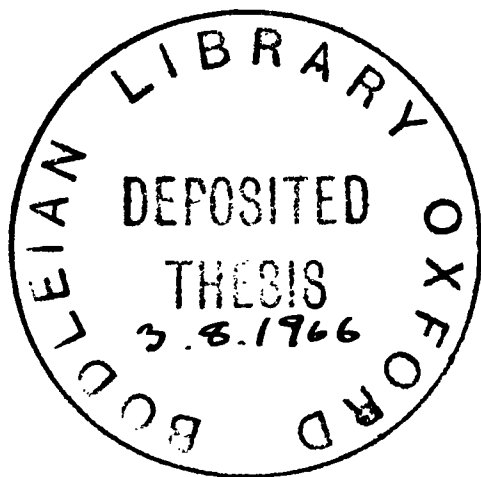


THE CHEMISTRY OF SOME WEST AFRICAN PLANTS

**A Thesis submitted to the
Board of the Faculty of Physical Sciences
in the
University of Oxford
in partial fulfilment of the requirements
for the
Degree of Doctor of Philosophy
by
Peter Toft**

**St. Catherine's College
Oxford**

December 1965



ACKNOWLEDGEMENTS

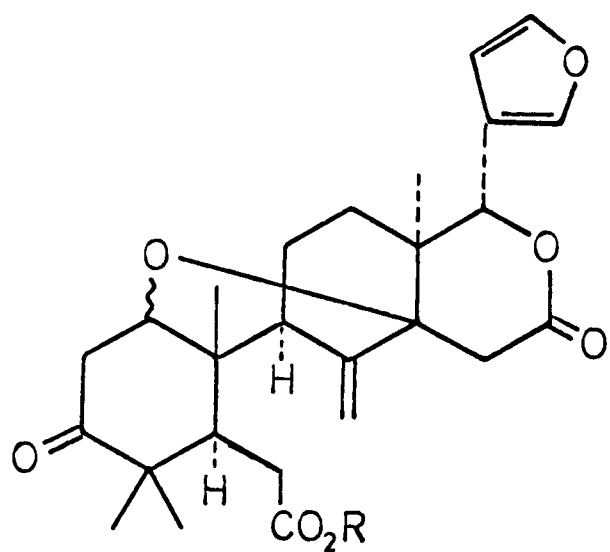
I wish to thank Dr. T. G. Halsall, Professor C. W. L. Bevan, and Dr. J. W. Powell for their supervision and generous advice during the course of this work. I should also like to thank my friends and colleagues for many helpful discussions.

I should like to express my gratitude to the technical staff of the Dyson Perrins Laboratory and the Chemistry Department of the University of Ibadan for the determination of the greater part of the physical data. Specific thanks are due to Mrs. R. E. Richards for the recording of nuclear magnetic resonance spectra, to Dr. R. T. Aplin for the determination of mass spectra, and to Mr. G. Adesida for extracting the timbers used in the work. The receipt of a university bursary from Messrs. Pfizer (Pharmaceutical) Ltd. is gratefully acknowledged. I also thank Mrs. Barbara Bunyan for typing this thesis.

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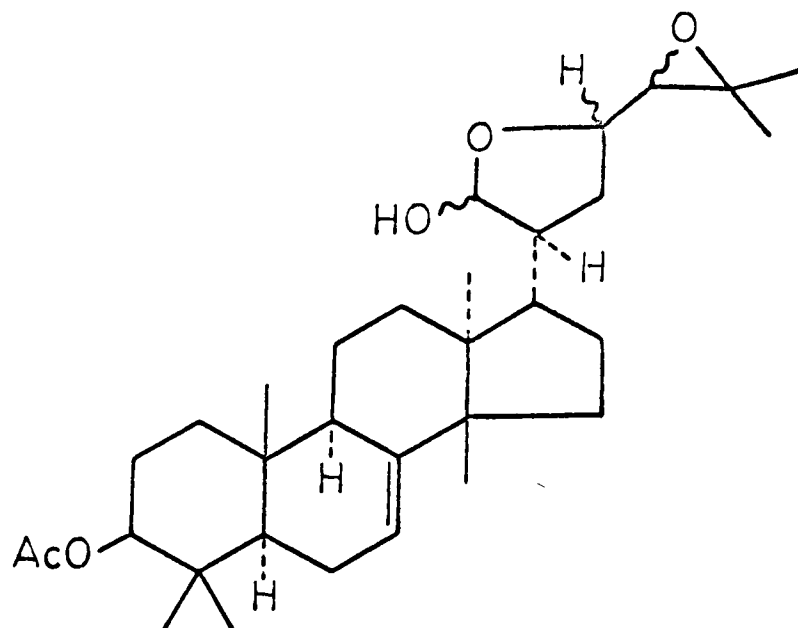
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ABSTRACT

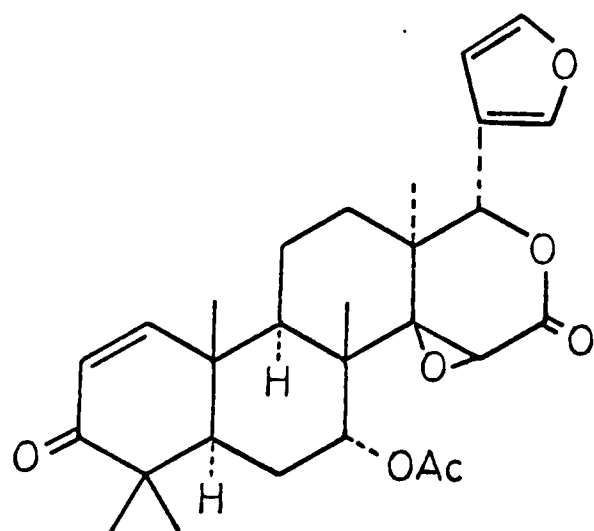


1 R = Me, methyl angolensate

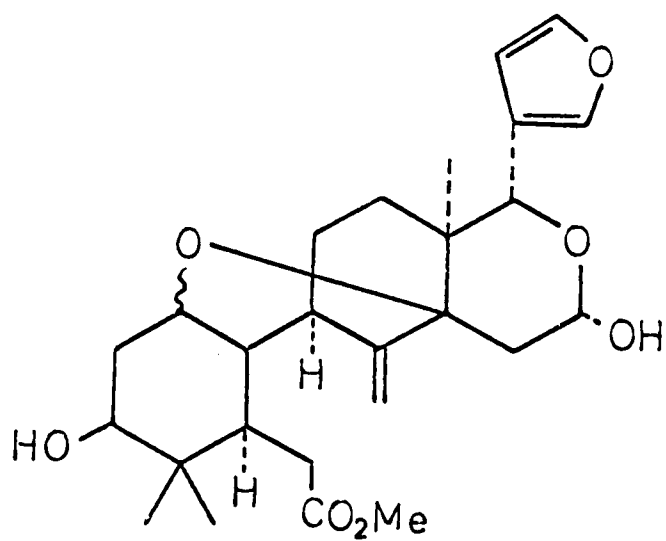
2 R = H, angolensic acid



2 Turraeanthin



3 Gedunin

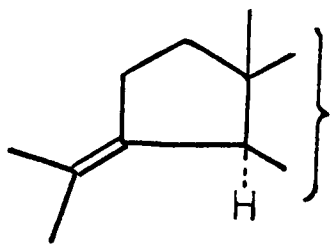


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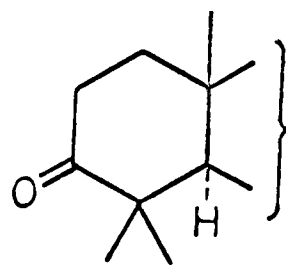
ABSTRACT

The main subjects of this thesis are the chemistry and structure of two triterpenes, methyl angolensate (1) and turraeanthin (2), which were isolated from species of the family Meliaceae. A review is included of other triterpenes isolated from this family and from the related plant families Rutaceae and Simaroubaceae.

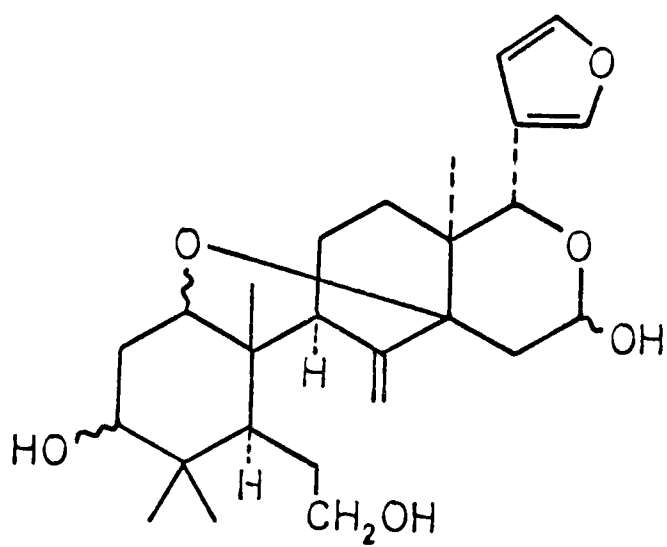
Methyl angolensate has been obtained from several species of the family Meliaceae found in West Africa,^{cf.1} the principal source being Entandrophragma angolense² where it occurs with gedunin (3).⁹ Initial studies had been carried out by Taylor and Powell³ and continued by Welford.⁴ Methyl angolensate was also isolated by Chan,⁵ from Cedrela odorata obtained from the West Indies, with whom there has been an interchange of information. Methyl angolensate was assigned the structure (1) on the basis of the following studies. Spectral evidence and chemical studies indicated the presence of a ketone, a methyl ester, a δ -lactone and a β -substituted furan, and showed the absence of a hydroxyl group. Reduction of methyl angolensate with potassium borohydride gave a diol (4) in which the 3-oxo group had



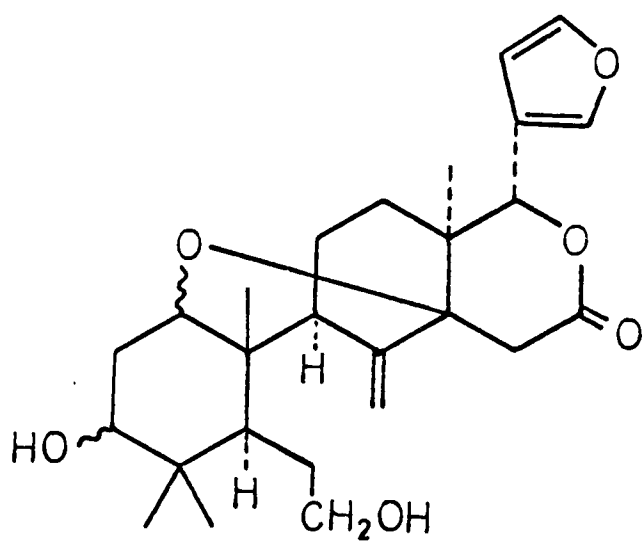
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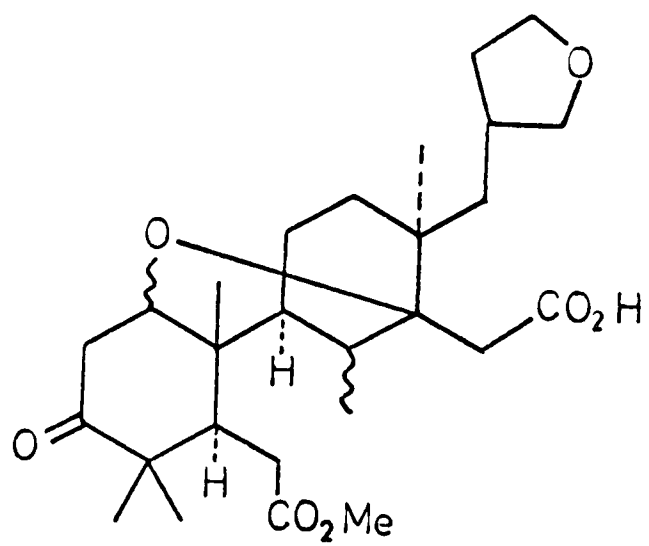
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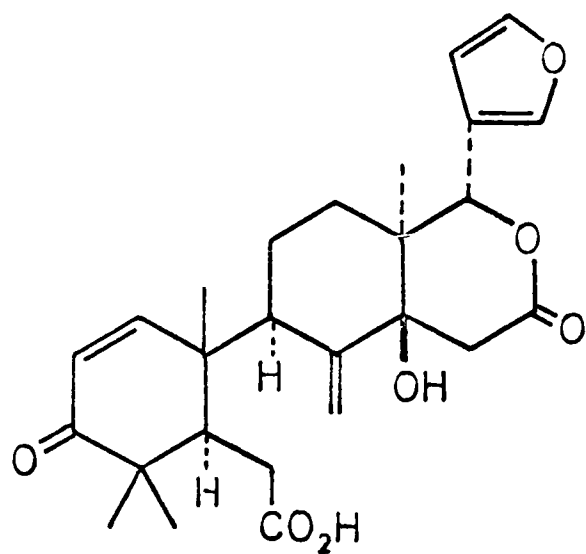


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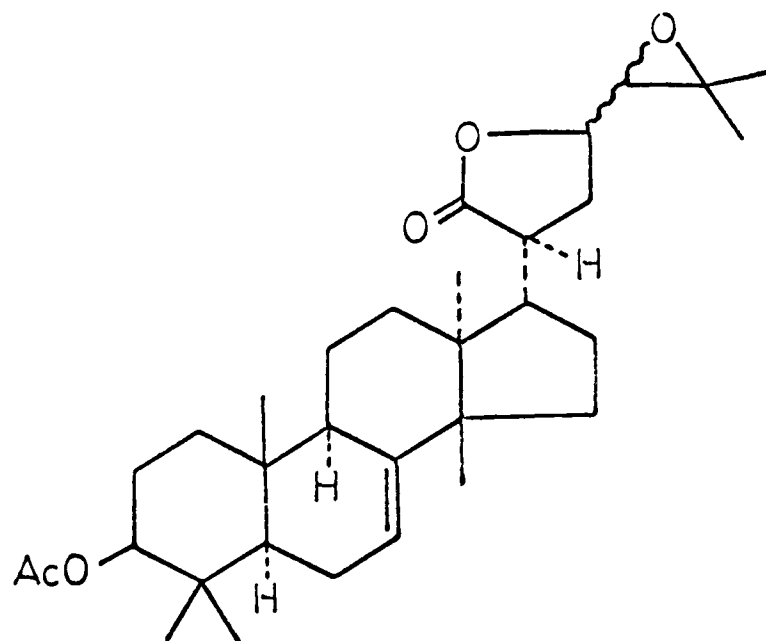
been reduced to an alcohol and the δ -lactone had been converted into a hemiacetal. The diol (4) underwent a retropinacol rearrangement in the presence of phosphorus pentachloride, and a product (5) was obtained which on ozonolysis afforded acetone and a cyclopentanone derivative. This indicated that methyl angolensate had the partial structure (6).⁶ Reduction of methyl angolensate with lithium aluminium hydride gave a mixture of two triols (7) and a diol (8). On oxidation with chromic acid all of these compounds gave angolensic acid (9).^{4,5} Oppenauer oxidation of the diol (8) gave a hydroxy-aldehyde.⁵ The n.m.r. spectrum of the latter compound showed the signal due to the aldehydic proton as a triplet, indicating the presence of $-\text{CH}_2\text{CHO}$ in this compound, and hence suggesting the grouping $-\text{CH}_2\text{CO}_2\text{Me}$ in methyl angolensate. Hydrogenation of methyl angolensate in acetic acid over palladised charcoal produced an octahydro acid (10) which was still a methyl ester but no longer a furan.^{cf.7} This reaction indicates the presence of the lactone - furan system as found in gedunin (3).⁹ The pK^*_{MCS} (7.2) of this acid showed that it was not an α -oxy-acid while the n.m.r. spectra of the methyl angolensate derivatives in which the lactone group had been reduced to a hemiacetal group showed that there was

a $-\text{CH}_2-$ group next to the carbonyl group of the lactone. The functional groups so far described account for six of the seven oxygen atoms. The n.m.r. spectrum of methyl angolensate had a band at 6.53τ (quartet) due to one proton which is indicative of the grouping $>\text{CHO}-$. This suggested that the seventh oxygen atom was in a cyclic ether. After allowance for the functional groups the formula $\text{C}_{27}\text{H}_{34}\text{O}_7$ requires that methyl angolensate has three carbocyclic rings and/or double bonds. Spectral evidence indicated the presence of an exocyclic methylene group which could be hydrogenated to give a secondary methyl group. The presence of the $-\text{CH}_2\text{CO}_2\text{Me}$ group and the $>\text{C}=\text{CH}_2$ group in methyl angolensate can be explained if ring B or ring C of the gedunin skeleton has been opened oxidatively. Evidence from the n.m.r. spectra indicated that ring C was intact, and therefore ring B must be open. The nature of the ether bridge was demonstrated by treating with sodium isobutoxide which caused a base-catalysed elimination of the ether linkage at $\text{C}_{(1)}$ to yield the α,β -unsaturated ketone (11).⁵ Biogenetic and steric considerations point to the other end of the ether bridge being at $\text{C}_{(14)}$. Thus the structure (1) was deduced for methyl angolensate.

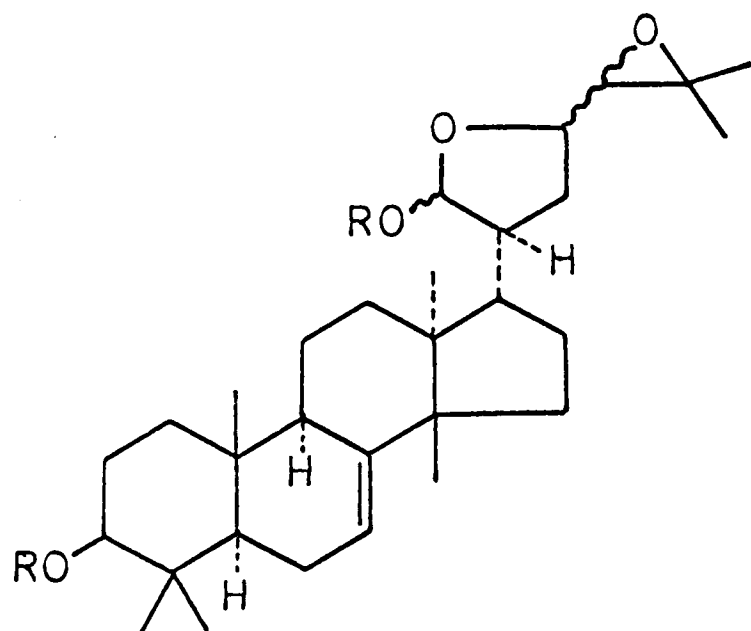
Extraction of the heartwood of Turraeanthus africanus



11

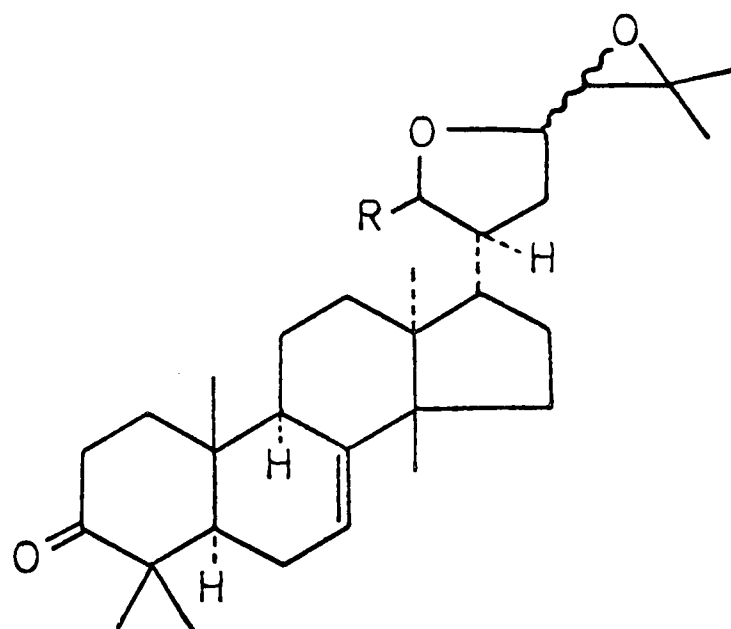


12 Turraeanthin lactone



13 $\text{R} = \text{H}$

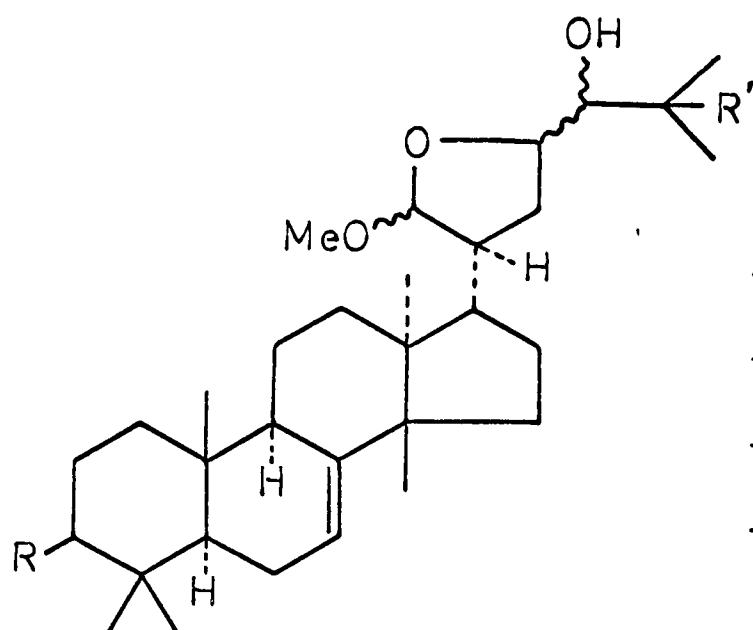
16 $\text{R} = \text{Ac}$



14 $\text{R} = \text{H}, \text{OH}$

15 $\text{R} = \text{O}$

afforded a new triterpene, turraeanthin, which was assigned the structure (2) on the basis of the following evidence. Mass spectral and combustion analyses indicated the formula $C_{32}H_{50}O_5$. Spectral evidence indicated the presence of a hydroxyl group, an acetoxy group, a trisubstituted double bond and an epoxy group. The n.m.r. spectrum showed that there were seven tertiary methyl groups. Mild oxidation with chromium trioxide - pyridine complex gave a γ -lactone (12). This indicated that a five-membered cyclic hemiacetal must be present in turraeanthin. The trisubstituted double bond could not be hydrogenated under mild conditions and ozonolysis did not afford any volatile fragment. The double bond is therefore in a ring. Alkaline hydrolysis of turraeanthin gave deacetylturraeanthin (13), the oxidation of which gave a ketone (14) and a keto-lactone (15). Acetylation of turraeanthin afforded an acetate (16), also obtained by acetylation of deacetylturraeanthin (13). Turraeanthin is therefore a monoacetate. The n.m.r. spectrum had a band at 5.45τ due to the proton on the acetoxy carbon atom. Its band width and shape were typical of that of the 3α -proton of triterpene 3β -acetates. Treatment of turraeanthin with methanolic hydrochloric acid converted the hemiacetal grouping to an acetal and opened the epoxide ring

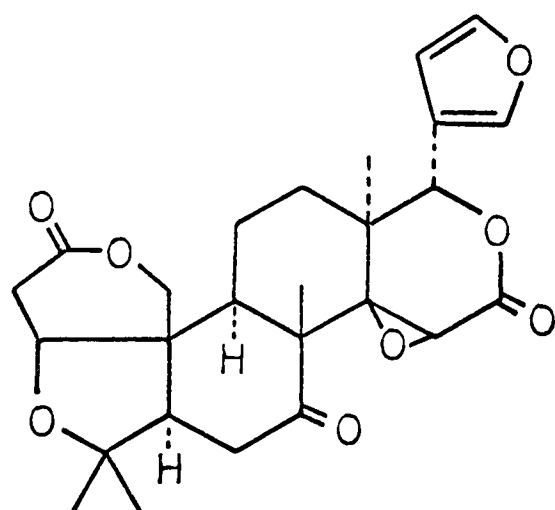


17 R = OAc, α H; R' = Cl

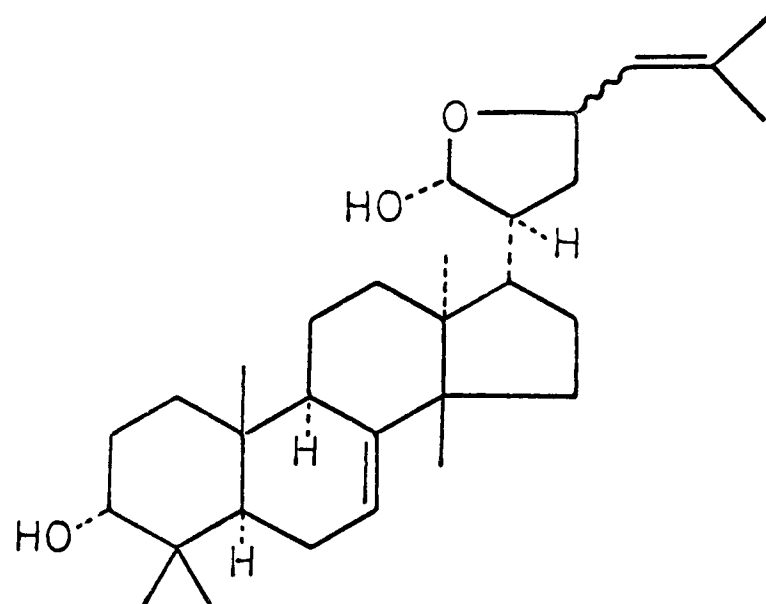
18 R = OAc, α H; R' = OMe

19 R = OH, α H; R' = OMe

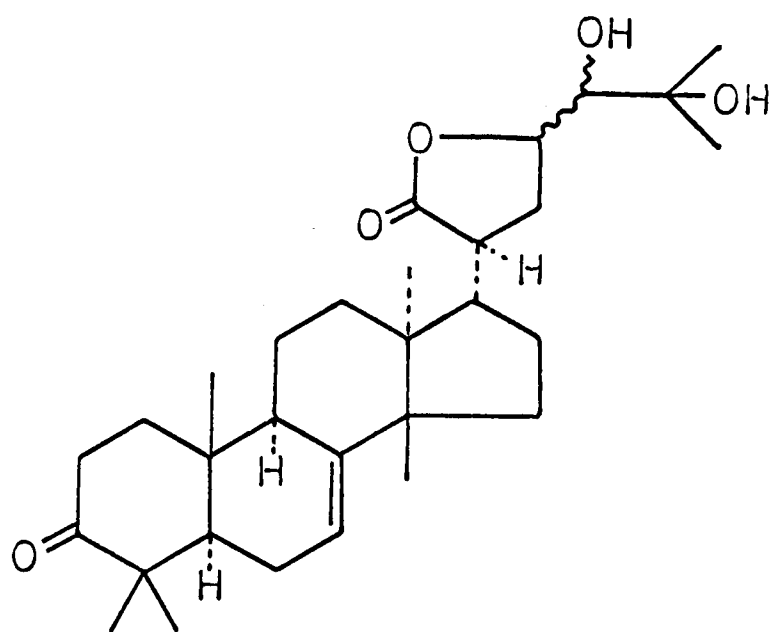
20 R = O ; R' = OMe



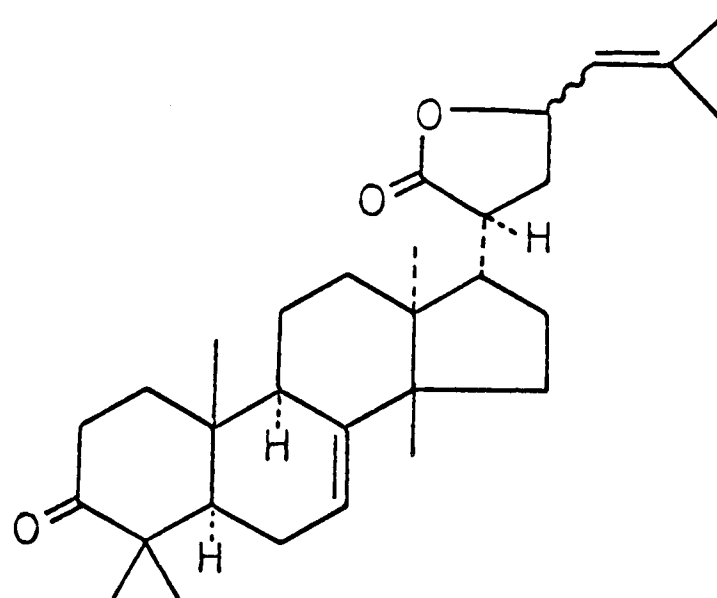
21 Limonin



22 Flindissol



23



24 Flindissone lactone

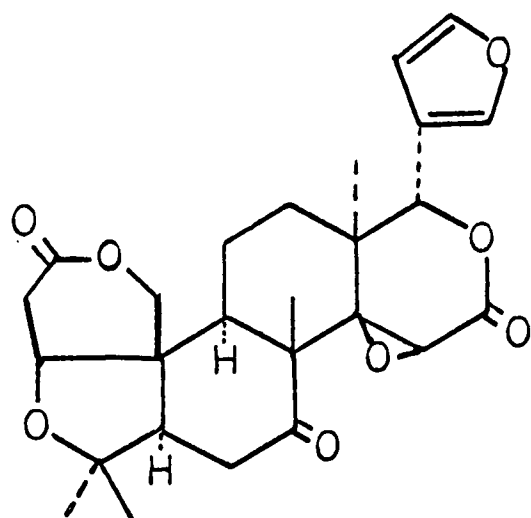
to give the chlorohydrin (17) and the methoxyhydrin (18).

A similar reaction with methanolic sulphuric acid also caused hydrolysis of the acetoxy group affording compound (19) which with chromium trioxide - pyridine gave the ketone (20). The negative Cotton curve of the latter compound (20) was almost superimposable upon that of flindissone lactone (24).⁸ The relationship of the epoxide group to the hemiacetal group was demonstrated by a spin decoupling experiment on the lactone (12). Irradiation of the proton at C₍₂₃₎ absorbing at 5.85 τ caused collapse of the doublet at 7.15 τ due to the epoxy proton at C₍₂₄₎. The presence in Meliaceae and the related Rutaceae of a number of degraded triterpenes such as limonin (21)⁷ and gedunin (3)⁹, all of which can be formally derived by oxidative degradation of tirucalla-7,24-dien-3 β -ol ($\equiv$ 20 α H-butyrospermol) together with the evidence described suggested that turraeanthin was (2) and closely related to flindissol (22).⁸ The relationship was established in the following way. The keto-lactone (15) on being treated with sulphuric acid in ether gave the glycol (23). This was converted^{cf.10} into the cyclic thionocarbonate and hence to a product which proved to be identical with flindissone lactone (24).⁸ No melting point depression was observed on admixture with an authentic sample, and the infrared, mass, and n.m.r. spectra were identical.

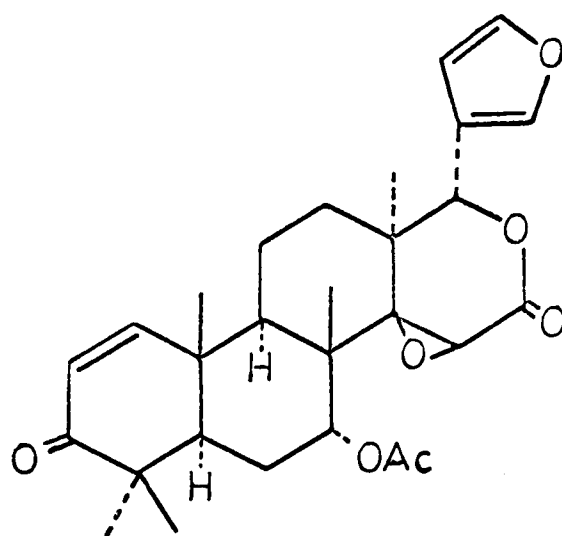
The possible biogenetic origin of turraeanthin (2), methyl angolensate (1) and other oxidised triterpenes found in the related Meliaceae, Rutaceae, and Simaroubaceae plant families is discussed.

References

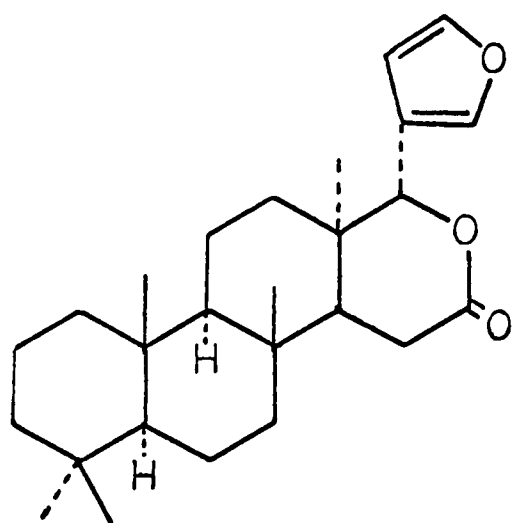
- 1 C.W.L. Bevan, D.E.U. Ekong, and D.A.H. Taylor, Nature, 1965, 206, 1323.
- 2 A. Akisanya, C.W.L. Bevan, J. Hirst, T.G. Halsall, and D.A.H. Taylor, J.Chem.Soc., 1960, 3827.
- 3 J.W. Powell and D.A.H. Taylor, personal communication.
- 4 M. Welford, D.Phil. thesis, (Oxford), 1964.
- 5 W.R. Chan, personal communication; B.S. Mootoo, Ph.D.thesis (Kingston, Jamaica), 1965.
- 6 J.F. Biellmann and G. Ourisson, Bull.Soc.Chim.France, 1962, 331; and the references cited therein.
- 7 D. Arigoni, D.H.R. Barton, E.J. Corey, O. Jeger, L. Caglioti, Sukh Dev, P.G. Ferrini, E.R. Glazier, A. Melera, S.K. Pradhan, K. Schaffner, S. Sternhell, J.F. Templeton, and S. Tobinaga, Experientia, 1960, 16, 41.
- 8 A.J. Birch, D.J. Collins, Sultan Muhammad, and J.P. Turnbull, J.Chem.Soc., 1963, 2762.
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- 10 E.J. Corey and R.A.E. Winter, J.Amer.Chem.Soc., 1963, 85, 2677.



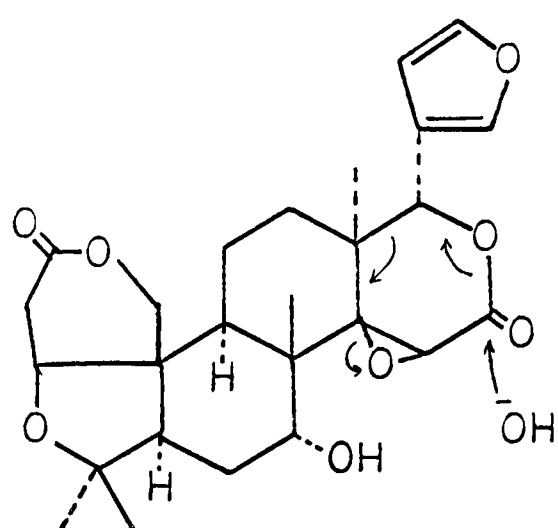
1 Limonin



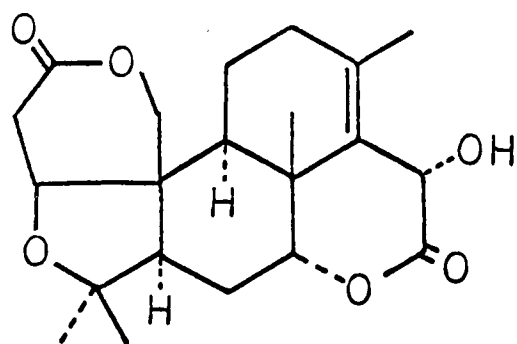
2 Gedunin



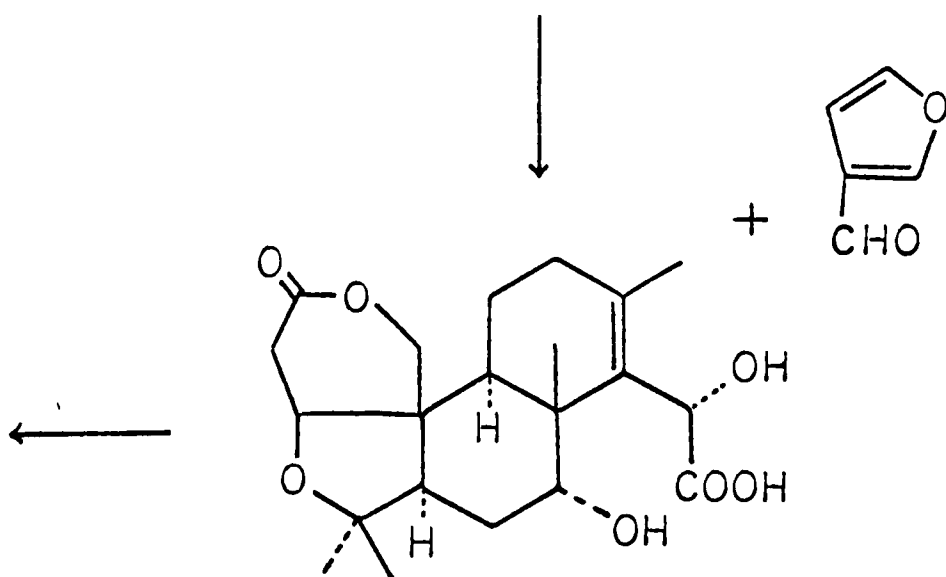
3 'Meliacin'



4 Limonol



5 Merolimonol



CHAPTER I

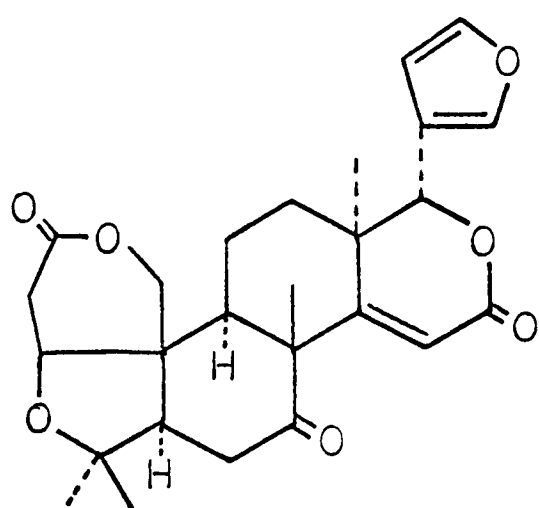
CHAPTER I INTRODUCTION

INTRODUCTION

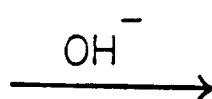
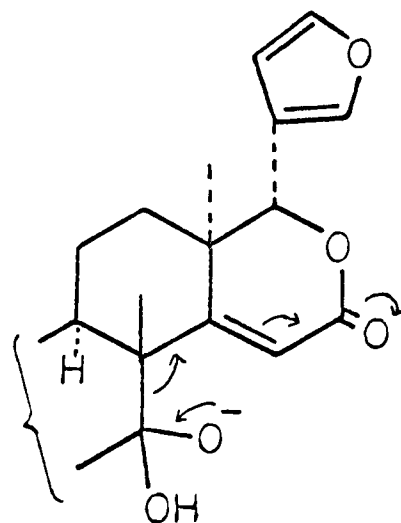
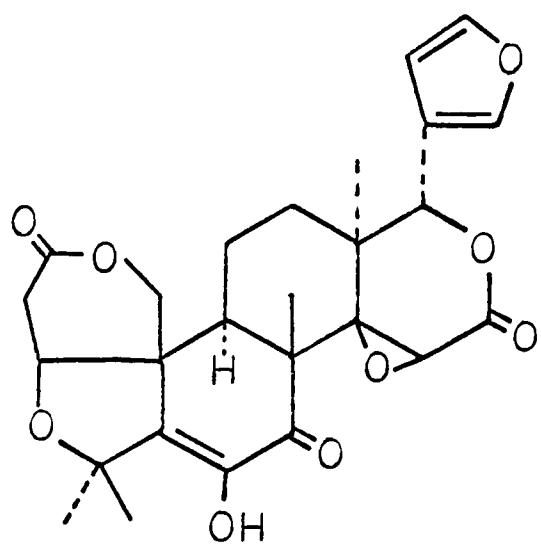
The main subjects of this thesis are the chemistry and structure of methyl angolensate and turraeanthin, two new triterpenes which have been isolated from the heartwoods of species of the family Meliaceae. These compounds are related, structurally and probably biogenetically, to other triterpenes ^{of 1,2} obtained from this family and from the related families Rutaceae and Simarubaceae, which contain a series of progressively oxygenated triterpenes related to limonin (1) and gedunin (2). It is therefore appropriate that a brief review of these compounds should be included. Compounds with the gedunin nucleus occur widely in the Meliaceae family and the name 'meliacin' has been suggested³ for a hypothetical parent substance (3).

Limonin

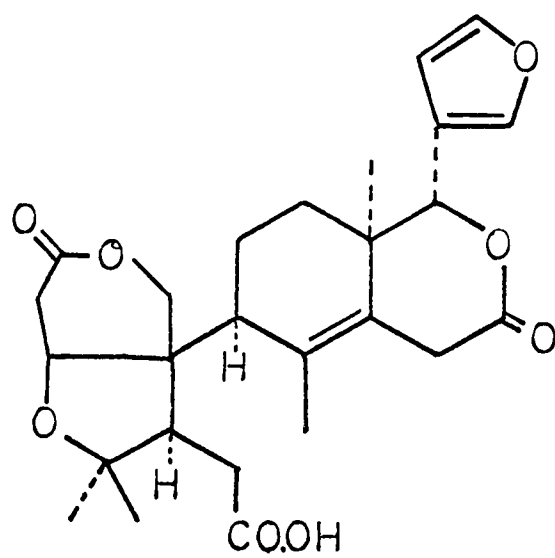
Limonin, the citrus bitter principle, was first isolated in 1841 from the seeds of several species of citrus, and has been found more recently in the fruit, seeds and roots of other species of Rutaceae^{4,9}. It was assigned the structure (1) on the basis of X-ray analysis⁵ and extensive chemical evidence^{6, 7,8}, and more recently an n.m.r. correlation of



6 Desoxylimonin



8 Limonin diosphenol



7 Desoxylimonic acid

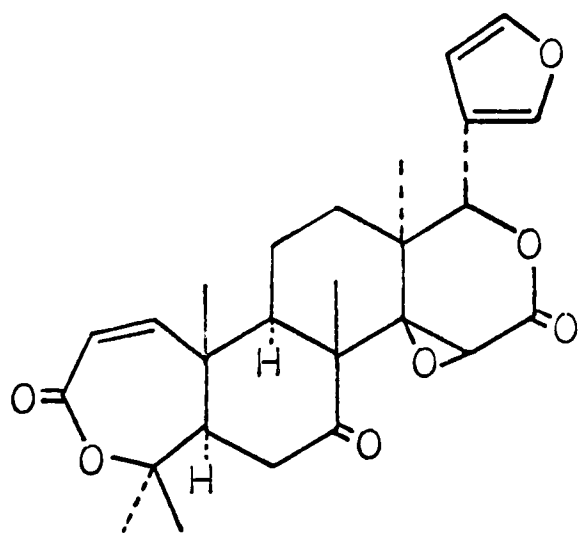
limonin, its derivatives, and nomilin and obacunone (see below) has been carried out^{9a}. The understanding of its chemistry was the starting point for much of the work done on the meliacins. A few aspects of its chemistry are summarised below.

The ketone group of limonin is stereospecifically reduced by the Meerwein-Ponndorf method to give the axial alcohol limonol (4). Mild alkaline hydrolysis of limonol produces cleavage of ring D with elimination of furan-3-aldehyde, and merolimonol (5) is obtained.⁸ Treatment of limonin with hydriodic acid or chromous chloride readily eliminates the conjugated epoxide to give desoxylimonin (6). Treatment of desoxylimonin under mild alkaline conditions produces cleavage of ring B to give desoxylimononic acid (7)⁶. In the presence of potassium *t*-butoxide limonin is readily autoxidised to the diosphenol (8) which proved useful in determining structural features of ring B.⁷ The elucidation of these and other deep-seated changes occurring under basic conditions was the key to the structure of limonin and its congeners.

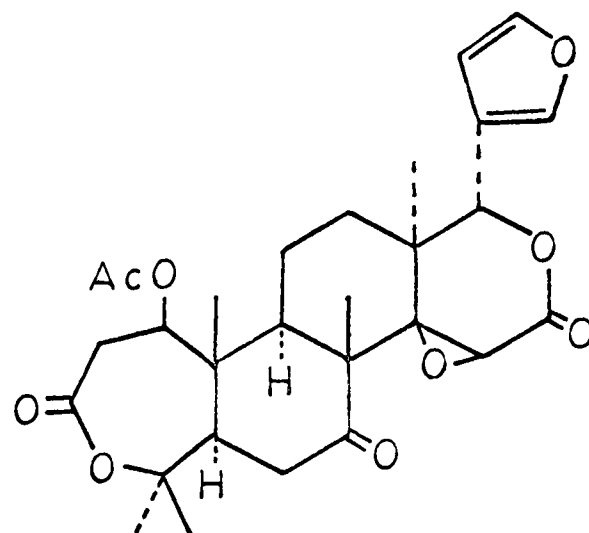
Obacunone and Nomilin

Obacunone was isolated from the bark of Phellodendron

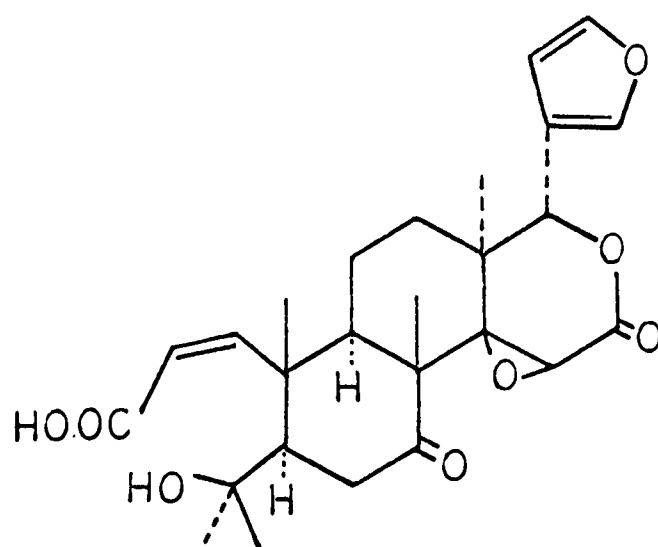
3a



9 Obacunone



10 Nomilin



11 Obacunoic acid

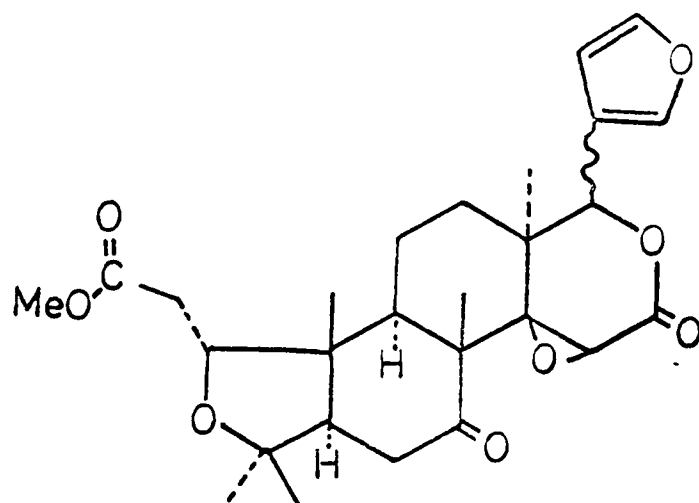
amurense, Rupr. (Rutaceae)¹⁰, and as 'casimirolide' from the seeds of Casimiroa edulis (Rutaceae)¹¹, and was also found together with nomilin, the chief bitter material, in the oil of Florida citrus seeds¹⁰. Structures very similar to limonin have been suggested^{6,7} for obacunone (9) and nomilin (10) on the basis of their analogous chemical behaviour, and obacunone¹² has since been chemically related to limonin through a route which correlates the stereochemistry at all positions except that at C₍₁₇₎. Furthermore, when nomilin is heated with γ -picoline the acetoxy group is eliminated β to the lactone giving obacunone¹³. Both nomilin and obacunone on treatment with mild alkali are converted into obacunonic acid (11)¹³. Relactonisation does not occur spontaneously, and this gives evidence for the presence of a seven-membered ring.

Evodol

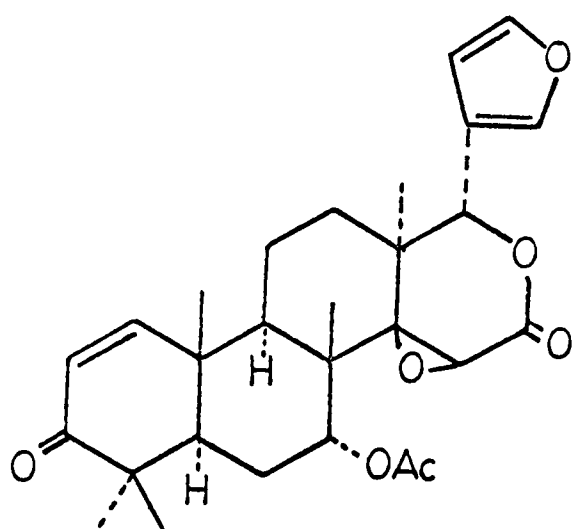
Evodol was found to occur with limonin in the plant Evodia rutseecarpa (Rutaceae)¹⁴. Comparison with an authentic sample established its identity with limonin diosphenol (8).

Veprisone

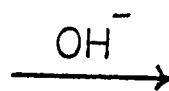
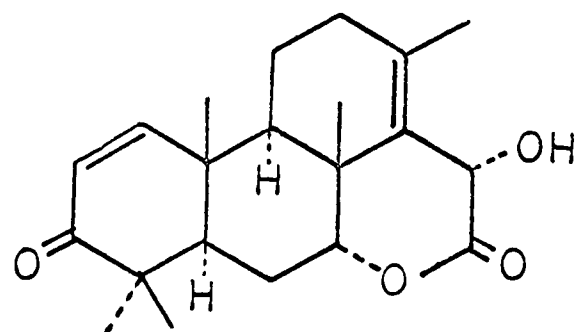
This compound was obtained from the bark of Vepris



12 Veprisone



2 Gedunin



13 Merogedunin

bilocularis (Rutaceae). Comparison of the infrared and n.m.r. spectra of veprisone and its derivatives proved that it is identical with methyl episoobacunoate (12).¹⁵

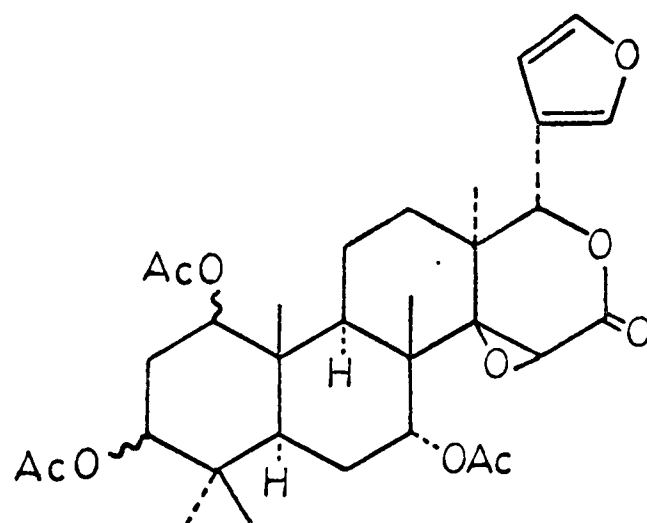
Deacetylnomilin and Desoxylimonin

Deacetylnomilin was isolated as a minor constituent of several citrus species, and desoxylimonin (6) was obtained in low yield from C.paradisi^{9b}. Limonin (1) was the major extractive in both cases.

