Investigations on the Terpenic Constituents of Costus Root Oil

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(S.V. Hiremath)

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[3]

CONTENTS

INTRODUCTION

The costus plant, Saussurea lappa Clarke (compositae family) is a valuable Indian raw material grown extensively in Punjab and Kashmir at high altitudes[1]. In India it is known under various names[2,3] such as Kuth, Kut, Kashmirja etc. The roots of the plant are reputed for medicinal properties and have been prescribed in indigenous system of medicine[2,3,4] as a remedy against various ailments such as cough, asthma, fever, ulcers, tumers, skin diseases etc. The roots are known to contain a fragrant principle also and used to be exported to China and Japan in large quantities for burning as incence in Buddhist temples[1]. The essential oil contained in the roots is used in high grade perfumary preparations.

The commercial method for extracting the oil is steam distillation[5,7,9] though solvent extraction[6-9] has been used for the isolation of the oil from roots, mostly for experimental purposes. The oil is known to be rich in lactonic constituents some of which are thermolabile and denature or polymerise on heating around 60-70° or more quickly at higher temperatures. The earlier workers, however, did not give adequate attention for the control of temperature during extraction or subjected this thermolabile oil to vacuum distillation at elevated temperatures for the isolation of constituents[6,9,11,12]. As a result the yield of the oil obtained by them is poor and many of the thermolabile constituents were lost due to denaturing or polymerisation and artefacts were also formed.

Semmler and Feldstein[11] were the first to study the chemistry of costus root oil (commercial). They subjected it to vacuum distillation at 11 mm and collected various fractions boiling within a range of 10 - 15° (between 60°-210°). By examining these fractions they reported the presence of the following compounds in the oil. Camphene, phellandrene, α-costene, β-costene, aplotaxene, costol, costus acid ($C_{15}H_{22}O_2$), costus lactone ($C_{15}H_{20}O_2$), dihydrocostus lactone ($C_{15}H_{18}O_2$). They were unable, however, to isolate any solid lactone.

Ukita[8], in 1939 extracted costus root oil with pet. ether, distilled the oil under vacuum, b.p. 175-90°/6 mm and isolated, in low yield, a crystalline lactone, $C_{15}H_{18}O_2$, m.p. 60.5°. Crablona[13] isolated probably the same lactone from the oil after several years standing. This lactone is presumably identical with dehydrocostus lactone, isolated in low yield (0.25%), by Naves[6] by vacuum distillation of the oil at 2 mm.

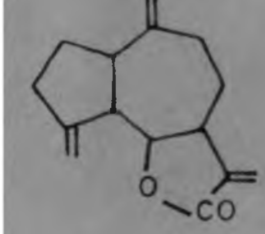
Recently Sorm and co-workers[12,14-16] have carried out investigations on the characterisation of the constituents of the commercial costus root oil and have examined some of them systematically and elucidated their structures. They also isolated, in 5.8% yield, the same dehydrocostus lactone of Naves by vacuum distillation of the oil and established its constitution as a guaianolide (I). Apart from dehydrocostus lactone they have reported the presence of the following compounds in the oil viz p-cymene, myrcene, humulene, β-elemene, caryophyllene, cedrene, aplotaxene, cedrol, costol and palmitic acid.

Taking into account the thermolabile nature of the constituents of the oil, it appeared necessary to use a mild extraction procedure to enable isolation of the oil in the form in which it exists in the roots, free from polymerisation and denaturing. Such a procedure was subsequently developed in National Chemical Laboratory, using pet. ether (40-60°) as the solvent and working under controlled temperature conditions[17].

The procedure gives a high yield of the oil i.e. about 6% from roots of Kashmir origin and about 4% from the roots of Punjab origin. The oil which is free from any polymerisation and denaturing differs considerably from the oil of commerce. It is very rich in lactonic constituents and the solid lactones can be isolated in the form of a mixture by stage-wise cooling of the pet. ether solution of the oil at 0° and - 18°. The oil has been critically examined for its constituents and the results have been published[17-25].

The mixture of lactones mentioned above amounts to the extent of about 50% of the oil. It consists of dehydrocostus lactone (I, 70%) and costunolide (II, 30%).

Costunolide, $C_{15}H_{20}O_2$, has been isolated for the first time in our laboratory and its structure and stereochemistry have been established independantly by Bhattacharyya et al.[21] and Sorm[26]. It is a parent compound of the series of medium sized ring lactones containing a ten-membered carbocyclic ring system, such as pyrethrosin[36], parthenolide[33] arctiopicrin[37] etc. Costunolide has a unique distribution of the trisubstituted double bonds and is capable of undergoing numerous



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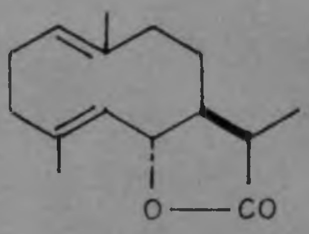

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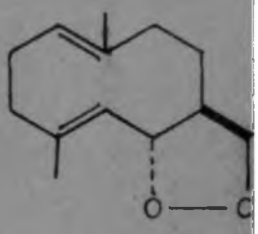

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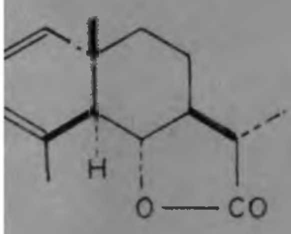

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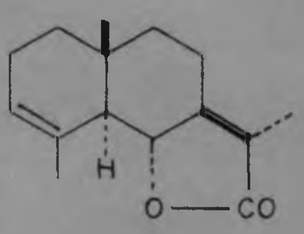

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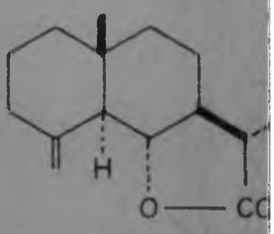

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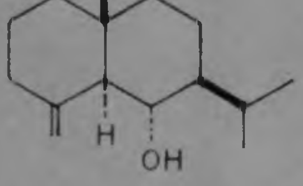

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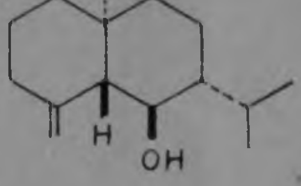

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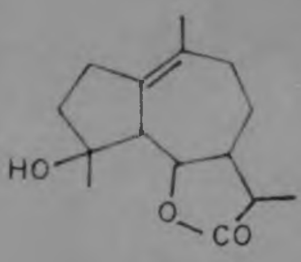

IX

interesting transformations. Its conversion into elemene[23] and selinene[27,31] type compounds by stereospecific reactions like thermal rearrangement and acid-catalysed trans-annular cyclisations has been extensively studied in our laboratory. The thermal rearrangement of dihydrocostunolide (III), for example, led to the formation of saussurea lactone[23] (IV) the structure and stereochemistry of which have been established in this laboratory by degradative and synthetic[29] methods. Dihydrocostunolide gives a mixture of α- and β-cyclodihydrocostunolides[27] (V and VI respectively) on acid catalysed cyclisation. The formation of VI has lead to the synthesis of d~~l~~-junenol[27] (VII), a secondary alcohol, isolated from juneper oil by Czech workers[28] who had established its structure only. Its synthesis in this laboratory has not only established stereochemistry of d-junenol at all asymmetric centres, but also that of l-junenol (VIII) an antipodal compound isolated from North Indian vetiver oil. The~~s~~re are, however, very few examples of the conversion of a ten-membered carbocyclic system into guaiane type compounds except for the formation of IX from parthenolide by BF_3-catalysed cyclisation[33].

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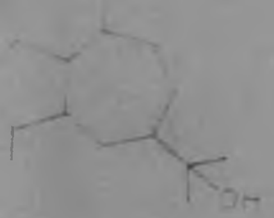

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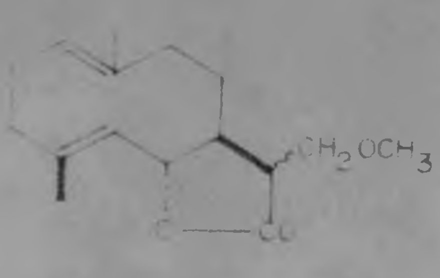

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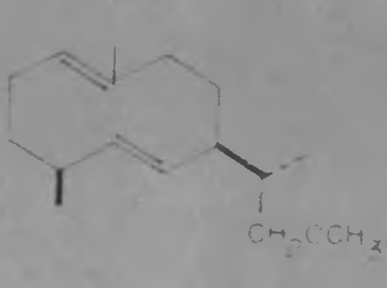

XXI

XXII

In the Part I and II of this thesis, is described the work in connection with the transformation of costunolide into compounds of the guaiane system via the thermal rearrangement of the compounds (X, XI and XII) containing a cyclodeca 1:6 diene system, obtainable from it. The structures of the rearranged products (XIII, XIV and XV) have been rigorously established by converting them into the parent hydrocarbon, namely guaiane, azulenes and also obtaining a cyclopentanone derivative by degradative experiments. The presence of cyclopentanone has been shown by IR spectrum of the latter compound. The guaiane structures for the rearranged products are further confirmed by converting one of them, namely the ester (XIII) into a dihydroguaiol (XVI) and showing its identity through comparison of its IR spectrum with those of known dihydroguaiols[34]. In addition, the compounds (XVII and XVIII) which are structurally related to bulnesol[35] and its C_{10} exocyclic double bond isomer have also been synthesised.

Part III deals with the work done on dehydrocostus lactone with a view to lend support to the structure proposed for it by Naves and Sorm, on the basis of IR spectrum and quantitative ozonolysis. However it needed further support based on the chemical reactions to establish the structure. This has been now done[32] by preparing (i) the basic hydrocarbon guaiane (ii) by obtaining higher yields of azulenes (iii) by showing unambiguously that the lactone attachment is at C_6- C_7. Additional evidence in support of guaiane structure of dehydrocostuslactone is obtained by preparing a cyclopentanone derivative from it. Further, some interesting reactions of the lactol (XIX), obtainable from dehydrocostus lactone, have been studied and the resulting products have been characterised.

Part IVA of the thesis deals with the preparation and characterisation of some Michael addition products obtained from dehydrocostus lactone and costunolide, both containing an α-β-unsaturated-γ-lactone grouping by addition of simple primary and secondary amines. These products have been prepared with a view to explore their physiological activity.

Part IVB deals with the stereochemistry of 12-methoxy dihydrocostunolide (XX) at the C_{11} position. The methoxy lactone, initially isolated[22] from the oil is not a primary constituent, but is an artefact, formed from costunolide by the action of methanol under mild basic conditions. Its synthesis from costunolide has revealed its stereochemistry at C_6 and C_7. However, there is no experimental proof as regards to its stereochemistry at C_{11}. The study of the ozonolysis products of the two methyl ethers (XXI and XXII) prepared from dihydrocostunolide (III) and 12-methoxy dihydrocostunolide indicates that the two ethers XXI and XXII are different which means that the $-CH_2-OCH_3$ group in 12-methoxy dihydrocostunolide is α-oriented.

During the course of these investigations liberal use of modern techniques such as infrared, ultraviolet spectroscopy, nuclear magnetic resonance, gas liquid chromatography, thin layer chromatography etc. have been made.

For the sake of brevity a general introduction to terpenes has been avoided in this thesis. The subject has already been covered adequately by a number of well-known publications, of which special mention may be made of the following.

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   Vol I - V (University Press, Cambridge)

2. Chemistry of carbon compounds
   (Edited by E.H. Rood), Vol. IIB,
   1953 edition (Elsevier Publishing Co.)
3. Mono and sesquiterpenoids by P.de Mayo
   (Interscience Publishers, N.Y.).
4. Progress in the Chemistry of
   Natural Products, Zechmeister,
   Vol XII (Springer-Vienna).
5. The Essential Oils (6 Volumes)
   by E. Guenther
   D. Van Nostrand Co. Inc., N.Y.

I gratefully acknowledge the help I received from these publications, during the course of the investigations.

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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. Unless otherwise stated, all rotations were taken in chloroform solutions. 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 were measured in τ units.

7. Acid washed activated alumina standardised as per Brockmann's procedure was employed for column chromatography.

8. Gas liquid chromatographic analyses (VPC) were carried out on a Griffin and George VPC apparatus MK IIA with polyester column employing hydrogen as carrier gas.

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 activated at 120° for 3 hr. Solvent systems used were pet.ether, benzene, ethylacetate and acetone or a suitable mixture of two or more of these solvents, depending upon the nature of the compounds. The plates were developed by keeping in an iodine chamber or by spraying with H_2SO_4.

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

11. The list of references pertaining to each Part has been given at the end of that Part.

PART I

TRANSFORMATION PRODUCTS OF COSTUNOLIDE: THERMAL REARRANGEMENT OF CYCLO DECA 1:6 DIENES TO A GUAIANE SYSTEM

***

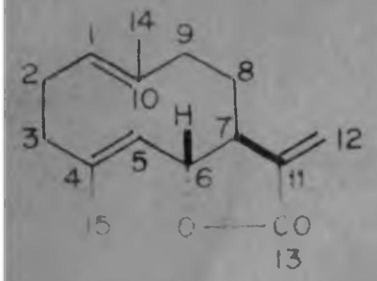
SUMMARY

The diethenoid monocyclic alcohol (XXIII), containing a cyclodeca 1:6 diene system, prepared from dihydrocostunolide (II), rearranges on heating in diethylene glycol and alkali at high temperatures. The rearranged product has been shown to possess the guaiane structure (L) on the basis of spectral data and chemical reactions. The stereochemistry of the rearranged alcohol (L) and closely related products (XLIX and LI) has been discussed.

Costunolide, (I) $C_{15}H_{20}O_2$, is a crystalline monocyclic sesquiterpenic lactone. It was isolated[1] for the first time in our laboratory from costus root (Saussurea Lappa, Clarke) oil, obtained by a low temperature solvent extraction procedure[2] using pet. ether (40-60°). It occurs to the extent of about 15% of the total extractive. It is rather unstable at room temperature and readily polymerises on heating above 50°. For this reason the earlier workers[4,5], who used high temperatures during extraction of the oil and isolation of its constituents, failed to isolate this lactone.

The structure of costunolide has been rigorously established by Bhattacharyya et al.[1] and also by the Czech workers[3] who isolated it from Artimisia balchanorum, a worm-wood species from Russian Central Asia. The stereochemistry of this lactone at C_6 and C_7 has been definitely proved[1,3] by its conversion into sant-3-enolide (α-cyclo-dihydrocostunolide) (V), santanolide 'c' (VII) and the lactone dicarboxylic acid (IX), all of known stereochemistry.

On account of the unique disposition of the two trisubstituted double bonds, costunolide



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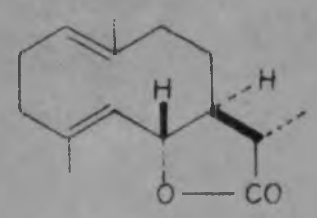

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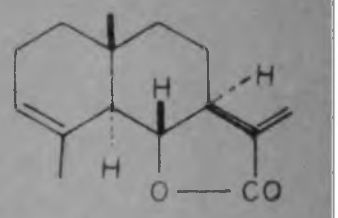

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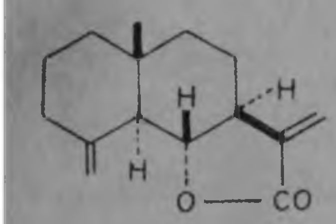

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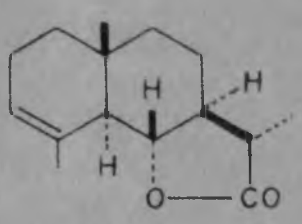

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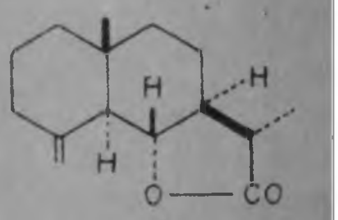

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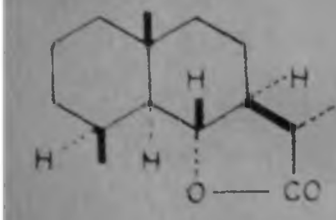

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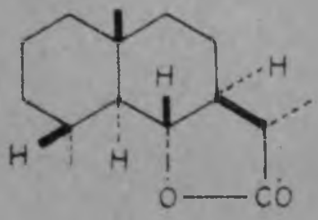

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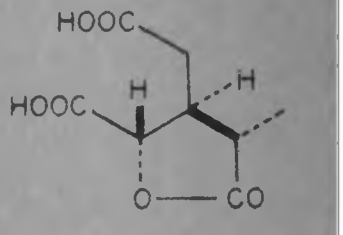

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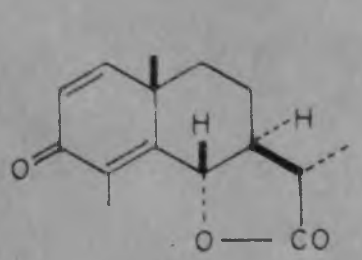
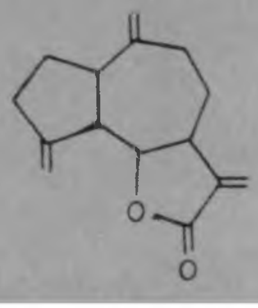
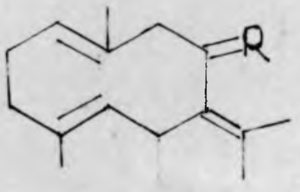




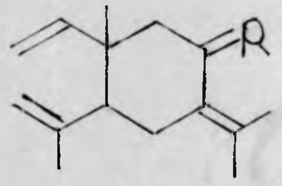
is capable of undergoing a number of interesting transformations some of which have been studied in our laboratory and elsewhere and are described below in brief.

1. **Cope's Rearrangement**

Germacrone (XXXV, R = O), a crystalline α-β-unsaturated sesquiterpenic ketone, (isolated from Bulgarian Zddravet's oil), containing a ten-membered carbocyclic ring system, on thermal rearrangement, gives β-elemenone[11].

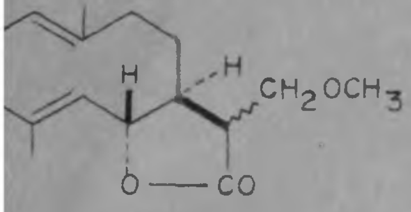


XXXV, R = O



β elemenone, R=O

Dihydrocostunolide (II), like germacrone (XXXV), contains the same cyclodeca 1:5 diene system and, therefore, undergoes thermal rearrangement to give saussurea lactone (XIV), an elemane type compound. The structure and stereochemistry of this lactone have been



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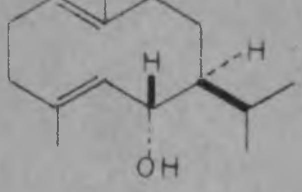
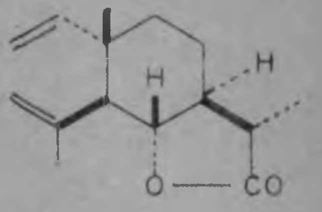


XIII



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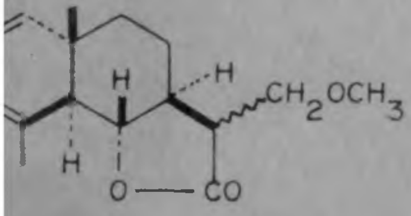
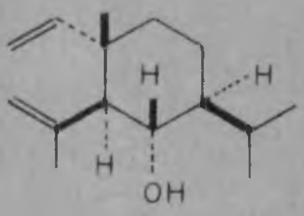
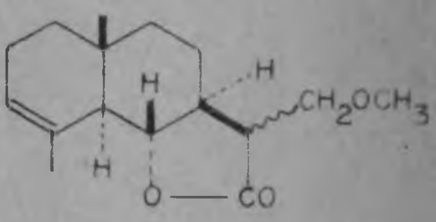


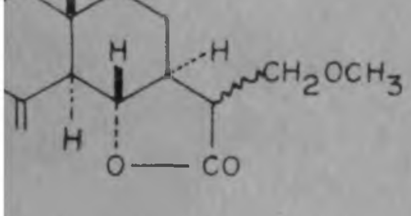
XV



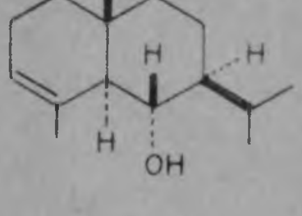
XVI



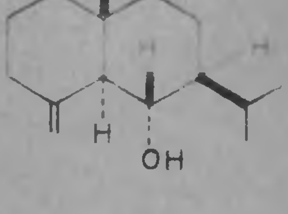
XVII



XVIII

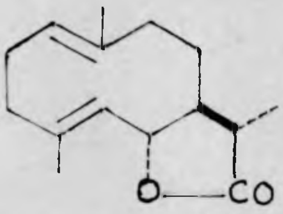


XIX

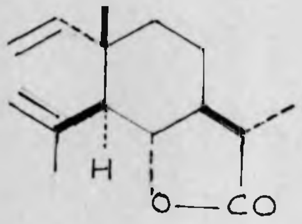


XX

established[6] in our laboratory, and has been confirmed by its synthesis[6a].



II

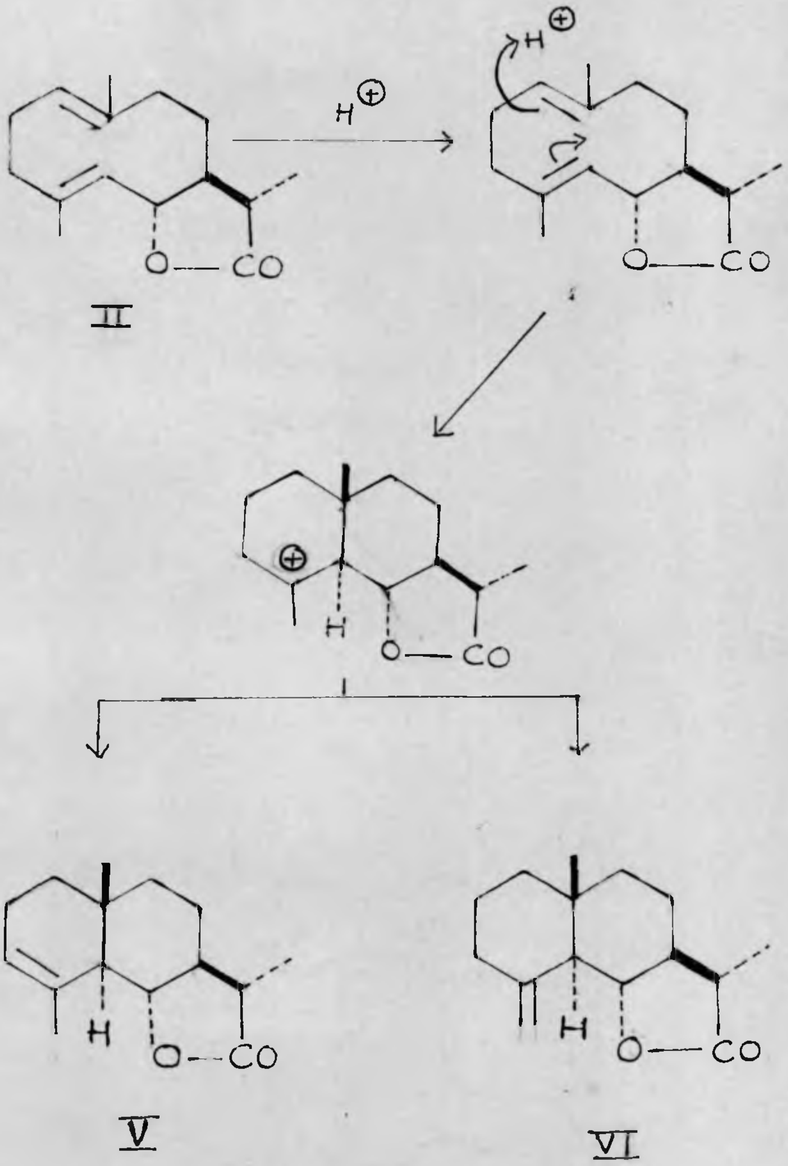


XIV

Similarly, the 12-methoxy dihydrocostunolide (XII) and the monol (XIII), obtainable from costunolide (I) and also containing cyclodeca 1:5 diene system, have been rearranged to the elemane type products XV and XVI respectively[7-8].

2. Trans-annular acid catalysed cyclisations

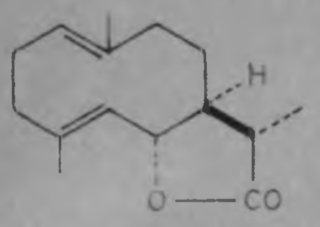
Costunolide and its derivatives undergo acid catalysed trans-annular cyclisation to give selinenic type of compounds. This reaction is stereospecific and invariably leads to trans-ring juncture. Thus solid dihydrocostunolide (II), on treatment with acetic anhydride[9] or acetic acid-perchloric[10] acid, gives a mixture of α- and β-cyclodihydrocostunolides[9] (V and VI) of which the α-isomer (V), containing a tri-substituted double bond, has been previously prepared[12] from α-santonin (X). The other isomer (VI), containing a $>C = CH_2$ grouping, had been prepared for the



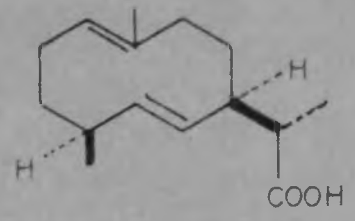
first time and its structure and stereo-chemistry are proved[9] by catalytic hydrogenation when it gives santanolide 'a' (VIII), a reference compound of known stereochemistry. Further the β-isomer (VI), on controlled LAH reduction followed by Huang-Minlon reduction affords α-junenol (XX), from which the stereochemistry of the latter follows[9]. Costunolide itself, with acetic acid-perchloric acid at 0°, affords a mixture of α- and β-cyclocostunolides (III and IV) of which only the α- isomer has been isolated in pure condition[10]. Similarly 12-methoxy-dihydrocostunolide (XII) and the monol XIII give the corresponding selinenic compounds (XVII), (XVIII) and (XIX), (XX) respectively[8].

3. Metal-amine reduction in the costunolide series

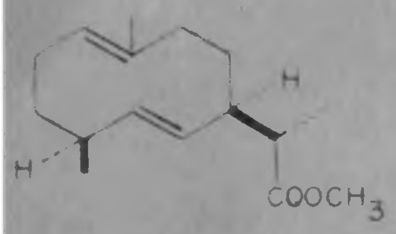
Solid dihydrocostunolide (II), which possesses a potential allylic hydroxyl group in the lactone moiety, on metal-amine (Li/NH_3) reduction, gives the acid (XXI) in about 85-90% yield[13], by hydrogenolysis followed by migration of the allylic double bond at C_4 - C_5 to C_5 - C_6. The methyl ester (XXII) on LAH reduction furnishes the alcohol (XXIII) which on subsequent tosylation and reduction with LAH affords the hydrocarbon



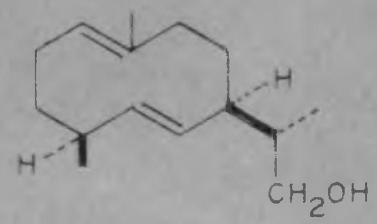
II



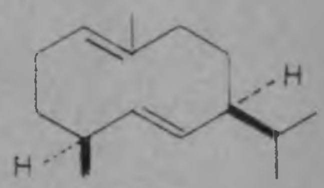
XXI



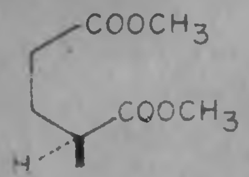
XXII



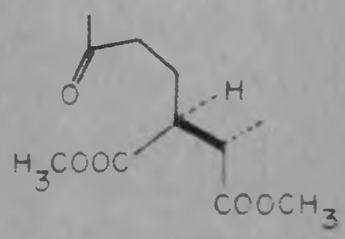
XXIII



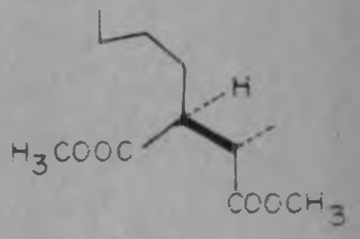
XXIV



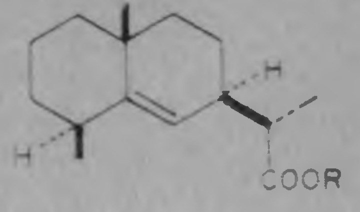
XXV



XXVI



XXVII



XX VIII R = CH_3

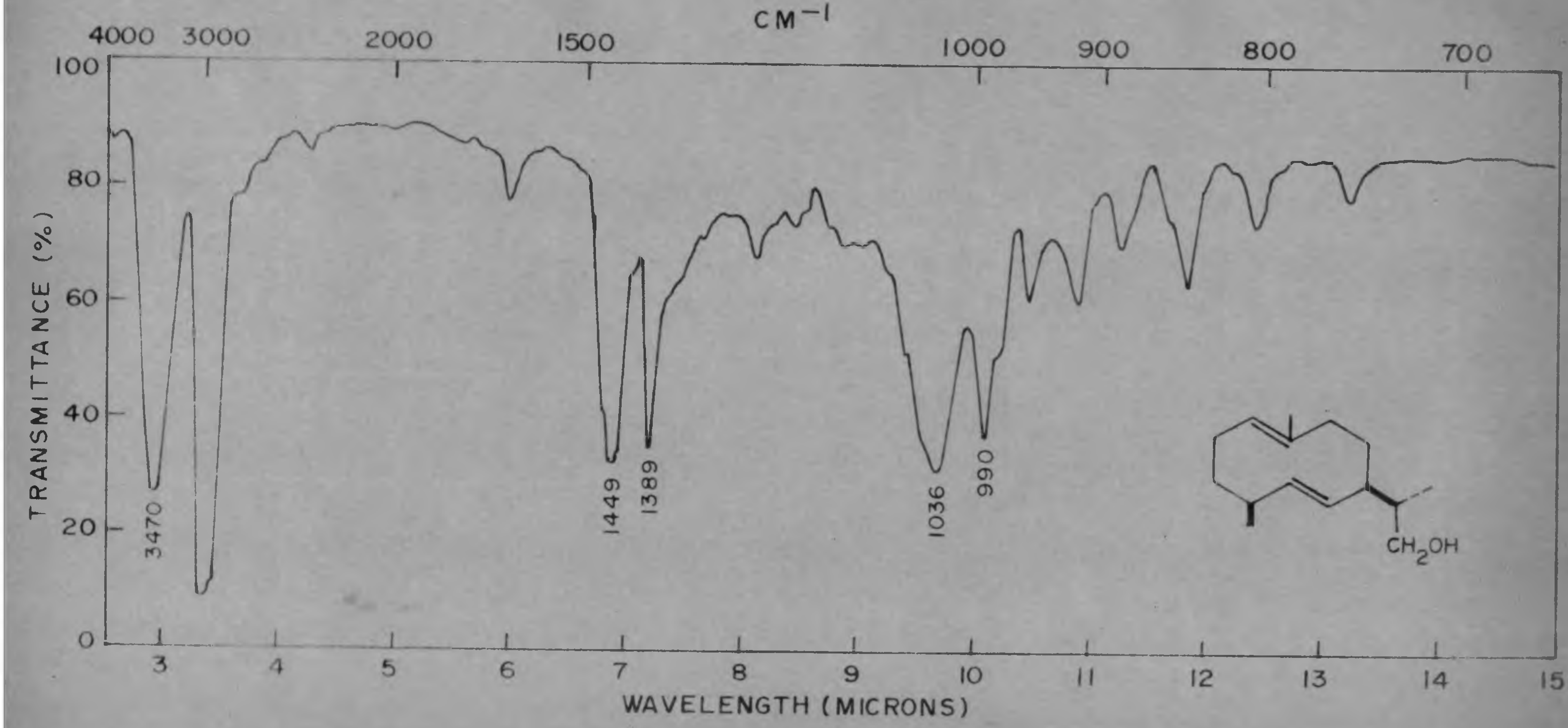


FIG. 2 - IR SPECTRUM OF ALCOHOL (LIQ. FILM)

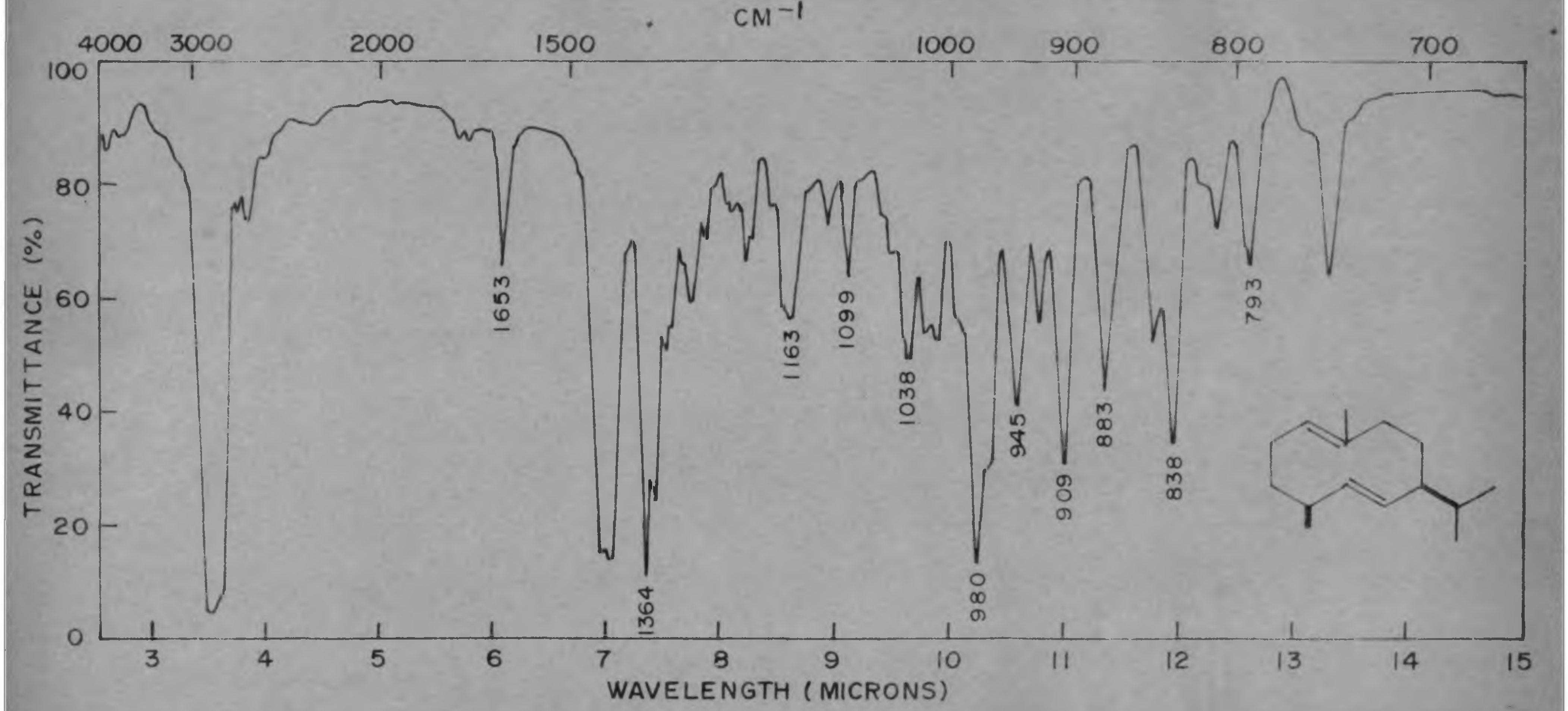


FIG. 3 - IR SPECTRUM OF HYDROCARBON (LIQ. FILM)

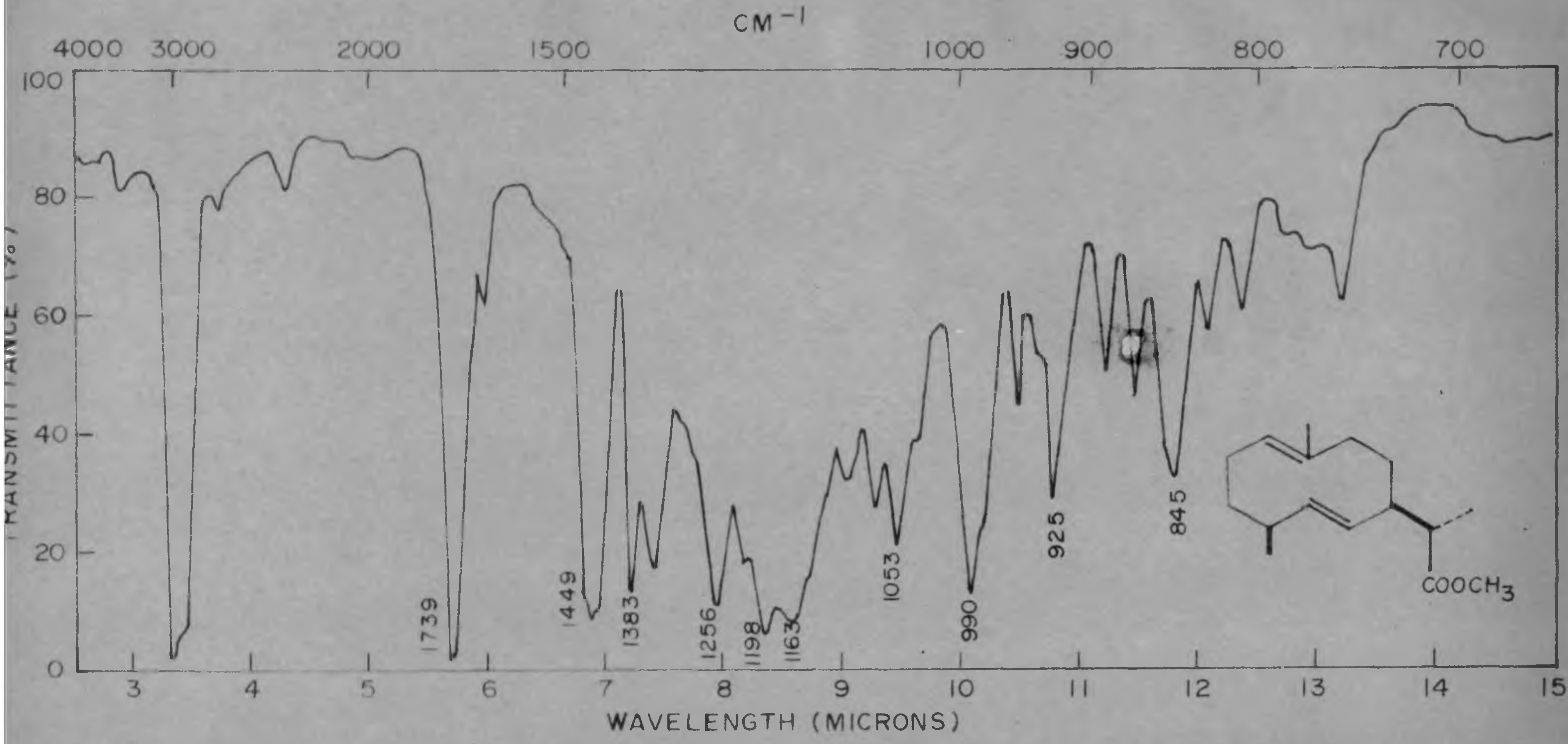
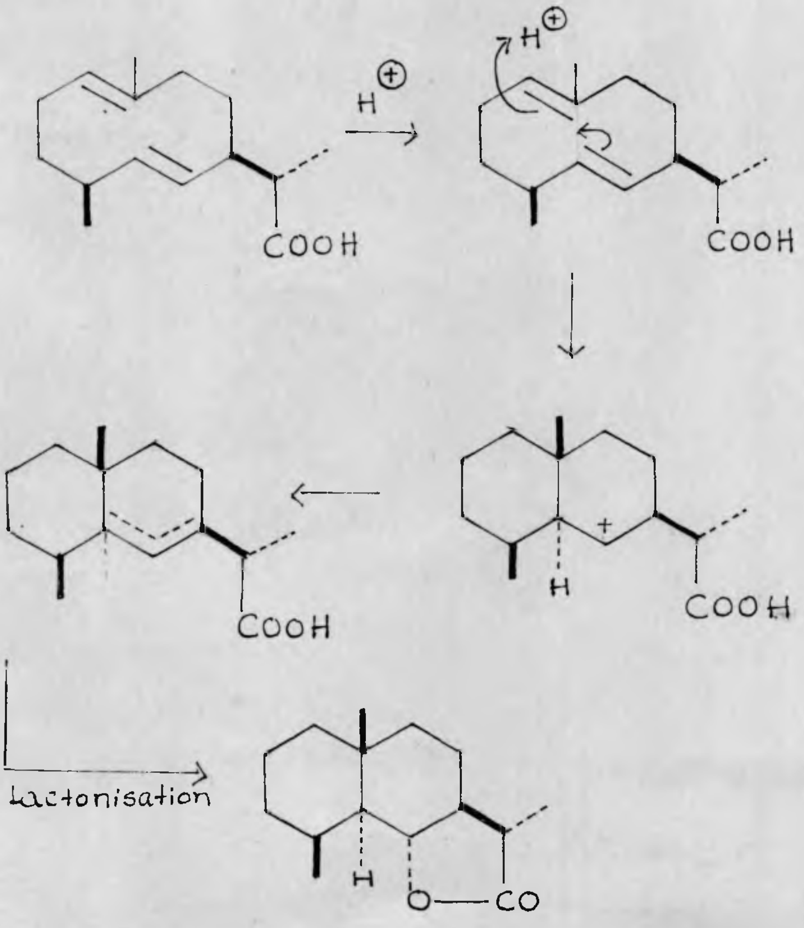


FIG I - IR SPECTRUM OF ESTER (LIQ. FILM)

(XXIV). The ester (XXII) on ozonolysis, followed by esterification of the resulting mixture of acids, gives, as one of the products, S - (+) -α-methyl glutaric acid dimethyl ester (XXV), a compound of known absolute configuration. The other product of ozonolysis, (-)-2-methyl-3-(3'-oxo) butyl succinic acid dimethyl ester (XXVI) gives on desulfurisation of its thioketal (Raney-Ni), (-)-2S-methyl-3S-butyl succinic acid dimethyl ester (XXVII). These findings[13] establish the position of the double bond at C_5 - C_6 and the stereochemistry at the centres C_4 and C_{11} of the ester (XXII) and subsequently confirm the α-assignment of the methyl group at C_{11} in dihydrocostunolide (II) and α-santonin (X).

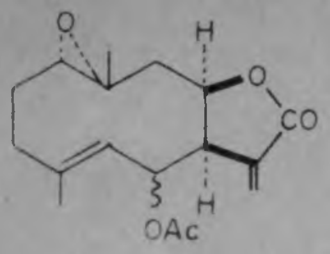
The acid (XXI) on treatment with acetic acid perchloric acid, undergoes <u>trans</u>-annular cyclisation, giving rise to santanolide 'c' (VII) and a bicyclic acid[13] (XXVIII, R = H). The formation of santanolide 'c' supports the β-orientation of the C_4-methyl group mentioned above and the course of the reaction has been explained as follows:



Santanolide 'c'

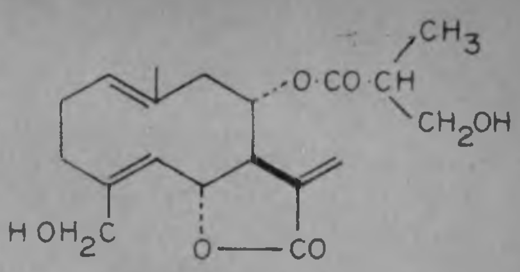
Biogenetic significance of costunolide

Recently a series of sesquiterpenic lactones, with a ten-membered carbocyclic ring system as their basic carbon skeleton, have been isolated from natural sources. Pyrethronsin[14] (XXIX), arctiopicrin[15] (XXX), cnicin (XXXI), scabiolide (XXXII), eupatoriopicrin[16] (XXXIII) parthenolide[17] (XXXIV) and salonitenolide (XXXIVa)[32] are some of the lactones belonging to this series. Costunolide



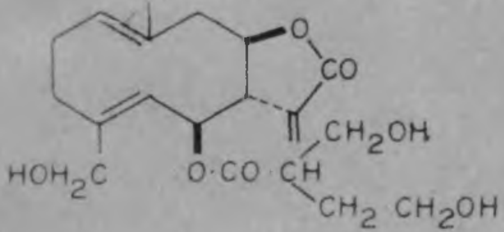
PYRETHROSIN

XXIX



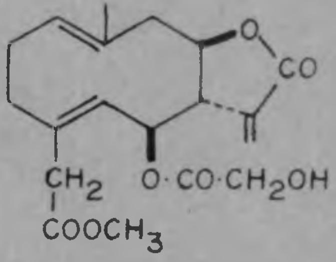
ARCTIOPICRIN

XXX



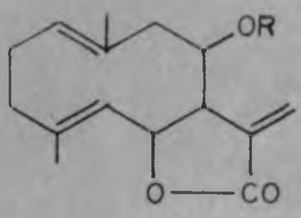
CNICIN

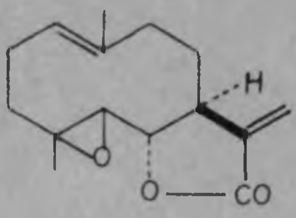
XXXI

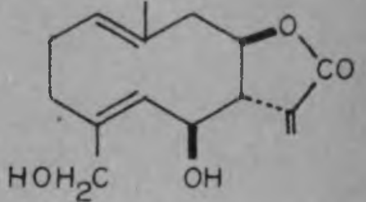


SCABIOLIDE

XXXII







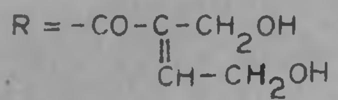
XXXIII

XXXIV

PARTHENOLIDE

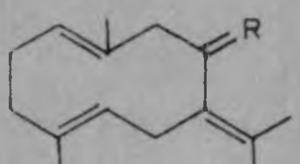
XXXIVa

SALONITENOLIDE



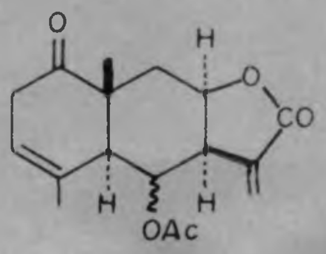
$$R = -CO-\underset{\underset{CH-CH_2OH}{\|}}{C}-CH_2OH$$

EUPATORIOPICRIN



XXXV

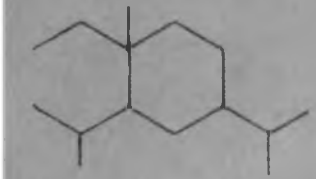
R=O, R= -OH



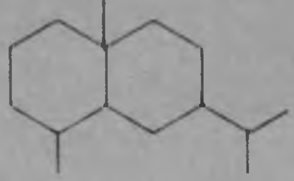
XXXVI

is the simplest amongst these and may be regarded as the parent lactone of the series. It is probably a biogenetic precursor of the mono- and bicyclic sesquiterpenic lactones such as dehydrocostus lactone (XI) and santonin. Such a view is based on the present belief[18] that a ten-membered carbocyclic ring system formed from an acyclic precursor of the farnesene type is an intermediate step in the biogenesis of certain mono and bicyclic sesquiterpenes belonging to elemane (XXXVII) selinane (XXXVIII), cadinane (XXXIX), guaiane (XL) and vetivane (XLI) series. The feasibility of such a view is experimentally illustrated by conversion of costunolide (I) into (III, IV, XIV)[6,8] (which has been already discussed), pyrethrosin XXIX into (XXXVI)[14] and germacrone (XXXV, R = O) into XXXVIII and XXXVII by chemical and thermal rearrangements.

