TERPENOIDS

A

THESIS

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BY

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C O N T E N T S

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INTRODUCTION

In the thesis some of the results of our experiments on terpenoids and allied products have been presented. It consists essentially of two parts.

(A) Elucidation of the chemistry of Indian 'Black Dammar Resin', obtained from the tree Canarium strictum Roxb.

(B) The stereochemistry of elemol and related compounds.

For the sake of brevity any general introduction on terpenoids has been avoided. Broad survey on the subject has been made from time to time through many important publications. Some of these are mentioned below.

Apart from the classical volumes 'The Terpenes' by Sir J.L. Simonsen published by the University Press at Cambridge, there are elaborate reviews by D.H.R. Barton in 'Chemistry of Carbon Compounds'[1] and 'Progress in Organic Chemistry'.[2] There are also the books by Paul de Mayo, 'Mono and Sesquiterpenoids'[3] and 'The Higher Terpenoids'.[4] Mention should be made of the monographs published in Zechmeister's 'Progress in the Chemistry of Organic Natural Products'[5-9] and also many other good reviews[10-12] which have appeared recently.

Literature survey on essential oils will be incomplete without the mention of the famous volumes - "The Essential Oils" by E. Guenther.

Indian Black Dammar Resin

The Black dammar tree, Canarium strictum Roxb., is a large handsome, lofty, deciduous tree native to South India. It is found abundantly in the dense forests of the West Coast from Konkan to Travancore and Cochin. It grows upto an altitude of 8000 ft.[13] The timber is soft and of inferior quality, but the black opaque nodular lumps* of resin fetches a good price because of its many uses, industrial and medicinal. The resin begins to exude from the tree during the months of April to November[14] when it is two years old and continues to do so for further ten years. A healthy tree yields about 5 to 7 kg of resin per year.[15] The Kerala State and the Madras State produce about 70,000 kg of resin annually. Because of the high price it fetches in the local market it is not exported, nor it is used to any large extent for any of the purposes for which it is admittedly well suited. The main uses of Black dammar

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* Several resins from different sources are known in Europe by the name 'dammar' but they are transparent, colourless or faint brown in colour.

resin are in the manufacture of varnishes, bottling wax and as a substitute for Burgundy pitch in plasters. It is also used for caulking boats.[16] Medicinally it is used in rheumatic pains when mixed with gingili oil.[17]

Dammar is a general name given to the group of natural resins, from Dipterocarpaceae family, very common in Malaya, Indonesia, East Indies and India.

Mills and Werner[18] have reported the isolation of some interesting triterpenes from 'Dammar' resin (Pale Bold Indonesian Dammar). By the use of column chromatography and reversed-phase paper chromatography[19] neutral and acidic triterpenes were isolated. They are listed below.

Neutral constituents of dammar

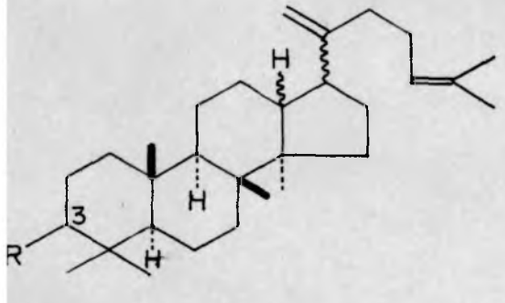
Name	Approx. Rf value	Formulae	M.P.	$(\alpha)_D$
Dammadienone	0.26	$C_{30}H_{48}O$	72-75	+ 81
Dammadienol	0.36	$C_{30}H_{50}O$	136-138	+ 47
Hydroxy-damma-renone (I)	0.62	$C_{30}H_{50}O_2$	145-147	+ 60
" (II)	0.62	$C_{30}H_{50}O_2$	134-136	+ 66
Hydroxy-hopanone	0.66	$C_{30}H_{50}O_2$	252-256	+ 64
Dammarene diol (I)	0.82	$C_{30}H_{52}O_2$	142-144	+ 27
" (II)	0.82	$C_{30}H_{52}O_2$	131-133	+ 33

Acidic constituents of dammar

Acid	Approx. Rf value	Formulae	M.P.	$(\alpha)_D$
Dammarolic	0.96	$C_{30}H_{48-50}O_6$	315*	+ 49
Dammarenolic	0.83	$C_{30}H_{50}O_3$	138-142	+ 43
Ursonic	0.74	$C_{30}H_{46}O_3$	270-275*	+ 80

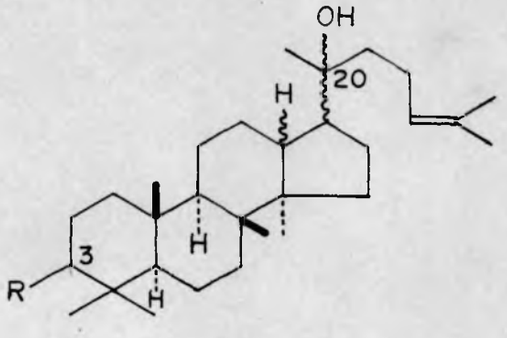
* With decomposition.

The constitution of some of these triterpenes, such as dammadienol (1) and its related 3-ketone dammadienone (2),[20] the dammarene diols I & II (3) which differ only in the configuration at C_{20} and the corresponding 3-ketones, hydroxy-dammarenones I & II,[21] have been elucidated.



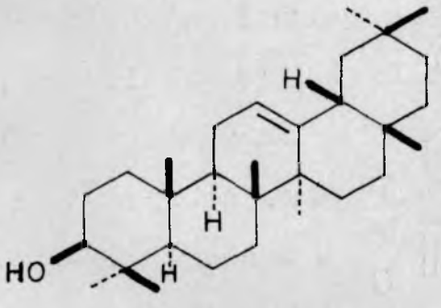
(1) R = (β) OH

(2) R = O



(3) R = (β) OH

Other important resins from India are 'white dammar' obtained from Vateria indica Linn., and 'shal resin' obtained from the plant Shorea robusta. Shal resin is highly aromatic and is burnt as an incense. It is used in medicine as astringent, antiseptic and aphrodisiac. This commercially important resin has been investigated in our laboratory.[22] The constituents of the parent resin were isolated mainly by using solvent partition and column chromatography. Apart from the mixture of sesquiterpene hydrocarbons and ketones in liquid component, the crystalline triterpene alcohols β-amyrin(4) and ψ -taraxasterol (5) were isolated in pure form.



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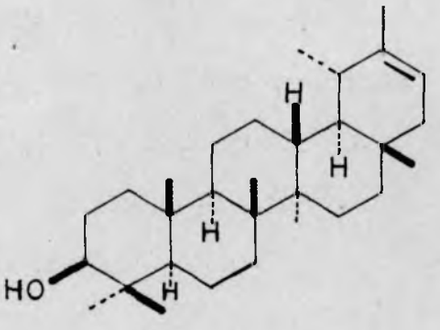
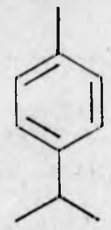


(5)

Also from the neutral fraction of the 'chua oil' obtained by destructive distillation of shal resin (Shorea robusta) the presence of p-cymene (6), ocimene (7), tetrahydro-γ-cadinene (8), three sesquiterpene hydrocarbons (9,10,11), cadalene (12), 1,6-dimethyl naphthalene (13) and 1,2,6,8-tetramethyl naphthalene (14)[22] was confirmed.



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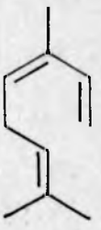

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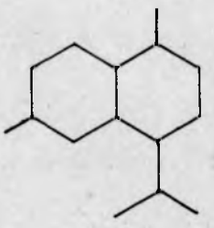

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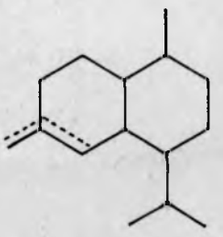

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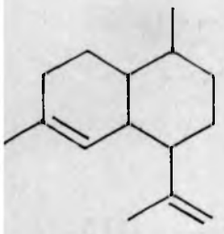

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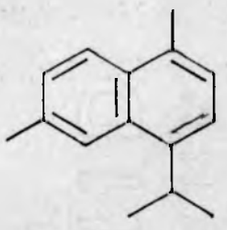

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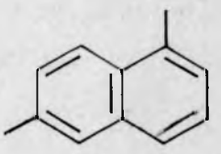

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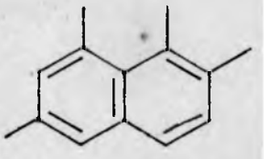

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PRESENT INVESTIGATION

As mentioned in the beginning the results incorporated in this thesis concern mainly two aspects. Firstly, elucidation of the chemistry of Black dammar resin (*Canarium strictum* Roxb.) and secondly solving the stereochemistry of elemol and related compounds.

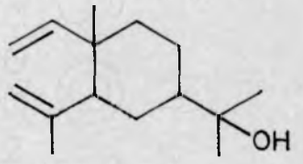
The constituents of Black dammar resin have been separated and isolated mainly by employing different solvent

partitions at room temperature, followed by chromatography over neutral alumina. The results of our investigation are incorporated in Chapters I & II.

In Chapter I, the properties of parent resin, elaborate procedure for separating the constituents and isolation and identification of the compounds are discussed in detail.

The results on the structure and absolute configuration of a new sesquiterpene ketone obtained in small quantity from the resin are presented in Chapter II.

The Stereochemistry of Elemol and Related Compounds



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Although the structure of the crystalline monocyclic sesquiterpene alcohol elemol (15) was established by Ruzicka and co-workers[23] and Sorm and co-workers,[24-26] the stereochemistry remained unsolved until very recently Halsall[27] established it by relating elemol to sesquiterpene (+)-epi-α-cyperone by a series of elaborate steps. We have been able to prove it unambiguously by its direct conversion to tetrahydrosaussurea lactone of known stereochemistry. The data of our results are presented in Chapter III.

GENERAL REMARKS

(1) All melting points and boiling points are uncorrected and are recorded on centigrade scale.

(2) Petroleum ether refers to the fraction, b.p. 60-80°.

(3) Specific rotations were taken in chloroform solution unless otherwise stated.

(4) The neutral alumina used for chromatography was prepared from commercial aluminium hydrate (200 mesh) which was treated with nitric acid, washed with water free from mineral acid, and heated at 450° for 6 hours. The required activity was obtained by mixing with requisite amount of water.[28]

(5) The numbers given to the structures and also the numbers given to the figures in each chapter of the thesis refer only to that particular chapter.

(6) Throughout the work liberal use of infrared and ultraviolet spectrophotometry, nuclear magnetic resonance spectra and rotatory dispersion studies has been made. Wherever necessary, the products, according to the specific requirements, were subjected to VPC analysis.

(7) The infrared spectra were recorded as liquid film or in nujol suspension on Perkin-Elmer infracord

spectrophotometer, Model 137B, with sodium chloride optics.

(8) The ultraviolet spectra were measured in ethanol solution on a Beckman Ratio-recording spectrophotometer, Model DK-2.

(9) The NMR spectra were taken in carbontetrachloride solution using tetramethylsilane as the internal reference on a 60 Mc Varian instrument, and the chemical shifts were measured in δ units.

(10) Gas-liquid chromatography analyses were carried out on Griffin VPC apparatus, MK II-A, with polyester column using hydrogen as the carrier gas.

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CHAPTER I

ELUCIDATION OF THE CHEMISTRY OF INDIAN BLACK DAMMAR RESIN (CANARIUM STRICTUM ROXB.)

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SUMMARY

The constituents of the Black dammar resin, Canarium strictum Roxb., have been isolated by solvent partition and column chromatography.

From the petroleum ether (40-60°) extract of the resin, by elaborate column chromatography over neutral alumina, the following compounds have been isolated and characterised. These include among the sesquiterpenoids, a hydrocarbon, a new monoethynoid ketone, canarone, D-junenol and a liquid alcohol, probably epi-Khusinol. Some related work has also been carried out on khusinol and is reported in this chapter. In addition to the sesquiterpenoids, the crystalline triterpene fractions were identified as α-amyrin, β-amyrin and β-amyrin acetate.

Natural resins have been the subject of extensive investigation for the last 150 years; the results which are described in the book by Tschirch and Stock[1] leave a picture of complexity together with considerable doubt as to the homogeneity of the compounds. This is due to the fact that the methods then available for the attempted isolation and purification of the resin components were not adequate.

Earlier work on Black dammar resin

The work on Indian Black dammar resin, Canarium strictum Roxb., was initiated by K.L. Moudgill.[2] He studied the components of the 'resin oil' obtained by destructive distillation and reported the presence of azulene, n-heptane, heptine (C_7H_{12}), d-α-pinene (1), bicyclic sesquiterpene hydrocarbons etc. From the acetone extract of the resin, the presence of a yellow crystalline compound (m.p. 105°) has been reported.

Later, Vasisth and Muthana[3] reported their work on the resin. The physical constants of the resin and the 'resin oil' as determined by these workers are given in TABLE-1 and TABLE-2 respectively.

TABLE - 1

Physical constants of Black dammar

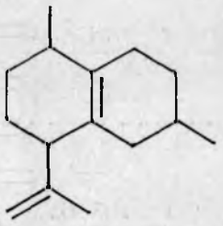
	Values reported by Vasisth & Muthana.	Values reported by Moudgill
Acid value	4.00 (Stock)	28.30
Ester value	17.7	-
Iodine value	42.3 (Huble)	-
Solubility in:		
Alcohol	16%	4.4%
Acetone	40	26.5
Pet. ether	34	-
Benzene, chloroform carbontetrachloride	- the resin completely soluble	

TABLE - 2

Physical constants of resin oil

Refractive index	1.6091	1.5070
Optical rotation	nil	invisible
Density	0.9257	0.9228
Acid value	0.115	-
Ester value	18.89	11.0
Iodine value	231.65	-

From the sesquiterpene fractions of the 'resin oil'[3] Vasisth and Muthana isolated a new sesquiterpene hydrocarbon,[4] Damarene (2).



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Present work on Black dammar resin

Black dammar resin consisting mainly of black nodular lumps was obtained from the Forest Department, Kerala State. The resin was finely powdered, sieved and used for the determination of acid value, volatile oil content and solubility in various solvents.

The acid value determined by direct method was 8.7.

The essential oil content in the resin was determined by hydro-distillation and was found to be 0.7%.

The resin is completely soluble in chloroform and carbontetrachloride and partly soluble in other solvents. The solubility data are shown in TABLE-3.

The separation of the constituents of the resin using both solvent partition and chromatography is outlined in Chart I (p. 35). The coarsely powdered resin was first extracted with acetone. The soluble portion

recovered from acetone was re-extracted with ethanol. The ethanol extract was then treated with methanol. The concentrated suspension from methanol was stirred with petroleum ether (40-60°). All the extractions were carried out at room temperature, under stirring with excess of solvents. The only practical method for further resolution of the components present in the petroleum ether extract* was chromatography over neutral alumina. The grades of alumina and series of solvents used during chromatographic separation are given in CHART 1 and in the relevant Chromatography Tables.

Solubility of Black dammar resin

The solubility of the resin in various solvents, listed below, was determined by taking each time powdered resin weighing approximately 10 g. and adding to it 100 ml. of the solvent. The mixture was shaken thoroughly in a well-stoppered bottle for a period of two hours at the room temperature of about 32°. The solubility data are collectively given in TABLE-3.

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* Petroleum ether extract refers only to the soluble part. The insoluble portion, alongwith other extracts of the same resin, is being investigated separately in our laboratory.

TABLE - 3

No.	Solvent	Solubility in %
1	Methanol	22
2	Ethanol	27
3	Acetic acid	38
4	Acetone	41
5	Ethyl acetate	50
6	Dioxan	66
7	Ether	80
8	Pet.ether (60-80°)	84
9	Benzene	90
10	Pet.ether (40-60°)	97
11	Carbon tetrachloride	100
12	Chloroform	100

The fractions eluted with petroleum ether (Chromatography Table-I, p. 36) were found to contain liquid hydrocarbons, triterpene esters and ketones, alongwith sesquiterpene oxides and carbonyl compounds in small proportion. Examination of the hydrocarbon fraction

revealed that it was composed of three or four components. A preliminary study of one of the fractions (Fr. 2, Chromatography Table - II, p. 38) indicated that the hydrocarbon belonged to sesquiterpene group having the molecular formula, $C_{15}H_{24}$. The infrared spectrum (Fig. 1) indicated the presence of $>C=CH_2$ grouping (1640 and 885 cm^{-1}), also bands at 785 and 836 cm^{-1} showed the presence of tri-substituted double bond. Perbenzoic acid titrations indicated the number of double bonds as 2.1-1.9 (24-72 hrs). Catalytic hydrogenation using Adams' catalyst gave the tetrahydro-product. The molecular refractivity determined was 66.12 ($C_{15}H_{24}\sqrt{2}$ = 66.14).[5] The hydrocarbon on selenium dehydrogenation gave a good yield of cadalene characterised as its s-trinitrobenzene adduct and picrate. Evidently it was a cadalenic hydrocarbon. The ozonolysis experiments showed the presence of formaldehyde and acetone in volatile part, while the non-volatile portion gave test for aldehyde (Fehling's test) and methyl ketone (iodoform reaction), but failed to give test for 1,3-diketone (Ferric chloride).

Further study of the hydrocarbon was discontinued because VPC analysis then showed that the hydrocarbon was only about 70% pure.

In addition to the liquid component obtained from the pet.ether eluted fraction (see CHART-I, p. 35), substantial amount of solid material was also obtained. With

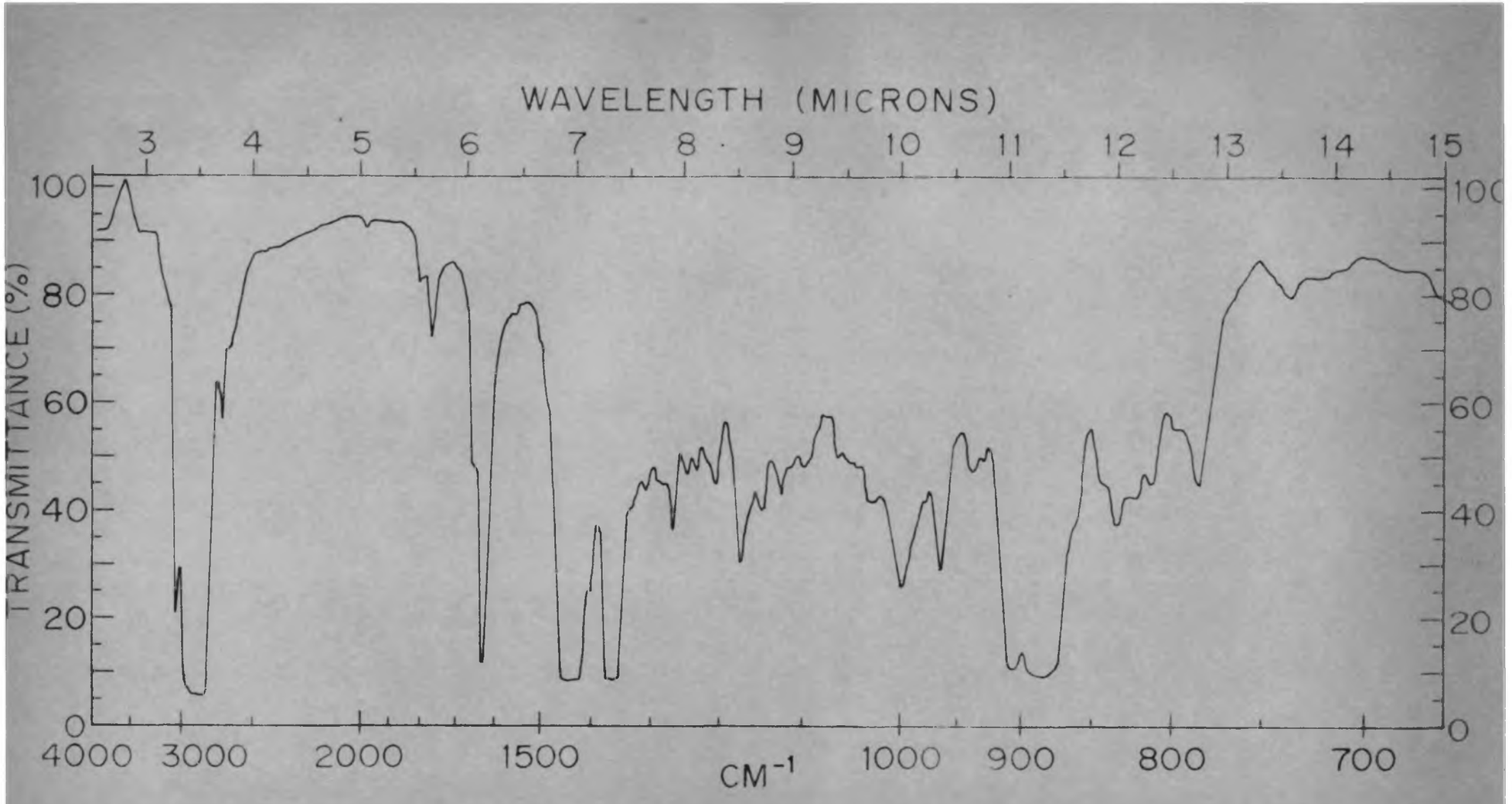
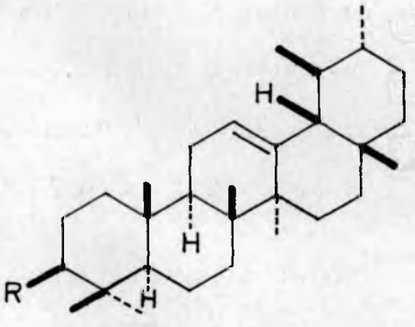


FIG. 1. IR SPECTRUM OF A HYDROCARBON FROM BLACK DAMMAR RESIN.

Liebermann-Burchardt test it gave violet pink colouration. The infrared spectrum of the material exhibited absorption band at 3400 cm^{-1} suggesting the presence of hydroxyl function. Since the substance could not be obtained in a crystalline form, it was suspected to be a mixture. In order to effect the separation, a small portion of the substance was chromatographed (Chromatography Table-III, p. 42). As the infrared spectrum suggested the presence of hydroxy- compound, the earlier fraction of the said chromatography was acetylated. The acetate was repeatedly crystallised from ethyl acetate till it gave constant melting point. It was found to be α-amyrin acetate (3b), m.p. 223-224°, $(\alpha)_D$ + 82.2°. Its IR spectrum (Fig. 2B) was superimposable with the IR spectrum of an authentic



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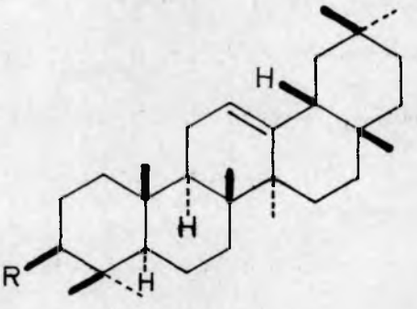


(4)

(3a) R=OH

(3b) R=OAc

(3c) R=OBz

(4a) R=OH

(4b) R=OAc

(4c) R=OBz

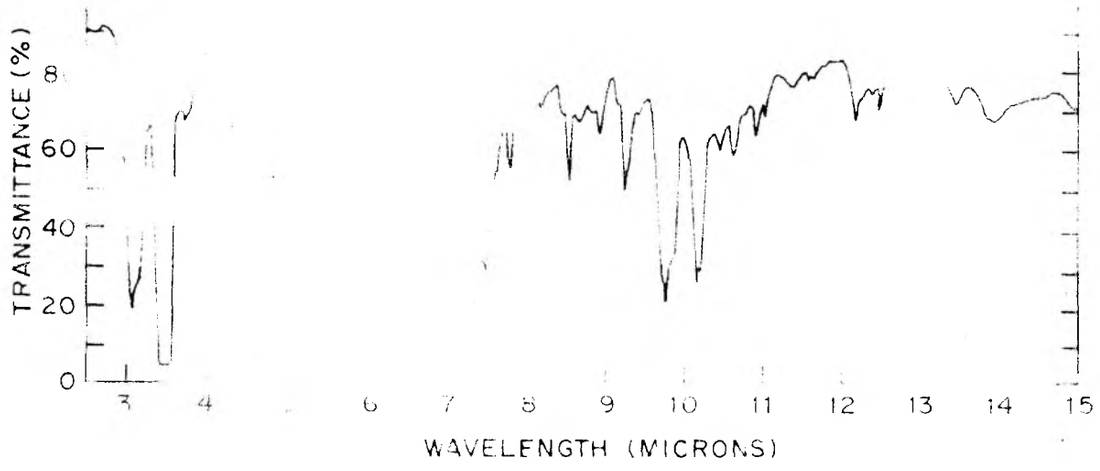


FIG. 2A. IR SPECTRUM OF THE α-AMYRIN (3a) FROM BLACK DAMMAR RESIN.

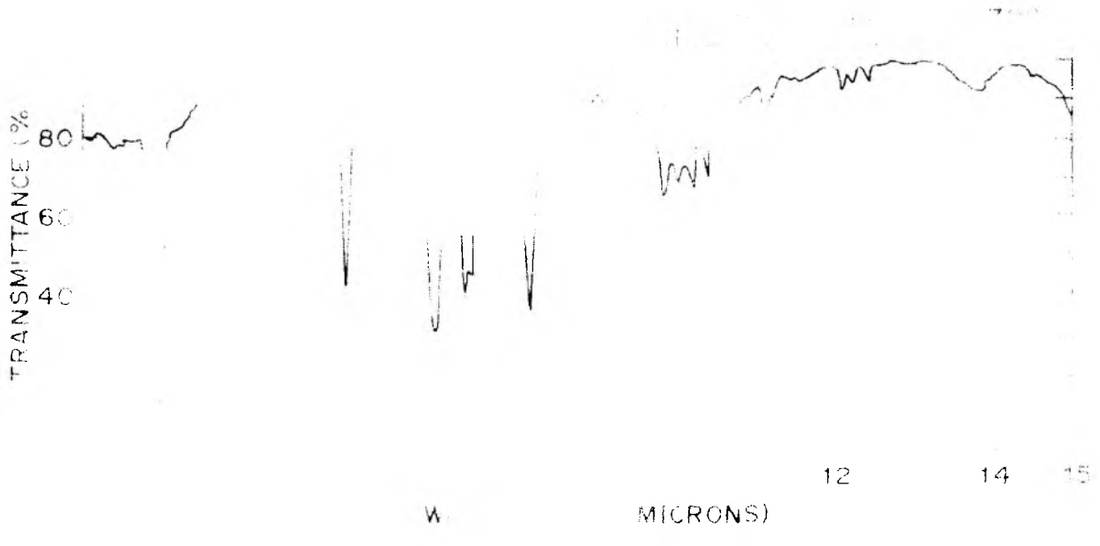


FIG. 2B. IR SPECTRUM OF THE α-AMYRIN-ACETATE (3b)

sample. On hydrolysis it afforded α-amyrin (3a), m.p. 182-184°, $(\alpha)_D$ + 91.2°. Infrared spectrum (Fig.2A) agreed with that of an authentic specimen.

It gave a benzoate derivative (3c), m.p.192-194°, $(\alpha)_D$ + 94°. The properties of the alcohol, its acetate and benzoate derivatives agreed with those reported for α-amyrin.[6]

The other product which could be separated from the mixture was another triterpene alcohol, β-amyrin (4a). Spring[7] has also reported the separation of α-amyrin from β-amyrin. The later fraction of the chromatography (Chromatography Table-III, p. 42) which showed hydroxyl function in its infrared spectrum was acetylated and the crude acetate was purified by crystallisation using ethyl acetate. It was characterised as β-amyrin acetate (4b), m.p. 238-239°, $(\alpha)_D$ + 83.5°. Its infrared spectrum is represented in Fig. 3B. On hydrolysis with alcoholic potash, β-amyrin (4a), (IR spectrum, Fig.3A) was obtained, m.p. 197-198°, $(\alpha)_D$ + 90°. It afforded a benzoate derivative (4c), m.p. 232-233°. The properties of β-amyrin, its acetate and benzoate derivatives agreed with those reported in the literature.[8]

Petroleum ether eluted fraction (Chromatography Table-I, p. 36) also contained a triterpenic substance

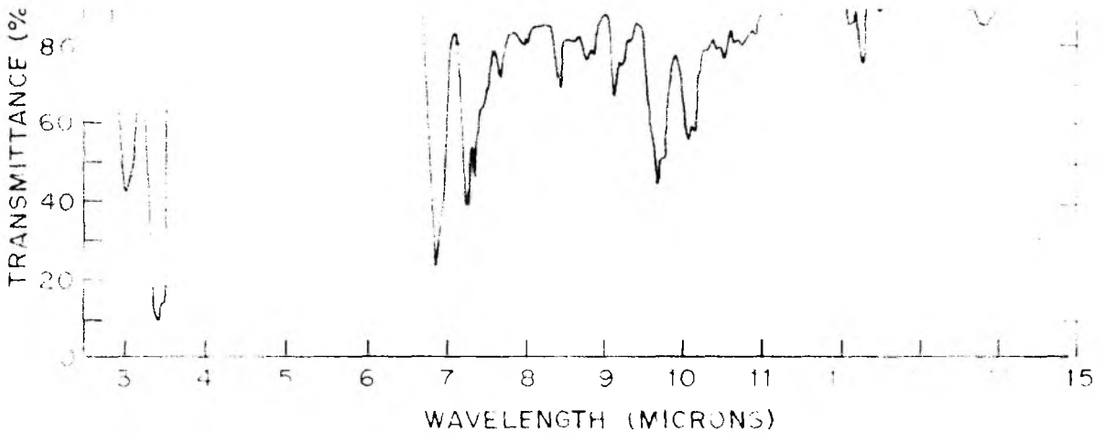


FIG. 3A. IR SPECTRUM OF THE β-AMYRIN (4c) FROM BLACK DAMMAR RESIN

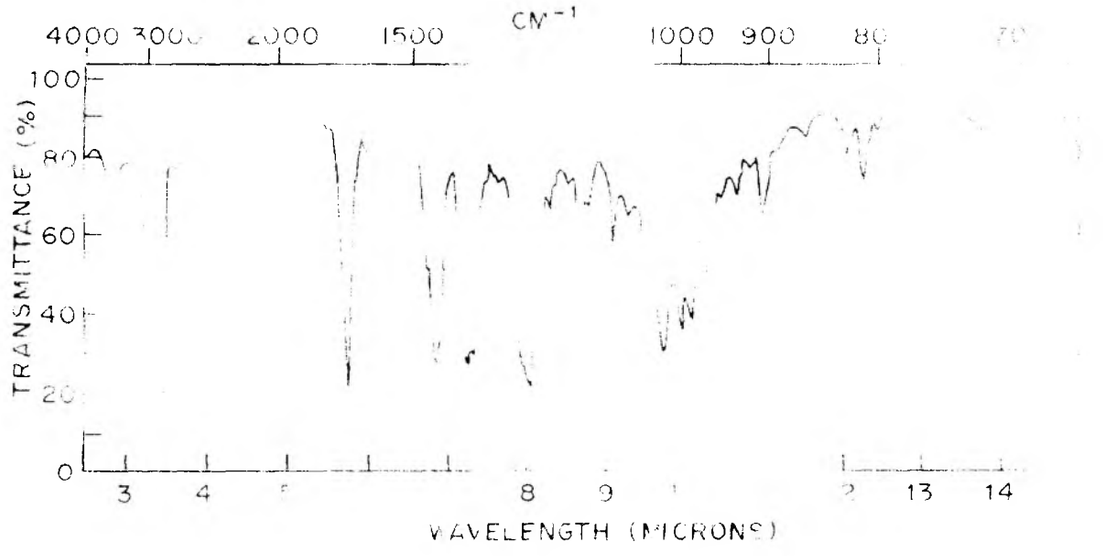


FIG. 3B. IR SPECTRUM OF THE β-AMYRIN-ACETATE (4b)

which appeared as a crystalline solid in chromatography fractions (Fr. 5 to 10). The infrared spectrum of the crude product exhibited bands at 1740 and 1280 cm^{-1} suggesting thereby the presence of ester function. The naturally occurring ester was purified by chromatography (Chromatography Table-IV, p.47) and crystallisation from ethyl acetate. It was identified as β-amyrin acetate (4b), (IR spectrum, Fig.4), m.p. 238-239°, $(\alpha)_D$ + 83.5°. On hydrolysis it afforded β-amyrin (4a), m.p.198-199°, $(\alpha)_D$ + 90°.

The yellow, viscous, benzene-eluted fractions (Fr. 22 to 24) (Chromatography Table-I, p.36) was distilled under vacuum. The distillate after elaborate column chromatography (Chromatography Table-V, p. 49) yielded a new liquid monoethynoid sesquiterpene ketone followed by a crystalline substance in small amount.

The structure and the stereochemistry of the ketone are discussed in the Chapter II.

The infrared spectrum of the crystalline substance showed the presence of -OH group (3500 cm^{-1}) and a methylenic double bond $\rangle C=CH_2$ (1645 and 885 cm^{-1}). It was purified by crystallisation from pet.ether and identified as the rare alcohol D-junenol[9] (5).

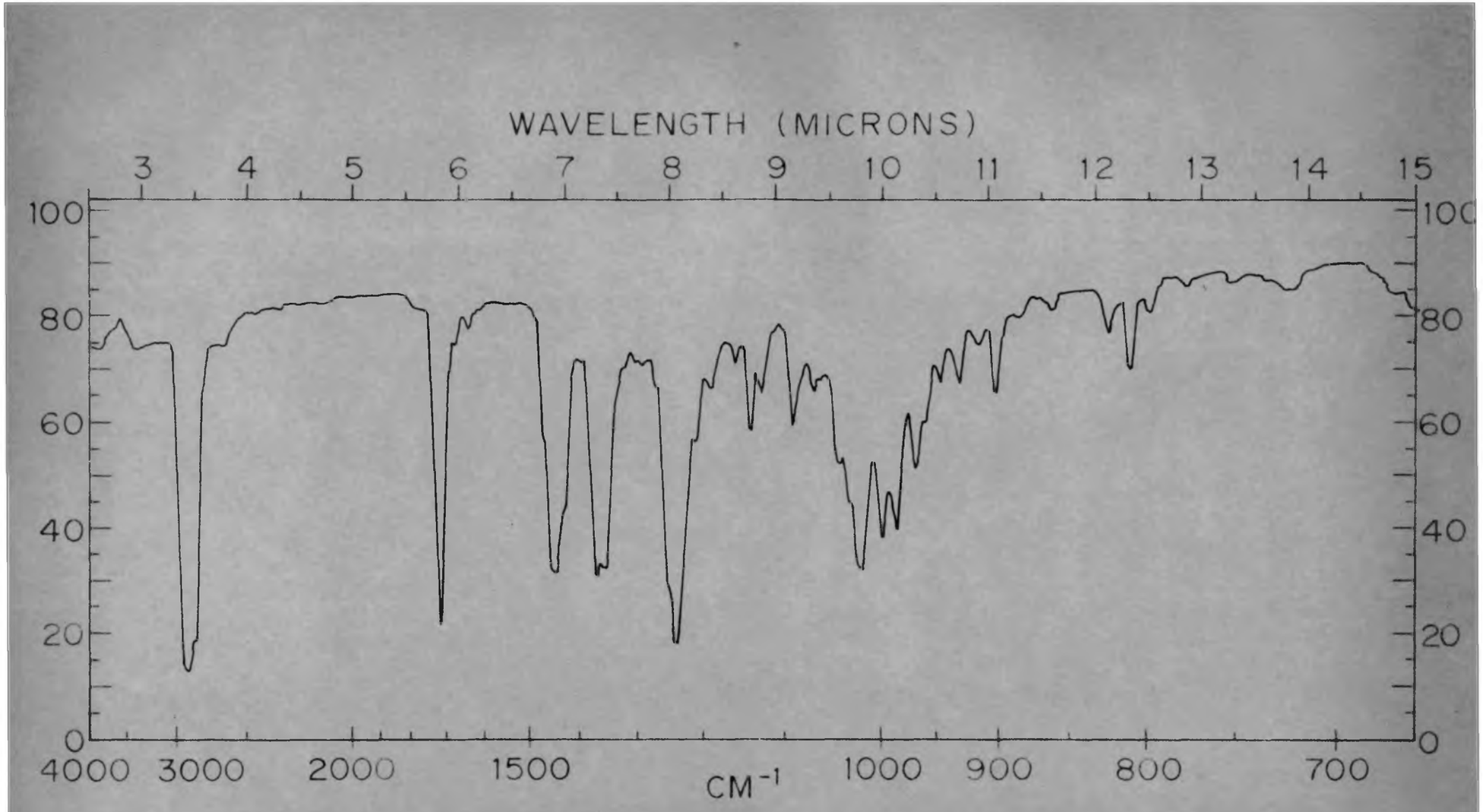
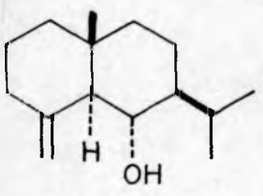
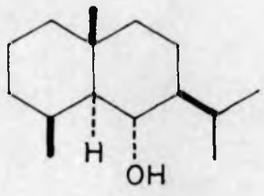


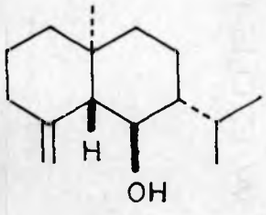
FIG. 4. IR SPECTRUM OF THE β-AMYRIN ACETATE FROM BLACK DAMMAR RESIN.



