Synthetic and Structural Studies on Natural Coumarins.

THESIS

presented to the University of Glasgow,

for the degree of Doctor of Philosophy.

by

Michael Sutcliffe

1973

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

Acknowledgments

To someone not conversant with the day-to-day atmosphere and work of an Organic Research Laboratory, the successful completion of a Ph.d thesis represents simply three years labour on behalf of its author. Nothing could be further from the truth. The very essence of successful research in Organic Chemistry lies in discussion with one's neighbours, and also in seeking the help and advice of one's superiors. In Glasgow, neither of these things is lacking. In particular I should like to thank my supervisor, Dr.R.D.H.Murray for his guidance, advice and unstinting help over the last three years. His enthusiasm for the subject was the source of much inspiration during my low periods. Outwith the realms of Chemistry his friendship, good humour and ready willingness to listen to any problems will be with me long after the content of this thesis is forgotten. I should also like to thank Dr.P.H.McCabe for much helpful discussion and advice in both the theoretical and practical aspects of the subject.

I owe the greatest debt of all to two people totally unconnected with the Chemistry Department. The first is my wife, Alison, who has suffered uncomplainingly for the whole three years and has helped me more than she knows; the second is my late Grandfather, without whose

help and encouragement I would never have taken the road to University. I shall be forever grateful to them both.

Technical assistance was freely rendered by Mrs.F.Lawrie and her staff; Mr.J.M.L.Cameron, Miss F.Cowan and their staffs; Mr.A.Ritchie and Miss M. Laing; and Mr.A.Haetzman and Mr.J.Gall. Their help is gratefully acknowledged.

Samples were kindly provided by: Dr.T.J.King, Nottingham; Professor M.Nakajima, Kyoto; Professor B.S.Joshi, Bombay and Professor M.Hasegawa, Tokyo.

I should also like to thank the Science Research Council for a maintenance award.

September, 1973.

Summary.

In the first part of the thesis, synthetic approaches to a number of natural coumarins are described. Oxidative cyclisation reactions of the prenylated phenolic coumarins osthenol and 7-demethylsuberosin are discussed. It has been found that, by varying the reaction conditions, cyclisation can be specifically directed to give either furanocoumarins or pyranocoumarins. In particular, the natural coumarins (±)-marmesin, (±)-columbianetin, (±)-decursinol and (±)-lomatin have each been synthesised in high yield.

The regioselective dehydration of (±)-columbianetin to give the naturally occurring isopropenyldihydrofuranocoumarin, masquin, has been investigated. Conditions for the regioselective dehydration of the linear hydroxyisopropyldihydrofuranocoumarin, (±)-marmesin, to the previously unknown isopropenyldihydrofuranocoumarin have been determined. The corresponding reaction with the angular hydroxyisopropyldihydrofuranocoumarin, (±)-columbianetin, has given synthetic (±)-masquin, which could not be separated from the isomeric isopropylfurocoumarin.

Selenium dioxide oxidation of osthenol acetate has been shown to result in exclusive oxidation of the allylic methyl group.

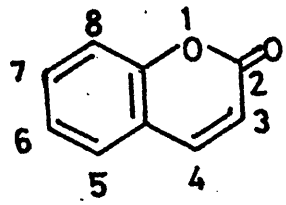
In the second section of the thesis, chemical evidence is presented which unequivocally establishes the structure of tomentin, the major aglycone of the wood of Prunus tomentosa, as 5-hydroxy-6,7-dimethoxycoumarin. Attempts were made to introduce a 1,1-dimethylallyl group at C-8 of

tomentin with a view to obtaining a direct correlation with nieshoutol, the sternutatory constituent of Ptaeroxylon obliquum. The key synthetic precursor, O-1,1-dimethylallyltomentin, was found to undergo a novel charge-induced ortho-Claisen rearrangement, at R.T., specifically to C-6. This blocked ortho-dienone failed to undergo a para-Claisen rearrangemsnt on heating, while on reduction followed by aromatisation, 6,7-dimethoxycoumarin was obtained.

The complex mixture resulting from 1,1-dimethylpropargylation of tomentin has been separated and structures assigned to all of the principle components. The structures of two novel, isomeric, blocked ortho-dienones, each containing an α-3.3-dimethylallenyl group, have been rigorously secured on the basis of spectroscopic evidence and the reduction and aromatisation of one of them to the known natural coumarin, alloxanthoxyletin.

Synthetic and Structural Studies on Natural Coumarins

Introduction to Part 1, Including a Short Review of the Biogenesis of Furocoumarins.



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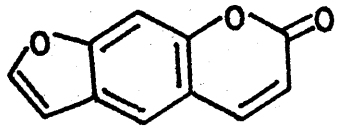

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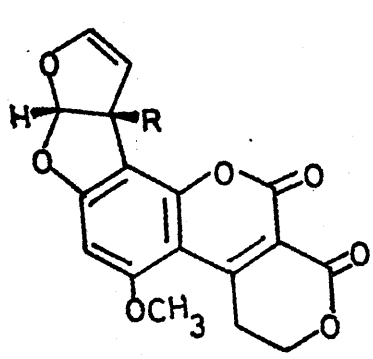
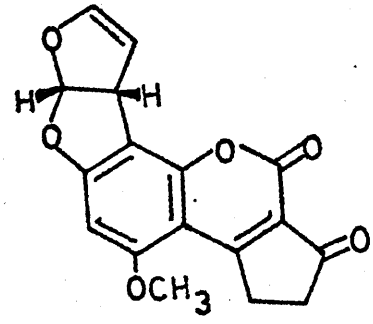


R = H ; G_1

R = OH ; M_1

(3)

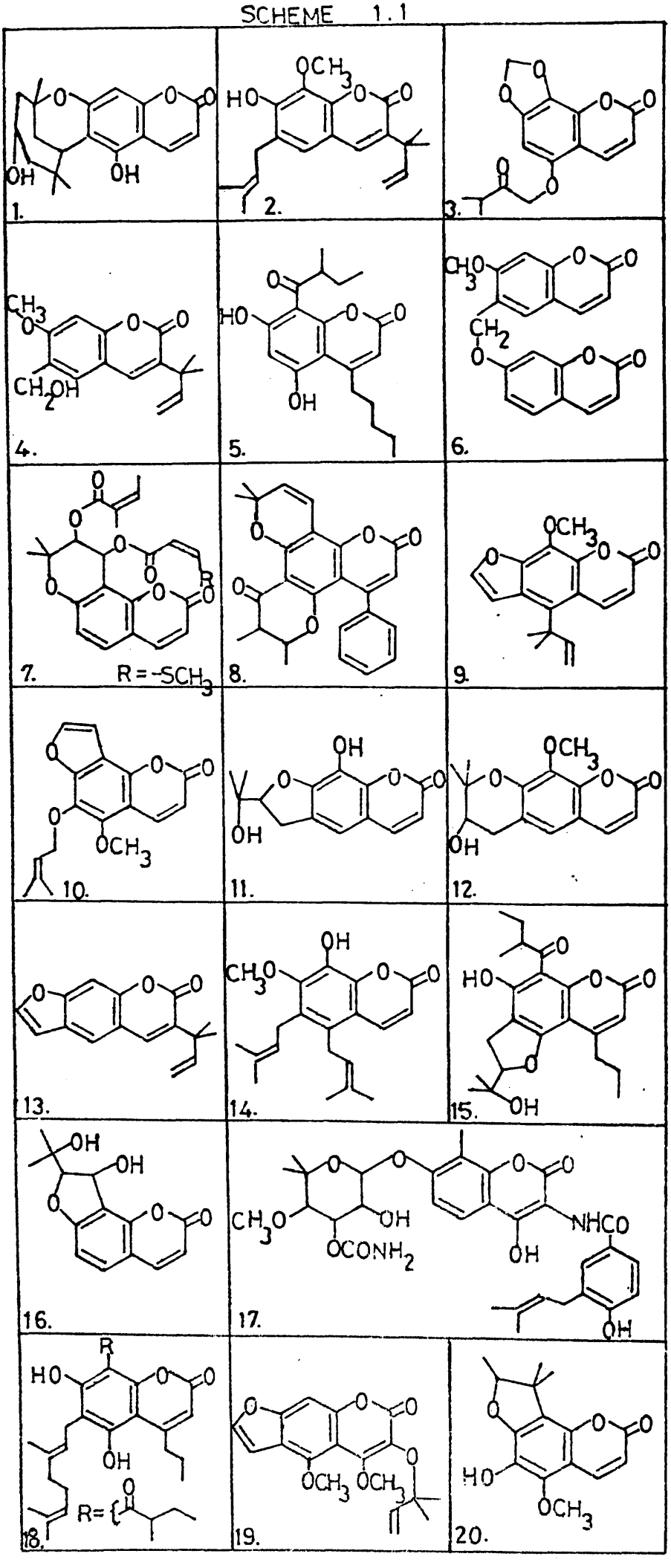


B_1

The well-established position of the coumarins as natural products has its origin in 1820, when the simplest member, coumarin(1)[1,2] was isolated by Vogel from Coumarouna odorata Willd.(Tonka beans). Since then its derivatives have been found to be widely distributed[3-5] throughout the plant kingdom as well as being present in some animals[6] and micro-organisms[7]. In 1963, Dean reported[5] that about ninety naturally occurring coumarins were known. By 1970[8] more than twice this number had been isolated, with a current approximate estimate being over three hundred. These large increases represent advances in isolation and separation techniques[3,4,9] and in physical methods for structure determination. Thus, recently, the seeds alone of Mammea americana L. have been shown[10] to contain at least twenty-eight new coumarins.

Much interest has centred on the diversity of physiological effect[3,4] which natural coumarins can exhibit; these range from the contraceptive activity of psoralen(2)[11] and the well-established[4] skin sensitising properties of some furocoumarins, through anticoagulant[4] and vasodilatory[4] activity, to behavior as antitumour[12] agents. The aflatoxins(3), on the other hand, are exceedingly toxic[13]. Whereas the synthesis of the aflatoxins has been the subject of some elegant work by Buchi[14], the synthesis of many natural coumarins still remains the province of the enzyme. To illustrate the problems facing the synthetic chemist, the structures of a few coumarins, chosen at random from the literature and as yet unsynthesised, are givenin Scheme 1.1.

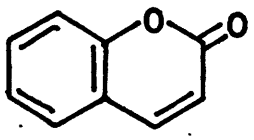
SCHEME 1.1



Index to Scheme 1.1

The numbering system refers only to Scheme 1.1 and not to that of the text.

Trivial Name	Reference	Trivial Name	Reference
1.Hydroxyeriobrucinol	15	11.Rutaretin	25
2.8-Methoxygravelliferone	16	12.Arnottianin	26
3.Sabandinone	17	13.Chalepensin	27
4.Pinnaterin	18	14.Brosiprenin	28
5. -	19	15. -	29
6.Lasiocephalin	20	16.Vaginidiol	30
7.Phloroseselin	21	17.Novobiocin	31
8.Tomentolide A	22	18.Surangin A	32
9.Benahorin	23	19.Halfordinin	33
10. -	24	20.Nieshoutol	34



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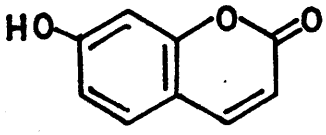

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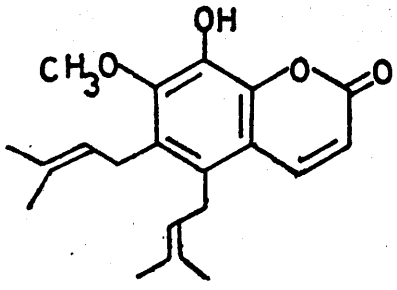


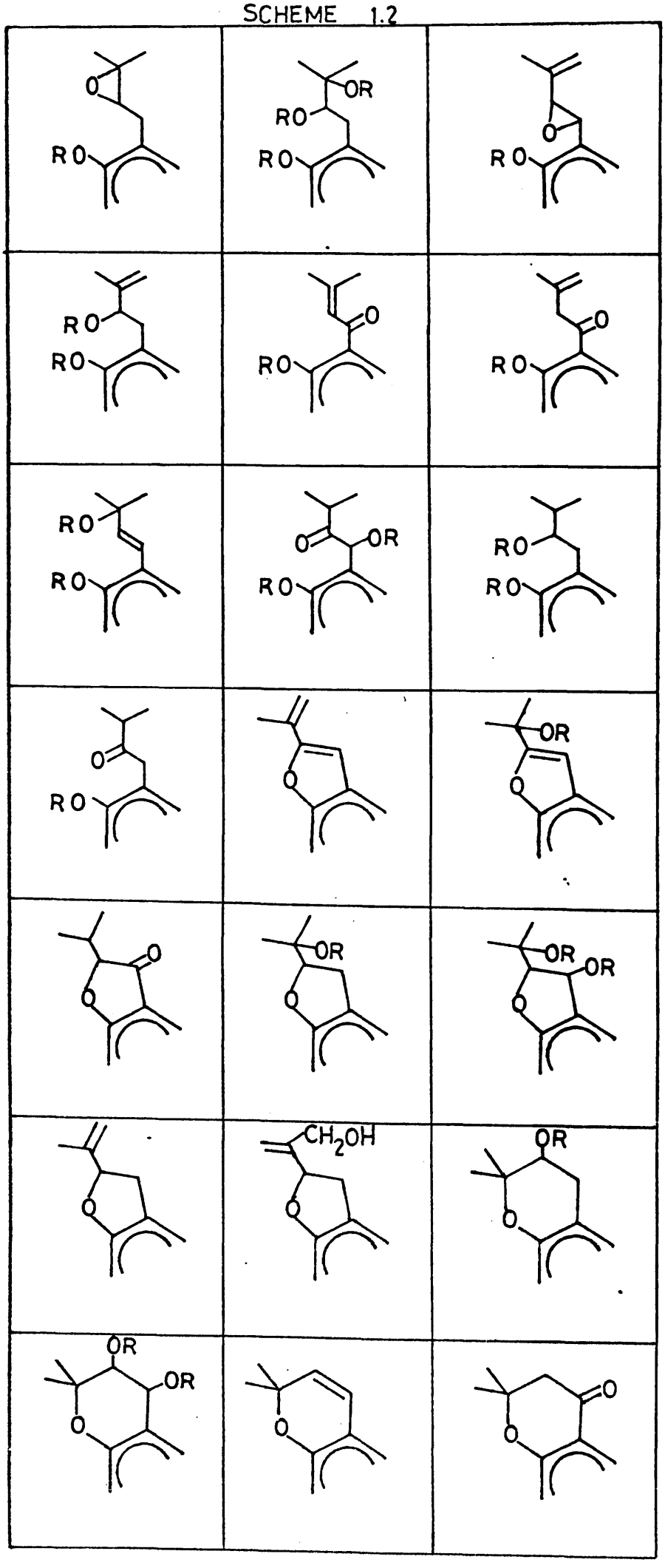
(5)

Examination of the basic coumarin nucleus (1) reveals that there are six possible sites at which oxygenation can occur, all of which are represented in nature. These oxygen functions can be present as phenols or ethers, as can be seen from Scheme 1.1, or as glycosidic ethers, or esters. The presence of one or more isoprenoid chains of variable length, attached to either carbon or oxygen, or to both, is also common feature. These isoprene units are often further elaborated by oxygenation and cyclisation, as shown in Scheme 1.2, imparting an apparently endless variety to natural coumarins.

The most common subdivision in coumarins is based on the oxygenation pattern of the nucleus, those having an oxygen atom at C-7 being by far the most numerous. For this reason, umbelliferone (4) is best regarded as the parent natural compound, rather than the structurally more basic coumarin (1).

Almost all known coumarins carrying an isoprene unit on nuclear carbon have this moiety ortho to an oxygen function[3-5]. This probably reflects the biosynthetic pathway leading to the prenylated coumarins, it being thought that [35-37] the C-5 unit is inserted directly by C-alkylation of a phenolic precursor, with dimethylallyl pyrophosphate as a likely candidate for this purpose. At least one exception, that of brosiprenin (5)[28], is known, in which the C-5 prenyl group may well arise by a biogenetic para-Claisen rearrangement.

SCHEME 1.2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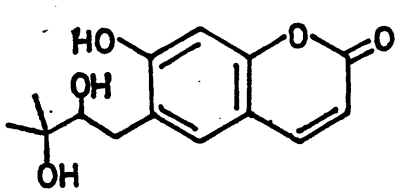

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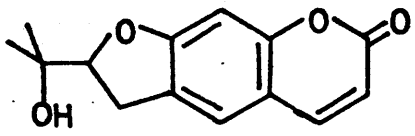

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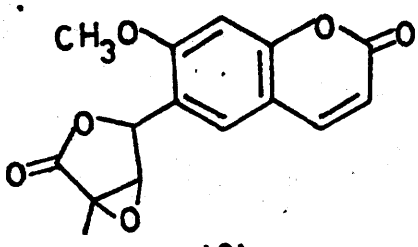
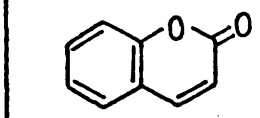


(8)

Progressive enzymatic elaboration of the 3,3-dimethylallyl unit is the probable[37] process by which compounds like peucedanol(6) marmesin (7) and more complex systems exemplified by micromelumin (8) are generated. This theory is supported by the co-occurrence in some plants of structurally related coumarins. A good sample is provided by Ruta pinnata , investigated[38] by Gonzalez et al. Scheme 1.3 illustrates some of the coumarins found in this plant.

The common occurrence of the isopentenyl unit and its oxygenated forms in many classes of compound has prompted various workers to search for general synthetic routes to ortho-prenylated phenols. Direct C-alkylation can be satisfactory in some cases[39,40], but generally fails with phenols containing a preformed coumarin nucleus. For this reason, Murray and Ballantyne developed the Claisen rearrangement[41] as a method to introduce this unit ortho to an existing phenolic hydroxyl grouping (vide infra). This section of the thesis deals with an extension of this work in which the newly formed-prenylated phenols were further elaborated by oxidative cyclisation and dehydration reactions. The possibility of further extension to give some of the partial structures illustrated in Scheme 1.2 was also considered.

SCHEME 1.3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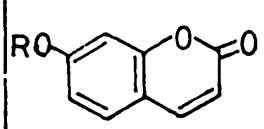
a : R = H
b : R = CH_3
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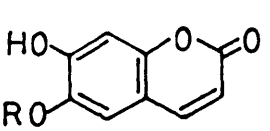
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b : R = CH_3
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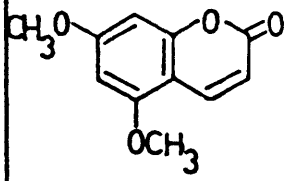
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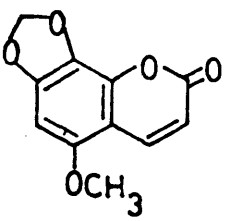
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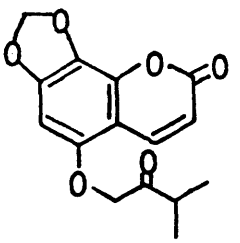
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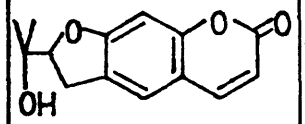
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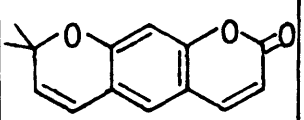
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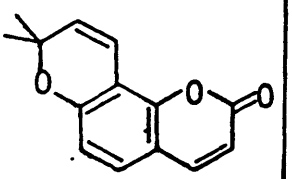
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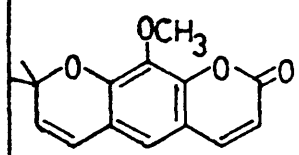
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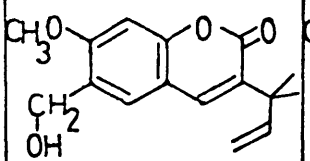
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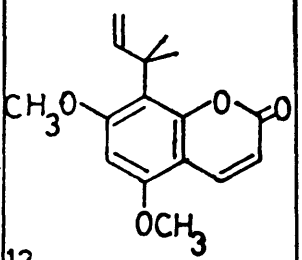
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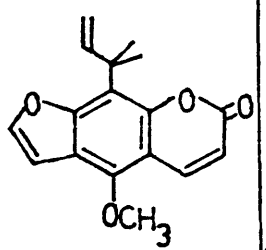
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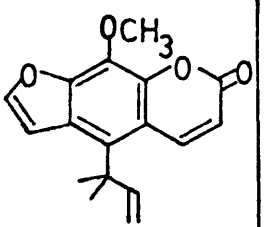
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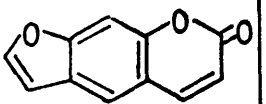
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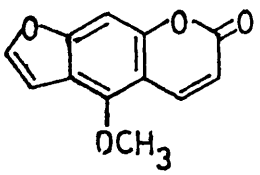
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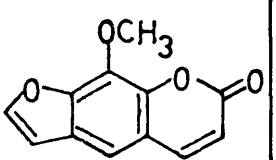
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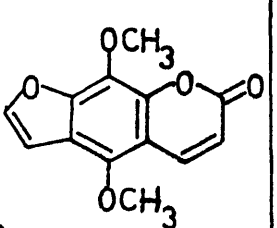
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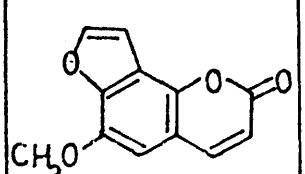
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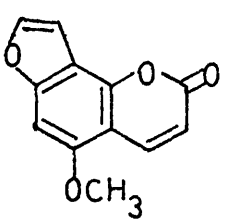
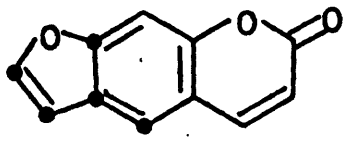

20.

Index to Scheme 1.3

The numbering system refers only to Scheme 1.3 and not to that of the text.

Trivial Name	Reference	Trivial Name	Reference
1. Coumarin	38	10. Luvangetin	38
2a. Umbelliferone	38	11. Pinnaterin	18
2b. Herniarin	38	12. Pinnarin	38
3a. Aesculetin	38	13. Furopinnarin	38
3b. Scopoletin	38	14. Benahorin	42
4. Limettin	42	15. Psoralen	38
5. Sabandinin	42	16. Bergapten	38
6. Sabandinone	17	17. Xanthotoxin	38
7. Marmesin	38	18. Isopimpinellin	38
8. Xanthyletin	38	19. Sphondin	38
9. Seselin	38	20. Isobergapten	38



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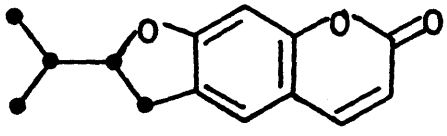

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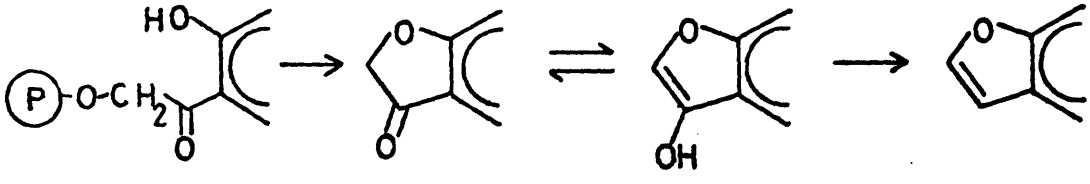

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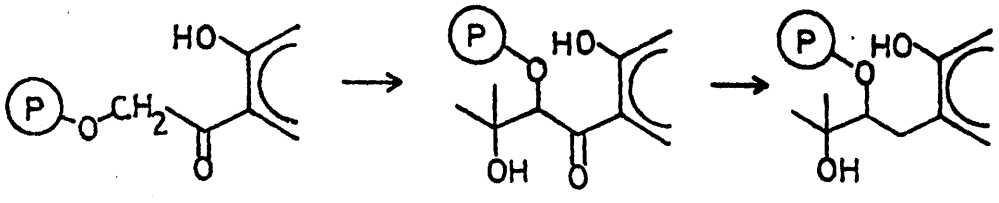
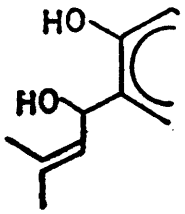


As will become clear later, it is relevant at this juncture to consider the biogenetic origin of another sub-division of natural coumarins, namely the furocoumarins.

The biosynthesis of benzofurans and specifically the furocoumarins has long been the subject of speculation and strenuous investigation. As long ago as 1937, Spath suggested in a review[43] that all the carbon atoms of the furan ring were derived from an isopentane unit as illustrated in(9), Howarth, on the other hand, envisaged[44] that the furocoumarins were theoretically derivable by elimination of propane from 2'-isopropyldihydrofurans, as in (10). It was considered that these could arise by cyclisation of ortho-isoprenylphenols.

Geissman and Hinreiner proposed[45] in 1952 that unsubstituted furan rings could be formed from a two-carbon phosphorylated keto-alcohol precurser(Scheme 1.4). The authors did not comment, however, on the means of attachment of this moiety to the aromatic ring. They did point out, though, that it might also be condensed with acetone, providing a system with potential for developing into many of the common modifications of an isopentenyl group (Scheme 1.5). This theory was extended to include hydrolysis of the phosphorylated hydroxyl group and subsequent cyclisation of the resultant glycol with an adjacent phenolic hydroxyl to account for the formation of hydroxyisopropyldihydrofurans and α,α-dimethylpyran moieties. The possible cleavage of the former as a route to unsubstituted furans was



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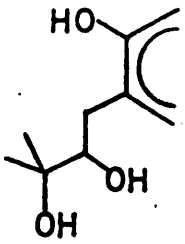

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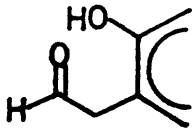

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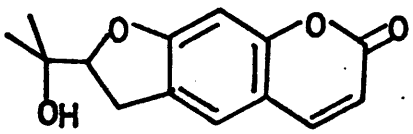

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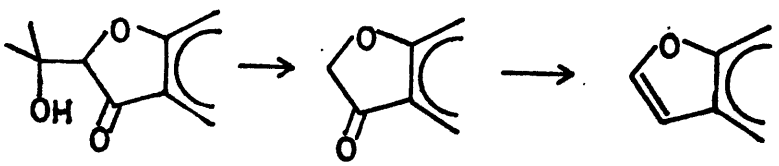

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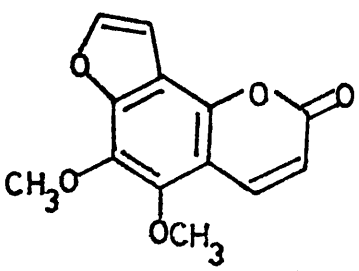

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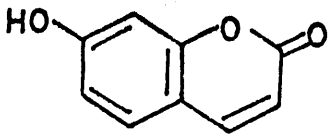


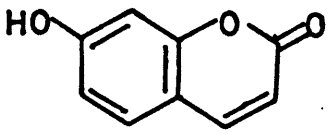
(4)

not considered.

Six years later two suggestions were put forward independently; both in favour of a C-5 unit as the starting point. The first[46], by Seshadri, required removal of a three-carbon fragment prior to formation of the five-membered ring. Starting with an allylic alcohol of type(11), reduction of which would lead to the ortho-isoprenylphenol, he proposed that transformation of the latter into a glycol (12), possibly via an epoxide intermediate, followed by oxidative cleavage to an aldehyde (13), cyclisation, and dehydration would lead to the benzofurans. It is interesting to note that in this paper Seshadri also commented upon the hydroxyisopropyldihydrofuran (7) as arising by interaction of an ortho-phenolic hydroxyl group with an oxygenated C-5 unit; however, like Geissman and Hinreiner[45] he did not consider the possibility that the furocoumarins could be derived by its further elaboration.

The second proposal[47], by Birch and Smith, differed from that of Seshadri in that loss of the three carbon fragment was considered to occur after cyclisation, the ketone (14) being a key compound (Scheme 1.6).

Floss and Mothes[35] provided the first real evidence for the origin of the two carbon atoms of the furan ring in furocoumarins. Feeding experiments with Pimpinella magna established mevalonic acid as the source of these atoms in pimpinellin(15). They had earlier shown[48] umbelliferone(4) to be the precurser of the furocoumarins in this plant. It was thought[35] that the furan ring was likely to be formed by prenylation of a precurser, followed by



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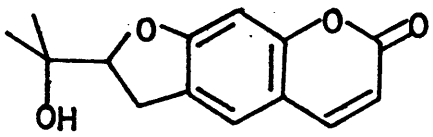

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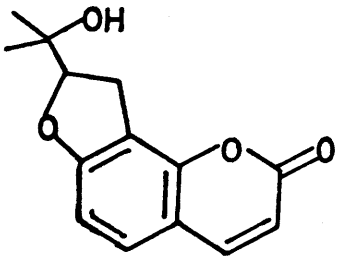

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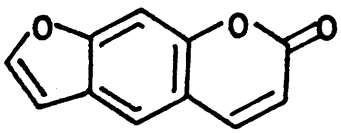

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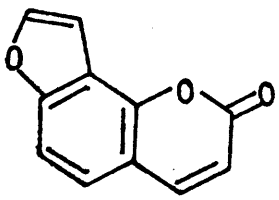

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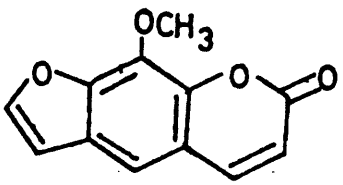

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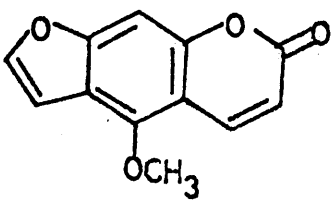


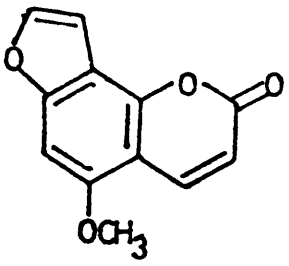
(17)

cyclisation and loss of a three-carbon unit. Oxygenation of the umbelliferone nucleus (4) was postulated to occur before these steps took place, this reasoning being based on a comparison of the specific activities of the various furanocoumarins isolated.

In a third paper[49], Floss and Paikert investigated the sequence of possible intermediates in going from umbelliferone (4) to furocoumarins in Pimpinella magna. In contrast to the earlier suggestion [35](vide supra) their results strongly indicated that the alternative pathway, that of initial prenylation of umbelliferone(4) with subsequent nuclear oxygenation, was more likely.

The work of Floss leaves little doubt that mevalonate can be incorporated into furocoumarins; although recent papers[37,50] have cast doubt on the generality of this statement. Poor incorporations of this metabolite are to be expected, however, owing to the large number of metabolic pathways available to this material compared with some of the more advanced intermediates in furocoumarin biosynthesis.

In 1969 Steck, Dakhakhny and Brown were able to show[51] that labelled umbelliferone (4), when fed to the shoots of Ruta graveolens (as the free phenol) and to Heracleum lanatum (as the glucoside), was incorporated into the dihydrofuranocoumarins marmesin (7) and columbianetin (16), respectively. In addition, feeding of tritiated marmesin (7) and columbianetin (16) strongly indicated their incorporation into the furanocoumarins psoralen (2), bergapten (17), xanthotoxin (18), angelicin(19),



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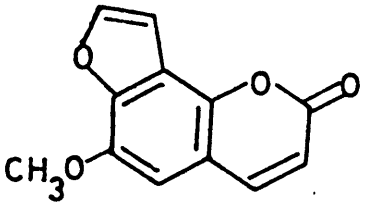

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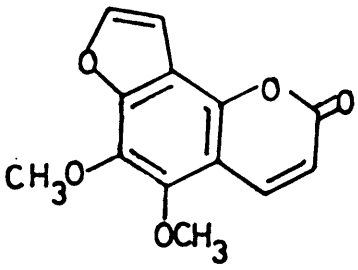

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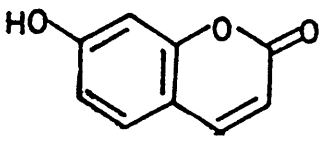
SCHEME 1.7



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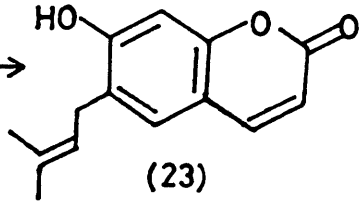

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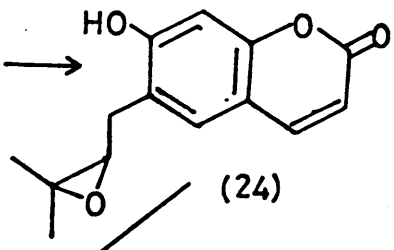

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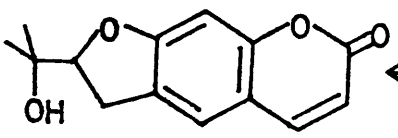

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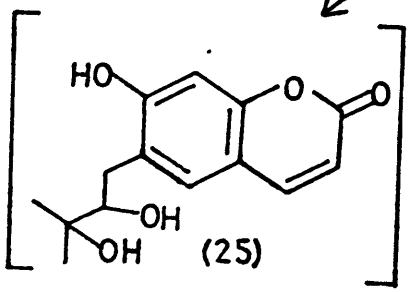

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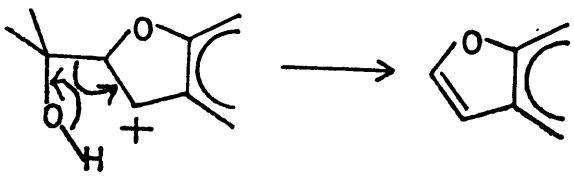

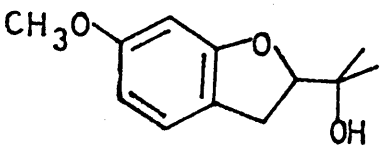

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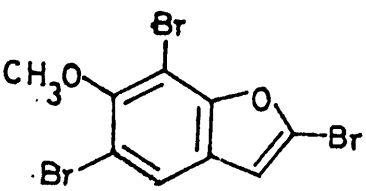

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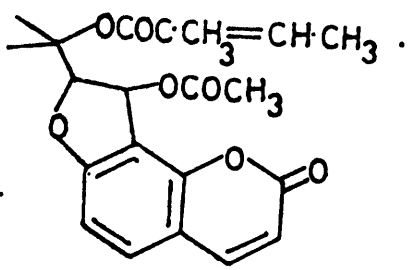

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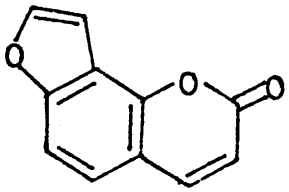

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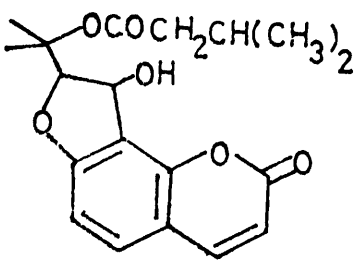

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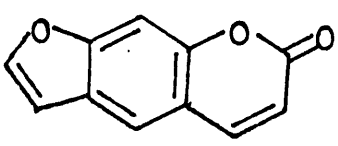
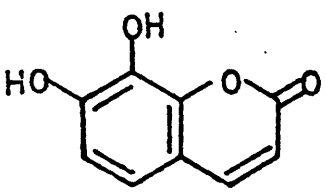


(2)

isobergapten(20), sphondin (21) and pimpinellin (22). This led Steck to propose Scheme 1.7 as the route from umbelliferone (4) to marmesin (7) with an analogous scheme for the biosynthesis of columbianetin (16).

Earlier that same year, Birch and his co-workers had published a paper[52] in which they elaborated on their earlier suggestions [47] with regard to the benzofurans. They pointed out that cleavage of a hydroxyisopropyldihydrofuran with concomitant loss of acetone (Scheme 1.8) required only a carbonium ion in the benzylic position, however generated. An indirect proof of the feasibility of this process was provided by their isolation of the brominated furan (27) in 55% yield from reaction of (26) with excess of N-bromosuccinimide. Other chemical evidence for this type of process was also accumulating by this time. Birch himself cited[52] the example of libanotin [53] (28) which, on treatment with methanolic sodium hydroxide, readily gave angelicin(19). A similar observation [54]was made by Seshadri who found that treatment of vaginidin (29) with alkali again furnished angelicin. (Structure (29) for vaginidin was later revised[30] to the alternative, having the isovaleryl grouping onthe benzylic hydroxyl).

More recently, Steck has published two papers [55,56] on the biosynthesis of furocoumarins of both the linearly and angularly fused varieties. In the first of these[55], the authors established unambiguously that the sequence: umbelliferone (4)⟶marmesin (7)⟶psoralen (2)→higher oxygenated coumarins operated in Ammi majus ,



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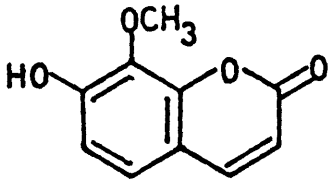

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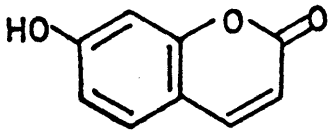

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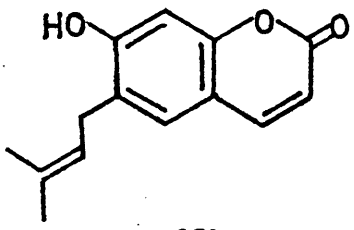

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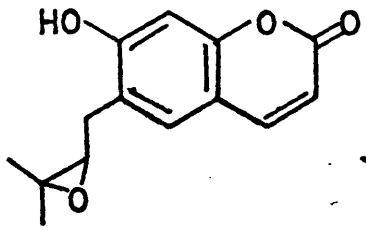

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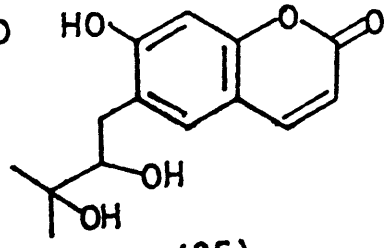

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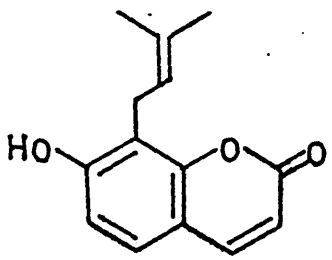

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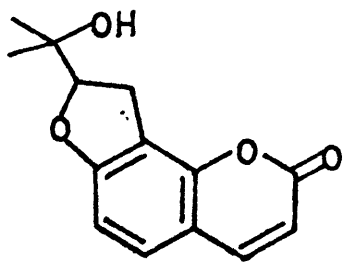

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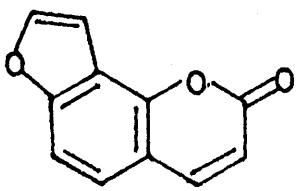

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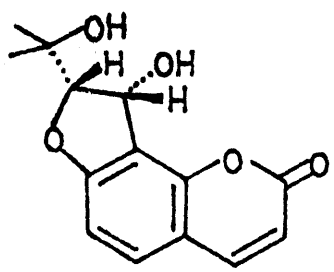
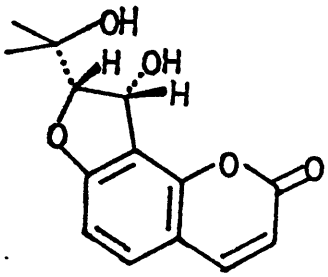


(33)

Angelica archangelica, Heracleum lanatum (Umbelliferae) and in Ruta graveolens (Rutaceae). Unfortunately, however, none of the biogenetic linking compounds was found in the plants. The fact that oxygenated umbelliferones, for example daphnetin (30) and its monomethyl ether (31), were poor precursors of furocoumarins led the authors to believe that prenylation at position 6 and not further oxygenation was the first step from umbelliferone (4) to linear furanocoumarins, thus strengthening the earlier proposal [51] of the possible intermediacy of 7- demethylsuberosin (23), the epoxyphenol (24), and the glycol (25). The natural occurrence of coumarins bearing the side chains of (23), (24) and (25) was used as the basis for this argument.

The second paper by Steck [56] resulted in a precisely analogous route being proposed for the biogenesis of the angular furocoumarins. Of the two possible intermediates between osthenol (32) and columbianetin (16), the authors favoured the 1,2 diol as this was a common structural feature in natural coumarins, frequently found with the related epoxide. In considering the pathway from columbianetin (16) to angelicin (19), the authors postulated the diol (33) as a probable intermediate. Although unknown at the time, its esters (thought to have the stereochemistry of (33)) were constituents of some umbelliferous plants[56] and (33)



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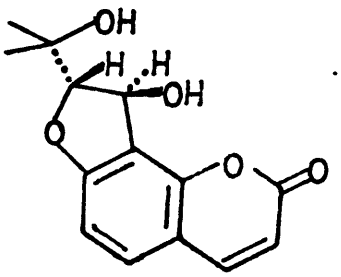

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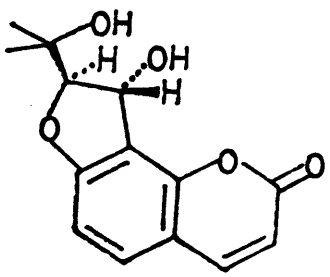

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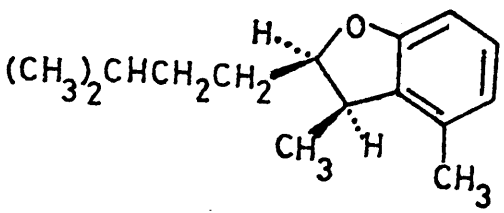

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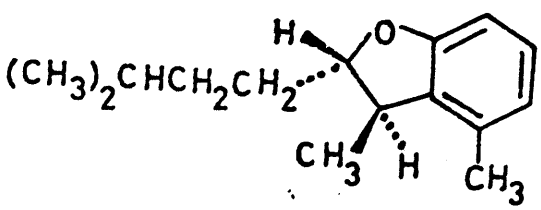

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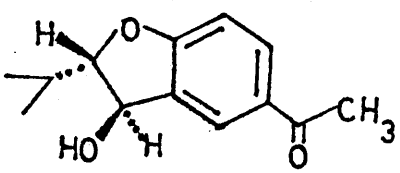

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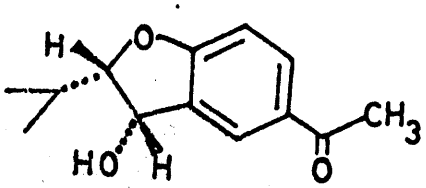
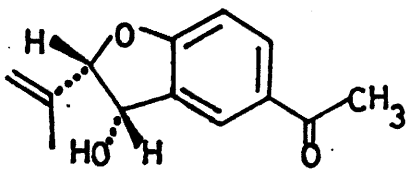


(38)

fitted in well with the Birch mechanism [52] for the biosynthesis of benzofurans (Scheme 1.8). Since Steck's paper was published, this diol, named vaginidiol has been reported [30] as being a constituent of Selinum vaginatum. It was assigned cis stereochemistry on the basis of the magnitude (6 Hz.) of the coupling constant between the two dihydrofurano-ring protons. This assignment was only possible because a diastereo-isomer, vaginol, had also been isolated [57] from the same source. Vaginol exhibited a coupling constant of 3.5 Hz. between the two five-ring protons. Seshadri's allocation of cis stereochemistry to vaginidiol (33) and trans stereo-chemistry to vaginol (34) depended on an observation by Bothner-By [58] that in five-membered rings, $J_{cis} > J_{trans}$, assuming dihedral angles of 0^{o} and 120^{o} between cis and trans protons respectively. Doubt can be cast on this assumption, however, especially in flexible molecules where stereochemical repulsion may alter the dihedral angles, but to confirm his assignment Seshadri used the known model compounds (35) and (36) whose coupling constants had previously been reported [59] as 7.0 Hz. and 4.8 Hz. respectively. The stereochemistry and coupling constants of a more closely related system to vaginidiol (33) had, however, been reported [60] by Zalkow and Ghosal . They synthesised compounds (37) and (38) and assigned



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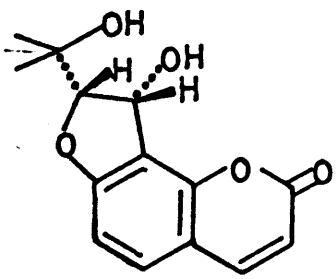

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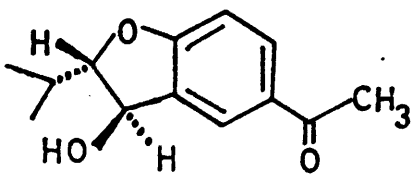

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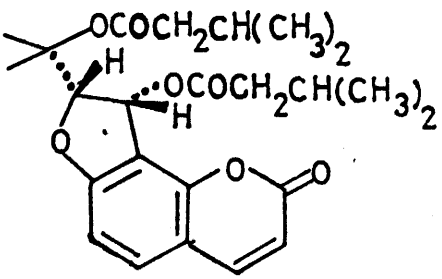

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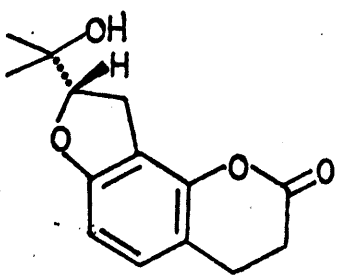
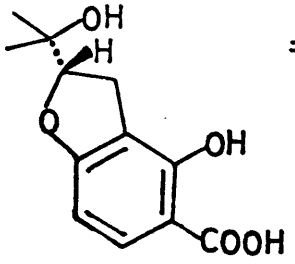


(16a)

cis stereochemistry to the latter on the basis of its identity with dihydrotoxol, prepared by hydrogenation of toxol [61] (39). The fact that toxol (39) yielded (+)-tartaric acid on ozonolysis had earlier implied [62] cis-stereochemistry. Zalkow found that, with his system, J_{trans} (6 Hz.) was greater than J_{cis} (4 Hz.) so that adoption of this system as a model for vaginidiol (33) would have led to an opposite stereochemical assignment. Lemmich, Lemmich and Nielsen commented [63] on the possible dubiety of the configuration at the benzylic carbon atom of several esters of vaginidiol just before Seshadri's paper [30] was published. Their paper contained a note to the effect that Zalkow had informed the authors of his discovery, by X-ray analysis, that the compound (37), earlier given trans stereochemistry was in fact cis. The erroneous conclusion reached previously could be explained if epimerisation had taken place during the ozonolysis of toxol (39).

