Synthetic Approaches to Complex Naturally Occurring Coumarins.

THESIS

presented to the University of Glasgow

for the degree of Doctor of Philosophy

by

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Summary of a Thesis Entitled :-

Synthetic Approaches to Complex Naturally Occurring Coumarins.

Synthetic routes to the naturally occurring coumarins glabralactone and the more complex dentatin have been developed to provide unequivocal proof of their structures. The structure assigned to angelicone, an isomer of glabralactone, has also been synthesised, by an unambiguous pathway. As a consequence of this work, the published structure of angelicone has been shown to be incorrect. A key step in each of these syntheses has been the base-catalysed retro-Michael opening of a chromanone ring, to generate a phenolic coumarin containing an ortho senecioyl grouping. Additionally, base treatment in this manner has provided, by coumarin ring opening and alternative reclosure, a method for the efficient synthesis of both 6- and 8- senecioyl-5,7-dioxygenated coumarins.

The above described chromanone ring opening and coumarin ring isomerisation processes have also been utilised in the synthesis of dentatin, a linear chromenocoumarin whose structure had been based on spectroscopic data only. The 1,1- dimethylallyl group at C-8 was introduced by the ortho-Claisen rearrangement of the 7- O- (3,3- dimethylallyl) ether derived from a readily available phenolic chromanocoumarin. The further rearrangements to which this type of alkenyl is prone, were deliberately prevented by having a senecioyl group at C-6. The rapid intramolecular cyclisation of this group with the 7- hydroxyl liberated during the Claisen rearrangement, resulted, in high yield, in the formation of a linear chromanocoumarin having the correct carbon skeleton and oxygenation pattern of the natural product. Further careful reduction and dehydration proceeded smoothly to give pure dentatin.

Preliminary investigations have been directed towards the syntheses of some structurally complex natural 4-alkyl coumarins which have recently been shown to possess important physiological activity. The reaction of 2,2-dimethyl-5,7-dihydroxychroman-4-one with acetylene dicarboxylic acid dimethyl ester has given two new isomeric 4-carbomethoxy chromanocoumarins. The structures of these have been assigned on both spectroscopic and chemical evidence. Attempts to modify the carbomethoxy group and to induce chromanone ring opening have been made. The corresponding 4-methyl analogues have been prepared and shown to be resistant to oxidation.

Acknowledgements

I would like to thank, most sincerely, my supervisor, Dr. R.D.H. Murray, for his assistance, guidance and his constant friendship during the course of this research. His enthusiasm has been a source of great encouragement to me and his words of advice on many diverse topics have been greatly appreciated.

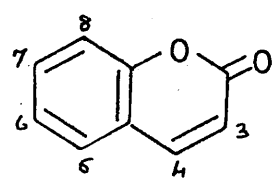
I would also like to thank all the members of staff in the Chemistry Department who supply the technical services, especially Miss F. Cowan, Mr. A. Haetzman and Mrs. F. Lawrie.

During the last three years, it has been my privilege to work beside some exceptional characters. Discussions with them on scientific matters and the problems of the world have proved most rewarding, and I wish to thank them all for their friendship.

I am also indebted to the Science Research Council for a maintenance award.

Contents.

A Short Review of 4-substituted Coumarins

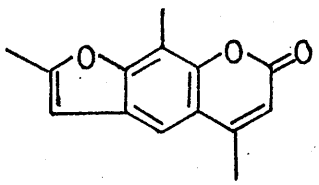


(1)

Since the isolation of coumarin (1) in 1820[1] from Coumarouna odorata (Willd) by Vogel, many compounds possessing this skeleton as a fundamental unit have been isolated from plant sources. There has been continual interest in the isolation and synthesis of novel natural coumarins due to the growing number of pharmacological properties associated with such oxygen heterocycles. Over the last ten years, there have been several reviews[2,3,4], of natural coumarins dealing with their isolation, structural elucidation and pharmacological properties. However one branch of the coumarin family which has failed to achieve prominence in the chemical reviews of the last decade, is that group of natural coumarins bearing a carbon substituent at C-4. This lack of recognition is due principally to their comparatively late emergence, although recent reports of the high insecticidal[5] and anti-tumour[6] activity of certain members of this class will undoubtedly stimulate interest in synthetic possibilities.

This class of natural coumarins can be conveniently divided into two major groups; I, those bearing a C-4 alkyl substituent; and II, those bearing a C-4 aryl substituent. This review does not include the C-4 oxygenated coumarins, as this would enlarge it beyond the scope of this thesis.

The simplest members of Group I are those bearing a methyl group at the C-4 position. When Dean[2] in 1963, and Soine[3] in 1964 reviewed natural coumarins, there were no examples of 4-methyl coumarins known to occur in plant sources. However Nielsen[4] mentions the 4-methyl furo-



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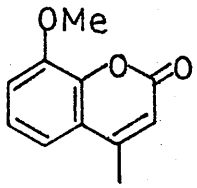

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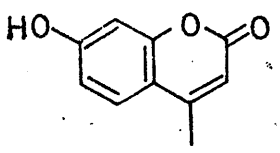

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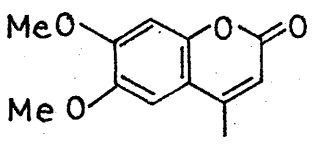


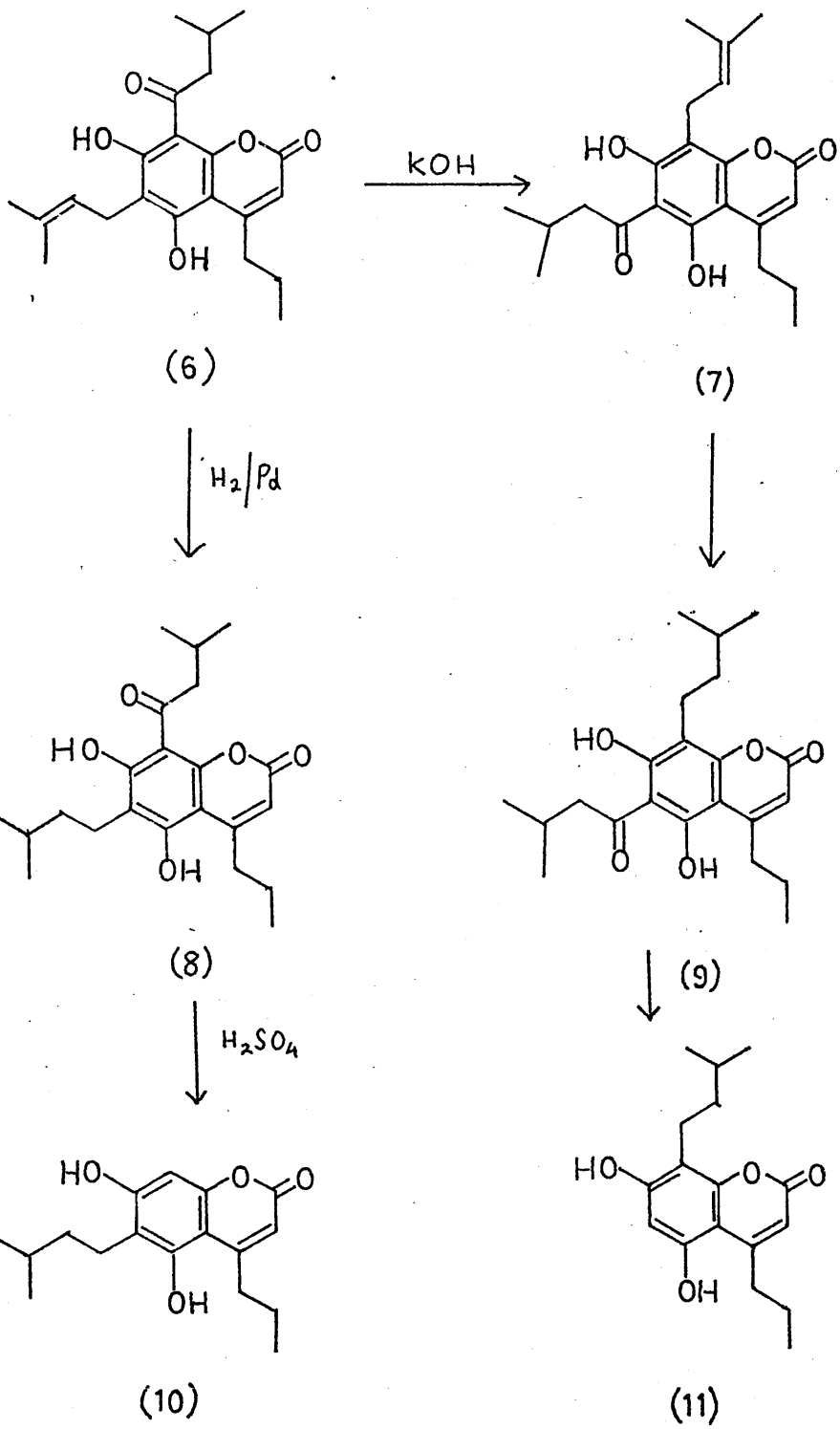
(5)

coumarin (2) isolated by Scheel[7] in 1963 from Apium graveolens L. This compound possesses the unusual feature of having another methyl group attached to the ring at C-8, whereas methyl groups are more frequently found attached to the aromatic ring as ethers. The coumarin (3) isolated[8] from Ekebergia senegalensis is also an unusual member of the coumarin family. The majority of natural coumarins possess an oxygen substituent at C-7, either as a phenolic-OH, an ether, or as part of a heterocylcic ring system, whereas 3 has no such substituent at C-7, but has a methoxyl group at C-8. The only other natural 4-methyl coumarins isolated to date are the phenol (4)[9] and the bis-ether siderin[10] (5), both isolated from Ruta pinnata. The former compound has been synthesised[11] by the Pechman condensation of ethylacetoacetate with resorcinol in the presence of a variety of acid catalysts.

It should be noted that a great number of synthetically derived 4-methyl coumarins appear in the literature. This is due to their ease of formation from ethyl acetoacetate by Pechman condensation[11], even when the aromatic portion of the molecule has been extensively functionalised.

The most abundant members of the natural 4-substituted coumarins are those bearing a n-propyl group. To date, the most prolific source of such compounds has been the West Indian tree, Mammea americana L. The fruit of the mammey tree has long been considered to be edible, but suspicion that it might contain toxic constituents, led to the examination of its constituents, and the isolation[12] of a coumarin named mammein. This compound was assigned

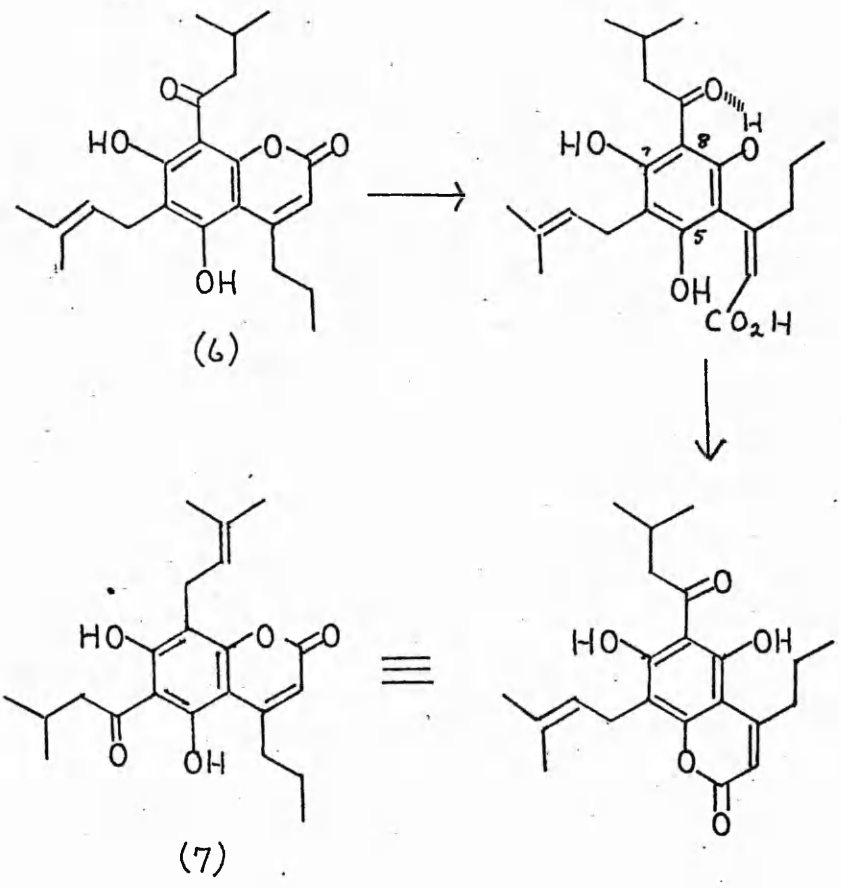
Scheme 1

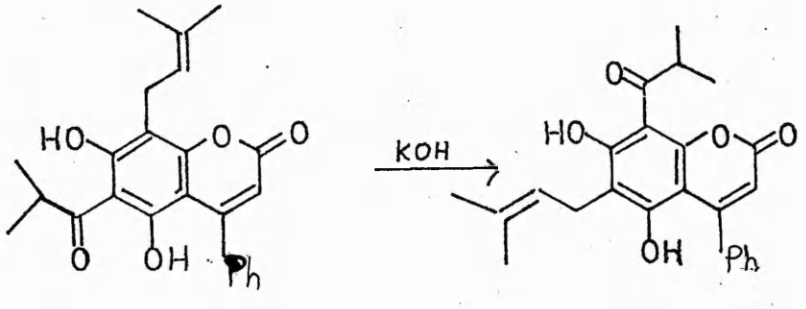


structure 6 on the basis of its spectroscopic properties and rigorous degradation by Djerassi[12] in 1960. Mammein is a 5,7-dihydroxycoumarin having a n-propyl substituent at C-4, an isopentenyl substituent at C-6 and an isovaleryl group at C-8. Whilst determining the positions of the latter pair of substituents, some general properties of this type of coumarin were observed, which proved useful in the determination of the structures of similar natural products, (Scheme 1). Mammein is a colourless crystalline solid which on treatment with methanolic KOH followed by acidification yielded a yellow crystalline isomer (7), in which the substituents at C-6 and C-8 have exchanged. The mechanism of this isomerisation involves the opening of the lactone ring, followed on acidification by closure with the alternative ortho OH at C-5. Chelation between the carbonyl at C-8 and the liberated lactone phenolic OH is sufficient to direct relactonisation to the non-chelated C-5 OH, (Scheme 2). In this case, there is a quantitative conversion to the C-6 acyl isomer (7), but in certain other examples[13], an equilibrium mixture is obtained in which the C-6 acyl isomer is predominant, but a small percentage of the C-8 acyl isomer remains. Two examples in which the isomerisation goes in the opposite direction have been reported[14,15]. Mesuol (12) is converted to iso-mesuol (13) on treatment with base, but some dubiety has arisen in that no yields are quoted for this reaction. Tomentolide B (55) is similarly isomerised by base to yield a C-8 acyl coumarin, which has been conclusively characterised.

In connection with synthetic studies[16] in this series it was observed that 75% H_2SO_4 represented an excellent

Scheme 2





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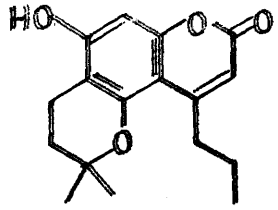

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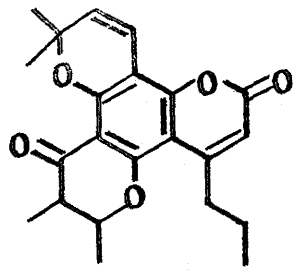

(55)

Scheme 3

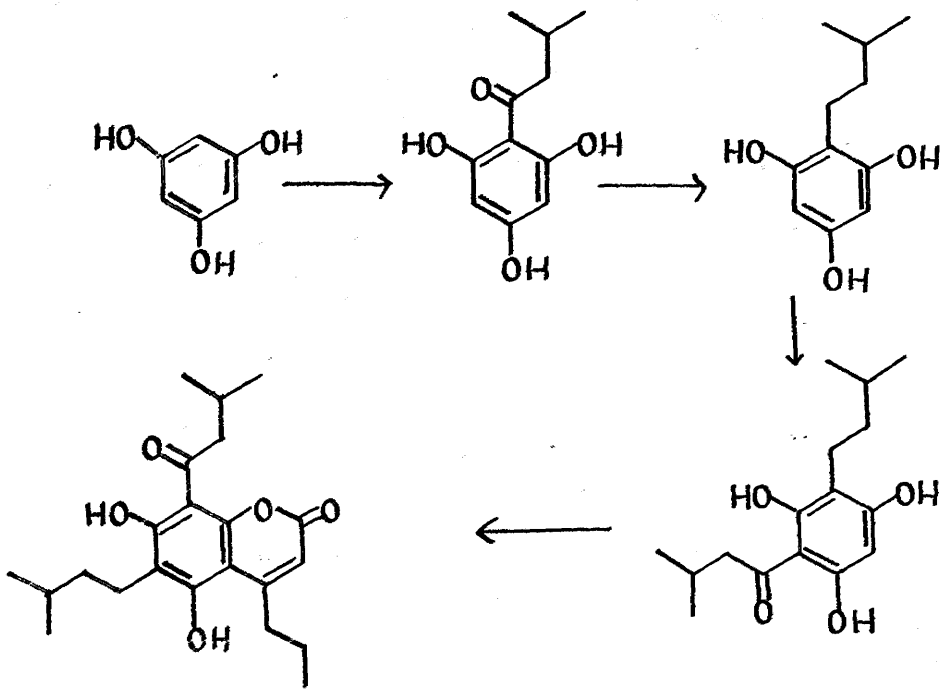

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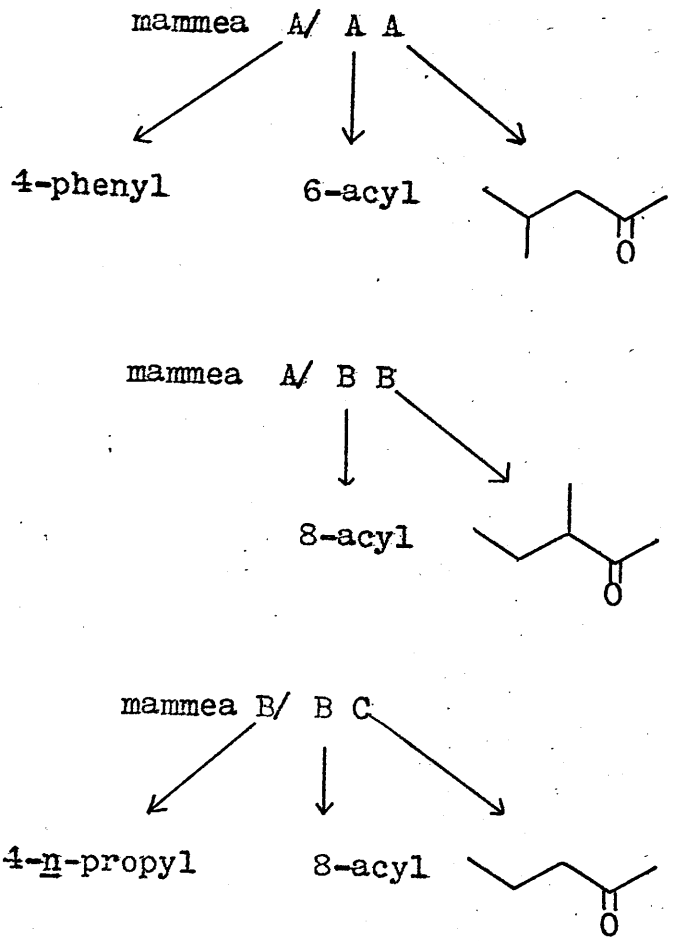
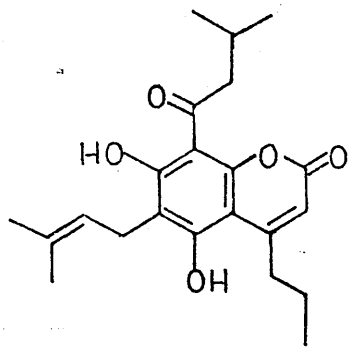
Table 1


mammea A/ A A
4-phenyl
6-acyl
O
mammea A/ B B
8-acyl
O
mammea B/ B C
4-n-propyl
8-acyl
O

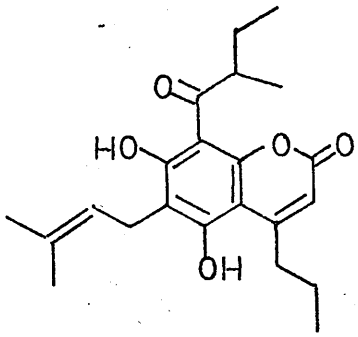
deacylating agent, without causing any rearrangement, since the reaction proceeded with the coumarin skeleton intact. It is possible that the ease of this reaction is due to the relief of steric compression about the aromatic ring. However, when this reaction is carried out in the presence of an ortho-isopentenyl phenol, as in mammein, a cyclised product (14) is formed[17]. This acid catalysed deacylation introduces complications with respect to the synthesis of this type of coumarin, as the acyl substituent now requires to be protected before acid catalysed coumarin ring formation can take place[16] and a protective method must also be found to halt the rearrangement of the acyl substituent in the presence of base. The low yield (1%) obtained by Djerassi[16] in his synthesis of dihydromammein can be readily explained by this type of deacylation, (Scheme 3).

Since the isolation of mammein, a further twenty seven related coumarins have been isolated from the same source, and a standard system of nomenclature has been devised by Crombie[18]. This system has been used in this thesis for naming coumarins isolated from Mammea americana L. Mammein (6) is named Mammea B/BA, the first letter referring to the C-4 substituent. When a 4-n-propyl group is present, the first letter is always B, and if a 4-phenyl group is present, the letter becomes A. The second letter refers to the position of the acyl substituent, A representing a 6-acyl and B an 8-acyl group respectively. The third letter refers to the nature of the acyl substituent, A representing a 3-methylbutyryl, B a 2-methylbutyryl and C a n-butyryl substituent. (This system is summarised in Table 1).



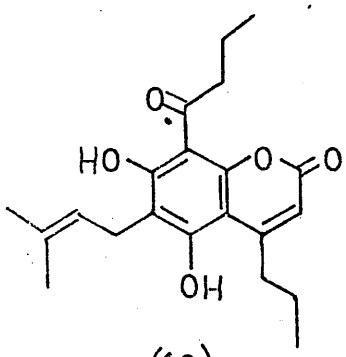
(6)

B/BA



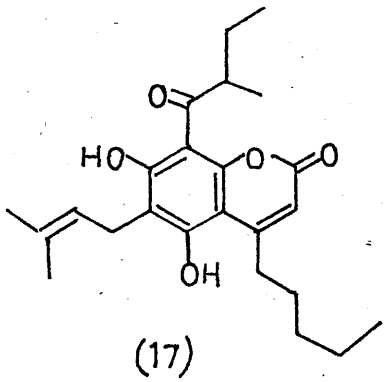
(15)

B/BB



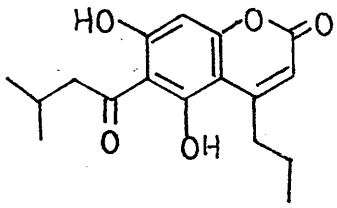
(16)

B/BC



(17)

C/BB



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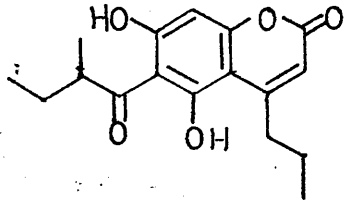

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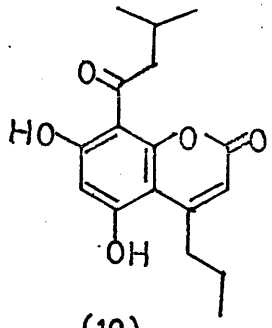

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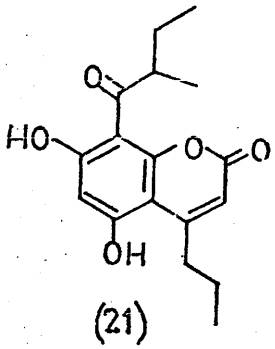
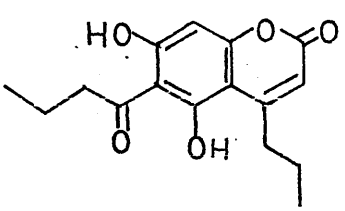


(21)

Crombie has reported[5] that the petroleum extracts of the seeds of Mammea americana L have strongly insecticidal properties, and his search for the active constituent(s) has led to the isolation of a great number of 4-substitued coumarins, all having related, although sometimes unusual, structural features. Initial investigation of the petroleum extracts of the seeds[19] led to the isolation of four 4-alkyl coumarins, named mammea B/BA(6), B/BB(15), B/BC(16) and C/BB(17) respectively. Accurate mass measurements showed that the first pair were isomers having the formula $C_{22}H_{28}O_5$, while the latter two have the formulae $C_{21}H_{26}O_5$ and $C_{24}H_{32}O_5$. Comparison of the IR and UV spectra of all four compounds with the spectra recorded[12] for mammein(6) showed that they are all very similar in structure. Detailed examination of the NMR spectra of mammea B/BA, B/BB and B/BC, revealed that all three compounds possess a 4-n-propyl substituent and an isopentenyl group. Combination of the mass spectral and NMR data revealed that these three coumarins each possess one acyl substituent, which was identified as a 3-methylbutyryl, 2-methylbutyryl and an n-butyryl group respectively. One of the principal problems in the structural determination of this group of compounds, is to find the correct location of the alkyl and acyl substituents. This can be found by degradation of the molecule to known compounds[12,19] or more simply by inspection of the UV spectrum of the natural coumarin[19]. It has been found that coumarins having 6- or 8-acyl substituents show characteristic base-shifts in the UV, and Table 2 shows the UV spectra of the synthetic coumarins (18)-(22)[19] and the four natural coumarins under consideration.

Table 2

coumarin		λ max.nm.					
(18)	acid	232		281	325		
	base	236		295		368	398
(19)	acid	219		289	317		
	base	221	253		329		
(20)	acid	237		282	325		
	base	237		297		368	400
(21)	acid	219		290	317		
	base	222	254		328		
(6)	acid	223	252	293	322		
	base	225	253		322		
(15)	acid	222		295	320		
	base	225	257		333		
(16)	acid	223	252	293	322		
	base	225	253		332		
(17)	acid	222		294	322		
	base	229	257		333		



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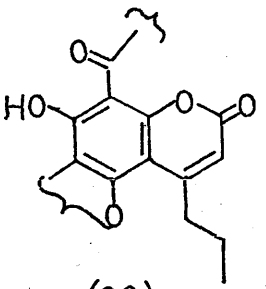
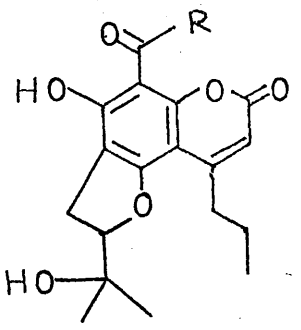


(23)

From this data, it is apparent that all four have the acyl substituent at C-8, and this is further verified by the presence of a chelated OH (τ-4.7) and an unchelated OH (τ2.8) in their NMR spectra. Therefore the coumarins mammea B/BA, B/BB and B/BC were assigned the structures 6, 14 and 15 respectively. The fourth coumarin, mammea C/BB was shown to differ from mammea B/BB only in the nature of the C-4 alkyl substituent, which was found by NMR and mass spectrometry to be a n-pentyl group. Thus mammea C/BB was assigned structure 17. Natural mammein, which was originally thought to be a pure compound, has since been shown[19] by comparison to consist of a mixture of the coumarins mammea B/BA(6), B/BB(15) and B/BC(16).