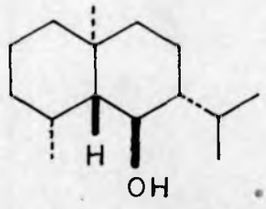
(5)



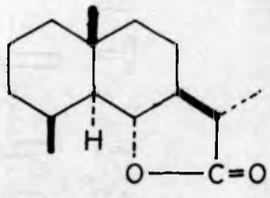
(6)



(7)



(8)



(9)

From its sign and magnitude of rotation, it was confirmed as dextro-junenol and not laevo-junenol[10] (7). Bhattacharyya and co-workers[11] elucidated the absolute configuration of D-junenol (5) and laevo-junenol (7) by synthesising dihydrojunenol (6) from santanolide 'c' (9) of known configuration.[12] The junenol isolated from this resin had, m.p. 60°, $(\alpha)_D$ + 82°. The mixed melting point with an

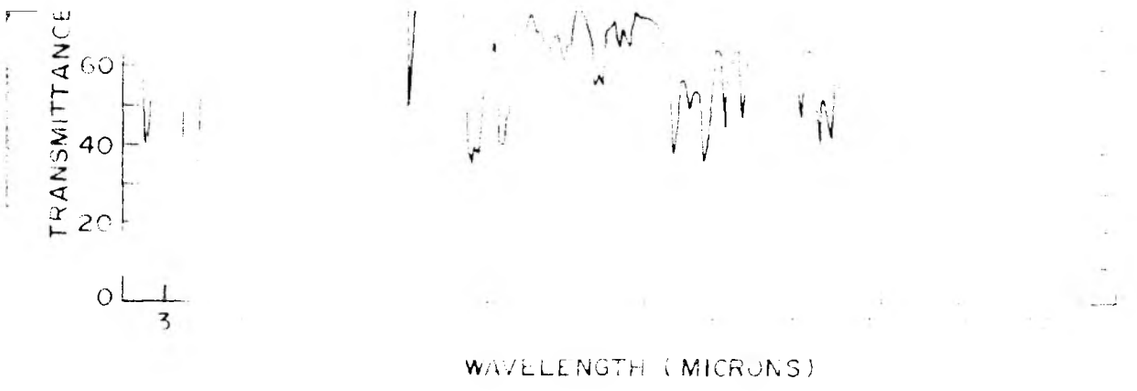


FIG. 5A. IR SPECTRUM UNENOL (5) FROM BLACK DAMMAR RESIN.

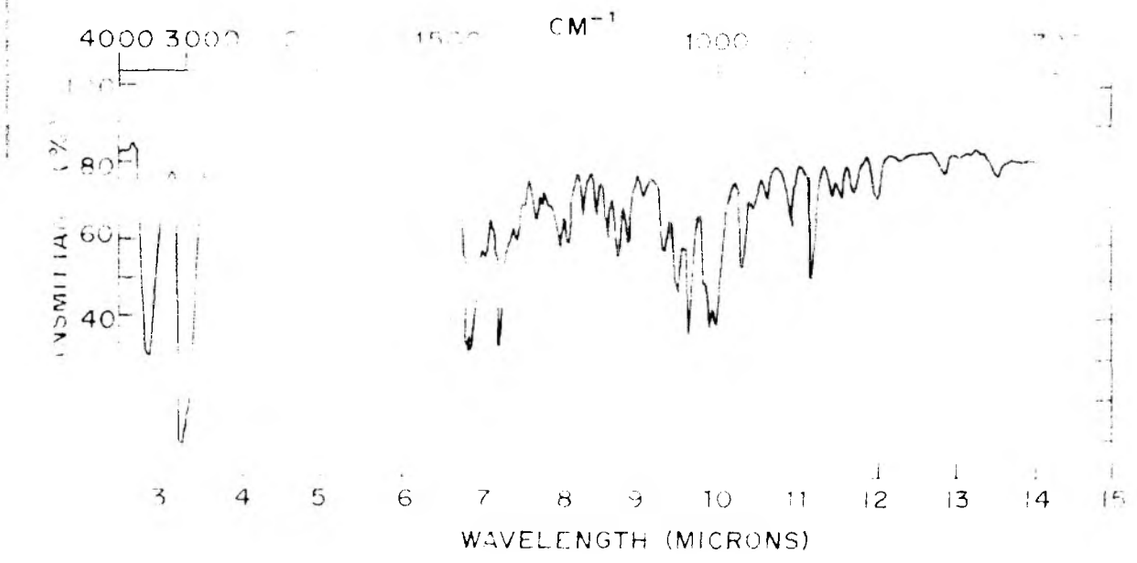


FIG. 5B. IR SPECTRUM OF THE DIHYDRO-JUNENOL (6).

authentic sample was undepressed. The infrared spectrum (Fig.5a) was completely identical with the spectrum of junenol. The identity was further confirmed by converting junenol to dihydrojunenol (6). The melting point and mixed melting point with authentic sample of dihydro-junenol was 113-114°. Mixed melting point with laevo-dihydrojunenol(8), however, gave a depression. Its infrared spectrum (Fig.5b) was identical with that of dihydrojunenol.

The sesquiterpene alcohol

The yellow, viscous, benzene-eluted fraction(Fr. 25) (Chromatography Table-I, p. 36) after distillation under vacuum yielded in small amount, a liquid component which on careful chromatography over neutral alumina gave a sesquiterpene alcohol, $C_{15}H_{24}O$, b.p.126°(bath)/0.5 mm., $(\alpha)_D$ - 96.8°. On the basis of the experimental evidences, this alcohol is represented by the gross structure (10). Because of its structural similarity with khusinol (11), the structure and absolute configuration of which was proved by Bhattacharyya and his colleagues,[13] the liquid alcohol is considered to be epi-khusinol, being epimeric at C_3 and is represented by the stereoformula (12). This however could not be rigorously established due to paucity of material.

Khusinol (11), as well as khusol (13),[14-16] belong to the unusual antipodal group of cadinenes. In the

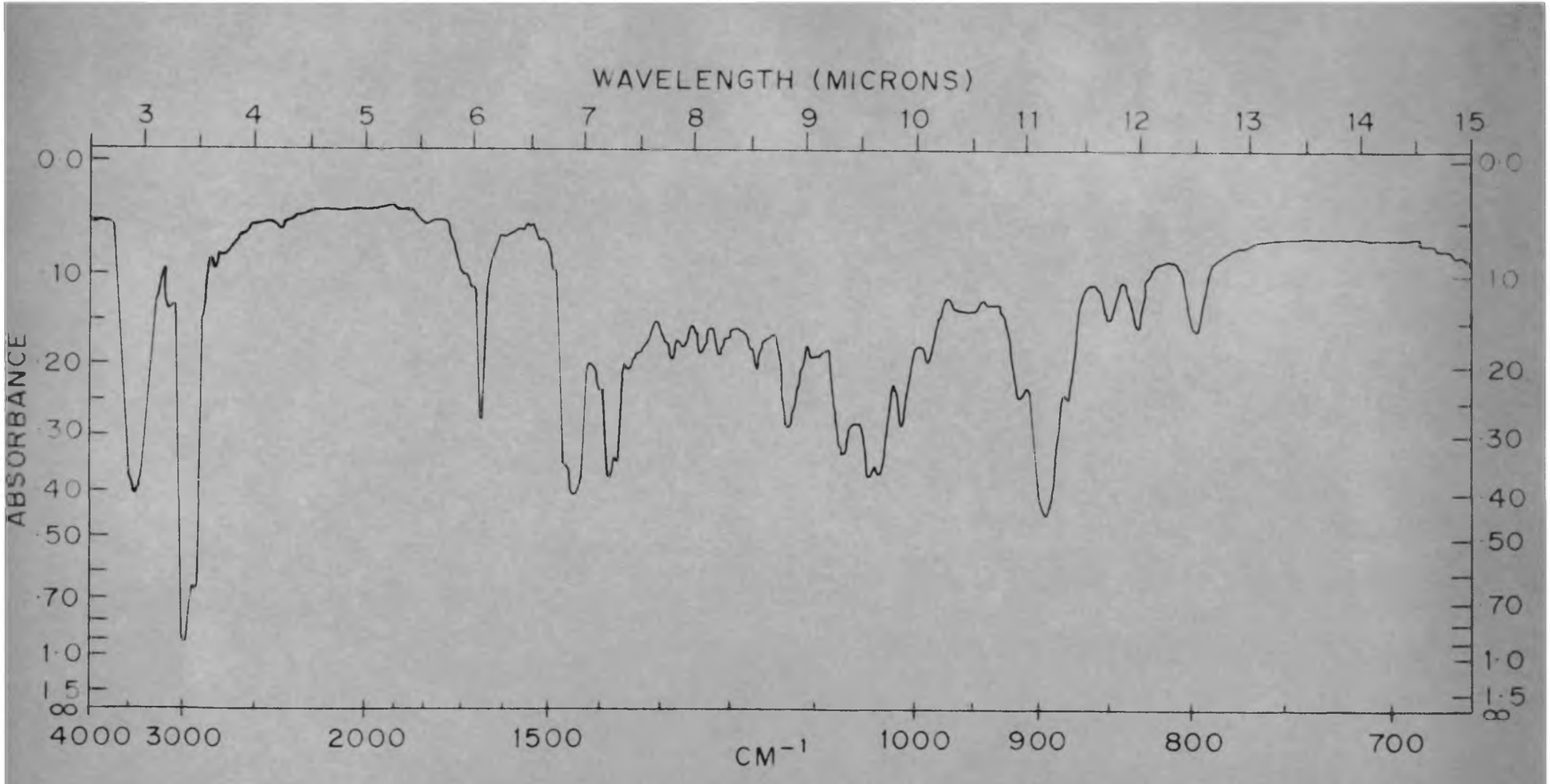
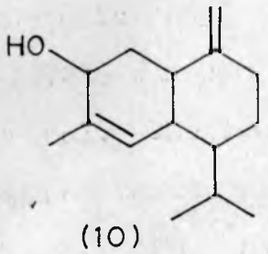
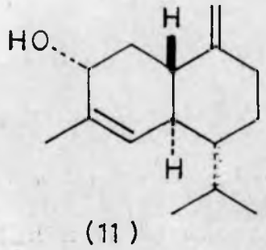


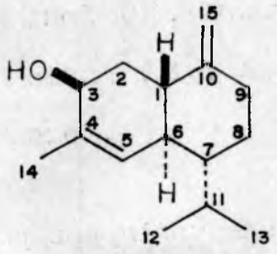
FIG. 6. IR SPECTRUM OF THE EPI-KHUSINOL (12) FROM BLACK DAMMAR RESIN.



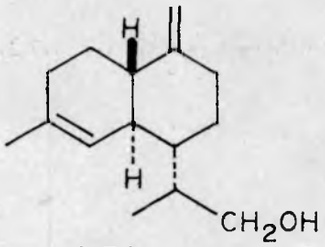
(10)



(11)



(12)



(13)

infrared spectrum (Fig.6), epi-khusinol showed bands at 3448, 1047 cm^{-1} (-OH group), 1640 and 896 cm^{-1} (exo-methylene double bond), 796 cm^{-1} (trisubstituted double bond) and 1360 and 1380 cm^{-1} (isopropyl group). It did not show any absorption in the ultraviolet region indicating the absence of conjugation.

The quantity of the alcohol (10), at our disposal being very small, we restricted our effort on only a few essential reactions and had often to depend on spectral and VPC characteristics since sufficient material for analyses and degradations were not always available.

epi-Khusinol easily furnished a crystalline 3,5-dinitrobenzoate, $C_{22}H_{26}O_6N_2$, m.p.186-187°. On catalytic hydrogenation with Adams' catalyst in glacial

acetic acid, it afforded the tetrahydroalcohol (14) by absorbing two moles of hydrogen, thereby confirming its bicyclic nature. On dehydrogenation with selenium at 280-290°, it afforded cadalene (15) in good yield. Cadalene was characterised through s-trinitrobenzene adduct, m.p. and mixed m.p. 109° and comparing the infrared spectra.

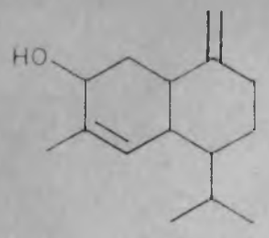
epi-Khusinol on oxidation with Jones reagent[17,18] gave a ketone which presumably was (16) containing α,β-conjugation. From our experience on the oxidation of khusinol, we knew that yields during this oxidation are not so satisfactory, as, much of the oxidation product is lost due to polymerisation. As the material at our disposal was extremely limited, we did not pursue this oxidative reaction further but were satisfied by collecting IR spectral evidences on the impure product which supported our contention. The location of the keto-group, however, was decided by hydrogenation of epi-khusinol and oxidising the reduced product to the corresponding saturated ketone (26). The same ketone could also be obtained from khusinol (11) via the same series of reactions. This has been discussed vide infra.

In this connection, we re-examined the oxidation of khusinol (11) with chromic acid. This has been previously carried out in our laboratory and it has been

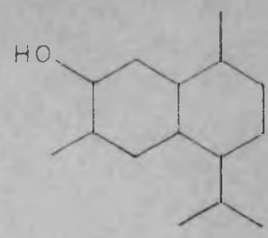
assumed that the liquid α,β-unsaturated ketone[13] obtained thereby, is represented by the structure (16). But on re-examination, we have found that the ketone obtained by oxidation of khusinol with chromic acid-acetic acid, chromic acid-pyridine or Jones chromic acid reagent, is actually a crystalline solid, $C_{15}H_{22}O$, m.p. 87°, and is represented by the structure (17) and not by the structure (16) as previously assumed. This structure is fully supported by IR, UV and NMR spectral evidences.

In the infrared spectrum (Fig. 7), the ketone (17) showed bands at 1665 and 1620 cm^{-1} due to α,β- unsaturated ketone and another band at 1430 cm^{-1} due to $-CO-CH_2-$ group.

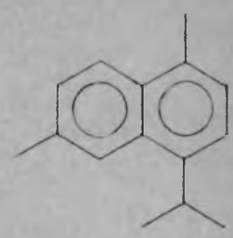
When khusinol (11) is hydrogenated under controlled conditions, it is converted to dihydrokhusinol (18), oxidation of which with chromic acid affords the α,β-unsaturated ketone (19) showing ultraviolet absorption at 233 mμ (ε_{max}, 13800) which is according to expectation. As against this, the conjugated ketone (17) obtained by oxidation of khusinol shows UV absorption at 244 mμ (ε_{max}. 10480) and at 278 mμ (ε_{max}, 7498). This is further supported by the IR spectrum of the compound (17) which shows absence of methylenic double bond.



(10)



(14)



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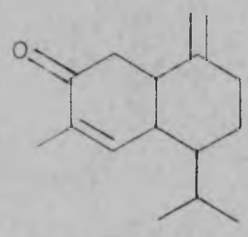
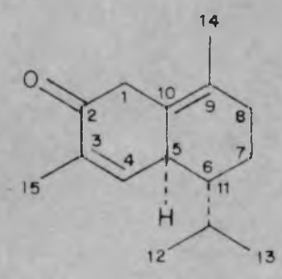


(16)



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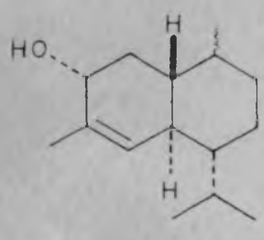

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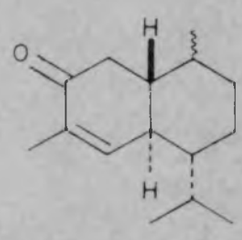

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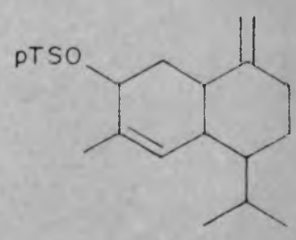

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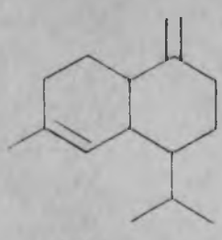

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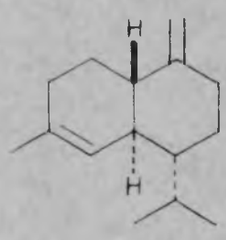

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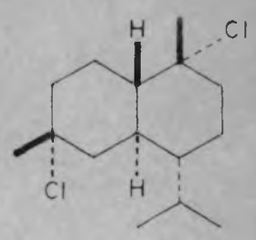

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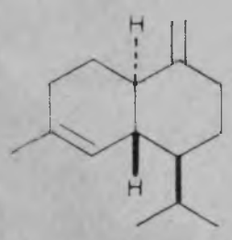

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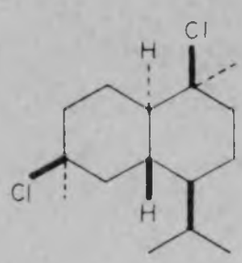

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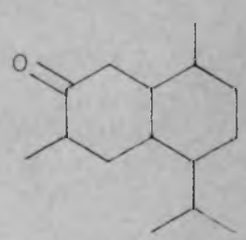

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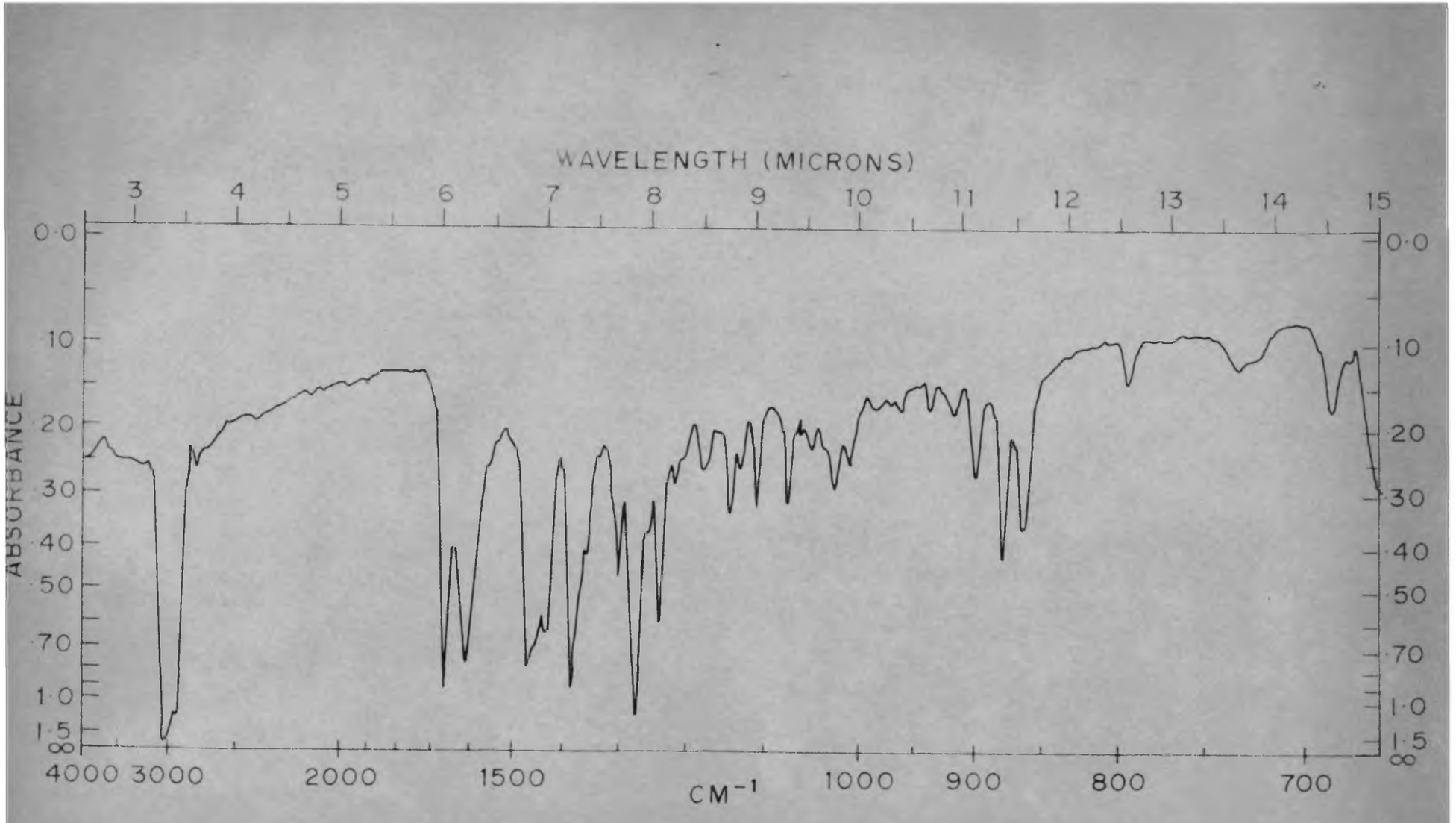


FIG. 7. IR SPECTRUM OF THE KETONE (17).

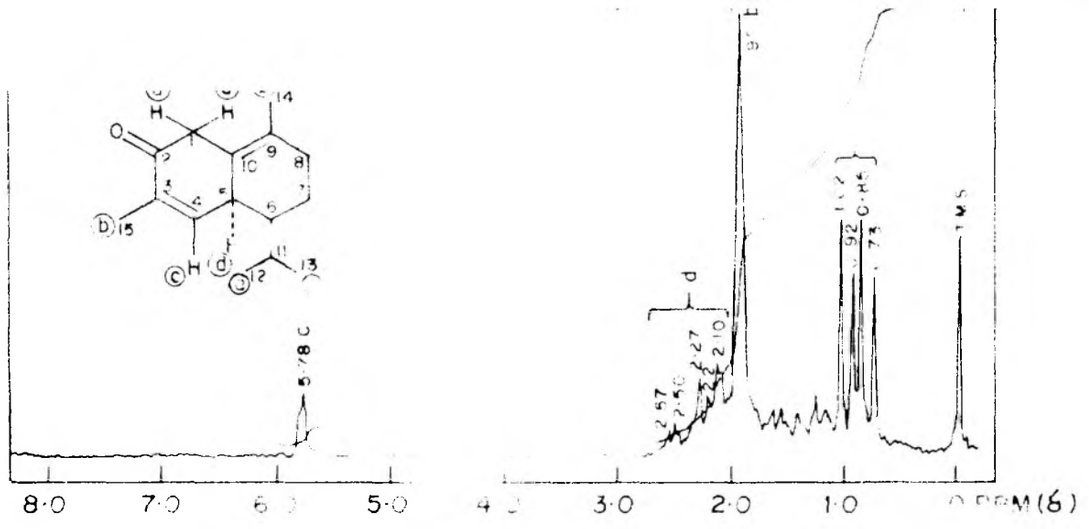


FIG. 8. NMR SPECTRUM OF THE KETONE (17)

In conformity with the structure (17), the NMR spectrum (Fig. 8) gave signals at 0.73, 0.85, 0.92, 1.02 δ (6H) due to two methyls at C_{12} and C_{13}, an intense signal at 1.92 δ (6H) due to two methyl groups on unsaturated carbon atoms at C_9 and C_3, a singlet at 5.78 δ (H) due to a proton at C_4 and signals at 2.1, 2.2, 2.37, 2.5, 2.67 δ (3H) due to two protons at C_1 and a proton at C_5.

With a view to know the placement of the double bonds in the basic skeleton of the epi-khusinol, it was converted into its tosyl derivative (20) by treating with tosylchloride in pyridine solution at room temperature for 48 hours. The crude tosylate on reduction with lithium aluminium hydride followed by subsequent chromatography gave a hydrocarbon (21). Its infrared spectrum (Fig. 9) and physico-chemical properties were identical with those of (-) γ-cadinene (22) of known stereochemistry.[13] The antipodal nature of the hydrocarbon (21) has been proved in our laboratory[13] by its conversion to crystalline dihydrochloride (23), m.p. 117.5°, $(\alpha)_D$ - 36.2°. The dihydrochloride (25) of the normal cadinene (24)[19] has m.p. 118° and $(\alpha)_D$ - 36°. The melting points are identical and specific rotation are equal but opposite in sign.

The location of the hydroxyl group was further proved in the following way. The tetrahydro alcohol (14)

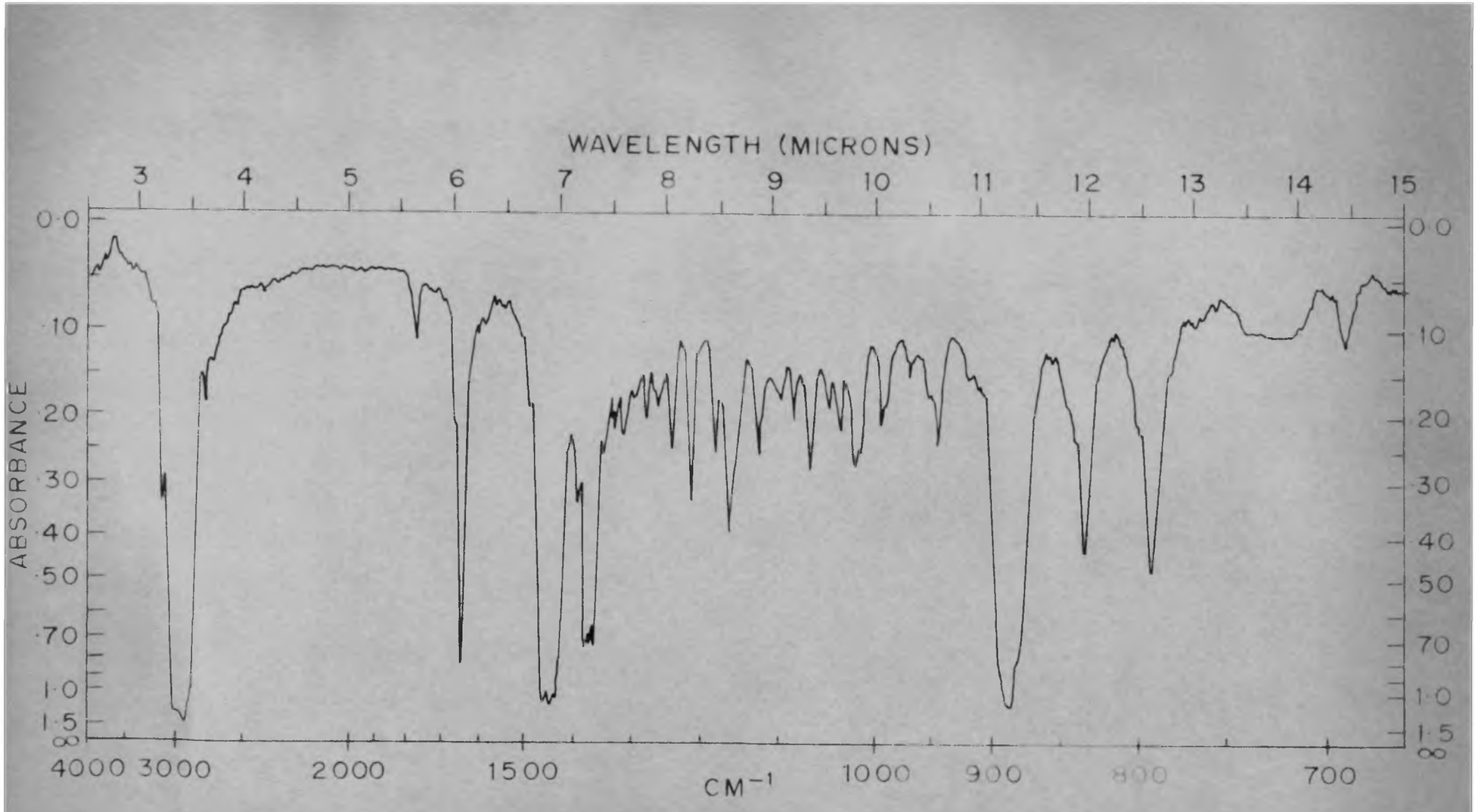
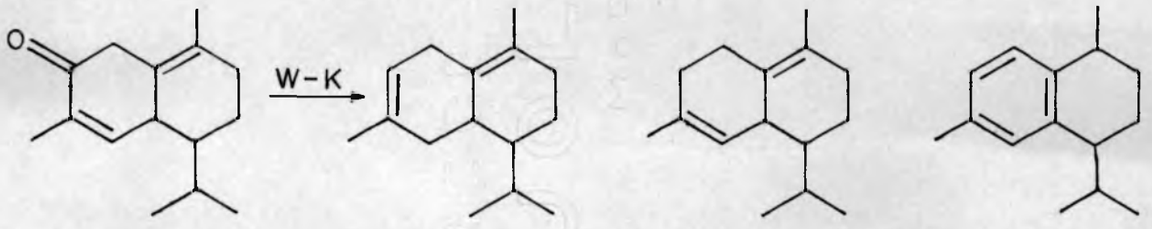


FIG. 9. IR SPECTRUM OF THE (−)-γ-CADINENE (21,22).

on oxidation with Jones reagent gave the saturated ketone (26), $C_{15}H_{28}O$. The infrared spectrum (Fig. 10A) was identical with the saturated ketone obtained from khusinol (Fig. 10B) and also VPC analysis gave the same retention time for both the ketones.

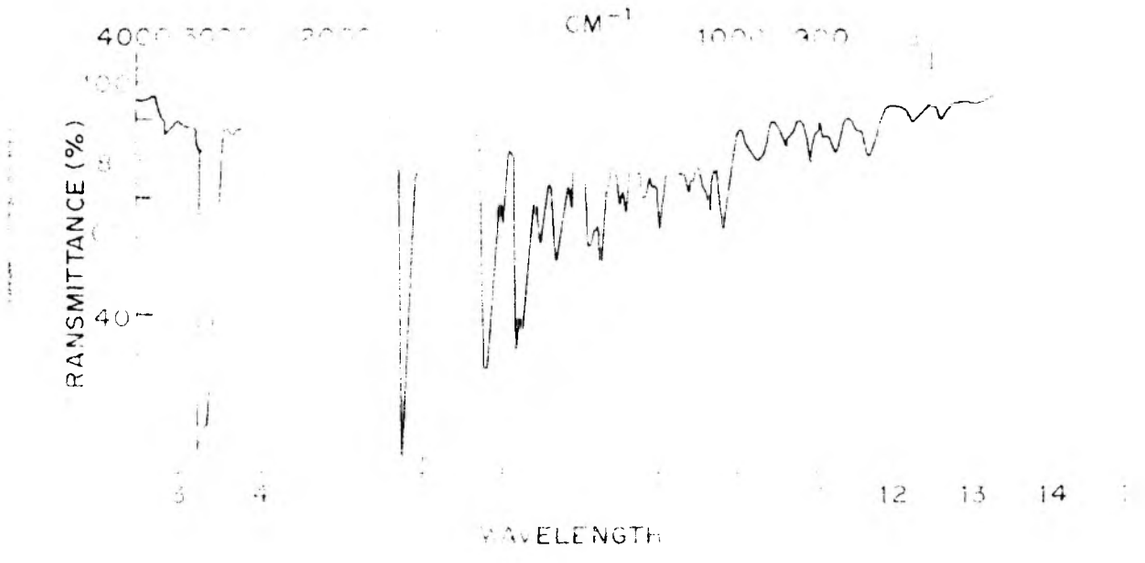
As mentioned earlier, khusinol (11) on chromic acid oxidation gave the crystalline ketone (17). In order to convert it to δ - cadinene (28)[30] it was subjected to Wolff-Kishner reduction. The reduction product was a mixture (VPC) of three distinct hydrocarbons possibly (27), (28) and (29).



(17) (27) (28) (29)

Although, it was not possible to isolate them individually, they were characterised by VPC analysis. The tetralenic hydrocarbon (29), has been previously obtained in our laboratory[21] by the reaction of lithioethylene diamine (LEDA) on khusinol (11).

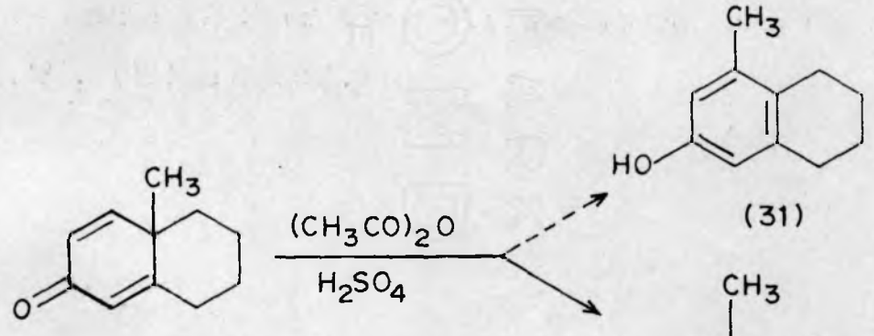
FIG. SPECTRUM OF THE SATURATED KETONE (26) FROM EPI-KHUSIN



F SPECTRUM OF THE SATURATED KETONE FROM KH

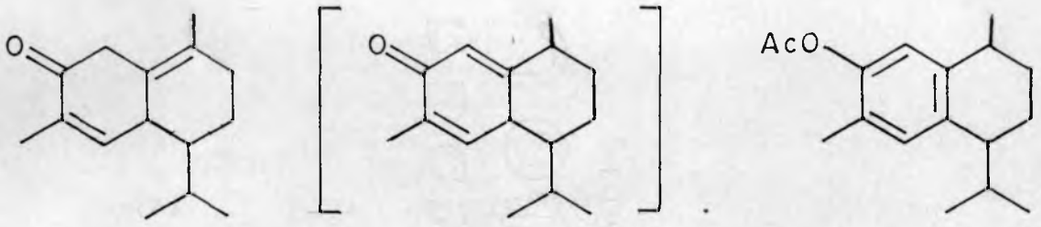
(11) (29)

Woodward et al.[32] subjected cyclohexadienone (30) to dienone-phenol rearrangement and instead of the expected product (31) obtained (32).