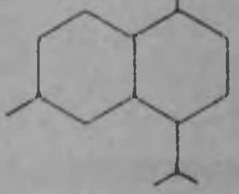
The fact that such compounds (containing a ten-membered carbocyclic ring system) could also be transformed into compounds of the guaiane series has been indicated in certain reactions like Se-dehydrogenation of pyrethrosin[14] (XXIX) giving some azulenes and parthenolide[17] (XXXIV)



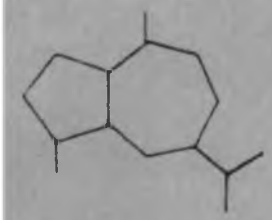
XXXVII



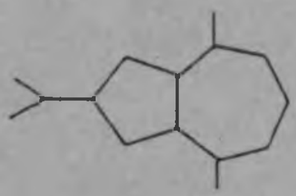
XXXVIII



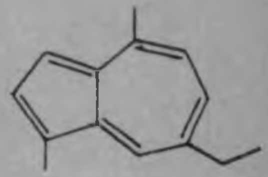
XXXIX



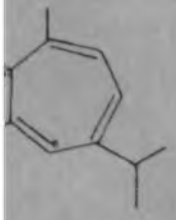
XL



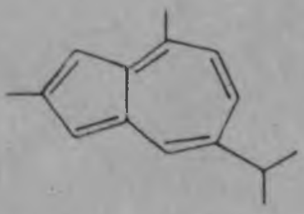
XLI



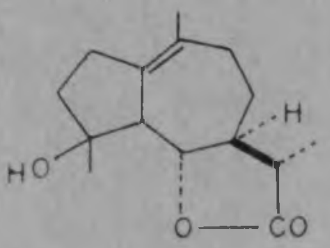
XLII



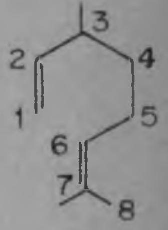
LIII



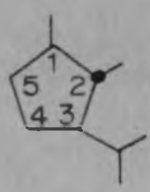
XLIV



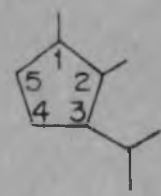
XLV



XLVI



XLVII



XLVIII

producing chamazulene(XLII) during the reaction. Germacrol (XXXV, R = OH) and its derivatives are similarly known to produce S-guaiazulene(XLIII) during sulphur dehydrogenation^{11a}.

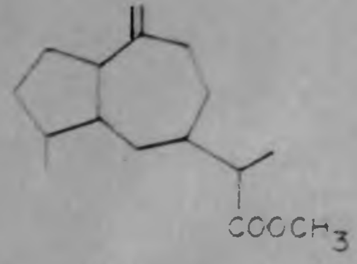
The formation of azulenes, from compounds which do not contain a perhydroazulene skeleton, can be explained only by assuming an initial rearrangement to such a system. In support of such a view parthenolide (XXXIV) has been actually reported to be converted into a guaianolide (XLV) by BF_3-catalysed-trans-annular cyclisation^{17b}.

Thus, "it is possible by establishing different bonds accross the ten-membered carbocyclic ring system to construct the carbon skeletons of most of the bicyclic sesquiterpenes"^{14}.

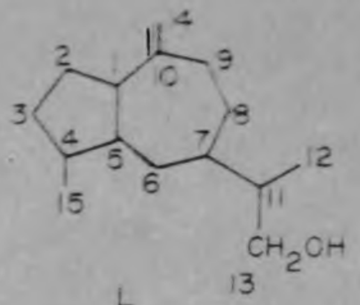
PRESENT WORK

In this part of the thesis is described the formation of compounds of the guaine series, by thermal rearrangement of cyclodeca 1:6 dienenes[13], (XXII, XXIII and XXIV) obtainable from costunolide (I) as described earlier.

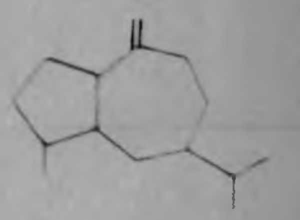
The thermal rearrangement of acyclic-1:6-diene systems at high temperatures viz. 400-500° to give cyclopentane derivatives has been reported by H. Pines et al.[19] It is observed[20] that 3:7 dimethyl octa-1:6 diene (XLVI) rearranges at 400-500° to give both 1-*trans*-2-dimethyl, *cis*-3-isopropenyl cyclopentane (XLVII) and 1-*cis*-2-dimethyl *cis*-3 isopropenyl cyclopentane (XLVIII). The mechanism of such a rearrangement, which was initially presumed to take place through a free radical, was later corrected by Huntsmann and Curry[21]. They explained the formation of the cyclopentane compounds as due to an intramolecular rearrangement involving hydrogen transfer. Such a rearrangement is assumed to take place through a cyclic transition state. The Cope rearrangement and the Claisen rearrangement of allylic ethers are examples of reactions belonging to this category.



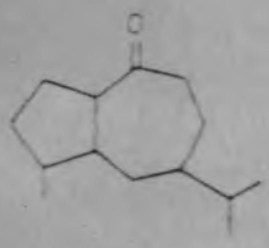
XLIX



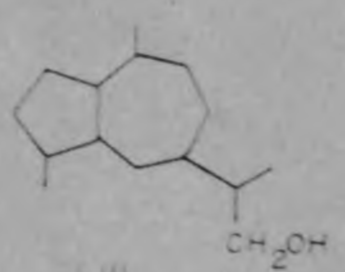
L



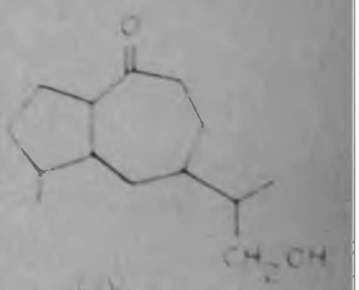
LI



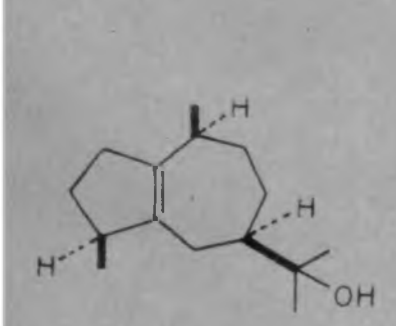
LII



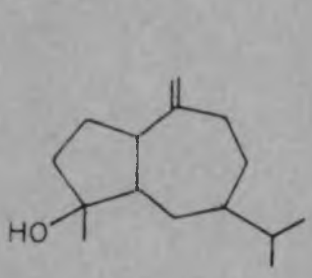
LIII



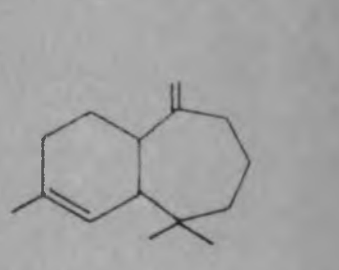
LIV



LV



LVI



LVII

The thermal rearrangement of cyclo-deca 1:6 diene systems was first studied in our laboratory by Bhattacharyya et al.[8] They carried out the rearrangement of the alcohol (XXIII) and the hydrocarbon (XXIV) at 220-240° in vacuum and obtained in low yield a mixture of compounds in which the presence of elemene type of compound was inferred on the basis of IR spectra. However, due to paucity of material, no further proof was given in support of this view.

The thermal-rearrangement of such compounds (XXIII, XXIV) has been now studied more critically and the results definitely indicate that they rearrange, in fact, to cyclopentane derivatives (guaiane system in the present case) as expected in analogy with acyclic 1:6 diene systems.

Since the thermal rearrangement of the alcohol (XXIII), at 220° under vacuum, did not proceed smoothly[8], different experimental conditions were tried to achieve this objective. It was found that by heating (XXIII) in diethylene glycol medium containing 5% alkali (potassium-hydroxide) in an atmosphere of nitrogen at 250° for five hours, a mono-ethenoid bicyclic alcohol is obtained

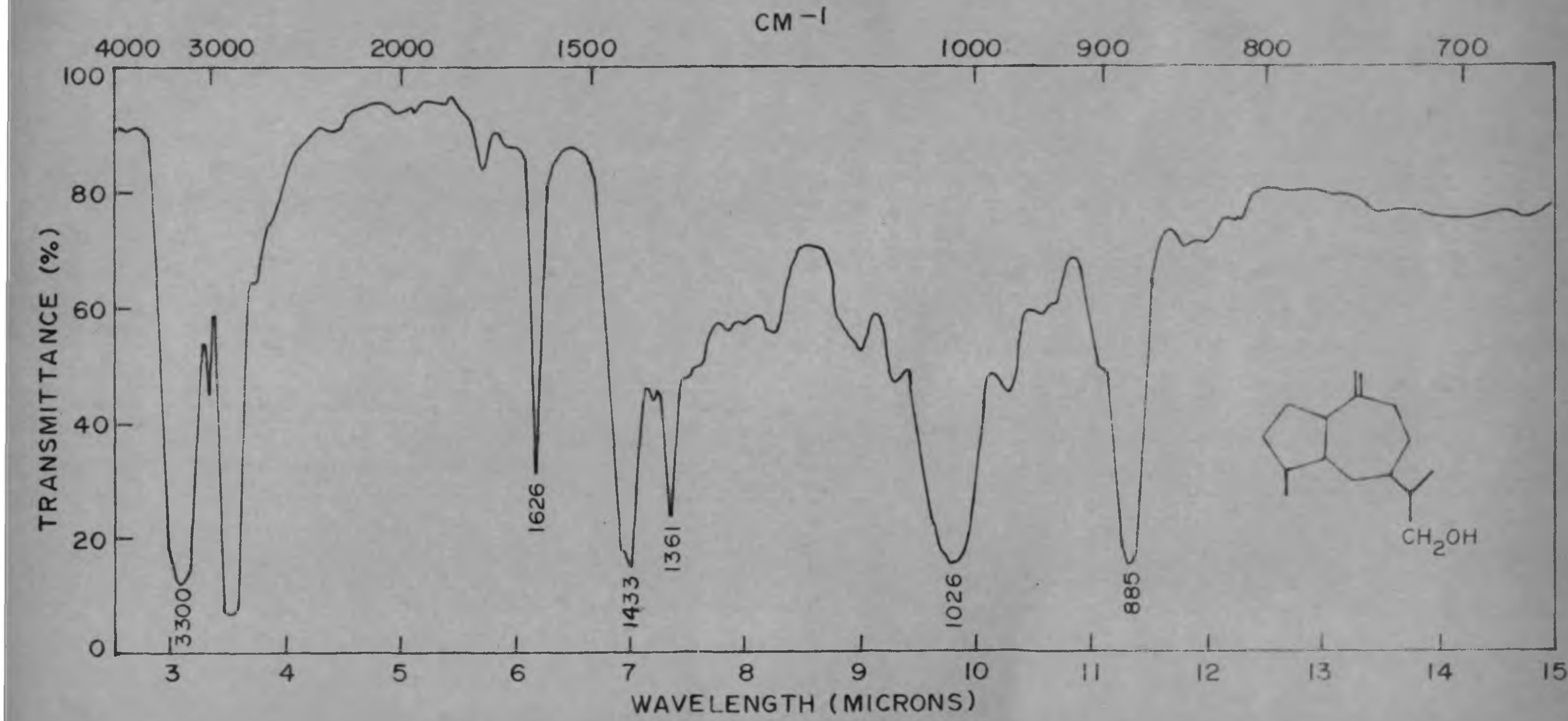


FIG. 4 - IR SPECTRUM OF THE REARRANGED ALCOHOL (LIQ. FILM)

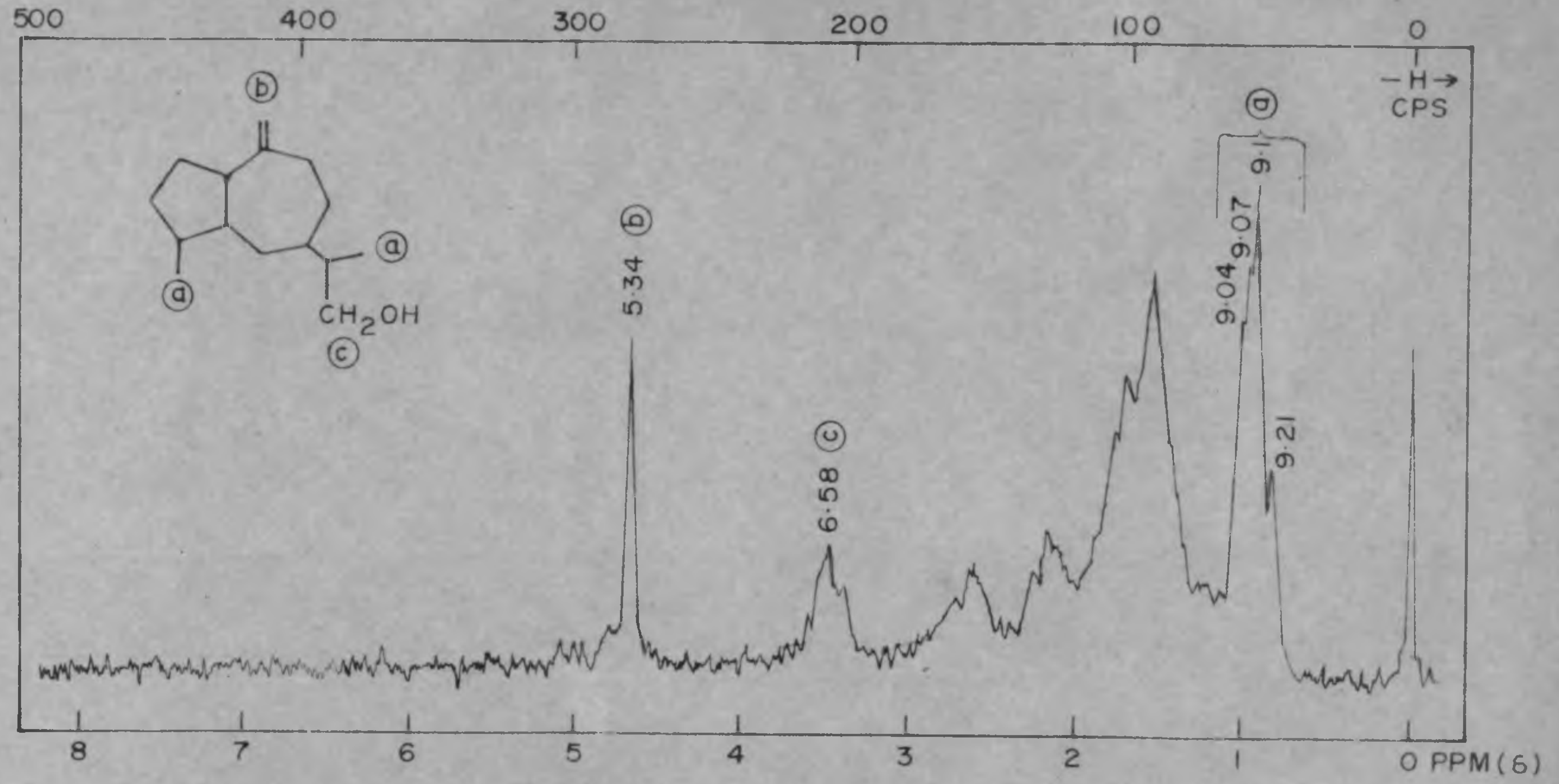
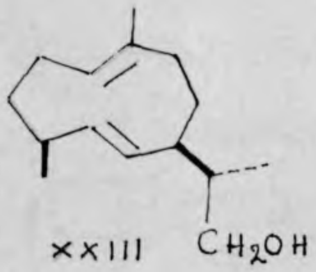
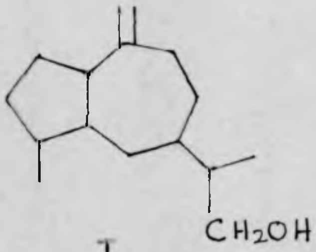


FIG. 5 - NMR SPECTRUM OF REARRANGED ALCOHOL

in 85 to 90% yield. On chromatography over alumina followed by distillation at reduced pressure, it was obtained in pure state (GLC/TLC) and shown to be (L) on the following grounds:


XXIII


L

It showed in its IR spectrum (Fig. 4) bands at 3300, 1026 cm^{-1} due to a primary hydroxyl function, and at 1626, 885 cm^{-1} due to $>C=CH_2$ group. The NMR spectrum (Fig. 5) of the alcohol showed signals at 9.04, 9.07, 9.1 and 9.21 τ (6 H) due to the secondary methyl groups at C_4 and C_{11}; around 6.54 τ (2 H) due to the two protons of the - CH_2OH group at C_{11} and at 5.34 τ (2 H) due to two olefinic protons at C_{14}.

Though for a compound containing an exocyclic double bond two separate signals are usually observed in the NMR spectrum, as in the case of nardol[22] (LVI), there are also examples like α-himachalene[23] (LVII), where only one signal is observed. The position of $>C=CH_2$ group in both the alcohol (L) and nardol (LVI) is the same;

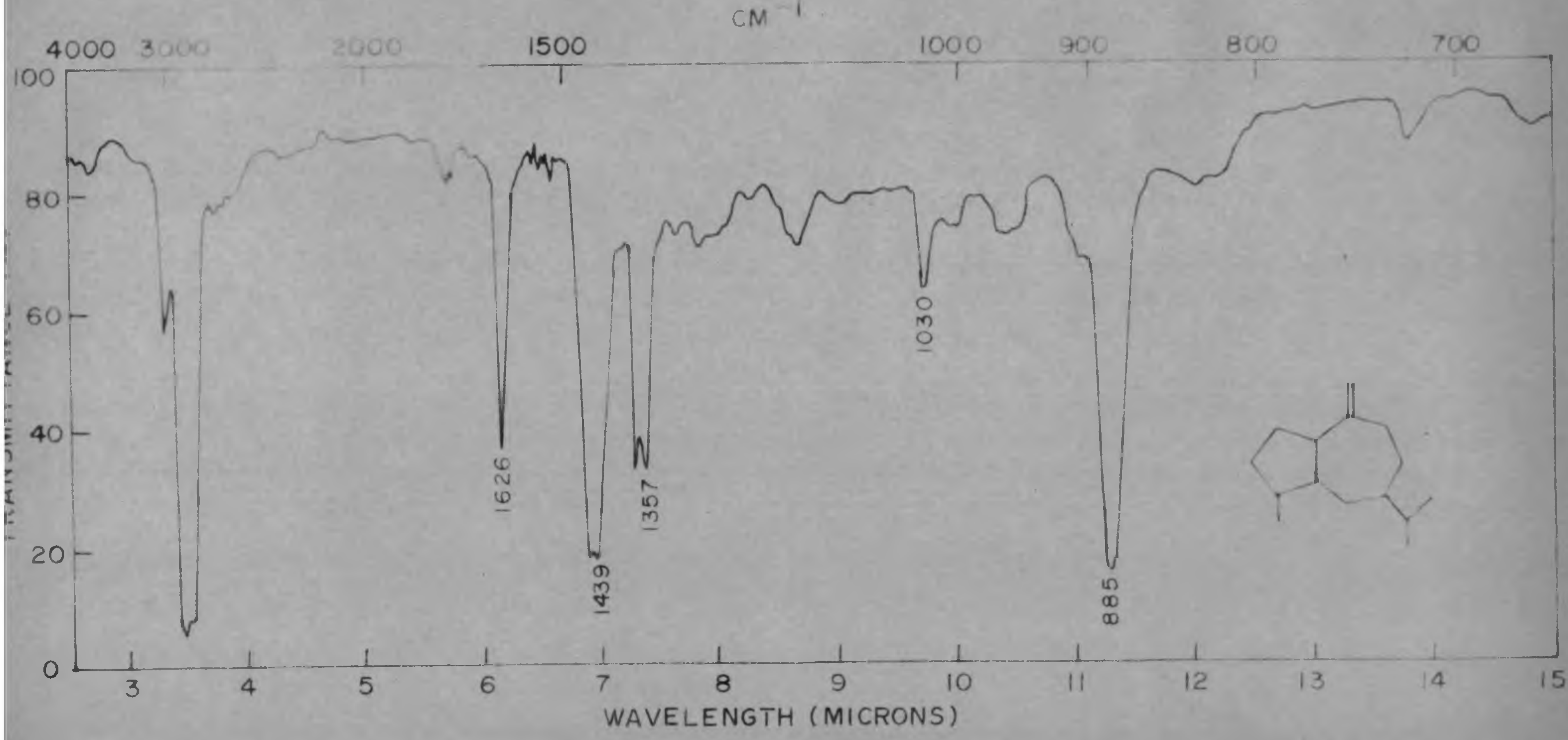


FIG. 6 – IR SPECTRUM OF HYDROCARBON (LIQ. FILM)

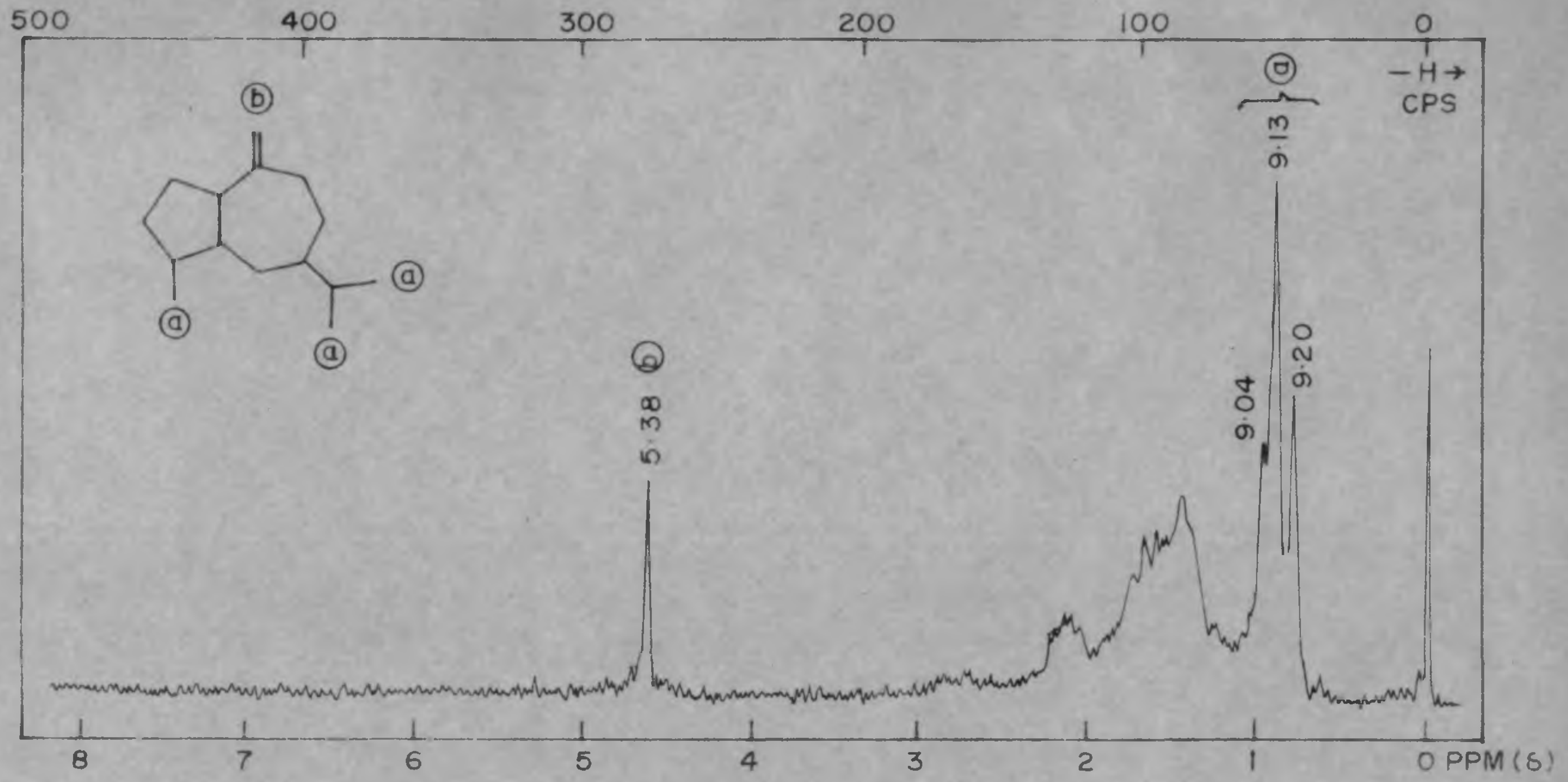


FIG. 7. NMR SPECTRUM OF REARRANGED HYDROCARBON

the difference in their NMR pattern may, therefore, be due to certain steric factors.

Quantitative catalytic hydrogenation of (L) in alcohol medium using PtO_2 catalyst gave a saturated dihydroderivative (LIII) indicating the presence of only one double bond.

The alcohol (L) was converted to the corresponding hydrocarbon (LI) via the LAH reduction of its tosylate. The hydrocarbon after purification by chromatography over alumina and distillation under vacuum showed in its IR spectrum (Fig. 6) bands at 1626, 885 cm^{-1} due to $>C = CH_2$ grouping. The NMR spectrum (Fig.7) showed signals at 9.04, 9.13 and 9.20 τ (9 H) due to the three methyl groups at C_4 and C_{11} and at 5.38 τ (2 H) due to the two olefinic protons at C_{14}.

Sulphur dehydrogenation of (LI) gave S-guaiazulene (XLIII) in 7% yield, characterised through its TNB adduct m.p. 150°-151°. Mixed m.p. with an authentic S-guaiazulene adduct was undepressed. Selenium dehydrogenation of the hydrocarbon (LI) produced a mixture of S- and Se-guaiazulenes in 8% yield, the latter predominating. The mixture of azulenes gave an

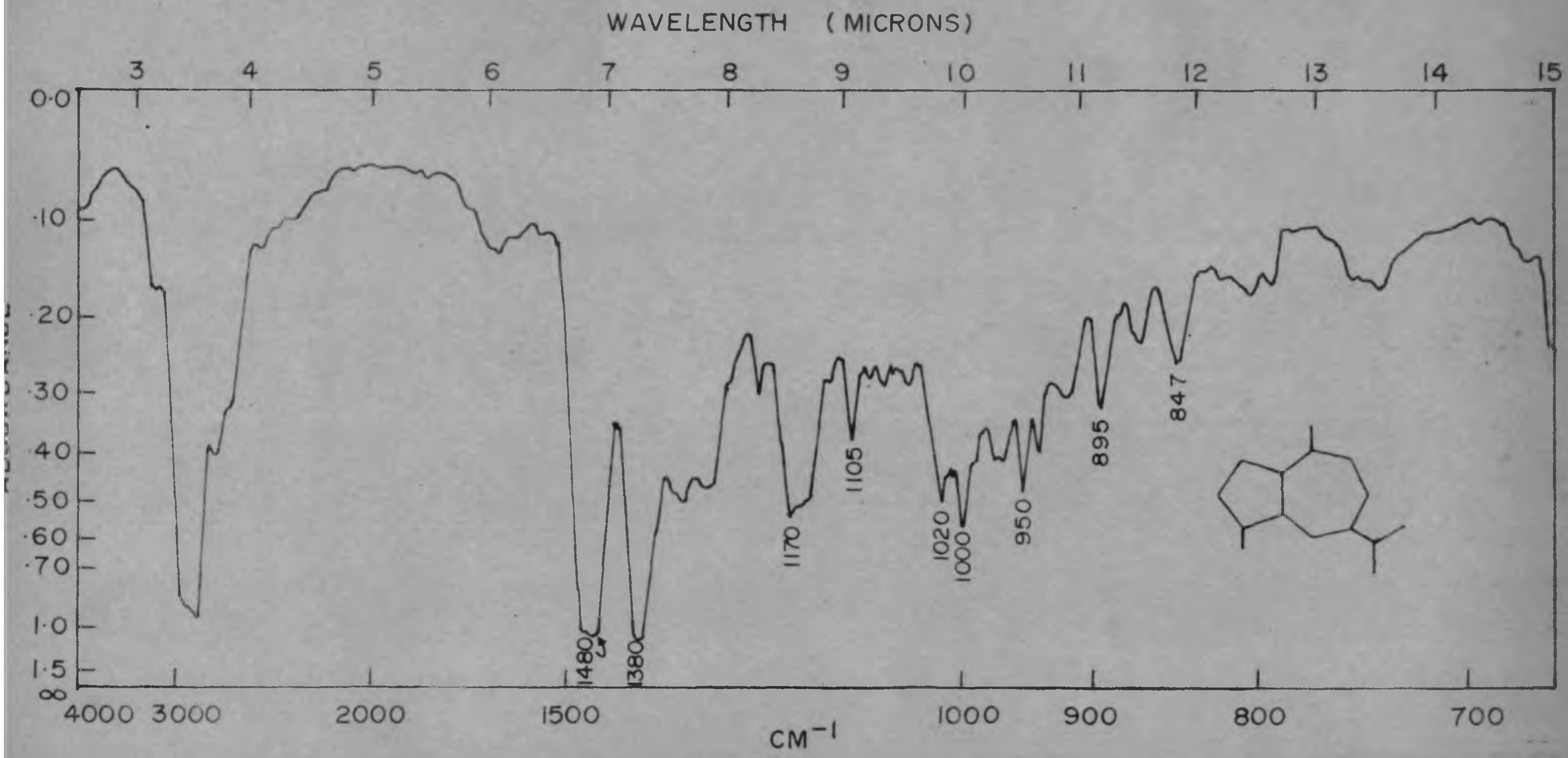


FIG. 8 - IR SPECTRUM OF SATURATED HYDROCARBON (0·1 mm CELL)

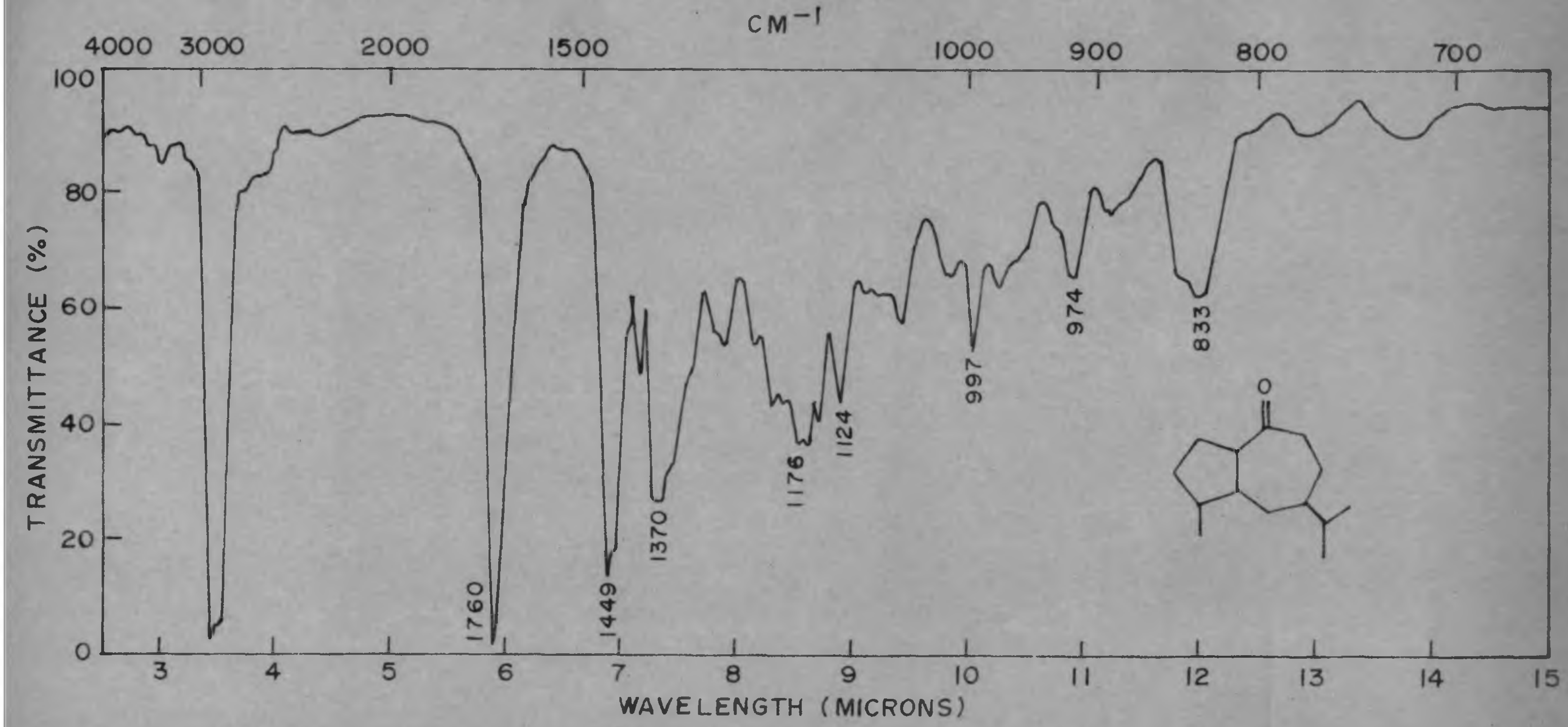


FIG. 9 – IR SPECTRUM OF KETONE (LIQ. FILM)

adduct with s-TNB, m.p. 147-148°, and mixed m.p. with an authentic Se-guaiazulene TNB-adduct was undepressed.

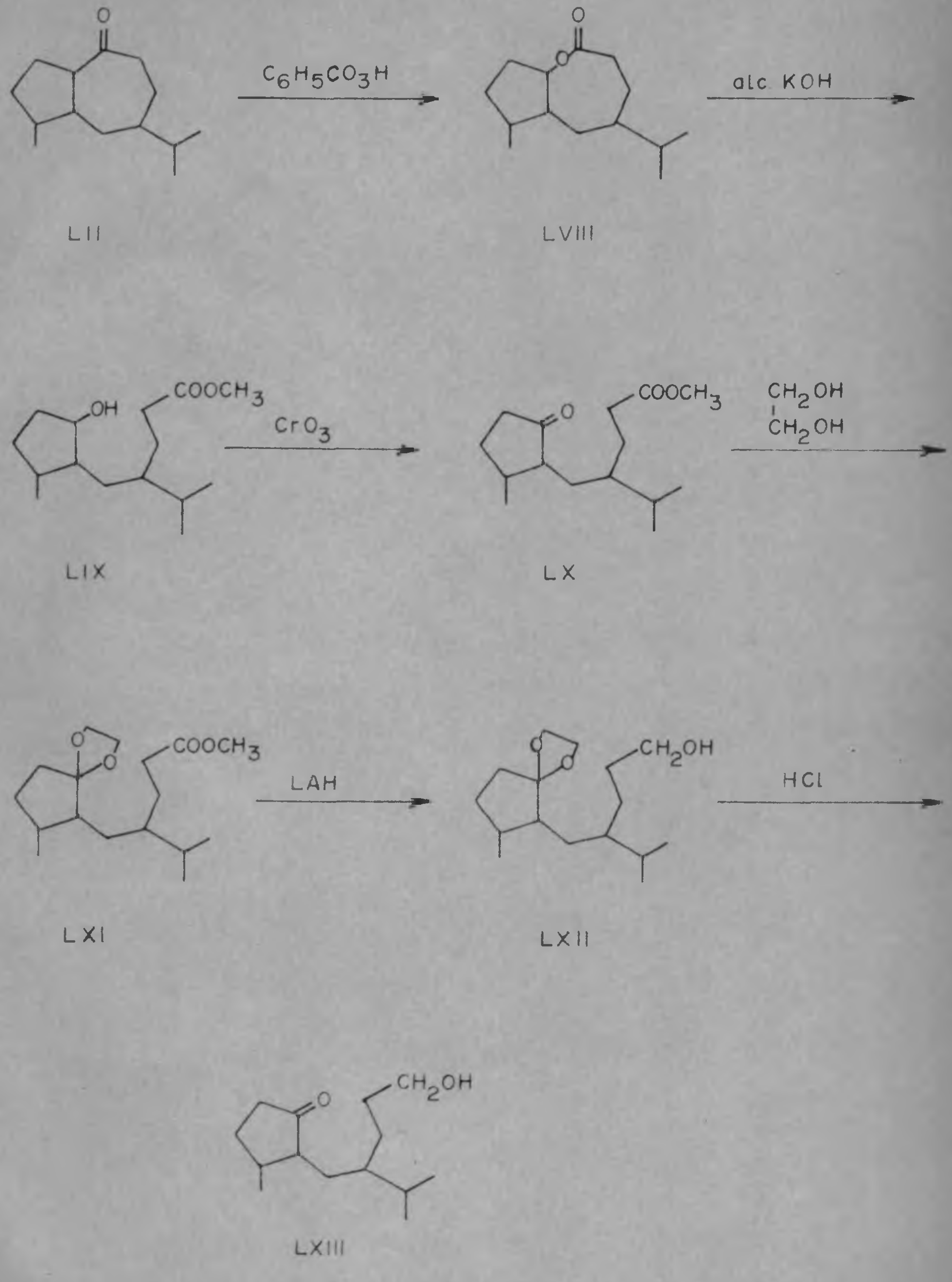
Catalytic hydrogenation of the hydrocarbon (LI) in acetic acid medium, using PtO_2 catalyst, gave a saturated (negative tetranitromethane test) dihydroderivative, identified as guaiane (XL) by comparison of its IR spectrum (Fig. 8) with those of guaianes prepared from guaiol[25] (LV), nardol[22] (LVI) and dehydrocostus lactone[24] (XI). These experiments suggested a guaiane skeleton for the alcohol (L).

The exact location of the double bond in (L) was then decided by ozonolysis of the hydrocarbon (LI), which gave a ketone (LII), $C_{14}H_{24}O$, along with formaldehyde (characterised as its dimedone derivative). The ketone (LII) furnished a semicarbazone, m.p. 175°. The IR spectrum (Fig. 9) of the ketone showed carbonyl absorption at 1700 cm^{-1}, consistent with a cycloheptanone system. Its NMR spectrum showed signals, at 8.96, 9.0, 9.06 and 9.1 τ (9 H) due to the methyls at C_4 and C_{11} and a multiplet around 7.72 τ (3 H) due to the protons at C_1 and C_9.

Similarly the alcohol (L), on ozonolysis, produced the ketoalcohol (LIV) and formaldehyde. The IR spectrum of the ketoalcohol showed carbonyl absorption at 1700 cm^{-1}. The formation of formaldehyde from (L) and (LI) clearly indicated the presence of $>CH = CH_2$ grouping in these compounds.

Some additional proof for the guaiane skeleton of the alcohol (L) was obtained in the following way. The ketone (LII) on Baeyer-Villiger oxidation gave a lactone (LVIII), which on hydrolysis and esterification furnished the hydroxy ester, $C_{15}H_{28}O_3$, (LIX). The latter was converted to the keto ester, $C_{15}H_{26}O_3$, (LX) by Jones' chromic acid oxidation. The NMR spectrum (Fig. 11) of the ketoester showed signals at 8.9, 9.04, 9.08, 9.15, 9.18 τ (9 H) due to methyls at C_4 and C_{11}; at 7.75 and 7.86 τ (3 H) due to protons at C_2 and C_5 and at 6.36 τ (3 H) due to the ester methyl at C_{10}.

Since in the IR spectrum (Fig. 10) of the keto-ester (LX) carbonyl absorptions of the keto and the ester groupings were merging no definite assignments could be made. The keto-ester was, therefore, converted into its ethylene ketal (LXI).


LII
$C_6H_5CO_3H$
LVIII
alc. KOH
LIX
CrO_3
LX
CH_2OH
CH_2OH
LXI
LAH
LXII
HCl
LXIII
OH
$COOCH_3$
CH_2OH
O

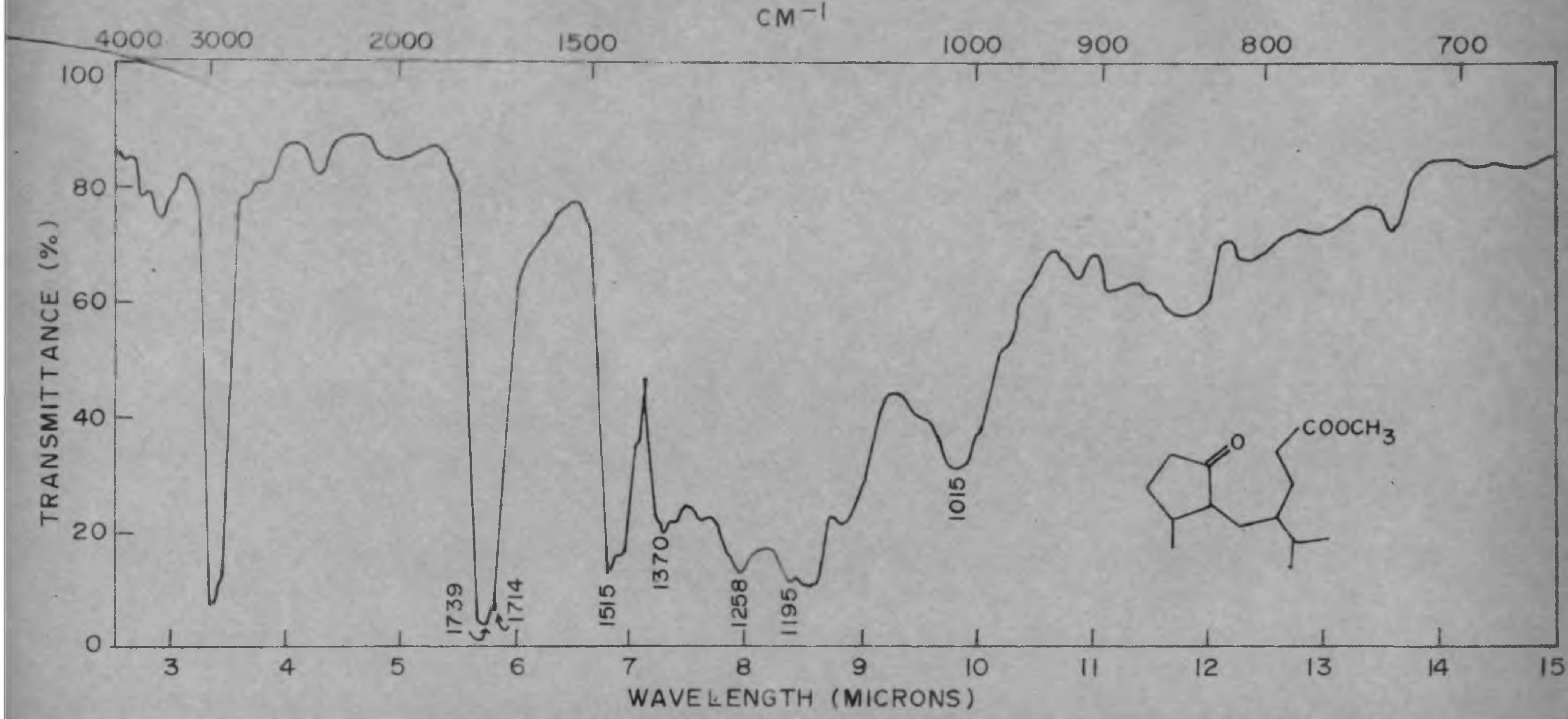


FIG. 10 - IR SPECTRUM OF KETO-ESTER (LIQ. FILM)

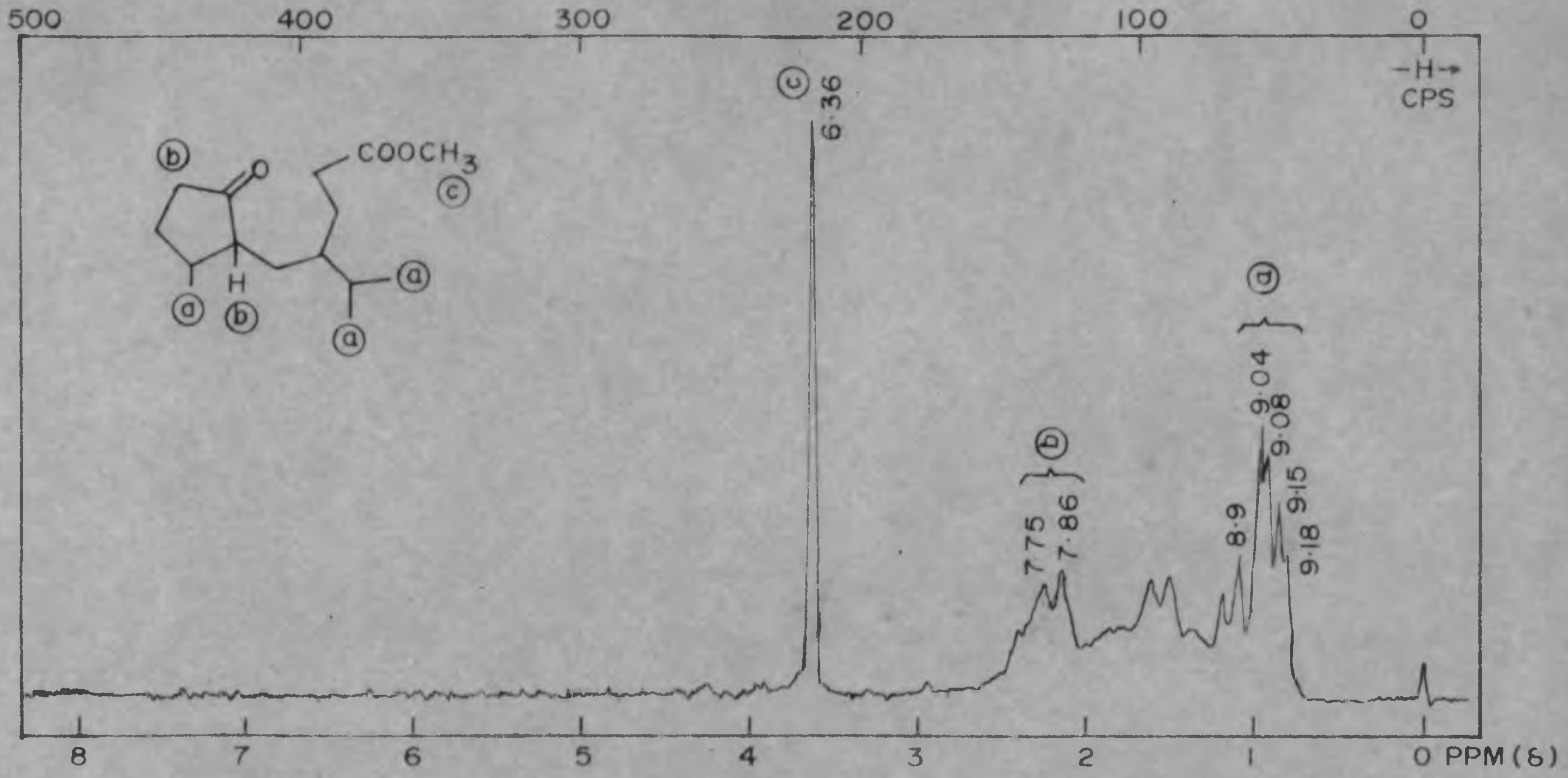


FIG. 11 - NMR SPECTRUM OF KETO ESTER

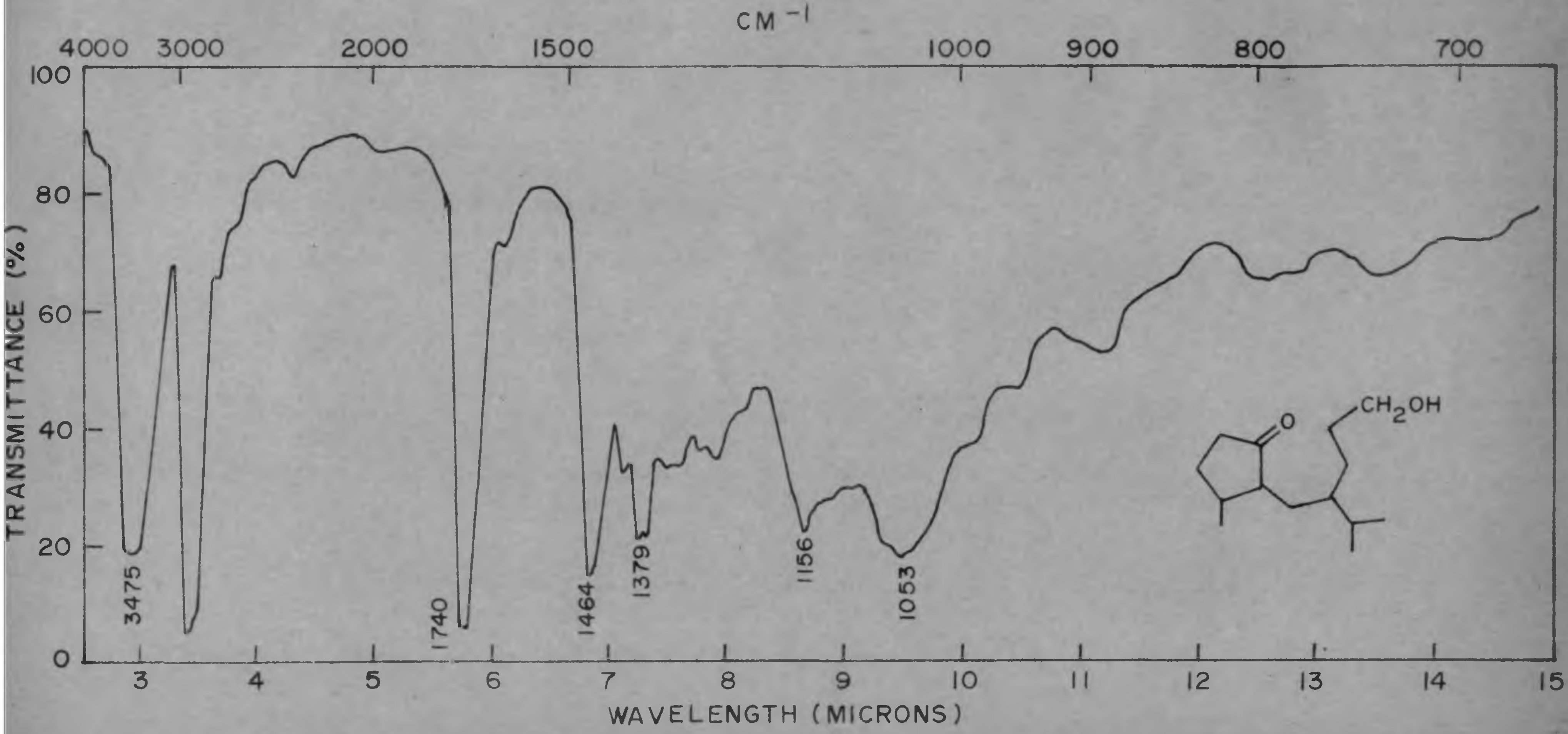
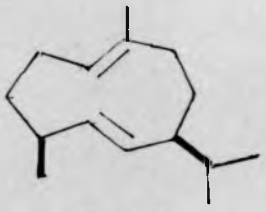


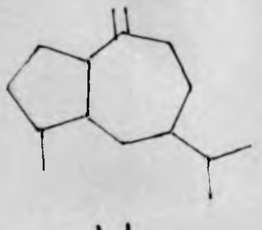
FIG. 12 - IR SPECTRUM OF KETO-ALCOHOL (LIQ. FILM)

which on reduction with LAH afforded the ketal-alcohol (LXII). The keto-alcohol (LXIII) regenerated from (LXII) showed in its IR spectrum (Fig. 12) carbonyl absorption at 1740 cm^{-1}, clearly indicating the presence of cyclopentanone system in (LXIII) and (LX) and cyclopentane ring in compounds LII, LI, L etc. These results supported the guaiane skeleton for the rearranged alcohol (L).

