TERPENOIDS

A
THESIS
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INTRODUCT

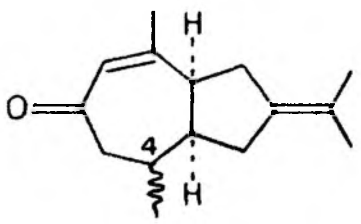
Vetiver oil isolated by steam distillation of the roots of the plant '*Vetiveria zizanioides*' Staph is of great commercial importance. The oil is one of the most valuable perfumery raw materials.[1] The vetiver grass grows as a wild, semi-wild and cultivated plant in many tropical countries.[1] It has been known to the oriental people, particularly in India, for many centuries.[2]

The regions which produce vetiver oil commercially, are Java, Brazil, Reunion Islands, Malaya, Indonesia, India and other tropical countries.

Chemical Composition of Vetiver Oil

Vetiver oil obtained from Java and Reunion Islands has been extensively studied by various workers.[3] Many of the constituents occurring therein have been found to be azulenic in nature. Pfau and Plattener[4] obtained from vetiver oil, two isomeric ketones, α- and β- vetivones. β-Vetivone, $C_{15}H_{22}O$, was assigned the structure (I).

From a consideration of the optical inactivity[4c,5b] of dihydro-β-vetivol (2) and its derivatives, it has been



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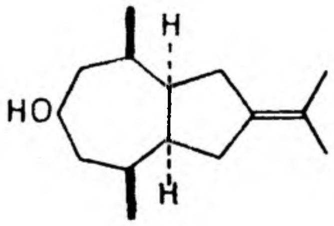

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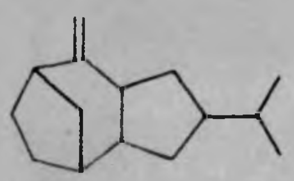
concluded that there must be a plane of symmetry in the molecule running through the isopropylidene and alcohol groups and thus the ring fusion is _cis_. Naves and Perrottet[5] in 1941 showed on the basis of physical properties and Raman spectra that α-vetivone differs from β-vetivone only in the orientation of the methyl group at C_4. The UV spectra of α- and β- vetivone and their derivatives have been published by Naves.[10] The strong odour of the vetiver oil is due to the ketones[4,6] rather than the alcoholic constituents of the oil.

In addition to these two ketones, the presence of other sesquiterpenic compounds has been reported by various workers,[7] though their structures have not been determined.

Chiurdoglu _et al_.[8a] isolated an interesting tricyclic hydrocarbon, tricyclo-vetivene, $C_{15}H_{24}$ (3), two sesquiterpenic alcohols,[8b] bicyclovetivenol, $C_{15}H_{26}O$ (4) and tricyclo-vetivenol $C_{15}H_{24}O$ (5) from Belgian Congo vetiver oil.



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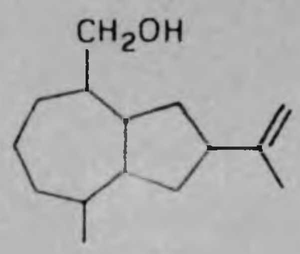

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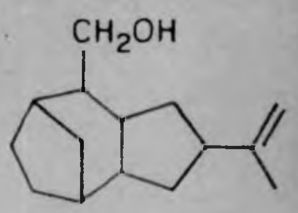
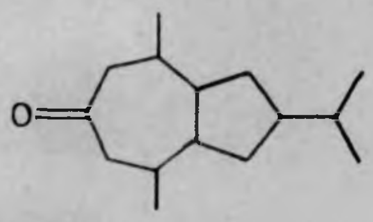


(5)

In 1960, Herout _et al_.[9] from Java vetiver oil reported the isolation of several sesquiterpenic hydrocarbons. They also published the IR spectra of α- and β- vetivones, $C_{15}H_{22}O$ (1), α- and β- vetivanones, $C_{16}H_{26}O$ (6) and the saturated hydrocarbons vetivane and isovetivane, $C_{15}H_{28}$ (7), prepared from α- and β- vetivones respectively. The IR spectra of vetivane and iso-vetivane were however found significantly different from each other. They assigned structure (8) to α-isovetivenene, $C_{15}H_{22}$, $(\alpha)_D^{20}$ - 120.4°, on the basis of spectral data (UV spectrum: $\lambda_{max.}$ 234 mμ, log ε 3.93) and its conversion to isovetivane (7), on hydrogenation.



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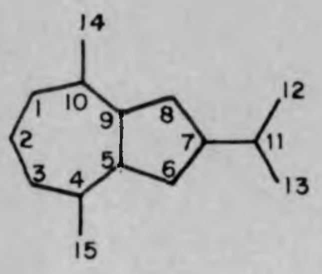

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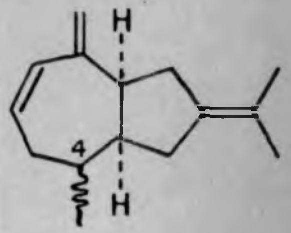

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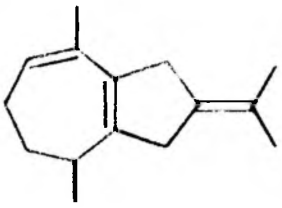
Since on hydrogenation the centres of asymmetry at C_5 and C_9 remained unchanged it was concluded that both the rings in α-isovetivenene (8) are _cis_-fused.

Another hydrocarbon which differs from α-isovetivenene only in specific rotation, $(\alpha)_D^{20}$ - 68°, and IR spectra has been named as β-isovetivenene (UV spectrum: $\lambda_{max.}$ 232 mμ, log ε 4.09) and therefore has been concluded to be different from α-isovetivenene only in the configuration at C_4. They have assigned tentatively two alternate structures (9 or 10) to another hydrocarbon β-vetivenene, $C_{15}H_{22}$, chiefly on the basis of spectral



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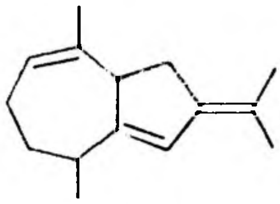


(10)

data (UV spectrum: $\lambda_{max.}$ 230, 238 and 246 mμ, log ε 4.33, 4.33, 4.20) and its conversion to vetivane (7 [illegible] complete hydrogenation. They have further isolated α-vetivenene in an impure form and a conjugated hydrocarbon, (UV spectrum: $\lambda_{max.}$ 246 mμ, log ε 3.79), $C_{15}H_{24}$, which they have named zizanene. It contains two double bonds and possess a new carbon skeleton, since the IR spectrum of its tetrahydroderivative could not be compared with any of the sesquiterpene types known so far.

In addition to the work reviewed above, vetiver oil collected from different areas has been somewhat inconclu- [illegible] ers.[11] [illegible] ke of brevity detailed reference [illegible] eir work is being avoided.

Indian Vetiver Oil

Vetiver oil in India is commonly known as 'khus' oil. The khus grass grows abundantly in the States of the Punjab, Uttar Pradesh, Madhya Pradesh, lower planes of the Himalayas in the North India and also in Kerala and Madras States in the South India. Highly priced varieties of the oil possessing superior aroma and exquisite blending properties are obtained from Bharatpur, Moosanagar and Kanpur areas in the North India. The botanical identification[12] of different varieties of Indian vetiver grass was carried out at the Forest Research Institute, Dehradun. From their examination, it appears that vetiver grass from North India is essentially Vetiveria zizanioides (Linn.) belonging to the family Gramineae.

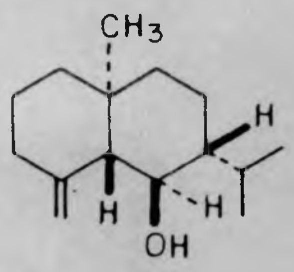
Recently Sadgopal[13] has published the physico-chemical properties of the controlled and the wild varieties of vetiver oil belonging to the different regions in the North India. While the vetiver oil of commerce, coming from Java and Reunion Islands is dextro-rotatory in nature, all the varieties of the North Indian vetiver oil are laevorotatory. This fundamental difference in the physico-chemical properties prompted a systematic examination of the Indian vetiver oil.

As regards the chemical examination of the oil, work done by earlier workers[14] is of a very preliminary nature.

A systematic study of essential oils was initiated in the National Chemical Laboratory during which many essential oils of Indian origin have been examined. The Indian Standards Institute, was particularly interested in determining the properties of different varieties of Indian vetiver oil for the guidance of the consumers. The systematic examination of Indian vetiver oil from five important regions was thus undertaken in this Laboratory. The study has led to the determination of the structures and absolute configurations of many new compounds. This includes structure and absolute configuration of laevo-junenol,[15] $C_{15}H_{26}O$ (11), which has been proved to be the optical antipode of the dextrorotatory alcohol, junenol(12) isolated and characterised by Sorm et al;[16] structure and absolute configuration of khusinol,[17] $C_{15}H_{24}O$ (13), which is the first secondary alcohol of the cadinane group so far reported and belongs to the unusual antipodal group of cadinenes; structure and absolute configuration of (-)-γ_2-cadinene,[18] $C_{15}H_{24}$ (14), a new sesquiterpene hydrocarbon also belonging to the antipodal group of cadinenes and a new cadalenic bicyclic sesquiterpene hydrocarbon,[19] $C_{15}H_{24}$ (15), isolated from South Indian variety of vetiver oil.

It is interesting to point out that so far vetivones (α- or β) have not been isolated from any variety of Indian vetiver oil although the odour of

Indian vetiver oil is closely similar to that of Java or Reunion Island vetiver oil. It is also possible that the odour of the Indian oil is due to the presence of compounds other than vetivones. North Indian varieties of vetiver oil seem to be fundamentally different from the vetiver oil from Java and Reunion Islands, since most of the compounds isolated and characterised from Java and Reunion Island vetiver oil have been found to be azulenic in nature, while the Indian vetiver oil consists chiefly of cadalenic and eudalenic components.



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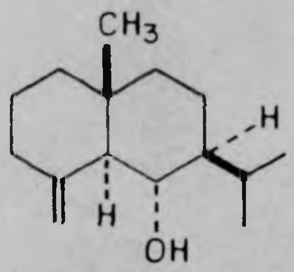

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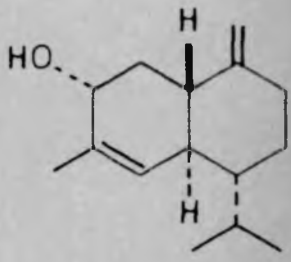

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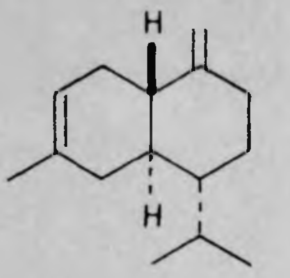

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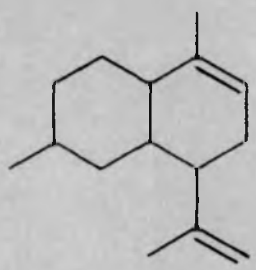

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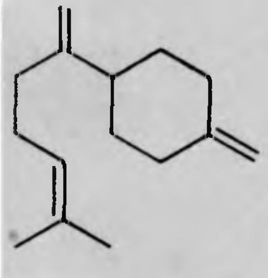
PRESENT INVESTIGATION

The thesis embodies the results of the chemical examination of the commercially available vetiver oil obtained from Bharatpur area in the North India. A study of the physico-chemical properties of the oil was made and the results recorded. Isolation of the different constituents by elaborate column chromatography of the oil over alumina (using different grades according to the requirements) is described in Chapter I of the thesis. Two new liquid sesquiterpene hydrocarbons isobisabolene[20] (16) and (-)-γ_2-cadinene[18] (14), a new liquid aldehyde, khusilal[21] (17), a secondary crystalline sesquiterpene alcohol, khusinol[17] (13) and a primary crystalline sesquiterpene alcohol, khusol[20] (18) have been isolated.



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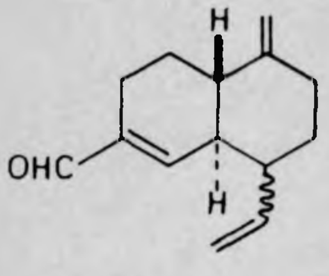

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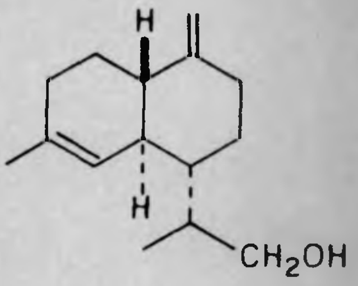

(18)

On VPC analyses, isobisabolene, $C_{15}H_{24}$ (16) has been found to be 90% pure. It belongs to the monocyclic bisabolane group of sesquiterpenes containing three double bonds. The results of the structural investigation of this hydrocarbon are reported in Chapter II of the thesis. The second hydrocarbon, (-)-γ_2-cadinene, $C_{15}H_{24}$, has been assigned the structure and stereochemistry[18] represented by (14). It also belongs to the unusual antipodal group of sesquiterpenes.

The Chapter III describes the results of a systematic reinvestigation on the structure of the crystalline primary sesquiterpene alcohol khusol,[22] $C_{15}H_{24}O$ (18). The absolute configuration[22] of khusol has also been established and it has been shown to belong to the unusual antipodal group of cadinenes.

In Chapter IV of the thesis, the results of structural investigation on a novel aldehyde khusilal,[21] $C_{14}H_{18}O$ (17), have been incorporated. It contains only fourteen carbon atoms.

One particularly striking feature of North Indian vetiver oil is the occurrance of a large number of antipodal terpenoids. This naturally is of obvious biogenetic significance.

Any general introduction to the chemistry of terpene compounds has been avoided for the sake of brevity and especially, since a large number of recent monographs and reviews[23] are already available.

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CHAPTER I

ISOLATION OF ISOBISABOLENE, (-)-γ_2-CADINENE, KHUSILAL, KHUSINOL, AND KHUSOL FROM VETIVER OIL

In this chapter the isolation of different constituents occurring in the North Indian vetiver oil has been described. The isolation was essentially carried out by column chromatography on neutral alumina. Purity of the components was determined by systematic application of ultraviolet and infrared spectra, VPC, TLC and other established practices. The details are described in the experimental part.

EXPERIMENTAL

All melting points and boiling points recorded in this thesis are uncorrected. Rotations were measured in chloroform solution. The alumina used for chromatography was acid-washed and activated and graded according to the Brockmann scale of activity.[1,2] The pet.ether refers to the fraction boiling between 60-80°, unless otherwise stated. UV spectra were measured in ethanol solution unless otherwise stated, on a Beckman ratio recording spectrophotometer, Model DK-2. The IR spectra were recorded as liquid films or in nujol suspension on a Perkin-Elmer Infracord Spectrophotometer, Model No. 137-B. NMR spectra were recorded with a Varian A-60 spectrometer operating at 60 mc. Tetramethyl silane was added as an internal standard. Microanalyses were carried out in the microanalytical section of the laboratory.

Vetiver oil (_Vetiveria zizanioides_, Linn.)[3] of North Indian origin from Bharatpur area was procured through Government agencies. A small portion of the oil (15 g) was dissolved in pet.ether (15 ml), dried over sodium sulphate and filtered. The solvent was removed and the oil was totally distilled; b.p. 200° (bath)/0.2 mm., n_D^{26} 1.5182; d^{30} 0.9914; $(\alpha)_D^{26}$ - 82.26°; acid value 9.45; ester value 22; ester value after acetylation 138; percentage of carbonyl components 20; UV spectrum: $\lambda_{max.}$ 232 $m\mu$.

Vetiver oil (1 kg, dried over anhydrous sodium sulphate) was mixed with pet.ether (200 ml) and chromatographed over alumina (grade III, 20 kg) in three batches. The results of the chromatography are presented in Table I.

TABLE I

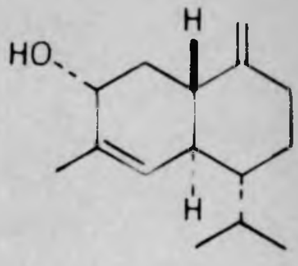
Fr.	Eluent (lit.)		Weight (g.)	n_D^{26}	$(\alpha)_D^{26}$
1	Pet.ether,	40	450	1.5165	-78.76°
2	Benzene,	45	250	1.5180	-91.0°
3	Ether,	30	260	1.5188	-64.5°

Further processing of these fractions ultimately resulted in the isolation of different components in the pure state.

Fraction 1: Isolation of isobisabolene (4), (-)-γ_2-cadinene (5) and khusilal(3)

From its IR spectrum (Fig.1.1) it was found to consist of hydrocarbons, carbonyl components and small amounts of alcohols. Percentage of carbonyl components 39.5 (hydroxyl amine hydrochloride method). The details of their isolations are given in pages (17,20,23)

Fraction 2: Isolation of khusinol (1)



(1)

From its IR spectrum (Fig.1.2) it was found to consist of alcohols. This fraction solidified on keeping at 0° for 6 hr. The crystals were separated and repeatedly crystallised from pet.ether, m.p.87° (50 g). From its IR spectrum (Fig.1.3) and mixed m.p. determination it was identified as khusinol (1) characterised by Bhattacharyya *et al.*[4]

Fraction 3: Isolation of khusol (2)

IR spectrum (Fig.1.4) of this fraction revealed the presence of alcoholic components in it. On keeping in a refrigerator for 36 hr., this fraction deposited crystals. These were filtered and washed with cold pet. ether. On crystallisation from pet.ether, white silky

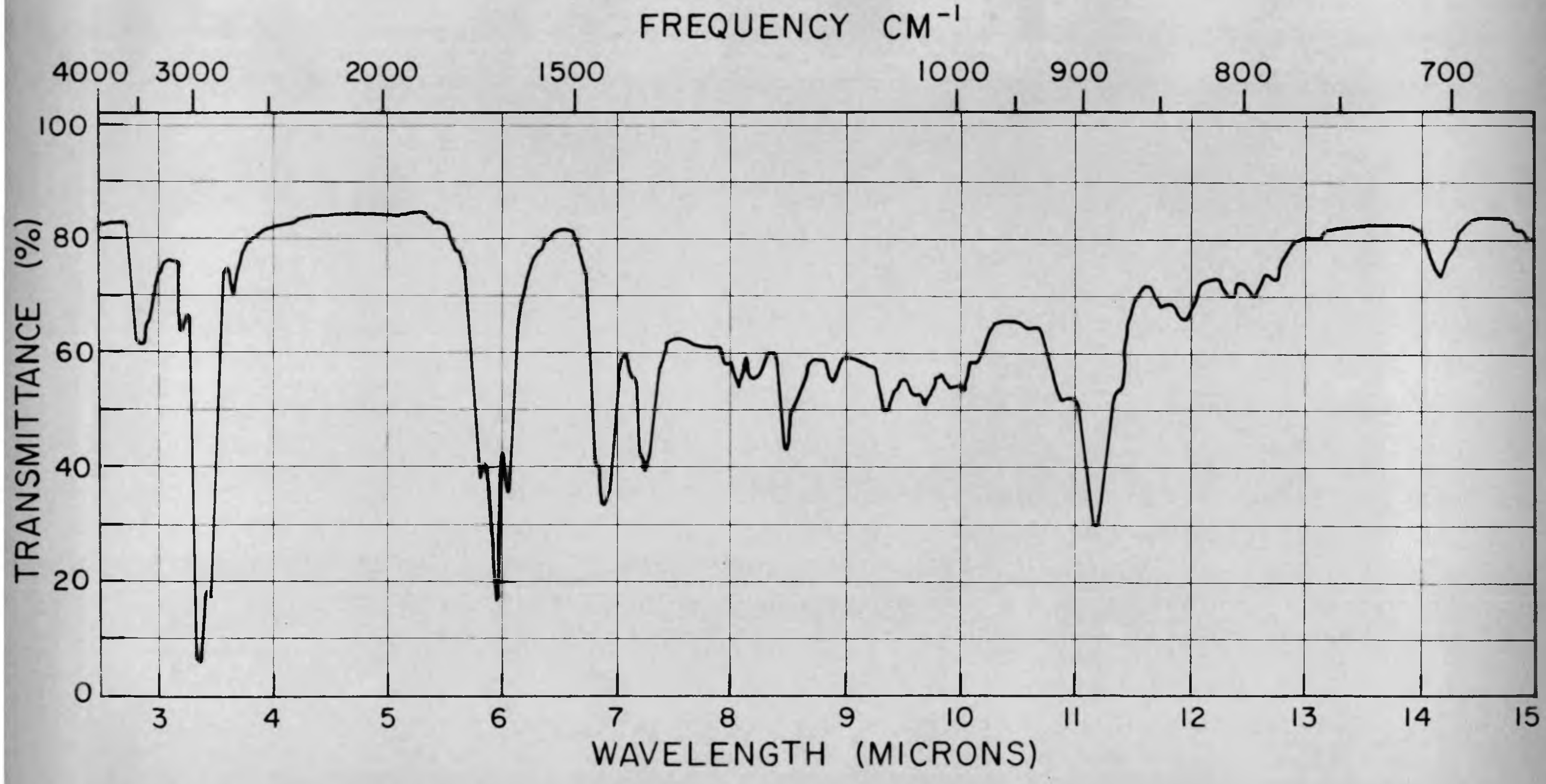
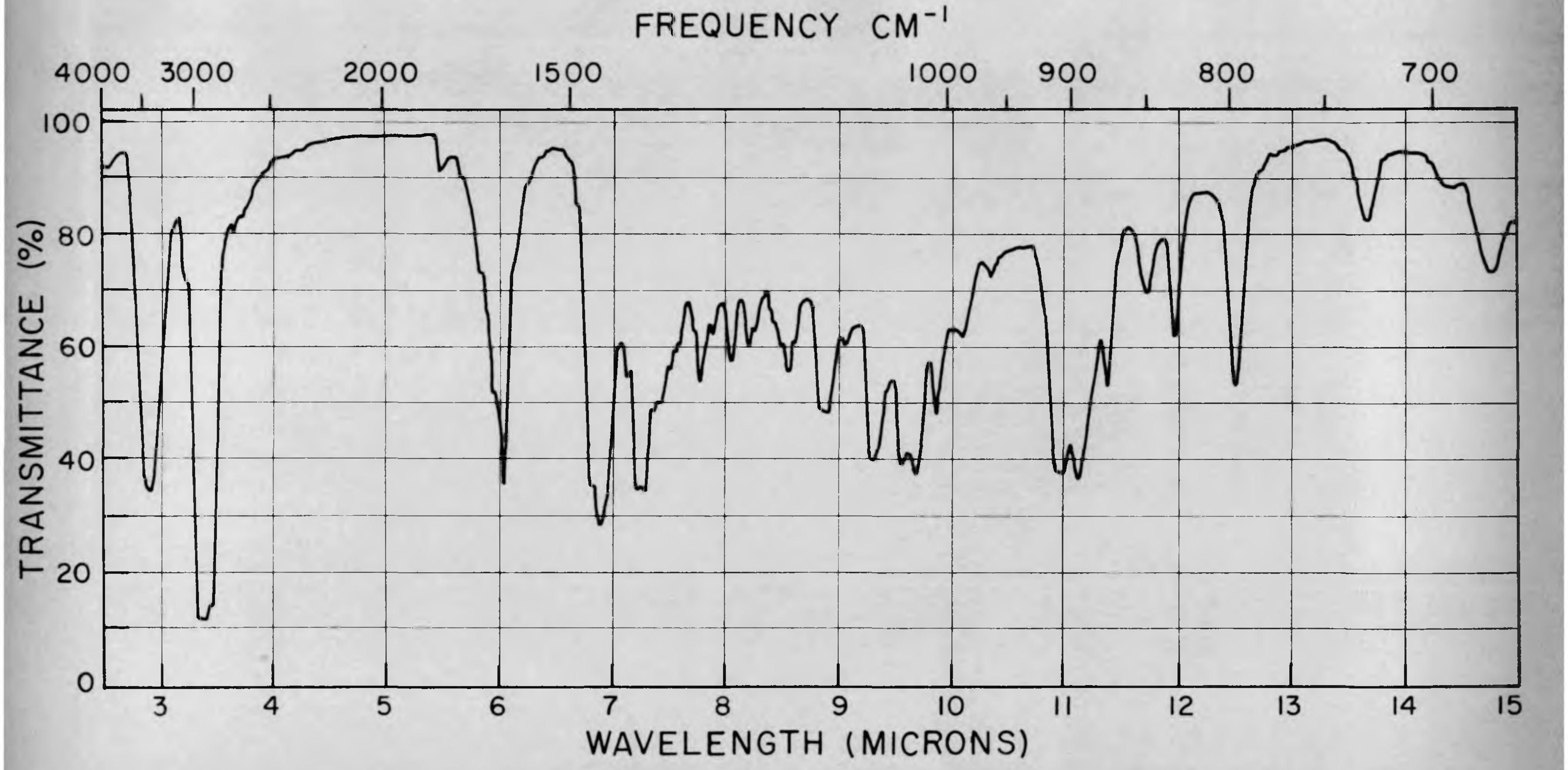


