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The Chemical Constituents of Australian *Zanthoxylum* Species. VII* Some Transformation Products of Suberosin

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Department of Organic Chemistry, University of Sydney, N.S.W. 2006.

Abstract

Photosensitized oxidation of suberosin yielded suberenol (2), isosuberenol (6) and, under certain conditions, 6,6′-ethylenebis(7-methoxy-2*H*-1-benzopyran-2-one). The epoxy alcohol (7a), its methyl ether and the aldehyde (3) were also obtained, but these are believed to be artefacts formed under the conditions of workup. Autoxidation of suberosin does not appear to occur readily. Other oxygenated derivatives of suberosin were prepared by chemical methods.

Dehydration of suberenol and isosuberenol yielded the diene (5) which on treatment with acid gave in low yield a bis-coumarin, isomeric with cyclobisuberodiene, for which structure (24) is suggested.

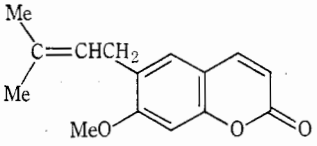
In a previous paper[1] the isolation of suberosin (1) in relatively high yield from the bark of *Zanthoxylum ovalifolium* Wight (Rutaceae) was reported; also isolated, *inter alia*, were suberenol (2), the aldehyde (3) and cyclobisuberodiene (4) (thamnosin),[2] all as minor products. The possibilities that (2) and (3) were artefacts derived from suberosin by oxidative processes occurring during the isolation procedures and that (4) was formed by a Diels–Alder reaction involving the diene (5), which could conceivably be formed by dehydration of suberenol, were then briefly discussed, but were discounted on the grounds that suberosin appeared to be a relatively stable substance, that the extracts were not subjected to prolonged manipulations, and that in preliminary experiments suberenol could not be converted into cyclobisuberodiene. However, the obvious structural similarities between (1), (2) and (3), and the fact that (4) was optically inactive, constituted *prima facie* evidence that the minor products were artefacts and made it desirable for us to attempt the conversion of (1) into (2), (3), (4) and (5).

In preliminary experiments the photosensitized oxidation of suberosin was studied in methanol and in chloroform with four different sensitizers to determine the optimal reaction conditions. A single incandescent light source was used and the products were isolated through careful chromatography on alumina after exposure of the initially formed hydroperoxides to acidified ferrous sulfate. Typically, after irradiation for 100 h in chloroform/Methylene Blue the products isolated were suberenol (5%), the aldehyde (3) (35%) and two new substances, isosuberenol (6) (30%) and the epoxy

* Part VI, *Aust. J. Chem.*, 1973, **26**, 687.

[1] Guise, G. B., Ritchie, E., Senior, R. G., and Taylor, W. C., *Aust. J. Chem.*, 1967, **20**, 2429.

[2] Kutney, J. P., Inaba, T., and Dreyer, D. L., *Tetrahedron*, 1970, **26**, 3171.



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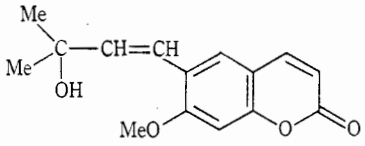

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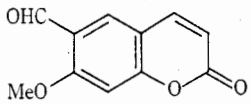

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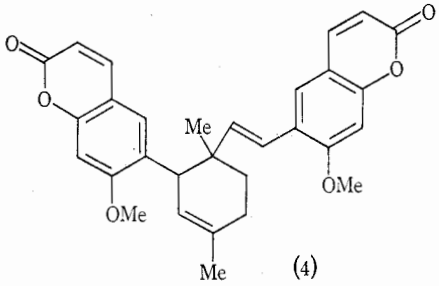

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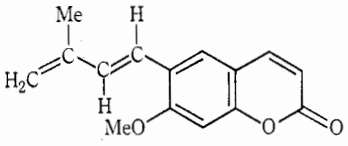

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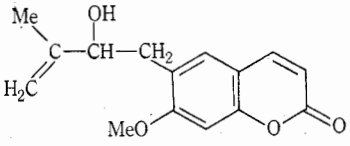

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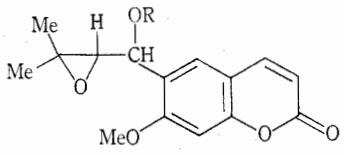

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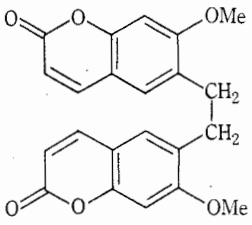
(7c) R = Ac



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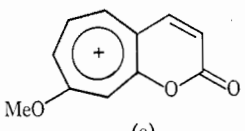

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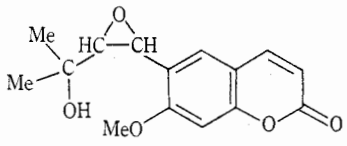

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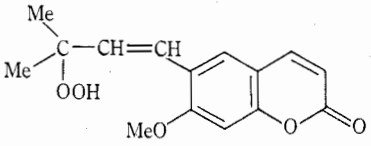

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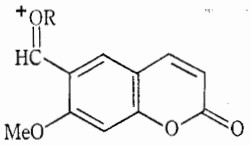

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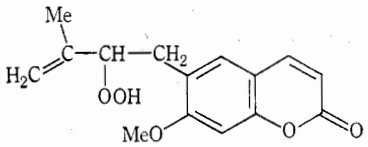

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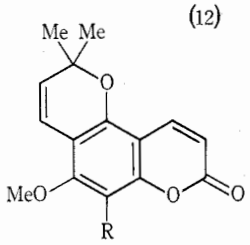

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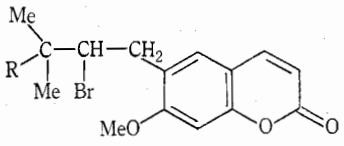
(14b) R = CH=CHC(Me)=CH$_2$



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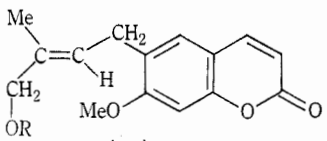

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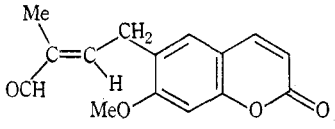

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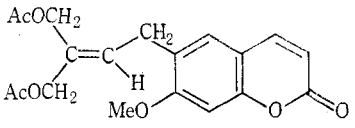

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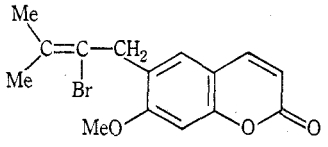

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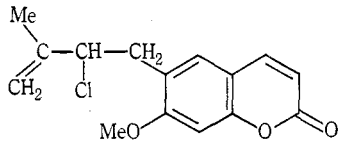

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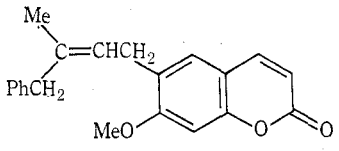

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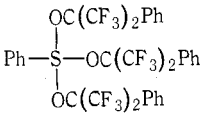

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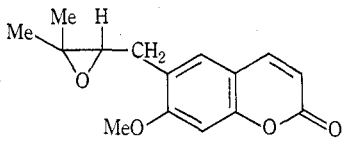

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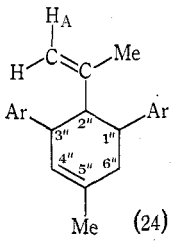

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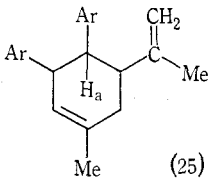

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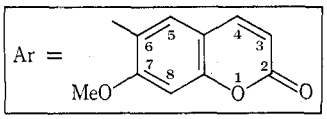
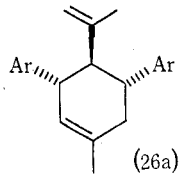
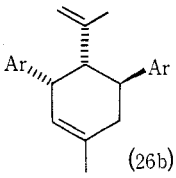




(26a)



(26b)

alcohol (7a) (5%), together with suberosin (10%). With other solvent/sensitizer combinations the product distribution for (2), (3), (6) and (7a) was approximately the same; methanol/Methylene Blue yielded in addition the methoxy epoxide (7b) (20%). From a reaction in methanol/haematoporphyrin another substance, 6,6′-ethylenebis(7-methoxy-2*H*-1-benzopyran-2-one) (8), was also isolated.

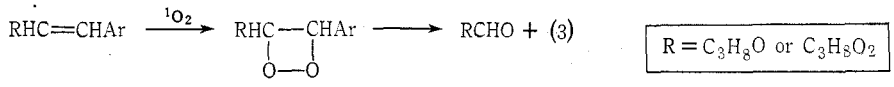
However, at this stage it became apparent that complete reduction of the initially formed hydroperoxide mixture was not being achieved with ferrous sulfate. The aldehyde (3) and the epoxides (7a,b) were in fact not genuine products of the photo-oxygenation reaction, but arose through decomposition of hydroperoxide intermediates on alumina (see below). Thus, when sodium borohydride was used in the reduction step, the photo-oxygenation yielded simply the expected mixture of allylic alcohols, suberenol (2) and isosuberenol (6), which was easily separated by chromatography. Indeed, by using the system chloroform/Methylene Blue and an improved light source (see Experimental) excellent yields of (2) and (6) could be obtained, approximately in the ratio 2 : 3.