In order to ascertain whether this thermal-rearrangement is due to simple heat or is due to chemical effect of diethylene glycol and/or alkali, we subjected the alcohol (XXIII) as well as the hydrocarbon (XXIV) and the ester (XXII) to simple thermal treatment. The hydrocarbon (XXIV) was heated at 250°-260° in an atmosphere of nitrogen for five hours. It was observed that it rearranges to the hydrocarbon (LI) in about 90% yield. The



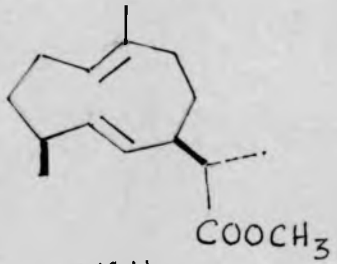
XXIV

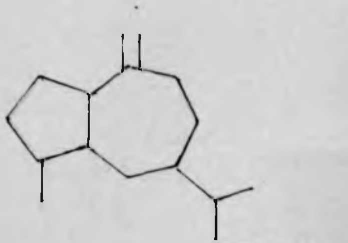


LI

IR and NMR spectra as well as the GLC/TLC analyses of this hydrocarbon were in complete agreement with those of (LI) prepared from (L). In confirmation of its structure, sulphur dehydrogenation produced S-guaiazulene characterised through its s-TNB adduct and ozonolysis produced formaldehyde and the same ketone (LII), the latter giving a semicarbazone, m.p. and m.m.p. 175°. This conclusively proved that the hydrocarbon obtained by direct thermal rearrangement of (XXIV) and the one from (L) were the same.

Similarly the ester (XXII), on heating at 250-260° for five hours in an atmosphere of nitrogen, rearranged to the ester (XLIX) in about 90% yield. Its IR spectrum (Fig. 13) showed bands


XXII


XLIX

at 1730 cm^{-1} due to the ester carbonyl and at 1626 and 885 cm^{-1} due to the $>C = CH_2$ grouping. The NMR spectrum (Fig. 14) showed signals, at 9.01, 9.07, 9.11 τ (6 H) due to the methyls at C_4 and C_{11}; at 6.38 τ (3 H) due to the ester methyl

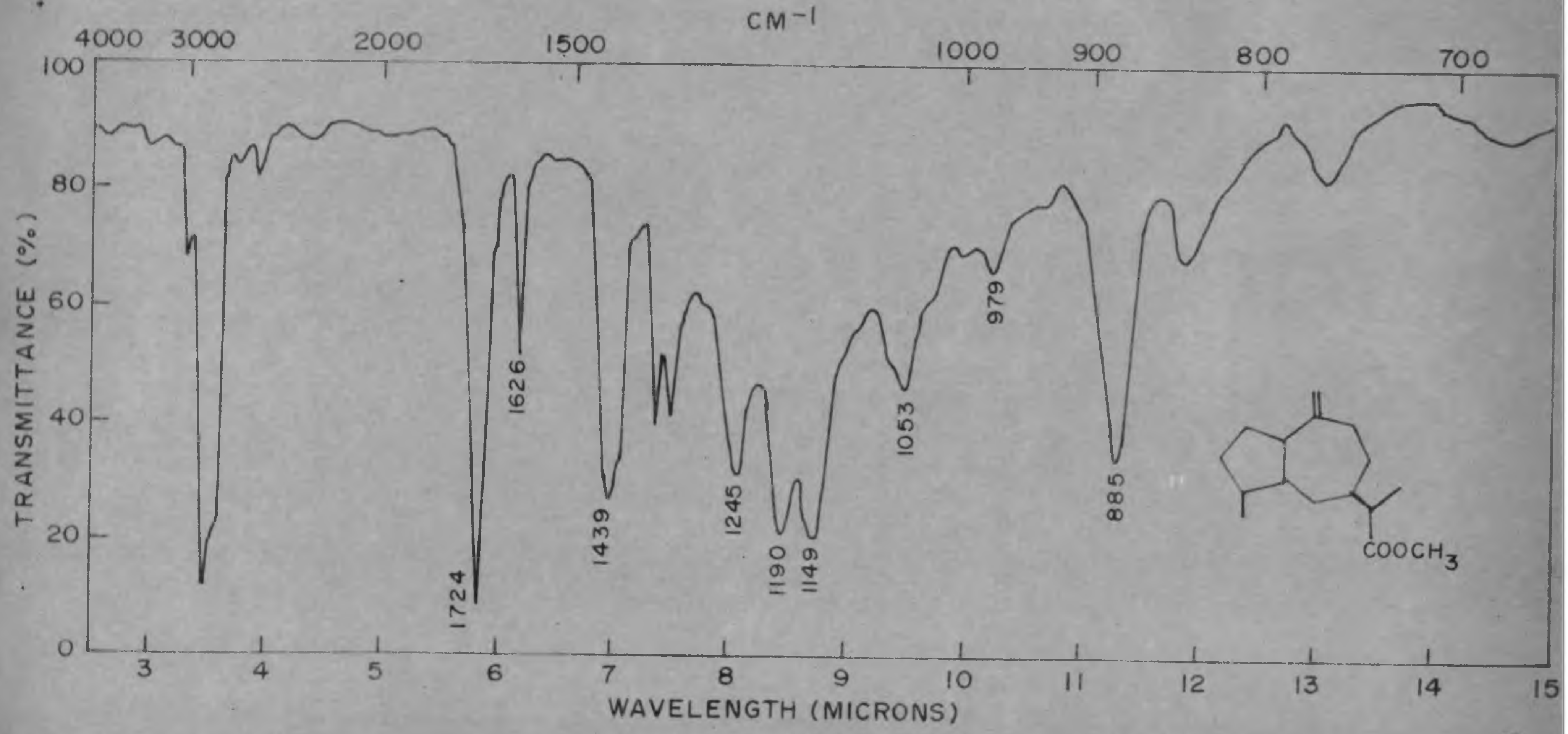


FIG. 13- IR SPECTRUM OF THE REARRANGED ESTER (LIQ. FILM)

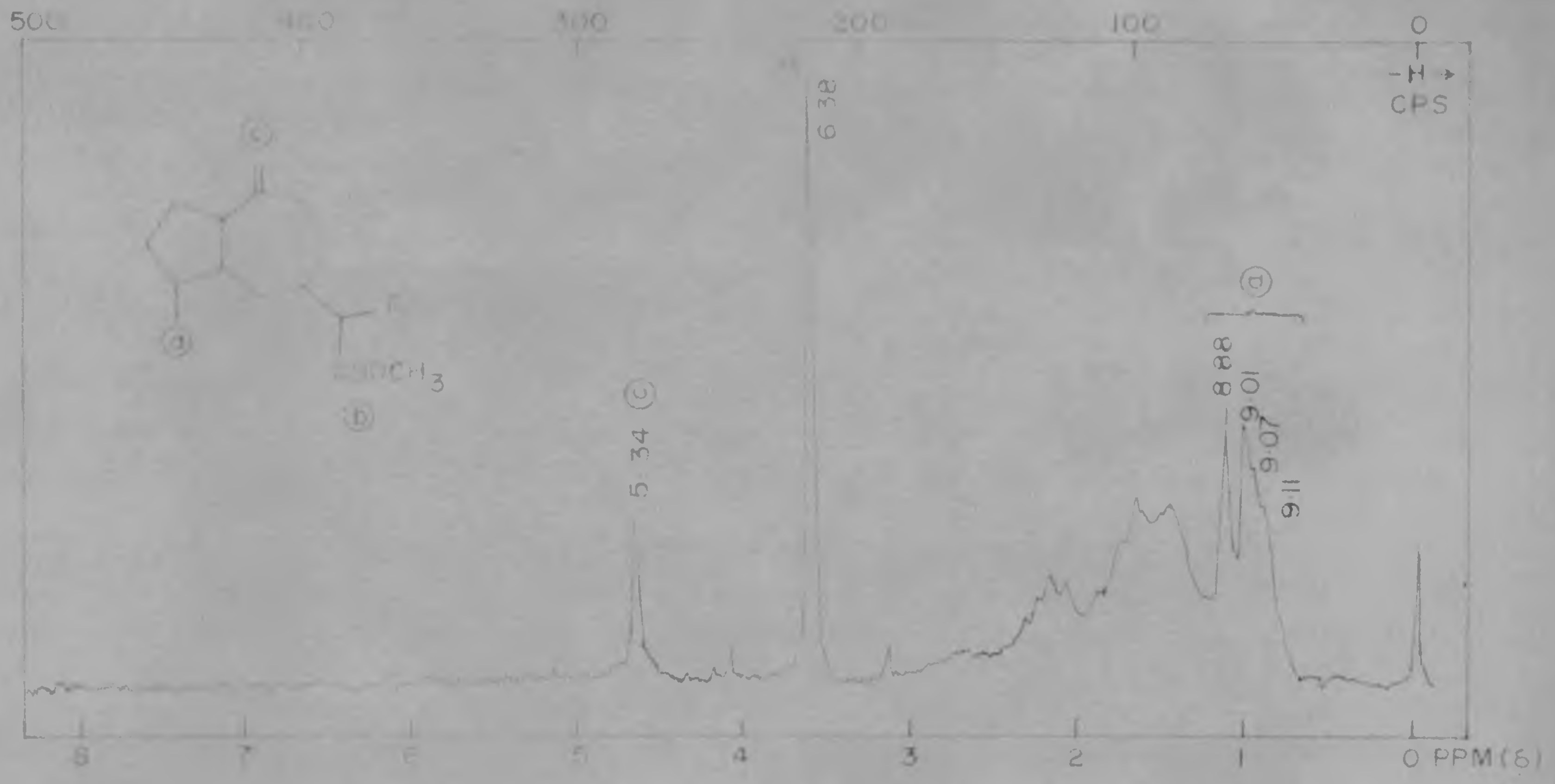


FIG 14 - NMR SPECTRUM REARRANGED ESTER

and at 5.34 τ (2 H) due to the olefinic protons at C_{14}. The ester (XLIX), on LAH reduction gave the alcohol which was identical in its IR spectrum and physical constants with the alcohol (L), obtained by the thermal rearrangement of (XXIII). This alcohol was converted to the hydrocarbon (LI) via LAH reduction of its tosylate. The hydrocarbon, on ozonolysis, gave the same ketone (LII), characterised through its semicarbazone m.p. and m.m.p. 175°.

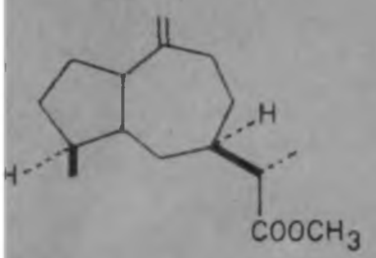
When the thermal rearrangement of the alcohol (XXIII) was carried out directly by heating at 250°-260° in an atmosphere of nitrogen, apart from (L) other products were also formed (as indicated by GLC analysis) from which it was difficult to isolate (L) in pure condition.

When the thermal rearrangement of (XXIII) was carried out in diethylene glycol alone (without alkali) a product was formed, which did not show any absorption ~~in~~ due to $>C = CH_2$ group in its IR spectrum. Further investigation of this aspect is in progress in our laboratory.

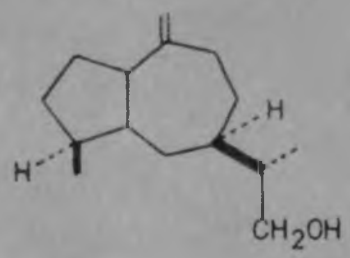
STEREOCHEMICAL CONSIDERATIONS

Although we could not obtain any definite proof for the stereochemistry of the thermally rearranged products (XLIX, L and LI) at the five asymmetric centres viz. C_1, C_4, C_5, C_7 and C_{11} some emperical deductions can be made based on analogy with certain observed facts.

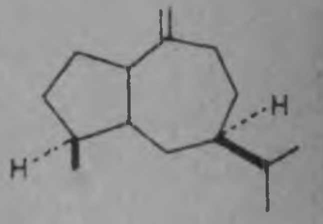
The stereochemistry of (XXII and XXIII) at C_4, C_7 and C_{11} and of (XXIV) at C_4 and C_7 is definitely known. The methyl group at C_4 and the isopropyl group at C_7 are both β-oriented and the methyl group at C_{11} is α-oriented. It is reasonable to assume, that the same stereochemistry as in the original compounds at these centres would be retained in (XLIX, L and LI), since these optical centres are not involved in the rearrangement. The conversion of dihydrocostunolide (II) into saussurea lactone[6] (XIV) and caryophyllene (LXVII) into (LXVIII)[26] by thermal rearrangement are some of the examples which lend support to such an assumption. Further the β-orientation of C_4 methyl and C_7 isopropyl groups in these rearranged products appear to be more stable in guaine series



LXIV

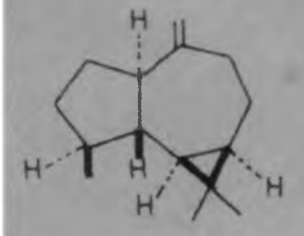


LXV

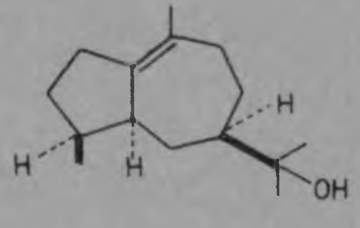


LXVI

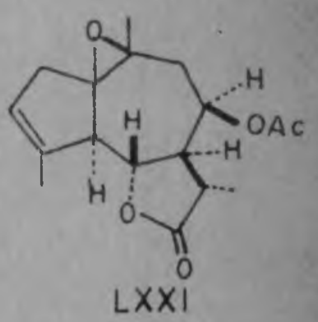
LXVII LXVIII



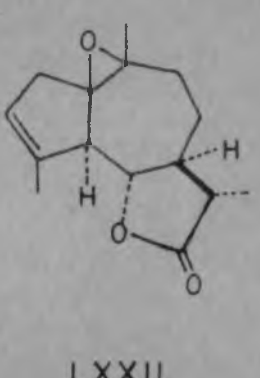
LXIX



LXX



LXXI



LXXII

also than the corresponding epimeric arrangements. In this connection it is worthwhile mentioning that the β-orientation of the methyl at C_4 and the isopropyl at C_7 are the most common in naturally occurring guaiane type compounds like aromadendrene[27] (LXIX) guaiol[28](LV), and bulnesol[29] (LXX) (containing both C_4 and C_7 β-substituents) and the guaianolides like globicin[30] (LXXI) arboresein[31] (LXXII) (for C_7 β-oriented substituent).

The rearranged ester (XLIX), the alcohol (L) and the hydrocarbon (LI) may, therefore, be represented by partial stereostructures LXIV, LXV and LXVI respectively.

EXPERIMENTAL

The ester XXII, the alcohol XXIII and the hydrocarbon XXIV were prepared from (I) by essentially the same procedure as previously reported[13] and were further purified by chromatography over alumina and distillation under reduced pressure. They showed the following properties:

The Ester XXII, b.p., 120-125°(bath)/0.3 mm n_D^{27} 1.4970; $(\alpha)_D$ - 97° (c, 2.6). IR spectrum, Fig. 1.

The Alcohol XXIII, b.p. 120-130°(bath)/0.1 mm; n_D^{28}, 1.5039; $(\alpha)_D$ - 114° (c, 3.2) IR spectrum, Fig.2

The Hydrocarbon XXIV, b.p. 100-105°(bath)/0.5 mm; n_D^{26} 1.4940; $(\alpha)_D$ - 106.8° (c, 2.81). IR spectrum Fig.3

Thermal rearrangement of the alcohol XXIII to L

The alcohol (10 g) was dissolved in diethylene-glycol (100 ml) containing potassium hydroxide (0.5 g) and was heated at 250° for five hours in an atmosphere of nitrogen. The product, after cooling, was diluted with water and extracted with ether. The ether layer was washed with dil. HCl (1%), water and was dried (Na_2SO_4). The product obtained on evaporation of ether was chromatographed on alumina (Gr.II, 250 g) and eluted with pet. ether, pet. ether-benzene mixture (1:1) and benzene. The fractions eluted with pet.ether-benzene and benzene gave L (GLC/TLC pure), (7.9 g), having the following constants:

b.p. 150-160°(bath)/1 mm; n_D^{25} 1.5040; $(\alpha)_D + 32^\circ$ (c, 2.9).

The IR spectrum (Fig. 4) of the alcohol (L) showed bands at: 3300, 3012, 2857, 1754, 1626, 1433, 1361, 1111, 1075, 1026, 970, 885 cm^{-1}.

Analysis:

Found: C, 80.54; H, 11.80%

$C_{15}H_{26}O$ requires: C, 81.02; H, 11.79%

Hydrogenation of the alcohol (L) to (LIII)

The alcohol (3.34 g) was hydrogenated in ethanol using Adams catalyst. The volume of hydrogen absorbed (340 ml at NTP) corresponded to one double bond. The residue, after filteration of the catalyst and evaporation of the solvent, gave (LIII) with the following properties:

b.p. 140-150°(bath)/0.7 mm, n_D^{26} 1.4920, $(\alpha)_D + 35^\circ$ (c, 2.8).

The IR spectrum showed bands at: 3440, 2990, 1470, 11388, 1040, 900 cm^{-1}.

Analysis:

Found: C, 80.00; H, 12.19%.

$C_{15}H_{28}O$ requires: C, 80.29; H, 12.58%.

The hydrocarbon LI from the alcohol L

a) Tosylation of L

The alcohol (4 g) was dissolved in pyridine (30 ml) and was treated with toluene-p-sulphonyl chloride (4 g). The reaction mixture was kept at room temperature for 48 hr. It was diluted with water and extracted with ether. Ether layer was washed with dil. HCl (5%), water and dried (Na_2SO_4). Evaporation of ether gave the crude tosylate (5.1 g).

b) LAH reduction of the tosylate

To an ice-cold solution of LAH (0.75 g) in dry-ether (100 ml) was added dropwise a solution of the above tosylate in dry ether (50 ml). The reaction mixture was stirred at room temperature for 12 hr. Excess of LAH was carefully decomposed by adding moist ether followed by water. The product was filtered and the organic layer separated, washed with dil. HCl (1%), water and dried (Na_2SO_4). The product (2.9 g) obtained on evaporation of ether showed two peaks (approximately in the proportion of 4:1) in GLC analysis. It was chromatographed over alumina (Gr. L, 300 g) and eluted as follows:

Fr.No.	Solvent	Volume (ml)	Weight (g)
1	Pet.ether	100	1.409
2	"	"	0.670
3	"	150	0.308
4	"	400	0.242

Fractions 1 and 2, on evaporation, gave the pure (GLC/TLC) hydrocarbon (LI) with the following properties:

b.p. 100-110°(bath)/1 mm; n_D^{26} 1.4870, $(\alpha)_D$ + 42° (c, 1·9)

<u>The IR spectrum (Fig. 6</u>) showed bands at: 3030, 2890, 1626, 1451, 1439, 1374, 1279, 1156, 1030, 961, 885 cm^{-1}.

<u>Analysis</u>:

Found: C, 86.88: h, 12.76%

$C_{15}H_{26}$ requires: C. 87.30; H, 12.70%.

Selenium dehydrogenation of the hydrocarbon (LI)

The hydrocarbon (1 g) was heated with selenium powder (1 g) in an atmosphere of nitrogen for 8 hr at 280°-310°. The product was taken in pet. ether and was chromatographed on alumina (Gr. I, 50 g), and the blue coloured fraction eluted with pet. ether was separated into azulenic and non-azulenic parts by treatment with phosphoric acid (80%). The azulenic part, regenerated from the phosphoric acid extract on treatment with s-TNB, gave a solid derivative which was crystalli~~sation~~sed from ethanol, m.p. 147-148°. It was identified as s-TNB adduct of Se-guaiazulene by mixed m.p. with an authentic sample.

Analysis

Found: C, 61.67; H, 4.80; N, 10.23%.

$C_{21}H_{21}N_3O_6$ requires: C, 61.36; H, 5.13; N, 10.21%.

The non-azulenic part did not show any maxima characteristic of naphthalenic compounds in its UV spectrum.

Sulphur dehydrogenation of the hydrocarbon LI

The reaction was carried out as mentioned above by heating the hydrocarbon (1 g) at 210-220° with sulphur (2 g) when S-guaiazulene was obtained in 7% yield. It gave s-TNB adduct m.p. 150-151°; mixed m.p. with an authentic S-guaiazulene. TNB adduct was undepressed.

Analysis:

Found: N, 10.34%

$C_{21}H_{21}N_3O_6$ requires: N, 10.21%.

Hydrogenation of the hydrocarbon (LI)

The hydrocarbon (0.5 g) was hydrogenated in acetic acid medium using Adams catalyst. The volume of hydrogen absorbed (57 ml at NTP) corresponded to one double bond. The product was filtered, diluted with water and extracted with ether. The ether layer was washed free of acid with Na_2CO_3 solution (5%), water and was dried. The product obtained after evaporation of ether was passed through a column of silica gel (25 g) and was eluted with pet. ether, which on evaporation furnished pure (GLC/TLC) guaiane (XL, 0.45 g) having the following properties:

b.p. 90-100°(bath)/1 mm; n_D^{25} 1.4735;
$(\alpha)_D$ + 44° (c, 2.7).

The IR spectrum (Fig.8) showed bands at: 1380, 1345, 1310, 1280, 1210, 1170, 1105, 1070, 1050, 1020, 1000, 975, 950, 940, 920, 895, 872, 847, 805 cm^{-1}.

Analysis

Found: C, 86.26; H, 13.10%

$C_{15}H_{28}$ requires: C, 86.46; H, 13.54%.

Ozonolysis of the hydrocarbon LI: Formation of LII and formaldehyde

A stream of ozonised O_2 was passed through an ice-cold solution of (LI, 0.9 g) in chloroform (25 ml), till the absorption was complete. Solvent was removed under suction at 40° and the resulting ozonide was decomposed by heating with water for 3 hr. in a flask with trap-arrangement to collect formaldehyde. The trap-water, on treatment with dimedone, gave a solid derivative which was identified as formaldimedone, m.p. and m.m.p. 187-188°. The non-volatile portion was extracted with ether. Ether layer was washed with Na_2CO_3 solution (10%), water and dried (Na_2SO_4). The crude product obtained on evaporation of ether was passed through alumina (Gr. III, 25 g) and was eluted with pet. ether which on evaporation afforded the pure (GLC/TLC) ketone LII (0.515 g) with the following properties:

b.p. 120-125°(bath)/0.5 mm; $n_D^{27.5}$ 1.4826, $(\alpha)_D$ + 38.5° (c, 1.8).

The IR spectrum (Fig. 9) showed bands at: 2915. 1700, 1449, 1439, 1399, 1370, 1266, 1225, 1205, 1176, 1156, 1124, 1106, 1020, 997, 975, 917, 833 cm^{-1}.

Analysis:

Found: C, 80.56; H, 11.67%

$C_{14}H_{24}O$ requires : C, 80.71; H, 11.61%,

With semicarbazide hydrochloride and sodium acetate ~~in aq. ethanol~~, the ketone gave a semicarbazone m.p. 175°.

Analysis:

Found: N, 15.36%

$C_{15}H_{27}N_3O$ requires: N, 15.8%

Ozonolysis of the alcohol L: Formation of LIV and formaldehyde

The alcohol (1 g) was ozonised and worked up as above to give formaldehyde (identified by dimedone derivative) and the keto alcohol LIV, b.p. 140-150°(bath)/0.5 mm.

IR spectrum showed bands at: 3500, 1695, 1404 and 1031 cm^{-1}.

Analysis:

Found: C, 74.66; H, 10.61%

$C_{14}H_{24}O_2$ requires: C, 74.95; H, 10.78%

Baeyer-Villiger oxidation of the ketone LII to LVIII and conversion of the latter to LIX

A mixture of the ketone (1.5 g) perbenzoic acid (2.5 g) in chloroform (25 ml) and toluene-p-sulphonic acid (10 mg) was stirred at room temperature for 48 hr. The product was washed with Na_2CO_3 solution (1%) and water and was dried (Na_2SO_4). Chloroform was evaporated to give crude lactone LVIII, which without further purification, was hydrolysed by heating under reflux with 1 N methanolic KOH (25 ml) for 4 hr. The acidic portion (1.3 g), obtained by working up in the usual way, was treated in cold with an excess of a dry solution of diazomethane in ether. Evaporation of ether gave the desired hydroxy ester (LIX; 1.32 g). It was purified by passing through alumina (Gr. III, 30 g) and eluting with benzene and by distillation under reduced pressure. It had the following properties: b.p. 160-165°(bath)/0.2 mm; $(\alpha)_D$ + 20.33° (c, 3.9). IR spectrum showed bands at: 3500, 2959, 1739, 1460, 1439, 1370, 1258, 1176, 1005 and 895 cm^{-1}.

Analysis:

Found: C, 70.59; H, 11.43%

$C_{15}H_{28}O_3$ requires: C, 70.27; H, 11.01%

Oxidation of the hydroxy ester LIX to the keto ester LX

The hydroxy ester (0.6 g) was dissolved in acetone (25 ml) and Jones reagent was added dropwise with shaking till brown colour persisted. The reaction product was kept at room temperature for 45 minutes, diluted with water and extracted with ether. The ether layer was washed with Na_2CO_3 solution (5%) followed by water and dried (Na_2SO_4). The neutral material (0.570 g), obtained after evaporation of ether, was chromatographed on alumina (Gr. III, 12 g) and eluted with pet. ether-benzene mixture (1:1), which on evaporation afforded the keto-ester (LX, 0.55 g) (TLC single spot) with the following properties:

b.p. 150-155°(bath)/0.1 mm; $(\alpha)_D$ - 6.9°(c, 1.3)

IR spectrum (Fig. 10) showed bands at: 2950, 1739, 1724, 1515, 1447, 1408, 1370, 1250, 1195, 1170, 1130, 1015, 925, 900 and 847 cm^{-1}.

Analysis:

Found: C, 70.82; H, 9.75%

$C_{15}H_{26}O_3$ requires:C, 70.83; H, 10.3%.

Conversion of the keto ester LX to the keto-alcohol LXIII

a) Formation of the ethylene ketal LXI

A mixture of the keto ester (0.4 g),

ethylene glycol (0.6 g; freshly distilled), dry benzene (30 ml) and toluene-p-sulphonic acid (5 mg) was heated under reflux with stirring for 12 hr with an arrangement to separate the water formed in the reaction by azeotropic distillation. The reaction product, after cooling, was washed with Na_2CO_3 solution (5%) and water and dried (Na_2SO_4). Evaporation of benzene furnished the ketal (LXI;0.430 g).

Conversion of the ketal LXI to the ketoalcohol LXIII

To an ice-cold solution of LAH (0.25 g) in dry ether (50 ml) the above ketal in dry-ether (25 ml) was added slowly with stirring. The reaction mixture was further stirred at room temperature for 8 hr. and worked up as usual. The resulting material (0.39 g, shows no carbonyl absorption in its IR spectrum), the ketal alcohol LXII was refluxed with concentrated HCl (2 ml), water (2 ml) and ethanol (5 ml) for 2 hr. The reaction product was diluted with water and extracted with ether. The ether layer was washed with Na_2CO_3 solution (5%), water and dried (Na_2SO_4). The ether was evaporated and the crude product obtained after purification by chromatography over alumina and distillation under reduced pressure gave the pure (GLC/TLC) keto alcohol (LXIII; 0.35 g) with the following constants:

b.p. 160-165°(bath)/0.2 mm; $(\alpha)_D$ - 3.85° (c, 3.25)

IR spectrum (Fig. 12) showed bands at: 3475 (hydroxyl) 2941, 1740 (cyclopentanone), 1464, 1408 ($-CO-CH_2-$), 1379, 1333, 1316, 1266, 1156, 1053, 990, 952 and 892 cm^{-1}.

Analysis:

Found: C, 74.66; H, 11.2%

$C_{14}H_{26}O_2$ requires:C, 74.28; H, 11.58%.

Thermal rearrangement of the ester XXII to the ester XLIX

The ester (1 g) was heated at 240-260° for 5 hr in an atmosphere of nitrogen. The resulting product was chromatographed over alumina (Gr. II, 30 g) and eluted with pet. ether and pet. ether benzene (3:1) mixture. The fractions on evaporation furnished the pure (GLC/TLC) ester XLIX, 0.77 g with the following properties:

b.p. 120.130°(bath)/0.2 mm; n_D^{29} 1.4860; $(\alpha)_D$ + 47° (c, 3.7).

The IR spectrum (Fig. 13) of the ester showed bands at: 3032, 2882, 1730, 1626, 1439, 1362, 1335, 1245, 1190, 1053, 970, 885 and 845 cm^{-1}.

Analysis:

Found: C, 76.54; H, 10.41%

$C_{16}H_{26}O_2$ requires: C, 76.75; H, 10.47%.

Conversion of the ester XLIX to the alcohol L

The ester (1 g) was reduced, by a solution of LAH (0.2 g) in dry ether (100 ml) under stirring for 12 hr. at room temperature. The reaction product was worked as usual to furnish the alcohol (L; 0.800 g) with the following properties:

b.p. 125-135°(bath)/0.2 mm; n_D^{30} 1.5030;
$(\alpha)_D$ + 33.6° (c, 2.5).

The IR and NMR spectra of the alcohol are identical with those of (L) prepared from XXIII.

Analysis:

Found: C, 81.23; H, 11.62%

$C_{15}H_{26}O$ requires : C, 81.02; H, 11.79%.

Conversion of the alcohol (L) into the hydrocarbon (LI)

The alcohol (prepared from the rearranged ester XLIX) (0.8 g) was dissolved in pyridine (25 ml) and toluene-p-sulphonyl-chloride (1 g) was added slowly with shaking and cooling. The reaction mixture was kept at room temperature for 48 hr and worked as usual. The p-toluene sulphonate (1.3 g) obtained was reduced by an ethereal solution of LAH (0.250 g in 100 ml of dry ether). The resulting hydrocarbon (0.840 g) after purification by chromatography over alumina and distillation under reduced pressure showed the following constants:

b.p. 100-105°(bath)/0.8 - 1 mm; $n_D^{28.5}$ 1·48-75, $(\alpha)_D$ + 40.4° (c, 2.7)

The IR and NMR spectra of this hydrocarbon were found to be in complete agreement with those of (LI) prepared from (L).

<u>Ozonolysis of the hydrocarbon (LI)</u>

Ozonolysis of the hydrocarbon (prepared from the rearranged ester XLIX) (0.5 g) as described previously furnished formaldehyde (dimedone derivative m.p. 189°) and a ketone, identical with LII, in its properties:

b.p. 120-130°(bath)/0.5 mm; n_D^{29} 1.4830; $(\alpha)_D$ + 37° (c, 1.9).

<u>Analysis</u>:

Found: C, 80.85; H, 11.90%

$C_{14}H_{24}O$ requires: C, 80.71; H, 11.61%.

The ketone furnished the semicarbazone (semicarbazide hydrochloride Na-acetate method) m.p. 175-176°. Mixed m.p. with an authentic sample was undepressed.

Analysis:

Found: C, 68.29; H, 10.03; N, 15.70%

$C_{15}H_{27}N_3O$ requires: C, 67.88; H, 10.26; N, 15.83%.

Thermal rearrangement of the hydrocarbon XXIV: Sulphur dehydrogenation and ozonolysis of the resulting hydrocarbon LI

a) Thermal rearrangement

The hydrocarbon (2 g) was heated at 250-260° for 5 hr in an atmosphere of nitrogen. The product was passed through alumina (Gr. I, 100 g) and eluted with pet. ether to furnish pure (GLC/TLC) hydrocarbon (1.7 g) with the following constants:

b.p. 105-110°(bath)/1 mm; n_D^{28} 4860;

$(\alpha)_D$ + 39.5° (c, 4.42).

The IR and NMR spectra of this hydrocarbon were found to be in complete agreement with those of (LI) prepared from the rearranged alcohol (L).

b) Sulphur dehydrogenation of the hydrocarbon LI

The hydrocarbon (0.5 g) was heated with sulphur (1 g) at 200-220° for 8 hr in an atmosphere of nitrogen. The product (0.025 g), obtained by working up as described before, gave s-TNB adduct, m.p. 149-150°. Mixed m.p. with an authentic sample of s-TNB adduct of S-guaiazulene was undepressed.

c) Ozonolysis of the hydrocarbon (LI)

The above hydrocarbon (0.5 g) was ozonised as described previously. It furnished formaldehyde (dimedone derivative m.p. 187°) and the ketone (LII) (0.180 g), semicarbazone m.p. 174-176°. Mixed m.p. with the authentic sample of semicarbazone was undepressed.

Analysis:

Found: C, 80.89; H, 11.85%.

$C_{14}H_{24}O$ requires: C, 80.71; H, 11.61%.

Thermal rearrangement of the alcohol XXIII

The alcohol (1 g) was heated at 240-260° in an atmosphere of nitrogen for 5 hr. GLC analysis of the product showed it to be a mixture of three compounds. From the mixture we could isolate (L) (0.215 g), of about 80% purity (GLC), by repeated chromatography over alumina. It showed the following constants:

b.p. 120-130°(bath)/0.2 mm; $(\alpha)_D$ + 25° (c, 2.4).

The IR spectrum of this product showed bands at: 3490, 1626, 1030, 885 cm^{-1}.

Analysis:

Found: C, 81.40; H, 11.90%

$C_{15}H_{26}O$ requires : C, 81.02; H, 11.79%.

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PART II

SYNTHESES OF COMPOUNDS STRUCTURALLY RELATED TO DIHYDROGUAIOLS AND BULNESOL

***

SUMMARY

Compounds structurally related to dihydroguaiols (III and IV) and bulnesol (II) have been synthesised starting from the ester (XXIXa) obtainable from costunolide (XXVII) via the thermal rearrangement of XXVIIIa.

Guaiol

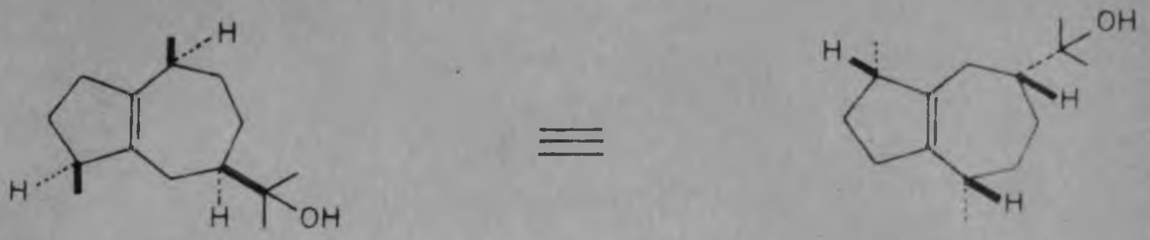
Guaiol, $C_{15}H_{26}O$, (I) is a crystalline bicyclic sesquiterpenic tertiary alcohol, possessing a guaiane skeleton. It constitutes one of the major components of guaiac wood oil[1] from which it was isolated for the first time by Plattner and co-workers[2]. It occurs in other essential oils[3] also, such as the oil of Callitris glauca.

The structure of guaiol was established by Plattner and co-workers[2]. On hydrogenation it furnished two isomeric dihydroguaiols. The levorotatory isomer (III), which was isolated in pure condition, is a crystalline solid m.p. 74-78°. The dextro-rotatory isomer (IV) is a liquid which has not been, so far, isolated in pure condition.

The absolute configuration of guaiol (I) was elucidated as follows:

Configuration at C_4 and C_{10} (Chart 1A and 1B)

Djerassi and co-workers[4] converted the (+) dihydroguaiol (IV), by a series of reactions (Chart 1A) into bis-homo-nepetalinic acid (VI). The same acid was also obtained from nepetalinic acid (VII) of known absolute configuration[21], by



I

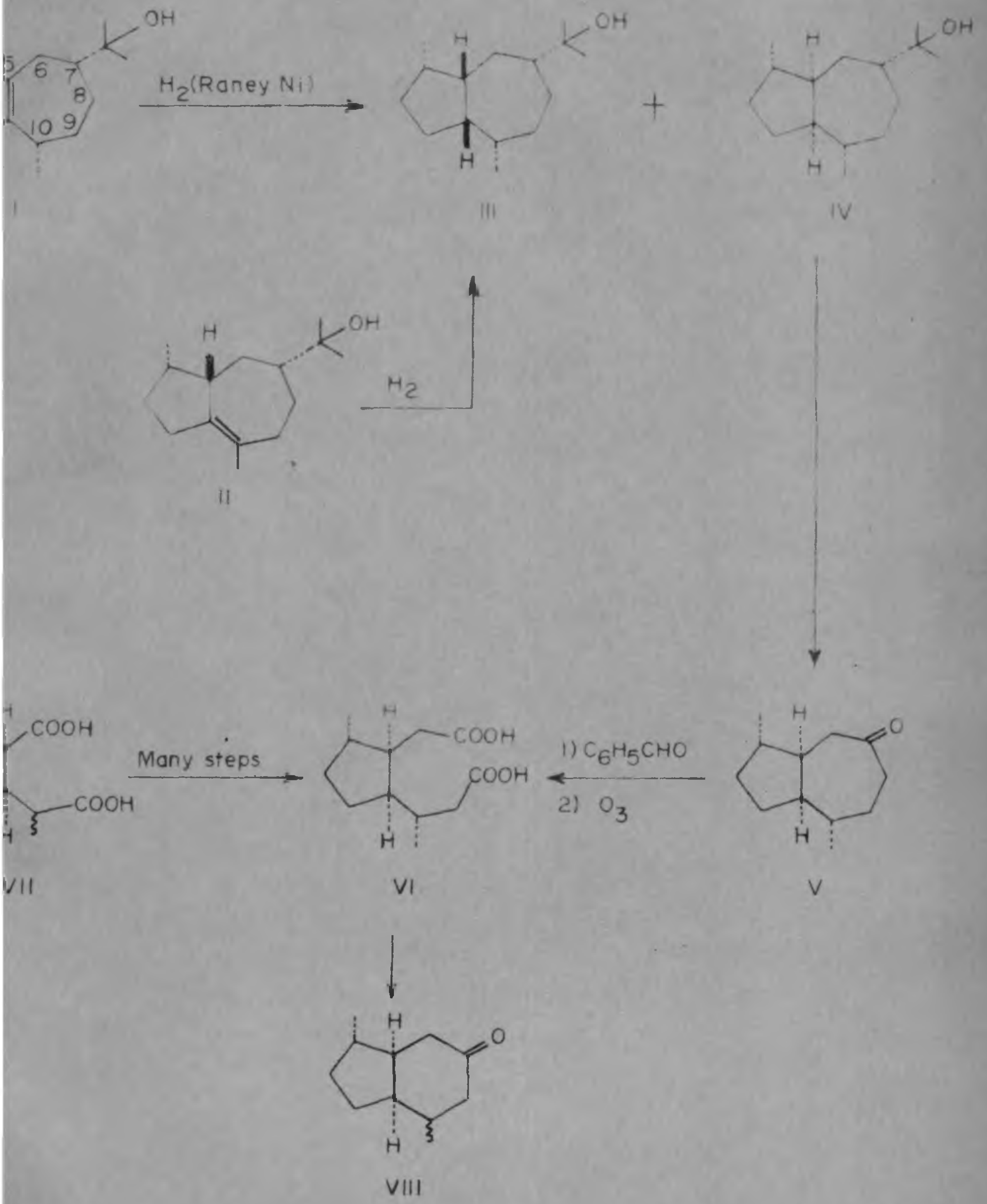
II

III

IV

CHART - I

CONFIGURATION OF GUAIOL AT C_4 AND C_{10}



CHART—1A

reactions which do not involve any epimerisation. Thus it follows that the absolute configuration at the carbon atoms 1, 4 and 5 in (+) dihydroguaiol (IV) should be the same as in nepetalinic acid (VII) (Chart 1A).

On the basis of these results and assuming the <u>cis</u>-addition of hydrogen to the double bond in guaiol (I), the absolute configuration at C_1, C_4 and C_5 in levorotatory crystalline dihydroguaiol was inferred as in III. The C_{10} methyl group was tentatively assigned β-orientation, on the basis of the ORD data of the indanone derivative VIII, obtained from VI. However, subsequently it has been shown to be α-oriented as given below.

Sorm and co-workers[8] during their work on bulnesol (II), a double bond isomer of guaiol, observed the identity between dihydrobulnesol and (-) dihydroguaiol (III) and inferred the configuration at C_{10} as in III (Chart 1A) i.e. the C_{10} methyl to be α-oriented, on the basis of <u>cis</u>-addition of hydrogen to the double bond in bulnesol (II).

Minato and co-workers[5] arrived at the same conclusion as follows: An intermediate product XI,

CONFIGURATION OF GUAIOL AT C_4 AND C_{10}

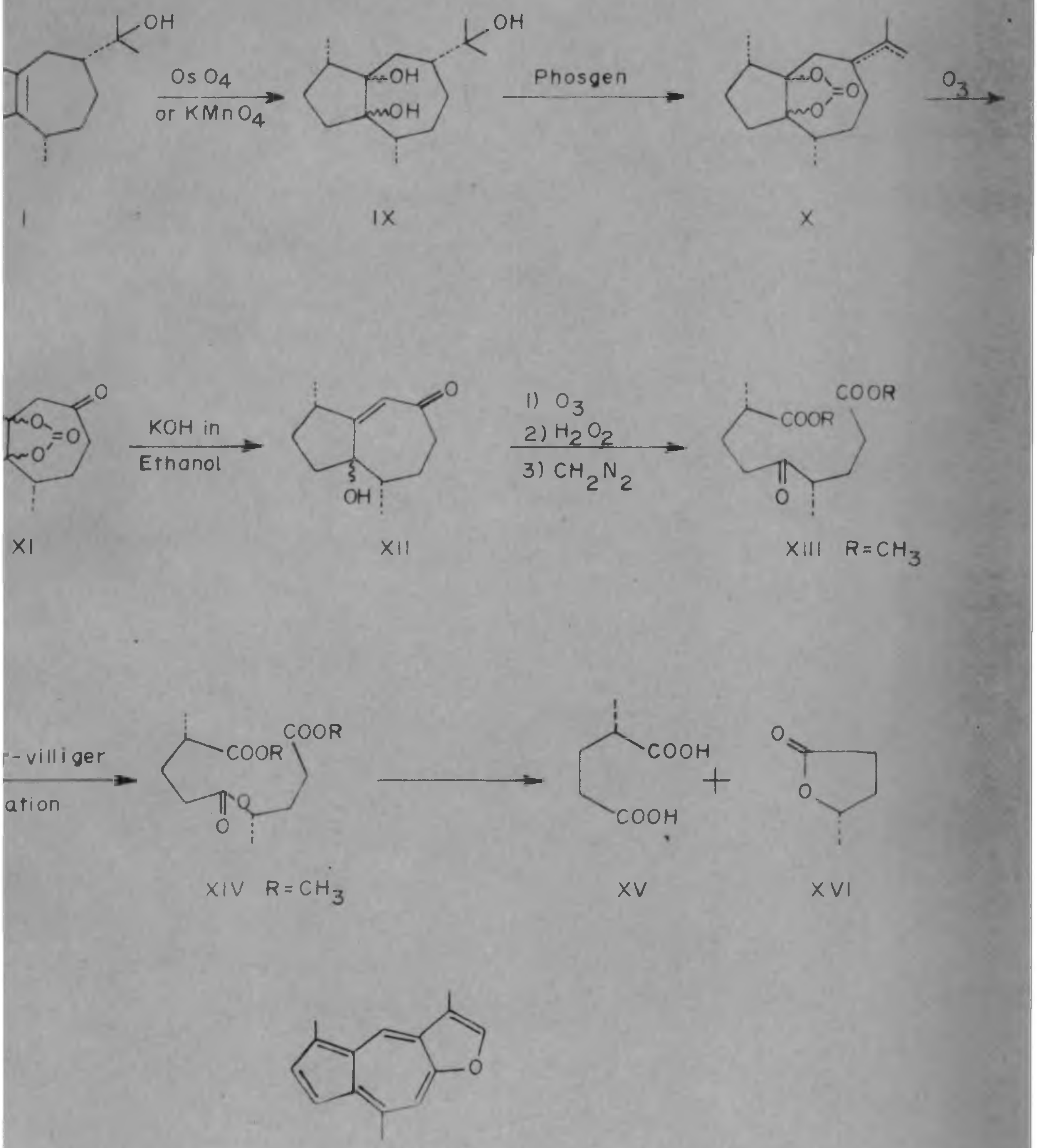


CHART-1B

obtained from guaiol during the synthesis of linderazulene[6] (XVII), was converted by a series of reactions into (+)-α-methyl glutaric acid (XV) and (-)-γ-methyl-butyrolactone (XVI). Since XV was correlated with R-(-)-lactic acid by A. Fredga[19] and XVI xxxx with S-(+) lactic acid by P.A. Lavene[20], both the C_4 and the C_{10} methyl groups in guaiol should possess α-configuration as in I (Chart 1A and 1B).

The configuration at C_7 (Chart 2)

The configuration of the C_7 hydroxy isopropyl group in guaiol was established by Minato[7] as follows.

The dihydroguaiene (XIX), obtained by dehydration of guaiol (I) followed by hydrogenation of the resulting guaiene (XVIII), was converted by a series of reactions, which involved no epimerisation, into levo-rotatory-α-isopropyl-γ-aceto butyric acid (XXV). This on oxidation furnished S-(-)-α-isopropyl glutaric acid (XXVI). It thus follows that, the C_7 hydroxy isopropyl group in guaiol should be α-oriented as in (I) (Chart 2).