(30) (31) (32)

With a view to explore the possibility of converting the ketone (17) via the intermediate dienone (17') to the phenolic compound (34), the ketone (17) was treated with acetic anhydride containing a drop of sulphuric acid. An acetate, $C_{17}H_{24}O_2$, no doubt, was obtained but on saponification it did not give the desired phenol (34).



(17) (17') (33)

(34) (35)

The examination of the IR spectrum (Fig. 11) and the NMR spectrum indicates that the acetate is represented by the enol acetate structure (35).

Although it was not possible to obtain the phenol (34) from the ketone (17) by the reaction described before, the ketone has been converted to the phenol (34) in excellent yield in our laboratory[23] by treating it with lithioethylenediamine (LEDA).

(17) (34)

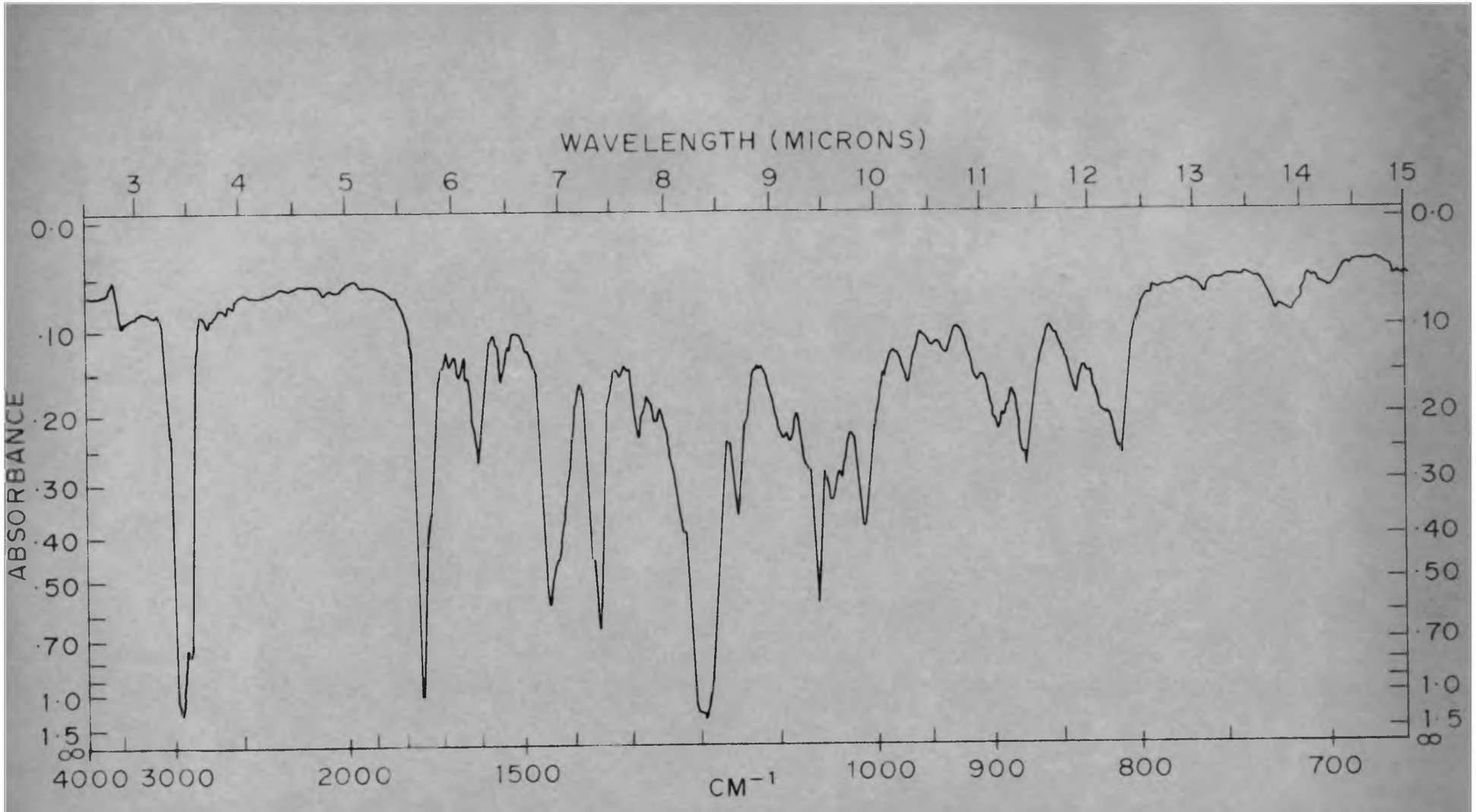
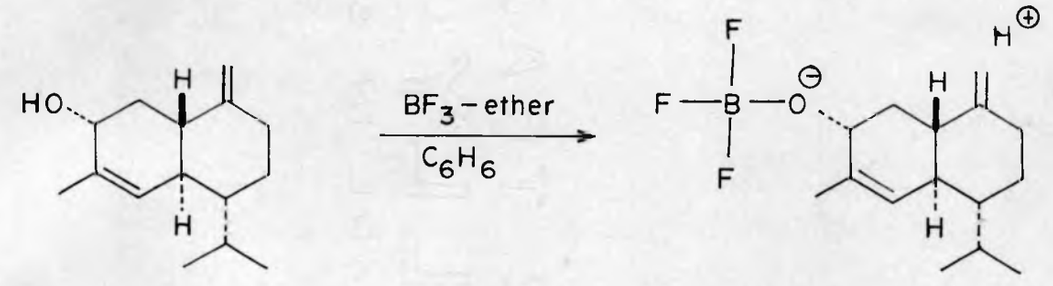


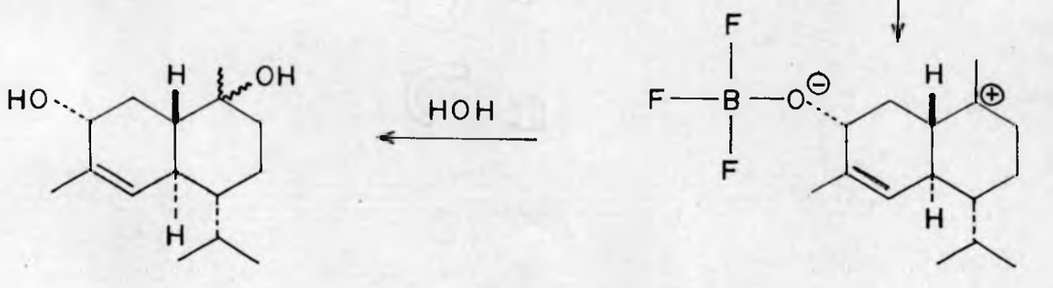
FIG. 11. IR SPECTRUM OF THE ENOL-ACETATE (35).

Khusinodiol

During the present investigation an interesting observation has been made by us. It has been found that khusinol (11) on treatment with borontrifluoride ethereate in benzene solution at room temperature is converted to crystalline 'khusinodiol' (36), $C_{15}H_{26}O_2$, m.p. 133°, $(\alpha)_D$ + 23.81° (vide, Chromatography Table VI, p. 59). The probable mechanism of the formation of khusinodiol is presented below. This is supported by experiments carried on model compounds.*



(11)



(36)

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* Unpublished work of Dr. S.N. Kulkarni.

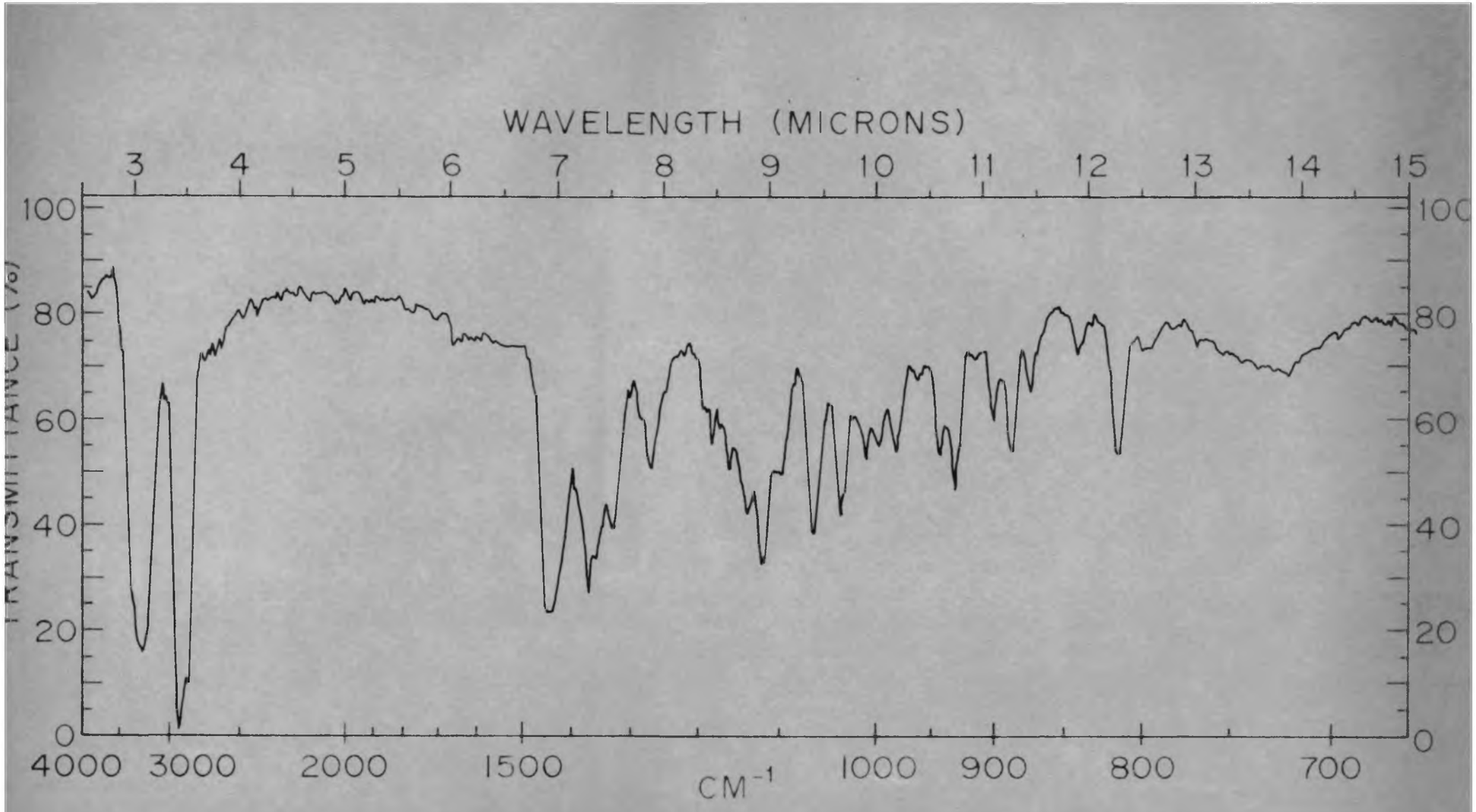


FIG. 12. IR SPECTRUM OF THE KHUSINODIOL (36).

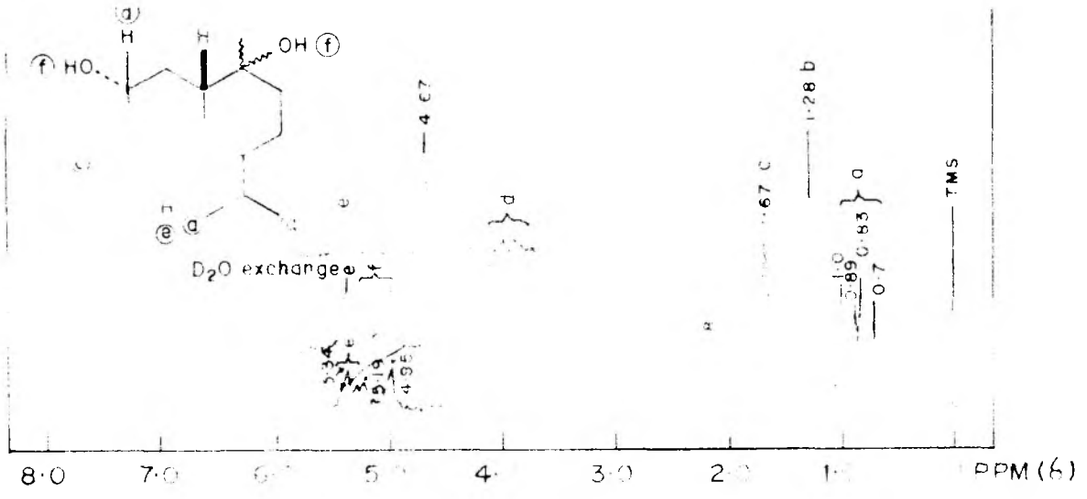


FIG. 13. NMR SPECTRUM OF KHUSINODIOL (36)

Its infrared spectrum (Fig. 12) exhibits absorption bands at 3300 and 1120 cm^{-1} due to hydroxyl group and 1360 and 1380 cm^{-1} due to isopropyl side chain. In the NMR spectrum (Fig. 13), the signals at 0.70, 0.83, 0.89, 1.0 δ (6H) are due to isopropyl group, a signal at 1.28 δ (3H) due to a methyl attached to carbon atom bearing oxygen, also the signal at 1.67 δ (3H) due to a methyl on unsaturated carbon atom. Triplet at 3.7, 3.85, 3.98δ(1H) is due to hydrogen on a carbon atom bearing oxygen. Signals at 4.95 and 5.19 δ (2H) are due to two hydrogens of hydroxyl groups, and a signal at 5.34 δ (one proton) is due to a hydrogen on unsaturated carbon atom (α-hydrogen). When the spectrum was taken in D_2O, the doublet at 4.95 and 5.19 δ due to the two hydroxyl protons disappeared and a signal at 4.67 due to water appeared.

The chromic acid oxidation in acetone of khusinodiol (36) afforded the keto-alcohol, $C_{15}H_{24}O_2$ (37), m.p. 89-90°, $(\alpha)_D$ + 163.2°. The infrared spectrum (Fig. 14) showed bands at 3500 and 1139 cm^{-1} (tertiary hydroxyl group), 1650 and 1630 cm^{-1} (α,β- unsaturated ketone) and 1420 cm^{-1} due to $-CO-CH_2-$ group. The ultraviolet spectrum gave absorption maximum at 236 mμ (ε_{max}, 14,640) indicating the presence of α,β-unsaturated ketone. On partial tosylation, the khusinodiol (36) gave corresponding tosyl derivative (38) which on lithium aluminium hydride reduction

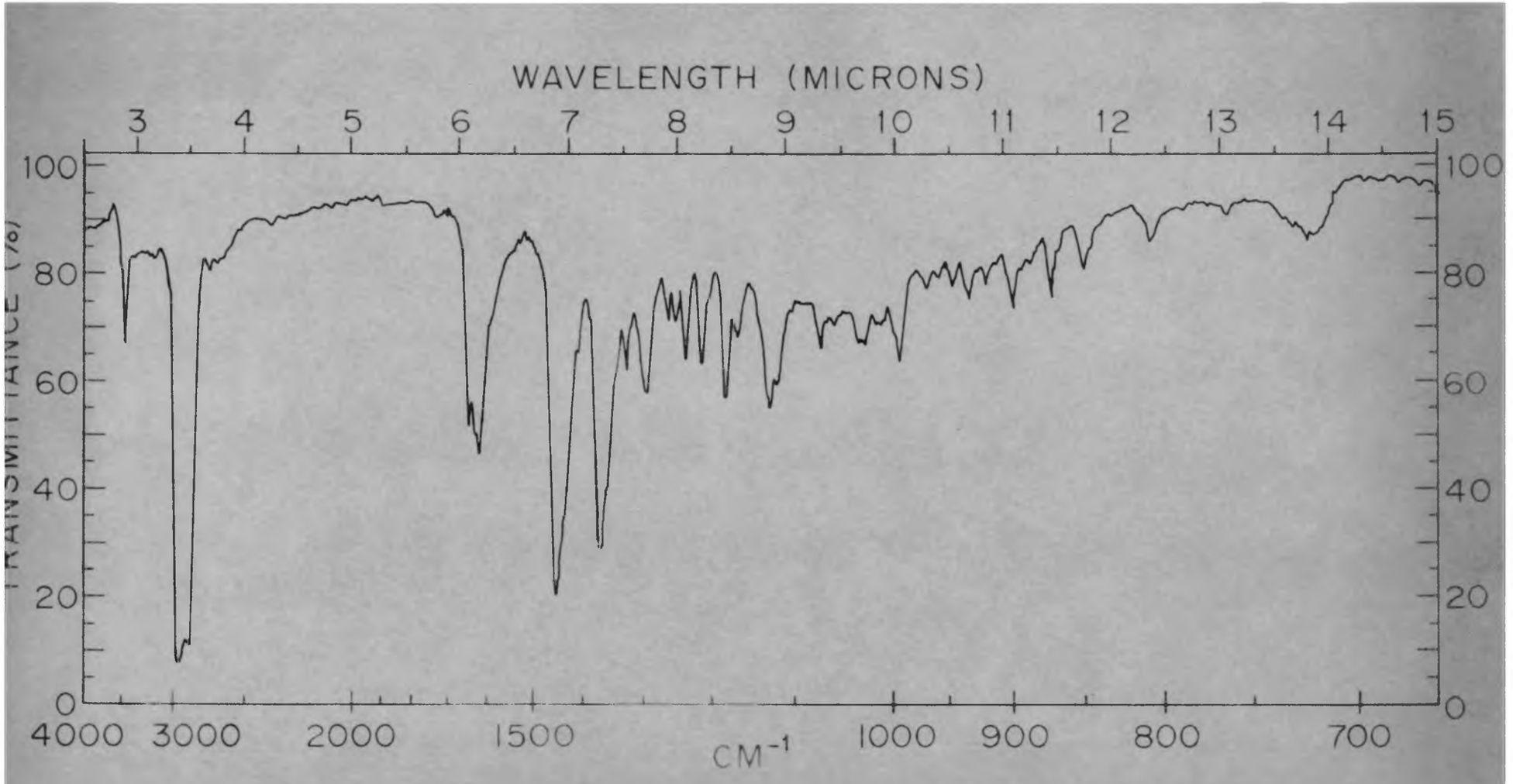


FIG. 14. IR SPECTRUM OF THE KETO-ALCOHOL (37).

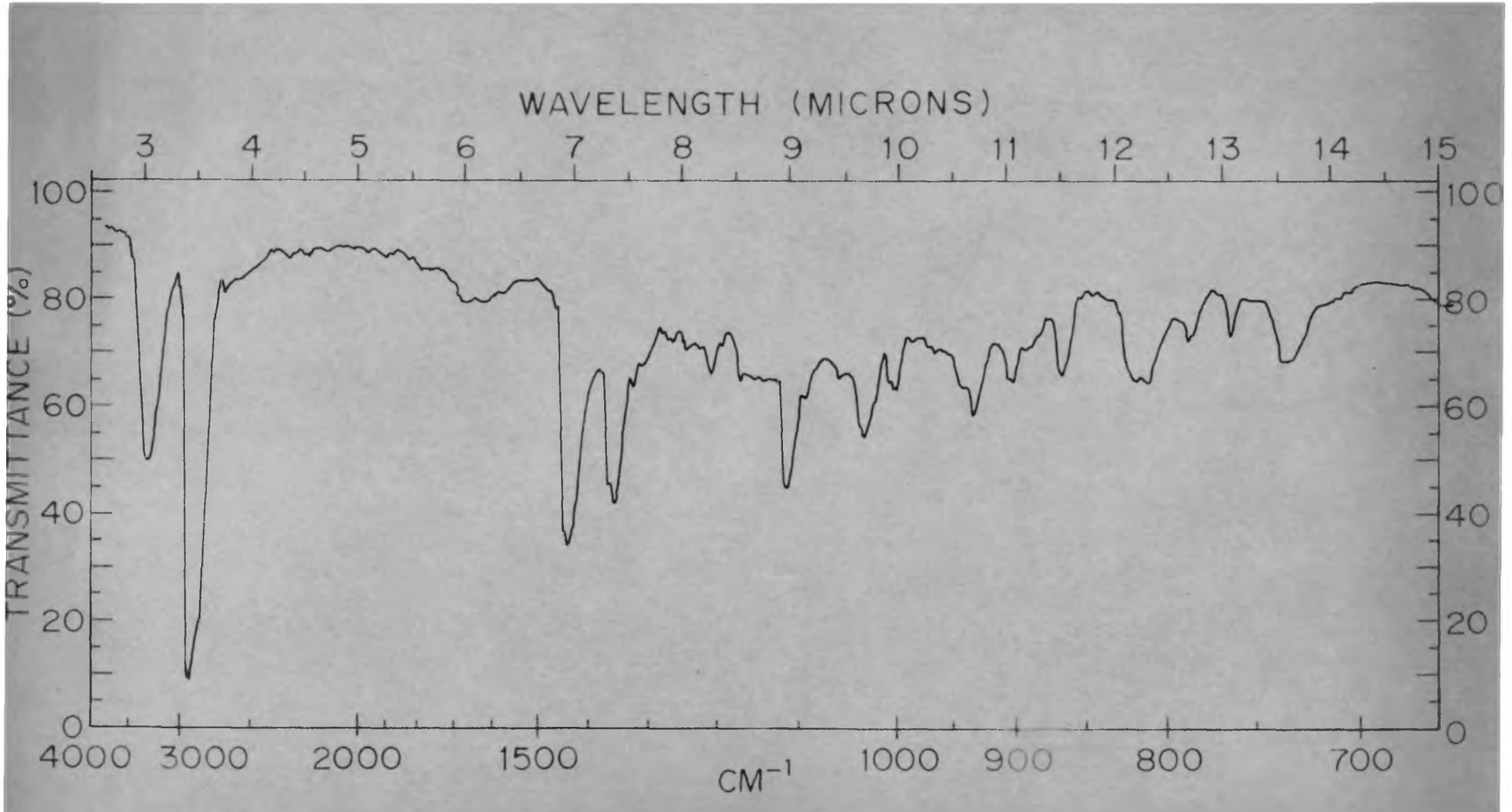
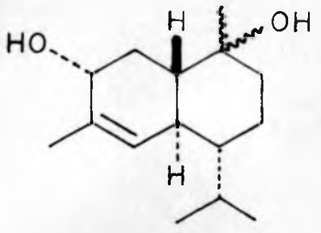
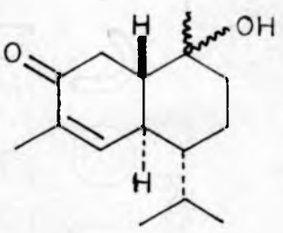


FIG. 15. IR SPECTRUM OF THE MONOL FROM KHUSINODIOL.

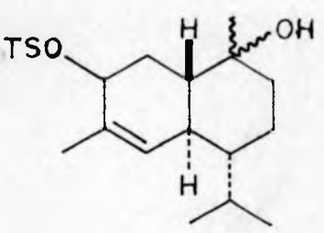
gave the monol, $C_{15}H_{26}O$ (39), m.p. 88-90°, $(\alpha)_D$ + 95.72° (c, 2.34). Its infrared spectrum (Fig. 15) closely resembled that of α-cadinol[20] (40). Its stereochemistry is now receiving our attention.



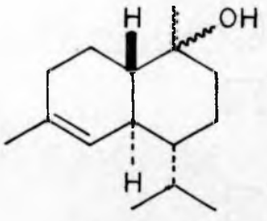
(36)



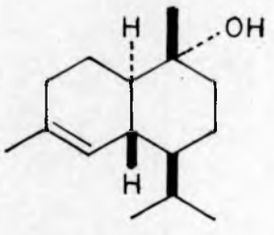
(37)



(38)



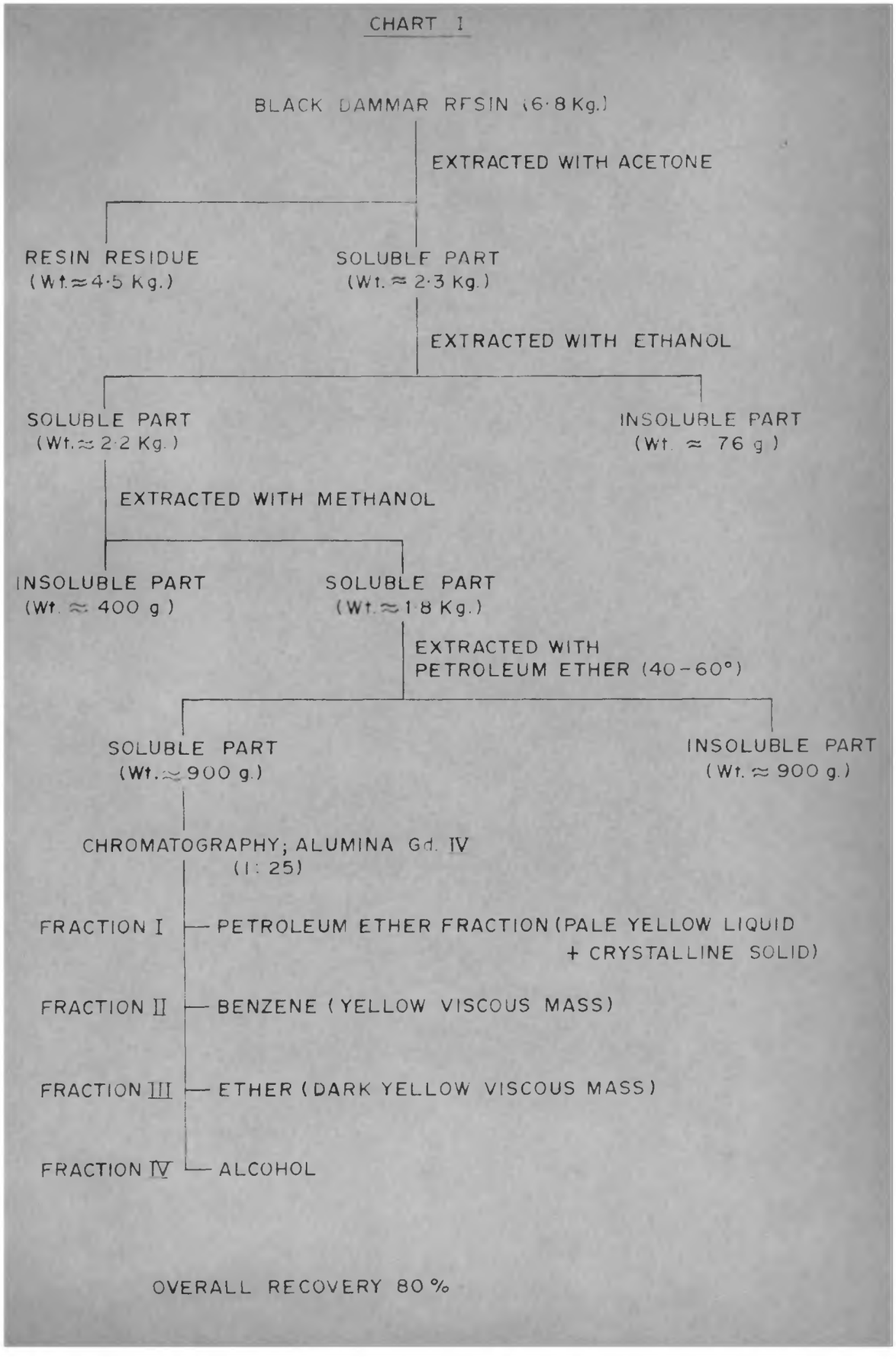
(39)



(40)

EXPERIMENTAL

CHART I


BLACK DAMMAR RESIN (6·8 Kg.)
EXTRACTED WITH ACETONE
RESIN RESIDUE (Wt.≈4·5 Kg.)
SOLUBLE PART (Wt.≈2·3 Kg.)
EXTRACTED WITH ETHANOL
SOLUBLE PART (Wt.≈2·2 Kg.)
INSOLUBLE PART (Wt. ≈ 76 g)
EXTRACTED WITH METHANOL
INSOLUBLE PART (Wt. ≈ 400 g)
SOLUBLE PART (Wt.≈1·8 Kg.)
EXTRACTED WITH PETROLEUM ETHER (40–60°)
SOLUBLE PART (Wt.≈900 g.)
INSOLUBLE PART (Wt. ≈ 900 g.)
CHROMATOGRAPHY; ALUMINA Gd. IV (1 : 25)
FRACTION I — PETROLEUM ETHER FRACTION (PALE YELLOW LIQUID + CRYSTALLINE SOLID)
FRACTION II — BENZENE (YELLOW VISCOUS MASS)
FRACTION III — ETHER (DARK YELLOW VISCOUS MASS)
FRACTION IV — ALCOHOL
OVERALL RECOVERY 80 %

EXPERIMENTAL

Chromatography Table-I

Chromatography of petroleum ether fraction (Chart I)

Weight of fraction 126 g.

Weight of alumina- 3780 g., grade III, ratio 1:30

Fr.	Eluent	No. of ml. collected	Weight (g)	n_D^{26}	Remarks
1	Pet.ether	500	8.5678	1.5030	Sesquiterpene hydrocarbons
2	"	"	1.7170	1.5040	
3	"	"	0.9176	1.5036	
4	"	"	1.3910	1.4975	
5	"	"	1.2590	1.4970	β - amyrin acetate
6	"	"	1.5485	-	
7	"	"	1.9031	-	
8	"	"	1.9857	-	
9	"	"	2.5690	-	
10	"	"	1.9170	1.5030	
11	"	"	2.0560	1.5060	Ester and ketonic fractions
12	"	"	1.6582	1.5090	
13	"	"	1.4298	1.5130	
14	"	"	1.3743	1.5160	
15	"	1000	2.0397	1.5180	

Chromatography Table-I (Contd.)

Fr.	Eluent	No. of ml. collected	Weight (g)	n_D^{26}	Remarks
16	Pet.ether	500	1.1363	1.5140	
17	"	1000	1.8370	1.5110	Ketonic
18	"	1000	1.5741	1.5120	fractions
19	"	1000	0.8998	1.5110	
20	"	1000	1.0891	1.5150	
21	"	3000	4.5329	1.5100	
22	Benzene	500	12.3127	-	Canarone and
23	"	"	13.3475	-	Junenol
24	"	"	14.7634	-	
25	"	"	9.9980	-	Epi-khusinol
26	"	"	2.7800	-	
27	"	"	5.9536	-	Crystalline solid
28	"	"	5.0111	-	α-amyrin
29	"	"	3.9314	-	
30	"	"	-	-	
31	Ether	500	0.4193	-	
32	"	"	0.3253	-	
33	"	1000	-	-	

Isolation of Hydrocarbon

Fraction 1 (Chromatography Table-I) (8.86 g) was rechromatographed over neutral alumina (grade II, 428 g., ratio 1:50). The column was eluted with petroleum ether and the chromatographic results are given in Chromatography Table-II.

Chromatography Table-II

Fr.	Eluent	No. of ml. collected	Weight (g)	n_D^{26}	$(\alpha)_D$
1	Pet.ether	50	0.3705	1.4920	+ 5.35°
2	"	"	4.3032	1.5020	+ 7.09°
3	"	"	1.2492	1.5030	-
4	"	"	1.2121	1.5030	-
5	"	"	0.5643	1.5040	- 3.82°
6	"	"	0.1333	1.5030	-
7	"	"	0.0547	1.4980	-
8	"	"	-	-	-

Fraction 2 (4.2 g) was chromatographed separately on alumina (grade I, 200 g) and 10 ml. fractions were collected. Fractions with the same refractive index(1.4970) were combined and was distilled over sodium under reduced

pressure and physico-chemical constants were determined: b.p. 90°/6 mm., $(\alpha)_D$ + 0.77° (c, 1.6), n_D^{26} 1.496, d_4^{25} 0.9074; $(R_L)_D$ = 66.12. $C_{15}H_{24}\sqrt{2}$ requires: 66.14.

Fig.1. IR spectrum (in 0.1 mm. liquid cell) bands at: 3077, 2710, 1765, 1637, 1274, 1176, 1150, 1130, 1000, 967, 940, 909, 886, 835, 785 cm^{-1}.

Ultraviolet spectrum showed no absorption maximum characteristic of a dienic system.

Analysis

Found: C, 88.10; H, 11.90.

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

Dehydrogenation of Hydrocarbon

The hydrocarbon (0.3 g) was heated with selenium (0.4 g) at 280-290° for 10 hrs. in nitrogen atmosphere. The dehydrogenated product was taken up in pet.ether. The extract was concentrated and chromatographed over alumina (grade I, 50 g) and the column eluted with pet.ether. The colourless non-azulenic product was eluted first from the column followed by violet coloured azulene.

The non-azulenic part gave an orange coloured complex with picric acid which after crystallisation from ethanol had m.p. 114°. Mixed melting point with an authentic sample of cadalene picrate (m.p. 116°) was undepressed.

Petroleum ether solution of the blue azulene after shaking with phosphoric acid and decomposing the complex with cold water and extracting with ether, finally yielded small amount of azulene. It gave a complex with s-trinitrobenzene which after crystallisation from ethanol had m.p. 107-110°; visible spectrum: λ_{max}. 580 and 630 mμ. Because of paucity of material the azulene could not be identified further.

Estimation of Unsaturation in the Hydrocarbon

(a) By hydrogenation

The hydrocarbon (0.25 g) in glacial acetic acid (20 ml) was hydrogenated in the presence of platinum catalyst (15 mg) at room temperature. It absorbed 2 moles of hydrogen. The hydrogenated product, after filtering off the catalyst, was diluted with water and extracted with pet.ether. The extract was washed with bicarbonate solution and finally with water and dried. Solvent was evaporated and the product was distilled over sodium, b.p.95°/7 mm., n_D^{25} 1.4750.

Analysis

Found: C, 86.30; H, 13.70.

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

(b) By perbenzoic acid

Hydrocarbon (i) 39 mg; (ii) 45 mg, was treated with perbenzoic acid solution (5 ml) on each occasion) in chloroform and was kept in the refrigerator. Blank experiments were run simultaneously. The excess of

perbenzoic acid was titrated against standardised sodium thiosulphate solution at different intervals of time. It absorbed (i) 2.3 moles after 24 hours and (ii) 1.9 moles after 72 hours.

Ozonolysis of Hydrocarbon

A stream of ozonised oxygen was bubbled through a solution of the hydrocarbon (0.5 g) in chloroform (10 ml) for 5 hours. The trap water collected during ozonolysis gave dimedone derivative (m.p. 189°) and iodoform test, indicating the presence of formaldehyde and acetone. The ozonide after removal of solvent at 40° was decomposed by heating with water (20 ml) on a water bath for 3 hours. It gave positive test for an aldehyde group (Fehling's solution), and for a methyl ketone (iodoform test in dioxan), but failed to give colour test with alcoholic ferric chloride.