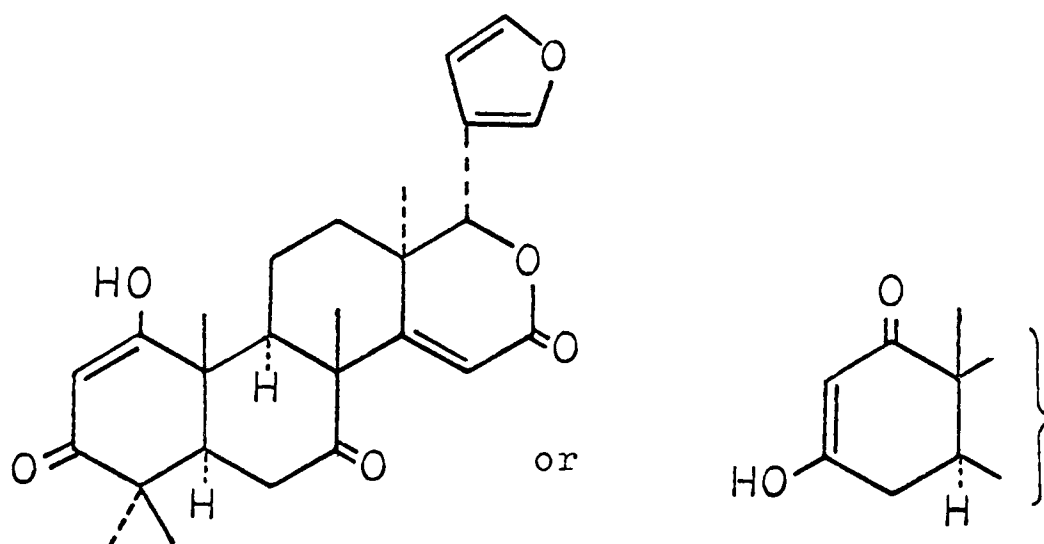
Gedunin

Gedunin (2) occurs in variable amounts in the heartwood of Entandrophragma angolense (Meliaceae)¹⁶ together with methyl angolensate (70) (see later) and in the heartwood of Guarea thompsonii (Meliaceae)¹⁷, and it was the first of the meliscins to have its structure elucidated¹⁸.

Its structure was confirmed by X-ray analysis¹⁹. When subjected to alkaline hydrolysis furan-3-aldehyde is eliminated in a reaction similar to the limonol (4) - merolimonol (5) transformation, and merogedunin (13) is produced¹⁸.



14 Khivorin



15

Derivatives of Gedunin

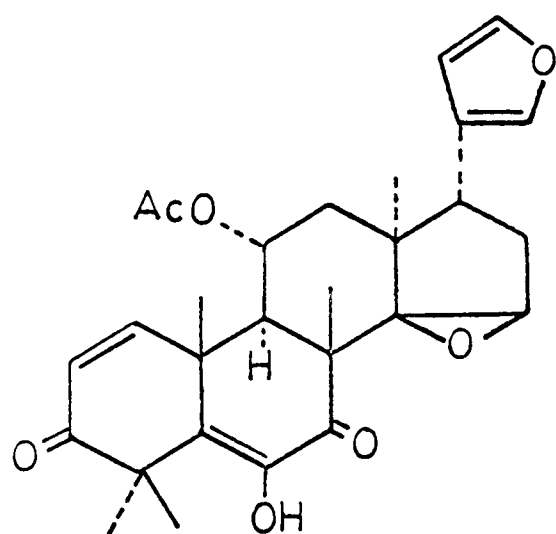
7-Oxodeacetoxygedunin has been obtained from Nigerian Cedrela odorata (Meliaceae)³ and Carapa guayanensis Aubl. (Meliaceae)³². 1,2-Dihydrogedunin^{3,17} and 7-oxodeacetoxy-1,2-dihydrogedunin¹⁷ were found in Guarea thompsonii.

Khivorin

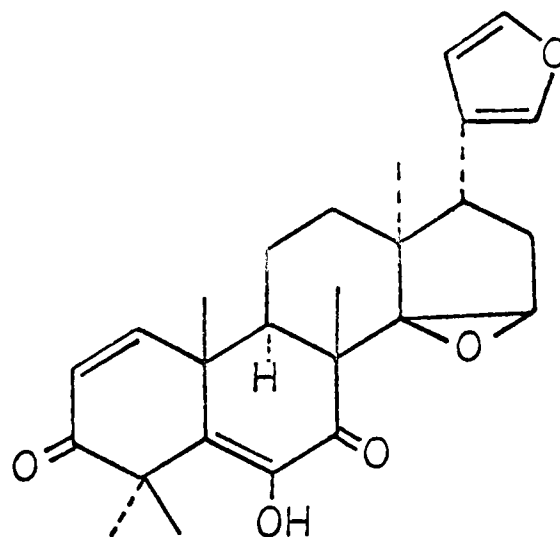
Khivorin was isolated from Khaya ivorensis (Meliaceae)²⁰ and K. grandifoliola³, and was assigned the structure (14) on the basis of its chemical reactions²⁰. In the presence of alkali furan-3-aldehyde is eliminated (cf. gedunin above). Treatment of khivorin with chromous chloride gives desoxykhivorin, analogous to desoxylimonin (6). Hydrolysis of the three acetoxy groups of desoxykhivorin followed by oxidation gives an enolic 1,3-diketone (15), thus placing the acetoxy groups at the 1,3, and 7 positions. Recently khivorin and gedunin (2) have been converted into a common derivative²¹.

Derivative of Khivorin

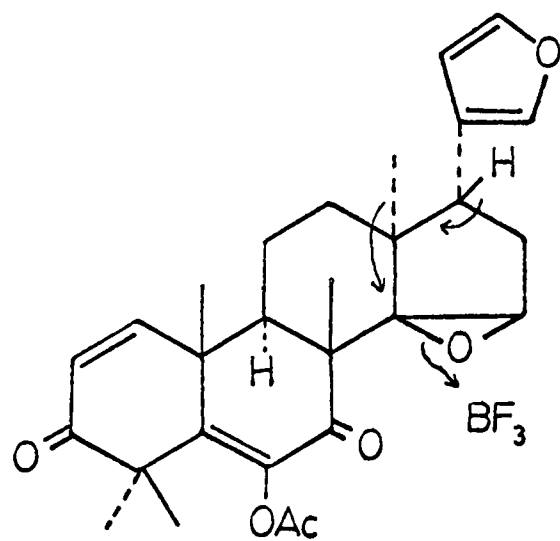
7-Oxodeacetoxykhivorin has been found in K. senegalensis³.



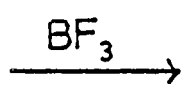
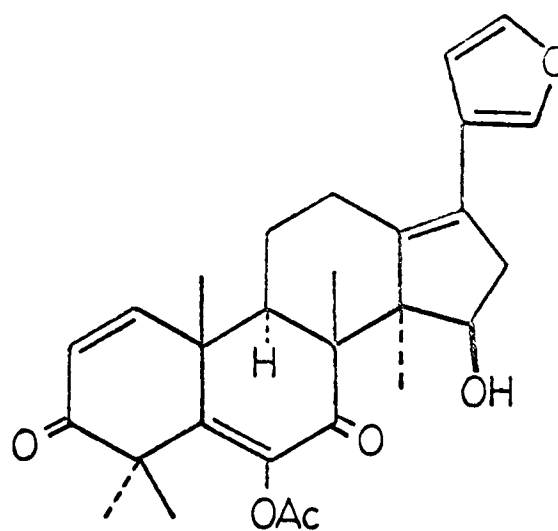
16 Anthothecol



17 Cedrelone



18 Cedrelone acetate



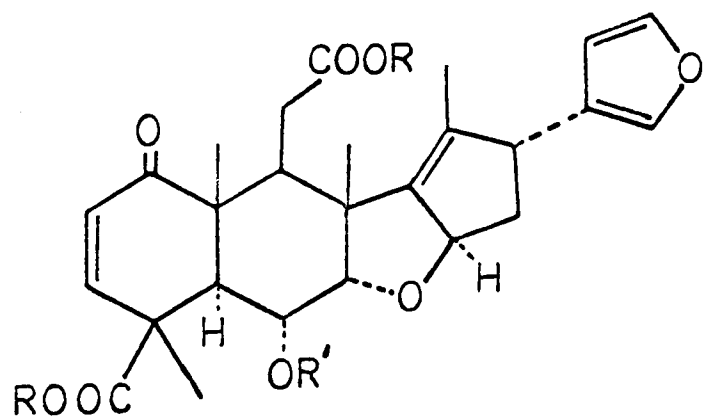
19 Isocedrelone acetate

Anthotheool

This compound was obtained from the heartwood of K. anthotheos³. The structure (16) was elucidated from its chemical reactions²², which are similar to those of cedrelone (see below). It is the 11α -acetoxy derivative of cedrelone.

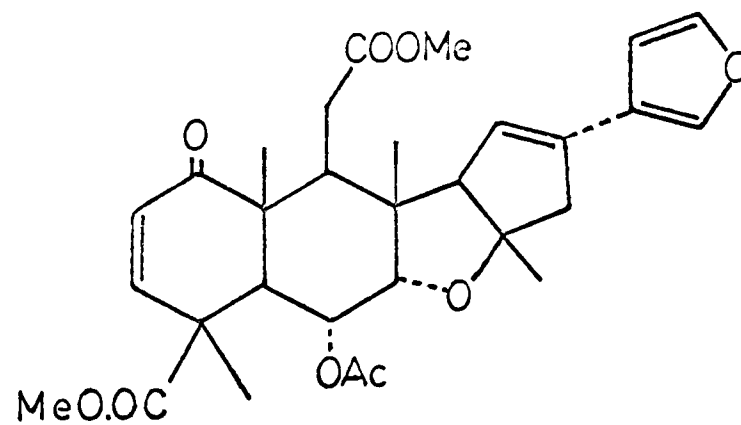
Cedrelone

Cedrelone was extracted from the heartwood of Cedrela toona Roxb. (Meliaceae)²³, and the structure (17) was determined by X-ray crystallography²⁴ and is in agreement with its chemistry²³. The X-ray examination showed that ring C is in the boat conformation, and it is thought that the driving force for the rearrangement of cedrelone acetate (18) to isocedrelone acetate (19) occurring under acidic conditions is the relief of steric strain as ring C becomes a chair. Recently an infrared study of the hydrogen bonding in cedrelone and related compounds has been carried out²⁵. This characterized the intramolecular hydrogen bonds closing the planar five-membered diosphenol in cedrelone, and the twisted seven-membered ring between the ring B carbonyl group and the ring D hydroxyl group in the isocedrelone series.

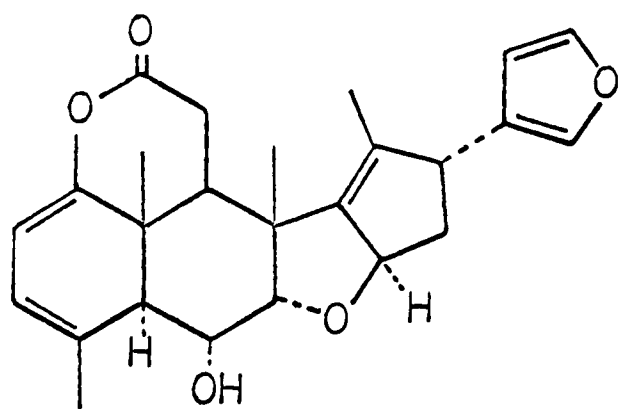


20 R = Me, R' = Ac, Nimbin

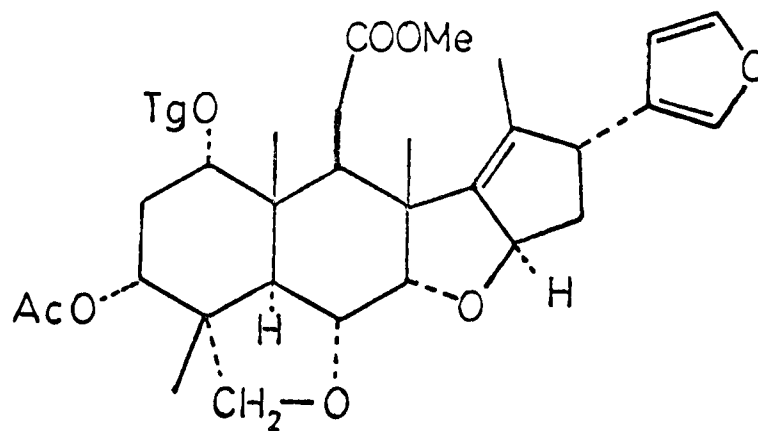
22 R = R' = H, Nimbic acid



21 Isonimbin



23 'Pyronimbic acid'



24 Salannin

Nimbin

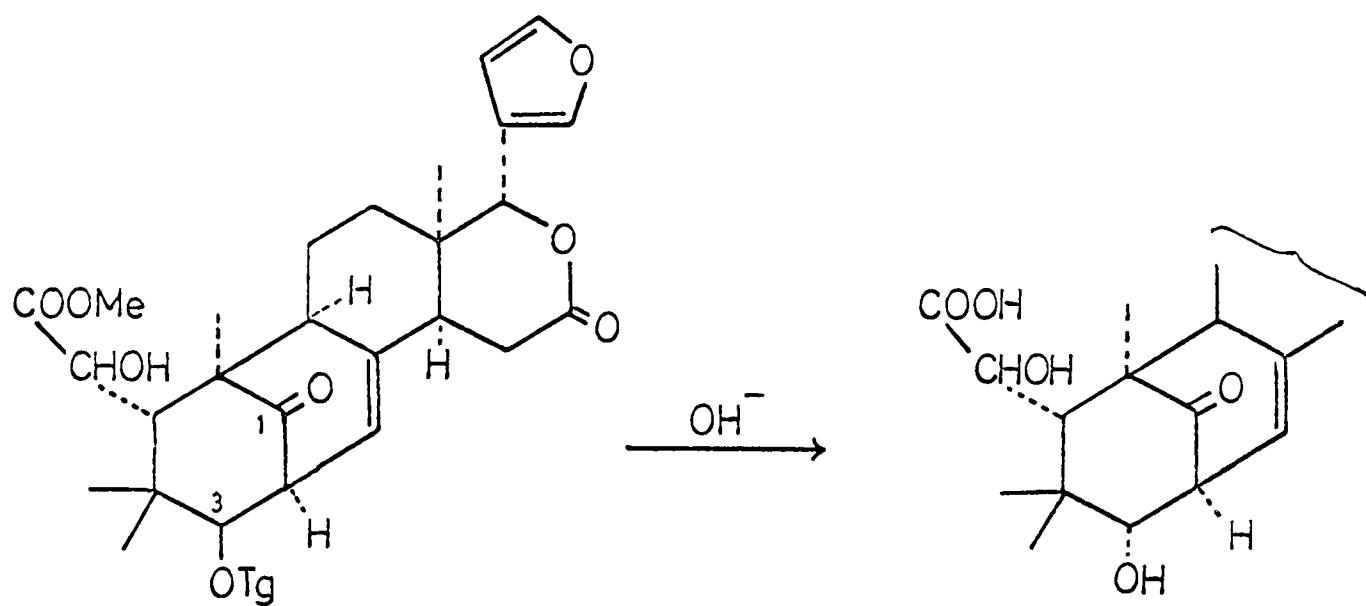
Nimbin was isolated from nim oil, the seed oil of Melia azadirachta Linn. (Meliaceae) and was assigned the structure (20) on the basis of chemical evidence^{26,27}. Nimbin isomerises under acidic conditions to isonimbin (21) in which the furan is in conjugation with a double bond. Pyrolysis of nimbic acid (22), obtained by alkaline hydrolysis of nimbin, results in decarboxylation and lactonisation to give a neutral substance, 'pyronimbic acid' (23).

Salannin

This compound was obtained as a minor constituent of nim oil during the isolation of nimbin (see above)²⁷. By analysis of the n.m.r. spectra of salannin and its derivatives, and by comparison of its chemistry with that of nimbin, salannin was assigned the structure (24)²⁷.

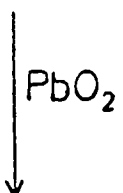
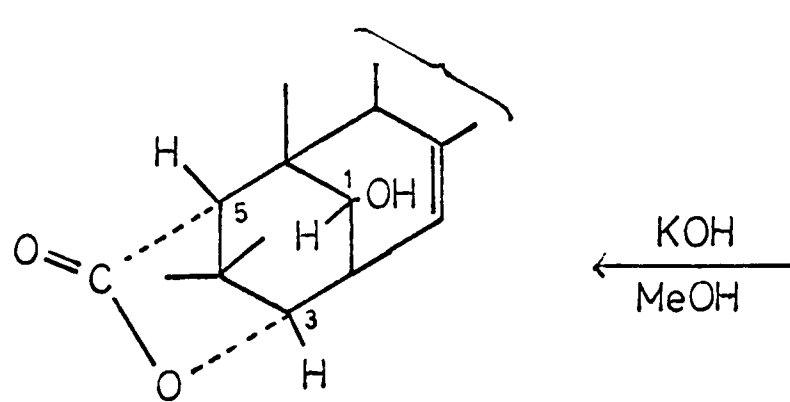
Swietenine

Swietenine was isolated from the seeds of Swietenia macrophylla King (Meliaceae)²⁸. Its constitution and stereochemistry were established as (25) by X-ray crystallography²⁹, and confirmed by its chemical reactions³⁰.



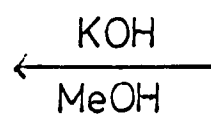
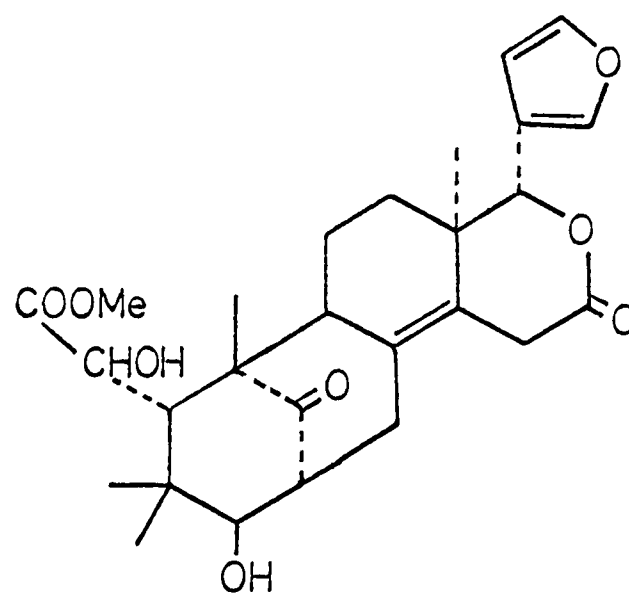
25 Swietenine

26



28

27



29 Swietenolide

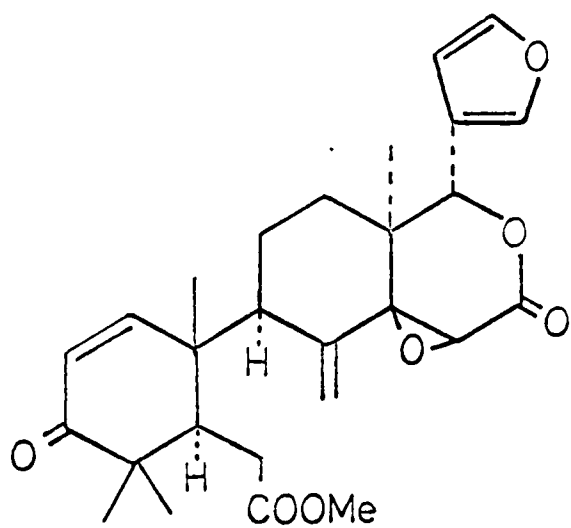
Alkaline hydrolysis of swietenine gives the α -hydroxy acid (26) with inversion of configuration at the 3 position by a retro- and re- aldolisation of the β -ketol system in ring A. Oxidation of this acid with lead dioxide gives the nor-aldehyde (27) which with methanolic potassium hydroxide undergoes an intramolecular Cannizzaro reaction with the C₍₁₎ carbonyl group to give a γ -lactone (28). Since the new carboxyl group can lactonise only with the C₍₃₎ hydroxyl group already present its configuration is defined.

Swietenolide

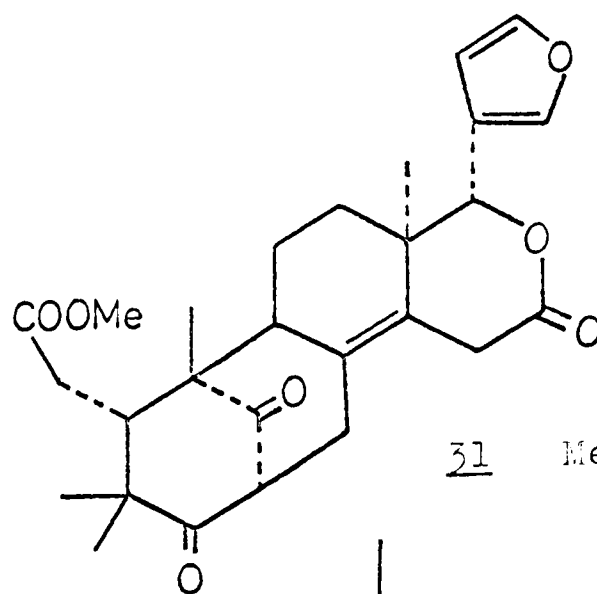
This compound occurs together with swietenine (25) in the seeds of Swietenia macrophylla²⁸. It was assigned the structure (29) on the basis of its chemical reactions³¹ which bear a close resemblance to those of mexicanolide (31) (see below) and swietenine. However, attempts to relate swietenolide to mexicanolide or swietenine directly have so far been unsuccessful.

Andirobin

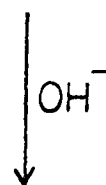
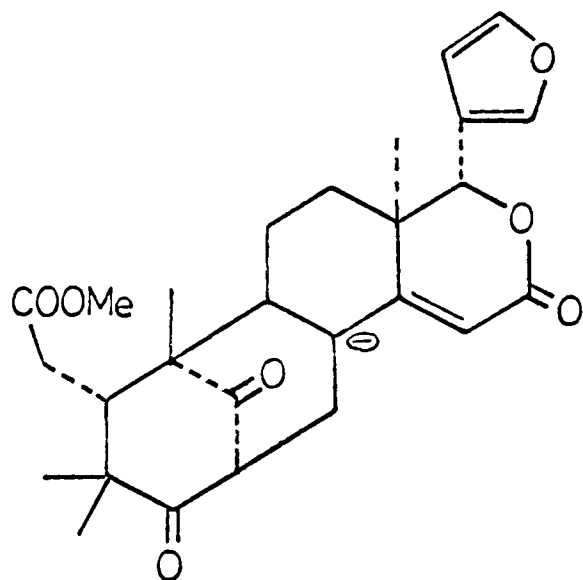
Andirobin was obtained from the seeds of Carapa guayanensis Aubl. (Meliaceae)³² together with 7-oxodeacetoxy-



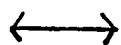
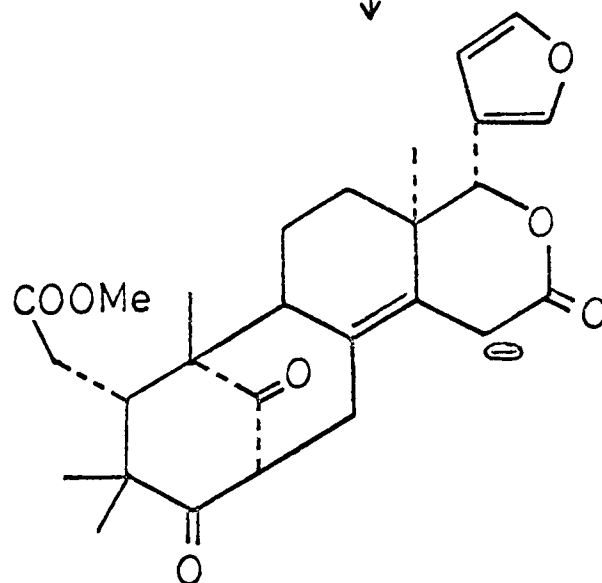
30 Andirobin



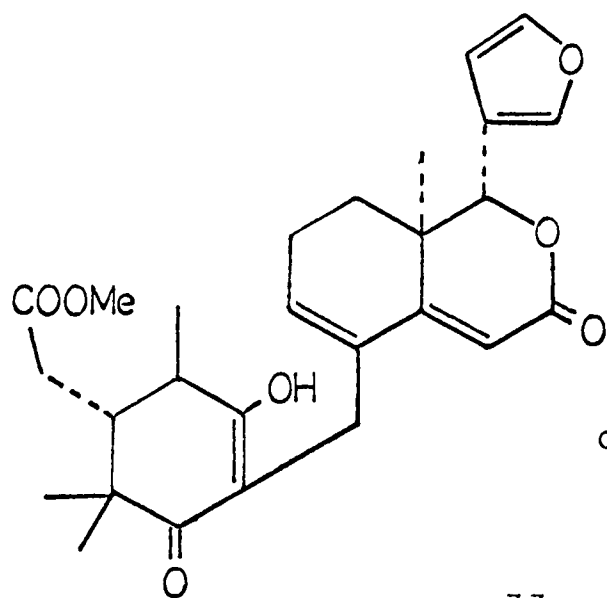
31 Mexicanolide



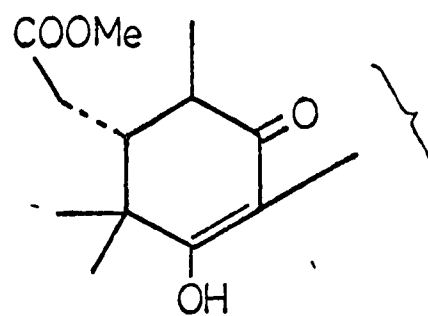
32b



32a



or

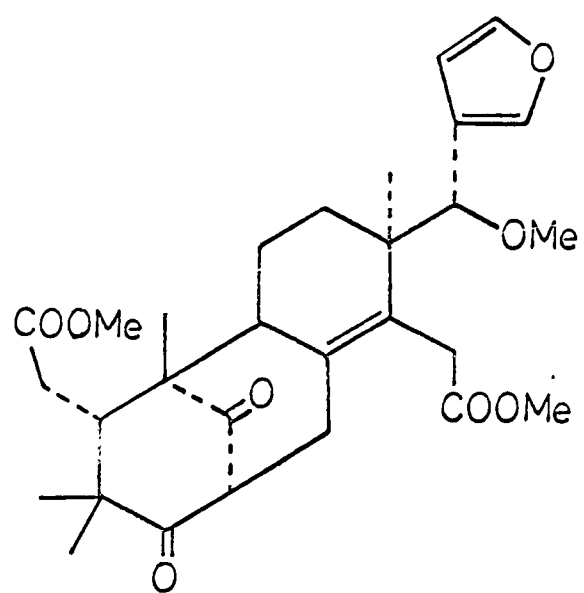
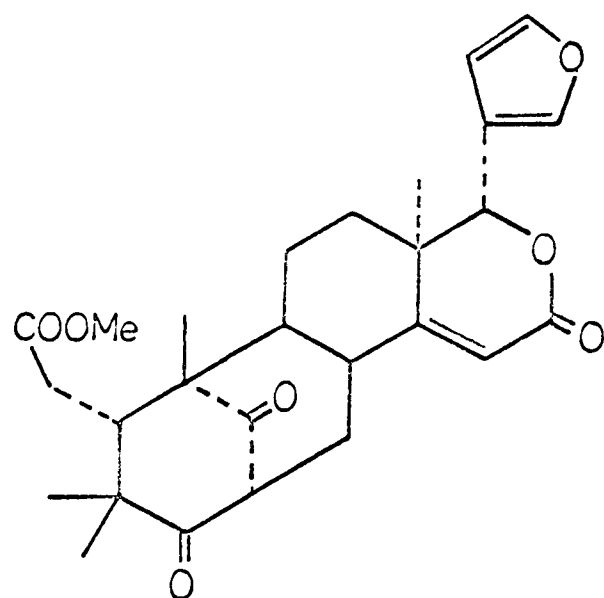
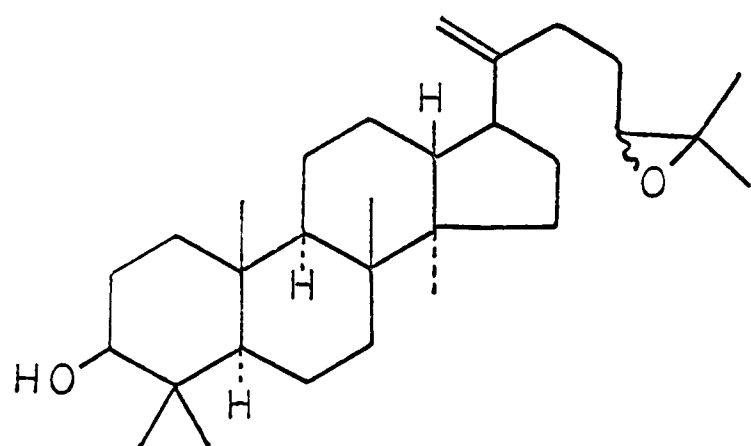
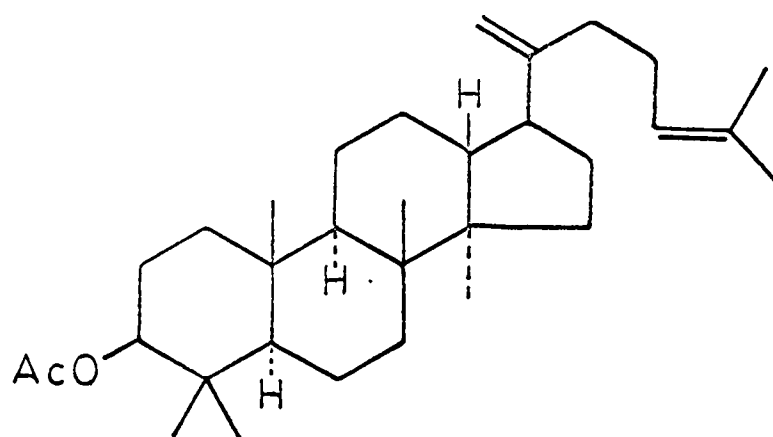


33

gedunin³. The structure (30) was deduced³² for andirobin on the basis of its chemical reactions and by comparison of its spectral properties with those of 1,2-dihydrogedunin^{3,17}. Its chemistry closely parallels that of methyl angolensate (70), the constitution of which was elucidated independently³³ and which will be discussed later.

Mexicanolide and Cedrela odorata Substance B

From the timber of Cedrela odorata (Meliaceae)³ were isolated two substances A and B. Compound A was shown to be 7-oxodesacetoxygedunin³. The structure (31) has been deduced³⁴ for compound B which is identical with the structure already suggested³⁵ for mexicanolide obtained from C. mexicana. The constitution and stereochemistry of compound B have been confirmed by X-ray crystallography³⁶. On the addition of a few drops of aqueous sodium hydroxide to an ethanolic solution of (31) an extremely rapid rearrangement occurs to give an enolisable β -diketone (33). Removal of a proton from C₍₁₅₎ would give a mesomeric anion (32a)³⁷ which could cleave by a retro-Michael fission to the β -diketone (33)³⁵. Swietenolide (29) also undergoes an analogous rearrangement³¹. Treatment of (31) with methanolic sulphuric acid opens the

3435 Carapin36 Aglaiol37 Dammaradienyl acetate

lactone to give (34)³⁴.

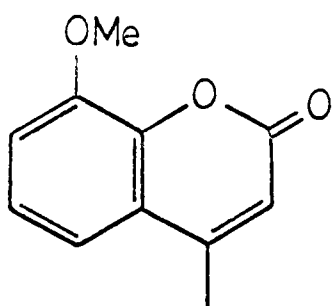
Carapin

Carapin was obtained from Carapa procera (Meliaceae) and the structure (35) has been deduced³⁷ for it. On chromatography over alumina carapin isomerises to (31). Alkaline hydrolysis affords (33) via the mesomeric anion (32b) but the rearrangement occurs 250 times more slowly than the corresponding transformation of compound B (31). This may be due to the C₍₈₎ position being more inaccessible to attack by hydroxide ion than the C₍₁₅₎ position. However, the comparatively large difference observed in the rates suggests³⁷ that the rearrangement of compound B is a concerted reaction aided by Grob's 'frangomeric acceleration'^{37,38}. Carapin is also distinguished from compound B (31) by not giving (34) with methanolic sulphuric acid.

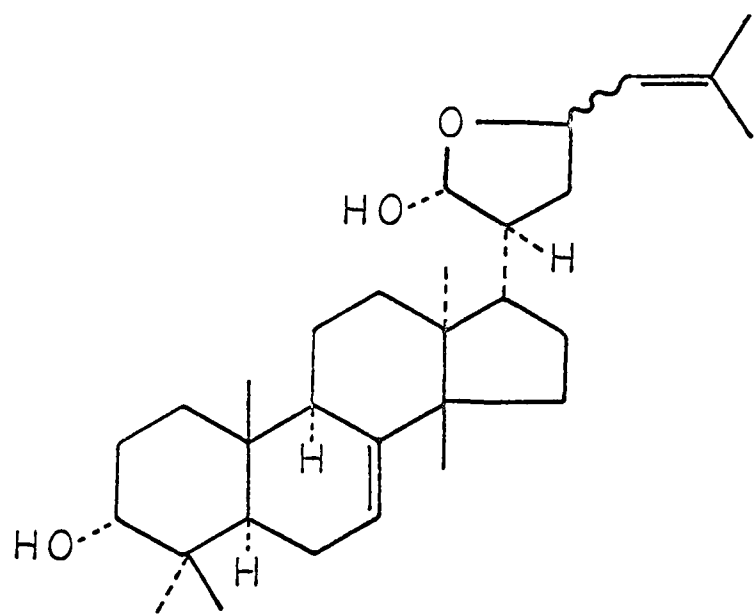
Aglaiol

Aglaiol was extracted from the leaves of Aglais odorata Lour. (Meliaceae). It was shown³⁹ to possess structure (36) on the basis of its chemical reactions and by analysis of its spectra. The formula was confirmed by direct correlation with dammaradienyl acetate (37).

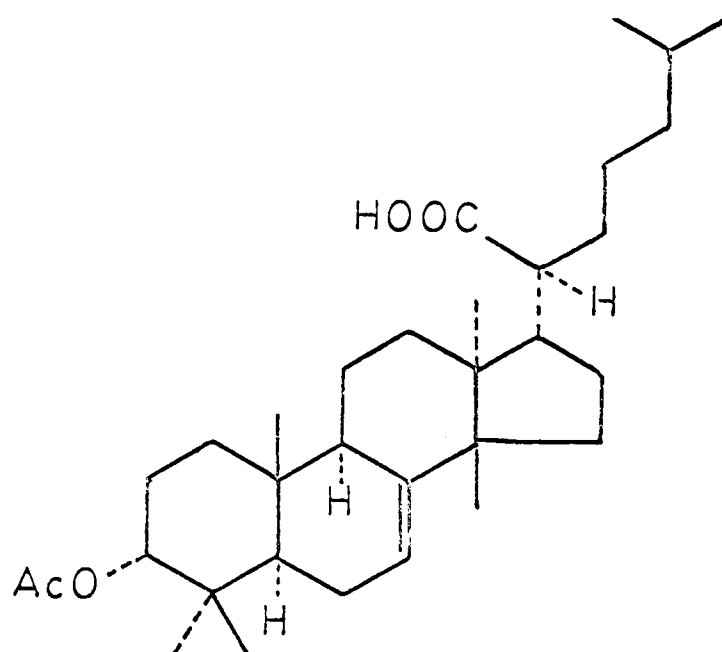
11a



38 8-Methoxy-4-methylcoumarin



39 Flindissol



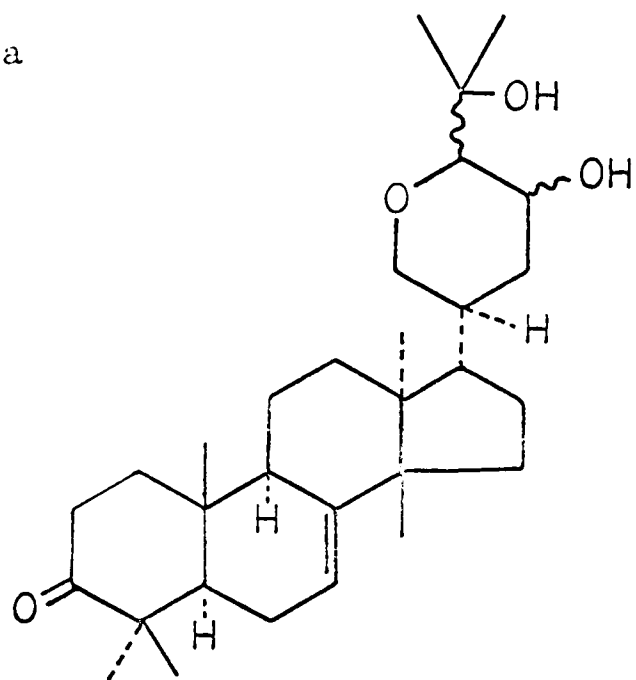
40 Acetyl dihydro-" α -elemolic acid"

8-Methoxy-4-methylcoumarin

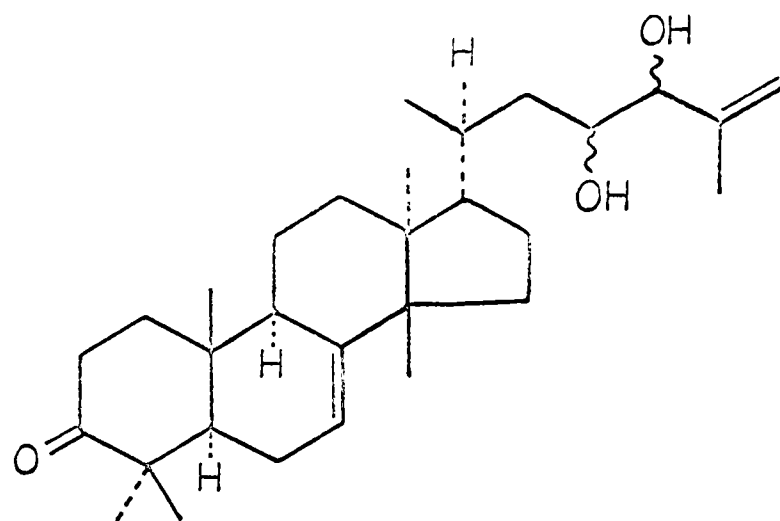
The presence of oxygenated triterpenes related to gedunin (2) is characteristic of the species of Meliaceae listed above. However, extraction of the heartwood of Ekerbergia senegalensis (Meliaceae) from Northern Nigeria afforded 8-methoxy-4-methylcoumarin⁴⁰ (38). The structure was confirmed by synthesis⁴⁰. E. senegalensis is the first member of the Meliaceae found to contain a coumarin. It is interesting to note that coumarins occur widely in the family Rutaceae⁴¹ which also contains oxygenated triterpenes such as limonin (1)⁸ (see above).

Flindissol

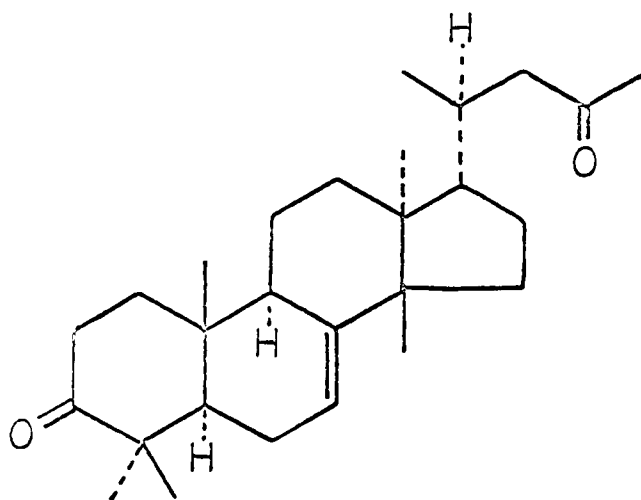
Flindissol was isolated from the bark and leaves of Flindersia dissosperma Domin. and from the bark of Flindersia maculosa Lindl.⁴² The structure (39) was assigned⁴³ to flindissol on the basis of its chemical reactions and spectral properties. It was confirmed by the conversion of flindissol to the known compound acetyl dihydro- "α-elemolic" acid (40)⁴³. Some aspects of the chemistry of flindissol are similar to that of turraeanthin which will be discussed later. Flindissol is of considerable biogenetic interest as it



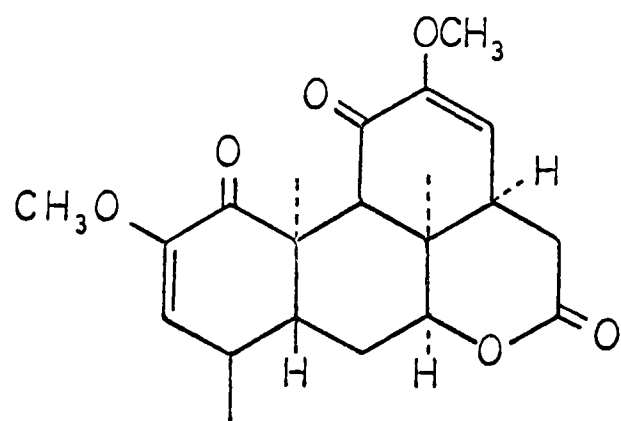
41 Bourjotinolone A



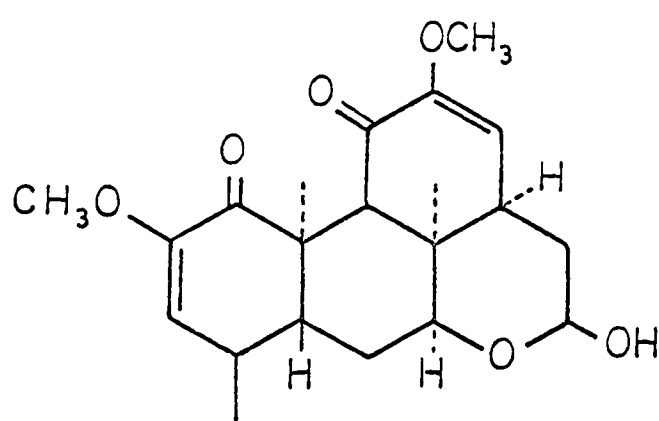
42 Bourjotinolone B



43 Bourjotone



44 Quassin



45 Neoquassin

corresponds to a possible hypothetical precursor for the biogenesis of the meliacin type of compounds.

Bourjotinolones A and B, and Bourjotone

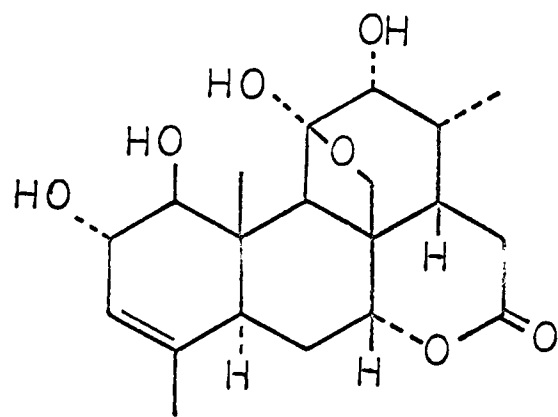
From Flindersia bourjotiana F. Muell.⁴⁴ were obtained three new triterpenes, bourjotinolone A (41), bourjotinolone B (42) and bourjotone (43). The structures were deduced from their chemical reactions, and bourjotinolone B was degraded to the known substance 24,25-dihydrotirucall-7-en-3 β -yl acetate⁴⁴.

Quassin and Neoquassin

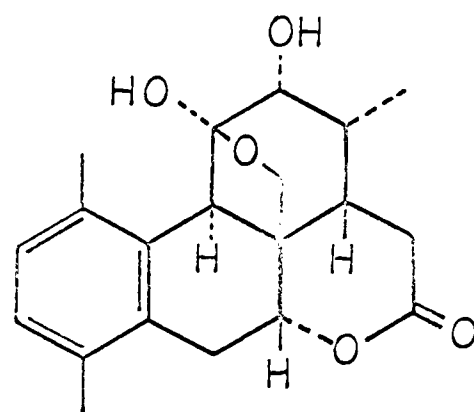
These compounds are the bitter components of quassia wood, Quassia amara Linn., and they were the first triterpenes from the Simaroubaceae family to have their structures established^{45,46}. The structure (44) was assigned to quassin on the basis of chemical evidence and extensive use of n.m.r. spectroscopy. Neoquassin (45) is the hemi-acetal of quassin, and can be converted into quassin by mild oxidation.

Chaparrin

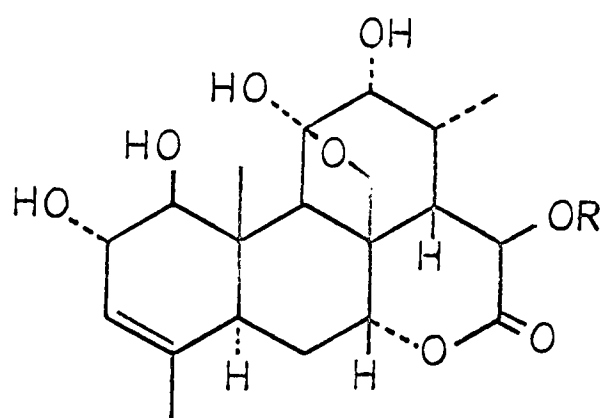
Chaparrin is the bitter principle of Castela nicholsoni



46 Chaparrin

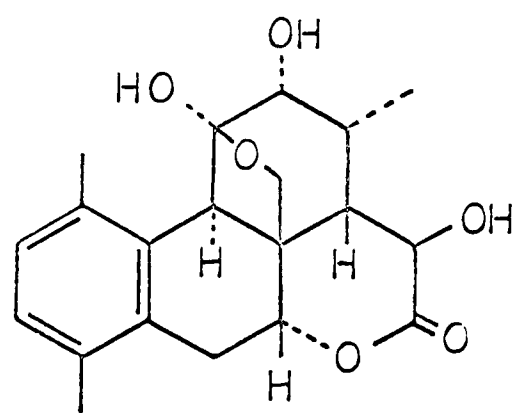


47 Chaparrol



48 R = $\begin{array}{c} \text{Et} \\ | \\ -\text{CO}-\text{C}-\text{OH} \\ | \\ \text{Me} \end{array}$, Glaucarubin

49 R = H, Glaucarubol

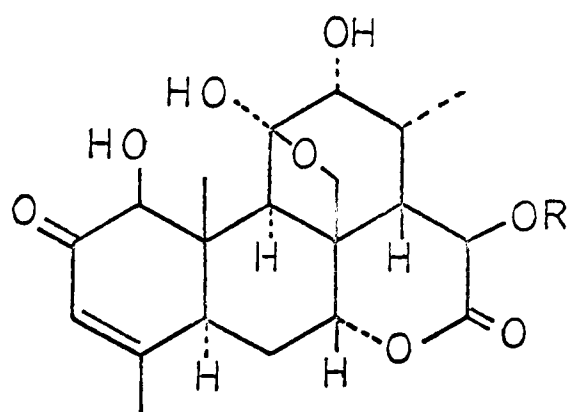


50 Glaucanol

Hook. (Simaroubaceae), and it has been assigned the structure (46)^{47,48,68}. Treatment of chaparrin with acid results in the ready loss of two molecules of water and concomitant aromatisation of ring A. The product, chaparrol (47), shows typical benzenoid absorption in its ultraviolet spectrum.

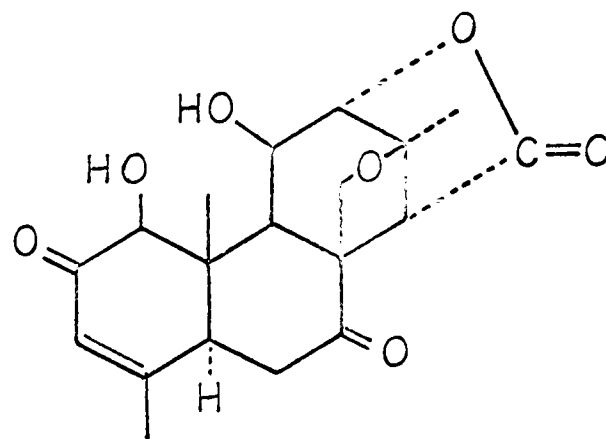
Glaucarubin and Glaucarubol

Extraction of the seeds of Simarouba glauca (Simaroubaceae)⁴⁹ gives the bitter principle glaucarubin (48) which is the 2-hydroxy-2-methylbutyric ester of glaucarubol (49). Glaucarubol was also isolated as the free hydroxy compound from Castela nicholsoni Hook.⁵⁰ The structure and stereochemistry of glaucarubin (48) were determined independently by chemical means⁴⁹ and X-ray crystallography⁵¹. Alkaline hydrolysis of glaucarubin gives (+)-2-hydroxy-2-methylbutyric acid, and thus the stereochemistry of the side chain can be written as in (48)⁵². Treatment of glaucarubol (49) with acid causes a rapid aromatisation of ring A to give glaucanol (50), from which the structure of glaucarubol was suggested by analogy with the chaparrin (46) - chaparrol (47) transformation.

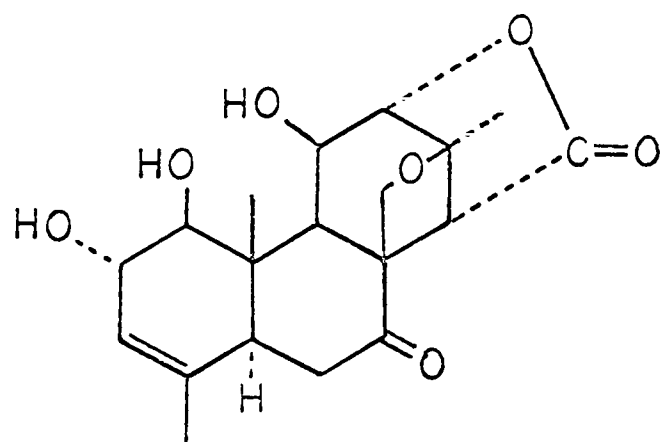


51 $R = -\text{CO}-\underset{\text{Me}}{\overset{\text{Et}}{\text{C}}}-\text{OH}$, Glaucarubinone

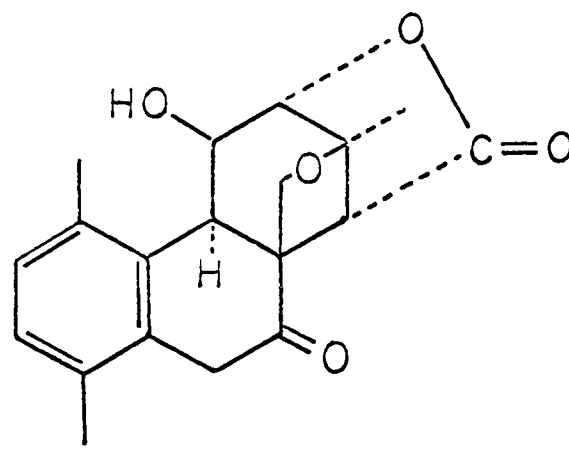
51a $R = \text{H}$, Glaucarubolone



52 Samaderin B



53 Samaderin C



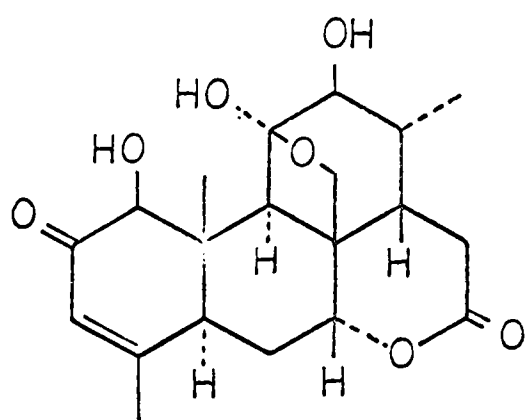
54 Samaderol

Glaucarubinone

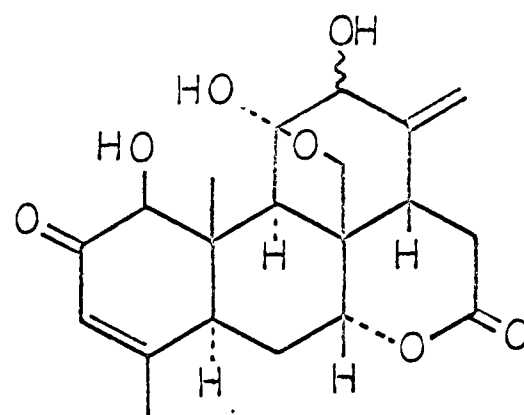
Glaucarubinone was obtained as the second bitter constituent of the seeds of Simarouba glauca and was found together with glaucarubin (48) in the seeds of Perriera madagascariensis⁵³. It was assigned the structure (51) on the basis of an n.m.r. spectral analysis and by comparison of its chemistry with that of glaucarubin (48)⁵⁴. The structure was confirmed by a synthesis from glaucarubin (48) by oxidation of the latter with manganese dioxide to give glaucarubinone (51)⁵⁴.