However, none of these compounds was found to possess insecticidal activity[19], and so the petroleum extract of the seeds was re-examined[20]. Careful chromatographic separation showed the presence of six new 4-n propyl coumarins, but separation of these proved difficult, and so identification was approached by resolving them into small groups of congeners. The structures of the individual members were then deduced from spectral data, and the compounds related to known coumarins by chemical conversions.

The IR, NMR and mass spectra indicated that each group had the partial structure (23), the position of the acyl group being determined from the UV spectrum. The acyl substituent was shown to be either a 3-methylbutyryl, 2-methylbutyryl or a n-butyryl group, but the nature of the alkyl substituent at C-6 was found to be more complex than that of any previously isolated Mammea coumarins. The NMR spectrum of the first group of congeners showed the



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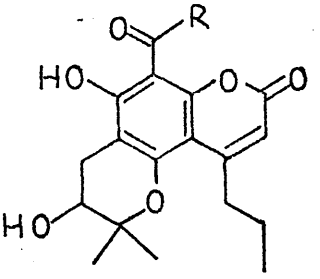

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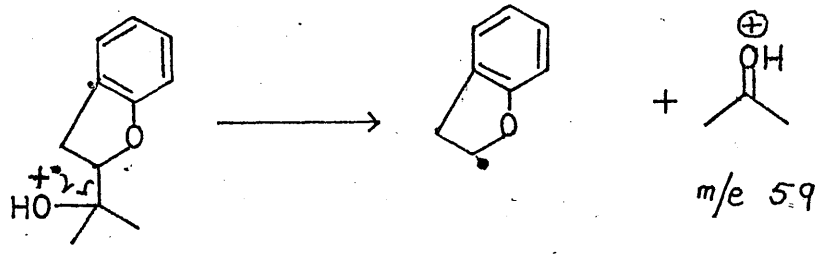
Scheme 4



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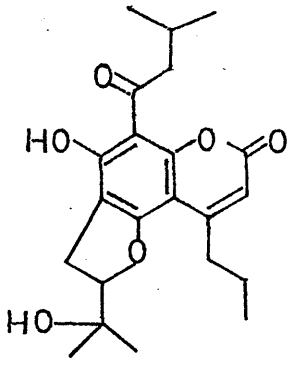

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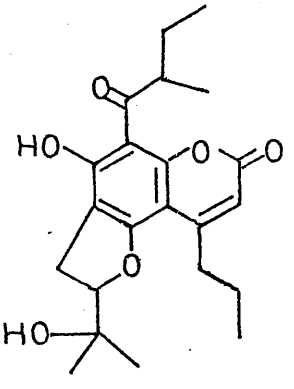

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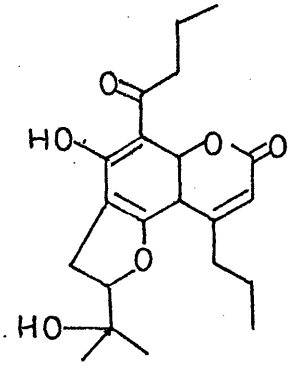

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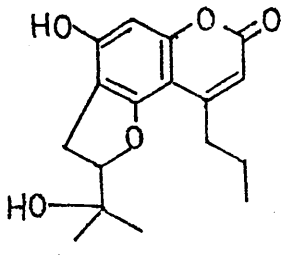

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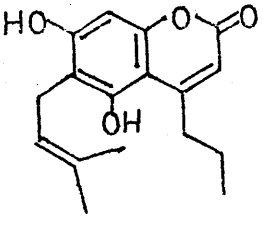

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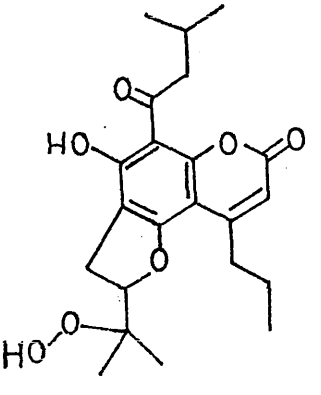
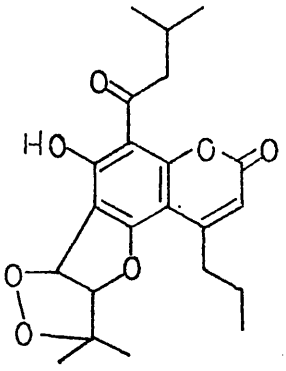


(33)

absence of the phenolic 5-OH, but did show a new OH signal at τ 8.06. This information, along with accurate mass measurements, suggested that the compounds could be either α-(hydroxyisopropyl) dihydrofurans (24) or the isomeric 3-hydroxy-2, 2-dimethyldihydropyrans (25). The presence of an abundant ion at M/E 59 in the mass spectrum (Scheme 4), favoured the former, and this was confirmed by the NMR spectrum of the diacetate of this compound. The methine proton showed a downfield shift of 0.27 p.p.m., in agreement with 24, a much larger shift being expected for the secondary alcohol (25). Thus the three coumarins in the first group of this extract were assigned the structures (26-28). Further confirmation of these assignments was obtained by the synthesis of the de-acylated product (29) from the coumarin (30)[20] by treatment with m-chloroperbenzoic acid.

The remaining three coumarins isolated by Crombie at this time proved to be further oxygenated coumarins (31-33). The first two gave a positive peroxide test[21] and spectral comparisons with the coumarins (26-28) confirmed their structures. The structure of the hydroperoxide (33) was assigned by similar spectral comparisons.

In view of the oxidation level of these new compounds, the aerial oxidation of mammea B/BA, B/BB and B/BC was examined[20]. Thus, when a mixture of these three coumarins was dissolved in $CHCl_3$, and left in light for ten weeks, (26-28) were shown to be present by TLC, along with other unidentified material. The problem of whether these natural coumarins originate from metabolism within the seed, or are formed during the isolation procedure, is as yet undetermined.



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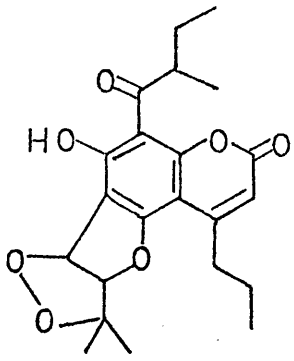

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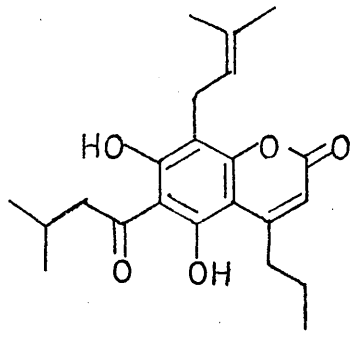

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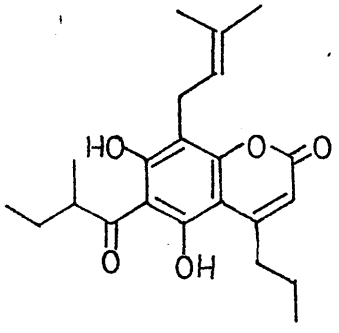

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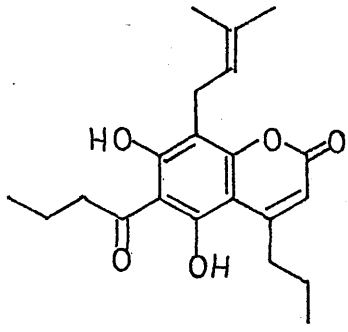

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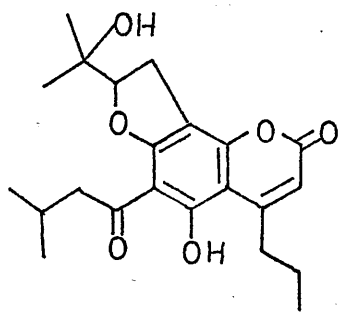

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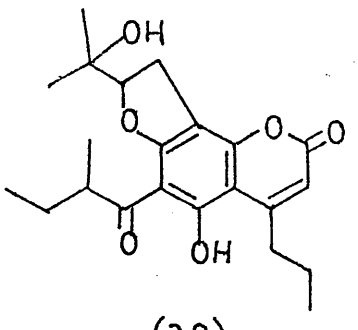

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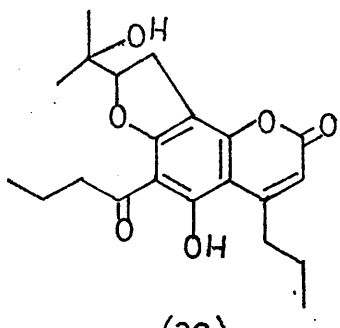

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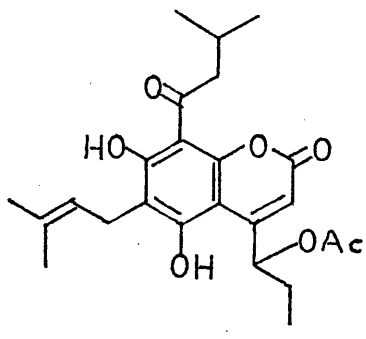

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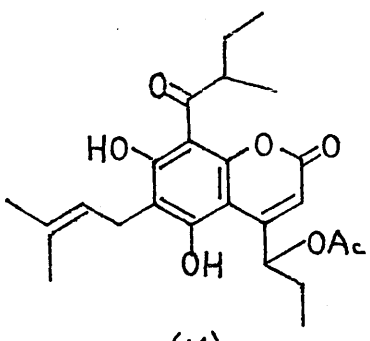

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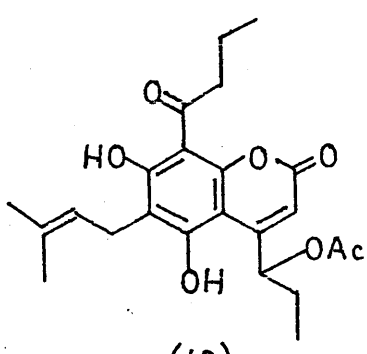

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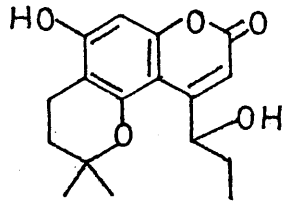
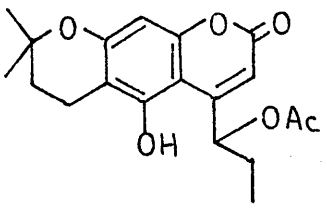


(43)

None of the above extracts had any insecticidal activity, and so further examination of the seed extract was undertaken[22]. This revealed the presence of some new 4-n-propyl compounds. These were all yellow crystalline phenols, whose UV spectra indicated that their acyl substituents were positioned at C-6[19]. The structures of these coumarins were determined by the same means used for their previously isolated isomers. The first three (34-36) are the isomers of natural mammein[12,19] and are named mammea B/AA, B/AB and B/AC respectively. The remaining three were the 7,8--annulated α-(hydroxyisopropyl) dihydrofurans (37-39), the structures being confirmed by their syntheses from mammea B/AA, B/AB and B/AC by treatment with m-chloroperbenzoic acid. The coumarins (34-36) were synthesised by the base--catalysed isomerisation of mammea B/BA(6), B/BB(14) and B/BC(15) respectively. However these six coumarins still showed no insecticidal activity, but a further two coumarins, isolated[5] as an inseparable mixture, possessed greater insecticidal activity than the non-crystalline concentrate from which they had been isolated. Spectral evidence suggested that these colourless coumarins were similar to the previously isolated mammea B/BA and B/BB differing only in the nature of the C-4 alkyl substituent. The loss of ketene and acetic acid in the mass spectrum suggested the presence of an acetate and NMR showed that this side chain was a 1-acetoxy-n-propyl group. Therefore the insecticidal components of the seed extract of Mammea americana have the structures (40) and (41). The authors comment that the mass spectrum of the mixture suggests



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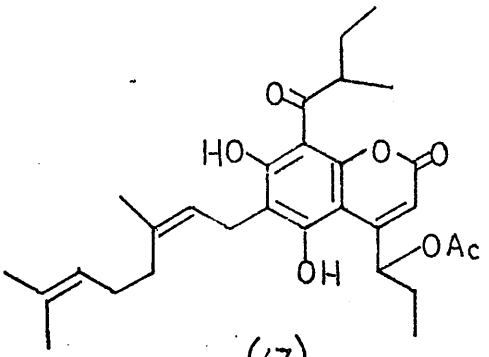
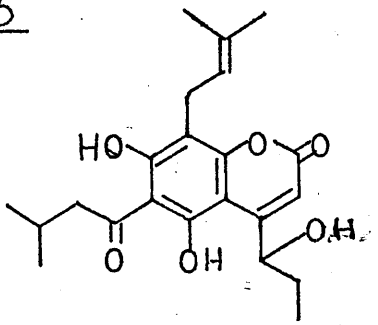


(47)

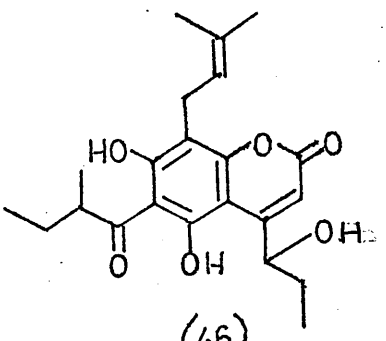
Scheme 5

(40) $\xrightarrow[MeOH]{KOH}$



(45)

(41) $\xrightarrow[MeOH]{KOH}$



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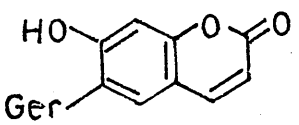
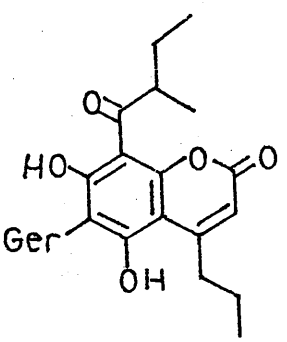


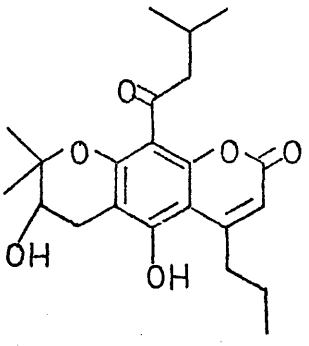
(48)



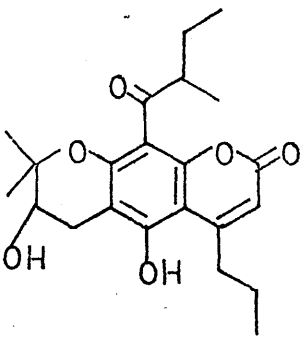
(49)

the presence of a small amount of 42, but no further evidence was found to support this. Treatment of 40 and 41 with 70% H_2SO_4 resulted in deacylation and cyclisation to give the chroman (43) whilst treatment with CF_3CO_2H gave 44, and treatment with methanolic KOH yielded the corresponding 6-acyl coumarins (45) and (46), (Scheme 5). The two coumarins (40) and (41) have been shown[5] to be uncouplers of oxidative phosphorylation, a property shared by the other natural Mammea coumarins, but the presence of the 1'-acetoxy group attached to the 4-alkyl substituent appears to be the important factor in the conferment of insecticidal properties. This was further confirmed, when the naturally occurring coumarin[23], surangin B (47) was tested[5], and found to be even more toxic to houseflies than the active coumarins (40) and (41). Surangin B was isolated from the roots of Mammea longifolia (Wight), and its structure was assigned on the basis of its spectral properties. The only difference between surangin B and 41 is the presence of a geranyl group at C-6. This substituent was suspected from the NMR spectrum and comparison of the mass spectral fragmentation pattern of surangin B with that of ostruthin (48) confirmed this. Surangin A (49), isolated from the same source, structurally is similar to 47, but without the acetoxyl group on the C-4 substituent.

A further group of highly oxygenated coumarins, isolated from Mammea americana by Finnegan[24], have been assigned the structures (50-52). These assignments were confirmed by their syntheses of 50-52 from the coumarins mammea B/BA, B/BB and B/BC, by treatment with m-chlorperbenzoic acid in the presence of p-toluenesulphonic



(50)



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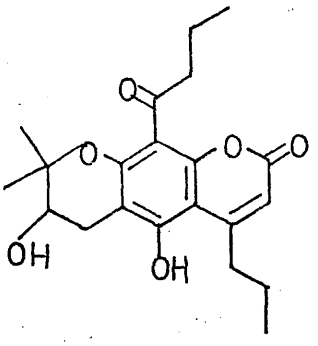

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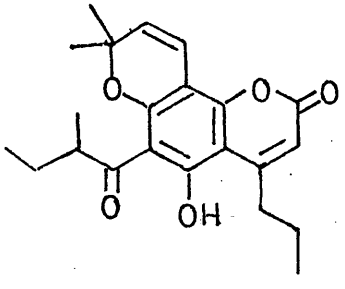

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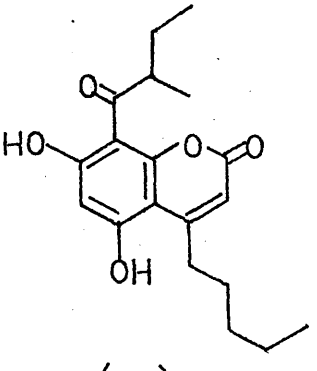

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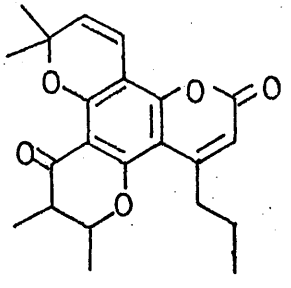
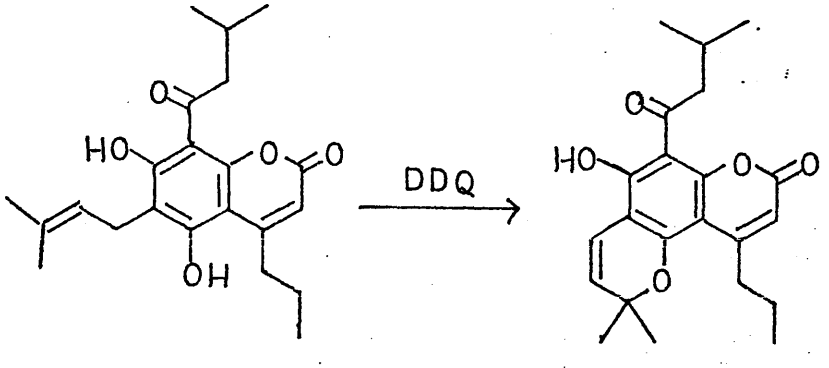


(55)

Scheme 6



acid[25].

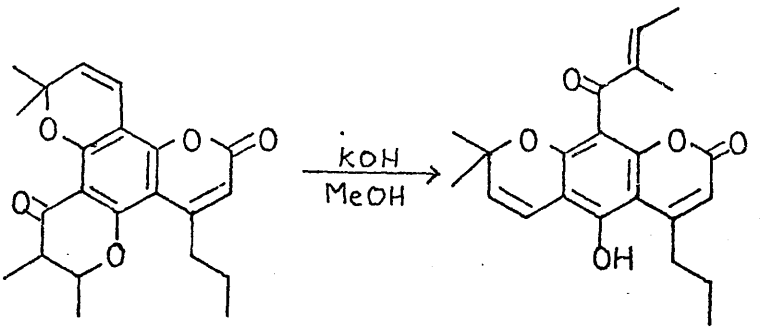
Investigations by Scheinmann[26,27] on the related tree, Mammea africana G Don, have shown the presence of similar 4-alkyl coumarins. Thus mammea B/BA, B/BB and B/BC have been extracted from the seeds of this tree[26], and the bark has yielded[27] the known mammea B/BB and B/AB along with two novel 4-alkyl coumarins. The first of these was shown by spectroscopic means, to be the chromeno-coumarin (53), and the second was assigned the structure (54). The latter is the second example of a natural coumarin bearing a n-pentyl substituent at C-4, the first being mammea C/BB (17)[19].

It is known that 2,2-dimethylchromene rings can be formed by oxidative cyclisation of an isopentyl group with an ortho-phenol, in the presence of dichlorodicyanobenzoquinone, and Finnegan[28] has used this reaction for the conversion of mammein to the corresponding chromene, (Scheme 6). It is interesting to note that acid catalysed cyclisations give linear derivatives, in contrast to the oxidative cyclised angular product.

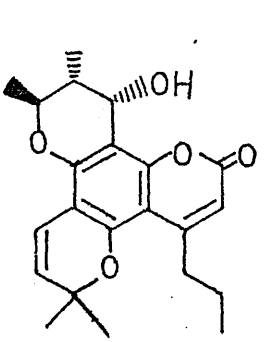
A further method for the synthesis of such, 2,2--dimethylchromenes has been reported by Games[29]. This involves heating the corresponding phenol with 3-hydroxy-1,1--dimethoxy-3 methylbutane, but the yields in this process are low, especially when the aromatic ring is highly substituted.

Other 4-alkyl coumarins possessing chromene rings are known, and tomentolide B (55), isolated from Calophyllum tomentosum[15], is an interesting example. In addition to having the C-8 alkyl substituent cyclised as a chromene

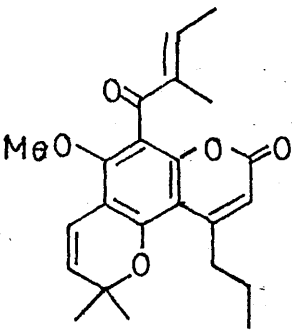
Scheme 9



(55) (56)

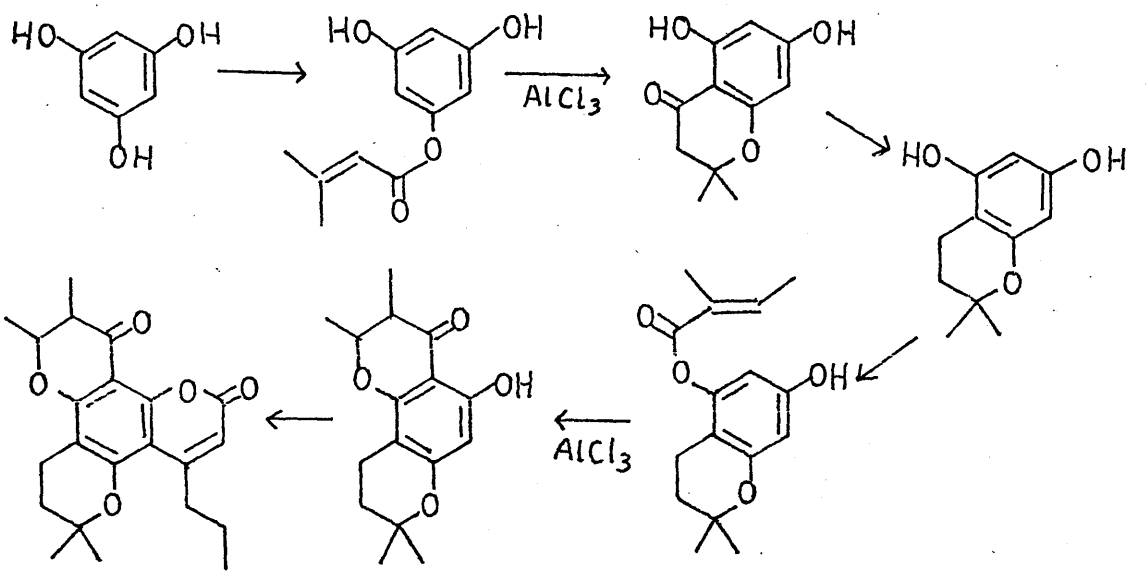


(57)



(60)

Scheme 7

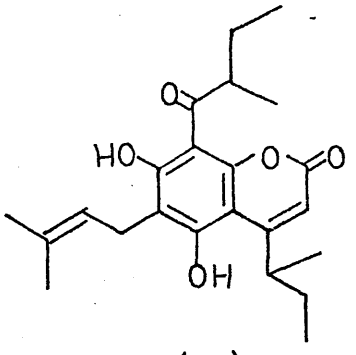


(58) (59)

ring, the C-6 acyl substituent is also cyclised, to form a 2,3-dimethylchromanone ring. The orientation of these two ring systems was confirmed by the base-catalysed isomerisation of tomentolide B. When 55 was treated with dilute KOH, the phenol (56) was obtained. This phenol must be formed by base-opening of the chromanone and coumarin rings followed by relactonisation of the coumarinic acid to the alternative ortho phenol, to yield the 5-hydroxy-8-(2',3'--dimethylacryloyl) coumarin (56), (Scheme 9). The direction of lactonisation in this case is unusual, as cyclisation accurs with the chelated phenol, and not as expected to the non chelated phenol, as in the case of mammein[12].

The coumarin, costatolide (57), isolated[30] from Calophyllum costatum Bail is similar to tomentolide B. In this compound, the relative orientation of the rings is reversed, and the chromanone ring has been reduced to the corresponding chromanol. The structure was verified by the synthesis of racemic oxodihydrocostatolide (58) (Scheme 7) by condensation of the phenol (59)[31] with ethyl butyroacetate in the presence of CF_3CO_2H. Detailed consideration of the NMR spectrum of costatolide has revealed that the two methyls of the chromanol ring are trans to each other, and that the -OH is cis to the neighbouring methyl. Therefore, costatolide should be represented as 57. Another related coumarin (60) has recently been isolated[32] from Calophyllum inophyllum. This compound possesses a chromene ring and a 2,3-dimethyl--acryloyl grouping at C-8, cyclisation of this acyl grouping to a chromanone ring being prevented by the presence of a methyl ether at C-7.