Separation of α-amyrin and β-amyrin

From the total crystalline substance obtained in petroleum ether fraction (Chart I), 5 g. of the substance was chromatographed on neutral alumina (grade III, 150 g). It was found that the crystalline substance contains both α-amyrin and β-amyrin. The results are recorded below.

Chromatography Table-III

Wt. of the substance 6 g.

Wt. of alumina 180 g., grade III, ratio 1:30

Fr.	Eluent	No. of ml. collected.	Wt. of fraction(g)	m.p. of crude fraction.	$(\alpha)_D$
1	Pet.ether	800	nil	-	-
2	Benzene	100	0.04	162-65°	-
3	"	100	1.5	165-68°	+ 83.33°
4	"	100	1.5	165-68°	-
5	"	100	0.7	165-68°	-
6	"	100	0.4	168-70°	+ 87.17°
7	Ether	800	0.5	viscous liquid.	

α-amyrin acetate (3b)

Fraction 3 (1 g) from the above chromatography was dissolved in anhydrous pyridine (30 ml) and acetic anhydride (20 ml) was added. The reaction mixture was allowed to stand overnight at room temperature. The acetate ester(1.5 g) was obtained by working up in the usual way. It was chromatographed on alumina (grade III, 40 g). Pet.ether eluted fractions were crystallised from ethyl acetate to yield α-amyrin acetate, m.p.223-224°, $(\alpha)_D$ + 82.2°.

Fig.2B. IR spectrum (in nujol) bands at: 1740, 1250, 1150, 1100, 1050, 1025, 1000, 983, 965, 950, 935, 902, 820, 808 cm^{-1}.

It was found to be identical with that of ∝-amyrin-acetate.

Analysis

Found: C, 82.00; H, 11.00.

$C_{32}H_{52}O_2$ requires: C, 81.99; H, 11.18%.

∝-amyrin (3a)

A portion of the acetate (500 mg) was refluxed with alcoholic KOH (10 ml; 10%) for 3 hr. The hydrolysed product (450 mg) was obtained in the usual way, filtered through a short column of alumina (grade III, 10 g), crystalline solid eluted in petroleum ether:benzene (1:1, 250 ml) on crystallisation from ethanol gave pure ∝-amyrin, m.p.182-184°, $(\alpha)_D$ + 91.2°.

Fig.2A. IR spectrum(in nujol) bands at: 3300, 1361, 1342, 1290, 1170, 1134, 1097, 1026, 990, 986, 943, 917, 823, 800 cm^{-1}.

It was found to be identical with ∝-amyrin.

Analysis

Found: C, 84.10; H, 11.36.

$C_{30}H_{50}O$ requires: C, 84.44; H, 11.81%.

<u>α-amyrin benzoate</u> (3c)

A solution of α-amyrin (100 mg) in dry pyridine (5 ml) was treated with benzoyl chloride (1 ml). The reaction mixture was heated on a water bath for 5 hr, and the product was worked up in the usual manner. Crystallisation from acetone gave pure α-amyrin benzoate, m.p.192-194°, $(\alpha)_D$ + 94°.

Its IR spectrum was identical with that of α-amyrin benzoate.

All the above evidences confirmed that Fraction 3 is α-amyrin.

<u>Analysis</u>

Found: C, 83.7; H, 10.4.

$C_{37}H_{54}O_2$ Requires: C, 83.72; H, 10.25%.

<u>β-amyrin acetate</u> (4b)

Fraction 6 (0.4 g) from the same chromatography (Chromatography Table-III) was acetylated by dissolving it in pyridine (12 ml) and acetic anhydride (8 ml). The reaction mixture was left overnight at room temperature. The crude acetate (0.45 g) obtained by working up in the usual manner, was filtered through a short column of alumina (grade III, 20 g) and elution with petroleum ether afforded a solid which on crystallisation from ethyl acetate yielded pure β-amyrin acetate, m.p.238-239°, $(\alpha)_D$ + 83.5°.

Fig.3B. IR spectrum(in nujol) bands at: 1740, 1280, 1145, 1090, 1025, 995, 978, 962, 899, 825, 810, 800 cm^{-1}.

The infrared spectrum was found to be identical with that of β-amyrin acetate.

β-amyrin (4a)

The acetate (200 mg) was hydrolysed by refluxing for 5 hrs with alcoholic KOH (10 ml, 5%). The hydrolysed product (170 mg) was filtered through a column of alumina (grade III, 10 g) and elution with pet.ether:benzene (1:1, 100 ml) afforded a solid which on crystallisation from ethanol gave pure β-amyrin, m.p.197-198°, $(\alpha)_D$ + 89°.

Fig.3A. IR spectrum(in nujol) bands at: 3300, 1370, 1361, 1299, 1183, 1136, 1095, 1034, 954, 823, 813, 800 cm^{-1}.

It was found to be identical with that of β-amyrin.

Analysis

Found: C, 84.16; H, 11.96.

$C_{30}H_{50}O$ requires: C, 84.44; H, 11.81%.

β-amyrin benzoate (4c)

β-amyrin (70 mg) was dissolved in dry pyridine (5 ml) and benzoyl chloride (1 ml) was added. The reaction mixture was heated on a water bath for 5 hr. and the product was worked up in the usual manner. The crude

benzoate after crystallisation from acetone gave pure β-amyrin benzoate, m.p.232-233°.

Its IR spectrum was found to be identical with that of β-amyrin benzoate.

In all the above cases, mixed melting points with the authentic samples of β-amyrin and its derivatives available in our laboratory, were taken and they showed no depression.

Fraction 6, therefore, is β-amyrin.

Isolation of pure β-amyrin acetate

Fractions 5 to 10 (10.2 g, Chromatography Table-I) were combined and rechromatographed over alumina. The results of the chromatography are presented in Chromatography Table-IV.

Chromatography Table-IV

Wt. of the fraction 10.9 g.

Wt. of alumina 400 g; grade III; ratio 1:36.

Fr.	Eluent	Vol. of eluent (ml)	Wt. of fraction. (g)	n_D^{26}	Remarks
1	Pet.ether	100	0.3284	1.4910	
2	"	50	0.9834	1.5010	
3	"	50	2.5510	-	
4	"	50	1.2890	-	β - amyrin
5	"	50	0.5532	-	acetate
6	"	50	0.3579	-	
7	"	100	0.4645	-	
8	"	150	0.4282	-	
9	"	250	0.4301	1.5090	
10	Benzene	500	0.2447	1.5160	
11	Ether	200	0.4049	1.5190	

Fractions 3 to 8. The crude solid material (5 g) obtained after combining the fractions 3 to 8 was found to be the acetate ester (from its IR spectrum). It was crystallised from ethyl acetate to yield β-amyrin-acetate as needles, m.p. 234-237°. Recrystallisation from the same

solvent raised the melting point to 240°, $(\alpha)_D$ + 85°. The mixed melting point with the authentic sample remained undepressed.

Fig.4. IR spectrum(in nujol) bands at: 1730, 1250, 1146, 1090, 1040, 1025, 995, 978, 962, 899, 825, 810, 800 cm^{-1}.

The IR spectrum was superimposable with the spectrum of the authentic sample of β-amyrin acetate.

Analysis

Found: C, 83.00; H, 11.37.

$C_{32}H_{52}O_2$ requires: C, 81.99; H, 11.18%.

α-amyrin

The crystalline substance obtained in benzene fractions (fractions 26 to 29) (Chromatography Table-I) was characterised as α-amyrin through its acetate and benzoate derivatives. The properties of the α-amyrin, its acetate and benzoate derivatives and their infrared spectra were exactly identical with those given in literature.[6]

Isolation of junenol (5)

Fractions 22 to 24 (Chromatography Table-I) were combined and the combined fraction (40 g) was distilled, b.p.130°(bath)/0.3 mm. The distillate (14 g, 35%) was chromatographed over alumina. The results are tabulated below.

Chromatography Table-V

Wt. of the distilled fraction 14 g.

Wt. of alumina 350 g., grade II; ratio 1:25

Fr.	Eluent	Vol. of eluent collected (ml)	Wt. of the fraction (g)	$(\alpha)_D$	
1	Pet.ether	50	0.52	+ 13.6°	
2	"	50	1.26	-	
3	"	50	0.92	-	
4	"	50	0.28	-	
5	"	50	0.25	-	
6	"	50	0.34	-	
7	"	500	0.85	+ 18.8°	
8	Pet.ether-benzene (1:1)	100	0.15	-	
9	Benzene	50	2.05	———	Junenol
10	"	50	1.22	-	
11	"	250	1.67	-	
12	"	250	1.56	-	
13	Ether	500	2.00	-	

Fraction 9 which solidified on keeping was crystallised from pet.ether, sublimed and identified as D-junenol. It had the following properties, m.p.60°, $(\alpha)_D$ + 52°.

The mixed melting point with an authentic sample of D-junenol was 60°.

Fig.5A. IR spectrum(in nujol) bands at: 3600, 1645, 1299, 1366, 1163, 1143, 1070, 1053, 1030, 1000, 980, 938, 912, 893, 885, 873, 854, 826 cm^{-1}.

It was found to be identical with that of D-junenol.

Analysis

Found: C, 80.63; H, 11.51.

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

Dihydrojunenol (6)

Junenol (0.2 g) dissolved in glacial acetic acid (30 ml) was hydrogenated in presence of Adams' catalyst (30 mg) at room temperature and atmospheric pressure. The hydrogenation continued till there was no further uptake of hydrogen. The catalyst was filtered off and the filtrate was diluted with water followed by extraction with ether. Ether layer was washed till neutral and dried. The crude dihydrojunenol was crystallised from pet.ether to give pure dihydrojunenol, m.p.113-114°. The mixed melting point with the authentic sample of dihydrojunenol remained undepressed.

Fig. 5B. IR spectrum(in nujol) bands at: 3400, 1366, 1242, 1190, 1170, 1156, 1136, 1080, 1058, 1042, 1015, 1005, 983, 948, 917, 897, 882, 869, 859, 840 cm^{-1}. The IR spectrum was identical with that of dihydrojunenol.

Analysis

Found: C, 80.20; H, 12.30.

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

epi-Khusinol (12)

The benzene eluted fraction (Fr.25, Chromatography Table-I) was distilled, b.p.140-160° (bath)/0.6 mm. The distillate (2.5 g) was further purified by passing over a column of alumina (grade II, 60 g). The fraction eluted with benzene gave pure epi-khusinol (1.8 g), b.p.120-125° (bath)/0.5 mm., n_D^{27} 1.5140, $(\alpha)_D$ - 86.80° (c, 7.88).

Fig.6. IR spectrum(in liquid film) bands at: 3448, 1640, 1382, 1342, 1320, 1170, 1130, 1071, 1047, 1034, 1012, 896, 850, 833, 795 cm^{-1}.

Analysis

Found: C, 81.40; H, 11.20.

$C_{15}H_{24}O$ requires: C, 81.76; H, 10.90%.

3,5-Dinitrobenzoate

The alcohol (0.15 g) was dissolved in dry pyridine (5 ml) and freshly prepared 3,5-dinitrobenzoyl chloride (0.3 g) was added. The mixture was kept at room temperature for 24 hours. The contents were poured into crushed ice and extracted with ether. The ether layer was washed free

from pyridine with dilute hydrochloric acid and water, then with aqueous sodium carbonate solution (5%) and finally with water till neutral and dried. The crude derivative was crystallised from pet.ether, m.p.186-187°.

IR spectrum (in nujol) bands at: 1739, 1650, 1639, 1550, 1471, 1379, 1365, 1316, 1290, 1176, 1080, 934, 917, 905, 794, 775, 735 and 721 cm^{-1}.

Analysis

Found: N, 6.91.

$C_{15}H_{23}O.C_7H_3O_8N_3$ requires: N, 6.76%.

Dehydrogenation

The alcohol (0.1 g) was heated with selenium powder (0.2 g) at 290° for 6 hr. in nitrogen atmosphere. The dehydrogenated product was extracted with ether and filtered through a short column of alumina (grade I, 10 g) when colourless dehydrogenation product was obtained. It gave trinitrobenzene complex m.p.108-109°. Mixed melting point with the authentic sample of TNB of cadalene showed no depression (108°).

Its IR spectrum was identical with that of TNB of cadalene.

Hydrogenation

The alcohol (0.1134 g) was hydrogenated in glacial acetic acid (15 ml) using platinum catalyst (74 mg). The

absorption of hydrogen (22.4 ml at NTP) corresponding to 2 moles of hydrogen was complete during 4 hours after which there was no further absorption. Catalyst was filtered off and the filtrate diluted with water and the hydrogenated product was taken up in ether. The ether extract was washed free from acid, dried and solvent evaporated. The residue was distilled, b.p.115-120°(bath)/0.5 mm., n_D^{26} 1.4930; $(\alpha)_D$ + 14.03° (c, 3.38).

IR spectrum (in liquid film) bands at: 3450, 1389, 1372, 1269, 1136, 1087, 1052, 1031, 994, 951, 862 cm^{-1}.

Analysis

Found: C, 79.90; H, 12.40.

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

Ketone (17) from khusinol (11)

Khusinol (3 g) was dissolved in pure acetone (75 ml) and Jones' chromic acid reagent (11.3 ml) was added dropwise to the stirring solution till persistant orange colour remained. The product was diluted with water, extracted with ether, washed with water, dried and the product thus obtained after removal of solvent was chromatographed on alumina (grade II, 90 g) to give the pure ketone (1.8 g) on elution with pet.ether-benzene (1:1) mixture, m.p.87° (sublimed) $(\alpha)_D$ + 79.75°.

UV spectrum $\lambda_{max.}$ 244 mμ (ε_{max}, 10,480) and $\lambda_{max.}$ 278 mμ (ε_{max}, 7,498).

Fig.7. IR spectrum (in nujol) bands at: 1667, 1613, 1420, 1382, 1274, 1239, 1176, 1143, 1111, 1072, 1024, 897, 878, 862, 793 cm^{-1}.

NMR spectrum is represented in Fig.8.

Analysis

Found: C, 82.73; H, 10.07.

$C_{15}H_{22}O$ requires: C, 82.51; H, 10.16%.

Tosylation of epi-khusinol

Alcohol (0.477 g) was dissolved in dry pyridine (10 ml) and freshly crystallised p-toluene sulphonyl chloride (0.609 g) in dry pyridine (10 ml) was added. The contents were kept in well stoppered flask for 48 hours at room temperature. It was processed in the usual way to obtain the crude tosylate.

IR spectrum (in liquid film) bands at: 1724, 1653, 1597, 1493, 1364, 1333, 1217, 1186, 1170, 1134, 1090, 1064, 1022, 943, 900, 864, 840, 820, 793, 725, 692 cm^{-1}.

Conversion of the tosylate (20) to (-)-γ-cadinene (22)

The crude tosylate (0.67 g) was dissolved in dry ether (25 ml) and added dropwise to a slurry of lithium

aluminium hydride (0.6 g) in dry ether (25 ml) at zero degree with stirring. The addition was done in 15 minutes. The reaction mixture was then refluxed for 12 hr. The excess of lithium aluminium hydride was decomposed with moist ether and finally with water. The ether layer was separated and the aqueous layer was extracted several times with ether. The combined ethereal extracts were washed with water till neutral and dried over sodium sulphate. The reaction product obtained after removal of solvent was filtered through a column of alumina (grade I, 20 g), elution with pet.ether gave the hydrocarbon (0.2 g), which was further purified by distillation in vacuo, over sodium b.p. 140° (bath)/4.5 mm., n_D^{26}, 1.5068, $(\alpha)_D$, - 130° (c, 1.82).

Fig.9. IR spectrum (in liquid film) bands at: 3077, 1796, 1642, 1408, 1389, 1370, 1250, 1220, 1186, 1171, 1130, 1070, 1020, 1000, 947, 889, 836, 798 cm^{-1}.

The IR spectrum was superimposable with that of (-)-γ-cadinene. VPC analysis showed a single peak. The identity was further confirmed by taking the mixed VPC with the authentic sample of (-)-γ-cadinene available in our laboratory.

Analysis

Found: C, 88.20; H, 11.80.

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

Ketone (25) from tetrahydroalcohol (14)

Chromium trioxide (0.3 g) was dissolved in pyridine (6 ml) at 0° to which a solution of the tetrahydro alcohol(0.3 g) in pyridine (6 ml) was added under cooling and shaking. The reaction mixture was left overnight at room temperature. Contents were diluted with water and extracted repeatedly with benzene-ether (1:1), using filtration through super-cel to break the emulsion formed. The solvent layer was washed successively with dilute hydrochloric acid, sodium carbonate solution (5%) and finally with water and dried. The residue (0.25 g) obtained after removal of solvent was chromatographed over alumina (grade II, 10 g). The pure ketone (0.2 g) was eluted with pet.ether-benzene (1:1) mixture. It was distilled in vacuo, b.p.130-135° (bath)/2.5 mm.

Fig.10A. IR spectrum(in liquid film) bands at: 1710, 1418, 1383, 1399, 1236, 1212, 1168, 1136, 1111, 1042, 1020, 980, 917, 893, 862 cm^{-1}.

IR spectrum was found to be identical with that of the saturated ketone obtained from khusinol (Fig.10B).

The identity was further confirmed by taking the mixed VPC with the sample of saturated ketone prepared from khusinol.

Analysis

Found: C, 80.69; H, 12.46.

$C_{16}H_{26}O$ requires: C, 81.02; H, 11.79%.

Wolff-Kishner reduction of ketone(17)

The ketone (0.3 g) was refluxed for 1 hr. at 180° under nitrogen atmosphere with a mixture of potassium hydroxide (0.9 g), hydrazine hydrate (99-100%; 1 ml) and diethylene glycol (10 ml). The temperature was then raised and kept at 210° for 5 hr. After cooling to room temperature, the reaction mixture was diluted with water (100 ml) and extracted with pet.ether. The extract was washed with water, dried and solvent evaporated. The hydrocarbon(0.1 g) obtained was purified by filtering over a short column of alumina (grade I, 5 g) and eluting with pet.ether.

VPC analysis of the hydrocarbon showed three distinct peaks. Theoretically, formation of the two hydrocarbons(27) and (28) was expected. However, the formation of the third hydrocarbon (29) though not antipipated, was confirmed by taking VPC and comparing the retention time under identical conditions with the hydrocarbon obtained by N-lithioethylene diamine reaction on khusimol.

Conversion of ketone (17) to the acetate (35)

The ketone (0.5 g) was dissolved in acetic anhydride (20 ml) and conc. sulphuric acid (1 ml) in acetic anhydride (6 ml) was added. The colour changed to bluish green. The reaction mixture was allowed to stand at room temperature for 6 hours. It was then diluted with cold water (100 ml)

to decompose the acetic anhydride and extracted with ether. The residue (0.4 g), after removal of solvent, was distilled under vacuo, to give the ester (0.15 g), b.p.140-150° (bath)/ 0.3 mm.

Fig.11. IR spectrum(in liquid film) bands at: 1776, 1613, 1582, 1299, 1205, 1160, 1064, 1053, 1018, 975, 900, 881, 843, 816 cm^{-1}.

Analysis

Found: C, 79.23; H, 9.67.

$C_{17}H_{24}O_2$ requires: C, 78.42; H, 9.29%.

Khusinodiol (36)

To a solution of khusinol (3.5 g) in dry benzene (50 ml), freshly distilled BF_3- etherate (2 ml) was added dropwise with stirring. The reaction mixture was allowed to stand at room temperature for 30 minutes. Contents were poured into water. Benzene layer was separated and the aqueous layer extracted with ether. The combined extract was washed with water and dried. Removal of solvent gave the residue (2.4 g) which on chromatography afforded khusinodiol. The chromatography data is given in Chromatography Table-VI.

Chromatography Table-VI

Wt. of the substance 2.4 g.

Wt. of alumina 75 g., grade II, ratio 1:30

Fr.	Eluent	Vol. of eluent (ml)	Wt. of fraction. (g)	Remarks
I	Pet.ether	100	0.5 ——	Hydrocarbon (VPC analysis showed four peaks)
2	Pet.ether	100	-	
3	Pet.ether - benzene (1:1)	100	1.0 ——	liquid alcohols
4	Benzene	50	-	
5	Ether	100	0.4 ——	Unreacted khusimol
6	Ether	tail fractions	0.5 ——	Khusinodiol (20%)

The tail fractions afforded crystalline substance which was crystallised (twice) from pet.ether-ether (1:1) and further purified by sublimation at 130-140°(bath)/1 mm. to give the pure diol, m.p.133°, $(\alpha)_D$ + 23.81° (c, 1.47).

TLC analysis (solvent phase - 15% ethyl acetate in benzene) showed one spot.

Fig.12. IR spectrum(in nujol) bands at: 3400, 3300, 1370, 1363, 1333, 1266, 1183, 1163, 1151, 1120, 1099, 1064, 1036, 1010, 990, 980, 943, 930, 900, 887, 873, 813 cm^{-1}.

NMR spectrum is represented in Fig.13 and agrees well with the structure.

Analysis

Found: C, 75.54; H, 11.39.

$C_{15}H_{26}O_2$ requires: C, 75.63; H, 10.92%.

Oxidation of khusinodiol (36) to the keto-alcohol(37)

Khusinodiol (100 mg) was dissolved in dry acetone (25 ml) and Jones' reagent was added slowly to a stirring solution till persistent orange colour was obtained. The product was worked up according to the procedure described earlier. The oxidation product after chromatography on alumina (grade III, 5 g) gave the keto-alcohol (80 mg) on elution with benzene. It was further purified by sublimation at 100°(bath)/1 mm. The keto-alcohol had the following properties, m.p. 90°, $(\alpha)_D$ + 163.2°.

Fig.14. IR spectrum(in nujol) bands at: 3500, 1650, 1620, 1430, 1333, 1299, 1243, 1214, 1186, 1129, 1075, 1031, 954, 922, 873, 851 cm^{-1}.

UV spectrum showed absorption maximum at 236 mμ, ε_{max}, 14,640.

Analysis

Found: C, 76.32; H, 10.34.

$C_{15}H_{24}O_2$ requires: C, 76.28; H, 10.17%.

Partial tosylation of khusinodiol

Khusinodiol (0.45 g) was dissolved in dry pyridine (10 ml) and freshly crystallised p-toluene sulphonyl chloride (0.85 g) in dry pyridine (10 ml) was added. The mixture was kept at room temperature for 48 hours. It was worked up in the usual way to obtain the crude tosylate (38)(0.6 g).

Lithium aluminium reduction of the tosylate (38)

The crude tosylate (0.6 g) was dissolved in dry ether (25 ml) and added slowly to a slurry of lithium aluminium hydride (0.4 g) in dry ether (25 ml) at 0°. Refluxing was then carried on for six hours. The excess of lithium aluminium hydride was decomposed with moist ether and finally with water. The product was isolated in the usual way and chromatographed over alumina (grade II, 15 g). Elution with a mixture of benzene-ether (1:1) gave the monol(0.332 g) which was distilled in vacuo, b.p.130-180°(bath)/2 mm. It was purified by sublimation at 85°(bath)/0.5 mm. The monol had the following properties, m.p.88-90°, $(\alpha)_D$ + 96.72° (c,2.34).

Fig.15. IR spectrum(in nujol) bands at: 3400, 1220, 1134, 1042, 1010, 943, 910, 877, 826, 813, 733, 769, 740 cm^{-1}.

Analysis

Found: C, 81.30; H, 11.20.

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

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CHAPTER II

STRUCTURE AND ABSOLUTE CONFIGURATION OF CANARONE, A NEW KETONE, FROM BLACK DAMMAR RESIN

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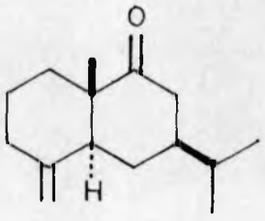
SUMMARY

From the petroleum ether extract of the Black dammar resin (Canarium strictum Roxb.), an eudalenic, monocethynoid sesquiterpene ketone, canarone, has been isolated in small amount. On the basis of chemical degradations, IR, UV, NMR spectral studies and optical rotatory dispersion measurements, the absolute configuration of canarone has been determined and is as shown below.



Canarone, $C_{15}H_{24}O$, $(\alpha)_D$ + 34.78°, is a new monoethynoid sesquiterpenoid ketone which has been isolated from the petroleum ether extract of the Black dammar resin (Canarium strictum Roxb.).

The infrared spectrum (Fig.1) of canarone, exhibited bands at 1700 cm^{-1} characteristic of 2,2-dialkyl cyclohexanone[1] and 1420 cm^{-1} due to $-CO-CH_2-$ grouping. Bands at 3080, 1640 and 890 cm^{-1} indicated the presence of terminal methylene group. Ultraviolet spectrum showed no characteristic absorption and hence canarone is not an α,β-unsaturated ketone. Canarone easily furnished a semicarbazone, m.p. 222-224° (IR spectrum, Fig. 2).

Nature of the carbon skeleton

Canarone (1) on lithium aluminium hydride reduction gave canarol, $C_{15}H_{26}O$ (5), which on selenium dehydrogenation gave good yield of eudalene (3). No azulene was detected or isolated from the product of dehydrogenation. From these experiments, it was possible to assign eudalenic skeleton to canarone, thereby accounting for 14 of the 15 carbon atoms in the molecule. Assuming that canarone follows the isoprene rule and that the remaining carbon atom was present as an angular methyl group, its elimination during selenium dehydrogenation[2] could be anticipated. The infrared spectrum

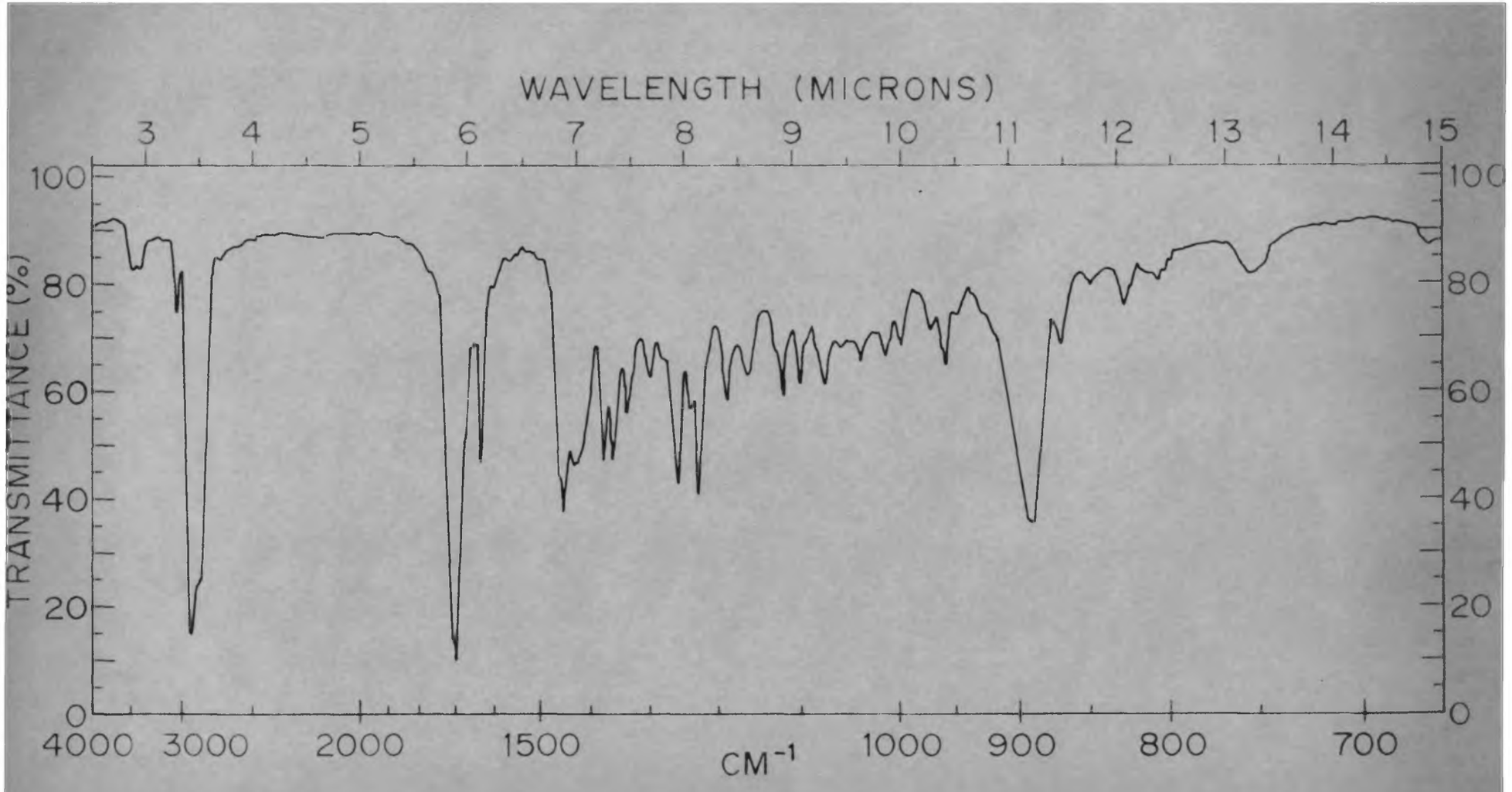


FIG. 1. IR SPECTRUM OF THE CANARONE (I) FROM BLACK DAMMAR RESIN.

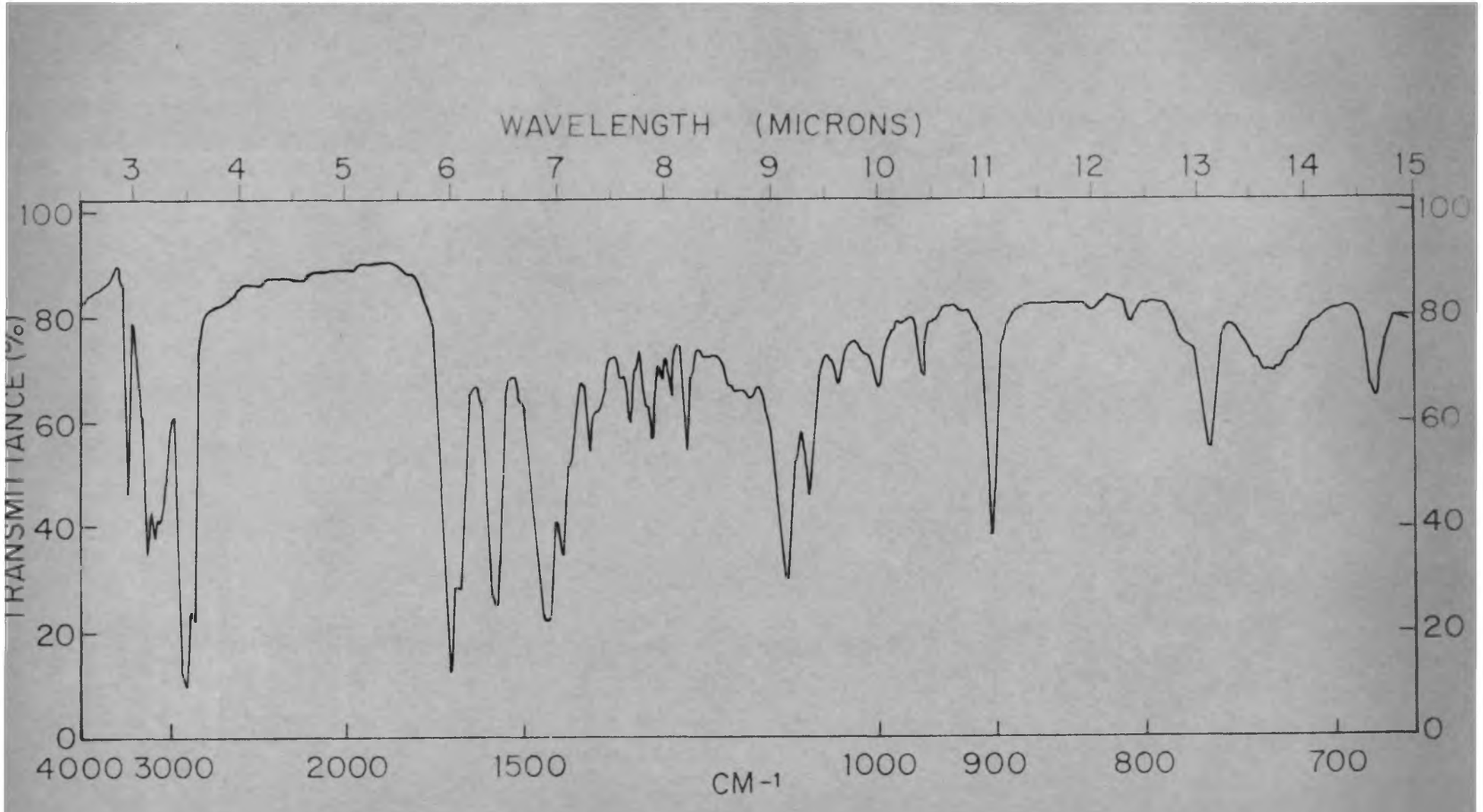


FIG. 2. IR SPECTRUM OF THE SEMICARBAZONE OF CANARONE.

of canarol (Fig.4A) showed prominent band at 3450 cm^{-1} indicating the presence of hydroxyl function and strong bands at 1640 and 890 cm^{-1} showing the presence of exo-cyclic double bond.

Nature of unsaturation

Catalytic hydrogenation of canarone with Adams' catalyst in acetic acid afforded a tetrahydro product, dihydrocanarol (6). Its infrared spectrum (Fig. 4B) showed absence of bands at 1700 cm^{-1} due to ketone and 1640 and 890 cm^{-1} due to the terminal methylene group, but instead showed a intense band at 3500 cm^{-1}.

Hydrogenation of canarol (6) in acetic acid over Adams' catalyst also afforded dihydrocanarol (6), showing the presence of one double bond in canarol (6), and hence in canarone (1). This was further confirmed by carrying out quantitative hydrogenation of canarone over palladium charcoal catalyst in methanol, furnishing the saturated ketone, dihydrocanarone, $C_{15}H_{26}O$ (4). The infrared spectrum (Fig. 3) of dihydrocanarone lacked the bands due to terminal methylene group. Canarone, having the molecular formula $C_{15}H_{24}O$ and one double bond, should therefore be a bicyclic ketone.