Samaderins A and B

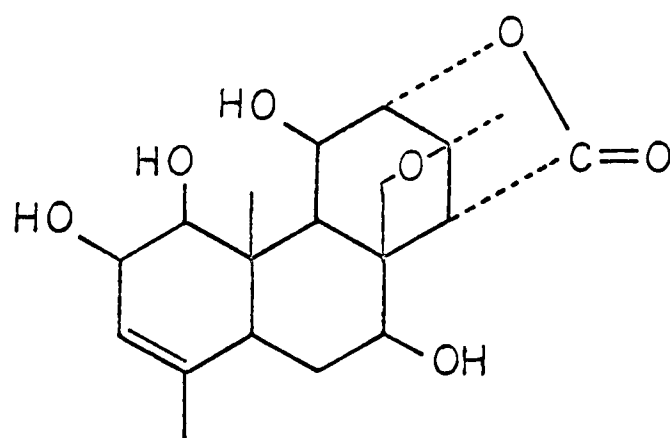
Extraction of the nuts from the tree Samadera indica Gartn (Simaroubaceae) gave two glycosides, samaderosides A and B⁵⁵. The former could be readily hydrolysed under acidic conditions. The bark of the same tree was shown to contain three new compounds, samaderins A, B and C⁵⁶. Samaderin C, the bitter constituent, has been identified with samaderoside A⁵⁵. The structures of samaderin B (52) and samaderin C (53) have been suggested on the basis of their chemical reactions and analysis of their spectra⁵⁷. Treatment of samaderin C (53) with acid readily results in a double



55 Chaparrinone



56 Ailanthone



57 Cedronyline

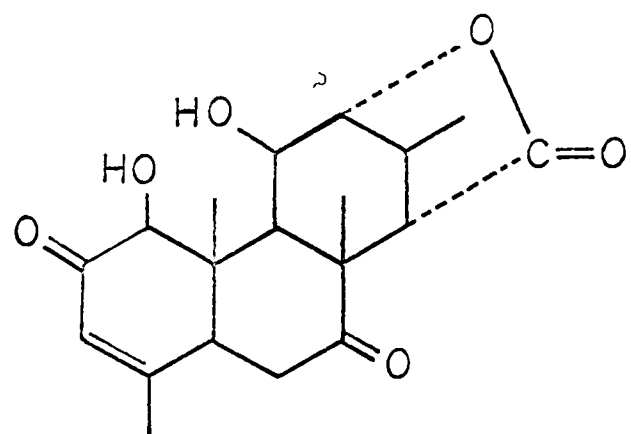
dehydration and aromatisation of ring A to give samaderol (54).

Ailanthone and Chaparrinone

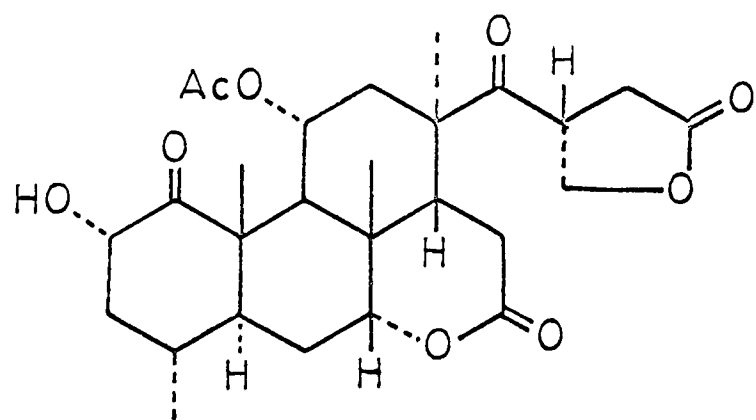
Three triterpene bitter principles were obtained by extraction of the seeds of Ailanthus altissima (Mill.) Swingle⁵⁸. The first was found to be identical with the bitter constituent chaparrinone (55) isolated from Hannoa Klaineana⁵⁸. The principal component, ailanthone (56), has also been obtained from A. glandulosa Desf.⁵⁹ (which is probably identical with A. altissima). The structure (56) has been proposed^{58,59} for ailanthone on the basis of its chemistry and spectral properties. This was confirmed by relating ailanthone directly to chaparrinone (55)⁵⁸. The name ailantholide has been suggested for the third bitter principle, but the structure has not yet been elucidated.

Cedronyline and Cedronine

Extraction of the nuts from the tree Simba cedron Planch. (Simaroubaceae)⁶⁰ gave cedronyline and cedronine. The structure (57) has been proposed for cedronyline on the basis of n.m.r. spectroscopic studies and chemical work^{61a}.



58 Eurycomalactone



59 Simarolide

Studies on cedronine have established that it has an α,β -unsaturated ketone, and a γ -lactone, and contains hydroxyl groups. However, a complete structure has not yet been reported.

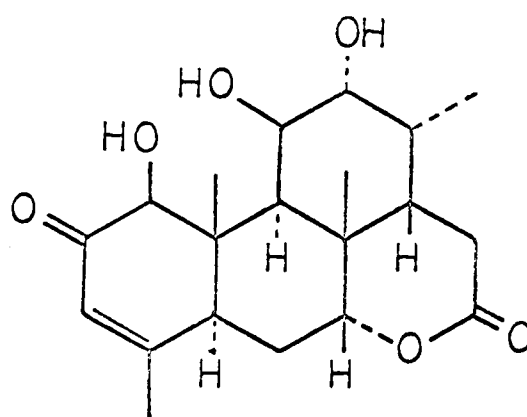
Eurycomalactone

Eurycomalactone was isolated from the bark of Eurycoma longifolia Jack. (Simaroubaceae). The structure (58) has been suggested^{61b} on the basis of chemical evidence and by comparison with samaderin compounds (see above).

Simarolide

Simarolide is the bitter principle obtained from the bark of Simarouba amara (Simaroubaceae)⁶². The structure and stereochemistry as in (59) were deduced from an X-ray crystallographic study⁶³ in conjunction with concomitant work on its chemical reactions⁶⁴. The compound seems to represent a structural type intermediate between that found in other members of the Simaroubaceae family and that of the limonin group of compounds obtained from the families Rutaceae and Meliaceae.

17a



. 60 Klaineaneone

Klaineane and Chaparrinone

Three triterpene bitter principles were isolated from the seeds of Hannonia klaineana (Simaroubaceae)⁶⁶. One of them has been identified as glaucarubolone (51a), the product of alkaline hydrolysis of glaucarubinone (51). The other two compounds, chaparrinone (55) and klaineane (60), had their structures determined on the basis of their chemical reactions and by analysis of their spectral properties.

Taxonomic Implications⁴¹

Early in the development of natural product chemistry it was realised that it should be possible to classify plants on the basis of their chemical constituents. Biosynthetic pathways leading to particular products are as characteristic of a plant species as are the morphological features. Indeed morphological features are in some sense themselves a product of biosynthetic pathways. The characteristic chemical constituents are genetically controlled and, unlike many morphological characteristics which are subjective, can be exactly described in terms of a definite chemical structure. The method of chemical taxonomy thus consists of the investigation of the distribution of chemical compounds,

or groups of biosynthetically related compounds, in related plant families. It is possible that in the future enzymes may be found to be more important for the classification of plants than their chemical end-products.

The Rutaceae, Meliaceae and Simaroubaceae plant families are considered to be closely related on morphological grounds. The Rutaceae has been divided into seven subfamilies which differ among themselves to such an extent that some have been regarded as independent families. However, on the basis of their chemical constituents the major subfamilies of the Rutaceae are a highly homogenous group. Furoquinoline alkaloids are found in four of the five subfamilies including the Flindersioideae, and have never been found in any other family. Chemically the genus Flindersia which has been classified elsewhere is a typical rutaceous species⁶⁵.

The occurrence of oxygenated triterpenes derivable from a tirucallol-type precursor in the Rutaceae, Meliaceae and Simaroubaceae provides further chemotaxonomic evidence that these families are closely related. This will become more evident when the possible biogenetic relationships are discussed later. The presence of coumarins is a well-known characteristic of the Rutaceae, and the recent isolation of

a coumarin⁴⁰ from a species of Meliaceae is another example of the close relationship between these two families.

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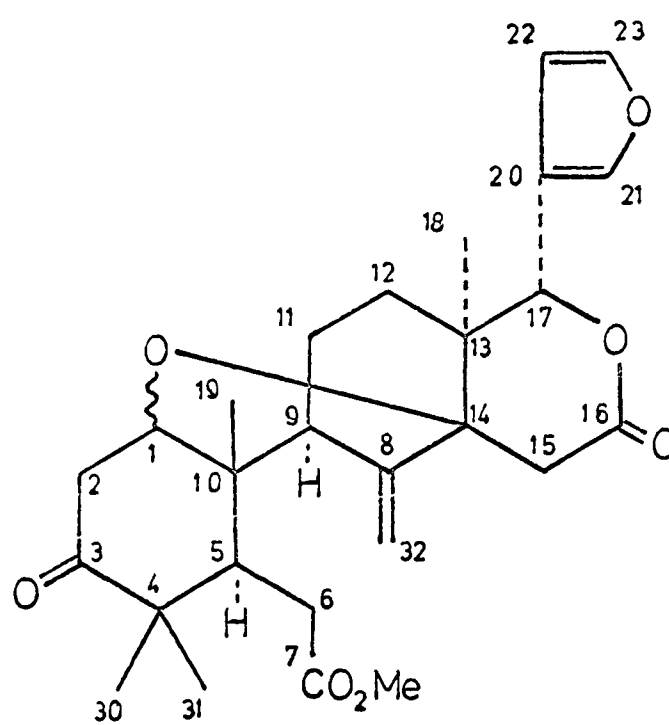
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CHAPTER II

THE STRUCTURE AND CHEMISTRY OF METHYL ANGOLENSATE

The Structure and Chemistry of Methyl Angolensate

Methyl angolensate has been found in several species of the family Meliaceae^{cf.1} obtained from Nigeria. It was first isolated from Entandrophragma angolense.² Extraction of the heartwood of this tropical tree with petroleum ether gave either methyl angolensate or gedunin (2) or a variable mixture of the two. It has since been found in the wood of Guarea thompsonii³ with dihydrogedunin and in the wood of E. utile² together with entandrophragmin and utilin. Khaya grandifoliola¹ usually contains khivorin (14) but extraction of some specimens yielded a mixture of methyl angolensate and Cedrela odorata substance B (31). Methyl angolensate has also been isolated from the wood of the West Indian Cedar, Cedrela odorata⁴ found in Jamaica. C. odorata does not occur naturally in West Africa but it is cultivated commercially for its valuable timber. When grown in Southern Nigeria it contains, not methyl angolensate, but Cedrela odorata substance B (31) and 7-oxodesacetoxygedunin⁵. The variations in the chemical constituents of the latter two species suggest a close biogenetic and probably structural relationship between these compounds. It is interesting to note that a sample of



70 Methyl angolensate

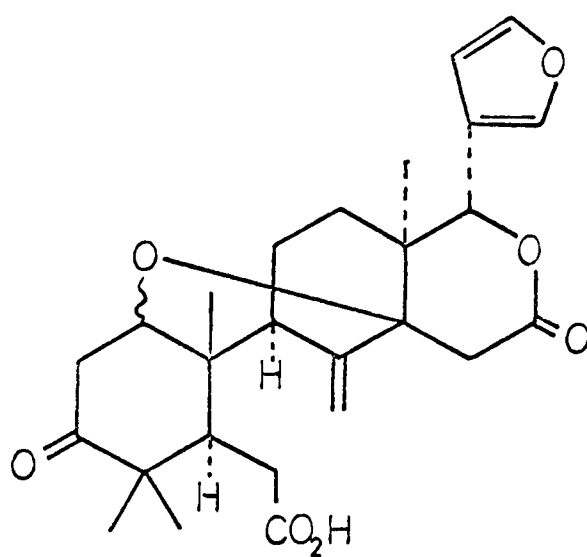
E. angolense⁶ obtained from Uganda did not contain methyl angolensate, gedunin or any other meliacin. However, the specimens from which the extracts were taken had some botanical differences from those found in West Africa, so it seems possible that they may belong to a different species.

Structural studies were started by Akisanya⁷ and carried on by Powell and Taylor⁸ in Ibadan. The work was continued by Welford⁹ and the author. Methyl angolensate was also isolated independently by Chan⁴ in Jamaica with whom there has been an interchange of information.

Methyl angolensate is a crystalline solid, m.p. 203-208°. King et al.³ proposed the formula $C_{27}H_{34}O_7$ which has since been confirmed by mass spectrometry. The constitution and stereochemistry as in (70) are proposed and the subsequent work will be discussed in terms of this structure.

Functional Groups

An absorption band at 1713 cm^{-1} in the infrared spectrum of methyl angolensate indicated the presence of a ketone group. Confirmation was obtained by the formation of an oxime and a 2,4-dinitrophenylhydrazone.³ It could be

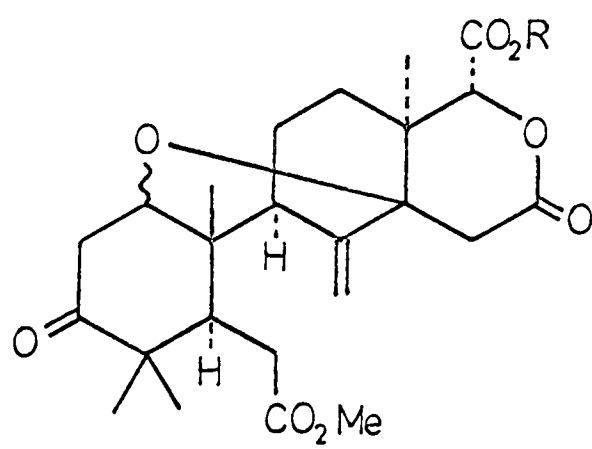


71 Angolensic acid

reduced with sodium borohydride to an alcohol which was reoxidised to the ketone with Jones' reagent.

The infrared spectrum had a strong band at 1735 cm^{-1} suggesting that methyl angolensate contained an ester and / or a lactone function, and showed the absence of a hydroxyl group. The n.m.r. spectrum had a singlet at 6.27τ due to the three methoxyl protons of the methyl ester. Mild hydrolysis with methanolic potassium hydroxide readily gave an acid, angolensic acid (71), from which methyl angolensate could be regenerated by treating with diazomethane, thus confirming the presence of a methyl ester⁹. Titration experiments with angolensic acid by dissolving it in an excess of alkali and titrating with acid revealed the presence of a second carboxyl group, presumably present in a lactone ring which could be reversibly opened⁹. Since there was no infrared absorption in the carbonyl region higher than 1735 cm^{-1} and the ultraviolet spectrum showed only absorption at $214\text{ m}\mu$, the lactone ring must be saturated and six-membered.

Methyl angolensate contains a furan ring which was identified by its characteristic infrared absorption at 1505 and 875 cm^{-1} and by the ultraviolet absorption at $214\text{ m}\mu$ ($\epsilon\ 5500$).



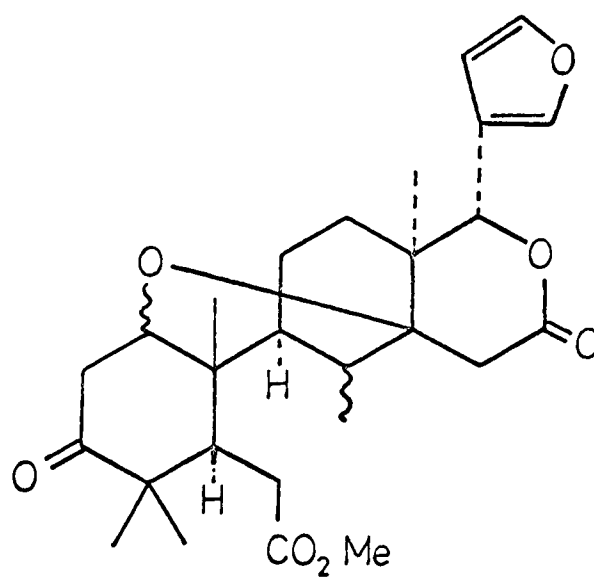
72 R = H

73 R = Me

The n.m.r. spectrum showed bands at 3.6 and 2.65 τ corresponding to one and two protons respectively. Therefore the furan ring has one β -proton and two α -protons and so must be β -substituted.²² This was confirmed by ozonolysis of methyl angolensate which cleaved the furan ring and gave the tris-nor carboxylic acid (72). Methylation with diazomethane gave the tris-nor ester (73) which had no infrared absorption at 1505 and 875 cm^{-1} . and showed no ultraviolet absorption at 214 $\text{m}\mu$. The loss of the corresponding furan bands in the n.m.r. spectrum was also observed, and a singlet appeared at 6.34 τ due to the three methoxyl protons of the new methyl ester. There was also an infrared absorption band at 1755 cm^{-1} due to this ester.

The presence of ketone, methyl ester, lactone, and furan groups so far described accounts for six of the seven oxygen atoms in methyl angolensate. The last oxygen atom gave no simple chemical reactions but the n.m.r. spectrum had a band at 6.46 τ (quartet) due to one proton which was indicative of the grouping $>\text{CH.O-}$. This suggested that the seventh oxygen was in a cyclic ether. After allowance for these functional groups the formula $\text{C}_{27}\text{H}_{34}\text{O}_7$ requires three double bond equivalents (carbocyclic rings or double bonds) in methyl angolensate.

29a



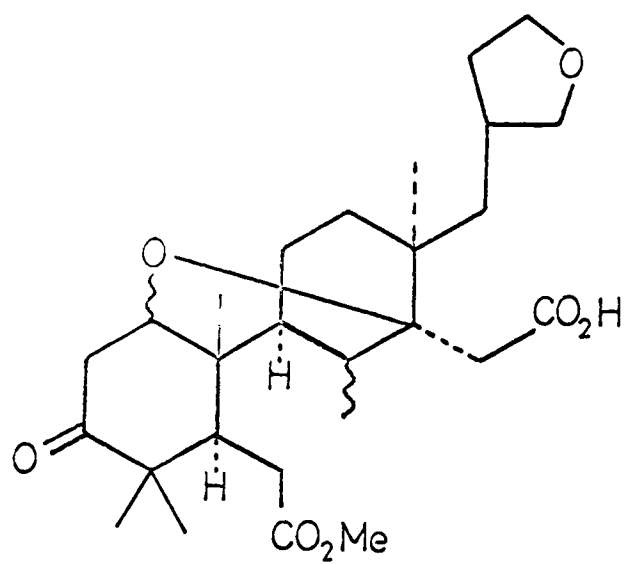
74 A mixture of epimers at $\text{C}_{(8)}$

Methyl angolensate has a C_{26} skeleton and a β -substituted furan ring and a δ -lactone group, and in addition it is found in four species of Meliaceae together with gedunin and dihydrogedunin. This suggests that it is a tetra-nor triterpene probably biogenetically closely related to gedunin.

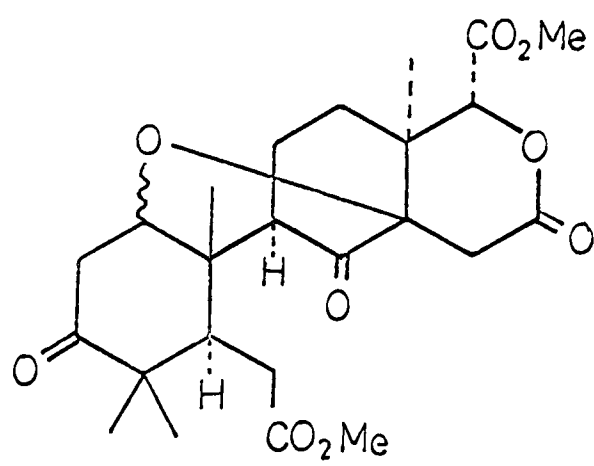
The n.m.r. spectrum of methyl angolensate showed the presence of four tertiary methyl groups as singlets at 9.12, 9.05, 8.94, and 8.80 τ in contrast with the five tertiary methyl groups found in gedunin (2). It also had three low field protons as singlets at 5.03, 4.88, and 4.36 τ .

On mild hydrogenation of methyl angolensate in ethanol over Adams' catalyst an inseparable mixture of two dihydro-compounds (74) was obtained. The infrared and ultraviolet spectra of the mixture were quite similar to those of methyl angolensate and the mixture could not be reoxidised to starting material with Jones' reagent. Thus there must be a double bond in methyl angolensate. The n.m.r. spectrum of the dihydro-product showed that it was a mixture of about equal amounts of two stereoisomers which gave rise to doubled bands in the spectrum. However, the two low field signals at 5.03 and 4.88 τ in the n.m.r. spectrum had disappeared and a new methyl signal had appeared at 8.72 τ . This could be seen more clearly when methyl angolensate was hydrogenated under

30a



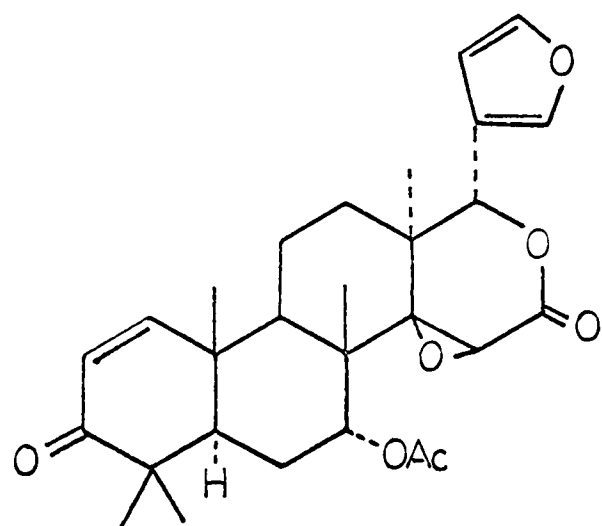
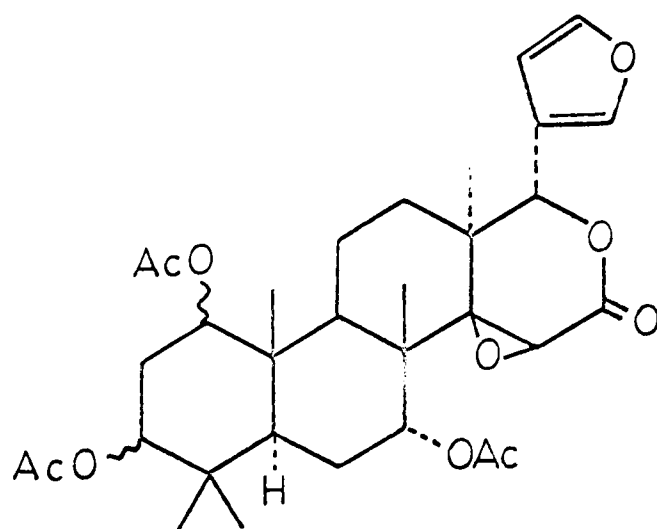
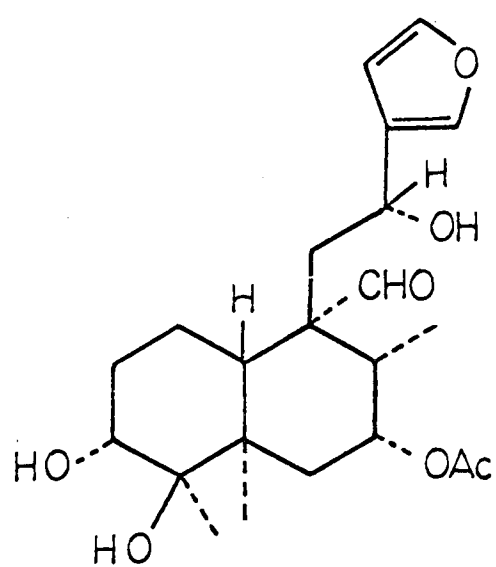
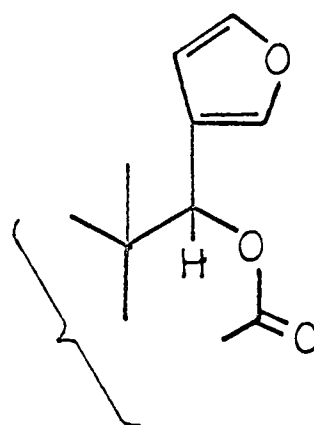
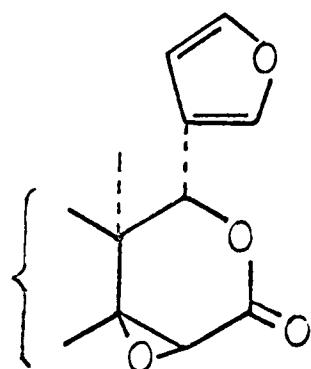
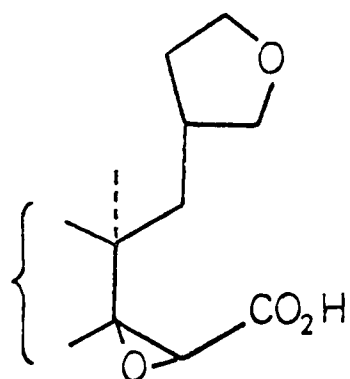
75



76

more vigorous conditions in acetic acid over palladised charcoal to give an octahydro-compound (75) which did not appear to be a mixture (see later). The n.m.r. spectrum of the latter compound had bands due to five methyl groups, one of which appeared as a doublet at 8.90τ (J 7.4. c.p.s.) and must therefore be due to a secondary methyl group. A secondary methyl group could only arise by hydrogenation of a terminal methylene group. Thus the two signals at 5.03 and 4.88τ in the n.m.r. spectrum of methyl angolensate must be due to the protons of the methylene group, and since these bands are singlets it must be present as $\begin{smallmatrix} \text{C} \\ | \\ \text{C} \end{smallmatrix} > \text{C} = \text{CH}_2$. Confirmation ~~fr~~ the presence of the methylene group was obtained by Chan and Mootoo¹⁰ who subjected the tris-nor ester (73) obtained by ozonolysis of methyl angolensate to further prolonged ozonolysis. The n.m.r. spectrum of the product (76) had the original four tertiary methyl bands but had lost the low field signals due to the methylene protons. In addition, distillation of the aqueous extract from the work-up of the reaction gave formaldehyde which was characterised as the 2,4-dinitrophenylhydrazone.

The presence of a terminal methylene group means that methyl angolensate is bicarbocyclic.

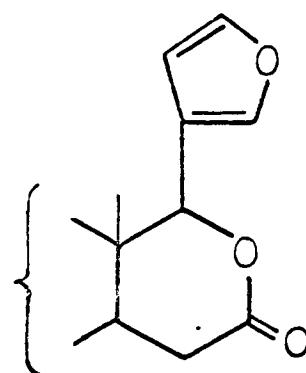
2 Gedunin14 Khivorin77 Cascarillin787980

The Furan and Lactone Rings

Two of the low field one-proton signals in the n.m.r. spectrum of methyl angolensate mentioned above have been assigned to the methylene group. The remaining band occurred at 4.36τ which is quite close to the position of the $C_{(17)}$ -proton in the n.m.r. spectra of gedunin (2) and Khivorin (14), both of which appeared at 4.43τ ⁹. In the n.m.r. spectrum of the tris-nor ester (73) obtained by ozonolysis of the furan ring the corresponding band appeared at 5.17τ . This shift is comparable with that observed in the n.m.r. spectra of cascarillin (77) and its corresponding ozonolysis product¹¹. Furthermore the pK_{MCS}^* ⁹ of the tris-nor acid (72) obtained by ozonolysis was found to be 5.42 which is consistent with the strength of an acid with an α -oxygen substituent. This suggested the presence of the partial structure (78) analogous to limonin (1), gedunin (2), khivorin (14), and several other meliacins.

Barton¹² showed in his work on limonin(1) that hydrogenation of a system such as (79) under suitable conditions produced hydrogenolysis of the lactone ring and saturation of the furan ring to give hexahydrolimonic acid (80). The opening of the lactone ring is due to its being

32a

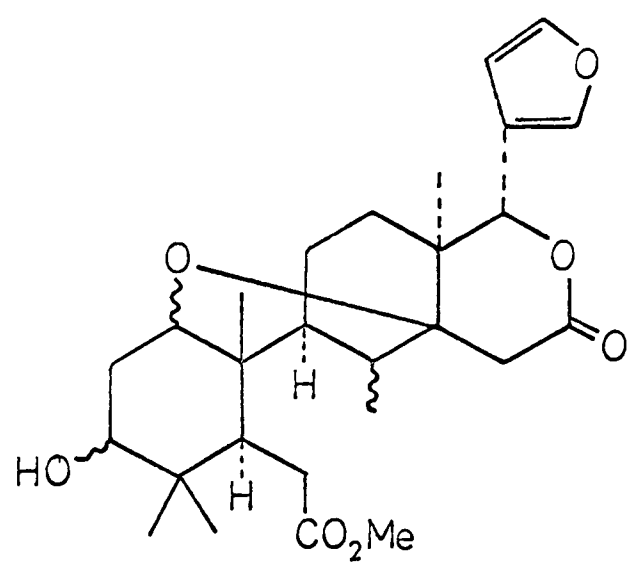


81

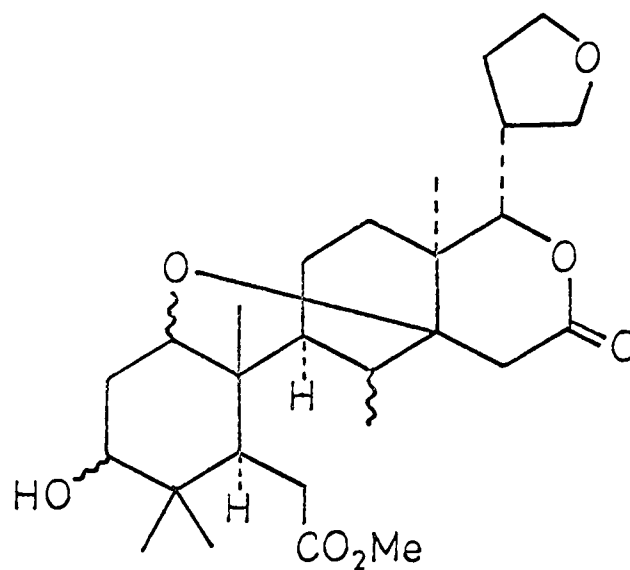
in a position allylic to the furan ring since when tetrahydrolimonin in which the furan ring was previously saturated was subjected to the hydrogenolysis conditions no acid was produced. When methyl angolensate was hydrogenated in acetic acid over palladised charcoal an octahydro-acid was obtained (75)⁹ (see above). Reduction and hydrogenolysis of the lactone-furan system accounted for three of the four molecules of hydrogen, while the fourth reduced the exocyclic double bond. The n.m.r. spectrum showed the loss of all of the low field signals including the bands due to the furan protons, the two methylene proton singlets and the C₍₁₇₎-proton singlet. The pK_{MCS}^* of this acid, which was 7.52, showed that it was not an α -oxy-acid unlike the corresponding hexahydrolimonio acid (80)¹². Thus the partial structure (81) can be inferred for methyl angolensate.

Chan and Mootoo¹⁰ obtained a similar hexahydro-acid by a milder hydrogenation of methyl angolensate in rectified spirit over palladised charcoal. Their compound was analogous to the octahydro-acid (75) mentioned above except that in this case the exocyclic double bond was not reduced.

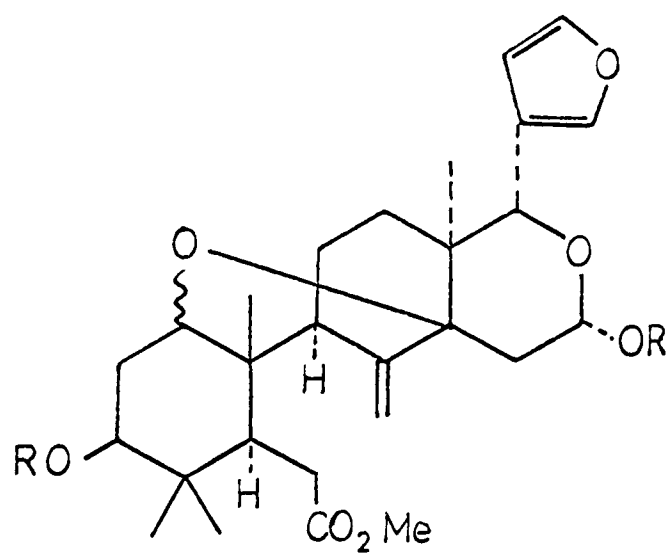
By variation of the conditions several other hydrogenation products of methyl angolensate could be obtained. The



82 A mixture of epimers at C₍₈₎



83 A mixture of epimers at C₍₈₎



84 R = H

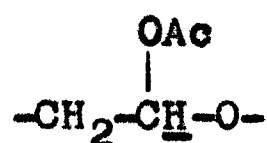
85 R = Ac

dihydro-compound (74) which has only the double bond reduced has been mentioned before. Hydrogenation of methyl angolensate in acetic acid over Adams' catalyst produced a tetrahydro-compound. The infrared spectrum of this compound had a band at 3450 cm^{-1} due to a new hydroxyl group and did not have any absorption due to a ketone group. Oxidation with Jones' reagent gave a compound identical in all respects with the dihydro-derivative (74). This suggested that the tetrahydro-compound had the ketone group reduced to an alcohol (82). Prolonged hydrogenation of methyl angolensate in acetic acid over Adams' catalyst gave an octahydro-compound in which the furan ring was also reduced (83). This was shown by the absence of the corresponding furan bands in the infrared, ultraviolet, and n.m.r. spectra.

Evidence from the Reduction of Methyl Angolensate with Potassium Borohydride

Treatment of methyl angolensate with potassium borohydride produced a tetrahydro-derivative (84). The infrared spectrum of this compound had hydroxyl absorption at 3600 cm^{-1} and only one carbonyl band at 1735 cm^{-1} . It could be oxidised with Jones' reagent back to methyl angolensate. Acetylation

of the tetrahydro-compound in the usual way gave a diacetate (85), the infrared spectrum of which did not show any absorption in the hydroxyl region. The n.m.r. spectrum of the diacetate had signals for two acetoxy groups at 7.92 and 7.96 τ and a band due to the carbomethoxy group at 6.33 τ . A new low field one-proton signal appeared at 3.82 τ as a double-doublet (J_1 8.5 c.p.s., J_2 4 c.p.s.). This must be due to the grouping



in which the neighbouring methylene hydrogen atoms are non-equivalent, as in the partial structure (81).

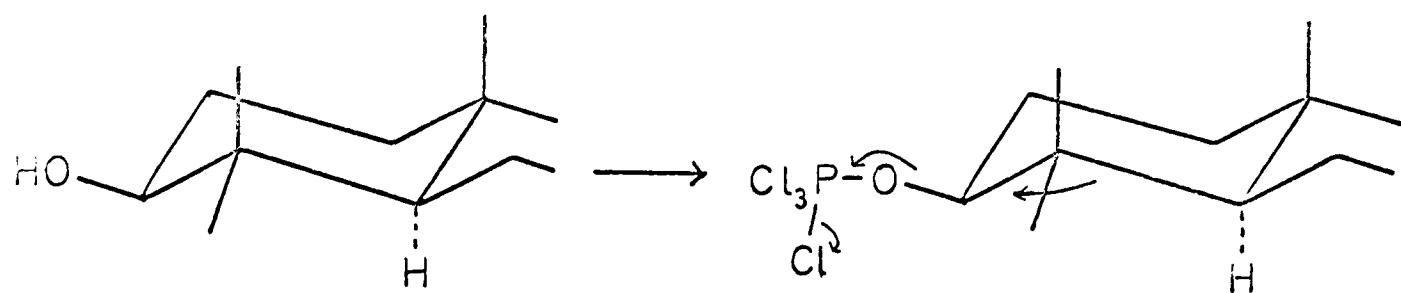
Therefore borohydride attack on methyl angolensate, in addition to reducing the ketone group as would be expected and which was shown by the loss of the ketone band in the infrared spectrum, must also have reduced the lactone to a hemiacetal. In agreement with this change in the lactone ring the band due to the $\text{C}_{(17)}$ -proton had shifted up-field in the n.m.r. spectra of both the diol (84) and the diacetate (85) and appeared at 5.31 and 5.26 τ respectively.

A six-membered cyclic hemiacetal can be compared to a

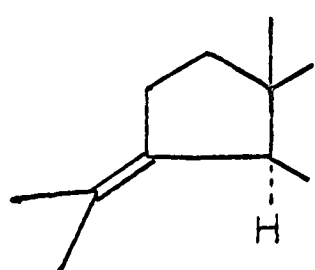
pyran system. Lemieux et al.¹³ have shown that in the n.m.r. spectra of acetylated pyranoses axial --- equatorial and equatorial --- equatorial couplings of protons have a J value of the order of 3 c.p.s. The corresponding coupling constant for axial - axial interaction is two to three times greater than this and is about 8 c.p.s. The signal at 3.82 τ in the n.m.r. spectrum of the diacetate (85) appeared as a double-doublet (J_1 8.5 c.p.s., J_2 4 c.p.s.). This must be due to the C₍₁₆₎-proton being in the axial conformation and being split by the neighbouring axial C₍₁₅₎-proton (J 8.5 c.p.s.) and split further by the equatorial C₍₁₅₎-proton (J 4 c.p.s.). This confirms that there is a -CH₂- group next to the carbonyl group of the lactone in methyl angolensate.

The Structure of Ring A

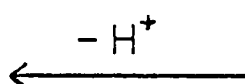
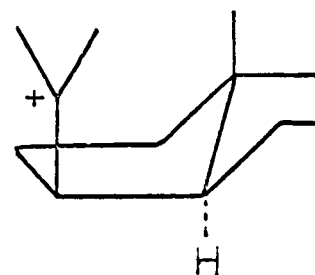
One of the characteristic reactions of triterpenes is the contraction of ring A when a 3 β -alcohol is treated with phosphorus pentachloride. The mechanism of this retropinacolic rearrangement has been investigated by Ourisson¹⁴ who showed that it occurred via the route (86) to (88). He also demonstrated that the O, C₍₃₎, C₍₄₎, and C₍₅₎ atoms had to be coplanar and that the O-C₍₃₎ and C₍₄₎-C₍₅₎



86

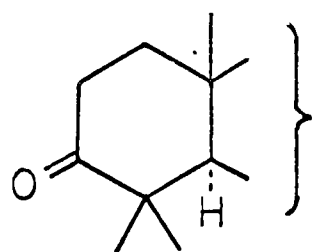


88



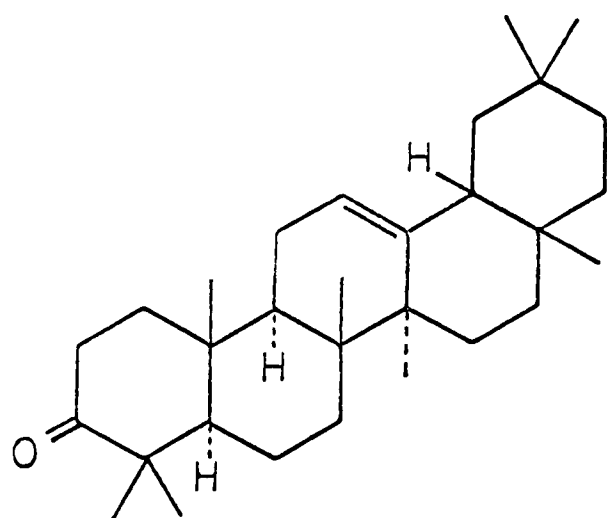
87

89

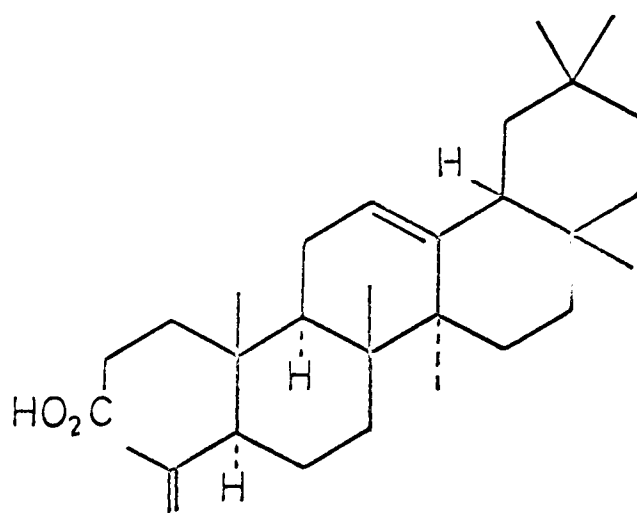


bonds should be antiparallel for the transformation to occur. Furthermore he observed that for a high conversion to the product (88) the presence of a β -oriented $C_{(10)}$ -methyl group was necessary. This was explained by a 1-3 quasi diaxial interaction in the carbonium ion (87) between the $C_{(10)}$ -methyl group and the isopropenyl group which could be relieved by elimination of a proton from $C_{(3)}$ to give (88). With 19-nor compounds a mixture of double bond isomers was obtained, the product analogous to (88) being obtained in about 40% yield.

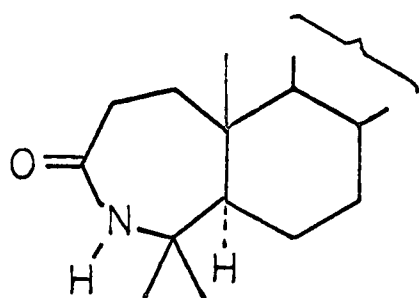
The diol (84) obtained by reducing methyl angolensate with potassium borohydride was treated with phosphorus pentachloride and the product was ozonised at -50° . Steam-distillation of the reaction mixture gave acetone which was characterised as the 2,4-dinitrophenylhydrazone. The yield of the latter compound indicated that at least 70% of the isopropylidene-cyclopentane-compound as in (88) had been produced. The residue after steam-distillation could not be crystallised but showed a band in the infrared spectrum at 1776 cm^{-1} which was assigned to a cyclopentanone. This means that the structure and stereochemistry of ring A in methyl angolensate must be as in (89), and that the $C_{(3)}$ -hydroxyl group in the diol (84) must be equatorial.



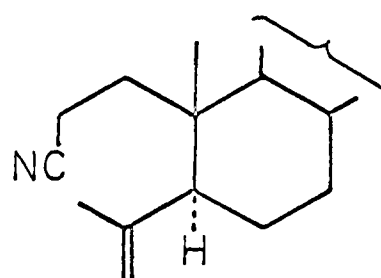
90 β -Amyrenone



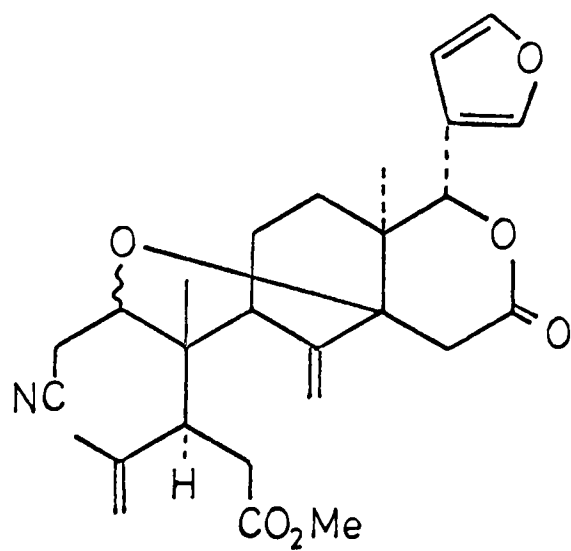
91 Nyctanthic acid



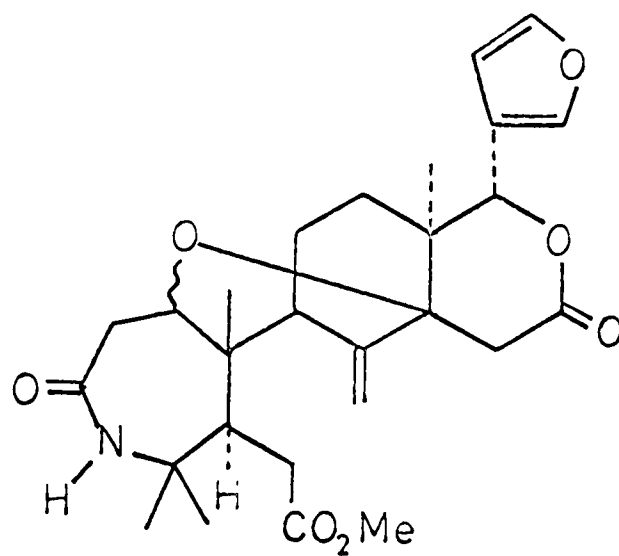
92



93



94

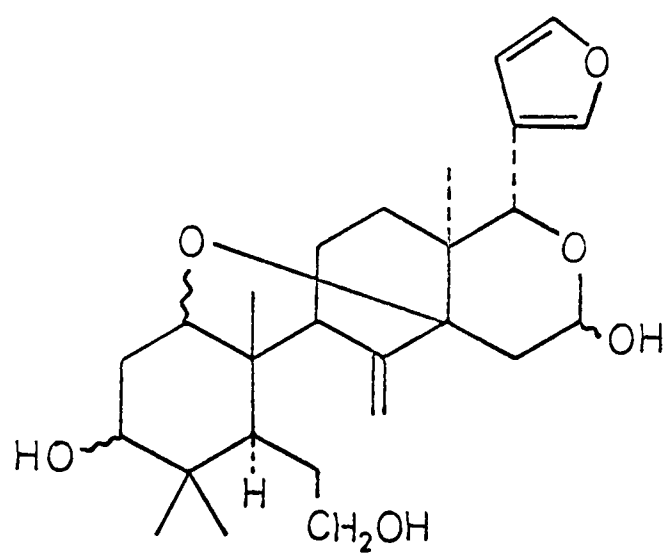


95

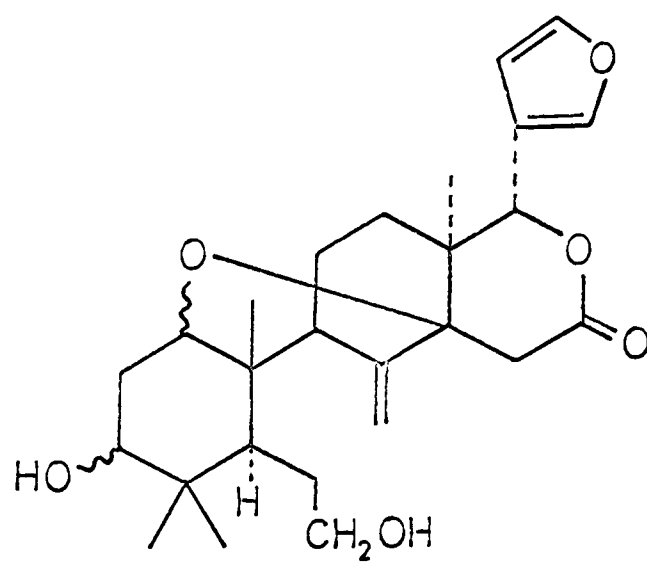
Further evidence for the structure of ring A was obtained by Chan and Mootoo¹⁰ who carried out a Beckmann rearrangement of methyl angolensate oxime. Whitham¹⁵ converted

β -amyrenone (90) into nyctanthic acid (91) via a Beckmann rearrangement of β -amyrenone oxime. He obtained two compounds, a lactam (92) and a nitrile (93), and the nitrile was hydrolysed to nyctanthic acid (91). It was hoped that methyl angolensate would undergo an analogous transformation.

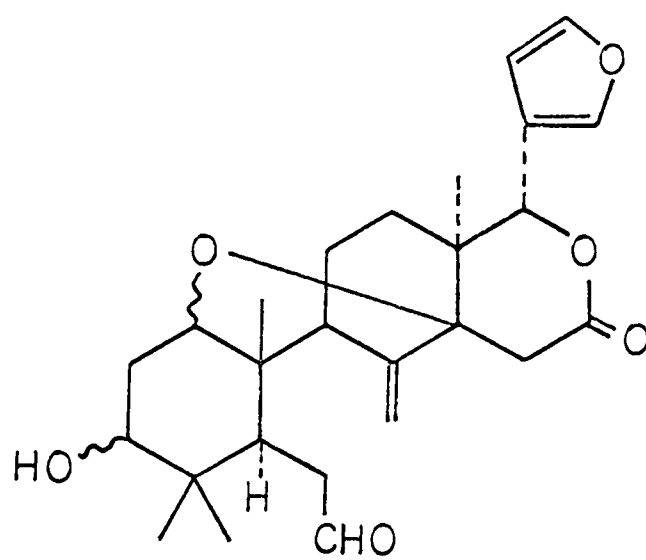
Treatment¹⁰ of methyl angolensate oxime with thionyl chloride gave two products (94) and (95). One compound (94) had a band in the infrared spectrum at 2247 cm^{-1} characteristic of a nitrile group, and its n.m.r. spectrum showed only two tertiary methyl signals at 9.03 and 9.09 τ . A band due to a methyl group attached to a double bond appeared at 8.13 τ , and there were four protons in the olefinic region at 5.04 to 4.80 τ . The structure (94) was assigned to this compound which must be the result of an 'abnormal' Beckmann rearrangement. The other product (95) had infrared absorption bands at 3509 and 3448 cm^{-1} which were assigned to N-H stretching. Its n.m.r. spectrum showed signals due to four tertiary methyl groups and had a new peak at 4.02 τ due to the proton attached to the nitrogen atom. This compound



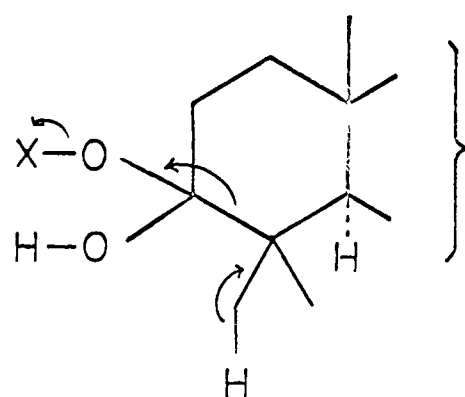
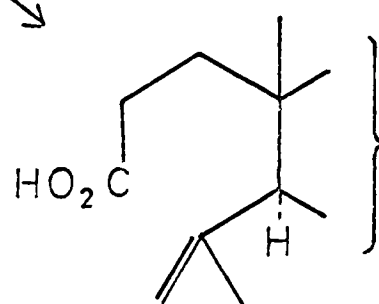
96



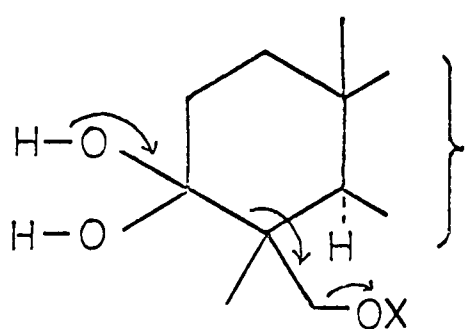
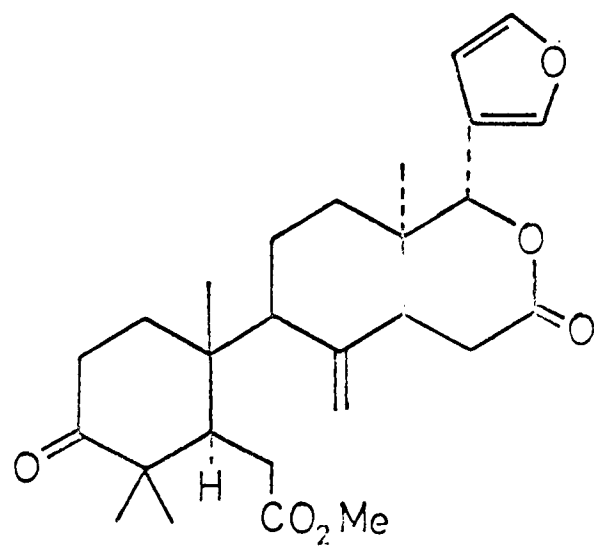
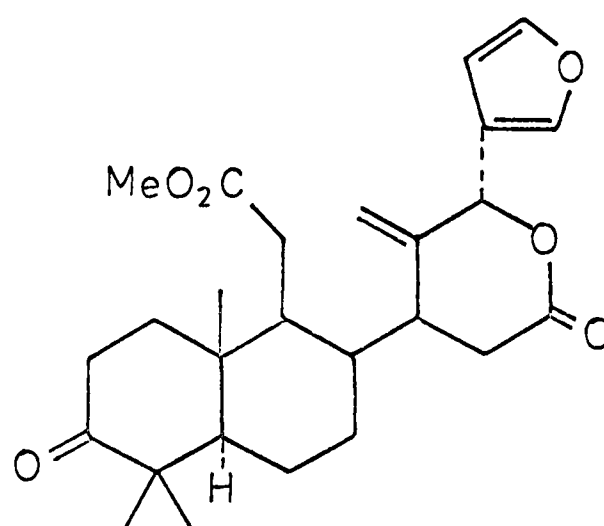
97



98

9991

X = a suitable leaving group

100101102

that there should be only two carbocyclic rings. Since the structure of ring A has been established this means that either ring B or C of the gedunin skeleton has been cleaved. Furthermore, the cleavage must be in such a way as to accommodate a primary ester and a terminal methylene group. This could be achieved if ring B or C were to be opened by oxidation of a grouping such as $-\text{CO}-\text{CH}-\text{CH}_3$ as has been postulated for the biogenesis of nystanthic acid (91) from β -amyrenone (90). Arigoni *et al.*¹⁶ suggested the scheme (99) for this, while Whitham¹⁷ proposed a similar mechanism as in (100). Application of either of these mechanisms to ring B or C of the gedunin skeleton would lead to the partial structures (101) and (102) respectively for methyl angolensate after methylation of the acid produced.