The conclusion reached by Seshadri [30] on the stereochemistry of vaginidiol (33) must, therefore, be correct; it has a cis substituted dihydrifurano-ring. The absolute configuration of vaginidiol (33) was shown[30] to be 2'-(S), 3'-(R) by conversion of a natural monoester (3'-isovalerate, vaginidin) into a natural diester (athamantin) with isovaleroyl chloride in pyridine. The absolute configuration of athamantin (40) was determined [64] by correlation, through hydrogenolysis, with optically active dihydrocolumbianetin (16a)[65-67], columbianetin itself being converted by way of ozonolysis and oxidation reactions [64] to



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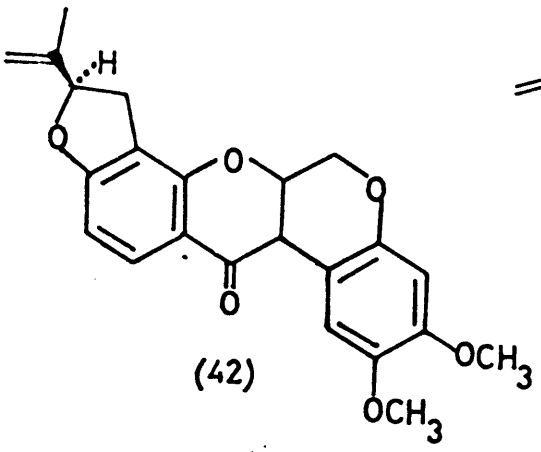

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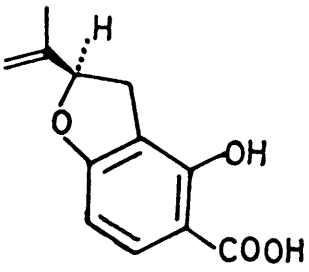

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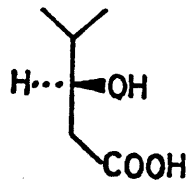

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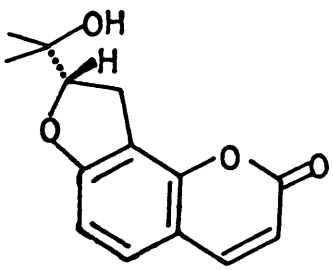

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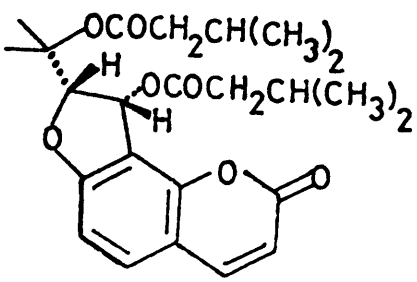

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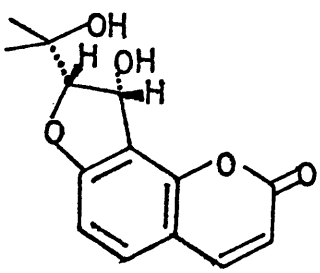

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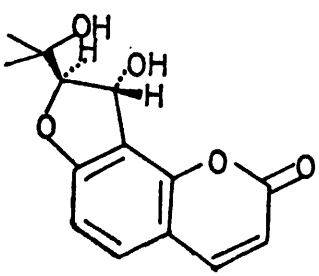

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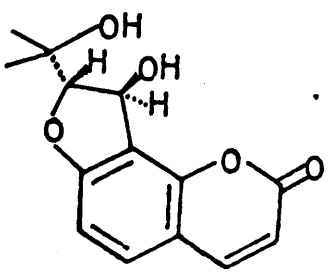

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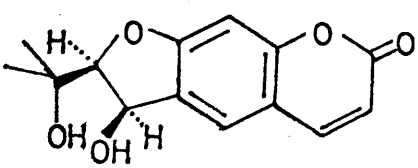

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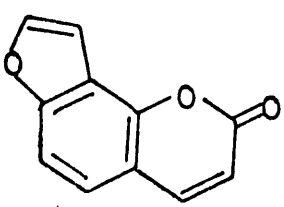

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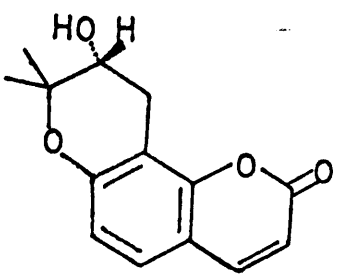


(46)

(+)-hydroxydihydrotubaic acid (41). A sample of (-)-hydroxydihydrotubaic acid was prepared for comparison by reaction of natural rotenone (42) with alkali followed by hydration of the resultant (-)-tubaic acid(43) with acid. (-)- Tubaic acid had been shown to be (R) previously [68] by relation with glyceraldehyde through degradation to the acid (44), so it followed that (+)-columbianetin (16) must have been (S). The 2'-(S), 3'-(R) stereochemistry of athamantin (40) then resulted from the cis arrangement of the substituents on the ring.

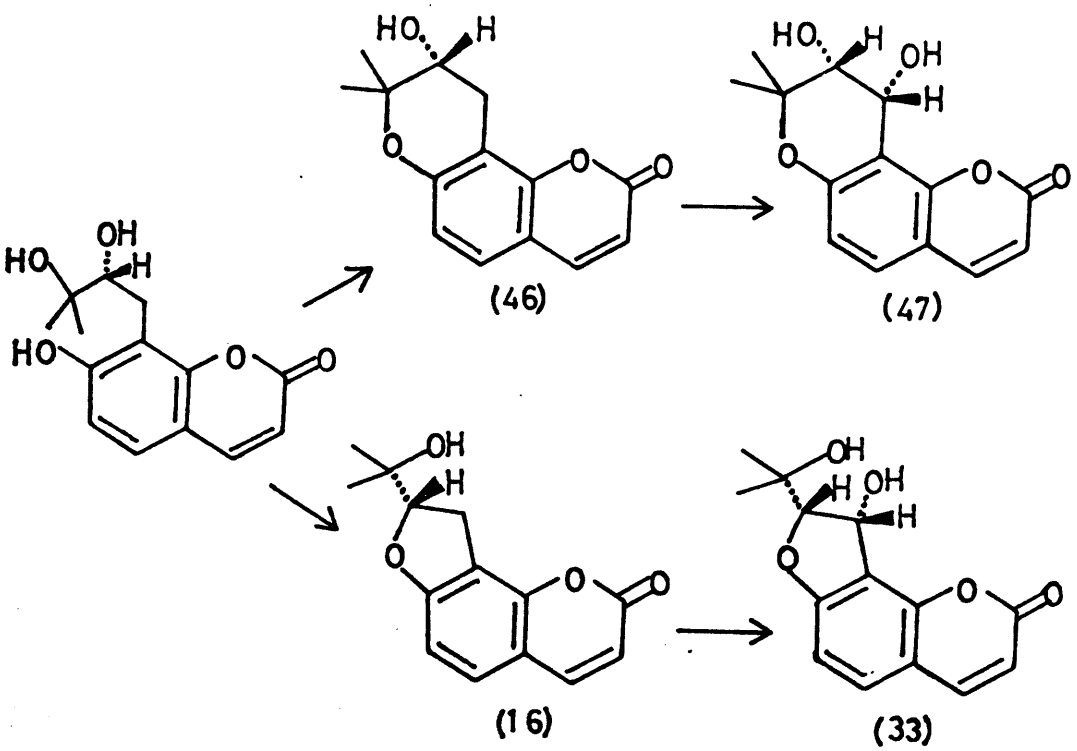
To account for the observed consistency in the configuration of both assymetric centres in the natural esters of the diol (33) known at that time, Steck suggested [56] a stereospecific hydroxylation of columbianetin (16) followed by esterification as the most probable biosynthesis of athamantin (40) and related compounds. This was confounded by Bhattacharyya's isolation of vaginol (34) (vide supra) with its apparently trans stereochemistry.

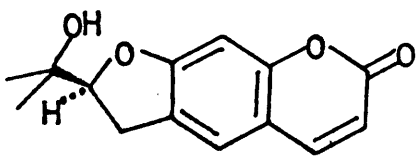
Th analogous diol (45) was also proposed [55] to occupy a similar role in the biogenesis of the linear furocoumarins. Surprisingly, however, neither (45) nor its esters have yet been isolated from a natural source.

The parallel with the linear furocoumarins was completed [56] when feedings of the sodium coumarinate salt of angelicin (19) indicated incorporation into all its methoxylated derivatives.

The co-occurrence of columbianetin (16) and lomatin (46) derivatives and the relative stereochemistry of natural

SCHEME 1.9.

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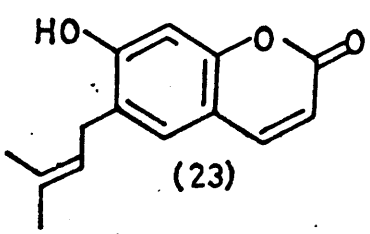
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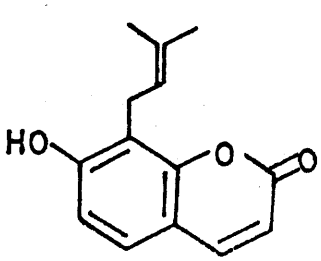
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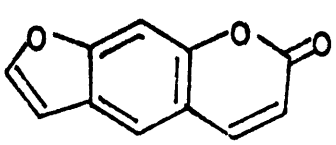
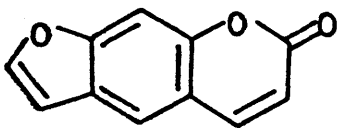

(2)

dihydrofuran and dihydropyran derivatives (for example the diol (47)) was used by Steck as support for the idea of a common precursor which could undergo ring closure in two ways [56] . Thus, either an epoxyphenol or a vicinal diol could produce a five- or a six-membered ring system (Scheme 1.9). The known configurations of both lomatin (46) and columbianetin (16) [69] placed stereochemical constraints on the configuration of any intermediate in their biosynthesis. In this respect it is interesting to note that whereas columbianetin (16) has only been found in the (S)-configuration naturally, its linear isomer, marmesin (7), is known in both antipodal forms [70]. Steck and Brown investigated[71] their relative efficiencies as furocoumarin precursors in Ruta graveolens, Heracleum lanatum and in Angelica archangelica. Their results clearly demonstrated that (S) (+)-marmesin (7) was incorporated in the three species, whereas its enantiomer was not. Whether or not R (-)-marmesin is a precursor of the furocoumarins in plants in which it is found is still unknown.

The roles of 7-demethylsuberosin (23) and osthenol (32) in the pathway were established later by Steck and Brown[36]. They showed conclusively that the former was a precursor of linear furocoumarins in Conium maculatum and Heraclium lanatum (Umbelliferae); and in Ruta graveolens (Rutaceae). (23), however, was not incorporated into psoralen (2) in Coronilla glauca (Leguminosae) but two possible reasons were given for this. It was feasible that



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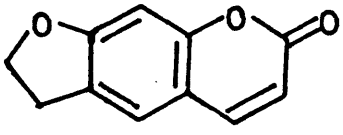

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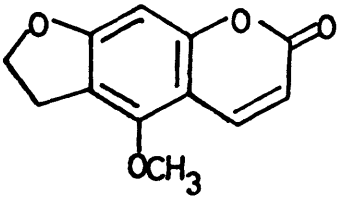

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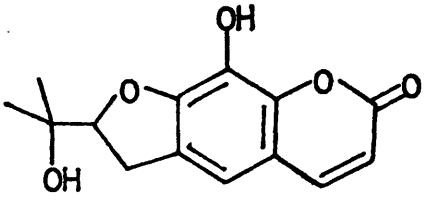

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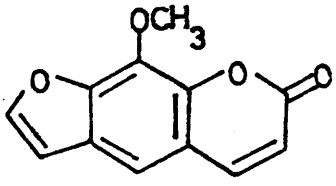

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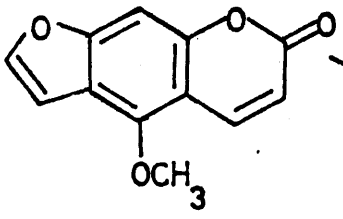

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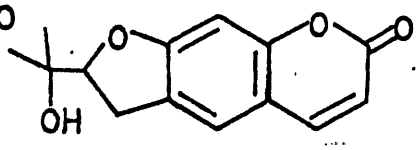
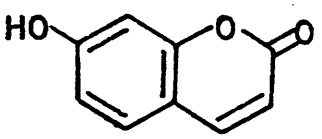


(7)

an alternative pathway could consume the phenol before it reached the site of furocoumarin biosynthesis. Alternatively, a completely different biogenetic sequence may have been operating in this plant. The authors' suspicions were aroused by the occurrence of psoralen (2) as the glycoside of the derived cinnamic acid. Simpler coumarins were often encountered in this form, but the phenomenon was much rarer in such an advanced metabolite.

Since 1970 a series of papers has been published on the subject by Caporale and co-workers. The leaves of Ficus carica (Moraceae) were used [72] to test the efficiency of the unsubstituted dihydrofurocoumarins(48) and (49) as possible furan precursors. Good incorporation into the corresponding furocoumarins was observed, dehydrogenation as the final step being postulated.

Caporale then turned his attention to Ruta graveolens[73] and observed good incorporation of rutaretin (50) into xanthotoxin (18), suggesting that perhaps hydroxylation might occur prior to cleavage of the C-5 unit. He was also able to demonstrate interconversions between psoralen (2), bergapten (17) and xanthotoxin (18) in the plant. In a second paper on Ruta graveolens[74], Caporale established the sequential roles of marmesin(7) and rutaretin(50); showing that whereas(7) was a highly efficient precursor of (50), the reverse was not the case. These results, taken in conjunction with those of Steck, imply that



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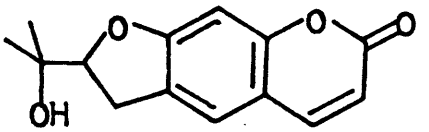

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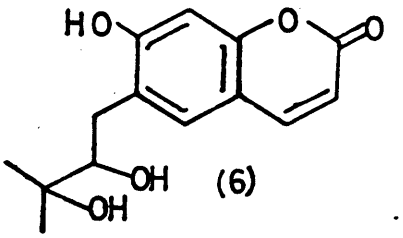

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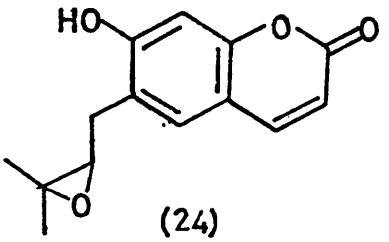

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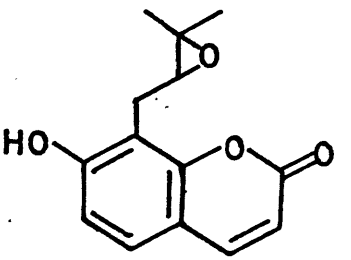

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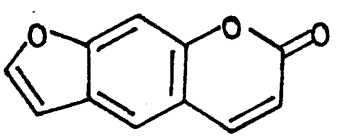

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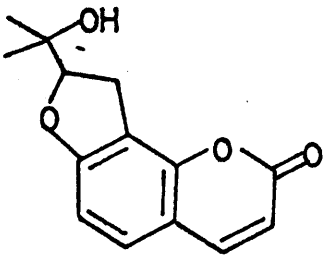

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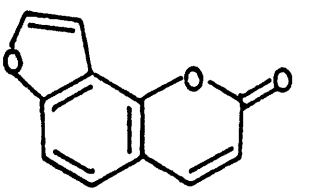


(19)

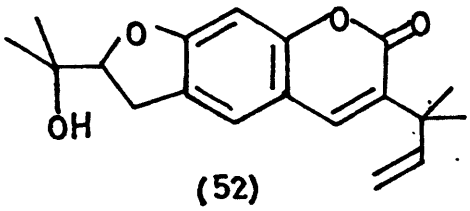
hydroxylation can take place either at the isopropyldihydrofuranocoumarin stage,or after the furan ring has been formed.

A very recent paper by Austin and Brown [37] on Ruta graveolens cell cultures rather than the free growing plant confirms the previous findings of Steck.

Other work implies that the biogenetic sequence elucidated over the last ten years must be fairly general. Thus, umbelliferone (4) was shown to be incorporated into furocoumarins in Pastinaca sativa L.[75] and Caporale showed marmesin (7) to be intermediate in the leaves of Ficus carica [76]. A very similar sequence of events is suspected to operate also in the biosynthesis of the furochromones [77] and of some furanoquinoline alkaloids [78]. The work of Grundon has bee especially prominent in the latter field [79].

From the aforegoing discussion it should be seen that the evidence so far adduced for some of the intermediates in furocoumarin biosynthesis is tenuous. Although either an epoxyphenol or a vicinal diol may in principle give rise to the dihydropyranocoumarins and dihydrofurocoumarins, neither has been shown to be a precursor. It is perhaps significant that the diol (6) has been isolated from natural sources [3], and is a stable compound whereas (24) and (51) have only been found as their methyl ethers [80,5].

The routes from marmesin (7) to psoralen (2) and from columbianetin (16) to angelicin (19) are still obscure. Other examples of similarly related compounds



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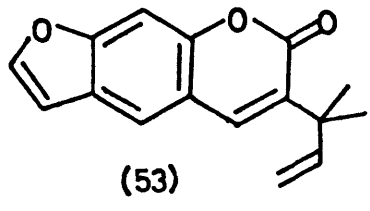

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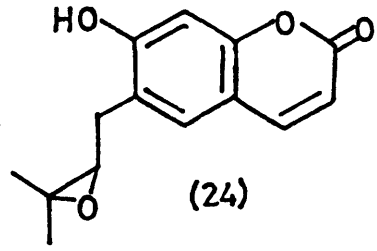

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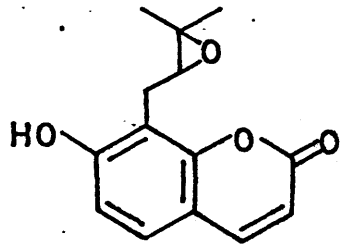

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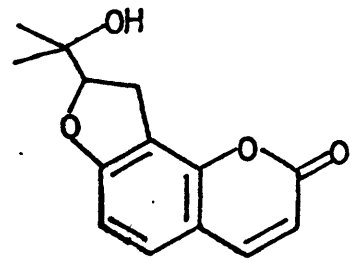

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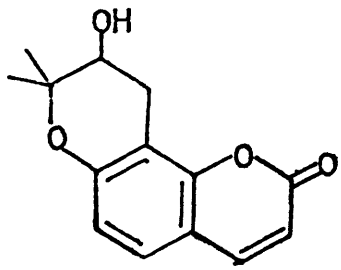

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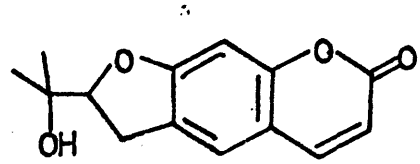

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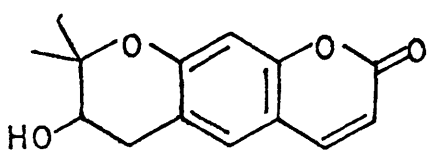

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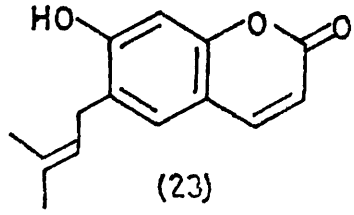

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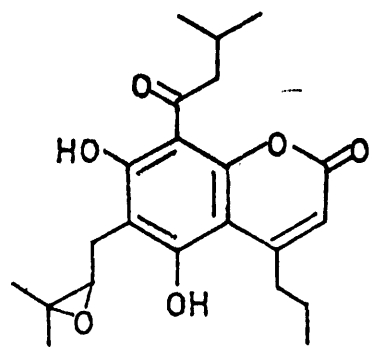


(55)

can be found in the literature. Chalepin (52) and Chalepensin (53) are found together in Clausena indica[27] and are almost certainly linked biogenetically. The former is also found [81], in racemic form, in Helietta longifoliata Britt. (Rutaceae)but is not accompanied by the furan in this case.

Clearly, a synthesis of some of the proposed intermediates would be of value in that isotopically labelled material could then be fed to plants and the efficiency of proposed precursors tested. Our main objectives were the epoxyphenols (24) and (51), which might then be induced to cyclise preferentially to either (±)-columbianetin [66] (zozimol [82])(16) or (±)-lomatin [83] (selinetin [84], jatamansinol [85] or xanthogalol [86])(46) in the former case ; or to either the corresponding compounds (±)-marmesin [70](7) or (±)-decursinol [87](54) in the latter case.

It was known that King et al had already failed to isolate (24) when,in 1954[88], they treated 7-demethylsuberosin (23) with monoperphthalic acid in ether at 0°, obtaining a good yield of (±)-marmesin(7) directly. No mention of the dihydropyranocoumarin (54) was given, however. On the other hand, recent papers by Finnegan et al [89] and by Crombie and co-workers [29] on compounds isolated from the seeds of Mammea americana L. claim the isolation and characterisation of the epoxyphenol (55) from reaction of the prenylated phenol with peracid. These latter publications were not available when the work described herein was carried out.

Part 1

Elaboration of the Coumarins, Osthenol and 7-Demethylsuberosin.

SCHEME 1.10

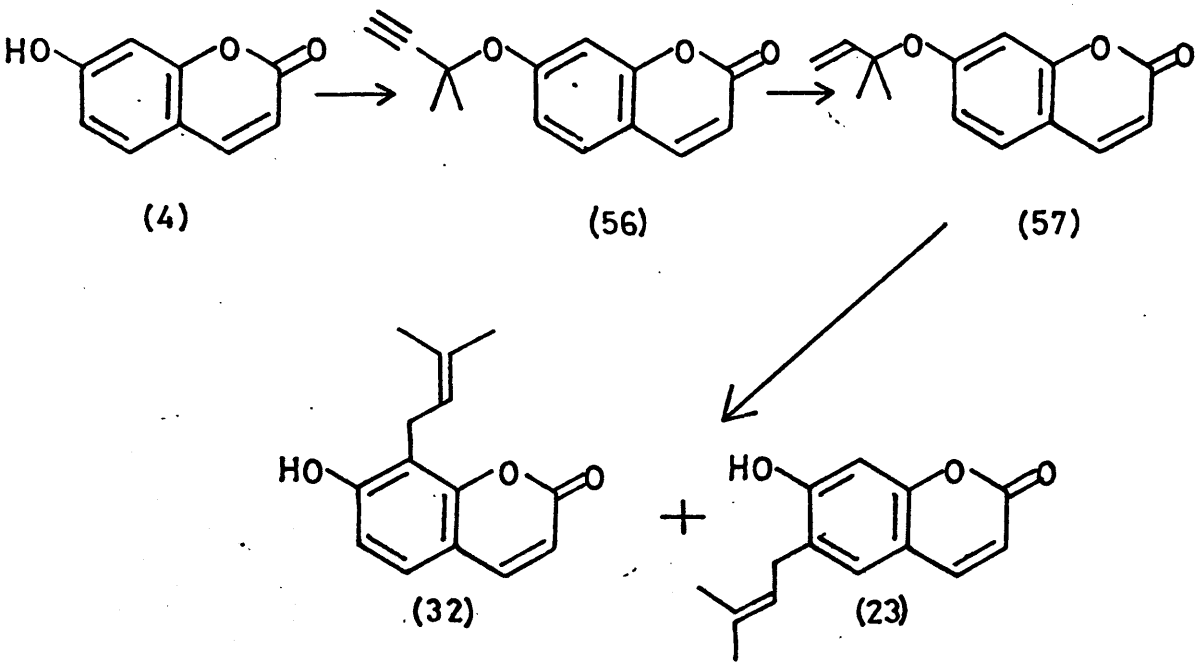
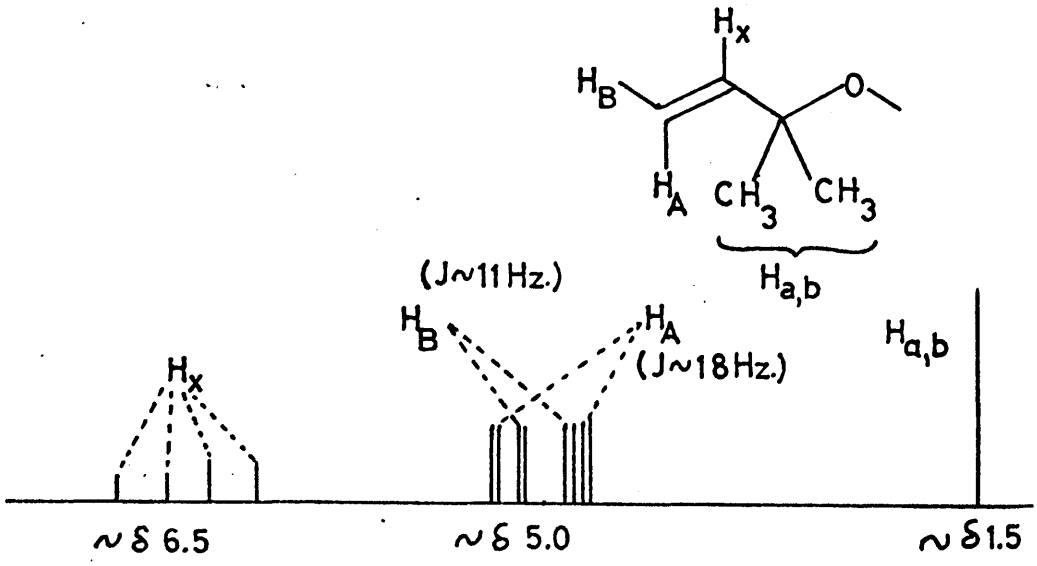


FIGURE 1.11



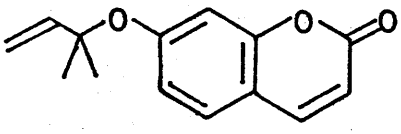
The chemical shift of H_A can be higher than that of H_B. When this happens, coalescence of the low-field portions of the two signals can occur.

As mentioned earlier, Murray and Ballantyne had already developed [41] a synthetic route to prenylated coumarins, the generality of which has now been put to the test[90]. They were able to obtain a good yield of osthenol (32) from umbelliferone by the reaction sequence outlined in Scheme 1.10[41], and this was utilised to prepare the phenol in reasonable quantities (~0.5g. per run).

Umbelliferone (4) was treated with 1,1-dimethylpropargyl chloride [91] in refluxing aqueous acetone in the presence of potassium carbonate and potassium iodide. The required propargyl ether (56) was obtained in yields averaging 70% . Its n.m.r. spectrum($CDCl_3$) is typical of coumarin 1,1-dimethylpropargyl ethers in that it exhibits a six-proton singlet at δ1.73 and a one proton singlet at δ2.68, attributable to the methyl and acetylenic proton resonances respectively.

Hydrogenation of (56) over 5% palladium - charcoal with a quinoline-sulphur poison[41] afforded 7-O-(1,1-dimethylallyl) umbelliferone (57) in virtually quantitative yield. This ether is quite stable in its crystalline form but has been shown [8] to melt over a fairly broad range, the phenomenon being attributed to slight rearrangement at the melting point.

The n.m.r. of the 1,1-dimethylallyl system is worthy of discussion at this point. A typical pattern produced by the system is illustrated in Figure 1.11. The ABX system of the three olefinic protons gives rise to two one-proton doublets at δ5.0 approximately, with J_{AX} 18 Hz. ; i.e. <u>trans</u> coupling and J_{BX} 11 Hz. ; i.e. <u>cis</u> coupling, and a one-proton double-doublet at lower field



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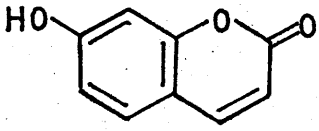

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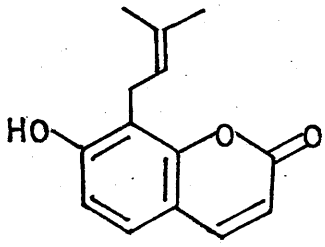

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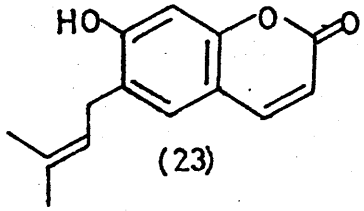
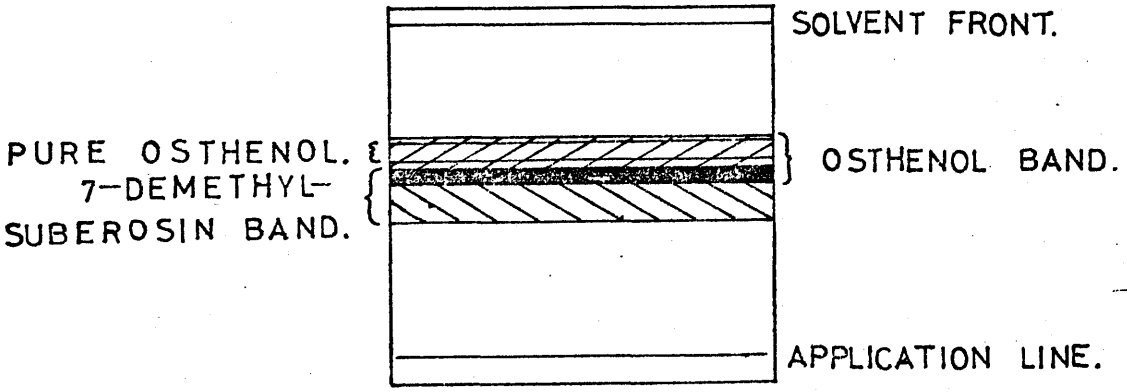


(23)

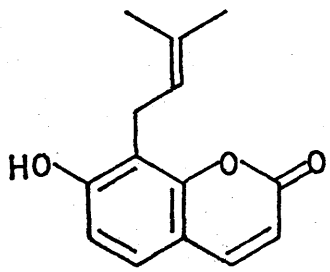
FIGURE 1.12



(J_{AX} 18 Hz.; J_{BX} 10 Hz.). There is also evidence of geminal coupling between the A and B protons in this system; J 1 Hz. These features make the system almost instantly recognisable from the n.m.r. alone.

Pyrolysis of the neat ether (57) at 130° for 1 hour at atmospheric pressure gave a mixture consisting mainly of three phenolic compounds. Umbelliferone (4) was present to a small extent, the other components being osthenol (32) and 7-demethylsuberosin (23) Separation was achieved by preparative t.l.c. as described by Murray and Ballantyne [41] with the following addition: it was often found that separation of the bands corresponding to (32) and (23) was not complete, despite great care in applying material to the plate. When this happened the "centre" of the main osthenol(32) band was removed as indicated in Figure 1.12. to furnish the pure phenol, and the remaining silica was eluted to afford a mixture of (32) and (23) which was re-chromatographed at a later date. Although the yield of pure osthenol (32) from the plate was significantly reduced by this technique, the sometimes infuriating presence of traces of (23) in the osthenol was obviated.

The typical resonances of the 3,3-dimethylallyl unit attached to an aromatic nucleus were present in the n.m.r. spectrum of osthenol (32). The two vinyl methyl groups show separate signals at δ 1,70 and 1.82 as broad singlets, and a doublet ascribable to the benzylic protons appears at δ 3.58 with J 7 Hz. A broad triplet at δ 5.28 (J 7Hz.) completes the resonances due to this moiety.



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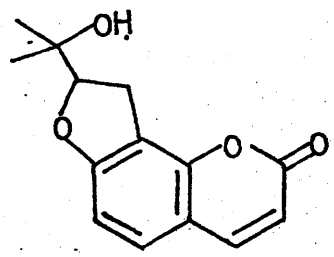

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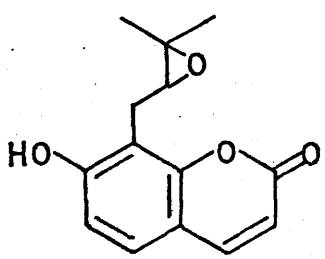

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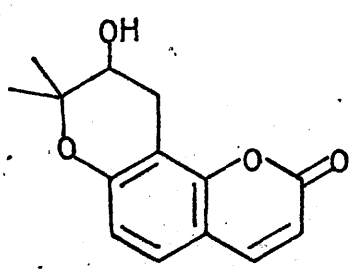
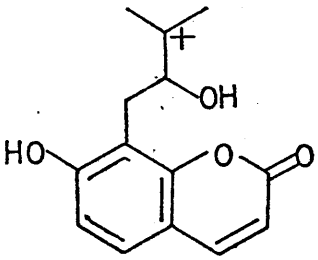


(46)

Osthenol (32), on reaction with m-chloroperbenzoic acid in ether at 0^{o} gave only one product, identified from spectroscopic evidence (vide infra) as (±)-columbianetin (16). Throughout the lengthy time involved in this conversion (~8 hr .), no evidence for the formation of (51) as a discrete reaction intermediate could be adduced. Analytical t.l.c. at various times throughout the reaction showed only the presence of starting material, product, and reagent. This seems to suggest that if the epoxyphenol (51) is formed as a discrete intermediate, its existence must be fleeting. Alternatively the substrate-peracid complex may undergo cyclisation with the ortho-hydroxyl group before dissociation is complete, in which case(51), as such, may never be formed. A third possibility is that cyclisation could be occurring during the work up procedure. If this process can take place on basic alumina (used to remove acidic material) then cyclisation on the chromatoplate might account for the absence of any t.l.c. evidence for the epoxyphenols.

The opening of the presumed epoxide ring at the less substituted carbon atom was expected [88,92] under the effectively neutral conditions employed. Identical results were obtained when ethyl acetate or carbon tetrachloride were used as solvent . With bench chloroform, however, a faster reaction ensued and the dihydropyranocoumarin (46) was now the sole product. This observation can be explained if the opening of the "epoxide" ring in this case is catalysed by traces of hydrochloric acid already present in the chloroform.



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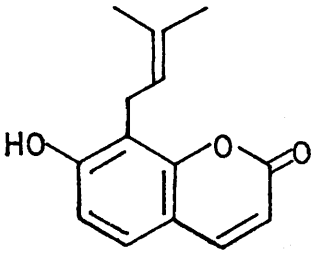

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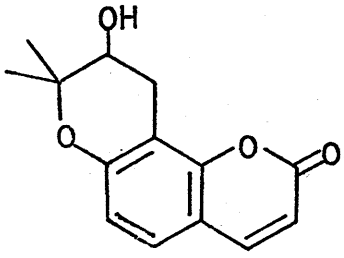

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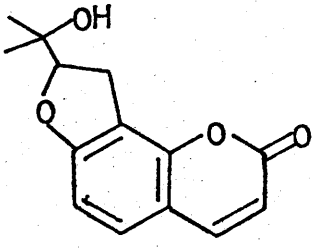

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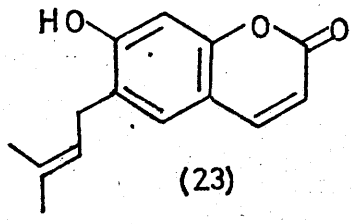

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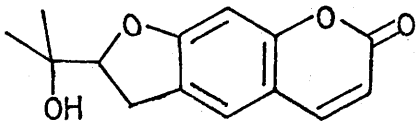

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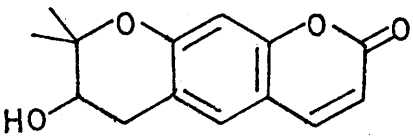
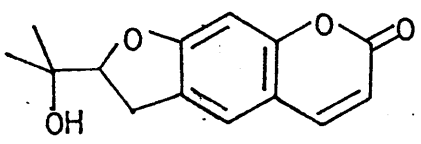


(54)

The reaction would then proceed [93] via the more stable tertiary carbonium ion (58), leading to the alternative six-membered ring. Confirmation of this hypothesis came when (32) was subjected to the epoxidation conditions in AnalaR chloroform which had been previously acidified with hydrochloric acid. (For details, see Experimental Section). The phenol was again converted exclusively to (±)-lomatin (46). The critical dependence of the reaction pathway on the presence of traces of acid was confirmed when AnalaR chloroform alone from a freshly opened bottle was used as solvent. The mixture of (16) and (46) isolated (~1:2) implied that enough acid was present even here to substantially influence the reaction.

The reaction of 7-demethylsuberosin (23), which is also available as a by-product in Murray's synthesis of osthenol (32)[41], with m-chloroperbenzoic acid showed a similar solvent dependence. Again, the products isolated were racemic variations of naturally occurring optically active compounds. Using ethyl acetate, ether, carbon tetrachloride or AnalaR chloroform, only (±)-marmesin (7) was formed. The dihydropyranocoumarin (±)-decursinol (54) was the sole product when chloroform acidified with hydrochloric acid was used. Reaction in chloroform acidified with 1-naphthalenesulfonic acid was not selective, a mixture (~3:1) of (7) and (54) being produced.

These results indicated that osthenol (32) and 7-demethylsuberosin (23) display different sensitivities



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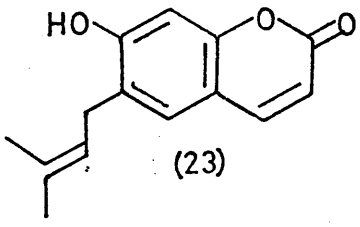

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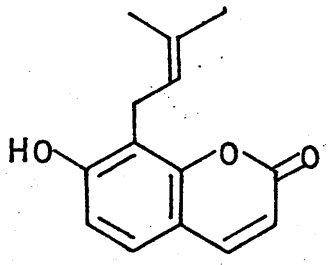

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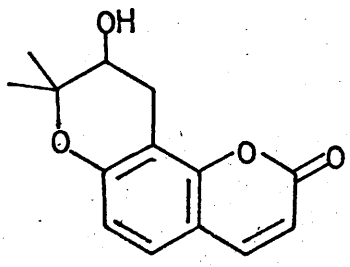

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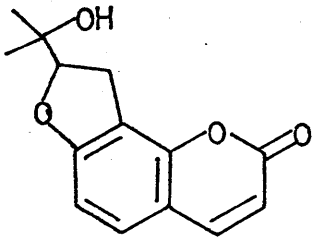

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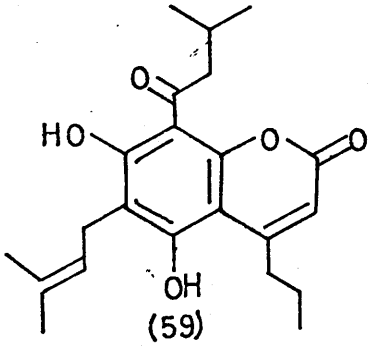

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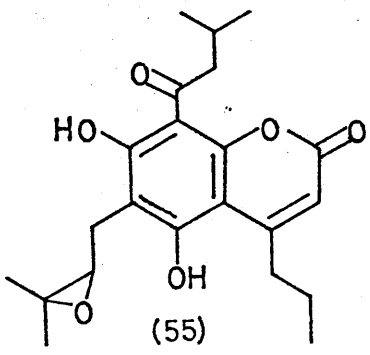

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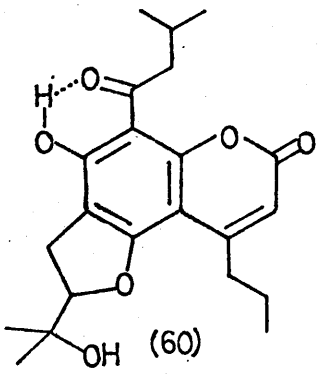

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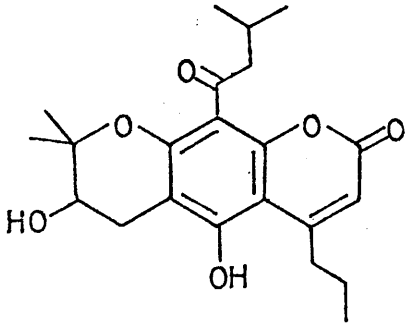

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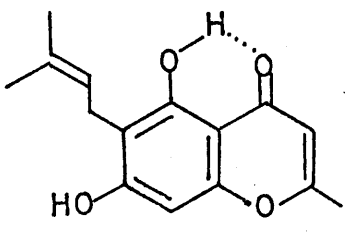
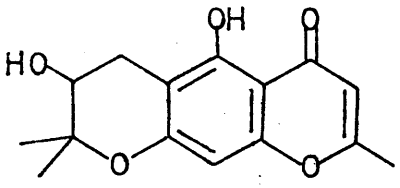
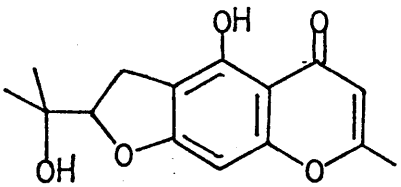


(62)

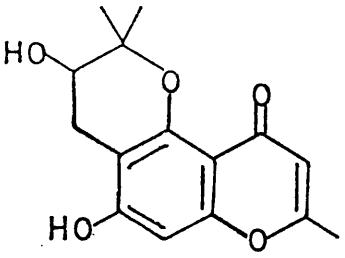
towards the acidity of the medium. The reaction in AnalaR chloroform produces a pure isopropyldihydrofuran(7) in the one case, and a mixture of five- and six-membered ring products in the other. These observations were substantiated when monoperphthalic acid was used as the oxidant. Thus, (23) gave only (±)-marmesin (7) as previously reported by King, Housley and King [88], whereas (32) under identical conditions gave a mixture of (46) and (16) (~3:7). It is evident that care should be exercised in the choice of solvent and reagent for epoxidations where the possibility of further acid-catalysed reaction exists. The point is well illustrated by the recent publications of Finnegan et al [89] in which (59) was epoxidised using m-chloroperbenzoic acid in chloroform at 0°. A mixture of dihydropyrano - and dihydrofuranocoumarins was obtained, as might have been expected from the work carried out in this laboratory. Also, by reducing the reaction time, the authors were able to isolate and characterise the unstable epoxyphenol intermediate (55); a result confirmed by Crombie's group [29]. Preferential cyclisation of (55) to (60) or (61) was achieved by heating the epoxide in ethanol, or alternatively by heating with acid. The different modes of cyclisation of (59) observed by both groups are worthy of comment. The angular products would have been expected to predominate owing to the chelation of the 7-hydroxy group with the 8-acyl substituent. A closely analogous system has been investigated by Steck [77]. He epoxidised the chromone peucenin (62) under acidic conditions and



(63)



(64)



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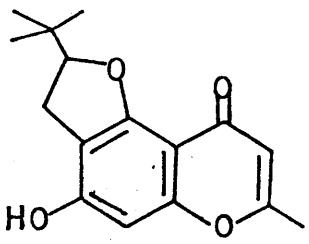

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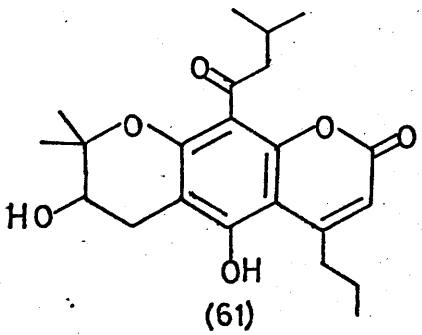

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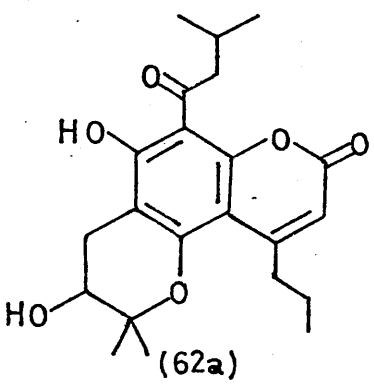
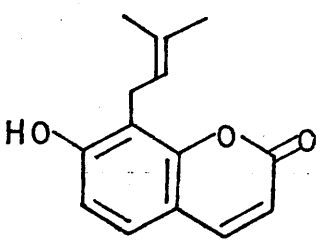


