'Claisen Rearrangement' of 7-O-(3,3-dimethylallyl)-5-methoxycoumarin(120) was undertaken as an extension of the studies discussed previously. This investigation was considered to be particularly relevant since a new coumarin, pinnarin, isolated[14] by Reyes and González from the root bark of Ruta pinnata, had been allocated structure 122. These workers had shown[14] conclusively that pinnarin is a limettin (121) derivative having a 1,1-dimethylallyl side chain attached to the benzenoid ring. The similarity between the u.v. spectrum of pinnarin and those of limettin derivatives known to possess a C_5 unit at C-8 prompted[14] Reyes and González to assign structure 122 to their new coumarin.

It has often proved difficult to establish, on spectroscopic evidence, whether the C_5 unit in such cases is attached to C-6 or to C-8. Structural determination has generally required a synthesis[67,114], chemical degradation[67,115] or the fact that one of the possible isomers is a known compound.

The appearance of pinnarin in the literature provided an excellent opportunity of demonstrating the potential of the 'Claisen Rearrangement' as a method of introducing a 1,1-dimethyl-allyl unit into a coumarin nucleus, and, if successful, the synthesis should provide confirmation of the structure proposed by Reyes and Gonzalez.

The work of Kaufman and others has shown[94,109,112,113] that

pyrolyses of 7-allyloxycoumarins, unsubstituted at C-6 and C-8, result exclusively in rearrangement to C-8. The results of Part II of this thesis were also available at the time of this present investigation and since the rearrangement of 7-O-(1,1-dimethylallyl)-5-methoxycoumarin had yielded only the C-8 substituted product, it seemed reasonable that the pyrolysis of 7-O-(3,3-dimethylallyl)-5-methoxycoumarin(120) would result at least predominantly in the required rearrangement to C-8. The possibility of an 'out-of-ring' rearrangement to C-3, analogous to that described in Part Ia, could not be discounted.

It was slightly more difficult to obtain the ether 120 required for the proposed synthesis than it had been to obtain 7-O-(3,3-dimethylallyl)scopoletin(61). In the latter case, it had been possible to utilise the more acidic nature of the C-7 hydroxyl of aesculetin(19), but, unfortunately, an analagous synthesis is not possible in the case of 120. However, Seshadri and his co-workers had investigated[116,117] the selective alkylation of several polyhydroxycoumarins and by the method outlined in Scheme 1.12, they had synthesised[117] 7-hydroxy-5-methoxycoumarin(127) from 5,7-diacetoxycoumarin(124) in a reasonable overall yield (55 %). Since this coumarin 127 could easily be converted to the required ether 120, its synthesis was undertaken.

5,7-Dihydroxycoumarin(123)[118] was obtained by heating a

mixture of phloroglucinol and ethyl propiolate in the presence

of zinc chloride. It was then converted to the diacetate 124

which, following the method[117] of Seshadri, was dissolved in

acetone and the solution refluxed with excess methyl iodide in

the presence of potassium carbonate. The crude product was

hydrolysed and the residue separated into a base insoluble and

a base soluble fraction. The base insoluble fraction yielded

5,7-dimethoxycoumarin (limettin) (6%), the n.m.r. spectrum of

which is consistent with the presence of two _meta_ aromatic

protons and two aromatic methoxyls. The base soluble fraction

appeared, from analytical t.l.c., to be a mixture of three

compounds, the most polar being probably 5,7-dihydroxycoumarin

present in very small amounts. This mixture[116a] was separated

by fractional crystallisation into 7-hydroxy-5-methoxycoumarin(127)

(41%) and a crystalline mixture of 127 and 7-methoxy-5-hydroxy-

coumarin (19%; ratio approximately 2:1). It was only possible

to separate very small amounts of the latter mixture by

preparative t.l.c. The two isomers were differentiated by

their u.v. spectra which indicated which coumarin possessed a

C-7 hydroxyl. A similar mixture of products was obtained when

aqueous acetone was used for the methylation. However, a much

shorter reflux time was sufficient in this case. Although the

above separation was tedious,it did enable a reasonable yield of

the required 7-hydroxy-5-methoxycoumarin to be obtained.

Dimethylallylation of this coumarin, using 3,3-dimethylallyl bromide and potassium carbonate, gave 7-O-(3,3-dimethylallyl)-5-methoxycoumarin(120). The n.m.r. spectrum of this compound possesses a doublet at τ 2.17 attributable to a C-4 proton peri to the oxygen at C-5. The chemical shift of a C-4 proton of 5-oxygenated coumarins is in the region of τ 2.1 whereas that of a coumarin unsubstituted at C-5 is generally at approximately τ 2.4.

It was decided, before continuing with the proposed synthesis of pinnarin, that the reaction of 5,7-dihydroxycoumarin with 3,3-dimethylallyl bromide should be investigated. Although it seemed unlikely that this would be an alternative route to the required ether 120, it was realised that even if both mono-ethers were obtained they could probably be separated by preparative t.l.c. In this way an authentic sample of 5-hydroxy-7-methoxycoumarin could be prepared for comparison with the very small amount of this compound which had been isolated previously.

Treatment of 5,7-dihydroxycoumarin with 3,3-dimethylallyl bromide in the presence of potassium carbonate, in an analogous manner to that employed for the synthesis of 7-O-(3,3-dimethylallyl)-aesculetin(65), yielded the bis-ether(128) (52%) and two phenolic compounds. One of the latter, obtained in 23% yield, possesses a hydroxyl (i.r. and n.m.r. spectra) at C-7 (u.v. spectrum; Appendix) and a 3,3-dimethylallyloxy unit (n.m.r. spectrum). The remainder

(128)

(130)

Scheme 1.13

(129)

(131)
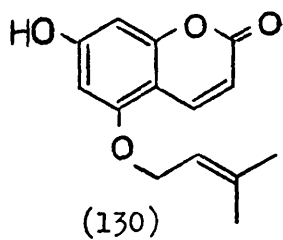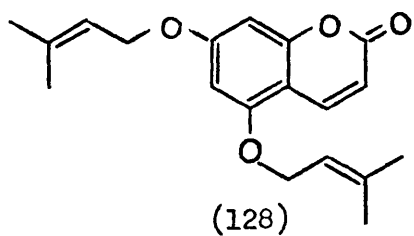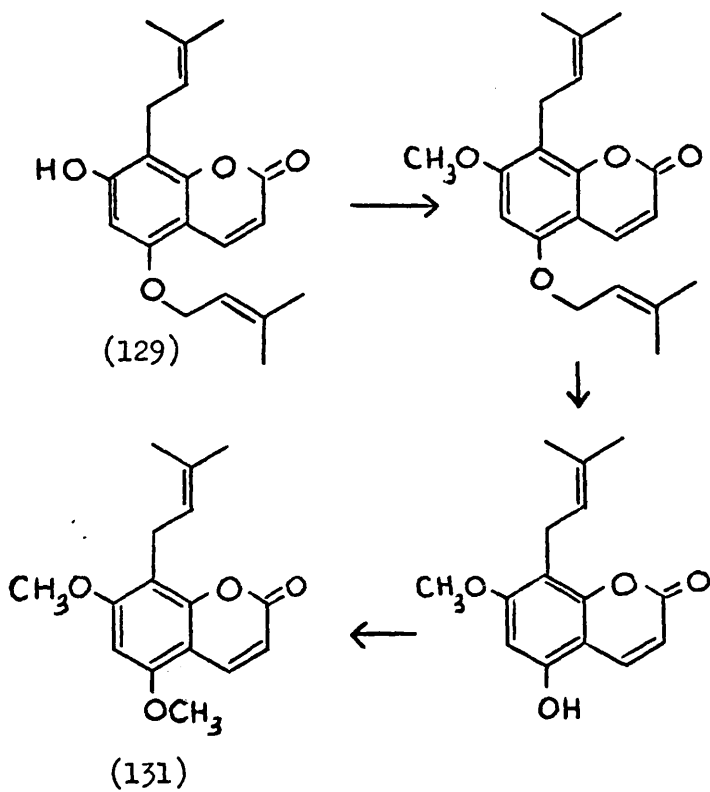
of the n.m.r. spectrum can be attributed to α-pyrone protons at C-3 and C-4, and to two <u>meta</u> aromatic protons. Thus, structure 130 is assigned to this product. The other phenolic product ($\sim$ 5%) appeared to contain two C_5H_9 units. The n.m.r. spectrum indicates a 3,3-dimethylallyl unit attached to oxygen and one attached to the benzene ring. Since the u.v. spectrum is characteristic of a C-7 hydroxyl, the former unit must be attached to the C-5 oxygen. The remaining unit could be attached to C-6 or to C-8. By the method outlined in Scheme 1.13 this minor product, the result of both C- and O-alkylation, was related to coumurrayin(131)[66] (synthesis; Part II) and can therefore be allocated structure 129. The intermediate compounds were identified only from n.m.r. and u.v spectra.

7-O-(3,3-Dimethylallyl)-5-hydroxycoumarin was not isolated from the dimethylallylation, although it might have been one of a mixture of two compounds ($\sim$ 2%) which were not identified. It was noticeable that when the experiment was stopped before all the starting material had been converted, a similar ratio of the bis-ether(128) and the mono-ether(130) was obtained. The high yield of 128 in the first reaction could therefore not have been a consequence of an overlong reflux.

Methylation of the mono-ether(130) yielded the methyl ether (132) which was hydrolysed under acidic conditions to 7-methoxy-5-hydroxycoumarin(133). This coumarin was identified by m.p., u.v.
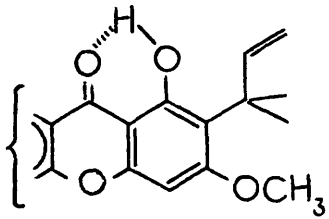
(134)
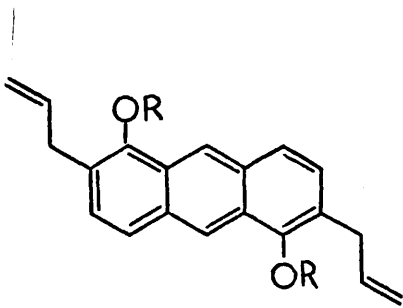
(135) R = H
(136) R = COCH₃
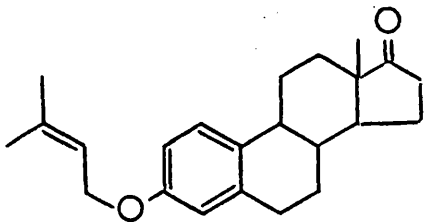
(137)
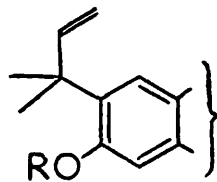
(138) R = H
(139) R = CO(CH₂)₂CH₃

and mass spectra and shown, by analytical t.l.c. and u.v. spectra, to be identical to the minor product obtained from the methylation of 5,7-diacetoxycoumarin.

A preliminary pyrolysis of 7-0-(3,3-dimethylallyl)-5-methoxy-coumarin(120) at $185 \pm 5^{\circ}$, in the absence of solvent, yielded not unexpectedly a mixture of products (as indicated by analytical t.l.c.). It is known that intramolecular hydrogen bonding as indicated in diagram 134 can prevent[97] the normal product rearranging to the abnormal. No such bonding is possible in the case of the first formed phenol(s) from the pyrolysis of 120.

It was, therefore, decided to trap the normal product(s) from 120 as the ester(s) since this should eliminate cyclisation to the dihydrofuran and rearrangement to the abnormal product. Such 'trapping' experiments are generally carried out using N,N-diethylaniline as solvent and acetic anhydride or butyric anhydride as the trapping agents. The unstable dihydroxy compound (135) was obtained[119] as the diacetate(136) by Fieser and Lothrop using the above procedure. In the case of oestrone 3,3-dimethylallyl ether (137), Jefferson and Scheinmann obtained[120] the normal product 138 only by trapping it as the butyrate(139) followed by hydrolysis.

Butyric anhydride was chosen as the trapping agent in the present instance since, although Jefferson and Scheinmann used fairly strong basic conditions to hydrolyse their butyrate, it was
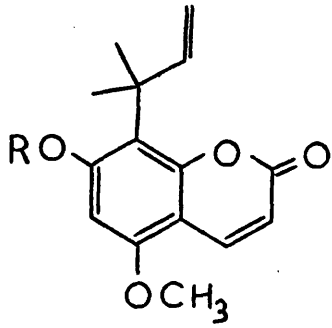
(140) R = CO(CH$_2$)$_2$CH$_3$
(141) R = H
(122) R = CH$_3$

hoped that a milder hydrolysis would be possible, in this case, in order to preserve the coumarin nucleus.

Thus, 7-O-(3,3-dimethylallyl)-5-methoxycoumarin was suspended in a small amount of N,N-diethylaniline in the presence of excess butyric anhydride. An oxygen-free nitrogen atmosphere was maintained throughout the experiment. The above suspension was immersed in an oil bath at 185°, shaken for 5 min. to ensure that the melt had dissolved and then kept at this temperature for 8 hr. After the reaction mixture had cooled to room temperature, a single butyrate was isolated in 92% yield. The n.m.r. spectrum clearly indicates that a 1,1-dimethylallyl unit had been inserted into the benzenoid ring and since it was know that coumarin 7-allyl and 7-(1,1-dimethylallyl)$^{Part II}$ ethers rearrange predominantly or exclusively to C-8 (vide supra), this butyrate was assigned structure 140. It would be interesting to discover now if under similar conditions 7-O-(3,3-dimethylallyl)-4-methylumbelliferone yields a mixture of both isomeric butyrates as a result of the absence of substitution at C-5 (vide infra).

It was surprising that the butyrate of the parent phenol, 7-hydroxy-5-methoxycoumarin, was not isolated from the pyrolysis of 120. It had been prepared, in anticipation, but could not be detected even by analytical t.l.c. The butyrate(140) which had been obtained, hydrolysed very readily under mild conditions to the phenol 141 (86%), the n.m.r. spectrum of which is consistent

with the proposed structure, indicating that no further rearrangement had taken place.

This phenol, m.p. 161-166°, was quite stable in the crystalline form but decomposed slightly to more polar material on heating. On account of this slight instability, an attempt was made to methylate this phenol(141) by treating it with excess diazomethane at room temperature overnight. An n.m.r. spectrum of the residue indicated that methylation had occurred but the signals for the 1,1-dimethylallyl unit had only approximately half the integration which they should have had. New signals had appeared at τ 9.70 and 9.57 perhaps due to cyclopropane formation.

Methylation of the phenol(141), in the usual way using methyl iodide and potassium carbonate, yielded a dimethyl ether in 84% yield. This result indicated that the previous fears on instability had been unfounded. This ether, 5,7-dimethoxy-8-(1,1-dimethylallyl)coumarin, was identical (m.p., m.m.p., t.l.c. behaviour and i.r. spectrum) with a sample of natural pinnarin(122) which had been very kindly provided by Professor Gonzalez[121].

The overall yield (67%) of pinnarin from 7-O-(3,3-dimethylallyl)-5-methoxycoumarin was even greater than had been anticipated and indicates that the 'Claisen Rearrangement' can be a very efficient method of incorporating a 1,1-dimethylallyl unit <u>ortho</u>
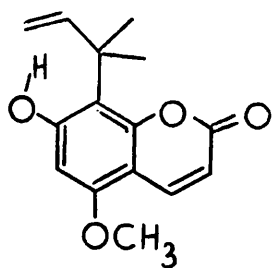
(141)
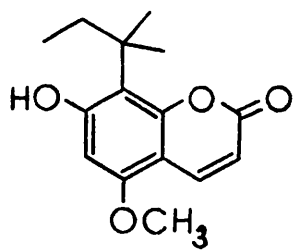
(142)
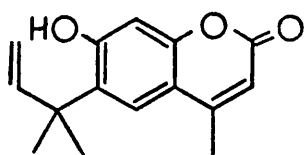
(117)
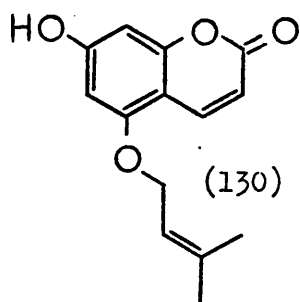
(130)
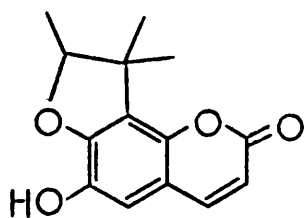
(93)

to a hydroxyl in a coumarin nucleus.

An interesting feature of the i.r. spectrum of 7-demethyl-pinnarin(141) is the remarkably low value, 3428 cm.$^{-1}$, of the hydroxyl stretching frequency. It has been reported[121] that ortho-(1,1-dimethylallyl)phenol displays both free (3615 cm.$^{-1}$) and intramolecularly hydrogen bonded (3494 cm.$^{-1}$) hydroxyl bands. The absence of any free hydroxyl stretching frequency in the spectrum of 141 and the stronger OH-π intramolecular hydrogen bond, are considered to be consequences of the acidity of the C-7 hydroxyl and of the restricted rotation of the bulky 1,1-dimethylallyl residue at C-8. It was noticeable that dihydrodemethylpinnarin(142), prepared by hydrogenation of 138, possesses two free hydroxyl stretching frequencies, 3629 and 3599 cm.$^{-1}$, in the i.r. spectrum. The latter is the normal value for a free hydroxyl in a coumarin system and the former value can be attributed to be a result of a steric buttressing effect[123]. Similar buttressing effects have been reported[124] by Cairns and Eglinton.

These results were compared with those obtained from coumarins which had already been synthesised. The spectrum of 117 (Part Ib), which possesses a similarly acidic hydroxyl but has the 1,1-dimethylallyl.residue in the sterically less crowded 6-position, displays two hydroxyl stretching frequencies, a weak free hydroxyl band at 3593 cm.$^{-1}$ and an intramolecularly hydrogen bonded hydroxyl

at 3475 cm.$^{-1}$.   Since the OH-π hydrogen bonding is considerably
weaker in this compound than in 141, and since the dihydro derivative
142 exhibits a steric buttressing effect, it is concluded that the
explanation of the exceptional OH-π bonding exhibited in
7-demethylpinnarin(138) can be justified.   The hydroxyl stretching
frequency (3600 cm.$^{-1}$) of the i.r. spectrum of 7-hydroxy-5-0-
(3,3-dimethylallyl)coumarin(130) (vide supra) can be used as a
standard for the free hydroxyl.   The value (3573 cm.$^{-1}$) obtained
from the spectrum of 6-demethylnieshoutin(93) is typical of a
hydroxyl bonded to an ortho oxygen.   All of the above results
were obtained from carbon tetrachloride solutions ($\sim$0.005 M).

Two preliminary investigations have been instigated to examine
further the use of butyric anhydride as a trapping agent for the
first formed phenol in the coumarin series.

It was decided that this might be a very good method of
preparing obliquetin(62) in sufficient quantities to enable further
investigations.   It was noted, however, that the ratio of
obliquetin(62) to the 'out-of-ring' compound (76) might alter
unfavourably on using N,N-diethylaniline since this solvent does
not favour[125] enolisation and might enhance the percentage of the
'out-of-ring' compound.

Using the same method as had been employed for the synthesis

of pinnarin, 7-0-(3,3-dimethylallyl)scopoletin(61) was heated

at 180° in N,N-diethylaniline and butyric anhydride. After

3 hr., analytical t.l.c. indicated that some starting material

remained and so the temperature was maintained at 180° for a

further 12 hr. During this period of time a faulty valve on

the nitrogen cylinder released all of the gas thus causing

evaporation of most of the diethylaniline and butyric anhydride.

The temperature apparently remained constant during this period.

The results, therefore, might not truly reflect the temperature

and time employed.

The pale amber oil found in the morning was separated, by

preparative t.l.c., into three components. The butyrates of

scopoletin(41) and the 'out-of-ring' compound (76) were obtained

in 38 and 22% yields respectively. These were identical to

the derivatives prepared on treating 41 and 76 with butyric

anhydride and pyridine. The third component was identified

as obliquetin butyrate (31%) since the n.m.r. spectrum indicates

the presence of a 1,1-dimethylallyl residue attached to the

benzenoid ring. The remainder of the spectrum is consistent

with the proposed structure. Although there was apparently an

increase in the percentage of 'out-of-ring' rearrangement and

of cleavage, when compared to that from the pyrolysis without

solvent, this was probably due to the ease with which such

butyrates can be recovered from preparative t.l.c. and to the

fact that these compounds can be purified by sublimation with little loss of material.

It only remains now to hydrolyse obliquetin butyrate and examine the product. If the latter were obliquetin, this would enable an investigation into its stability under basic and thermal conditions to be made. Similar conditions (0.2% w./v. NaOH/EtOH; ~ 1 min.) to that employed for the hydrolysis of 7-demethylpinnarin butyrate failed to hydrolyse obliquetin butyrate and approximately 98% of the starting material was recovered. As stronger hydrolysing conditions were used the recovery of the starting butyrate decreased but neither obliquetin nor its isomer could be detected either by analytical t.l.c. or n.m.r. The difficulties experienced in hydrolysing this butyrate were totally unexpected. The compound appeared to be decomposing rather than hydrolysing, perhaps due to base attack at the lactone carbonyl. It could also be that the hydrolysis product is unstable under basic conditions.

A second preliminary investigation was made into the pyrolysis of 7-0-(3,3-dimethylallyl)-4-methylumbelliferone(116). Since the structure of pinnarin, as far as the synthesis is concerned, is dependent upon rearrangement having taken place to C-8, it was felt that it would be confirmatory evidence to show that 116 rearranges to both C-6 and C-8. It will be remembered that from the pyrolysis, without solvent, the major rearrangement product isolated was 6-(1,1-dimethylallyl)-4-methylumbelliferone.

Figure 1.2

N.m.r. spectrum (τ) at 60 MHz.
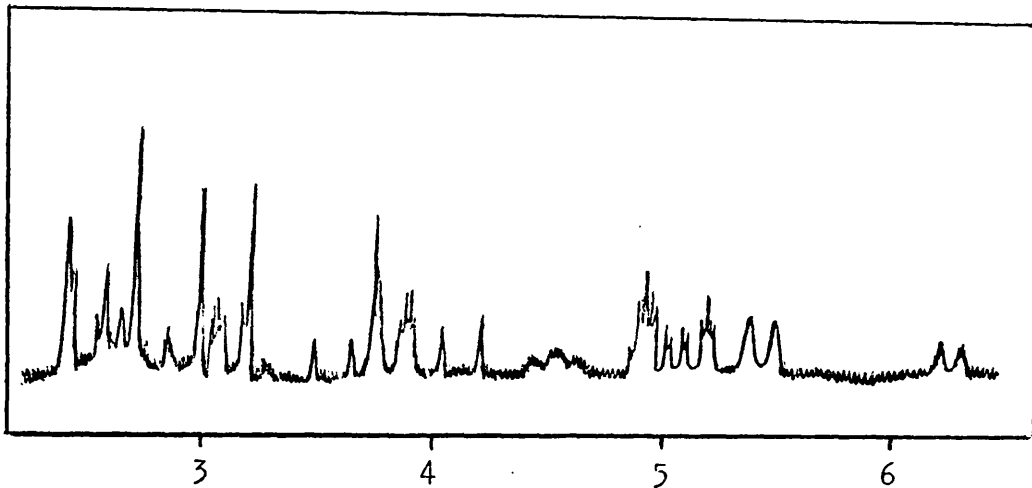
Figure 1.3

Expansion of $\sim 5\tau$ from Figure 1.2 and attempted interpretation.
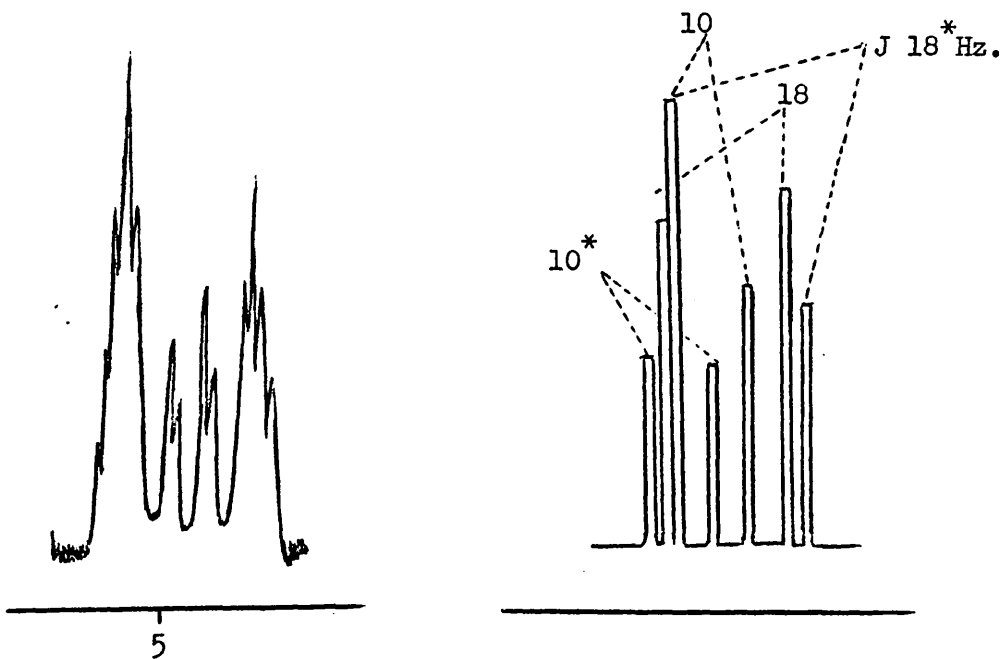
The ether(116) was heated at 180° for 36 hr. in N,N-diethylaniline and butyric anhydride. After work up, the residue gave the butyrate of the parent phenol and a mixture which from the n.m.r. spectrum (Figure 1.2) appeared to consist of four compounds. The presence of the starting ether was indicated by the doublet and triplet characteristic of a 3,3-dimethylallyl ether. The n.m.r. spectrum also appeared to contain two 1,1-dimethylallyl units (Figure 1.3) which would indicate that rearrangement had taken place to both C-8 and C-6. A doublet (J 6.5 Hz.) at τ 6.26 could be due to a small amount of a coumarin containing a 3,3-dimethylallyl unit attached to the benzenoid ring.

Unfortunately, lack of time prevented any further examinations of these two preliminary investigations. The results have been included since those from 7-O-(3,3-dimethyl-allyl)-4-methylumbelliferone, although based on insubstantial evidence, appear to conform with those obtained previously (Parts Ib, Ic and II) and since the inability to hydrolyse obliquetin butyrate was a problem that might not be expected. This might be overcome by trapping obliquetin as the acetate.

The synthesis of pinnarin has been summarised in a publication[133].

Summary

The pyrolyses of coumarin 3,3-dimethylallyl ethers can give

unpredictable results.   The efficiency of the 'Claisen Rearrange-

ment' as a method of introducing a 1,1-dimethylallyl residue

ortho to a phenol, in the coumarin series, varies tremendously.

However, problems involving the abnormal rearrangement and

cyclisation can be fairly easily overcome by trapping the first

formed phenols as esters, which should generally be easily hydrolysed

under fairly mild conditions.

The direction of rearrangement required in the synthesis of

pinnarin was fortunate since it might have been more difficult

to insert a C_5 unit at C-6. The corresponding ether, 5-0-(3,3-

dimethylallyl)-7-methoxycoumarin could easily have been synthesised

but in this case the para-Claisen might have competed strongly

with the ortho-Claisen.

By choosing the coumarin 3,3-dimethylallyl ethers carefully,

it might be possible to utilise the 'Claisen Rearrangement' to

synthesise more highly substituted coumarins and natural 'out-of-

ring' compounds.

General Experimental

and Abbreviations.

Melting points are uncorrected and were determined on a Kofler hot-stage apparatus. Microanalyses were obtained by Mr. J.M.L. Cameron and his staff. Mass spectra were recorded by Mr. A. Ritchie on an A.E.I.-G.E.C. MS 12 mass spectrometer. Infra-red spectra were recorded by Mrs. F. Lawrie and her staff on a Unicam SP 100 Mark II spectrophotometer or on a Perkin-Elmer 225 instrument, using carbon tetrachloride as solvent. Routine infra-red spectra were recorded for chloroform solutions on a Unicam SP 200 instrument. All ultra-violet spectra were recorded for ethanol solutions on a Unicam SP 800 spectrophotometer; λ_{max}(base) refers to the above solutions to which two drops of 4N sodium hydroxide had been added. Nucleur magnetic resonance spectra were recorded by Mrs. S. Hamilton, Mrs. M. Kirkland, Mr. A. Haetzman or Mr. J. Gall on a Perkin-Elmer R 10, a Varian T-60 or a Varian HA 100 spectrometer, using tetramethylsilane as an internal standard. Unless otherwise stated, deuterochloroform was used as solvent for these spectra. All spectra, recorded on the Varian HA 100, are indicated by 100 MHz. Kieselgel G (Merck) was used for preparative thin layer chromatography (t.l.c.).

Light petroleum refers to the fraction of b.p. 60-80°. All solvents, unless otherwise stated, were dried over anhydrous magnesium sulphate or anhydrous sodium sulphate and were 'removed' under partial pressure.

Distillation of an oil was carried out using a sublimation apparatus.