FIG. 1·1 IR SPECTRUM OF FRACTION 1. TABLE I



FIG·1·2 IR SPECTRUM (LIQUID FILM) OF FRACTION 2· TABLE I

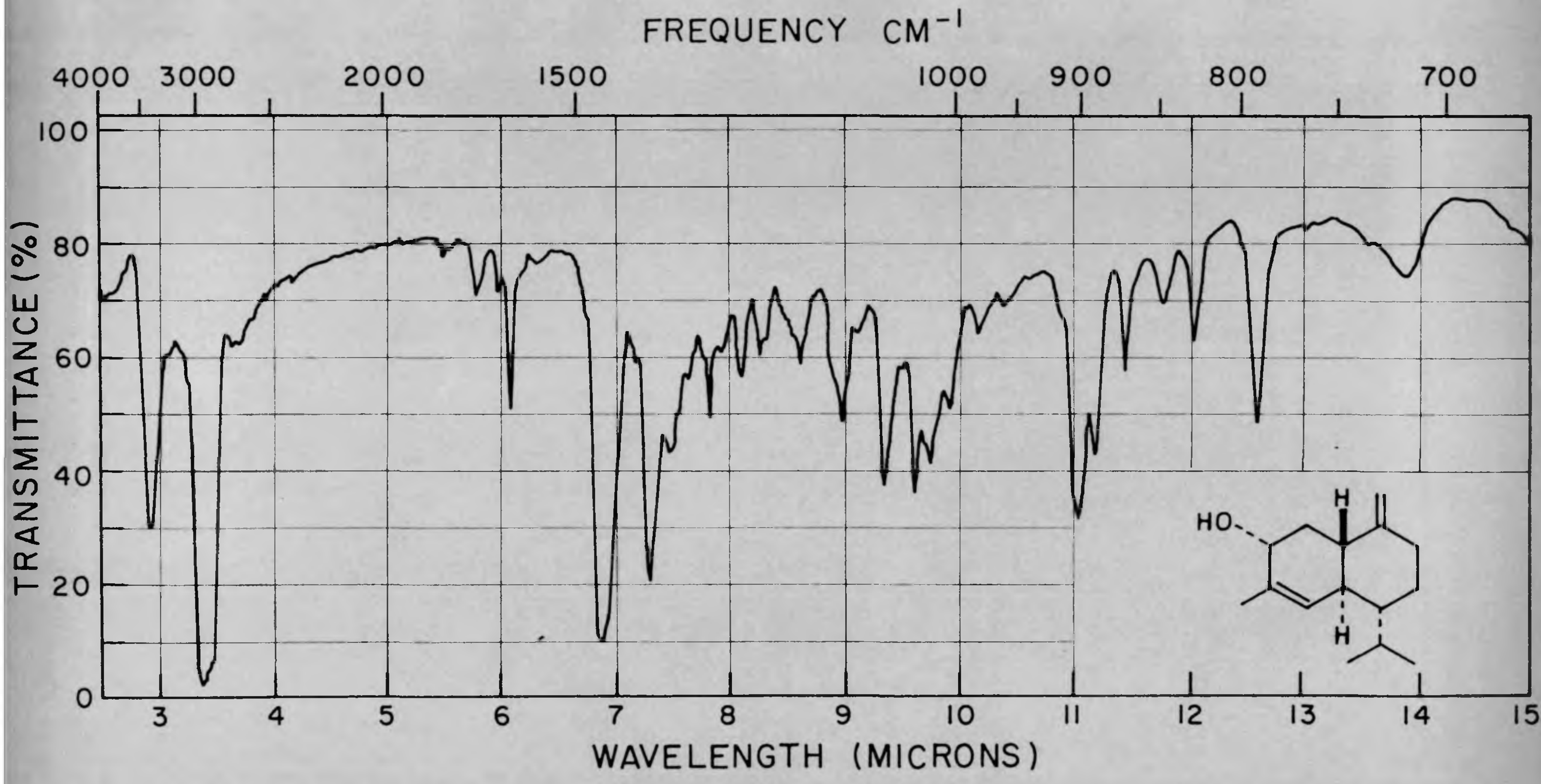


FIG. 1·3· IR SPECTRUM (IN NUJOL) OF KHUSINOL 1

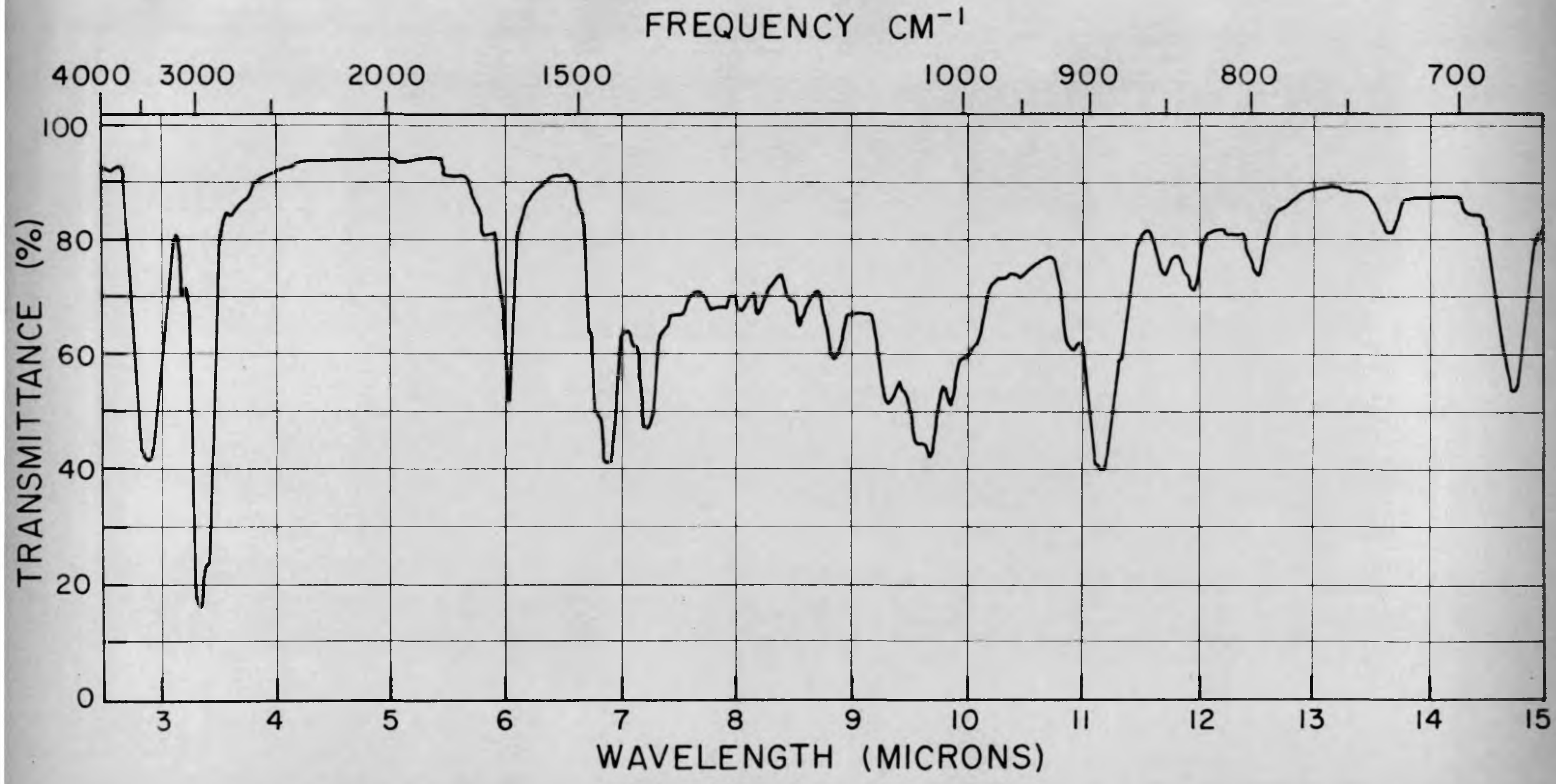
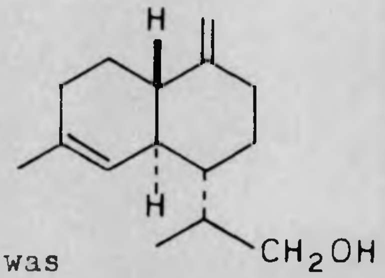


FIG. 1·4. IR SPECTRUM (LIQUID FILM) OF FRACTION 3. TABLE I needles were obtained (15 g), m.p.101-102°. By a mixed m.p. determination, it was identified as the primary cadalenic alcohol, khusol. Its structure and absolute configuration^{5} is shown to be represented by (2). Details of this investigation are represented in Chapter III of this thesis.



(2)

Treatment of Fraction 1 (Table I)

Isolation of khusilal (3)

Fraction 1 (Table I), 450 g. was further rechromatographed over alumina (grade II, 30 kg) in four batches. The results of the chromatography are presented in Table II.

TABLE II

Fr.	Eluent (lit.)	Weight (g.)	n_D^{27}	$(\alpha)_D^{27}$
1	Pet.ether, 40	100	1.5012	- 40°
2	Benzene, 28	168	1.5190	-111°
3	Ether, 22	90	1.5185	- 73°
4	Alcohol, 10	50	-	-

Fraction 2 (Table II)

Its IR spectrum (Fig.1.5) indicated that it chiefly consisted of carbonyl components; bands at: 2710 (-CHO), 1725 and 1709 ($\rangle C{=}O$) and at 1680 cm^{-1} ($-C{=}C{-}C{=}O$); UV spectrum: $\lambda_{max.}$ 232 $m\mu$, ϵ 5,000. The pale yellow colour of this fraction showed signs of darkening on keeping. Direct chromatography of a test portion (15 g) of this carbonyl fraction over alumina was relatively ineffective for the separation of its components. In all these chromatographic separations, the ratio of the alumina (grade II) used was usually kept low (40:1) but a considerable loss of the material was observed. With high ratios of alumina (grade III), the fractions collected on the basis of their IR spectra and optical rotations differed from each other only in the relative proportion of the components, but there was no clear cut separation. Fortunately, however, the components could be easily and conveniently separated via their semicarbazones at low temperature. This treatment separated the α,β-unsaturated carbonyl component of the fraction in the form of its crystalline semicarbazone.

The carbonyl fraction (150 g) was mixed with ethanol (50 ml) and a solution of semicarbazide hydrochloride (60 g) and sodium acetate (90 g)in water(400 ml).

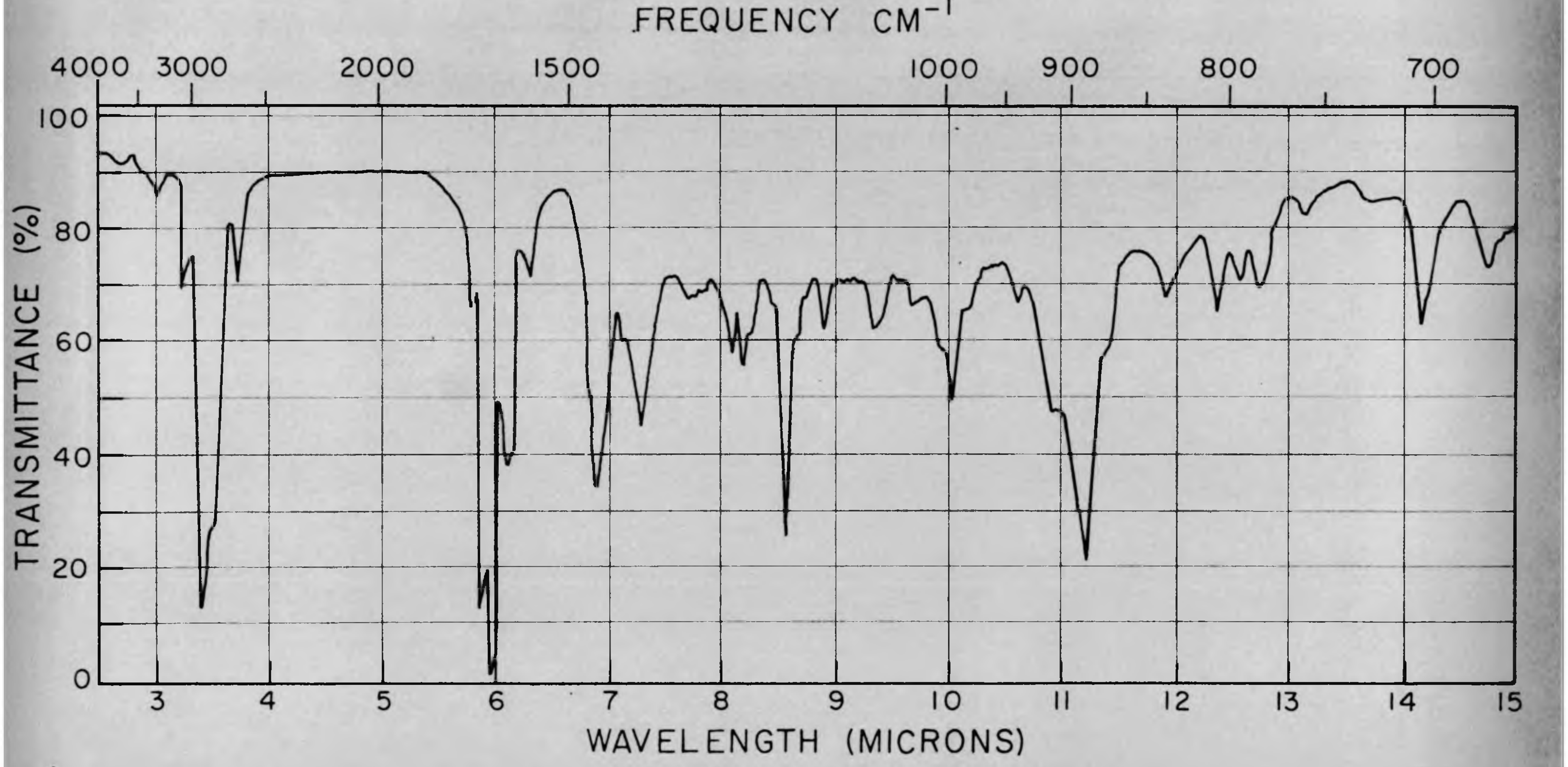
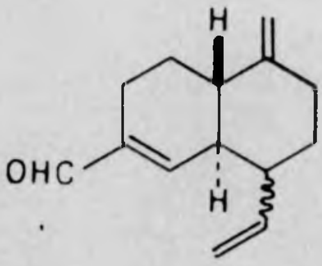


FIG. 1·5 IR SPECTRUM (LIQUID FILM) OF FRACTION 2 TABLE II

The mixture was kept at 0° for 24 hr. with occasional shaking. The semicarbazone was obtained in the form of a yellow cake. This was washed repeatedly with ice cold pet.ether when white solid (80 g) was obtained. On crystallisation from dilute alcohol long white needles were obtained, m.p.161° (sample dried for 4 hr. at 95°, 8 mm) (Found: N, 15.92; $C_{15}H_{21}ON_3$ requires: N, 16.2%). UV spectrum: $\lambda_{max.}$ 265 mμ, ϵ 28,850. This semicarbazone on treatment with oxalic acid according to the method of McQuillin *et al.*[6] gave a colourless mobile liquid in a (VPC) pure form. Laevulenic acid was also used for the decomposition of the semicarbazone but the use of oxalic acid according to the procedure described below was found to be the most convenient and gave high yields of pure product with reproducible results.

Semicarbazone (10 g) in ethanol (100 ml), pet. ether (80 ml) and water (100 ml) was refluxed for 11 hr. with oxalic acid (30 g) and 40% aqueous formaldehyde (50 ml). Pet.ether layer was separated and the aqueous layer was extracted several times with pet.ether. Combined pet.ether extracts (200 ml) were washed with water till neutral, dried and pet.ether evaporated. The residue (5 g) was chromatographed over alumina (grade II, 100 g) and the column eluted with pet.ether (250 ml) to give the carbonyl compound (4.5 g), which could be reconverted to the same semicarbazone, indicating that no change had taken place during these operations, b.p. 115° (bath)/ 0.3 mm., n_D^{25} 1.5349; $(\alpha)_D^{25}$ - 261° (c, 9.7). (Found: C, 83.18; H, 9.04. $C_{14}H_{18}O$ requires: C, 83.12; H, 8.97%). Neutralisation equivalent of its crystalline acid, $C_{14}H_{18}O_2$ (Found: 219. Calc. 218.8). UV spectrum: $\lambda_{max.}$ 232 mμ, ε 13,320. IR spectrum shows bands at: 2703 and 1678 cm^{-1}, typical of an α,β-unsaturated aldehyde.

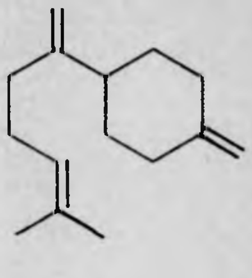


(3)

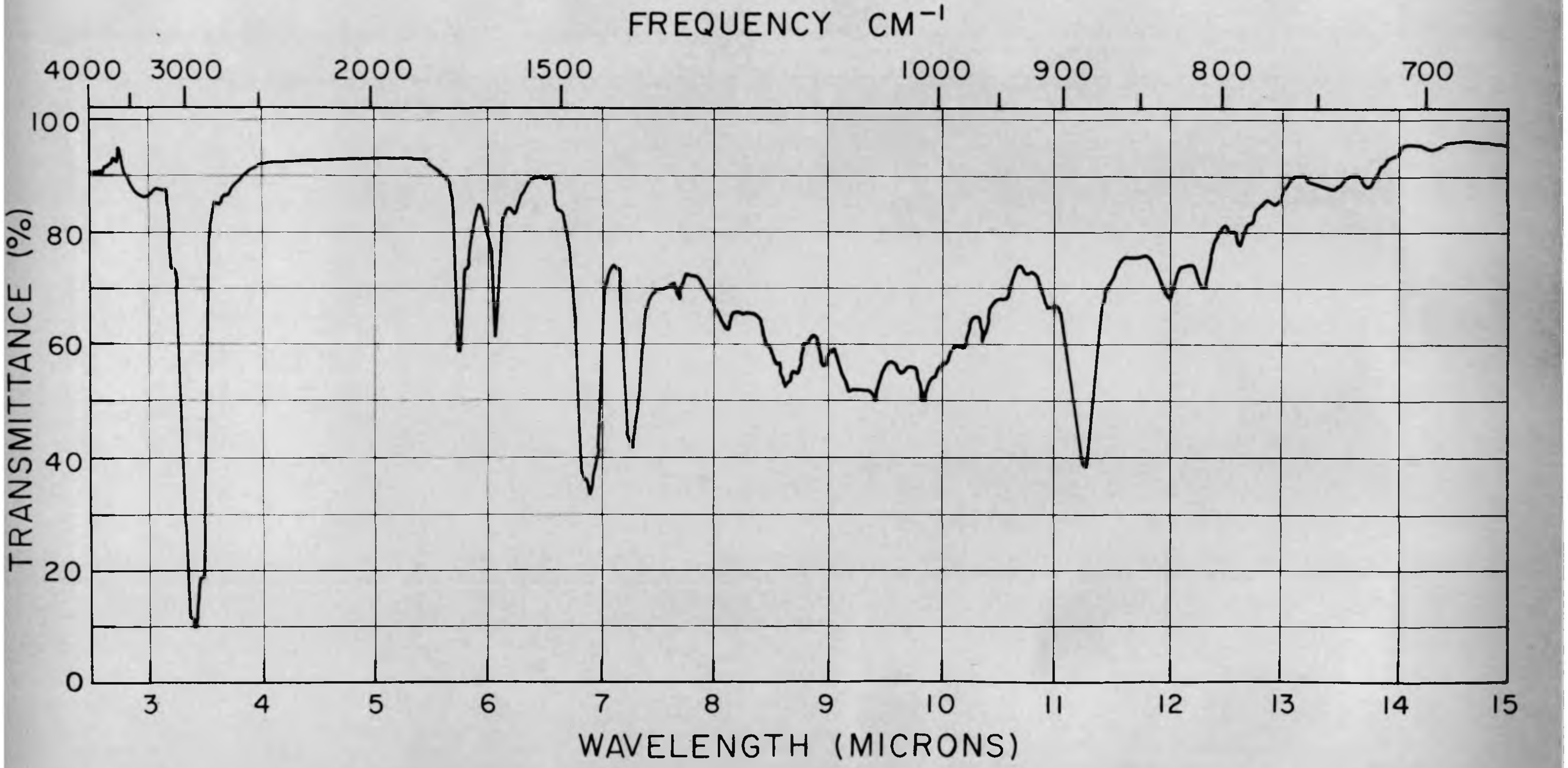
This is for the first time that an aldehyde has been isolated from vetiver oil. Evidences which show that this novel aldehyde has the structure[7] (3) are represented in Chapter IV of the thesis.

Isolation of Isobisabolene (4)

The hydrocarbon rich fraction 1 (Table II) still contained small amounts of carbonyl components (IR spectrum, Fig. 1.6). For the isolation of the hydrocarbons the ratio of alumina to the substance was kept high. In each case the column was eluted with pet.ether first; this removed most of the hydrocarbons. The oxygenated constituents retained in the column were then eluted with suitable solvents of higher polarity. Fraction1 (Table II) (100 g) was mixed with pet.ether (25 ml) and chromatographed over alumina(grade II,10 kg) in two batches.



(4)



FIG· 1·6· IR SPECTRUM (LIQUID FILM) OF FRACTION 1· TABLE II

The results of chromatography are shown in Table III.

TABLE III

Fr.	Eluent (lit.)	Weight (g.)	n_D^{28}	$(\alpha)_D^{28}$
1	Pet.ether, 1/2	20	1.5021	-7°
2	"	15	1.5056	-17°
3	"	13	1.5057	-28°
4	"	5	1.5020	-41°
5	" 2 X 1/2	4	1.4970	-48°
6	Benzene, 2	12	--	--
7	" 2 X 2	16	--	--

The fraction (5) from Table III (4 g) was further chromatographed over alumina (grade I, 400 g) and the results of the chromatography are shown in Table IV.

TABLE IV

Fr.	Eluent (ml.)	Weight (g.)	n_D^{28}	$(\alpha)_D^{28}$
1	Pet.ether, 50	0.20	1.4980	-41°
2	"	0.35	1.4965	-47.2°
3	"	0.82	1.4965	-48.0°
4	"	1.00	1.4966	-47.5°
5	" 2X50	0.41	1.4965	-47.6°
6	" 2X50	0.22	1.4970	-48.6°
7	" 5X50	0.20	1.5000	-52°

The fractions (3 to 5) from Table IV were combined (2.2 g) and rechromatographed over alumina (grade I, 230 g). The results indicated that even with the use of hundred fold alumina, the refractive indices and optical rotations remained almost constant. This showed that the near limit of purification attainable by chromatography had been reached. It was distilled over sodium, b.p. 99-102°/8 mm., $(\alpha)_D^{26}$ - 47° (c, 4.6), n_D^{26} 1.4966, d_4^{26} 0.8859 (Found: C, 88.33; H, 12.09. $C_{15}H_{24}$ requires: C, 88.16; H, 11.84%).