(62a)



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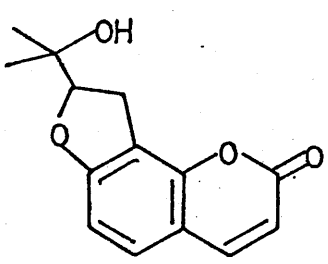

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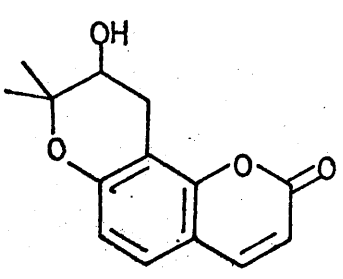
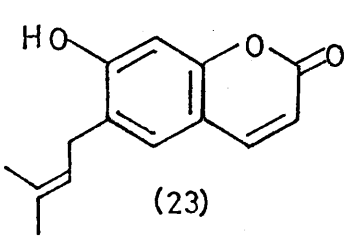


(46)



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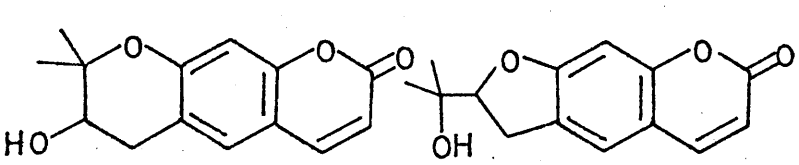


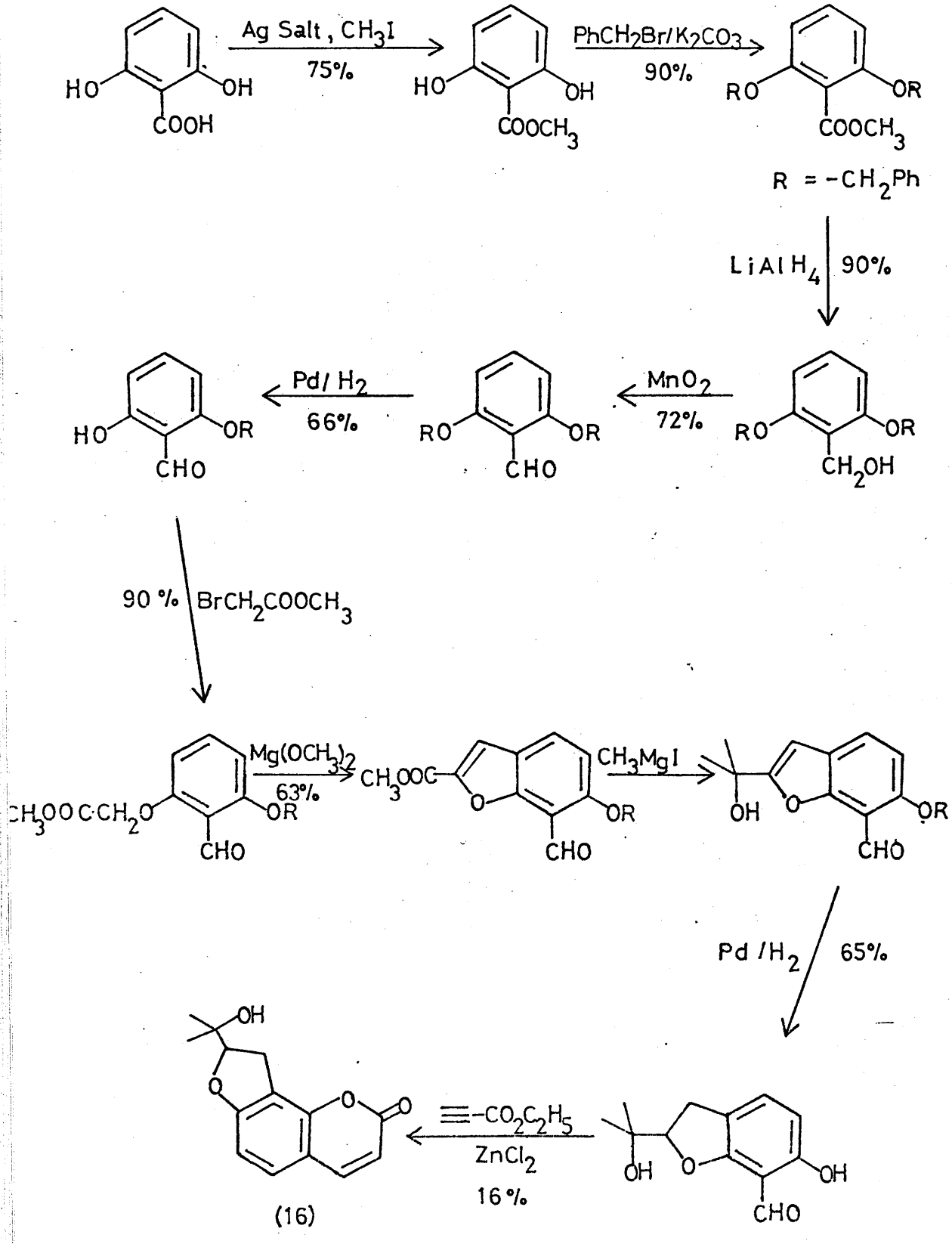
(54)

(7)

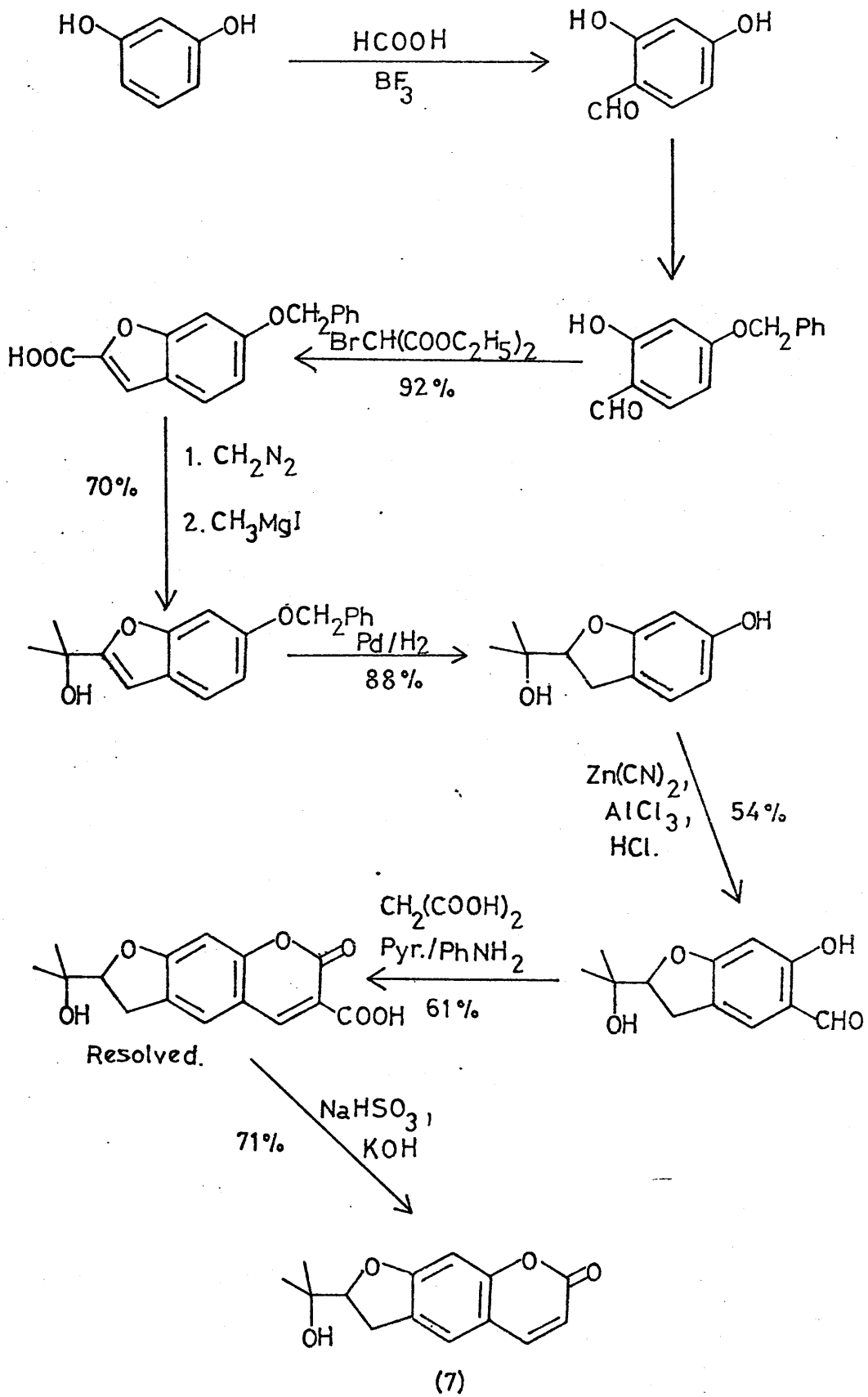
reported (±)-hamaudol (63) as the sole product. These results are at variance with the observations made in this laboratory [94] when, under identical conditions, all four possible products were found. As well as hamaudol (63), visamminol (64) (7-8%) and the angular analogues (65) and (66) (5% in total) were isolated. These products were minor, however, and the linear dihydropyranocoumarin (61) isolated by Finnegan et al remains a surprising observation. Undoubtedly, the angular isomer (62a) would have been the predicted product from this reaction. The assignment of the linear structure depended on the chemical shift of the hydroxyl proton resonance; a chelated proton would have resonated at δ 11-14, a signal at δ 5.35 being observed.

By careful choice of solvent and reagent, therefore, it was possible to convert osthenol (32) into (16) or (46) selectively and almost quantitively. 7-Demethylsuberosin (23) was converted to (7) or (54) by entirely analogous reactions ; again very selectively. The overall yield of the secondary and tertiary alcohols (46),(54),(7) and (16) was approximately 20% from umbelliferone. This compares well with earlier syntheses of columbianetin [95](16) and marmesin (7)[96] and with more recent syntheses of all four (vide infra). Soine's synthesis of columbianetin (16) is illustrated in Scheme 1.13, and that of marmesin (7) by Nakajima in Scheme 1.14. The syntheses of (16) and (46) from osthenol (32) were also described by Bohlmann [97] after our work was completed. Toluenesulphonic acid in chloroform was used to generate

SCHEME 1.13

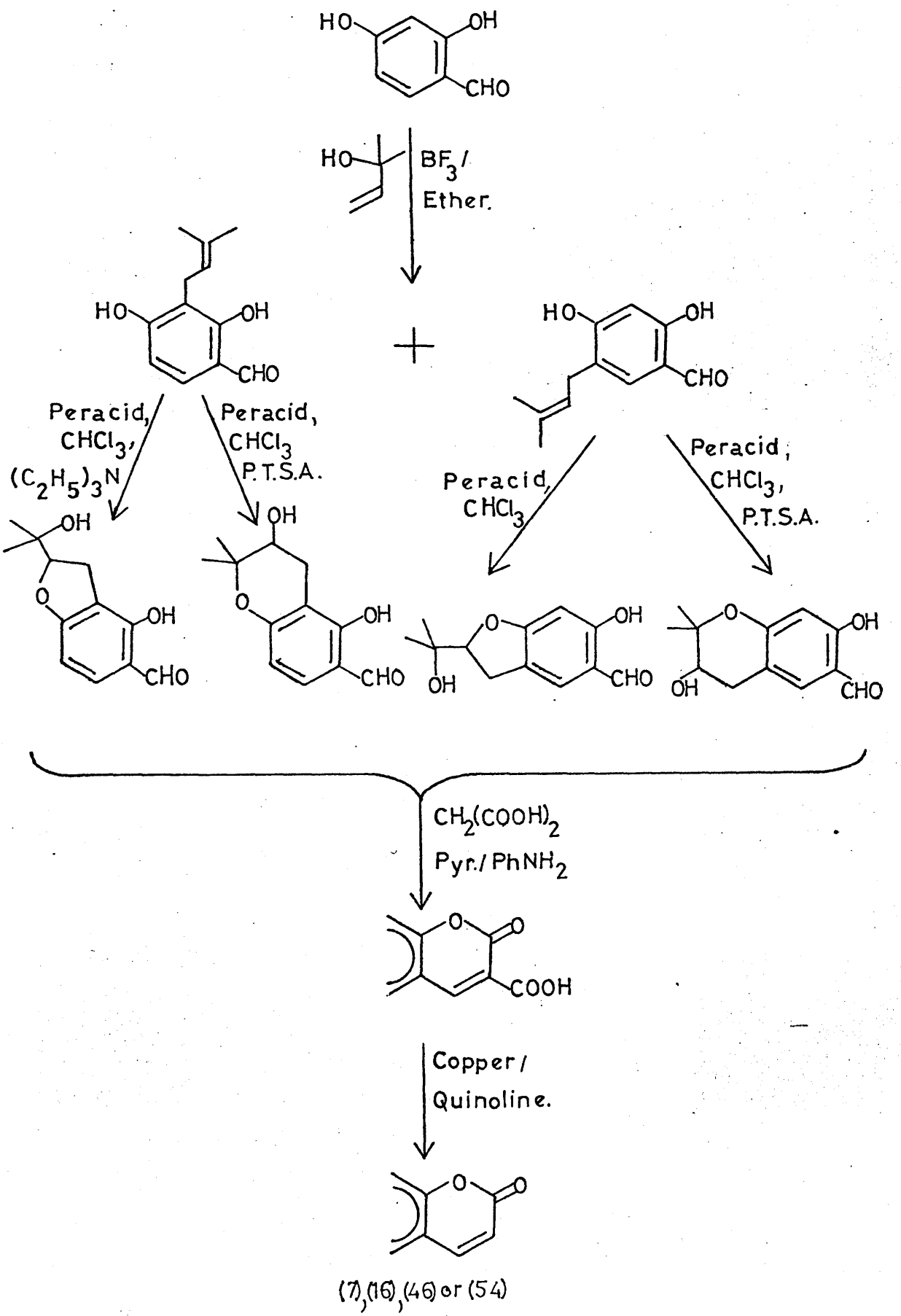

Ag Salt, CH3I
75%
PhCH2Br/K2CO3
90%
R = -CH2Ph
LiAlH4
90%
MnO2
72%
Pd/H2
66%
90 %
BrCH2COOCH3
Mg(OCH3)2
63%
CH3MgI
Pd/H2
65%
ZnCl2
16 %
(16)

SCHEME 1.14


HO
OH
HCOOH
BF3
CHO
OCH2Ph
BrCH(COOC2H5)2
92%
HOOC
O
70%
1. CH2N2
2. CH3MgI
OH
Pd/H2
88%
Zn(CN)2,
AlCl3,
HCl.
54%
CH2(COOH)2
Pyr./PhNH2
61%
COOH
Resolved.
NaHSO3,
KOH
71%

(7)

SCHEME 1.15



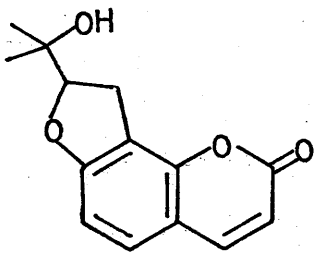
(7),(16),(46) or (54)

the six-membered ring from reaction of the phenol (32) with perbenzoic acid, and Bohlmann went on to describe how it was possible for him to generate the five-ring compound by treating the epoxydation reaction mixture with aqueous sodium carbonate solution. His experimental details are brief,no indication of the grade of chloroform being given, but the implication was that a stable solution of the epoxyphenol (51) in chloroform was produced by the action of perbenzoic acid on osthenol (32). This is surprising in the light of the work described earlier in this thesis. The epoxyphenol was neither characterised nor isolated by Bohlmann.

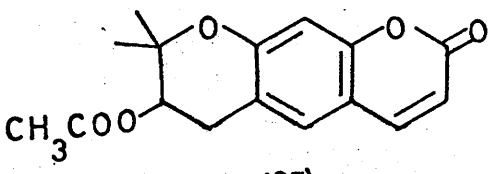
The syntheses of the four alcohols (7), (16),(46) and (54) was also achieved by Steck [98] concurrently with our work. His approach was to construct the pyrone ring last of all. The syntheses, bearing little relation to the biogenesis of these compounds are shown in Scheme 1.15. Overall yields for these processes are markedly inferior to those obtained using Murray's osthenol synthesis and the cyclisation methods herein described.

It should be noted that two papers containing relevant information about the cyclisation reactions outlined above have appeared very recently. The first, by Ritchie et al [99], contains results which appear to be at variance with our findings, whereas the second, from Crombie's group [100], only serves to confirm the generality of the reaction.

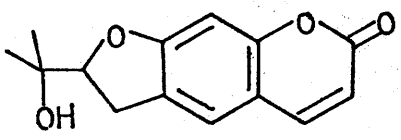
Each of the alcohols (7), (16), (46) and (54) is known to occur naturally in one, or both, enantiomeric



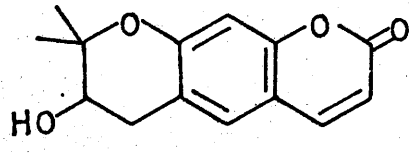
(16)



(67)



(7)

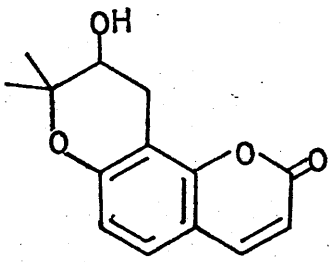


(54)

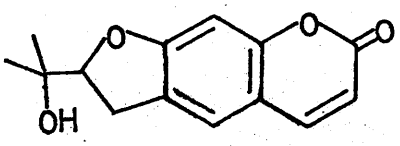
forms . Their esters, however, are much more frequently encountered. As an illustration, columbianetin (16) is found as its acetate [101] (libanoridine [102]), isovalerate[63], senecioate [63,103](libanorin [104]), angelate(columbianadin[66] or zozimin [82]), epoxyangelate (columbianadin oxide)[105] and also as more complex esters (peulustrin [106] and isopeulustrin [105]).

It was possible to differentiate between isomers containing the hydroxyisopropyldihydrofuran and hydroxydimethyldihydropyran moieties by a variety of spectroscopic methods. In the n.m.r. spectra of the former, the methylene and methine protons constitute an A_2X system with signals at δ 3.3(2H;d.) and δ 5.2(1H;t.) ; J 9-10 Hz. The corresponding dihydropyran protons form an ABX system at δ 2.8(2H;m.), and δ 3.7 (1H;t.)[105,107,108]. When the n.m.r. spectra were measured in dimethylsulphoxide it was possible also to distinguish the tertiary from the secondary hydroxyl proton resonance. The latter signal appeared as a doublet through coupling with the adjacent methine proton [109]. This phenomenon was occasionally observed when using deuterochloroform as solvent.

The secondary alcohol (54) was found to acetylate much more readily than the isomeric tertiary alcohol(7). Thus (54), in acetic anhydride and pyridine, furnished an acetate (67) after refluxing for five minutes. (7), on the other hand, required a five-hour reflux with sodium acetate in acetic anhydride, as previously described [70]. The downfield shifts of the methine protons in the acetates, $\sim$ 1.2 and $\sim$ 0.25 ppm for the secondary and tertiary alcohols respectively,



(46)



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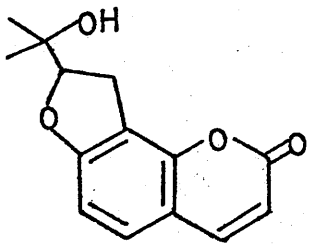

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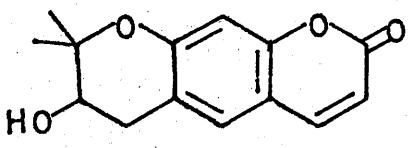
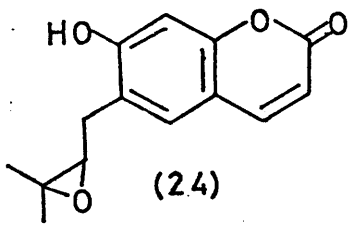


(54)

served as additional n.m.r. evidence[110] in assignment of structures.

The two types of ring system were also readily distinguished by mass spectrometry. The principal pathway of fragmentation in the dihydrofuran moiety [111] is loss of the elements of acetone, giving rise to an ion (M-58) which loses a hydrogen atom to give the base peak at M-59. An abundant ion at m/e 59 is also characteristic [111-113]. In the dihydropyran spectra the m/e59 species is not significant. Fission of the chroman ring here gives the fragment ion M-70 and M-71 (base peak) [114]. The spectrum of (46) published[115] by Das et al is of interest as it bears little resemblance to that of synthetic (46) produced by us.

High resolution infra-red studies on the alcohols(7), (16), (46) and (54) showed that each exhibits a free and an intramolecularly hydrogen-bonded hydroxyl stretching absorption. For the secondary alcohols,the free hydroxyl bands appear at 3630cm.$^{-1}$, 10 cm.$^{-1}$ higher than those of the tertiary alcohols, while the corresponding bonded hydroxyl stretch at 3590 cm.$^{-1}$ in the former is somewhat lower in frequency than that of its isomer. There are also readily discernible differences in the relative intensities of the free and bonded hydroxyl absorptions which can be explained from conformational studies. From an examination of the molecular models, the secondary hydroxyl maybe either equatorial or axial in the half-chair conformations[110] of the dihydropyran ring. In the former, which should be more



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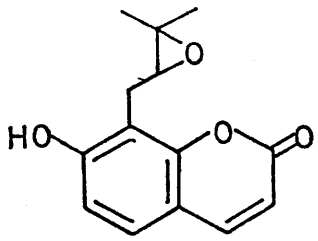

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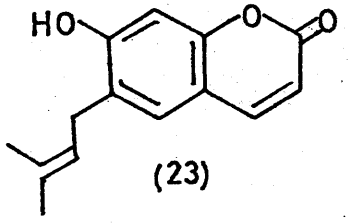

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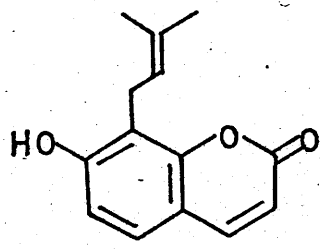

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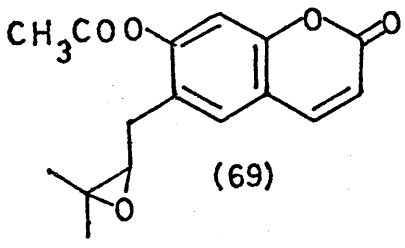

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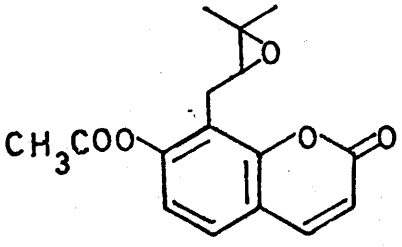

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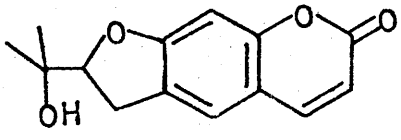

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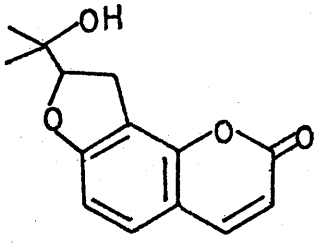
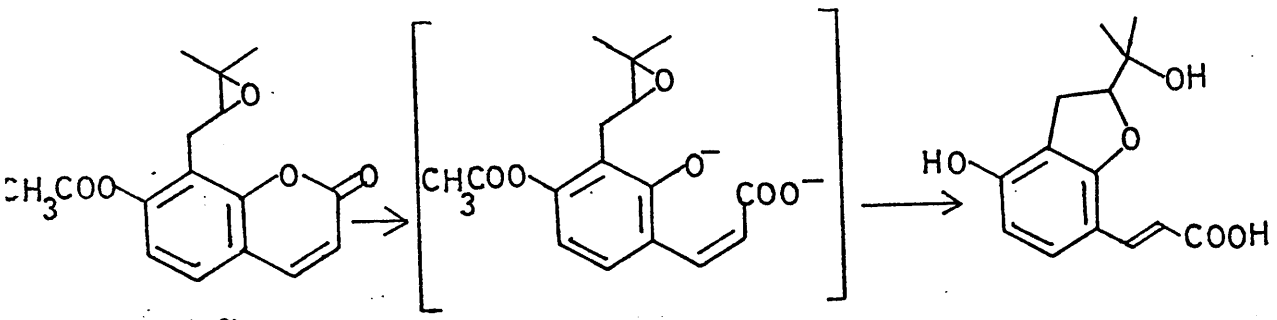


(16)

favourable on energetic grounds, intramolecular hydrogen-bonding to the dihydropyran oxygen is not possible, thus accounting for the observed, more intense free hydroxyl stretch (ratio of free:bonded hydroxyl approx. 1.8:1, based on observed optical density measurements). In the dihydrofurans, however, in which intramolecular hydrogen-bonding is more important (ratio of free:bonded hydroxyl 1:2.7) models show that the side chain will probably exist preferentially in a conformation conducive to hydrogen bonding between the tertiary hydroxyl group and the dihydro-furan oxygen atom.

Our failure to obtain any evidence for (24) or (51) prompted us to attempt their preparation indirectly. Both the phenols (23) and (32) readily afforded an acetate on treatment with acetic anhydride and pyridine . Epoxidation of these acetates using m-chloroperbenzoic acid in either ether or ethyl acetate at 0^{o} went very smoothly to afford the epoxyacetates(69) and (68) in high yield. Both were colourless gums and were substantially pure by t.l.c. and n.m.r., the ABM system of the epoxide proton and the two benzylic methylene protons giving rise to a complex multiplet for both compounds in the region δ 2.6-3.4. However, neither could be obtained crystalline, nor freed from a small quantity of(7)or(16) respectively. Both (68) and (69) were very sensitive to hydrolysis, not only by mild base, but also on the t.l.c. plate, producing exclusively in each case the dihydrofuranocoumarin (16) or(7), the product which would have been anticipated from cyclisation of(24)

SCHEME 1.16



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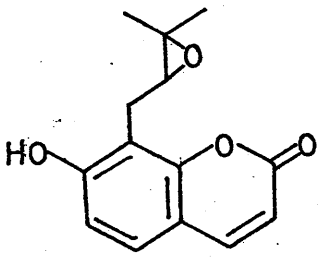

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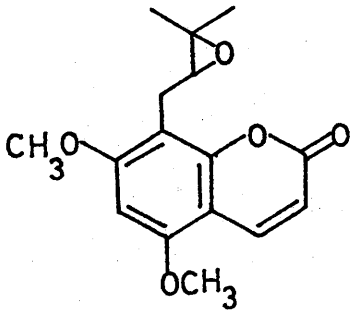

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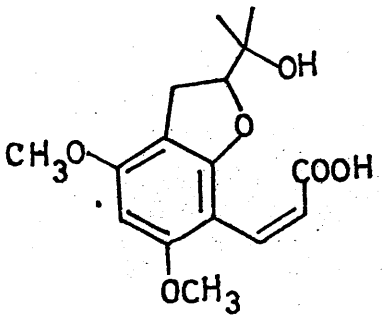

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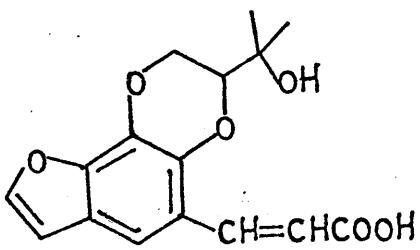
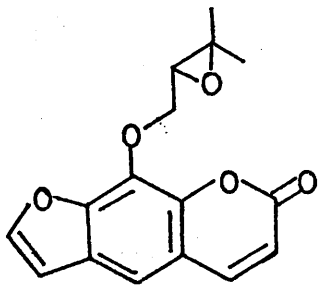


(72)



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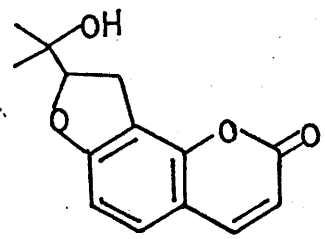

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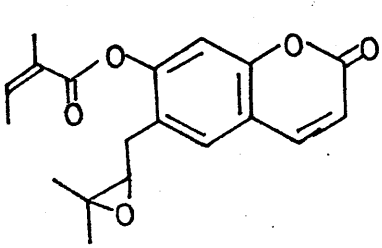

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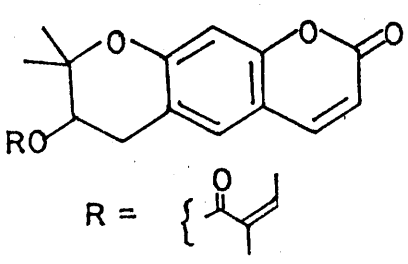

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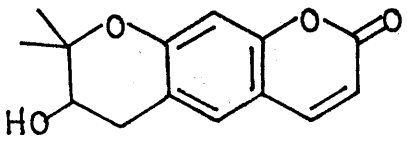


(54)

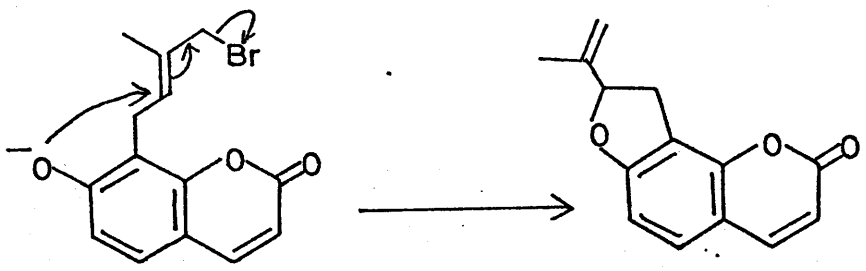
or (51) under alkaline conditions [92]. No evidence for these compounds could be adduced from the hydrolysis reactions.

It is interesting to note that the alternative reaction of the epoxyacetate (68) with base (Scheme 1.16), prcceeding via cleavage of the lactone ring, did not take place. This cyclisation has been reported by Seshadri et al[116] for sibiricin (70), a constituent of Seseli sibiricum. On treatment with 10% aqueous sodium hydroxide solution, sibiricin (70) yielded sibiricic acid, formulated as (71). A similar observation was reported by Noguti and Kawanami [117] who isolated isobyakangelicolic acid (72) on treatment of byakangelicol (73) with alcoholic potassium hydroxide at 220°. Undoubtedly the mild base(2% aqueous sodium carbonate) used in the hydrolysis of (68) to (16) prevented cleavage of the lactone ring.

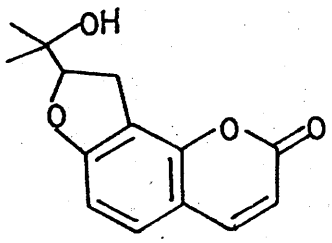
On the basis of our results a suggestion [110] by Lemmich and Nielsen can now be firmly discounted. (75) on saponification afforded, as its hydrolysis product, the pyranocoumarin (54). They suggested epoxyester (74) as a possible alternative structure for(75) on the supposition that hydrolysis would lead to an epoxyphenol which might cyclise to (54) under alkaline conditions. Clearly, from our observations,this could not occur, for a five-membered ring would be formed.

The successful total synthesis of (±)-columbianetin(16)

SCHEME 1.17



(76)



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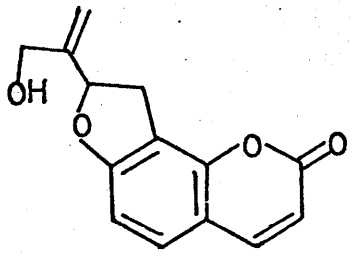

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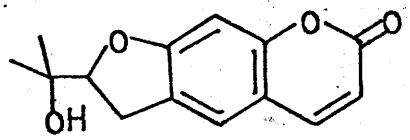

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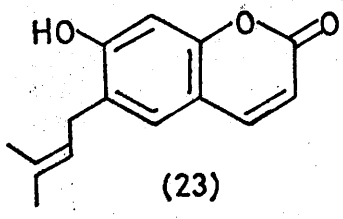
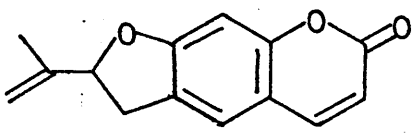


(23)

in this laboratory prompted investigation of its dehydration to the natural coumarin masquin [118](76) (angenomalin [119]). At the time the work was being carried out, this compound had also been isolated [120] as the glycoside of the corresponding ortho-hydroxycinnamic acid (majurin) from the fruits of Ammi majus by Abu-Mustafa, El-Bay and Fayez. Its synthesis, albeit in very low yield, was accomplished by Bohlmann [97] (Scheme 1.17) but it was felt that dehydration of the tertiary alcohol (16) might constitute a much more convenient pathway to this natural coumarin. The possibility of further oxidative elaboration of the side chain to discophoridin (77), a constituent of Velleia discophora[121], was then anticipated.

It was decided at the outset to try the reaction sequence first on (±)-marmesin (7) as this was much more readily available than columbianetin from a very generous gift of 7 - demethylsuberosin (23) made to this laboratory by Dr. T.J. King (Nottingham).

Treatment of (±)-marmesin (7) with thionyl chloride in pyridine at 0^{o} furnished a brown residue which, on purification by preparative t.l.c., gave two compounds. The major component of the reaction mixture (48%) had informative n.m.r. signals at δ 1.80 (3H;s.) (vinyl methyl group) 3.03 (1H;d.d.J 15 and 8Hz.) and 3.37 (1H;d.d.J 15 and 8Hz.) (benzylic methylene protons AB quartet coupled to the angular proton), 4.93 (1H;bd.;J 1Hz.) and 5.10 (1H; bd.;J 1Hz.) (olefinic protons exhibiting a typically small



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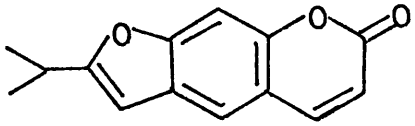

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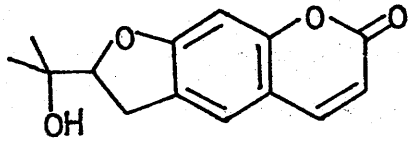

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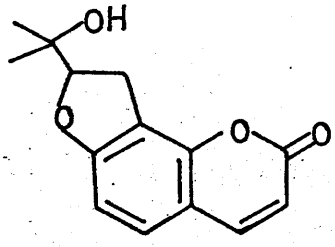

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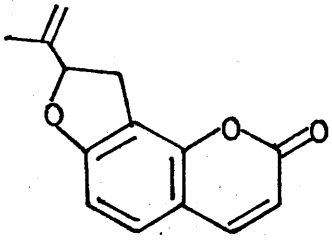

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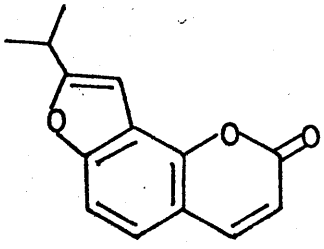

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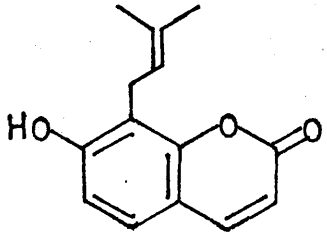


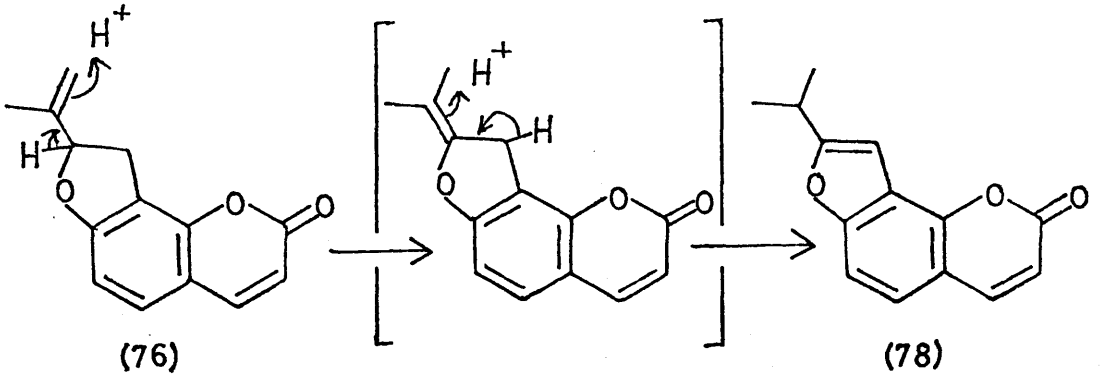
(32)

geminal coupling constant [122]) and finally 5.27(1H;t.;J 8Hz.)(angular proton resonance) in addition to the normal resonances of the coumarin nucleus. This compound was assigned structure (78).

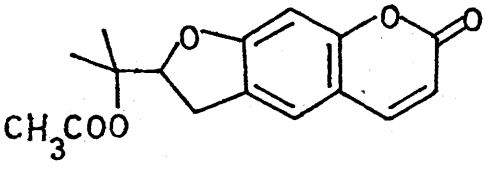
The minor component of the reaction mixture (24%) exhibited n.m.r. resonances at δ 1.38(6H;d.J 7Hz.), 3.10(1H;m.;J 7Hz.) attributable to an isopropyl grouping and an extra singlet(one proton) in the aromatic region. Structure (79) was given to this material on the basis of its melting point (133-136°)(lit.[88] m.p. 136-137°) and the n.m.r. data. This compound alone was isolated [88]by King on dehydration of (±)-marmesin (7) by refluxing for 5 hr. with phosphoric oxide in benzene.

This result encouraged us to try the dehydration conditions on (±)-columbianetin (16). Taking care in the work up to avoid excessive exposure to acid, thionyl chloride-pyridine treatment of (16) afforded no better than a 1:1 ratio of the corresponding angular compounds (76) and (80), as determined by n.m.r. These were inseparable by preparative t.l.c. even when silver nitrate-impregnated silica was used. This disappointing observation seemed to parallel the general acid-sensitivity displayed by osthenol (32) towards oxidative cyclisation. That the dehydration conditions and work up procedure were acidic was beyond doubt,and it was considered that acid-catalysed migration of the double-bond from its exocyclic position to the furan ring was taking place.

SCHEME 1.18



(76) (78)



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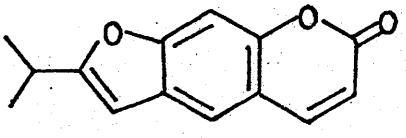

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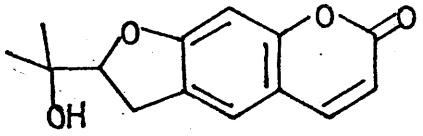

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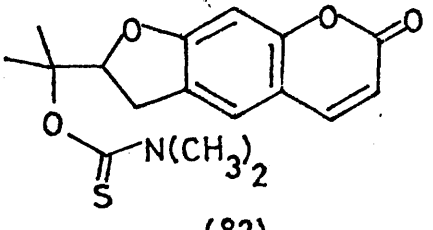
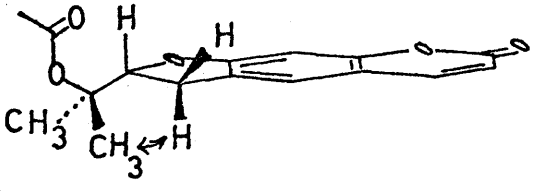


(82)

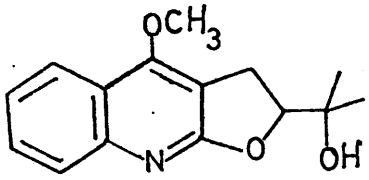
FIGURE 1.19



The conformational requirement for isopropylidene formation introduces steric repulsion.

(Scheme 1.18) Previous workers have isolated isopropylfurocoumarins in good yield from highly acidic dehydration conditions[66,67,123]. Unfortunately the double bond seemed to be more sensitive in the case of masquin(76), than it was for the linear isomer(78).

Examination of molecular models led us to believe that acetate pyrolysis might favour exomethylene double-bond formation over the competing reaction which produced the isopropylidene system. Consideration of the cyclic mechanism involved[124] and the preferred conformation of the acetate (81) seemed to indicate that there might be a preference for the former (Figure 1.19). With this in mind the acetate (81) was pyrolysed at 260° for 5 mins. on a very small scale. Examination of the products by analytical t.l.c. indicated only partial conversion of the starting acetate but the ratio of (78) to (79) seemed to be much higher than in the thionyl chloride reaction, in accordance with the prediction. It was decided at this stage to attempt the preparation of a derivative, in practice a dimethylthiocarbamate[125], which would eliminate at a much lower temperature than the acetate, but by a similar mechanism. Unfortunately , however, despite several attempts, reaction of the alcohol (7) with sodium hydride in dimethylformamide followed by dimethylthiocarbamoyl chloride failed to produce any of the hoped-for derivative (82). Newman, in his paper on the subject[125], described successful derivative formation for mainly primary and secondary



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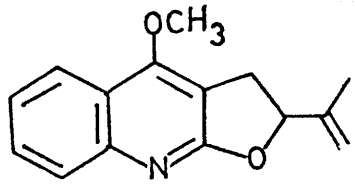

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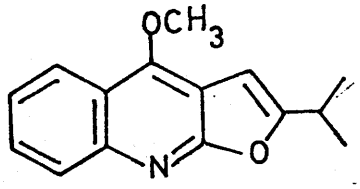

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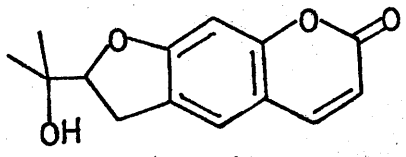

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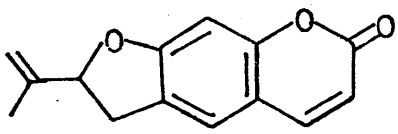

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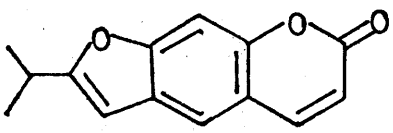

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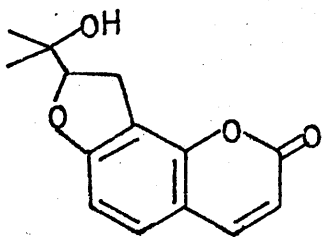

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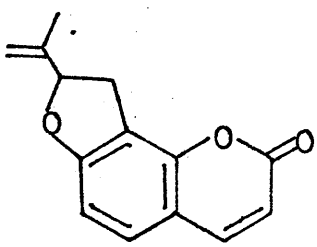

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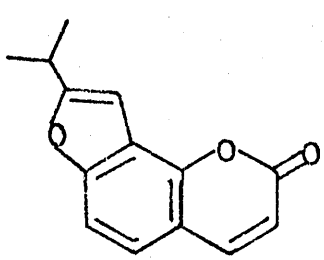


(80)

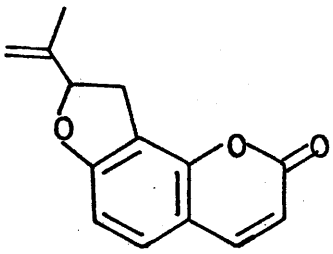
alcohols. One tertiary alcohol, namely 2-phenylpropan-2-ol was, however, successfully taken through the procedure.

Grundon and James[126], in an analogous system, used triphenylphosphite dibromide to dehydrate the tertiary alcohol (83) to the olefin (84) in 48% yield, producing 23% of the isopropylfuran (85) as by-product. This reagent seemed to offer no advantage over thionyl chloride for the reaction in hand as their yields were very similar to ours.

In 1972 Lomas et al published a paper[127] in which they stated that tertiary alcohols could be dehydrated when refluxed with hexamethylphosphoramide. Furthermore, they were of the opinion that the mechanism of the dehydration was like that of ester pyrolysis, but much less severe in that elimination proceeded smoothly at the boiling-point (220^{o}).

When this reaction was tried on (±)-marmesin (7) the advantages of having a non-acidic work up became apparent. The yields were 60% for the major olefin (78) and 30% for the unwanted furan (79), after chromatography, representing a substantial increase in the yield of the exomethylene isomer as compared with the thionyl chloride dehydration.