Analytical and preparative t.l.c. plates were viewed under an ultra-violet (254 and 350 nm.) lamp.   Analytical t.l.c. plates were developed by iodine vapour and/or spraying the plates with a solution of ceric ammonium sulphate and then heating the plates at approximately 150°.   The solution of ceric ammonium sulphate was made by dissolving ceric ammonium nitrate (5g.) in conc. sulphuric acid (50ml.) and making the solution up to 500ml. with water.

The solvents used for preparative chromatography are expressed as a percentage volume,e.g. 10% chloroform-methanol is equivalent to chloroform and methanol in a volume ratio of 1:9.   The number of elutions required for separation are indicated, after the solvent, by e.g. $x \frac{1}{2} x 1$.   This infers that the chromatoplate (20cm. x 20cm.) was eluted to a distance of $\sim$ 10cm., allowed to dry and then eluted to a distance of $\sim$ 20cm. from the application line (N.B. x 2 $\equiv$ x 1 x 1).

The compounds isolated from a mixture by preparative t.l.c. are given in order of decreasing chromatoplate mobility with respect to the elution procedure employed.

Analytical t.l.c. was automatically employed for comparison purposes.   It is therefore assumed that if two compounds are said to be identical, this includes with respect to t.l.c. behaviour.

The following abbreviations and symbols have been employed primarily in the experimental sections:-

t.l.c.	thin layer chromatography
i.r.	infra-red
u.v.	ultra-violet
n.m.r.	nuclear magnetic resonance
r.a.	relative abundance (in mass spectra)
sh.	shoulder (in u.v. or i.r. spectra)
s.	singlet :
d.	doublet :
t.	triplet :
q.	quartet : (in n.m.r. spectra)
m.	multiplet :
b.	broad :

R.T.   room temperature ($\sim 20^{o}$)

w./v.   e.g. 20% w./v.; this refers to a solution of 20g. in 100ml. solvent.

$\neq$ e.g. 100 m.g.; this refers to the weight of a compound which has only been purified by preparative t.l.c.

•   e.g. τ 3.52 ; this refers to a signal in an n.m.r. spectrum which disappears on addition of deuterium oxide to the solution.

dil.   dilute; $\sim$4N.

p.   page number

Two methods of working up a crude reaction mixture were frequently employed during the course of this research. In the experimental sections, they have been referred to as 'work up (I)' and 'work up (II)'.

Work up (I)

Methylation (or 3,3-dimethylallylation) of a hydroxy-coumarin was carried out by refluxing an acetone solution of the coumarin with methyl iodide (or 3,3-dimethylallyl bromide) in the presence of potassium carbonate. After the reflux, the inorganic solids were filtered off and the acetone solution evaporated. The residue was dissolved in a mixture of ethyl acetate and brine. The organic layer was washed with aqueous potassium carbonate ($\sim 0.5\%$ w./v.), if it was necessary to remove any starting material, brine to neutrality, dried and evaporated. The residue was treated as specified in each preparation.

Work up (II)

This refers to any reaction in which pyridine was employed. The solution, on cooling after the reaction, was poured into iced water (pyridine : water ratio approximately 1 : 100) or had iced water added to it. This aqueous mixture was allowed to stand at R.T. for 1-2 hr. and, then, ethyl acetate extracted. The organic layer was washed repeatedly with brine, dried and

evaporated.   Any pyridine which remained in the residue was
removed as an azeotrope with benzene.   The residue was treated
as specified in each preparation.

PART I

Experimental

Aesculetin(19)

A solution of aesculin(74)(10g.) in methanol(750ml.) and conc. hydrochloric acid (150ml.) was refluxed for 6 hr., allowed to cool and then neutralised with dil. sodium hydroxide. After removal of most of the solvent, the resulting yellow precipitate was filtered, washed with water and then recrystallised from aqueous methanol. This gave aesculetin as pale yellow needles (4.4g.), m.p. 269-271° (lit.[126] m.p. 276°); λ_{max} 229, 254(sh.), 297 and 350nm. (logε 4.06, 3.64, 3.63 and 3.97); λ_{max} (base) 406nm. (log ε 4.11).

Aesculetin dimethyl ether (scoparin) (95)

Potassium carbonate (50mg.) was added to a solution of aesculetin(19)(25mg.) in acetone(50ml.) and the mixture stirred at R.T. for 1 hr. Methyl iodide (0.5ml.) was then added and the solution refluxed gently for 12 hr. Work up (I) gave a yellow solid which, on crystallisation from methanol, yielded scoparin as colourless needles (24mg.; 82%), m.p. 143.5-145° (lit.[127] m.p. 144-146°); mass spectral peaks at m/e 206 (M^+), 191, 178, 163, 135, 120, 107, 92, 79, 69 and 51 (r.a. 100, 52, 25, 52, 39, 18, 37, 24, 37, 40 and 42%); n.m.r. signals at τ 6.10 (3H ; s.), 6.07 (3H ; s.), 3.75 (1H ; d.; J 9.5 Hz.), 3.19 (1H ; s.), 3.17 (1H ; s.) and 2.41 (1H ; d.; J 9.5 Hz.).

5,7-Dihydroxycoumarin and its dimethyl ether p.81,83.

4-Methyl-5,7-dihydroxycoumarin

Prepared by the method[111] of John and Israelstam using phloroglucinol, ethyl acetoacetate and a cation exchange resin (Amberlite I.R. 120). This gave the above coumarin which crystallised from methanol as pale yellow needles, m.p. 277-279° (lit.[111] m.p. 284.5-285°).

4-Methyl-5,7-dimethoxycoumarin

Using the same procedure as that employed for the synthesis of scoparin (p.64), 4-methyl-5,7-dihydroxycoumarin (25mg.) was converted to the bis-methyl ether which crystallised from methanol as colourless needles (26mg. ; 90%), m.p. 171-173° (lit.[132] m.p. 172-173°); n.m.r. signals at τ 7.51 (1H ; d.; J 1 Hz.), 6.15 (6H ; s.), 4.10 (1H ; b.s.), 3.75 (1H ; d.; J 2 Hz.) and 3.62 (1H ; d.; J 2 Hz.).

4-Methyl-7,8-dihydroxycoumarin

Prepared by the method[111] of John and Israelstam using pyrogallol, ethyl acetoacetate and a cation exchange resin (Amberlite I.R. 120). This yielded the required coumarin which crystallised from aqueous ethanol as colourless needles, m.p. 231-236° (lit.[111] m.p. 234-235°).

4-Methyl-7,8-dimethoxycoumarin

Using the same procedure as that employed for the synthesis of scoparin (p.64), 4-methyl-7,8-dihydroxycoumarin (25mg.) was

converted to the bis-methyl ether which crystallised from aqueous methanol as colourless cubes (24mg.; 84%), m.p.133-134° (lit.[132] m.p. 135°); n.m.r. signals at τ 7.61 (3H ; d.; J 1 Hz.), 6.02 (6H ; s.), 3.87 (1H ; b.s.), 3.14 (1H ; d.; J 9.5 Hz.) and 2.72 (1H ; d.; J 9.5 Hz.).

1-Bromo-3-methyl-but-2-ene (3,3-dimethylallyl bromide)[129]

Isoprene (100ml.; 68g.) and a solution of hydrogen bromide in glacial acetic acid (50% w./v.; 168ml.) were cooled to ~0° and then mixed together.   The solution was kept for three days at ~5° and then diluted with iced water (1500ml.).   The yellowish oil which separated, was washed with iced water and dried over anhydrous calcium chloride.   Distillation (standard apparatus) of this oil at 65-68°/~68mm. yielded 3,3-dimethylallyl bromide (108g.; 72%).

This reagent could be stored at ~ -25° for 1-2 months before distillation was required.

Dimethylallylation of aesculetin(19)

Potassium carbonate (1g.) was added to a solution of aesculetin (1g.) in acetone (200ml.) and the mixture stirred at R.T. for 2 hr.   Dimethylallyl bromide (1g.) was added and the solution refluxed for 20 hr.   The inorganic solids were filtered off, washed with hot acetone and the filtrant evaporated.   The residue was taken up in ethyl acetate and this solution washed repeatedly with aqueous sodium hydroxide (~ 0.5% w./v.) until the

basic layer was colourless. The combined aqueous washings were carefully neutralised with dil. hydrochloric acid and set aside. The organic layer was washed with brine to neutrality, dried and evaporated. Crystallisation of the residue from ether-light petroleum yielded the <u>bis-ether</u>(75) as pale yellow needles (0.40g.; 23%), m.p. 79.5-81°. (Found: C, 72.30 ; H, 7.10. $C_{19}H_{22}O_4$ requires C, 72.60 ; H, 7.05%); λ_{max} 231, 254, 260, 296 and 344 nm. (logϵ 4.27, 3.79, 3.72, 3.77 and 4.07); n.m.r.signals at τ 8.24 (12H ; b.s.), 5.46 (2H ; d.; J 6 Hz.), 5.38 (2H ; d.; J 6 Hz.), 4.56 (1H ; b.t.; J 6 Hz.), 4.53 (1H ; b.t.; J 6 Hz.), 3.78 (1H ; d.; J 10 Hz.), 3.21 (1H ; s.), 3.16 (1H ; s.) and 2.43 (1H ; d.; J 10 Hz.).

The ethyl acetate extract of the acidified aqueous layer was washed with brine, dried and evaporated. Crystallisation of the residue from methanol yielded 7-0-(3,3-dimethylallyl)aesculetin (65) as colourless needles (0.86g.; 63%), m.p. 143-144° (lit.[45] m.p. 145-146°). (Found: C, 68.35; H, 5.60. Calc. for $C_{14}H_{14}O_4$ C, 68.30; H, 5.75%); ν_{max} 3556, 1742 and 1631 cm.$^{-1}$; λ_{max} 231, 254, 260, 297 and 348 nm. (logϵ 4.37, 3.91, 3.91, 3.96 and 4.22); λ_{max} (base) 254, 279 (sh.), 314 and 401 nm. (log ϵ 4.46, 4.06, 3.98 and 4.00); n.m.r. signals at τ 8.23 (6H ; b.s.), 5.35 (2H ; b.d.; J 7 Hz.), 4.52 (1H ; b.t.; J 7 Hz.), 4.30 (1H ; s.), 3.74 (1H ; d.; J 10 Hz.), 3.19 (1H ; s.), 3.05 (1H ; s.) and 2.41 (1H ; d.; J 10 Hz.).

7-O-(3,3-Dimethylallyl)scopoletin(61)

7-O-(3,3-Dimethylallyl)aesculetin(65) (1.7g.) was converted
(see scoparin p.64) to its methyl ether, using potassium carbonate
(2g.), methyl iodide (2.5ml.) and acetone (200ml.).   After
refluxing for 20 hr., work up (I) gave a low melting solid which,
on crystallisation from ether-light petroleum, yielded the ether
61 as colourless needles (1.66g.; 91%), m.p. 82-83° (lit.[43] m.p.
80-81°).   (Found: C, 69.10; H, 6.10.   Calc. for $C_{15}H_{16}O_4$ C, 69.20;
H, 6.20%); $\nu \, ^{CHCl_3}_{max}$ 1720-1710, 1615 and 1560 cm.$^{-1}$; λ_{max} 231,
252, 259, 296 and 346 nm. (logε 4.25, 3.77, 3.71, 3.77 and 4.10);
n.m.r. signals at τ 8.24 (6H ; b.s.), 6.12 (3H ; s.), 5.33 (2H ; b.d.;
J 7 Hz.), 4.48 (1H ; b.t.; J 7 Hz.), 3.71 (1H ; d.; J 10 Hz.),
3.12 (2H ; s.) and 2.34 (1H ; d.; J 10 Hz.).

Scopoletin(41)

A solution of 61 (1g.) in methanol (20ml.) and dil. hydro-
chloric acid (20ml.) was refluxed for 2 hr., and then neutralised
with dil. sodium hydroxide.   Most of the solvent was removed and
the residue diluted with iced water (100ml.).   The precipitate
was filtered, washed with brine and crystallised from methanol.
This gave scopoletin as colourless needles (0.65g.; 88%), m.p.
203-205° (lit.[93] m.p. 202-203°); λ_{max} 230, 254, 260, 299 and
346 nm. (logε 4.12, 3.68, 3.63, 3.69 and 4.06); λ_{max} (base)
242, 278 (sh.), and 400 nm. (logε 4.03, 3.64 and 4.36); n.m.r.
(deuteropyridine) signals at τ 6.23 (3H ; s.), 3.74 (1H ; d.;
J 9.5 Hz.), 2.99 (1H ; s.), 2.93 (1H ; s.) and 2.36 (1H ; d.;J 9.5 Hz.).

Pyrolyses of 7-O-(3,3-dimethylallyl)scopoletin(61)

[1.] The ether, 61, (500mg.) was pyrolysed in a sublimation block at 195° with a partial pressure of 0.05 mm. Initially the material tended to sublime and so the tube was pushed further into the block. After 2 hr., the oil was allowed to cool to room temperature and then separated by careful preparative t.l.c. into:-

i) nieshoutol(63), from ether-light petroleum as pale yellow needles (106mg.; 21%), m.p. 124-125° (lit.[43] m.p. 125-127°). (Found: C, 69.15; H, 6.35. Calc. for $C_{15}H_{16}O_4$ C, 69.20; H, 6.20%); $\nu_{max}^{CHCl_3}$ 1720, 1615 and 1578 cm.$^{-1}$; λ_{max} 232, 253, 262, 309 (sh.) and 346 nm. (logε 4.12, 3.47, 3.46, 3.72 and 4.09); mass spectral peaks at m/e 260 (M^+) and 245 (r.a. 100 and 65%); n.m.r. signals at τ 8.71 (3H ; s.), 8.57 (3H ;d.;J 6.5 Hz.), 8.44 (3H ; s.), 6.11 (3H ;s.), 5.45 (1H ; q.;J 6.5 Hz.), 3.82 (1H ; d.; J 10 Hz.), 3.27 (1H ;s.) and 2.42 (1H; d.; J 10 Hz.).

ii) starting material (21mg.; 4%) (m.p.,m.m.p.,n.m.r.).

iii) obliquetin(62), from ether-light petroleum as colourless needles (44mg.; 9%), m.p. 136-138° (lit.[43] m.p. 141-143°); λ_{max} 230, 254, 262, 308 (sh.) and 346 nm. (log ε 4.10, 3.61, 3.57, 3.76 and 4.01); λ_{max} (base) 410 nm. (log ε 4.31); n.m.r. signals at τ 8.29 (6H ; s.), 6.09 (3H ; s.), 5.02 (1H ; b.d.; J 11 Hz.), 5.00 (1H ; b.d.; J 18 Hz.),3.79 (1H ; d.; J 9.5 Hz.), 3.62 (1H ; d./d.; J 11 & 18 Hz.), 3.36 (1H ; s.), 3.27 (1H ; s.) and 2.45 (1H ; d.: J 9.5 Hz.).

iv) 3-(1,1-dimethylallyl)scopoletin(76), from light

petroleum as pale yellow needles (71mg.; 14%), m.p. 132-135°.

(Found: C, 69.05; H, 6.25. $C_{15}H_{16}O_4$ requires C, 69.20; H, 6.20%);

$\nu_{max}^{CHCl_3}$ 3515, 1715-1705, 1612 and 1585 cm.$^{-1}$; λ_{max} 231, 255,

262, 298 and 344 nm. (logε 4.25, 3.76, 3.72, 3.80 and 4.21);

λ_{max} (base) 243, 279 (sh.) and 390 nm. (logε 3.99, 3.67 and

4.40); mass spectral peaks at m/e 260, 245, 217 and 205 (r.a.83,

83, 100 and 58%); n.m.r. signals at τ 8.55 (6H ; s.), 6.09

(3H ; s.), 4.96 (1H ; b.d.; J 18 Hz.), 4.93 (1H ; b.d.; J 10 Hz.),

3.82 (1H ; d./d.; J 18 & 10 Hz.), 3.65 (1H ; b.s.), 3.18 (1H ; s.),

3.14 (1H ; s.) and 2.51 (1H ; s.).

v)   scopoletin(41), from methanol as colourless needles

(105mg.; 30%) (m.p.; m.m.p.; u.v.).

2.   The residue from a similar pyrolysis of 61 (500mg.; 193°/

0.06mm.; 2hr.) was separated into a base insoluble fraction and a

base soluble fraction (see p.66).   The former yielded a pale

yellow oil (130mg.; 26%) which by n.m.r. and t.l.c. was mainly

nieshoutin(63) with a small amount of starting material.   The

base soluble fraction was separated by preparative t.l.c.

(chloroform x 2) into :-

i)   8-(1,2-dimethylallyl)scopoletin(91), from ether-light

petroleum as pale yellow needles (7.5%), m.p. 135-137°.   (Found:

C, 69.10; H, 6.20. $C_{15}H_{16}O_4$ requires C, 69.20; H, 6.20%); $\nu_{max}^{CHCl_3}$

3500, 3400, 1715, 1610 (weak) and 1580 cm.$^{-1}$; n.m.r. signals at

τ 8.49 (3H ; d.; J 7 Hz.), 8.30 (3H ; s.), 6.09 (3H ; s.), 5.78

(1H ; q.; J 7 Hz.), 5.03 (2H ; b.s.), 3.75 (1H ; d.; J 10 Hz.),
3.60 (1H ; s.), 3.24 (1H ; s.) and 2.42 (1H ; d.; J 10 Hz.).

      ii)   3-(1,1-dimethylallyl)scopoletin(76) (13%).

      iii) scopoletin(41) (26%).

$\boxed{3.}$ The residue from a pyrolysis of 61 (950mg.; 195°/0.02 mm.;
4 hr.) was separated by preparative t.l.c. and resulted in the
isolation of 8-(1,2-dimethylallyl)scopoletin(91) (10%).

3-(1,1-Dimethylallyl)scoparin(77)

Methylation was carried out using 3-(1,1-dimethylallyl)-
scopoletin(76) (35mg.), potassium carbonate (40mg.) and methyl
iodide (0.1ml.) in refluxing acetone (10ml.). After 4 hr., work
up (I) gave a residue which, on crystallisation from light petroleum,
yielded 3-(1,1-dimethylallyl)scoparin as pale yellow needles, m.p.
103-104°. (Found: C, 70.10; H, 6.65. $C_{16}H_{18}O_4$ requires C, 70.05;
H, 6.60%); λ_{max} 231, 252, 260, 288, 295 and 342 nm. (log ϵ 4.18,
3.78, 3.73, 3.71, 3.78 and 4.12); mass spectral peaks at m/e
274 (M^+), 259, 231 and 219 (r.a. 100, 80, 95 and 46%); n.m.r.
signals at τ 8.52 (6H; s.), 6.10 (6H ; s.), 4.97 (1H ; b.d.; J 18 Hz.),
4.95 (1H ; b.d.; J 10 Hz.), 3.82 (1H ; d./d.; J 18 & 10 Hz.), 3.23
(1H ; s.), 3.17 (1H ; s.) and 2.53 (1H ; s.).

Cyclisation of 8-(1,2-dimethylallyl)scopoletin(91)

A solution of 91 (20mg.) in methanol (1ml.) and dil. hydro-
chloric acid (1ml.) was refluxed for 1 hr. On cooling, the solution
was diluted with iced water (50ml.), neutralised with dil. sodium

hydroxide and extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated. The residue, after purification by preparative t.l.c. (chloroform x 1), yielded the cyclic ether(92) as a pale yellow oil (17 mg.); n.m.r. signals at τ 8.66 (3H ; d.; J 7 Hz.), 8.54 (6H ; s.), 6.59 (1H ; q.; J 7 Hz.), 6.13 (3H ; s.), 3.83 (1H ; d.; J 9.5 Hz.), 3.27 (1H ; s.) and 2.43 (1H ; d.; J 9.5 Hz.).

Pyrolyses of 7-O-(3,3-dimethylallyl)aesculetin(65)

1. The hydroxy-ether(65) (150mg.) was pyrolysed in a sublimation tube at 198° under partial pressure. After 15 min. the oil solidified as a pale yellow solid and after a further 25 min. at 198°, on cooling, was separated by preparative t.l.c. (1% methanol-chloroform x 3) into:-

   i)   a mixture ($\sim$ 30mg.) of at least three compounds.

   ii)   6-demethylnieshoutin(93), from ether-light petroleum as colourless plates (15mg.; 10%), m.p. 157-159°. (Found: C, 68.35; H, 5.65. $C_{14}H_{14}O_4$ requires C, 68.30; H, 5.75%); $\nu_{max}^{CHCl_3}$ 3570, $\sim$3250, 1720 and 1660 cm.$^{-1}$; $\nu_{max}^{CCl_4}$ 3573, 1738 and 1626 cm.$^{-1}$; λ_{max} 228, 257, 264, 313 (sh.) and 349 nm. (log ε 4.17, 3.48, 3.48, 3.85 and 4.09); λ_{max} (base) 220, 252, 278, 326 and 399 nm. (log ε 4.44, 4.28, 3.73, 3.80 and 3.92); n.m.r. signals at τ 8.71 (3H ; s.), 8.59 (3H ; d.; J 6.5 Hz.), 8.43 (3H ; s.), 5.44 (1H ; q.; J 6.5 Hz.), 4.50 (1H ; v.b.s.), 3.80 (1H ; d.; J 9.5 Hz.), 3.18 (1H ; s.) and 2.47 (1H ; d.; J 9.5 Hz.).

   iii) A mixture ($\sim$23mg.) of at least two compounds.

iv)   3-(1,1-dimethylallyl)aesculetin(94) as a white solid (15ʹmg.; 10%);   n.m.r. signals (deuterodimethylsulphoxide) at τ 8.62 (6H ; s.), 5.01 (1H ; d.; J 18 Hz.), 5.00 (1H ; d.; J 10 Hz.), 3.83 (1H ; d./d.; J 18 & 10 Hz.), 3.27 (1H ; s.), 2.98 (1H ; s.) and 2.29 (1H ; s.).

v)   aesculetin(19) (20mg.; 19%) (m.p.; m.m.p.; u.v.)

2.   Similarly, pyrolysis of 65 (625mg.) at 170° under partial pressure for 1 hr. gave a yellow solid (564mg.) which was methylated by the usual procedure [potassium carbonate (1.2g.), methyl iodide (2ml.) in acetone (30ml.) for 20 hr.] .   Work up (I) gave a low melting solid which was separated by preparative t.l.c. (5% ethyl acetate-light petroleum x 1, then 10% x 1, 15% x 1 and finally 20% x 2) into:-

i)   a mixture (~75mg.) of at least four compounds.

ii)   8-(3,3-dimethylallyl)scoparin(96) as a pale yellow solid, from ether-light petroleum as colourless plates (19ʹmg.), m.p. 97-99°;   n.m.r. signals at τ 8.29 (3H ; b.s.), 8.17 (3H ; b.s.), 6.42 (2H ; d.; J 6.5 Hz.), 6.20 (3H ; s.), 6.07 (3H ; s.), 4.92 (1H ; b.t.; J 6.5 Hz.), 3.73 (1H ; d.; J 9.5 Hz.), 3.25 (1H ; s.) and 2.23 (1H ; d.; J 9.5 hz.).

iii)   3-(1,1-dimethylallyl)scoparin(77) (69mg.; 11%) (m.p., m.m.p., n.m.r.).

iv)   a mixture (~88mg.) of at least four compounds including some starting material (as indicated by the n.m.r. spectrum).

v)   scoparin(95) (151mg.; 29%) (m.p., m.m.p., n.m.r.).

4-Methylaesculetin(97)[105]

Quinone (20g.) was slowly added to a mixture of conc. sulphuric acid (4g.) and acetic anhydride (60g.), the temperature being kept at between 40 and 50°. When no external cooling was required to keep the reaction in this temperature range, the mixture was poured into iced water (100ml.). The resulting precipitate was filtered, washed with water to neutrality and recrystallised from ethanol. This gave hydroxyhydroquinone triacetate as colourless needles (42g.), m.p. 96-97.5° (lit.[105] m.p. 96-97°).

Sulphuric acid (75% w./v.; 150ml.) was added with stirring to a smooth paste of the triacetate (42g.) in ethyl acetoacetate (20g.). The resulting deep red solution was heated on a steam bath for $\frac{1}{2}$ hr. and then, on cooling, poured into iced water (600ml.). The precipitate was filtered, washed with water and recrystallised from methanol to give 4-methylaesculetin as yellowish green needles (21.5g.), m.p. 272-281°. Further purification by sublimation at 260°/0.05 mm. gave 97 as pale yellow needles, m.p. 272-276° (lit.[105] m.p. 272-274°), with little loss of material.

4-Methyl-7-0-(3,3-dimethylallyl)aesculetin(98)

Potassium carbonate (7g.) was added to a solution of 4-methyl-aesculetin(97) (6g.) in acetone (1500ml.) and the mixture stirred at R.T. for 1 hr. Dimethylallyl bromide (8g.) was then added and the solution refluxed for 18 hr. Work up (I) gave a yellowish solid which was washed repeatedly with cold methanol. The residue was crystallised from methanol yielding the required ether (98) as

colourless needles (5.6g.; 69%), m.p. 170-171.5°.   (Found:

C, 69.25; H, 6.20. $C_{15}H_{16}O_4$ requires C, 69.20; H, 6.20%); λ_{max}

231, 252, 258, 292 and 346 nm. (log ϵ 4.20, 3.59, 3.55, 3.72 and

4.00); λ_{max} (base) 254, 309 and 396 nm. (log ϵ 4.30, 3.84 and

3.89);   n.m.r. signals at τ 8.24 (3H ; s.), 8.20 (3H ; s.),

7.67 (3H ; s.), 5.37 (2H ; b.d.; J 7 Hz.), 4.55 (1H ; b.t.; J 7 Hz.),

4.37 (1H ; s.), 3.87 (1H ; b.s.), 3.20 (1H ; s.) and 2.93 (1H ; s.).

4-Methyl-7-O-(3,3-dimethylallyl)scopoletin(99)

Using the same procedure as that employed for scoparin (p.64),

4-methyl-7-O-(3,3-dimethylallyl)aesculetin(98) (400mg.) was

converted to its methyl ether(99) by using potassium carbonate

(500mg.), methyl iodide (3ml.) and acetone (100ml.).   After

refluxing for 24 hr., work up (I) gave a low melting solid which

crystallised from ether-light petroleum, yielding 4-methyl-7-O-(3,3-

dimethylallyl)scopoletin as colourless needles (398mg.; 94%),

m.p. 116-117.5°.   (Found: C, 70.20; H, 6.70. $C_{16}H_{18}O_4$ requires

C, 70.05; H, 6.60%); λ_{max} 230, 247, 254, 290 and 342 nm. (log ϵ

4.29, 3.75, 3.63, 3.76 and 4.12);   n.m.r. signals at τ 8.20 (6H;

b.s.), 7.60 (3H ; s.), 6.07 (3H ; s.), 5.38 (2H ; b.d.; J 7 Hz.),

4.53 (1H ; b.t.; J 7 Hz.), 3.90 (1H ; b.s.), 3.25 (1H ; s.) and

3.10 (1H ; s.).

Pyrolyses of 4-methyl-7-0-(3,3-dimethylallyl)scopoletin(99)

1. Pyrolysis of the ether 99 (250mg.), for 1 hr. in a sublimation block at 200° under partial pressure, yielded a yellow solid which was separated by preparative t.l.c. (50% ethyl acetate-light petroleum x 3) into:-

i) 4-methylnieshoutin(102), from ether-light petroleum as colourless plates (36mg.; 15%), m.p. 162-165°. (Found: C, 69.85; H, 6.55. $C_{16}H_{18}O_4$ requires C, 70.05; H, 6.60%); $\nu_{max}^{CHCl_3}$ 1715, 1615 and 1590 cm.$^{-1}$; λ_{max} 230, 258, 304 (sh.) and 344 nm. (log ε 4.27, 3.44, 3.74 and 4.12); n.m.r. signals at τ 8.71 (3H ; s.), 8.54 (3H ; d.; J 6.5 Hz.), 8.43 (3H ; s.), 7.63 (3H ; d.; J 1.5 Hz.), 6.10 (3H ; s.), 5.45 (1H ; q.; J 6.5 Hz.), 3.91 (1H ; b.s.) and 3.15 (1H ; s.).

ii) A mixture (104mg.) of starting material (99) and 4-methylobliquetin(103) (ratio ~5:1) (identification and estimation of ratio from the n.m.r. spectrum of the mixture).

iii) 4-methylscopoletin(101), from methanol as colourless plates (55mg.; 29%), m.p. 213.5-215° (lit.[128] m.p. 216°). (Found: C, 63.95; H, 5.00. Calc. for $C_{11}H_{10}O_4$ C, 64.05; H, 4.90%); λ_{max} 228, 251 (sh.), 257, 293 and 343 nm. (log ε 4.28, 3.68, 3.64, 3.76 and 4.17); λ_{max} (base) 241, 271 (sh.) and 391 nm. (log ε 4.15, 3.68 and 4.39).

2. Similarly, pyrolysis of the ether (99) (180mg.) at 200° for 3 hr. under partial pressure gave:-

i) 4-methylnieshoutin(102) (50mg.; 28%) (m.p., m.m.p., n.m.r.)

ii)   A mixture (17 mg.) of 8-(1,2-dimethylallyl)- and 8-(3,3-dimethylallyl)-4-methylscopoletin, (104) and (105), (ratio ∼2:1) (identification and estimation of ratio from the 100 MHz. n.m.r. spectrum of the mixture).

iii)   4-methylscopoletin(101) (52mg.; 38%).

