Synthetic Studies of Natural Coumarins and Chromones

THESIS

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by

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SUMMARY

A variety of methods have been investigated by many workers for the synthesis of ortho-3,3-dimethylallylphenols. However, all of these synthetic routes have their limitations. One method, developed in this laboratory for the synthesis of naturally occurring oxygenated coumarins, besides being more efficient, has the advantages of utilising a preformed coumarin nucleus and mild conditions for the three step isoprenoid insertion process. In this present study, the method has been extended to the synthesis of two natural coumarins, sesibiricin and toddaculin and now provides a viable synthetic route to substitution at C-6 or C-8 of the coumarin nucleus through Claisen rearrangement of the appropriate 1,1-dimethylallyloxy ether.

As an alternative synthetic route to sesibiricin, the para Claisen rearrangement of 5-O-(3,3-dimethylallyl)-7-methoxycoumarin has been used for isoprenylation at C-8.

Thermal pyrolyses of the 3,3-dimethylallyl ethers of 7-mono and 5,7-dioxygenated chromones, as in the analogous coumarin series, can give a complex mixture of products resulting from cyclisation and abnormal Claisen rearrangement. However, these disadvantages have been overcome by trapping the first formed phenol as the butyrate ester followed by mild hydrolysis which generally affords the phenol.

The major drawback to the synthesis of ortho-3,3-dimethylallyl phenols via Claisen rearrangement of 1,1-dimethylallyl ethers has been the initial propargylation step. Attempts were made to improve the efficiency of this step and eventual application of the route to

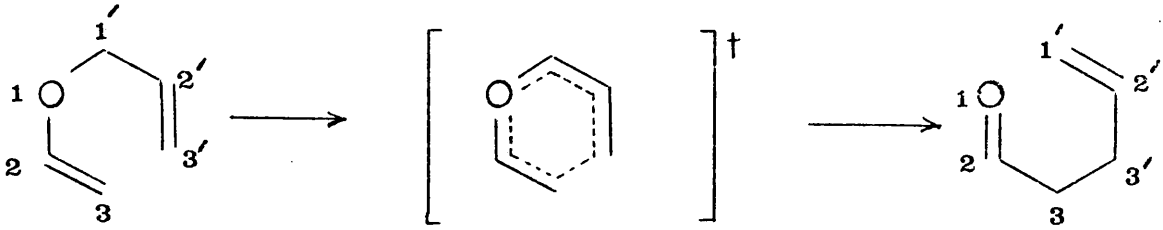
5,7-dihydroxy-2-methylchromone afforded the isopentenylchromones, peucenin and heteropeucenin.

Oxidative cyclisation of peucenin and its 7-methyl ether was achieved through epoxidation of the isoprenoid chain *in situ* followed by selective nucleophilic ring opening by the *ortho* hydroxyl groups. Cyclisation with the 7-hydroxyl of peucenin gave a mixture of the secondary alcohol, hamaudol and the tertiary alcohol, visamminol which were separable by acetylation. Oxidative cyclisation of peucenin-7-methyl ether showed that angular cyclisation with the chelated 5-hydroxyl group of the chromone was also a competitive reaction.

These results have been confirmed by numerous epoxidation experiments are in complete disagreement with a recent publication which suggests that hamaudol is the sole product of the epoxidation of peucenin.

Synthetic Studies of Natural Coumarins and Chromones

SCHEME 1



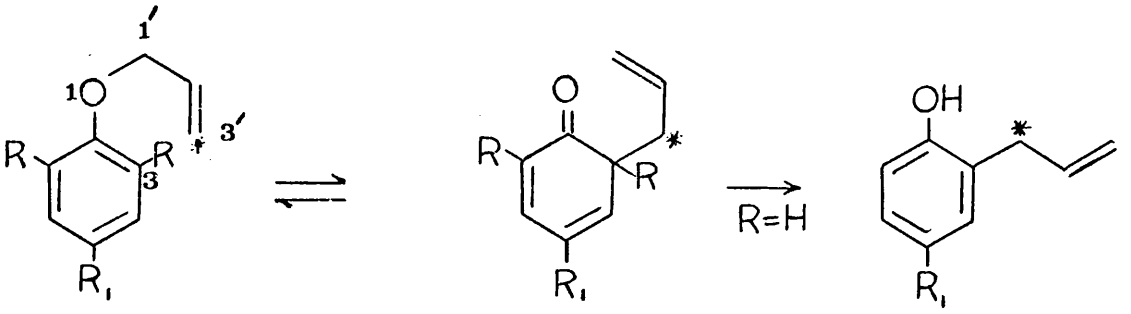
(1) (2)

In its long and distinguished history since 1912, the Claisen rearrangement has proved to be of great synthetic value and mechanistic interest. The rearrangement involves the thermal transformation of an allyl vinyl ether (1) into a γ,δ-unsaturated carbonyl compound (2), the reaction proceeding by a intramolecular pathway (Scheme 1). The synthetic utility of this facile rearrangement has been enhanced by efficient methods of synthesis of various allyl ethers[2(b),3] and by extension of the reaction to nitrogen[1,4], sulphur[1,38] and phosphorus[1] analogues.

One of the properties which has been particularly useful in synthesis stems from the stereochemical consequences of the rearrangement for, no matter what stereochemistry is exhibited at C-1′ (Scheme 1), the concerted pathway of the reaction leads to a predominantly trans-substituted olefin[5] as product. On the mechanistic front, the rearrangement can be readily explained by the Woodward-Hoffmann selection rules for sigmatropic shifts[6].

The major part of the experimental work in this thesis deals with the application of the Claisen rearrangement to the synthesis of naturally occurring oxygenated coumarins (86) and chromones (160) containing isoprenoid side-chains. Consequently, the purpose of this short review of the Claisen rearrangement has been to exemplify how the rearrangement, through the elucidation of its mechanistic pathway, has become an accepted tool in the synthesis of many natural products.

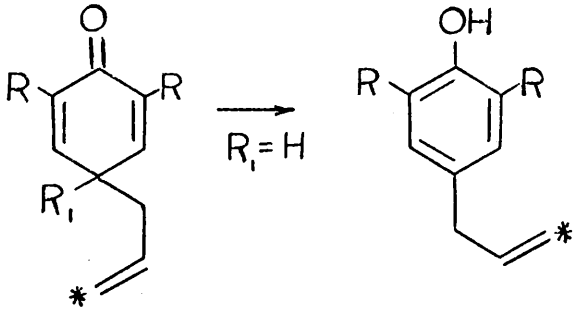
SCHEME 2



(3) (4) (5)

$1 \not\downarrow R \neq H$

* ^{14}C label



(6) (7)

The main headings of the review cover:-

(i) the mechanism and structural features of the Claisen rearrangement.

(ii) sigmatropic rearrangements.

(iii) stereochemistry.

(iv) the abnormal Claisen rearrangement.

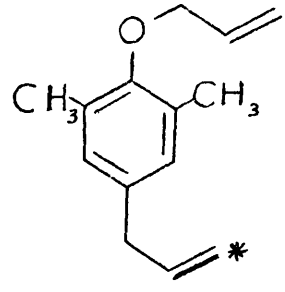
(v) the effects of solvent and acid catalysis on the rearrangement.

(vi) synthetic applications.

(i) Mechanism and structural features of the Claisen rearrangement

The term 'Claisen rearrangement' is frequently associated with the thermal rearrangement of allyl aryl ethers[1] where the vinyl group is an integral part of the aromatic ring. It is within this system that most mechanistic studies have been performed.

In Scheme 2, when the ether (3) is heated neat or in a solvent at 180-200°, a reversible intramolecular cyclic process[7,8] occurs with migration of the allyl group to the ortho position affording an ortho-dienone intermediate (4)[9,10]. This dienone usually enolises rapidly to the phenol (5) when R=H. In the migration, the allyl group has undergone a so-called 'inversion' with the γ-carbon now becoming attached to the aromatic ring. This inversion, a characteristic of the reaction, has been demonstrated by labelling[1,2] or by substituting the α or the γ position[9] of the allyl chain. Thus, Schmid[11] found that rearrangement of the ether (3 ; $R_1 = CH_3$, R=H) labelled with ^{14}C



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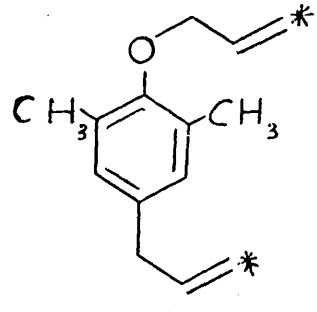


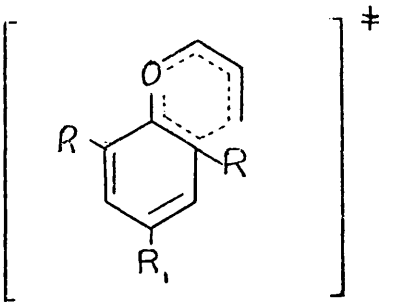
(9)

on the γ-carbon resulted in the formation of the appropriately labelled allylphenol (5 ; $R_1 = CH_3$, $R = H$).

When both ortho positions are substituted, the enolisation step becomes impossible, and a Cope rearrangement[2], the all-carbon analogue of the Claisen rearrangement, takes place to generate the para-dienone (6) which again can enolise rapidly when $R_1 = H$ to give the para-substituted aromatic allyl ether (7)[10]. The above migration constitutes the para-Claisen rearrangement and further labelling experiments[2,11] have shown that a double inversion occurs with the carbon atom which was attached to the oxygen now being attached to the aromatic ring.

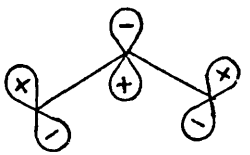
The reversibility of the dienone intermediate has also been neatly demonstrated by a radioactive labelling technique[11]. Thus, allyl 2,6-dimethyl-4-allyl-γ-^{14}C-phenyl ether (8) which has no enolisable hydrogens, gave only starting ether (9) on equilibration at 170°. Significantly however, the radio-active tracer was now uniformly distributed between the O- and C-allyl groups showing that rearrangement had indeed taken place with the formation of a symmetrical intermediate. This experiment therefore also provides indirect evidence for the formation of a para-dienone intermediate.

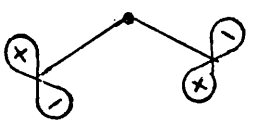
The kinetics of the reaction mechanism show that both ortho- and para- Claisen rearrangements are first-order reactions with negative entropies of activation supporting the involvement of highly ordered transition states[1,2]. The rate-determining step

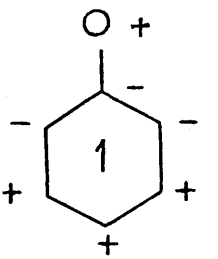


(8)

SCHEME 3

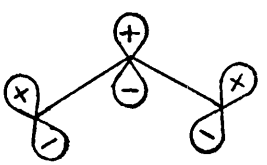
ψ_3  — Antibonding

ψ_2  ↿ Non-bonding



ψ_4

The phase of the wave function on the side of the benzene ring.

ψ_1  ↿⇂ Bonding

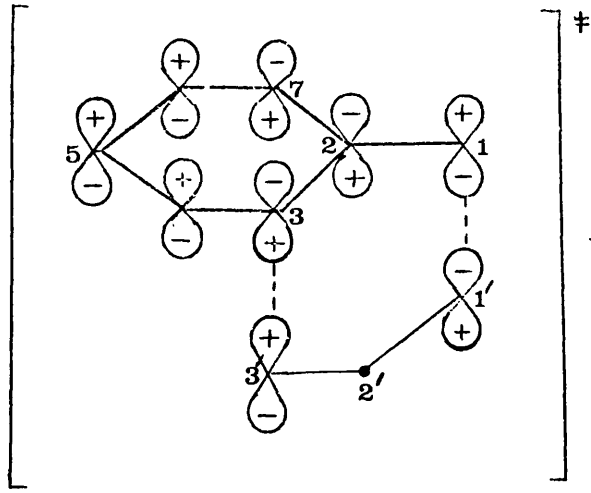
is probably the formation of the dienone intermediate, followed by a rapid enolisation step. Evidence of the intramolecular pathway of the reaction was demonstrated by the absence of any "cross-over" products when two different ethers were rearranged in the same vessel[7,12]. The Claisen rearrangement however is relatively inert to free radical or ionic probes and this lack of response to the usual diagnostic tests for heterolytic or homolytic fissions has resulted in the Claisen rearrangement being labelled a "no-mechanism" reaction[2(a)].

(ii) Sigmatropic rearrangements

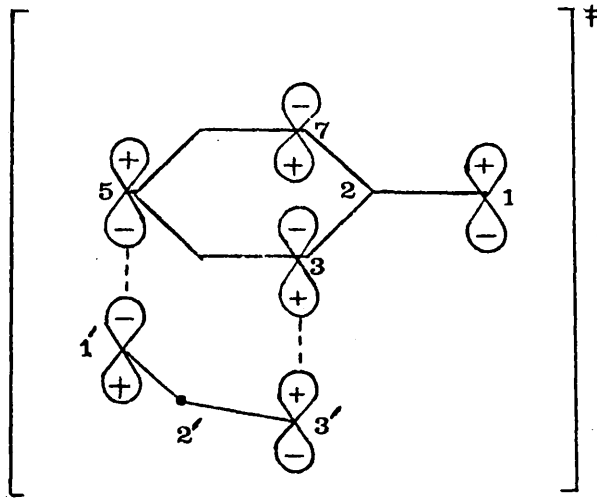
A sigmatropic rearrangement can be defined as a unimolecular one-step process whereby a σ-bond may migrate to a new position when it is flanked by one or two π-electron systems[6]. The Claisen and Cope rearrangements can each be classified as concerted electrocyclic reactions proceeding through a [3,3] sigmatropic rearrangement[6]. In Scheme 2, the C-O bond designated 1-1′, is broken with synchronous formation of a new 3-3′ bond in the dienone (4).

The transition state (8) in the concerted migration can conveniently, albeit incorrectly, thought of as the interaction between a quasi-allyl, and a quasi-phenoxy radical. Hückel molecular orbital treatment[13] of the π-allyl system (Scheme 3) demonstrates that the system consists of three molecular orbital levels, the bonding level ψ_1, the non-bonding level ψ_2 and the anti-bonding molecular orbital level ψ_3, with the highest occupied molecular orbital level ψ_2 containing one electron.

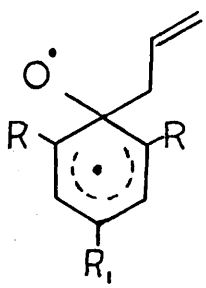
SCHEME 4



‡ → ortho-substitution



‡ → para-substitution



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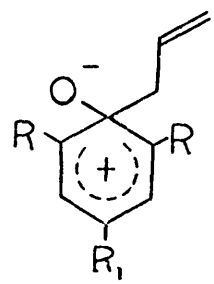


(10)

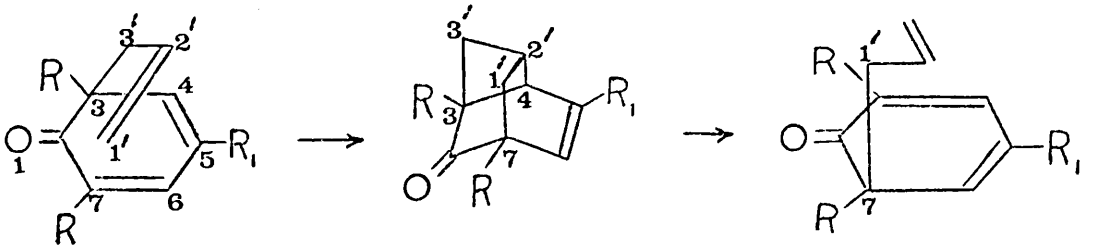
A similar treatment of the quasi-phenoxy radical shows that of the seven molecular orbital levels only four are occupied by electrons, with ψ_4 (shown in Scheme 3) being the highest occupied level ψ_4 the system[6,13].

The course of the rearrangement is determined by the interaction of the two highest occupied molecular orbital levels and by the concept that bonding can only occur between levels of the same phase with conservation of orbital symmetry. This is shown diagramatically in Scheme 4.

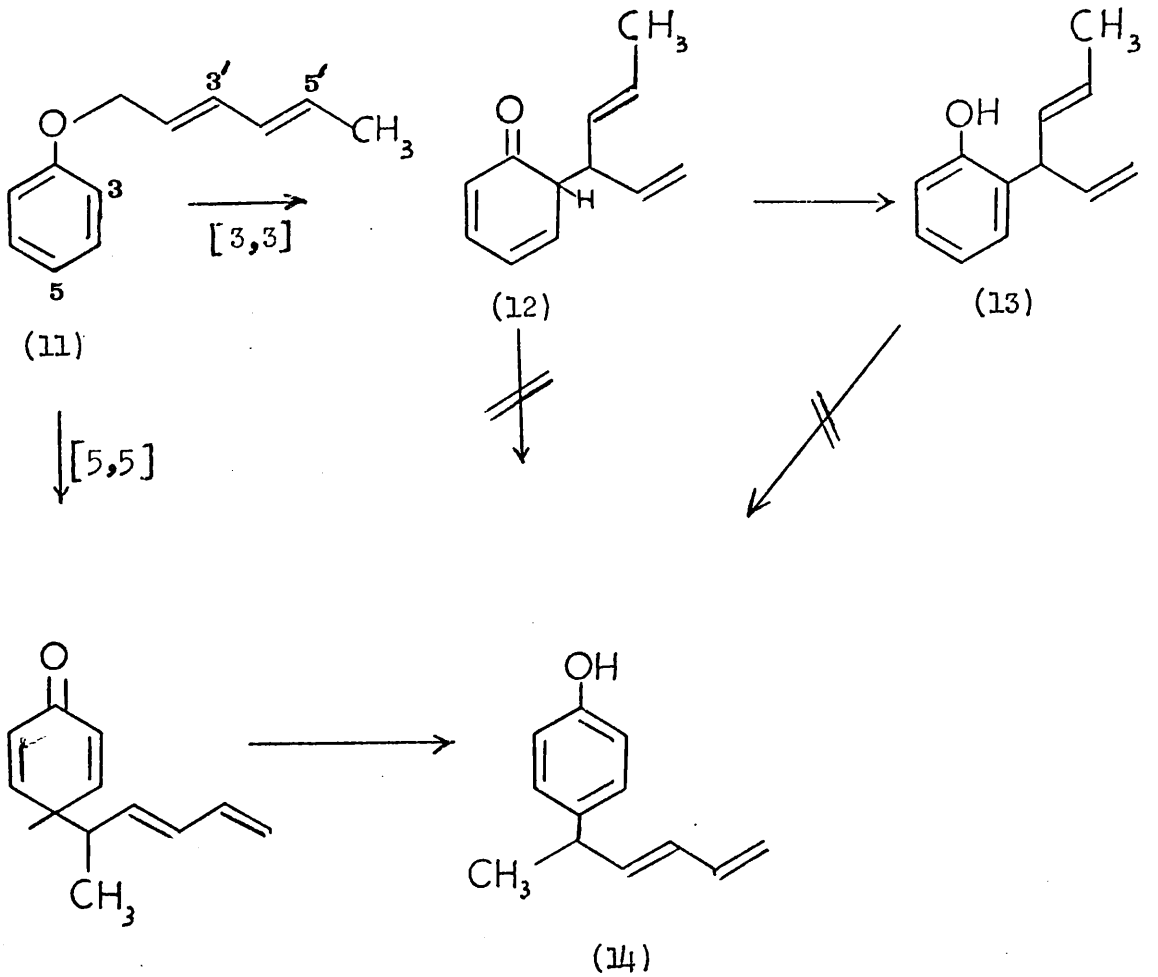
By considering the transition state of the Claisen rearrangement, (Scheme 4), it follows that the [3,3] sigmatropic shift (3) $\rightleftharpoons$ (4) shown in Scheme 2, must occur with inversion of the allyl group in a suprafacial movement[6] i.e. the bonds broken and formed are on the same side of the molecule. The resulting dienone intermediate (4) could either return to the starting ether by the reverse procedure, enolise if there were an available hydrogen to form the ortho substituted phenol, or undergo another suprafacial migration between C-5 and C-1′, with double inversion of the allyl moiety therefore constituting a para- Claisen rearrangement.

On theoretical grounds, a suprafacial [2,3] shift is also possible, i.e. the migration of the allyl group from oxygen to C-2 in Scheme 4 with inversion[6]. However, such a pathway would lead to a diradical (9) or a zwitterion (10) and niether is likely to occur since both (9) and (10) would have to arise from

SCHEME 5



SCHEME 6



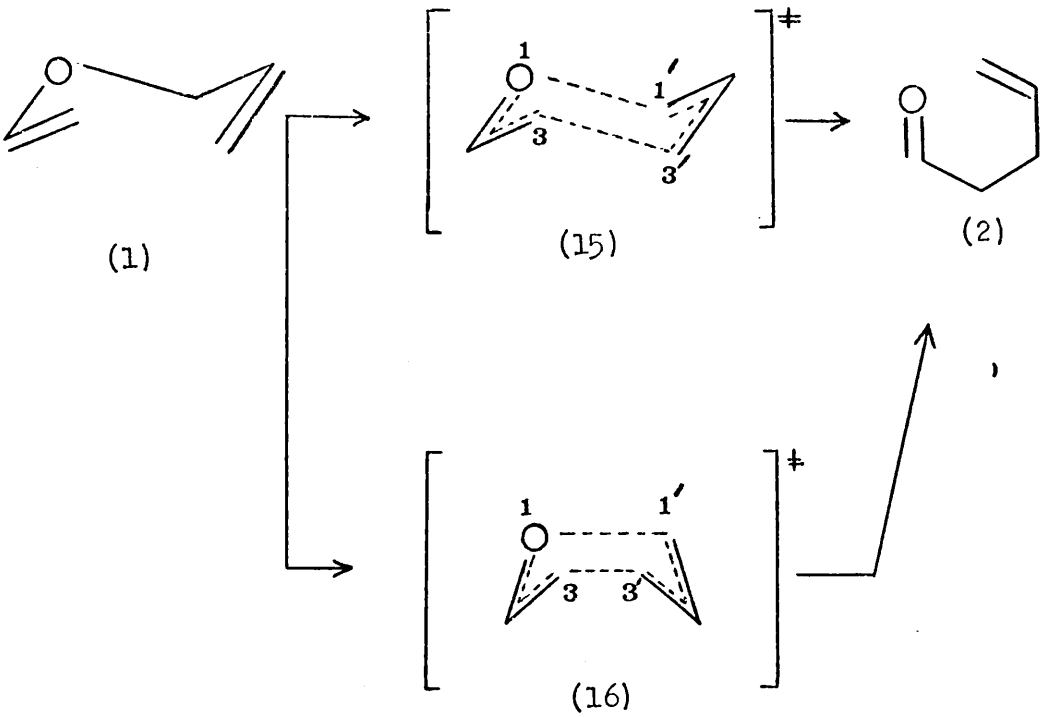
a transition state which lies essentially higher in energy than the rearrangement of (3)⇌(4). No products or chemical evidence for such a pathway has yet been found. However, a possible competitive reaction to the [3,3] sigmatropic shift is homolytic fission[14] of the aryl allyl ether to the allyl and phenoxyl radicals which can occur during thermal pyrolysis though this generally requires a high activation energy.

In Scheme 4, the ortho-ortho migration[1,6] from C-3 to C-7 would require to be antarafacial i.e. the bond being formed is on the opposite side of the molecule to the one being broken. This reaction is said to be 'forbidden' within the framework of the Woodward-Hoffmann rules[6]. However, within the literature, a number of ortho-ortho rearrangements have been postulated[1]. Most of these examples can be explained by the formation of internal Diels-Alder adducts which then reopen possibly by homolytic fission (Scheme 5).

An interesting example of a [5,5] sigmatropic shift is shown in the rearrangement of pentadienyl phenyl ethers (Scheme 6). The pentadienyl group can migrate suprafacially in the normal manner such that the C-3′ bonds with the aromatic C-3 position. In addition, a [5,5] sigmatropic rearrangement with inversion of the pentadienyl group is also possible with the formation of a bond between the C-5′ and the C-5 of the aromatic ring.

Frater and Schmid[15] found that on rearrangement of the phenyl ether (11) a [3,3] sigmatropic shift through the intermediacy

SCHEME 7



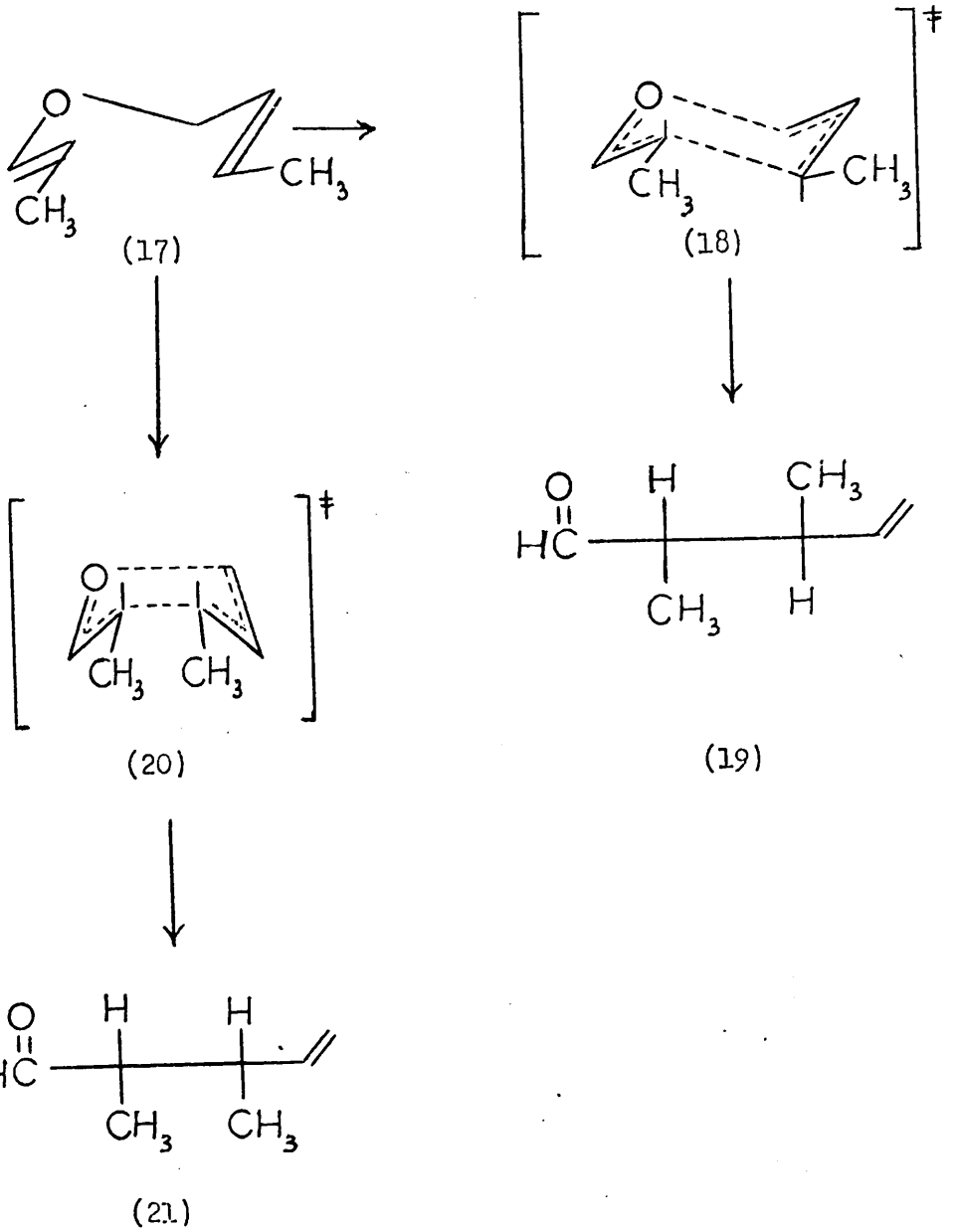
of the ortho-dienone (12) led to the ortho-substituted phenol (13). However, as predicted, the [5,5] suprafacial sigmatropic rearrangement also occurred giving rise to the para-substituted phenol (14). The workers also provided evidence that (12) and (13) could be excluded as intermediates in the formation of (14) and that the rate of [5,5] migration was four times as fast as the [3,3] rearrangement to the ortho-position.

(iii) Stereochemistry

During the course of the Claisen rearrangement there is a direct stereochemically induced relationship between the reactant and the product. The exact configuration[16] of the product is determined by the transition state geometry and the degree of hybridisation at the reacting centres. Thus, in the transition state the six atoms concerned in the rearrangement can adopt a quasi-chair (15) or a quasi-boat conformation (16) with the stereochemistry of the reaction centres 1-1′ and 3-3′ lying between tetrahedral and trigonal geometry (Scheme 7).

To determine the stereochemistry of the transition state, Schmid[17] examined the products obtained from the rearrangement of trans, trans-crotyl propenyl ether (17) (Scheme 8). If the ether (17) were to rearrange through a chair-like transition state (18) then the threo-2,3-dimethylpent-4-en-1-al (19) would be formed, whereas if the alternative boat-like transition state (20) were adopted, the erythro-aldehyde (21) would result. It was found that the mixture of diastereoisomeric aldehydes formed from the

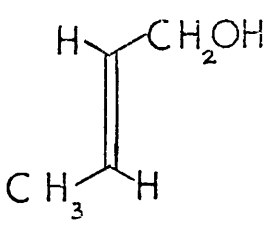
SCHEME 8



rearrangement contained 98% of the threo-product (19) and consequently the chair-like transition state was considered to be the favoured pathway.

A similar type of result was obtained by Sucrow and Richter[18] when they examined the rearrangement products of the allyl ether (22) formed in situ by the reaction of 1-dimethylamino-1-methoxy-prop-1-ene (23) and 3-hydroxy-1-methyl-prop-1-ene (24). The German workers found that the trans form of the allylic alcohol (24) gave the corresponding erythro amide of (25) on rearrangement of the appropriate ketene acetal (22), whereas the cis alcohol (24) gave the threo amide of (25). These results favour the formation of a chair-like transition state provided the ether (22) formed in situ is assumed to retain the geometry shown around the ketene O,N-acetal double bond.

It has been more difficult to obtain unambiguous evidence regarding the transition state stereochemistry for the aromatic Claisen rearrangement. For a concerted pathway to the ortho position, the γ-carbon of the allyl side chain should lie directly above or directly below the ortho-carbon of the aromatic ring (Scheme 9)[19]. This can be achieved by two orientations of the allyl side chain. If the β-carbon lies above, or below the ring carbon bearing oxygen then a quasi-boat transition state (26) will be formed whereas if the β-carbon is directed away from the ring a quasi-chair conformation (27) will ensue.



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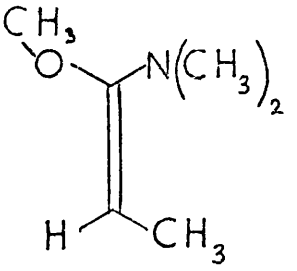

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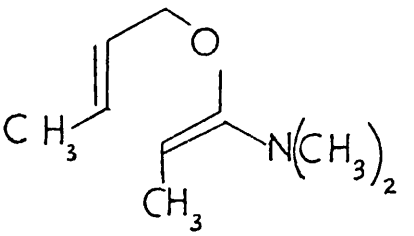

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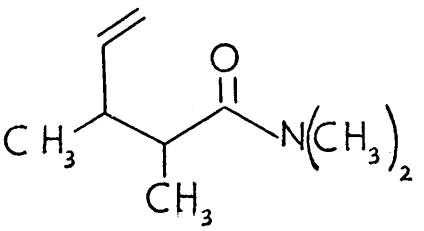

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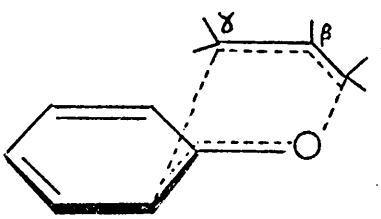
SCHEME 9



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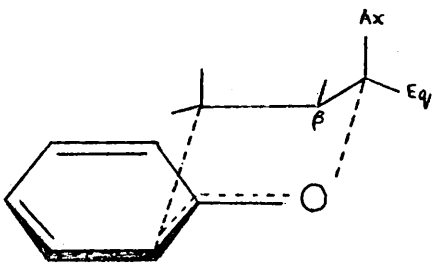


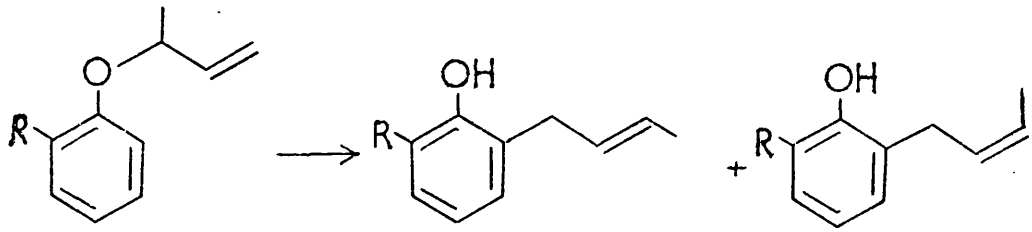
(27)

In α-methylallyl-2-alkylphenyl ethers (28) substitution of the methyl group in the α-position means that two chair and two boat forms of transition state stereochemistry[19] have to be considered (Scheme 10). A substituent which is equatorial in this chair conformation will lead to a product containing a trans double bond, i.e. trans-(29). However, if the substituent is axial in the chair conformation this will result in a cis double bond, i.e. cis-(29), being produced. From models, it can be shown that an ortho-substituent R will have a greater steric interaction with an axial α-methyl group than the equatorial conformer, if the rearrangement is assumed to take place through a chair-like transition state. Thus, the bulkier the ortho substituent becomes the greater should be the predominance of trans-(29) over cis-(29). On investigation, Frater and Schmid[19] found that for the rearrangement of the ether (28) where R was H, CH_3, C_2H_5 and tert-butyl, the trans : cis ratio was 14, 37.5, 39 and 99:1 respectively in complete accord with a chair-like pathway. Models show that the reverse trend would be expected if the rearrangement were to proceed through a boat-like transition state.

(iv) The abnormal Claisen rearrangement

Lauer and Filbert[20] in 1936 reported that the rearrangement of γ-ethylallyl phenyl ether (30) in N,N-diethylaniline yielded 2-(α,γ-dimethylallyl)phenol (31) instead of the 'normal' ortho-rearrangement product (32) (Scheme 11). Since this did not

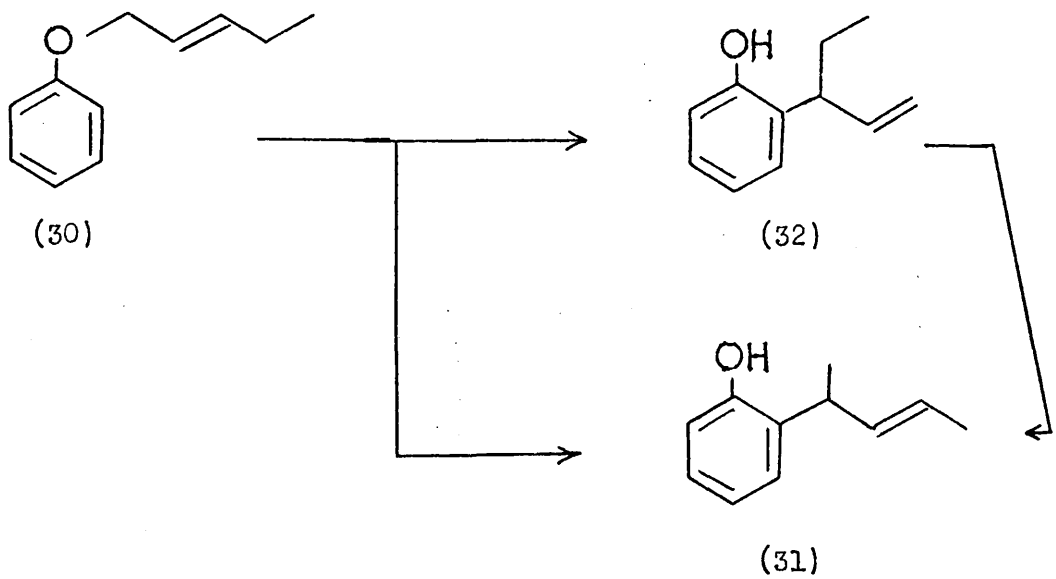
SCHEME 10



(28) trans-(29) cis-(29)

R= H, CH_3, C_2H_5 or tert butyl

SCHEME 11



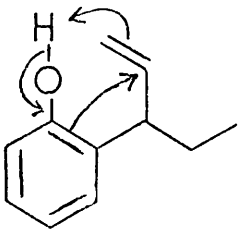
(30) (32) (31)

correspond with the general scheme of the aromatic Claisen rearrangement, the transformation was called the 'abnormal' Claisen rearrangement. This is really a misnomer as it implies that the 'abnormal' rearrangement competes with the 'normal' process which is not the case.

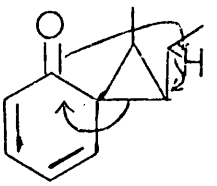
In 1962, Marvell et al[21] reported that the abnormal Claisen rearrangement of the above phenyl ether (30) was in fact a consecutive reaction of the primarily formed 'normal' rearrangement product (2-α-ethylallyl) phenol (32). Kinetic analysis of the reaction showed that the abnormal rearrangement of the phenol (32) proceeded more slowly than the normal rearrangement of the starting ether (30). In consequence, through control of the rearrangement by heating at 175°, pure 2-(α-ethylallyl) phenol (32) was obtained which on pyrolysis in diphenyl ether at 200-225° was slowly converted to the abnormal product (31).

An important factor in the abnormal Claisen rearrangement is the ortho relationship between the free hydroxyl group and the allyl side-chain. Marvell and his collaborators[21] suggested the now accepted mechanism for the formation of abnormal products, shown in Scheme 12. The mechanism is characterised by a reversible [1,5] sigmatropic hydrogen transfer from the phenolic hydroxyl group to the allyl side-chain resulting in an ortho spiro-octadienone intermediate of cis geometry[22], which by a further [1,5] homosigmatropic hydrogen shift leads to the formation of the abnormal product (31).

SCHEME 12



(32)



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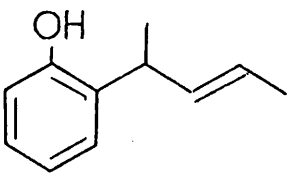

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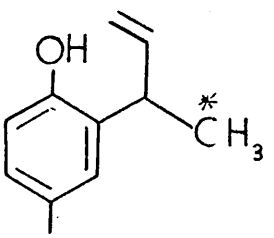


(34)

* ^{14}C label

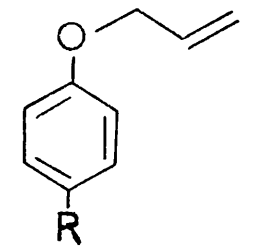
This mechanism has been supported by labelling experiments[23]. Rearrangement of 2-(α-methylallyl)-4-methyl phenol (34) labelled with ^{14}C at the α-methyl group resulted in the label becoming distributed between the α-methyl position and the γ-carbon of the side-chain in the abnormal product, indicating that these two carbons had become equivalent during the rearrangement.

Unsuccessful attempts to detect the cis-spirodienone intermediate spectroscopically[24] have been made, implying that the stationary concentration of the intermediate in the rearrangement must be small and that the phenolic compound must be strongly favoured thermodynamically. However, characterisation of the spirodienone by deuterium incorporation[22] into the butene side-chain of abnormal product formed when 2-(α-methylallyl)-4-methyl phenol (34) was heated in deuterium oxide provides further support for the postulated mechanism.

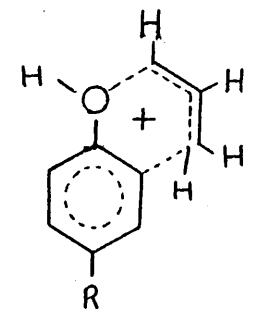
The abnormal Claisen rearrangement is also found in aliphatic[24,25] and alicyclic systems[26] and products arising from this rearrangement must be expected whenever the allyl group of the ether contains a γ-alkyl substituent. An excellent review of the abnormal Claisen rearrangement by H.-J. Hansen[27] has recently been published.

(v) The effects of solvent and acid catalysis on the Claisen rearrangement

At one time the Claisen rearrangement[2] was thought to be insensitive to solvent and catalytic effects. However, investigations[28] have shown that this is not the case and the



(35) $R = CH_3$
(36) $R = OCH_3$

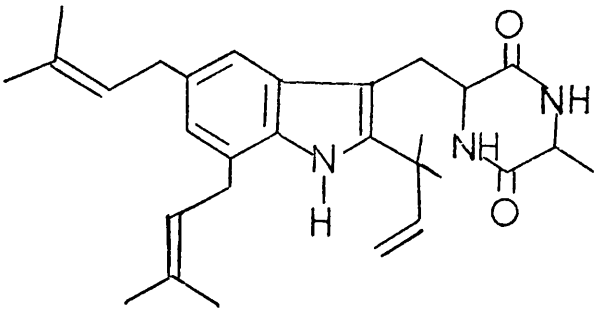


(37)

reaction rate can be influenced by both the medium and the reaction conditions.

White and his co-workers[28] found that in hydroxylic solvents such as carbitol and ethylene glycol the rates of rearrangement of allyl para-tolyl ether were in general faster than in solvents such as tetradecane and n-butyl ether. This led White to conclude that the sensitivity of the rearrangement to solvent media could be attributed to either the hydrogen-bonding abilities or the 'polar' characteristics of the solvents. This interpretation however does not account for all the factors involved in the solvent dependence of the reaction rate.

Acid catalysis[29] can also promote a rate enhancement in the Claisen rearrangement. A recent communication by Svanholm and Parker[29] shows that the rearrangement of allyl phenyl ethers can be achieved under mild conditions and at room temperature by dissolving the appropriate ether in trifluoroacetic acid. The allyl ethers (35) and (36) in trifluoroacetic acid were estimated to rearrange to the corresponding O-allylphenols at rates $\sim 10^5$ times greater than those observed when the ethers were rearranged by the normal thermal manner. Various substituent effects have led these authors to postulate an intramolecular pathway for this acid-catalysed rearrangement through a possible transition state (37).



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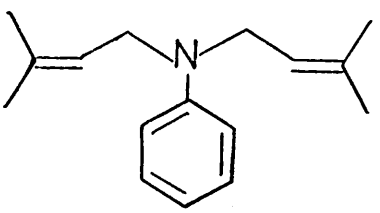

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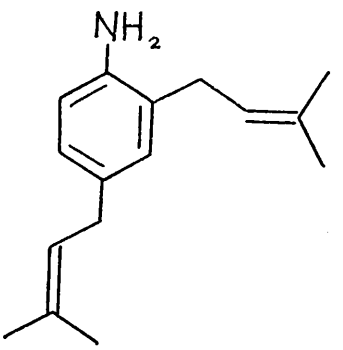


(40)

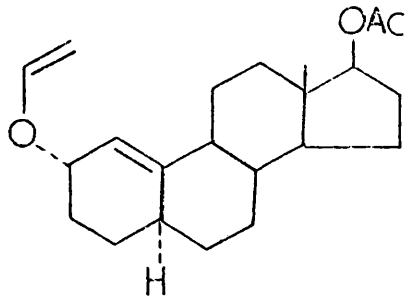
Other workers have reported that Lewis acids such as boron trifluoride-acetic acid complex[30], boron trichloride[31] and zinc chloride[32] also catalyse the Claisen rearrangement. A recent extension to this type of catalysis has been reported by Sonnenberg[33]. He found that treatment of various allyl ethers in hexane with an excess of diethylaluminium chloride at room temperature resulted in the quantitative conversion of the ethers to the ortho-allylphenols. As a further example, Kishi et al[34] have reported a synthesis of the alkaloid echinulin (38) incorporating an acid-catalysed amino-Claisen rearrangement of 2,4-di(3,3-dimethylallyl) aniline (39) to prepare the synthon (40).

The facile nature of the acid-catalysed Claisen rearrangement has biogenetic[35] as well as synthetic implications and certainly future developments in this sphere will provide a valuable extension to the synthetic utility of the rearrangement.

(vi) Synthetic applications

The synthetic applications of the Claisen rearrangement span many areas of chemistry and the following examples have been selected from the literature in order to show the degree of versatility the reaction has reached in the hands of many organic chemists.

The aromatic Claisen rearrangement has been studied in most detail and, as an obvious consequence, the rearrangement has been extended to the synthesis of ortho-allylphenols which can be used



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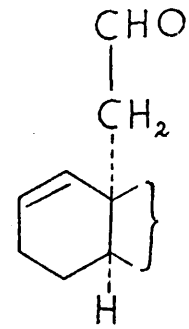

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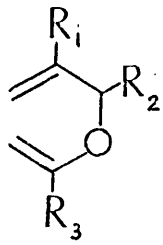
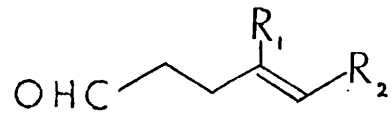
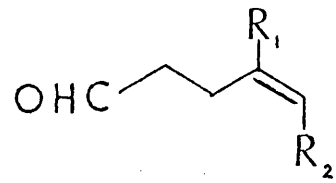


(43)



trans-(44)

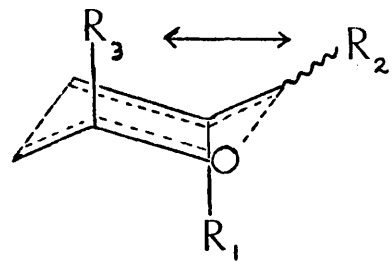


cis-(44)

(a) $R_1 = CH_3$, $R_2 = Et$, $R_3 = H$

(b) $R_1 = CH_3$, $R_2 = i\text{-}Pr$, $R_3 = H$

(c) $R_1 = Et$, $R_2 = Et$, $R_3 = H$



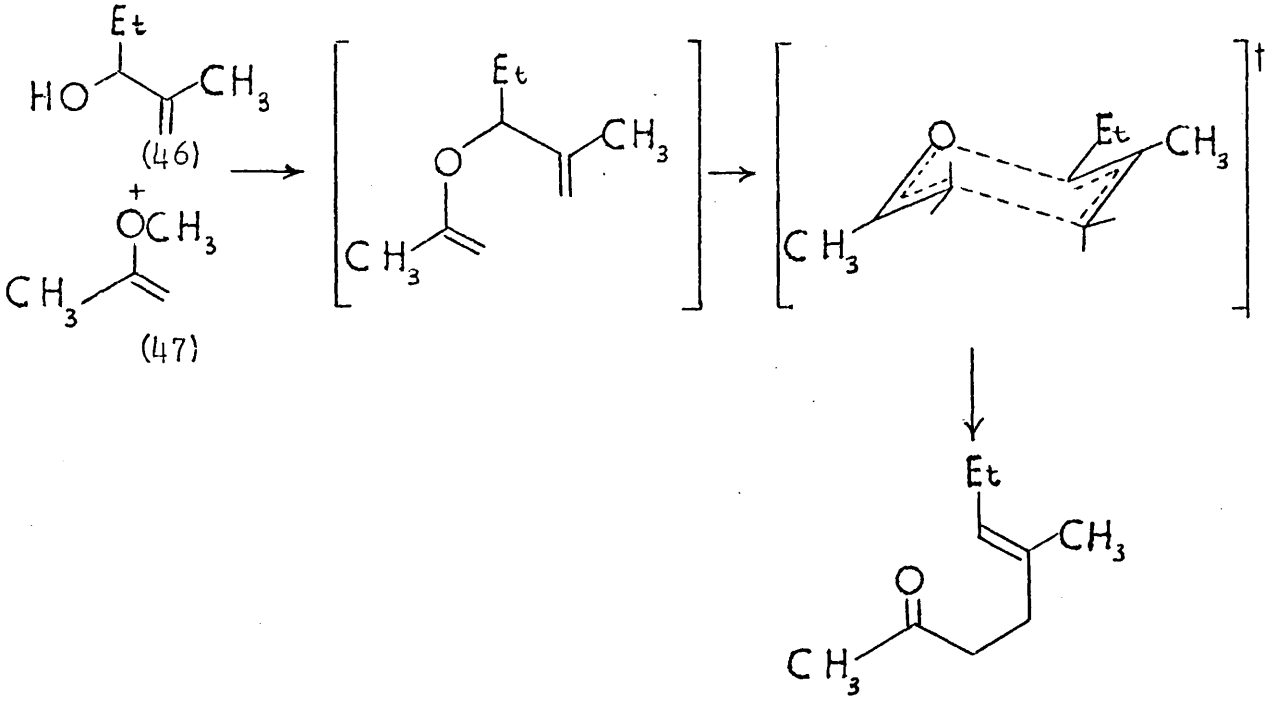
(45)

for many further synthetic manipulations. Thus, by oxidative cleavage of the double bond, interaction of the phenol with the aldehyde formed from the cleavage, followed by dehydration, a method is available for the synthesis of aromatic benzofurans[36,37].