Evidences which led to structure (4) for this hydrocarbon which has been named isobisabolene[8] are presented in Chapter II of the thesis.

Isolation of (-)-γ_2-cadinene (5)

Fraction 4 (5 g) from Table III was chromatographed over alumina (grade I, 500 g) and the results of the chromatography are shown in Table V.

TABLE V

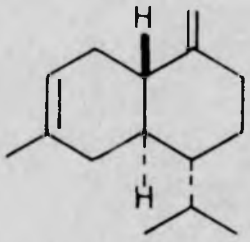
Fr.	Eluent (ml.)	Weight (g.)	n_D^{26}	$(\alpha)_D^{26}$
1	50	0.2	1.5007	-16°
2	"	1.0	1.5040	-38°
3	"	1.8	1.5061	-42°
4	"	1.3	1.5059	-41°
5	"	0.15	1.5041	-49.6°
6	3X50	0.21	1.4980	-50°
7	3X50	0.10	1.4977	-

Fractions 3 and 4 from Table V were combined (3.1 g) and rechromatographed over alumina (grade I, 350 g) and the results of the chromatography are shown in Table VI.

TABLE VI

Fr.	Eluent	Weight	n_D^{26}	$(\alpha)_D^{26}$
1	Pet.ether, 30	0.35	1.5047	-38.9°
2	"	0.90	1.5049	-40.4°
3	"	1.05	1.5049	-39.9°
4	"	0.41	1.5049	-40.1°
5	" 2X30	0.20	-	-

Fractions 2, 3 and 4 from Table VI were combined and distilled over sodium, b.p.115-116°/3 mm., $(\alpha)_D^{26}$ - 40°, n_D^{26} 1.5050, d_4^{30} 0.9169, (Found: C, 87.8; H, 12.00. $C_{15}H_{24}$ requires: C, 88.16; H, 11.89%). This hydrocarbon from its physico-chemical properties and IR spectrum(Fig.1.7) was found to be identical with (-)-γ_2-cadinene (5) isolated and characterised by Bhattacharyya <u>et al.</u>[9]



(5)

Further work on other fractions of the oil is in progress.

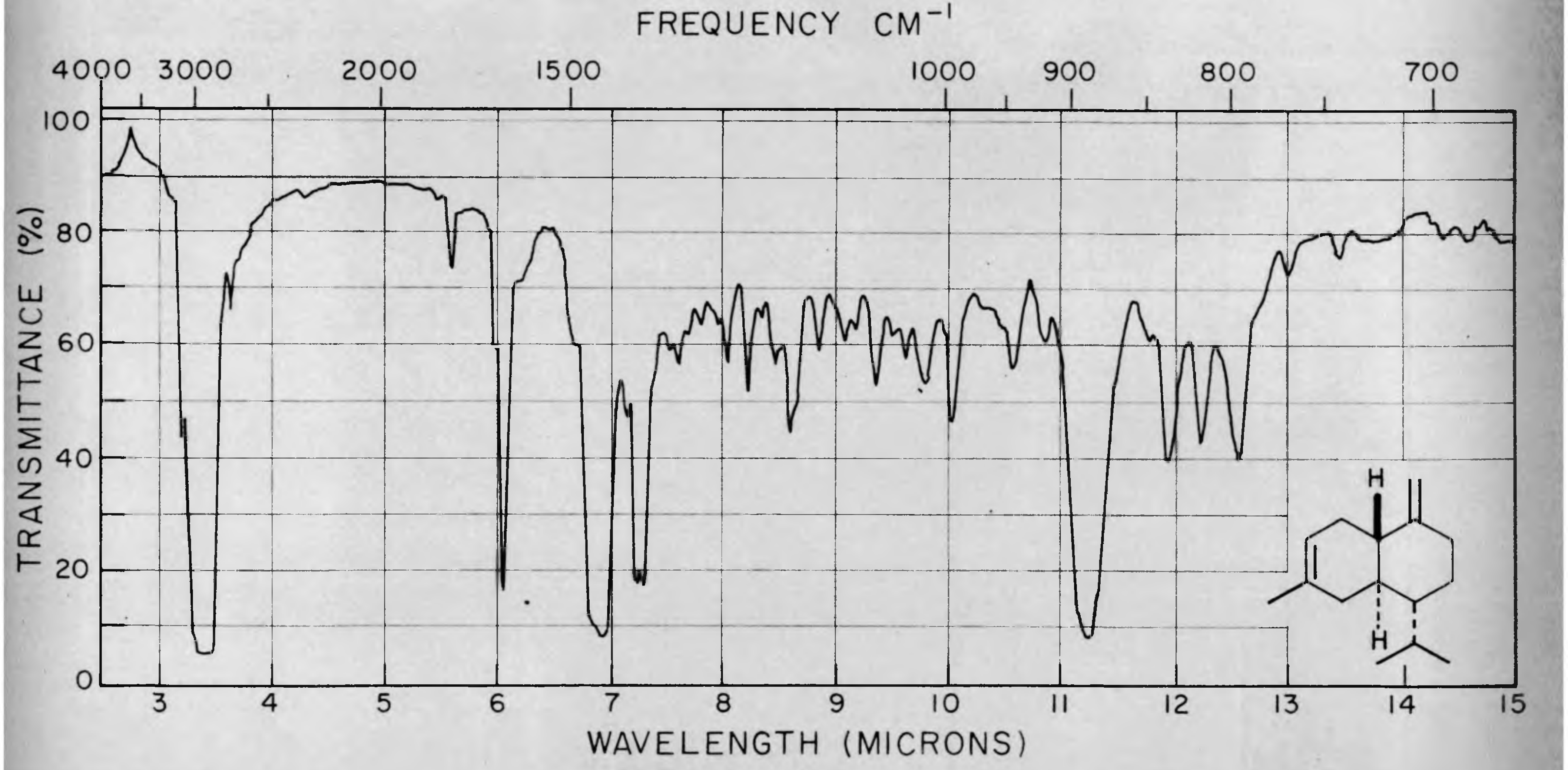


FIG.1.7 IR SPECTRUM (LIQUID CELL, 0.05 mm) OF (–) – γ_2 – CADINENE 5

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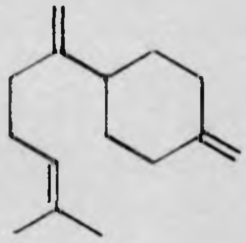
CHAPTER II

THE STRUCTURE OF ISOBISABOLENE
A NEW SESQUITERPENE HYDROCARBON
FROM VETIVER OIL

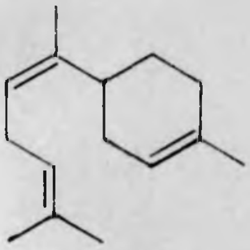
S U M M A R Y

On subjecting vetiver oil to elaborate column chromatography over alumina, a new liquid hydrocarbon isobisabolene[1] has been isolated in pure form (VPC and TLC analysis). Structure (I) has been assigned to it on the basis of dehydrogenation, ozonolysis and the formation of bisabolane on hydrogenation. Infrared and NMR spectra confirm this structure.

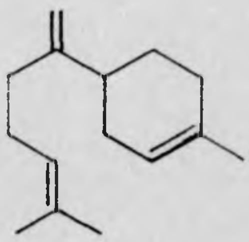


(1)

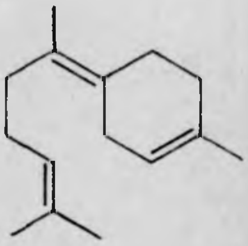
A number of monocyclic sesquiterpene hydrocarbons belonging to the bisabolane[2] group which afford cadalene or structurally related type skeleton on aromatisation have been known.[3] α,β- and γ-Bisabolene, $C_{15}H_{24}$ (2,3 & 4), zingiberene, $C_{15}H_{24}$ (5), α-curcumenes, $C_{15}H_{22}$ (6) and β- and γ-curcumenes $C_{15}H_{24}$ (7 & 8) belong to this group. Ruzicka and Capato[3] showed on the basis of chemical studies that bisabolenes should be represented by (2, 3 & 4) of which the γ-isomer predominates. All of them however give the same trihydrochloride, m.p. 79-80°.



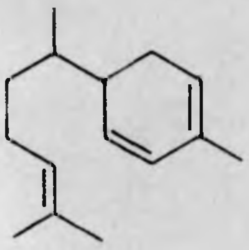
α-2



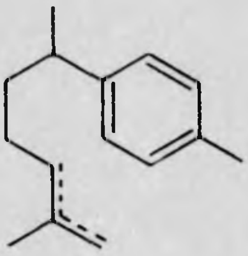
β-3



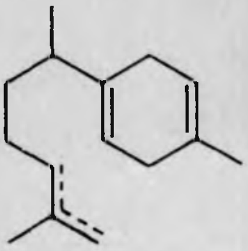
γ-4



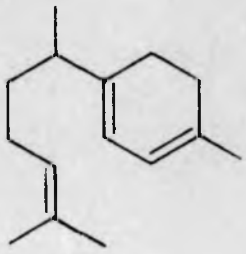
5



α-6



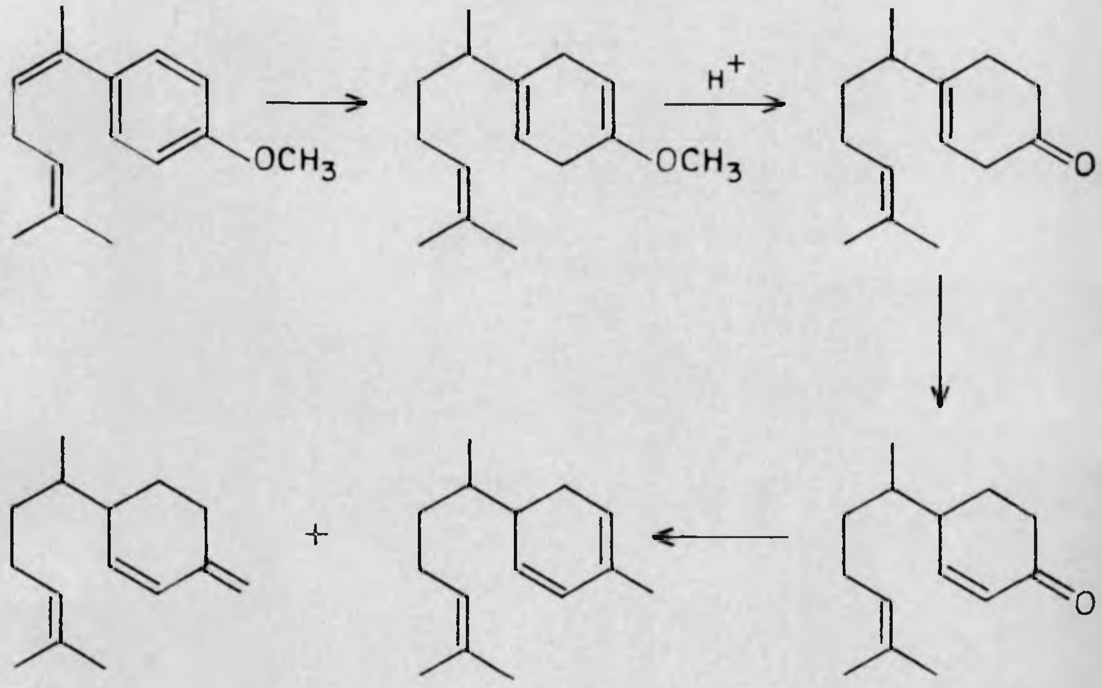
β-7



γ-8

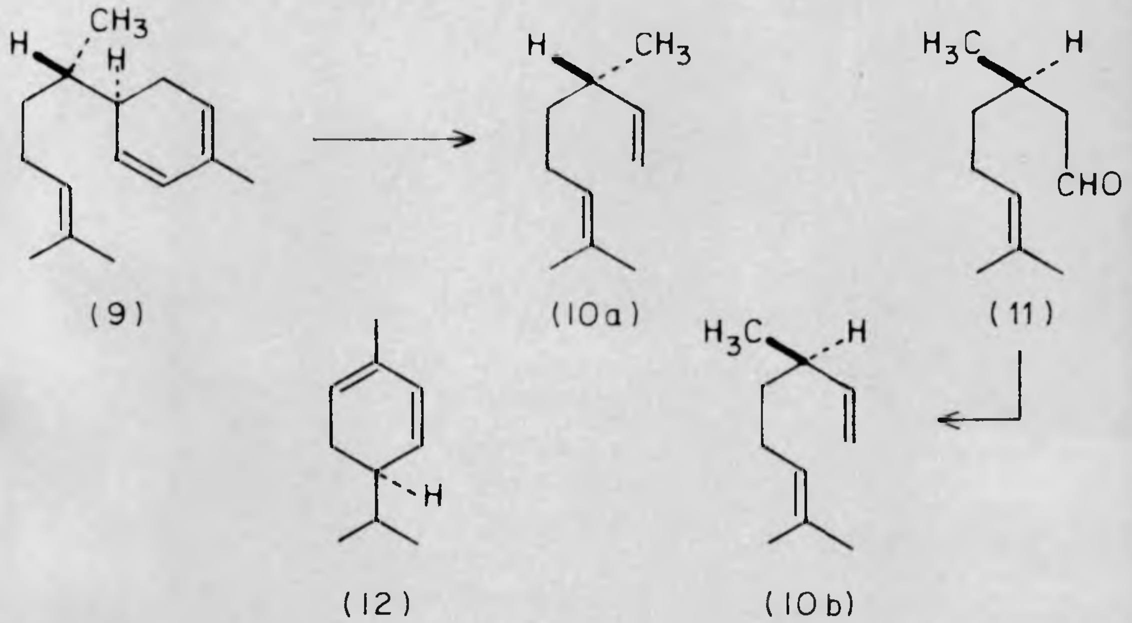
The structure of zingiberene (5) has been verified by synthesis[5] as shown in scheme (1). The absolute configuration of zingiberene[6,7] has been established as shown in (9), chiefly from its degradation to α- 2:6 -dimethyl-octa-2:7-diene (10a) which has now been correlated with d-citronellal (11). On the basis of rotatory powers, Mills[7] has shown that the ring asymmetric centre is identical with that in α-d-phellandrene (12).

SCHEME-1

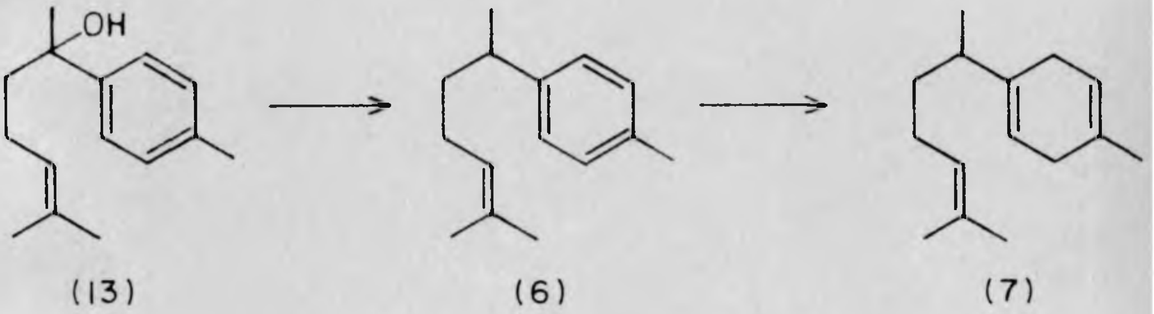


(5)

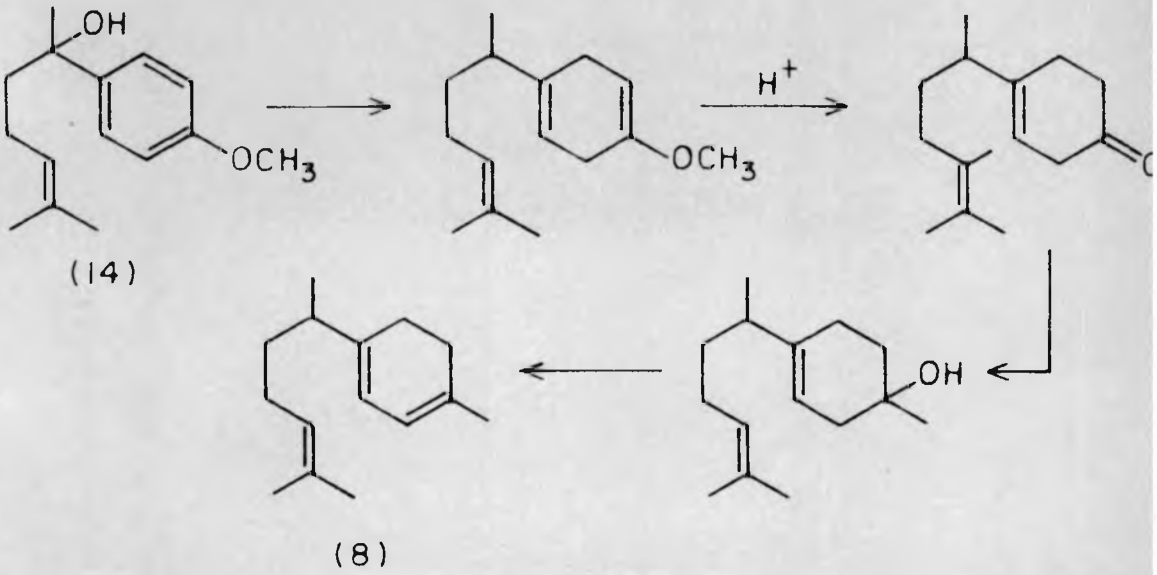
Birch and Mukherji[8] have reported the synthesis of dl-α,β- and -γ-curcumenes. α- and β- Hydrocarbons were prepared by the hydrogenolysis of the allylic alcohol (13)



SCHEME-2

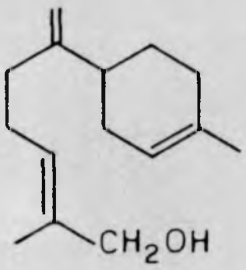


SCHEME-3

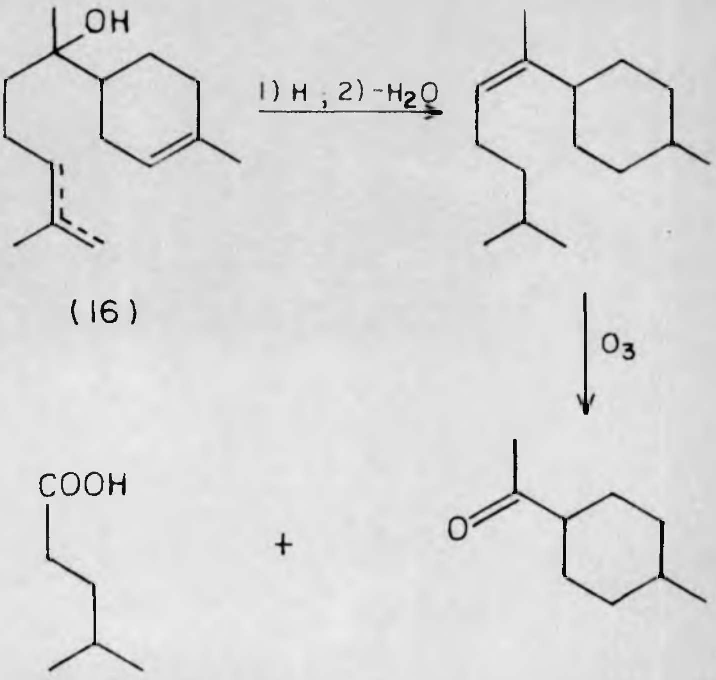


with sodium in liquid ammonia and ethanol according to the scheme (2). dl-γ-Curcumene was prepared from (14) in accordance with the scheme (3).

Among the recently investigated members particular mention may be made of lanceol$^{9-11}$, $C_{15}H_{24}O$, which is represented by structure (15). It gives β-bisabolene (3) by reduction with sodium in liquid ammonia/ethanol. Sorm et al.[12] isolated bisabalol, $C_{15}H_{26}O$ (16) from the oil of Camomille and showed its relation with bisabolene by the formation of bisabolene trihydrochloride. They found that the alcohol gave on ozonolysis both acetone and formaldehyde, while after hydrogenation, dehydration and ozonolysis it gave p-methyl hexahydro-acetophenone (17) and isocaproic acid (18). In confirmation with the structure (16), their tetrahydrobisabalol, $C_{15}H_{30}O$ (19) was identical with the synthetic product.



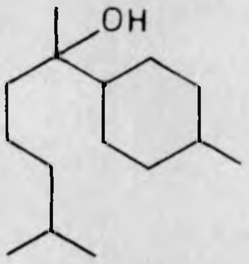
(15)



(16)

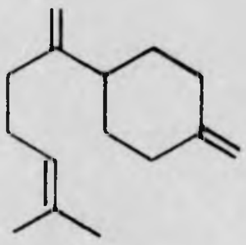
(18)

(17)



(19)

On subjecting vetiver oil (Bharatpur variety, North India) to elaborate column chromatography over alumina we have now isolated another monocyclic sesquiterpene hydrocarbon, $C_{15}H_{24}$. We propose to name it as isobisabolene.[1] Evidences put forward in this part of the thesis show that isobisabolene is represented by the structure (1).


(1)

Isobisabolene (isolation vide Chapter I, p. 20) analysed correctly for $C_{15}H_{24}$, $(\alpha)_D^{26}$ - 47°; n_D^{26} 1.4966, d_4^{26} 0.8859, b.p. 99-102°/8 mm. It shows 90% purity on VPC analysis.

Nature of Unsaturation

The IR spectrum of isobisabolene (Fig.2.1) showed absorptions at 892 and 1640 cm^{-1} due to a methylenic double bond ($>C=CH_2$) and at 791, 813 and 833 cm^{-1} due to a tri-substituted ethylenic linkage ($-CH=CR_1R_2$). Isobisabolene did not show any characteristic UV absorption, thus the double bonds present in the hydrocarbon are not conjugated. Its molecular refractivity (67.5) is in good agreement with that of a monocyclic sesquiterpene hydrocarbon (67.8) containing three double bonds. Catalytic hydrogenation confirmed the presence of three double bonds in isobisabolene.