Umbelliferone(4)

Prepared by the method[110] of Dey, Rao and Seshadri using resorcinol, malic acid and conc. sulphuric acid. The crude product was sublimed at 160-200°/0.1mm. and then crystallised from methanol. This gave umbelliferone as pale yellow needles, m.p. 228-230° (lit.[110] m.p. 223-224°); λ_{max} 216, 244, 253 and 326 nm. (log ε 4.08, 3.49, 3.38 and 4.18); λ_{max} (base) 233, 242 (sh.) and 375 nm. (logε 3.96, 3.88 and 4.31).

Herniarin(16)

Treatment of umbelliferone(4) (60mg.) in methanol (10ml.) with excess ethereal diazomethane for 18 hr. gave a solid which was purified by preparative t.l.c. (chloroform x 2) and then crystallised from ether-light petroleum to give herniarin as pale yellow needles (50mg.; 78%), m.p.117-119° (lit.[110] 117-118°); λ_{max} 217, 241, 251, 298 (sh.) and 322 nm. (log ε 4.11, 3.49, 3.34, 3.91 and 4.15); n.m.r. signals at τ 6.17 (3H ; s.), 3.80 (1H ; d.; J 10 Hz.), 3.23 (1H ; d.; J 2 Hz.), 3.21 (1H ; d./d.; J 2 & 9 Hz.), 2.68 (1H ; d.; J 9 Hz.) and 2.42 (1H ; d.; J 10 Hz.).

7-O-(3,3-Dimethylallyl)umbelliferone(113)

Potassium carbonate (1g.) was added to a warm solution of umbelliferone (1g.) in acetone (100ml.) and the mixture stirred at R.T. for 1 hr. Dimethylallyl bromide (1g.) was then added and the solution refluxed for 40 hr. Work up (I) gave a white solid which, on crystallisation from ether-light petroleum, yielded

the ether(113) as colourless needles (1.24g.; 87%), m.p. 76-78°
(lit.[87] m.p. 77-78°); λ_{max} 216, 242, 252, 299 and 323 nm.
(log ϵ 4.09, 3.43, 3.26, 3.86 and 4.11);   n.m.r. signals at
τ 8.23 (6H ; b.s.), 5.51 (2H ; b.d.; J 7 Hz.), 4.60 (1H ; b.t.;
J 7 Hz.), 3.95 (1H ; d.; J 10 Hz.), 3.35 (1H ; d.; J 2 Hz.),
3.34 (1H ; d./d.; J 2 & 9 Hz.), 2.79 (1H ; d.; J 9 Hz.) and
2.53 (1H ; d.; J 10 Hz.).

4-Methylumbelliferone(115)

Prepared by the method[111] of John and Israelstam using
resorcinol, ethyl acetoacetate and a cation exchange resin
(Amberlite I.R. 120).   This yielded crude 115 which crystallised
from methanol as colourless needles, m.p. 180-182° (lit.[111] m.p.
185°).

7-O-(3,3-Dimethylallyl)-4-methylumbelliferone(116)

As for the synthesis of 113 (p.78), 4-methylumbelliferone (1g.)
was converted to the ether(116) which crystallised from ether as
colourless needles (1.1g.; 80%), m.p. 86-88°.   (Found: C, 73.65;
H, 6.75. $C_{15}H_{16}O_3$ requires C, 73.75; H, 6.60%); $\nu_{max}^{CHCl_3}$ 1715-1710
and 1615 cm.$^{-1}$; λ_{max} 217 (sh.), 240, 252, 292 (sh.) and 322 nm.
(log ϵ 4.31, 3.56, 3.34, 3.91 and 4.23);   n.m.r. signals at
τ 8.23 (6H ; b.s.), 7.63 (3H ; s.), 5.45 (2H ; b.d.; J 6.5 Hz.),
4.53 (1H ; b.t.; J 6.5 Hz.), 3.89 (1H ; s.), 3.23 (1H ; d.; J 2 Hz.),
3.14 (1H ; d./d.; J 2 & 9.5 Hz.) and 2.53 (1H ; d.; J 9.5 Hz.).

Pyrolysis of the ether 116

Pyrolysis of the ether(116) (1g.) for 2 hr. in a sublimation block at 196° under partial pressure gave a solid which was separated by preparative t.l.c. (chloroform) into:-

i)   a mixture (363mg.) of at least four compounds including starting material (from the n.m.r. spectrum).

ii)   <u>6-(1,1-dimethylallyl)-4-methylumbelliferone</u>(117), from ether as colourless needles (152mg.; 15%), m.p. 191-195° decomp. (Found: C, 73.70; H, 6.40. $C_{15}H_{16}O_3$ requires C, 73.75; H, 6.60%); $\nu_{max}^{CCl_4}$ 3593, 3475, ~ 3347, 1747, 1735, 1705 and 1629 cm.$^{-1}$ (ϵ 25, 170, 45, 640, 620, 340 and 490); λ_{max} 221, 242 (sh.), 252 and 329 nm. (log ϵ 4.25, 3.55, 3.43 and 4.19); λ_{max} (base) 236 and 389 nm. (log ϵ 4.10 and 4.36);   n.m.r. signals at τ 8.46 (6H ; s.), 7.58 (3H ; d.; J 1.5 Hz.), 4.72 (1H ; d.; J 18 Hz.), 4.71 (1H ; d.; J 11 Hz.), 3.90 (1H ; b.s.), 3.76 (1H ; d./d.; J 18 & 11 Hz.), 3.18 (1H ; s.), 3.13 (1H ; s.) and 2.55 (1H ; s.).

iii) 6-(1,2-dimethylallyl)-4-methylumbelliferone(118) as a white solid (22 mg.;~2%);   n.m.r. signals at τ 8.60 (3H ; d.; J 7 Hz.), 8.31 (3H ; s.), 7.61 (3H ; s.), 6.20 (1H ; q.; J 7 Hz.), 5.01 (2H ; b.s.), 3.86 (1H ; b.s.), 2.91 (1H ; s.), 2.59 (1H ; s.) and 2.35 (1H ; v.b.s.).

iv)   6-(3,3-dimethylallyl)-4-methylumbelliferone(119) as a colourless oil (14 mg.;~1.4%);   n.m.r. signals at τ 8.25 (~6H ; s.), 7.62 (~3H ; d.; J 1.5 Hz.), 6.62 (~2H ; b.d.; J 7 Hz.), 4.66 (~1H ; t. ?), 3.88 (~1H ; b.s.), 2.94 (~1H ; s.) and 2.69 (~1H ; s.).

v)   4-methylumbelliferone (216mg.; 22%) (m.p., m.m.p., u.v.).

Ethyl propiolate[130]

A mixture of propiolic acid (20g.), dry ethanol (60ml.) and conc. sulphuric acid (3.3ml.) was kept at R.T. for 40 hr. It was then diluted with water (200ml.) and extracted with ether. The organic layer was washed with dil. sodium carbonate, brine to neutrality and dried. Distillation yielded ethyl propiolate (14g.; 50%), b.p. 117-118° (lit.[130] b.p. 119°/745 mm.).

5,7-Dihydroxycoumarin(123)[109]

Phloroglucinol dihydrate (8.10g.), ethyl propiolate (7.35g.) and zinc chloride (6.80g.) were mixed together and heated in an oil bath at 115±5° for 2 hr. The resulting solid was dissolved in a mixture of ethyl acetate (∼750ml.) and dil. hydrochloric acid (∼250ml.). The organic layer was washed with dil. hydrochloric acid, brine to neutrality, dried and evaporated. The residue was crystallised from water to give 5,7-dihydroxycoumarin as a light tan solid (6.58g.; 74%), m.p. 267-270° decomp. (lit.[109] m.p. 280° decomp.).

5,7-Diacetoxycoumarin(124)[109]

A solution of 5,7-dihydroxycoumarin (6.5g.) in acetic anhydride (25ml.) with a few drops of conc. sulphuric acid was heated on a steam bath for 20 min. On cooling, the solution was diluted with iced water (250ml.), left for 2 hr. and then extracted with ethyl acetate. The organic layer was washed with brine to neutrality, dried and evaporated. The residue, on crystallisation from ethyl

acetate, yielded 5,7-diacetoxycoumarin as colourless needles

(8.23g.; 86%), m.p. 139-140.5° (lit.[109] m.p. 139.5-141°);

$\nu_{max}^{CHCl_3}$ 1778, 1730 and 1630 cm.$^{-1}$; n.m.r. signals at τ 7.67

(3H ; s.), 7.60 (3H ; s.), 3.64 (1H ; d.; J 9.5 Hz.), 3.05 (1H ; d.;

J 1.5 Hz.), 2.99 (1H ; d.; J 1.5 Hz.) and 2.31 (1H ; d.; J 9.5 Hz.).

Sublimation of the crude diacetate at 160°/0.02 mm. provided

a fast and efficient method of purification but the yield was $\sim$ 20%

lower than that obtained by crystallisation.

5-Methoxy-7-hydroxycoumarin(127)

§1. Potassium carbonate (7g.) and methyl iodide (7ml.) were added

to a solution of 5,7-diacetoxycoumarin (3.5g.) in acetone (350ml.).

After refluxing for 40 hr., further methyl iodide (3.5ml.) was

added and refluxing continued.   This was repeated 46 hr. after

the start of reflux.   After 49 hr., the inorganic solid was

filtered off and washed with hot acetone.   The acetone was evapor-

ated and since analytical t.l.c. indicated that some starting

material still remained, the residue was dissolved in acetone

(350ml.) with potassium carbonate (7g.) and methyl iodide (3.5ml.).

After refluxing for 6 hr., the solvent was evaporated and the

residue dissolved in aqueous methanol (50% v./v.; 200ml.).   The

solution was heated on a steam bath for 15 min., allowed to cool

and neutralised with dil. hydrochloric acid.   Most of the solvent

was then removed and the residue dissolved in a mixture of ethyl

acetate and aqueous sodium hydroxide (0.5% w./v.).   The organic

layer was washed with aqueous sodium hydroxide (0.5%) until the

basic washings were colourless. The combined washings were carefully neutralised with dil. hydrochloric acid and set aside. The ethyl acetate solution was washed with brine to neutrality, dried and evaporated. The residue was crystallised from methanol yielding 5,7-dimethoxycoumarin(126) as pale yellow needles (0.16g.; 6%), m.p. 145-147° (lit.[117] m.p. 145°); n.m.r. signals at τ 6.15 (3H ; s.), 6.12 (3H ; s.), 3.89 (1H ; d.; J 9.5 Hz.), 3.75 (1H ; d.; J 2 Hz.), 3.62 (1H ; d.; J 2 Hz.) and 2.11 (1H ; d.; J 9.5 Hz.).

The neutralised washings were extracted with ethyl acetate and the organic layer washed with brine, dried and evaporated. The residue was fractionally crystallised from methanol yielding 5-methoxy-7-hydroxycoumarin as colourless needles (1.04g.; 41%), m.p. 241-244° (lit.[117] m.p. 243-245°); λ_{max} 221, 247, 257 and 330 nm. (logϵ 4.02, 3.72, 3.74 and 4.14); λ_{max} (base) 236, 271 and 374 nm. (logϵ 3.96, 3.79 and 4.29).

The mother liquors yielded a crystalline mixture (0.48g.; 19%) of 5-methoxy-7-hydroxycoumarin and the isomer 5-hydroxy-7-methoxy-coumarin (ratio ~2:1) (identification from t.l.c. behaviour and the u.v. spectra of small amounts of the two separated).

5-Methoxy-7-hydroxycoumarin(127)

§ 2. In a similar manner to the procedure above, a mixture of 5,7-diacetoxycoumarin (2g.), potassium carbonate (2g.), methyl iodide (1.5ml.) and acetone (100ml.) was refluxed for 24 hr. Analytical t.l.c. indicated only starting material. Water (2ml.) was added and after refluxing for a further 6 hr., work up, hydrolysis and

fractional crystallisation (as above) yielded:-

    i)   5,7-dimethoxycoumarin(126) (0.10g.; 6.5%).

    ii)   5-methoxy-7-hydroxycoumarin(127) (0.57g.; 39%).

    iii) a mixture of the two isomers, 127 and 133, (0.36g.; 24%).

Dimethylallylation of 5,7-dihydroxycoumarin

Potassium carbonate (200mg.) was added to a solution of 5,7-dihydroxycoumarin (200mg.) in acetone (20ml.) and the mixture stirred at R.T. for 1 hr. Dimethylallyl bromide (400mg.) was then added and the solution refluxed for $4\frac{1}{2}$ hr. Work up (I) gave an oily solid which was separated by preparative t.l.c. (chloroform x 1) into:-

    i)   <u>the bis-ether</u>(128), from ether-light petroleum as colourless needles (182mg.; 52%), m.p. 79-81°. (Found: C, 72.80; H, 7.15. $C_{19}H_{22}O_4$ requires C, 72.60; H, 7.05%); $\nu_{max}^{CHCl_3}$ 1725-1715 and 1608 cm.$^{-1}$; mass spectral peaks at m/e 314 (M^+), 244, 178, 149, 69 and 41 (r.a. 2, 5, 59, 9, 100 and 72%); n.m.r. signals at τ 8.20 (12H ; b.s.), 5.46 (4H ; b.d.; J 6.5Hz.), 4.53 (2H ; b.t.; J 6.5 Hz.), 3.94 (1H ; d.; J 9.5 Hz.), 3.74 (1H ; d.; J 2 Hz.), 3.65 (1H ; d.; J 2 Hz.) and 2.10 (1H ; d.; J 9.5 Hz.).

    ii) the hydroxy-ether(129) as a white solid (22′mg.; 5%); λ_{max} 226 (sh.), 255 (sh.), 262 and 334 nm.; λ_{max} (base) 249, 277 and 390 nm. (390 nm. ε > 331 nm. ε); mass spectral peaks at m/e 314 (M^+); n.m.r. signals at τ 8.22 (12H ; b.s.), 6.47 (2H ; b.d.; J 7 Hz.), 5.45 (2H ; b.d.; J 6.5 Hz.), ~ 4.63 (2H ; b.m.), 3.88 (1H ; d.; J 9.5 Hz.), 3.68 (1H ; s.), ~ 3.55° (1H ; b.s.) and 2.00 (1H ; d.; J 9.5 Hz.).

iii) a mixture (13mg.) of at least two compounds (by analytical t.l.c.).

iv) <u>5-0-(3,3-dimethylallyl)-7-hydroxycoumarin</u>(130), from ether as colourless plates (66mg.; 23%), m.p. 143.5-145°. (Found: C, 68.00; H, 5.60. $C_{14}H_{14}O_4$ requires C, 68.30; H, 5.75%); $\nu \frac{CCl_4}{max}$ (saturated solution) 3600, $\sim$ 3330 (broad), 1745, 1716 and 1705 cm.$^{-1}$; $\nu \frac{CHCl_3}{max}$ (S.P.100) 3585, $\sim$ 3287, 1721, 1697, 1613 and 1575 cm.$^{-1}$ (ε 100, 120, 740, 610, 1440 and 260); λ_{max} 249, 258 and 333 nm. (logε 3.79, 3.81 and 4.13); λ_{max} (base) 239, 274 and 386 nm. (logε 3.83, 3.74 and 4.25); mass spectral peaks at m/e 246 (M^+), 231, 191, 179, 178, 150, 69 and 41 (r.a. 8, 5, 15, 10, 89, 36, 100 and 67%); n.m.r. signals at τ 8.27 (3H ; s.), 8.22 (3H ; s.), 5.45 (2H ; b.d.; J 6.5 Hz.), 4.53 (1H ; b.t.; J 6.5 Hz.), 3.88 (1H ; d.; J 9.5 Hz.), 3.65 (1H ; d.; J 2 Hz.), 3.39 (1H ; d.; J 2 Hz.), 1.97 (1H ; d.; J 9.5 Hz.) and 1.50$^\bullet$ (1H ; b.s.).

This experiment was repeated using a shorter reflux time ($3\frac{1}{2}$ hr.). This gave the bis-ether(128) (46%), the C-alkylated compound (129) (3%) and the mono-ether (130) (20%).

Confirmation of structure assigned to 129

Methylation of the C-alkylated compound 129 (21′mg.), using methyl iodide (0.1ml.) and potassium carbonate(20mg.) in refluxing acetone (2ml.), gave after 2 hr. an oily methyl ether (20′mg.); n.m.r. signals at τ 8.35 (3H ; b.s.), 8.18 (9H ; b.s.), 6.57 (2H ; b.d.; J 7 Hz.), 6.07 (3H ; s.), 5.40 (2H ; b.d.; J 6.5 Hz.), 4.79 (1H ; b.t.; J ?), 4.51 (1H ; b.t.; J ?), 3.90 (1H ; d.; J 9.5 Hz.), 3.67 (1H ; s.)

and 2.03 (1H ; d.; J 9.5 Hz.).

A solution of this methyl ether (20 mg.) in methanol (1ml.) and conc. hydrochloric acid (5 drops) was refluxed for $1\frac{1}{2}$ hr. On cooling, the solution was neutralised with dil. sodium hydroxide and then most of the solvent evaporated.   The remainder was diluted with iced water (10ml.) and extracted with ethyl acetate.   The organic layer was washed with brine, dried and evaporated.   The residue, after purification by preparative t.l.c. (chloroform x 1) yielded 5-hydroxy-7-methoxy-8-(3,3-dimethylallyl)coumarin as an off-white solid (11 mg.); λ_{max} 225 (sh.), 255 (sh.), 261 and 322 nm.; λ_{max} (base) 238 (sh.), 275, 325 and 391 nm. (391 nm.ε $<$ 322 nm.ε).

Treatment of this phenol (11 mg.) with methyl iodide and potassium carbonate (10mg.) in refluxing acetone (1ml.) for 2 hr. gave a pale yellow oil which was distilled at $160^{o}/0.04$ mm.   On standing the distillate solidified as a pale yellow solid (6mg.). The physical properties (m.p., m.m.p., i.r.) of this compound were identical with those of coumurrayin(131) (synthesis p. 112-114).

5-O-(3,3-Dimethylallyl)-7-methoxycoumarin(132)

5-O-(3,3-Dimethylallyl)-7-hydroxycoumarin(130) (49mg.) was converted (see scoparin p.64) to the methyl ether 132, using potassium carbonate (95mg.), methyl iodide (0.5ml.) and acetone (10ml.).   After refluxing for 3 hr., work up (I) gave a yellow solid which, on crystallisation from light petroleum, yielded the methyl ether (132) as pale yellow needles (48 mg.; 92%), m.p. 93-95° (lit.[65b]90-92°).(Found: C, 69.20; H, 6.10.   Calc. for $C_{15}H_{16}O_4$ C, 69.20; H, 6.20%);

$\nu_{max}^{CHCl_3}$ 1720, 1610 and 1560 (very weak) cm.$^{-1}$; mass spectral peaks at m/e 260 (M$^+$), 192, 164, 149, 135, 69 and 41 (r.a. 7, 80, 40, 13, 9, 100 and 92%); n.m.r. signals at τ 8.27 (3H ; b.s.), 8.23 (3H ; b.s.), 6.17 (3H ; s.), 5.44 (2H ; b.d.; J 6.5 Hz.), 4.53 (1H ; b.t.; J 6.5. Hz.), 3.89 (1H ; d.; J 9.5 Hz.), 3.74 (1H ; d.; J 2 Hz.), 3.62 (1H ; d.; J 2 Hz.) and 2.05 (1H ; d.; J 9.5 Hz.).

5-Hydroxy-7-methoxycoumarin(133)

A solution of 132 (10mg.) in methanol (5ml.) and conc. hydrochloric acid (5 drops) was refluxed for 2 hr. On cooling, it was neutralised with dil. sodium hydroxide and most of the solvent evaporated. The remainder was diluted with water (10ml.) and extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated. The residue after sublimation at 180°/0.03 mm., yielded 5-hydroxy-7-methoxycoumarin as a white solid (6.5mg.) (88%), m.p. 227-230° (lit.[131] m.p. 228-229°); λ_{max} 249, 258 and 327 nm. (log ε 3.70, 3.73 and 4.05); λ_{max} (base) 235 (sh.), 271, 325 and 390 nm. (log ε 3.82, 3.92, 3.84 and 3.79).

5-Methoxy-7-O-(3,3-dimethylallyl)coumarin(120)

This ether was made from 5-methoxy-7-hydroxycoumarin(127) (150mg.) by using potassium carbonate (150mg.), 3,3-dimethylallyl bromide (200mg.) and acetone (50ml.). After refluxing for 12 hr., work up (I) yielded a low melting solid which, on crystallisation from ether-light petroleum, gave the ether(120) as colourless needles (174mg.; 85%), m.p. 101-102°. (Found: C, 69.35; H, 6.10. $C_{15}H_{16}O_4$ requires

C, 69.20; H, 6.20%); $\nu_{max}^{CHCl_3}$ 1720, 1603 and 1560 (very weak) cm.$^{-1}$;

mass spectral peaks at m/e 260, 245, 205, 193, 192, 164, 69 and 41

(r.a. 5, 5, 6, 12, 100, 47, 35 and 31); n.m.r. signals at τ 8.32

(6H ; b.s.), 6.20 (3H ; s.), 5.55 (2H ; b.d.; J 6.5 Hz.), 4.62

(1H ; b.t.; J 6.5 Hz.), 3.99 (1H ; d.; J 9.5 Hz.), 3.80 (1H ; d.;

J 2 Hz.), 3.70 (1H ; d.; J 2 Hz.) and 2.17 (1H ; d.; J 9.5 Hz.).

5-Methoxy-7-hydroxycoumarin n-butyrate

A solution of 5-methoxy-7-hydroxycoumarin(127) (25mg.) and

n-butyric anhydride (0.1ml.) in dry pyridine (0.2ml.) was left at

R.T. for 2 hr. Work up (II) yielded a white solid which was

sublimed at 145°/0.15 mm. This gave the required butyrate as

colourless needles (31mg.; 91%), m.p. 116-118°. (Found: C, 64.30;

H, 5.30. $C_{14}H_{14}O_5$ requires C, 64.10; H, 5.40%); $\nu_{max}^{CHCl_3}$ 1765,

1730 and 1610 cm.$^{-1}$; mass spectral peaks at m/e 262 (M$^+$), 192,

165, 71 and 43 (r.a. 11, 100, 39, 23 and 40%); n.m.r. signals at

τ 8.95 (3H ; t.; J 7 Hz.), 8.22 (2H ; sextet ; J 7 Hz.), 7.43

(2H ; t.; J 7 Hz.), 6.10 (3H ; s.), 3.76 (1H ; d.; J 9.5 Hz.),

3.54 (1H ; d.; J 2 Hz.), 3.34 (1H ; d.; J 2 Hz.) and 2.05 (1H ; d.;

J 9.5 Hz.).

Pyrolysis of 5-methoxy-7-0-(3,3-dimethylallyl)coumarin(120)

Oxygen-free nitrogen was passed over a suspension of 120 (60mg.) in N,N-diethylaniline (0.5ml.) and n-butyric anhydride (0.3ml.) for 1 hr. With a continuous nitrogen flow, the suspension was shaken at $185 \pm 5^{\circ}$ for 5 min. to ensure that the melt had gone into solution. The temperature was then maintained at this level for 8 hr. On cooling, large colourless crystals precipitated. The mixture was diluted with iced water (10ml.), left at R.T. for 2 hr. and then extracted with ethyl acetate. The organic layer was washed with dil. hydrochloric acid (1% w./v.) to pH 2, dil. potassium carbonate (5% w./v.) to pH 11, brine to neutrality, dried and evaporated. The residue was purified by preparative t.l.c. (30% ethyl acetate-light petroleum x $\frac{1}{2}$ x 1; then chloroform x 1) which removed the remaining diethylaniline and butyric anhydride, and then sublimed at $155^{\circ}/0.02$ mm. This yielded the butyrate(140) as colourless needles (70mg.; 92%), m.p. 162-164°. (Found: C, 68.80; H, 6.45. $C_{19}H_{22}O_5$ requires C, 69.05; H, 6.70%); $\nu_{max}^{CHCl_3}$ 1755, 1720, 1625 (weak) and 1598 cm.$^{-1}$; mass spectral peaks at m/e 330 (M$^+$), 315, 261, 260, 246, 245, 217, 205, 71 and 43 (r.a. 23, 14, 9, 47, 16, 100, 16, 40, 27 and 42%); n.m.r. signals at τ 8.97 (3H ; t.; J 7 Hz.), 8.39 (6H ; s.), $\sim$8.31 (2H ; m.), 7.51 (2H ; t.; J 7 Hz.), 6.14 (3H ; s.), 5.14 (1H ; b.d.; J 10 Hz.), 5.11 (1H ; b.d.; J 18 Hz.), 3.76 (1H ; d./d.; J 10 & 18 Hz.), 3.74 (1H ; d.; J 9.5 Hz.), 3.74 (1H ; s.) and 1.98 (1H ; d.; J 9.5 Hz.).

5-Methoxy-7-hydroxy-8-(1,1-dimethylallyl)coumarin(141)

The butyrate 140 (32mg.) was dissolved in ethanol (5ml.) with gentle heating. Sodium hydroxide in ethanol (1% w./v.; 1ml.) was added and the solution heated on a steam bath until a bright blue-green fluorescence appeared ($\sim$1 min.). The solution was then carefully neutralised with dil. hydrochloric acid ($\sim$1% w./v.) and most of the solvent evaporated. The residue was diluted with water (25ml.) and extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated. After preparative t.l.c. (30% ethyl acetate-light petroleum x 2), the residue was crystallised from ether to give the hydroxy-ether(141) as colourless needles (22mg.; 86%), m.p. 161-166° decomp. (Found: C, 69.05; H, 6.25. $C_{15}H_{16}O_4$ requires C, 69.20; H, 6.20%); $\nu_{max}^{CHCl_3}$ 3410, 1720-1710, 1620 (sh.) and 1592 cm.$^{-1}$; $\nu_{max}^{CCl_4}$ 3428, 1755 (sh.), 1739, 1626 and 1599 cm.$^{-1}$ (ε 310, 350, 1140, 490 and 1110); λ_{max} 225, 255, 262 and 332 nm. (log ε 4.02, 3.87, 3.89 and 4.11); λ_{max} (base) 253, 281 and 400 nm. (log ε 3.91, 3.96 and 4.30); mass spectral peaks at m/e 261, 260, 246, 245, 217, 205 and 189 (r.a. 10, 53, 22, 100, 43, 50 and 20%); n.m.r. signals at τ 8.29 (6H ; s.), 6.13 (3H ; s.), 4.63 (1H ; d.; J 10.5 Hz.), 4.54 (1H ; d.; J 18 Hz.), 3.86 (1H ; d.; J 9.5 Hz.), 3.74 (1H ; s.), 3.51 (1H ; d./d.; J 10.5 & 18 Hz.), 2.71 (1H ; s.) and 1.98 (1H ; d.; J 9.5 Hz).

5-Methoxy-7-hydroxy-8-(1,1-dimethylpropyl)coumarin(142)

The hydroxy-ether 141 (25mg.) in ethyl acetate (20ml.) was hydrogenated at R.T. over palladium-barium sulphate (5% w./w.; 15mg.). After 2 hr., filtration of the catalyst and removal of solvent yielded the dihydro compound(142) which crystallised from ether as pale yellow needles (20mg.; 80%), m.p. 222-226° decomp. (Found: C, 68.85; H, 6.85. $C_{15}H_{18}O_4$ requires C, 68.70; H, 6.90%); $\nu_{max}^{CCl_4}$ (saturated solution) 3629, 3599, 1738 and 1625 cm.$^{-1}$; n.m.r. signals (deuteropyridine) at τ 9.03 (3H ; t.; J 7 Hz.), 8.08 (6H ; s.), 7.73 (2H ; q.; J 7 Hz.), 6.30 (3H ; s.), 3.78 (1H ; d.; J 9.5 Hz.), 3.43 (1H ; s.) and 2.01 (1H ; d.; J 9.5 Hz.).

5,7-Dimethoxy-8-(1,1-dimethylallyl)coumarin (pinnarin) (122)

The hydroxy-ether(141) (34mg.) was converted (see scoparin p.64) to its methyl ether, using potassium carbonate (100mg.), methyl iodide (0.2ml.) and acetone (5ml.). After refluxing for 12 hr., work up (I) yielded a dimethyl ether which crystallised from ether as colourless needles (30mg.; 84%), m.p. 166-167° (lit.[14] m.p.162-163°). (Found: C, 70.05; H, 6.45. Calc. for $C_{16}H_{18}O_4$ C, 70.05; H, 6.60%); $\nu_{max}^{CCl_4}$ 1736, 1622 and 1598 cm.$^{-1}$; λ_{max} 223, 254, 261 and 328 nm. (log ε 4.09, 3.96, 3.98 and 4.15); mass spectral peaks at m/e 275, 274 (M$^+$), 260, 259, 231 and 219 (r.a. 12, 63, 17, 100, 35 and 29%); n.m.r. signals at τ 8.34 (6H ; s.), 6.15 (3H ; s.), 6.07 (3H ; s.), 5.15 (1H ; d.; J 10 Hz.), 5.14 (1H ; d.; J 18 Hz.), 3.87 (1H ; d.; J 9.5 Hz.), 3.71 (1H ; d./d.; J 10 & 18 Hz.), 3.67 (1H ; s.) and 2.03 (1H ; d.; J 9.5 Hz.). This compound was shown to be identical with an authentic sample of pinnarin (m.p.,m.m.p.,i.r.).