In the terpene[5] and steroid field[38], the stereochemical control of the rearrangement has been harnessed to provide a synthetic pathway for the introduction of an angular group in a stereospecific manner. For example, Claisen rearrangement of the vinyl ether (41) of 17-β-acetoxy-1(10)-oestren-2-one rearranges in a stereospecific manner to give the 10α-angular aldehyde (42)[38]. However, with the application of the reaction to other hetero-analogues[39], the general utility of the rearrangement has been extended to the synthesis of various other natural products.

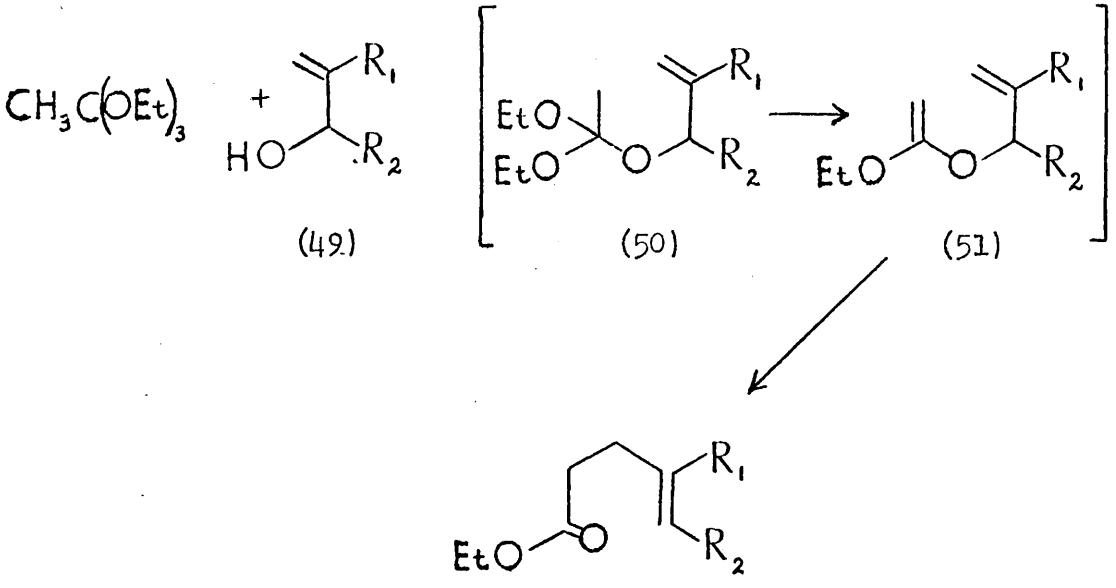
An important advance in the aliphatic Claisen rearrangement has been the development of a selective method for the preparation of compounds containing trans-trisubstituted[5] double bonds. Faulkner and Petersen[40] synthesised various allyl ethers of the type (43) which on pyrolysis gave a stereoisomeric mixture of the unsaturated aldehydes (44). Examination of the trans : cis isomer ratio led to the hypothesis that if the rearrangements were proceeding through a chair transition state (45), then a bulky axial substituent at R_3 would introduce a relatively large 1,3-diaxial interaction with the R_2 substituent and lead to the preferential formation of the trans-alkene (44).

SCHEME 13



(46) (47) (48)

SCHEME 14



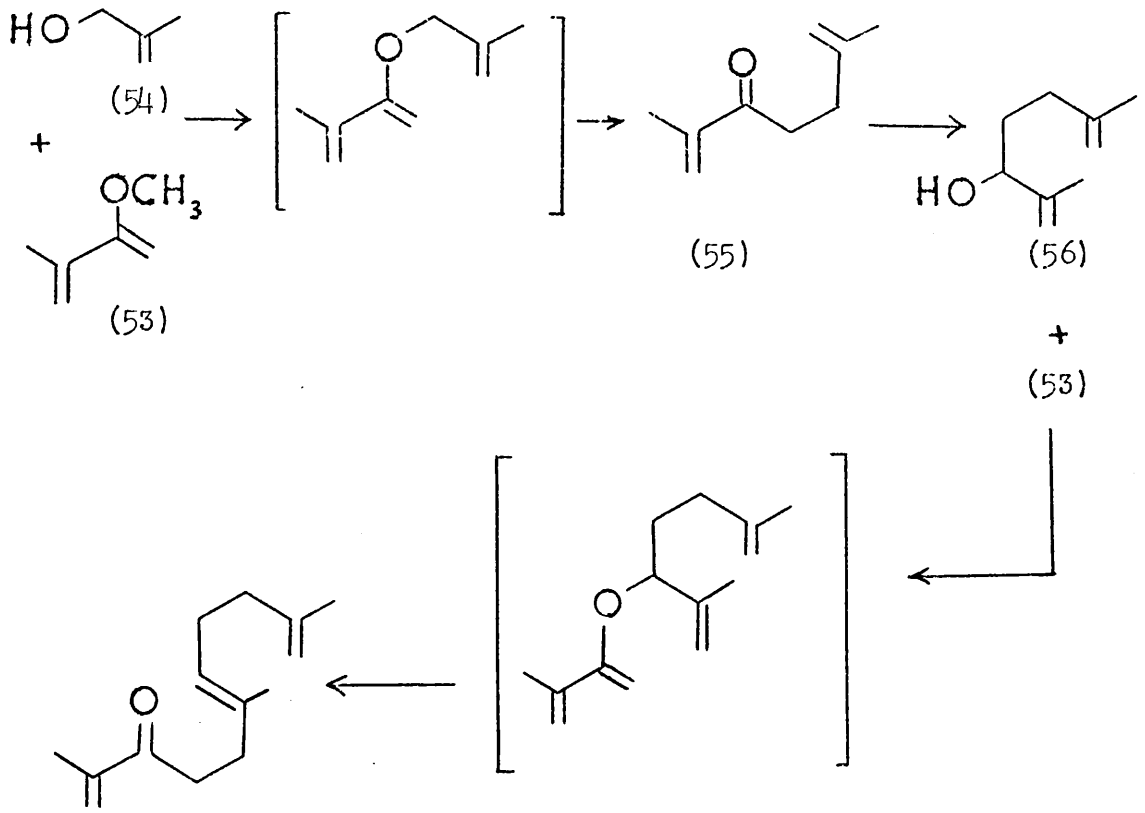
(49) (50) (51) (52)

In fact, when 2-methylpent-1-en-3-ol (46) and isopropenyl methyl ether (47) (R_3 now a methyl group) were heated in a sealed tube at 110°, in the presence of an acid catalyst, the ketone (48) was obtained in good yield containing 99% of the trans-isomer (Scheme 13). The above result demonstrates that the introduction of a substituent R_3 was sufficient to cause a profound increase in the stereoselectivity of the Claisen rearrangement.

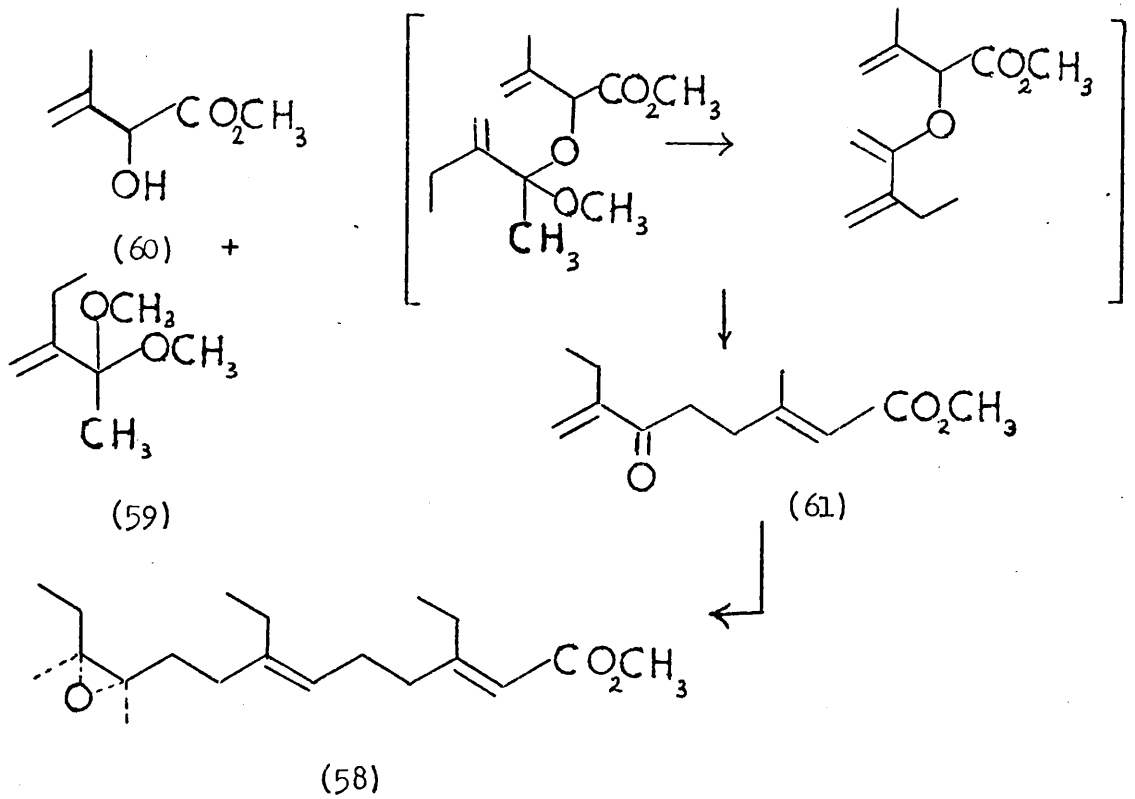
An important extension to this work has been made by Johnson et al. His group developed the so-called 'orthoester' Claisen rearrangement[41] and utilised this reaction in their recent elegant approaches to the synthesis of squalene. The 'orthoester' method involves heating an allylic alcohol (49) with an excess of ethyl orthoacetate in the presence of a weak acid (Scheme 14). The presumed first-formed mixed orthoester (50) eliminates ethanol to form the unsaturated ketal (51) which subsequently underwent Claisen rearrangement to form the trans-trisubstituted olefin (52).

A modification of the above procedure utilised 3-methoxy-isoprene (53)[41] as the potential vinyl component of the allyl vinyl ether. Scheme 15 shows two consecutive applications of the 'methoxyisoprene' Claisen rearrangement leading to a 'head-to-tail' insertion of isoprene units with a trans stereochemistry. The dienone (55), formed from the rearrangement of the vinyl ether from 3-methoxyisoprene (53) and 3-hydroxy-2-methyl-prop-1-ene (54), was easily reduced to the allylic alcohol (56). The 'methoxy-

SCHEME 15



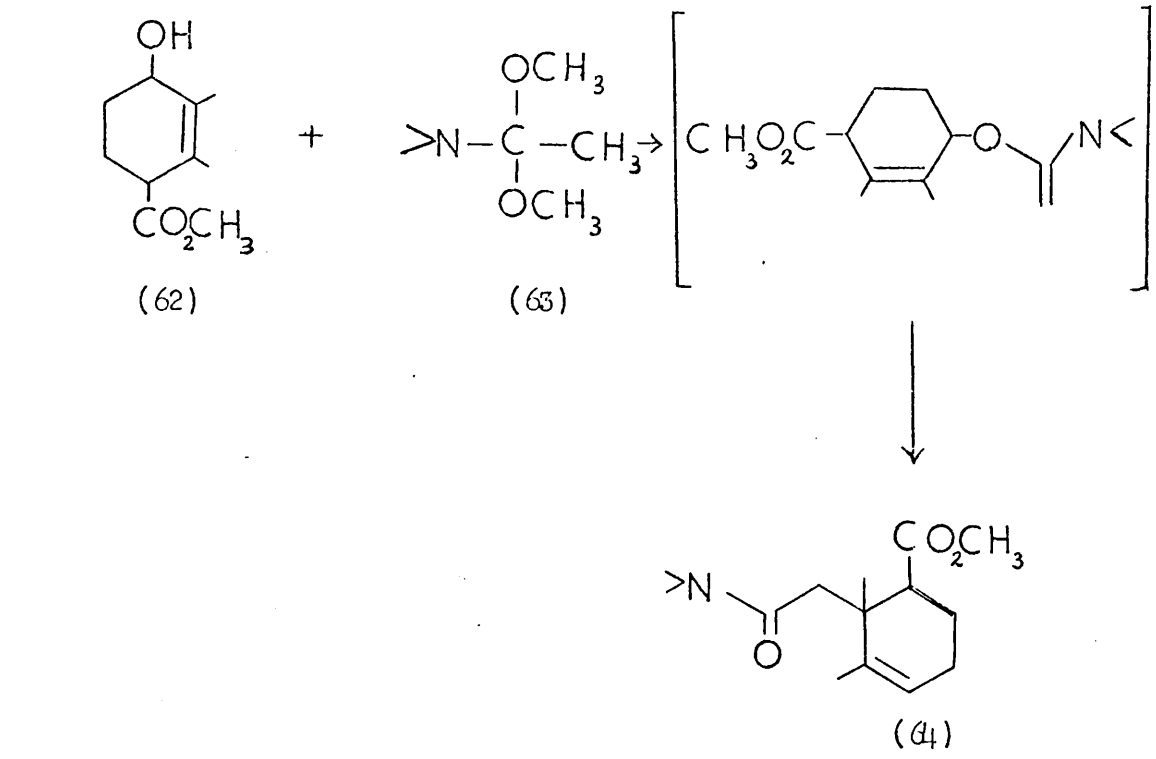
SCHEME 16



isoprene' reaction was repeated and further rearrangement afforded the trienone (57) with an all-trans geometry. Ultimately, successive linkages of this type and modification of the skeletal framework led to a stereospecific synthesis of squalene[41].

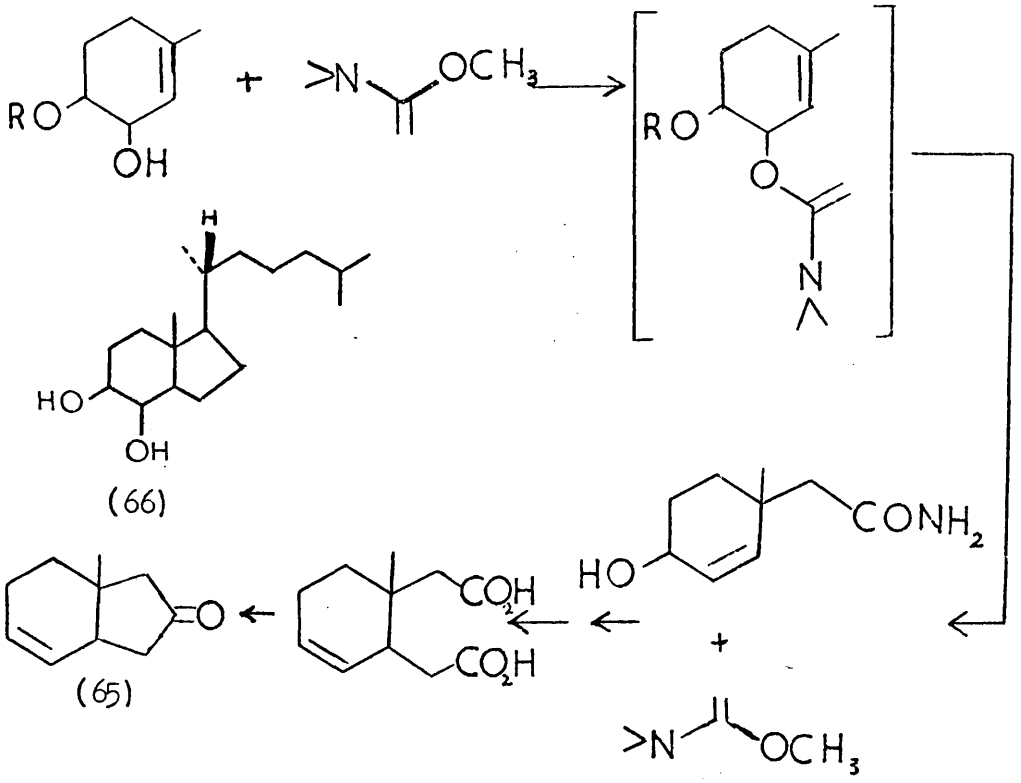
Johnson et al[42] have also reported a facile route to the juvenile hormone (58) through additional modification of the methoxyisoprene method. In this case, the vinyl synthon is in the form of the olefinic ketal (59) which on reaction with the hydroxy-ester (60) gave the keto-ester (61). Reduction of (61) to the allylic alcohol, followed by a further 'ketal' Claisen rearrangement gave a precursor which, on modification, provided a neat and highly stereoselective route to the juvenile hormone (58) (Scheme 16).

Eschenmoser and his collaborators[43] have used the Claisen rearrangement to form, N,N-dimethylamides of γ,δ-unsaturated acids and arylacetic acids. In a similar manner to the 'orthoester' rearrangement of Johnson, the vinyl ether formed in situ by the reaction of methyl-4-hydroxy-2,3-dimethylcyclohex-2-encarboxylate (62) and N,N-dimethylacetamide-dimethylacetal (63) pyrolysed at 140° gave the γ,δ-unsaturated amide (64). The aryl acetamides were synthesised via a similar rearrangement by the reaction of (63) with various benzyl alcohols. Bolton, Harrison and Lythgoe[44] have extended this type of rearrangement to the stereospecific synthesis of hydrind-4-en-2-ones (65) shown in the partial reaction scheme 17. A further modification afforded the synthesis of des-AB-cholestane-8β,9α-diol (66)[44].



(62) (63) (64)

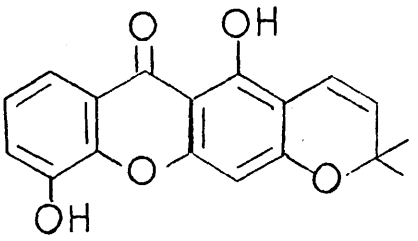
SCHEME 17



(66) (65)

In the field of xanthone chemistry, Scheinmann and his co-workers[45] have reported the isolation, elucidation and syntheses of some natural products extracted from the Guttiferae family, including 1-hydroxy-2-(3-methylbut-2-enyl)-3,5-dimethoxy xanthone (73), the biogenetic precursor of the pyranoxanthone, 6-deoxyjacareubin (67) isolated from Calophyllum scriblitifolium (Scheme 18). Claisen rearrangement of 1-allyloxy-3,5-dimethoxyxanthone (68) gave 2-allyl-1-hydroxy-3,5-dimethoxyxanthone (69). Modification of the side-chain by ozonolysis of the methyl ether (70) gave the aldehyde (71), which, in a Wittig reaction with the phosphorane generated from isopropyltriphenylphosphonium iodide and n-butyl-lithium followed by selective demethylation of (72) afforded the natural product (73).

A later communication by Scheinmann and Quillinan[46] described the synthesis of a heterocyclic bicyclo [2,2,2] octenone structure found in the morellins (74) (metabolites from Garcinia species of the Guttiferae family) and gambogic acid (75). Thus, Claisen rearrangement of 1-hydroxy-5,6-diallyloxyxanthone (76) and jacareubin-5,6-diallyl ether (77) in decalin resulted in products which on spectroscopic examination contained the bicyclo [2,2,2] octenone system (78). The postulated reaction mechanism to this novel system is shown in Scheme 19. Although Diels-Alder adducts[1,6] of the type (78) have been predicted as intermediates in some ortho-ortho Claisen rearrangements (see p. 6) these are the first examples isolated from the rearrangement of allyl ethers.



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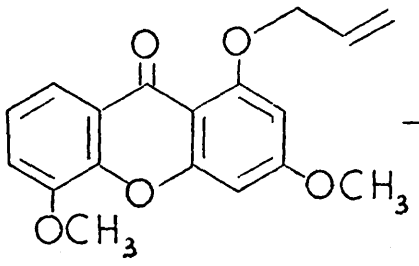
SCHEME 18



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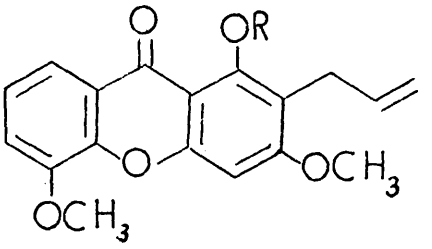
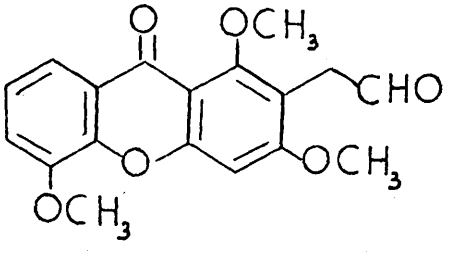
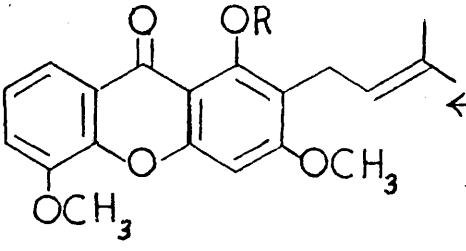


(69) R = H

(70) R = CH_3



(71)



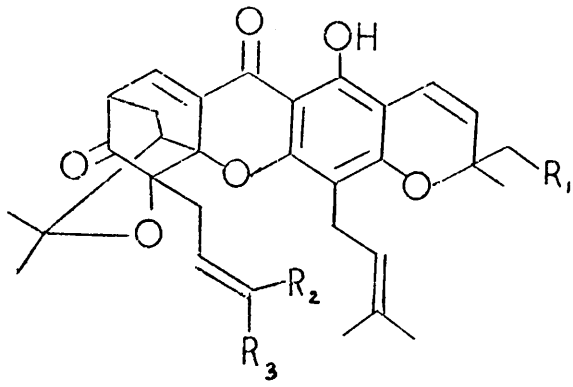
(72) R = CH_3

(73) R = H

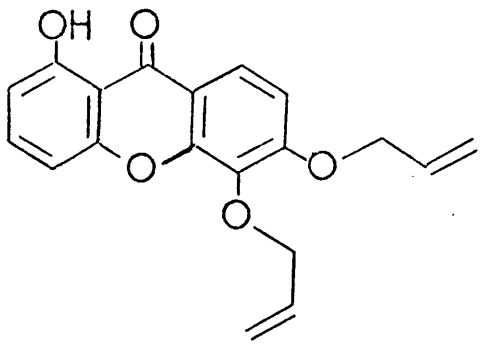
Claisen rearrangement has also been applied extensively in nitrogen heterocyclic systems, the main work being carried out in substituted pyrimidines, pyridines and quinolines. An overall review of the use of the rearrangement in these and other nitrogenous systems has been compiled by Thyagarajan[4].

Within the quinoline alkaloid field, Grundon and his co-workers[47] have investigated the biosynthesis of the 1,1-dimethylallyl 'inverted isoprene' unit occurring in these natural products. The alkaloids (82) and (84) have been isolated[47,48] from Flindersia ifflaiana F. Muell, and (79), (83) and (84) from Ravenia spectabilis Engl.[49] On the basis of this and other chemo-taxonomic evidence, Grundon[47,51] has proposed that the biosynthesis of the 1,1-dimethylallyl and the 1,2-dimethylallyl side-chains could be formed through Claisen rearrangement of a 3,3-dimethylallyl unit. In support of this postulate, he found that after feeding[47] labelled ravenine (79) to R. spectabilis, radioactive ravenoline (83) could be isolated and that this result was not a consequence of rearrangement of labelled (79) during isolation. Significantly, pyrolysis of the ether (79) also gave the 'abnormal' products ravenoline (83) and spectabiline (84). However, refluxing the ether (79) in the presence of acetic anhydride trapped the 'normal' phenol (81) as the acetate (80) and cyclisation afforded the natural alkaloid ifflaiamine (82)[50,51].

The above examples have been selected to illustrate the



	R_1	R_2	R_3	
(74)	H	CH_3	CHO	Morellin
(75)	$CH_2CH{:}C(CH_3)_2$	CH_3	CO_2H	Gambogic acid



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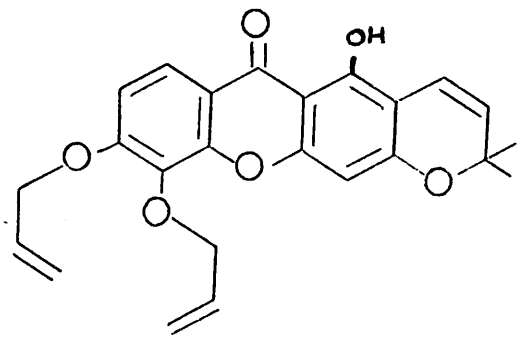

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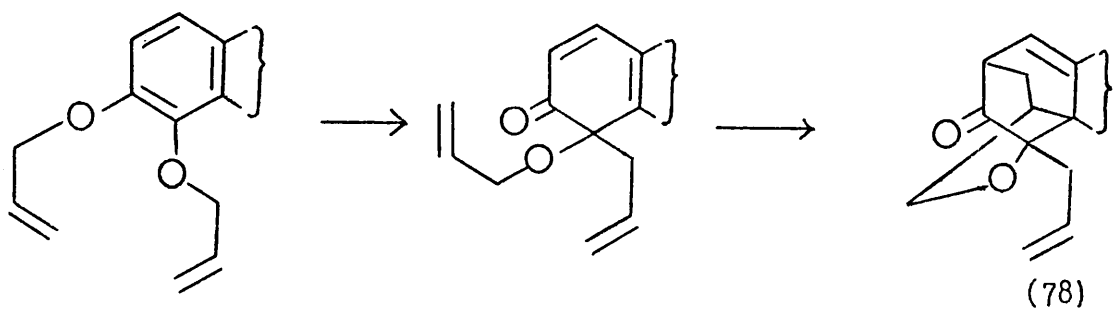
SCHEME 19



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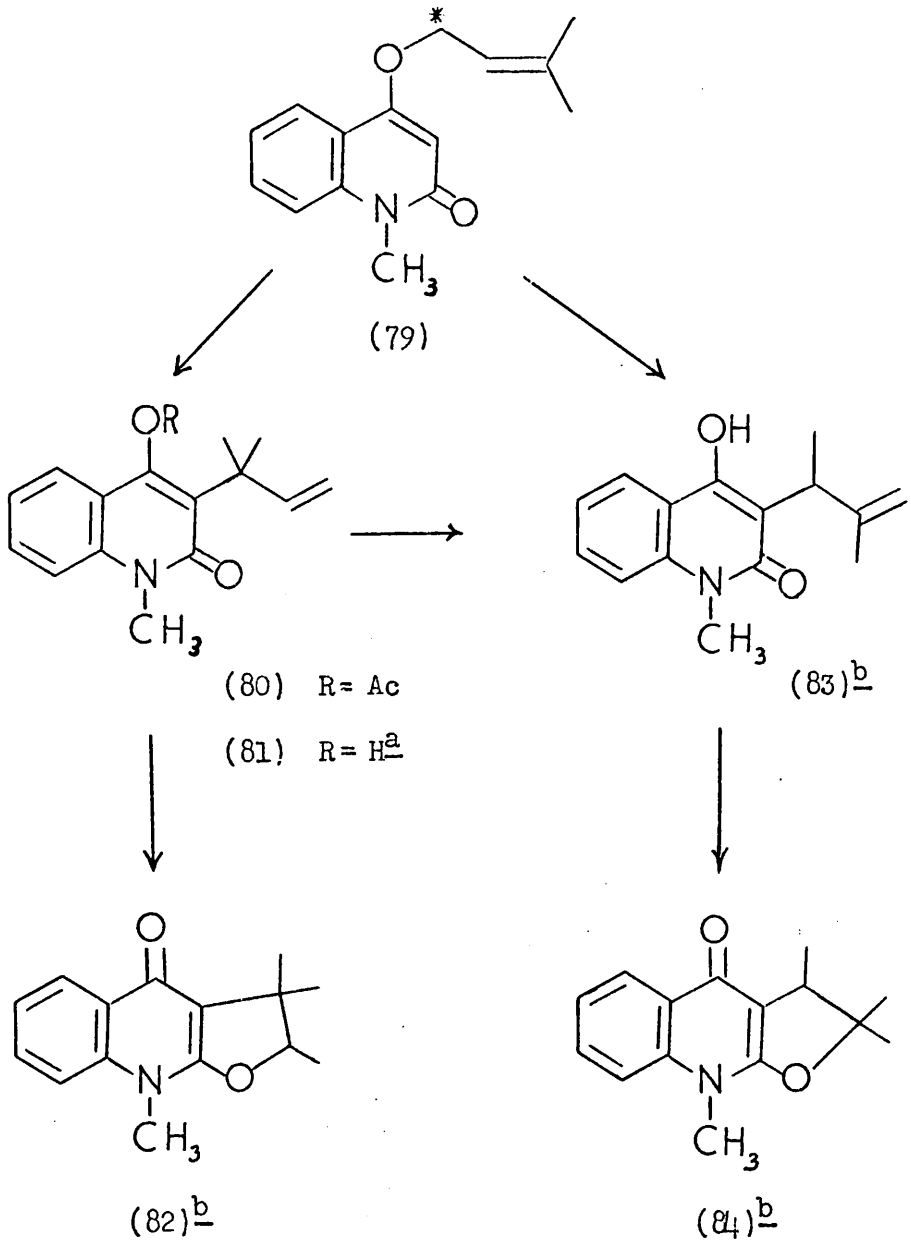
SCHEME 20



[a] has not been isolated from a natural source

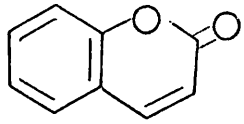
[b] optically active natural alkaloids

* position of ^{14}C in the labelling experiment

potential of the Claisen rearrangement in synthesis. Other relevant examples, particularly those associated with the synthesis of isoprenoid side-chains, will be cited later in the text.

Finally, it should be said that the scope of the Claisen rearrangement is being continually widened and many other valuable synthetic contributions to organic chemistry from the application of this simple electrocyclic reaction undoubtedly remain to be discovered.

Introduction to Part I



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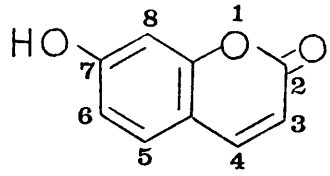

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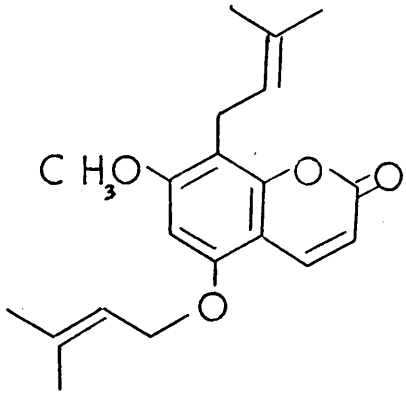

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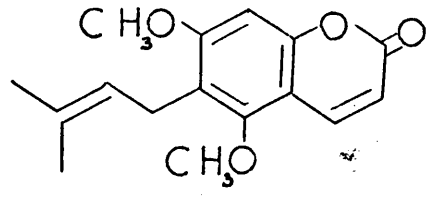


(87)

Coumarin (84)[52], isolated by Vogel in 1820 from Coumarouna adorata Willd (Tonka beans) represents the simplest member of the benzo-α-pyrones. The term 'coumarin' has been adopted universally as the parent name for the group of naturally occurring compounds possessing this structural skeleton as a fundamental unit. Since, coumarin derivatives have been found to be widely distributed[53,54] throughout the plant kingdom. For example, in 1963 when Dean[54] reviewed the subject of oxygen heterocycles, ninety natural representatives of this class of compound were known. At the present time, this number has more than doubled and is increasing rapidly.

One of the main reasons for this continued and growing interest stems from reports of physiological activities[53] associated with the compounds. As pharmacologically active agents, coumarins have found uses as anticoagulants, vasodilators[53] and recently as contraceptives[55]. Further, as a consequence of the rapid expansion of knowledge concerning naturally occurring coumarins a number of comprehensive reviews have appeared in the literature particularly from the U.S.S.R.[56]

Coumarin (84) is a typical as it contains no oxygen at C-7. Thus, since 7-oxygenation is found in virtually every known coumarin isolated from natural sources, 7-hydroxycoumarin (umbelliferone) (85) is often regarded as the parent of these heterocycles.

In fact, oxygenation is known to occur at any of the six available positions on the coumarin nucleus, with these oxygen

atoms being present as phenols, ethers or glycosides. Another common feature found in many natural coumarins is the occurrence of isoprenoid chains[54] in one, two or three units. These may appear bonded to the oxygen or to the carbon of the coumarin nucleus. In some instances, the isoprenoid chains may also be involved in the formation of heterocyclic ring systems with adjacent phenolic groups.

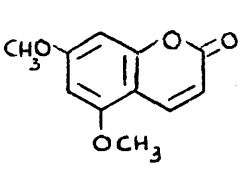
The biogenesis[57] of these C-5 units in phenolic isoprenoids is thought to arise from direct C-alkylation of a precursor by a moiety such as 3,3-dimethylallyl pyrophosphate. Subsequent modifications of the isoprenoid chain, usually by biogenetic oxidation, can then give rise to a variety of C-5 side-chains.

Since a 3,3-dimethylallyl grouping present as such, or in an oxygenated form is found in coumarins and in many other compounds of natural origin[54,57], methods of synthesis of the residue are important. One particular method, developed by Murray and Ballantyne[58], for the introduction of a 3,3-dimethylallyl group ortho to a phenol has been applied to the synthesis[58] of a number of naturally occurring coumarins. As an extension to this work, Part I of this thesis deals mainly with the application of this method to the synthesis of two other natural coumarins, sesibiricin (86)[59] and toddaculin (87)[60].

Both these coumarins show a 5,7-dioxygenation pattern and are frequently clasified as 'simple coumarins' on the basis that C-3 and C-4 of the α-pyrone ring are unsubstituted.

Within this category of 5,7-dioxygenated 'simple coumarins' many interesting skeletal variations of the isoprenoid chain are found. Scheme 1.1 illustrates a number of these modifications.

SCHEME 1·1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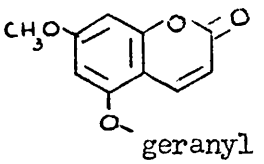

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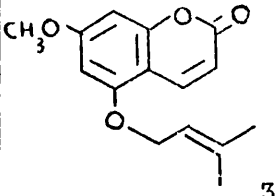
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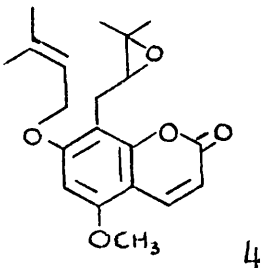
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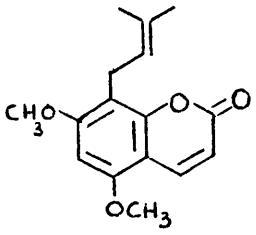
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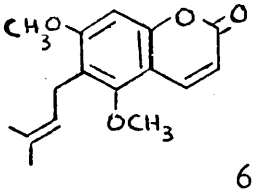
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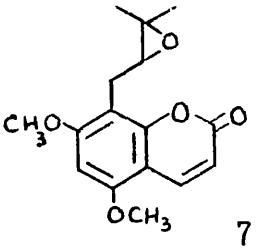
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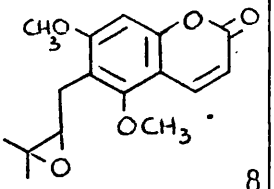
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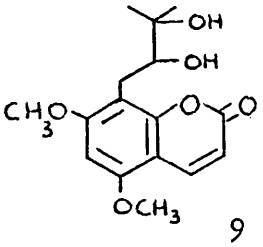
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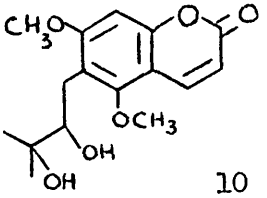
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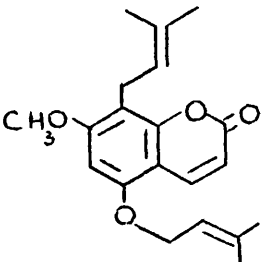
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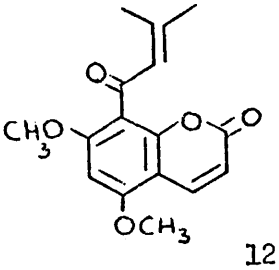
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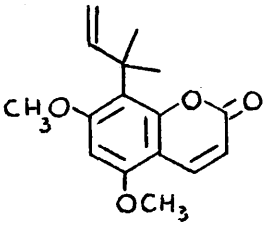
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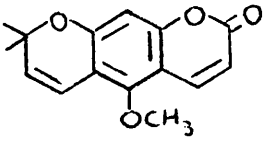
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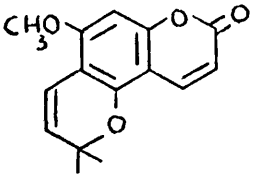
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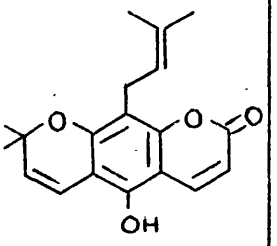
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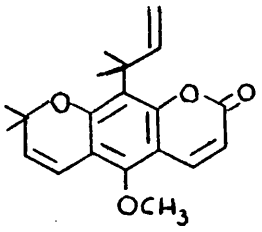
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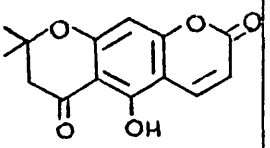
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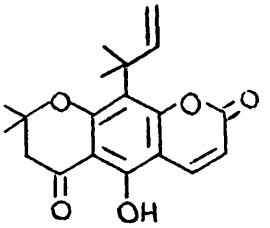
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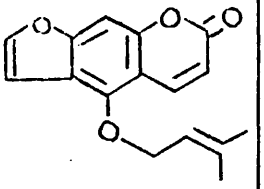

20

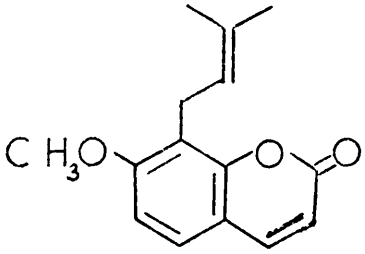
Index to Scheme 1.1

The numbering system refers to Scheme 1.1 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.

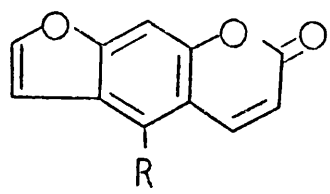
	Trivial Names	References
1.	limettin	
	citropten	53,54
2.	-	53,54
3.	-	61
4.	-	62
5.	coumurrayin	63
6.	toddaculin	64
7.	sibiricin	
	isoaculeatin	62,65
8.	aculeatin	54,66
9.	mexoticin	67
10.	toddalolactone	
	aculeatin hydrate	53,54
11.	sesibiricin	68
12.	glabralactone	
	angelicone	69
13.	pinnarin	70
14.	xanthoxyletin	53,54
15.	alloxanthoxyletin	53,54
16.	trachyphyllin	71
17.	poncitrin	
	dentatin	72
18.	clausenin	73
19.	clausenidin	72
20.	isoimperatorin	53,54

Part I

The Synthesis of the Coumarins, Sesibiricin and Toddaculin

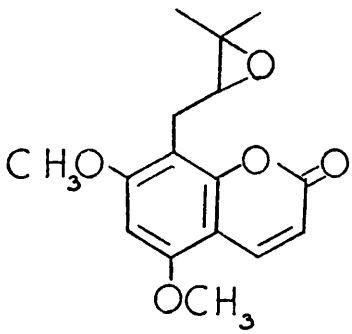


(88)



(89) R = $OCH_2CH{:}C(CH_3)_2$

(90) R = OCH_3



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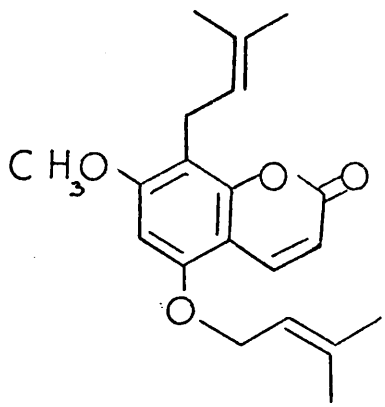
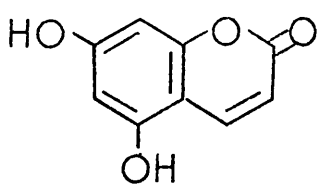


(86)



(92)

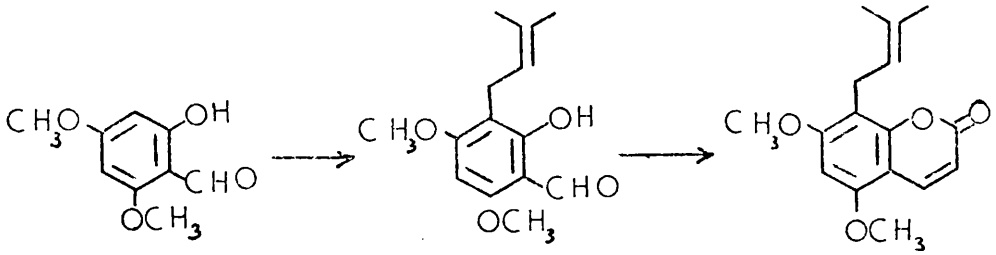
The coumarin, sesibiricin (86) was isolated[68] from the roots and rhizomes of the Indian plant Seseli sibiricin Benth (Umbelliferae) by Seshadri and Viswapaul. Other studies of the roots[74] revealed the presence of a number of terpenoids but only one other coumarin, osthol (88). However, although the roots and rhizomes appear to contain few coumarins, the extracts[75] of the umbels afforded osthol (88), imperatorin (89), bergapten (90) and sibiricin (91).

The structure of sesibiricin (86) is unusual in that it possesses two 3,3-dimethylallyl substituents, one bonded to oxygen and the other attached to carbon. Seshardri[68] established the structure of the coumarin as 5-O-(3,3-dimethylallyl)-7-methoxy-8-(3,3-dimethylallyl) coumarin (86) on the basis of chemical degradation and spectral evidence. In order to extend the synthetic utility of the isoprenyl insertion method developed by Murray and Ballantyne[58], and also to confirm the structure of sesibiricin, a synthesis of this natural coumarin was embarked upon.

A projected synthesis of sesibiricin (86) from 5,7-dihydroxy-coumarin (92) would necessitate both regioselective O-prenylation and C-prenylation of this diphenol. However, direct C-alkylation of the benzene ring has always been difficult and as such, the subject has received considerable attention[76].

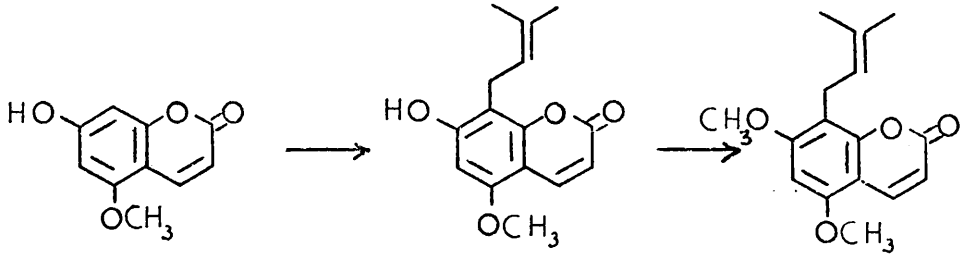
Two main methods, based on direct C-prenylation, have been developed to synthesise ortho-(3,3-dimethylallyl) coumarins. The first, developed by Späth[77], involves C-alkylation of a substituted salicylaldehyde followed by formation of the α-pyrone ring, as

SCHEME 1.2



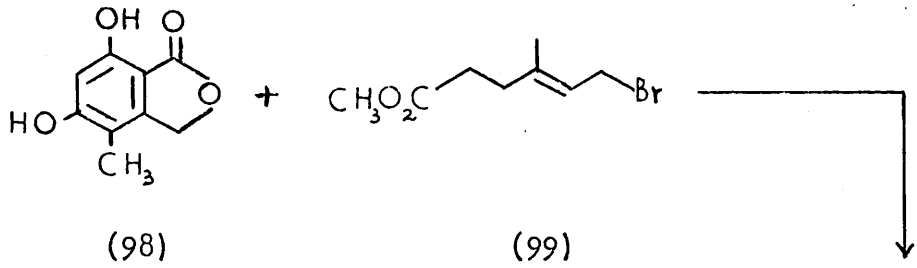
(95)

SCHEME 1.3

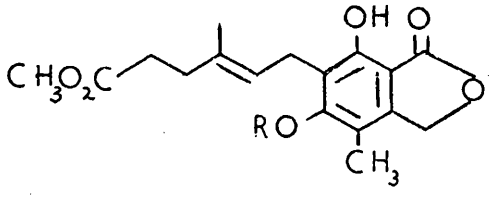


(95)

SCHEME 1.4



(98) (99)



(100) R = H

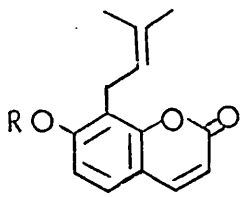
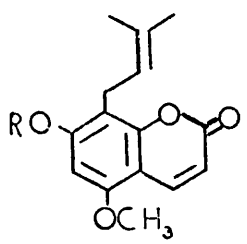
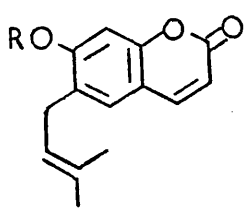
(101) R = CH_3

outlined in Scheme 1.2. When applied to the synthesis of mono- and 5,7-dioxygenated coumarins, this method suffers from poor yields and the difficulty of preparing the correctly substituted aldehyde. The second method[65,78,79] requires direct C-prenylation of a preformed hydroxycoumarin nucleus and, as in the first case, tends to present similar problems (Scheme 1.3). The mode of prenylation in both methods involves the reaction[2(b)] of the sodium or potassium salt of the appropriate phenol with an allylic halide in a heterogeneous media. Extensive studies[3,80] on the conditions for alkylation have established that the use of non-polar solvents and a heterogeneous reaction media usually favour direct C-alkylation. However, as Table 1.1 shows, these conditions do not provide efficient synthetic routes to isoprenyl side-chains in coumarins and salicylaldehydes.