Use of the same procedure with (±)-columbianetin (16) as substrate, established the hexamethylphosphoramide method as being the best to date. After chromatography, a 64% overall yield of a mixture of the olefin (76) and (80) (n.m.r.) was obtained. The n.m.r. spectrum of the mixture



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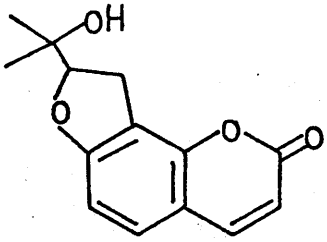

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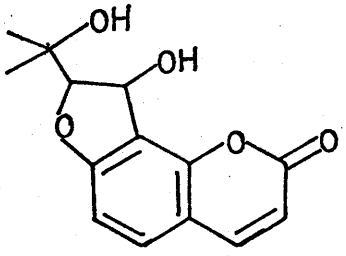

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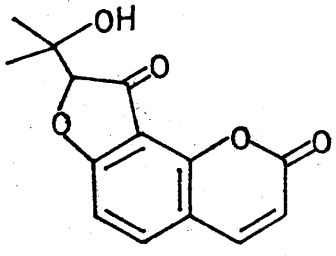

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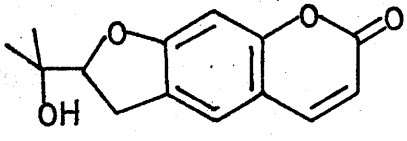
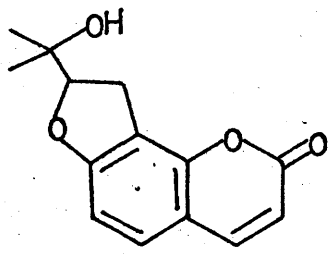


(7)

indicated the predominance of masquin (76) by ~3:1. Unfortunately, as before, this mixture, although just separable on an analytical t.l.c. plate (chloroform x 1 or 30% ethyl acetate-light petroleum x 1 or 30% ether-light petroleum x 1) could not be resolved by preparative t.l.c. on either conventional plates or on plates made with silica impregnated with siver nitrate. This procedure remains the most efficient method of dehydrating (±)-columbianetin (16) to masquin (76). The problem of separation of the product from the unwanted isopropylfuran was never solved.

Another type of intermediate postulated [56] to be a biogenetic link in the formation of furocoumarins in plants was the diol (33). Again, the availability of labelled material would greatly expedite the elucidation of the *in vivo* pathway. It should be seen that only one step, a benzylic oxidation, is necessary to convert (±)-columbianetin (16) to (33). Several approaches to this were considered, namely :- direct oxidation to either the alcohol (33) or the ketone (86) by chemical means, photolytic oxidation, and benzylic bromination followed by displacement of the bromine atom with hydroxide ion.

The first of the direct oxidation methods to be tried was selenium dioxide in 20% aqueous dioxan. (±)-Marmesin (7) was recovered unchanged after refluxing for 14hr. under these conditions, and (±)-columbianetin (16) was totally resistant to attack over a 5-day reflux, despite addition of freshly-sublimed reagent at various intervals.



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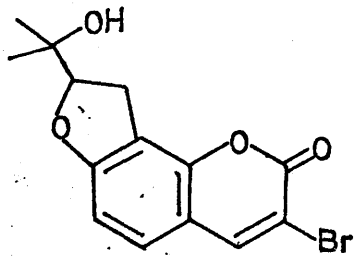


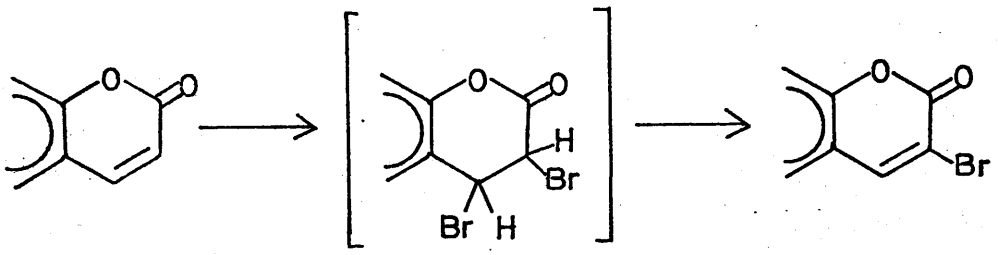
(87)

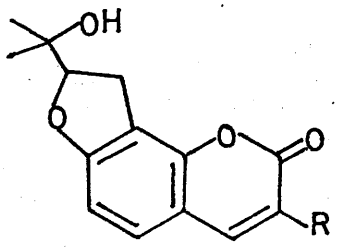
Nor was any useful oxidation of (16) achieved with lead tetra-acetate. After 1 day at R.T. no reaction occurred at all. Heating the reaction mixture only produced extensive decomposition of the starting alcohol (16) to give a multiplicity of products, none of which was isolated.

Various chromium reagents were tried on (±)-columbianetin (16). Sodium chromate-acetic anhydride-acetic acid at 40° had little effect over a 2-day period. Although recovery of starting material was low (23%), no products were detectable on t.l.c. Direct Jones reagent oxidation again gave a very low recovery of organic material (~15%) after 2 days at R.T. The reaction mixture here consisted of at least three components and was not investigated further. Reaction of (±)-columbianetin (16) with a 2% solution of chromyl chloride in carbon tetrachloride-acetic acid for 1hr. at R.T. yielded mainly the starting alcohol (16) and very polar decomposition products.

Attention was then directed to bromination of the benzylic methylene group. Reaction of N-bromosuccinimide with (16) in 20% aqueous dioxan resulted in almost instantaneous conversion to a new compound. The n.m.r. of this material was unusual in that the pyrone ring of the coumarin nucleus had undergone modification, the usual AB quartet system exhibited by the 3- and 4-protons was missing, and a singlet had appeared at δ8.00, close to the position of the 4-proton resonance of (±)-columbianetin (16). The compound was, therefore, assigned structure (87), that

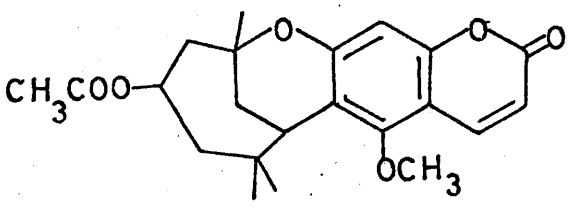
SCHEME .1 20





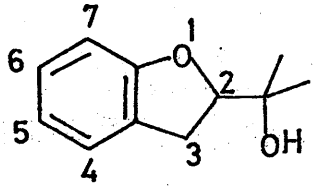
(16) : R = H

(87) : R = Br

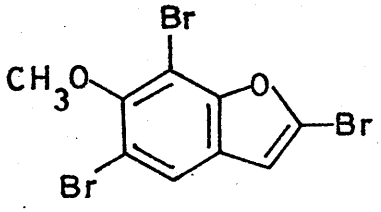


(88)

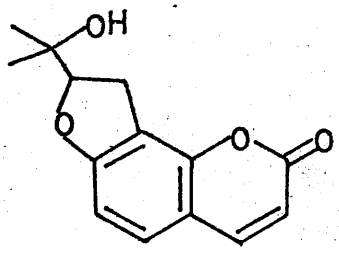
of 3-bromocolumbianetin. This reaction is well documented for coumarins [128] and is thought to proceed [5] by initial addition of bromine across the 3-4 double bond of the pyrone ring, followed by elimination of the elements of hydrogen bromide from the resulting dibromo-compound (Scheme 1.20). The reason it occurred here was presumed to be the essentially ionic conditions employed. Breakdown of the N-bromosuccinimide under visible light irradiation must have been exceedingly fast in the presence of the relatively large amount of water. Consequently a second experiment was tried in which steps were taken to remove water from the dioxan before use. After refluxing the solvent over solid potassium hydroxide pellets for 12hr., followed by distillation, repetition of the reaction of (±)-columbianetin (16) with N-bromosuccinimide resulted in much slower product formation, even with tungsten lamp irradiation. After 16hr., however, work up afforded only 3-bromocolumbianetin (87) again. A third reaction was attempted using carbon tetrachloride as solvent. After refluxing the alcohol (16) with N-bromosuccinimide in carbon tetrachloride for 19hr. under visible irradiation, no observable reaction had then taken place. Here it must be presumed that the hoped-for decomposition of the reagent to bromine atoms had not taken place, or else was exceedingly slow. In this context, a very recent paper by Jeffries and Worth [15] includes a successful benzylic bromination of the coumarin (88) using N-bromosuccinimide in carbon tetrachloride in conjunction with a radical



(89)



(27)

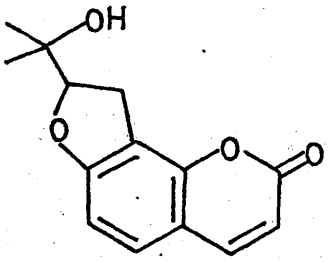


(16)

initiator, benzoyl peroxide. This would undoubtedly have speeded up radical decomposition of the reagent. Birch[52], on the other hand was unable to isolate any benzylic bromides when he used these conditions. He also encountered the stability of the hydroxyisopropyldihydrofuran system towards benzylic functionalisation when he unsuccessfully tried to oxidise (89). One equivalent of N-bromosuccinimide with benzoyl peroxide in carbon tetrachloride gave only the nuclear substituted 5-bromoderivatives of (89), whereas an excess caused dehydrgenation to the benzofuran with the hydroxyisopropyl side chain remaining intact. Activation of the system by the introduction of a para-methoxyl substituent was necessary before any evidence of the required reaction was obtained. Even then, the required product could not be isolated. When one equivalent of reagent was used, mononuclear bromination was the only reaction observed, as before. Use of a four-fold excess, however, resulted in 55% yield of the tribromo-compund(27). Presumably a benzylic bromide was an intermediate in the formation of this material, but the extent of nuclear substitution may have been a reflection on the forcing conditions found necessary to achieve the required benzylic functionalisation.

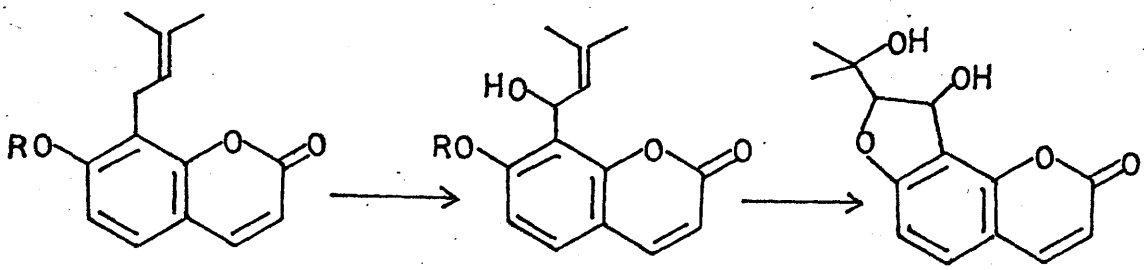
Substitution of this type on (16) had already been observed by us without the use of a radical initiator to decompose the N-bromosuccinimide.

The successful benzylic bromination achieved by Jeffries and Worth [15] is a strong indication, however, that this



(16)

SCHEME 1.21



90 : R = -OCCH$_3$ (91) (33)

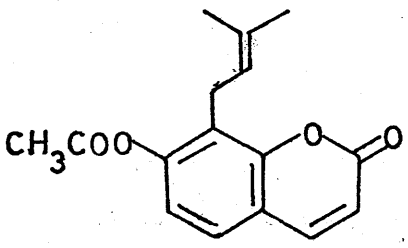
combination of reagents holds the most promise for the required functionalisation of (±)-columbianetin (16), despite the failure of Birch to isolate a compound of the hoped-for type. Unfortunately, these conditions were not tried on the alcohol (16).

Cobalt acetate bromide has been reported [129] as a very efficient oxidising agent for benzylic methylene groups. Accordingly, (±)-columbianetin (16) was added to a blue solution of the reagent generated from cobalt acetate and benzyl bromide in acetic acid. Oxygen was bubbled through the mixture during the 1½hr. reflux but unfortunately work up yielded only starting material as oily crystals, contaminated with products derived from benzyl bromide (n.m.r.).

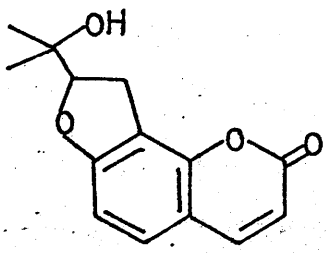
A similar resistance to oxidation was exhibited towards the conditions of Daniher[130]. Thus, exposure of the alcohol (16) to ammonium persulphate and silver nitrate in 50% aqueous ethanol for 5hr. at 65-75° gave only starting material on work up.

As a last resort, the photo-oxidation reaction of Mazur[131] was tried. A very dilute solution of (16) in t-butanol containing mercuric bromide was photolysed using a high pressure Hanovia lamp (254nm.). After work up, t.l.c. indicated extensive decomposition, which was confirmed by n.m.r.

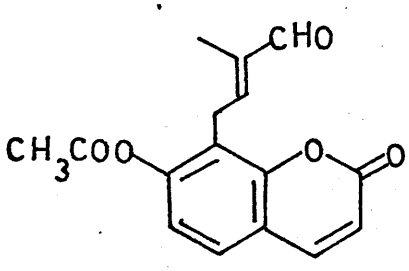
At this point it was decided that a better approach to the diol (33) might be made by attempting the benzylic oxidation prior to the cyclisation reaction (Scheme 1.21),



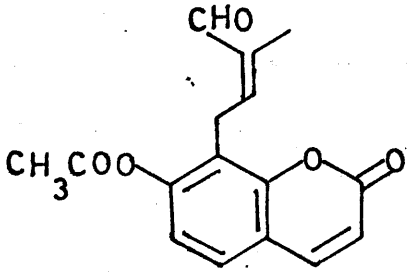
(90)



(16)



(92)

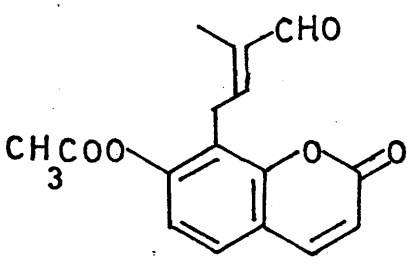


(93)

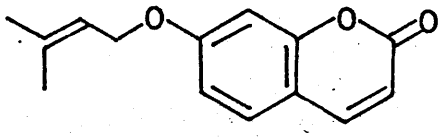
when the methylene group is doubly activated. Osthenol acetate (90) was chosen as the substrate. Lead tetra-acetate in benzene-acetic acid gave the same disappointing results as for (±)-columbianetin (16), a 2-day reflux producing only decomposition products and starting material.

On reaction with selenium dioxide, however, (90) gave a very good yield (92%) of a new compound having an n.m.r. signal at δ 9.36(1H;s) attributed to an aldehydic proton resonance, and a single vinyl methyl group resonance at δ 1.95 which could be resolved as a very close doublet (J 1.5 Hz.). The characteristic resonance of the acetate protons was also present at δ 2.34 but the triplet typical of the olefinic proton of the 3,3-dimethylallyl moiety had undergone a significant shift downfield from δ 5.15 in osthenol acetate (90) to δ 6.44 in this new compound, and appeared as a multiple resonance with the secondary coupling constant 1.5 Hz. The presence of the aldehyde grouping was confirmed by the appearance of a weak band at 2710cm.$^{-1}$ in the infra-red, and also a strong band at 1694cm.$^{-1}$, due to a new $\alpha\beta$-unsaturated system.

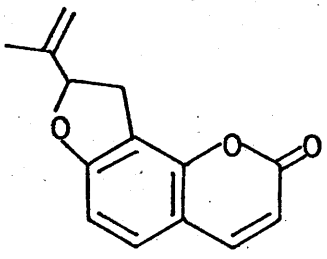
Evidently, allylic oxidation had taken place, not at the doubly activated methylene group, but at one of the terminal methyl groups, giving either (92) or (93). Coupling between the methyl group and the vinyl proton was established by decoupling experiments. Irradiation at the methyl resonance collapsed the



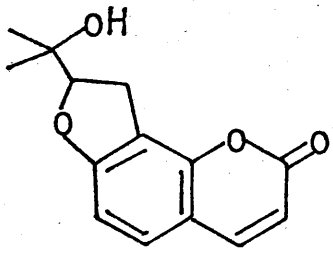
(92)



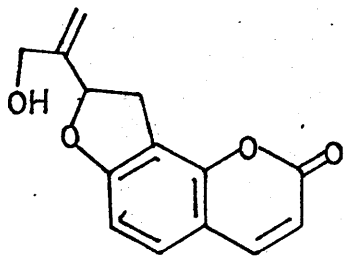
(94)



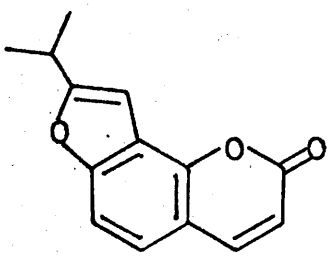
(76)



(16)



(77)



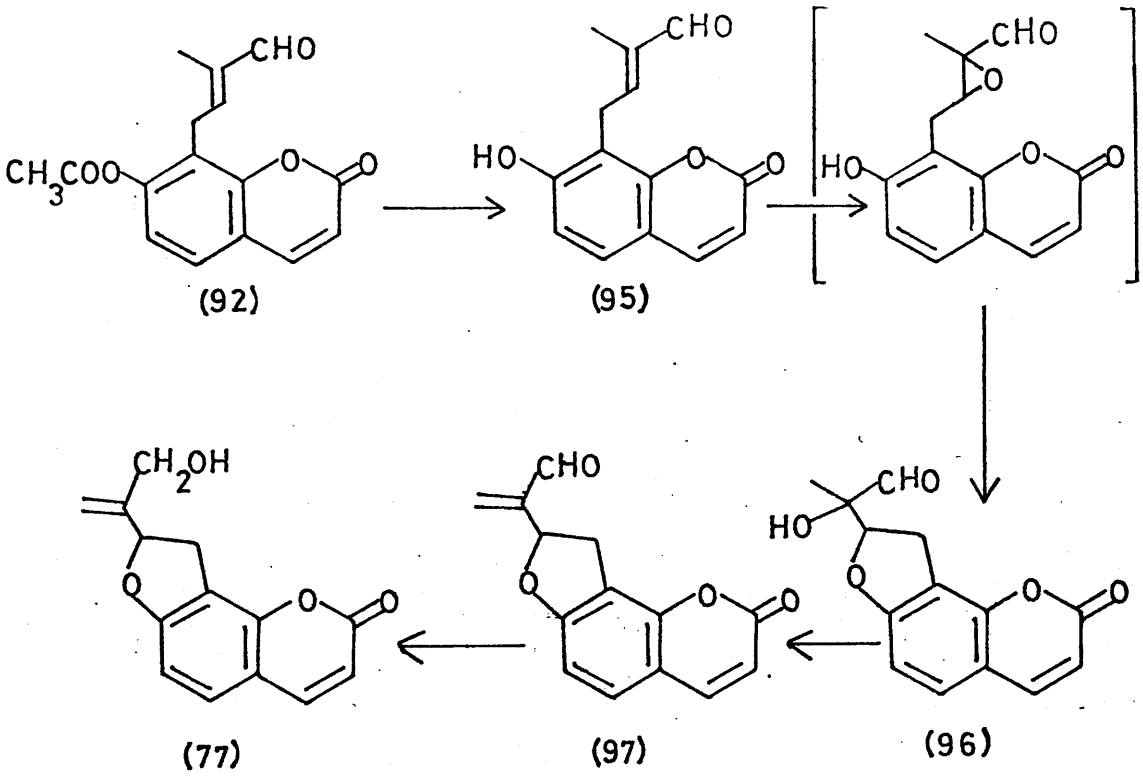
(78)

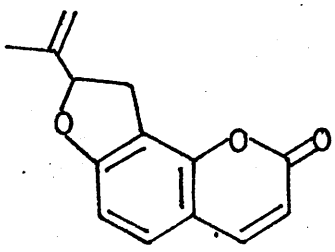
multiplet to the"normal" triplet shape seen for the 3,3-dimethylallyl group, whereas irradiation at the benzylic methylene proton resonance caused its collapse to a close quartet. That the aldehyde group and the benzylic carbon had a trans relationship was established by the chemical shift of the aldehyde proton[132] (δ 9.36), cis aldehydes giving a signal in the δ 9.9 region. The aldehyde was, therefore, assigned structure (92).This is in accord with Rapoport's findings[133] for oxidation of other isopentenyl moieties, and with a recent publication[134] by Lassak and Southwell who carried out the same reaction on umbelliferone 3,3-dimethylallylether (94). They arrived at the same conclusion with regard to the molecular geometry from nuclear Overhauser Studies.

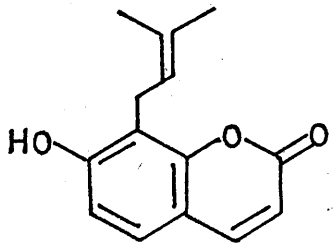
The possible application of this reaction became immediately obvious. It had been hoped earlier in the work that masquin (76), obtained by dehydration of columbianetin (16), could be allylically oxidised to the natural coumarin discophoridin (77). Two serious drawbacks to this approach were apparent. Not only was masquin (76) found to be inseparable from the isomeric furan (78), but also its double-bond was exceedingly labile in the acidic conditions normally used for allylic oxidation. The aldehyde (92) represented a much more viable starting point.

The projected route to discophoridin (77) from the

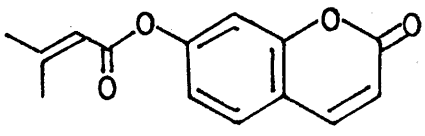
SCHEME 1.22



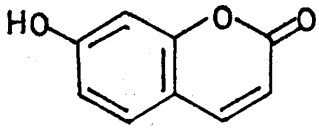

(76)



(32)



(98)



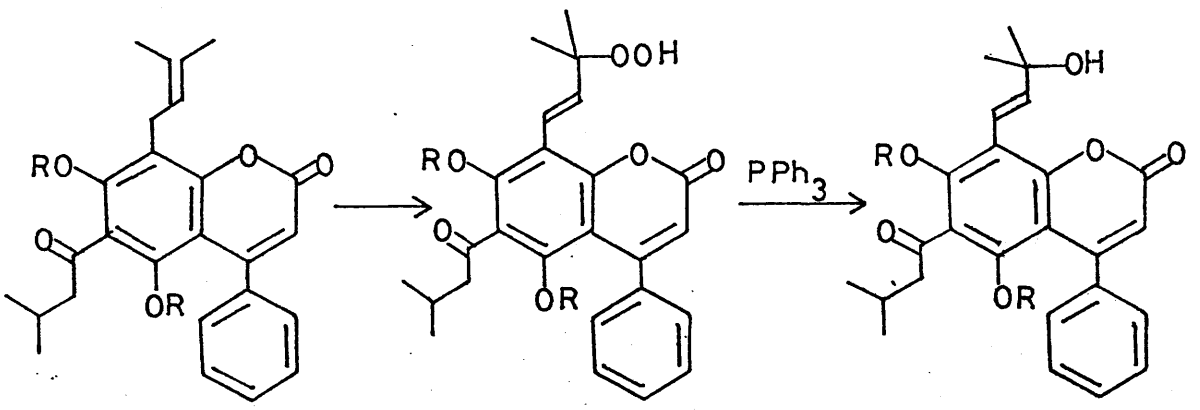
(4)

aldehyde (92) is shown in Scheme 1.22. Preliminary studies have indicated that the acetate grouping in (92) is readily hydrolysed under the normal epoxidation conditions employed [135] for $\alpha\beta$-unsaturated carbonyl compounds. Reaction of (92) with 2% sodium carbonate and 30% hydrogen peroxide for 10 mins. furnished a compound with no acetate proton resonance in its n.m.r. and with the $\alpha\beta$-unsaturated aldehyde system apparently still intact (n.m.r., i.r. and molecular weight from mass spectrum). This compound almost certainly has structure (95). Slightly more forcing conditions in the epoxidation should lead to the tertiary alcohol (96) which hopefully would dehydrate into conjugation to (97), without the concomitant rearrangement of the double bond into the furan ring which takes place so readily for masquin (76). A straightforward borohydride reduction would then afford synthetic discophoridin (77). This last reaction has ample precedent in the coumarin field [97,136] and no complications are envisaged.

A third general method of approach to a benzylically substituted osthenol (32) derivative has been made in this laboratory [137]. 7-O-Senecionylumbelliferone(98) was prepared by reaction of the free phenol (4) with senecionyl chloride. All attempts at Fries rearrangement of this material, however, have so far failed.

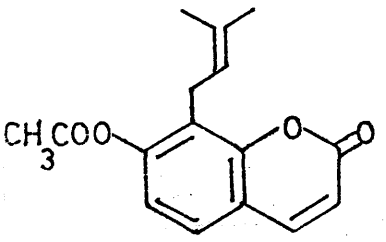
Another method for benzylic functionalisation was

SCHEME 1.23

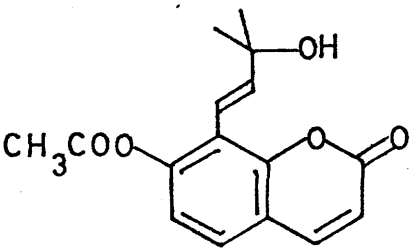


(99) (100) (101)

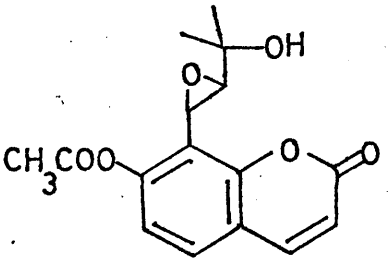
R = -OCCH$_3$



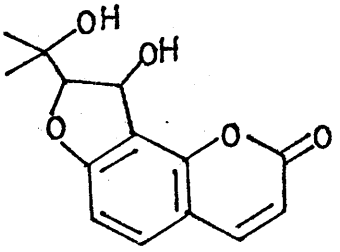
(90)



(102)



(103)



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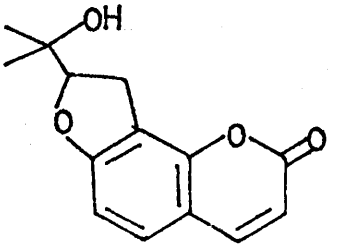

(16)

suggested by the work of Polonsky[138]. She was able to carry out an oxidation/rearrangement on the coumarin (99) (Scheme 1.23) using a haematoporphyrin-catalysed photo-oxidation. Reduction of the intermediate hydroperoxide (100) led to the isolation of the allylic alcohol (101). If this sequence were carried out on osthenol acetate (90), the alcohol (102) would be the expected product. Subsequent epoxidation and hydrolysis might then lead, through (103), to the diol (33).

Although (33) has eluded all attempts at synthesis, it is possible that one of the many allylic oxidations outlined earlier in this discussion will have the required affect on osthenol acetate (90) and will satisfactorily functionalise the benzylic methylene group.

The peroxide-initiated radical decomposition of N-bromosuccinimide and its reaction with (16) remains a promising, but tantalisingly unknown, quantity.

Some of the work described in Part 1 of this thesis has been summarised in a publication[139].

General Experimental

and abbreviations.

Melting points are uncorrected and were determined on a Kofler hot-stage apparatus. Microanalyses were obtained by Mr. J.M.L. Cameron, Miss F. Cowan and their staff. Mass spectra were recorded by Mr. A. Ritchie and Miss M.Laing on an A.E.I. - G.E.C. MS 12 instrument. Infra-red spectra were recorded by Mrs. F. Lawrie and her staff on a Perkin Elmer 225 spectrophometer or on a Unicam SP100 instrument, using either carbon tetrachloride or chloroform as solvent. All ultra-violet spectra were recorded for ethanol solutions on a Unicam SP800 spectrophotometer; λ_{max}(base) refers to the above solution to which two drops of 4N sodium hydroxide had been added. Nuclear magnetic resonance spectra were recorded by Miss S.Cathcart, Miss M. Laing, Miss J. MacSwan, Mr. A. Haetzman or Mr. J. Gall on a Varian T-60, a Jeol C60 HL or a Varian HA 100 spectrometer, using tetramethylsilane as internal standard. Unless otherwise stated, nuclear magnetic resonance spectra were recorded using deuterochloroform as solvent. All spectra recorded on the Varian HA100 are indicated by 100 MHz. Kieselgel G (Merck) was used for preparative thin layer chromatography (t.l.c.). Alumina refers to Woelm basic, grade 1.

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

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

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

The solvents used for preparative chromatography are expressed as a percentage volume, e.g. 30% ethyl acetate-light petroleum is equivalent to ethyl acetate and light petroleum in a volume ratio of 3:7. The number of elutions required for separation are indicated, after the solvent, by e.g. $x\frac{1}{3}$ x1. This infers that the chromatoplate was eluted to a distance of one-third of its length from the application line, allowed to dry and then eluted again to its full length (N.B. $x2 \equiv x1x1$).

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

Analytical t.l.c. was always employed for comparison purposes. If two compounds are said to be identical, this includes with respect to t.l.c. behaviour.

During the course of this research, crude reaction

mixtures were often worked up by one of two methods. These have been refered to in the Experimental Section as "work up (1)" and "work up (11)".

Work up (1)

O-alkylation of a hydroxy-coumarin was achieved by refluxing an acetone solution of the coumarin with the alkylating agent in the presence of potassium carbonate. When the reaction was complete, all solid material was removed by filtration and the filtrate evaporated. The residue was then dissolved in a mixture of ethyl acetate and brine, and the organic layer washed with 0.5%w./v. aqueous potassium carbonate solution to remove any starting material. Subsequent washing with brine to neutrality, drying and evaporation of solvent gave a residue which was treated as specified in each preparation.

Thr remaining inorganic solids (vide supra) were acidified with dil. hydrochloric acid and the whole extracted with ethyl acetate. The organic layer was then washed to neutrality with brine, dried and evaporated, to yield unreacted starting material.

Work up (11)

This was employed for any reaction mixture containing pyridine or hexamethylphosphoramide. The reaction was allowed to cool to R.T., poured into a large excess of iced water, and left for at least three hours. Extraction into ethyl acetate, followed by repeated washings with brine, drying and evaporation yielded a residue which was treated as specified in each preparation.

The following abbreviations and symbols have been used in the Experimental Sections:-

b.	broad :
d.	doublet :
m.	multiplet :(in n.m.r. spectra)
q.	quartet :
s.	singlet :
t.	triplet :
i.r.	infra-red.
r.a.	relative abundance(in mass spectra).
R.T.	room temperature ($\sim 20^{\circ}$).
sh.	shoulder (in u.v. spectra).
u.v.	ultra-violet.
n.m.r.	nuclear magnetic resonance.
t.l.c.	thin layer chromatography.
w./v.	e.g. 1% w./v.; this refers to a solution of 1g. in 100ml. solvent.
dil.	dilute; 4N.
p.	page number.
•	e.g. 6.31°;this refers to a signal in an n.m.r.spectrum which disappears on addition of deuterium oxide to the solution.

PART 1

Experimental

Umbelliferone (4)

Prepared [140] by the method of Dey, Rao and Seshadri using resorcinol, malic acid and conc. sulphuric acid. The crude product was sublimed at 160-200°/0.1mm. and then crystallised from methanol. This gave umbelliferone (4) as pale yellow needles, m.p. 228-230°(lit.[140] m.p. 223-224°); λ_{max} 216, 244, 253 and 326 nm.(log.ϵ 4.08, 3.49, 3.38 and 4.18); λ_{max}(base) 233, 242(sh.) and 375 nm.(log.ϵ 3.96, 3.88 and 4.31).

Osthenol (32)

The reaction sequence described by Murray, Ballantyne and Mathai[41] was used to prepare the phenolic coumarin(32). In a typical synthesis, umbelliferone (4)(4.42g.) on reaction with 2-methyl-2-chloro-3-butyne furnished the acetylenic ether (56)(4.29g., 69%) which was hydrogenated over 5% w./w. palladium-charcoal poisoned with sulphur-quinoline to yield the allyl ether (57) (4.32g., 98%). After pyrolysis and subsequent purification by preparative t.l.c., (30% v./v. ether-light petroleum x3, then 80% v./v. chloroform-light petroleum x2) pure osthenol (32)(1.43g.,33%) and a mixture of osthenol and 7-demethylsuberosin (23)(1.05g., 24%) were obtained. This latter mixture was stockpiled and repurified at a later date to afford more osthenol. (32) had n.m.r. signals at δ 1.70(3H;bs.), 1.82(3H;bs.), 3.58(2H;d.;J 7Hz.), 5.28(1H;bt.;J 7Hz.), 6.25(1H;d.;J 9.5Hz.), 6.87(1H;d.;J 9Hz.), 7.20(1H; d.;J 9Hz.) and 7.63(1H;d.;J 9.5Hz.).

(±)-Columbianetin (16)

A cooled solution of m-chloroperbenzoic acid (62mg.) in dry ether (2ml.) was added to a solution of osthenol (32) (60mg.) in ether (15ml.) at 0^{0}. After 2½hr. more peracid (15mg.) was added and the mixture stirred at 0^{0} for 5hr. when t.l.c. indicated complete reaction. The mixture was filtered through a short column of alumina(0.5g) which was further eluted with ethyl acetate. Evaporation of the combined eluates gave (±)-columbianetin (16)(53mg.,83%) as needles (cloroform-light petroleum), m.p. 169-171° (lit.[95] 170-171°);n.m.r. signals at δ1.27(3H;s.), 1.37(3H;s.), 2.10°(1H;bs.), 3.30(2H; d,;J 10Hz.), 4.77(1H; t.;J 10Hz.), 6.15(1H; d.; J 9.5Hz.), 6.72(1H; d.;J 9Hz.), 7.22(1H; d.;J 9Hz.), and 7.58(1H;d.;J 9.5Hz); $\nu_{max}^{CCl_4}$ 3620, 3598 and 1745cm.$^{-1}$, mass spectral peaks at m/e 246 (M^{+}), 213, 188, 187, 176, 175, 160, 159, 131, 77 and 59(r.a. 43, 17, 86, 100, 15, 16, 37, 16,24, 17 and 70%).

(±)-Lomatin (46)

A solution of m-chloroperbenzoic acid (50mg.) in AnalaR chloroform (2ml.) was added to a solution of osthenol (32) (49mg.) in acidified chloroform (1ml.)(prepared by shaking AnalaR chloroform (50ml.) with 2 drops of conc. hydrochloric acid) at 0^{0}. After 20mins. work up as above gave (±)-lomatin (46) (40mg. 76%) as colourless needles (ethyl acetate-light petroleum), m.p. 163-164° (lit.[141] 165-166°); n.m.r. signals at

δ 1.35(3H;s.), 1.38(3H;s.), 2.42°(1H;bs.), 2.98 and 3.05(2H;dd;J 17 and 5Hz.), 3.87(1H;t.;J 5Hz.), 6.20 (1H;d.;J 9.5Hz.), 6.75(1H;d.;J 9Hz.), 7.22(1H;d.;J 9Hz.), and 7.57(1H;d.;J 9.5Hz.); mass spectral peaks at $^{m}/e$ 246(M^+), 213, 188, 187, 177, 176, 175, 147, 91, 77, 71 and 43 (r.a. 43, 12, 14, 12, 13, 100, 62, 13, 17, 11, 22 and 42%); $\nu_{max}^{CHCl_3}$ 3630, 3592, 1722 and 1605 $cm.^{-1}$

(±)- Marmesin (7)

7-Demethylsuberosin (23)(23mg.) was dissolved in ethyl acetate (3ml.) and a solution of m-chloroperbenzoic acid (20mg.) in ethyl acetate (3ml.) added at 0°. After 4hr. at this temperature work up by elution through a short alumina column afforded (±)-marmesin(7) (17mg. 71%) as colourless plates after crystallisation from benzene, m.p. 150-152°(lit.[88] m.p. 152-153°); n.m.r. signals at δ 1.27(3H;s.), 1.38(3H;s.), 2.33°(1H; bs.), 3.22(2H;d.;J 9.5Hz.), 4.73(1H;t.;J 9.5Hz.), 6.13 (1H;d.;J 9.5hZ.), 6.62(1H;s.), 7.17(1H;s.) and 7.53 (1H;d.;J 9.5Hz.); mass spectral peaks at $^{m}/e$ 246(M^+), 213, 189, 188, 187, 175, 160, 159, 131, 77 and 59 (r.a. 49, 24, 12, 85, 100, 16, 34, 14, 24, 15 and 60%); $\nu_{max}^{CCl_4}$ 3621, 3596, 1740 and 1625 $cm.^{-1}$ All spectral data for this compound were identical with that obtained from a natural sample of (±)-marmesin.

(±)-Decursinol (54)

A solution of m-chloroperbenzoic acid (210mg.) in acidified chloroform (3ml.)(prepared by shaking AnalaR chloroform (50ml.) with 2 drops of conc. hydrochloric

acid) and a solution of 7-demethylsuberosin (23) (207mg.) in acidified chloroform (3.5ml.) were mixed and kept at 0° for 1hr. Work up as above gave (±)-decursinol (54)(169mg., 76%) as a colourless solid. Crystallisation from ethyl acetate-light petroleum furnished needles, m.p. 167-168°(lit.[110] 167.5-168.5°); n.m.r. signals at δ 1.38(6H;s.), 2.63°(1H;d.;J 6Hz.), 2.87 and 3.00(2H;dd.;J 17 and 5Hz.), 3.85(1H;m.; collapses to t.,J 5Hz., on addition of D_2O), 6.12 (1H;d.;J 9.5Hz.), 6.68(1H;s.), 7.12(1H;s.) and 7.52 (1H;d.;J 9.5Hz.); mass spectral peaks at $^m/_e$ 246(M^+), 213, 188, 187, 177, 176, 175, 148, 147, 91, 77, 71, 69, 51 and 43(r.a. 59, 10, 18, 13, 13, 100, 100, 11, 28, 15, 17, 27, 18, 17 and 53%); $\nu_{max}^{CCl_4}$ 3632, 3588, 1742, 1625 and 1129 $cm.^{-1}$

Decursinol acetate (67)

A solution of the alcohol (54) (90mg.) in acetic anhydride (0.9ml.) and pyridine (0.9ml.) was refluxed for 5mins. with stirring. Work up 11 afforded the acetate (67) as a pale yellow solid (96mg.,91%) which, on crystallisation(aqueous ethanol), gave colourless needles, m.p. 182-183°; n.m.r. signals at δ 1.37(6H;s.), 2.07(3H;s.), 2.83(1H;d.d.;J 17 and 5Hz.), 3.23(1H;d.d.;J 17 and 5Hz.), 5.07(1H;t.;J 5Hz.), 6.23(1H;d.;J 9.5Hz.), 6.78(1H;s.), 7.17(1H;s.) and 7.58(1H;d.;J 9.5Hz.); $\nu_{max}^{CCl_4}$ 1740, 1624 and 1134 $cm.^{-1}$

Marmesin acetate (81)

The alcohol (7) (24mg.) in acetic anhydride (1.5ml.)

to which had been added sodium acetate (57mg.) was refluxed for 5hr. Work up 11 gave the acetate as a brownish solid (30mg.); n.m.r. signals at δ 1.50 (3H;s.), 1.55(3H;s.), 1.97(3H;s.), 3.20(3H;d.;J 8Hz.), 5.10(1H;t.;J 8Hz.), 6.20(1H;d.;J 9.5Hz.), 6.73(1H;s.), 7.20(1H;s.) and 7.60(1H;d.;J 9.5Hz.).

Monoperphthalic acid

Prepared by the method of Payne [142]. Phthalic anhydride (28g.) was added to a mixture of 30% v./v. hydrogen peroxide (26ml.) and a solution of sodium carbonate (24.2g.) in water (95ml.) at 0°. Work up gave a solution of monoperphthalic acid in ether (900ml.), estimated as being 0.17M with respect to peracid by treating a known volume (2ml.) with potassium iodide solution and titrating the liberated iodine against 0.1N sodium thiosulphate solution. This solution was used for epoxidation reactions without further treatment.

Pilot scale epoxidations

A cooled (0°) solution of the phenol (5mg.) in solvent (0.5-3ml.) and a cooled solution of m-chloroperbenzoic acid (5mg.)(unless otherwise stated) in solvent (0.5-3ml.) were mixed and kept at 0° for 25-60 min. until no starting material could be detected by t.l.c. The dihydrofurocoumarins,(16)or (7)were readily distinguished from the dihydropyranocoumarins,(46)or(54),by t.l.c. in 0.5% v./v. methanol-chloroform (X1) with examination of the plate under

u.v. light (354nm.) and development with iodine.

(i) 7-Demethylsuberosin(23)

(a) With ethyl acetate, carbon tetrachloride, ether and AnalaR chloroform, only (7) was formed;

(b) with "bench" chloroform or AnalaR chloroform acidified with conc. hydrochloric acid, the mixture turned yellow after 10sec. After 5min. reaction was complete, the colour faded and only (54) was formed;

(c) with AnalaR chloroform and 1ml. of a saturated chloroform solution of 1-naphthalenesulphonic acid there was no colour change but after 1hr. a mixture of (7) and (54) (~3:1) was formed;

(d) with monoperphthalic acid in ether, only (7) was formed.

(ii) Osthenol (32)

(a) With ethyl acetate, carbon tetrachloride, and ether only(16) was formed;

(b) with "bench" chloroform only (46) was formed;

(c) with AnalaR chloroform a mixture (~1:2) of (16) and (46) was formed;

(d) with monoperphthalic acid in ether a mixture of (16) and (46)(~7:3) was produced.

Osthenol acetate

A solution of osthenol (32)(44mg.) in acetic anhydride (0.2ml.) containing pyridine (2 drops) was refluxed for 20mins. Work up 11 gave a colourless solid which, on crystallisation from aqueous ethanol, afforded the acetate as needles (44mg.,85%), m.p. 94-95°. (Found:

C,70.65;H, 5.85. $C_{16}H_{16}O_4$ requires C,70.57;H, 5.92%); n.m.r. signals at δ 1.68(3H;bs.), 1.82(3H;bs.), 2.35 (3H;s.), 3.48(2H;bd.J 7Hz.), 5.15(1H;bt.;J 7Hz.), 6.37 (1H;d.;J 9.5Hz.), 6.98(1H;d.;J 9Hz.), 7.33(1H;d.;J 9Hz.) and 7.63(1H;d.;J 9.5Hz.); $\nu_{max}^{CHCl_3}$ 1764, 1735 and 1605cm.$^{-1}$; mass spectral peaks at $^m/_e$ 272(M^+), 230, 229, 215, 201, 187 and 175 (r.a. 11, 87, 27, 32, 18, 43 and 100%).

7-Demethylsuberosin acetate.

7-Demethylsuberosin (23)(43mg.) was dissolved in acetic anhydride (0.2ml.) to which pyridine (2 drops) had been added and the mixture refluxed for 20mins. Work up 11 afforded the acetate (47mg.,92%) as prisms, m.p. 97-98° (lit.[88] m.p. 98-100°);n.m.r. signals at δ 1.70(3H;bs.), 1.77(3H;bs.), 2.35(3H;s.), 3.27(2H;bd.; J 7Hz.), 5.27(1H;bt.J 7Hz.), 6.35(1H;d.;J 9.5Hz.), 7.03(1H;s.), 7.28(1H;s.), and 7.63(1H;d.;J 9.5Hz.); $\nu_{max}^{CHCl_3}$ 1760, 1735 and 1630cm.$^{-1}$

Epoxidation of osthenol acetate.

A solution of osthenol acetate (450mg.) in ethyl acetate (15ml.) and a solution of 85% m-chloroperbenzoic acid (457mg.) in ethyl acetate (10ml.) were mixed at R.T. and stirred for 20 mins., when t.l.c. showed complete reaction. Any excess peracid was removed by diluting with ethyl acetate (30-40ml.) and washing the organic layer with half its volume of freshly prepared sodium sulphate solution (10% W./V.). Washing with brine to neutrality, drying and evaporation of solvent afforded the epoxyacetate (51) (500mg.,94%) as a colourless

glass which could be separated from traces of a polar compound also present by preparative t.l.c. (0.25% methanol-chloroform X1). The recovered epoxy-acetate, however, was always found to contain small amounts of this compound, identified as the alcohol (16)(t.l.c.).(51) shows n.m.r. signals at δ 1.32(3H;s.), 1.50(3H;s.), 2.38(3H;s.), 2.7-3.4(3H;m.), 6.37(1H;d.; J 9.5Hz.), 7.02(1H;d.;J 9Hz.), 7.38(1H;d.;J 9Hz.) and 7.65(1H;d.;J 9.5Hz.); $\nu_{max}^{CCl_4}$ 1770, 1747, 1605, 1188 and 1111cm.$^{-1}$; mass spectral peaks at $^{m}/e$ 288(M^+), 228, 213, 188, 187, 176, 175, 160, 131, 91, 77, 71, 44 and 43 (r.a. 4, 33, 73, 29, 20, 79, 73, 19, 17, 27, 23, 31, 73 and 100%).

Epoxidation of 7-demethylsuberosin acetate.