Scopoletin n-butyrate

A solution of scopoletin(41) (25 mg.) and n-butyric anhydride (0.1ml.) in dry pyridine (0.2ml.) was left at R.T. for 4 hr. Work up (II) gave a colourless oil which, after preparative t.l.c. (chloroform x 1), was distilled at 135°/0.03 mm. On standing the distillate partially solidified to give the butyrate as a colourless oily solid (31mg.; 91%). (Found: C, 64.35; H, 5.35. $C_{14}H_{14}O_5$ requires C, 64.10; H, 5.40%); n.m.r. signals at τ 8.96 (3H ; t.; J 7 Hz.), 8.21 (2H ; m.), 7.43 (2H ; t.; J 7 Hz.), 6.16 (3H ; s.), 3.65 (1H ; d.; J 9.5 Hz.), 3.06 (1H ; s.), 2.97 (1H ; s.) and 2.38 (1H ; d.; J 9.5 Hz.).

3-(1,1-Dimethylallyl)scopoletin n-butyrate

A solution of the 'out-of-ring' compound (76) (18mg.) and n-butyric anhydride (0.1ml.) in dry pyridine (0.2ml.) was left at R.T. for 4 hr. Work up (II) gave a colourless oil which, after preparative t.l.c. (chloroform x 1) was distilled at 140°/0.03 mm. On standing the distillate solidified to yield the butyrate as colourless plates (26mg.; 84%), m.p. 98-99°. (Found: C, 69.25; H, 6.70. $C_{19}H_{22}O_5$ requires C, 69.05; H, 6.70%); n.m.r. signals at τ 8.94 (3H ; t.; J 6.5 Hz.), 8.50 (6H ; s.), 8.19 (2H ; b.m.), 7.41 (2H ; t.; J 6.5 Hz.), 6.13 (3H ; s.), 4.91 (1H ; d.; J 18 Hz.), 4.88 (1H ; d.; J 10 Hz.), 3.79 (1H ; d./d.; J 18 & 10 Hz.), 3.06 (1H ; s.), 2.98 (1H ; s.) and 2.48 (1H ; s.).

Pyrolysis of 7-0-(3,3-dimethylallyl)scopoletin(61)

Using the same procedure as that employed for the pyrolysis of 7-0-(3,3-dimethylallyl)-5-methoxycoumarin(120) (p.89), the ether(61) (120mg.) was heated at 180° in N,N-diethylaniline (1ml.) and n-butyric anhydride (0.6ml.). After 3 hr. analytical t.l.c. indicated that some starting material remained. The temperature was, therefore, maintained at 180° for a further 12 hr. During this period of time, an excess flow of nitrogen resulted in the evaporation of most of the diethylaniline and butyric anhydride. The pale amber oil which remained was separated by preparative t.l.c. (35% ethyl acetate-light petroleum x ½ x 1) into:-

i) 3-(1,1-dimethylallyl)scopoletin n-butyrate (34mg.; 22%) (m.p., m.m.p., n.m.r.).

ii) obliquetin n-butyrate as a colourless oil which, after distillation at 150°/0.008 mm., solidified as a white solid (48mg.; 31%), m.p. 104-106°. (Found: C, 69.30; H, 6.65. $C_{19}H_{22}O_5$ requires C, 69.05; H, 6.70%); n.m.r. signals at τ 8.97 (3H ; b.t.; J 6.5 Hz.), 8.34 (6H ; s.), 8.24 (2H ; b.m.), 7.49 (2H ; b.t.; J 6.5 Hz.), 6.19 (3H ; s.), 5.12 (1H ; d./d.; J 10 & 1.5 Hz.), 5.07 (1H ; d./d.; J 18 & 1.5 Hz.), 3.71 (1H ; d./d.; J 10 & 18 Hz.), 3.66 (1H ; d.; J 9.5 Hz.), 3.17 (1H ; s.) and 2.40 (1H ; d.; J 9.5 Hz.).

iii) scopoletin n-butyrate (46mg.; 38%) (n.m.r.).

Attempted hydrolyses of obliquetin n-butyrate

a) Sodium hydroxide in ethanol (1% w./v.; 1ml.) was added to a warm
solution of obliquetin butyrate (36mg.) in ethanol (5ml.).   The
mixture was heated on a steam bath for 1 min.   The same procedure
as that employed in the hydrolysis of 7-demethylpinnarin butyrate
(p.90) yielded an oil which, after preparative t.l.c. (chloroform x 1)
gave recovered starting material (33´mg.) (identified from n.m.r.
spectrum).

b) This was repeated using obliquetin butyrate (33´mg.), ethanol (5ml.)
and sodium hydroxide in ethanol (1% w./v.; 2ml.).   After heating
the solution on a steam bath for 1 min., the same procedure as before
yielded a yellow oil from which starting material (28´mg.) was
recovered.   The n.m.r. spectrum of the oil before purification did
not indicate the presence of obliquetin.

c) Aqueous sodium carbonate (2% w./v.; 10ml.) was added to a solution
of obliquetin butyrate (28´mg.) in methanol (10ml.).   After refluxing
for 30 min., the same procedure as before yielded a brown oil from
which starting material (16´mg.) was recovered.   The n.m.r. spectrum
of the brown oil, before purification,did not indicate the presence
of obliquetin.

4-Methylumbelliferone n-butyrate

Using the same procedure as that employed for the synthesis of scopoletin butyrate, 4-methylumbelliferone (115) (25mg.) was converted to the butyrate (33´mg.; 94%); n.m.r. signals at τ 8.93 (3H ; b.t.; J 6.5 Hz.), 8.27 (2H ; b.m.), 7.57 (3H ; d.; J∼1 Hz.), 7.42 (2H ; b.t.; J 6.5 Hz.), 3.74 (1H ; b.s.), 2.96 (1H ; d./d.; J 9.5 & 2.5 Hz.), 2.87 (1H ; b.s.) and 2.40 (1H ; d.; J 9.5 Hz.).

Pyrolysis of 7-0-(3,3-dimethylallyl)-4-methylumbelliferone(116)

Using the same procedure as that employed for the pyrolysis on p.89, the ether(116) (60mg.) was heated at 180° in N,N-diethyl-aniline (0.5ml.) and n-butyric anhydride (0.3ml.) for 36 hr. After work up, the yellow oil was separated, by preparative t.l.c. (50% ethyl acetate-light petroleum x 2), into:-

    i)   a mixture (60mg.) of four compounds (estimated from the n.m.r. spectrum).

    ii)   4-methylumbelliferone butyrate (18´mg.) (n.m.r. spectrum).

PART II

Pyrolyses of 1,1-Dimethylallyloxycoumarins.

Scheme 2.1

(146)

Scheme 2.2

(41)   (143)
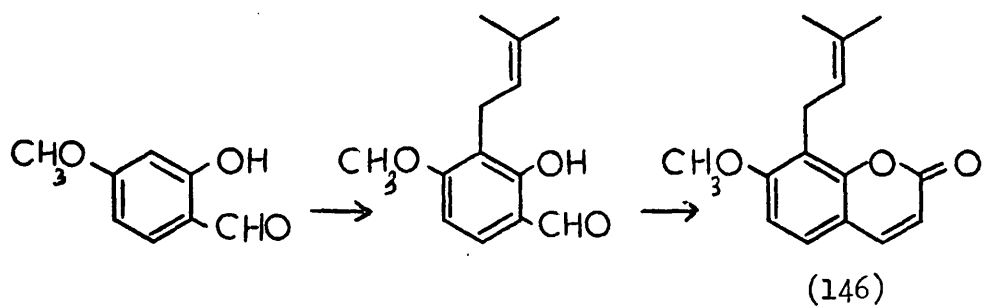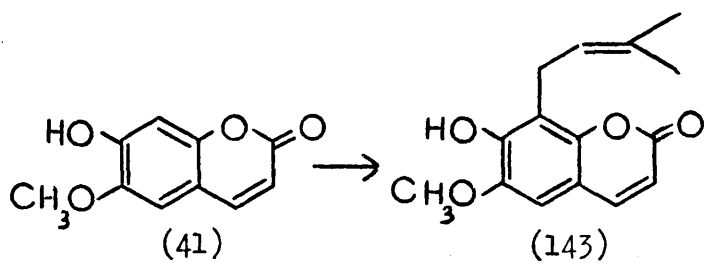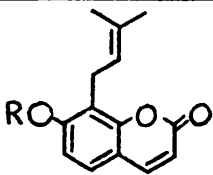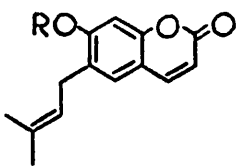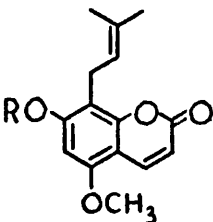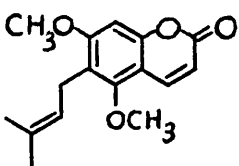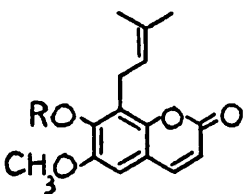
The 3,3-dimethylallyl residue is a unit commonly encountered among natural compounds which are essentially non-terpenoid. The synthesis of such a unit, attached to a benzenoid ring, has received considerable attention.

Two methods have been developed to synthesise ortho-(3,3-dimethylallyl)hydroxycoumarins. The first, developed by Spath[134], involves C-alkylation of a substituted salicylaldehyde, followed by formation of the ∝-pyrone ring, as outlined in Scheme 2.1. This method suffers from the necessity of preparing a correctly substituted aldehyde. The second general method involves C-alkylation of a preformed hydroxycoumarin nucleus (Scheme 2.2). The yields in this case are generally very poor. Only scopoletin(41) has been found[135,136] to give reasonable results on C-alkylation. Table 2.1 summarises the results obtained for the syntheses of several simple coumarins by these methods.

It was felt that an obvious extension to the work on 3,3-dimethylallyl ethers would be the rearrangement of 1,1-dimethylallyl ethers. In this way, a 3,3-dimethylallyl residue could be inserted into the benzenoid ring and thus provide an alternative to the methods discussed above.

There should be many advantages to the 'Claisen Rearrangement' of coumarin 1,1-dimethylallyl ethers. Apart from being able to utilise a preformed coumarin nucleus, problems such as cyclisation, cleavage and the abnormal rearrangement, which hindered the use of

| Table 2.1 | A C-alkylation of a salicylaldehyde |
| | B C-alkylation of a hydroxycoumarin |

Structure	Method / Yield
(21) R=H, osthenol (146) R=CH$_3$, osthol	A 1% of 146 from 4-methoxy-2-hydroxy-benzaldehyde[134]. B ~5% of the cyclic ether of 21 from umbelliferone[138].
(22) R=H (147) R=CH$_3$, suberosin	A 3% of 22 from 2,4-dihydroxy-benzaldehyde[138]. B ~5% of the cyclic ether of 22 from umbelliferone[138].
(155) R=H (131) R=CH$_3$, coumurrayin	A 1-2% of 155 from 2-hydroxy-4,6-dimethoxybenzaldehyde[67,114a]. B ~8% of 155 from 7-hydroxy-5-methoxycoumarin[114b]. B ~0.4% of the cyclic ether of 155 from 7-hydroxy-5-methoxycoumarin[67].
(148) toddaculin[115a]	not synthesised
(143) R=H, cedrelopsin (149) R=CH$_2$CH:C(CH$_3$)$_2$ brayleanin	A - B 50% of 143 from scopoletin[135,136].

Scheme 2.3

(4)   (144)   (145)
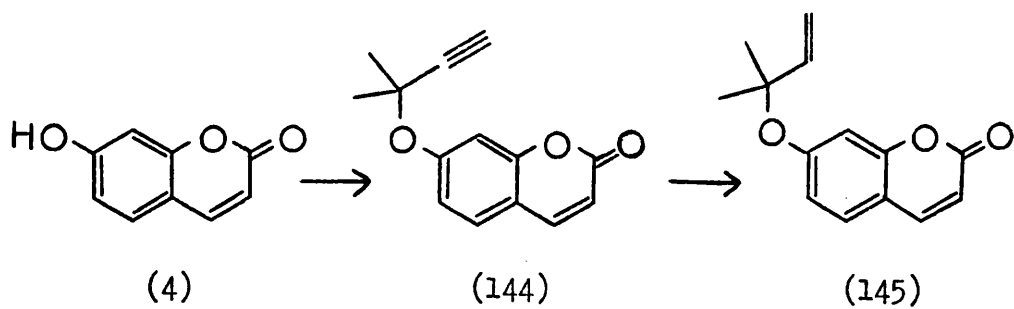
Scheme 2.4

(144) $\xrightarrow{\Delta}$
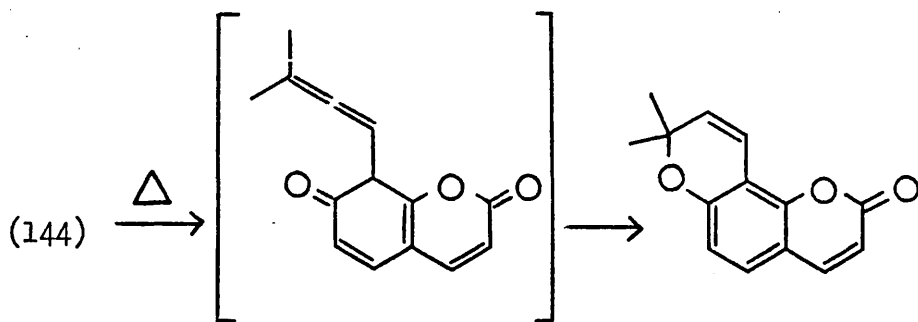
3,3-dimethylallyl ethers, should be absent.

A method of synthesising 1,1-dimethylallyl ethers was suggested by Professor R. A. Raphael. He felt that such ethers might be synthesised via the corresponding 1,1-dimethylpropargyl ethers (Scheme 2.3). At that time, while pursuing another line of research, Murray and Gillies synthesised[137] 7-0-(1,1-dimethylallyl)-scopoletin by this method. Although as a synthetic route the results did not appear promising, it was felt that by modifying the propargyl ether formation conditions and those for the selective reduction, it might be possible to make Scheme 2.3 a viable proposition.

Thus, by refluxing a solution of umbelliferone(4) in aqueous acetone with 1,1-dimethylpropargyl chloride[140] in the presence of potassium carbonate and potassium iodide, the required propargyl ether (144) was obtained in 77% yield. The n.m.r. spectrum of this coumarin contains a six proton singlet at τ 8.27 and a one proton singlet at τ 7.32, indicative of a 1,1-dimethylpropargyloxy unit. A by-product ($\sim$3%), M^+ 228, from this reaction has not yet been identified. It appears to be neither an allene nor a chromene.

The melting point of 144 is fairly broad, 136-140°, and the n.m.r. spectrum obtained after allowing this compound to melt on a Kofler hot-stage apparatus, contains a pair of doublets (J 10 Hz.) at τ 4.32 and 3.30. Hlubucek, Ritchie and Taylor have since shown[141] that the propargyl ether 144, prepared in a similar manner, readily rearranges by a 'Claisen Rearrangement'[80, 84, 141, 142] to C-8 to give the corresponding 2,2-dimethylchromene (Scheme 2.4).

It could, therefore, be that the doublets observed in the n.m.r. spectrum of the above melt are due to a very small amount of rearrangement which takes place at the melting point.

Hydrogenation of 7-O-(1,1-dimethylpropargyl)umbelliferone(144), over palladium-barium sulphate with thiourea as a poison, gave poor and variable results. However, if quinoline-sulphur[143] was employed as the poison, hydrogenation afforded 7-O-(1,1-dimethyl-allyl)umbelliferone(150) in 96% yield. Consistently good results were obtained by this procedure. Hydrogenolysis occurs during the reduction but only to a slight extent (~1.5%).

The n.m.r. signals of a 1,1-dimethylallyloxy unit are similar to those of the C_5H_9 unit attached to the benzenoid ring the gem-dimethyls appearing at τ 8.45 instead of approximately τ 8.3 . 7-O-(1,1-Dimethylallyl)umbelliferone is quite stable in the crystalline form but has a broad melting point, 75-78°. Analytical t.l.c. of the melt revealed the presence of a very small amount of more polar material which was later shown, by analytical t.l.c., to be probably the result of rearrangement.

Pilot pyrolyses of the allyl ether (150) indicated that a lower temperature than had been employed for the 3,3-dimethylallyl ethers would be sufficient for rearrangement. Thus, pyrolysis of 7-O-(1,1-dimethylallyl)umbelliferone at 130° for 1 hr. yielded three phenolic compounds. Umbelliferone(4) was isolated in approximately 5% yield and identified by its u.v. spectrum and t.l.c. behaviour. The remaining two coumarins had very similar t.l.c. mobilities but could
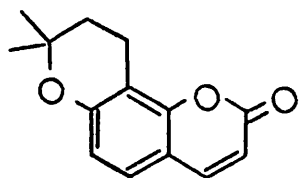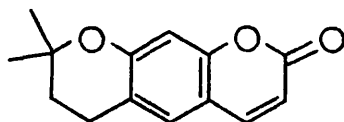
(151)   (152)

be separated by fractional preparative t.l.c.

The n.m.r. spectrum of the major product (74%) possesses an
α-pyrone AB system (τ 3.75, τ 2.35 ; J 9.5 Hz.), a pair of
doublets (τ 3.12, τ 2.78 ; J 9 Hz.) which can be attributed to
two ortho aromatic protons, and a one proton singlet (τ 2.67) which
disappears on addition of deuterium oxide to the solution. The
remainder of the spectrum can be accounted for by the presence of
a 3,3-dimethylallyl unit [(τ 8.27 ; 3H ; b.s.), (8.14 ; 3H ; b.s.),
(6.40 ; 2H ; b.d.; J 7 Hz.) and (4.72 ; 1H ; b.t.; J 7 Hz.)] attached
to the benzenoid ring. From this spectrum and other data collected,
it was deduced that this product was osthenol(21)[139], the result of
a 'Claisen Rearrangement' to C-8. This coumarin has not to our
knowledge been previously synthesised.

The minor product, 14% of the pyrolysis, possesses an n.m.r.
spectrum very similar to that of osthenol, the two ortho aromatic
proton signals being replaced by two para signals at τ 2.93 and
2.81. This coumarin was identical with an authentic sample of
7-demethylsuberosin(22)[138,144] kindly supplied by Dr. T. J. King[145].

The structure of the major product osthenol was confirmed by
the synthesis of its methyl ether, osthol(146)[134], and its cyclic
ether, dihydroseselin(151)[138]. Correspondingly, 7-demethylsuberosin
(22) was converted to suberosin(147)[133] and dihydroxanthyletin(152)[138].

Although not so selective as 7-0-(allyl)umbelliferone, the
above rearrangement did go predominantly to C-8 and enabled osthenol·
to be synthesised in a 55% yield from umbelliferone. These results

Scheme 2.5

Scheme 2.6

ratio ~2:3
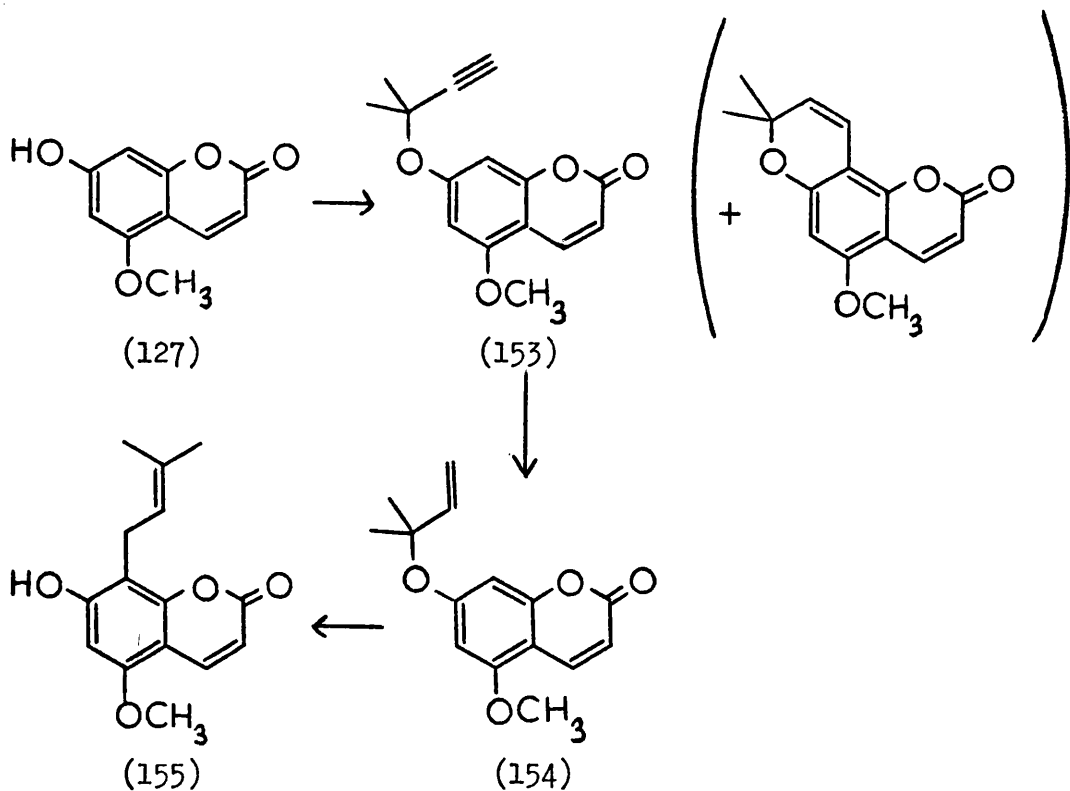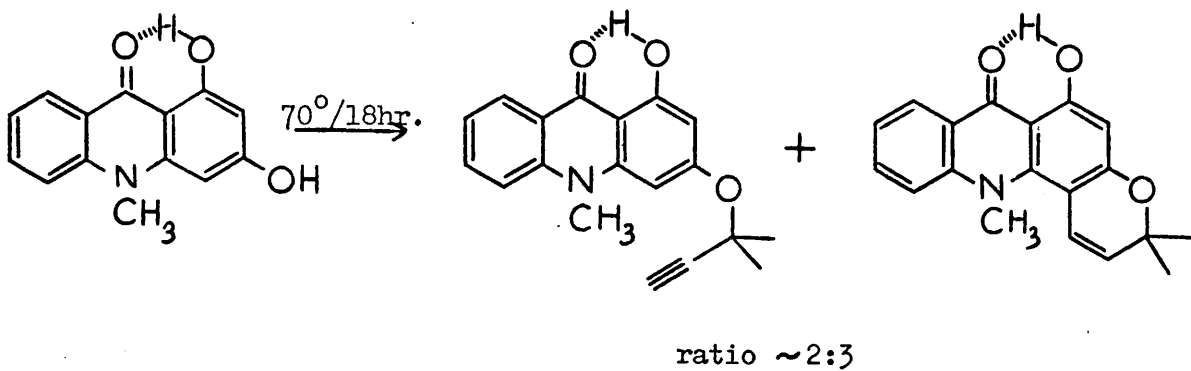
were sufficiently encouraging to promote a further investigation
into this route as a method for introducing a 3,3-dimethylallyl
grouping ortho to a phenol.

Unlike 7-demethylpinnarin(141) (Part Ic), 7-demethylsuberosin
and osthenol possess both free and bonded hydroxyl stretching
frequencies in their i.r. spectra.   Intermolecular hydrogen
bonding is very persistent in 7-demethylsuberosin.   However, at
very low concentrations, the values of 3598 and 3449 cm.$^{-1}$ can be
attributed to free and intramolecular hydrogen bonded hydroxyl
bands.   These results are similar to the values (3614 and 3486 cm.$^{-1}$)
reported[122] for ortho-(3,3-dimethylallyl)phenol.

The corresponding values obtained for osthenol are 3601 and
3408 cm.$^{-1}$.   The latter value is surprisingly low but unfortunately
only one dilution was made, and so it could be due to persistent
intermolecular hydrogen bonding.   Without a further examination
no conclusions can be reached.

Concurrently, preliminary investigations by Dr. K. P. Mathai,
of this department, had shown that coumurrayin(131)[66, 114] could
be synthesised from 7-hydroxy-5-methoxycoumarin in an analogous
manner (Scheme 2.5) to that employed for osthenol.   For publication,
this synthesis was repeated.

The parent phenol, 127, was prepared by the method of Seshadri
et al as described in Part Ic, and the propargyl ether by a similar
procedure to that described previously for 7-O-(1,1-dimethylpropargyl)-
umbelliferone.   It was found, however, that the method employed by

the author for the synthesis of 153, although providing a good
yield (74%) of the propargyl ether, also resulted in the production
of the corresponding chromene, 5-methoxyseselin, (10%).   A
similar rearrangement of a 1,1-dimethylpropargyl ether at low
temperature has been reported[142] by Hlubucek et al (Scheme 2.6).

Hydrogenation of the propargyl ether (153) over 'poisoned'
palladium-barium sulphate (p.99) yielded the allyl ether (154).
The minimum heating was employed while removing the solvent after
reduction.   The n.m.r. spectrum of the crude hydrogenation product
confirmed that a selective reduction had taken place.   One unusual
aspect of this allyl ether, noted by Dr. K. P. Mathai, was that it
appears to rearrange more readily than the umbelliferone counterpart.
Small traces of 'poison' can make crystallisation of these allyl
ethers difficult and so they were normally purified by preparative
t.l.c. prior to crystallisation.   However, in the case of 7-O-(1,1-
dimethylallyl)-5-methoxycoumarin, rearrangement appeared to occur
during this preliminary purification procedure.   Therefore,
although 154 was characterised by its n.m.r. spectrum, no analytical
data was obtained.

The crude product from hydrogenation was heated for 1 hr. in
a sublimation block at 160°.   The resulting solid was crystallised
from ethyl acetate-light petroleum and yielded 7-demethylcoumurrayin
(155)[114b] in 88% yield from 153.   The n.m.r. spectrum of 155 in
deuteropyridine confirms that a 3,3-dimethylallyl unit has been
inserted into the coumarin nucleus.   The physical and spectroscopic

data of this compound and of its methyl ether, coumurrayin, agree with the published figures[114b].

The mother liquors from the crystallisation of 7-demethyl-coumurrayin(155) contain, as estimated by analytical t.l.c., a small amount (~ 4%) of 7-hydroxy-5-methoxycoumarin, the result of a small amount of hydrogenolysis during the reduction and, perhaps, cleavage during the pyrolysis. The isomeric rearrangement product, 7-hydroxy-5-methoxy-6-(3,3-dimethylallyl)coumarin, was not detected.

Rearrangement has, therefore, proceeded exclusively to C-8. The overall yield (58%) of coumurrayin from the starting phenol is far superior to either of the C-alkylation methods (Table 2.1).

So far this method of introducing a 3,3-dimethylallyl unit ortho to a hydroxycoumarin has produced very promising results. However, an investigation into the scopoletin series was not so profitable.

Scopoletin(41) was prepared by hydrolysis of the corresponding dimethylallyl ether, 61, (Part Ia). The yield of 7-0-(1,1-dimethyl-propargyl)scopoletin(156) was only 41% using the same conditions as was described previously. It is perhaps significant that scopoletin is the only hydroxycoumarin which gives reasonable yields of direct C-dimethylallylation.

Only one hydrogenation of 156 was undertaken. The material was, unfortunately, over-hydrogenated and the mixture obtained was separated, by preparative t.l.c., into scopoletin (24%) and a less polar yellow oil. After distillation, it was apparent that the oil

Scheme 2.7
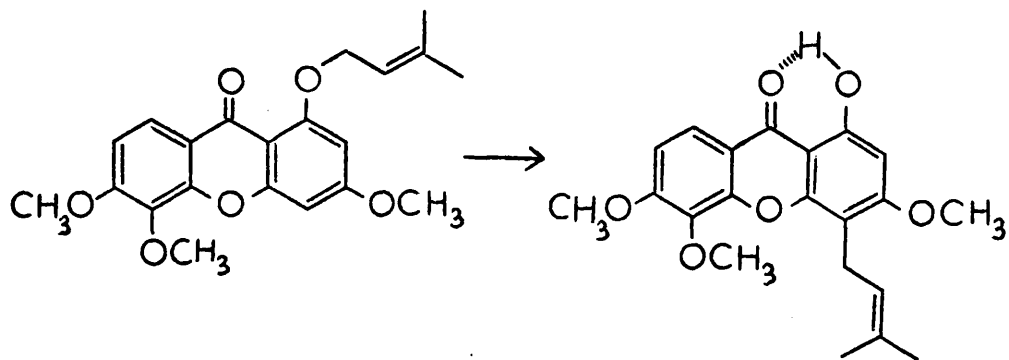
Scheme 2.8
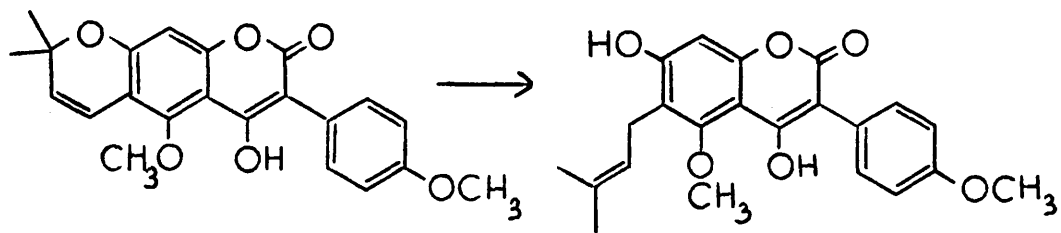
must have been a mixture of two components, namely 7-O-(1,1-dimethylpropyl)scopoletin(157) and 7-O-(1,1-dimethylallyl)scopoletin (158). This was deduced from the fact that the distillate was separated, by preparative t.l.c., into 157 (42%) and a phenol (15%), the latter being identified by m.p. and n.m.r. spectrum as 8-(3,3-dimethylallyl)scopoletin, cedrelopsin[136].

