THE CONSTITUENTS OF THE RESIN OF EURYOPS FLORIBUNDUS. N.E.Br.

by

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A C K N O W L E D G E M E N T S.

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C O N T E N T S.

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S U M M A R Y.

The aerial portions of the plant Euryops floribundus were extracted and shown to contain Euryopsonol and another sesquiterpenoid for which the name Euryopsol is proposed. An extraction of Euryops tenuissimus contained Euryopsol only.

Euryopsonol, of empirical formula $C_{15}H_{20}O_3$, was previously shown to contain a hydroxyl group and a keto-group and to be doubly unsaturated. The hydroxyl group has been shown to be secondary, while the keto-group is α, β, γ, δ-unsaturated. Spectroscopic and Mass spectrosmetric measurements showed euryopsonol to possess a furan ring and to be member of the eremophilane-type of sesquiterpenoids. These proposals were confirmed by the conversion of euryopsonol to furanoeremophilone -9, thus establishing the stereochemistry at C_4, C_5 and C_{10}. The free hydroxyl group has been placed at C_3, but its stereochemistry is still unknown.

Euryopsol, of empirical formula $C_{15}H_{22}O_4$, possesses an unstable furan ring and readily undergoes antoxidation, probably to a more stable γ-lactone. It contains two vicinal hydroxyl groups, one of which was placed by Mass spectrometry at C_9. If euryopsol possesses the eremophilane skeleton the other hydroxyl group must be at C_{10}.

1. PREVIOUS WORK ON THE RESIN OF EURYOPS FLORIBUNDUS.

In 1954 Horn, Nunn and Rivett published the results of an investigation of the constituents of the resin of Euryops floribundus.[1] The resin obtained on acetone extraction was subdivided into free acids, combined acids and unsaponifiable matter. The combined acids were found to consist mainly of anisic, iso-butyric, angelic and tiglic acids. Tiglic acid, however, was absent in the mixture of free acids. The main crystalline substance isolated from the unsaponifiable matter was Euryopsonol of molecular formula $C_{15}H_{20}O_3$. It was doubly unsaturated, contained a ketone and an alcoholic group, but the nature of the third oxygen atom remained unknown.

2. A SURVEY OF SESQUITERPENOID-LACTONES AND RELATED FURANO-COMPOUNDS OCCURRING IN THE COMPOSITAE.

Recent investigations into the bitter principles of plants of the Compositae, of which Euryops is a member, have revealed the presence of five distinct groups of γ-lactones, viz:- the germacranolides, the santanolides, the alantanolides, the guaianolides and the eremophilenolides.[2]

Excepting for the santanolides, none of these groups has been extensively reviewed. For this reason the literature survey, which follows, is more lengthy than is usual for an M.Sc. thesis.

2.1. The Germacranolides have not been reviewed and hence this is dealt with in detail.

This group is characterised by a ten-membered carbocyclic ring, methyl groups at C_4 and C_{10}, a γ-lactone (generally with the lactonic hydroxyl group at C_6) and a hydroxyl group at C_8. A few of these compounds have the methyl group at C_{10} oxidised to a primary hydroxyl, while the C_3 hydroxyl is often esterified.

There is/.....

There is only one exception to this generalisation, namely aristolactone,[3] which has the unusual structure (1).[4]

The structures of the following germacranolides have been elucidated; they are based on that of germacrone (2).[5]

2.1.1. Pyrethrosin (3)[5] from Chrysanthemum cineriafolium was first isolated by Thoms in 1891. It was the first germacranolide to be chemically characterised.

Mild hydrogenation formed a mixture of dihydrostereoisomers, whereas the fully saturated stereoisomers were obtained on more vigorous reduction. Although chromium trioxide oxidation afforded a ketone, indicative of a secondary hydroxyl group, pyrethrosin could not be acetylated. The presence of a 1,2 oxide ring was demonstrated by the treatment of one of the above tetrahydropyrethrosins with an ethereal solution of borontrifluoride, whereby the ring was split and a ketone formed.[7]

The presence of the ten-membered carbocyclic nucleus was demonstrated by nitric acid oxidation of the mixture of tetrahydropyrethrosins to β-methyladipic acid (4).

The infrared spectrum of pyrethrosin showed frequencies due to the following functional groups:- an α, β-unsaturated γ-lactone (1760 cm^{-1}), two ethylenic linkages (1670 and 1650 cm^{-1}) and acetate residues (1735 and 1242 cm^{-1}). Comparison of the ultra-violet spectra of pyrethrosin, dihydro- and isodihydro-pyrethrosins, together with the products obtained from quantitative ozonolysis, showed that the methylenic double bond of the α, β-unsaturated γ-lactone is saturated on mild hydrogenation. This defined the lactonic function as 5.

In the presence of p-toluenesulphonic acid and acetic anhydride, pyrethrosin cyclised to the diacetate (6), which on selective hydrogenation followed by controlled hydrolysis, afforded an acetoxy-alcohol (7). Chromium trioxide oxidation of 7 led to 8, which on treatment with a base, yielded a

conjugated/.....

conjugated ketone (9), indicative of the presence of a β, γ-unsaturated ketone in 8. The position of the ethylenic linkage in 8 was verified by bromination followed by dehydrobromination to give 10, which was characterised by its ultra-violet absorption.

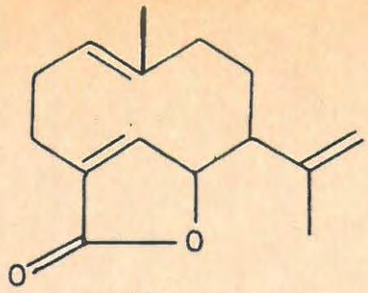
From the above base treatment of 8, two further products, 11a and 11b, were isolated, the former being reactylated to 8. Treatment of 11b with chromium trioxide gave a diketone, which with alkali afforded 12, a degredation product of ψ-santomin.[8] Similar treatment of 11a failed to give dienone absorption in the ultra-violet, and as it is reactylated to starting material, the lactonic function must be present as in pyrethrosin, which must be represented by 3. This structure is supported by further chemical evidence, molecular rotations and nuclear magnetic resonance studies.[6]

2.1.2. Arctiopicrin [9,10] of suggested structure (13) was isolated from Arctium minus (Bernh) and shown to be an ester of β-hydroxybutyric acid and arctiolide, a monocyclic-dihydroxy sesquiterpenic-γ-lactone. Hydrogenation afforded a mixture of hydrogenated and hydrogenolysed products, the ease of hydrogenolysis being due to the free allylic hydroxyl group. Tetrahydroarctiopicrin was hydrolysed to tetrahydroarctiolide (14), which on chromium trioxide oxidation afforded a hydroxy-keto-lactone (15). The product of hydrogenolysis was saponified and the free hydroxy-lactone 16 oxidised with chromium trioxide to a keto-lactone (17).[11] Compound 16 has also been obtained from hydrogenation of balchanolide.

The position of the ketonic frequency in the infrared spectrum of the various keto-derivatives of tetrahydro-arctiolide shows arctiopicrin to possess a medium sized carbocyclic ring. This was confirmed by its relation to balchanolide.

The mutual positions of the γ-lactone and the esterified hydroxyl group in arctiopicrin were inferred[9] from analogy

with matricin[12]/.....



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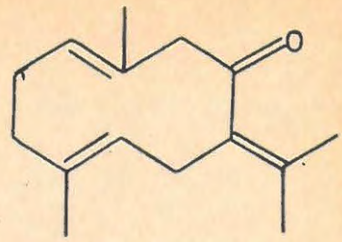

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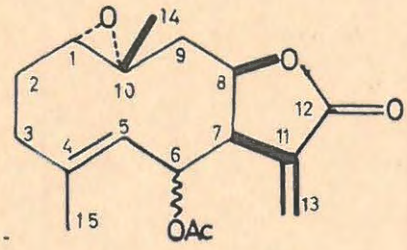

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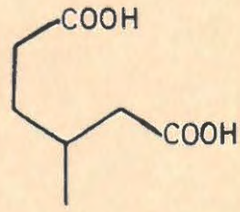

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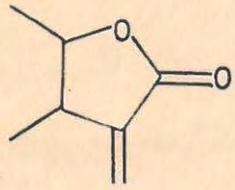

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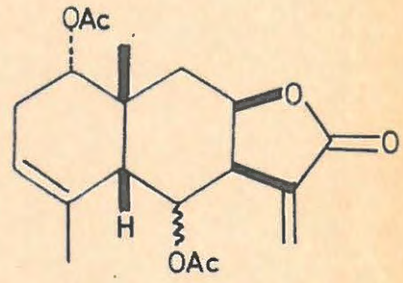

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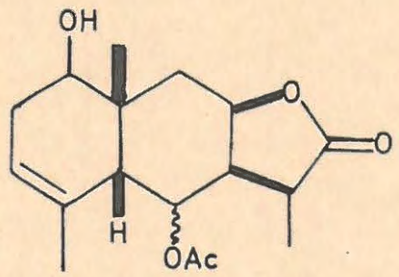

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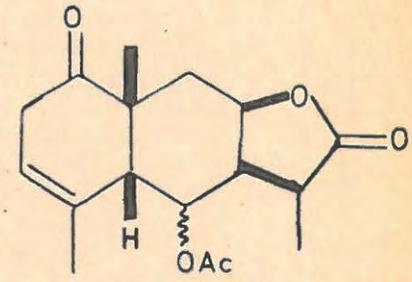

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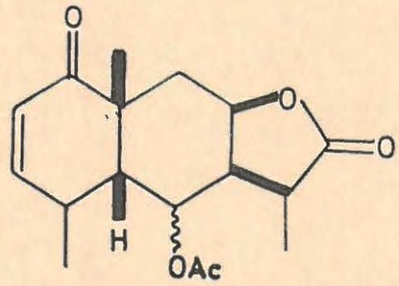

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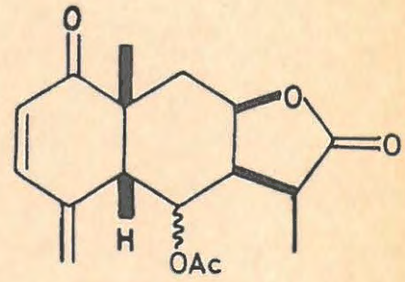


(10)

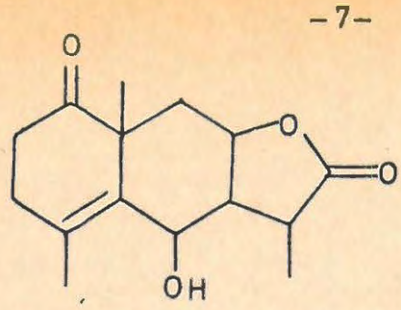
with matricin[12] in which a characteristic shift in the infrared occurs on hydrolysis. Their positions were found to be the same as in artemisin, for hydrogenation in the presence of perchloric acid resulted in 18, identical with the product obtained from the Clemmensen reduction of artemisin. This correlation with artemisin allows the same stereochemical arrangement at C_6, C_7 and C_8 to be assigned. Since santanolide "a" (19) was obtained as a by-product, Clemmensen reduction was assumed not to alter the orientation of the C_{13} methyl group, which was assigned an α-orientation.

Since oxidation of polymeric arctiopicrin with nitric acid afforded (-) methylsuccinic acid (20), the methyl group at C_4 is assigned the β-configuration. An optically inactive hydroxygermacranolide, isomeric with 15 has been isolated from the chromium trioxide oxidation of arctiopicrin. The latter might therefore be represented by a structure where both methyl groups are α. The absolute configuration of arctiopicrin is thus being revised.

2.1.3. Parthenolide (21)[13] from Chrysanthemum parthenium (L) Bernh showed maxima in its infrared spectrum due to the following functional groups:- a γ-lactone (bands at 1768 cm^{-1} (lactonic carbonyl) and 1142 cm^{-1} (lactonic hydroxyl group) and an exocyclic methylenic double bond (band at 1408 cm^{-1}) conjugated with the lactonic carbonyl group.[14]

On mild hydrogenation, parthenolide afforded a dihydroderivative, which lacked the frequency at 1408 cm^{-1}, but still showed that due to the γ-lactone. The end absorption in the ultraviolet spectrum of parthenolide at 225 mμ ($\log \varepsilon = 3.53$) had disappeared. These results, together with the low yield of formaldehyde[10] on ozonolysis, is confirmation of the exocyclic methylenic double bond at C_{11}.

Parthenolide/.....



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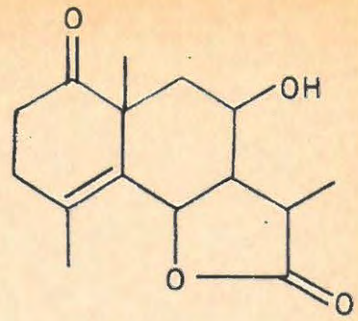

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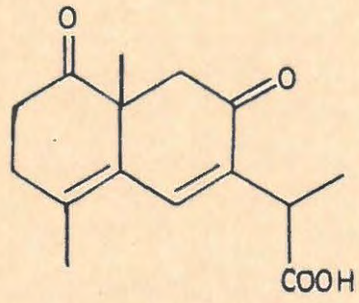

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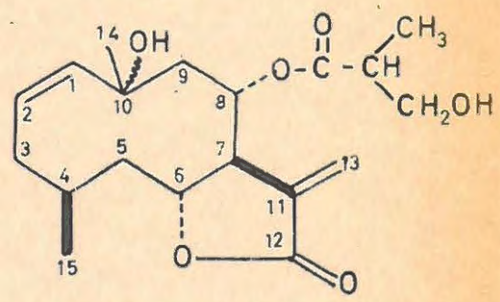

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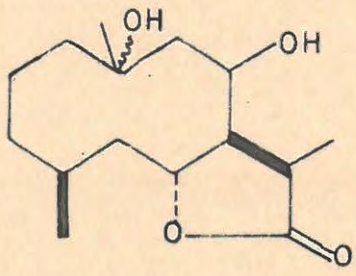

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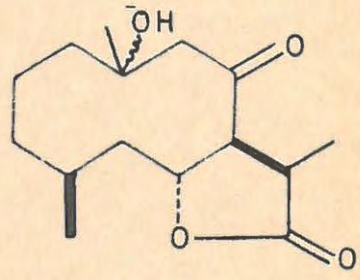

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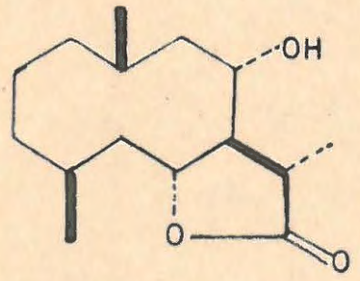

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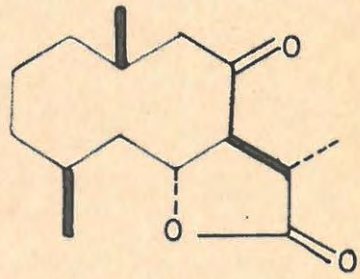

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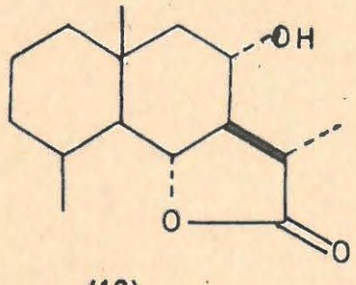

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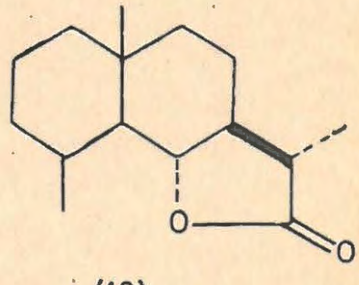


(19)

Parthenolide was converted on hydrogenation over Adam's catalyst to a hexahydro-compound containing a hydroxyl group. The third oxygen atom must thus be present as an epoxide, which splits on hydrogenation to form 22. In an attempt to define the position of the hydroxyl group, 22 was oxidised with chromium trioxide to a ketone, which failed to form a dinitrophenylhydrazone and its unusually high frequency (1717 cm^{-1}) in the infrared spectrum suggested intensive interaction with the lactone group. It must therefore be positioned at C_5 or C_8. Lithium aluminium hydride reduction converted 22 into a triol, which in turn absorbed one mole of periodic acid. The hydroxyl group must thus be adjacent to the lactonic hydroxyl, i.e. at C_5.

Parthenolide failed to cyclise to a santonin-type compound as did arctiopicrin, cnicin and dihydrocostunolide, but it was oxidised to β-methyladipic acid with nitric acid. As the double bond in dihydroparthenolide is disubstituted and one C-O bond of the oxide ring is vicinal to the lactonic hydroxyl, structure 21 is ascribed to parthenolide. Ozonolysis of dihydroparthenolide afforded products which confirmed this structure.

2.1.4. Costunolide, balchanolide, isobalchanolide and hydroxybalchanolide from Artemisia balchanorum H. Krasch[15] and acetylbalchanolide from Achillea Millefolium[16] have also been investigated. Costunolide (23)[15] showed strong infrared bands due to a γ-lactone (1757 cm^{-1}) conjugated with a methylenic double bond (1408 cm^{-1}) as well as of two further double bonds (1663 cm^{-1}). Mild hydrogenation afforded dihydro-costunolide (24), in which the exocyclic methylenic double bond had been saturated.[13] Vigorous hydrogenation converted costunolide to the hexahydro-derivative identical with 25 also obtained from 17 by desulphurisation of the ethylenethioketal. Hydrogenation of costunolide over Adam's catalyst in the presence of

perchloric acid/.....

perchloric acid resulted in a bicyclic compound (26), identical with santanolide "c".

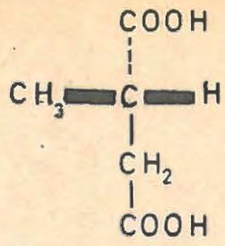
In acetic acid and acetic anhydride, dihydro-costunolide cyclised to a bicyclic, unsaturated sesquiterpene (27), identical with 3-santenolide.[17] Hydrogenation of 27 afforded santanolides "a" and "c".[18] These results corroborated the location of the lactonic function and the double bonds in the ten-membered carbocyclic ring, as in 22. Dihydrocostunolide (24) was converted by ozonolysis and oxidation with nitric acid to the same lactonic dicarboxylic acid (28) obtained from santonin, artabsin and absinthin.[19]

As the absolute configurations of 3-santenolide, santanolides "a" and "c" are known, that for costunolide could be assigned.[20] The validity of 23 has also been shown by synthesis.[21]

2.1.5. Balchanolide (29)[15] exhibited frequencies due to a γ-lactone (1760 cm^{-1}), hydroxyl groups (3490 and 3620 cm^{-1}) and a double bond (1666 cm^{-1}). The acetyl derivative 30 showed frequencies due to the carbonyl in an ester group (1244 and 1738 cm^{-1}) as well as a γ-lactonic carbonyl (1767 cm^{-1}). This derivative was found to be identical with an acetylbalchanolide, isolated from the common yarrow.[16] Furthermore, tetrahydro-acetylbalchanolide (31) is identical with tetrahydro-acetyliso-balchanolide. Saponification of 31 afforded a non-crystalline hydroxylactone, which was oxidised with chromium tioxide to 17, also obtained from arctiopicrin. This relationship defined the size of the carbocyclic ring, the positions of the methyl groups, the γ-lactone and the hydroxyl function.

Permanganate oxidation of balchanolide gave succinic and laevulic acids, while chromium tioxide oxidation led to the formation of a keto-lactone (32). As the ultraviolet

spectrum of/.....



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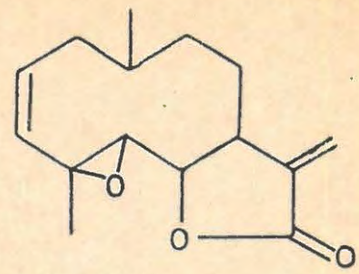

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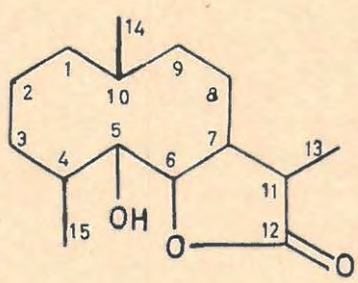

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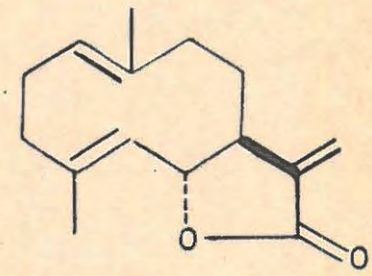

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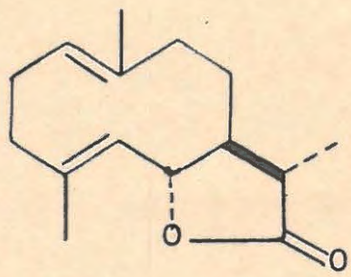

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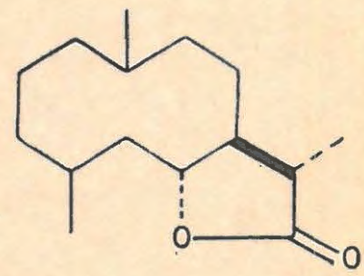

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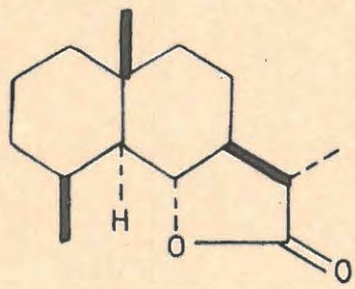

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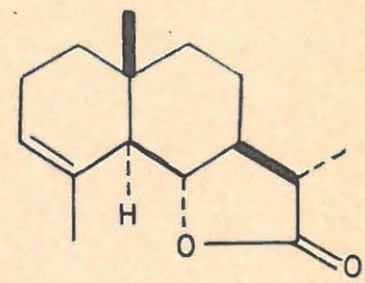

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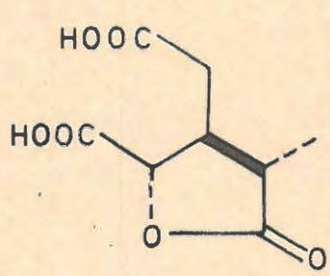

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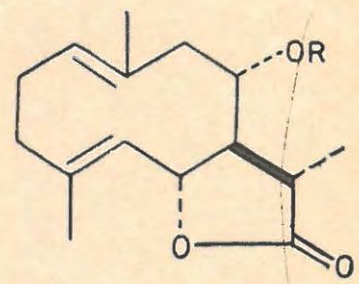


(29) R = H

(30) R = Ac

spectrum of balchanolide lacked conjugated unsaturated ketonic absorption, it has structure 29.

As expected, balchanolide is cyclised in acidic medium (BF_3 in benzene) to a crystalline hydroxysantenolide (33). Hydrogenation of 33 gave 34 identical with 8-hydroxysantanolide, prepared by Clemmensen reduction of artemisin.

2.1.6. Isobalchanolide showed frequencies in the infrared due to the following fuctional groups:- a γ-lactone (1768 cm^{-1}), unsaturation (1640 cm^{-1}) and a hydroxyl group (3600 and 3430 cm^{-1}). It formed a crystalline acetate 30 or 35, which was hydrogenated to tetrahydroacetylbalchanolide (31).

Potassium permanganate oxidation of isobalchanolide afforded succinic and laevulic acids. The formation of laevulic acid shows the mutual positions of the double bonds, and isobalchanolid is thus 36 or 29.

As tetrahydroacetylbalchanolide is identical with tetrahydroacetylisobalchanolide, balchanolide and isobalchanolide differ only in the location of the double bonds or in their steric arrangements. Chromium trioxide oxidation of isobalchanolide did not lead to a uniform product and thus the positions of the double bonds have not been established with certainty.

As balchanolide, isobalchanolide and acetylbalchanolide were correlated via the same tetrahydroacetyl derivative (31), they must possess the same configuration at C_6, C_7, C_8 and C_{11}.

2.1.7. Hydroxybalchanolide[15] is a diol and exhibited maxima in the infrared due to a γ-lactone (1761 cm^{-1}), hydroxyl groups (3610 and 3420 cm^{-1}) and a double bond (1669 cm^{-1}). It was hydrogenated to a tetrahydro-derivative, which was oxidised with chromium tioxide to a hydroxyketo-lactone. Thus one hydroxyl group is secondary and the other is tertiary. The infrared frequencies at 3500 and 3620 cm^{-1} in the spectrum of

the above/.....

the above hydroxyketo-lactone are indicative of hydrogen bonding of the hydroxyl group.

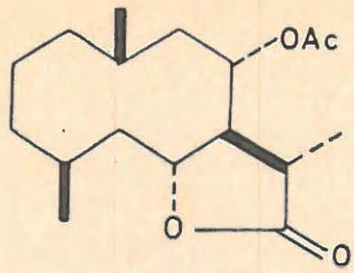
Oxidation of hydroxybalchanolide with potassium permanganate gave succinic and laevulic acids. Hence the double bonds are probably arranged as in isobalchanolide. As hydroxybalchanolide is stable towards periodate oxidation, the tertiary hydroxyl group must be located at C_{11} rather than C_7. Structures (37) or (38) have been suggested for hydroxybalchanolide.

2.1.8. Cnicin (39)[11, 22, 23] is a triol from Cnicus benedictus (L) and showed maxima in the infrared due to the following functional groups:- a γ-lactone (1766 cm^{-1}), a conjugated ester (1713 cm^{-1}), double bonds (1694 and 1632 cm^{-1}) and hydroxyl groups (3450 cm^{-1}). The ultraviolet spectrum showed end absorption at 220 mμ (log ξ = 4.34).

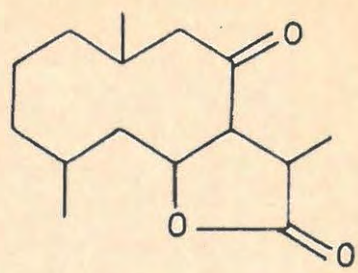
Quantitative ozonolysis of cnicin afforded 0.46 mol. formaldehyde, in agreement with a methylenic double bond, α, β to the lactonic carbonyl group.[10] As lithium aluminium hydride reduction followed by selenium dehydrogenation afforded chamazulene and artemazulene, cnicin was first thought to be a guaianolide.

Cnicin was hydrogenated over Adam's catalyst to a mixture of hydrogenated and hydrogenolysed products. The normal hydrogenation product, hexahydrocnicin (40) was separated and its infrared spectrum showed maxima at 1781 cm^{-1} (γ-lactone), 1728 cm^{-1} (unconjugated ester) and 3465 cm^{-1} (hydroxyl groups). The mother liquors from 40 were saponified, acidified and steam distilled to afford ethylmethylacetic acid. Cnicin is thus formulated as an ester of α, β (bis-hydroxymethyl) acrylic acid, although the latter acid was too unstable to be isolated. The residue from the steam distillation gave the expected product 41 "a".

Saponification/.....



(31)



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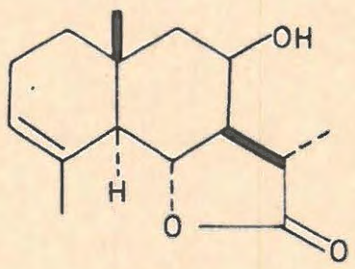

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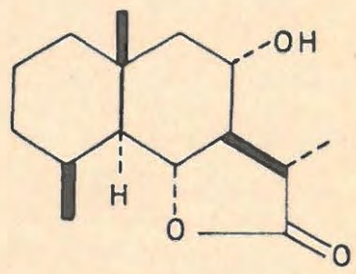

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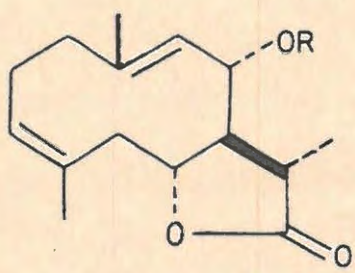
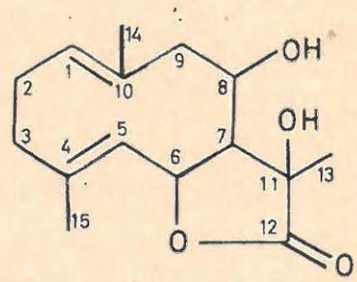


(35) R = Ac

(36) R = H



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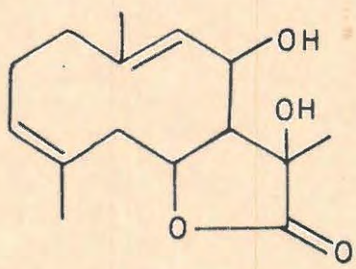

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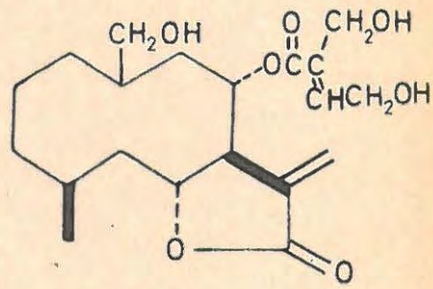

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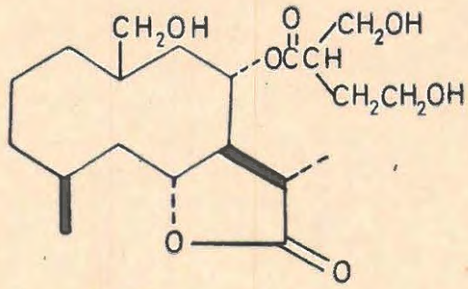

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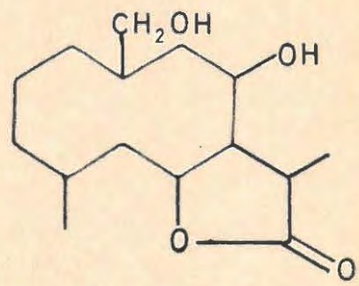


(41a,b,c)

Saponification of the non crystalline hydrogenation products afforded two further hydroxylactones (41 "b") and (41 "c"). Chromium trioxide oxidation of these gave two keto-lactone acids (42 "a") and (42 "b"). Thus these hydroxy-lactones posses both a primary and a secondary hydroxyl group. The position of the keto-group absorption in the infrared spectrum (band at 1720 cm^{-1}) suggests that it is present in a middle-sized carbocyclic ring.

Oxidation of 41 "a" gave a neutral compound 17, identical with that obtained from arctiopicrin.[19] Thus the size of the carbocyclic ring, the position of the methyl groups, the γ-lactone and the secondary hydroxyl are defined.

Since hydrogenolysis of cnicin occurs with ease, the primary hydroxyl group is probably in an allylic position. This suggestion is supported by the fact that the acid obtained on oxidation of this hydroxyl group is α, β-unsaturated. The single endocyclic double bond is thus present at C_9 - C_{10}.

Cnicin has been converted into tetrahydroacetylbalchanolide of known stereochemical configuration, while the keto-lactone (17), which has been related to artemisin, allows the configuration as in 39 to be assigned. Salonitolide, the alcohol which in cnicin is esterified with α, β-bishydroxymethyl acrylic acid, has been isolated from centaurea salonitana Vis.[24]

2.1.9. Scabiolide (43) [11,22,25] from Centaurea scabiosa (L) Presl showed bands in the infrared due to a γ-lactone (1767 cm^{-1}) conjugated with a methylenic double bond (1435 cm^{-1}),[10,22] superimposed ester carbonyl groups (intense band at 1740 cm^{-1}), an acetoxy-group (1260 cm^{-1}), unsaturation (1663 cm^{-1}) and hydroxyl groups forming a hydrogen bridge (3530 cm^{-1}). Ozonolysis of the methylenic double bond afforded 0.34 mol. formaldehyde, the low yield being observed in analogous cases.[10,22]

Dihydroscabiolide,/.....

Dihydroscabiolide, obtained on mild hydrogenation, absorbed one mole of perphthalic acid, indicating the presence of a second double bond. Saponification confirmed the fact that it is a diester, as two acids, glycollic and acetic acids, were obtained.

On hydrogenation over Adam's catalyst scabiolide absorbed more than two moles of hydrogen. A complicated mixture of hydrogenated and hydrogenolysed products was obtained; only the hydroxyester γ-lactone (44) could be crystallised. The non-crystalline material was saponified, acidified and the neutral products (re-lactonised) separated into stereoisomeric monohydroxylactones and stereoisomeric dihydroxylactones. Chromium trioxide oxidation of the mixture of monohydroxylactones gave (45 "a") identical with 17 obtained from arctiopicrin [9] cnicin [22] and (45"b"). Similar oxidation of the mixture of dihydroxylactones afforded the ketolactonic acid (42) obtained from cnicin. Hence the size of the carbocyclic ring and the positions of the two methyl groups, the γ-lactone, the esterified secondary hydroxyl and the esterified primary hydroxyl groups are defined.

Since hydrogenolysis occurs with ease, the esterified primary hydroxyl group must be allylic. Dihydroscabiolide, which retained the double bond in the carbocyclic ring, was subjected to mild hydrolysis. The resultant dihydroxylactone (46) and a product of hydrogenolysis 47 were subjected to chromium trioxide oxidation. From 46, a crystalline ketolactone (48) was obtained. This was shown by its ultraviolet absorption to lack an α, β-unsaturated ketone, and the increase in R-band intensity (log ξ = 2.48 at 290 mμ) is indicative of a β, γ-unsaturated ketone.[26] The double bond is thus located between C_1 and C_{10}. Hydrogenated scabiolide after chromatography on slightly alkaline alumina afforded an oily polar fraction, which was oxidised with chromium trioxide to an

acetoxy-keto-γ-lactone/.....

acetoxy-keto-γ-lactone(49) Accordingly the secondary hydroxyl group must be esterified with the more readily saponifiable glycollic moiety.

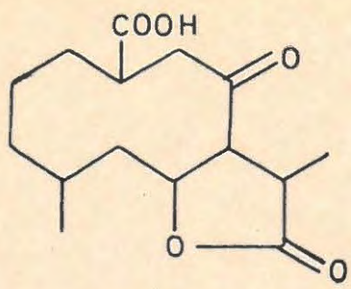
The unsaturated hydroxy-lactone (47) formed a dihydro-derivative, which on acetylation gave tetrahydroacetylbalchanolide (31). As 31 has been related to artemisin, the absolute configuration of scabiolide at C_6, C_7 and C_8 is established.

2.1.10. Eupatoriopicrin (50)[11,27] a diol from Eupatorium canabium, possesses a cis lactone ring. It shows frequencies in the infrared due to a γ-lactone (1764 cm^{-1}) conjugated with a methylenic double bond (1148 and 1419 cm^{-1}), an ester group (1711 cm^{-1}) and a hydroxyl group (3400 and 3620 cm^{-1}). The ultraviolet spectrum showed end absorption at 211 mμ (log ξ = 4.4).

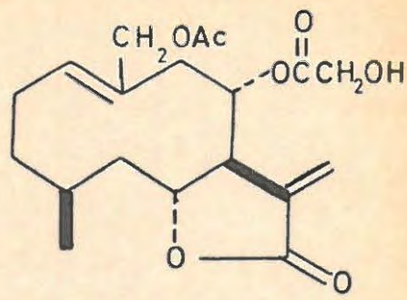
On alkaline hydrolysis, eupatoriopicrin afforded eupatolide, an unsaturated hydroxylactone (51), which was hydrogenated to 52. The hydroxylactone was oxidised with chromium trioxide to a ketogermacranolide (53). The α-isopropyl group, shown by optical rotatory dispersion, was converted to the more stable β-configuration on heating with sodium acetate to give the ketogermacranolide (17), which has been obtained from scabiolide [22,25], arctiopicrin[9, 11] and cnicin.[22] This demonstrated the size of the carbocyclic ring and the positions of the methyl groups, the γ-lactone and the secondary hydroxyl group.

Hydrogenation of eupatoriopicrin was accompanied by hydrogenolysis to 54, saponification of which gave tetrahydroeupatolide and methylethylacetic acid. This fact, together with the isolation of a C_5 unstable hydroxy-acid from eupatoriopicrin shows that the latter is esterified with α,β-(bishydroxymethyl) acrylic acid.