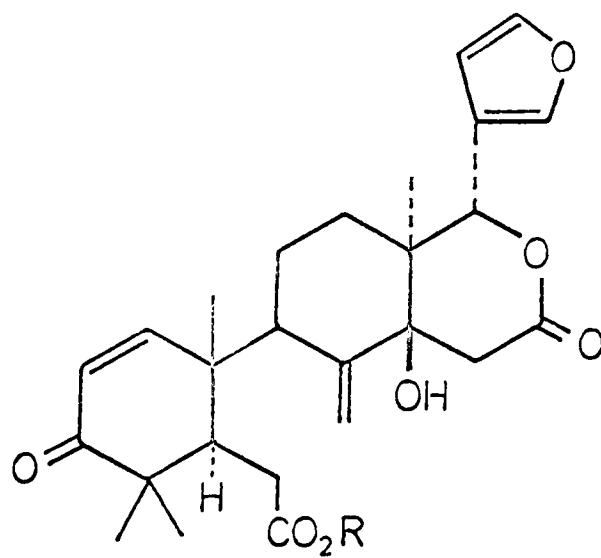
The position of the signal due to the $\text{C}_{(17)}$ -proton (4.36τ) in the n.m.r. spectrum of methyl angolensate is very close to the corresponding peak in the n.m.r. spectra of limonin (1) (4.55τ)¹⁸, gedunin (2) (4.43τ), and khivorin (14) (4.43τ)⁹. This favours an intact ring C (101) since a cleaved ring C would create a methylene group at $\text{C}_{(13)}$ as in (102) and would be expected to cause a downfield shift of the $\text{C}_{(17)}$ -proton in the n.m.r. spectrum.

More convincing evidence was provided by the dihydro-product (74) mentioned above obtained by mild hydrogenation of methyl angolensate. Its n.m.r. spectrum showed that it was a mixture of about equal amounts of two stereoisomers which gave rise to doubled bands in the spectrum. However the signals due to the C₍₁₇₎-protons appeared as singlets at 4.29 τ . Hydrogenation of the seco-ring C structure (102) would lead to a product which should show a doublet for the C₍₁₇₎-proton in the n.m.r. spectrum. Therefore the partial structure as in (101) was suggested for methyl angolensate.

The Ether Bridge

The presence of a cyclic ether in methyl angolensate has already been mentioned. The n.m.r. spectrum had a one-proton signal at 6.46 τ (multiplet) which is characteristic of the grouping $>\text{CH.O-}$. This was assigned to one end of the ether bridge, but there was no signal in the n.m.r. spectrum which might be due to the other end. Treatment of methyl angolensate under a variety of acidic conditions failed to give any material which could be characterised. However, Chan and Mootoo¹⁰ treated methyl angolensate under strong basic conditions using sodium isobutoxide in isobutanol.

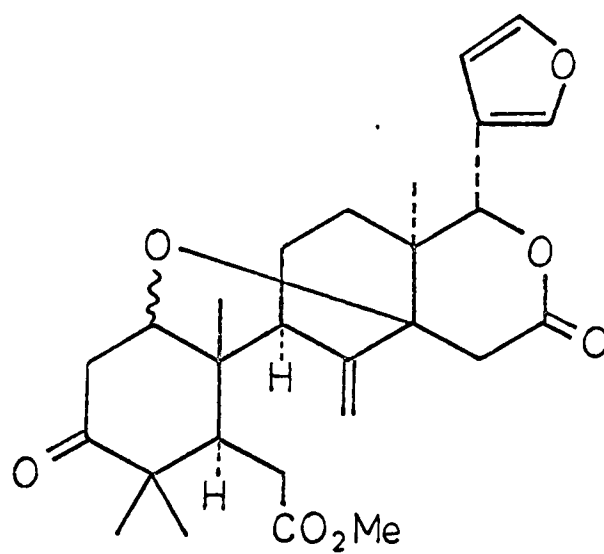
41a



103 R = H

104 R = Me

An acidic compound (103) was obtained, and the same compound was produced when angolensic acid (71) was subjected to the same conditions. This acid (103) was methylated with diazomethane to give the methyl ester (104). The infrared spectrum of the ester had a band at 3425 cm^{-1} due to a hydroxyl group and had absorption at 1745 and 1731 cm^{-1} assigned to the lactone and ester functions. There was also an infrared band at 1664 cm^{-1} and the ultraviolet spectrum had $\lambda_{\text{max.}}\ 235\text{ m}\mu$ ($\epsilon\ 11,000$), which are characteristic of an α,β -unsaturated ketone. The n.m.r. spectrum had a new band at 6.17 which was shown to be due to a hydroxyl proton by deuterium exchange, and there was no signal corresponding to a proton attached to the carbon atom bearing this hydroxyl group. Therefore the new hydroxyl group must be tertiary. The signal at 6.46 τ in the n.m.r. spectrum of methyl angolensate had disappeared and there were two new doublets at 4.03 and 2.25 τ (J 11 c.p.s.) which were assigned to the grouping $-\text{CO}.\text{CH}=\text{CH}.\text{O}-$. The generation of an α,β -unsaturated ketone and a hydroxyl group must have been due to the base-catalysed opening of the ether bridge which is therefore attached at $\text{C}_{(1)}$, to the ketone group. On treatment with acid the unsaturated ketone (104) recyclised to give methyl angolensate.



70 Methyl angolensate

The other end of the cyclic ether must be attached at one of the tertiary centres $C_{(5)}$, $C_{(9)}$ or $C_{(14)}$. An ether ring from $C_{(1)}$ to $C_{(5)}$ or $C_{(9)}$ would be four-membered and therefore strained. Furthermore, once opened, it would probably not reclose in the presence of acid as readily as was found with the unsaturated ketone (104). A $C_{(1)} - C_{(14)}$ link would be a more stable six-membered ring. All of the meliacin compounds characterised so far (see Introduction) have an oxygen function at $C_{(14)}$. So steric and biogenetic considerations point to a bridge between $C_{(1)}$ and $C_{(14)}$ and the structure (70) is therefore proposed for methyl angolensate.

Stereochemical Considerations

It has been assumed that methyl angolensate is derived biogenetically from gedunin or from a gedunin-like compound, or that both gedunin and methyl angolensate are derived from a common precursor relatable to euphol or tirucallol (see later). If this is so then the stereochemistry of methyl angolensate can be represented as in (70) with the configuration of $C_{(1)}$ undefined. As was mentioned earlier a signal at 6.46 τ in the n.m.r. spectrum of methyl angolensate was attributed to the proton at $C_{(1)}$. It

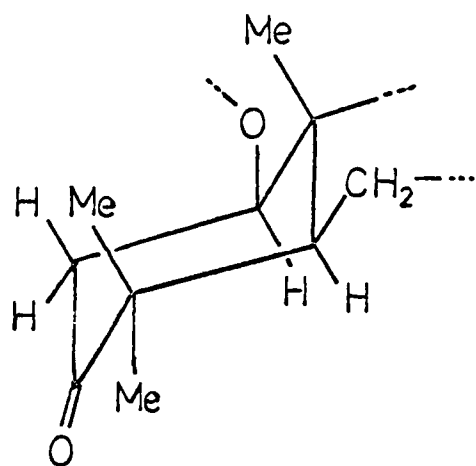
appeared as a double-doublet with coupling constants of 6.0 and 4.2 c.p.s. due to coupling with the neighbouring hydrogen atoms on C₍₂₎. These values of J may be compared with those predicted on theoretical grounds from a knowledge of the dihedral angles. The original equation describing the relationship between the vicinal coupling constant and ϕ , the dihedral angle between the protons, was derived by Karplus¹⁹. More recently a slightly modified version has been calculated by Williamson and Johnson²⁰ using derivatives of cholestane as their model:

$$J = 10 \cos^2 \phi \quad (0 \leq \phi \leq 90^\circ)$$

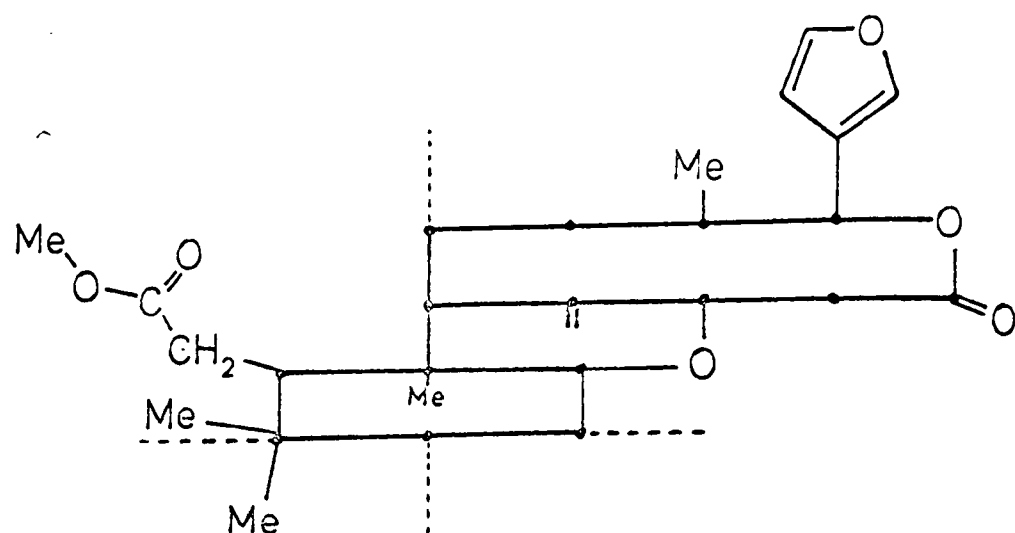
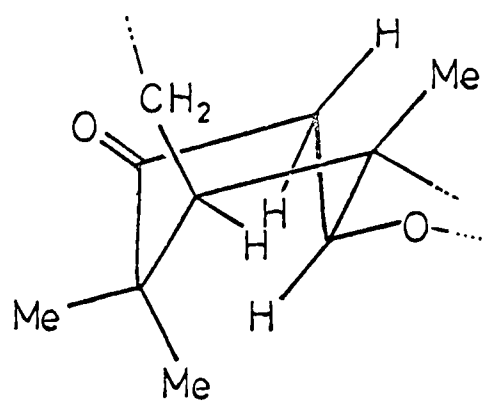
$$J = 16 \cos^2 \phi \quad (90^\circ \leq \phi \leq 180^\circ)$$

The oxygen link at C₍₁₎ may be or and in each case ring A can formally adopt either a chair or one of two boat conformations, (105) — (110). An attempt can be made to determine which of these is present in methyl angolensate by applying these n.m.r. considerations. The octant rule 21 can also be used to predict the sign of the Cotton effect in the optical rotatory dispersion (O.R.D.) curve by using a Dreiding model. It must be remembered, however, that Dreiding models do not represent the true conformation of a compound and that slight distortions are to be expected.

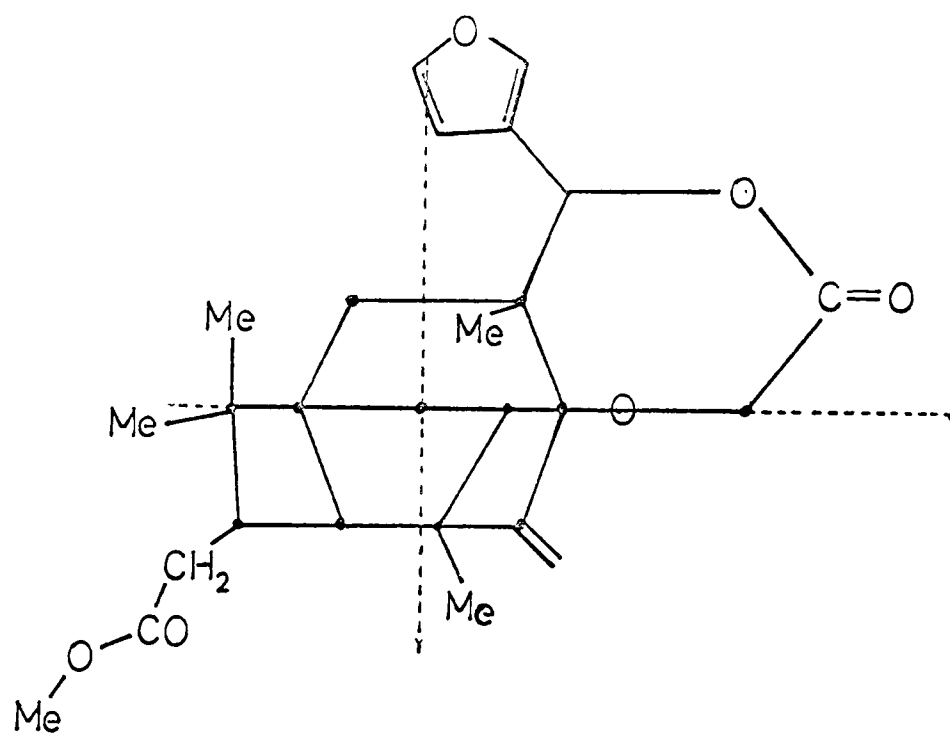
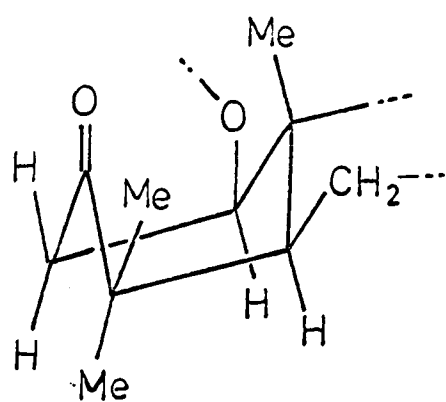
Methyl angolensate showed no Cotton effect in the O.R.D.,



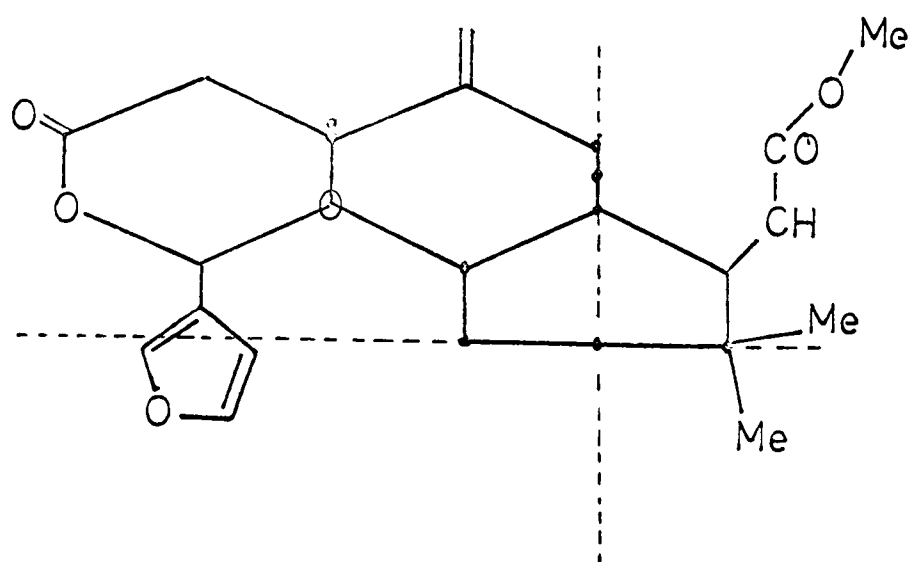
105



106

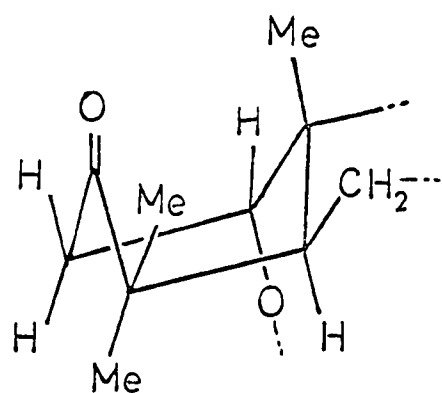
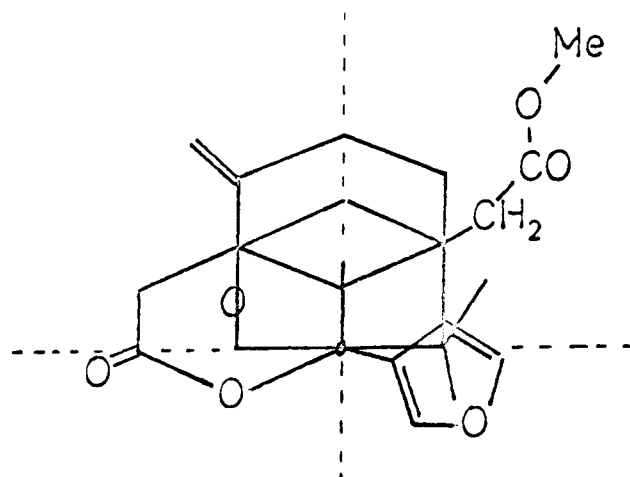
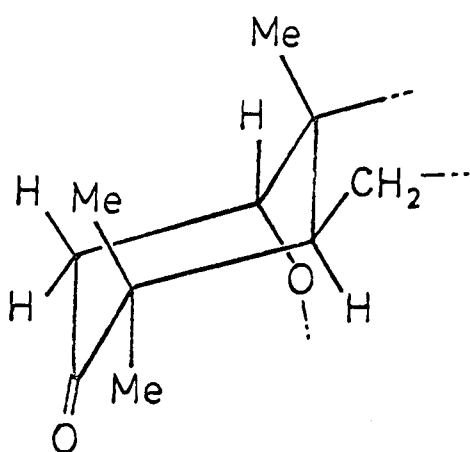
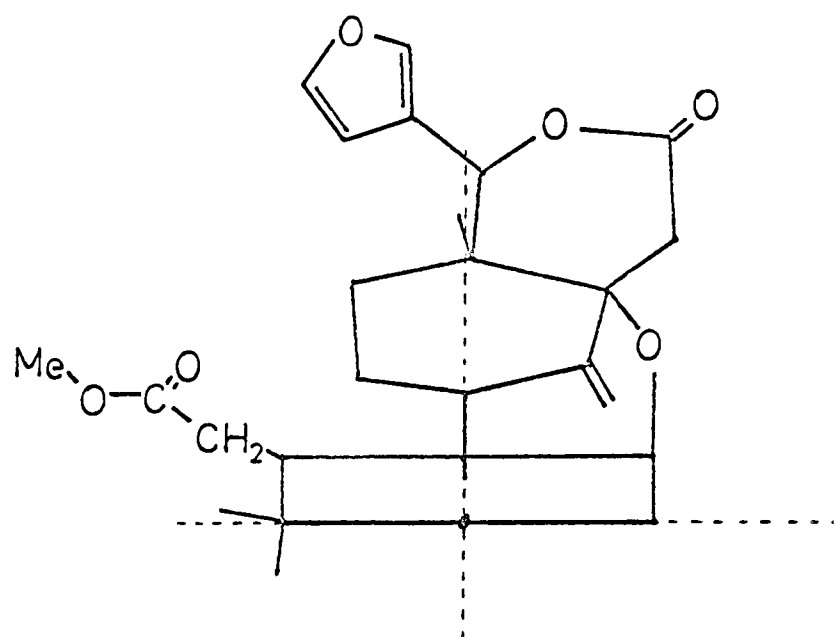
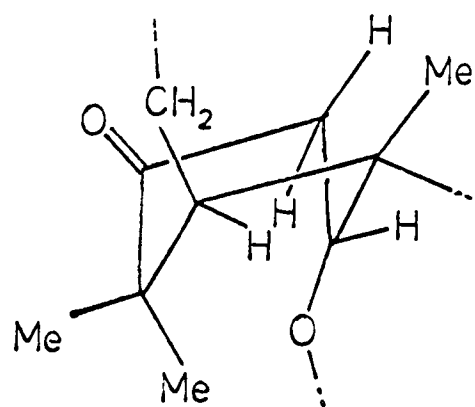
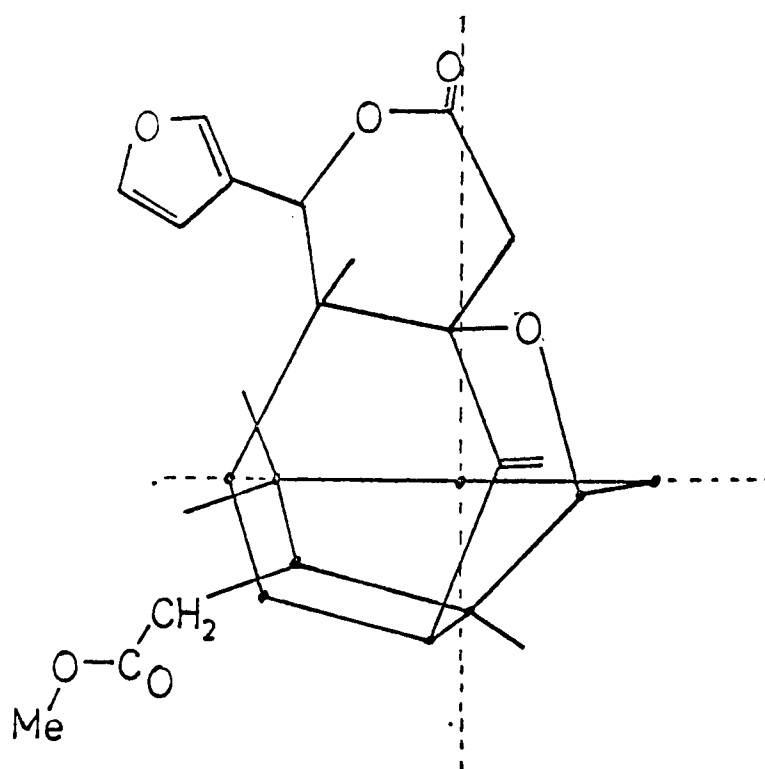


107



but the tris-nor ester (73) produced by ozonolysis of the furan ring had a negative Cotton effect⁹. It must therefore be assumed that the furan ring is placed in such a way that it makes a positive contribution to the Cotton curve.

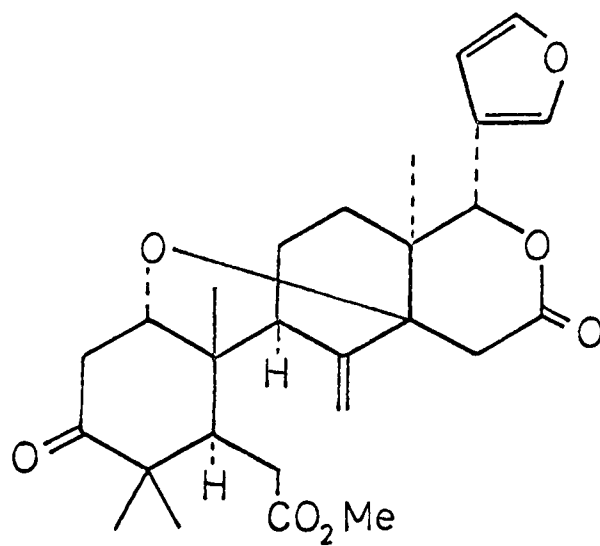
The structures in which the oxygen link at C₍₁₎ is attached in the β -configuration are considered first, (105) — (107). In all these cases the cyclic ether is in the more stable chair conformation. However, in both (105) and (106) the C₍₁₎ proton is axial and the dihedral angles with the C₍₂₎ protons would be in the region of 60° and 180°. This would give rise to coupling constants of the order of 2.5 and 8-14 c.p.s. respectively. There would also be considerable steric interaction in structure (106). Furthermore the predicted Cotton effects would be negative with the furan ring in a negative octant in both cases. Therefore structures (105) and (106) may be rejected. In the third case (107) the C₍₁₎ proton is again axial and the dihedral angles would be about 5° and 125°. This would give rise to coupling constants of the order of 9 and 4 c.p.s., although a suitable distortion of the boat would probably enable angles to be attained which correspond to coupling constants similar to those observed. However, the Cotton effect would probably be fairly strongly positive with the furan ring making either

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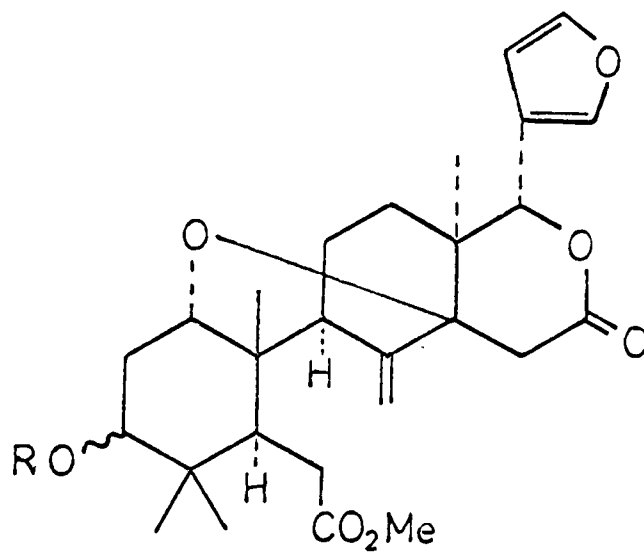
a small negative or no contribution. So structure (107) may also be rejected.

When the oxygen is considered to be α at C₍₁₎, structure (108) would have the dihedral angles in the region of 120° and 0° which would make the coupling constants about 4 and 8-10 c.p.s. The predicted Cotton effect would be small but the furan ring would probably make no contribution. The two structures (109) and (110) would both have dihedral angles of the order of 50 - 70° which would lead to rather low coupling constants, about 4.5 and 1.5 c.p.s. However, the Cotton effect would be small, probably slightly positive, and in each case the furan ring is found in a positive octant as expected. Perhaps, therefore, the most likely structure is an α -C₍₁₎ ether linkage with ring A in a distorted boat conformation somewhere between structures (108) and (110), which would enable 'suitable' dihedral angles to be attained and which would minimise steric interactions. Therefore structure (111) is proposed for methyl angolensate with the ether bond at C₍₁₎ placed tentatively in the α -configuration.

It is hoped that this problem will be solved by an X-ray analysis of a heavy-atom derivative which will be carried out at the University of Ibadan. In connection with this an



111 Methyl angolensate



112 R = H

113 R = Ac

attempt was made to prepare a suitable derivative. Methyl angolensate was reduced by the Meerwein - Ponndorf method, which should only attack the ketone group, to a hydroxy compound (112). This was then to be treated with *p*-bromobenzoyl chloride in order to make the *p*-bromobenzoate. However, the n.m.r. spectrum of the acetate (113) of this hydroxy compound had doubled bands indicating that it was a mixture of about 50% each of two isomers, presumably the 3α - and 3β - epimers. The hydroxy compound (112) was also presumably a mixture of epimers at the 3-position, which would not give a derivative suitable for X-ray work.

EXPERIMENTAL SECTION

General

The work was carried out partly in the University of Oxford and partly in the University of Ibadan.

Melting points were determined on a Kofler block, and rotations were measured in chloroform solution, unless otherwise stated, with a N.P.L. automatic polarimeter.

Infrared spectra were recorded with a Perkin-Elmer 237 spectrophotometer or a Perkin-Elmer 21B spectrophotometer. All the spectra were determined using a 'Nujol' mull of the material, unless otherwise indicated. Ultraviolet spectra were recorded on a Cary Recording Spectrophotometer Model 14M or a Unicam SP 700 spectrophotometer using solutions in ethanol.

Unless otherwise stated, nuclear magnetic resonance spectra were determined at 60 mc/s on a Perkin-Elmer R-10 instrument fitted with an automatic integrator, using tetramethylsilane as internal standard. The spectra were determined with ca. 10-15% w/v solutions in deuteriochloroform. Hydroxyl protons were characterised by exchange with deuterium oxide. The notation used for recording the spectra is s = singlet, d = doublet, t = triplet, q = quartet,

and m = multiplet. The chemical shifts are given in units and the coupling constants (J) in cycles per second (c.p.s.).

Mass spectra were obtained using an A.E.I. M.S.9 double-focussing mass spectrometer. Samples were introduced directly into the ion chamber, without vaporisation.

Measurements of optical rotatory data were carried out in Professor Klyne's laboratory.

Microanalyses were carried out by Drs. G. Weiler and F.B. Stauss (Oxford), P.I. Mowete and F.M. Ozoh (Ibadan), Dr. F. Pascher and E. Pascher (Bonn), and A. Bernhardt (Mulheim).

The alumina used in column chromatography was Peter Spence Grade H, 5% or 10% deactivated by the addition of 5% or 10% of 10% acetic acid.²³ Thin-layer plate chromatography (t.l.c.) was conducted according to the method of Stahl²⁴ using an unbaked silica gel (Merck Kieselgel H) stationary phase deposited on glass, with benzene - ethyl acetate, or ethyl acetate, as eluant. The plates were developed by exposure to iodine vapour, or by spraying with saturated aqueous toluene-p-sulphonic acid and drying at 150°. Purity of materials was checked by this means.

Solutions in organic solvents were dried over anhydrous

magnesium sulphate or sodium sulphate. Pyridine was dried over potassium hydroxide pellets.

Petroleum ether (b.p. $40-60^{\circ}$) has been referred to as light petroleum; petroleum ether (b.p. $60-80^{\circ}$) has been referred to as petroleum ether.

A stock solution of Jones' reagent²⁵ was prepared by dissolving chromium trioxide (133.5 g.) in sulphuric acid (115 ml.) which had been diluted with water (385 ml.).

Extraction of Methyl Angolensate (70)

The methyl angolensate used in this work was isolated in Professor Bevan's laboratory at the chemistry department of the University of Ibadan. The heartwood of Entandrophragma angolense was ground up and extracted in a Soxhlet apparatus with petroleum ether for 24 hours. The solvent was evaporated off, and the residue was crystallised from methanol to give prismatic needles of methyl angolensate, m.p. 203-208°, $[\alpha]_D^{30} - 43^\circ$ (c 1.90), (lit.², m.p. 197° $[\alpha]_D^{20} - 43^\circ$), $\nu_{\max.}$ 1735, 1713, 1655, 1505, 910, and 875 cm^{-1} , and $\lambda_{\max.}$ 214 $\text{m}\mu$ (ϵ 5500).

Angolensic Acid (71)

Methyl angolensate (4.798 g.) in methanol (50 ml.) was treated with potassium hydroxide (5 g.) in water (20 ml.). The solution was heated under reflux on a steam-bath for 90 minutes and then poured into water. The alkaline aqueous solution was washed with ether (2 x 100 ml.), and was then acidified with dilute hydrochloric acid which produced a precipitate. The precipitate was filtered off, washed with water, and crystallised from aqueous methanol as needles of angolensic acid (4.353 g.), m.p. 250-253°, (lit.², m.p. 272°), $[\alpha]_D^{25} - 46^\circ$ (c 1.00), $\nu_{\max.}$ 3430, 1735, 1715, 910, and

875 cm^{-1} , and $\lambda_{\text{max.}}$ 214 $\text{m}\mu$ (ϵ 5500).

(Found: C, 68.4; H, 6.9; O, 24.4;
calc. for $\text{C}_{26}\text{H}_{32}\text{O}_7$ C, 68.4; H, 7.1; O, 24.5%).

Treatment of Methyl Angolensate with Peracid

Methyl angolensate (77.8 mg.) was weighed into a 50 ml. standard flask and dissolved in dry chloroform (5 ml.). Monoperphthalic acid (5 ml. of an ethereal solution containing 0.5175 moles / l.) was added to this flask and to a similar empty one (as blank). Both flasks were made up to 50 ml. with dry chloroform, and kept in the dark at 19° . At intervals samples were withdrawn and treated with excess aqueous potassium iodide, and the iodine liberated was estimated with 0.050N aqueous sodium thiosulphate. The number of moles of peracid which reacted with one mole of methyl angolensate were:
after 16 hours, 0.4; after 42 hours, 0.9; after 72 hours, 1.3; and after 306 hours, 1.4 moles.

Ozonolysis of Methyl Angolensate

Methyl angolensate (3.376 g.) in ethyl acetate (100 ml.) was cooled in an acetone - 'Drikold' bath. Ozonised oxygen

was passed through the solution until a deep blue colour was produced due to the presence of excess ozone (approximately 1 hour). The solution was allowed to warm to room temperature (20°), and hydrogen peroxide (100 vol., 100 ml.) was added, and the mixture was heated under reflux on a water-bath for 1 hour. Salt was added to the cooled solution to saturate the aqueous phase, and the two layers were separated, the aqueous layer being extracted with a further quantity of ethyl acetate (2 x 50 ml.). The combined organic solutions were extracted with saturated aqueous sodium bicarbonate (8 x 50 ml.). The combined aqueous extracts were acidified with dilute sulphuric acid and extracted with ethyl acetate (5 x 50 ml.). The organic extract was washed with water and dried. Evaporation of the solvent and crystallisation of the residue (2.95 g.) from aqueous methanol afforded needles of the tris-nor acid (72), m.p. $238-241^{\circ}$, $[\alpha]_D^{24} - 55^{\circ}$ (g 0.71), (lit.⁹ m.p. $241-244^{\circ}$, $[\alpha]_D^{22} - 52^{\circ}$), $\nu_{\max}$. 3600, 1750, 1720, 1010, and 915 cm^{-1} .

(Found: C, 64.3; H, 7.2;
Calc. for $\text{C}_{24}\text{H}_{32}\text{O}_8$ C, 64.3; H, 7.2%).

The acid was taken up in ether (100 ml.) and methylated with ethereal diazomethane in the usual way. Crystallisation from aqueous methanol afforded needles of the tris-nor ester

(73) (2.87 g.), m.p. 174-177°, $[\alpha]_D^{23} - 53^\circ$ (d 1.00),
 (lit.⁹ m.p. 176-178°, $[\alpha]_D^{22} - 55^\circ$), $\nu_{\max}$. 1755, 1740,
 1715, and 920 cm^{-1}

(Found: C, 64.7; H, 7.8;
 calc. for $\text{C}_{25}\text{H}_{34}\text{O}_8$ C, 64.9; H, 7.4%).

The semicarbazone had m.p. 241-243°.

(Found: C, 59.8; H, 6.9;
 $\text{C}_{26}\text{H}_{37}\text{O}_8\text{N}_3$ requires C, 60.1; H, 7.2%).

Reduction of Methyl Angolensate with Potassium Borohydride

Methyl angolensate (2.178 g.) in methanol (50 ml.) was treated with potassium borohydride (0.54 g.) and the mixture was heated under reflux on a steam-bath for 1 hour. About 75% of the methanol was distilled off and the residue was poured into water (100 ml.). The aqueous solution was extracted with ethyl acetate (3 x 50 ml.), and the organic extract was dried. The solvent was removed by distillation and the residue, the diol (84), (2.05 g.) was recrystallised from benzene - light petroleum as needles, m.p. 119-123°, (lit.⁹ m.p. 200-203°), $[\alpha]_D^{20} - 35^\circ$ (d 1.00), $\nu_{\max}$. 3600, 1735, 1505, 1025, and 875 cm^{-1}

(Found: C, 68.2; H, 8.2;
 calc. for $\text{C}_{27}\text{H}_{38}\text{O}_7$ C, 68.3; H, 8.1%).

Treatment of the Borohydride Reduction Product (84) with Phosphorus Pentachloride

The diol (84) (2.0 g.) was taken up in dry benzene (100 ml.) and phosphorus pentachloride (13 g.) was added. The mixture was kept at room temperature (27°) for 24 hours. It was then poured into water (100 ml.) and the mixture was extracted with ethyl acetate (2 x 50 ml.). The organic extract was dried and the solvent was distilled off. The residue was taken up in ethyl acetate (50 ml.) and ozonised at -50° for 12 hours. Water (100 ml.) was added and the solution was steam-distilled into a solution of 2,4-dinitrophenylhydrazine (1 g.) in methanol (30 ml.) containing sulphuric acid (1 ml.). The distillate was extracted with chloroform and dried. The solvent having been distilled off, the residue was taken up in benzene and adsorbed on to a column of alumina (Spence grade H, 40 g.). Elution with benzene (200 ml.) afforded acetone-2,4-dinitrophenylhydrazone which was crystallised from methanol as prisms (0.68 g.), m.p. 124-126°, $\lambda_{\max}$ 366 m μ .

(Found: C, 45.2; H, 4.4; N, 23.6;

calc. for $C_9H_{10}O_4N_4$ C, 45.4; H, 4.2; N, 23.5%)

The infrared spectrum was identical with that of an authentic specimen of acetone-2,4-dinitrophenylhydrazone,

m.p. 126-127°, and mixed m.p. 125-127°.

The residue left after steam-distillation was extracted with ethyl acetate and the organic solution was dried. The solvent was distilled off leaving a solid which would not crystallise, but which had no infrared absorption at 1715 cm^{-1} , but had an absorption at 1776 cm^{-1} in CH_2Cl_2 .

Acetylation of the Diol (84)

Acetic anhydride (5 ml.) was added to the diol (84) (0.845 g.) in dry pyridine (20 ml.). The mixture was heated on a steam-bath for 1 hour, and then kept at room temperature overnight. The pyridine and excess acetic anhydride were removed by distillation in vacuo, and the residue was taken up in benzene and adsorbed on to a column of alumina (10% deaot., 75 g.). Elution with benzene afforded the diacetate (85) (0.610 g.), which crystallised from aqueous ethanol as needles, m.p. 195-199°, (lit.⁹ m.p. 198-200°), $[\alpha]_D^{20} - 39^\circ$ (c 1.35), $\nu_{\text{max.}}$ 1745, 1650, 1503, 1245, 900, and 875 cm^{-1} .

(Found: C, 66.3; H, 7.7;
calc. for $\text{C}_{31}\text{H}_{42}\text{O}_9$ C, 66.7; H, 7.6%).

Meerwein-Ponndorf Reduction of Methyl Angolensate

Aluminium foil (5.6 g.) and isopropanol (100 ml.) were heated under reflux on a steam-bath for 15 hours in the presence of mercuric chloride (0.25 g.) and carbon tetrachloride (1 ml.). Methyl angolensate (2.148 g.) was then added and the mixture was slowly fractionally distilled for 7 hours to remove acetone formed in the reaction. Residual solvent was distilled off, and the residue was treated with excess dilute sulphuric acid and then extracted with chloroform. The organic solution was dried and the solvent distilled off. The residue was taken up in benzene and adsorbed on to a column of alumina (10% deactivated, 150 g.). Elution with benzene - ether (3:1) afforded methyl 3-hydroxyangolensate (112) (1.92 g.), which was crystallised from aqueous ethanol as needles, m.p. $257 - 260^{\circ}$, ν_{max} 3500, 1735, 1505, and 875 cm^{-1}

(Found:	C, 68.3; H. 7.8; O, 23.9;
$\text{C}_{27}\text{H}_{36}\text{O}_7$ requires	C, 68.6; H. 7.7; O, 23.7%).

Acetylation of Methyl 3-Hydroxyangolensate (112)

Methyl 3-hydroxyangolensate (1.23 g.) in dry pyridine (10 ml.) was treated with acetic anhydride (3 ml.), and the solution was kept at room temperature (25°) for 24 hours.

After working up in the usual way, the product methyl 3-acetoxyangolensate (113) (0.93 g.) was crystallised from aqueous ethanol as plates, m.p. 192-194°, $\nu_{\max}$. 1735, 1505, 1245, and 875 cm^{-1}

(Found: C, 67.2; H, 7.5; OAc, 8.6;

$\text{C}_{29}\text{H}_{38}\text{O}_8$ requires C, 67.7; H, 7.4; OAc, 8.4%).

Catalytic Hydrogenation of Methyl Angolensate over Adams'

Catalyst

(1) Methyl angolensate (0.609 g.) in ethanol (50 ml.) was hydrogenated at room temperature and pressure over Adams' catalyst (49 mg.) which was reduced in situ. The reaction ceased after 1 hour when approximately 0.9 mole equivalents of hydrogen had been absorbed. The catalyst was removed by filtration and the solvent was distilled off. The residue (0.607 g.) was crystallised from aqueous ethanol, and then recrystallised from ethyl acetate - light petroleum to give the dihydro-product (74) as prisms, m.p. 186-189°,

$[\alpha]_{\text{D}}^{20} + 14^\circ$ (c 1.52), $\nu_{\max}$. 1735, 1715, 1505, 910 and 875 cm^{-1} , and $\lambda_{\max}$. 212 $\text{m}\mu$ (ϵ 5,500).

(Found: C, 68.7; H, 7.7;

$\text{C}_{27}\text{H}_{36}\text{O}_7$ requires C, 68.2; H, 7.7%).

(ii) Methyl angolensate (1.050 g.) in acetic acid, (50 ml.) was hydrogenated at room temperature and pressure over Adams' catalyst (52 mg.). The reaction was stopped after 7 hours when 2.6 mole equivalents of hydrogen had been absorbed and the rate of uptake of hydrogen had been considerably reduced. The catalyst was removed by filtration and the solvent was distilled off in vacuo. The residue (0.95 g.) crystallised from aqueous methanol to give needles of the tetrahydro-product (82), m.p. 229-233°, $\nu_{\max}$. 3450, 1735, 1505, and 875 cm^{-1}

(Found: C, 68.2; H, 8.0;
 $\text{C}_{27}\text{H}_{38}\text{O}_7$ requires C, 68.3; H, 8.1%).

(iii) Methyl angolensate (0.451 g.) in acetic acid (50 ml.) was hydrogenated at room temperature and pressure over Adams' catalyst (55 mg.). The reaction was stopped after 2 days when 4.2 mole equivalents of hydrogen had been taken up and the reaction seemed to be complete. The solution was worked up as before, and the residue (0.410 g.) was crystallised from aqueous methanol to give the octahydro-product (83) as needles, m.p. 253-257°, $\nu_{\max}$. 3450, 1737, and 920 cm^{-1}

(Found: C, 68.1; H, 8.9;
 $\text{C}_{27}\text{H}_{42}\text{O}_7$ requires C, 67.8; H, 8.9%).

Attempted Oxidation of the Dihydro-Product (74)

The dihydro-product (74) (202 mg.) in acetone (40 ml.) was treated with Jones' reagent²⁵ (2 ml.). The mixture was shaken at room temperature for 15 minutes and then poured into water (100 ml.). Extraction with ether and isolation of the product in the usual way afforded unchanged starting material, identified by mixed m.p. and by comparison of the infrared spectrum with an authentic specimen of the dihydro-product (74).

Hydrogenation of the tris-nor Ester (73)

The tris-nor ester (73) (1.806 g.) in acetic acid (50 ml.) was hydrogenated as before over Adams' catalyst (50 mg.) which was reduced in situ. The catalyst was removed by filtration and as much as possible of the solvent was distilled off in vacuo. The residue was taken up in ethyl acetate (100 ml.) and washed with saturated aqueous sodium bicarbonate and water. The organic solution was dried and the solvent was distilled off. The residue was crystallised from aqueous methanol to give needles of the dihydro-product, m.p. 225-226°,

$[\alpha]_D^{20} - 12^\circ$ (c 0.50), $\nu_{\max.} (\text{CH}_2\text{Cl}_2)$ 1755, 1740, 1715, and 910 cm^{-1}

(Found: C, 64.3; H, 7.8;

$\text{C}_{25}\text{H}_{36}\text{O}_8$ requires

C, 64.6; H, 7.8%).

References to Chapter II

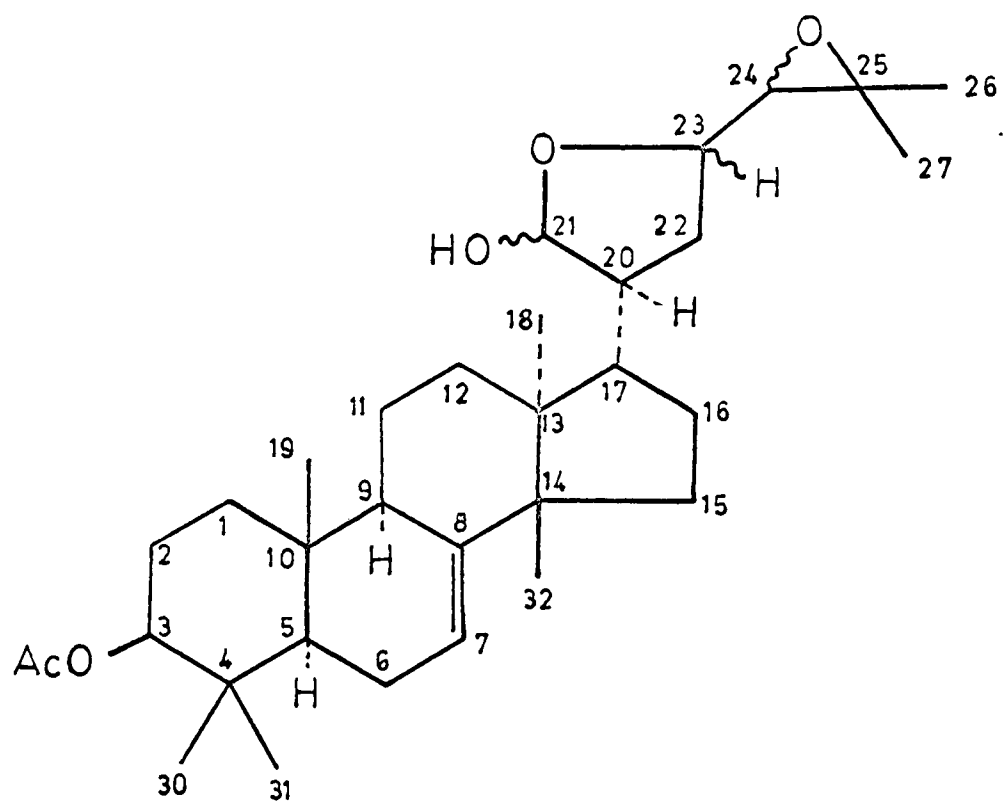
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CHAPTER

CHAPTER III

THE STRUCTURE AND CHEMISTRY OF TURRAZANTHIN



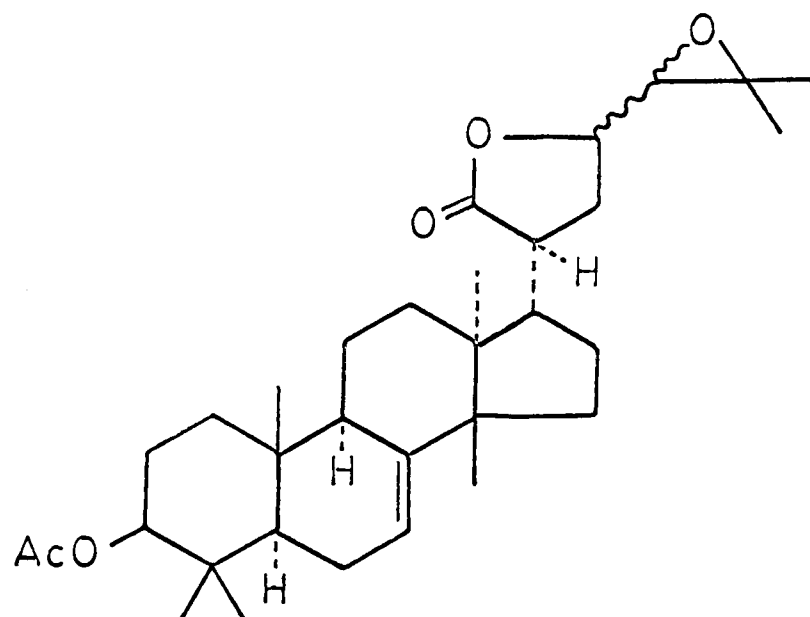
120 Turraeanthin

24 ϵ ,25 ϵ :21 ϵ ,23 ϵ -Diepoxytirucall-7-en-3 β ,21 ϵ -diol 3 β -monoacetate

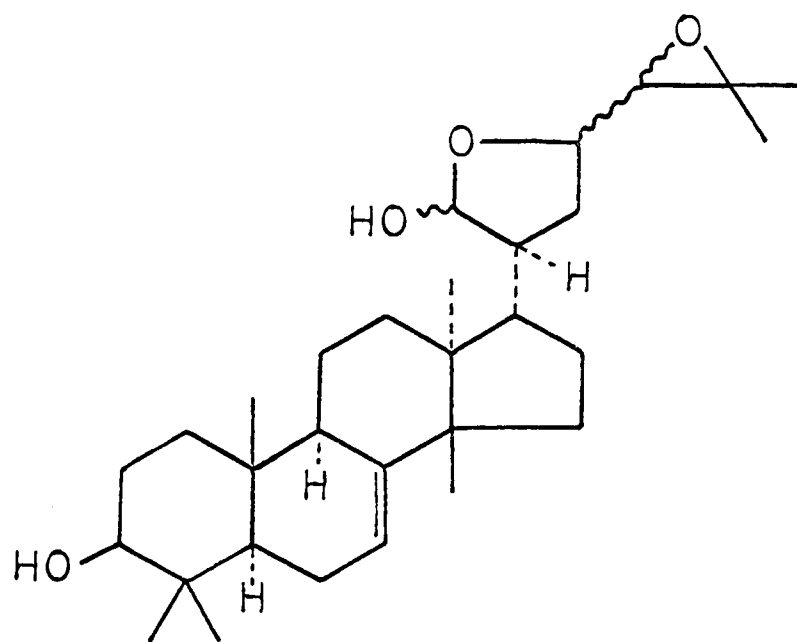
The Structure and Chemistry of Turraeanthin

Turraeanthus africanus is a member of the family Meliaceae which is found in West Africa, particularly in Ghana.^{of.1} Extraction of the heartwood with petroleum ether gave as the chief constituent (0.12%) needles of turraeanthin, a new triterpene, m.p. 218-220°, $[\alpha]_D^{20} + 3^\circ$. Combustion analysis indicated the formula $C_{32}H_{50}O_5$ which was confirmed by mass spectral studies of turraeanthin (M 514) and its derivatives. For simplicity its chemistry will be discussed in terms of the structure (120) which ultimately will be shown to represent it. A 100 mc/s n.m.r. spectrometer was used for some of this work, but unless otherwise stated the spectra were recorded on a 60 mc/s instrument (see Experimental Section for details).

