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UNIVERSITY OF POONA
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Studies in Sesquiterpenic Compounds



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A Thesis submitted to the
University of Poona

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For the Degree of
Doctor of Philosophy
(In Chemistry)

by
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M. Sc.

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I am also grateful to Dr. V.S. Pansare and his colleagues for microanalysis, to Mr. V.K. Bhalerao, Mrs. N.V. Bhalerao and Mr. K.G. Deshpande for IR and UV spectral measurements, to Mr. I.S. Mulla and Mr. G. Samuel for recording the NMR spectra, to Dr. B.V. Bapat and Mr. V.K. Kulkarni for GLC analyses and to Dr.C.A. Chinchwadkar and Mr. P.S. Kulkarni for recording mass spectra for this work.

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(Miss R.N. Sathe)

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I N T R O D U C T I O N

The costus plant, Saussurea lappa Clarke (compositae family) is a valuable Indian raw material grown extensively in Punjab and Kashmir at high altitudes¹. In India, it is known by various names^{2,3} such as Kuth, Kut, Kashmiraja etc. The roots of the plant are said to possess medicinal properties and have been prescribed in indigenous system of medicine^{2,3,4}, as a remedy against various ailments such as cough, fever, ulcers, asthma, tumors, skin diseases etc. The root powder is used for preserving woollen fabrics. The roots contain a fragrant principle also and they used to be exported to China and Japan in large quantities for burning as incense in Buddhist temples¹. The essential oil contained in roots is used in high grade perfumery preparations.

The commercial method for extracting the oil is steam distillation^{5,7,9}, though solvent extraction has been occasionally used for isolation of the oil from roots, mostly for experimental purposes. The oil is known to be rich in lactic constituents, some of which are thermolabile and denature or polymerise on heating around 60-70° or more quickly at high temperatures. The earlier workers, however, did not pay adequate attention

to the control of temperature during extraction or subjected this thermolabile oil to vacuum distillation at elevated temperature for the isolation of the constituents^{6,9,11,12}. As a result, the yield of the oil obtained by them was poor and many of the thermolabile constituents were lost due to denaturing and polymerisation and artefacts were formed as well.

Taking into consideration these results, a mild extraction procedure was considered necessary for isolation of the oil in the form in which it exists in the roots. Such a procedure has been developed in this laboratory in which pet. ether (40-60°) was used as the solvent and the bath-temperature does not exceed 40-45° in any operation in the process¹⁰.

This procedure gives a high yield of the oil i.e. about 6.5% from the roots of Kashmir origin and about 4% from the roots from Punjab. The oil is free from polymerisation and denaturing as compared to the commercial oil. It is very rich in lactonic constituents and the solid lactones can be isolated by stage-wise cooling of the pet. ether extractive at 0° and - 18°. The oil has been critically examined for its constituents and the results have been published^{10,13-20}.

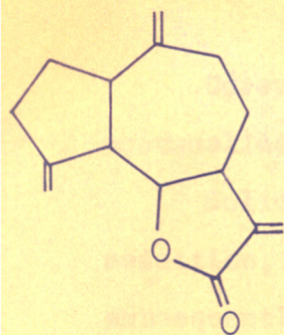
The lactonic constituents mentioned above are isolable to the extent of about 50% of the oil, and dehydrocostus lactone (I, 70%) and costunolide (II, 30%) are the major components.

Costunolide (II), $C_{15}H_{20}O_2$, is a new sesquiterpenic

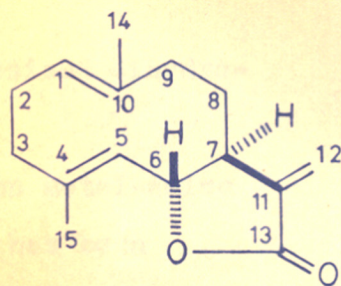
lactone, isolated for the first time in this laboratory and its structure and stereochemistry have been established by Bhattacharyya et al.¹⁶ and Sorn and co-workers²¹. It is the parent lactone of a series of ten-membered carbocyclic ring compounds, such as parthenolide²², pyrethrosin²³, arctiopicrin²⁴ etc. It has a unique distribution of two trisubstituted double bonds and is capable of undergoing numerous interesting transformations.

It can be converted into elemene¹⁸ and selinene^{25,26} type compounds by stereospecific thermal rearrangement and acid catalysed transannular cyclisation respectively. The thermal rearrangement of dihydrocostunolide (III) led to the formation of saussurea lactone¹⁸ (IV), the structure and stereochemistry of which have been established in this laboratory by degradative and synthetic methods²⁷. On acid catalysed cyclisation, dihydrocostunolide (III) gives a mixture of α and β -cyclodihydrocostunolides (V and VI respectively).

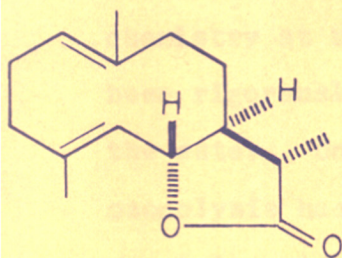
Starting from the lactone (VI) d-junenor (VII), isolated from Juniper oil by Czech workers²⁸, has been synthesised in this laboratory and its stereochemistry established.²⁵ This work helped elucidation of the stereochemistry of l-junenor (VIII), isolated from the South Indian variety of vetiver oil, which is the optical antipode of d-junenor.



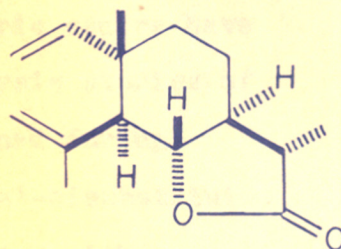
(I)



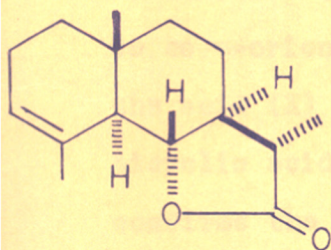
(II)



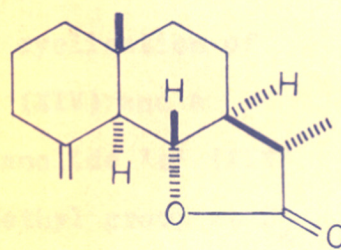
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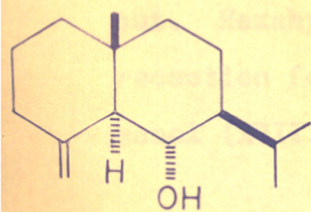
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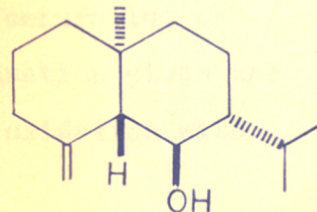
(V)



(VI)



(VII)

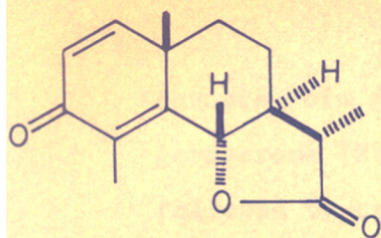


(VIII)

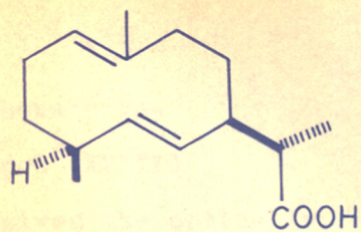
Corey and Hortmann²⁹ have synthesised dihydro-costunolide (III) from santonin (IX).

Solid dihydrocostunolide (III) on metal-amine reduction, gives an acid (X)³⁰. This has been subsequently converted into the ester (XI) and the corresponding primary alcohol (XII) and hydrocarbon (XIII). The exact position of the double bonds and stereochemistry at the newly formed asymmetric centre have been rigorously established by ozonolysis studies of the ester. One of the products obtained during ozonolysis has been converted into α,α' -disubstituted succinic acid, which has been correlated with roccellic acid of known absolute configuration. From these considerations the methyl group at C₁₁ in dihydrocostunolide (III) and (-) santonin (IX) has been shown to be α -oriented. The acid catalysed cyclisation of the acid (X) leads to santanolide 'c' (XIV) and a bicyclic acid. The formation of santanolide 'c' (XIV) confirms the stereochemistry of the methyl group at C₄ in the acid.

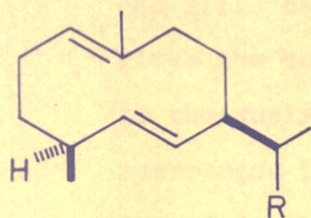
Conversion of costunolide (II) into hexahydrogermacrone (XV) and germacrane (XVI) has also been carried out. Hexahydrocostunolide (XVII) on controlled LAH reduction followed by Huang-Milon reduction gives the monol (XVIII). The monol (XVIII) on oxidation with



(IX)



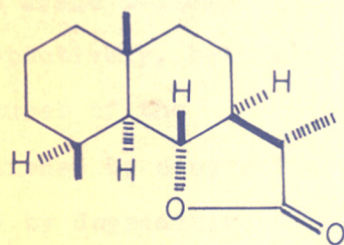
(X)



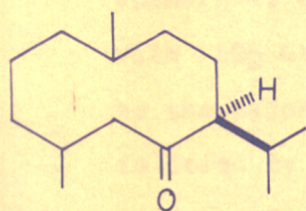
XI : R - COOCH₃

XII : R - CH₂OH

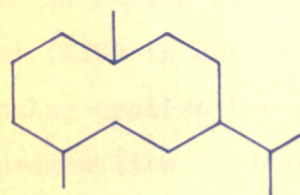
XIII : R - CH₃



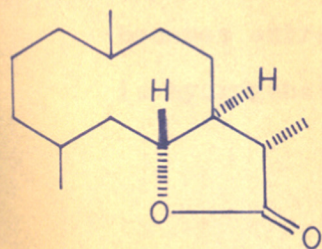
(XIV)



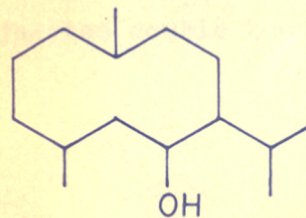
XV



XVI



(XVII)



(XVIII)

chromic acid gives optically active hexahydro-germacrone (XVI). Dehydration of monol (XVIII) followed by catalytic hydrogenation gives the optically inactive germacrane (XVI).

Thermal rearrangement of the compounds (XI, XII and XIII) containing a cyclodeca 1,6 diene system, gives the compounds XIX, XX, XXI respectively, belonging to the guaiane system³². The structures of the rearranged products have been established by converting them into the parent hydrocarbon and by degradative experiments.

When hydrogenated at atmospheric pressure in alcoholic medium using palladium charcoal, costunolide (II) gives solid and liquid dihydrocostunolides, which are epimers at the C₁₁ asymmetric centre. In acetic acid, with PtO₂ as catalyst, santanolide 'c' (XIV) is obtained as the major product due to trans-annular cyclisation followed by hydrogenation¹⁶. When hydrogenation is done under pressure (1000 p.s.i.g.) in alcohol medium and with PtO₂, hexahydrocostunolide (XVII) is formed.

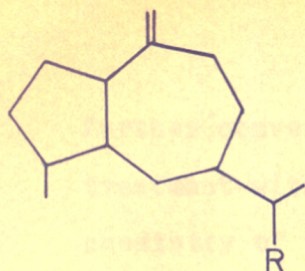
Hydrogenation of costunolide (II) at atmospheric pressure and in alcohol medium using PtO₂ as catalyst becomes extremely slow after the conjugated double bond is hydrogenated.

The two trisubstituted double bonds of dihydrocostunolide have been observed to possess different affinities towards epoxidation; the $C_1 - C_{10}$ double bond being more easily epoxidised than the $C_4 - C_5$ double bond³³.

In part I of this thesis are described the results of partial hydrogenation of dihydrocostunolide (III). It gives two solid tetrahydrocostunolides, (XXII) as major product, along with (XXIII) and a liquid tetrahydrocostunolide probably (XXIV). The structures of these have been established by chemical reactions and spectroscopic data. The position of the double bond has been determined by metal-amine reduction of (XXII) and (XXIII). The compound XXII does not give any acid, so it does not contain any double bond allylic to the potential hydroxy group, while XXIII gives an acid showing that it contains a double bond at $C_4 - C_5$.

Previous attempts in this laboratory for converting costunolide into tetrahydrosantonins via α -cyclodihydrocostunolide (V) have not been successful.

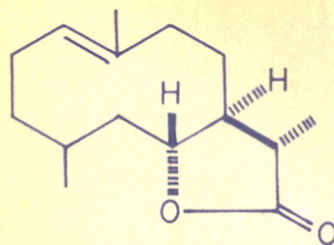
However such a conversion has now been achieved and Part II of the thesis deals with it. On hydroboration-oxidation α -cyclodihydrocostunolide (V) gives a hydroxylactone (XXVII). The latter on chromic acid/pyridine oxidation gives β -tetrahydrosantonin (XXVI) which is



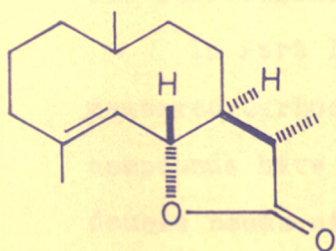
XIX : R - COOCH₃

XX : R - CH₂OH

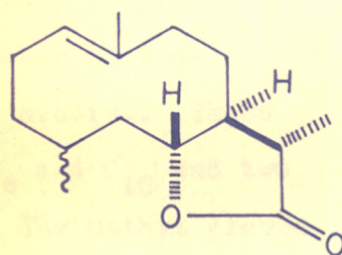
XXIX : R - CH₃



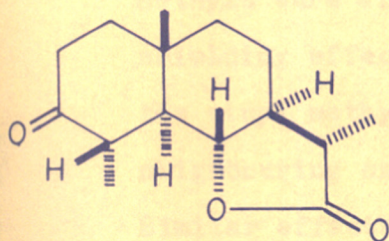
(XXII)



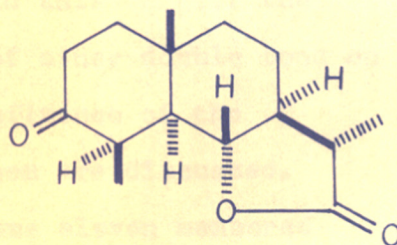
(XXIII)



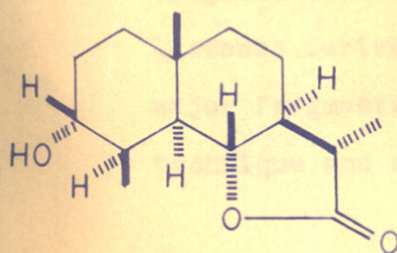
(XXIV)



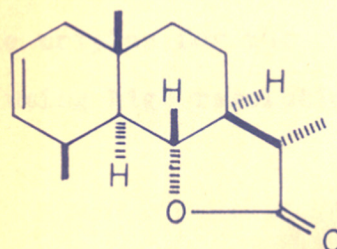
(XXV)



(XXVI)



(XXVII)



(XXVIII)

further converted into α -tetrahydrosantonin (XXV) by treatment with an acid. The structure and stereochemistry of the hydroxylactone (XXVII) have been established by chemical and spectroscopic data. The hydroxy lactone (XXVII) on dehydration gives exclusively the unsaturated lactone (XXVIII) which on catalytic hydrogenation gives santanolide 'c' (XIV). This proves the stereochemistry of the C₄ methyl group as β .

In Part III, NMR spectra of a number of ten-membered carbocyclic systems have been studied. These compounds have two vinyl methyls, at C₄ and C₁₀ and two double bonds at C₁ - C₁₀ and C₄ - C₅. The methyl groups show two distinct signals in the NMR spectra. So far, no definite assignments were made and high values for such methyls were also not explained. In this Chapter the shielding effects of π -electrons of other double bond on the vinyl methyl and deshielding influence of the neighbouring oxygen functions on them are discussed. Similar effects were observed in some eleven membered carbocyclic systems also.

Part IV deals with the correlation between the fragmentation modes and the structures of costunolide and lactones derived from it. The possible origins for the major fragments have been determined, using high resolution technique and deuterium labelling.

11

During the course of these investigations liberal use has been made of the modern techniques, such as infrared, ultraviolet, nuclear magnetic resonance and mass spectrometry, for structural identification.

For separation and purification of individual compounds, extensive column chromatography over alumina, silica gel and silica gel impregnated with silver nitrate have been employed and compounds have been tested for purity by thin-layer and gas-liquid chromatographic analysis.

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GENERAL REMARKS

1. All melting points and boiling points are uncorrected.
 2. All temperatures are recorded on the centigrade scale.
 3. All rotations were taken in chloroform solutions unless stated otherwise. Concentrations are expressed in g/100 ml of the solution.
 4. The ultraviolet spectra were recorded in ethanol solution on a Beckman DK-II ratio recording spectrophotometer.
 5. The infrared spectra were recorded on a Perkin-Elmer infracord spectrophotometer, Model 137B and Model 221, with sodium chloride optics.
 6. The NMR spectra were taken in carbon-tetrachloride solution, unless otherwise mentioned, using tetramethylsilane as the internal reference on a A-60 MC Varian instrument and the chemical shifts have been measured in τ units.
 7. The Mass Spectra were recorded on a CEC-21-110B mass spectrometer on photographic paper.
 8. Acid washed activated alumina standardised as per Brockmann's procedure was employed for column chromatography.
 9. TLC analyses were carried out on glass plates coated with a mixture of silicic acid and plaster of Paris (85:15; 200 mesh) and a mixture of silicic acid, plaster of Paris and silver nitrate (78:12:10, 200 mesh) and activated at 120° for 3 hours. Solvent systems used were pet.-ether, benzene and ethyl acetate or suitable mixture of two of these solvents depending on the nature of the compounds.
- The plates were developed by keeping in an iodine chamber or by spraying with H_2SO_4 .

10. Gas liquid chromatographic analysis (GLC) were carried out on a Griffin and George VPC apparatus, MK IIA, with polyester column employing hydrogen as the carrier gas.

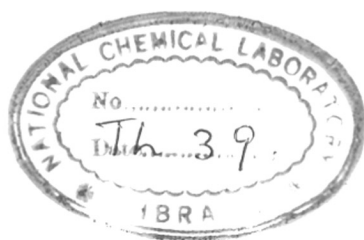
11. Numbers given to charts, figures and structures in each part of the thesis refer to that particular part only.

12. The list of references pertaining to each part has been given at the end of that part.

13. In the list of IR bands given for each compound in the experimental section, the significant bands described in the theory, are underlined.

Part - I

Partial Hydrogenation
of Costunolide



S U M M A R Y

Partial hydrogenation of solid dihydro-costunolide (I), leads to three isomeric tetrahydrocostunolides, of which two are solids. The structures of these compounds have been arrived at, by chemical reactions and spectral data.

Compound IV, is the predominant product of partial hydrogenation thus indicating greater reactivity of the $C_4 - C_5$ double bond in (I), towards hydrogenation.

Partial hydrogenation of dihydrocostunolide

Solid dihydrocostunolide (I) m.p. 78° obtained from costunolide¹ (II) by selective hydrogenation of the conjugated exocyclic double bond, contains two trisubstituted double bonds at C_4-C_5 and $C_{10}-C_1$. Of these, the one at C_4-C_5 is allylic to the potential hydroxy group at C_6 of the lactone moiety. The two double bonds, therefore, can be theoretically expected to show difference in their chemical reactivity.

Sorm² and co-workers have recently reported that the $C_{10}-C_1$ double bond in (I) can be preferentially epoxidised.

It was, therefore, felt desirable to ascertain whether they show any difference in their reactivity towards hydrogenation also.

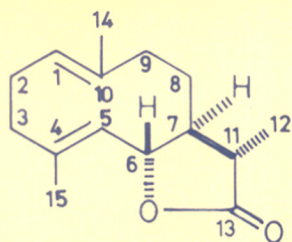
Dihydrocostunolide (I) is subjected to catalytic hydrogenation (in alcohol) using Adams' catalyst at atmospheric pressure and temperature. The hydrogenation is stopped when the absorption corresponds to one double bond. The reaction product, worked up in the usual way, shows three spots in TLC analysis. The least polar spot corresponds to liquid hexahydrocostunolide¹ (XXXI) and the more polar one to unchanged dihydrocostunolide (I). Attempts to separate the components by extensive chromatography over neutral alumina are not entirely

successful though the hexahydrocostunolide (XXXI) and dihydrocostunolide (I) can be separated from the rest. Initially as an alternative course it was thought advisable to separate the partially hydrogenated products in the form of their epoxides by subjecting the mixture, as such, to epoxidation (PBA).

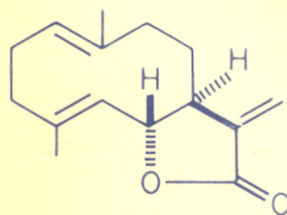
Isolation of an epoxide from the mixture

The mixture of epoxides, however, fails to give any solid by crystallisation. It is, therefore, chromatographed over alumina when an epoxide (III) $C_{15}H_{24}O_3$, m.p. 136-137°, (α)_D - 85°, can be isolated in rather low yield from the earlier fractions. The later fractions of chromatography yield a mixture of hydroxy-lactones, possibly produced by the rearrangement of the epoxide on the column, under the mild alkaline action of alumina. The epoxide (III) shows the following properties:

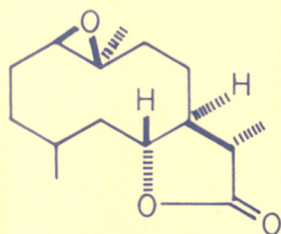
IR Spectrum (Fig. 1) shows bands at: 1767 (γ -lactone), 1236 and 870 cm^{-1} (epoxide). NMR, (Fig. 2) signals at: 8.72, 8.74, 8.84 τ (6H, methyls at C_{10} and C_{11}); 8.9 and 9.0 τ (3H, C_4 methyl); a triplet at 6.98, 7.08 and 7.2 τ (1H, C_1 proton) and a multiplet around 5.78 τ (1H, C_6 proton).



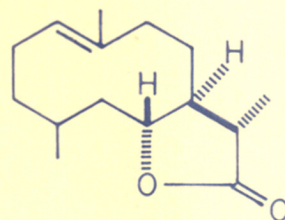
(I)



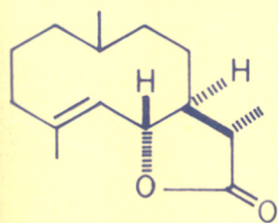
(II)



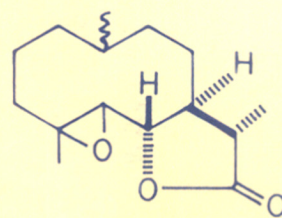
(III)



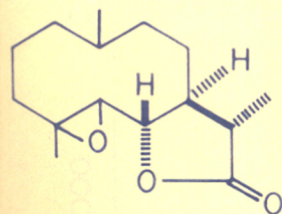
(IV)



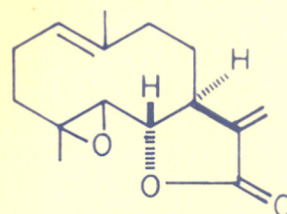
(V)



(VI)



(VII)



(VIII)

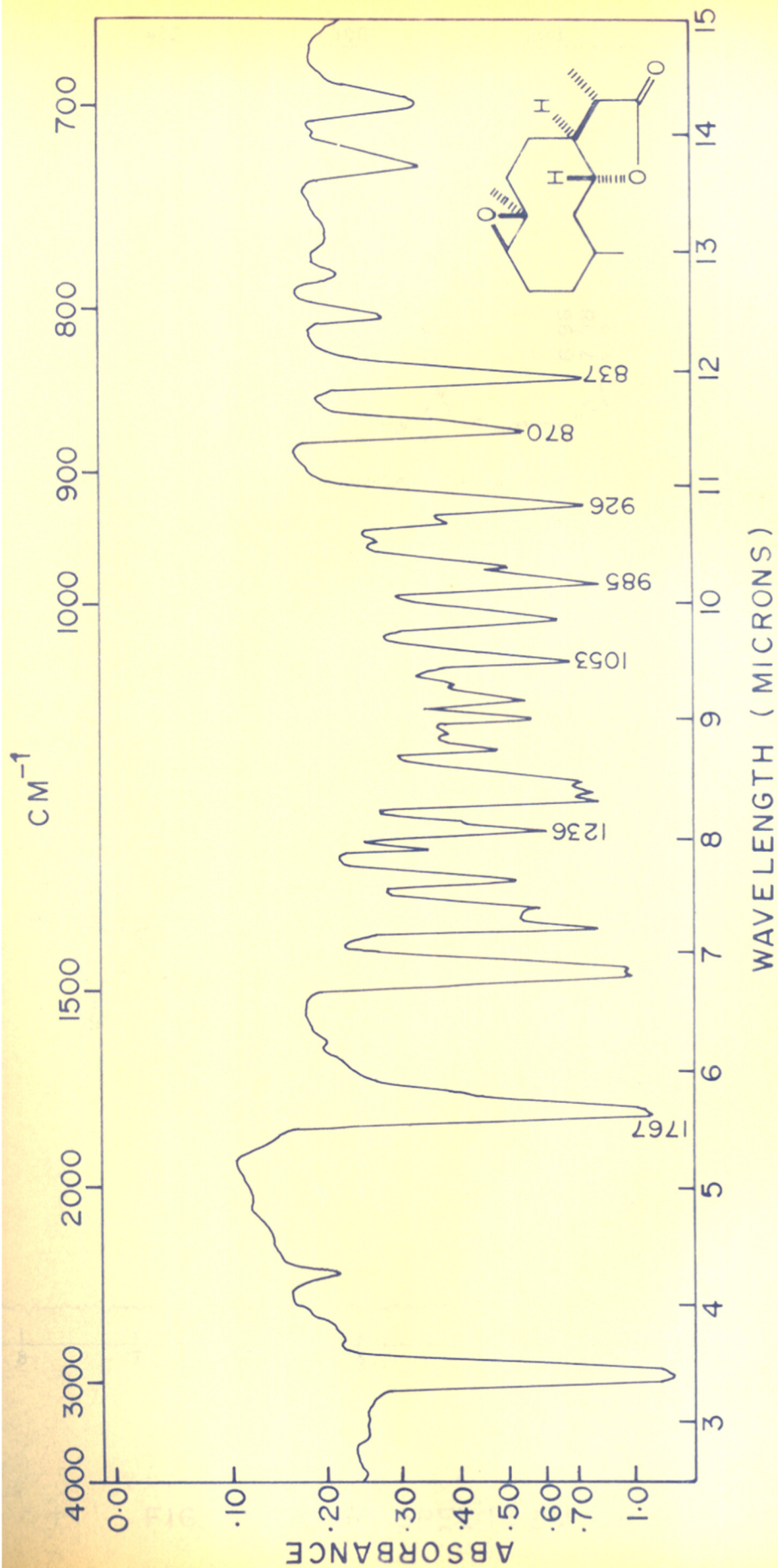


FIG. 1. IR SPECTRUM OF THE EPOXIDE

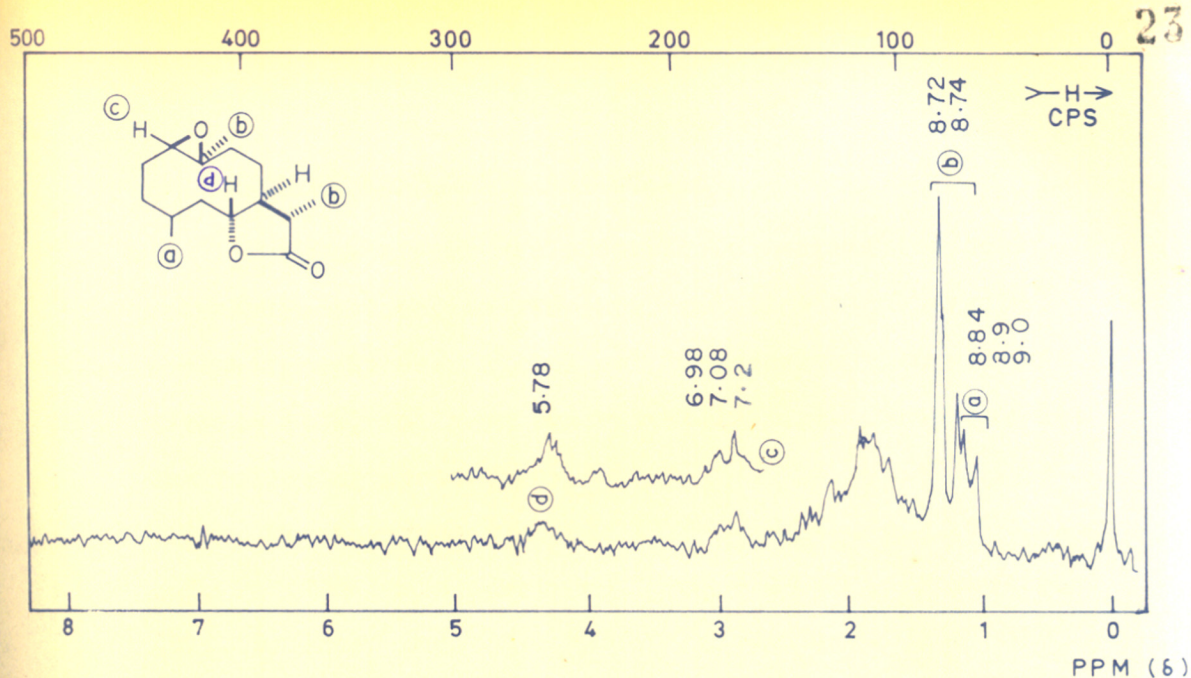


FIG. 2. NMR SPECTRUM OF THE EPOXIDE

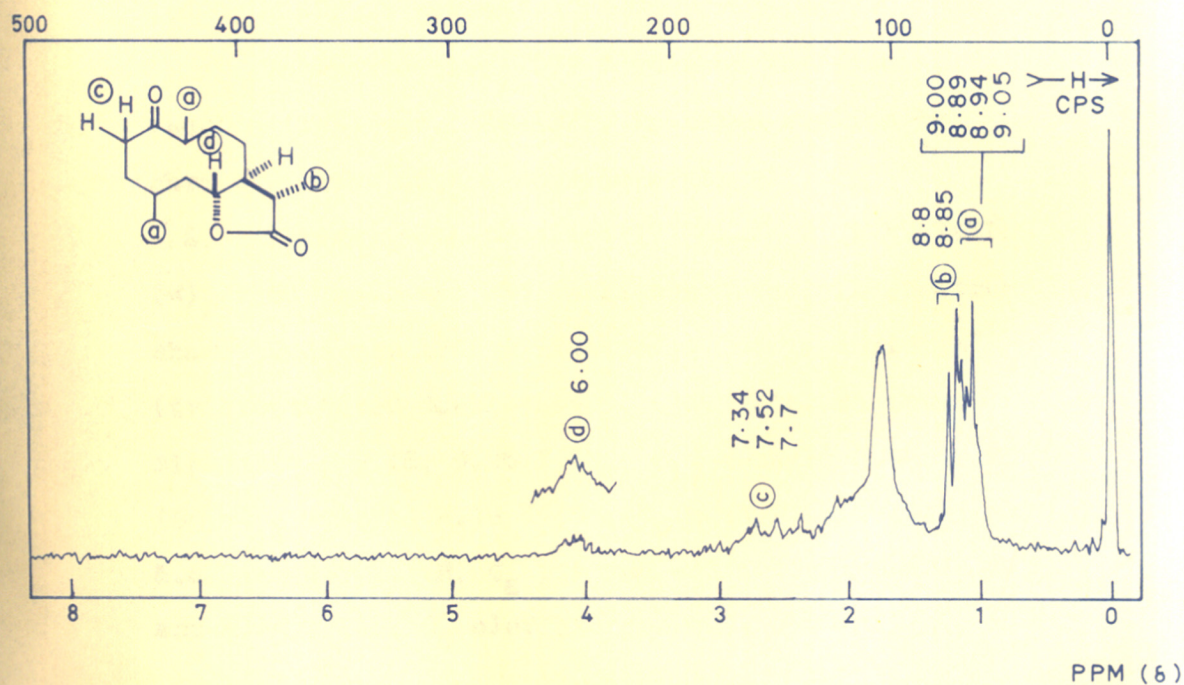


FIG. 17. NMR SPECTRUM OF THE KETOLACTONE

Isolation of tetrahydrocostunolides

Ultimately it was possible to isolate two solid tetrahydrocostunolides in pure condition by extensive chromatography over silica gel impregnated with silver nitrate (10%) followed by crystallisation. They possess the following properties:

1. Tetrahydrocostunolide (IV) $C_{15}H_{24}O_2$, m.p. 76° , mol. wt. 236 (mass spectrum), $(\alpha)_D - 14.42^{\circ}$, IR spectrum (Fig. 3) shows bands at: 1754, (γ -lactone), 1658, 820 and 804 cm^{-1} (trisubstituted double bond). NMR (Fig. 4) shows signals at: 8.97, 9.07 τ (3H, C_4 methyl) 8.75, 8.85 τ (3H, C_{11} methyl), 8.32 τ (3H, C_{10} methyl) a multiplet around 6.0 τ (1H, C_6 proton) and a triplet around 4.62 τ (1H C_1 olefinic proton).

On epoxidation (IV) furnishes the same epoxide (III) m.p. $136-137^{\circ}$, isolated earlier by chromatography of the epoxide mixture.

2. Tetrahydrocostunolide (V) $C_{15}H_{24}O_2$ m.p. 148° , $(\alpha)_D + 60^{\circ}$, mol. wt. 236 (mass spectrum), IR spectrum (Fig. 5) shows bands at: 1767 (γ -lactone), 1667 and 819 cm^{-1} (trisubstituted double bond). NMR (Fig. 6) shows signals at: 9.15, 9.25 τ (3H, C_{10} methyl) 8.88, 8.92 τ (3H, C_{11} methyl) 8.18 τ (3H, C_4 methyl) a triplet at 5.4, 5.52 and 5.7 τ (1H, C_6 proton) and a doublet at 4.67 τ and 4.84 τ (1H, C_5 olefinic proton).