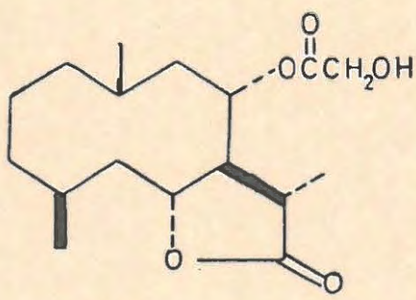
Ozonolysis of eupatoriopicrin and eupatolide, resulting in low yields of formaldehyde[10,22,25] and the infrared spectra



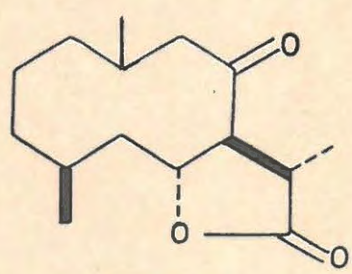
(42a, b)



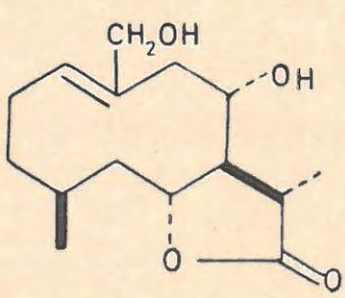
(43)



(44)



(45a,b)



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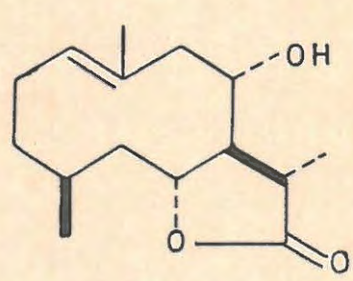

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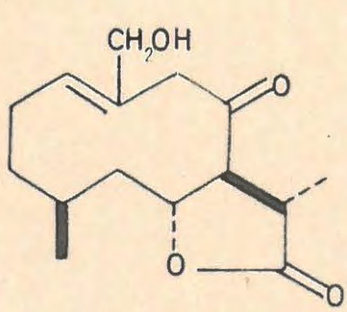

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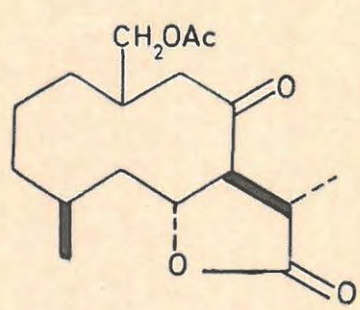

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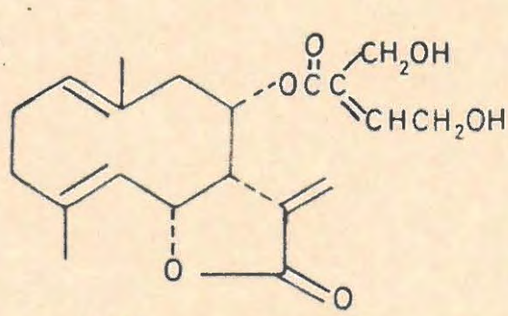

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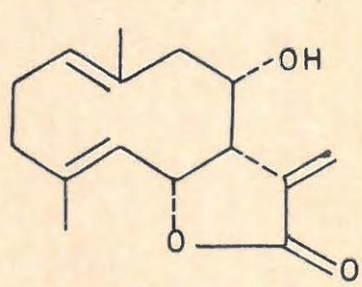


(51)

of these compounds (eupatoriopicrin and eupatolide) (bands at 1148 and 1419 cm^{-1})[28] indicated that the methylenic double bond is conjugated with the carbonyl of the γ-lactone.

Eupatolide afforded a methyl ether (55), which was shown by N.M.R. studies to possess two double bonds, each substituted with a methyl group. Chromium tioxide oxidation of eupatolide converted the C_8 hydroxyl group to a ketone, which showed the infrared absorption frequency (1708 cm^{-1}) of an unconjugated keto-group. The increase in the R-band absorption in the ultraviolet spectrum is due to a β, γ-unsaturated keto-group.

The conversion of eupatoriopicrin to 17 and the optical rotatory dispersion curve defines the absolute configuration as in (50).

2.1.11. Nobilin [29] from Anthemis nobilis (L) showed infrared absorption due to a γ-lactone (1760 cm^{-1}), a methylenic double bond conjugated with the lactonic carbonyl (1405 and 1137 cm^{-1}), a conjugated ester (1714 cm^{-1}), a hydroxyl group (3500 and 3610 cm^{-1}) and a double bond (1651 and 1662 cm^{-1}).

Saponification and N.M.R. studies showed that nobilin is esterified with tiglic acid. The non-volatile product of saponification consisted of an acid and a hydroxy-oxido-lactone, containing one molecule of water more than expected. Their infrared spectra showed that both these compounds possessed an exocyclic methylene group, different from that in natural nobilin. It is thus assumed that the C_{11} double bond disappears when an oxide ring is formed.

Nobilin was oxidised with chromium trioxide to dehydronobilin, indicating the secondary nature of the free hydroxyl group. Hydrogenation of dehydronobilin afforded a mixture, which was converted to deoxydehydro-octahydro-nobilin via its thioketal.[30] This ester-lactone was saponified to a hydroxy-lactone, which was oxidised with chromium trioxide to a keto-lactone (17), identical with that obtained from arcticpicrin.[10]

This proved/.....

This proved the size of the carbon skeleton, the positions of the γ-lactone and methyl groups and that the esterified hydroxyl group is in position 8.

As nobilin is not oxidised to laevulic, succinic [15,22] or any other dicarboxylic acid containing four or more carbon atoms, nor cyclised to a santonin-type sesquiterpene, [10,15] the positions of the free hydroxyl group and of the double bonds are uncertain. Partial structure 56 can be ascribed to nobilin.

2.1.12. Gafrinin [31] (57) from Geigeria africana Gries. contains a readily reducible trisubstituted double bond (infrared maximum at 813 cm^{-1}). Since dihydrogafrinin retains its end absorption in the ultraviolet (λ max 219 mμ, log ξ = 3.84), the second double bond is in conjugation with the carbonyl group of the γ-lactone and must be at C_7 - C_{11}. This is supported by its resistance to hydrogenation.

Oxidation of dihydrogafrinin with chromium trioxide gave deacetyldehydrodihydrogafrinin containing a ketone group and a hydroxyl group, stable to oxidation. As gafrinin is readily acetylated, the hydroxyl group is not tertiary and must be the precursor of the ketone group in deacetyldehydrodihydrogafrinin, while the hydroxyl group resistant to oxidation must be formed by the hydrolysis of the acetoxy-group present in gafrinin. Since deacetyldehydrodihydrogafrinin reduced one mol. of periodate, the ketone and hydroxyl groups are vicinal.

Sublimation from alumina afforded anhydrogafrinin (58), whose ultraviolet absorption (λ max 226 mμ, log ξ = 4.3) showed that both an α, β-unsaturated lactone and a conjugated diene must be present. Treatment of gafrinin with sodium methoxide in dry methanol gave methyl deacetylgafrinate, which lacked ultraviolet absorption due to the α, β-unsaturated ester, methyl deacetylgafrinate reduced two mols. of periodate and

possesses two/.....

possesses two hydroxyl groups, one at C_3 and the other either at C_6 or at C_8. Methyldeacetylgafrinate lost only the C_3 hydroxyl group on dehydration and the position of the second hydroxyl group is thus uncertain chemically. However, from the examination of models and the preparation of an isopropylidene derivative, the hydroxyl group must be located at C_6. Gafrinin thus has structure (57).

2.2. The Santanolides.

The santanolides are characterised by a naphthalenic nucleus, a γ-lactone at C_6 - C_7, two methyl groups, one at C_4 and the other at C_{10}, and a keto-group at C_3. All these groups, excepting the C_3 ketone are in the same positions as in the germacranolides and are obtained from the latter on cyclisation.[6,10,15,22]

2.2.1. Santonin (59) is obtained from various species of Artemisia and its chemistry has been ably summarised.[32,33,34,35]

X-Ray crystallography,[36] as well as a detailed study of isophoto-α-santonic-lactone [37,38] (60) showed that santonin possesses an α-orientated methyl group at C_{11},[39,40] opposite to that accepted until recently.[41,42] The absolute configuration of this methyl group has been confirmed by degradative work[39] and by total synthesis of santonin.[43]

2.2.2. (-)-β-Santonin [44] occurs together with (-)-α-santonin in many of the Artemisia species and is a stereoisomer of it.

Barton's suggestion [45] that (-)-α- and (-)-β-santonin differ only at C_{11} has been demonstrated.[46] The recent synthesis [43] of (-)-α-santonin therefore confirms the β-configuration of the C_{13} methyl group in (-)-β-santonin.

2.2.3. Artemisin (61) (8-hydroxy-santonin) from Artemisia maritima was shown to be an unsaturated hydroxy-keto-lactone,

closely related/.....

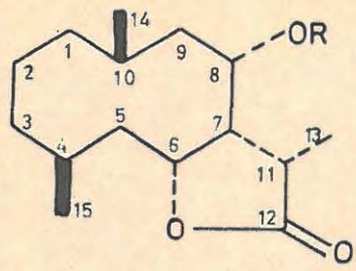
closely related to santonin, and was converted, as expected, by selenium dehydrogenation to 1-methyl-7-ethylnaphthalene. On treatment with dilute acids, artemisin formed a phenolic compound, desmotropo-artemisin, analogous to desmotropo-santonin.

The tertiary hydroxyl group was placed at C_7, because dehydration in formic acid afforded artemisene, for which structure (62) was proposed. Barton discussed the stereochemistry of artemisin in terms of molecular rotations and concluded that the configurations at C_6, C_7, C_{10} and C_{11} are the same as those in (-)-α-santonin. He therefore proposed structure (63).

The Japanese chemist, Sumi, synthesised two racemic isomers 64a, b, both of which rearranged to their desmotropo-compounds (65a, b) by the action of 55% sulphuric acid. Although the trans-isomers do exist, they are converted to the cis-isomers under the rearrangement conditions and only the two (65a, b) were therefore considered. If artemisin possessed the arrangement in structure 63, one of the phenolic compounds 65a, b must be the racemate of desmotropo-artemisin. Owing to the low solubilities of these phenolic products, the diacetates (66a, b) were compared; the diacetate of desmotropo-artemisin was found to be distincly different from either 66a or b.

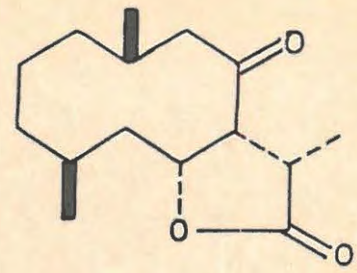
The tertiary nature of the free hydroxyl group was previously inferred from its stability to acetylation but Sumi[47] showed it to be easily acetylated in acetic anhydride and sodium acetate. Furthermore, it formed a cathylate, a tosylate and a formate, showing that this hydroxyl group cannot be tertiary, for tertiary hydroxyl groups do not react with tosyl chloride,[48,49] or ethylchlorocarbonate.[50] Chromium trioxide oxidation converted artemisin into a diketone (67), the infrared (band at 1727 cm^{-1}) and the ultraviolet (no band at 240 mμ) spectra of which showed that the newly formed carbonyl group

is unconjugated/.....



(52) R = H

(54) R = $COC(CH_3)-CH_2CH_3$



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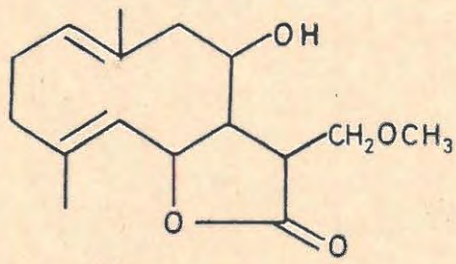

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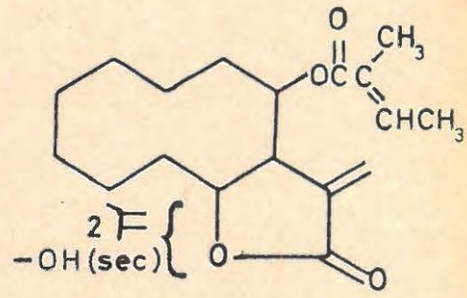

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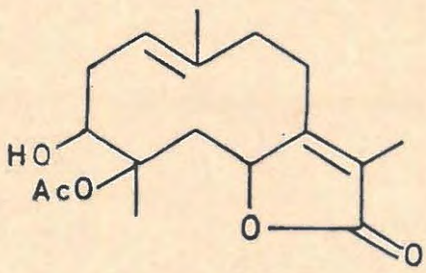

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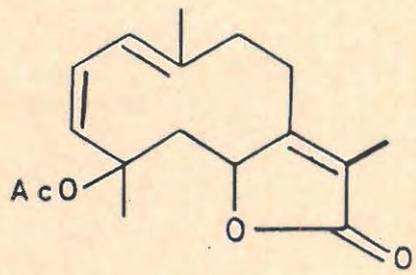

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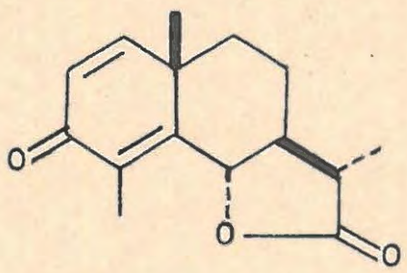

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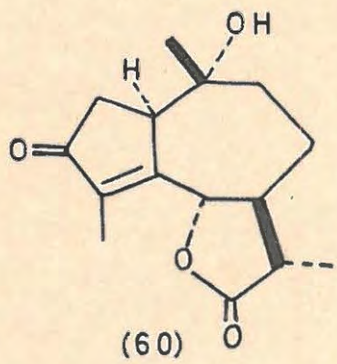

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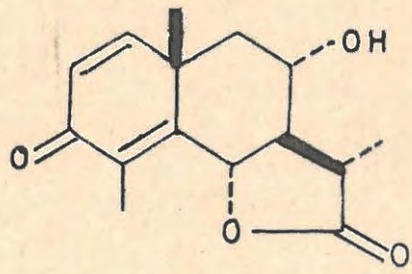

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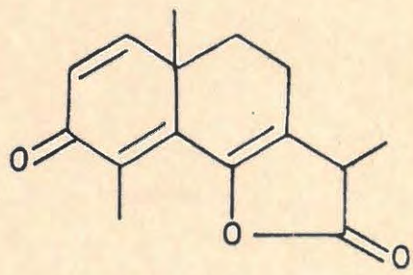


(62)

is unconjugated and therefore not at C_6. Decinormal sodium hydroxide converted the diketo-lactone (67) to the diketo-acid (68) in which the carboxyl group is β- with respect to the keto-group formed on oxidation of artemisin. Furthermore, the presence of an absorption band at 317 mμ shows that the newly formed double bond is conjugated with the carbonyl group and with the cross-conjugated dienone system. These facts suggested the secondary hydroxyl group is attached at C_8 and the lactonic hydroxyl group at C_6.

Treatment of α-tetrahydroartemisin with chromium trioxide in pyridine gave a diketone (69), which was converted into the unsaturated diketo-acid (70) with dilute alkali. These results offer conclusive proof that the free hydroxyl group is secondary and attached at C_8. Structure (61) shows the absolute stereochemistry of artemisin.[47]

2.2.4. ψ - Santonin [51,52,53,54] from the flower heads of Artemisia maritima, is closely related to santonin. The presence in ψ-santonin of the same ring system as that in (-)-α-santonin as well as of an unsaturated γ-lactone, containing carbonyl and hydroxyl groups, was readily demonstrated.

ψ-santonin is insoluble in cold alkali, but it dissolves on warming, being reprecipitated on acidification. Catalytic hydrogenation gave a dihydroderivative, which was converted by Clemmensen reduction and selenium dehydrogenation to 1-methyl-7-ethylnaphthalene. The presence of a carbonyl group was shown by the preparation of an oxime, which formed a quinoline derivative with o-aminobenzaldehyde, indicating that a methylene group is α to the ketone. In 55% sulphuric acid ψ-santonin gave a phenolic lactone d-β-desmotropo-ψ-santonin, which on dehydrogenation afforded 2,4-dimethyl-7-ethylnaphth-1-ol (71), confirming the presence of the carbonyl group at C_1 in ψ-santonin. An isomer, d-α-isodesmotropo-ψ-santonin was also obtained. On heating with potassium carbonate in xylene,

d-β-desmotropo-/.....

d-β-desmotropo-ψ-santonin was partly isomerised to d-α-desmotropo-ψ-santonin, while d-α-isodesmotropo-ψ-santonin was partly isomerised to d-β-isodesmotropo-ψ-santonin. These reactions in the ψ-santonin series paralled the reactions of the structurally analogous desmotropo-α-santonin in the α-santonin series.

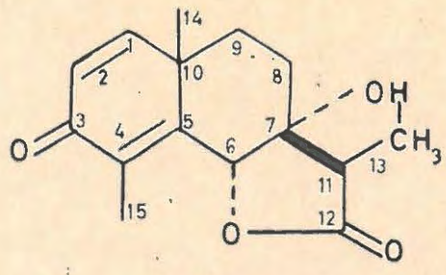
Mild treatment of ψ-santonin with acid afforded ψ-santonic acid, which was converted to the tetrahydroderivative on mild hydrogenation, and a hexahydroderivative under more vigorous conditions. With bromine in sodium carbonate solution, dihydro-ψ-santonin was converted to the mono-bromo-lactone, which regenerated dihydro-ψ-santonin on reduction with zinc in alcoholic solution. On the grounds of the resistance of the free hydroxyl group to acetylation, Cocker and co-workers[51,52,53] suggested that it is tertiary and probably at C_5. They proposed that the ethylenic linkage is α, β or β, γ to the lactonic carbonyl group.

Dauben and Hance have since shown that the hydroxyl group is attached at C_8 [55] and the ethylenic linkage is positioned between C_4 and C_5.[56] Reinvestigations into the reactivity of the free hydroxyl group[55] showed that ψ-santonin froms a liquid acetate which regenerated ψ-santonin on hydrolysis. ψ-santonin formed a cathylate and a tosylate,[48,49] and thus the free hydroxyl group cannot be tertiary. Chromium trioxide oxidation afforded a diketone (72) with a wide melting point. Infrared and ultraviolet spectral studies showed that both carbonyl functions are contained in a six-membered ring. The hydroxyl group in ψ-santonin is thus secondary.

The reaction of 1-keto-8-hydroxyantenic acid (73), a hydrogenolysis product of ψ-santonin, also suggested that the free hydroxyl group is secondary. On boiling with 98% formic acid 73 was stable to dehydration and a formate was formed.

A study of the lactones in the ψ-santonin series indicated

that both/.....



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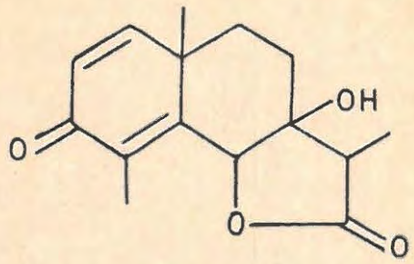
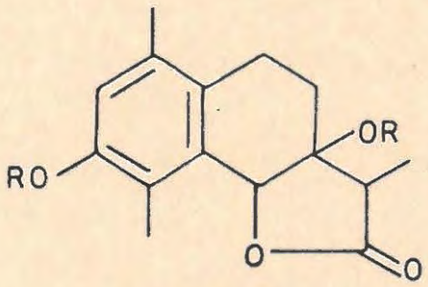
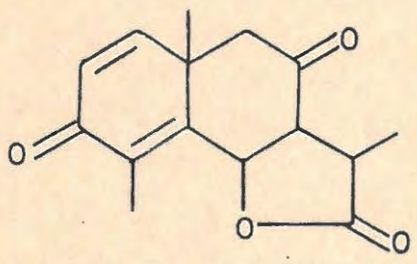


(64a,b)



(65a,b) R = H
(66a,b) R = Ac



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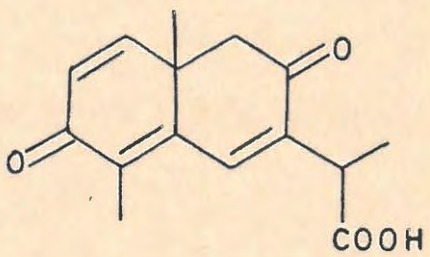

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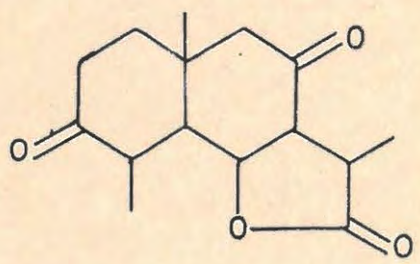

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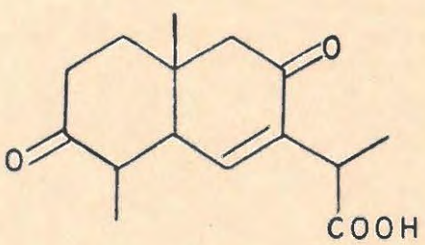

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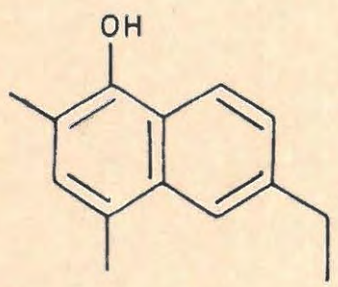

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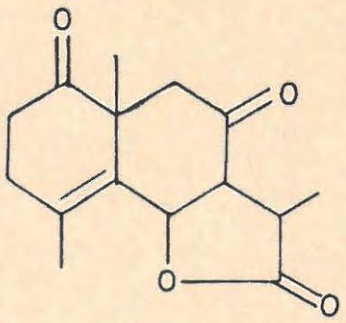

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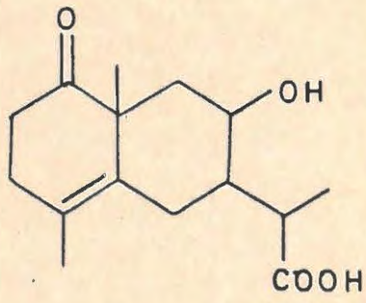


(73)

that both the free and lactonic hydroxyl groups must be in the γ - position relative to the α-propionic side chain. Hence partial structure 74 must be present in ψ-santonin. As the olefinic centre is allylic,[56,57] partial structure 75 must be present. Structure (76) was therefore proposed for ψ-santonin.

ψ-Santonin has been related to tetrahydroalantolactone[58,59] and its absolute configuration is shown in structure (76).

2.2.5. Tauremisin (77) from Artemisia taurica Willd.[60] and vulgarin from Artemisia vulgaris (L)[61] appear, by comparison of their various derivative, to be alike. A study of tauremisin follows:-

Tauremisin is an α, β-unsaturated ketone possessing a γ-lactone and an hydroxyl group (infrared bands at 1685, 1790 and 3580 cm^{-1}; ultraviolet absorption λ_{max} 216 $m\mu$, log ξ = 3.81). The hydroxyl group is resistant to acetylation and undergoes dehydration to the anhydroderivative (78), which was shown by ultraviolet spectrum (λ max 269 $m\mu$, log ξ = 4.10) to be a conjugated dienone.

Tauremisin was hydrogenated to the saturated dihydroderivative (79), possessing a carbonyl group in a six-membered ring (infrared band at 1710 cm^{-1}). Vigorous reduction over Adam's catalyst gave a dihydro-lactone (80), which was dehydrogenated to 1-methyl-7-ethylnaphthalene. These facts are explained by the presence of either of the systems 81 or 82 in tauremisin. Since it is converted in acid medium to a dienone, the hydroxyl group must be in the vicinity of the unsaturated keto-group. As tauremisin is stable to alkali, the hydroxyl group must be α to either the double bond or the keto-group. The tertiary character of the hydroxyl function was confirmed by attempted oxidation of dihydrotauremisin with chromium trioxide, when only starting material was recovered. Partial structure 82 is at variance with the stability of tetrahydrotauremisin towards lead tetra acetate. Also, partial structure 81 is in

accordance with/.....

accordance with the production of a non-conjugated ketone (83) on treatment of tauremisin with zinc in acetic acid. Treatment of 83 with osmium tetroxide gave a dihydroxy-lactone (84), which was dehydrated to tauremisin (77).

On ozonolysis anhydrotauremisin (78) gave formaldehyde and a lactone-dicarboxylic acid (85). Hydrogenation of 83 gave a dihydroderivative, which was converted to the deoxyderivative by desulphuration of the ethylene thioketal. This deoxy-compound was identical with santanolide "c" (26).[18]

The correlation of tauremisin with santanolide "c" proves the location of the lactonic group, the trans-configuration of the six-membered rings and the absolute configuration at C_5, C_6, C_7, C_{10} and C_{11}. The absolute configuration at C_4 follows from the osmium tetroxide oxidation of 83 to 84, which gives tauremisin on dehydration.

2.2.6. Balchanin (86) [62] occurs together with costunolide, balchanolide and hydroxybalchanolide in artemisia balchanorum.[15]

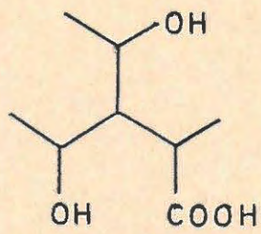
The infrared spectrum exhibited absorption bands at 1140 and 1418 cm^{-1} due to an exocyclic vinylidene double bond, conjugated with a carbonyl group in a γ-lactone ring (1767 cm^{-1}); frequencies at 3518 and 3628 cm^{-1} are due to a hydroxyl group.

On mild hydrogenation balchanin was converted to dihydrobalchanin (87), which was oxidised [63] to tetrahydroanhydrotauremisin (88).[60] This conversion proved not only the carbon skeleton and the location of the functional groups, but also the configuration at C_4, C_5, C_6, C_7 and C_{10}. The β-configuration of the hydroxyl group at C_1 was shown by stereo-specific reduction[64] of the keto-lactone (88) with lithium tri (tert-butoxy) alumino-hydride to the equatorial alcohol (87).

2.3. The Alantanolides.

The group is characterised by a naphthalenic nucleus, two methyl groups, one at C_4 and the other at C_{10}, and a γ-lactone

with the/.....



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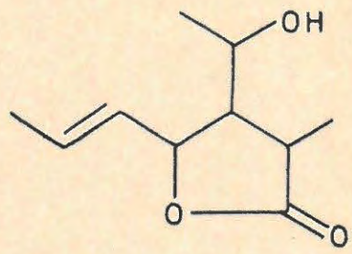

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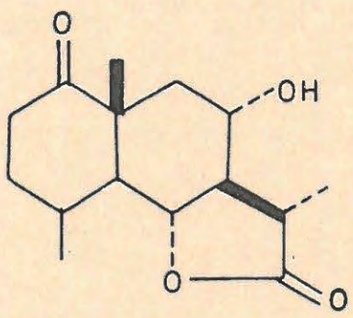

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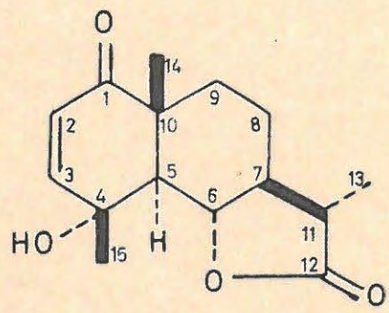

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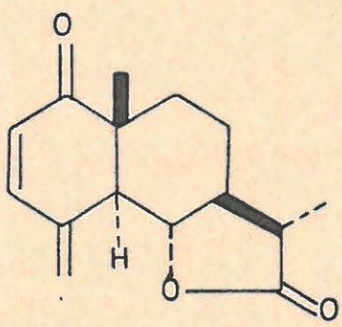

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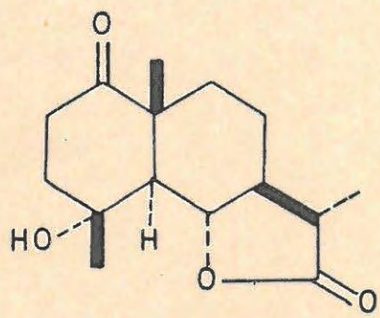

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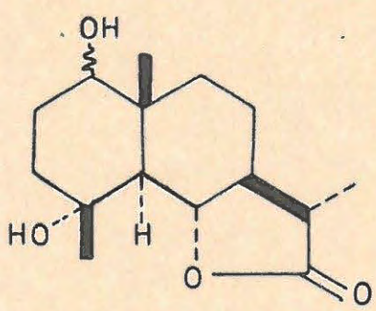

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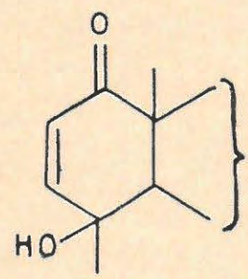

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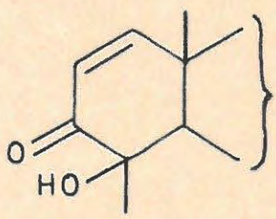

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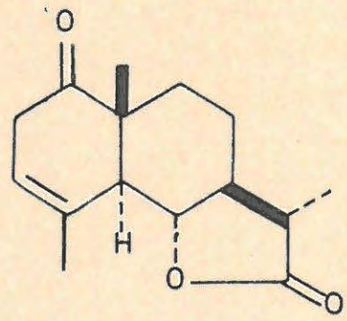


(83)

with the lactonic hydroxyl at C_8. They differ from the santanolides in that the lactonic hydroxyl group is at C_8 rather than at C_6.

2.3.1. Alantolactone[65,66] (89), its isomer isoalantolactone (90) and dihydroisoalantolactone occur in the roots of Inula helenium. They all afforded the same tetrahydroalantolactone (91) on calalytic hydrogenation and must therefore have identical carbon skeletons.

Ruzicka suggested in 1931 that alantolactone possessed the structure (92) but attempts to correlate it with santonin were without success.[18,67] Tetrahydroalantolactone was believed to be an isomer of deoxytetrahydrosantonin, but Tsuda and coworkers[65] showed the existence of a number of marked differences between these two compounds.

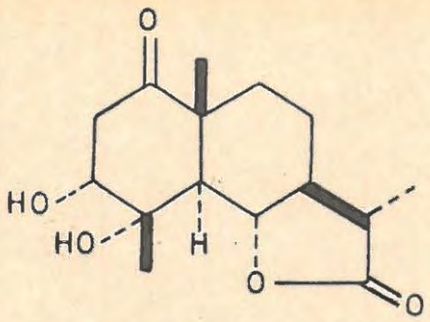
Dehydrogenation of alantolactone with selenium afforded 1-methyl-7-ethylnaphthalene thus fixing the position of the propionic side chain at C_7 as in santonin and artemisin. The position of the double bond was shown by the preparation of derivatives and degredative work.[66]

Tetrahydroalantolactone (91) was converted to the methyl ester of alantonic acid (93), which was oxidised with sodium dichromate in acetic acid to methyl-8-keto tetrahydroalantonate (94) and converted to 8-methyl-tetrahydroalantolactone (95) with methyl magnesium iodide. Dehydrogenation of 95 with selenium gave 2,5-dimethyl-7-ethyl naphthalene (96), showing the lactonic hydroxyl group is positioned at C_8.

Sodium amalgam reduction of isoalantolactone (90) afforded dihydroisoalantolactone, indicating the relationship between the two compounds.

The stereochemistry of tetrahydroalantolactone has been related to that of artemisin and ψ-santonin.[58] The stereochemistry of alantolactone was elucidated by comparing it with tetrahydroalantolactone.[59] The absolute configuration of

alantolactone/.....



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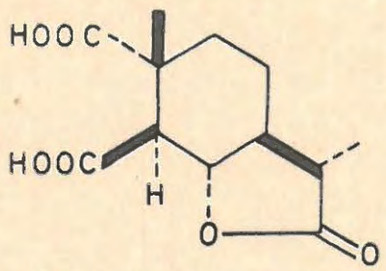

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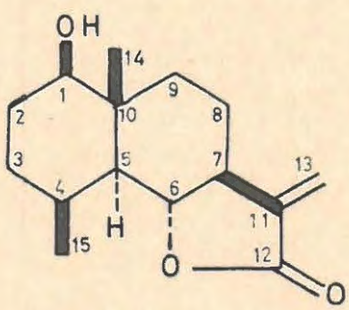

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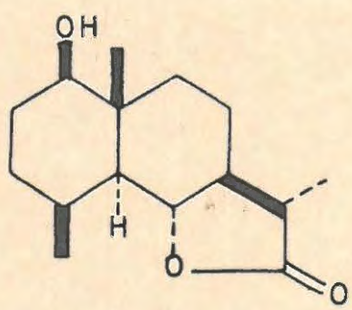

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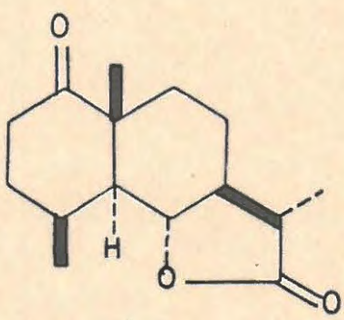

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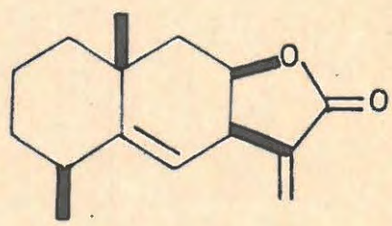

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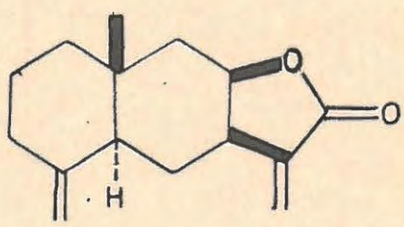

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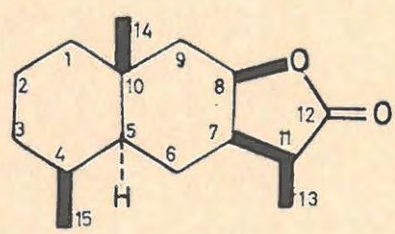

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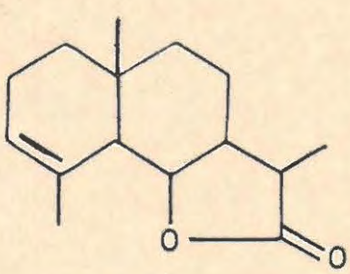

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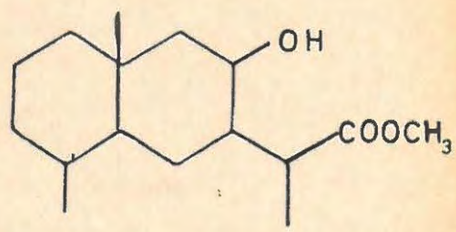


(93)

alantolactone and tetrahydroalantolactone are shown in structures (89) and (91) respectively. Alantolactone has recently been totally synthesised.[68]

2.3.2. Ivalin (97) from Iva microcephala Nutt[69] was shown to possess a hydroxyl group (infrared absorption bands at 3700 and 3500 cm^{-1}), two double bonds (bands at 1600 and 1645 cm^{-1}, and catalytic hydrogenation), and a γ-lactone (infrared bands at 1750 cm^{-1}), conjugated with one of the double bonds (λmax 208 mμ, log ξ = 4.04).

Ozonolysis of ivalin afforded an amount of formaldehyde (94%) indicative of more than one exocyclic double bond. Dihydroivalin (98) was obtained on partial hydrogenation and lacked the double bond conjugated with the carbonyl group of the γ-lactone. Formaldehyde was obtained on ozonolysis of 98, thus confirming the presence of two exocyclic methylenic groups. The hydroxyl group was oxidised to a ketone flanked by at least one methylene group (positive Zimmerman test). Thus the free hydroxyl group is secondary. Dihydroivalin was ozonised to a β-hydroxy-ketone (99) and converted with methanesulphonyl chloride in pyridine to an α, β-unsaturated ketone (100).

The mesylate of tetrahydroivalin was converted in boiling lutidine to its anhydroderivative (101), which was catalytically hydrogenated to tetrahydroalantolactone (91), thus establishing the absolute configuration at C_5, C_7, C_8 and C_{10}. Sodium borohydride reduction[70] of 2-keto tetrahydroivalin and rates of chromium trioxide oxidation,[71] inability to effect dehydration with phosphorusoxychloride in pyridine[72] and N.M.R. studies on ivalin, showed that it is 2-α-hydroxyisoalantolactone (97).