The infrared spectrum of turraeanthin had a band at 3590 cm^{-1} due to the presence of a hydroxyl group. A strong peak appeared in the mass spectrum at m/e 496 corresponding to the ready loss of water (M - 18).² The n.m.r. spectrum had a band at 6.50 τ due to one proton which disappeared in the presence of deuterium oxide and must therefore be due to a hydroxyl proton. Turraeanthin therefore contains one hydroxyl group. The band due to the hydroxyl proton appeared at 6.25 τ in the 100 mc/s n.m.r. spectrum, but this



121 Turraeanthin lactone



122 Deacetylturraeanthin

is not surprising since the position of a hydroxyl proton signal is dependent upon concentration³ and the two spectra were not determined at the same concentration.

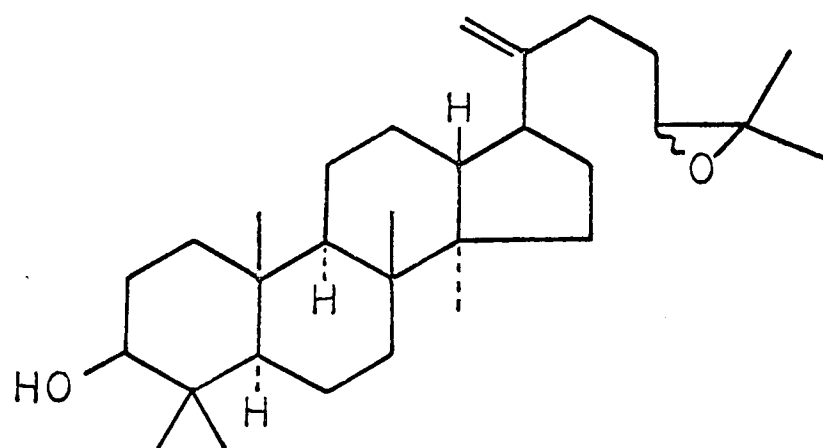
Mild oxidation with chromium trioxide - pyridine complex⁴ gave a γ -lactone, turraeanthin lactone (121). This compound had an infrared absorption band at 1780 cm^{-1} due to the

γ -lactone, and there was no absorption in the hydroxyl region. The mass spectrum had its parent peak at m/e 512 indicating that two hydrogen atoms had been removed by the oxidation and it did not show a peak corresponding to the loss of water ($M - 18$). The n.m.r. spectrum had lost the band corresponding to the hydroxyl proton. This means that a five-membered cyclic hemiacetal structure must be present in turraeanthin. The 100 mc/s n.m.r. spectrum of turraeanthin had a band at 4.63τ due to one proton, but this band did not appear in the 100 mc/s n.m.r. spectrum of turraeanthin lactone (121). Therefore this signal can be attributed to the proton on the carbon atom to which the hydroxyl group is attached, $-\text{C}_{(21)}\text{H}(\text{OH})\cdot\text{O}-$ in the cyclic hemiacetal.

The presence of an acetoxy group in turraeanthin was suggested by the bands at 1724 and 1245 cm^{-1} in the infrared spectrum. The mass spectrum had a peak at m/e 454 corresponding to the loss of acetic acid ($M - 60$),² and the

corresponding peak ($M - 60$) was observed at m/e 452 in the mass spectrum of turraeanthin lactone (121). The 100 mc/s n.m.r. spectrum of turraeanthin had a singlet at 7.90 due to the acetoxy methyl group, and there was a multiplet at 5.47τ due to one proton. The latter signal is assigned to the grouping $-C_{(3)}\underline{H}(OAc)-$.⁵ Hydrolysis of turraeanthin with methanolic potassium hydroxide removed the acetoxy group to give the hydroxy compound desacetylturraeanthin (122). The mass spectrum of this compound had its parent peak at m/e 472 indicating the loss of 42 mass units which corresponds to the hydrolysis of one acetoxy group. The infrared spectrum had a strong band at 3400 cm.^{-1} due to the hydroxyl groups and did not have any absorption in the carbonyl region. The n.m.r. spectrum of desacetylturraeanthin (122) had lost the band at 7.90τ due to the acetoxy group. The signal which appeared at 5.47τ in the n.m.r. spectrum of turraeanthin assigned to the grouping $-CH(OAc)-$ now appeared at 6.1τ and is assigned to the grouping $-C_{(3)}\underline{H}(OH)-$.⁵ Therefore turraeanthin is a mono-acetate.

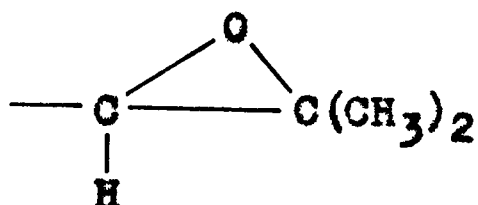
The presence of a cyclic hemiacetal group and an acetoxy group in turraeanthin accounts for four of the five oxygen atoms in the formula $C_{32}H_{50}O_5$. The fifth oxygen atom is present in an epoxy group. The 100 mc/s n.m.r. spectrum of



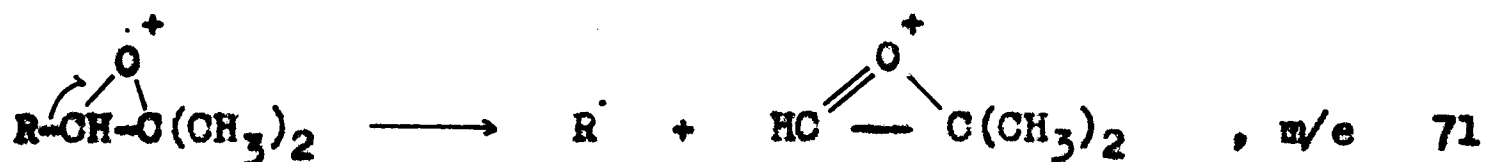
36 Aglaiol

turraesanthin had a signal at 7.09τ due to the proton at $C_{(24)}$ on the epoxy ring. The corresponding signal appeared at 7.20τ in the 100 mc/s n.m.r. spectrum of turraesanthin lactone (121). Furthermore, a singlet due to six protons appeared at 8.63τ in the 100 mc/s n.m.r. spectra of both turraesanthin and its lactone. This is assigned to the two methyl groups on the epoxy group at $C_{(25)}$.

Thus the presence of the group



is suggested. This was supported by the presence of a strong peak at m/e 71 in the mass spectrum of turraesanthin lactone (121) which can be attributed to the fragmentation shown below.



A similar epoxy group occurs in aglaol (36)⁷. Its n.m.r. spectrum had a signal due to the $C_{(24)}$ proton at 7.25τ , and bands due to the methyl groups at $C_{(25)}$ appeared at 8.73

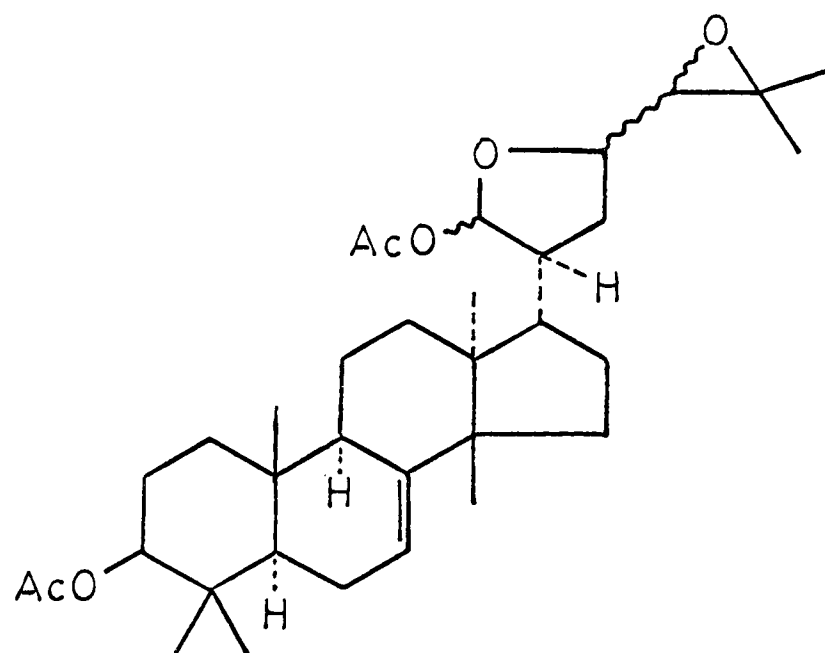
and 8.70 τ .

All of the oxygen atoms in turraesanthin have now been accounted for. The remaining functional group is a double bond whose presence was suggested by a band at 4.73 τ due to one proton in the 100 mc/s n.m.r. spectrum of turraesanthin. The corresponding signal appeared at 4.70 τ in the 100 mc/s n.m.r. spectrum of the lactone (121). These bands are assigned to the proton at C₍₇₎ on the double bond,³ which must be trisubstituted since the signals were due to only one proton. This was supported by a band at 823 cm.⁻¹ in the infrared spectrum of turraesanthin characteristic⁶ of a trisubstituted double bond. It could not be hydrogenated under mild conditions and ozonolysis did not give any volatile fragment, which would be expected if the double bond were in the side-chain. Therefore the double bond is in a ring.

Since the presence of a cyclic hemiacetal, an acetoxy group, an epoxide, and a cyclic double bond has been established, the formula C₃₂H₅₀O₅ for turraesanthin requires that there should be four carbocyclic rings.

The Side-Chain

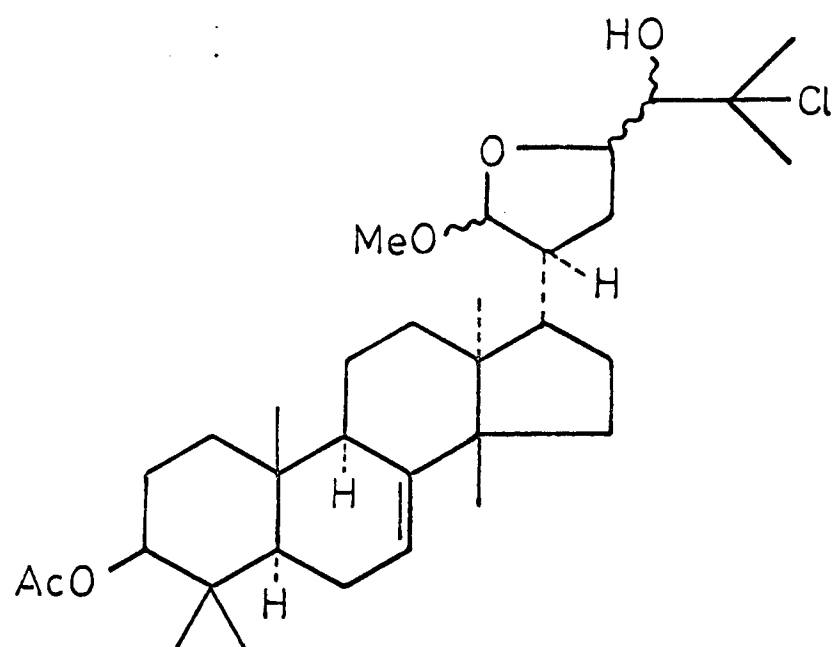
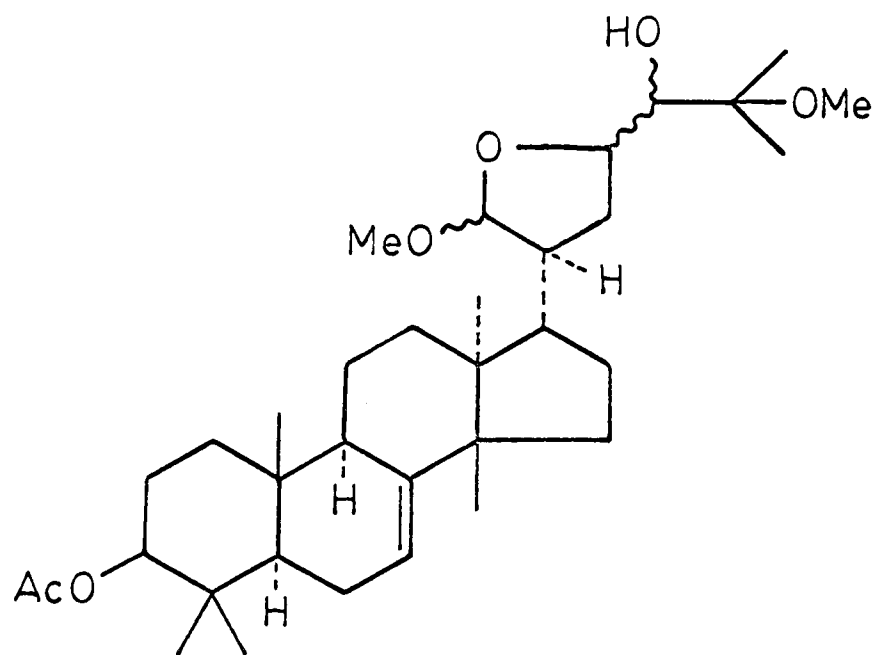
The hydroxyl group of turraesanthin could be acetylated



123 Turraeanthin acetate

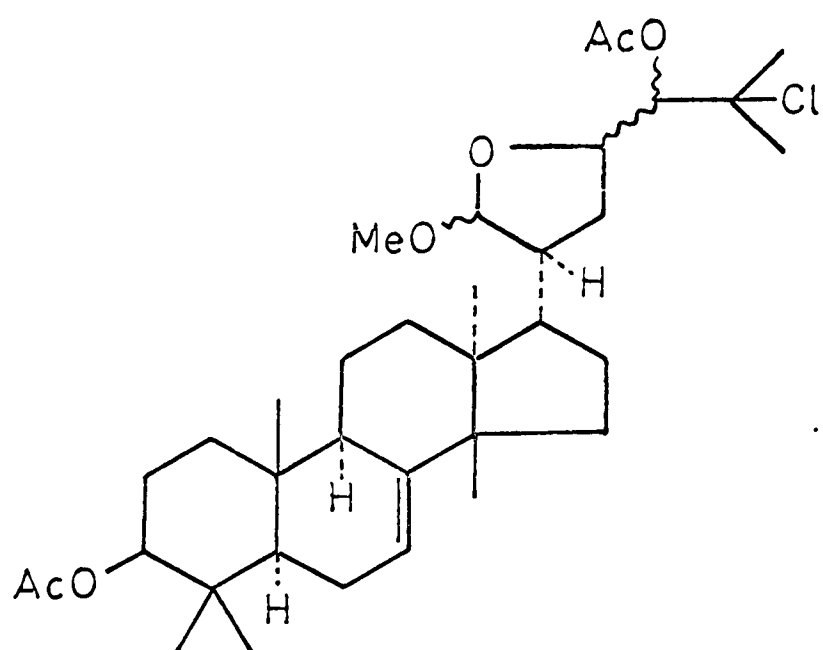
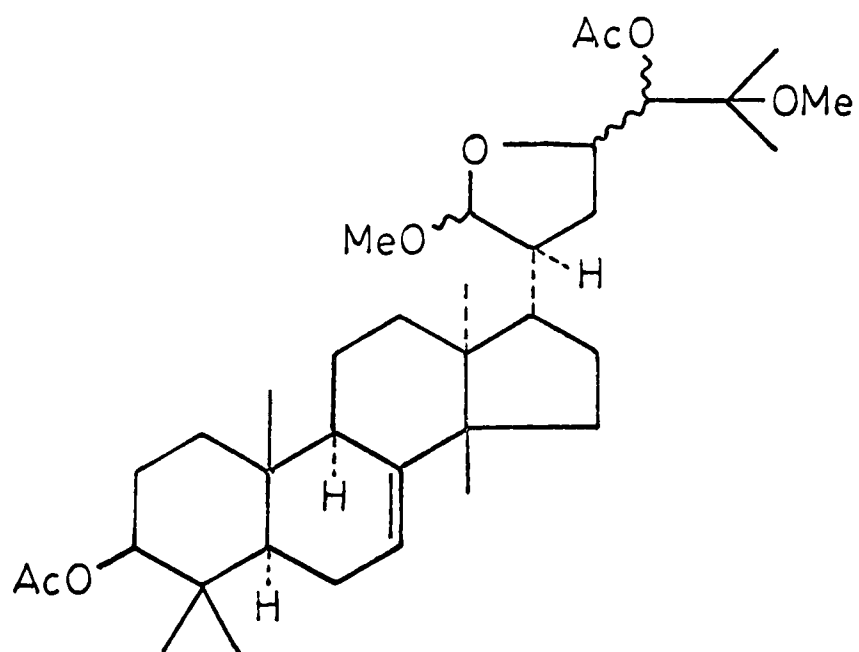
to give turraeanthin acetate (123). The same product was also obtained by acetylation of deacetylturraeanthin (122) as expected. Its infrared spectrum did not have any absorption in the hydroxyl region, but had bands at 1753 and 1225 cm^{-1} attributed to the new acetoxy group at $\text{C}_{(21)}$ and bands at 1745 and 1245 cm^{-1} assigned to the original acetoxy group at $\text{C}_{(3)}$. The mass spectrum had its parent peak at m/e 556, an increase of 42 mass units due to the acetylation of the hydroxyl group. It also showed a strong peak at m/e 496 due to the ready loss of acetic acid ($M - 60$).² The 100 mc/s n.m.r. spectrum had a singlet at 7.95 τ due to six protons which is assigned to the two acetoxy methyl groups. The proton at $\text{C}_{(21)}$ gave rise to a signal at 4.63 τ in the 100 mc/s n.m.r. spectrum of turraeanthin, and this band shifted to lower field on acetylation of the $\text{C}_{(21)}$ hydroxyl group and now appeared at 3.77 τ . This latter band was a doublet (J 3 c.p.s.) which indicates that there must be one proton at $\text{C}_{(20)}$.

In the 100 mc/s n.m.r. spectrum of turraeanthin the epoxy proton at $\text{C}_{(24)}$ appeared at 7.09 τ as a sharply defined doublet with a coupling constant of 8 c.p.s. The 100 mc/s n.m.r. spectrum of the lactone (121) similarly had a doublet at 7.20 τ (J 8 c.p.s.). Since there is no

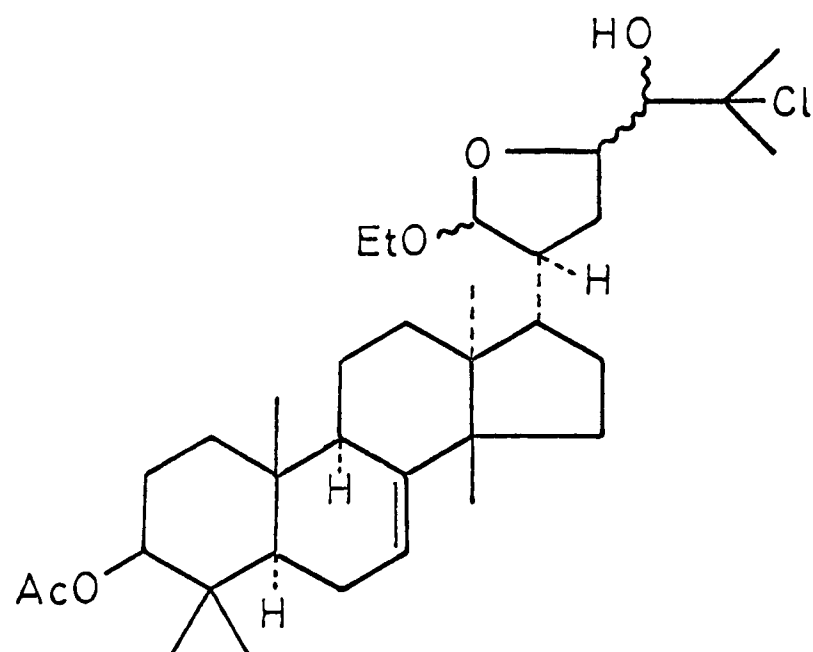
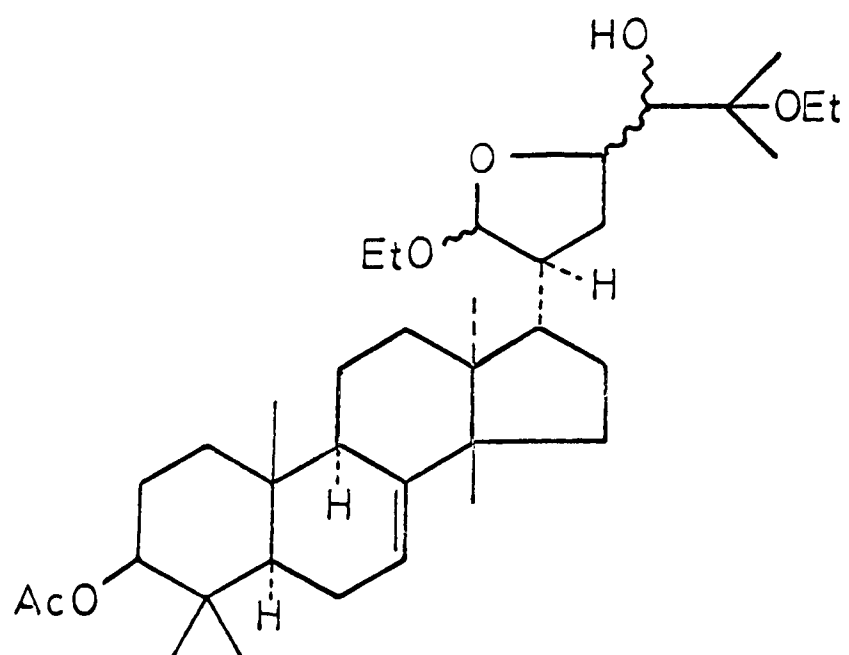
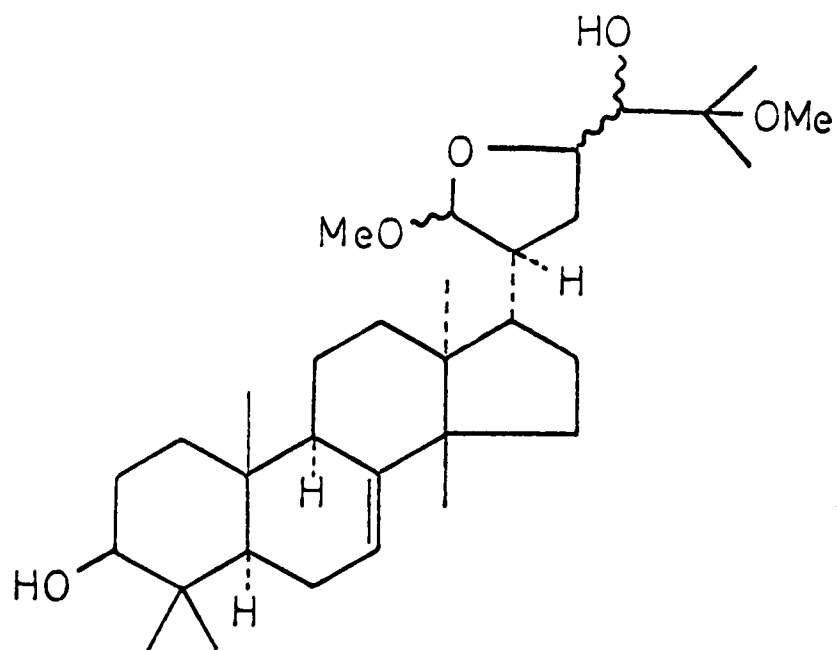
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proton at $C_{(25)}$ there must be one proton at $C_{(23)}$ to which the epoxy proton is coupled. A multiplet signal appeared at 6.15τ in the 100 mc/s n.m.r. spectra of turraeanthin and its acetate (123) which is assigned to the hydrogen at $C_{(23)}$. In the 100 mc/s n.m.r. spectrum of turraeanthin lactone (121) this signal shifted to slightly lower field and appeared at 5.85τ . The latter signal was an ill-defined six-line pattern owing to the $C_{(23)}$ proton being coupled to the $C_{(24)}$ proton and in addition split further by the methylene group at $C_{(22)}$. The assignment of the signals at 7.20 and 5.85τ in the n.m.r. spectrum of the lactone (121) to protons on neighbouring carbon atoms was demonstrated conclusively by a spin-decoupling experiment. Irradiation of the proton at $C_{(23)}$ absorbing at 5.85τ caused collapse of the doublet at 7.20τ due to the epoxide proton at $C_{(24)}$.

Treatment of turraeanthin with hydrochloric acid in methanol converted the hemiacetal grouping to an acetal and opened the epoxide ring to give the chlorohydrin (124) and the methoxyhydrin (125). The n.m.r. spectrum of the chlorohydrin (124) had a singlet at 6.62τ due to the methoxy group at $C_{(21)}$. The signals due to the methyl groups at $C_{(25)}$ now appeared at 8.34 and 8.40τ and are

126127

assigned to the grouping $-C_{(25)}Cl(CH_3)_2$. The infrared spectrum had a band at 3420 cm^{-1} due to the new hydroxyl group at $C_{(24)}$. The mass spectrum of the chlorohydrin (124) had its parent peak at m/e 564 in agreement with the formula $C_{33}H_{53}O_5Cl$. Similarly, the methoxyhydrin (125) had two singlets at 6.64 and 6.74 τ in the n.m.r. spectrum due to the methoxy groups at $C_{(21)}$ and $C_{(25)}$. The signals due to the methyl groups at $C_{(25)}$ appeared at 8.83 and 8.77 τ and are assigned to the grouping $-C_{(25)}(OMe)(CH_3)_2$. A band at 3550 cm^{-1} in the infrared spectrum was due to the $C_{(24)}$ hydroxyl group. The mass spectrum had its parent peak at m/e 560 corresponding to the formula $C_{34}H_{56}O_6$ for the methoxyhydrin (125). Attempted oxidation of the $C_{(24)}$ hydroxyl group in both the chlorohydrin (124) and the methoxyhydrin (125) failed, presumably because the $C_{(24)}$ position is highly hindered. However, acetylation of both compounds gave the chlorohydrin acetate (126) and the methoxyhydrin acetate (127) respectively. Neither of these acetates had absorption in the hydroxyl region of their infrared spectra. The n.m.r. spectrum of the methoxyhydrin acetate (127) had two singlets at 7.95 and 7.84 τ corresponding to the acetoxy methyl groups at $C_{(3)}$ and $C_{(24)}$.

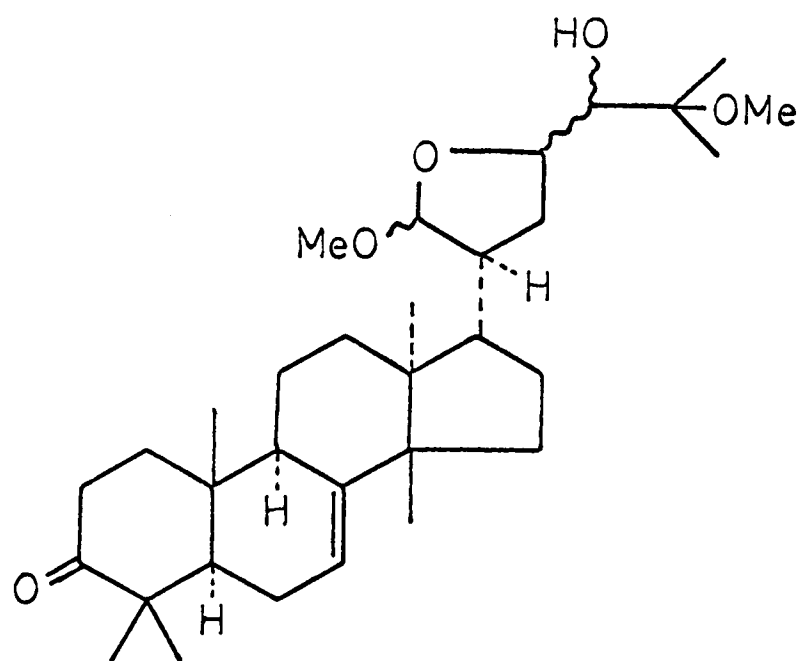
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By treating turraeanthin with hydrochloric acid in ethanol the hemiacetal grouping was converted to an acetal and the epoxide ring opened to give the chlorohydrin (128) and the ethoxyhydrin (129). These compounds are analogous to the chlorohydrin (124) and methoxyhydrin (125) respectively obtained by treating turraeanthin with hydrochloric acid in methanol.

Rings A and B

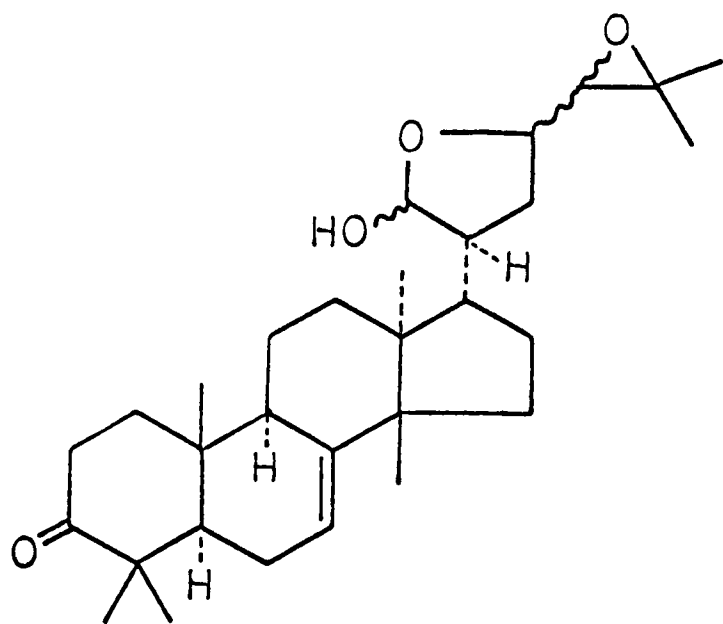
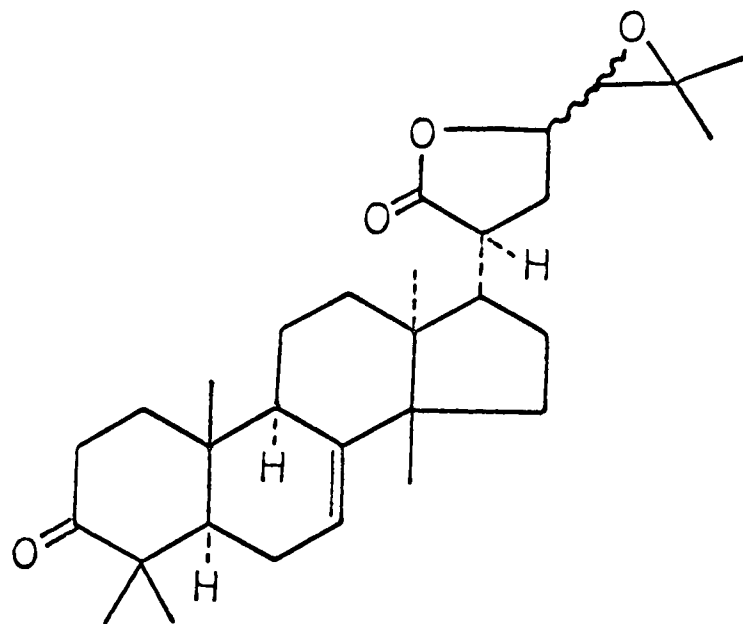
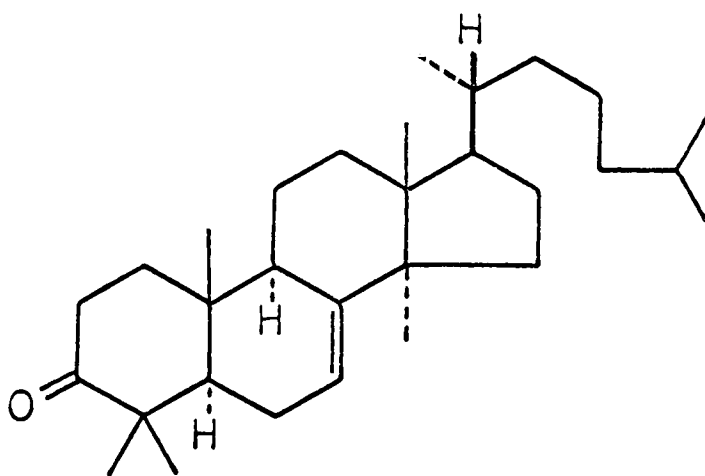
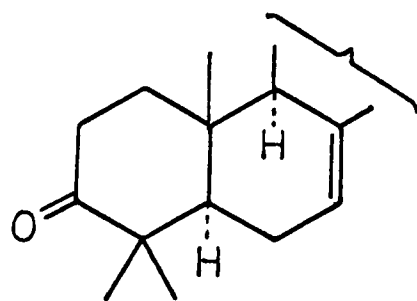
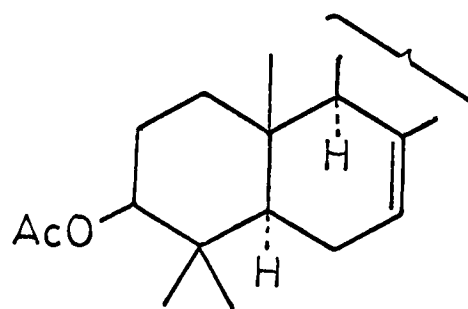
Treatment of turraeanthin with sulphuric acid in methanol gave two compounds. The minor product was shown to be identical with the methoxyhydrin (125) mentioned above. Their infrared spectra were superimposable and a mixed melting point gave no depression. The major product (130) was similar to the methoxyhydrin (125) in that the side-chain hemiacetal had been converted into the acetal and the epoxide ring had been opened to give the methoxyhydrin group. In addition the acidic conditions caused hydrolysis of the acetate group at C₍₃₎ affording the hydroxy compound (130). The infrared spectrum of this compound had a strong band at 3480 cm.⁻¹ due to the hydroxyl groups, and did not have any absorption in the carbonyl region indicating that the acetoxy group had been lost. Oxidation of compound (130)

71a



131

with chromic acid - pyridine⁴ gave the methoxyhydrin ketone (131) in which the C₍₃₎ hydroxyl group was oxidised to the ketone, but the C₍₂₄₎ hydroxyl group did not react under the conditions of the experiment. The infrared spectrum of this compound had an absorption band at 3540 cm⁻¹ due to the C₍₂₄₎ hydroxyl group, and a peak appeared at 1705 cm⁻¹ due to the ketone at C₍₃₎. The mass spectrum had its parent peak at m/e 516 in agreement with the formula C₃₂H₅₂O₅, and had a strong peak at m/e 484 corresponding to the ready loss of methanol (M - 32). Reduction of the ketone (131) with sodium borohydride gave a product which was identical with the hydroxy compound (130) from which the ketone (131) was originally prepared. Their infrared spectra were identical and a mixed melting point gave no depression. Since the reduction process should give a 3 β -hydroxyl group,⁹ the hydroxy compound (130) must contain a 3 β -hydroxyl group. Therefore the acetoxy group at C₍₃₎ in turraeanthin, from which the hydroxyl group was obtained by hydrolysis, must be β -oriented. Further evidence for this was obtained by an examination of the 100 mc/s n.m.r. spectra of turraeanthin and its lactone (121). In both of these spectra the signals due to the protons at C₍₃₎ appeared as triplets centred at 5.47 and 5.50 τ respectively, with

132133134 Lanost-7-en-3-one135136

observed splittings of 8 and 8 c.p.s. giving an overall band width of 16 c.p.s. This is the X portion of an ABX system.³ The proton at C₍₃₎ is axial and is coupled with the neighbouring axial and equatorial protons at C₍₂₎. In such a system diaxial interaction leads to a splitting of about 10 c.p.s. and axial - equatorial interaction has a splitting of the order of 5 c.p.s.³ This would lead to a double-doublet which would overlap thus appearing as an apparent triplet with an overall bandwidth of 15 c.p.s. and apparent splittings of 7.5 and 7.5 c.p.s. This is quite close to the observed values and the proton at C₍₃₎ in turraeanthin is therefore placed in the axial conformation which makes the acetoxy group at C₍₃₎ β -equatorial.

Alkaline hydrolysis of turraeanthin gave deacetylturraeanthin (122) mentioned above. Oxidation of this with chromium trioxide - pyridine⁴ gave a mixture of two compounds, a minor product 3-oxodeacetoxyturraeanthin (132) and the major component 3-oxodeacetoxyturraeanthin lactone (133). The infrared spectrum of 3-oxodeacetoxyturraeanthin (132) had a band at 3400 cm.⁻¹ due to the C₍₂₁₎ hydroxyl group, and there was a band at 1705 cm.⁻¹ corresponding to the ketone group at C₍₃₎. The mass spectrum

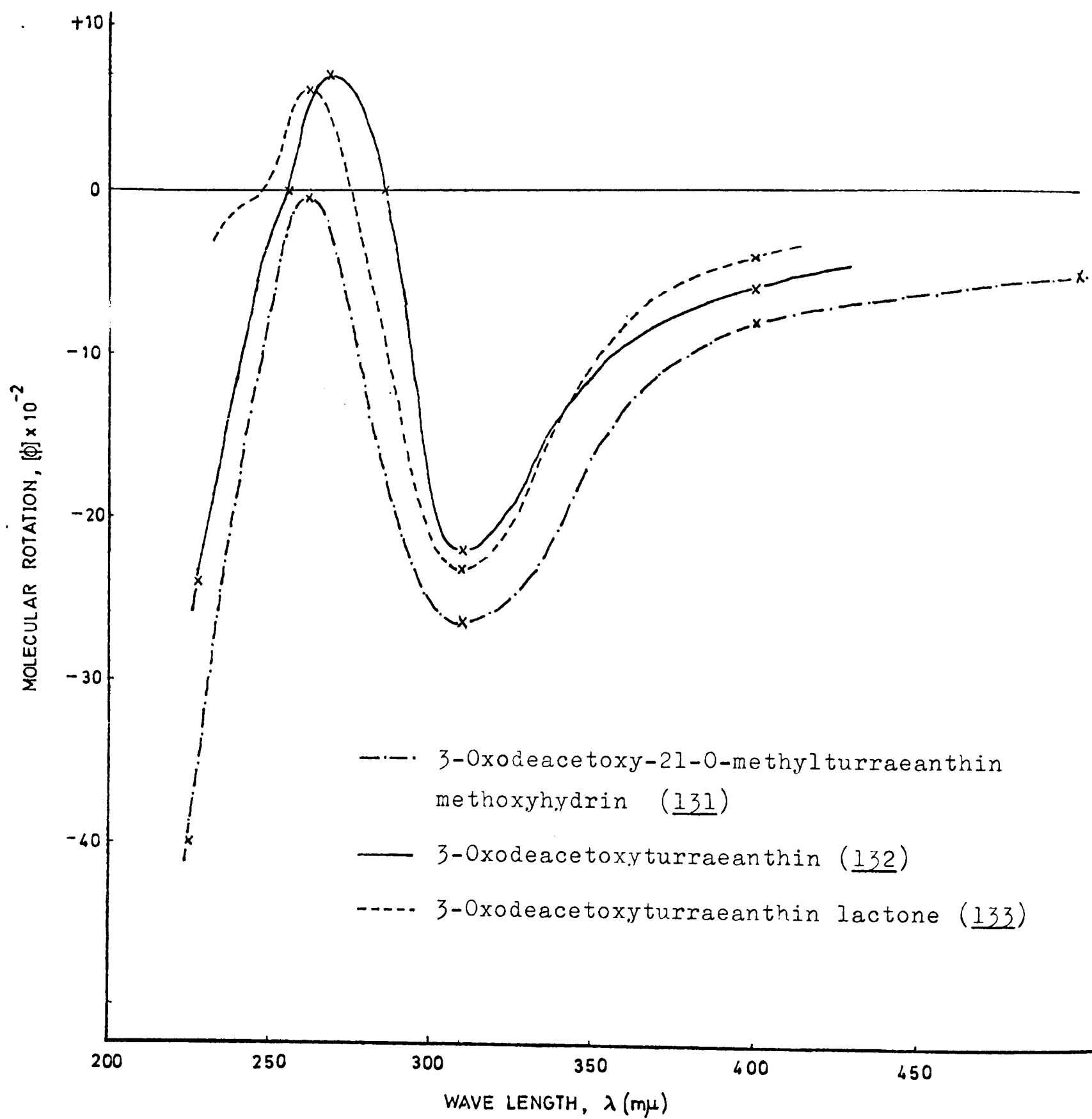
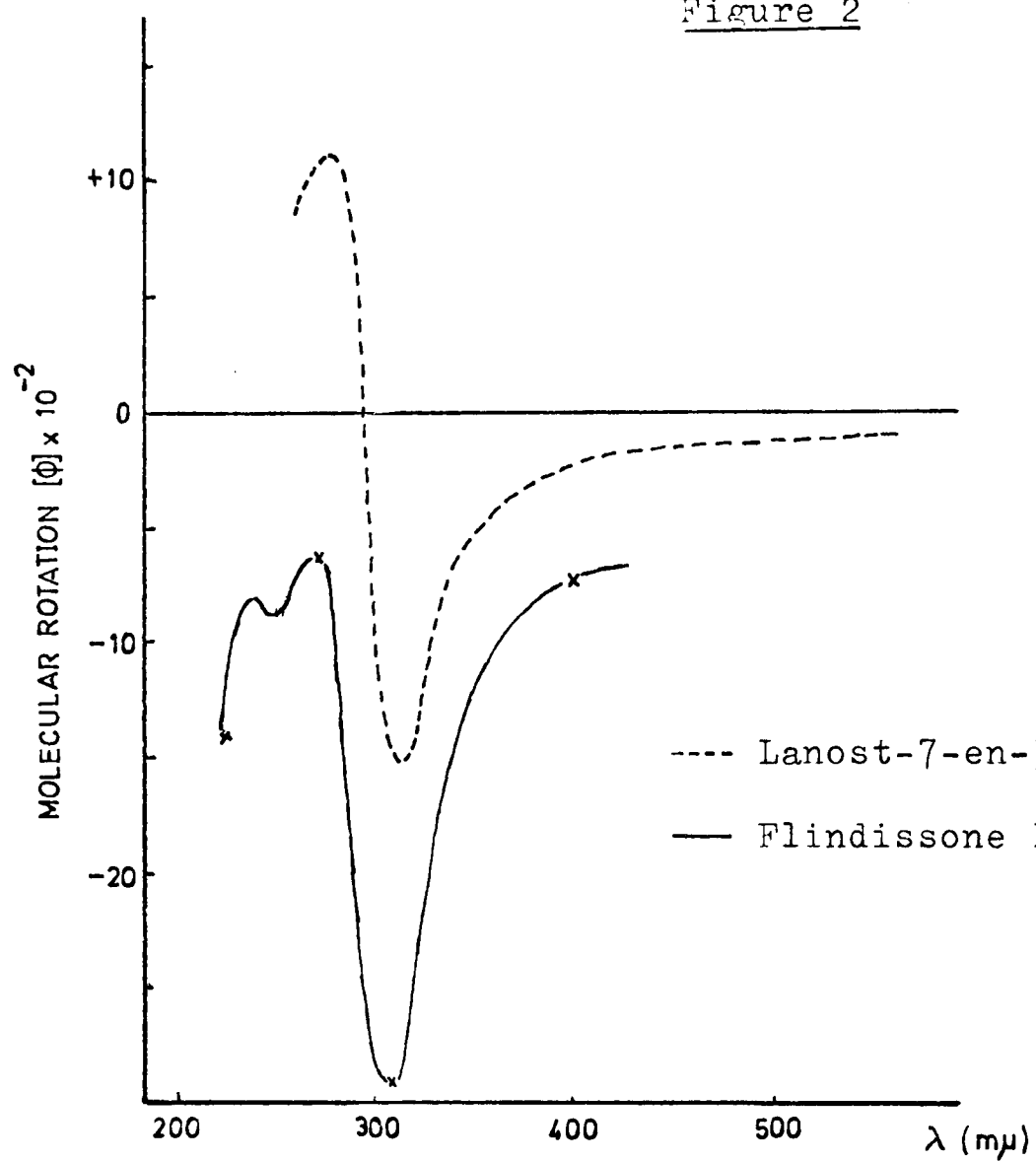
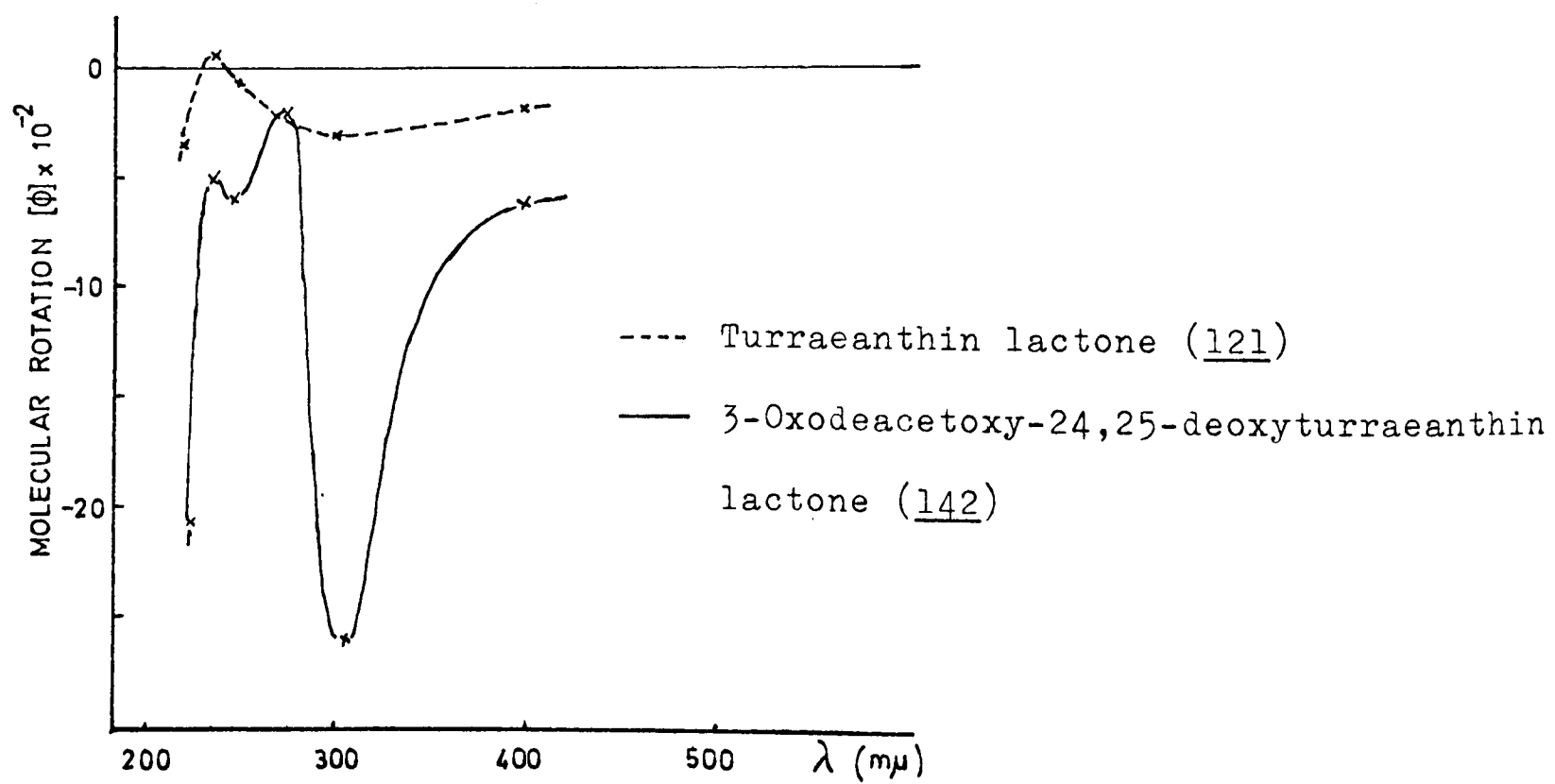


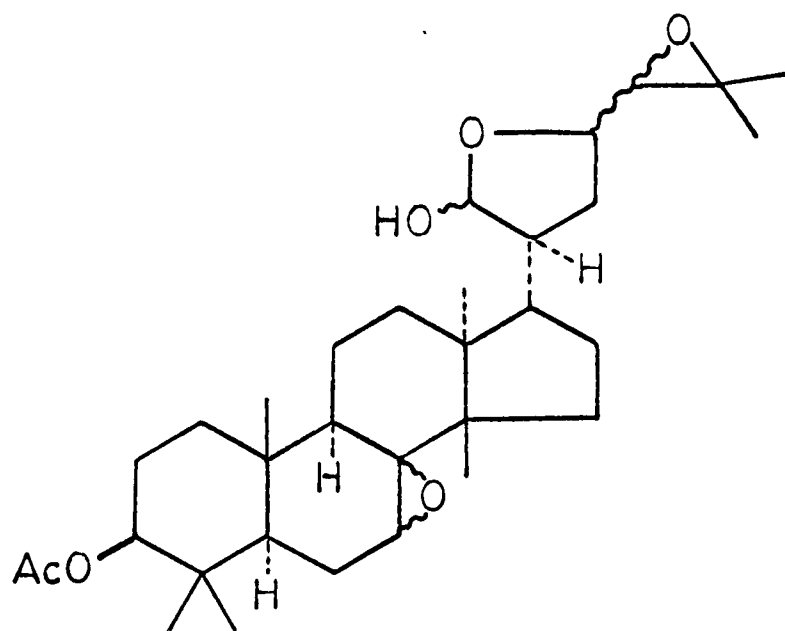
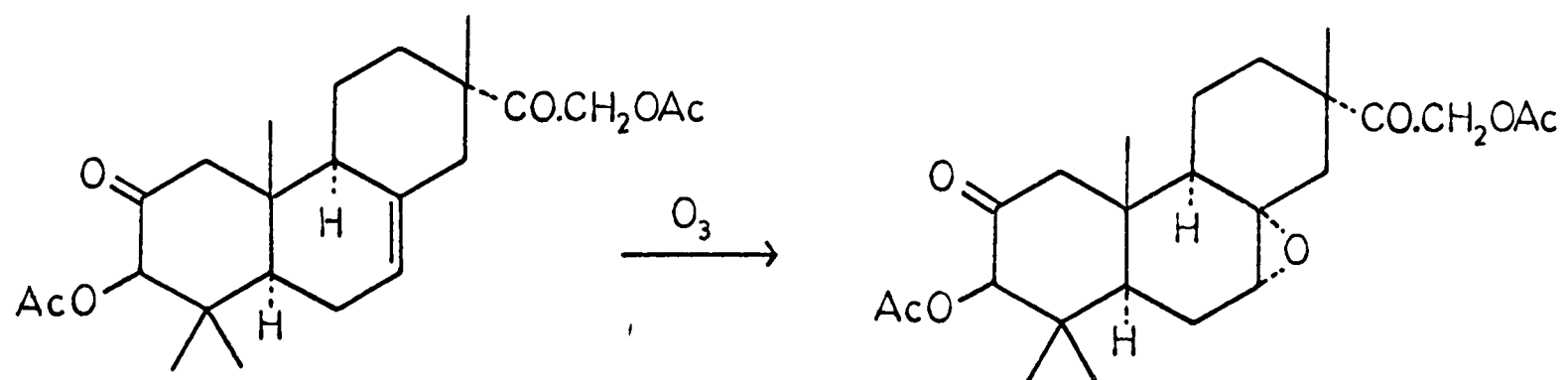
Figure 1

Figure 2



had its parent peak at m/e 470 in agreement with the formula $C_{30}H_{46}O_4$ and had a strong peak at m/e 452 corresponding to the loss of water ($M - 18$).² The major product, 3-oxodeacetoxyturraeanthin lactone (133), had absorption bands in its infrared spectrum at 1775 and 1710 cm^{-1} due to the γ -lactone and the ketone group respectively. There was no absorption in the hydroxyl region. The mass spectrum had its parent peak at m/e 468 in agreement with the structure (133). The n.m.r. spectrum had only two signals at low field below 7τ at 5.7 and 4.6 τ due to the proton at $C_{(23)}$ and the vinyl proton at $C_{(7)}$ respectively.