Suberenol and the aldehyde (3) were identical with the respective products from natural sources.[1] The structure of isosuberenol (6), $C_{15}H_{16}O_4$, was evident from its spectral properties. In particular the n.m.r. spectrum showed signals from H 4 at δ 7·62 and H 3 at 6·23 as an AB quartet (J 9·5 Hz); from H 5 and H 8 as singlets at 7·32 and 6·82 respectively; from $(H\,4')_2$ at 4·94 and 4·84 as singlets broadened by coupling to 3′-Me and H 2′ (proven by double irradiation); from OH as a singlet at 1·92; and from 3′-Me as a broadened singlet at 1·82. Protons H 2′ and $(H\,1')_2$ gave rise to a 12-line ABX pattern which was analysed to give δ_A 3·01 and δ_B 2·65 [$(H\,1')_2$], and δ_X 4·31 (H 2′); J_{AB} 13·6, J_{AX} 8·2, J_{BX} 4·6 Hz. The mass spectrum had a molecular ion peak at m/e 260, a peak at 219 corresponding to the loss of C_3H_5 by an α-cleavage, and a base peak at 189 corresponding to the ion (9).

The structure of the epoxy alcohol (7a), $C_{15}H_{16}O_5$, was also established by its spectral properties. In addition to signals from the coumarin nucleus, the n.m.r. spectrum showed signals from H 1′ at δ 4·85, a broadened doublet which sharpened to a doublet of doublets ($J_{1',2'}$ 7·5, $J_{1',5}$ 0·6 Hz) on exchange with D_2O, and which sharpened further on simultaneous irradiation of H 5; from H 2′ as a doublet at 2·95 (J 7·5 Hz); from OH at 2·92; and from $(H\,4')_3$ and 3′-Me as sharp singlets at 1·42 and 1·30. The chemical shift value for H 1′, and the fact that the signal showed benzylic *and* hydroxylic coupling, allowed the alternative structure (10) to be ruled out (see below). In addition, the base peak in the mass spectrum was at m/e 205 corresponding to the ion (11a) which could readily be formed an by α-cleavage with loss of the fragment C_4H_7O. The derived acetate (7c) had the expected spectral properties; in particular the signal from H 1′ occurred at δ 5·97.

The methoxy compound (7b) had spectral properties similar to those of (7a) except that in the n.m.r. spectrum the signal from H 1′ was at δ 4·48 and there was a new signal at 3·36 from the introduced methoxy group. The base peak in the mass spectrum was at m/e 219, corresponding to the ion (11b).

The n.m.r. spectrum of the substance (8), $C_{22}H_{18}O_6$, showed signals from H 4 at δ 7·73 and H 3 at 6·11 as an AB quartet (J 9·5 Hz); from H 5 and H 8 as singlets at 7·25 and 6·85 respectively; from OMe as a singlet at 3·80; and from the four methylene protons as a singlet at 2·84. In the mass spectrum the base peak was at m/e 189 corresponding to the ion (9), and there were only a few weak peaks between it and the molecular ion peak at 378.



Scheme 1

The formation of suberenol (2) and isosuberenol (6) is readily explicable by the well known Schenck mechanism, involving a concerted 'ene' reaction, though a perepoxide intermediate is also possible.[3] At the outset it seemed that suberenol or (12) was a source of the aldehyde (3) via a dioxetan[4] (Scheme 1). In fact, photosensitized oxidation of suberenol for an extended period in methanol with Rose Bengal gave the aldehyde (3) as the major product, and a similar result was obtained

[3] For recent reviews see Denny, R. W., and Nickon, A., *Org. React.*, 1973, **20**, 133; Kearns, D. R., *Chem. Rev.*, 1971, **71**, 395.

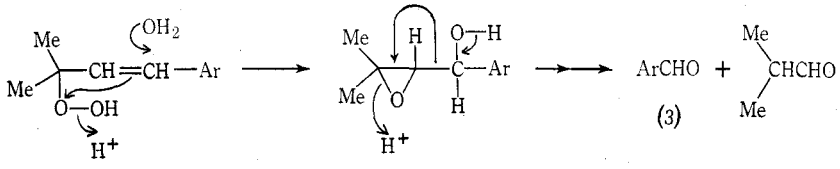
[4] Fencial, W., Kearns, D. R., and Radlick, P., *J. Am. Chem. Soc.*, 1969, **91**, 3396, 7771; Kopecky, K. R., Van de Sande, J. H., and Mumford, C., *Can. J. Chem.*, 1969, **47**, 709.

with 7-methoxy-6-vinylcoumarin. The latter substance was prepared, though in low yield, from the aldehyde (3) and the Wittig reagent generated from methyltriphenylphosphonium bromide.

However, the above mechanism was untenable under the improved conditions subsequently developed for the photo-oxygenation. The n.m.r. spectrum of the initial product of the reaction showed it to be simply a mixture of the two hydroperoxides (12) and (13). Chromatography of the mixture on alumina or silica led to the separation of the hydroperoxide (13) corresponding to isosuberenol, but the other one (12) could not be isolated. Instead there was obtained the aldehyde (3) in significant quantity, and a small amount of the epoxide (7a).

The hydroperoxide mixture was then subjected to a countercurrent distribution between methanol/water and ethyl acetate/light petroleum. Partial separation was achieved, but even under these mild, non-acidic conditions isolation of the hydroperoxide (12) was thwarted by its decomposition to the aldehyde (3). Hydroperoxide (13) was isolated readily, after chromatography of enriched fractions.

It therefore appeared that the major route to the aldehyde (3) involved the hydroperoxide (12), presumably via the epoxide (7a) (Scheme 2).



Scheme 2

This mechanism is supported by the fact that the epoxide (7a) on rechromatography on alumina was converted into the aldehyde (3), and the reaction could also be effected by brief treatment with boron trifluoride etherate.

The epoxide (7a) presumably arises by an acid-catalysed decomposition of the hydroperoxide (12) as shown in Scheme 2; this could easily occur on alumina during chromatography. It is not clear at present when the methoxy compound (7b) is formed, but it would appear to involve the addition of methanol rather than water to the double bond in (12).

Isosuberenyl hydroperoxide (13) had spectral properties very similar to those of isosuberenol except that in the n.m.r. spectrum the signals from $(H1')_2$ and $H2'$ were very nearly a first-order doublet and triplet respectively (J 6·5 Hz). The base peak in the mass spectrum was again at m/e 189 [the ion (9)] arising by an α-cleavage from the molecular ion at 276. The substance was converted quantitatively into isosuberenol on treatment with sodium borohydride. It could be recovered unchanged from an alumina column; this confirmed that it was not the progenitor of the aldehyde (3).

It is not clear how the ethane (8) arises, but presumably a coupling of benzylic radicals is involved.

While this work was in progress several other groups of researchers reported relevant results. Polonsky and coworkers[5] studied the photosensitized oxidation of a variety of natural products containing alkenyl substituents; mammeisin, a 4-phenylcoumarin with a prenyl (3′-methylbut-2′-enyl) group at position 8, gave in methanol/

[5] Fourrey, J. L., Rondest, J., and Polonsky, J., *Tetrahedron*, 1970, **26**, 3839.

haematoporphyrin a low yield of the suberenol type of derivative after reduction—no mention was made of the isosuberenol type of product. Murray and Forbes[6] have prepared avicennol (14a) in 50% yield as the single product of haematoporphyrin-sensitized photo-oxygenation of the corresponding prenyl precursor (after reduction); under the same conditions (pyridine as solvent), 7-acetoxy-8-prenylcoumarin gave cleanly a 52% yield of the corresponding suberenol analogue as the sole product. Other workers[7] have reported briefly the formation in rather low yields of suberenol (11%) and isosuberenol (22%) by photo-oxygenation of suberosin, using Rose Bengal as sensitizer followed by reduction.

Abyshev[8] claimed that when a chloroform solution of suberosin was left for 4 h 'in an illuminated place at room temperature' a 28% yield of suberenol was obtained after preparative t.l.c. of the crude product (no reduction step). Unspecified amounts of two other compounds were produced by allowing a chloroform solution of the residual material to stand under the same conditions for 24 h. Only one of the products was characterized, and it was recognized as being identical with the coumarin, lophopterol, isolated from *Prangos lophoptera* Boiss and originally assigned[9] the structure (10) because of an erroneous interpretation of the spectral data. Lophopterol had in fact physical constants and spectral data (optical activity unspecified) identical with those of the product (7a), and it seemed to us that this was the correct structure for the substance. Abyshev subsequently[10] came to the same conclusion after reinterpretation of the n.m.r. spectrum and the preparation of certain derivatives. In view of the present results, it would appear most likely that the substance arises from the hydroperoxide (12) during the preparative t.l.c. on silica employed for isolation purposes, and is not a direct product of photo-oxidation in this case either.