2.3.3. Asperilin[73] (102) from Iva asperifolia Less. and I. texensis Jackson is very similar to ivalin, differing only in the position of the hydroxyl group. Asperilin was hydrogenated to/.....

nated to tetrahydroasperilin, which was oxidised with chromium trioxide to 1-keto-tetrahydroasperilin (103). Dehydrotetrahydroasperilin was different from dehydrotetrahydroivalin (2-keto-tetrahydroalantolactone) and dehydrotetrahydroisotelekin (3-keto-tetrahydroalantolactone)[74] and must thus be, by elimination, 1-keto-tetrahydroalantolactone.

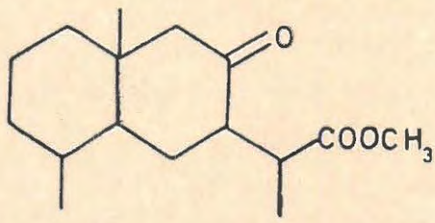
Dehydrotetrahydroasperilin (103) was converted via the thioketal to deoxydehydrotetrahydroasperilin identical with tetrahydroalantolactone (91). This conversion established the configuration at all the asymetric centres excepting that at C_1. Sodium borohydride reduction[70] of 103 showed asperilin to posses a β-orientated hydroxyl group as in (102).

2.3.4. Ivasperin[73] (104) from Iva asperifolia Less. and I. texensis Jackson was shown from its infrared and ultraviolet spectra to be a dihydroxy-γ-lactone similar to asperilin and ivalin. It formed a diacetate and the two hydroxyl groups were shown to be vicinal because ivasperin (and it reduction products) consumed one mol. of periodate.

Dihydroivasperin was converted to the 4-keto-derivative on ozonolysis, which in turn formed a dimesylate. Heating the dimesylate in pyridine converted it into an α, β-unsaturated ketone (105), which was catalytically reduced to the saturated compound obtained on ozonolysis of dihydroasperilinmesylate. This interconversion established the gross structure as well as the absolute configuration at all asymetric centres excepting at C_2. This was shown to be as in 104 for lead tetraacetate oxidation[75] of dehydrotetrahydroasperilin (106) afforded an acetate (107), which on sodium borohydride reduction was converted to tetrahydroivasperin.

2.3.5. Microcephalin[76] (108) from Iva microcephala Nutt. was shown to contain two hydroxyl groups (infrared absorption band at 3400 cm^{-1}) and a double bond (infrared band at 1660 cm^{-1})

conjugated with/.....



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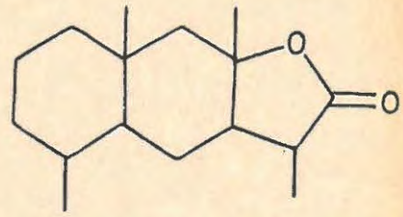

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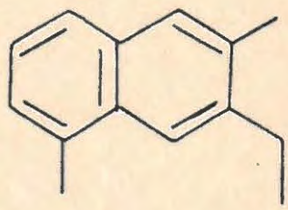

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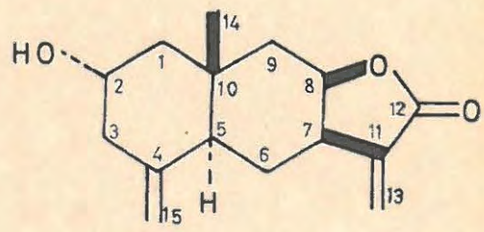

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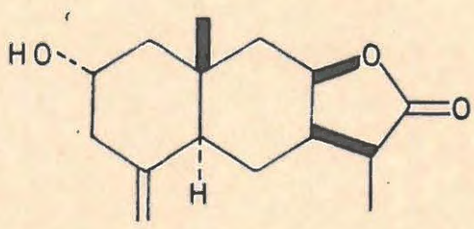

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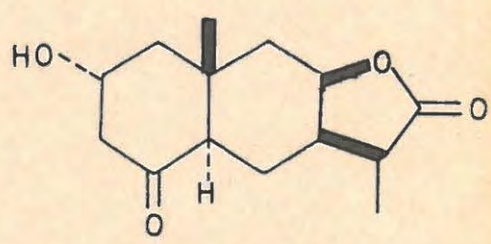

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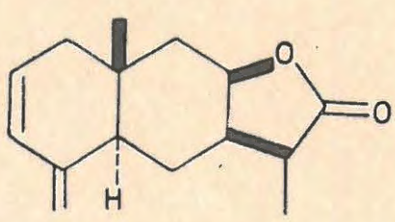

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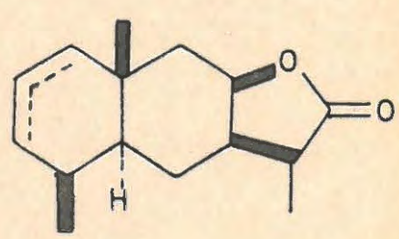

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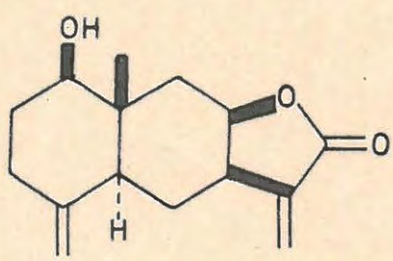

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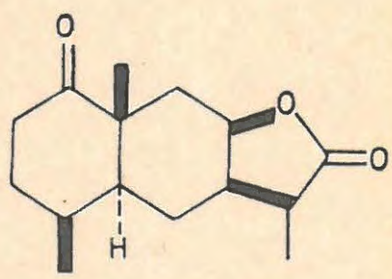


(103)

conjugated with a γ-lactone (infrared band at 1760 cm^{-1} and end absorption at 212 mμ, (log ξ = 3.86) in the ultraviolet). Ozonolysis afforded formaldehyde, indicative of an exocyclic methylenic linkage, and the enolic α-keto-butyrolactone (109). Chromium trioxide oxidation of dihydromicrocephalin afforded a C_1-ketone, which was converted via the ethylenethioketal to tetrahydroalantolactone (91), thereby establishing the basic structure of microcephalin. Since dehydromicrocephalin gave a positive Zimmerman test, the secondary hydroxyl group must be present in ring A. Microcephalin did not react with lead tetra-acetate nor periodic acid, thus limiting the position of this hydroxyl group to C_1 or C_2.

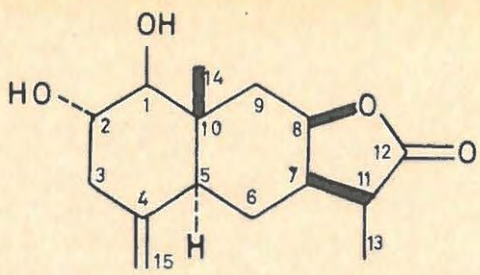
Dihydromicrocephalin formed an unsaturated mesylate (110), possessing an exocyclic methylenic group. The mesylate (110) was different from the mesylate of ivalin (111), but as the C_2 β-epimer was unknown, the latter could not be excluded. Treatment of 110 with lutidine afforded an unconjugated diene, different from the conjugated diene (112) obtained from 111. That no rearrangement had taken place was shown by catalytic hydrogenation of the above dienes to tetrahydroalantolactone (91).

Dehydrodihydromicrocephalin was reduced with sodium borohydride to the dihydroxylactone, epimeric with dihydromicrocephalin, showing that the C_1-hydroxyl group is axial and thus as in (106). The epimer formed a mesylate (113) identical with the mesylate obtained from dihydroasperilin (114). The steriochemistry at C_4 follows from the direction taken by various bimolecular eliminations.[77]

2.3.6. Telekin (115), isotelekin (116) and isoalantolactone (90) were isolated from Telekin speciosa Schreb Baumg.[74]

The infrared spectrum of telekin exhibited a frequency at 1758 cm^{-1} due to a γ-lactone, this band together with frequencies at 1411 and 1143 cm^{-1} shows the presence of a methylene

double bond/.....



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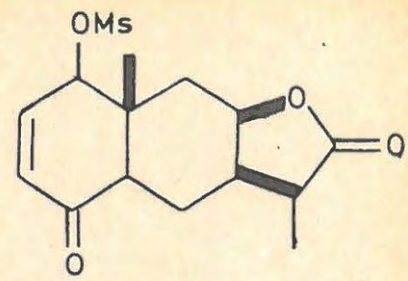

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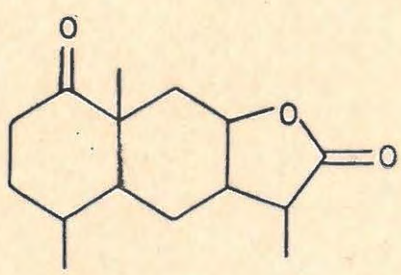

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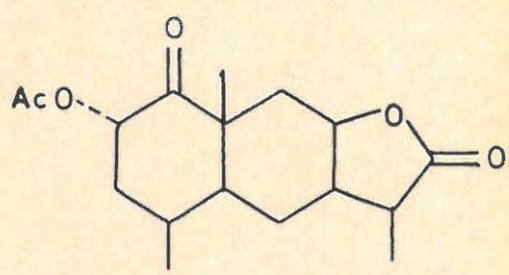

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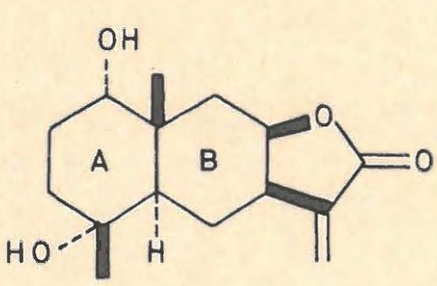

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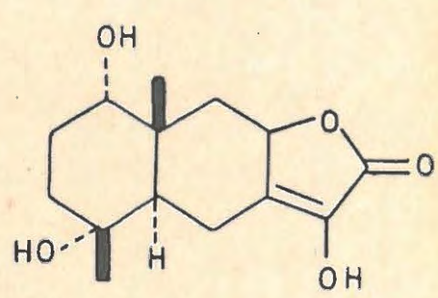

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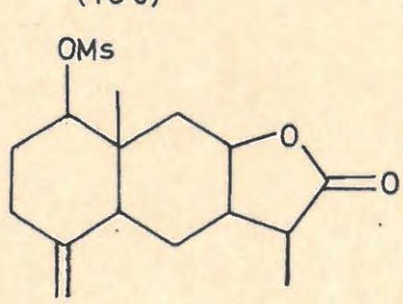

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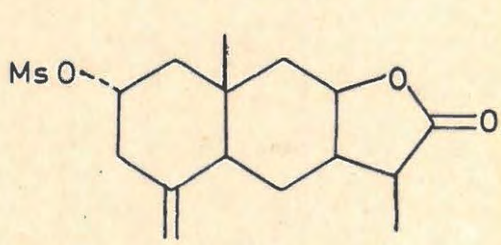

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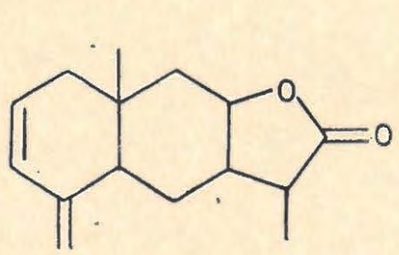

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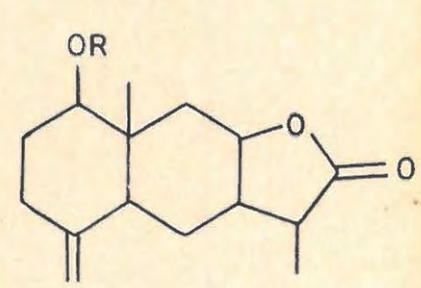


(113) R = Ms
(114) R = H

double bond conjugated with the lactonic carbonyl group.[20] Absorption bands at 1645 and 3090 cm^{-1} are due to a second methylenic double bond, while that at 3601 cm^{-1} indicates the presence of a hydroxyl group.

Telekin was converted to a tetrahydroderivative, while quantitative ozonolysis and colourimetric determinations showed the presence of two methylenic double bonds. Dihydrotelekin (117), in which the double bond conjugated with the γ-lactone has been saturated, shows a characteristic shift in the infrared absorption band of the γ-lactone.[28]

On dehydration in thionyl chloride, telekin formed a mixture of isomers, which was catalytically reduced to tetrahydroalantolactone (91). The hydroxyl group is tertiary, being stable to chromium trioxide oxidation, and its location was demonstrated by osmium tetroxide oxidation of dihydrotelekin (117) to a triol (118), which consumed 1.9 mols. of periodate. The tertiary hydroxyl group must therefore be at C_5. The configurations at C_7, C_8 and C_{10} follows from the conversion of telekin to tetrahydroalantolactone (91).

Comparison of their similar infrared spectra suggests that isotelekin is probably an isomer of telekin, differing only in the position of the hydroxyl groups. Mild hydrogenation converted isotelekin to dihydroisotelekin (119), while vigorous reduction gave tetrahydroisotelekin (120) in low yield. A non-crystalline tetrahydroisomer was also isolated. These isomeric tetrahydroderivatives were oxidised with chromiun trioxide to a ketone (121), which had an unsharp melting point. Treatment of this ketone with potassium carbonate in methanol converted it to 3-oxo-4β(H),-5α(H)-tetrahydroalantolactone (122), which had a sharp melting point. These compounds differed only in their stereochemical arrangements and possessed identical frequencies in the infrared spectrum (an absorption band at 1766 cm^{-1} due to a γ-lactone and a band at 1706 cm^{-1} due to a

ketone)/.....

ketone).

Dehydrotetrahydroisotelekin (121) was converted via the ethylenethioketal to isoalantolactone (90). This establishes the absolute configuration at all asymetric carbon atoms excepting at C_3. The absolute configuration of this hydroxyl group is based on molecular rotations.[78]

2.4. Furano-compounds related to the Alantanolides.

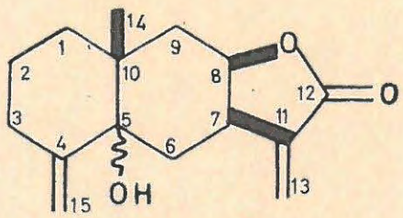
The isolation of these γ-lactones from plants belonging to the Compositae has led to the hypothesis that the most probable precursors of these lactones are furans, which are transformed according to SCHEME I.[79] This hypothesis is based on the proved formation of γ-lactones from substances of the atractylon-type and from the furanoeremophilanes. Linderene is possibly the precursor of the guaianolides.

2.4.1. Atractylon (123)[80] from Atractylodes japonica Koidzumi showed an infrared absorption peak at 1134 cm^{-1} due to an ether. The spectrum lacked bands due carbonyl or hydroxyl functions. The presence of a furan ring system was inferred from the colour reactions with vanillin-hydrochloride, pine-stick, Ehrlichs reagent and Liebermann and Burchard reactions, as well as from the end absorption at 220 mμ in the ultraviolet spectrum.

The third ethylenic linkage was exocyclic, (infrared absorption bands at 3077, 1639 and 866 cm^{-1}) as atractylon afforded formaldehyde on ozonolysis. Dihydroatractylon (124), obtained on hydrogenation over Adam's catalyst in methanol still retained the furan system as indicated by the abovementioned colour reaction and end absorption at 221 mμ in the ultraviolet spectrum. On hydrogenation in ethyl acetate over palladiun, atractylon was converted to octahydrodesoxylinderene (125).

Atractylon underwent antoxidation on standing in air to

give two/.....



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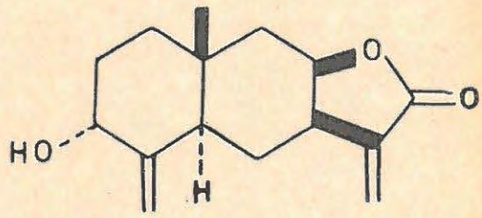

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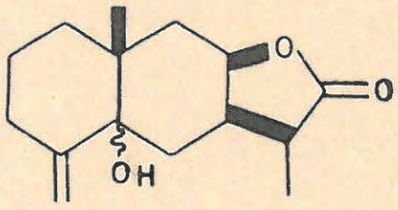

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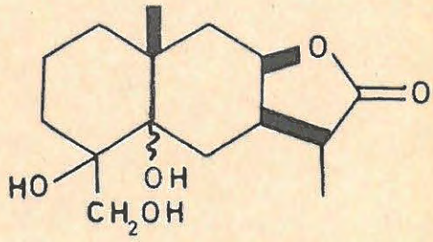

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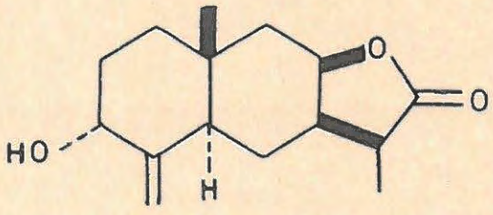

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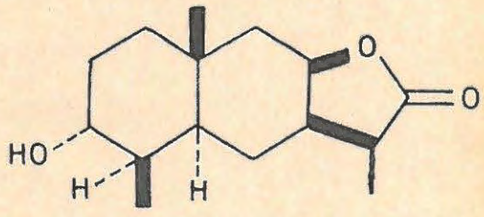

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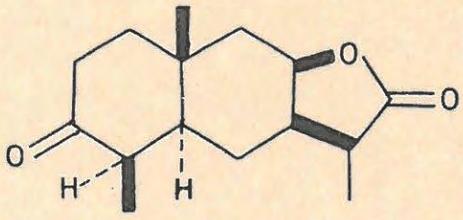

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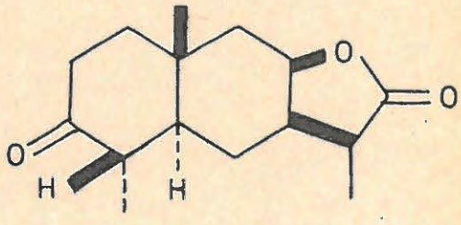

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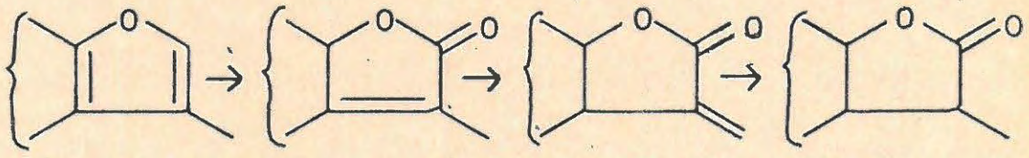


SCHEME 1

give two crystalline products 126 and 127, both of which contained an α, β-butenolide system as inferred from spectral studies (both showed λ max = 220mμ and infrared absorption bands at 1733 and 1672 cm^{-1} in 126 and at 1736 and 1695 cm^{-1} in 127). They also displayed bands at 900 and 877 cm^{-1} (vinylidene) and yielded formaldehyde on ozonolysis. Hydrogenation of 126 and 127 in methyl acetate over palladium afforded two dihydro-derivatives (128) and (129) respectively, both of which retained the properties due to the α, β-butenolide, but lacked the exocyclic methylenic double bond. The remaining oxygen atom in 127 was present as a hemiketal in the α, β-butenolide system (ultraviolet - λmax = 264, infrared absorption band at 3333 cm^{-1}). It exhibited weakly acidic properties and was easily dehydrated to an anhydroderivative (130) (ultraviolet - λmax = 275 mμ), from which 127 was regenerated by dissolution in alkali, followed by acidification. Hydrogenation in acetic acid over Adam's catalyst in the presence of hydrochloric acid converted 127 into tetrahydroalantolactone (91). The dihydroderivative (128) was identical with the butenolide obtained from alantolactone.[81]

The interconversion to tetrahydroalantolactone defines the carbon skeleton and the absolute configuration at C_5 and C_{10}. Atractylon has now been totally synthesised.[82]

2.5 The Guaianolides.

This is by far the largest group and is characterised by a guaiazulene nucleus containing a γ-lactone with the lactonic hydroxyl group at either C_6 or C_8. All lactones isolated from Ambrosia and Pathenium species are biogenetically "abnormal" and possess an errant methyl group at C_5.

As this group includes too many compounds to be reviewed here, only a few examples will be chosen to illustrate the differences between the "normal" and the "abnormal" guaianolides.

2.5.1. The Normal Guaianolides/.....

2.5.1. The Normal Guaianolides.

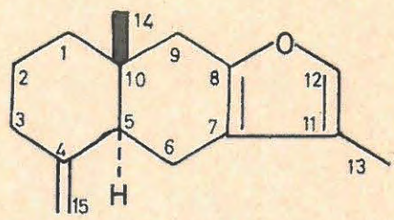
2.5.1.1. Costus lactone, dihydrocostus lactone and dehydrocostus lactone (131)[83] from Saussurea lappa Clarke, all afforded the same fully saturated lactone. They lack other functional groups and are the simplest members of this series.

Dehydrocostus lactone[84] showed infrared absorption bands at 1764, 3125, 1639 and 893 cm^{-1}, the latter two frequencies being due to the methylene groups. Quantitative ozonolysis indicated the presence of three methylene groups, while dehydrogenation converted it into guaiazulene and chamazulene. Dehydrocostus lactone (131) was catalytically reduced to tetrahydromokko lactone (132), while sodium borohydride reduction converted it into mokko lactone (133).

2.5.1.2. Artabsin (134) from Artemisia absinthum L [85] was shown to be a bicyclic hydroxy-γ-lactone (infrared absorption band at 1785 cm^{-1}). On hydrogenation in the presence of palladium, artabsin was converted to a complex mixture of hydrogenated and hydrogenolysed products from which four isomeric hydroxyguaianolides (135 a,b,c and d) were separated. The ease of hydrogenolysis showed a hydroxyl group to be allylic and as no acidic product was obtained, it must be the free hydroxyl group and not the lactonic hydroxyl group which is allylic to one of the conjugated double bonds. Artabsin was oxidised with potassium permanganate to a trihydroxyoxidolactone (136), which in turn was cleaved with periodate to give formaldehyde.

Correlation with matricin (137) placed the free hydroxyl group at C_4, but a study of the ultraviolet spectrum (λmax = 248 mμ, log ξ = 3.65) indicated the presence of two cis-conjugated double bonds in a five-membered ring, rather than a system of trans-conjugated double bonds as in matricin (λmax = 247 mμ, log ξ = 4.32).

For structure/.....



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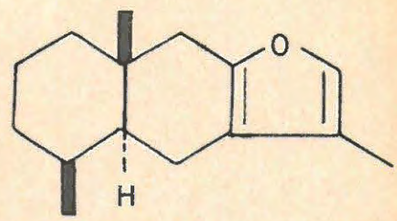

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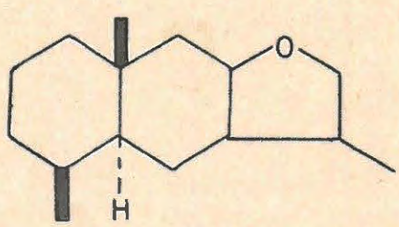

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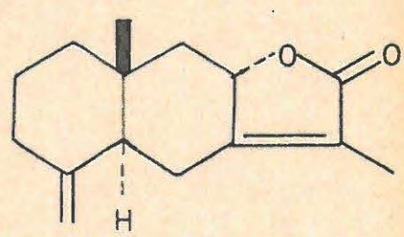

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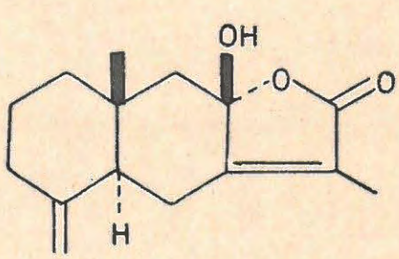

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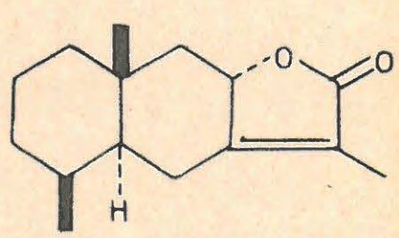

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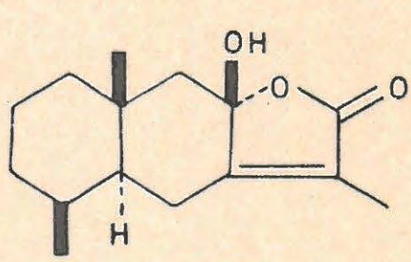

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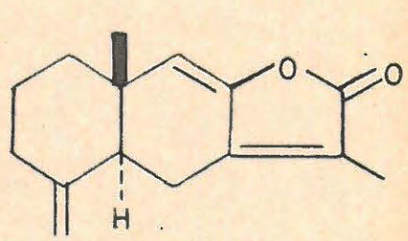

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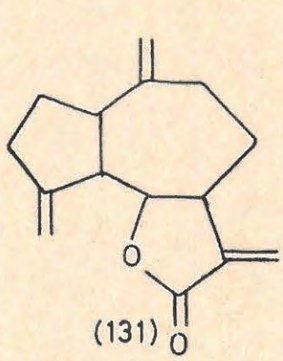

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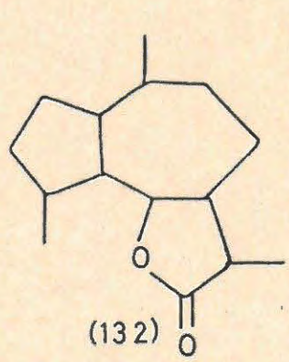


(132)

For structure 134 to be valid, one of the hydroxyguaianolides (135) might be identical with a product obtained by reduction of isophotosantonim lactone acetate (138). The keto-group in dihydro-isophotosantomin lactone acetate was removed by desulphuration of the thioketal. During these reactions, the acetoxy-group at C_{10} was split off. N.M.R. studies showed the product 139 to possess a tetrasubstituted double bond in position C_1(10).

Dehydration of isomers 135"c" and "d" afforded two isomers, that of "d" being identical with 139. This defined the gross structure for artabsin as well as the stereochemistry at C_5, C_6, C_7 and C_{11} as expressed in (134).

2.5.1.3. Arborescin(140) from Artemisia arborescens L[85] and Matricaria globiferra THUMB[86] is closely related to artabsin for hydrogenation of the former afforded the same hydroxyguaianolides (135) as artabsin.

Arborescin was shown to posses a trisubstituted double bond (infrared absorption bands at 823 and 1652 cm^{-1}) and to be an epoxy-lactone (band at 1760 cm^{-1}). The absence of high intensity absorption in the ultraviolet showed the γ-lactone to be fully saturated. The position of the γ-lactone was shown by the isolation of artemazulene on dehydrogenation. Treatment with sulphuric acid converted arborescin to a diol, which could not be oxidised with chromium trioxide nor acetylated. The ether oxygen must thus be attached to two tertiary carbon atoms.

Arborescin was catalytically reduced to a mono-ol, which was dehydrated to a lactone containing a tetra-substituted double bond. This double bond is not part of the γ-lactone and is therefore not attached at C_6, C_7 or C_{11}. The oxide is not attacked by lithium aluminium hydride, while the diol obtained from acid treatment was resistant to periodate. These facts are all explained by structure (140), which is supported

by the isolation/.....

by the isolation of globicin (141), the structure of which has been elucidated,[87] from the same plant.

The structure of arborescin has been elucidated by its synthesis from isophotosantonin lactone acetate (138). Dihydroisophotosantonin lactone acetate was reduced with sodium borohydride to a mixture of two epimeric hydroxy acetoxylactones, which was benzoylated to 142. The benzoate was treated with borontifluoride etherate to give 143, which was oxidised with perbenzoic acid to an epoxylactone, which on mild pyrolysis gave arborescin (140).

These results corroborated the biogenetical relationship between artabsin and arborescin, while the synthesis from isophotosantonin lactone acetate showed the stereochemistry to be as in 140.

2.5.1.4. Globicin (141) from Matracaria globiferra Thumb [87] is isomeric with matricin. A detailed study of its chemistry has shown globicin to be acetoxyarborescin.

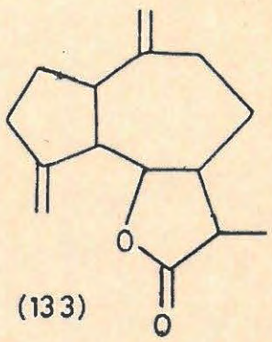
The stereochemistry of globicin follows from a study of the N.M.R. spectrum.

2.5.2. The Abnormal Guaianolides.

2.5.2.1. Tenulin, the bitter principle of several Helenium species,[88] was shown to be either (144) or (145).[89]

Tenulin isomerised in mild alkali to isotenulin, both compounds forming the corresponding dihydroderivatives. Saponification of isotenulin converted it to deacetylisotenulin, which could be reacetylated to isotenulin. Both tenulin and isotenulin were oxidised with potassium permanganate or alkaline hydrogen peroxide to tenulinic acid, which afforded an acetyl derivative.

The ultraviolet spectrum (λmax 226mμ, log ξ = 3.85) and infrared spectrum [bands at 1772 cm^{-1} (γ-lactone), 1700 and 1595 cm^{-1} (cyclopentenone) and 3620 cm^{-1} (hydroxyl group)] indicated that/.....



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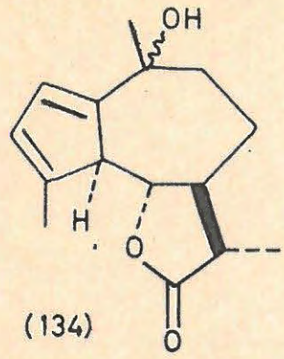

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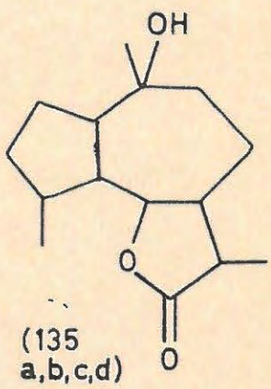
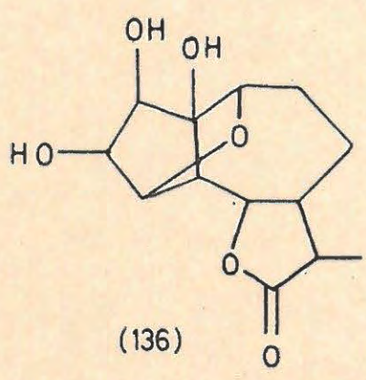


(135 a,b,c,d)



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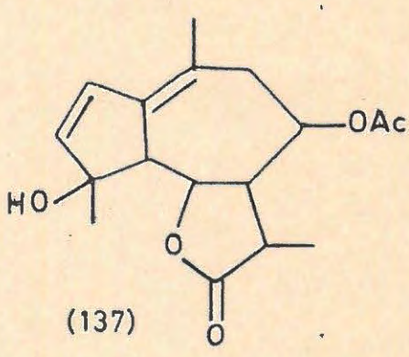

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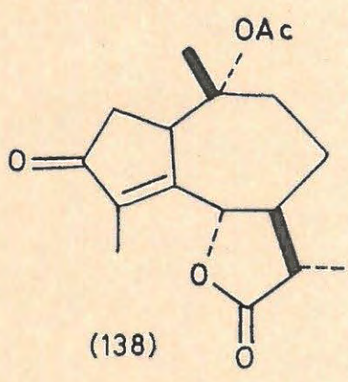
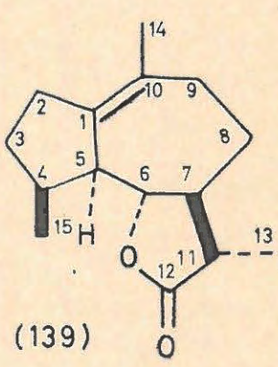


(138)



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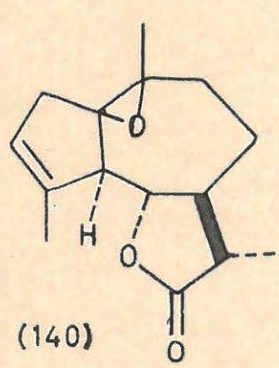
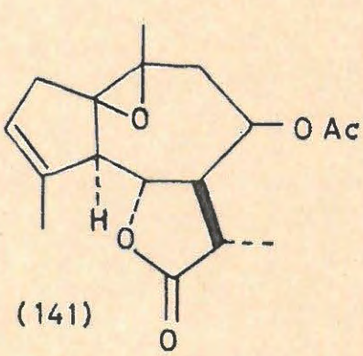
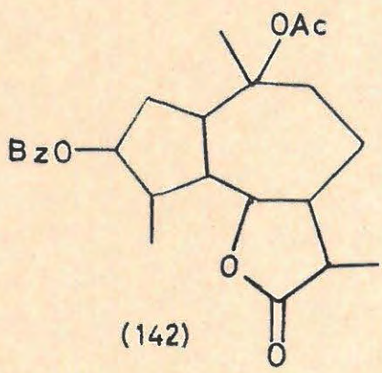


(140)



(141)



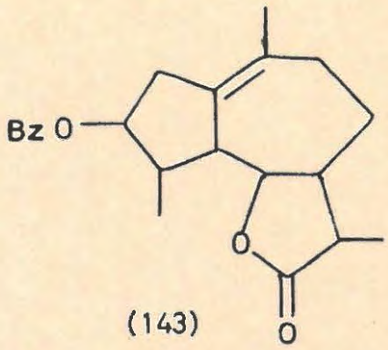
(142)

indicated that tenulin possessed a monosubstituted cyclopentenone system. The infrared spectrum of isotenulin showed bands at 1778 cm^{-1} (γ-lactone), 1705 and 1588 cm^{-1} (cyclopentenone) and 1748 and 1238 cm^{-1} (acetate group), while the band due to the hydroxyl group was absent. The spectrum also showed that the cyclopentenone system remained intact in the conversion of tenulin to isotenulin and therefore the masked acetate in tenulin must be attached β to the lactone grouping as in 146, which rearranges to 147 on very mild treatment with base. Both potential hydroxyl groups are secondary and attached to a six-membered or larger alicyclic ring, while both tenulin and isotenulin are bicyclic. Because of the formation of chamazulene and linderazulene on reduction and dehydrogenation of isotenulin and dihydroisotenulin[90] (148) respectively, tenulin was assumed to be based on a guaiane skeleton.

N.M.R. studies have shown that tenulin possesses an angular methyl group at C_5, placing it into the group of abnormal guaianolides. The positions of the methyl group at C_{10} and the isopropyl residue at C_7 were inferred from the above formation of azulenes. The positions of both groups were confirmed by N.M.R. studies, indicating that (149) is the correct structure of tenulin and (150) of isotenulin. This is supported by the conversion of dehydrodesacetyldihydroisotenulin (151) to a dibasic α, β-unsaturated keto-acid, (153) which may now be interpreted as being due to the clearage of a β-diketone via (152). On the otherhand, dehydrodesacetyldihydroalloisotenulin (154), formed in the hydrolysis of dihydroisotenulin and having the lactone ring closed at C_6, forms an α, β-unsaturated diketo-acid (155) only.

Treatment of the mesylates of desacetyldihydroisotenulin and desacetyldihydroalloisotenulin with lutidine afforded two different anhydroderivatives, providing chemical evidence for the different orientation of the lactone groups. The isolation

of 156 from/.....