A solution of m-chloroperbenzoic acid (450mg.) in ethyl acetate (10ml.) and a solution of the acetate (464mg.) in ethyl acetate (18ml.) were mixed and kept at R.T. for 1½hr. The mixture was then diluted with ethyl acetate (50ml.) and washed with its own volume of 10% w./v. sodium sulphite solution. Repeated washing with brine to neutrality, drying and removal of solvent gave the epoxyacetate (69)(432mg.88%) as a colourless gum after purification by preparative t.l.c. (chloroform X1). (69) always contained small amounts of a very polar compound, later identified as the alcohol (7) and shows n.m.r. signals at δ 1.37(3H;s.); 1.40(3H;s.), 2.40(3H; s.), 2.6-3.1(3H;m.), 6.28(1H;d.;J 9.5Hz.), 7.02(1H;s.), 7.40(1H;s.), and 7.60(1H;d.;J 9.5Hz.); $\nu_{max}^{CCl_4}$ 1772, 1748,

1629, 1193 and 1110cm.$^{-1}$; mass spectral peaks at $^{m}/_{e}$ 288(M^{+}), 228, 213, 176, 175, 147, 91, 77, 73, 71, 61, 45, 43 and 41(r.a. 2, 15, 24, 39, 43, 14, 12, 12, 69, 27, 51, 28, 100 and 22%).

Hydrolysis of the epoxyacetate (51)

The epoxyacetate (51)(50mg.) in methanol (10ml.) was stirred for 1 min. with 2% w./v. sodium carbonate solution (1ml.) at R.T. Careful acidification with 0.1N hydrochloric acid followed by dilution with water (100ml.), extraction with ethyl acetate, washing to neutrality with brine, drying and evaporation of solvent furnished (16) as a colourless solid (43mg., 94%). Sublimation at 170°/0.02mm. and crystallisation (chloroform-light petroleum) afforded (±)-columbianetin (16) as colourless needles (m.p., n.m.r. and t.l.c.).

Hydrolysis of the epoxyacetate (69)

Using the same procedure as that employed for the hydrolysis of (51)(vide supra), the epoxyacetate (69) (70mg.), in methanol (5ml.), was stirred for 1 min. with 2% w./v. sodium carbonate solution (1 ml.) at R.T. Work up afforded (±)-marmesin (7)(57mg.;95%) as a colourless solid (m.p., n.m.r. and t.l.c.).

Dehydration of (±)-marmesin (7)

(a) A solution of (7)(18mg.) in dry pyridine (3ml.) was cooled to 0° and thionyl chloride (0.3ml.) added. After 15min. at 0°the reaction mixture was poured into iced water (100ml.) and stirred with solid sodium bisulphate until the mixture was in the range pH 3-4.

Extraction twice with ether, followed by washing to neutrality with brine, drying and evaporation of solvent gave a brownish residue (12mg.,72%) which, after purification by preparative t.l.c. (chloroform X1) furnished :-

(i) the olefin (78)(8mg.,48%) as a colourless solid (m.p.94-95°) from aqueous ethanol. (Found:C, 73.48; H, 5.35. $C_{14}H_{12}O_3$ requires C, 73.67; H, 5.30%);n.m.r. signals (CCl_4) at δ1.80(3H;s.), 3.03(1H;dd.J 15 and 8Hz.), 3.37(1H; dd.J 15 and 8Hz.), 4.93(1H;bd.;J 1Hz.), 5.10 (1H;bd.;J 1Hz.), 5.27(1H;t.;J 8Hz.), 6.03(1H;d.;J 9.5Hz.), 6.63(1H;s.), 7.13(1H;s.) and 7.45(1H;d.;J 9.5Hz.); $\nu_{max}^{CCl_4}$ 1740, 1626 and 1118cm.$^{-1}$; mass spectral peaks at m/e 228(M^+), 213, 185, 97, 95, 83, 81, 71, 69, 57, 55, 44, 43 and 41,(r.a. 75, 85, 35, 24, 23, 29, 27, 29, 49, 56, 63, 100, 70 and 75%).

(ii)the furanocoumarin (79)(4mg.,24%) as colourless prisms, m.p. 133-136°(lit.[88] m.p. 136-137°); n.m.r. signals (CCl_4) at δ 1.38(6H;d.;J 7Hz.), 3.10(1H;m.;J 7Hz), 6.18(1H;d.;J 9.5Hz.), 6.28(1H;s.), 7.25(1H;s.), 7.37(1H;s.) and 7.57(1H;d.;J 9.5Hz.).

(b) The alcohol (7)(18mg.) was dissolved in hexamethylphosphoramide (1.0ml.) and heated to reflux for 30 mins. Work up 11 gave yellow crystals (16mg.) which were then purified by preparative t.l.c. (30% v./v. ethyl acetate-light petroleum) into :-

(i) the olefin (78)(10mg.,60%),(n.m.r. and t.l.c. behaviour).

(ii) the furanocoumarin (79)(5mg.,30%), as a colourless crystalline solid (m.p., and t.l.c. behaviour).

Pilot pyrolysis of marmesin acetate (81)

A very small sample of the acetate (81)(1-2mg.) was heated to 260° for 5 mins. at atmospheric pressure in a sublimation block. Examination of the residue by analytical t.l.c. revealed that the major components of the reaction mixture were the starting acetate and the olefin (78). The furanocoumarin (79), although detectable by examination of the plate under a u.v. lamp (354nm.), was only present in trace quantities.

N,N-Dimethylthiocarbamoyl chloride.

Prepared from bis(dimethylaminothiocarbamoyl)-disulphide by the method of Newman and Hetzel[125]. The disulphide (7.2g.) on reaction with gaseous chlorine(2-3g.) in carbon tetrachloride (25ml.) yielded the chloride (5.0g.,68%). This reagent was freshly sublimed immediately prior to use.

Attempted formation of the dimethylthiocarbamate of the alcohol (7).

To a well stirred, cooled solution of (7)(32mg.) in dry dimethylformamide (5ml.) was added a suspension of sodium hydride in benzene (60% w./v.;20mg.). After 30 mins. the deep yellow solution was allowed to warm to R.T. and freshly sublimed dimethylthiocarbamoyl chloride (45mg.) was added. The solution was kept at

80° for 3½hr. and allowed to cool. Work up 11 then gave a dark brown gummy residue (48mg.) which contained only the starting materials and very polar decomposition products (n.m.r. and t.l.c.).

Dehydration of (±)-columbianetin (16)

(a) Thionyl chloride (0.5ml.) was added to a solution of the alcohol (16)(30mg.) in pyridine (2ml.) at 0° and left at this temperature for 20 mins. when t.l.c. showed complete conversion. After pouring into iced water (100ml.),the solution was stirred with solid sodium bisulphate until the pH range 3-4 was reached, and extracted twice with ether. Washing the organic layer to neutrality with brine, drying and evaporation gave a yellow solid (25mg.,90%) consisting of a mixture of two compounds, approximately in the ratio 1:1 (n.m.r.). This mixture could not be separated by preparative t.l.c., either by conventional means or by using silica impregnated with silver nitrate.

(b) A solution of the alcohol (16)(42mg.) in hexamethylphosphoramide (1.2ml.) was refluxed for 30 mins. Work up 11 gave a brown semi-solid residue (42mg.), still containing a trace of solvent, which, after preparative t.l.c. (chloroform X1), furnished a (3:1) mixture of the olefins (76) and (80) as a colourless crystalline solid (25mg.,64%). This mixture could not be further separated by preparative t.l.c.

Attempted benzylic oxidation of (±)-marmesin (7)

Selenium dioxide (8mg.) was added to a solution of (±)-marmesin (15mg.) in 20% v./v. aqueous dioxan(2.5ml). After refluxing the reaction mixture for 14hr. no detectable products were present by analytical t.l.c. After cooling and dilution with water (100ml.) the product was extracted with ethyl acetate,the organic layer washed repeatedly with brine, dried and evaporated to yield unreacted starting material(7) (13mg.,87%)(t.l.c. and n.m.r.)

Attempted benzylic oxidations of (±)-columbianetin(16).

(a) Selenium dioxide

A solution of the alcohol (16)(11mg.) in aqueous dioxan (20% v./v.;5ml.) was refluxed with freshly sublimed selenium dioxide (21mg.) for 2 days, when more selenium dioxide was added (20mg.). After a further 24 hr., this addition was repeated and the reflux continued for another 2 days. The reaction mixture was then allowed to cool and worked up as above to furnish only the starting alcohol (16)(11mg.)(t.l.c. and n.m.r.).

(b) Lead tetra-acetate.

(±)-Columbianetin (16)(9mg.), dissolved in 50% v./v. benzene-acetic acid, (1 ml.)was added to a solution of an excess of lead tetra-acetate in the same solvent (1 ml.). No product could be detected by t.l.c. after stirring at R.T. for 1 day, so the

solution was heated to reflux for 12hr. and then allowed to cool. After work up by dilution with ethylene glycol (2ml.) and then water (100ml.), followed by extraction with ethyl acetate, washing and drying of the organic layer, evaporation afforded a brownish gum (9mg.) containing starting material and a plethora of products (t.l.c.). No isolable product was, however, obtained.

(c) Sodium chromate-acetic anhydride-acetic acid.

The alcohol (16)(13mg.), dissolved in acetic acid (1 ml.) and acetic anhydride (0.5ml.) was kept at 40° for 2 days with anhydrous sodium chromate (24mg.). Work up 11 gave a low recovery (3mg.,23%) of a colourless gum containing only starting material (t.l.c.).

(d) N-Bromosuccinimide-aqueous dioxan.

Oxygen was bubbled through a solution of the alcohol (16)(11mg.) in 20% v./v. aqueous dioxan(5ml.) to which recrystallised N-bromosuccinimide (18mg.) had been added. After a few seconds at R.T. the solution turned yellow and t.l.c. indicated complete conversion. Work up 11 yielded a pale yellow crystalline solid (12mg.,83%) having n.m.r. signals at δ 1.27(3H;s.), 1.37(3H;s.), 2.30°(1H;vb), 3.32(2H; d.;J 8.5Hz.), 4.80(1H;bt.;J 8.5Hz.), 6.77(1H;d.;J 8Hz.), 7.23(1H;d.;J 8Hz.) and 8.00(1H;s.). This compound was assigned structure (87) on this basis.

(e) Jones reagent.

(±)-Columbianetin (12mg.) was dissolved in acetone (2ml.) and Jones reagent (0.5ml.) added at R.T. After 2 days more reagent (1 ml.) was added and the solution left a further 5hr. when t.l.c. indicated absence of starting material. Work up 11 yielded a solid brown material (~2mg.) consisting of at least three compounds. No further investigation was carried out.

(f) Photo-oxidation.

A solution of the alcohol (16)(25mg.) in t-butanol (25ml.) containing mecuric bromide (28mg.) was photolysed for 18hr. (254nm.). The reaction mixture was then poured on to a large volume of water and solid sodium chloride added. After extraction with 50% v./v. ether-ethyl acetate, washing with brine, drying and evaporation, a yellow gum (17mg.) was obtained which contained no isolable product (t.l.c. and n.m.r.).

(g) Cobalt acetate bromide.

Cobalt acetate (90mg.) was dissolved in a warmed solution of benzyl bromide (85mg.) in acetic acid (0.5ml.). When the blue colour of cobalt acetate bromide had developed, the alcohol (16)(25mg.) was added, oxygen bubbled through the solution, and the whole refluxed for 1½hr. with continual addition of more benzyl bromide and acetic acid (0.1 ml. containing

17mg. bromide every 10 mins.). Work up 11 afforded oily crystals (53mg.) containing only starting materials and decomposition products of benzyl bromide (n.m.r. and t.l.c.). No other product could be detected.

(h) Ammonium persulphate-silver nitrate.

A mixture of the alcohol (16)(55mg.), ammonium persulphate (102mg.) and silver nitrate (1-2mg.) was dissolved in 50% v./v. aqueous ethanol and the whole kept at 65-75° for 5hr. Work up 11 furnished only starting material (40mg.)(n.m.r. and t.l.c.)

(i) N-Bromosuccinimide-carbon tetrachloride.

A solution of the alcohol (16)(24mg.) and recrystallised N-bromosuccinimide (21mg.) in carbon tetrachloride (25ml.) was refluxed for 19hr. under irradiation by visible light. After cooling, solvent was removed by evaporation and the residue taken up in ethyl acetate to give a solution whose t.l.c. revealed the presence of starting material only.

(j) N-Bromosuccinimide-dioxan.

(±)-Columbianetin (17mg.) was added to a solution of N-bromosuccinimide (34mg.) in dioxan (4ml.) which had been refluxed over potassium hydroxide for 12hr. and then freshly distilled. The solution was irradiated with a tungsten lamp for 16hr., when work up 11 gave a yellow semi-crystalline residue (20mg., 89%) whose n.m.r. indicated structure (87) and which was indentical with the compound obtained from this alcohol by reaction with N-bromosuccinimide in aqueous dioxan (vide supra).

(k) Chromyl chloride.

A solution of 2% v./v. chromyl chloride in carbon tetrachloride (1 ml.) was added to the alcohol (16) (29mg.) in carbon tetrachloride (1 ml.) and acetic acid (0.5ml.) and left for 1hr. at R.T. Work up 11 gave only a very impure sample of starting material. No isolable product was obtained.

Allylic oxidation of osthenol acetate (90).

(a) Selenium dioxide.

Osthenol acetate (90)(114mg.) and freshly sublimed selenium dioxide (114mg.) were dissolved in 20% v./v. aqueous dioxan (10ml.) and refluxed for 2hr. After cooling, work up 11 gave a pale yellow highly crystalline solid (110mg.,92%) which afforded the aldehyde (92) as colourless needles from ethyl acetate-light petroleum, m.p.156-157°.(Found:C,67.20; H,5.11. $C_{16}H_{14}O_5$ requires C,67.12; H,4.93%); n.m.r. signals (100 MHz.) at δ 1.95(3H;d.;J 1.5Hz.), 2.34(3H;s.), 3.82(2H;d.;J 7Hz.), 6.39(1H;d.;J 9.5Hz.), 6.44(1H;dt; J 7 and 1.5Hz.), 7.05(1H;d.;J 9Hz.), 7.43(1H;d.;J 9Hz.), 7.70(1H;d.;J 9.5Hz.) and 9.36(1H;s.); $\nu_{max}^{CCl_4}$ 2710 (v.weak), 1771, 1752, 1694, 1185 and 1109cm.$^{-1}$; λ_{max} 311 and 281nm.(log.ϵ 3.75 and 3.96); mass spectral peaks at m/e 286(M^+), 244, 215, 199, 187, 176, 175, 115, 91, 82, 65, 63, 58, 44 and 43(r.a. 31, 67, 30, 39, 50, 19, 30, 17, 19, 22, 17, 17, 17, 17, and 100%).

(b) Lead tetra-acetate.

A solution of the acetate (90)(43mg.) in 50% v./v. benzene-acetic acid (5ml.) was added to a solution of excess lead tetra-acetate in the same solvent (5ml.) at R.T. and stirred for 1 day, when analytical t.l.c. showed starting material to be the only compound present. After a further 10hr. at 40° there was no change, and a subsequent 2 day reflux only gave rise to some decomposition of the starting acetate. No isolable product was obtained.

Attempted epoxidation of the aldehyde (92)

The aldehyde (92)(35mg.) was dissolved in redistilled tetrahydrofuran(5ml.) and 2% v./v. sodium carbonate solution (0.5ml.) added. To this mixture was added 30% v./v. hydrogen peroxide (0.5ml.) and the reaction left at R.T. for 10mins. when t.l.c. showed complete reaction. Work up by acidifying with 0.1N hydrochloric acid, diluting with water (100ml.), extracting with ethyl acetate, washing the organic layer to neutrality with brine, drying and evaporation of solvent furnished a yellow crystalline solid (30mg.,90%);n.m.r. signals (100MHz.,d_6-acetone) at δ 1.92(3H;bs.), 3.86 (2H;d.;J 7.5Hz.), 6.14(1H;d.;J 9.5Hz.), 6.59(1H;t.;J 7.5Hz.), 6.92(1H;d.;J 8Hz.), 7.38(1H;d.;J 8Hz.), 7.82 (1H;d.;J 9.5Hz.) and 9.39(1H;s.); λ_{max}346(sh.), 323, and 260nm.; λ_{max}(base)388 and 277(sh.)nm.;$\nu_{max}^{CCl_4}$ 3687, 3590, 1730, 1682 and 1604cm.$^{-1}$; mass spectral peaks at

m/e 244(M^+), 213, 187, 186, 176, 175, 131, 115, 91, 77, 65, 63, 57, 55, 51, 43 and 41(r.a.26, 100, 53, 47, 54, 53, 33, 32, 49, 43, 43, 57, 38, 32, 46, 92 and 59%). This compound has been tentatively assigned structure (95).

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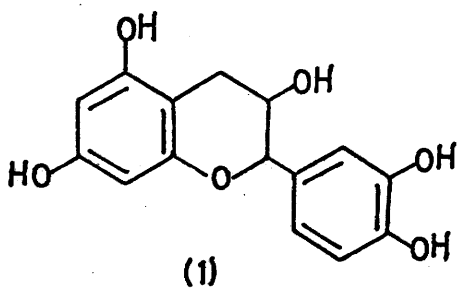
PART II

The Chemistry of the Coumarin, Tomentin.



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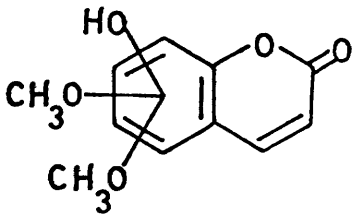

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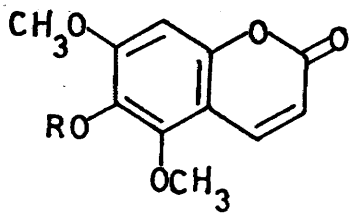
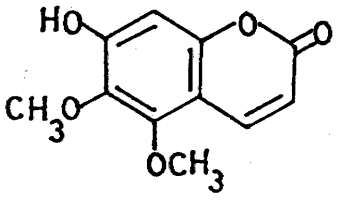
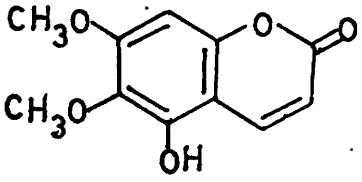


(3): R = $-OCCH_3$

(4) R = $-CH_3$



(5)

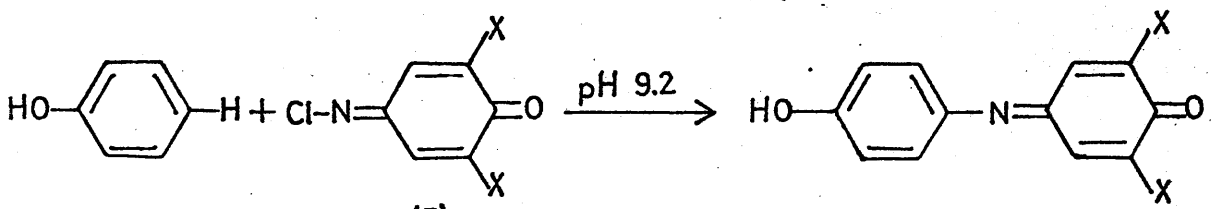


(6)

During a routine examination of the wood constituents of the shrub Prunus tomentosa , Hasegawa isolated [1] two compounds from the methanolic extract. The first was identified as d-catechin (1). The other was a glycoside (tomenin) which, on acid hydrolysis, yielded glucose and a new phenolic aglycone, tomentin, having the molecular formula $C_{11}H_{10}O_5$. The acetate of the latter compound exhibited n.m.r. resonances typical of a coumarin AB quartet [2] at δ6.31 (d) and 7.68 (d) along with two separate $-OCH_3$ signals (δ3.86 and 3.98) and a single aromatic proton resonance at δ 6.82, giving partial structure (2) for the aglycone. Comparison of the acetate with fraxinol acetate (3) revealed their non-identity, but the oxygenation pattern of the coumarin nucleus in tomentin was established when it was shown that its methyl ether and fraxinol methyl ether (4) were the same compound. The structure of the coumarin was, therefore, either (5) or (6). To distinguish between these two possibilities, Hasegawa relied [1] on a colour test, namely the formation of a red colour with Gibbs' reagent[3], concluding that, in tomentin, the phenolic hydroxyl group and the aromatic proton enjoy a para-relationship. On this basis, (5) was eliminated and tomentin assigned the alternative structure (6).

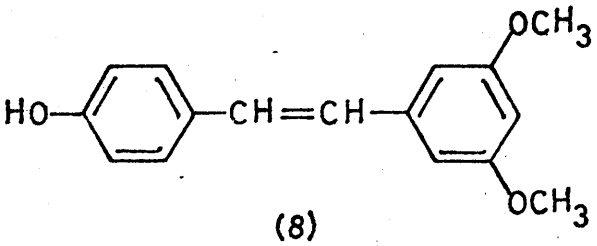
The reliability of the Gibbs' test as a means of structural assignment has been called into question

SCHEME 2.1



(7)

X = -Br or -Cl



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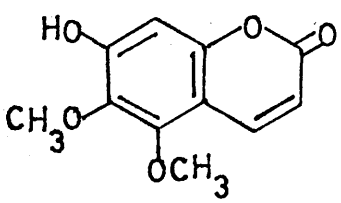
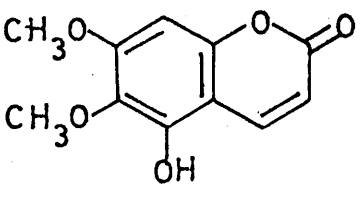


(5)

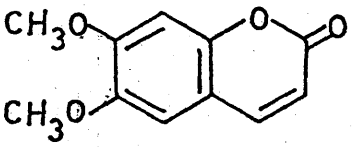


(6)

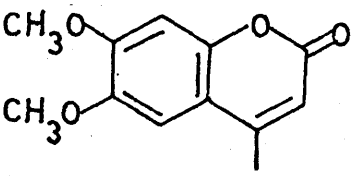
several times in the past [4-6]. The colour observed is supposedly that of the sodium salt of the indophenol formed when a substrate is reacted with 2,6-dichloro- or 2,6-dibromoquinonechloroimide (7), as in Scheme 2.1. Colour reaction have been observed, however, for compounds having a blocked <u>para</u> - position [6]. The situation has, to a large extent, been clarified [6] by the work of King, King and Manning, who were able to show that the reaction was more reliable when the products were examined spectrophotometrically. A large number of phenols were examined under the reaction conditions employed for the test, the simplest (phenol itself) giving an absorption at 605nm. Thus, although a colour was obtained for pterostilbene (8), its λ_{max} lay outwith the 500-700 nm. range and, therefore, (8) was not regarded as having given a positive test.

In this form, more reliance can be placed on the results obtained from the Gibbs' test, a recent example[7] coming from the work of Crombie. Unfortunately, however, Hasegawa had not used this refinement in his application of the test to tomentin. His observation of a red colour alone was not, in our opinion, sufficient grounds for eliminating structure (5). Accordingly, a small sample of tomentin was obtained from Japan in order that the situation might be resolved.

The first attempt to distinguish between (5) and (6) was based on the u.v. behaviour of tomentin in neutral



(9)



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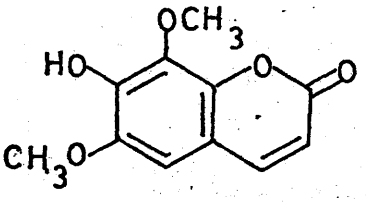

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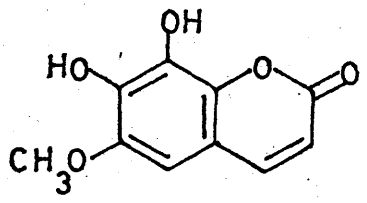

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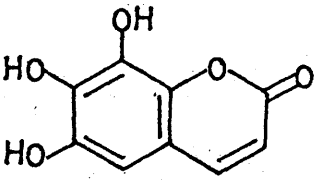

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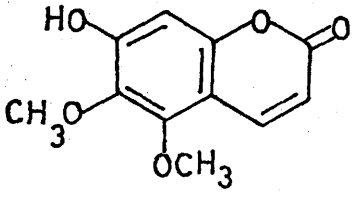
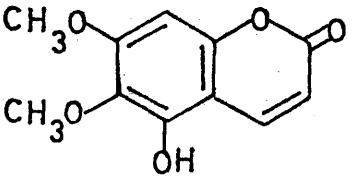


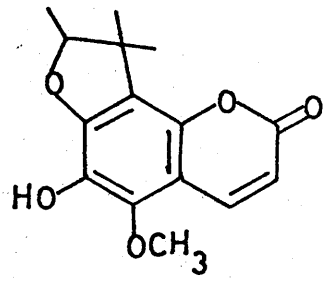
(5)



(6)

and basic media. It was known [8] from earlier work that it is often possible to distinguish between coumarins carrying a free phenolic hydroxyl at C-7 and those with this substituent elsewhere in the benzene ring, on the basis of the u.v. base shift alone. In the mono-oxygenated series a hyperchromic effect is observed for the former, a hypochromic effect being usual for coumarins hydroxylated in the 5-,6- or8-positions. Additionally, all types showed a significant red shift. Unfortunately the situation becomes more complex for higher oxygenated coumarins. 6,7-Dihydroxy-coumarin (9) and its 4-methyl analogue (10) were reported[8] to behave as simple 7-hydroxycoumarins, producing the expected hyperchromic effect in basic solution with respect to the neutral solution spectrum. Also, isofraxedin (11), with a trioxygenated nucleus and a free7-hydroxyl group, gave the expected effect. Fraxetin (12) and 6,7,8-trihydroxycoumarin (13), however, produced hypochromic effects,despite the presence of a C-7 hydroxyl group. Tomentin was found to show a pronounced hypochromic effect when its u.v. was run in basic solution. Although indicative of a C-5 phenol and, therefore, structure (6), the above exceptions still left considerable doubt as to whether or not this was the correct assignment.

An alternative method for distinguishing (5) from (6) was suggested by work carried out in this laboratory



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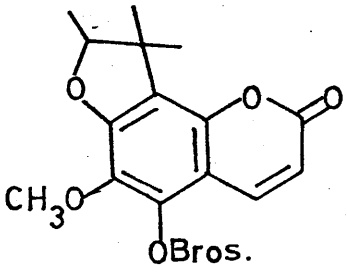

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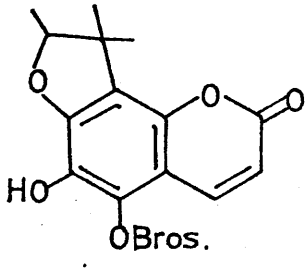

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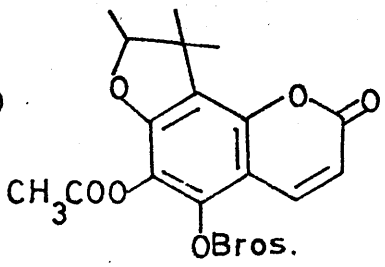

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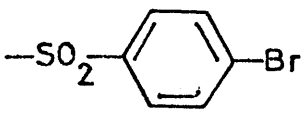
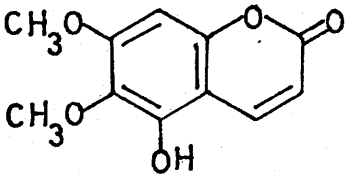
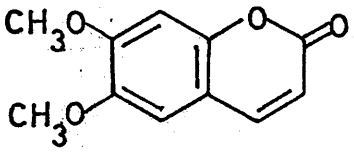
Bros. ≡ 



(6)

several years ago. During an investigation into the constituents of Ptaeroxylon obliquum, McCabe, McCrindle and Murray isolated[9] a coumarin which was given the name nieshoutol. In a later paper[10] the structure of this compound was elucidated as (14). Three brosylates, (15),(16) and (17), were prepared in the course of the structural proof. A significant shielding (0.17, 0.22 and 0.28 ppm respectively) of the 4-proton with respect to that of nieshoutol (14) was observed in the n.m.r. of these compounds. Presumably this can be explained as a through-space effect, the local magnetic field produced by circulation of the π -electrons of the pendant aromatic ring opposing the applied magnetic field in the neighbourhood of the 4-proton, resulting in a higher chemical shift for the latter. A similar effect has been reported[11] for a tosylate in a related system. Prolonged treatment of tomentin(6) with toluene p-sulphonyl chloride in pyridine afforded the tosylate, which was purified by preparative t.l.c. In the n.m.r. of this compound, the 4-proton resonance was found to occur at δ 7.75 (J 9.5Hz.). The corresponding value for the parent phenol was δ 7.98, representing an upfield shift of 0.23 ppm for the tosylate with respect to the phenol. This evidence would strongly indicate structure (6) for tomentin, the structure originally proposed by Hasegawa.

In an attempt to obtain firmer evidence for the structure of tomentin, it was noted that removal of the



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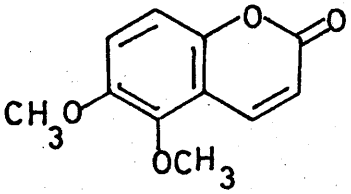

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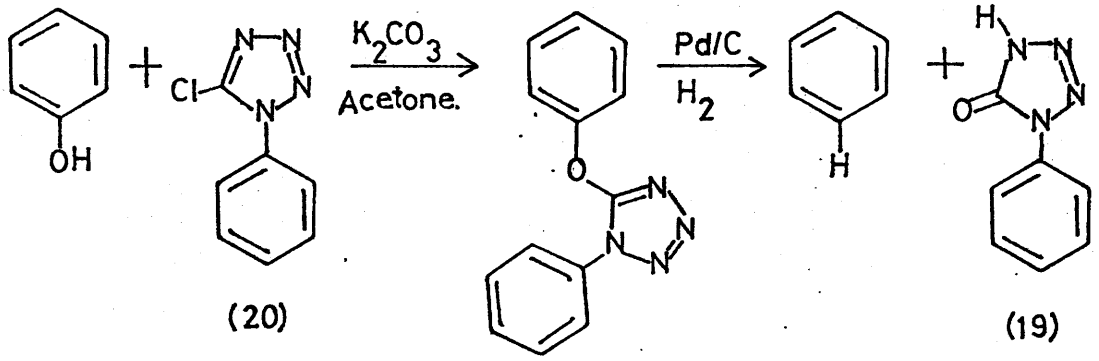
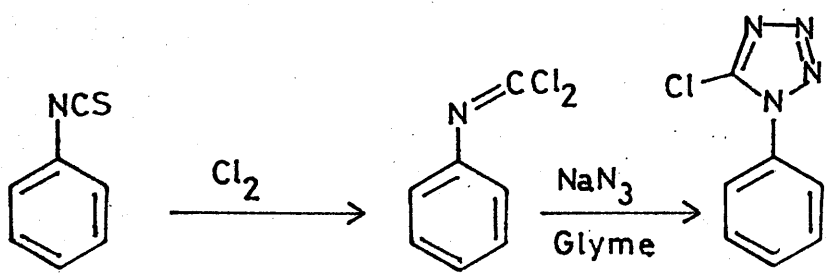
SCHEME 2.2



(20) (19)

SCHEME 2.3



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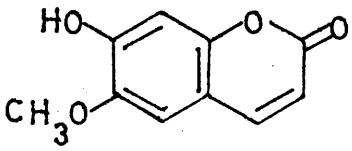


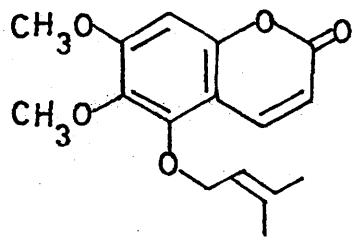
(21)

phenolic hydroxyl group would result in a compound with two aromatic protons having a para-relationship in the one case (compound(9)), or a compound with two such protons in an ortho-relationship in the other (18). It was considered that these products would be readily distinguished by n.m.r.

A facile method for the dehydroxylation of phenols has been reported[12] by Musliner and Gates, who prepared the 1-phenyl-5-chlorotetrazolyl ethers of several phenols in very good yield. Subsequent hydrogenolysis cleaved the ether to the parent aromatic compound, giving 1-phenyl-5- tetrazolone (19) as a by-product (Scheme 2.2).

1-Phenyl-5-chlorotetrazole (20) was prepared, as described by Kauer and Sheppard[13], from N-phenyldichloro-azomethine, the latter compound being obtained[14] by the action of chlorine on phenyl isothiocyanate. (Scheme 2.3). As supplies of tomentin were limited, it was decided to try the etherification reaction on scopoletin (21) first. Unfortunately, prolonged refluxing of (21) with 1-phenyl-5-chlorotetrazole and potassium carbonate in acetone resulted in no detectable products, only starting materials being obtained on work up. Rather than risk this apparently unsuccessful procedure on tomentin, an alternative chemical structural proof was employed.

It was felt that the structure of tomentin could



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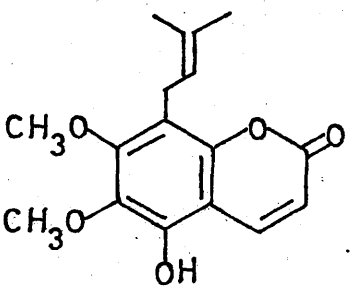

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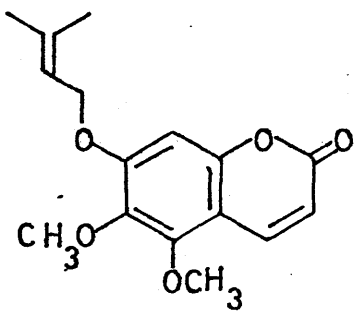

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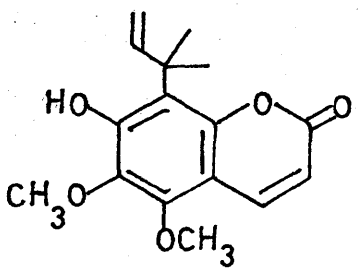

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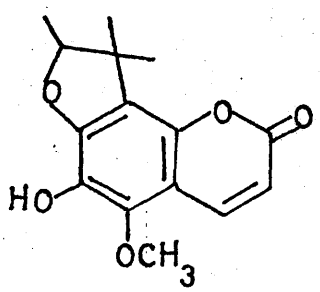
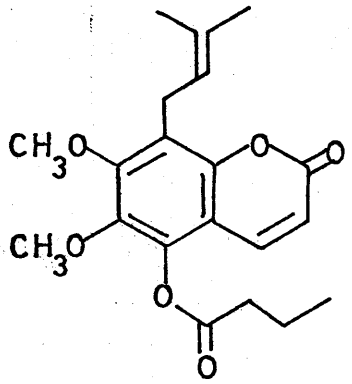


(14)

be determined by examination of the product arising from a Claisen rearrangement of an unsymmetrically substituted allyl ether. Thus, from the readily-prepared 3,3-dimethylallyl ether, a *para*-rearrangement[15] should occur for (22) with a consequent double inversion of the ends of attachment of the allyl group, giving (23) whereas (24) should undergo an *ortho* rearrangement[16] to (25). The n.m.r. spectrum of the product would readily indicate which pathway was followed. Moreover, the Claisen rearrangement could serve a dual purpose for if (25) were by chance produced it would possess the same carbon framework and oxygenation pattern as nieshoutol[10](14).

From the practical viewpoint, the *ortho*-Claisen rearrangement product of a 3,3-dimethylallyl aryl ether is prone to cyclise[17] to a dihydrofuran on heating and may also undergo further rearrangement, while fission of the ether to isoprene and the parent ether can also occur[18]. Such reactions have been simplified considerably in the past[19] by carrying out pyrolysis in the presence of butyric anhydride which traps the first formed phenol as its butyrate ester.

Tomentin, on refluxing with 3,3-dimethylallyl bromide in the presence of potassium carbonate and acetone for 3hr. readily furnished the ether as a single product. The n.m.r. of this compound exhibited signals at δ 1.70 (3H;bs.), 1.78(3H;bs.), 4.73(2H;d.;J 7.5Hz.) and 5.52



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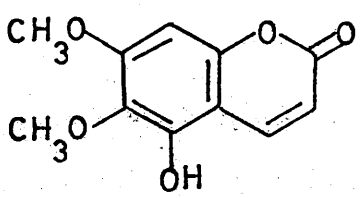
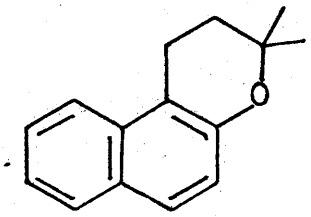
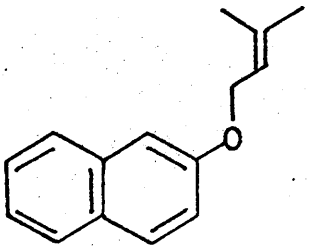


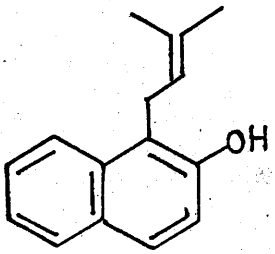
(6)



(27a)



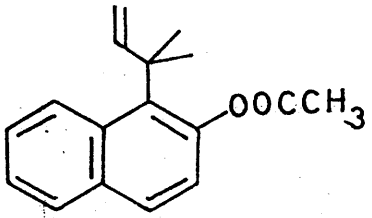
(28a)



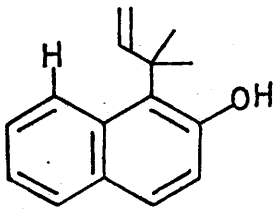
(29a)

(1H;bt.; J 7.5 Hz.), indicative of a 3,3-dimethylallyl group attached to oxygen, in addition to the resonances of the methoxylated benzo-α-pyrone nucleus. Slight broadening of the vinyl proton signal was attributed to allylic coupling[20] with the protons of the C-3 methyl group. Loss of the C_5H_9 unit from the molecular ion gave rise to the base peak in the mass spectrum of the ether.

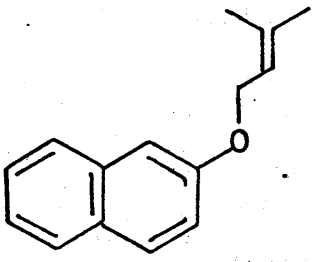
Pyrolysis of O-(3,3-dimethylallyl) tomentin in N,N-diethylaniline and n-butyric anhydride was carried out for 7hr. at 175° under nitrogen. After work up the residue was purified by preparative t.l.c. and distillation to yield the butyrate (26) as a colourless gum, exhibiting n.m.r. signals characteristic of a 3,3-dimethylallyl group[23]. However, the methylene group resonance had moved upfield from δ4.73 in the ether to δ 3.50 in the butyrate, indicating its attachment to carbon. A para-Claisen rearrangement had presumably occurred, constituting strong chemical evidence that Hasegawa's original proposal of structure (6) for tomentin was correct. It was conceivable, however, that the C-isoprenyl group could have arisen from an anomalous ortho - rearrangement. Buckle and Waight obtained[21] compound (27a) on pyrolysis of β-naphthyl 3,3-dimethylallyl ether (28a). This appeared to have arisen from cyclisation of the corresponding ortho-isoprenylphenol (29a). The authors were able to isolate



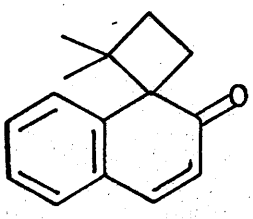
(30a)



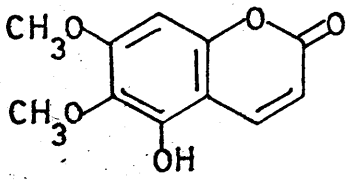
(31a)



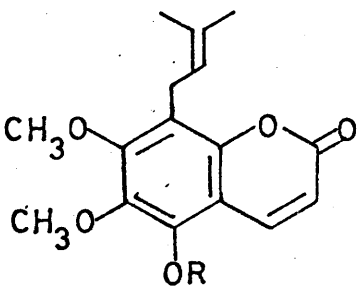
(28a)



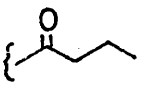
(32a)

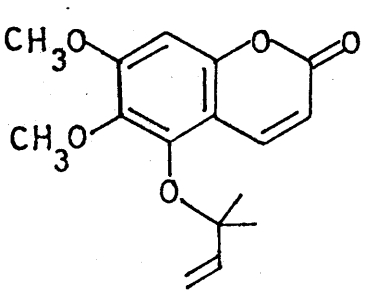


(6)



(23) : R = H

(26) : R = 



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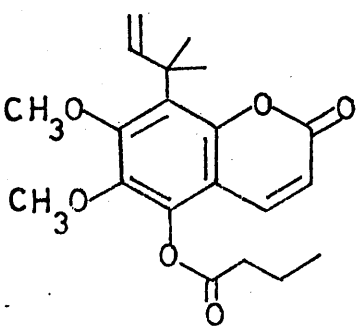
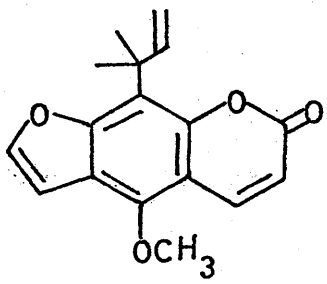


(28)

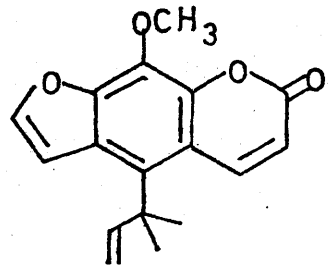
the expected product (30a) by carrying out the reaction in the presence of acetic anhydride, and suggested the corresponding phenol (31a) as the initial product of the pyrolysis of (28a). Subsequent rearrangement of the allylic side-chain was postulated to occur for steric reasons, cyclisation of the first-formed phenol being hindered by the proximity of the gem-dimethyl group to the peri-hydrogen atom. The rearrangement was considered to involve the spirocyclobutane intermediate (32a).

It seemed unlikely that this could be occurring in the case of tomentin (6) in view of the fact that the reaction had been carried out in n-butyric anhydride, but the possibility was readily discounted for the phenol (23) obtained on hydrolysis of the butyrate (26), showed no OH-π hydrogen bonding in its infra-red spectrum[22]. This phenol was also stable to hot acid; conditions which would have resulted in cyclisation to a dihydrofuran if the phenol and the allyl moiety were ortho-related. This reaction is known to proceed readily and in high yield for 7-hydroxy-8-isopentenylcoumarins[23].

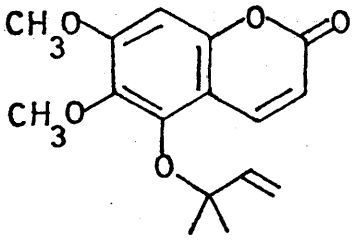
The structure of tomentin was, therefore, shown to be (6) by Claisen rearrangement of its 3,3-dimethylallyl ether. Hasegawa's assignment had, fortuitously, been correct. The interesting correlation with nieshoutol (14), however, had yet to be carried out. This would require preparation of the1,1-dimethylallyl ether(27), subsequent rearrangement to the butyrate (28), followed by demethylation, hydrolysis of the butyrate, and acid-



(29)



(30)



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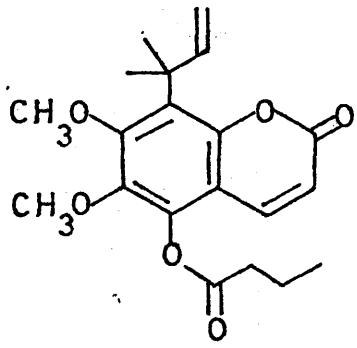

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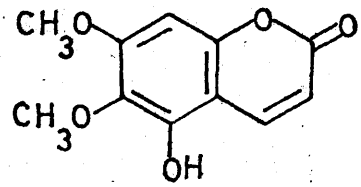


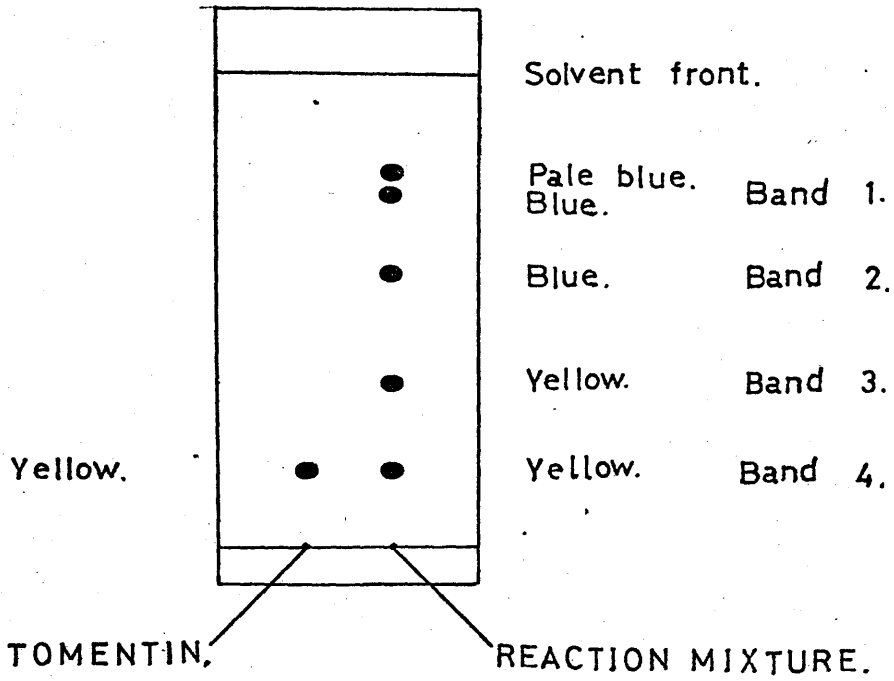
(6)

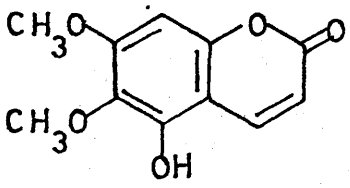
catalysed cyclisation. Interestingly enough, although para-Claisen rearrangements of 3,3-dimethylallyl-aryl ethers are fairly common[24], there are no reported para-Claisen rearrangements for the 1,1-dimethylallyl-aryl ether system, to our knowledge. Also, some natural coumarins, for example furopinnarin[25] (29) and benahorin (30)[26], have a carbon skeleton which might be obtained synthetically by this route; so it was felt that the ether (27) and its rearrangement to (28) would be a worthwhile objective.