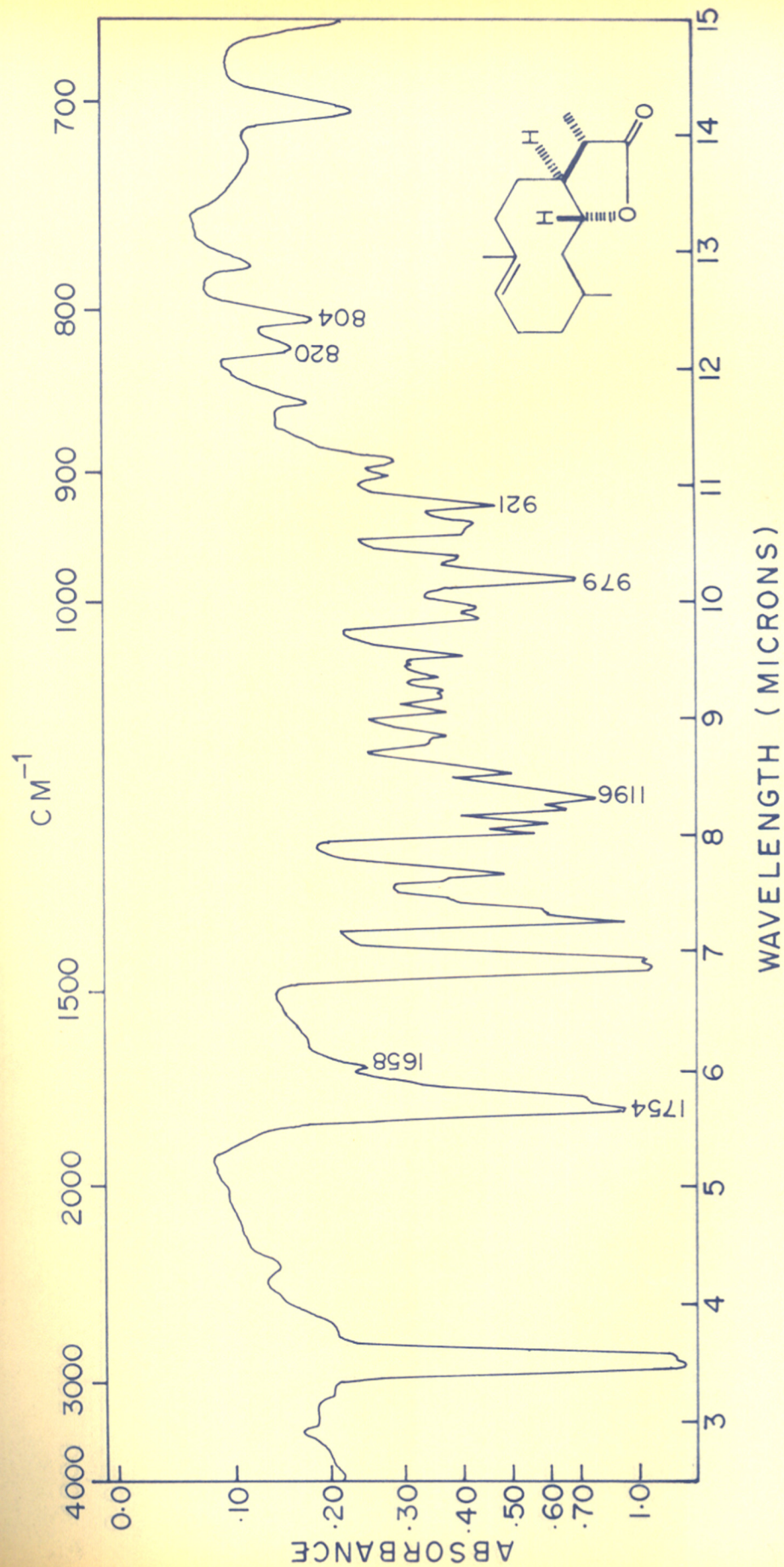


FIG. 3. IR SPECTRUM OF TETRAHYDRO COSTUNOLIDE

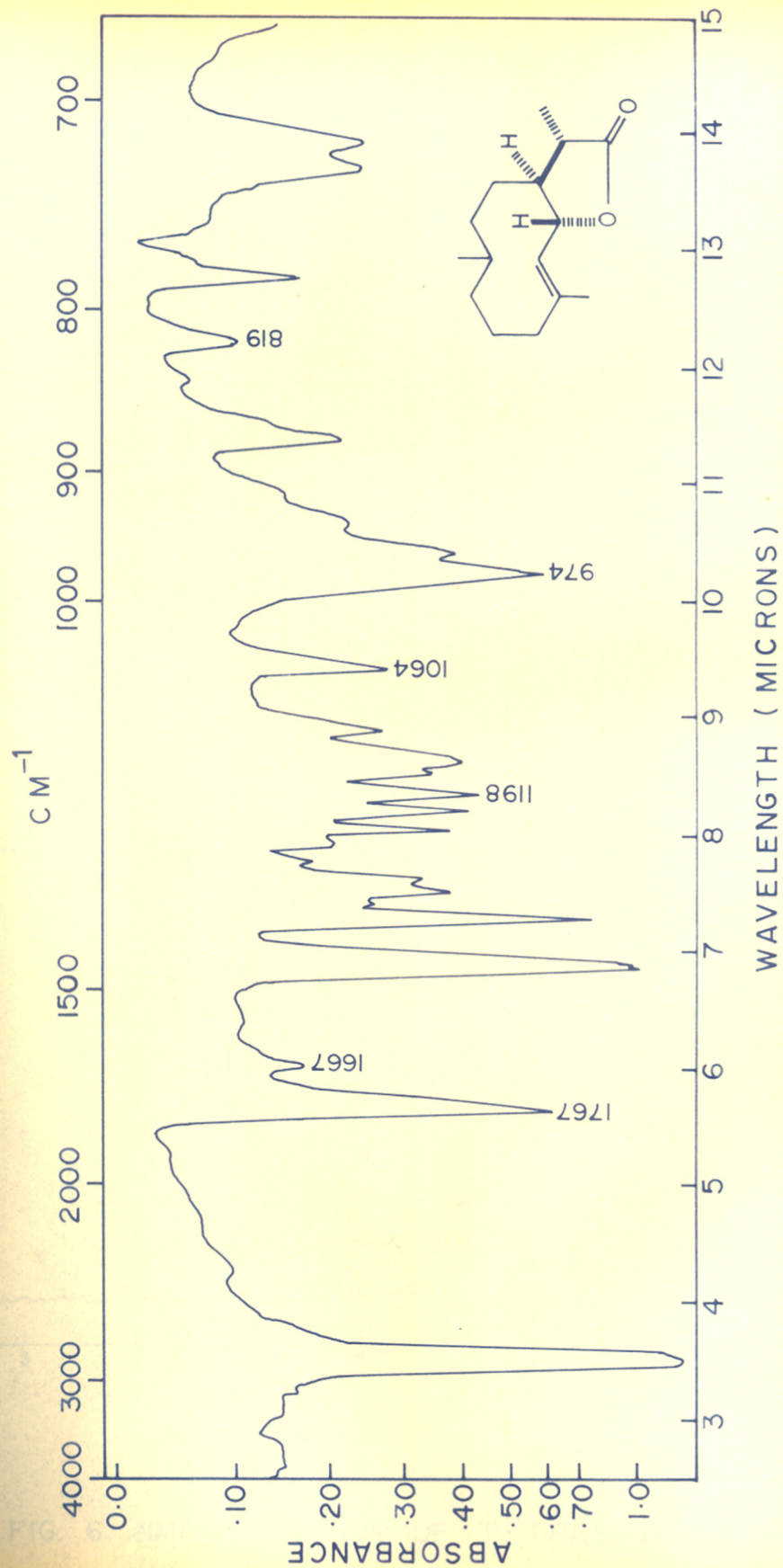


FIG. 5. IR SPECTRUM OF THE TETRAHYDROCOSTUNOLIDE

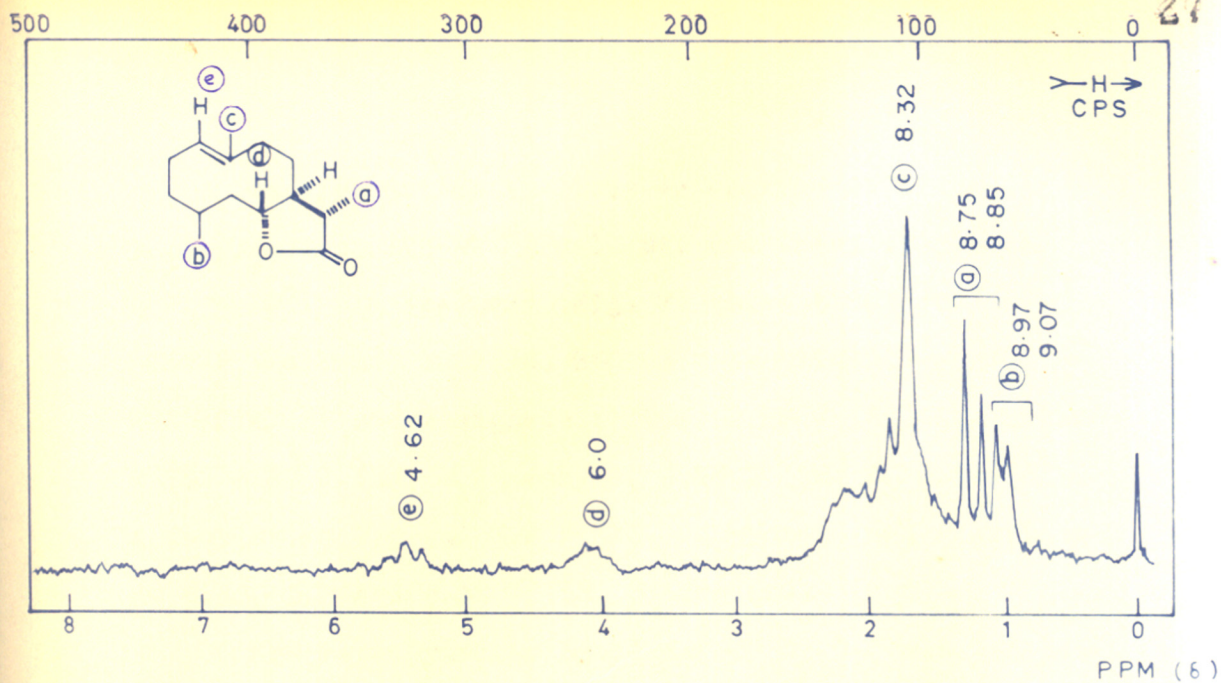


FIG. 4 . NMR SPECTRUM OF TETRAHYDROCOSTUNOLIDE

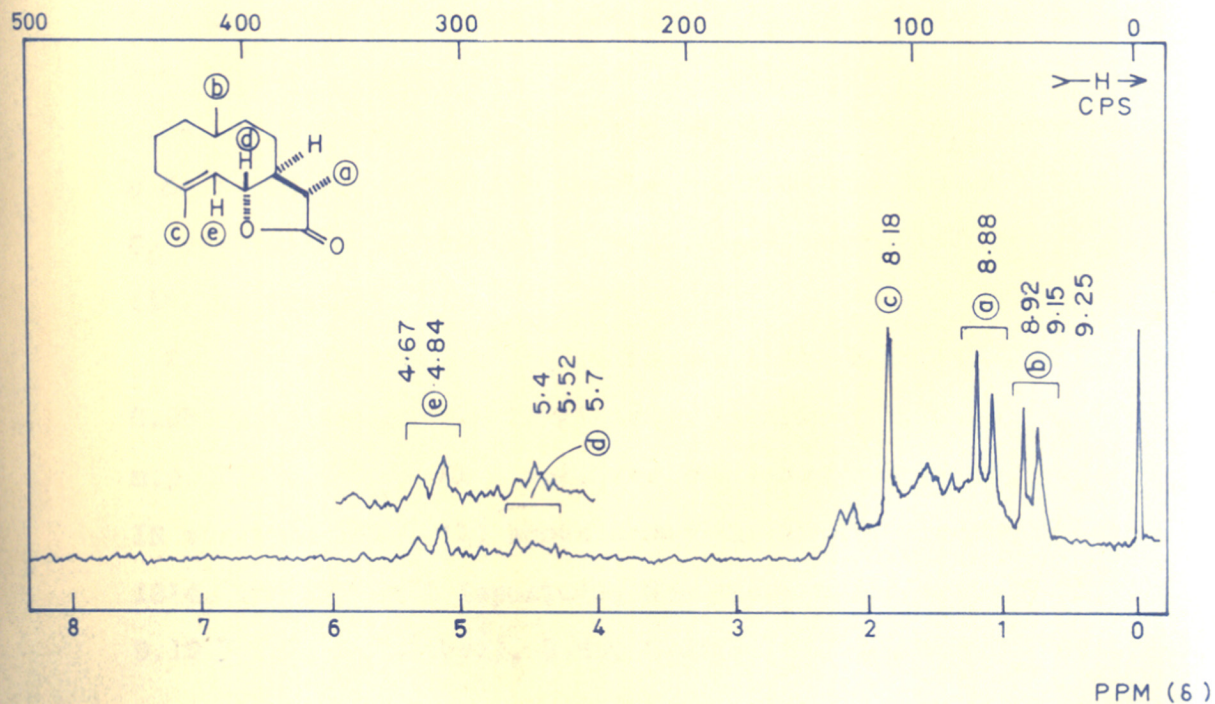


FIG. 6. NMR SPECTRUM OF TETRAHYDROCOSTUNOLIDE

On epoxidation it gives an epoxide (VI)

$C_{15}H_{24}O_3$, m.p. 176-177°, mol. wt. 252 (mass spectrum),

$(\alpha)_D - 79^\circ$. IR spectrum (Fig. 7) shows bands at:

1767 (γ -lactone) 1235 and 869 cm^{-1} (epoxide).

NMR (Fig. 8) shows signals at 9.1, 9.18 τ (3H, C_{10} methyl)

8.75, 8.85 τ (3H, C_{11} methyl), 8.55 τ (3H, C_4 methyl)

a doublet at 7.0 and 7.2 τ (1H, C_5 proton) and a triplet

at 6.13, 6.3 and 6.42 τ (1H, C_6 proton).

Now, tetrahydroparthenolide³ $C_{15}H_{24}O_3$, m.p. 146-147°,

$(\alpha)_D - 20^\circ$, obtained by complete hydrogenation of

parthenolide³ (VIII) possesses the structure (VII). The

epoxide (VI) m.p. 176-177° differs from (VII) in physical

properties but resembles it in IR and NMR spectra. IR

spectrum (Fig. 9) shows bands at: 1772 (γ -lactone) 1242

and 885 cm^{-1} (epoxide). NMR (Fig. 10) shows signals at:

9.08, 9.18 τ (3H, C_{10} methyl) 8.76, 8.88 τ (3H, C_{11} methyl),

8.54 τ (3H, C_4 methyl) a doublet at 7.06 and 7.23 τ (1H,

C_5 proton) and a triplet at 6.11, 6.27 and 6.41 τ

(1H, C_6 proton).

3. In addition, a liquid isomer (IX), b.p. 160-170°(bath)/

0.25 mm is isolated. It gives an epoxide (X), $C_{15}H_{24}O_3$,

m.p. 175°, $(\alpha)_D - 81^\circ$, mol. wt. 252 (mass spectrum),

IR spectrum (Fig. 11) shows bands at: 1754 (γ -lactone)

1214, and 877 cm^{-1} (epoxide); NMR shows signals at: 9.01,

9.10 τ (3H, C_4 methyl), 8.68, 8.81 τ (6H, C_{10} and C_{11} methyls)

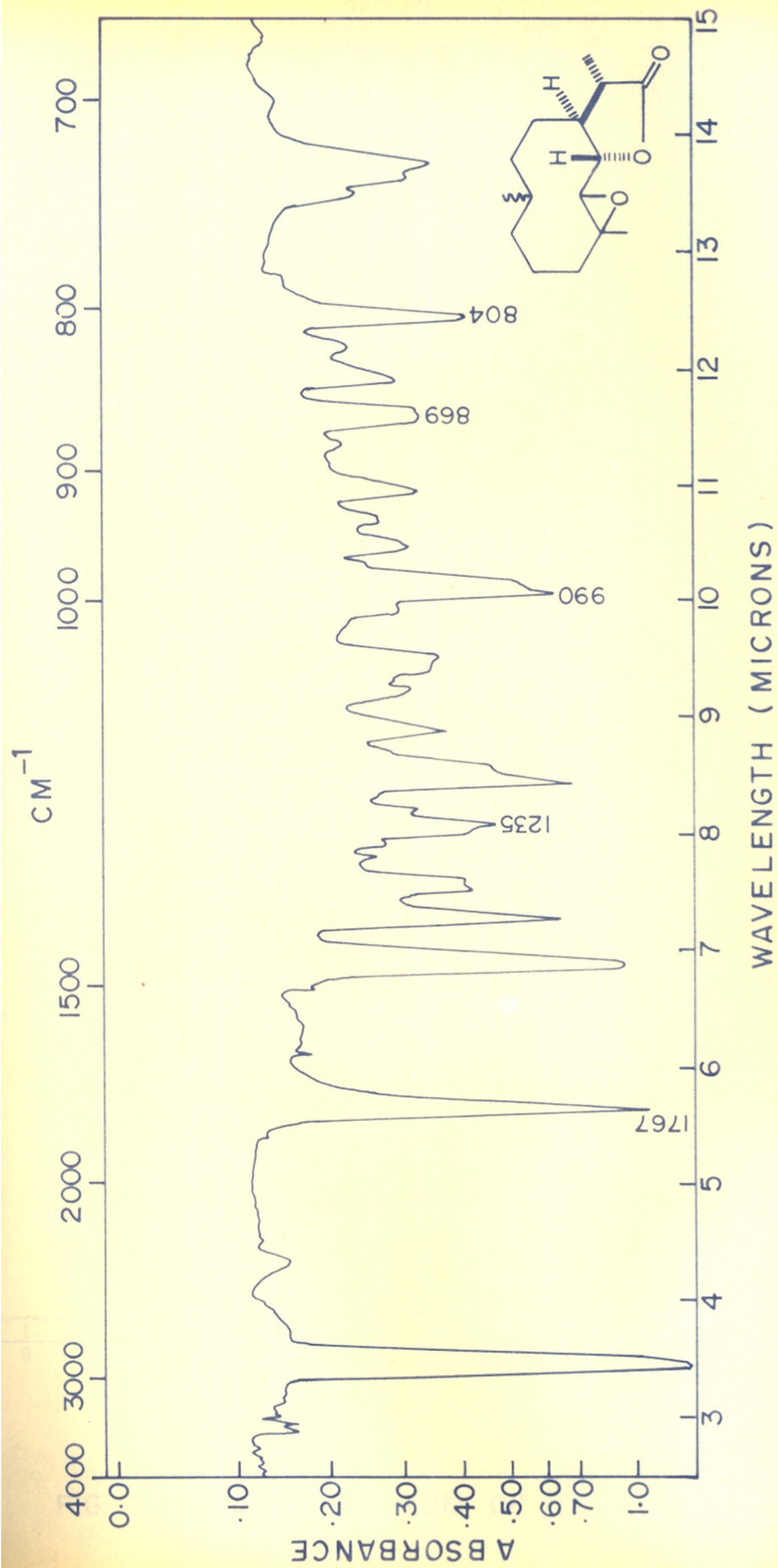


FIG. 7. IR SPECTRUM OF THE EPOXIDE

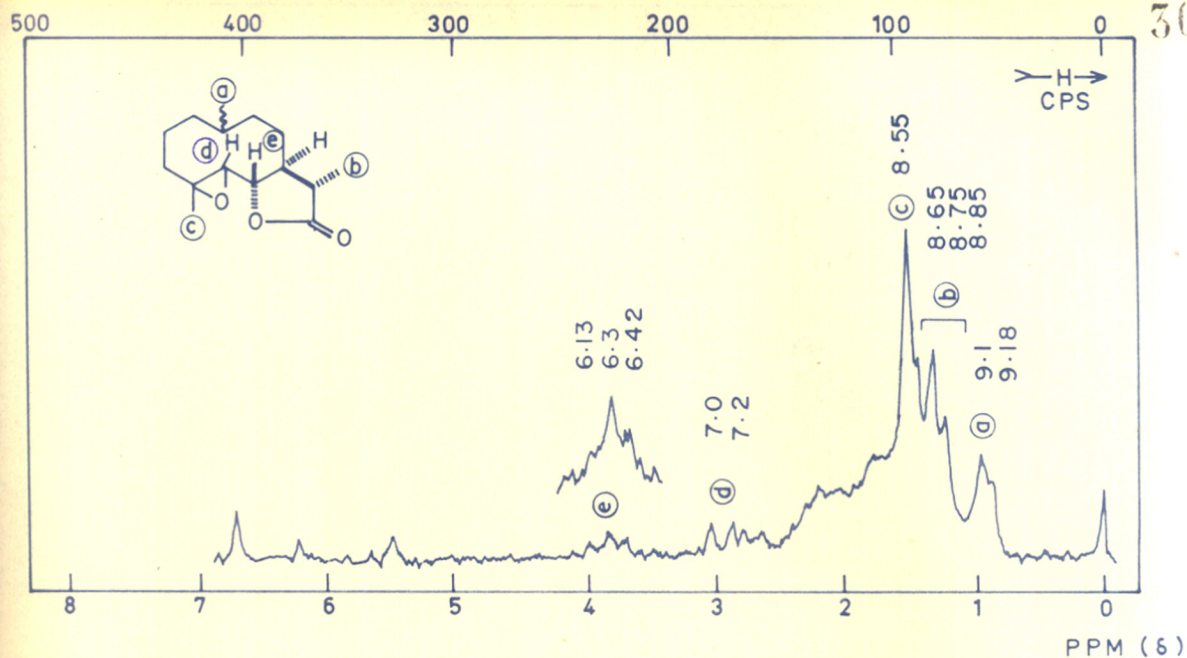


FIG. 8 . NMR SPECTRUM OF THE EPOXIDE

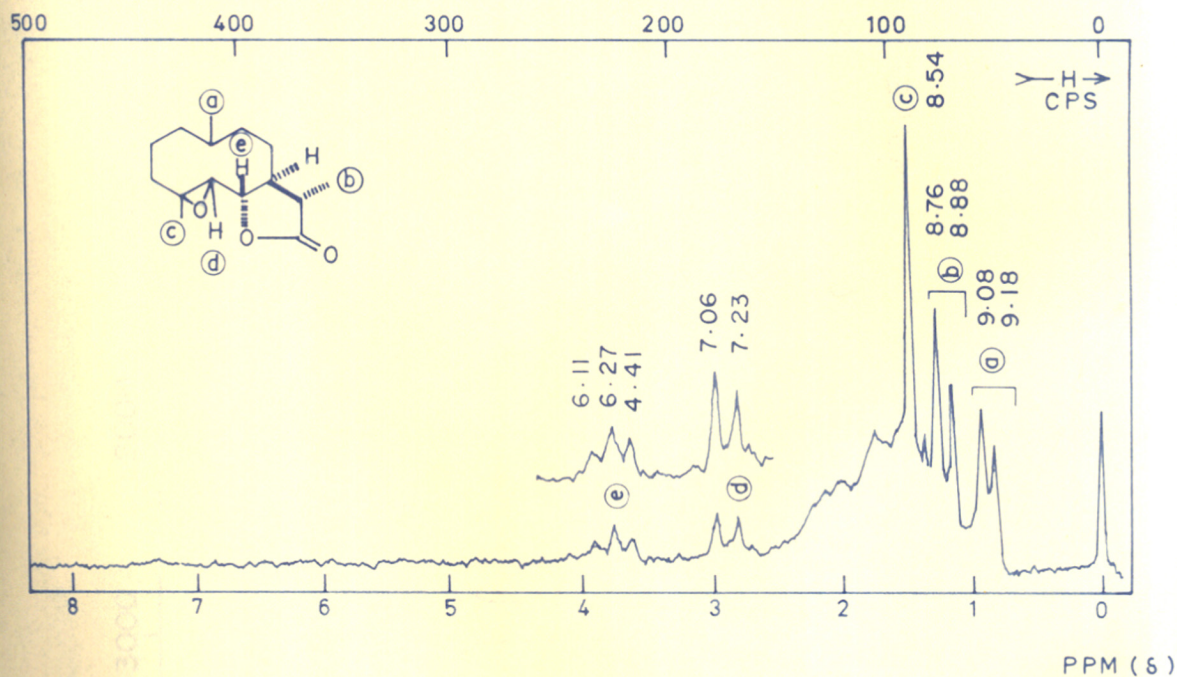


FIG. 10 . NMR SPECTRUM OF TETRAHYDROPARTHENOLIDE

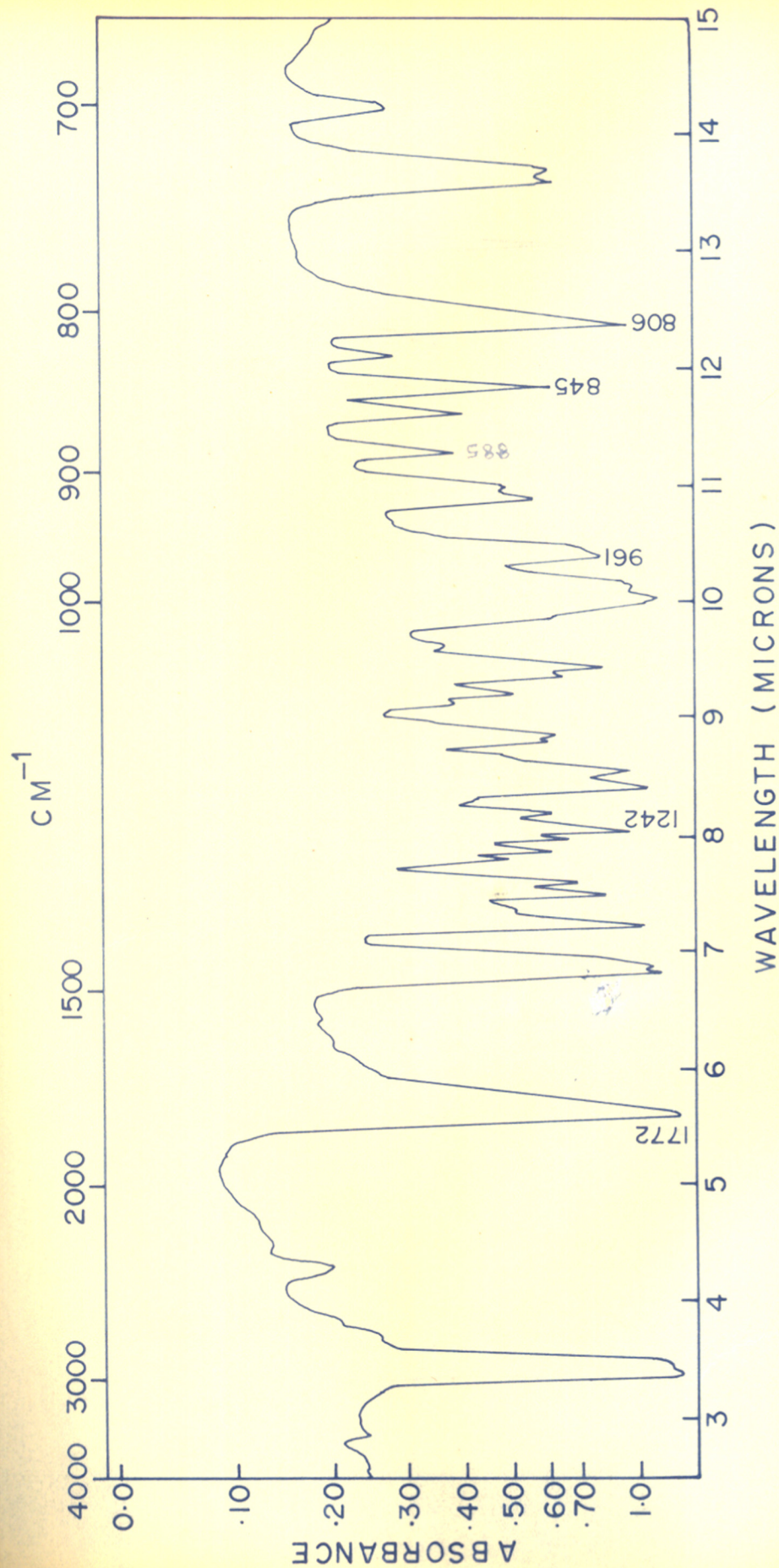


FIG. 9 . IR SPECTRUM OF THE TETRAHYDROPARTHENOLIDE

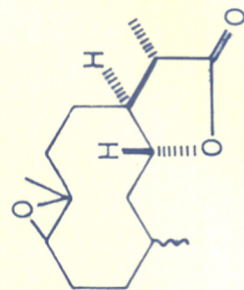
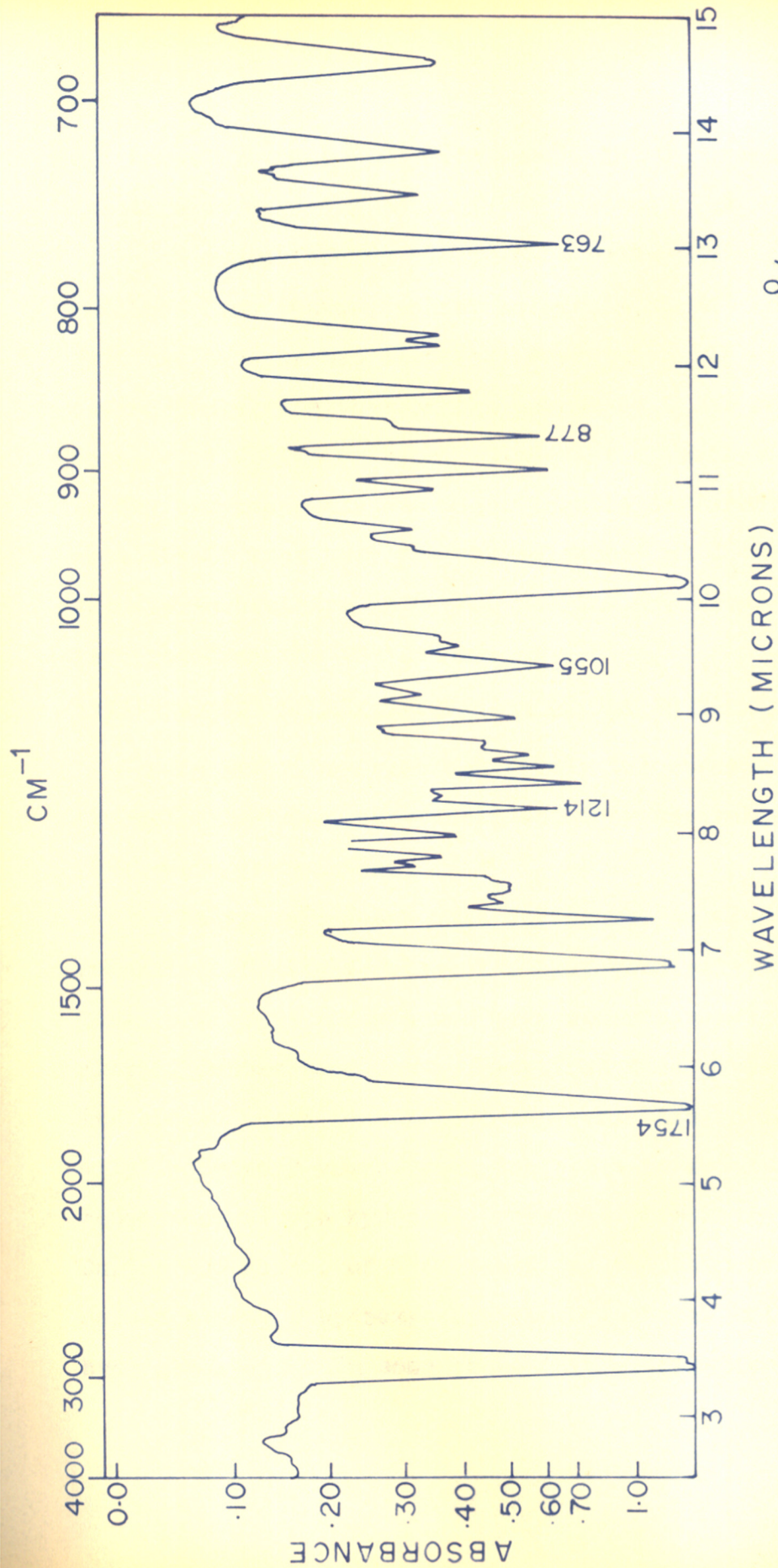


FIG. 11. IR SPECTRUM OF THE EPOXIDE

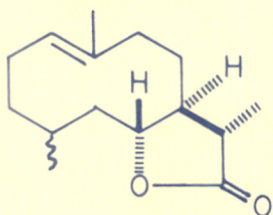
a triplet at 7.04, 7.22 and 7.42 τ (1H, C_1 proton) and a multiplet around 5.64 τ (1H, C_6 proton).

A comparison of the above epoxide (X) with that obtained from tetrahydrocostunolide, m.p. 76° indicates that the two possess identical structures but differ in stereochemistry either of the methyl at C_4 or of the epoxide at C_1-C_{10} or both. Since the C_4 methyl signals in the two compounds are significantly different, it is more likely that they are stereoisomers at C_4 . As regards the stereochemistry at C_1-C_{10} nothing definite can be inferred from the NMR spectra.

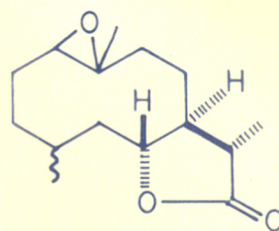
Establishment of the structures of the tetrahydrocostunolides

In order to establish firmly the structures of the two solid tetrahydrocostunolides, they are subjected to metal-amine reduction.

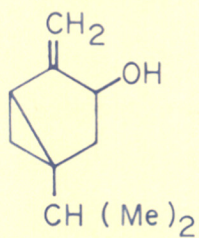
It is well known that during the metal-amine reduction of allylic alcohols, hydrogenolysis takes place⁴. Sometimes it is accompanied by a rearrangement of the allylic double bond⁴; e.g. d-sabinol (XI) gives α -thujene(XII). It is also known that γ -lactones containing a potential allylic hydroxy group, when subjected to metal-amine reduction undergo hydrogenolysis and give rise to acids⁵. During the course of this reaction, the lactone ring is opened giving a hydroxy-acid ion which then suffers hydrogenolysis. In some cases this elimination of the



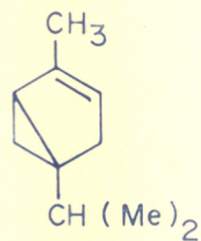
(IX)



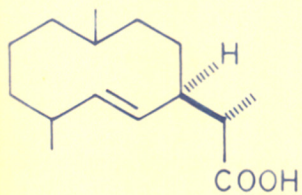
(X)



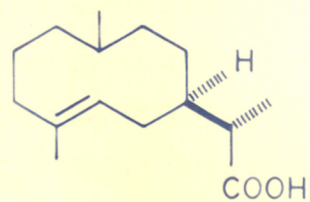
(XI)



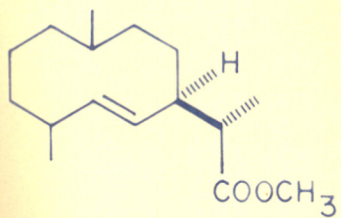
(XII)



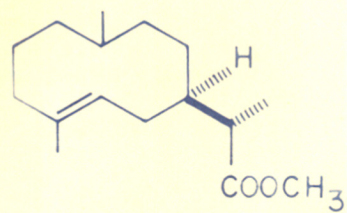
(XIII)



(XIV)



(XV)



(XVI)

allylic hydroxy group is also accompanied by migration of the allylic double bond⁶.

When tetrahydrocostunolide (V), m.p. 148° is subjected to metal-amine reduction, it gives a mixture of two acids (XIII and XIV) which are separated by chromatography of their methyl esters (XV and XVI) over silica gel impregnated with silver nitrate (10%).

The ester (XV), $C_{16}H_{28}O_2$, possesses the following properties: b.p. 170-180°(bath) at 1 mm, $(\alpha)_D + 42^\circ$, $n_D^{29} 1.4752$, IR spectrum (Fig. 12) shows bands at: 1748 (ester), 997 cm^{-1} (trans disubstituted double bond). This value is somewhat high for a trans disubstituted double bond. Such a high value is also observed in Humulene-dioxide⁷. Presence of disubstituted double bond is established from the NMR data which shows presence of two olefinic protons at C_5-C_6 . NMR spectrum (Fig. 13) shows signals at: 9.12, 9.22 τ (3H; C_{10} methyl) 8.9, 9.02 τ (3H; C_4 methyl) 8.69, 8.79 τ (3H; C_{11} methyl) 6.4 τ (3H, ester methyl) and a triplet at 4.5, 4.6 and 4.65 τ (2H, C_5 and C_6 protons).