As previously mentioned, the insecticidal components (40)



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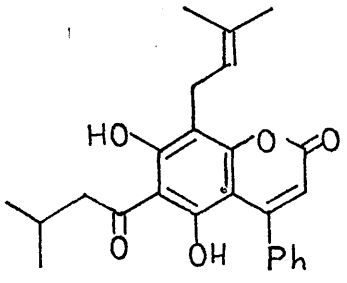

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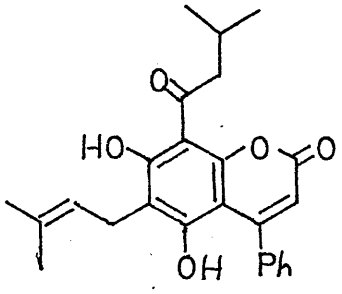

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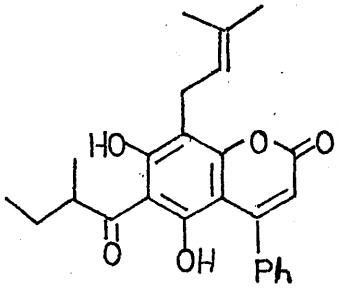

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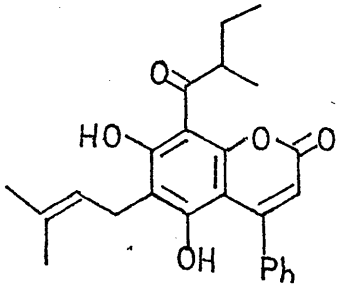

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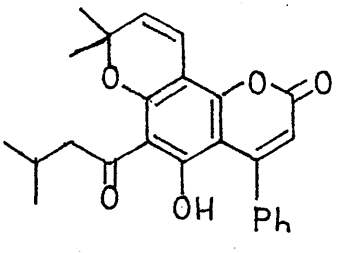

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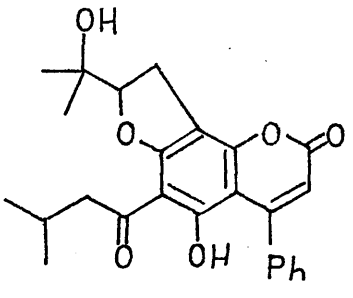

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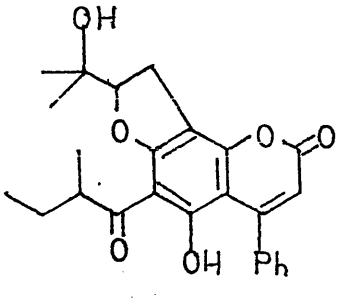

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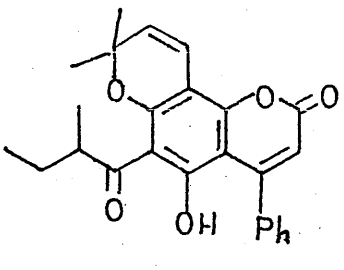

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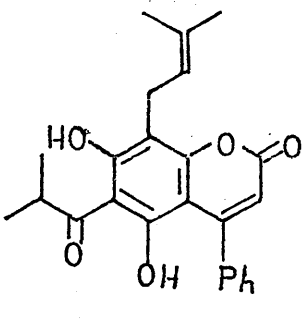


(70)

Table 3

Compound.	Trivial Names.	Source.	Reference.
(6)	Mammein	Mammea americana	12, 19
	Mammea B/BA	Mammea africana	26, 27
	Ferruol C	Mesua ferrea	14.
(7) (34)	Mammea B/AA	Mammea americana	12, 19
		Mammea africana	26, 27
(12)	Mesuol	Mesua ferrea	14
(15)	Mammea B/BB	Mammea americana	12, 19
		Mammea africana	26, 27
(16)	Mammea B/BC	Mammea americana	19
		Mammea africana	26, 27
(17)	Mammea C/BB	Mammea americana	19
(26)		" "	20
(27)		" "	20
(28)		" "	20
(31)		" "	20
(32)		" "	20
(33)		" "	20
(35)	Mammea B/AB	" "	22
		Mammea africana	26,27
(36)	Mammea B/AC	Mammea americana	22
(37)		" "	22
(38)		" "	22
(39)		" "	22
(40)		" "	5
(41)		" "	5

Table 3 contd.

(47)	Surangin B	Mammea longifolia	23
(49)	Surangin A	" "	23
(50)		Mammea americana	24
(51)		" "	24
(52)		" "	24
(53)		Mammea africana	26, 27
(54)		" "	26, 27
(55)	Tomentolide B	Calophyllum tomentosum	15
(57)	Costatolide	" costatum	30
(60)		" inophyllum	32
(61)	Ferruol A	Messua ferrea	33

Table 4

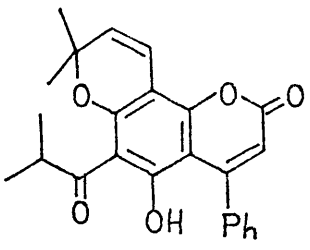
(62)	Mammeisin	Mammea americana	13 ,22, 34
	Mammea A/AA		
(63)	Mammea A/BA	" "	13, 22, 34
(64)	Mammea A/AB	" "	13, 22, 34
(65)	Mammea A/BB	" "	13, 22, 34
(66)	Mammea A/Acyclo D	" "	13, 22, 34
	Mammeigin		
(67)		" "	13, 22, 34
(68)			13, 22, 34

Table 5

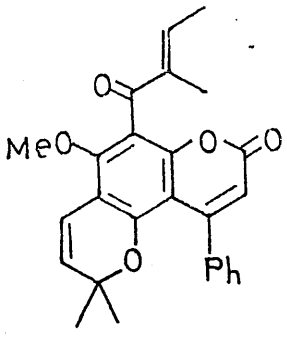
Compound	Trivial Name	Source	Reference
(62)	Mammea A/AA	Mammea africana	26, 27
(63)	Mammea A/BA	" "	26, 27
(64)	Mammea A/AB	Mammea africana	26, 27
(68)		" "	26, 27
(69)		" "	26, 27
(70)		" "	26, 27
	Mesuol	Mesua ferrea	14

and (41) of the Mammea americana seed extract and surangin B (47) have oxygen substituents on the n-propyl group at C-4. One further variation of this side chain has been found, and is exhibited by the coumarin feruol A (61) isolated[33] from Mesua ferrea L. The NMR and mass spectrum of this compound revealed the presence of a 1-methyl n-propyl group situated at C-4, the remainder of the molecule being similar to mammea B/BB. Table 3 gives a summary of these 4-n-propyl substituted coumarins.

The second major group of 4-substituted coumarins possess a 4-aryl substituent. Once again, the most abundant source of these has been Mammea americana L, and the compounds exhibit the same general properties as their 4-alkyl analogues. Thus the 8-acyl isomers can be converted to the 6-acyl isomers by treatment with methanolic KOH, and the acyl substituents can be removed by treatment with strong acid. The structures of these coumarins were assigned by the same means as their 4-alkyl analogues. Table 4 lists the seven 4-arylcoumarins (62-68) isolated from Mammea americana L[13,22,34] and Table 5 lists those from Mammea africana G Don[26,27], (62-64, 68-70). The coumarin (70) was shown to be identical with mesuol (12) a coumarin previously isolated[14] from Mesua ferrea L. Three other coumarins isolated[35] from this latter source are mammeisin (mammea A/AA) (62), mammeigin (mammea A/A cyclo D) (66) and the chromenocoumarin, mesuagin (70a). The position of the acyl group at C-8 in 71 was suggested by its UV spectrum, and this was confirmed by the chemical shift of the two tertiary methyls of the chromene ring. These resonate at τ8.42 and are therefore not shielded by the 4-phenyl ring.



(70 a)



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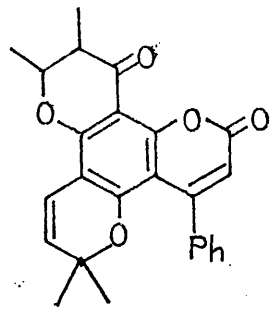

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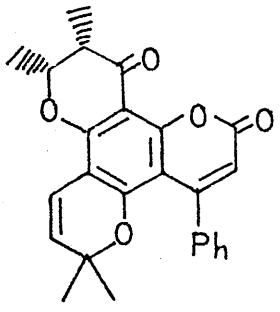

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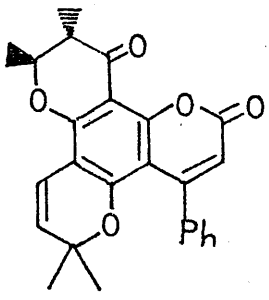

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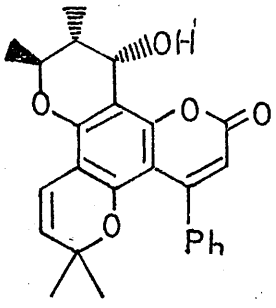

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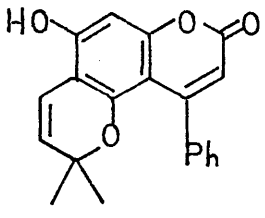

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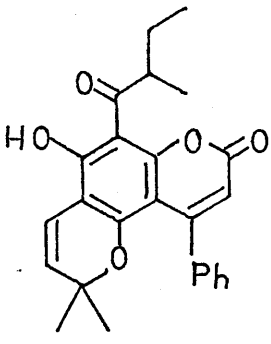

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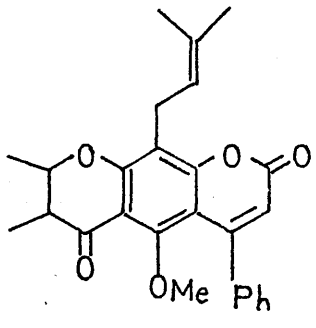

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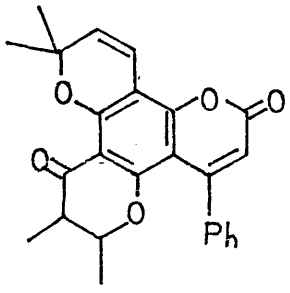

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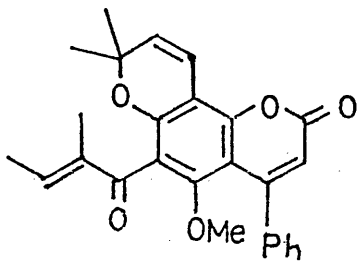
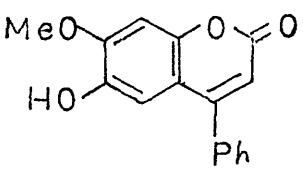


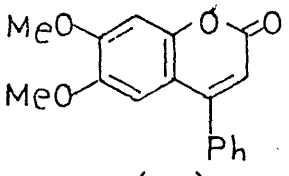
(80)

In the case of a 5,6-fused chromene, the tertiary methyls have been reported[15] as being significantly shielded by the neighbouring aryl group. The shielding effect of the 4-phenyl group is shown in Table 6. The relationship between mesuol (12≡70) and mesuagin (70a) was proved by the oxidative cyclisation of 12 with DDQ to give 70a in high yield.

Another source of 4-phenyl coumarins, Calophyllum inophyllum, has been studied by several authors. The coumarin calphyllolide[36] (71) is analogous to 60, containing a chromene ring and a 2,3-dimethylacryloyl side chain. Inophyllolide[36] (72) is closely related to calophyllolide, and indeed has been synthesised from 68 by $AlCl_3$ catalysed demethylation, followed by ring closure. Other investigators[37] have shown that both cis-(73) and trans-(74) inophyllolide occur in the same tree, along with the reduced form 75, which is analogous to costatolide (57). These three inophyllolide derivatives all show piscidal activity[37], but are only a fifth as active as pentachlorophenol. The fifth coumarin isolated from Calophyllum inophyllum ponnalide, was originally thought[38] to have the structure (76), but this was later revised[39] to 77 after careful examination of its NMR and mass spectra. A further related coumarin isolated from Calophyllum australianum[40], was assigned the linear structure 78, on spectral grounds. The chemical shift values of the chromanone ring substituents in the NMR confirms the linear structure as the proximity of the phenyl ring causes a marked change in their chemical shift from their normal values[15]. This shielding effect was again found in the NMR of the coumarin tomentolide A (79), isolated[15] from Calophyllum tomentosum. The directly related coumarin apetalolide (80), isolated[15] from Calophyllum apetalum is



(81)



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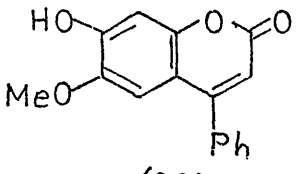

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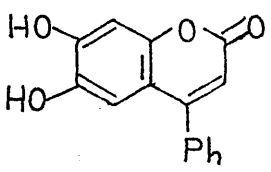

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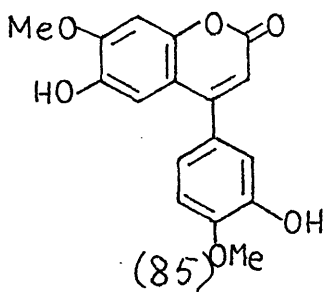

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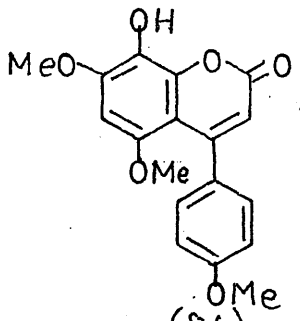

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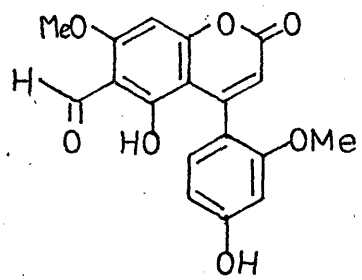
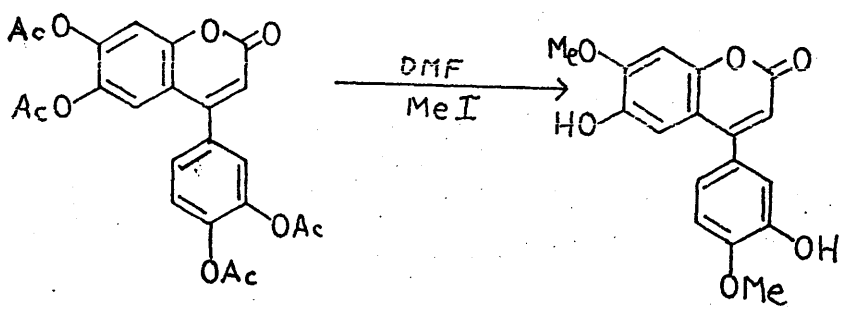
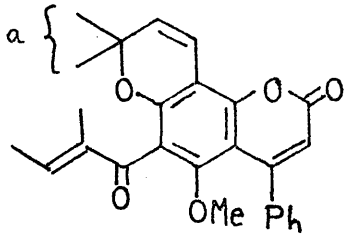


(87)

Scheme 8





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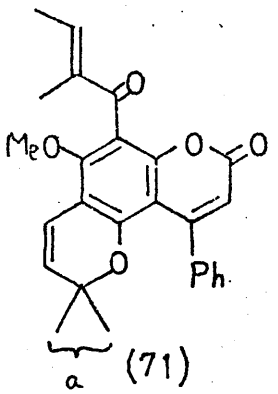


(71)

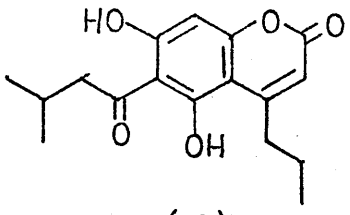
Table 6

Compound	NMR values τ	
(71)	-OMe 6.28	Ha 9.06
(80)	-OMe 6.97	Ha 8.62

isomeric with calophyllolide (71) and a comparison of the NMR spectra of these two coumarins demonstrates the shielding effect of the 4-phenyl group (Table 6). It should be noted that all these 4-phenyl coumarins possessing alkyl and acyl substituents were isolated from the same plant family, the Guttiferae.

Some simple 4-phenyl coumarins are known, the first to be isolated[41] being dalbergin (81). This coumarin occurs along with its methyl ether (82) in the heartwood of Dalbergia sissoo, and its structure was proved by degradation and synthesis. Investigation of the stem bark of the same tree led to the isolation[42] of isodalbergin (83) and nor-dalbergin (84) along with 81 and 82. The first coumarin possessing a substituted phenyl group at C-4 was melannein (85), isolated[43] from Dalbergia baroni and Dalbergia melanoxylon. The structure of this coumarin was based on spectroscopic evidence, and it has since been confirmed by synthesis[44]. Exostemin (86), isolated[45] from Exostemma caribaeum has also been synthesised by the same type of route (Scheme 8). The only other similar coumarin isolated to date is sisafolin (87) from[46] Dalbergia latifolia. On the basis of chemical and physical properties, the tentative structure (87) has been proposed. The presence of the formyl group at C-6 is unusual, and a synthesis of this compound would be useful to confirm the structure.

Since the isolation of mammein (6)[12], there have been several attempted syntheses of similar related coumarins. In 1960, Djerassi synthesised[16] dihydromammein (8), (Scheme 3),



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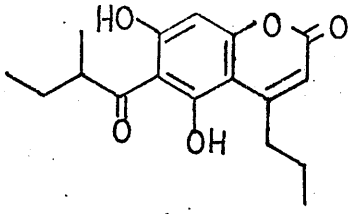

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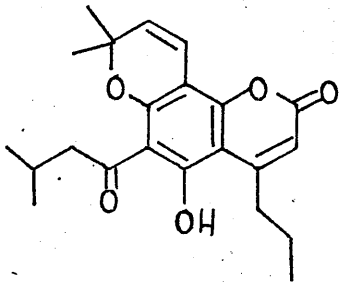

(88)

from phloroglucinol, but the yield of 8 was never greater than 1%. The principal difficulty encountered in this route was the final stage Pechman condensation on the substituted phenol, which went only in low yield. It is possible that the acid catalyst required for this reaction, initiated deacylation of the phenolic precursor, or even of the dihydromammein formed in the reaction.

This problem of deacylation was overcome by Stout[30] in his synthesis of oxodihydrocostatolide(58). The phenolic precursor (59) has the acyl group protected as a chromanone ring. The naturally occurring coumarins, Mammea B/AA and B/AB, (34) and (35), have been synthesised[29] from the substituted coumarins (18) and (20), using 2-methylbut-3-en-2-ol and boron trifluoride-etherate to introduce the isopentenyl substituent, although once again the yields are low. Seshadri has also reported the synthesis of mammeisin (62)[35] by a similar method.

Games and Haskins have also reported[29] the syntheses of the naturally occurring coumarins, mammeigin (66),(53) and the non-natural coumarin (88). The 2,2-dimethylchromene ring was introduced by condensation of the corresponding phenols with 3-hydroxy-1,1-dimethoxy-3-methylbutane, and the yields in these reactions are between 30-80%. These latter syntheses are the most successful that have been reported to date.

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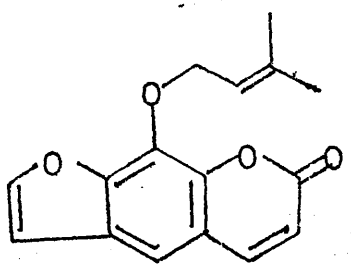
Syntheses of the coumarins dentatin and glabralactone.



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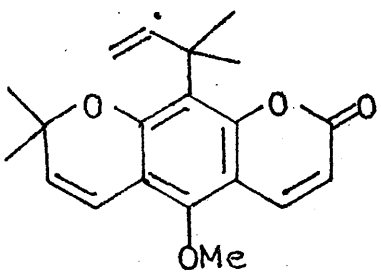

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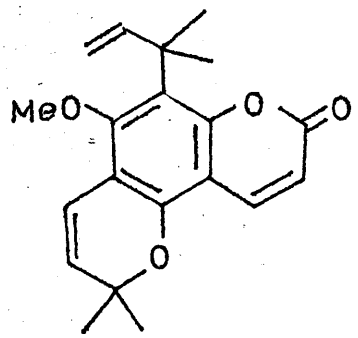

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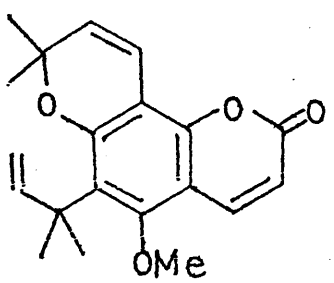

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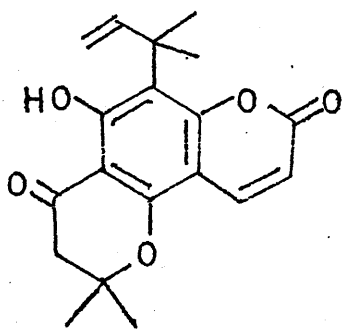
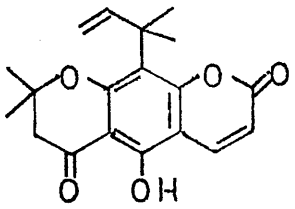


(5)

Clausena dentata (Willd) is a small tree found in the south of India. In 1969 the extraction of its roots with hexane[1], yielded a mixture which was separated by chromatography into three crystalline compounds, melting at 102°, 95° and 182° respectively. The first was shown by direct comparison with an authentic sample to be the substituted furocoumarin, imperatorin (1)[2]. The remaining two compounds were named dentatin and nor-dentatin respectively.

Analytical data and mass spectral molecular weight determination (M^+326) indicated that dentatin had the molecular formula $C_{20}H_{22}O_4$. Its IR spectrum (νmax 1720cm^{-1}) and UV spectrum (λmax 230, 270 and 330nm) suggested that it was a substituted coumarin and the NMR spectrum confirmed this. The NMR also showed the presence of a 2,2-dimethylchromene ring, a 1,1-dimethylallyl group and a methoxyl group, and thus dentatin could be formulated as 2,3 or 4. From the available physical data, it was not possible for the authors to choose between these three possibilities, but they favoured 3 on the following grounds. From a related plant, Clausena heptaphylla, another new coumarin, clausenidin, has been isolated[3]. Moreover, it was possible to obtain a direct interrelation of dentatin with the methyl ether of clausenidin by reduction of the chromanone ring followed by dehydration.

Thus 3 was the structure allocated to dentatin on the evidence that it had been interrelated with clausenidin for which the structure (5) had been proposed[3]. The angular structure (5) of clausenidin had been preferred to the linear possibility (11) for two main reasons. When



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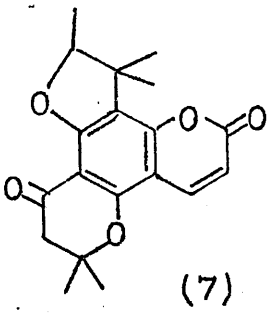

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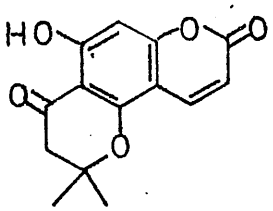

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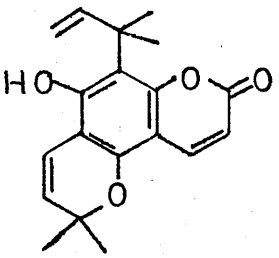
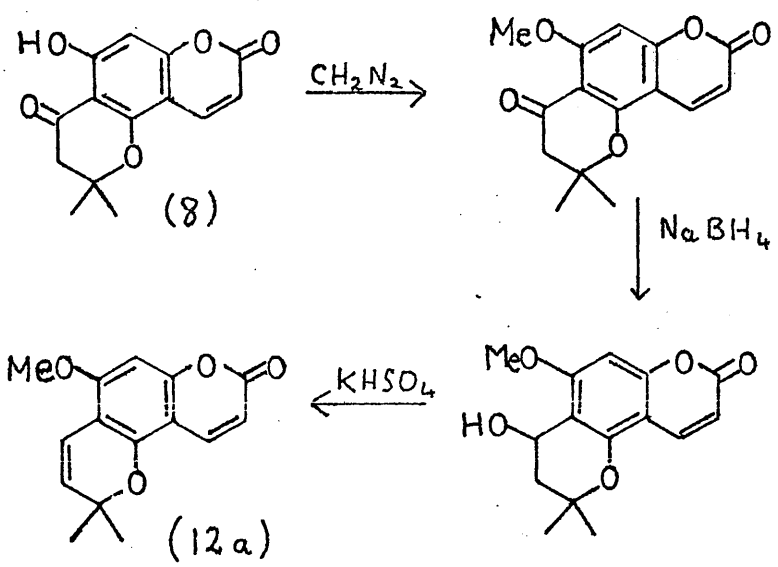
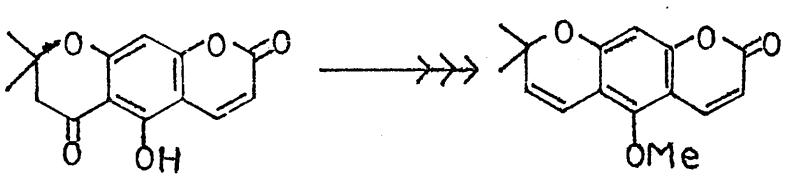


(9)

Scheme 1

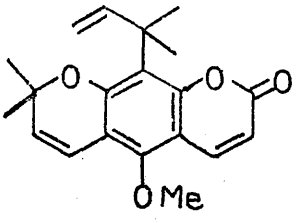




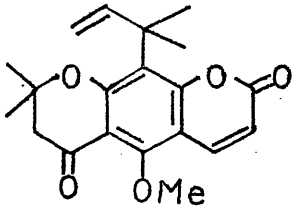
clausenidin was reacted with conc. H_2SO_4, a non-phenolic isomer was obtained, which no longer possessed a vinyl grouping. The presence of a new secondary methyl group in the NMR spectrum of this compound showed that it was a 2', 3', 3'-trimethyl dihydrofuran which must have arisen by the interaction of the double bond of the alkenyl side chain with an ortho phenolic group. Thus 7 was necessarily the structure of cycloclausenidin, and the Indian authors[3] logically, but erroneously, assumed that clausenidin must be 5, and did not consider any other possibilities. Normally one would have predicted[4] an almost quantitative conversion of clausenidin to cycloclausenidin, even where the OH is chelated to a carbonyl, but the yield of cycloclausenidin was only 30%. In retrospect, this should have led the Indian workers to query their structure of clausenidin.

The second reason for assuming the angular structure (5) to be correct, was that clausenidin, on heating with $AlCl_3$, underwent a retro Friedel-Crafts alkylation. The product of this reaction, obtained in only 10% yield, was shown by comparison with an authentic sample to be the chromanocoumarin (8). The angular structure of this coumarin had been conclusively proved by its conversion[5] to alloxanthoxyletin (12a) (Scheme 1). Having assigned the structure (3) to dentatin, the authors then assigned the structure (9) to nor-dentatin on the basis that simple methylation (MeI/K_2CO_3) afforded dentatin.

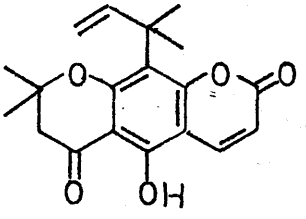
More recently, a fluorescent crystalline compound, isolated[6] from the roots of Poncirus trifoliata Rafinesque was shown, solely from spectroscopic evidence, to be the



(2)



(10)



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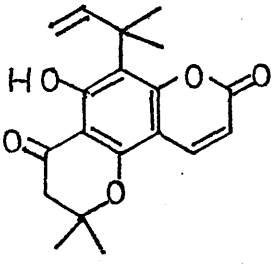


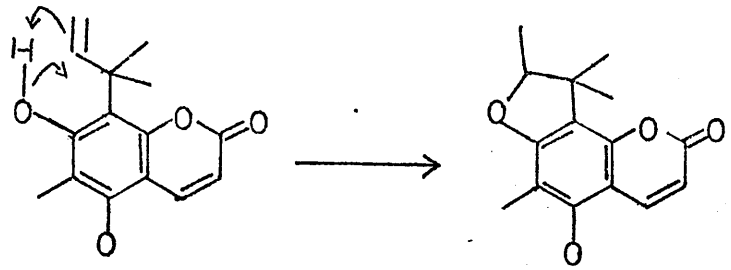
(5)

chromenocoumarin (2). The linear structure (2) of this coumarin, named poncitrin, was established by the use of the nuclear Overhauser effect (NOE). Thus when the NMR signal of the methoxyl group was saturated by double irradiation, the integrated intensities of the coumarin C-4 proton and the benzylic proton of the chromene ring were appreciably increased. This necessitated a close spatial relationship between the OMe and each of these protons. Consequently the methoxyl group must be attached to C-5, with the chromene ring attached through oxygen at C-7 to C-6. Therefore poncitrin was assigned the linear structure (2).