Various other conditions have been used in attempts to increase the efficiency of direct C-alkylation. The use of 2-methyl-but-3-en-2-ol and a Lewis acid e.g. boron trifluoride etherate[81], has provided a mild synthetic step for C-prenylation in a number of natural products. However, this method usually results in multiprenylation and poor yields (~10% in most examples).

Recently Canonica[82] and his co-workers have reported the synthesis of mycophenolic acid (101) through prenylation of a 5,7-dihydroxynapthalide (98) (Scheme 1.4). The prenylation was performed by treatment of a dioxane solution of the napthalide (98) at room temperature in the presence of silver oxide and the proper allylic bromide (99). The side-chain was introduced

TABLE 1·1

	A C-alkylation of a salicylaldehyde B C-alkylation of a hydroxycoumarin
 (93) R=H, osthenol (88) R=CH_3, osthol	A 1% of (88) from 4-methoxy-2-hydroxy benzaldehyde[77] B 5% of the cyclic ether of (93) from umbelliferone[78]
 (94) R=H (95) R=CH_3, coumurrayin	A 1-2% of (94) from 2-hydroxy-4,6-dimethoxy benzaldehyde[65,79(a)] B 8% of (94) from 7-hydroxy-5-methoxycoumarin[79(b)] B 0.4% of the cyclic ether of (94) from 7-hydroxy-5-methoxycoumarin[65]
 (96) R=H (97) R=CH_3, suberosin	A 3% of (96) from 2,4 dihydroxy-benzaldehyde[78] B 5% of the cyclic ether of (96) from umbelliferone

at C-6 to yield (100) which on methylation afforded mycophenolic acid (101).

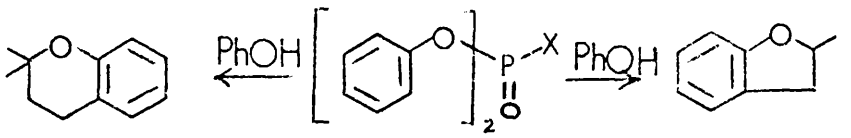
At this point, it would be appropriate to note the attempted syntheses of ortho-isopentenylphenols patterned on biosynthetic pathways. Studies[83] of isoprenylation of phenols in buffered protic acids e.g. citric and acetic acid buffer have been investigated with varying results. Miller and Wood[84] have also reported that the interaction of phenols with allyl diphenyl phosphates results in C-alkylation (Scheme 1.5). However, in all of these studies the products usually cyclise in the acid media to chromans (102) or coumarans.

An alternate synthetic route to phenolic isoprenoids has been suggested by Birch and his associates[85] through the intermediacy of the 2,2-dimethylchromenes (Scheme 1.6). Reductive ring opening with lithium in liquid ammonia of robustic acid (103) resulted in a high yield of (104).

Thus in the light of the above studies, regioselective direct C-prenylation of 5,7-dihydroxycoumarin (92) as a synthetic step towards sesibiricin would likely prove to be unfruitful.

As an alternative, the method developed by Murray et al[58] for the introduction of a 3,3-dimethylallyl unit ortho to a phenol, requires Claisen rearrangement of the appropriate 1,1-dimethylallyl coumarin (Scheme 1.7). Through this route, three natural coumarins osthenol (93), demethylsuberosin (96) and coumurrayin (95) have already been synthesised. In addition, the yields of osthenol (93)

SCHEME 1.5

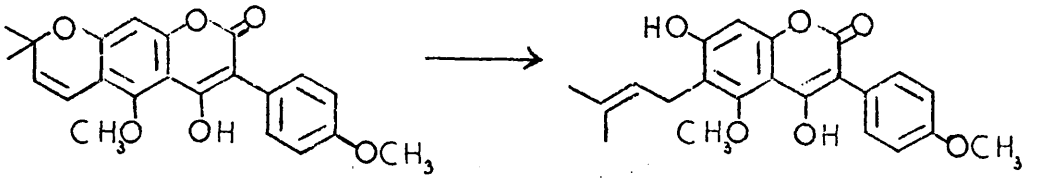


(102)

when X = $OCH_2CH{:}C(CH_3)_2$

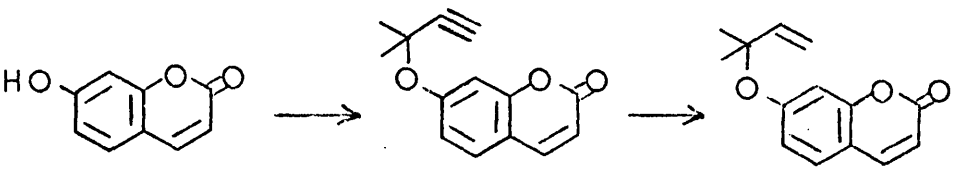
when X = $OCH_2CH{:}CH_2$

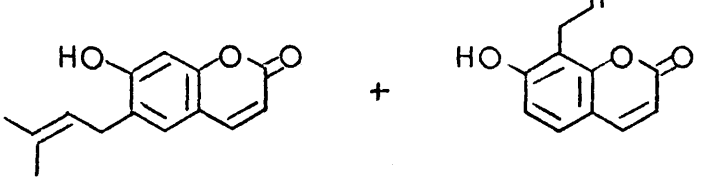
SCHEME 1.6



(103) (104)

SCHEME 1.7





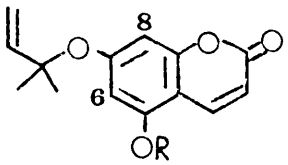
(96) (93)

and coumurrayin (95) were appreciably greater (~55-60%) than by the direct C-alkylation methods.

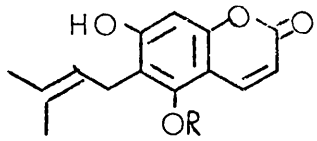
There are also many other advantages gained from the use of this synthetic route towards hydroxycoumarins. The three-step method is performed under mild conditions and, as a result, a preformed coumarin nucleus is unaffected. Moreover, it overcomes the problems such as cyclisation, cleavage and abnormal Claisen rearrangement associated with the thermal pyrolyses of 3,3-dimethylallyl ethers.

In applying this method to the synthesis of sesibiricin (86), the pathway to the introduction of the isoprenoid unit specifically at C-8 would be through Claisen rearrangement of the ether (105). There is also the possibility that rearrangement would occur to C-6 of the coumarin nucleus with the formation of the isomeric C-6 phenol (106). However, it would seem reasonable to assume that the rearrangement of the ether (105) would result in exclusive migration to C-8 from the following evidence. In the synthesis[70] of pinnarin (109), the 3,3-dimethylallyl ether of 7-hydroxy-5-methoxycoumarin (107) underwent exclusive migration to C-8 to form the ortho-1,1-dimethylphenol (108). Further work by Kaufmann and his co-workers[36], on the pyrolyses of 7-allyloxycoumarins unsubstituted at C-6 and C-8, showed the same direction of rearrangement.

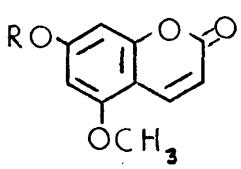
However, selective functionalisation of the C-7 hydroxyl group as a 1,1-dimethylallyl ether necessitates the protection of the C-5 hydroxyl, preferably as a 3,3-dimethylallyl unit as this substituent is present in sesibiricin (86) itself. The question arises as to



(105)

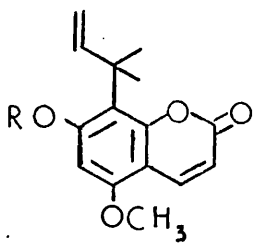


(106)



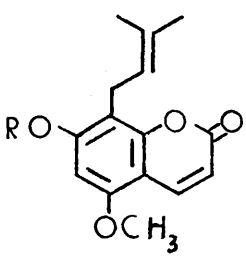
(107) $R = CH_2CH{:}C(CH_3)_2$

(110) $R = C(CH_3)_2CH{:}CH_2$



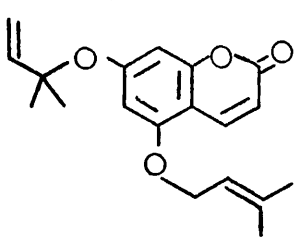
(108) $R = H$

(109) $R = CH_3$



(111) $R = H$

(95) $R = CH_3$



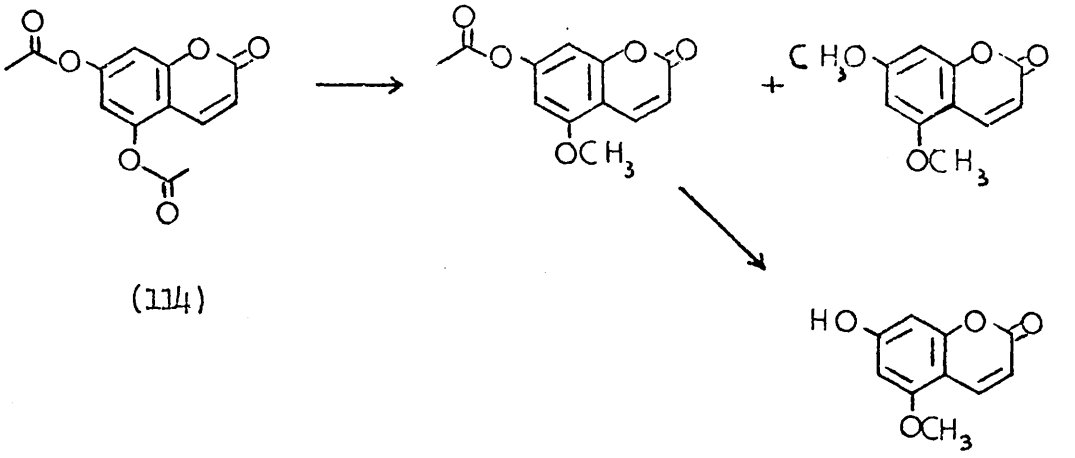
(112)

whether this function would survive the three step insertion of the isoprenyl group at C-8, in particular, the Claisen rearrangement step, since such ethers are unstable at $\sim 190^{\circ}$. However, during the synthesis of coumurrayin (95) by this method, facile rearrangement of the ether (110) to the phenol (111) was found to occur very rapdily at 160°. Therefore, it was hoped that if the bis-ether (112) could be prepared, selective rearrangement of the 1,1-dimethylallyl group by careful temperature control might be possible.

Unfortunately, there is little difference between the reactivities of the 5- and the 7- hydroxyl functions in 5,7-dihydroxycoumarin (92) and allylation and alkylation result in the formation of a mixture of mono- and bis- ethers with a predominance of the latter. Seshadri[86] and his co-workers had investigated the selective alkylation of several polyhydroxycoumarins and by the method outlined in Scheme 1.6 had synthesised[87] 7-hydroxy-5-methoxycoumarin (113) from 5,7-diacetoxycoumarin (114) in a reasonable overall yield ($\sim 55\%$). If 3,3-dimethylallylation of 5,7-diacetoxycoumarin (114) were to give similar results, this would mean that the 5-hydroxyl would be protected as a dimethylallyl ether and would leave the 7-hydroxyl free for further synthetic manipulation.

5,7-Dihydroxycoumarin (92) was obtained[88] by heating a mixture of phloroglucinol and ethyl propiolate[89] in the presence of zinc chloride, then converted[89] to the diacetate (114). Following the method of Seshadri[88], an acetone solution of the diacetate (114)

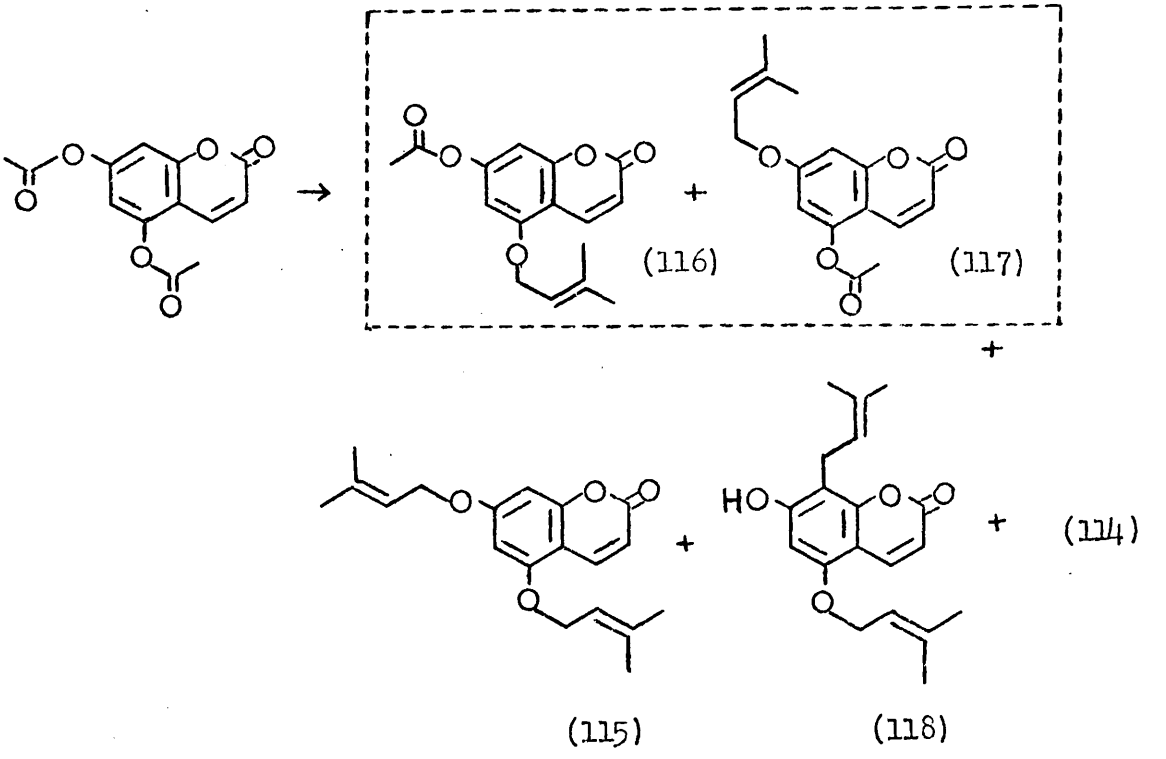
SCHEME 1·6



(114)

(113)

SCHEME 1·7



(116)

(117)

(115)

(118)

(114)

as a mixture

was refluxed with excess of 3,3-dimethylallyl bromide in the presence of potassium carbonate and the products separated by preparative t.l.c. The major product from the reaction was an isomeric mixture of the acetates (116) and (117) (Scheme 1.7). The other products isolated were the bis-ether (115) (6%) which was found to be identical with a synthetic sample[90], the starting acetate (114) (30%) and a C-prenylated ether (118) (2%).

At this time, Büchi[91] reported that the use of base stable 1,2-dimethoxyethane (glyme) as solvent for the O-alkylation of phenols normally resulted in more efficient yields and no C-alkylation. When the dimethylallylation was repeated using glyme as solvent the yield of the mixture of the isomeric acetates increased by 19% (see Table 1.2). Moreover, using a shorter reflux time (27 hr. in glyme compared with 45 hr. in acetone), no C-alkylated ether (118), and considerably less starting acetate was isolated.

From the n.m.r. spectrum of the isomeric mixture of the acetates (116) and (117), the required isomer 5-O-(3,3-dimethylallyl)-7-acetoxycoumarin (116) was found to predominate in a ratio of ~3:1. With glyme as solvent this ratio has increased to ~4:1. On careful examination of the t.l.c. chromoplate, a band lower in polarity than that of the isomeric acetate mixture was detected. The u.v. spectrum of this coumarin indicates a 5,7-dioxygenation pattern with a free 7-hydroxyl, thereby suggesting the phenol (119).

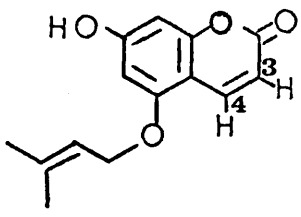
TABLE 1·2

Dimethylallylation of 5,7-diacetoxycoumarin (114)

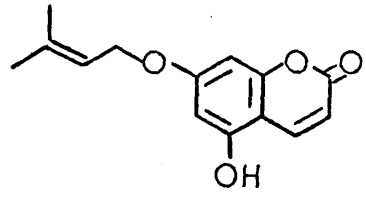
Solvent	(115)[A]	(116)[B]	(118)	(114)
1,2-dimethoxyethane	2	60	-	11
acetone	6	41	2	30

A percentage yields from 5,7-diacetoxycoumarin (114)

B isolated as a mixture with the acetate (117)



(119)



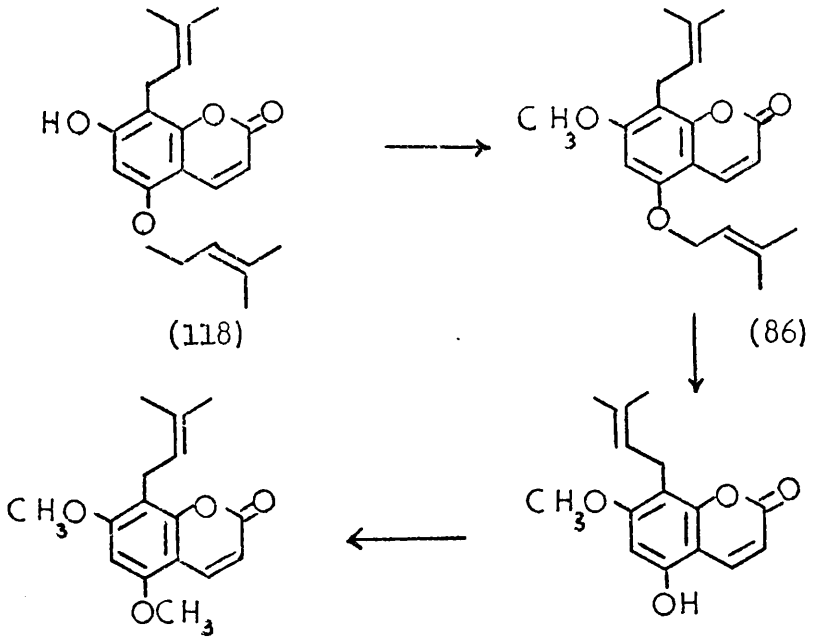
(120)

Further scrutiny of the n.m.r. spectrum of the isomeric acetates (116) and (117) indicates that, besides the signals at τ1.95 and τ 2.36 respectively for the C-4 protons of the AB system of these acetates, a signal for the C-4 proton of a third coumarin at τ 2.04 exists. Comparison with the n.m.r. spectrum of an actual sample of 7-hydroxy-5-O-(3,3-dimethylallyl)coumarin (119) shows these signals to be identical. Since no evidence for a free 5-hydroxyl is detected from the u.v. spectrum, it must follow that during the work up conditions of the dimethylallylation selective hydrolysis of one isomer, namely (116) occurs. Other workers[92], investigating this reaction obtained the same results. In addition, they found that they were unable to separate the isomeric acetates by preparative t.l.c. and in each separation attempt, regioselective hydrolysis occurred during work up.

On the evidence of the above failure, attempts were made to selectively hydroyse the 7-acetoxy isomer (116) in the presence of the other (117). Unfortunately, no suitable base was found and from each attempt an isomeric mixture of the phenols (119) and (120) resulted.

As an alternative, fractional crystallisation did provide a sample of the predominant isomer (116), the spectral data of which were in complete accord with the above structure. However, as a structural confirmation, the acetate (116) was hydrolysed in mild base to the phenol (119) and correlated with a synthetic sample.

SCHEME 1·8



(118) (86) (95)

Previous studies[92,93] of the dimethylallylation of 5,7-dihydroxycoumarin (92) in acetone indicated that the major component of the reaction was the bis-ether (115). Among the minor products, the C-alkylated ether (118) was isolated and its structure confirmed by conversion[58,93] to coumurrayin (95)[63] (Scheme 1.8).

The C-alkylated ether isolated from the dimethylallylation of 5,7-diacetoxycoumarin possesses similar spectral characteristics to the above ether (118) and, if these ethers were identical, methylation would yield sesibiricin (86). Indeed, during the structural confirmation route to coumurrayin (Scheme 1.8) sesibiricin must have been an intermediate. However, at that time the coumarin had not been isolated and, in the previous studies, the low yield of the C-alkylated ether (118) (~5%) resulted in the intermediate compounds not being fully characterised.

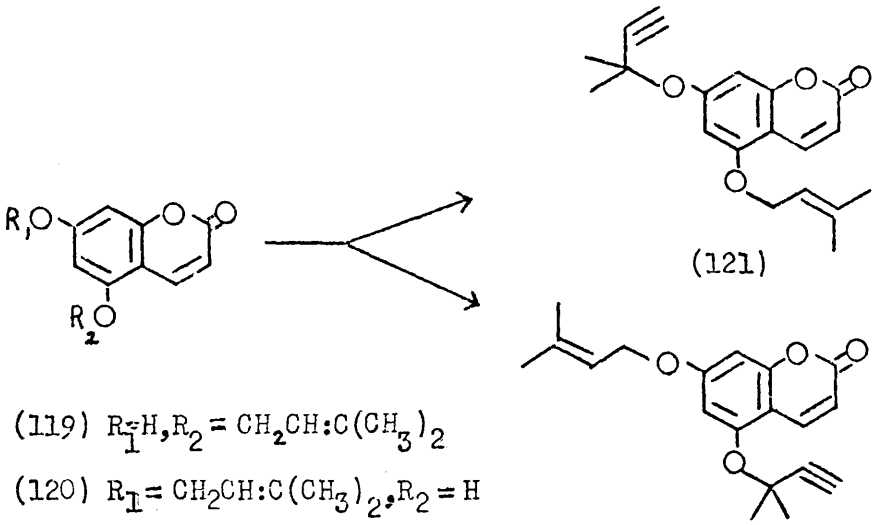
In order to provide at least a sample of sesibiricin through this route, the reaction of 5,7-dihydroxycoumarin with 3,3-dimethylallylbromide was repeated. The crude reaction product was hydrolysed and the residue separated into a base soluble and a base insoluble fraction. The latter fraction yielded the bis-ether (115) (57%), and the base soluble fraction the phenols (119) (23%) and (118) (2%). The n.m.r. and u.v. spectra of the C-alkylated ether (118) is identical with that obtained from the minor product isolated from the dimethylallylation of 5,7-diacetoxycoumarin. The ether was methylated and the product obtained possesses physical

properties (m.p., m.m.p. and n.m.r.) identical with those of sesibiricin (synthesis p.35). In the C-alkylated ether, direct prenylation occurred at C-8 and no C-6 alkylated isomer was found. Indeed, this again provides indirect evidence that Claisen rearrangement of the 1,1-dimethylallyloxy ether at C-7 should migrate preferably to the C-8 position.

Since no separation of the acetates (116) and (117) either by preparative t.l.c.[92] or by selective hydrolysis could be found, they were both hydrolysed to the phenols (119) and (120). It was hoped that at a later stage in the synthesis that suitable functionalisation of the C-7 and C-5 hydroxyl would provide some difference in chromoplate mobility, in order to affect a separation. In fact, after dimethylpropargylation, the next synthetic step, this separation could be achieved.

Refluxing a solution of the isomeric phenols in aqueous acetone with 2-methyl-2-chloro-but-3-yne[94] in the presence of potassium carbonate and potassium iodide[58] gave an isomeric mixture of the propargyl ethers (121) and (122) (Scheme 1.9). Separation by preparative t.l.c. afforded the required propargyl ether (121) (72%) and the isomer (122) (21%). Most of the physical properties of these isomers, with the exception of m.p. were similar (Table 1.3). One significant difference in the n.m.r. spectra of these isomers is in the chemical shift of the C-4 proton of the α-pyrone ring. The 1,1-dimethylpropargyl group apparently can act as a more efficient proton shield at C-5 than the

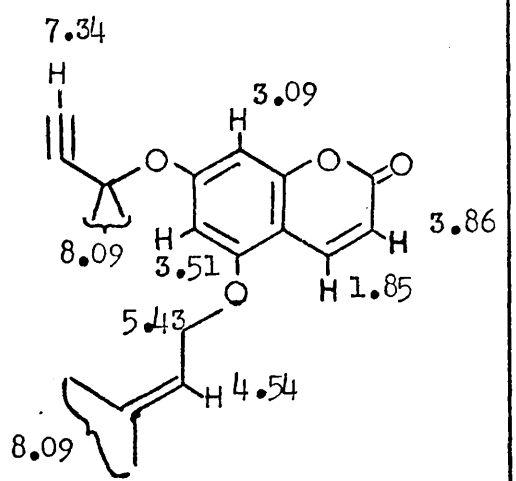
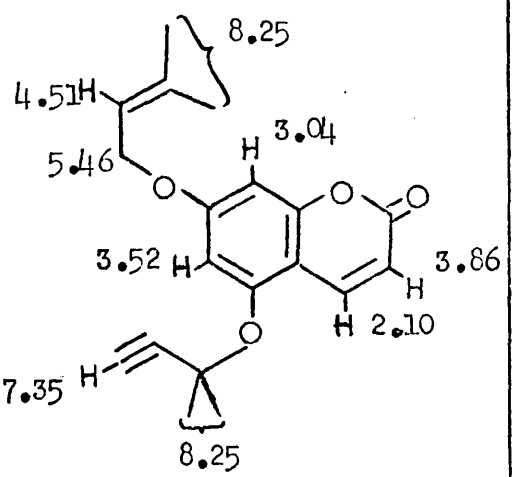
SCHEME 1·9



(119) R_1=H, R_2 = $CH_2CH{:}C(CH_3)_2$

(120) R_1 = $CH_2CH{:}C(CH_3)_2$, R_2 = H

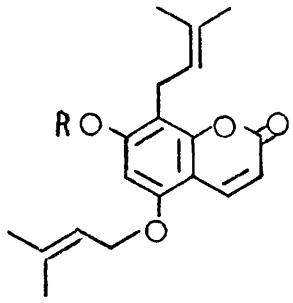
TABLE 1·3

(121)	(122)
	
m.p. 114-116°	m.p. 84-86°
i.r. 3295, 1725 and 1610 cm.$^{-1}$	i.r. 3596, 1720 and 1603 cm.$^{-1}$
u.v. 219, 246, 254, and 329 nm.	u.v. 219, 246, 254 and 323 nm.

3,3-dimethylallyl group and consequently the C-4 signal in (121) appears at τ 1.85, at considerably lower field than the C-4 signal of (122) (τ 2.10). One unique feature is that both the compounds analyse for $C_{19}H_{20}O_4 \cdot \frac{1}{2}H_2O$. A more detailed discussion of the mechanism of dimethylpropargylation is found in Part II (p.p. 98-99).

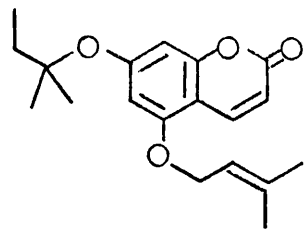
At this step, it was assumed that the major acetylenic ether would be (121) since it was already known that the predominant isomer of the phenolic mixture was (119).

Hydrogenation of the propargyl ether (121) over palladium-barium sulphate catalyst with quinoline-sulphur as poison[95] afforded the bis-ether (112) in 88% yield. In order to remove traces of sulphur-quinoline poison, preparative t.l.c. was employed as a purification procedure. Examination of the chromatoplate revealed the presence of a small amount (2%) of a more polar compound. From the i.r. and u.v. spectra, this compound appears to possess a free 7-hydroxyl. Comparison with the C- prenylated ether (118) isolated from the 3,3-dimethyl-allylation of 5,7-dihydroxy- and 5,7-diacetoxycoumarin shows that both compounds are identical. Obviously, on purification, a small amount of rearrangement occurs, presumably to the C-8 position since only one product is present. Also during the hydrogenation, hydrogenolysis occurs to a slight extent (2%) with the formation of 7-hydroxy-5-O-(3,3-dimethylallyl)coumarin (119).

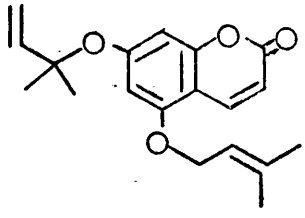


(118) R= H

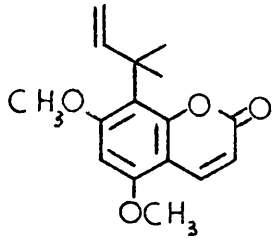
(86) R= CH_3



(124)



(112)

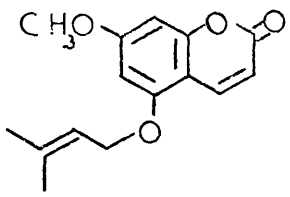


(109)

With the preparation of the 1,1-dimethylallyl ether (112) it remained to be seen whether selective rearrangement of the dimethylallyloxy group would occur in the presence of a 3,3-dimethylallyl ether. Fortunately, pilot pyrolyses of (112) indicated that a lower temperature than had been employed for the rearrangement of 3,3-dimethylallyl ethers would be sufficient, and at a temperature of 130° pyrolysis resulted in two products which were separated by preparative t.l.c.

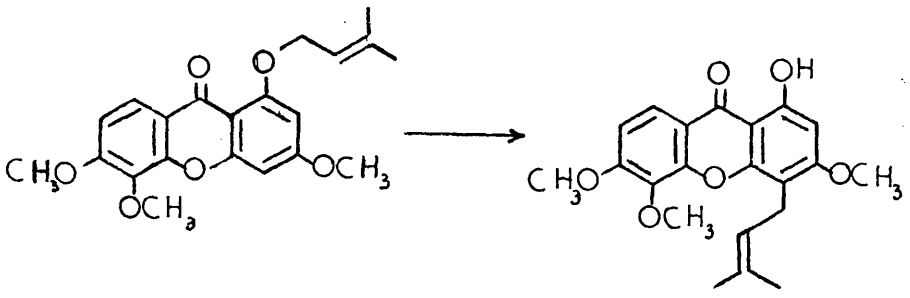
The u.v. spectrum of the major product (77%) shows a free 7-hydroxyl. The n.m.r. spectrum indicates an α-pyrone AB system (τ 3.96 and 2.10 ; 2H ; J 9.5 Hz.), a 3,3-dimethylallyl residue bonded to the benzene ring (τ 8.22 ; 6H ; b.s.), (τ 6.73 ; 2H ; d./d. ; J 6.5 Hz.) and (τ 4.85 ; 1H ; b.t. ; J 6.5 Hz.), a 3,3-dimethylallyl unit attached to oxygen (τ 8.35 ; 3H ; b.s.), (τ 8.22 ; 3H ; b.s.), (τ 5.43 ; 2H ; d./d. ; J 6.5 Hz.) and (τ 4.56 ; 1H ; b.t. ; J 6.5 Hz.) with an aromatic proton at τ 3.60 (s.). On the above evidence the product was assigned the structure 7-demethylsesibiricin (118). Comparison with the product obtained during the hydrogenation work up indicated that the two compounds were identical. (vide supra)

The i.r. spectrum of 7-demethysesibiricin (118) possesses both free and bonded hydroxyl stretching frequencies. From the evidence of dilution studies, the values at 3597 and ~3398 $cm.^{-1}$ can be attributed to intermolecular and intramolecular hydrogen bonding respectively. These values are similar to those reported[70]

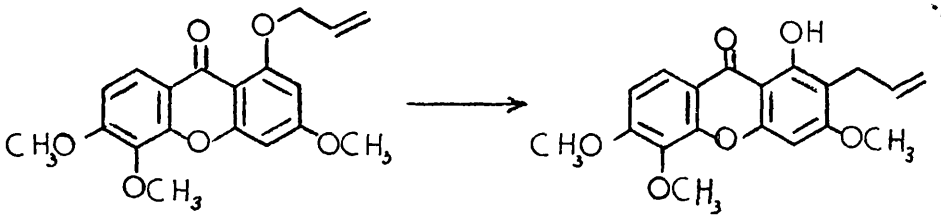


(125)

SCHEME 1·10



(126) (127)



(128) (129)

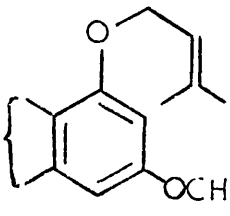
for pinnarin (109) (3598 and 3449 $cm.^{-1}$) and for[96] ortho-(3,3-dimethylallyl) phenol (3614 and 3486 $cm.^{-1}$).

The other product isolated from the pyrolysis, from its u.v. spectrum, appears to be non-phenolic. The n.m.r. spectrum shows that the 1,1-dimethylallyloxy residue has been replaced by a 1,1-dimethylpropyl unit (τ 9.03 ; 3H ; t. ; J 6 Hz.), (τ 8.62 ; 6H ; s.) and (τ 8.22 ; 2H ; q. ; J 6 Hz.) whereas the 3,3-dimethylallyl unit appears unchanged. Mass spectral analysis indicates a parent peak at m/e 316 (M^+). On this evidence, the structure (124) was assigned to the product. Obviously during hydrogenation, the presence of a small amount of 'unpoisoned' catalyst totally reduced the 1,1-dimethylallyl group.

Methylation of 7-demethylsesibiricin (118) with methyl iodide in the presence of potassium carbonate afforded sesibiricin (86) in high yield. Comparison with a natural sample kindly donated by Professor Seshadri showed that both samples were identical in all respects.

An alternative synthesis of sesibiricin (86) was envisaged through para-Claisen rearrangement[1,2] of 5-O-(3,3-dimethylallyl)-7-methoxycoumarin (125). This rearrangement as a method of C-alkylation had previously been investigated by Scheinmann and his group[45,97] in their studies in the xanthone field. They reported the synthesis of ugaxanthone trimethyl ether (127) through para-Claisen rearrangement of the 3,3-dimethylallyl ether (126) (Scheme 1.10). However, pyrolysis of 1-allyloxy-

SCHEME 1·11



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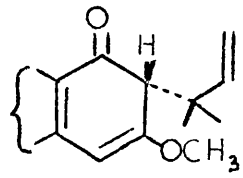
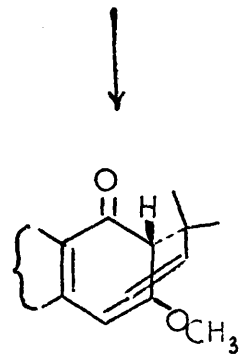
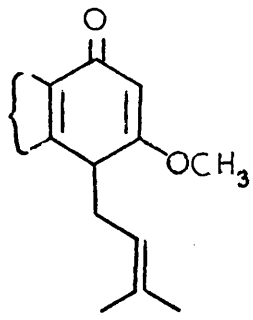


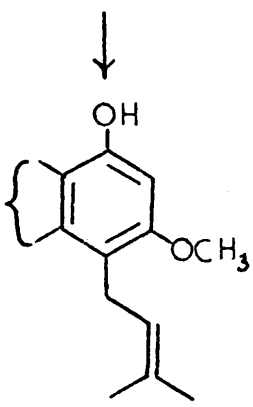
(130)



(132)



(133)



(127)

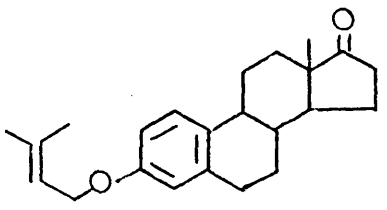
3,5,6-trimethyoxyxanthone (128) afforded the ortho-substituted xanthone (129) only (Scheme 1.10). These results suggest that the 3,3-dimethylallyl group is largely responsible for the formation of the para product (127) since meta substituents do not appreciably influence a Claisen rearrangement. Similar findings were reported by Schmid et al[19] with meta-substituted phenylallyl ethers.

Scheinmann[97] suggested the mechanism shown in Scheme 1.11 for the rearrangement. The 'buttressing effect' of the gem-dimethyl groups on the allyl side chain hinders enolisation to such an extent in the ortho-dienone intermediate that rearrangement to the para position becomes a competitive process. Thus, in Scheme 1.11, rearrangement of the allyl ether (126) to the vacant ortho site gives the dienone (130) in which interaction of the dimethyl group with the neighbouring meta methoxyl group hinders the formation of the pseudo equatorial conformer (130). Free rotation of the side-chain allows the formation of a conformer (132) which possesses the correct orientation for Cope rearrangement to the para position, to yield the thermodynamically more stable para-dienone (133) which enolises to the phenol (127).

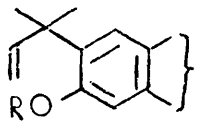
Other studies by Schmid[98] et al on meta-substituted aryl crotyl ethers showed that solvent significantly influences the course of the rearrangement. They suggest that migration to the para position is favoured by non-polar solvents such as decalin and N,N-diethylaniline whereas polar solvents such as dimethylformamide favour enolisation of the ortho-dienone (130).

Therefore, it seems likely that Claisen rearrangement of the allyl ether (125) could possibly lead to another method of introducing the isoprenoid unit at C-8 and hence afford sesibiricin (86). However, thermal pyrolyses of 3,3-dimethylallyl ethers are often unpredictable and often accompanied by side-reactions. One of the problems results from the dissociation[14] of the starting ether into isoprene and the parent phenol. Moreover, once the rearrangement occurs, the first-formed ortho-(1,1-dimethylallyl) phenol can cyclise[99] to a 2,3,3-trimethyldihydrofuran (or coumaran) system. Further, with the presence of a γ-alkyl substituent, abnormal Claisen rearrangement (see p. 9)[27] can arise.

One method of eliminating the last two processes would be to trap the product(s) of the pyrolysis. Such 'trapping' experiments are usually carried out using N,N-diethylaniline as solvent and acetic or n-butyric anhydride as the trapping agent. In the pyrolysis of oestrone 3,3-dimethylallyl ether (134), Jefferson and Scheinmann[100] obtained the normal product (135) by trapping it as the butyrate (136). Murray and Ballantyne[70] have also utilised this method in the synthesis of pinnarin (109). Rearrangement of the allyl ether (137) in N,N-diethylanine and n-butyric anhydride gave the butyrate (138) which on hydroylsis and methylation afforded pinnarin (109). In the alkaloid field, Grundon and his co-workers[50] reported the use of acetic anhydride as a trapping agent in the synthesis of ifflaiamine (82) (see p. 18).

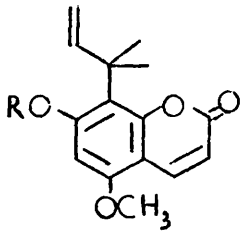


(134)



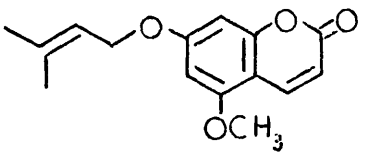
(135) R = H

(136) R = $CO(CH_2)_2CH_3$

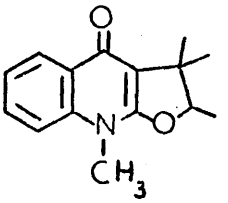


(138) R = $CO(CH_2)_2CH_3$

(109) R = CH_3



(137)

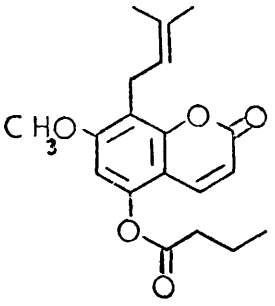


(82)

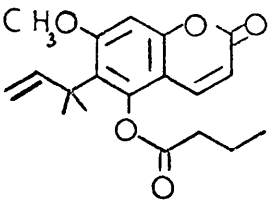
In the present case, butyric anhydride was chosen for the rearrangement of (125) since, in the synthesis[70] of pinnarin (109) (vide supra) hydrolysis of the butyrate ester (138) was achieved under very mild conditions.

The ether (125) was obtained by the methylation of a mixture of the isomeric phenols (119) and (120) obtained from the dimethylallylation of 5,7-diacetoxycoumarin in glyme (see p.29). The n.m.r. spectrum indicated that the methyl ethers (125) and (137) were in the ratio of 82:18 respectively and complete separation by preparative t.l.c. was not possible. However a partial chromatographic separation, followed by fractional crystallisation gave the major isomer (125) in 61% yield.

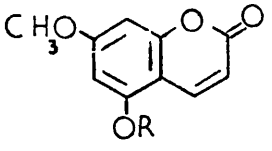
The ether (125) was pyrolysed at $175 \pm 5^{\circ}$ under nitrogen for 2 hr. in the presence of a small amount of N,N-diethylaniline and excess n-butyric anhydride. One major butyrate was isolated in 86% yield, the n.m.r. spectrum of which indicates that a 3,3-dimethylallyl group is present attached to the benzene ring. Assuming that under the conditions of the pyrolysis a para-Claisen rearrangement[1,2] occurs, the most likely position for the isoprenoid unit would be at C-8. On this evidence the butyrate was assigned the structure (139). No trace of the ortho-substituted butyrate (140)was found. The only other product isolated was the butyrate (141) of the parent phenol, 5-hydroxy-7-methoxycoumarin (142) (2%). The structure of the



(139)

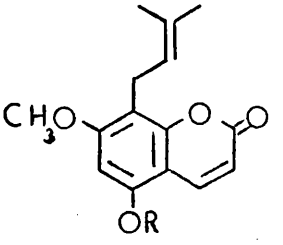


(140)



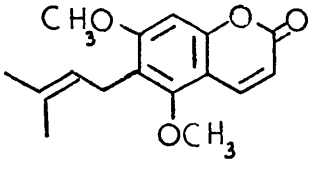
(141) R= $CO(CH_2)CH_3$

(142) R = H



(143) R= H

(86) R= $CH_2CH{:}C(CH_3)_2$



(87)

butyrate (141) was confirmed by its synthesis from (142).

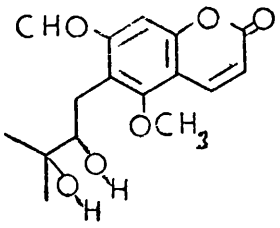
In using this method, there is surprisingly little cleavage of the ether in comparison with thermal pyrolysis.

The butyrate (139) was hydrolysed under mild conditions to 5-hydroxy-7-methoxy-8-(3,3-dimethylallyl) coumarin (143). The u.v. spectrum[93] of this product indicates a free 5-hydroxyl group and further evidence that the isoprenoid unit is located at C-8 is indicated from the i.r. spectrum which shows a free hydroxyl stretching frequency at 3599 $cm.^{-1}$ and no intramolecular stretching frequency. If the isoprenoid unit had been inserted by some other rearrangement process at C-6, ortho to the phenol group at C-5, then, as in 7-demethylsesibiricin (118) (see p. 34), the i.r. spectrum should possess both bonded and free hydroxyl stretching frequencies.

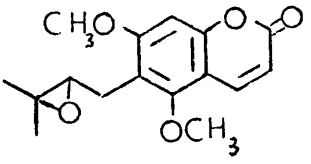
Treatment of the methyl ether (143) with 3,3-dimethylallyl bromide in the usual manner afforded sesibiricin (86). The overall yield by this method was ~37% from the phenol (119) and is comparable with that from the dimethylpropargylation route (~40%).

Synthesis of Toddaculin (87)

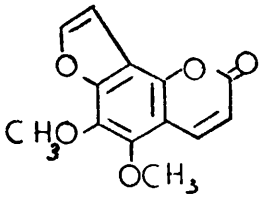
Toddaculin (87) was first isolated by Combes, Pernet and Pierre[64] from the ethanolic extracts of the roots and the trunk bark of Toddalia aculeata Pers. (Rutacea). The chemical constituents of the plant have long been a subject of extensive investigations[101] which have resulted in the isolation of a number



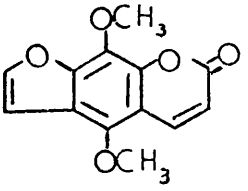
(144) Toddalolactone
(≡ Aculeatin hydrate?)



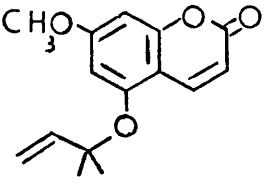
(145)



(146)



(147)

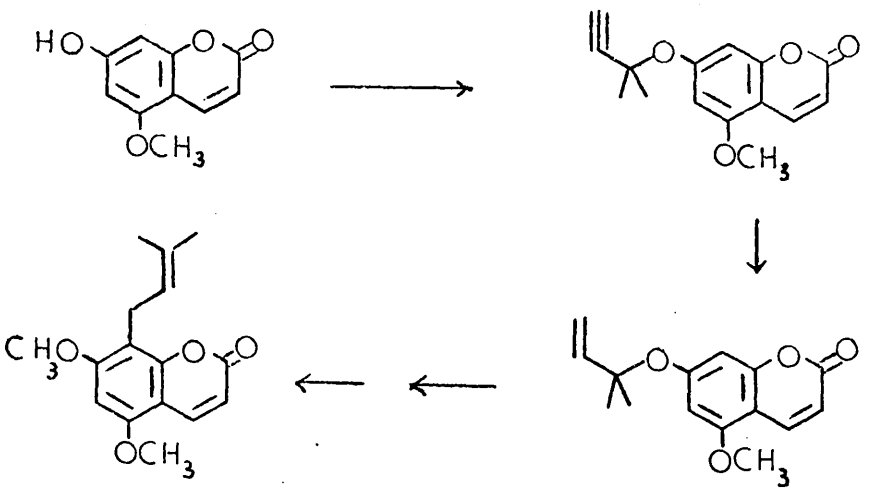


(148)

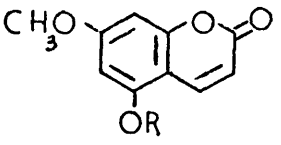
of other coumarins and some alkaloids. As early as 1938, Späth, Dey and Tyray[102] reported the isolation of a vicinal diol toddalolactone (144) and established its structure by chemical degradation. From later studies of the plant extracts, Dutta[66] isolated an epoxycoumarin, aculeatin (145) and the related glycol, aculeatin hydrate reported as having the same structure as toddalolactone (144) but slightly different physical properties. At the present time it is not known whether toddalolactone and aculeatin hydrate are in fact the same compound[54] or, as Combes[64] suggests, optical isomers. Toddaculin (87) is obviously the biogenetic parent of aculeatin (145), aculeatin hydrate, and toddalolactone (144). In the most recent investigation of T. aculeata[101(b)], two furanocoumarins pimpinellin (146) and isopimpinellin (147) have been isolated.