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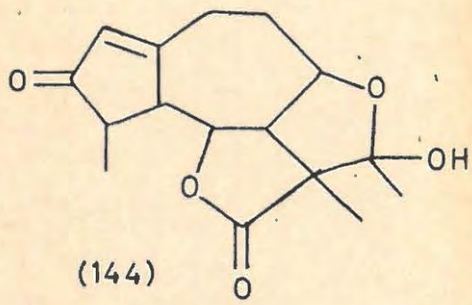

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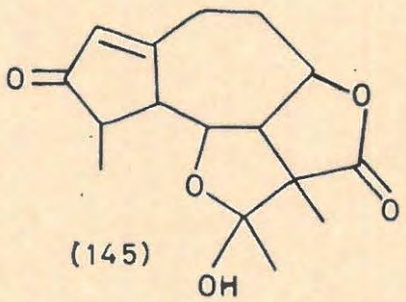

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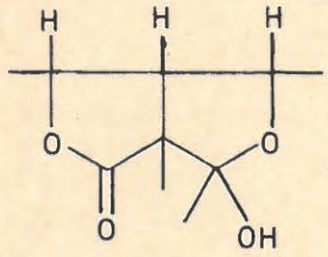
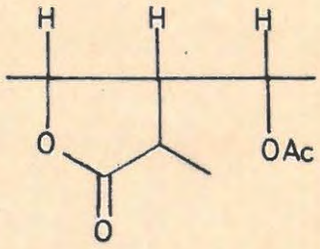


(146)



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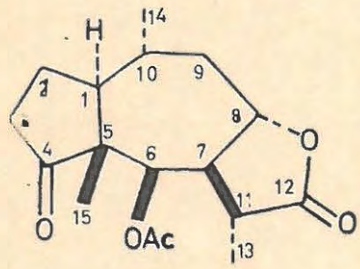
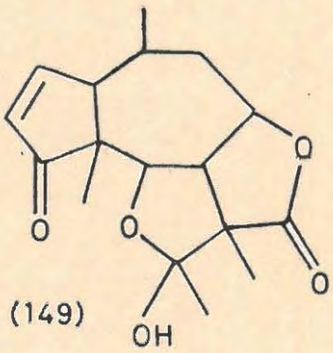
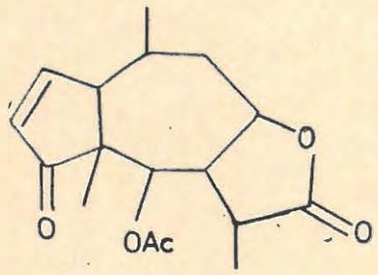


(148)



(149)



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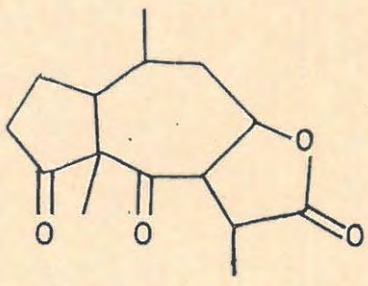
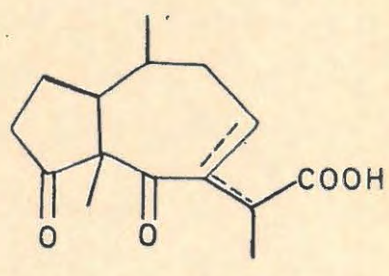


(151)



(152)

of 156 from the latter corroborated the orientation of the lactone ring in tenulin.

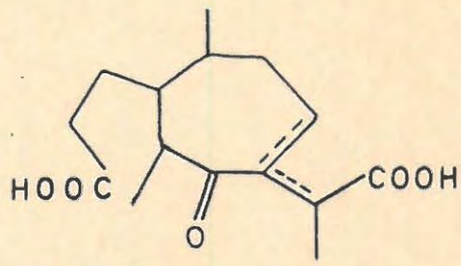
Dihydroisotenulin (148) was converted to the thioketal and the latter desulphurised to give an oily hydroxy-lactone (157), which was oxidised with chromium trioxide to 158, which failed to give a positive Zimmerman test. Base catalysed clearage of the keto-lactone (158) gave an α, β-unsaturated keto-acid (159), different from the keto-acid (160) prepared from dehydrodesoxodesacetyldihydroalloisotenulin or from similar compounds of the Helenium species.

Further chemical evidence supported the conclusion that isomerisation of the normal to the allo-series involves reorientation of the lactone ring.

The stereochemistry of tenulin has been determined by an X-ray study of bromoisotenulin (161).[91]

2.5.2.2. Parthenin (162) from Parthenium hysterophorus L [92] possesses a methylenic double bond (infrared absorption bands at 1655 and 1592 cm^{-1}) conjugated with a γ-lactone (bands at 1755 and 1408 cm^{-1}) and a cyclopentenone system (infrared bands at 1592 and 1718 cm^{-1}). The ultraviolet spectrum (λmax 215 and 340 mμ, log ξ = 4.18, 1.34; high intensity absorption at 206 - 210 mμ) was similar to that of helenalin and baldulin and is due to the α, β-unsaturated ketone and α, β-unsaturated γ-lactone. The infrared spectrum of tetrahydroparthenin showed two carbonyl maxima, one at 1760 cm^{-1} due to the γ-lactone and the second at 1742 cm^{-1} characteristic of a cyclopentanone carbonyl. The bands at 1655 and 1592 cm^{-1} in parthenin disappeared on catalytic hydrogenation to tetrahydroparthenin (163). Comparison of the N.M.R. spectra of 162 and 163 indicated that an additional C- methyl group was present in 163, while ozonolysis of 162 gave rise to formaldehyde and norparthenone (164).

Although parthenin/.....



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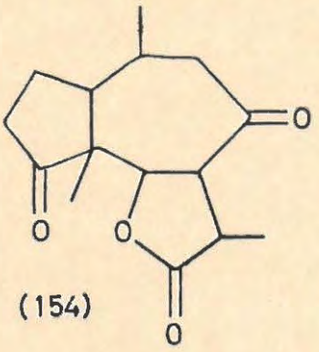

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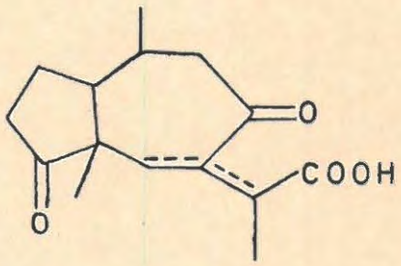

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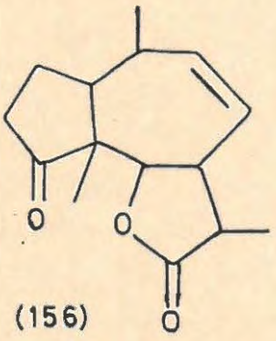
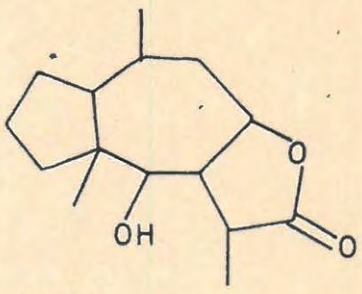


(156)



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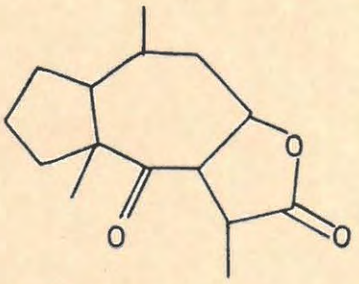
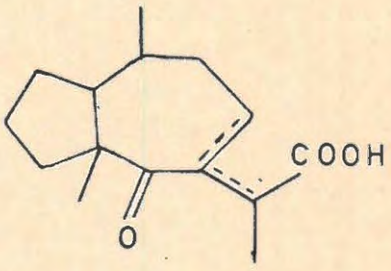


(158)



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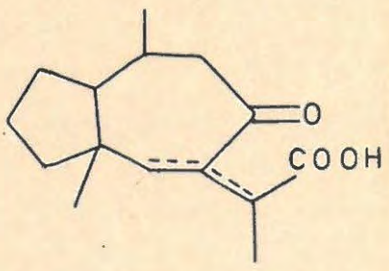

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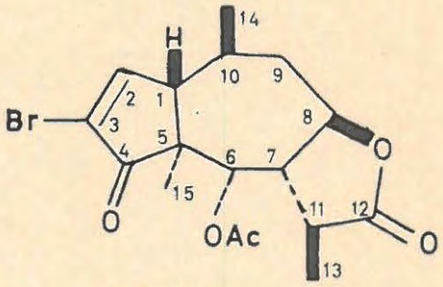

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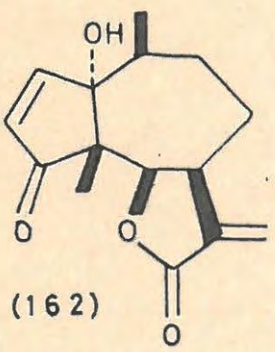


(162)

Although parthenin formed the tetrahydroderivative, the main hydrogenation product was dihydroisoparthenin (165), which resisted further hydrogenation. The double strength of the carbonyl band in the infrared spectrum at 1745 cm^{-1} indicated that the cyclopentenone chromophore had been reduced, while a band at 1668 cm^{-1} in the infrared and end absorption in the ultraviolet pointed to the continued presence of conjugation. The presence of the lactone in 165 is based on N.M.R. studies.

The tertiary nature of the hydroxyl group was inferred from its resistance to acetylation and chromium trioxide oxidation and from the ease with which parthenin and its derivatives are dehydrated. Dehydration of parthenin gave 166, while norparthenone was dehydrated to a product, which was shown by spectral studies to possess a dienone system unconjugated with the enolic α-ketobutyro-lactone. The tertiary hydroxyl group is either γ or δ to the α, β-unsaturated ketone. That the hydroxyl group is at the γ - position was demonstrated by the facile deoxygenation of parthenin and neoparthenin in zinc and acetic acid solution. Further chemical evidence supported the positioning of this group at C_1.

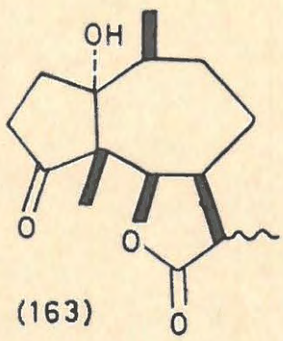
Lithium aluminium hydride reduction followed by dehydrogenation afforded artemazulene, but N.M.R. studies of parthenin and its derivatives indicated the presence of an errant methyl group at C_5.

Anhydroparthenin (166) was reduced to two dihydroderivatives, two tetrahydroderivatives and two hexahydroderivatives, one of which (167 b) was identical with tetrahydroambrosin. Ambrosin (168) is thus also an abnormal guaianolide.

2.6. Furano Compounds Related to the Guaianolides.

2.6.1. Linderene (169)[93], linderane (170), linderalactone (171) and isolinderalactone (172), all furano-sesquiterpenoids, were isolated from the roots of Lindera Strychnifolia Vill.

Dehydrogenation/.....



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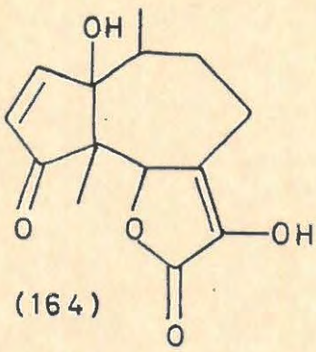
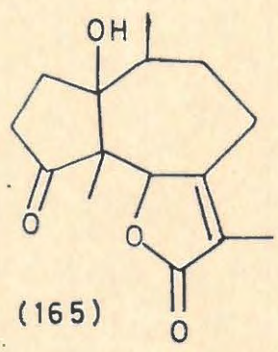


(164)



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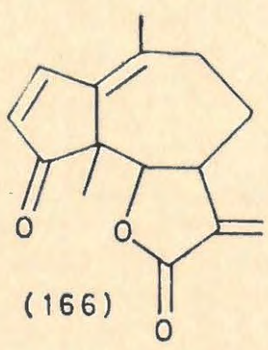
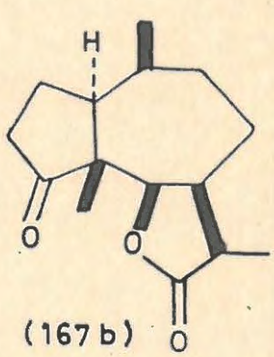
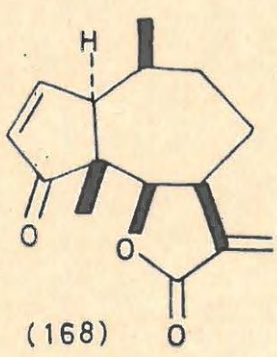


(166)



(167b)



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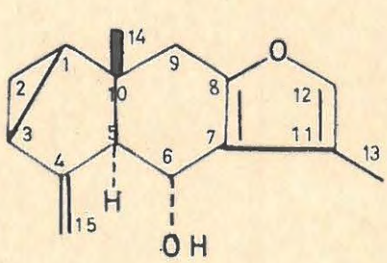

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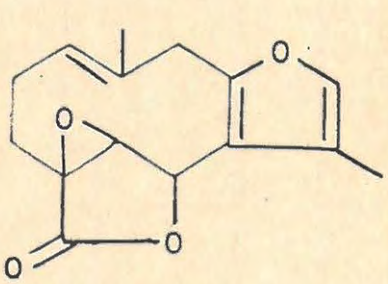

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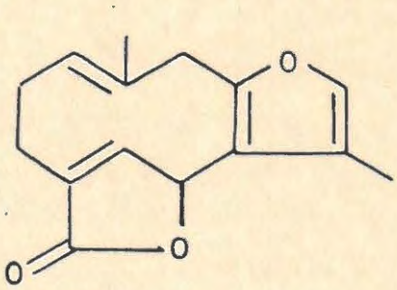

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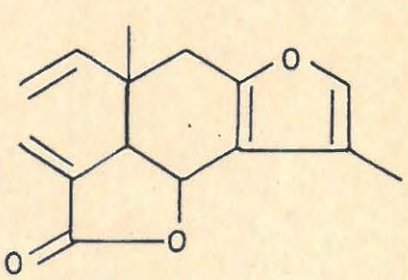


(172)

Dehydrogenation of 169 afforded linderazulene (173), which suggested that these compounds are the probable precursors of the guaianolides.

The ultraviolet spectra of linderene and dihydrolinderene (174) showed end absorption at 206 and 219 $m\mu$ respectively, indicating the presence of a conjugated chromophore, besides the furan ring. N.M.R. studies showed linderene to possess structure (169).

The hydroxyl group in linderene was placed at C_6 because octahydrolinderene, obtained on vigorous reduction of linderene, was dehydrated to 175, which could be reduced to octahydrodehydroxylinderene (176). The latter has been synthesised from alantolactone.[94]

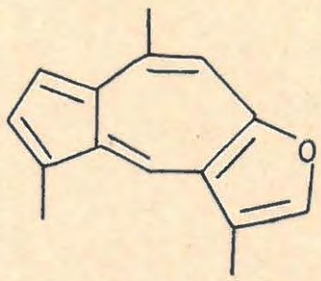
The formation of linderazulene (173) from linderene (169) can be rationalised by the two routes shown in SCHEME II.

2.6.2. Lindestrene (177) from Lindera strychnifolia Vill.[95] was shown by N.M.R. studies to possess two double bonds and a furan ring and was hydrogenated to octahydrodehydroxylinderene (176).

The furan ring in lindestrene is unstable, being converted to the stable γ-lactonic function as shown in SCHEME III. The intermediate (178) was converted to 181, which could be reduced to tetrahydroalantolactone. Thus the methyl group at C_{11} is β-orientated.[59]

The position of the exocyclicmethylenic double bond was demonstrated by osmium tetroxide oxidation of 181 to a dihydroxy derivative (182) - characterised by its N.M.R. spectrum - which on sodium periodate oxidation gave a non-conjugated ketone (183), converted by acid to two α, β-unsaturated ketones (184) and (185). The double bond is thus at C_{1-2} in lindestrene. Optical rotatory dispersion studies showed lindestrene to possess the stereochemistry as in 177.

2.7. The Eremophilenolides/...



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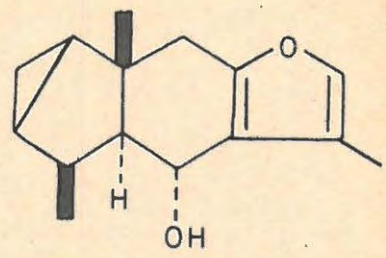

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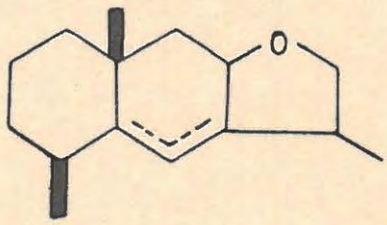
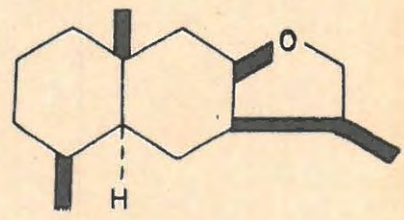
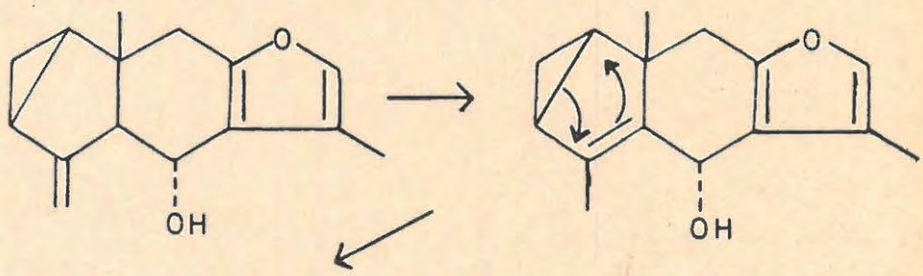


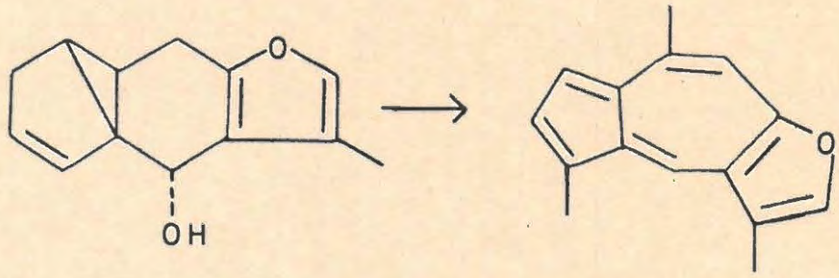
(175)



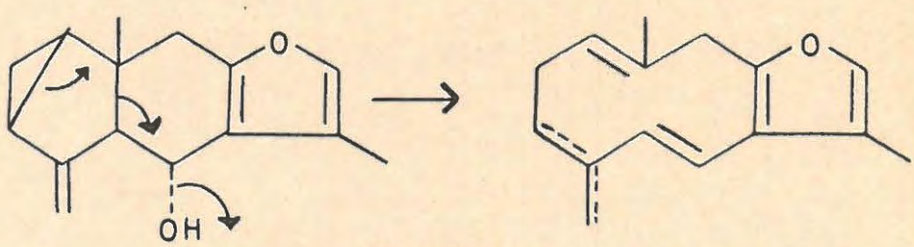
(176)

(i)





(ii)



SCHEME 2

2.7. The Eremophilenolides and Petasitolides.

These contain a naphthalenic nucleus and possess two methyl groups, one at C_4 and the other at C_5. The γ-lactonic hydroxyl group is positioned at C_8. Free hydroxyl or ketonic groups occur at C_2, C_3 or C_9.

Early work on eremophilone narrowed the structures to a choice between (186) which conformed to the isoprene rule or (187) which did not.[96] Both structures contain an α, β-unsaturated ketone and account for:-

(i) the formation of eudalene on sodium/alcohol reduction and dehydrogenation;

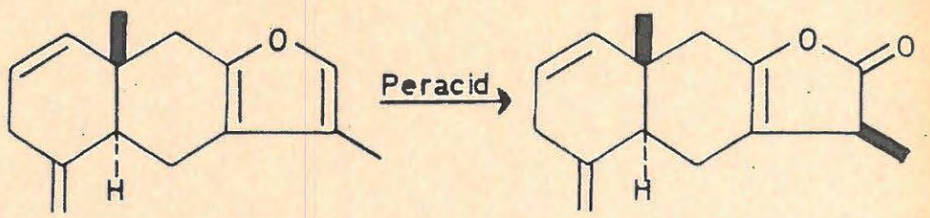
(ii) the presence of a methylene group adjacent to the carbonyl group and

(iii) the results of hydrogenation and oxidative experiments.

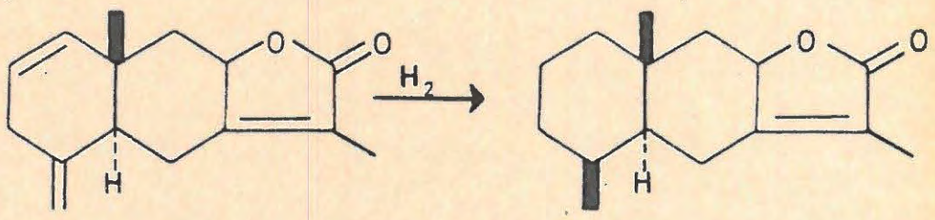
The problem was resolved by converting tetrahydroeremophilone, by reaction with methyl magnesium iodide and selenium dehydrogenation into, 1,5-dimethyl-3-isopropylnaphthalene, clearly derived from 187. Eremophilone had an ultraviolet absorption band at 243 mμ (log ξ = 3.90). This wavelength is closer to the calculated value, 242 mμ for 187 than to 239 mμ calculated for 186. The low value of the extinction coefficient is consistant with the system as in 187 rather than that of 186.

2.7.1. Eremophilenolide (188) from Petasites officinalis Moench[97] is related to petasin (189), isopetasin (190) and S-petasin (191) from Petasites hybridus L. Eremophilenolide exhibited infrared bands at 1760 and 1693 cm^{-1}, typical of an α, β-unsaturated 5-membered lactone, and the ultraviolet spectrum (λmax = 220 - 224, log ξ = 4.16) was compatible with such a chromophore. Confirmation was adduced by catalytic hydrogenation to dihydroeremophilenolide (192), the infrared spectrum of which (bands at 1780 cm^{-1}) showed that it was a

saturated γ-lactone./.....

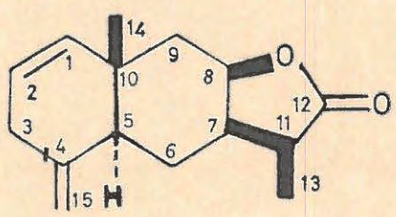


(177) (178)

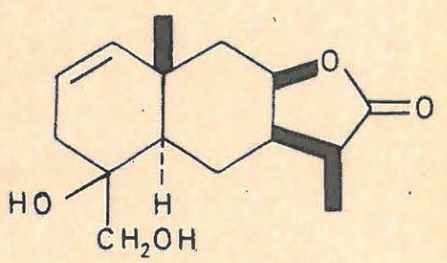


(179) (180)

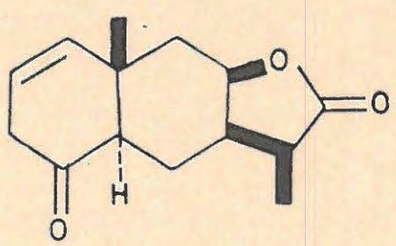
SCHEME 3



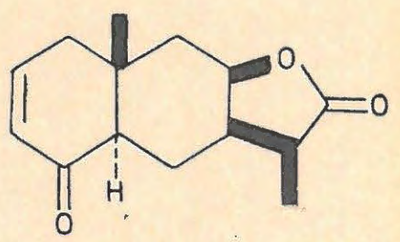
(181)



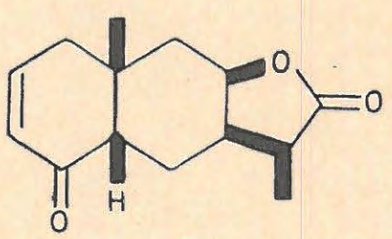
(182)



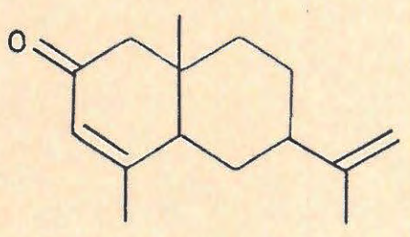
(183)



(184)



(185)



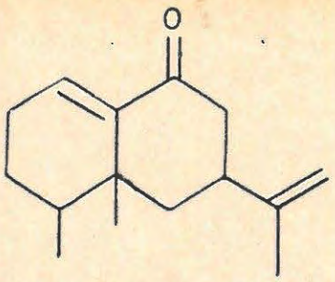
(186)

saturated γ-lactone. Reduction of 192 with lithium aluminium hydride afforded 193, which on tosylation and reduction with lithium aluminium hydride gave a mixture of a hydrocarbon ($C_{15}H_{26}$) and an ether ($C_{15}H_{26}O$). The hydrocarbon (194) was catalytically reduced to eremophilane (195)[98], while the ether was identical with tetrahydrofuranoeremophilane (196). When dihydroeremophilenolide (192) was reduced, under controlled conditions, with lithium aluminium hydride[99], and the intermediate hydroxyaldehyde (197) subjected to Huang Minlon reduction,[100] there was isolated the crystalline hydroxyeremophilane (198). This was oxidised with chromium trioxide to a ketone (199a), which isomerised with a base to (200). The infrared spectrum of the unstable ketone (199a) exhibited a band at 1430 cm^{-1}, indicative of a methylene group adjacent to a ketone function (band at 1711 cm^{-1}), an observation which pointed towards C_8 as the termination point of the lactone ring. This supposition, as well as that concerning the stereochemistry of the ketones (199a) and (200), was supported by the following evidence.

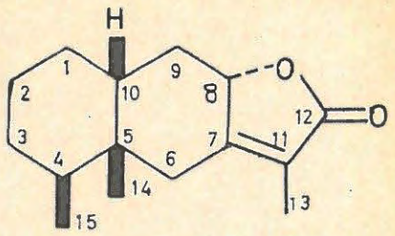
In the proof of the absolute configuration of eremophilone,[101] the methyl ether (201c) of hydroxyeremophilone was hydrogenated, and after base equilibration at C_7, the methoxyl function was removed and the intermediate C_8 hydroxyl group reoxidised. The resulting ketone (202) exhibited a positive Cotton effect,[102] typical of A/B trans-fused 3-keto-steroids and proved to be identical with a synthetic specimen of known absolute configuration.

In order to put this interconversion of eremophilenolide and hydroxyeremophilone (201a) on a firm footing, attempts were made to increase the proportion of cis-fused hydrogenation product. Catalytic hydrogenation of 201a gave an oily tetrahydroderivative (203a), which contained substantial amounts of the cis-fused isomer. Acetylation of 203a provided an isomeric mixutre of tetrahydroeremophilone acetate (204 a,b), the

infrared spectrum/.....



(187)



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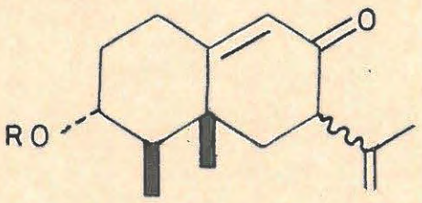
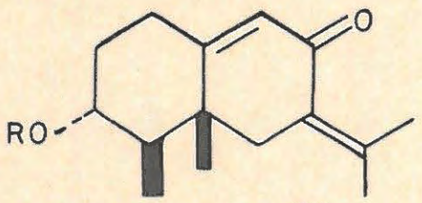
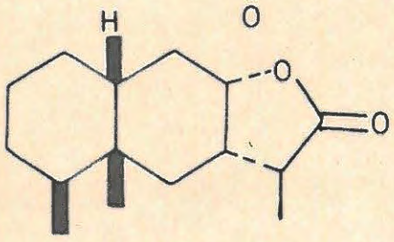




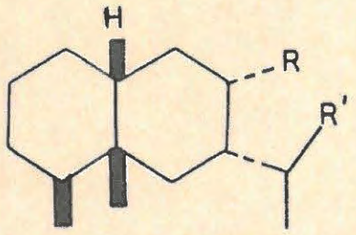
(189) R= $-\overset{O}{\overset{\|}{C}}-\overset{CH_3}{\overset{|}{C}}=CH\,CH_3$

(190) R= $-\overset{O}{\overset{\|}{C}}-\overset{CH_3}{\overset{|}{C}}=CHCH_3$

(191) R= $-\overset{O}{\overset{\|}{C}}CH=CHSCH_3$



(192)

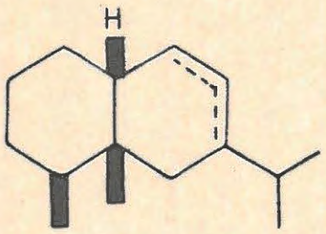


(193) R = OH ; R' = CH_2OH

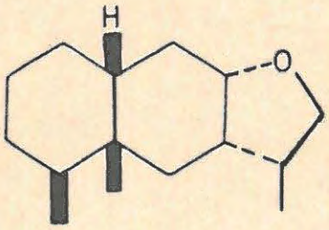
(195) R = H ; R' = CH_3

(197) R = OH ; R' = CHO

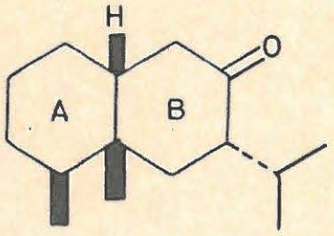
(198) R = OH ; R' = CH_3



(194)



(196)



(199a)

infrared spectrum and optical rotatory dispersion of which were virtually identical with those of direct hydrogenation of hydroxyeremophilone acetate (201b). Deacetoxylation of 204 a,b afforded an approximate 1:1 mixture of cis and trans isomers of 199a and b, identical with those originating from eremophilenolide. Their optical rotatory dispersion curves exhibited a typical negative Cotton[102] effect superimposed upon a positive background, characteristic of A/B cis-fused 3-keto-steroids. This interconversion of eremophilenolide and hydroxyeremophilone (201a) completely settles the configuration of the former. Furthermore, the isolation of the base labile (199a) and base-stable (200) cis-fused ketones permits unequivocal stereochemical arrangement to C_7 in dihydroeremophilenolide. The cis-ring fusion in eremophilenolide points towards the α-orientation of the C_8-oxygen atom.

The presence of the C_4 equatorial methyl group makes a "steroid-like" conformation of the decalin clearly preferred over a "non-steroid" conformation. In the "steroid-like" conformation the lactone ring in 188 can only be formed with a hydroxyl at C_8 α-orientated. A β-connection would require the ring to exist in a very unfavourable boat form. This latter conformation is not impossible, but molecular rotation values of -12° for 192 and 42° for 196 also favour a C_8 - α - orientated substituent.

2.7.2. Petasitolide A and B and S-Petasitolide A and B, isolated from the rhizomes of Petasites officinalis Moench,[2] all possess an α, β-unsaturated γ-lactone and are derived from the same eremophilane-type sesquiterpenoid.[2,79,103]

Petasitolide A (205a) exhibited bands in the infrared spectrum at 1762 cm^{-1} (α, β-unsaturated γ-lactone) and 1712 and 1650 cm^{-1} (α, β-unsaturated ester). In the ultraviolet, the compound showed end absorption at 218 $m\mu$ ($\log \xi = 4.42$). Petasitolide A

was hydrogenated/.....

was hydrogenated in acetic acid over Adam's catalyst to tetrahydropetasitolide A, which showed bands at 1778 cm^{-1} (saturated γ-lactone) and 1739 cm^{-1} (saturated ester group).

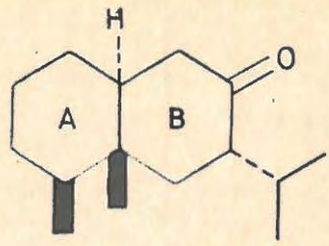
Petasitolide A was saponified to angelic acid and an α,β-unsaturated hydroxy-lactone (205e), which was catalytically reduced to a dihydrohydroxy lactone (206). Chromium trioxide oxidation of 206 afforded a keto-lactone (207), which showed infrared absorption bands at 1711 cm^{-1} due to a carbonyl group and at 1767 cm^{-1} due to a saturated-γ-lactone. The keto-lactone (207) was converted via the thioketal to dihydroeremophilenolide (192).

The location of the hydroxyl group was confirmed by N.M.R. studies of the keto-lactone (207). A singlet at 8.71 τ corroborated the presence of an angular methyl group, while a doublet at 9.00 and 9.11 τ is due to a methyl group in the $=CHCH_3$ grouping. The good resolution is due to the presence of a carbonyl group in the vicinity.[104]

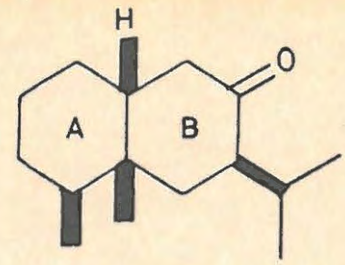
S-Petasitolide A (205c) on saponification was converted to β-methylthioacrylic acid, m.p. 124°, while pyrolysis gave an isomeric acid, m.p. 99 - 100°, which was converted into the acid of m.p. 124° with alkali. Spectroscopic measurements showed S-petasitolide A to be esterified by the less stable cis-β-methylthioacrylic acid. Transesterification of S-petasitolide A in methanol in the presence of sulphuric acid led to the hydroxy-lactone (205e).

Petasitolide B (205b) and S-petasitolide B (205 d) afforded tiglic acid and trans β-methylthioacrylic acid, m.p. 124°, respectively, on pyrolysis,[105] and the same hydroxylactone on transesterification. As both these substances were isolated in very low yields, they are probably not present in the natural material and are more likely artifacts, formed by isomerisation during isolation.

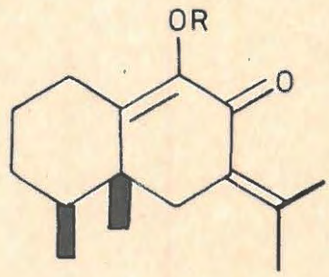
2.8. Furano Compounds/.....



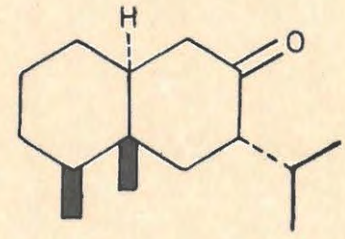
(199b)



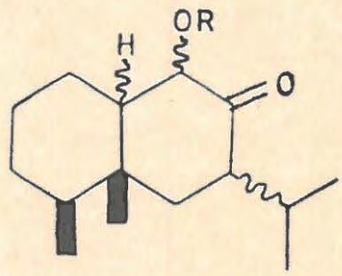
(200)



(201) (a) R = H
(b) R = Ac
(c) R = CH_3

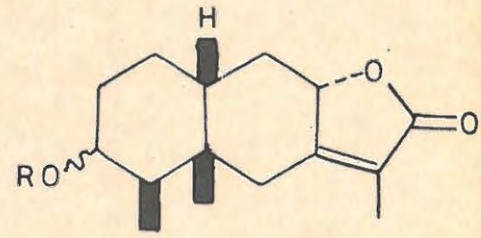


(202)



(203) (a) R = H

(204) (a,b) R = Ac



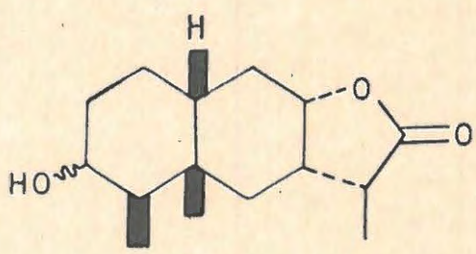
(205) (a) R = $OCC(CH_3)=CHCH_3$ (cis)

(b) R = $OCC(CH_3)=CHCH_3$ (trans)

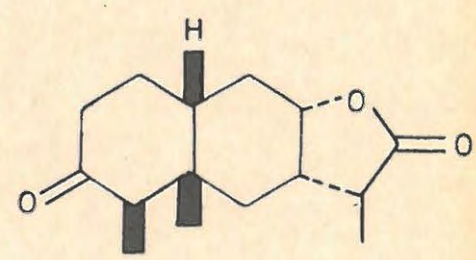
(c) R = $OCCH=CHSCH_3$ (cis)

(d) R = $OCCH=CHSCH_3$ (trans)

(e) R = OH



(206)



(207)

2.8. Furano Compounds Related to the Eremophilenolides.

2.8.1. Furanoeremophilane (208) from Petasites officinalis[2,97,98], and P. albus L showed infrared absorption bands at 1576, 1660, 1776 and 1810 cm^{-1}. The presence of a furan ring was confirmed by a positive test with Ehrlich's reagent, while the ultraviolet spectrum showed end absorption at 222 $m\mu$ (log ξ = 3.78), typical of a furan ring. Furanoeremophilane was catalytically hydrogenated to tetrahydrofuranoeremophilane (196). This allows the stereochemistry in (208) to be assigned to furanoeremophilane.

Autoxidation of furanoeremophilane[79] has demonstrated that this compound is the precursor of eremophilenolide. A light petroleum solution of furanoeremophilane, when exposed to air, was converted to eremophilenolide. The latter may also be prepared by oxidation of furanoeremophilane with oxygen in the presence of platinum prepared by reduction of Adam's catalyst. Hydroxyeremophilenolide (209) was obtained as a by-product.