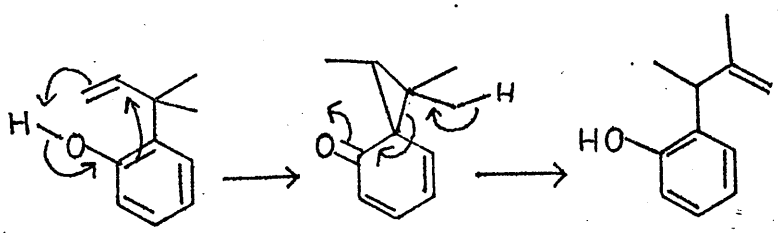
This result prompted a reinvestigation[7] of the structure of dentatin, and in particular, that of clausenidin, on which the structure of dentatin had been based. NOE experiments on clausenidin methyl ether again revealed a peri relationship between the OMe and the C-4 hydrogen. This necessitated the reformulation of clausenidin methyl ether as 10, and therefore dentatin as 2. Consequently dentatin and poncitrin must be identical, confirmed later by direct comparison of their IR spectra, and thus the chemical transformations of clausenidin, now 11, must proceed with isomerisation. It would appear that the strongly acidic conditions employed in these reactions must have caused opening of the chromanone ring with recyclisation to the C-5 OH leading to the angular compounds (5)

Since the currently accepted structure (2) of dentatin-poncitrin is largely dependant on the interpretation of spectroscopic data, we felt that it would be useful to provide additional support of a synthetic nature. The 1,1-dimethylallyl unit of dentatin, could in principle be

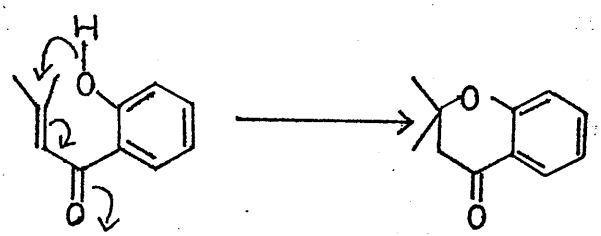
Scheme 2



Scheme 3

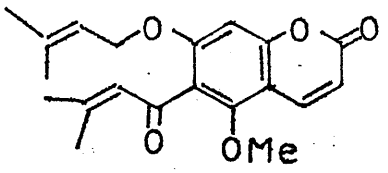


Scheme 4



introduced at C-8 by the ortho Claisen rearrangement of a 7-O-(3,3-dimethylallyl) ether. Examples of this process have previously been reported[8], but in general yields were low. The newly formed desired product has an ortho phenolic OH which can interact directly with the double bond of the alkenyl side chain to yield a dihydrofuran, (Scheme 2). Alternatively, the ortho phenol could react indirectly with the 1,1-dimethylallyl side chain giving a 1,2-dimethylallyl phenol. The mechanism of this latter reaction, known as the abnormal Claisen rearrangement[9], is shown in Scheme 3. It requires participation of the phenolic OH with the alkenyl group to form a spirocyclohexadienone by a [1,5] sigmatropic hydrogen transfer. If this is then followed by a further [1,5] sigmatropic hydrogen shift from one of the benzylic methyl groups, the 1,2-dimethylallyl phenol is formed.

Since these undesired side reactions are initiated by the newly liberated phenolic OH, these problems can be obviated by carrying out the rearrangement in the presence of an anhydride, thus trapping the phenol as it is formed as an ester[10]. We envisaged that rather than having an external anhydride present, similar trapping might be obtained by the intramolecular cyclisation of a C-6 senecioyl group with the newly formed ortho OH to give a chromanone ring (Scheme 4). Cyclisations of senecioyl groups with ortho phenolic groups have previously been reported to occur during the Fries rearrangement of senecioate esters[11], and if similar cyclisation occurred during the Claisen rearrangement described above, the product would have, as an added advantage, the required linear framework of dentatin.



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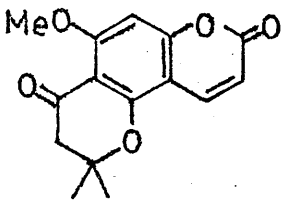

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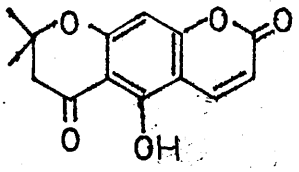

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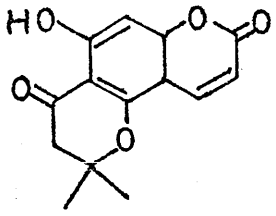

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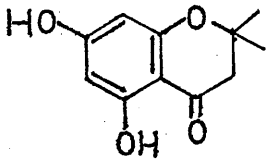
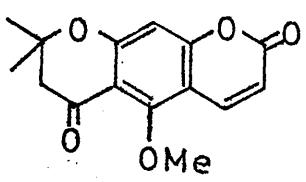


(16)

Thus from a synthetic viewpoint, the key intermediate was the bis-ether (13). This coumarin was potentially derivable from the synthetically available[5] phenol (8) by dimethylallylation of the C-7 OH, if it were then possible to effect a retro-Michael opening of the chromanone ring and prevent recyclisation by methylation of the newly formed C-5 OH. In order to study the possibility of chromanone ring opening, it was decided to examine the behaviour of the methylether (14) with various bases.

The angular chromanocoumarin (8) and its linear isomer, clausenin (15), have been synthesised[5] by the condensation of ethyl propiolate with 2,2-dimethyl-5,7-dihydroxychroman-4-one (16) in the presence of $ZnCl_2$. The Indian workers suggest in their paper that only two compounds are formed and that their separation by chromatography is simple, but by following their conditions, a viscous gum was obtained, which contained a minimum of ten compounds. Column chromatography was completely unsuccessful in separating these, while preparative TLC gave apparently homogeneous bands, which were later shown to be mixtures. Analytical TLC did show however that the major product was a pale yellow compound which gave a positive $FeCl_3$ test. By dissolving the total gum in EtOAc, and leaving the resulting solution in a deep freeze for 3-4 days, a pure sample of a coumarin was obtained in 13% yield, m.p. 215-220° whose spectral properties were identical with those published for 8[5].

An alternative synthesis of 8 has since been reported[12], involving the Pechman condensation of the chromanone (16) with malic acid, using conc. H_2SO_4 as the catalyst. This



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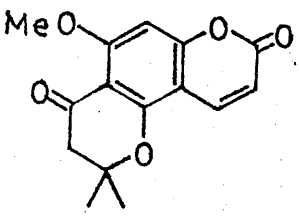
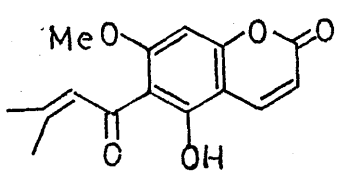


(14)

method was much cleaner, and gave 8 in 27% yield. Also repeated chromatography of the mother liquors of crystallisation of 8 yielded the linear coumarin, clausenin (15), (7%) m.p. 156-158°. The linear relationship of the three rings of clausenin had been established by its conversion to the known coumarin, xanthoxyletin (12b), (see Scheme 1). Treatment of these phenols (8) and (15) with MeI and K_2CO_3 in acetone gave high yields of the corresponding methyl ethers (14) and (17).

It was hoped that either of these ethers could be induced to undergo a retro-Michael chromanone ring opening by reacting them with non-nucleophilic bases. The advantage of using a non-nucleophilic base would be that coumarin ring isomerisation could be prevented. However, when the ethers (14) and (17) were treated with the base NaH, $KOBu^t$ and diaza-bicyclo-undecane in anhydrous solvents, no reaction was found to take place.

During an attempted methylation of the phenol (8), the solvent was accidently evaporated to dryness, and as a result, the organic material and the K_2CO_3 were slightly charred. When this reaction mixture was worked-up and purified by T.L.C, a yellow crystalline coumarin, m.p. 151-153° was obtained in 12% yield. This compound gave a positive $FeCl_3$ test, indicating the presence of a phenol, but analytical data and mass spectral molecular weight determination showed that its molecular formula was $C_{15}H_{14}O_5$. This information suggested that the phenol (8) had in fact been methylated, and that a further rearrangement had taken place on heating with K_2CO_3 in the absence of the solvent. The bathochromic shift observed in the UV spectrum when dil.



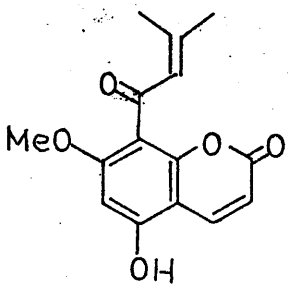
(18)

NaOH was added, showed that this compound possessed a phenolic OH located at C-5[13]. The NMR spectrum showed the presence of two vinyl methyl groups (τ 8.00 and 7.80) and a multiplet at τ 3.13 (J 1Hz) suggested that retro-Michael chromanone ring opening had occurred and that a senecioyl group had resulted. The location of this acyl substituent at C-6 was confirmed by the presence of a chelated OH in the NMR (τ-4.77) and from the IR by the presence of a peak at 1620cm^{-1} due to a chelated α,β-unsaturated ketone. Thus, the yellow coumarin was allocated the structure (18). The yellow colour of 18 is in agreement with the acyl substituent being at C-6, as Crombie has reported[14] that phenolic coumarins possessing a C-6 acyl side chain are generally yellow, whereas if the acyl group is at C-8, the coumarins are usually colourless.

As the yield of 18 in this 'accidental' reaction was low, the coumarin (14) was heated with K_2CO_3 in a sublimation tube at various temperatures to try to improve it, but in no case, was any chromanone ring opening observed.

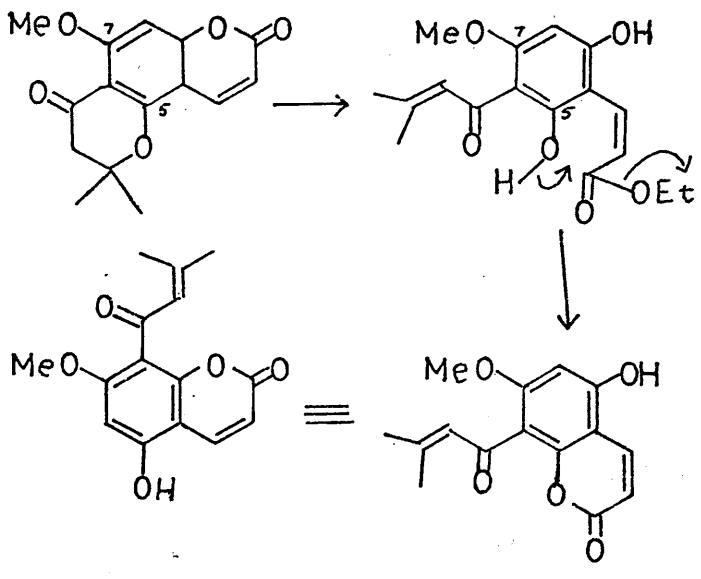
At this stage, it was felt that the chromanone might possibly have been opening in the presence of these various bases, but that the phenolic product was so unstable that it was recyclising on contact with acid, in the work-up procedure, or in contact with silica on TLC. In order to prevent this type of ring closure, an experiment was devised whereby any phenolic products formed would be trapped as esters. Thus the chromanone (14) was refluxed in acetic anhydride in the presence of anhydrous sodium acetate, but the absence of any ester products suggested that no ring opening had occurred.

While characterising the chromanone (14), it was



(19)

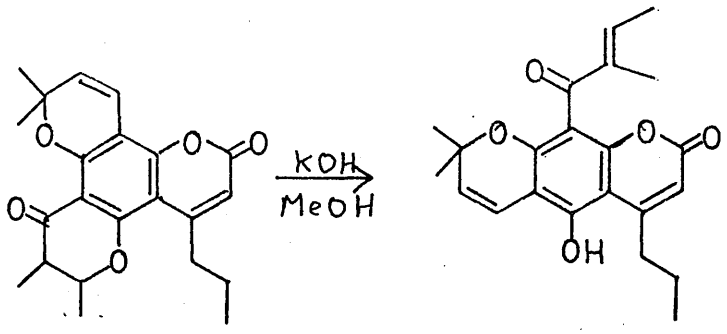
Scheme 5



observed that its UV spectrum was significantly altered when dil. NaOH was added to the ethanolic solution. This result was surprising, as non-phenolic coumarins do not generally show base shifts in their UV spectra. However, this effect proved to be the key to the synthetic problem, as the altered spectrum suggested that a C-5 OH was present in the solution[13]. The possibility that a nucleophilic base was causing rapid chromanone ring opening led to 14 being heated at 40° in ethanolic NaOEt. After $4\frac{3}{4}$ hours, TLC showed that a mixture of at least two compounds had been formed. The least polar of these was a yellow crystalline phenol, identical with that previously isolated (18), but now present in 28% yield. The other compound isolated was found to be unreacted starting material (33%), but as this only accounted for 61% of the material involved, the preparative TLC plates were re-examined. It was observed that a further band of a very polar material had remained on the base line of the plates, and this contained the missing 39% of the organic material. This compound was shown by mass spectrometry and micro-analysis to be isomeric with 14 and 18, and its UV spectrum showed that it was a 5-OH coumarin. Its NMR spectrum showed the presence of a methoxyl signal and a senecioyl group, and the peak at 1670cm^{-1} in the IR spectrum indicated that the senecioyl carbonyl was unchelated, and that the structure of this coumarin must be 19. The fact that this phenolic coumarin was colourless, also supported the location of the acyl substituent at C-8.

This compound must arise by base induced chromanone and coumarin ring opening, followed by lactonisation of the coumarinic ester with the alternative C-5 <u>ortho</u> OH, on

Scheme 6



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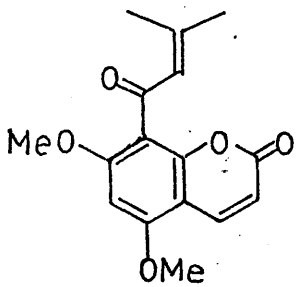

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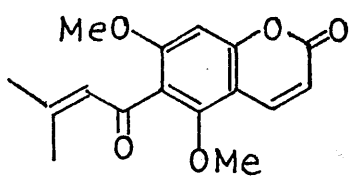

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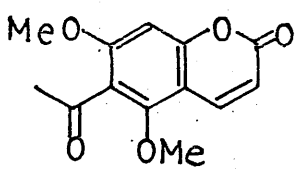
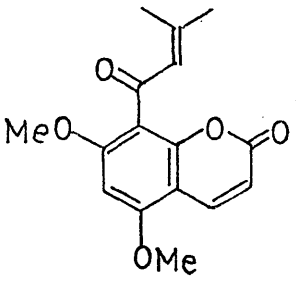


(24)

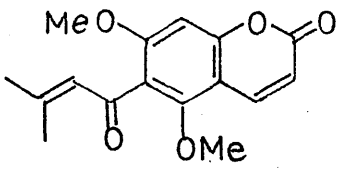
acidification. (Scheme 5). This type of coumarin ring isomerisation has previously been reported by Djerassi[15] and Crombie[16] in their studies on the coumarins isolated from Mammea americana. However, a more closely related example is the base induced isomerisation of the coumarin, tomentolide B (20)[17] (Scheme 6). In this case both the chromanone and coumarin rings have opened on contact with the base, and acidification resulted in the cyclisation of coumarinic acid intermediate with the newly liberated C-5 OH to yield the phenol (21). In the isomerisation of 20, the base used was KOH, and when the chromanone (14) was treated with KOH in methanol, results similar to the NaOEt reaction were obtained. The only disadvantage of KOH as a base for this ring opening was that the yields of all three products were slightly lower.

Further confirmation of the structures of the phenols (19) and (18) could be obtained by their methylation to give the coumarins glabralactone (22) and (23) respectively[18,19]. Treatment of 19 with MeI and K_2CO_3 in acetone quantitatively afforded a bis methyl ether, m.p. 128-130°, whose physical properties were identical with those published for natural glabralactone[18,20]. Unfortunately, an authentic sample of glabralactone could not be obtained for direct comparison purposes.

The structure (23) is that assigned to natural angelicone and quoted in the three most recent comprehensive coumarin reviews[21,22,23]. Angelicone was assigned this structure on the basis of its physical properties, and by its degradation to the known 6-acetyl-5,7-dimethoxycoumarin (24). However, methylation of 18 yielded a bis methyl ether,



(22)



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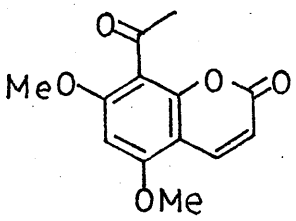

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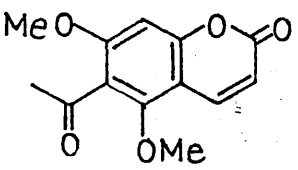

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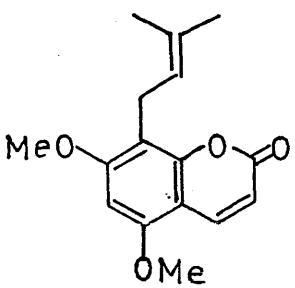

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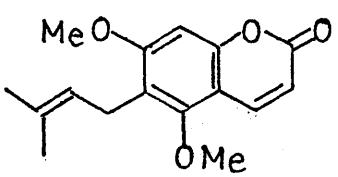
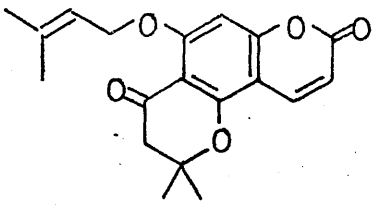


(27)

m.p. 120°, which was not identical to natural angelicone (m.p. 130°). This ether analysed for $C_{16}H_{16}O_5$, and its NMR spectrum revealed that it was a 5,7-dimethoxycoumarin possessing a senecioyl substituent. This compound undoubtedly has the structure (23), and thus the published structure of angelicone must be wrong. A detailed inspection of the literature has since shown that the physical properties of angelicone and glabralactone are identical and also a somewhat inaccessible publication[24] has been found in which the structure of the angelicone retro-aldol product was revised from 6-acetyl (24) to 8--acetyl-5,7-dimethoxycoumarin (25). The structure (25) had been proved by further unambiguous degradations[20], and as the structure of angelicone had been based primarily on its conversion to the retro-aldol product, it is now certain that angelicone and glabralactone are identical, possessing the 8-acyl structure (22).

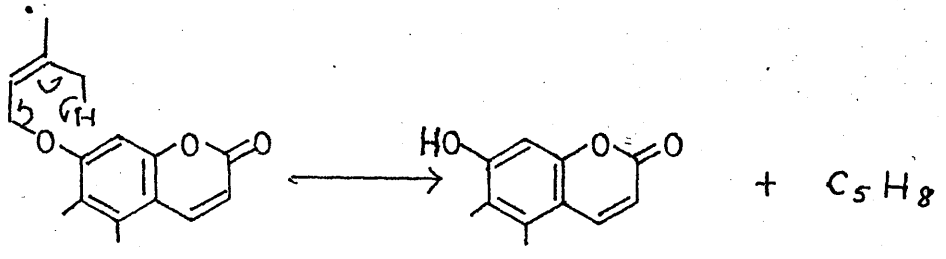
Comparison of the NMR spectra of 22 and 23 shows that in the former, the methoxyl signals are split at τ6.10 and 6.05, whilst in the latter, they are identical at τ6.17 There is also a significant difference in the chemical shifts of the aromatic protons of 22 and 23, (τ3.68 and 3.40 respectively), which is comparable to that observed[26,27] for the similar coumarins, coumurrayin (26) and toddaculin (27) (τ3.70 and 3.38 respectively).

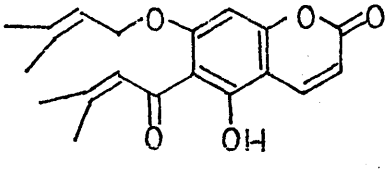
The first stage in the synthesis of dentatin (2) required the dimethylallylation of the phenolic chromanocoumarin (8). Thus 8 was refluxed in acetone with 3,3-dimethylallyl bromide and K_2CO_3, and a colourless



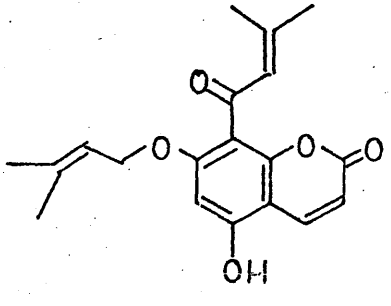
(28)

Scheme 7





(30)



(31)

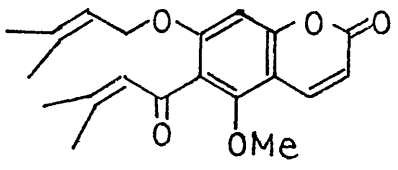
crystalline compound, m.p. 128° was obtained. This coumarin gave a negative $FeCl_3$ test, and was identified as 28 from its NMR spectrum which shows a 3,3-dimethylallyl group attached to oxygen (τ8.23; 6H; s), (τ5.27; 2H; bd; J6 Hz) and (τ4.36; 1H; bt; J6 Hz). The mass spectrum of this compound shows the loss of a C_5H_8 (Scheme 7) thus confirming the presence of a 3,3-dimethylallyloxy moiety.

As found in the 7-methoxy series[25], treatment of 28 with ethanolic NaOEt resulted in the formation of a mixture of three coumarins. This mixture was separated by TLC to give a yellow crystalline phenol (34%), m.p. 136-138°, unreacted starting material (31%) and a polar phenol (34%), m.p. 137-140°. The spectral properties of the two phenolic products were very similar to those of 18 and 19, and they were assigned the structures (30) and (31) respectively.

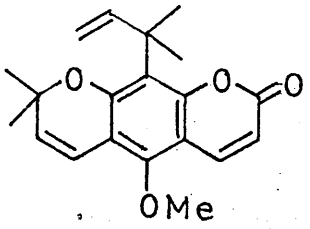
While studying the base catalysed isomerisation of the chromanones (14) and (28), several reactions were carried out on a micro-scale in UV cells. The course of these reactions was followed by the changes observed in the resulting UV spectra. The results obtained for the methyl ether series were identical with those obtained from the dimethylallyl series. Thus, when the chromanone (28) was treated with two drops of an ethanolic solution of NaOEt, the principal peak of the neutral spectrum (274nm) collapsed rapidly, and a new peak commenced to grow at 390nm. This altered spectrum now resembled that expected for a 5-hydroxycoumarin in basic solution[13]. Acidification with dil. HCl did not initially restore the original spectrum, but after heating at 60°, the spectrum of 28 began to re-appear. When base was added to solutions of the phenols

(30) and (31), the resultant spectra were almost identical, and similar to that obtained when base was added to 28. Thus it appeared that these three isomeric coumarins were converted on treatment with base to the same equilibrium mixture, and that it should be possible, on a preparative scale, to increase the yield of the synthetically useful isomer (30) by subjecting the other isomers (28) and (31) to further reaction with base. In order to confirm this, a solution of 31 in ethanol was treated with ethanolic NaOEt, and a mixture of 28, 30 and 31 was isolated in the same proportions as previously mentioned.

Further experiments on a micro scale revealed that, on the addition of a few drops of dil. HCl, the chelated phenol (30) was only slowly converted to 28, but when the reaction was repeated at 60°, ring closure was complete after only a few hours. It was also observed that 30 was completely converted to 28 after standing for four days in neutral ethanolic solution, and once again, heating to 60° considerably enhanced the rate of this reaction. One further effect observed while carrying out these micro scale reactions was that the phenols (30) and (31) were more stable at room temperature to base, than the chromanone (28). Thus, when solutions of the phenols were made basic, and then immediately re-acidified, the spectrum of the starting phenol was restored, but when 28 was treated in a similar fashion, a complex spectrum was obtained. In conclusion, it appears that the three isomers (28), (30) and (31) are each converted by NaOEt to an equilibrium mixture containing all three in approximately equal proportions, but that in the presence of acid, the chromanone isomer (28) is more stable.

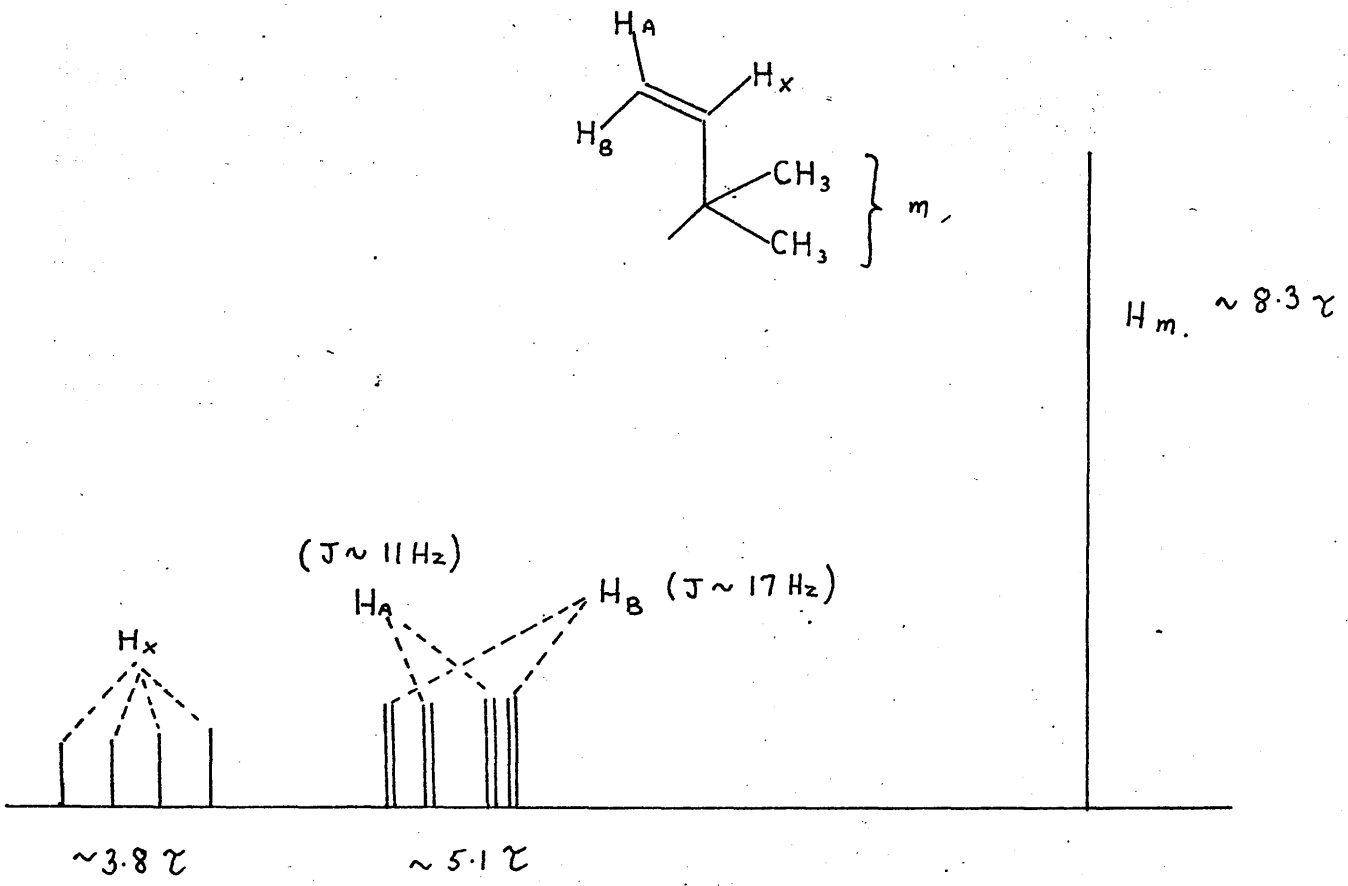


(13)



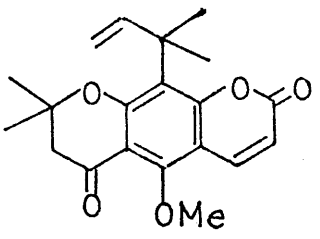
(2)

Figure 1.