The structure of toddaculin was established by Combes et al[64] as 5,7-dimethoxy-6-(3,3-dimethylallyl) coumarin (87) by spectral evidence and by conversion to aculeatin (145)[66] and toddalolactone (144)[102]. However, the determination of the exact position of an isoprenoid chain in 5,7-dioxygenated coumarins has always proved difficult and an unambiguous synthesis of the parent coumarin toddaculin through Claisen rearrangement of the 1,1-dimethylallyl ether (148) to C-6, would provide an exact structural placement of the isoprenoid group and would also serve as a structural verification for toddaclactone (144) and aculeatin (145). Moreover, the isomer coumurrayin (95) isolated from Murraya paniculata[63,79(a)] has been synthesised

SCHEME 1·12



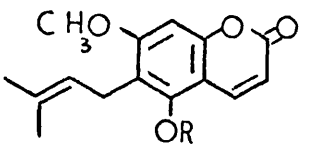
(95) (149)



(142) R = H

(149) R= $C(CH_3)_2C{\equiv}CH$

(148) R= $C(CH_3)_2CH{:}CH_2$



(150) R= H

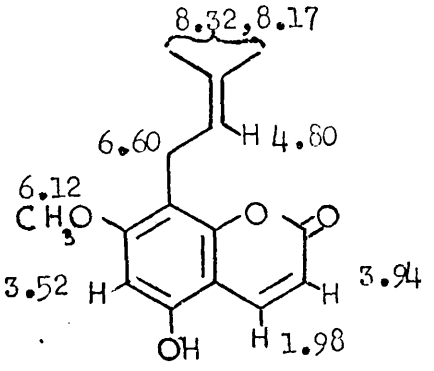
(87) R= CH_3

by Murray et al[58] through rearrangement of the ether (149) (Scheme 1.12) and as an extension to the above method a synthesis of toddaculin (87) was attempted.

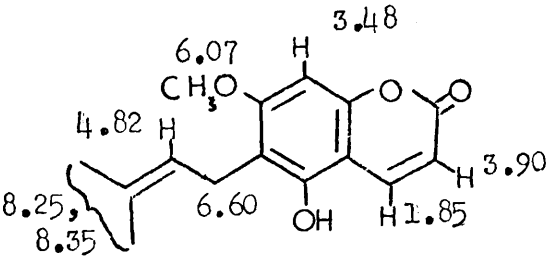
However, at this time, all rearrangements of the 1,1-dimethylallyl ethers at C-7 in 5,7-dioxygenated coumarins[70] were known to rearrange exclusively to C-8 and as a consequence rendered rearrangement to the C-6 useless. Thus, by synthesising the ether (148) it was hoped that ortho migration to C-6 would occur regioselectively.

Hydrolysis of 5-O-(3,3-dimethylallyl) 7-methoxycoumarin (125) afforded the phenol (142) which on treatment with 2-methyl-2-chlorobut-3-yne gave the propargyl ether (149). As before, catalytic hydrogenation yielded the 1,1-dimethylallyloxy ether (148). A small amount of rearrangement of the ether (148) again occurred during purification although rearrangement this time appears less than in the ether (112) used in the sesibiricin synthesis (see p.33).

Pyrolysis at 114° afforded one major phenolic product (identified as a 5-hydroxycoumarin from its u.v. spectrum). The n.m.r. spectrum of this product possesses a 3,3-dimethylallyl unit attached to the benzene ring. From dilution studies of the i.r. spectrum, the product exhibits free and intramolecular hydrogen bonding at 3606 and ~3388 $cm.^{-1}$ consistent with the introduction of the isoprenoid side-chain at C-6 ortho to the 5-hydroxyl. On the basis of the above evidence the product was assigned the structure of 5-demethyltoddaculin (150).

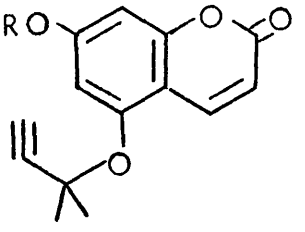


(143)



(150)

Both spectra in d_6 acetone



(151) R= $COCH_3$

(152) R= H

Comparison of the n.m.r. values shown opposite for 5-demethyltoddaculin (150) and 5-demethylcoumurrayin (143) (see p.39) indicates that both structures are virtually identical. However, there are slight differences in the aromatic protons (τ 3.52 and 3.48) and in the C-4 hydrogens of the α -pyrone rings (τ 1.98 and 1.85) in (143) and (150) respectively.

Methylation of (150) afforded toddaculin (87) which was identical in all physical and spectral data with a natural sample[84] kindly provided by Dr. G. Combes.

In this instance, comparing the n.m.r. spectra of toddaculin (87) and coumurrayin (95) shows that in the former the methoxyl signals are split at τ 6.18 and 6.14 whilst in the latter they are identical (τ 6.68). There is also a significant difference in the aromatic protons of (87) and (95) (τ 3.38 and 3.70 respectively).

A more direct, though somewhat less efficient route to the key intermediate (149) in the toddaculin synthesis was established by direct dimethypropargylation of 5,7-diacetoxycoumarin (114). From the complex mixture of products, the acetoxy-ether (151) was isolated in 14% yield. Hydrolysis of this ether (151) gave the phenol (152) which on methylation gave (149) identical in all respects with a synthetic sample (see p41 for synthesis). The complex nature of this reaction and the low overall yield ($\sim$20%) of the desired ether (149) makes this synthetic route less viable.

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 or chloroform as solvent. Routine infra-red spectra were recorded for chloroform solutions on a Unicam SP 1000 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. Nuclear magnetic resonance spectra were recorded by Mrs. S. Hamilton, Mr. A. Haetzman or Mr. J. Gall on 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. 40-60°. 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 /cr 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 500 ml. 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 (20 cm. x 20 cm.) was eluted to a distance of ~10 cm., allowed to dry and then eluted to a distance of ~ 20 cm. from the application line (N.B. x 2≡ 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	: (in n.m.r. spectra)
q.	quartet	:
m.	multiplet	:
b.	broad	:
R.T.	room temperature (~20°)	
w./v.	e.g. 20% w./v. ; this refers to a solution of 20 g. in 100 ml. solvent.	
†	e.g. 100 mg.† ; 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 ;~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 hydroxycoumarin or hydroxychromone was carried out by refluxing an acetone solution of the coumarin or chromone 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 (~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

Ethyl Propiolate [88]

A mixture of propiolic acid (20 g.), dry ethanol (60 ml.) and conc. sulphuric acid (3.3 ml.) was kept at R.T. for 40 hr., then diluted with water (200 ml.) and extracted with ether. The organic layer was washed with dil. sodium carbonate, brine to neutrality and dried. Distillation yielded ethyl propiolate (14 g. ; 50%), b.p. 117-118° (lit.[89] b.p. 119°/745 m.m.).

5,7-Dihydroxycoumarin (92) [88]

Phloroglucinol dihydrate (8.10 g.) ethyl propiolate (7.35 g.) and zinc chloride (6.80 g.) 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 (~750 ml.) and dil. hydrochloric acid (~250 ml.). 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 dihydroxy-coumarin as a light tan solid (6.58 g. ; 74%) m.p. 267-270° decomp. (lit.[88] m.p. 280° decomp.).

5,7-Diacetoxycoumarin (114)

A solution of 5,7-dihydroxycoumarin (6.5 g.) in acetic anhydride (25 ml.) containing 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 (250 ml.) 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 (8.23 g. ; 86%), m.p. 139-140.5° (lit.[88] 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.).

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

Isoprene (B.D.H.) (100 ml. ; 68 g.) and a solution of hydrogen bromide in glacial acetic acid (B.D.H.) (45% w./v. ; 168 ml.) were cooled to ~0° and then mixed. The solution was kept for 3 days at -5°, then diluted with iced water (1500 ml.). The yellowish oil which separated, was washed with iced water and dried over anhydrous calcium chloride. Distillation of this oil at 65-68°/68 mm yielded 3,3-dimethylallyl bromide (108 g. ; 72%).

Dimethylallylation of 5,7-dihydroxycoumarin (92)

Potassium carbonate (1.4 g.) was added to a solution of 5,7-dihydroxycoumarin (1.5 g.) in acetone (100 ml.) and the mixture refluxed for 1 hr. Dimethylallyl bromide (3.7 g.) was then added and the solution refluxed for 3½ hrs. Work up (I) gave an oily solid which was dissolved in a mixture of ethyl acetate and aqueous sodium hydroxide (0.8% w./v.). The organic layer was washed with aqueous sodium hydroxide (0.8% w./v.) 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, dried and evaporated. The residue was crystallised from ether-light

petroleum yielding the bis-ether (115) as colourless needles (1.46 g. ; 55%), m.p. 78-80° (lit.[93] m.p. 79-81°); n.m.r. signals at τ 8.20 (12H ; b.s.), 5.43 (4H ; b.d. ; J 6.5 Hz.), 4.50 (2H ; b.t. ; J 6.5 Hz.), 3.90 (1H ; d. ; J 9.5 Hz.), 3.70 (1H ; d. ; J 2 Hz.), 3.60 (1H ; d. ; J 2 Hz.) and 2.04 (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 only solid obtained (0.7 g.) was separated by preparative t.l.c. (15% ethyl acetate-light petroleum x 3) into:-

(i) the bis-ether (115), a crystalline solid (53 mg.† ; 2%).

(ii) the hydroxy ether (118), an amorphous solid (55 mg. ; 2%); λ_{max} 226 (sh.), 258 (sh.), 264 and 337 nm. (log. 4.18, 3.98, 4.00 and 4.14); λ_{max} (base) 249 (sh.), 280, 396 nm. (log. ε 3.93, 4.00 and 4.25); n.m.r. signals at τ 8.20 (12H ; b.s.), 6.46 (2H ; b.d. ; J 7 Hz.), 5.45 (2H ; b.d. ; J 7 Hz.), 4.62 (2H ; b.m.), 3.90 (1H ; d. ; J 9.5 Hz.), 3.70 (1H ; s.), 2.29* (1H ; b.s.) and 2.00 (1H ; d. ; J 9.5 Hz.).

(iii) 5-O-(3,3-dimethylallyl)-7-hydroxycoumarin (119), from ether as colourless plates (460 mg. ; 23%), m.p. 142-144° (lit.[93] m.p. 143-145°); λ_{max} 248, 256 and 330 nm. (log. ε 3.71, 3.85 and 4.13); λ_{max} (base) 236, 271 and 384 nm. (log. ε 3.80, 3.71 and 4.23); n.m.r. signals at τ 8.27 (3H ; s.), 8.20 (3H ; s.), 5.41 (2H ; b.d

J 6.5 Hz.), 4.52 (1H ; b.t. ; J 6.5 Hz.), 3.85 (1H ; d. ; J 9.5 Hz.), 3.61 (1H ; d. ; J 2 Hz.), 3.37 (1H ; d. ; J 2 Hz.), 2.30° (1H ; b.s.) and 1.94 (1H ; d. ; J 9.5 Hz.).

Dimethylallylation of 5,7-diacetoxycoumarin

Potassium carbonate (2.43 g.) was added to a solution of 5,7-diacetoxycoumarin (1.35 g.) in 1,2-dimethoxyethane (25 ml.) and the mixture stirred at R.T. for 1 hr. Dimethylallyl bromide (2.76g.) was then added and the solution refluxed for 21 hr. More potassium carbonate (0.5 g.) and dimethylallyl bromide (1 g.) were added and refluxing continued for a further 21 hr. Work up (I) gave an oily solid which was separated by preparative t.l.c. (30% ethyl acetate-light petrol x 1) into:-

(i) the bis ether (115), a crystalline solid (165 mg. ; 9%).

(ii) the hydroxy ether (118) as an amorphous solid (43 mg. ; 2%).

(iii) a mixture of the isomeric acetates (116) and (117) as a yellow solid (974 mg. ; 58%). The main isomer 5-O-(3,3-dimethylallyl)-7-acetoxycoumarin (116) was fractionally crystallised from ether-acetone giving fine colourless needles, m.p. 127-129° (Found: C, 66.88 ; H, 5.58. $C_{16}H_{16}O_5$ requires C, 66.66 ; H, 5.59%); $\nu_{max}^{CCl_4}$ (S.P. 100) 1773, 1749, 1623 and 1612 cm.$^{-1}$. (439, 1002, 432 and 540); λ_{max} 211, 240, 248 and 303 n.m. (log.ϵ 4.44, 3.79, 3.76 and 4.18); mass

spectral peaks at m/e 288 (M^+), 220, 178 150, 69, and 41 (r.a. 3, 20, 34, 36, 100 and 96); n.m.r. signals at τ 8.21 (6H ; s.), 7.65 (3H ; s.), 7.32 (1H ; s.), 3.72 (1H ; d. ; J 9.5 Jz.), 3.23 (1H ; s.), 2.84 (1H ; s.) and 2.04 (1H ; d. ; J 9.5 Hz.).

This experiment was repeated using:-

(i) a shorter reflux time (27 hr.). This gave the bis-ether (115) (2%), no C-alkylated ether (118), and the mixture of the isomeric acetates (116) and (117) in 60% yield.

(ii) with acetone as solvent. This gave the bis-ether (6%), the C-alkylated ether (118) (2%), the mixture of isomeric acetates (41%) and starting material 5,7-diacetoxycoumarin (~30%).

Confirmation of structure assigned to the hydroxy-ether (118)

Methylation of the C-alklylated compound (43 mg.†) using methyl iodide (0.5 ml.) and potassium carbonate (56 mg.) in refluxing acetone (4 ml.) gave after 4 hr. an oily methyl ether, which was purified by preparative t.l.c. (15% ethyl acetate-light petroleum x 2) affording 5-O-(3,3 dimethylallyl)-7-methoxy-8-(3,3 dimethylallyl) coumarin (86) as an amorphous solid (34 mg. : 75%). The physical properties (m.p., m.m.p., n.m.r.) of this compound were identical with those of sesibiricin (86) (synthesis p. 57).

Hydrolysis of the isomeric acetates (116) and (117)

The isomeric acetates (116) and (117) (900 mg.) were dissolved in methanol (12 ml.) and sodium bicarbonate (0.3 ml. ; 1% w./v.)

added. A bright orange fluorescence appeared. The solution was then refluxed on a steam bath for 3/4 hr., allowed to cool, and carefully neutralised with dil. hydrochloric acid (~ 1% w./v.). After evaporation of most of the solvent, the residue was diluted with water 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 1), the residue, a mixture of 5-O-(3,3-dimethylallyl)-7-hydroxycoumarin (119) and 5-hydroxy-7-O-(3,3 dimethylallyl) coumarin (120) (ratio 3 : 1) was crystallised from ether as colourless plates (640 mg. ; 77%). The isomers did not fractionally crystallise from ether, nor were they separable by preparative t.l.c.

Confirmation of the structure assigned to (116)

The acetate (116) (32 mg.) was dissolved in methanol (2 ml.), sodium bicarbonate (0.1 ml. ; 1% w./v.) added and the solution refluxed for 1/2 hr. After a similar work up to that above the residue (23 mg. ; 81%) was crystallised from ether as colourless needles. The physical properties (m.p., m.m.p., i.r.) were identical with those of 5-O-(3,3-dimethylallyl)-7-hydroxycoumarin (119).[93]

2-Methyl-2-chloro-3-butyne

Prepared by the method of[94] Hennion and Boisselle. 2-Methyl-3-butyn-2-ol (100 g.) yielded 2-methyl-2-chloro-3-butyne (63 g. ; 52%), b.p. 78-81° (lit.[94] b.p. 73-76°).

5-O-(3,3-Dimethylallyl) 7-O-(1,1-dimethylpropargyl) coumarin (121)

Potassium carbonate (0.42 g.) was added to a solution of a mixture of 5-O-(3,3-dimethylallyl)-7-hydroxycoumarin (119) and its 7-O-(3,3-dimethylallyl)-5-hydroxycoumarin (120) (0.30 g.) in aqueous acetone (3% v./v. ; 25 ml.) and the mixture stirred at R.T. for 30 min. 2-Methyl-2-chloro-3-butyne (2 g.) and potassium iodide (0.16 g.) were added and refluxing continued for a further 12 hr. More potassium carbonate (0.25 g.) and 2-methyl-2-chloro-3-butyne (1.10 g.) were added and refluxing continued for another 6 hr. Work up (I) gave a yellow oil (0.53 g.) which was separated by preparative t.l.c. (15% ethyl acetate-light petroleum x 2) into:-

(i) an unidentified product as an oil (21 mg.).

(ii) a mixture (45 mg.) of (i) and 7-O-(1,1 dimethyl propargyl)-5-O-(3,3-dimethylallyl) coumarin (121).

(iii) the propargyl ether (121), recrystallised from ether-light petroleum to yield colourless needles (262 mg. ; 72%) m.p. 114-116°. (Found : C, 71.05 ; H, 6.59 $C_{19}H_{20}O_4\frac{1}{2}H_2O$ requires C, 71.01 ; H 6.59%) ; $\nu_{max}^{CHCl_3}$ 3295, 1725 and 1610 cm.$^{-1}$; λ_{max} 219 (sh.), 246, 254 and 320 nm. (log. ϵ 3.99, 3.59, 3.57 and 3.93); mass spectral peaks at m/e 312 (M^+), 244, 229, 178, 150, 69 and 41 (r.a. 6, 14, 16, 87, 27, 87 and 100); n.m.r. signals at τ 8.09 (12H ; m.), 7.34 (1H ; s.), 5.43 (2H ; d/d. ; J 6.5 Hz.), 4.54 (1H ; b.t. ; J 6.5 Hz.), 3.86 (1H ; d. ; J 9.5 Hz.), 3.51 (1H ; d. ; J 2 Hz.),

(iv) the isomeric ether (122) crystallised from ether-light petroleum as colourless plates (73 mg. ; 21%) m.p. 84-86° (Found : C, 71.46 ; H 6.32. $C_{19}H_{20}O_4\frac{1}{2}H_2O$ requires C, 71.01 ; H, 6.59%); $\nu_{max}^{CHCl_3}$ 3296, 1720 and 1603 cm.$^{-1}$; λ_{max} 219, 246, 254 and 323 nm. (log ϵ 4.12, 3.79, 3.73 and 4.12); mass spectral peaks at m/c 312 (M^+), 244, 229, 178, 150, 69 and 41 (r.a. 6, 12, 22, 80, 30, 86 and 100%); n.m.r. signals at τ 8.25 (12H ; m.), 7.35 (1H ; s.), 5.46 (2H ; d/d ; J 6.5 Hz.), 4.51 (1H ; b.t. ; J 6.5 Hz.), 3.86 (1H ; d. ; J 9.5 Hz.), 3.52 (1H ; d. ; J 2 Hz.), 3.04 (1H ; d. ; J 2 Hz.) and 2.10 (1H ; d. ; J 9.5 Hz.).

Quinoline-sulphur poison[95]

A mixture of sulphur (1 g.) and commercial quinoline (6 g.) 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, 0.7 ml. of this xylene solution was diluted to 70 ml. with ethyl acetate and used in this diluted form as a partial poison for the catalyst, 5% palladium-barium sulphate.

Reduction of 5-O-(3,3-dimethylallyl)-7-O-(1,1-dimethylpropargyl) coumarin (121)

The propargyl ether (121) (200 mg.) was dissolved in ethyl acetate (~25 ml.) and palladium-barium sulphate catalyst (5% w./w. ; 96 mg.) added. The quinoline-sulphur poison (0.95 ml.) was then syringed into the mixture. After

hydrogenation for 1½ hr. at R.T., the uptake of hydrogen was approximately one mole. The catalyst was filtered off and the solvent evaporated using very little heat. The residue (209 mg.) was separated by preparative t.l.c. (15% ethylacetate-light petroleum x 2) into:-

(i) 5-O-(3,3-dimethylallyl)-7-O-(1,1-dimethylallyl) coumarin (112) as an impure oil (176 mg. ; 88%), n.m.r. signals at τ 8.45 (6H ; s.), 8.23 (3H ; s.), 8.18 (3H ; s.), 5.45 (2H ; d./d. ; J 6.5 Hz.), 4.77 (1H ; d. ; J 18 Hz.), 4.71 (1H ; d. ; J 10 Hz.), 4.50 (1H ; b.t. ; J 6.5 Hz.), 3.88 (1H ; d. ; J 9.5 Hz.), 3.84 (1H ; d./d. ; J 18 10 Hz.), 3.66 (1H ; d. ; J 2 Hz.), 3.42 (1H ; d. ; J 2 Hz.) and 2.02 (1H ; d. ; J 2 Hz.).

(ii) a hydroxy ether (5 mg.† ; 2%) as an amorphous solid m.p. 192-196° (Found: $\nu_{max}^{CHCl_3}$ ~3400 (broad), 1713 and 1616 cm^{-1}; λ_{max} 222 (sh.), 260, 263 and 323 nm. λ_{max} (base) 226, 248, 280 and 396 nm.). This compound has the same chromoplate mobility, staining, i.r. and u.v. as that of 7-demethyl sesibiricin (118) (see p.56).

(iii) 5-O-(3,3-dimethylallyl)-7-hydroxycoumarin (119), from u.v. (4 mg.† ; 2%).

Pyrolysis of 5-O-(3,3-dimethylallyl)-7-O-(1,1-dimethylallyl) coumarin (112)

The allyl ether (112) (120 mg.) was heated for 1¾ hr. at 130° in a sublimation block under partial vacuum. The residue

was separated by preparative t.l.c. (15% ethyl acetate-light petroleum x 1 ; chloroform x 1) into:-

(i) 5-O-(3,3-dimethylallyl)-7-O-(1,1-dimethylpropyl) coumarin (124) as a colourless oil (11 mg. ; 8%) distilled at 145°/.02 mm. (Found: C, 72.46 ; H, 7.43. $C_{19}H_{24}O_4$ requires C, 72.12 ; H 7.65%); $\nu_{max}^{CHCl_3}$ ~ 2970, 1725 and 1608 cm.$^{-1}$; mass spectral peaks at m/e 316 (M^+), 248, 178, 149, 69 and 41 (r.a. 6, 23, 100, 39, 90 and 46%); n.m.r. signals at τ 9.03 (3H ; t. ; 6 Hz.), 8.62 (6H ; s.), 8.22 (2H ; q. ; J 6 Hz.), 8.18 (3H ; s.), 8.23 (3H ; s.), 5.43 (2H ; d./d. ; J 6.5 Hz.), 4.52 (1H ; b.t. ; J 6.5 Hz.), 3.85 (1H ; d. ; J 9.5 Hz.), 3.71 (1H ; d. J2 Hz.), 3.45 (1H ; d. ; J 2 Hz.) and 2.05 (1H ; d. ; J 9.5 Hz.).

(ii) 7-demethylsesibiricin (118) from acetone as colourless needles (91 mg. ; 77%), m.p. 196-198°. (Found : C, 72.48 ; H, 6.85. $C_{19}H_{22}O_4$ requires C, 72.59 ; H, 7.05%); $\nu_{max}^{CHCl_3}$ (S.P. 100) 3597, ~3398 (broad), 1720, 1627 and 1598 cm.$^{-1}$. (ϵ 64, 77, 937, 410 and 1360); λ_{max} 226 (sh.), 258 (sh.), 264 and 337 nm. (log ϵ 4.18, 3.98, 4.00 and 4.14); λ_{max} (base) 226, 249 (sh.), 280 and 396 nm. (log ϵ 4.18, 3.93, 4.00 and 4.25); mass spectral peaks at m/e 314 (M^+), 246, 231, 203, 191, 69 and 41 (r.a. 6, 83, 10, 9, 100, 98 and 40%); n.m.r. signals (d_6-dimethylsulphoxide) at τ 8.35 (3H ; s.),

8.22 (9H ; s.), 6.73 (2H ; d./d. ; J 6.5 Hz.), 5.43 (2H ; d./d. ; J 6.5 Hz.), 4.85 (1H ; b.t. ; J 6.5 Hz.), 4.56 (1H ; b.t. ; J 6.5 Hz.), 3.96 (1H ; d. ; J 9.5 Hz.), 3.60 (1H ; s.) and 2.10 (1H ; d. ; J 9.5 Hz.).

Sesibiricin (86)

Potassium carbonate was added to a solution of 7-demethylsesibiricin (118) (46 mg.) in acetone (~5 ml.) and the mixture stirred at R.T. for 1 hr. Methyl iodide (1 ml.) was then added and the solution refluxed gently for 4 hr. Work up (I) gave a residue which was separated by preparative t.l.c. (15% ethylacetate-light petroleum; chloroform x 1) to yield sesibiricin (86) as a colourless solid which crystallised from ether-light petroleum as colourless needles (39 mg. ; 81%), m.p. 121-122°(lit.[87] m.p. 120-122°) (Found: C, 73.21 ; H, 7.20. Calculated for $C_{20}H_{24}O_4$. C, 73.14 ; H, 7.37%); $\nu_{max}^{CHCl_3}$ (S.P. 100) 1720, 1617 and 1603 cm.$^{-1}$. (ϵ 650, 372 and 1062); ν_{max}^{KBr} 1715, 1617 and 1598 ; λ_{max} 225 (sh.), 255, 261 and 329 nm. (log ϵ 3.18, 3.07, 3.10 and 3.15); mass spectral peaks at m/e 328 (M^+), 260, 245, 220, 191, 69 and 41 (r.a. 6, 26, 64, 23, 22, 100 and 66%); n.m.r. signals at τ 8.33 (3H ; s.), 8.17 (9H ; s.), 6.56 (2H ; d./d. ; J6.5 Hz.), 6.07 (3H ; s.), 5.40 (2H ; d./d. ; J 6.5 Hz.), 4.78(1H ; b.t. ; J 6.5 Hz.), 4.52 (1H ; b.t. ; J 6.5 Hz.), 3.93 (1H ; d. ; J 9.5 Hz.), 3.69 (1H ; s.) and 2.05 (1H ; d. ; J 9.5 Hz.). This compound was shown to be identical with an authentic sample of sesibiricin (m.p., m.m.p., i.r.) kindly provided by Professor Seshardri.[87]

Preparation of 5-O-(3,3-dimethylallyl)-7-methoxycoumarin (125)

A mixture (600 mg.) of 5-O-(3,3-dimethylallyl)-7-hydroxycoumarin (119) and the isomer 5-hydroxy-7-O-(3,3-dimethylallyl) coumarin (120) was methylated using potassium carbonate (709 mg.), methyl iodide (1 ml.) and acetone (~25 ml.). After refluxing for 2 hr., work up (I) gave a yellow oil, which was a mixture of the isomeric methyl ethers (125) and (137) [82% of (125) from n.m.r. integration.] This residue was separated by preparative t.l.c. (15% ethyl acetate-light petroleum x 2) into:-

(i) the methyl ether (125), from ether-light petroleum as colourless needles (139 mg. ; 23%), m.p. 91-94° (lit.[61] m.p. 90-92°), $\nu_{max}^{CHCl_3}$ (S.P. 100) 1726, 1611 and 1567 (weak) cm.$^{-1}$ (ϵ 965, 1650 and 165); n.m.r. signals at 8.22 (3H ; s.), 8.17 (3H ; s.), 6.14 (3H ; s.), 5.42 (2H ; d./d. ; J 6.5 Hz.), 4.50 (1H ; b.t. : J 6.5 Hz.), 3.89 (1H ; d ; J 9.5 Hz.), 3.71 (1H ; d. ; J 2 Hz.), 3.60 (1H ; d. ; J 2 Hz.) and 2.41 (1H ; d. ; J 9.5 Hz.).

(ii) a mixture (345 mg. ; 57%) of the two isomeric ethers (125) and (137) which on fractional crystallisation from ether-light petroleum gave the ether (125) in 72% yield. On trituration of the evaporated mother liquors with ether, the other isomer (137) was obtained as colourless plates (15 mg. : 5%), m.p. 99-102° (lit.[70] m.p. 101-102°) $\nu_{max}^{CHCl_3}$ 1724, 1608 and 1562 (weak) cm.$^{-1}$; n.m.r. signals at τ 8.32 (6H ; b.s.), 6.12 (3H ; s.), 5.44 (2H ; d./d. ; J 6.5 Hz.), 4.50 (1H ; b.t. ;

J 6.5 Hz.), 3.89 (1H ; d. ; J 9.5 Hz.), 3.71 (1H ; d. ; J 2 Hz.), 3.60 (1H ; d. ; J 2 Hz.) and 2.07 (1H ; d. ; J 9.5 Hz.).

5-Hydroxy-7-methoxycoumarin (142)

5-O-(3,3-Dimethylallyl)-7-methoxycoumarin (125) (64 mg.) in methanol (1 ml.) and conc. hydrochloric acid (6 drops) was refluxed for 2 hr. On cooling, the solution was neutralised with dil. sodium carbonate (0.5% w./v.), and most of the solvent evaporated. The residue was diluted with water (10 ml.) and extracted with ethyl acetate. The organic layer was washed with brine, dried, and evaporated to yield 5-hydroxy-7-methoxycoumarin (142) as a yellow solid (47 mg. ; 87%), m.p. 224-228° (lit.[104] m.p. 228-229°); λ_{max} 249, 257 and 327 nm. (log ϵ 3.71, 3.73 and 4.09); λ_{max} (base) 237 (sh.), 270, 325 and 388 nm. (log ϵ 3.80, 3.89, 3.81 and 3.79).

5-hydroxy-7-methoxycoumarin n-butyrate (141)

A solution of 5-hydroxy-7-methoxycoumarin (142) (24 mg.) and n-butyric anhydride (0.25 ml.) in dry pyridine (0.5 ml.) was stirred at R.T. for 2 hr. Work up (II) gave the butyrate (141) (29 mg. 86%) crystallised from ether as colourless plates, m.p. 108-109°, (Found: C, 64.11 ; H, 5.31. $C_{14}H_{14}O_5$ requires C, 64.11 ; H, 5.38%); $\nu_{max}^{CHCl_3}$ 1760, 1728 and 1620 cm.$^{-1}$; λ_{max} 216 (sh.), 243, 353 and 320 nm. (log ϵ 4.40, 3.77, 3.69 and 4.23); mass spectral peaks at m/e 262 (M^+), 192, 164, 71, 69 and 41 (r.a. 14, 100, 34, 52, 7 and 18%); n.m.r. signals at τ 8.93 (3H ; t. ; J 7 Hz.), 8.17 (2H ; sextet ; J 7 Hz.), 7.36 (2H ; t. ; J 7 Hz.), 6.14 (3H ; s.), 3.75 (1H ; d. ;

J 9.6 Hz.), 3.34 (2H ; d. ; J 2 Hz.) and 2.41 (1H ; d. ; J 9.5 Hz.).

Pyrolysis of 5-O-(3,3-dimethylallyl)-7-methoxycoumarin(125)

Oxygen-free nitrogen was passed over a suspension of (125) (70 mg.) in N N-diethylaniline (0.5 ml.) and butyric anhydride (0.2 ml.) for 15 min. The suspension was then shaken at 175±5° for a few minutes until the first formed melt had dissolved. The temperature was maintained at this level for 2 hr. The mixture was then diluted with iced-water (~20 ml.), left at R.T. for 2 hr. and extracted with ethyl acetate. The organic layer was washed with dil. HCl (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. (20% ethyl acetate-light petroleum x 1) into:-

(i) the butyrate (139) as a yellow oil which crystallised from ether as colourless needles (76 mg. ; 86%), m.p. 98-100° (Found: C, 68.90 ; H, 6.78. $C_{19}H_{22}O_5$ requires C, 69.07 ; H, 6.71%); $\nu_{max}^{CHCl_3}$ (S.P. 100) 1763, 1740 (sh.), 1728 and 1614 $cm.^{-1}$ (ϵ 239, 606, 803 and 1264); λ_{max} 218, 250, 258 and 320 nm. (log ϵ 4.06, 3.72 and 4.03); mass spectral peaks at m/e 330 (M^+), 260, 245, 217, 202, 189, 71, 43 and 41 (r.a. 18, 84, 62, 14, 14, 18, 38, 100 and 46%); n.m.r. signals at τ 8.92 (3H ; t. ; J 7 Hz.), 8.32 (3H ; s.), 8.17 (3H ; s.), 8.18 (2H ; sextet ; J 7 Hz.), 7.35 (2H ; t. ; J 7 Hz.), 6.50 (2H ; d. ; J 6.5 Hz.), 6.08 (3H ; s.), 4.78 (1H ; b.t. ; J 6.5 Hz.), 3.77 (1H ; d. ; J 9.5 Hz.)

3.35 (1H ; s.) and 2.40 (1H ; d. ; J 9.5 Hz.).

(ii) 5-hydroxy-7-methoxy n-butyrate (141) as a brown oil (12 mg.† ; 2%) (identified from t.l.c. behaviour).

5-Hydroxy-7-methoxy-8-(3,3-dimethylallyl) coumarin (143)

The butyrate (139) (37 mg.) was dissolved in methanol (3 ml.) and sodium hydroxide (1% w./v. ; 1 ml.) added. The solution turned yellow. After refluxing for 15 min., the solution was carefully acidified with dil. HCl (1% w./v.) and most of the solvent evaporated. The residue was diluted with water (25 ml.) and extracted with ethyl acetate. The organic layer was washed with brine, dried, and evaporated. After preparative t.l.c. (chloroform x 1), crystallisation from methanol yielded (25 mg. ; 86%) the hydroxy methyl ether (143) as colourless needles, m.p. 195-197° (Found: C, 69.17 ; H, 6.30. $C_{15}H_{16}O_4$ requires C, 69.21 ; H, 6.20%); $\nu_{max}^{CHCl_3}$ (S.P. 100) 3599, 1730, 1719 and 1616 cm.$^{-1}$ (ϵ 161, 572, 724 and 125); λ_{max} 223 (sh.), 258 (sh.) 263 and 324 nm. (log ϵ 4.15, 4.08, 4.12 and 4.14); λ_{max} (base) 224, 238, 276, 324 and 399 nm. (log ϵ 4.35, 4.10, 4.18, 3.89 and 3.85); mass spectral peaks at m/e 260 (M^+), 245, 217, 205 and 189 (r.a. 66, 96, 100, 72 and 56%); n.m.r. (d_6-acetone) signals at τ 8.32 (3H ; s.), 8.17 (3H ; s.), 6.76 (1H ; b.s.), 6.60 (2H ; d. ; J 6.5 Hz.), 6.12 (3H ; s.), 4.80 (2H ; b.t. ; J 6.5 Hz.), 3.94 (1H ; d. ; J 9.5 Hz.), 3.52 (1H ; s.) and 1.98 (1H ; d. ; J9.5 Hz.)

The hydroxy methyl ether (143) was converted to sesibiricin (86) in the usual manner, using potassium carbonate, dimethylallyl bromide and acetone. The product obtained was identical[87] in all

respects (n.m.r., i.r., m.m.p.) with sesibiricin.

5-O-(1,1-Dimethylpropargyl)-7-methoxycoumarin (149)

Potassium carbonate (0.71 g.) was added to a solution of 5-hydroxy-7-methoxycoumarin (0.34 g.) in aqueous acetone (3% v./v. ; 25 ml.) and the solution stirred at R.T. for 1 hr. 2-Methyl-2-chloro-3-butyne (3.28 g.) and potassium iodide (0.22 g.) were added and the mixture refluxed for 14 hr. Work up (I) gave a light brown oil which was separated by preparative t.l.c. (development 15% ethyl acetate x 2) into:-

(i) an unidentified product as an oil (30 mg.)

(ii) 5-O-(1,1-dimethylpropargyl)-7-methoxycoumarin (149) crystallised as yellow plates from ether (0.31 g. ; 69%), m.p. 89-91°. (Found: C, 69.60 ; H, 5.47. $C_{15}H_{14}O_4$ requires C, 69.75 ; H, 5.46%); $\nu_{max}^{CCl_4}$ (S.P. 100) 3304, 1746, 1609 and 1564 (weak) $cm.^{-1}$ (ϵ 263, 1660, 2670 and 188); λ_{max} 220 (sh.), 246, 255 and 324 nm. (log ϵ 3.91, 3.61, 3.57 and 3.84); mass spectral peaks at m/e 258 (M^+), 244, 193, 164, 149, 68, 42 (r.a. 16, 58, 94, 100, 31, 66, 66%); n.m.r. signals at τ 8.23 (6H ; s.), 7.32 (1H ; s.), 6.16 (3H ; s.), 3.89 (1H ; d. ; J 9.5 Hz.), 3.55 (1H ; d. ; J 2 Hz.), 3.05 (1H ; d. ; J 2 Hz.) and 2.13 (1H ; d. ; J 9.5 Hz.).

(iii) 5-hydroxy-7-methoxycoumarin (142) identified from u.v. evidence (7 mg. ; 2%).

Reduction of 5-O-(1,1-dimethylpropargyl)-7-methoxycoumarin (149)

The propargyl ether (149) (60 mg.) was dissolved in ethyl

acetate (~25 ml.) and palladium-barium sulphate catalyst (5% w./w. ; 35 mg.) added. The quinoline-sulphur poison (0.33 ml.) (see p.54) was injected and the solution hydrogenated for 2½ hr. at R.T. (uptake of hydrogen approximately 1 mole). The catalyst was filtered off and the solution evaporated carefully.
The residue was separated by preparative t.l.c. (15%-ethyl acetate-light petroleum x 2) into:-

(i) 5-O-(1,1-dimethylallyl)-7-methoxycoumarin (148) as a yellow oil (49 mg. ; 84%) with n.m.r. signals at τ 8.43 (6H ; s.), 6.20 (3H ; s.), 4.76 (1H ; d. ; J 18 Hz.), 4.75 (1H ; d. ; J 10 Hz.), 3.88 (1H ; d./d. ; J 18 Hz. and 10 Hz.), 3.85 (1H ; d. ; J 9.5 Hz.), 3.60 (1H ; d. ; J 2 Hz.), 3.45 (1H ; d. ; J 2 Hz.) and 2.05 (1H ; d. ; J 9.5 Hz.).

(ii) 5-hydroxy-7-methoxycoumarin (142) identified from u.v. evidence (2 mg.; 4%).

Pyrolysis of 5-O-(1,1-dimethylallyl)-7-methoxycoumarin (148)

The allyl ether (148) (35 mg.) was heated for 2 hr. at 114° in a sublimation block under partial vacuum. The residue was separated by preparative t.l.c. (chloroform x 1) into:-

(i) 5-demethyltoddaculin (150) crystallised as colourless plates from ether-acetone (24 mg. ; 70%), m.p. 150-153° (Found: C, 69.02 ; H, 6.04. $C_{15}H_{16}O_4$ requires C, 69.21 ; H, 6.20%); $\nu_{max}^{CHCl_3}$ (S.P. 100), 3606, ~3388 (broad), 1732 (sh.), 1719, 1632 and 1569 $cm.^{-1}$ (ϵ 154, 346, 496,

724, 1122 and 231); λ_{max} 230, 255 and 328 nm. (log ϵ 4.33, 3.78 and 4.23); λ_{max} (base) 226, 273, 336 and 396 nm. (log ϵ 4.45, 4.05, 4.10 and 3.76); mass spectral peaks at m/e 260 (M^+), 245, 217, 205 and 177 (r.a. 52, 14, 8, 100 and 62%); n.m.r. signals (d_6-acetone) at τ 8.35 (3H ; s.), 8.25 (3H ; s.), 6.60 (2H ; d. ; J 6.5 Hz.), 6.07 (3H ; s.), 6.02* (1H ; b.m.), 4.82 (1H ; b.t. ; J 6.5 Hz.), 3.90 (1H ; d. ; J 9.5 Hz.), 3.48 (1H ; s.) and 1.85 (1H ; d. ; J 9.5 Hz.).

(ii) a mixture of two unidentified compounds (6 mg.†).

Toddaculin (87)

5-Demethyltoddaculin (150) (20 mg.) was converted (see sesibiricin p.57) into the methyl ether using potassium carbonate (40 mg.), methyliodide (0.5 ml.) and acetone (~5 ml.). After refluxing for 2 hr., work up (I) yielded toddaculin which crystallised from ether as colourless plates m.p. 93-94° (lit.[64] m.p. 95°); $\nu_{max}^{CCl_4}$ (S.P. 100)1745 and 1611 cm.$^{-1}$ (ϵ 1810 and 1950); $\nu_{max}^{CHCl_3}$ 1743, 1609 and 1378 cm.$^{-1}$; λ_{max} 226, 244, 254 and 328 nm. (log ϵ 4.29, 3.79, 3.68 and 4.19); mass spectral peaks at m/e 274 (M^+), 259, 244, 219, 216 and 188 (r.a. 88, 100, 45, 38, 32 and 29%); n.m.r. signals at τ 8.32 (3H ; s.), 8.22 (3H ; s.), 6.64 (2H ; d. ; J 6.5 Hz.), 6.18 (3H ; s.), 6.14 (3H ; s.), 4.84 (1H ; b.t. ; J 6.5 Hz.), 3.70 (1H ; d. ; J 9.5 Hz.) 3.38 (1H ; s.) and 2.15 (1H ; d. ; J 9.5 Hz.). This compound was shown to be identical with an authentic sample of toddaculin (m.p., m.m.p., i.r.) kindly given by Dr. G. Combes.[64]

Direct dimethylpropargylation of 5,7-diacetoxycoumarin (114)

Potassium carbonate (213 mg.) was added to a warm solution of 5,7-diacetoxycoumarin (211mg.) in aqueous acetone (4% v./v. ; 15 ml.). After stirring for 1 hr., 2-methyl-2-chloro-3-butyne (2.24 g.) and potassium iodide (78 mg.) were added and the reflux continued for another 24 hr. Work up (I) yielded a yellow oil which was separated by preparative t.l.c. (15% ethylacetate-light petroleum x 2) into:-

(i) a mixture of three products (18 mg.).

(ii) 5-O-(1,1-dimethylpropargyl)-7-acetoxycoumarin (152) crystallised as colourless needles from ether-light petroleum (38 mg. ; 14%), m.p. 104-106°. (Found: C, 66.99 ; H, 5.03. $C_{16}H_{14}O_5$ requires C, 67.12 ; H, 4.93%); $\nu_{max}^{CCl_4}$ 3309, 1776, 1751, 1621 and 1614 cm.$^{-1}$ (ϵ 190, 625, 1180, 596 and 588); λ_{max} 238, 248 and 300 nm. (log ϵ 3.77, 3.69 and 4.16); mass spectral peaks at m/e 286 (M^+), 271, 243, 229, 201, 178 and 150 (r.a. 14, 14, 13, 100, 11, 55 and 27%); n.m.r. signals at τ 8.21 (6H ; s.), 7.65 (3H ; s.), 7.32 (1H ; s.), 3.72 (1H ; d. ; J 9.5 Hz.), 3.23 (1H ; s.), 2.84 (1H ; s.) and 2.04 (1H ; d. ; J 9.5 Hz.).

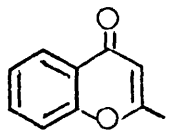
Evidence of the structure of (151).

The acetate (151) (30 mg.) was dissolved in methanol (5 ml.), sodium bicarbonate (0.1 ml. ; 1% w./v.) added and the solution refluxed for $\frac{1}{2}$ hr. After cooling, the solution was carefully acidified with dil. hydrochloric acid ($\sim$1% w./v.) and most of

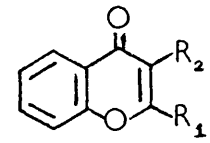
the solvent evaporated. The residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated to yield 5-O-(1,1-dimethylpropargyl)-7-hydroxycoumarin (152) as a yellow solid which did not crystallise (27 mg. ; 95%), m.p. 190-200°; $\nu_{max}^{CHCl_3}$ 3586, ~ 3290 (broad), 3300, 1727, 1613 and 1575 cm.$^{-1}$ (ϵ -, -, 780, 756, 1100 and 195); λ_{max} 221 (sh.), 249, 258 and 327 nm. (log ϵ 4.09, 3.70, 3.60 and 4.09); λ_{max} (base) 225, 235, 273 and 380 nm. (log ϵ 4.29, 4.00, 3.76 and 4.25); mass spectral peaks at m/e 244 (M^+), 229, 178, 150 and 68 (r.a. 18, 46, 100, 92 and 98%); n.m.r. signals (d_6-acetone) at τ 8.23 (6H ; s.), 6.73 (1H ; s.), 3.90 (1H ; d. ; J 9.5 Hz.), 3.54 (1H ; d. ; J 2 Hz.), 2.95 (1H ; d. ; J 2 Hz.) and 2.00 (1H ; d. ; J 9.5 Hz.).

The hydroxy-ether(152) (15 mg.) was methylated using methyl iodide (0.3 ml.), potassium carbonate (20 mg.) and acetone (3 ml.) to yield 5-O-(1,1-dimethylpropargyl)-7-methoxycoumarin identical in all respects (i.r., m.p. and m.m.p.) with a synthetic sample (see p. 62 for synthesis).

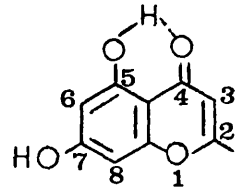
Introduction to Part II



(153)



(154) R_1 = Ph, R_2 = H
(155) R_1 = H , R_2 = Ph



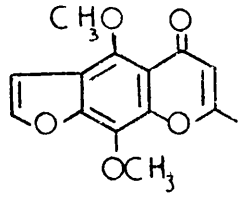
(156)

The chromone nucleus (153), the benzo-homologue of 4-pyrone is widely represented in natural products. A majority of chromones possess a phenyl group at C-2 or C-3 and are generally classified as flavones (154) or isoflavones (155). However, a small remaining group of about forty-five compounds contain a methyl (or hydroxymethyl) group at C-2 and are generally unsubstituted at C-3. These are often regarded as the naturally occurring chromones[54].