The ester (XVI), $C_{16}H_{28}O_2$, possesses the following properties: b.p. 120-130°(bath)/0.25 mm, $(\alpha)_D + 23.5^\circ$, $n_D^{29} 1.4793$; IR spectrum (Fig. 14) shows bands at: 1730 (ester) and 841 cm^{-1} (trisubstituted double bond);

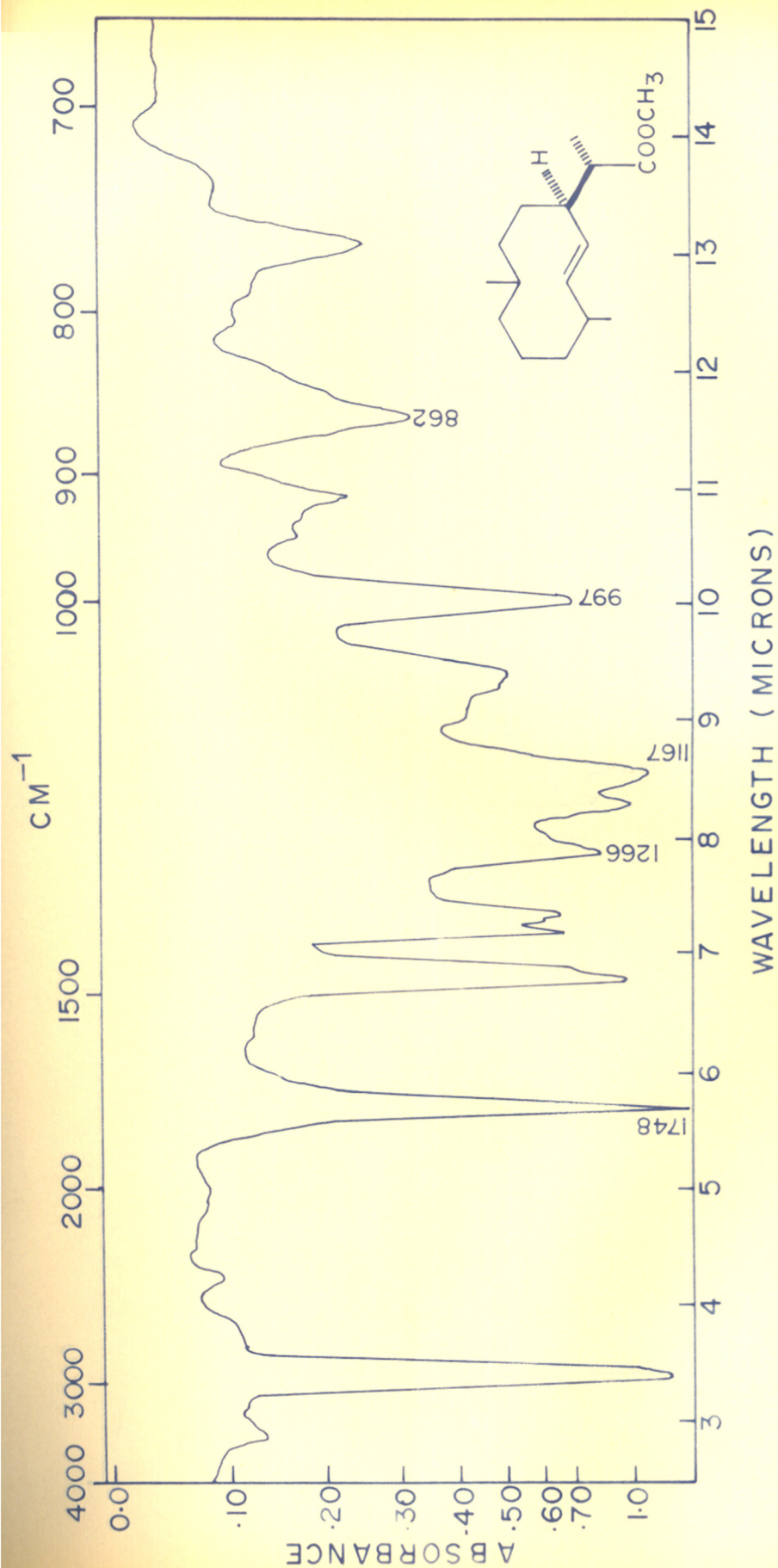


FIG. 12 . IR SPECTRUM OF THE ESTER

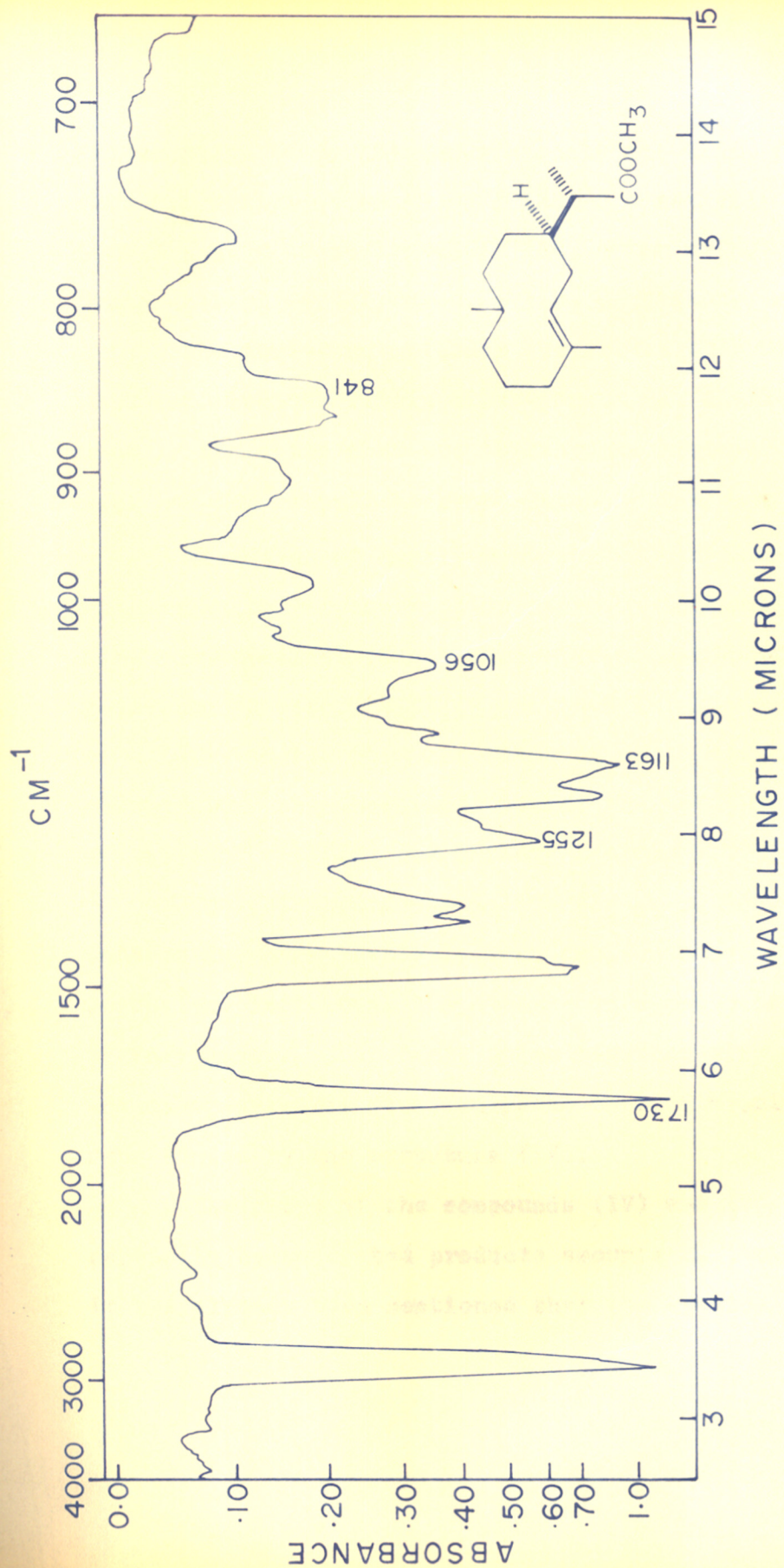


FIG. 14 . IR SPECTRUM OF THE ESTER

NMR spectrum (Fig. 15) shows signals at: 9.18, 9.3 τ (3H; C₁₀ methyl) 8.86, 8.98 τ (3H; C₁₁ methyl) 8.37 τ (3H; C₄ methyl) 6.39 τ (3H, ester methyl) and broad doublet at 4.7 and 4.84 τ (1H, C₅ proton).

The formation of these two esters by hydrogenolysis with and without allylic migration of the double bond clearly indicates that the tetrahydrocostunolide, m.p. 147-148^o should be represented by the structure (V).

Migration of double bond during hydrogenolysis is well-known in the costunolide series. Thus when dihydrocostunolide (I) is subjected to metal-amine reduction an acid (XVII) is obtained in which the migration of allylic double bond has taken place⁵. Similar observations have been made during the metal-amine reduction of the diol⁶ (XVIII) and methoxy lactone⁸ (XIX).

The tetrahydrocostunolide (IV) m.p. 76^o, does not undergo any hydrogenolysis when subjected to metal-amine reduction, indicating the absence of a potential allylic hydroxy group. This fact, taken together with the IR and other spectral data, suggests that it should be represented by the structure (IV).

The ratio of the compounds (IV) and (V) in the partially hydrogenated products amounts to about 8:1. It has already been mentioned that the epoxide of (IV)

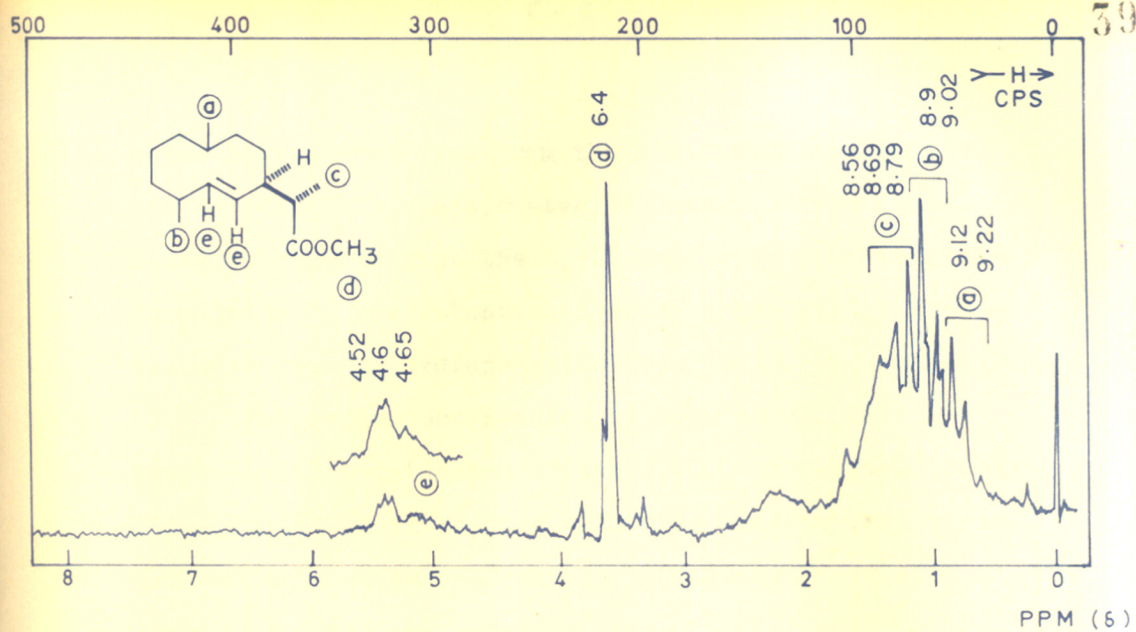


FIG. 13. NMR SPECTRUM OF THE ESTER

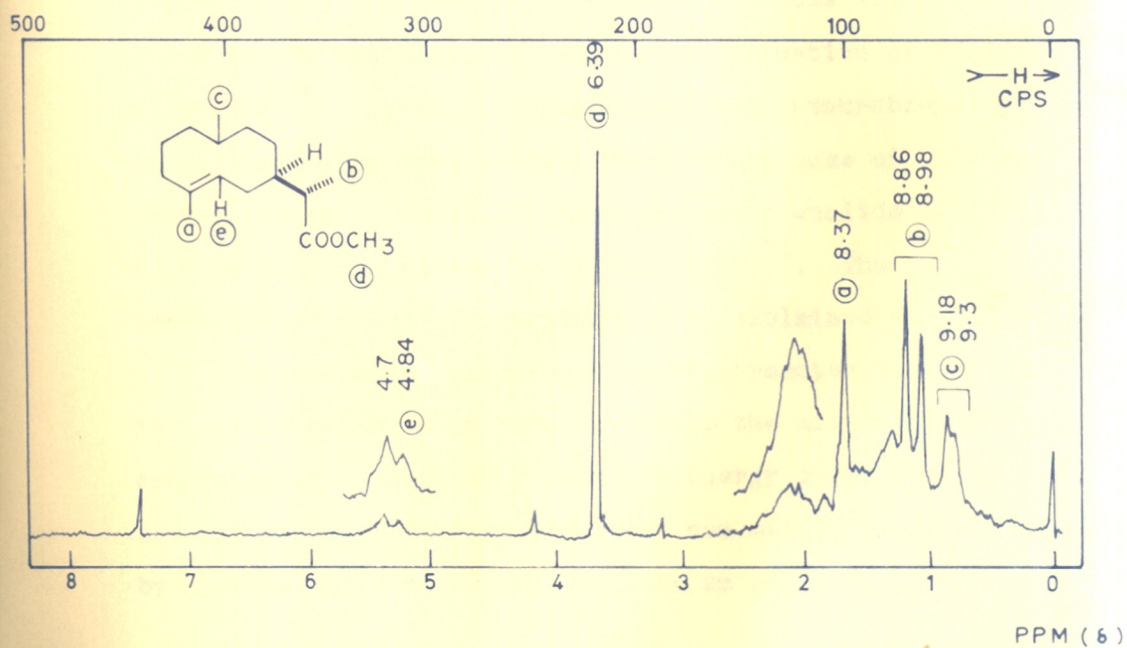


FIG. 15. NMR SPECTRUM OF THE ESTER

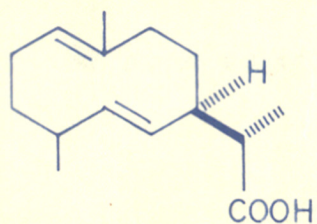
could be isolated even from the mixture of epoxides of the partially hydrogenated products. These facts clearly indicate that the C_4-C_5 double bond in (I), which is allylic to the potential hydroxy group at C_6 , is more reactive towards hydrogenation than the C_1-C_{10} double bond.

The recent observation of Sorm et al.² that a preferential epoxidation of the C_1-C_{10} double bond takes place in (I) is in keeping with this observation, since double bonds which are readily hydrogenated are slow towards epoxidation and vice versa.

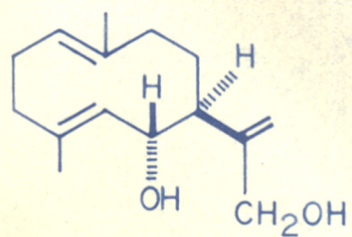
Borontrifluoride rearrangement of epoxides

It is well known that epoxides derived from steroids and terpenoids give rise to ketones on treatment with borontrifluoride⁹. In some cases allylic alcohols are formed in place of the ketones; for example the formation of (XXV) from (VII)¹⁰. Further if conditions are favourable, ring closure may also take place. Thus in the case of dihydroparthenolide (XXIV) the hydroxyguaianolide (XXIII) is formed by the action of BF_3 on (XXIV)¹¹. The mechanism of these rearrangements are explained as follows.

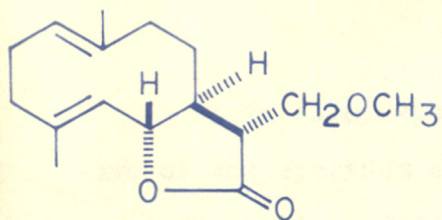
The powerful electrophilic BF_3 promotes considerable ionisation of the bond from oxygen to the more alkylated carbon centre. Depending upon the energy paths available, the intermediate represented below can either yield a ketone by hydride shift as at (a), or lose an adjacent proton



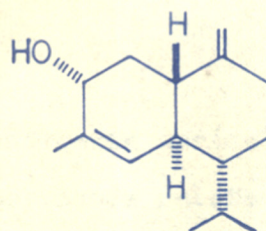
(XVII)



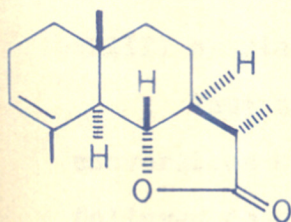
(XVIII)



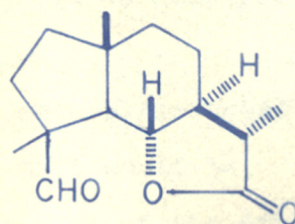
(XIX)



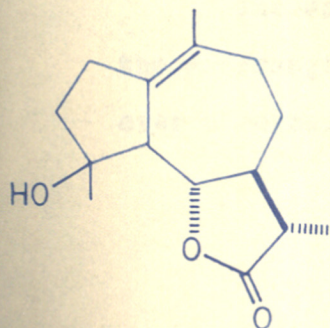
(XX)



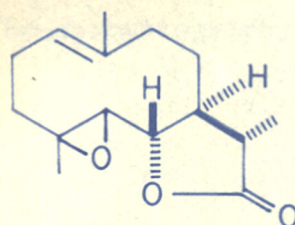
(XXI)



(XXII)

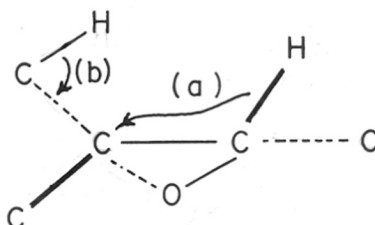


(XXIII)



(XXIV)

as shown at (b) to give an allylic alcohol.



It is also reported in the cadinenic series¹² that some of the epoxides derived from compounds related to (XX), under the action of BF_3 , rearrange to ring-contracted aldehydes instead of the normal expected ketones. Similarly α -cyclodihydrocostunolide (XXI), belonging to the selinenic series, has been found to form an aldehyde (XXII) by ring contraction¹².

Thus there are several limiting factors for these conversions and the course of reactions that would be followed depends upon the nature and position of the double bond from which the epoxy compound is derived.

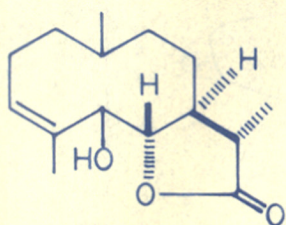
Borontrifluoride rearrangement of epoxide (III)

The epoxide (III) is treated with BF_3 -etherate and the rearranged products are separated by chromatography over alumina.

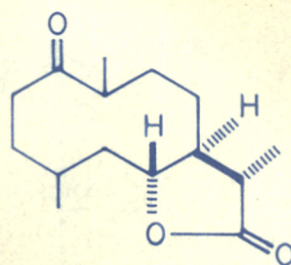
The earlier fractions of chromatography furnish a solid, $C_{15}H_{24}O_3$, m.p. 88° , $(\alpha)_D + 21^\circ$, mol.wt. 252 (mass spectrum), which is found to be a ketolactone (XXVI) from IR spectrum. IR Spectrum (Fig. 16) shows bands at: 1764 (γ -lactone), 1695 cm^{-1} ($>C=O$). NMR spectrum (Fig. 17) shows signals at: 8.89 , 8.94 , 9.00 , $9.05\text{ } \tau$ (6H; methyls at C_4 and C_{10}) 8.8 and $8.85\text{ } \tau$ (3H; methyl at C_{11}) 7.34 , 7.52 , $7.7\text{ } \tau$ (2H; C_2 methylene protons) and a multiplet around $6.0\text{ } \tau$ (1H; C_6 proton).

The later fractions of chromatography furnish another solid, $C_{15}H_{24}O_3$, m.p. 160° , $(\alpha)_D - 123.3^\circ$, mol. wt. 252 (mass spectrum). This is indicated to be a hydroxylactone (XXVII) according to IR spectrum. IR spectrum (Fig. 18) shows bands at: 3546 ($-OH$), 1764 (γ -lactone) and 1639 cm^{-1} (trisubstituted double bond). NMR spectrum (Fig. 19) shows signals at: $8.28\text{ } \tau$ (3H; C_{10} methyl) 8.73 , $8.85\text{ } \tau$ (3H; C_{11} methyl) 9.0 , $9.05\text{ } \tau$ (3H; C_4 methyl) a triplet around $5.66\text{ } \tau$ (1H; C_1 proton) a quartet centered at $5.14\text{ } \tau$ (1H; C_6 proton) and a triplet centered at $4.6\text{ } \tau$ (1H; olefinic proton at C_9).

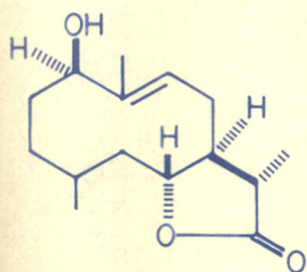
Chromic acid oxidation of the hydroxylactone (XXVII) affords a conjugated ketolactone (XXVIII), $C_{15}H_{22}O_3$, m.p. 138° , $(\alpha)_D + 0^\circ$. IR Spectrum (Fig. 20) shows bands at: 1764 (γ lactone) 1681 (conju. $>C=O$), 1653 and



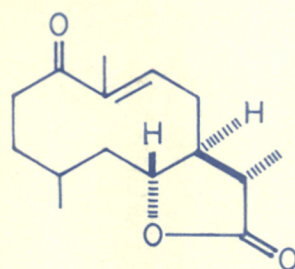
(XXV)



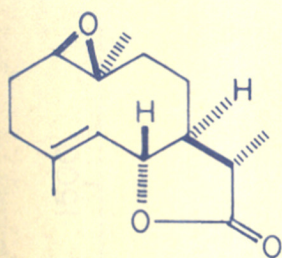
(XXVI)



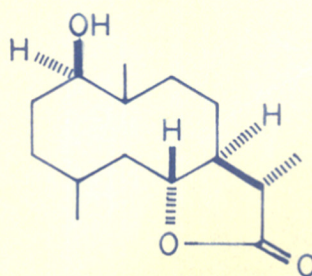
(XXVII)



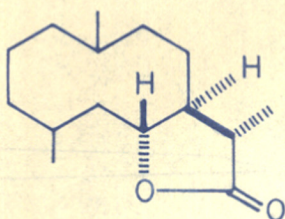
(XXVIII)



(XXIX)



(XXX)



(XXXI)

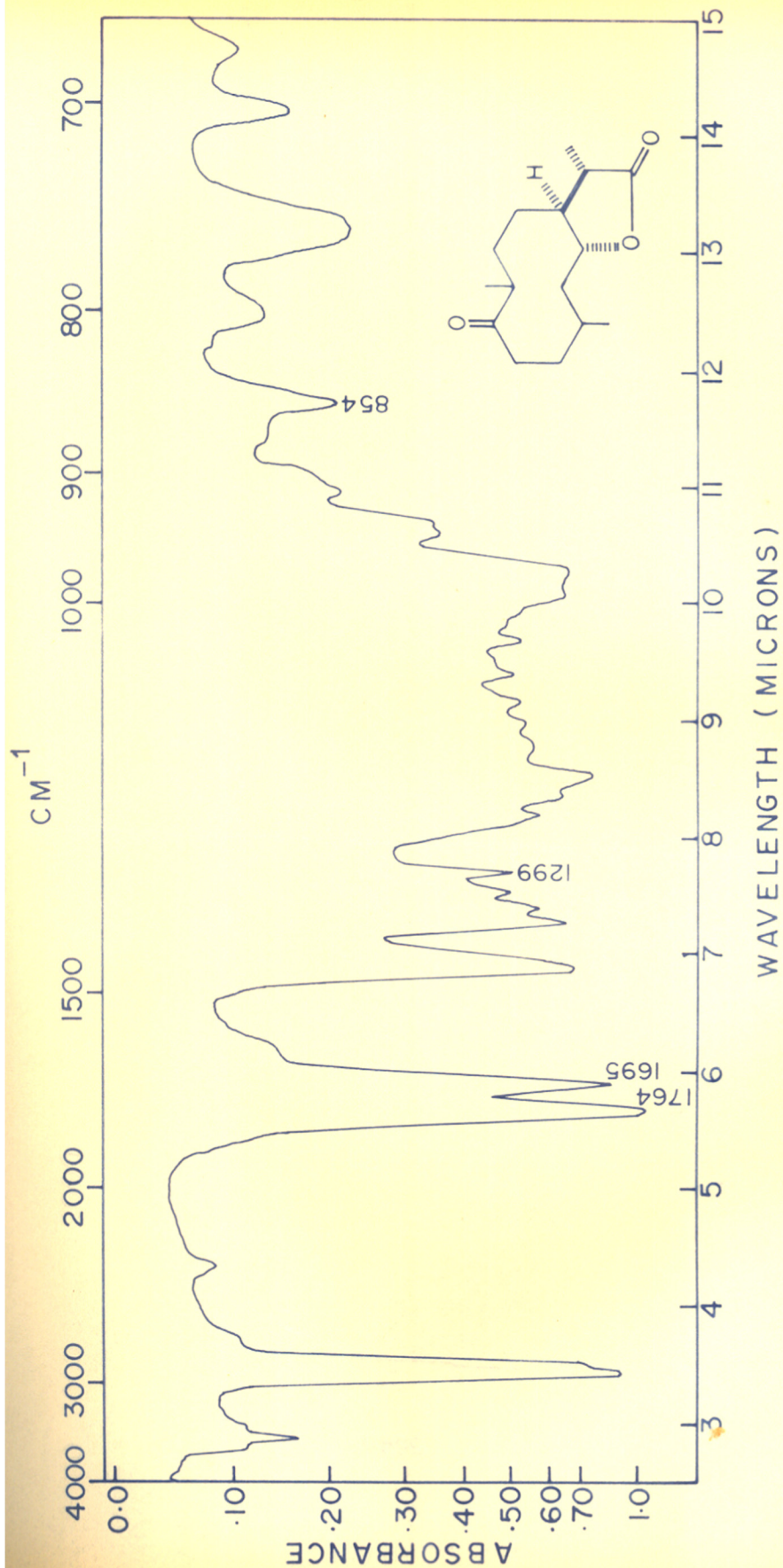


FIG. 16. IR SPECTRUM OF THE KETOLACTONE

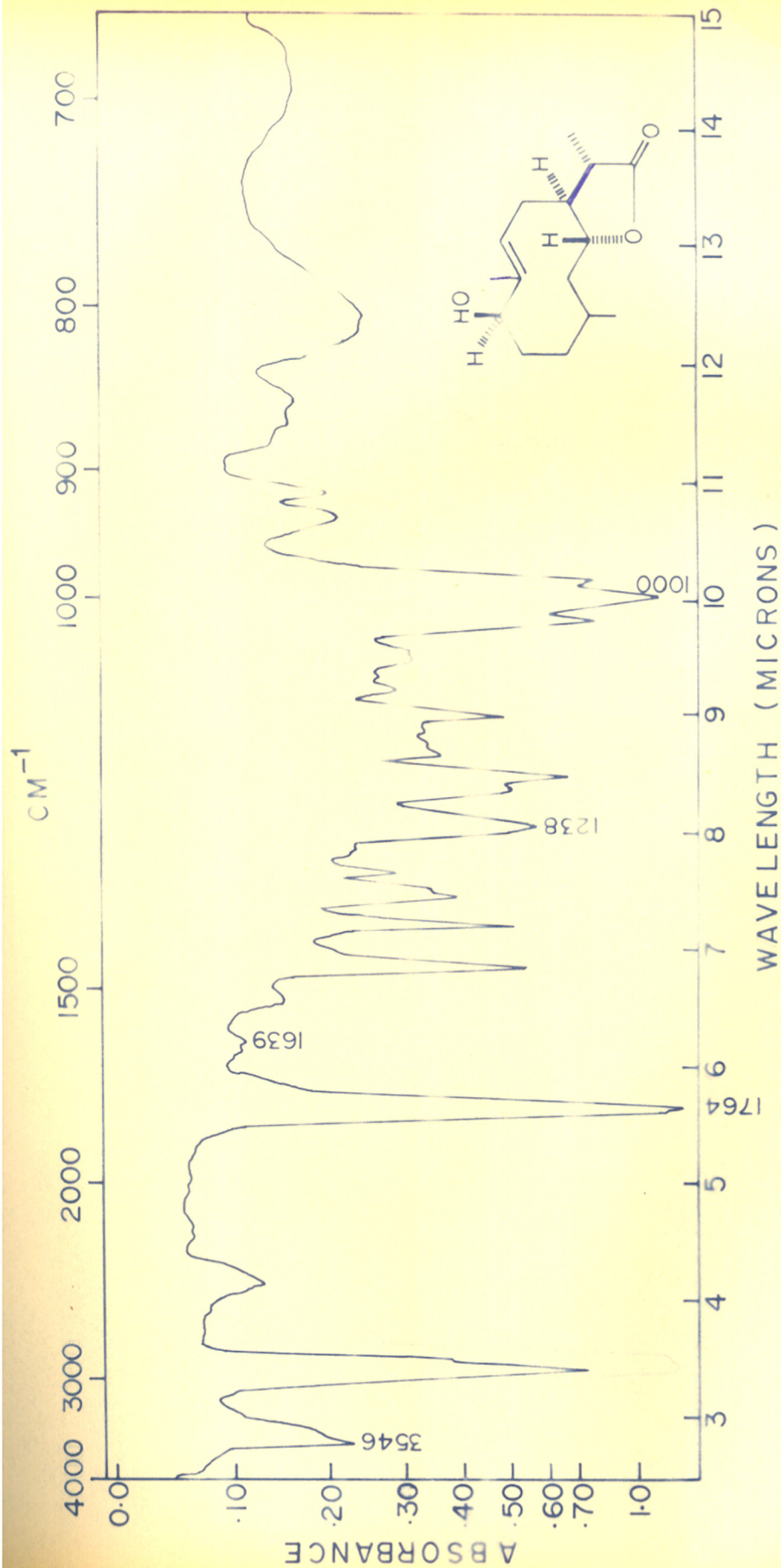


FIG. 18. IR SPECTRUM OF THE HYDROXYLACTONE

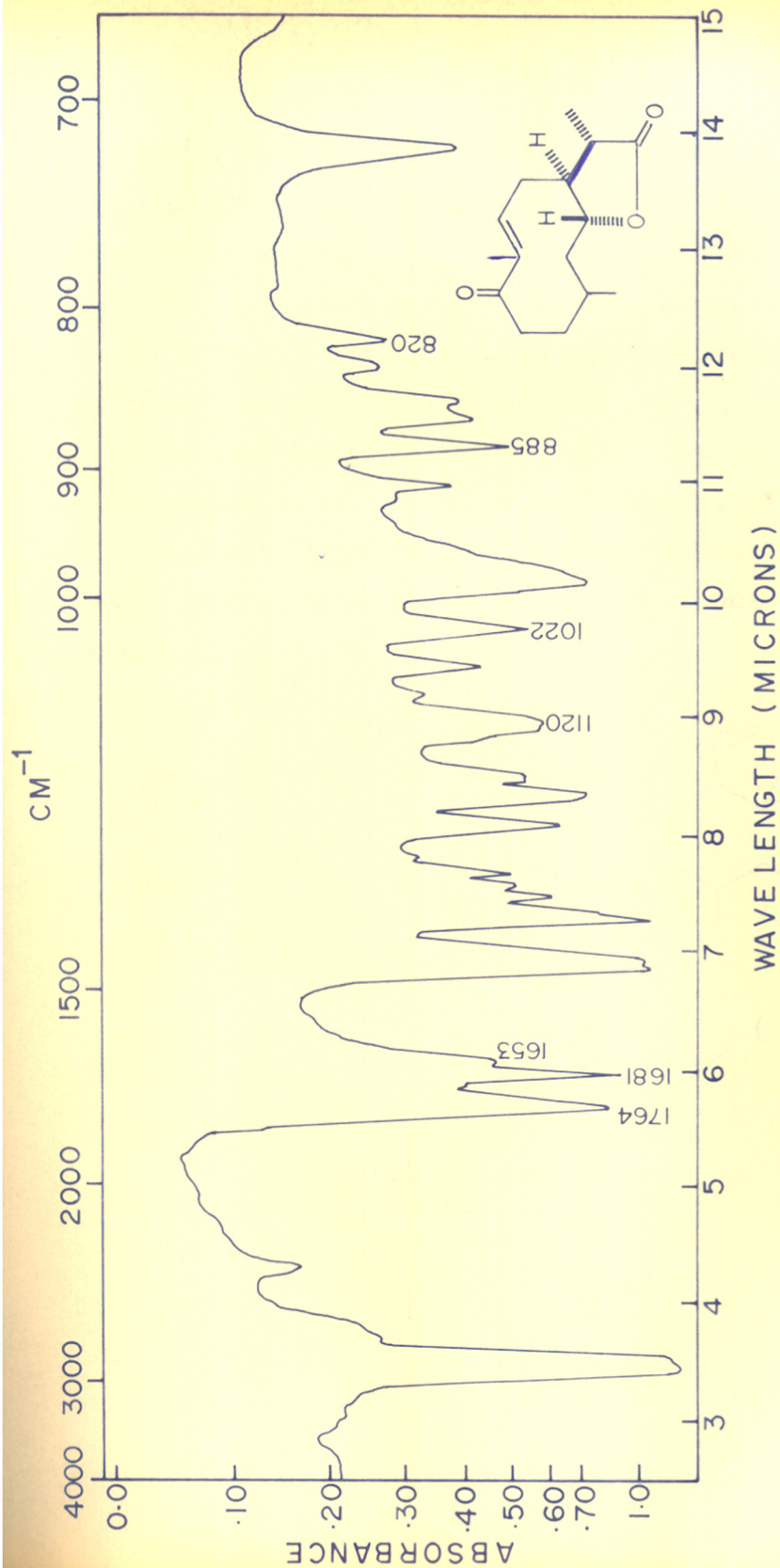
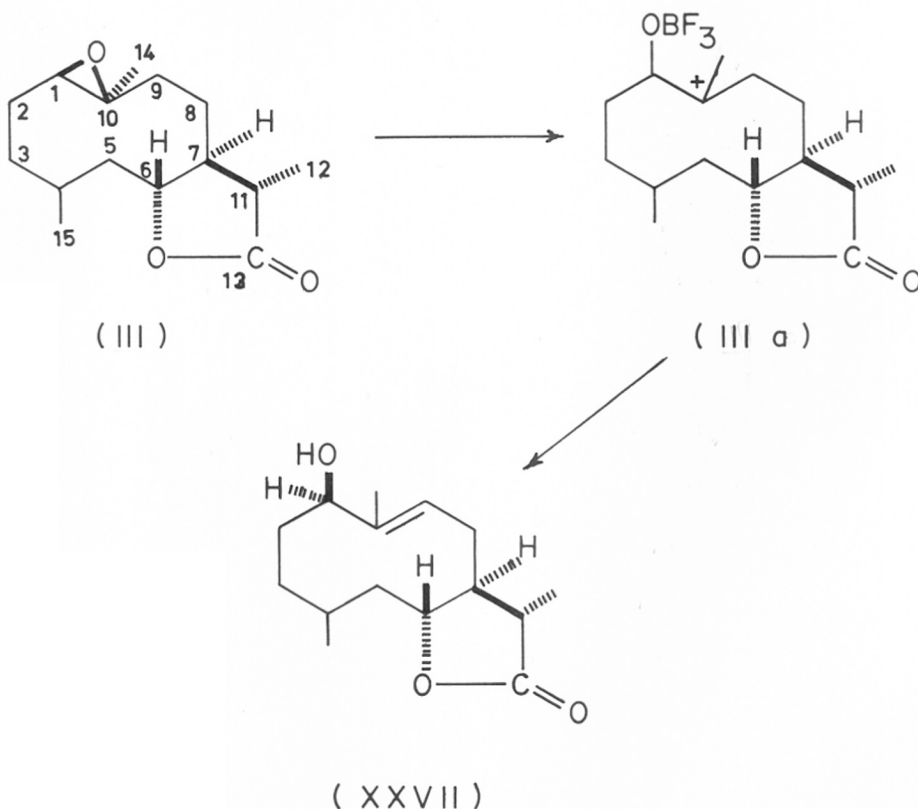


FIG. 20. IR SPECTRUM OF THE CONJUGATED KETOLACTONE

820 cm^{-1} (trisubstituted double bond). NMR spectrum (Fig. 21) shows signals at: 8.76, 8.86, 8.96 τ (6H; methyls at C_4 and C_{11}) 8.08 τ (3H; C_{10} methyl) a multiplet around 5.84 τ (1H; C_6 proton) and a triplet around 4.46 τ (1H; olefinic proton at C_9). In the UV spectrum it shows λ_{max} 230 $\text{m}\mu$, ϵ_{max} 3500.