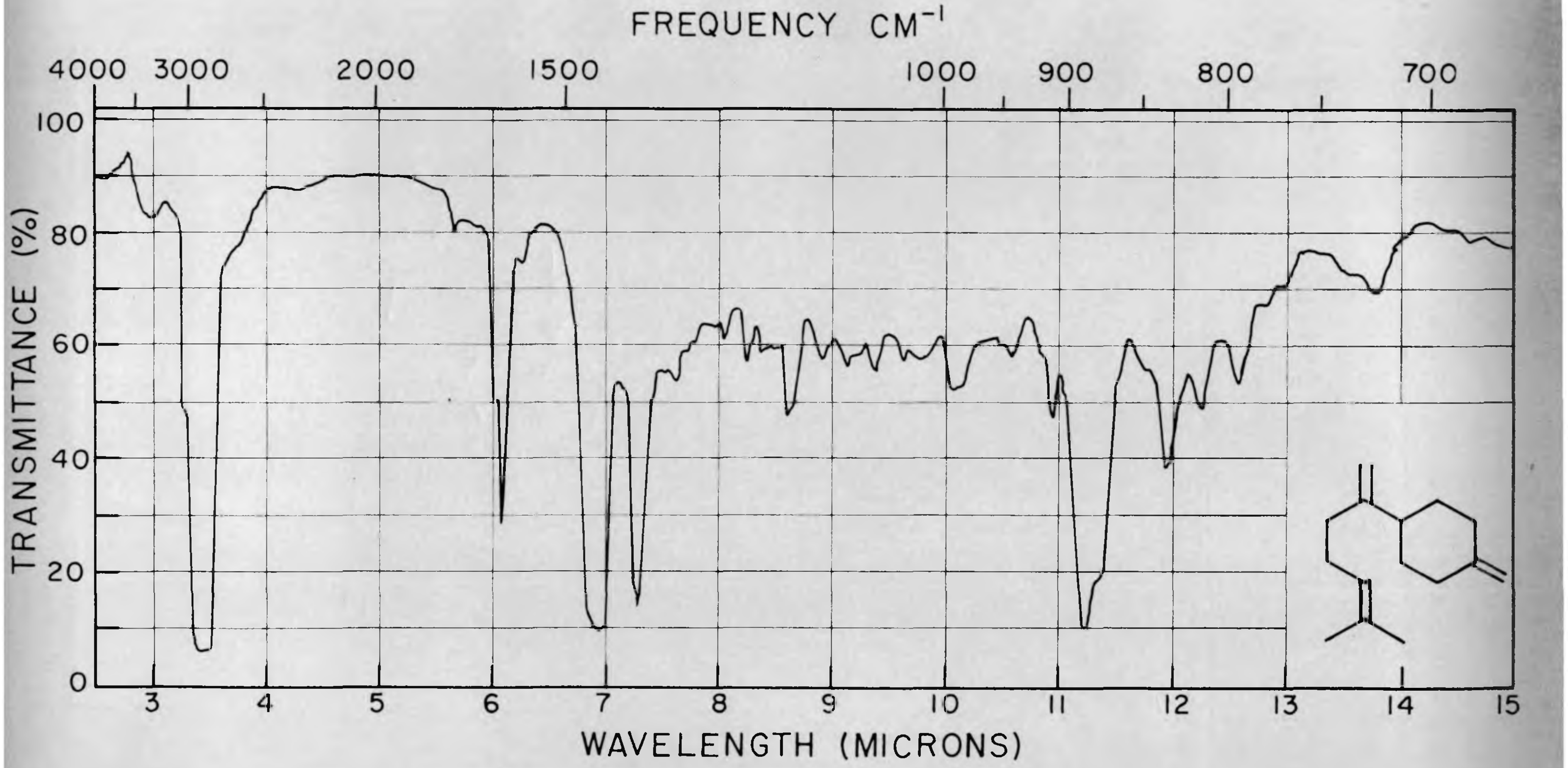
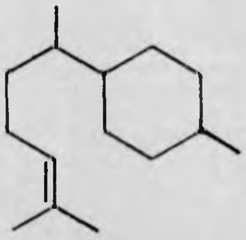


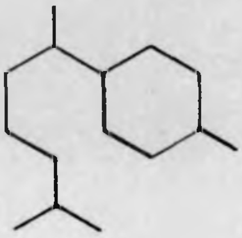
FIG. 2.1 IR SPECTRUM (LIQUID FILM, 0·05 mm) OF ISOBISABOLENE I

Selective hydrogenation of isobisabolene with palladised-charcoal in alcohol gives the tetrahydro derivative (20) of the molecular formula, $C_{15}H_{28}$. IR spectrum (Fig.2.2) of this product shows the presence of trisubstituted double bond (791, 813 and 825 cm^{-1}), absorptions due to methylenic double bonds being absent. Hence the hydrocarbon contains two methylenic double bonds and one trisubstituted double bond. This fact was further confirmed by ozonolysis of the hydrocarbon when it gave two moles of formaldehyde, the other volatile component of ozonolysis being acetone. The non-volatile product of ozonolysis had reducing properties (Fehling's solution) due to the presence of an aldehydic group, but failed to give iodoform test indicating the absence of a methyl ketonic group. The volatile product of ozonolysis of the tetrahydro derivative (20) of isobisabolene consisted only of acetone.



(20)

On complete hydrogenation with platinum oxide in acetic acid isobisabolene yielded a hexahydro product (21) of the molecular formula, $C_{15}H_{30}$ (IR spectrum Fig. 2.3).



(21)

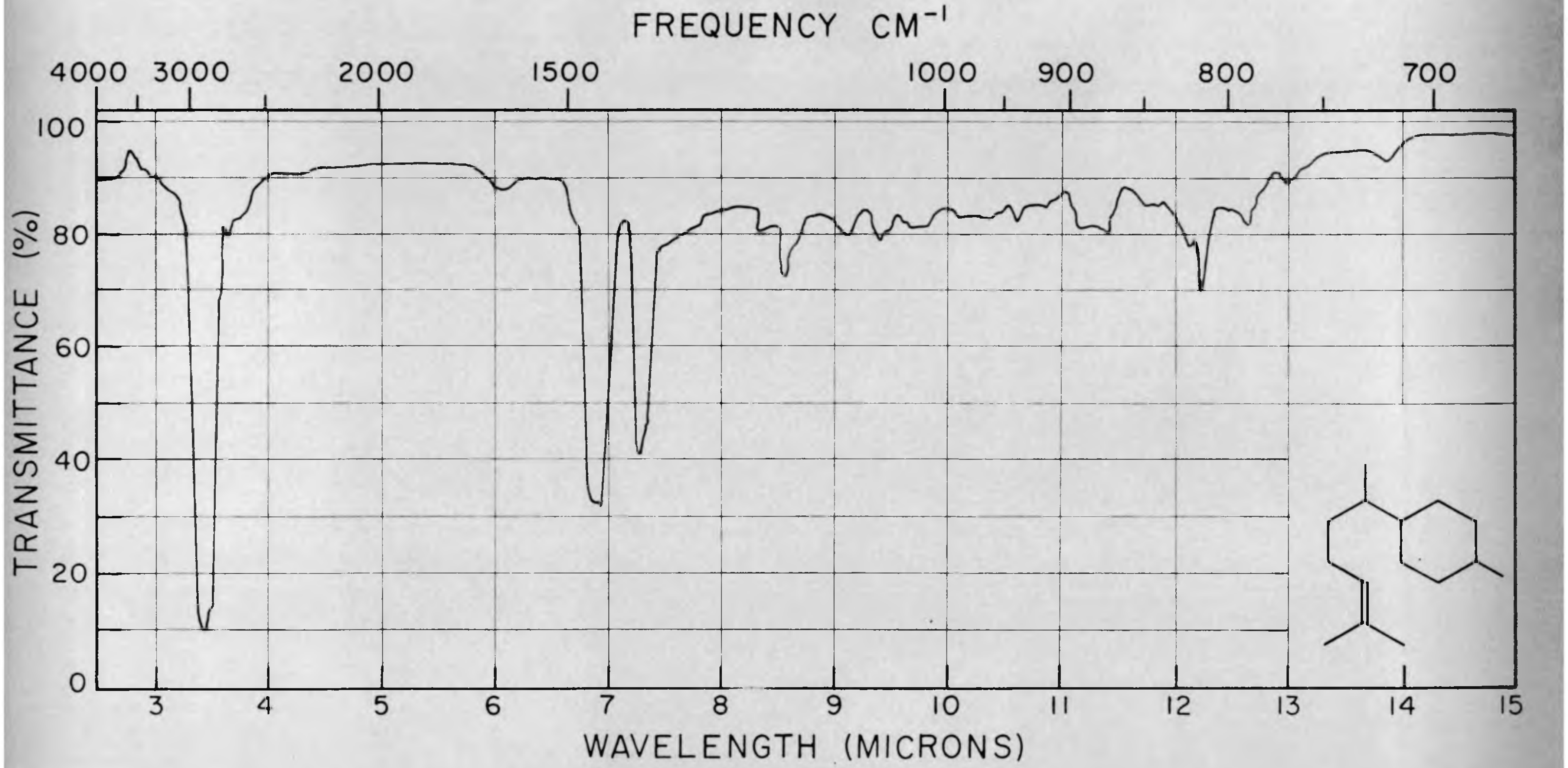


FIG. 2.2 IR SPECTRUM (LIQUID FILM) OF TETRAHYDROISOBISABOLENE 20

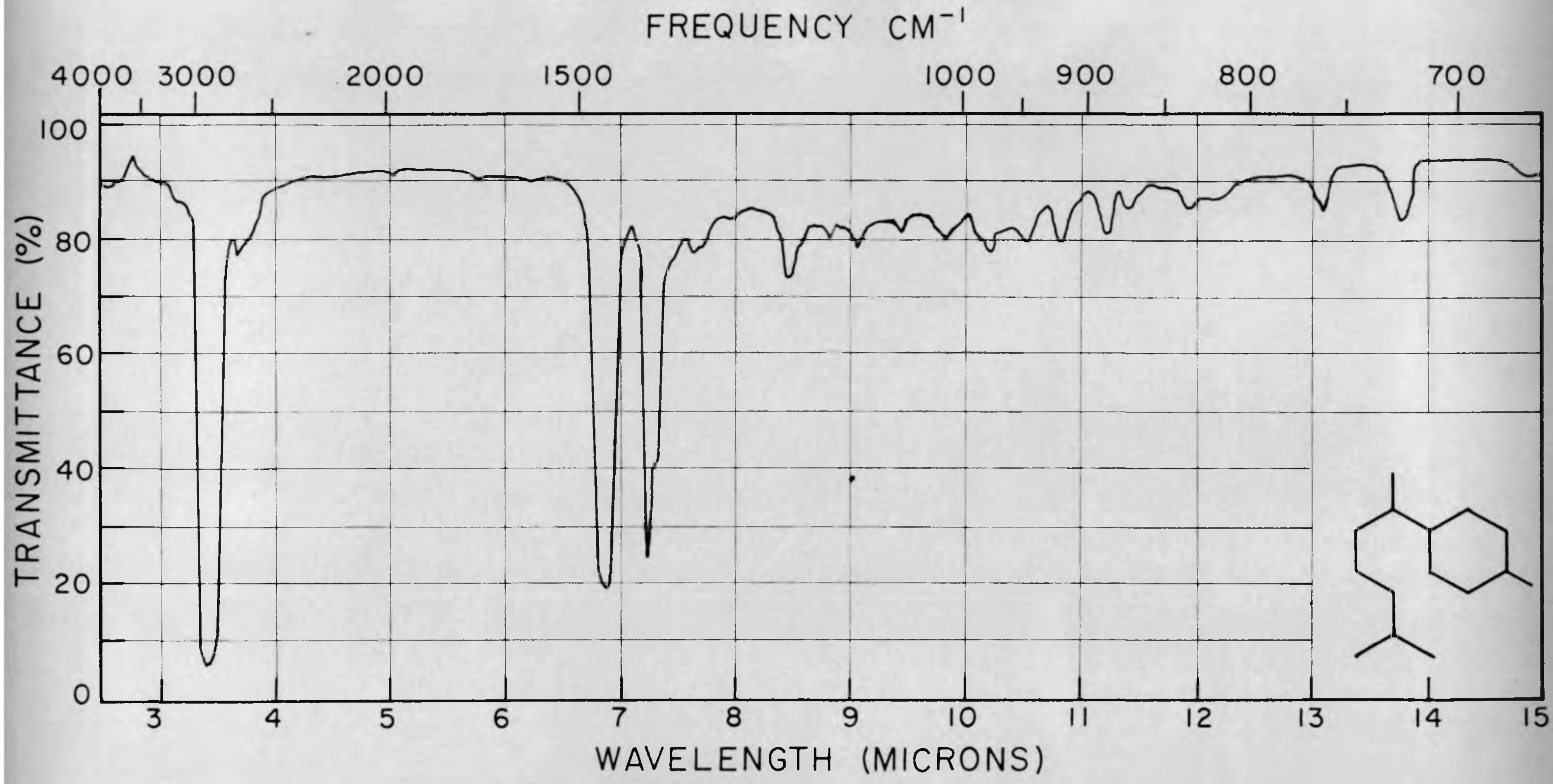
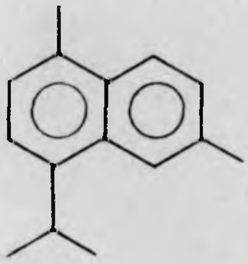


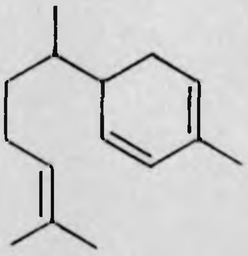
FIG. 2.3 IR SPECTRUM (LIQUID FILM) OF HEXAHYDROISOBISABOLENE 21

Nature of Carbon skeleton

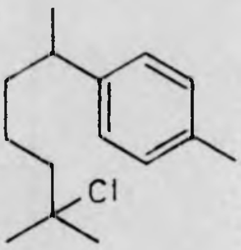
Isobisabolene on selenium dehydrogenation yielded cadalene (22) in a yield of 50%, together with a trace of unidentified azulene. Cadalene evidently was formed by migration of double bonds followed by ring closure during dehydrogenation. This is reminiscent of zingiberene[13] (5), α-curcumene monohydrochloride[14] (23) and γ-curcumene[4] (8). It however did not give any crystalline hydrochloride. The infrared spectra of its hexahydro derivative was compared[2] with that of the fully hydrogenated terpenic hydrocarbons and found to be identical with the IR spectrum (Fig. 2.4)



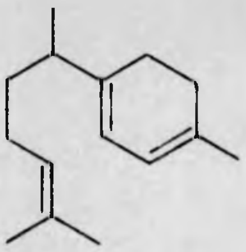
(22)



(5)



(23)



(8)

of bisabolane[15] (31) obtained by total reduction of ar-curcumene. These facts established structure (1) for isobisabolene.

Such a structure of isobisabolene is expected to make the compound optically inactive since there is a plane of symmetry in the molecule. As the compound in our hand (90% by VPC) was showing an optical rotation of -47°, evidently the laevo-rotation was due to the presence of small amount of a highly laevo-rotatory impurity. The compound was subjected to intensive chromatography through silicic acid impregnated with silver nitrate.[16] Eluting the column with pet. ether, a sample of isobisabolene was obtained in the tail fractions which showed low rotation of -4.1°. Further purification with a view to obtain a product with zero rotation was not possible. This sample was found to be sufficiently pure by VPC and TLC analysis. NMR spectrum of this sample of isobisabolene (Fig.2.5) further confirmed its structure. A singlet centred at 8.44 τ (6H) is due to the isopropylidene group and at 5.52 τ (4H) is due to the methylenic groups. The triplet centred at 4.3 τ has been assigned to the grouping $-CH_2-CH=C<$, the further fine structure of the triplet is probably due to the coupling with the adjacent methyl groups.

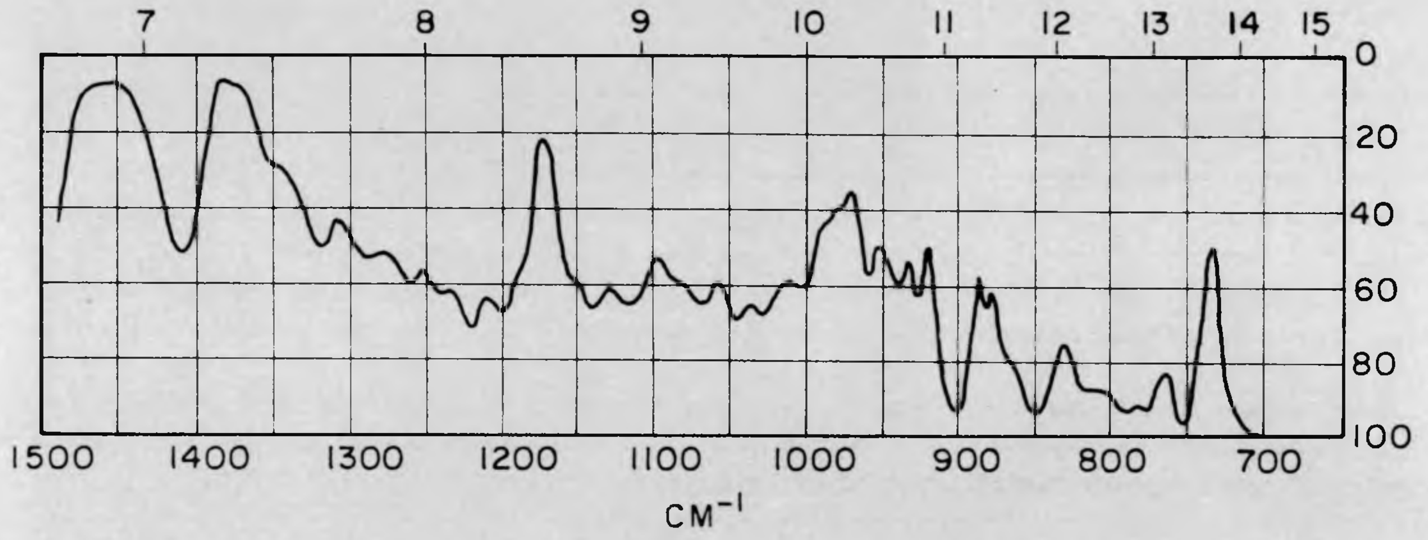


FIG. 2·4 I R SPECTRUM OF BISABOLANE 21 PREPARED FROM ar - CURCUMENE

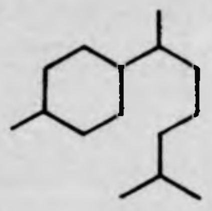
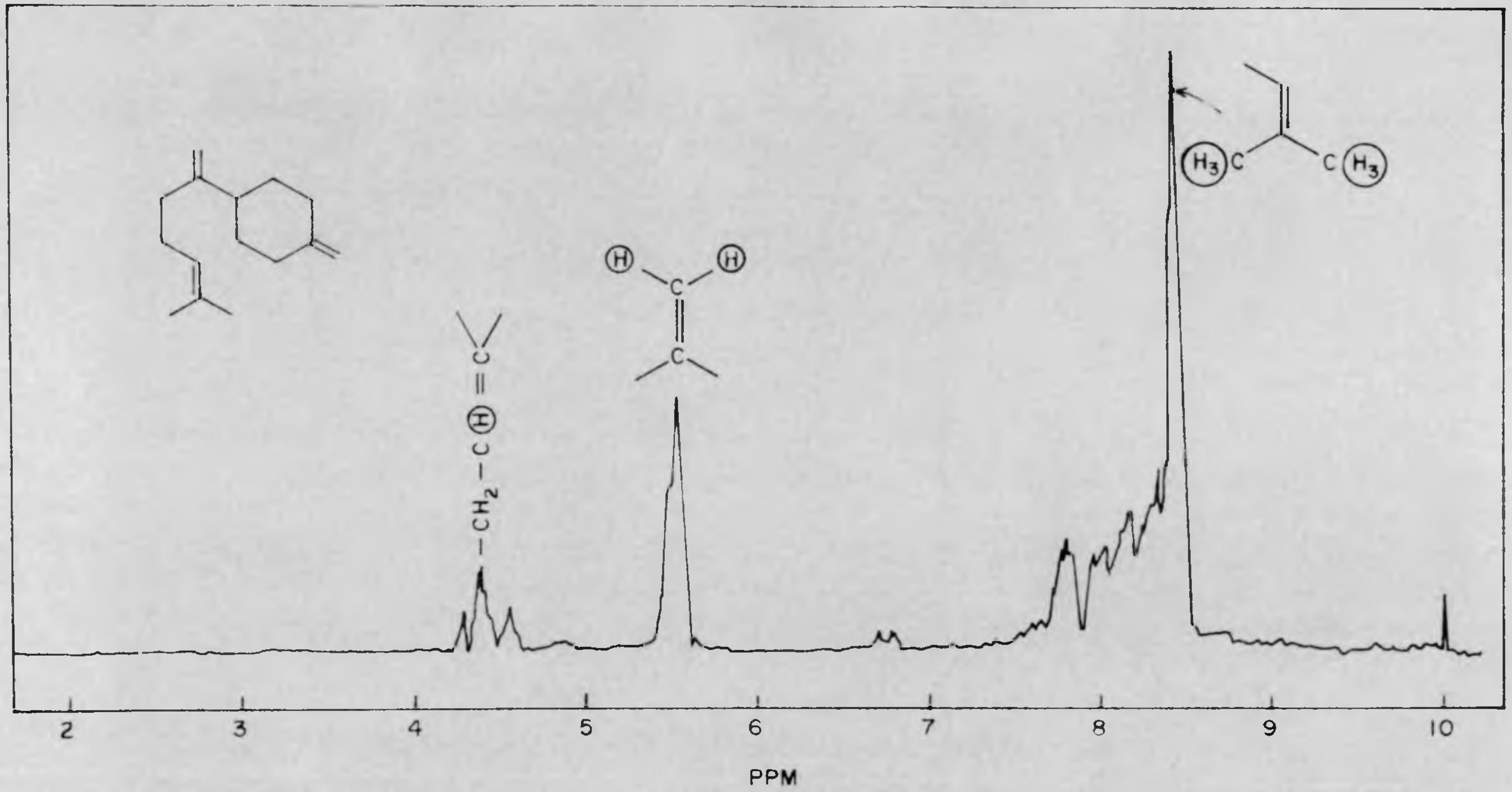


FIG.2·5



NMR SPECTRUM OF ISOBISABOLENE 1

EXPERIMENTAL

Isobisabolene had b.p. 99-102°/8 mm., n_D^{26} 1.4966; d_4^{26} 0.8859; $(\alpha)_D^{26}$ - 47° (c, 4.6) (Found: C, 88.33; H,12.09. $C_{15}H_{24}$ requires: C, 88.16; H, 11.84%). VPC shows 90% purity. IR spectrum in liquid cell 0.05 mm (Fig.2.1) bands at: 1640, 892, 791, 813 and 833 cm^{-1}.

Tetrahydroisobisabolene (20)

Isobisabolene (0.125 g) in alcohol (40 ml) was hydrogenated using 5% palladium-charcoal (0.05 g) as catalyst. The hydrogenation became extremely slow after the absorption of 28.5 ml hydrogen (temp. 22°, press 716 mm), which corresponded to 1.81 moles hydrogen. The hydrogenation was stopped at this stage (2 hr). The catalyst was filtered off and the alcohol removed under suction. The residue was chromatographed over neutral alumina (grade I, 10 g), eluting with pet.ether (40-60°). The first fraction(25 ml) gave tetrahydro-iso-bisabolene (0.06 g) which showed the following properties: b.p.118°(bath)/8 mm., $(\alpha)_D^{26}$ + 28.8° (c, 4.05), n_D^{26} 1.4780. (Found: C, 86.7; H, 13.39. $C_{15}H_{28}$ requires: C, 86.46; H, 13.54%). IR spectrum (Fig.2.2) bands at 825, 813 and 791 cm-1.

Hexahydroisobisabolene (bisabolane) (21)

A solution of isobisabolene (0.032 g) in acetic acid (20 ml) was hydrogenated in the presence of platinum oxide (0.01 g) catalyst. The hydrogenation was complete after the absorption of 12 ml hydrogen (temp. 21.5°, press. 713 mm) corresponding to 2.97 moles hydrogen. The product was isolated in the usual manner and distilled to give hexahydro-isobisabolene, b.p. 90° (bath)/0.3 mm. $(\alpha)_D^{26}$+2.9° (c, 5.2), n_D^{26} 1.4573 (Found: C, 86.3; H, 14.58. $C_{15}H_{30}$ requires: C, 85.71; H, 14.28%). IR spectrum (Fig. 2.3) in liquid cell 0.025 mm. Bands at: 724, 764, 833, 870, 885, 917, 943, 970, 1020, 1052, 1100, 1124, 1176, 1250 and 1299 cm-1.

Bisabolane obtained by the total reduction of ar-curcumene,[15] IR spectrum (Fig.2.4) in liquid cell 0.15 mm. cell at: 725, 763, 828, 875, 895, 917, 933, 947, 970, 1017, 1057, 1085, 1125, 1176, 1208, 1258 and 1308 cm-1.

Ozonolysis of Isobisabolene

Isobisabolene (0.68 g) was dissolved in chloroform (80 ml), cooled to 0° and a stream of ozonised oxygen (0.3 g ozone per hr) was passed until ozonisation was complete. The ozonised solution was steam distilled. The distillate was treated with dimedone solution and the chloroform was removed by distillation. The formaldimedone, m.p. 188-190° which separated weighed (0.7858 g), 0.84 moles. After one crystallisation the sample of formaldimedone melted alone or on admixture with an authentic sample at 190-191° under identical conditions camphene (0.2915 g) yielded formaldimedone (0.26 g) corresponding to 0.41 moles. The other volatile component was identified as acetone (iodoform test).