The optical rotatory dispersion (O.R.D.) curves of the three compounds 3-oxodeacetoxy-21-O-methylturraeanthin methoxyhydrin (131), 3-oxodeacetoxyturraeanthin (132), and 3-oxodeacetoxyturraeanthin lactone (133), are shown in fig. 1. They all exhibit a negative Cotton effect and are almost superimposable upon the corresponding curves of flindissone lactone¹⁰ (142) and lanost-7-en-3-one (134).¹¹ This fixes the stereochemistry of the A/B ring system as in (135) in these compounds (131), (132) and (133), and means that turraeanthin must have the partial structure as in (136). It is not possible to determine the geometry of the rest of the molecule from O.R.D. data since the tetracyclic

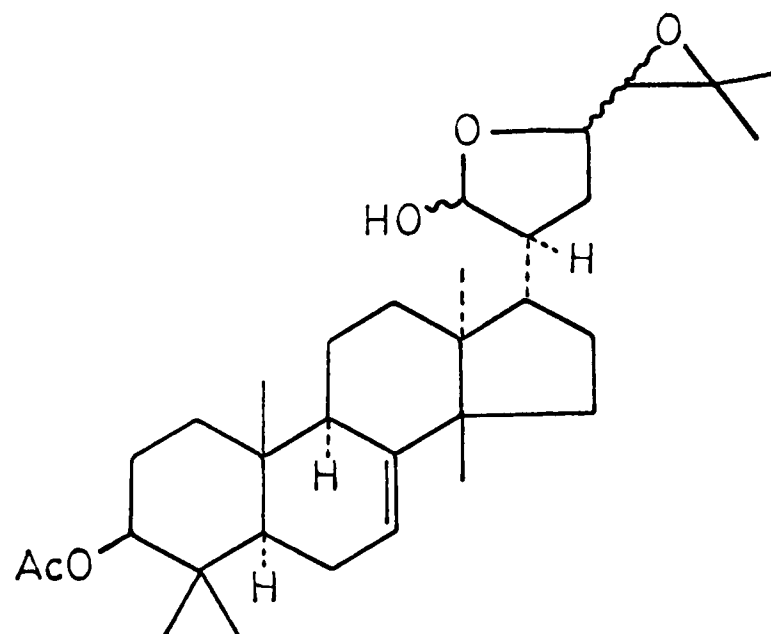
137138 Araucarolone diacetate139

triterpenes lanost-7-en-3-one and dihydrobutyrospermone have very similar Cotton curves even though their C/D ring junctions have different configurations.¹¹

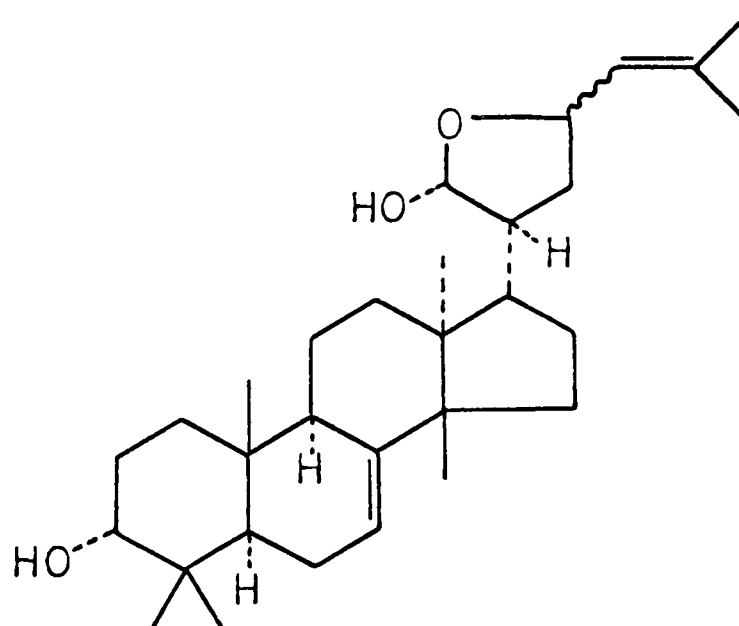
The ozonolysis of turraeanthin has been mentioned before when it was stated that no volatile fragment was produced. However, the residue from ozonolysis was an epoxy compound (137). The n.m.r. spectrum of this compound had signals in the region 7.1 τ due to two protons corresponding to the epoxy protons at C₍₂₄₎ and C₍₇₎, and there was no signal due to a vinyl proton. Enzell and Thomas¹² obtained a similar epoxide by ozonolysis of araucarolone diacetate (138) when the epoxy compound (139) was produced. By analogy with this, turraeanthin oxide (137) is probably a 7 α , 8 α -epoxide, although since the signals at 7.1 τ in the n.m.r. spectrum were confused it was not possible to decide this from n.m.r. considerations.

Relationship to Flindissol

The presence in the Meliaceae and the related Rutaceae and Simaroubaceae species of a number of degraded triterpenes such as limonin¹³ (1), gedunin¹⁴ (2), and simarolide¹⁵ (59) (see Introduction), all of which can be



120 Turraeanthin

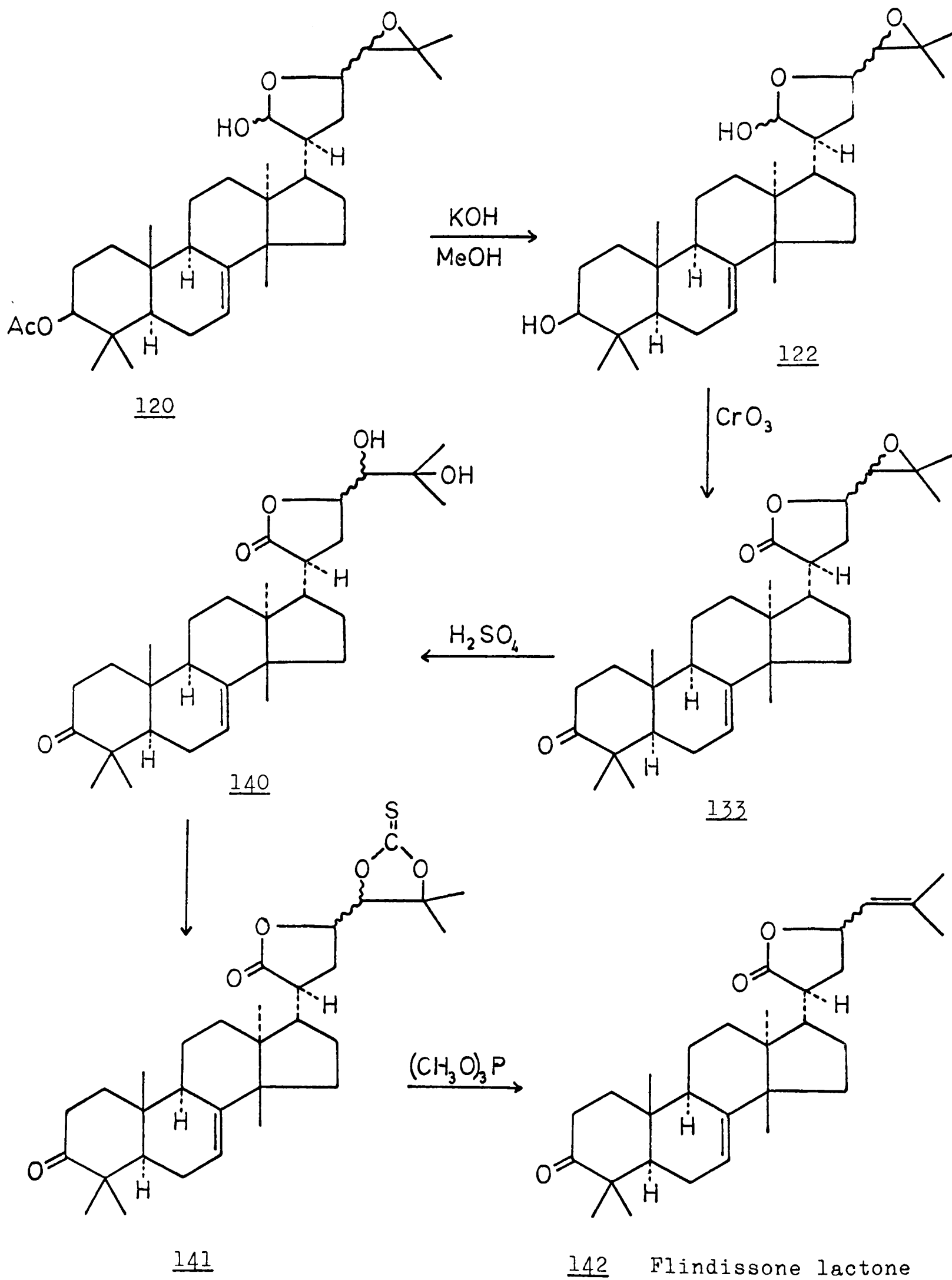


39 Flindissol

formally derived by oxidative degradation of tirucall-7,24-dien-3 β -ol (equivalent to 20- α H-butyropermol) (see later) together with the evidence described above suggested that turraeanthin was (120) and closely related to flindissol (39). Flindissol was isolated^{10,17} from Flindersia dissosperma Domin. and F. maculosa Lindl., species of the Rutaceae family related to the Meliaceae species.

The relationship between turraeanthin and flindissol (39) was established by the following route. Alkaline hydrolysis of turraeanthin gave deacetylurraeanthin (122), oxidation of which afforded 3-oxodeacetyturraeanthin lactone (133) mentioned above. The latter compound was treated with sulphuric acid in ether for two hours in order to open the epoxy ring, and the glycol (140) was obtained. The infrared spectrum of this compound (140) had absorption at 3500 cm^{-1} due to the hydroxyl groups at C₍₂₄₎ and C₍₂₅₎, and there were bands at 1750 and 1700 cm^{-1} due to the

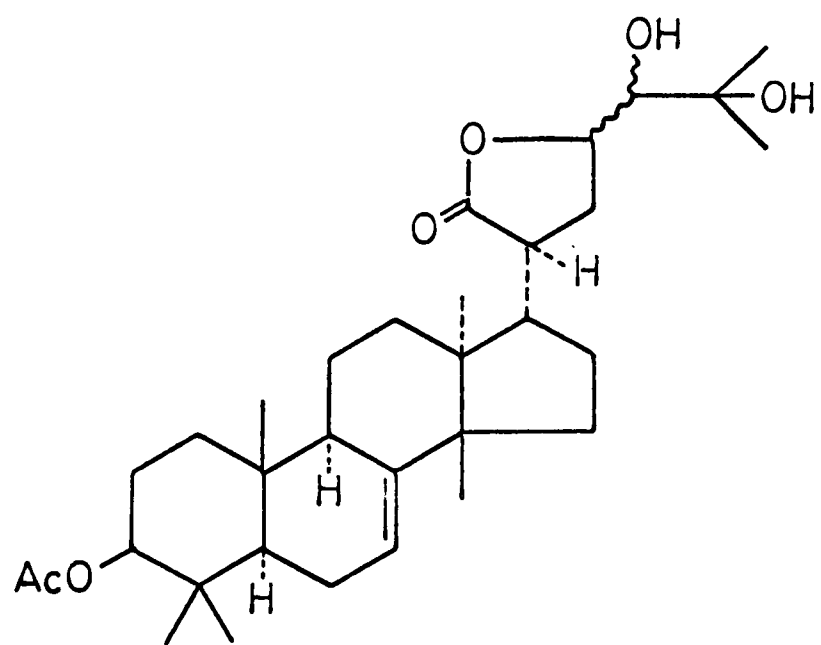
γ -lactone and the C₍₃₎ ketone groups respectively. The mass spectrum had its parent peak at m/e 530 in agreement with the formula C₃₀H₄₆O₅. The glycol (140) was converted¹⁶ into the cyclic thionocarbonate (141) by treatment with thiocarbonyl diimidazole.⁸ The product was refluxed with trimethylphosphite which caused¹⁶ desulphurisation-



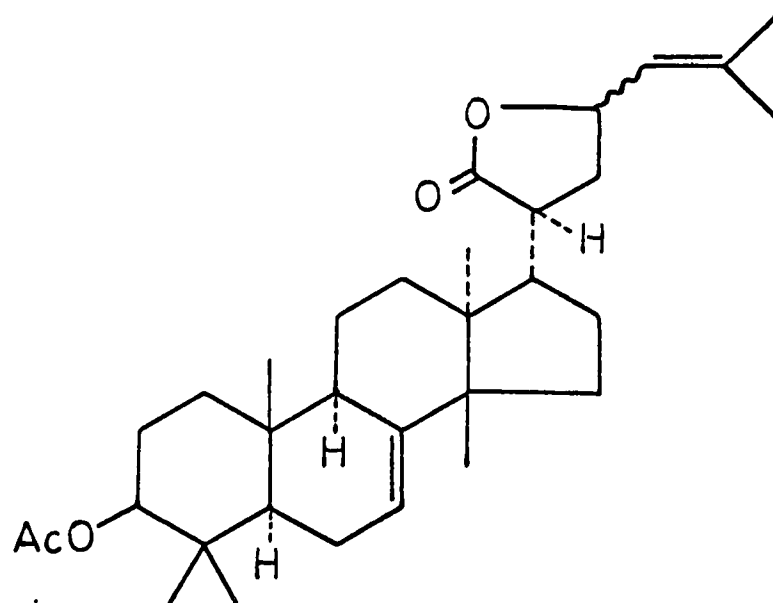
decarboxylation of the thionocarbonate group to give the 24,25-olefin, 3-oxodesacetoxy-24,25-deoxyturraeanthin lactone (142). Extensive purification, including chromatography and several recrystallisations, was necessary to remove residual traces of trimethylphosphite. The product (142) had a melting point ($190-194^{\circ}$) identical with that of flindissone lactone,¹⁰ obtained by a mild oxidation of flindissol (39) with chromium trioxide-pyridine, and no depression of the melting point was observed on admixture with an authentic sample. Their optical rotations were found to be $[\alpha]_D^{20} - 81^{\circ}$ and $[\alpha]_D^{20} - 83^{\circ}$ which are within experimental error, and their O.R.D. curves were identical within experimental error. Their infrared, n.m.r., and mass spectra were superimposable. This means that turraeanthin can be written as in (120) with the stereochemistry at $C_{(21)}$, $C_{(23)}$ and $C_{(24)}$ undefined.

The compound (142), 3-oxodesacetoxy-24,25-deoxyturraeanthin lactone, was also approached via another slightly different route. Turraeanthin lactone (121) was treated with sulphuric acid in ether for twenty-four hours to give the glycol (143), 24,25-dihydroxyturraeanthin lactone. The infrared spectrum of this compound had bands at 3580, 1775,

77a

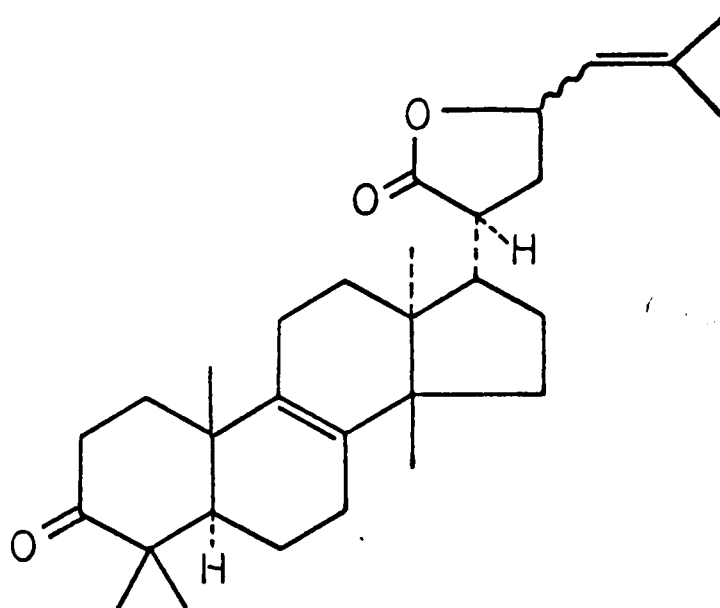


143

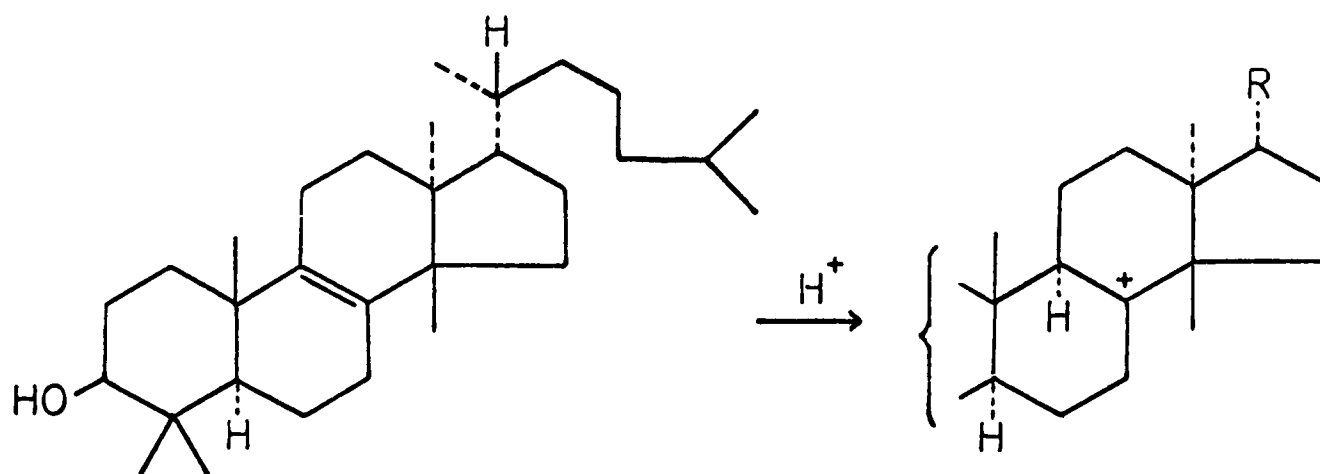


144

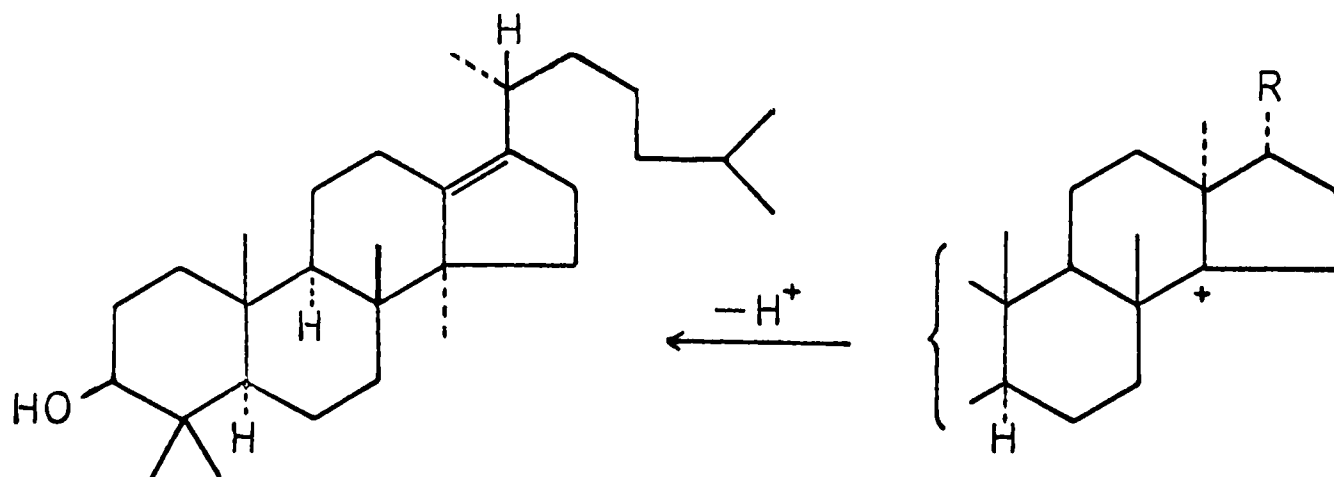
and 1728 cm.^{-1} corresponding to the $C_{(24)}$ and $C_{(25)}$ hydroxyl groups, the γ -lactone group and the $C_{(3)}$ acetoxy group. This glycol (143) was converted into its thionocarbonate by treating with thiocarbonyl diimidazole and hence into the 24,25-olefin (144) by refluxing the product with trimethylphosphite in a reaction analogous to the one above.^{cf. 16} Alkaline hydrolysis and oxidation of this compound (144) converted the $C_{(3)}$ acetoxy group into a ketone group and gave 3-oxodeacetoxy-24,25-deoxyturraesanthin lactone (142). However, this compound was seen to be impure when compared with the product of the former route. Its melting point ($180-185^{\circ}$) was lower and the optical rotation was different, $[\alpha]_D^{20} - 45^{\circ}$. This can probably be explained by the fact that in the preparation of the glycol (143) leading to the latter compound, turraesanthin lactone (121) was treated with sulphuric acid in ether for twenty-four hours instead of for only two hours in the analogous step of the former route. Under these conditions the double bond at $C_{(7)}$ could easily migrate to the $C_{(8)}$ position. Thus the final product of the second route could contain some of the $\Delta^{8(9)}$ isomer, and this is supported by the optical rotation, $[\alpha]_D^{20} - 45^{\circ}$, which is between that of



145 Isoflindissone lactone



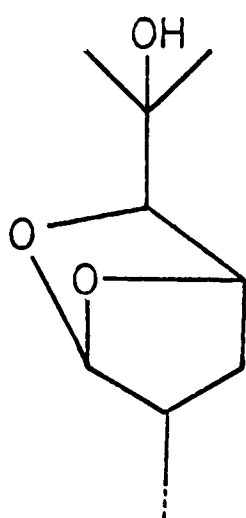
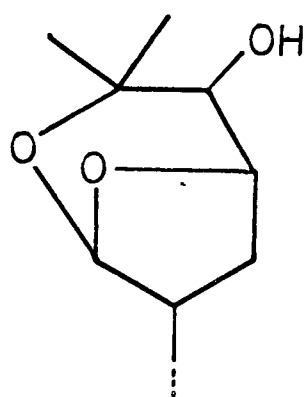
146 Dihydroeuphol



147

flindissone lactone, $[\alpha]_D^{20} - 83^\circ$, and that of isoflindissone lactone (145), $[\alpha]_D^{25} + 38^\circ$.¹⁰ An analogy for this rearrangement is provided by isoflindissone lactone (145)¹⁰ itself which was prepared by isomerisation of flindissone lactone (142) in the presence of hydrogen chloride in chloroform. In the euphol series, more drastic acid treatment leads to a more profound rearrangement involving the migration of methyl groups. Thus dihydroeuphol (146) rearranges¹⁸ to give isoeuphol (147), and it is also possible that an analogous transformation may have occurred to some extent in the preparation of 24,25-dihydroxyturraeanthin lactone (143) above subsequent to the Δ^7 to $\Delta^{8(9)}$ isomerisation.

When turraeanthin was treated with sulphuric acid in ether for twenty-four hours a product, isoturraeanthin, was obtained. The mass spectrum had its parent peak at m/e 514 indicating that it had the same molecular weight as turraeanthin. The infrared spectrum was quite similar to that of turraeanthin, the only major difference being the loss of the band at 822 cm^{-1} corresponding to the double bond at $C_{(7)}$. The n.m.r. spectrum did not have a signal due to an epoxide proton or a vinyl proton. Instead a new singlet due to one proton appeared at 4.75τ and there was

148149

a multiplet signal at 6.2 τ . The signals due to the methyl groups at $C_{(25)}$ now appeared as singlets at 8.45 and 8.72 τ . One possible explanation is that the epoxide ring had been opened to give a glycol as would be expected by analogy with the reactions mentioned above. Then acetal formation could have occurred between the hemiacetal hydroxyl group at $C_{(21)}$ and either of the new hydroxyl groups at $C_{(24)}$ or $C_{(25)}$. The former would give a new five-membered ring while the latter would produce a six-membered ring as in the partial structures (148) and (149) respectively. Perhaps the latter is the more likely since in this structure (149) the methyl groups at $C_{(25)}$ would be in different environments. This would account for the appearance of separate signals at 8.45 and 8.72 τ for these two methyl groups in the n.m.r. spectrum. In addition the double bond originally at $C_{(7)}$ must have migrated either to $C_{(8)}$ or to $C_{(13,17)}$ (see above).

Stereochemical Considerations

All of the stereochemical features of turraesanthin have been fixed by its relationship to flindissol (39) except those at $C_{(21)}$, $C_{(23)}$, and $C_{(24)}$.

In the 60 mc/s n.m.r. spectra of turraesanthin and

deacetylturraeanthin (122) but not in the spectra of any other derivatives there were four peaks in the region 7.1 τ which have been assigned to the epoxy proton at C₍₂₄₎. In the 100 mc/s spectrum there was primarily a doublet but there were also two other peaks. If these peaks are called A, B, C, and D the following figures were obtained (in units):

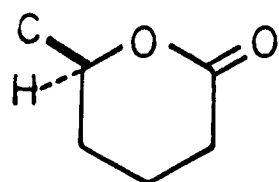
	100 mc/s	60 mc/s
A	7.04	7.02
B	7.11	7.13
C	7.24	7.20
D	7.32	7.32

If A is assumed to be coupled with C, and B with D, the coupling constants are 20 and 21 c.p.s. (100 mc/s), and 11 and 11 c.p.s. (60 mc/s). Alternatively if A and B are coupled, and C and D, the coupling constants are 7 and 8 c.p.s., and 7.5 and 8.5 c.p.s. respectively. These figures indicate that A is coupled with B and C with D, and suggests that the bands C and D have arisen from a different proton from that giving rise to bands A and B.

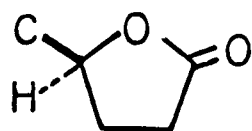
However, the integration indicated that the signals between 7.0 to 7.4 τ were due to approximately one proton. One possibility is that in solution turraesanthin gives rise to an equilibrium mixture of the two hemiacetal structures. An analogy for this is glucose.¹⁹ If two hemiacetal isomers existed, the hydroxyl group at C₍₂₁₎ would be either cis or trans to the C₄ side-chain at C₍₂₃₎ which has the epoxy group. This might well affect the chemical shift of the C₍₂₄₎ epoxy proton and the spectrum would show two doublets. The proton at C₍₂₁₎ might also be expected to show slightly different absorption peaks and it was observed that the band at 4.65 τ in the 100 mc/s n.m.r. spectrum of turraesanthin due to this proton was not as sharp as might be expected.

An attempt can be made to determine the stereochemistry at C₍₂₃₎ in turraesanthin by examining the derivatives in which the hemiacetal function has been oxidised to a lactone. Klyne²⁰ has extended Hudson's lactone Rule²¹ to the molecular rotations of compounds in which lactone rings are fused with other rings, and the modified rule is now stated:

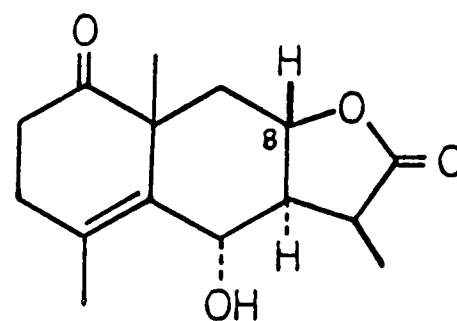
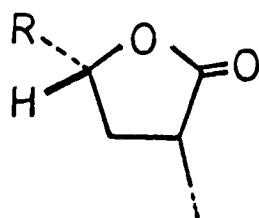
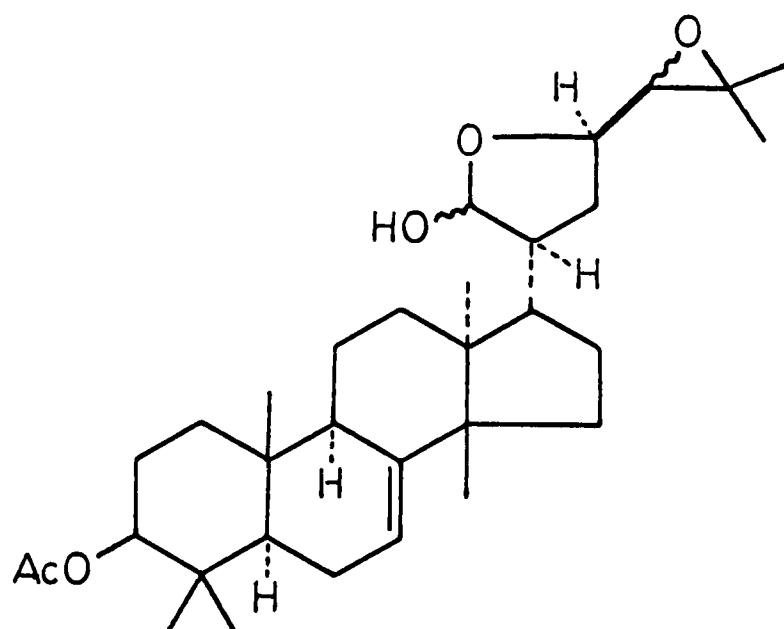
"If the hydrogen atom attached to the carbon atom bearing the potential hydroxyl group is below the plane of the lactone ring (150) the Δ value will be positive; if



(a)



(b)

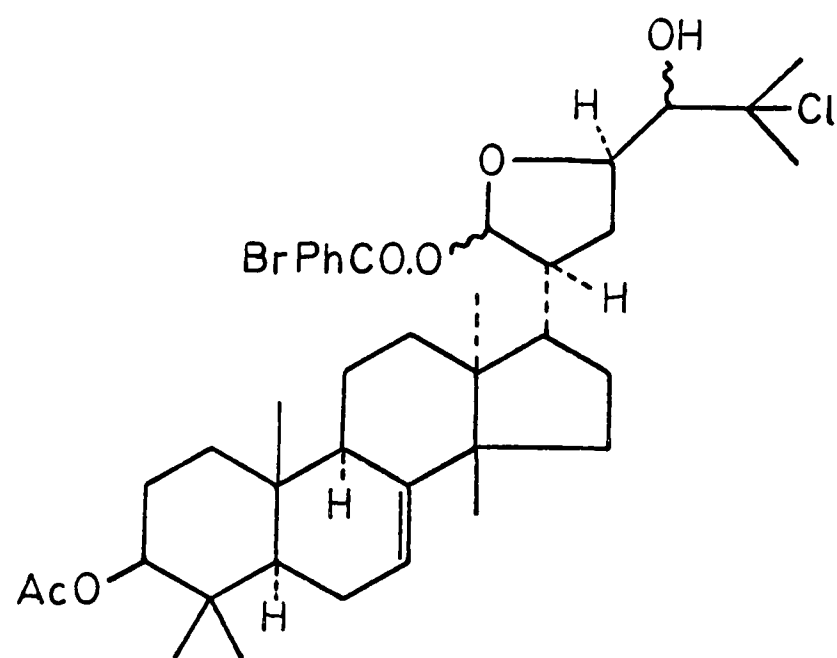
150151 Iso-ψ-santonin152153 Turraeanthin

the hydrogen atom is above the plane, the Δ value will be negative."

[Δ = the rotational difference, $[M]_D$ (lactone) - $[M]_D$ (acid)]. This modified lactone rule was used by Cocker et al.²² to determine the stereochemistry of the C₍₈₎ position in iso- ψ -santonin (151). The optical rotations of several lactones were measured, firstly in a mixture of methanol - chloroform alone, and then in methanol - chloroform containing potassium hydroxide so that the lactone was present in the open form as the potassium salt. The following results were obtained:

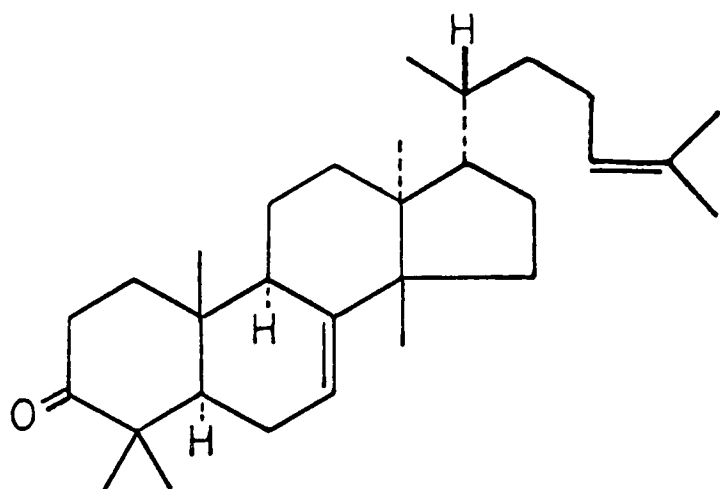
	$[M]_D^{20}$ (lactone)	$[M]_D^{20}$ (acid)
Turraeanthin lactone (<u>121</u>)	- 423°	-154°
3-Oxodeacetylturraeanthin lactone (<u>133</u>)	- 159°	- 8°
Flindissone lactone (<u>142</u>)	- 425°	- 376°

All of these results show a negative Δ value, which indicates that the configuration of the lactones in these compounds may be written as in (152). Hence turraeanthin itself may be written as in (153). The optical rotatory dispersion (O.R.D.) curves of these three compounds have also

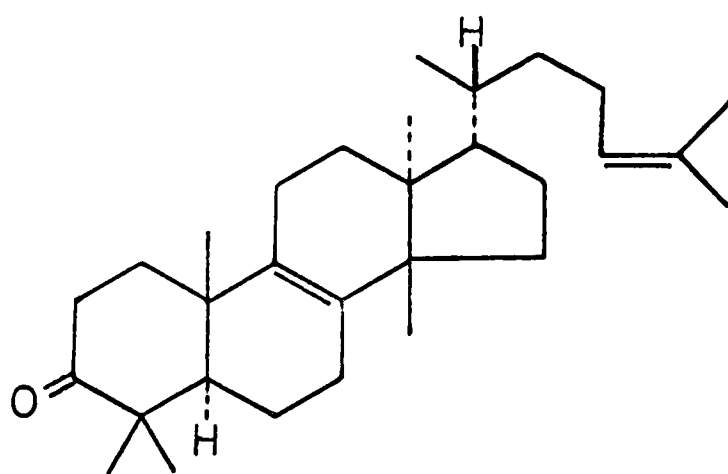


been measured. The Cotton effect of the lactone group was partly masked in the curves of 3-oxodesacetoxyturraeanthin lactone (133) and flindissone lactone (142) by the Cotton effect of the 3-oxo-7-ene grouping. However, the latter grouping is not present in turraeanthin lactone (121) and the Cotton curve of the lactone group could be seen. It was negative and much smaller than that due to the 3-oxo-7-ene system. This may be due to the additional Cotton effect of the double bond.²⁵ The Cotton effects of this and other lactones are being studied further by Professor W. Klyne and Dr. D.M. Scopes.

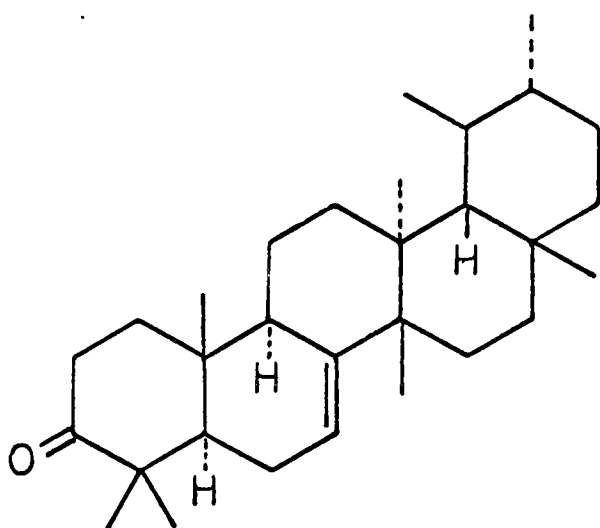
It is hoped that the remaining stereochemical features at C₍₂₁₎ and C₍₂₄₎ will be determined by an X-ray crystallographic examination of the p-bromobenzoate derivative (154). This compound was prepared by treating turraeanthin with p-bromobenzoyl chloride. In addition to forming the p-bromobenzoate ester at the C₍₂₁₎ hydroxyl group, the hydrogen chloride liberated from this reaction opened the epoxy ring to give the chlorohydrin. The n.m.r. spectrum had singlets at 8.30 and 8.23 τ due to the methyl groups at C₍₂₅₎ [of. the chlorohydrin compound (124)], and there was a broad singlet at 3.95 τ due to the proton



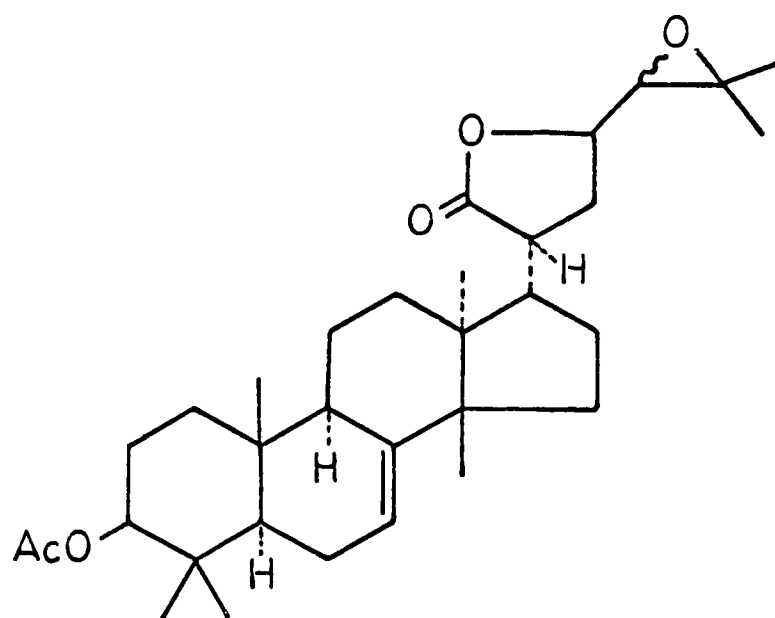
155 Butyrospermone



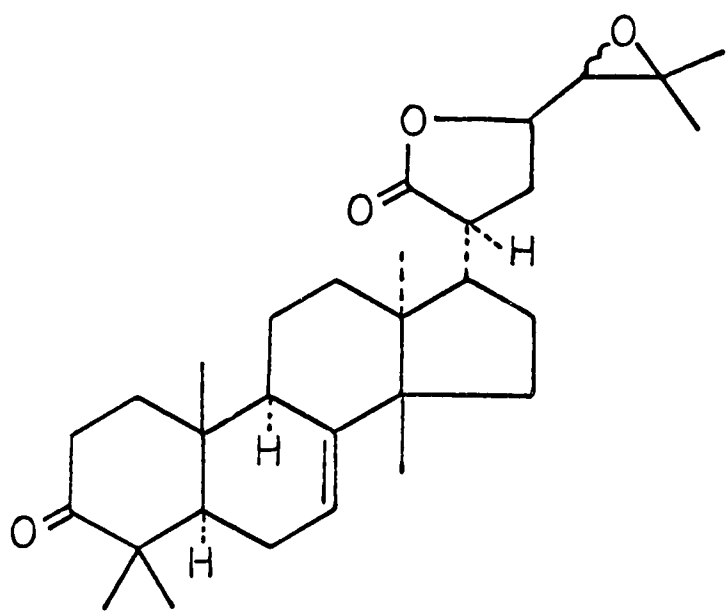
156 Euphone



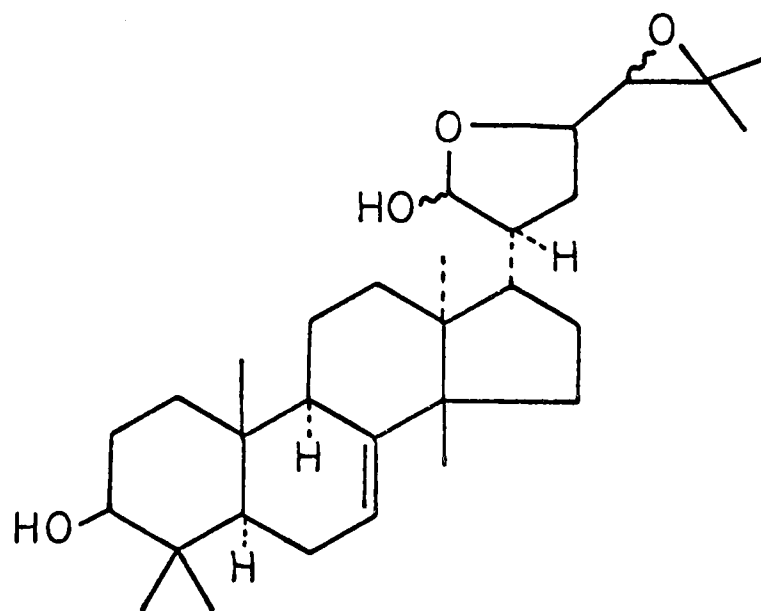
157 Bauerenone



121 Turraeanthin lactone



133 3-Oxodeacetoxyturraeanthin
lactone

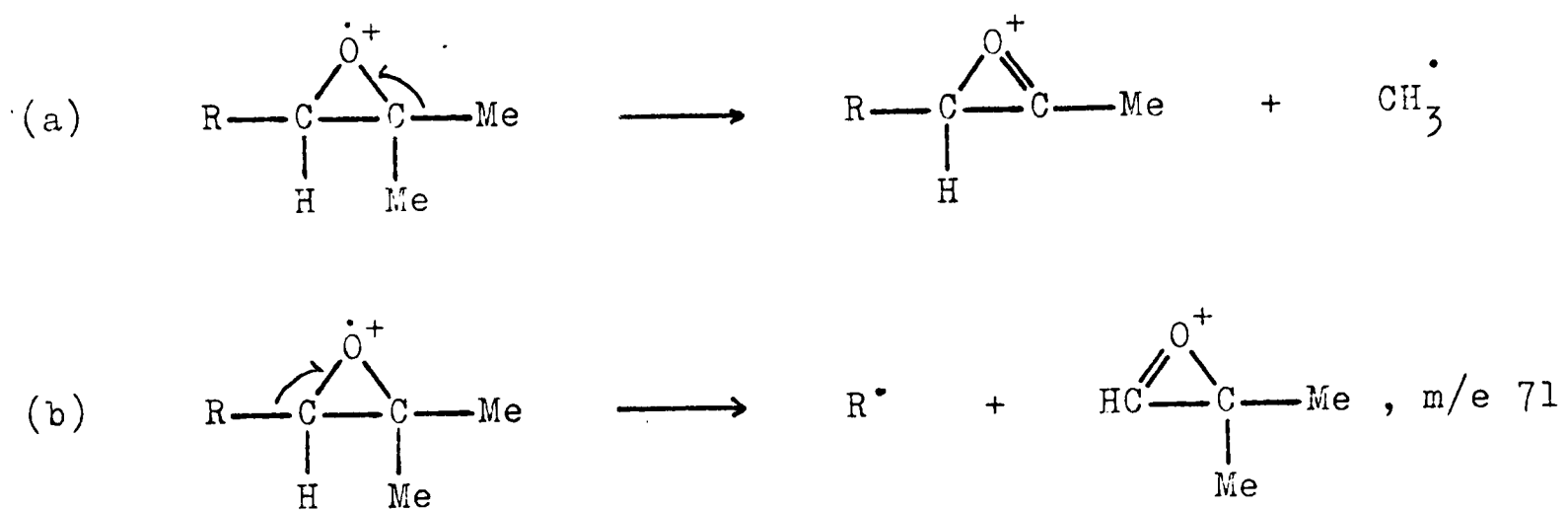
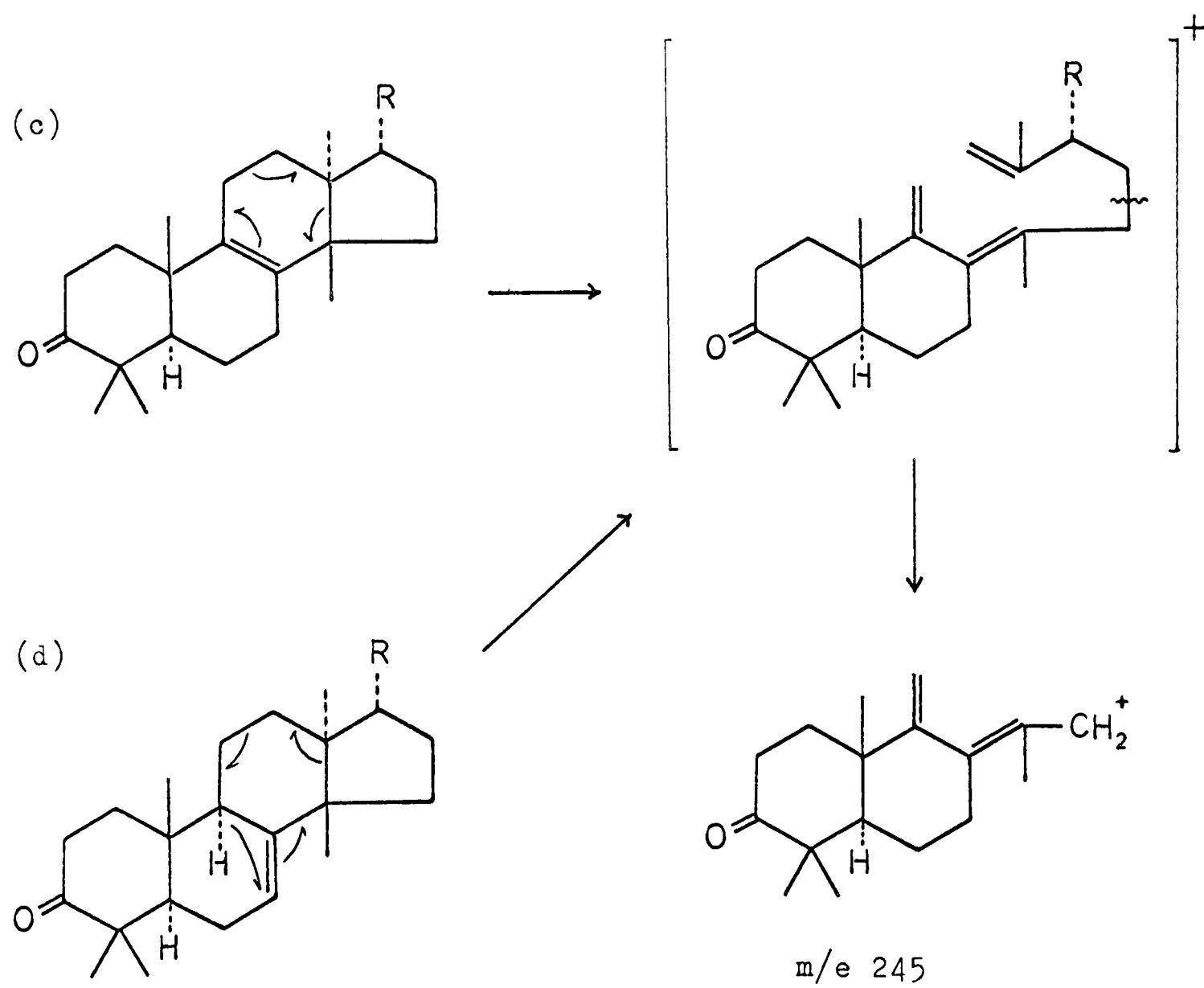


122 Deacetylturraeanthin

at C₍₂₁₎ to which the *p*-bromobenzoate ester group is attached. The aromatic protons of this ester group gave rise to signals at 2.20 τ .

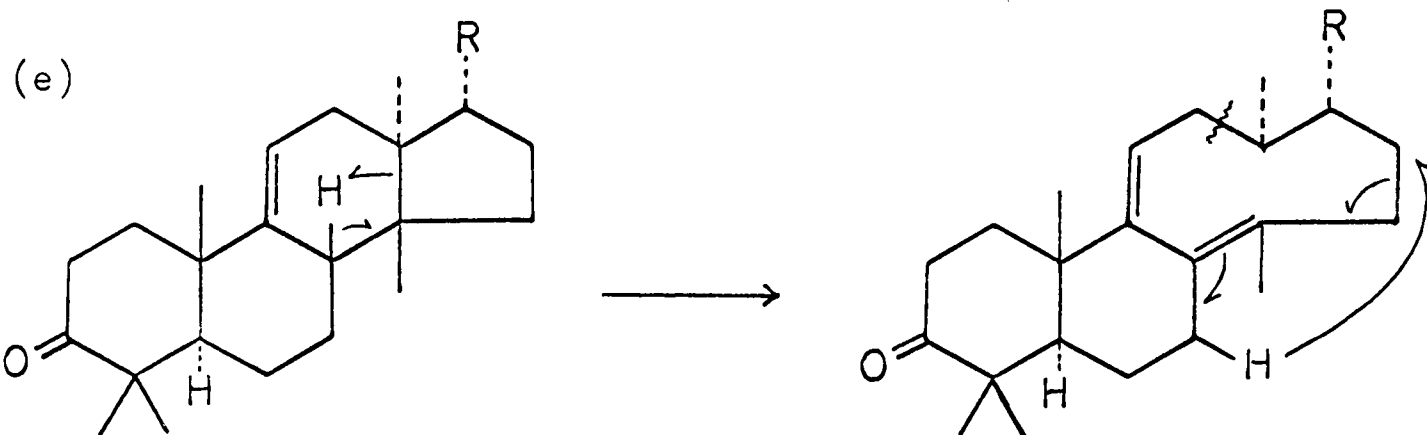
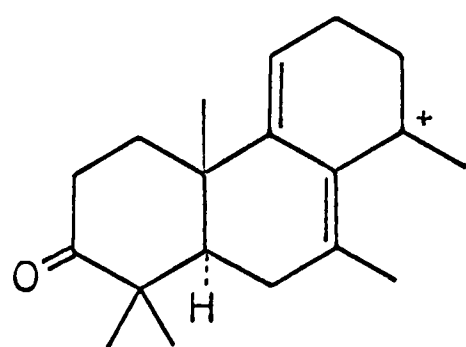
Mass Spectral Studies

In attempting to interpret the mass spectra of turraeanthin (153) and its derivatives, the mass spectra of butyrospermone (155) and euphone (156) will also be considered. Butyrospermone has the same stereochemistry as turraeanthin (153) at all positions except that at C₍₂₀₎,²³ and serves as a model compound. The mass spectra of tetracyclic triterpenes have not been discussed in detail in the literature, but Djerassi *et al.*²⁴ have analysed the mass spectra of the pentacyclic triterpene baurenone (157) and related compounds. The stereochemistry of baurenone at the A, B, and C ring junctions is similar to that of butyrospermone (155) and turraeanthin (153), and these compounds appeared to fragment in similar ways. There is enhanced strain due to the methyl groups at C₍₁₃₎ and C₍₁₄₎, and most of the fragmentation of the nucleus occurred in the environment of the C/D ring junction. The position of the double bond (Δ^7 or Δ^8) affected only the relative abundance of certain fragments and not the breakdown pattern.²⁴

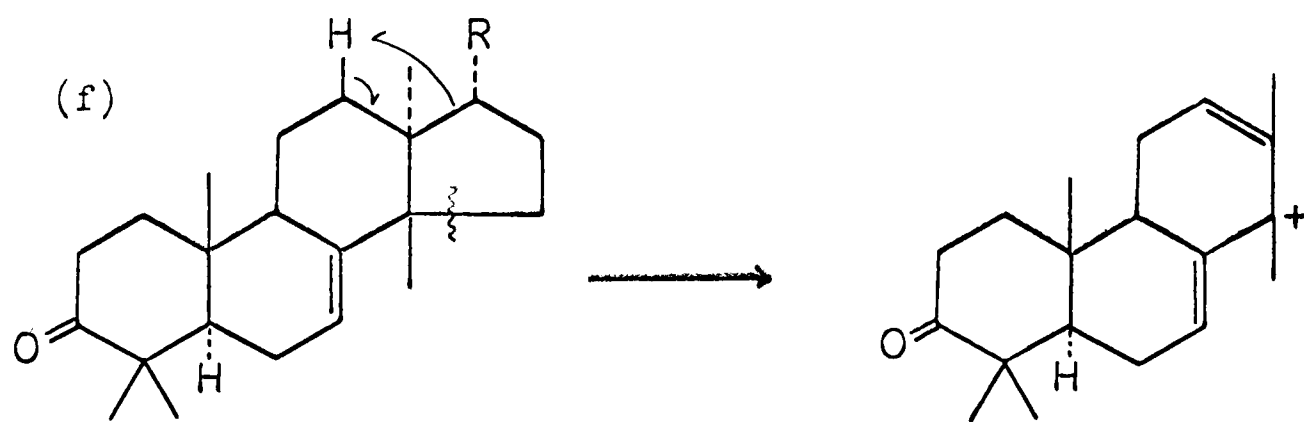


Fragmentations of the nucleus will be considered first. All of the spectra under consideration showed a strong peak, often the base peak, at $M - 15$ which is due to the loss of a methyl radical. This is probably the loss of a methyl group placed in a position allylic to the double bond,² i.e. the $C_{(14)}$ methyl group in butyrospermone (155) and turraeanthin derivatives, and the $C_{(14)}$ and $C_{(10)}$ methyl groups in euphone (156). In addition, turraeanthin derivatives with the side-chain epoxy intact could also lose a methyl radical by the mechanism (a). The alternative fragmentation (b) would give rise to a fragment m/e 71 which was observed in the mass spectra of turraeanthin lactone (121) and 3-oxodeacetoxyturraeanthin lactone (133), and provided evidence for the presence of the epoxy side-chain in turraeanthin. By analogy with the cracking pattern of baurenone (157),²⁴ most of the other major fragments arising from the nucleus comprised rings A and B.