2.8.2. Petasalbin and albopetasin have been isolated from the rhizomes of Petasites albus,[106,107,108] P.spurius BCHL. and P.tomentosus D.C. Petasalbin (210) exhibited absorption bands in the infrared at 1565 cm^{-1} due to a furan ring, and at 3485 and 3615 cm^{-1} due to a hydroxyl group. The ultraviolet spectrum showed end absorption at 220 $m\mu$ (log ξ = 3.84). The N.M.R. spectrum corroborated the presence of all the protons in 210. Catalytic hydrogenation in ethanol over Adam's catalyst converted petasalbin to the tetrahydroderivative (211), while hydrogenation in glacial acetic acid gave a mixture of hydrogenated and hydrogenolysed products. Chromatography separated the mixture into eremophilane (212), tetrahydrofuranoeremophilane (196), tetrahydropetasalbin (211) and tetrahydropetasalbin acetate (213). Petasalbin must thus possess an eremophilane skeleton, with the furan ring attached at C_8 and

be substituted/.....

be substituted by a hydroxyl group in an allylic position.

The position of the hydroxyl group was ascertained by oxidation of petasalbin with chromium trioxide to furanoeremophilone - 6 (214), which was unlike natural furanoeremophilone - 9 (215).[2] The former had the following physical properties:- m.p. 62°, infrared absorption bands at 1568, 1615 and 1675 cm^{-1}, ultraviolet maximum at 269 $m\mu$ (log ξ = 3.6). The latter (215) had:- m.p. 150°, infrared absorption bands at 1537, 1667 (probably due to a keto-group-conjugated with a furan ring) and 3000 cm^{-1}, ultraviolet maximum at 280-282 $m\mu$, (log ξ = 4.15-4.33).

The position of the free hydroxyl group was unambiguously proved by elucidation of the structure of hydroxyeremophilenolide (216), an antoxidation product of petasalbin, also isolated from the rhizomes of P. albus.[108] Hydroxyeremophilenolide was shown by spectroscopic measurements to be a hydroxy-γ-lactone (infrared bands at 1755, 1690, 3450 and 3600 cm^{-1}, ultraviolet absorption at 220 $m\mu$ (log ξ = 4.12)). Chromium trioxide oxidation converted 216 to a keto-eremophilenolide (217), the infrared spectrum of which indicated the presence of an α, β-unsaturated-γ-lactone conjugated with a keto-group (maxima at 1760, 1665 and 1690 cm^{-1} in the infrared). Maxima at 240 $m\mu$ and 328 $m\mu$ (log ξ = 4.03, 1.90) in the ultraviolet is also indicative of this chromaphore. The N.M.R. spectrum confirmed this structure.

The lactonic hydroxyl group was shown to be α-orientated by measurement of molecular rotatory increments.

Albopetasin (218) on saponification afforded petasalbin (210) and tiglic acid together with traces of angelic acid. That albopetasin was the tiglate of petasalbin was demonstrated by pyrolysis when tiglic acid only was obtained.

2.8.3. Albopetasol [106] showed maxima in the infrared spectrum

at 3320 and/.....

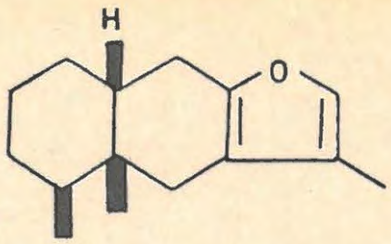
at 3320 and 3370 cm^{-1} due to hydroxyl groups, and at 1568 and 1652 cm^{-1} due to a furan ring. The ultraviolet spectrum showed end absorption, λ max = 220 $m\mu$ (log ξ = 3.82), indicative of a furan ring. Active hydrogen analysis showed albopetasol to be a diol. No structure has as yet been proposed.

2.8.4. Furanopetasin (219) from the rhizomes of Petasites officinalis Moench [2,103,109] showed maxima in the infrared spectrum due to a hydroxyl group (3608 and 3540 cm^{-1}), an α, β-unsaturated ester (1718 and 1655 cm^{-1}) and a furan ring (1567 cm^{-1}). The ultraviolet absorption peak at 222 $m\mu$ (log ξ = 4.17) is also indicative of the presence of a furan ring. Furanopetasin displayed an intense blue-green colour with Stahl-Müller reagent, characteristic of a furan ring. Mild alkaline hydrolysis afforded furanopetasol (220), which also gave a blue-green colour with Stahl-Müller reagent. The acidic fraction consisted chiefly of angelic acid, contaminated with some tiglic acid, formed by isomerisation of angelic acid.

Furanopetasin was catalytically hydrogenated to the non-crystalline hexahydrofuranopetasin (221), which gave a crystalline tosyl derivative (222). The tosyl derivative (222) was converted to tosyloxytetrahydrofuranopetasol (223), which was oxidised with chromium trioxide[110] to tosyloxytetrahydrofuranopetasone (224). The keto-group was removed by desulphurisation of the thioketal and the resulting deoxyderivative (225) converted to tetrahydrofuranoeremophilane (196) by reduction with lithium aluminium hydride. Hydrogenation of 223 in the presence of MoS_2 at 300-320° and 150 atm pressure afforded eremophilane (212), thus confirming the nature of the carbon skeleton.

The two hydroxyl groups in furanopetasol were first judged to be primary and secondary, for chromium trioxide oxidation of tetrahydrofuranopetasol afforded a lactone-keto-acid (226)

which on/.....



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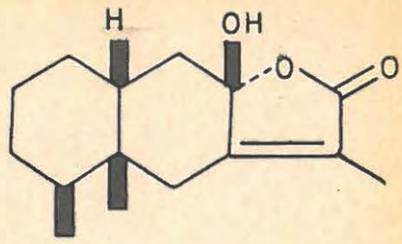

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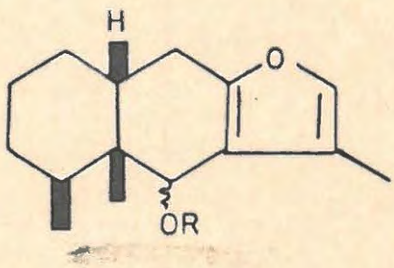
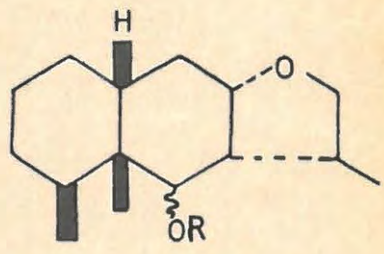
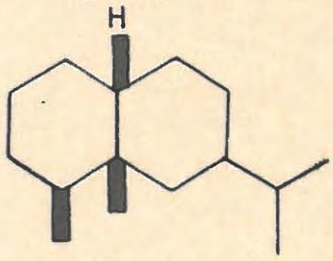


(210) R = H
(218) R = OC C= CHCH$_3$(cis)



(211) R = H
(213) R = Ac



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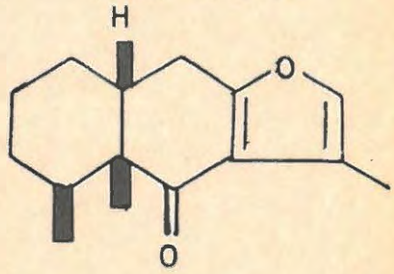

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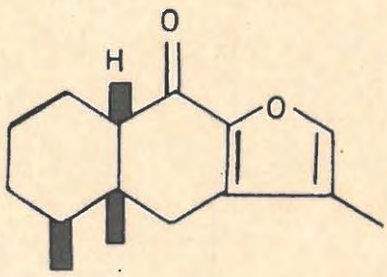

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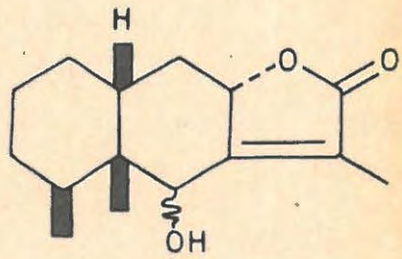

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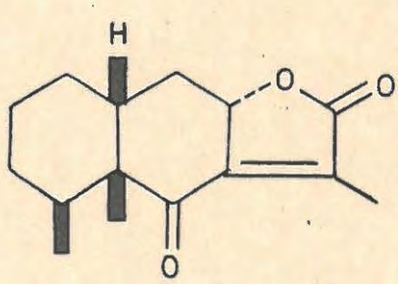

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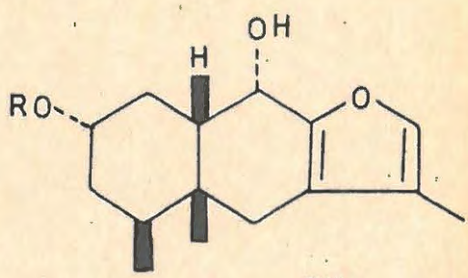
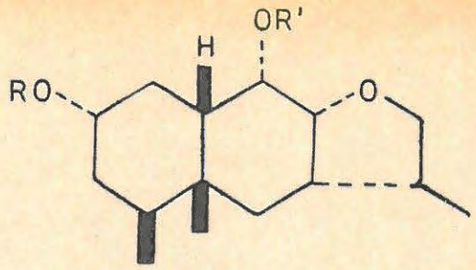


(219) R= OC CH$_3$ C=CHCH$_3$(cis)
(220) R = H

which on elemental analysis contained two more hydrogens than was supposed and should have possessed a primary hydroxyl group. The formation of 226 can only arise from oxidative cleavage of one of the rings and not merely by oxidation of a primary hydroxyl group. The absence of a primary hydroxyl group in furanopetasin and its derivatives was verified by N.M.R. studies.

As furanopetasol and tetrahydrofuranopetasol readily afforded a diacetate, both hydroxyl groups were considered to be secondary. That one of the hydroxyl groups is in the vicinity of the ether part of the furan ring was shown by the above oxidative cleavage of one of the rings, for this does not occur in furanoeremophilane. Furanopetasol (220) was selectively oxidised with manganese dioxide[111] to a furano-keto-alcohol (227), the infrared spectrum of which exhibited bands at 1560 cm^{-1} due to a furan ring, at 1678 and 1023 cm^{-1} due to an α, β, γ, δ-unsaturated ketone in a six-membered ring and at 3600 cm^{-1} due to a hydroxyl group. The ultraviolet absorption peak at 280 $m\mu$ ($\log \xi = 4.37$) is characteristic of a keto-group at C_9 in conjugation with a furan ring.[103,104] Saponification and chromium trioxide oxidation of the desoxyderivative (225) afforded a lactonic acid (228). Hence the free hydroxyl group in furanopetasin is attached at C_9 and the other one is acylated by angelic acid. The acid (226) was not a β-keto-acid for it gave no colour with methanolic ferric chloride and no decarboxylation took place at elevated temperatures in the presence of acids. It was esterified with diozomethane and the resulting methyl ester reduced to a γ-lactone (229), which was hydrolysed to the corresponding lactone-hydroxy-acid. Pyrolysis of the latter afforded 230, which possessed an absorption band in the infrared spectrum at 1774 cm^{-1} characteristic of a γ-lactone. Hence the acylated hydroxyl group in furanopetasin is at C_2. This supposition was confirmed by mass spectrometry of the deuterated diketone (231).

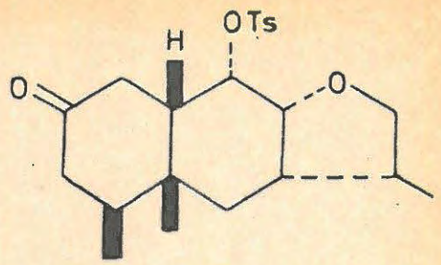
The absolute/.....



(221) R = $\overset{O}{\overset{\|}{C}}\overset{CH_3}{\overset{|}{C}}HCH_2CH_3$; R' = H

(222) R = $\overset{O}{\overset{\|}{C}}\overset{CH_3}{\overset{|}{C}}HCH_2CH_3$; R' = tosyl

(223) R = H ; R' = tosyl



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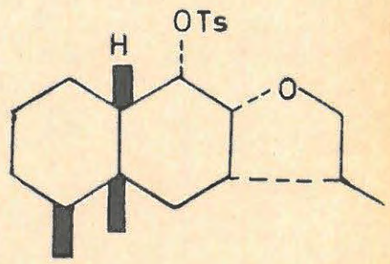

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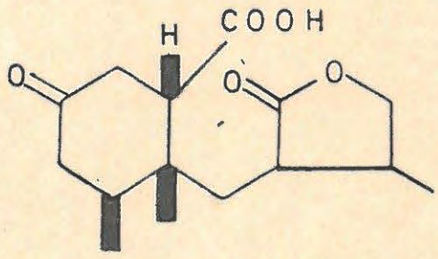

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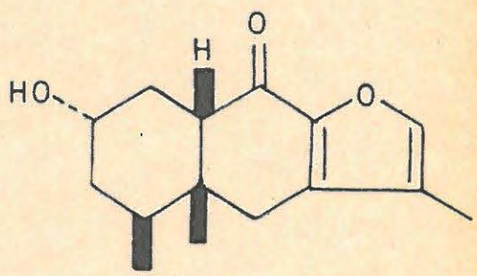

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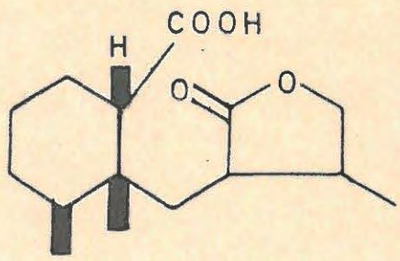

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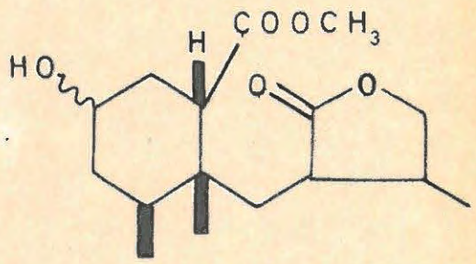

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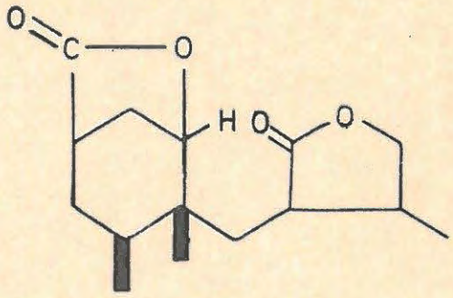

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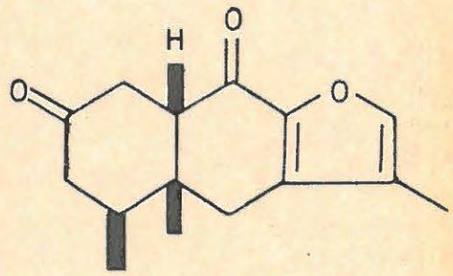


(231)

The absolute configuration of both hydroxyl groups followed from the reaction of tetrahydrofuranopetasol with thionyl chloride in pyridine. A cyclic sulphite (232), which can only arise when both hydroxyls are α-orientated, was obtained.

3. DISTRIBUTION, ECOLOGY, GENERAL INFORMATION AND AFFINITIES.

3.1. Distribution.

Xalanga, Queenstown, Glen Grey, Wodehouse and Graaff Reinet districts.

3.2. Ecology and General Information.

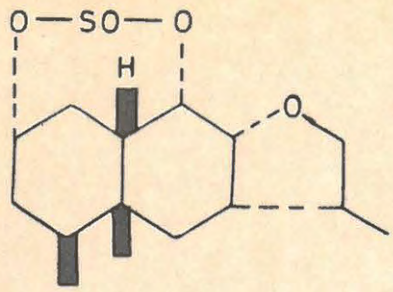
Euryops floribundus is a greyish shrub, commonly called "Harpuisbos". It grows from 2 - 5 feet high, but may reach 7 feet under more favourable conditions. It grows mainly on sandstone slopes.

The plant is declared a noxious weed in certain of the above areas and where it infests the soil, the grass is ousted, increasing the rate of soil erosion. The plant has conspicuous yellow flowers and blooms mainly in Spring and Winter. The flowers, but not the foliage, are eaten by sheep. A decoction of the resin from Euryops species is taken by the Nama in fevers

3.3. Affinities.

In the original description,[112] based on a specimen collected by Galpin (Number 1536) from the Queenstown Division (in valeys near Queenstown, Alt. 3500 ft.), Brown states:- "Affinis E. pendunculato N.E.Br., pendunculis tripoli brevioribus facile distinguitur."

According to the Chief Botanist, Pretoria, E.tenuissimus Less is the closest affinity. Other closely related species in order of affinity are: E. linifolius D.C. and E.brevipappus M.D. Henderson. E. floribundus N.E.Br. differs from E. tenuissimus Less. by its broader and lesser (8-9) involucre scales (E.tenuissimus has 12-20) and by the fact that its old stems are not so rough.



(232)

4. EXPERIMENTAL.

4.1. The Extraction of Euryops floribundus.

The plant material was collected on the farm "Sondagsrivier Hoek" about 25 miles to the west of Graaff Reinet during the period October, 1962 to November, 1964.

The extraction of IV(c) is discussed:-

Undried stems (16.8 kg.) were cut into small pieces and steeped in cold acetone (110 L.) for 2 days. The extract was filtered and the solvent removed by flash distillation. The resulting aqueous resin was extracted with ether (3 L.) and washed with water. Evaporation of the solvent afforded a sticky gum (399g) (2.38% of undried plant), which was dissolved in 25% ethanolic potassium hydroxide (500 ml.) containing water (50 ml.). After heating under reflux for six hours, water (500 ml) was added and the alcohol removed under reduced pressure. The residue was then extracted with ether (8 x 400 ml), washed with water (5 x 200 ml) and dried (Na_2SO_4). The filtered solution was concentrated to 300 ml., whereupon a crystalline solid separated.

4.2. The Extraction of Euryops tenuissimus.

The plant material was collected, approximately ten miles from Grahamstown along the Cradock road, during late November. The extraction was carried out as for E.floribundus (7.1)

In Table I are recorded the results of extractions carried out over two years.

Table I/.....

TABLE I.

TABLE OF EXTRACTIONS.

Date collected.	Extraction Number.	Weight of plant.	Weight of resin.	Weight of crystalline solid.	m.p. °C.	% Euryopsol obtained from crystalline solid.	% Euryopsonol obtained from crystalline solid.
E. floribundus.							
29.10.1962	I(A)	3.7kg. dried	106.5 g	1.4 g	200 - 215	---	21
	(B)	8.7kg. "	319.0 g	3.4 g	207 - 209	---	19
26.2.1963	II(A)	18.8kg. undried	248.3 g	4.3 g	200 - 205	55	---
	(B)	17.4kg. "	331.3 g	16.2 g	205 - 209		
	(C)	17.7kg. "	330.5 g	13.2 g	197 - 207		
	(D)	12.0kg. "	249.4 g	8.3 g	192 - 203		
20.5.1963	III(A)	17.9kg. "	248.2 g	7.2 g	194 - 197	45	10
	(B)	16.4kg. "	327.0 g	5.4 g	195 - 198		
	(C)	12.0kg. "	285.0 g	3.5 g	190 - 196		
2.12.1963	IV(A)	16.8kg. "	305.8 g	8.2 g	190 - 203	15	53
	(B)	17.0kg. "	406.0 g	7.0 g	197 - 206		
	(C)	16.8kg. "	399.4 g	12.0 g	195 - 210	16	46
	(D)	15.8kg. "	365.0 g	6.5 g	198 - 207	---	63

TABLE I cont/.....

TABLE I cont.

Date collected.	Extraction Number.	Weight of plant.	Weight of resin.	Weight of crystalline solid.	m.p. °C	% Euryopsol obtained from crystalline solid.	% Euryopsonol obtained from crystalline solid.
20.4.1964	V(A)	18.1kg. undried	332.0 g	15.9 g	175 - 210	16	47
	(B)	20.1kg. "	---	22.3 g	185 - 197	30	59
	(C)	9.5kg. "	---	6.6 g	190 - 210		
20.5.1964	VI(A)	20.0kg. "	---	10.4 g	---	45	---
	(B)	19.5kg. "	---	10.0 g	---		
	(C)	19.5kg. "	---	12.2 g	---	75	---
	(D)	17.2kg. "	---	8.7 g	---	46	12
	(E)	19.1kg. "	---	13.0 g	---	49	11
24.11.1965	VII(A)	18.7kg. "	267.0 g	5.2 g	173 - 175	100	---
	(B)	22.4kg. "	353.5 g	5.5 g	169 - 170	100	---
	(C)	21.4kg. "	414.0 g	8.7 g	174 - 175	100	---
E. tenuissimus.							
30.11.1963	VIII(A)	10.1kg. "	328.0g	7.8 g	162 - 164	100	---

4.3 The Purification of the Crystalline Solid from Euryops floribundus.

The purification of IV(C) is typical.

The crude extract (12.0 g) was dried under reduced pressure. The ultraviolet spectrum showed a maximum at λ = 280 mμ., (log ξ = 4.033). Since pure euryopsonol has a maximum at λ = 280, (log ξ = 4.16), this crystalline material contained 75% euryopsonol. The crude extract was dissolved in dry tetrahydrofuran (150 ml) and the solution poured onto a column (4" in diameter) of neutral alumin (325 g) (treated with dilute hydrochloric acid and activated at 180 - 190° for 24 hours). Details of the chromatogram are given in Table 2 (300 ml. eluates being collected).

TABLE 2.

Fraction	Solvent.	Weight.
1	Dry ether	1.06 g
2	Dry ether	4.76 g
3	Dry ether	0.11 g
4	Dry ether	0.23 g
5	Ether + 1% ethyl alcohol.	0.20 g
6	Ether + 1% ethyl alcohol.	0.48 g
7	Ether + 1% ethyl alcohol.	1.20 g
8	Ether + 1% ethyl alcohol.	0.68 g
9	Ether + 5% ethyl alcohol.	1.37 g
10	Ether + 5% ethyl alcohol.	1.30 g
11	Ether + 5% ethyl alcohol.	0.30 g
12	Ether + 25% ethyl alcohol.	0.06 g

Fractions 1 - 2 were combined and crystallised from benzene (60 ml) to give yellow needle-like crystals (3.41 g), mp.223 - 229°; λmax = 280 mμ (log ξ = 4.12). Concentration of the mother liquors afforded a further 0.48 g, m.p. 214 - 218°.

Fraction 3 - 6/.....

Fractions 3 - 6 were combined and crystallised from benzene (30 ml) to give yellow needles (0.89 g), m.p. 223 - 225°.

Fraction 7 crystallised from benzene (30 ml) as yellow needles (0.69 g), m.p. 222 - 224°.

Fraction 8 crystallised from methyl alcohol (15 ml) as fine, white needle-like crystals (0.55 g) m.p. 173 - 174°

Fractions 9 - 12 were combined and crystallised from methyl alcohol (35 ml) to give fine, white needle-like crystals (1.41g) m.p. 173 - 174°. The ultraviolet spectrum (λ = 280 mμ, (log ξ = 1.82)) indicated a maximum of 0.4% euryopsonol.

Euryopsonol.

Recrystallised from ethyl alcohol (charcoal) to give large colourless crystals m.p. 230 - 231° (decomp.).

Found: C = 72.6, 72.6, 72.3, 72.81%

H = 8.2, 8.1, 8.1, 7.84%

C - methyl = 6.1,

Molecular Weight (Rast) 216, 225

(Mass spectrogram) 248.

Two double bonds

$[\alpha]_D^{22}$ = - 36 (chloroform)

λ max = 280 mμ (log ξ = 4.16)

λ max = 212 mμ (log ξ = 3.22)

Calculated for $C_{15}H_{20}O_3$:

C = 72.55%, H = 8.12%

One C - methyl = 6.05%

Molecular weight = 248.

Euryopsol.

Crystallised as fine white needles from ethyl alcohol, slightly soluble in benzene (0.4 g/100 ml) and ether, m.p. 169 - 171°.

Found/.....

Found: C = 67.78, 67.59, 67.59%

H = 8.38, 8.33, 8.32%

C - methyl = 17.29%

Molecular weight (ebullioscopic) 205, 234, 254.

(Mass spectrogram) 266.

Active hydrogen = 0.80, 0.84%

$[\alpha]_D^{17}$ = + 14° (ethanol)

λ max = 220 mμ (log ξ = 3.68)

Calculated for $C_{15}H_{22}O_4$:

C = 67.65%, H = 8.33%

Three C - methyl groups = 16.94%

Molecular weight = 266

Active hydrogen - two hydroxyl groups = 0.76%

4.4. Purification of Crystalline Extract from E.tenuissimus.

Crystallised from methyl alcohol as white needles, m.p. 167 - 169°.

Mixed melting point and infrared and ultraviolet spectra showed it to be identical with Euryopsol isolated from E. floribundus.

4.5. Lithium Aluminium Hydride Reduction of Euryopsonol.

A solution of euryopsonol (2.03 g, dried for 18 hours at 80°/2.0 m.m.) in 65 ml. of tetrahydrofuran (dried first over sodium and distilled over lithium aluminium hydride) was added dropwise, over a period of 50 minutes, to a stirred slurry of lithium aluminium hydride (4.96 g) in dry tetrahydrofuran (50 ml). The mixture was stirred for 3 hours and then refluxed for 7 hours. The excess hydride was decomposed by adding wet ether (50 ml) followed by 50 ml. of dilute sulphuric acid, the aqueous layer separated and extracted with ether (5 x 50 ml). The combined extracts were washed with saturated sodium bicarbonate solution and water, and dried (Na_2SO_4).

Removal of/.....

Removal of the solvent left a yellow oil (1.79 g), λ max 280 mμ (log ξ = 2.77), which could not be crystallised. From the ultraviolet absorption, the oil contained a maximum of 4.5% unreacted euryopsonol.

4.6 Dehydrogenation of the Lithium Aluminium Hydride Reduction Product.

The above oil (1.79 g) was intimately mixed with 30% palladised charcoal[113] (0.99 g) in a 25 ml. flask, fitted with an air condenser 30 cm. in length. The apparatus was flushed with pure nitrogen for 30 minutes and heated at 305 - 310° for 5 hours, when 235 ml. of gas was evolved, chiefly during the first 1 1/2 hours. The reaction product was extracted with hexane (5 x 40 ml.), filtered through a celite pad and dried (Na_2SO_4). The filtered extract was poured onto a column (2 cm. diameter) of neutral alumina (30 g) and eluted with dry hexane. Details of the chromatogram are given in Table 3.

TABLE 3.

Fraction	Solvent.	Weight	Remarks.
1	Dry hexane (150 ml.)	48.8 mg.	oil
2	Dry hexane (150 ml.)	63.8 mg.	oil
3	Dry hexane (150 ml.)	20.0 mg.	oil
4	Dry hexane (150 ml.)	1.5 mg.	oil
5	Hexane/Benzene 1:1 (150 ml.)	16.3 mg.	oil
6	Hexane/Benzene 1:1 (150 ml.)	6.0 mg.	oil

Fractions 1 and 2 were dissolved in hot ethyl alcohol (1 ml.) and added to a hot solution of trinitrobenzene (21.5 mg.) in ethyl alcohol (1 ml.). Reddish yellow crystals (18.7 mg), m.p. 99 - 101°, separated on cooling and were recrystallised from methyl alcohol to give 9.3 mg. of adduct, m.p. 104.5 - 106°.

Found: C = 60.61%; H = 4.88%; N = 10.47%

λ max 228 mμ (log ξ = 5.0371)

λ max 282 mμ (log ξ = 3.7971)

Calculated/.....

Calculated for $C_{20}H_{19}O_6N_3$:

C = 60.45%; H = 4.82%; N = 10.57%.

Further dehydrogenation experiments are summarised in Table 4.

TABLE 4.

Dehydrogenation of Euryopsonol and Euryopsol.

M.p. of Trinitrobenzene adduct:-	Elemental Analyses of adduct. %C.	%H.	%N.	Ultraviolet spectrum of hydrocarbon obtained from adduct.
(i) Obtained from Euryopsonol.				
81 - 91°	59.28	4.81	8.70	---
(ii) Obtained from Euryopsol.				
(a) 82.5°	59.41	4.41	---	λmax 220 mμ (log ξ = 4.26) λmax 253 mμ (log ξ = 3.99) λmax 283 mμ (log ξ = 3.50)
167 - 168°	--	--	---	---
(b) 75 - 76°	58.69	5.24	9.74	---
(c) 79 - 81°	57.38	4.95	16.72	---
(d) 81 - 82°	59.57	4.44	---	λmax 215 mμ (log ξ = 4.25) λmax 252 mμ (log ξ = 4.29) λmax 282 mμ (log ξ = 3.77)

4.7. Hydrogenation of Euryopsonol.

Euryopsonol was hydrogenated on a micro scale with various catalysts in different solvents. The results are summarised in Table 5.

TABLE 5/.....

TABLE 5.

Weight of euryopsonol.	Catalyst	Solvent	Volume of hydrogen absorbed at N.T.P.	Mols. H_2 absorbed per mol. euryopsonol.	Remarks.
12.50 mg.	2% Pd/$CaCO_3$	ethanol	2.34 ml.	2.0[1]	
9.70 mg.	2% Pd/$CaCO_3$	ethanol	1.69 ml.	2.0[1]	
15.35 mg.	30% Pd/$BaSO_4$	ethanol	2.70 ml.	1.97	
19.60 mg.	30% Pd/$BaSO_4$	ethanol	3.36 ml.	1.90	
21.75 mg.	30% Pd/$BaSO_4$	ethanol	4.17 ml.	2.12	λ = 280 mμ (log ξ = 2.64) (3.5% unreacted euryopsonol)
21.32 mg.	PtO_2	ethanol	3.80 ml. over 3 hours.	---	No end point. (11% unreacted euryopsonol).
13.25 mg.	PtO_2	acetic acid	3.34 ml. over 1.25 hours.	2.8	No end point.

A macro hydrogenation was carried out by shaking a mixture of euryopsonol (0.350 g), 10% palladium /$BaSO_4$[114] (0.65 g) and ethyl alcohol (100 ml) under hydrogen for 3.5 hours, when 57 ml. of hydrogen at N.T.P. (1.90 mols.) were absorbed. After the catalyst had been filtered off, the filtrate showed λ max = 280 mμ (log ξ = 2.76), corresponding to the presence of about 4% unchanged euryopsonol. Thin layer chromatography on silica gel plates, run in 30% ethyl acetate in benzene and developed by spraying with 30% chlorosulphonic acid in acetic acid, showed a major spot at R_F = 0.27, with a minor spot at 0.43 relating to euryopsonol. Removal of the solvent left an oil, which was extracted with peroxide free ether and dried (Na_2SO_4). Removal of the solvent left a completely clear oil (200 mg), which could not be induced to crystallise and failed to form a 2, 4-dinitrophenylhydrazone derivative.

4.8. Hydrogenation of Euryopsol.

Hydrogenations were carried out in ethyl alcohol and acetic acid over Adam's catalyst and palladium /$BaSO_4$, but no definite volume of hydrogen was absorbed. A solution of euryopsol in chloroform showed no colour change with tetranitromethane,[115] suggesting the absence of unsaturation.

4.9. Preparation of Euryopsonol Acetate.[1]

Euryopsonol (208.5 mg.) was dissolved in redistilled acetic anhydride (3 ml) and dry pyridine (4 drops) added. The mixture was left at room temperature for 20 hours and the solvent removed under reduced pressure. The crystalline residue, after two recrystallisations from methyl alcohol, had m.p. 196-197 (recorded m.p. 196 - 198°.

Found[1]: C = 70.4, 70.4%

H = 7.7, 7.9%

λ max = 280 mμ (log ξ = 4.17)

Calculated for $C_{17}H_{22}O_4$:

C = 70.32%, H = 7.64%

4.10. Hydrolysis of Euryopsonol Acetate.

A solution of euryopsonol acetate (58.0 mg) in methyl alcohol (5 ml) containing KOH (0.2 g) was refluxed for 2 hours. Water (10 ml) was added and the methyl alcohol removed under reduced pressure. The mixture was extracted with ether (4 x 15 ml), the extract washed with water and dried (Na_2SO_4). Removal of the solvent afforded a crystalline product (36 mg) m.p. 226 - 227°, identical with authentic euryopsonol.

4.11. Tetrahydroeuryopsonol Acetate.

A solution of euryopsonol acetate (20.7 mg) in ethyl alcohol (10 ml) was shaken under hydrogen with 30% Pd/$BaSO_4$[114] (39.8 mg), 3.11 ml. (1.95 mols.) hydrogen at N.T.P. being absorbed. Filtration and removal of the solvent left 17.4 mg. of solid m.p. 128 - 138°. Repeated recrystallisation raised

the m.p./.....

the m.p. to 135 - 140°.

Found: C = 68.57%, H = 8.74%

λ max = 280 mμ (log ξ = 2.55) indicating the presence of about 2.3% unreacted euryopsonol acetate.

Calculate for $C_{17}H_{26}O_4$:

C = 69.36%, H = 8.90%.

4.12. Attempted Oxidation of Euryopsonol Acetate with Sodium Dichromate.[116,117].

Euryopsonl (286.5 mg) was converted to its acetate by heating at 100° in acetic anhydride (3 ml.) for 6 hours. The excess acetic anhydride was decomposed with water (2 ml.) and the solution added to a solution of sodium dichromate dihydrate (507.4 mg) in acetic acid (7 ml.). The mixture was heated in a glycerine bath at 100 - 103° for 5.25 hours and ethyl alcohol (1.5 ml) and hot water(40 ml) added. The resulting crystalline precipitate (86 mg) had m.p. unchanged on admixutre with euryopsonol acetate.

4.13. Euryopsonol Acetate 2,4 Dinitrophenylhydrazone.

A solution of euryopsonol acetate (54.9 mg) in ethyl alcohol (3 ml) was added to a warm solution of 2,4 dinitrophenylhydrazine (40 mg) in ethyl alcohol (2 ml), containing one drop of concentrated sulphuric acid.[118] After 24 hours the crystalline product (47.5 mg) was filtered off and recrystallised to a constant melting point of 278 - 279°, from ethyl acetate (4 ml).

Found: C = 58.41, 57.90%

H = 5.76, 5.45%

N = 11.14, 11.80%

λ max 390 mμ, (log ξ = 4.51).

Calculated for $C_{23}H_{26}N_4O_7$:

C = 58.72%, H = 5.57%, N = 11.91%

4.14 Euryopsol/.....

4.14. Euryopsol acetate.

A solution of euryopsol (237.3 mg), m.p. 165-167°, in redistilled acetic anhydride (3 ml) and dry pyridine (10 drops) was heated at 120-125° for 4 hours, then left at room temperature for 12 hours. The excess acetic anhydride was decomposed with water (2 ml) and the mixture extracted with ether (5 x 15 ml). The ethereal solution was washed with a dilute solution of sodium carbonate and with water, then dried (Na_2SO_4). Filtration and removal of the solvent left a clear yellow oil, which could not be crystallised. The oil was distilled at 10^{-3} cm pressure, between 110-120° as a viscous fluorescent oil.

Found: C = 70.69%, H = 7.72%.

The acetate was prepared in acetyl chloride-pyridine and acetic anhydride-pyridine (room temperature), but in each case, the oily product failed to crystallise.

4.15. Hydrolysis of Euryopsol Acetate.

A solution of euryopsol acetate (90 mg) in methyl alcohol (5 ml) containing potassium hydroxide (0.2 g) was refluxed for 4 hours. Water (5 ml) was added to the resulting dark brown solution and the solvent removed under reduced pressure. The precipitate, which formed, was filtered off, m.p. 200-203°.

A solution of euryopsol (12.0 mg), m.p. 170-173°, was heated in hot ethyl alcohol for 30 minutes. Addition of water resulted in a precipitate, m.p. 175°.

Euryopsol (30 mg) m.p. 169-170°, was refluxed in ethyl alcohol (2 ml) and water (0.5 ml) containing KOH (0.15 g) for 1.5 hours. The solution, which had darkened slightly, was diluted with water (4 ml) and cooled in ice. The resulting precipitate, m.p. 184°, showed an intermediate melting point on admixture with authentic euryopsol.

The infrared spectra of euryopsol and the hydrolysis product, m.p. 200-203°, showed these compounds to be identical.

On recrystallisation/.....

On recrystallisation from water-ethyl alcohol, the melting point dropped to 174-175°.