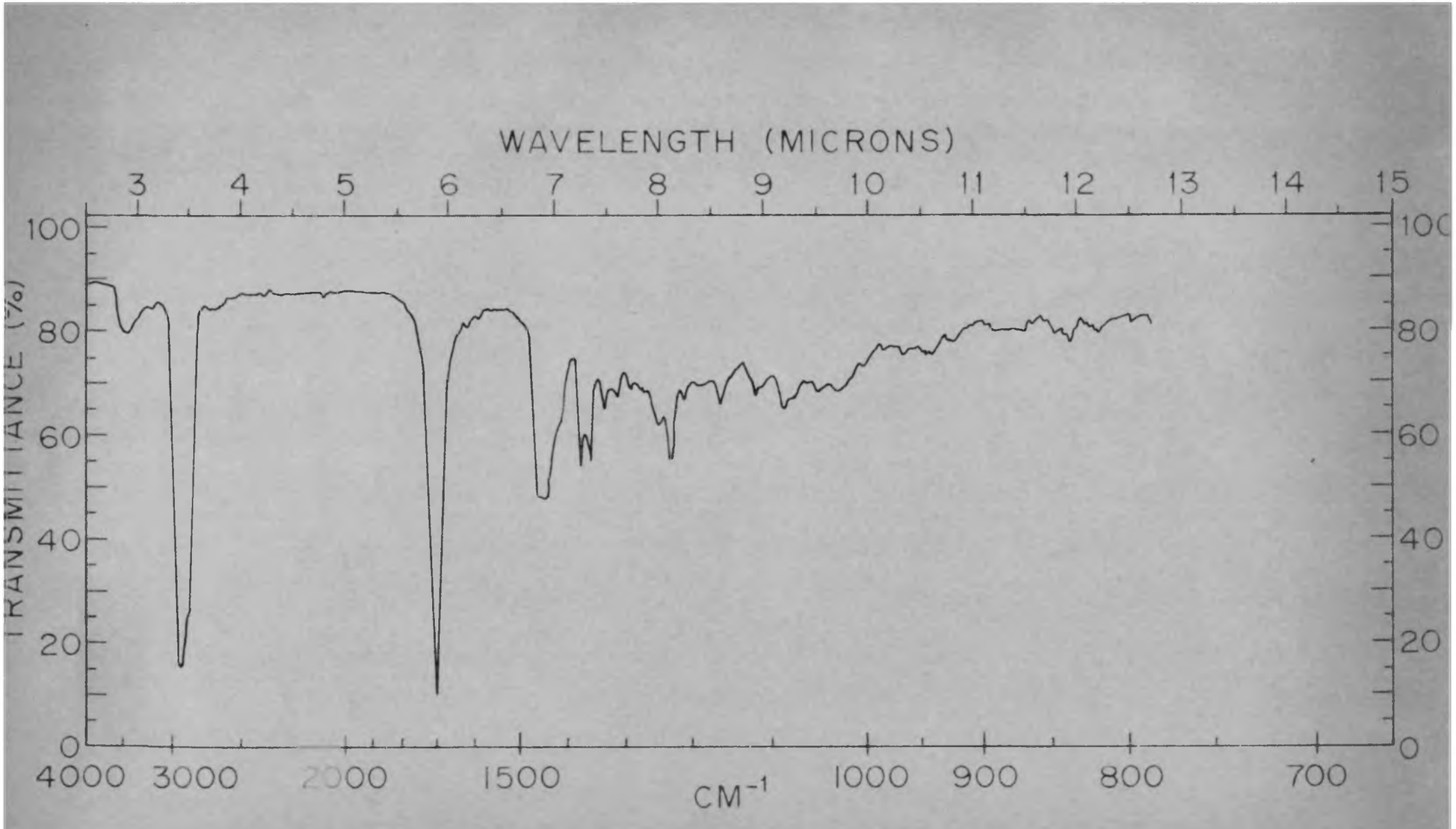


FIG. 3. IR SPECTRUM OF THE DIHYDROCANARONE (4).

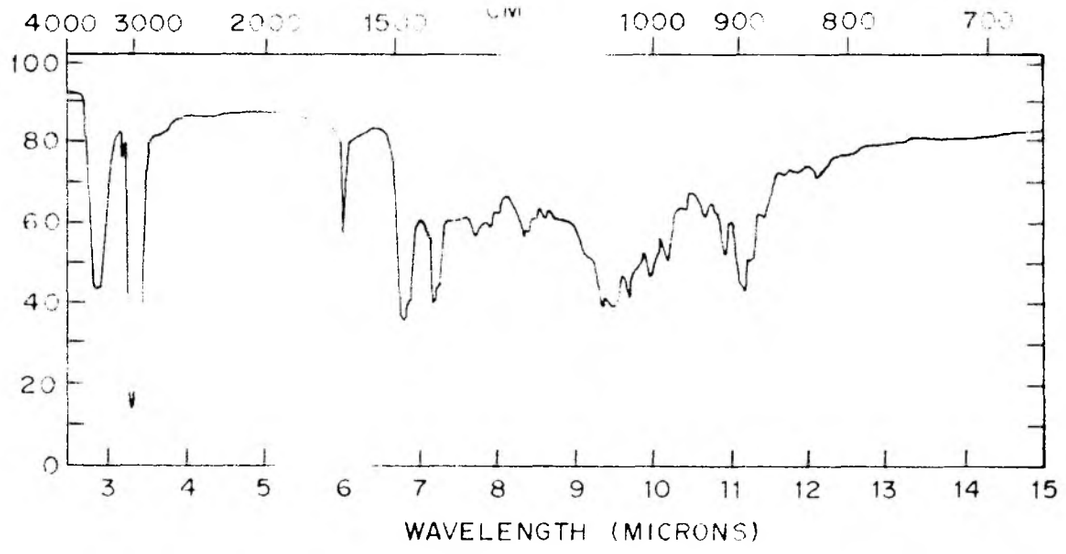


FIG. 4A. IR SPECTRUM OF THE CANAROL (5).

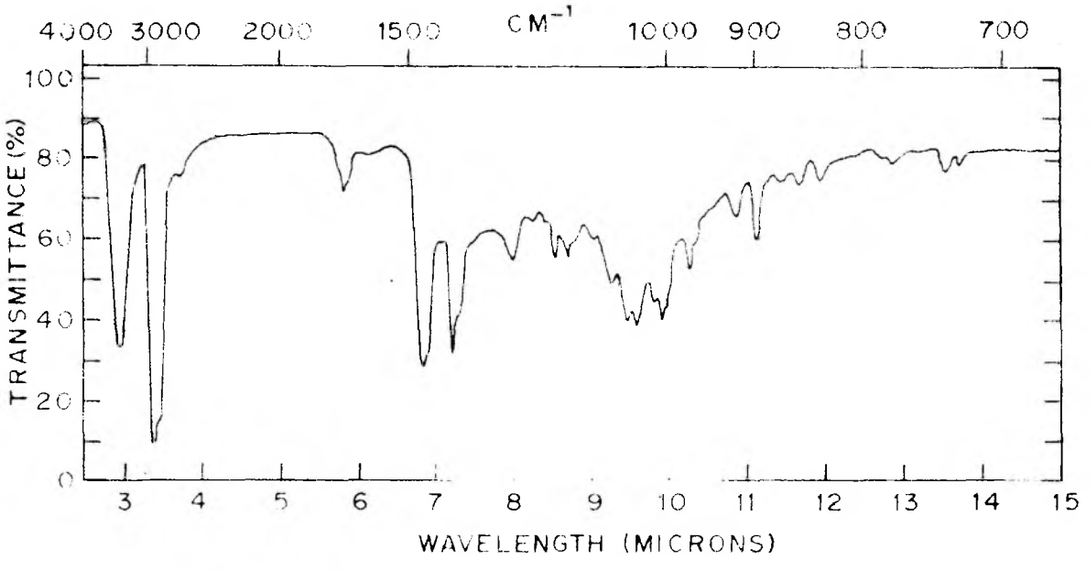


FIG. 4B. IR SPECTRUM OF THE DIHYDRO CANAROL (6).

Ozonolysis

When canarol (5) was ozonised in chloroform solution, it afforded entirely formaldehyde as the volatile fragment and did not give any acetone. Thus the possibility of the methylenic double bond in the isopropyl side chain is ruled out, as some acetone is usually obtained from such products due to migration of the double bond to the isopropylidine form. The non-volatile portion consisted of the hydroxy-nor-ketone, $C_{14}H_{22}O_2$ (7), which gave a negative iodoform test.

In its infrared spectrum (Fig. 5), the hydroxy nor-ketone (7) showed strong absorption bands at 3400 cm^{-1} (hydroxyl), 1710 cm^{-1} (six-membered ring ketone), 1420 cm^{-1} ($-CO-CH_2$) and a doublet at 1360 and 1375 cm^{-1} (isopropyl). This locates the position of the ethylenic linkage between C_4-C_{15} carbon atoms and not in the isopropyl side chain. In further support for this, canarone* and all the products derived from it, exhibited a doublet (between 1360 and 1380 cm^{-1}) in the methyl bending region. It is therefore safe to assume the

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* Infrared spectrum of canarone also showed presence of bands at 1183, 1160 cm^{-1} attributable to isopropyl group, c.f. R.L.MacMurry and V.Thornton, Analyt.Chem., 24, 318 (1952).

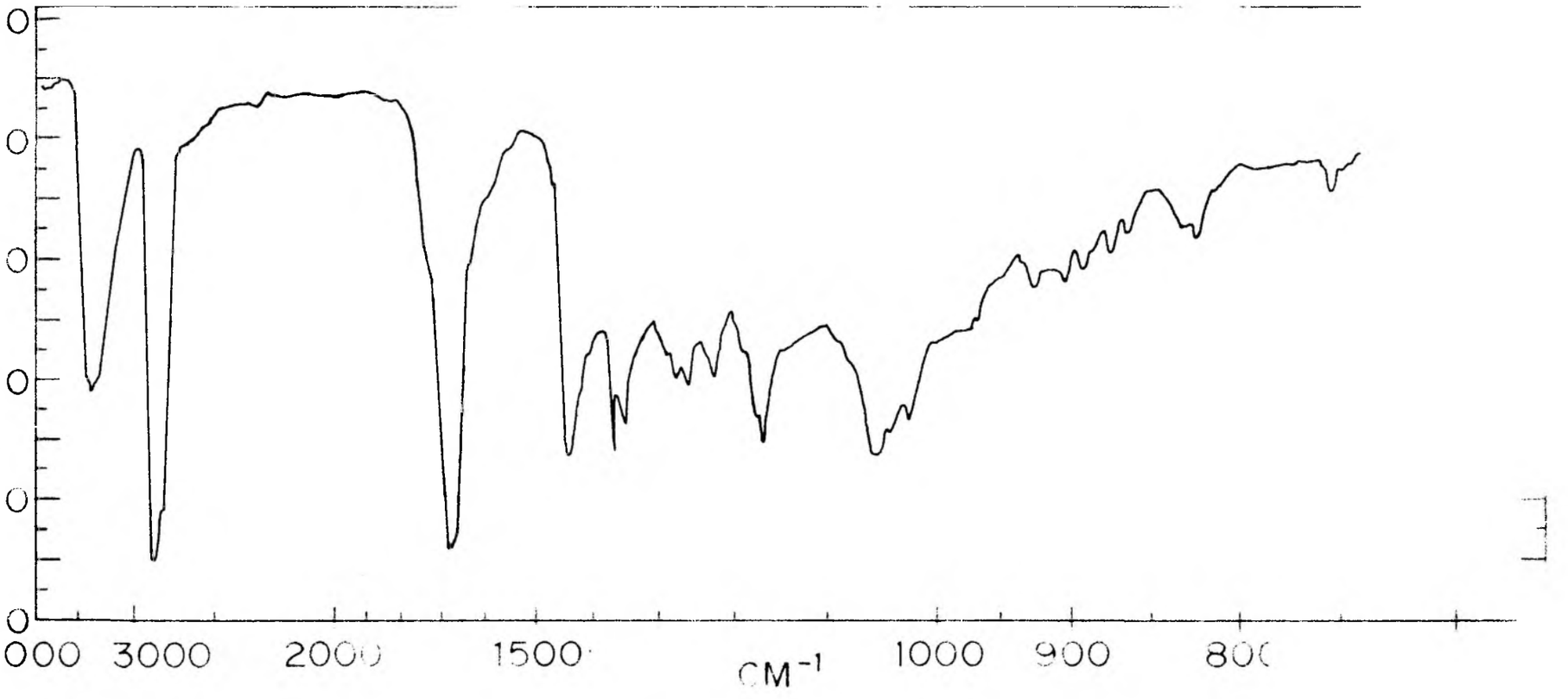
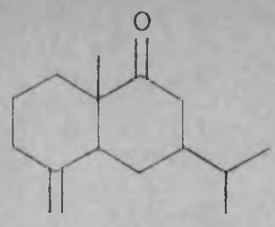
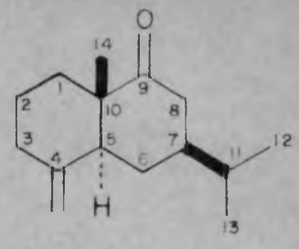


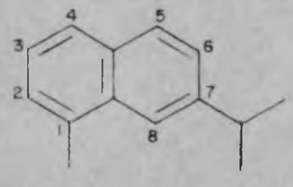
FIG. 5. IR SPECTRUM OF HYDROXY NOR KETONE (7).



(1)



(2)



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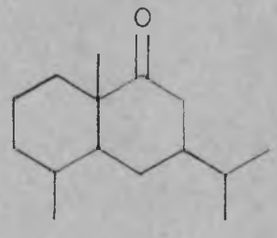

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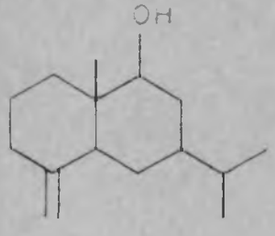
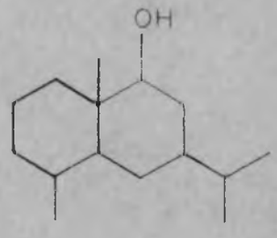
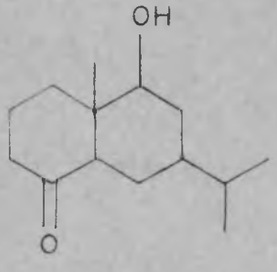


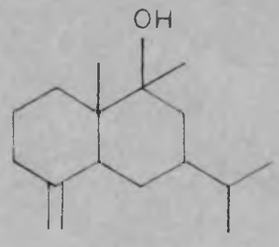
(5)



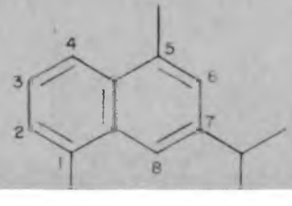
(6)



(7)



(8)



presence of isopropyl group[3] in hydroxy nor-ketone (7) and hence the location of the exocyclic double bond at C_4 carbon atom in canarone (1).

Position of the carbonyl function in canarone

The position of the carbonyl function* at C_9 - carbon atom was fixed by reacting canarone with methyl magnesium iodide and dehydrogenating the resulting carbinol (8) to furnish 6-methyl eudalene (9) which was identified by preparing its picrate and its m.p. and mixed m.p. with the picrate derivative of the authentic sample+ of 1,6-dimethyl-7-isopropyl naphthalene[4,5] (9). Thus the location of the carbonyl function at C_9 carbon atom was established. From this it was possible to conclude that canarone is represented by the structure (1).

NMR spectral data of canarone are completely in accord with the structure (1).

The NMR spectrum of canarone (Fig. 6) showed signals at 0.90 and 0.98 δ (6H) due to two methyls in

---

* Initially we had assumed the location of the carbonyl group in canarone at the C_1-carbon atom, but subsequent verification showed that the carbonyl function is actually located at the C_9 carbon atom and not at C_1.

+ We are grateful to Professor G. Buchi for supplying an authentic sample.

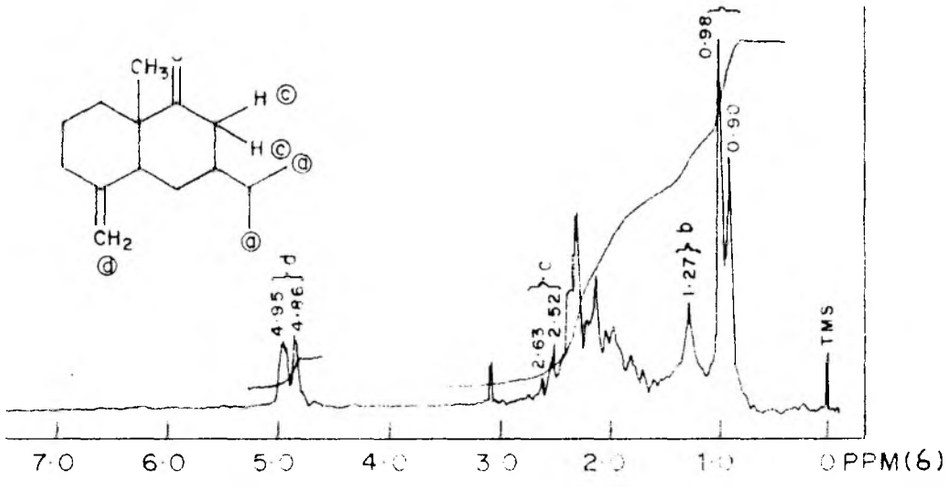
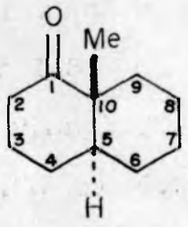


FIG. 6. NMR SPECTRUM OF THE CANARONE (1)

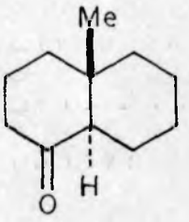
isopropyl side chain; a singlet at 1.27 δ (3H) due to an angular methyl group (adjacent to carbonyl) and signals at 2.62 and 2.63 δ (2H) due to two protons adjacent to the carbonyl function. In the olefinic region a doublet at 4.86 and 4.95 δ (2H) is observed due to the exocyclic double bond.

Absolute configuration of canarone

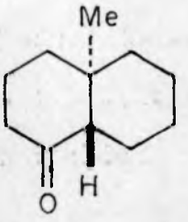
One of the important applications of the rotatory dispersion method, developed by Djerassi et al.[6] has been the determination of the absolute configuration[7] of cyclic ketones by comparison of rotatory dispersion curves with suitable model compounds of known absolute configuration. Steroids of known and well defined absolute configuration with respect to D-glyceraldehyde[8] have been used as the most suitable model compounds for such comparison. The exceptions to these premise are 10-methyl-1-decalones which are not comparable with 1-keto-steroids where rest of the polycyclic system of the steroids makes an important contribution. In order to explain this anomaly many of the key bicyclic ketones of known absolute configuration have been synthesised and their rotatory dispersion curves determined.[9] Important among the trans-decalones are trans-10-methyl-1-decalone (10), trans-10-methyl-4-decalone (11), trans-10-methyl-2-decalone (12) and trans-10-methyl-3-decalone (13).



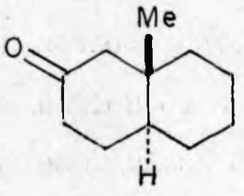
(10)



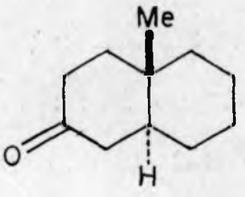
(11)



(11')

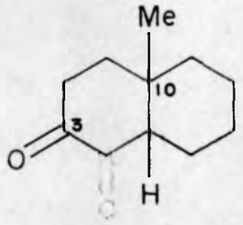


(12)

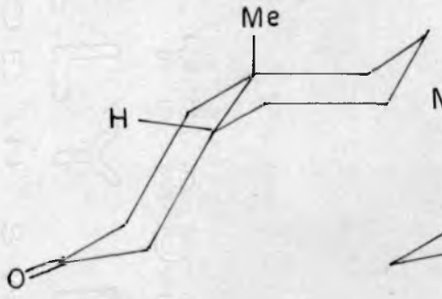


(13)

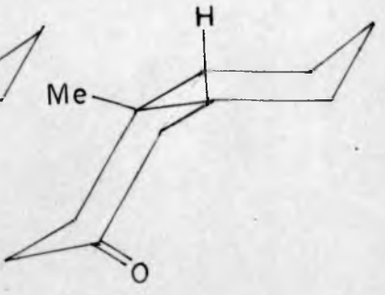
The trans-decalones exist in only one favoured double chaired conformation. The cis-decalone derivatives usually exist in two possible two-chair conformations, and in many cases the cotton effect of the two forms of the same cis-decalone will be of opposite sign. The determination of ORD curve of cis-decalone is often useful in detecting the preferred conformation. The cis-10-methyl-3-decalone (14) for example, can exist in steroid-like conformation (14a) and non-steroid conformation (14b).



(14)



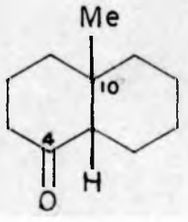
(14a)



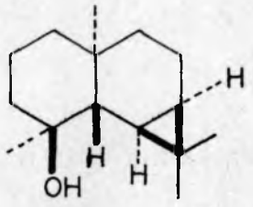
(14b)

It had been suggested[9] that cis-10-methyl-3-decalone (14) exists in non-steroid form (14b), but similarity of the ORD curves of 3-keto-5β steroids with that of cis-10-methyl-3-decalone (14), proved that the latter should be represented by the steroid-like conformation (14a). This has been further supported by the octant rule.

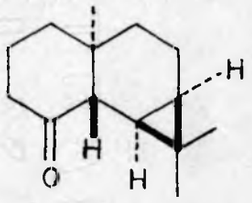
The cis-10-methyl 4-decalone (15) has symmetrical cotton effect curve, identical in sign but distinct in shape as compared to that of the steroid analogue coprostan-4-one. These considerations supported by the octant rule favour non-steroid conformation for (15).



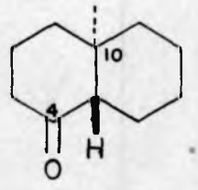
The sesquiterpene maaliol (16) has been transformed[10] into nor-maalione (17) which exhibits a strong positive cotton effect.



(16)



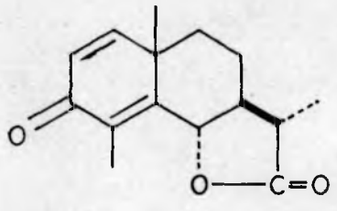
(17)



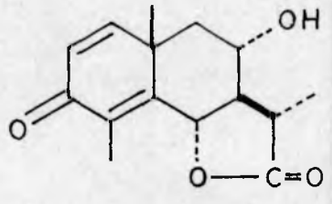
(11')

The coincidence of the positive cotton effect with that of trans-10-methyl-4-decalone (11') leads to the conclusion that maaliol should be represented by stereo-formula (16).

Also, the rotatory dispersion curves were of great significance for solving the stereochemical problems of hydrogenation products of santonin (18),[7a,11,12] C-11 isomeric santonins[13] and artemisin (19).[14]



(18)



(19)

The rotatory dispersion curve (Fig.7A)* of canarone (1) showed a positive cotton effect (a = + 30). The curve is of the same type as the curve given by trans-10-methyl-1-decalone (10). The hydroxy nor-ketone (7) on the other hand, showed the negative cotton effect curve (Fig. 7B)* (a = -30) which is of antipodal type as compared to trans-10-methyl-1-decalone (10) and is of the same type as compared to trans-10-methyl-4-decalone (11). The molecular amplitude values 'a' for canarone (1) and hydroxy nor-ketone (7) are in better agreement with those reported[7a,15] for trans-1-decalones from eudesmanic group than from eremophilane group. Comparison of the ORD curves of canarone and hydroxy nor ketone with that of known decalones, indicates that the canarone belongs to trans-decalone group. The octant rule[16] also points to the trans-fusion of the rings.

The Octant diagrams of canarone (1) and hydroxy-nor-ketone (7) depicted on the next page, also predict the following cotton effect curves; in canarone, positive; and in hydroxy nor ketone, negative.

The customary β-orientation is assigned to the C_7-isopropyl side chain[17] in analogy with the other eudesmanic compounds. Hence the absolute configuration of canarone must be represented as 9-oxo-5:7α(H) eudesm-4(15)-en.

Canarone can therefore be represented by the stereo-formula (2).

The numbering used here is according to Cocker & Cahn.[18]

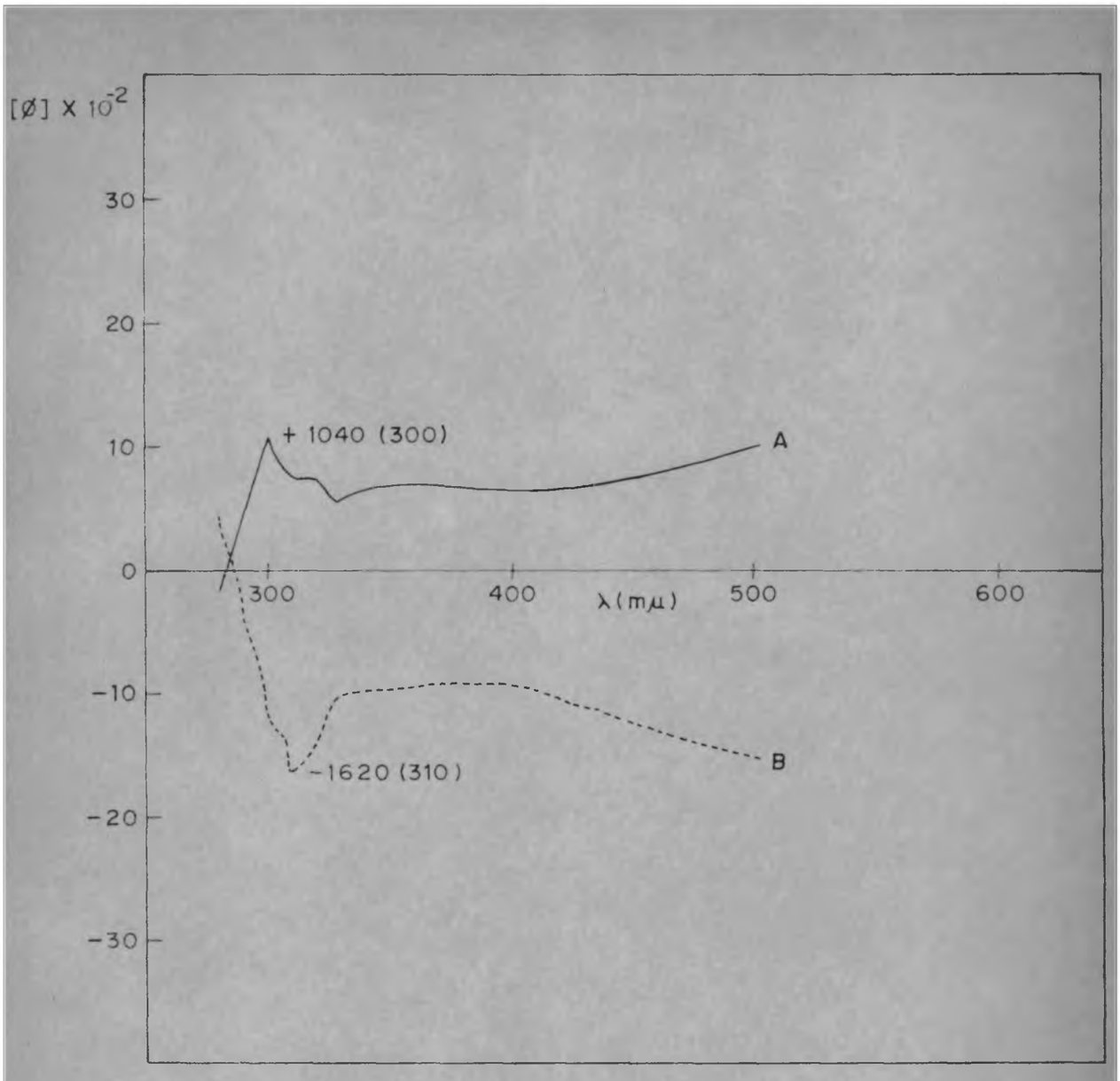
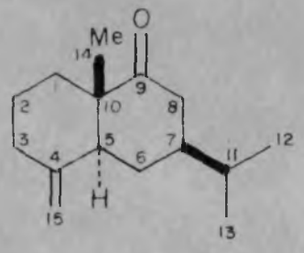


FIG. 7A. ROTATORY DISPERSION CURVE OF CANARONE (1).

FIG. 7B. ROTATORY DISPERSION CURVE OF HYDROXY NOR KETONE (7)

OCTANT DIAGRAMS

Canarone



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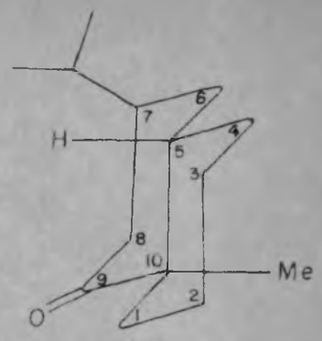
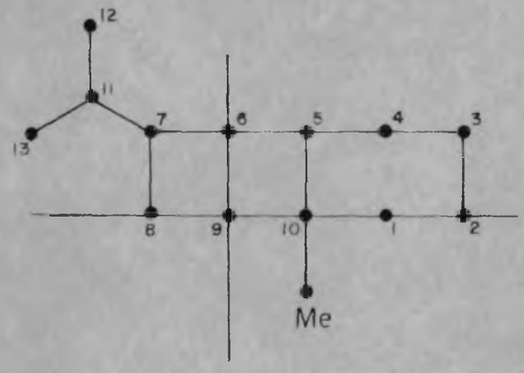
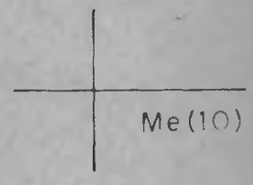
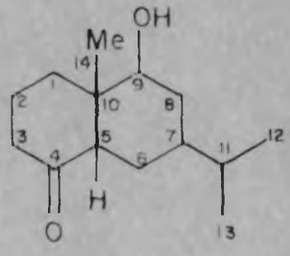






Predicts positive contribution

Hydroxynor-ketone



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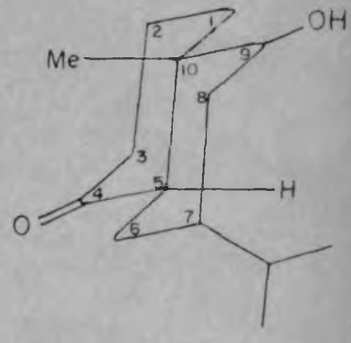

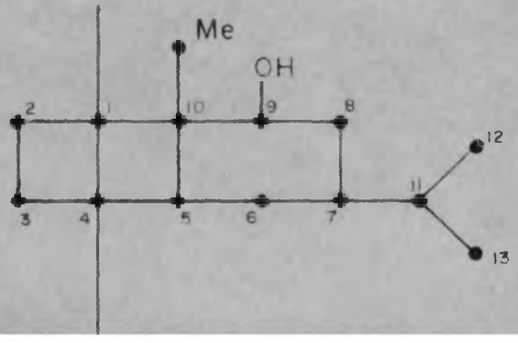

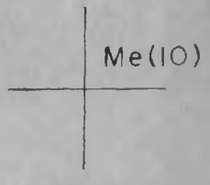

EXPERIMENTAL

EXPERIMENTAL

Isolation of canarone (1)

The sesquiterpene ketone, canarone, was obtained by chromatography of the distilled component of the benzene eluate of the pet.ether extract. The details of the chromatography are described in Chapter I (vide Chromatography Table-V, page 49). Fractions 1 to 7 of this chromatography were combined and fractionated. The fraction (2.5 g) which distilled at 140°(bath)/3 mm. was rechromatographed on alumina (grade II, 70 g). The pure ketone (1.8 g) obtained from the benzene eluent had following properties, b.p.130-135° (bath)/1 mm., n_D^{28} 1.5020, $(\alpha)_D$ + 34.78° (c, 3.45) and d_{29}^{29} 0.9819. Properties did not effectively change after regeneration from the semicarbazone.

Fig.1. IR spectrum (in liquid film) bands at: 3080, 1700, 1640, 1420, 1360, 1375, 1260, 1225, 1183, 1160, 890 cm^{-1}.

The NMR spectrum is represented in Fig. 6.

Analysis

Found: C, 81.00; H, 10.98.

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

The ketone easily formed a semicarbazone by acetate method, m.p.222-224°.

Fig.2. IR spectrum(in nujol) bands at: 3400, 3225, 3135, 1667, 1552, 1449, 1428, 1370, 1299, 1266, 1098, 1066, 900, 763, 680 cm^{-1}.

Analysis

Found: N, 15.58.

$C_{16}H_{27}ON_3$ requires: N, 15.15%.

Lithium aluminium hydride reduction of canarone(1) to canarol (5)

To a suspension of lithium aluminium hydride (0.9 g) in dry ether (50 ml) was added a solution of ketone (1.03 g) in dry ether (35 ml). During addition the temperature was maintained between 0 to 5°. The solution was stirred at 0° for 1 hr., and refluxed for 5 hours. The excess of lithium aluminium hydride was destroyed at 0° with moist ether and water and the gelatineous precipitate of aluminium hydroxide was filtered off. The ether layer was washed with water, dried and on evaporation furnished the secondary alcohol, canarol (5), b.p.110-115°(bath)/0.2 mm., n_D^{28} 1.5040, $(\alpha)_D$ + 23.81° (c, 1.26 in ethanol).

Fig.4A. IR spectrum(in liquid film) bands at: 3450, 1640, 1385, 1380, 1285, 1190, 1070, 1045, 1025, 1000, 912, 890 cm^{-1}.

Analysis

Found: C, 80.65; H, 11.58.

$C_{15}H_{26}O$ requires: C, 80.04; H, 11.74%.

Dehydrogenation of canarol (5)

The secondary alcohol canarol (0.4 g) was heated with selenium (0.4 g) at 390° for 7 hrs. in an atmosphere of nitrogen. No blue colour was observed during the process of dehydrogenation. The dehydrogenated product was taken up in petroleum ether and concentrated to a small volume (5 ml). This was passed over a column of alumina (grade I, 20 g) and eluted with pet.ether; UV spectrum: absorption maxima at 287 mμ ($\varepsilon_{max.}$ 79430) and at 279 mμ ($\varepsilon_{max.}$ 6905) indicating the presence of naphthalenic compounds.

The above dehydrogenation product (150 mg) was dissolved in ethanol (3 ml) and a hot solution of TNB(150 mg) in ethanol (3 ml) was added to it. The mixture was heated on a water bath for a short time and cooled. The TNB derivative formed was filtered off and crystallised two times from ethanol. It melted at 110° and mixed melting point with an authentic sample of TNB derivative of eudalene (113°) was also 110°.

Quantitative determination of unsaturation of canarone(1)

Canarone (30 mg) was dissolved in methanol (10 ml) and stirred in an atmosphere of hydrogen with palladium on charcoal (5%, 30 mg) for 1 hr. The total uptake of hydrogen was equivalent to one double bond (3.5 ml, 24°,710 mm).

After removal of the catalyst, the filtrate afforded after usual processing, dihydrocanarone (4).

Fig.3. IR spectrum(in liquid film) bands at: 1704, 1420, 1383, 1366, 1250, 1235, 1163 cm^{-1}.

Analysis

Found: C, 80.17; H, 11.57.

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

Hydrogenation of canarone (1) to dihydrocanarol (6)

Canarone (130 mg) was dissolved in glacial acetic acid (20 ml) and hydrogenated using platinum catalyst. The hydrogenation stopped after absorption corresponding to 2 moles of hydrogen. The catalyst was filtered off and acetic acid was removed by distillation in vacuum. The hydrogenation product was taken up in ether, washed with sodium bicarbonate solution, water and dried. The evaporation of the solvent afforded dihydrocanarol (90 mg). It had the following properties, b.p.105-110° (bath)/0.2 mm., n_D^{28} 1.4940, $(\alpha)_D$ + 8.43° (c, 1.78).

Fig.4. IR spectrum(in liquid film) bands at: 3500, 1380, 1370, 1250, 1170, 1150, 1080, 1065, 1040, 1010, 975, 930, 897 cm^{-1}.

Analysis

Found: C, 80.62; H, 12.81.