One of the characteristic fragmentations²⁴ of $\triangle^8$ compounds is a retro-Diels-Alder decomposition of ring C, followed by cleavage of the activated $C_{(15)} - C_{(16)}$ bond as in (c). This gives rise to an ion m/e 245 which was observed in the spectrum of euphone (156). The same



m/e 257



m/e 271

fragmentation occurred to a smaller extent with butyrospermone (155) and 3-oxodeacetoxyturraeanthin lactone (133). One then has to assume²⁴ either a double bond migration prior to this special fragmentation process, or a rearrangement of the C₍₉₎ hydrogen atom to yield the same intermediate as in (d).

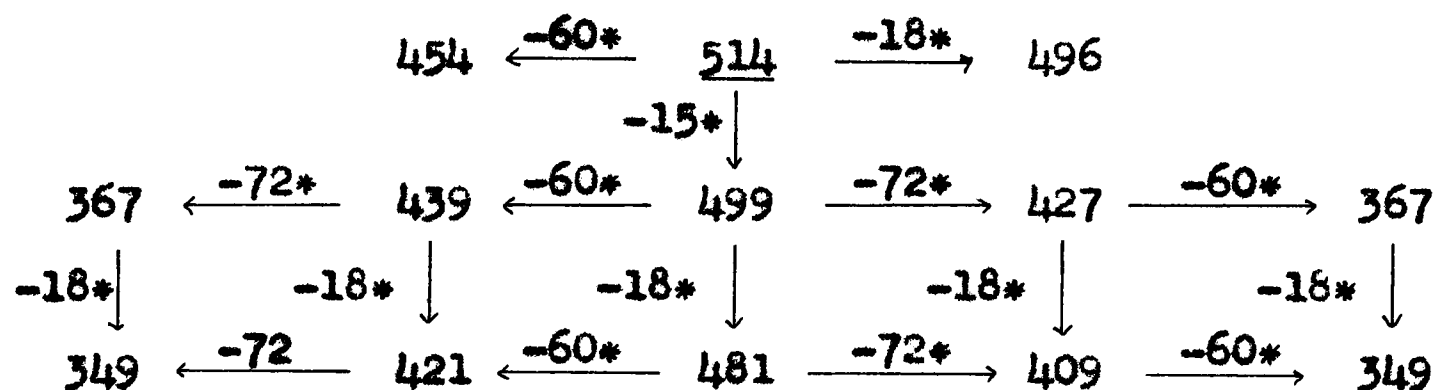
A fragment m/e 257 which could be observed as a strong peak in the spectrum of euphone (156) but which was weaker in the mass spectra of 3-oxodeacetoxyturraeanthin lactone (133) and butyrospermone (155) requires the prior migration of the double bond to the C₍₉₎ position.²⁴ A possible mechanism for the subsequent fragmentation is as in (e).

A fragment at m/e 271 which was observed in the spectra of butyrospermone (155), euphone (156), and 3-oxodeacetoxyturraeanthin lactone (133) can be explained by cleavage of the C₍₁₃₎ - C₍₁₇₎ and C₍₁₄₎ - C₍₁₅₎ bonds with migration of a hydrogen atom probably from C₍₁₂₎ to C₍₁₇₎ by the mechanism as in (f).²⁴ The corresponding peak was observed at m/e 315 in the spectra of turraeanthin and its lactone (121), and at m/e 273 in the spectrum of deacetylturraeanthin (122).

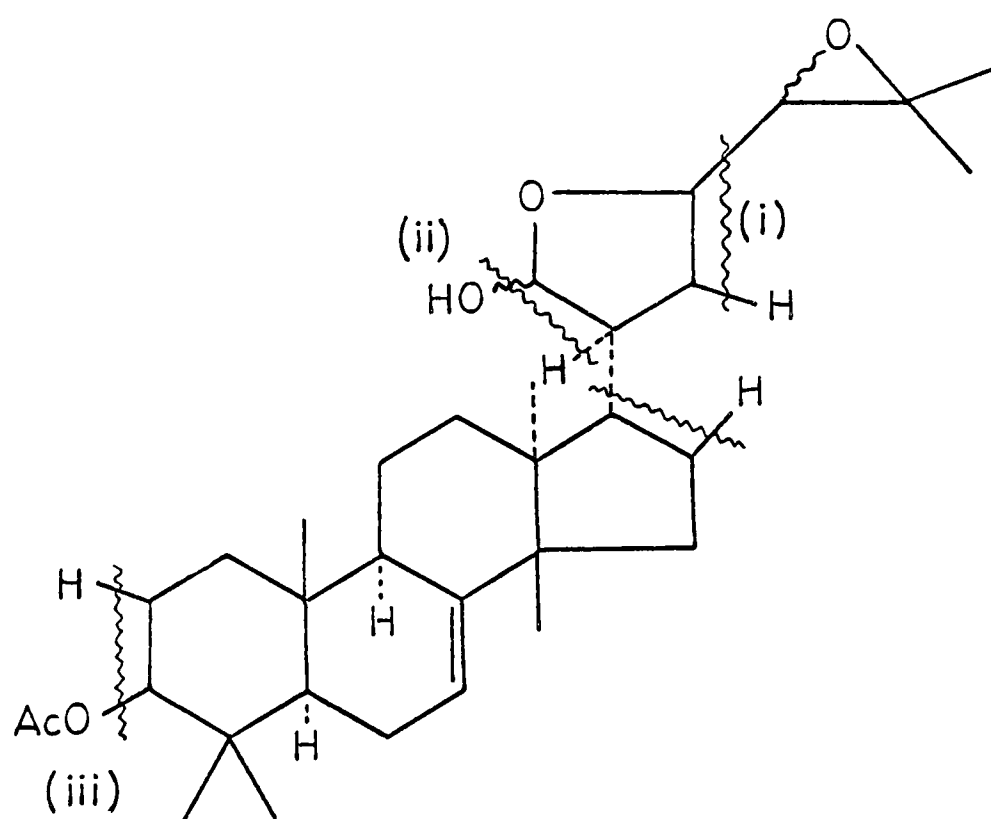
The mass spectrum of turraeanthin furnished useful information about the functional groups. However, since the spectrum was complex an attempt was made to assign the

composition of only a few of the more intense peaks. The following interpretation of the breakdown pattern was substantiated, where possible, by the presence of corresponding metastable peaks, the observation of which is denoted by an asterisk (*).

As has been mentioned before turrseanthin readily loses a methyl radical (- 15), probably mainly from the C₍₁₄₎ position, to yield the ion m/e 499, and most of the subsequent fragmentation seems to stem from this latter ion. The fragmentations involve:



Mass spectral fragmentation of turrseanthin.



Turraeanthin

- (i) the fission of the $C_{(23)} - C_{(24)}$ bond giving the loss of a C_4 - unit together with a neighbouring proton from $C_{(22)}$, (- 72),
- (ii) the loss of water, which when considered together with (i), generates a furan ring in the side-chain, (- 18), and
- (iii) the loss of acetic acid from $C_{(3)}$, (- 60).

Furthermore it appears that these three processes can occur in any order.

Another major breakdown process appears again to stem from the $M - 15$ ion, m/e 499. This involves the cleavage of the $C_{(17)} - C_{(20)}$ bond together with the loss of a hydrogen atom, possibly from the $C_{(16)}$ position, giving loss of the side-chain (- 158) leading to an ion m/e 341. Loss of acetic acid from this ion then leads to the peak at m/e 281.

However, it must be pointed out that in the absence of high resolution data this cracking pattern is only tentative.

Experimental Section

General

The same procedures were adopted as recorded in the Experimental Section of Chapter II. In addition, 100 mc/s n.m.r. spectra were recorded either on a Varian A 100 instrument or on a Japan Electron Optics JNM-4H-100 instrument.

Extraction of Turraeanthin (120)

The turraeanthin used in this work was isolated in Professor Bevan's laboratory at the chemistry department of the University of Ibadan. The heartwood of Turraeanthus africanus (21.28 kg.) was ground up and extracted in a Soxhlet apparatus with petroleum ether for 24 hours. Evaporation of the solvent afforded a thick oil. The oil was shaken with methanol (200 ml.) and the solvent was decanted off leaving a brown precipitate. The brown residue was washed with ether (100 ml.) leaving a dirty-white solid (25 g.). This was crystallised from methanol using a little decolourising charcoal and afforded needles of crude turraeanthin, m.p. 205-209°. Crude turraeanthin (4.037 g.) was taken up in benzene and adsorbed on to a column of

alumina (5% deact., 250 g.). Elution with ether - light petroleum (1:3) gave a compound (10 mg.) which crystallised from aqueous methanol as needles, m.p. 204-206°, $\alpha_{\text{max.}}$ (KCl) 3400, 1730, 1445, 1380, 1248, 1100, 1030, 960, 905, 875, and 815 cm^{-1} , and M 528 (mass spectrum), which was not further investigated.

Further elution with ether - light petroleum (1:1) afforded turraecanthin (24%, 25:21%, 23%-diepoxytirucall-7-en-3 β , 21 β -diol 3 β -monoacetate) (3.932 g.), which crystallised from methanol - chloroform as needles, m.p. 218-220°, $[\alpha]_{\text{D}}^{20} + 3^\circ$ (d 1.00), $\nu_{\text{max.}}$ (CH_2Cl_2) 3590, 1724, 1245, 1118, 1090, 1033, 980, and 823 cm^{-1} , $\lambda_{\text{max.}}$ 214 m μ (ϵ 2000), 100 mc/s n.m.r. : τ 9.16 (3H), 9.07 (6H), 8.99 (3H), 8.93 (3H) [s, tertiary CH_3], 8.63 [6H; s, $\text{RCH}-\overset{\text{O}}{\text{C}}(\text{CH}_3)_2$], 7.90 (3H; s, $\text{CH}_3\text{CO.O-}$), 7.09 [1H; d, J 8 c.p.s., $\text{RCH}-\overset{\text{O}}{\text{C}}(\text{CH}_3)_2$], 6.25 (1H; m, OH , D_2O), 6.15 [1H; bm, $-\text{CH}(\text{OR})-$], 5.47 [1H; t, J 8 c.p.s., $-\text{CH}(\text{OAc})-$], 4.73 (1H; m, $-\text{CH}=\text{}$), and 4.63 [1H; m, $-\text{CH}(\text{OH}).\text{O-}$] p.p.m., and M 514 (mass spectrum).

(Found: C, 74.6; H, 9.8; OAc, 7.0;

$\text{C}_{32}\text{H}_{50}\text{O}_5$ requires C, 74.7; H, 9.8; OAc, 8.4%).

The specimen of Turraecanthus africanus was kindly supplied by Professor F. G. Torto of the University of Legon, Ghana.

Turraeanthin Lactone (121)

Chromium trioxide (5.8 g.) was carefully added to dry pyridine⁴ (90 ml.) at 10° with cooling to maintain the temperature below 15°. Turraeanthin (4.190 g.) in pyridine (20 ml.) was added and the mixture was kept at room temperature (20°) for 48 hours with occasional shaking. Water (200 ml.) was added and the mixture was then extracted with ether. The combined organic extracts were washed with water and dried. The solvent was distilled off and the residue was taken up in benzene and adsorbed on to a column of alumina (5% desot., 300 g.). Elution with benzene - ether (19:1) afforded turraeanthin lactone (3.70 g.) (3 β -acetoxy-24 ϵ , 25-epoxy-23 ϵ -hydroxytirucall-7-en-21-oic acid 23 ϵ , 21-lactone), which crystallised from aqueous ethanol as needles, m.p. 215-220°, $[\alpha]_D^{23} - 33^\circ$ (d 0.49), $\nu_{\max}$. 1780, 1735, 1162, 1015, 925, 902 and 815 cm^{-1} , 100 mc/s n.m.r.: τ 7.20 [1H; d, J 8 c.p.s., $\text{RCH}=\text{C}(\text{CH}_3)_2$], 5.85 [1H; m, $-\text{CH}(0.60.R)-$], 5.50 [1H; t, J 8 c.p.s., $-\text{CH}(\text{OAc})-$], and 4.75 (1H; m, $-\text{CH}_2-$) p.p.m., M 512 (mass spectrum), $[\alpha]_D^{20} - 31^\circ$ (d 0.51 in MeOH - CHCl_3 , 4:1), and $[\alpha]_D^{20} - 1.5^\circ$ (d 0.75 in MeOH - CHCl_3 , 4:1 containing 1% KOH).
 (Found: C, 75.3; H, 9.6;
 $\text{C}_{32}\text{H}_{48}\text{O}_5$ requires C, 75.0; H, 9.4%).

Further elution with benzene - ether (3:1) gave turraeanthin (1.10 g.), recrystallised from aqueous ethanol as needles, m.p. and mixed m.p. 218-220°.

Acetylation of Turraeanthin

Turraeanthin (1.060 g.) in dry pyridine (10 ml.) was heated on a steam-bath with acetic anhydride (3 ml.) for 30 minutes. The solution was kept at room temperature (20°) for a further 24 hours. The pyridine and residual acetic anhydride were removed by distillation under vacuum, and the residue was taken up in light petroleum - benzene (3:1) and adsorbed on to a column of alumina (5% deact., 130 g.). Elution with light petroleum - benzene (3:1) (450 ml.) afforded turraeanthin acetate (123) (665 mg.) (24, 25:21, 23 - diepoxytirucall-7-en-3, 21 -diol diacetate), which crystallised from aqueous ethanol as needles, m.p. 214-215°, $[\alpha]_D^{20} - 35^\circ$ (c 1.01), $\nu_{\max}$. 1753, 1732, 1245, 1225, 1084, 1030, 960, 871, and 815 cm^{-1} , 100 mc/s n.m.r. : 7.95 (2 x 3H; s, $\text{CH}_3\text{CO.O-}$), 7.25 [1H; d, J 8 c.p.s., $\text{RCH}=\text{C}(\text{CH}_3)_2$], 4.70 (1H; m, $-\text{CH}_2-$), and 3.77 [1H; d, J 3 c.p.s., $-\text{CH}(\text{OAc}).\text{O-}$] p.p.m., and M 556 (mass spectrum).

(Found: C, 73.4; H, 9.4;
 $\text{C}_{34}\text{H}_{52}\text{O}_6$ requires C, 73.3; H, 9.4%).

Further elution with benzene gave turraeanthin (190 mg.), which crystallised from aqueous ethanol as needles, m.p. 214-218°.

Hydrolysis of Turraeanthin

Turraeanthin (446 mg.) in methanol (40 ml.) was heated under reflux with potassium hydroxide (1.26 g.) for 30 minutes. The mixture was diluted with ether and the solution was washed with dilute aqueous sulphuric acid and water, and then dried. The solvent was distilled off, and the residue was taken up in benzene and adsorbed on to a column of alumina (5% deact., 30 g.). Elution with benzene - ether (1:1) afforded deacetylturraeanthin (122) (335 mg.) (24 ξ , 25:21 ξ , 23 $\frac{1}{2}$ -diepoxy-tirucall-7 α -en-3 β , 21 ξ -diol), which crystallised from aqueous methanol as needles, m.p. 182-184°, $[\alpha]_D^{21}$ -35° (c 0.51),

$\nu_{\max}$. 3400, 1025, 970, and 813 cm^{-1} , n.m.r. : τ 6.1 [2H; bm, -CH(OH)- and -CH(OR)-] p.p.m., and M 472 (mass spectrum).

(Found: C, 74.4; H, 9.9;

$\text{C}_{30}\text{H}_{48}\text{O}_4 \cdot \frac{1}{2}\text{H}_2\text{O}$ requires C, 74.8; H, 10.2%).

Acetylation of Deacetylturraeanthin (122)

Deacetylturraeanthin (25 mg.) in dry pyridine (4 ml.)

was heated on a steam-bath with acetic anhydride (1 ml.) for 10 minutes, and the solution was kept at room temperature for a further 24 hours. The pyridine and residual acetic anhydride were removed by distillation under vacuum, and the residue was taken up in ether and washed with aqueous sodium bicarbonate and water, and then dried. The solvent was distilled off, and the residue was taken up in benzene and adsorbed on to a column of alumina (5% deact., 10 g.). Elution with benzene afforded turraeanthin acetate (123) (14 mg.), which crystallised from aqueous ethanol as needles, m.p. and mixed m.p. 212-215°, and the i.r. spectra were superimposable.

Oxidation of Deacetylturraeanthin (122)

Deacetylturraeanthin (250 mg.) in pyridine (10 ml.) was added to a slurry⁴ of chromium trioxide (2 g.) and pyridine (30 ml.) cooled in an ice-bath. The mixture was kept at room temperature for 24 hours and then poured into water, and extracted with ether. The ethereal solution was dried and the solvent was distilled off. The residue was taken up in benzene - light petroleum (1:3) and adsorbed on to a column of alumina (5% deact., 20 g.). Elution with benzene

afforded 3-oxodeacetoxyturraeanthin lactone (133) (155 mg.) (3-oxo-24 ξ , 25-epoxy-23 ξ -hydroxytirucall-7-en-21-olc acid 23 ξ , 21-lactone), which crystallised from aqueous methanol as needles, m.p. 181-184 $^{\circ}$, $[\alpha]_D^{20} - 76^{\circ}$ (g 0.53), $\nu_{\max}$. 1775, 1710, 1170, 995, 970, 900 and 817 cm^{-1} , n.m.r. : τ 7.18 [1H; d, J 8 c.p.s., $\text{ROCH}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}(\text{CH}_3)_2$], 5.7 [1H; bm, $-\text{CH}(\text{O.CO.R})-$], and 4.6 (1H; m, $-\text{CH}=\text{}$) p.p.m., M 468 (mass spectrum), $[\alpha]_D^{20} - 83^{\circ}$ (g 0.48 in MeOH - CHCl_3 , 4:1), and $[\alpha]_D^{20} - 30^{\circ}$ (g 0.63 in MeOH - CHCl_3 , 4:1 containing 1% KOH).

(Found: C, 76.8; H, 9.1;

$\text{C}_{30}\text{H}_{44}\text{O}_4$ requires C, 76.9; H, 9.5%).

Further elution with benzene - ether (9:1) gave

3-oxodeacetoxyturraeanthin (132) (81 mg.) (3-oxo-24 ξ , 25:21 ξ , 23 ξ -diepoxytirucall-7-en-21 ξ -ol) which crystallised from aqueous methanol as needles, m.p. 171-173 $^{\circ}$, $[\alpha]_D^{20} - 52^{\circ}$ (g 0.54), $\nu_{\max}$. 3400, 1705, 1020, 970 and 820 cm^{-1} , and M 470 (mass spectrum).

(Found: C, 74.0; H, 9.7;

$\text{C}_{30}\text{H}_{46}\text{O}_4 \cdot \text{H}_2\text{O}$ requires C, 73.7; H, 9.9%).

Ozonolysis of Turraeanthin

Turraeanthin (1.594 g.) in ethyl acetate (100 ml.) was

cooled in an acetone - 'Drikold' bath. Ozonised oxygen was passed through the solution until a deep blue colour was produced due to the presence of excess ozone (approximately 1 hour). Water (75 ml.) and zinc dust (10 g.) were added and the mixture was steam-distilled into a solution of 2,4-dinitrophenylhydrazine (1 g.) in methanol (30 ml.) containing sulphuric acid (1 ml.). No steam-volatile carbonyl compound was obtained. The residue was filtered and extracted with chloroform, and the organic extract was washed with water and dried. The solvent was distilled off and the residue was taken up in benzene and adsorbed on to a column of alumina (5% desicc., 100 g.). Elution with benzene - ether (3:1) afforded 7,8-epoxyturraeanthin (137) (0.72 g.) (7 ξ , 8 ξ :24 ξ , 25:21 ξ , 23 ξ -tri-epoxytirucall-3 β , 21 ξ -diol 3 β -mono-acetate), which crystallised from aqueous methanol as needles, m.p. 191-194°, $[\alpha]_D^{20} - 33^\circ$ (c 1.02), $\nu_{\max}$. (CHCl₃) 3580, 1730, 1245, 1025, 975 and 900 cm.⁻¹, and n.m.r. δ 7.15 (2H; m, RCH₂-CR₂) p.p.m.

(Found: C, 71.2; H, 9.4;
 C₃₂H₅₀O₆· $\frac{1}{2}$ H₂O requires C, 71.2; H, 9.5%).

Treatment of 7,8-Epoxyturraeanthin (137) with Hydrochloric Acid

7,8-Epoxyturraeanthin (110 mg.) in methanol (15 ml.) was

treated with hydrochloric acid (1 ml.) and the solution was heated under reflux on a water-bath for 1 hour. Water was added and the mixture was extracted with chloroform. The organic solution was dried and the solvent distilled off, leaving a gum which could not be crystallised. It had λ_{max} . 233, 239, and 248 μ (ϵ 8900, 9400, and 6000).

Treatment of Turraeanthin with Perbenzoic Acid

Turraeanthin (375 mg.) in dry chloroform (10 ml.) was treated with perbenzoic acid in chloroform (14 ml. of a solution containing 7.9 g./l.). The solution was kept at 20° for 5 days, and was then washed with aqueous sodium bicarbonate and water. The organic solution was dried and the solvent distilled off. The residue was taken up in benzene and adsorbed on to a column of alumina (5% deact., 20 g.). Elution with benzene - ether (9:1) gave a gum (73 mg.), which had ν_{max} . 3400, 1724, 1245, 1025, 905 and 820 cm^{-1} , λ_{max} . 232, 239 and 247 μ (ϵ 15340, 16120 and 11000).

Treatment of Turraeanthin with Hydrochloric Acid in Methanol

Turraeanthin (1.052 g.) in methanol (75 ml.) was

treated with hydrochloric acid (7 ml.) with cooling in ice during the addition. The solution was kept at room temperature (20°) for 3 hours during which crystals were deposited. Water was added and the mixture was extracted with chloroform. The combined organic extracts were washed with water and dried. The solvent was distilled off, and the residue was taken up in benzene - light petroleum (1:1) and adsorbed on to a column of alumina (5% deact., 75 g.). Elution with benzene - light petroleum (1:1) afforded

21-O-methylturraeanthin chlorohydrin (124) (354 mg.)

(25-chloro-21 ξ -methoxy-21 ξ ,23 ξ -epoxytirucall-7-en-3 β ,24 ξ -diol 3 β -monoacetate), which crystallised from methanol - chloroform as needles, m.p. $197-198^{\circ}$, $[\alpha]_D^{23} + 3^{\circ}$ (d 0.43), $\nu_{\max}$. 3420, 1733, 1240, 1098, 1025 and 985 cm^{-1} , n.m.r. : τ 8.40, 8.34 [2 x 3H; s, $(\text{CH}_3)_2\text{CCl-}$], and 6.62 (3H; s, $\text{CH}_3\text{O-}$) p.p.m., and M 564 (mass spectrum).

(Found: C, 70.1; H, 9.6; Cl, 6.5;

$\text{C}_{33}\text{H}_{53}\text{O}_5\text{Cl}$ requires C, 70.1; H, 9.5; Cl, 6.3%).

Further elution with benzene - ether (9:1) gave

21-O-methylturraeanthin methoxyhydrin (125) (539 mg.)

(21 ξ ,25-dimethoxy-21 ξ ,23 ξ -epoxytirucall-7-en-3 β ,24 ξ -diol 3 β -monoacetate), which crystallised from aqueous methanol

as needles, m.p. 171-173°, $[\alpha]_D^{23} + 23^\circ$ (c 0.56), $\nu_{\max}$. 3550, 1730, 1245, 1098, 1028, 900 and 818 cm^{-1} , n.m.r. : τ 8.83, 8.77 [2 x 3H; s, $(\text{CH}_3)_2\text{C}(\text{OCH}_3)-$], 6.74, 6.64 (2 x 3H, s, $\text{CH}_3\text{O}-$) p.p.m., and M 560 (mass spectrum).

(Found: C, 72.5; H, 10.2;
 $\text{C}_{34}\text{H}_{56}\text{O}_6$ requires C, 72.8; H, 10.1%).

Acetylation of 21-O-Methylturraeanthin Chlorohydrin (124)

21-O-Methylturraeanthin chlorohydrin (41 mg.) in dry pyridine (4 ml.) was treated with acetic anhydride (1.5 ml.), and the solution was warmed on a water-bath for 5 minutes and then kept at room temperature overnight. The solvents were evaporated off under vacuum, and the residue was taken up in benzene and adsorbed on to a column of alumina (5% desot., 15 g.). Elution with benzene afforded 21-O-methylturraeanthin chlorohydrin acetate (126) (25-chloro-21 β , -methoxy-21 β , 23 β -epoxytirucall-7-en-3 β , 24 β -diol 3 β , 24 β -diacetate) (35 mg.) which crystallised from aqueous methanol as needles, m.p. 183-185°, $[\alpha]_D^{20} + 22^\circ$ (c 0.94), $\nu_{\max}$. (KCl) 1748, 1735, 1375, 1250, 1235, 1030, 980, 885 and 827 cm^{-1} .

(Found: C, 69.6; H, 9.3;
 $\text{C}_{35}\text{H}_{55}\text{O}_6\text{Cl}$ requires C, 69.2; H, 9.1%).

Acetylation of 21-O-Methylturraeanthin Methoxyhydrin (125)

21-O-Methylturraeanthin methoxyhydrin (114 mg.) in dry pyridine (6 ml.) was treated with acetic anhydride (2 ml.), and the solution was warmed on a water-bath for 15 minutes and then kept at room temperature (20°) for 24 hours. The solvents were evaporated off under vacuum, and the residue was taken up in light petroleum - benzene (1:1) and adsorbed on to a column of alumina (5% deact., 20 g.). Elution with benzene gave 21-O-methylturraeanthin methoxyhydrin acetate (127) (21 β ,25-dimethoxy-21 β ,23 ξ -epoxytirucall-7-en-3 β ,24 ξ -diol 3 β ,24 ξ -diacetate) (88 mg.) which crystallised from aqueous ethanol as needles, m.p. 162-165°, $[\alpha]_D^{20}$ -3° (c 0.48), $\nu_{\max}$. 1730, 1245, 1100, 990, and 835 cm^{-1} , n.m.r. ; τ 7.95 (3H; s, $\text{CH}_3\text{CO.O-}$), 7.84 (3H; s, $\text{OH}_3\text{CO.O-}$), 6.80, 6.65 (2 x 3H; s, $\text{CH}_3\text{O-}$) p.p.m.

(Found: C, 71.3; H, 9.3;

$\text{C}_{36}\text{H}_{58}\text{O}_7$ requires C, 71.7; H, 9.7%).

Treatment of Turraeanthin with Hydrochloric Acid in Ethanol

Turraeanthin (1.170 g.) in ethanol (75 ml.) was treated with hydrochloric acid (7 ml.) with cooling in ice during the addition, and the solution was kept at room temperature for 3

hours. Water was added and the mixture was extracted with chloroform, and the combined organic extracts were washed with water and dried. The solvent was distilled off, and the residue was taken up in light petroleum - ether (19:1) and adsorbed on to a column of alumina (5% deact., 75 g.). Elution with light petroleum - ether (19:1) (400 ml.) gave 21-O-ethylturraeanthin chlorohydrin (128) (25-chloro-21 ϵ -ethoxy-21 ϵ ,23 ϵ -epoxytirucall-7-en-3 β ,24 ϵ -diol 3 β -monoacetate) (834 mg.), which crystallised from aqueous ethanol as needles, m.p. 152-156°, $[\alpha]_D^{21} - 6^\circ$ (c 0.53), $\nu_{\max}$. 3440, 1735, 1240, 1100, 1025, 985, and 820 cm^{-1} , n.m.r. : τ 8.36, 8.43 [2 x 3H; s and d, J 2 c.p.s., $(\text{CH}_3)_2\text{CCl}-$] p.p.m.

(Found: C, 70.1; H, 9.4; Cl, 6.4;

$\text{C}_{34}\text{H}_{55}\text{O}_5\text{Cl}$ requires C, 70.5; H, 9.6; Cl, 6.1%).

Further elution with light petroleum - ether (9:1) afforded 21-O-ethylturraeanthin ethoxyhydrin (129) (21 ϵ ,25-diethoxy-21 ϵ ,23 ϵ -epoxytirucall-7-en-3 β ,24 ϵ -diol 3 β -monoacetate) (272 mg.), which crystallised from aqueous ethanol as needles, m.p. 136-139°, $[\alpha]_D^{20} - 14^\circ$ (c 0.53), $\nu_{\max}$. 3430, 1735, 1245, 1025, 980, and 820 cm^{-1} , n.m.r. : τ 8.86, 8.75 [2 x 3H; s, $(\text{CH}_3)_2\text{C}(\text{OEt})-$] p.p.m.

(Found: C, 73.4; H, 10.7;

$\text{C}_{36}\text{H}_{60}\text{O}_6$ requires C, 73.4; H, 10.3%).

Treatment of Turraeanthin with Sulphuric Acid in Methanol

Turraeanthin (1.017 g.) in methanol (70 ml.) was treated with sulphuric acid (4 ml.) with cooling in ice during the addition. The solution was kept at room temperature for 4 hours. Water was added and the mixture was extracted with chloroform, and the combined organic extracts were washed with aqueous sodium bicarbonate and water, and then dried. The solvent was distilled off, and the residue was taken up light petroleum - ether (9:1) and adsorbed on to a column of alumina (5. desct., 100 g.). Elution with light petroleum - ether (3:1) (400 ml.) afforded 21-O-methylturraeanthin methoxyhydrin (125) (240 mg.), which crystallised from aqueous methanol as needles, m.p. 169-173°,

$\nu_{\text{max.}}$ 3550, 1730, 1245, 1098, 900, and 818 cm^{-1}

(Found: C, 72.5; H, 10.2;

calc. for $\text{C}_{34}\text{H}_{56}\text{O}_6$ C, 72.8; H, 10.1%).

The mixed m.p. with the sample prepared previously gave no depression, 169-173°, and the infrared and n.m.r. spectra were identical.

Further elution with light petroleum - ether (1:1) (400 ml.) gave 3-desoethyl-21-O-methylturraeanthin methoxyhydrin (130) (21½, 25-dimethoxy-21½, 23½-epoxytirucall-7-en-3β, 24½-diol)

(730 mg.), which crystallised from aqueous methanol as needles, m.p. 106-108°, $[\alpha]_D^{20} - 35^\circ$ (c 0.51), $\nu_{\max.}$ (CHCl₃) 3480, 1388, 1368, 1095, 1030, 980, and 915 cm.⁻¹
 (Found: C, 73.2; H, 10.9;
 C₃₂H₅₄O₅ · $\frac{1}{2}$ H₂O requires C, 72.8; H, 10.5%).

Oxidation of 3-deacetyl-21-O-methylturraeanthin Methoxyhydrin
 (130)

3-Deacetyl-21-O-methylturraeanthin methoxyhydrin (430 mg.) in pyridine (20 ml.) was added to a slurry⁴ of chromium trioxide (2.8 g.) and pyridine (40 ml.) cooled in an ice-bath. The mixture was kept at room temperature (20°) for 20 hours, and was then poured into water and extracted with ether. The ethereal solution was dried and the solvent was distilled off. The residue was taken up in light petroleum - ether (3:1) and adsorbed on to a column of alumina (5% deact., 70 g.). Elution with light petroleum - ether (3:1) (200 ml.) afforded

3-oxodeacetoxy-21-O-methylturraeanthin methoxyhydrin (131)

(3-oxo-21 $\frac{1}{2}$, 25-dimethoxy-21 $\frac{1}{2}$, 23 $\frac{1}{2}$ -epoxytirucall-7-en-24 $\frac{1}{2}$ -ol) (264 mg.), which crystallised from aqueous methanol as needles, m.p. 171-175°, $[\alpha]_D^{20} - 70^\circ$ (c 0.48), $\nu_{\max.}$ 3540, 1705, 1100, 1035, 984, and 838 cm.⁻¹, n.m.r. : τ 8.72, 8.62 (2 x 3H; s, CH₃O-), and 8.65 (1H; m, -CH=) p.p.m., and M 516 (mass

spectrum).

(Found: C, 74.7; H, 10.1;
 $C_{32}H_{52}O_5$ requires C, 74.4; H, 10.1%).

Reduction of 3-Oxodesacetoxy-21-O-methylturraeanthin
 Methoxyhydrin (131) with Sodium Borohydride

3-Oxodesacetoxy-21-O-methylturraeanthin methoxyhydrin (39 mg.) in methanol (15 ml.) was heated under reflux on a steam-bath with sodium borohydride (150 mg.) for 2 hours. The solution was poured into water and extracted with ether. The ethereal solution was washed with dilute sulphuric acid and water, and then dried. The solvent was distilled off, and the residue (31 mg.) was crystallised from aqueous methanol to give 3-deacetyl-21-O-methylturraeanthin methoxyhydrin (130) as needles, m.p. and mixed m.p. 106-108°, and the infrared spectra were superimposable.

Treatment of Turraeanthin Lactone (121) with Sulphuric Acid
 in Ether

Turraeanthin lactone (165 mg.) in ether (30 ml.) was treated with sulphuric acid (1 ml.) with cooling in ice during the addition, and the solution was kept at room

temperature for 24 hours. Water was added and the mixture was extracted with chloroform; the organic extract was washed with water and then dried. The solvent was distilled off, and the residue was taken up in benzene and adsorbed on to a column of alumina (5% deact., 20 g.). Elution with benzene - ether (3:1) afforded 24,25-dihydroxyturraeanthin lactone (143) (3β -acetoxy-23 ϵ ,24 ϵ ,25-trihydroxytirucall-7-en-21-oic acid 23 ϵ ,21-lactone) (110 mg.), which crystallised from aqueous methanol as needles, 219-222°, $[\alpha]_D^{20} = 39^\circ$ (c 0.48), $\nu_{\max.}$ (CHCl₃) 3580, 1775, 1728, 1260, 1160, 1130, and 922 cm.⁻¹, n.m.r. : τ 8.71, 8.66 [2 x 3H; s, (CH₃)₂C(OH)-], 7.55 (2H; s, OH, D₂O), 6.68 [1H; d, J 2 o.p.s., -CH(OH)-], and 4.7 (1H; m, -CH=) p.p.m., and M 530 (mass spectrum).
 (Found: C, 72.3; H, 9.6;
 C₃₂H₅₀O₆ requires C, 72.4; H, 9.5%).

24,25-Deoxyturraeanthin Lactone (144)

24,25-Dihydroxyturraeanthin lactone (143) (370 mg.) in dry xylene (50 ml.) was treated with thiocarbonyl diimidazole⁸ (1.33 g.), and the mixture was heated under reflux in an atmosphere of nitrogen for 30 minutes. The mixture was taken up in chloroform (200 ml.), and the solution was washed with water and then dried. The solvent was distilled off, and the residue was taken up in freshly

distilled trimethylphosphite (40 ml.). The solution was heated under reflux in an atmosphere of nitrogen for 24 hours. Excess of trimethyl phosphite was distilled off on a rotary evaporator and the residue was taken up in chloroform. The organic solution was washed with water and then dried. The solvent was distilled off, and the residue was taken up in benzene and adsorbed on to a column of alumina (5% deact., 30 g.). Elution with benzene afforded 24,25-deoxyturraeanthin lactone (144) (3β -acetoxy-23 ξ -hydroxytirucall-7,24(25)-dien-21-oic acid 23 ξ ,21-lactone) (250 mg.), which crystallised from aqueous methanol as needles, m.p. 158-160°, $[\alpha]_D^{20} - 28^\circ$ (c 0.50), $\nu_{\max.}$ (CHCl₃) 1770, 1725, 1380, 1138, 1029, 1010, 980, and 920 cm.⁻¹, n.m.r. : τ 8.27 [2 x 3H; s, (CH₃)₂C=], 7.97 (3H; s, CH₃.60.0-), 5.5 [1H; m, -CH(OAc)-], and 4.8 (2H; m, -CH=) p.p.m., M 496 (mass spectrum).

(Found: C, 77.3; H, 9.7;
 C₃₂H₄₈O₄ requires C, 77.4; H, 9.7%).

3-Oxodesacetoxy-24,25-deoxyturraeanthin Lactone (142)

24,25-Deoxyturraeanthin Lactone (144) (180 mg.) in methanol (15 ml.) was heated under reflux on a water-bath for 30 minutes with potassium hydroxide (160 mg.). The

solution was poured into water and acidified with dilute aqueous sulphuric acid, and the mixture was extracted with chloroform. The organic solution was washed with water and then dried, and the solvent was distilled off. The residue was taken up in pyridine (10 ml.) and added to a slurry of chromium trioxide (1.5 g.) in pyridine (30 ml.) cooled in ice. The mixture was kept at room temperature overnight, and was then poured into water and extracted with ether. The ethereal solution was washed with water and dried, and the solvent was distilled off. The residue was taken up in light petroleum - benzene (1:1) and adsorbed on to a column of alumina (5% deactivated, 20 g.). Elution with benzene afforded 3-oxodesacetoxy-24,25-deoxyturracanthin lactone

(142) (3-oxo-23 $\frac{1}{2}$ -hydroxytirucall-7,24(25)-dien-21-oic acid 23 $\frac{1}{2}$,21-lactone) (133 mg.), which crystallised from aqueous methanol as needles, m.p. 180-185°, $[\alpha]_D^{20} - 45^\circ$ (c 0.51),

$\nu_{\max.}$ (KCl) 1771, 1706, 1450, 1387, 1178, 995, 958, and 840 cm^{-1} , n.m.r. : τ 8.26 [2 x 3H; s, $(\text{CH}_3)_2\text{C}=\text{}$], and 4.8 (2H; m, $-\text{CH}=\text{}$) p.p.m.

(Found: C, 79.5; H, 9.5;

$\text{C}_{30}\text{H}_{44}\text{O}_3$ requires C, 79.6; H, 9.8%).

Treatment of 3-Oxodeacetoxyturraeanthin Lactone (133) with Sulphuric Acid in Ether

3-Oxodeacetoxyturraeanthin lactone (420 mg.) in ether (100 ml.) was treated with sulphuric acid (3 ml.) with cooling in ice during the addition, and the solution was kept at room temperature for 2 hours. The solution was washed with water and dried. The solvent was distilled off, and the residue was taken up in benzene and adsorbed on to a column of alumina (5% desat., 50 g.). Elution with benzene - ether (1:1) afforded 3-oxodeacetoxy-24,25-dihydroxyturraeanthin lactone (140) (310 mg.) (3-oxo-23 ξ ,24 ξ ,25-trihydroxytirucall-7-en-21-oic acid 23 ξ ,21-lactone), which crystallised from aqueous methanol as needles, m.p. 187-189°, $[\alpha]_D^{20} - 89^\circ$ (c 0.55), $\nu_{\max.}$ (KCl) 3500, 1750, 1700, 1210, 1158, 1050, 1010, and 840 cm^{-1} , and M 530 (mass spectrum).

(Found: C, 73.7; H, 9.4;
 $\text{C}_{30}\text{H}_{46}\text{O}_5$ requires C, 74.0; H, 9.5%).

3-Oxodeacetoxy-24,25-deoxyturraeanthin Lactone (142)

3-Oxodeacetoxy-24,25-dihydroxyturraeanthin lactone (140) (290 mg.) in dry xylene (50 ml.) was treated with thiocarbonyl diimidazole⁸ (1.57 g.) and the mixture was heated under reflux

in an atmosphere of nitrogen for 30 minutes. The mixture was taken up in ether (200 ml.), and the solution was washed with water and then dried. The solvent was distilled off, and the residue was taken up in freshly distilled trimethylphosphite (40 ml.). The solution was heated under reflux in an atmosphere of nitrogen for 20 hours. Excess of trimethylphosphite was distilled off on a rotary evaporator and the residue was taken up in chloroform. The organic solution was washed with water, and then dried. The solvent was distilled off, and the residue was taken up in light petroleum - benzene (3:1) and adsorbed on to a column of alumina (5% desat., 20 g.). Elution with light petroleum - benzene (1:1) gave 3-oxodeacetoxy-24,25-deoxyturrseanthin lactone (142) (195 mg.), which crystallised from aqueous methanol as needles, m.p. 175-180°. Repeated recrystallisation from methanol to remove traces of trimethyl phosphite gave needles, m.p. 190-194°, $[\alpha]_D^{20} = 81^\circ$ (c 0.65), $\nu_{\max}$. 1770, 1703, 1450, 1390, 1330, 1175, 1138, 1010, 1000, 920, and 840 cm^{-1} , and M 452 (mass spectrum).

(Found: C, 79.6; H, 9.7;
calc. for $\text{C}_{30}\text{H}_{44}\text{O}_3$ C, 79.6; H, 9.8%).

The infrared, n.m.r., and mass spectra were identical with those of an authentic sample of flindissone lactone (142),

and the mixed m.p. gave no depression.

Flindissone Lactone (142)

Flindissol (39) (147 mg.) in pyridine (10 ml.) was treated with a slurry of chromium trioxide (2 g.) and pyridine (40 ml.), and the mixture was kept at room temperature (20°C) overnight. The mixture was poured into water and then extracted with ether. The ethereal solution was dried and the solvent was distilled off. The residue was taken up in benzene and adsorbed on to a column of alumina (5% deactivated, 20 g.). Elution with benzene afforded flindissone lactone (142) (110 mg.), which crystallised from aqueous methanol as needles, m.p. 191-193°C, $[\alpha]_D^{20} - 83^\circ$ (c 0.47), (lit.¹⁰ m.p. 193-195°C; $[\alpha]_D^{24} - 87^\circ$), $\nu_{\max}$ (CHCl₃) 1770, 1703, 1450, 1390, 1330, 1175, 1138, 1010, 1000, 920, and 840 cm.⁻¹, M 452 (mass spectrum), and $[\alpha]_D^{20} - 83^\circ$ (c 0.46 in MeOH - CHCl₃, 4:1) and $[\alpha]_D^{20} - 71^\circ$ (c 0.52 in MeOH - CHCl₃, 4:1 containing 1% KOH).

(Found:

C, 79.8; H, 9.7;

calc. for C₃₀H₄₄O₃

C, 79.6; H, 9.8%).

The flindissol was kindly supplied by Professor A. J. Birch.

Treatment of Turraeanthin with Sulphuric Acid in Ether

Turraeanthin (360 mg.) in ether (30 ml.) was treated with sulphuric acid (1 ml.) with cooling in ice during the addition. The solution was kept at room temperature (20°) for 24 hours. Ether (100 ml.) was added and the solution was washed with saturated aqueous sodium bicarbonate and water. The solution was dried and the solvent was distilled off. The residue was taken up in benzene and adsorbed on to a column of alumina (5% desot., 30 g.). Elution with benzene - ether (19:1) gave isoturraeanthin (233 mg.), which crystallised from acetone as needles. Recrystallisation from methanol - chloroform afforded needles, m.p. 333-336°,

$[\alpha]_D^{20} - 8^\circ$ (c 0.49), $\nu_{\max.}$ (CHCl₃) 3600, 1730, 1115, 1020, 960, 930, and 900 cm.⁻¹, n.m.r. : τ 6.2 [1H; m, -CH(OR)-] and 4.75 [1H; bs, -CH(OR).O-] p.p.m., M 514 (mass spectrum).

(Found: C, 74.5; H, 9.6;
C₃₂H₅₀O₅ requires C, 74.7; H, 9.8%).

Turraeanthin p-Bromobenzoate Chlorohydrin (154)

Turraeanthin (0.627 g.) in dry pyridine (30 ml.) was treated with p-bromobenzoyl chloride (2.2 g) and the solution was heated on a steam-bath for 90 minutes. The

mixture was kept at room temperature for 48 hours and then chloroform (200 ml.) was added. The organic solution was washed with saturated aqueous sodium bicarbonate, dilute aqueous sulphuric acid and water, and then dried. The solvent was distilled off and the residue was adsorbed from benzene on to a column of alumina (10% desat., 100 g.). Elution with benzene afforded turraeanthin p-bromobenzoate chlorohydrin (154), which crystallised from ethanol as needles, m.p. 333-336°, $\nu_{\text{max.}}$ 1730, 1592, 1260, 1245, 1095, 1011, 845, and 755 cm^{-1} , n.m.r. τ 8.30, 8.23 [2 x 3H; s, $(\text{CH}_3)_2\text{OCl-}$], 3.95 [1H; bs, $-\text{CH}(\text{O.CO.Ph}).\text{O-}$], and 2.20(4H; m, Ar-H) p.p.m.

(Found:

C, 64.5; H, 7.5;

$\text{C}_{39}\text{H}_{54}\text{O}_6\text{BrCl}$ requires

C, 63.8; H, 7.4%).