4.16. Euryopsonol Benzoate.[119]

A mixture of euryopsonol (81.6 mg), dry pyridine (3 ml) and benzoyl chloride (6 drops) was kept at room temperature for 24 hours. Water (15 ml) was added and the mixture extracted with ether. The ether extract was washed with N H_2SO_4 to remove traces of pyridine, then with 10% aqueous Na_2CO_3, water and dried (Na_2SO_4). Removal of the solvent and recrystallisation from ethyl alcohol afforded 52.9 mg of white needles, m.p. 164-165°.

Found : C = 74.32, 74.42, 74.22%

H = 7.01, 7.01, 7.08%.

Calculated for $C_{22}H_{24}O_4$:

C = 74.98%, H = 7.19%

4.17. Attempted Preparation of Euryopsol Benzoate.

A mixture of euryopsol (563 mg), dry pyridine (15 ml) and redistilled benzoyl chloride (3 ml) was kept at room temperature for 36 hours. Water (25 ml) was added and the mixture extracted with dichloromethane (5 x 25 ml) which was washed with N HCl, 10% aqueous sodium carbonate and water. The extract was decolourised with charcoal, dried (Na_2SO_4) and evaporated to give a clear light-yellow oil (722 mg), which was distilled at 120°/5 x 10^{-4} m.m. It crystallised partly, but could not be satisfactorily purified.

4.18. Attempted Tosylation of Euryopsol.[120]

p-Toluene sulphonyl chloride (267.3 mg) was added to a solution of euryopsol (60.4 mg) in dry pyridine (2 ml), the mixture shaken at room temperature for 0.5 hour, then heated on a steam bath for a further 0.5 hour. The excess chloride was decomposed with ice and extracted as in 7.16. Removal of the solvent left 48.5 mg. of clear oil which could not be crystallised.

4.19. Euryopsonol 2,4-Dinitrophenylhydrazone.[121]

A solution of euryopsonol (49 mg) in hot ethyl alcohol (1 ml) was added to a solution of 2,4-dinitrophenyldrazone (49 mg) in hot diglyme (1 ml). Concentrated hydrochloric acid (2 drops) and methyl alcohol (1 ml) were added and the mixture left at room temperature overnight. The orange crystals (52 mg) which separated, were filtered off and recrystallised from ethyl acetate, m.p. 285-286° (dec). Recorded m.p. 288.5-289°.

Found: C = 53.80%, H = 5.74%, N = 12.48%

λ max = 391 mμ (log ξ = 4.51)

Calculated for $C_{21}H_{24}O_6N_4$:

C = 58.89%, H = 5.65%. N = 13.08%

4.20. Periodic Acid Oxidation of Euryopsol.[122]

(i) To a solution of euryopsol (137.7 mg) in ehtyl alcohol (10 ml), 0.1936 N periodic acid (15 ml) was added, the mixture left at room temperature for 42 hours, 0.9576 N sodium arsenite solution (30 ml) added and the excess arsenite titrated with 0.09326 N iodine solution (12.70 ml). It was found that 1.23 mols. periodic acid oxidised one mol. euryopsol. Steam distillation into a solution of 2,4-dinitrophenylhydrazine did not give a precipitate, thus no formaldehyde was formed.

(ii) A solution of euryopsol (383.1 mg) and periodic acid (967.7 mg) in ethyl alcohol (15 ml) and water (2 ml) was kept at room temperature for 58 hours. The excess acid was decomposed with ethylene glycol (1.5 ml) at room temperature for 36 hours. Water (60 ml) was added and the product extracted with ether (5 x 20 ml), washed with 10% aqueous sodium carbonate water and dried (Na_2SO_4). Removal of the solvent left an oil (265.2 mg) which was subjected to distillation at 6 x 10^{-3} m.m. Raising the temperature to 70° caused the oil to darken into a green resinous gum, which failed to distil.

4.21. Dehydroeuryopsonol.

To a solution of euryopsonol (1.000 g), m.p. 227-230°, in

pure acetone/.....

pure acetone (70 ml) (distilled over potassium permanganate), the oxidant, a solution of chromium trioxide in dilute sulphuric acid[123] (8N with respect to oxygen), (1.6 ml) was added dropwise from a microburette until a peristant orange-brown colouration indicated that oxidation was complete. The mixture was kept at 17° for 5 minutes, after which period, water (100 ml) and ethyl alcohol (2 ml) was added. After reduction of the volume to 110 ml, the mixture was left at 5° overnight. The white crystals (0.370 g) m.p. 215-217° were filtered off and dried in vacuo. The product crystallised as white needles (.650 g) m.p. 221 - 3° from methyl alcohol (40 ml). Concentration of the mother liquors afforded a further .220 g, m.p. 214-215°. Dehydroeuryopsonol sublimed readily at 150°/ 15×10^{-4} m.m.,the sublimate melting at 224-5°.

Found: C = 72.91, 72.97%

H = 7.65, 7.50%

λ max (EtOH) = 280, (log ξ = 4.16)

λ max (EtOH - NaOH) = 280, (log ξ = 4.16)

$[\alpha]_D^{16}$ = - 69°

Calculated for $C_{15}H_{18}O_3$:

C = 73.17%, H = 7.36%

4.22. Colour tests on Dehydroeuryopsonol.

(a) When a drop of aqueous $FeCl_3$ was added to a solution of dehydroeuryopsonol (5 mg) in ethyl alcohol (0.5 ml), the colour was unchanged, accordingly dehydroeuryopsonol is not an α-diketone[124] nor an enolic β-diketone.

(b) Dehydroeuryopsonol (3 mg) in freshly prepared Tollens reagent[124] gave a negative result, thus it is not an aldehyde.

(c) Zimmerman test[123]:- A solution of dehydroeuryopsonol (1 mg) in 2 N ethanolic potassium hydroxide, when mixed with 1% m-dinitrobenzone (1 ml) gave a light purple colour, which intensified after five minutes. As euryopsonol on similar treatment gave a/.....

ment gave a negative test, dehydroeuryopsonol thus contains an unhindered methylene group adjacent to the newly formed ketone.

4.23. Dehydroeuryopsonol Oxime.[125]

A solution of dehydroeuryopsonol (33 mg) in ethyl alcohol (1 ml) was added to a solution of sodium acetate (112 mg) and hydroxylamine hydrochloride (45 mg) in ethyl alcohol (1 ml) and water (3 drops) and the mixture refluxed for 1.5 hours. The volume was reduced to 1 ml, the solution cooled and the crystals, which separated, filtered off. Recrystallisation from methyl alcohol-water (1:1) gave 26.5 mg. of dehydroeuryopsonol oxime, m.p. 198-200°.

Found: C = 69.00%, H = 7.62%, N = 4.71%,

Calculated for $C_{15}H_{19}O_3N$:

C = 68.94%, H = 7.33%, N = 5.36%

4.24. Attempted Preparation of Euryopsonol Oxime.

Euryopsonol was treated and worked up as in 4.23 and gave unchanged material.

4.25. Attempted Preparation of Euryopsonol Semicarbazone.

A solution of euryopsonol (42 mg) in ethyl alcohol (1 ml) was added to a solution of sodium acetate (100 mg) and semicarbazine hydrochloride (60 mg) in ethyl alcohol (2 ml) and water (3 drops). The mixture was refluxed and worked up as usual. The crystalline precipitate m.p. 228-230° did not contain nitrogen and the melting point was unchanged on admixture with euryopsonol.

4.26. Attempted Preparation of Dehydroeuryopsonol 2,4-Dinitrophenylhydrazone.

Dehydroeuryopsonol (21 mg) was dissolved in ethyl alcohol (1 ml) and the solution added to a solution of 2,4 dinitrophenylhydrazine (34 mg) in ethyl alcohol (2 ml) and concentrated sulphuric acid (3 drops).

The orange/.....

The orange precipitate was quite insoluble in normal solvents and could not be recrystallised.

4.27. Furfurylidene Derivative of Dehydroeuryopsonol.[126,127]

A mixture of freshly distilled furfural (0.2 ml) and 30% aqueous sodium hydroxide (0.4 ml) was added to a solution of dehydroeuryopsonol (120 mg) in ethyl alcohol (15 ml) and the mixture kept at room temperature for 4.5 hours. The volume was reduced to 4 ml. and the mixture kept at 5° overnight. The yellow crystals (111 mg) after recrystallisation from ethanol had m.p. 213-214.5°. Thin layer chromatography, on silica gel plates, run in 30% ethyl acetate in hexane and developed by spraying with 30% chlorosulphonic acid in acetic acid and heating to 100°, showed that no dehydroeuryopsonol was present in this material.

Found : C = 73.62%, H = 6.23%

λ max = 285 mμ (log ξ = 4.26)

(α, β, γ, δ-unsaturated ketone).

λ max = 326 mμ (log ξ = 4.34)

(α, β-unsaturated furfurylidene ketone).

Calculated for $C_{20}H_{20}O_4$:

C = 74.06%, H = 6.21%

4.28. Attempted Dehydration of Euryopsonol.

Euryopsonol (52.8 mg) was intimately mixed with alumina (151 mg)[31] and heated at 190°/0.05 m.m. over three hours. The sublimate (34.5 mg), m.p. 215-218°, which formed was shown by mixed melting point and infrared spectrum to be identical with authentic euryopsonol.

4.29. Dehydration of Euryopsol.

(a) Euryopsol (98.4 mg) was intimately mixed with alumina[31] (200.6 mg) and heated at 140° as in 4.28. The sublimate

(63 mg) was/.....

(63 mg) was recrystallised as white needles from ethyl alcohol (32 mg) m.p. 174-5°, identical with starting material. The residue was shaken with alcohol and filtered. The filtrate had an intense green colour and the oil, obtained on removal of the solvent, could not be induced to crystallise.

(b) Euryopsol (100 mg) was mixed with anhydrous potassium hydrogen sulphate[128] (210.5 mg) and heated at 140° /0.05 m.m. for three hours in a sublimation apparatus. The green oil, which collected on the cold finger, failed to crystallise.

4.30. Reaction of Euryopsonol with Borontrifluoride diethyl etherate.[129]

Borontrifluoride diethyl etherate (6 drops) was added to a solution of euryopsonol (98 mg) in tetrahydrofuran and the mixture was heated under reflux for 1 hour, then kept at room temperature for 74 hours. Water (10 ml) was added and the mixture extracted with ether. The ethereal extract was washed with 10% aqueous sodium bicarbonate, water, dried (Na_2SO_4) and the solvent removed to give a solid, which recrystallised from ethyl alcohol; yield 63 mg. This was shown by mixed melting point and infrared spectrum to be identical with authentic euryopsonol.

4.31. Reaction of Dehydroeuryopsonol with Borontrifluoride diethyl etherate.[129]

Dehydroeuryopsonol (100 mg) was treated with borontrifluoride diethyl etherate as in 4.30 to afford a white crystalline product (95 mg) identical in all respects with authentic dehydroeuryopsonol.

4.32. Attempted Preparation of Acetonide[130] of Euryopsol.

Euryopsol (303 mg) was dissolved in pure dry acetone (15 ml) and decinormal hydrochloric acid (4drops) added. The mixture was heated at 55° for 3 minutes and kept at room

temperature for/.....

temperature for 26 hours. The intensely green solution was diluted with water (50 ml), the acetone removed under reduced pressure and extracted with chloroform (4 x 20 ml). The extract was washed with 10% aqueous sodium carbonate, water, dried (Na_2SO_4) and the solvent removed to give a dark gum (196 mg), which could not be decolourised nor induced to crystallise.

4.33. Reaction of Euryopsonol and Euryopsol with Sodium hypoiodite Solution.[131-134]

(a) To a solution of euryopsonol (31 mg) in dioxane (3 ml) containing 10% sodium hydroxide (0.5 ml), an iodine-potassium iodide solution (2 g iodine and 1 g potassium iodide dissolved in 8 ml. water) was added until a permanent iodine colour persisted. The mixture was kept at room temperature for five minutes, then heated at 60° for 2 hours.

Euryopsonol did not deposit iodoform under these conditions.

(b) Euryopsol (32 mg) was treated as in (a) and also failed to deposit iodoform.

4.34. Reaction of Euryopsol with 0.2 N Hydrochloric Acid in Ethyl Alcohol in the Presence of Adam's Catalyst under Hydrogen.

A mixture of euryopsol (167.8 and 147.2 mg), Adam's Catalyst (180 mg) and 0.2 N hydrochloric acid in ethyl alcohol was shaken under hydrogen for 4 hours at 60°, when 71.4 and 66.0 ml. of hydrogen (5.1 and 5.3 mols) were absorbed. All attempts to extract the product from the colourless solution resulted in a green gum, which failed to crystallise and could not be decolourised with charcoal.

4.35. Action of Concentrated Hydrochloric Acid on Euryopsol.

Concentrated hydrochloric acid (4 ml.) was added to a solution of euryopsol (215 mg) in ethyl alcohol (4 ml) and the mixture heated under reflux for 0.5 hours. The green precipitate (180 mg), m.p. 200-220°, was filtered off (filtrate colourless) and found/.....

less) and found to be readily soluble in ethyl alcohol and aqueous sodium hydroxide. All attempts to decolourise or recrystallise this precipitate failed. The ultraviolet spectrum showed a broad shoulder with

λ max EtOH - HCl = 295 mμ (log ξ = 3.70).

4.36. Action of p-Toluensulphonic Acid on Euryopsonol and Euryopsol.

(a) To a solution of euryopsonol (103.7 mg) in acetic anhydride (10 ml), p-toluensulphonic acid (25 mg) was added. The mixture was heated at 120° for 2 hours in which time it turned green. The excess anhydride was decomposed with water and the solution extracted with chloroform. The extract was washed with 10% aqueous sodium carbonate, water, dried (Na_2SO_4) and the solvent removed to give a green gum (85 mg), which failed to crystallise.

(b) A solution of euryopsol (248 mg) and p-toluenesulphonic acid (43 mg) in benzene (5 ml) was refluxed under nitrogen for 3 hours. The green solution was washed with water and dried (Na_2SO_4). Removal of the solvent afforded a brown gum (248 mg) which could not be crystallised.

4.37. Action of 10% Sulphuric Acid in Acetic Acid on Euryopsonol.

A solution of euryopsonol (184 mg) in a mixture of concentrated sulphuric acid and acetic acid (1:10) (1 ml) was heated at 80° for 12 minutes. The green solution was cooled, diluted with water (4 ml) and the precipitate (180 mg), m.p. 186-188°, filtered off and washed with water. Recrystallisation of the dried product in benzene-hexane (1:2) (2ml) gave long colourless needles (142 mg), m.p. 198-199°. Mixed melting point, elemental analysis and infrared spectrum showed this product to be identical with euryopsonol acetate.

Found: C = 70.13%, H = 7.67%

Calculated for $C_{17}H_{22}O_4$:

C = 70.32%, H = 7.64%

4.38 Action of/.....

4.38. Action of 10% Sulphuric Acid in Acetic Anhydride on Euryopsonol, its derivatives and on Euryopsol.

(i) Euryopsonol. A solution of euryopsonol (32 mg) in a mixture of sulphuric acid and acetic anhydride (1:10) (0.5 ml) was heated at 80° for 12 minutes. The green solution was cooled and diluted with water (5 ml) but failed to afford any crystalline material.

(ii) Dehydroeuryopsonol under the same conditions as (i) gave a green colour more intense than euryopsonol and also failed to afford any crystalline product.

(iii) Euryopsonol acetate gave a green colour comparable to the intensity obtained from euryopsonol.

(iv) Euryopsol. A solution of euryopsol (16 mg) in the above sulphuric acid - acetic anhydride mixture (0.5 ml) was heated as in (i). It turned a wine red colour, changing to pale blue after about 4 hours.

4.39. Ehrlichs Test.[95,135]

The reagent was prepared by dissolving p-dimethylaminobenzaldehyde (100 mg) in ethyl alcohol (3 ml), cooling and adding concentrated hydrochloric acid (3 ml).

(i) Euryopsonol. The above reagent was added to a solution of euryopsonol (10 mg) in ethyl alcohol (0.5 ml). No colour was produced.

(ii) Euryopsol under the same conditions as (i) gave an intense purple colour which turned brown after half an hour.

(iii) Euryopsol Acetate was prepared by refluxing euryopsol (30 mg) in acetic anhydride (2 ml) and pyridine (3 drops) for 0.5 hour. The solvent was removed under high vacuum and the residue dissolved in ethyl alcohol (1 ml). On adding the reagent, the solution turned an intense indigo-blue colour.

4.40. Perbenzoic Acid oxidation of Euryopsonol and Euryopsol.

The perbenzoic acid was prepared in chloroform[136] and the

content determined/.....

content determined[137] as follows:- To perbenzoic acid (5 ml), acetic acid (15 ml) and a solution of potassium iodide (500 mg) in water (3 ml) were added, and the mixture allowed to stand for 5 minutes. Water (60 ml) was added and the free iodine titrated with a 0.1 N standard solution of sodium thiosulphate.

(i) The rate of reaction was determined by allowing 0.1 m. mole (25 mg) to react with 0.35 m.mole. perbenzoic acid at room temperature for varying times and back titrating the unchanged perbenzoic acid. The results are summarised in Table 6.

TABLE 6.

		Time of reaction.	Mols. perbenzoic acid absorbed per mol. of compound.
(a) Euryopsenol	1.	4.25 hours.	No absorption.
	2.	22.5 hours,	No absorption.
	3.	70.0 hours.	No absorption.
(b) Euryopsol	1.	16.0 hours.	1.73
	2.	33.25 hours.	1.79
	3.	40.0 hours.	1.70
	4.	66.0 hours.	2.08

(ii) Euryopsol (1.013 g; 3.8 m.mols.) was dissolved in perbenzoic acid solution (120 ml), (8.0 m.mols.) and stored at 5° for 42 hours. The chloroform solution was washed with 3N sodium hydroxide, water and dried. Removal of the solvent left a pale yellow oil, which was refluxed with 10% ethanolic potassium hydroxide (20 ml) under nitrogen for 2 hours. The solution, which had darkened on saponification, was diluted with water (100 ml) and extracted with peroxide-free ether (3 x 60 ml). This ethereal extract afforded a clear yellow oil (0.24 g), which was not investigated further.

The aqueous layer was acidified with 5N HCl (8 ml) and

extracted with/.....

extracted with ether (3 x 70 ml). The brown ethereal extract was washed with water and dried (Na_2SO_4). Removal of the solvent left a light brown crystalline solid (0.74 g), which on sublimation (80-85° /5 x 10^{-3} m.m.) afforded colourless needles (0.50 g), m.p. 120-121° of benzoic acid (mixed m.p. and equivalent weight).

(iii) Ehrlich test. Euryopsol (39 mg) was treated with excess perbenzoic acid for 41 hours, after which time, it failed to give a colour with Ehrlich's reagent.

4.41. Perbenzoic Acid Oxidation of Acetylated Euryopsol.

(i) The rate of reaction was determined by heating a solution of euryopsol (25 mg portions) in acetic anhydride (0.5 ml) and dry pyridine (4 drops) at 120° for 0.5 hours. The excess anhydride was removed under high vacuum and the residue allowed to react with perbenzoic acid (0.35 m.mol.) at 5° for varying times. The results are summarised in Table 7.

TABLE 7.

Time of reaction.		Mols. perbenzoic acid absorbed per mol. euryopsol.
1.	13 hours.	1.12
2.	41 hours.	1.16
3.	65 hours.	1.07
4.	(acetylated at room temperature. 22.5 hours.	0.99

(ii) Euryopsol (500 mg) was acetylated in acetic anhydride (11 ml) and dry pyridine (0.5 ml) at room temperature for 24 hours. (No colouration occurred at this low temperature). The solvent was removed under reduced pressure and 50°, leaving a clear yellow oil, which was dissolved in chloroform (2 ml). Perbenzoic acid solution (1.1 mols.) was added, the mixture kept at 5° for 27 hours, washed with 3N sodium hydroxide

(5 x 30 ml), water/.....

(5 x 30 ml), water and dried (Na_2SO_4). Removal of the chloroform left a yellow oil, which was refluxed with 5% ethanolic sodium hydroxide (20 ml) under nitrogen for 1 hour, then kept at room temperature for 22 1/2 hours. Tne saponification product was worked up as in 4.40 (ii). The sublimate (126 mg) was also found to be benzoic acid.

(iii) Ehrlich test. Euryopsol (39.2 mg) was acetylated and treated with perbenzoic acid solution for 41 hours as in 4.41(i). The solution was diluted with ethyl alcohol (0.5 ml) and failed to give a colour with Ehrlich's reagent.

4.42. Preparation of Thioketal of Dehydroeuryopsonol.

To a solution of dehydroeuryopsonol (300 mg) in analar acetic acid (8 ml), ethanedithiol (0.5 ml) and borontrifluoride diethyletherate (0.2 ml) were added and the mixture kept at room temperature for 45 hours. The mixture was diluted with water (40 ml) and cooled in ice. A solution of potassium hydroxide (13 g) in water (25 ml) was added and the precipitate filtered and dried. The crude precipitate (300 mg) was dissolved in boiling ethyl alcohol (50 ml) the solution filtered and the volume reduced to 15 ml. to give 230 mg. of dehydroeuryopsonolthioketal, m.p. 184-186°. This product sublimed readily at 110-120°/1 x 10^{-3} m.m. (3hours); the sublimate melting at 186-7°.

Found: C = 63.46%, H = 6.92%

Calculated for $C_{17}H_{22}O_2S_2$:

C = 63.30%, H = 6.88%

4.43. Raney Nickel Desulphuration of Dehydroeuryopsonolthioketal. Preparation of Deoxydehydroeuryopsonol.

A solution of dehydroeuryopsonolthioketal (123 mg) in methyl alcohol-acetone (18 ml, 1:1) was heated under reflux for 9 hours with freshly prepared Raney nickel (2 g).[138] The solution was filtered through a celite pad, the solvent

removed and/.....

removed and the product dissolved in acetone (5 ml) and then kept at 5°. The crystalline precipitate (87 mg) was filtered off and chromatographed on neutral alumina (5 g), using benzene-hexane 1:1 as eluant. Thin layer chromatography of the product (41 mg) on silica gel in benzene-ethyl acetate (3:2) and spraying with 30% chlorosulphonic acid in acetic acid showed a single spot, R_F = 0.70. Crystallisation from hexane-benzene (5:1) followed by sublimation at 90°/1 x 10^{-2} m.m. afforded needles of deoxydehydroeuryopsonol, m.p. 145°.

Found: C = 78.02%, H = 8.76%

$[\alpha]_D^{17}$ = - 20°

λ max = 280 mμ, (log ξ = 4.17).

Calculated for $C_{15}H_{20}O_2$:

C = 77.55%, H = 8.36%.

4.14 Preparation of 2,4-Dinitrophenylhydrazone of Deoxydehydroeuryopsonol.[121]

To a solution of deoxydehydroeuryopsonol in ethyl alcohol (1 ml) a solution of 2,4 dinitrophenylhydrazine (32 mg) in hot diglyme (1 ml) and concentrated hydrochloric acid (2 drops) were added. After being kept at room temperature for 36 hours, the crystalline product was filtered off and recrystallised from ethyl acetate (15 ml) to afford orange needles (20 mg) of deoxydehydroeuryopsonol 2,4-dinitrophenylhydrazone m.p. 283° (dec.)

Found: C = 62.18%, H = 6.21%, N = 13.94%.

Calculated for $C_{21}H_{24}O_5N_4$:

C = 61.16%, H = 5.87%, N = 13.58%.

4.15. Manganese Dioxide Oxidation of Euryopsol.[111]

(i) A solution of euryopsol (33 mg) in chloroform (8 ml) was shaken with freshly prepared manganese dioxide (4.0 g) for 1 hour. The mixture was filtered and the solvent removed under reduced pressure. Thin layer chromatography of the residue

on silica gel/.....

on silica gel, run in ethyl acetate-benzene (1:1) and developed by spraying with 30% chlorosulphonic acid in acetic acid, showed 2 spots R_F = 0.21 (intense), and 0.50 (faint).

(ii) A solution of euryopsol (32 mg) in benzene (10 ml) was shaken and worked up as in (i). Thin layer chromatography showed 2 spots identical to those of euryopsol.

5. DISCUSSION OF RESULTS.

The aerial portions of Euryops floribundus N.E.Br. were extracted thoughout the year, Table 1, and the content of resinous extract found to vary with season. A maximum content of euryopsonol was found during midsummer and a maximum content of euryopsol during the autumn months.

The leaves were removed and the undried stems and branches cut into small pieces and extracted by steeping in cold acetone for 48 hours. After filtration, the extract was concentrated by flash distillation, the aqueous residue extracted with ether and washed with water. Removal of the solvent left a brown, sticky gum, which was saponified with hot ethanolic potassium hydroxide. Water was added and the alcohol removed under reduced pressure. The residue was extracted with ether, washed with water and dried (Na_2SO_4). Filtration and concentration of the dark red solution afforded a crystalline precipitate, which was clearly a mixture of yellow rhombs and white needles.

The crystalline solid was dissolved in dry tetrahydrofuran, absorbed onto neutral alumina and eluted with dry ether, evaporation of which gave euryopsonol. The column was then eluted with ether containing ethyl alcohol to give relatively pure euryopsol.

5.1. Euryopsonol.

Previous workers showed euryopsonol to have the empirical formula $C_{15}H_{20}O_3$. It formed crystalline acetate and 2,4-dinitrophenylhydrazone/.....

trophenylhydrazone and thus possesses a free hydroxyl group and a keto-group. Euryopsonol is doubly unsaturated affording a non-crystalline tetrahydroderivative, and possesses a single-C-methyl group. Euryopsonol absorbed 1.48 mols. perbenzoic acid, but the epoxide could not be isolated in a pure state.

The infrared spectrum ($CHCl_3$) of euryopsonol (fig 1) showed absorption bands at 3640 cm^{-1} due to a free hydroxyl group, 1670 and 1025 cm^{-1} due to an α, β, γ, δ-unsaturated ketone, while bands at 1563, 1126, 1080 and 880 cm^{-1} were attributed to the ether mode of a furan ring. Euryopsonol did not possess an infrared absorption band due to an exocyclic methylene group and the absence of such a function was confirmed by ozonolysis; no formaldehyde was produced.

The ultraviolet spectrum of euryopsonol showed a maximum at 280 $m\mu$, ($\log \xi = 4.16$),[2] indicative of an α, β, γ, δ-unsaturated ketone and end absorption at 212 $m\mu$ ($\log \xi = 3.32$) corresponding to the above mentioned chromaphores.

Although euryopsonol failed to give a colour with Ehrlich's reagent, it did form a green colour with mineral acids as did the extractives of Petasites officinalis Moench.[2] When euryopsonol was heated with acetic anhydride containing p-toluene sulphonic acid, a light green colour was produced. Solutions of euryopsonol and of euryopsol in 10% sulphuric acid in acetic anhydride turned green; an intense green colour formed with dehydroeuryopsonol. Euryopsonol, refluxed with 10% sulphuric acid in acetic acid, readily afforded euryopsonol acetate.

Two of the oxygen atoms present in euryopsonol had previously been characterised as a hydroxyl group and as a ketone:- The presence of a single hydroxyl group was confirmed by the formation of a mono-acetate and a mono-benzoate and the absence of absorption bands due to a hydroxyl group in the infrared spectrum of euryopsonol acetate (fig.2). The presence of a single keto-group was likewise demonstrated by the formation of a mono-2,4-dinitrophenylhydrazone for both euryopsonol and

euryopsonol acetate/.....

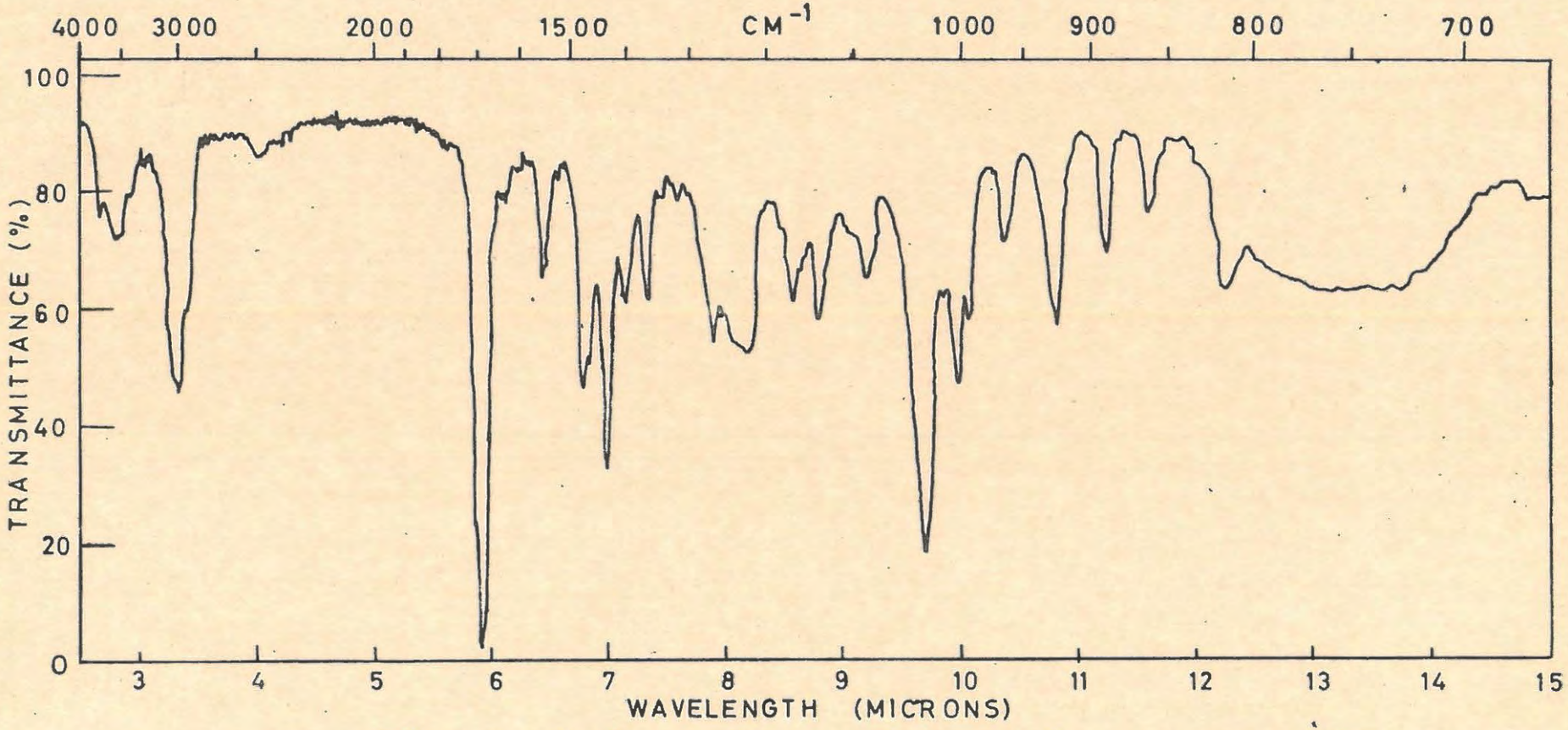


Fig. 1 Infrared spectrum of euryopsonol.

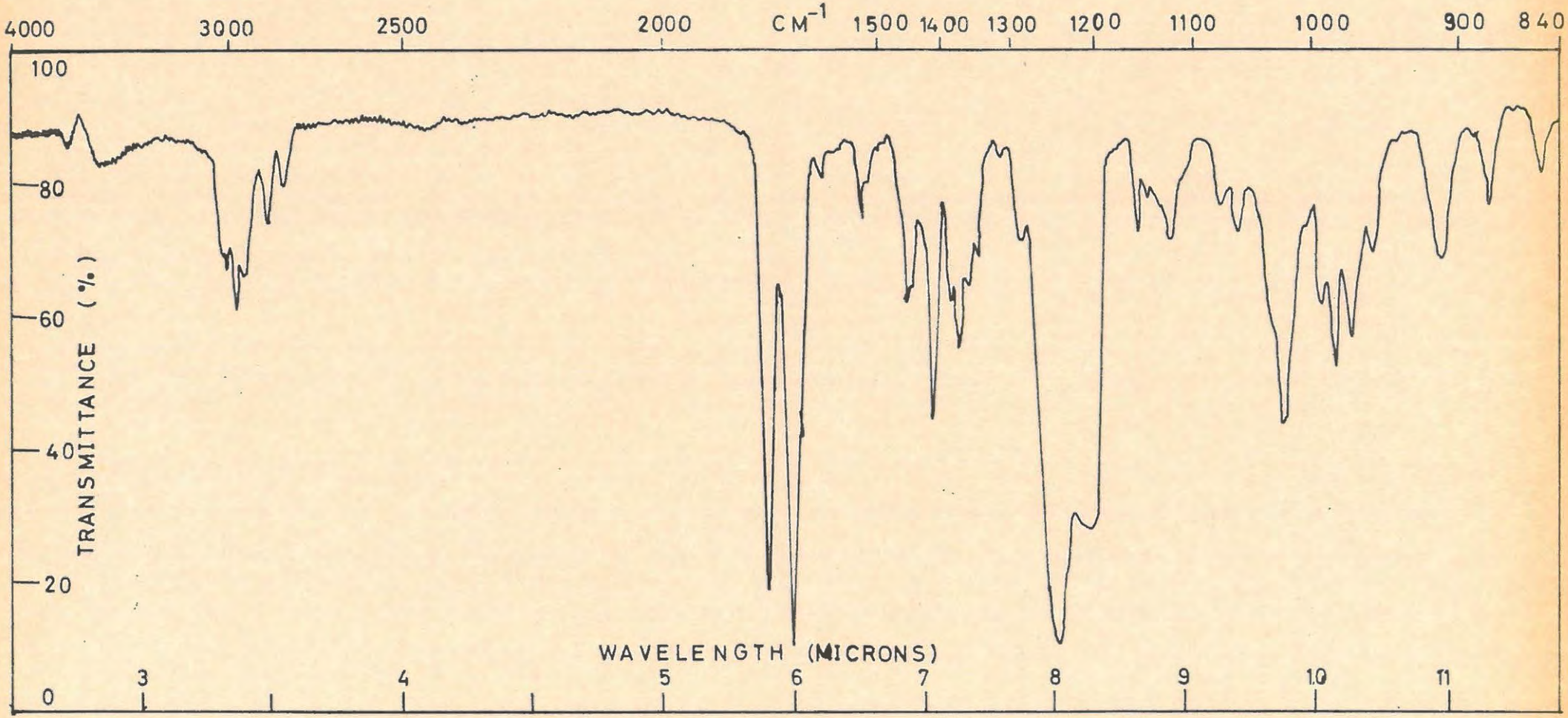


Fig. 2 Infrared spectrum of euryopsonol acetate.

euryopsonol acetate. The infrared spectrum of euryopsonol acetate 2,4-dinitrophenylhydrazone (fig 3) showed a band due to the carbonyl of the acetate group, but lacked the frequencies due to the α, β, γ, δ-unsaturated ketone. The analyses of both these dinitrophenyldrazones ruled out any possibility of them being pyrazolines.[139,140] Accordingly the hydroxyl group is not adjacent to the keto-group. The ultraviolet spectrum of the 2,4-dinitrophenylhydrazones of both euryopsonol and euryopsonol acetate showed broad bands at 330-450 $m\mu$ with maxima at 390 $m\mu$, ($\log \xi = 4.51$), indicative of an α, β, γ, δ-unsaturated ketone.[141]

Acetylation of euryopsonol did not alter the stereochemistry of the free hydroxyl group, for saponification of the acetate regenerated euryopsonol. Euryopsonol acetate was converted to the tetrahydroderivative on mild hydrogenation.

The absence of an epoxide function in euryopsonol was shown by the stability of euryopsonol and dehydroeuryopsonol towards boron trifluoride diethyl-etherate[129]; only unchanged starting material being recovered.

Lithium aluminium hydride reduction of euryopsonol afforded an oily product, which showed absorption at 279 $m\mu$ ($\log \xi = 2.77$) and failed to absorb hydrogen on catalytic reduction. The infrared spectrum of this oil possessed a maximum at 1730 cm^{-1}, attributed to a keto-group in a six-membered ring.