During the formation of (XXVII) from (III) the bond connecting the oxygen to C_{10} is cleaved giving rise to a carbonium ion on C_{10} as in IIIa. This is then stabilised by the formation of a $\text{C}_{10}-\text{C}_9$ double bond to give (XXVII).



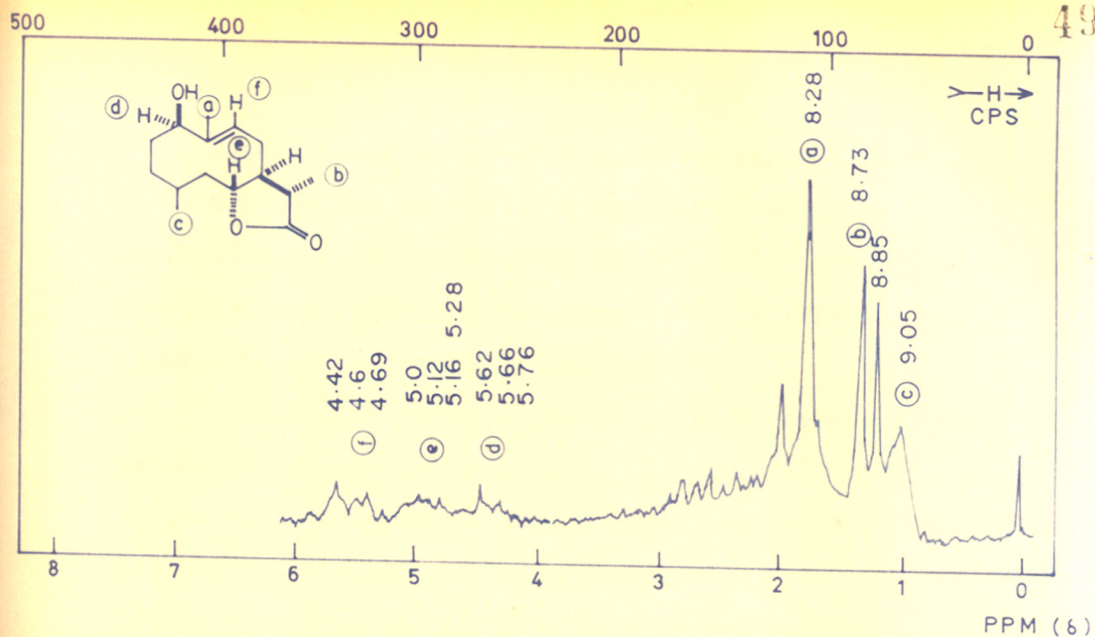


FIG. 19. NMR SPECTRUM OF THE HYDROXYLACTONE

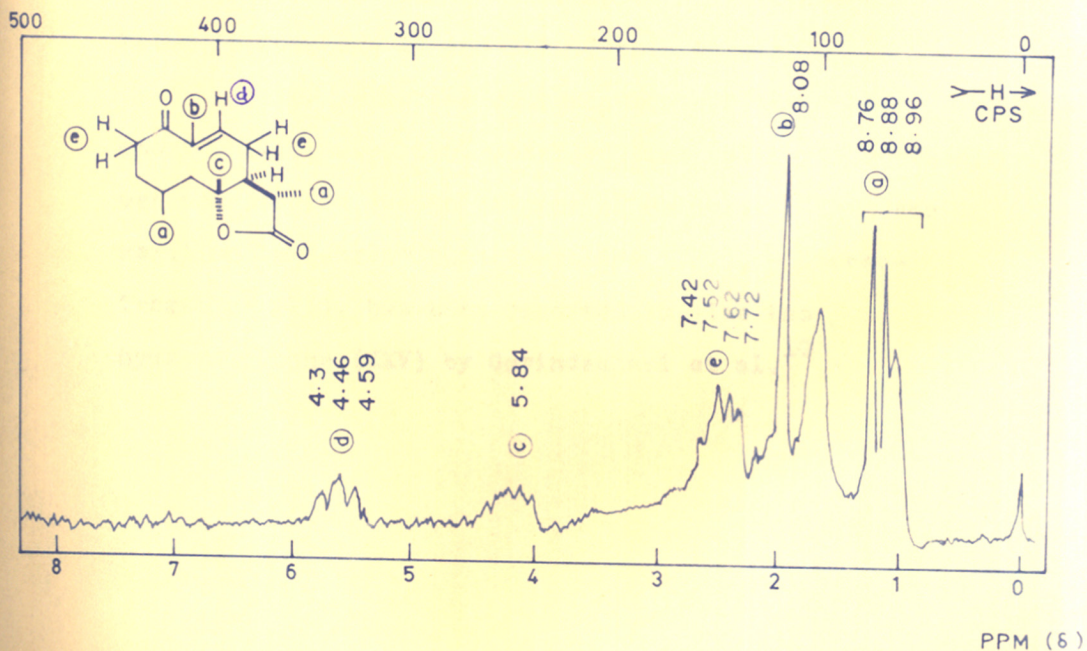


FIG. 21. NMR SPECTRUM OF THE CONJUGATED KETOLACTONE

Since the stereochemistry of the epoxide ring at C₁-C₁₀ and its mode of cleavage by BF₃ etherate in (III) and epoxydihydrocostunolide² (XXIX) are expected to be the same, the hydroxy group at C₁ in (XXVII) appears to be β-oriented by analogy.

Catalytic hydrogenation of (XXVII) gives a liquid saturated hydroxy lactone (XXX), C₁₅H₂₆O₃ (TLC single spot), (α)_D - 38°. IR spectrum showed bands at: 33448 (-OH), 1754 cm⁻¹ (γ-lactone). It is accompanied by hexahydrocostunolide (XXXI) formed by hydrogenolysis.

Oxidation of (XXX) by Jones' chromic acid reagent yields the same ketolactone (XXVI), m.p. 88°.

Further evidences regarding the structures of (IV) and (V) based on NMR and mass spectral data are described later in Chapters II and III of this thesis.

The BF₃ etherate rearrangement of the other epoxide (VI), m.p. 175° obtained from tetrahydrocostunolide was not studied, due to paucity of material. The same reaction on tetrahydroparthenolide (VII), a stereoisomer of (VI), has been reported to give the hydroxylactone (XXV) by Govindachari et al.¹⁰

EXPERIMENTAL

Partial hydrogenation of dihydrocostunolide (I) to tetrahydrocostunolide and preparation of epoxide (III)

Dihydrocostunolide (I, 4.0 g) in ethyl alcohol (100 ml) was hydrogenated using PtO_2 (150 mg). Hydrogenation was stopped after absorption of 460 ml of hydrogen at N.T.P., corresponding to 1.01 moles. The catalyst was filtered, alcohol was removed under suction and residue taken up in ether. The ether layer was washed with sodium carbonate solution, followed by water and dried (Na_2SO_4). Removal of ether furnished a liquid (3.92 g) (mixture of tetrahydrocostunolides).

To the liquid (3.92 g) dissolved in chloroform (7 ml) a chloroform solution of perbenzoic acid (2.5 N; 20 ml, 1.5 moles) was added and the mixture kept at -15° for 48 hours. After dilution with chloroform (50 ml) it was extracted with sodium bicarbonate solution (calculated quantity), to remove the acids, washed with water and dried (Na_2SO_4). After removal of chloroform the residue (4.0 g) was chromatographed on neutral alumina (120 g; grade III) and eluted as follows:

Fr.No.	Solvent	Volume in ml	Weight in g
1	Hexane + benzene 2:1	200	0.56
2	Hexane + benzene 1:1	200	0.36
3	Benzene	200	1.02
4	Chloroform	200	0.65
5	Ether	200	0.36
6	Methyl alcohol	200	0.47

Fraction 3, when crystallised from ether-hexane mixture (10:1) gave (III), (0.38 g); m.p. 136-137°, (α)_D - 85° (c, 1.34), mol. wt. 252 (mass spectrum).

Analysis

Found: C, 71.34; H, 9.66%.

$C_{15}H_{24}O_3$ requires: C, 71.31; H, 9.59%.

IR Spectrum (Fig. 1) showed bands at: 2907, 1767, 1462, 1379, 1348, 1307, 1263, 1236, 1202, 1111, 1087, 1053, 1012, 985, 926, 870, 837, 807, 730 and 700 cm^{-1} .

Extensive chromatography of tetrahydrocostunolide over neutral alumina

Tetrahydrocostunolide mixture (3.8 g) was chromatographed on neutral alumina (190 g; grade II) and eluted as follows:

Fr.No.	Solvent	Volume in ml	Weight in g
1	Hexane	400	0.01
2	Hexane + Benzene 4:1	500	0.01
3	Hexane + benzene 3:1	200	0.38
4	" "	300	0.46
5	Hexane + benzene 2:1	100	0.34
6	" "	100	0.24
7	" "	250	0.34
8	Hexane + benzene 1:1	150	0.26
9	" "	100	0.20
10	Benzene	200	0.74
11	"	200	0.42
12	Ether	200	0.13

Fractions: 1, 2 and 3 - TLC ($\text{SiO}_2 + \text{AgNO}_3$) single spot.

Fractions: 4 to 9 - Two spots on TLC ($\text{SiO}_2 + \text{AgNO}_3$)

Fractions: 11 and 12 - TLC ($\text{SiO}_2 + \text{AgNO}_3$) single spot.

Fractions 4 to 9 (1.8 g) were rechromatographed on neutral alumina (90.0 g; grade I) and eluted as follows:

Fr.No.	Solvent	Volume in ml	Weight in g
1	Hexane + benzene 3:1	100	0.02
2	" "	100	0.21
3	" "	100	0.15
4	" "	100	0.12
5	" "	100	0.06
6	Hexane + benzene 2:1	100	0.16
7	" "	100	0.14
8	" "	150	0.10
9	" "	200	0.07
10	Hexane + benzene 1:1	150	0.11
11	" "	150	0.07
12	" "	200	0.05
13	" "	250	0.04
14	Benzene	200	0.03
15	Ether	400	0.03

Fractions: 1 to 11 - Two spots on TLC ($\text{SiO}_2 + \text{AgNO}_3$)

Fractions: 12 to 15 - single spot on TLC ($\text{SiO}_2 + \text{AgNO}_3$)

Epoxidations of fractions 2 to 11

To the fractions 2 to 11 (1.2 g) dissolved in chloroform (4 ml) a chloroform solution of perbenzoic acid (2.5 N; 6 ml, 1.5 moles) was added and mixture

kept at -15° for 48 hours. It was worked up as in the above epoxide. Removal of chloroform gave a liquid (0.134 g) which was chromatographed on neutral alumina (60 g; grade II) and eluted as follows:

Fr.No.	Solvent	Volume in ml	Weight in g
1	Hexane + benzene 2:1	200	0.36
2	Hexane + benzene 1:1	200	0.31
3	Benzene	200	0.47
4	Chloroform	150	0.13

Fractions 2 and 3 were crystallised from ether-hexane mixture (10:1) to furnish a solid (0.25 g), m.p. $136-137^{\circ}$, mixed m.p. with above epoxide (III) showed no depression.

Separation of tetrahydrocostunolides by chromatography over silica gel/silver nitrate

Tetrahydrocostunolide mixture (11.0 g) was chromatographed on silica gel (165 g) impregnated with silver nitrate (16.5 g) and eluted as follows:

Fr.No.	Solvent	Total volume in ml	Weight in g
1	Hexane + benzene 2:1	1000	2.65
2	Hexane + benzene 1:1	1500	2.35
3	Benzene	1000	2.64
4	Ether	700	2.95

Fraction 1 was purified by chromatography and distillation to give a liquid isomer (IX), TLC single spot. B.p. $160-170^{\circ}$ (bath)/0.25 mm; $(\alpha)_D - 38^{\circ}$ (c, 2.77), $n_D^{24} 1.4933$.

Analysis

Found: C, 75.95; H, 10.65%

$C_{15}H_{24}O_2$ requires: C, 76.22; H, 10.21%.

IR Spectrum showed bands at: 2941, 1786, 1660, 1460, 1385, 1340, 1235, 1190, 998, 977, 937 and 890 cm^{-1} .

Fraction 2 was crystallised from hexane. On cooling at -15° a solid separated (0.15 g, V).

m.p. $147-148^{\circ}$, $(\alpha)_D + 60^{\circ}$ (c, 1.97)

mol. wt. 236 (mass spectrum)

Analysis

Found: C, 76.67; H, 10.24%.

$C_{15}H_{24}O_2$ requires: C, 76.22; H, 10.21%.

IR Spectrum (Fig. 5) showed bands at: 2887, 1767, 1667, 1451, 1370, 1332, 1248, 1217, 1198, 1159, 1124, 1064, 974, 961, 880, 819, 784, 729 and 719 cm^{-1} .

Fraction 3 was crystallised from hexane. On cooling at 0° a solid (1.2 g, IV) was obtained; m.p. 76° , $(\alpha)_D - 14.42^{\circ}$ (c, 2.63), mol. wt. 236 (mass spectrum).

Analysis

Found: C, 76.21; H, 9.82%

$C_{15}H_{24}O_2$ requires: C, 76.22; H, 10.21%

IR Spectrum (Fig. 3) showed bands at: 2857, 1754, 1653, 1449, 1370, 1299, 1242, 1227, 1209, 1196, 1164, 1125, 1099, 1043, 1010, 1000, 979, 961, 921, 900, 890, 820, 804 and 704 cm^{-1} .

Epoxidation of liquid tetrahydrocostunolide (IX)

To the liquid tetrahydrocostunolide (0.86 g) dissolved in chloroform (2 ml), a chloroform solution of perbenzoic acid (2.7N; 5 ml, 1.5 moles) was added and mixture kept at 0° for 72 hours and worked up as ^{for} above epoxide. After removal of chloroform, the residue (0.72 g) was chromatographed on neutral alumina (24 g; grade II) and eluted as follows:

Fr.No.	Solvent	Volume in ml	Weight in g
1	Hexane	150	0.09
2	Hexane + benzene 2:1	200	0.38
3	Hexane + benzene 1:1	200	0.03
4	Benzene	200	0.09
5	Chloroform	200	0.05
6	Ether	150	0.01

Fraction 4 when crystallised from ether-hexane (10:1) mixture furnished a solid (X) m.p. 175° , $(\alpha)_D - 81^\circ$ (c, 2.5), mol. wt. 252 (mass spectrum).

IR Spectrum (Fig. 11) showed bands at: 2941, 1754, 1449, 1370, 1282, 1250, 1214, 1183, 1163, 1111, 1055, 990, 943, 912, 900, 877, 847, 820, 813, 763, 742, 722 and 685 cm^{-1} .

Epoxidation of tetrahydrocostunolide (V)

To the tetrahydrocostunolide (0.17 g) dissolved in chloroform (1 ml), a chloroform solution of perbenzoic acid (2N; 2 ml; 1.5 moles) was added and mixture kept at 0° for 60 hours and then worked up as usual to give a solid (0.17 g). This was crystallised from acetone-hexane (1:2); m.p. $176-177^{\circ}$, $(\alpha)_D - 79^{\circ}$ (c, 1.81), mol. wt. 252 (mass spectrum).

IR spectrum (Fig. 7) showed bands at: 2890, 1767, 1449, 1374, 1235, 1183, 990, 934, 869, 804 and 727 cm^{-1} .

Epoxidation of tetrahydrocostunolide (IV)

To the tetrahydrocostunolide (0.4 g) dissolved in chloroform (1 ml), chloroform solution of perbenzoic acid (1.5 N; 4 ml; 2 moles) was added and mixture kept at -15° (48 hours), then worked up as usual to give a solid (0.41 g) which was chromatographed on neutral alumina (20 g, grade II) and eluted as follows:

Fr.No.	Solvent	Volume in ml	Weight in g
1	Hexane + benzene 2:1	100	0.03
2	Hexane + benzene 1:1	150	0.26
3	Benzene	100	0.05
4	Chloroform	100	0.05

Fraction 2 was crystallised from ether-hexane (10:1) m.p. 136-137°, mixed m.p. with (III) showed no depression.

Metal-amine reduction of tetrahydrocostunolide (V)

In a three necked 250 ml flask fitted with a mercury seal, mechanical stirrer and air condenser, liquid ammonia (100 ml) was drawn after insulating the flask with saw dust, Li (0.8 g) was added in small pieces. Tetrahydrocostunolide (0.9 g) dissolved in dry ether (40 ml) was added slowly from a dropping funnel. After complete addition, the solution was stirred for four hours. The reaction mixture was kept overnight to allow the ammonia to escape. The reaction flask was then cooled in ice and the lithium complex was decomposed by addition of alcohol and ammonium chloride solution. The mixture was acidified with dil. HCl and kept for two hours. It was then extracted with ether. Ether layer was extracted with sodium carbonate solution and finally with water and dried (Na_2SO_4). Ether was removed to furnish a neutral product as a thick liquid (0.57 g).

The carbonate extract was acidified with dil. HCl and extracted with ether. Ether layer was washed with water and dried (Na_2SO_4). Removal of ether furnished the acidic product as a liquid (0.33 g) (XIII and XIV).

Esterification of the above acid mixture

To the acid mixture (0.33 g) dissolved in dry ether (20 ml) and cooled to 0° , a solution of diazomethane cooled to 0° was added till yellow colour persisted. The solution was washed with sodium carbonate solution followed by water and dried (Na_2SO_4). Removal of ether furnished a liquid (0.32 g) which was chromatographed on silica gel (7.0 g) impregnated with silver nitrate (0.7 g) and eluted as follows:

Fr.No.	Solvent	Volume in ml	Weight in g
1	Hexane	170	0.12
2	Hexane + benzene 4:1	100	0.04
3	Hexane + benzene 2:1	70	0.14

Fraction 1 - single spot on TLC ($\text{SiO}_2 + \text{AgNO}_3$) (XV),
 b.p. $170-180^{\circ}$ (bath)/1 mm, $(\alpha)_D + 42^{\circ}$ (c, 1.045)
 n_D^{29} 1.4752.

Analysis

Found: C, 75.86; H, 11.63%

$\text{C}_{16}\text{H}_{28}\text{O}_2$ requires: C, 76.14; H, 11.18%.

IR Spectrum (Fig. 12) showed bands at: 2924, 1748, 1471, 1389, 1359, 1266, 1205, 1167, 1074, 997, 917, 862 and 763 cm^{-1} .

Fraction 3 - single spot on TLC ($\text{SiO}_2 + \text{AgNO}_3$) (XVI); b.p. $120-130^\circ$ (bath)/0.25 mm, $(\alpha)_D + 23.5^\circ$ (c, 1.28), n_D^{29} 1.4793.

Analysis

Found: C, 76.83; H, 10.8%

$\text{C}_{16}\text{H}_{28}\text{O}_2$ requires: C, 76.14; H, 11.18%

IR Spectrum (Fig. 14) showed bands at: 2874, 1730, 1449, 1374, 1348, 1255, 1196, 1163, 1126, 1056, 985, 862, 841 and 763 cm^{-1} .

Borontrifluoride rearrangement of epoxylactone (III)

To the epoxylactone (0.5 g) dissolved in benzene (5 ml) and cooled to 0° , borontrifluoride etherate solution (0.1 g in 2 ml benzene) was added and mixture kept at room temp. for 20 minutes. It was then diluted with water and extracted with ether. Ether layer was washed with sodium carbonate solution, followed by water and dried (Na_2SO_4). On evaporation, ether layer furnished a semisolid (0.54 g) which was washed repeatedly with hexane. The insoluble solid was crystallised from acetone-hexane (1:2) to give (XXVII, 0.22 g).

M.p. 160° , $(\alpha)_D - 123.3^\circ$ (c, 2.956),
mol. wt. 252 (mass spectrum).

Analysis

Found: C, 71.04; H, 9.6%.

$C_{15}H_{24}O_3$ requires: C, 71.31; H, 9.59%.

IR Spectrum (Fig. 18) (in chloroform solution in cell 0.1 mm) showed bands at: 3546, 2899, 1764, 1639, 1458, 1385, 1238, 1176, 1110, 1018, 1000, 985, 926, 905 and 806 cm^{-1} .

Hexane washings mentioned above on removal of hexane furnished a semisolid (0.2 g) which was chromatographed on neutral alumina (10 g, grade III) and eluted as follows:

Fr.No.	Solvent	Volume in ml	Weight in g
1	Hexane + benzene 3:1	50	0.03
2	Hexane + benzene 1:1	50	0.03
3	Benzene	50	0.06
4	Ether	50	0.05

Fraction 3 was crystallised from hexane to furnish (XXVI),

m.p. 38° , $(\alpha)_D + 21^{\circ}$ (c, 2.47)

mol. wt. 252 (mass spectrum)

IR Spectrum (Fig. 16) showed bands at: 2890, 1764, 1695, 1449, 1370, 1351, 1325, 1299, 1221, 1170, 971, 950, 854, 803, 769 and 704 cm^{-1} .

Oxidation of hydroxylactone (XXVII) by Jones' reagent

To the hydroxy lactone (0.15 g) dissolved in acetone (10 ml) and cooled to 0° , Jones' reagent was added drop by drop till a brown colour persisted. The solution was kept at 0° for two hours, diluted with water and extracted with ether. Ether layer was washed with sodium carbonate solution followed by water and dried (Na_2SO_4). On evaporation, the ether layer furnished a solid (0.13 g) which was crystallised from ether-hexane (5:1) (XXVIII).

M.p. 138° , $(\alpha)_D^{20} \pm 0^{\circ}$ (c, 2.00),

mol. wt. 250 (mass spectrum)

Analysis

Found: C, 71.87; H, 8.86%

$\text{C}_{15}\text{H}_{22}\text{O}_3$ requires: C, 71.40; H, 8.74%.

IR Spectrum (Fig. 20) showed bands at: 2899, 1764, 1681, 1653, 1460, 1374, 1339, 1299, 1238, 1205, 1179, 1120, 1064, 1022, 986, 910, 885, 820 and 722 cm^{-1} .

Hydrogenation of hydroxylactone (XXVII)

The hydroxylactone (0.44 g) dissolved in glacial acetic acid (15 ml) was hydrogenated using PtO_2 (100 mg). The volume of hydrogen absorbed (65 ml of hydrogen at N.T.P.)

corresponded to 1.3 moles. After working up in the usual way it furnished a liquid (0.4 g) which was chromatographed on neutral alumina (40 g; grade III) and eluted as follows:

Fr.No.	Solvent	Volume in ml	Weight in g
1	Hexane	100	0.02
2	Hexane + benzene 2:1	100	0.01
3	Hexane + benzene 1:1	100	0.03
4	Benzene	200	0.25
5	Chloroform	100	0.05

Fraction 1 - TLC single spot (α) - 23.4° (c, 1.42)

IR Spectrum showed bands at 2899, 1770, 1449, 1370, 1179, 990, 971 and 719 cm^{-1} . It was identified as hexahydrocostunolide (XXXI).

Fraction 4 - TLC single spot, (α)_D - 38° (c, 1.844).

IR Spectrum showed bands at: 3448, 2941, 1754, 1449, 1370, 1333, 1294, 1190, 1100, 1036, 990, 961, 934 and 862 cm^{-1} . This was identified as dihydroderivative (XXX).

Chromic acid oxidation of saturated hydroxylactone (XXX)

The hydroxylactone (0.124 g) dissolved in acetone (10 ml), solution cooled to 0° and Jones'

reagent was added drop by drop till brown colour persisted. Solution was kept at 0° for one hour and worked up as usual to give a solid (0.12 g) which was crystallised from hexane, m.p. 88° , mixed m.p. with the above saturated ketone (XXVI) showed no depression.

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Part-II

Conversion of Costunolide
into Tetrahydrosantonins

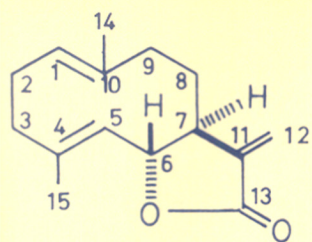
S U M M A R Y

Hydroboration-oxidation of α -cyclo-dihydrocostunolide (IV) obtainable from costunolide (I) leads to 3- α -hydroxy santanolide 'c' (XIX). Oxidation of XIX by CrO_3/Py gives the known β -tetrahydrosantonin (XII), which is further converted to α -tetrahydrosantonin (XIII) by acid.

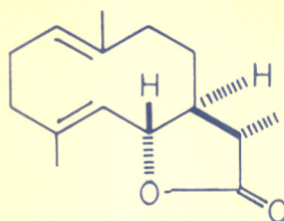
Dehydration of (XIX), exclusively yields, the unsaturated lactone (XX) containing the disubstituted double bond, thus confirming the assignment of stereochemistry of (XIX), at $\text{C}_3 - \text{C}_4$.

Costunolide¹ (I) isolated from the solvent extracted costus root oil, is a sesquiterpenic lactone, containing a ten-membered carbocyclic system with a unique distribution of two trisubstituted double bonds. This arrangement of the double bonds is very favourable for conversion of costunolide into elemene type compounds by thermal rearrangement (Cope rearrangement) of the cyclodeca-1:5-diene system² and the selenene type compounds by acid catalysed trans annular cyclization³. The conversion of dihydrocostunolide (II) into saussurea lactone² (III) and α - and β -cyclodihydrocostunolides³ (IV and V) may be cited as examples. Some interesting transformation of the latter two compounds have also been carried out which have led to valuable information about the stereochemistry of the naturally occurring compounds like d-junenol (VI), isolated from Juniper oil, (Juniperus Communis L.)⁴ and l-junenol (VII), isolated from South Indian Vetiver oil (Vetiveria zizanioides, Linn)⁴ as well as to the synthesis of isojunenol⁵ (VIII), related to α -verbesinol⁶ (IX) isolated from the plant Verbesina virginica L._{called} (ice plant).

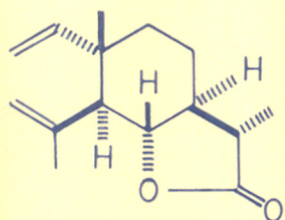
Although (-) santonin (X) has been converted into dihydrocostunolide (II) by Corey et al.⁷, conversion of dihydrocostunolide (II) into (-) santonin (X) or any of



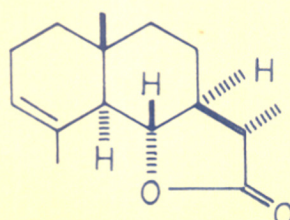
(I)



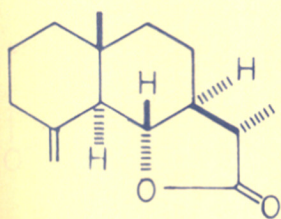
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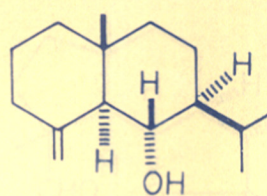
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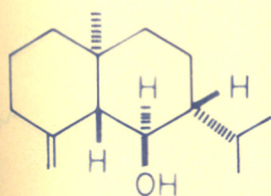
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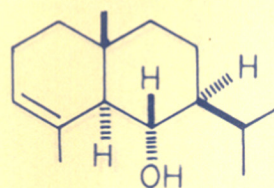
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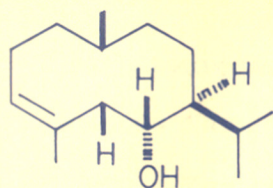
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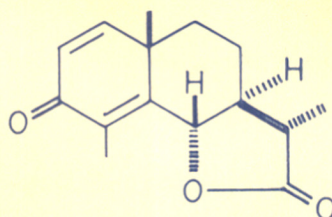
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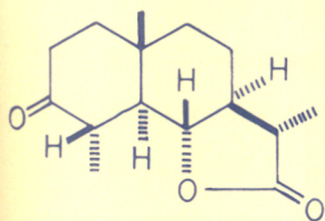
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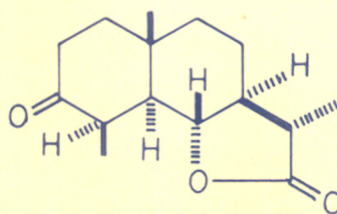
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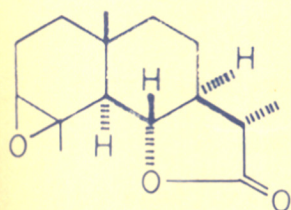
(X)



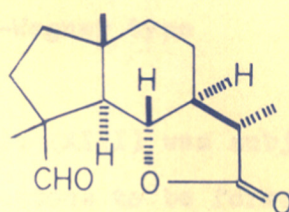
(XI)



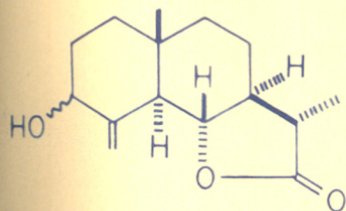
(XII)



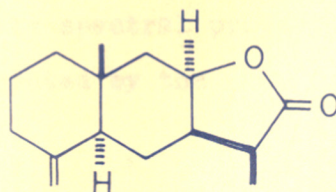
(XIII)



(XIV)



(XV)



(XVI)

tetrahydrosantonins (XI and XII) has not been carried out so far.

For such conversions the α - and β -cyclo-dihydro-costunolides³ (IV and V) appear to be suitable starting materials.

Previous work

In the earlier attempts made in this direction in our laboratory, α -cyclodihydrocostunolide (IV) was epoxidised (PBA) to furnish a crystalline epoxide (XIII, m.p. 142°). Since it is known that BF_3 -etherate rearranges epoxides to ketones, the above epoxide was subjected to BF_3 treatment in the hope of getting a tetrahydrosantonin (XI or XII). But contrary to the expectation this led to a ring-contracted aldehyde-lactone⁸ (XIV) possibly by Meerwein-Wagner type rearrangement.

In another attempt the epoxide (XIII) was subjected to acetolysis expecting a hydroxy-lactone to be formed. However, the major reaction product was found to be the same ^{ring} contracted aldehyde (XIV) together with a small proportion of a hydroxy-lactone. Though the latter could not be isolated in pure condition, its spectral properties indicated that it is probably represented by the structure⁹ (XV).

Present work

As another approach to the conversion, hydroboration-oxidation of α -cyclodihydrocostunolide (IV) was considered to be a suitable reaction, provided the lactone ring of the product so obtained remained unaffected. Although hydroboration-oxidation has been widely used in a variety of unsaturated compounds with different functional groups, for addition of H and OH at the double bond, in the anti-Markownikoff fashion, very few unsaturated lactones appear to have been subjected to this reaction. The only example appears to be dihydroisocalantolactone¹⁰ (XVI) in which the lactone ring was unaffected.

By following a procedure for hydroboration-oxidation, essentially similar to the one employed for dihydroisocalantolactone¹⁰ (XVI), a saturated hydroxylactone, m.p. 147°, is obtained from α -cyclodihydrocostunolide (IV). It shows the following properties: $(\alpha)_D + 56^\circ$, $C_{15}H_{24}O_3$, mol.wt. 252 (mass spectrum), IR spectrum (Fig. 1) shows bands at 3521 (OH), 1754 cm^{-1} (γ -lactone); NMR spectrum (Fig. 2) shows signals at 8.74, 8.86 τ (3H, C_{11} methyl); 8.94, 8.96 and 9.05 τ (6H, methyls at C_4 and C_{10}) and a multiplet around 6.14 τ (2H, protons at C_3 and C_6). It gives an acetate, $C_{17}H_{26}O_3$, m.p. 143-144°, $(\alpha)_D + 15^\circ$, IR spectrum (Fig. 3)

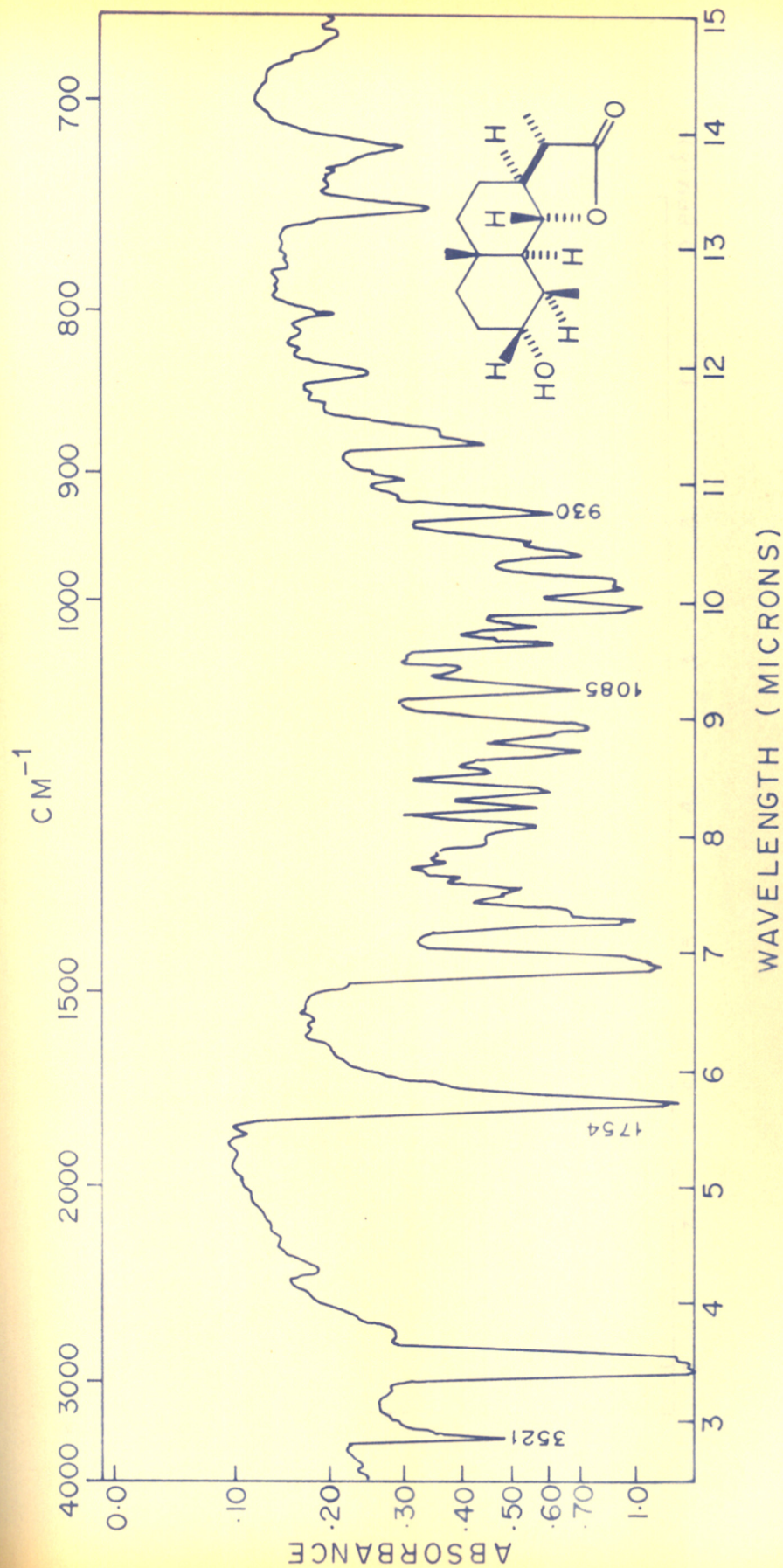


FIG. 1. IR SPECTRUM OF THE HYDROXYLACTONE.