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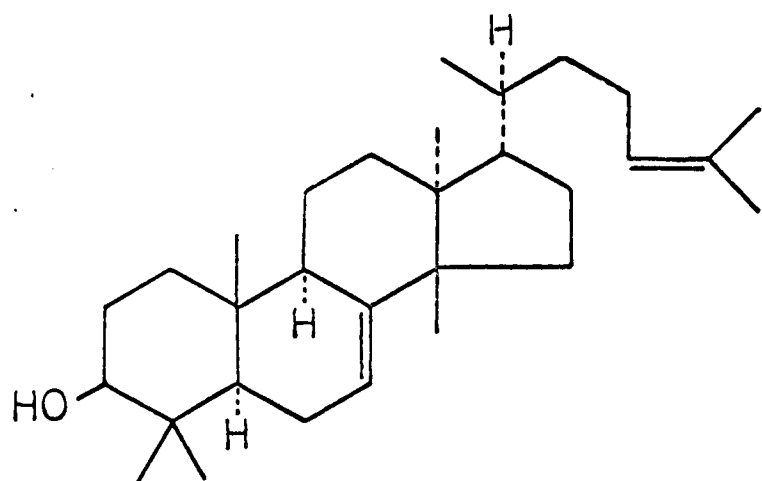
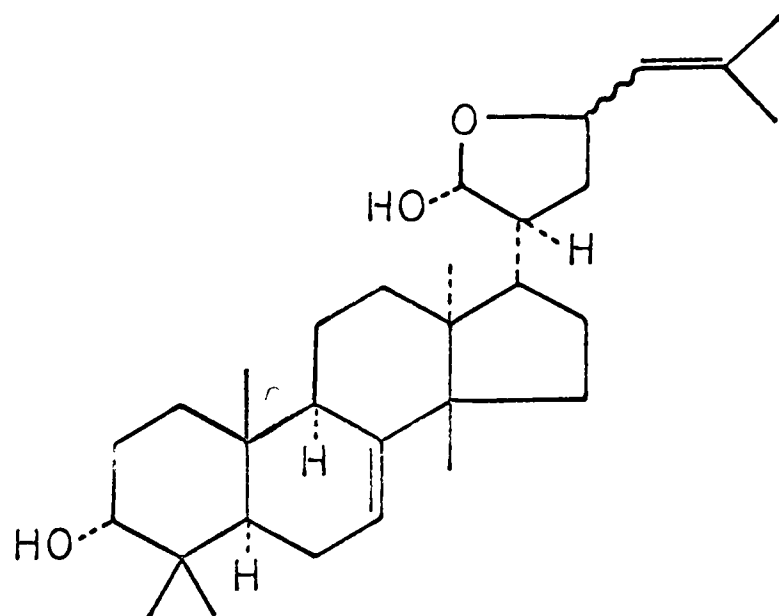
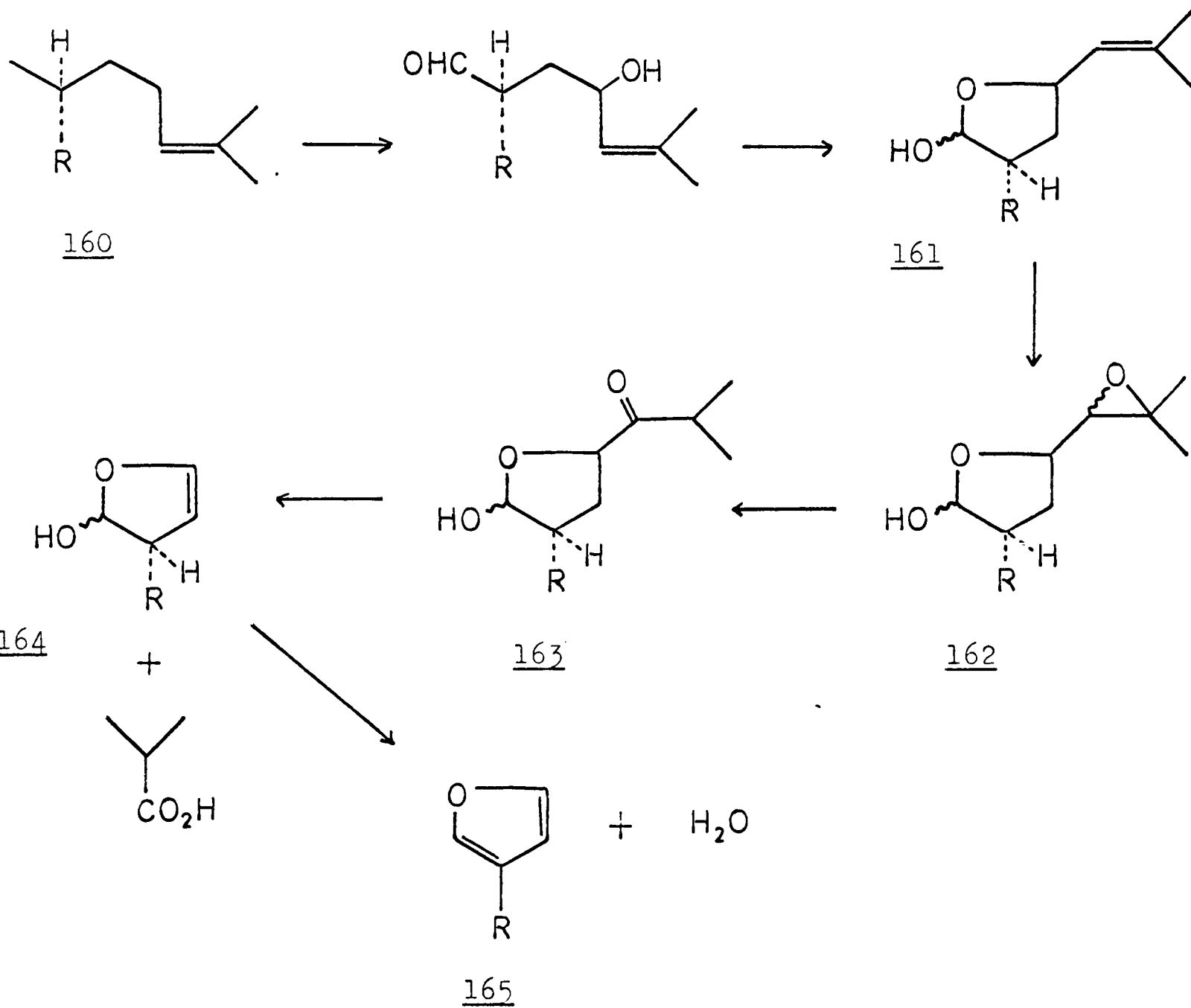
CHAPTER IV

BIOGENESIS OF THE LIMONENE GROUP OF COMPOUNDS

Biogenesis of the Limonin Group of Compounds

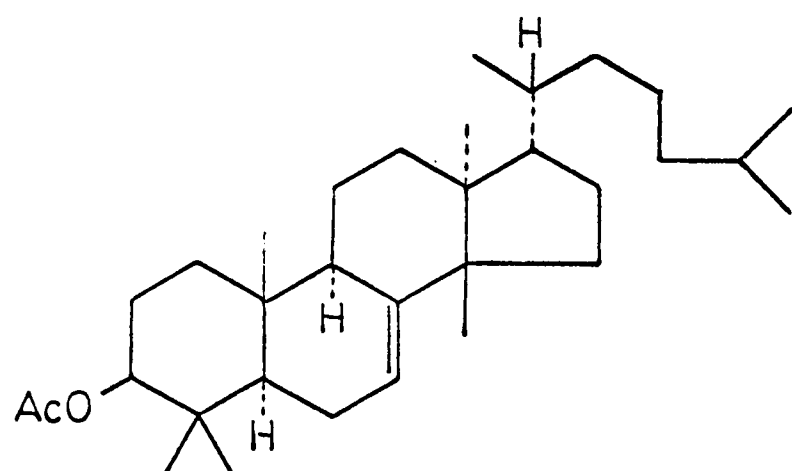
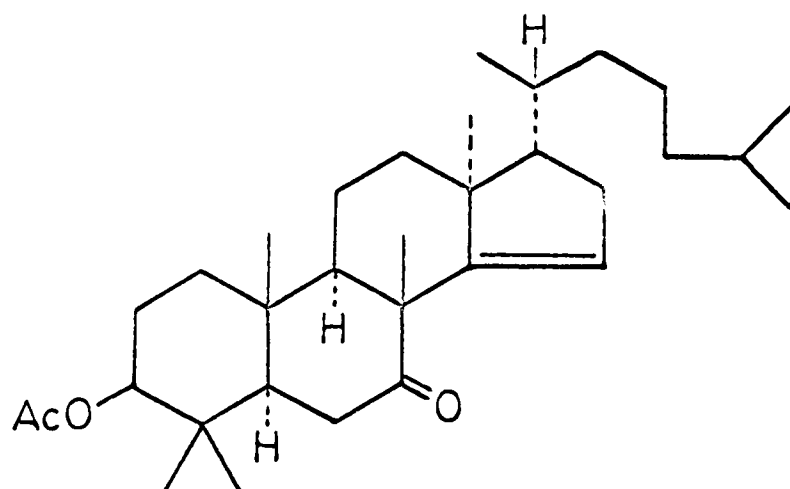
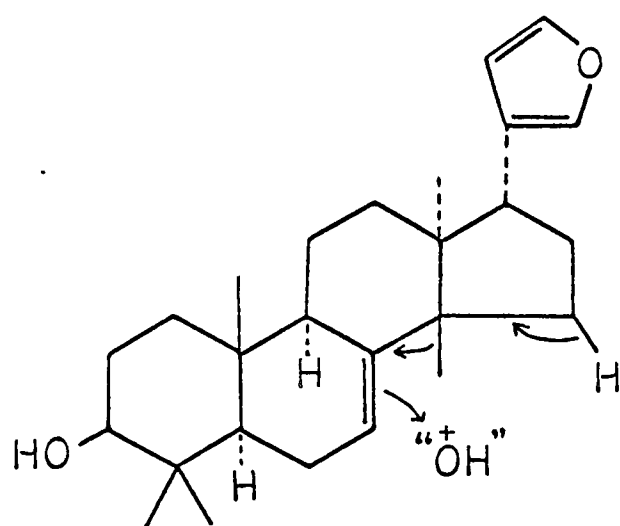
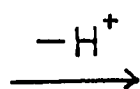
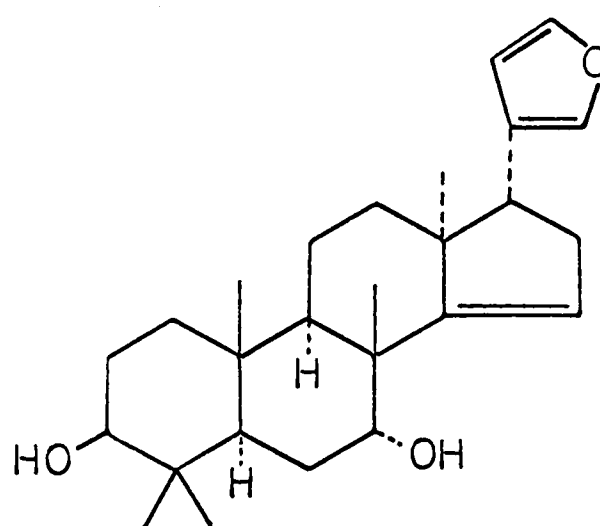
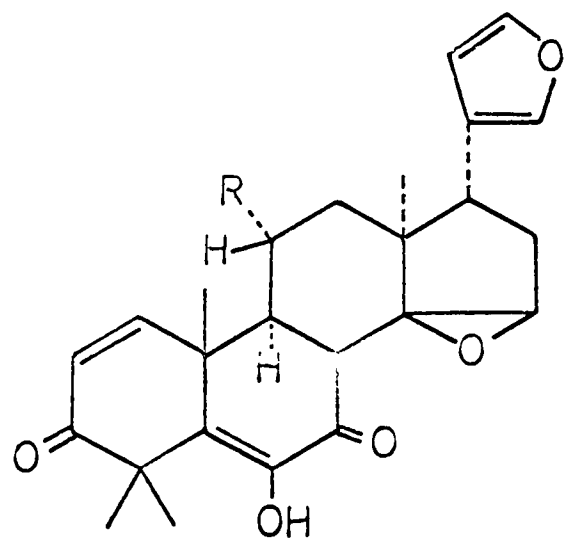
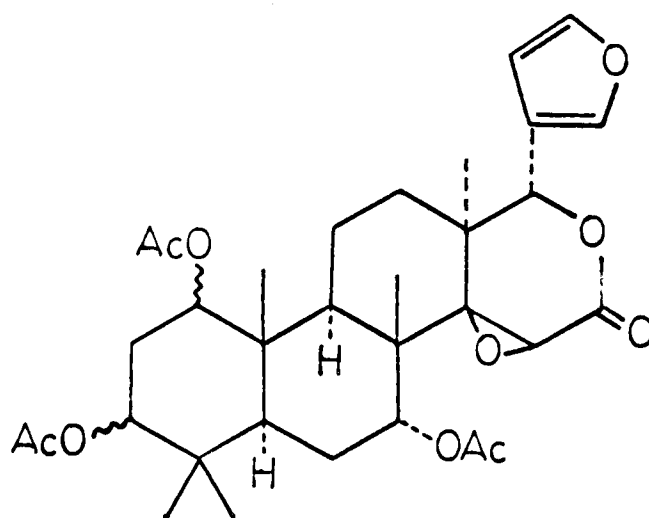
Many of the essential features of the biogenesis of terpenoids and steroids have been elucidated by intensive studies of the biogenesis of cholesterol, particularly those carried out in the laboratories of Bloch, Cornforth and Popjak, and Lynen. Their results have been reviewed elsewhere¹⁻⁵. Triterpenes are formed by a concerted cyclisation of squalene, and the stereochemistry of the product depends upon the type of folding of the original squalene chain, presumably on an enzyme surface. The positive charge remaining after the ring closures often stimulates the migrations of angular methyl groups, and oxidations at various positions can also occur, leading to a wide range of products.

It has been proposed⁶ that the limonin type of compounds are derived biogenetically from a tirucalla-7,24-dien-3 β -ol (equivalent to 20-epi-butyrospermol) (160) type of precursor by a series of oxidative degradations. Many of these oxidations involve the hydroxylation of saturated carbon atoms that are unactivated in any classical sense. These and other oxidations are postulated to proceed via the attack

16039 Flindissol

of the hypothetical "OH⁺" species.⁵ The nature of the latter species has not yet been elucidated, but it has been shown that many hydroxylations utilise molecular oxygen,^{7,8} and that this often requires the presence of ferrous iron.⁹

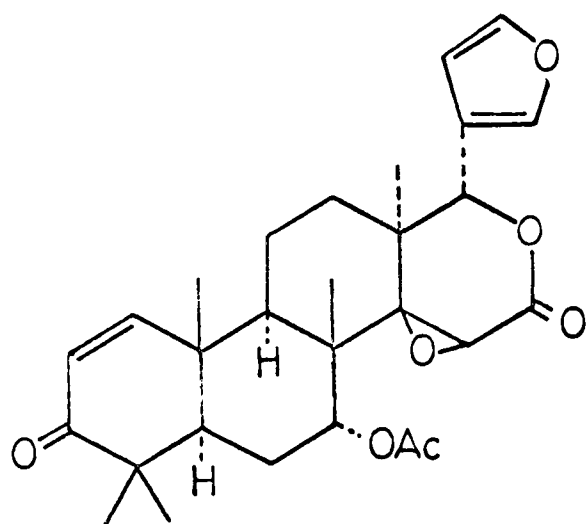
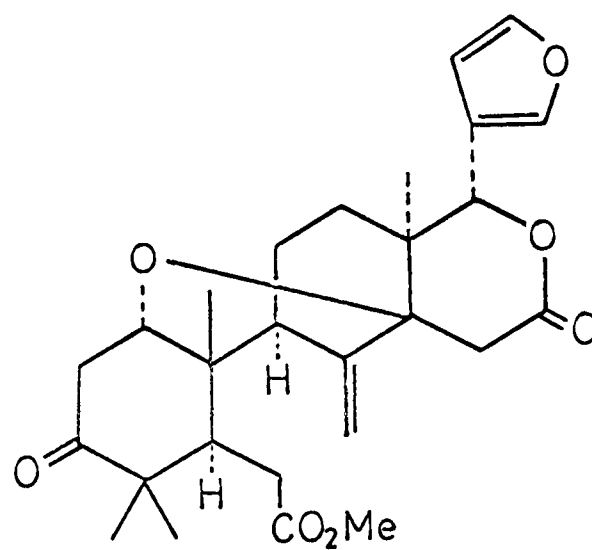
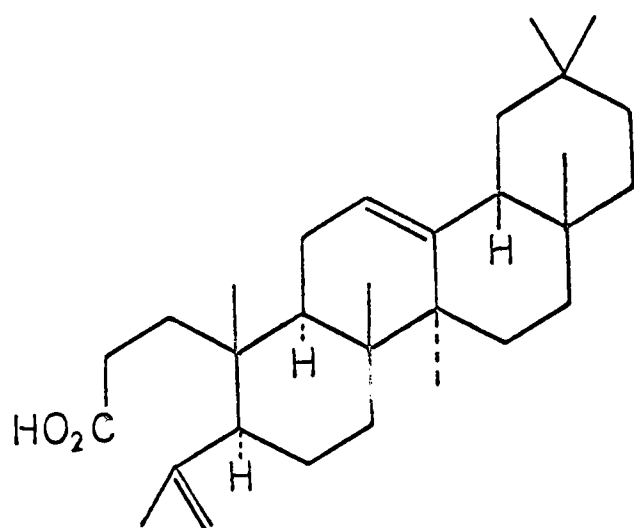
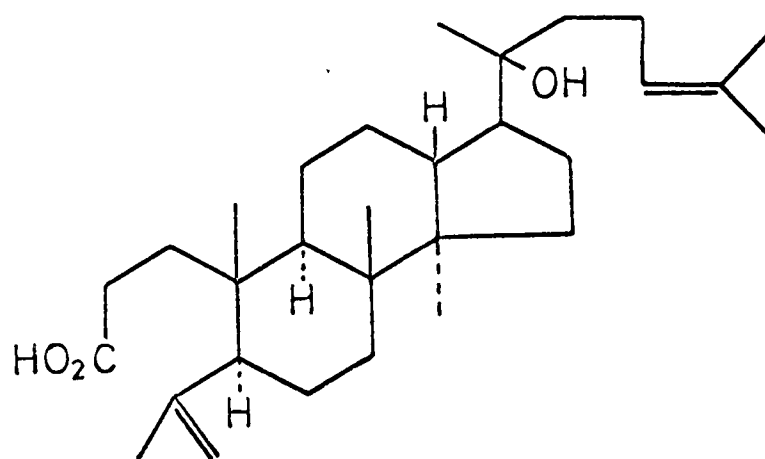
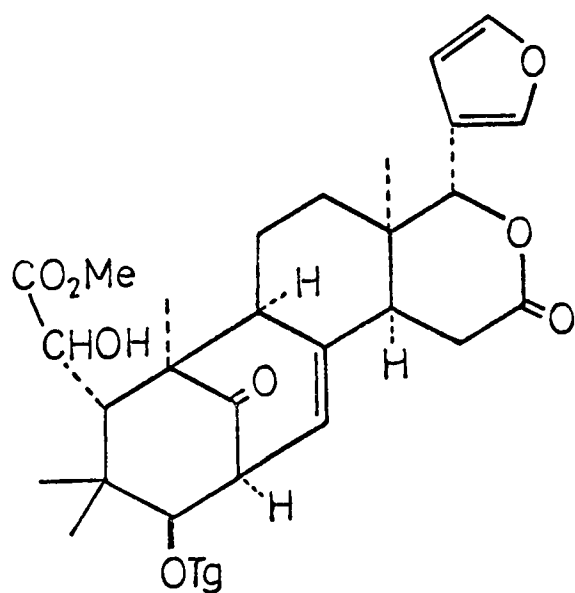
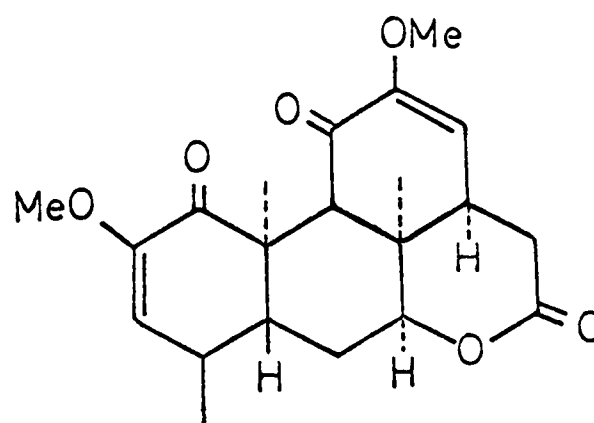
It has been proposed⁶ that the β -furan group found in limonin (1) and its congeners is derived by oxidation of the tirucallosol type of side-chain. Flindissol¹⁰ (39) has been suggested as a possible biogenetic intermediate in this sequence since it contains a potential furan ring and an intact side-chain. Turraeanthin (153) now appears to represent the next biogenetic intermediate since it again has its side-chain intact but it is at a higher level of oxidation than flindissol (39). The oxidative sequence leading to a furan ring could be envisaged as proceeding in the following manner. Oxidation of the tirucallosol side-chain at C₍₂₁₎ and C₍₂₃₎ to an aldehyde and a hydroxyl group respectively would be followed by cyclisation to the hemiacetal, (160) to (161). This would give the flindissol side-chain (39). Epoxidation of the 24-25 double bond would then yield a turraeanthin type of compound (162). This epoxide group could rearrange to give the C₍₂₄₎ ketone, (163) the oxidation of which would result in a cleavage of the C₍₂₃₎ - C₍₂₄₎ bond yielding the

16616716816917 R = H, Cedrelone16 R = AcO, Anthothecol14 Khivorin

compound (164).^{of.18,19} Dehydration of this latter compound leads to the -furan (165).

Barton⁶ has proposed that the modification of the ring system of the tirucall-7,24-dien-3 β -ol (160) precursor to give limonin (1) commences by an oxidative rearrangement similar to that found¹¹ when dihydrobutyrospermyl acetate (166) was treated with chromic acid to give 7-oxoapocoeuphenyl acetate (167). This rearrangement can be envisaged as being brought about biogenetically by the attack of "OH⁺", by the mechanism (168) to (169). The product (169) can then be transformed into the individual members of the meliacin group of compounds present in the Meliaceae and Rutaceae families. In order to achieve this it is only necessary to carry out simple oxidations, sometimes including ring cleavages of the Baeyer-Villiger type. Thus cedrelone¹² (17) may be considered to arise from such a compound by epoxidation of the 14-15 double bond, oxidation at C₍₆₎, C₍₇₎ and C₍₃₎ and dehydrogenation at C₍₁₎ - C₍₂₎. Anthothecol¹³ (16) could be obtained from cedrelone by hydroxylation and acetylation at C₍₁₁₎.

In khivorin¹⁴ (14) ring D has been expanded to a six-membered lactone by an oxidative cleavage of the Baeyer-

2 Gedunin70 Methyl angolensate91 Nyctanthic acid170 Dammarenolic acid25 Swietenine44 Quassin

Villiger type upon a 16-ketone. Gedunin¹⁵ (2) could then be derived from khiivorin (14) by further oxidation at C₍₃₎ to the ketone and elimination of the C₍₁₎ acetoxy group to give a 1-2 double bond. Methyl angolensate¹⁶ (70) and andirobin¹⁷ (30) represent a further stage of oxidation beyond that of gedunin (2). In these compounds ring B has been oxidatively cleaved, possibly by a mechanism similar to that postulated for the biogenesis of nyctanthic acid¹⁸ (91) and dammarenolic acid¹⁹ (170). Cleavage of ring B has also occurred in the formation of swietenine²⁰ (25) and the related compounds swietenolide²¹ (29) and mexicanolide²² (31). In these compounds it is interesting to note that the C₍₂₎ position has become linked to the methyl group at C₍₈₎. Limonin⁶ (1) itself has ring B intact while ring A has been oxidatively cleaved and the C₍₃₎ carboxyl group produced oxidatively cyclised on to C₍₁₉₎.

In order to obtain the type of compounds found in the Simaroubaceae family such as quassin²³ (44), chaparrin²⁴ (46), and glaucarubin²⁵ (48) more extensive changes are necessary. Their carbon skeleton closely resembles that of merogedunin¹⁵ (13), apart from the extra carbon atom at C₍₄₎, obtained by a base-catalysed transformation of gedunin (2).

It has been suggested²⁶ that this group of so-called diterpenes obtained from the Simaroubaceae family might arise biogenetically from gedunin-type precursors. Simarolide²⁷ (59) represents a possible type of intermediate and lends further support for this theory.

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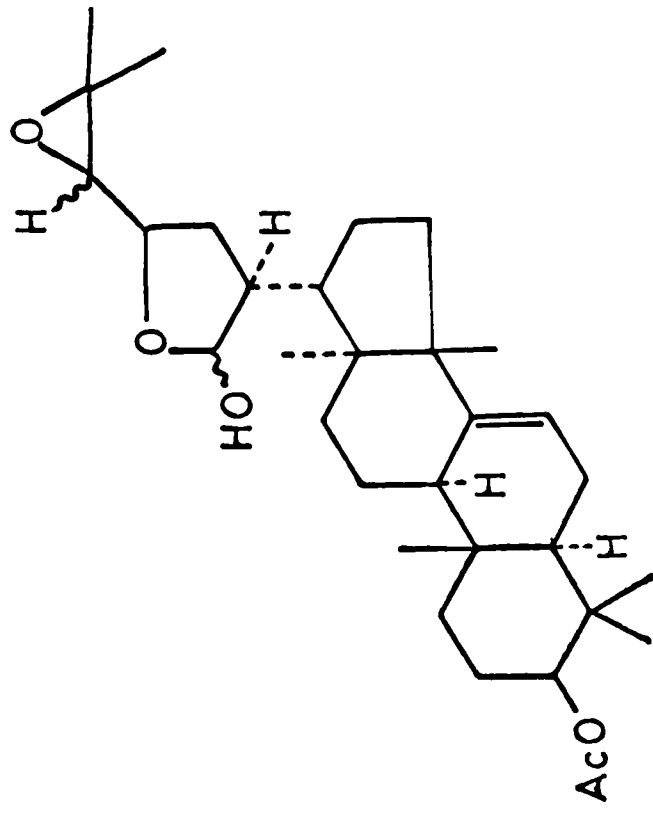
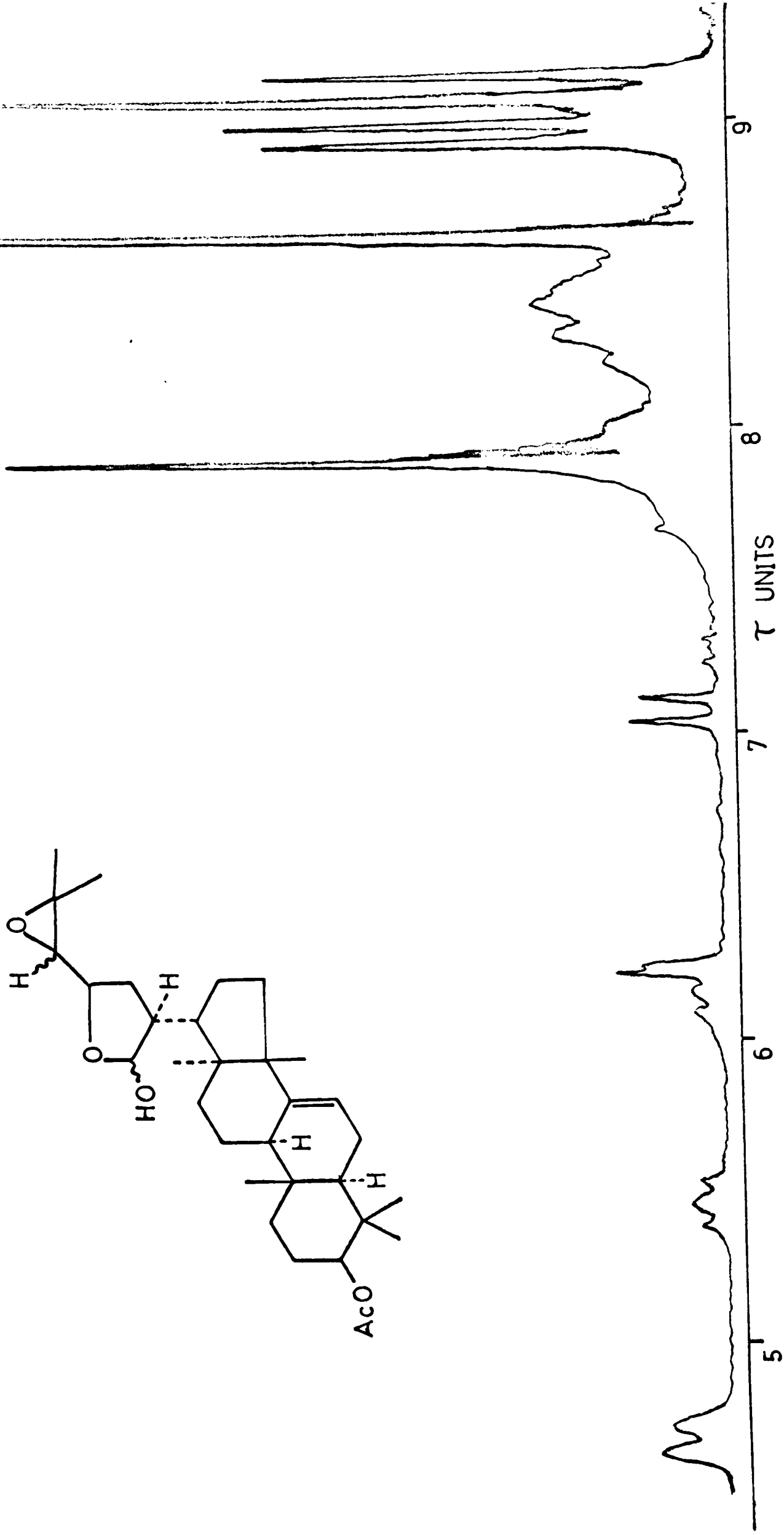
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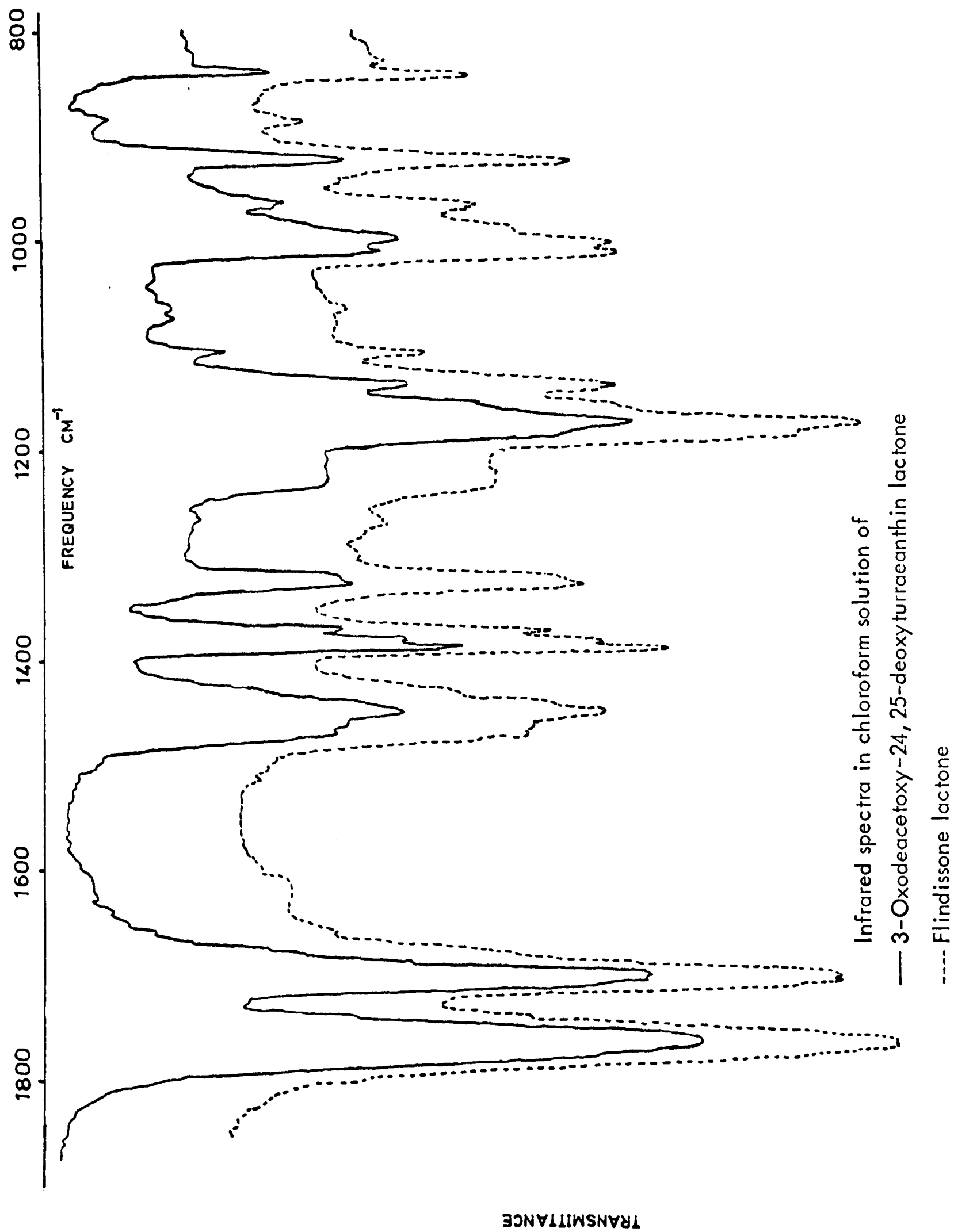
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APPENDIX

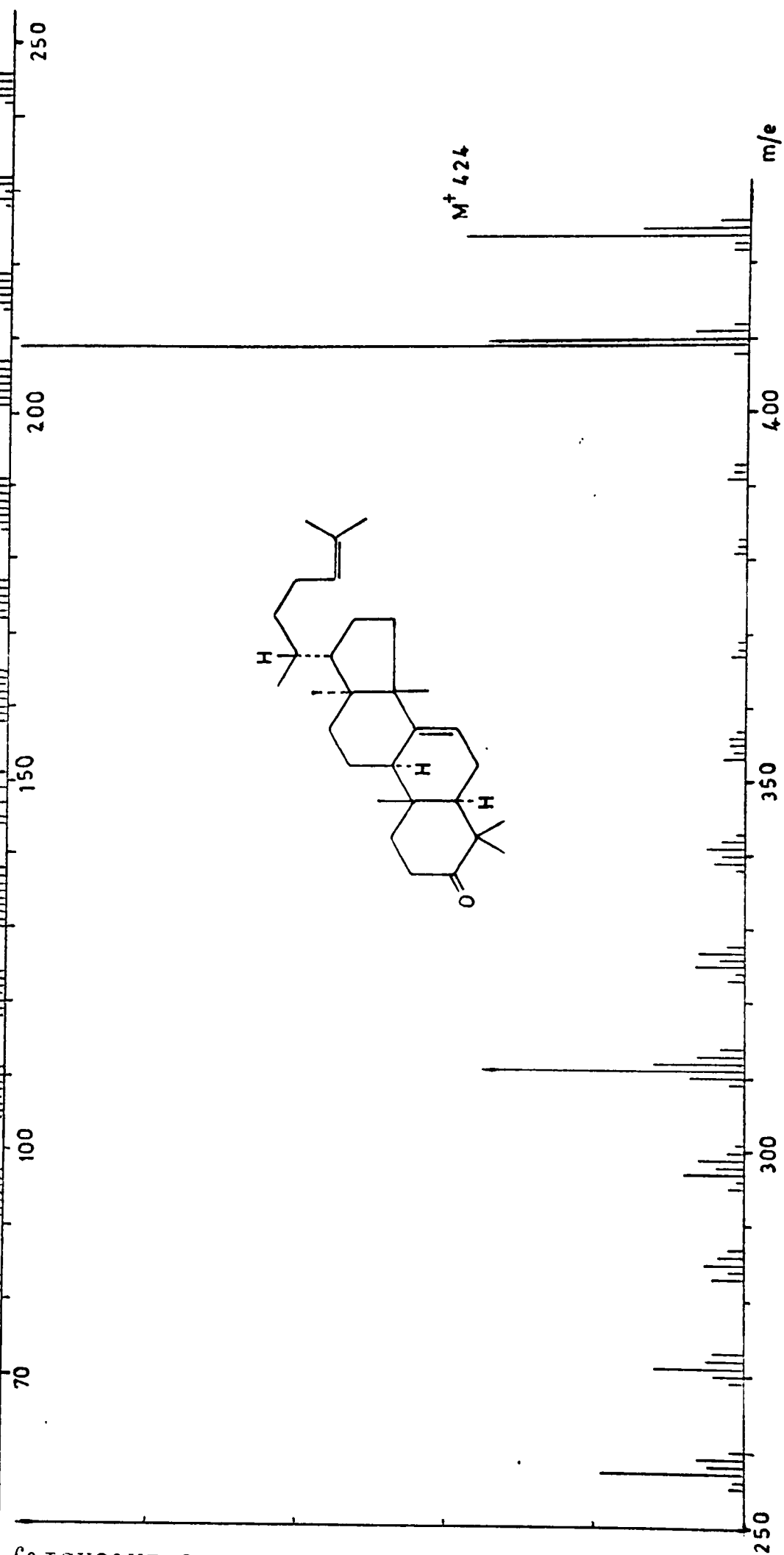
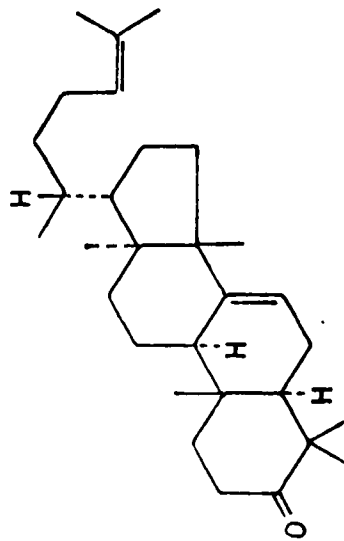
100 MC/S NMR SPECTRUM OF TURRAEANTHIN



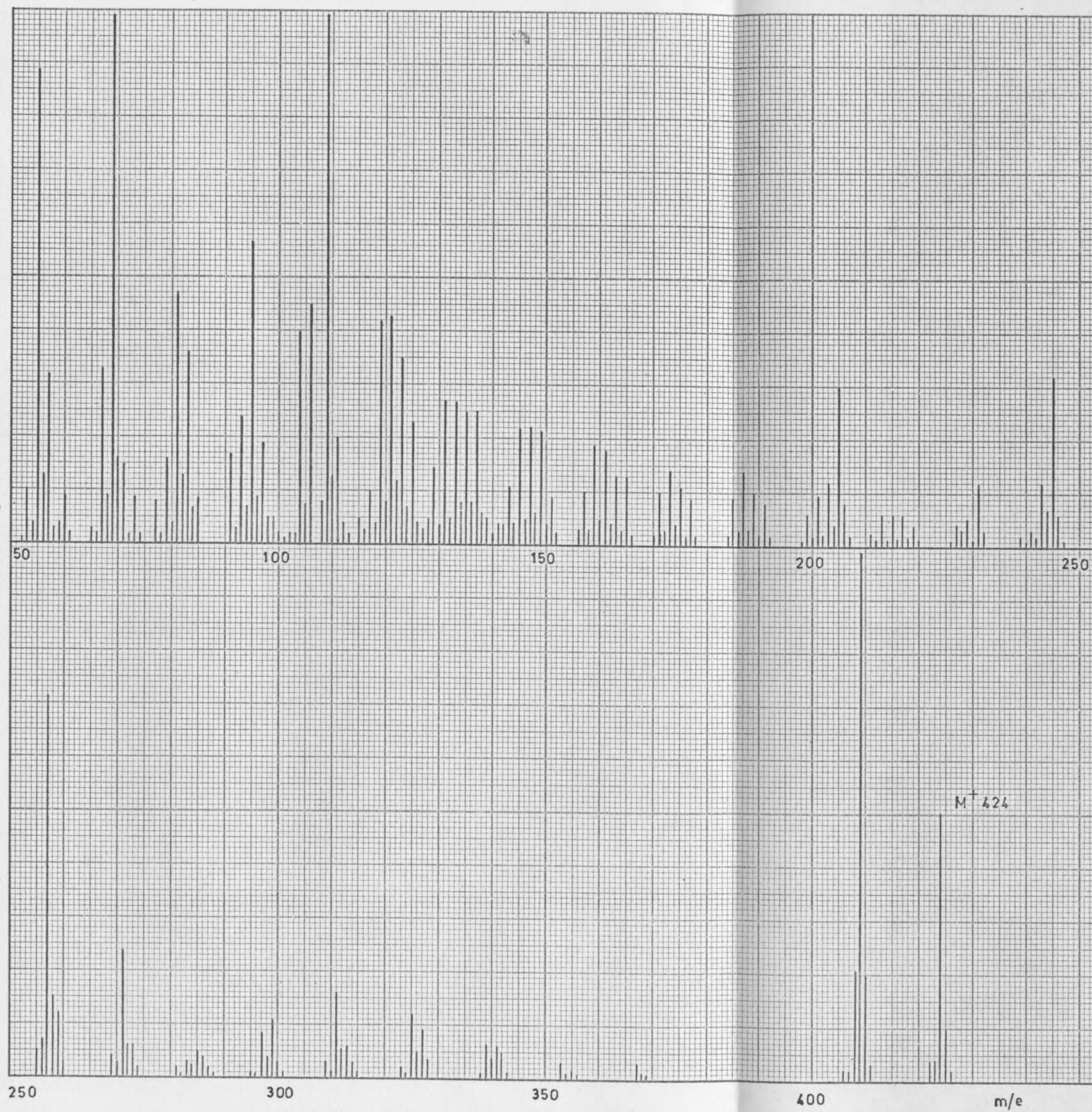
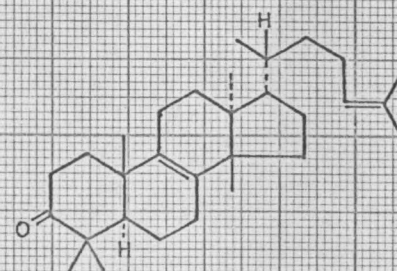


BUTYROSPERMONE

Relative Intensity



Relative Intensity



EUPHONE

Relative Intensity.

300

350

400

450

500

m/e

50

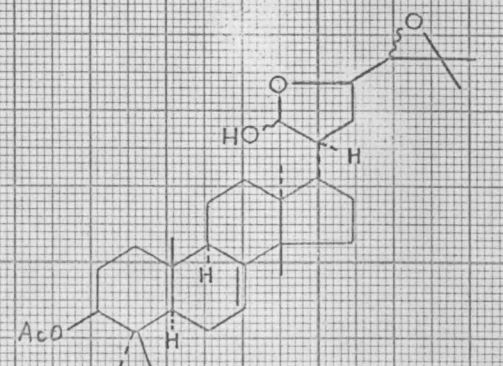
100

150

200

250

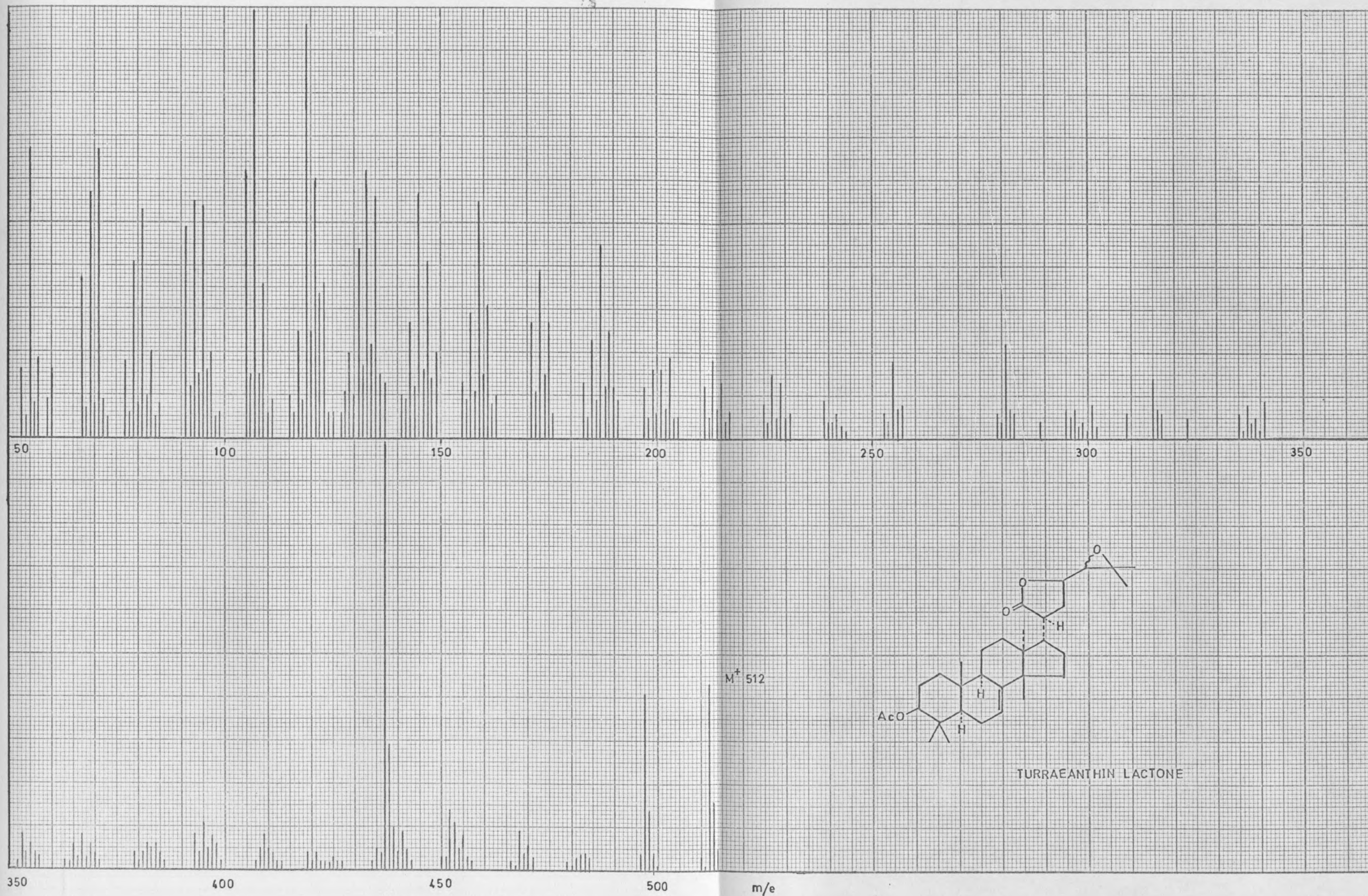
300



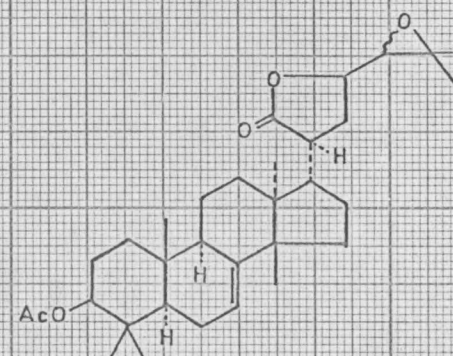
TURRAEANTHIN

M^+ 514

Relative Intensity

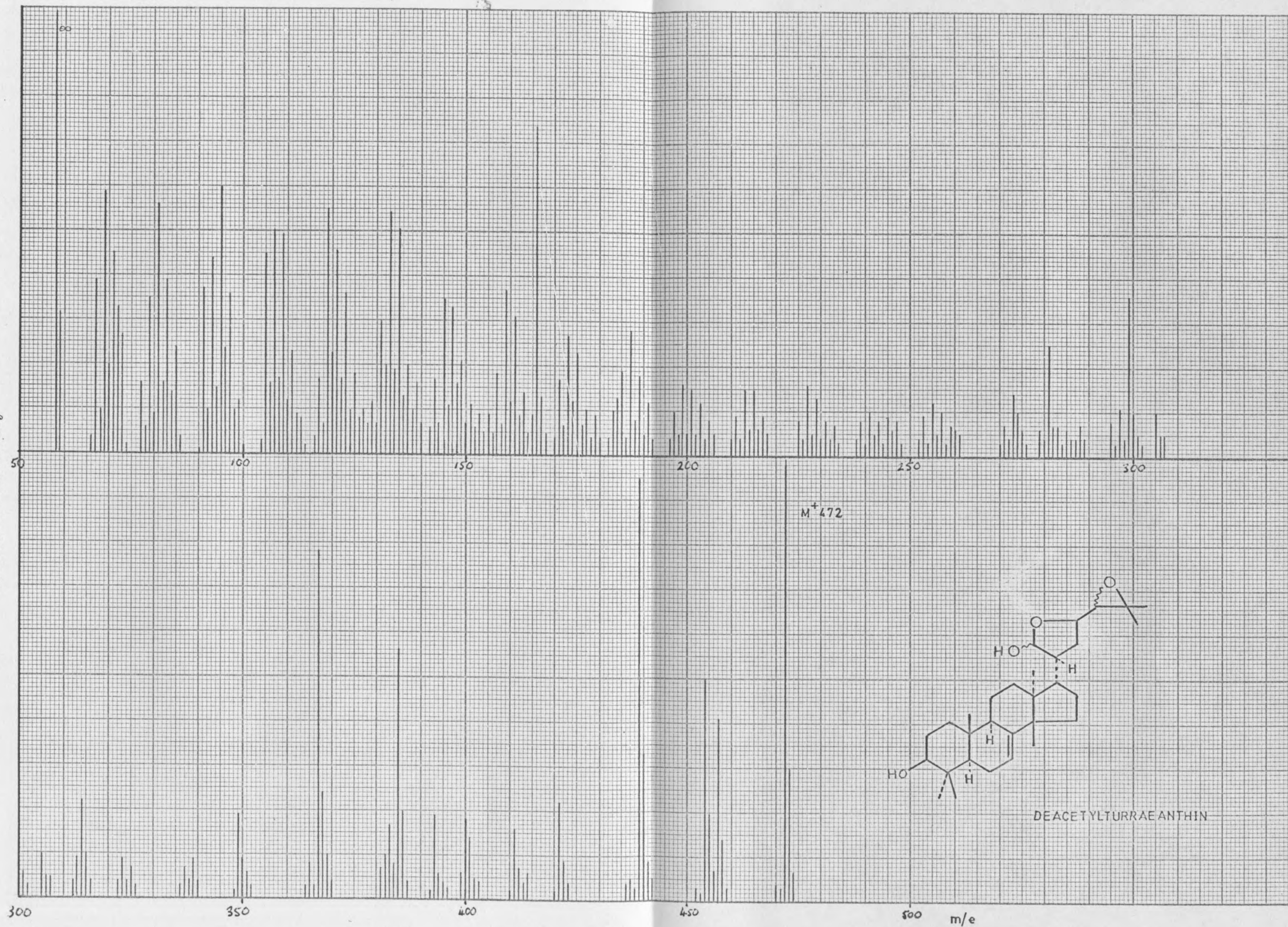


M^+ 512

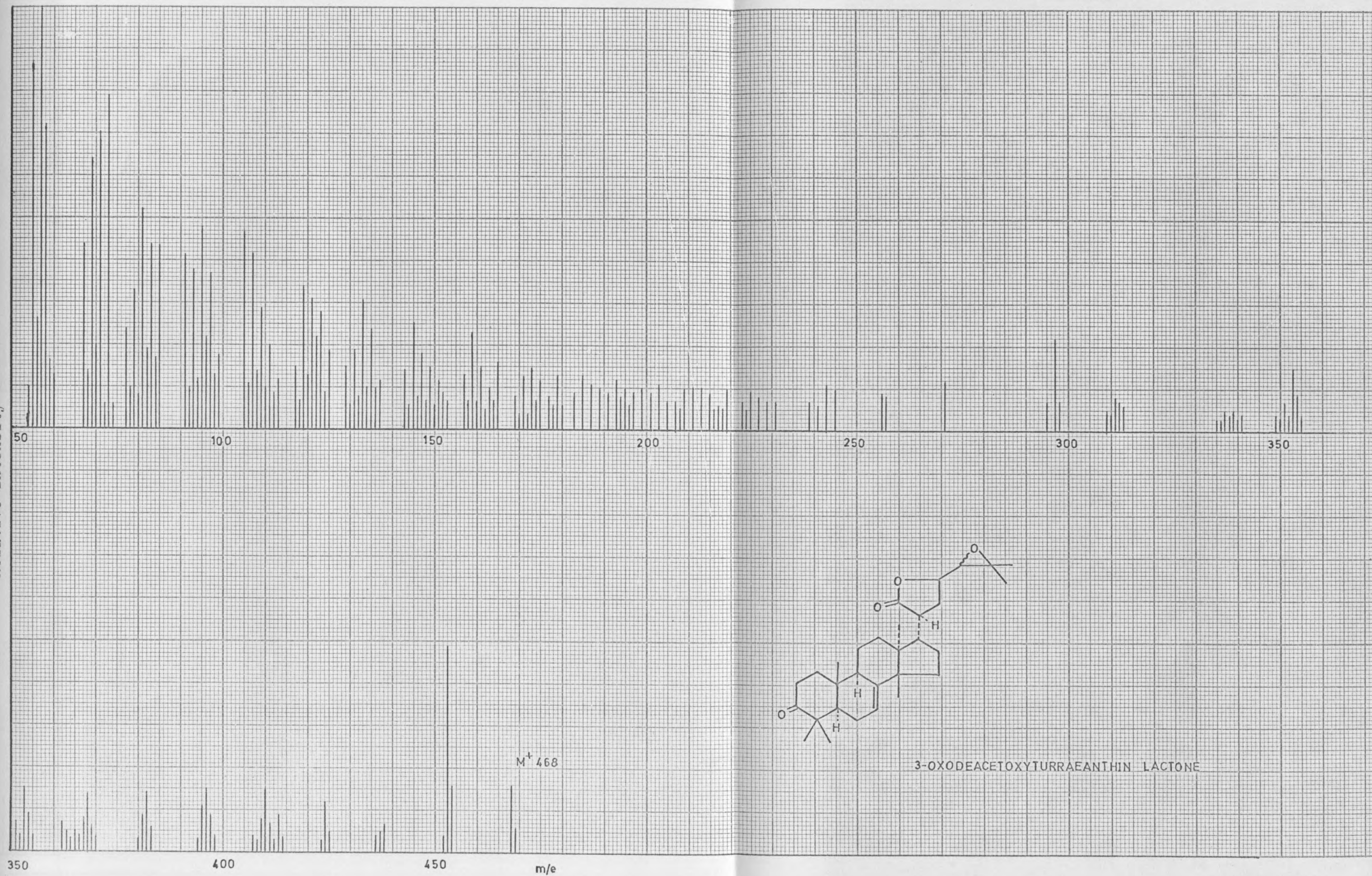
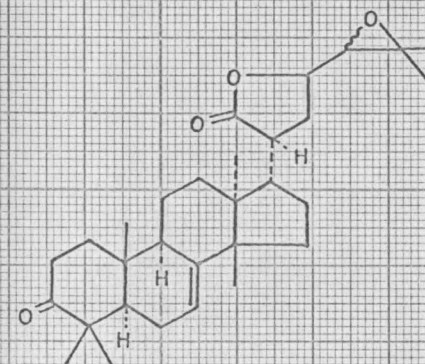


TURRAEANTHIN LACTONE

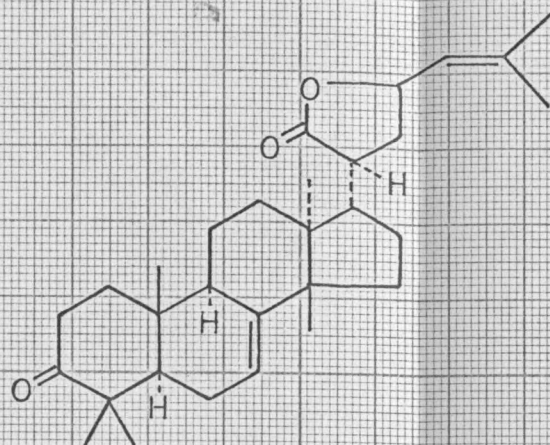
Relative Intensity



Relative Intensity



3-OXODEACETOXYTURRAEANTHIN LACTONE



3-OXODEACETOXY-24,25-DEOXY TURRAEANTHIN LACTONE

M⁺ 45

150

200

250

300

350

400

m/e

450

FLINDISSONE LACTONE

M⁺

150

200

250

300

350

400

m/e

450