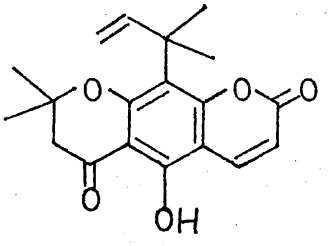


In order to synthesise the key intermediate (13) in the synthetic route to dentatin (2), the coumarin (30) was reacted with MeI and K_2CO_3 in acetone solution. The product of this reaction was an oily solid which was crystallised from CCl_4, only after great difficulty, to give a pure compound (67%), m.p. 57-60°. The spectral properties of this coumarin were very similar to those of 23, and so its structure was assigned as the bis ether (13). In order to induce this ether to undergo a thermal ortho Claisen rearrangement, it was heated at 180° in N,N--diethylaniline under a nitrogen atmosphere, and a colourless crystalline coumarin, m.p. 87-88° was obtained in 74% yield. The NMR spectrum of this compound clearly shows the presence of a 1,1-dimethylallyl substituent attached to the aromatic ring, with a six proton singlet at τ8.30, attributable to the gem-dimethyls attached to a carbon which is both allylic and benzylic and an ABX system of three olefinic protons. This ABX system gives rise to a one proton broadened doublet at τ5.10 (Jax 11 Hz; cis coupling) due to H_A, a one proton broadened doublet at τ5.07 (J_{BX} 17 Hz: trans coupling) due to H_B and a one proton doublet of doublets at τ3.77 (Jax 11 Hz: Jbx 17 Hz). The broadening of the doublets is due to a small coupling between H_A and H_B of about 1 Hz. The NMR spectrum of a typical 1,1--dimethylallyl unit attached to an aromatic ring is shown in Figure 1.

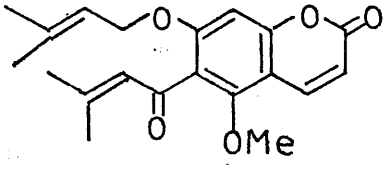
The NMR of this coumarin, obtained by pyrolysis of 13, also reveals that a chromanone ring has been regenerated, with signals at τ8.50 (gem dimethyl) and at τ7.30 (methylene group α to a carbonyl). Therefore, the ortho



(10)



(11)



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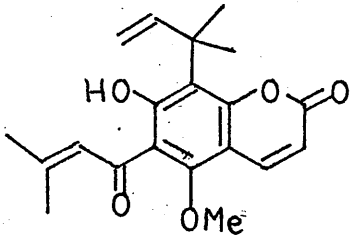
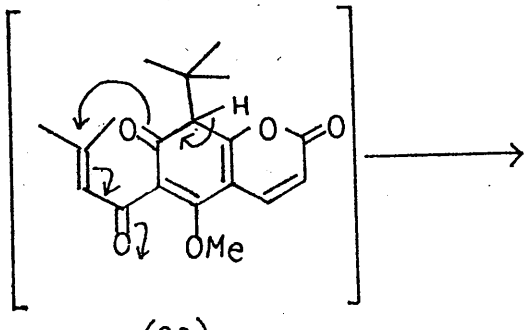


(32)

Scheme 8



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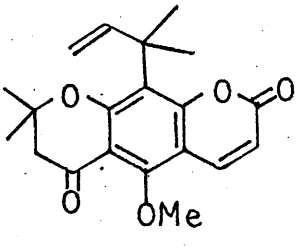

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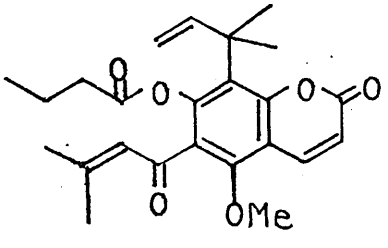

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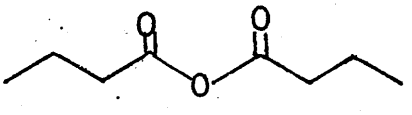


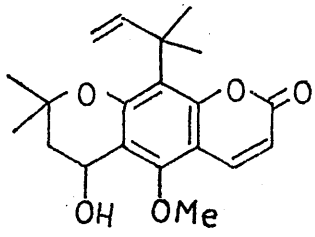
(35)

senecioyl group must have acted, as anticipated, as an efficient trapping agent for the newly formed C-7 phenolic OH, and thus prevented further rearrangements of the alkenyl side chain.

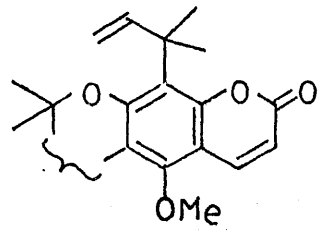
This new coumarin was assigned the linear structure (10) and comparison of its physical properties with those of the methyl ether derived from clausenidin (11) confirmed that this latter phenol is indeed the linear isomer.

During the pyrolysis of 13, no trace of the intermediate phenol (32) was observed, and so the reaction was repeated in the presence of butyric anhydride in order to trap this phenol as its butyrate ester[10] (34). However, no ester was isolated from the reaction mixture, and the yield of 10 remained constant. This implies that the phenol (32), derived from the cyclohexadienone (33), interacted very rapidly with the ortho senecioyl group, or alternatively, that 33 cyclised spontaneously, as shown (Scheme 8).

When the chromanocoumarin (10) was reacted with $NaBH_4$ in ethanol, two products were obtained, each in 50% yield. The more polar product, m.p. 155-158° was an alcohol (νmax 3590cm^{-1}), and the presence in the NMR spectrum of a doublet at τ 7.97 (J6Hz) and a triplet at τ 4.97 (J6Hz) suggested that this compound was the known[1] chromanol (36). Comparison of the physical properties of our synthetic material with the published data for this alcohol confirmed the assignment. The UV spectrum of the less polar product, m.p. 87-89°, was very similar to that of 36, and its IR spectrum showed that although the coumarin ring was still intact (νmax 1740cm^{-1}), the chromanone carbonyl was not present. The NMR spectrum shows four tertiary methyls at



(36)



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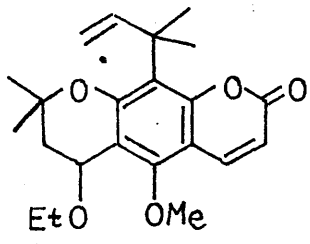

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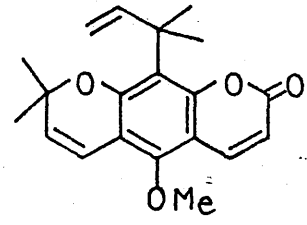
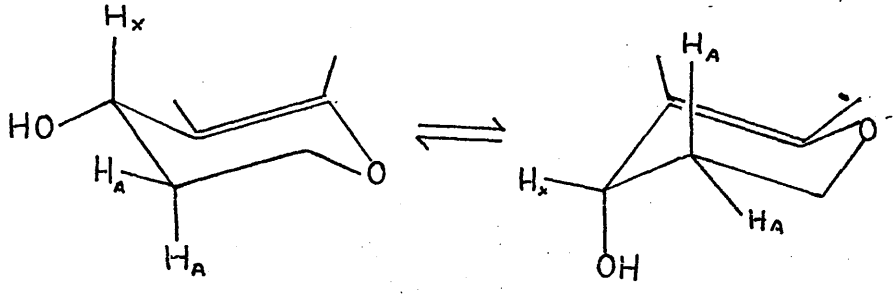


(2)

Figure 2.



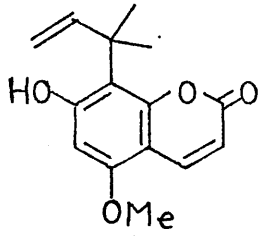
(40a)

(40b)

τ8.60, 8.53, 8.37 and 8.33, one aromatic methoxyl at τ6.07, a three proton ABX system at τ 5.18, 5.12 and 3.72, and a two proton AB quartet at τ 3.85 and 2.17, and this suggested that this product had the partial structure (37). The molecular weight, found by mass spectrometry, was 372, and this indicated a possible molecular formula of $C_{22}H_{28}O_5$. This requires the addition of C_4H_8O to the partial structure (37), and so the structure (38) was considered for this product. The remaining signals in the NMR spectrum of this compound are complex, and as a pure sample of this product could not be obtained, a detailed analysis of this spectrum could not be made. However, the presence of a peak at M-46 in the mass spectrum due to the loss of ethanol supports the assignment of structure (38) to this new coumarin.

The NMR spectrum of the chromanol (36) is unusual in that the chromanol ring protons give rise to an A_2X system. Normally one would expect to see an ABX system for these protons, but in this case there must be a rapid interconversion of the pseudo-axial and pseudo-equatorial hydroxyl, thus giving rise to a time averaged NMR spectrum (Figure 2).

The alcohol (36) has previously[1] been converted to dentatin (2) using alumina as the dehydrating agent, but the yield of dentatin was not high and so an alternative method was sought. On treatment with thionyl chloride in pyridine, the alcohol gave no recognisable products, but when it was heated to reflux in hexamethyl phosphoric tri-amide (HMPT)[28] a small sample of dentatin was isolated. However this reaction was not reproducable, and so the search for a suitable dehydrating reagent was continued. Joshi has reported[3] that



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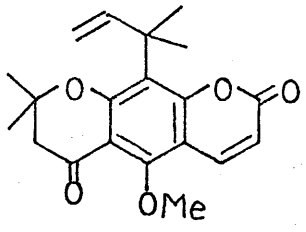

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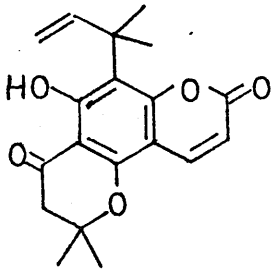

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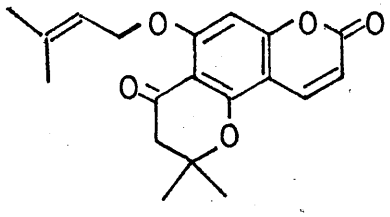
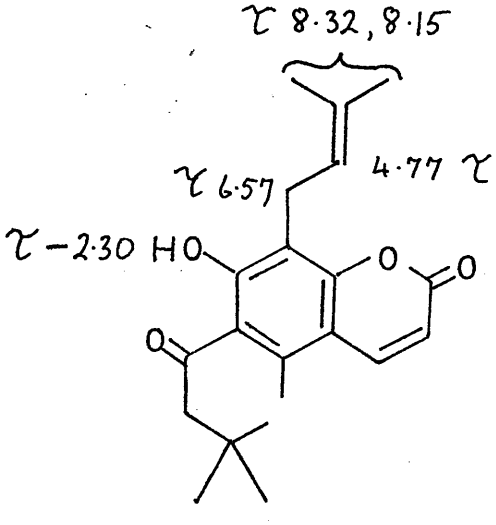


(28)

Figure 3.

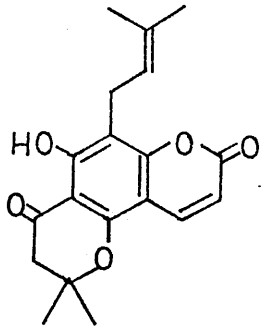


(29)

chromanols can be converted to the corresponding chromenes by heating in the presence of $KHSO_4$. Thus, when an intimate mixture of 36 and $KHSO_4$ was heated at 105° under vacuum a colourless crystalline compound sublimed out in 85% yield. This compound, m.p. 93-95° was identical (mixed m.p., TLC, m.p., IR, UV and mass spectrum) with an authentic sample of natural dentatin, m.p. 93-95°[91], kindly supplied by Professor B.R. Pai.

An alternative preparation of clausenidin methyl ether (10) which also confirms the linear structure of this coumarin, has recently been published[29]. This involves heating norpinnarin[30] (39) with senecioic acid and polyphosphoric acid, but the yield in this process is very low. For comparison purposes, it was decided to synthesise the compound having the original wrong angular structure (5) of clausenidin, by pyrolysing the 3,3-dimethylallyl ether (28), and so inducing an ortho Claisen rearrangement.

Whilst preparing the ether (28), an experiment was carried out using 1,2-dimethoxyethane (glyme) as solvent instead of acetone. It has been reported[31], that glyme is a better solvent than acetone for promoting O-alkylation in preference to C-alkylation, but when 8 was refluxed in glyme with dimethylallyl bromide and K_2CO_3, a yellow crystalline phenol m.p. 151-152° was obtained in 39% yield. The IR and UV spectra of this compound were similar to those recorded for 8, but it analysed for $C_{19}H_{20}O_5$, thus showing that one dimethylallyl unit had been incorporated. The NMR spectrum showed the presence of a chelated OH (τ-2.30), which the UV spectrum indicated to be at C-7, and a 3,3 dimethylallyl unit attached to an aromatic ring (Figure 3). This evidence, coupled with the absence of an aromatic proton in the NMR indicated that



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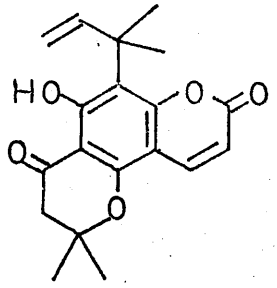

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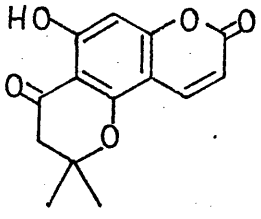

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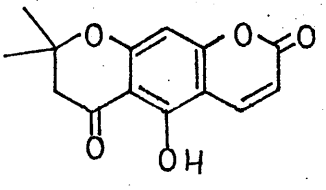
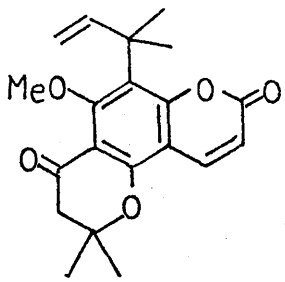


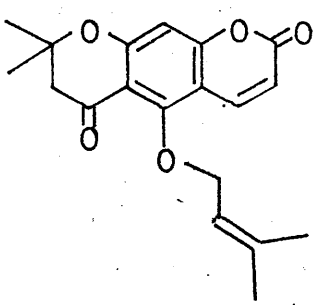
(15)

this product was the C-alkylated phenol (29). This result, which was not repeatable, was probably due to the presence of impurities in the solvent, but the compound was useful for comparison purposes. However when acetone was employed as solvent the desired ether (28) was obtained. 28, on heating to 180° gave a yellow phenol (τ-3.02), m.p. 151-152°, whose spectral properties were very similar to those of the phenol (29). The NMR spectrum of this new coumarin shows the characteristic signals of 1,1-dimethylallyl group attached to an aromatic ring, and the compound was therefore assigned the structure (5). Comparison of the physical properties of this compound with those published for natural clausenidin proved beyond all doubt that the angular structure (5) was incorrect for the natural compound.

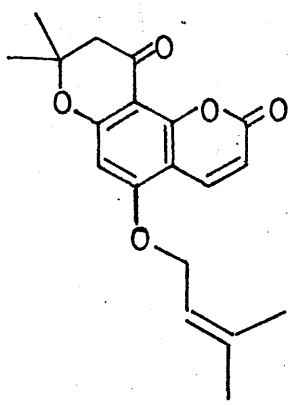
When the pyrolysis of 28 was carried out in this fashion, there was no trace of any products arising from the abnormal Claisen rearrangement. This was presumably due to the chelation of the phenolic OH with the chromanone carbonyl preventing the OH from interacting with the alkenyl side chain. However when the reaction was carried out using N,N-diethylaniline as solvent, the yield of 5 was considerably reduced (43%), and when butyric anhydride was added, to act as a trapping agent for the phenol, the principal product was the de-alkylated phenol (8) (56%) and only 40% of the required product (5) was obtained. It is unusual for the products of such a reaction to be isolated as phenols rather than esters. Another example of the reluctance in functionalisation of this phenol was found when 8 could not be converted to its corresponding tosylate. Joshi[3] has reported the preparation of the tosylate of clausenin (15), but even following his conditions, no tosylate was formed for the angular isomer (8).



(6)



(41)



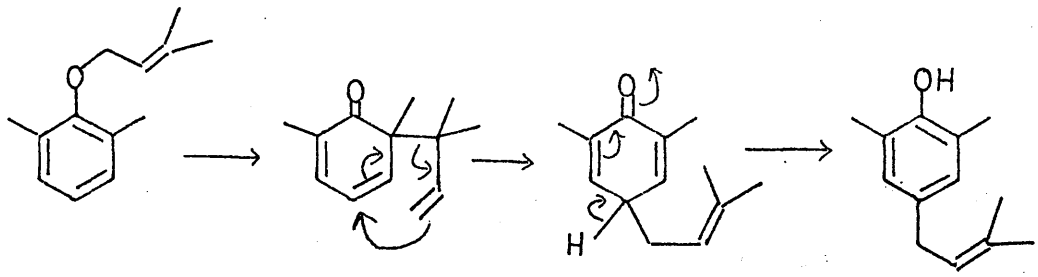
(42)

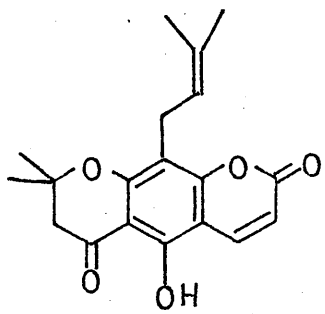
Methylation of the rearranged coumarin (5) with MeI and K_2CO_3 gave the ether (6) which is isomeric with the derived methyl ether of clausenidin, and once again comparison of their physical properties confirmed the linear structure for the naturally derived compound.

As previously stated, the chromanocoumarin (8) was synthesised by the Pechman condensation of the chromanone (16) with malic acid in the presence of conc. H_2SO_4. However, when the crude phenolic product of this reaction was reacted with 3,3-dimethylallyl bromide and K_2CO_3 in the usual way, the ether (28) was obtained as the major product, along with two other new compounds. The IR and UV spectra of these two compounds were similar to those recorded for 28, and suggested that they were also coumarins. Each of these coumarins analysed for $C_{19}H_{20}O_5$, and comparison of the spectral properties of the least polar isomer with those published[3] for clausenin dimethylallyl ether (41) showed that they were in fact identical. The other more polar product, m.p. 177-179°, (11%) was deduced to have the structure (42), on spectroscopic grounds. The NMR spectrum showed the presence of a 3,3-dimethylallyl ether, τ8.23 and 8.18 (each 3H, bs), 5.42 (2H, bd, J=7Hz) and 4.52 (1H, bt, J=7Hz) and a chromanone ring, τ 8.37 (6H, s) and 7.30 (2H, s). The mass spectrum showed the molecular weight to be 328, in accord with the molecular formula, $C_{19}H_{20}O_5$. Thus the only possible structure for this compound is that of the angular ether (42), as the only other two possibilities are the known ethers (28) and (41).

It has been reported that aromatic allyl ethers with both <u>ortho</u> positions blocked, can undergo a para Claisen

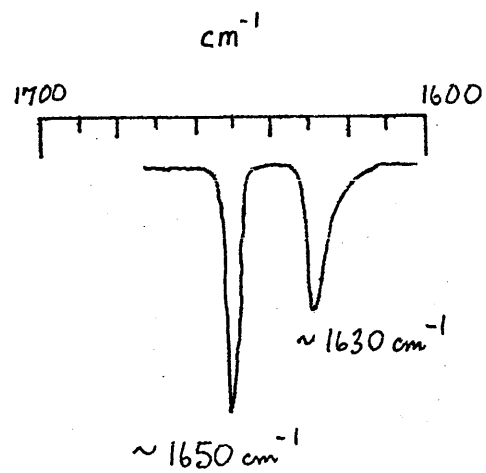
Scheme 9





(43)

Figure 4.



rearrangement. The proposed mechanism for this reaction[32] involves the normal rearrangement to an ortho-dienone intermediate followed by a Cope rearrangement[33] to generate a para-dienone. This species can then rapidly enolise to give the para-substituted allylphenol (Scheme 9). The stereochemistry of this process is such that a 3,3-dimethylallyl ether will give a para-3,3-dimethylallyl phenol. Thus when clausenin dimethylallyl ether (41) was heated in N,N-diethylaniline, two products were formed, both giving positive $FeCl_3$ tests. The NMR of the least polar product, present in 68% yield, showed signals at 8.33 and 8.18 (each 3H, bs), 6.60 (2H, d, J=7Hz) and 4.82 (1H, bt, J=7Hz) indicating a 3,3-dimethylallyl unit attached directly to an aromatic ring, and at -2.65 (1H, s) indicating a chelated OH. This compound was clearly the phenol (43) and the other product (23%) was found by spectroscopic data to be identical with clausenin (15), having been formed by cleavage of the allylic side chain.

In order to provide a means of assigning linear or angular structures to chromanocoumarins, a comparison of the physical properties of some phenols, methyl ethers and dimethylallyl ethers was carried out. Some useful differences in the spectral properties of the linear and angular isomers soon became evident. The most useful property for the identification of the structures of the phenols proved to be the IR spectrum. The spectra of the angular phenols (5), (8) and (29) show a characteristic pattern in the region 1600--1700cm^{-1} (Figure 4). However, in the linear isomers (11), (15) and (43) these two signals always appear as a single peak, and in addition, they all show a very intense signal in the region of 1150cm^{-1} which is absent in the angular isomers.

Table 1

Angular phenols.

Compound	IR max cm^{-1}	
(5)	1755, 1642, 1630 and 1592	(CCl_4)
(8)	1740, 1650, 1632 and 1595	($CHCl_3$)
(29)	1749, 1642, 1630 and 1590	(CCl_4)

Table 2

Linear phenol

(15)	1740, 1635 and 1100	($CHCl_3$)

Table 3

Angular ethers

(14)	1732, 1682, 1614 and 1594	($CHCl_3$)
(6)	1735, 1680, 1615 and 1560	(Nujol)
(28)	1740, 1690 and 1610	(Nujol)

Table 4

Linear ethers

(17)	1729, 1639, 1600 and 1148	(Nujol)
(41)	1735, 1690, 1610 and 1145	(Nujol)

Table 5

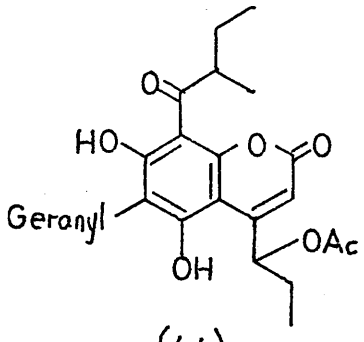
Compound	NMR signals of	phenolic ,	aromatic,	C-4 protons.
(8)	angular	-2.10	3.56	2.10
(5)	"	-3.02	-	2.08
(15)	linear	-2.75	3.66	2.00
(43)	"	-2.65	-	2.02

Table 6

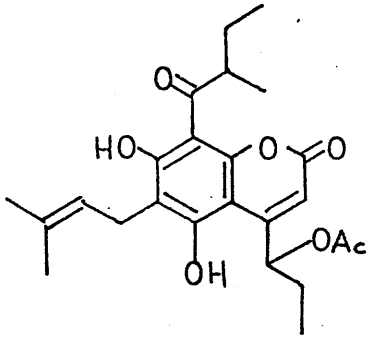
Compound	NMR signals of the	aromatic and	C-4 protons
(6)	angular	-	1.98
(14)	"	3.62	2.00
(28)	"	3.60	2.05
(17)	linear	3.40	2.08
(41)	"	3.40	2.08

This strong signal, at approximately 1150cm^{-1}, also appears in the spectra of the linear methyl and 3,3-dimethylallyl ethers (17) and (41) but not in the spectra of their angular counterparts (14) and (28). The NMR spectra of the above compounds show that the phenolic protons of the linear isomers resonate at lower fields than the angular ones. The phenolic proton of natural clausenidin (11) is the only exception to this trend, as the signal from the angular phenol (5) has the same chemical shift. Unfortunately, a sample of natural clausenidin could not be obtained, and thus the reported value of this signal could not be verified. Also, with the linear phenols, the C-4 proton is found to be deshielded by about 0.1 relative to the angular phenols. This deshielding is consistent with the presence of a phenolic OH at C-5, and when the phenols are methylated, this relative deshielding is not observed. In the case of the angular phenols, the C-8 aromatic proton is also slightly deshielded by the neighbouring OH group, compared to the linear phenols. However, this effect is reversed when the phenol is alkylated with either MeI or 3,3-dimethylallyl bromide. The presence of an ether at C-5 results in deshielding of the C-8 aromatic proton, while the presence of a C-7 ether results in the aromatic proton being slightly shielded. These spectroscopic findings are summarised in Tables 1 to 6.

Synthetic approaches to 4-substituted coumarins.


O
HO
O
O
Geranyl
OAc
OH

(44)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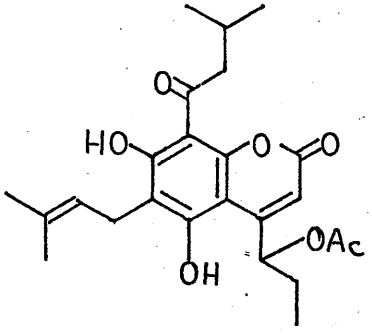
HO
O
O
OAc
OH

(45)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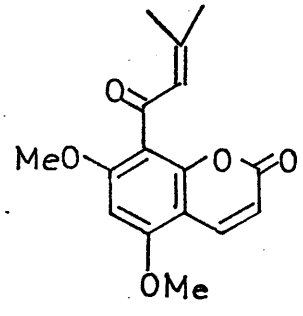
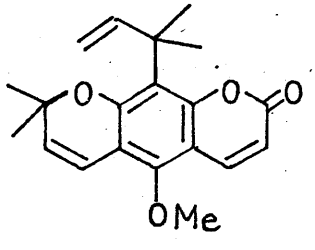
O
O
OAc
OH

(46)


O
MeO
O
O
OMe

(22)

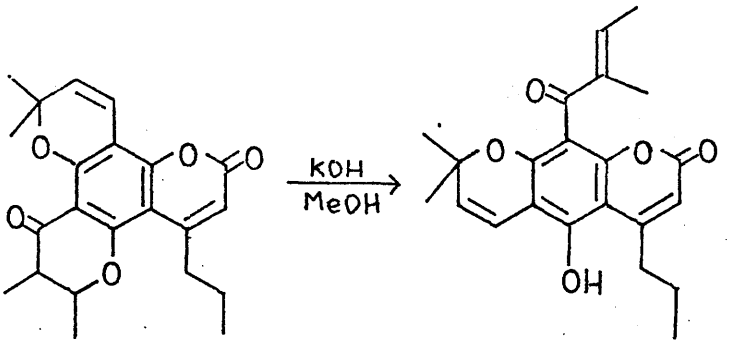

O
O
O
OMe

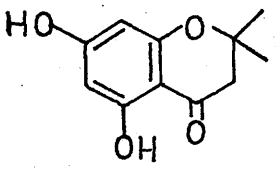
(2)

The recent isolation of pharmacologically active 5,7--dioxygenated coumarins bearing C-4 substituents has given a new impetus to the search for high yield synthetic routes to such compounds. The coumarin, surangin B (44) isolated[34] by Govindachari from Mammea longifolia (Wight) Planch and Triana, has been shown[35] to be extremely toxic to houseflies, even at very low concentrations. Crombie has also isolated[35] two similar coumarins (45) and (46) from Mammea americana L seeds which show similar activity to surangin B. Many related coumarins have been isolated from the same source, differing only in the non-oxygenated form of their C-4 side chain, but these coumarins do not appear to have the same insecticidal properties as those already mentioned. The recent report[36] of the anti-tumour activity of the Mammea coumarins gives additional importance to research into the synthesis of such compounds.