The reaction of suberosin with singlet oxygen generated by the following chemical methods was also investigated: (A) from sodium hypochlorite and hydrogen peroxide;[11] (B) by decomposition of the triphenyl phosphite–ozone adduct in methylene chloride at $-30°$;[12] (C) by the thermal decomposition of the *endo* transannular peroxide of 9,10-diphenylanthracene;[13] and (D) by the thermolysis of potassium perchromate.[14] All of these reactions were rather inefficient, giving only low yields of oxygenated products; they were not pursued further. A second possible mode of transformation of suberosin into (2) and (6) was by autoxidation. Suberosin was recovered unchanged when a chloroform or methanol solution was kept for extended periods (several weeks) in the dark. In diffuse sunlight a methanol solution slowly gave a trace of suberenol and a chloroform solution gave low yields of suberenol and the aldehyde (3). When a chloroform solution of suberosin which was 0·1 M with respect to salcomine [α,α′-ethylenedinitrilodi-*o*-cresolato(2−)cobalt(II), which reversibly absorbs molecular oxygen in the solid state or in solution and which has been shown to catalyse the autoxidation of phenols][15] was exposed to diffuse sunlight for extended

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[7] Raj, K., Kapil, R. S., and Popli, S. P., *Indian J. Chem.*, 1975, **13**, 404.
[8] Abyshev, A. Z., *Chem. Nat. Compd. (USSR)*, 1975, **11**, 147 (*Khim. Prir. Soedin.*, 1975, 131).
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[13] Wasserman, H. H., and Sheffer, J. R., *J. Am. Chem. Soc.*, 1967, **89**, 3073.
[14] Peters, J. W., Pitts, J. N., Rosenthal, I., and Fuhr, H., *J. Am. Chem. Soc.*, 1972, **94**, 4348.
[15] Van Dort, H. M., and Guersen, H. J., *Recl Trav. Chim. Pays-Bas Belg.*, 1967, **86**, 520.

periods, a low yield of the aldehyde (3) and a trace of suberenol were formed. Irradiation of a chloroform solution of suberosin with passage of oxygen gave, after a few days, low yields of suberenol, the aldehyde (3) and isosuberenol. These experiments showed that suberosin does not undergo autoxidation at an appreciable rate but that it can photosensitize itself, although inefficiently, to oxidation (cf.[8]).

The combined results suggest that both suberenol and the aldehyde (3) may be artefacts rather than genuine natural products. Against this possibility are the considerations advanced previously[1] and the fact that isosuberenol was not isolated from plant extracts. As in other such cases it would be difficult to decide the question without prolonged experimentation.

The functionalization of the prenyl residue in suberosin by chemical methods was also examined. Reaction with *N*-bromosuccinimide in carbon tetrachloride gave a complex mixture which yielded no crystalline products but, in aqueous dioxan, 6-(2′-bromo-3′-hydroxy-3′-methylbutyl)-7-methoxycoumarin (15a) and, in methanol, 6-(2′-bromo-3′-methoxy-3′-methylbutyl)-7-methoxycoumarin (15b) were obtained. The structures of both substances were apparent from their spectral properties. Acetoxylation of suberosin with mercuric acetate in acetic anhydride/acetic acid was unsuccessful, but selenium dioxide in the same solvent mixture gave 6-[(*E*)-4′-acetoxy-3′-methylbut-2′-enyl]-7-methoxycoumarin (16a) together with low yields of aldehyde (17) and the diacetate (18). The n.m.r. spectrum of the acetate (16a) revealed its structure; in particular, the signal from H 2′ was a triplet of quartets at δ 5·66 (J 7·5, 1·4 Hz), and that from $(H\,4')_2$ was a broadened singlet at 4·56. Simon's rules[16] predict similar chemical shifts for H 2′ in both *E* (δ 5·41) and *Z* (δ 5·39) isomers. However, a decision in favour of the former, i.e. configuration (16a), was readily made from the results of a nuclear Overhauser effect experiment. Irradiation of the signal from $(H\,4')_2$ enhanced the intensity of the signal from H 2′ by 17%. Similarly, the structure of the aldehyde (17) was established; the low-field position of the H 2′ signal, a triplet of quartets at δ 6·56, suggested it was *cis* to the aldehyde function. This was confirmed by n.O.e. experiments: no enhancement of intensity of the H 2′ signal was observed on irradiating 3′-Me or vice versa, but irradiation of the H 4′ signal enhanced that of H 2′ by 27%. The diacetate (18), a gum, had spectral properties consistent with its structure.

Hydrolysis of the acetate (16a) under mild conditions gave the related alcohol (16b), together with a small amount of isosuberenol (6). When the selenium dioxide oxidation of suberosin was effected in methanol, the alcohol (16b) was the major product; also formed in fair yield was the aldehyde (17).

In connection with a synthesis of the minor coumarin, arnottin, selenium dioxide oxidation of osthol has been found to give a derivative corresponding to (16a).[17]

Attention was next turned to the preparation of the diene (5), with the object of dimerizing it to achieve a synthesis of cyclobisuberodiene (4). Firstly, the treatment of suberosin dibromide with a wide range of bases gave no useful result, but with potassium t-butoxide in dimethylformamide the bromo olefin (19) was obtained. Dehydration of isosuberenol with phosphoryl chloride, methanesulfonyl chloride or trifluoromethanesulfonyl chloride in the presence of pyridine also proved unsatisfactory, the only isolable product being the chloro derivative (20). The structures of (19) and (20) were readily apparent from their n.m.r. spectra.

[16] Matter, U. E., Pascual, C., Pretsch, E., Pross, A., and Sternhell, S., *Tetrahedron*, 1969, 691.
[17] Ishii, H., and Ishikawa, T., *Chem. Pharm. Bull.*, 1975, **23**, 936.

In one attempt to prepare the diene (5), (16b) was treated with boron trifluoride in acetic acid, but the product was the acetate (16a). The alcohol (16b) was substantially unaffected by boron trifluoride in tetrahydrofuran, but in benzene a Friedel–Crafts alkylation occurred to yield (21).

In contrast, the tertiary alcohol, suberenol, was dehydrated smoothly by phosphoryl chloride and pyridine at 0° to the diene. However, as isosuberenol was in somewhat more plentiful supply, it was still desirable to find a method to effect its dehydration, under mild conditions and without intrusion of the competing allylic substitution reaction observed above. These requirements were met by the sulfur(IV) compound (22) (cf.[18]). Exposure of isosuberenol to (22) in dichloromethane at room temperature gave the desired diene instantaneously and in good yield. It has been reported that the suberenol-like substrate, avicennol (14a), gave no useful result on treatment with acid or base but it was readily dehydrated by phosgene to the naturally occurring diene, avicennin (14b).[19]

The structure of the diene (5) was supported by its spectral properties. The u.v. spectrum (λ_{max} 220, 276, 283, 341 nm, ε 16000, 22000, 21000, 10600) showed evidence of extended conjugation, and the n.m.r. spectrum ([D_6]acetone) contained, in addition to coumarin signals, peaks which could be assigned to the unsaturated side chain [δ 6·99, 6·85, AB q, $J_{1',2'}$ 16·2 Hz, H 1′, H 2′; 5·19, m, $J_{4',4'}$ 2·2, $J_{4',Me}$ 0·8, $J_{4',Me}$ 1·2 Hz, (H 4′)$_2$; 2·00, dd, Me]. The substance readily formed an adduct with maleic anhydride.

In preliminary experiments to effect the synthesis of cyclobisuberodiene, treatment of (16a), (16b), or suberosin epoxide (23) with *p*-toluenesulfonic acid in refluxing benzene, toluene or xylene gave low yields of a bis-coumarin isomeric with the desired product. With the putative intermediate in the reaction, the diene (5), in hand, it was of interest to study its reactivity. In the event, refluxing the substance in benzene with or without *p*-toluenesulfonic acid led to much decomposition and the only product isolated was again the bis-coumarin. There was no sign of cyclobisuberodiene.

The bis-coumarin, $C_{30}H_{28}O_6$, could have been formed either by an acid-catalysed dimerization of the diene (5) or by a Diels–Alder reaction. The former reaction, if cationic intermediates of the normal type are involved and if consideration is limited to five- and six-membered rings, could yield six products. Of these, two contain the residue ArCH=CH–, and two the residue –C(Ar)=CH–, but, since the n.m.r. spectrum showed no signals corresponding to protons in such environments, these products could be immediately excluded. The two remaining products have structures (24) and (25). From a Diels–Alder reaction four products could arise: two if the C 3′=C 4′ residue acted as the dienophile, and two if the C 1′=C 2′ residue did so. The former pair (one of which is cyclobisuberodiene) contain the grouping ArCH=CH– and so may also be excluded. The latter pair, it transpires, have structures (24) and (25). Both contain the grouping –C(Me)=CH_2, and in fact the n.m.r. spectrum of the bis-coumarin had signals arising from two terminal olefinic protons at about δ 4·7.