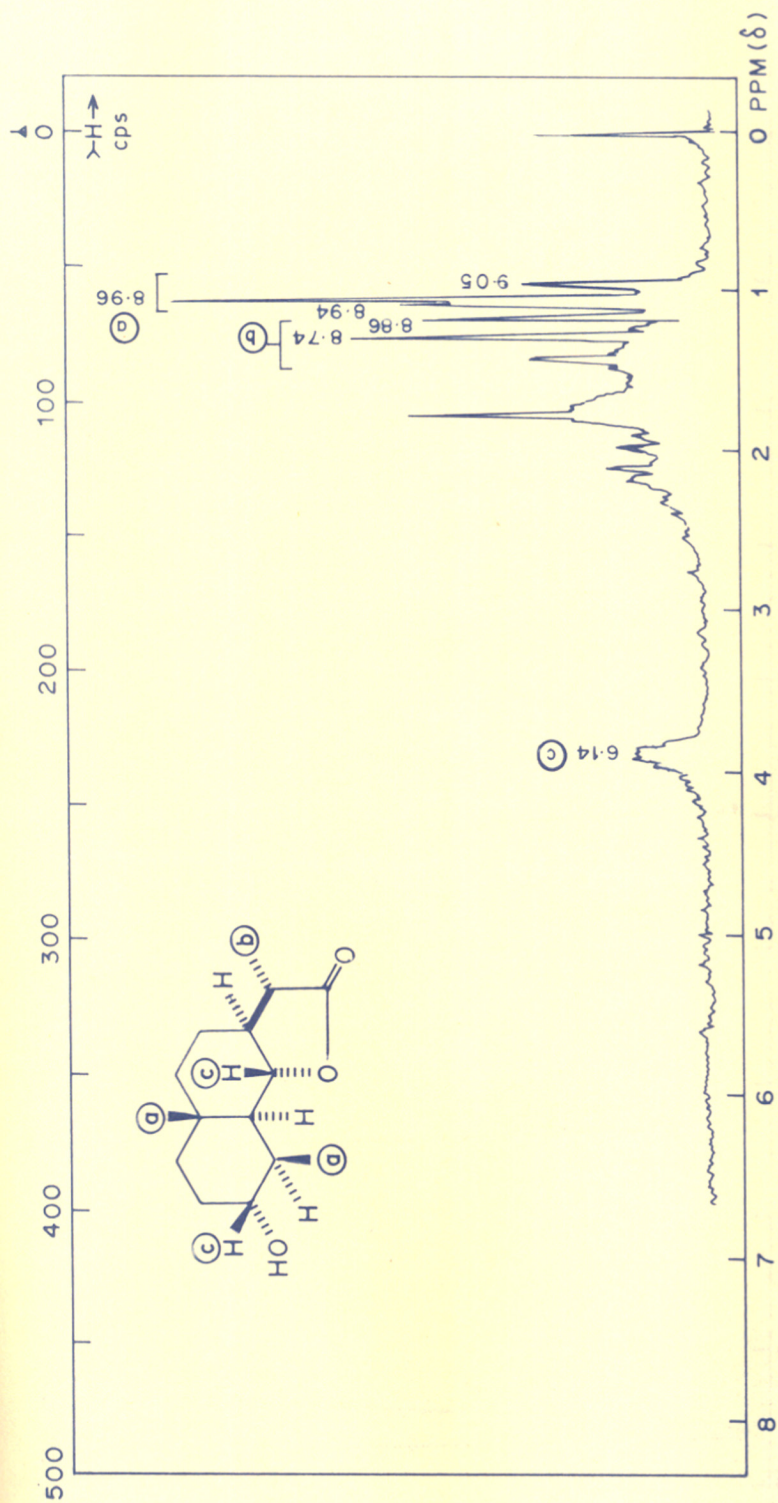
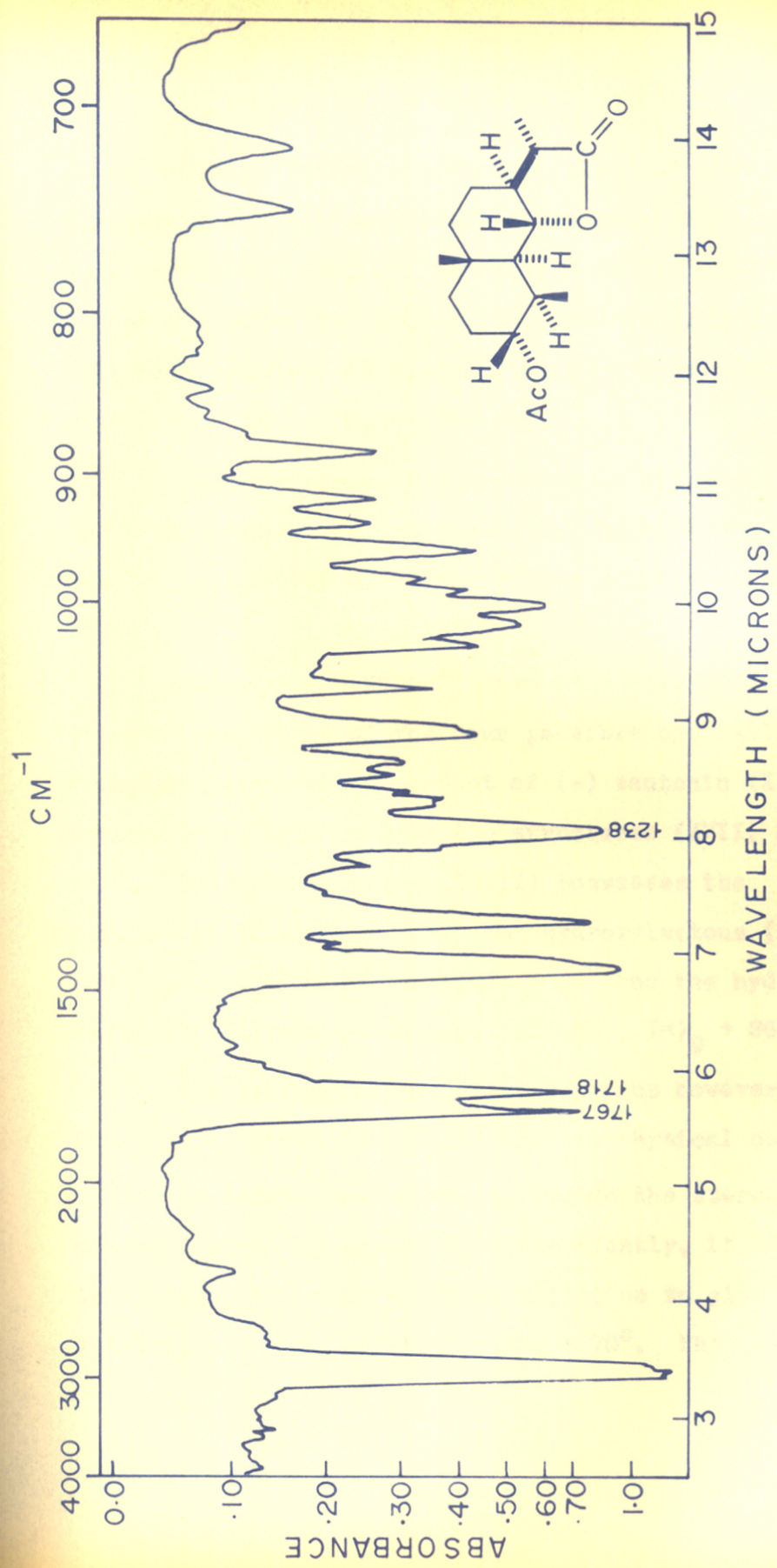


FIG. 3. IR SPECTRUM OF THE ACETATE LACTONE.



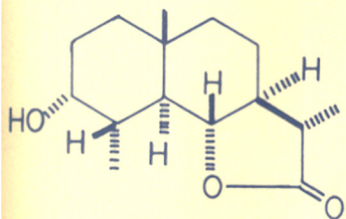
shows bands at 1767 (γ -lactone), 1718 and 1238 cm^{-1} (acetate); NMR spectrum (Fig. 4) shows signals at: 8.81 and 8.91 τ (3H, C_{11} methyl); 8.98 and 9.04 τ (6H, C_4 and C_{10} methyls); 8.01 τ (3H, acetate methyl); a multiplet centered at 6.25 τ (1H, C_6 proton) and a broad signal at 5.22 τ (1H, C_3 proton).

Since hydroboration proceeds by cis addition to the double bond, the hydroxylactone in the present case may be represented by either of the structures (XVIII or XIX).

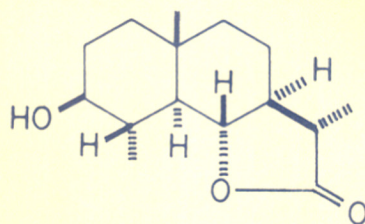
Cocker and McMurtry¹¹ have been able to isolate and characterise three of the four possible hydroxylactones from the hydrogenated product of (-) santonin (X) which according to them possess the structures (XVII, XVIII and XIX). The hydroxylactone (XVII) possesses the m.p. 142-143 $^{\circ}$, $(\alpha)_{\text{D}} + 16^{\circ}$. The hydroxylactone (XVIII) has the m.p. 175-176 $^{\circ}$ and $(\alpha)_{\text{D}} + 48^{\circ}$ and the hydroxylactone (XIX) shows the m.p. 107-108 $^{\circ}$, $(\alpha)_{\text{D}} + 36^{\circ}$.

The hydroxylactone obtained by us however differs from the lactones (XVIII and XIX) in physical constants.

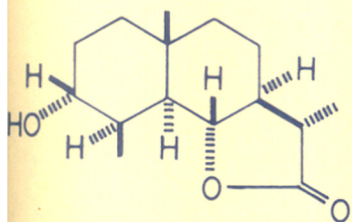
In order, therefore, to decide the stereochemistry of our lactone at C_3 and C_4 independantly, it was subjected to chromium trioxide/pyridine oxidation to give a ketolactone, m.p. 143-144 $^{\circ}$, $(\alpha)_{\text{D}} + 70^{\circ}$. This was



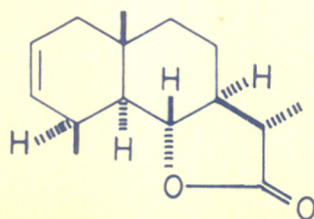
(XVII)



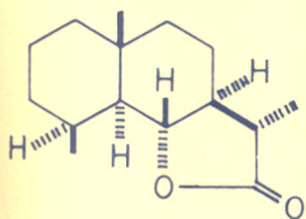
(XVIII)



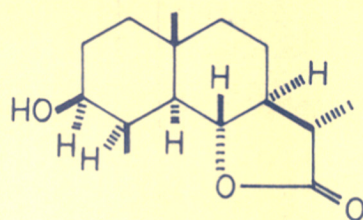
(XIX)



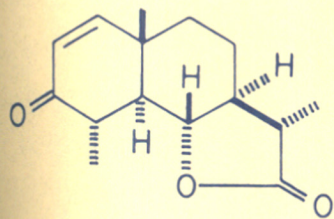
(XX)



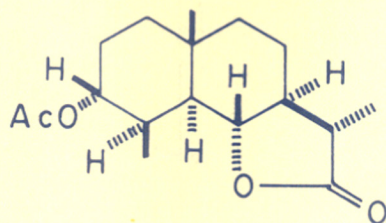
(XXI)



(XXII)



(XXIII)



(XXIV)

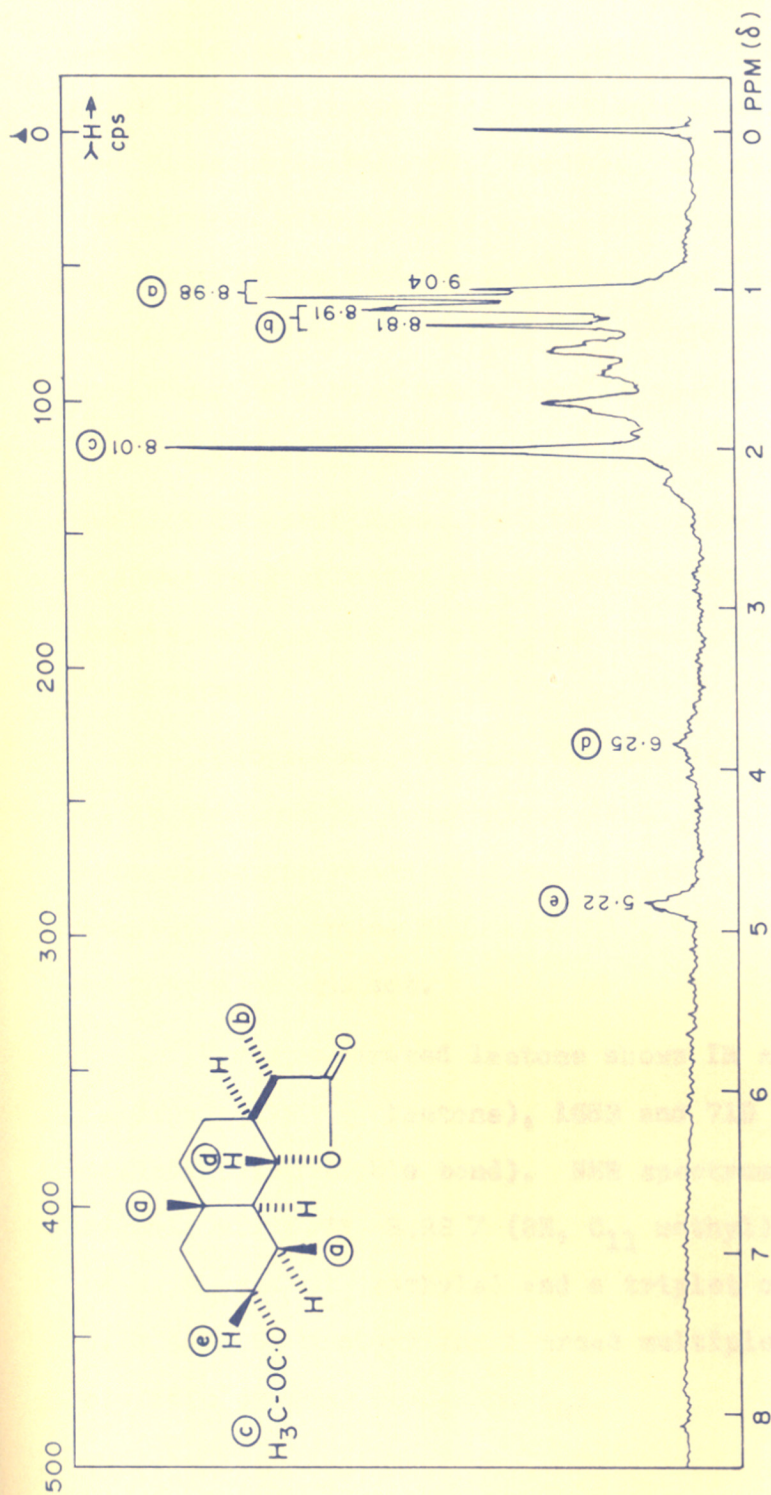


FIG. 4. NMR SPECTRUM OF THE ACETATE LACTONE.

identified as β -tetrahydrosantonin (XII) by m.p. and mixed m.p. determination, rotation and comparison of the IR spectra (Fig. 5). Further, the oxidation product was treated with an acid when, by epimerisation¹² at C_4 ¹² it gave the known α -tetrahydrosantonin¹¹ (XI) m.p. and mixed m.p. 154° , $(\alpha)_D + 25^\circ$. This was further confirmed by comparison of the IR spectra (Fig. 6).

The formation of β -tetrahydrosantonin (XII) definitely establishes that the C_4 methyl group in our lactone is β -oriented and therefore the C_4 hydrogen is α -oriented and the OH at C_3 is expected to be α -oriented.

Independent evidence for the stereochemistry at C_3 is obtained by dehydration ($POCl_3/Py$) of the hydroxylactone under mild conditions¹³, when an unsaturated lactone m.p. $120-121^\circ$, $(\alpha)_D + 210^\circ$ was obtained as the major product.

The unsaturated lactone shows IR spectrum (Fig. 7) bands at: 1767 (γ -lactone), 1653 and 719 cm^{-1} (cis disubstituted double bond). NMR spectrum (Fig. 8) shows signals at: $8.76, 8.83\tau$ (3H, C_{11} methyl); $8.86, 8.95\tau$ (6 H, C_4 and C_{10} methyls) and a triplet centred at 6.15 (1H, C_6 proton) and a broad multiplet at 4.37 (2H, olefinic protons at C_2 and C_3).

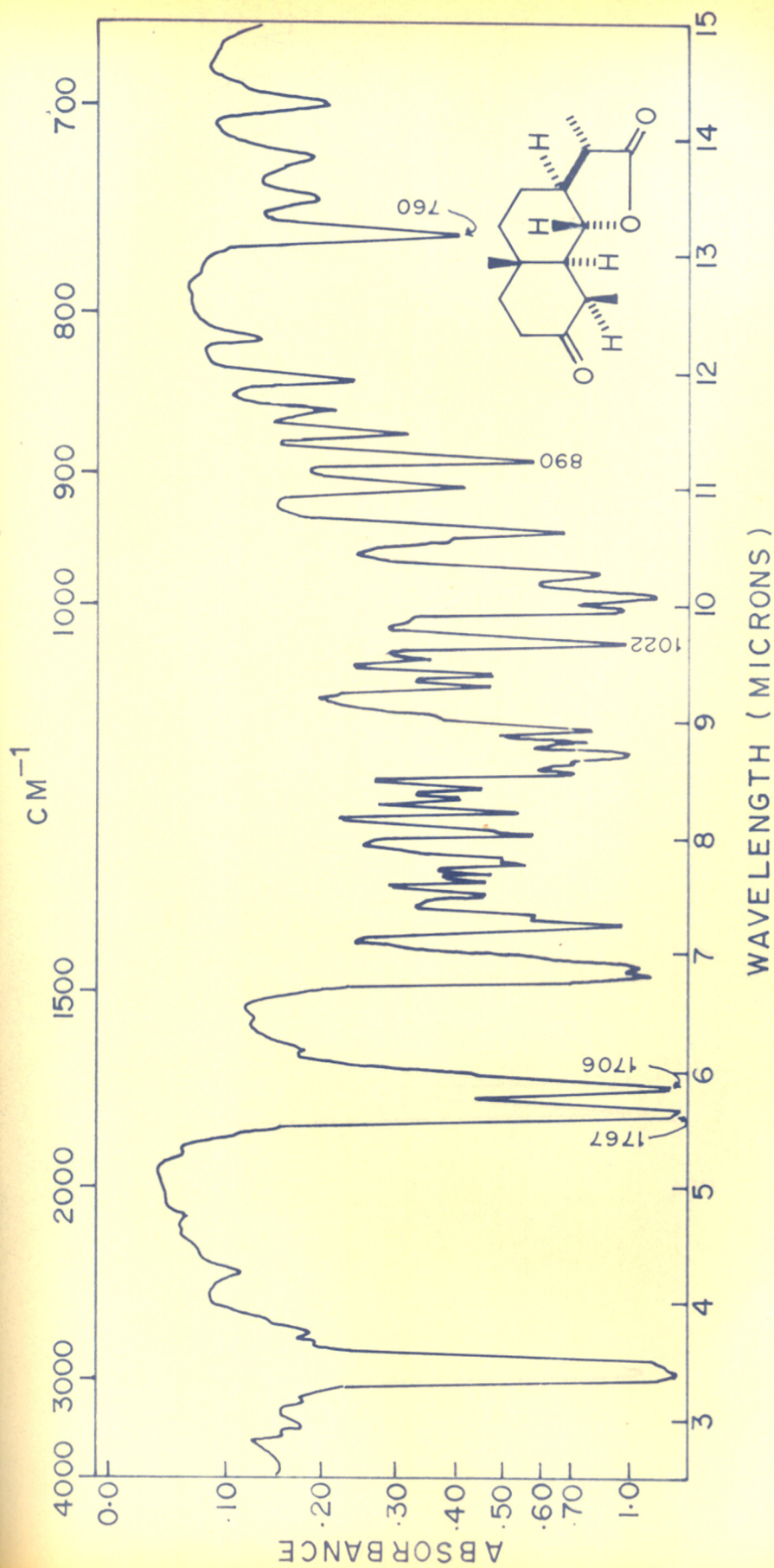


FIG. 5. IR SPECTRUM OF THE β -TETRAHYDROSANTONIN.

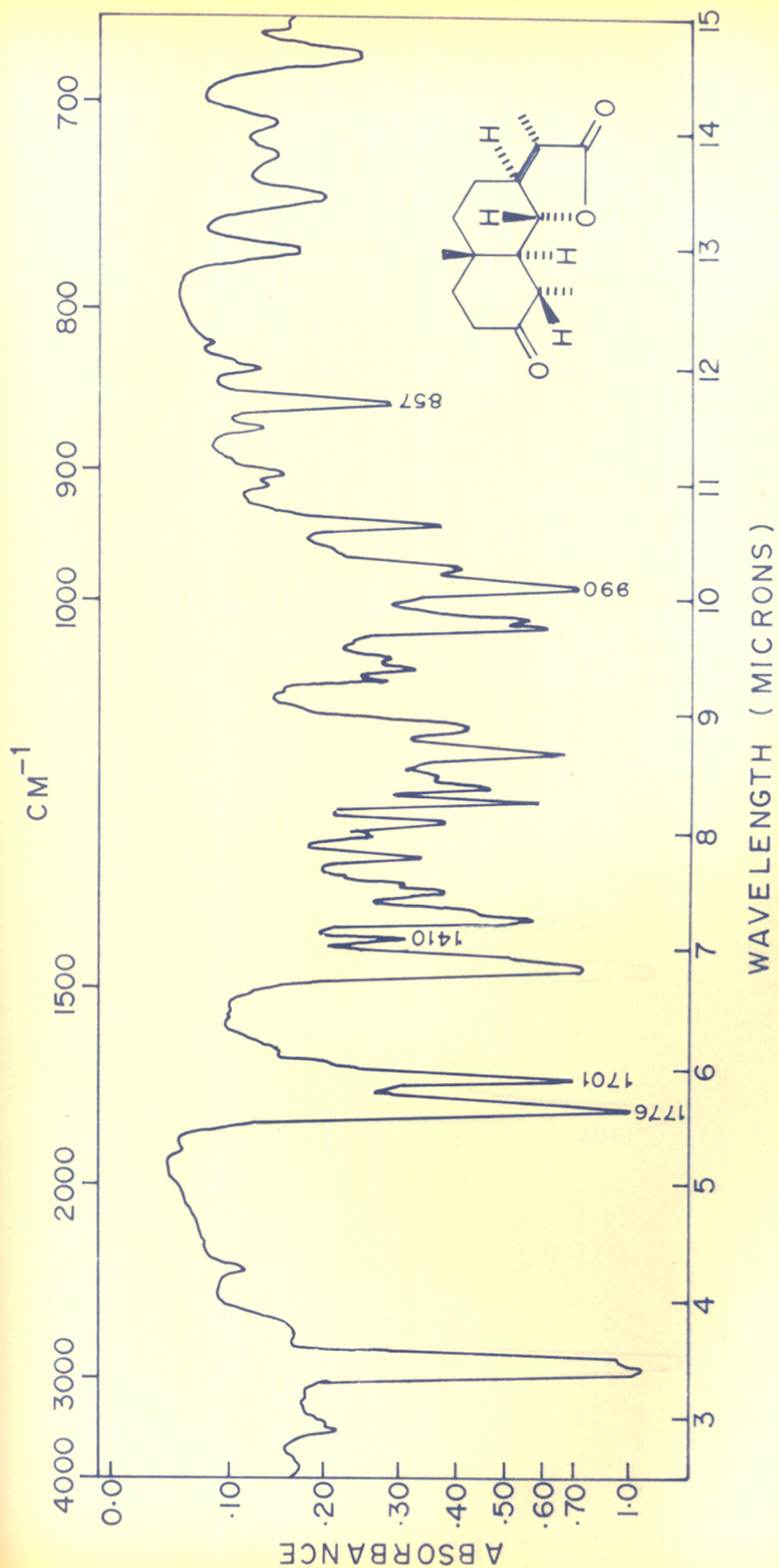


FIG. 6. IR SPECTRUM OF THE α -TETRAHYDROSANTONIN.

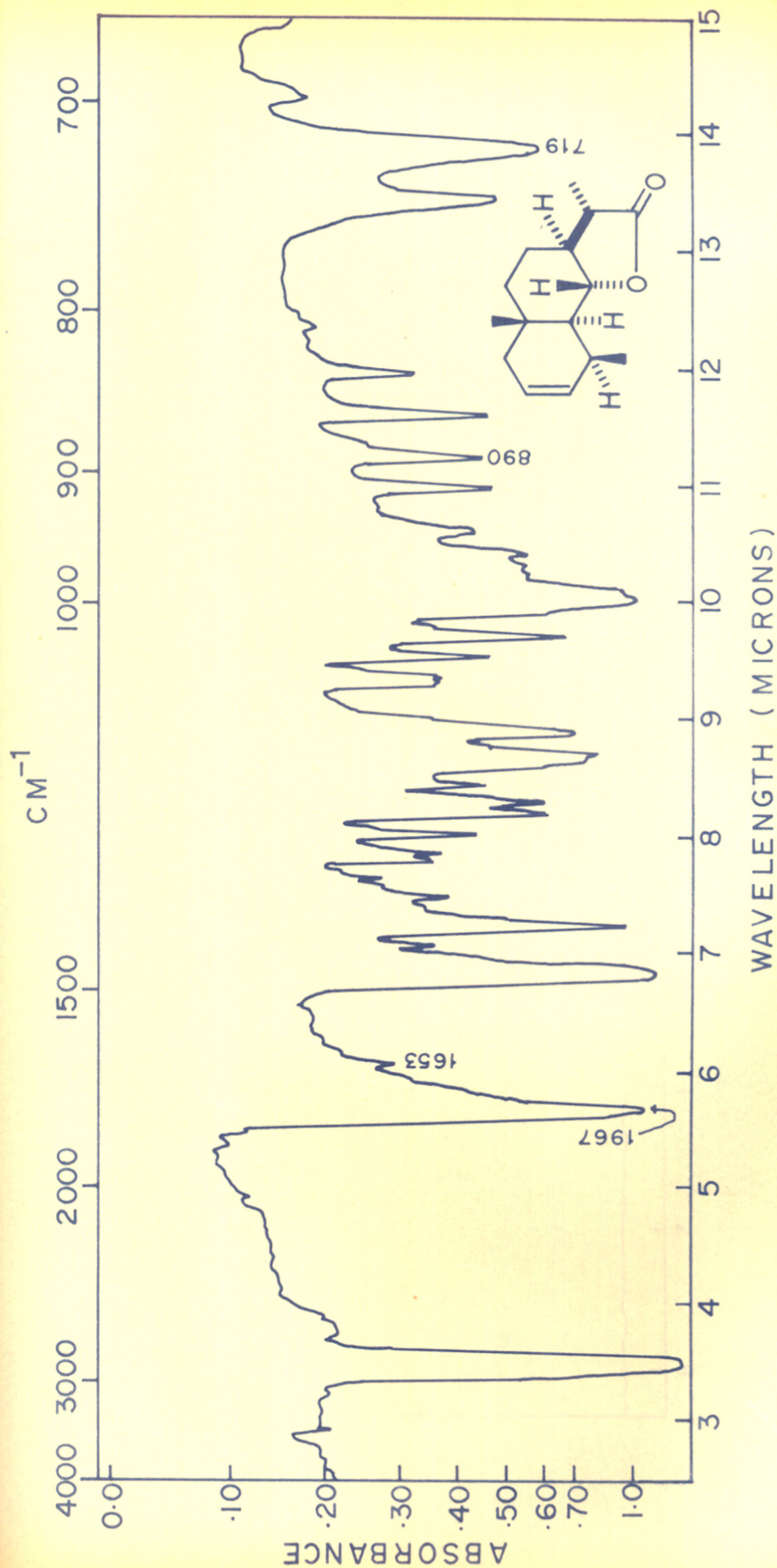


FIG. 7. IR SPECTRUM OF THE UNSATURATED LACTONE.

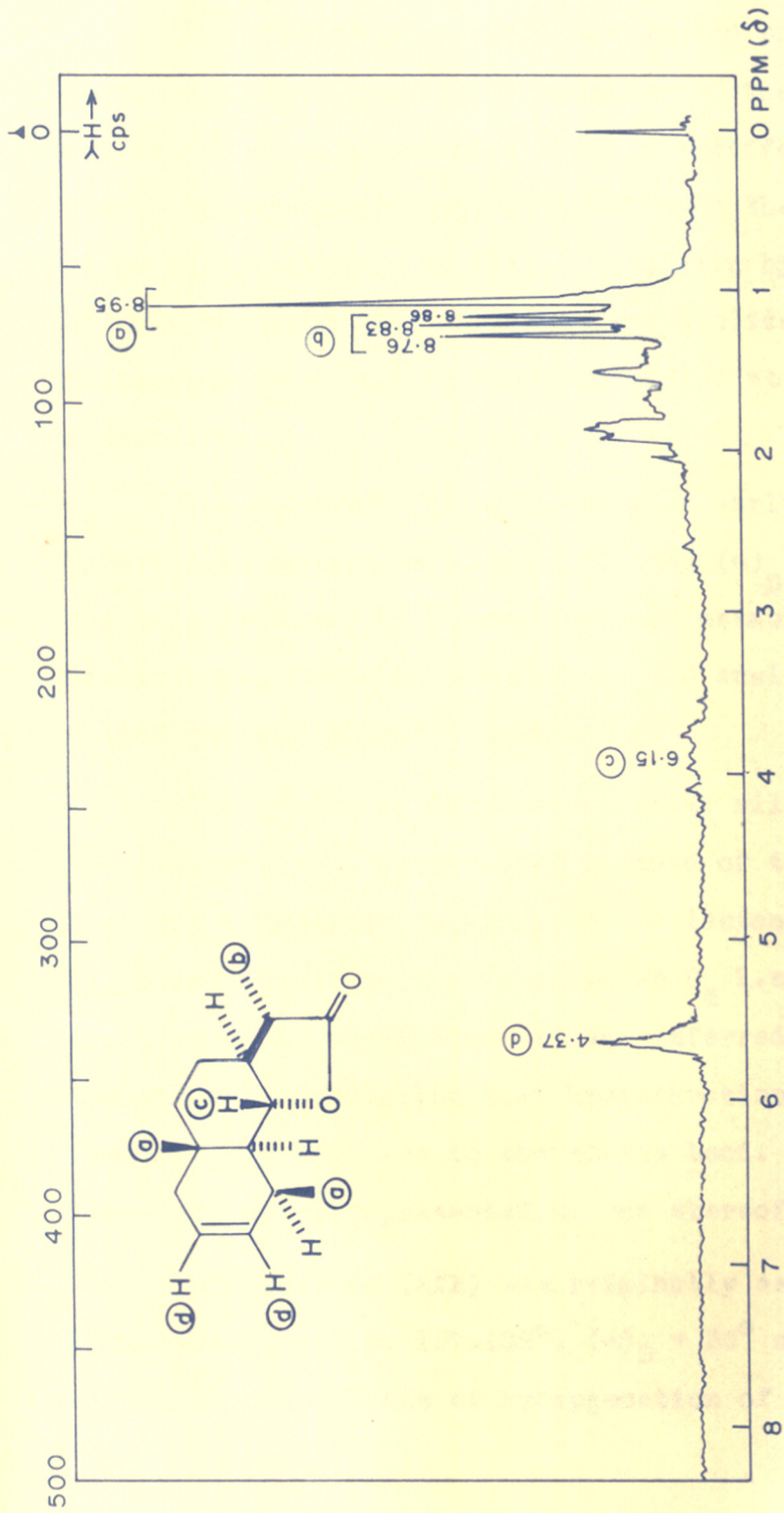


FIG. 8. NMR SPECTRUM OF UNSATURATED LACTONE.

The absence of a vinyl methyl and presence of olefinic protons in the NMR spectrum of the compound and the physical properties which are different from the α -cycloclidihydrocostunolide (IV) indicate that the lactone is to be represented by (XX). Catalytic hydrogenation of this compound (XX) furnished santanolide 'c' (XXI)(Fig.9) indicating no change in stereochemistry at C₄ during the dehydration.

The compound (XX) was obtained earlier¹¹ and was reported to possess m.p. 106-107° and $(\alpha)_D + 90^\circ$. It has now been obtained in a pure state as established from higher m.p., rotation and also by TLC analysis on silica gel-10% silver nitrate.

The preferred dehydration under mild conditions to the disubstituted isomer (XX) instead of to (IV) suggests that the hydroxy group at C₃ in the lactone is in cis relationship to the hydrogen at C₄ i.e. the hydroxy group at C₃ is α -oriented as was inferred in keeping with the general observation that hydroboration-oxidation involves cis addition to the double bond. Our lactone is therefore to be represented by the stereoformula (XIX).

The formula (XIX) was originally assigned to a hydroxylactone m.p. 107-108°, $(\alpha)_D + 36^\circ$ obtained as one of the major products of hydrogenation of (-) santonin.