Selenium dehydrogenation of isobisabolene

Isobisabolene (0.3 g) was mixed with selenium (1 g) and heated in nitrogen atmosphere at 290° for 24 hr. The reaction product was dissolved in pet.ether and filtered. Traces of azulene were removed by usual treatment with phosphoric acid. Non-azulenic product (cadalene content-50% on the basis of UV spectrum) was chromatographed over alumina (grade I). The product thus obtained was characterised as cadalene through the picrate, m.p. and mixed m.p. with an authentic sample 115°, and TNB complex, m.p. and mixed m.p. with an authentic sample 112-113°.

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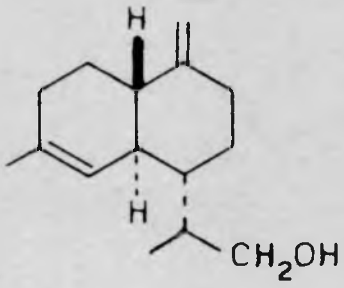
CHAPTER III

STRUCTURE AND ABSOLUTE CONFIGURATION OF KHUSOL THE FIRST CADALENIC PRIMARY SESQUITERPENE ALCOHOL

SUMMARY

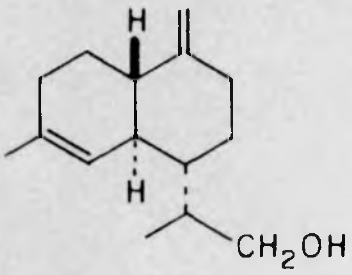
From the alcoholic fraction of the Indian vetiver oil, khusol, a crystalline cadalenic primary sesquiterpene alcohol, $C_{15}H_{24}O$, has been isolated. On the basis of chemical studies and physical measurements, it has been assigned the structure and absolute configuration[1] represented by (1). It belongs to the unusual antipodal group of cadinenes, such as γ_1-cadinene,[2] γ_2-cadinene[3] and the crystalline secondary alcohol khusinol.[4]



(1)

In this part of the thesis, the results of a systematic reinvestigation[1] of the structure of khusol (2) (isolation vide Chapter I, p. 16) are represented together with its stereochemical studies, which establish its absolute configuration as shown by (1).

Zutshi and Sadgopal in 1956, isolated from vetiver oil a crystalline alcohol[5] having the molecular formula, $C_{15}H_{24}O$, m.p. 101-102°. In another communication in the same year Bhattacharyya et al.[6] suggested a tentative structure (3) to it and named it khusol after the common name (khus) of vetiver oil in India. The structure (3) was assigned at that time chiefly on the basis of preliminary colour tests and the oxidation of khusol to a somewhat impure aldehyde khusal (4)



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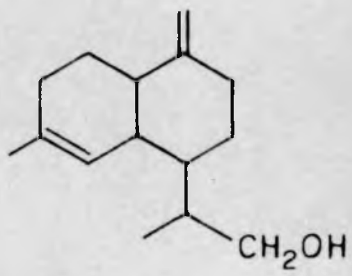

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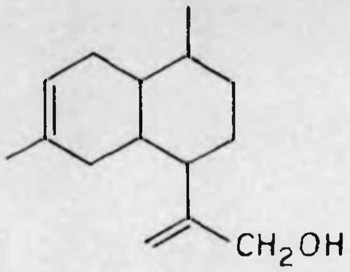

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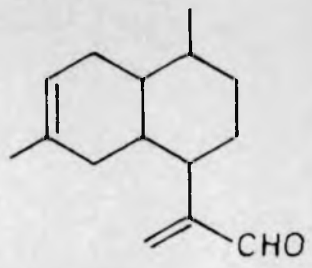


(4)

(semicarbazone, m.p. 178-179°, UV spectrum: $\lambda_{max.}$ 228 mμ, log ϵ 3.90). The NMR spectrum of khusol (Fig. 3.1) was subsequently examined in this Laboratory. It showed a very well formed doublet at 268 and 273.8 cps due to the presence of a $-CH-CH_2OH$ group. Consequently a systematic reinvestigation of its structure was undertaken.

Khusol was obtained in a yield of about 3% by chromatography of vetiver oil. It analysed correctly for the molecular formulae $C_{15}H_{24}O$, m.p.101-102° $(\alpha)_D^{25}$ - 137°.

Nature of Unsaturation

The IR spectrum of khusol (Fig.3.2) shows absorption bands due to an end methylenic group $>C{=}CH_2$ (1942, 892 cm-1) and a trisubstituted double bond $-CH{=}CR_1R_2$ (798, 840 cm-1). The NMR spectrum of khusol (Fig.3.1) further confirmed the presence of both types of double bonds. A signal at 99.4 cps indicated the presence of a methyl group on a double bond, $(-C{=}\overset{CH_3}{\overset{|}{C}}<)$ and a doublet at 41.9 and 49.05 cps showed the presence of $(>\overset{CH_3}{\overset{|}{C}}H)$ grouping in khusol. Catalytic hydrogenation of khusol confirmed the presence of two double bonds. On partial hydrogenation in presence of palladium-charcoal in ethanol, khusol absorbs only one mole of hydrogen and furnishes a liquid dihydro-khusol, $C_{15}H_{26}O$ (5) having IR bands only due to a trisubstituted double bond (793 and 831 cm-1). On catalytic hydrogenation in glacial acetic acid in the presence of Adams catalyst khusol furnished a

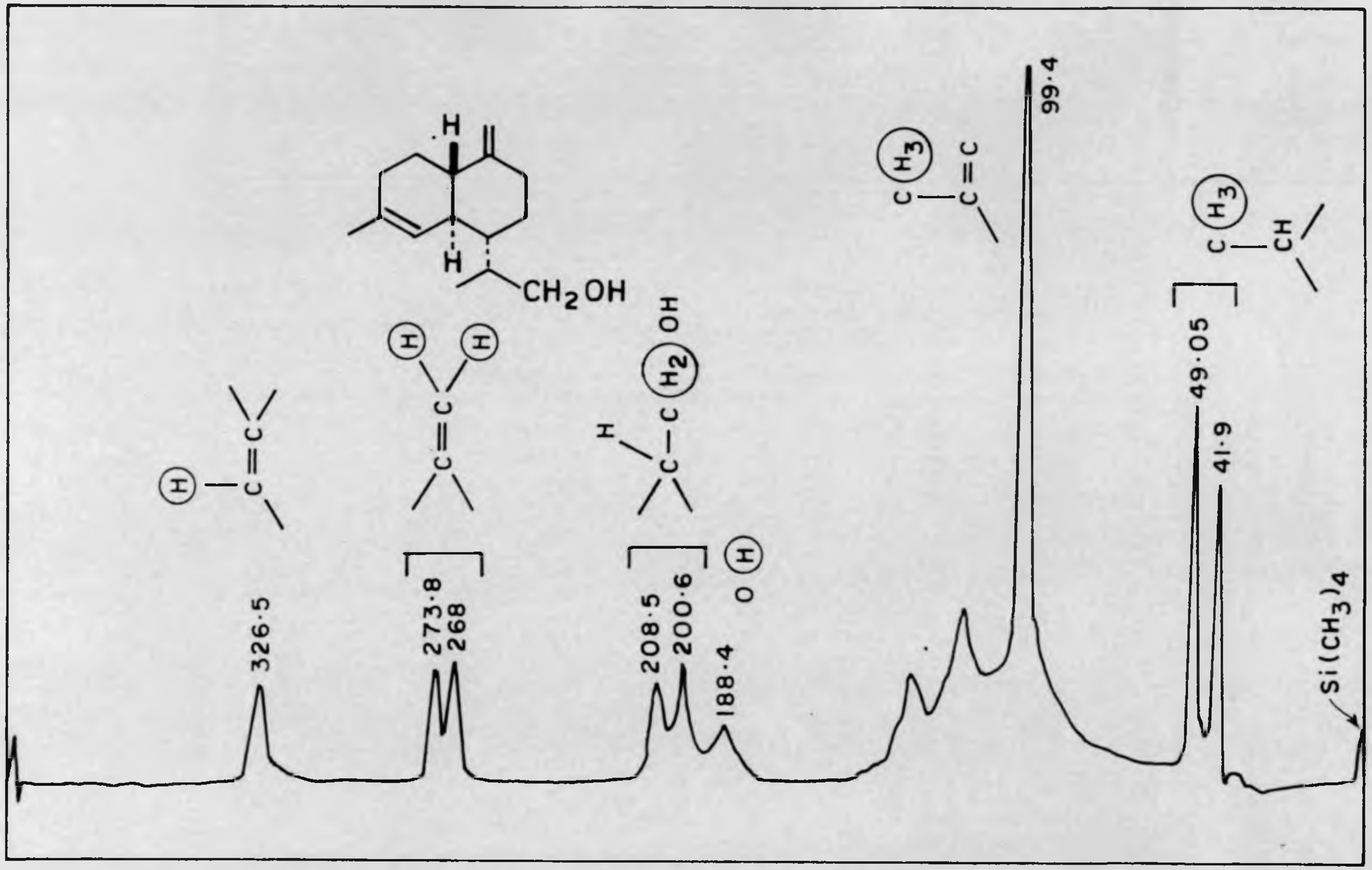


FIG. 3·1 NMR SPECTRUM OF KHUSOL 1.

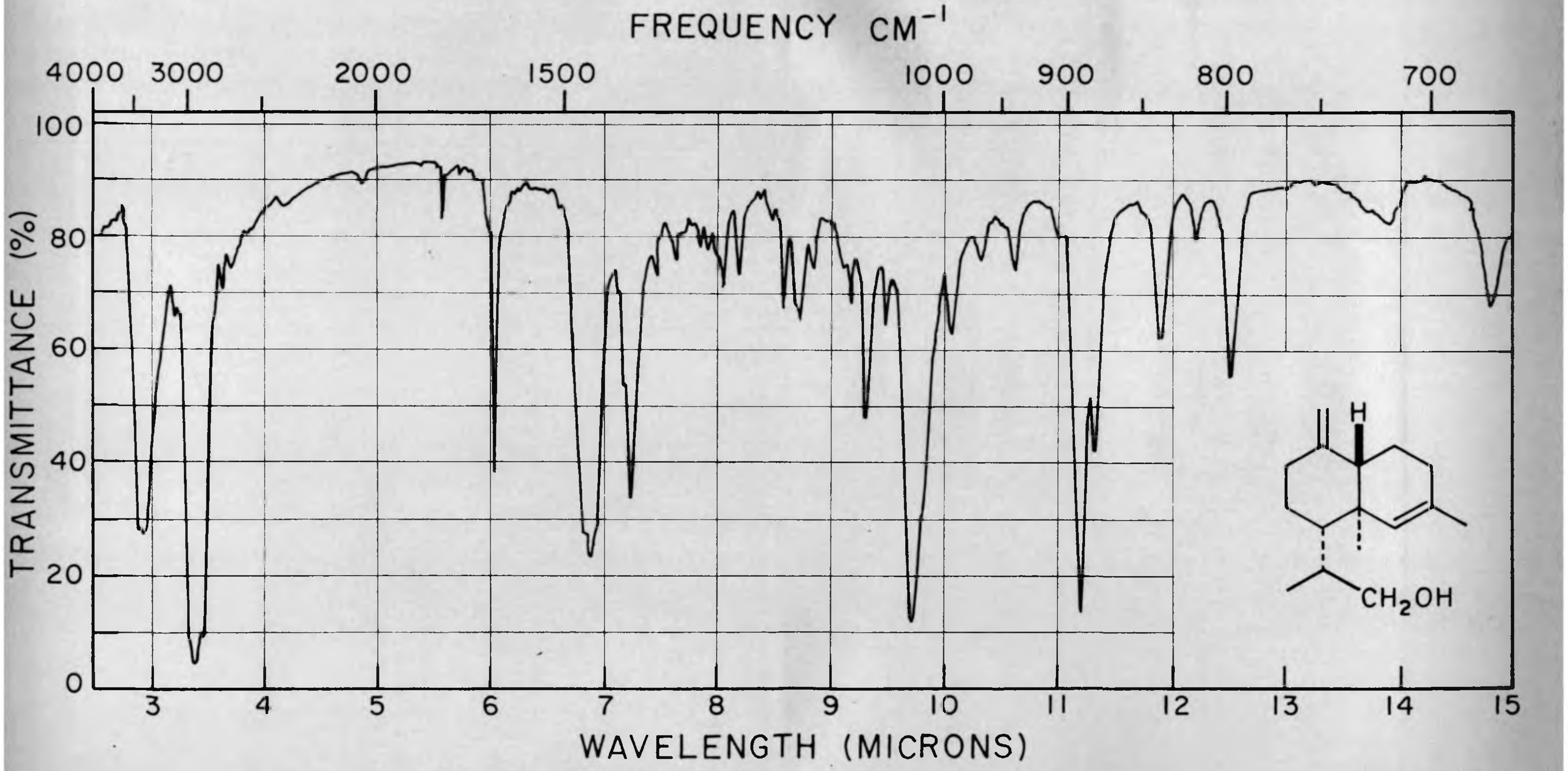
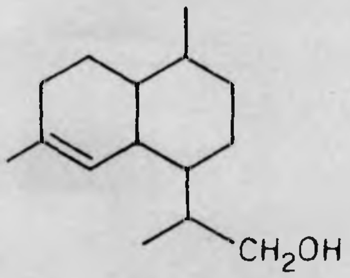
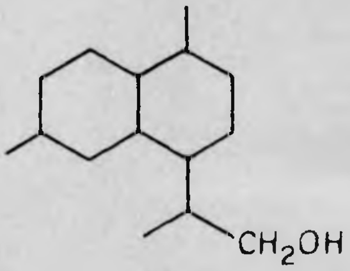


FIG. 3.2 IR SPECTRUM (IN NUJOL) OF KHUSOL I

liquid tetrahydrokhusol, $C_{15}H_{28}O$ (6), along with a small amount of its acetate. Inspite of repeated column chromatography over alumina neither dihydro nor tetrahydrokhusol cauld be obtained in a crystalline form.



(5)



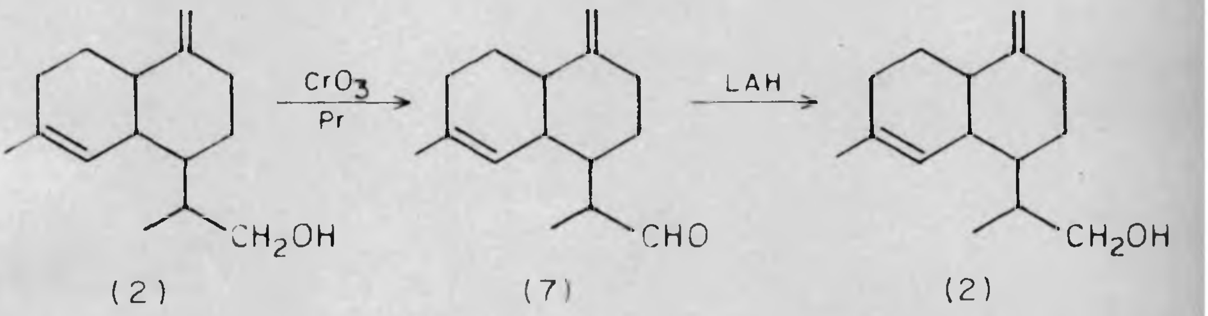
(6)

On ozonolysis in a dry stream of ozonized oxygen khusol yields formaldehyde as the only volatile product, confirming the presence of an exocyclic methylenic double bond. The non-volatile portion gave positive tests for methyl ketone and an aldehyde function. Khusol did not show any UV absorption maximum indicating absence of conjugation.

Nature of Oxygen function

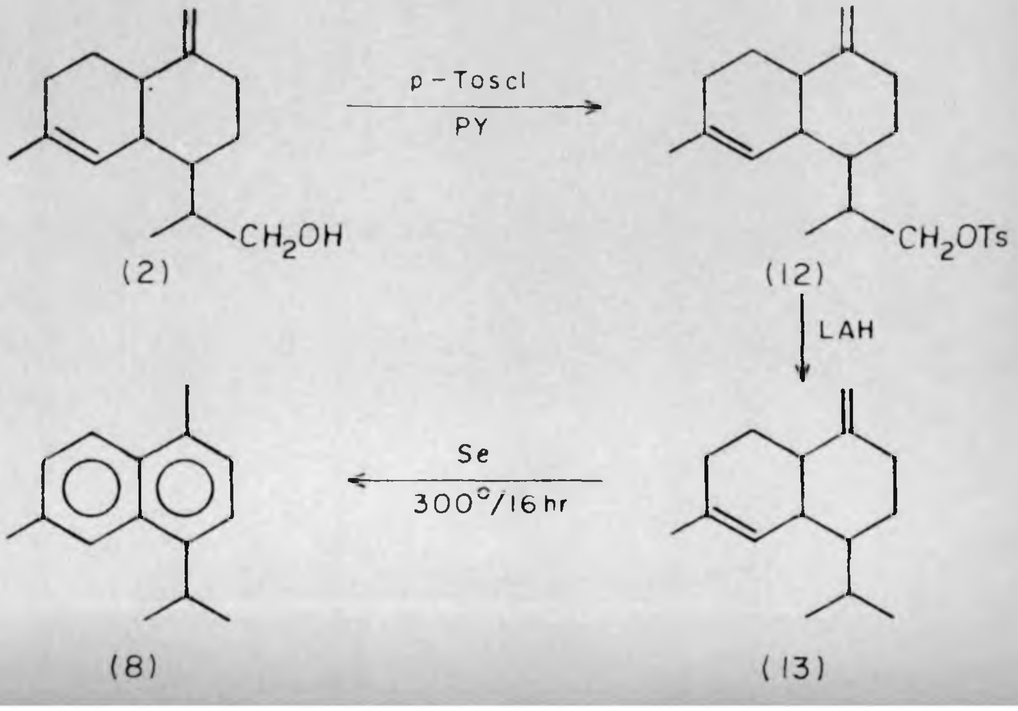
As shown by molecular formula, $C_{15}H_{24}O$, khusol contains one oxygen function. Its IR spectrum (Fig. 3.2) shows characteristic bands for a primary hydroxyl group (3340 and 1028 cm^{-1}). It easily forms a liquid acetate. The primary nature of the hydroxyl group in khusol was further proved by its oxidation with pyridine-chromic acid complex,[7] to a liquid aldehyde, $C_{15}H_{22}O$ (7, semicarbazone, $C_{16}H_{25}ON_3$, m.p. 165°). The IR spectrum of this aldehyde

(Fig.3.3) showed bands at: 2710 and 1724 cm-^{1} typical of a saturated aldehyde function. It readily reduced Fehling's solution and ammonical silver nitrate. The UV absorption spectra of the aldehyde or its semicarbazone did not show any characteristic absorption due to α,β-unsaturated aldehyde function. Khusol could be regenerated on reduction of the aldehyde with lithium aluminium hydride.



Nature of Carbon skeleton

The gross structural feature of khusol was determined by the dehydrogenation of its parent hydrocarbon (13). The tosyl derivative of khusol (12) (m.p. 114-115^{o}; IR spectrum in nujol, Fig.3.4) on reduction



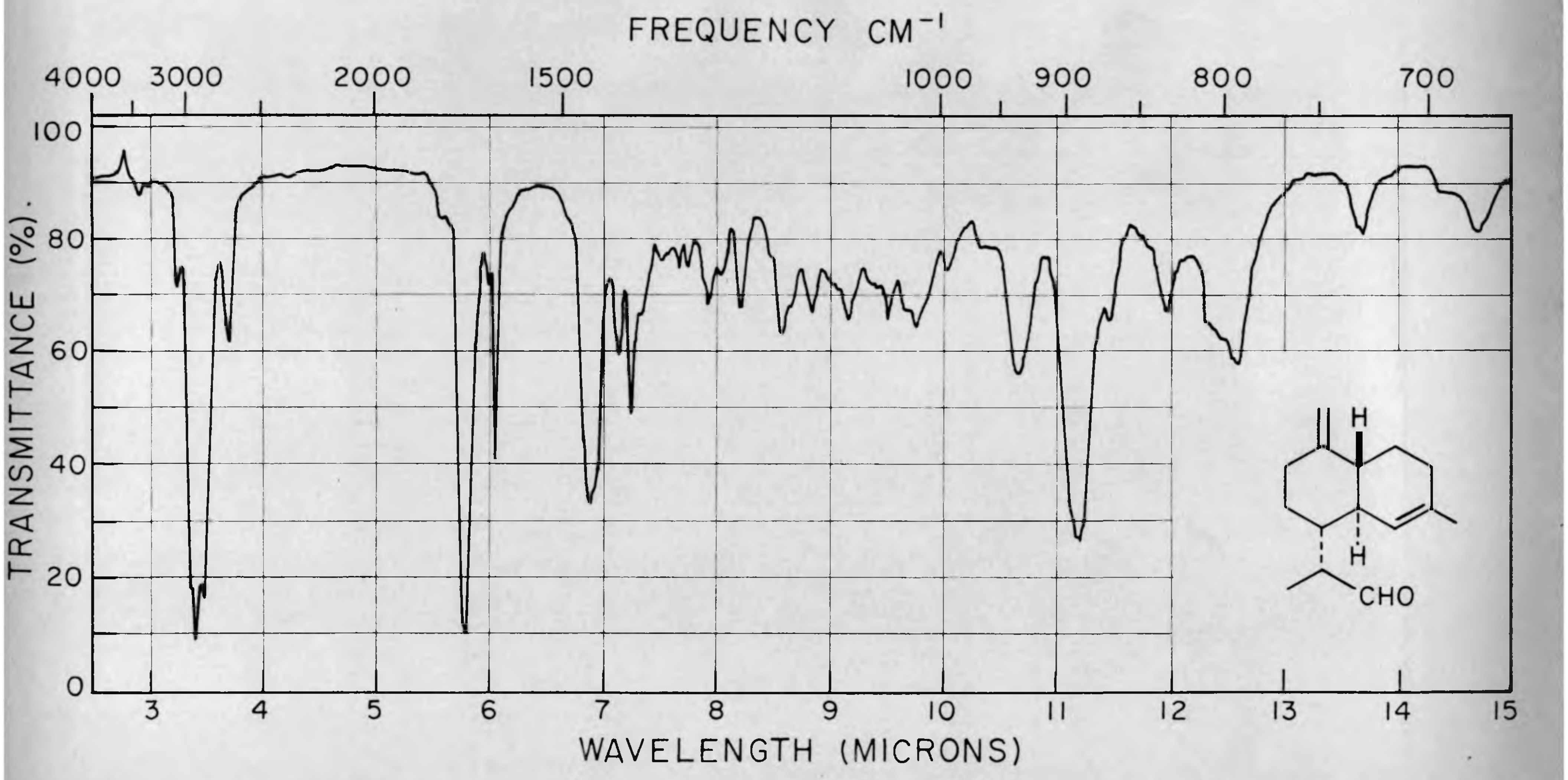


FIG. 3·3 IR SPECTRUM (LIQUID FILM) OF ALDEHYDE 7

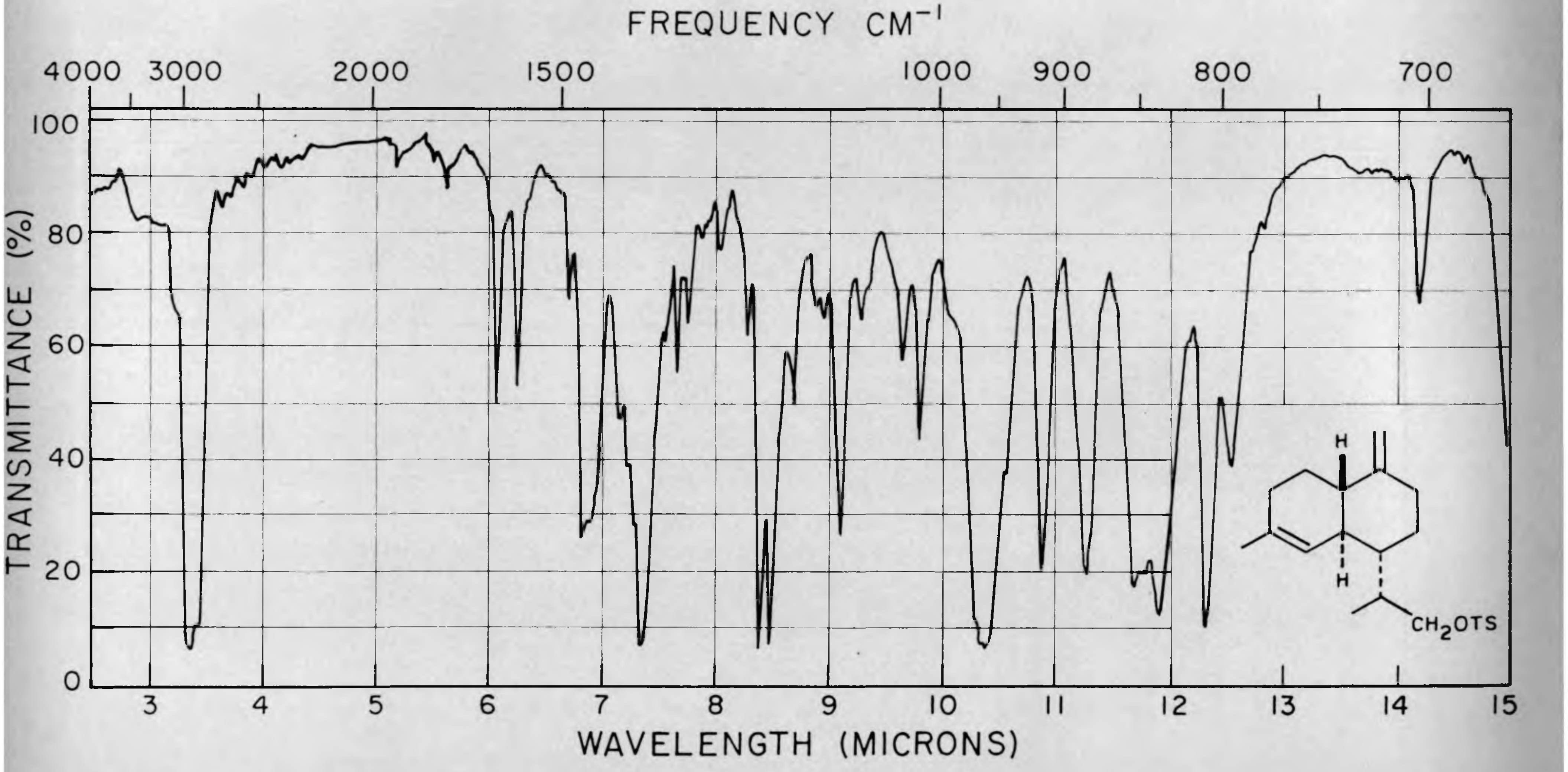
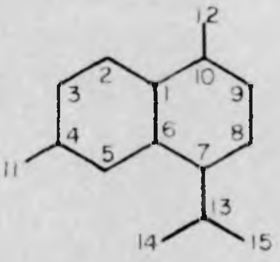