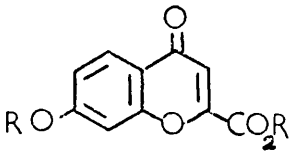
The oxygenation pattern is similar to that of the coumarins (see p. 21), with 5,7-dioxygenated chromones predominating. The chromone nucleus is often substituted in positions 5-8 by methyl or isopentenyl groups, the latter often appearing in a cyclised fashion. A particularly unusual type of cyclisation found in the natural chromones is the seven-membered oxepin ring. Examples of this ring system along with other natural chromones and their origin can be found in Table 2.1.

The occurrence of natural chromones is by no means widespread with no less than twenty-seven being found in five plants and the remainder mainly from fungal metabolites. In all cases, chromones co-occur with other phenolic compounds notably acetophenones, flavanoids and coumarins.

Unlike the coumarins, which have a well established biogenetic route through the shikimate-prephenic acid pathway[54,105], the biogenesis of hydroxylated chromones until recently was largely speculative. Studies[106] have now shown that for 5,7-dihydroxy-2-methylchromone (156) the most plausible route is through the



(157)



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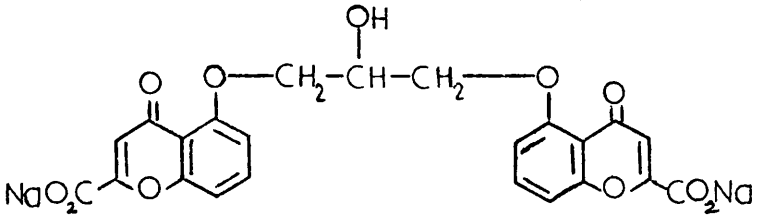
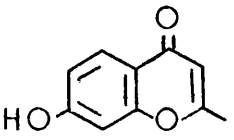
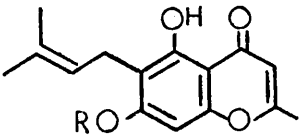


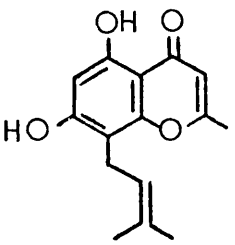
(159)



(163)



(160) R = H
(161) R = CH_3

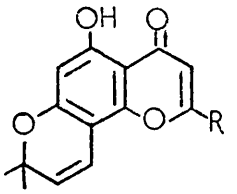
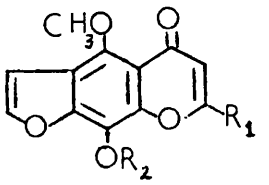
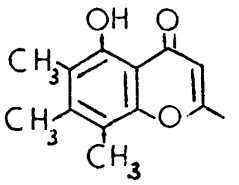
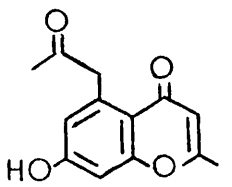
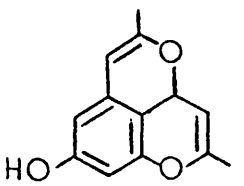
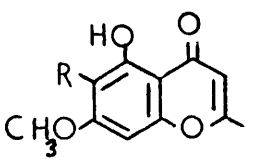


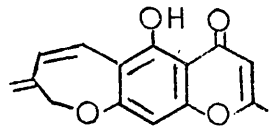
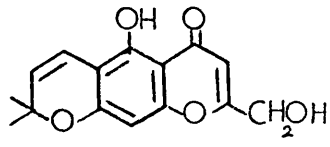
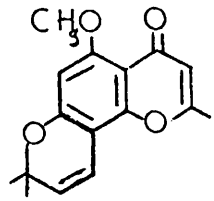
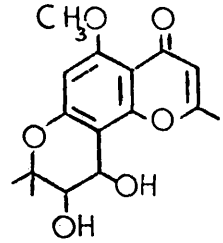
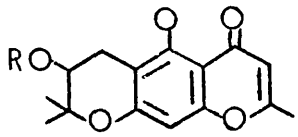
(162)

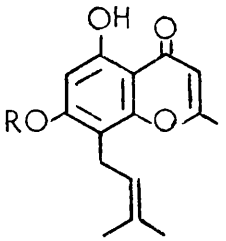
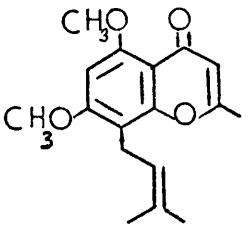
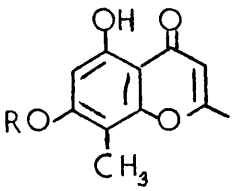
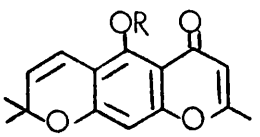
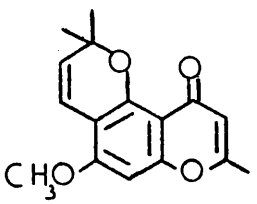
acetate-malonate pathway.

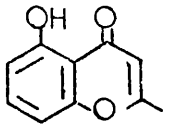
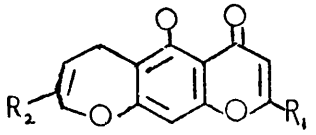
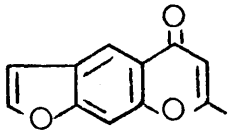
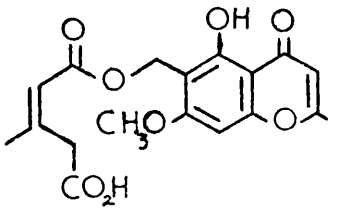
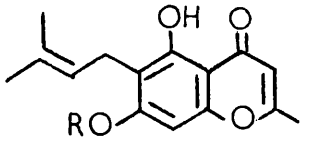
Until 1963 only seventeen natural chromones had been reported[54] and, therefore this class of compound had received relatively little attention. However, an upsurge of interest has resulted from the discovery of the physiological activities[107] of some of the natural chromones. Khellin (157) for example[106], exhibits strong vasodilatory action and has proved useful in the treatment of angina and some circulatory disorders. Moreover, although the natural chromones show only limited therapeutic properties, synthetic chromone derivatives particularly 2-carbethoxychromones (158) have proved extremely effective[108] in the treatment of practically all allergic airway diseases (a term covering the various asthmatic and bronchial disorders). One drug, brand-named Intal developed by Fisons Pharmaceuticals Limited is almost exclusively prescribed by the medical profession for the above disorders. Chemically, the compound is the disodium salt of 1,3-bis (2-carboxychromon-5-yloxy)-2-hydroxypropane (159). Any mild, efficient, synthetic method capable of attaching an alkyl or C-5 unit to the benzenoid portion of the chromone nucleus could effectively enhance the lipid solubility of the molecule. An ideal means of achieving such an insertion would be through Claisen rearrangement of various allyl ethers. Furthermore, by applying the ortho-isopentenyl insertion method developed in this laboratory[58] to 5,7-dihydroxy-2-methylchromone (156) it was hoped to synthesise peucenin (160) and heteropeucenin (162)[109,110]. Thus, studies of the rearrangement of various dimethylallyl ethers of 7-hydroxy-2-methylchromone (163) and its 5,7-dioxygenated analogue (156)

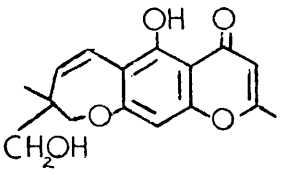
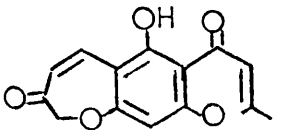
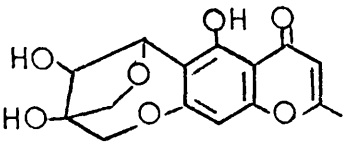
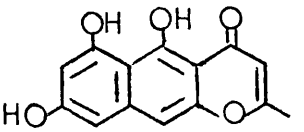
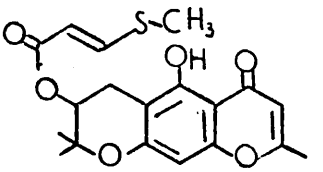
TABLE 2·1

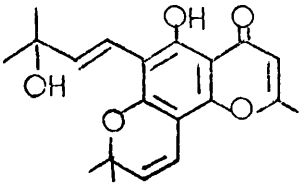
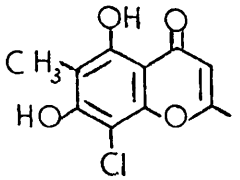
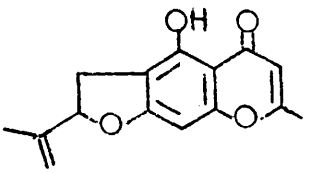
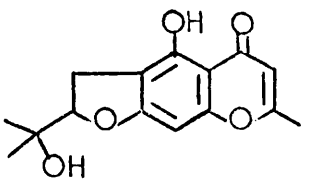
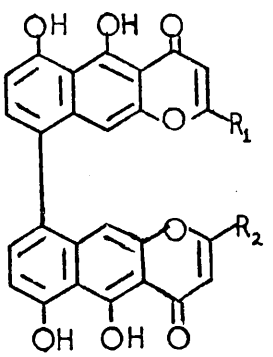
Chromone	Structure	Origin	Ref.
Alloptaeroxylin ($R = CH_3$) Ptaerochromenol ($R = CH_2OH$)		Ptaeroxylon obliquum (Thunb.) Radlk.	110
Ammiol ($R_1 = CH_2OH$, $R_2 = OCH_3$) Visnagin ($R_1 = CH_3$, $R_2 = OCH_3$)		Ammi visnaga	54
Angustifolionol		Backhousia angustifolia Benth.	111
5-Acetonyl-7-hydroxy-2-methylchromone		Cassia siamea	112
Barakol		C. Siamea	113
Eugenetin ($R = CH_3$) Eugenin ($R = H$)		Eugenia caryophyllata Thunbg.	54

Chromone	Structure	Origin	Ref.
Dehydroptaeroxylin		P. Obliquum	110
Greveichromenol		Cedrelopsis grevei	114
Alloptaeroxylin 5-methyl ether		C. grevei	114
Greveiglycol		C. grevei	114
Hamaudol (R = H) Hamaudol acetate (R = $COCH_3$)		Seseli tenuisectum Angelica japonica Libanotis lehmanniana	115 116 117

Chromone	Structure	Origin	Ref.
Heteropeucenin (R = H) Heteropeucenin-7-methyl ether (R = CH_3)		P. obliquum	110
Heteropeucenin-5,7-dimethyl ether		P. obliquum	110
Isoeugenitin (R= CH_3) Isoeugenitol (R = H)		E. caryophyllata	54
Spatheliachromenes A (R = H) B (R = $COCH{:}C(CH_3)_2$) C (R = $CH_2CH{:}C(CH_3)_2$)		Spathelia sorbifolia	118
Isospathelia-7-methoxy-chromene		S. sorbifolia	118

Chromone	Structure	Origin	Ref.
5-Hydroxy-2-methyl-chromone		Daldinia concentrica	119
Karenin (R_1= CH_2OH, R_2= CH_3) Ptaeroxylin (R_1= R_2= CH_3) Ptaeroxylinol (R_1= CH_3, R_2= CH_2OH)		P. obliquum	109 110
Khellin (R_1= R_2= OCH_3) Khellinol (R_1= OH, R_2= OCH_3)		A. visnaga	120
Lepraric acid		Rocella fusiformis	121
Peucenin (R= H) Peucenin-7-methyl ether (R= CH_3)		P. obliquum	109

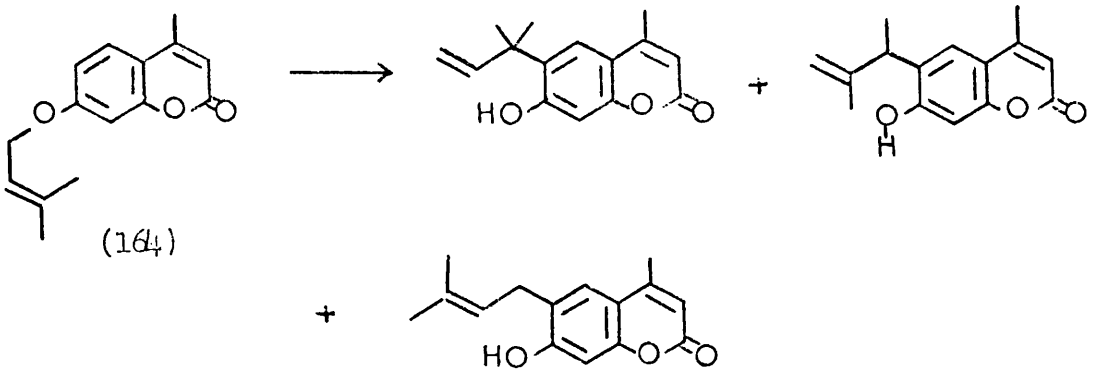
Chromone	Structure	Origin	Ref.
Ptaeroglycol		P. obliquum	110
Ptaeroxylone		P. obliquum	110
Ptaerocyclin		P. obliquum	110
Rubrofusarin (nor)		Fusarium culmorum Sacc.	122
Seselirin		Seseli sessiliflorum	123

Chromone	Structure	Origin	Ref.
Sorbifolin		S. sorbifolia	124
Sordidone		Lecanora sordida (Pers.) Th. Fr.	125
Umtatin		P. obliquum	110
Visamminol		A. visnaga	120
Ustilaginoidin A (R_1=R_2=CH_3) B (R_1=CH_2OH, R_2=CH_3) C (R_1=R_2=CH_2OH)		Ustilaginoidea virens (Cooke) Takahashi	122

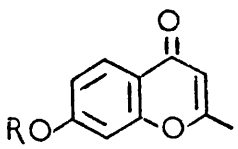
Pyrolyses of 3,3-Dimethylallyl Ethers

(a) 7-Mono-oxygenated Series

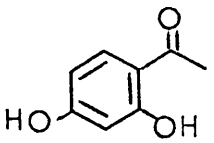
SCHEME 2·1



(164)

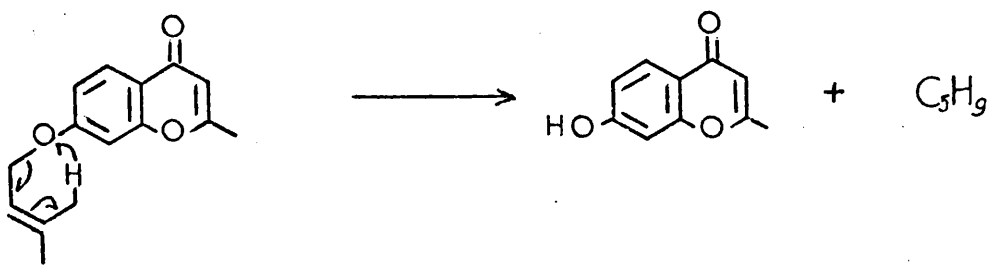


(163) R = H
(165) R = $CH_2CH{:}C(CH_3)_2$



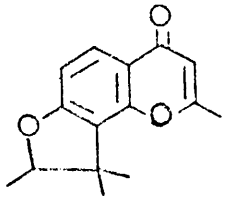
(166)

SCHEME 2·2



A study[93] of the Claisen rearrangement of 7-O-(3,3-dimethylallyl)-4-methyl umbelliferone (164) determined that on thermal pyrolysis a complex mixture of products resulted (Scheme 2.1). The analogous isomer in the chromone series is the 3,3-dimethylallyl ether of 7-hydroxy-2-methylchromone (165). Rearrangement of the ether (165) would provide an interesting product comparison with that of the coumarin series and possibly indicate the preferred direction of migration of the dimethylallyl group, a result particularly useful in future studies in the chromone series.

7-Hydroxy-2-methylchromone (163) was synthesised from 2,4-dihydroxyacetophenone (166) through the Kostanecki acylation[126] procedure with sodium acetate and acetic anhydride. Dimethylallylation resulted in the formation of the ether (165) which was identified from its n.m.r. spectrum which possesses a 3,3-dimethylallyl group attached to oxygen (τ 8.23 ; 6H ; b.s.), (τ 5.42 ; 2H ; b.d. ; J 6.5 Hz.) and (τ 4.66 ; 1H ; b.t., J 6.5 Hz.) and three aromatic protons, two ortho coupled at τ 3.09 and 1.96 (J 9.5 Hz.) and one meta coupled (J 2 Hz.) at τ 3.20. The n.m.r. characteristics of the chromone γ-pyrone nucleus are typical of the series with signals for the C-2 methyl group and the C-3 vinyl proton at τ 7.66 and 3.91 respectively. The vinyl proton signal is slightly broadened by allylic coupling[114] to the C-3 methyl group. In the mass spectrum, cleavage of the C_5H_9 unit through Scheme 2.2 is also indicative of the presence of a 3,3-dimethylallyloxy moiety.

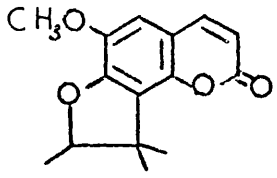


(167)

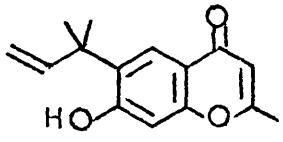
As found in the coumarin series[93], pyrolysis of the ether (165) at 200° resulted in a complex mixture of products. Many of these products (at least eleven as estimated from analytical t.l.c.) were of similar chromatoplate polarity which rendered separation by preparative t.l.c. difficult. However, from the complex mixture five identifiable compounds were isolated.

The major product (20%) has an identical chromatoplate polarity to that of the starting ether (165) and attempted separation by preparative t.l.c. failed. The n.m.r. spectrum of the mixture indicates the signals of a 2,3,3-trimethyl dihydrofuran system[127] and those of the starting ether (165) in the ratio of 2:1. As a means of separation, acid hydrolysis resulted in the cleavage of the 3,3-dimethylallyl group which allowed the mixture of the chromone (163) and the cyclised ether to be separated by preparative t.l.c.

The cyclised ether was assigned the structure (167) from the following evidence. The n.m.r. spectrum possesses two ortho coupled aromatic protons at τ 3.31 and 2.01 (J 9.5 Hz.) and signals for the 2,3,3-trimethyl dihydrofuran system (τ 8.70 ; 3H ; s.), (τ 8.46 ; 3H ; s.), (τ 8.58 ; 3H ; d. ; J 7 Hz.) and (τ 5.56 ; 1H ; q. ; J 7 Hz.) . The chemical shift of the methine proton a τ 5.56 is characteristic of a secondary methyl system on a carbon bearing oxygen while the tertiary methyl resonating at higher field[128] may be that cis to the secondary



(168)



(169)

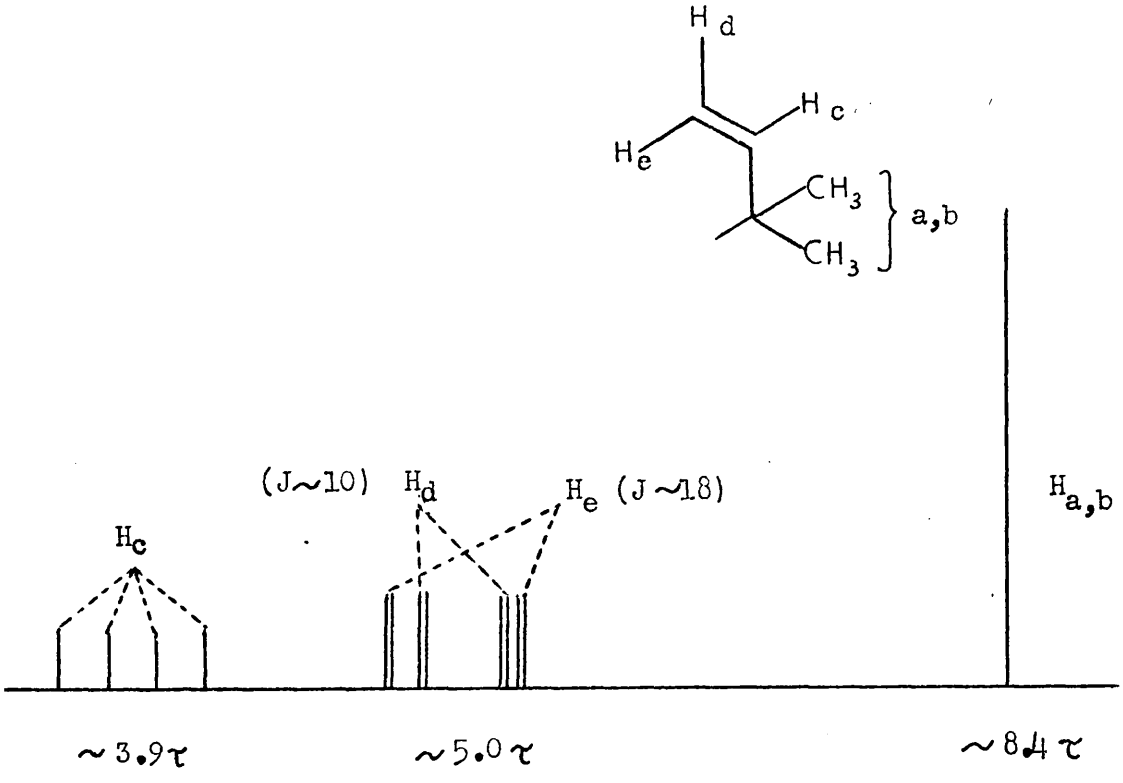
methyl. From this evidence the unit is fused[5',4' ; 7,8] to the chromone nucleus. The remainder of the spectrum indicates the characteristic signals for the 2-methyl-γ-pyrone at τ 7.64 and 3.95. In the coumarin series the 2,3,3-trimethyldihydrofuran unit is present in nieshoutin (168)[127] and comparison of the two n.m.r. spectra show clearly that they have this unit in common.

The second product (3%) isolated from the reaction mixture was obviously phenolic from the evidence of the hydroxyl stretching frequency at ~3400 cm.$^{-1}$ in the i.r. spectrum. However, unlike the cyclised ether (167) the n.m.r. spectrum of this product shows two one proton singlets at τ 3.14 and 1.92 indicating the presence of two <u>para</u> aromatic protons. Moreover, the C-5 unit is now present as an easily recognisable 1,1-dimethylallyl group (Fig. 2.1) with signals for a six proton singlet at τ 8.50 attributable to the gem-dimethyls situated at a carbon which is both allylic and benzylic. The ABX system of the three olefinic protons gives rise to a one proton doublet at τ 4.73 (J_{AX} 10 Hz. ; i.e. <u>cis</u>-coupling) (H_A), a one proton doublet at τ 4.69 (J_{BX} 18 Hz. ; i.e. <u>trans</u>-coupling) (H_B) and a one proton double-doublet at τ 3.74 (J_{AX} 10 Hz. ; J_{BX} 18 Hz.) (H_X). In this system there is usually evidence of J_{AB} coupling in the region of 1 Hz. On the above analysis, the product was assigned the structure (169), the 1,1-dimethylallyl group being inserted at position 6.

The third component (3%) was characterised from its n.m.r. spectrum only. The signal at τ 1.65 disappears on addition of deuterium oxide indicating the presence of a 7-hydroxychromone.

FIG. 2·1

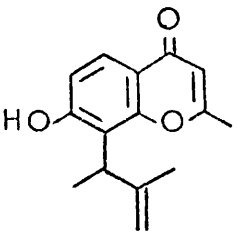
N.m.r. spectrum of a 1,1-dimethylallyl unit attached to a benzenoid ring. (J Hz.)



The two aromatic protons at τ3.09 and 2.05 appear to be ortho coupled (J 9.5 Hz.) and on this evidence the chromone nucleus is possibly substituted at C-8. Besides the C-2 methyl signal at τ 7.58 and the vinyl proton at 3.85 for the 2-methyl- δ -pyrone, the spectrum possess the characteristic resonances of a 1,2-dimethyl allyl group arising from abnormal Claisen rearrangement[27] with signals at (τ 8.48 ; 3H ; d. ; J 7 Hz.), (τ 8.22 ; 3H ; s.), (τ 5.77 ; 1H ; q. ; J 7 Hz.) and (τ 4.78 ; 2H ; b.s.) . The n.m.r. spectrum is consistent with the structure (170) assigned to the product.

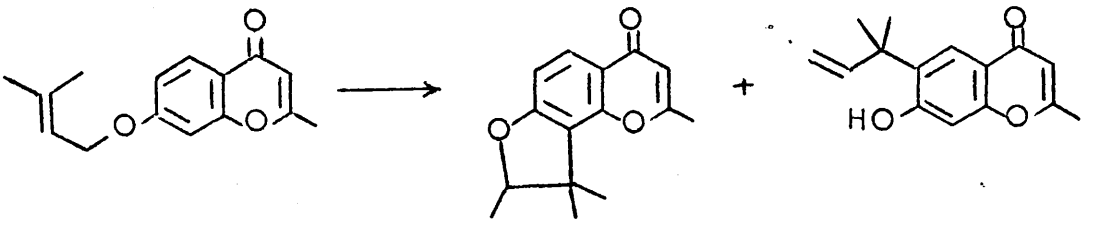
The fourth and last compound isolated from the reaction mixture was identified at 7-hydroxy-2-methylchromone (18%) formed from the cleavage of the isoprene unit.

Scheme 2.3 summarises the results of the pyrolysis and it should be compared with Scheme 2.1 for the analogous coumarin series. There are some obvious differences; all the coumarins isolated were substituted at C-6 whereas two of the products in the chromone rearrangement were C-8 substituted and the other C-6 substituted. Thus, in the 7-mono-oxygenated chromone series it would appear that although competition between the two sites occurs, the preferred site is C-8. Nevertheless, since there are a number of unidentified components in the reaction mixture which could possibly be substituted at C-6, no definite conclusion as to the exact distribution between the two vacant ortho positions can be reached.

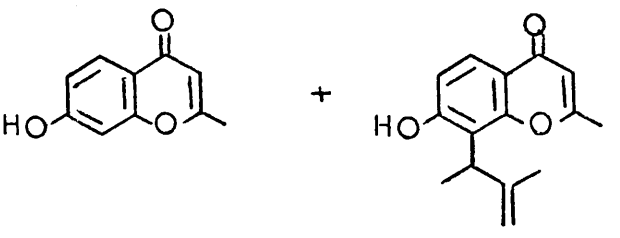


(170)

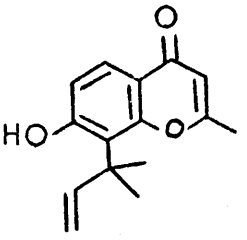
SCHEME 2·3



(165) (167) (169)



(163) (170)

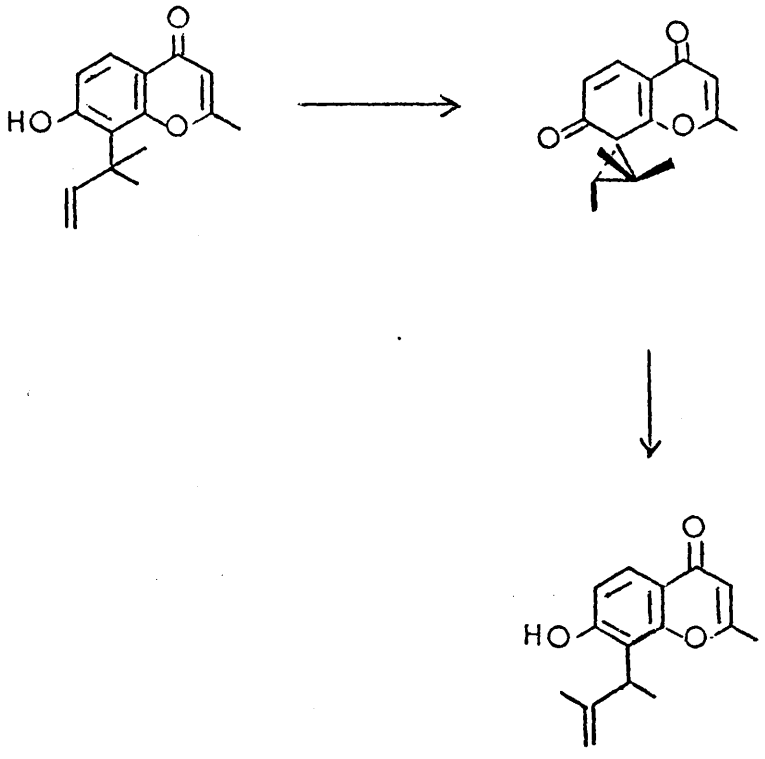


(171)

Both the cyclised ether (167) and the abnormal product (170) are formed from the normal C-8 rearranged product (171) which was not isolated from the pyrolysis. However, some evidence for its presence was revealed through careful examination of the n.m.r. spectrum of the abnormal product (170), which possesses additional signals attributable to a 1,1-dimethylallyl unit substituted at C-8. It appears that the normal product (171) suffers considerable steric strain at this position from the interaction between the gem-dimethyls and the surrounding substituents. As a means of reducing this steric compression, the product either cyclises with the ortho phenol or, through the spirocyclo-octadiene shown in Scheme 24, rearranges to the abnormal product (170). From the ratio of (167) and (170) (20:3), it appears that the rate of cyclisation is faster than that of abnormal rearrangement. The cyclisation process[99] may be thermally induced or catalysed by the acidic phenolic components of the reaction. The abnormal product on the other hand, being less sterically congested, does not appear to cyclise so readily. The C-6 substituted phenol (169) neither rearranges nor cyclises since at this less sterically hindered C-6 position the driving force for both these processes is absent.

The disadvantages of the pyrolyses of 3,3-dimethylallyl ethers have already been discussed in Part I (see p. 27) and it is now quite apparent that such pyrolyses are not only inefficient at substituting C_5-units into the benzene ring (from the amount of cleavage obtained) but result in a complex mixture of products.

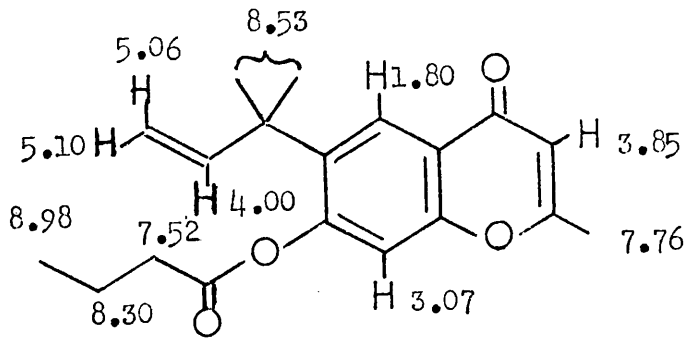
SCHEME 2·4



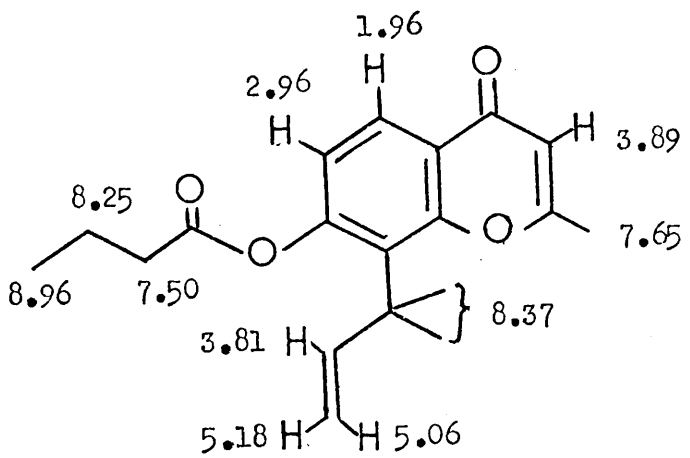
In an attempt to simplify the chromone reaction mixture, the above pyrolysis was repeated in dimethylsulphoxide. This resulted in an altered product ratio but the same complex mass of products.

The use of n- butyric anhydride and N,N-diethylaniline as a media for the Claisen rearrangement has already proved useful in the synthesis of sesibiricin (86) (see p.37), where para rearrangement resulted in the insertion of a 3,3-dimethylallyl group. However, the original intention of this trapping technique[100] was to prevent the occurrence of the abnormal rearrangement of the first-formed ortho-1,1-dimethylallylphenol by esterification and hence, removal of the phenolic proton necessary for the [1,5] homosigmatropic shift (Introduction: see p. 9). By employing this technique in the pyrolysis of the ether (165), it was hoped to trap the normal rearrangement products as butyrates, and consequently isolate a less complex reaction mixture which would perhaps facilitate chromatographic separation. In addition, the results of previous rearrangements showed that cleavage of the isoprene unit in this media only occurred to a small extent ($\sim$ 1-2%).

Pyrolysis of the ether (165) in the presence of butyric anhydride and N,N-diethylaniline at a lower temperature (175°) than that of the neat thermal pyrolysis gave three butyrates. From the n.m.r. spectrum, the first product (10%) appears to possess the structure of the 1,1-dimethylallyl butyrate (172) with the C-5 unit inserted at C-6 indicated by the presence of the


8.53
5.06
H
1.80
O
5.10 H
H 3.85
4.00
8.98
7.52
O
7.76
O
H 3.07
8.30
O

(172)


1.96
H
2.96
O
H
H 3.89
8.25
O
O
7.65
8.96
7.50
8.37
3.81 H
5.18 H
H 5.06

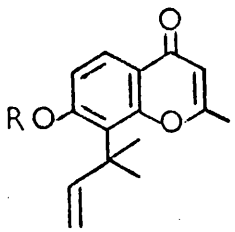
(173)

singlets at τ 3.07 and 1.80 for the two para aromatic protons. The major product of the pyrolysis (68%) possesses an n.m.r. spectrum which is almost identical to the butyrate (172), however, from the presence of the two ortho coupled aromatic protons at τ 2.96 and 1.96 (J 9 Hz.), the product was assigned the structure of the isomeric butyrate (173). A diagramatic comparison of the n.m.r. signals of both the butyrates (172) and (173) is shown opposite.

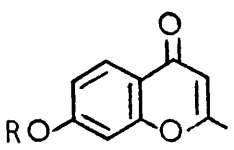
As predicted, a small amount of cleavage occurred with the isolation of the butyrate (174) ($\sim$1%). Comparison with the butyrate synthesised from 7-hydroxy-2-methylchromone (163) showed that both compounds were identical.

The above study confirms that pyrolysis under these conditions certainly furnishes, as a consequence of the ease of separation of the butyrates (172) and (173), and of the less complex reaction mixture, more efficient yields of isolable products. Moreover, the ratio of migration to the vacant ortho positions can now be judged more accurately and the results indicate migration to the C-8 position is favoured.

Hydrolysis of the butyrate (173) was achieved under relatively mild conditions (aqueous 2% w./v. sodium carbonate). However, even under these conditions cyclisation resulted and a mixture of the cyclised ether (167) and the normal phenol (171) resulted. Separation gave the cyclised ether (167) which was identical with that obtained from the thermal pyrolysis. By using a shorter



(173) R = $CO(CH_2)_2CH_3$
(171) R = H
(175) R = CH_3

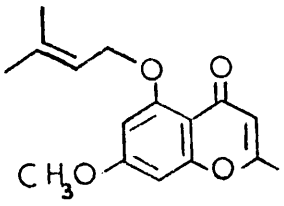


(163) R = H
(174) R = $CO(CH_2)_2CH_3$

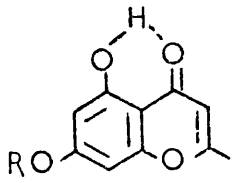
reflux time, only the normal phenol (171) was isolated. The facile nature of cyclisation made characterisation of the phenol (171) difficult. Consequently, it was characterised as its methyl ether (175), all spectral and analytical data being consistent with the proposed structure.

Hydrolysis of the C-6 substituted butyrate (172) under the same conditions afforded the phenol (169) which appeared to be identical with that obtained from the thermal pyrolysis. Unfortunately, poor recovery of this phenol from preparative t.l.c. meant that only a comparison of chromatoplate polarity and staining properties could be made.

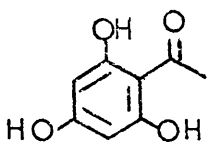
(b) 5,7-Dioxygenated Series



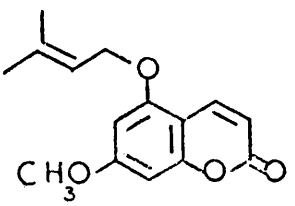
(176)



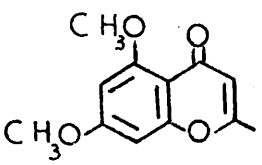
(156) R = H
(177) R = CH_3



(178)



(125)

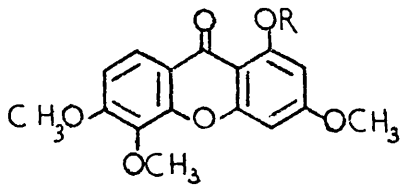


(179)

As an extension to the previous study, an investigation of the Claisen rearrangement of 5-O-(3,3-dimethylallyl)-7-methoxy-2-methylchromone (176) was undertaken. The obvious precursor to the ether (176) is 5,7-dihydroxy-2-methylchromone (156). The 5-hydroxyl grouping in this compound is strongly chelated[129] to the γ-pyrone carbonyl and consequently alters the chemistry of this chromone series considerably. Furthermore in Part I, rearrangement of the coumarin ether (125) provided a route to sesibiricin (86); it would be an interesting comparison to examine the analogous chromone system.

Synthesis of the ether (176) necessitates regioselective methylation and dimethylallylation of 5,7-dihydroxy-2-methylchromone (156). Fortunately, the 5- and 7- position of the dihydroxychromone (156), unlike 5,7-dihydroxycoumarin (114), are not equivalent. The chelated 5-hydroxyl group remains 'protected' by the intramolecular hydrogen bonding and as a result the more acidic 7-hydroxyl becomes the more active substituent.

Thus, diazomethylation of 5,7-dihydroxy-2-methylchromone (156) which was prepared from Kostanecki acylation[126] of phloroacetophenone (178) was expected to generate mainly 5-hydroxy-7-methoxy-2-methylchromone (eugenin) (177). However, mono-methylation to eugenin (177) only partly occurred, the main product being the dimethylated species (179). At first this appeared anomalous, since other stronger methylation procedures such as methyl iodide and dimethyl sulphate[130] normally resulted in a predominance of eugenin (177), indicating that methylation of the 5-position was relatively difficult

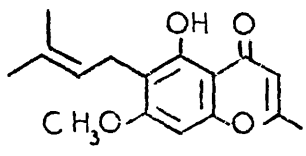


(181) R= $CH_2CH{:}C(CH_3)_2$
(182) R= $CH_2CH{:}CH_2$

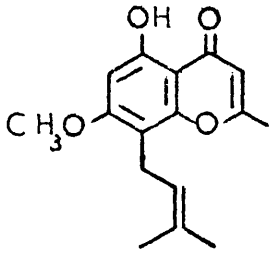
It would appear that the explanation for the ease of methylation at position 5 by diazomethane stems from the particular solvent media used in this case. The dihydroxychromone (156) is relatively insoluble in most organic solvents and for the reaction a mixture of ether and ethanol was needed for homogeneity. The alcoholic media opens the chelate ring of the first formed product eugenin (177) thus promoting a facile methylation of the 5-hydroxyl. This effect has also been observed by Geissman[131] while studying the methylation of ortho-hydroxy ketones. However, selective demethylation[132] of the ether (179) at position 5 with boron trichloride, effectively converted it to eugenin (177).

It would be appropriate at this point to note some of the characteristics exhibited by the chelated 5-hydroxyl group of 5-hydroxychromones. For instance, in the n.m.r. spectrum the hydroxyl proton signal usually appears at low field (τ -2.5) as a singlet in deuterochloroform, which disappears on addition deuterium oxide. In the i.r. spectrum, the appearance of a broad absorption envelope[133] centred around 2970 $cm.^{-1}$ is attributed to the stretching frequency of the strongly[129] chelated 5-hydroxyl. The chelation effect also increases the chromatoplate mobility and as a result 5-hydroxychromones usually appear above the corresponding chromones substituted at C-5 by other groups.

The next step in the synthesis of the ether (176) was that of dimethylallylation of the 5-hydroxyl of eugenin (177). According to previous investigations, the xanthones (181) and (182) were prepared[97] in good yield by the usual conditions of dimethylallyl-



(161)



(180)

bromide, potassium carbonate and acetone. Thus, eugenin (177) was treated in a similar manner. However, no dimethylallylation occurred even after several additions of dimethylallyl bromide and after a reaction time of 72 hr. From the reaction mixture, besides the majority of unconverted starting material two C-alkylated products were isolated in minor yield (1% of each). The first was identified as peucenin-7-methyl ether (161) from comparison with an actual sample. The second, identified again from a synthetic sample[134] was assigned the structure of the C-8 prenylated isomeric ether[134], heteropeucenin-7-methyl ether (180). Small amounts of C-prenylation from the use of this media had already been experienced during the dimethylallylation of 5,7-dihydroxycoumarin (82) (see p. 31).

As the normal dimethylallylation procedure appears to be unsuccessful in this case, an alternative method for the preparation of 5-O-(3,3-dimethylallyl)-7-methoxy-2-methylchromone (176) was investigated. To a suspension of eugenin and sodium hydride in tetrahydrofuran, dimethylallyl bromide was added and the reaction gently heated under nitrogen. Work up gave the required ether (176) in 52% yield which is less than that obtained from the usual method (~70-80%). There were a number of unidentified compounds in this reaction which may arise from C-prenylation.

The n.m.r. spectrum of the ether (176) shows the presence of a 3,3-dimethylallyl group attached to oxygen and no evidence of

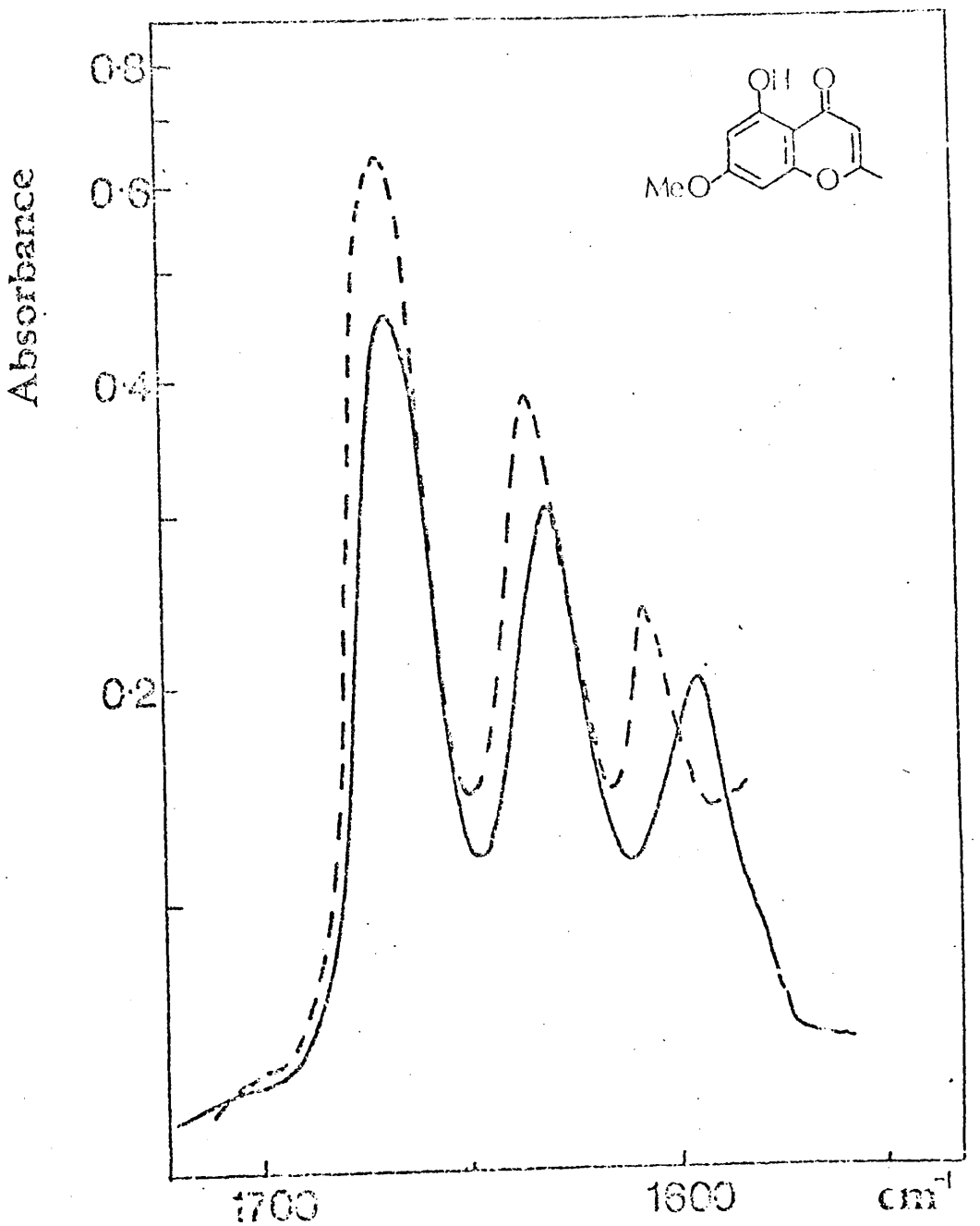


Fig. 2.2

(——) Chloroform soln.

(- - - -) Carbon tetrachloride soln.