Under more suitable conditions, this reduction and subsequent rearrangement would perhaps have been as successful as the previous ones. However, the poor yield of the propargyl ether 156 was a strong indication that this method of introducing a 3,3-dimethyl-allyl unit ortho to a phenol could have its limitations.

Two procedures for synthesising the type of compound in question, which were known at the time of this investigation, have not been mentioned previously since both are more limited in their application than the two direct C-alkylation methods. The para-Claisen Rearrangement has been cleverly manipulated[97] by Burling, Jefferson and Scheinmann in the synthesis of the dimethyl ether of ugaxanthone[146] (Scheme 2.7), and the use of lithium in liquid ammonia has been investigated[29] by Birch, Maung and Pelter as a method of reducing a chromene to an ortho-isopentenylphenol (Scheme 2.8).

When the present investigation had been completed, Hlubucek, Ritchie and Taylor published[142,147] work based on very similar lines. The only discrepancy is the fact that only osthenol was isolated[147] from their pyrolysis. Since our work is reproducible[151], it might be a result of the fact that their pyrolysis was carried out in

Scheme 2.9
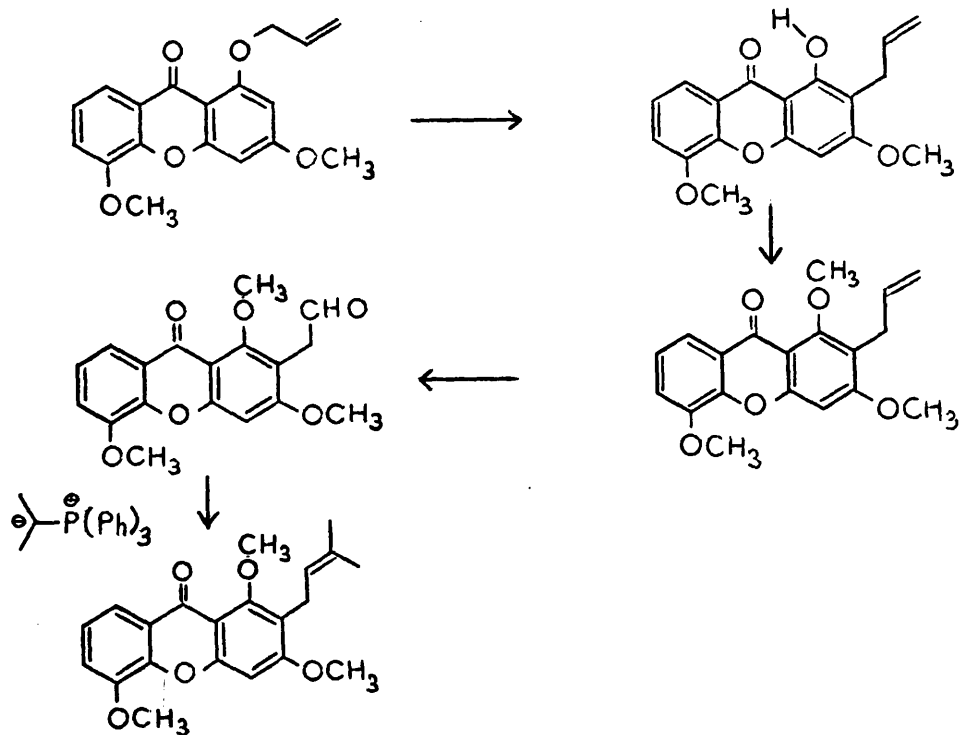
Scheme 2.10
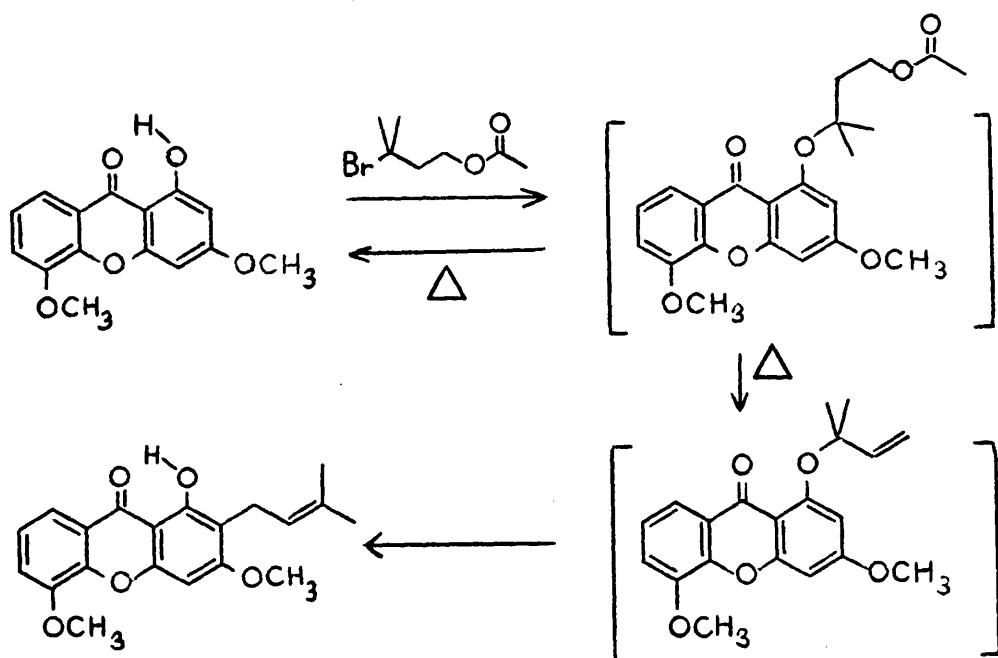
diethylaniline.

To our knowledge, the effect of conditions on the distribution between two vacant _ortho_ positions has not been investigated. It was for this purpose that the methyl ethers and cyclic ethers of osthenol and 7-demethylsuberosin were prepared. It had been hoped that it might be possible to investigate this aspect of the pyrolysis of 7-O-(1,1-dimethylallyl)umbelliferone by gas liquid chromatography but a suitable column could not be found to further this project.

Two new methods of synthesising _ortho_-isopentenylphenols have recently been introduced[148] by Scheinmann and his co-workers. The first involves the rearrangement of an allyl ether, followed by oxidative cleavage and then reaction of the aldehyde, so formed, with an ylide to complete the isoprene unit (Scheme 2.9). This method seems to have great potential although the necessity of protecting the _ortho_ hydroxyl might limit the further use of this function. It might, however, be extremely useful in cases where an intramolecularly hydrogen bonded hydroxyl can be converted to an allyl ether but not so readily to the 1,1-dimethylpropargyl ether. The second innovation by Scheinmann has been an attempt to form the 1,1-dimethylallyl ether _in situ_ by treating a hydroxy-xanthone with excess 3-methyl-3-bromo-butyl acetate (Scheme 2.10). Although their evidence shows that the required ether is formed, the major pyrolysis product is cleavage of the intermediate acetate.

Summary

The variety of methods which have been investigated for the synthesis[135,138,147-149] of ortho-(3,3-dimethylallyl)phenols is a guage of the intense interest invested in this 'simple' problem. All of these synthetic routes have their limitations.

The method developed in the present study could be of use. The major drawback at the moment is the initial propargyl ether formation. Although the technique employed was more than adequate for the syntheses of osthol and coumurrayin, the propargyl ether formation was a rather slow step, even for the free hydroxls involved in these cases.

An investigation into methods of improving this first step has been instigated[150] in this department, since the method, as a whole, has advantages such as the utilisation of a preformed coumarin nucleus for certain syntheses, and mild conditions which enable further manipulations of the skeleton.

Part of the above research has been summarised in a preliminary communication[114c].

PART II

Experimental.

2-Methyl-2-chloro-3-butyne

Prepared by the method[140] of Hennion and Boisselle. 2-Methyl-3-butyne-2-ol (100g.) yielded 2-methyl-2-chloro-3-butyne (63g.; 52%), b.p. 78-81° (lit.[140] b.p. 73-76°).

7-O-(1,1-Dimethylpropargyl)umbelliferone(144)

Potassium carbonate (0.85g.) and potassium iodide (0.15g.) were added to a solution of umbelliferone(4) (0.80g.) in aqueous acetone (2% v./v.; 100ml.) and the mixture stirred at R.T. for 1 hr. 2-Methyl-2-chloro-3-butyne (1g.) was added and the solution refluxed for 6 hr. More potassium carbonate (0.85g.) and 2-methyl-2-chloro-3-butyne (1g.) were added and the reflux continued for a further 24 hr. Work up (I) gave a yellow solid which, on crystallisation from ethyl acetate-light petroleum, yielded the ether 144 as pale yellow needles (0.71g.; 63%), m.p. 136-140°. (Found: C, 73.70; H, 5.45. $C_{14}H_{12}O_3$ requires C, 73.65; H, 5.30%); $\nu_{max}^{CHCl_3}$ 3300, 1730 and 1616 cm.$^{-1}$; mass spectral peak at m/e 228 (M^+), 213, 162 and 134 (r.a. 10, 18, 100 and 81%); n.m.r. signals at τ 8.27 (6H ; s.), 7.32 (1H ; s.), 3.74 (1H ; d.; J 9.5 Hz.), 2.98 (1H ; d./d.; J 8.5 & 2 Hz.), 2.70 (1H ; b.s.), 2.65 (1H ; d.; J 8.5 Hz.) and 2.36 (1H ; d.; J 9.5 Hz.).

The residue from this crystallisation was separated by preparative t.l.c. (chloroform x 2) into:-

    i)   an unidentified product as a yellow oil (0.03g.).

    ii)   a mixture (0.06g.) of i) and iii) (by t.l.c. behaviour).

    iii)   the ether 144 (0.16g.; 14%).

Quinoline-sulphur poison[143]

A mixture of sulphur (1g.) and quinoline (6g.) were heated at 160 ± 5° for 6 hr. On cooling, the dark brown mixture was made up to 70 ml. with xylene. This stock solution was stored at ~ 5°. Immediately prior to use, 0.7ml. of this xylene solution was diluted to 70ml. with ethyl acetate and used in this diluted form as a partial poison for the catalyst, 5% palladium-barium sulphate.

Reduction of 7-0-(1,1-dimethylpropargyl)umbelliferone(144)

Palladium-barium sulphate (5% w./w.; 30mg.) was added to a solution of the propargyl ether(144) (100mg.) in ethyl acetate (40ml.) and the quinoline-sulphur poison (0.3ml.). After hydrogenation at R.T. for 1 hr., the uptake of hydrogen was approximately one mole. The catalyst was then filtered off and the solvent evaporated using as little heat as possible. The residue was separated by preparative t.l.c. (40% ether-light petroleum x 2) into:-

i) 7-0-(1,1-dimethylallyl)umbelliferone(150), from ether-light petroleum as colourless needles (96mg.; 96%), m.p. 75-78°. (Found: C, 73.30; H, 6.35. $C_{14}H_{14}O_3$ requires C, 73.00; H, 6.15%); mass spectral peaks at m/e 230 (M^+), 163, 162, 134, 169 and 41 (r.a. 4, 12, 100, 60, 54 and 51%); n.m.r. signals at τ 8.45 (6H ; s.), 4.77 (1H ; d.; J 18 Hz.), 4.77 (1H ; d.; J 10 Hz.), 3.85 (1H ; d./d.; J 18 & 10 Hz.), 3.77 (1H ; d.; J 9.5 Hz.), 3.15 (1H ; d./d.; J 10 & 2 Hz.), 3.07 (1H ; b.s.), 2.72 (1H ; d.; J 10 Hz.) and 2.40 (1H ; d.; J 9.5 Hz.).

ii) umbelliferone(4) (~ 1$^{\prime}$mg.; ~1.5%) (u.v.).

Pyrolyses of 7-0-(1,1-dimethylallyl)umbelliferone(150)

The allyl ether, 150, (69mg.) was heated for 1 hr. in a sublimation block at 130°. The residue was separated by preparative t.l.c. (30% ether-light petroleum x $\frac{1}{3}$ x $\frac{1}{2}$ x $\frac{2}{3}$ followed by 80% chloroform-light petroleum x 2) into:-

i) osthenol(21), from ethyl acetate-light petroleum as colourless needles (51mg.; 74%), m.p. 129-131° (lit.[139] m.p. 124-125°). (Found: C, 73.10; H, 6.15. Calc. for $C_{14}H_{14}O_3$ C, 73.00; H, 6.15%); $\nu_{max}^{CHCl_3}$ 3580, ~3340 (broad), 1725-1715, 1605 and 1580 cm.$^{-1}$; $\nu_{max}^{CCl_4}$ 3601, 3408 and 1747 cm.$^{-1}$; mass spectral peaks at m/e 230 (M^+), 215, 187, 175 and 146 (r.a. 68, 25, 27, 100 and 24%); n.m.r. signals at τ 8.27 (3H ; b.s.), 8.14 (3H ; b.s.), 6.40 (2H ; b.d.; J 7 Hz.), 4.72 (1H ; b.t.; J 7 Hz.), 3.75 (1H ; d.; J 9.5 Hz.), 3.12 (1H ; d.; J 9 Hz.), 2.78 (1H ; d.; J 9 Hz.), 2.67$^{\bullet}$ (1H ; b.s.) and 2.35 (1H ; d.; J 9.5 Hz.).

ii) 7-demethylsuberosin(22),from benzene as pale yellow plates (10mg.; 14%), m.p. 133-134° (lit.[144] m.p. 133.5-134°); $\nu_{max}^{CHCl_3}$ 3580, ~3260 (broad), 1720-1710, 1625 and 1575 cm.$^{-1}$; $\nu_{max}^{CCl_4}$ 3598, 3449 and 1744 cm.$^{-1}$; mass spectral peaks at m/e 230 (M^+), 215, 176, 175 and 147 (r.a. 42, 16, 11, 100 and 14%); n.m.r. signals at τ 8.27 (3H ; b.s.), 8.22 (3H ; b.s.), 6.63 (2H ; b.d.; J 7 Hz.), 4.67 (1H ; b.t.; J 7 Hz.), 3.78 (1H ; d.; J 9.5 Hz.), 2.93 (1H ; s.), 2.81 (1H ; s.), 2.33 (1H ; d.; J 9.5 Hz.) and 1.96$^{\bullet}$ (1H ; b.s.). The physical properties of this compound agreed with those of an authentic sample of 7-demethylsuberosin.

iii) umbelliferone(4) ($\sim 2^{\prime}$mg.; ~ 5%) (u.v.).

Derivatives of osthenol(21)

1. Osthol(146)

Osthenol (48mg.) was converted (see scoparin p.64) to its methyl ether, using potassium carbonate (50mg.), methyl iodide (0.1ml.) and acetone (5ml.). After refluxing for 4 hr., work up (I) yielded osthol which crystallised from light petroleum as colourless needles (44mg.; 86%), m.p. 82-84° (lit.[134] m.p. 83-84°); mass spectral peaks at m/e 244 (M^+), 229, 213, 201, 189 and 131 (r.a. 100, 85, 42, 65, 53 and 44%); n.m.r. signals at τ 8.32 (3H ; b.s.), 8.15 (3H ; b.s.), 6.47 (2H ; b.d.; J 7 Hz.), 6.07 (3H ; s.), 4.73 (1H ; b.t.; J 7 Hz.), 3.79 (1H ; d.; J 9.5 Hz.), 3.18 (1H ; d.; J 9 Hz.), 2.72 (1H ; d.; J 9 Hz.) and 2.41 (1H ; d.; J 9.5 Hz.).

2. Dihydroseselin(151)

A solution of osthenol (25mg.) in methanol (1ml.) and conc. hydro-chloric acid (5 drops) was refluxed for 2 hr. and then diluted with iced water (25ml.). The ethyl acetate extract of the aqueous mixture was washed with dil. potassium carbonate to pH 11, brine to neutrality, dried and evaporated. Crystallisation of the residue from ether-light petroleum yielded dihydroseselin as pale yellow needles (21mg.; 82%), m.p. 101-103° (lit.[138] m.p. 103-104°); mass spectral peaks at m/e 230 (M^+), 215, 201, 187, 176, 175, 174 and 146 (r.a. 68, 24, 13, 21, 12, 100, 21 and 21%); n.m.r. signals at τ 8.62 (6H ; b.s.), 8.14 (2H ; t.; J 7 Hz.), 7.08 (2H ; t.; J 7 Hz.), 3.82 (1H ; d.; J 9.5 Hz.), 3.30 (1H ; d.; J 8.5 Hz.), 2.80 (1H ; d.; J 8.5 Hz.). and 2.41 (1H ; d.; J 9.5 Hz.).

Derivatives of 7-demethylsuberosin(22)

1. ### Suberosin(147)

   Using the same procedure as was employed for the synthesis of osthol
   (p.110), 7-demethylsuberosin (24mg.) was converted to its methyl
   ether, suberosin.   The oil obtained was distilled at $100°/0.05$ mm.
   On standing, the distillate solidified to give suberosin as colour-
   less plates (23mg.; 90%), m.p. 85-87° (lit.[138] m.p. 86-87°);   mass
   spectral peaks at m/e 245, 244 (M^+), 230 and 229 (r.a. 12, 76, 18
   and 100%);   n.m.r. signals at τ 8.28 (3H ; b.s.), 8.23 (3H ; b.s.),
   6.70 (2H ; b.d.; J 7 Hz.), 6.09 (3H ; s.), 4.72 (1H ; b.t.; J 7 Hz.),
   3.80 (1H ; d.; J 9.5 Hz.), 3.25 (1H ; s.), 2.85 (1H ; s.) and 2.42
   (1H ; d.; J 9.5 Hz.).

2. ### Dihydroxanthyletin(152)

   Using the same procedure as was employed for the synthesis of
   dihydroseselin (p.110), 7-demethylsuberosin (20mg.) was converted
   to the cyclic ether, dihydroxanthyletin, which crystallised from
   ethanol as colourless plates (18mg.; 88%), m.p. 123.5-125° (lit.[138]
   m.p. 124-125°);   mass spectral peaks at m/e 231, 230 (M^+), 215, 176,
   175 and 147 (r.a. 27, 65, 40, 46, 100 and 56%);   n.m.r. signals at
   τ 8.63 (6H ; b.s.), 8.16 (2H ; t.; J 7 Hz.), 7.17 (2H ; t.; J 7 Hz.),
   3.85 (1H ; d.; J 9.5 Hz.), 3.31 (1H ; s.), 2.87 (1H ; s.) and 2.45
   (1H ; d.; J 9.5 Hz.).

7-O-(1,1-Dimethylpropargyl)-5-methoxycoumarin(153)

A solution of 7-hydroxy-5-methoxycoumarin (300mg.) in aqueous acetone (2% v./v.; 60ml.) was refluxed in the presence of 1,1-dimethylpropargyl chloride (600mg.), potassium carbonate (600 mg.) and potassium iodide (60mg.) for 24 hr. Further 1,1-dimethylpropargyl chloride (600mg.) was then added and reflux continued for another 24 hr. Work up (I) yielded a pale yellow solid which was separated by the procedure employed for 7-O-(1,1-dimethylpropargyl)umbelliferone (p.107) into:-

a) 5-methoxyseselin, sublimed at 140°/0.005 mm. as pale yellow needles (39mg.; 10%), m.p. 156-158°. (Found: C, 69.85; H, 5.50. $C_{15}H_{14}O_4$ requires C, 69.75; H, 5.45%); n.m.r. signals at τ 8.54 (6H ; s.), 6.12 (3H ; s.), 4.43 (1H ; d.; J 10 Hz.), 3.88 (1H ; d.; J 9.5 Hz.), 3.77 (1H ; s.), 3.20 (1H ; d.; J 10 Hz.) and 2.07 (1H ; d.; J 9.5 Hz.).

b) 7-O-(1,1-dimethylpropargyl)-5-methoxycoumarin, from ether-light petroleum as pale yellow needles (292mg.; 74%), m.p. 140-144°. (Found: C, 69.85; H, 5.55. $C_{15}H_{14}O_4$ requires C, 69.75; H, 5.45%); n.m.r. signals at τ 8.27 (6H ; s.), 7.33 (1H ; s.), 6.12 (3H ; s.), 3.85 (1H ; d.; J 9.5 Hz.), 3.53 (1H ; d.; J 2 Hz.), 3.06 (1H ; d.; J 2 Hz.) and 2.05 (1H ; d.; J 9.5 Hz.).

Reduction of 153 and subsequent pyrolysis

7-0-(1,1-Dimethylpropargyl)-5-methoxycoumarin(153) (50mg.) in ethyl acetate (20ml.) was hydrogenated over 'poisoned' palladium-barium sulphate (5% w./w.; 16mg.) (for procedure see p.108) for 1 hr. at R.T.   Filtration of catalyst and careful removal of solvent gave a pale yellow oil (49mg.); n.m.r. signals at τ 8.51 (6H ; s.), 6.17 (3H ; s.), 4.79 (1H ; b.d.; J 10 Hz.), 4.78 (1H ; b.d.; J 18 Hz.), 3.90 (1H ; d.; J 9.5 Hz.), 3.86 (1H ; d./d.; J 10 & 18 Hz.), 3.67 (1H ; d.; J 2.5 Hz.), 3.43 (1H ; d.; J 2.5 Hz.) and 2.10 (1H ; d.; J 9.5 Hz.).

This oil was heated in a sublimation block at 160° for 1 hr. The resulting solid was crystallised from ethyl acetate-light petroleum and yielded 7-demethylcoumurrayin(155) as pale yellow needles (44mg.; 88% from 153), m.p. 197-199° (lit.[114b] m.p. 196-197°).   (Found: C, 68.90; H, 6.15.   Calc. for $C_{15}H_{16}O_4$ C, 69.20; H, 6.20%); n.m.r. signals (deuteropyridine) at τ 8.33 (3H ; b.s.), 8.04 (3H ; b.s.), 6.31 (3H ; s.), 6.21 (2H ; b.d.; J 6.5 Hz.), 4.35 (1H ;b.t.; J 6.5 Hz.), 3.80 (1H ; d.; J 9.5 Hz.), 3.42 (1H ; s.) and 2.01 (1H ; d.; J 9.5 Hz.); n.m.r. signals (deutero-pyridine - D_2O) at (following same order as above signals) τ 8.33, 8.07, 6.13, 6.32, - , 3.80, 3.17 and 2.12.

The mother liquors of this crystallisation contained some 7-hydroxy-5-methoxycoumarin ($\sim$4%).

Coumurrayin(131)

7-Demethylcoumurrayin(155) (32mg.) was converted (see scoparin p.64) to the methyl ether by using potassium carbonate (50mg.), methyl iodide (0.5ml.) and acetone (10ml.). After refluxing for 5 hr., work up (I) yielded coumurrayin which crystallised from carbon tetrachloride as pale yellow plates (30mg.; 89%), m.p. 155-157° (lit.[66] m.p. 157°). (Found: C, 70.10; H, 6.55. Calc. for $C_{16}H_{18}O_4$ C, 70.05; H, 6.60%); mass spectral peaks at m/e 274 (M^+), 259, 231, 219 and 206 (r.a. 66, 100, 25, 20 and 21%); n.m.r. signals at τ 8.34 (3H ; b.s.), 8.18 (3H ; b.s.), 6.58 (2H ; b.d.; J 6.5 Hz.), 6.08 (3H ; s.), 4.82 (1H ; b.t.; J 6.5 Hz.), 3.80 (1H ; d.; J 9.5 Hz.), 3.69 (1H ; s.) and 2.08 (1H ; d.; J 9.5 Hz.).

7-O-(1,1-Dimethylpropargyl)scopoletin(156)

Potassium carbonate (400mg.) was added to a warm solution of scopoletin(41) (192mg.) in aqueous acetone (2% v./v.; 25ml.). After stirring at R.T. for 1 hr., 2-methyl-2-chloro-3-butyne (500mg.) was added and the reaction refluxed for 24 hr. Potassium iodide (40mg.) and the propargyl chloride (500mg.) were then added and reflux continued for another 24 hr. Further dimethylpropargyl chloride (500mg.) was added and reflux continued for 24 hr. (i.e. total 72 hr.). Work up (I) yielded a yellow sold which was separated by preparative t.l.c. (30% ethyl acetate-light petroleum x 2) into:-

i)   an unidentified product (10'mg.) as a pale yellow oil.

ii) 7-O-(1,1-dimethylpropargyl)scopoletin, from ether-light petroleum as pale yellow needles (107mg.; 41%), m.p. 139-143°.

(Found: C, 69.65; H, 5.60. $C_{15}H_{14}O_4$ requires C, 69.75; H, 5.45%);
$\nu_{max}^{CHCl_3}$ 3295, 1720-1710, 1610 and 1555 cm.$^{-1}$;   mass spectral peaks
at m/e 258 (M^+), 243, 192, 177, 164 and 149 (r.a. 12, 38, 100, 42,
29 and 25%);   n.m.r. signals at τ 8.27 (6H ; s.), 7.35 (1H ; s.),
6.14 (3H ; s.), 3.71 (1H ; d.; J 9.5 Hz.), 3.12 (1H ; s.), 2.47
(1H ; s.) and 2.39 (1H ; d.; J 9.5 Hz.).

Reduction of 7-O-(1,1-dimethylpropargyl)scopoletin
and subsequent pyrolysis

The propargyl ether, 156, (60mg.) in ethyl acetate (40ml.) was
hydrogenated over 'poisoned' palladium-barium sulphate (5% w./w.;
30mg.) (for procedure see p.108).   After 2 hr., there was no
appreciable uptake of hydrogen.   The catalyst was filtered off and
the solvent carefully evaporated.   The n.m.r. spectrum of the
residue indicated that only a small amount of reduction had taken
place.   The crude residue was set up again for hydrogenation using
'poisoned' palladium-barium sulphate (60mg.).   After 2 hr., the
catalyst was filtered off and the solvent carefull evaporated.   The
residue was separated by preparative t.l.c. (chloroform x 1) into
scopoletin(41) (11mg.; 24%) (m.p., m.m.p., n.m.r.) and a less polar
yellow oil (43mg.).

This oil was distilled at 140°/ 0.5 mm. and the distillate
separated by preparative t.l.c. (40% ethyl acetate-light petroleum)
into:-

i)   7-O-(1,1-dimethylpropyl)scopoletin(157), which was
distilled at 140°/0.05 mm. as a colourless oil (26mg.; 42%).

(Found: C, 68.50; H, 6.80. $C_{15}H_{18}O_4$ requires C, 68.70; H, 6.90%);

n.m.r. signals at τ 8.98 (3H ; b.t.; J 7.5 Hz.), 8.64 (6H ; s.),

8.22 (2H ; q.; J 7.5 Hz.), 6.15 (3H ; s.), 3.72 (1H ; d.; J 9.5 Hz.),

3.15 (1H ; s.), 3.01 (1H ; s.) and 2.40 (1H ; d.; J 9.5 Hz.).

ii)   cedrelopsin(143) from ethanol as pale yellow needles

(9mg.; 15%), m.p. 169-171° (lit.[136] m.p. 170-174°);   n.m.r. signals

at τ 8.32 (3H ; b.s.), 8.16 (3H ; b.s.), 6.43 (2H ; d.; J 7 Hz.),

6.07 (3H ; s.), 4.72 (1H ; b.t.; J 7 Hz.), 3.79 (1H ; d.; J 9.5 Hz.),

3.77 (1H ; s.), 3.29 (1H ; s.) and 2.46 (1H ; d.; J 9.5 Hz.).