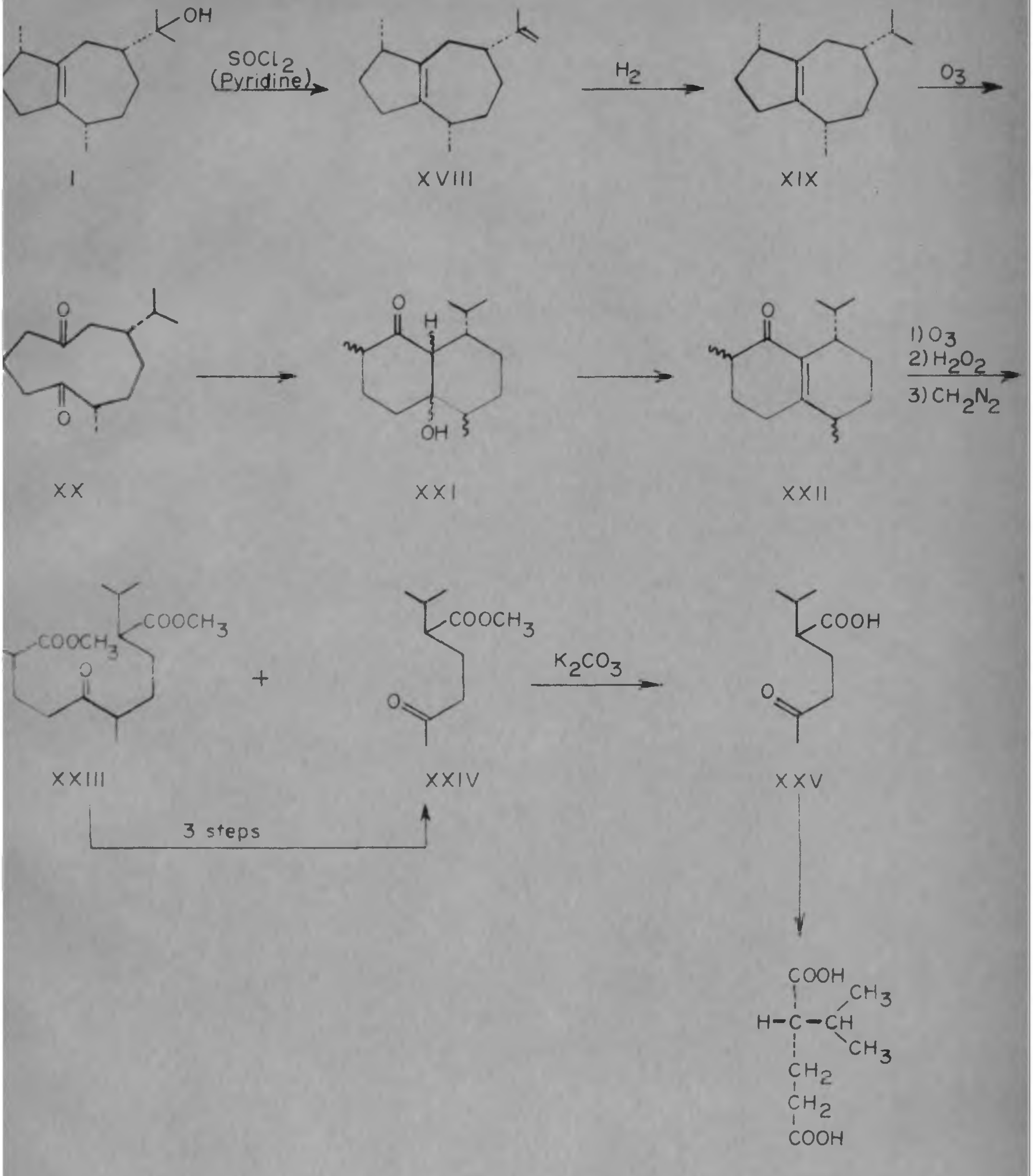
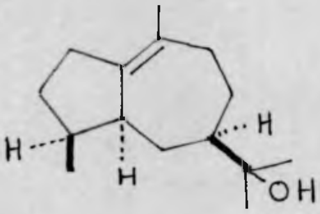


CHART- 2

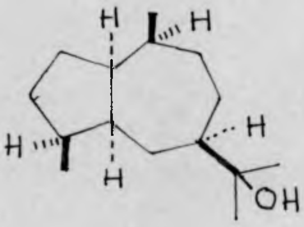
CONFIGURATION OF GUAIOL AT C_7

Bulnesol

Bulnesol, $C_{15}H_{26}O$ (II), is another crystalline, sesquiterpenic, tertiary alcohol which accompanies guaiol (I) in guaiac wood oil and was isolated by Czech worker[8]. On hydrogenation, it gave a solid dihydroderivative, which was identified as (-) dihydroguaiol (III) by m.p. and mixed m.p. On this basis as well as by other degradation studies[8] it was assigned the structure II.



II



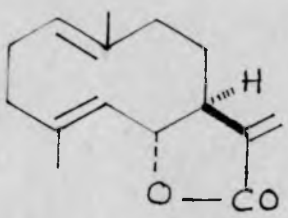
III

Recently, the conversion of bulnesol (II) to guaiol (I), by the action of acetic acid-sulphuric acid, has been reported by R.B. Bates et al.[9]

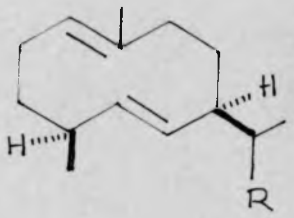
In the last few years, apart from guaiol and bulnesol, numerous other sesquiterpenoids of guaiane series have been isolated from various natural sources. Although the structures of these compounds have been determined by unambiguous methods, the stereochemical knowledge in majority of these compounds is still meagre. Hence, guaiol (I), bulnesol (II) and the compounds derived from them viz. the dihydroguaiols (III & IV), all with known absolute configuration, are useful in stereochemical deductions of compounds belonging to the guaiane series.

PRESENT WORK

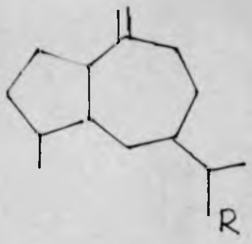
The conversion of costunolide (XXVII) into compounds XXIX$_{a,b \text{ and } c}$ of guaiane series via the thermal rearrangement of compounds XXVIII$_{a,b \text{ and } c}$ respectively has been described in Part I of the thesis. Further in analogy with certain observed cases, the configuration at C$_4$ and C$_7$ in the rearranged products (XXIX$_{a,b \text{ and } c}$) has been assumed to be the same, as in the original compounds (XXVIII$_{a,b \text{ and } c}$) since these optical centres are not involved in the rearrangement.



XXVII



XXVIII a, R = COOCH$_3$.
b, R = CH$_2$OH
c, R = CH$_3$



XXIX
a, R = COOCH$_3$
b, R = CH$_2$OH
c, R = CH$_3$

The work described in this part of the thesis deals with the conversions of the rearranged

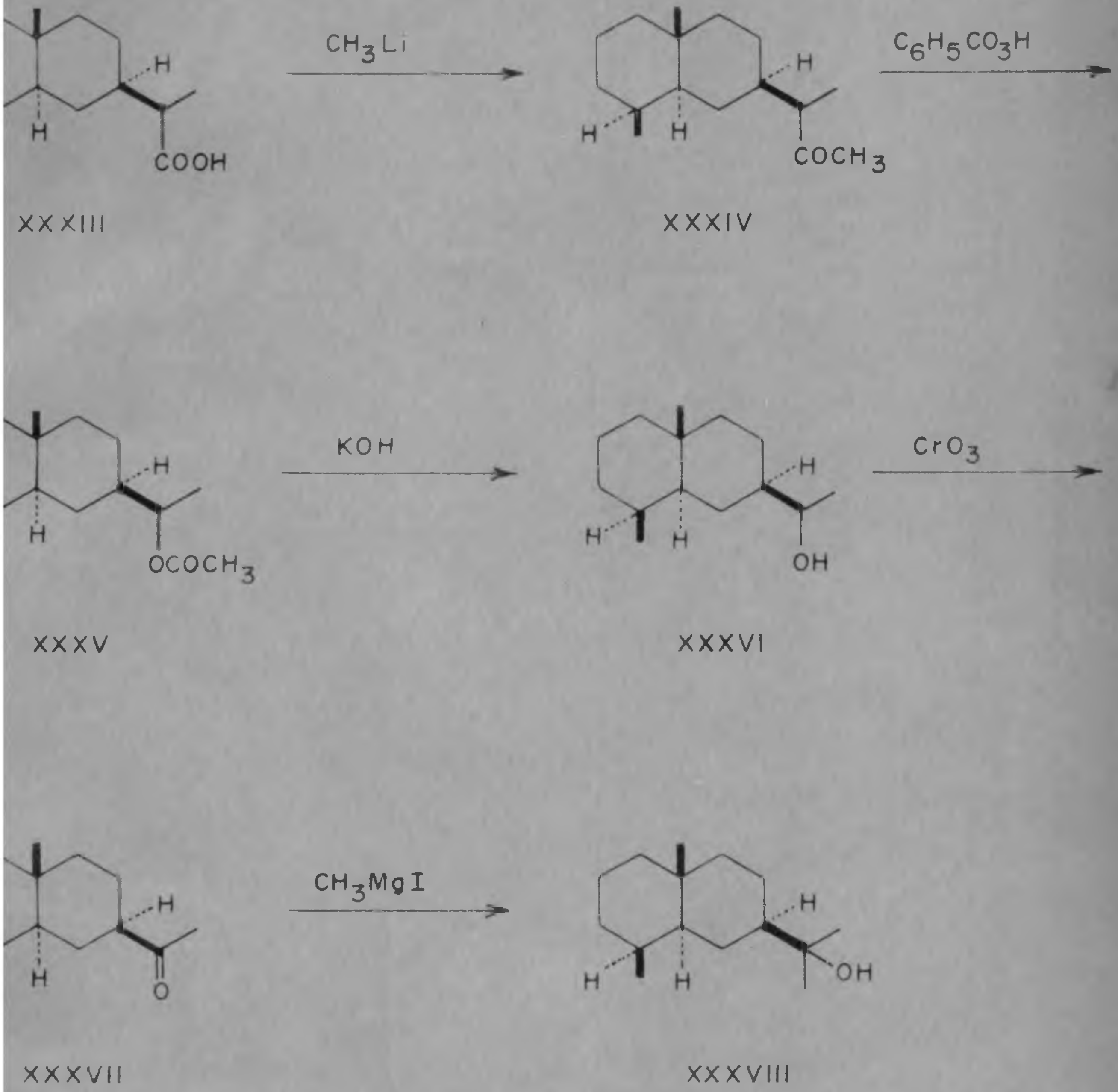
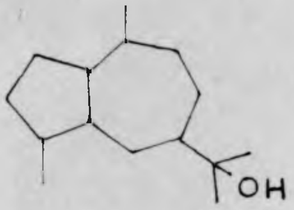


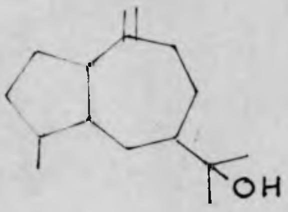
CHART-3

SYNTHESIS OF DIHYDRO-EUDESMOL

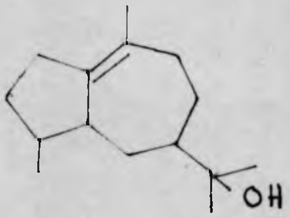
ester $XXIX_a$ into compounds XXX, XXXI and XXXII which are structurally related to dihydroguaiols (III and IV) and bulnesol (II) respectively.



XXX



XXXI



XXXII

The aim in carrying out these conversions was to gain more insight into the stereochemical aspects of the rearranged products $XXIX_{a,b}$ and c.

Conversion of the ester $XXIX_a$ into the alcohol XXX

Starting from tetrahydrocostic acid (XXXIII) dihydroeudesmol (XXXVIII) was synthesised by Kelkar et al.[10], as outlined in Chart 3. Following the same sequence of reactions, we have been able to convert the ester ($XXIX_a$) into the desired alcohol (XXX) as described below.

The ester ($XXIX_a$) was hydrogenated (PtO/EtOH) to the saturated dihydroderivative (XXXIX) (see Chart 4). The corresponding acid (XL)

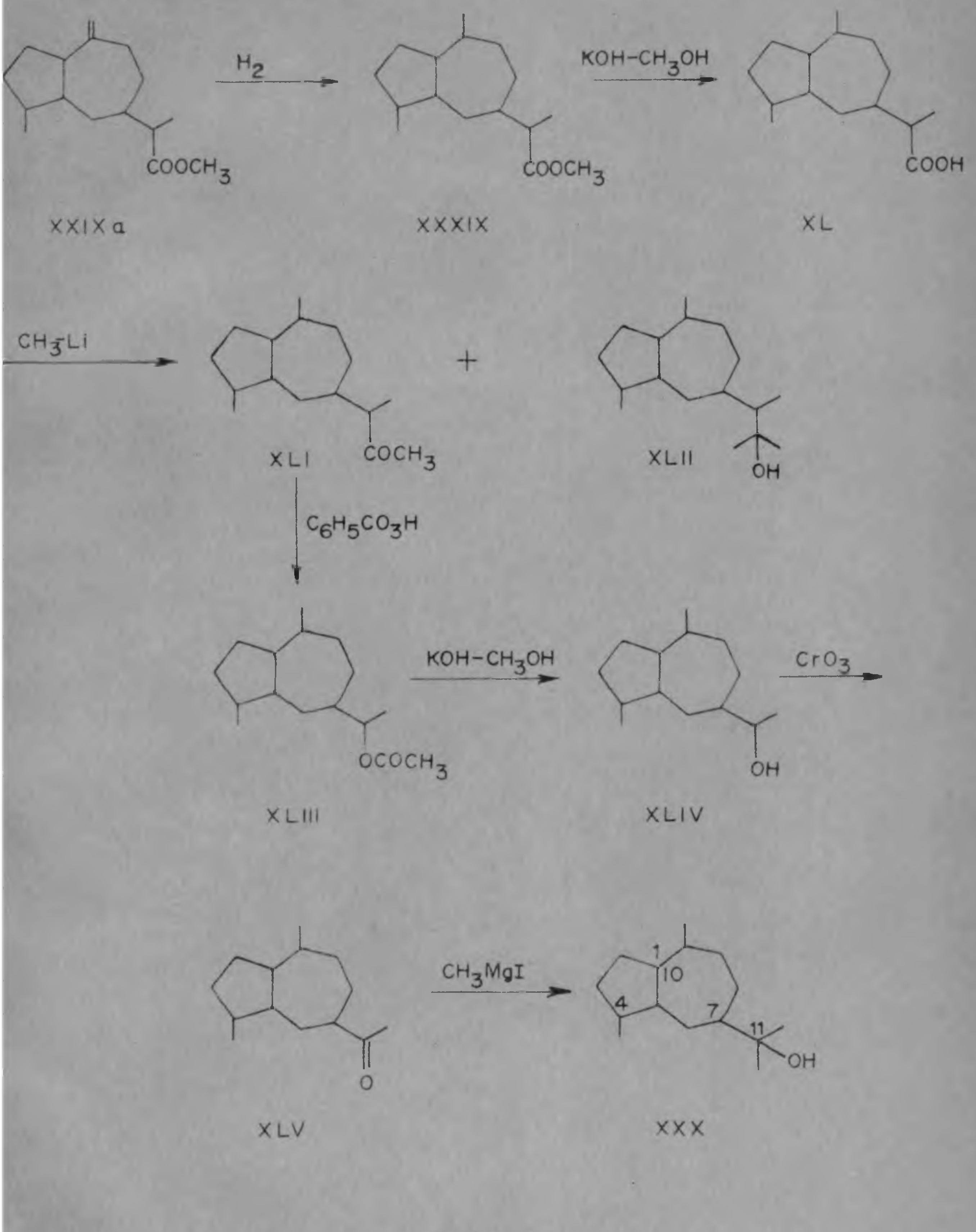

COOCH3
XXIXa
H2
COOCH3
XXXIX
KOH-CH3OH
COOH
XL
CH3Li
XLI
COCH3
+
XLII
OH
C6H5CO3H
OCOCH3
XLIII
KOH-CH3OH
OH
XLIV
CrO3
O
XLV
CH3MgI
1
10
4
7
11
OH
XXX

CHART-4

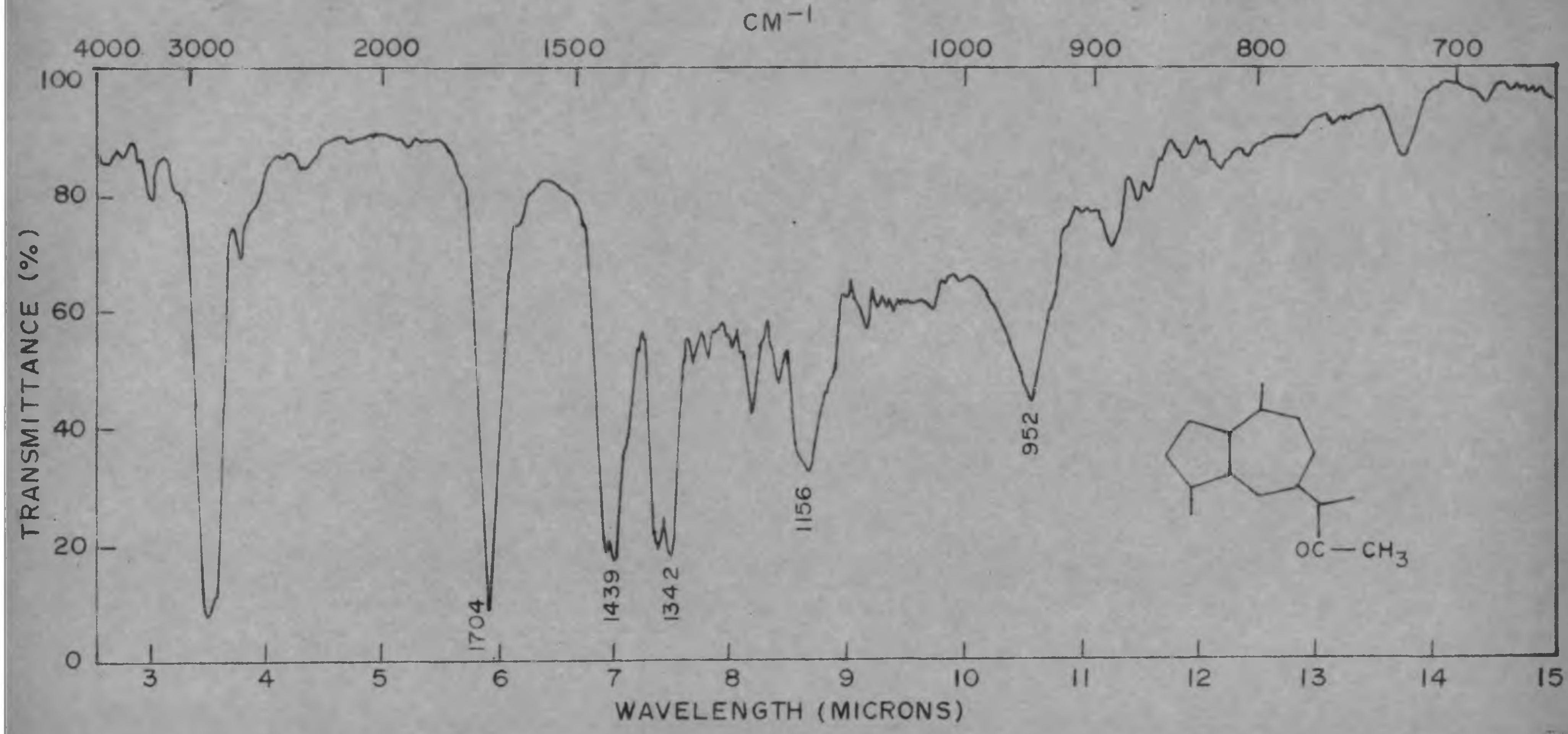


FIG. 1 - IR SPECTRUM OF C_{16}- KETONE (LIQ. FILM)

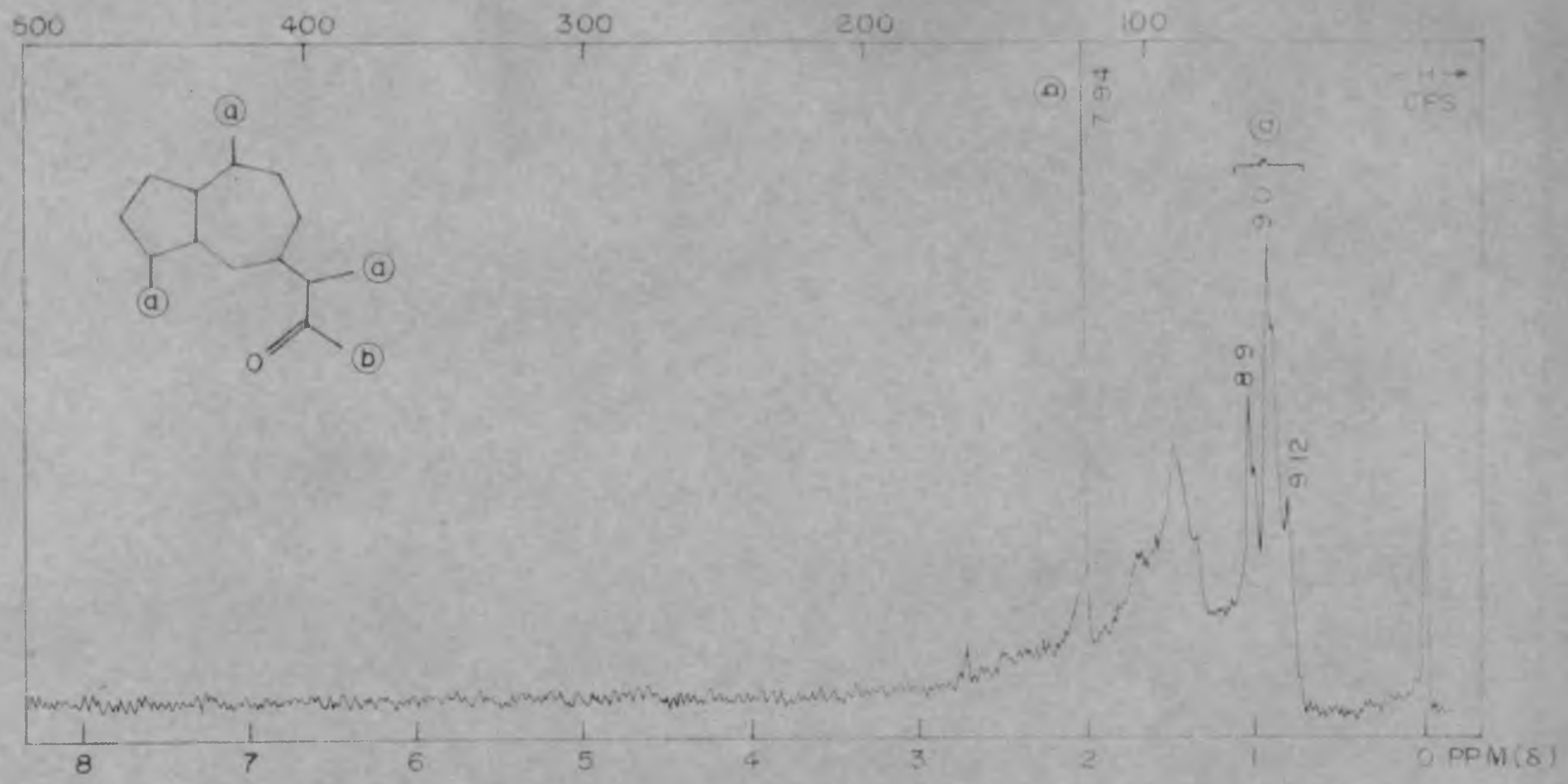


FIG 2 NMR SPECTRUM OF C_{16} - KETONE

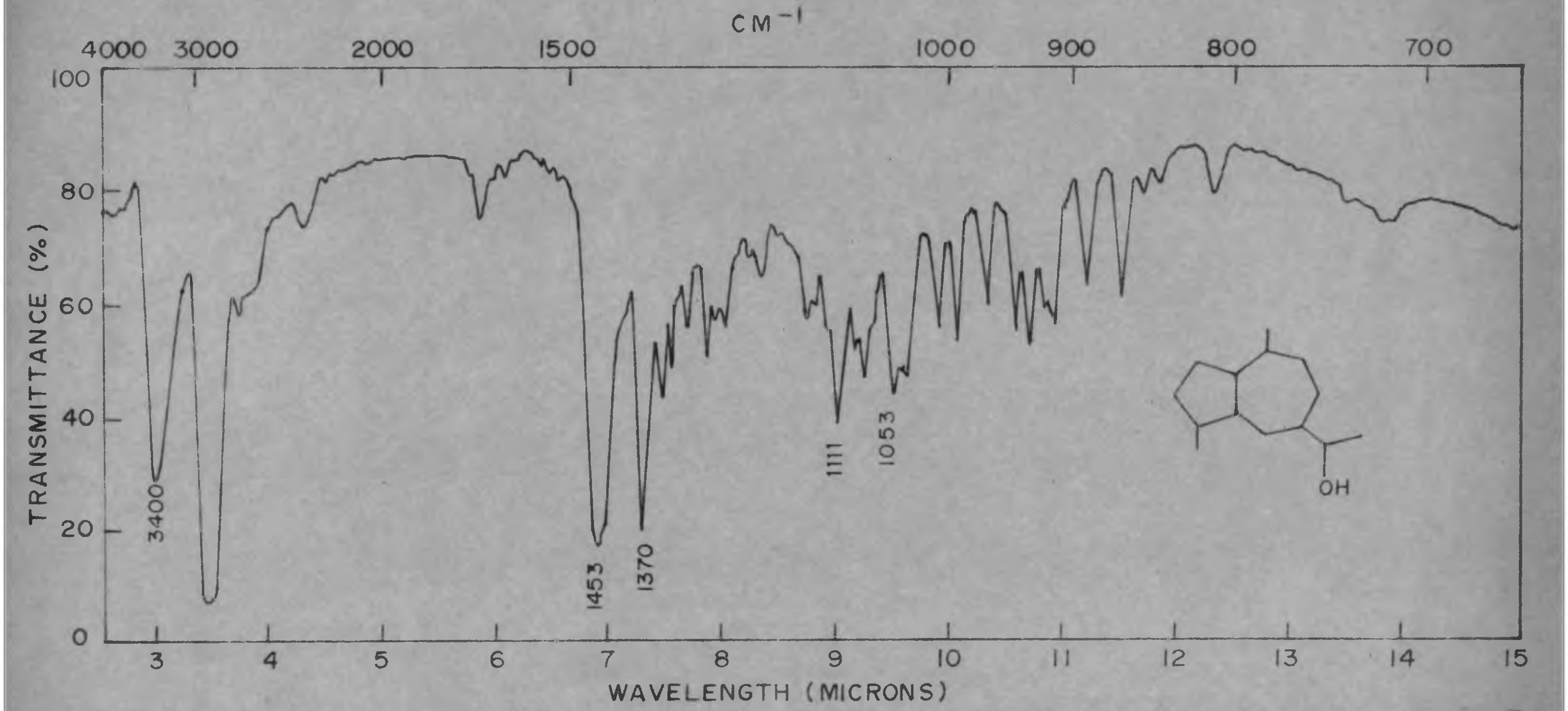


FIG. 3-IR SPECTRUM OF C_{14}- ALCOHOL (LIQ. FILM)

on treatment with methyl-Li, furnished the C_{16}-methyl ketone (XLI) along with some tertiary alcohol (XLII). The two compounds were separated by chromatography over alumina. The ketone (XLI) was characterised through its semicarbazone, m.p. 190-191°. IR spectrum (Fig. 1) of the ketone indicated carbonyl absorption at 1704 cm^{-1}. The NMR spectrum (Fig. 2) showed signals at 8.9, 9, 9.12 τ (9 H) due to methyl groups at C_4, C_{10} and C_{11} and a signal at 7.94 τ (3 H) due to the methyl ketone group at C_{11}.

Baeyer-Villiger oxidation of the ketone (XLI) with perbenzoic acid gave the acetate (XLIII) which on saponification furnished the crystalline secondary alcohol (XLIV) (IR spectrum, Fig. 3). This alcohol (XLIV) on oxidation by Jones' chromic acid reagent gave the C_{14}-methyl ketone (XLV) (IR spectrum, Fig. 4) (semicarbazone, m.p. 124-125°). The ketone (XLV) on treatment with methyl magnesium iodide furnished the tertiary alcohol (liquid) (XXX) in good yields. The IR spectrum (Fig. 5) of the tertiary alcohol (XXX) was identical with the IR spectra[15] (Fig. 5) of solid and liquid dihydroguaiols (III and IV). However, the optical rotation value of the synthetic

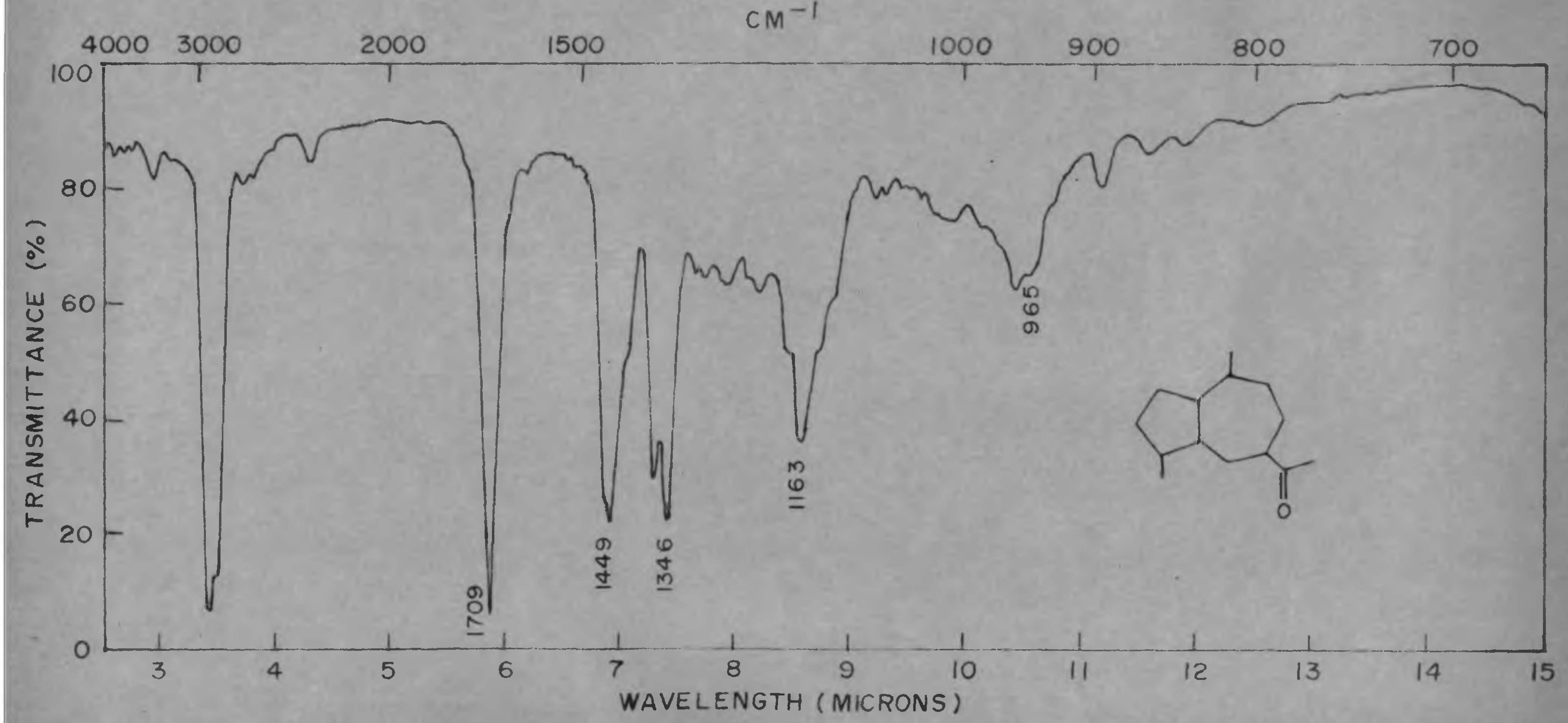


FIG. 4 - IR SPECTRUM OF C_{14}- METHYL KETONE (LIQ. FILM)

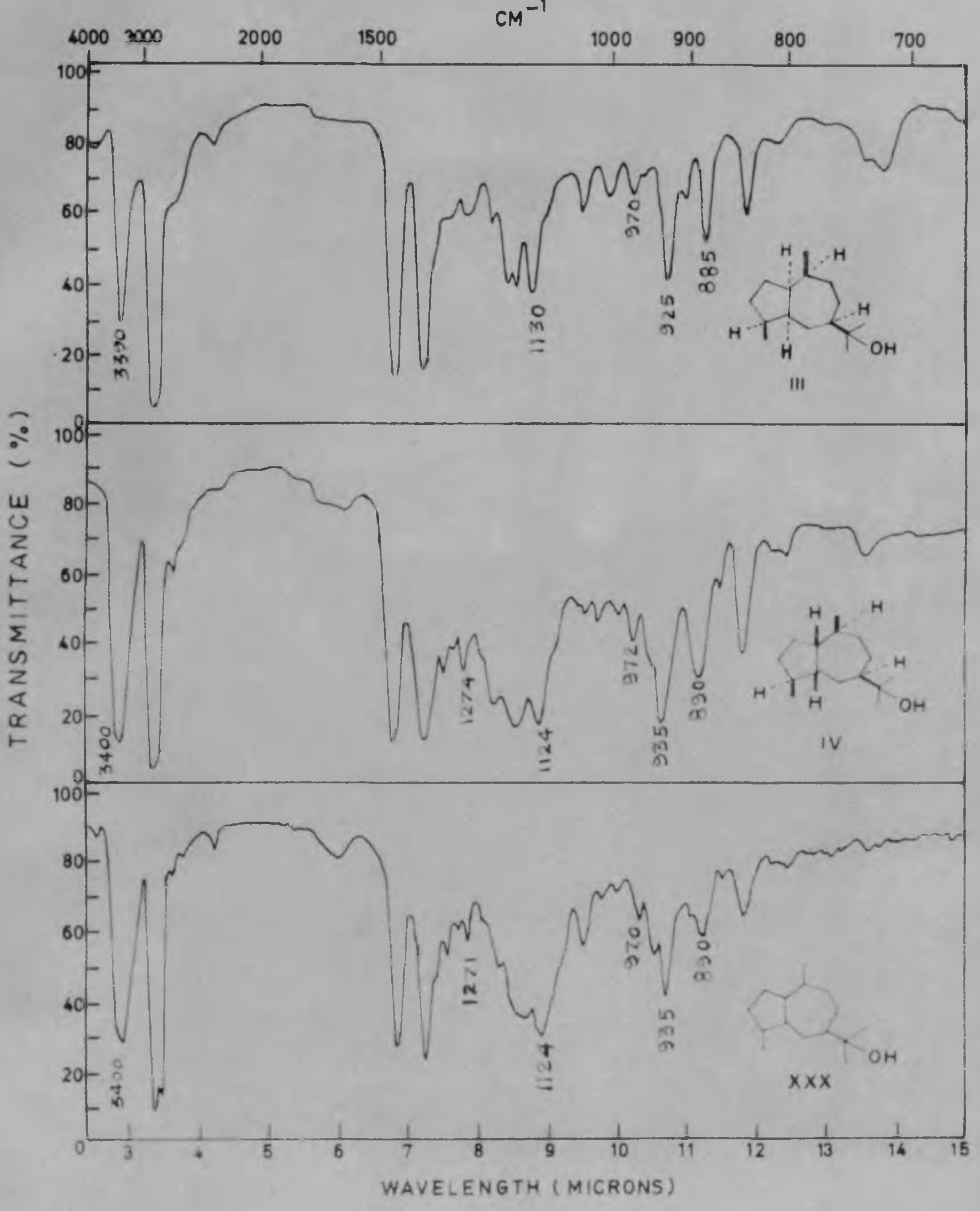
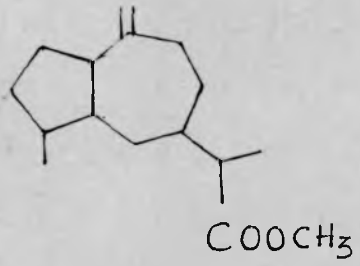


FIG. 5. IR SPECTRA OF DIHYDROGUAIOLS

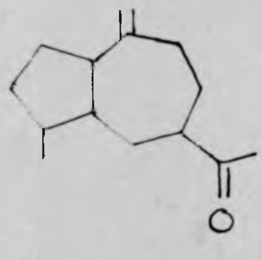
product was different from those reported for (III) and (IV). Hence, it is sterechemically different from the two dihydroguaiols. This was also supported by GLC analysis in which it differed from the two dihydroguaiols in its retention time.

Conversion of the ester $XXIX_a$ into the alcohol XXXI (Chart 6)

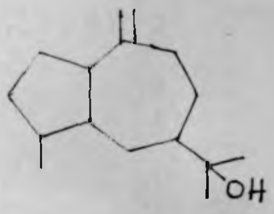
An important part of the synthesis is the conversion of the ester ($XXIX_a$), without affecting its double bond, into the C_{14}-methyl ketone (LVI), which would give the desired product (XXXI) on treatment with methyl magnesium iodide.



XXIXa

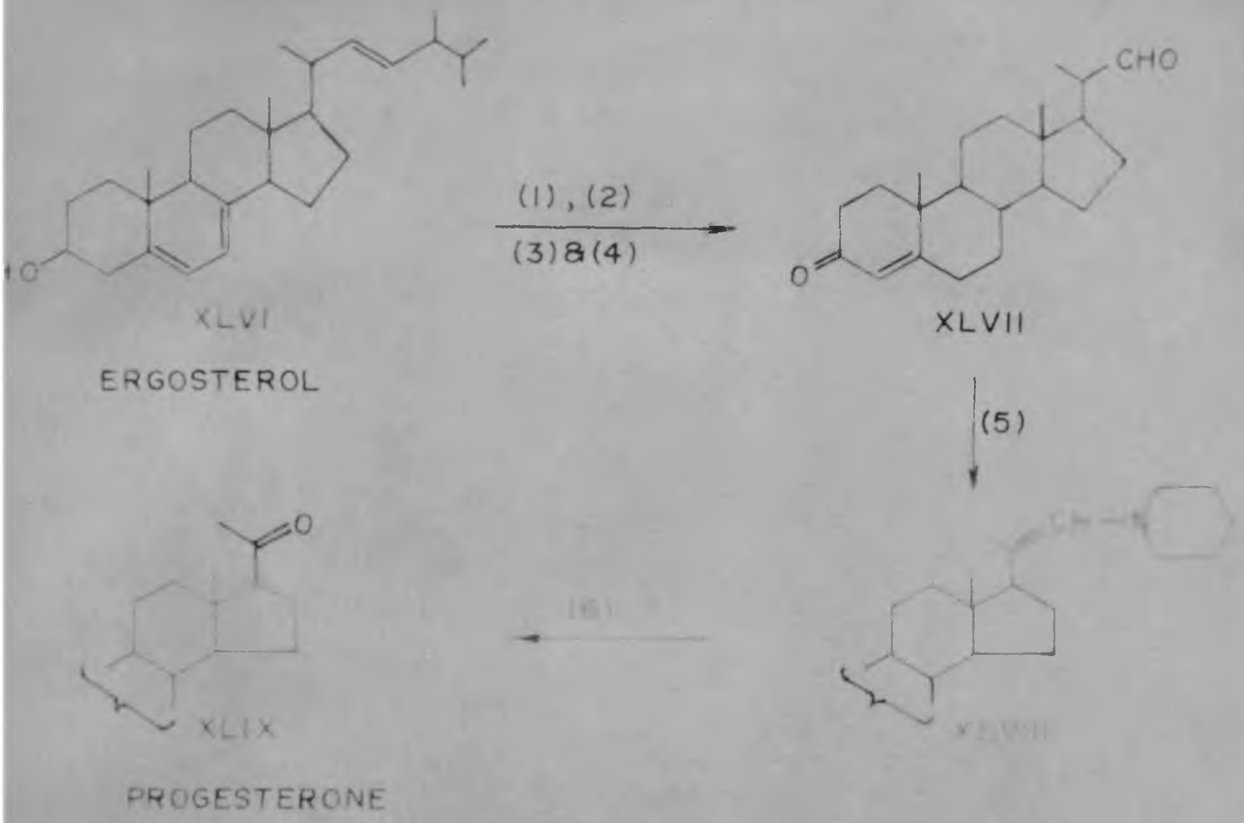


LVI



XXXI

The procedure (Chart 4) employed for the preparation of the saturated ketone (XLV), an intermediate in the synthesis of XXX from $XXIX_a$ could not be used here, since it involves



(1) OPPENAUER OXIDATION, (2) HCl IN CH_3OH & HEAT, (3) HYDROGENATION
(4) Ozonisation
(5) PIPERDINE, (6) $Na_2Cr_2O_7$ – BENZENE – AcOH

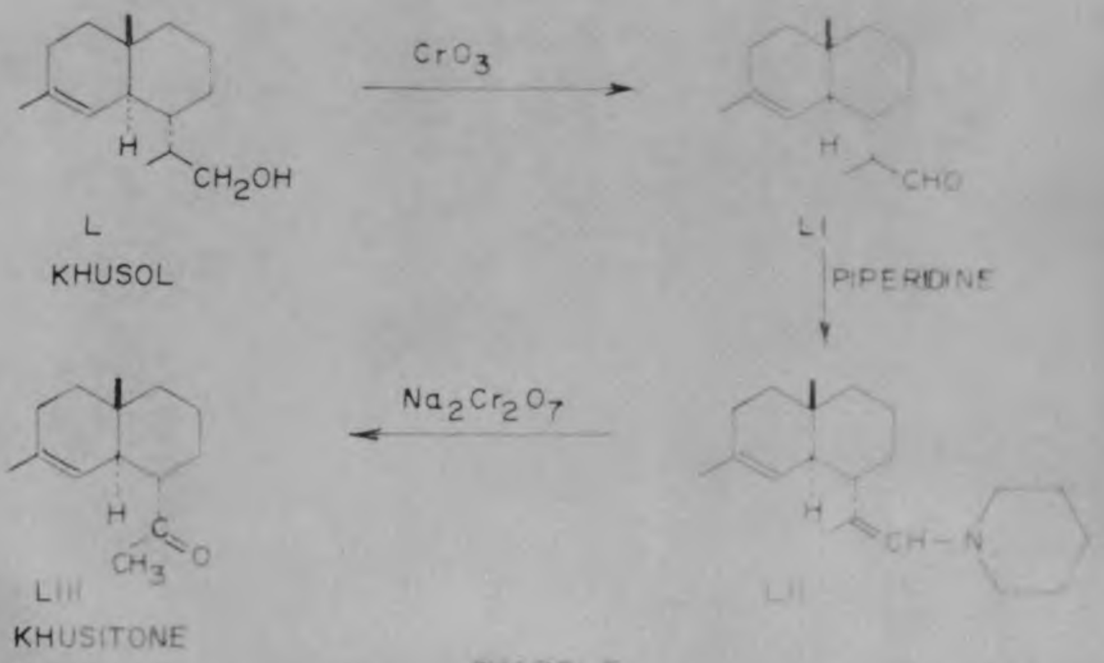
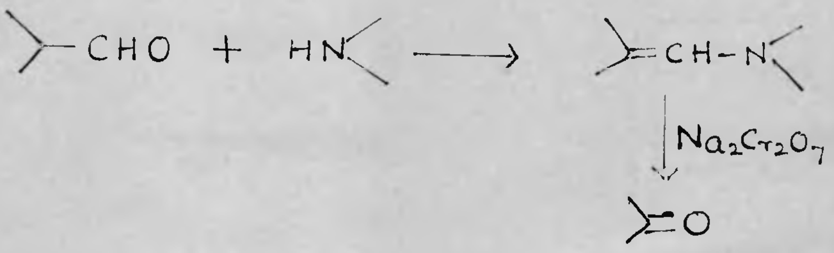


CHART-5

SYNTHESES OF PROGESTERONE AND KHUSITONE

Baeyer-Villiger oxidation by PBA, which would affect the double bond as well. An alternate procedure was, therefore, essential.

The procedure involving the formation of an enamine followed by its oxidation by sodiumdichromate has been conveniently employed in the synthesis of many nor-ketones. For example,



in the synthesis[11] of progesterone (XLIX) (Chart 5) from ergosterol (XLVI), 3-keto-bis-nor-4-cholenaldehyde (XLVII) obtained (as shown in Chart 5), was converted into its piperidine enamine (XLVIII) by modified Herr and Heyl procedure[12]. The crude enamine on oxidation with sodiumdichromate-benzene-acetic acid system furnished progesterone (XLIX).

Proceeding along similar lines, pregnane-3, 20 dione was also synthesised[13] from stigmasterol and ergosterol. In our laboratory the procedure has been used in the synthesis of khusitone (LIII) from khusol (L)^{14} (Chart 5).

Following the same procedure (see Chart 6), we have been able to convert the alcohol (XXIX$_b$) prepared from XXIX$_a$ into the C_{14}-methyl ketone (LVI) as described below.

The alcohol (XXIX$_b$) was oxidised at 0° with Jones' chromic acid reagent to furnish the aldehyde LIV (IR spectrum, Fig. 6) in about 40% yield. The aldehyde was converted into its piperidine enamine (LIII), by modified Herr and Heyl procedure. The crude enamine on oxidation at 0° with sodium dichromate-benzene-acetic acid system afforded the desired C_{14}-methyl ketone (LVI), in about 30% yield. The ketone was separated from the reaction mixture by repeated chromatography over alumina. It was obtained in pure condition (GLC/TLC) by regenerating it from its semicarbazone (m.p. 194-195°) and by distillation under reduced pressure.