Much effort was expended in attempting to obtain recognisable products from the dehydrogenation of euryopsonol, but without success. Thus, the material obtained on reduction of euryopsonol with lithium aluminium hydride was dehydrogenated directly with 30% Pd/C[113] for 5 hours at 305-310°. Chromatography of the product on alumina gave a fraction reacting with trinitrobenzene to give a small amount of adduct, m.p. 104.5-106°. Analysis showed it be formed from a hydrocarbon $C_{14}H_{16}$. The adduct was decomposed on alumina to the oily hydrocarbon,

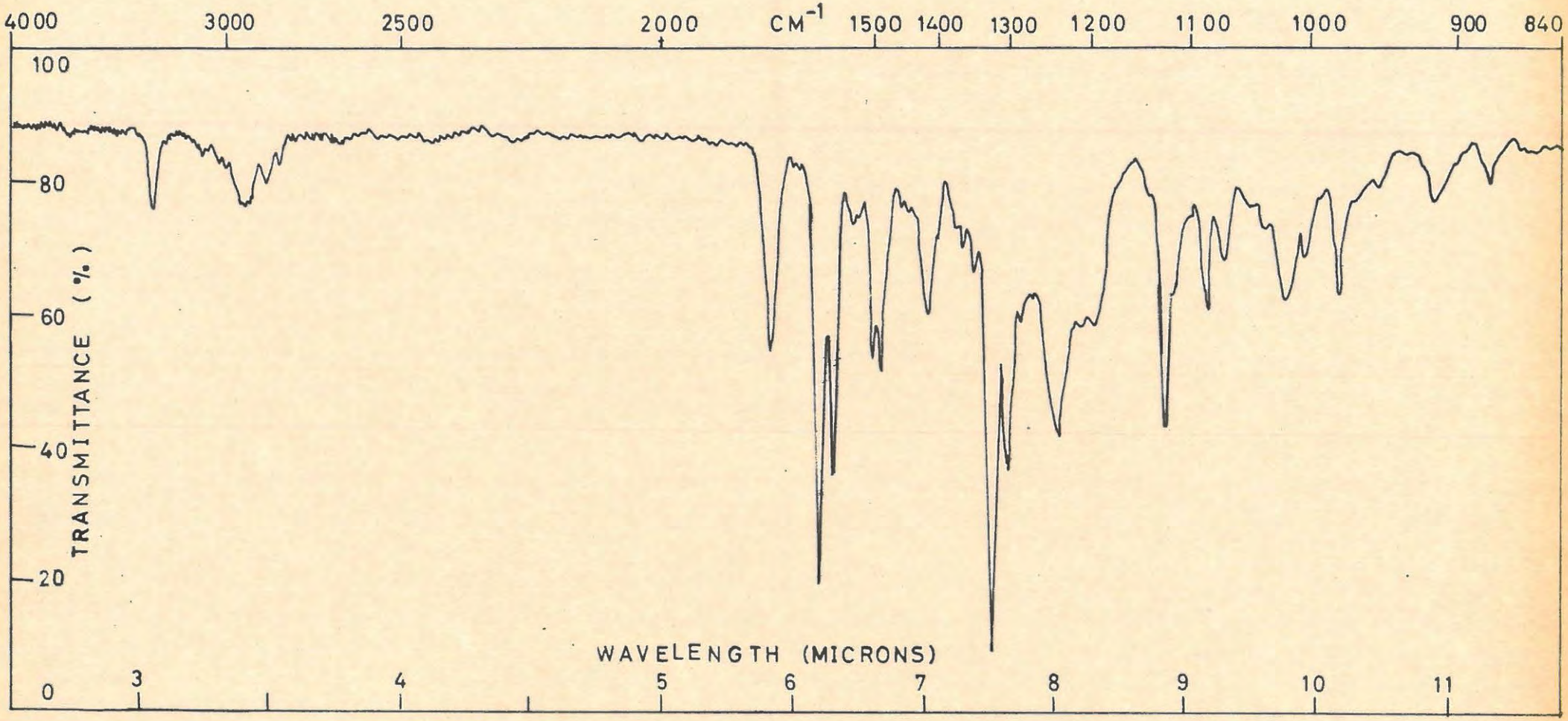


Fig. 3 Infrared spectrum of euryopsonol acetate 2,4-dinitrophenyl-hydrazone.

the ultraviolet spectrum of which indicated that it was a substituted naphthalene.[142] A mixed melting point determination showed that the trinitrobenzene adduct was dissimilar to that obtained from eudalene.[143] Another experiment afforded an adduct with a lower melting point, which could not be raised on repeated recrystallisation. These results together with those obtained from euryopsol are summarised in Table 4.

Euryopsonol was hydrogenated over various catalysts (Table 5). Mild hydrogenation in ethyl alcohol over $Pd/BaSO_4$[114] afforded a non-crystalline tetrahydroeuryopsonol (λ max 279 mμ, log ξ = 2.73), while more vigorous hydrogenation in acetic acid over Adam's catalyst resulted in the uptake of 2.8 mols. of hydrogen, presumably due to both hydrogenation and hydrogenolysis.

The presence of a furan ring in euryopsonol was confirmed by N.M.R. studies of euryopsonol, euryopsonol acetate and tetrahydroeuryopsonol acetate. The spectra of these compounds are shown in figs. 4, 5 and 6 respectively.

<u>The N.M.R. spectrum of euryopsonol</u> (in $CDCl_3$) showed the following bands:-

A. τ = 9.18 (J = 5 c.p.s.) a singlet; an area of three protons due to a tertiary methyl group at C_5.

B. τ = 8.88 (J = 6 c.p.s.) a doublet; an area of three protons due to a secondary methyl group at C_4.

C. τ = 7.98 (J = 6 c.p.s.) a doublet; an area of three protons. The small splitting is due to a methyl group attached at an olefinic carbon atom (C_{11}), shielded at the α position by a quaternary carbon atom and split by a single olefinic proton at the α' carbon atom. Partial structure (233) can thus be assigned to euryopsonol.

D. τ = 6.6 (J = 20 c.p.s.) appears to be a symmetrical multiplet; an area of one proton due to a secondary hydroxyl group.

E. τ = 2.60 (J = 4 c.p.s.) a doublet; an area of one proton present as a vinyl proton, is attributed to the olefinic proton in the furan ring at C_{12}.

F. τ = 7.16 and 7.60/.....

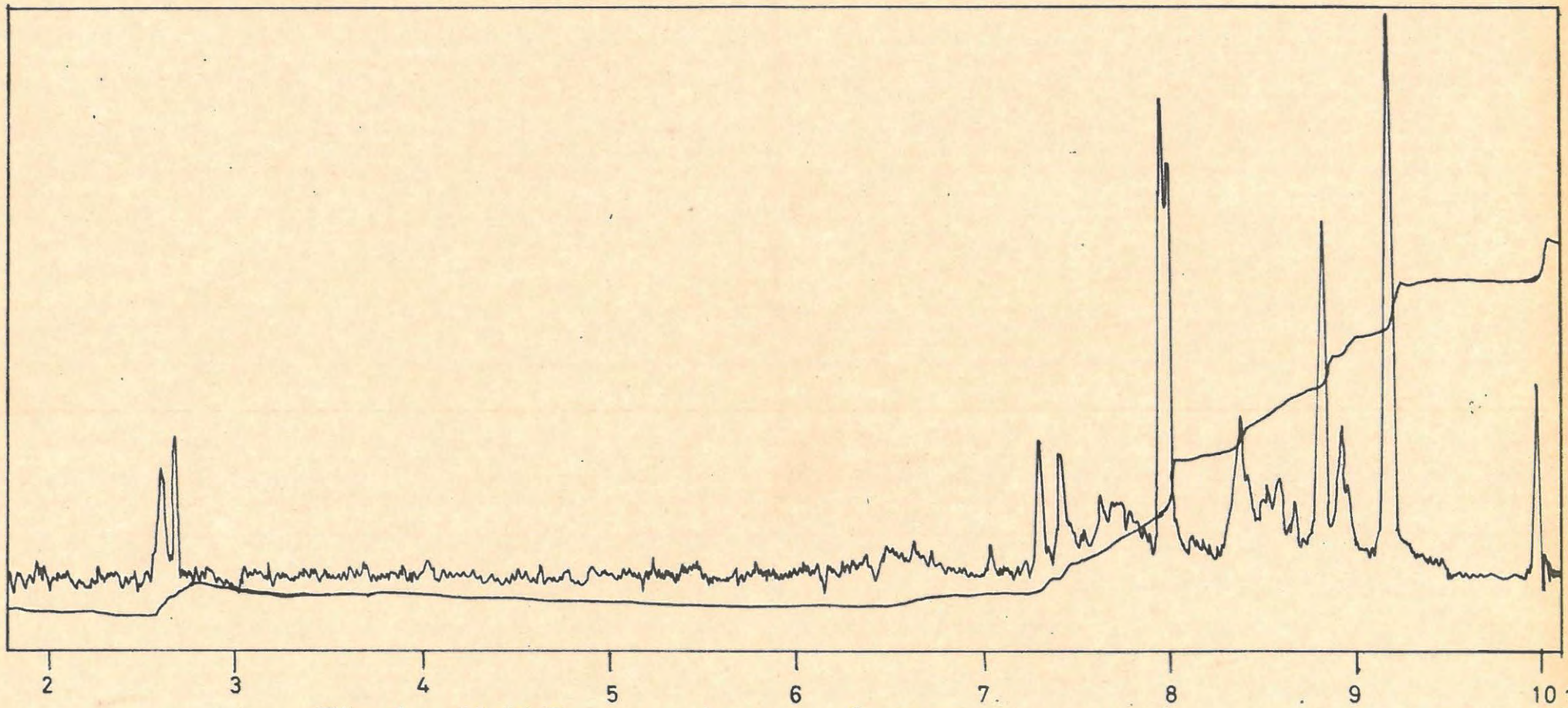


Fig. 4 N.M.R. spectrum of euryopsonol.

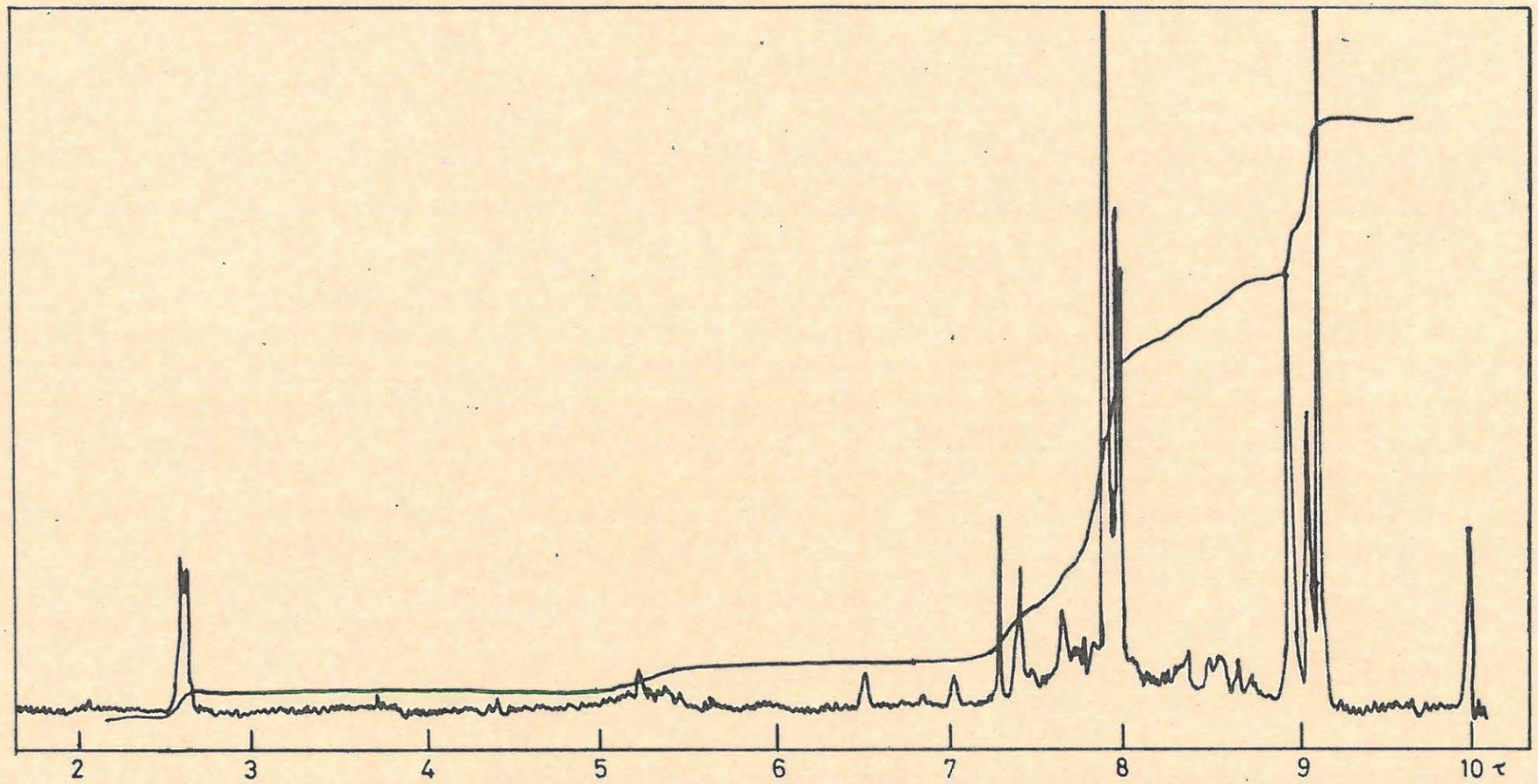


Fig. 5 N.M.R. spectrum of euryopsonol acetate.

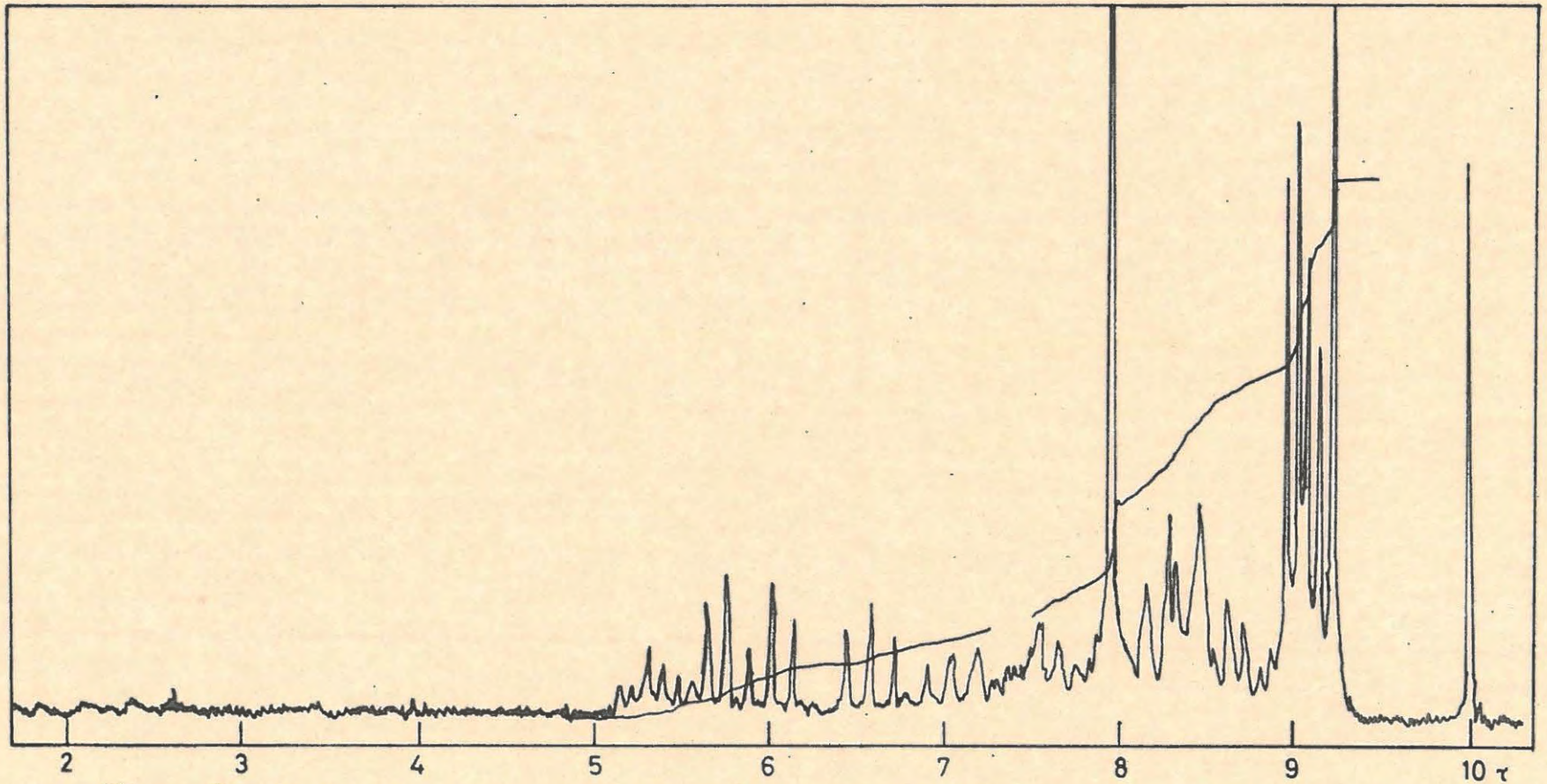


Fig. 6 N.M.R. spectrum of tetrahydroeuryopsonol acetate

F. τ = 7.16 and 7.60 (a group of signals) (J = 16 c.p.s.) could arise from a methylene group attached to a furan ring with a tertiary centre on the next carbon atom.

The N.M.R. spectrum of Euryopsonol Acetate showed the following bands.

A. τ = 9.13 (J = 5 c.p.s.) a singlet; an area of three protons due to a tertiary methyl group at C_5.

B. τ = 8.99 (J = 8 c.p.s.) a doublet; an area of three protons due to a secondary methyl group at C_4.

C. τ = 7.91 - 7.98 an area of six protons:-

τ = 7.91 (J = 4 c.p.s.) a singlet; an area of three protons attributed to an acetoxy methyl group.

τ = 7.98 (J = 4 c.p.s.) a doublet; an area of three protons. The very small splitting could be attributed to the acetate being a mixture of very closely related compounds (e.g. stereoisomers, but is more likely due to a methyl group attached to an olefinic carbon atom (C_{11}), shielded in the α position by a quaternary carbon atom and split by a single olefinic proton at the α' carbon atom (C_{12}).

D. τ = 7.30 (J = 13 c.p.s.) an area of two protons shielded at the α and α' positions.

E. τ = 5.35 (J = 22 c.p.s.) a multiplet; an area of one proton α to an acetoxy-group.

F. τ = 2.63 (J = 5 c.p.s.) a doublet (split by long range coupling); an area of one proton present as a vinyl proton similar to the α proton of an α, β-unsaturated ketone. The small coupling constant indicates coupling with an allyl hydrogen. This signal is thus attributed to the olefinic proton at C_{12}.

The N.M.R. spectrum of Tetrahydroeuryopsonol Acetate showed the following bands:-

A. τ = 9.21/.....

A. τ = 9.21 (J = 4 c.p.s.) a singlet; an area of three protons due to a tertiary methyl group at C_5.

B. τ = 9.10 (J = 7 c.p.s.) a doublet; an area of three protons due to a secondary methyl group at C_4.

C. τ = 8.95 (J = 7 c.p.s.) a doublet; an area of three protons due to a secondary methyl group at C_{11}.

D. τ = 7.96 (J = 5 c.p.s.) a singlet; an area of three protons due to the methyl of an acetoxy group.

E. τ = 6.43-6.72 a triplet; an area of two protons.

F τ = 5.6-6.15 a multiplet; an area of two protons.

G τ = 5.35 a triplet of doublets; an area of one proton due to the proton α to the acetoxy group.

Discussion of the N.M.R. spectra.

1. All spectra show the presence of one tertiary methyl group.
2. All spectra show the presence of one secondary methyl group.

Since the sesquiterpenoids of all five groups have the secondary methyl group attached at C_4, this group is placed at the same position in euryopsonol. The tertiary methyl group is attached at C_{10}, excepting in the eremophilenolides, where it occurs at C_5. Since the keto-group in euryopsonol is conjugated with the furan ring, partial structures (234) or (235) may be assigned. The system (234) is present in the transformation product (227) of furanopetasin (219)[109] and is also contained in furanoeremophilone - 9 (215).[2] This chromophore exhibits an absorption peak at 280 - 282 mμ (log ξ = 4.15 - 4.33), whereas the chromophore of the type (235), prepared from petasalbin (210) and albopetasin (218),[106,107,108] shows a maximum at 269 mμ (log ξ = 3.6). As euryopsonol and its 2,4-dinitrophenylhydrazone showed absorption peaks at 280 mμ, (log ξ = 4.16) and 391 mμ, (log ξ = 4.51) respectively, it contains an α, β, γ, δ-unsaturated ketone, and partial structure

(236) was/.....

(236) was assigned to it.

3. The N.M.R. spectra of euryopsonol and euryopsonol acetate showed bands at τ = 7.16 and 7.60 and τ = 7.30 respectively. These signals are attributed to two protons shielded on both sides either in systems (237) or (238). For this system to be present in euryopsonol, the tertiary methyl group must be attached at C_5 as in (239), and the hydroxyl group cannot be in ring B. Euryopsonol is thus a member of the eremophilane type of sesquiterpenoids.

4. The hydroxyl group is secondary for the band at τ = 5.35 is due to a proton α to the acetoxy-group in both euryopsonol acetate and tetrahydroeuryopsonol acetate. The hydroxyl group in euryopsonol may thus be present at either C_1, C_2 or C_3.

5. The N.M.R. spectrum of tetrahydroeuryopsonol acetate showed a band (a doublet) at τ = 8.95, which was not present in either euryopsonol or euryopsonol acetate and is due to the secondary methyl group formed on hydrogenation of the double bond bearing the methyl group at C_{11}.

6. The appearance of bands at τ = 5.6 - τ = 6.72 in tetrahydroeuryopsonol acetate, equivalent to four protons, is proof that euryopsonol acetate is converted to the tetrahydroderivative on reduction.

7. The disappearance of the band at τ = 7.30 in tetrahydroeuryopsonol acetate indicates the de-shielding of the two protons at C_6.

8. The disappearance of the doublet at τ = 2.63 and the splitting of the methyl signal at τ = 8.95 shows that the double bond at C_{11} has been saturated in tetrahydroeuryopsonol acetate.

The mass spectrum of euryopsonol (fig 7) showed a base peak m/e 122 due to the fragment (240) suggesting, in agreement

with deductions/.....

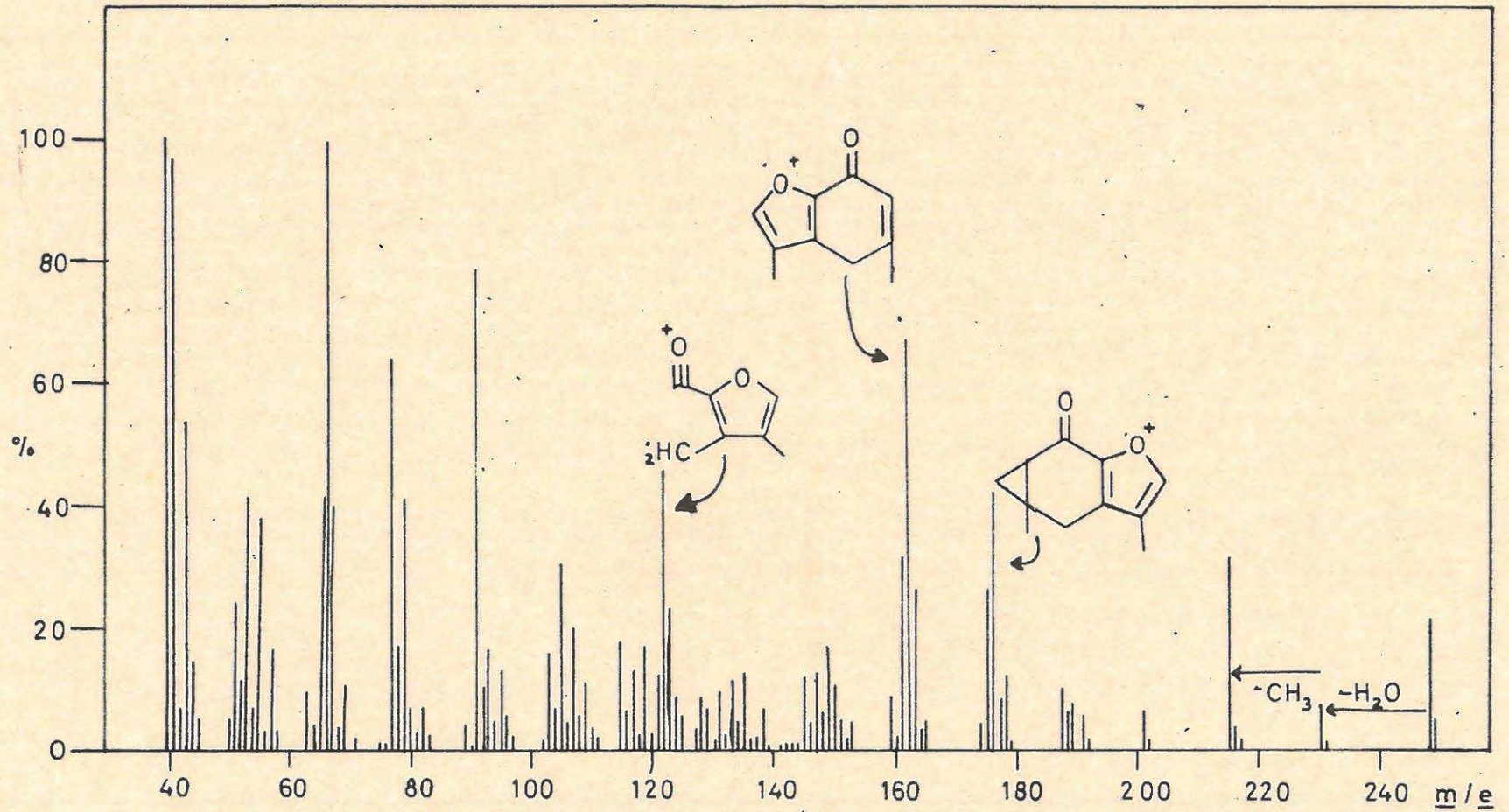


Fig. 7. Mass spectrum of euryopsonol.

with deductions from the ultraviolet spectrum, that the carbonyl group is positioned at C_9. This species (240) corresponds to the base peak (241; m/e 108) in the mass spectrum of alexandrofuran.[144]

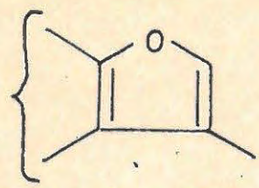
These proposals concerning the structure of euryopsonol are all based on spectroscopic and mass spectrometric measurements. They were placed on a surer footing by converting euryopsonol to furanoeremophilone - 9 (215)[2].

Euryopsonol was oxidised with chromium trioxide in acetone to dehydroeuryopsonol (242). The infrared spectrum of 242 lacked absorption bands due to a hydroxyl function, but showed maxima at 1670 cm^{-1} (α, β, γ, δ-unsaturated ketone); 1550 and 870 cm^{-1} (furan ring) and a newly formed band at 1715 cm^{-1} (ketone in a six-membered ring or open chain). Since Dehydroeuryopsonol did not react with Tollen's reagent, the carbonyl group is not present as an aldehyde. It gave a positive Zimmerman test (euryopsonol gave a negative test) andformed a monofurfurylidene derivative, indicating that an unhindered methylene group is adjacent to the newly formed keto-group. Since the absorption band at 280 $m\mu$ (log ξ = 4.16) in euryopsonol was unchanged on oxidation to 242, the hydroxyl group cannot be present at C_6; this is in agreement with the N.M.R. studies.

The ultraviolet spectrum of dehydroeuryopsonol was unchanged on addition of alkali and it failed to give a colour with ferric chloride. Accordingly, dehydroeuryopsonol is not an enolic β-diketone and the hydroxyl group in euryopsonol is not attached at C_1. Dehydroeuryopsonol formed a mono-oxime, whereas euryopsonol failed to react with hydroxylamine hydrochloride.

Dehydroeuryopsonol was converted to a monothioketal (243). The optimum period of reaction was found to be 45 hours, shorter times affording a mixture of the ketal and unchanged dehydroeuryopsonol, the rate of reaction being followed by thin layer

chromatography./.....



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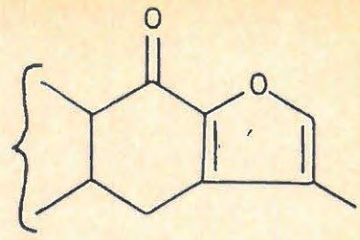

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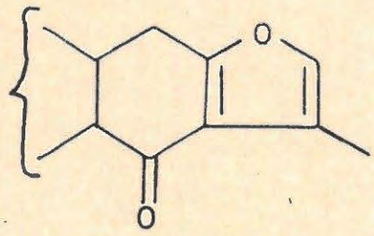

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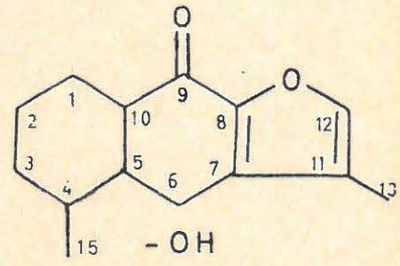

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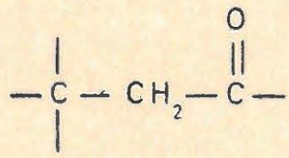

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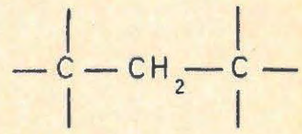

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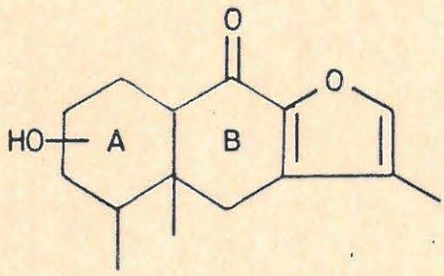

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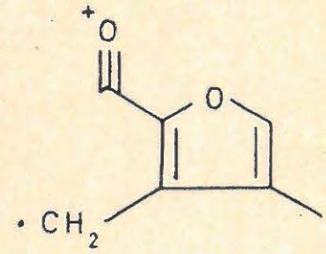
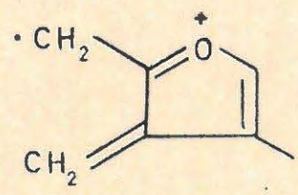
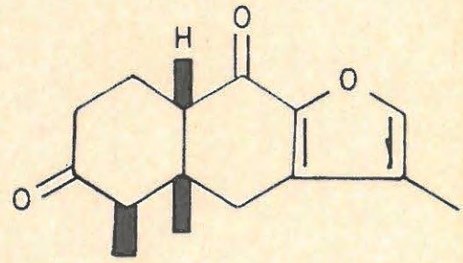


(240) m/e 122



(241) m/e 108



(242)

chromatography. The thioketal showed infrared absorption bands at 1680 cm^{-1} due to the α, β, γ, δ-unsaturated ketone; 1550 and 867 cm^{-1} due to a furan ring, but lacked the maximum due to the ketone in the six-membered ring. It was converted to deoxydehydroeuryopsonol (215) by treatment with Raney-nickel. The infrared spectrum of deoxydehydroeuryopsonol showed absorption bands at 1666 cm^{-1} due to an α, β, γ, δ-unsaturated ketone and at 1540 and 876 cm^{-1} due to a furan ring, while the ultraviolet spectrum showed a peak at 280 $m\mu$, ($\log \xi = 4.17$). The infrared spectrum of deoxydehydroeuryopsonol was identical with that of furanoeremophilone - 9. Unfortunately the Czechoslovakian chemists, who had isolated furanoeremophilone - 9, did not have any left for a mixed melting point determination. Furanoeremophilone - 9 obtained from dehydroeuryopsonol showed $[\alpha]_D = -20^{\circ}$, while that isolated from natural sources was optically inactive.

The position of attachment of the hydroxyl group in euryopsonol was judged from a study of dehydroeuryopsonol. Dehydroeuryopsonol, m.p. 217-218°, is clearly different from 2-ketofuranoeremophilone - 9 (231), m.p. 149° a transformation product of furanopetasin (219).[109] Since C_1 has already been eliminated as a possible position for the new keto-group in dehydroeuryopsonol, this group (and hence the hydroxyl group in euryopsonol) must be at C_3. Dehydroeuryopsonol thus has structure (242) and euryopsonol has structure (244). The position of the keto-group at C_3 in dehydroeuryopsonol was confirmed by N.M.R. studies, the spectrum (fig 8) possessing the following bands:-

A. τ = 9.24 (J = 7 c.p.s.) a singlet; an area of three protons due to a tertiary methyl group at C_5.

B. τ = 8.90 (J = 11 c.p.s.) a doublet; an area of three protons due to a secondary methyl group at C_4.

C. τ = 7.98/.....

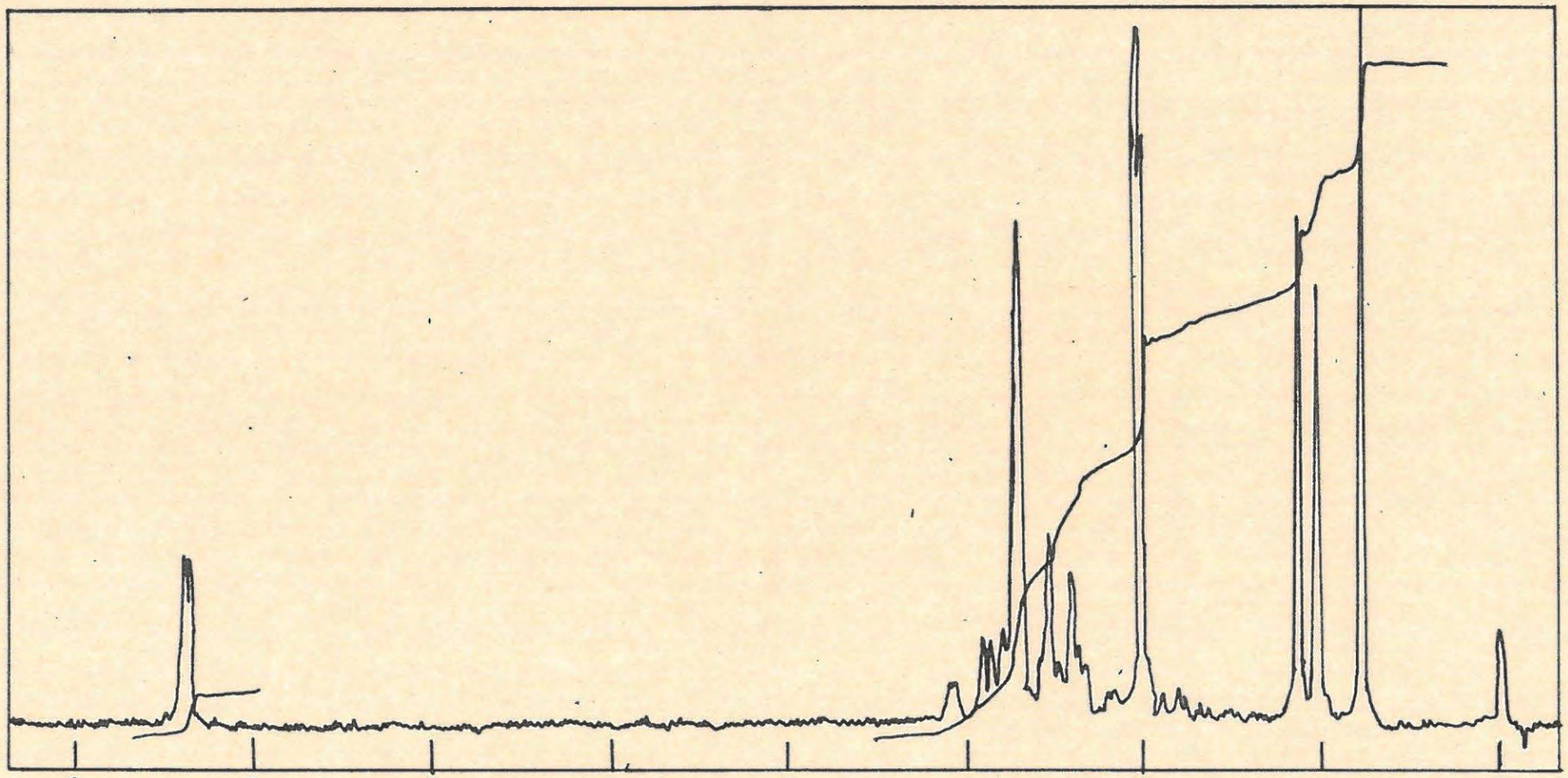


Fig. 8 N.M.R. spectrum of dehydroeuryopsonol.