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

Hydrogenation of canarol (5) to dihydrocanarol (6)

A solution of canarol (100 mg) in glacial acetic acid (20 ml) was hydrogenated over pre-reduced Adams' catalyst (50 mg). The absorption (11 ml at NTP) corresponded to one double bond. The hydrogenation product obtained after usual processing and purification gave infrared spectrum identical with the infrared spectrum of the product obtained by direct hydrogenation of canarone over Adams' catalyst, and had identical properties.

Ozonolysis of canarol (5) to keto-alcohol (7)

Canarol (0.13 g) was dissolved in pure chloroform (10 ml) and ozonised to completion in a dry stream of ozonised oxygen at -5°. The volatile component was collected in cold water during ozonolysis. The presence of formaldehyde in this trap water was confirmed by its dimedone derivative, m.p. and mixed m.p. 189°. The trap water did not give test for acetone. The chloroform was removed at 40° under reduced pressure and the ozonide was decomposed by adding water(25 ml) and heating on a water bath for 4 hours. The aqueous layer was extracted with ether, washed with water and dried. On evaporation it gave a residue (100 mg) which was purified by filtering through a short column of alumina (grade III) to give keto-alcohol (60 mg). It did not give test for methyl ketone. It was further purified by distillation under vacuum, b.p. 138° (bath)/6 mm.

Fig.5. IR spectrum(in nujol) bands at: 3400, 1710, 1425, 1370, 1385, 1180, 1065, 1030, 985, 930, 829 cm^{-1}.

Analysis

Found: C, 76.80; H, 10.60.

$C_{14}H_{24}O_2$ requires: C, 75.04; H, 10.78%.

Due to paucity of material, better analysis could not be obtained.

Grignard reaction on canarone(1) and isolation of 6-methyl eudalene (9) by dehydrogenation

The ketone (0.5 g) in dry ether (20 ml) was added dropwise to a solution of methyl magnesium iodide (prepared from 0.40 g. magnesium and 2.8 ml. of methyl iodide) in dry ether (50 ml) and the reaction mixture was refluxed for 12 hours. The product was worked up in the usual way and the derived tertiary alcohol (8) was separated from the traces of unreacted ketone by chromatography.

The crude tertiary alcohol (8) (0.25 g), was heated with selenium (0.3 g) at 290° for 6 hrs. under nitrogen atmosphere. The reaction product was extracted with pet. ether and filtered through a column of alumina (grade I, 10 g). Ultraviolet spectrum of the dehydrogenated product indicated 90% naphthalenic product. It was identified as 1,6-dimethyl-7-isopropyl naphthalene (8) by its picrate derivative, m.p. 112-113° (lit. 113-114°).[4] Mixed melting point with the authentic sample of picrate of 1,6-dimethyl-7-isopropyl naphthalene remained undepressed.

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1. E.J. Corey, T.H.Topie and W.A.Wozniak,J. Amer.Chem.Soc., 77, 5415 (1955).
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3. Infrared spectrum of canarone also showed presence of bands at 1183, 1160 cm^{-1}, attributable to isopropyl group, c.f. H.L.MacMurry and V.Thornton, Analyt. Chem., 24, 318 (1952).
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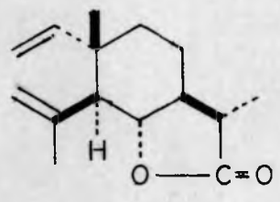
CHAPTER III

THE ABSOLUTE CONFIGURATION OF BISNOL AND RELATED PRODUCTS.

***

SUMMARY

The biogenesis of terpenes would suggest two possible enantiomeric configurations for the elemane type sesquiterpenoids, one of which corresponds to saussurea lactone (A). However, the stereochemistry of elemol (B) remained unsolved so far due to lack of direct chemical proof. In this connection, we examined the lactone formed by the lactonisation of the hydroxy acid (D) obtained by ozonisation of dihydroelemol (C). It was found on the basis of IR and NMR spectral evidences that the lactone so formed is a γ-lactone (E) and not the δ - lactone (F) as previously assumed.



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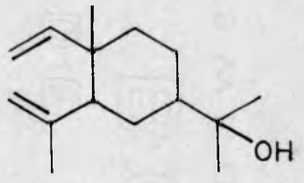

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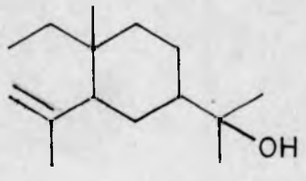

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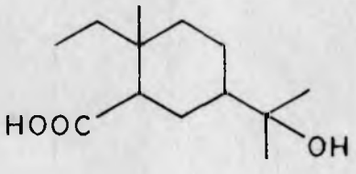

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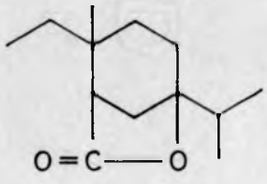

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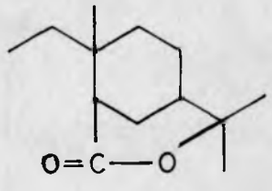
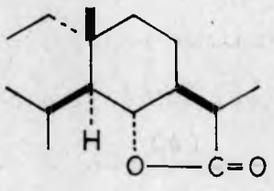
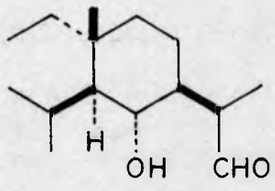


(F)

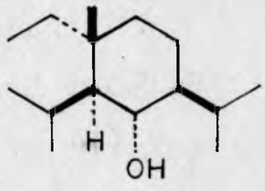
In order to clafify the stereochemistry of elemol, we initially converted tetrahydrosaussurea lactone (G) to elemane (K). Tetrahydrosaussurea lactone by controlled lithium aluminium hydride reduction gave the hydroxy - aldehyde (H) which on Wolff-Kishner reduction afforded a low melting crystalline monol (I). The benzoate of the monol on pyrolysis furnished a mixture of two unsaturated hydrocarbons (J) which on hydrogenation gave elemane (K).



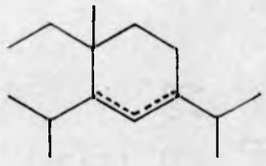
(G)



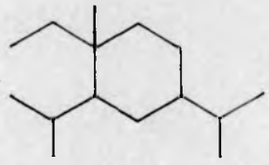
(H)



(I)



(J)

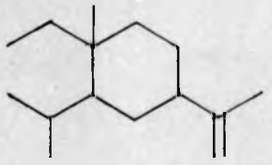


(K)

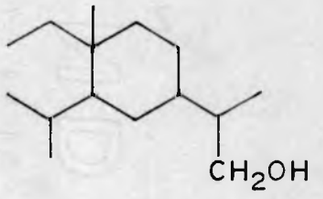
Although the elemane thus formed showed identical physical properties and infrared spectrum with an authentic sample of elemane prepared from elemol, the NMR spectral characteristics indicated that it was a mixture of stereoisomers.

Since it was not possible to draw clear conclusion regarding the stereochemistry of elemol from the above

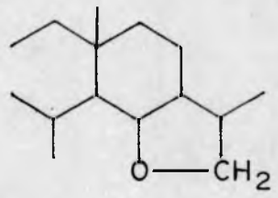
experiments, we decided to convert elemol (B) to tetrahydrosaussurea lactone (G) which is a product of definite stereochemistry, high melting point and good rotation. This was achieved in the following way. Elemol was converted to tetrahydroelemene (L) via pyrolysis of tetrahydroelemol benzoate. The tetrahydroelemene on hydroboration gave the primary alcohol (M), Lead tetraacetate oxidation of which afforded an oxide (N) which on chromic acid oxidation yielded tetrahydrosaussurea lactone (G).



(L)

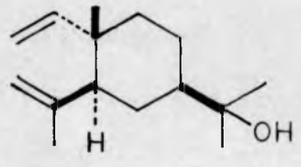


(M)



(N)

This unambiguous conversion of elemol to tetrahydrosaussurea lactone convincingly proves that the stereochemistry of elemol* is represented by the structure (O).



(O)

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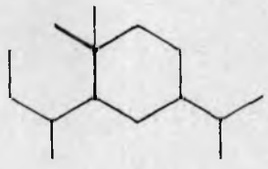
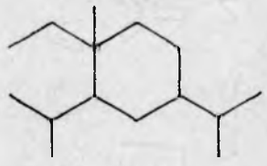
* T.G.Halsall, D.W.Theobald and K.B.Walshaw in a recent communication (J.Chem.Soc., 1029(1964) have arrived at the same conclusion by correlating elemol with (+) epi-α-cyperone by an elaborate series of experiments.

Elemol

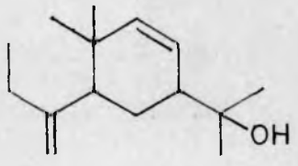
The crystalline sesquiterpene monocyclic alcohol elemol, $C_{15}H_{26}O$, was originally isolated by Clover[1] from Manilla Elemi oil. Later it has also been obtained from the higher boiling fractions of Java citronella oil.[2] Many workers[3-6] have worked to elucidate its structure. Ruzicka and van Veen[6] suggested two alternative carbon skeletons (1) and (2) for elemol. From degradative experiments, formula (3) was put forward by them as a likely structure for elemol. From oxidative degradation of dihydroelemol, Ruzicka obtained acetaldehyde and a hydroxy acid, $C_{13}H_{24}O_3$. These findings led them to the conclusion that the elemol is presumably ad-mixture of compounds represented by (4) or partial formula (4') having a different carbon skeleton.



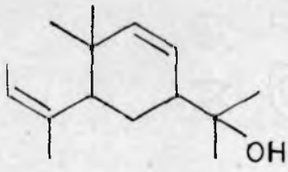
(1)

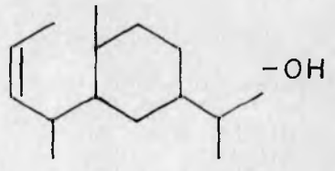


(2)

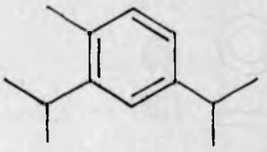


(3)





Sorm and co-workers[7] disproved the basic skeleton (1) by synthesising 1,1-dimethyl-2-sec-butyl-4-isopropyl cyclohexane and showing its non-identity with elemane. They synthesised 1-methyl-2,4-di-isopropyl benzene (5) and showed it to be identical with the product of dehydrogenation of elemol, on the basis of which they concluded that the basic skeleton elemane is represented by (2).

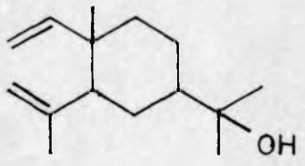


(5)

In a subsequent paper,[8] they converted 3-isopropyl-4-methyl-4-ethyl cyclohexanone (6) to tetrahydroelemol (7) which on chromic acid oxidation yielded back (6).

(6) (7)

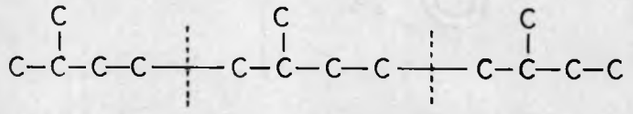
Infrared spectrum of elemol showed the presence of vinyl -CH=CH$_2$ and methylene $>$C=CH$_2$ groups. From these evidences the structural formula (8) was assigned to elemol.



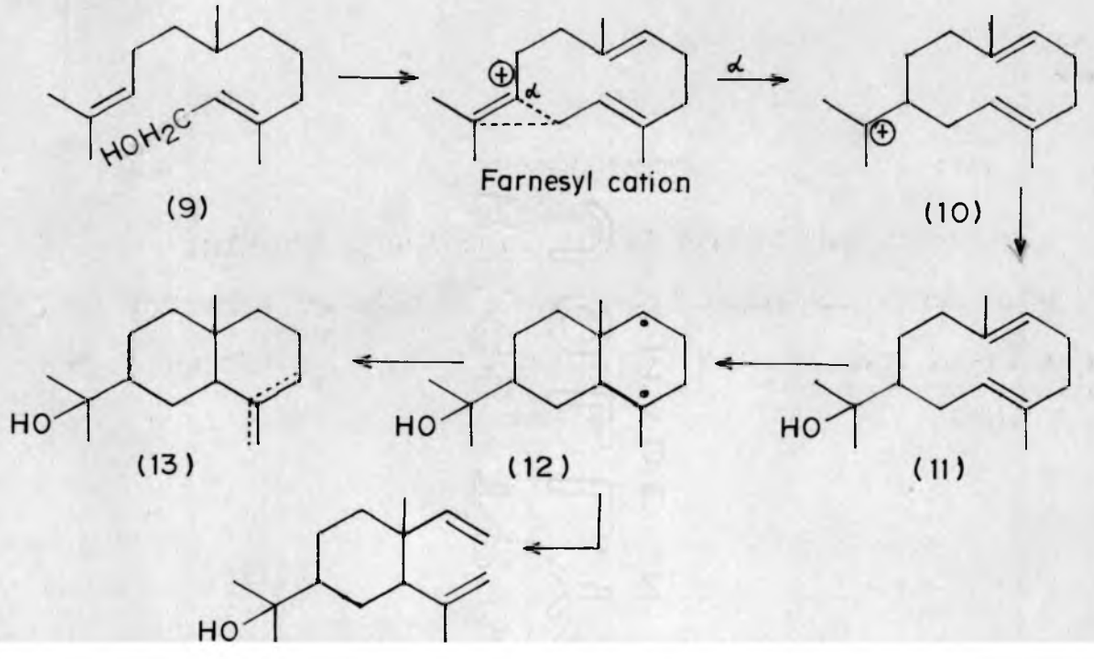
(8)

Biogenetic approach towards the stereochemistry of elemol

Ruzicka[9] has described that the structure of hydroaromatic sesquiterpenes such as cadanine and eudesmol can be deduced from farnesol. The sesquiterpenoids derived from farnesol contain three isoprene units in regular head-to-tail arrangement as shown below.

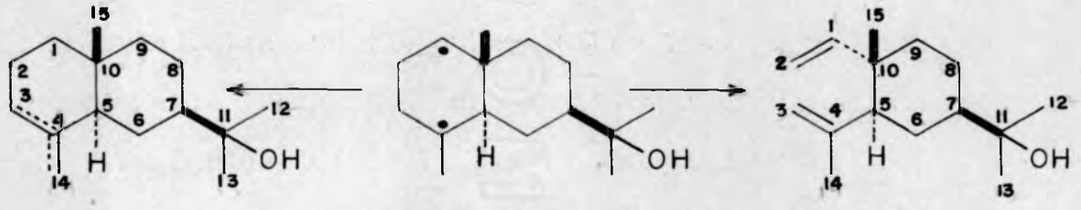


Two types of biogenetic cyclisations of farnesol may be considered, one leading to the formation of 6-membered ring intermediates and the other 10- or 11-membered ring intermediates. Eudesmol (α or β) (13) was assumed to be formed from farnesol (9) via the π -complex of the farnesyl cation through the intermediates (10, 11, 12).



The bi-radical (12) could then undergo ring opening forming elemol (8).

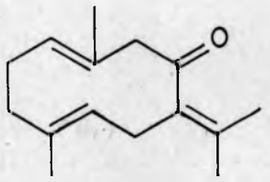
If we apply Hendrickson's[10] conception of biogenesis to Ruzicka's observation of the derivation of eudesmol and elemol from farnesol, it should be possible to draw certain conclusions regarding the stereochemistry of these compounds which then are expected to be represented by the stereoformula (13a) and (8a) for eudesmol and elemol respectively, originating through the intermediate (12a).



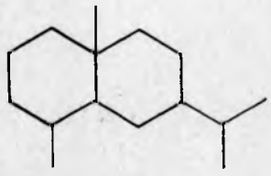
(13a) (12a) (8a)

Eudesmol α- and β- have been shown to possess the absolute configuration as represented by stereoformula (13a).[11-13]

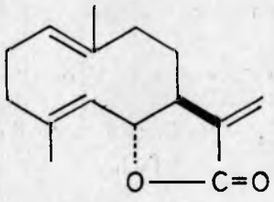
According to the accepted biogenetic conception many monocyclic sesquiterpenes undergo facile cyclisation to bicyclic derivatives. For example, germacrone (14)[14] is known to form selinane (15), and also the ten-membered cyclic lactone, costunolide (16) on hydrogenation in acetic acid in the presence of Adams' catalyst affords santanolide 'c' (17).[15]



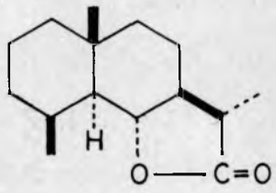
(14)



(15)



(16)

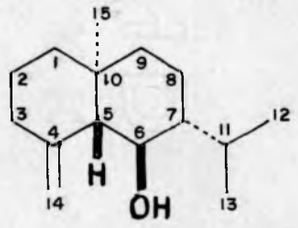


(17)

Analogous transannular cyclisations in presence of acid are known to occur with pyrethrosin,[10] aretiopicrin[14] etc.

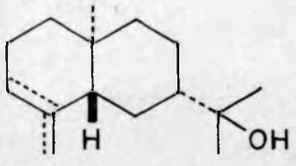
By considering the stereochemistry of the cyclised products thus obtained, it can be seen that the compounds belong to eudesmane group. According to the present knowledge of the eudesmanic compounds, the absolute configuration of the C_{10}- angular methyl and the C_7 isopropyl-groups in such compounds are always found to be in the same direction, usually in β-orientation with the two rings in trans-fusion. But there are certain exceptions to this premise such as the naturally occurring

laevo-junenol[16] where C_{10}- angular methyl and C_7- isopropyl groups are α-oriented and due to regular trans-fusion of the rings, H-atom at C_6 is β-oriented, as represented by formula (18).

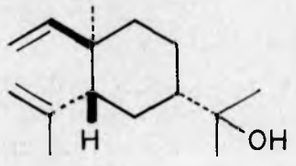


(18)

The existence of the antipodal eudesmanic skeleton like laevojunenol in nature would suggest the possible occurrance of eudesmol and the elemol isomers as represented by (13b) and (8b).



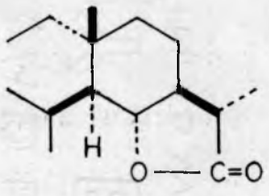
(13b)



(8b)

Biogenesis of elemol as postulated by Ruzicka and extended by Hendrickson finds easy analogy in the laboratory. Thus dihydrocostunolide (19) on pyrolysis afforded saussurea lactone (20)[17] in high yields.

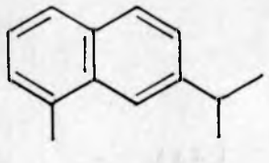
(19) (20)



(21)

The absolute configuration of saussurea lactone (20) was established by Bhattacharyya and co-workers[17] by converting it to santanolide 'c' (17). This has been further confirmed by a total synthesis of tetrahydro-saussurea lactone (21).[18]

Elemol (8) is connected with eudesmol (13a) not only through common eudalene (22) formed during selenium dehydrogenation but also through eudesmane (23) obtained by acid catalysed cyclisation at elevated temperature followed by hydrogenation.[19]



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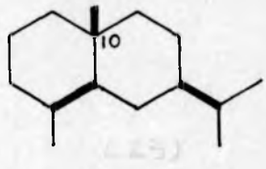
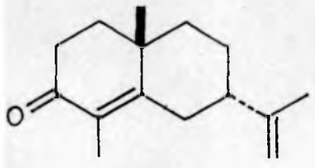


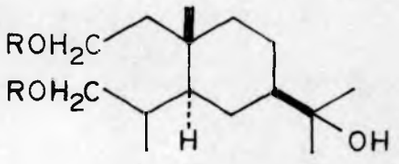
(23)

THE PRESENT WORK

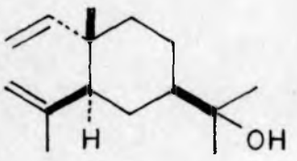
In a recent communication Halsall et al.[20] proved the absolute configuration of elemol (8a) by synthesising eleman-2,3,11-triol (25) from (+)-epi-α-cyperone (24) and correlated it with elemol derivative. Elemol was converted by hydroboration to the same triol (25) which afforded a crystalline ditrityl ether (26) identical with that obtained from the triol synthesised from (+)-epi-α-cyperone of known stereochemistry.



(24)



(25, R=H)
(26, R=CPh3)



(8a)

The absolute configuration of elemol and related compounds

Ruzicka and van Veen[6] obtained a crystalline hydroxy acid, $C_{13}H_{24}O_3$ (29), m.p.146°, by ozonisation of dihydroelemol (27). The hydroxy acid on heating with formic acid afforded a δ -lactone, $C_{13}H_{22}O_2$, m.p. 37°, presumed to be (32). According to Sorm and co-workers[8] the lactonisation of the hydroxy acid is possible only if the carboxyl and the

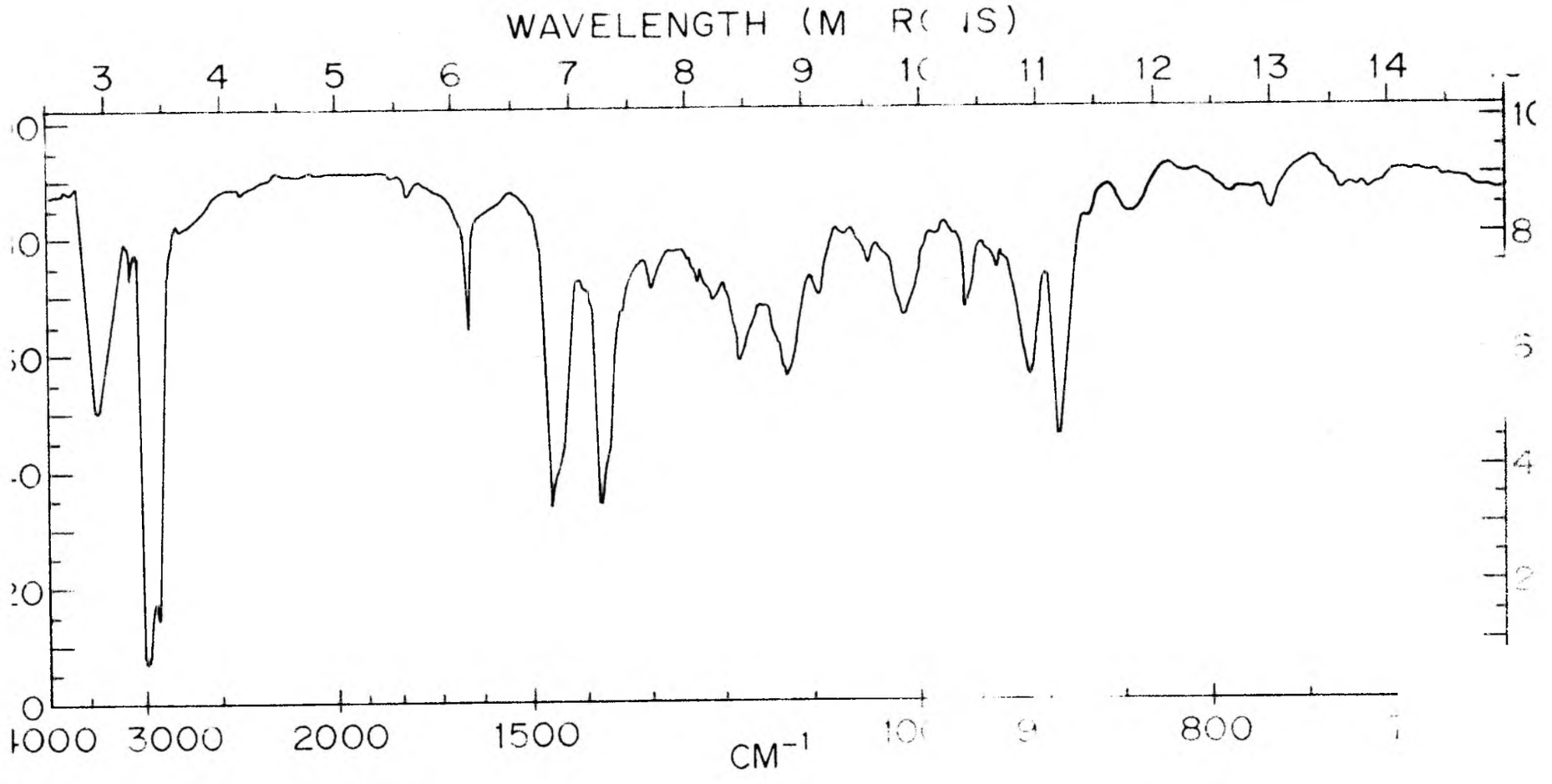


FIG. 1. IR SPECTRUM OF THE DIHYDROELEMOL (27).

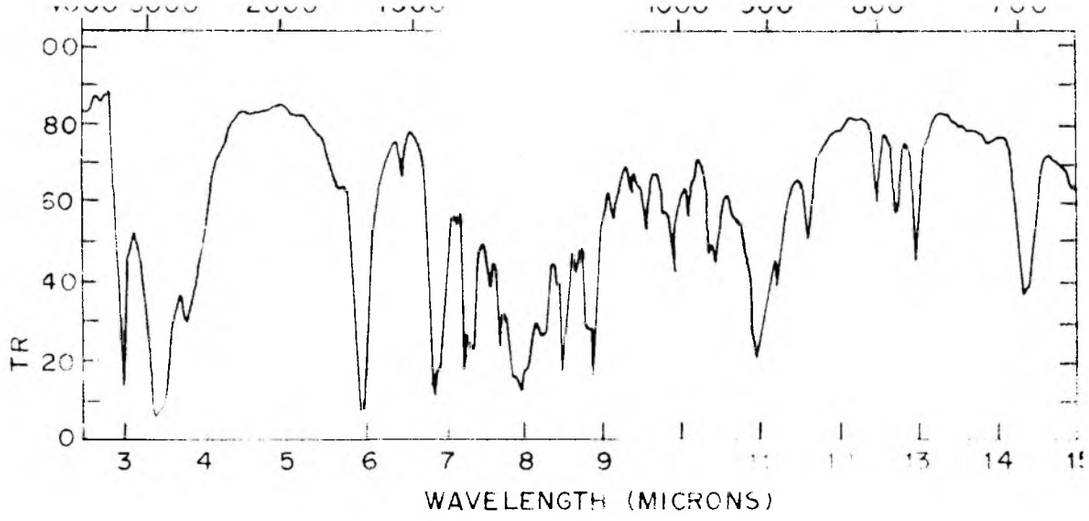


FIG. 2. IR SPECTRUM C[illegible] HYDROXY-ACID (29).

hydroxy-isopropyl groups have the axial conformation and cis-disposition. This is, however, unexpected according to the biogenesis rules[9,10] discussed earlier, and is evident from both the enantiomeric structures (8a) and (8b) for elemol where the C_7 and C_8 side chains are equitorially oriented.

We have examined this point critically. Elemol(8) on partial hydrogenation in ethanol with palladised carbon (5%) gave dihydroelemol, $C_{15}H_{28}O$ (27), m.p.45-46° (IR spectrum, Fig.1) which on ozonisation afforded the mixture of hydroxy methyl ketone (28) and the hydroxy acid (29). The neutral portion was separated in the usual way from the acidic portion by aqueous sodium bicarbonate extraction. The neutral portion was identified as the hydroxy methyl ketone (28) by its infrared spectrum. The pure hydroxy-acid, $C_{13}H_{24}O_3$ (29), m.p.146° (IR spectrum, Fig.2), obtained from the acidic portion, on heating with concentrated formic acid afforded the previously described lactone, $C_{13}H_{22}O_2$ which is not a δ - lactone but γ-lactone and is represented by the structure (31).

Its infrared spectrum (Fig.3) exhibited bands at 1770 cm^{-1} characteristic of γ-lactone and a doublet at 1380, 1380 cm^{-1} in methyl bending region indicating the presence of an isopropyl group. The NMR spectrum (Fig.4) showed

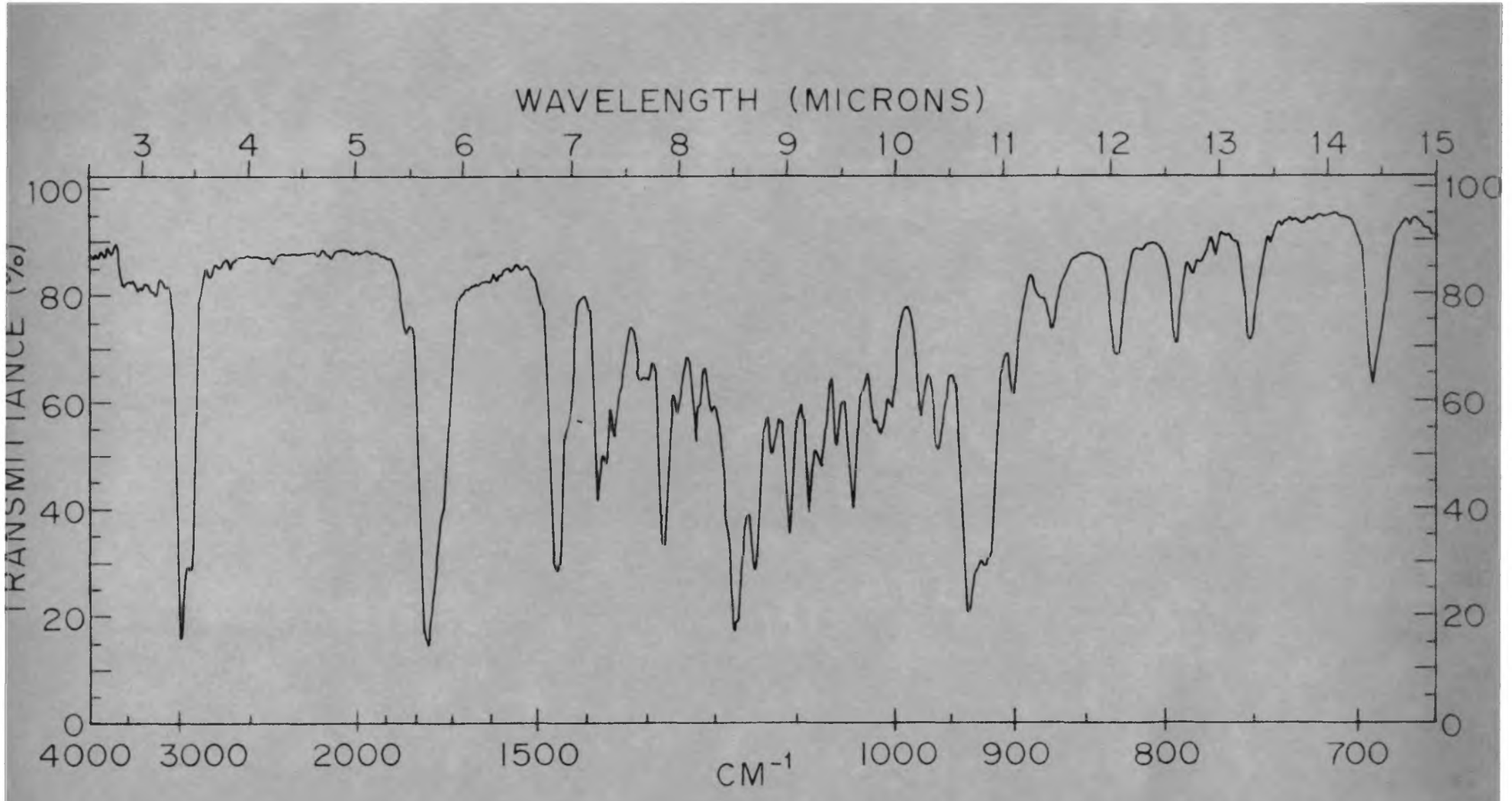
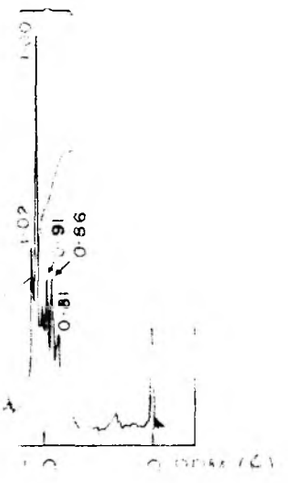
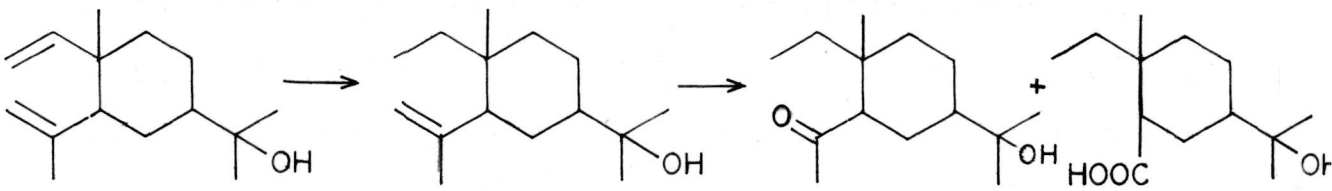


FIG. 3. IR SPECTRUM OF THE γ-LACTONE (31).

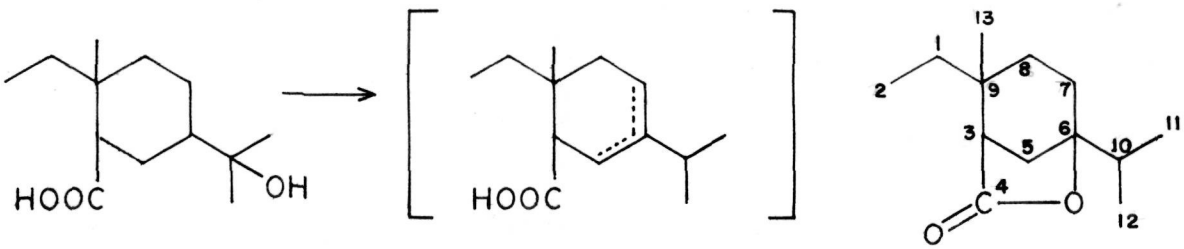


4. NMR SPEC OF THE γ-LACTONE (31).

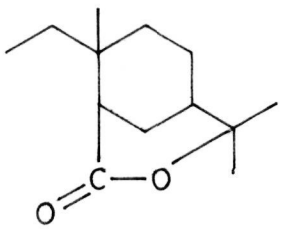
signals at 0.81, 0.86, 0.91, 0.93, 1.0, 1.02 δ (12H) due to four methyl groups at C_2, C_{11}, C_{12} and C_{13}. Two signals at 1.8 and 1.85 δ (2H) are due to two protons at C_5, and a singlet at 2.2 δ due to a proton at C_3. The evidences given by the infrared and the NMR spectra suggest beyond doubt that the lactone formed is not the δ -lactone (32) but the γ-lactone (31). Evidently it can be seen that the lactone is not formed by simple lactonisation of the carboxyl and the hydroxyl groups in (29) but through an intermediate (30) obtained via dehydration of the hydroxyl group followed by migration[21] of the resultant double bond to the ring and subsequent lactonisation to form γ-lactone(31).