The IR spectrum (Fig. 7) of the ketone (LVI) showed bands at 1709 ($>$CO), 1639 and 890 cm^{-1} ($>C=CH_2$). Its NMR spectrum (Fig. 8) showed signals at 8.95 τ (3 H) due to the methyl group at C_4 and at 7.95 τ (3 H) due to the methyl-ketone group

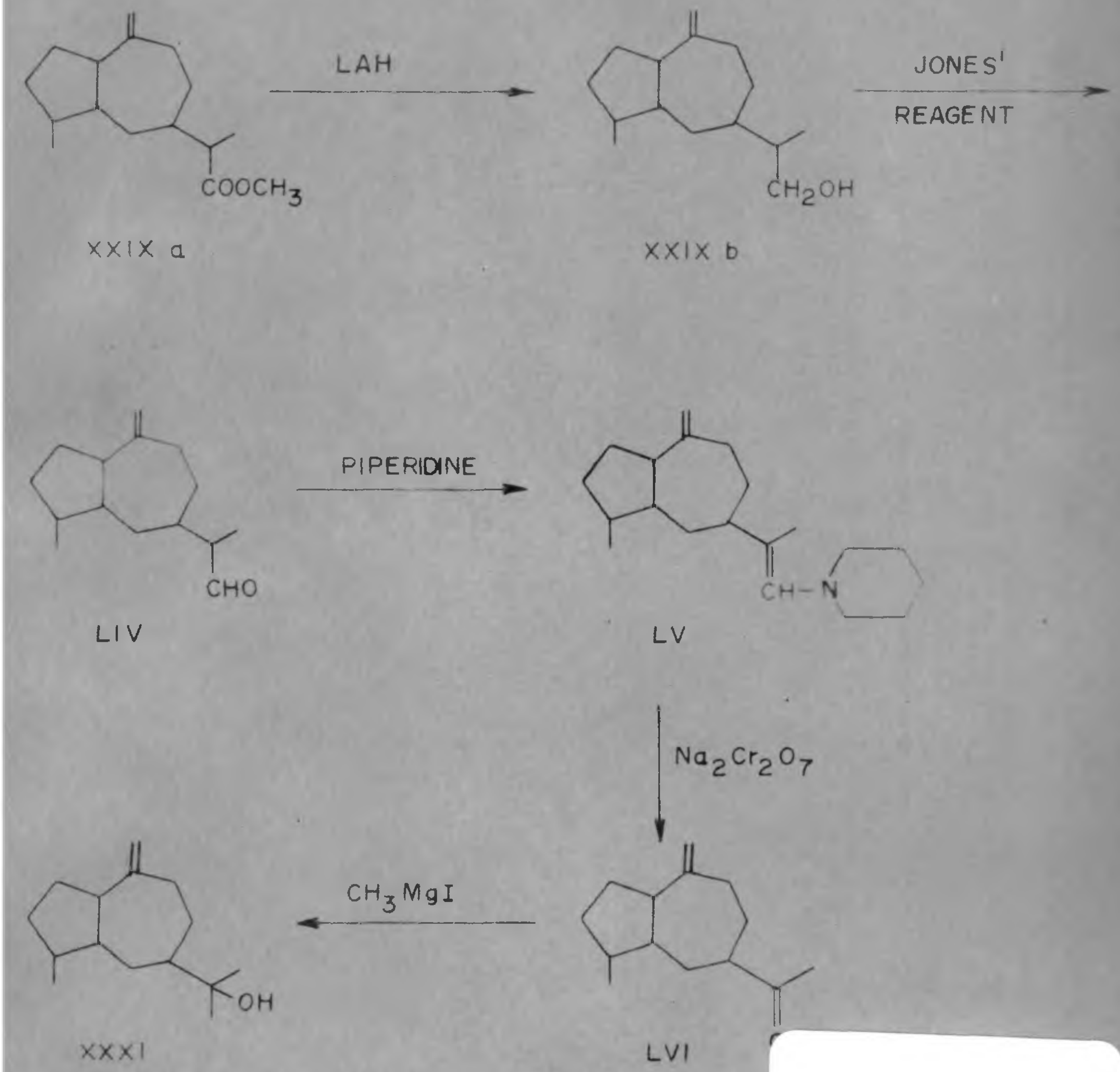

COOCH3
XXIX a
LAH
CH2OH
XXIX b
JONES'
REAGENT
CHO
LIV
PIPERIDINE
CH–N
LV
Na2Cr2O7
CH3MgI
OH
XXXI
LVI

CHART-6

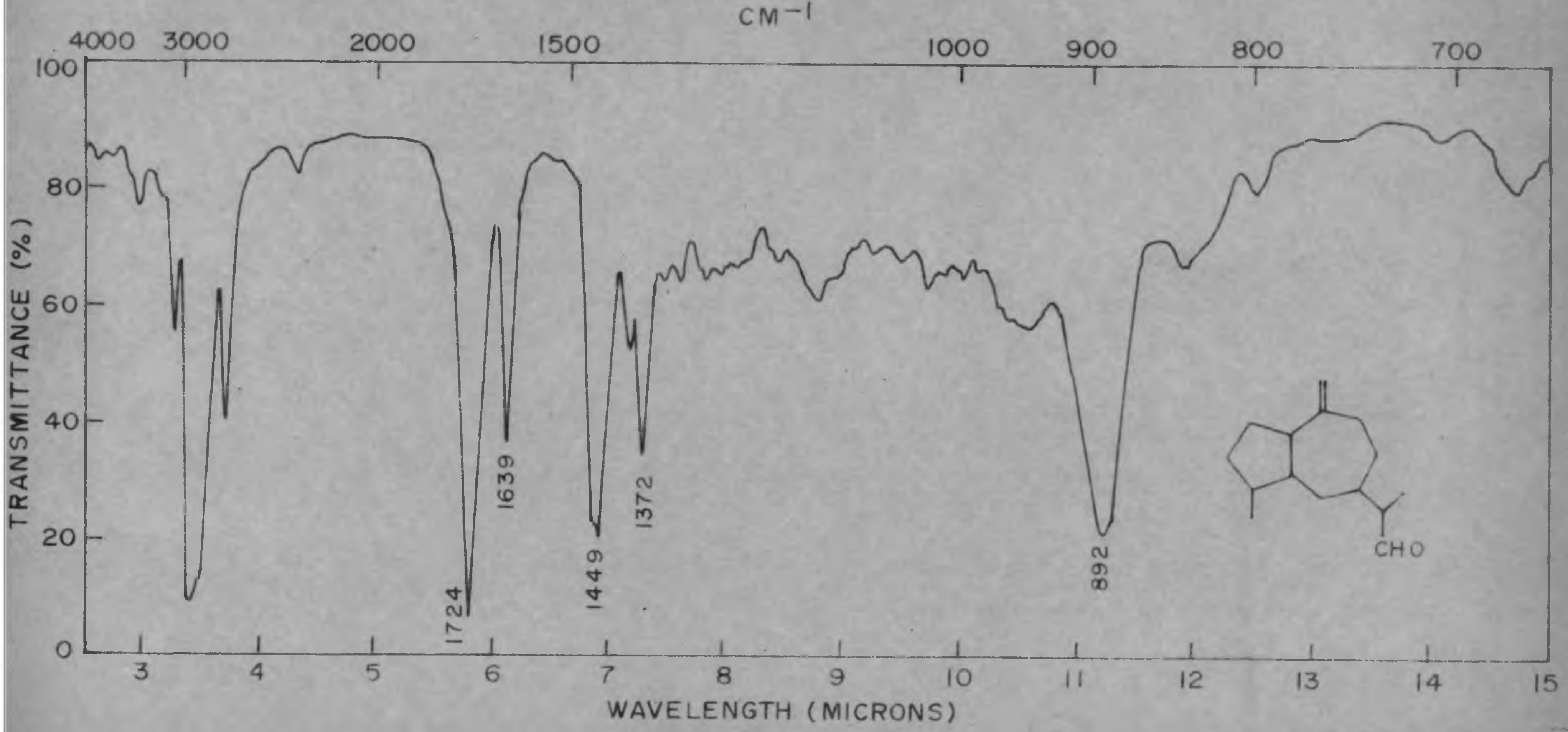


FIG. 6 - IR SPECTRUM OF AIDEHYDE (LIQ.FILM)

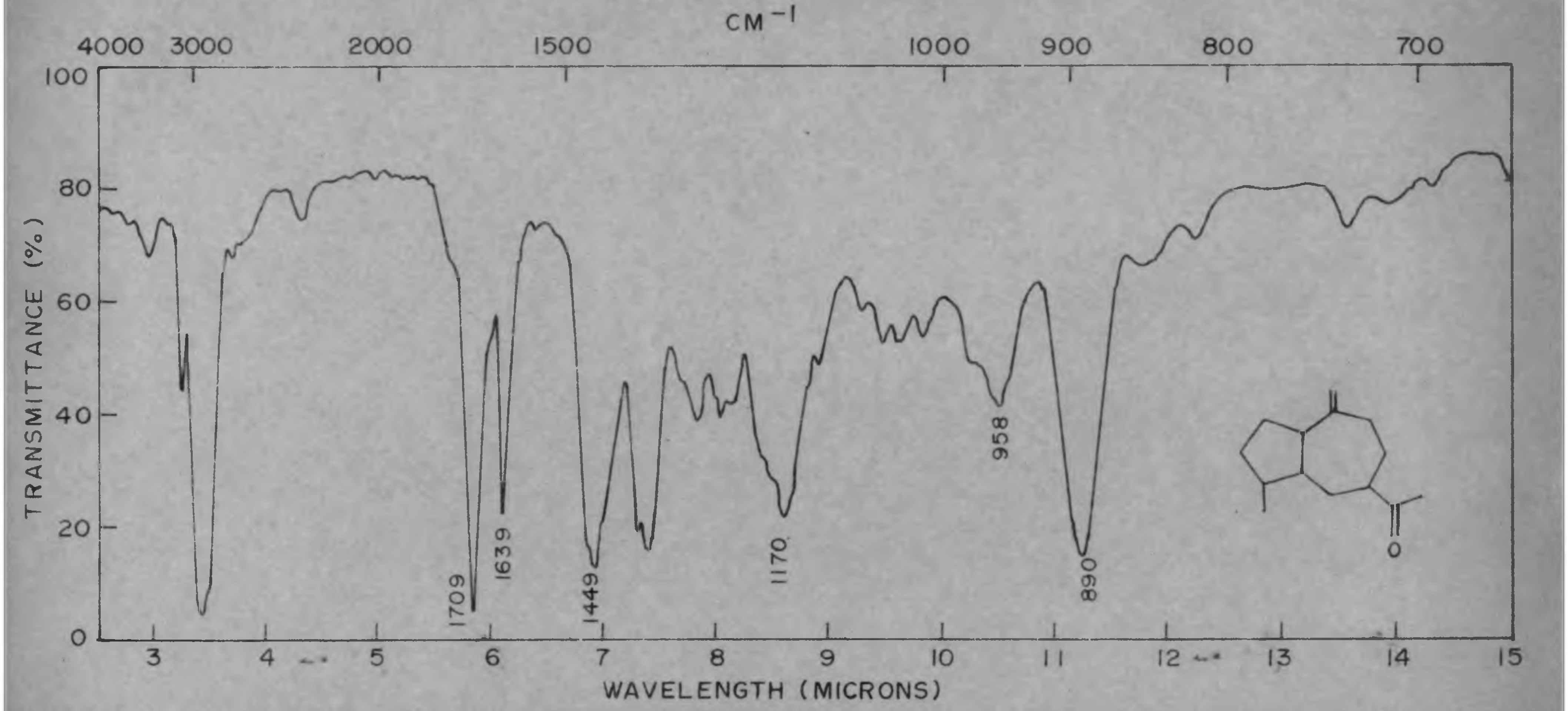


FIG. 7 - IR SPECTRUM OF C_{14}- KETONE (LIQ. FILM)

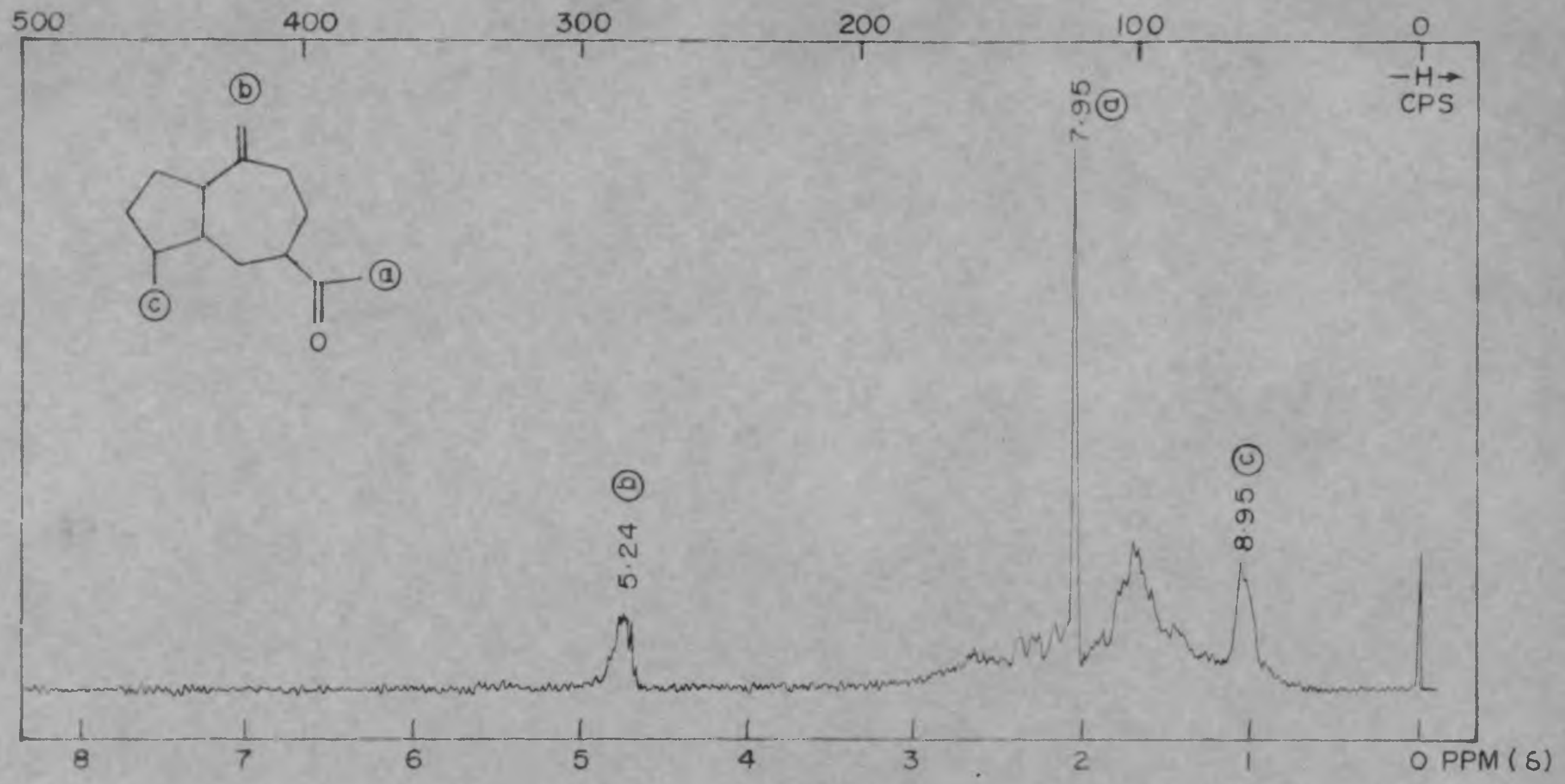


FIG 8. NMR SPECTRUM OF C_{14} - KETONE

at C_7. It also showed signals around 5.24 τ (2 H) due to the olefinic protons of the exocyclic double bond at C_{10}.

The ketone (LVI), on treatment with methyl magnesium iodide in dry ether, afforded the tertiary alcohol XXXI (liquid). It was obtained in pure condition (GLC/TLC) by chromatography. Its IR spectrum (Fig. 9) indicated bands at 3400 (- OH), 1639 and 890 cm^{-1} ($>C = CH_2$).

The NMR spectrum of the alcohol (XXXI) showed signals at 9.06, 9 τ (3 H) due to the methyl at C_4, 8.9 τ (6 H) due to the methyl groups at C_{11} and at 5.35 τ (2 H) due to the olefinic protons of the exocyclic double bond at C_{10}.

Conversion of the ester ($XXIX_a$) to the alcohol (XXXII) (Chart 7)

An important step in this conversion is the transformation of the ester $XXIX_a$, with an exocyclic double bond, into its corresponding isomer LXI with a tetrasubstituted double bond. The latter can be converted to the tertiary alcohol XXXII by employing the same sequence of reactions (Chart 6) which have been used for the synthesis of XXXI.

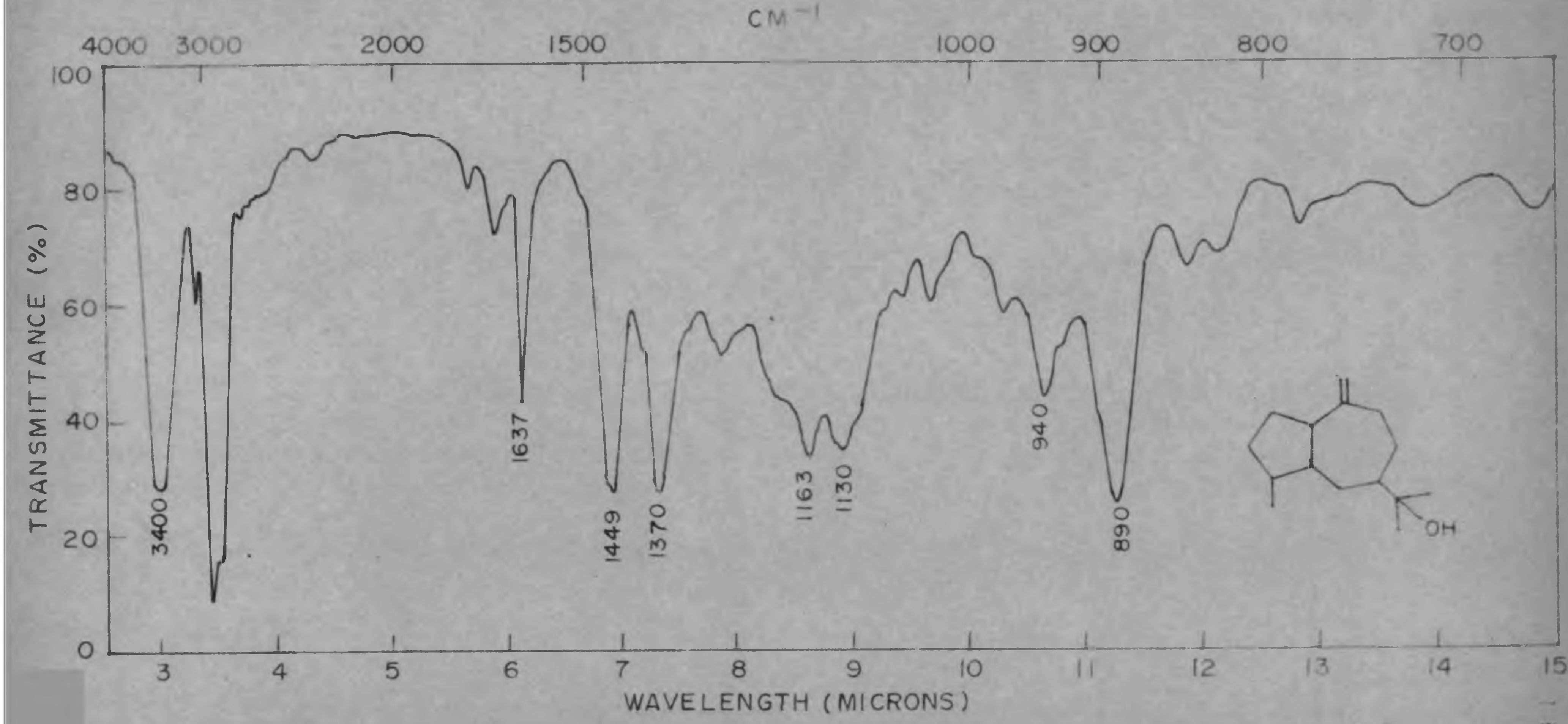
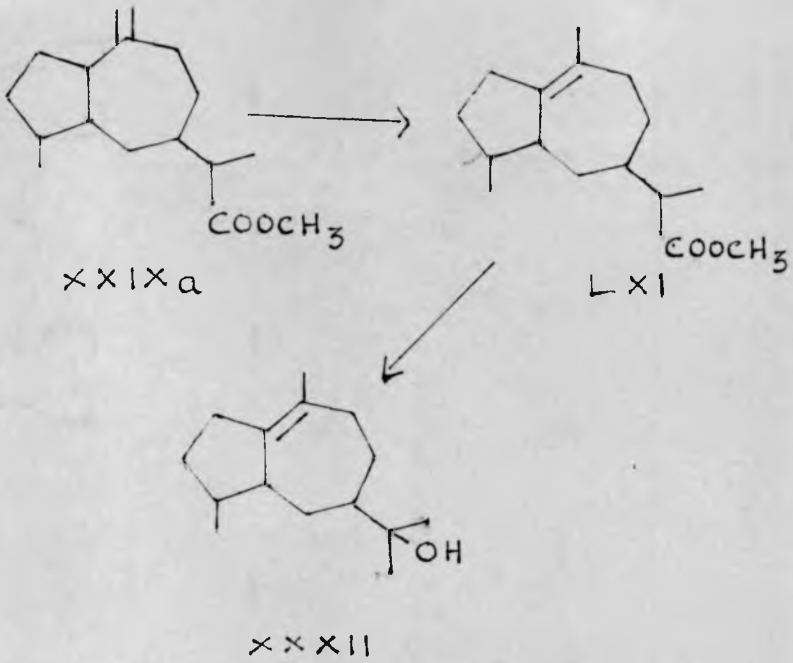
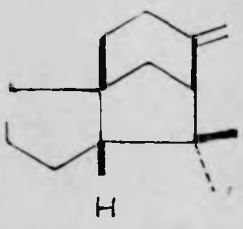


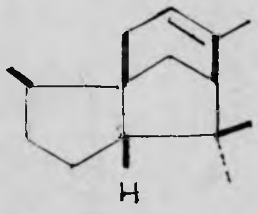
FIG. 9- IR SPECTRUM OF TERTIARY ALCOHOL (LIQ FILM)



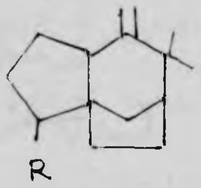
The isomerisation of an exocyclic double bond to either trisubstituted or tetrasubstituted double bond, by the action of formic acid, has been observed in many cases viz. β-cedrene LVII with an exocyclic double bond was found to afford[16] its corresponding α-isomer (LVIII) with a trisubstituted double bond on treating with formic acid. Similarly, khusimol (LIX_a) and its derivatives LIX_b and c were converted[17] to their corresponding isomers ($LX_{a,b}$ and c) by the action of formic acid.



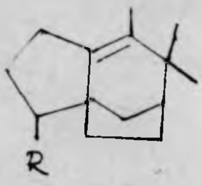
LVII



LVIII



LIX a, R = CH_2OH
b, R = H
c, R = $COOCH_3$



LX a, R = CH_2OH
b, R = H
c, R = $COOCH_3$

When the ester $XXIX_a$ (Chart 7) was treated with formic acid (98-100%) for 12 hours at room temperature it rearranged to the corresponding isomer LXI, in about 80% yield. It could be obtained in about 95% purity (GLC) by chromatography and distillation. The IR

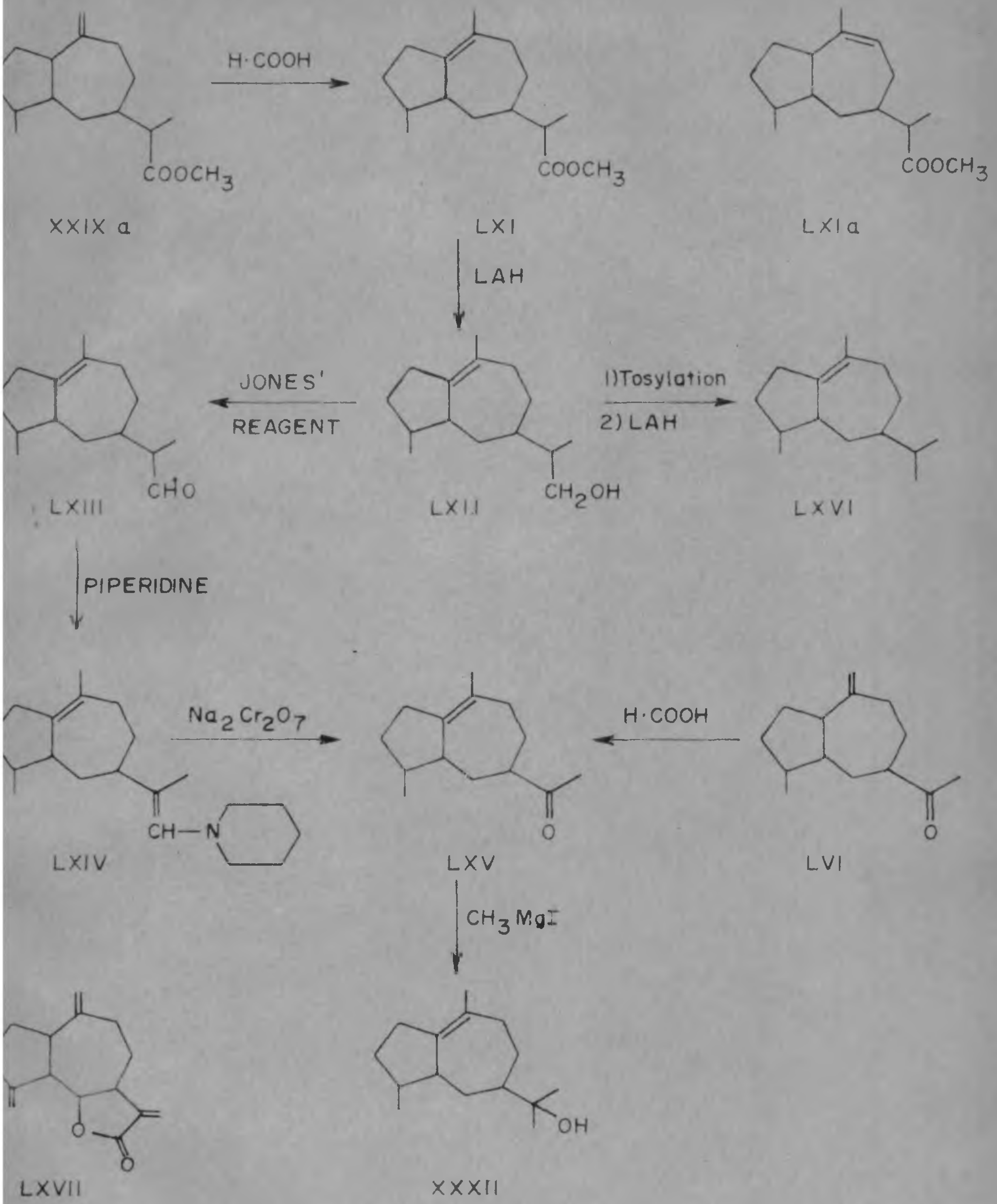

H·COOH
COOCH$_3$
XXIX a
COOCH$_3$
LXI
COOCH$_3$
LXIa
LAH
JONES' REAGENT
CHO
LXIII
CH$_2$OH
LXII
1)Tosylation
2) LAH
LXVI
PIPERIDINE
Na$_2$Cr$_2$O$_7$
CH—N
LXIV
O
LXV
H·COOH
O
LVI
CH$_3$MgI
O
O
LXVII
OH
XXXII

CHART-7

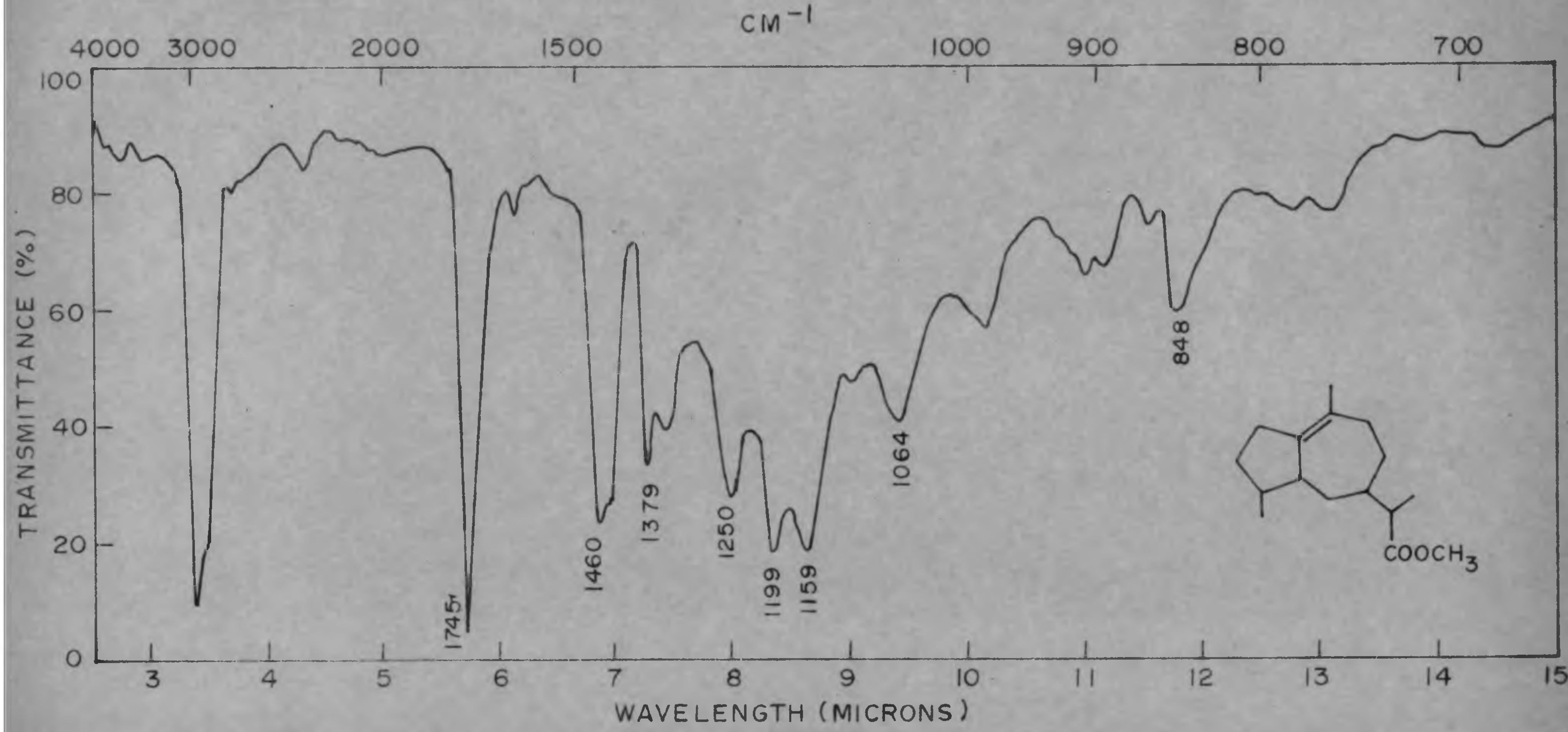
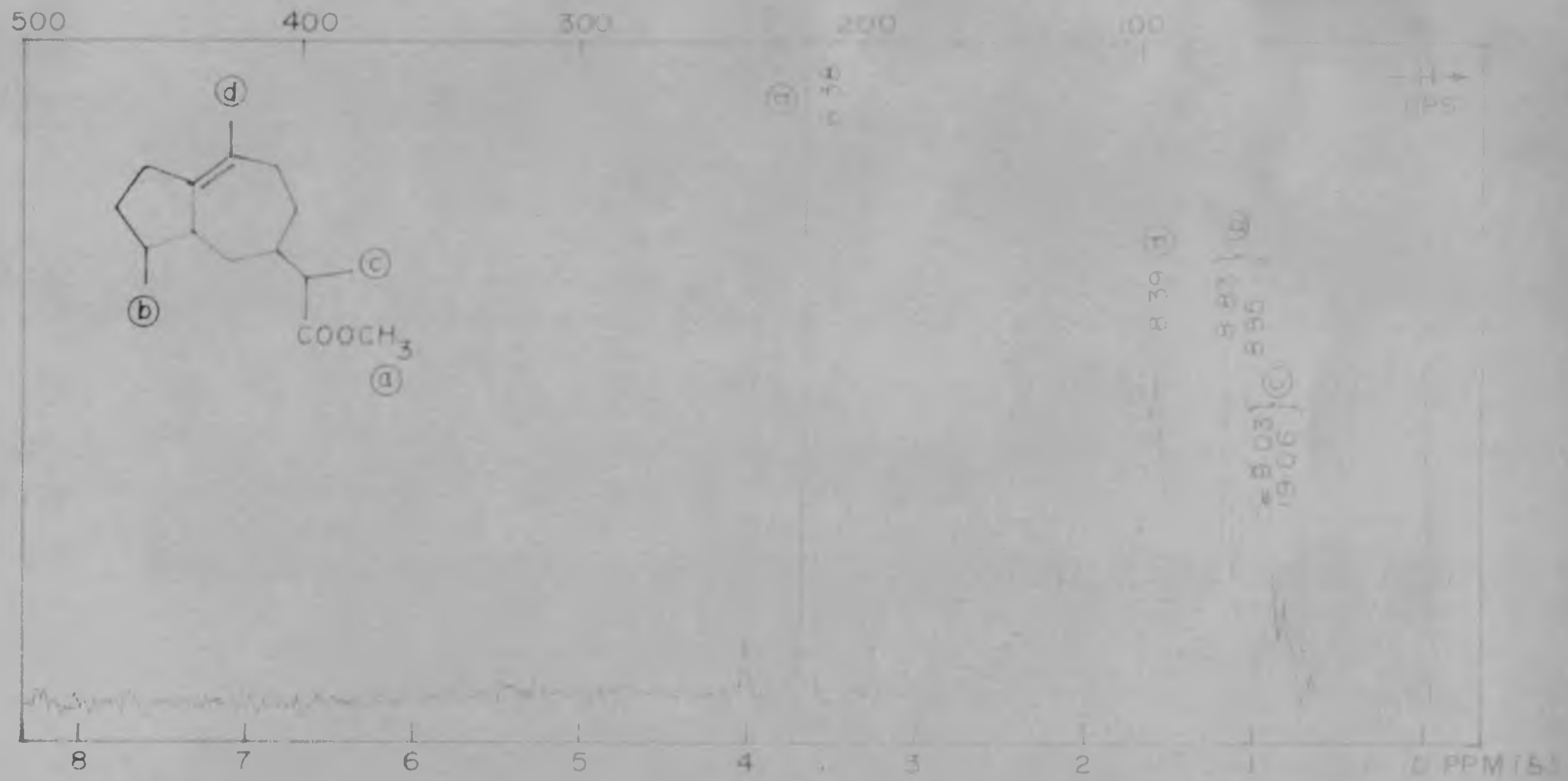


FIG. 10 - IR SPECTRUM OF THE ESTER (LIQ. FILM)



F 11 NMR SPECTRUM OF ESTER

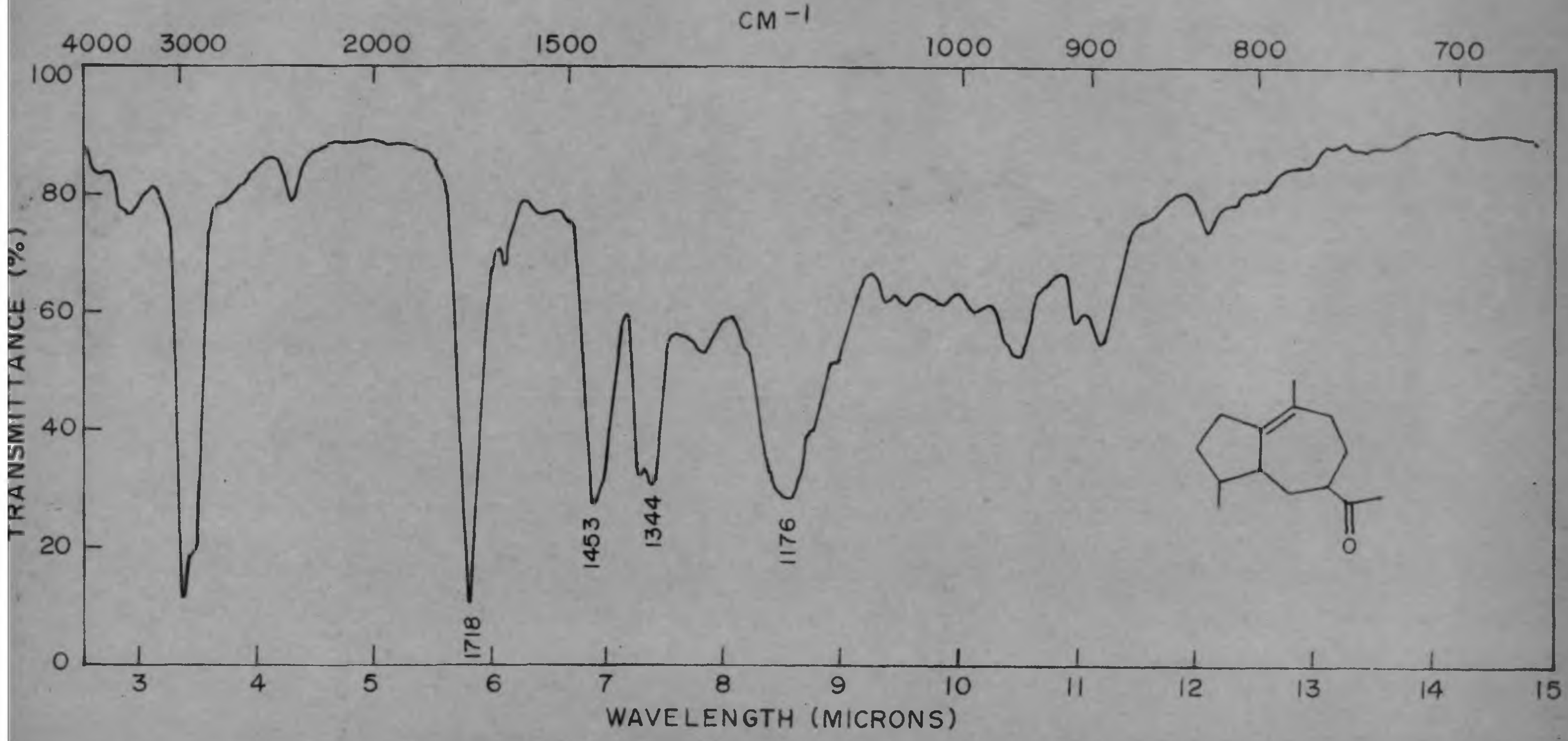


FIG. 12 - IR SPECTRUM OF C_{14}-METHYL KETONE (LIQ. FILM)

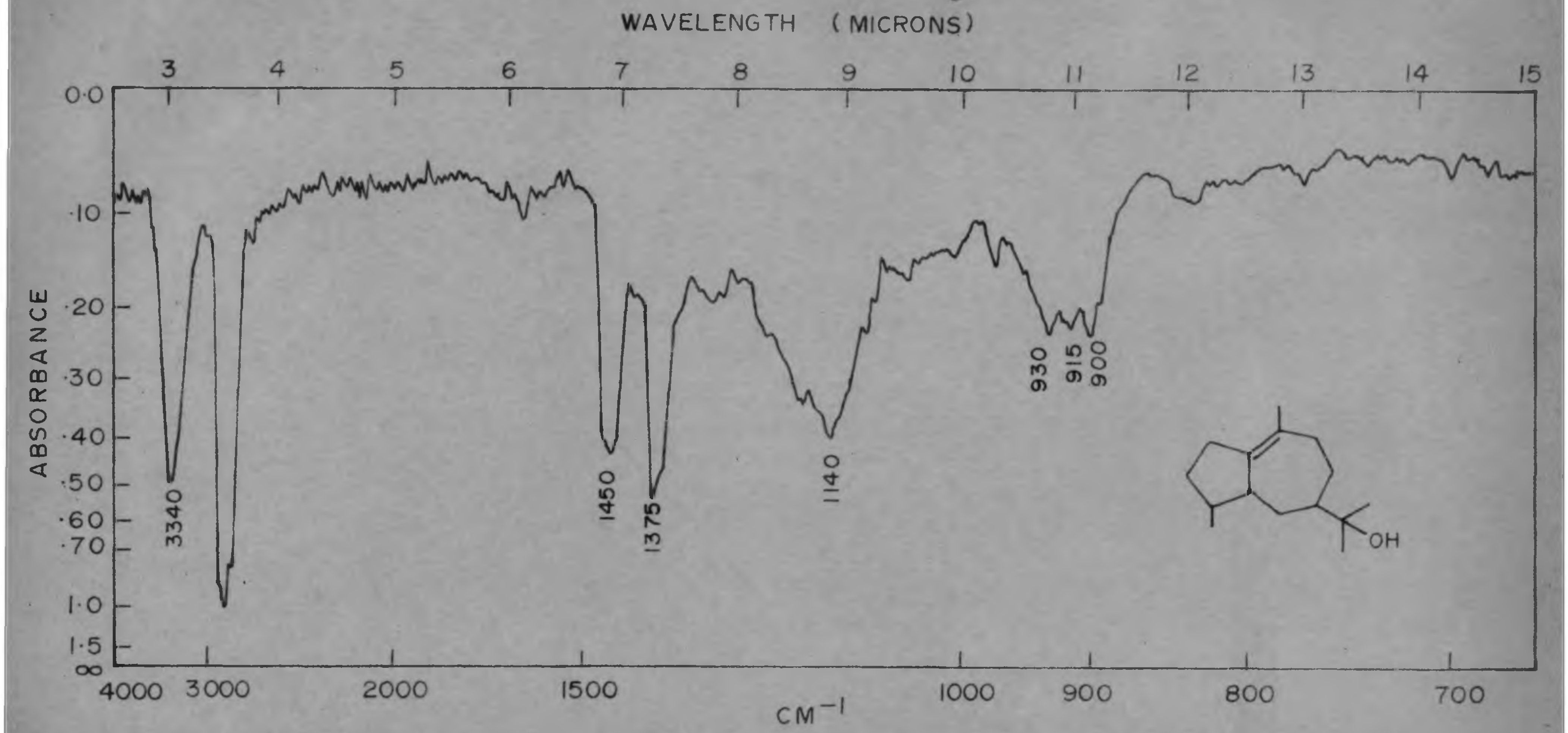


FIG. 13- IR SPECTRUM OF TERTIARY ALCOHOL (LIQ. FILM)

spectrum (Fig. 10) of the ester did not show any absorption due to $>C = CH_2$ group. The NMR spectrum (Fig. 11) of the ester (LXI) indicated the presence of a methyl group on a tetrasubstituted double bond (signal at 8.39 τ, (3 H) and no signals in the olefinic region) thus excluding the possibility of a trisubstituted double bond as in LXI_a. It also showed signals at 9.19, 9.06 9.03 τ (3 H) due to the methyl at C_4, at 8.95, 8.83 τ (3 H) due to the methyl at C_{11} and at 6.38 τ due to the ester methyl group.

The ester (LXI) on LAH reduction gave the corresponding alcohol (LXII) which on controlled oxidation with Jones' chromic acid at 0° furnished the aldehyde (LXIII). The aldehyde was converted into its piperidine enamine (LXIV). The crude enamine on oxidation with sodium-dichromate-benzene-acetic acid system gave the C_{14}-methyl ketone (LXV), which was isolated in pure condition (GLC/TLC) in about 30% yield, by chromatography over alumina and distillation at reduced pressure. The IR spectrum of the ketone is shown in (Fig. 12). The NMR spectrum of the ketone indicated signals, at 9.01, 8.97 τ (3 H) due to the methyl group at

C_4, at 8.36 τ (3 H) due to methyl group on a double bond and at 7.96 τ (3 H) due to the methyl ketone group at C_7.

The ketone (LVI) with an exocyclic double bond on treatment with formic acid for 1 hr. gave a product, the GLC/TLC analysis of which indicated it to be a mixture of at least four products almost in equal proportion. Although the comparative GLC/TLC analysis indicated the presence of the ketone (LXV) in the reaction product, it could not be isolated in pure condition even after elaborate column chromatography. It was also observed that the complexcity of the reaction product increased by increasing the reaction period above one hour.

The ketone (LXV), obtained by the enamine procedure, on treatment with methyl-magnesium iodide afforded a liquid tertiary alcohol (XXXII) (GLC single peak, TLC single spot). Its IR spectrum is shown in (Fig. 13)*. NMR spectrum of the alcohol showed signals at 8.9, 8.94, 9.03,

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*The IR spectrum (Fig. 13) of the synthetic product (XXXII) resembles closely with that of bulnesol (II) reported by Sorm and co-workers[3]. An exact comparison between the two was, however, not possible as the spectra were recorded on different instruments. Our attempt to obtain an authentic sample of bulnesol from Sorm and co-workers was not fruitful.

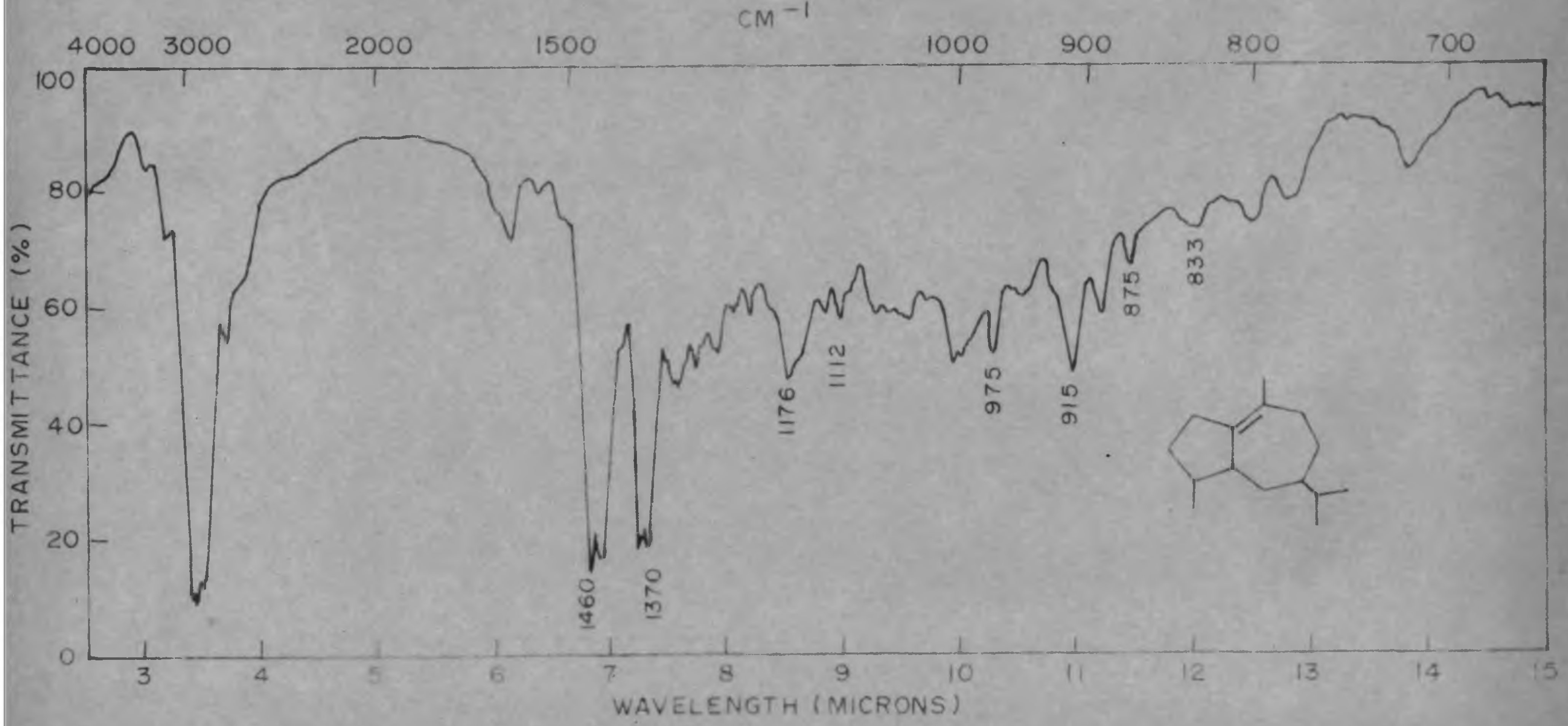


FIG 14 - IR SPECTRUM OF HYDROCARBON (LIQ FILM)

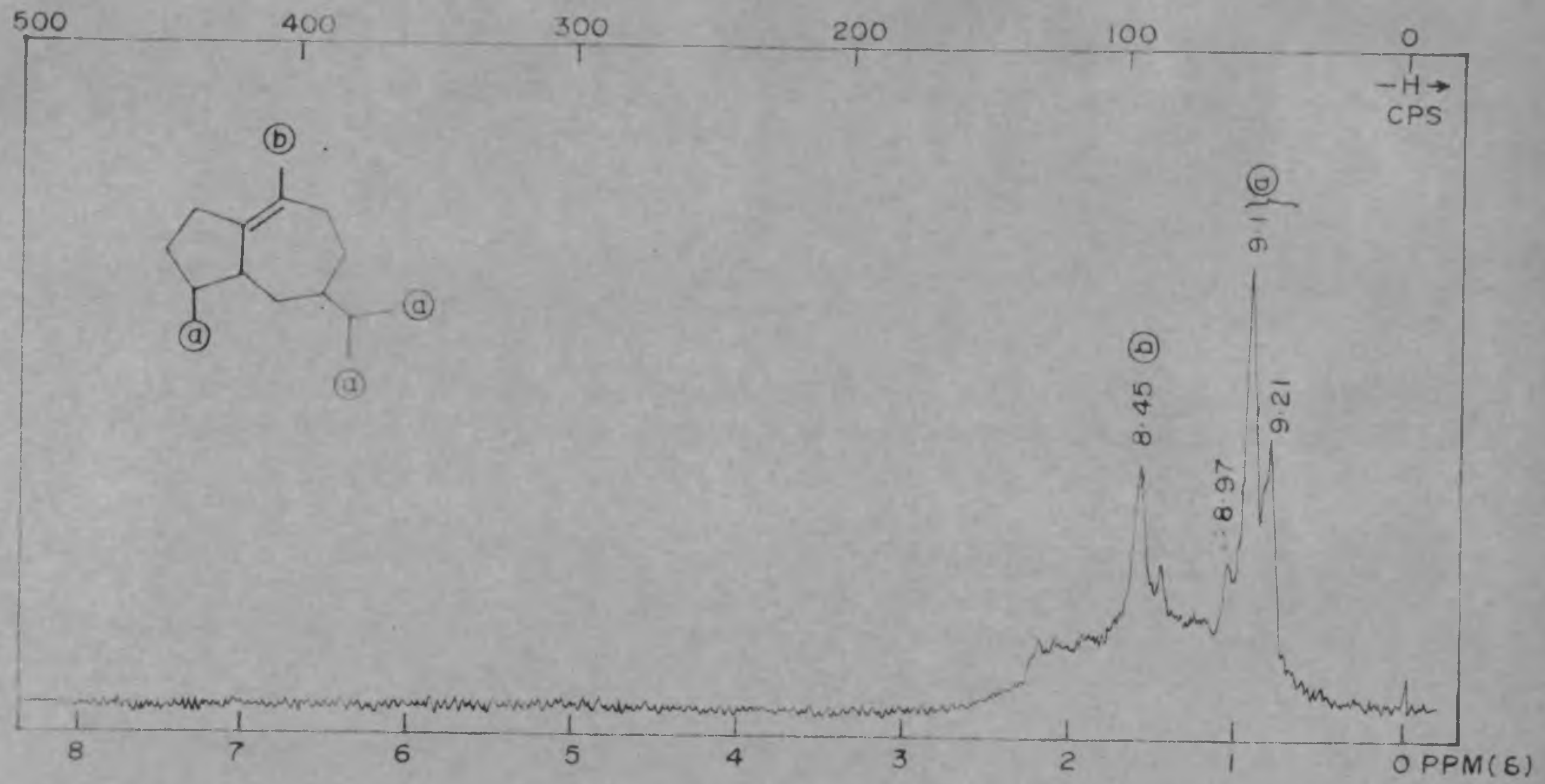


FIG. 15. NMR SPECTRUM OF HYDROCARBON

9.07 τ (9 H) due to methyl groups at C_4 and C_7 and at 8.4 τ (3 H) due to the methyl group on a double bond.