The n.m.r. spectrum [in $CDCl_3/C_6D_6$ (1 : 3) for maximum dispersion] supported structure (24) rather than (25). The heterocyclic ring protons resonated as two overlapping AB quartets (δ 7·02 and 6·98, *J* 9·5 Hz, H 4, H 4′; 6·0 and 5·94, *J* 9·5 Hz, H 3, H 3′); H 5 and H 5′ as singlets at 7·16 and 7·00; H 8 and H 8′ as singlets at 6·53 and 6·33; and the two methoxy group protons as singlets at 3·25 and 2·90.

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[19] Gray, A. I., Waigh, R. D., and Waterman, P. G., *J. Chem. Soc., Perkin Trans. 1*, 1975, 485.

The signal from the olefinic proton, H 4″, was an envelope ($W_{h/2}$ 9·0 Hz) at δ 5·48; two broadened singlets at 4·87 and 4·78 were assigned to H_2C=. The signal from H 3″ appeared as a broadened sextet at δ 3·49. A broadened three-proton signal at δ 2·00 was assigned to 5″-Me and a second three-proton signal at 1·35 to H_2C=C**Me**. The remainder of the spectrum consisted of two sets of broadened doublets of doublets centred at δ 2·02 and 2·38 and a triplet at 2·58. These signals could be assigned to $(H\,6'')_2$ and H 2″ respectively. Double irradiation at δ 1·35 caused sharpening in the signals at 4·87 and 4·78, and so this signal could be attributed to H_2C=C**Me**. In the reverse experiment, the signal at δ 1·35 sharpened more when the signal at 4·87 was selectively irradiated than when the signal at 4·78 was; the former signal was therefore due to H_A. The upfield position of the signal from H_2C=C**Me** at δ 1·35 [δ ($CDCl_3$) 1·31] can be explained on the basis of shielding by one or both of the coumarin rings.

Having established the gross structural features of the bis-coumarin from the n.m.r. spectra, we performed extensive multiple-irradiation experiments to distinguish between isomeric structures (24) and (25). Because of the presence of allylic and homoallylic couplings, signals from protons associated with the cyclohexene ring were considerably broadened and some decouplings were observed only with difficulty. An envelope at δ 3·94 could be assigned to the benzylic–allylic proton H 3″ since irradiation of it produced a distinct narrowing of the signals at 7·16 (H 5) and 5·47 (H 4″); in addition the triplet at 2·58 collapsed to a doublet (J 3·5 Hz). The proton associated with this latter signal must be either the allylic H 2″ in (24) or the benzylic H_a in (25). On chemical shift grounds the former is preferred and indeed no benzylic coupling was observable between this proton and any of the aromatic protons, but allylic coupling could be shown to be operating with H_2C= as follows: irradiation of the methyl group at δ 1·35 caused the two broad signals from H_2C= to collapse to an AB quartet with the upfield doublet still noticeably broadened; simultaneous irradiation of H 2″ removed this broadening. The multiplet centred at δ 3·49 can therefore be assigned to H 1″ in (24). As expected then irradiation of H 1″ caused the H 2″ triplet to collapse to a doublet (J 3·5 Hz), the signals due to $(H\,6'')_2$ to change to an AB quartet (J 18 Hz), and the signal due to H 5′ (δ 7·00) to sharpen distinctly (benzylic coupling); there was no change in the H_2C= signals.

The mass spectrum of the bis-coumarin was very similar to that of cyclobisuberodiene. Between the molecular ion peak and the base peak at *m/e* 242, corresponding to the ion of the diene (5) arising from a retro-Diels–Alder fragmentation, there were only a few small peaks. The remainder of the spectrum could be accounted for in terms of further fragmentation of the diene ion.

The balance of evidence therefore clearly favoured (24). On the assumption of a concerted process, the dimerization of diene (5) would be suprafacial on the diene and either suprafacial–*endo* or –*exo* (e.g. with respect to the aryl group) on the dienophile, leading to the two isomers (26a) and (26b) respectively, with the relative configurations indicated. It is not possible at this stage to distinguish between the two structures. Both can exist in boat-like conformations so that H 1″, H 2″, H 3″ and $(H\,6'')_2$ are correctly disposed to produce the vicinal coupling constants observed in the n.m.r. spectrum; chair-like conformations are unsatisfactory in this respect.

The orientation effects (regioselectivities) that are observed in Diels–Alder reactions when the diene and dienophile are unsymmetrically substituted are intriguing and are

not well understood even in simple systems,[20] though in some instances frontier orbital theory has been used successfully in a qualitative sense.[21,22] In the case of 1-substituted dienes there is strong preference for '*ortho*' adducts of the type (25) over '*meta*' adducts of the type (24). Most studies have been concerned with dienophiles bearing electronegative substituents, but it has been reported that 1-phenylbutadiene dimerizes to give 3,4-diphenyl-5-vinylcyclohex-1-ene.[23] On the whole steric factors do not appear to be important except perhaps in extreme situations with very bulky groups, when the isomer distribution approaches the statistical value.[24] The exclusive formation of (24) from suberodiene is, therefore, remarkable but at this stage no further comment can be made except to invoke the possibility of severe steric repulsions between the coumarin rings. Also puzzling is the relationship between the bis-coumarin (24) and cyclobisuberodiene (4); it is not clear why the styrene double bond should be involved in the formation of (24) whereas the terminal methylene bond of (5) serves as the dienophile to produce (4).

The failure to convert suberosin or its oxygenated derivatives into cyclobisuberodiene (4) suggests that the latter is probably not formed during manipulation of the plant extracts but is a genuine natural product. Phebalin has recently been shown to have a structure isomeric with (4), having the aryl rings attached through the 8,8′-positions from an osthol-type precursor.[25]

Note on Nomenclature

The names suberosin, suberenol etc. were coined before the publication of the IUPAC Rules on the Nomenclature of Natural Products and Related Compounds (Section F). They have been retained here to preserve continuity with the previous literature. Their systematic synonyms are listed in the Chemical Abstracts Index Guide.

IUPAC Rule C 473.1 permits the use of coumarin as a trivial name for 2*H*-1-benzopyran-2-one. For simplicity, and to permit ready comparison of n.m.r. assignments, we have named our new compounds as substituted coumarins, except in those cases where overriding IUPAC rules make this impossible. Systematic names of the key compounds are given in the Experimental section.

Experimental

Except where otherwise stated the following generalizations apply.

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. Ultraviolet spectra were measured in 95% ethanol on a Perkin–Elmer 402 spectrometer, and infrared spectra in Nujol mulls on a Perkin–Elmer 221 spectrometer. Mass spectra were obtained at 70 eV with an A.E.I. MS902 mass spectrometer. Proton nuclear magnetic resonance spectra were measured in deuterochloroform solutions on Varian HA-100 or XL-100 100-MHz instruments.

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[23] Onishenko, A. S., 'Diene Synthesis' p. 606 (Israel Program for Scientific Translations: Jerusalem 1964).
[24] Huisgen, R., Grashey, R., and Sauer, J., in 'The Alkenes' (Ed. S. Patai) p. 914 (Interscience: London 1964).
[25] Brown, K. L., Burfitt, A. I. R., Cambie, R. C., Hall, D., and Mathai, K. P., *Aust. J. Chem.*, 1975, **28**, 1327.

Merck silica gel $HF_{254+366}$ was used for thin-layer chromatography and $PF_{254+366}$ for preparative layer chromatography, benzene/ether (8 : 2) being used for development. Merck silica gel (80–120 mesh) and alumina (type H) were used for column chromatography. Deactivated alumina was prepared by treatment with ethyl acetate. Gas–liquid chromatography was carried out on an F & M 400 instrument with a flame ionization detector and nitrogen as carrier gas. The column used was 1% Xe60 on Gas-Chrom P (100–400 mesh) support in a tube of length 3·5 m and diameter 0·002 m. At a column temperature of 220° the following retention times were recorded: suberosin, 2·5 min; suberenol, 4·3 min; isosuberenol, 7·5 min; the aldehyde (3), 2·6 min.

Light petroleum had b.p. 40–60°. Known substances were identified by direct comparison (mixed m.p. and comparison of i.r. and n.m.r. spectra) with authentic specimens. Analyses were performed by the Australian Microanalytical Service, Melbourne.

Photo-oxygenation of Suberosin [7-Methoxy-6-(3'-methylbut-2'-enyl)coumarin] (1)

(A) In initial experiments, the solution of suberosin contained in a round-bottom flask fitted with a water-cooled condenser was irradiated by a single 500-W tungsten lamp located immediately below the flask. A stream of oxygen was passed through the solution by means of a sintered glass bubbler. The heat generated by the lamp was generally sufficient to cause the solution to reflux.