PART III

Elucidation of the Structure of the Coumarin, Nieshoutol.
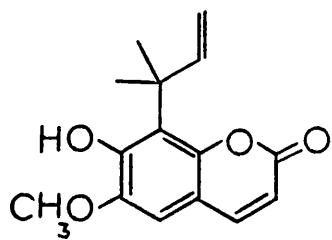
(62)
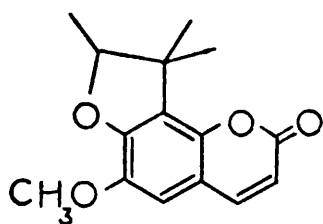
(63)
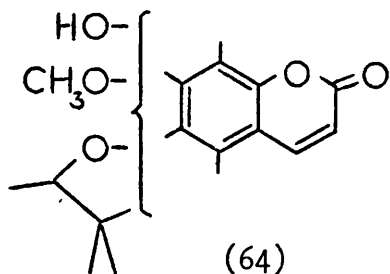
(64)

One of the new coumarins, isolated[43] by McCabe, McCrindle

and Murray from the ethyl acetate extract of the heartwood of

Ptaeroxylon obliquum, was given the trivial name nieshoutol from

the African word, nieshout, for the tree.   It contains one more

oxygen than the other coumarins which they isolated from this

source and therefore has the molecular formula $C_{15}H_{16}O_4$.   The

n.m.r. spectrum possesses signals typical of a coumarin unsubstituted

at C-3 and C-4 $\left[\tau \; 3.81 \; (1H \; ; \; d.; \; J \; 9.5 \; Hz.), \; 2.13 \; (1H \; ; \; d.; \; J \; 9.5 \; Hz.)\right]$,

of an aromatic methoxyl $\left[\tau 6.03 \; (3H \; ; \; s.)\right]$ and of an acidic proton

$\left[\tau 4.83^{\bullet} \; (1H \; ; \; s.)\right]$.   The remainder of the spectrum $\left[\tau 5.43 \; (1H \; ; \; q.;\right.$

J 6.5 Hz.), 8.59 (3H ; d.; J 6.5 Hz.), 8.46 (3H ; s.), 8.72 $\left. (3H \; ; \; s.)\right]$

can be attributed to a 2,3,3-trimethyldihydrofuran system[11,14,43-45]

fused to the benzenoid ring.   This system had already been

encountered[43-45] in the co-occurring coumarin, nieshoutin(63) (Part Ia).

The phenolic nature of nieshoutol was evident from the disappear-

ance of a one proton singlet ($\tau 4.83$) in the n.m.r. spectrum when

D_2O was added to the solution, and from the facile conversion[62]

of this compound to an aromatic bis-methyl ether.   The partial

structure 64 was, therefore, allocated to this coumarin.   It is

generally difficult to establish[70], purely on spectroscopic evidence,

the relative orientation of substituents when the benzenoid ring is

fully substituted.

It was noted[62] that nieshoutol and its derivatives are optically

inactive.   This leaves open the possibility that nieshoutol is an

artefact, arising perhaps from the cyclisation of the corresponding

Table 3.1

U.v. spectra (nm.)

nieshoutol				isofraxidin			
EtOH		1% NaOH/EtOH		EtOH		basic soln.	
λmax	log ε	λ max	log ε	λmax	log ε	λmax	logε
230	4.18	255	4.26	230	4.5	245	4.2
251	3.64	340	3.98	254	3.9	271	4.1
258	3.55	400	3.79	345	4.5	405	4.7
340	4.08						
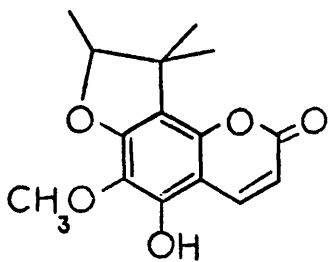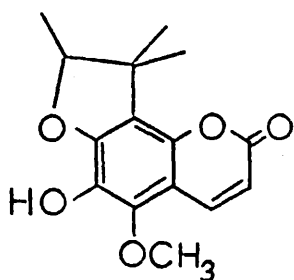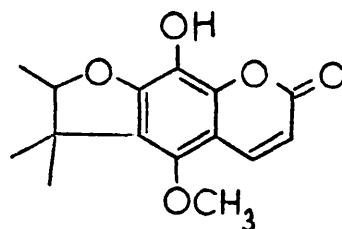
(159)　　　(160)　　　(161)
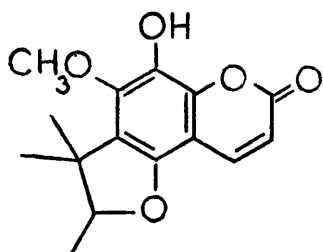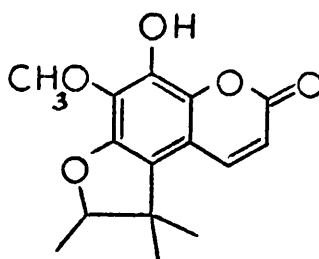
(162)　　　(163)

1,1-dimethylallylphenol during isolation. However, using the analogy of obliquetin(62) and nieshoutin(63), this phenol should have similar chromatographic properties to the corresponding cyclic ether, nieshoutol, but it was not detected in the extract.

The i.r. and u.v. spectra of nieshoutol give information which limits the structural possibilities. The band at 3569 cm.$^{-1}$ in the i.r. spectrum indicates that the hydroxyl is intramolecularly hydrogen bonded (Part Ic; p.54). But, unlike the case of nieshoutin, the u.v. spectrum of nieshoutol gave no information on the oxygen substitution pattern. However, when this spectrum was compared with that obtained from a basic solution of nieshoutol, the difference, characteristic of a 7-hydroxycoumarin, was not observed (Appendix). This method of placing a hydroxyl at C-7 undoubtedly holds in mono-oxygenated and di-oxygenated systems. It appears, moreover, from the u.v. spectra of isofraxidin[152] (6,8-dimethoxy-7-hydroxycoumarin) (Table 3.1) that this premise is also viable in tri-oxygenated systems.

Thus, assuming that nieshoutol is a normal 7-oxygenated coumarin and that the phenolic hydroxyl is not at C-7, only five structures, 159 - 163, in which the hydroxyl can be intramolecularly hydrogen bonded, are possible for nieshoutol. Structure 163 is unlikely since C_5 units are almost exclusively located[4,157] ortho to the C-7 oxygen in natural coumarins.

The close similarity between the n.m.r. spectrum of nieshoutol and that of nieshoutin led Murray and McCabe to postulate[62] that the

Scheme 3.1

(159) → → →

(63) ←

Scheme 3.2

(93) → →

(159) ←

(160)
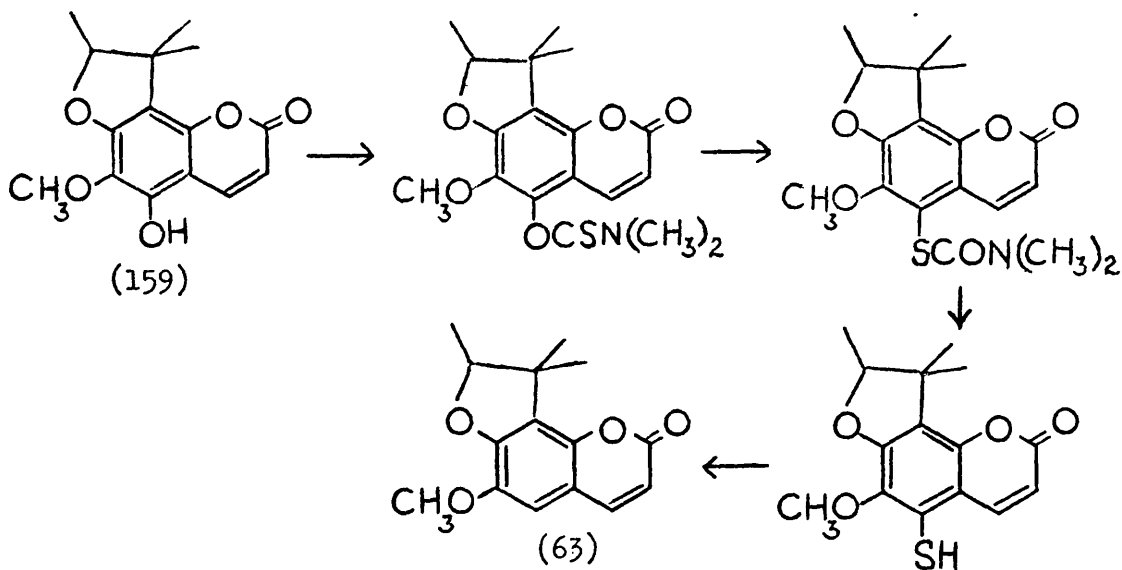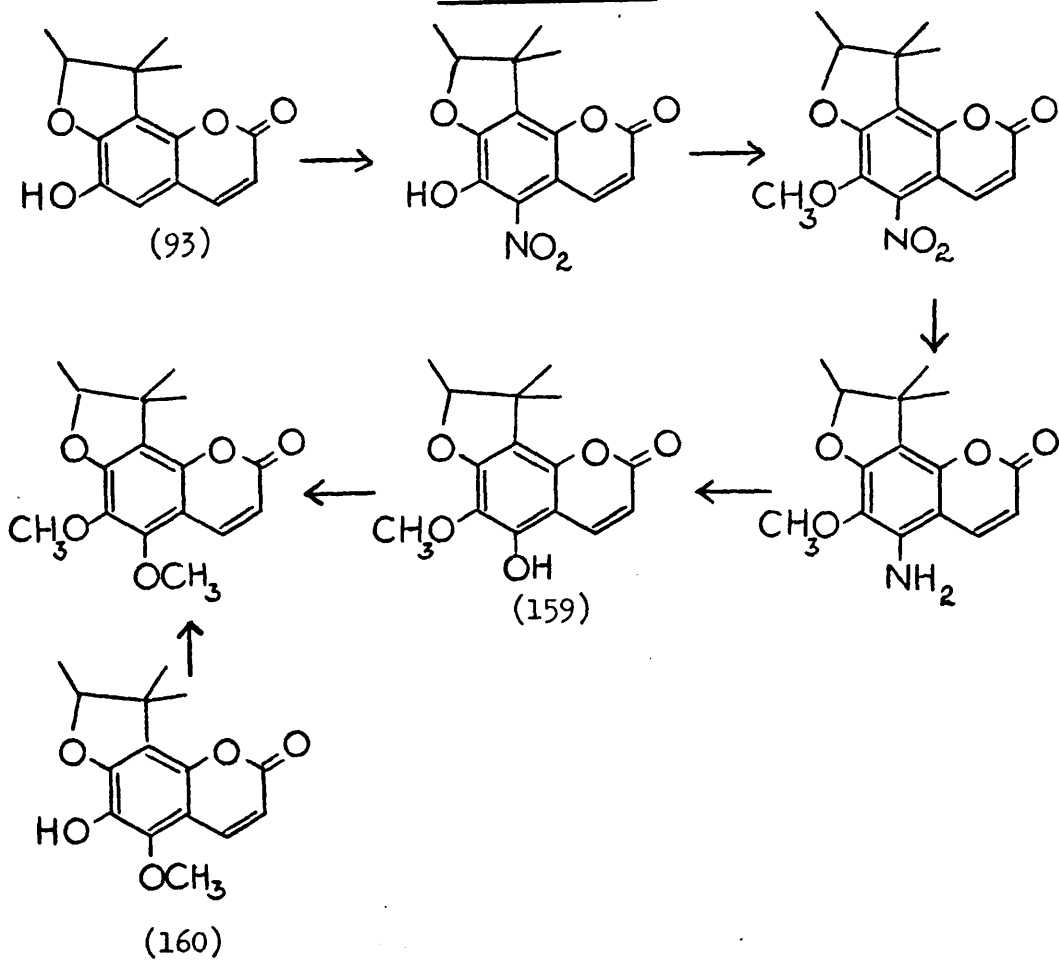
former might arise, biosynthetically, by in vivo oxygenation of the latter.   On this basis, they proposed structure 159 for nieshoutol and attempted to interconvert the two co-occurring coumarins.

O-Aryldimethylthiocarbamates are known to rearrange[153] on pyrolysis to the corresponding thiol derivatives.   Scheme 3.1 was therefore proposed[62] as a method of relating the two coumarins. Unfortunately, they found that pyrolysis of nieshoutol O-dimethyl-thiocarbamate, in the absence of solvent, at 250° failed to give either the required product or recovered starting material.   This approach was reinvestigated unsuccessfully by the author, a temperature range of 185-285° being examined.   The following is typical of the results obtained when other than starting material was recovered.

Pyrolysis of nieshoutol O-dimethylthiocarbamate, in the absence of solvent at 250°, yielded a small amount of starting material (11%) and of the cleavage product, nieshoutol (~2%). The remainder of the reaction mixture consisted of numerous minor products, none of which were isolated in sufficient quantities to permit identification.

With a view to determining the structure of nieshoutol by X-ray crystal structure analysis, McCabe and Murray prepared[62] three heavy atom derivatives.   However, the bromo-acetate is unstable, the crystals of the p-bromobenzoate possesses pseudo-symmetric properties and those of the p-bromobenzenesulphonate

(brosylate) are imperfectly formed. These derivatives were, therefore, unsuitable for X-ray analysis but, as will be seen later, they provided the first clue which led to the elucidation of the structure of nieshoutol.

An alternative approach to the interconversion of nieshoutol and nieshoutin would have been the synthesis of the former from the latter. Since it is known[154a] that 6-hydroxycoumarin can be converted to 5-nitro-6-hydroxycoumarin, Scheme 3.2 was envisaged as being a feasible method of carrying this out. This method would have the added bonus that either structure 159 or structure 160 for nieshoutol could be determined by it.

Unfortunately, 6-demethylnieshoutin(93) (Part Ia) was not available at this time. Numerous attempts were made to nitrate a model compound, 6-hydroxy-7-methoxycoumarin(42). Although 42 was perhaps not a very good model, it had been hoped that the C-6 hydroxyl would have the strongest directing influence and at least a small amount of the 5-nitro derivative would have been isolated. This was not found to be the case, nitration either yielding a plethera of products (H_2SO_4/HNO_3) or recovered starting material $(HOAc/HNO_3)$.

Nitration (H_2SO_4/HNO_3) of nieshoutin(63) smoothly yielded a bright yellow dinitro derivative, $C_{14}H_{14}N_2O_8$. The insertion of two nitro groups is apparent from the n.m.r. spectrum which possesses a one proton singlet at τ 1.44 instead of the usual α-pyrone AB system and which has no signal for an aromatic proton. The i.r.
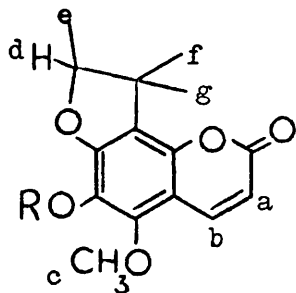
(160) R = H

Table 3.2

Chemical shifts (τ) (J Hz.) at 60 MHz. of nieshoutol and its derivatives based on structure 160.

	H_a 1H, d. J 9.5	H_b 1H, d. J 9.5	H_c 3H, s.	H_d 1H, q. J 6.5	H_e 3H, d. J 6.5	H_f 3H, s.	H_g 3H, s.
nieshoutol	3.81	2.13	6.03	5.43	8.59	8.46	8.72
brosylate	3.80	2.16	6.05	5.71	8.80	8.52	8.82
tosylate	3.85	2.15	6.08	5.73	8.82	8.52	8.82
mesylate	3.80	2.13	5.98	5.36	8.57	8.43	8.67
methyl ether	3.87	2.12	6.01 or 6.06	5.45	8.58	8.45	8.73
acetate	3.83	2.15	6.08	5.45	8.62	8.45	8.70
benzyl ether	3.86	2.15	6.05	5.51	8.61	8.47	8.75
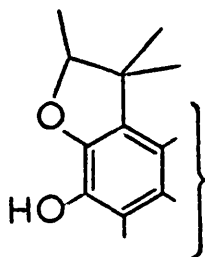
(164)

spectrum $(CHCl_3)$ displays a pyrone carbonyl stretching frequency at 1770 cm.$^{-1}$, instead of $\sim$1730 cm.$^{-1}$, and a strong band at 1540 cm.$^{-1}$ which can be attributed to a conjugated C-NO$_2$ grouping. The nitration product must therefore be 3,5-dinitronieshoutin. Coumarins are known[154] to nitrate at C-3 as well as at the benzenoid nucleus. Modification of the nitrating conditions yielded only a mixture of this dinitro derivative and unreacted nieshoutin. It appeared that 6-demethylnieshoutin(93) would be essential for the reaction sequence outlined in Scheme 3.2.

While the synthesis of 93 was being investigated (Part Ia), it was noted that there is a marked difference between the n.m.r spectrum of nieshoutol brosylate (previously prepared[62] by Dr. P. H. McCabe for X-ray analysis) and that of the parent phenol, nieshoutol. The spectra of the bromo-acetate and the p-bromobenzoate are very similar to that of nieshoutol but the spectrum of the brosylate reveals a significant shielding of the secondary methyl system of the 2',3',3'-trimethyldihydrofuran (C-2' hydrogen 0.28 ppm and C-2' methyl 0.21 ppm). In order to investigate the phenomenon further, the following derivatives of nieshoutol were made, namely, the acetate[70], the methanesulphonate (mesylate), the benzyl ether and the p-toluenesulphonate (tosylate).

The first three possess n.m.r. spectra almost identical to that of nieshoutol. It had been hoped that since the benzyl group is known[155] to cause shielding, that a similar effect might have been observed in this case. Only the tosylate, however, shows a shielding of the secondary methyl system (Table 3.2) comparable to that of the
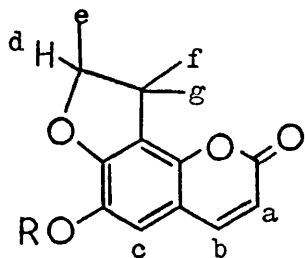
(63) R = CH$_3$
(93) R = H
(165) R = brosyl
(166) R = mesyl

Table 3.3

Chemical shifts (τ) (J Hz.) at 60 MHz.

	H$_a$ 1H, d. J 9.5	H$_b$ 1H, d. J 9.5	H$_c$ 1H, s.	H$_d$ 1H, q. J 6.5	H$_e$ 3H, d. J 6.5	H$_f$ 3H, s.	H$_g$ 3H, s.
(63)	3.81	2.44	3.27	5.43	8.55	8.42	8.70
(93)	3.80	2.47	3.18	5.44	8.59	8.43	8.71
(165)	3.75	2.43	2.75	5.80	8.84	8.52	8.84
(166)	3.75	2.43	2.75	5.36	8.56	8.42	8.67

Scheme 3.3

glu = glucose residue
R = " "
or H etc.

(167)

(63)

(161)

(160)
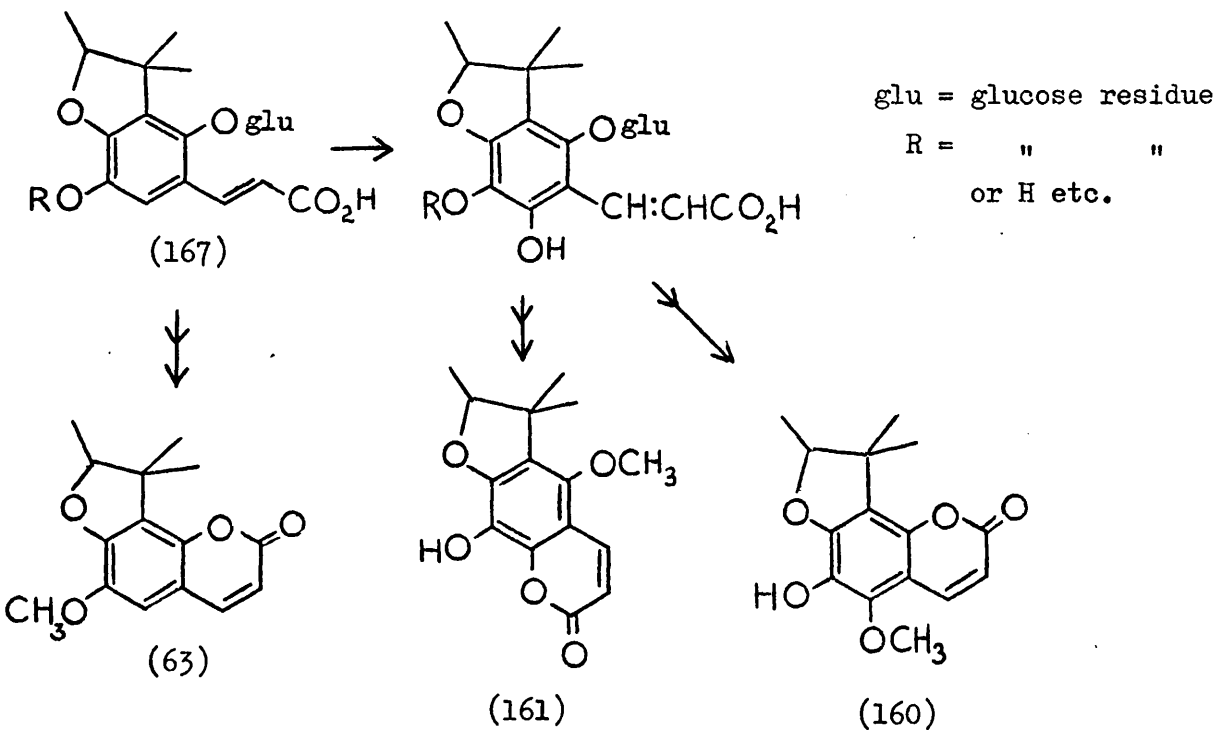
brosylate.

From a study of models, it seemed likely that to account for the observed effects, partial structure 164 is required, since only in this environment might the brosyl (or tosyl) grouping be expected to exert such a specific effect.

The reason for the shielding is not yet clear. The sulphoxide grouping has approximately the same geometry as an sp^3 hybridised carbon. It was, therefore, disappointing that the benzyl ether failed to produce any shielding effects. One possible explanation is that the size of the sulphoxide group in the aryl sulphonates induces the benzenoid rings to take up a preferred conformation.

6-Demethylnieshoutin(93) had, meanwhile, been synthesised by 'Claisen Rearrangement' of 7-0-(3,3-dimethylallyl)aesculetin(65) (Part Ia). In order to ascertain the viability of partial structure 164, the brosylate(165) and mesylate(166) of 93 were prepared. Comparison of the n.m.r. spectrum (Table 3.3) of the brosylate(165) with that of its parent phenol(93) shows that once again a shielding of the secondary methyl system occurs (0.36 and 0.25 ppm for the hydrogen and methyl respectively). The downfield shift (0.43 ppm) of the aromatic proton signal of 165 is as expected for a strong electron withdrawing group in the ortho position. In the spectrum of the corresponding mesylate(166), a similar effect on the aromatic proton is observed but unlike the brosylate the remainder of the spectrum is unaffected.

The above evidence strongly supports the proposed partial structure 164 and suggests that nieshoutol could be best represented
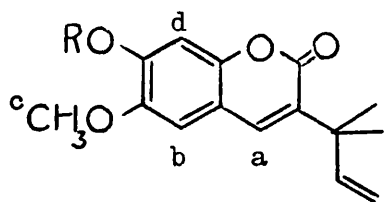
(76) R = H
(77) R = CH$_3$
(168) R = brosyl
(169) R = mesyl

Table 3.4

Chemical shifts (τ) at 60 MHz.

	H$_a$ 1H, s.	H$_b$ 3H, s.	H$_c$ 1H, s.	H$_d$ 1H, s.
(76)	2.53	6.07	3.16	3.17
(77)	2.53	6.10	3.17	3.23
(168)	2.53	6.36	3.14	2.91
(169)	2.49	6.07	3.00	2.75

Scheme 3.4
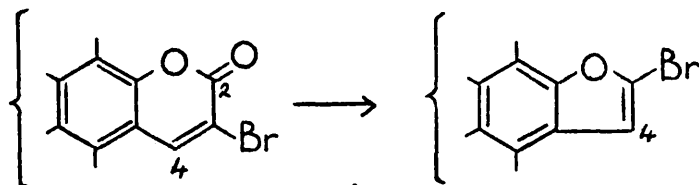
by either 160 or 161. Both fulfil the requirements of the
evidence presented so far. Scheme 3.3 represents possible
biosynthetic routes to these structures. Since many coumarins,
including e.g. psoralen, are known[156] to exist in the plant as
the ortho-glucoside of the corresponding coumarinic acid, 167
is a feasible starting point. An alternative could be C-5
oxygenation of a nieshoutin-type precursor either leading directly
to 160 or to 161 after opening the pyrone ring and reclosing it in
the opposite direction.

It was noticeable that the chemical shifts of the ∝-pyrone
olefinic protons and the methoxyl protons remain essentially the
same in the n.m.r. spectra (Table 3.2) of all the nieshoutol
derivatives which have been prepared so far. This tends to favour
the linear structure (161) for nieshoutol over the angular one (160).
To investigate the effect of an arylsulphonyl group on an ortho-
methoxyphenol, the brosylate(168) and mesylate(169) of 3-(1,1-
dimethylallyl)scopoletin(76) (Part Ia) were made. The parent
phenol, 76, was selected on account of its availability and high
solubility in chloroform. The n.m.r. spectrum of the derived
brosylate, 168, displays a marked shielding (0.29 ppm) of the
ortho methoxyl (Table 3.4) when compared with that of 76. Both
the brosylate(168) and mesylate(169) show a downfield shift of the
ortho aromatic proton primarily. Although the effect of a brosyl
group on an ortho methoxyl function favours 161 as the structure
of nieshoutol, it is difficult to explain this result on the basis
of the size of the $-SO_2-$ grouping. A study of models, in this case,

indicates that other conformations might be less sterically

hindered than the one with the benzenoid ring of the arylsulphonate

orientated above the methoxyl grouping.

However, since the hydroxyl and methoxyl of nieshoutol must

be either ortho or para to one another, no matter what the structure,

it was realised that conclusive information might be obtained if

nieshoutol were converted to the corresponding diol. With this

in view, a solution of nieshoutol in glacial acetic acid was

treated with a commercial solution of hydrogen bromide in glacial

acetic acid. After refluxing gently for $2\frac{1}{2}$ hr., eight compounds

were isolated from the reaction mixture. Four of these, present

in small amounts, were identified as the 3-bromo derivatives of the

remaining four, on the basis of the n.m.r. spectra which contain

one proton singlet at $\sim \Upsilon$ 1.7 instead of the usual olefinic

pair of doublets; and of the mass spectra in which the bromine

atom is retained for some time in the fragmentation pattern.

It has been postulated[158] that after expulsion of carbon monoxide

(Scheme 3.4) from 3-bromocoumarins under electron impact, the

resulting 2-bromofurans are fairly stable to loss of the bromine

atom. The four major components were readily identified but since

the four minor were undoubtedly due to a slight trace of bromine in

the slightly yellow commercial HBr/HOAc, the experiment was repeated

using freshly prepared HBr/HOAc. This time only the expected four

compounds were isolated, namely, nieshoutol acetate (5%), recovered

starting material (22%), a hydroxy-acetate (22%) and a diol (40%).

The two new compounds, on treatment with diazomethane, gave nieshoutol acetate and nieshoutol methyl ether respectively. Thus, no skeletal rearrangement had taken place during the demethylation.

The i.r. spectrum of the hydroxy-acetate shows an absorption band at 3570 cm.$^{-1}$, consistent with the hydroxyl being intra-molecularly hydrogen bonded. Since this hydroxyl had been derived from the methoxyl of nieshoutol, the linear structure, 161, can no longer be a possibility for the natural coumarin. This is slender evidence, in itself, on which to allocate the alternative structure 160, but, since this assignment was ultimately shown to be the correct one, the structure of all the derivatives of nieshoutol will be based on 160 from now on.

It must be noted that the demethylation products of nieshoutol, namely, the hydroxy-acetate and the diol, were slightly unstable and were used for synthetic purposes immediately after purification by preparative t.l.c. They appeared to be perfectly stable under the demethylating conditions, but whenever the ethyl acetate extract of the carefully neutralised reaction mixture was left standing or was heated under partial pressure, a pale lavender colour appeared which intensified as the solvent was removed. The relatively high recovery of the four compounds from the demethylation and the percentage conversions of the hydroxy-acetate and the diol to stable derivatives confirm that decomposition was not a competing reaction under these conditions. Nevertheless,

several unsuccessful attempts were made to eliminate it, e.g.
the ethyl acetate extract was kept at ~5° during the extraction;
as much air as possible was removed from the solution prior to
the evaporation of solvent with minimum heating. Despite the
use of different solvent systems and/or neutral silica, decomposition
appeared to continue during preparative t.l.c. The decomposition
product(s), characterised by its dark green appearance on silica,
was less polar than the compounds being isolated, did not markedly
interfere with their separation and represented only a very small
percentage of the total weight.

It is thought that the hydroxy-acetate hydrolyses to the
diol which itself undergoes aerial oxidation. This might account
for the intense colouring which was observed. A milder form of
this apparent decomposition occurs even with simple 6,7-dihydroxy-
coumarin (aesculetin). The crystals of this compound are almost
colourless, but, if even gentle heating (40-50°) is used, the
crystals become quite yellow over a period of time.

A more efficient method of synthesising the hydroxy-acetate
was provided by treating nieshoutol acetate with HBr/HOAc. This
yielded, in addition to recovered starting material (13%) and
nieshoutol (15%), the hydroxy-acetate (37%) and the diol (20%).

This type of demethylation incidentally provided a convenient
synthesis of 6-demethylnieshoutin(93). Since nieshoutin(63) was
more readily synthesised from the corresponding dimethylallyl ether
than its demethyl analogue (Part Ia), it was found to be more

convenient to prepare nieshoutin by a 'Claisen Rearrangement'
and then to demethylate it.   Nieshoutin proved slightly more
resistant to demethylation than nieshoutol under the same
conditions, but after heating nieshoutin with HBr/HOAc for
18 hr., three compounds were isolated.   In addition to 6-demethyl-
nieshoutin (36%) and unreacted starting material (30%), a highly
crystalline acetate (13%) was obtained.   The n.m.r. spectrum
is consistent with the identification of this compound as 6-demethyl-
nieshoutin acetate.   The u.v. spectrum of this compound is slightly
unusual and will be discussed with the u.v. spectra of the simple
coumarins in general in the appendix.   The percentage of demethyl-
ation in this experiment, however, was not very high.   If 6-demethyl-
nieshoutin had been required as part of a synthetic sequence, as
was originally intended, a more efficient synthesis might have been
provided by one of several reagents, known[159] to demethylate
aromatic methyl ethers in high yield.