These coumarins, in addition to their C-4 substituent, all possess alkyl and acyl substituents at C-6 and/or C-8 of the nucleus. The alkyl units are present as either 3,3-dimethylallyl units, (45) and (46) or as a geranyl unit (44). The former could in principle be inserted by the Claisen rearrangement of a 1,1-dimethylallyl ether situated on a neighbouring phenolic OH[37], or alternatively by the para-Claisen rearrangement of a 3,3-dimethylallyl ether[32]. The acyl units are present as either 2-methyl or 3-methyl butyryl groups, and these are potentially derivable from the corresponding 2,3-dimethyl and 2,2-dimethyl chromanones, as in the glabralactone (22) and dentatin (2) syntheses. The unsaturated acyl groups thus formed can be readily reduced to the required substituents by catalytic hydrogenation[19,20]. The positioning of the acyl groups at C-6 or C-8 would depend on the position of the equilibrium set up in the

Scheme 6.





(16)

base catalysed chromanone ring opening. Crombie[38] and Djerassi[39] have both reported that the 6-acyl isomer is predominant in this type of base catalysed reaction, but the rearrangement of tomentolide B in methanolic KOH (Scheme 6) is a more closely related analogy and in this case, a 2,3-dimethylacryloyl grouping is found at C-8 exclusively.

The principal problem in the synthesis of the afore mentioned active coumarins would therefore be the introduction of an oxygen substituent into the 1' position of a 4-alkyl grouping. The reaction of acetylenic esters with phenols is known to give the corresponding coumarins, and such reactions involving dimethyl acetylenedicarboxylate have been reported[40] as giving 4-CO_2Me phenols when $ZnCl_2$ was used as the acid catalyst. Thus it was felt that if the chromanone (14) could be induced to react in a similar manner, the resulting phenols would be useful starting materials in a projected synthesis of either of the coumarins (45, 46). The additional advantage of this chromanone as a starting material, is its ability to avoid acid-catalysed deacylation as undergone by the Mammea coumarins mentioned earlier.

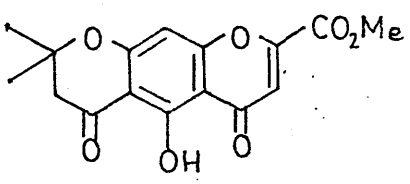
When the chromanone (16) was reacted with dimethyl acetylene dicarboxylate using the conditions of Woods and Hollands[40], a viscous gum, which appeared from TLC to be predominantly unreacted starting material, was obtained. However, when both the reaction temperature and time were increased, the resultant gummy product could be purified by TLC to give two main products. Each of these compounds gave a positive $FeCl_3$ test, and their NMR spectra indicated that the chromanone ring was still present. Both analysed for $C_{16}H_{14}O_7$, and their IR and UV spectra suggested that they were coumarins. The NMR spectrum of the less polar isomer showed the presence of a CO_2Me group (τ6.03, 3H, s)

Table 7

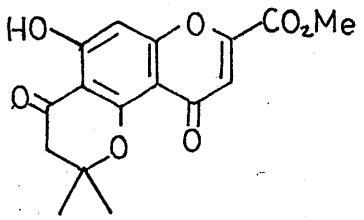
Compound	ν max.	τ -OH	τ aromatic
(50)	1740, 1629 and 1147	-4.85	3.67
(15)	1740, 1635 and 1100	-2.75	3.66

Table 8

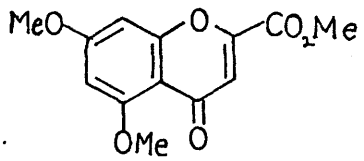
(51)	1740, 1650, 1622 and 1580	-2.12	3.60
(8)	1740, 1650, 1632 and 1595	-2.10	3.56



(48)



(49)



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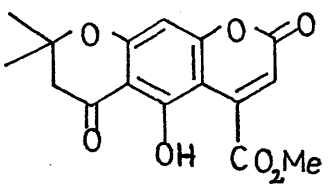

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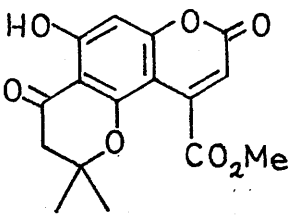

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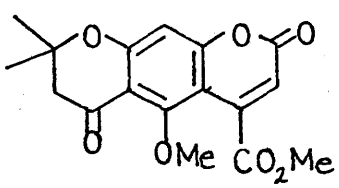

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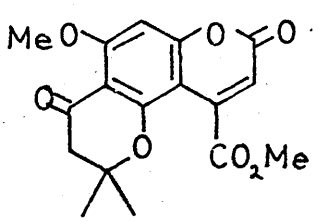
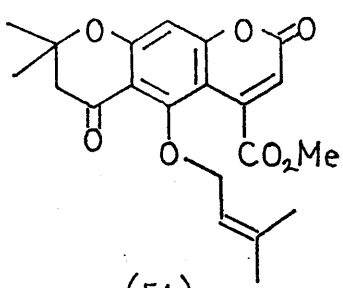


(53)

a chelated phenol (τ-4.85*, 1H, s), one aromatic proton (τ3.67, s) and only one vinyl proton (τ3.9, s). Comparison of the spectral properties of this phenol with those of clausenin (15) led to its structure being assigned as 50, (Table 7). Similar comparison between the more polar isomer and the known angular chromenocoumarin (8), (Table 8), led to its structure being assigned as 51. However the possibility still remained that the two compounds could be the corresponding isomeric chromones (48) and (49). In order to confirm their identity as coumarins, the IR and UV spectra of the methyl ethers (52) and (53) were compared with those recorded for the chromone (47), kindly donated by Fisons Ltd. These comparisons indicated that the two phenols were definitely coumarins and not chromones.

The more polar phenol had been assigned the angular structure (51) by spectral comparisons, and for confirmation of this assignment, 51 was reacted with 3,3-dimethylallyl bromide and K_2CO_3 in the presence of acetone. This reaction did not proceed as cleanly as expected, but the major product isolated was shown to be the angular 3,3-dimethylallyl ether (55). TLC of the crude reaction product suggested that the reaction had not gone to completion, and that some isomerisation of the starting phenol had occurred. The angular nature of the major product was confirmed by the nature of the phenolic product obtained after 55 had been heated at 170° in the presence of N,N-diethylaniline. This new yellow coumarin showed the characteristic NMR spectrum of a chelated (1,1-dimethylallyl) phenol (57), with signals at τ8.37 (6H, s), 5.07 (1H, bd, J11Hz), 5.03 (1H, bd, J17Hz), 3.70 (1H, d/d, J11 and 17Hz) and -3.05* (1H, s). Had the starting phenol been the linear isomer (50), then on rearrangement, a <u>para</u>-(3,3-dimethylallyl) phenol



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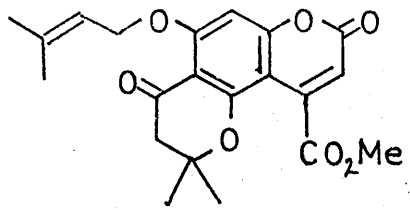

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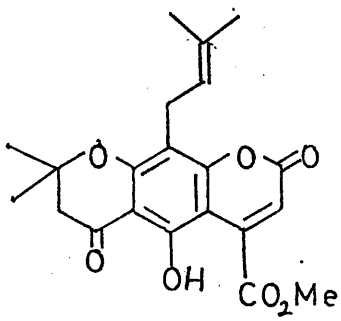

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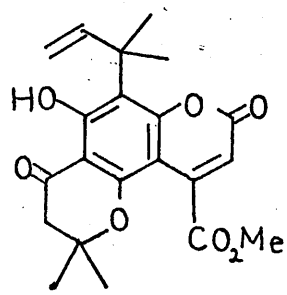

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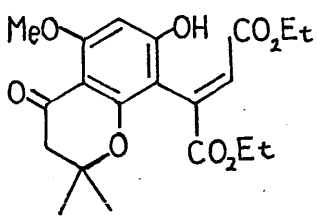

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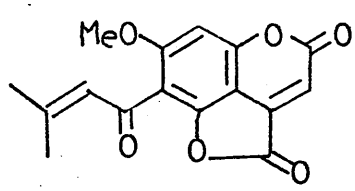


(59)

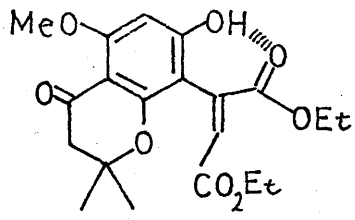
(56) would have resulted.

In order to study the base-catalysed rearrangements of such 4-substituted chromanocoumarins, the phenol (51) was converted to its methyl ether (53). However, methylation of 51 with MeI and K_2CO_3 in acetone gave a mixture of the linear and angular methyl ethers, (52) and (53). The angular phenol gave the angular ether in 57% yield and the linear ether in 38% yield. Also it was found that the linear phenol gave a mixture of the linear ether (66%) and the angular ether (28%) when subjected to similar methylation. The reason for this isomerisation is not clear, and certainly there was no evidence of similar rearrangement when 8 and 15 were methylated under the same conditions. Although difficulty was experienced in separating the starting phenols, the purity of the samples used for these methylations is not in doubt, as contamination of one isomer by the other to the extent of 30% would clearly show in their NMR and IR spectra. This isomerisation does however help to explain the number of products formed in the 3,3-dimethylallylation of the angular phenol (51).

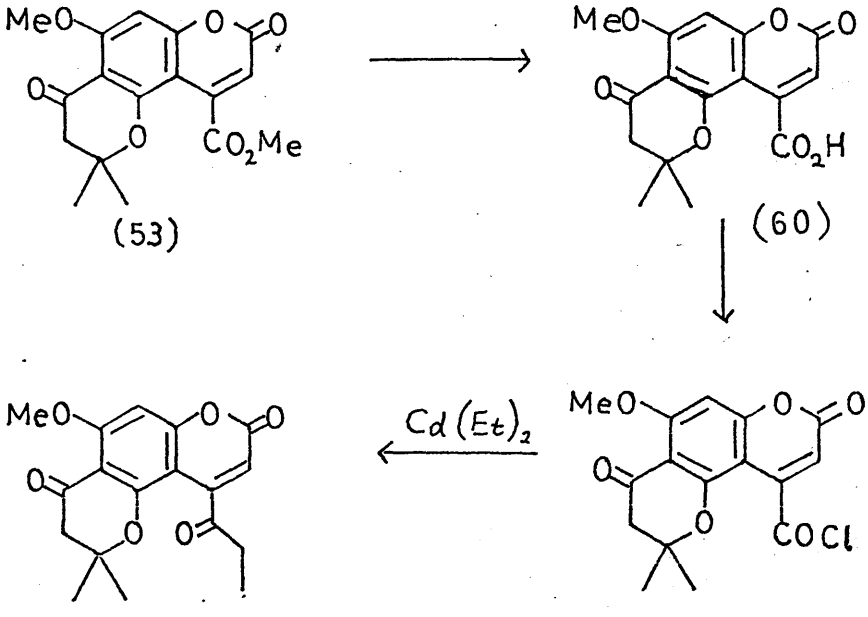
It was hoped that the angular methyl ether (53) could be converted by treatment with base[25] to a coumarin bearing either a C-6 or a C-8 senecioyl group and a C-5 phenolic OH. The possibility of this latter OH reacting with the C-4 ester to form the lactone (59) was considered, but inspection of molecular models suggested that the strain involved was too great for such cyclisation to occur. However it seemed possible that hydrogen bonding between the newly formed C-5 OH and the ester carbonyl might allow the reaction to go to completion by hindering chromanone ring closure.

When the ether (53) was added to an ethanolic solution of NaOEt[25] TLC showed that initially no reaction was taking place.

Figure 3.



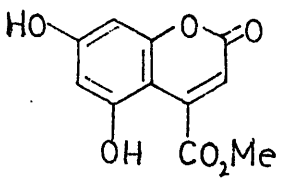
Scheme 10



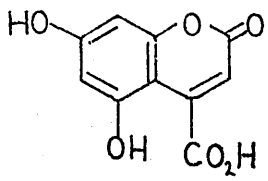
However, after prolonged stirring in the basic solution, a polar product was formed. This colourless crystalline compound was shown, from its NMR spectrum to contain an unopened chromanone ring, τ 8.63 (6H, s) and 7.40 (2H, s) . The NMR also showed the presence of two ethoxy groups, τ 8.82 6H, t, J7Hz) and 5.88 (4H, q, J7Hz) and one methoxyl signal, τ 6.23 (3H, s) . This evidence suggested that the compound concerned was the coumarinic acid ethyl ester (58), with the 4-CO_2Me ester being exchanged to its corresponding ethyl ester. This was confirmed by the molecular weight of 392 found by mass spectrometry. The isolation of coumarinic acids and their esters is not common, as lactonisation occurs fairly rapidly. However, Dean has reported that if a coumarin possesses a carbonyl or a nitro group at C-8 then chelation between these groups and the neighbouring phenol slows down lactonisation and the coumarinic acid can be isolated. In the case of the ester (58) it is possible that chelation between the 4-ester group and the phenol (Figure 3) is sufficient to hinder lactonisation. When this reaction was repeated using other bases, no reaction was observed.

With the failure to induce chromanone ring isomerisation in the presence of a C-4 ester grouping, it was felt that further modification of this substituent was required. If the ester (58) could be converted to the corresponding acid (60), it is possible that this could then be functionalised, via the acid chloride and diethyl cadmium, to give a 1' propionyl substituent at C-4, (Scheme 10). The advantage of this route, is that the other functional groups in the molecule should remain untouched.

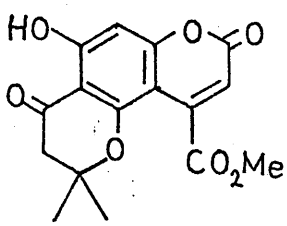
Woods and Hollands[40] have reported that esters such as 61 can be hydrolysed to the corresponding acid (62) by



(61)

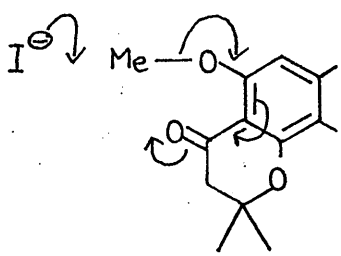


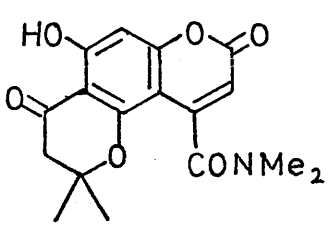
(62)



(51)

Scheme 11.



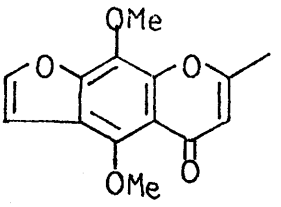


(63)

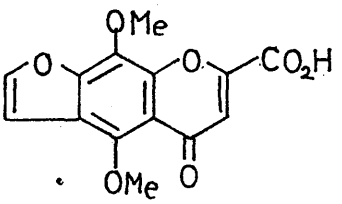
refluxing them with dil. HCl in ethanol for 48 hours. When these conditions were followed using the esters (52) and (53) no hydrolysis was observed, even when conc. HCl was added to the solution. Similar results were observed when conc. H_2SO_4 was employed. It was also found that these esters would not hydrolyse under basic conditions, and even after prolonged stirring with aqueous NaOH, only unreacted starting material was recovered.

However, it has been reported[41] that in cases where ester hydrolysis by aqueous acid or base has failed, the use of LiI in a solvent such as N,N-dimethylformamide or pyridine has yielded the corresponding acid. When the ester (53) was refluxed in N,N-diethylaniline in the presence of $LiI \cdot 2H_2O$, a yellow crystalline product was obtained. The NMR spectrum of this compound showed it to be the phenol (51) and this was confirmed by TLC comparisons. This product is formed by the demethylation of the C-7 OMe, the ease of the reaction being due to the electron with drawing effect of the neighbouring chromanone carbonyl (Scheme 11). Attempts to hydrolyse the phenolic ester (51) with LiI also failed, but when the reaction time was considerably increased, a polar product was isolated, whose NMR spectrum suggested that it was the amide (63) formed by reaction of the ester with the solvent.

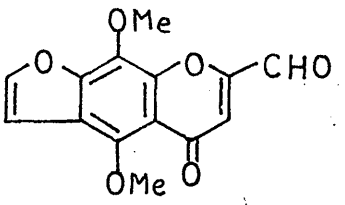
It has been reported[42] that the allylic C-2 methyl group of the chromone, khellin (64), can be oxidised with selenium dioxide to give a mixture of the acid (65a) and the aldehyde (65b). This result prompted an investigation into the possibility of similarly oxidising the C-4 methyl group of a suitably substituted coumarin, to give a 4-CO_2H coumarin. With this in mind, the chromanone (16) was reacted with ethyl



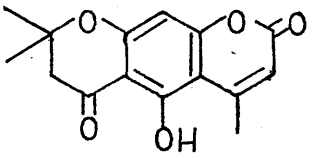
(64)



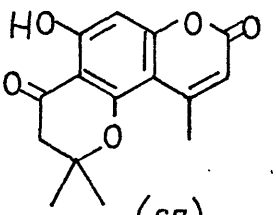
(65a)



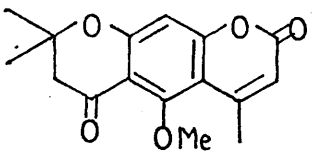
(65b)



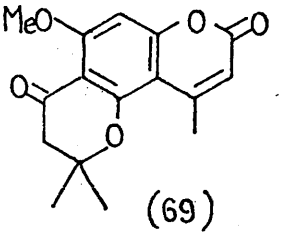
(66)



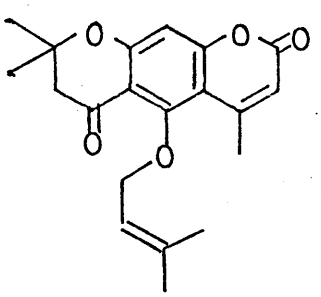
(67)



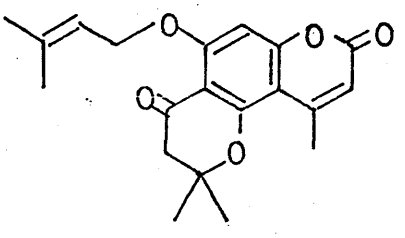
(68)



(69)



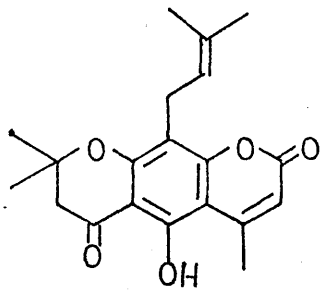
(70)



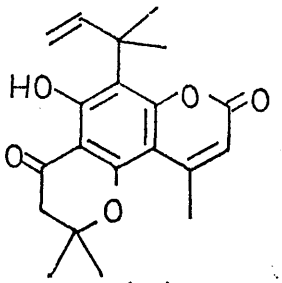
(71)

acetoacetate in the presence of an ion-exchange resin[43]. This reaction afforded a mixture of two phenolic coumarins which were only separated after repeated preparative TLC. The NMR spectra of these isomers indicated that they were the 4-methyl chromanocoumarins (66) and (67), the allylic methyl group giving rise to a doublet at approximately τ7.4 (J1Hz) and the C-3 proton resonating as a multiplet at approximately τ4.0. The assignment of the linear and angular structures to these two phenols was determined by spectral comparisons with similar compounds of known structure, and confirmed by synthesis of the 3,3-dimethylallyl ether of (67). When this compound was heated in N,N-diethylaniline under N_2, it underwent a Claisen rearrangement to give the phenol (73). The NMR spectrum of this compound clearly showed the presence of a 1,1-dimethylallyl unit attached to an aromatic ring, thus indicating that an ortho-Claisen rearrangement had taken place (Scheme 12). Had the starting phenol been the linear isomer (66) the 3,3-dimethylallyl phenol (72) would have resulted.

Due to the difficulty found in separating the phenols, the crude reaction product was normally methylated with MeI and K_2CO_3 and the ethers (68) and (69) separated by TLC and it appears that no rearrangement takes place in these reactions. When the ether (69) was treated with freshly sublimed SeO_2 using the conditions of the khellin oxidation[42], no reaction was observed to take place, and when aqueous dioxan was employed as solvent in place of EtOAc as solvent, a similar result was obtained. Attempts to oxidise the allylic methyl group using chromyl chloride[44] were also unsuccessful. It therefore appears that the C-4 methyl of the coumarin (69) is less reactive towards oxidising agents than the C-2 methyl group of khellin

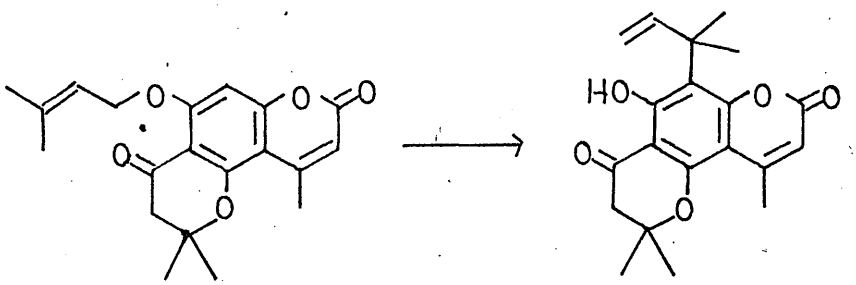


(72)

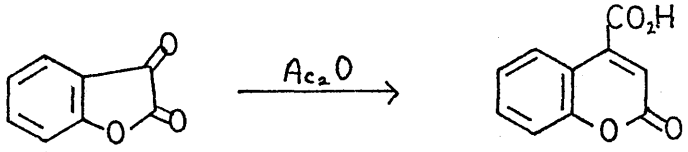


(73)

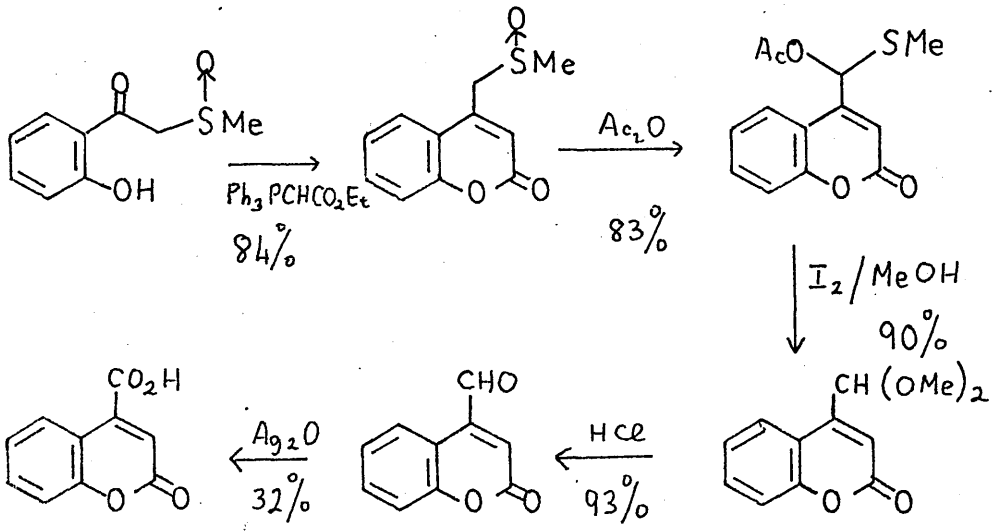
Scheme 12.



Scheme 13.



Scheme 14.



Scheme 15.

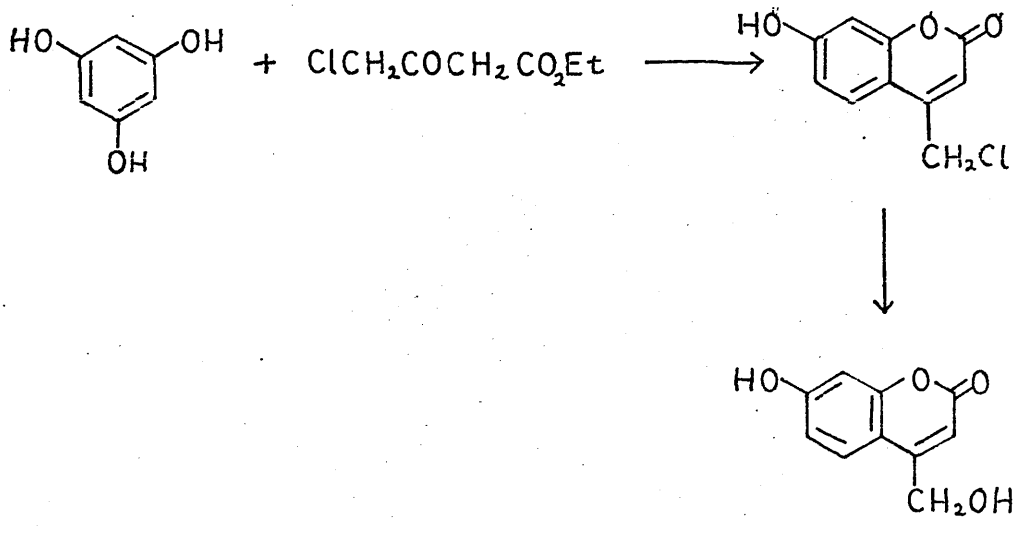


Table 9

Compound	ν max.					
(5)	1755,	1642,	1630 and	1592	(CCl_4)	angular
(8)	1740,	1650,	1632 and	1595	($CHCl_3$)	"
(51)	1740,	1650,	1622 and	1580	($CHCl_3$)	"
(67)	1735,	1649,	1625 and	1581	($CHCl_3$)	"
(15)	1740,	1635,	and	1100	($CHCl_3$)	linear
(50)	1740,	1629,	and	1147	($CHCl_3$)	"
(66)	1730,	1630,	1561 and	1150	($CHCl_3$)	"

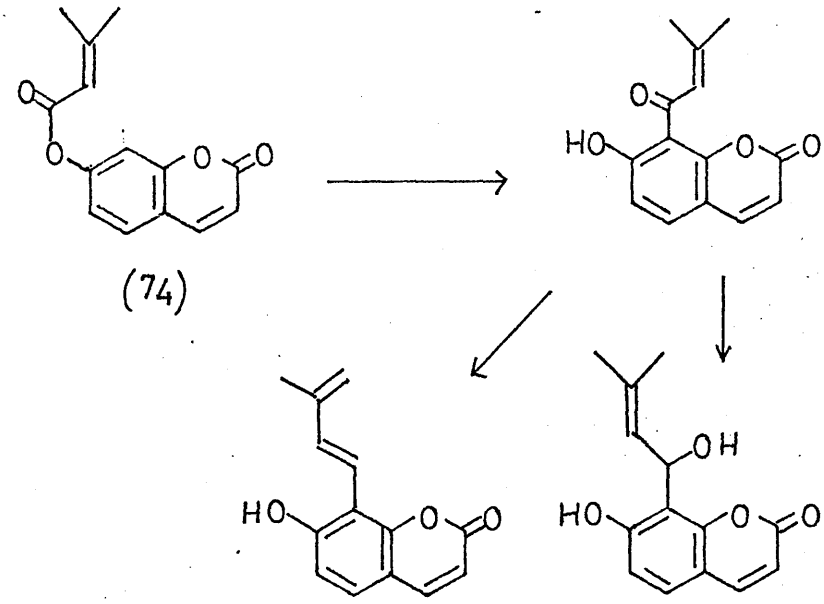
(64). The C-2 methyl of 64 is vinylogously conjugated to a ketone carbonyl, whereas the C-4 methyl of 69 is similarly conjugated to a lactone carbonyl and is thus less acidic, which could explain the lack of reactivity of the coumarin 4-methyl towards oxidising agents.