As outlined in Part 1 of this thesis, ethers of the type (27) are conveniently prepared by partial hydrogenation of the corresponding acetylenic ether, obtained by direct O-alkylation of the phenolate anion with 2-methyl-2-chloro-3-butyne (1,1-dimethylpropargyl chloride).

Accordingly, tomentin (6) was refluxed with a solution of 1,1-dimethylpropargyl chloride[27] in 2% aqueous acetone in the presence of potassium carbonate and potassium iodide for a total of 54hr., additional acetylenic chloride being added after 6hr. and after30 hr. Very little conversion was seen after 30 hr. (t.l.c. examination) but the extra one-day reflux resulted in the formation of several products, all of which fluoresced when the t.l.c. plate was examined under a 354nm. u.v. lamp, prior to development. Their relative mobility and colour of fluorescence is given in Fig. 2.4. Increasing the reaction time did not increase the conversion of tomentin (6) but only served to cause

FIGURE 2.4





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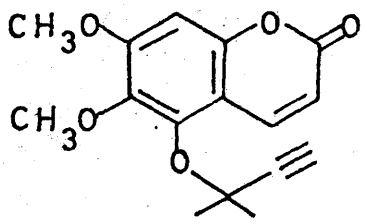
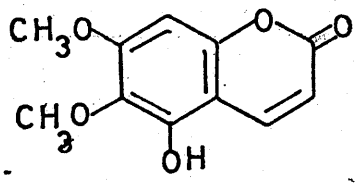


(31)

deterioration of the products. As conversion was, at best, only partial and the starting phenol was only available in limited quantities, a procedure for quick recovery of the latter was employed. This involved filtration of the reaction mixture through Celite, elution with ethyl acetate and then acidification of the Celite followed by re-elution with ethyl acetate. The second organic washing contained pure starting material, the first the product mixture.

At this time it was noticed that Buchi had reported[28] increased yields of O-alkylation products by using 1,2-dimethoxyethane (glyme) as solvent. This was tried as a means of increasing the yield from the propargylation of tomentin (6). T.l.c. examination of the reaction mixture after 4hr., however, indicated the presence of decomposition products with no trace of the expected reaction mixture.

After work up the product mixture was separated by preparative t.l.c. into four main bands (Fig. 2.4). The major component of the mixture (band 2, Fig 2.4) was found to be the required ether (31) and was isolated in yields averaging 45%, based on reacted tomentin (6). Its spectral data were completely in accord with the structural assignment, n.m.r. signals at δ1.72(6H;s.) and δ2.43(1H;s.) being ascribed to the O-1,1-dimethyl-propargyl moiety. Confirmation of the latter's presence in the molecule came from the i.r. which showed bands



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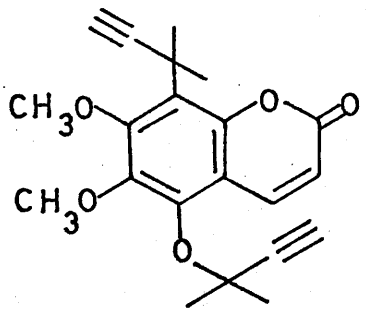


(32)

at 3310 and 2125 cm^{-1}.

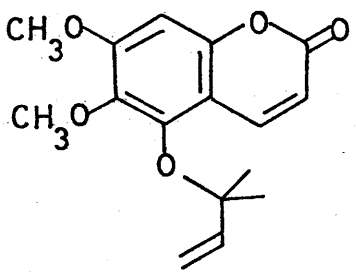
A small quantity of tomentin (6) was also isolated from the reaction mixture (band 4, Fig.2.4) as expected. Most of the starting material was, however, removed by the isolation procedure described above (see also Experimental Section), the total recovery being about 35%.

The remaining products (bands 1 and 3, Fig. 2.4) were interesting in that their composition was not immediately obvious from their spectral data. Band 1 (Fig. 2.4) consisted of two very close spots on analytical t.l.c. but its n.m.r. was evidently that of a substantially pure compound. Very careful preparative t.l.c. resulted in the successful isolation of the major component as a pale yellow gum; but the accompanying compound was never isolated. The major constituent of band 1 exhibited no aromatic proton resonances in the n.m.r., indicating that position 8 in tomentin (6) had been substituted. Two one-proton singlets were present in the acetylenic region, however, at δ 2.30 and 2.47, as well as two six-proton singlets at δ 1.73 and 1.92. These signals suggested that two 1,1-dimethylpropargyl moieties had been incorporated into the tomentin (6) molecule, and this theory was confirmed by the molecular ion at m/e 354 in the mass spectrum. Structure (32) immediately suggested itself and is consistent with all the data obtained for the compound. Some chemical evidence for this structure was obtained later (*vide infra*). This material

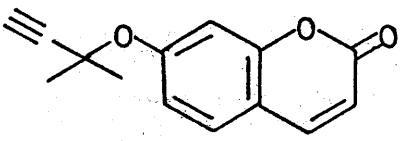
represented 6% of the reacted tomentin (6) in the propargylation reaction, and the significance of its formation will be commented on later in the text.

The composition of band 3 remained a mystery for some time. It was isolated as a bright yellow glass which was found to crystallise slowly over a period of several weeks. Although it ran as one spot on analytical t.l.c. plates in various solvent systems, it was possible, on occasion, to detect a slight lengthening effect in the spot, suggesting the band was, in fact, a mixture. These suspicions were confirmed by the n.m.r. of this material, which showed a pair of one-proton septets (J 3 Hz.in each case) at δ 5.17 and 5.45 and a pair of one-proton singlets at δ 5.70 and 5.73. These were at considerably higher field than the aromatic proton singlet in tomentin(6) (δ 6.42). Two AB-quartet systems were also in evidence at δ 6.07, 6.18, 7.80 and 7.88 (J 9.5Hz, in each case) which suggested the band was a 1:1 mixture of two compounds (within the limits of the accuracy of the integrator), inseparable by t.l.c. No further investigation was carried out at the time of the initial isolation of this mixture, but its components were instrumental in solving a structural elucidation problem encountered later. It is proposed to describe the sequence of events chronologically, and to return to the composition of this mixture at a suitable point later in the text.

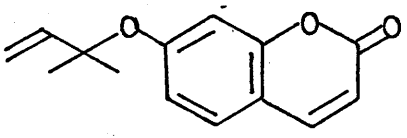
Having successfully synthesised the ether (31) in



(27)



(33)



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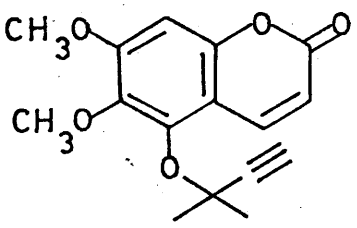

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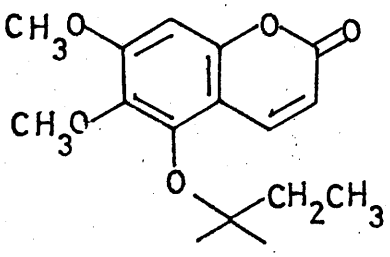
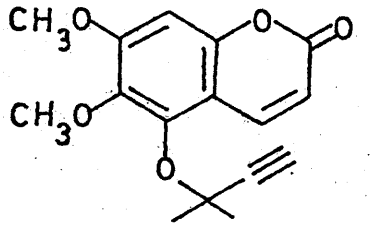


(35)

moderate yield, the next step was partial hydrogenation to the 1,1-dimethylallyl ether (27). As described in Part 1 of this thesis, this can best be achieved by hydrogenation of the substrate over a catalyst comprising 5% palladium on charcoal, poisoned with a carefully determined quantity of sulphur and quinoline in xylene[54]. Murray, Ballantyne and Mathai [23] found that the best ratio of catalyst to diluted poison was 1mg.:0.01 ml. This was found to work very well for the hydrogenation of (33) to the ether (34), and was successfully repeated on several occasions by the author. Several attempted hydrogenations on (31) with this ratio failed, however; starting material being recovered. After some experimentation it was found that the hydrogenation of (31) became reproducible when slightly less poison than the above-mentioned ratio was used (see Experimental Section for details), the reaction being carried out in the absence of bright sunlight. When the quantity of poison was reduced even further, the saturated ether (35) (identified by n.m.r. and mass spectrum) was formed very quickly. Great care had to be taken in calculating the volume of poison solution to add to the reaction mixture for this reason. A summary of precautions to be taken is given in the Experimental Section.

Using the correct conditions, the ether (31) took up 1 mole of hydrogen in 1-2 hr. Removal of the catalyst was effected by filtration through Celite, a procedure



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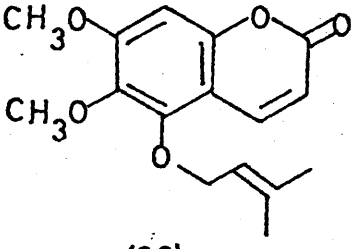
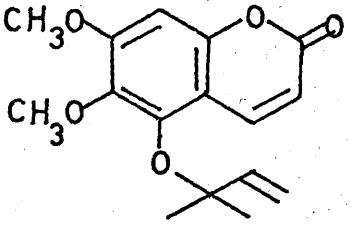


(22)

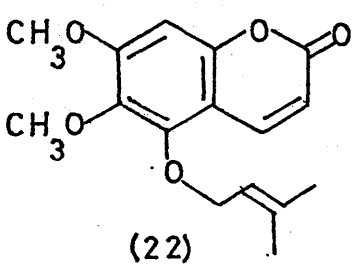


(27)

later shown to play a major role in the identity of the product isolated. After purification by preparative t.l.c. the reaction mixture was separated into a little starting ether(31), and a single bright yellow crystalline solid which constituted the sole product of the hydrogenation of (31). The spectral data of this compound were not at all like that of other coumarin 1,1-dimethylallyl ethers. In the u.v. for example, in contrast to the ether (22),a compound which might have been expected to resemble the ether (27) in this respect, the yellow solid showed peaks at 380, 316 and 257 nm. (log ϵ 3.70, 3.95 and 3.82)which shifted to 338, 276 and 254nm. (log ϵ 3.84, 3.73 and 4.04) in a basic medium. The corresponding values for (22) were 319 and 255 (sh.) nm., with no base shift being shown.

The i.r. of the yellow solid was unusual in that a very strong peak at 1535cm.$^{-1}$ was observed, and also a strong absorption at 1678cm.$^{-1}$. No such bands appear in the i.r. of (22). The α-pyrone carbonyl stretch at 1760cm.$^{-1}$ was, however, still present in the yellow hydrogenation product.

A mass spectrum indicated the compound had the correct molecular weight for $C_{16}H_{18}O_5$ exhibiting a molecular ion at m/e 290, but the most revealing evidence came from its n.m.r. spectrum. That it was a single compound, and not a mixture, was already suspected from its homogeneity on t.l.c. and sharp melting-point (111-113°). The n.m.r. confirmed this suspicion. Signals were observed at δ1.53 (3H;bs.), 1.60(3H;bs.), 2.70(2H;d.;J 8.5Hz.), 3.15 (3H;s.),



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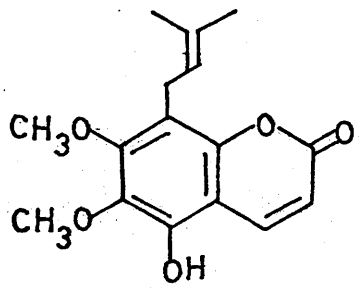

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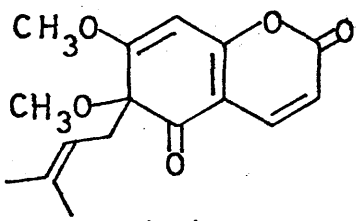

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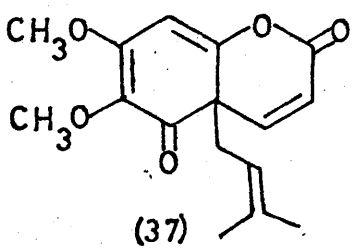

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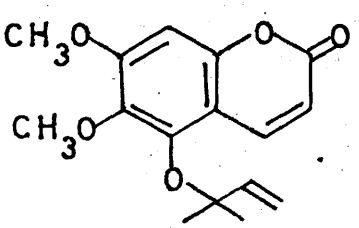
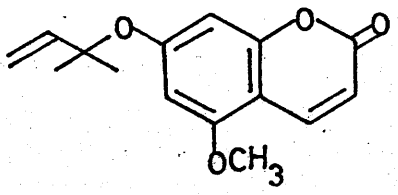


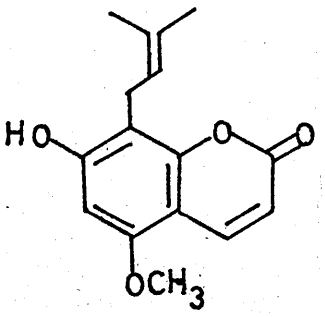
(27)

3.93(3H;s.), 4.87(1H;bt.;J 8.5Hz.), 5.77(1H;s.), 6.08 (1H;d.;J 9.5Hz.) and 7.82(1H;d.; J 9.5Hz.). Several points became immediately apparent from this spectrum. Firstly, the expected pattern of the 1,1-dimethylallyl unit (Fig. 1.11) was missing, and was apparently replaced by that of a 3,3-dimethylallyl unit. Secondly, as in the yellow mixture obtained from the propargylation reaction (*vide supra*), the aromatic singlet had undergone an up-field shift from δ 6.42 to δ 5.77. Thirdly, the two methoxyl resonances were now well split (δ 3.15 and 3.93) as compared with tomentin (6) (δ 3.83 and 3.85) and its 3,3-dimethylallyl ether (22) (δ 3.87 and 3.93), a phenomenon which again had been noticed in the yellow propargylation by-products. Fourthly, the methylene protons of the 3,3-dimethylallyl unit were at δ 2.70. This compares with δ 4.73 for the ether (22) and δ 3.47 for the prenylated phenol (23). Either these protons were undergoing a significant shielding effect or else were attached to saturated carbon.

Two possible structures fitted all the data. These were the enones (36) and (37) and, in confirmation, a positive reaction was obtained when a t.l.c. plate was sprayed with 2,4-dinitrophenylhydrazine solution. The problem of structural assignment then arose, and also the problem of accounting for the isolation of this compound. It appeared as though the 1,1-dimethylallyl ether (27), when formed, had undergone Claisen rearrangement



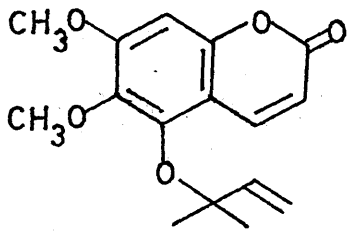
(37a)



(37b)

either spontaneously or during the isolation procedure. With this in mind the hydrogenation was repeated, but precautions were taken to minimise the number of external influences which might have been causing the rearrangement. In particular, care was taken so that the product mixture was never heated above room temperature, a temperature gradient being used to facilitate evaporation of solvent on the rotary evaporator. This had no effect, however, none of the hoped-for ether being isolated.

At this point it was noticed that the crude reaction mixture, when spotted on a small, analytical t.l.c. plate gave rise to considerable streaking. An intensely blue fluorescent non-polar spot seemed to be giving rise to the yellow enone. The possibility that rearrangement could be taking place on the silica then occured to us. A similar observation has been recorded [23] in this laboratory for the ether (37a), when (37b) was the sole product. Several short experiments confirmed that this was happening. A spot of the reaction mixture (very pale yellow) on a t.l.c. plate (without elution) was seen to turn yellow over a period of a few seconds; and no allylic ether was ever isolated from a preparative t.l.c. plate. Its presence in the reaction mixture was proved, however, when the reaction was worked up using the minimum Celite as a filtration pad. Unfortunately no other method of removing the finely divided catalyst was found, but rapid filtration at the pump resulted in



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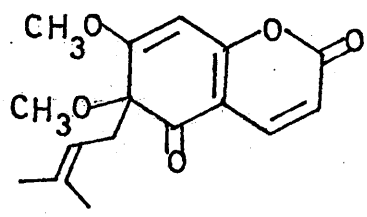

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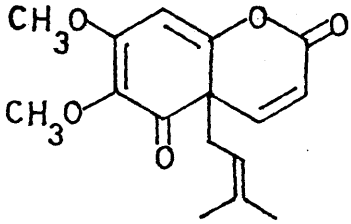

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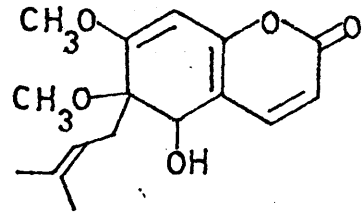

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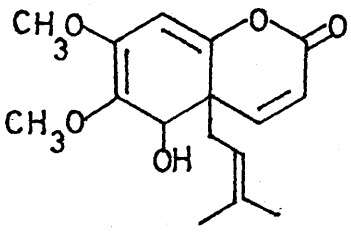

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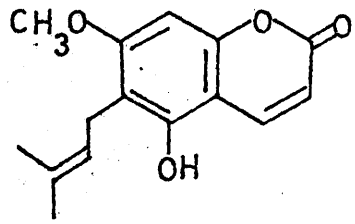
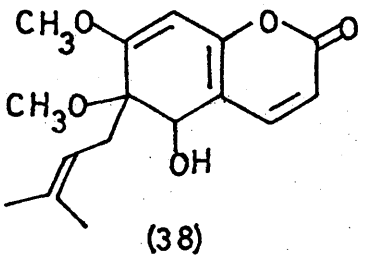


(40)

only slight rearrangement. When the solvent had been removed from the filtrate, the residue gave n.m.r. signals typical [29] of a 1,1-dimethylallyl ether, along with signals due to small amounts (10-20%) of the enone. When a few milligrams of Celite were added to an ethyl acetate solution of the ether (27) at room temperature and the mixture stirred, substantial conversion to the enone was seen after 5 mins., when the n.m.r. spectrum was re-run. Leaving the mixture to stir for 1 hr. with Kieselgel G resulted in complete conversion.

Although the allyl ether (27) was never isolated, an attempt to rearrange it thermally was made. A solution of (27), in ethyl acetate, was refluxed on a steam bath for a few minutes and the n.m.r. of the product compared with that of the material prior to heating. No conversion was observed, within the limits of the n.m.r. integrator accuracy. Evidently the ether (27) was stable to 77° but underwent a clean, high yield conversion to either (36) or (37) on silica at room temperature. An attempt to rationalise these findings will be made later in the text.

It was proposed to differentiate between structures (36) and (37) for the enone by means of reduction of the ketone with sodium borohydride, followed by attempted elimination of methanol from the resulting alcohol(38) or (39). Structure (38) would give rise to (40), a compound previously prepared[30] in this laboratory by Dr.T.C. Hogg.



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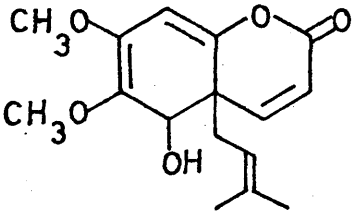

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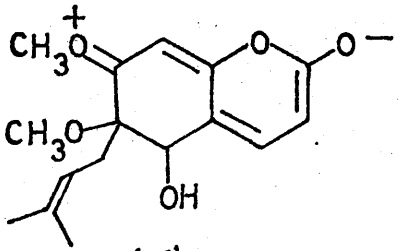
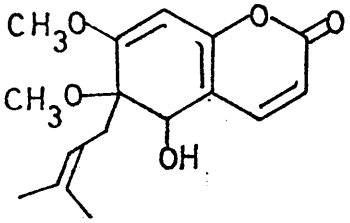


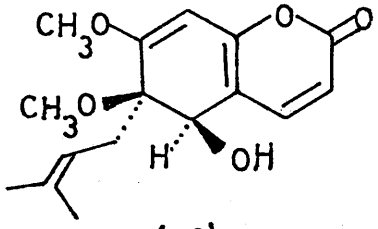
(41)

Reaction of the enone with sodium borohydride in ethanol took place very smoothly at R.T. in a few minutes to afford a pale yellow gum, after purification by preparative t.l.c. The spectral data of this compound were consistent with either structure (38) or (39). In the u.v. the λ_{max} had shifted from 380 to 325nm.; the i.r. showed both bonded and non-bonded hydroxyl stretches in addition to a very strong band at 1525cm^{-1}. This band was also present in the parent enone but evidently was not connected with the carbonyl group of the latter, owing to its presence in the derived alcohol. One theory suggested that this was due to a contribution from the resonance hybrid (41), the strength of the band being attributed to the large dipole moment present in this structure. Such extended conjugation is not possible for the alternative (39), and, therefore, if the theory were correct, some evidence for (38) had been adduced.

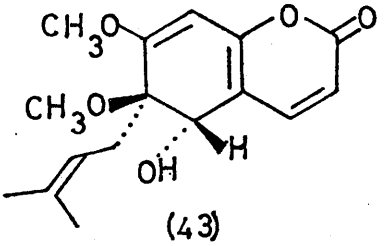
Further support for (38) came from dilution studies on the hydroxyl region of the borohydride product. It was found that progressive dilution of the i.r. solution resulted in weakening and eventual disappearance of the bonded hydroxyl stretching band. This was taken as being indicative of inter-as opposed to intramolecular hydrogen-bonding. If structure (39) were correct, some residual intramolecular bonding between the hydroxyl and the methoxyl group would be expected from a consideration of models,regardless of stereochemistry at the tetrahedral



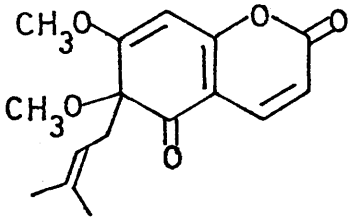
(38)



(42)



(43)



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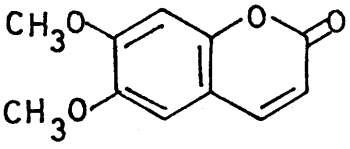
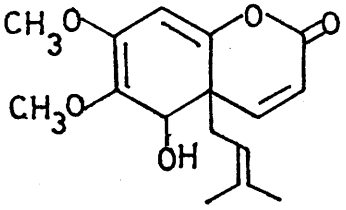
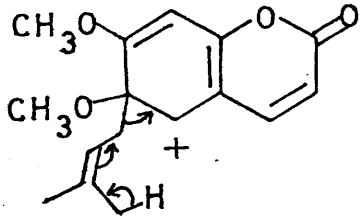


(9)

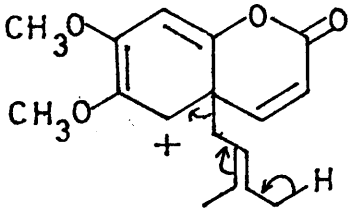


(39)

FIGURE 2.5

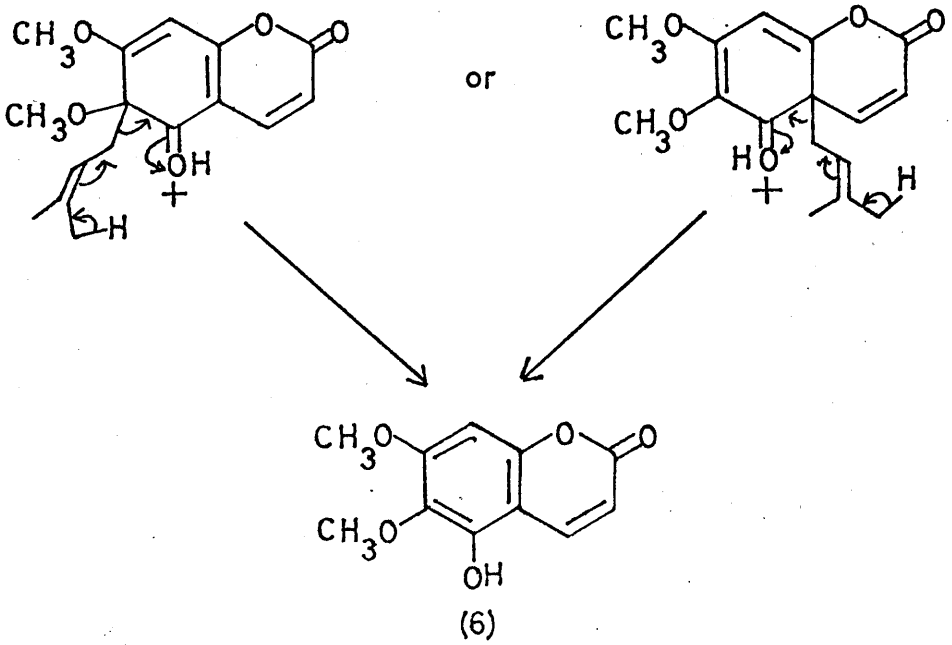


(44)



(45)

SCHEME 2.6

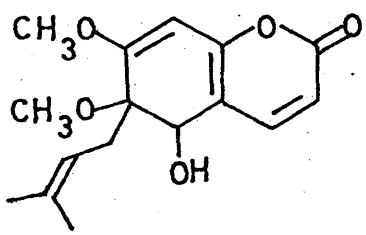


(6)

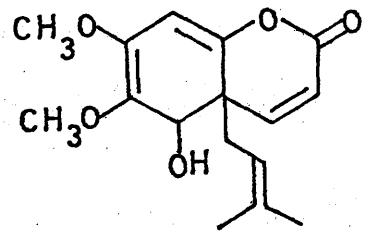
carbon atoms. Structure (38), however, results in two markedly different situations in the diastereomeric alcohols (42) and (43). (42) greatly favours intramolecular hydrogen-bonding and, therefore, can be ruled out. (43) on the other hand completely precludes it. Moreover, this latter structure might be the expected product if the hydride nucleophile were delivered from the less sterically crowded "methoxyl side" of the enone (36). Such an attack would result in the methoxyl group and the proton being cis as shown in (43).

Treatment of the alcohol with hot methanolic acid bore out the stereochemical theories outlined above. Elimination of methanol did not take place, 6,7-dimethoxycoumarin (9) being formed instead. This was identified by u.v., i.r., n.m.r. and mass spectrum, and by comparison with a genuine sample (m.p.,m m.p.)made by methylation of 6,7-dihydroxycoumarin[8]. The mode of formation of this compound from (38) (or (39)) presumably involved the relatively stable allylic secondary carbonium ion(44) (or (45)), followed by further fragmentation, shown in Fig. 2.5. No conclusion as to the structure of the enone could,therefore,be drawn from this observation.

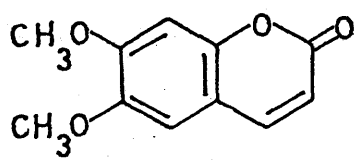
The ease of loss of the isoprene unit from this system was confirmed by similar treatment of the parent enone (36) (or (37)) with ethanolic acid, when tomentin (6) was obtained (Scheme 2.6). It seemed that this facile cleavage was being initiated by protonation of



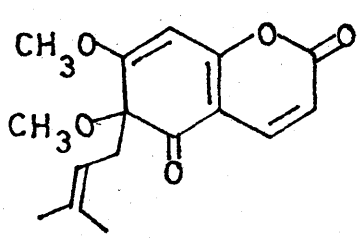
(38)



(39)



(9)



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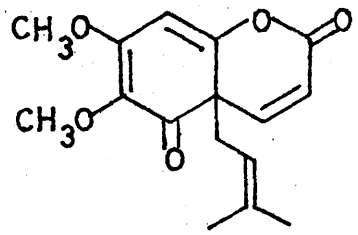
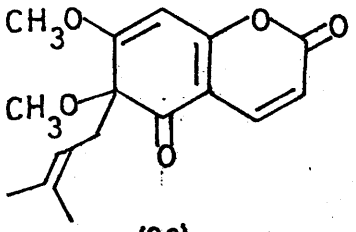


(37)

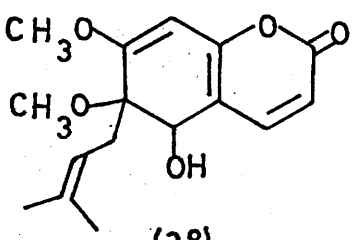
the oxygen function at position 5, and therfore, it was decided to attempt a simple pyrolytic elimination from (38) (or (39)).

Accordingly, a very small sample of the alcohol was heated to 195° in a sublimation block at atmospheric pressure for 5 mins. Examination of the residue by analytical t.l.c. unfortunately showed that, whereas the starting alcohol was the main constituent, 6,7-dimethoxycoumarin(9) was the sole reaction product. No products derived from elimination of methanol were observed.

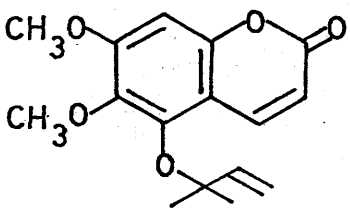
It was felt that fission of the resonance-stabilised alkenyl group from the ring in preference to the desired carbon-oxygen cleavage could be obviated by hydrogenation of the 3,3-dimethylallyl group double-bond. Prolonged hydrogenation of (36) (or (37)) over 5% palladium - charcoal, however, produced no reaction. One possible explanation for this lies in the theory of heterogeneous catalysis. It is thought[31] that hydrogenation proceeds by adsorption of the alkene onto the catalyst surface followed by transfer of adsorbed hydrogen to the participating carbon atoms. Consideration of models of (36) and (37) reveals that such adsorption of the 3,3-dimethylallyl double bond might be very difficult. Preferential adsorption of the dienone-pyrone double bonds might lead to a situation where the 3,3-dimethylallyl unit lies well above the catalyst surface, thereby precluding hydrogenation.



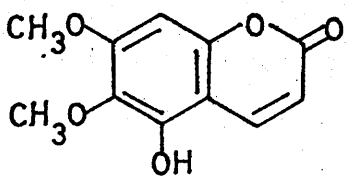
(36)



(38)



(27)



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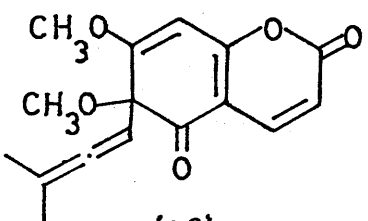
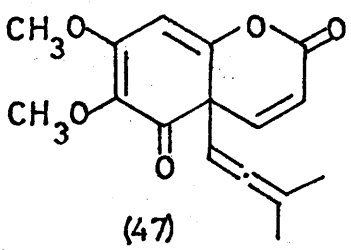


(46)



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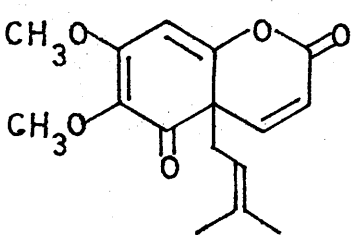

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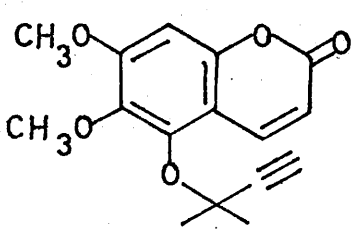
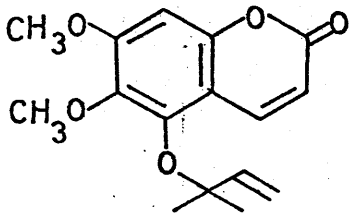


(31)

Although a little evidence for (36) as the structure of the enone had been obtained from the i.r. data of the derived alcohol(38), no firm conclusions had yet been drawn. Before going on to present the conclusive evidence obtained finally to resolve the situation, it is necessary to return to the problem of the composition of the yellow mixture isolated from the propargylation reaction(vide supra).

The similarity between the n.m.r. spectra of the enone obtained from the rearrangement of (27) and the yellow 1:1 mixture obtained as a by-product from the reaction of tomentin (6) with 1,1-dimethylpropargyl chloride prompted a suggestion as to the constituents of the latter mixture. A spot of this material also gave a positive test with 2,4-dinitrophenylhydrazine when a t.l.c. plate was sprayed with this reagent, suggesting that one or both of its constituents was also ketonic. The two allenyl dienones (46) and (47) were postulated to account for the spectral data obtained for the mixture, giving rise to the problem of accounting for their formation. It was known (vide supra) that the allyl ether (27), on Claisen rearrangement, gave a single product whose structure was (36) (or (37)). If the corresponding allene compounds were also formed by this route, the question of accounting for the formation of both (46) and (47) had to be answered. It seemed unlikely that the acetylenic ether (31) could undergo both possible



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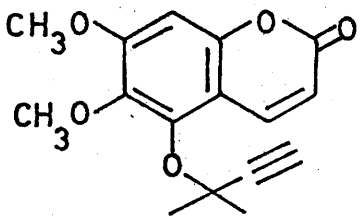

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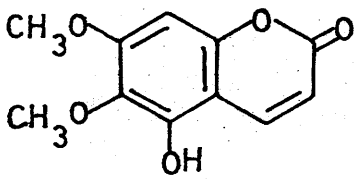

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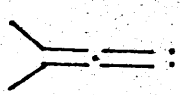
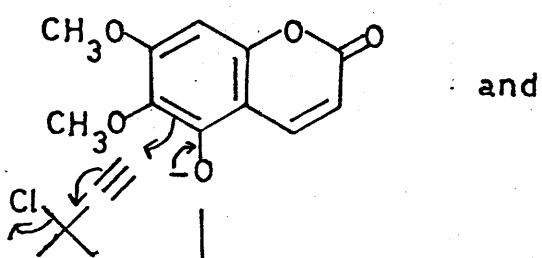


(48)

SCHEME 2.7



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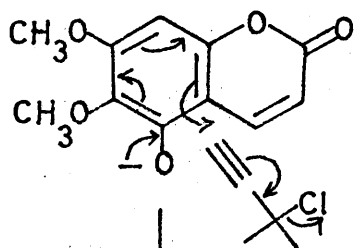

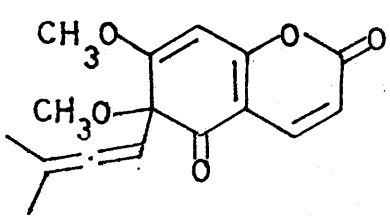

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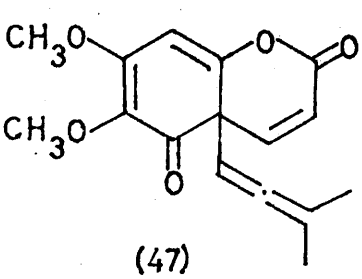


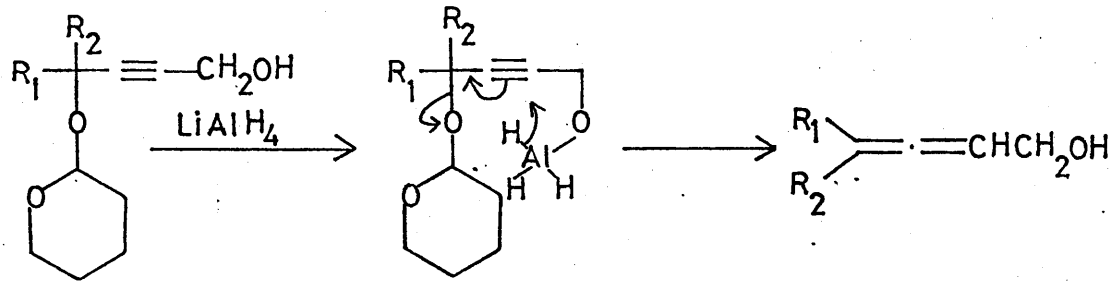
(47)

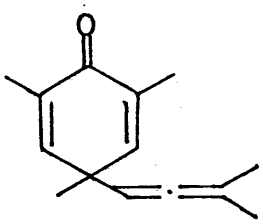
modes of rearrangement, while the allyl ether (27) rearranged exclusively in one direction.

A partial answer came from an experiment in which the propargyl ether (31) was refluxed with potassium carbonate and potassium iodide in 2% aqueous acetone for 50 hr. This was an attempt to simulate the propargylation conditions used for tomentin (6). Any allene mixture formed could only come from rearrangement of (31). Although some decomposition of (31) was observed on t.l.c. after work up, the allene mixture was totally absent, proving that some mechanism other than Claisen rearrangement of the ether (31) had to be invoked to account for its formation during the synthesis of (31).

Two possibilities remain. One theory is that the allenes arise by direct C-alkylation; effected by a species derived from 1,1-dimethylpropargyl chloride. It is known [32] that this reagent can be used as a source of the carbene (48) when used in conjunction with strong base, but this hardly seems a likely intermediate under the mildly basic conditions used. It is conceivable, however, that an electrophilic substitution reaction could take place by attack at the less hindered acetylenic carbon atom of either a carbonium ion, an ion-pair, or a partly dissociated species (Scheme 2.7). Precedent for this exists in the work of Landor [33], who recently

SCHEME 2.8





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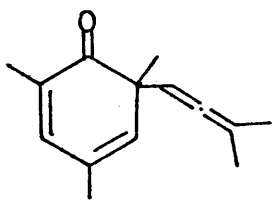

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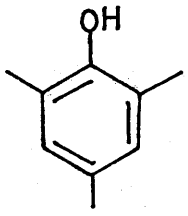

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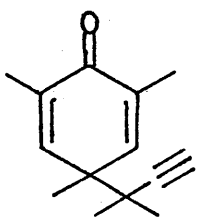

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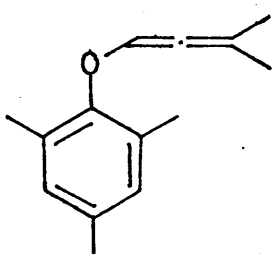

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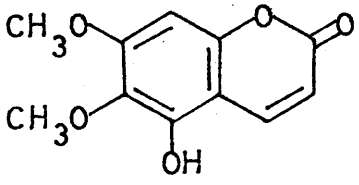

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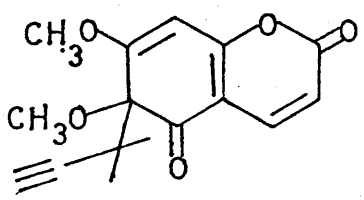
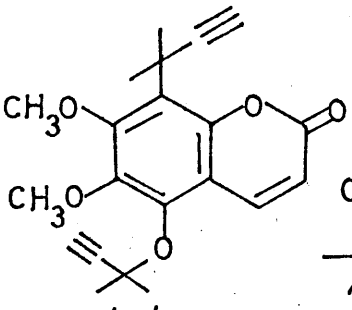


(54a)



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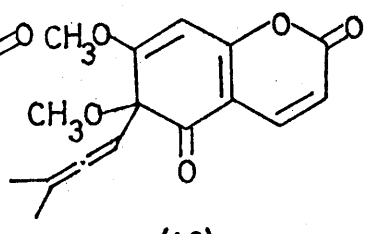

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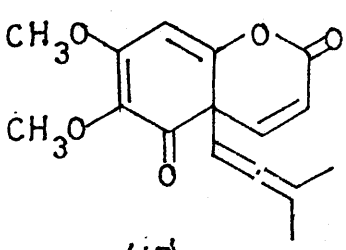

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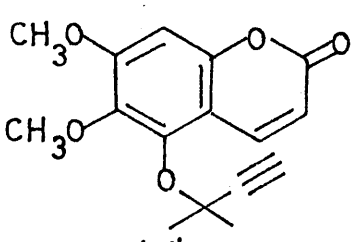
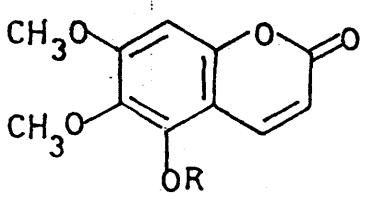


(31)

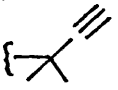
carried out the reaction sequence outlined in Scheme 2.8., and in the work of Roumestant and Gore[34]. Schmid also explained[35] the formation of the allenes (49) and (50), obtained by treatment of the phenol (51) with strong base and 1,1-dimethylpropargyl chloride, as being the result of an $SN2'$ process. Other products obtained from this reaction by Schmid were : a low yield of the para-dienone (52) and,surprisingly,significant amounts of the allenyl ether (53). No product corresponding to this latter compound was isolated by us when tomentin(6) was reacted with 1,1-dimethylpropargyl chloride, although the basic conditions used were much less severe than those of Schmid.

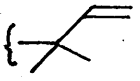
The fact that no products of type (54a) were isolated might be expected for steric reasons. Although more electrophilic in nature, the tertiary centre may not be able to approach the site of alkylation sufficiently closely owing to its bulk. This situation evidently does not apply to the 8-position of the nucleus, however, as the bis-alkylated compound (32) was isolated from the mixture (vide supra). The presence of this material gave rise to an alternative theory to account for the formation of the allenes (46) and (47).

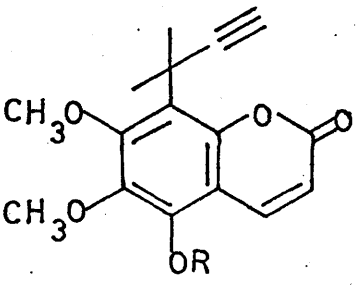
It may be safely assumed the C-alkylation must occur before O-alkylation during the formation of (32). An experiment to verify that the ether (31) could not be C-alkylated unfortunately met with failure. The "normal"propargylation mixture was obtained when



(6) R = H

(31) R = 

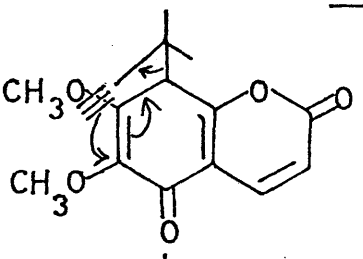
(27) R = 



(54) R = H

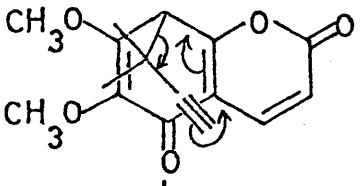
(32) R = 

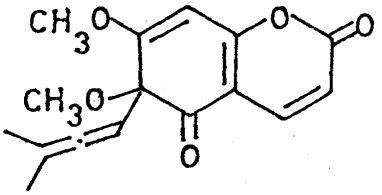
SCHEME 2.9



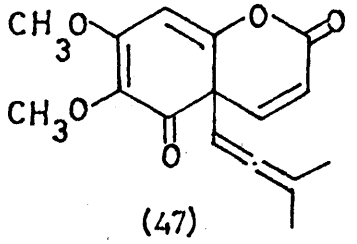
or

(55)

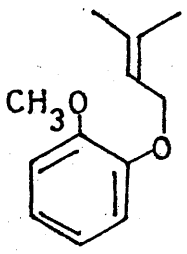




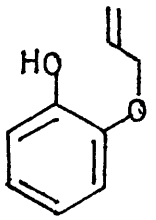
(46)



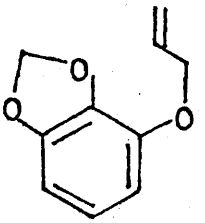
(47)



(56)



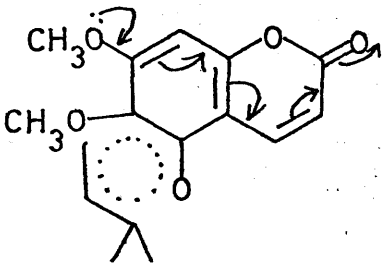
(57)

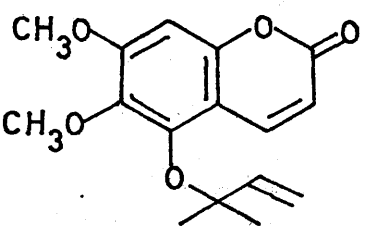


(58)

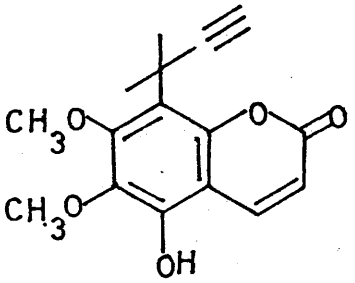
(31) was treated with 1,1-dimethylpropargyl chloride, suggesting that cleavage of (31) had taken place to tomentin (6) which could then react in the presence of excess 1,1-dimethylpropargyl chloride to produce all expected products. If compound (54) constituted part of the reaction mixture, however, as it must have done to account for the isolation of (32), it is possible that it could undergo, via the dienone (55), a Cope-rearrangement to the allenes (46) and (47). The fact that no preference for the site of the allene substituent in the final product was observed must be taken as meaning that the proposed rearrangement could go equally well in either direction (Scheme 2.9). The presence of oxygen in both positions ortho-to-C-8 in the nucleus supports this hypothesis. Examples are known [15,36] where the ortho-para product distribution, obtained from Claisen rearrangement carried out on a substrate having an oxygen substituent in one ortho-position, indicates that the allyl group prefers to migrate via the oxygenated position. Thus, Tarbell reports [36] significant rearrangement to the para-position in the ethers (56), (57) and (58), Sethi and Rao [37] comment on their finding that the monoallyl ether of catechol (57) gives an ortho-para product ratio of 55/45 on rearrangement. In the case of the dienone (55) therefore, the rearrangement could go in either direction as both ortho-positions carry oxygen. For the allyl ether (27), however, some preference for migration onto

FIGURE 2.10

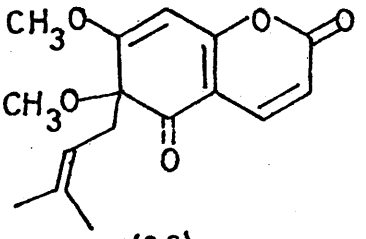




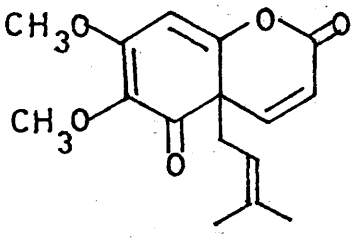
(27)



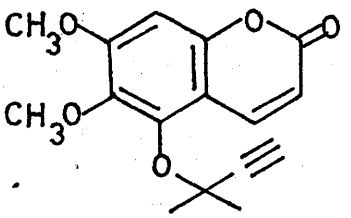
(54)



(36)



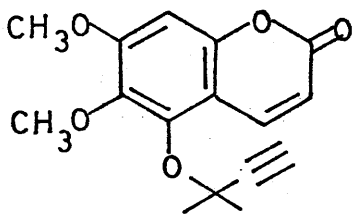
(37)



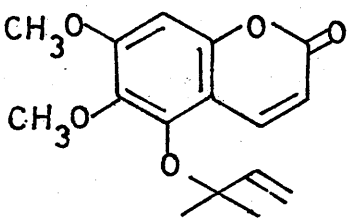
(31)

carbon bearing methoxyl would be expected, but the observed regiospecificity of this rearrangement is still a surprising result. Stabilisation of the transition state through the longer conjugated system involving the 7-methoxyl group (Fig. 2.10) may be of some importance in explaining this observation. A close examination of space-filling models reveals little steric difference between the quasi-chair conformations[38] necessary for the two possible modes of rearrangement of the ether (27). Interconversion between the two by rotation about the carbon-oxygen single bonds is a feasible process. The same was found to apply to the phenol (54). It must be assumed, therefore, that any observed preference for the direction of rearrangement is a direct result of the electronic factors operating, and not due to steric reasons. The second proposed mode of formation of the allene mixture i.e. by Cope rearrangement of an 8-1,1-dimethylpropargylated compound, seems the most attractive to the author.