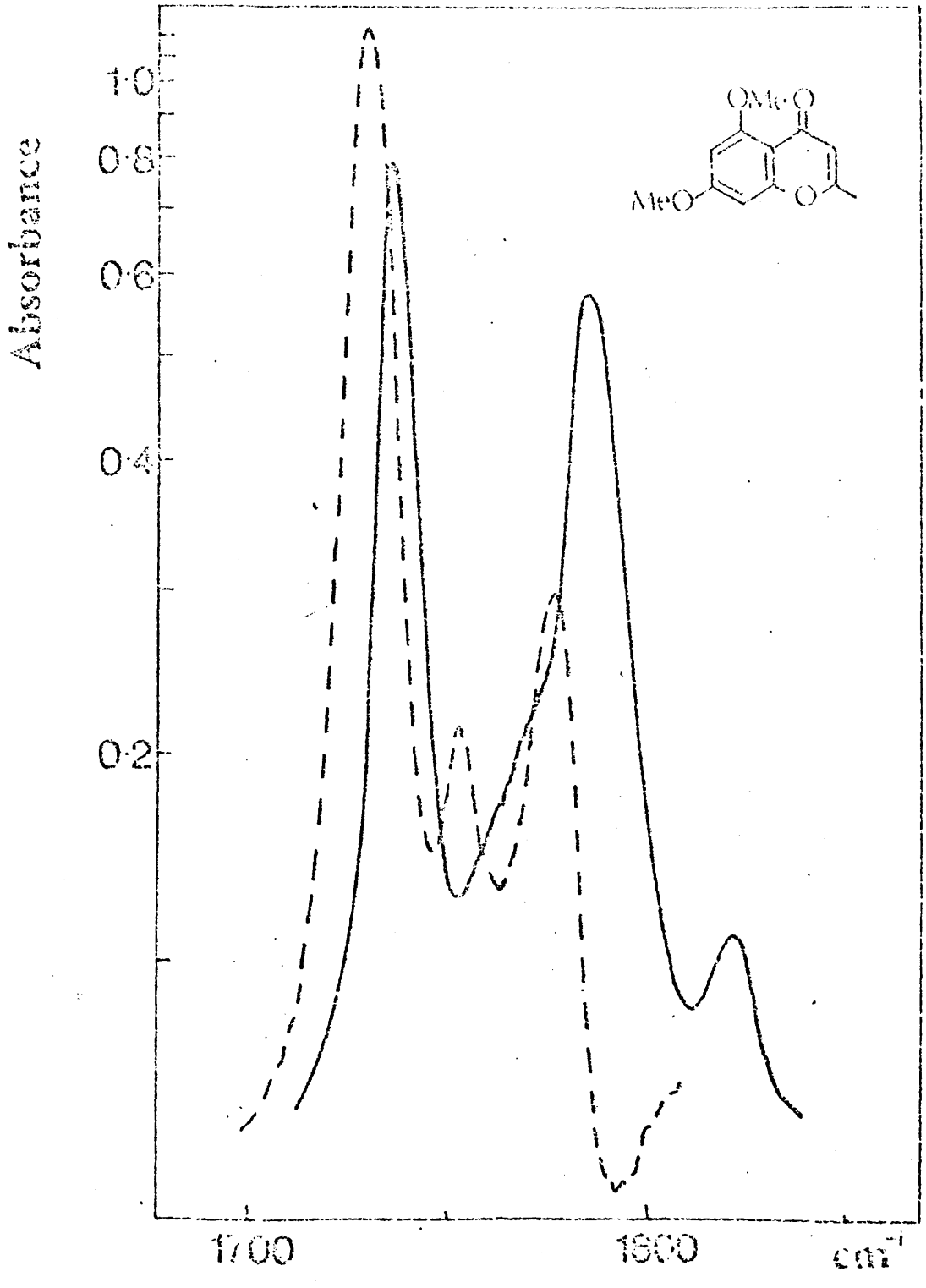
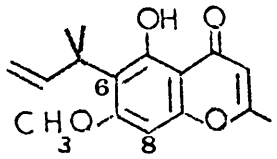


Fig. 2.3

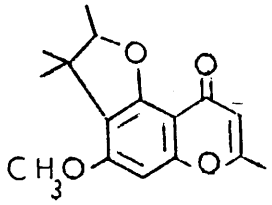
the chelated 5-hydroxyl. The i.r. spectrum of the hydroxyl region shows the absence of any intramolecular hydrogen bonding. Moreover, the spectral profile of the peaks of the carbonyl stretching frequences in the i.r. spectrum provides further evidence that the 5-hydroxyl group is now substituted.

Extensive high resolution i.r. studies of the spectral characteristics of 5-hydroxychromones have already been reported[129,134] from this laboratory. It was found that diagnostically useful contour changes in the i.r. spectral profile of the carbonyl stretching fequencies of 5,7-dioxygenated chromones occurs when substitution of the C-5 hydroxyl takes place. Usually, the γ-pyrone carbonyls of 5-hydroxychromones exhibit complex i.r. spectra showing three main maxima at $\sim$1663, $\sim$1630 and $\sim$1605 cm.$^{-1}$ (spectra recorded in carbon tetrachloride). The two highest absorptions have been shown to possess carbonyl stretching character, the twin peaks arising from Fermi resonance involving a low energy vibrational mode of the carbon-hydrogen bond at C-3. The other maximum at $\sim$1600 cm.$^{-1}$ is probably an aromatic mode.

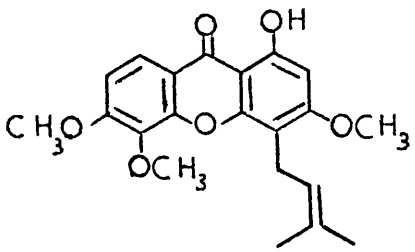
For example the i.r. spectrum of eugenin (177) (Fig. 2.2) shows absorptions at 1660, 1626 and 1590 cm.$^{-1}$, the spectral profile of which is markedly different from that of the 5,7-dimethoxy analogue (179) (Fig. 2.3) which shows only two intense maxima in this region at 1659 and 1574 cm.$^{-1}$ The allyl ether (176) shows a similar spectral pattern as (179) with two absorptions at 1659 and 1609 cm.$^{-1}$



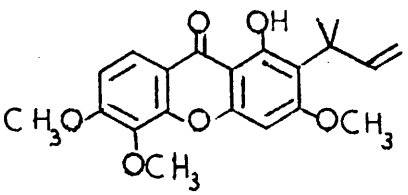
(183)



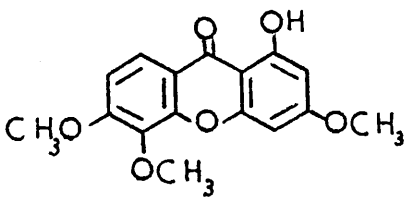
(184)



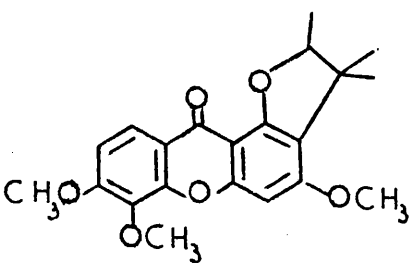
(185)



(186)



(187)



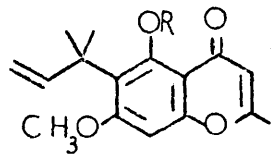
(188)

Thermal pyrolysis of the ether (176) at 200° gave two major products. The first product from the appearance of the characteristic broad absorption envelope at ~2980 cm.$^{-1}$ in the i.r. spectrum contains a chelated 5-hydroxyl. Signals in the n.m.r. spectrum indicates the presence of a 1,1-dimethylallyl unit attached to the benzene ring of the chromone and the resonance at τ -3.50 which disappears on the addition of deuterium oxide provides further evidence of the presence of a chelated 5-hydroxyl. The product was assigned the structure (183) on the assumption that ortho rearrangement of the dimethylallyl ether has occurred.

The major product (87%) of the pyrolysis was assigned the structure (184) mainly from the characteristic signals of the 2,3,3-trimethyldihydrofuran system[127] exhibited by the n.m.r. spectrum. The ether (184) results from cyclisation of the phenol (183) and indicates that ortho rearrangement has indeed occurred.

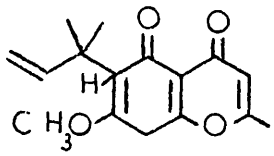
During the study, no evidence of para-rearrangement to position 8 was found. This appears unusual when compared with the results of Jefferson and Scheinmann[97] who found that rearrangement of the xanthone (181) in N,N-diethylaniline gave a 2:1 ratio of the phenols (185) and (186) with only trace amounts of the cleavage product (187) and the cyclised xanthone (188) being detected.

An a matter of comparison, and in order to reduce the amount of cleavage (14%) obtained during thermal pyrolysis, rearrangement of the ether (176) was carried out in n-butyric anhydride and diethylaniline. The results of this pyrolysis confirm the findings of the thermal study in that only ortho rearrangement occurs, the



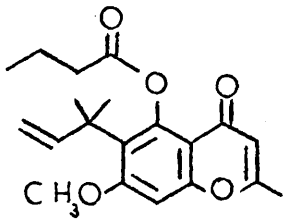
(183) R = H
(189) R = $CO(CH_2)_2CH_3$

SCHEME 2·5



(190)

(183)



(189)

major product being the phenol (183) (41%) which was identical with the sample obtained from the thermal pyrolysis.

The butyrate (189) of the phenol (183) was found at lower chromatoplate polarity and identified from its n.m.r. and i.r. spectrum. Obviously, during the work up facile hydrolysis of the butyrate (189) occurs with regeneration of the chelated system.

From consideration of the results of both the thermal and the butyric anhydride pyrolyses, it would appear the ortho rearrangement to position 6 is the predominant, if not exclusive migration and unlike the coumarin series (see p. 38) no para rearrangement to position 8 occurs. The essential difference in the chromone system compared with that of the 5,7-dioxygenated coumarin series is that enolisation of the first formed ortho-dienone intermediate (190) to the phenol (183) is enhanced by the presence of the γ-pyrone carbonyl (Scheme 2.5). The driving force for this enolisation[97,98] is greater than that for the release of the steric buttressing effect of the gem-dimethyl substituents. Consequently, the required rotamer for Cope rearrangement[2] does not form and the rearrangement halts at the phenol (183).

However, it is difficult to relate these results to those found in the xanthones by Jefferson and Scheinmann[97]. One argument would be that the chelation effect is stronger in 5-hydroxychromones than in 1-hydroxyxanthones (187) and consequently no para rearrangement occurs. This may be borne

out by a number of reactions of 5-hydroxychromones. For example, on applying the normal dimethylallylation procedure to eugenin (177) no ether linkage was formed. Furthermore, in order to achieve dimethylallylation it was necessary to generate the ambident anion by sodium hydride.

Experimental

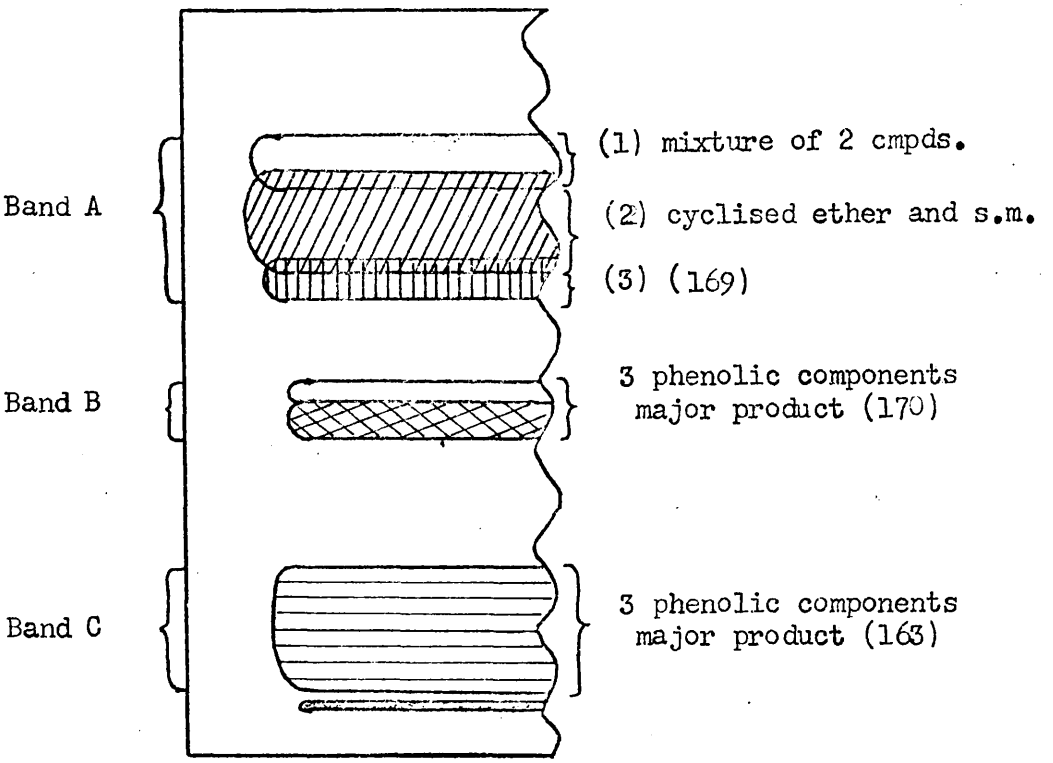
7-Hydroxy-2-methylchromone (163)

2,4-Dihydroxyacetophenone (166) (10 g.) and fused sodium acetate (20 g.) were refluxed for 15 hr. in acetic anhydride (100 ml.). The reaction was poured on to ice, left at R.T. for 2 hr., and extracted with ethyl acetate. After removal of the solvent, the brown residue was refluxed in aqueous sodium carbonate (10% w./v. ; 40 ml.) for 2 hr. Acidification with dil. hydrochloric acid, precipitated a light brown solid which was filtered, and purified by boiling with activated charcoal. Crystallisation from methanol gave 7-hydroxy-2-methylchromone (163) (7.3 g. ; 63%) as light brown plates m.p. 247 - 249° (lit.[135] m.p. 248 - 249°). ν_{max}^{KBr} (S.P. 100) 1651, 1633 (weak), 1614, 1576 (sh.) and 1568 $cm.^{-1}$; λ_{max} 226, 253 and 326 nm. (log ϵ 4.19, 3.99 and 3.55); λ_{max} (base) 236, 260, 295 and 370 nm. (log ϵ 4.20, 3.99, 2.89 and 3.63); mass spectral peaks at m/e 176 (M^+), 148 and 120 (r.a. 100, 57 and 39%); n.m.r. signals (d_6-dimethylsulphoxide) at τ 7.74 (3H;s.), 3.90 (1H ; s.), 3.18 (1H ; s.), 3.12 (1H ; d./d. ; J 9.5 & 2 Hz.), 2.13 (1H ; d./d. ; J 9.5 & 2 Hz.) and -0.70* (1H ; s.).

The 2,4-dihydroxyacetophenone (166) used in this synthesis was prepared by heating resorcinol with zinc chloride and acetic anhydride[136]

Dimethylallylation of 7-hydroxy-2-methylchromone (163)

Potassium carbonate (1.05 g.) was added to a solution of 7-hydroxy-2-methylchromone (0.89 g.) in acetone (200 ml.) and the


Band A
Band B
Band C
(1) mixture of 2 cmpds.
(2) cyclised ether and s.m.
(3) (169)
3 phenolic components
major product (170)
3 phenolic components
major product (163)

mixture stirred at R.T. for 1 hr. Dimethylallyl bromide (1.5 g.) was added and the solution refluxed for a further 40 hr. Work up (I) gave a brown oil which solidified on standing. Crystallisation of this solid from ether-light petroleum yielded pale yellow crystals (0.94 g. ; 74%) of 7-O-(3,3-dimethylallyl)-2-methyl-chromone (165) m.p. 74-76° (Found: C, 73.74 ; H, 6.56. $C_{15}H_{16}O_3$ requires C, 73.75 ; H, 6.60%); $\nu_{max}^{CCl_4}$ (S.P. 100) 1661, 1638 (weak) and 1613 $cm.^{-1}$ (ϵ 1270, 256 and 873); mass spectral peaks at m/e 244 (M^+), 176, 148, 69 and 41 (r.a. 13, 100, 39, 98 and 84%); n.m.r. signals at τ 8.23 (6H ; b.s.), 7.66 (3H ; s.), 5.42 (2H ; b.d. ; J 6.5 Hz.), 4.66 (1H ; b.t. ; J 6.5 Hz.), 3.91 (1H ; s.), 3.20 (1H ; s.), 3.09 (1H ; d./d. ; J 2 & 9.5 Hz.) and 1.96 (1H ; d./d. ; J 9.5 & 2 Hz.).

Pyrolysis of 7-O-(3,3-dimethylallyl)-2-methylchromone (165)

Pyrolysis of the ether (165) (607 mg.) for 2 hr. in a sublimation block at 200° under partial pressure gave an oily solid which was separated by preparative t.l.c. (chloroform x 1) into three main bands (see diagram opposite) which needed further purification:-

(I) Band A (261 mg.) as a mixture of at least four compounds. Further separation of these components by preparative t.l.c. (60% ethyl acetate-light petroleum x 3) gave:-

(i) a mixture (13 mg.) of at least two compounds (from n.m.r. spectrum).

(ii) the cyclised ether (167) and the starting ether (165) as a mixture (206 mg. ; 2:1 ratio from n.m.r. spectrum).

(iii) 7-hydroxy-6-(1,1-dimethylallyl)-2-methylchromone (169) (18 mg. ; 3%) crystallised from ethyl acetate as colourless needles m.p. 202-205° $\nu_{max}^{CHCl_3}$ ~ 3,400 (br.), 1642 and 1605 cm.$^{-1}$; mass spectral peaks at m/e 244 (M^+), 229, 214, 201 and 189 (r.a. 40, 100, 24, 14 and 22%); n.m.r. signals at τ 8.50 (6H ; s.), 7.67 (3H ; s.), 4.73 (1H ; b.d. ; J 10 Hz.), 4.69 (1H ; b.d. ; J 18 Hz.), 3.90 (1H ; s.), 3.14 (1H ; s.), 3.74 (1H ; d./d. ; J 10 and 18 Hz.), 2.68 (1H ; b.s.) and 1.92 (1H ; s.).

Separation of the cyclised ether (167) and the starting material (165)

The mixture (164 mg.) from Band A (ii) was dissolved in methanol, conc. hydrochloric acid (1 ml.) added and the solution refluxed for 1½ hr. After removal of most of the solvent, the residue was extracted with ethyl acetate. The organic layer was washed with aqueous sodium bicarbonate (10% w./v.) and brine, then dried and evaporated. The residue was separated by preparative t.l.c. (chloroform x 1) into:-

(a) the cyclised ether (167) (123 mg. ; 20%) crystallised from ether-light petroleum as colourless needles m.p. 132-135°. (Found: C, 73.69 ; H, 6.47. $C_{15}H_{16}O_3$ requires C, 73.75 ; H, 6.60%); $\nu_{max}^{CHCl_3}$ 1602, 1645 and 1048 cm.$^{-1}$; mass spectral peaks at m/e 244 (M^+), 229, 201, 189 and 173 (r.a. 82, 100, 12, 10 and 14%); n.m.r. signals at τ 8.70 (3H ; s.), 8.58 (3H ; d. ; J 7 Hz.), 8.46 (3H ; s.), 7.64 (3H ; s.), 5.56 (1H ; q. ; J 7 Hz.), 4.77 (1H ; s.), 3.31 (1H ; d. ; J 9.5 Hz.) and 2.01 (1H ; d. ; J 9.5 Hz.).

(b) 7-hydroxy-2-methylchromone (163) identified from t.l.c. staining.

Band B (63 mg.) as a mixture of approximately three phenolic compounds (identified from u.v. evidence). Further separation of the components by preparative t.l.c. (60% ether-light petroleum x 3, chloroform x 1 x $\frac{1}{2}$) gave:-

7-hydroxy-8-(1,2-dimethylallyl)-2-methylchromone (170) (18 mg. ; 3%) as a pale yellow solid; n.m.r. signals at τ 8.48 (3H ; d. ; J 7 Hz.), 8.22 (3H ; s.), 7.58 (3H ; s.), 5.77 (1H ; q. ; J 7 Hz.), 4.78 (2H ; b.s.), 3.85 (1H ; s.), 3.09 (1H ; d. ; J 9.5 Hz.), 2.05 (1H ; d. ; J 9.5 Hz.) and 1.65 (b.s.).

Band C (190 mg.) as a mixture of at least three phenolic compounds. Further separation by preparative t.l.c. and soxhlet extraction (2% methanol-chloroform x 1) gave only one compound, 7-hydroxy-2-methylchromone (163) (75 mg. ; 18%) crystallised from methanol as yellow plates (m.p., m.m.p., u.v. identical with synthetic sample).

Pyrolysis of the ether (165) in dimethylsulphoxide at 159° for 3 hr. gave an altered product ratio (identified from t.l.c. evidence) but the same complex mixture of compounds.

7-O-(n-Butyloxy-2-methylchromone (174)

A solution of 7-hydroxy-2-methylchromone (163) (64 mg.), n-butyric anhydride (0.1 ml.) in dry pyridine (0.2 ml.) was stirred at R.T. overnight. Work up (II) afforded a light-brown oil which was purified by preparative t.l.c. (chloroform x 1) followed by distillation at 90°/.001 mm. On standing, the distillate solidified

to give the required n-butyrate (174) (79 mg. ; 89%) as colourless plates m.p. 73-75° (Found: C, 68.18 ; H, 5.61. $C_{14}H_{14}O_4$ requires C, 68.28 ; H, 5.73%); $\nu_{max}^{CHCl_3}$ 1750, 1659, 1650 and 1611 cm.$^{-1}$; mass spectral peaks at m/e 246 (M^+), 169, 141 and 71 (r.a. 68, 78, 43 and 100%); n.m.r. signals at τ 8.96 (3H ; t. ; J 7 Hz.), 8.20 (2H ; m.), 7.63 (3H ; s.), 7.44 (2H ; t. ; J 7 Hz.), 3.86 (1H ; s.), 2.99 (1H ; d. ; J 2 Hz.), 2.81 (1H ; d./d. ; J 2 and 9 Hz.) and 1.80 (1H ; d. ; J 9 Hz.).

Pyrolysis of the ether (165) in n-butyric anhydride

Oxygen-free nitrogen was passed over a mixture of the ether (165) (472 mg.), N,N-diethylaniline (1 ml.) and n-butyric anhydride (1.5 ml.) for ½ hr. Under a continuous nitrogen flow, the mixture was shaken at 175 ± 5° for 5 minutes to ensure that the first formed melt had gone into solution, then maintained at that temperature for 20 hr. The mixture was diluted with water, left at R.T. for 2 hr. and extracted with ethyl acetate. The organic layer was washed with dil. hydrochloric acid (1% v./v.)to pH 3, aqueous sodium bicarbonate (1% w./v.) to pH 10, brine to neutrality, dried and evaporated to give a brown oil. Purification by preparative t.l.c. (30% ethyl acetate-light petroleum x 4) gave:-

(i) 6-(1,1-dimethylallyl)-7-O-(n-butyloxy)-2-methylchromone (172) (61 mg. ; 10%) crystallised from light petroleum as colourless prisms, m.p. 89-91° (Found: C, 72.57, H, 6.92. $C_{19}H_{22}O_4$ requires C, 72.59 : H, 7.05%); $\nu_{max}^{CHCl_3}$ 1761, 1650 and 1613 cm.$^{-1}$; mass spectral

peaks at m/e 314 (M^+), 243, 228, 200 and 43 (r.a. 22, 44, 100, 27 and 54%); n.m.r. signals at τ 8.98 (3H ; t. ; J 7 Hz.), 8.53 (6H ; s.), ~ 8.30 (2H ; m.), 7.76 (3H ; s.), 7.52 (2H ; t. ; J 7 Hz.), 5.10 (1H ; b.d. ; J 10 Hz.), 5.06 (1H ; b.d. ; J 17 Hz.), 4.00 (1H ; d./d. ; J 10 & 17 Hz.), 3.85 (1H ; s.), 3.07 (1H ; s.) and 1.80 (1H ; s.).

(ii) 8-(1,1-dimethylallyl)-7-O-(n-butyloxy)-2-methylchromone (173) (410 mg. ; 68%) crystallised from ether-light petroleum as colourless plates m.p. 75-77° (Found: C, 72.52 ; H, 6.99. $C_{19}H_{22}O_4$ requires C, 72.59 ; H, 7.05%); $\nu_{max}^{CHCl_3}$ 1754, 1659, 1639 (sh.), 1609 and 1598 $cm.^{-1}$; mass spectral peaks at m/e 314 (M^+), 243, 228, 213 and 200 (r.a. 22, 54, 100, 34 and 16%); n.m.r. signals at τ 8.96 (3H ; t. ; J 7 Hz.), 8.37 (6H ; s.), ~ 8.25 (2H ; m.), 7.65 (3H ; s.), 7.50 (2H ; t. ; J 7 Hz.), 5.18 (1H ; b.d. ; J 10 Hz.), 5.15 (1H ; b.d. ; J 17 Hz.), 3.89 (1H ; s.), 3.81 (1H ; d./d. : J 10 17 Hz.), 2.96 (1H ; d. ; J 9 Hz.) and 1.96 (1H ; d. ; J 9 Hz.).

(iii) 7-O-(n-butyloxy)-2-methylchromone (174) (41 mg. ; ~1%) identified from u.v. and t.l.c. evidence.

Attempted hydrolyses and methylation of the n-butyrate (173)

(a) The n-butyrate (173) (61 mg.) in methanol (2 ml.) and aqueous sodium carbonate (5 ml. ; 2% w./v.) was refluxed on a steam-bath for ½ hr. The solution was allowed to cool, carefully

neutralised with dil. hydrochloric acid (~1% v./v.) and most of the solvent evaporated. The residue was diluted with water (20 ml.) and extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated. Preparative t.l.c. (40% ethyl acetate-light petroleum x 3) gave :-

(i) the cyclised ether (167) (19 mg. ; 40%) crystallised as colourless needles from ether-light petroleum identical (m.p., m.m.p., and n.m.r.) with the compound obtained from the thermal pyrolysis. (see p. 85).

(ii) 7-hydroxy-8-(1,1-dimethylallyl)-2-methylchromone (171) (25 mg. ; 53%) as an impure oil with n.m.r. signals at τ 8.32 (6H ; s.), 7.64 (3H ; s.), 4.80 (1H ; b.d. ; J 10 Hz.), 4.75 (1H ; b.d. ; J 17 Hz.), 3.91 (1H ; s.), 3.56 (1H ; d./d. ; J 10 & 17 Hz.), 3.10 (1H ; d. ; J 9 Hz.), 2.16 (1H ; s.) and 2.06 (1H ; d. ; J 9 Hz.).

Methylation of (171) with acetone, potassium carbonate (57 mg.) and methyl iodide (1 ml.), followed by work up (I) gave 7-methoxy-8-(1,1-dimethylallyl)-2-methylchromone (175) (21 mg. ; 81%) crystallised from ether-light petroleum as colourless plates m.p. 63-66° (Found: C, 74.66 ; H, 6.95. $C_{16}H_{18}O_3$ requires C, 74.39 ; H, 7.02%); $\nu_{max}^{CHCl_3}$ 1648, 1601 and 1408 $cm.^{-1}$; mass spectral peaks at m/e 258 (M^+), 243, 228, 213, 200 and 189 (r.a. 74, 100, 14, 21, 47 and 25%); n.m.r. signals at τ 8.36 (6H ; s.), 7.68 (3H ; s.), 6.13 (3H ; s.), 5.68 (1H ; b.d. ; J 10 Hz.), 5.16 (1H ; b.d. ; J 10 Hz.), 3.94 (1H ; s.), 3.75 (1H ; d./d. ; J 10 & 17 Hz.), 3.05 (1H : d. J 9 Hz.) and 1.94 (1H ; d. ; J 9 Hz.).

No cyclised ether was detected when the n-butyrate (173) was heated gently at 60° for 15 min. in methanol (2 ml.) and aq. sodium carbonate (2 ml. ; 2% w./v.). Work up (I) yielded the phenol (171) which was methylated by the above procedure.

5,7-Dihydroxy-2-methylchromone (156)

Phloroacetophenone (178) (20 g.) and fused sodium acetate (19 g.) were refluxed for 18 hr. in acetic anhydride (170 ml.). The reaction was poured on to ice, left at R.T. overnight, and extracted with ethyl acetate. The organic layer was washed with aqueous sodium carbonate (satd. solution), brine to neutrality, dried and evaporated to give a brown solid. This residue was then refluxed in aqueous sodium carbonate (satd. solution) for $2\frac{3}{4}$ hr. Acidification with dil. hydrochloric acid precipitated a dark brown solid (9.2 g. ; 40%) which crystallised from methanol as dark brown plates, m.p. 282-286° (lit.[137] m.p. 290°). Due to the insolubility of this compound, it was characterised after methylation (vide infra).

5-Hydroxy-7-methoxy-2-methylchromone (177)

5,7-Dihydroxy-2-methylchromone (156) (1.07 g.) in ethanol was reacted with an excess of ethereal diazomethane for 40 hr. The polymethylene formed was removed by filtration through Celite-625. After evaporation of the solvent to dryness, the crude product was separated by preparative t.l.c. (chloroform x 1) into:-

(i) 5-hydroxy-7-methoxy-2-methylchromone (eugenin) (177) (147 mg. ; 14%) crystallised from ether as pale yellow needles, m.p. 118-119° (lit.[138] m.p. 120°); $\nu_{max}^{CHCl_3}$ ~ 3300, 1660, 1626 and 1590 $cm.^{-1}$; n.m.r. signals at τ 7.70 (3H ; s.), 6.15 (3H ; s.), 3.98 (1H ; s.), 3.34 (2H ; s.) and -2.70 (1H ; s.).

(ii) 5,7-dimethoxy-2-methylchromone (179) (672 mg. ; 55%) crystallised from ether as pale yellow needles m.p. 122-124° (lit.[138] m.p. 124°); n.m.r. signals at τ 7.74 (3H ; s.), 6.14 (3H ; s.), 6.09 (3H ; s.), 4.02 (1H ; s.), 3.71 (1H ; d. ; J 2 Hz.) and 3.62 (1H ; d. ; J 2 Hz.)

To a methylene chloride solution of 5,7-dimethoxy-2-methylchromone (179) (640 mg.), boron trichloride in methylene chloride (1 ml. ; 25% w./v.) was added and the solution stirred at R.T. for 20 min. Water (10 ml.) was added and the resulting precipitate filtered off. The filtrate was washed with brine to neutrality, dried and evaporated to yield a light tan solid which crystallised from methanol to give yellow plates of 5-hydroxy-7-methoxy-2-methylchromone (177) (467 mg. ; 85%).

Attempted preparation of 5-O-(3,3-dimethylallyl)-7-methoxy-2-methylchromone (176)

Method A

Potassium carbonate (439 mg.) was added to a solution of 5-hydroxy-7-methoxy-2-methylchromone (320 mg.) in acetone ($\sim$ 20 ml.) and the mixture stirred at R.T. for 2 hr. Dimethylallyl bromide (749 mg.) and potassium iodide (34 mg.) were added and the solution refluxed for 72 hr. Work up (I) gave an oil which was separated by preparative t.l.c. (20% ethyl acetate-light petroleum x 2) into:-

(i) peucenin-7-methyl ether (161) (43 mg. ; 1%) crystallised from ether-light petroleum as colourless needles, m.p.

107-110° (lit.[110] m.p. 108-109°). This compound was identical (m.p., m.m.p., u.v. and i.r.) with a natural sample kindly provided by Dr. P.H. McCabe.

(ii) heteropeucenin-7-methyl ether (180) (42 mg. ; 1%) from ether-light petroleum as colourless needles, m.p. 105-107° (lit.[110] 110°). The compound was identical (m.p., m.m.p. and u.v.) with a synthetic sample (see p.119).

(iii) 5-hydroxy-7-methoxy-2-methylchromone (177) (269 mg. ; 88%).

Method B

5-Hydroxy-7-methoxy-2-methylchromone (177) (306 mg.) in tetrahydrofuran (10 ml.) was added dropwise under nitrogen to a stirred suspension of sodium hydride in tetrahydrofuran (~4 ml.) at 0°. The reaction was stirred at R.T. for 24 hr. Dimethylallyl bromide (780 mg.) was then added and the mixture heated at 50° for 23 hr. After the careful addition of water, most of the solvent was evaporated and the remainder extracted with ethyl acetate. The organic layer was separated, washed with brine to neutrality, dried and evaporated. The residue was separated by preparative t.l.c. (chloroform into:-

(i) an oil (~30 mg.) comprising of at least three compounds (identified from t.l.c. evidence).

(ii) 5-O-(3,3-dimethylallyl)-7-methoxy-2-methylchromone (176) (212 mg. ; 52%) crystallised from ether as colourless plates, m.p. 78-80° (Found: C, 70.11 ; H, 6.37. $C_{16}H_{18}O_4$ requires C, 70.05 ; H, 6.61%); $\nu_{max}^{CHCl_3}$ 1659 and 1609 $cm.^{-1}$; mass spectral peaks at m/e 274 (M^+),

259, 206 and 178 (r.a. 23, 30, 100 and 91%); n.m.r. signals at τ 8.23 (6H ; s.), 7.84 (3H ; s.), 6.14 (3H ; s.), 5.02 (2H ; b.d. ; J 7 Hz.), 4.61 (1H ; b.t. ; J 7 Hz.), 4.06 (1H ; s.), 3.74 (1H ; d. ; J 2 Hz.) and 3.66 (1H ; d. ; J 2 Hz.).

Pyrolyses of 5-O-(3,3-dimethylallyl)-7-methoxy-2-methylchromone (176)

Thermal Pyrolysis

The dimethylallyl ether (176) (114 mg.) was pyrolysed in a sublimation block at 200° for 1½ hr. under partial pressure. On cooling, the residue was separated by preparative t.l.c. (chloroform x 1) into:-

(i) an unidentified brown solid (~5 mg.).

(ii) 5-hydroxy-7-methoxy-6-(1,1-dimethylallyl)-2-methylchromone (183) (20 mg. ; 18%) crystallised from ether-light petroleum as colourless needles, m.p. 90-91°. (Found: C, 69.92 ; H, 6.79. $C_{16}H_{18}O_4$ requires C, 70.05 ; H, 6.61%); $\nu_{max}^{CCl_4}$ (S.P. 100) ~ 2980, 1666, 1615 and 1606 cm.$^{-1}$ (ε 60, 1580, 600 and 670); λ_{max} 210, 233, 254, 259 and 293 nm. (log. ε 3.53, 3.44, 3.31, 3.33 and 3.02); λ_{max} (base) 214, 233, 253, 260 and 290 nm. (log. ε 3.46, 3.33, 3.29, 3.30 and 2.98); mass spectral peaks at m/e 274 (M^+), 259, 244, 231 and 219 (r.a. 34, 100, 31, 43 and 34%); n.m.r. signals at τ 8.41 (6H ; s.), 7.66 (3H ; s.), 6.22 (3H ; s.), 5.20 (1H ; b.d. ; J 10 hz.), 5.16 (1H ; b.d. ; J 17 Hz.), 4.00 (1H ; s.), 3.72 (1H ; d./d. ; J 10 & 17 Hz.), 3.69

(1H ; s.) and -3.50 (1H ; s.).

(iii) 5-hydroxy-7-methoxy-2-methylchromone (177) (12 mg. ; 14%)(identified from u.v. evidence).

(iv) the cyclised ether (184) (65 mg. ; 57%) crystallised from ether as colourless needles, m.p. 146-148°. (Found: C, 70.33 ; H, 6.30. $C_{16}H_{18}O_4$ requires C, 70.05 ; H, 6.11%); $\nu_{max}^{CHCl_3}$ 1648 and 1606 $cm.^{-1}$; mass spectral peaks at m/e 274 (M^+), 259, 231 and 43 (r.a. 29, 100, 24 and 21%); n.m.r. signals at τ 8.82 (3H ; s.), 8.58 (3H ; s.), 8.55 (3H ; d. ; J 6.5 Hz.), 7.74 (3H ; s.), 6.12 (3H ; s.), 5.45 (1H ; q. ; 6.5 Hz.), 4.05 (1H ; s.) and 3.70 (1H ; s.).

Pyrolysis in n-butyric anhydride and N,N-diethylaniline

Using a similar procedure to that for 7-O-(1,1 dimethylallyl)-2-methylchromone (163) (see p.8), the ether (176) (70 mg.) in N,N-diethylaniline (0.5 ml.) and n-butyric anhydride (0.1 ml.) was heated at 170 5° for 6 hr. under oxygen-free nitrogen. The work up employed on p. 88 gave a brown oil contaminated with a small amount of N,N-diethylaniline. This was removed by distillation at 150°/0.001 mm. The residue was separated by preparative t.l.c. (20% ethyl acetate-light petroleum x 1) into:-

(i) 5-hydroxy-7-methoxy-6-(1,1-dimethylallyl)-2-methylchromone (183) (29 mg. ; 41%) crystallised from ether-light petroleum as colourless needles, m.p. 88-90°. This compound was identical with the synthetic sample isolated from the thermal pyrolyses (see p.95).

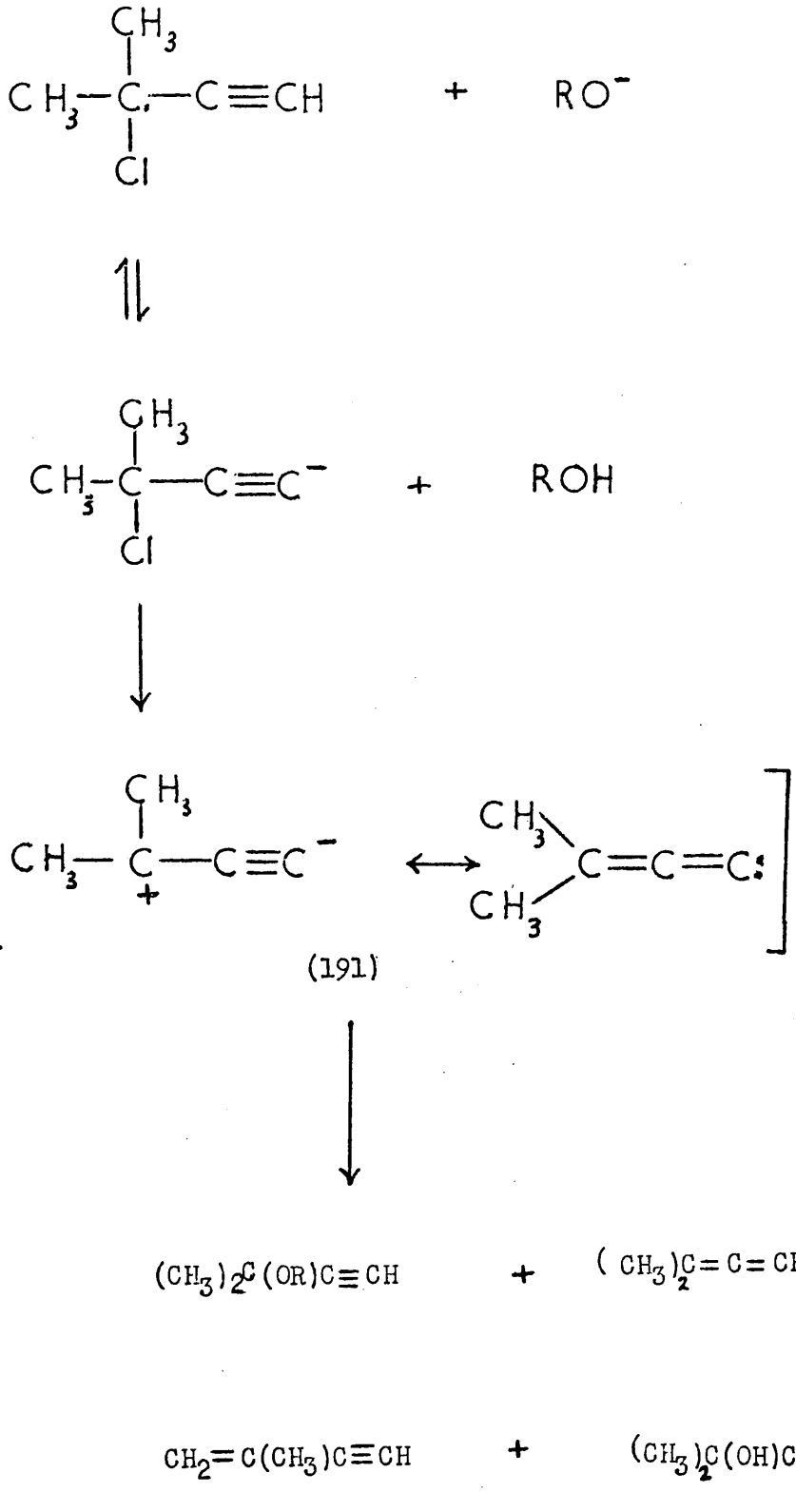
(ii) 5-O-(n-butyloxy)-7-methoxy-6-(1,1-dimethylallyl)-2-methylchromone (189) (19 mg. ; 22%) crystallised from ether-light petroleum as colourless prisms, m.p. 75-80°; $\nu_{max}^{CCl_4}$ 1768, 1662 and 1605 cm.$^{-1}$; mass spectral peaks at m/e 314 (M^+), 273, 258, 243, 230, 215 and 204 (r.a. 13, 75, 100, 78, 81, 79 and 90%); n.m.r. signals at τ 8.97 (3H ; t. ; J 7 Hz.), 8.48 (6H ; s.), 8.26 (2H ; b.m. ; J 7 Hz.), 7.74 (3H ; s.), 7.30 (2H ; t. ; J 7 Hz.), 6.14 (3H ; s.), 5.23 (1H ; d. ; J 11 Hz.), 5.16 (1H ; d. ; J 17 Hz.), 4.06 (1H ; s.), 3.90 (1H ; d./d. ; J 11 and 17 Hz.) and 3.20 (1H ; s.).

(iii) starting chromone (177) (3 mg.; 4%) identified from t.l.c. behaviour.

Pyrolyses of the 1,1-Dimethylallyl Ethers

(a) 7-Mono-oxygenated Series

SCHEME 2·6


CH3
CH3—C—C≡CH
Cl
+
RO⁻
CH3
CH3—C—C≡C⁻
Cl
+
ROH
CH3
CH3—C—C≡C⁻
+
CH3
CH3
C=C=C:
(191)
(CH3)2C(OR)C≡CH
+
(CH3)2C=C=CHCl
CH2=C(CH3)C≡CH
+
(CH3)2C(OH)C≡CH

The method for the introduction of an isoprenyl group ortho to a phenol developed in this laboratory[58] has already been applied successfully to the syntheses of a number of natural coumarins (see Part I). However, the major drawback which limits the utility of this method is the initial propargyl ether formation from the reaction of a phenolic inorganic salt with 2-methyl-2-chloro-but-3-yne.

The mechanism for t-propargylic ether formation[140,141] is now generally accepted to involve an intermediate (neutral) zwitterion-allene carbene (191) which is notably electrophilic at the tertiary carbon (Scheme 2.6). Various nucleophiles, including solvents such as alcohols[142] and many amines[143] react at this centre. However, the zwitterion-allene carbene (191) is an ambident electrophile, capable of yielding both t-propargylic and allenic products with the result that efficiency of ether formation can be impaired. Good evidence for the validity of the mechanism has come from the kinetics (regarded as second order)[141] and from the nature of the reaction products. Moreover, the allene-carbene (191) has been trapped by stereospecific reaction with olefins[140] in the manner typical of other carbenes.

In order to generate the species (191) and allow the reaction to proceed at a suitable rate, the presence of a strong base is usually necessary with many of the solvolysis reactions[142] being carried at 15-20° in sodium hydroxide and aqueous ethanol. However,

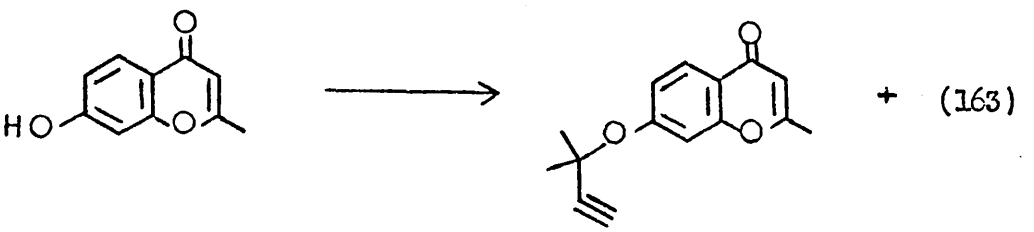
TABLE 2·2

Experiments to determine maximum propargylic ether formation

Experiment	+Yield%	Time(hr	%H_2O/Acetone ‡	Unreact.*
A	46	50	-	14
B	41	80	-	18
C	26	22	2	64
D	44	80	5	12
E	56	80	3	8

+%yield of (192) ‡ %v./v. * % of (163) unreacted.

REACTION.

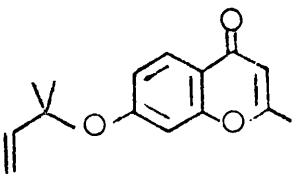


(163) (192)

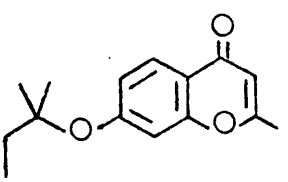
the α -and the γ -pyrone rings of coumarins and chromones tend to undergo ring opening[144] when in a strongly alkaline media. Thus, in order to minimise this fission a medium of potassium carbonate, potassium iodide and aqueous acetone was used. Inevitably, the weakly basic conditions decreased the reaction rate and necessitated refluxing the solution over a longer period. As a result, various side-reactions[140] associated with t-propargylic halide decomposition (Scheme 2.6) began to decrease the overall yield of the ether.

Although the conditions employed in the coumarin series provided more than adequate amounts of the propargylic ethers, it was decided that an investigation, via a number of control experiments, would perhaps reveal ideal conditions whereby maximum efficiency of t-propargylic ether formation could be achieved. The substrate used was 7-hydroxy-2-methylchromone (163) and in each experiment either the time, or the percentage of water present in the acetone solution, was varied. Further additional amounts of potassium carbonate and 2-methyl-2-chloro-but-3-yne were usually made after 24 hr. of reflux, and each reaction was monitored by analytical t.l.c. The results of experiments A-E are shown in Table 2.2.

From the results it was difficult to determine optimum conditions for propargyl ether formation. General observation showed that the greater the length of time of the reaction, the greater was the proportion of impurities formed. There also appeared to be a critical water:acetone ratio ($\sim$3%), and a



(193)



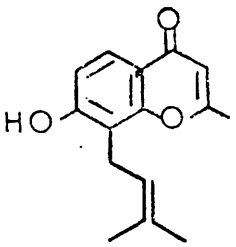
(194)

dependence on the purity of the 2-chloro-2-methyl-but-3-yne which was usually distilled before use for best results.

However, from the above observations it was clear that the reaction of 2-chloro-2-methyl-but-3-yne with the chromone (163) to give the ether (192) was not as efficient as that in the analogous coumarin series[58], which showed yields of ~77%. Moreover, dimethylallylation of the chromone series also gave lower yields (~74%) than that of umbelliferone (~80%)[93]. The reason for this lack of reaction[3] may be attributed to the acidity of the 7-hydroxyl of the chromone (163) which is enhanced by the mesomeric and inductive effects of the para substituted carbonyl group. Thus, formation of the ambident anion in this series may be more difficult than that in the coumarins.

Reduction of the propargyl ether (192) with palladium-barium sulphate catalyst poisoned with sulphur-quinoline gave a high yield of the 1,1-dimethylallyl ether (193). As in the coumarin series (see p. 33), a small amount of hydrogenolysis to (163) and some total reduction to (194) occurred. However, unlike the coumarin series, the ether (193) did not appear to rearrange on the chromoplates or during work up conditions and it was possible to crystallise and to obtain full analytical data for the compound.

The increased stability of the ether (193) was also reflected in the slightly higher temperature needed for pyrolysis (~150°), which yielded only one product (86%). The n.m.r. spectrum of this compound possesses the signals for a 3,3-dimethylallyl unit (τ 8.21 ; 3H ; s.), (8.18 ; 3H ; s.), (6.44 ; 2H ; b.d. J 9.5 Hz.)