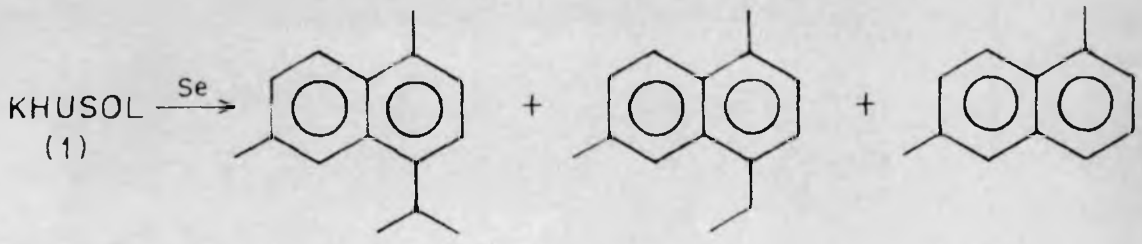
FIG. 3.4 IR SPECTRUM (IN NUJOL) OF TOSYLATE 12.

with lithium aluminium hydride gave the parent hydrocarbon (13). This afforded cadalene (8) in very good yield on dehydrogenation with selenium in an atmosphere of nitrogen. Cadalene was characterised as its picrate and TNB derivatives. Formation of cadalene accounts for all the fifteen carbon atoms of khusol and consequently its basic skeleton can be represented by (9). The numbering of the carbon skeleton is in accordance with the principle formulated by Barton et al.[8]



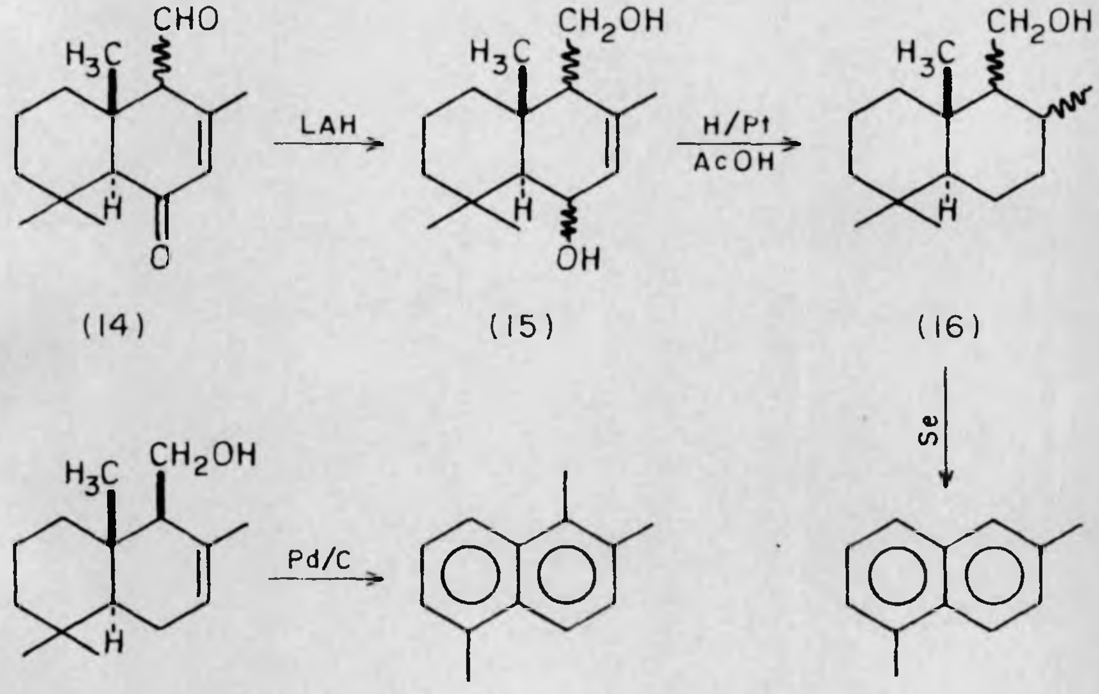
(9)

Product of direct selenium dehydrogenation of khusol itself was difficult to characterise through the usual derivatives, as has been already reported by earlier authors.[6] This has now been proved to be due to the non-homogeneous nature of the dehydrogenation product. It has now been possible to identify 1,6-dimethyl naphthalene (11), 1,6-dimethyl-4-ethylnaphthalene (10) and cadalene (8) from the dehydrogenation product of khusol on the basis of VPC analysis with authentic samples.



(8) (10) (11)

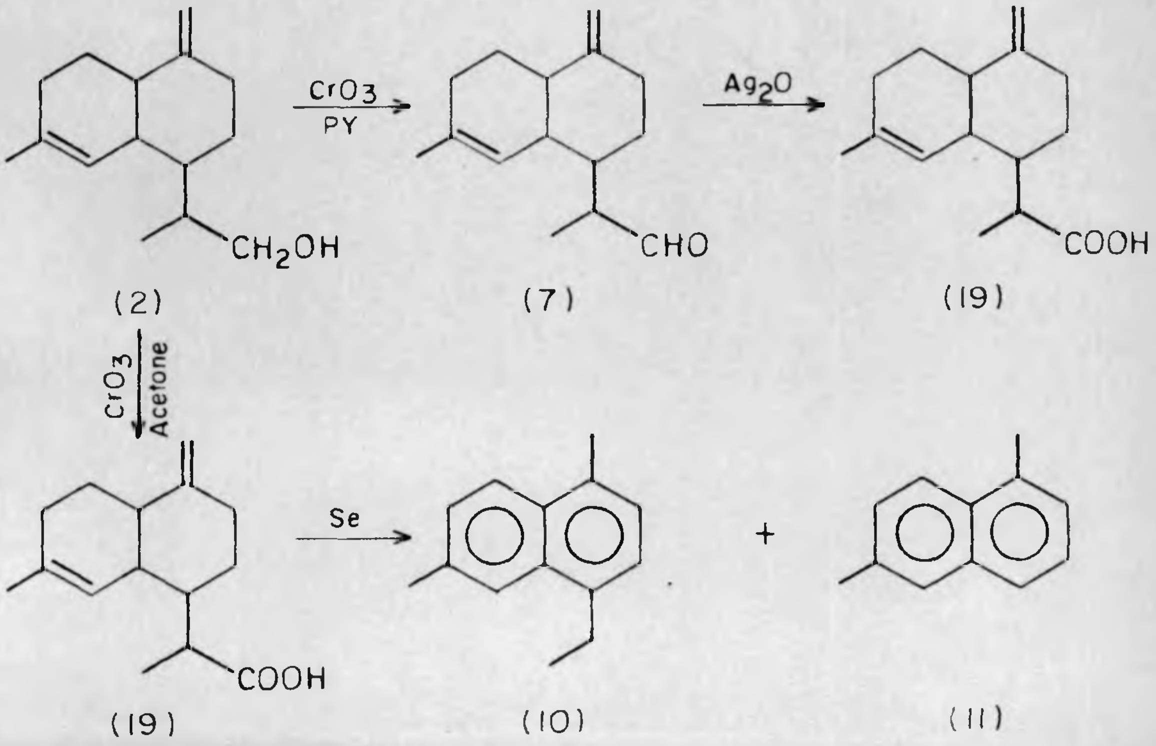
A similar unusual elimination of (-CH_2OH) group during the selenium dehydrogenation of the alcohol (15) prepared from tadeonal (14) has also been recorded recently[9a] to afford 1,6-dimethylnaphthalene (11). Dehydrogenation of drimenol,[9b] (17) with palladised charcoal at 350° however affords the expected 1,2,5-trimethyl naphthalene (18).



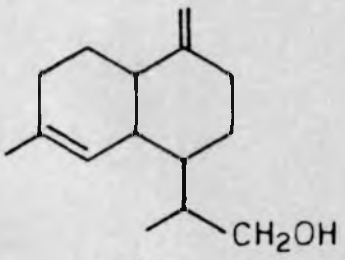
Position of the Primary hydroxyl group

As already mentioned khusol on oxidation with pyridine-chromic acid complex gives an unconjugated aldehyde (7). This coupled with the NMR data establishes the position of the primary hydroxyl group as -CH(CH_2OH)CH_3 moiety as shown in (1). This fact was further confirmed by the dehydrogenation of the acid, $C_{15}H_{22}O_2$ (19), m.p.118-19°, prepared by the silver oxide oxidation of the aldehyde (7).

The acid (19) could, however, be prepared[10] in almost quantitative yields by the oxidation of khusol during a period of 15 min. with chromic acid in acetone.[11] (ca. 8 N). As reported in the literature[12] no attack on the double bonds was observed. The acid thus prepared was identical in all respects with the one prepared by the silver oxide oxidation of the aldehyde (7). The acid (19) on dehydrogenation with selenium gave 1,6-dimethyl-4-ethylnaphthalene (10) together with equal amounts of 1,6-dimethyl naphthalene (11). 1,6-Dimethyl naphthalene in the dehydrogenation product was detected by means of VPC analysis with an authentic specimen. 1,6-Dimethyl-4-ethyl naphthalene was isolated from the mixture via its TNB derivative, m.p.134°, purified through repeated crystallisations.



On the basis of this data, khusol can be represented by one of the three possible structures (2, 20, 21).



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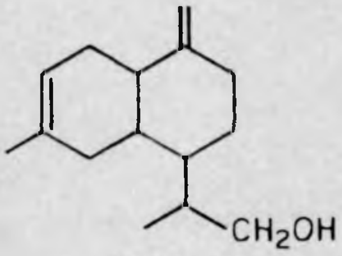
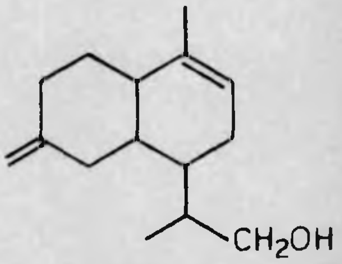


(20)



(21)

Position of Unsaturation

In order to determine the position of the trisubstituted double bond in khusol, it was subjected to the labelling procedure of Campbell and Soffer.[13] Khusol on treatment with p-toluene sulphonyl chloride in pyridine gives the crystalline tosyl derivative, $C_{22}H_{30}O_3S$ (12, m.p.114-115°, IR spectrum in nujol Fig.3.4). This on reduction with lithium aluminium hydride gives the hydrocarbon (13, IR spectrum Fig. 3.5). The dihydro derivative (22) obtained by the hydrogenation of the hydrocarbon (13) with palladium charcoal in ethanol on treatment with perbenzoic acid furnished an epoxy compound (23). The epoxy compound on prolonged treatment with methyl magnesium iodide yielded an alcohol which on dehydrogenation with selenium afforded 1,2,5-trimethyl naphthalene (18). Introduction of a methyl group at C_5 position eliminated[14]

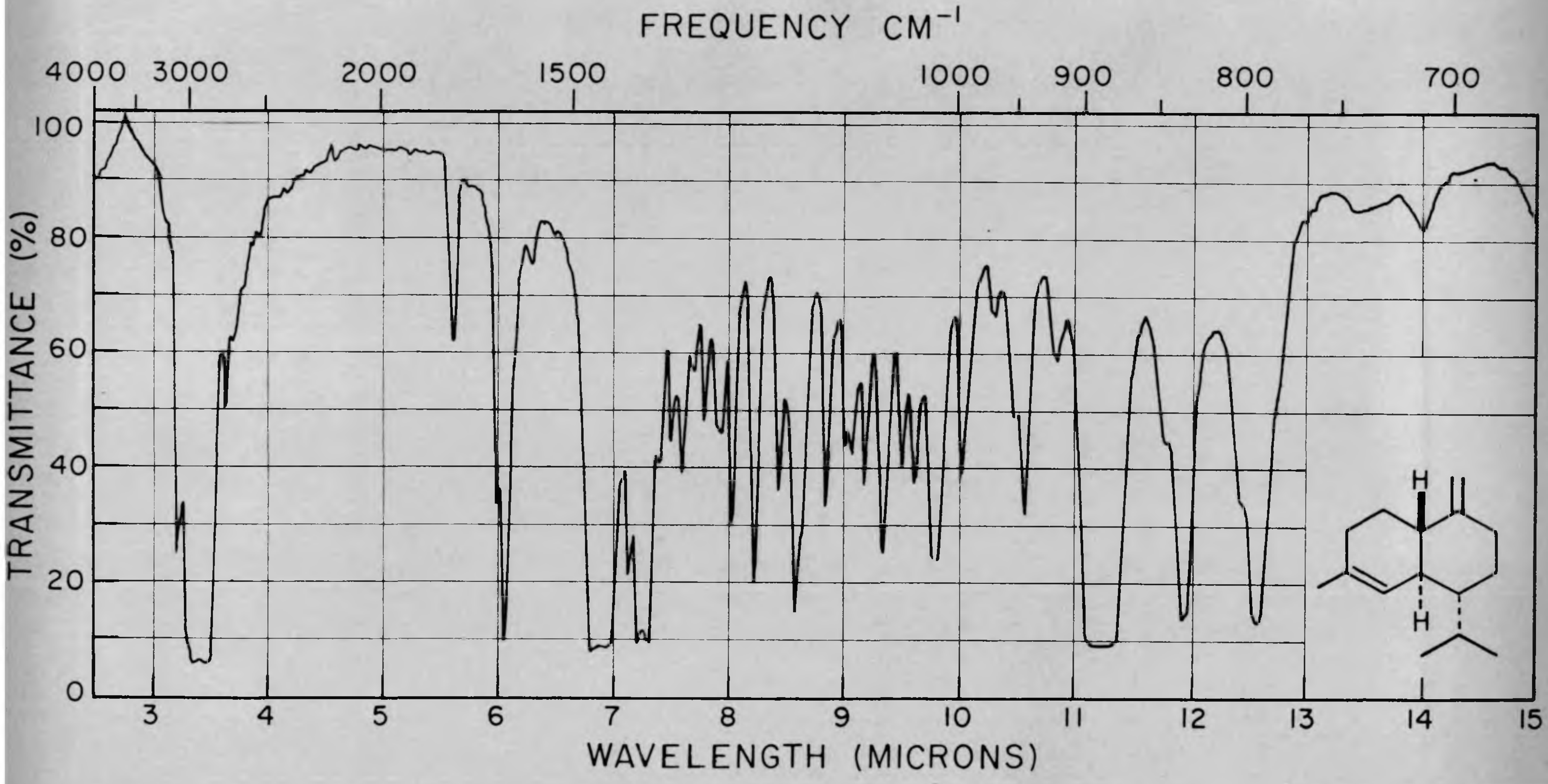
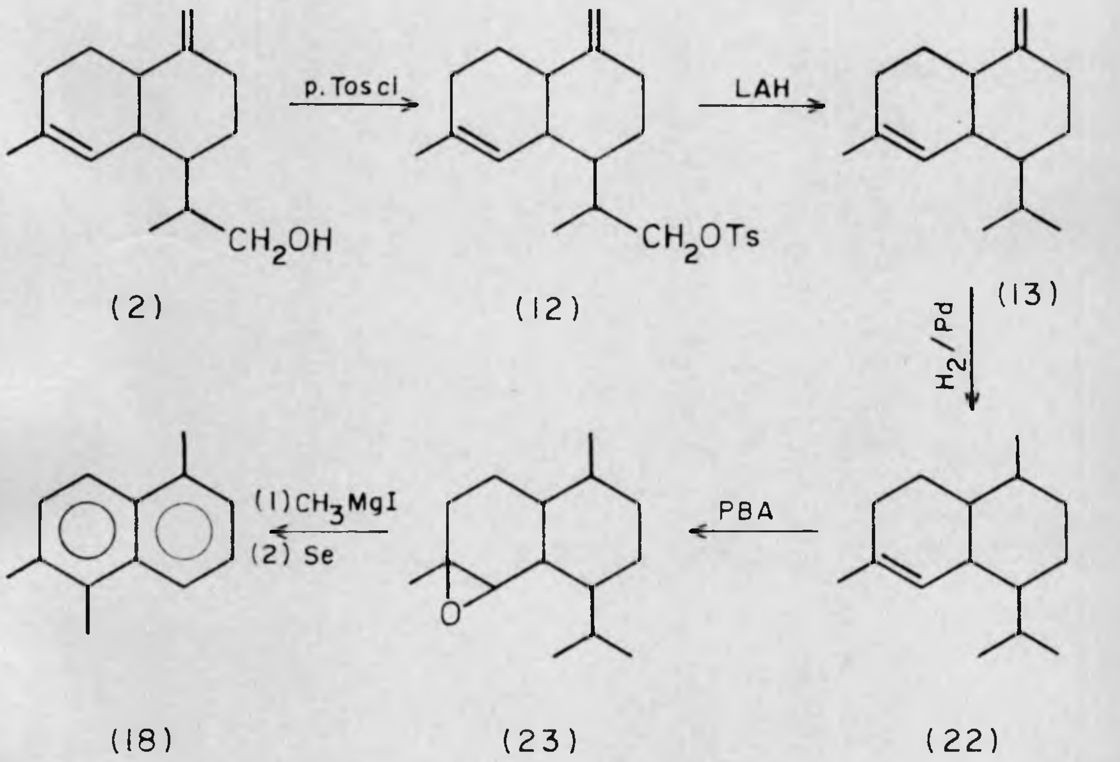


FIG. 3.5 IR SPECTRUM (LIQUID FILM, 0·1 mm) OF (–)–γ–CADINENE 13

the bulky isopropyl group at C_7 during dehydrogenation. A number of instances are mentioned in the literature where non-angular alkyl groups get eliminated during



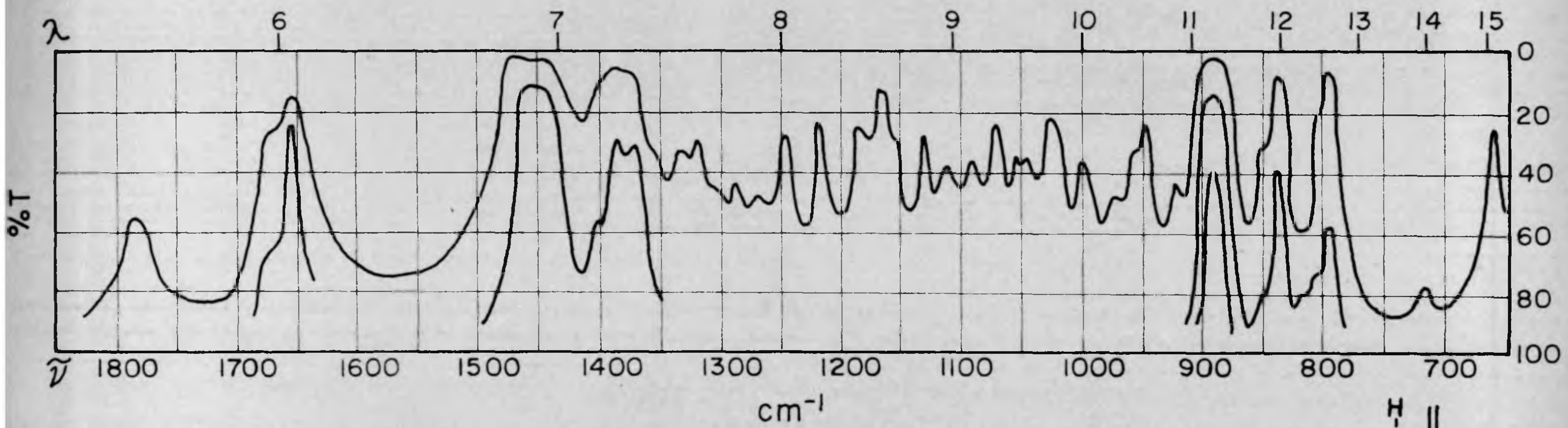
dehydrogenation reactions[15] (Ref. Chapter IV, p.91). The isolation of 1,2,5-trimethyl-naphthalene (18) fixed the position of the trisubstituted double bond and hence of the exocyclic methylene as shown in structure (2). The properties of the laevorotatory hydrocarbon (13) and its IR spectrum were identical with that of the already known dextrorotatory γ-cadinene[16] (24, IR spectrum Fig. 3.6), except that their rotations were identical but opposite.

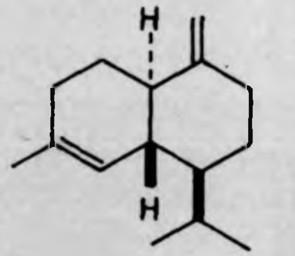
(+)-γ-Cadinene natural(24) NORMAL	(-)-γ-Cadinene from Khusol(13) ANTIPODAL
d_4^{20} 0.9239	d_4^{24} 0.9182
n_D^{20} 1.5075	n_D^{31} 1.5060
$(\alpha)_D$ + 148°	$(\alpha)_D^{26}$ - 145°
(-)-Cadinene dihydrochloride	(+)-Cadinene dihydrochloride
m.p. 118°, $(\alpha)_D$ - 36°	m.p. 117°, $(\alpha)_D$ + 38°

This further confirmed the position of double bonds in khusol as shown in (2).