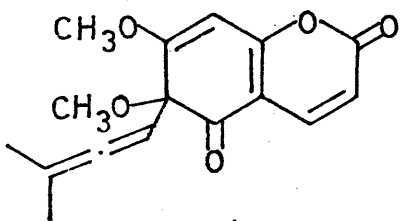
As a partial verification of these theories, and in order to facilitate the assignment of structure (36) or, less likely, (37) to the enone formed by silica-catalysed rearrangement of (27), it was decided to attempt a thermal rearrangement of the propargyl ether (31), when a Claisen-like process would be expected [38] to occur, giving, in the first instance, an allene. When the ortho-position is free, enolisation takes place, followed



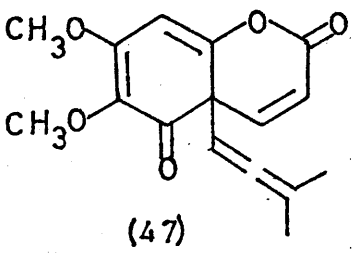
(31)



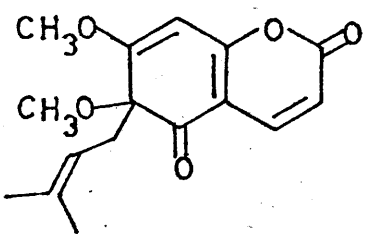
(27)



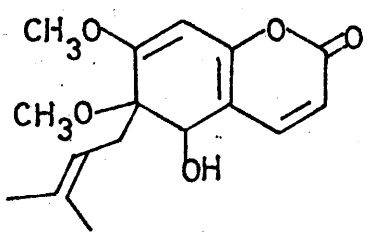
(46)



(47)



(36)



(38)

by rapid cyclisation to a chromene[38,39].

Heating the ether (31) to 130° for 20 mins. under high vacuum produced a deep yellow oil which distilled up the sublimation tube. After preparative t.l.c. on the distillate and subsequent re-distillation, a bright yellow solid was obtained whose n.m.r. indicated that only one allene had been formed. Thus, as in the case of the silica-catalysed rearrangement of the ether(27), migration had occurred exclusively in one direction to give (46) (or (47)). This observation reaffirmed the earlier finding (vide supra) that the mixture of (46) and (47) formed during the synthesis of (31) could not have arisen by Claisen rearrangement of the latter.

The spectral data obtained for this pure allene are worthy of discussion. In the i.r. a very weak band was present at 1970cm.$^{-1}$, indicative of the allene grouping, along with the significantly strong band at 1538cm.$^{-1}$ encountered earlier for (36) and (38). If the theory of the origin of this band were correct (vide supra), the allene produced in the pyrolysis of (31) must be (46). Very significant evidence came from the u.v. of the pure allene, which was almost superposable on the u.v. of the 3,3-dimethylallyl enone (36), indicating identical chromophores. In this respect it was interesting that the u.v. spectrum of the 1:1 mixture of (46) and (47) was very complex, and is illustrated in

FIGURE 2.11

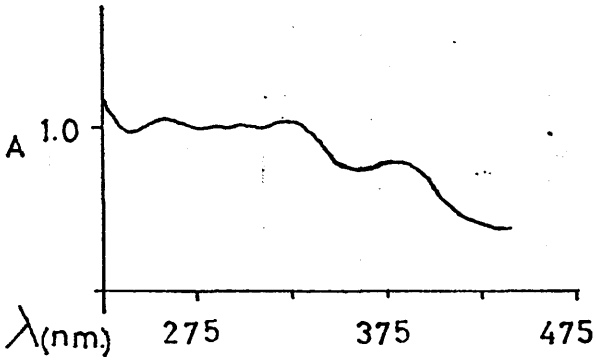
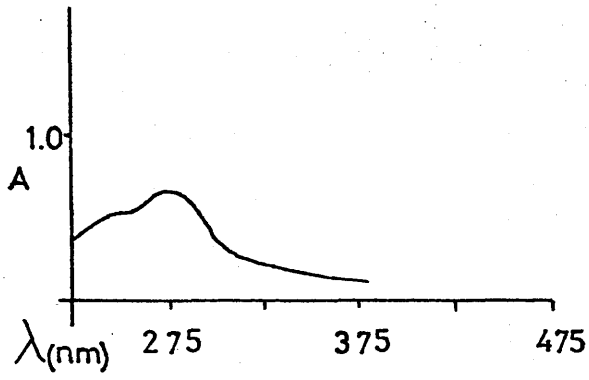
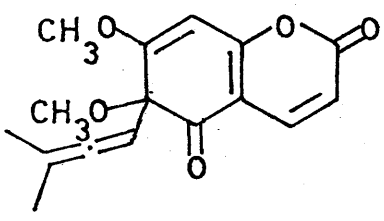
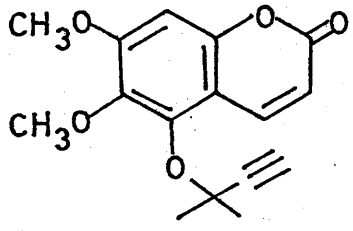


FIGURE 2.12

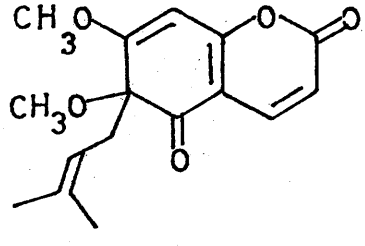




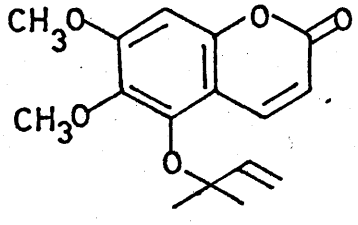
(46)



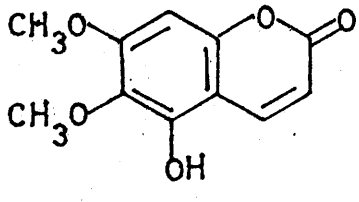
(31)



(36)



(27)



(6)

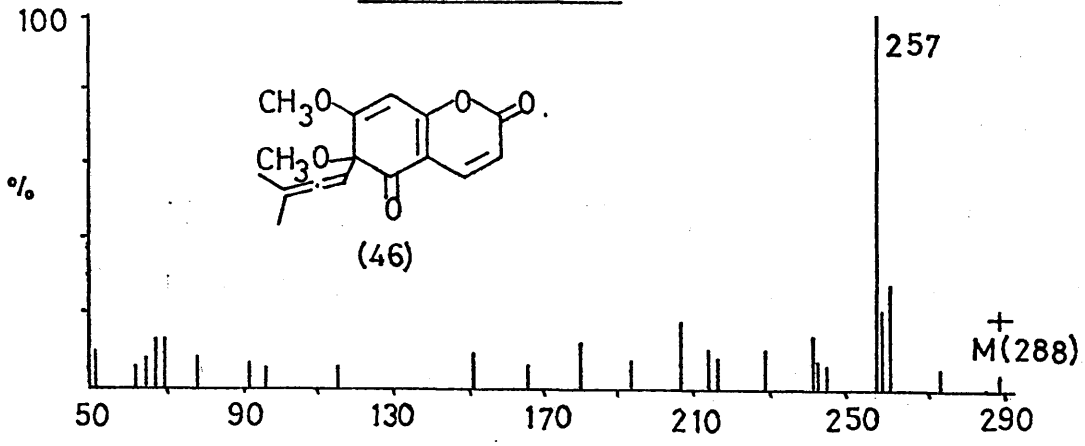
Fig. 2.11. After correcting for concentration, it was possible to subtract the u.v. of (46) from the u.v. of the mixture mathematically. Subtracting absorbances at 2nm. intervals resulted in the curve shown in Fig. 2.12 for the other allene. Evidently the chromophore in this latter case was not as extended as in the allene obtained by pyrolysis of (31). Structure (46) was, therefore,confidently assigned to the yellow allene isolated, and structure (36) to the enone isolated from rearrangement of (27). This latter assignment was possible owing to the strong similarity between the u.v.'s of the pure allene (46) and the enone (36).

The n.m.r.of(46)was instructive in that the allenic proton resonated as a septet, J=3Hz., through coupling to the methyl groups. This observation is typical of the system, according to the findings [40] of Snyder and Roberts and was confirmed by irradiation at the methyl resonance, when the allenic proton signal collapsed to a sharp singlet.

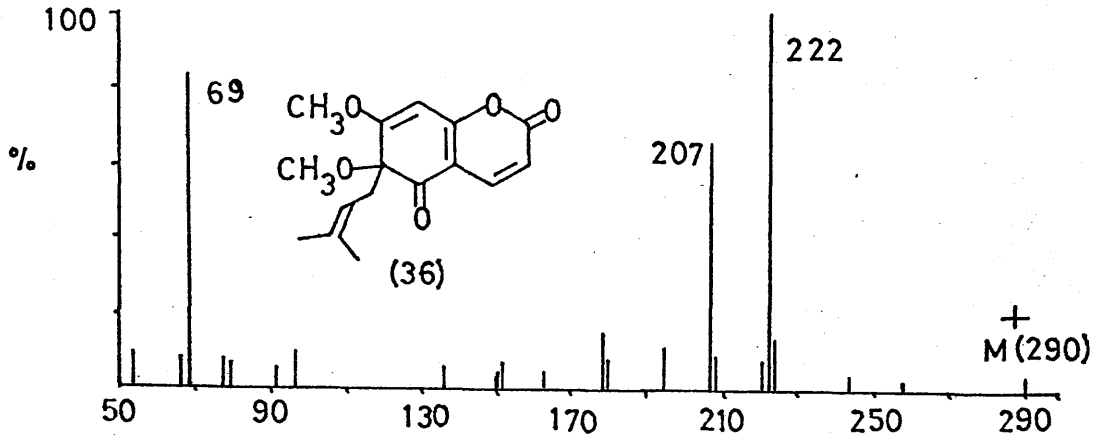
A comparison of the mass spectra of (36) and (46) led to some very interesting conclusions. The principal fragmentation pathway in the former is by rapid loss of the five-carbon unit, borne out by treatment with acid when tomentin (6) is the sole product.

The spectrum of (46), however, indicates that loss of methoxyl was a facile process, the dimethylallenyl unit being retained until a fairly late stage in the

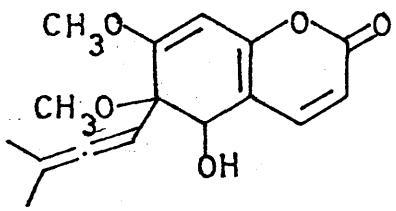
FIGURE 2.13



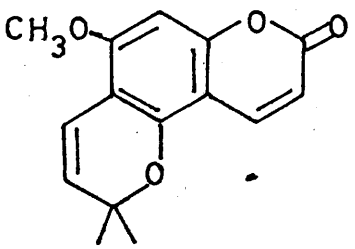
(46)



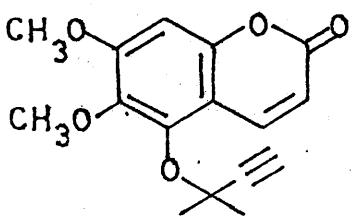
(36)



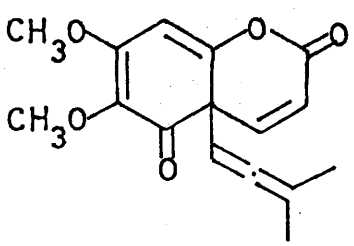
(59)



(60)



(31)

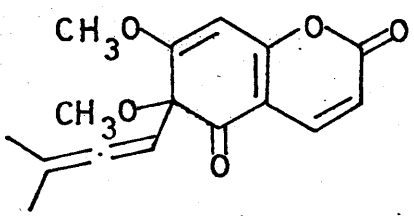


(47)

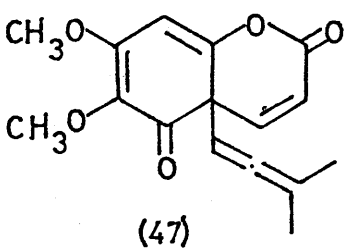
breakdown. The two fragmentation patterns are given in Fig. 2.13 for comparison.

These observation encouraged us to try the elimination of methanol from (59). Reduction of (46) with sodium borohydride again went cleanly and in high yield, affording a semi-solid yellow material which rapidly decomposed at R.T. but whose n.m.r. and u.v. were consistent with structure (59). Warming a methanolic solution of this compound with dil. hydrochloric acid afforded colourless needles after work up and purification by sublimation. The m.p., i.r., n.m.r. and mass spectrum of this compound presented very strong evidence for structure (60), that of alloxanthoxyletin [41], and this was confirmed (m.p., m.m.p., t.l.c. and mass spectrum) by comparison with a natural sample of (60) kindly supplied by Professor B.S.Joshi, CIBA, Bombay. The orientation of the allene (46) and the enone (36) were, therefore, established unequivocally by spectral and by chemical means.

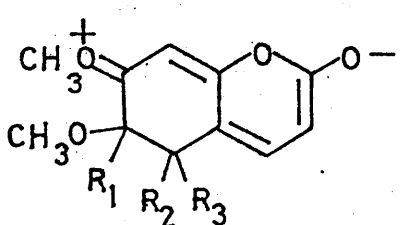
Having obtained (46) as a pure compound by rearrangment of (31), the possible isolation of its isomer (47) from the 1:1 mixture of the two was investigated. As stated earlier, thin layer chromatography had proved ineffective for this and so an alternative was sought. A little experimentation revealed that a partial separation could be achieved by very careful distillation of the mixture, the required allene (47) being slightly more volatile than



(46)



(47)



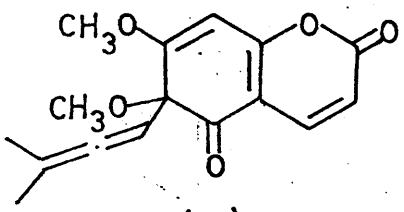
(61)

(46). Although still contaminated with a little of the bright yellow (46), the purest sample of (47), obtained from the upper end of the tube, could be freed from its isomer by washing the cooled material with a little ice-cold ether until all traces of yellow compound had been removed. The colourless residue remaining crystallised very slowly on standing, and gave pure (47) after one further sublimation.

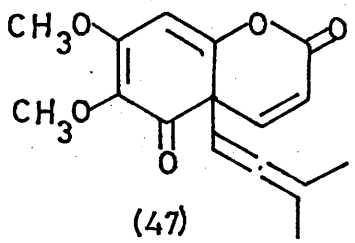
As expected, the shorter chromophore in (47), as compared with (46), resulted in a significantly different u.v. spectrum, accounting for the fact that (47) is colourless whereas (46) is bright yellow. The curve obtained for (47) was identical with that derived mathematically by subtraction of the u.v. of (46) from the spectrum of the 1:1 mixture (vide supra).

In the i.r., (47) exhibited a very weak band at 1968cm.$^{-1}$, along with other bands at 1760, 1663, 1640 and 1604cm.$^{-1}$. No strong band was found in the 1530-1540cm.$^{-1}$ region, however, providing further support for the idea of structures of type (61) being responsible for this band in compounds having the extended chromophore present in (46).

The n.m.r. spectra of (46) and (47) were very similar. The septet structure observed for the allenyl proton in (46) was again in evidence, irradiation at the methyl resonance causing collapse to a sharp singlet. Again,

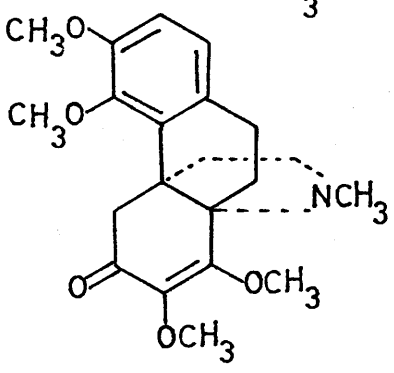


(46)

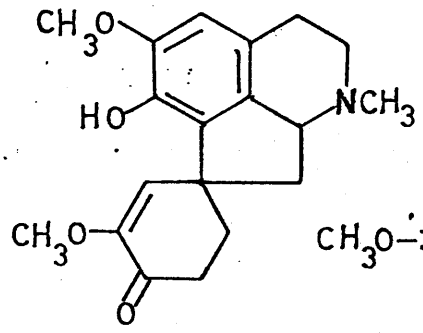


(47)

CH_3O– :– δ 4.08
3.91
3.80
3.64

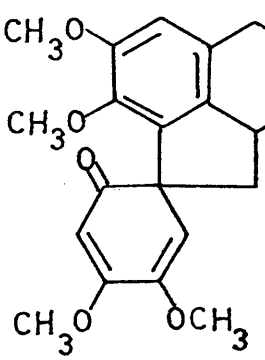


(62)



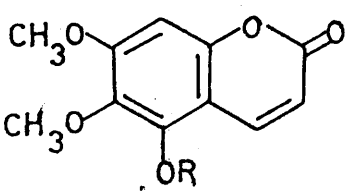
CH_3O– :– δ 3.78
3.54

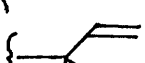
(63)



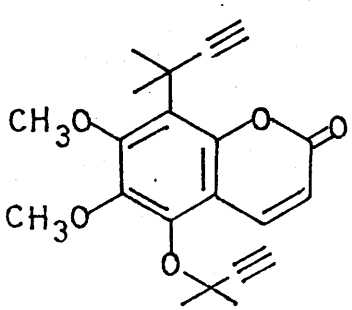
CH_3O– :– δ 3.88
3.79
3.67
3.63

(64)

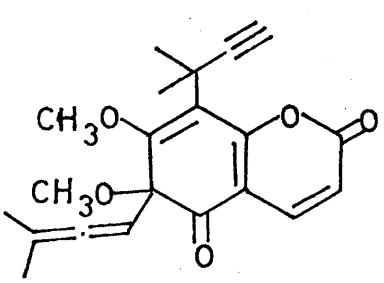


(27) R = 

(31) R = 



(32)

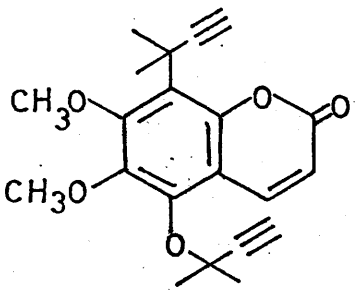


(65)

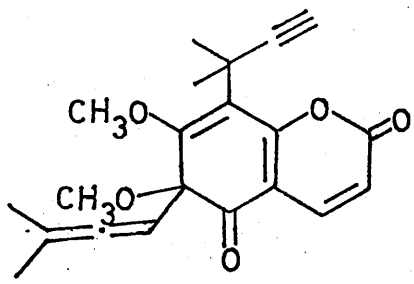
as in (46) the two methoxyl resonances in (47) were well separated (δ 3.22 and 3.86 as compared with δ 3.21 and 3.87). Whereas in (46) the signal at δ 3.87 is probably the C-7 vinyl methoxyl and δ 3.21 the methoxyl on tetrahedral carbon, it is much less easy to account for the substantial difference in chemical shift observed for the two methoxyls in (47). In the latter, both are attached to the double-bond of a conjugated ketone and consequently might be expected to show some difference in chemical shift, with the β-methoxyl resonating at lower field (cf.(62)[42], (63)[43] and (64)[44]). It must be concluded that in (47) the methoxyl α to the carbonyl group is significantly shielded. One possible, though from models not completely convincing, explanation is a through-space effect produced by the diamagnetic circulation of the π-electrons of the allene system.

The mass spectra of (46) and (47) differ markedly in that the molecular ion from (47) loses the C-5 moiety immediately to give rise to the base peak, whereas in (46) the C-5 unit is retained until a late stage in the fragmentation.

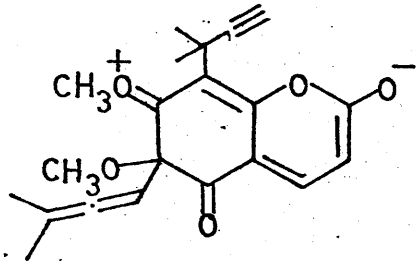
An interesting extension to the regiospecific rearrangements of (27) and (31) was the action of heat on the bis acetylene (32). The expected product would be the enone (65), if the proposed structure for the bis acetylene (vide supra) were correct.



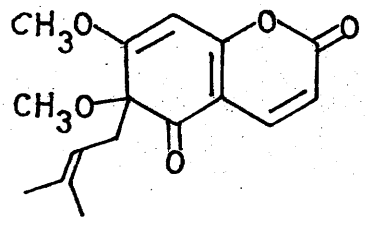
(32)



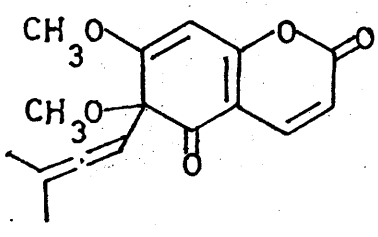
(65)



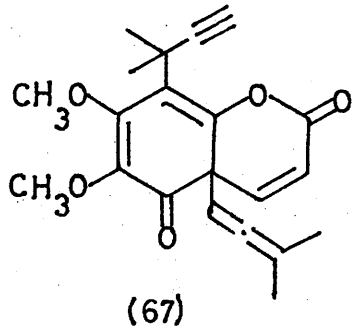
(66)



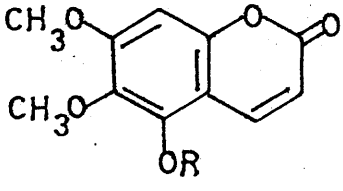
(36)

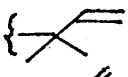


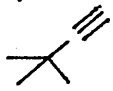
(46)

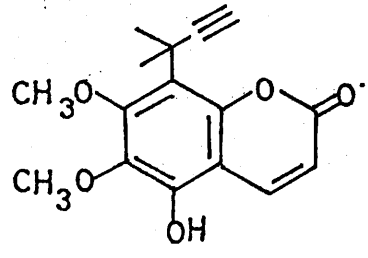


(67)



(27) R = 

(31) R = 

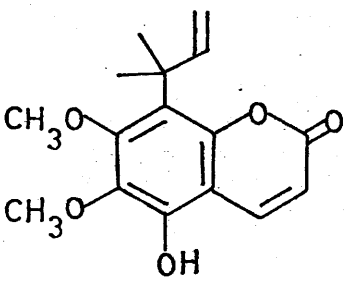


(54)

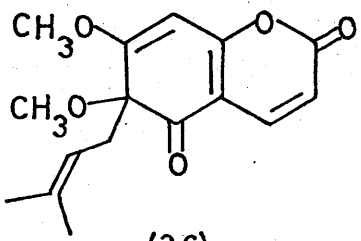
On heating (32) in a sublimation block to 150° for 20 mins., a deep orange liquid distilled slowly up the tube. Elemental analysis and all spectral data were completely in accord with structure (65) for this compound. In the i.r. bands were present at : 3310, 2103 (w), 1966(w), 1757, 1679, 1614 and 1510(vs)cm.$^{-1}$ the last again being attributed to a contribution from the resonance hybrid (66). N.m.r. signals were present at δ 1.57(3H;s), 1.70(3H;s.), 1.73(3H;s.), 1.78(3H;s.), 2.30(1H;s.), 3.32(3H;s.), 4.10(3H;s.), 5.12(1H;m.;J 3Hz.), 6.12(1H;d.;J 9.5Hz.), and 7.90(1H;d.;J 9.5Hz.). Again marked shielding of one methoxyl group was well in evidence.

The u.v. spectrum of (65) was similar in general appearance to that of the enones (36) and (46), confirming the presence of the extended chromophore, and ruling out (67) as a possible structure for this compound. The molecular weight was confirmed by the peak at m/e 354 in the mass spectrum.

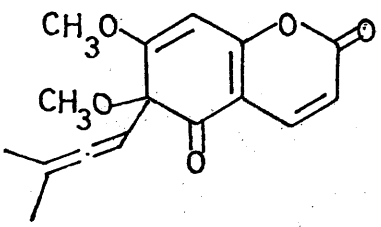
It should be seen, therefore, that each of the three ethers (27), (31) and (32) rearranges exclusively into the 6 - position of the coumarin nucleus. In the case of (27), the reaction took place rapidly and at R.T. when silica was present. Although high temperatures were used in the conversion of (31) to (46), it is interesting to note that none of compound(54) was isolated from the reaction. The action of heat on the enone (36) remained to be investigated,



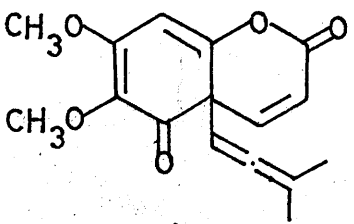
(68)



(36)



(46)



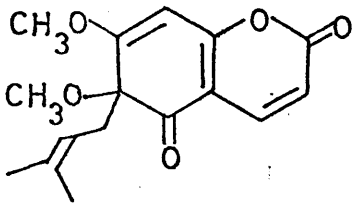
(47)

in order that the originally hoped-for phenol (68) might be produced.

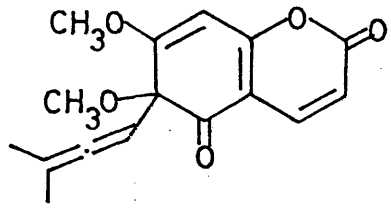
A small sample of (36) was heated in a sublimation block for 15min., at 150°. Examination of the residue by t.l.c. revealed the sample to be substantially unchanged. On raising the temperature to 200° for a further 10mins., t.l.c. still showed (36) to be the major component of the residue, which had by this time undergone some charring. A spot corresponding to a compound more polar than (36) had also appeared on the plate, however. Owing to shortage of material this compound was never isolated, but the experiment served to illustrate the remarkable thermal stability of the enone (36).

In another experiment to detect rearrangement to position 8, the mixture of allenes (46) and (47), in tetrachloroethylene, was heated to 155° for 40mins. in a sealed n.m.r. tube. The spectrum was then run immediately, the tube and contents being kept at 100° during the scanning period, but no detectable acetylenic resonance was observed.

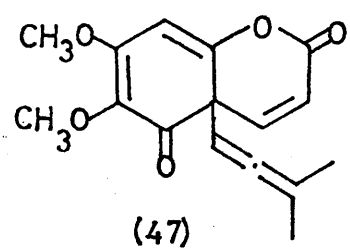
Heating the allenes (46) and (47) individually in a sublimation block to 145° for 45mins. also left them apparently unchanged. U.v. spectra of both distillates and residues were identical with those of the starting materials.



(36)

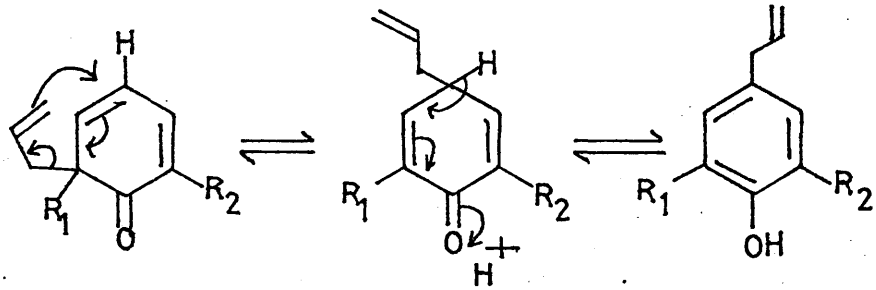


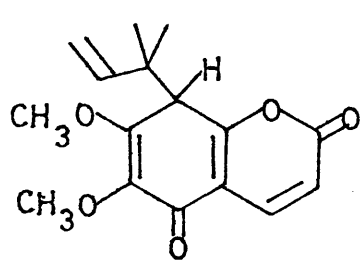
(46)



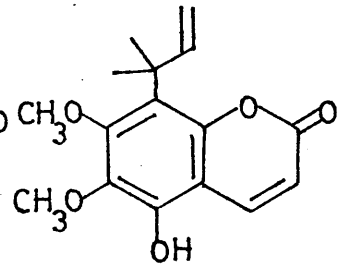
(47)

SCHEME 2.14

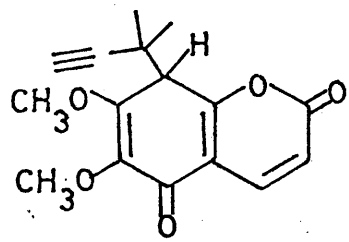




(69)



(70)



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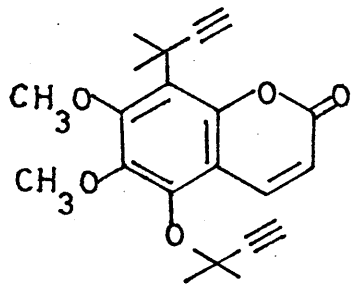

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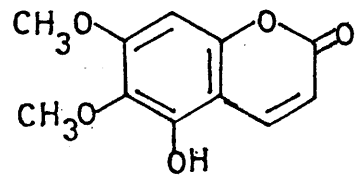
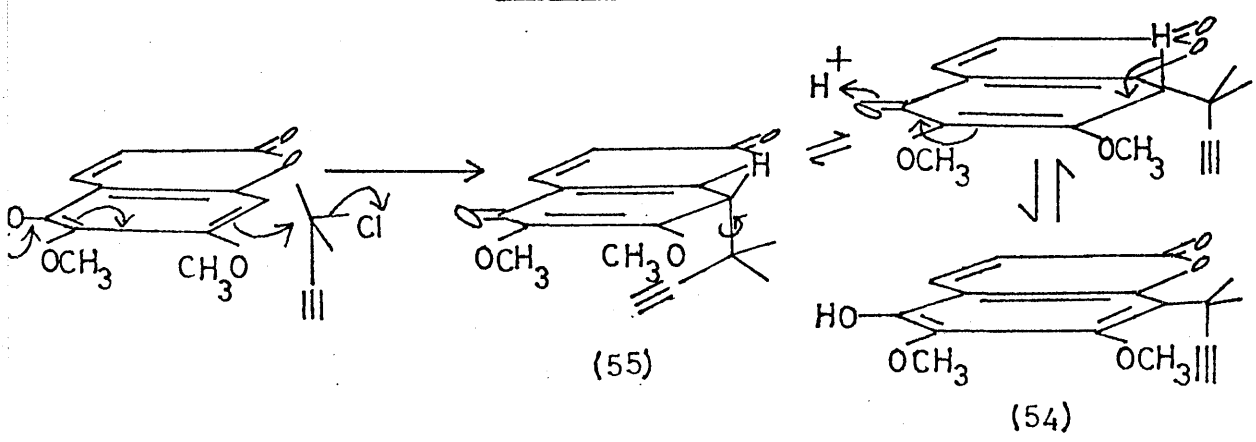


(6)

FIGURE 2.15

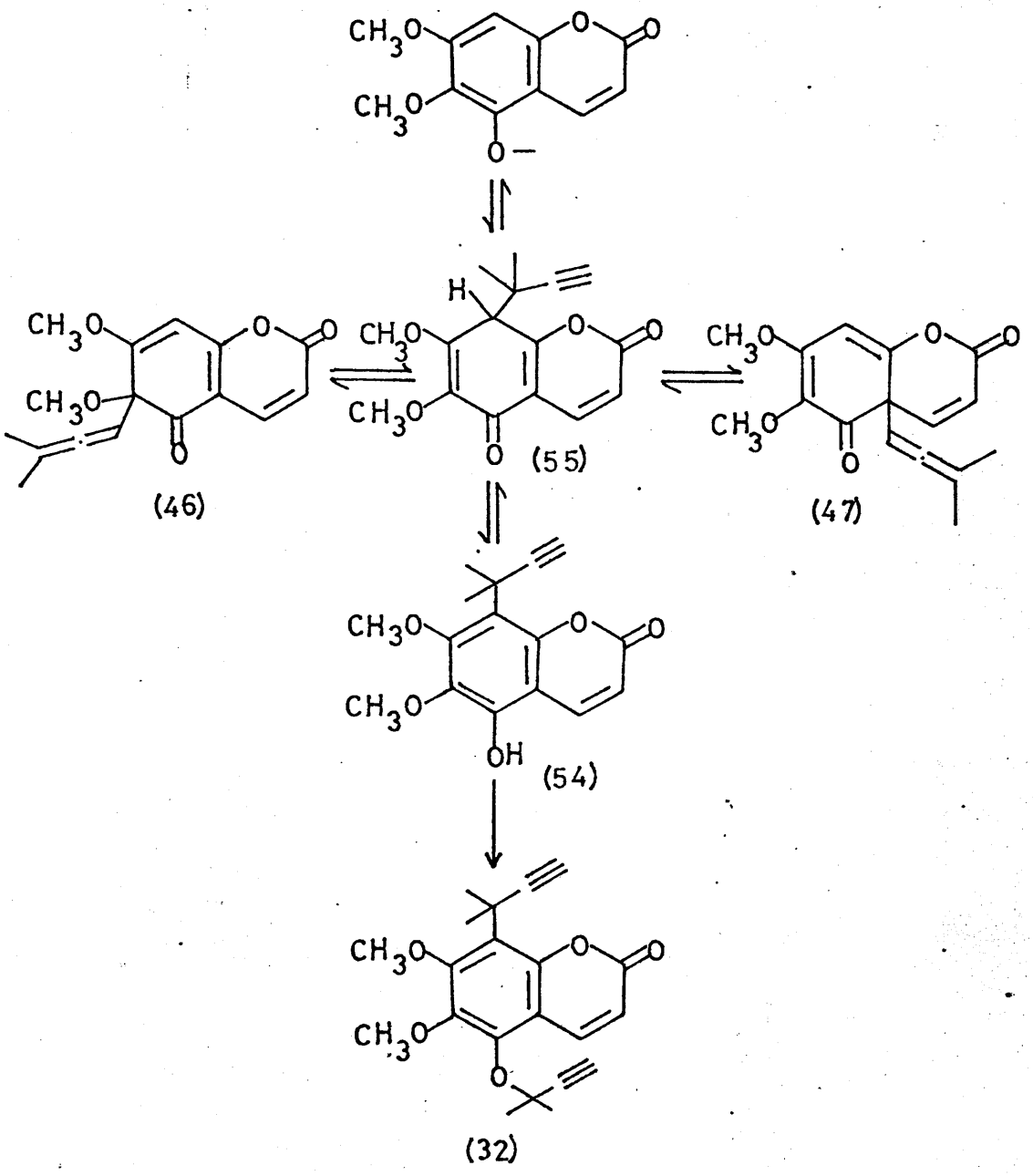


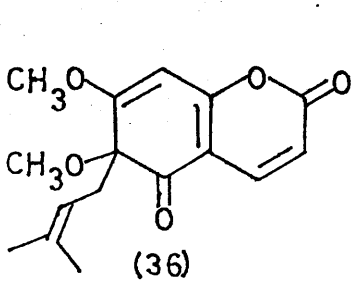
(55)

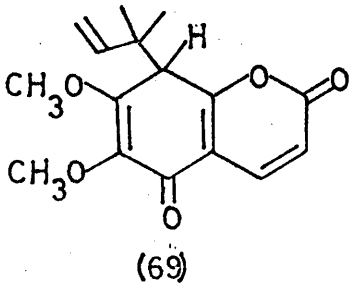
(54)

The above observations indicate that the enones (36), (46), and (47) exhibit pronounced thermal stability. Normally[15], in a Claisen rearrangement of an allyl ether blocked in the ortho-positions, the ortho-dienone is not isolated, but a further (3,3) sigmatropic shift occurs, leading to a para-dienone which can enolise to the p-allylphenol if it possesses a para-hydrogen (Scheme 2.14). Surprisingly, this does not occur for the cases in question, implying that either the Cope rearrangement to C-8 does not take place, or that, if an equilibrium is set up between the o- and p-dienones (36) and (69), then the proportion of the latter is very small. Enolisation to (70) would not be a very favourable process[15] owing to the presence of steric interaction between the gem-dimethyl group and the neighbouring methoxyl substituent in the necessary conformation. The para-dienone (55) is almost necessarily a reaction intermediate in the formation of (32), obtained during the propargylation of tomentin(6). In the first-formed conformation of (55), the 1,1-dimethylpropargyl group would be pseudo-axial[45] and would be able to adopt the conformations necessary for the Cope rearrangement to the two allene dienones (46) and (47) by simple rotation (Fig. 2.15). Alternatively, a conformational change in which the 1,1-dimethylpropargyl group became psuedo-equatorial(and hence in a sterically unfavoured position) would allow the

FIGURE 2.16



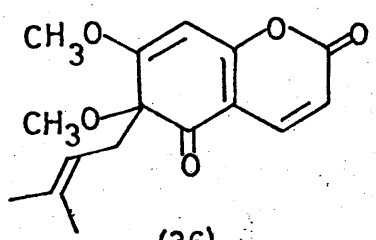




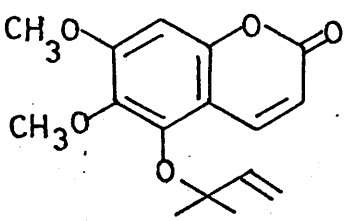
pendant hydrogen atom to become pseudo-axial, and, therefore, in the correct conformation for enolisation to (54), a compound which is trapped as its 1,1-dimethylpropargyl ether. The system of equilibria is illustrated in Fig. 2.16.

If, during the pyrolysis of the dienones (36) and (46), there had been a substantial amount of the para-dienones (69) and (55) at equilibrium (Fig. 2.16), then products derived from the pathways described above should have been detected. However, no changes in the u.v. spectra were observed; nor was any acetylenic proton resonance observed in the high temperature n.m.r. experimental on the 1:1 mixture of (46) and (47).

An explanation for the apparent difficulty in forming the para-dienone (55) is suggested by a consideration of its stability as compared with the ortho-dienone (46), and also by a consideration of the transition state between them. Space-filling models reveal that the C-8 substituent in (55) viz. $(CH_3)_2C-C\equiv CH$ is markedly bulkier than the almost linear $(CH_3)_2C=C=CH-$ substituent at C-6 in (46). Thus, without taking into consideration the differences due to different types of conjugation, the para-dienone (55) would be expected to have a higher ground state free energy than the ortho-dienone (46) on steric grounds alone. In



(36)

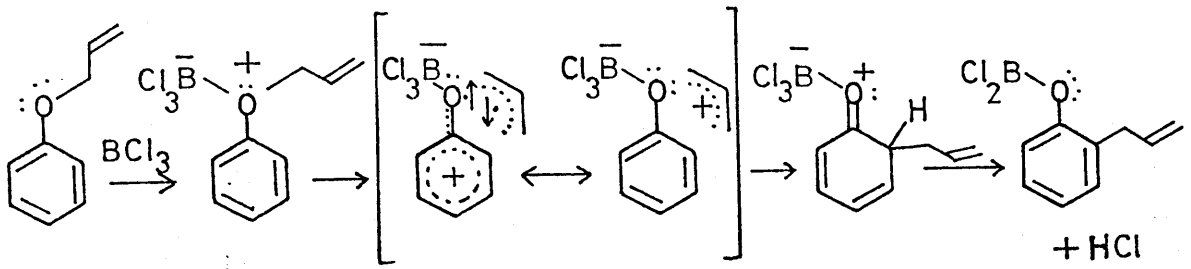


(27)

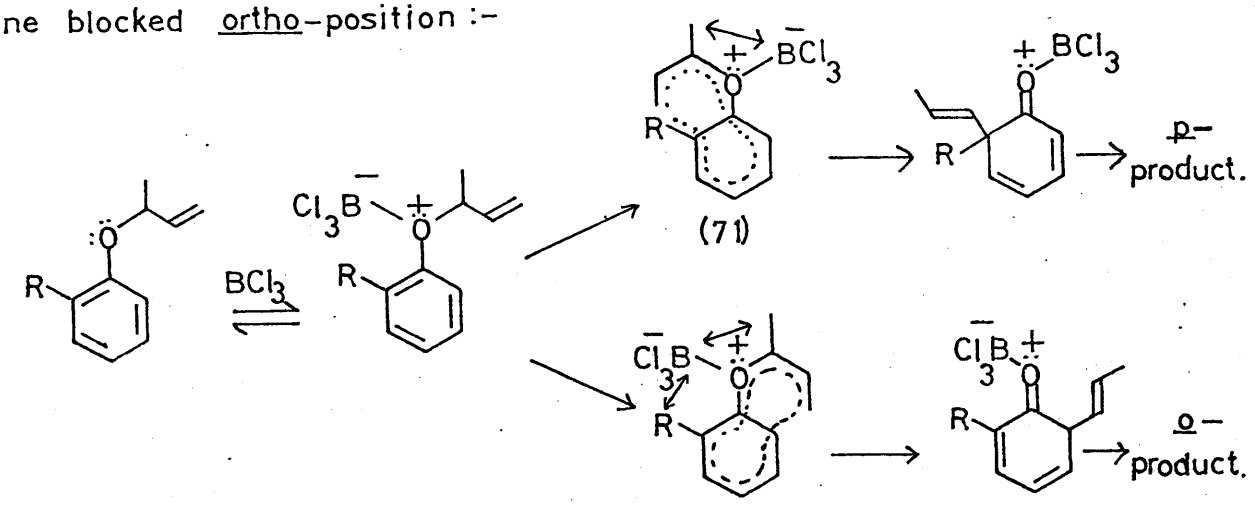
considering a rearrangement from C-8 to C-6 i.e. from the para-dienone to the ortho-dienone, the bond broken is between ring-carbon and a tertiary carbon atom. This should be an energetically favourable process owing to the release of strain. The new bond being formed at C-6 suffers no steric contraints during the appraoch of the terminal acetylenic carbon. The reverse process, however, requires the breaking of a bond which suffers no weakening influences and the making of a bond which gets progessively more difficult as the tertiary carbon approaches C-8. This effect, which has also been observed by Schmid [35] and is almost certainly due to the size of the gem-dimethyl group, has been invoked in the past [46] to account for the rate of thermal cyclisation of aryl-1,1-dimethylpropargyl ethers to chromenes. A similar argument is thought to apply to the 3,3-dimethylallyl enone (36).