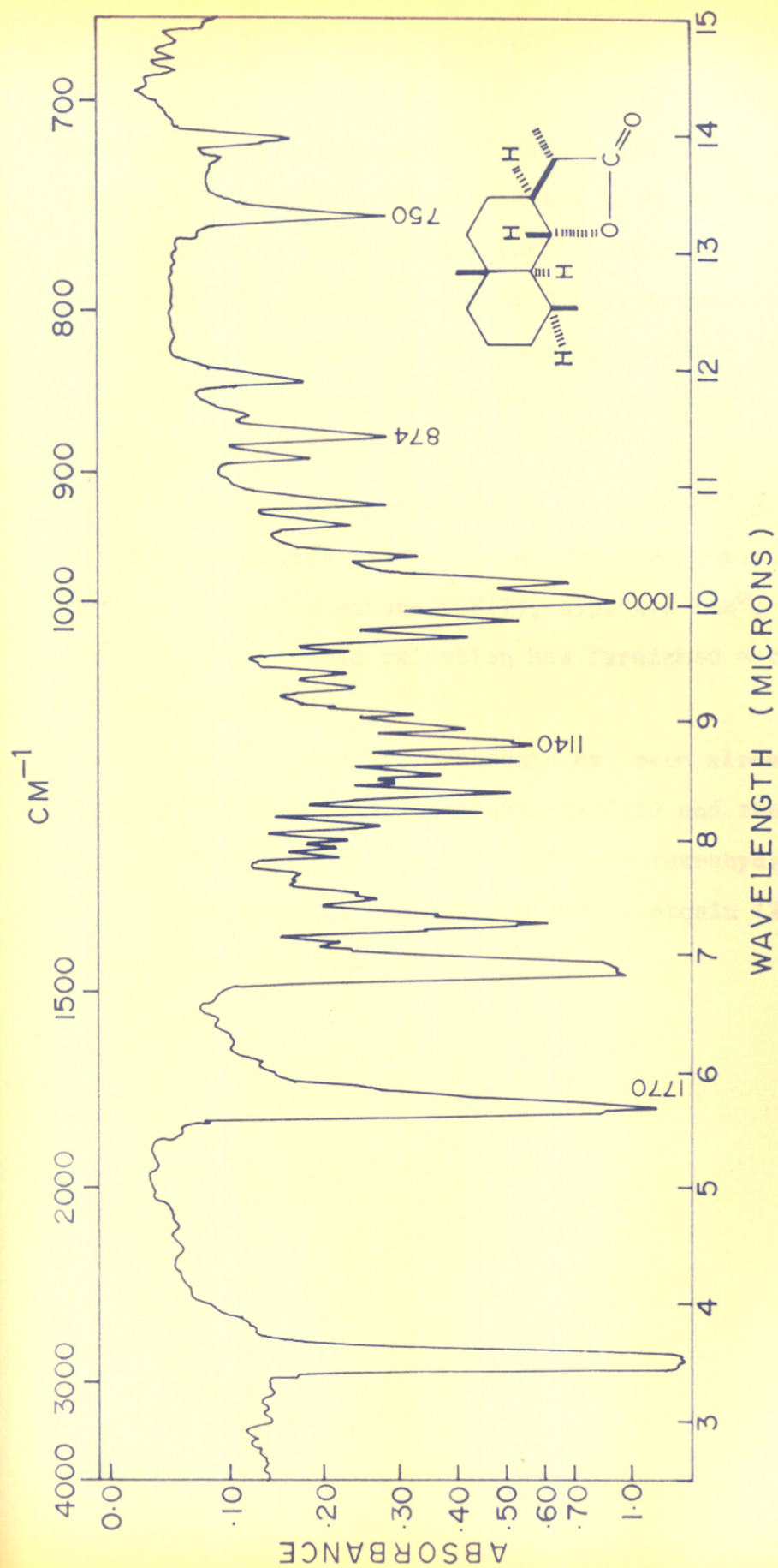


FIG. 9. IR SPECTRUM OF THE SANTANOLIDE 'C'

However, the stereoformula of this lactone has been recently corrected to (XXII) on the basis of predominant formation of (IV) by elimination reactions.¹¹ This structure has also been confirmed by the sodium borohydride reduction of β -tetrahydrosantonin (XII) to give (XXII) which contains a β -oriented (equatorial) hydroxy group¹⁴.

Recently by employing SeO_2 oxidation¹⁵ β -cyclo-dihydrocostunolide (V) has been converted into the saturated hydroxylactone (XVII), m.p. 142-143°, $(\alpha)_D + 16^\circ$. This on chromic acid oxidation has furnished α -tetrahydrosantonin (XI).

Since α -tetrahydrosantonin has been already converted¹² into dihydrosantonin (XXIII) and santonin (X), the conversion of costunolide (I) into tetrahydrosantonin also constitutes its conversion into santonin (X) and dihydrosantonin (XXIII).

EXPERIMENTAL

Hydroboration of α -cyclodihydrocostunolide (IV) to hydroxylactone (XIX)

Through a solution of α -cyclodihydrocostunolide (3.0 g) in dry tetrahydrofuran (30 ml), diborane gas, prepared from sodium borohydride (1.5 g) in diglyme (25 ml) and a solution of borontrifluoride etherate (20 ml) in diglyme (20 ml), was passed at 0° for one hour and then at room temperature for further one hour. The reaction was carried out in an atmosphere of nitrogen. The excess of diborane was then decomposed immediately by adding small pieces of ice and the mixture left overnight at 0°. Hydrogen peroxide (30%, 20 ml) was added gradually followed by potassium hydroxide solution (5%, 20 ml) and the mixture left at room temperature for 24 hours. It was then acidified with HCl (1:1), extracted with ether, and ether layer washed successively with water and dried (Na_2SO_4). The product obtained on removal of ether, was purified by chromatography and crystallised from pet. ether to furnish a solid (2.1 g), m.p. 146-147°; $(\alpha)_D + 56^\circ$ (c, 2.32).

Analysis

Found: C, 71.58; H, 9.65%.

$\text{C}_{15}\text{H}_{24}\text{O}_3$ requires: C, 71.31; H, 9.59%.

IR spectrum (Fig. 1) showed bands at: 3521, 2900, 1754, 1449, 1380, 1241, 1215, 1193, 1147, 1124, 1085, 1008, 990, 961, 930, 883, 740 and 720 cm^{-1} .

Acetate of the hydroxylactone (XIX)

A mixture of hydroxylactone (0.5 g), acetic anhydride (2.7 ml) and pyridine (0.5 ml) was kept at room temp. for 48 hours. The reaction mixture was diluted with water and extracted with ether. Ether layer was washed with dilute HCl and successively with water and dried (Na_2SO_4). On evaporation it furnished a solid (0.38 g) which was crystallised from hexane, (0.25 g). It showed the following properties:

m.p. $146-147^\circ$; $(\alpha)_D + 15^\circ$ (c, 1.923)

Analysis

Found: C, 69.44; H, 9.18%

$\text{C}_{17}\text{H}_{26}\text{O}_4$ requires: C, 69.39; H, 8.90%.

IR spectrum (Fig. 3) showed bands at: 2941, 1767, 1718, 1452, 1370, 1232, 1126, 1076, 1023, 1000, 954, 934, 916, 884, 747 and 716 cm^{-1} .

Chromic acid oxidation of the hydroxylactone (XIX) to β -tetrahydrosantonin (XII)

The hydroxy lactone (1.0 g) in pyridine (15 ml) was treated with chromium trioxide (1.2g) in pyridine (30 ml) at 0° during 20 minutes with occasional shaking.

The contents were kept at room temp. for 48 hours and poured into water and extracted with ether. Ether layer was washed with dilute HCl and water, dried (Na_2SO_4). On evaporation, ether^{layer} furnished a solid which was crystallised from hexane to give β -tetrahydrosantonin (0.5 g), m.p. and mixed m.p. with authentic β -tetrahydrosantonin $143-144^\circ$, $(\alpha)_D + 70.76^\circ$ (c, 1.72).

Analysis

Found: C, 71.99; H, 9.03%

$\text{C}_{15}\text{H}_{22}\text{O}_3$ requires: C, 71.97; H, 8.86%.

IR spectrum (Fig. 5) was found to be superimposable on that of the authentic sample and displays bands at: 2941, 1767, 1706, 1462, 1379, 1333, 1243, 1217, 1149, 1120, 1075, 1022, 990, 943, 909, 890, 872, 839 and 760 cm^{-1} .

Oxidation by Jones' reagent

The hydroxylactone (0.2 g) was dissolved in acetone (5 ml) Jones' reagent (0.2 ml) was added and the mixture kept at room temp. for two hours, poured in water and extracted with ether. Ether layer was washed with sodium bicarbonate solution and finally with water and dried (Na_2SO_4). Removal of ether furnished β -tetrahydrosantonin (XII) m.p. and mixed m.p. with authentic sample $143-144^\circ$.

Conversion of β -tetrahydrosantonin (XII) to α -tetrahydrosantonin (XI)

β -Tetrahydrosantonin (0.2 g) was dissolved in alcohol (20 ml) and HCl (5%, 30 ml) was added. The clear solution was warmed on waterbath for one hour and alcohol was removed. The residue was extracted with ether, the ether layer washed several times with water and dried (Na_2SO_4). The product, on evaporation of ether, was crystallised from hexane to furnish α -tetrahydro-santonin (XI, 0.12 g) m.p. and mixed m.p. with an authentic sample 153-154°, $(\alpha)_D + 25.4^\circ$.

Analysis

Found: C, 71.91; H, 9.33%.

$\text{C}_{15}\text{H}_{22}\text{O}_3$ requires: C, 71.97; H, 8.86%.

IR Spectrum (Fig. 6) was superimposable on that of an authentic sample and displays bands at: 2941, 1776, 1701, 1466, 1410, 1379, 1212, 1152, 1124, 1064, 1026, 990, 942, 857, 770, 744 and 682 cm^{-1} .

Dehydration of hydroxylactone (XIX) with POCl_3 /pyridine to dehydrated lactone (XX)

Hydroxylactone (0.6 g) was dissolved in pyridine (1.5 ml) and POCl_3 (0.7 ml) was added at 0° and the mixture kept at room temp. for 60 hours. It was then poured in ice water and extracted with ether. Ether layer

was washed with dilute HCl and successively with water and dried (Na_2SO_4). On evaporation, ether furnished a solid (0.55 g) which was chromatographed on silica gel (11 g) and eluted as follows:

Fr.No.	Solvent	Volume in ml	Weight in g
1	Hexane	200	0.141
2	Hexane+benzene 2:1	200	0.314
3	Ether	150	0.081

Fractions 1 and 2 when crystallised from hexane gave XX (0.4 g), m.p. $120\text{--}121^\circ$; $(\alpha)_D^{20} + 210^\circ$ (c, 2.05).

Analysis

Found: C, 76.52; H, 9.17%

$\text{C}_{15}\text{H}_{22}\text{O}_2$ requires: C, 76.88; H, 9.46%

IR Spectrum (Fig. 7) showed bands at 2857, 1767, 1653, 1466, 1412, 1383, 1247, 1220, 1205, 1149, 1124, 1072, 1031, 980, 909, 890, 855, 833, 743 and 719 cm^{-1}

Dehydration by alumina-pyridine

Hydroxylactone (XIX, 0.2 g) was mixed with alumina/pyridine catalyst, (1.5 g; 100 g alumina + 2 g pyridine) and heated for 5 hours at 230°C . The mixture was then

passed over a column of alumina (Gr. III, 10 g) and eluted with ether. Ether solution was washed with water and dried (Na_2SO_4). Removal of ether and crystallisation of the residue from hexane furnished (XX), m.p. and mixed m.p. with above lactone (XX) 121° .

Hydrogenation of lactone (XX) to santanolide 'c' (XXI)

The lactone (0.12 g) was dissolved in ethyl alcohol (18 ml) and hydrogenated with PtO_2 (50 mg) as catalyst. Absorption of hydrogen stopped after absorption of ~~hydrogen~~ (18 ml) corresponding to one mole at N.T.P. The catalyst was filtered off and the solvent removed on water-bath under suction. The residue was dissolved in ether and washed with water. Ether layer was dried (Na_2SO_4) and evaporated to yield a solid, which was crystallised from hexane, m.p. 156° , mixed m.p. with authentic santanolide 'c' $155-156^\circ$.

IR Spectrum (Fig. 9) showed bands at: 2900, 1770, 1464, 1380, 1340, 1220, 1195, 1159, 1139, 1120, 1070, 1008, 1000, 982, 960, 937, 922, 890, 874, 840, 750 and 715 cm^{-1} .

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Part-III

Study of NMR Spectra of
some Ten-membered Carbocyclic Compounds

S U M M A R Y

A number of naturally occurring germacranolides possess vinyl methyls at C₄ and C₁₀ and double bonds at C₁ - C₁₀ and C₄ - C₅.

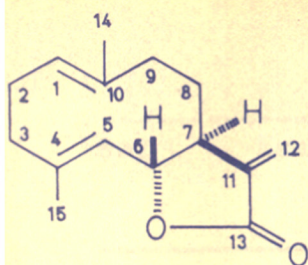
The somewhat higher values (8.5 τ and above instead of the usual 8.2 to 8.4 τ) for the vinyl methyls in the NMR spectra of such compounds has been shown to be due to the shielding effect by the π -electrons of the other double bond. It is now possible to make definite assignments for the individual vinyl methyls.

The NMR spectra of compounds, ester (XIV), alcohol (XV), hydrocarbon (XVI) and their dihydro-products (XVII, XVIII and XIX), along with the study of the spectra of other similar compounds have corroborated the above view.

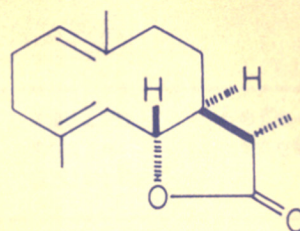
A number of sesquiterpenic lactones containing a ten-membered carbocyclic system with vinyl methyls at C₄ and C₁₀ and double bonds at C₁ - C₁₀ and C₄ - C₅ have been isolated and their NMR spectra studied. They show two distinct signals (as shown in the table) for the C₄ and C₁₀ methyls, of which one is invariably observed above 8.5 τ and the other between 8.2 to 8.4 τ . The normal value¹ observed for a vinyl methyl is between 8.2 and 8.4 τ . The higher value i.e. 8.5 τ and above, for such methyls has been suggested as due to the shielding of the protons of the vinyl methyl by the π electrons of the other double bond. However, no particular assignment for each of the vinyl methyls has been made so far.

Table-1

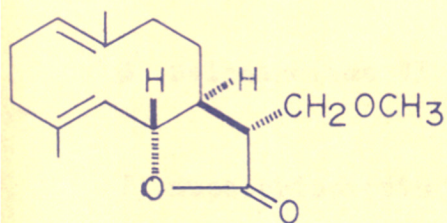
No.	Name	Signal for C ₄ , C ₁₀ methyl τ	Assignments proposed τ	Ref- erence
1	Costunolide I	8.59	C ₁₀ 8.59	1
		8.32	C ₄ 8.32	
2	Dihydrocostunolide II	8.6	C ₁₀ 8.6	2
		8.33	C ₄ 8.33	
3	12-Methoxy-dihydro- costunolide III	8.58	C ₁₀ 8.58	3
		8.32	C ₄ 8.32	



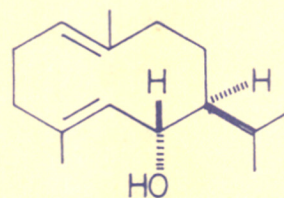
I



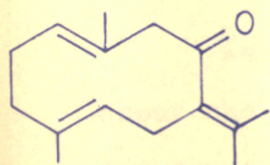
II



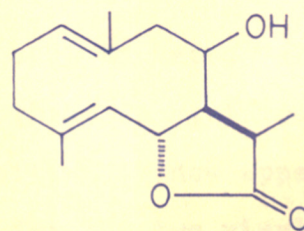
III



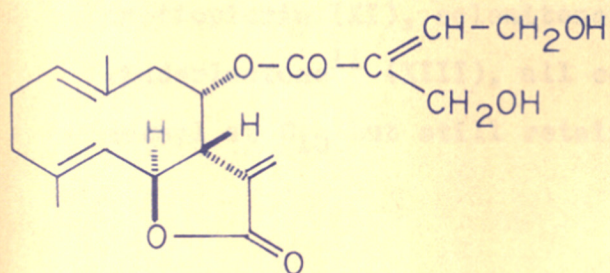
IV



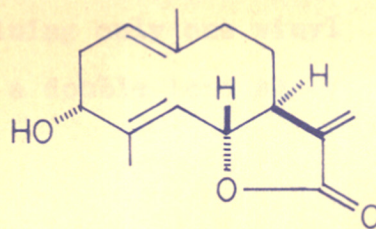
V



VI



VII



VIII

No.	Name	Signal for C ₄ , C ₁₀ methyl γ	Assign- ments proposed	Refer- ence
4	Monol IV	8.6	C ₁₀ 8.6	4
		8.34	C ₄ 8.34	
5	Germacrone V	8.58	C ₄ 8.58	1
		8.395	C ₁₀ 8.395	
6	Balchanolide VI	8.57	C ₁₀ 8.57	3
		8.34	C ₄ 8.34	
7	Eupatoriopierin VII	8.52	C ₁₀ 8.52	5
		8.23	C ₄ 8.23	
8	Tamaulipin b VIII	8.56	C ₁₀ 8.56	6
		8.37	C ₄ 8.37	

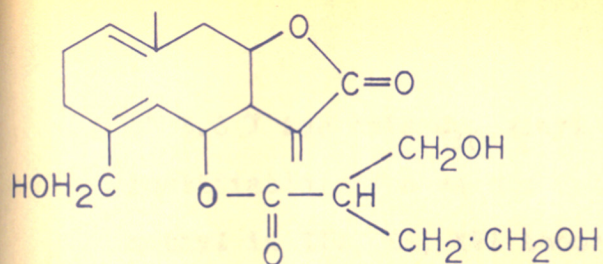
In this chapter the assumption made by Bates¹ et al. about the higher value of such vinyl methyls is verified and found to be substantiated. In addition it now appears possible to make definite assignments for the two vinyl methyls.

The NMR spectra of Cnicin⁷ (IX), aristolactone⁸ (X), arctiopierin (XI), salonitenolide¹⁰ (XII) and linderlactone¹¹ (XIII), all containing only one vinyl methyl at C₁₀ but still retaining a double bond at

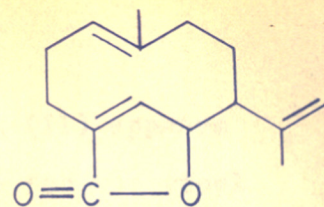
$C_4 - C_5$ show signals at 8.48, 8.52, 8.67 and 8.72 τ respectively for the C_{10} vinyl methyl. This suggests that the higher value in similar compounds (Table I) may be assigned to C_{10} vinyl methyls. Bates et al.¹ have suggested that the higher value is due to the shielding of the methyl protons by the π electrons of the other double bond. In the examples mentioned above (IX to XIII) the shielding is due to the π electrons of the $C_4 - C_5$ double bond.

In order to verify this assumption, we started with dihydrocostunolide² (II), which shows the signals for the two vinyl methyls at 8.6 and 8.33 τ . It was subjected to metal-amine reduction to get an acid, which was converted into its methyl ester (XIV) ~~XXXXXX~~₃. The structure and stereochemistry of these compounds have been rigorously established¹². The ester (XIV) contains only the C_{10} vinyl methyl, the C_4 vinyl methyl originally present in II being changed into a methyl on a saturated carbon. This compound contains the other double bond at $C_5 - C_6$ instead of at $C_4 - C_5$ as present in II.

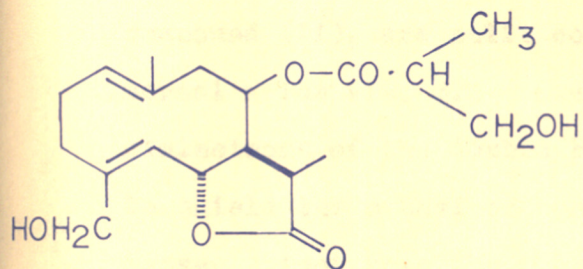
The ester¹² (XIV), as well as the alcohol¹² (XV) and the hydrocarbon¹² (XVI) prepared from (XIV) show for the C_{10} methyl signals at 8.51, 8.5, 8.5 τ respectively. From these figures also the higher value



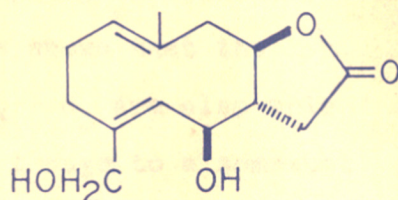
IX



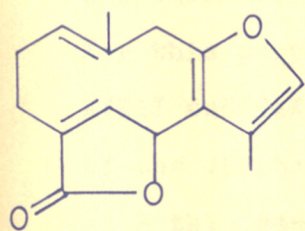
X



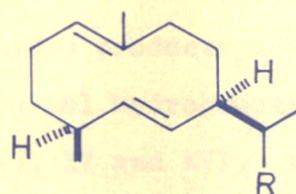
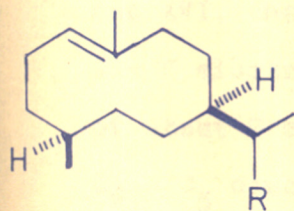
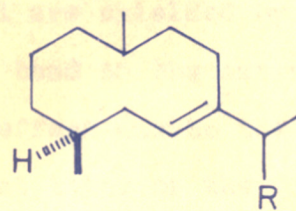
XI



XII



XIII

XIV, $\text{R} - \text{COOCH}_3$ XV, $\text{R} - \text{CH}_2\text{OH}$ XVI, $\text{R} - \text{CH}_3$ XVII, $\text{R} - \text{COOCH}_3$ XVIII, $\text{R} - \text{CH}_2\text{OH}$ XIX, $\text{R} - \text{CH}_3$ XX, $\text{R} - \text{COOCH}_3$ XXI, $\text{R} - \text{CH}_2\text{OH}$ XXII, $\text{R} - \text{CH}_3$

of 8.6 τ for this C_{10} vinyl methyl in (II) appears justifiable. The values 8.51 and 8.5 for the vinyl methyl in XIV, XV, XVI though somewhat lower as compared to 8.6 τ observed in the spectrum of the parent compound (II), are still considerably higher than the normal value viz. 8.2 - 8.4 τ . This shows that the π electrons of the double bond at $C_5 - C_6$ are also able to shield the methyl protons at C_{10} though to a somewhat lesser extent than the π electrons of the $C_4 - C_5$ double bond.

We then thought of eliminating altogether the shielding effect of the electrons of the double bond. For this purpose the corresponding dihydro products XVII, XVIII and XIX were prepared by preferential hydrogenation of the disubstituted double bond in XIV, XV and XVI. Along with this ~~xxx~~ other isomers XX, XXI, XXII were also isolated.

The compounds XVII, XVIII and XIX show signals for the C_{10} methyl at 8.36, 8.35 and 8.37 τ respectively, the normal values for a vinyl methyl on a trans double bond.

From these facts it is obvious that in XIV, XV and XVI, the protons of the C_{10} methyl are shielded by the π electrons of the $C_5 - C_6$ double bond to the extent of about 9 cps. while the shielding effect due to the $C_4 - C_5$ double bond is more significant, being of the

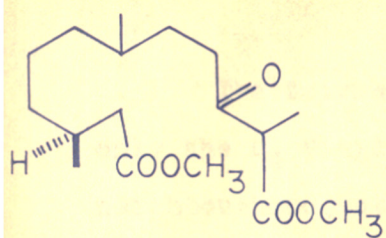
order of 15 cps.

These results taken together with the value of the C_{10} vinyl methyl in compound IX to XIII enables one to assign the higher values of 8.5 τ and above in compounds I to VIII to the C_{10} vinyl methyls. The lower value around 8.34 τ in such compounds is due, therefore, to the C_4 vinyl methyl.

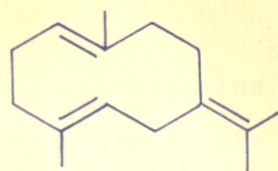
Although Bates et al.¹ have suggested the shielding effect of the $C_4 - C_5$ double bond on C_{10} methyl they have not commented about any such influence of the C_4 methyl protons by the $C_1 - C_{10}$ double bond. Two reasons can possibly be ascribed for the comparatively lower value for the C_4 methyl. (1) The combined effect of the deshielding influence of the oxygen function at C_6 and the shielding influence of the π electrons of $C_1 - C_{10}$ double bond on the C_4 methyl and (2) absence of any shielding and deshielding influences of the $C_1 - C_{10}$ double bond and the oxygen function at C_6 . In order to clarify this point the NMR spectrum of the hydrocarbon¹³ (XXIV) obtained from germacrone (V) was examined. In this hydrocarbon both the C_4 and C_{10} vinyl methyls together with the double bonds at $C_1 - C_{10}$ and $C_4 - C_5$ are present and there being no oxygen function at C_6 , the deshielding influence due to the oxygen function is altogether eliminated. The only possible

deshielding influence, if at all, may arise from the double bond at C₇. This hydrocarbon shows signals at 8.52 τ for both the C₁₀ and C₄ vinyl methyls clearly indicating that the π electrons of the C₁ - C₁₀ double bond are shielding the protons of the C₄ methyl to an equal extent. The somewhat lower value viz. 8.52 τ as compared to 8.6 τ in (II) for the vinyl methyl appears to be due to the possible deshielding influence of the double bond at C₇. It is therefore clear that the lower value of 8.34 τ for the C₄ methyl in II is due only to the deshielding influence of the oxygen function at C₆.

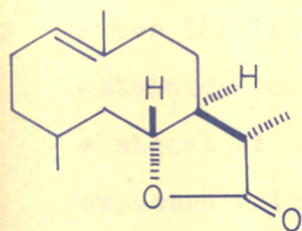
We then studied the NMR spectra of the two tetrahydrocostunolides (XXV) and (XXVI) obtained by partial hydrogenation of dihydrocostunolide (II) as described earlier in Chapter I of this thesis. The compound (XXV), which contains only the C₁₀ vinyl methyl which is almost free from any deshielding influence due to neighbouring oxygen functions or double bonds, shows a signal at 8.32 τ which is the normal value expected for a vinyl methyl. The corresponding ester (XVII) containing only the C₁₀ vinyl methyl shows a signal at 8.36 τ , indicating that the deshielding influence of the C₆ oxygen function on the C₁₀ methyl is insignificant.



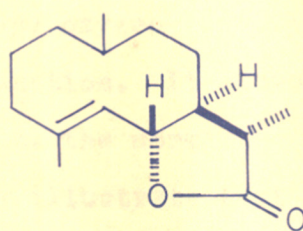
XXIII



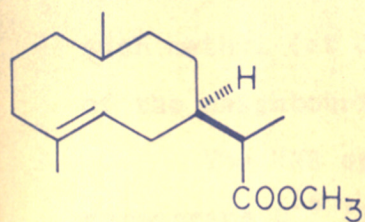
XXIV



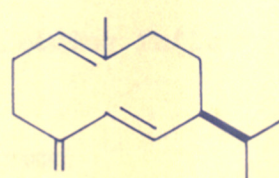
XXV



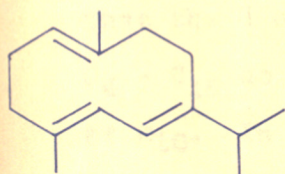
XXVI



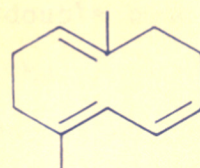
XXVII



XXVIII



XXIX



XXX

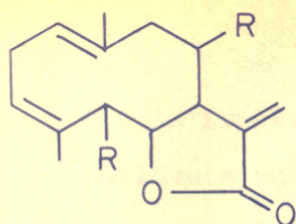
The tetrahydrocostunolide (XXVI) which contains only the C_4 vinyl methyl and an oxygen function in the neighbourhood, at C_6 , shows a signal at 8.14 τ , which is lower than the normal value. This is due to the deshielding influence of the oxygen function at C_6 as confirmed by the NMR spectrum of the corresponding ester (XXVII), which does not contain any oxygen function, obtained from (XXVI) by metal-amine reduction. It shows a signal at 8.37 τ for the C_4 methyl i.e. the normal expected value. These examples clearly illustrate that the higher value observed in dihydrocostunolide and the other similar compounds for the vinyl methyl (at C_{10}) is due to the shielding influence of the π electrons of the other double bond and the lower value observed for one such methyl (at C_4) is due to the deshielding influence of the neighbouring oxygen function.

The NMR spectrum of the hydrocarbon germacrane D^{14} , (XXVIII) shows a signal at 8.48 τ for the C_{10} vinyl methyl. While the dihydroproduct⁴ (XVI) which is also obtained from dihydrocostunolide (II) shows a signal at 8.5 τ for the same. It therefore appears that the π electrons of the exocyclic double bond at $C_4 - C_{15}$ do not shield the protons of the vinyl methyl at C_{10} . In fact such a double bond appears to deshield

the vinyl methyl protons though to an insignificant extent.

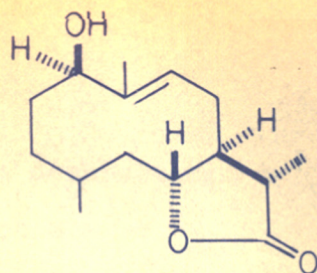
In germacrane C^{14b} , (XXIX) and pregeijerene C^{14c} (XXX) the $C_4 - C_5$ double bond is conjugated with the $C_6 - C_7$ double bond. They show values for the $-C_{10}$ vinyl methyls at 8.85 and 8.83 respectively. While the C_4 methyl signals are observed at 8.44 and 8.45 τ respectively. The somewhat higher values for the C_{10} methyls in both the compounds appear to be due to the shielding influence of the π electrons of the $C_4 - C_5$ as well as $C_6 - C_7$ double bonds.

In Chamissonin C^{15} (XXXI) and its diacetate one of the double bonds is present between $C_3 - C_4$, in place of the $C_4 - C_5$ in the naturally occurring compounds examined so far, and two vinyl methyls at C_4 and C_{10} . In addition they contain oxygen functions at C_5 and C_8 . The compound (XXXI) shows signals at 8.33 and 7.74 τ for the two vinyl methyls. The higher value, 8.33 τ , can be assigned to the C_{10} methyl, since there is no oxygen function in the immediate neighbourhood, though some deshielding influence is likely from the C_8 oxygen function. It appears therefore that the π electrons of the $C_3 - C_4$ double bond do not shield the protons of the C_{10} vinyl methyl to any significant extent. Alternatively the

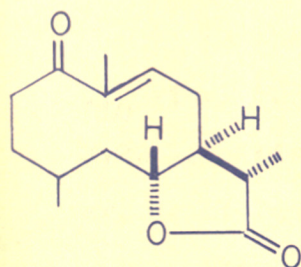


XXXI, R - OH

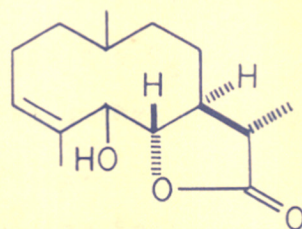
XXXII, R - OAc



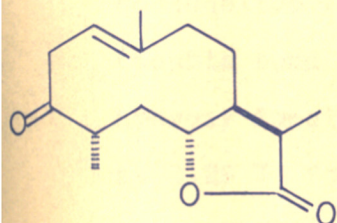
XXXIII



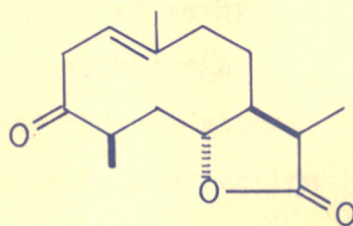
XXXIV



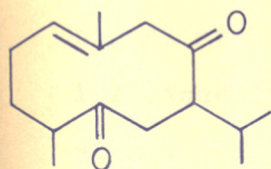
XXXV



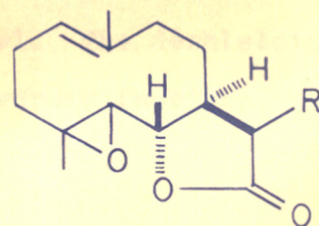
XXXVI



XXXVII



XXXVIII

XXXIX, R = CH₂XL, R = CH₃

oxygen function at C_5 may be having a deshielding influence on the C_{10} vinyl methyl which may be counteracting the shielding effect if any, of the π electrons of the $C_3 - C_4$ electrons. The C_4 vinyl methyl, however, appears to be deshielded both by the oxygen function at C_5 and the double bond at $C_1 - C_{10}$.

In the spectrum of the diacetate¹⁵ (XXXII) the C_{10} vinyl methyl is observed at 8.27 τ and the C_4 at 8.20 τ . This suggests that the C_{10} vinyl methyl protons are deshielded by the oxygen function at C_5 .

Some more examples of the deshielding influence of the neighbouring oxygen function are described below:

The hydroxylactone (XXXIII) obtained by the BF_3 rearrangement of the epoxide of the tetrahydro-costunolide (XXV), contains only a C_{10} vinyl methyl (double bond being at $C_9 - C_{10}$) and a neighbouring hydroxy function at C_1 . This compound shows a signal at 8.28 τ for the C_{10} methyl. Chromic acid oxidation of (XXXIII) results in the formation of the conjugated ketone (XXXIV) which shows signal at 8.08 τ for the C_{10} methyl. A similar hydroxy lactone (XXXV) obtained by BF_3 rearrangement of tetrahydroparthenolide²¹ shows a signal at 8.28 τ for the C_4 vinyl methyl. The deshielding influence in this case is due to the hydroxy function at C_5 .

The NMR spectra of ketopalenolide¹⁷ 'a' (XXXVI) and ketopalenolide¹⁷ 'b' (XXXVII) in which the keto function is situated in the β position to the double bond show signals for the C₁₀ vinyl methyl at 8.345 and 8.365 τ respectively indicating that the deshielding influence of the keto function is negligible. In curdione¹⁸, (XXXVIII) which shows the value 8.4 τ , the keto function at C₃ which is in the β position of the double bond is not likely to have much deshielding influence on the vinyl methyl. This slightly higher value, for the C₁₀ methyl therefore appears to be due to the shielding influence of the π electrons of the keto group at C₅.

These facts would enable one to make assignments for the C₄ and the C₁₀ vinyl methyls in the other compounds mentioned in the table, in the beginning of this Chapter.

The above considerations would enable assignments to be made also for the C₄ and C₁₀ methyls in other compounds. also.

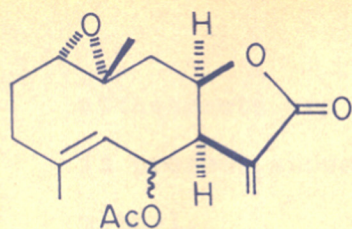
Thus in germacrone¹ (V) which shows signals at 8.58 and 8.395 τ , the higher value can be assigned to the C₄ methyl, considering its remoteness from the C₃ oxygen function, as compared to the C₁₀ methyl. In balchanolide (VI), eupatoriopicrin (VII) the higher values

are due to the C₁₀ methyl. The deshielding influence of the C₆ allylic oxygen on the C₄ methyl appears to be more than that of the C₈ oxygen function on the C₁₀ methyl, considering the values for the C₄ methyl in similar compounds.