The availability of the hydroxy-acetate, now formulated as
170, which had been obtained from the demethylation of nieshoutol
(160), provided an excellent opportunity for introducing a group
at the position which had originally been the methoxyl in 160.
Thus, treatment of 170 with brosyl chloride in pyridine gave two
compounds.   The first was the expected brosyloxy-acetate(172)
(41%), the n.m.r. of which shows a significant shielding (0.35 ppm)
of the C-4 proton when compared with that of the hydroxy-acetate
(170) (Table 3.5).   The _ortho_ relationship of the brosyl and
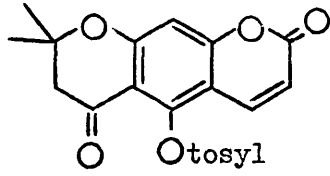
(173)

(160)   (170)   (172)

(176)   (174)

R = brosyl

(175)
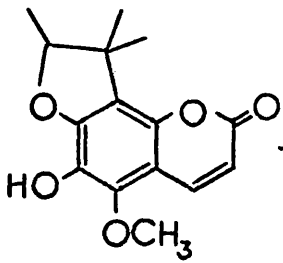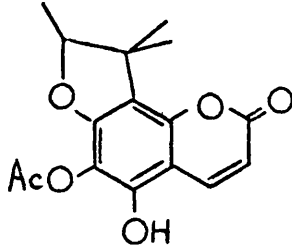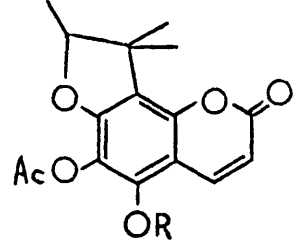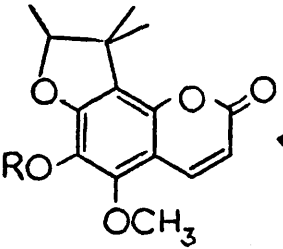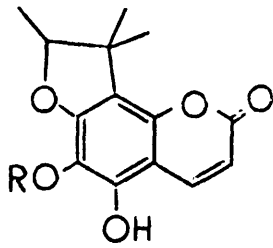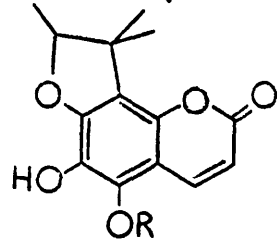
acetyl functions is strongly indicated by the upfield shift of the
acetate signal (0.33 ppm).   No such effect could have been expected
if they have a _para_ relationship.   Recently, Joshi, Kamat and
Saksena recorded[74], without comment, the n.m.r. spectrum of clausenin
tosylate (173) and by comparing it with that of clausenin a similar
effect on the C-4 proton (0.25 ppm) by the C-5 tosyl grouping can
be observed.

The second compound which was recovered from the brosylation
of the hydroxy-acetate(170), was a brosyloxy-phenol (35%) which
can be assigned structure 174 on the basis of its n.m.r. spectrum
(Table 3.5) which indicates the presence of a brosylate at C-5.
From the i.r. spectrum of 174, the hydroxyl is intramolecularly
hydrogen bonded (3555 cm.$^{-1}$).   This is consistent with the idea
that the hydroxyls of both 174 and nieshoutol occupy the same
position, i.e. C-6.

When this brosylation experiment was repeated, analytical
t.l.c. of the crude reaction mixture indicated that only the brosyl-
acetate was present but after work up both brosylates were isolated
in approximately the same yields as before.   It would appear,
therefore, that some acetate hydrolysis takes place during isolation.
The structure assigned to the brosyloxy-phenol(174) was confirmed
by hydrolysis of 172 to 174 in high yield.   Methylation of this
phenol, using methyl iodide and potassium carbonate, gave primarily
a compound isomeric with nieshoutol brosylate.   In the n.m.r.
spectrum of the latter, the brosyl grouping shields the secondary
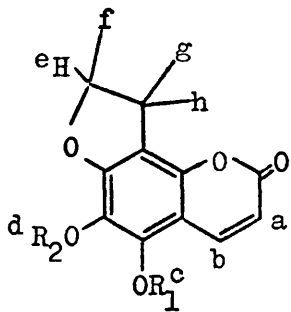
(160) $R_1 = CH_3$ $R_2 = H$

(170) $R_1 = H$ $R_2 = $ acetyl

(171) $R_1 = H$ $R_2 = H$

(172) $R_1 = $ brosyl $R_2 = $ acetyl

(174) $R_1 = $ brosyl $R_2 = H$

(175) $R_1 = $ brosyl $R_2 = CH_3$

(176) $R_1 = H$ $R_2 = $ brosyl

Table 3.5

Chemical shifts (τ) (J Hz.) at 60 MHz.

	H_a 1H,d. J9.5	H_b 1H,d. J9.5	H_c 3H,s.	H_d 3H,s.	H_e 1H,q. J6.5	H_f 3H,d. J6.5	H_g 3H,s.	H_h 3H,s.
(160)	3.81	2.13	6.03	-	5.43	8.59	8.46	8.72
(170)	3.85	2.02	-	7.60	5.45	8.62	8.48	8.73
(171)	3.85	2.02	-	-	5.47	8.62	8.48	8.76
(172)	3.78	2.41	-	7.93	5.39	8.60	8.42	8.67
(174)	3.82	2.35	-	-	5.40	8.58	8.44	8.70
(175)	3.77	2.30	-	6.31	5.44	8.59	8.44	8.71
(176)	3.83	2.03	-	-	5.89	8.88	8.58	8.92

methyl system of the 2,3,3-trimethyldihydrofuran but in that

(Table 3.5) of the former(175), using the diol 171 as a standard,

the brosyl grouping shields the C-4 proton and the methoxyl protons

in a manner analogous to that observed for the acetoxy-brosylate

(172).

Structure 160 can now confidently be allocated to nieshoutol.

Nevertheless, the brosyloxy-phenol, 174, discussed above, produced

a result which is worthy of comment.   174 is slightly unstable

but does not decompose to coloured material as do 170 and 171.

It is merely a non-crystalline fawn solid which darkens markedly at

its melting point.   It was noted that on treatment with methyl

iodide and potassium carbonate, this compound did not give the

required methyl ether, 175, exclusively.   A small amount ($\sim$ 5%)

of the isomer nieshoutol brosylate was also isolated.   Although

there is a possibility that a small percentage of the isomeric

hydroxy-brosylate(176) had been present, an alternative explanation

is favoured.   It is possible that a slight amount of ester inter-

change had occurred under the reaction conditions.   The exchange

of arylsulphonates is known[160] to take place in catechol systems.

The ability of the brosyl group in 174 to migrate on to the adjacent

hydroxyl was clearly indicated when an attempted sublimation of 174

gave rise to two compounds.   The n.m.r. spectrum of the mixture

confirms the evidence of analytical t.l.c. which indicated that

unreacted starting material was one of the components.   The remaining

n.m.r. signals can be readily accounted for by the presence of the

Scheme 3.5

R = brosyl

(177)

(178)

(179)

(120)

hydroxy-brosylate(176). By using the diol as a standard, the brosyl group in this case has a marked effect on the secondary methyl system (Table 3.5). This ester interchange was confirmed when methylation of the mixture gave both nieshoutol brosylate and the isomer, 175, in approximately equal amounts. These results can, once again, be explained only by an _ortho_ relationship of the functionalities involved. Scheme 3.5 summarises the above inter-conversions.

The original intention of using the diol(171) to show this _ortho_ relationship was also carried out. A solution of the diol (171) in pyridine and dichlorodiphenylmethane[161] was kept for 15 hr. After removing benzophenone which had been produced during the work up, a colourless oil was obtained, which solidified as a white solid on standing. The n.m.r. spectrum of this compound clearly indicates that it is the required cyclic ketal, 177. The mass spectrum, in addition to the molecular ion at m/e 426 (81%), shows a strong M^+-15 (95%), a base peak at m/e 105 and $C_6H_5^+$ at m/e 77 (20%). A similar yield (55%) of the cyclic ketal, 178, had been obtained when 4-methylaesculetin(97) was used as a model compound.

The _peri_ relationship of the methoxyl group and the C-4 proton of nieshoutol was independently established by using the nuclear Overhauser effect[162]. Saturation of the C-4 proton by double irradiation caused a 12% increase of the integrated intensity of the methoxyl protons when compared with the intensity on irradiating at approximately 50 Hz. upfield from the C-4 proton signal.

Conversely, an 11% increase of the integrated intensity of the C-4 proton resulted from the saturation of the methoxyl signal. These results were reproduceable when different samples of nieshotol were used.

A similar nuclear Overhauser effect has been observed[71] by Tori and his co-workers who deduced the arrangement of substituents in poncitrin(179) by this method. Saturation of the methoxyl protons of 179 produced an 11% increase for C-4 and a 16% increase for C-4′. It is noted that in both poncitrin and nieshoutol, the methoxyl is flanked by at least one peri hydrogen. Poncitrin, having two peri hydrogens, is well set up to produce the two nuclear Overhauser effects quoted. Since there is presumably some intra-molecular hydrogen bonding of the hydroxyl of nieshoutol(160) to the oxygen of the methoxyl, the methyl protons of that grouping will at some time be orientated towards the C-4 proton. If the dihydrofuran ring had not been competing for the hydroxyl, an even greater effect might have been observed since in that case the methoxyl might have been predominantly orientated towards the C-4 proton.

To examine the contribution played by the hydroxyl in nieshoutol to the N.O.E. and the possibility of identifying a methoxyl at C-5 when the ortho aromatic position is vacant, 7-O-(3,3-dimethylallyl)-5-methoxycoumarin(120) (Part Ic) was subjected to the same saturation procedure. In this case, however, there was no marked enhancement of the integrated intensity of the C-4 proton. The small effect

observed ($\sim 3\%$) is not significant with respect to the accuracy

of the determination. Nevertheless, if it could be shown that

a bulky group at C-6 induces a N.O.E. similar to that observed

for nieshoutol, this could be extended to provide a first

approximation method for distinguishing between the C-6 and

C-8 isomers of 5,7-dioxygenated coumarins which were discussed

earlier (Part Ic).

Part of this work has been summarised in a publication[164].

Scheme 3.6

(141)   (180)   (160)
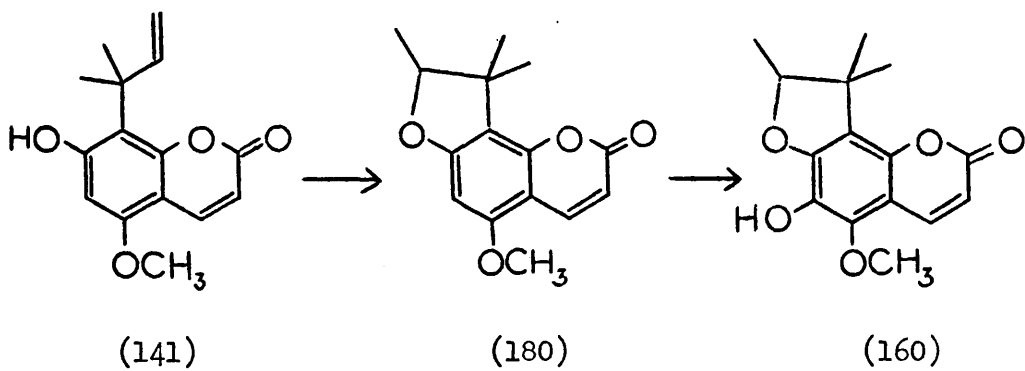
<u>Summary</u>

The results obtained eliminate every possible structure for

nieshoutol except 160. Even those having no oxygen at C-7 can

be discarded. From the subsequent studies of the u.v. spectra

of coumarins, it is quite possible that more information could

have been obtained from that of nieshoutol. This aspect will

be discussed in the appendix. Although the structure of nieshoutol

is not totally dependent on the shielding effects produced by the

arylsulphonates, they added considerable interest to the problem

and could have a potential use in this field. The synthesis of

nieshoutol can now readily be envisaged (Scheme 3.5). The phenol

(141) has already been prepared (Part Ic) in a reasonable yield

and the cyclisation to 180[14] would undoubtedly go well. The

last step, an Elb's persulphate oxidation [132], would probably give

a low yield ($\sim$20%) but the recovery of starting material should

be high, thus enabling recyclisation.

It was originally postulated[62] that nieshoutol, the only tri-

oxygenated coumarin which has been isolated so far from <u>P.obliquum</u>,

might be one of the sternutatory factors of this wood. During

the isolation of this coumarin, it was noted[62] that inhilation of

finely divided chromatographic silica, containing adsorbed nieshoutol,

caused violent sneezing. None of the other constituents of the

wood, either in the pure state or in mixtures, had this effect.

However, the author, although susceptible to sneezing on exposure

to the sawdust of this wood, did not find nieshoutol, adsorbed on

silica, to be an irritant.   It might, therefore, be that the

sternutatory factor, originally isolated in very small amounts

with nieshoutol, was inadvertently removed by crystallisation

and was not present in the sample of nieshoutol inherited by

the author.

PART III

Experimental.

Nieshoutol(160)

Nieshoutol, $C_{15}H_{16}O_5$, which occurred[62] as 0.1% of the dried heartwood of <u>Ptaeroxylon obliquum</u>, crystallised from carbon tetrachloride as pale yellow plates, m.p. 143-144°; $\nu \, ^{CCl_4}_{max}$ 3569, 1736, 1620 and 1578 cm.$^{-1}$; mass spectral peaks at m/e 276 (M^+), 261, 247, 246, 243, 233, 229, 220 and 205 (r.a. 98, 100, 9, 15, 7, 32, 56, 12 and 10%).

Nieshoutol methyl ether.

The oil obtained[62] by diazomethylation of an ethereal solution of nieshoutol was distilled at 120°/0.05mm. On standing, the distillate solidified to yield the methyl ether as colourless needles, m.p. 99-100°.

Nieshoutol O-(dimethylthiocarbamate).

Sodium hydride(50mg.) (from a 50% w./w. oil dispersion washed with anhydrous light petroleum) was added to a solution of nieshoutol(160)(500mg.) in dry dimethylformamide(25ml.). When effervescence had ceased (~90min.), dimethylthiocarbamoyl chloride(350mg.) was added and the solution heated at 110° for 10 min., and then at 95° for 60 min. The variation in temperature was accidental and 95° for 60-90 min. would have sufficed[62]. On cooling, the reaction mixture was diluted with aqueous potassium hydroxide (0.2% w./v.; 25ml.) and, after 15 min., extracted with ether. The organic layer was washed with aqueous potassium hydroxide (0.2%), water to neutrality and dried. Removal of solvent gave a yellow solid which, on

crystallisation from methanol, yielded the thiocarbamate as pale yellow plates (333mg.; 50%), m.p. 182-183°. The physical properties of this compound agreed in all respects with those of the derivative previously prepared[62].

Neutralisation and ethyl acetate extraction of the basic washings gave crude nieshoutol(125mg.).

Pyrolyses of nieshoutol O-(dimethylthiocarbamate).

Numerous pilot pyrolyses ($\sim$10mg. scale) were carried out in a sublimation block with temperatures ranging from 185° to 285° and times from 15 to 60 min. Analytical t.l.c. indicated that pyrolyses carried out under reduced pressure or in a nitrogen atmosphere gave similar results to those obtained when the thiocarbamate was heated in a tube open to the atmosphere.

Almost total recovery of starting material was obtained at lower temperatures (185-220°; 30-60 min.). At higher temperatures (275-285°; 15-30 min.) rapid charring took place and analytical t.l.c. indicated a large number of products. At temperatures around 250° (30-60 min.), less charring took place and, although there still appeared to be a large number of products, several preparative scale pyrolyses were carried out. The following results are typical of those obtained.

The thiocarbamate(100mg.) was heated in a sublimation block at 250° for 50 min. The residue was adsorbed on to preparative chromatoplates and, after eluting with chloroform, 6 bands were removed. One of these was shown to contain

starting material(11mg.)(m.p., m.m.p., i.r., n.m.r.) and

another nieshoutol(160)(3mg.)(m.p., m.m.p., i.r.).

Analytical t.l.c. indicated that the remaining bands contained

a complex mixture of compounds(total weight 46mg.).

Nitration of nieshoutin(63).

A cold mixture (2 drops; $\sim$120mg.) of conc. sulphuric and

conc. nitric acids (molar ratio 2:1) was added to a stirring

solution of nieshoutin(24mg.) in conc. sulphuric acid(1ml.) at

0°. After 45 min. at that temperature, a further 3 drops of

the acid mixture was added and the solution kept at 0° for a

further 15 min. Iced water(25ml.) was added and the resulting

yellow precipitate filtered, washed with water to neutrality,

dried and then adsorbed onto a preparative chromatoplate.

Elution with chloroform and extraction of the major band gave

a yellow solid which, on crystallisation from ether-light

petroleum, yielded 3,5-dinitronieshoutin as yellow needles

(25mg.; 76%), m.p. 165.5-167°. (Found: C, 51.15; H, 3.90;

N, 7.85. $C_{15}H_{14}N_2O_8$ requires C, 51.45; H, 4.05; N, 8.00%);

$\nu \frac{CHCl_3}{max}$ 1780, 1765, 1620 and 1575 cm.$^{-1}$; λ_{max} 224, 243, 337

and 390 nm. (log ε 4.09, 3.78, 3.78 and 3.96); mass spectral

peaks at m/e 350 (M^+), 335, 320, 290, 275 and 44 (r.a. 35, 6,

29, 6, 9 and 100%); n.m.r. signals at τ 8.66 (3H; s.), 8.51

(3H; d.; J 6.5 Hz.), 8.42 (3H; s.), 5.96 (3H; s.), 5.24 (1H; q.;

J 6.5 Hz.) and 1.44 (1H; s.).

6-Hydroxy-7-methoxycoumarin (isoscopoletin) (42)

After treatment of aesculin, the 6-β-glucoside of

aesculetin(19), (3g.) in methanol (100ml.) with a large excess

of ethereal diazomethane for 24 hr., removal of solvent gave a

white solid.   This was dissolved in methanol (300ml.) and

conc. hydrochloric acid (35ml.) and the solution refluxed

for 18 hr.   Most of the solvent was then removed and the

remainder diluted with iced water (250ml.).   The resulting

precipitate was filtered, washed with water to neutrality

and crystallised from methanol.   This gave isoscopoletin as

pale yellow needles (0.85g.), m.p. 184-186° (lit.[163] m.p. 185°);

λ_{max} 231, 253, 259, 296 and 348 nm. (log ε 4.22, 3.75, 3.73,

3.78 and 4.02); λ_{max} (base) 253, 277 (sh.), 313 and 401 nm.

(log ε 4.41, 4.00, 3.92 and 3.92);   mass spectral peaks at m/e

192, 177, 164, 149, 121, 79, 69 and 51 (r.a. 100, 17, 84, 99,

42, 33, 49 and 44%).

Derivatives of nieshoutol(160)

1. Acetate

A solution of nieshcutol(300 mg.) and acetic anhydride(0.15 ml.) in dry pyridine(1 ml.) was kept at R.T. for 1 hr. Work up (II) yielded a white solid which, on crystallisation from ether–light petroleum, gave nieshoutol acetate as colourless plates(316 mg.; 93%), m.p. 126–128°. (Found: C, 64.40; H, 5.85. $C_{17}H_{18}O_6$ requires C, 64.15; H, 5.70%); $\nu \, ^{CHCl_3}_{max}$ 1775–1765, 1730, 1613 and 1580 cm^{-1}; λ_{max} 223, 249, 259 and 328 nm. (log$\mathcal{E}$ 4.19, 3.78, 3.80 and 4.16); mass spectral peaks at m/e 318 (M^+), 276 and 261 (r.a. 16, 100 and 66%).

2. Methanesulphonate (mesylate)

A solution of nieshoutol(27 mg.) and methanesulphonyl chloride (65 mg.) in dry pyridine(0.5 ml.) was kept at R.T. for 3 hr. Work up(II) yielded a dark yellow oil which, after preparative t.l.c. (chloroform x 2), was distilled at 160°/0.05 mm. On standing the distillate solidified to give the mesylate as colourless needles(28 mg.; 81%), m.p. 140–142°. (Found: C, 54.00; H, 5.15. $C_{16}H_{18}O_7S$ requires C, 54.25; H, 5.10%); $\nu \, ^{CHCl_3}_{max}$ 1745–1735, 1618 and 1583 cm^{-1}; λ_{max} 224, 252, 260 and 325 nm. (log$\mathcal{E}$ 4.16, 3.74, 3.77 and 4.09); mass spectral peaks at m/e 354 (M^+), 276, 275, 260, 245 and 221 (r.a. 16, 16, 100, 22, 28 and 16%).

3. p-Toluenesulphonate (tosylate)

A solution of nieshoutol(27 mg.) and p-toluenesulphonyl chloride (25 mg.) in dry pyridine (1ml.) was kept at R.T. for 20 hr. Since analytical t.l.c. indicated that the reaction was not complete, further tosyl chloride(20 mg.) was added and the temperature raised to 75° for 3 hr. Work up (II), followed by preparative t.l.c. (chloroform x 1), gave a white solid which on crystallisation from chloroform-light petroleum gave neishoutol tosylate as colourless plates(38 mg.; 89%), m.p. 153-155°. (Found: C, 60.90; H, 5.05. $C_{22}H_{22}O_7S$ requires C, 61.40; H, 5.15%); mass spectral peaks at m/e 430 (M^+), 276, 275, 260, 245, 221 and 91 (r.a. 10, 18, 100, 15, 15, 10 and 10%).

4. Benzyl ether

Potassium carbonate(20 mg.) and benzyl bromide(40 mg.) were added to a solution of nieshoutol(20 mg.) in acetone(5 ml.) and the solvent refluxed for 6 hr. Work up (I) gave a yellow solid which was kept at 35°/0.05 mm. for 4 hr. to remove excess benzyl bromide and then crystallised from ether-light petroleum. This gave nieshoutol benzyl ether as colourless plates(25 mg.; 91%), m.p. 119-121.5°. (Found: C, 72.05; H, 6.10. $C_{22}H_{22}O_5$ requires C, 72.10; H, 6.05%); λ_{max} 228, 250, 259 and 324 nm. (logε 4.25, 3.82, 3.75 and 4.16); mass spectral peaks at m/e 366 (M^+), 276, 275, 260, 245, 221 and 91 (r.a. 15, 18, 100, 16, 18, 10 and 44%).

Derivatives of 6-demethylnieshoutin(93)

1. p-Bromobenzenesulphonate (brosylate)(165)

A solution of 6-demethylnieshoutin(18 mg.) and brosyl chloride (45 mg.) in dry pyridine(1 ml.) was kept at 84° for 18 hr. Work up (II), followed by preparative t.l.c. (chloroform x 1), gave an oil which was distilled at $150^{\circ}/0.02$ mm. On standing the distillate solidified to give the brosylate(165) as colourless needles(27 mg.; 79%), m.p. 128-129.5°. (Found: C, 51.40; H, 3.75. $C_{20}H_{17}O_6S.Br$ requires C, 51.60; H, 3.70%); $\nu_{max}^{CHCl_3}$ 1750-1730, 1625 and 1580 cm.$^{-1}$; λ_{max} 222, 237, 259, 280 and 325 nm. (logϵ 4.36, 4.34, 3.70, 3.68 and 4.19); mass spectral peaks at m/e 466 (M^+), 464 (M^+), 246, 245, 230, 191 and 79 (r.a. 8, 8, 15, 100, 19, 10 and 9%).

2. Methanesulphonate (mesylate)(166)

A solution of 6-demethylnieshoutin(20 mg.) and methanesulphonyl chloride(65 mg.) in dry pyridine(1 ml.) was kept at R.T. for 2 hr. Work up (II), followed by preparative t.l.c. (chloroform x 1), gave a white solid which, on crystallisation from ether-light petroleum, gave the sulphonate(166) as colourless plates (23 mg.; 87%), m.p. 128-130°. (Found: C, 55.50; H, 5.05. $C_{15}H_{16}O_6S$ requires C, 55.55; H, 4.95%); $\nu_{max}^{CHCl_3}$ 1745-1735, 1625 and 1585 cm.$^{-1}$; λ_{max} 219, 248, 259 and 325 nm. (log ϵ 4.28, 3.60, 3.63 and 4.20); mass spectral peaks at m/e 324 (M^+), 246, 245, 230, 223, 221, 191 and 79 (r.a. 34, 22, 100, 50, 19, 14, 29 and 36%).

Derivatives of 3-(1,1-dimethylallyl)scopoletin(76)

1. p-Bromobenzenesulphonate (brosylate)(168)

A solution of 76 (50 mg.) and brosyl chloride (124 mg.) in

dry pyridine (2 ml.) was kept at 80° for 18 hr. Work up (II)

yielded the brosylate which crystallised from carbon tetrachloride

as pale yellow needles (76 mg.; 81%), m.p. 203.5-205°. (Found:

C, 52.70; H, 4.00. $C_{21}H_{19}O_6S$ Br requires C, 52.60; H, 3.95%);

$\nu \frac{CHCl_3}{max}$ 1735-1725, 1615 (very weak) and 1580 cm.$^{-1}$; λ_{max}

228, 235, 259, 273, 278, 285 and 337 nm. (logϵ 4.45, 4.30, 3.93,

4.08, 4.13, 4.03 and 3.93); mass spectral peak at m/e 480 (M^+),

478 (M^+), 260, 259, 231, 217 and 203 (r.a. 16, 16, 23, 100, 24,

25 and 20%).

2. Methanesulphonate (mesylate)(169)

A solution of 76 (26 mg.) and methanesulphonyl chloride (75 mg.)

in dry pyridine (1 ml.) was kept at R.T. for 2½ hr. Work up (II),

followed by preparative t.l.c. (chloroform x 1), yielded the

mesylate which crystallised from ether as colourless needles

(27 mg.; 80%), m.p. 118-120°. (Found: C, 56.80; H, 5.50.

$C_{16}H_{18}O_6S$ requires C, 56.80; H, 5.35%); $\nu \frac{CHCl_3}{max}$ 1735-1725, 1620

(very weak) and 1585 cm.$^{-1}$; λ_{max} 226, 250, 259, 271, 278, 284

and 335 nm. (logϵ 4.31, 3.78, 3.86, 4.02, 4.09, 4.02 and 3.94);

mass spectral peaks at m/e 338 (M^+), 323, 260, 259, 231, 217 and

203 (r.a. 31, 10, 18, 100, 22, 20 and 18%).

Demethylation of nieshoutol(160)

Hydrogen bromide in glacial acetic acid (B.D.H. Chemicals Ltd.) (50% w./v.; 10ml.) was added to a solution of nieshoutol (150mg.) in glacial acetic acid (10ml.) and the mixture heated for $2\frac{1}{2}$ hr. on a steam bath. On cooling, the solution was poured into iced water (100ml.), carefully neutralised with dil. sodium hydroxide and then extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated. The resulting brown-green oil, after preparative t.l.c. (chloroform x 2) yielded:-

i)   3-bromonieshoutol acetate, as a pale yellow solid (5'mg.); mass spectral peaks at m/e 356 (M^+-42) and 354 (M^+-42); n.m.r. (100 MHz.) signals at τ 8.69 (3H ; s.), 8.58 (3H ; d.; J 6.5 Hz.), 8.43 (3H ; s.), 7.62 (3H ; s.), 6.07 (3H ; s.), 5.45 (1H ; q.; J 6.5 Hz.) and 1.76 (1H ; s.).

ii)   nieshoutol acetate (7mg.) (m.p., m.m.p., i.r., n.m.r.).

iii) 3-bromonieshoutol, as a yellow oily solid (15'mg.); $\nu_{max}^{CHCl_3}$ 3540, 1730-1720, 1630 and 1572 cm.$^{-1}$; mass spectral peaks at m/e 356 (M^+) and 354 (M^+); n.m.r. signals at τ 8.73 (3H ; s.), 8.58 (3H ; d.; J 6.5 Hz.), 8.47 (3H ; s.), 6.00 (3H ; s.), 5.42 (1H ; q.; J 6.5 Hz.), 5.00$^\bullet$ (1H ; b.s.) and 1.80 (1H ; s.).

iv)   nieshoutol(160) (16mg.) (m.p., m.m.p., i.r., n.m.r.).

v)   3-bromo derivative of the hydroxy-acetate(170), as a yellow solid (12'mg.); $\nu_{max}^{CHCl_3}$ 3540, 1775, 1730, 1630 and 1570 cm.$^{-1}$; n.m.r. (100 MHz.) signals at τ 8.73 (3H ; s.), 8.62 (3H ;

d.; J 6.5 Hz.), 8.48 (3H ; s.), 7.58 (3H ; s.) and 1.68 (1H ; s.).