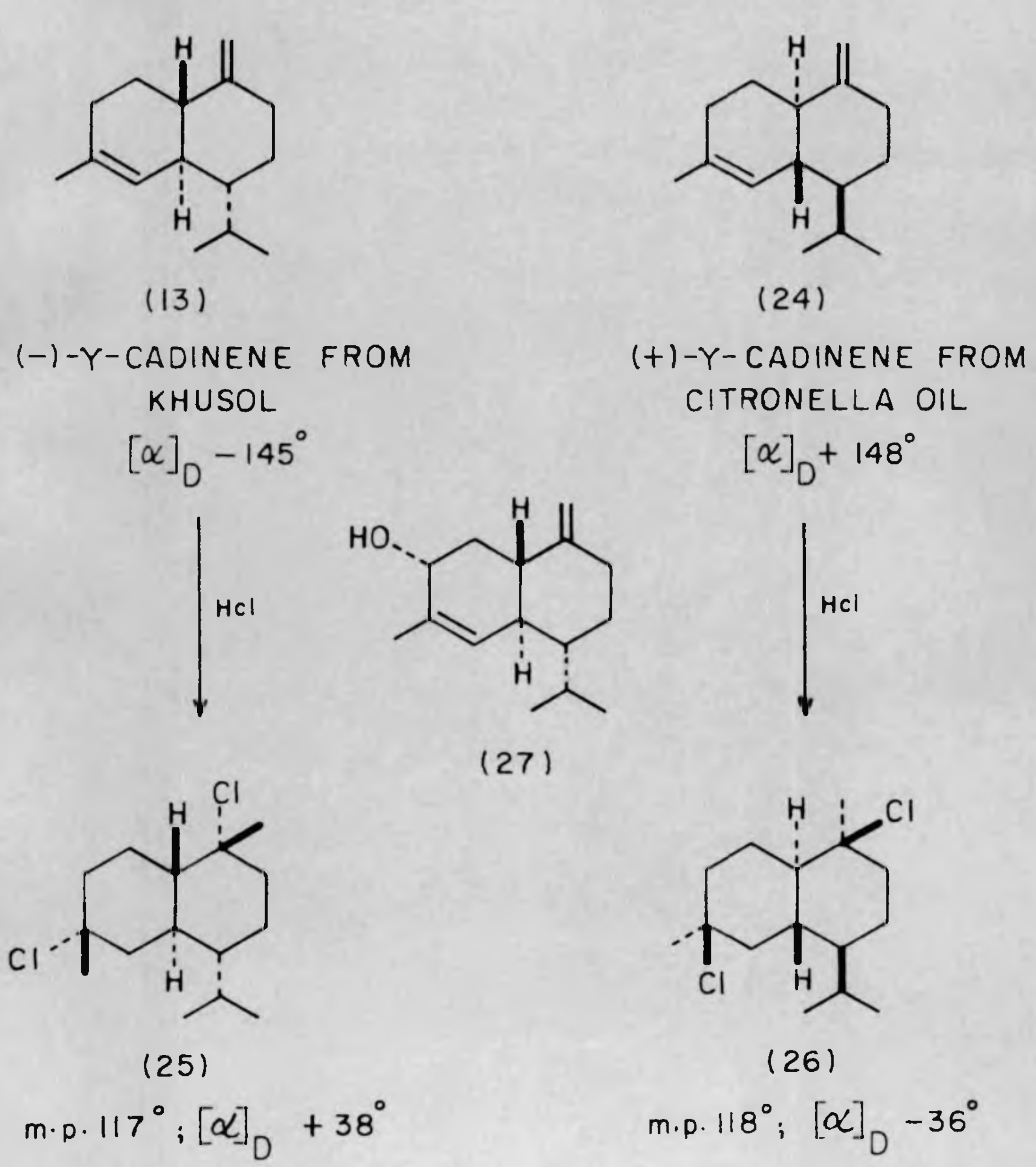
Absolute configuration of khusol

The IR spectrum (Fig. 3.5) and physico-chemical properties of the hydrocarbon (13) prepared from khusol are identical with those of (+)-γ-cadinene (24), $(\alpha)_D$ + 148°, (IR spectrum Fig. 3.6), isolated from citronella oil by Pliva *et al.*[16] However, its specific rotation, $(\alpha)_D^{26}$ -145° clearly indicated that the hydrocarbon (13) is the optical antipode of (+)-γ-cadinene (24). To further confirm the





FIG·3·6 IR SPECTRUM OF (+)−γ− CADINENE 24 FROM CITRONELLA OIL antipodal nature of the hydrocarbon (13), it was converted to its crystalline dihydrochloride (25). Its melting point 117^{o} was identical with that of normal (-)-cadinene dihydrochloride (26), m.p.118^{o}, but its specific rotation (+ 38^{o}) was almost equal but opposite in sign to that of normal cadinene dihydrochloride (-36^{o}).



(13)

(-)-γ-CADINENE FROM KHUSOL

$[\alpha]_D$ -145°

(24)

(+)-γ-CADINENE FROM CITRONELLA OIL

$[\alpha]_D$ + 148°

(27)

(25)

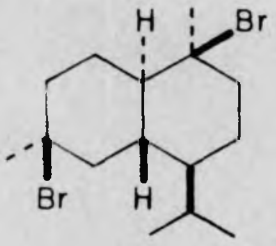
m.p. 117°; $[\alpha]_D$ +38°

(26)

m.p. 118°; $[\alpha]_D$ -36°

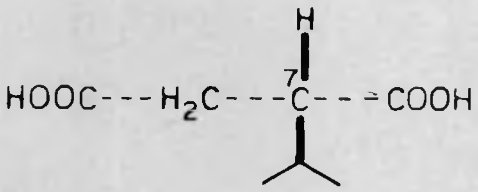
Mixed m.p. of (+) cadinene dihydrochloride from khusol with an authentic sample of (-)-cadinene dihydrochloride showed depression (102°), which is in accordance with expectation, since (±)-cadinene dihydrochloride, m.p. 105-106°, has been prepared[17] from optically inactive δ-cadinene and also has been synthesised.[18] Mixed m.p. of (+) cadinene dihydrochloride (25) prepared earlier from khusinol[4] (27) with that of (+) cadinene dihydrochloride prepared from khusol however remained undepressed.

Absolute configurations of cadinenes and cadinols[19] yielding (-) cadinene dihydrochloride (26) have been determined on the basis of X-ray diffraction measurements of (-)-cadinene dihydrobromide by Hanic[20] and it has been shown to be represented by (28). Thus the two rings are transfused, the three alkyl groups are equatorial and the two halogen atoms are axial and lie on the same side of the molecule. Thus all the compounds which afford (-)-cadinene dihydrobromide or the dihydrochloride have been shown to possess the same configuration at C_1, C_6 and C_7 which are not involved in the formation of the derivative. Isolation[21] of D-(+) isopropyl-succinic acid (29) from the products of oxidation of β-cadinene(30) supported the configuration at C_7. Same conclusion has

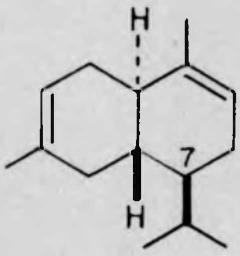


(28)

been drawn by the rotatory dispersion studies[19] of the ketones (31) and (32) prepared[22] from α-cadinol (33) and

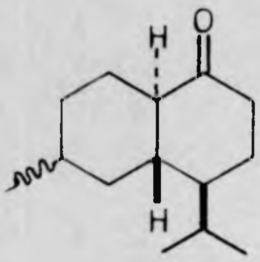

$$HOOC{-}{-}{-}H_2C{-}{-}{-}\overset{H}{\underset{CH(CH_3)_2}{C^7}}{-}{-}{-}COOH$$

(29)



(30)

their comparison with that of the ketone (34), whose absolute configuration[23] is known. ORD curves of (+)-cadinene- dihydrochloride (25) from khusol and (-)-cadinene dihydrochloride (26) further confirmed their antipodal nature. These facts pointed out that khusol, its derived hydrocarbon (-)-γ-cadinene and its corresponding (+)-cadinene dihydrochloride should be represented by (1), (13) and (25) respectively; and hence are antipodal to



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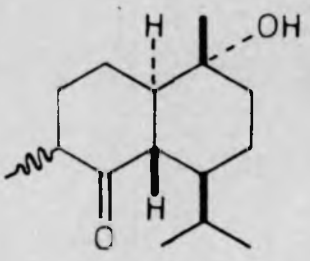

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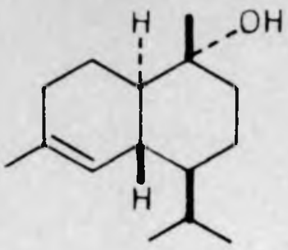
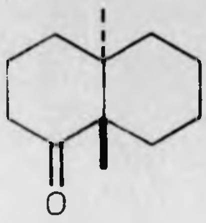
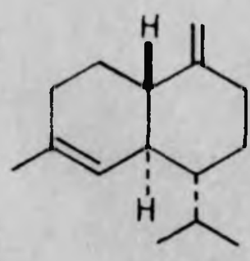


(33)

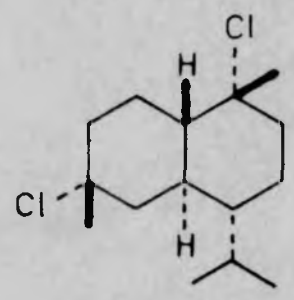


(34)

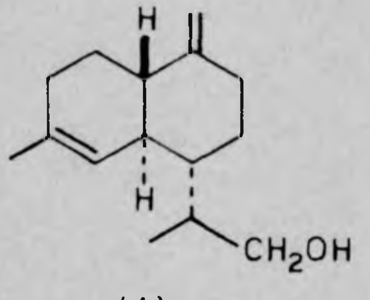
the normal (+)-γ-cadinene (24) and its corresponding (-)-cadinene dihydrochloride (26).



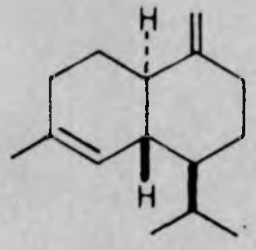
(13)



(25)



(1)



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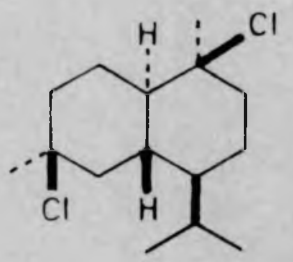
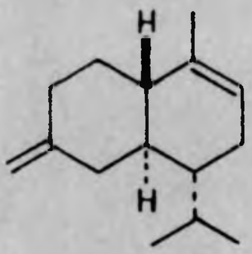
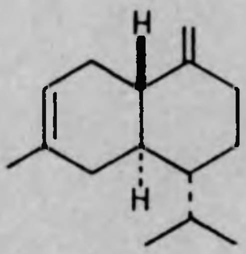


(26)

Previously γ_1-cadinene[2] has been isolated in this Laboratory from Malabar lemongrass oil and its structure elucidated. It also gives cadinene dihydrochloride, m.p. 118°. Its specific rotation which was not determined at that time has now been found to be + 36.8°. It does not depress the m.p. of (+) cadinene dihydrochloride obtained from (-)-γ-cadinene, but depresses the m.p. of (-)-cadinene dihydrochloride. γ_1-Cadinene, therefore, also belongs to the antipodal group and is assigned the absolute configuration (35). Very recently we have isolated yet another hydrocarbon (-)-γ_2-cadinene[3] from vetiver oil. On the basis of formation of (+)-cadinene dihydrochloride it has been assigned the absolute configuration (36).



(35)

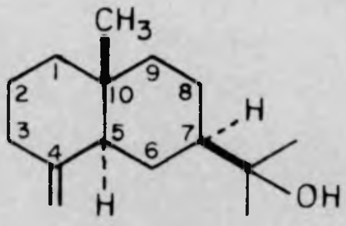


(36)

Although the above described cadinenes yielding (+)-cadinene dihydrochloride are few, as compared to those yielding (-)-cadinene dihydrochloride, the existance in separate plants of the appropriate enzyme systems for the production of the enantiomorphs renders it statistically likely that some plants will have both systems and may produce cadinenes, at least partially raecimic, as it frequently happens with the monoterpenes α-pinene, limonene etc. The production of pure racemates however by the enzyme systems of a plant would necessarily be an extraordinary coincidence. O. Motl and V. Lukes have isolated for the first time (±)γ-cadinene[25] from the oil of Lindera strychnifolia (F) Will leaves (Lauraceae).

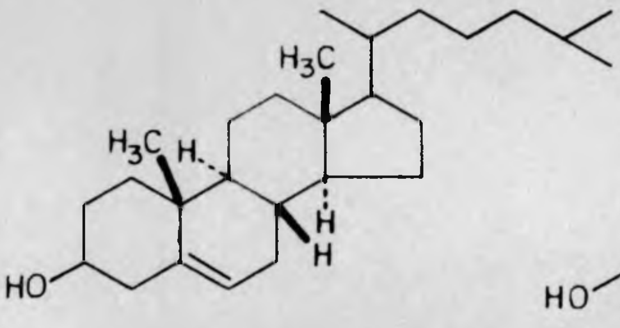
Other antipodal compounds

In a review dealing with the stereochemical relationships in the eudesman group of compounds, Cocker and McMurry[26] have shown the angular methyl group at C_{10}, having β-configuration, while the C_5 hydrogen is α-oriented. They have further stated that in all eudesmanic compounds, where the configuration is known, the isopropyl group is β-oriented as shown in β-eudesmol(37).



(37)

The C_{10} centre is the most important and is comparable with the asymmetric centre at C_{10} in the steroids e.g. cholesterol (38) and triterpenes e.g. β-amyrin (39). But recently some compounds from sesqui, di, and triterpene series have been isolated which possess the 'wrong' configuration at C_{10} as compared to steroids.



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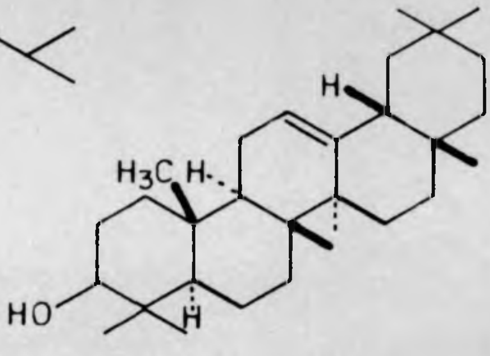
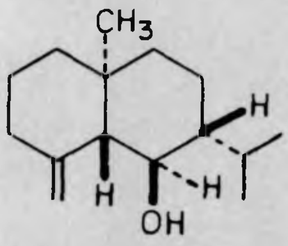
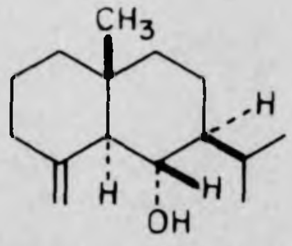


(39)

Laevojunenol[27] (40) has opposite configuration at C_{10}, C_5 and C_7 as compared to eudesmol and is thus antipodal to the naturally occurring junenol (41), isolated by Sorm *et al.*[28] Buchi[29] has shown that the sesquiterpene alcohol maaliol (42) differs in absolute configuration from eudesmol at C_{10} and C_5 but not at C_7 position.



(40)



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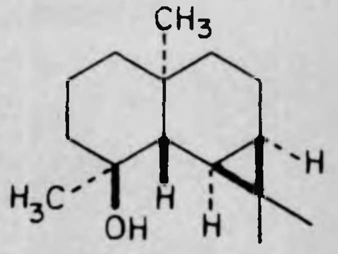
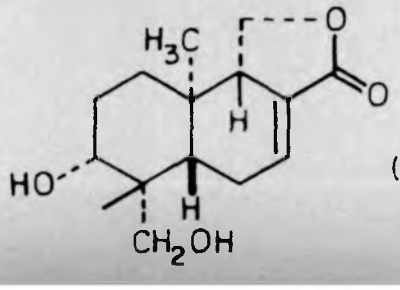
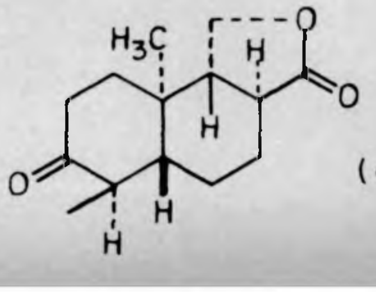


(42)

Iresin[30a] (43) also possesses the absolute configuration opposite to that of steroids and higher terpenes. Iresin was converted into the norketone (44), the rotatory dispersion curve of which exhibited a negative cotton effect curve in contrast to the positive one of 4-methyl-3-keto-5α-steroids.[30b] Eperuic acid[31] (45a) is the first authentic case of a diterpene with the wrong absolute configuration, which followed from the comparative rotatory dispersion measurements of the keto esters (45b) and (46b), derived from the corresponding eperuic acid (45a) and labdanolic acid (46a) respectively, although it has been suggested[34] that the two keto esters may perhaps not be

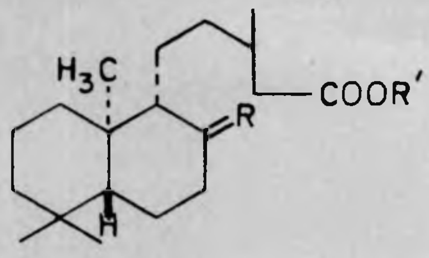


(43)



(44)

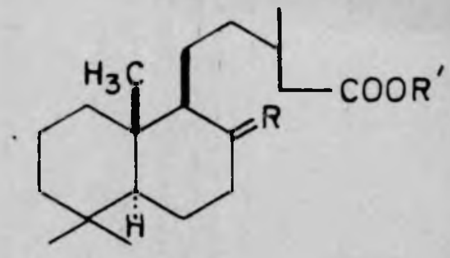
antipodal at every asymmetric centre, since there exists a large discrepancy in the m.ps of the oximes of the keto esters (45b and 46b) 223° and 180° respectively.



(45)

(a) R=CH$_2$, R′=H

(b) R=O R′=CH$_3$

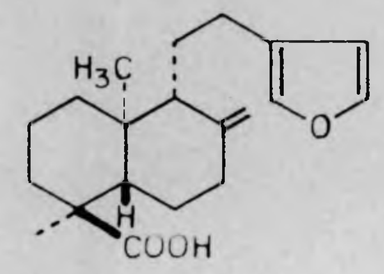


(46)

(a) R= $\overset{HO}{\text{—}}CH_3$,R′=H

(b) R = O R′=CH$_3$

Govindachari et al.[32] have isolated a new crystalline diterpene acid polyalthic acid (47) from Polyalthia fragrans (BTH) a large tree belonging to the family of Anonaceae. Wrong configuration in polyalthic acid was proved by its conversion into the keto dicarboxylic acid (49) which was found to be antipodal to the keto-dicarboxylic acid (50) prepared from neoabietic acid (48) of known configuration. Daniellic acid[33] (51) differs from polyalthic acid only in having an axially oriented carboxyl



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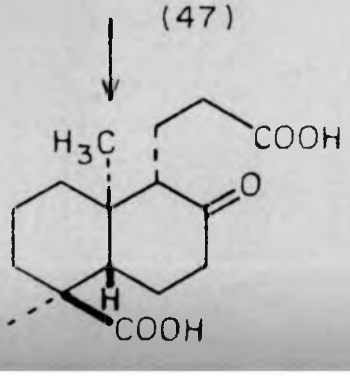

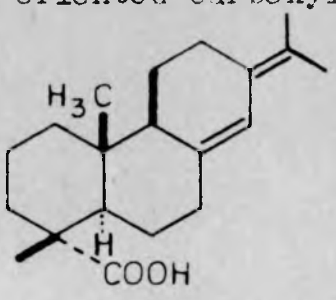

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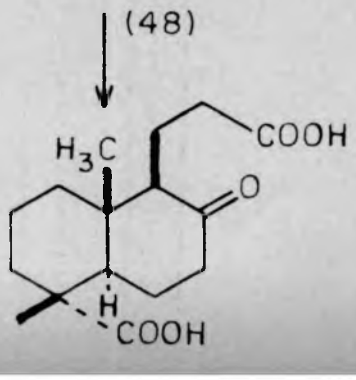
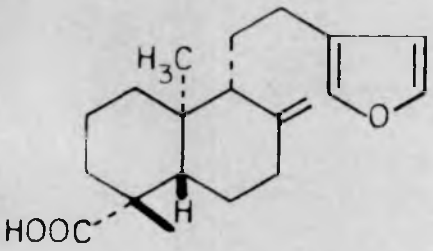
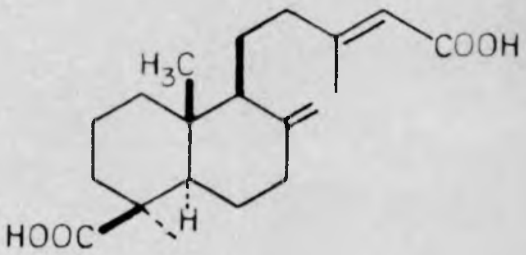


group, a conclusion derived from its correlation with agathic acid (52).

Copalic acid^{34} (53) has been shown to consist of several double bond isomers. On the basis of optical rotatory dispersion results and correlation of its derivatives with that of labdanolic acid (46), antipodal stereochemistry of the A/B ring juncture of copalic acid has been adduced. The wrong configuration of the diterpene lactone andrographolide^{35} (54) has been confirmed since the derived methyl ester (55) shows a positive rotatory dispersion curve.



(51)



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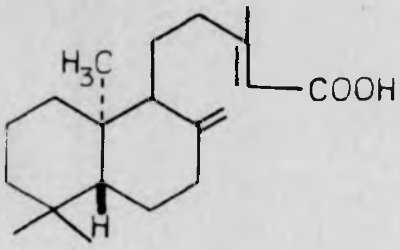
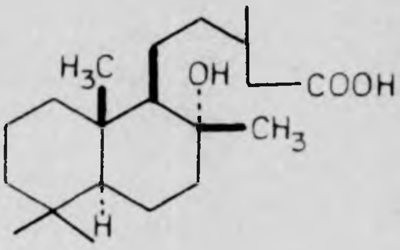
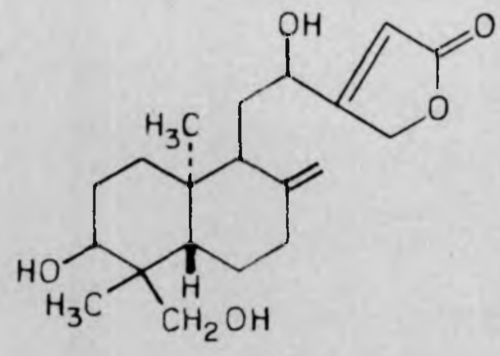


(53)

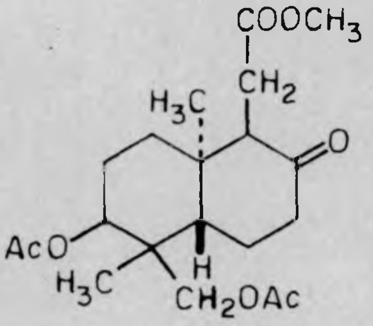


(46)

Djerassi et al.[36] in 1959 on the basis of comparative rotatory dispersion measurements assigned the absolute

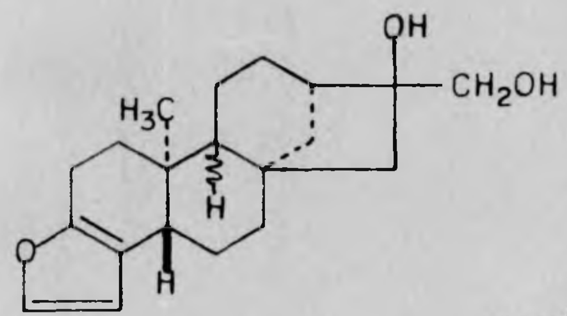


(54)



(55)

configuration at C_5 and C_{10} of cafestol (56) and showed it to be antipodal to that of the steroids or diterpenes of the abietic acid class. Farnesiferol A[37] (57) also possess a wrong configuration since the derived ketone(58) is antipodal to the ketone (59).