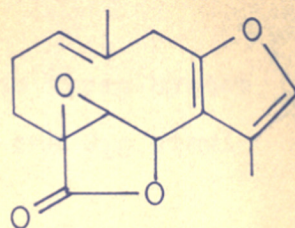
Epoxy lactones

Parthenolide¹⁶ (XXXIX), dihydroparthenolide¹⁶ (XL), pyrethrosin¹ (XLI) and linderane¹⁹ (XLII) are some of the compounds in which an epoxy ring has taken the place of one of the two double bonds in the usual arrangement. The NMR spectra of (XXXIX), (XL) and (XLII) show signals for the C₁₀ methyl at 8.29, 8.28, 8.43 τ indicating slight deshielding influence due to the epoxy ring at C₄ - C₅.

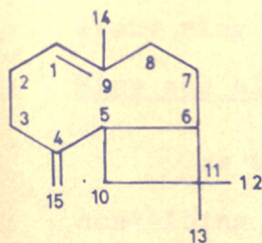
In the case of linderane¹⁹ (XLII) the higher value of 8.43 τ , in spite of the absence of C₄ - C₅ double bond and in addition a deshielding influence due to the epoxy ring at C₄ - C₅, is justified if a comparison is made with the corresponding value (8.72 τ) for the C₁₀ methyl in linderlactone (XIII). The abnormally high value of 8.72 τ for the C₁₀ vinyl methyl in linderlactone¹¹ (XIII) appears to be due to the shielding influence of the furan system since ~~for~~ aristolactone⁸ (X), where the position of the double bond and the lactone



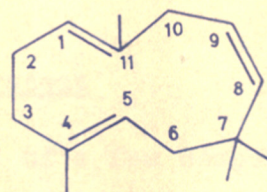
XL I



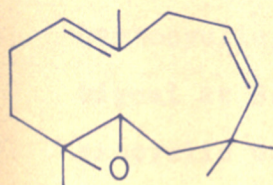
XL II



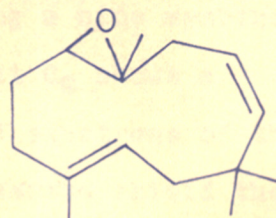
XL III



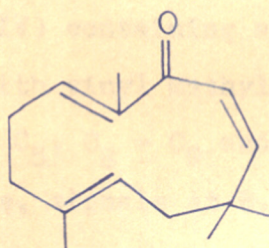
XL IV



XL V



XL VI



XL VII

attachments are identical but wherein no furan system is present, shows a value of 8.52 τ for the C₁₀ vinyl methyl.

In the case of pyrethrosin¹ (XLI) the lower value of 8.14 τ for the C₄ vinyl methyl is due to the deshielding influences of the C₆ acetate function and epoxy ring at C₁ - C₁₀.

Nine and eleven membered carbocyclic systems

We then examined the NMR spectra of a few compounds containing the nine membered and eleven membered carbocyclic systems with a view to ascertain whether such shielding influence of the π electrons on the vinyl methyls can be observed in these compounds also.

Caryophylline³ (XLIII) containing a nine membered carbocyclic system and a vinyl methyl at C₉ shows a signal at 8.4 τ . It appears that the π electrons of the exocyclic double bond at C₄ do not ~~xxxxxxxx~~ shield the methyl protons to any appreciable extent, which is in keeping with the observation made in the case of germacrane D¹⁴ (XXVIII).

Humulene³ (XLIV) containing an eleven membered carbocyclic system with vinyl methyls at C₄ and C₁₁ and double bonds at C₄ - C₅, C₈ - C₉ and C₁₁ - C₁, it shows, for the vinyl methyls, signals at 8.57 τ and 8.37 τ

respectively. The higher value (8.57 τ) can be ascribed to the C_4 methyl and the lower one (8.37 τ) to the C_{11} methyl on considerations similar to those used for the ten membered systems. The somewhat lower value for the C_{11} methyl may be due to the deshielding influence of the disubstituted double bond which is comparatively nearer to it.

The above assignments are supported when the NMR spectra of humulene epoxides are taken into consideration. The humulene epoxide²⁰ (XLV) containing the epoxy ring at $C_4 - C_5$ show for the C_{11} methyl a signal at 8.32 τ . The slight lowering in the value is due to the deshielding influence of the epoxy ring at $C_4 - C_5$ as described earlier. The other humulene epoxide (XLVI) which contains the epoxy ring at $C_1 - C_{11}$ shows for the C_4 methyl a signal at 8.46 τ and the lowering in the value can be attributed to the deshielding influence of the epoxy ring at $C_1 - C_{11}$. Since the trans disubstituted double bond is present in both (XLIV) and (XLVI) the lowering in value can be ascribed to the epoxy ring at $C_1 - C_{11}$ which is somewhat more significant as compared to the epoxy ring at $C_4 - C_5$.

Zerumbone³ (XLVII) is another example of an eleven membered carbocyclic system which contains an additional keto group at the C_{10} position in the humulene skeleton.

It shows signals at 8.46 τ and 8.2 τ for the vinyl methyls. The 8.46 τ value can be ascribed to the C₄ methyl and lower value to the C₁₁ methyl. The lowering in value, as expected, is due to the neighbouring keto function at the C₁₀ position.

EXPERIMENTALPartial hydrogenation of the ester (XIV):~~XXXXXXXXXX~~₃

The ester (5.7 g) in ethyl alcohol (150 ml) was hydrogenated using PtO_2 (200 mg) as catalyst. Hydrogenation was stopped after absorption of 600 ml hydrogen at N.T.P. which corresponds to one mole of hydrogen. After filtration, the solvent was removed under suction and the residue was diluted with water and extracted with ether. The ether layer was dried (Na_2SO_4) and ether on evaporation, gave a liquid (5.3 g) which was chromatographed on silica gel-silver nitrate (145 g, 15 g) and eluted as follows:

Fr.No.	Solvent	Total volume in ml	Weight in g
1	Hexane	700	3.25
2	Hexane + benzene 2:1	200	0.23
3	Hexane + benzene 1:1	400	0.99
4	Benzene	200	0.12
5	Ether	400	0.60

Fr. 1 (XX) TLC ($\text{SiO}_2 + \text{AgNO}_3$) single spot,
GLC - single peak, b.p. 135-140°(bath)/0.15 mm.,
 $n_D^{25.5}$ 1.473 (α)_D + 10.7° (c, 3.01).

Analysis

Found: C, 76.03; H, 11.19%. $C_{16}H_{28}O_2$

requires: C, 76.14; H, 11.18%.

IR Spectrum showed bands at: 2907, 1730, 1660, 1449, 1429, 1370, 1252, 1190, 1160, 1053, 986, 909 and 854 cm^{-1} .

NMR spectrum showed signals at: 9.3, 9.2, 9.1, 8.94, 8.87 τ (9H, C_4 , C_{10} , C_{11} methyls), 6.38 τ (3H, ester methyl), a multiplet around 4.62 τ (1H, C_6 olefinic proton).

Fr. 3 (XVII) TLC ($SiO_2 + AgNO_3$) single spot, GLC one peak; b.p. $120-125^\circ$ (bath)/0.1 mm. $n_D^{25.5}$ 1.481 (α)_D + 12.7° (c, 3.00).

Analysis

Found: C, 76.07; H, 11.2%.

$C_{16}H_{28}O_2$ requires: C, 76.14; h, 11.18%.

IR spectrum showed bands at 2900, 1733, 1667, 1449, 1370, 1250, 980, 906, 835, 862, 847, 820, 757, 730 and 694 cm^{-1} .

NMR spectrum showed signals at: 9.16 τ (3H, C_4 methyl), 8.94, 8.88 τ (3H, C_{11} methyl). 8.35 τ (3H, C_{10} methyl), 6.37 τ (3H, ester methyl) and a triplet at 4.68 τ (1H, C_1 olefinic proton).

LAH reduction of ester (XVII) to (XVIII)

The ester (0.8 g) was dissolved in dry ether (70 ml) and LAH (0.4 g) in dry ether (50 ml) was added at 0°. The solution was stirred at room temp. for 16 hours. The solution was cooled and excess of LAH was decomposed by alcohol and then cold water. Ether layer was washed with dil. HCl, water and dried (Na₂SO₄). On evaporation, ether^{layer} furnished a thick liquid (0.74 g). TLC - single spot, GLC - single peak; b.p. 140-150°(bath)/0.25 mm.; $n_D^{27.5}$ 1.4947; (α)_D + 5.8° (c, 2.76).

Analysis

Found: C, 79.88; H, 12.7%.

C₁₅H₂₈O requires: C, 80.29; H, 12.58%.

IR spectrum showed bands at : 3390, 2941, 1667, 1449, 1370, 1031, ⁹⁸⁰909, 870, 850, 820 and 757 cm⁻¹.

NMR spectrum showed signals at: 9.19, 9.09 τ (6H, C₄ and C₁₁ methyl), 8.35 τ (3H, C₁₀ methyl), 6.51, 6.6 τ (2H, C₁₃ methylene), a triplet at 4.55, 4.66, 4.81 τ (1H, C₁ - olefinic proton).

Conversion of alcohol (XVIII) to hydrocarbon (XIX)(a) Tosylate of the alcohol

The alcohol (0.6 g) was dissolved in pyridine (7 ml), toluene p-sulphonyl chloride (0.6 g)

added and reaction mixture was kept at room temp. for 48 hours. It was diluted with water and extracted with ether. The ether layer was washed with dil. HCl and water and dried (Na_2SO_4). On removal, ether furnished the tosylate, a liquid (0.72 g).

(b) LAH reduction of the tosylate

The tosylate (0.72 g) was dissolved in ether (50 ml) and LAH (0.5 g) in dry ether (50 ml) was added at 0° and solution was stirred by magnetic stirrer at a temp. of $35-40^\circ$, maintained by an IR lamp, for 24 hours. Then it was worked up as usual. Ether^{layer}, on evaporation, furnished a liquid (0.5 g), which was chromatographed on alumina (Gr. I, 25 g) and eluted with hexane. Hexane_{fraction}, on evaporation, gave the hydrocarbon, (0.3 g). It showed the following properties:

TLC - single spot, GLC - single peak;
b.p. $100-110^\circ$ (bath)/0.2 mm; $n_D^{26.5}$ 1.48 (α)_D + 10.2°
(c, 3.16).

Analysis

Found: C, 86.37; H, 13.75%.

$\text{C}_{15}\text{H}_{28}$ requires : C, 86.46; H, 13.54%.

IR Spectrum showed bands at: 2924, 1449, 1383, 980, 860 and 847 cm^{-1} .

NMR Spectrum showed signals at: 9.04, 9.15 τ (9H, C_4 and C_{11} methyls), 8.37 τ (3H, C_{10} methyl) and a triplet

at 4.54, 4.67 and 4.87 (1H, C₁ olefinic proton).

LAH reduction of the ester (XX) to the alcohol (XXI)

The ester (1.76 g) was similarly reduced to the alcohol (1.6 g) using LAH (1.0 g). GLC - single peak, TLC - single spot; b.p. 140-150° (bath)/0.3 mm
 $n_D^{27.5}$ 1.48 g (α)_D + 39° (c, 3.07).

Analysis

Found: C, 79.82; H, 12.83%

C₁₅H₂₈O requires: C, 80.29; H, 12.58%.

IR Spectrum showed bands at: 3333, 2941, 1667, 1449, 1370, 1031, 990, 909, 757 and 725 cm⁻¹.

NMR spectrum showed signals at: 9.09, 9.18 (9H, C₄, C₁₀ and C₁₁ methyls), 6.52, 5.6 (2H, C₁₃ methylene), a multiplet at 4.58 (1H, C₆ olefinic proton).

Conversion of the alcohol (XXI) to the hydrocarbon (XXII)

Alcohol (1.2 g) was similarly converted to hydrocarbon (0.7 g) and chromatographed on alumina (Gr. I, 35 g) and eluted with hexane. Hexane ^{fraction} 4, on evaporation gave a hydrocarbon (0.63 g). TLC - single spot, GLC - single peak; b.p. 100-110° (bath)/0.4 mm.
 $n_D^{26.5}$ 1.4749, (α)_D + 7.5° (c, 4.75).

Analysis

Found: C, 86.38; H, 13.71%.

C₁₅H₂₈ requires: C, 86.46; H, 13.54%.

IR spectrum showed bands at: 2941, 1460, 1374, 986, 790, 730 cm^{-1} .

NMR spectrum showed signals at: 9.1, 9.2 (12H, C_4 , C_{10} and C_{11} methyls) and a doublet at 4.6, 4.7 τ (1H, C_6 olefin proton).

Ozonolysis of the ester (XX)

A stream of ozonised oxygen was passed through a solution of the ester (2.0 g) in chloroform (30 ml) at -10° . After complete ozonization chloroform was removed at 40° in vacuum and the product was decomposed by heating with water and hydrogen peroxide (30% 60 ml) on water bath for five hours. The solution was extracted with ether. Ether layer was extracted with sodium carbonate and finally washed with water and dried (Na_2SO_4). The carbonate solution was acidified with dil. HCl and extracted with ether. Ether layer was washed with water and dried (Na_2SO_4). Removal of ether furnished the acid (0.9 g) which was esterified to the ester XXIII as follows:

Esterification

To the acid (0.9 g) dissolved in dry ether (30 ml) and cooled to 0° , solution of diazomethane cooled at 0° was added till yellow colour persisted. The solution was kept at 0° for two hours. It was washed with sodium carbonate solution followed by water and dried (Na_2SO_4). Removal of ether furnished a liquid (0.85 g) which was chromatographed

on alumina (Gr. III, 25 g) and eluted as follows:

Fr.	Solvent	Volume in ml	Weight in g
1	Hexane	100	0.15
2	Hexane + benzene 2:1	200	0.60
3	Hexane + benzene 1:1	100	0.02
4	Benzene	50	0.03

Fraction 2 - TLC - single spot; b.p.170-180°(bath)/
0.5 mm.; n_D^{33} 1.4442.

IR spectrum showed bands at: 2941, 1724, 1449, 1422,
1370, 1250, 1190, 1156 and 813 cm^{-1} .

NMR spectrum showed signals at: 9.21, 9.11 τ (3H,
 C_{10} methyl), 8.93, 8.82, 8.73 (6H, C_4 and C_{11} methyls)
and 6.4 τ (6H, ester methyls).

NMR spectrum did not show any methyl ketone signal, so
(XX)
the double bond in the ester was in the $\text{C}_6 - \text{C}_7$ position.

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Part – IV

Fragmentation of Costunolide and
its Derivatives under Electron Impact

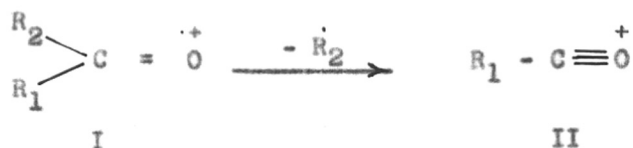
S U M M A R Y

An attempt has been made to correlate the fragmentation modes on electron impact and structure of costunolide (IX) and its derivatives, containing a ten membered carbocyclic system. The possible origins for the major fragments have been determined, using high resolution mass spectrometry and deuterium labelling.

In recent times, mass spectrometry has become a particularly effective physical method for structure elucidation.

The first process in mass spectrometry is the removal of a single electron from the molecule to provide a molecular ion, which then undergoes bond-fission. Fragment ions are also found which can be formed from the parent ions by bond rupture and rearrangement processes closely resembling those which occur in reaction mechanisms of thermally excited neutral molecules. The molecular ion is of fundamental importance to ascertain the correct molecular weight of the compound. In the substances possessing a heteroatom, one of the non-bonding electrons of the heteroatom is the first to be removed.

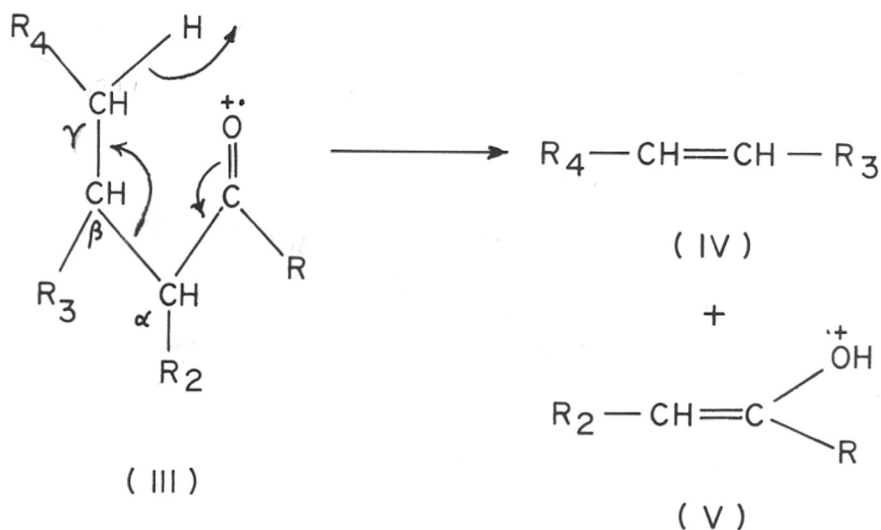
In the case of carbonyl compounds, the predominant ion will be I which will direct the fragmentation process.



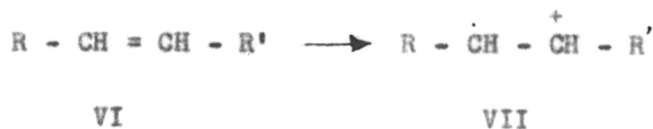
A favourable fragmentation of the ion (I) will result from the cleavage of the bond between the carbonyl group and α -carbon atom. This is referred to as α -cleavage. The charge remains with the oxygen containing fragment (II) and

it will be stabilised by formation of a triple bond.

Alternatively the molecular ion represented as III can fragment by a cleavage of the bond between α and β -carbon atoms with the migration of γ hydrogen to oxygen. It is referred to as β -cleavage. This will result in the formation of olefine molecule^{e-} (IV) and charged enol ion (V).



In the unsaturated hydrocarbons ionisation of double bond occurs through the removal of a π electron, thus an ion radical(VII) will be obtained from(VI).

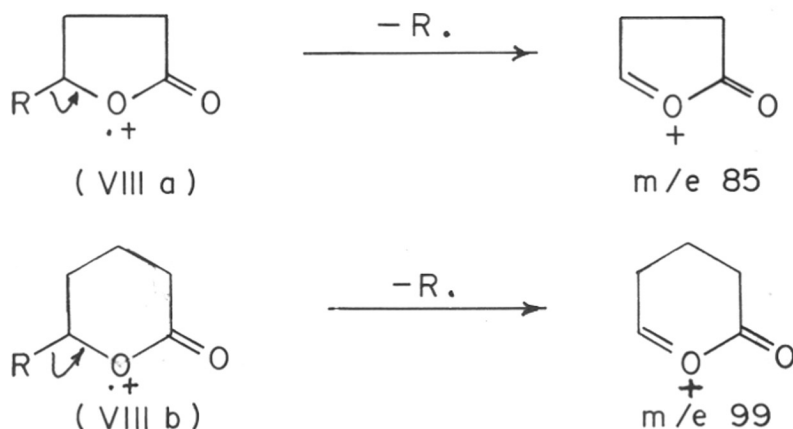


In the electron impact reactions, two types of rearrangements are possible, viz. (i) those involving migration of a hydrogen atom and (ii) migration of groups. The latter class can lead to skeletal rearrangements. Migration occurs to electron deficient centres, generated by removal of an electron in the ionisation process.

In the interpretation of mass spectrometric fragmentation processes, isotopic labelling has proved very helpful. Deuterium is one of the most important isotopes. The replacement of a specific hydrogen atom by deuterium, not only labels a given portion of the molecule but also provides information on the occurrence and origin of hydrogen transfer reactions. Exchange with enolisable hydrogens is one of the procedures employed for introducing deuterium.

High resolution mass spectrometry is helpful in the differentiation of isobaric fragments. It offers the possibility of separating peaks with a very low mass difference. When more than one ion species are existing, it makes possible the measurement of the mass of any ion in the spectrum with sufficient precision to deduce its empirical formula or at least to restrict the number of such possible formulae.

In the aliphatic γ and δ lactones of the general formulae VIIIa and VIIIb respectively (in which R is a saturated alkyl group) peaks at m/e 85 and m/e 99 arise due to cleavage of the bond adjacent to oxygen^{1,2}.



This fragmentation helps in differentiating isomeric γ and δ lactones of this type.

Recently the mass spectra of santonins and their derivatives^{3,4} have been investigated in order to obtain information on the fragmentation of fused ring lactones. The most common feature of the spectra of the santonins is associated with an abundant ($M-73$) ion, shown by high resolution measurements to arise from the expulsion of $C_3H_5O_2$. Hence elimination of the γ -lactone ring occurs in association with one additional hydrogen atom.

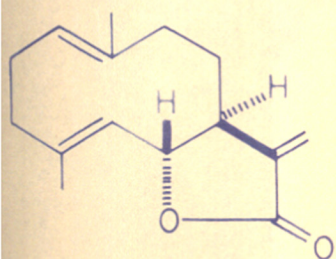
Present work

So far, the behaviour, under electron impact, of sesquiterpenic lactones, with a ten membered carbocyclic system, does not seem to have received much attention and hence mass spectrometric study of costunolide (IX) (Fig. 1), the parent lactone of such a group and its derivatives was undertaken. The results are described in this part of the thesis.

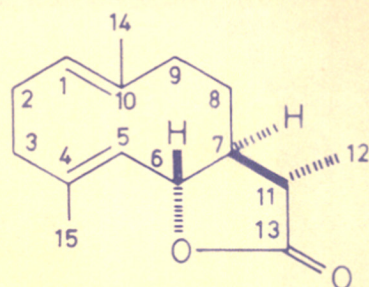
From costunolide (IX), the dihydrocostunolide (X)⁵ (Fig. 2) tetrahydrocostunolides (XI and XII) (Fig. 3 and Fig. 4), hexahydrocostunolide (XIII)⁵ and 12-methoxy dihydrocostunolide (XIV)⁷ are prepared by known procedures described in Part I of this thesis.

A comparative study of the mass spectra of lactones IX to XII, has revealed some common fragmentation modes and a few significant differences of diagnostic value in structure elucidation.

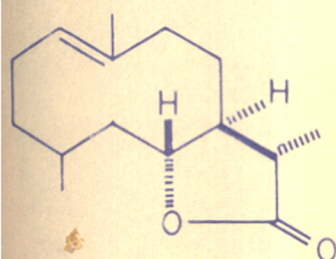
The thermal rearrangement⁶ of X and the transannular acid catalysed cyclization^{8,9} of IX and X are known. In order to explain satisfactorily some fragmentation modes induced by electron impact in IX, X and XII, it is necessary to assume that similar processes are operating in the vapour state. Table 1 gives the relative intensities of some significant ions observed in the



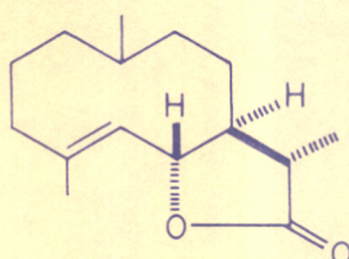
(IX)



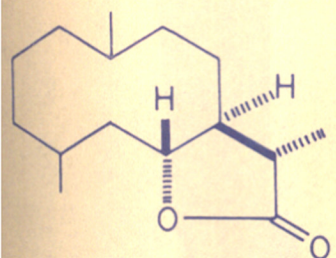
(X)



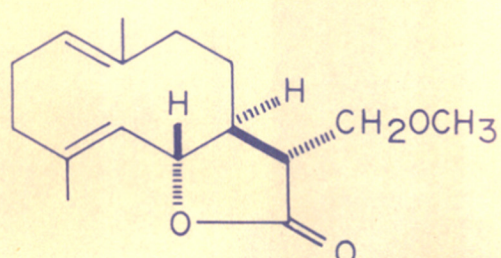
(XI)



(XII)



(XIII)



(XIV)

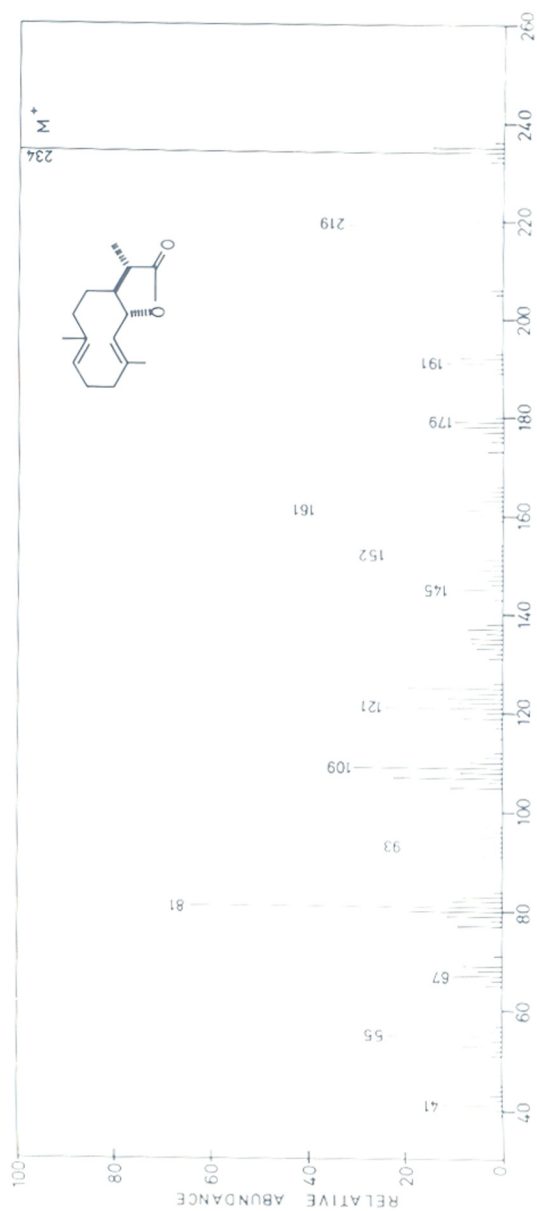


FIG. 2. MASS SPECTRUM OF DIHYDROCOSTONOLIDE

spectra of these lactones. For comparison, values for the saturated lactone (XIII) are also included.

Table 1

Percentage relative intensities

Ions	IX	X	XI	XII	XIII
M ⁺	27.6	100.0	90.8	97.8	4.8
(M - 15) ⁺	8.7	32.0	9.7	27.1	<1
(M - 28) ⁺	4.0	2.3	1.0	27.1	17.7
(M-43) ⁺	7.8	11.3	5.5	100.0	3.8
(M - 57) ⁺	11.9	4.3	5.9	73.0	1.4
(M - 71) ⁺	12.5	5.3	100.0	75.0	2.8
(M - 73) ⁺	7.6	38.0	33.5	64.6	21.2
(M - 85) ⁺	15.1	5.0	33.0	63.0	1.9

In lactones IX to XII, the double bond appears to trigger the primary fragmentation process. Depending on its location, differences are observed in the fragmentation patterns or in the relative intensities of some fragments. Sometimes, the migration of double bonds, induced by electron impact alters the expected cleavages¹⁰.

The insignificant value of (M - 15)⁺ ion in XIII, suggests that the contribution from the methyl groups at C₄, C₁₀ and C₁₁, to the formation of this ion is negligible.

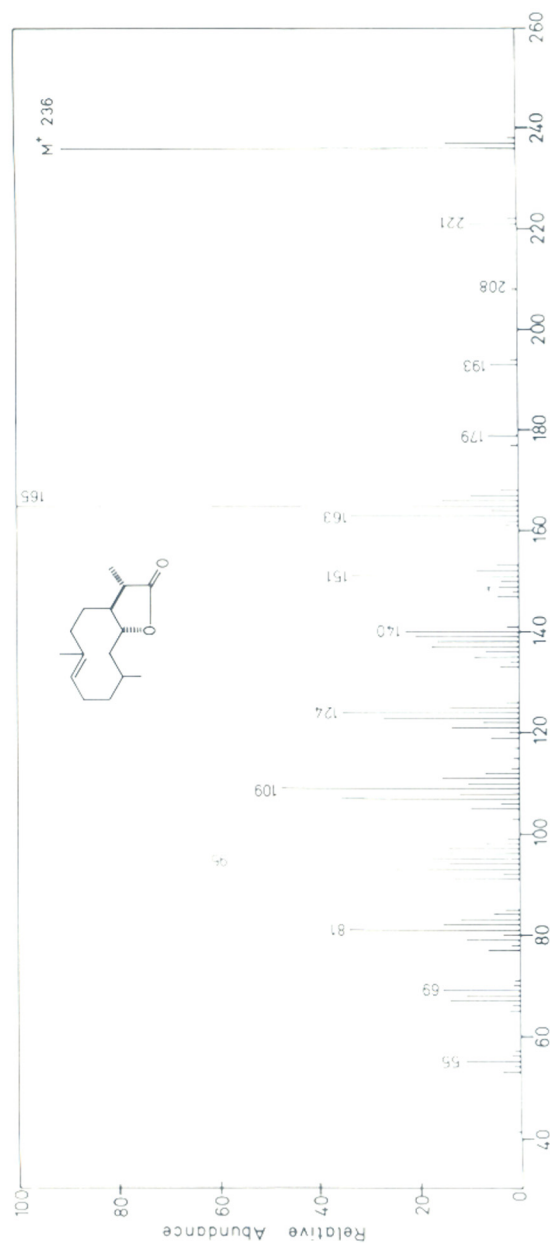
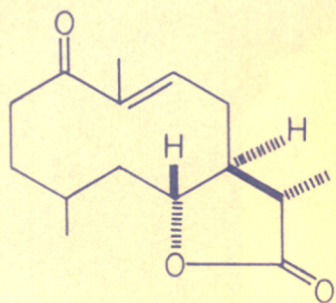
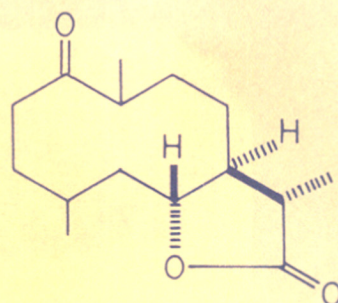


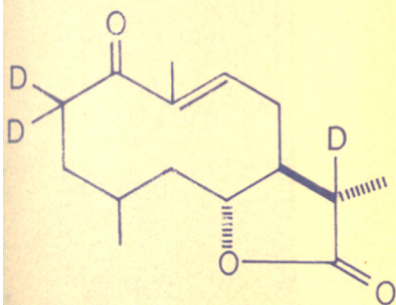
FIG. 3. MASS SPECTRUM OF TETRAHYDROCOSTUNOLIDE



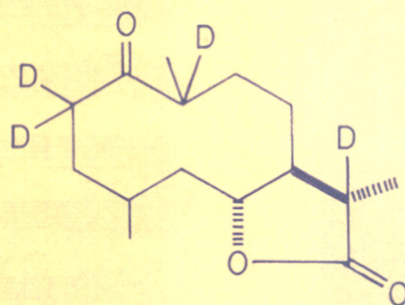
(XV)



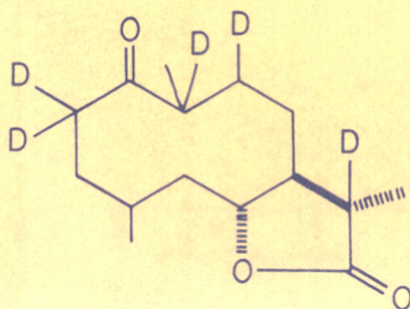
(XVI)



(XVII)



(XVIII)



(XIX)

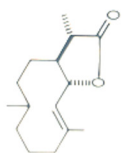
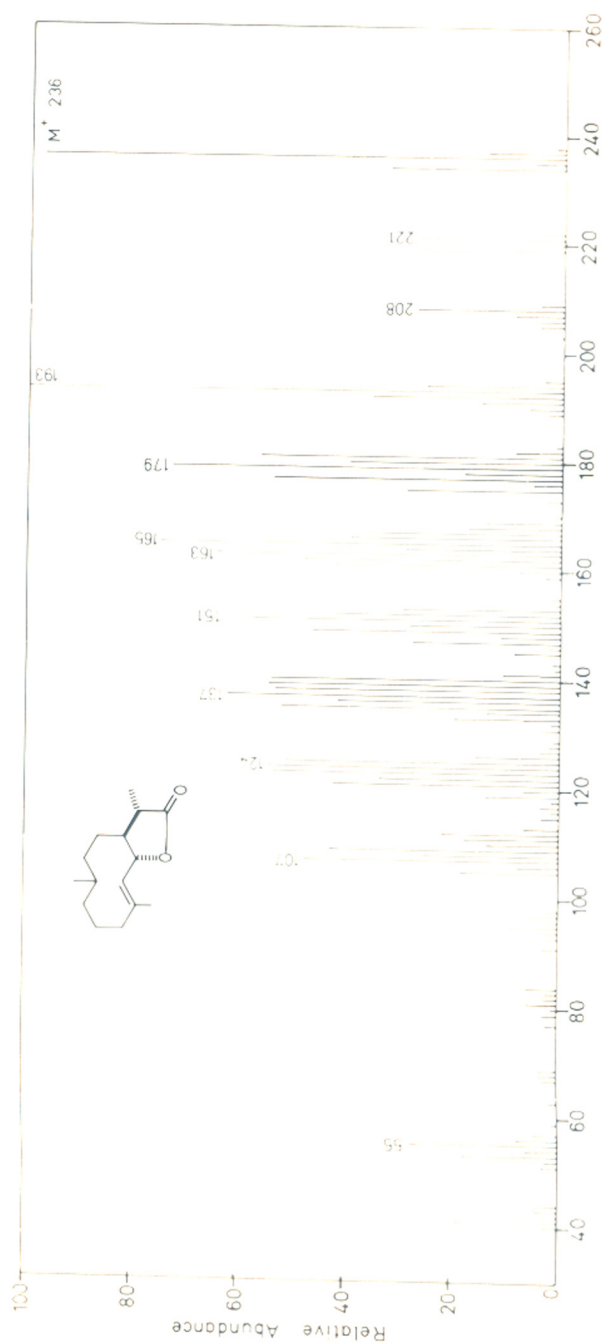


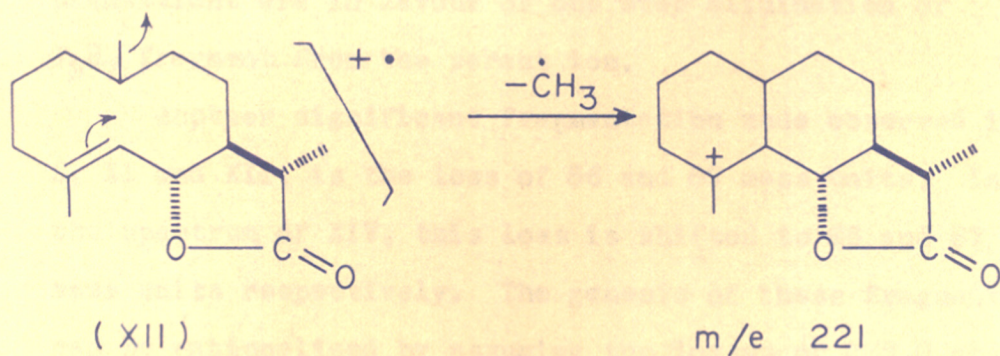
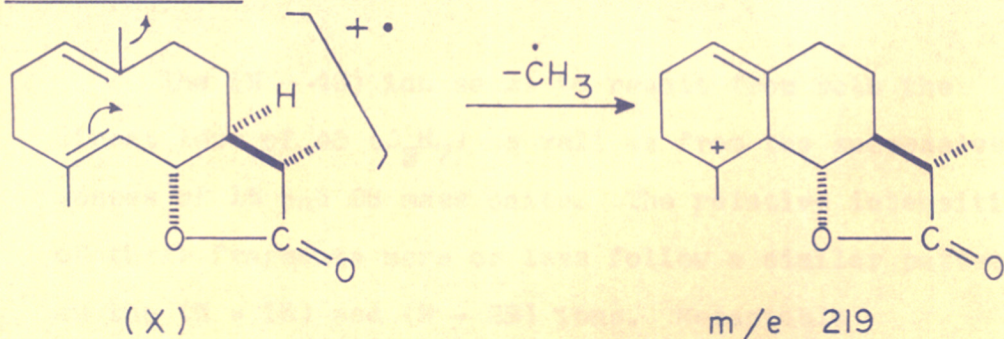
FIG. 4. MASS SPECTRUM OF TETRAHYDROCOSTONOLIDE

This ion is, however, significant in the lactones IX to XII, which is difficult to rationalise. The intensities of these ions in X and XII are comparable with that observed in (-) santonin (33%), where the major contribution has been proposed to come from the angular methyl group³. A concerted cyclisation mechanism, leading to the elimination of a methyl radical, appears to contribute considerably to the formation of this ion in X and XII as indicated in Scheme 1.