In a typical experiment suberosin (1·0 g) dissolved in chloroform (100 ml) was irradiated for 100 h in the presence of Methylene Blue (0·005 g) as sensitizer. From time to time solvent was added to maintain the original volume and sensitizer added to maintain the original colour. At the end of the reaction the solution was washed with aqueous ferrous sulfate, then water, and brine. The dried solution was evaporated and the crude residue chromatographed on deactivated alumina. Elution with light petroleum/benzene (1 : 1) gave suberosin (0·1 g) followed by the aldehyde (3) (0·29 g). Elution with light petroleum/benzene (1 : 2) and benzene gave suberenol (2) (0·05 g). Isosuberenol (6) (0·32 g) was eluted by benzene/ethyl acetate mixtures (95 : 5, 90 : 10, 80 : 20). The epoxy alcohol (7a) (0·05 g) was obtained from fractions eluted by benzene/ethyl acetate (7 : 3 and 6 : 4).

The effectiveness of methanol and chloroform as solvents was studied, in combination with the sensitizers Rose Bengal, eosin, haematoporphyrin, and Methylene Blue. No marked variation in the yields of the major products was observed; in each case a significant amount (*c.* 20%) of the product could not be crystallized, presumably being decomposition material produced in the long reaction periods involved.

In one experiment suberosin (3 g) in methanol (300 ml) was irradiated for 170 h (haematoporphyrin as sensitizer). A solution of the crude product in benzene, on standing, deposited the derivative (8) (0·3 g). Chromatography of the remaining material as above gave, in addition to the products (2), (3) and (6), a fraction eluted by benzene/ethyl acetate (7 : 3) which contained the methoxy epoxide (7b). This was purified by p.l.c. to give the pure substance (0·08 g).

(B) In subsequent work, an improved irradiation apparatus was used. This consisted of a light source made up of eight 20-W 'white' fluorescent tubes encircling (diam. 20 cm) a vertical, tubular reaction vessel equal in length to that of the light tubes. The bottom of the vessel tapered to a sintered glass frit which served to introduce a steady stream of oxygen. Ambient temperature was maintained by means of air cooling from a small fan located at the base of the apparatus.

In a typical experiment, a solution of suberosin (6 g) in chloroform (500 ml) was irradiated in the presence of oxygen (Methylene Blue as sensitizer). After 2·5 h practically all of the suberosin had been consumed (t.l.c. and n.m.r.). The solution was then evaporated and the residue taken up in methanol (100 ml). After the solution had been stirred with sodium borohydride (1·0 g) for 1 h, the solvent was removed and the crude product (which n.m.r. spectroscopy showed to be essentially a mixture of suberenol and isosuberenol in the ratio of 2 : 3) was chromatographed on deactivated alumina. Benzene/light petroleum (1 : 2 and 1 : 1) eluted suberenol; benzene and benzene/ethyl acetate (9 : 1) eluted isosuberenol. The yields of the two products, after recrystallization, were 2·2 g (34%) and 3·1 g (48%) respectively.

Suberenol [(E)-6-(3'-Hydroxy-3'-methylbut-1'-enyl)-7-methoxycoumarin] (2)

The pure substance, prisms for methanol, had m.p. 172–173°, and was identical with the natural product.

Isosuberenol [6-(2′-Hydroxy-3′-methylbut-3′-enyl)-7-methoxycoumarin] (6)

Isosuberenol crystallized from benzene as colourless *needles*, m.p. 123–124° (Found: C, 69·1; H, 6·0. $C_{15}H_{16}O_4$ requires C, 69·2; H, 6·2%). λ_{max} 224, 244sh, 254, 298sh, 330 nm; ε 19000, 5900, 4600, 6900, 13800. ν_{max} 3500, 1700, 1620 cm^{-1}. N.m.r. δ 3·92, s, OMe. Mass spectrum *m/e* 260 (17%), 219 (4), 190 (86), 189 (100), 161 (6), 159 (13), 131 (12), 103 (3), 78 (7).

The Epoxy Alcohol (7a)

The pure substance [6-(2′,3′-epoxy-1′-hydroxy-3′-methylbutyl)-7-methoxycoumarin] formed colourless *prisms* from methyl acetate/diisopropyl ether, m.p. 183–185° (Found: C, 65·2; H, 5·7. $C_{15}H_{16}O_5$ requires C, 65·2; H, 5·8%). λ_{max} 223, 243, 252, 297, 326, 344sh nm; ε 19200, 5500, 4000, 8300, 14300, 7800. ν_{max} 3420, 1726, 1620, 1560, 1500 cm^{-1}. N.m.r. δ 3·92, s, OMe; 6·30, d, *J* 9 Hz, H3; 6·83, s, H8; 7·60, s, H5; 7·69, d, *J* 9 Hz, H4; data for side chain in text. Mass spectrum *m/e* 276 (11%), 218 (7), 205 (100), 204 (40), 203 (14), 175 (15), 71 (10), 57 (12), 43 (18), 41 (45), 39 (13).

The acetate, formed with pyridine/acetic anhydride at room temperature, crystallized from hexane as *needles*, m.p. 147–148° (Found: C, 64·0; H, 5·6. $C_{17}H_{18}O_6$ requires C, 64·1; H, 5·7%). N.m.r. δ 1·28, 1·39, s, 2×Me; 2·12, s, OAc; 3·11, d, *J* 8·5 Hz, H2′; 3·92, s, OMe; 5·97, d, *J* 8·5 Hz, H1′; 6·29, d, *J* 9·5 Hz, H3; 6·83, s, H8; 7·47, s, H5; 7·65, d, *J* 9·5 Hz, H4.

The Methoxy Epoxide (7b)

The pure substance [6-(2′,3′-epoxy-1′-methoxy-3′-methylbutyl)-7-methoxycoumarin] formed colourless *prisms* from ethyl acetate/hexane, m.p. 152–154° (Found: C, 66·5; H, 6·3. $C_{16}H_{18}O_5$ requires C, 66·2; H, 6·3%). λ_{max} 242sh, 252sh, 292, 325 nm; ε 6200, 4400, 7800, 13000. ν_{max} 1730, 1620 cm^{-1}. N.m.r. δ 1·25, 1·28, 2×s, $(H4')_3$, 3′-Me; 3·02, d, *J* 7·5 Hz, H2′; 3·36, s, 1′-OMe; 3·91, s, 7-OMe; 4·48, d, *J* 7·5 Hz, H1′; 6·26, d, *J* 9·5 Hz, H3; 6·83, s, H8; 7·52, s, H5; 7·69, d, *J* 9·5 Hz, H4. Mass spectrum *m/e* 290 (8%), 220 (15), 219 (100), 189 (3), 84 (6), 78 (44).

The Dicoumarinylethane (8)

The substance [6,6′-ethylenebis(7-methoxy-2*H*-1-benzopyran-2-one)] crystallized from acetic acid in white *prisms*, m.p. 330–335° (Found: $M^{+\cdot}$, 378·110. $C_{22}H_{18}O_6$ requires $M^{+\cdot}$, 378·110). ν_{max} 1725, 1612, 1612, 1558, 1270, 1140, 1120, 1008, 819 cm^{-1}. Mass spectrum *m/e* 378 (17%), 189 (100), 159 (10), 131 (10), 102 (7).

7-Methoxy-6-vinylcoumarin

Methyltriphenylphosphonium bromide (0·85 g) was added slowly to butyllithium (1·1 ml of a 20% solution in hexane) in ether (20 ml). The mixture was stirred for 4 h at room temperature and then the aldehyde (3) (0·5 g), dissolved in tetrahydrofuran (200 ml), was added slowly. After the mixture had been stirred overnight, it was diluted with water and the crude product isolated with the aid of chloroform. Purification was achieved by p.l.c. to give *7-methoxy-6-vinylcoumarin* (0·21 g), buff prisms from methanol, m.p. 118-120° (Found: C, 71·2; H, 4·9. $C_{12}H_{10}O_3$ requires C, 71·3; H, 5·0%). λ_{max} 221sh, 253, 295sh, 305, 338 nm; ε 13100, 17600, 6100, 6800, 9300. ν_{max} 1730, 1618, 1560, 1270, 1132, 919, 825 cm^{-1}. N.m.r. δ 3·87, s, OMe; 5·27, dd, J_Z 11, J_{gem} 1·5 Hz, H2′; 6·6, dd, J_E 18, J_{gem} 1·5 Hz, H2′; 6·21, d, *J* 9·5 Hz, H3; 6·70, s, H8; 7·05, dd, J_Z 11, J_E 18 Hz, H1′; 7·45, s, H5; 7·57, d, *J* 9·5 Hz, H4. Mass spectrum *m/e* 202 (100%), 187 (18), 159 (16), 131 (28), 77 (8).

Photo-oxygenation of Suberenol and 7-Methoxy-6-vinylcoumarin

(i) Suberenol (0·15 g) in methanol (80 ml) and Rose Bengal (0·001 g) as sensitizer were irradiated [method (A)] for 120 h. P.l.c. of the crude reaction product gave the aldehyde (3) (0·08 g).