The observation which initiated this investigation, namely the silica-catalysed rearrangement of the allyl ether (27) to the enone (36) still remains to be explained. The most reasonable rationalisation of this exceedingly facile high-yield conversion comes from the elegant work of Professor Hans Schmid. In a recent publication [47] he pointed out that the rate of the Claisen rearrangement can be increased by a factor of $\sim 10^{10}$, relative to the thermal reaction, by charge induction. Allyl aryl ethers were shown to undergo

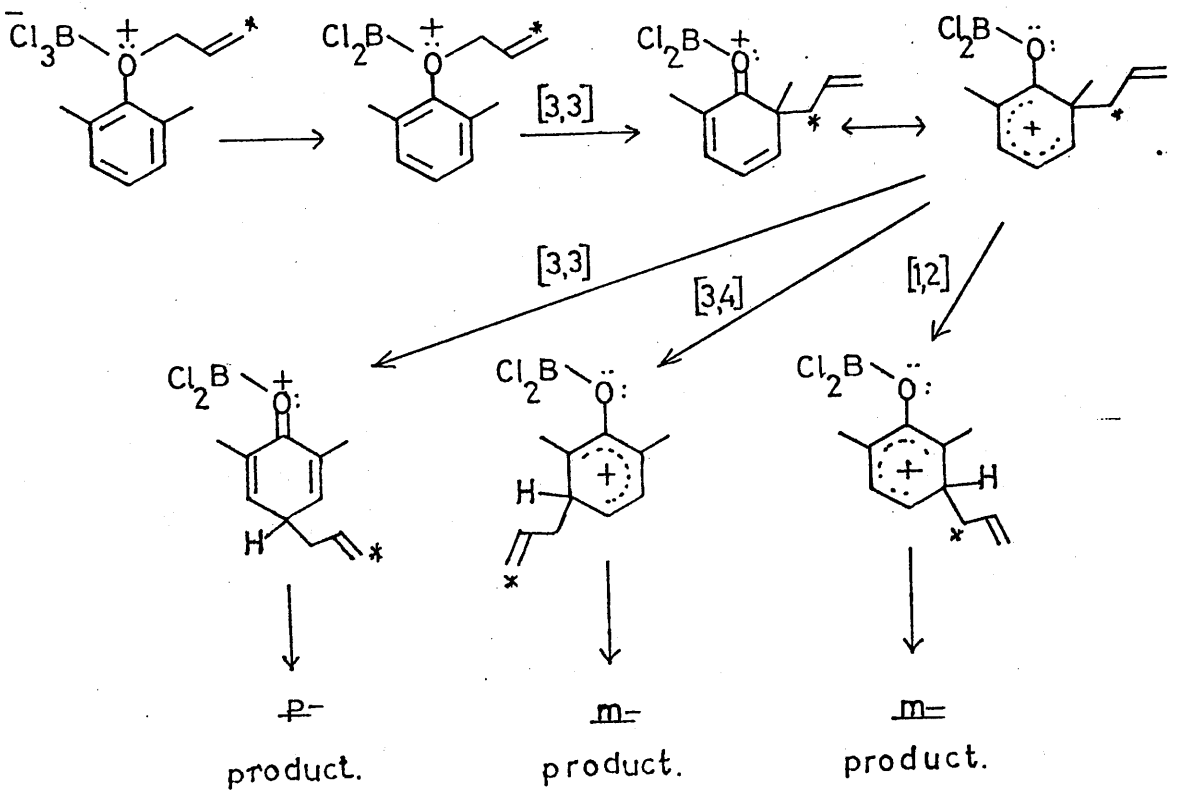
SCHEME 2.17



One blocked ortho-position :-



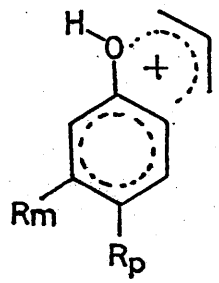
Both ortho-positions blocked :-



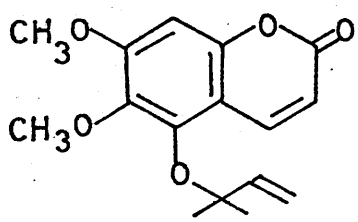
conversion to ortho-allyl phenols, in chlorobenzene at low temperatures, in the presence of boron trichloride. When one of the ortho-positions was substituted, a mixture of ortho and para- products were produced, with more of the para- product than in the corresponding thermal rearrangement.

To account for his observations, Schmid invoked the sequence shown in Scheme 2.17. Presumably, cleavage of the oxygen-carbon bond is facilitated by the complexing of the oxygen atom with the Lewis acid, accounting for the increase in the rate of the reaction. When both ortho- positions are substituted the ortho-Claisen took place and was then followed by a (1,2),-(3,3)-, or (3,4)- shift of the allyl moiety, thus accounting for the observed products. The predominance of the para-product in compounds with one ortho-substituent was explained by Schmid by invoking steric hinderence. The conformer (71), leading to a para-rearrangement, was regarded as predominating over the alternative (72) which would be expected to yield an ortho-substituted product.

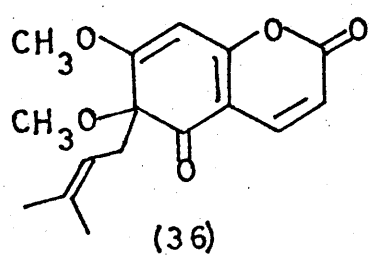
Other workers have also noticed the effect of acid on the speed of the Claisen rearrangement. Svanholm and Parker [48] studied the rate of rearrangement of phenyl allyl ethers in trifluoroacetic acid and obtained increases of the order of 10^5 times the rate of



(73)



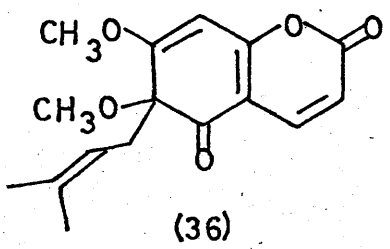
(27)



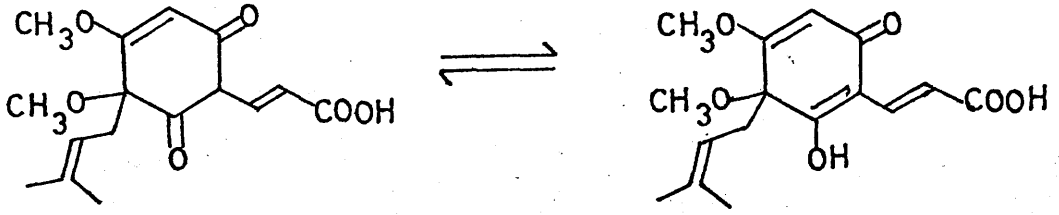
(36)

the thermal rearrangement. They concluded that a transition state such as (73) in which the positive charge is spread over several atoms best describes this reaction. Miller also descibes [49] the acid-catalysed sigmatropic shifts of allyl groups in cyclohexa-2,4-dien-1-ones, methanolic hydrochloric acid being used to promote the reaction at R.T. He observed both Cope and reverse-Claisen rearrangement under these conditions. Diethylaluminium chloride was used by Sonnenberg [50] to carry out Claisen rearrangement of allyl phenyl ethers at R.T. in hexane, but no explanation of its apparent catalytic effect was given.

In the case of the ether (27), it would seem that silica is bringing about the same carbon-oxygen bond weakening as boron trichloride is thought to do[35], although the precise mechanism in our case remains obscure. Presumably, the relief of considerable steric strain in going from the ether(27) to the enone (36) also contributes to driving the reaction to completion. That none of the other shifts observed by Schmid i.e. (3,3)-, (3,4)- or (1,2)- took place is probably a reflection on the weakness of any oxygen-silica bond formed. Whether such a bond ever exists or whether the silica serves to stretch and polarise the carbon-oxygen bond by virtue of adsorption of the substrate on to its surface, is unknown.



(36)



(74)

One further aspect of the chemistry of (36) was investigated. It had been noted that (36) showed a base shift on running its u.v. spectrum. The original curve was not, however, generated on re-acidification. Treatment of (36) with dil. sodium hydroxide solution in ethanol produced a pale yellow glass after acidification, having n.m.r. signals at δ 1.55(6H;bd.), 2.65(2H;d.;J 7.5Hz.), 3.08(3H;s.), 3.78(3H;s.), 4.78(1H; bt.;J 7.5Hz.), 5.57(1H;s.), 7.00(1H;d.;J 16Hz.)and 7.77(1H;d.;J 16Hz.). An attempt to purify this material by preparative t.l.c. resulted in loss of the sample, no isolable product being eluted from the silica. It would appear from the n.m.r., however, that cleavage of the pyrone ring had occurred to furnish a trans-unsaturated carboxylic acid, to account for[51] the observed coupling constant of 16Hz. Under normal circumstances, ortho-hydroxycinnamic acids recyclise on acidification[52]. It must be assumed, therefore, that the system has probably tautomerised to a structure of type (74). No further work was carried out on this reaction.

Throughout this work, progress was held up because of lack material, owing to the fact that the starting compound is a natural product with only one known source. After some effort, a growing specimen of Prunus tomentosa was located in Britain[53]; but, on obtaining a fairly substantial sample of the wood,

close examination revealed that no tomentin was present in it. I am, therefore, extremely grateful to Professor Masao Hasegawa, Tokyo, for his generosity in supplying samples of the glycone tomenin.

PART II

Experimental

Hydrolysis of tomenin.

Tomenin (1.046g.) was heated with 26ml. 5% v./v. hydrochloric acid on a steam bath for 3 hours. After cooling, the colourless needles were filtered off, washed with cold water and dried at 40° for 2 days. The yield of tomentin (6) was 531mg (88%), m.p. 182-185°(lit.[1] m.p. 185°);n.m.r. signals (100MHz.) at δ 3.83(3H;s.), 3.85(3H;s.), 6.19(1H;d.;J 9.5Hz.), 6.31°(1H;s.), 6.42 (1H;s.), and 7.98(1H;d.;J 9.5Hz.); λ_{max} 323, 255(sh.) and 230(sh.)nm.(logϵ 4.13, 3.54 and 4.06); λ_{max}(base) 390, 333, 269 and 245(sh.)nm.(Logϵ3.68, 4.02, 3.88 and 3.95);mass spectral peaks at $^{m}/_{e}$ 222(M^{+}),208, 207, 179, 151, 95 and 69(r.a.73, 12, 100, 19, 42, 19 and 18%).

N-phenyldichloroazomethine.

Prepared according to the method of Murphy[14] from phenyl isothiocyanate (22.5g.) and gaseous chlorine. Fractionation of crude material at 117°(15 mm.) gave the pure product as a colourless oil (20g.,69%).

1-Phenyl-5-chlorotetrazole (20).

Made from N-phenyldichloroazomethine (1.74g.) and sodium azide (0.7g.) according to the method of Kauer and Sheppard[13]. (20) crystallised from benzene-hexane as a colourless solid (1.1g.61%) m.p. 121-123°(lit.[13] m.p.123.4-124.6°).

Attempted formation of 7-O-(N-phenyltetrazolyl)scopoletin.

Potassium carbonate (20mg.) and 1-phenyl-5-chloro-tetrazole(12mg.) were added to a solution of scopoletin

(21)(12mg.) in dry acetone (2ml.) and the mixture refluxed for 8hr. Work up 1 yielded pure (20) from the organic filtrate and unreacted scopoletin (21) (8mg.) on acidifaction of the solid inorganic material. Close examination by t.l.c. revealed no trace of any product.

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

Isoprene (100ml.;68g) and a solution of hydrogen bromide in glacial acetic acid (50%w./v.;168ml) were cooled to $\sim 0^{\circ}$ and then mixed. After three days at $\sim 5^{\circ}$ the solution was diluted with iced water (1500ml.), when a yellowish oil separated. This was washed with iced water and dried over anhydrous calcium chloride. Distillation at $65\text{-}68^{\circ}/\sim 68$mm. yielded 3,3-dimethyl-allyl bromide (108g.;72%).

This material could be stored at $\sim -25^{\circ}$ for several weeks before further distillation was necessary.

5-O-(3,3 Dimethylallyl) tomentin (22)

Tomentin (6)(70mg) was added to a stirred suspension of potassium carbonate (50mg.) in acetone (12ml.) and left at R.T. for 1hr. Dimethylallyl bromide (60mg.) was then added and the solution refluxed for 2 hr. Work up 1 gave (22) as a yellowish crystalline solid (84mg, 92%) which crystallised from methanol-water as colourless plates, m.p. 80-81°. (Found:C,66.16;H,6.14. $C_{16}H_{18}O_5$ requires C,66.19;H,6.25%); $\nu_{max}^{CCl_4}$ 1744, 1608 and

1140 cm.$^{-1}$; λ_{max} 319 and 255 (sh.) n.m. (log ϵ 4.07 and 3.66) ; n.m.r. signals at δ 1.70 (3H;bs.), 1.78(3H; bs.), 3.87 (3H;s.), 3.93(3H;s.), 4.73(2H;d.;J 7.5Hz.), 5.52(1H;bt.;J 7.5Hz.), 6.23(1H;d.; J 9.5Hz.), 6.63(1H; s.) and 7.93(1H;d.;J 9.5Hz.); mass spectral peaks at m/e 290(M^+), 223,222,207,193,179,176,151,150,135,95 and 69 (r.a. 7,15,100,90,19,16,18,15,15,14,16 and 92%).

Pyrolysis of 5-O-(3,3-dimethylallyl) tomentin (22)

A solution of (22) (22mg.) in N,N-diethylaniline (0.3ml.) and n-butyric anhydride (0.3ml.) was kept at 175° under nitrogen for 7 hr. On cooling, the mixture was diluted with iced water (15ml), left at R.T. for 3 hr. and then extracted with ethyl acetate. The organic layer was washed with 1%w./v. hydrochloric acid, 0.5% w./v. potassium carbonate solution, brine to neutrality, and then dried and evaporated. The residue was purified by preparative t.l.c. (30% ethyl acetate-light petroleum) which removed any remaining diethylaniline and butyric anhydride, and then distilled at 170°/0.4mm. This yielded the butyrate (26) as a colourless glass (18mg.; 66%). (Found:C, 66.65;H, 7.38.$C_{20}H_{24}O_6$ requires C, 66.65; H, 6.71%); $\nu_{max}^{CCl_4}$ 1770,1746 and 1608cm.$^{-1}$; n.m.r. signals (CCl_4solution) at δ 1.08(3H;t.; J 7Hz.), 1.70 (3H;bs.), 1.85(3H;bs), 1.60-2.10(2H;m), 2.60(2H;t.; J 7Hz.), 3.50(2H;d.; J 7.5Hz.), 3.78(3H;s.), 3.90 (3H;s.), 5.17(1H; bt.;J 7.5Hz.), 6.20(1H;d.;J 9.5Hz.), and 7.48(1H;d.;J 9.5 Hz.) ; λ_{max} 346(sh.), 328(sh.), and 294nm. (log ϵ 3.35,

3.65 and 3.86);mass spectral peaks at $^{m}/_{e}$ 360(M^{+}), 291, 290, 276, 259, 204, 185, 176, 129, 71, 57, 43 and 41(r.a. 24, 24, 86, 60, 36, 23, 43, 26, 21, 41, 21, 100 and 50%).

8-(3,3-Dimethylallyl) tomentin (23)

The butyrate (26)(27mg) was dissolved in ethanol (10ml.) with heating. To the warm solution was added 1 ml. 0.5% w./v. aqueous potassium carbonate and the mixture heated on a steam bath for 5 mins. After cooling and careful acidification with 0.1N hydrochloric acid, the solvent was removed by evaporation to give a residue which was dissolved in a mixture of water and ethyl acetate. The organic layer was washed repeatedly with brine to neutrality, dried and evaporated to yield a crystalline solid (19mg.87%) which furnished (23) as colourless needles, m.p.154-158°, after crystallisation from ether-light petroleum. (Found:C,66.18;H,6.13. $C_{16}H_{18}O_5$ requires C,66.19;H,6.25%); $\nu_{max}^{CCl_4}$ 3530, 1747, 1626, and 1618cm.$^{-1}$; λ_{max}315, 256 and 232(sh.)nm.(log ϵ4.02, 3.95 and 4.03; λ_{max}(base) 406, 340(sh.),326, 275 and 243(sh.)nm.(log ϵ3.56, 3.80, 3.89, 3.91 and 3.96); n.m.r. signals at δ 1.70(3H;bs.), 1.83(3H;bs.), 3.47(2H;d;J 8Hz.), 3.93(6H;s), 5.22(1H;bt.;J 8Hz.), 6.18°(1H;s.), 6.25(1H;d;J 9.5Hz.), and 7.98(1H;d.;J 9.5Hz.); mass spectral peaks at $^{m}/_{e}$ 290(M^{+}), 276, 275, 260, 259, 247, 245, 235, 233 and 219(r.a.100, 16, 79, 11, 17, 27, 12, 14, 11 and 11%).

Attempted cyclisation of (23)

(23)(4mg.) was dissolved in 1 ml. methanol to which 2 drops of conc. hydrochloric acid had been added, and the mixture refluxed for 90mins. The mixture was diluted with iced water, extracted into ethyl acetate and the organic layer washed with 0.5% w./v. potassium carbonate solution, brine to neutrality, dried and evaporated to yield unreacted starting material(3mg) (m.p. and t.l.c.) as the sole product.

Tomentin tosylate

A solution of tomentin(6)(23mg) and toluene p-sulphonyl chloride (25mg.) in dry pyridine (1 ml.) was kept at R.T. for 75hr. when t.l.c. showed only partial conversion. A further 20mg.of toluene p-sulphonyl chloride was, therefore, added and the mixture left for another 4 days. Work up 11 yielded 34mg. of a pale yellow glass which, after preparative t.l.c. (0.5% v./v. methanol-chloroform X1), afforded:-

i) tomentin tosylate, as colourless plates from ethyl acetate (19mg.; 49%. 94%conversion), m.p. 176-177°. (Found:C,57.23;H,4.40. $C_{18}H_{16}O_7S$ requires C,57.44; H,4.29%); mass spectral peaks at $^m/_e$ 376, 222, 193, 178, 150, 91, 69 and 65(r.a. 31, 77,100, 15, 15, 41,15 and 15%); n.m.r. signals at δ 2.48(3H;s.), 3.63(3H;s), 3.93 (3H;s); 6.25(1H;d.;J 9.5Hz.), 6.78(1H;s.), 7.37(2H;d.; J 8Hz.), 7.75(1H;d.;J 9.5Hz.), and 7.88(2H;d.;J 8Hz.);

$\nu_{max}^{CCl_4}$ 1748, 1615, 1382 and 1065cm.$^{-1}$; λ_{max} 331, 296 and 255(sh.)nm.(log ϵ 4.03, 3.98 and 3.96).

ii) tomentin(6) (11mg.;30%)(n.m.r.).

2-Methyl-2-chloro-3-butyne.

Prepared by the method of Hennion and Boiselle[27], 2-methyl-3-butyne-2-ol (100g.) yielded 2-methyl-2-chloro-3-butyne (63g.;52%),b.p. 78-81°(lit.[27] b.p.73-76°). This reagent could be stored over solid anhydrous potassium carbonate at ~-20° for at least 6 months without requiring redistillation.

5-O-(1,1-Dimethylpropargyl) tomentin(31).

Potassium carbonate (0.83g.) and potassium iodide (0.14g.) were added to a solution of tomentin(6) (0.56g.) in aqueous acetone (2% v./v.;66ml.) and the mixture stirred at R.T. for 1hr. 2-Methyl-2-chloro-3-butyne (0.83g.) was added and the solution refluxed for 6hr. More potassium carbonate (0.83g.) and 2-methyl-2-chloro-3-butyne (0.83g.) were added and the reflux continued for a further 24hr. Additional 2-methyl-2-chloro-3-butyne (0.83g.) was then put into the mixture, and a final 24hr. reflux carried out. Work up 1 gave, from the recovered inorganic solids, a brown crystalline material, identified as tomentin (6)(0.19g.;34%)(m.p.,n.m.r. and t.l.c. behavior), and from the filtrate, a brown oil which, after preparative t.l.c.(50% v./v. ether-light petroleum X1), yielded:-

i) the ether (32) as a pale yellow glass (33mg.4%, 6% conversion), b.p. 135°/0.1mm.(decomposes).(Found: C,71.02;H,6.47. $C_{21}H_{22}O_5$ requires C,71.17;H,6.26%); $\nu_{max}^{CCl_4}$ 3309, 2110 (very weak), 1740, 1618, 1583 and 1551cm.$^{-1}$; mass spectral peaks at m/e 354(M^+), 289, 288, 287, 274, 273, 245, 243, 229, 202, 193, 115, 91, 77 and 67(r.a.11, 11, 55, 12, 18, 100, 36, 11, 16, 12, 12, 12, 15, 19 and 54%)n.m.r. signals at δ 1.73(6H;s), 1.92 (6H;s), 2.30(1H;s.), 2.47(1H;s.), 3.80(3H;s.), 3.98 (3H;s.), 6.23(1H;d.;J 10Hz.) and 8.10(1H;d.;J 10Hz.), $\lambda_{max}^{CCl_4}$ 348(sh.), 335(sh.), 303, 253(sh.), and 232(sh.) nm.(logϵ 3.61, 3.86, 4.08, 3.72 and 4.19).

ii) 5-O-(1,1-dimethylpropargyl) tomentin(31)(221mg.,30%, 46% conversion), as colourless plates (m.p. 85-86°) from aqueous ethanol. (Found:C,66.56;H,5.93. $C_{16}H_{16}O_5$ requires C,66.66;H,5.59%); $\nu_{max}^{CCl_4}$ 3310, 2125(very weak), 1747 and 1612cm.$^{-1}$; mass spectral peaks at m/e 288(M^+), 260, 257, 223, 222, 208, 207, 193, 179, 151, 135, 95, 69, 67, 65, 53 and 51 (r.a. 12, 13, 45, 14, 100, 13, 100, 23, 17, 18, 13, 17, 28, 41, 16, 14 and 21%); n.m.r. signals at δ 1.72(6H;s.), 2.43(1H;s.), 3.78(3H;s.), 3.90(3H;s.), 6.18(1H;d.;J 9.5Hz.), 6.65 (1H;s.), and 8.07(1H;d.;J 9.5Hz.); λ_{max} 350(sh.), 329, 313, 255(sh.), 246(sh.), and 225(sh.)nm.(logϵ 3.78, 4.01, 3.98, 3.60, 3.71 and 3.03).

iii) the allene mixture (46 and 47) (54mg.;7%, 11% conversion) as a yellow oil which crystallised on

standing for several weeks. The mixture had n.m.r. signals at δ 1.48-1.70 (12H;m.), 3.23(6H;s.), 3.88 (3H;s.), 3.93(3H;s.), 5.17(1Hseptet;J 3Hz.), 5.45(1H; septet;J 3Hz.), 5.70(1H;s.), 5.73(1H;s.), 6.07(1H;d.; J 9.5Hz.), 6.18(1H;d.;J 9.5Hz.), 7.80(1H;d.;J 9.5Hz.), and 7.88(1H;d.;J 9.5Hz.); λ_{max}382, 316, 290, 282 and 255 nm.

iv) tomentin(6)($\sim$10mg., $\sim$2%);identified by n.m.r. and t.l.c. behavior.

Attempted formation of the ether(31) in glyme.

A solution of tomentin (6) (10mg.) and 2-chloro-2-methyl-3-butyne (24mg.) in glyme (3ml.) to which had been added potassium carbonate (11mg.) and potassium iodide (1 small crystal) was kept at 75^{o}in an oil bath for 4 hr. Work up 1 gave a yellow oily residue (8mg.) containing mainly the starting phenol (6) and traces of decomposition products (t.l.c.), which were not isolated. None of the expected products, (31), (32), (46) or (47) was present in observable quantities.

Quinoline-sulphur poison[54]

A mixture of sulphur (1g.) and quinoline (6g.) were heated at 160$^{o}\pm5^{o}$ for 6hr. On cooling the dark brown mixture was made up to 70ml. with xylene. This stock solution was stored at $\sim5^{o}$. Immediately prior to use, 0.7ml. of this solution was diluted to 70ml. with ethyl acetate and used in this form as a partial poison for the catalyst, 5% w./w. palladium-charcoal.

Reduction of 5-O-(1,1-dimethylpropargyl) tomentin(31).
(a) Palladium-charcoal (5% w./w.;9mg.) was added to a solution of the propargyl ether (31)(22mg.) in ethyl acetate (15ml.) and the quinoline-sulphur poison (0.07ml.). After hydrogenation at R.T. for 1-2hr. when the uptake of hydrogen was approximately 1 mole, the catalyst was removed by filtration through Celite 535 and the solvent evaporated using as little heat as possible, to yield 29mg. of a yellow oily material, still containing a little of the poison mixture. The residue was separated by preparative t.l.c.(chloroform X1) into:-

i)5-O-(1,1-dimethylpropargyl) tomentin(31)(6mg.;27%) (n.m.r. and t.l.c. behavior)

ii)the enone (36)(11mg.;50%),from ether as yellow prisms, m.p. 111-113°.(Found: C, 66.44;H,6.23. $C_{16}H_{18}O_5$ requires C,66.19; H,6.25%); $\nu_{max}^{CCl_4}$ 1763, 1678, 1635, 1592 and 1535(very strong)cm^{-1}; n.m.r. signals at δ 1.53(3H;bs.), 1.60(3H;bs.), 2.70(2H;d.;J 8.5Hz.), 3.15(3H;s.), 3.93(3H;s.), 4.87(1H;bt.;J 8.5Hz.), 5.77 (1H;s.), 6.08(1H;d.;J 9.5Hz.) and 7.82(1H;d.;J 9.5Hz.); mass spectral peaks at $^{m}/e$ 290(M^+), 223, 222, 207, 193, 176, and 69(r.a. 3, 13, 100, 65, 10, 14 and 82%); λ_{max}380, 316 and 257nm.(logϵ3.70, 3.95 and 3.82); λ_{max}(base) 338, 276 and 245nm.(logϵ3.84, 3.73 and 4.04); λ_{max}(reacidification) 281nm. (logϵ3.66).

(b) In another experiment, carried out in an identical fashion to the one described above, the propargyl ether (31)(48mg.) gave rise to a pale yellow oil(45mg., 92%) on hydrogenation with palladium-charcoal (5%w./w.; 57mg.) poisoned with sulphur-quinoline (0.55ml.). Distillation at 170°/0.1mm. afforded the saturated ether (35) as a pale yellow glass; $\nu_{max}^{CCl_4}$ 1742, 1604 and 1558cm.$^{-1}$; n.m.r. signals at δ 1.05(3H;t.;J 7.5Hz.), 1.32(6H;s.), 1.82(2H;q.;J 7.5Hz.), 3.78(3H;s.), 3.93 (3H;s.), 6.20(1H;d.;J 10Hz.), 6.63(1H;s.), and 7.90 (1H;d.;J 10Hz.); mass spectral peaks at m/e 292(M^+), 263, 223, 222, 208, 207, 193, 151, 71, 69 and 55(r.a. 4, 11, 19, 94, 14, 100, 16, 11, 13, 12 and 11%).

Comments on the partial hydrogenation of propargyl ethers.

During the course of this research several Lindlar reductions of coumarin propargyl ethers have been carried out. The results obtained from this reaction are reproducible, but care had to be taken to make sure the procedure was followed exactly. In particular, hydrogenation of the ether (31) was found to be very sensitive to certain variables; whereas reduction of 7-O-(1,1-dimethylpropargyl) umbelliferone, whilst still tricky, was somewhat less sensitive. Important factors were:-

i) the degree of catalyst poisoning employed. For the 7-O-ether (Part 1,) 0.01ml. of sulphur-quinoline poison

(freshly diluted for each reaction) per mg. of 5% w./w. palladium-charcoal was ideal. In the case of the 5-O-ether (31), however, a reaction mixture made up with this poison concentration would never proceed. Here it was necessary to calculate the quantity of dilute poison as above, and then subtract 0.02ml. from the figure obtained (e.g. 20mg. of catalyst was poisoned with 0.18ml. of diluted sulphur-quinoline). Slight over-poisoning resulted in a very slow reaction, under-poisoning carried the danger of over hydrogenation.

ii) the order of addition of reagents to the reaction flask. The following sequence was used for best results:-

a) crystalline starting material.

b) AnR. ethyl acetate.

c) catalyst.

d) diluted poison.

iii) incident radiation. The hydrogenation apparatus utilised for these reactions was positioned next to a window in the laboratory and over two years it was noticed that satisfactory hydrogenation of the ether (31) would not proceed in bright sunlight. No explanation can be offered for this observation, but when the effect was eventually noticed, a hitherto erratic and unpredictable reaction became reproducible.

Evidence for the ether (27) as the first product of hydrogenation.

The hydrogenation of the ether (31) was carried out exactly as described (vide supra) but with the following modification to the work-up:- the reaction mixture was filtered at the pump through a very thin pad of Celite 535 to minimise contact with the constituents of the reaction mixture. Subsequent evaporation of solvent, with minimal heating, afforded (27) as a pale yellow oil, which was not purified; n.m.r. signals at δ 1.53(6H;s.), 3.83(3H;s.), 3.97 (3H;s.), 5.20(1H;d.;J 18Hz.), 5.10(1H;d.;J 10Hz.), 6.17(1H; dd.;J 18 and 10Hz.); 6.23(1H;d.;J 10Hz.), 6.67(1H;s.) and 7.92(1H;d.;J 10Hz.) in addition to signals due to small traces of the enone (36).

Attempted thermal rearrangement of the ether (27)

The allyl ether (27)($\sim$20mg.), contaminated with small amounts of (36) was dissolved in ethyl acetate (5ml.) and allowed to reflux gently on a steam bath for 5mins. After evaporation of solvent, the n.m.r. of the residue was identical with that of the starting ether (27). No conversion to the enone (36) was observed within the limits of the integrator accuracy.

Silica-catalysed rearrangement of the ether (27)

An unpurified residue (75mg.) from the hydrogenation of the ether (31) containing the allyl ether (27) and traces of the enone (36) was dissolved in ethyl acetate

(10ml.) and stirred with solid Celite 535 at R.T. for 5mins. After filtration and evaporation of solvent from the filtrate, the n.m.r. of the residue indicated substantial rearrangement (30%) to the enone (36). A repeat of the experiment using Kieselgel G instead of Celite 535 and stirring for 1hr. resulted in complete conversion to the dienone.

Borohydride reduction of the enone (36)

To a solution of the enone (36)(45mg.) in ethanol (10ml.) at R.T. was added solid sodium borohydride in small portions (3mg each) until t.l.c. indicated complete reaction. The mixture was then carefully neutralised with 0.1N hydrochloric acid, diluted with saturated brine (20ml) and extracted twice into ether-ethyl acetate (50% v./v.). Washing with brine, drying and evaporation of solvent furnished (38) as a yellow oil (35mg.;77%). Purification by preparative t.l.c. gave the alcohol (38) as a pale yellow glass; n.m.r. signals at δ 1.65(3H;bs.), 1.73(3H;bs.), 2.45 (2H;bm;J 8.5Hz.), 3.17(3H;s.), 3.77(3H;s.), 4.30(1H;s.), 5.27(1H; bm.;J 8.5Hz.), 5.33(1H;s.), 5.80(1H;d.;J 9.5Hz.), and 7.22(1H;d.;J 9.5Hz.); $\nu_{max}^{CCl_4}$ 3595, 3425, 1740, 1600 and 1525(very strong)$cm.^{-1}$; λ_{max} 325, 300 and 257(sh.) nm.; mass spectral peaks at $^{m}/e$ 292(M^+), 224, 223, 222, 208, 207, 206, 191, 164, 163, 135, 123, 107, 95, 79, 77, 69, 55, 53 and 51(r.a.23, 22, 42, 13, 12, 90, 25, 53, 15, 100, 27, 17, 12, 17, 17, 17, 36, 16, 19, 19 and 15%).

Aromatisation of the alcohol (38)

A solution of (38)(16mg.) in methanol (5ml.) containing concentrated hydrochloric acid (0.3ml.) was refluxed for 10mins. After cooling, the mixture was poured into iced water (15ml.), extracted into ethyl acetate and the organic layer washed with 2% w./v. sodium bicarbonate solution and brine to neutrality. Subsequent drying and solvent evaporation yielded 6,7-dimethoxycoumarin (9) as a colourless solid (10mg.;88%) identical in all respects (m.p., m.m.p., u.v., i.r., n.m.r. and mass spectrum) with synthetic material. (9) crystallised as needles, m.p.138-139° (lit.[55] m.p. 143-143.5°).

Synthesis of 6,7-dimethoxycoumarin (9)[8]

Potassium carbonate (100mg.) was added to a solution of 6,7-dihydroxycoumarin (50mg.) in acetone (100ml.) and stirred at R.T. for 1hr. Methyl iodide (1 ml.) was then added and the mixture refluxed gently for 4hr. Work up 1 afforded a colourless crystalline solid, m.p. 139-140°(lit.[55] m.p.143-143.5°); $\nu_{max}^{CCl_4}$ 1740, 1619 and 1514cm.$^{-1}$; n.m.r. signals(100 MHz.) at δ 3.88(3H;s.), 3.90(3H;s.), 6.26(1H;d.;J 10Hz.), 6.84(2H; bs.), and 7.62(1H;d.;J 10Hz.); λ_{max} 343, 294, 258(sh.) and 230 nm.; mass spectral peaks at m/e 206(M^+), 191, 178, 163, 135, 120, 107, 92, 79, 69 and 51(r.a.100, 50, 23, 44, 31, 14, 28, 15, 23, 25 and 24%).

Aromatisation of the enone (36)

The enone (36)(15mg.) in ethanol-water (80%v./v.) (10ml.) to which had been added 2ml. dil. sulphuric acid, was warmed on a steam bath for 5 mins. After dilution with water (20ml.) and extraction into ethyl acetate, the organic layer was washed to neutrality with brine, dried and evaporated to yield 5mg.(43%) of a colourless crystalline solid, identified as tomentin (6)(t.l.c., u.v., and mass spectrum).

Attempted hydrogenation of the enone(36)

A solution of (36)(42mg.) in ethyl acetate (15ml.) to which had been added 5% w./w. palladium-charcoal (9mg.)(no poison) was hydrogenated for 2½hr. At the end of this time there had been no measurable uptake of gas and, after removal of catalyst by filtration through Celite 535 and evaporation of solvent, the residue was found to contain only unreacted starting material (t.l.c. and n.m.r.)

Action of base on the enone (36)

The enone (36)(20mg.) was dissolved in ethanol(2ml.) to which 2 drops of dil. sodium hydroxide solution had been added. After gently warming for 5 mins. during which the yellow colour faded considerably, the solution was acidified until just neutral with 0.1N sulphuric acid,diluted with water(20ml.), extracted into ethyl acetate, and the organic layer washed with brine, dried, and evaporated to furnish a pale yellow glass

(23mg.) still containing a trace of ethanol(n.m.r.); n.m.r. signals (CCl_4) at δ 1.55(6H; bd.), 2.65(2H;d.; J 7.5Hz.), 3.08(3H;s.), 3.78(3H;s.), 4.78(1H; bt.;J 7.5Hz.), 5.57(1H;s.),7.00(1H;d.;J 16Hz.), and 7.77(1H; d.;J 16Hz.).

Attempted purification by preparative t.l.c.(ethyl acetate X1) failed; no isolable product could be eluted from the silica.

Pyrolysis of the ether (31)

5-O-(1,1-Dimethylpropargyl) tomentin (31) was pyrolysed for 20mins. at 130° in a sublimation tube at 0.1mm. pressure.

The product, which distilled up the tube, yielded the following after preparative t.l.c.(40% ethyl acetate-light petroleum X1):-

i) the allene (46) (22mg.;88%) which, on redistillation and allowing the distillate to stand for a week, slowly solidified as yellow plates, m.p. 110-112°. (Found: C,66.51;H,5.38. $C_{16}H_{16}O_5$ requires C,66.66;H, 5.59%); $\nu_{max}^{CCl_4}$ 1970(very weak), 1763, 1681, 1638, 1594 and 1538 (very strong)$cm.^{-1}$;n.m.r. signals (100 MHz.) at δ 1.60(3H;d.;J 3Hz.), 1.65(3H;d.;J 3Hz.), 3.21(3H;s.), 3.87(3H;s.), 5.12(1H;septet;J 3Hz.), 5.64(1H;s.), 6.04(1H;d.;J 9.5Hz.), and 7.79(1H;d.;J 9.5Hz.); λ_{max} 382, 318 and 255nm. (log ϵ 3.78, 3.99 and 3.82); mass spectral peaks at $^m/_e$ 288(M^+), 260, 258, 257, 242, 207, 179, 69 and 67(r.a. 3, 25, 20, 100, 12, 15, 10,

12 and 12%)

ii) the ether (31)(~1mg.;~4%)(t.l.c.).

Isolation of the allene(47)from the 1:1 mixture with(46).

The 1:1 mixture of allenes (20mg.), obtained as a by-product from the synthesis of (31), was heated slowly in a sublimation tube at 0.1mm. pressure until (47) just began to distil. The tube was then slowly withdrawn from the sublimation block as distillation proceeded until the block temperature reached 145°, when heating was stopped. On cooling, the material at the upper end of the tube crystallised as a colourless solid, and any contamination from the yellow isomer (46) was removed by washing with ether. One further sublimation furnished a very small sample of the allene (47), m.p. 148-150°. $\nu_{max}^{CCl_4}$ 1968(very weak), 1760, 1663, 1640 and 1604cm.$^{-1}$; λ_{max}278 and 252(sh.)nm. (log ϵ 4.06 and 3.98); λ_{max}(base) 340 and 255(sh.).nm. (log ϵ 3.91 and 3.93); n.m.r. signals (100 MHz.) at δ 1.64(3H;s.), 1.66(3H;s.), 3.22(3H;s.), 3.86(3H;s.), 5.45(1H;septet;J 3Hz.), 5.71(1H;s.), 6.33(1H;d.;J 9.5Hz.), and 7.91(1H;d.;J 9.5Hz.); mass spectral peaks at m/e 288(M^+), 273, 257, 223, 222, 221, 207, 193, 179, 77, 69, 67, 65, 63 and 51(r.a.43, 18, 21, 13, 100, 23, 98, 27, 13, 17, 24, 39, 16, 16 and 21%).

Reduction of the allene (46)

To a solution of the allene (46)(25mg.) in ethanol (4ml.) at R.T. was added small portions (~3mg.each) of solid sodium borohydride until t.l.c. showed complete reaction (about 5mins.) After careful neutralisation with 0.1N hydrochloric acid, the mixture was diluted with sat. brine (10ml.) and extracted into ethyl acetate. Subsequent washing to neutrality with brine, drying and evaporation of solvent furnished 24mg. (95%) of semi-solid pale yellow material (59) which decomposed quickly at R.T.; n.m.r. signals (100 MHz.) at δ 1.60(3H;d.;J 3Hz.), 1.68(3H;d.;J 3Hz.), 3.41(3H;s.), 3.71(3H;s.), 4.71(1H;s.), 5.10(1H;m.;J 3Hz.), 5.32(1H;s.), 5.97(1H;d.;J 9.5Hz.), and 7.43(1H;d.;J 9.5Hz.); λ_{max} 370, 325(sh.), and 258(sh.)nm.

Aromatisation of the alcohol (59)

The alcohol (59)(18mg.) was dissolved in methanol (2ml.) and 0.3ml. dil. hydrochloric acid added. The mixture was then warmed on a steam bath to ~50° and left to cool for 2hrs., after which it was diluted with water (10ml.), extracted into ethyl acetate, washed to neutrality with brine, dried and the solution evaporated to yield a pale yellow glass which crystallised on standing. Sublimation at 130°/0.1mm. gave the chromene (60) as colourless needles (6mg.38%) m.p.110-112°(lit.[41] m.p.116°). $\nu_{max}^{CCl_4}$ 1742, 1638, 1610

and 1597cm.$^{-1}$; n.m.r. signals (100 MHz.) at δ 1.46 (6H;s.), 3.86(3H;s.), 5.42(1H;d.;J 10Hz.), 5.99(1H;d.; J 10Hz.), 6.26(1H;s.), 6.52(1H;d.;J 10Hz.), and 7.77 (1H;d.;J 10Hz.); λ_{max}323, 302, 292(sh.), 282 and 273 (sh.)nm.(log ϵ4.04, 4.05, 4.10, 4.21 and 4.14); mass spectral peaks at $^{m}/e$ 258(M^{+}), 244, 243, 228 and 200 (r.a. 16, 16, 100, 11 and 13%).

Rearrangement of the ether (32)

The bis acetylene (32)(18mg.) was heated slowly from R.T. to 140^{o} at 0.4mm. pressure in a sublimation block and held at this temperature for 20mins. The pure product (65) was distilled out of the reaction mixture at 145-150^{o}/0.4mm as a deep orange glass(14mg.78%) (Found:C,71.14;H,6.38. $C_{21}H_{22}O_{5}$ requires C,71.17;H, 6.26%); $\nu_{max}^{CCl_4}$ 3310, 2103(v.weak), 1966(v.weak), 1757, 1679, 1614 and 1510(v.strong)cm.$^{-1}$; n.m.r. signals at δ 1.57(3H;s.), 1.70(3H;s.), 1.73(3H;s.), 1.78(3H;s.), 2.30(1H;s.), 3.32(3H;s.), 4.10(3H;s.), 5.12(1H;m.;J 3Hz.), 6.12(1H;d.;J 9.5Hz.), and 7.90(1H;d.;J 9.5Hz.); λ_{max} 400, 320 and 270nm.; (log ϵ3.47, 3.81 and 3.89); λ_{max} (base) 396, 285 and 243nm.(log ϵ3.70, 4.01 and 4.11); mass spectral peaks at $^{m}/e$ 354(M^{+}), 340, 339, 326, 324, 323, 309, 307, 293, 287, 279, 273, 272, 259, 229, 201, 194, 193, 115, 91, 77, 67 and 65(r.a.27, 17, 75, 15, 18, 56, 21, 22, 24, 34, 16, 24, 14, 17, 14, 12, 15, 100, 14, 14, 20, 34 and 16%).

Attempted C-alkykation of the ether (31)

Potassium carbonate (45mg.), potassium iodide(8mg.) and 2-methyl-2-chloro-3-butyne (45mg.) were added to a solution of the ether (31)(30mg.) in 2% v./v. aqueous acetone (5ml.) and the whole refluxed for 6hr. More 2-methyl-2-chloro-3-butyne (60mg.) was then added and the reflux continued for a further 24hr., when a t.l.c. examination of the reaction mixture showed the presence of the ether (32), starting material, the allenes (46) and (47) and tomentin (6).

Attempted interconversion of the allenes(46) and (47)

(a) 20mg. of the 1:1 allene mixture was dissolved in freshly distilled tetrachloroethylene (0.4ml.) and the solution heated to 155° for 40mins. in a sealed pyrex n.m.r. tube. The spectrum was then run (100 MHz.) immediately whilst the whole n.m.r. tube assembly was kept at a temperature of 100°. The resulting spectrum was exactly identical with the spectrum of the starting mixture, and exhibited no measurable acetylenic resonance.

(b) In a second experiment, small samples of the allenes (46)and(47) were heated individually in a sublimation block to 145° for 45mins. Some distillation occurred, but u.v. examination of both residues and both distillates showed the compounds to have remained completely unchanged.

Attempted rearrangement of the ether(31) under propargylation conditions.

Potassium carbonate (20 mg.) and potassium iodide(1 crystal) were added to a solution of 5-O-(1,1-dimethyl-propargyl) tomentin (31)(6mg.) in 2% v./v. aqueous acetone (10ml) and the solution refluxed for a total of 50hr. Work up 1 yielded an oily residue whose t.l.c. indicated some decomposition of the ether (31) to give both polar and non-polar products, none of which were isolated. The 1:1 mixture of (46) and (47) was, however, absent.

Pyrolysis of the enone (36)

The yellow dienone (36) (~1mg.) was heated to 150° for 15mins. at atmospheric pressure in a sublimation block, when t.l.c. examination revealed it to be substantially unchanged. After a further 10mins. at 200° the material had charred but a polar product could be detected by analytical t.l.c., although the sample still contained the enone (36) as major constituent. Data for this product were not obtained.

Attempted pyrolytic aromatisation of the alcohol(38).

A very small sample (~1 mg.) of (38) was heated to 195° at atmospheric pressure in a sublimation block for 5 mins. Examination by analytical t.l.c. revealed the starting alcohol(38) as major component accompanied by some 6,7-dimethoxycoumarin (9).

Extraction of British Prunus tomentosa[53].

The wood was cut into small chips, dried at 40°,

ground thoroughly and finally dried again for several days at 40°. This material(134g.) was extracted for 4hr. with hot methanol (2.5l.) in a Soxhlet extractor and the extract evaporated as far as possible under reduced pressure. The resultant residue was extracted three times with ether (150 ml. portions) leaving a green residue. The ethyl acetate soluble portion was evaporated under reduced pressure, affording a brown tarry residue; a small portion of which was dissolved in 5% v./v. hydrochloric acid and boiled for 3hr. After cooling and dilution with water, the reaction mixture was extracted with ethyl acetate, washed to neutrality with brine, dried and evaporated to give a residue which was found to contain no tomentin on close t.l.c. examination.

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