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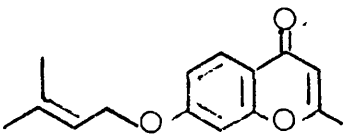
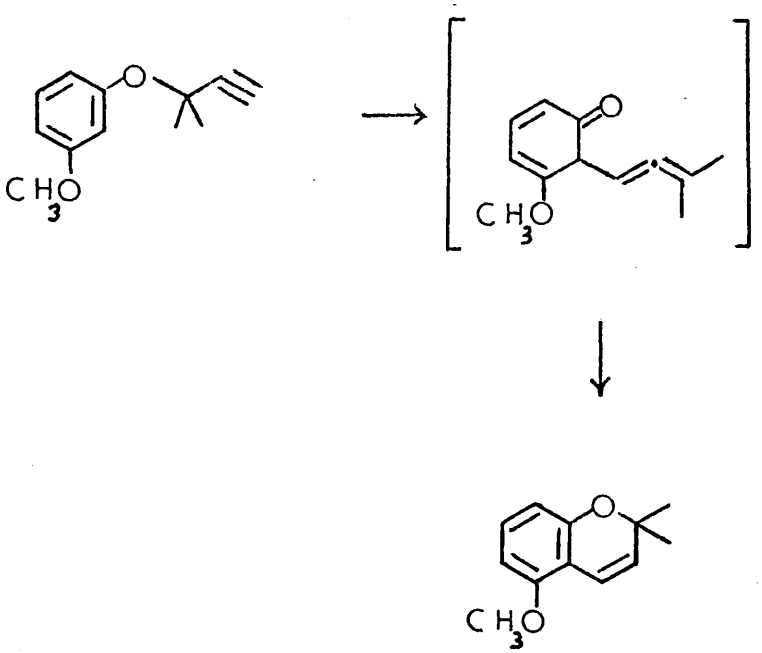


(165)

SCHEME 2·7



and (4.70 ; 1H ; b.t. ; J 9.5 Hz.) attached to the benzene ring. Besides the characteristic γ-pyrone signals at τ 7.62 and 3.85, the remainder of the spectrum shows the presence of two ortho aromatic protons (τ2.97 ; 1H ; d. ; J 9.5 Hz.) and (τ2.06 ; 1H ; d. ; J 9.5 Hz.) and a one proton singlet at τ0.96 which disappears on addition of deuterium oxide. From this, and other data the compound was assigned the structure (195).

Obviously, migration to C-8 is again favoured during the rearrangement and this correlates with the findings of the pyrolysis of the 3,3-dimethylallyl ether (165). However, although it would appear that no C-6 migration occurs, two components formed in small yield during the pyrolysis of (193) were not identified and these may possess C-6 substituted structures.

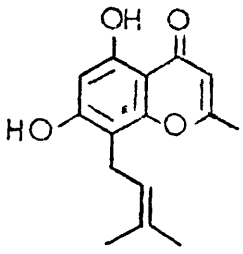
At this point, it would be appropriate to note the work of Hlubucek, Ritchie and Taylor[76,145] reported while this investigation was in progress. These workers prepared α,α-dimethylpropargyl ethers of various phenolic derivatives in a similar manner. Claisen rearrangement of these ethers in diethylaniline provided a facile route to 2,2-dimethylchromenes (Scheme 2.7). The authors have also extended the reaction to the synthesis of ortho-isopentenylphenols[76] utilising the same route as that developed by Murray and Ballantyne[58].

The ease of chromene formation from rearrangement of the propargylic ethers illustrates another side-reaction which may lead to a decrease in the efficiency of ether formation. Hlubucek et al[145] found that even at low reaction temperature

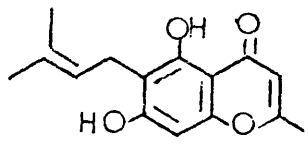
($\sim 70^{\circ}$), Claisen rearrangement to the 2,2-dimethylchromene system occurred readily.

Undoubtedly, in chromone propargylic ether synthesis, the longer reaction time accentuates chromene formation. In fact some evidence for the formation of the 2,2-dimethylchromene system was found in the n.m.r. spectrum of a minor product isolated from the synthesis of the ether (192) which possesses signals attributable to the AB system of the chromene ring at τ4.33 and 3.29 (J 10 Hz.).

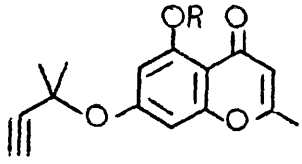
(b) 5,7-Dioxygenated Series



(162)



(160)

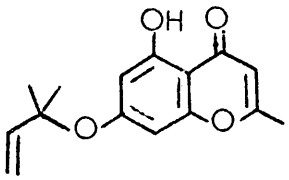


(196) R = H
(198) R = CH_3

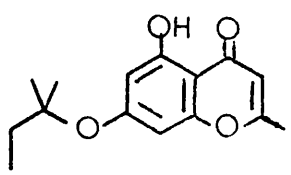
Almost all naturally occurring 2-methylchromones have varied 5,7-dioxygenation patterns (see Table 2.1) which usually contain modified isoprenoid units. It has been suggested[106,146] that the parents for these chromones are heteropeucenin (162) and peucenin (160) both of which appear amenable to synthesis by the method developed in this laboratory. Both heteropeucenin (162) and peucenin (160) have been isolated from the heartwood of Ptaeroxylon obliquum by Dean et al[110] and by Murray, McCrindle and McCabe[109] respectively.

Thus, 5,7-dihydroxy-2-methylchromone (156) was treated with 2-chloro-2-methyl-but-3-yne in the usual manner and afforded one major product (66%) which was assigned the structure (196), with etherification of the C-5 hydroxyl being precluded by virtue of its hydrogen bonding with the carbonyl group. This is confirmed by the n.m.r. spectrum which possesses a singlet resonance at τ -2.60 which disappears on addition of deuterium oxide. The spectrum also indicates the presence of a 1,1-dimethylpropargyl unit with signals at τ 8.28 (6H ; s.) for the gem-dimethyl groups on carbon attached to oxygen and at τ7.32 for the acetylenic proton.

One difficulty experienced during the above reaction was the limited solubility of 5,7-dihydroxy-2-methylchromone (156) in aqueous acetone. This was overcome by the addition of a small amount of methanol in order to create a more homogeneous reaction[3,80] media and this may account for the increased efficiency of acetylenic ether formation. Since the increased solubility appeared to enhance the efficiency, the reaction was repeated in dimethyl sulphoxide[147]. However, recovery of the propargyl ether (196) proved difficult and



(197)



(198)

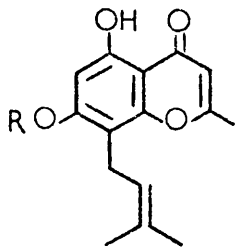
even after constant ether extraction only 37% of the ether could be isolated.

Hydrogenation in the usual manner over palladium-barium sulphate catalyst poisoned with sulphur- quinoline[95] did not yield the required ether (196).

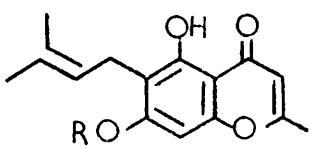
At first it was thought that the reaction had been 'over-poisoned' or, that either the catalyst or the poison had become inactive. However, after repeating the experiment using different catalyst:poison ratios, freshly prepared poison, and varying time intervals for the hydrogenation, no appreciable amount of Lindlar reduction was achieved. The hydrogenation was repeated using a different catalytic poison i.e. 'conditioned' palladium-calcium carbonate catalyst[148], again with no success.

It was suspected that the 5-hydroxy substituent of the propargyl ether (196) was affecting the hydrogenation in some way by perhaps forming a metal chelate with the palladium of the catalyst which could hinder the acetylene unit bonding to the vacant surface sites. This would not appear too unreasonable as 5-hydroxychromones are known to chelate fairly readily with various metals[149] including palladium[150] and they have been used in this field as analytical reagents in the estimation of metals.

By breaking the chelation through methylation of the 5-hydroxyl it was hoped to resolve this problem. Treatment of the ether (196) with methyl iodide and potassium carbonate gave a surprisingly easy conversion (97%) to the desired ether (198). However, on hydrogenation there was no reduction which may indicate



(162) R = H
(200) R = CH_3



(160) R = H
(199) R = CH_3

that the above postulate may not be the reason for the lack of reaction.

Finally, hydrogenation was achieved through using the procedure of Cram and Allinger[151] in which the modified poison for the palladium -barium sulphate catalyst was synthetic quinoline[152] obtained from Skraup synthesis. The authors reported that commercial quinoline available from coal-tar inhibits the reaction since it contains trace quantities of sulphur. Hydrogenation via this method gave the required 1,1-dimethylallyl ether (197) which was relatively stable and complete analytical and spectral data in accord with the proposed structure were recorded.

Pyrolysis of the ether (197) at 180° gave two major products. The n.m.r. spectrum of the minor product(18%) possesses characteristic chromone signals for the C-2 methyl at τ 7.72 and the C-3 vinyl proton at τ4.04 and a singlet at τ-3.02 which disappears on addition of deuterium oxide. The remainder of the spectrum contains signals for an aromatic proton at τ3.71 and a 3,3-dimethylallyl group (τ 8.30 ; 3H ; s.), (τ 8.31 ; 3H ; s.), (τ 6.62 ; 2H ; b.d. ; J=7 Hz.) and (τ 4.78 ; 1H ; b.t. ; J=7 Hz.) attached to the benzene ring. Although the presence of another hydroxyl group was not detected in the n.m.r. spectrum, i.r. data clearly shows that besides the broad intramolecularly bonded C-5 hydroxyl stretching frequency at $\sim$ 2970 cm.$^{-1}$, other maxima at 3588 and 3386 cm.$^{-1}$ are present, which are characteristic of a 7-hydroxyl group, showing free and intramolecular OH$\rightarrow\pi$ stretching

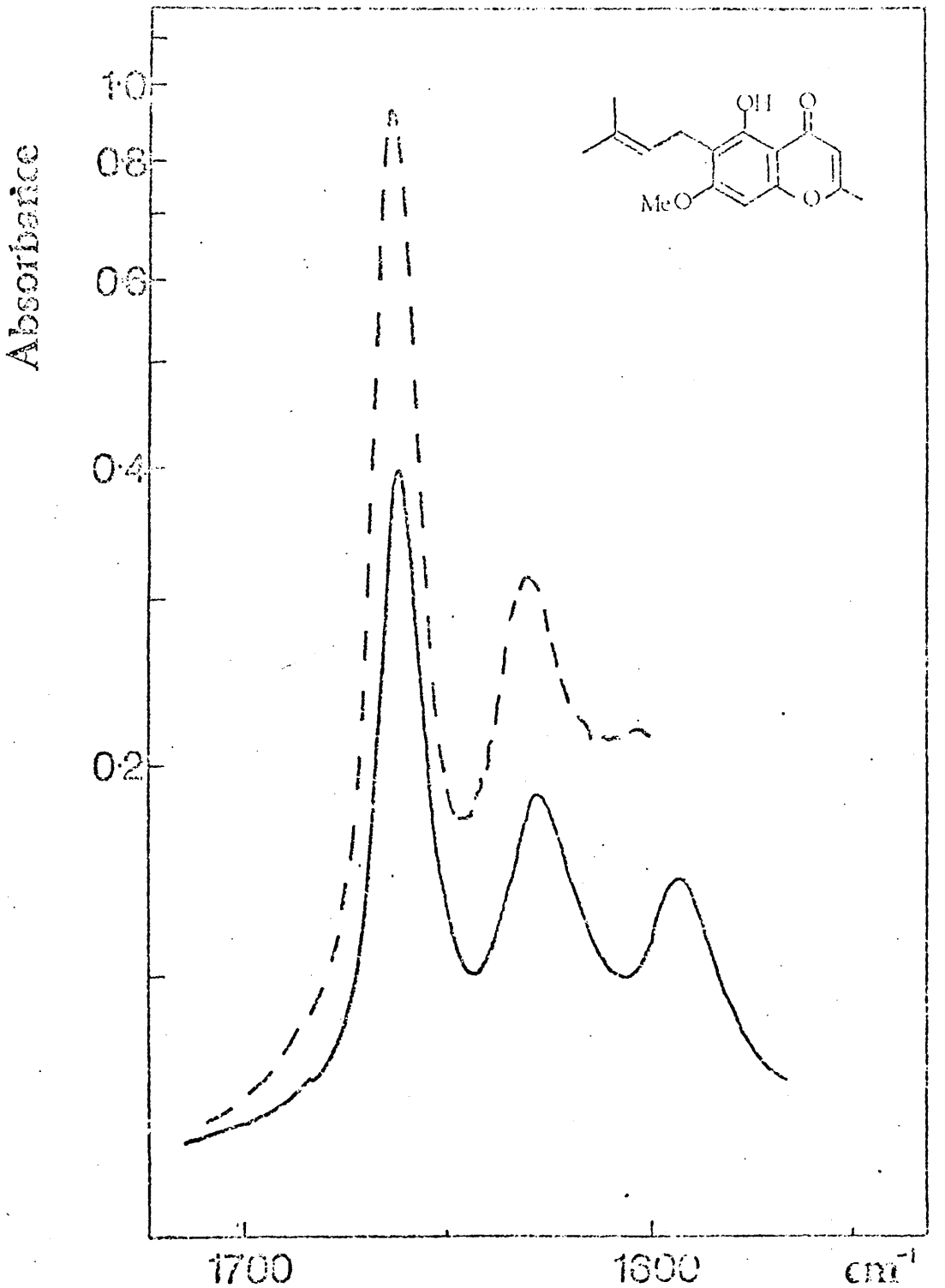


Fig.2.3

(——) $CHCl_3$ solution.

(- - -) CCl_4 solution.

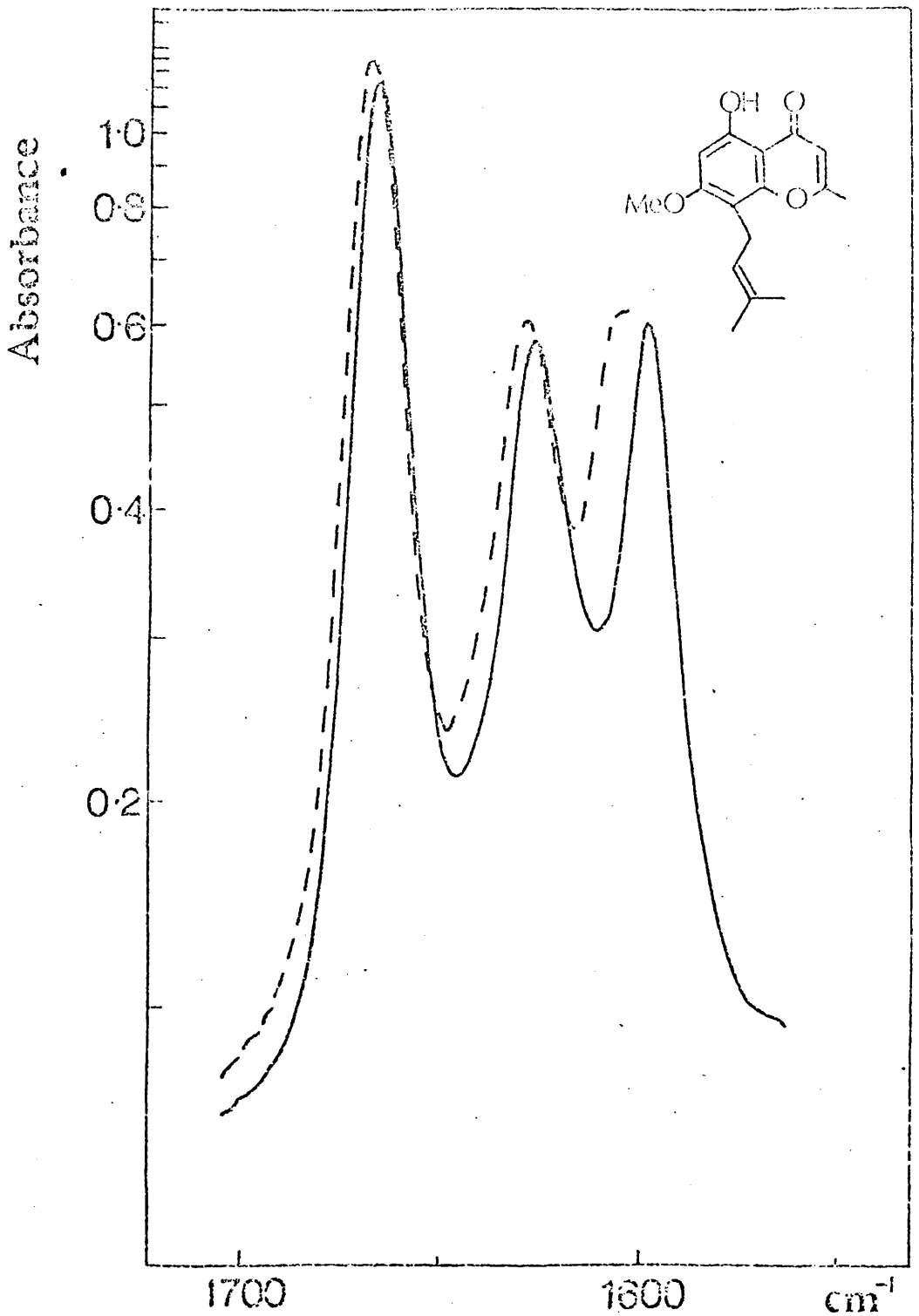


Fig. 24

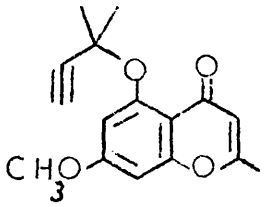
frequencies. Comparison with the spectral and physical properties of this compound with that of peucenin (160) showed that both were identical.

The major product (51%) from the pyrolysis appears to possess similar spectral characteristics to that of peucenin (160) with the exception of the u.v. data. However, from the melting point and on comparison with the spectral data of heteropeucenin (162) both compounds were found to be identical.

As a confirmation that the above structures were assigned correctly both (162) and (160) were converted to their respective methyl ethers and compared with authentic samples[134] of heteropeucenin-7-methyl ether (200) and peucenin-7-methyl ether (199).

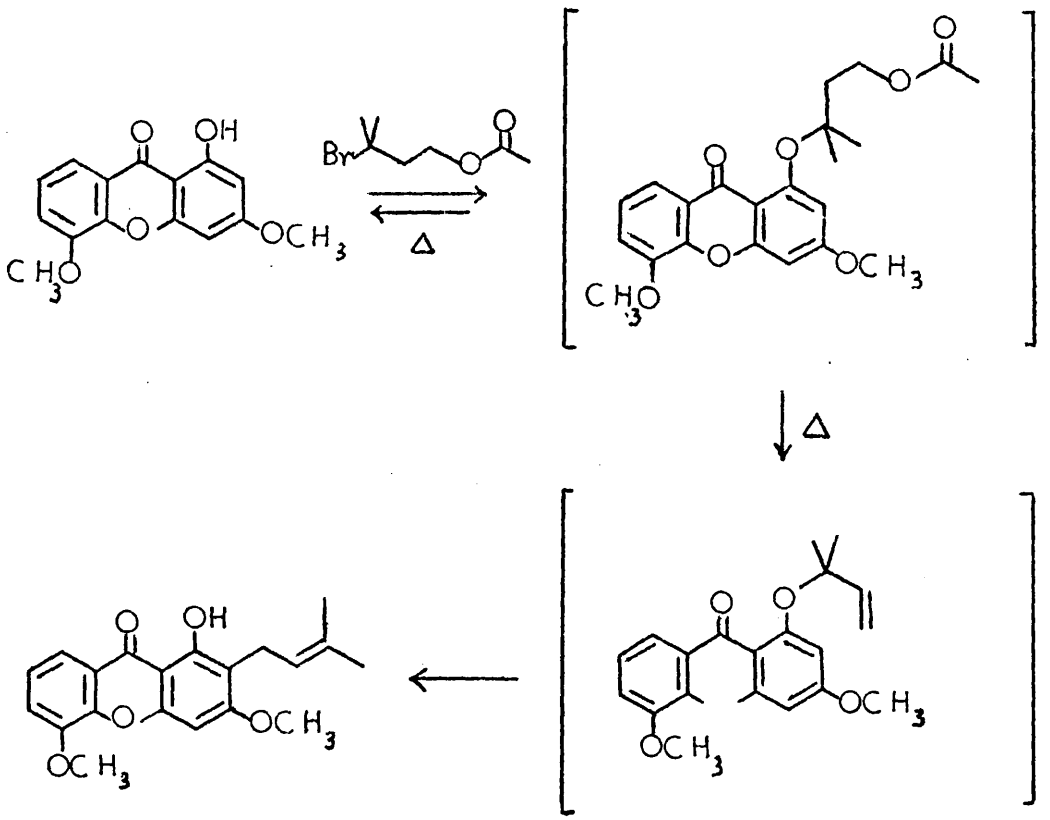
High resolution i.r. spectral profiles of the carbonyl regions (1580-1700 $cm.^{-1}$) of the natural ethers (199) and(200) provide an interesting comparison, and prove to be of diagnostic value (see Fig. 2.3 and Fig. 2.4). In peucenin-7-methyl ether (199) where the isopentenyl group is at C-6, the i.r. spectrum exhibits decreasing intensity maxima at 1657, 1633 and 1590 $cm.^{-1}$ whereas in heteropeucenin-7-methyl ether (200) where the isoprenoid unit is at C-8, the absorption of the band at 1590 $cm.^{-1}$ is notably more intense than that of the neighbouring 1620 $cm.^{-1}$ band.

From the results of the pyrolysis, it appears that migration to C-8 is again favoured over C-6. This route yields heteropeucenin (162) and peucenin (160) in 33% and 11% respectively from the chromone (156) and, although the efficiency compared with that of the coumarin



(201)

SCHEME 2·8



series is less, the route provides a mode of synthesis of (162) and (160) considerably better than that through direct C-alkylation. For example, Schmid et al[153] isolated heteropeucenin (162) and peucenin (160) in low yield (~4% of each) from direct dimethylallylation of 5,7-dihydroxy-2-methylchromone (156). Later, Seshadri et al[154] by a similar method, managed to improve the efficiency of the alkylation and isolated peucenin in 11% yield.

From the toddaculin synthesis (see Part I : p.39), it was found that pyrolysis of a 1,1-dimethylallyl ether at C-5 resulted in migration to C-6 exclusively. Thus, if the analogous ether (201) could be prepared in the 5,7-dioxygenated chromones, rearrangement should lead to a more efficient synthesis of peucenin-7-methyl ether (199). However, as dimethylallylation at the chelated 5-hydroxyl had already proved difficult it was expected that dimethylpropargylation would prove an even greater obstacle.

Two methods of synthesising ortho-isopentenyl phenols through alkylation of a chelated hydroxyl have recently been introduced with varying degrees of success by Jefferson and Scheinmann. The first[155] involves an attempt to synthesise a 1,1-dimethylallyl ether in situ by treating a hydroxyxanthone with an excess of 3-methyl-3-bromo-butyl acetate (Scheme 2.8). Although their evidence shows that the required ether is formed, the major pyrolysis product is cleavage of the intermediate acetate. The second method has already been discussed (see Introduction: p. 17 : Scheme 18). Although the latter method seems to have great potential, the necessity of protecting the ortho hydroxyl group might limit the

use of this function.

Thus, attempts were made to synthesise the t-propargyl ether (201) from eugenin (177) and 2-chloro-2-methyl-but-3-yne. No less than five various methods were applied, each experiment being designed to change the conditions[3] governing the O-alkylation of ambident anions. It is not proposed to discuss in great detail each of the methods; what follows is a short summary of the conditions which were applied and the reasons for doing so.

Probably the most important choice[3] that has to be made is that of the solvent or media. In phenols, ketones and β-dicarbonyl compounds O-alkylation occurs to the highest degree when the oxygen anion is free. As the anion becomes bound or partially bound, for example to strongly hydrogen-bonding molecules in the solvent, reaction at the less electronegative site, i.e. C-alkylation, gains importance. Thus, for O-alkylation an aprotic solvent[147] should be chosen. In fact, in the experiments no t-propargyl ether (201) was detected when dimethylformamide or tetrahydrofuran was used as solvent.

By changing the counterion and using the silver salts in place of the alkali metal salts, it was hoped to achieve through the methods used by Kornblum et al[161] to achieve propargylation. However, the reaction mixtures with silver salts tend to be heterogeneous and as a result favour C-alkylation.

An attempt to generate the dimethylallene-carbene (191) through the treatment of 2-chloro-2-methyl-but-3-yne with potassium tert-butoxide[160] in the presence of the potassium salt of eugenin (177)

again gave no O-alkylation.

As a last resort, eugenin (177) in an aqueous acetone solution was refluxed in the presence of 2-chloro-2-methyl-but-3-yne, potassium carbonate and potassium iodide and strangely enough a small amount (2%) of the required ether (201) was isolated. It was assigned this structure on the evidence of its i.r. and n.m.r. spectra. The i.r. spectrum shows an acetylene C-H stretching frequency at 3304 $cm.^{-1}$ and, in the carbonyl region, twin maxima at 1662 and 1616 $cm.^{-1}$ are characteristic of a 5-substituted chromone (see p. 81). The n.m.r. spectrum shows signals at τ 7.70 and 4.06 for the chromone resonances of the γ-pyrone ring and for a three proton methoxyl singlet at τ 6.12. The remainder of the spectrum possesses signals at τ 8.22 (6H) and τ 7.37 (1H) indicative of a 1,1-dimethyl propargyl unit. Unfortunately, the sample appeared to decompose rapidly in deuterochloroform solution and, as a result of the combination of the weakness of the solution and of the decomposition products, the aromatic signals were not discernible. Indeed, in order to record the acetylene signal (τ 7.37) a time average computer technique was utilised to eliminate background noise.

Experimental.

2-Methyl-2-chloro-3-butyne - see p. 52 for preparation.

Control experiments in the preparation of 7-O-(1,1-dimethyl-propargyl-2-methylchromone (192)

Experiment A (Reflux time 50 hr.)

Potassium carbonate (168 mg.) and potassium iodide (11 mg.) were added to a solution of 7-hydroxy-2-methylchromone (163) (157 mg.) in acetone (100 ml.) and the mixture stirred at R.T. for 1 hr. 2-Methyl-2-chloro-3-butyne (303 mg.) was added and refluxing continued for another 50 hr. Work up (I) gave a yellow oil which was separated by preparative t.l.c. (chloroform x 1 followed by 60% ether-light petroleum x 1) into:-

(i) an unidentified product as a yellow oil (22 mg.)

(ii) the acetylenic ether (192) (99 mg. ; 46%) crystallised from ether-light petroleum as colourless plates, m.p. 112-114°. (Found: C, 74.13 ; H, 5.91. $C_{15}H_{14}O_3$ requires C, 74.36 ; H, 5.83%); $\nu_{max}^{CHCl_3}$ 3295, 1654, 1644, 1639 (sh.) and 1604 $cm.^{-1}$; mass spectral peaks at m/e 242 (M^+), 227, 176 and 148 (r.a. 22, 100, 73 and 46%); n.m.r. signals at τ 8.27 (6H ; s.), 7.65 (3H ; s.), 7.36 (1H ; s.), 3.94 (1H ; s.), 2.90 (1H ; d. ; J 2 Hz.), 2.73 (1H ; d./d. ; J 2 & 9.5 Hz.) and 1.99 (1H ; d. ; J 9.5 Hz.).

(iii) 7-hydroxy-2-methylchromone (163) (22 mg.; 14%).

Experiment B (Reflux time 80 hr.)

Potassium carbonate (329 mg.) and potassium iodide (15 mg.) were added to an acetone solution of 7-hydroxy-2-methylchromone

(163) (225 mg.) and the mixture stirred for 1 hr. 2-Methyl-2-chloro-3-butyne (448 mg.) was added and the solution refluxed for 22 hr. More potassium carbonate (361 mg.) and 2-methyl-2-chloro-3-butyne (726 mg.) were added and refluxing continued for a further 58 hr. Following the same work up conditions as in Experiment A, preparative t.l.c. yielded the desired ether (192) (145 mg. ; 41%) and the starting chromone (163) (40 mg.; 18%).

Experiment C (2% v./v. aqueous acetone)

Potassium carbonate (710 mg.), potassium iodide (39 mg.), 2-methyl-2-chloro-3-butyne (765 mg.) and 7-hydroxy-2-methylchromone (163) (619 mg.) were refluxed for 22 hr. in aqueous acetone (2% v./v. ; 150 ml.). Work up (I), followed by preparative t.l.c. yielded the ether (192) (173 mg. ; 22%) and the starting chromone (163) (398 mg. ; 64%).

Experiment D (5% v./v. aqueous acetone)

Potassium carbonate (424 mg.), potassium iodide (18 mg.), 2-methyl-2-chloro-3-butyne (558 mg.) and 7-hydroxy-2-methyl-chromone (163) (262 mg.) were refluxed (22 hr.) in aqueous acetone (5% v./v. ; 100 ml.). After this time, further additions of 2-methyl-2-chloro-3-butyne (545 mg.) and potassium carbonate (362 mg.) were made and refluxing continued for another 58 hr. Work up (I) followed by preparative t.l.c. gave the ether (192) (161 mg. ; 41%) and the starting chromone (163) (31 mg. ; 12%).

Experiment E (3% v./v. aqueous acetone)

Potassium carbonate (416 mg.), potassium iodide (25 mg.), 2-methyl-2-chloro-3-butyne (480 mg.) and 7-hydroxy-2-methylchromone (163) (278 mg.) were refluxed (22 hr.) in aqueous acetone (3% v./v. ; 100 ml.). Further additions of potassium carbonate (235 mg.) and 2-methyl-2-chloro-3-butyne (586 mg.) were made and refluxing continued for a further 58 hr. Work up (I) and preparative t.l.c. gave the ether (192) (212 mg. ; 56%) and the starting chromone (23 mg. ; 8%).

Quinoline-sulphur poision - see p. 54 for the preparation of the Lindlar poison.

Reduction of 7-O-(1,1-dimethylpropargyl)-2-methylchromone (192)

Palladium-barium sulphate (5% w./w. ; 30 mg.) was added to a solution of the propargyl ether (192) (70 mg.) in ethyl acetate ($\sim$30 ml.) and the quinoline-sulphur poison (0.2 ml.). After hydrogenation at R.T. for 50 min., the correct volume of hydrogen uptake was observed ($\sim$7 ml.) and the reaction stopped. The catalyst was filtered off and the solvent carefully evaporated under reduced pressure. The residue was separated by preparative t.l.c. (30% ethyl acetate-light petroleum x 1) into:-

(i) 7-O-(2-methylbutyl)-2-methylchromone (194) (2 mg. ; 3%) which was distilled at 160°/.005 mm. as a colourless oil; 1652, 1648 (sh.) and 1609 $cm.^{-1}$; mass spectral peaks at m/e 246 (M^+), 218, 176, 148 and 43 (r.a. 9, 11, 100, 24 and 36); n.m.r. signals at τ 9.07 (3H ; t. ; J 7 Hz.),

8.67 (6H ; s.), 8.26 (2H ; q. ; J 7 Hz.), 7.70 (3H ; s.), 3.95 (1H ; s.), 3.10 (2H ; m.) and 2.00 (1H ; d. ; J 9.5 Hz.).

(ii) 7-O-(1,1-dimethylallyl)-2-methylchromone (193) crystallised from ether-light petroleum as colourless plates (60 mg. ; 85%), m.p. 74-76°. (Found: C, 73.58 ; H, 6.53. $C_{15}H_{16}O_3$ requires C, 73.75 ; H, 6.60%); $\nu_{max}^{CHCl_3}$ 1654 (sh.), 1644, 1639 (sh.), and 1604 cm.$^{-1}$; mass spectral peaks at m/e 244 (M^+), 229, 189 and 176 (r.a. 35, 23, 52 and 100%); n.m.r. signals at τ 8.55 (6H ; s.), 7.76 (3H ; s.), 4.83 (1H ; d. ; J 10 Hz.), 4.79 (1H ; d. ; J 18 Hz.), 4.03 (1H ; s.), 3.92 (1H ; d./d. ; J 10 & 18 Hz.), 3.11 (2H ; m.) and 2.09 (1H ; d. ; J 9.5 Hz.).

(iii) 7-hydroxy-2-methylchromone (163) (2 mg.† ; 3%) (identified from u.v.)

Pyrolysis of 7-O-(1,1-dimethylallyl)-2-methylchromone (193)

The allyl ether (193) (70 mg.) was heated for $1\frac{3}{4}$ hr. at 150° under partially reduced pressure in a sublimation block. The residue, on purification by preparative t.l.c. (30% ethyl acetate-light petroleum x 3), gave 7-hydroxy-8-(3,3-dimethylallyl)-2-methylchromone (195) (58 mg. ; 83%) crystallised from methanol as colourless prisms, m.p. 193-195°. (Found: C, 73.68 ; H, 6.48. $C_{15}H_{16}O_3$ requires C, 73.75 ; H, 6.60%); $\nu_{max}^{CHCl_3}$ 3506, 1650 (sh.), 1644, 1638 (sh.) and 1599 cm.$^{-1}$; mass spectral peaks at m/e 244 (M^+),

229, 189 and 148 (r.a. 57, 34, 100 and 17%); n.m.r. signals at τ 8.21 (3H ; s.), 8.18 (3H ; s.), 7.62 (3H ; s.), 6.44 (2H ; b.d. ; J 6.5 Hz.), 4.70 (1H ; b.t. ; J 6.5 Hz.), 3.85 (1H ; s.), 2.97 (1H : d. ; J 9.5 Hz.), 2.06 (1H ; d. ; J 9.5 Hz.) and 0.96 (1H ; b.s.).

Preparation of 5-hydroxy-7-O-(1,1-dimethylpropargyl)-2-methylchromone (196).

Method A

Potassium carbonate (120 mg.), potassium iodide (27 mg.), 2-methyl-2-chloro-3-butyne (168 mg.) and 5,7-dihydroxy-2-methylchromone (156) (134 mg.) were refluxed for 19 hr. in an aqueous acetone (4% v./v. ; 100 ml.) and methanol (2 ml.) solution. Further additions of 2-methyl-2-chloro-3-butyne (197 mg.) and potassium carbonate (124 mg.) were made and refluxing continued for 19 hr. Work up (I), followed by preparative t.l.c. (40% ethyl acetate-light petroleum x 2) gave:-

(i) an unidentified colourless oil (12 mg.†).

(ii) 5-hydroxy-7-O-(1,1-dimethylpropargyl)-2-methylchromone (196) (118 mg. ; 66%) crystallised from ether as fine colourless needles, m.p. 152-154°. (Found: C, 70.00 ; H, 5.39. $C_{15}H_{14}O_4$ requires C, 59.75 ; H, 5.46%); $\nu_{max}^{CHCl_3}$ 3307, 1660, 1626 and 1591 cm.$^{-1}$; mass spectral peaks at m/e 258 (M^+), 243, 215, 192 and 164 (r.a. 35, 100, 16, 75 and 23%); n.m.r. signals at τ 8.28 (6H ; s.), 7.65 (3H; s.), 7.32 (1H ; s.), 3.96 (1H ; s.), 3.38 (1H ; d. ; J 2 Hz.), 3.30 (1H ; d. ; J 2 Hz.), -2.60 (1H ; s.).

(iii) 5,7-dihydroxy-2-methylchromone (156) (16 mg.† ; 2%).

Method B

A mixture of potassium carbonate (106 mg.), potassium iodide (28 mg.), 2-methyl-2-chloro-3-butyne (112 mg.) and 5,7-dihydroxy-2-methylchromone (156) (179 mg.) was heated at 55° for 39 hr. in

dimethyl sulphoxide. As in method A, after 19 hr., further additions of 2-methyl-2-chloro-3-butyne and potassium carbonate were made. The reaction was allowed to cool and water and ether added. After constant ether extraction (24 hr.), the organic layer was separated, washed with brine to neutrality, dried and evaporated to yield a brown oil. Purification by preparative t.l.c. (40% ethyl acetate-light petroleum x 2) gave the propargyl ether (196) (89 mg. ; 37%) and the starting chromone (156) (59 mg. ; 27%).

5-Methoxy-7-O-(1,1-dimethylpropargyl)-2-methylchromone (198)

The 5-hydroxypropargyl ether (196) (76 mg.) was converted to its methyl ether (198) using potassium carbonate (534 mg.), methyl iodide (0.2 ml.) and acetone (7 ml.). After refluxing for 8 hr., work up (I) gave a yellow solid which on crystallisation from acetone yielded 5-methoxy-7-O-(1,1-dimethylpropargyl)-2-methyl-chromone (78 mg. ; 97%) as colourless needles m.p. 161-164°. (Found: C, 70.69 ; H, 5.93. $C_{16}H_{16}O_4$ requires C, 70.57 ; H, 5.92%); $\nu_{max}^{CHCl_3}$ 3303, 1712, 1660 and 1609 cm.$^{-1}$; mass spectral peaks at m/e 270 (M^+), 257, 217, 206 and 178 (r.a. 34, 100, 22, 21 and 16%); n.m.r. signals at τ 8.25 (6H ; s.), 7.75 (3H ; s.), 7.28 (1H ; s.), 6.28 (3H ; s.), 4.04 (1H ; s.), 3.50 (1H ; d. ; J 2 Hz.) and 3.14 (1H ; d. ; J 2 Hz.).

Attempted methods of reduction of 5-hydroxy-7-O-(1,1-dimethyl-propargyl)-2-methylchromone (196) and its methyl ether (198).

Method A

1) Palladium-barium sulphate (5% w./w. ; 57 mg.) was added to a solution of the propargyl ether (196) (66 mg.) in ethyl acetate

(~40 ml.) and the quinoline-sulphur poison (0.52 ml.) (see p. 54 for preparation). After hydrogenation for 1¼ hr., no uptake of hydrogen was observed. The catalyst was then filtered off and the solvent carefully evaporated under reduced pressure.

The n.m.r. and i.r. spectrum of the residue showed that no hydrogenation to the olefin had taken place.

The experiment was repeated using different catalyst/poison ratios, freshly prepared sulphur-quinoline poison and varying time intervals for the reaction. However, in each case, there was no appreciable hydrogenation.

2) Palladium-barium sulphate (5% w./w. ; 32 mg.) was added to a solution of 5-methoxy-7-O-(1,1-dimethylpropargyl)-2-methyl-chromone (198) (77 mg.) in ethyl acetate (~40 ml.) and the quinoline-sulphur (0.32 ml.) poison. No reduction to the olefin occurred.

Method B

No hydrogenation was seen to occur on using a 'conditioned' palladium-calcium carbonate catalyst, prepared by the method of Lindlar and Dubuis.[148]

Method C[151]

The propargyl ether (196) (110 mg.) in ethyl acetate (~30ml.) was hydrogenated over palladium-barium sulphate (5% w./w. ; 57 mg.) 'poisoned' with pure synthetic quinoline[152](0.53 ml.). After hydrogenation for 1½ hr. at R.T., the catalyst was filtered off, and cadmium chloride (saturated solution) added to precipitate the quinoline from the ethyl acetate solution. The precipitate

was then removed by passage through Celite-625. On separation of the filtrate, the organic layer was washed with brine, dried and evaporated. Residual traces of quinoline were removed by preparative t.l.c. (chloroform x 1) to give:-

(i) 5-hydroxy-7-O-(1,1-dimethylallyl)-2-methylchromone (197) (107 mg. ; 96%) crystallised from light petroleum as colourless needles, m.p. 99-102°. (Found: C, 69.23 ; H, 6.20. $C_{15}H_{16}O_4$ requires C, 69.21 ; H, 6.20%); $\nu_{max}^{CHCl_3}$ 3010 (wk.), 1664, 1615 and 1590 cm.$^{-1}$; mass spectral peaks at m/e 260 (M^+), 245, 217, 205, 192 and 164 (r.a. 100, 46, 49, 60, 31 and 92); n.m.r. signals at τ 8.46 (6H ; s.), 7.66 (3H ; s.), 4.80 (1H ; b.d. ; J 10 Hz.), 4.78 (1H ; b.d. ; J 17 Hz.), 4.02 (1H ; s.), 3.96 (1H ; d./d. ; J 10 & 17 Hz.), 3.64 (1H ; d. ; J 2 Hz.), 3.56 (1H ; d. ; J 2 Hz.) and-2.50 (1H ; s.).

(ii) 5,7-dihydroxy-2-methylchromone (156) (2 mg.; ~2%).

Pyrolysis of 5-hydroxy-7-O-(1,1-dimethylallyl)-2-methylchromone (197)

The allyl ether (197) (101 mg.) was pyrolysed in a sublimation block at 180° under partial vacuum (~ 0.08 mm.) for 1½ hr. On cooling, the residual oil was separated by preparative t.l.c. (chloroform x 1 30% ethyl acetate-light petroleum x 2) into:-

(i) peucenin (160) (18 mg. ; 18%) crystallised from methanol as yellow plates, m.p. 210-212° (lit.[153] m.p. 212°); $\nu_{max}^{CHCl_3}$ (S.P. 100) 3588, 3386, 1657, 1633 and 1590 cm^{-1}. (ϵ 79, 81, 917, 722 and 437); λ_{max} 212, 232, 254, 259 and 298 nm. (log ϵ 4.32, 4.13, 4.05, 4.06 and 3.80);

mass spectral peaks at m/e 260 (M^+), 245, 217 and 205 (r.a. 40, 25, 87 and 100%); n.m.r. signals at τ 8.30 (3H ; s.), 8.21 (3H ; s.), 7.72 (3H ; s.), 6.62 (2H ; b.d. ; J 7 Hz.), 4.78 (1H ; b.t. ; J 7 Hz.), 4.04 (1H ; s.), 3.71 (1H ; s.) and -3.02° (1H ; b.s.).

(ii) heteropeucenin (162) (51 mg. ; 51%) crystallised from methanol as yellow needles, m.p. 187-193° (lit.[110] m.p. 193°); $\nu_{max}^{CHCl_3}$ 1655, 1630 and 1585 $cm.^{-1}$; n.m.r. signals at τ 8.31 (3H ; s.), 8.21 (3H ; s.), 7.68 (1H ; s.), 6.61 (2H ; b.d. ; J 7 Hz.), 4.82 (1H ; b.t. ; J 7 Hz.), 4.03 (1H ; s.), 3.71 (1H ; s.) and -2.57° (1H ; b.s.).

Peucenin-7-methyl ether (199)

Diazomethylation (24 hr.) of peucenin (160) (10 mg.) gave on purification by preparative t.l.c. (chloroform x 1) peucenin-7-methyl ether (199) (7 mg. ; 63%) crystallised from methanol as colourless needles m.p. 108-110° (lit.[162] m.p. 108-109°); $\nu_{max}^{CHCl_3}$ ~ 3400, 1661, 1628 and 1594 $cm.^{-1}$; λ_{max} 211, 233, 255, 258 and 293 (log ϵ 4.42, 4.30, 4.26 and 3.91); mass spectral peaks at m/e 274 (M^+), 259, 231 and 219 (r.a. 46, 32, 100, 91 and 16%); n.m.r. signals at τ 8.32 (3H ; s.), 8.20 (3H ; s.), 7.65 (3H ; s.), 6.67 (2H ; b.d. ; J 7 Hz.), 6.14 (3H ; s.), 4.83 (1H ; b.t. ; J 7 Hz.), 4.00 (1H ; s.), 3.69 (1H ; s.) and -2.60° (1H ; s.).

The compound was shown to be identical with an authentic sample of peucenin-7-methyl ether (m.p., m.m.p., u.v.) kindly provided by Dr. P.H. McCabe.

Heteropeucenin-7-methyl ether (200)

Diazomethylation of heteropeucenin gave heteropeucenin-7-methyl ether (200) crystallised from ether-light petroleum as colourless needles, m.p. 107-109° (lit.[110] m.p. 110°); $\nu_{max}^{CHCl_3}$ ~3400, 1663, 1625 and 1596 cm.$^{-1}$; λ_{max} 253, 259, 294 and 329 nm. (log. ϵ 4.07, 4.09, 3.34 and 3.27); n.m.r. signals at τ 8.33 (3H ; s.), 8.21 (3H ; s.), 7.65 (3H ; s.), 6.62 (2H ; b.d. ; J 7 Hz.), 6.12 (3H ; s.), 4.85 (1H ; b.t. ; J 7 Hz.), 4.01 (1H ; s.), 3.65 (1H ; s.) and -2.50 (1H ; s.).

The compound was identical with a natural sample of heteropeucenin methyl ether. (m.p., m.m.p. and u.v.).

Attempted preparation of 5-O-(1,1-dimethylpropargyl)-7-methoxy-2-methylchromone (201)

(1) Sodium hydride method

Eugenin (177) (174 mg.) in tetrahydrofuran was added dropwise under nitrogen to a suspension of sodium hydride (23 mg.) in tetrahydrofuran at 0° and the reaction stirred at R.T. for 24 hr. 2-Methyl-2-chloro-3-butyne (262 mg.) and potassium iodide (16 mg.) were added and the mixture heated for 43 hr. at 55° using the same work-up procedure as was employed in the synthesis of 5-O-(3,3-dimethylallyl)-7-methoxy-2-methylchromone (176) (see p. 94), no propargylic ether was detected.

(2) Silver oxide method [156]

Silver oxide was prepared by precipitation from silver nitrate and aqueous sodium hydroxide by the method of Pearl.[157]

Eugenin (177) (40 mg.) and silver oxide (50 mg.) were stirred in dimethylformamide for 48 hr. at R.T., with the exclusion of light. 2-Chloro-2-methyl-3-butyne (60 mg.) and potassium iodide (14 mg.) were added and the reaction heated at 55° for 26 hr. No reaction occurred and only starting material was recovered.

The experiment was repeated using chloroform as solvent and a small addition of water. Again, no reaction occurred.

(3) Silver tetrafluoroborate method [158,161]

Silver tetrafluoroborate was prepared by the method of Birch and Keaton.[159]

Eugenin (177) (40 mg.) in chloroform (5 ml.) was added dropwise to the silver tetrafluoroborate (74 mg.) prepared *in situ* under nitrogen. The solution was stirred for 20 hr., before the addition of 2-chloro-2-methyl-3-butyne (62 mg.) and potassium iodide (12 mg.). After stirring for another 20 hr., the silver salts formed were filtered off, most of the solvent removed, and the remainder extracted with ether. On work up of the organic layer, starting material was the major product.

(4) Potassium tert-butoxide method[160]

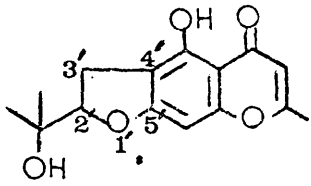
A benzene solution (20 ml.) of eugenin (100 mg.) and potassium tert-butoxide (110 mg.) was stirred under nitrogen for ½ hr. 2-Chloro-2-methyl-3-butyne (55 mg.) in benzene was then added dropwise to the solution at -45°. After the reaction was allowed to come to R.T., the solution was stirred for 6 hr.