(8) (27) (28) (29)



(29) (30) (31)

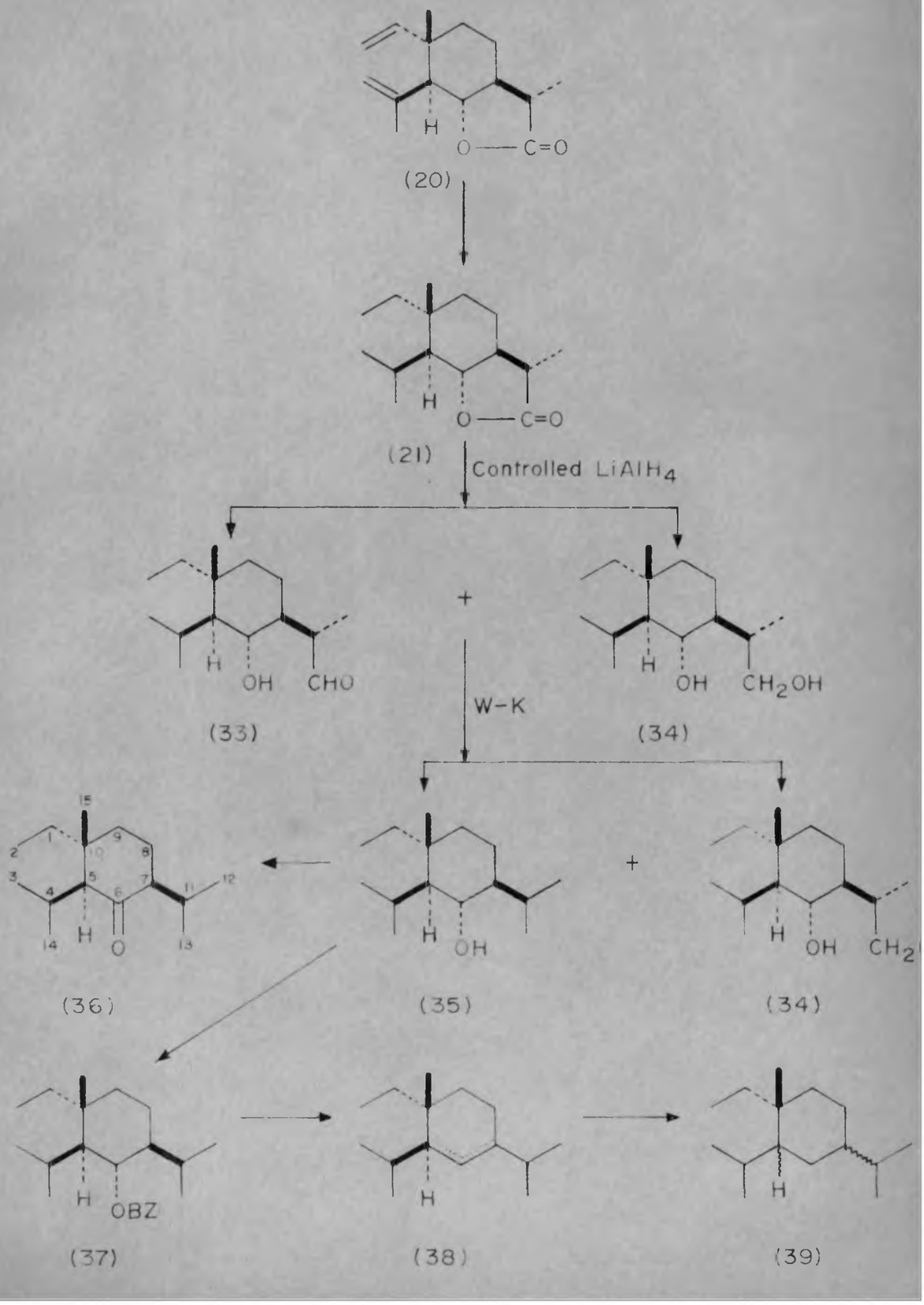


(32)

Jeger and co-workers[19] reported the isolation of eudesmane (23) on hydrogenation of mixed hydrocarbons obtained by pyrolysis of elemol benzoate. This suggests but does not prove the absolute configuration of elemol. For this purpose we initially used tetrahydrosaussurea lactone as the starting material, because of its known and well established stereochemistry.[18,22] Tetrahydrosaussurea lactone (31) was reduced by lithium aluminium hydride under controlled conditions[23] with a view to get the corresponding hydroxy-aldehyde (33). The reaction product obtained was found to be the mixture of the diol (34) and the hydroxy aldehyde (33). Without making an attempt to separate the two products at this stage, the mixture as such was subjected to Wolff-Kishner reduction to give a mixture of the secondary alcohol (35) and the diol (34) (vide, CHART-I). The monol (35) was separated from the diol by chromatography over neutral alumina. The diol was identified through its infrared spectrum (Fig.5B) while the monol, $C_{15}H_{30}O$, m.p.36-37° was purified by rechromatography, distillation in vacuuo and sublimation. VPC analysis showed a sharp single peak indicating its purity of a high order. Its infrared spectrum is represented in Fig. 5A. Bhattacharyya and co-workers[24] obtained the same monol (VIII) by the metal amine reduction of costunolide derivatives (vide CHART-II). Costunolide (I) on reduction

CHART - I

CONVERSION OF SAUSSUREA LACTONE TO ELEMANE



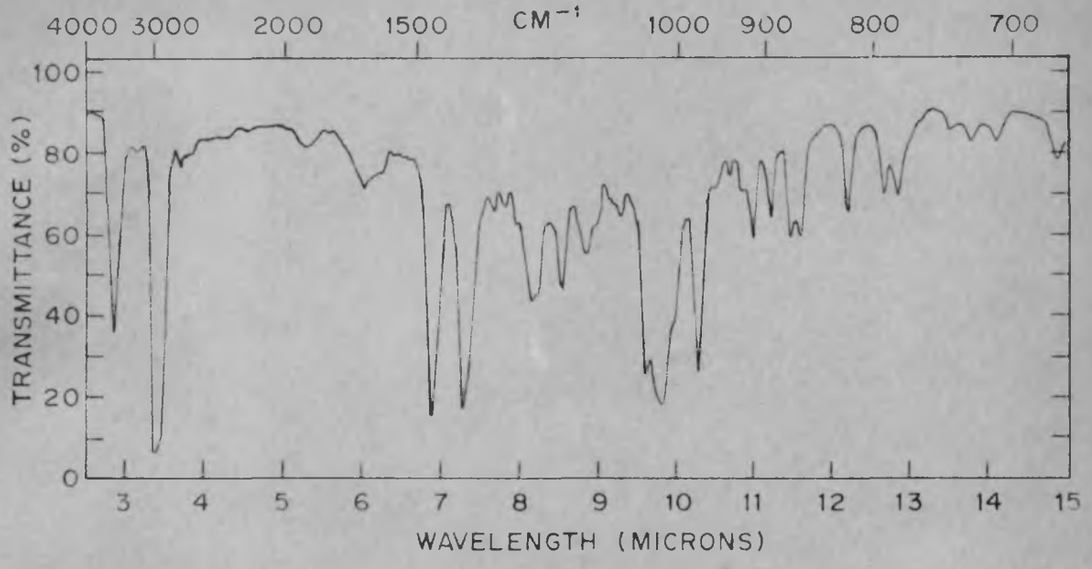


FIG. 5A. IR SPECTRUM OF THE MONOL (35).

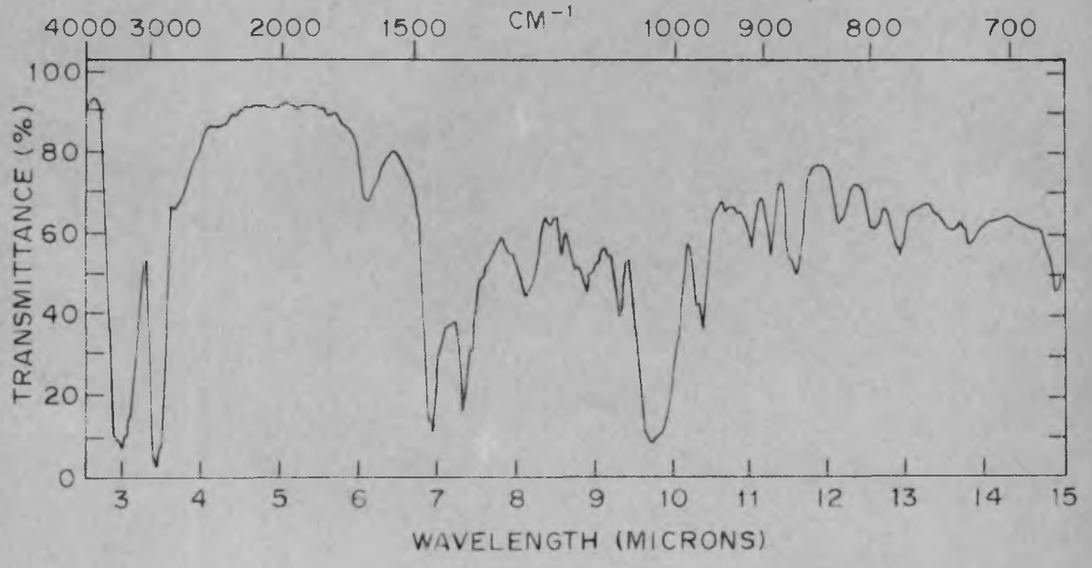
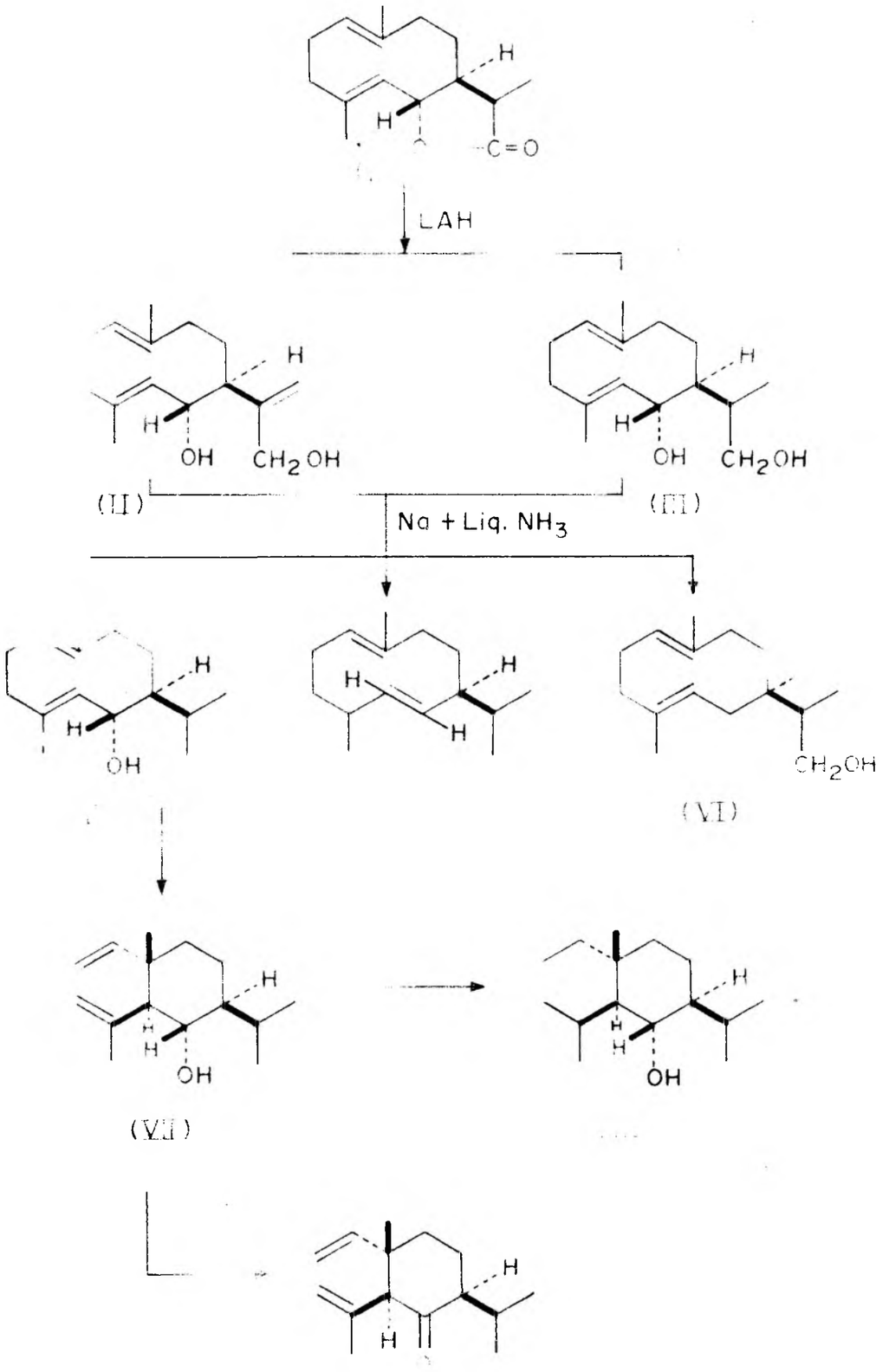


FIG. 5B. IR SPECTRUM OF THE DIOL (34).

with lithium aluminium hydride afforded a mixture of diols (II & III). The mixture as such was subjected to metal amine reduction which resulted in the formation of the hydrocarbon (IV), the secondary alcohol (V) and the primary alcohol (VI). The secondary alcohol, separated in the pure form by repeated chromatography over neutral alumina, was completely rearranged pyrolytically to the monol (VII) which on catalytic hydrogenation gave a tetrahydro product (VIII) identical in all respects with the monol (35) of known stereochemistry prepared from tetrahydrosamsaurea lactone. The complete identity of the two products enabled them to decide the stereochemistry of compounds (VII), (VIII) and (IX) as shown in CHART-II.

The monol (35) was found stable towards mesityl sulphonyl chloride or p-toluene sulphonyl chloride, as it did not form the corresponding mesitylate or tosylate adduct. On oxidation with chromic acid (Jones' reagent),[25] it was converted to a ketone, $C_{15}H_{28}O$ (36), which after purification by chromatography showed a sharp single peak on VPC analysis. The infrared spectrum (Fig.6) of the ketone exhibited bands at 1700 cm^{-1} due to >C=O and a doublet at 1380, 1365 cm^{-1} due to isopropyl group. Its NMR spectrum (Fig.7) was found to be in complete agreement with its structure (36) and gave indication of six methyl


C=O
LAH
OH
CH2OH
(II)
(III)
Na + Liq. NH3
(VI)
(VII)

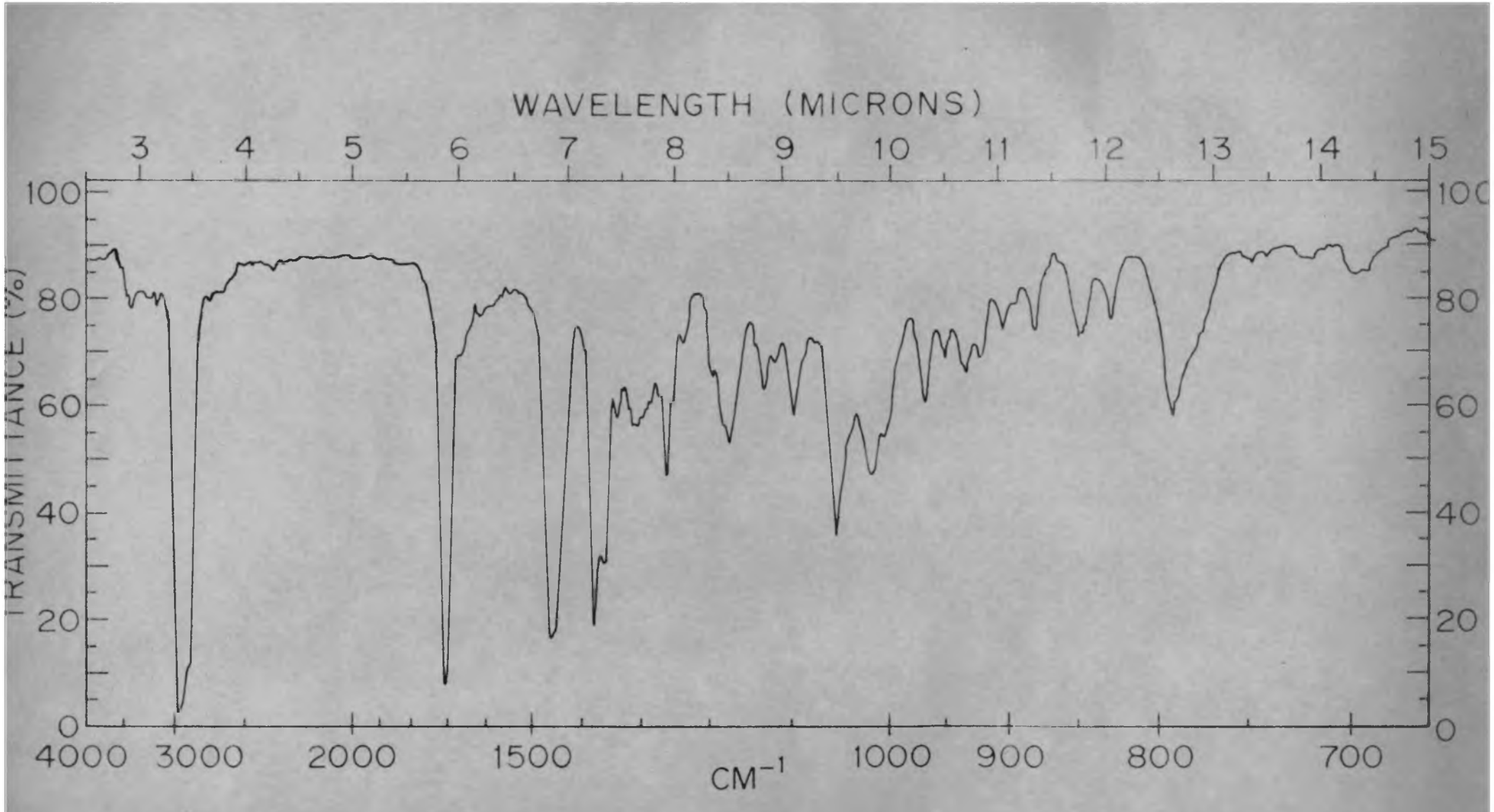


FIG. 6. IR SPECTRUM OF THE KETONE (36).

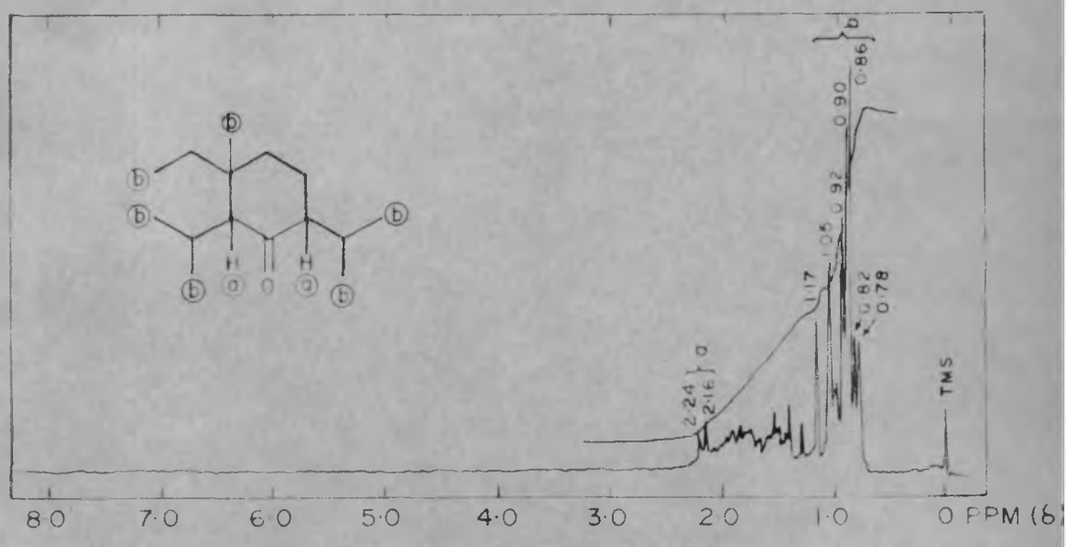


FIG. 7. NMR SPECTRUM OF THE KETONE (36).

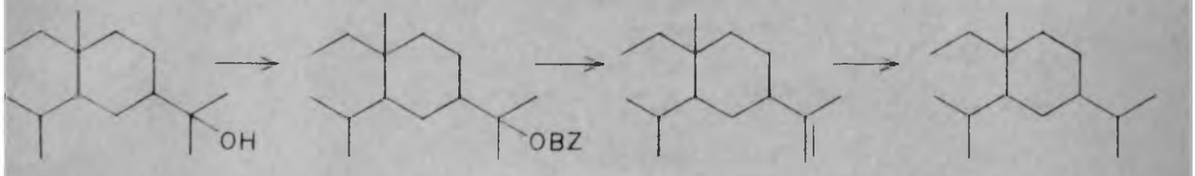
groups of the type -C-CH_3 (0.80, 0.82, 0.86, 0.92, 1.05 and 1.17 δ units) and two protons situated adjacent to the carbonyl group (2.16 and 2.24 δ units). The alcohol (35) with benzoyl chloride and pyridine forms a benzoyl derivative (37) which on pyrolysis at elevated temperature afforded a mixture of two (TLC) unsaturated hydrocarbons $C_{15}H_{28}$ (38). On catalytic hydrogenation in ethyl acetate solution with Adams' catalyst it afforded a saturated hydrocarbon, $C_{15}H_{30}$ (39) identical in all respects with elemane. A similar hydrocarbon (39a) (vide CHART-III) was obtained by hydrogenation of tetrahydroelemene (42) obtained via pyrolysis of tetrahydroelemol benzoate (41).[5,21]

Although the elemane (39) obtained from tetrahydrosaussurea lactone showed identical physical properties and infrared spectrum (Fig. 8) with that of pure elemane (39a) obtained from tetrahydroelemol (40) (vide CHART-III) and a single peak on mixed VPC analysis, its NMR spectrum showed some difference, suggesting thereby that the elemane (39) is possibly a mixture of stereoisomers formed during hydrogenation of the mixture of two unsaturated hydrocarbons (38).

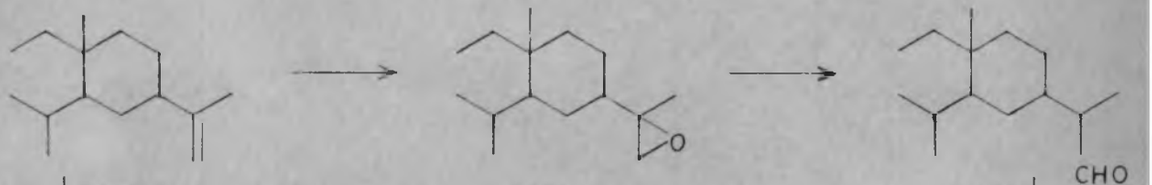
Since it was not possible to draw clear conclusion regarding the stereochemistry of elemol from the above experiments, we decided to convert elemol to tetrahydrosaussurea lactone (21), which is a product of definite

CHART – III

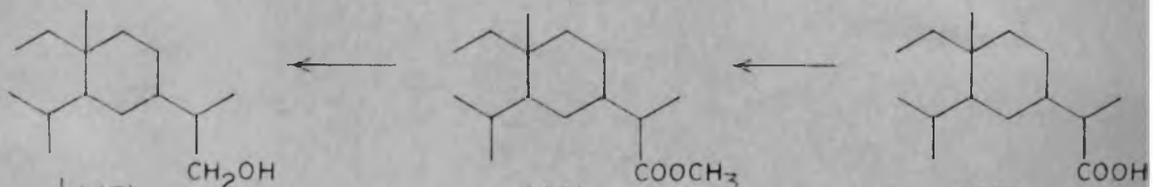
CONVERSION OF ELEMOL TO TETRAHYDRO SAUSSUREA LACTONE



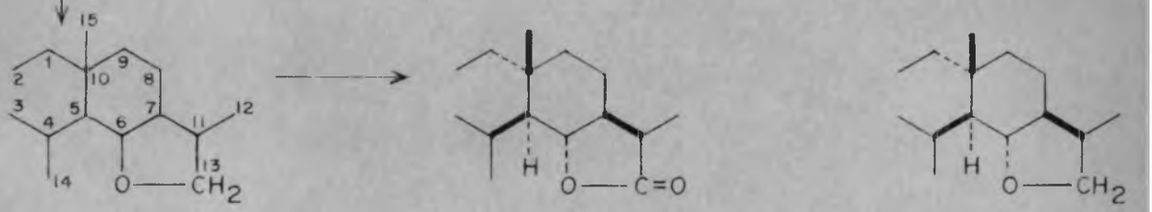
(40) (41) (42) (39a)



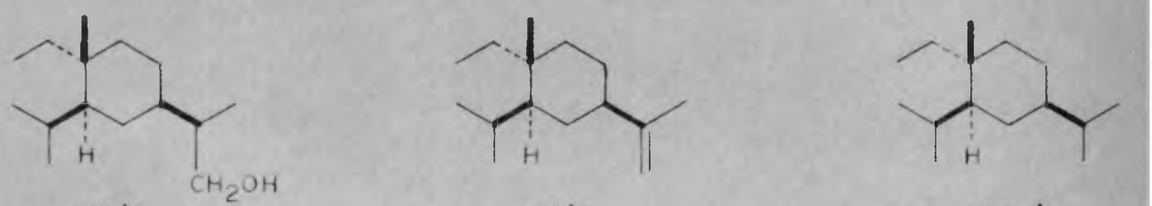
(42) (43) (44)



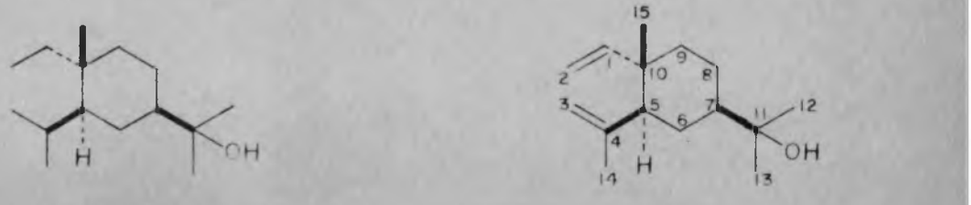
(47) (46) (45)



(48) (21) (49)



(47') (42') (39a')



(40') (8a)

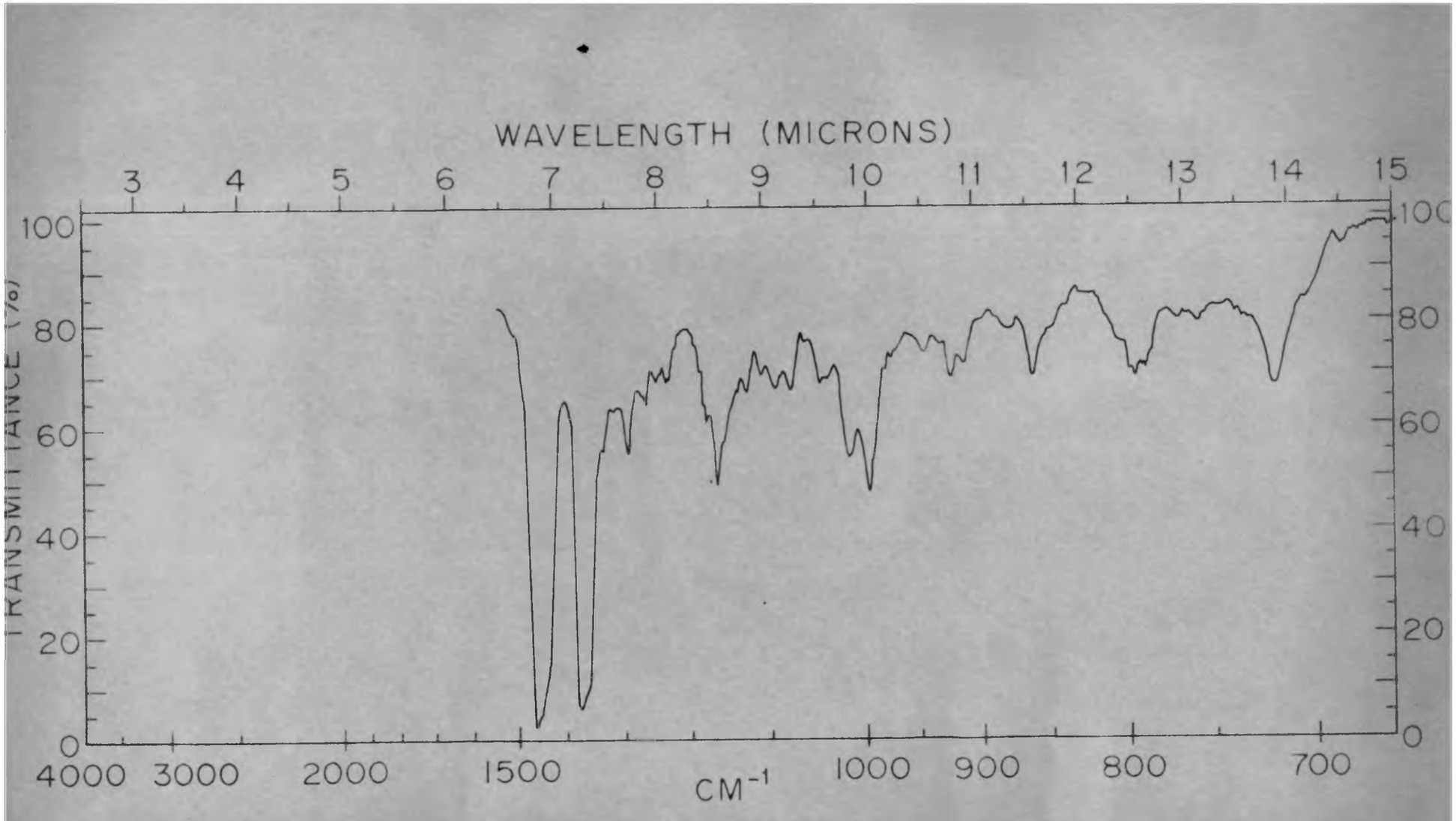


FIG. 8. IR SPECTRUM OF THE ELEMANE (39).

stereochemistry, high melting point (123-125°) and good rotation (+42°). As mentioned earlier, elemol was converted to tetrahydroelemene (42) via pyrolysis of tetrahydroelemol benzoate (CHART-III). The VPC analysis showed essentially one peak (98% by VPC). Its infrared spectrum (Fig. 9) showed bands at 3080,1775, 1639 and 890 cm^{-1} indicating the presence of terminal methylene group. On treatment with perbenzoic acid, the hydrocarbon (42) gave an epoxide (43) which on reacting with borontrifluoride etherate under controlled conditions afforded the aldehyde (44). The aldehyde was oxidised to the corresponding acid (45) with potassium permanganate or with silver oxide. The acid (IR spectrum, Fig.10A) was converted to its methyl ester, $C_{16}H_{30}O_2$ (46) on treatment with excess of ethereal diazomethane. The VPC analysis ascertained the purity of (46). Its infrared spectrum (Fig.10B) showed bands at 1739 and 1193 cm^{-1} due to methyl ester. On reduction with lithium aluminium hydride, the methyl ester afforded the alcohol, $C_{15}H_{30}O$, $(\alpha)_D$ + 3.84° (47). Hydroboration[26] of tetrahydroelemene afforded more conveniently the same alcohol, $C_{15}H_{30}O$, $(\alpha)_D$ + 3.84° (47) with superimposable infrared spectrum(Fig.11) Mixed VPC analysis gave a single peak. The alcohol (47), on refluxing in benzene solution with freshly prepared lead tetracetate[27] under nitrogen atmosphere, was converted to the oxide (48), which from VPC analysis was found to be

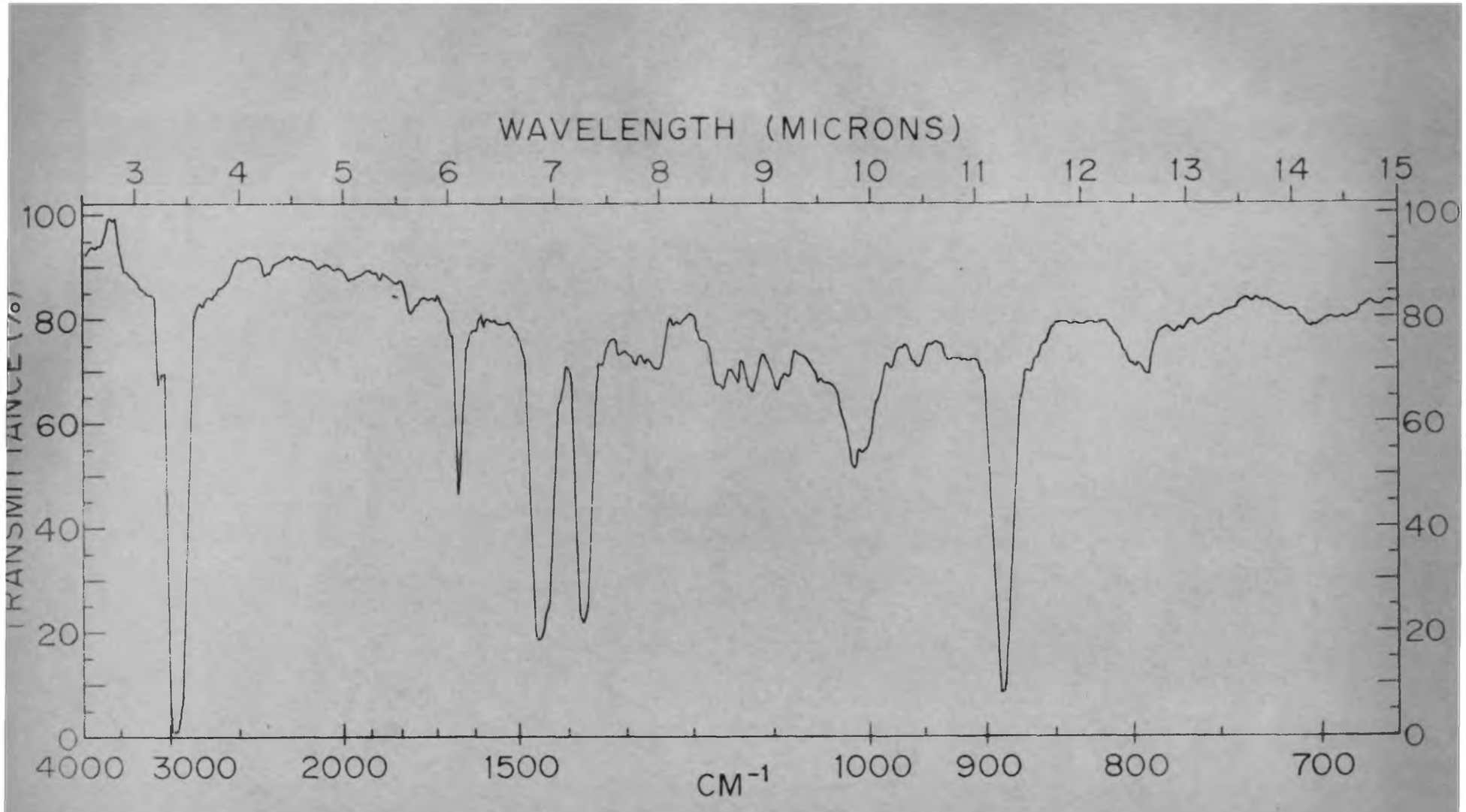


FIG. 9. IR SPECTRUM OF THE TETRAHYDROELEMENE (42).