C. τ = 7,98 (J = 4 c.p.s.) a doublet; an area of three protons. The small splitting is due to the methyl group attached at the olefinic carbon atom (C_{11}), shielded by the quaternary C_7 atom and split by the olefinic hydrogen at C_{12}.

D. τ = 7.48 (J = 14 c.p.s.) a doublet; an area of two protons shielded in the α and α' positions, due to the methylene group at C_6.

E. τ = 7,15 (J = 24 c.p.s.) a multiplet; an area of five protons due to the two methylene groups at C_1 and C_2 and the angular proton at C_{10}.

F. τ = 2.63 (J = 5 c.p.s.) a doublet; an area of one proton due to the olefinic proton at C_{12}.

As the band at τ = 9.24 showed good resolution, the carbonyl group must be in the vicinity.[104]

The conversion of euryopsonol to furanoeremophilone - 9 confirmed all proposals regarding its structure (244). Excepting for the hydroxyl group, the stereochemistry of which is still unknown, the structure of euryopsonol is settled.

5.2. Euryopsol.

Difficulties were encountered at the start of investigations in the separation of this compound from euryopsonol due to its insolubility in non-polar solvents.

Elemental analysis showed an empirical formula of $C_{15}H_{22}O_4$, while ebullioscopic determinations put the molecular weight between 205 and 254. The mass spectrogram confirmed the molecular weight of 266. Euryopsol failed to form any crystalline derivative, thus this formula is not established chemically.

An extraction of Euryops tenuissimus Less. yielded euryopsol free of any euryopsonol. This was unexpected, as the extraction was carried out during the period of maximum content

of euryopsonol/.....

of euryopsonol in Euryops floribundus.

The infrared spectrum of euryopsol in nujol (fig.9) showed maxima at 1160, 1560, 1340, 1280, 1078, 1051, 1038, 1000, 892 and 884 cm^{-1}, while the spectrum in K.Br. (fig 10) showed further maxima at 3400 and 3020 cm^{-1}. The bands at 3400, 1340, 1280, 1050, 1038 and 1000 cm^{-1} are attributed to hydroxyl groups, and the bands at 3020, 1560, 1126, 1078, 892 and 884 cm^{-1} are due to a furan ring. The band at 1660 cm^{-1} is attributed to an ethylenic double bond, but this has not been proved as euryopsol failed to absorb hydrogen on catalytic reduction and did not show a colour change with tetranitromethane.[115] Judging from its infrared spectrum and failure to form derivatives, euryopsol does not contain a keto-group.

The ultraviolet spectrum showed end absorption at 220 $m\mu$, ($\log \xi = 3.68$), characteristic of sesquiterpenoids containing a non-conjugated furan ring. The absence of absorption at 269 or 280 $m\mu$ shows that euryopsol is not a conjugated ketone.

Active hydrogen determinations showed euryopsol to possess two hydroxyl groups and since it absorbed 1.2 mols. of periodate, these groups are vicinal; no formaldehyde was obtained from the periodate oxidation. Analysis also showed the presence of three C-methyl groups, thus a primary hydroxyl group is not present in euryopsol.

Euryopsol formed a non-crystalline acetate, which showed infrared absorption bands at 1730 and 1250 cm^{-1} due to an acetoxy-group. The elemental analysis of this acetate failed to fit any likely formula and it is probably a mixture of products in which partial dehydration has occurred during the heating in acetic anhydride. Hydrolysis of this acetate gave a crystalline product, m.p. 200-203°, which showed an intermediate melting point on admixture with starting material. A sample of euryopsol was refluxed in alcoholic potassium hydroxide and the crystalline product found to melt at 184°.

On recrystallisation/.....

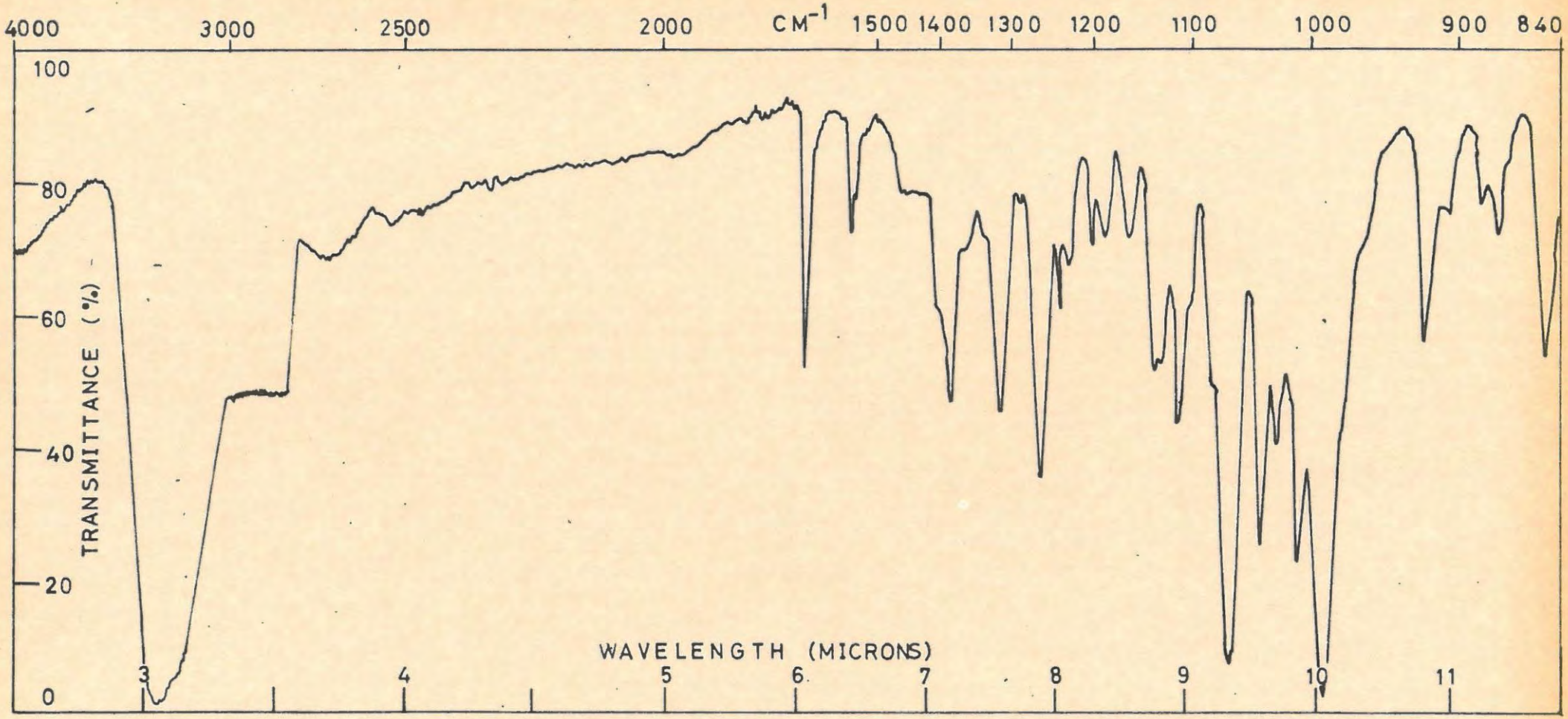


Fig. 9 Infrared spectrum of euryopsol (nujol).

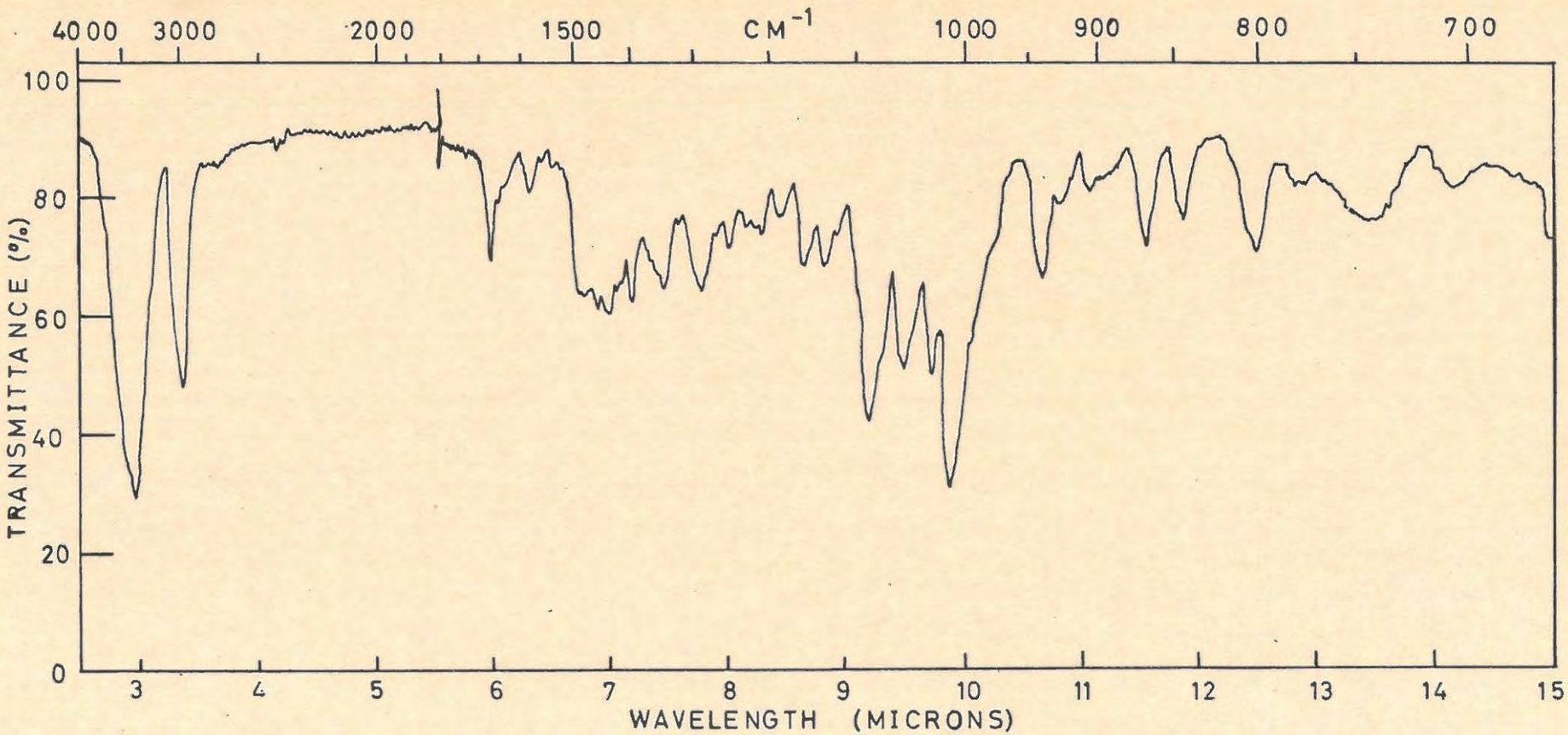


Fig. 10 Infrared spectrum of euryopsol (KBr)

On recrystallisation from water-ethyl alcohol, the melting point dropped to 174-5°, the normally observed melting point of euryopsol. This phenomenon is probably due to hydration of euryopsol during the saponification and subsequent dehydration in an ethanolic medium.

Euryopsol as well as its oily acetate displayed an intense purple colour with Ehrlich's reagent, confirming the presence of a furan ring. Euryopsol also gave an intense red colour with sulphuric acid and an intense green colour with hydrochloric acid.[2]

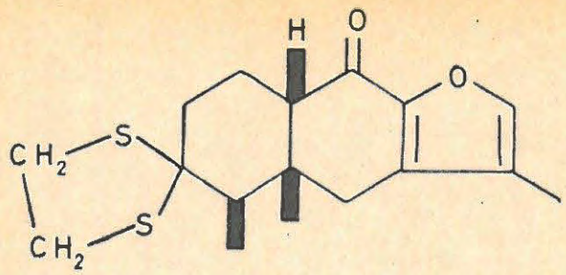
Euryopsol is unstable in chloroform solution and is probably converted to a more stable hydroxyeremophilenolide. Perbenzoic acid oxidation of euryopsol and euryopsol acetate resulted in the uptake of approximately two and one mols. of acid respectively. Saponification of the product resulted in benzoic acid, which probably results from saponification of the diol monobenzoate (245) obtained on cleavage of one of the double bonds of the furan ring.[145]

The N.M.R. spectrum is uninformative, showing a band at τ = 7.82 due to a methyl group attached to an olefinic carbon atom.

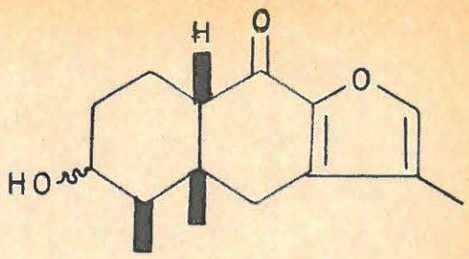
The mass spectrum of euryopsol (fig.11) is very similar to that of euryopsonol and the base peak (246) at m/e = 124 is two mass units higher than the fragment (240) observed for euryopsonol. This suggests that the carbonyl group in euryopsonol is replaced by a hydroxyl group in euryopsol, and hence partial structure (247) may be assigned to euryopsol. However, the portulated allylic hydroxyl group could not be oxidised by shaking euryopsol in either chloroform or benzene; thin layer chromatography showed that no reaction had occurred.

The character of the fourth oxygen atom and the positions of the two methyl groups are still unknown.

6. BIBLIOGRAPHY/.....



(243)



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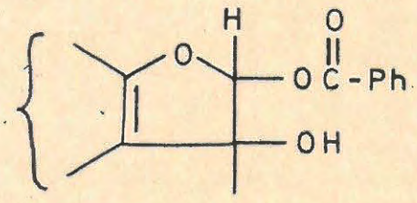

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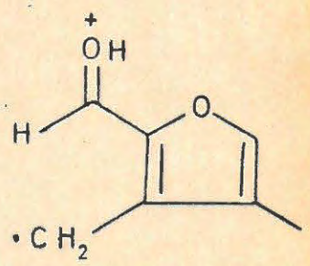
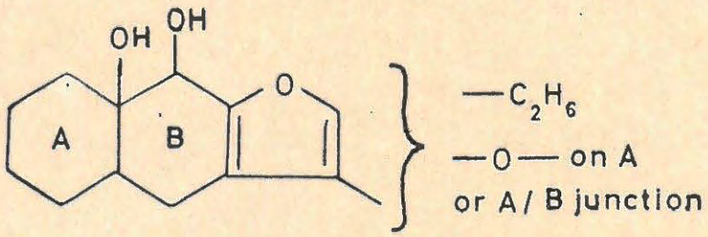


(246) m/e 124



(247)

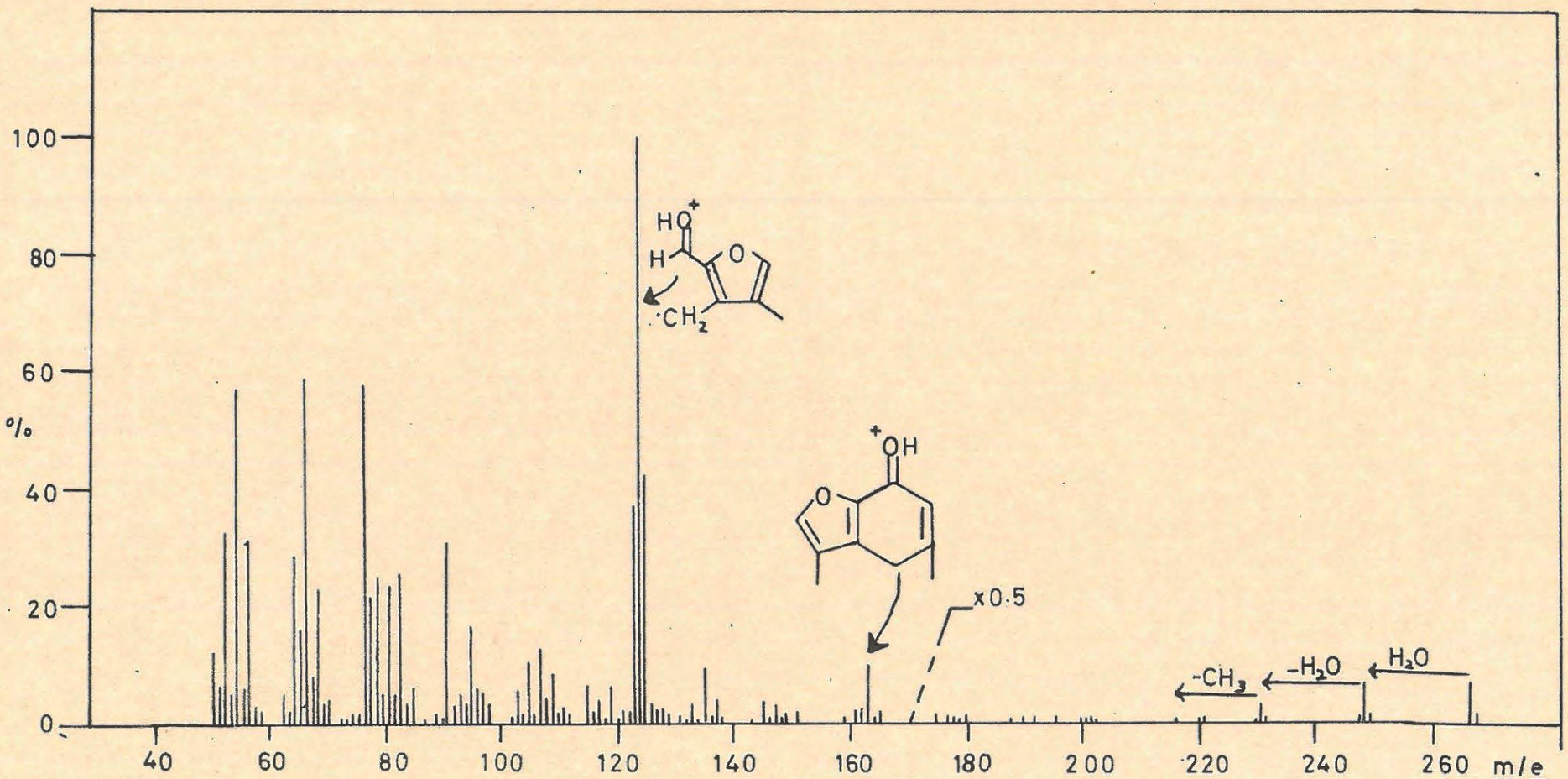


Fig. 11 Mass spectrum of euryopsol.

6. BIBLIOGRAPHY.

1. D.H.S. Horn, J.R. Nunn, and D.E.A. Rivett, J.S. African Chem. Inst., 8, 22, (1954).

2. L. Novotny, J. Jizba, V. Herout, and F. Sorm, Collection Czech. Chem. Commun., 27, 1393, (1962).

3. M. Martin-Smith, S.J. Smith, J.B. Stenlake, and W.D.Williams, Tetrahedron Letters, 24, 1639, (1963).

4. M. Martin-Smith, P. de Mayo, S.J. Smith, J.B. Stenlake, and W.D. Williams, Tetrahedron Letters, 35, 2391 (1964).

5. M. Suchy, V. Herout, and F. Sorm, Collection Czech, Chem. Commun., 26, 1358, (1961).

6. D.H.R. Barton, O.C. Bockman, and P. de Mayo, J. Chem. Soc., 2263, (1960).

7. H.O. House, J. Am. Chem. Soc., 76, 1235, (1954).

8. W.G. Dauben and P.D. Hance, J. Am. Chem. Soc., 77, 2451, (1955).

9. M. Suchy, M. Horak, V. Herout, and F. Sorm, Chem. and Ind. (London), 894, (1957).

10. M. Suchy, V. Herout, and F. Sorm, Collection Czech. Chem. Commun., 24, 1542, (1959).

11. M. Suchy, V. Herout, and F. Sorm, Collection Czech. Chem. Commun., 28, 1715 (1963)

12. Z. Cekan, V. Herout, and F. Sorm, Chem. and Ind. (London), 1234, (1956).

13. M. Soucek, V. Herout, and F. Sorm, Collection Czech. Chem. Commun., 26, 803, (1961).

14. M. Soucek, V. Herout, and F. Sorm, Chem. and Ind. (London), 1069 (1959).

15. V. Herout, M. Suchy, and F. Sorm, Collection Czech. Chem. Commun., 26, 2612, (1961).

16. J. Hochmannova, V. Herout, and F. Sorm, Collection Czech. Chem. Commun., 26, 1826 (1961).

17. W. Cocker/.....

17. W. Cocker and T.B.H. McMurry, J. Chem. Soc., 4549 (1956).

18. O. Kovacs, V. Herout, and F. Sorm, Collection Czech. Chem. Commun., 21, 225, (1956).

19. L. Novotny, V. Herout, and F. Sorm, Collection Czech. Chem. Commun. 25, 1500, (1960).

20 A.S. Rao, G.R. Kelkar, and S.C. Bhattacharyya, Tetrahedron, 9, 275, (1960).

21. S.B. Mathur, G.H. Kulkarni, G.R. Kalkar, and S.C. Bhattacharyya, Tetrahedron, 13, 2903, (1964).

22. M. Suchy, V. Benesova, V. Herout, and F. Sorm, Chem. Ber., 93, 2449, (1960).

23. M. Suchy, V. Herout, and F. Sorm, Collection Czech. Chem. Commun., 27, 2398, (1962).

24. M. Suchy, V. Herout, and F. Sorm, Collection Czech. Chem. Commun., 30, 2363, (1965).

25. M. Suchy, V. Herout, and F. Sorm, Collection Czech. Chem. Commun. 27, 1905, (1962).

26. H. Labhart and G. Wagniere, Helv. Chim. Acta, 42, 2219 (1959).

27. L. Dolejs and V. Herout, Collection Czech. Chem. Commun., 27, 2654, (1962).

28. M. Horak and J. Pliva, Chem. and Ind. (London), 102, (1960).

29. V. Benesova, V. Herout, and F. Sorm, Collection Czech. Chem. Commun., 29, 3096, (1964).

30. L.F. Fieser, J. Am. Chem. Soc., 76, 1945, (1954).

31. J.P. de Villiers, J. Chem. Soc., 2049, (1961).

32. J. Simonsen and D.H.R. Barton, The Terpenes, Cambridge Univ. Press, 1952, Vol. III, pg. 250.

33. G.R. Clemo, R.D. Haworth, and E. Walton, J. Chem. Soc., 2368, (1929).

34. G.R. Clemo, R.D. Haworth, and E. Walton, J. Chem. Soc., 1110, (1930).

35. G.R. Clemo and R.D. Haworth, J. Chem. Soc., 2579, (1930).

36. J.D.M. Asher and G.A. Sim, Proc. Chem. Soc., 111, (1962).

37. D.H.R. Barton/.....

37. D.H.R. Barton, T. Mike, J.T. Pinhey, and R.J. Wells, Proc. Chem. Soc., 112, (1962)

38. D.H.R. Barton, P. de Mayo, and M. Shafiq, J. Chem. Soc., 929, (1957).

39. M. Nakazaki and H. Arakawa, Proc. Chem. Soc., 151, (1962).

40. Y. Abe, T. Mike, M. Sumi, and T. Toga. Chem. and Ind. (London), 953, (1956).

41. W. Cocker, H. Gobinsingh, T.B.H. McMurry, and M.A. Nisbet, J. Chem. Soc., 1432, (1962).

42. W. Cocker and T.B.H. McMurry, Tetrahedron, 8, 181, (1960).

43. Wei-Shan Chow, Tse-Hwa Yin, and Huang Minlon, Chem. Abstracts, 60, 1664 e, (1964).

44. G.R. Clemo, J. Chem. Soc., 1343, (1934).

45. D.H.R. Barton, J. Org. Chem., 15, 466, (1950).

46. Y. Abe and M. Sumi, Chem. and Ind. (London), 253, (1955).

47. M. Sumi, J. Am. Chem. Soc., 80, 4869, (1958).

48. C.M. Suter, "The Organic Chemistry of Sulphur", John Wiley and Sons, Inc. New York, N.Y. (1949) pg. 514.

49. L.E. Fieser, J.E. Herz, M.W. Klochs, M.A. Romero, and T. Utne. J. Am. Chem. Soc., 74, 3309, (1952).

50. A.J.N. Bolt, W. Cocker, and T.B.H. McMurry, J. Chem. Soc., 5235, (1963).

51. W. Cocker, J. Chem. Soc., 36, (1946).

52. W. Cocker and C. Lipman, J. Chem. Soc., 533, (1947).

53. W. Cocker, B.E. Cross, and C. Lipman, J. Chem. Soc., 1170 (1949)

54. W. Cocker, B.E. Cross, A.K. Fateen, C. Lipman, E.R. Stuart, W.H. Thompson, and D.R.A. Whyte, J. Chem. Soc., 1781, (1950).

55. W.G. Dauben and P.D. Hance, J. Am. Chem. Soc., 77, 606, (1955)

56. W.G. Dauben and P.D. Hance, J. Am. Chem. Soc., 75 3352, (1953).

57. P. Bladon, H.B. Henbest, and G.W. Woods, J. Chem. Soc., 2737, (1952).

58. W. Cocker, T.B.H. McMurry, and L.O. Hopkins, J. Chem. Soc., 1998, (1959).

59. W. Cocker/.....

59. W. Cocker and M.A. Nisbet, J. Chem. Soc., 534, (1963).

60. K.S. Rybalko and L. Dolejs, Collection Czech. Chem. Commun., 26, 2909, (1961).

61. T.A. Geissman and G.A. Ellestad, J. Org. Chem., 27, 1855, (1962).

62. M. Suchy, Collection Czech. Chem. Commun., 27, 2925, (1962).

63. C. Djerassi, R. Engle, and A. Bowers, J. Org. Chem., 21, 1547, (1956).

64. O.H. Wheeler and J.L. Matoes, Chem. and Ind. (London), 395 (1957).

65. K. Tsuda, K. Tanabe, I. Iwai, and K. Funakoshi, J. Am. Chem. Soc., 79, 5721 (1957).

66. J. Simonsen and D.H.R. Barton, The Terpenes, Cambridge Univ. Press. 1952, Vol. III, pg. 240.

67. M. Matsumura, I. Iwai, E. Ohki, and K. Kanzaki, J. Pharm. Soc., Japan, 75, 689, (1955).

68. J.A. Marshall and N. Cohen, J. Am. Chem. Soc., 87, 2773 (1965).

69. W. Herz and G. Högenauer, J. Org. Chem., 27, 905, (1962).

70. W.G. Dauben, E.J. Blanz, J. Jiu, and R.A. Micheli, J. Am. Chem. Soc., 78, 3752, (1956).

71. J. Schreiber and A. Eschenmoser, Helv. Chim. Acta, 38, 1529, (1955)

72. D.H.R. Barton, J. Chem. Soc., 1027, (1953).

73. W. Herz and N. Viswanathan, J. Org. Chem., 29, 1022, (1964).

74. V. Benesova, V. Herout, and F. Sorm, Collection Czech. Chem. Commun., 26, 1350, (1961).

75. K. Yamakawa, J. Org. Chem., 24, 897, (1959).

76. W. Herz, G. Högenauer, and A.R. de Vivar, J. Org. Chem., 29, 1700, (1964).

77. D.H.R. Barton and R.C. Cookson, Quart. Rev. (London), 10, 44, (1956).

78. K. Tanabe, Chem. Abstracts, 53, 304, (1959).

79. L. Novotny, V. Herout, and F. Sorm, Collection Czech. Chem. Commun., 29, 2182, (1964).

80. H. Hikino/.....

80. H. Hikino, Y. Hikino, and I. Yosioka, Chem. and Pharm. Bull. (Tokyo), 10, 641, (1962).

81. R.B. Woodward and R.H. Eastman, J. Am. Chem. Soc., 72, 399, (1950)

A. Melera, K. Schaffner, D. Arigoni and O. Jeger, Helv. Chim. Acta, 40, 1420, (1957).

82. H. Minato and T. Nagasaki, Chem. Commun. (London), 377, (1965).

83. M. Romanuk, V. Herout, and F. Sorm, Collection Czech. Chem. Commun., 21, 894, (1956).

84. H. Hikino, K. Meguro, G. Kusano, and T. Takemoto, Chem. Abstracts, 61, 5698, (1964).

85. M. Suchy, V. Herout, and F. Sorm, Collection Czech, Chem. Commun., 29, 1829, (1964).

86. Z. Cekan, V. Prochazka, V. Herout, and F. Sorm, Collection Czech, Chem. Commun., 25, 2553, (1960).

87. V. Prochazka, Z. Cekan, and R.B. Bates, Collection Czech. Chem. Commun., 28, 1202, (1963).

88. W. Herz, W.A. Rhode, K. Rabindran, P. Jayaraman, and N. Viswanathan, J. Am. Chem. Soc., 84, 3857, (1962).

89. D.H.R. Barton and P. de Mayo, Quart. Rev. (London), 11, 189, (1957).

90. W. Herz, A.R. de Vivar, J. Romo, and N. Viswanathan, Tetrahedron, 19, 1359 (1963).

91. D. Rogers and Mazar-ul-Haque, Proc. Chem. Soc., 92 (1963).

92. W. Herz, H. Wanatabe, M. Miyazaki, and Y. Kishida, J. Am. Chem. Soc., 84, 2601, (1962).

93. K. Takeda, M. Ikuta, and M. Miyawaki, Tetrahedron, 20, 2991 (1964).

94. K. Tanabe, Chem. Pharm. Bull. Japan 6, 214 (1958).

95. K. Takeda, H. Minato, M. Ishikawa, and M. Miyawaki, Tetrahedron, 20, 2655 (1964).

96. L.F. Fieser/.....

96. L.F. Fieser and M. Fieser, Topics in Organic Chemistry, Reinhold, 1963, pg. 186.

97. L. Novotny, J. Jizba, V. Herout, F. Sorm, L.H. Zalkow, S.Hu, and C. Djerassi, Tetrahedron, 19, 1101 (1963).

98. J. Hochmannova, L. Novotny and V. Herout, Collection Czech. Chem. Commun., 27, 1870, (1962).

99. S.C. Bhattacharyya, A.S. Rao, and M. Shaligram, Chem. and Ind. (London), 469, (1960).

100. Huang Minlon, J. Am. Chem. Soc., 68, 2487, (1946).

101. L.H. Zalkow, F.X. Markley, and C. Djerassi, J. Am. Chem. Soc., 81, 2914 (1959).

102. C. Djerassi, "Optical Rotatory Dispersion: Applications to Organic Chemistry" McGraw-Hill Book Co. New York, (1960).

103. L. Novotny, V. Herout, and F. Sorm, Tetrahedron Letters, 697 (1961).

104. F.A. Anet, Can. J. Chem., 39, 2262 (1961).

105. D.H.R. Barton, P. de Mayo, E.W. Warnhoff, O. Jeger, and G.W. Perold, J. Chem. Soc., 3689 (1954).

106. L. Novotny, V. Herout, and F. Sorm, Collection Czech, Chem. Commun., 27, 1400 (1962).

107. L. Novotny, V. Herout, Collection Czech Chem. Commun., 27, 2462 (1962).

108. L. Novotny, V. Herout, and F. Sorm, Collection Czech. Chem. Commun., 29, 2189 (1964).

109. L. Novotny, C.H. Tabacikova-Wlotzka, V. Herout, and F. Sorm, Collection Czech. Chem. Commun., 29, 1922 (1964).

110. A.W. Schrecker and J.L. Hartwell, J. Am. Chem. Soc., 77, 432 (1955).

111. O. Mancera, G. Rosenkranz, and F. Sondheimer, J. Chem. Soc. 2189 (1953).

112. N.E. Brown, Kew Bulletin pg. 125 (1901).

113. R.P. Linstead and S.L.S. Thomas, J. Chem. Soc., 1130 (1940).

114. C. Weygand, Organic Preparations, Interscience Publishers Inc. N.Y. (1945) pg. 16.

115. Weisberger/.....

115. Weisberger, Techniques of Organic Chemistry, Interscience Publishers Inc. (1949), Vol. XI, Part I, pg. 34.

116. E.J. Corey and J.J. Ursprung, J. Am. Chem. Soc., 78, 183 (1956).

117. E.J. Corey and J.J. Ursprung, J. Am. Chem. Soc., 78, 5041 (1956).

118. Openshaw. A Laboratory Manual of Qualitative Organic Analysis, Cambridge Univ. Press (1959) pg. 46.

119. Openshaw, A Laboratory Manual of Qualitative Organic Analysis, Cambirdge Univ. Press (1959) pg. 36.

120. Hopkins and Williams (Ltd), Organic Reagents for Organic Analysis, Hopkins and Williams (Ltd) (1944), pg. 97.

121. A.J. Shine, J. Chem. Educ., 575 (1959)
J. Org. Chem., 24, 252 (1959).

122. E.L. Jackson, Organic Reactions, John Wiley & Sons. Inc. (N.Y.) 1944, pg. 341.

123. A. Bowers, T.G. Halsall, E.R.H. Jones, and A.J. Lemin. J. Chem. Soc., 2548 (1953).

124. Weisberger, "Technique of Organic Chemistry" Interscience Publishers Inc. N.Y. (1949) Vol. XI Part I, pg. 36.

125. Hopkins and Williams (Ltd) Organic Reagents for Organic Analysis Hopkins and Williams (Ltd) (1944) pg. 58.

126. W.S. Johnson, B. Bannister, and R. Pappo, J. Am. Chem. Soc., 78, 6331 (1956).

127. W.S. Johnson, D.S. Allen, R.P. Hindersinn, G.N. Sausen and R. Pappo, J. Am. Chem. Soc. 84, 2181 (1962).

128. K. Sato and Y. Kurihara, J. Org. Chem., 28, 45 (1963).

129. F. Sanchez-Viesca and J. Romo, Tetrahedron 19, 1285 (1963).

130. S. Bernstein, R. Littell, J.J. Brown, and I. Ringler, J. Am. Chem. Soc., 81, 4573 (1959).

131. R.C. Fuson and C.W.T. Tullock, J. Am. Chem. Soc., 56, 1638, (1934).

132. H. Booth and B.C. Saunders, Chem. and Ind. (London), 824 (1950).

133. B.T. Gillis/.....

133. B.T. Gillis, J. Org. Chem., 1027, (1959).

134. D.H.R. Barton, S.K. Pradhan, S. Sternhell, and J.F. Templeton, J. Chem. Soc., 255, (1961).

135. D.L. Dreyer, J. Org. Chem., 30, 749, (1965).

136. J.R. Moyer and N.C. Manley, J. Org. Chem., 29, 2099, (1964).

137. B.C. McKusick (Editor). Organic Syntheses, John Wiley and Sons. Inc. N.Y., 43, 93, (1963).

138. N.L. Drake (Editor). Organic Syntheses, John Wiley and Sons. Inc. N.Y., 21, 15, (1941).

139. H.J. Shine and J.Y-F. Tsai, J. Org. Chem., 29, 443, (1943).

140. W.L. Williams and M.L. Willard, J. Am. Chem. Soc., 82, 3373, (1960).

141. J.P. Phillips, J. Org. Chem. 27, 1443 (1962).
D. Johnson, J. Am. Chem. Soc., 75, 2720 (1953)
E.A. Braude and E.R.H. Jones, J. Chem. Soc., 498 (1945).

142. A. Gillam and E.S. Stern "Electronic Absorption Spectroscopy" Edward Arnold (1954), pg. 122.

143. E. de B. Barnett and F.G. Saunders, J. Chem. Soc., 434 (1933).

144. H. Budzikicz, C. Djerassi, and D.H.W. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry", Holden-Day, Inc., San Francisco (1964) Vol. II, pg.152

145. L.F. Fieser and M. Fieser, "Advanced Organic Chemistry", Reinhold, (N.Y.) (1961), pg. 160.