The inorganic salts were filtered off, and the filtrate evaporated to yield starting material (10 mg.). Acidification of the inorganic salts, followed by extraction with ethyl acetate furnished the remainder of the starting material (177).

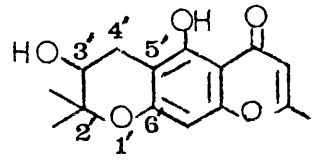
(5) Potassium carbonate method

Potassium carbonate (70 mg.), potassium iodide (9 mg.), 2-chloro-2-methyl-3-butyne (63 mg.) were added to a solution of eugenin (177) (39 mg.) in aqueous acetone (4% v./v. ; 25 ml.) for 43 hr. As before (see p.110) further additions of 2-chloro-2-methyl-3-butyne and potassium iodide were made after 24 hr. of refluxing. Work up (I), followed by preparative t.l.c. (chloroform x 1) yielded 5-O-(1,1-dimethylpropargyl)-7-methoxy-2-methylchromone (201) (6 mg. ; 2%); $\nu_{max}^{CHCl_3}$ 3304, 1662 and 1616 $cm.^{-1}$; n.m.r. signals at τ 8.22 (6H ; s.), 7.70 (3H ; s.), 7.37 (1H ; s.), 6.12 (3H ; s.) and 4.06 (1H ; s.).

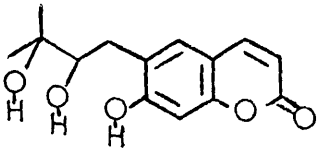
(c) Oxidative Cyclisations of Peucenin and Peucenin-7-methyl Ether



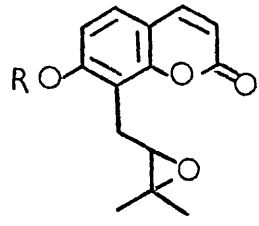
(222)



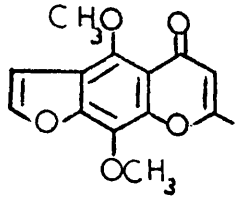
(223)



(202)



(203) R = H
(204) R = CH_3



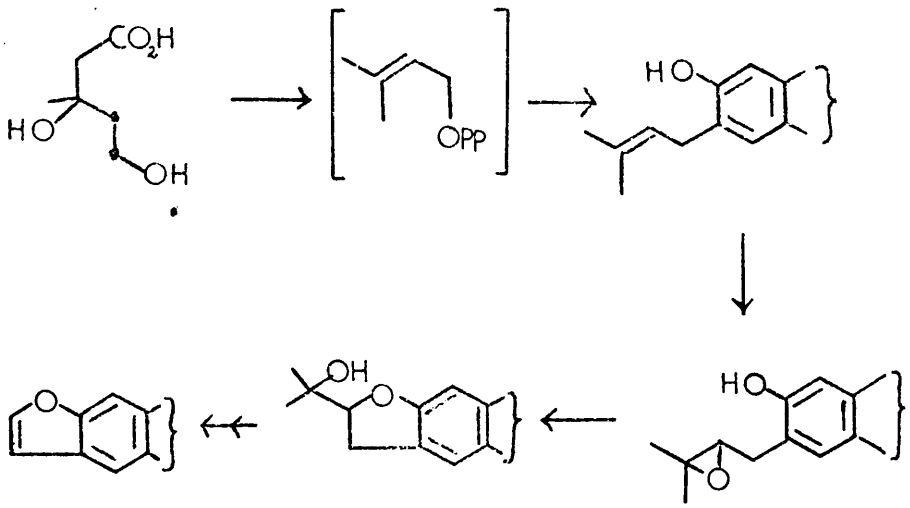
(205)

Many natural products are known[54] in which the oxygenated heterocyclic nucleus is elaborated by attachment on oxygen or carbon of at least one isoprenyl substituent. In chromones, as in other natural oxygen heterocycles, the parent 3,3-dimethylallyl group attached to the aromatic ring is located ortho to an oxygen function as in peucenin (160) and heteropeucenin (162). As a result of this close proximity, it is common to find the C-5 unit cyclised through an interaction with the ortho hydroxyl usually in the form of a 5- or 6-membered ring, exemplified by visamminol (222)[120] and hamaudol (223)[116] respectively.

The problem of the biogenesis of the 2'-(hydroxyisopropyl) dihydrofuran and the 3'-hydroxy-2',2'-dimethyldihydropyran systems found in visamminol (222) and hamaudol (223) has instigated[163,164] many studies. It is generally accepted that these cyclised units may result from a biologically induced interaction with an epoxide or a vicinal diol formed from the 3,3-dimethylallyl precursor. The exact intermediate leading to cyclisation is not known at the present time. However, in the coumarin series, the presence of the vicinal diol (202) isolated as a stable product[165] is significant, whereas the epoxyphenol (203) is only found[53] naturally as its methyl ether (204).

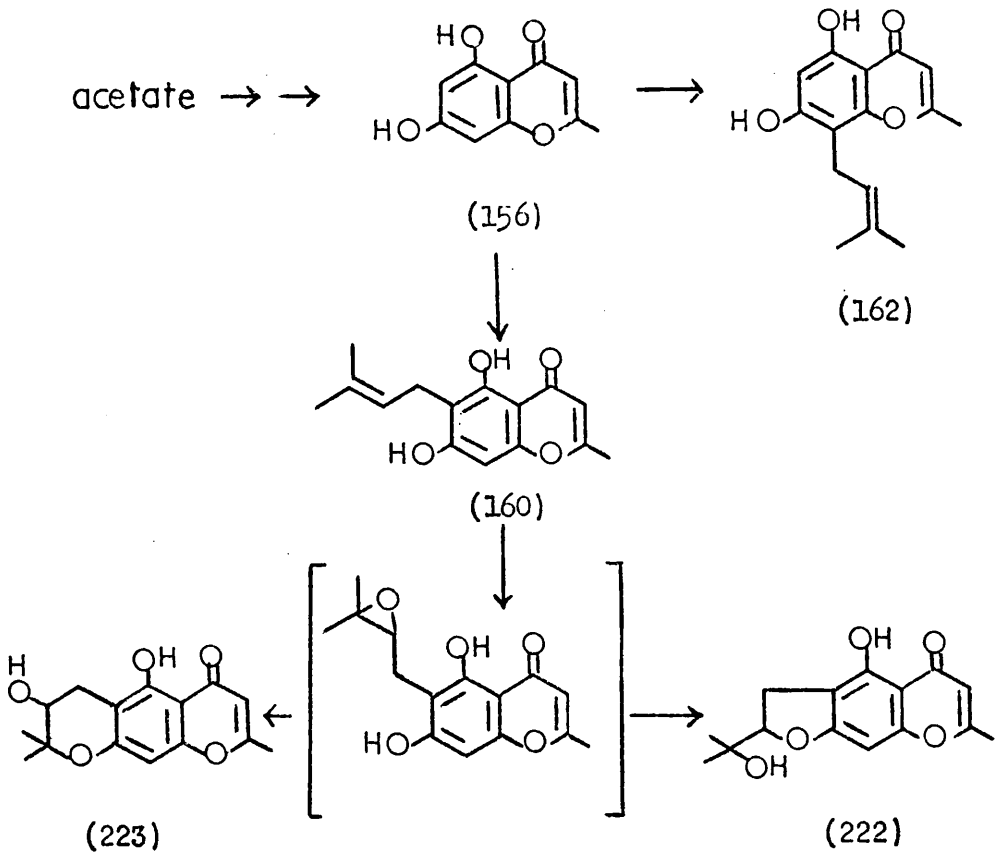
Another common unit found in many natural products[54] is the furanoid skeleton exemplified[106] in the chromones by khellin (205). The biogenesis of this unit is thought to be derived from the isopropylfurano system by loss of the terminal C-3 unit (Scheme 2.9). This origin has been substantiated in furanocoumarins,[166] furano-

SCHEME 2·9



PP = pyrophosphate

SCHEME 2·10



(156)

(162)

(160)

(223)

(222)

chromones[106,146] and furanoquinolines[164] by *in vivo* studies and long since demonstrated *in vitro* by oxidative cleavage of the C_3 unit. The speculative biogenetic pathway to hamaudol (223) and visamminol (222) through 5,7-dihydroxy-2-methylchromone (156) suggested by Steck[106] is shown in Scheme 2.10.

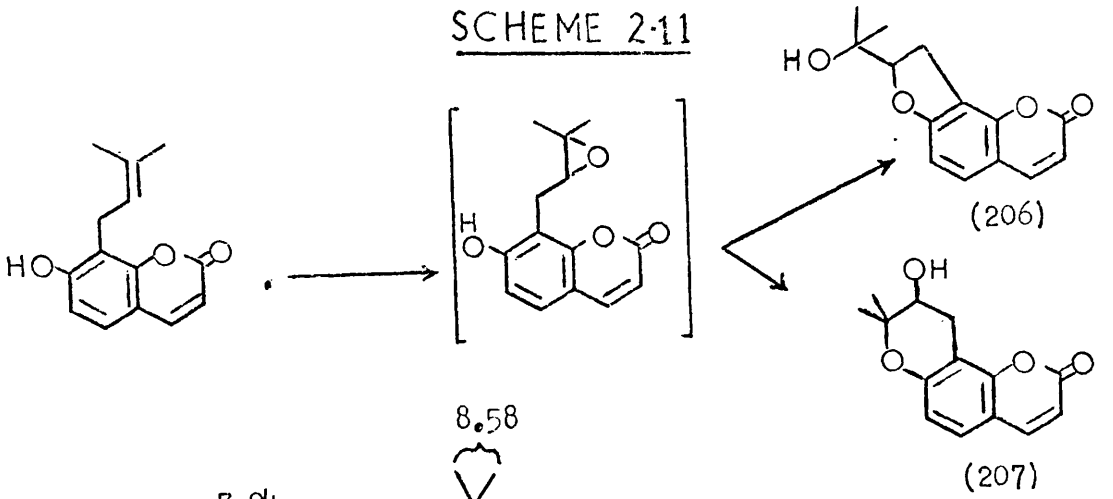
It would appear that epoxidation of peucenin (160) followed by nucleophilic ring opening by the *ortho* phenolic substituent could provide a synthetic route to natural chromones with the dihydrofurans or dihydropyrano skeleton of visamminol (222) or hamaudol (223). Successful studies[167] in this laboratory on the oxidative cyclisations of osthenol (93) has already provided efficient routes to columbianetin (206) and lomatin (207) (Scheme 2.11). With this coumarin series, by careful choice of solvent and epoxidising agent, the dihydrofurano or the dihydropyrano system could be selectively prepared.

(i) The epoxidation of peucenin-7-methyl ether (199)

The 5-hydroxyl of peucenin is chelated and it would be interesting to observe whether it would compete as a nucleophile in oxidative cyclisation. One way of detecting this would be to examine the product(s) obtained from the epoxidation of peucenin-7-methyl ether (199).

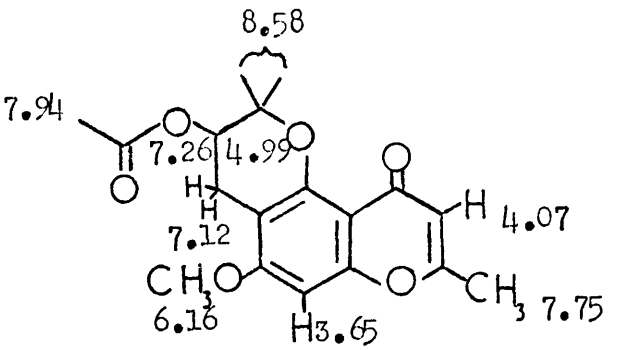
The ether (199) was prepared by diazomethylation of peucenin (160). Epoxidation with *m*-chloroperbenzoic acid in AnalaR chloroform gave two products with similar chromatoplate polarity. From the position of these products, which was well below that of the polarity of the starting ether (199), it was obvious that the

SCHEME 2·11

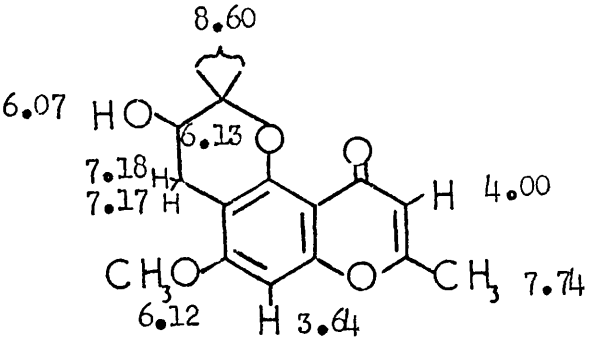


(206)

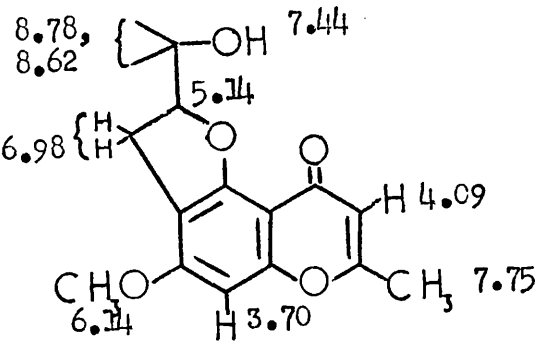
(207)



(210)



(209)



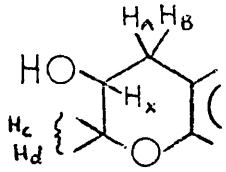
(208)

chelated 5-hydroxyl had been involved in the oxidative cyclisation. However, no separation of these products could be achieved on preparative t.l.c.

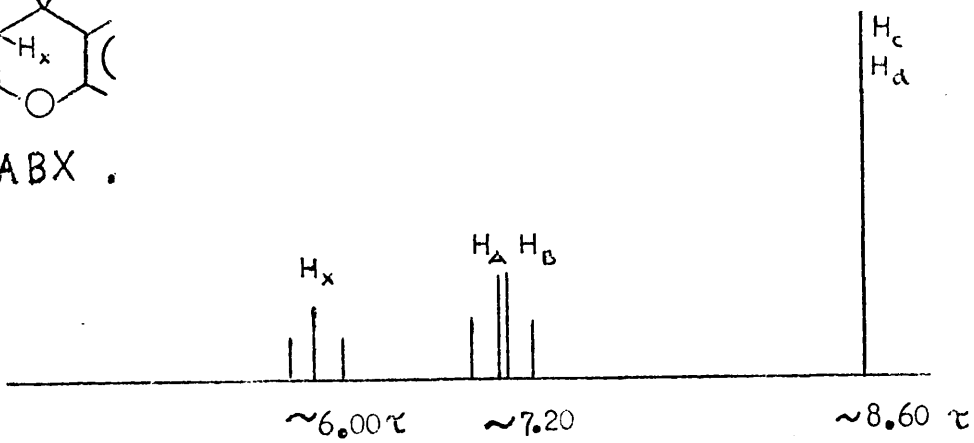
From the signals in the n.m.r. spectrum, the products of epoxidation appear to be a mixture of the 2′-(hydroxyisopropyl) dihydrofuran (208) and the isomeric 3′-hydroxy-2′,2′-dimethyl-dihydropyran ether (209) which should be separable by acetylation. Under these conditions, the tertiary hydroxyl of the isopropyl-dihydrofuran system (208) should be unreactive whereas the secondary alcohol of (209) should acetylate fairly readily, with the result that separation by preparative t.l.c. might be possible. In fact, on applying this procedure to the isomeric mixture of (208) and (209), two products were obtained.

The major product (75%) was assigned the structure of the dihydropyrano acetate (210) on the following evidence. From the i.r. spectrum the product appears to be non-phenolic by the absence of the broad absorption envelope of the chelated hydroxyl. The stretching frequency at 1763 $cm.^{-1}$ is characteristic of an acetate carbonyl function, and the other maxima at 1660, 1630 and 1607 $cm.^{-1}$ show the spectral profile associated with a substituted C-5 hydroxyl on the chromone nucleus (see p. 81). The resonances from the n.m.r. spectrum indicated alongside the structure (210) show the methylene protons at τ 7.26 and 7.12 as doublets (J~6 Hz.) and the methine proton as a triplet at τ 4.99 (J~6 Hz.) which constitute the familiar ABX system associated[164,168] with the 3′-hydroxy-dimethyldihydropyran system (see Table 24).

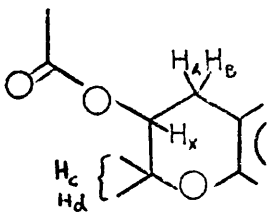
TABLE 2·4



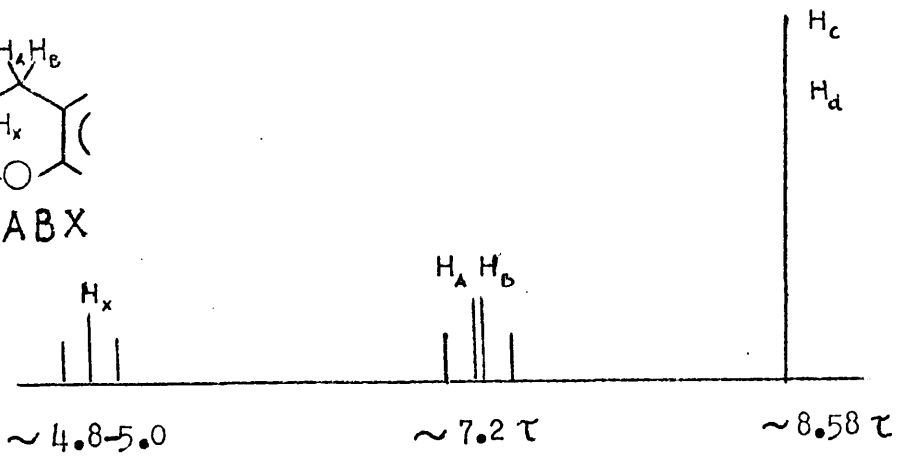
ABX .



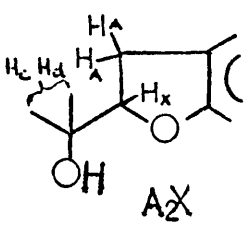
J~ 6Hz.



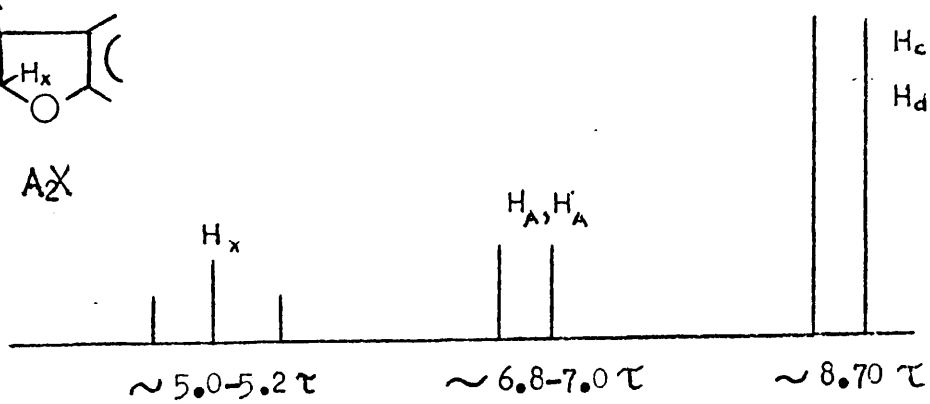
ABX



J~6 Hz.



A_2X

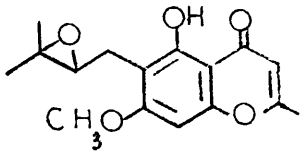


J~9-10 Hz.

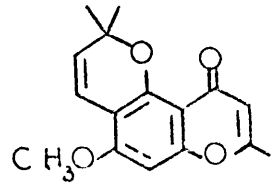
Mild hydrolysis of the acetate (210) regenerated the alcohol (209) which possesses a similar n.m.r. spectral pattern to that of the acetate. However, comparison of the two spectra reveals one primary difference; the methine proton in acetate (210) shows a downfield shift of ~1.14 ppm compared with that of the alcohol (209). This has been used as an additional method of discriminating between the alcohols (208) and (209) as the methine proton of a tertiary acetate should only show a downfield shift[169] of ~0.25 ppm compared with that of the tertiary alcohol.

The minor product (8%) isolated from the reaction mixture was the angular 2'-(hydroxyisopropyl)-dihydrofuran (208) which did not acetylate under the mild conditions. The n.m.r. signals of this alcohol are shown alongside its structure. The methine and methylene protons at τ 5.14 and 6.98 (J~10 hz.) constitute an A_2X system typical of that exhibited by the hydroxyisopropyldihydrofuran moiety. The gem-dimethyl signals are now split into resonances at τ 8.78 and 8.62 whereas in the secondary alcohol (209) and the acetate (210) they appear as singlets. Table 2.4 compares the general n.m.r. resonances of the ABX and A_2X systems found in this series. The i.r. spectrum of the carbonyl region of the alcohol (208) again shows an absence of a broad absorption envelope for the chelated 5-hydroxyl and in addition, that angular cyclisation to position 5 has occurred from the spectral profile of the maxima at 1655, 1640 and 1613 $cm.^{-1}$

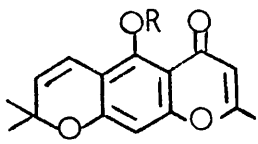
From the results it would seem that the epoxychromone (211) formed <u>in situ</u> undergoes nucleophilic ring opening by the <u>ortho</u> 5-hydroxyl affording the angularly cyclised alcohols (208) and (209).



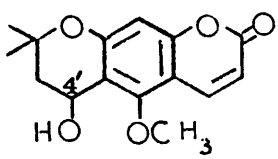
(211)



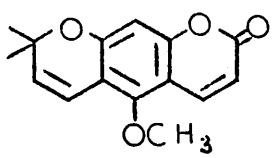
(212)



(213) R = H
(214) R = $COCH{:}C(CH_3)_2$
(215) R = $CH_2CH{:}C(CH_3)_2$



(216)



(217)

However, we hoped to utilise this reaction further, for at that time the structure of a natural chromone, isospathelin-7-methoxy-chromene (212) appeared in the literature[118], isolated from Spathelia sorbifolia. Three other natural chromones (213), (214) and (215) were also isolated although they possess linearly cyclised structures. It would seem likely that dehydration of the angular secondary alcohol (209) synthesised from peucenin-7-methyl ether (199) would lead to the angular chromene (212).

When the epoxidation of (199) was repeated in chloroform acidified[106] with a trace of p-toluenesulphonic acid, nucleophilic ring opening proceeded via the more stable tertiary carbonium ion and led to the preferential formation of the dihydropyran alcohol (209). The result was that a more efficient yield of the alcohol (209) (~92%) was obtained. However, attempts[170-175] to dehydrate the alcohol under a variety of conditions were singularly unsuccessful.

For instance, attempted dehydration of the alcohol (209) with phosphoryl chloride and pyridine[170], followed by the usual work up procedure, gave no isolable reaction products with only a small quantity of starting material (209) being recovered even after constant ethyl acetate extraction. Similarly, when hexamethyl-phosphorous triamide[171] was employed as the dehydrating agent, little starting alcohol (209) and no dehydration products were isolated. These suggest that some water soluble complex of the chromone (209) with the reaction media may be formed thus making product recovery difficult.

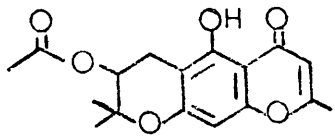
Potassium bisulphate[172] is known to smoothly dehydrate the

alcohol (216) to the chromene (217). However, when a finely ground mixture of the alcohol (209) and freshly fused potassium bisulphate was heated at 160-190° under reduced pressure, only pure starting material was recovered. In the former alcohol (216), the hydroxyl is situated at the more reactive benzylic position which possibly accounts for the facile elimination in this case. A similar lack of success was found when acid catalysed dehydration of the alcohol (209) was attempted using napthalene-β-sulphonic acid.[173]

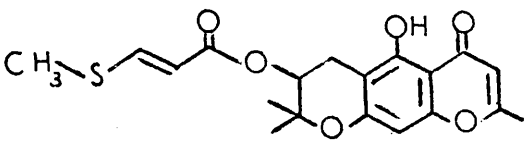
Alumina is known to dehydrate[174] benzylic alcohols and perhaps not surprisingly was ineffective as a dehydrating agent for (209).

Finally, a number of attempts to synthesise the tosylate of the alcohol (209) were made[175] which resulted in only starting material being recovered. As in some of the other medias, the recovery of the starting material was inefficient, even after constant ethyl acetate extraction.

It would be appropriate to note at this point that although the alcohol (209) forms an acetate (210), the yield from this reaction (70-80%) is certainly not as high as that expected from the acetylation of a simple secondary alcohol.



(218)



(219)

(ii) The epoxidation of peucenin (160)

As an extension to the series, the oxidative cyclisation of peucenin (160) was investigated, in the hope that it would selectively lead, through control of the reaction media, to hamaudol (223) or visamminol (222). Although the results from peucenin-7-methyl ether (199) had shown that the chelated 5-hydroxyl would compete in the nucleophilic cyclisations, it was expected that the more acidic 7-hydroxyl function would permit the linear isomers to predominate.

Visamminol (222) was first isolated from Ammi visnaga by Schmid et al[120]; hamaudol (223) was found by Nitta[116] in Angelica japonica. Recently, on further examination of the extracts of A. visnaga, Steck[106] has reported the detection of hamaudol (223), however structural proof is incomplete. The acetate of hamaudol (218) has been reported[117] to be a constituent of Libanotis lehmanniana but, at the present time, it has not been isolated in A. visnaga nor A. japonica. One unusual derivative of the hamaudol series is the sulphur containing analogue, seselirin (219) isolated from seseli sessiliflorum (Schrenk).

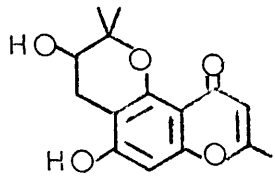
The epoxidation of peucenin (160) was first effected in chloroform as solvent and the products separated by preparative t.l.c. into two main bands. The less polar band from g.l.c. analysis appears to contain two compounds. Acetylation of the mixture followed by chromatographic separation gave two products.

The major compound (78%) was assigned the structure of hamaudol acetate (218) on the following evidence. The i.r. spectrum

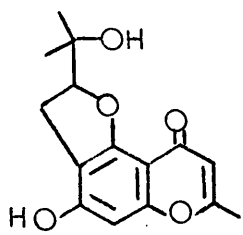
shows stretching frequencies at ~2970 cm.$^{-1}$ assigned to the chelated 5-hydroxyl and at 1738 cm.$^{-1}$ for the 3′-acetoxy carbonyl. The remaining maxima in the carbonyl region at 1658, 1631 and 1584 cm.$^{-1}$, show a spectral profile typical of a 5-hydroxychromone. The n.m.r. spectrum confirms the presence of a chelated 5-hydroxyl and also indicates a characteristic ABX system associated with the 3′-acetoxydihydropyran system (see Table 2.4). The analytical and spectral data of the compound compares favourably with that of (217) synthesised by Nitta[116] during the structural elucidation of hamaudol.

The minor compound (5%) was assigned the structure of visamminol (222). The n.m.r. spectrum shows the presence of a low field proton singlet at τ -1.31 and a broad singlet at τ 8.15, both of which disappear on addition of deuterium oxide. Other resonances in the spectrum indicate an A_2X system which is associated with the 2′-hydroxyisopropyldihydrofuran moiety. When compared with a natural sample[176] of visamminol both compounds were found to be identical.

The more polar band from the chromatoplate again consists of two products which, from the solubility and polarity, appear to contain a free 7-hydroxyl. The n.m.r. spectrum in deuteropyridine indicates the presence of signals attributable to an ABX and A_2X system with the former predominating. The absence of any low field protons for the chelated 5-hydroxyl indicates that angular cyclisation has occurred. On the above evidence, the compounds were assigned the structures (220) and



(220)



(221)

(221).

Confirmation that the structural assignments were indeed correct was obtained through diazomethylation of the 7-hydroxyl. Fractional crystallistion, followed by sublimation gave the major isomer (209) which was found to be identical with a synthetic sample from another source (see p. 125).

The epoxidation of peucenin was repeated in chloroform acidified[106] with p.t.s.a., and afforded an isomeric mixture of hamaudol (223) and visamminol (222) in the ratio of 92:8 (calculated from g.l.c. data). Fractional crystallisation of the mixture gave hamaudol (223) which was identical in all respects with a synthetic sample kindly provided by Professor Kun Ying Yen. The competitive cyclisation to give the angular isomers (220) and (221) was also found to occur (5%).

The acidic conditions utilised above were also employed by Steck[106] in a synthesis of hamaudol (223) from peucenin (160). However, he reported from g.l.c. evidence, that hamaudol (223) was the sole product of reaction. On repeated epoxidations of peucenin (160) using identical conditions to those of Steck, but different g.l.c. conditions for product analysis, we have found that, besides the major product hamaudol (223), a small quantity of visamminol (222) (7-8%) is formed. Moreover, angularly cyclised products (220) and (221) are also formed (~5%) which on g.l.c. appear to have longer retention times than that of hamaudol (223) and visamminol (222). This would be expected from the acidic nature of the free 7-hydroxyls of the angular isomers (220) and

TABLE 2·6

Comparison of i.r. hydroxyl stretching frequencies of hamaudol (223) and visamminol (222)

	ν cm.$^{-1}$	ϵ	
Hamaudol (223)	3616	71	Free hydroxyl stretch
	~3590	~39	Bonded " "
Visamminol (222)	3590	35	Free hydroxyl stretch
	~3100	~60	Bonded " "

(221).

High resolution i.r. studies of visamminol (222) and hamaudol (223) provide an interesting comparison (see Table 2.6). Each exhibits a free and an intramolecularly hydrogen-bonded hydroxyl maxima, besides the broad stretching envelopes of the chelated 5-hydroxyls common to both at $\sim$2970 cm.$^{-1}$. For the secondary alcohol (223) the free hydroxyl band appears at 3616 cm.$^{-1}$, which is 26 cm.$^{-1}$ higher than that of visamminol (222), while the corresponding intramolecularly bonded hydroxyl at $\sim$3590 cm.$^{-1}$ in the former is considerably higher than that of visamminol (222) which is at $\sim$3100 cm.$^{-1}$ Moreover, there are readily discernible differences in the relative intensities of the free and bonded hydroxyl absorptions which show additional diagnostic value. Thus, for hamaudol (223) the free hydroxyl is more intense than the bonded hydroxyl, based on optical density measurements, whereas for visamminol (222) the reverse is true.

The reason for this can be seen from an examination of the molecular models of hamaudol (223) and visamminol (222). In hamaudol, the quasi-chair conformation of the dihydropyran ring with the hydroxyl group in the equatorial position is probably energetically more favoured. With this conformation, intramolecular hydrogen bonding to the dihydropyran is not possible thus accounting for the more intense free hydroxyl stretching frequency. In visamminol (222) in which intramolecular hydrogen bonding is found to be more important, models show that the hydroxyisopropyl group will possibly exist preferentially in a conformation in which

TABLE 2·5

Solvent	+ Hamaudol (%)	Visamminol (%)
$CHCl_3$	89	11
$CHCl_3$/ p.t.s.a.	92	8
EtOAc/ Na_2HPO_4	58	42
EtOAc	66	34
$CHCl_3$/ Na_2HPO_4	73	27
EtOAc/ Na_2HPO_4/ Pyridine	74	53

+ % calculated from g.l.c. data.

the tertiary hydroxyl is hydrogen bonded to the dihydrofuran ring.

The dihydrofuran and dihydropyran system can readily be distinguished using mass spectrometry. A comparison of the mass spectra of visamminol (222) and hamaudol (223) reveals that in the former the principle pathway of fragmentation[177] is the loss of C_3H_6O giving rise to an ion at M-58 which loses a hydrogen atom to give a base peak at M-59. In the dihydropyran series the principal loss is through fission of the chroman ring giving the fragment ions at M-70 and M-71 (base peak).

It remained now to find a suitable solvent system such that visamminol (222) would result as the major cyclised product from the epoxidation of peucenin (160). Previous studies[167] in the coumarin series revealed that under neutral conditions such as the use of ethyl acetate as the solvent media, nucleophilic ring opening favoured in the formation of the 2′-(hydroxyisopropyl) dihydrofuran system. However, in the case of peucenin the use of ethyl acetate as the solvent in the epoxidation still resulted in hamaudol (223) being the major component of the isomeric mixture (see Table 2.5). Even in various 'buffered' chloroform and ethyl acetate solutions no better than a 58:42 ratio of hamaudol: visamminol could be obtained. However, as a means of preparation of visamminol (222) separation from hamaudol (223) was achieved by acetylation and visamminol obtained in 39% yield from peucenin.

Experimental

General Experimental

The epoxidation reactions were carried out using m-chloroperbenzoic acid (85% purity) (Digby Chemicals).

Gas-liquid chromatography was carried out using a Pye Argon Gas Chromatograph equipped with a 1% or-1 Chromosorb-G, 100-120 mesh column operated at 175° with an argon flow rate of 60 ml./min.

Method of Epoxidation

To the solution of m-chloroperbenzoic acid (m.c.p.b.a.) (1.5 x molar equivalent of chromone used) at 0°, the substrate in the minimum volume of solvent was added dropwise over 10 min. The reaction was then allowed to stir at R.T. between 3-6 hr. Excess peracid was destroyed by the addition of aqueous sodium sulphite (10% w./v.) until a test with starch-iodide paper was negative. The reaction mixture was then transferred to a separating funnel and the organic layer washed with sodium bicarbonate solution (5% w./v.), brine to neutrality, dried and evaporated.

In some experiments, disodium hydrogen phosphate was used. This was filtered off before the addition of aqueous sodium sulphite.

Method of Acetylation

The mixture of the cyclised ethers formed in the epoxidation was dissolved in the minimum volume of pyridine (distilled at 115° from KOH and stored over B.D.H. Linde type 4A molecular sieves), AnalaR acetic anhydride (2 fold excess) added and the solution stirred at R.T. overnight.

The reaction was worked up by the procedure employed in work up (II) (see p. 46) or by pouring the reaction mixture on to ice

in order to hydrolyse the excess acetic anhydride, followed by the addition of copper sulphate solution to remove the pyridine.

Under these mild acetylation conditions followed by preparative t.l.c., it was possible to separate the acetates of the dihydropyran secondary alcohols from the unreacted dihydrofuran tertiary alcohols.

Preparation of peucenin-7-methyl ether (199) - see p. 119

1. Epoxidation of peucenin-7-methyl ether (199)

Chloroform

Peucenin-7-methyl ether (199) (100 mg.) and m.c.p.b.a. (182 mg.) in AnalaR chloroform (~6 ml.) were stirred at R.T. for 3 hr. Work up followed by preparative t.l.c. to remove excess reagent (40% ethyl acetate-ether x 3) gave an unresolved mixture of the secondary and tertiary alcohols (209) and (208) (85 mg. ; 76%).

This mixture was separated by acetylation followed by preparative t.l.c. (2% methanol-chloroform x 2) into:-

(i) 5,6-(2',2'-dimethyl-3'-acetoxy-[6',5']-dihydropyrano)-7-methoxy-2-methylchromone (210) (73 mg. ; 75%) crystallised from acetone as colourless plates, m.p. 186-188° (Found: C, 64.97 ; H, 6.01. $C_{18}H_{20}O_6$ requires C, 65.05 ; H, 6.07%); $\nu_{max}^{CHCl_3}$ 1736, 1660, 1631 and 1607 cm.$^{-1}$ (ϵ 214, 760, 159 and 715); mass spectral peaks at m/e 332 (M^+), 289, 272, 257, 229 and 218 (r.a. 3, 19, 48, 26, 25 and 100%); n.m.r. signals at τ 8.58 (6H ; s.), 7.94 (3H ; s.), 7.75 (3H ; s.), 7.26 (1H ; d. ; J 6 Hz.), 7.12 (1H ; d. ; J 5 Hz.), 6.16 (3H ; s.), 4.99 (1H ; t. ; J 6 Hz.), 4.07 (1H ; s.), 3.65 (1H ; s.).

(ii) 5,6-(2′-hydroxyisopropyl-[5′,4′]-dihydrofurano)-7-methoxy-2-methylchromone (208) (7 mg. ; 8%) crystallised from acetone as colourless needles, m.p. 201-204°; $\nu_{max}^{CHCl_3}$ (S.P. 100) 3580, ~3410, 1655, 1640 and 1613 cm.$^{-1}$ (ε 64, 40, 971, 108 and 470); n.m.r. signals at τ 8.78 (3H ; s.), 8.62 (3H ; s.), 7.75 (3H ; s.), 7.44° (1H ; b.m.), 6.98 (2H ; d. ; J 9 Hz.), 6.14 (3H ; s.), 5.14 (1H ; t. ; J 9 Hz.), 4.09 (1H ; s.) and 3.70 (1H ; s.).

Hydrolysis of the acetate (210)

The acetate (210) (40 mg.) in methanol was stirred at R.T. for 8 hr. with aqueous sodium carbonate (2% w./v. ; 2 ml.). Most of the solvent was evaporated off and the remainder extracted with ethyl acetate. The organic layer was separated, washed with brine to neutrality, dried and evaporated. The residue, 5,6-(2′,2′-dimethyl-3′-hydroxy-[6′,5′]-dihydropyrano)-7-methoxy-2-methylchromone (209) (30 mg. ; 86%) was crystallised from acetone as colourless prisms, m.p. 247-248°. (Found: C, 66.02 ; H, 6.12. $C_{16}H_{18}O_5$ requires C, 66.19 ; H, 6.25%); $\nu_{max}^{CHCl_3}$ 3621, 3590, 1735, 1662, 1630 and 1608 cm.$^{-1}$; mass spectral peaks at m/e 290 (M^+), 272, 257, 229 and 219 (r.a. 9, 19, 20, 15 and 100% ; n.m.r. signals at τ 8.60 (6H ; s.), 7.74 (3H ; s.), 7.18 (1H ; d. ; J 6 Hz.), 7.17 (1H ; d. ; J 6 Hz.), 6.13 (1H ; t. ; J 6 Hz.), 6.12 (3H ; s.), 6.07 (1H ; b.s.), 4.00 (1H ; s.) and 3.64 (1H ; s.).

The epoxidation was repeated using chloroform acidified with p-toluenesulphonic acid (2 mg.). Work up, purification by t.l.c.

and acetylation yielded the acetate (210) (~82%) and a small amount of the tertiary alcohol (208) (2%).

Attempted dehydrations of the alcohol (209)

Method 1 Phosphoryl chloride/pyridine[170]

To a solution of the alcohol (209) (39 mg.) at -5°, redistilled phosphoryl chloride (0.25 ml.) was added dropwise. The solution was kept at this temperature for 24 hr., allowed to warm to R.T. and allowed to stand for another 36 hr. Work up (II) followed by a constant ethyl acetate extraction yielded starting material (identified from t.l.c. evidence and from m.p.).

Method 2 Hexamethylphosphorous triamide[171]

A solution of the alcohol (209) (20 mg.) in hexamethylphosphorous triamide (B.D.H. ; 4 ml.) was refluxed for ½ hr. After a few minutes the solution turned dark brown and dimethylamine distilled off. The reaction mixture on work up gave starting material.

Method 3 Potassium bisulphate[172]

An intimate mixture of the alcohol (209) (15 mg.) and 'fused' potassium bisulphate was heated in a sublimation block under reduced pressure for ~3 hr. The sublimate isolated proved to be starting material.

Three other methods (4), (5) and (6) were equally unsuccessful in achieving dehydration.

Method 4 Napthalene-β-sulphonic acid[173]

Method 5 Napthalene-β-sulphonic acid/potassium bisulphate

Method 6 Alumina-pyridine.[174]

Attempted tosylation of alcohol (209)

To a solution of the alcohol (209) (56 mg.) in pyridine at 0°, p-toluenesulphonyl chloride in pyridine was added dropwise. The solution was left at -5° for 2 days. Water was then added and the aqueous layer extracted with ether, washed with dil. hydrochloric acid (50% v./v.), brine to neutrality and dried. On evaporation at R.T., an oily residue was isolated which contained starting material only.

2. Epoxidation of Peucenin

A) Chloroform

A solution of peucenin (100 mg.), m.c.p.b.a. (90 mg.) in chlroform (~100 ml.) gave after 4 hr.:-

1] a mixture of the linear isomers (223) and (222) (86 mg. ; 81%) in the ratio 89 : 11 (calculated from g.l.c. data). After acetylation, these were separated by preparative t.l.c. (2% methanol-chloroform x 2) into:-

(i) hamaudol acetate (218) (77 mg. ; 78% based on the linear isomers) crystallised from methanol as colourless needles, m.p. 152-154°. (Found: C, 64.27 ; H, 5.59. $C_{17}H_{18}O_6$ requires C, 64.14 ; H, 5.70%); $\nu_{max}^{CHCl_3}$ (S.P. 100) 1738, 1658, 1631 and 1584 cm.$^{-1}$ (ϵ 504, 1040, 526 and 450); mass spectral peaks at m/e 318 (M^+), 275, 256, 243, 218 and 203 (r.a. 3, 44, 6, 9, 14 and 100%); n.m.r. signals at τ 8.67 (6H ; s.), 7.94 (3H ; s.), 7.66 (3H ; s.), 7.17 (1H ; d. ; J 5 Hz.), 7.08 (1H ; d. ; J 5 Hz.), 4.92 (1H ; t. ; J 5 Hz.), 4.04 (1H ; s.), 3.70 (1H ; s.) and -3.00 (1H ; s.).

(ii) visamminol (222) (5 mg. ; 5%) crystallised from methanol as colourless needles, m.p. 158-160 (lit.[120] m.p. 160-160.5); λ_{max} 232, 249, 255 and 298 nm. (log ϵ 4.27, 4.23, 4.22 and 4.06); $\nu_{max}^{CHCl_3}$ (S.P. 100) 3590, ~3100, 1670, 1635 and 1593 cm.$^{-1}$ (ϵ 35, ~60, 930, 730 and 420); mass spectral peaks at m/e 276 (M^+), 248 and 218 (r.a. 38, 29 and 100%); n.m.r. signals at τ 8.82 (3H ; s.), 8.67 (3H ; s.), 8.15•

(1H ; b.s.), 8.00 (3H ; s.), 6.86 (2H ; d. ; J 9 Hz.), 5.25 (1H ; t. ; J 9 Hz.), 4.02 (1H ; s.), 3.73 (1H ; s.) and -1.31 (1H ; b.s.)

This compound was identical (m.p., m.m.p., i.r.) with a natural sample supplied by Penick Chemicals, New York.

2] a mixture of the similar angular isomers (220) and (221) (5 mg. ; 5%) with the 5,6-(2',2'-dimethyl-3'-hydroxy-[6',5]-dihydropyrano)-7-hydroxy-2-methylchromone (220) predominating (~94%) (calculated from the n.m.r. spectrum); n.m.r. (d_5-pyridine) signals at τ 8.33 (3H ; s.), 8.27 (3H ; s.), 8.00 (3H ; s.), 6.75 (1H ; d. ; J 7 Hz.), 6.64 (1H ; d. ; J 7 Hz.), 5.82 (1H ; t. ; J 7 Hz.), 3.92 (1H ; s.), 3.30 (1H ; s.) and 3.08 (1H ; b.m.).

Diazomethylation gave a mixture of the 7-methyl ethers (220) and (221). Fractional crystallisation from acetone, followed by sublimation at 180°/.01 mm. gave (209) identical (m.p., m.m.p., n.m.r.) with a synthetic sample (see p.136).

B) Chloroform/p.t.s.a.

Using the conditions of Steck , peucenin (160) (213 mg.) in AnalaR chloroform (~100 ml.) and p.t.s.a. (3 mg.) was epoxidised with m.c.p.b.a. (200 mg.) for 6 hr. The usual work up followed by preparative t.l.c. (2% methanol-chloroform x 2) gave:-

(i) a mixture of hamaudol (223) and visamminol (222) (137 mg. ; 61%). The main product hamaudol (223) (92% ; calculated from g.l.c.) was fractionally crystallised from methanol as fine colourless needles, m.p. 192-196° (lit.[116] m.p.

197-197.5°); $\nu_{max}^{CHCl_3}$ 3616, ~3590, 1658, 1630 and 1583 cm.$^{-1}$ (ε 71, ~60, 973, 661 and 525); mass spectral peaks at m/e 276 (M^+), 243, 217 and 202 (r.a. 56, 10, 100 and 19); n.m.r. signals at τ 8.65 (3H ; s.), 8.62 (3H ; s.), 7.68° (1H ; b.d.), 7.69 (3H ; s.), 7.22 (1H ; d. ; J 6 Hz.), 7.12 (1H ; d. ; J 6 Hz.), 6.15 (1H ; t. ; J 6 Hz.), 4.02 (1H ; s.), 3.71 (1H ; s.) and -2.90° (1H ; s.).

This compound was identical (m.p., m.m.p., n.m.r.) with a natural sample of hamaudol kindly supplied by Professor Kun Ying Yen.

(ii) the angular isomers (220) and (221) (11 mg. ; 5%).

C) Chloroform and 'buffered' m.c.p.b.a.

Peucenin (160) (53 mg.), Na_2HPO_4 (92 mg.), m.c.p.b.a. (52 mg.) and AnalaR chloroform were stirred at R.T. for 6 hr. Work up, followed by preparative t.l.c. gave:-

(i) hamaudol (223) and visamminol (222) (45 mg. ; 89%) in the percentage ratio 73 : 27 (calculated from g.l.c.).

(ii) the angular cyclised products (220) and (221) (7 mg.; 2%).

D) Ethyl Acetate

Peucenin (208 mg.), m.c.p.b.a. (211 mg) in AnalaR ethyl acetate stirred at R.T. for 6 hr. Work up, followed by preparative t.l.c. gave:-

(i) hamaudol and visamminol mixture (163 mg. ; 70%) in the

percentage ratio 66 : 34 (calculated from g.l.c.).

(ii) the angular cyclised products (220) and (221) (11 mg.; 5%).

E) Ethyl Acetate and 'buffered' m.c.p.b.a.

Peucenin (51 mg.), m.c.p.b.a. (58 mg.), Na_2HPO_4 (97 mg.) in AnalaR ethyl acetate (10 ml.) stirred at R.T. for 6 hr. Work up, followed by preparative t.l.c. gave:-

(i) hamaudol and visamminol(39 mg. ; 69%) in the percentage ratio 58 : 42 (calculated from g.l.c.).

(ii) the angular cyclised products (220) and (221) (4 mg. ; 2%).

Separation by acetylation (see p.139) furnished hamaudol acetate and visamminol (39% from peucenin).

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