While studying this 4-methyl coumarin system, it was found that, as with the 4-CO_2Me coumarins, the ethers (68) and (69) do not undergo base catalysed chromanone ring isomerisation. This observation is indeed intriguing, as the analogy with the base catalysed isomerisation of tomentolide B[17] (Scheme 6) would seem reasonable.

As previously noted, there are some striking differences in the spectral properties of the linear and angular isomeric phenols and their ethers. All the angular phenols studied, whether or not they bear a C-4 substituent, show a characteristic pattern in the region 1750-1580cm^{-1} of their IR spectra which is readily distinguishable from the linear isomer, (Table 9). Also the NMR spectra of these compounds show similar effects in the chemical shifts of the aromatic and phenolic protons to those previously mentioned for non 4--substituted coumarins.

Two other methods are known[45,46] for the synthesis of 4-CO_2H coumarins. The first involves treatment of a 2,3-coumarandione with acetic anhydride in pyridine, to give the acid in moderate yield (Scheme 13), and the second longer synthesis (Scheme 14) gives high yields in all stages. One third possible method[47] of synthesising coumarins bearing oxygenated alkyl groups at C-4, involves condensing ethyl chloroacetoacetate with a phenol, followed by hydrolysis, (Scheme 15).

Scheme 16.



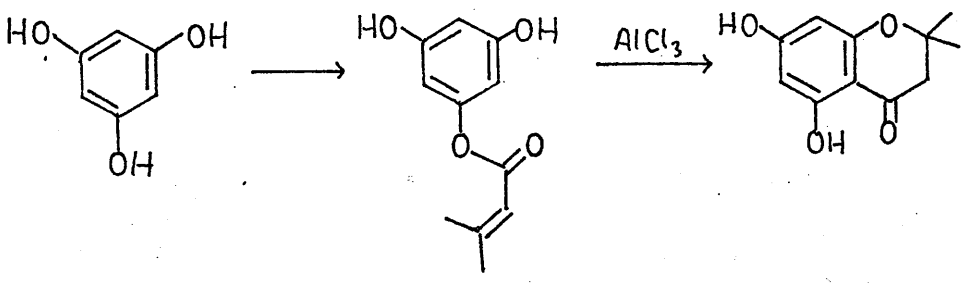
(74)

Whereas in the synthesis of glabralactone and dentatin it was possible to open the dimethyl chromanone ring to give an ortho senecioyl phenol, this could not be repeated in the 4-substituted series mentioned above. An alternative method of introducing a senecioyl group into the aromatic ring could be the use of the Fries rearrangement. Although this reaction was not attempted on 5,7-dioxygenated coumarins, preliminary investigations were carried out on 7-hydroxycoumarin. Had this reaction been successful, synthetic routes to coumarins of the type shown in Scheme 16 could have been examined.

The recent report[48] of the Fries rearrangement of unsaturated esters of naphthols prompted an investigation of similar rearrangements of the dimethylacryloyl ester of umbelliferone (74). This ester was prepared by stirring senecioyl chloride and umbelliferone in refluxing, ethanol--free, chloroform, and the product was shown by its NMR and IR spectra to be 74 . Several attempts using various conditions were then made to induce a Fries rearrangement to occur, but no success was achieved. The reason for this failure is hard to find, as saturated esters of umbelliferone[49] are known to undergo such rearrangements.

However, further attempts were made to introduce a senecioyl group into the umbelliferone molecule. When umbelliferone was treated with senecioic acid following the conditions of Miyano and Matsui[50] no reaction was found to take place, and when polyphosphoric acid was used as the catalyst, the umbelliferone was consumed, but no recognisable product was isolated. However a recent report[51] suggests trichloroacetic acid as a good Friedel Crafts acid catalyst and so umbelliferone was heated with senecioic acid in the presence

Scheme 17.



of this acid, and a white crystalline product was obtained. However, comparison of the physical properties of this compound with those of the ester (74) showed them to be identical. In a similar experiment, 5,7-dihydroxycoumarin was treated with the same reagents, and a mixture of the two chromanocoumarins (8) and (15) was obtained, albeit in low yield. Similar cyclisations have been reported[11] in the synthesis of calophyllolide and costatolide derivatives, (Scheme 17).

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General Experimental

and Abbreviations.

Melting Points are uncorrected and were determined on a Kofler hot-stage apparatus. Microanalyses were carried out by Mr. J.M.L. Cameron and Miss F. Cowan and their staffs. Mass spectra were recorded on an A.E.I.-G.E.C. M.S.12 mass spectrometer by Mr. A. Ritchie and Miss M. Laing. Infra-red spectra were recorded by Mrs. F. Lawrie and her staff on a Perkin-Elmer 225 instrument, and routine infra-red spectra were recorded on a Unicam SP 1000 instrument. All ultra-violet spectra were recorded for ethanol solutions on a Unicam SP 800 spectro-photometer; 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 Mr. A. Haetzman on a Varian T-60 spectrometer, using tetramethylsilane as an internal standard. Unless otherwise stated, these spectra were run using deuterochloroform as a solvent.

Kieselgel G(Merck) was used for all thin layer chromatography. Light petroleum refers to the fraction boiling between 60-80°. All solutions were dried over anhydrous magnesium sulphate or anhydrous sodium sulphate, and solvents were evaporated under reduced pressure. Analytical and preparative TLC plates were viewed under an ultra-violet (254 and 350nm) lamp. Analytical TLC plates were developed by iodine vapour, followed by spraying with ceric ammonium sulphate solution and heating to approximately 150°. The compounds isolated from a mixture by preparative TLC are given in order of increasing polarity with respect to the elution procedure employed.

The following abbreviations have been used, primarily in the experimental sections:-

MS	Mass spectrum
TLC	thin layer chromatography
IR	infra-red
UV	ultra-violet
NMR	nuclear magnetic resonance
sh	shoulder (in UV spectra)
s	singlet
d	doublet
t	triplet
q	quartet
m	multiplet
b	broad
w/v	e.g. 20% w/v refers to a solution of 20g in 100 ml solvent.
/	e.g. 100mg/ refers to the weight of a compound purified by TLC only.
o	e.g. 3.52^{o} refers to an NMR signal which disappears on addition of D_2O.
conc.	concentrated
dil.	dilute
p.	page number

A standard method of working up alkylation reactions, often employed during the course of this research, is referred to as work-up procedure I, in this thesis. The full details of this procedure are as follows :-

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

EXPERIMENTAL.

2,2-Dimethyl-5,7-dihydroxychroman-4-one (16)

This was prepared by the method of Miyano and Matsui[50] using phloroglucinol (3.2g), zinc chloride (2.0g) and senecioic acid (2.0g). This gave the required chromanone (1.6g, 38%), m.p. 196-197°.

Ethyl Propiolate

A mixture of propiolic acid (20g), dry ethanol (60ml) and conc. sulphuric acid (3.3ml) was kept at R.T. for 40 hr, then diluted with water (200ml) and extracted with ether. The organic layer was washed with dil. sodium carbonate, brine to neutrality and dried. Distillation yielded ethyl propiolate (14g, 50%), b.p. 117-118° (lit[52] b.p. 119°/745 m.m.).

Preparation of the chromanone (8)

(i) 2,2-Dimethyl-5,7-dihydroxychroman-4-one (3g), malic acid (2g) and conc. H_2SO_4 (8ml) were heated at 125° for 1 hr[12] to give 8, (1g, 27%), needles, m.p. 215-220° (from EtOAc) (lit[12] m.p. 218-220°); $\nu_{max}^{CHCl_3}$ 1740, 1650, 1632 and 1595 cm^{-1}; λmax 278 and 323 nm (log ε 4.38 and 4.02); NMR signals at τ 8.40 (6H, s), 7.16 (2H, s), 3.75 and 2.10 (each 1H, d, J 10 Hz), 3.56 (1H, s) and -2.10• (1H, s).

(ii) 2,2-Dimethyl-5,7-dihydroxychroman-4-one (2.15g), $ZnCl_2$ (1.4g) and ethyl propiolate (1ml) were heated at 100° for 1½ hr.[5] The cooled residue was extracted with EtOAc, washed with dil. HCl, brine to neutrality and dried. Evaporation yielded a viscous gum which crystallised from EtOAc to give 8 (350mg, 13%), m.p. 215-220°.

Clausenin (15)

By repeated preparative TLC (1 x $CHCl_3$ and 1 x 20% EtOAc: light petroleum) on the mother liquors of crystallisation of 8, it was possible to obtain synthetic clausenin (15), (175mg, 7%), m.p. 156-158° (lit[3] m.p. 157-158°); $\nu_{max}^{CHCl_3}$ 1740, 1635 and 1100 cm^{-1}; λ max 277 and 321 nm (log ε 4.42 and 4.02); NMR signals at τ 8.43 (6H,s), 7.16 (2H,s), 3.77 and 2.00 (each 1H, d, J 10Hz), 3.66 (1H,s) and -2.75• (1H,s).

Methylation of 8

K_2CO_3 (80mg) was added to a solution of 8 (125mg) in acetone (25ml) and the mixture stirred at R.T. for ½ hr. MeI (0.75 ml) was added and the mixture refluxed for 20hr. Work-up procedure I gave the methyl ether (14), (100mg, 76%), plates, m.p. 190-191°, (from $CHCl_3$ - ether), (lit[5] m.p. 193-194°); $\nu_{max}^{CHCl_3}$ 1732, 1682, 1614 and 1594 cm^{-1}; λ max 230 (sh), 273 and 318 nm (log ε 3.80, 4.15 and 3.87); NMR signals at τ 8.47 (6H,s), 7.25 (2H,s), 6.02 (3H,s), 3.83 and 2.07 (each 1H, d, J 10Hz) and 3.62 (1H,s).

Methylation of clausenin (15)

K_2CO_3 (150mg) was added to a solution of clausenin (150mg) in acetone (25ml) and the mixture stirred at R.T. for ½ hr. MeI (0.75 ml) was added and the mixture refluxed for 22 hr. Work-up procedure I gave the methyl ether (17), (80mg, 50%), white plates, m.p. 147-149° (from CH_2Cl_2-pentane), (lit[3] m.p. 147-149°); ν_{max}^{Nujol} 1729, 1639 and 1600 cm^{-1}; NMR signals at τ 8.50 (6H,s), 7.25 (2H,s), 6.00 (3H,s),

3.77 and 2.08 (each 1H, d, J 10Hz) and 3.40 (1H,s).

Isomerisation of the chromanone (14)

A solution of 14 (100mg) in EtOH (15 ml) was added to a solution (5ml) of ethanolic NaOEt, [made from Na (100mg) and EtOH (15ml)] and stirred at 40° for 4¾ hr. After dilution with water and acidification with dil. HCl, the mixture was extracted with EtOAc, washed with brine to neutrality and dried. Evaporation gave an oily solid which was separated by TLC (1 x $CHCl_3$) into:-

(i) the phenol (18), (28mg, 28%), yellow needles, m.p. 151-153° (from MeOH). (Found: C, 65.75; H, 5.3. $C_{15}H_{14}O_5$ requires C, 65.7; H, 5.15%); $\nu_{max}^{CHCl_3}$ 1741, 1620 and 1610 cm^{-1}; λ max 235(sh) and 300 nm (log ε 3.78 and 3.54), (after 3 days at R.T. or 3 hr at 65°, this spectrum changed to that of 14); λ_{max}^{base} 240, 313 and 392 nm (log ε 3.73, 3.56 and 3.39); mass spectral peaks at m/e 274 (5%, M^+), 259 (100%), 218 (10%), 189 (19%) and 54 (25%); NMR signals at τ 8.00 and 7.80 (each 3H, bs), 6.07 (3H,s), 3.82 and 1.97 (each 1H, d, J 10Hz), 3.72 (1H,s), 3.13 (1H,bs) and -4.77• (1H,s).

(ii) recovered starting material (14), (33mg, 33%).

(iii) the polar phenol (19), (39mg, 39%), prisms, m.p. 203-206° (from EtOAc-light petroleum). (Found: C,65.55; H,5.3. $C_{15}H_{14}O_5$ requires C,65.7; H,5.15%); $\nu_{max}^{CHCl_3}$ 1735, 1670 and 1612 cm^{-1}; λ max 218 (sh), 251 and 318 nm (log ε 4.13, 4.08 and 4.00); λ_{max}^{base} 255, 325 and 360 nm (log ε 4.05, 3.91 and 3.83); mass spectral peaks at m/e 274 (25%, M^+), 243 (70%), 150 (40%), 83 (60%), 55 (100%), 43 (85%)

and 41 (70%); NMR (in deuteroacetone) signals at τ 8.15 and 7.92 (each 3H, d, J 1Hz), 6.25 (3H,s), 3.97 and 2.02 (each 1H, d, J 10Hz), 3.75 (1H, m, J 1Hz) and 3.50 (1H,s).

Reaction of 17 wit NaOEt.

A solution of 17 (50mg) in EtOH (15ml) was added to a solution (5ml) of ethanolic NaOEt [made from Na (100mg) and EtOH (15ml)] and the mixture stirred at 40° for 4 hr. Similar work-up to that described above gave:-

(i) unreacted 17 (20mg, 40%)

(ii) clausenin (15) (28mg, 56%)

Methylation of 18

K_2CO_3 (80mg) was added to a solution of 18 (40mg) in acetone (15ml) and the mixture stirred at R.T. for 15 minutes. MeI (0.6ml) was added and the mixture refluxed for 3 hr. Work-up procedure I yielded the ether (23), (40mg, 97%), plates, m.p. 120°, (from ether-light petroleum). (Found: C,66.6; H,5.7. $C_{16}H_{16}O_5$ requires C,66.7; H,5.7%); ν_{max}^{KBr} 1740, 1670 and 1610 cm^{-1}; λ max 218 (sh), 247, 268 (sh) and 332 nm (log ε 4.09, 4.16, 4.09 and 4.10); mass spectral peaks at m/e 288 (26%, M^+), 257 (10%), 149 (40%), 83 (50%), 69 (40%) and 55 (100%); NMR signals at τ 8.05 and 7.77 (each 3H, d, J 1.5 Hz), 6.17 (6H,s), 3.78 and 2.15 (each 1H, d, J 10 Hz), 3.70 (1H, m, J 1.5 Hz) and 3.40 (1H,s).

Methylation of 19

Similar methylation of 19 (40mg), followed by purification by TLC (1 x $CHCl_3$), gave glabralactone (22), (33 mg, 75%), m.p. 128-130° (from EtOAc-light petroleum), (lit[18] m.p.127-129°).

(Found: C,66.6; H,5.6. Calc. for $C_{16}H_{16}O_5$: C,66.7; H, 5.7%); ν_{max}^{KBr} 1730, 1660, 1615 and 1595 cm^{-1}; λ max 221, 247 and 320 nm (log ε 4.13, 4.21 and 4.18); mass spectral peaks at m/e 288 (20%, M^+), 257 (100%), 83 (50%) and 55 (50%); NMR signals at τ 8.05 and 7.75 (each 3H, d, J 1.5 Hz), 6.10 and 6.05 (each 3H, s), 3.90 and 2.10 (each 1H, d, J 10 Hz) and 3.68 (2H, bs, resolves into a multiplet and a singlet in deuteroacetone). The IR and UV spectra were identical with those published[19] for natural angelicone, m.p. 130°.

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

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

Dimethylallylation of the chromanone (8)

K_2CO_3 was added to a solution of 8 (1.1g) in acetone (100ml) and the mixture stirred at R.T. for 1 hr. Freshly distilled dimethylallyl bromide (1g) was added and the mixture allowed to reflux for 20 hr. Work-up procedure I yielded an oil which, after purification by TLC (1 x $CHCl_3$), afforded the ether (28), (0.8g, 60%), needles, m.p. 128-129° (from ether). (Found: C,69.25; H,6.15. $C_{19}H_{20}O_5$ requires C,69.5; H,6.15%); ν_{max}^{Nujol} 1740, 1690 and 1610 cm^{-1}; λ max 235, 274 and 325 nm (log ε 3.76, 4.37 and 4.09); mass spectral peaks at m/e 328 (5%, M^+), 260 (52%), 245 (100%), 205 (33%), 69 (28%) and 41 (55%); NMR signals at τ 8.50 (6H,s), 8.23 (6H, bs), 7.24 (2H,s), 5.27 (2H, d, J 6Hz), 4.36 (1H, bt, J 6Hz), 3.80 and 2.05 (1H, d, J 10Hz) and 3.60 (1H,s).

Isomerisation of the chromanone (28)

A solution of 28 (350mg) in EtOH (25ml) was added to a stirred solution of NaOEt [made from Na (65mg) in EtOH (25ml)] at 45°. After 3 hr, the yellow solution was diluted with cold water, acidified with dil. HCl and

extracted thoroughly with EtOAc. The organic layer was washed with brine to neutrality, dried and the residue from evaporation separated by TLC (1 x $CHCl_3$) into:-

(i) the phenol (30), (120mg, 34%), yellow needles, m.p. 136-138° (from MeOH). (Found: C, 69.25; H, 6.2. $C_{19}H_{20}O_5$ requires C, 69.5; H, 6.15%); $\nu_{max}^{CHCl_3}$ 1739, 1617 and 1608 cm^{-1}; λ max 239 and 302 nm (log ε 3.52 and 4.31); λ_{max}^{base} 240, 315 and 393 nm (log ε 4.20, 4.13 and 3.93); mass spectral peaks at m/e 328(5%, M^+), 260 (17%), 245 (82%), 69 (100%) and 41 (50%); NMR signals at τ 8.22 (6H, s), 8.03 and 7.83 (each 3H, d, J 1Hz), 5.40 (2H, bd, J 6Hz), 4.48 (1H, bt, J 6Hz), 3.87 and 1.97 (each 1H, d, J 10Hz), 3.75 (1H, s), 3.10 (1H, m, J 1Hz) and -4.70 (1H, s).

(ii) recovered starting material (28), (110mg, 31%).

(iii) the phenol (31), (120mg, 34%), m.p. 137-140° (from EtOAc - light petroleum). (Found: M^+ 328 by mass spectrum; $C_{19}H_{20}O_5$ requires M^+328); $\nu_{max}^{CHCl_3}$ 3590, 1734, 1670 and 1611 cm^{-1}; λ max 220 (sh), 250 and 320 nm (log ε 4.29, 4.23 and 4.15); mass spectral peaks at m/e 328 (12%, M^+), 313 (70%), 257 (45%), 245 (100%), 217 (23%), 205 (18%) and 83 (30%); NMR signals at τ 8.37 and 8.30 (each 3H, s), 8.05 and 7.80 (each 3H, bs), 5.78 (2H, bd, J 6Hz), 4.70 (1H, bt, J 6Hz), 3.95 and 2.05 (each 1H, d, J 10Hz) and 3.63 (2H, m).

Isomerisation of the phenol (31)

The phenol (31) (100mg) was added to a stirred ethanolic solution of NaOEt [made from Na (20mg) in EtOH (25 ml)]. The solution was kept at R.T. for 1 hr and at 40° for 2½ hr. After cooling, the solution was

diluted with water, acidified with dil. HCl and extracted with EtOAc. The organic layer was washed with brine to neutrality and dried. Evaporation yielded an oil which was separated by TLC (1 x $CHCl_3$) into:-

(i) the phenol (30), (31mg, 31%)

(ii) the chromanone (28), (30mg, 30%)

(iii) the phenol (31), (39mg, 39%)

Methylation of 30

K_2CO_3 (110mg) was added to a solution of 30 (80 mg) in acetone (30ml) and the mixture stirred at R.T. for 1 hr. MeI (0.5ml) was added, and refluxing continued for another 2 hr. Work-up procedure I gave an oil which was purified by TLC (1 x $CHCl_3$) to give the ether (13), (83mg, 67%), m.p. 57-60° (from CCl_4). (Found: C,70.0; H,6.65; $C_{20}H_{22}O_5$ requires C,70.2; H,6.5%); $\nu_{max}^{CCl_4}$ 1749, 1615 and 1602 cm^{-1}; λ max 246, 270 (sh) and 324 nm (log ε 4.08, 3.95 and 4.05); mass spectral peaks at m/e 342 (5%, M^+), 274 (10%), 259 (100%), 69 (50%) and 41 (40%); NMR signals at τ 8.23 (6H, bs), 8.05 and 7.78 (each 3H, d, J 1Hz), 6.15 (3H, s), 5.44 (2H, d, J 6Hz), 4.65 (1H, bt, J 6Hz), 3.82 and 2.15 (each 1H, d, J 10Hz), 3.72 (1H, bs) and 3.47 (1H, bs).

Claisen rearrangement of 13

A solution of 13 (243mg) in N,N-diethylaniline (1ml) was heated at 180° for 3 hr under N_2. The cooled solution was poured into ice-water, extracted with EtOAc, washed with dil. HCl to pH 1, brine to neutrality, dried and evaporated. The residual oil was purified by TLC (1 x $CHCl_3$)

to give clausenidin methyl ether (10), (183mg, 75%), m.p. 87-88° (from ether), (lit [3,29] m.p. 86-87°); ν_{max}^{Nujol} 1735, 1690, 1612 and 1575 cm^{-1}; λ max 289, 290 (sh), 320 and 335 (sh) nm (log ε 4.39, 4.13, 4.11 and 4.00); mass spectral peaks at m/e 342 (40%, M^+), 327 (23%), 272 (100%), 243 (30%) and 230 (28%); NMR signals at τ 8.50 (6H,s), 8.30 (6H,s), 7.30 (2H,s). 6.04 (3H,s), 5.10 (1H, bd, J 11 Hz), 5.07 (1H, bd, J 17Hz), 3.77 (1H d/d, J 11 and 17 Hz), 3.78 and 2.02 (each 1H, d, J 10 Hz).

When this reaction was repeated in the presence of butyric anhydride [10], no trace of any butyrate ester was observed, while the yield of 10 was the same.

Reduction of the chromanone (10)

$NaBH_4$ was added portionwise over 1 hr to a solution of 10 (180mg) in EtOH (15ml), the reaction being monitored by TLC until all of 10 had been consumed. The solution was then diluted with dil. HCl, extracted with EtOAc, washed with brine to neutrality and dried. Evaporation afforded an off-white solid which was separated by TLC (1 x CHCl) to give:-

(i) the ether 38, (90mg, 50%), m.p. 87-89° (from light petroleum). (Found: M^+372 by mass spectrum. $C_{22}H_{28}O_5$ requires M^+372); $\nu_{max}^{CCl_4}$ 1740, 1591 and 1145 cm^{-1}; λ max 225 (sh), 255, 264 and 330 nm (log ε 4.16, 3.87, 3.91 and 4.17); mass spectral peaks at m/e 372 (3%, M^+), 326 (22%), 312 (23%) and 311 (100%); NMR signals at τ 8.60, 8.53, 8.37 and 8.33 (each corresponding to a tertiary methyl, 8.80 (3H, d, J 8Hz), 8.47-7.67 (2H,m), 3.68 and 3.62 (2H, q, J 8Hz), 6.07 (3H,s), 5.33 (1H,m), 5.18 (1H, bd, J 11Hz), 5.12 (1H, bd, J 18Hz),

3.85 and 2.17 (each 2H, d, J 10Hz) and 3.72 (1H, d/d, J 11 and 18Hz).

(ii) the alcohol, (36), (90mg, 50%), colourless plates, m.p. 155-158° (from EtOAc - light petroleum), (lit [1] m.p. 157-158°). (Found: C, 69.85; H, 7.3. Calc. for $C_{20}H_{24}O_5$: C, 69.75; H, 7.0%); $\nu_{max}^{CHCl_3}$ 3570, 1720 and 1595 cm^{-1}; λ max 228, 257, 266 and 332 nm (log 4.03, 3.84, 3.92 and 4.14); mass spectral peaks at m/e 344 (15%, M^+), 326 (25%), 311 (100%), 281. 18%), 273 (63%), 243 (16%) and 233 (25%); NMR signals at τ 8.63 and 8.55 (each 3H,s), 8.33 (6H,s), 7.97 (2H, d, J 6Hz); 6.05 (3H,s), 4.97 (1H, t, J 6Hz), 5.18 (1H, bd, J 11Hz), 5.13 (1H, bd, J 18Hz), 3.73 (1H, d/d J 11 and 18 Hz), 3.80 and 2.18 (each 1H, d, J 10Hz).

Dehydration of the alcohol (36)

An intimate mixture of the alcohol (36) (20mg) and freshly fused $KHSO_4$ (45mg) was heated at 105°/0.01 m.m. for 6 hr. A colourless solid, (17mg, 85%), m.p. 93-95°, sublimed from the mixture. (Found: C, 73.6; H, 6.9. Calc. for $C_{20}H_{22}O_4$: C, 73.6; H, 6.8%); ν_{max}^{KBr} 1723, 1609, 1583 and 1130 cm^{-1}; λ max 227, 265, 272, 328 and 347 (log ε 4.22, 4.33, 4.54, 4.01 and 4.00); mass spectral peaks at m/e 326 (18%, M^+), 312 (22%), 311 (100%), 281 (16%) and 69 (10%); NMR signals at τ 8.55 and 8.33 (each 6H,s), 5.12 (1H, bd, J 11Hz), 5.05 (1H, bd, J 18Hz), 4.31, 3.83, 3.43 and 2.15 (each 1H, d, J 10Hz) and 3.50 (1H, d/d, J 11 and 18Hz). This compound was shown to be identical with an authentic sample of natural dentatin (m.p., m.m.p., IR, UV, NMR and MS) kindly donated by Professor B.R. Pai and Dr. S. Narayanaswami.

Dimethylallylation of the crude product of the Pechman condensation of the chromanone (16) and malic acid.

K_2CO_3 (1.0g) was added to a solution of the crude phenol mixture (1.1g) in acetone (100ml) and the mixture stirred at R.T. for 1 hr. Freshly distilled dimethylallyl bromide (1.0g) was added and the mixture refluxed for 20 hr. Work-up procedure I yielded a yellow oil which was separated by TLC (1 x $CHCl_3$) into:-

(i) clausenin dimethylallyl ether (41), (377 mg', 27%), needles, m.p. 124-125° (from EtOAc - light petroleum), (lit[5] m.p. 118-121°); ν_{max}^{Nujol} 1735, 1690, 1610 and 1590 cm^{-1}; λ max 264 and 315 nm (log ε 4.35 and 4.09); mass spectral peaks at m/e 328 (2%, M^+), 266 (47%), 245 (100%), 205 44%), 204 27%), 176 (23%), 68 (34%) and 41 (85%); NMR Signals at τ 8.52 (6H,s), 8.33 and 8.23 (each 3H, d, J 1.5Hz), 7.27 (2H,s), 5.38 (2H, bd, J 7Hz), 4.45 (1H, bt, J 7Hz), 3.78 and 2.08 (each 1H, d, J 10Hz) and 3.40 (1H,s).