Treatment of this compound in the usual way with methyl iodide and potassium carbonate yielded a methyl ether (87% conversion by crude weight), which was identical to 3-bromonieshoutol acetate with respect to mass spectrum and n.m.r. spectrum).

vi)   the <u>hydroxy-acetate</u>(170) (17′mg.), from ether as pale yellow needles, m.p. 176-178.5°.   (Found: C, 62.65; H, 5.20. $C_{16}H_{16}O_6$ requires C, 63.10; H, 5.30%); $\nu_{max}^{CHCl_3}$ 3550, 1775-1770, 1730-1720, 1625 and 1580 cm.$^{-1}$; $\nu_{max}^{CCl_4}$ 3570,∼3310, 1786 and 1740 cm.$^{-1}$ (ε 130, 40, 245 and 1060); λ_{max} 226, 252, 260 and 335 nm. (logε 4.03, 3.67, 3.70 and 3.95); mass spectral peaks at m/e 304 (M^+), 262, 247, 234, 229, 219 and 43 (r.a. 24, 100, 82, 67, 20, 42 and 60%); n.m.r. signals at τ 8.73 (3H ; s.), 8.62 (3H ; d.; J 6.5 Hz.), 8.48 (3H ; s.), 7.60 (3H ; s.), 5.45 (1H ; q.; J 6.5 Hz.), 3.93• (1H ; b.s.), 3.85 (1H ; d.; J 9.5 Hz.) and 2.02 (1H ; d.; J 9.5 Hz.).   Treatment of 170 in the usual way with methyl iodide and potassium carbonate or with diazomethane yielded nieshoutol‾acetate (82-86%) (m.p., m.m.p., n.m.r.).

vii) 3-bromo derivative of the diol(171), as grey needles (29′mg.); mass spectral peaks at m/e 342 (M^+) and 340 (M^+); n.m.r. signals at τ 8.76 (3H ; s.); 8.63 (3H ; d.; J 6.5 Hz.), 8.49 (3H ; s.), 5.47 (1H ; q.; J 6.5 Hz.), 4.22• (2H ; b.s.) and 1.62 (1H ; s.).

viii) the <u>diol</u>(171) (54′mg.), from ether-light petroleum as a pale yellow solid, m.p. 121-126° ; $\nu_{max}^{CHCl_3}$ 3540, 1730-1720, 1630

and 1585 cm.$^{-1}$; mass spectral peaks at m/e 262 (M^+), 247, 234, 229 and 219 (r.a. 92, 98, 74, 57 and 100%); n.m.r. signals at τ 8.76 (3H ; s.), 8.62 (3H ; d.; J 6.5 Hz.), 8.48 (3H ; s.), 5.47 (1H ; q.; J 6.5 Hz.), 4.00 (2H ; b.s.), 3.85 (1H ; d.; J 9.5 Hz.) and 2.02 (1H ; d.; J 9.5 Hz.). After treatment of 171 in methanol with excess ethereal diazomethane for 18 hr., removal of solvent gave an oil which was distilled at 120°/0.04 mm. On standing the distillate solidified to give nieshoutol methyl ether (84%) as colourless needles (m.p., m.m.p., i.r.).

Preparation of hydrogen bromide in glacial acetic acid

Bromine was added dropwise to tetrahydronaphthalene (tetralin) (200ml.). The solution was stirred and kept at ~25° by external cooling. The hydrogen bromide produced was passed twice through tetralin and then into glacial acetic acid (200ml.). After ~4 hr., a solution of HBr/HOAc (45% w./v.) was obtained.

If stored at ~5°, the solution became slightly yellow after only a few days, but if stored at ~-20°, the frozen mixture could be kept for at least two months before use. Other percentages were prepared and stored in the same way.

Demethylation of nieshoutol(160)

Using the same method as for the previous demethylation, nieshoutol (100mg.) in glacial acetic acid (8ml.) was treated with hydrogen bromide/acetic acid (45%w./v.; 8ml.) (cf. p.145) for 6 hr.   This yielded nieshoutol acetate (6mg.; 5%), nieshoutol (22mg.; 22%), the hydroxy-acetate(170) (24'mg.; 22%) and the diol (171) (38'mg.; 40%).

Modification of conditions, e.g. higher or lower percentages of HBr/HOAc and/or longer refluxed times, did not improve the yields of 170 and 171.

Demethylation of nieshoutol acetate

A solution of nieshoutol acetate (230mg.) in hydrogen bromide / acetic acid (40% w./v.; 20ml.) was heated on a steam bath for 3 hr. Using the same isolation procedure as for the previous demethylations, this reaction yielded nieshoutol acetate (30mg.; 13%), nieshoutol(160) (29mg.; 15%), the hydroxy-acetate(170) (81'mg.; 37%) and the diol(171) (39'mg.; 20%).

Demethylation of nieshoutin(63)

A solution of nieshoutin (105mg.) in hydrogen bromide / acetic acid (22% w./v.; 14ml.) was heated at 75° for 18 hr.   Work up of the reaction mixture (cf. p.143) gave an oil which was resolved by preparative t.l.c. (80% ether-light petroleum x 1) into:-

i) 6-demethylnieshoutin acetate, from ether-light petroleum as colourless needles (15mg.; 13%), m.p. 96.5-98°.   (Found:

C, 66.70; H, 5.70. $C_{16}H_{16}O_5$ requires C, 66.65; H, 5.60%);

λ_{max} 248, 258 and 329 nm. (log ε 3.53, 3.53 and 4.13);   n.m.r.

signals at τ 8.67 (3H ; s.), 8.58 (3H ; d.; J 6.5 Hz.), 8.41

(3H ; s.), 7.66 (3H ; s.), 5.42 (1H ; q.; J 6.5 Hz.), 3.79

(1H ; d.; J 9.5 Hz.), 2.97 (1H ; s.) and 2.46 (1H ; d.; J 9.5 Hz.).

      ii)   nieshoutin (32mg.; 30%) (m.p., m.m.p., i.r.).

      iii) 6-demethylnieshoutin(93) (38mg.; 36%) (m.p., m.m.p.,

i.r., n.m.r.).

Treatment of the hydroxy-acetate(170) with brosyl chloride

A solution of the hydroxy-acetate(170) (40mg.) and brosyl chloride (100mg.) in dry pyridine (1ml.) was kept at 85° for 18 hr. Work up (II) gave a yellow solid which was separate by preparative t.l.c. (chloroform x ½ x 1) into:-

i)   the brosyloxy-acetate(172), from chloroform-methanol as colourless plates (28 mg.; 41%), m.p. 209-211.5°.   (Found: C, 50.35; H, 3.60. $C_{22}H_{19}O_8S$ Br requires C, 50.50; H, 3.65%); $\nu_{max}^{CHCl_3}$ 1785, 1745-1735, 1627 and 1580 cm.$^{-1}$; λ_{max} 226, 239, 258, 279 and 328 nm. (logε 4.18, 4.16, 3.73, 3.41 and 3.93); mass spectral peaks at m/e 524 (M^+), 522 (M^+), 482, 480, 262, 261 and 246 (r.a. 2, 2, 25, 25, 21, 100 and 19%); n.m.r. signals at τ 8.67 (3H ; s.), 8.60 (3H ; d.; J 6.5 Hz.), 8.42 (3H ; s.), 7.93 (3H ; s.), 5.39 (1H ; q.; J 6.5 Hz.), 3.78 (1H ; d.; J 9.5 Hz.), 2.41 (1H ; d.; J 9.5 Hz.) and 2.20 (4H ; s.).

ii)   the brosyloxy-phenol(174), (22′mg.; 35%), from chloroform-carbon tetrachloride as a fawn solid, m.p. 209° decomp.; $\nu_{max}^{CHCl_3}$ 3555, 1735-1725, 1625 and 1585 cm.$^{-1}$; mass spectral peaks at m/e 482 (M^+) and 480 (M^+); n.m.r. signals at τ 8.70 (3H ; s.), 8.58 (3H ; d.; J 6.5 Hz.), 8.44 (3H ; s.), 5.40 (1H ; q.; J 6.5 Hz.), 4.67*(1H ; b.s.), 3.82 (1H ; d.; J 9.5 Hz.), 2.35 (1H ; d.; J 9.5 Hz.), 2.22 (2H ; b.s.) and 2.16 (2H ; b.s.).

Hydrolysis of the brosyloxy-acetate(172)

The brosylate, 172, (25mg.) was dissolved in cold ($\sim 0^{\circ}$),
conc. sulphuric acid (1ml.). Iced water (25ml.) was added
immediately and the aqueous mixture extracted with ethyl acetate.
The organic layer was washed with brine to neutrality, dried and
evaporated. The residue, after purification by preparative
t.l.c. (chloroform x 1), gave a yellow solid (20 mg.) whose
n.m.r. and i.r. spectra were identical to those of the sulphonate
174 isolated in the previous reaction.

Methylation of the brosyloxy-phenol(174)

Potassium carbonate (50mg.) and methyl iodide (0.1ml.) were
added to a solution of 174 (50mg.) in acetone (10ml.). After
refluxing for 18 hr., work up (I) gave an oil which was separated
by preparative t.l.c. (40% ether-light petroleum x 3) into:-

i) the methoxy-brosylate(175), from chloroform-light
petroleum as pale yellow plates (38 mg.; 73%), m.p. 103-104°.
(Found: C, 50.85; H, 3.95. $C_{21}H_{19}O_7S$ Br requires C, 50.90;
H, 3.90%); $\nu_{max}^{CHCl_3}$ 1740-1730, 1618 and 1580 cm.$^{-1}$; λ_{max} 235,
255, 278 and 336 nm. (log ϵ 4.32; 3.80, 3.38 and 3.92); mass
spectral peaks at m/e 496 (M^+), 494 (M^+), 276, 275, 259, 258,
244 and 243 (r.a. 20, 20, 23, 100, 29, 23, 29 and 24%); n.m.r.
signals at τ 8.71 (3H ; s.), 8.59 (3H ; d.; J 6.5 Hz.), 8.44
(3H ; s.), 6.31 (3H ; s.), 5.44 (1H ; q.; J 6.5 Hz.), 3.77 (1H ; d.;
J 9.5 Hz.), 2.30 (1H ; d.; J 9.5 Hz.), 2.22 (2H ; b.s.) and 2.16
(2H ; b.s.).

ii) nieshoutol brosylate (3 mg.; 5%) (t.l.c. and i.r.).

Attempted sublimation of the brosyloxy-phenol(174)

and subsequent methylation.

An attempted sublimation of 174 (20 mg.) at $190^{o}/0.05$ mm.

gave a yellowish oil which was shown to be a mixture of two

compounds by analytical t.l.c.   Treatment of the crude oil in

methanol (1ml.) with excess ethereal diazomethane for 5 hr. gave

a mixture which was separated by preparative t.l.c. into:-

   i) the methoxy-brosylate(175) (8 mg.) (t.l.c. behaviour, i.r.).

   ii) nieshoutol brosylate (6 mg.) (t.l.c. behaviour, i.r.).

Dichlorodiphenylmethane

An equimolar mixture of benzophenone and phosphorus penta-

chloride was heated at 150° for $1\frac{1}{2}$ hr.   Distillation yielded

dichlorodiphenylmethane, b.p. $161-162^{o}/\sim12$ mm.

Benzophenone cyclic ketal of 5-demethylnieshoutol

A solution of 5-demethylnieshoutol(171) (81 mg.) and dichloro-

diphenylmethane (200mg.) in dry pyridine (1ml.) was left at R.T.

for 15 hr.   Work up (II) gave a solid which was separated by

preparative t.l.c. (25% ethyl acetate-light petroleum x 1) into

benzophenone and the ketal, 177.   The latter was distilled at $170^{o}/$

0.05 mm. and on standing the distillate solidified to give 177 as

a white solid (76mg.; 58%), m.p. $194-195^{o}$.   (Found: C, 76.00;

H, 5.10. $C_{27}H_{22}O_{5}$ requires C, 76.05; H, 5.20%); $\nu_{max}^{CHCl_3}$ 1725,

1645 and 1585 cm.$^{-1}$; mass spectral peaks at m/e 427, 426 (M^{+}), 412,

411, 165, 105 and 77 (r.a. 23, 81, 27, 95, 53, 100 and 20%);

n.m.r. signals at τ 8.77 (3H ; s.), 8.61 (3H ; d.; J 6.5 Hz.), 8.48 (3H ; s.), 5.48 (1H ; q.; J 6.5 Hz.), 3.88 (1H ; d.; J 9.5 Hz.), 2.60 (10H ; b.m.) and 2.25 (1H ; d.; J 9.5 Hz.).

Benzophenone cyclic ketal of 4-methylaesculetin

A solution of 4-methylaesculetin(97) (96mg.) and dichlorodiphenylmethane (354mg.) in dry pyridine (2ml.) was left at R.T. for 20 hr. Work up (II) gave a white solid which was separated by preparative t.l.c. (chloroform x $\frac{1}{2}$ x 1) into benzophenone and the ketal(178). The latter sublimed at 180°/0.05 mm. as a white solid (100mg.; 55%), m.p. 221-222°. (Found: C, 77.45; H, 4.55. $C_{23}H_{16}O_4$ requires C, 77.50; H, 4.55%); $\nu_{max}^{CHCl_3}$ 1710, 1625 and 1585 cm.$^{-1}$; mass spectral peaks at m/e 356 (M$^+$), 280, 279, 251, 165, 105 and 77 (r.a. 60, 19, 100, 15, 45, 41 and 17%); n.m.r. signals at τ 7.67 (3H ; b.s.), 3.87 (1H ; b.s.), 3.12 (1H ; s.), 2.97 (1H ; s.) and 2.57 (10H ; b.m.).

Nuclear Overhauser Effects

Measurements were made on a Varian HA-100 spectrometer at a speed of 1 Hz.sec using a degassed solution of the compound (40mg.) in question, in deuterochloroform ($\sim$0.4ml.). Determinations to within $\sim\pm$2%.

APPENDIX

Ultra-Violet Spectra of Simple Coumarins.
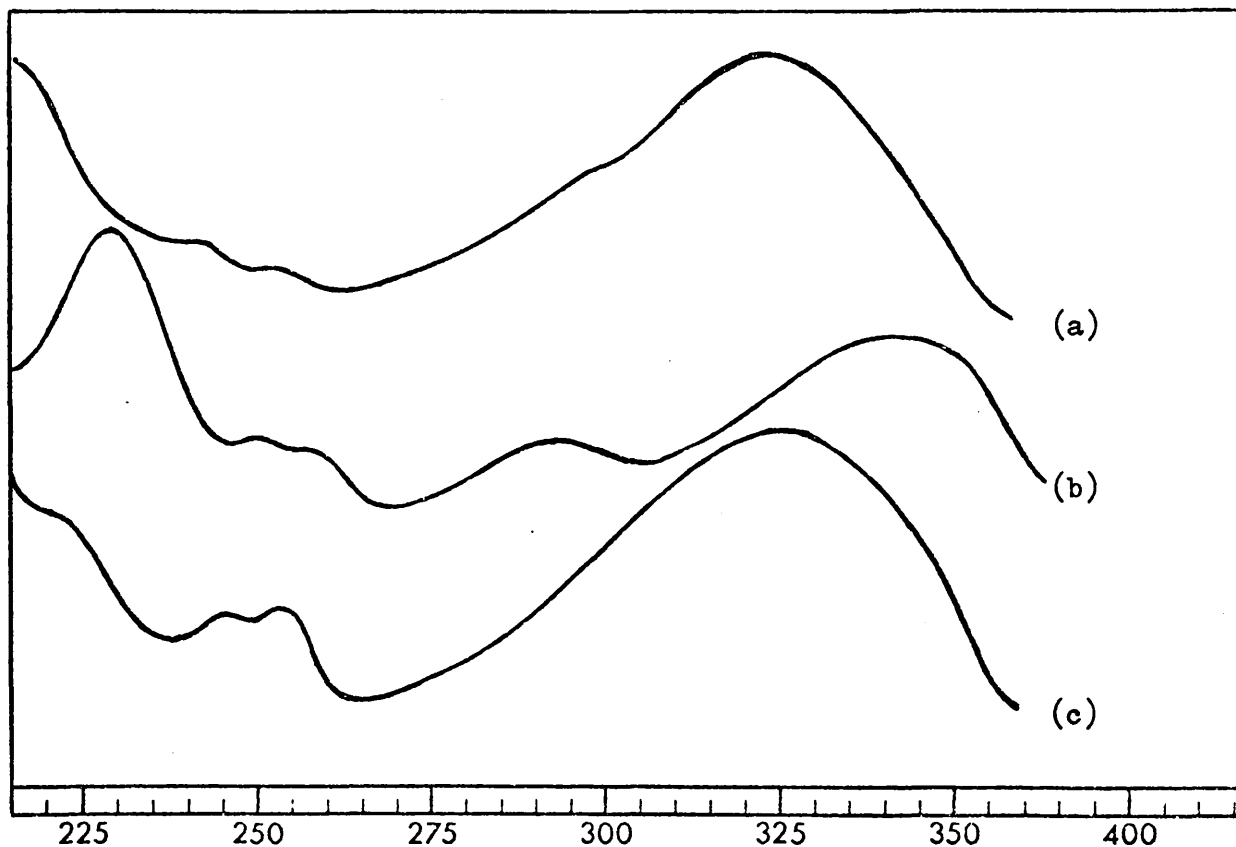
Figure A.1

U.v. spectra (nm.). Ethanol solutions.

(a) 7-methoxycoumarin

(b) 6,7-dimethoxycoumarin

(c) 5,7-dimethoxycoumarin

N.B. The spectra illustrated in Figures A.1, A.2 and A.3
do _not_ correlate with respect to absorption.

The u.v. spectra of simple coumarins can provide[165-168] useful information with regards to structural elucidation. Coumarin, itself, behaves as an α-pyrone[165,169] absorbing ultra-violet light at 275, 284 and 310 nm. (log ϵ 4.03, 3.96 and 3.72). However, the effects, observed on introducing hydroxyl or methoxyl groups, are difficult to explain on the basis of simple electronic interactions. The empirical rules of resonance might have suggested that a C-7 or C-5 hydroxyl (or methoxyl) would produce the largest bathochromic shift relative to coumarin. Table A.1 demonstrates that this position is actually held by 6-hydroxycoumarin.

Table A.1

U.v. spectra (nm.) *shoulder.

	λ max (log ϵ)				solvent	references
5-hydroxycoumarin	251 (3.8)	300 (4.1)			methanol	171
5-methoxycoumarin	243 (3.7)	300 (4.1)			"	172
6-hydroxycoumarin	224 (4.3)	277 (4.1)	349 (3.6)		"	171
6-methoxycoumarin	226 (4.4)	276 (4.0)	344 (3.6)		ethanol	173
7-hydroxycoumarin	217 (4.1)	240* (3.5)	325 (4.2)		methanol	171
7-methoxycoumarin	218 (4.1)	243* (3.4)	252 (3.3)	323 (4.2)	ethanol	173
8-hydroxycoumarin	211 (4.0)	255 (3.9)	286 (4.1)		methanol	171
8-methoxycoumarin	220 (4.1)	260 (3.9)	290 (4.1)		ethanol	174
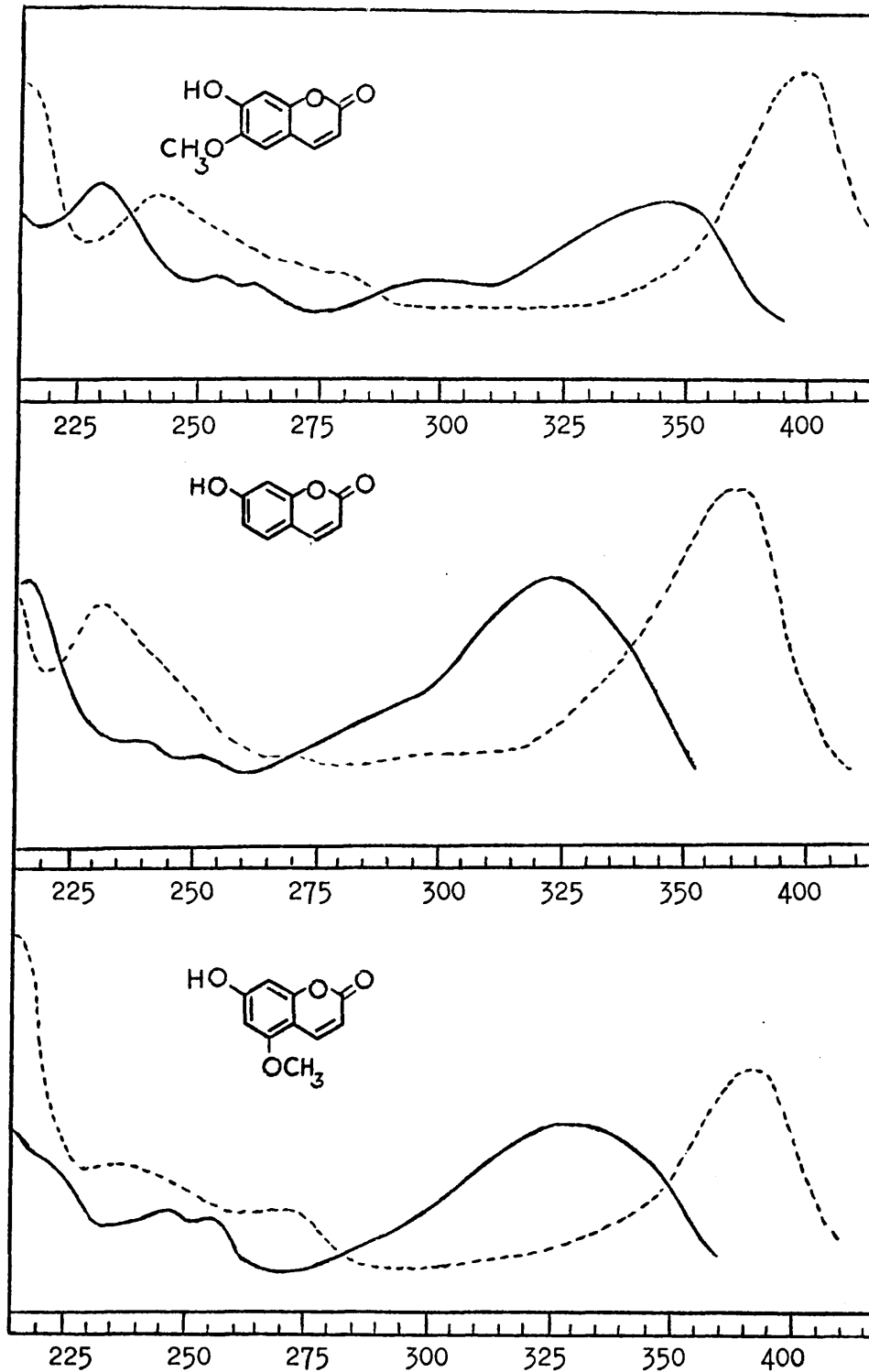
Figure A.2

—————— ethanol solution.

- - - - - - ethanol solution to which base has been added.

The spectra of 5,7-dioxygenated and 7,8-dioxygenated coumarins are generally very similar to that of the 7-monooxygenated series (partly illustrated in Figure A.1). Only 6,7-dioxygenated coumarins are easily recognisable, presumably due to the presence of an oxygen at C-6. It is noticeable that the presence of an electron withdrawing group, such as acetyl, on the oxygen at C-6 nullifies the effect produced by the C-6 oxygen. The spectrum produced, in this case, is similar to a) or c) in Figure A.1 . The u.v. spectrum of 6-demethylnieshoutin acetate (p. 127 & 146) is one of the few observed in the course of this research, which was not typical of its 6,7-dioxygenated skeleton.

It was realised that this effect, produced by a C-6 oxygen on u.v. spectra, could probably be extended to tri-oxygenated systems. Table A.2 indicates how it might have been deduced from the u.v. spectrum that nieshoutol (Part III) was not a 5,7,8-trioxygenated coumarin.

Table A.2

U.v. spectra (nm.) Ethanol solutions.

	λ_{max} (log ε)				
nieshoutol	230 (4.2)	251 (3.6)	258 (3.5)	340 (4.1)	
nieshoutol acetate	223 (4.2)	249 (3.8)	259 (3.8)	328 (4.2)	
6,7,8-trimethoxy-coumarin	229 (4.2)	–	296 (4.0)	338 (3.8)	ref.175
isopimpinellin, 2′,3′-dihydro	–	253 (3.8)	262 (3.8)	326 (4.2)	ref.176
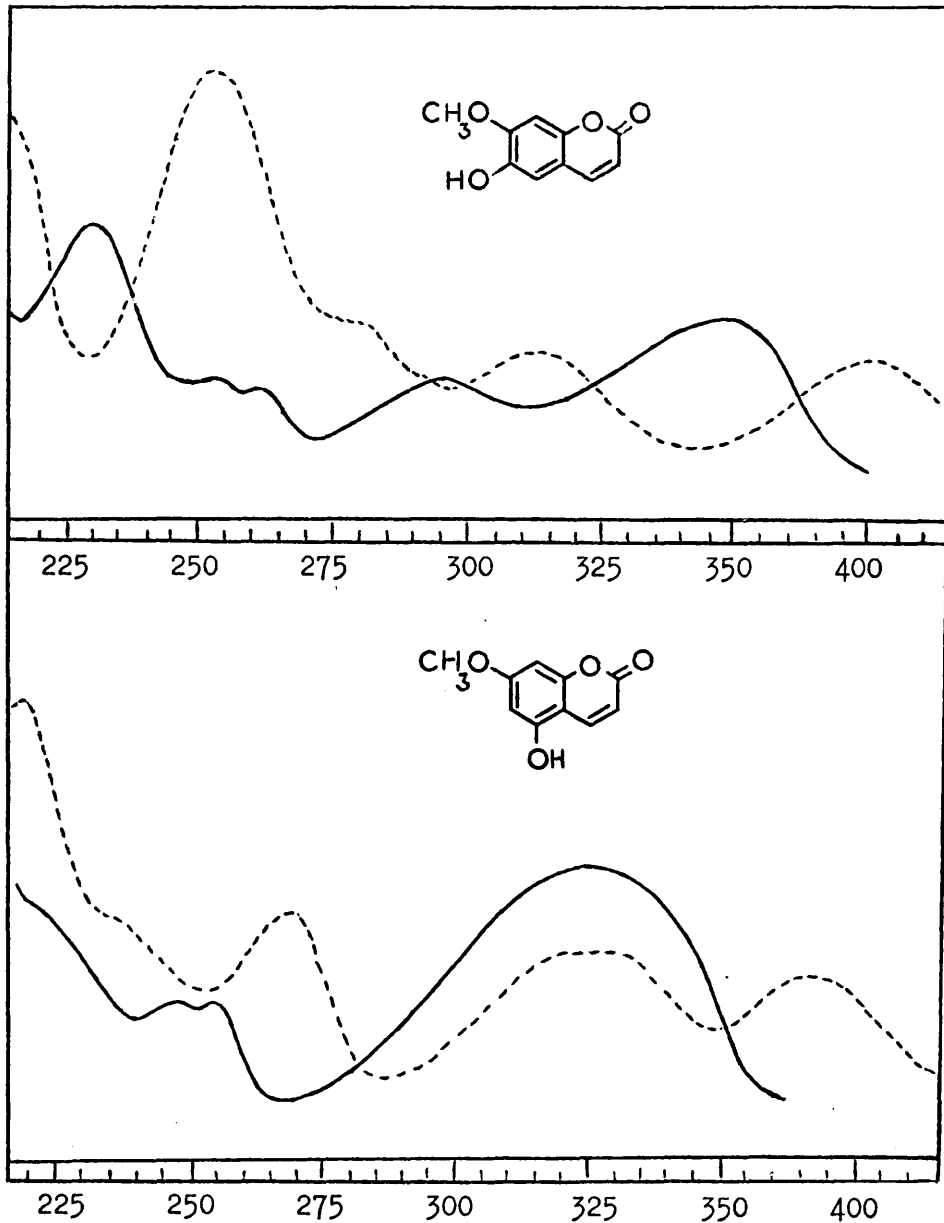
Figure A.3

——————— ethanol solution.

------- ethanol solution to which base has been added.

Furthermore, from the hypsochromic shift observed in nieshoutol acetate, relative to nieshoutol, it might have been suspected that the hydroxyl could be placed at C-6.

Changing from a neutral to a basic medium, enables the u.v. spectrum of a hydroxycoumarin to be compared with that of the corresponding phenoxide anion. The bathochromic shift produced can be used in locating the position of the hydroxyl. The effect of a hydroxyl at C-7[48] in mono-hydroxycoumarins is both bathochromic and hyperchromic (Figure A.2), whereas at C-5, C-6 or C-8 the effect produced is hypochromic in addition to bathochromic (partly illustrated in Figure A.3). This difference can obviously be very useful in distinguishing between isomers. The hypochromic shift observed in the u.v. spectra (p.118) of nieshoutol allowed valuable deductions to be made.

The u.v. spectra of other than mono-hydroxycoumarins in basic media do not appear to be quite so simple. 6,7-Dihydroxycoumarin and 6,7-dihydroxy-4-methylcoumarin behave as simple 7-hydroxycoumarins, producing hyperchromic shifts in basic, relative to neutral media. However, although isofraxidin, (7-hydroxy-6,8-dimethoxycoumarin), (p.118), behaves as a 7-hydroxycoumarin, fraxetin (7,8-dihydroxy-6-methoxycoumarin)[152] and 6,7,8-trihydroxycoumarin produce hypochromic shifts despite the presence of a C-7 hydroxyl.

Thus, the u.v. spectrum of a simple coumarin can often provide a useful hypothesis on which to base further investigations into its structure.

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