(ii) 7-Methoxy-6-vinylcoumarin (0·06 g) in methanol (70 ml), with Rose Bengal (0·001 g) as sensitizer, was irradiated for 96 h. P.l.c. of the crude product gave the aldehyde (3) (0·025 g) and starting material (0·019 g).

The Hydroperoxide (13)

Suberosin (2 g) in chloroform (500 ml) was irradiated [method (B)] for 2 h in the presence of oxygen, with Methylene Blue as sensitizer. The solvent was removed by distillation and the crude residue subjected to a countercurrent distribution in a machine of 120 tubes (20 ml each phase). The stationary phase was methanol/water (1 : 0·5) and the mobile phase ethyl acetate/light petroleum (15 : 1); the two phases were equilibrated before use. After 220 transfers isosuberenyl hydroperoxide (13) was concentrated in tubes 90–120 (by n.m.r.); tubes 105–120 contained small amounts also of suberenyl hydroperoxide (12), but in none was it present alone, unmixed with (13). Tubes 115–130 contained the aldehyde (3) (0·3 g). The contents of tubes 90–120 were combined and chromatographed on deactivated alumina. The aldehyde (3) (0·25 g) was eluted by benzene/light petroleum (2 : 1). Benzene/ethyl acetate (95 : 5 and 90 : 10) eluted isosuberenyl hydroperoxide (0·9 g). The pure substance [6-(2′-hydroperoxy-3′-methylbut-3′-enyl)-7-methoxycoumarin] formed colourless *needles* from benzene/light petroleum, m.p. 120–121° (Found: C, 65·2; H, 6·0. $C_{15}H_{16}O_5$ requires C, 65·2; H, 5·8%). λ_{max} 224, 244, 254, 299sh, 330, 347sh nm; ε 19600, 5900, 4900, 8500, 14200, 9200. ν_{max} 3300, 1700, 1620, 1563, 1505 cm^{-1}. N.m.r. δ 1·30, s, OOH; 1·83, br s, Me; 2·90, d, J 6·5 Hz, CH_2; 3·93, s, OMe; 4·59, t, J 6·5 Hz, CH; 5·0, br s, $=CH_2$; 6·20, d, J 9 Hz, H 3; 6·77, s, H 8; 7·27, s, H 5; 7·60, d, J 9 Hz, H 4. Mass spectrum *m/e* 276 (3), 260 (3), 258 (5), 204 (10), 190 (35), 189 (100), 159 (15), 131 (14), 103 (10), 79 (11), 70 (50), 41 (80), 39 (60).

The hydroperoxide was recovered quantitatively after passage through a column of deactivated alumina (elution with benzene/ethyl acetate 9 : 1). Treatment of it in methanol solution with sodium borohydride produced isosuberenol in good yield.

Conversion of the Epoxy Alcohol (7a) into 7-Methoxy-2-oxo-2H-1-benzopyran-6-carbaldehyde (3)

(i) When the epoxy alcohol (7a) (14 mg) was passed in benzene/light petroleum (1 : 1) solution through a column of deactivated alumina (8 g), the aldehyde (3) (3 mg) was the first substance eluted (by the initial solvent and by benzene). Benzene/ethyl acetate (9 : 1) eluted starting material (9 mg). With normal alumina the yield of aldehyde increased to 45%.

(ii) A solution of the epoxy alcohol (15 mg) in benzene (5 ml) at 5° was treated with boron trifluoride etherate (2 drops). No starting material remained after 2 h (t.l.c.). The solution was washed with water, dried and evaporated to give the aldehyde (3) quantitatively.

Reaction of Suberosin with $^1O_2$ Generated Chemically

(i) To a solution of suberosin (0·1 g) in methanol (10 ml) containing hydrogen peroxide (30%; 0·2 ml) was added aqueous sodium hypochlorite (1 M, 1·5 ml) dropwise over 0·5 h with vigorous stirring. The mixture was then acidified and the organic product isolated with the aid of chloroform.

(ii) A stream of ozone was passed through a solution of triphenyl phosphite (0·64 g) in dichloromethane (20 ml) at −78° until ozone was no longer absorbed. The cold solution was then swept with dry nitrogen to remove the excess ozone. To this solution was added a cold solution of suberosin (0·1 g) in dichloromethane (10 ml) and the mixture transferred to a bath at −25°. After 2 h it was allowed to come to room temperature slowly and the crude product obtained by evaporation of the solvent.

(iii) Suberosin (0·2 g) and 9,10-diphenylanthracene *endo*-peroxide (0·6 g) were refluxed in benzene (30 ml) under nitrogen for 72 h.

(iv) A solution of potassium chromate (0·69 g) and potassium hydroxide (0·15 g) in water (8 ml) was added slowly at 0° to a solution of suberosin (0·25 g) in methanol/water (60 : 40, 50 ml) containing hydrogen peroxide (30%, 1·2 ml). After 1 h the mixture was diluted with water and extracted with chloroform to give the crude product.

In each reaction the crude product was reduced in methanol with sodium borohydride and the product obtained as described above for the photo-oxygenations. G.l.c. analysis of each total reaction product indicated that the major component was the starting material; the amount of oxygenation products (suberenol and isosuberenol) amounted to less than 10%. Of the four methods, method (iii) gave the best result, but was still much less efficient than the photo-oxygenation method.

Autoxidation of Suberosin

(i) Suberosin was recovered unchanged (g.l.c.) from chloroform or methanol solutions (10%) kept in the dark but exposed to air.

(ii) A methanol solution (10%) of suberosin, allowed to stand for 2 months in diffuse light with access to air, was found (after treatment of the crude product with ferrous sulfate) to contain only a trace of suberenol together with unchanged suberosin. A chloroform solution treated in the same manner yielded suberosin (84%), suberenol (8%) and the aldehyde (3) (8%).

(iii) After a chloroform solution of suberosin (10%) which was 0·1 M with respect to salcomine had been kept in diffuse daylight for 2 months, g.l.c. indicated the presence of a trace of suberenol, suberosin (92%) and the aldehyde (3) (8%). There was no appreciable change to this result when the solution was shaken with oxygen.

(iv) A chloroform solution of suberosin (1%) was irradiated [method (B) above] for 80 h. G.l.c. analysis of the crude product, after reduction ($FeSO_4$), indicated the presence of suberosin (24%), suberenol (20%), isosuberenol (18%), the aldehyde (3) (20%) and unidentified material (18%).

Reaction of Suberosin with N-*Bromosuccinimide*

(i) When suberosin was refluxed in carbon tetrachloride for 4 h in the presence of *N*-bromosuccinimide, a complex mixture resulted which could not be separated satisfactorily. The use of azobisisobutyronitrile or t-butyl hydroperoxide/copper laurate as radical initiator did not improve the result.

(ii) To a stirred solution of suberosin (0·5 g) in dioxan (20 ml) and water (10 ml) was added portionwise *N*-bromosuccinimide (0·365 g) over 0·5 h. The mixture was stirred overnight, diluted with water, and then extracted with chloroform. Evaporation of the chloroform gave the crude product which was filtered in benzene solution through a short column of silica gel to give *6-(2′-bromo-3′-hydroxy-3′-methylbutyl)-7-methoxycoumarin* (15a) (0·35 g), colourless needles from methanol, m.p. 146–147° (Found: C, 52·6; H, 5·1; Br, 22·7. $C_{15}H_{17}BrO_4$ requires C, 53·0; H, 5·0; Br, 23·2%). λ_{max} 222, 242, 252, 295, 327 nm; ε 16800, 5600, 4300, 6800, 12700. ν_{max} 3650–3400, 1725, 1620, 1562, 1275, 1131 cm^{-1}. N.m.r. δ 1·48, s, 2×Me; 2·27, s, OH; 2·73, dd, J_{gem} 14·5, J_{vic} 11·0 Hz, H1′; 3·55, dd, J_{gem} 14·5, J_{vic} 2·0 Hz, H1′; 3·92, s, OMe; 4·38, dd, J 2·0, 11·0 Hz, H2′; 6·28, d, J 9·5 Hz, H3; 6·82, s, H8; 7·32, s, H5; 7·68, d, J 9·5 Hz, H4. Mass spectrum *m/e* 342 (17%), 340 (17), 243 (75), 203 (67), 189 (100), 159 (5), 131 (5), 59 (50).