(ii) the ether (28), (800mg', 60%)

(iii) the ether (42), (150mg', 11%), plates, m.p. 177-179° (from EtOAc - light petroleum). (Found: C, 69.7; H, 6.2. $C_{19}H_{20}O_5$ requires C, 69.5; H, 6.15%); $\nu_{max}^{CCl_4}$ 1750, 1698, 1623 and 1590 cm^{-1}; λ max 220, 235 (sh), 278 (sh), 285, 320 and 328 (sh) (log ε 4.27, 3.86, 4.01. 4.11, 4.05 and 3.93); mass spectral peaks at m/e 328 (6%, M^+), 260 (22%), 245 (45%), 205 (24%), 204 (40%), 176 (26%), 69 (53%) and 41 (100%); NMR signals at τ 8.37 (6H,s), 8.23 and 8.18 (each 3H, bs), 7.30 (2H,s), 5.42 (2H, bd, J 7Hz), 4.52 (1H, bt, J 7Hz), 3.85 and 2.07 (each 1H, d, J 10Hz) and 3.77 (1H,s).

Claisen Rearrangement of 28

The ether (28) (140mg) was heated at 180° for 3 hr at atmospheric pressure. The resultant oil was purified by TLC (1 x $CHCl_3$) to give the phenol (5), (100mg, 71%), needles, m.p. 151-152° (from EtOAc - light petroleum). (Found: C, 69.5; H, 6.2. $C_{19}H_{20}O_5$ requires C, 69.5; H, 6.15%); $\nu_{max}^{CCl_4}$ 1755, 1642, 1630 and 1582 cm^{-1}; λ max 215, 233 (sh), 284 and 330 nm (log ε 4.09, 3.91, 4.48 and 4.02); λ_{max}^{base} 248, 278, 292, 309 (sh), 370 and 415 nm (log ε 4.13, 4.01, 4.05, 4.00, 4.09 and 4.17); mass spectral peaks at m/e 328 (47%, M^+), 313 (57%), 272 (29%), 257 (100%), 245 (11%), 244 (21%) and 229 (14%); NMR signals at τ 8.45 and 8.32 (each 6H, s), 7.17 (2H, s), 5.10 (1H, bd, J 11Hz), 5.02 (1H, bd, J 18Hz), 3.90 and 2.08 (each 1H, d, J 10Hz), 3.72 (1H d/d, J 11 and 18 Hz) and -3.02$^{\bullet}$(1H, s).

Methylation of 5

K_2CO_3 (70mg) was added to a solution of 5 (80mg) in acetone (50ml) and the mixture stirred at R.T. for ½ hr. MeI (1ml) was added and the mixture refluxed for 11 hr. Work-up procedure I gave an off-white solid which was purified by TLC (1 x $CHCl_3$) to give the ether 6 (54mg, 61%), prisms, m.p. 160-162° (from EtOAc - light petroleum). (Found: C, 69.95; H, 6.5. $C_{20}H_{22}O_5$ requires C, 70.15; H, 6.5%); ν_{max}^{Nujol} 1735, 1680, 1615 and 1560 cm^{-1}; λ max 214, 272, 315 and 341 (sh) (log ε 4.25, 4.50, 4.06 and 3.80); mass spectral peaks at m/e 342 (39%. M^+), 327 (69%), 271 (100%), 243 (56%) and 41 (72%); NMR signals at τ 8.50 and 8.37 (each 6H, s), 7.26 (2H, s), 6.32 (3H, s), 5.15 (1H, bd, J 10Hz),

5.10 (1H, bd, J 18Hz), 3.77 and 1.98 (each 1H, d, J 10Hz) and 3.63 (1H, d/d, J 10 and 18 Hz).

Dimethylallylation of 8 using 1,2-dimethoxyethane (glyme) as solvent

K_2CO_3 (76mg) was added to a solution of 8 (115mg) in dry glyme (50ml) and the mixture allowed to reflux for 1 hr. Dimethylallyl bromide (70mg) was added and the mixture refluxed for 21 hr. Work-up procedure I yielded a yellow oil which gave, after purification by TLC (1 x $CHCl_3$), the phenol 29, (55mg, 39%), prisms, m.p. 151-152° (from MeOH). (Found: C,69.6; H,6.1. $C_{19}H_{20}O_5$ requires C,69.5; H, 6.15%); $\nu_{max}^{CCl_4}$ 1749, 1642, 1630 and 1590 cm^{-1}; λ max 215, 233 (sh), 283 and 331 nm (log ε 4.15, 3.95, 4.43 and 3.98); λ_{max}^{base} 245, 278, 297, 308 (sh), 370 and 410 nm (log ε 4.10, 4.04, 4.03, 4.00, 4.05 and 3.98); mass spectral peaks at m/e 328 (70%, M^+), 315 (60%), 273 (63%), 257 (100%), 229 (32%) and 218 (72%); NMR signals at τ 8.45 (6H,s), 8.32 and 8.15 (each 3H,bs), 7.18 (2H,s), 6.57 (2H, bd, J 7Hz), 4.77 (1H, bt, J 7Hz), 3.90 and 2.13 (each 1H, d, J 10Hz) and -2.30° (1H,s).

Pyrolysis of clausenin dimethylallyl ether (41)

The ether (41) (72mg) was dissolved in N,N-diethylaniline (1ml) and heated at 135° for 1 hr, and for a further 3 hr at 170°, under N_2. The cooled solution was poured into ice-water, extracted with EtOAc, washed with dil. HCl to pH1, brine to neutrality, dried and evaporated. The residual oil was separated by TLC (1 x $CHCl_3$) to give:-

(i) the phenol (43) (49mg, 68%); NMR signals at τ 8.52 (6H,s), 8.33 and 8.18 (each 3H, bs), 7.22 (2H,s),

6.60 (2H, bd, J 7Hz), 4.82 (1H, bd, J 7Hz), 3.87 and 2.02 (each 1H, d, J 10Hz) and -2.65$^{\circledast}$ (1H, s).

(ii) clausenin (15) (17mg, 23%).

Synthesis of the 4-CO_2Me phenols (50) and (51).

Acetylene dicarboxylic acid dimethyl ester (100mg) was added to a mixture of 2,2-dimethyl-5, 7-dihydroxychroman-4-one (50mg) and $ZnCl_2$ (80mg) and the solution heated at 130° for 3 hr.[40] . The cooled solution was extracted with EtOAc, washed with dil. HCl, with brine to neutrality and dried. Evaporation yielded a viscous gum which was separated by TLC (1 x $CHCl_3$ and 1 x 30% EtOAc: light petroleum) to give:-

(i) the linear phenol (50), (15mg✓, 20%), yellow needles, m.p. 205-208° (Dec.), (from EtOAc-light petroleum). (Found: C, 60.4; H,4.55. $C_{16}H_{14}O_7$ requires C, 60.4; H,4.4%); $\nu_{max}^{CHCl_3}$ 1740, 1629, 1562 and 1147 cm^{-1}; λ max 210 (sh), 281 and 325 nm (log ε 4.20, 4.27 and 3.94); λ_{max}^{base} 243 (sh), 283, 311 and 414 (log ε 4.00, 4.02, 4.00 and 4.00); mass spectral peaks at m/e 318 (92%, M^+), 303 (89%), 271 (93%), 231 (100%), 230 (95%), 203 (53%) and 174 (51%); NMR signals at τ 8.48 (6H,s), 7.18 (2H,s), 6.03 (3H,s), 3.90 (1H,s), 3.67 (1H,s) and -4.85° (1H,s).

(ii) the angular phenol (51), (10mg✓, 14%), yellow needles, m.p. 178-180° (from EtOAc-light petroleum). (Found: C, 60.3; H, 4.6. $C_{16}H_{14}O_7$ requires C, 60.4; H, 4.4%); $\nu_{max}^{CHCl_3}$ 1740, 1650, 1622 and 1580 cm^{-1}; λ Max 215, 279 and 320 nm (log ε 4.12, 4.28 and 3.95); λ_{max}^{base} 247, 275, 314, 354 and 400 nm (log ε 4.07, 3.82, 3.98 3.88 and 3.95); mass spectral peaks at m/e 318 (57%. M^+), 303 (86%), 271 (86%), 231 (100%), 203 (78%), 176 (70%), 93 (100%), and 69 (100%); NMR signals at τ 8.50 (6H,s), 7.18 (2H,s), 6.03 (3H,s), 3.93 (1H,s), 3.60 (1H,s) and -2.12° (1H,s).

Methylation of the linear phenol (50)

K_2CO_3 (30mg) was added to a solution of 50 (20mg) in acetone and the mixture stirred at R.T. for ½ hr. MeI (0.5ml) was added and the mixture refluxed for 18 hr. Work-up procedure I afforded an off-white solid which was separated by TLC (1 x 30% EtOAc : light petroleum) to give:-

(i) the linear methyl ether (52), (14mg, 66%), m.p. 182-183° (from EtOAc - light petroleum). (Found: C, 61.5; H, 4.9. $C_{17}H_{16}O_7$ requires C, 61.45 ; H, 4.85%); $\nu_{max}^{CHCl_3}$ 1740, 1691, 1605 and 1150 cm^{-1}; λ max 224, 262, 280, 320 and 335 (sh) nm (log ε 3.60, 4.09, 3.70, 3.85 and 3.78); mass spectral peaks at m/e 332 (46%, M^+), 317 (46%), 314 (92%), 285 (47%), 277 (57%), 276 (97%), 205 (48%), 83 (57%) and 69 (100%); NMR signals at τ 8.50 (6H,s), 7.28 (2H,s), 6.18 (3H,s), 6.08 (3H,s), 3.92 (1H,s) and 3.32 (1H,s).

(ii) the angular methyl ether (53), (6mg, 28%).

Methylation of the angular phenol (51)

K_2CO_3 (20mg) was added to a solution of 51 (20mg) in acetone (50ml) and the mixture stirred at R.T. for ½ hr. MeI (0.5ml) was added and the mixture refluxed for 18 hr. Work-up procedure I afforded a cream coloured solid which was separated by TLC (1 x 30% EtOAc:light petroleum) to give:-

(i) the linear methyl ether (52), (8mg, 38%).

(ii) the angular methyl ether (53), (12mg, 57%), plates, m.p. 209-211° (dec.) (from EtOAc - light petroleum). (Found: C, 61.65; H,5.00. $C_{17}H_{16}O_7$ requires C, 61.45; H, 4.85%); $\nu_{max}^{CHCl_3}$ 1740, 1682 and 1598 cm^{-1}; λ max 218,

235 (sh), 273 and 325 nm (log ε 3.82, 3.51, 4.29 and 4.04); mass spectral peaks at m/e 332 (54%, M^+), 317 (43%), 276 (100%), 245 (62%), 218 (46%), 190 (62%) and 93 (46%); NMR signals at τ 8.55 (6H,s), 7.28 (2H,s), 6.05 (6H,s), 3.90 (1H,s) and 3.55 (1H,s).

Dimethylallylation of the angular phenol (51)

K_2CO_3 (100mg) was added to a solution of 51 (90mg) in acetone (40ml) and the mixture stirred at R.T. for ½hr. Dimethylallyl bromide (0.5ml) was added and the solution refluxed for 17 hr. Work-up procedure I gave the ether (55), (55mg, 53%), needles, m.p. 143-145° (from EtOAc - light petroleum). (Found: M^+ 386 by mass spectrum. $C_{21}H_{22}O_7$ requires M^+ 386); $\nu_{max}^{CHCl_3}$ 1740, 1685 and 1595 cm^{-1}; λ max 273 and 325 nm (log ε 4.15 and 3.94); mass spectral peaks at m/e 386 (6%, M^+), 318 (41%), 313 (62%), 271 (45%), 203 (20%), 93 (23%) and 41 (100%); NMR signals at τ 8.55 and 8.23 (each 6H, s), 7.30 (2H,s), 6.05 (3H,s), 5.30 (2H, bd, J 6Hz), 4.50 (1H, bt, J 6Hz), 3.93 and 3.60 (each 1H,s).

Claisen rearrangement of 55

A solution of 55 (23 mg) in N,N-diethylaniline(0.5ml) was heated at 180° for 3 hr under N_2. The cooled solution was poured into ice-water, extracted with EtOAc, washed with dil. HCl to pH1, brine to neutrality, dried and evaporated. The residual oil was purified by TLC (1 x 25% EtOAc:light petroleum) to give the phenol (57), (14mg, 61%) as a yellow oily solid. (Found: M^+386 by mass spectrum. $C_{21}H_{22}O_7$ requires M^+386); $\nu_{max}^{CHCl_3}$ 1740, 1640, 1618 and 1572 cm^{-1}; λ max 220, 283 and 335 nm (log ε 4.21, 4.33 and 3.97);

mass spectral peaks at m/e 386 (4%, M^+), 371 (3%), 315 (4%), 283 (3%), 69 (26%), 59 (50%), 55 (26%) and 43 (100%); NMR signals at τ 8.53 and 8.37 (each 6H,s), 7.23 (2H,s), 6.07 (3H,s), 5.07 (1H, bd, J 11Hz), 5.03 (1H, bd, J 17Hz), 3.93 (1H,s), 3.70 (1H, d/d, J 11 and 17 Hz) and -3.05* (1H,s).

Base catalysed isomerisation of 53

53 (55mg) was added to a stirred solution of Na (12mg) in EtOH (10ml) and the mixture stirred at R.T. for 4 hr. The solution was diluted with dil. HCl, extracted with EtOAc, washed with brine to neutrality, dried and evaporated. The residue gave the phenol (58) (60mg; 93%), needles, m.p. 128-131° (from EtOAc - light petroleum). (Found: M^+392 by mass spectrum. $C_{20}H_{24}O_8$ requires M^+392); $\nu_{max}^{CHCl_3}$ 1725, 1670, 1600, 1250 and 1103 cm^{-1}; λ max 283 and 320 nm (log ε 3.95 and 3.54); λ_{max}^{base} 248 and 325 (log ε 3.85 and 4.19); mass spectral peaks at m/e 392 (4%, M^+), 379 (23%), 346 (27%), 332 (50%), 317 (38%), 276 (84%), 249 (84%), 245 (92%) and 218 (100%); NMR signals at τ 8.82 (6H, t, J 7Hz), 8.63 (6H,s), 7.40 (2H,s), 6.23 (3H,s), 5.88 (4H, q, J 7Hz), 3.88 (1H,s) and 3.05 (1H,s).

Attempted hydrolysis of the ester (53)

(i) Dil. HCl (10ml) was added to a stirred solution of 53 (20mg) in EtOH (30ml) and the mixture refluxed for 48 hr. TLC showed that no reaction had taken place, and so conc. HCl (2.5ml) was added, and refluxing continued for a further 24 hr. The cooled solution was poured into ice-water, extracted with EtOAc, washed with brine to neutrality and dried. Evaporation yielded unreacted starting material (18mg, 90%).

(ii) When the above reaction was repeated using conc. H_2SO_4, the only compound recovered, was unreacted starting material.

(iii) 53 (20mg) was added to dil. aqueous NaOH (10ml) and the resultant yellow solution stirred at R.T. for 24 hr. The solution was then neutralised with dil. HCl, extracted with EtOAc, washed with brine to neutrality and dried. Evaporation yielded only the unreacted starting ester (53), (15mg, 75%).

(iv) $LiI \cdot 2H_2O$ (60mg) was added to a solution of 53 (35mg) in dimethylformamide (1ml) and the mixture refluxed for 3 hr. The cooled solution was diluted with ice-water, washed with brine to neutrality and dried. Evaporation afforded a semi-crystalline oil which was purified by TLC (1 x 30% EtOAc:light petroleum) to give the angular phenol (51), (20mg, 60%).

Attempted hydrolysis of 51

$LiI \cdot 2H_2O$ (60mg) was added to a solution of the phenol 51 (60mg) in dimethylformamide (5ml) and the mixture refluxed for 16 hr. Similar work-up to that described above yielded a light brown polar oil (55mg)

Synthesis of the 4-methyl phenols (66) and (67)

Freshly ground Amberlite resin IR-120 (H) (64mg) was added to a solution of 2,2-dimethyl-5, 7-dihydroxychroman-4-one (100mg) and ethyl acetoacetate (200mg) and the mixture heated at 170° for 3 hr. The cooled solution was diluted with EtOAc and filtered. Evaporation afforded a yellow solid which was separated by TLC (1 x $CHCl_3$ and 1 x 20% EtOAc:light petroleum) to give:-

(i) the linear phenol (66), (44mg, 34%), yellow plates, m.p. 210-214° (from EtOAc - light petroleum). (Found: C, 65.8; H, 5.3. $C_{15}H_{14}O_5$ requires C, 65.7; 5.15%); $\nu_{max}^{CHCl_3}$ 1730, 1630, 1561 and 1150 cm^{-1}; λ max 218, 233 (sh), 281 and 318 nm (log ε 4.08, 3.77, 4.42 and 4.01); mass spectral peaks at m/e 274 (43%, M^+), 259 (100%), 231 (28%), 219 (43%), 190 (67%) and 134 (32%); NMR signals at τ 8.50 (6H,s), 7.38 (3H, d, J 1Hz), 3.68 (1H,s) and -3.48* (1H,s),4.05 (1H, m).

(ii) the angular phenol (67), (35mg, 27%), yellow needles, m.p. 170-173° (from EtOAc - light petroleum). (Found: C, 65.45; H, 5.2. $C_{15}H_{14}O_5$ requires C, 65.7; H, 5.15%); $\nu_{max}^{CHCl_3}$ 1735, 1649, 1625, 1581 and 1155 cm^{-1}; λ max 233, 278 and 318 nm (log ε 3.78, 4.42 and 4.00); mass spectral peaks at m/e 274 (59%, M^+), 259 (100%), 219 (42%) and 190 (47%); NMR signals at τ 8.33 (6H,s), 7.43 (3H, d, J 1Hz), 7.17 (2H,s), 4.05 (1H, m, J 1Hz), 3.62 (1H,s) and -2.30* (1H,s).

Methylation of the linear phenol (66)

K_2CO_3 (20mg) was added to a solution of 66 (18mg) in acetone (20ml) and the mixture stirred at R.T. for $\frac{1}{2}$hr. MeI (1ml)

was added and the mixture refluxed for 18 hr. Work-up procedure I gave the ether (68), (16mg, 93%), prisms, m.p. 142-144° (from EtOAc - light petroleum). (Found: C, 66.8; H, 5.65; $C_{16}H_{16}O_5$ requires C, 66.65; H, 5.6%); $\nu_{max}^{CHCl_3}$ 1730, 1688, 1610, 1595 and 1153 cm^{-1}; λ max 220, 262, 277 (sh), 310 and 332 (sh) (log ε 3.54, 4.24, 4.00, 3.89 and 3.80); mass spectral peaks at m/e 288 (98%, M^+), 273 (65%), 233 (86%), 232 (100%), 204 (82%) and 190 (82%); NMR signals at τ 8.50 (6H,s), 7.40 (3H, d, J 1Hz), 6.10 (3H,s), 3.97 (1H,m) and 3.37 (1H,s).

Methylation of the angular phenol (67)

K_2CO_3 (30mg) was added to a solution of 67 (20mg) in acetone and the mixture stirred for ½ hr. MeI (1ml) was added and the mixture refluxed for 18 hr. Work-up procedure I gave the ether (69), (18mg, 85%), needles, m.p. 222-223° (from EtOAc - light petroleum). (Found C, 66.8; H, 5.5. $C_{16}H_{16}O_5$ requires C, 66.65; H, 5.6%;) $\nu_{max}^{CHCl_3}$ 1733, 1680, 1609 and 1592 cm^{-1}; λ max 215, 235 (sh), 273 and 316 nm (log ε 4.02, 3.53, 4.47 and 4.13); mass spectral peaks at m/e 288 (43%, M^+), 273 (35%), 233 (33%) and 204 (100%); NMR signals at τ 8.47 (6H,s), 7.45 (3H, bs), 7.30 (2H,s), 6.07 (3H,s), 4.02 (1H,m) and 3.58 (1H,s).

Dimethylallylation of the angular phenol (67)

K_2CO_3 (60mg) was added to a solution of 67 (35mg) in acetone and the mixture stirred at R.T. for ½ hr. Freshly distilled dimethylallyl bromide (0.5ml) was added and the mixture refluxed for 18 hr. Work-up procedure I yielded a yellow oil which was purified by TLC (1 x 20% EtOAc : light

petroleum) to give the ether (71), (20mg; 47%), needles, m.p. 138-140° (from EtOAc - light petroleum). (Found: M^+342 by mass spectrum. $C_{20}H_{22}O_5$ requires M^+342); $\nu_{max}^{CHCl_4}$ 1746, 1650 and 1590 cm^{-1}; λ max 273 and 318 nm (log ε 4.12 and 3.89); mass spectral peaks at m/e 342 (2%, M^+), 327 (2%), 279 (6%), 265 (9%), 167 (18%), 149 (100%), 57 (41%), 55 (26%) and 43 (38%); NMR signals at τ 8.47 (6H,s), 8.22 (6H,bs), 7.43 (3H, d, J 1Hz), 7.28 (2H,s), 5.33 (2H, d, J 6Hz), 4.50 (1H,bt, J 6Hz), 4.05 (1H,m) and 3.62 (1H,s).

Claisen rearrangement of the ether (71)

A solution of 71 (45mg) in N,N-diethylaniline (0.6ml) was heated at 170° for 3 hr under N_2. The cooled solution was poured into ice-water, extracted with EtOAc, washed with dil. HCl to pH1, brine to neutrality, dried and evaporated. The residual oil was purified by TLC (1 x 20% EtOAc:light petroleum) to give the phenol 73 (29mg, 24%) as an oily semi-crystalline solid. (Found: M^+342 by mass spectrum. $C_{20}H_{22}O_5$ requires M^+342). $\nu_{max}^{CHCl_3}$ 1735, 1638, 1618 and 1565 cm^{-1}; λ max 283 and 321 nm (log ε 4.27 and 3.79); mass spectral peaks at m/e 342 (24%, M^+), 327 (29%), 271 (41%), 258 (21%), 243 (24%) and 41 (100%); NMR signals at τ 8.45 and 8.33 (each 6H,s), 7.45 (3H, d, J 1Hz), 5.12 (1H, bd, J 12Hz), 5.07 (1H, bd, J 18Hz), 4.08 (1H, m, J 1Hz), 3.68 (1H, d/d, J 12 and 18 Hz) and ~3.28 (1H,s).

Attempted base catalysed isomerisation of 69.

The ether (69) (100mg) was added to a solution of NaOEt [made from Na (20mg) in EtOH (25ml)] and the mixture stirred at R.T. for 3 hr and at 40° for 3 hr. After acidification

with dil. HCl, unreacted starting material was recovered (95mg, 95%). Similar results were obtained when NaH was used as the base catalyst.

Attempted Oxidation of the Coumarin (69)

(a) Freshly sublimed SeO_2 (50mg) was added to a solution of 69 (25mg) in EtOAc (25ml) and the mixture refluxed for 3hr. The cooled mixture was then filtered through celite, washed with brine, dried and evaporated. TLC of the crystalline residue (20mg) showed that no reaction had taken place and that the residue was unreacted starting material.

(b) This reaction was repeated using 20% aqueous dioxan as solvent, but once again no reaction was found to take place.

(c) When chromyl chloride in CCl_4 was used as the oxidising medium, similar negative results were obtained.

7-Hydroxycoumarin (75) (umbelliferone)

Umblliferone was prepared by the method of Dey, Rao and Seshadri [52] using resorcinol, malic acid and conc. sulphuric acid. The crude product was crystallised from methanol to give umbelliferone as pale yellow needles, m.p. 228-229° (lit.[52] m.p. 223-224°).

Umbelliferone senecioate (74)

Senecioyl chloride (400mg) was added to a solution of umbelliferone (300mg) in ethanol-free $CHCl_3$, and the mixture refluxed for 3hr. The solution was then poured into ice-water, extracted with $CHCl_3$, washed with brine to neutrality and dried. The white solid residue obtained after evaporation was crystallised from EtOAc-light petroleum to give the ester (74), (420mg, 87%) as colourless needles, m.p.118-120°. (Found: M^+244; $C_{14}H_{12}O_4$ requires M^+244); $\nu_{max}^{CCl_4}$ 1750 and 1118 cm^{-1}; λ max 280 and 312 nm (log ε 3·49 and 3·48); mass spectral peaks at m/e 244 (3%, M^+), 162 (2%), 134 (2%), 83(100%) and 55 (26%); NMR signals at τ 7·97 and 7·73 (each 3H, d, J 1Hz) 4·10 (1H, m, J 1Hz), 3·65 and 2·32 (each 1H, d, J 10Hz), 2·95 and 2·67 (each 1H, bd, J 8Hz) and 2·88 (1H, bs).

Attempted Fries rearrangement of umbelliferone senecioate

(a) A solution of the ester (74) (50mg) in CH_2Cl_2 (20ml) was added dropwise to a suspension of freshly sublimed $AlCl_3$ (20mg) in CH_2Cl_2 (20ml) at 0°. The mixture was then stirred at room temperature until TLC showed the absence of any starting material. The mixture was then poured into ice-water and extracted with CH_2CL_2 . After washing with brine to neutrality, drying and evaporating, the brown solid residue was purified by TLC, and the only product obtained was umbelliferone (15mg; 45%).

(b) The ester(50mg) and freshly sublimed $AlCl_3$ (10mg) were heated at 120° for four minutes in a sublimation tube. After the liberation of all HCl gas had ceased, the mixture was washed with EtOAc and these washings

further washed with brine to neutrality, dried and evaporated. Purification of the residue by TLC ($CHCl_3$) yielded only umbelliferone (20mg; 53%).

(c) The ester (74), (100mg) was added to a stirred mixture of $AlCl_3$ in tetrachloro-ethane, and the solution heated at 100° for 4hr. The cooled solution was poured into ice-water, extracted with EtOAc, washed with brine to neutrality and evaporated. The residual solvent was then removed by steam distillation, and the solid residue purified by TLC. The only material isolated was unreacted starting material (80mg; 80%). Similar reactions using CS_2 and nitro-benzene as solvents gave identical results.

(d) The ester (74) (400mg) was stirred in refluxing CF_3COOH (100ml) for 24hr. The solution was then poured into ice-water and the precipitate collected. This was found by comparison to be umbelliferone (200mg).

Attempted acylation of umbelliferone.

(a) Umbelliferone (200mg), $ZnCl_2$ and senecioic acid (124mg) were heated at 160° for 1hr. The mixture was extracted with EtOAc, washed with dil. HCl, brine to neutrality, dried and evaporated. TLC showed that the residue contained only umbelliferone and senecioic acid.

(b) Umbelliferone (50mg), trichloro-acetic acid (100mg) and senecioic acid (100mg) were heated together at 180° for 1½hr. The viscous residue was extracted with EtOAc, washed with dil. $NaHCO_3$, brine to neutrality, dried and evaporated. Purification of the resultant solid by TLC ($CHCl_3$) gave umbelliferone (20mg; 40%) and the senecioate ester (74), (20mg; 25%).

Acylation of 5,7-dihydroxycoumarin with senecioic acid.

5,7-Dihydroxycoumarin (50mg), trichloro-acetic acid (100mg) and senecioic acid (50mg) were heated together at 180° for 1½hr. The viscous residue was then extracted with EtOAc, washed with dil. $NaHCO_3$, brine to neutrality, dried and evaporated. The resultant oil was purified by TLC ($CHCl_3$) to give a mixture (15mg) of clausenin (15) and its angular isomer (8).