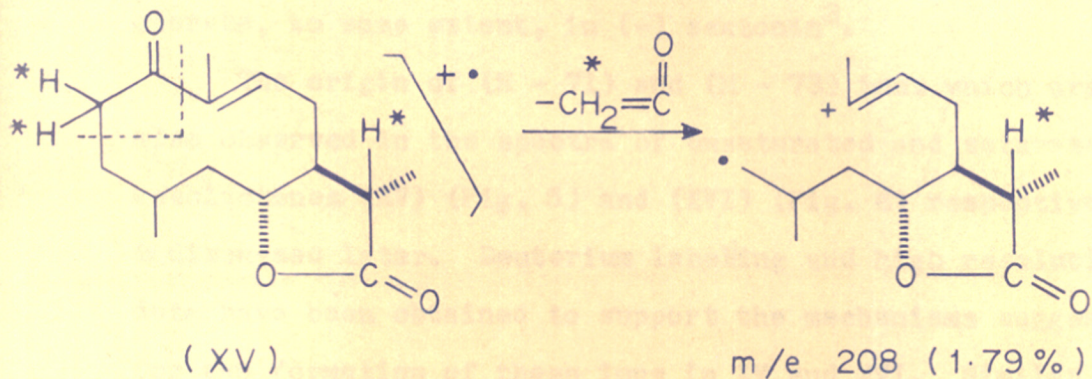
In lactone XI, such concerted mechanism cannot lead to the elimination of a methyl radical. The known tendency of lactone (IX) to polymerise even at room temperature, makes an absolute comparison difficult.

The loss of carbon monoxide (loss of 28 mass units) from the lactone moiety has been shown to be a minor fragmentation mode¹ in aliphatic lactones. The lower intensities of (M - 28) ions in the spectra of X and XI corroborate this fact. The slightly higher intensity of this ion in IX, however, is probably due to the presence of the conjugated exocyclic double bond. Similar observations were made in the spectra of some conjugated pseudoguaianolides¹⁵. In lactones IX to XII, the major contribution to this ion appears to come from the loss of CO as indicated by high resolution data. The high value of this ion in XII arising from the loss of CO, is remarkable, however.

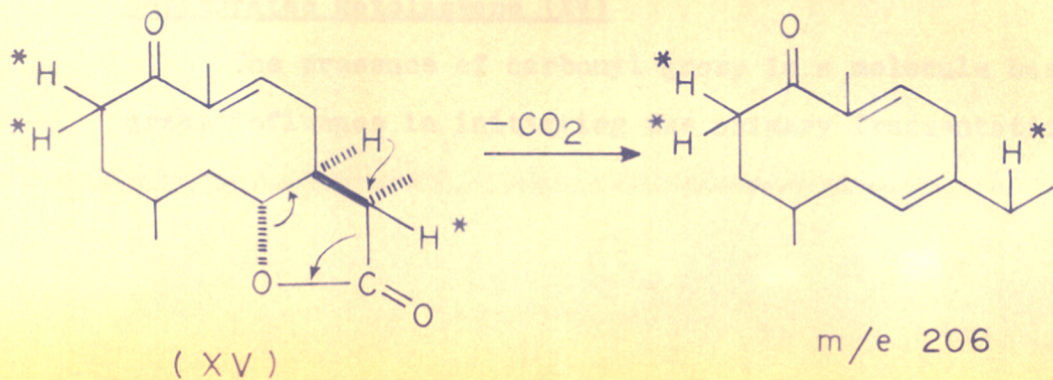
SCHEME - 1.



SCHEME - 2.



SCHEME - 3.



The ($M - 43$) ion seems to result from both the direct loss of 43 (C_3H_7) as well as from the successive losses of 15 and 28 mass units. The relative intensities of these fragments more or less follow a similar pattern as the ($M - 15$) and ($M - 28$) ions. Metastable transitions are in favour of one step elimination of C_3H_7 fragment from the parent ion.

Another significant fragmentation mode observed in X, XI and XII, is the loss of 56 and 57 mass units. In the spectrum of XIV, this loss is shifted to 86 and 87 mass units respectively. The genesis of these fragments can be rationalised by assuming the losses of C_3H_4O and C_3H_5O from the lactone moiety from IX to XII by α -cleavage. Similar mechanism has been suggested to operate, to some extent, in (-) santonin³.

The origin of ($M - 71$) and ($M - 73$) ions which are also observed in the spectra of unsaturated and saturated ketolactones (XV) (Fig. 5) and (XVI) (Fig. 6) respectively is discussed later. Deuterium labeling and high resolution data have been obtained to support the mechanisms suggested for the formation of these ions in XV and XVI. Similar mechanisms can operate in lactones, IX to XII.

Unsaturated ketolactone (XV)

The presence of carbonyl group in a molecule has a great influence in initiating the primary fragmentation

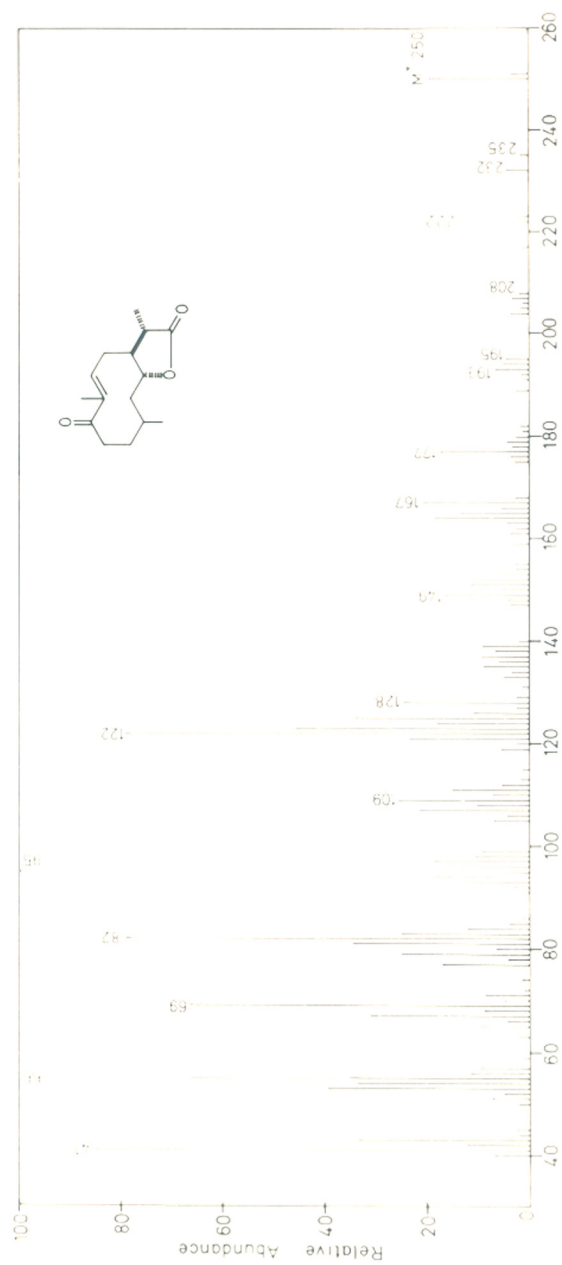


FIG 5. MASS SPECTRUM OF UNSATURATED KETOLACTONE

modes. As expected the stability of the molecular ion is considerably reduced (X, 100%, XI 90.8% but XV 19%).

The loss of a CH_3 radical is not significant (1.5%), suggesting that a cyclisation mechanism is not a favoured process.

The loss of H_2O ($M - 18$) (4.16%) can arise from (a) carbonyl group at C_1 and (b) from the lactone ethereal oxygen as suggested by McFadden et al.¹, due to the availability of hydrogen atom for a favourable transfer. Since in lactones IX to XII, the loss is negligible ($< 1\%$), it appears that the major contribution to this ion in XV is from the carbonyl group.

The loss of 28 mass units appears to be mostly due to carbon monoxide (and not C_2H_4 from C_2 and C_3) since, the same loss is observed in the deuterated compound (XVII). This is further confirmed by high resolution data.

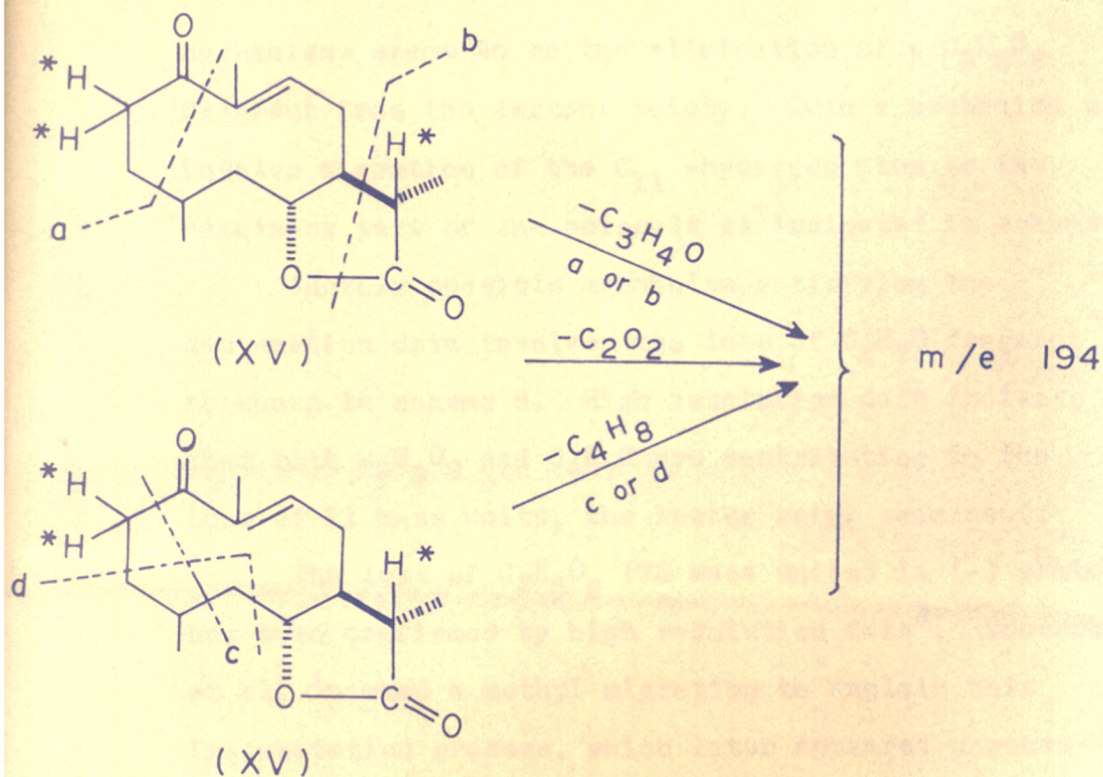
One of the characteristic fragmentation modes of cyclic α , β -unsaturated ketones¹¹ is the intense ($M - 42$) ($\text{C}_2\text{H}_2\text{O}$ i.e. CH_2CO) peak. This process is relatively insignificant (1.8%) in the fragmentation of (XV). Since this ion is shifted by only one mass unit (becomes 209) in the trideuterated analogue (XVII), the carbon atoms C_1 and C_2 are involved in the process, as indicated in scheme 2.

A rearrangement process leading to the expulsion of carbon dioxide (44) operates in (XV) to a small extent. The spectrum of the deuterated analogue shows the same loss. In this respect, it resembles (-) santonin as shown in scheme 3.

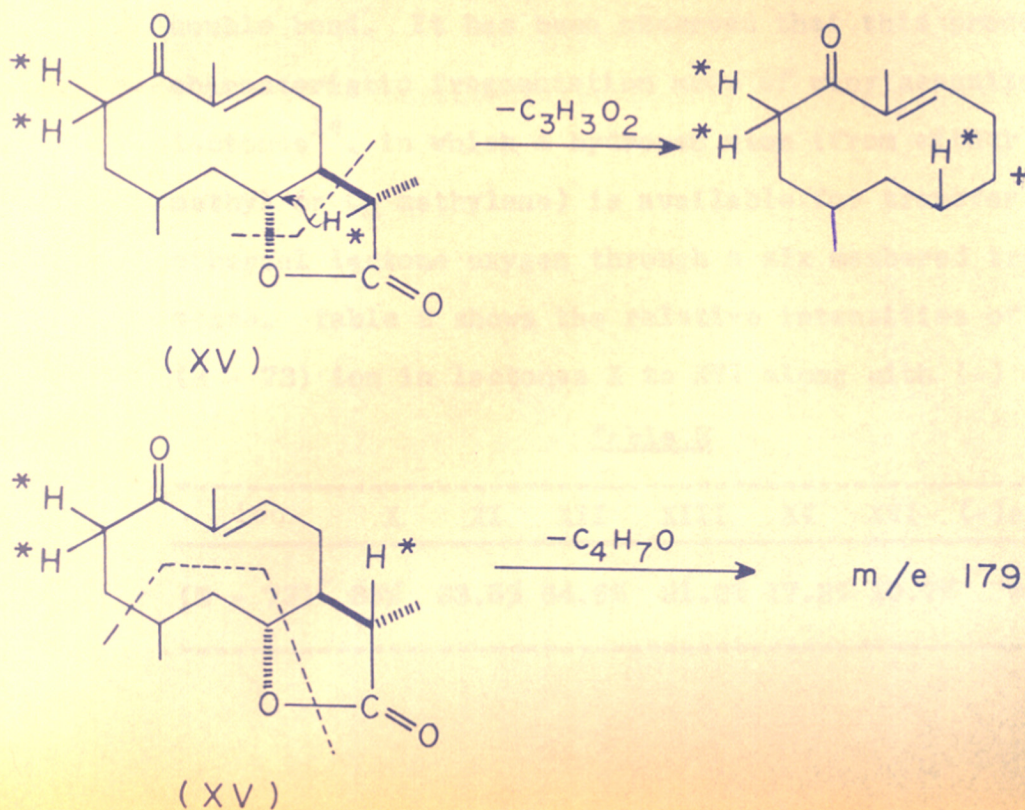
The fragmentation reactions leading to the loss of 56 and 57 mass units appear to be very complex processes. Attempts are made to analyse these fragments to find out the contribution from various competing processes. Deuteration and high resolution studies indicate that this fragmentation mode is due to the loss of C_3H_4O , C_4H_8 and C_2O_2 (insignificant) fragments as indicated in scheme 4. This is followed by the loss of one hydrogen atom to give the $(M - 57)^+$ ion. The elimination of C_3H_4O can take place either from the lactone moiety as mentioned earlier in lactones X to XII or from the ten-membered ring involving carbon atoms C_1 , C_2 and C_3 . Similarly the C_4H_8 fragment can be lost in two different ways as indicated in scheme 4. The loss of 56 mass units due to C_2O_2 is considerable.

It is not possible to assume the formation of m/e 179 ($M - 71$) fragment by a successive loss of 56 and 15 mass units as in (-) santonin. Since, the same loss is observed in the deuterated analogue, one of the possible

SCHEME - 4 .



SCHEME - 5 .



mechanisms seems to be the elimination of a $C_3H_3O_2$ fragment from the lactone moiety. Such a mechanism would involve migration of the C_{11} -hydrogen atom to the remaining part of the molecule as indicated in scheme 5.

Another possible mechanism satisfying the deuteration data involves the loss of C_4H_7O fragment as shown in scheme 5. High resolution data indicate that both $C_3H_3O_2$ and C_4H_7O are contributing to the loss of 71 mass units, the latter being prominent.

The loss of $C_3H_5O_2$ (73 mass units) in (-) santonin has been confirmed by high resolution data⁴. Boocock et al.³ invoked a methyl migration to explain this fragmentation process, which later appeared unnecessary¹². It was suggested, however, that the process is triggered by removal of one of the π electrons from the $C_4 - C_5$ double bond. It has been observed that this process is a characteristic fragmentation mode of many sesquiterpenic lactones¹⁴, in which a hydrogen atom (from either C_4 methyl or C_8 methylene) is available for transfer to the ethereal lactone oxygen through a six membered transition state. Table 2 shows the relative intensities of the (M - 73) ion in lactones X to XVI along with (-) santonin.

Table 2

ion	X	XI	XII	XIII	XV	XVI	(-)-santonin
(M - 73) ⁺	38%	33.5%	64.6%	21.2%	17.2%	10.7%	20.6% 90.6%

It is obvious from the table that the presence of a double bond in the $C_4 - C_5$ position is not a rigid structural requirement for this process, though it does facilitate such a reaction. Although both lactones X and XII fulfil these structural requirements, the intensity of this ion is lower in X than in XII. This can only be rationalised by assuming that a competing cyclisation mechanism, involving this double bond, is operating in X to a greater extent as suggested earlier for explaining the loss of methyl.

In compound XIV, which contains a $-CH_2OCH_3$ group at C_{11} , a loss of 103 ($C_4H_7O_3$) mass units is observed instead of a loss of 73, in IX - XII, while in the deuterated analogue (XVII) the loss is shifted to 74 mass units. Hence, both C_{11} and C_{13} carbon atoms are involved in the loss. This is further supported by high resolution data which indicate that loss of 73 is due to $C_3H_5O_2$ fragment.

The m/e 168 ion ($M - 82$) can result by a loss of C_5H_6O fragment involving cleavage α - to the carbonyl and β - to the double bond as indicated in scheme 6. Since the fragment with mass 82 (79%) is prominent, it is possible that the charge is carried by both the fragments.

The m/e 167 ion may be considered to be formed by a rearrangement process involving the transfer of a hydrogen atom to the C_1 - carbonyl, resulting in the

rupture of the $C_1 - C_2$ bond, followed by cleavage of the $C_7 - C_8$ bond. Deuteration studies indicate that these peaks are shifted by 3 mass units, suggesting that the hydrogen atoms at C_2 and C_{11} are not participating. High resolution data supported the above view. The successive loss of 73 ($C_3H_5O_2$) and 28 (CO) mass units, satisfactorily explains the genesis of the m/e . 149 ion, which was shifted to m/e 151 in the spectrum of the deuterated analogue.

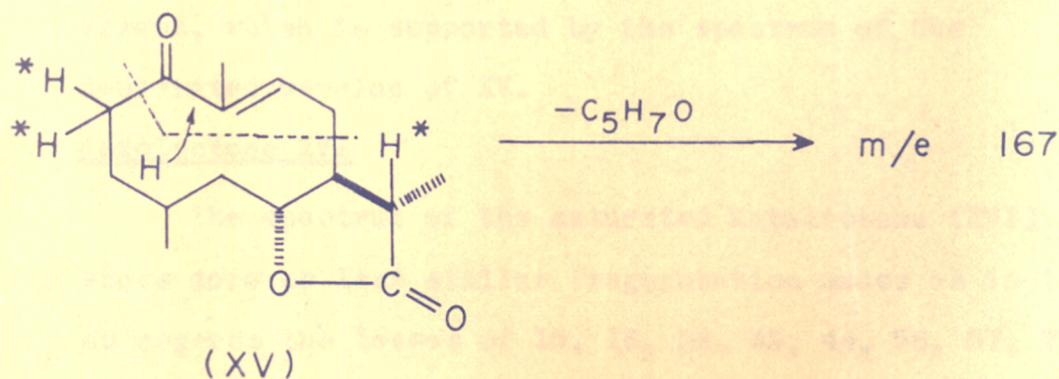
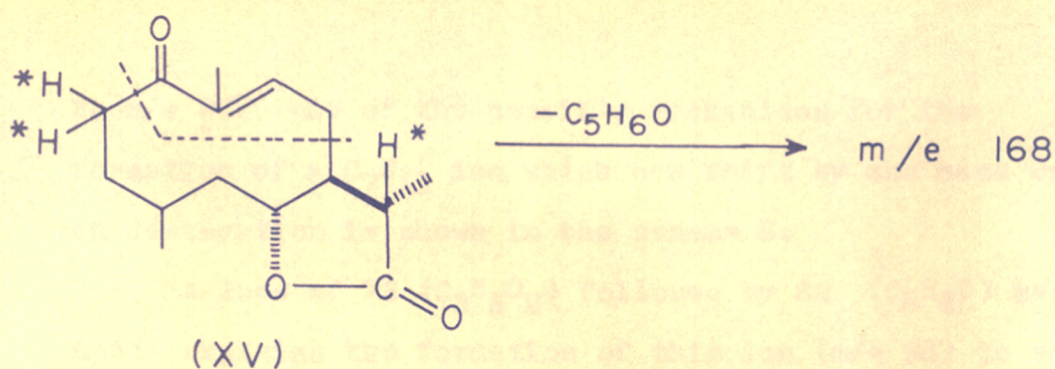


High resolution data indicate that the peak at m/e 122 is a doublet comprising of $C_8H_{10}O$ and C_9H_{14} ions in the ratio 10:1. On deuteration this peak is partly shifted to m/e 123, while a considerable portion remains unaffected. The C_9H_{14} ion can arise by the successive loss of 71 ($C_3H_3O_2$) and 57 (C_3H_5O) mass units as indicated in scheme 7.

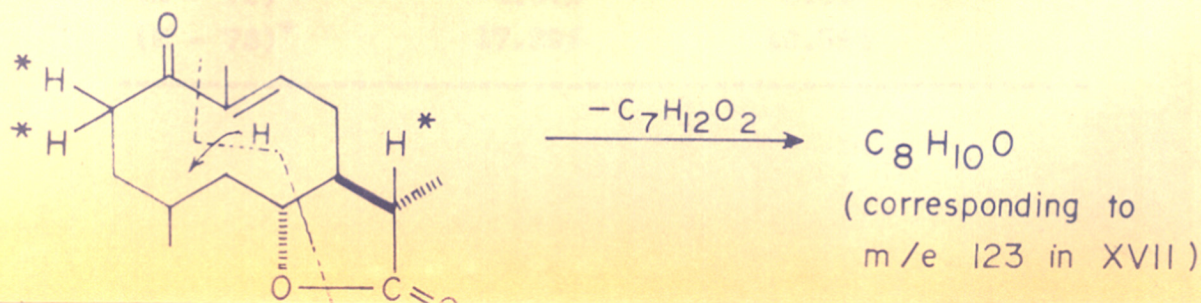
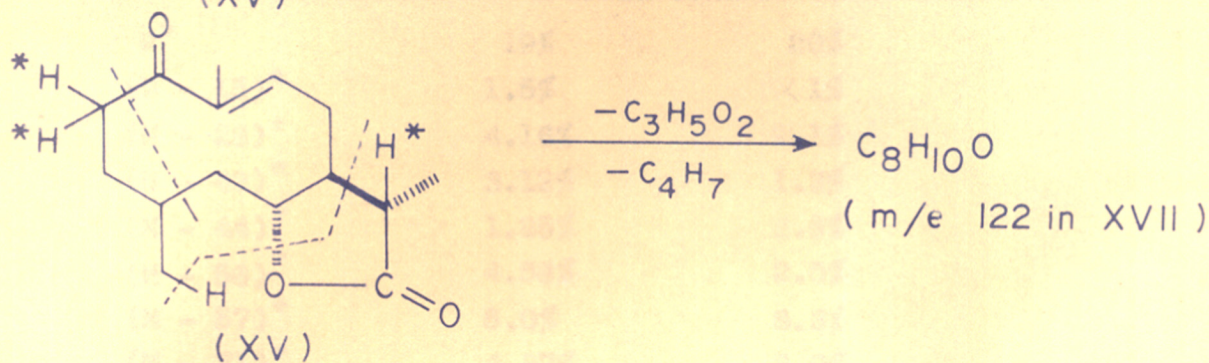
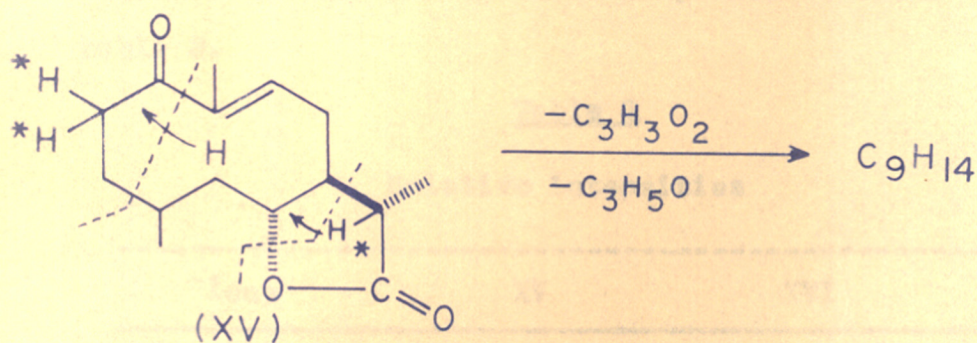
The ion $C_8H_{10}O$ can result by two different mechanisms involving hydrogen transfer, which corroborate the data obtained by deuteration studies, as shown in scheme 7.

The peak at m/e 95 (base peak) is also a doublet, comprising of C_7H_{11} and C_6H_7O in the ratio 3:1. In the spectrum of the deuterated compound it is partly shifted

SCHEME - 6.



SCHEME - 7



to m/e 96. One of the possible mechanisms for the formation of a C_7H_{11} ion which can shift by one mass unit on deuteration is shown in the scheme 8.

A loss of 73 ($C_3H_5O_2$) followed by 82 (C_5H_8O) mass units explains the formation of this ion (m/e 95) to some extent, which is supported by the spectrum of the deuterated version of XV.

Ketolactone XVI

The spectrum of the saturated ketolactone (XVI) shows more or less similar fragmentation modes as in (XV) as regards the losses of 15, 18, 28, 43, 44, 56, 57, 71 and 73 mass units. Differences are observed in the relative intensities of these fragments as shown in table 3.

Table 3

Relative intensities

Ions	XV	XVI
M^+	19%	20%
$(M - 15)^+$	1.5%	< 1%
$(M - 28)^+$	4.16%	2.1%
$(M - 43)^+$	3.12%	1.3%
$(M - 44)^+$	1.25%	2.9%
$(M - 56)^+$	4.58%	2.0%
$(M - 57)^+$	5.0%	8.3%
$(M - 71)^+$	4.37%	8.0%
$(M - 73)^+$	17.29%	10.58%

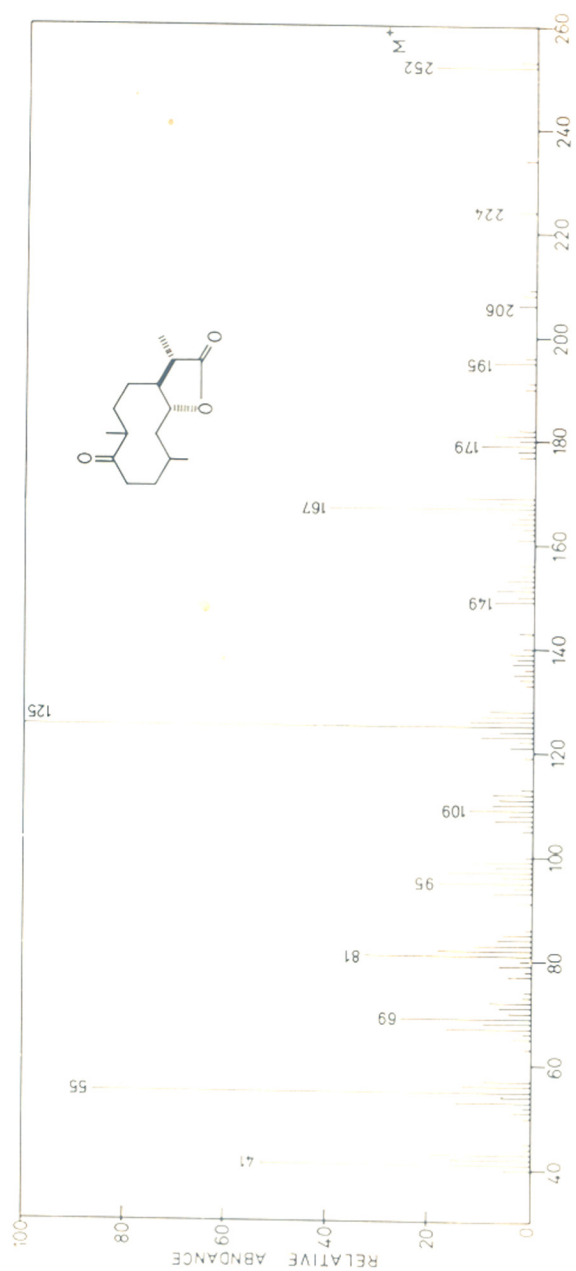
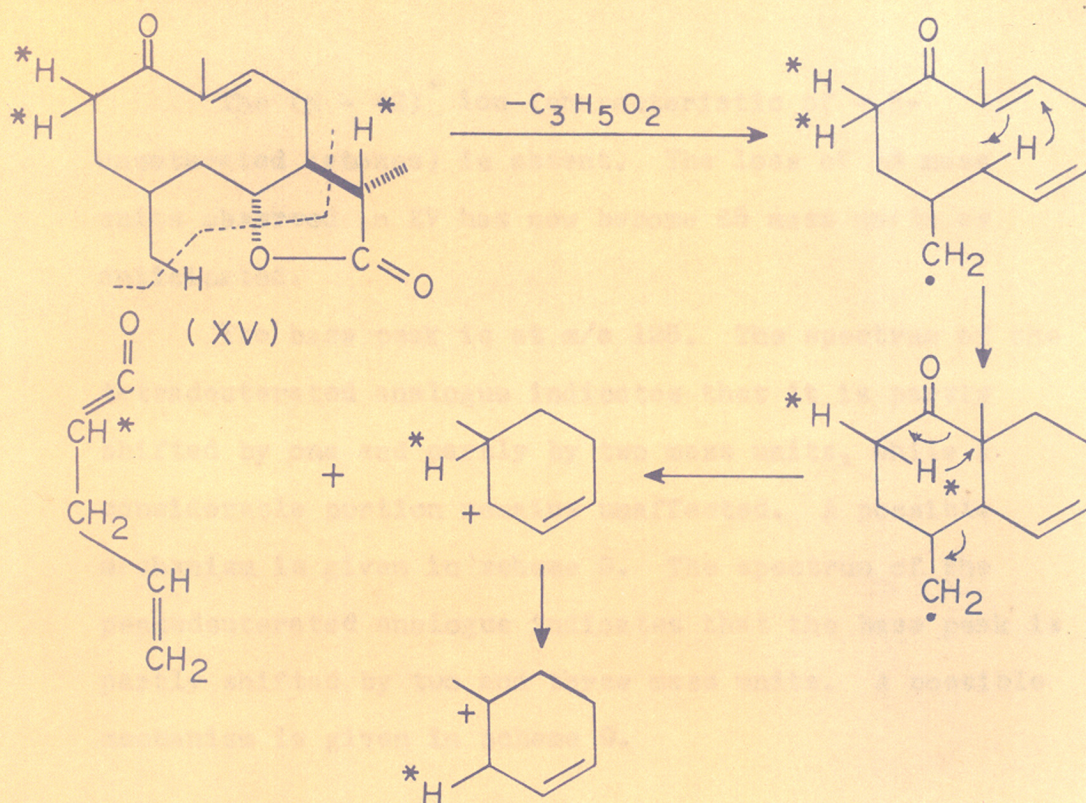
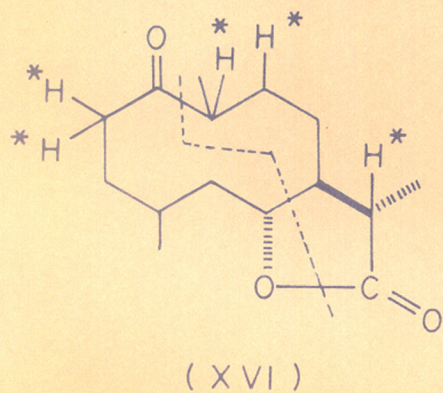
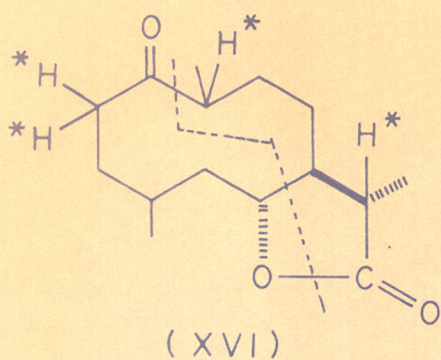


FIG. 6. MASS SPECTRUM OF SATURATED KETOLACTONE

SCHEME - 8 .



SCHEME - 9 .



The $(M - 42)^+$ ion (characteristic of α,β -unsaturated ketones) is absent. The loss of 83 mass units observed in XV has now become 85 mass units as anticipated.

The base peak is at m/e 125. The spectrum of the tetradeuterated analogue indicates that it is partly shifted by one and partly by two mass units, while a considerable portion remains unaffected. A possible mechanism is given in scheme 9. The spectrum of the pentadeuterated analogue indicates that the base peak is partly shifted by two and three mass units. A possible mechanism is given in scheme 9.

EXPERIMENTAL

Lactone X⁵, XV¹³ and XVI¹³ were prepared from costunolide (IX)⁵ isolated from the oil of costus roots (*Saussurea lappa* Clarke).

The tetrahydrocostunolides (XI) and (XII) were obtained by partial hydrogenation of (X) and separated by extensive chromatography over alumina and silver nitrate-impregnated silica gel as already described in Part I of this thesis. The structures of these compounds have been established from spectral data and chemical reactions as described in Part I.

Complete hydrogenation of X gave XIII.

Deuteration of XV and XVI

It was carried out by repeated equilibration of XV with CH₃OD and Na, to yield a mixture XVII, consisting of 60% trideuterated, 34% dideuterated and 6% monodeuterated analogues (mass spectral analytical data).

The tetradeuterated analogue of XVI viz. XVIII was similarly obtained and consists of 27% tetradeuterated, 37% trideuterated, 23% dideuterated, 11% monodeuterated and 2% unchanged. XVI.

For obtaining the pentadeuterated analogue (XIX), the lactone XV was initially catalytically deuterated in CH_3OD solution to a product containing a major portion of the dideuterated analogue (mass spectrum). This was then equilibrated as above to furnish the pentadeuterated product having 48% pentadeuterated, 34% tetra-deuterated, 14% trideuterated and 4% dideuterated analogues.

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