The alcohol showed a rotation of - 11.4° (c, 4.4) while that reported for bulnesol is + 3°. So it appears, that the synthetic product is a stereoisomer of bulnesol (II).

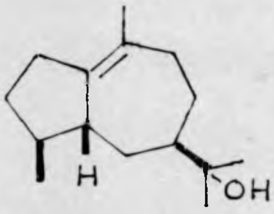
The primary alcohol (LXII), on intermediate product in the above synthesis, was converted to the corresponding hydrocarbon LXVI by LAH reduction of its tosylate. The IR and the NMR spectra (Fig. 14 and Fig. 15 respectively) of this hydrocarbon closely resembled with the IR and NMR spectra of a similar hydrocarbon ($LXVI_a$) obtained[18] from dehydro-costus lactone (LXVII). However, the two hydrocarbons differed in their optical rotation.

<u>Stereochemistry</u>

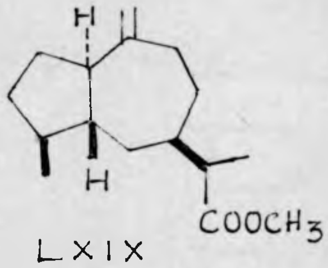
No definite conclusions could be drawn about the stereochemistry of the synthetic products (XXX and XXXII) since they were found to be stereochemically different from dihydroguaiols (III and IV) and bulnesol (II) respectively.

However, some tentative inferences can be drawn.

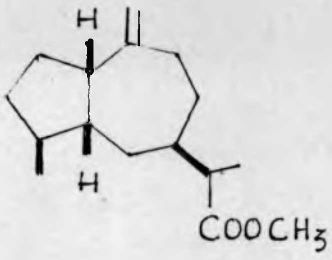
It has been already stated that the C_4-methyl and C_7-isopropyl groups in $XXIX_a$ may be assumed to be β-oriented. The same stereochemistry would be retained in XXX, XXXI and XXXII at these centres. Since the methyl at C_4 and the isopropyl at C_7 in bulnesol are also β-oriented, the optical rotational difference between this compound and the synthetic product XXXII could be only attributed to their stereochemiel difference at C_5. Hence the probable stereostructure for XXXII would be (LXVIII) and that for $XXIX_a$ would be LXIX or LXX.



LXVIII



LXIX



LXX

EXPERIMENTAL

The ester XXIXa was prepared from costunolide (XXVII) as described in Part I of the thesis. It showed the following properties:

b.p. 120-130°(bath)/0.2 mm

n_D^{29} 1.4860; $(\alpha)_D$ + 47° (c, 3.7)

Hydrogenation of the ester XXIXa

The ester (3 g) was hydrogenated with Adams catalyst (0.150 g) in absolute ethanol (100 ml) when the absorption of hydrogen was complete, the product was filtered to remove the catalyst, alcohol was removed under suction and the product was distilled to obtain pure (GLC/TLC) dihydroproduct (XXXIX) with the following properties, b.p. 120-130°(bath)/0.2 mm; n_D^{25} 1.4792; $(\alpha)_D$ + 38.7° (c, 3.5).

IR spectrum showed bands at: 2915, 1730, 1447, 1370, 1344, 1252, 1190, 1156, 1075, 1053, 987, 943, 848 and 768 cm^{-1}.

Analysis

Found: C, 76.32; H, 11.74%

$C_{16}H_{28}O_2$ requires: C, 76.14; H, 11.88%

Conversion of the ester (XXXIX) into the C_{16}-methyl ketone (XLI)

The ester (2 g) was saponified by refluxing with methanolic -KOH (10%, 25 ml) for 3 hr. The product was diluted with water and extracted with ether. The aqueous portion was acidified with dil. HCl (5%), extracted with ether, washed with water and dried (Na_2SO_4). The acid (XL), 1.5 g, obtained by evaporation of ether was taken in dry ether (20 ml) and was added at 0°, to a solution of MeLi (prepared from 1 g of Li and 10 g MeI) in dry ether during 5 min. The reaction mixture was stirred at 0° for 5 min. after the addition and excess of the reagent was carefully destroyed by addition of moist ether followed by water. The organic layer was separated, washed with Na_2CO_3 solution (5%), dil. HCl (5%), water and dried (Na_2SO_4). Evaporation of ether gave a liquid product (1.3 g) which was chromatographed on alumina (Gr. III, 35 g) and eluted with pet. ether to furnish the ketone (XLI) (0.92 g). It showed the following properties:

b.p. 130-135°(bath)/0.1 mm; n_D^{22} 1.4810; $(\alpha)_D$ + 52.44° (c, 2.2).

<u>The IR spectrum</u> (Fig. 1) showed bands at: 2907, 1704, 1370, 1342, 1316, 1290, 1229, 1198, 1156, 1099, 952, 892 cm^{-1}.

<u>Analysis</u>

Found: C, 81.70; H, 11.98%

$C_{16}H_{28}O$ requires: C, 81.29; H, 11.94%.

The ketone (XLI) gave a semicarbazone (Na acetate method) m.p. 190-191°.

<u>Analysis</u>

Found: N, 13.88%

$C_{17}H_{35}ON_3$ requires: N, 14.32%

Baeyer-Villiger oxidation of the ketone (XLI) and saponification of the resulting acetate (XLIII)

The ketone (0.85 g) was dissolved in chloroform (20 ml) and 1.2 N perbenzoic acid (10 ml) and toluene-p-sulphonic acid (0.15 g) were added. The mixture was stirred mechanically at room temperature for 48 hr. The chloroform solution was then washed with Na_2CO_3 solution (5%), water and dried (Na_2SO_4). The acetate (XLIII), 0.790 g, obtained on evaporation of chloroform was saponified by refluxing with 1 N methanolic KOH solution (25 ml) for 3 hr. The reaction product was worked up as usual and the neutral material (0.75 g) obtained was chromatographed on alumina (Gr. III, 25 g) and eluted with pet. ether and benzene. Benzene fraction on evaporation afforded a solid (0.51 g), which on crystallisation from pet. ether furnished the crystalline alcohol (XLIV) (TLC, single spot), m.p. 82-83°, $(\alpha)_D$ + 30.4° (c, 0.23).

<u>IR spectrum</u> (Fig. 3) of the alcohol (XLIV) showed bands at: 3400, 2915, 1453, 1447, 1370, 1339, 1328, 1302, 1274, 1250, 1200, 1144, 1111, 1081, 1053, 1042, 1010, 995, 970, 948, 935, 918, 893, 870, 855, 845, 812 cm^{-1}.

Analysis

Found: C, 79.58; H, 12.43%

$C_{14}H_{26}O$ requires: C, 79.93; H, 12.46%

Chromic acid oxidation of the alcohol XLIV

To the alcohol (0.4 g) in acetone (25 ml), Jones reagent was added dropwise till a brown colour persisted. The reaction mixture was kept at room temperature for 45 min. It was diluted with water and extracted with ether. The ether layer washed with Na_2CO_3 aq. (5%), water and dried (Na_2SO_4). The product (0.38 g) obtained on evaporation of ether was chromatographed on alumina (Gr. II, 10 g) and eluted with pet.ether to give the pure (GLC/TLC) ketone (XLV) which showed the following properties:

b.p. 120-125°(bath)/0.5 mm; n_D^{25} 1.4789; $(\alpha)_D$ - 8.7° (c, 2.85).

The IR spectrum (Fig. 4) of the ketone (XLV) showed bands at: 2964, 1709, 1449, 1370, 1346, 1266, 1220, 1163, 965, 895 cm^{-1}.

Analysis

Found: C, 80.60; H, 11.73%

$C_{14}H_{24}O$ requires: C, 80.71; H, 11.61%

The ketone gave a semicarbazone (Na-acetate method) m.p. 124-125°.

Analysis

Found: N, 15.91%

$C_{15}H_{27}ON_3$ requires: N, 15.7%

Conversion of the ketone (XLV) into the tertiary alcohol (XXX)

The ketone (0.25 g) dissolved in dry ether (20 ml) was added under stirring to an ice-cold solution of MeMgI (prepared from 0.25 g of Mg. wire and 4 g of MeI) in dry ether. The reaction mixture was stirred at 0° for 1 hr. and at room temperature for another 2 hrs. It was then poured into an ice-cold saturated solution of ammonium chloride. The organic layer was separated. The aqueous layer was extracted with ether. The organic layer combined with the ether extract was dried (Na_2SO_4) and the ether evaporated. The product (0.24 g), was chromatographed on alumina (Gr. III, 6 g) and eluted with pet. ether and ether. The pet. ether fraction gave the unreacted ketone (XLV; 0.040 g). The ether fraction furnished the pure (GLC/TLC) tertiary alcohol (XXX) (0.180 g), with the following constants:

b.p. 120-125°(bath)/0.08 mm; n_D^{25} 1.4850

$(\alpha)_D$ + 34.93° (c, 2.4).

<u>IR spectrum</u> (Fig. 5) of the alcohol (XXX) showed bands at: 3400, 2941, 1460, 3474, 1391, 1271, 1205, 1124, 1047, 970, 950, 935, 890, 845 cm^{-1}.

Analysis

Found: C, 80.27; H, 12.63%

$C_{15}H_{28}O$ requires: C, 80.29; H, 12.58%

Chromic acid oxidation of the alcohol (XXXIXb)

To an ice-cold solution of the alcohol (8 g) in acetone (100 ml) Jones[1] chromic acid reagent was added dropwise till a brown colour persisted. The reaction mixture was kept at 0° for 2 hr., diluted with water and extracted with ether. Ether layer was washed with Na_2CO_3 aq., water and dried (Na_2SO_4). The neutral material (6.5 g) obtained on evaporation of ether was chromatographed on alumina (Gr. II, 200 g) and eluted with pet. ether and ether. The pet.ether fraction which consisted of mostly the aldehyde (LIV) was further purified by rechromatography and distillation to obtain the pure (GLC/TLC) aldehyde LIV, (2.4 g) with the following properties:

b.p. 120-130°(bath)/0.2 mm; n_D^{24} 1.5145;
$(\alpha)_D$ + 42.3° (c, 3.07).

<u>IR spectrum</u> (Fig. 6) showed bands at: 3058, 2941, 2703, 1724, 1639, 1449, 1397, 1372, 1143, 945, 892 cm^{-1}.

<u>Analysis</u>

Found: C, 81.58; H, 11.24%

$C_{15}H_{24}O$ requires: C, 81.76; H, 10.98%

<u>The enamine (LV) from the aldehyde (LIV)</u>

To a solution of the aldehyde (2.2 g) in dry benzene (45 ml) was added piperidine (1.02 g) and toluene-p-sulphonic acid (7 mg). The reaction mixture was heated under brisk reflux in nitrogen atmosphere for 10 hr. using a water separator to remove the water formed during the reaction. Benzene was removed under vacuo to afford the crude enamine (LV) (2.7 g), b.p. 160-170°(bath)/0.1 mm.

Sodium dichromate oxidation of the enamine (LV)

The oxidising reagent was prepared by adding gradually powdered sodium dichromate dihydrate (5 g) to glacial acetic acid (25 ml) taken in a 2-necked flask equipped with an efficient stirrer and a dropping funnel. After the addition of dichromate salt was complete, dry benzene (15 ml) was added through dropping funnel and the resulting solution was cooled to 0 - 5° by means of ice-salt mixture. A solution of the enamine (2.5 g) in benzene (25 ml) was then added over a period of 1 hr. keeping the temperature below 5°. The dark reaction mixture was stirred for additional 2 hrs. and was diluted with water and the organic layer was separated. The dark-brown aqueous layer was extracted with benzene. This extract and the original benzene solution were combined and the resulting solution was washed successively with water, cold NaOH soln. (10%), water, dil HCl (10%) and water and dried. Removal of benzene gave a liquid product (1.9 g) which was chromatographed on alumina (Gr. II, 60 g) and eluted with pet. ether to furnish the ketone (LVI) (GLC, about 95%) (0.650 g). It was obtained in pure condition (GLC/TLC) by regenerating it from its semicarbazone, m.p. 194-195°).

The ketone indicated the following properties:

b.p. 120-125°(bath)/0.2 mm; $(\alpha)_D$ - 3.48° (c, 3.16)

IR spectrum (Fig. 7) of the ketone (LVI) showed bands at: 3067, 2941, 1709, 1639, 1449, 1370, 1351, 1279, 1247, 1170, 1081, 1057, 1042, 958 and 890 cm^{-1}.

Analysis

Found: C, 81.47; H, 10.81%

$C_{14}H_{22}O$ requires: C, 81.50; H, 10.75%

Analysis of the semicarbazone

Found: C, 68.25; H, 8.88; N, 15.92%

$C_{15}H_{25}ON_3$ requires: C, 68.4; H, 9.57; N, 15.96%

Conversion of the ketone (LVI) into the tertiary alcohol XXXI

The ketone (0.400 g) was dissolved in dry ether (50 ml) and was added to an ice-cold solution of MeMgI (prepared from 1.20 g of Mg wire and 6 g of MeI) in dry ether. The reaction mixture was stirred at 0° for 1 hr and at room temperature for 6 hr. Excess of the reagent was destroyed carefully by adding saturated solution of ammonium chloride. The organic layer was separated and the aqueous layer was extracted with ether. The organic layer combined with the ether extract was washed with water and dried (Na_2SO_4). Evaporation of ether gave a thick liquid (0.380 g) which was chromatographed on alumina (Gr. III, 12 g) and eluted with pet. ether, benzene and ether. The pet. ether fraction on evaporation gave the unreacted ketone (LVI; 0.11 g). Benzene and ether fractions gave the alcohol XXXI (TLC single spot) with the following properties:

b.p. 125-130°(bath)/0.1 mm; n_D^{26} 1.5000;
$(\alpha)_D$ + 32° (c, 2.09).

IR spectrum (Fig. 9) showed bands at: 3400, 2900, 1637, 1448, 1370, 1280, 1163, 1130, 1037, 975, 940, 890, 845, 822 cm^{-1}.

Analysis

Found: C, 80.63; H, 11.64%.
$C_{15}H_{26}O$ requires: C, 81.02; H, 11.79%.

Rearrangement of the ester XXIXa to the ester LXI

To the ester (10 g) was added formic acid (98-100%; 100 ml), and the mixture was kept for 12 hr at room temperature with occasional shaking. It was diluted with water and extracted with ether. Ether layer was washed with water, Na_2CO_3 aq. (5%) and water and dried (Na_2SO_4). Evaporation of ether gave a product (9.7 g) which was chromatographed on alumina (Gr. II, 300 g) and eluted with pet.ether to furnish LXI (7.3 g) (GLC, about 95%) with the following properties:

b.p. 120-125°(bath)/0.2 mm; $n_D^{25.5}$ 1.5065

$(\alpha)_D$ + 15.46° (c, 4.26).

IR spectrum (Fig. 10) showed bands at: 2941, 1745, 1460, 1379, 1351, 1250, 1199, 1159, 1064, 985, 910, 848 cm^{-1}.

Analysis

Found: C, 76.70; H, 10.53%

$C_{16}H_{26}O_2$ requires: C, 76.75; H, 10.47%

Conversion of the ester LXI into the alcohol LXII

The ester (5 g) in dry ether (50 ml) was added to an ice-cold solution of LAH (0.8 g) in dry ether (100 ml). The reaction mixture was stirred at room temperature for 12 hr. and worked up in the usual way to furnish the alcohol LXII (4.3 g), which showed the following properties:

b.p. 125-135°(bath)/0.1 - 0.2 mm; $n_D^{29.5}$ 1.5012

$(\alpha)_D$ + 3.93° (c, 2.5).

IR spectrum of the alcohol showed bands at: 3400, 2941, 1449, 1379, 1036, 910 cm^{-1}.

Analysis

Found: C, 80.83; H, 11.67%

$C_{15}H_{26}O$ requires: C, 81.02; H, 11.79%

Chromic acid oxidation of the alcohol (LXII)

To an ice-cold solution of the alcohol (10 g) in acetone (125 ml) Jones' chromic acid reagent was added till a brown colour persisted. The reaction mixture was kept at 0° for 2 hr. and worked up in the usual way to furnish a neutral product (8.2 g) which was chromatographed on alumina (Gr. II, 240 g) and eluted with pet. ether and ether. From the ether fraction, alcohol (LXII, 4 g) was recovered. Pet. ether fraction afforded the aldehyde LXIII (4.1 g) (GLC about 90%) b.p. 120-125°(bath)/0.2 mm; $(\alpha)_D$ + 7.2° (c, 1.7).

IR spectrum of the aldehyde showed bands at: 2900, 2700, 1724, 1449, 1370, 1176, 1149, 990, 920.

Analysis

Found: C, 81.13; H, 11.68%

$C_{15}H_{24}O$ requires: C, 81.76; H, 10.98%

Enamine LXIV from the aldehyde (LXIII)

To a solution of the aldehyde (3.5 g) in dry benzene (70 ml) was added piperidine (1.7 g) and toluene-p-sulphonic acid (0.012 g). The reaction mixture was refluxed in nitrogen atmosphere for 12 hr. with an arrangement to separate the water formed in the reaction by azeotropic distillation. From the reaction product benzene was removed under vacuo and the crude enamine (LXIV) (3.6 g) obtained was used for further reaction, without purification.

Sodiumdichromate oxidation of the enamine LXIV

The above enamine (3.6 g) was oxidised by sodium dichromate-acetic acid-benzene system as described previously and worked up in the usual way to furnish the ketone (LXV, 0.850 g) with the following properties:

b.p.125-135°(bath)/0.8 mm; n_D^{32} 1.4935

$(\alpha)_D$ - 31.15° (c, 1.74).

IR spectrum (Fig. 12) of the ketone showed bands at: 1718, 1453, 1379, 1344, 1282, 1176, 953, 915 895 and 830 cm^{-1}.

Analysis

Found: C, 82.13; H, 11.05%

$C_{14}H_{22}O$ requires: C, 81.50; H, 10.75%

Conversion of the ketone (LXV) into the tertiary alcohol (XXXII)

A solution of the ketone (0.350 g) in dry ether (25 ml) was added to an ice-cold solution of MeMgI (prepared from 1.25 g of Mg wire and 6.2 g of MeI) in dry ether. The reaction mixture was stirred at 0° for 1 hr and at 30° for 6 hr. After destroying excess of the reagent with saturated solution of ammonium chloride, the organic layer was separated, and the aqueous layer extracted with ether; the organic layer combined with the ether extract was dried (Na_2SO_4) and ether evaporated. The thick liquid (0.335 g) obtained was chromatographed on alumina (Gr. III, 10 g) and eluted with hexane and ether. From the hexane fraction the unreacted ketone (LXV, 0.13 g) was recovered. The ether fraction afforded the tertiary alcohol (XXXII; 0.180 g) (TLC, single spot) which showed the following properties:

b.p. 120-128° (bath)/0.1 mm; n_D^{32} 1.4970,
$(\alpha)_D$ - 11.14° (c, 4.04).

The IR spectrum (Fig. 13) showed bands at: 3340, 2900, 1450, 1375, 1280, 1170, 1140, 930, 915, 900 cm^{-1}.

Analysis

Found: C, 80.72; H, 11.95%

$C_{15}H_{26}O$ requires: C, 81.02; H, 11.79%

Conversion of the alcohol (LXII) into the hydrocarbon (LXVI)

a) Tosylation of the alcohol: The alcohol (1 g) dissolved in pyridine (15 ml) was treated with toluene-p-sulfonyl chloride (1 g) and the reaction mixture was kept at room temperature for 48 hr. It was diluted with water and extracted with ether. The ether layer was washed with water, dil. HCl (5%), water and dried (Na_2SO_4). Evaporation of ether furnished the crude tosylate (1.45 g) (IR-spectrum showed absence of hydroxyl group).

b) LAH reduction of the tosylate: The above tosylate (1.45 g) in dry ether (25 ml) was added to an ice-cold solution of LAH (0.400 g) and the reaction mixture stirred at room temperature for 12 hr. The reaction product was worked up as usual to afford the hydrocarbon (LXVI; 700 mg). It was purified by passing through a column of alumina (Gr. I, 40 g) and eluting with hexane (60-70°).

The hydrocarbon (GLC, 90%) showed the following properties:

b.p. 100-105°(bath)/0.8 to 1 mm; $n_D^{27°}$ 1.4885
$(\alpha)_D$ = - 1.5° (c, 3.1).

IR spectrum (Fig. 14) showed bands at: 2933, 1460, 1370, 1325, 1290, 1258, 1176, 1112, 1000, 975, 955, 915, 895, 833 cm^{-1}.

Analysis

Found: C, 87.02; H, 12.86%

$C_{15}H_{26}$ requires: C, 87.30; H, 12.70%

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PART III

STRUCTURE AND TRANSFORMATION PRODUCTS OF DEHYDROCOSTUS LACTONE

***

SUMMARY

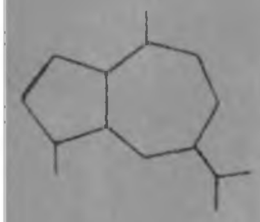
The ketocarboxylic acid, obtained during the chromic acid oxidation of the monol (XV), has been shown to possess the structure (XX) on the basis of spectral data and chemical reactions.

The crystalline lactol (XXXI) obtainable from (III), on Huang-Minlon reduction at 135-140°, gives a mixture of two monols (XXXVII and XXXVIII) the structures of which have been established by physical and chemical methods.

Dehydrocostus lactone III, $C_{15}H_{18}O_2$, is a crystalline guaianolide which constitutes one of the major components of costus root oil. The presence of this lactone in the oil was first reported by Ukita[1] in 1939. He isolated the lactone in low yield by vacuum distillation of the oil, obtained by extracting the roots with pet. ether. Crabalona[2] later on obtained probably the same lactone from the oil after several years ~~of~~ standing. Subsequently it was isolated by Naves[3] in a very low yield (0.125%) by vacuum distillation of the oil at 2 mm. Though Naves records that the lactone isomerises at 66°, the method of isolation adopted by him involved drastic temperature treatment and as a result major portion of the lactone must have been denatured.

The constitution of dehydrocostus lactone was initially studied by Naves. On the basis of its quantitative ozonolysis as well as the results of Se-dehydrogenation of its saturated derivative which furnished a mixture of S- and Se-guaizulenes, he concluded that the lactone contains two exocyclic double bonds and possesses a guaiane skeleton.

During the course of the investigations of the constituents of commercial costus root oil Sorm et al.[4] were able to isolate the same dehydrocostus lactone of Naves in 5.8% yield by vacuum distillation of the oil at one stage (140-143°/0.5 mm) followed by subsequent crystallisation of the particular fraction. They repeated the ozonolysis experiment of Naves and came to the conclusion that it contains three exocyclic double bonds and not two as previously reported. Examination of the IR spectrum[5] of dehydrocostus lactone showed the presence of only exomethylene double bonds (890, 1640 cm^{-1})[9,10] and no absorption due to $-CH_3$ bending vibrations around 1380 cm^{-1}, indicating the absence of any methyl groups in the molecule. The presence of an α-β unsaturated α-methylene, γ-lactone was indicated by the IR (peaks at 1760, 1400 and 815 cm^{-1}) and UV (high end absorption at 210 mμ) spectra. A comparison of the IR spectrum of the completely saturated lactone viz. hexahydrodehydrocostus lactone (VI) with that of dihydrodeoxy carpesia lactone obtained form carpeis lactone (II) indicated that the two compounds are identical in their carbon skeleton.



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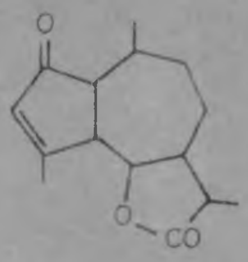

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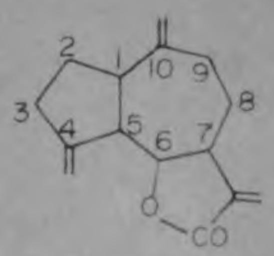

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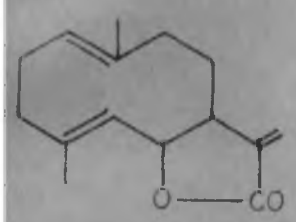

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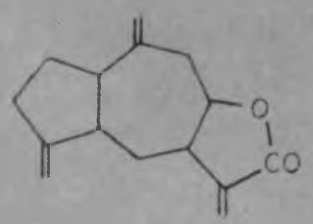

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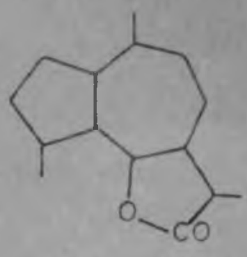

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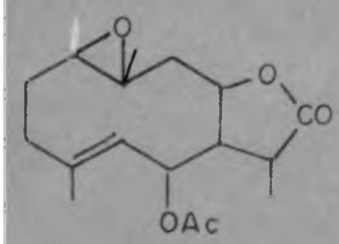

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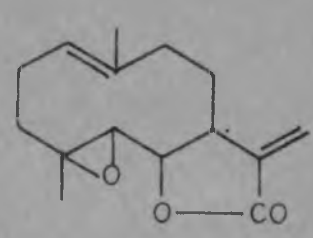

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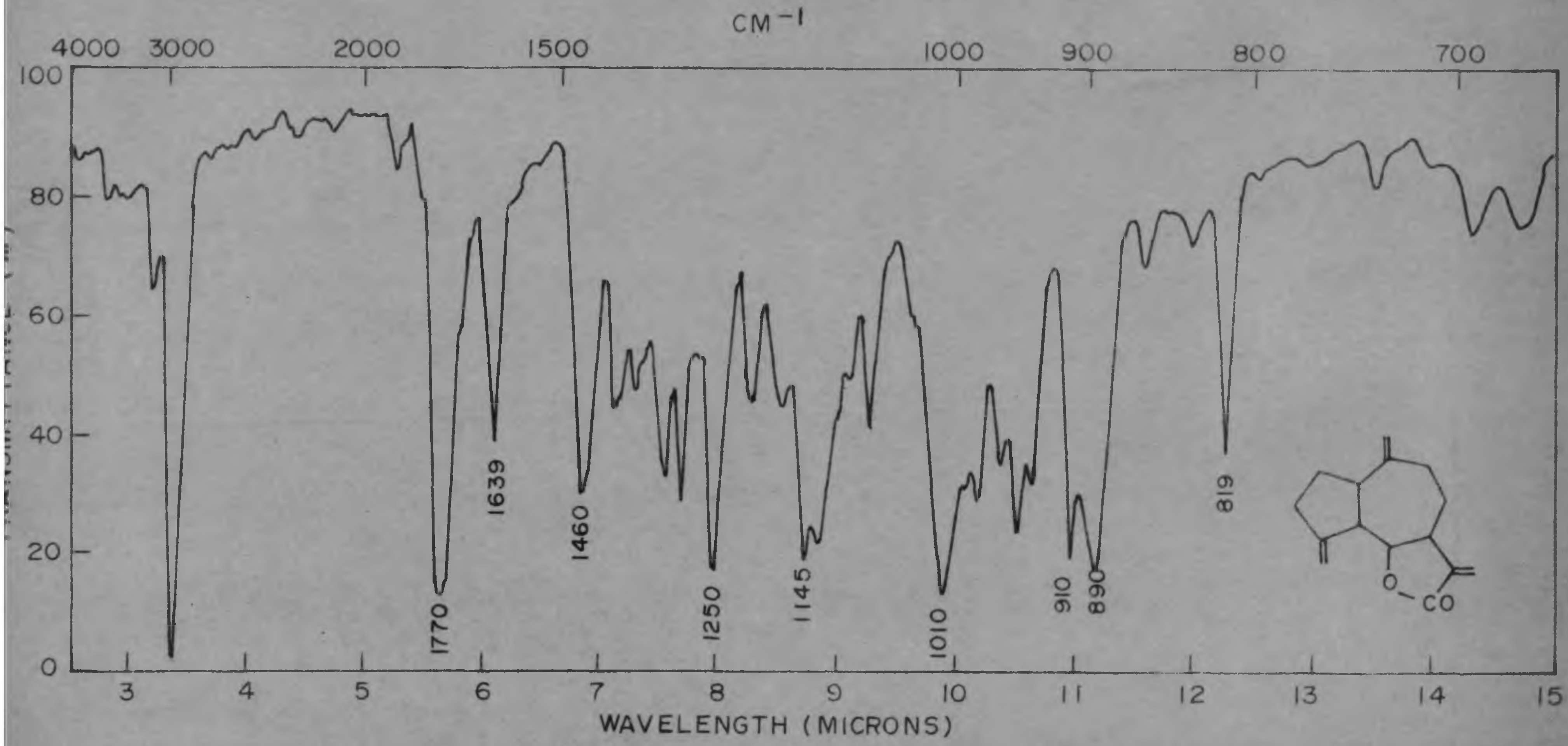


FIG. I- IR SPECTRUM OF DEHYDROCOSTUS LACTONE (IN NUJOL)

Se-dehydrogenation of hexahydrodehydrocostus lactone (VI) was reported to give a mixture of four azulenes, in low yield, identified by paper chromatography to consist of S- and Se-guaiazulenes and S- and Se-chamazulenes. On the basis of these results, the structure of dehydrocostus lactone was represented by them as III.

Though structure III for dehydrocostus lactone appears reasonable there are some points which need further evidence in support of it.
(i) Low yields of azulenes as obtained by Naves, Sorm and also by us[5] do not lend adequate support for the guaiane skeleton especially when many terpenoids such as pyrethrosin VII and parthenolide (VIII), which do not possess a perhydroazulene skeleton are also known to yield comparable amounts of azulenes on dehydrogenation.
(ii) An alternative structure (V) with the lactone attachment at C_7 - C_8 for the compound could not be ruled out, as most of the deductions viz. formation of azulenes, ozonolysis results, interpretation of IR and UV data will also hold good for structure (V) as well.

The only evidence given in favour of structure III is based on the comparison of the

IR spectrum of hexahydrodehydrocostus lactone, a non-homogenous material (GLC 4 peaks), with that of dihydrodeoxy carpesia lactone.

It was, therefore, thought desirable to collect data to confirm the structure assigned to dehydrocostus lactone.

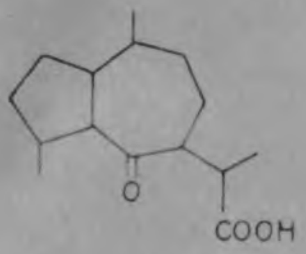
The low temperature solvent extraction procedure for extracting costus root oil furnished a mixture of two crystalline lactones in about 2-3% yield[5]. This consisted of (1) costunolide IV 30% and (2) dehydrocostus lactone 70%.

The availability of dehydrocostus lactone in high yield enabled us to undertake a detailed investigation of its structure.

For the sake of convenience it is assumed that dehydrocostus lactone is represented by the structure (III).

Previous work done in our laboratory

With the ultimate object of getting a product related to nepetalinic acid (X) via the intermediate ketocarboxylic acid IX, hexahydrodehydrocostus lactone, obtained by direct hydrogenation of dehydrocostus lactone, was oxidised with chromic acid in acetic acid. But instead of the desired ketocarboxylic acid, the



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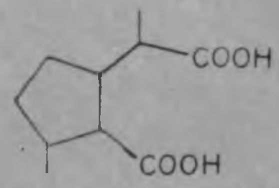

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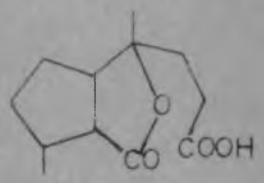

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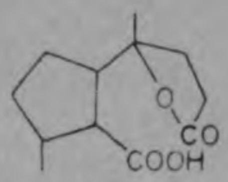
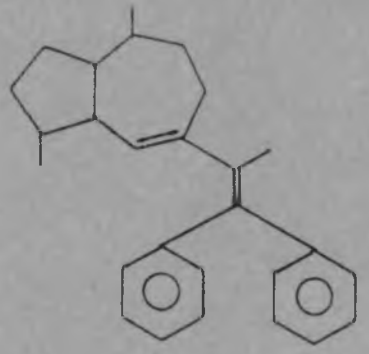


XII



XIII

product obtained was a lactone-carboxylic acid possibly represented by XI or XII, or a mixture of both. Much of the VI was recovered unchanged.

Subsequently VI was reacted with phenyl-magnesium-bromide and the product dehydrated to yield, presumably, the diene XIII. But contrary to expectation its oxidation did not lead to any conclusive results.*

Our approach towards solving the structure of dehydrocostus lactone is based on the following considerations:

1) Conversion of dehydrocostus lactone into the basic hydrocarbon guaiane (I).
2) Obtaining higher yields of azulenes from suitable derivatives of dehydrocostus lactone
3) Establishing the presence of cyclopentane ring in the molecule.
4) Showing that the lactone attachment is at $C_6 - C_7$.

The materials used in this investigation were of established purity.

1. Formation of guaiane

Hexahydrodehydrocostus lactone (VI) was reduced by LAH under controlled conditions[7] and the

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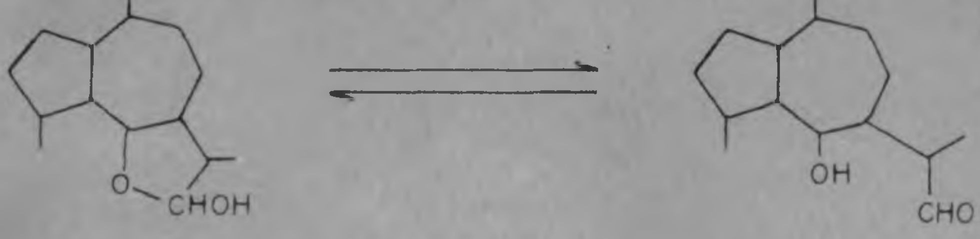
*This work was carried out by D. Simonovic and A.S. Rao



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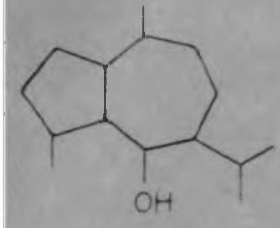
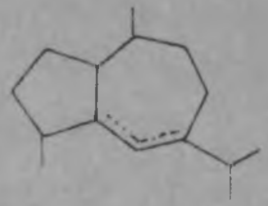
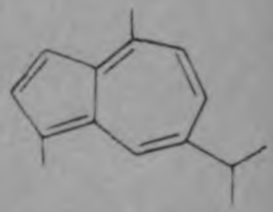


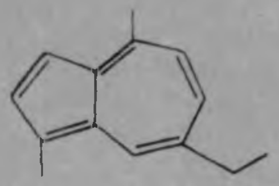
XV



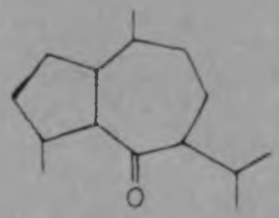
XVI



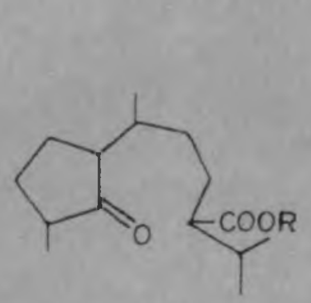
XVII



XVIII

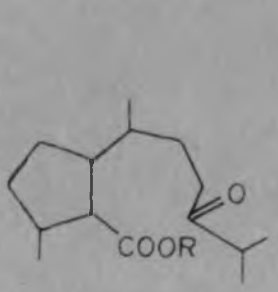


XIX



XX

R=H, R= CH_3



XXI

R=H, R=CH_3

resulting hydroxyaldehyde (XIV) was subjected to Huang-Minlon reduction to furnish in good yield, the pure (GLC/TLC) crystalline monol (XV) $C_{15}H_{28}O$, m.p. 54°. Dehydration of the monol by $KHSO_4$ gave a mixture (GLC) of two unsaturated hydrocarbons (XVI), $C_{15}H_{26}$, both containing a trialkylated double bond (IR and NMR evidences). Hydrogenation of this mixture (XVI) gave a saturated hydrocarbon, $C_{15}H_{28}$, (GLC, two isomers 80:20), identified as guaiane (I) by comparison of its IR spectrum with that of decahydro S-guaiazulene[15] and physical constants. Formation of guaiane from III, therefore, supports the guaianolide structure for dehydrocostus lactone.

2. Formation of azulenes

Sulphur dehydrogenation of the monol (XV) afforded S-guaiazulene in 8% yield. It was characterised through its TNB adduct. Dihydrodehydrocostus lactone obtained by $NaBH_4$ reduction of (III), on heating with alkali in diethylene glycol at high temperatures furnished chamazulene XVIII in about 7-8% yield[*]

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[*] More recently a method has been developed in our laboratory to produce azulenes from dehydrocostus lactone wherein the yield of azulenes is as high as 30%.

3. Presence of a cyclopentane ring

Previous work: The monol (XV) on oxidation with Jones' chromic acid reagent furnished a crystalline ketone, $C_{15}H_{26}O$, m.p. 54-55° (XIX). Along with the normal oxidation product (XIX), it also gave a ketocorboxylic acid, $C_{15}H_{26}O_3$, characterised through its methyl ester.

The ketone (XIX) showed in its IR spectrum carbonyl absorption at 1705 cm^{-1} consistant with a cycloheptanone system. It did not show any absorption around 1420 cm^{-1} characteristic of $-CO-CH_2-$ grouping. The ketone failed to give any semicarbazone and 2:4-dinitrophenyl hydrazone. It was also resistant to reduction by $NaBH_4$ and LAH. The ORD curve of this ketone showed positive cotton effect (a, + 64 units) which did not alter much on addition of hydrochloric acid indicating thereby that the carbonyl is in a hindered position.

These observations clearly suggest that the carbonyl group in the ketone is at C_6 and not at C_8 and hence the lactone attachment in dehydrocostus lactone is at C_6 - C_7. A chemical proof in this connection is also available and described in the sequel.

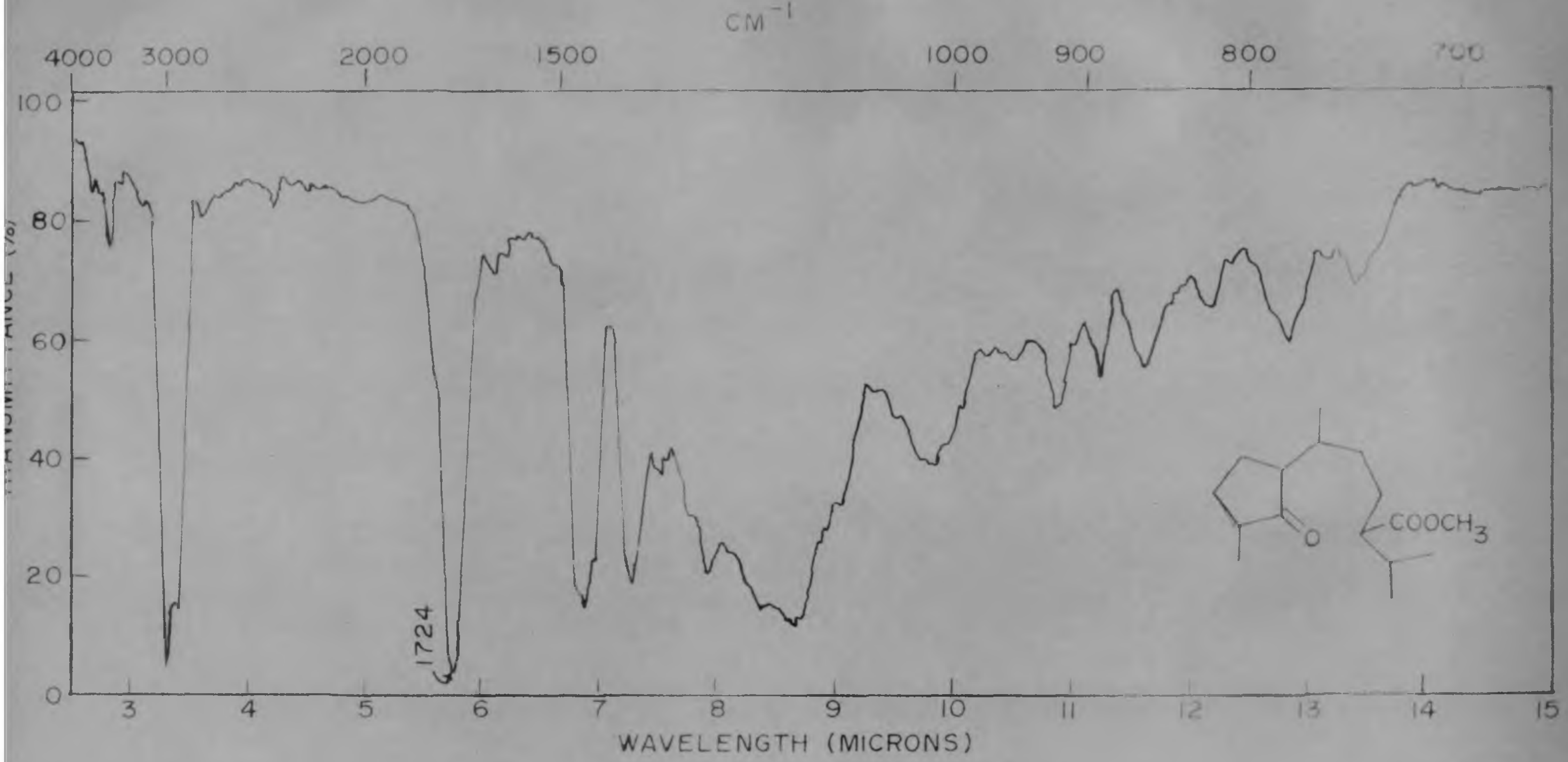
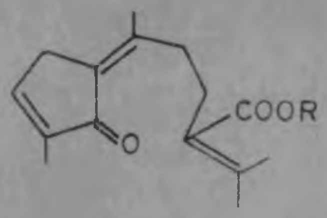


FIG 2- IR SPECTRUM OF KETO ESTER (LIQ FILM)

The IR and NMR spectra of the keto ester mentioned above suggested that it could be represented by either of the alternative structures XX or XXI. It was not possible, from the IR spectrum (Fig. 2), to decide whether the keto-group is located in the side-chain as in XXI or in the cyclopentane ring as in XX, since the carbonyl absorptions due to the keto-group and the ester group were merging. However, the absence of any absorption around 1420 cm^{-1} characteristic of $-CO-CH_2-$ grouping in the IR spectrum of the keto-ester suggests that XX is more likely to be its structure.

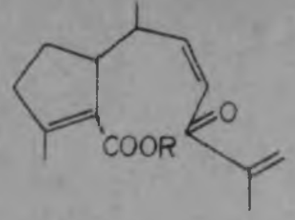
With a view to decide the structure of the ketocarboxylic acid its methyl ester was brominated with excess of N-bromosuccinimide[8] when a tribromo (bromine estimation) compound was obtained. This on dehydrobromination by refluxing with pyridine afforded among other products ~~of~~ a crystalline solid, $C_{16}H_{22}O_3$, m.p. 95-96°. The IR spectrum of this compound showed peaks at 1705 (ester carbonyl) 1672 (α-β-unsaturated keto group) and 1639 and 1629 cm^{-1} ($-C = C-$ stretching). Since the peaks at 1672, 1639 and 1629 cm^{-1} were not much differing in intensity[12-13], it is quite probable that one of the chromophores present in the molecule is a cisoid α-β-unsaturated ketone. The UV spectrum of the product showed λ_{max} 258 mμ (ϵ_{max} 12,900). No definite conclusion, however, could be drawn from these data regarding the exact location of the keto-group.

The NMR spectrum of the product, however, clearly indicated the absence of any methyl groups on saturated carbon atoms (no signals above 9.0 τ) and showed that all the four methyl groups present in the molecule are situated on carbon atoms carrying double bonds ($- C = C - CH_3$ type; signals at 8.29, 8.24, 8.03 and 7.92 τ; 12 H). It also showed signal at 6.32 τ (3 H) due to an ester methyl group and at 3.02 τ (1 H) due to and olefinic proton on a conjugated trisubstituted double bond. This NMR data cannot be explained by the structure XXI for the original keto acid, as it would have given a compound containing at least one methyl group on a saturated carbon atom and more than one olefinic proton as in XXIII and XXIV on bromination and dehydrobromination. Thus from the NMR spectrum it appears obvious that the keto acid cannot be represented by XXI and has, therefore, to be represented by XX.



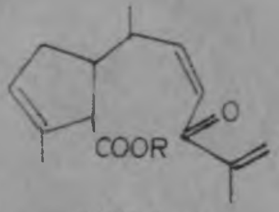
XXII

R = CH_3



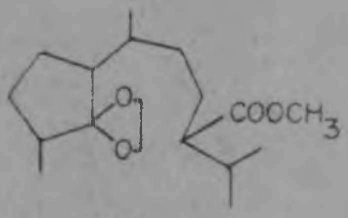
XXIII

R = CH_3

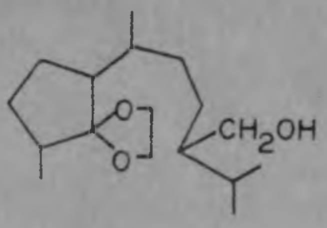


XXIV

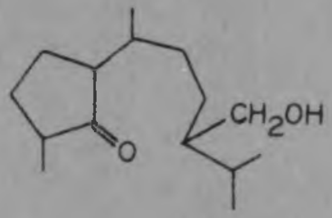
R = CH_3



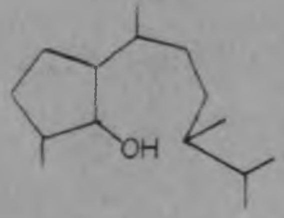
XXV



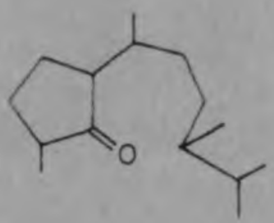
XXVI



XXVII



XXVIII



XXIX

Present work: With a view to confirm the structure XX for the keto-acid it was felt desirable to show the presence of cyclopentanone system in it, which would ultimately prove the presence of a cyclopentane ring in dehydrocostus lactone also.