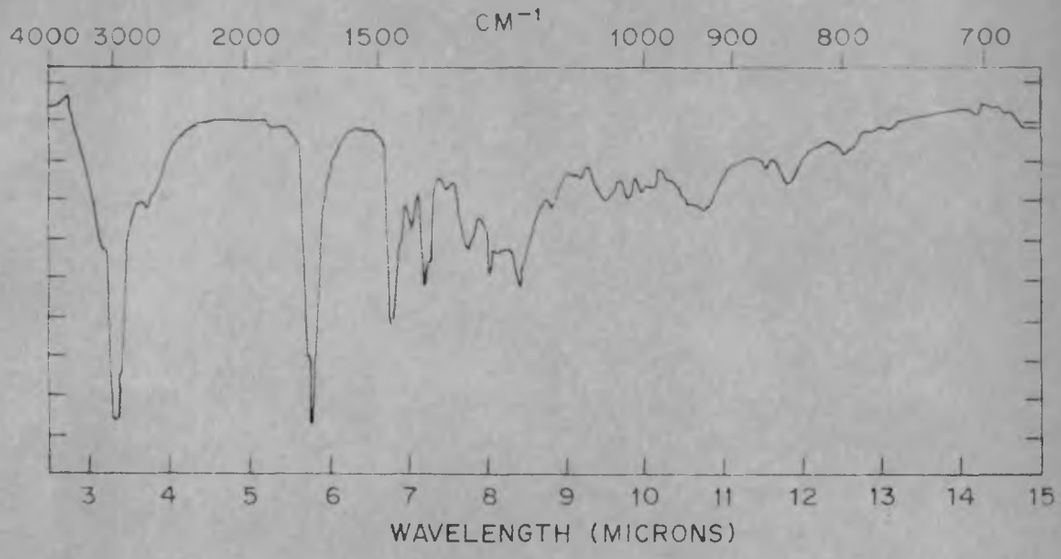


FIG. 10 A. IR SPECTRUM OF THE ACID (45)

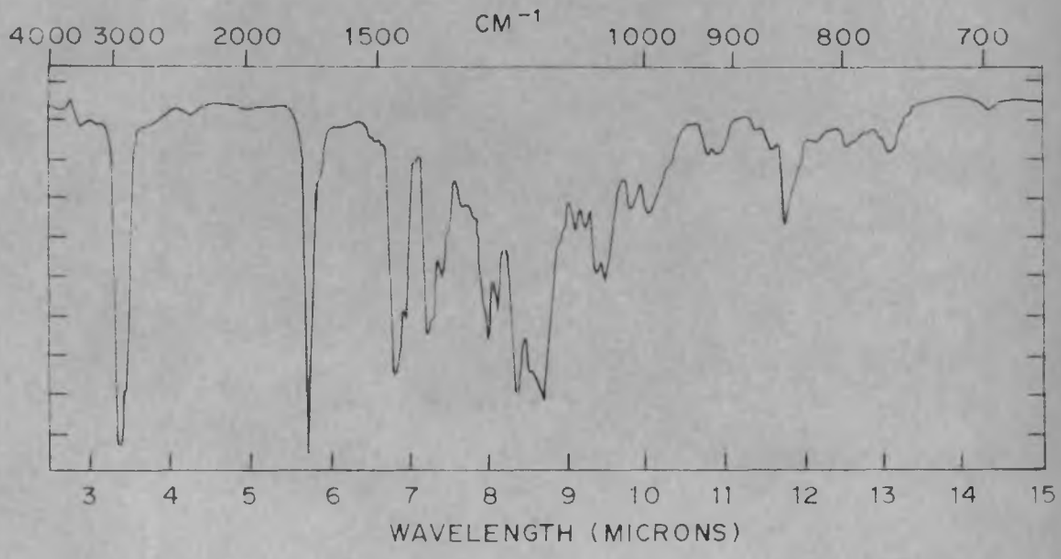


FIG. 10B. IR SPECTRUM OF THE METHYL ESTER (46) OF AN ACID (45).

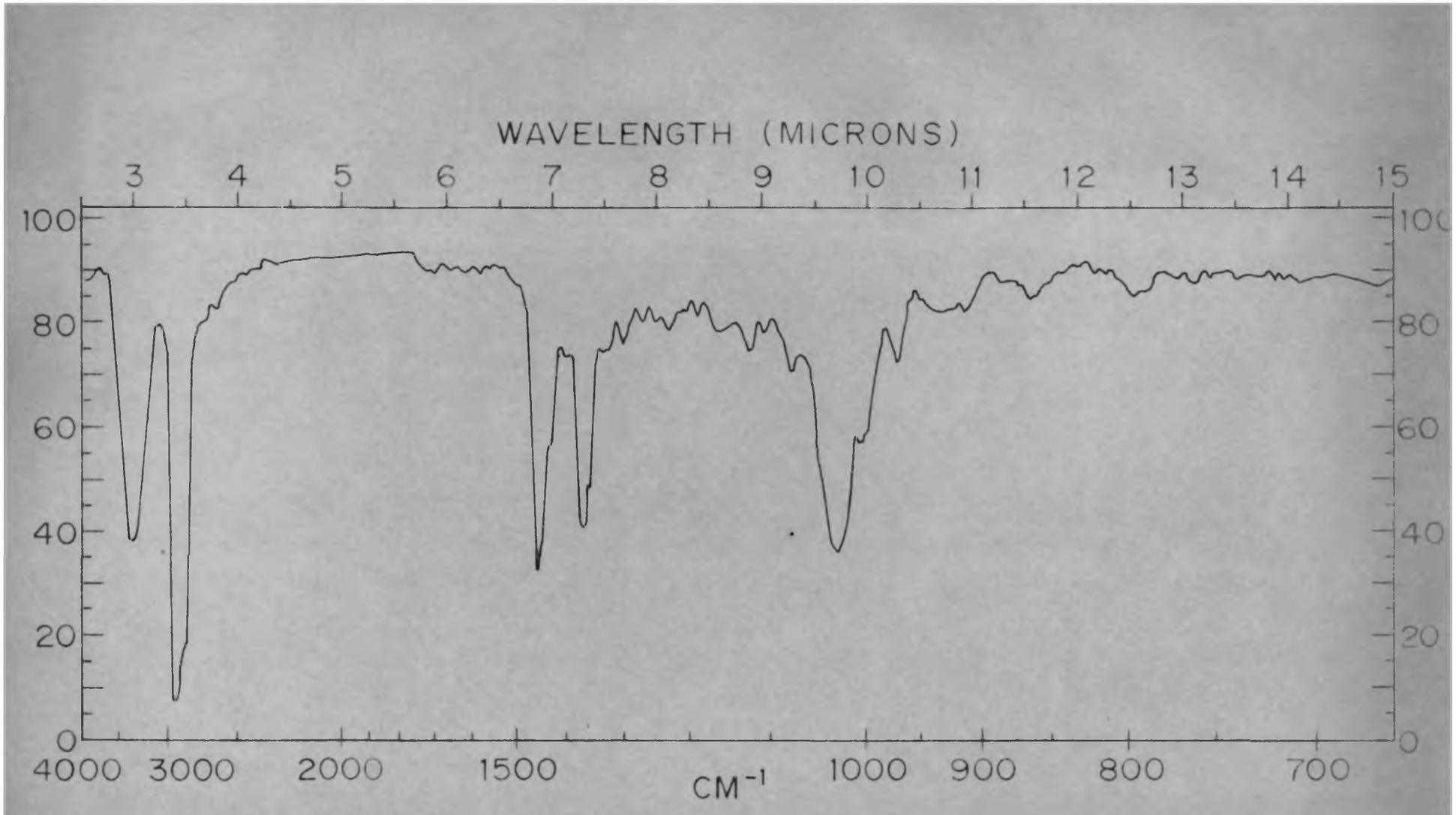


FIG. 11. IR SPECTRUM OF THE PRIMARY ALCOHOL (47).

composed of two isomers in nearly equal proportions (probably epimeric at C6). Its infrared spectrum(Fig.12A) although not completely identical showed some similarity with the IR spectrum (Fig.12B) of the oxide (49) obtained from tetrahydrosaussurea lactone (21).[18] The oxide (48) was carefully chromatographed over neutral alumina(grade I) and 28 fractions (5 ml. each) with pet.ether were collected. VPC analysis and infrared spectra were taken of the alternate fractions. The VPC analysis of the first three fractions showed four distinct peaks while the remaining 17 fractions showed essentially two peaks. The infrared spectrum of Fr.10 (Fig.12C) was superimposable with that of the oxide (49) prepared from tetrahydrosaussurea lactone. The combined fractions (Fr. 4 to 14) on chromic acid oxidation afforded tetrahydrosaussurea lactone (21), the identity of which was proved beyond doubt by melting point (122-123°), mixed melting point (123°),optical rotation (+ 40.14°) and superimposable infrared spectrum (Fig.13A) with an authentic sample of tetrahydrosaussurea lctone (Fig.13B) available in our laboratory.

Since the stereochemistry of tetrahydrosaussurea lactone is thoroughly established on the basis of degradative and synthetic experiments, it is clear that the alcohol (47), tetrahydroelemene (42), elemane (39a), tetrahydroelemol (40) and elemol (8) can be represented

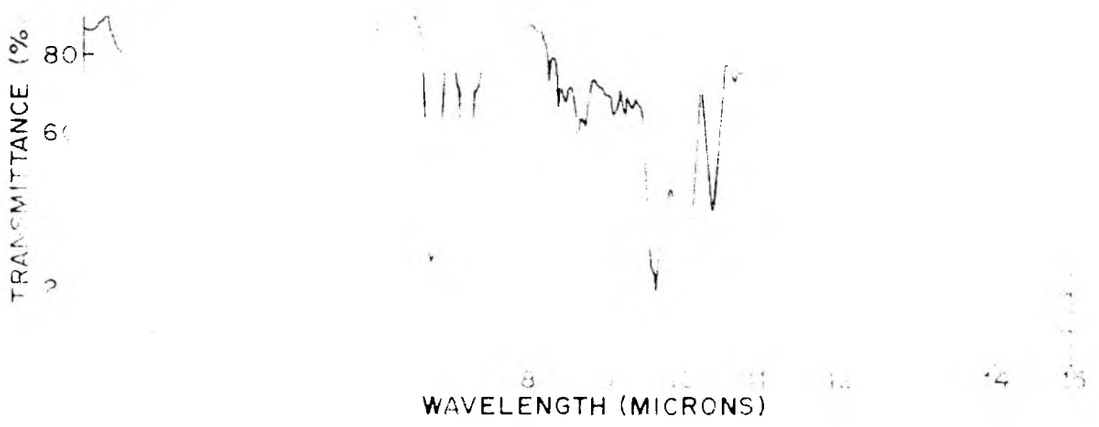


FIG. 12 A. IR SPECTRUM OF THE OXIDE (48) FROM ELEMOL (BEFORE PURIFICATION

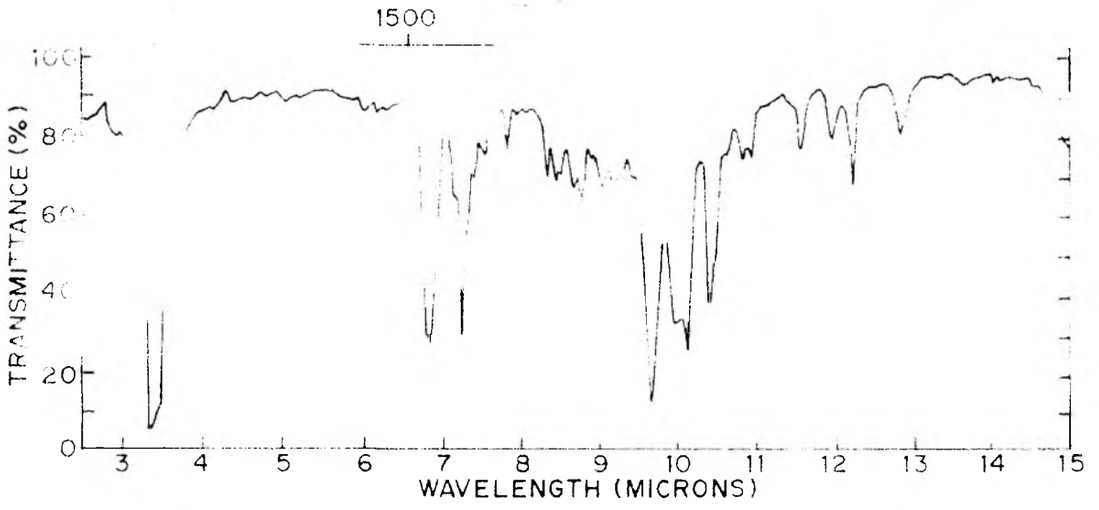


FIG. 12 B. IR SPECTRUM OF THE OXIDE (49) FROM TETRAHYDRO SAUSSUREA LACTONE

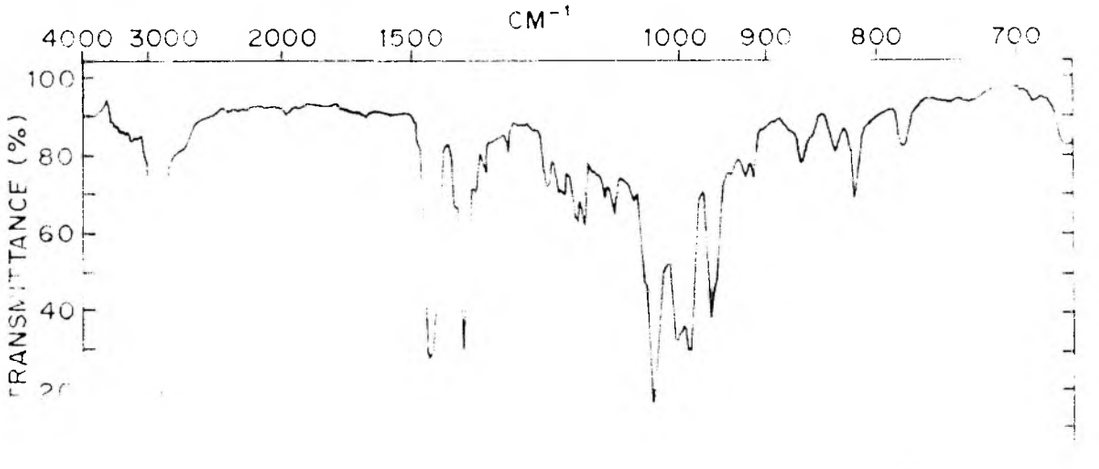


FIG. 12 C. IR (48) FROM
(AFTER PURIFICATION BY CHROMATOGRAPHY)

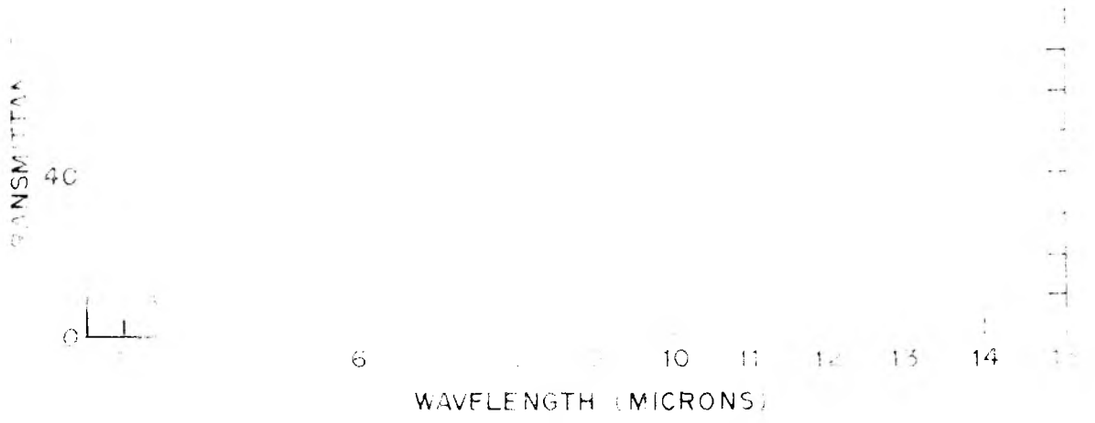


FIG. 13A. IR SPECTRUM OF THE TETRAHYDRO SAUSSUREA LACTONE (21), FROM ELEMOL.

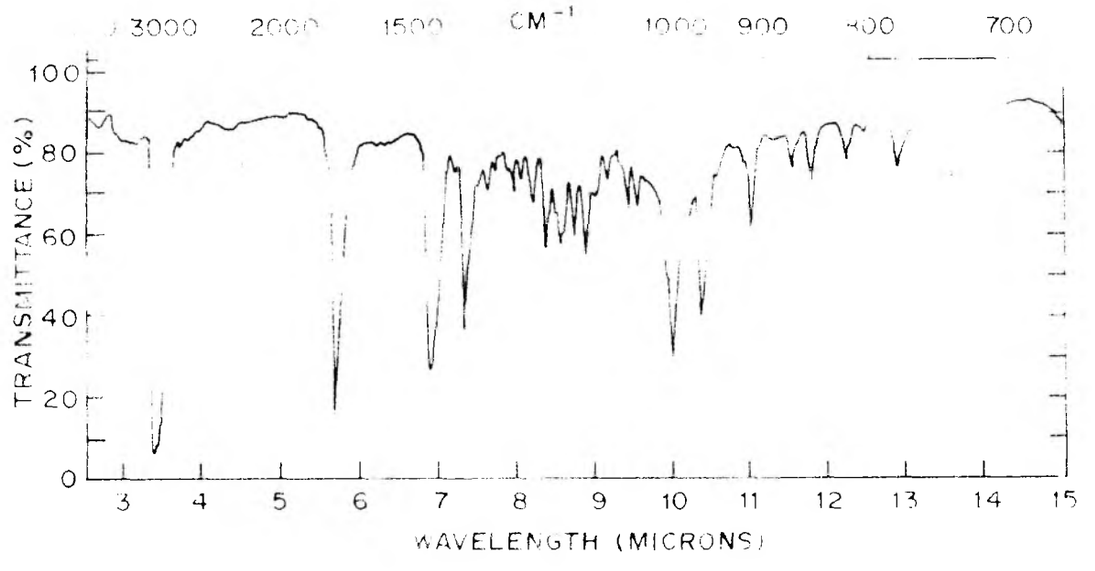


FIG. 13B. IR SPECTRUM TRAHYDRO SAUSSUREA LACTONE (21), AUTHENT

by stereoformula (47'), (42'), (39a') (40') and (2a) respectively. These observations conclusively prove the stereochemistry of elemol and the related compounds and show the stereochemical similarity[22] between elemane type of compounds and the eudesmane group of sesquiterpenoids.

EXPERIMENTAL

EXPERIMENTAL

Isolation of elemol (8)

The tail fractions of Java citronella oil were used for isolation of elemol, m.p.52-53°, $(\alpha)_D$ - 5.82° (c, 3.4).

Infrared spectrum showed complete identity with the spectrum of the authentic elemol available in literature.

Dihydroelemol (27)

A solution of elemol (4.35 g) in ethanol (75 ml) was partially hydrogenated over palladised carbon (1.35 g, 5%) until the absorption corresponded to one mole of hydrogen. The catalyst was filtered off; the filtrate after removal of solvent afforded dihydroelemol (4.1 g) which was purified by sublimation under vacuum, m.p.45-46°, $(\alpha)_D$ + 1.53° (c, 1.96).

Fig.1. IR spectrum(in nujol) bands at: 3400, 1639, 1300, 1176, 1124, 1090, 1010, 961, 910, 892 cm^{-1}.

Analysis

C, 80.30; H, 12.53.

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

Ozonolysis of dihydroelemol (27) to hydroxy-methyl ketone (28) and hydroxy-acid (29)

A stream of ozonised oxygen was passed through a solution of dihydroelemol (4.1 g) in chloroform (20 ml) at -10°.

The ozonisation was carried out in four batches. The combined ozonide after removal of chloroform at 40° in vacuo, was decomposed by heating with water on a water bath for 3 hours, and extracted with ether. The organic material was then separated in the neutral (3.5 g) and acidic portion (0.51 g) by extracting with aqueous bicarbonate solution. The neutral portion was hydroxymethyl ketone (28).

IR spectrum(in liquid film) bands at: 3450,1720, 1124,1063, 1015, 952, 934, 893, 854, 813, 800, 787 cm^{-1}.

The crystalline hydroxy acid (29) obtained from the acidic portion was crystallised two times from pet. ether, m.p.145°, $(\alpha)_D$ + 28.57° (c, 0.7).

Fig.2. IR spectrum(in nujol) bands at: 3400(hydroxyl), 2640, 1681 cm^{-1} (carbonyl), 1370, 1360, 1299, 1250, 1176, 1124, 1047, 1010, 964, 957, 912, 862, 800, 787, 769, 697 cm^{-1}.

Analysis

Found: C, 68.48; H, 10.62.

$C_{13}H_{24}O_3$ requires: C, 68.38; H, 10.59%.

Cyclisation of hydroxy-acid (29) to γ-lactone (31)

The hydroxy-acid (400 mg) in formic acid (5 ml) was heated on a water bath for 2 hours. After cooling to room temperature, it was diluted with water and extracted

with ether. The organic layer washed free from acid and dried. Removal of solvent yielded the lactone (0.32 g) which was purified by chromatography over alumina (grade III, 20 g) and then distilled in vacuo, b.p.128-130° (bath)/1 mm., $(\alpha)_D$ + 17.18° (c, 3.61).

Fig.3. IR spectrum(in liquid film) bands at: 1770 cm^{-1} (γ-lactone), 1360, 1380 cm^{-1} (isopropyl group), 1380, 1361, 1274, 1244, 1176, 1150, 1111, 1087, 1042, 961, 934, 917, 900, 874, 829, 793, 750, 692 cm^{-1}.

The NMR spectrum is shown in Fig.4.

Analysis

Found: C, 74.33; H, 10.69.

$C_{13}H_{22}O_2$ requires: C, 74.24; H, 10.59%.

Controlled lithium aluminium hydride reduction of tetrahydrosaussurea lactone (21) and Wolff-Kishner reduction of the resulting hydroxy-aldehyde (33) to alcohol (36)

To a stirred solution of tetrahydrosaussurea lactone (3 g) in dry ether (30 ml) was added at -5° over a period of 30 minutes, an ethereal solution of lithium aluminium hydride* (21.4 ml, 1 ml = 5.63 mg $LiAlH_4$). After the addition was over, the solution was stirred for 1 hr. at -5° and then allowed to come to room temperature.

* A commercial sample of lithium aluminium hydride was analysed[29] and found to contain 40-42% of the active part. The quantity of the reagent used was calculated accordingly.

Water was added carefully to the reaction mixture and the tether layer which separated out was washed with water and dried. The removal of ether furnished a product (2.3 g) which gave a positive Fehling's test.

The above partially reduced product (2.3 g) was dissolved in freshly distilled diethylene glycol (30 ml) and hydrazine hydrate (3 ml, 100%) by heating on a steam bath for 2 minutes. The solution was kept at room temperature for 30 minutes with occasional shaking; potassium hydroxide pellets (3 g) were added and the solution was heated at 110-115° for 2 hours in an atmosphere of nitrogen. The water was removed by raising the temperature to 190° and the reaction mixture was then refluxed at 190° for further 4 hours. The viscous reaction product was cooled, diluted with water and repeatedly extracted with ether, the ethereal layer washed with water and dried. Removal of ether gave a viscous mass (1.6 g).

The combined reaction product (5.1 g) from four batches was chromatographed over neutral alumina (grade IV, 100 g) and eluted as follows:

Chromatography

Fr.	Solvent	Volume in ml.	Wt. in g.
1	Pet.ether	500	2.8
2	Ether	500	3.2

Fraction 1 was purified by rechromatography on alumina (grade II, 60 g). Elution with pet.ether + benzene (1:1) gave the desired monol (35) (2.3 g) which was purified by distillation and sublimation, b.p.105-108° (bath)/0.5 mm., m.p. 36-37°, $(\alpha)_D$ + 1.84° (c, 6.516). VPC analysis showed a single peak.

Fig.5A. IR spectrum(in nujol) bands at: 3497, 1237, 1177, 1136, 1040, 1020, 970, 909, 892, 871, 862, 820, 790, 777 cm^{-1}.

Analysis

Found: C, 79.91; H, 13.47.

$C_{16}H_{30}O$ requires: C, 79.87; H, 13.36%.

Fraction 2 was identified as diol (34) through the infrared spectrum (Fig.5B), bands at: 3400, 1460, 1370, 1235, 1124, 1076, 1031, 966, 909, 893, 862, 825, 792, 772 cm^{-1}.

Oxidation of the monol (35) to the ketone (36)

The monol (0.15 g) was dissolved in pure acetone (25 ml), Jones' reagent[35] (2 ml) was added dropwise into it until a persistant orange colour was formed. After 10 minutes at room temperature, the product was diluted with water and extracted with ether. The ether layer was washed with water till neutral and dried. Removal of ether afforded the ketone (0.14 g) which after elution of the

chromatographic column (grade II, 30 g) with pet.ether, was further purified by distillation under vacuum, b.p. 90°(bath)/0.4 mm., n_D^{26} 1.4655, $(\alpha)_D$ + 60.84° (c, 6.509).

VPC analysis gave a single peak.

Fig.6. IR spectrum(in liquid film) bands at: 1706, 1380, 1369, 1333, 1307, 1258, 1171, 1130, 1096,1049, 1016, 966, 952, 934, 921, 906, 882, 847, 830, 797 cm^{-1}.

The NMR spectrum is represented in Fig.7.

Analysis

Found: C, 80.32; H, 12.64.

$C_{15}H_{29}O$ requires: C, 80.29; H, 12.58%.

Benzoyl derivative of the alcohol (35) and pyrolysis of the benzoate (37) to the mixture of hydrocarbons(38)

The alcohol (2.1 g) was dissolved in dry pyridine (15 ml) and benzoyl chloride (5 ml) was added. The mixture was shaken thoroughly and left at room temperature for 48 hours, and worked up in the usual way to furnish the benzoate of the alcohol.

IR spectrum(in liquid film), bands at: 1706, 1283, 704 cm^{-1}.

The benzoate was heated in a distillation flask at 210-230°(bath)/100 mm. The distillate was taken up in ether and freed from benzoic acid by washing with sodium bicarbonate solution. The ethereal extract containing the

neutral portion, was washed with water, dried and solvent evaporated. The hydrocarbon obtained was further purified by chromatography over alumina (grade I, 20 g) and distilled in vacuo over sodium, b.p.110-115°(bath)/2 mm., n_D^{28} 1.4676, $(\alpha)_D$ - 30.42° (c, 4.24).

TLC analysis indicated it to contain two components.

IR spectrum(in liquid film) bands at: 1380, 1360 1325, 1290, 1198, 1163, 1136, 1111, 1081, 1015, 885, 864 cm^{-1}.

Analysis

Found: C, 86.32; H, 13.67.

$C_{15}H_{28}$ requires: C, 86.46; H, 13.64%.

Hydrogenation of (33) to elemane (39)

A solution of the hydrocarbon (0.19 g) in ethyl-acetate (30 ml) was hydrogenated over prereduced Adams' catalyst until 1 mole of hydrogen was absorbed and further absorption ceased. The product (0.17 g) worked up in usual way was purified by chromatography over alumina (grade I, 20 g) and distilled in vacuo over sodium, b.p.120-126°(bath)/6.5 mm., n_D^{25} 1.4630, $(\alpha)_D \pm 0°$.

VPC analysis showed a single peak.

Fig.8. IR spectrum (in liquid film) was identical with that of elemane described in the literature.[30]

Tetrahydroelemol benzoate (41)

Tetrahydroelemol benzoate was obtained via hydrogenation of elemol benzoate according to known procedure.[31]

Tetrahydroelemene (42)

The hydrocarbon was prepared by pyrolysis of tetrahydroelemol benzoate according to the procedure previously followed in this laboratory.[21] It had the following properties, b.p.128-130°/9 mm., n_D^{26} 1.4748.

VPC analysis indicated 98% purity.

The infrared spectrum(in liquid film) represented in Fig.9 was identical with that of tetrahydroelemene described in the literature.[21]

Hydroboration of tetrahydroelemene(42) to alcohol(47)

Through a solution of the hydrocarbon (2 g) dissolved in dry tetrahydrofuran (25 ml), diborane gas B_2H_6 was passed at 0° for 1 hr., and then for a further one hour at room temperature. The diborane gas was prepared separately by adding slowly a solution of sodium-borohydride (1.6 g) in pure dry diglyme (20 ml) to a mixture of freshly distilled BF_3- ethereate (10 ml) in dry diaglyme (10 ml). Nitrogen gas was used as the carrier-gas. Excess of diborane in the

reaction flask was decomposed by adding small pieces of ice. The mixture was cooled in the ice-bath, potassium hydroxide solution(25 ml, 3 N) was added, followed by slow addition of hydrogen peroxide (35 ml, 30%, 1 hr). After a further period of 1 hr. at room temperature, the upper layer was separated; the aqueous layer was extracted repeatedly with ether and the combined extracts were dried over sodium sulphate. Removal of solvent gave the alcohol (1.5 g) which was purified by chromatography and distillation in vacuo, b.p.140° (bath)/0.7 mm., n_D^{32} 1.4770, $(\alpha)_D$ 3.84° (c, 3.91).

VPC analysis showed a single peak.

Fig.11. IR spectrum(in liquid film) bands at: 3380, 1380, 1360, 1299, 1235, 1150, 1075, 1031, 1000 and 970 cm^{-1}.

Analysis

Found: C, 79.97; H, 13.10.

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

Aldehyde (44) from tetrahydroelemene (42)

Tetrahydroelemene (42) (10.3 g) was treated with chloroform solution containing perbenzoic acid (100 ml, 6.90 g) and kept over night at 0°. The product was then worked up in usual way to give the crude epoxide (43). The epoxide (8.18 g) was dissolved in dry benzene (300 ml) to which was added a mixture of BF_3-ether complex (1.5 ml)

in dry benzene (50 ml) under stirring. After 10 minutes, sodium-hydrogen carbonate solution (10%, 100 ml) was added to it. The benzene layer was separated, washed with water and dried. The product (5.5 g) thus obtained after removal of solvent was distilled under vacuum, b.p.125-135° (bath)/ 0.5 mm.

Its infrared spectrum showed bands at 2730 and 1720 cm^{-1} due to aldehyde carbonyl. The product was not further purified.

Analysis

Found: C, 81.16; H, 13.36.

$C_{16}H_{28}O$ requires: C, 80.29; H, 12.56%

The semicarbazone prepared was crystallised from aqueous ethanol, m.p.167-168°.

Analysis

Found: N, 14.30.

$C_{16}H_{31}ON_3$ requires: N, 14.93%.

Conversion of aldehyde (44) to acid (45)

The aldehyde (44) (1.5 g) was dissolved in acetone (15 ml) and aqueous sodium carbonate solution (0.62 g. in 5 ml. water) was added. Potassium permanganate (0.62 g) solution in water (15 ml) was added to it slowly over a period of 2 hours under stirring. After a further period of

half an hour, the manganese dioxide formed was dissolved by means of sulphur dioxide and the organic material was extracted with chloroform. The acidic material was separated by extracting with aqueous sodium-carbonate solution which on acidification and extraction with ether gave the acid (0.7 g).

Fig.10A. IR spectrum(in liquid film) bands at: 3125, 2632, 1734, 1471, 1408, 1380, 1282, 1260, 1183, 1083, 1020, 939, 847 cm^{-1}.

Methyl ester (46)

The methyl ester was prepared by treatment of the acid (45) with excess of ethereal solution of diazomethane. The ester was purified by chromatography on alumina(grade II, 10 g) and distillation in vacuo, b.p.115-118°(bath)/0.4 mm., n_D^{29} 1.4643.

VPC analysis showed a single peak.

Fig.10B. IR spectrum(in liquid film) bands at: 1739, 1471, 1429, 1390, 1260, 1236, 1193, 1180, 1070, 1053, 1020, 1000, 864 cm^{-1}.

Analysis

Found: C, 75.97; H, 11.96.

$C_{16}H_{30}O_2$ requires: C, 75.53; H, 11.89%.

Lithium aluminium hydride reduction of ester(46) to alcohol (47)

The ester (0.68 g) was dissolved in dry ether (25 ml) and added dropwise to a slurry of lithium aluminium hydride (0.3 g) in dry ether (25 ml) at 0° with stirring. The reaction mixture was refluxed for 5 hours. The excess $LiAlH_4$ was decomposed with moist ether and finally with water. It was worked up in the usual way and purified by chromatography (grade III, 15 g) and distillation under vacuum. The product (0.54 g) obtained was found to be identical in all respects with the alcohol (47) obtained via hydroboration of tetrahydroelemene (42).

Mixed VPC analysis showed a single peak.

The infrared spectrum was superimposable with that represented in Fig.11.

Lead tetracetate oxidation of the alcohol (47) to the oxide (48)

A mixture of the alcohol (3.1 g), freshly prepared dry lead tetraacetate (6 g) and anhydrous benzene (75 ml) was refluxed on a water-bath for 1 hour with mechanical stirring in nitrogen atmosphere. After cooling to room temperature, the lead tetraacetate was filtered off. The filtrate on processing afforded the oxide (1.1 g) which was purified by chromatography over alumina (grade I, 50 g)

and distilled in vacuo, b.p.90-92° (bath)/1 mm., n_D^{30} 1.4718, $(\alpha)_D$ - 2.7° (c, 3.7).

VPC analysis showed two peaks in nearly equal proportion.

Fig.12A. IR spectrum (in liquid film) bands at: 1480, 1370, 1345, 1325, 1277, 1198, 1178, 1149, 1136, 1112, 1087, 1068, 1031, 1004, 986, 961, 926, 911, 866, 833, 816, 781 cm^{-1}.

Analysis

Found: C, 79.73; H, 12.26.

$C_{15}H_{28}O$ requires: C, 80.39; H, 12.68%.

The oxide (1 g) was rechromatographed on alumina (grade I, 50 g) and 25 fractions (5 ml, each) with pet. ether were collected. Fractions 4-14 were combined on the basis of VPC analysis and IR spectra to give the oxide (0.48 g) suitable for oxidation.

Chromic acid oxidation of the oxide (48) to tetrahydrosassausrea lactone (21)

The oxide (0.48 g) in acetic acid (12 ml) was oxidised with chromic acid (0.507 g) dissolved in water (2 ml) and acetic acid (10 ml). The mixture was heated on a water bath at 70-80° for 15 minutes, cooled and methyl-alcohol (3 ml) was added. After dilution with water, the mixture was extracted with ether and the ether extract

washed with aqueous sodium carbonate solution and water. The residue obtained after removal of ether was saponified by refluxing with alcoholic potash (12 ml; 10%; 1 hr). The alcohol was then removed and the residue diluted with water and extracted with ether. The aqueous solution on acidification gave white crystals (60 mg) of tetrahydrosaussurea lactone which was purified by chromatography and crystallisation from pet.ether. It had m.p. and mixed m.p. with an authentic sample 122-123°, $(\alpha)_D$ + 40.14° (c, 2.018).

Fig.13A. IR spectrum(in nujol) was superimposable with that of an authentic sample (Fig.13B).

Analysis

Found: C, 75.60; H, 11.45.

$C_{15}H_{26}O_2$ requires: C, 75.58; H, 11.00%.

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