(iii) When the reaction was repeated in anhydrous methanol as solvent a nearly quantitative yield of 6-(2′-bromo-3′-methoxy-3′-methylbutyl)-7-methoxycoumarin (15b) was obtained. The substance crystallized from methanol in colourless *needles*, m.p. 131–132° (Found: C, 54·0, H, 5·5; Br, 22·6. $C_{16}H_{19}BrO_4$ requires C, 54·2; H, 5·4; Br, 22·3%). λ_{max} 222, 242, 252, 294, 327 nm; ε 16500, 5400, 4000, 6900, 12800. ν_{max} 1722, 1619, 1560, 1272, 1130 cm^{-1}. N.m.r. δ 1·42, s, 2×Me; 2·75, dd, J_{gem} 14·5, J_{vic} 11·5 Hz, H1′; 3·32, s, 3′-OMe; 3·60, dd, J_{gem} 14·5, J_{vic} 2·0 Hz, H1′; 3·90, s, 7-OMe; 4·33, dd, J 2·0, 11·5 Hz, H2′; 6·27, d, J 9 Hz, H3; 6·82, s, H8; 7·32, s, H5; 7·65, d, J 9 Hz, H4. Mass spectrum *m/e* 356 (5%), 354 (5), 243 (83), 203 (3), 189 (27), 159 (4), 131 (5), 73 (100).

Reaction of Suberosin with Selenium Dioxide

(i) A solution of suberosin (1·0 g) in acetic acid (5 0·ml) and acetic anhydride (2·0 ml) was stirred at 90–95° while selenium dioxide (0·445 g) was added slowly over 1 h. The mixture was stirred and heated for a further 48 h. After the selenium produced had been filtered off, the filtrate was diluted with water and extracted with chloroform. This solution was washed thoroughly with aqueous $NaHCO_3$ and then worked up in the usual way. P.l.c. of the crude product (benzene/ether 7 : 3) separated the acetate (16a) (0·7 g), the aldehyde (17) (0·07 g) and the diacetate (18) (0·05 g).

6-[(E)-4′-Acetoxy-3′-methylbut-2′-enyl]-7-methoxycoumarin (16a) crystallized from methanol as buff needles, m.p. 140–141° (Found: C, 67·7; H, 6·0. $C_{17}H_{18}O_5$ requires C, 67·5; H, 6·0%). λ_{max} 223, 243sh, 253, 298sh, 330 nm; ε 20000, 6000, 4500, 7100, 14500. ν_{max} 1728, 1640, 1264, 1120, 1015, 820 cm^{-1}. N.m.r. δ 1·76, br s, Me; 3·41, br d, J 7·5 Hz, $(H1')_2$; 3·91, s, OMe; 4·52, tq, J 7·5, 1·4 Hz, H2′; 6·23, d, J 9·5 Hz; 6·82, s, H8; 7·18, s, H5. Mass spectrum *m/e* 302 (22%), 259 (4), 243 (31), 242 (100), 229 (25), 227 (75), 211 (28), 199 (13), 190 (17), 189 (41), 171 (6), 159 (12), 155 (5), 131 (14), 128 (6), 115 (9).

6-[(*E*)-3′-Formylbut-2′-enyl]-7-methoxycoumarin* (17) crystallized from methanol as straw-coloured *needles*, m.p. 133–134° (Found: $M^{+\cdot}$, 258·0881. $C_{15}H_{14}O_4$ requires $M^{+\cdot}$, 258·0892). λ_{max} 226, 284, 295, 318sh, 325 nm; ε 25300, 6100, 7600, 13400, 14100. ν_{max} 1730, 1685, 1621, 1561

* (*E*)-4-(7′-Methoxy-2′-oxo-2′*H*-1′-benzopyran-6′-yl)-2-methylbut-2-enal.

1276, 1130 cm^{-1}. N.m.r. spectrum δ 1·87, dt, J 1·4, 0·8 Hz, Me; 3·68, br d, J 7·5 Hz, (H1′)$_2$; 3·90, s, OMe; 6·26, d, J 9·5 Hz, H3; 6·58, tq (br), J 7·5, 1·4 Hz, H2′; 6·82, s, H3; 7·21, s, H5; 7·62, d, J 9·5 Hz, H4; 9·43, br s, CHO. Mass spectrum *m/e* 258 (100%), 241 (9), 229 (40), 189 (25), 176 (19), 159 (9), 148 (9), 131 (9), 82 (27), 77 (9), 69 (11).

6-(4′-Acetoxy-3′-acetoxymethylbut-2′-enyl)-7-methoxycoumarin was obtained as a gum. N.m.r. δ 2·03, s, 2×OAc; 3·47, d, J 7·5 Hz, (H1′)$_2$; 3·88, s, OMe; 4·6, 4·8, br s, 2×CH_2O; 5·88, br t, J 7·5 Hz, H2′; 6·20, d, J 9·5 Hz, H3; 6·78, s, H8; 7·18, s, H5; 7·60, d, J 9·5 Hz, H4.

(ii) The acetate (16a) (0·2 g) in methanolic potassium bicarbonate (5%, 10 ml) was warmed on a steam bath for 2 h and then left overnight at room temperature. After acidification with dilute sulfuric acid, extraction of the mixture with chloroform in the usual way gave a crude product which was separated by p.l.c. (benzene/ether 7 : 3). The alcohol (16b) (0·12 g) and isosuberenol (6) (0·03 g) were obtained.

6-[(E)-4′-Hydroxy-3′-methylbut-2′-enyl]-7-methoxycoumarin (16b) crystallized from methanol as colourless prisms, m.p. 85–86° (Found: C, 69·4; H, 6·4. $C_{15}H_{16}O_4$ requires C, 69·3; H, 6·2%). λ_{max} 224, 244sh, 254, 298, 331 nm; ε 20100, 5800, 4600, 7300, 15200. ν_{max} 1727, 1622, 1564, 1275, 1130, 1020, 822 cm^{-1}. N.m.r. δ 1·77, s, Me; 2·60, s, OH; 3·37, d, J 7·0 Hz, (H1′)$_2$; 3·90, s, OMe; 4·08, s, (H4′)$_2$; 5·58, t, J 7·0 Hz, H2′; 6·22, d, J 9·5 Hz, H3; 6·77, s, H8; 7·22, s, H5; 7·62, d, J 9·5 Hz, H4. Mass spectrum *m/e* 260 (67%), 229 (100), 189 (21), 159 (8), 131 (8).

(iii) When suberosin (0·5 g) and selenium dioxide (0·23 g) were refluxed in ethanol for 24 h the products isolated were the aldehyde (17) (0·1 g) and the alcohol (16b) (0·33 g).

6-(2′-Bromo-3′-methylbut-2′-enyl)-7-methoxycoumarin (*19*)

A solution of suberosin dibromide (0·1 g) in dimethylformamide (1 ml) was added to potassium t-butoxide (0·4 g) in dimethylformamide (1 ml) at 0°. The orange solution was kept at 0° for 3 h and the reaction then quenched with dilute H_2SO_4. Extraction with dichloromethane gave the crude product which was chromatographed on alumina (5 g). Benzene/light petroleum (1 : 1) eluted the bromo olefin (19) (0·07 g), colourless *rosettes* from ethyl acetate/hexane, m.p. 134° (Found: $M^{+\cdot}$, 324·0180, 322·0201. $C_{15}H_{15}BrO_3$ requires $M^{+\cdot}$, 324·0184, 322·0203). λ_{max} 224, 239, 253, 298, 328, 347sh nm; ε 22000, 7000, 5600, 8200, 15300, 9100. ν_{max} 1730, 1620, 1560, 1500, 815 cm^{-1}. N.m.r. δ 1·91, s, Me; 2·0, s, Me; 3·85, br s, CH_2; 3·95, s, OMe; 6·26, d, J 9 Hz, H3; 6·80, s, H8; 7·27, s, H5; 7·70, d, J 9 Hz, H4. Mass spectrum *m/e* 324 (92%), 322 (96), 243 (100), 227 (55), 213 (12), 199 (18), 189 (62), 177 (30), 176 (53), 159 (12), 148 (16), 131 (20), 128 (20), 115 (18), 103 (14), 89 (14), 77 (25), 69 (23).

Isosuberenyl Chloride [*6-(2′-Chloro-3′-methylbut-3′enyl)-7-methoxycoumarin*] (20)

Phosphoryl chloride (0·13 g) was added to a chilled solution of isosuberenol (0·125 g) in dichloromethane (5 ml) containing pyridine (0·6 g). After the mixture had stood at 0° for 4 h, it was left at room temperature for 6 h by which time no starting material remained (t.l.c.). The solution was then washed with ice-water, dilute sulfuric acid, water, and finally brine. The dried solution was evaporated to dryness and the residue chromatographed on silica gel (15 g). Elution with benzene/light petroleum (2 : 1) gave isosuberenyl chloride (20) (0·085 g), colourless *rods* from ethyl acetate/light petroleum, m.p. 117° (Found: C, 64·7; H, 5·5. $C_{15}H_{15}ClO_3$ requires C, 64·9; H, 5·4%). λ_{max} 224, 243, 253, 298, 327, 345sh nm; ε 20000, 6100, 4400, 8000, 14500, 8800. ν_{max} 1730, 1620, 1562, 1510 cm^{-1}. N.m.r. δ 1·88, s, Me; 3·15, m, CH_2 (AB of ABX); 3·90, s, OMe; 4·70, dd, J_{AX+BX} 14·5 Hz, CHCl (X of ABX); 4·85, 4·95, 2× br s, =CH_2; 6·24, d, J 9 Hz, H3; 6·78, s, H8; 7·22, s, H5; 7·60, d, 9 Hz, H4. Mass spectrum *m/e* 280 (4%), 278 (13), 243 (7), 242 (5), 229 (5), 227 (4), 189 (100), 159 (14), 131 (11), 103 (7), 77 (6).