To achieve this objective the keto ester (XX) was converted into the ethylene ketal-ester XXV by reacting it with ethyleneglycol. The ketal ester (XXV) on reduction with LAH gave the corresponding ketal-alcohol (XXVI) from which the ketoalcohol XXVII was generated by treatment with acid.

The ketoalcohol (XXVII) showed in its IR spectrum bands at 1730 cm^{-1} (cyclopentanone) and 3436 cm^{-1} (hydroxyl). It did not show any absorption around 1420 cm^{-1} characteristic of $- CO - CH_2$ grouping thus eliminating the structure (XXI) which contains such a moiety. The carbonyl absorption at 1730 cm^{-1} though reasonably satisfactory for cyclopentanone, leaves some doubt, as open chain ketones[14] are also capable of giving absorptions upto 1725 cm^{-1}. The somewhat low value for the cyclopentanone absorption in the IR spectrum of the ketol XXVII may possibly be due to hydrogen bonding with the

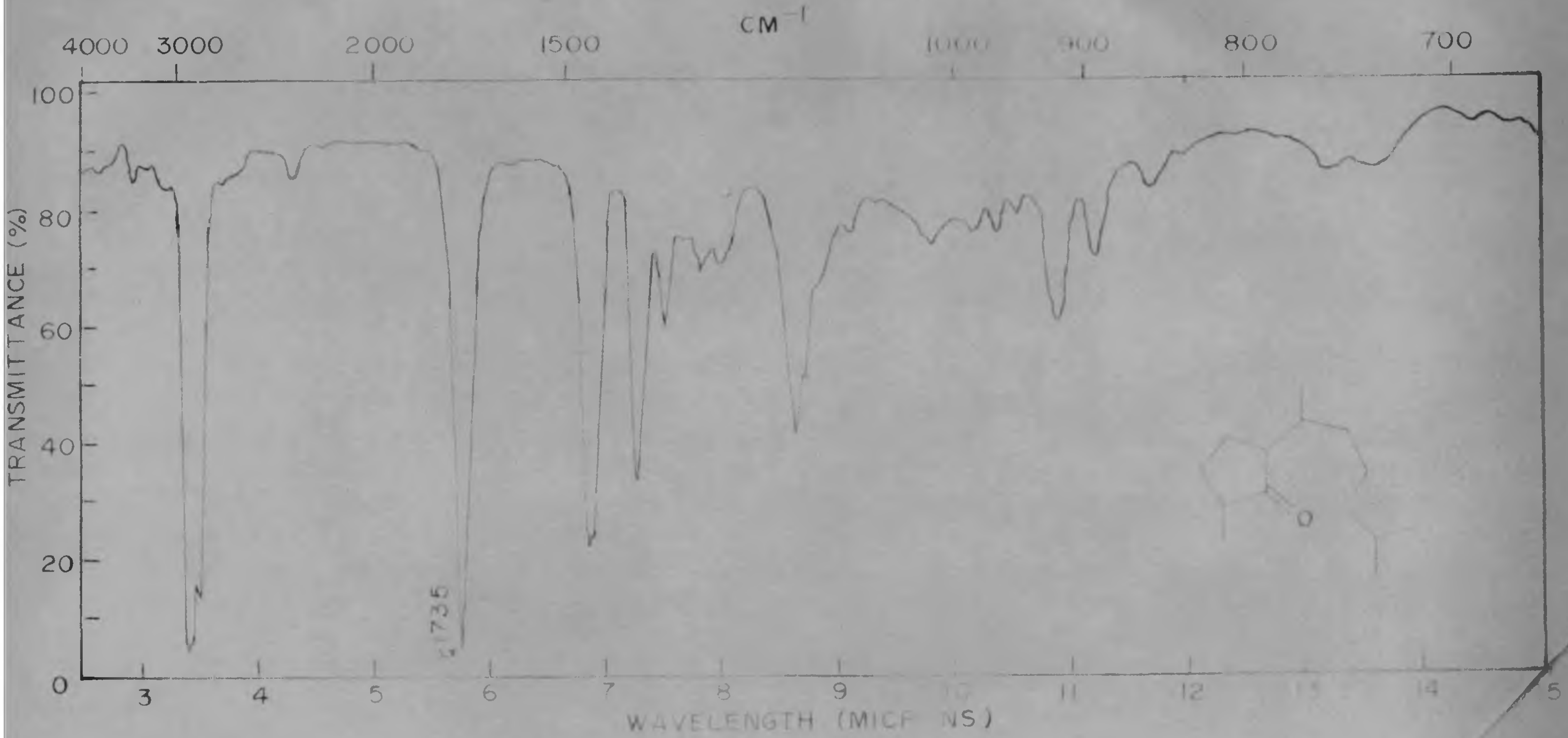


FIG 3 -IR SPECTRUM OF KETONE (LIQ FILM)

primary hydroxyl function. It was therefore decided to convert the CH_2OH into CH_3 and then examine the IR of the resulting product.

The ketol (XXVII) was converted into its tosylate and the latter reduced by LAH to give a mixture of two C_5 epimeric monols(XXVIII), chromic acid oxidation of which furnished the ketone (XXIX).

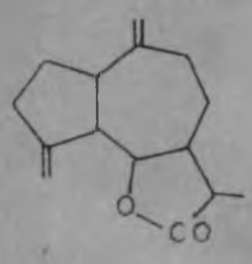
The ketone in its IR spectrum (Fig. 3)showed carbonyl absorption at 1736 cm^{-1}, firmly establishing the presence of cyclopentanone and ultimately confirming structure (XX) for the keto acid.

The NMR spectrum of the ketone XXIX is in agreement with the structure assigned to it [five secondary methyl groups, signals at: 8.91, 8.98, 9.03, 9.11, 9.17 and 9.24 τ (15 H)].

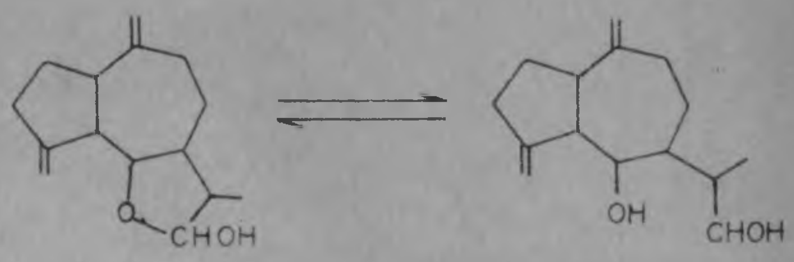
These findings clearly indicate that during the formation of the keto acid from XV initial hydroxylation (oxidation) takes place at C_5 and not at C_7.

4. Lactone attachment at C_6 - C_7
Reactions of Lactol (XXXI)

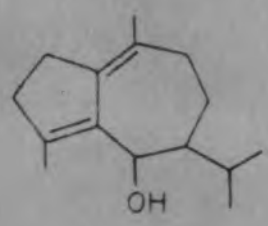
Previous work: Following the method of the Japanese workers[6] dehydrocostus lactone was converted



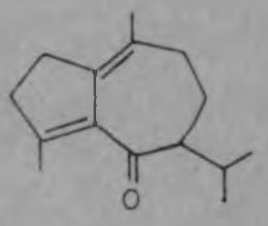
XXX



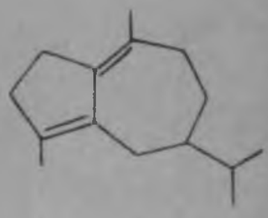
XXXI



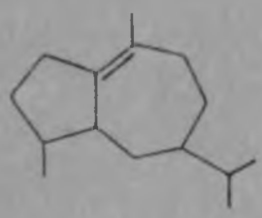
XXXII



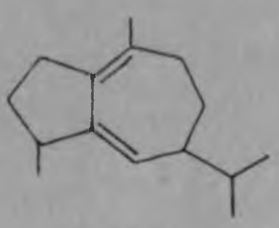
XXXIII



XXXIV



XXXV



XXXVI

to the crystalline lactol XXXI by prolonged reduction with $NaBH_4$. The lactol on oxidation with chromic acid afforded pure (GLC/TLC) dihydrodehydrocostus lactone XXX (our previous attempts to obtain the same in epimerically pure condition by reduction of III with Na-alcohol and Na- liq. ammonia had failed). The dihydroderivative (XXX) could also be obtained in 80% purity by direct reduction of III with $NaBH_4$. It was also observed by us that the crystalline lactol (XXXI) could be obtained more conveniently on preparative scale by controlled reduction of XXXI (80%) with LAH.

Huang-Minlon reduction of XXXI at 170° afforded along with other products, the pure (TLC) hetero-annular dienic monol (XXXII) in which both the original methylenic double bonds have migrated inside the rings. The IR spectrum of XXXII did not show the presence of exomethylene double bonds. The NMR spectrum indicated the presence of two methyl groups on double bonds (signals at 8.41 and 8.18 τ, 6 H) and did not show any signals due to trialkylated protons. In confirmity with this, it showed characteristic UV absorption at 252 mμ (ϵ_{max}, 9000).

Among the other products of Huang-Minlon reduction of XXXI, S-guaiazulene (characterised as its TNB adduct) was isolated in about 2% yield.

Oxidation of the monol XXXII with Jones' chromic acid reagent as well as with other oxidising agents like CrO_3-pyridine and activated MnO_2, however, failed to give the expected conjugated dienone XXXIII in pure condition, although indication of its formation as one of the products was observed in the UV spectrum of the oxidation product (λ_{max} 290, ϵ_{max} 3000). Much of the monol XXXII remained unaffected even when the reaction was carried out for a longer period, suggesting that the alcoholic group is in a hindered position. The indication of the formation of XXXIII from the dienic monol XXXII suggested that 'OH' group in the latter is at C_6. This was further confirmed in the following way:

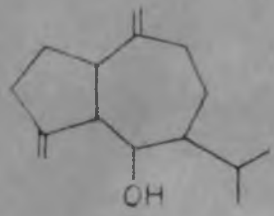
When the dienic monol XXXII was subjected to metalamine (Na or Li/Liq.NH_3) reduction[11], a hydrocarbon XXXV was formed along with traces of the hydrocarbon XXXIV. The structure of the hydrocarbon XXXV is supported by its NMR spectrum [signals at 9.13, 9.07, 8.97, 8.9 τ (9 H) due to three saturated methyl groups; at 8.38 τ (3 H) due to methyl on a double bond. The hydrocarbon

XXXV must have been formed by further reduction of the conjugated hydrocarbon XXXIV obtained as a primary product of hydrogenolysis. The possibility of any allylic migration of the double bond leading to the formation of XXXVI during the metalamine reduction is not likely, as a heteroannular dienic system is expected to be more stable. The formation of the hydrocarbon (XXXV) via the intermediate XXXIV can only be explained if the position of the hydroxyl group is at C_6 in XXXII and hence attachment of lactone moiety in III is at C_6.

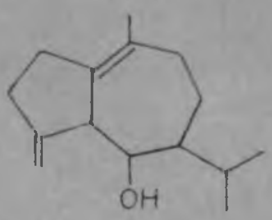
__Present work__: In order to ascertain whether more proof in favour of the structure III could be obtained, some transformations of dehydrocostus lactone were carried out. Since the Huang-Minlon reduction of the lactol (XXXI) at 170° and higher temperatures gave rise to the monol (XXXII), with both the double bonds migrated inside the rings along with S-guaiazulene, the reaction was tried at lower temperatures with a view to ascertain whether the normal reduction product (XXXVII), with both the exocyclic double bonds intact, as also the monols with one of the double bonds migrated inside the ring, could be obtained.

When the reaction was carried out at 135-140° a mixture of two monols was obtained in good yield. These were separated by repeated chromatography over alumina. The monol (XXXVII), $C_{15}H_{24}O$, (GLC/TLC pure) eluted in earlier fractions of the chromatography showed the presence of exomethylene double bonds in its IR spectrum (Fig. 4). The NMR spectrum (Fig. 5) of the monol showed signals at 9.3, 9.13, 9.04 τ (6 H) due to the methyls of the isopropyl group at C_7. In the olefinic region it showed signals at 5.34, 5.23 and 4.9 τ (4 H) due to the protons on the exomethylene double bonds at C_4 and C_{10}; a triplet at 7.11, 6.95 and 6.82 τ (1 H) was also observed which is due to the proton at C_6. The NMR spectrum is, thus, in agreement with structure XXXVII. Ozonolysis of the monol gave a diketo alcohol (XLIII). In the IR spectrum of this product (XLIII), a broad carbonyl absorption was observed, from which it was not possible, however, to conclude the presence of cyclopentanone system.

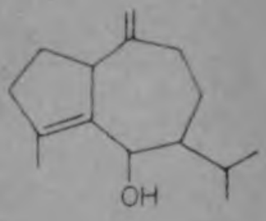
From the middle fractions of the chromatography, another pure (GLC/TLC) monol XXXVIII, $C_{15}H_{24}O$, was isolated. Its IR spectrum (Fig. 4) clearly indicated the presence of exomethylene group (1639, 885 cm^{-1}). Its NMR spectrum (Fig. 5), however, indicated the



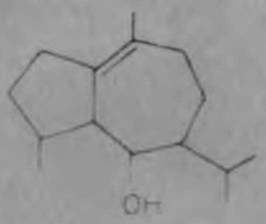
XXXVII



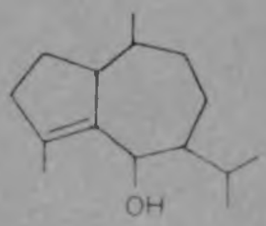
XXXVIII



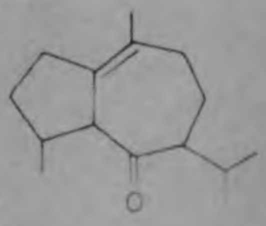
XXXIX



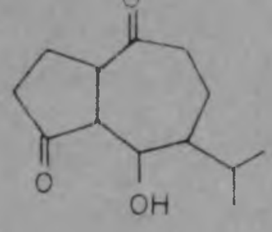
XL



XLI



XLII



XLIII

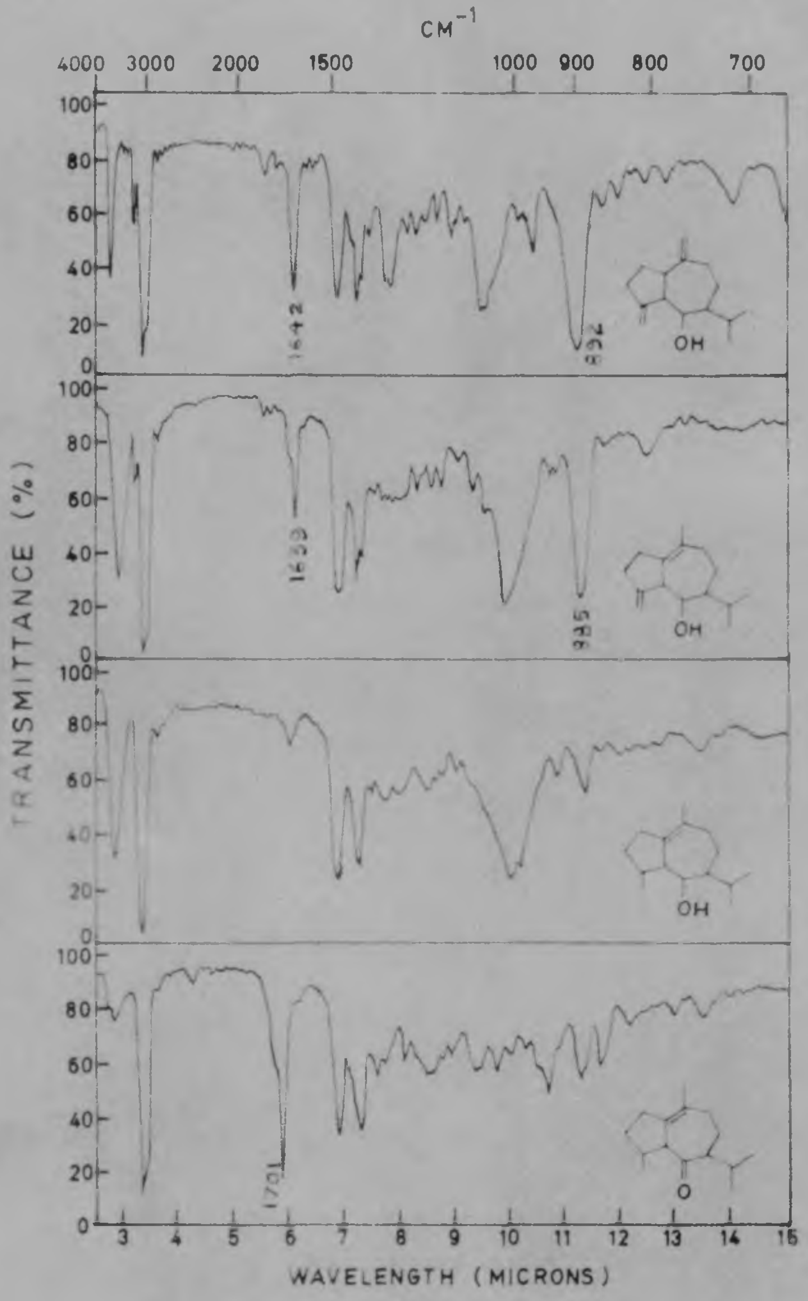


FIG. 4 - IR SPECTRA

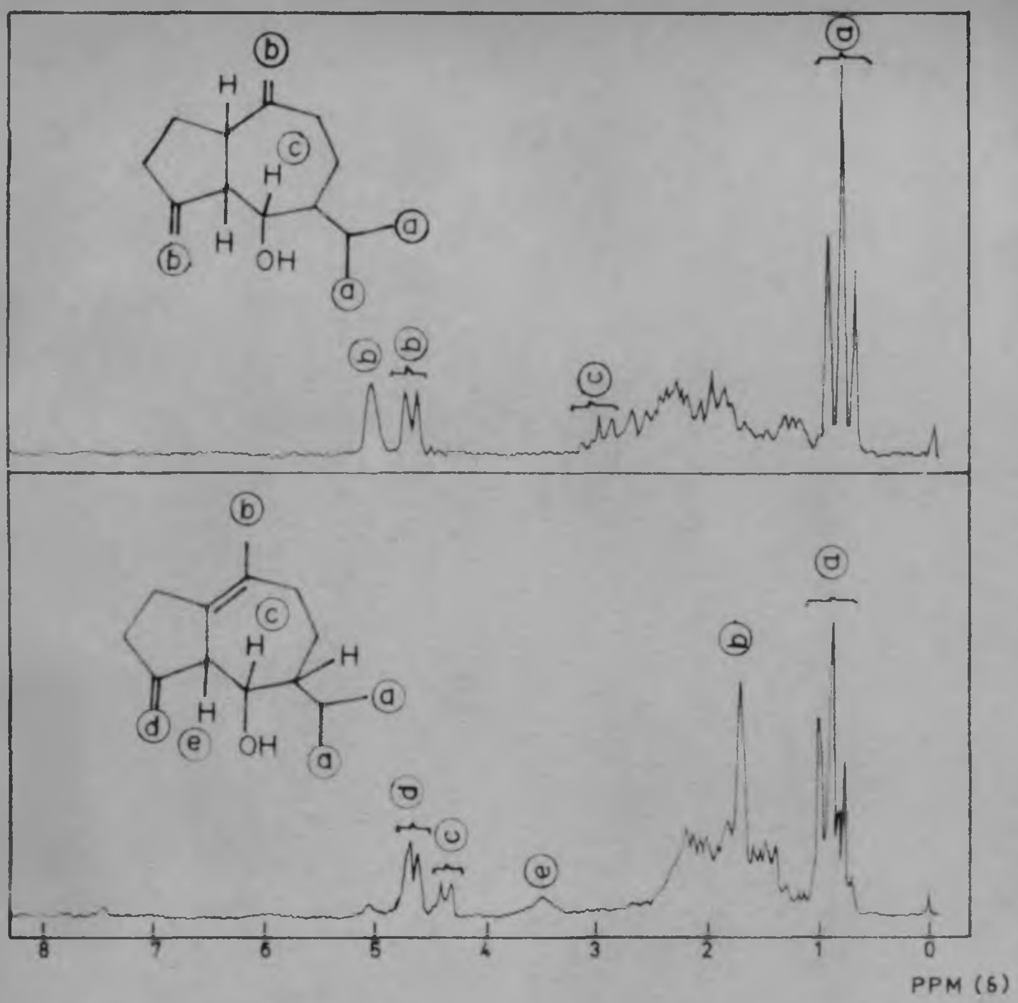


FIG. 5 - NMR SPECTRA

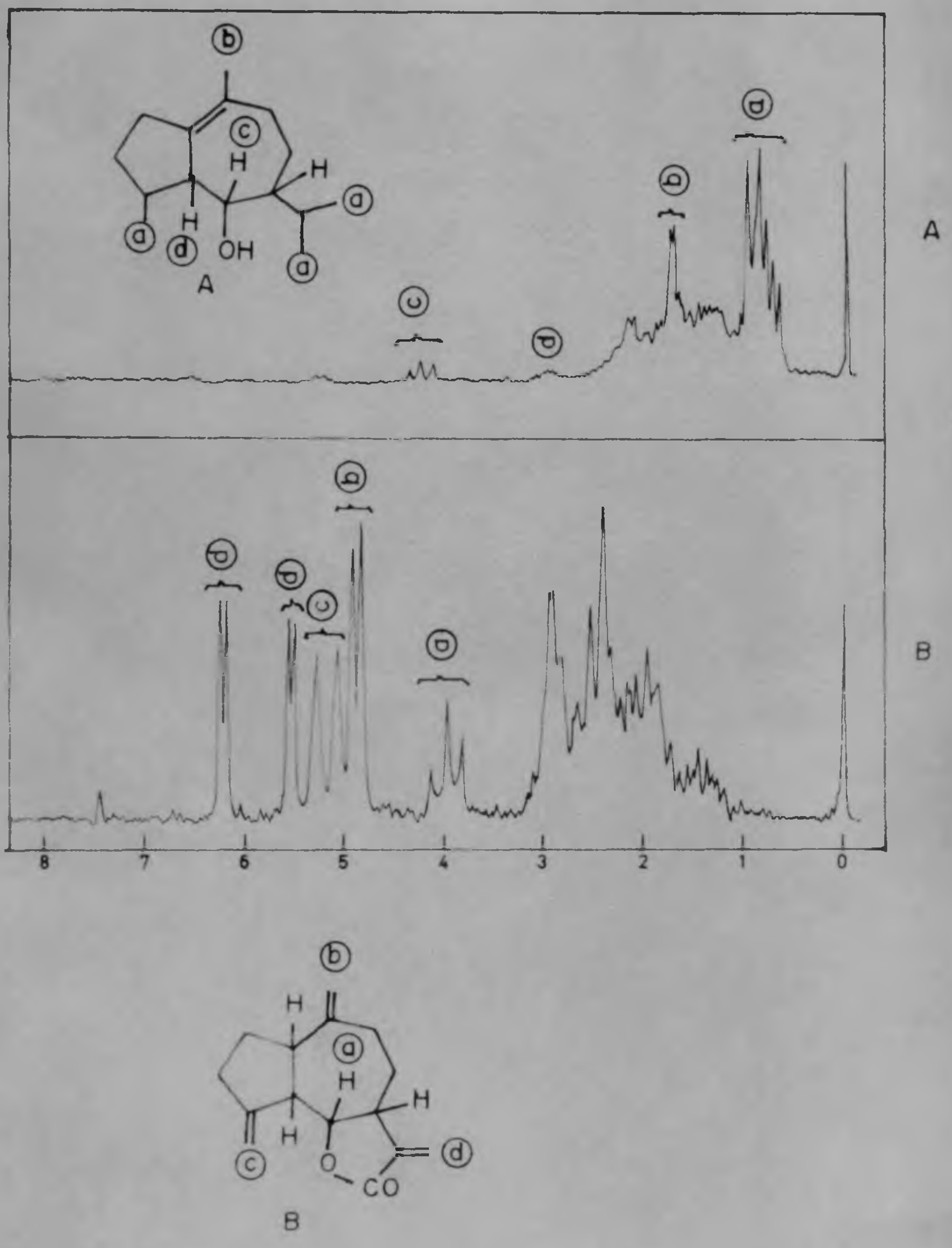
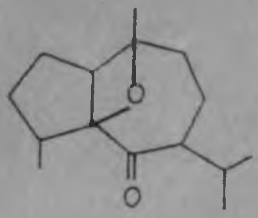


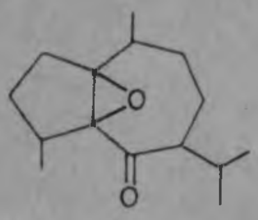
FIG. 6 NMR SPECTRA

presence of only one exomethylene group (signals at 5.45, 5.35 τ; 2H) and a methyl group on a double bond (signal at 8.35 τ; 3 H). The spectrum did not show any signal due to a proton on trialkylated double bond. It is, therefore, obvious, that one of the two original exomethylene double bonds in XXXI has migrated inside the ring during the reaction. The above spectral data would suggest that the alcohol could be represented by either of the structures XXXVIII or XXXIX. Preferential hydrogenation of the exomethylene group with 5% Pd on charcoal in alcohol medium, followed by chromic acid oxidation of the resulting dihydromonol (XL or XLI) afforded a number of products from which a fraction rich in ketone was obtained by chromatography. The IR (Fig. 4) and UV spectra of this fraction indicated the presence of a non-conjugated ketone in it, necessarily represented as (XLII). The original monol should be, therefore, represented by XXXVIII and its dihydro derivative by the structure (XL) (IR spectra Fig. 4).

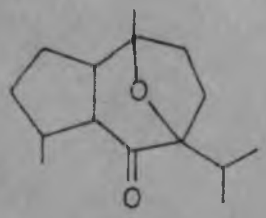
The other products of chromic acid oxidation of the monol XXXVIII include an oxido-ketone, $C_{15}H_{24}O_2$, m.p. 95°, with a keto group located in



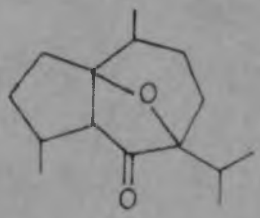
XLIV



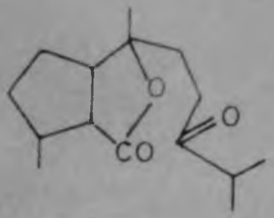
XLIVa



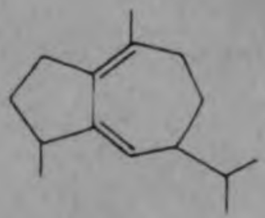
XLV



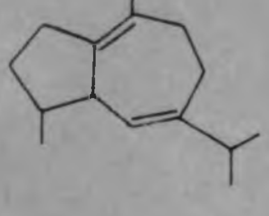
XLVa



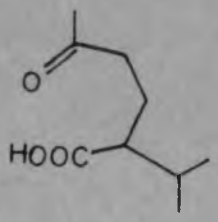
XLVI



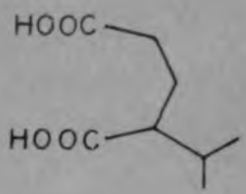
XLVII



XLVIII



XLIX



L

a seven membered ring (IR spectrum band at 1705 cm^{-1}). This oxido-ketone is possibly formed from an intermediate keto-alcohol containing an 'OH' group, either at C_5 or at C_7 formed by further oxidation of the ketone (XLII). So the oxido-ketone may be represented by any of the four structures viz. (XLIV and XLIVa) or (XLV and XLVa). The NMR spectrum of the oxido-ketone showed signals at 9.16, 9.12, 9.08, 9.01, 8.97 τ (9 H) due to the three methyl groups at C_4 and C_{11}. It also showed a signal at 8.68 (3 H) due to the methyl group at C_{10} which is carrying the oxygen bridge. The NMR spectrum thus suggests the structure XLIV or XLIVa for the oxido-ketone. In view of the formation of the keto-acid XX (R = H) from the monol XV in which the oxidation has taken place at C_5 it is very probable that the oxidation of the monol XL also should have taken place at C_5. In view of these considerations the structure XLIV appears to be more probable for the oxido-ketone.

Another product of the oxidation of the monol XL was a liquid keto-lactone showing IR bands at 1773, 1706 and 1408 cm^{-1} indicating the presence of a γ-lactone, a keto-group and a

$CO-CH_2$ grouping. The IR data suggest that this is formed by oxidation of the monol XL at C_7 to give an intermediate diol which on further oxidation gives rise to a keto-lactone by rupture of the C_6-C_7 bond followed by lactone ring closure of the resulting β-γ unsaturated acid. Thus it may be represented by the structure XLVI.

The dihydromonol (XL) on dehydration with alumina-pyridine at 180-200° in an atmosphere of nitrogen afforded a mixture of hydrocarbons, $C_{15}H_{24}$ (XLVII and XLVIII; GLC, 70:30) in about 60-65% yield. The hydrocarbon mixture was chromatographed and a fraction rich in XLVII (GLC, about 85-90%; λ_{max} 242; ϵ_{max} 20,000)* was obtained, which showed in its NMR spectrum signals at 8.94, 9.03, 9.15, 9.26 and 9.38 τ (3 H) due to methyls at C_4 and C_{11} and at 8.3 τ (3 H) due to methyl on a double bond at C_{10}. It also showed signals at 4.4 and 4.63 τ (1 H) due to a proton at C_6.

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*Simple cycloheptadine system without any substituent on chromophore absorbs at 248 mμ, and the compound in question though containing 3-substituents on the chromophore absorbs at a lower value (242 mμ). Reference compounds in this series were not available for comparison purposes. The structure XLVII, however, is confirmed by consideration of its NMR spectrum.

The hydrocarbon (XLVII) on ozonolysis would give the keto-acid (XLIX) which on subsequent oxidation would furnish α-isopropyl glutaric acid (L). This compound is expected to yield valuable information about the stereochemistry at C_7 in dehydrocostus lactone (III). However, due to paucity of the compound XLVII this work could not be carried out at present.

As such the examination of the NMR spectrum of dehydrocostus lactone suggests that the point of attachment of the hydroxyl oxygen atom of the lactone moiety is at C_6 and not at C_8 as the spectrum shows a triplet at 5.88, 6.04 and 6.17 τ (1 H) and not a quartet as would have been expected if the attachment were at C_8. Similar triplets are also observed in the NMR spectra of dihydrodehydrocostus lactone (XXX) and the monols XXXVII, XXXVIII and XL. This spectral data coupled with the chemical evidence previously obtained (formation of XXXIII and XXXV from XXXII) conclusively establishes the position of the lactone attachment at C_6 - C_7 in dehydrocostus lactone.

EXPERIMENTAL

Hexahydrodehydrocostus lactone (VI)

Dehydrocostus lactone (III), m.p. 60-61°, $(\alpha)_D$ - 13°, (50 g) dissolved in alcohol (250 ml) was hydrogenated under pressure (1000 lbs/sq.in) using platinum catalyst initially at room temperature (6 hr) and then at 50° (6 hr). Alcohol was removed under suction, the residue diluted with water and extracted with ether. Removal of ether furnished a liquid, purified by distillation, when it showed the following properties: b.p. 130-135°(bath)/ 0.5 mm, n_D^{32} 1.4980, $(\alpha)_D$ + 36° (c,4.2).

Analysis

Found: C, 76.68; H, 9.89%

$C_{15}H_{24}O_2$ requires: C, 76.22; H, 10.24%

Controlled LAH reduction of VI

The lactone (VI, 27 g) was reduced by gradual addition of an ethereal solution of LAH (75%, 2.6 g; in 200 ml) under cooling at - 10°. The reaction mixture was stirred for 3 hr at - 10° and for another 3 hr at room temperature. It was decomposed by alcohol and water and worked up to give crude hydroxy aldehyde XIV (26 g) containing some unreacted lactone (IR spectrum).

Huang-Minlon reduction of the hydroxyaldehyde (lactol) (XIV)

A mixture of the above hydroxyaldehyde (26 g), diethylene-glycol (150 ml), KOH (27 g) and hydrazine hydrate (26 ml), was heated at 200-220° for 5 hr in an atmosphere of nitrogen. After cooling, it was diluted with water and extracted with ether. Ether layer was washed with dil. HCl (5%), water and dried (Na_2SO_4). Evaporation of ether furnished a liquid (21 g) which was chromatographed on alumina (Gr. II, 1100 g) and eluted as follows:

Fr. No.	Solvent	Vol. in ml	Wt. in g
1	Pet.ether	600	6.155
2	Pet.ether + Benzene (2:1)	4500	10.8
3	Pet.ether + Benzene (1:1)	2000	0.8
4	Ether	500	1.5

Fraction 2 which solidified was crystallised from dilute alcohol to a const. m.p. to give XV (GLC/TLC, pure) m.p. 53-54°, $(\alpha)_D + 6.3^\circ$ (c, 2.1)

Analysis

Found: C, 80.37; H, 12.58%

$C_{15}H_{28}O$ requires: C, 80.29; H, 12.58%

Chromic acid oxidation of the monol (XV)

The monol (1 g) was dissolved in acetone (20 ml) and Jones' reagent was added dropwise till a brown colour persisted. The product was diluted with water and extracted with ether. The ether layer was washed with water and extracted with Na_2CO_3 aq. (5%). The Na_2CO_3 extract was acidified with dil. H_2SO_4 and extracted with ether. The acid obtained after removal of ether (0.3 g) was esterified with diazomethane to give XX, R = CH_3 (GLC pure), b.p. 150-155°(bath)/0.6 mm, n_D^{25} 1.5200, $(\alpha)_D$ + 20° (c, 2.5). IR spectrum (Fig. 2).

Analysis

Found: C, 71.60; H, 10.93%

$C_{16}H_{28}O_3$ required: C, 71.60; H, 10.52%

The residual ether layer after Na_2CO_3 extraction furnished the ketone (XIX; 0.5 g).

Ketalisation of XX (R = CH_3)

A mixture of the keto-ester (0.8 g), dry benzene (80 ml) ethylene-glycol (5 ml) and toluene-p-sulphonic acid (10 mg) was refluxed (24 hr) with stirring, with an arrangement to separate azeotropically water formed in the reaction. The reaction mixture was cooled and washed with

Na_2CO_3 aq. (5%) and water and dried (Na_2SO_4) Removal of benzene gave the ketal ester XXV (0.82 g).

LAH reduction of the ketal-ester (XXV) and deketalisation of the resulting ketal-alcohol (XXVI)

The ketal-ester (0.82 g) in dry ether (30 ml) was reduced by LAH (0.12 g in 50 ml of dry ether) under stirring for 10 hr. The reaction product worked up in the usual way to give the ketal alcohol (XXVI) (0.936 g) which did not show any carbonyl absorption in the IR spectrum. The ketal alcohol (0.936g) without further purification was dissolved in benzene (50 ml) and conc. HCl (2 ml) was added. The resulting mixture was refluxed for (1 hr). The benzene layer was separated, washed with water and dried (Na_2SO_4). Removal of solvent and purification of the resulting product by chromatography and distillation gave the keto-alcohol (XXVII; 0.47 g), with the following properties: b.p. 145-160 (bath)/0.1 mm. n_D^{25} 1.4750, $(\alpha)_D$ - 3^o (c, 0.4). IR spectrum showed carbony absorption at 1730 cm^{-1}.

Analysis

Found: C, 74.77; H, 11.71%

$C_{15}H_{28}O_2$ requires: C, 74.95; H, 11.74%

Tosylation of XXVII and LAH reduction of the tosylate

To the keto-alcohol XXVII, (0.4 g) dissolved in pyridine (10 ml) toluene-p-sulphonyl chloride (0.5 g) was added and the reaction product kept at room temperature for 48 hr. The product was worked up to give the tosylate (0.52 g) which was reduced by an ethereal solution of LAH (0.77 g in 100 ml) under stirring for 10 hr at room temperature. Excess of LAH was decomposed by addition of alcohol and water and the product worked up in the usual way to furnish a mixture of epimeric alcohols, (XXVIII, 0.3 g) (TLC, 2 spots), with the following properties:

b.p. 125-130°/0.2 mm.; n_D^{25} 1.4640, $(\alpha)_D$ - 28° (c, 0.85).

Analysis

Found: C, 79.43; H, 13.38%

$C_{15}H_{30}O$ requires: C, 79.57; H, 13.36%

Chromic acid oxidation of the alcohol (XXVIII)

To the alcohol (0.215 g) in acetone (30 ml) Jones' chromic acid reagent was added dropwise till a brown colour persisted. After keeping for 1 hr. at room temperature it was worked up to give a product (0.155 g) purified by chromatography and distillation to give XXIX (GLC, 95%) with the following properties: b.p. 150-155° (bath)/0.6 mm.; n_D^{26} 1.4900, $(\alpha)_D$ - 33° (c, 6.6). IR spectrum, Fig. 3. It showed carbonyl absorption at 1736 cm^{-1}.

Analysis

Found: C, 80.41; H, 12.25%

$C_{15}H_{28}O$ requires: C, 80.29; H, 12.58%

$NaBH_4$ reduction of dehydrocostus lactone (III)

To dehydrocostus lactone (23 g) dissolved in methanol (70 ml) was added $NaBH_4$ (1 g) in instalments during 1 hr., and the reaction mixture kept at room temperature for 24 hr. After dilution with water containing HCl it was extracted with ether. The ether layer was washed with water and dried. Removal of ether gave the crude dihydro-dehydrocostus lactone (XXX) (22 g).

Controlled LAH reduction of XXX

The lactone (XXX, 22 g) in dry ether (200 ml) was reduced by gradual addition of an ethereal solution of LAH (75%; 1.6 g) under cooling (- 10°). The reaction mixture was stirred for 3 hr at - 10° and for another 3 hr at room temperature. It was then worked up to give a solid (21 g) m.p. 90-95° which was crystallised from pet. ether to give the pure lactol XXXI (9 g), m.p. 110-111°, $(\alpha)_D$ - 32° (c, 3.5).

Analysis

Found: C, 77.45; H, 9.77%

$C_{15}H_{22}O_2$ requires: C, 76.88; H, 9.46%

Huang-Minlon reduction of the lactol (XXXI) at 135°

The lactol (20 g) was dissolved in freshly distilled diethylene-glycol (200 ml) and hydrazine hydrate (25 ml) and KOH (20 g) were added. The mixture was heated at 135°-140° for 5 hr. in an atmosphere of nitrogen. It was diluted with water and extracted with ether to furnish a liquid (14 g) which was chromatographed on alumina (Gr. II, 420 g) and eluted as follows:

Fr.No.	Solvent	Vol. in ml	Wt. in g
1	pet. ether	500	2.5
2	pet.ether + Benzene (1:1)	1000	4.2
3	Benzene	500	3.0
4	Ether	500	0.7

Fr. 1 was purified by rechromatography over alumina and distillation to give the monol XXXVII, b.p. 120-125° (bath)/0.5 mm; n_D^{28} 1.5090; $(\alpha)_D$ +28.3° (c,4.4) **IR spectrum** (Fig. 4) showed bands at 3610, 2985, 1642, 1449, 1387, 1389, 1370, 1274, 1205, 1115.

1053, 960, 890 cm^{-1}.

Fractions 2 and 3 which contain essentially the monol (XXXVIII) were mixed and purified by distillation to give the pure XXXVIII (GLC, TLC) with the following properties:

b.p. 120-125°(bath)/0.3 mm., $n_D^{28.5}$ 1.5126; $(\alpha)_D$ + 32° (c, 2.18).

IR spectrum (Fig. 4) showed bands at: 3425, 1639, 1449, 1385, 1370, 1198, 1163, 1138, 1070, 1005, and 885 cm^{-1}.

Analysis

Found: C, 81.08; H, 10.98%

$C_{15}H_{24}O$ requires: C, 81.76; H, 10.98%

Partial hydrogenation of the monol XXXVIII

The monol (1.53 g) absorbed 158 ml hydrogen at NTP, corresponding to one double bond, on hydrogenation in alcohol medium using 5% Pd charcoal catalyst. The product was worked up in the usual manner and purified by distillation, to yield (XL), b.p. 140-150°(bath)/0.5 mm; n_D^{24} 1.5000, $(\alpha)_D$ + 39.3° (c, 1.9).

IR spectrum (Fig. 4) showed bands at: 3500, 3030, 1667, 1471, 1389, 1050, 1005, 920, 800 cm^{-1}.

Analysis

Found: C, 81.02; H, 11.70%

$C_{15}H_{26}O$ requires: C, 81.12; H, 11.79%

Chromic acid oxidation of the monol (XL)

The monol (5 g) was dissolved in acetone (50 ml) and Jones' reagent was added till a brown colour persisted. It was kept at room temperature for 2.5 hr. and worked up to give a liquid (4.8 g) which was separated into acidic and neutral parts by $NaHCO_3$ aq. The neutral part (4 g) was chromatographed on alumina (Gr. II, 200 g) and eluted with pet. ether, pet. ether-benzene, benzene and ether. The pet. ether-benzene fraction (0.6 g) was rechromatographed to give the ketone, XLII (0.13 g) eluted with pet. ether and purified further by distillation (70% by GLC), b.p. 120°(bath)/0.6 mm. In the UV it did not show any absorption in the region 220-340 mμ, indicating it to be a non-conjugated ketone.

IR spectrum (Fig. 4) of the ketone showed bands at: 2985, 1704, 1453, 1370, 1316, 1163, 1117, 1064, 1020, 1000, 975, 935, ~~895~~ and 885 cm^{-1}.

From the later fractions of the rechromatography, a crystalline oxido-ketone (XLIV) m.p. 95°, was isolated. It showed negative TNM test.

IR spectrum (~~Fig. ——~~) showed bands at: 2995, 1705, 1460, 1404, 1389, 1370, 1307, 1235, 1202, 1185, 1075, 1047, 1009, 952, 869, 818, 800 and 735 cm^{-1}.

Analysis

Found: C, 76.49; H, 10.44%

$C_{15}H_{24}O_2$ requires: C, 76.22; H, 10.24%

From the ether fractions of the rechromatography was isolated a keto-lactone possibly represented by XLVI and having, b.p. 140-145°(bath)/0.8 mm., $(\alpha)_D$ + 8.7 (C, 2.3). The IR spectrum showed bands at 1776 (γ-lactone), 1710 cm^{-1} (carbonyl group).

Dehydration of the monol (XL)

The monol (0.5 g) was mixed with alumina (1 g, made basic by pyridine) and heated at 180-200° for 5 hr in an atmosphere of nitrogen. The product was taken in pet. ether and passed through a column of alumina (Gr. I, 25 g) and eluted with pet. ether to give a mixture of hydrocarbons (XLII and XLVIII; 70:30 by GLC) (0.28 g). It was rechromatographed and a fraction (0.140 g) was obtained by eluting with pet. ether. (GLC, about 90%); it showed b.p. 110-115°(bath)/2 mm., $(\alpha)_D$ - 21.10° (c, 2.56) n_D^{28} 1.5113; UV, λ_{max} 242, ϵ_{max} 20,000.

Analysis

Found: C, 88.09; H, 11.43%

$C_{15}H_{24}$ requires: C, 88.16; H, 11.84%.

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PART IVA

MICHAEL ADDITION PRODUCTS FROM DEHYDROCOSTUS LACTONE AND COSTUNOLIDE

***

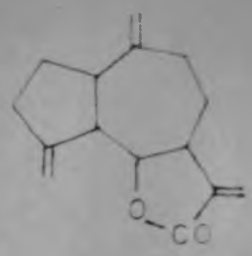
SUMMARY

Michael addition products have been prepared from dehydrocostus lactone and costunolide both containing an α-β-unsaturated γ-lactone grouping, by addition of primary and secondary amines. The products have been characterised by their elemental analysis and spectral data. In many cases, suitable crystalline derivatives have been prepared and characterised.

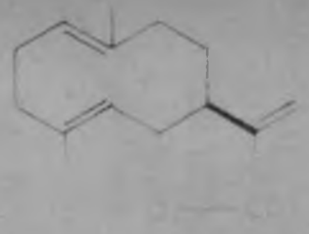
The wide range of physiological activity exhibited by lactones is well-known[1,2]. In particular, unsaturated lactones are able to inhibit selectively both tissue growth and seed germination and many of them possess antibiotic, cardiac, anthelmintic, hemorrhagic and insecticidal activity[1]. Recently their ability to act as carcinogens has also been demonstrated[3].

During the extraction of costus root oil by low temperature solvent extraction procedure[9], the two sesquiterpenic lactones viz. dehydrocostus lactone (I) and costunolide (II) were isolated in substantial quantities from the oil. As a part of our research programme, on the utilisation of lactonic constituents of the oil, we undertook the preparation of amine adducts from these lactones, with a view to evaluate their physiological activity.

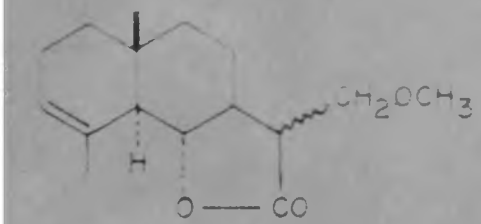
The addition of methanol, ammonia, and hydrocyanic acid to conjugated ketones and esters is well-known[4,5]. Such type of reactions involving 1:4 addition to the conjugated chromophore are classified under Michael addition reactions. The addition of methanol to conjugated α-methylene-γ-lactones, studied in our laboratory initiated with the isolation of 12-methoxy dihydrocostunolide[6] (XVI) from costus root oil. It was subsequently shown[6]



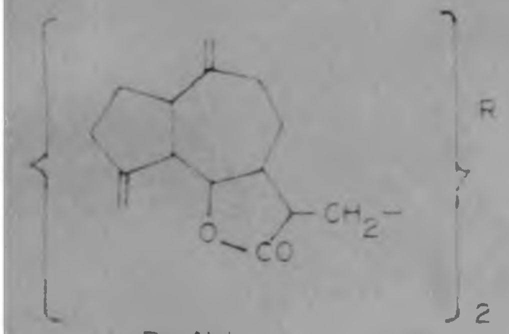
I



II

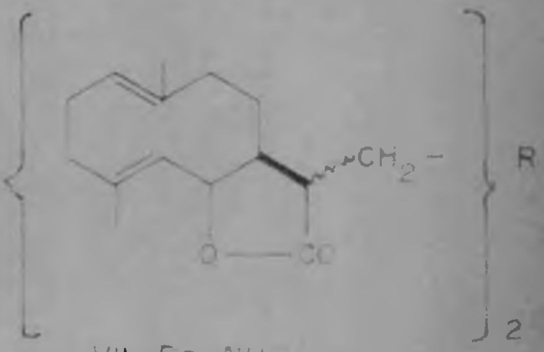


IV



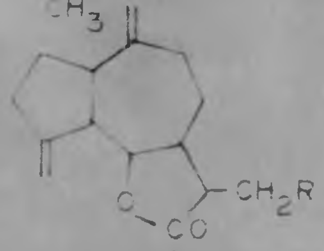
V, R=-NH-

VI, $R=-\underset{CH_3}{N}-$



VII, R=-NH-

VIII $R=-\underset{CH_3}{N}-$



IX $R=-OCH_3$

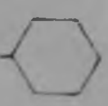
X $R=-N\begin{array}{l}CH_3\\CH_3\end{array}$

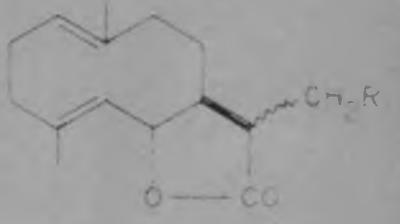
XI $R=-NH-CH_2-CH_3$

XII $R=-N\begin{array}{l}CH_2-CH_3\\CH_2-CH_3\end{array}$

XIII $R=-NH-CH_2-CH_2-CH_3$

XIV $R=-NH-CH(CH_3)_2$

XV R= - HN-



XVI $R=-OCH_3$

XVII $R=-N\begin{array}{l}CH_3\\CH_3\end{array}$

XVIII $R=-NH-CH-(CH_3)_2$

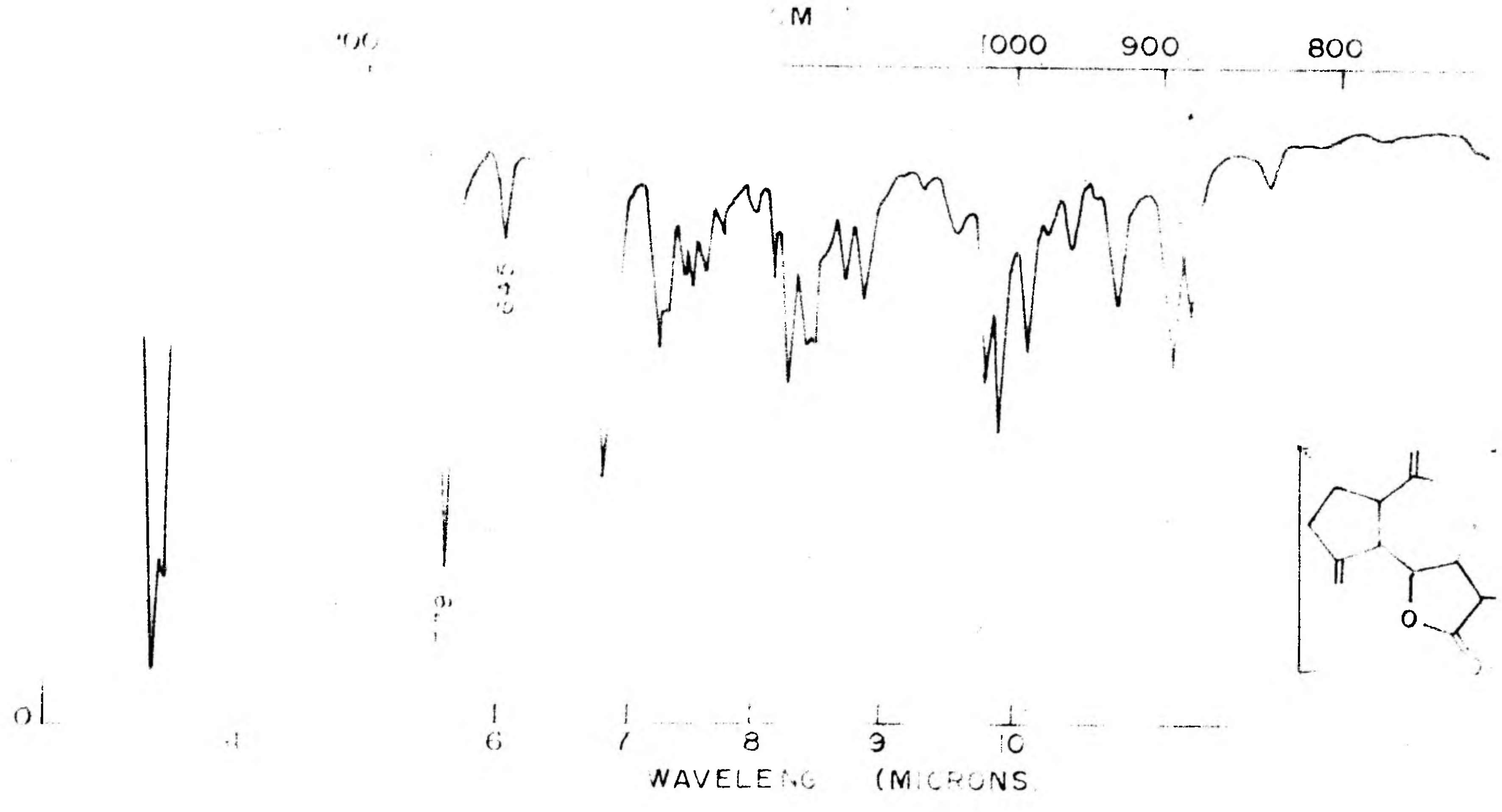
that (XVI) is not a primary constituent of the oil but an artefact produced by the action of methanol on costunolide (II) under mild basic conditions. The methoxy lactone (XVI) can be obtained in good yield from costunolide by the action of methanol and traces of alkali at lower temperatures. Subsequently the methoxy lactones IV[7] and IX[8] from dehydrocostus lactone (I) and α-cyclocostunolide (III) respectively were prepared and characterised.

With ammonia in alcoholic solution both (I) and (II) gave bis adducts (V)[9] and (VII)[10] respectively which were characterised through the picrates.

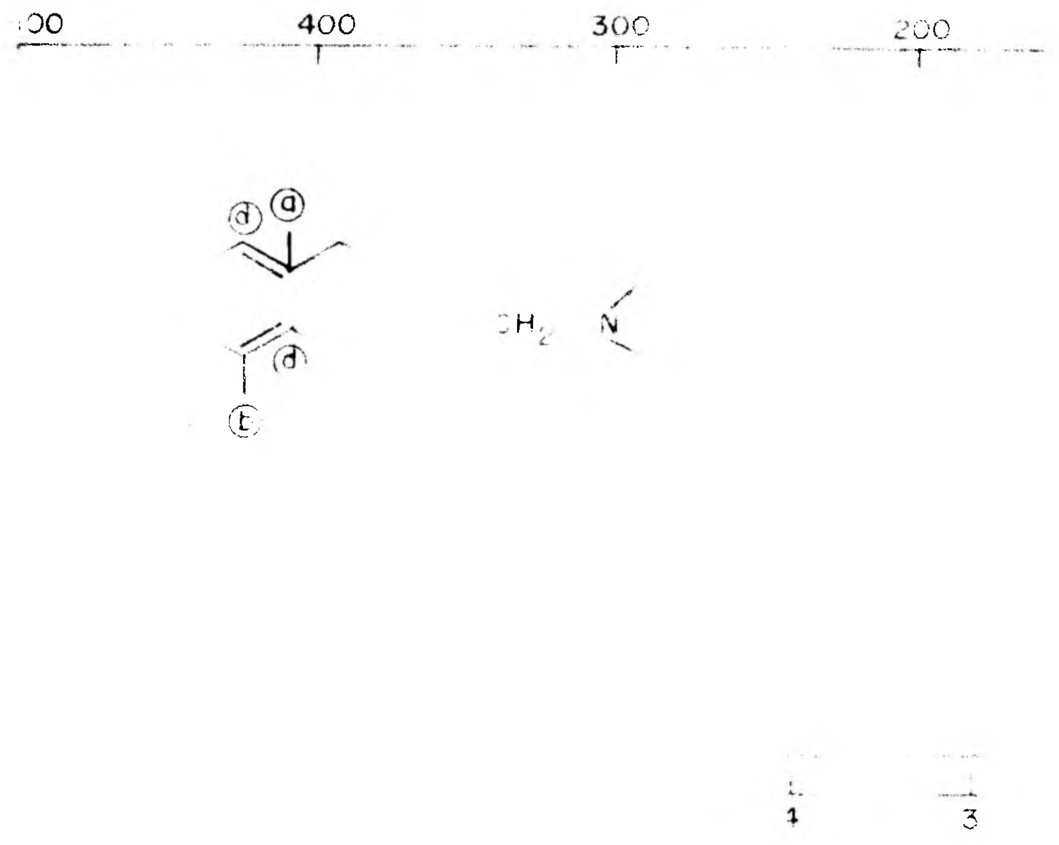
<u>Present work</u>

In this part of the thesis is described the preparation and characterisation of some of the adducts obtainable from dehydrocostus lactone and costunolide by the action of simple primary and secondary amines such as methyl amine, dimethyl amine etc.

The adducts have been prepared by treating an alcoholic solution of the lactone (1 mole) with the amine (3 moles) at 0° for 72 hr. The formation of the adduct was followed by IR spectra of the adducts. The peaks at 1400 - 1410[11] cm^{-1} and



IR SPECTRUM OF METHYL AMINE ADDUCT [illegible] DEHYDROCOSTUS LACTONE [illegible]OL)



2 DIMETHYLAMINE ADDUCT OF COSTUNOLIDE

also at 815^{12} cm^{-1} which are characteristic of conjugated α-methylene γ-lactones disappear in the IR spectra of adducts.

With the exception of methylamine which furnished a bis adduct (VI), all other primary amines namely ethylamine, n-propylamine, isopropylamine and cyclohexylamine gave mono-adducts (XI, XIII, XIV and XV respectively) on reacting with dehydrocostus lactone. Similarly in the case of costunolide methylamine furnished a bis adduct (VIII) while isopropylamine furnished a mono adduct (XVIII).

Some of these adducts (VI, X, XIV, XVI, XVII and XVIII) are crystalline solids while the others are liquids. All of them have been characterised by their elemental analysis and by IR and NMR spectra. In certain cases suitable crystalline derivatives have also been prepared and characterised.

The evaluation of biological activity of these compounds is in progress.

EXPERIMENTAL

A general procedure for the preparation of the adducts

The lactone (1 mole) is dissolved in alcohol and the amine (3 moles) is added. The reaction mixture is allowed to stand at 0° for 72 hr. after which it is diluted with water and extracted with ether. The product obtained after evaporation of ether is factionally distilled to remove excess of amine. The adduct is purified by dissolving in dilute HCl (5%) and regenerating it from the solution. The yields of the adduct is 80-85% of the theoretical.

The properties and elemental analysis of the adducts are summarised in the following table.

Adducts of Dehydrocostus Lactone

Adduct	m.p.	$(\alpha)_D$	Analysis N*		Derivative	Analysis	
			Found %	Requires %		Found %	Requires %
VI	144-146°	+ 39.5°	3.03	2.85	-	-	-
X	50-52°	+ 43°	4.92	5.09	Picrate 155-56°	N, 10.63	N, 11.11
XI	(Liquid)	+ 4°	4.79	5.09	Picrate 152-53°	N, 11.13	N, 11.11
XII	(Liquid)	+ 42.8°	4.80	4.62	Methiodide 189-90°	N, 3.04	N, 3.14
XIII	(Liquid)	+ 48°	4.97	4.84	Hydrochloride 195-96°	Cl, 11.31	Cl, 10.94
XIV	51-52°	+ 3.5°	5.2	4.84	-	-	-
XV	(Liquid)	- 1.67°	4.39	4.25	Hydrochloride 224-25°	Cl, 9.65	Cl, 9.94
				Adducts of Costunolide			
VIII ~~XVI~~	118-19°	+ 158°	2.71	2.83	-	-	-
XVII	109-10°	+ 114°	4.73	5.05	Picrate 173-4°	N, 10.91	N, 11.06
XVIII	68-70°	+ 83.8°	5.11	4.81	-	-	-

*The samples were analysed for Nitrogen after getting satisfactory analyses for C and H

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PART IVB

STEREOCHEMISTRY OF 12-METHOXY DIHYDROCOSTUNOLIDE AT THE C_{11} POSITION

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ABSTRACT

The methyl-ether (XVII) obtainable from solid dihydrocostunolide (II) on ozonolysis gave S (+) α-methyl-glutaric acid (XXI, R = H), a keto-carboxylic acid (XXIII, R = H) and a partially ozonised product (XXIV, R = H). The methyl ester (XXIII, R = CH_3) of the keto-carboxylic acid failed to furnish a solid semicarbazone indicating it to be different from the one XXII, R = CH_3 (semicarbazone m.p. 81-82°) obtained previously by ozonolysis of the methyl-ether (XX) prepared from 12-methoxy dihydrocostunolide (III). Hence the stereochemistry of the two methyl ethers (XVII and XX) at C_{11} is different and not the same as concluded by previous workers. This is also supported by the NMR study of the two partially ozonised products (XXIV, R = CH_3 and XXV, R = CH_3).

These findings indicate that the methoxy methylene group in 12-methoxy dihydrocostunolide is α-oriented as in (III).

During the investigations in our laboratory, on the chemical composition of costus root oil obtained by the low temperature solvent extraction procedure, a crystalline methoxy lactone, $C_{16}H_{24}O_3$, was isolated[1]. On the basis of degradative studies and comparison with analogous compounds it was shown[1] to be 12-methoxydihydrocostunolide represented by the stereostructure IIIa. It was also shown that the methoxy lactone can be obtained from costunolide (I) by the action of methanol in the presence of a trace of base. Since the absolute configuration of costunolide has been established[2,2a] as in (I), it follows that the stereochemistry of 12-methoxydihydrocostunolide at the centres C_6 and C_7 should also be the same as in costunolide. There was, however, no experimental proof regarding the stereochemistry of the methoxy-methylene group at the C_{11} position. It was assumed to be β-oriented (IIIa) in analogy with solid dihydrocostunolide in which the methyl group at the C_{11} position was taken, at that time, to be β-oriented[3] (IIa). Such an assignment of the stereochemistry for dihydrocostunolide at C_{11} was based on the then accepted stereochemistry of (-) santonin at C_{11} (IVa), since

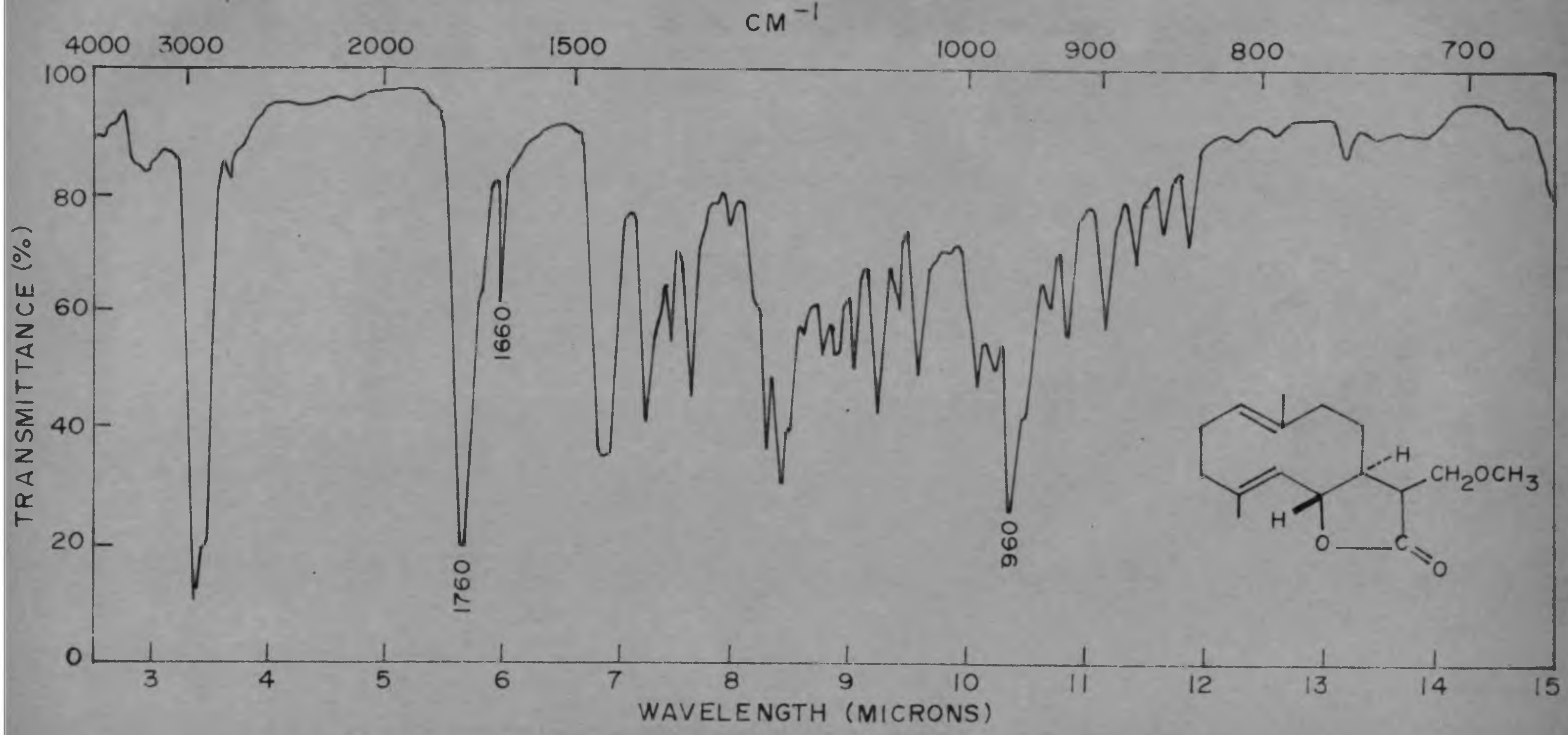
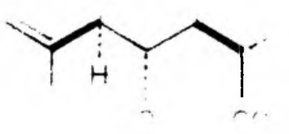


FIG.1 - IR SPECTRUM OF-12-METHOXY DIHYDROCOSTUNOLIDE (IN NUJOL)

both santonin and dihydrocostunolide could be converted into santanolide 'c'.

The recent crystallographic study[4] on (-) santonin, however, indicated that the methyl group at C_{11} is in fact α-oriented (as in IV) and not β (as in IVa) as was assumed previously. Consequently the C_{11} methyl group in dihydrocostunolide is also α-oriented and hence, in view of these findings, the methoxy methylene group at C_{11} in 12-methoxy-dihydrocostunolide should also be α-oriented (III). Such a view is supported by the close similarity between dihydrocostunolide (II) and 12-methoxy-dihydrocostunolide in their spectral and optical rotation data.

During the course of study, in our laboratory, on the stereospecific pyrolytic rearrangement[5,6] and the acid catalysed trans-annular cyclisation[7] of dihydrocostunolide (II) and 12-methoxydihydrocostunolide[8] two series of lactones were prepared viz. (i) derived from (II) and hence which contain an α-oriented-methyl group at C_{11} (ii) derived from 12-methoxy dihydrocostunolide in which the orientation of the methoxy-methylene group at C_{11} is assumed to be α-oriented. The stereochemistry at C_5, C_6, C_7 and C_{10}, in the two



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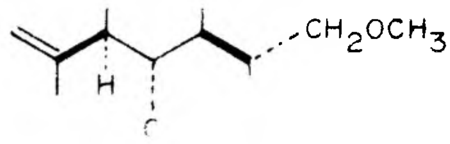
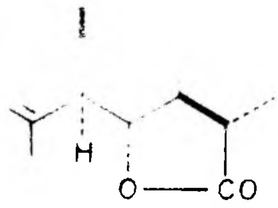
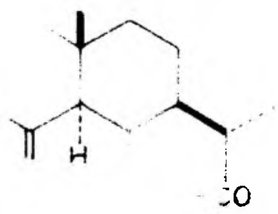
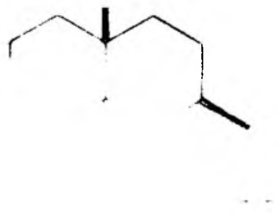


X

XI







XIII

series of lactones is identical[5-8], the only difference, if any, should be at C_{11}.

A comparison (Table 1) of the rotation contribution of the various mono- and bicyclic lactones obtained from II viz V, VI, VII, VIII and IX with those of the corresponding compounds prepared from 12-methoxy dihydrocostunolide viz. X, XI, XII XIII and XIV also suggests that the methoxy-methylene group in 12-methoxy dihydrocostunolide and in related compounds (X, XI, XII, XIII and XIV) should be α-oriented as shown in the formulae.

With a view to obtain some convincing chemical evidence for the α-orientation of the methoxy-methylene group at C_{11} in 12-methoxy-dihydrocostunolide certain reactions were carried[11] out in our laboratory. They are as follows.

Dihydrocostunolide (II) was subjected to metal-amine (Li/liq. NH_3) reduction to furnish the acid (XV, R = H), the structure and stereochemistry of which has been already established[9]. The acid was converted into its methyl-ester (XV, R = CH_3) which on LAH reduction furnished the known alcohol[9] XVI. The alcohol (XVI) was methylated at 0° by diazomethane[10] in presence

Table No.1

Lactones from dihydrocostunolide	$(\alpha)_D$	M_D	Lactones from 12-methoxy dihydrocostunolide	$(\alpha)_D$	M_D
1. Dihydrocostunolide(II)	$+113^{\circ}$	$+264.2^{\circ}$	12-methoxydihydrocostunolide(III)	$+115^{\circ}$	$+303.6^{\circ}$
2. Saussurea lactone (V)	$+ 66^{\circ}$	$+154.5^{\circ}$	12-methoxy saussurea lactone (X)	$+ 78^{\circ}$	$+205.3^{\circ}$
3. Tetrahydro saussurea lactone (VI)	$+ 42^{\circ}$	$+ 99.58^{\circ}$	Tetrahydro-12-methoxy saussurea lactone (XI)	$+ 39^{\circ}$	$+117.9^{\circ}$
4. α-Cyclodihydrocostunolide (VII)	$+ 84^{\circ}$	$+195.6^{\circ}$	α-Cyclo 12-methoxy dihydrocostunolide (XII)	$+ 83^{\circ}$	$+218.4^{\circ}$
5. β-Cyclodihydrocostunolide (VIII)	$+140^{\circ}$	$+327.1^{\circ}$	β-Cyclo-12-methoxy dihydrocostunolide (XIII)	$+146^{\circ}$	$+385.5^{\circ}$
6. Santanolide 'c' (IX)	$+ 56^{\circ}$	$+132.1^{\circ}$	12-Methoxy santanolide 'c' (XIV)	$+ 69^{\circ}$	$+182.5^{\circ}$

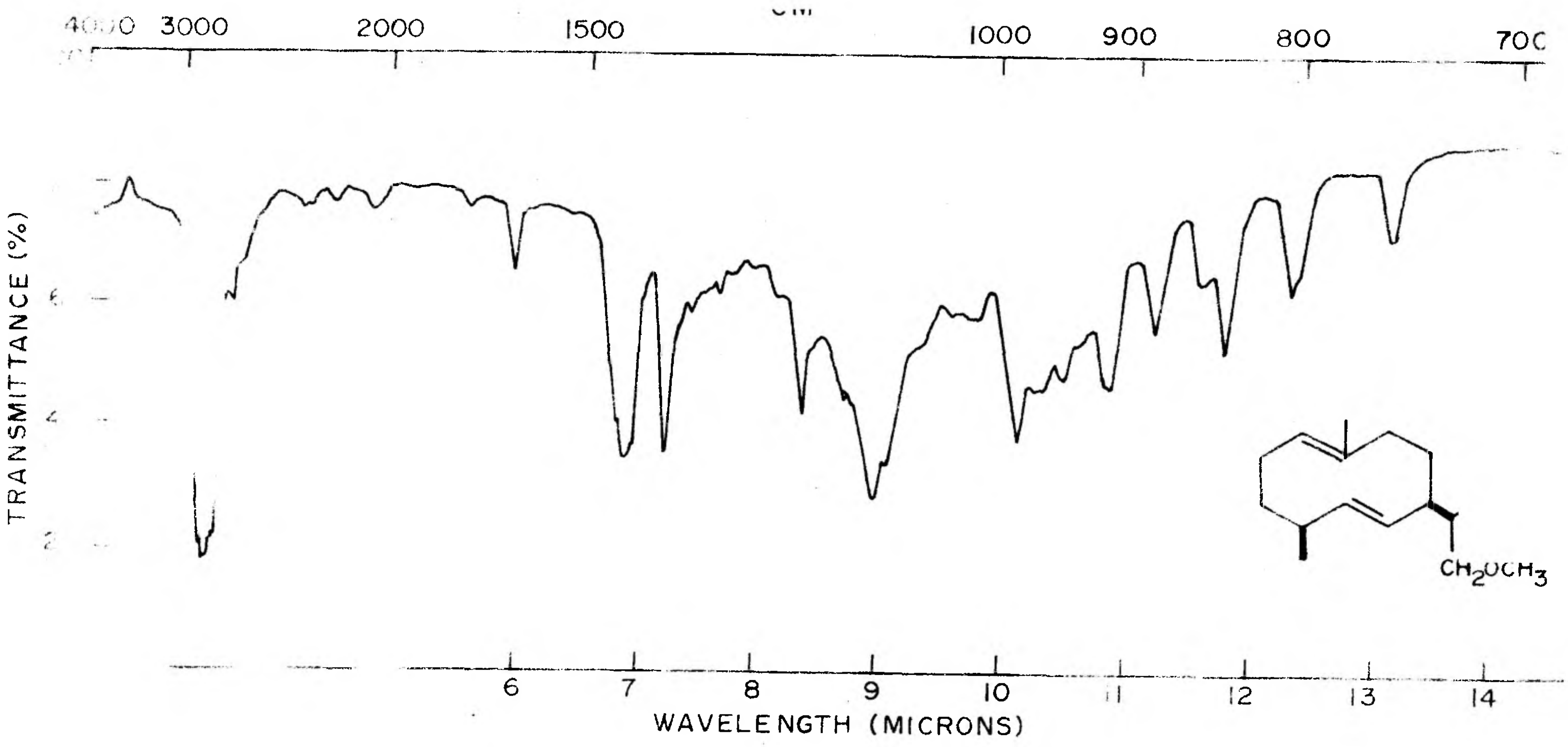


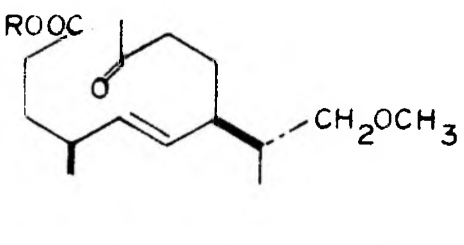
FIG 2 R SPECT M METHYL ETHER FROM DIHYDROCOSTUNOLIDE (LIQ FILM)

of traces of BF_3 etherate to give the ether (XVII) with $(\alpha)_D$ - 133°. Since methylation by this procedure takes place with retention of configuration[10], the original stereochemistry of the alcohol (XVI) at C_{11} is also retained in the methyl ether (XVII).

In another series of reactions[11] 12-methoxydihydrocostunolide was subjected to metal amine ($Li/Liq.NH_3$) reduction when the methoxy acid (XVIII, R = H) was obtained as a major product along with two other demethylated products [presumably epimeric mixture of acids (XV, R = H) at C_{11}] as minor constituents. The acid was converted into its methyl ester (XVIII, R = $COOCH_3$) which furnished the alcohol (XIX) by LAH reduction. The latter gave the methyl ether XX on LAH reduction of its tosylate. The methyl ether showed $[\alpha)_D$ - 133° and its IR and NMR spectra were identical with those of XVII; GLC/TLC analysis also showed that the two compounds were identical.

The methyl ether XX on ozonolysis furnished S (+) α-methyl glutaric acid (XXI, R = H) and the ketocarboxylic acid (XXII, R = H). The ketocarboxylic acid methyl ester (XXII, R = CH_3) gave a semicarbazone m.p. 81-82°.

These findings indicated that the two methoxy



XXV R=H, R=CH$_3$

ethers (XVII and XX) have the same stereochemistry at C_4, C_7 and C_{11}. Hence it was concluded[11] that the methoxy-methylene group at C_{11} in 12-methoxy dihydrocostunolide is β-oriented.

Present work

These conclusions indicating that the methoxy-methylene group in 12-methoxydihydrocostunolide is β-oriented were, however, contradictory to the assignment arrived at from the comparison of the rotation contributions of a number of mono- and bicyclic lactones as already shown in table 1. In addition, the proof given for the β-orientation by the previous workers[11] was based entirely on the comparison of properties of two liquid materials. The same optical rotation value shown by the two ethers (XVII and XX) is no doubt an important criterian for concluding their identity, but it is quite possible that the two ethers which are likely to be epimeric only at C_{11} may not differ much in their rotation, in case the contribution due to the C_{11} centre is not substantial. A comparison of the optical rotations of costunolide (I) $(\alpha)_D$ + 128° (with no

C_{11} asymmetric centre) and dihydrocostunolide (II) $(\alpha)_D + 115^\circ$ shows that the rotation contribution due to C_{11} centre is not significant. Similarly the ester (XV) $(\alpha)_D - 116^\circ$ and the hydrocarbon (XVa, without C_{11} asymmetric centre) $(\alpha)_D - 103^\circ$ also do not differ much.

It was therefore felt desirable to furnish further evidence to show the identity of the two ethers or otherwise, by other methods.

We initially tried to see if any suitable solid derivative could be obtained from both the ethers. Since the ether XX from methoxy lactone is reported, by previous workers, to give on ozonolysis S (+) α-methyl-glutaric acid and a keto-carboxylic acid (XXII, R = H). The methyl ester (XXII, R = CH_3) of which, gives a solid semicarbazone m.p. 81-82°, ~~that~~ this latter was considered suitable for comparison purposes.

The ether XVII obtained from solid dihydrocostunolide was subjected to ozonolysis to give S (+) α-methyl glutaric acid and a keto-carboxylic acid (XXIII, R = H; $C_{10}H_{18}O_4$) characterised as the methyl ester. The keto-ester (XXIII, R = CH_3) which showed $(\alpha)_D - 2^\circ$, however, failed to give a solid semicarbazone. This indicates that it is different from the one (XXII, R = CH_3) obtained from 12-methoxydihydrocostunolide which showed a rotation of + 6.8°. The difference in optical rotation value is not substantial enough so as to lead to any definite conclusion.

The ozonolysis of XVII also furnished a partially ozonised keto-acid (XXIV, R = H) characterised through its methyl ester (XXIV R = CH_3; $C_{17}H_{30}O_4$; $(\alpha)_D$ + 18°). As expected, the trisubstituted double bond in the ether (XVII) is only ozonised, leaving the disubstituted double bond intact. The IR spectrum of XXIV, R = CH_3, shows a strong band at 980 cm^{-1} due to trans-disubstituted double bond. Its NMR spectrum (Fig. 3) showed signals at 8.96, 9.07, 9.17 τ (6 H) due to methyl groups at C_4 and C_{11}; though for the C_4 methyl group a doublet is observed at 8.96, 9.07 τ the C_{11} methyl doublet was not clearly discernable. It ~~was~~ also showed signals at 7.99 τ (3 H) due to the methyl-ketone group at C_9, at 6,79, 6.84, 6.94 τ (5 H) due to $-CH_2OCH_3$ group at C_{11}, at 6.4 τ (3 H) due to ester methyl group and at 4.8, 4.85, 4.93 τ (2 H) due to protons on disubstituted double bond. The NMR spectrum is in agreement with the structure XXIV. The compound

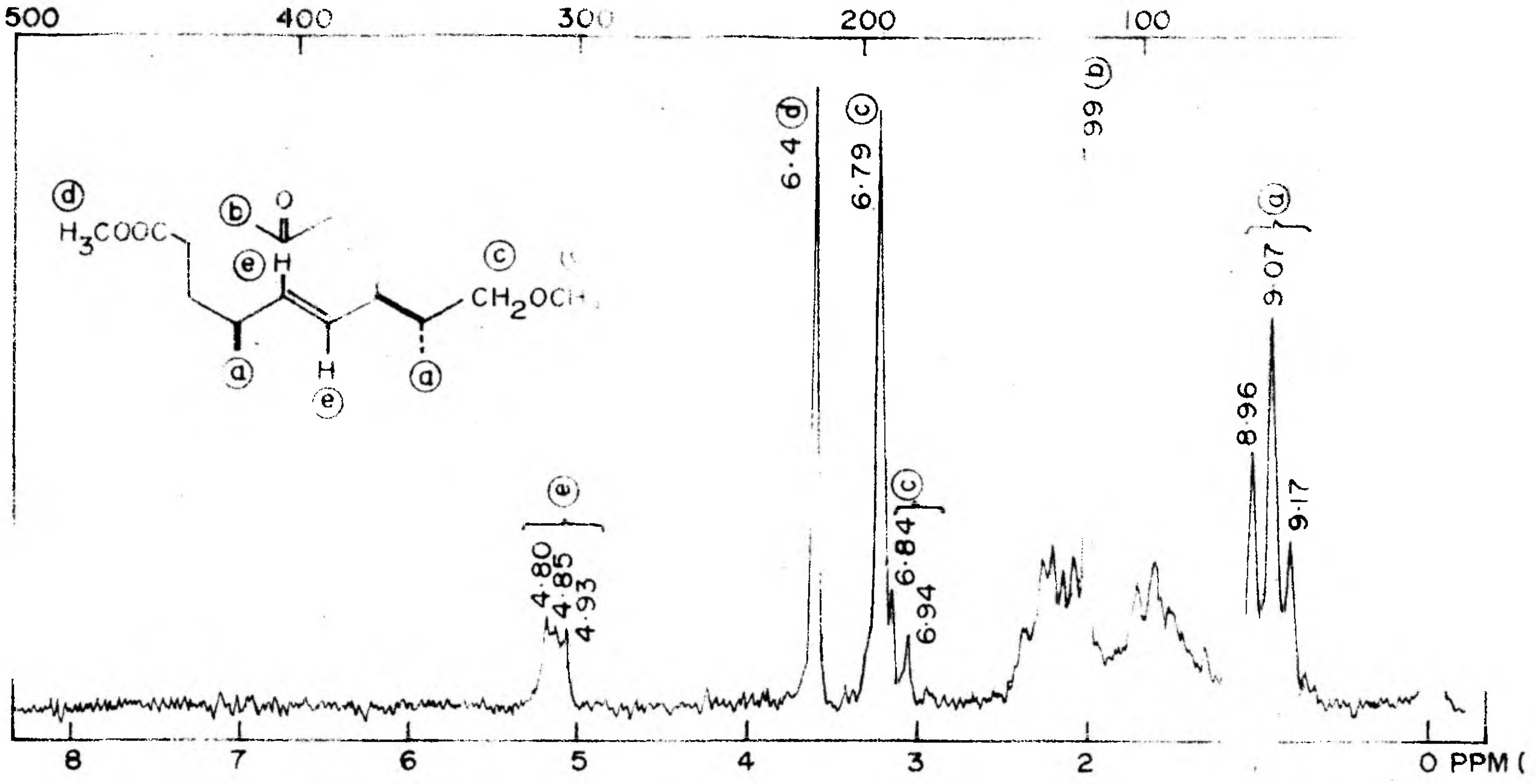


FIG. 3. NMR SPECTRUM OF PARTIALLY OZONISED PRODUCT FROM THE METHYL ETHER XVII

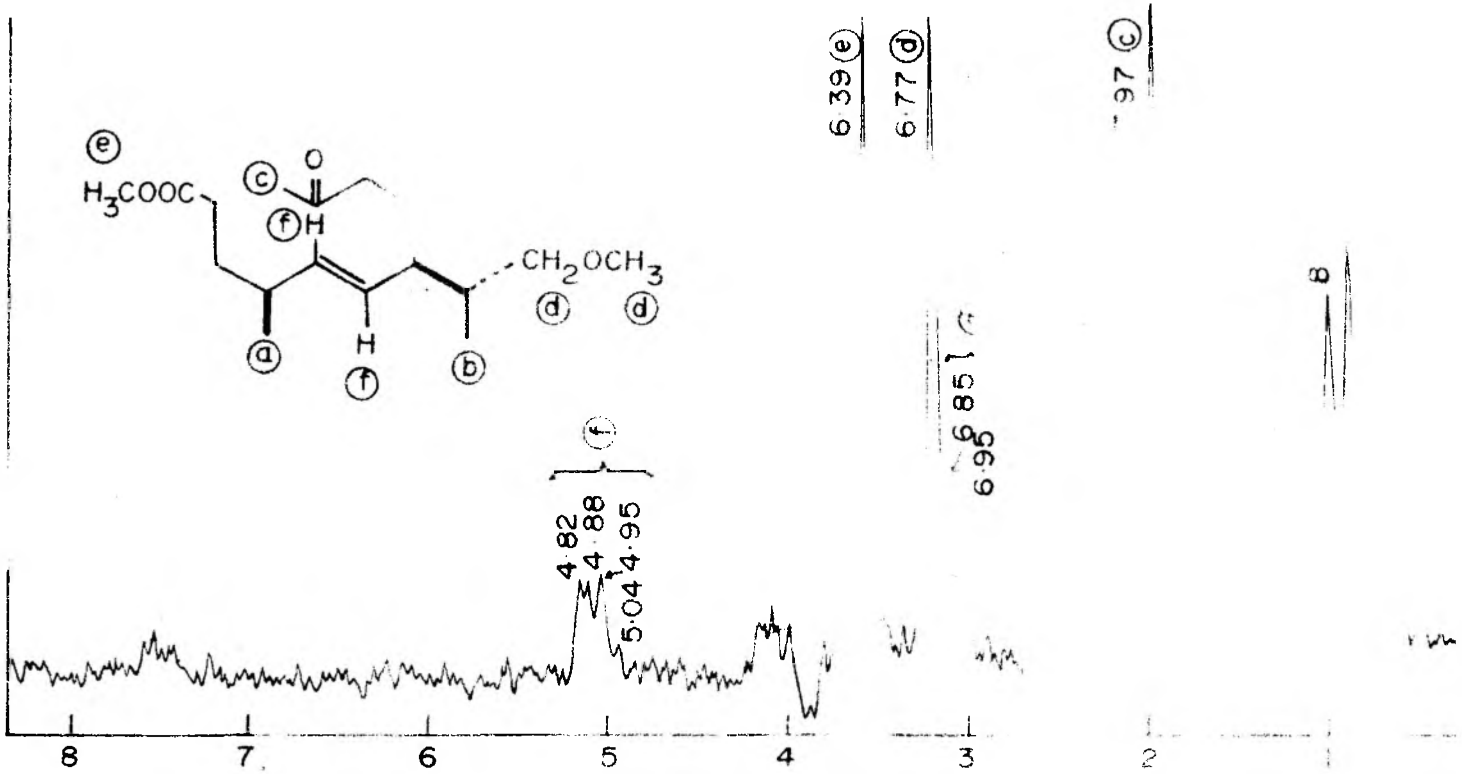


FIG. 4. NMR SPECTRUM OF PARTIALLY OZONISED PRODUCT FROM THE METHYL ETHER XX

XXIV failed to give any solid semicarbazone or 2:4 DNP derivative.

A similar partially ozonised product was also obtained during the ozonolysis of the ether XX prepared from the methoxy lactone, whose methyl ester (XXV, R = CH_3; $C_{17}H_{30}O_4$) showed $(\alpha)_D$ + 10°. Its IR spectrum showed a strong band at 980 cm^{-1} due to trans disubstituted double bond. The IR spectra of the two compounds (XXIV and XXV) were mostly identical. The NMR (Fig. 4) spectrum of XXV showed signals at 8.96, 9.06 τ (3 H) due to C_4- CH_3 and at 9.15, 9.28 τ (3 H) due to C_{11}- CH_3; the C_4 and C_{11} CH_3 are properly resolved, in this case, each showing a separate doublet.

This is in contrast with the NMR spectrum of XXIV where the main signal due to C_{11}-CH_3 is probably merging with the splitting signal of the C_4-CH_3. In addition the NMR spectrum of XXV showed signals at 7.98 τ (3 H) due to methyl-ketone group at C_9, at 6.77, 6.85, 6.95 τ (5 H) due to $-CH_2-OCH_3$ group at C_{11}, at 6.39 due to ester methyl group and at 4.82, 4.88, 4.95 and 5.04 (2 H) due to protons on disubstituted double bond. In the NMR spectrum of XXIV three distinct signals were observed for the $-CH_2-O-CH_3$ group whereas in case of XXV though the signal at 6,77 τ was clearly discernible as mentioned above the other two signals were not properly resolved.

These observations indicated that the two partially ozonised products are different and this is possible only if they differ in their stereochemistry at C_{11} as the stereochemistry at C_4 in both is the same.

Hence the two ethers (XVII) and (XX) appear to be different though they do not differ much in their optical rotation. This means that the $-CH_2.OCH_3$ group in the methoxy lactone is α-oriented as arrived at by consideration of rotation contribution. However, a more rigorous proof showing non-identity of the two ethers preferably through mixed m.p. determination of solid derivatives obtainable from both is essential for making a final assignment of the stereochemistry at the centre C_{11} in 12-methoxydihydrocostunolide.

EXPERIMENTAL

Metalamine (Li/Liq.NH$_3$) reduction of dihydrocostunolide (II)

Liquid ammonia (500 ml) was drawn in a 3-necked flask fitted with a mercury sealed mechanical stirrer, a dropping funnel and a condenser. Lithium pieces (2 g) were added during a period of 10 minutes with stirring. Formation of Li-NH$_3$ complex was indicated by development of blue colour. Dihydrocostunolide (11 g) in dry ether (200 ml) was added slowly through the dropping funnel and the reaction mixture stirred for 3 hr. Excess of ammonia was allowed to evaporate and excess of Li was decomposed by addition of alcohol. It was then diluted with water, acidified with dilute HCl (5%) and extracted with ether. Ether layer was washed with water and extracted with Na$_2$CO$_3$ aq. (10%). The Na$_2$CO$_3$ aq. layer was acidified with dil HCl (5%), and extracted with ether. Ether layer after washing with water was dried (Na$_2$SO$_4$). The acid (9.2 g) obtained on evaporation of ether was esterified with diazomethane in usual manner to furnish the ester (XV, R = CH$_3$; 9.3 g). It was purified by chromatography and distillation under reduced pressure. It indicated the following properties:

b.p. 115-120°(bath)/0.1 mm., n_D^{28} 1.4892;
$(\alpha)_D$ - 91.8° (c, 2.3).

The IR spectrum of the compound was identical with that of the authentic sample.

Analysis

Found: C, 76.39; H, 10.52%
$C_{16}H_{26}O_2$ requires: C, 76.75; H, 10.47%

LAH reduction of the ester (XV, R = CH_3)

The ester (9 g) in dry ether (100 ml) was added slowly with stirring to an ice-cold suspension of LAH (1.5 g) in dry ether (100 ml). The reaction mixture was stirred for 15 hr. at room temperature and worked up in the usual way to furnish the alcohol (XVI, 7.9 g) with the following properties:

b.p. 120-130°(bath)/0.1 mm; $(\alpha)_D$ - 115° (c, 2.8)

Analysis

Found: C, 81.29; H, 11.82%
$C_{15}H_{26}O$ requires: C, 81.02; H, 11.79%

Methylation of the alcohol (XVI)

To an ice-cold solution of the alcohol (6 g) in dry ether (100 ml) containing freshly distilled BF_3-etherate (0.2 ml), an ethereal solution of diazomethane was added slowly with shaking ~~till~~

till a yellow colour persisted. The reaction mixture was allowed to stand at room temperature for half an hour, washed with Na_2CO_3 aq. (5%), water and dried (Na_2SO_4). The product (5.9 g) obtained after evaporation of ether was chromatographed on alumina (Gr. I, 180 g) and eluted with pet. ether to furnish the methyl ether XVII, (4.1 g; GLC, TLC pure). It showed the following properties:

b.p. 115-120°(bath)/0.5 mm; n_D^{25} 1.4912, $(\alpha)_D$ - 132.8° (c, 2.7). IR spectrum is shown in Fig. 2.

Analysis

Found: C, 81.39; H, 12.05%

$C_{16}H_{28}O$ requires: C, 81.29; H, 11.94%

Ozonolysis of the methyl-ether (XVII)

The ether (4 g) was dissolved in chloroform (50 ml) and the solution cooled to - 10° by ice-salt mixture. A stream of ozonised O_2 was passed through the solution till the absorption was complete. Chloroform was removed at 40° under suction and the ozonide was decomposed by heating on a water-bath with water (20 ml) and H_2O_2 (30%, 10 ml). It was separated into acidic and neutral parts by Na_2CO_3. The acidic part (1.9 g) was esterified with diazomethane in the usual way and the resulting mixture of esters was fractionated in the following way.

<u>Fraction 1</u> (0.3 g), b.p. 95-100°(bath)/5~~.5~~ mm

<u>Fraction 2</u> (0.51 g), b.p. 120-125°(bath)/0.5 mm

<u>Fraction 3</u> (0.67 g), b.p. 160-170°(bath)/0.1 mm

Fraction 1 showed the following properties: n_D^{25} 1.4319; $(\alpha)_D$ + 19.2° (c, 0.91).

<u>Analysis</u>

Found: C, 54.85; H, 8.5%

$C_8H_{14}O_4$ requires: C, 55.16; H, 8.10%

It was identified as dimethyl ester of α-methyl glutaric acid (XXI, R = CH_3).

Fraction 2 (GLC 90%) was chromatographed on alumina (Gr. II, 15 g) and eluted with pet.ether and benzene. The benzene fraction gave the keto-ester (XXIII, R = CH_3; 0.38 g) (GLC, single peak), n_D^{25} 1.4421, $(\alpha)_D$ - 2° (c, 4.4).

<u>Analysis</u>

Found: C, 61.46; H, 9.72%

$C_{11}H_{20}O_4$ requires:C, 61.09; H, 9.32%

It failed to give a solid semicarbazone and 2:4 DNP derivative.

Fraction 3 (GLC, single peak) was identified as XXIV by IR and NMR (Fig. 3) spectra. It showed the following properties:

n_D^{30} 1.4590; $(\alpha)_D$ + 18.11° (c, 2.8).

Analysis

Found: C, 68.44; H, 10.07%

$C_{17}H_{30}O_4$ requires: C, 68.44; H, 10.07%.

It did not give a solid semicarbazone with semicarbazide hydrochloride and Na-acetate or pyridine.

Li/Liq.ammonia reduction of 12-methoxy-dihydrocostunolide (III)

The methoxy lactone III, (m.p. 125-126°; $(\alpha)_D$ + 115°, 12 g) in dry ether (400 ml) was reduced by Li (2 g) in liquid ammonia (800 ml) as per procedure described previously. The reaction product was worked up as usual to furnish a mixture of acids (10.2 g) which was esterified with diazomethane. The resulting mixture of esters (10.25 g) was chromatographed on alumina (Gr. II, 300 g) and eluted with pet. ether, pet.ether + benzene (3:1) and benzene. The benzene fraction on evaporation furnished the methoxy ester XVIII (7.1 g; GLC pure). It showed the following properties:

b.p. 140-145°(bath)/0.1 mm; n_D^{25} 1.4916

$(\alpha)_D$ - 99.8° (c, 2.93).

Analysis

Found: C, 72.68; H, 9.82%

$C_{17}H_{28}O_3$ requires: C, 72.83; H, 10.06%.

LAH reduction of the methoxy ester (XVIII, R = CH_3)

The methoxy ester (7 g) in dry ether (150 ml) was reduced by a solution of LAH (1.5 g in 100 ml of ether). The reaction mixture after stirring for 15 hr. at 30° was worked up in the usual way to furnish the alcohol (XIX, 6.6 g), b.p. 140-145°(bath)/0.08 mm.; n_D^{25} 1.5047; $(\alpha)_D$ - 105° (c, 2.1).

Analysis

Found: C, 75.98; H, 11.32%

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

Tosylation of the alcohol (XIX) and LAH reduction of the tosylate

The alcohol (6.5 g) dissolved in freshly distilled dry pyridine (50 ml) was treated with toluene-p-sulphonylchloride (6.5 g). The reaction mixture was kept at room temperature for 48 hr. and worked up to furnish the tosylate (8.3 g). The crude tosylate (8.3 g) in dry ether (100 ml) was reduced by LAH (2 g, in 100 ml of dry ether) to furnish the ether (XX; 4.8 g). The ether (XX) was purified by passing through alumina (Gr.I, 150 g) and eluting with pet. ether. It showed the following properties:

b.p. 120-125°(bath)/0.4 mm; n_D^{24} 1.4911;
$(\alpha)_D$ - 133.4° (c, 2.4).

Analysis

Found: C, 81.19; H, 12.00%

$C_{16}H_{28}O$ requires: C, 81.29; H, 11.94%.

Ozonolysis of the ether (XX)

The ether XX (4 g) was ozonised as described previously. The acidic fraction (1.73 g) was esterified with diazomethane and the mixture of esters was fractionated as follows:

Fraction 1 (0.298 g) b.p. 95-100°(bath)/6 mm

Fraction 2 (0.415 g) b.p. 110-115°(bath)/0.5 mm

Fraction 3 (0.520 g) b.p. 160-170°/0.1 mm.

Fr. 1 showed the following properties:

n_D^{23} 1.4321; $(\alpha)_D$ + 19.2° (c, 0.75).

Analysis

Found: C, 54.9; H, 8.50%

$C_8H_{14}O_4$ requires: C, 55.16; H, 8.10%.

It was identified as dimethyl ester of α-methyl glutaric acid (XXI R = CH_3).

Fraction 2 was identified as (XXII, R = CH_3) by m.p. and mixed m.p. (80-81°) of its semicarbazone with that of the authentic sample.

Fr. 3 (GLC, single peak) showed the following properties: n_D^{29} 1.4595; $(\alpha)_D$ + 10.66° (c, 1.96).

Analysis

Found: C, 67.49; H, 10.66%

$C_{17}H_{30}O_4$ requires: C, 67.98; H, 10.13%

Its IR and NMR spectra (Fig. 4) indicated it to be (XXV, R = CH_3)

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