The compound was also prepared in good yield by allowing a solution of isosuberenol (0·15 g) and triphenylphosphine (0·25 g) in carbon tetrachloride (1·5 ml) to stand at room temperature for 48 h. Removal of the solvent and precipitation of triphenylphosphine oxide with benzene gave a crude product which was purified by chromatography on silica gel.

Reaction of isosuberenol with methanesulfonyl chloride and with trifluoromethanesulfonyl chloride in the presence of pyridine also gave the chloride as the only isolable product.

Reaction of the Alcohol (*16b*) *with Boron Trifluoride Etherate*

(i) The alcohol (16b) (0·15 g) in acetic acid (10 ml) was treated at room temperature with boron trifluoride etherate (1 ml) for 2 h. The mixture was diluted with water and extracted with chloroform.

The extract was washed with saturated $NaHCO_3$ and then worked up in the usual way. P.l.c. (benzene/ether 8 : 2) gave the acetate (16a) (0·09 g).

(ii) The alcohol (16b) (0·1 g) in benzene (30 ml) was treated with boron trifluoride etherate (1 ml) and the mixture refluxed (N_2) for 48 h in a flask connected to a Soxhlet apparatus containing molecular sieves, type 4A, to remove water. The cooled solution was then washed with aqueous $NaHCO_3$ and worked up in the usual manner. P.l.c. of the crude product gave 7-methoxy-6-(3′-methyl-4′-phenylbut-2′-enyl)coumarin (21) (0·06 g). The pure substance crystallized from methanol as colourless *needles*, m.p. 104–105° (Found: C, 78·5; H, 6·5. $C_{21}H_{20}O_3$ requires C, 78·7; H, 6·3%). λ_{max} 243, 254, 300, 330 nm; ε 6500, 5100, 7100, 13800. ν_{max} 1722, 1620, 1560, 1270, 1128, 1018, 820 cm^{-1}. N.m.r. δ 1·63, s, Me; 3·33, m, 4H, $(H1')_2$, $(H4')_2$; 3·85, s, OMe; 5·43, m, H2′; 6·17, d, *J* 9 Hz, H3; 6·75, s, H8; 7·16, s, H5; 7·21, s, 5H, Ph; 7·56, d, *J* 9 Hz, H4. Mass spectrum *m/e* 320 (38%), 230 (17), 229 (100), 189 (14), 159 (5), 131 (5), 129 (5), 91 (6).

The Diene (5) [(E)-*7-Methoxy-6-(3′-methylbuta-1′,3′-dienyl)coumarin*]

(i) Phosphoryl chloride (0·22 g) was added to a solution, chilled in ice, of suberenol (0·18 g) in dichloromethane (6 ml) containing pyridine (0·80 g). After 6 h at 0° there was no starting material remaining (t.l.c.). The yellow solution was washed with dilute H_2SO_4, water, and brine, and then dried. Removal of the solvent gave a yellow crystalline residue which was chromatographed on silica gel. Elution with light petroleum/benzene (2 : 3) gave the diene (5) (0·12 g), yellow *rosettes* from carbon tetrachloride, m.p. 105° (dec.) (Found: $M^{+\cdot}$, 242·0941. $C_{15}H_{14}O_3$ requires $M^{+\cdot}$, 242·0942). λ_{max} 220, 276, 283sh, 341 nm; ε 16000, 22000, 21000, 10600. ν_{max} 1730, 1630, 1610, 1560, 1500 cm^{-1}. N.m.r. δ 2·0, br s, Me; 3·94, s, OMe; 5·14, br s, $=CH_2$; 6·28, d, *J* 9·5 Hz, H3; 6·80, s, H8; 6·85, s, H1′, H2′ (accidental equivalence, removed in [D_6]acetone); 7·55, s, H5; 7·65, d, *J* 9·5 Hz, H4. Mass spectrum *m/e* 242 (100%), 227 (70), 211 (22), 199 (14), 183 (6), 171 (9), 168 (6), 155 (12), 128 (12), 115 (9).

(ii) To a stirred solution of isosuberenol (0·38 g) in dichloromethane (20 ml) (dried over molecular sieves) at room temperature was added the sulfur(IV) compound (22) (2·5 g, 2·5 equiv.). After 6 min the reaction was complete and no starting material remained (t.l.c.). The solution was evaporated to dryness, and the residue taken up in light petroleum/benzene (5 : 2). Passage of this solution through a column of silica gel (25 g) and elution with the same solvent mixture afforded the fluoro alcohol [$PhC(CF_3)_2OH$] formed from (22). Elution with light petroleum/benzene (3 : 2) gave the diene (0·32 g).

A solution of the diene (0·023 g) and maleic anhydride (0·01 g) in benzene (0·5 ml) was heated on the steam bath for 1 h. The adduct separated on cooling the solution; the substance was recrystallized from ethyl acetate as colourless *rods*, m.p. 225° (Found: C, 67·1; H, 4·9. $C_{19}H_{16}O_6$ requires C, 67·1; H, 4·8%). λ_{max} 225, 245, 255, 300, 331, 348sh nm; ε 18300, 6900, 5500, 7850, 14900, 9300. ν_{max} 1840, 1780, 1730, 1620, 1565, 1500, 945 cm^{-1}. N.m.r. δ 1·92, br s, Me; 2·24–2·85, m, 2×CH; 3·4–4·1, m, 3×CH; 3·92, s, OMe; 5·90, br s, =CH; 6·27, d, *J* 9·5 Hz, H3; 6·95, s, H8; 7·29, s, H5; 7·66, s, H4. Mass spectrum *m/e* 340 (70%), 312 (30), 267 (25), 253 (10), 242 (78), 227 (100), 211 (28).

The Bis-coumarin (24) (*6,6′-[5″-Methyl-2″-(1‴-methylethenyl)cyclohex-4″-ene-1″,3″-diyl]bis(7-methoxy-2H-1-benzopyran-2-one)*)

(i) The alcohol (16b) (0·2 g) was refluxed in benzene (30 ml) containing *p*-toluenesulfonic acid (0·075 g) for 36 h. The flask was fitted with a Soxhlet apparatus containing molecular sieves, type 4A, to remove water. The cooled solution was then washed with aqueous sodium hydrogen carbonate and the crude product isolated in the usual manner. P.l.c. (benzene/ether 8 : 2) gave the dimer (24) (0·035 g) as the only isolable product; the yield was similar when toluene or xylene was used as solvent for the reaction. The bis-coumarin separated from methanol as colourless *plates*, m.p. 273–274° (Found: C, 74·1; H, 6·1. $C_{30}H_{28}O_6$ requires C, 74·4; H, 5·8%). λ_{max} 255, 299, 333 nm; ε 11350, 13650, 24000. ν_{max} 1720, 1616, 1559, 1270, 1150, 1120, 820 cm^{-1}. N.m.r. δ ($CDCl_3$) 1·32, s, Me; 1·92, br s, Me; 1·8–2·5, m, $(H6'')_2$; 2·55, br t, *J* 3·5 Hz, H2″; 3·50, 3·90, s, 2×OMe; 3·5, m (obscured), H1″; 3·9, m (obscured), H3″; 4·61, 4·77, br s, $=CH_2$; 5·70, br s, H4″; 6·23, 6·26, d, *J* 9·5 Hz, H3, H3′; 6·64, 6·84, s, H5, H5′; 7·22, 7·32, s, H8, H8′; 7·63, 7·68, H4, H4′. Mass spectrum *m/e* 484 (9%), 429 (2), 283 (4), 282 (19), 281 (8), 277 (9), 243 (16), 242 (100), 228 (4), 227 (16), 211 (7), 203 (3), 199 (3), 190 (4), 189 (26), 171 (3), 159 (4), 155 (2), 131 (4).

(ii) Treatment of the acetate (16a) (0·2 g) under the same conditions gave a similar yield of (24), as did suberosin epoxide (23) with *p*-toluenesulfonic acid or boron trifluoride etherate as catalyst.

(iii) A solution of the diene (5) (0·11 g) in benzene (50 ml) containing *p*-toluenesulfonic acid (0·05 g) was refluxed in a flask attached to a Dean–Stark apparatus. After 5 h no diene remained (t.l.c.). The reaction was worked up as above and the crude product purified by p.l.c. (light petroleum/acetone 75 : 25, triple development). The diene (0·025 g) was the only homogenous product isolated; all other fractions recovered were examined by n.m.r. spectroscopy but there was no indication of the presence of cyclobisuberodiene.

When suberodiene alone was refluxed in benzene conversion into other products occurred slowly, as indicated by t.l.c.; after 10 h the only isolable product was again (24), in low yield.

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