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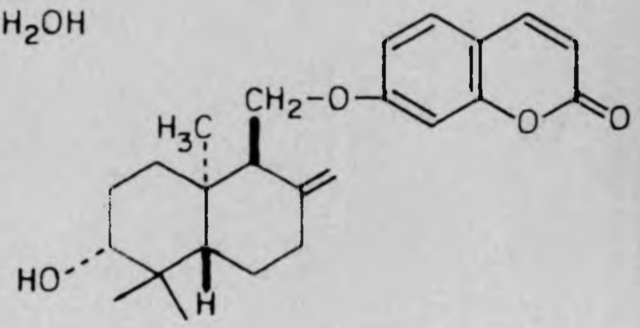

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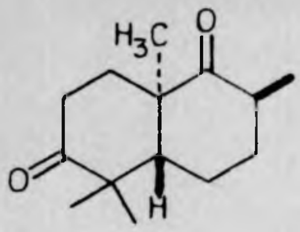

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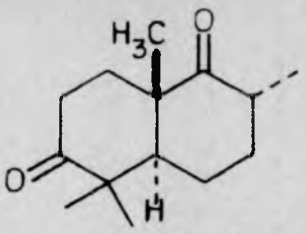
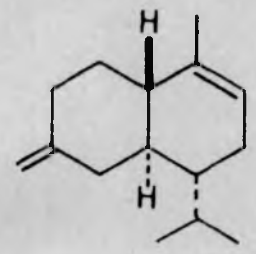


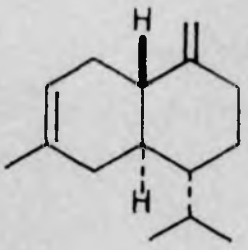
(59)

Other cadinenes and cadinols

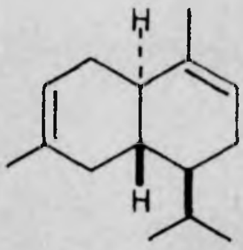
Out of the nine theoretically possible isomers of cadinenes which are capable of yielding the same cadinene dihydrochloride, including (-)-γ_1 (35) and (-)-γ_2 (36) cadinenes isolated by Bhattacharyya *et al.*[2,3] isolation of β (30), γ (24) δ (50) and ϵ (61) cadinenes[19] has proved the existance of six isomers in nature.



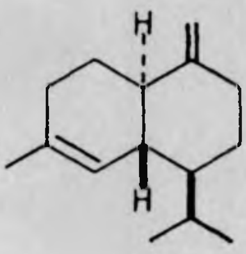
γ_1-(35)



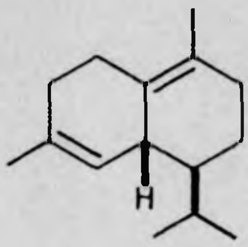
γ_2-(36)



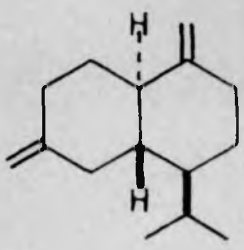
β-(30)



γ-(24)

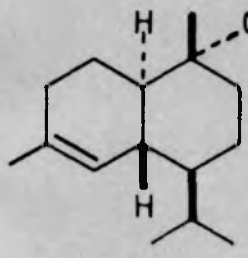


δ-(60)

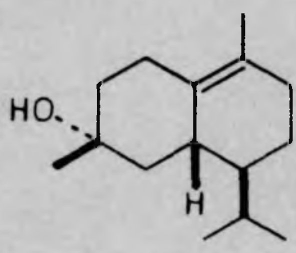


ϵ-(61)

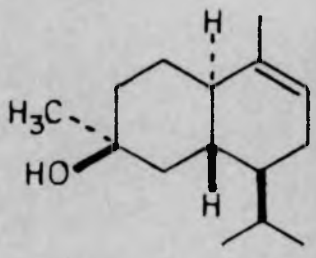
The twelve theoretically possible cadinols which can give rise to the same cadinene dihydrochloride, three isomers have been found in nature so far. α-Cadinol[22] (62) was isolated from the oil of *Juniperus communis* L. and also from Java citronella oil. The position of trisubstituted double bond in α-cadinol was fixed by labelling experiments.^{14,22} Sorm *et al*. suggested the structure^{22} (63) for another crystalline alcohol, m.p.140° named δ -cadinol by them. It was shown to possess a tetrasubstituted double bond on the basis of IR spectra and since on ozonolysis it afforded a material which lacked aldehydic properties. Subsequently Anderson *et al*.^{38} showed that δ-cadinol in its NMR spectrum clearly showed the presence of one vinyl proton (4.43τ) This coupled with other chemical data showed that δ-cadinol instead contains a trisubstituted double bond and must be represented by (64). Another cadinol, m.p. 79° has been isolated by Sorm *et al*.^{22} from the oil of *Juniperus communis* and its structure is being investigated.



α-(62)

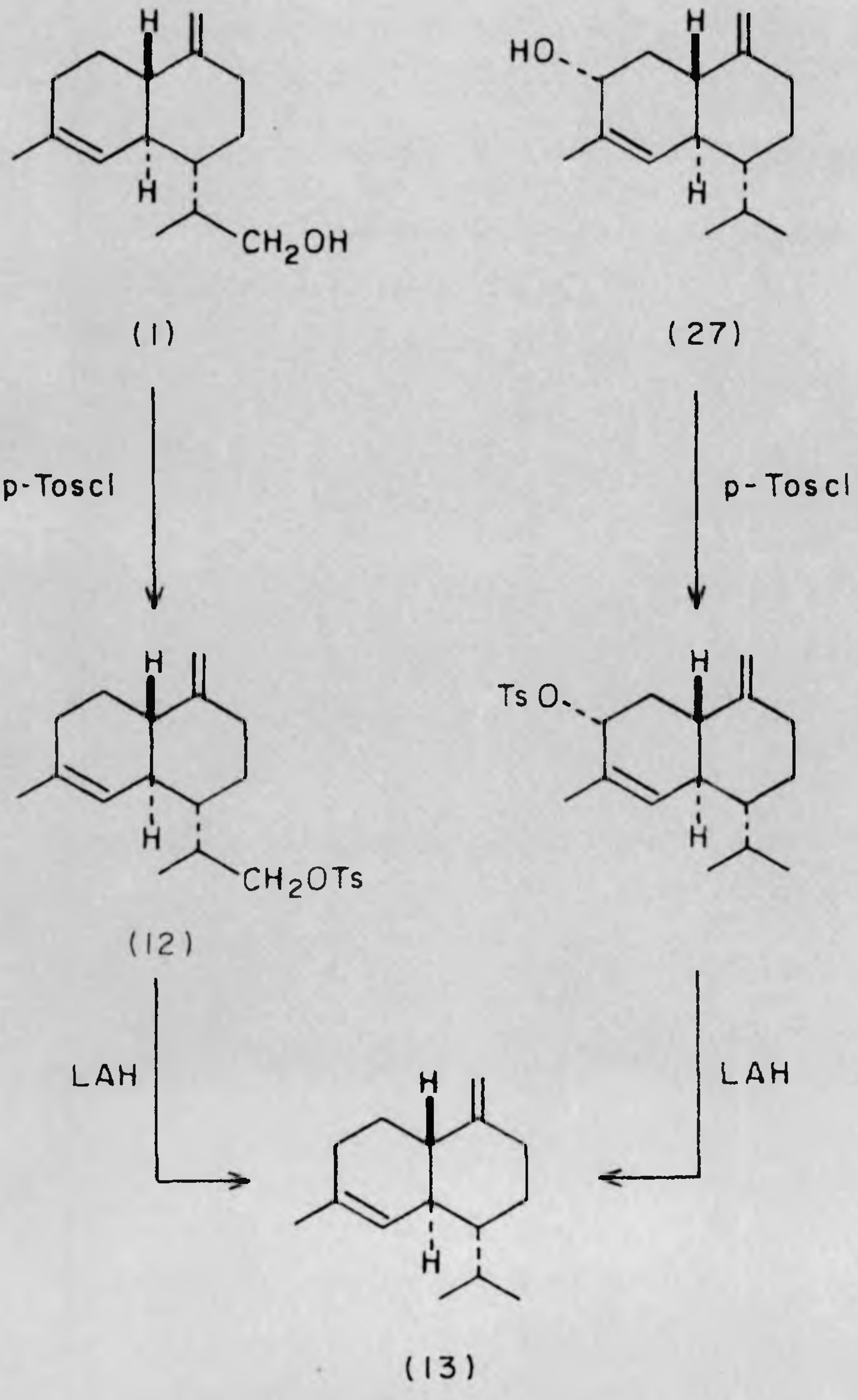


(63)



δ-(64)

Khusol^{1} (1), m.p. 102° and khusinol,^{4} (27), m.p. 87°, occurring in the Indian vetiver oil seem to be the only cadalenic primary and secondary alcohols known so far. Both on treatment with p-toluene sulphonyl chloride and the subsequent reduction of the resulting tosyl derivatives with lithium aluminium hydride give the same (-)-γ-cadinene (21) which has already been shown to be antipodal to the naturally occurring (+)-γ-cadinene.[13]



EXPERIMENTAL

Khusol was crystallised from pet. ether, m.p.101-102°; $(\alpha)_D^{27}$ - 137° (c, 2.9) (Found: C, 81.77; H, 11.10. $C_{15}H_{24}O$ requires: C, 81.76; H, 10.98%). IR spectrum in nujol (Fig. 3.1) bands at: 3340, 1642, 1028, 892, 840 and 798 cm^{-1}.

Isolation (vide Chapter I, p. 16).

Dihydrokhusol (5)

A solution of khusol (0.5 g) in ethanol (15 ml) was hydrogenated in the presence of 10% palladium-charcoal catalyst (200 mg). The hydrogen absorbed (63 ml at 25° and 711 mm in 1 hr), corresponded to one double bond, further absorption being extremely slow. The catalyst was filtered off, the ethanol removed from the filtrate on a steam bath in vacuo and the residue in pet.ether chromatographed over alumina (20 g, grade II) to give dihydrokhusol (5), b.p.155° (bath)/1.5 mm., $(\alpha)_D^{27}$ + 60° (c, 1.7), n_D^{27} 1.5080 (Found: C, 80.80; H, 11.90. $C_{15}H_{26}O$ requires: C, 81.02; H, 11.79%). IR spectrum bands at: 3338, 1030, 831 and 793 cm^{-1}.

Tetrahydrokhusol (6)

A solution of khusol (0.266 g) in acetic acid (20 ml) was hydrogenated in presence of 55 mg pre-reduced Adams catalyst (61.9 ml hydrogen at 25° and 711 mm in 11 hr) which corresponded to 2 moles of hydrogen. The product was chromatographed over alumina (grade II, 10 g) to give tetrahydrokhusol (6, 0.211 g), b.p.140° (bath)/0.5 mm., $(\alpha)_D^{27}$ + 34° (c, 2.0); n_D^{28} 1.4951 (Found: C, 80.00; H, 12.50. $C_{15}H_{28}O$ requires: C, 80.29; H, 12.58%).

Ozonolysis of khusol

A stream of dry ozonised oxygen was passed through a solution of khusol (0.5 g) in dry chloroform (55 ml) cooled to 0°, until ozonisation was complete. Solvent was removed under reduced pressure and the ozonide decomposed by heating with water. The volatile portion was characterised as formaldehyde by its dimedone derivative (m.p. and mixed m.p. 189-190°). The non-volatile portion gave a positive iodoform test for methyl ketone group and Fehling's solution test for aldehyde function.

Aldehyde (7)

Khusol (2 g) in pyridine (20 ml) was oxidised with pyridine-chromic acid complex (40 ml, pyridine and 2 g. chromic acid) at room temperature for 24 hr with shaking. The product after chromatography over alumina (grade II, 30 g) gave the pure aldehyde (0.98 g). An analytical sample had b.p. 135° (bath)/1.5 mm., n_D^{27} 1.5173; $(\alpha)_D^{27}$ - 165° (c, 2.5) (Found: C, 82.70; H, 10.1. $C_{15}H_{22}O$ requires: C, 82.51; H, 10.16%). IR spectrum (Fig.3.3) bands at: 2710, 1724, 1630, 892, 832 and 795 cm^{-1}. The semicarbazone was obtained as fine needles on crystallisation from ethanol, m.p. 165° (Found: N, 14.96. $C_{16}H_{25}N_3O$ requires: N, 15.26%).

(-)-γ-Cadinene (13)

A mixture of khusol (5 g) in dry pyridine (20 ml) and freshly crystallised p-toluene sulphonyl chloride (6 g) in dry pyridine (40 ml) was kept at room temperature for 94 hr. It was poured into crushed ice, taken up in ether and the ether layer washed successively with dilute hydrochloric acid, sodium-bicarbonate solution and finally with water and dried. After the removal of the solvent the crystalline tosylate (12, 6.2 g) crystallised from pet. ether in white shining needles, m.p. 114-115° (Found: C, 70.6; H, 7.9; S, 8.1. $C_{20}H_{30}O_3S$ requires: C, 70.9; H, 8.0; S, 8.5%). IR spectrum in nujol (Fig. 3.4) bands at: 1600, 1490, 1190, 1176 and 1100 cm-1.

The tosyl derivative (5 g) in dry ether (20 ml) was added dropwise to a slurry of well powdered lithium aluminium hydride (2 g) in dry ether (45 ml) at 0° with stirring 1/2 hr. The contents were then refluxed for 7 hr., the mixture decomposed with moist ether and worked up to afford (-)-γ-cadinene (2.6 g) which was chromatographed over alumina (grade I, 50 g) with pet.ether, and distilled over sodium, b.p.100° (bath)/0.5 mm., n_D^{31} 1.5060; $(\alpha)_D^{26}$ - 145° (c, 3.8); d_4^{24} 0.9182 (Found: C, 88.10; H, 12.10. $C_{15}H_{24}$ requires: C, 88.16; H, 11.84%). IR spectrum in liquid cell 0.1 mm. (Fig. 3.5) bands at: 1786, 1639, 1389, 1370, 892, 835 and 795 cm-1.

Cadalene (8) on dehydrogenation

The hydrocarbon (13, 0.35 g) was mixed with selenium (0.5 g) and heated in nitrogen atm. at 300° for 16 hr. The product in pet.ether was chromatographed over alumina (grade I, 50 g) and characterised as cadalene by picrate, m.p. and mixed m.p. with an authentic sample 114-115°.

Dehydrogenation of khusol

Khusol (0.5 g) was mixed with selenium (1.g) and heated in nitrogen atmosphere at 290° for 18 hr. The product in pet.ether was chromatographed over alumina (grade I, 70 g). On subjecting to VPC analysis, it showed the presence of three major products, 1,6-dimethyl naphthalene (11), 1,6-dimethyl-4-ethyl naphthalene (10) and cadalene (8) in the ratio of (3:2:1).

1,2,5-Trimethyl naphthalene (18)

A solution of (-)-γ-cadinene (13, 0.473 g) in ethanol (20 ml) was hydrogenated in the presence of 10% palladium charcoal catalyst (300 mg) at 710 mm and 25° (0.94 mole hydrogen absorbed in 1.5 hr), and the product on distillation over sodium yielded dihydro-(-)-γ-cadinene (22), b.p.90° (bath)/0.8 mm., n_D^{27} 1.4900; $(\alpha)_D^{27}$ + 70° (c,0.9). (Found: C, 87.49; H, 12.52. $C_{15}H_{26}$ requires: C, 87.30; H, 12.70%). Dihydro (-)-γ-cadinene (0.45 g) was reacted with excess perbenzoic acid in chloroform for 16 hr. at 0°. The resulting epoxide (23, 0.42 g) was refluxed with stirring for 48 hr. with Grignard's reagent prepared from magnesium (0.8 g) and methyl iodide (3.7 g) in dry ether (45 ml). After decomposition with ice and dilute sulphuric acid, the desired carbinol was isolated in the usual way (0.38 g) and purified through chromatography over alumina (grade I, 12 g). The IR spectrum showed absorption at 3445 cm-1; absorption in the vicinity of 1700 cm-1 being absent.

The carbinol (0.25 g) was heated with selenium (0.5 g) at 290-300° for 16 hr. The product was extracted with pet.ether and filtered through alumina (grade I). The oily material thus obtained gave a TNB complex m.p. 159°. The mixed m.p. with an authentic sample of TNB complex of 1,2,5-trimethylnaphthalene remained undepressed.

Acid (19) from Aldehyde (7)

(i) Oxidation with alkaline silver oxide

To a cold solution of aldehyde (7, 0.8 g) and powdered silver nitrate (1.6 g) in ethanol, was added dropwise a solution of sodium hydroxide (0.9 g) in aqueous ethanol (20 ml) with stirring. After 24 hr at room temp. the mixture was diluted with water and acidified with cold dilute sulphuric acid. It was extracted with ether and the ethereal solution washed repeatedly with cold water and dried. After removal of the solvent, the acid (19, 0.6 g), crystallised from pet.ether, m.p.118-119°; $(\alpha)_D^{24}$ - 123° (c, 1.7) (Found: C, 76.42; H, 9.55. $C_{15}H_{22}O_2$ requires: C, 76.88; H, 9.46%).

IR spectrum in nujol bands at: 3175, 1712, 1639, 892, 832 and 795 cm-1.

(ii) Oxidation with chromic acid in acetone

To a solution of khusol (3.4 g) in dry acetone (250 ml) chromic acid solution was added dropwise at room temp. till the solution retained the reddish colour of the oxidation reagent (15 min). The mixture was diluted with water (200 ml), and the reaction product isolated with ether, solvent was evaporated and the product (3.2 g) treated with saturated aqueous solution of sodium carbonate. It was extracted with ether (2 X 50 ml) to remove unreacted khusol. The sodium carbonate solution was acidified with cold dil. hydrochloric acid. It was extracted with ether and ethereal solution washed repeatedly with cold water and dried. After removal of the solvent, the acid (19, 3.1 g) was crystallised from pet.ether, m.p.119° $(\alpha)_D^{27}$ - 120° (c, 2); mixed m.p. with an authentic sample prepared by the silver oxide oxidation of aldehyde (7) remained undepressed.

Methyl ester of the acid (19)

Acid (19, 0.2 g) in dry ether was converted into its methyl ester (ethereal solution of diazomethane) and chromatographed over alumina (grade II, 5 g) and eluted with pet.ether; benzene mixture (1:1) and distilled b.p. 135° (bath)/1.7 mm. (Found: C, 77.20; H, 10.00. $C_{16}H_{24}O_2$ requires: C, 77.37; H, 9.74%). IR spectrum: bands at 1740, 1645, 1250, 1200, 1175, 1165, 892, 835 and 790 cm^{-1}.

1,6-Dimethyl-4-ethylnaphthalene (10)

The acid (19, 0.3 g) was heated with selenium(0.4 g) in nitrogen atmosphere at 290-300° for 16 hr. The dehydrogenation product in pet.ether was chromatographed over alumina (grade I, 20 g) using pet.ether as eluent. The product on VPC examination showed the presence of two major products, 1,6-dimethyl naphthalene (11) and 1,6-dimethyl-4-ethyl naphthalene (10) in the ratio of (1:1). The product was converted into its TNB complex, repeated crystallisations of which with ethanol gave the TNB of 1-6, dimethyl naphthalene, m.p.135° (Found: N, 10.79. $C_{20}H_{19}O_6N_3$ requires: N, 10.58%); picrate m.p. 94-95° (Lit.[24] picrate m.p.99-100°; TNB derivative m.p.134.5-136°).

(+)-Cadinene dihydrochloride (25)

A solution of (-)-γ-cadinene (13, 1 g) in dry ether (60 ml) was saturated with dry hydrogen chloride, and the solvent removed at 30° under suction. The product deposited on cooling and was crystallised from pet.ether as the dihydrochloride, m.p.116-117°, $(\alpha)_D^{27}$ + 38° (c,1.2). Mixed m.p. with an authentic sample of (+)-cadinene dihydrochloride obtained via khusinol (27) (m.p. 117.5°, $(\alpha)_D^{24}$ + 36.27°) remained undepressed.

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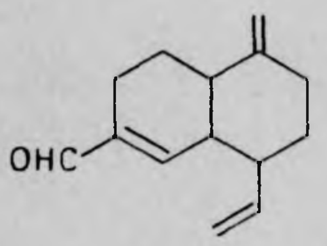
CHAPTER IV

STRUCTURE OF KHUSILAL

A NOVEL C_{14} ALDEHYDE FROM VETIVER OIL

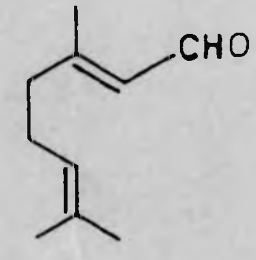
SUMMARY

North Indian vetiver oil has yielded a new laevorotatory aldehyde in a pure form containing only fourteen carbon atoms, which has been named as khusilal. Structure[1] (1) has been assigned to it on the basis of ultraviolet, infrared and NMR spectra and chemical evidences.



(I)

The occurrance of a large number of lower aldehydes C_1 to C_{10} (aliphatic, aromatic, cyclic and heterocyclic types) in essential oils is well known.[2] Aromatic aldehydes, as compared to the aliphatic aldehydes play a much more important role in essential oils and sometime occur as major constituents in them. Cinnamaldehyde, a valuable ingredient in flavours and in perfumes for imparting spicy notes, is the main constituent of cassia leaf and bark oil.[2] From the open chain C_{10} group of terpene aldehydes mention may be made of citral (2), the major constituent of lemongrass oil, as the key substance for the commercial synthesis of vitamin A. An interesting cyclic terpene dialdehyde anisomorphal (3), $C_{10}H_{14}O_2$ has been recently isolated by Eisner *et al*.[3] from the Southern walking stick insect (*Anisomorpha buprestoides*, Stoll).



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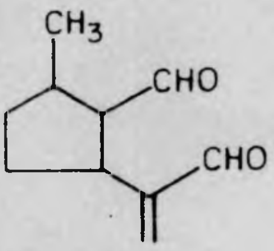
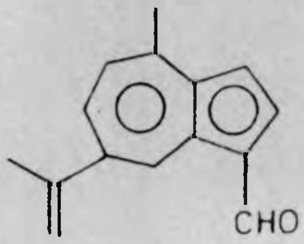


(3)

On the other hand only a few C_{15} sesquiterpene aldehydes are known and their structures have been determined only very recently. Particular mention may be made of lactaroviolin (4). This azulenic aldehyde, $C_{15}H_{14}O$, m.p. 59^o, was isolated by Willstaedt[4] in 1935 from the organge agaric (Lactarius deliciosus, L.). Heilbronner *et al.*[5] presented physico-chemical evidences for its structure (4) in 1954. In the same year Sorm *et al.*[6] presented the direct chemical proof for its structure by converting it to known 1-ethyl-4-methyl-7-isopropyl azulene (5).

A novel dialdehyde helminthosporal, $C_{15}H_{22}O_2$ (6), a toxin produced by the fungus (Helminthosporium sativum) has been isolated and characterised by de Mayo *et al.*[7] The structure (6) followed from its conversion to 6-isopropyl-3-methyl phthalic anhydride (7) by the dehydrogenation of the derived lactone (8) and from the NMR studies of its derivatives. Its biogenesis[7c,8] has also



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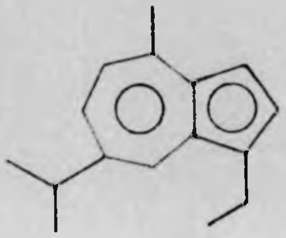

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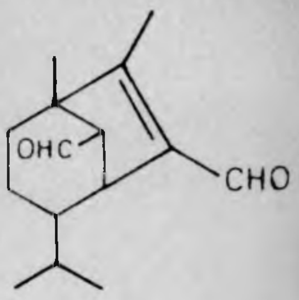
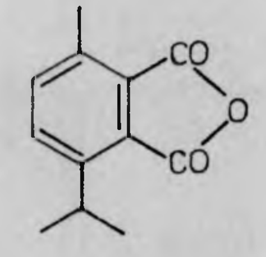


(6)

been suggested from an isoprenoid precursor (9) which has been shown to be formed from farnesyl cyclisation and then by subsequent steps similar to those suggested



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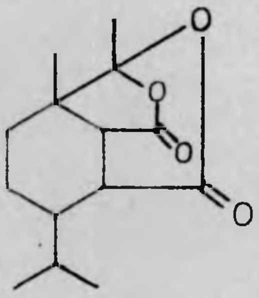
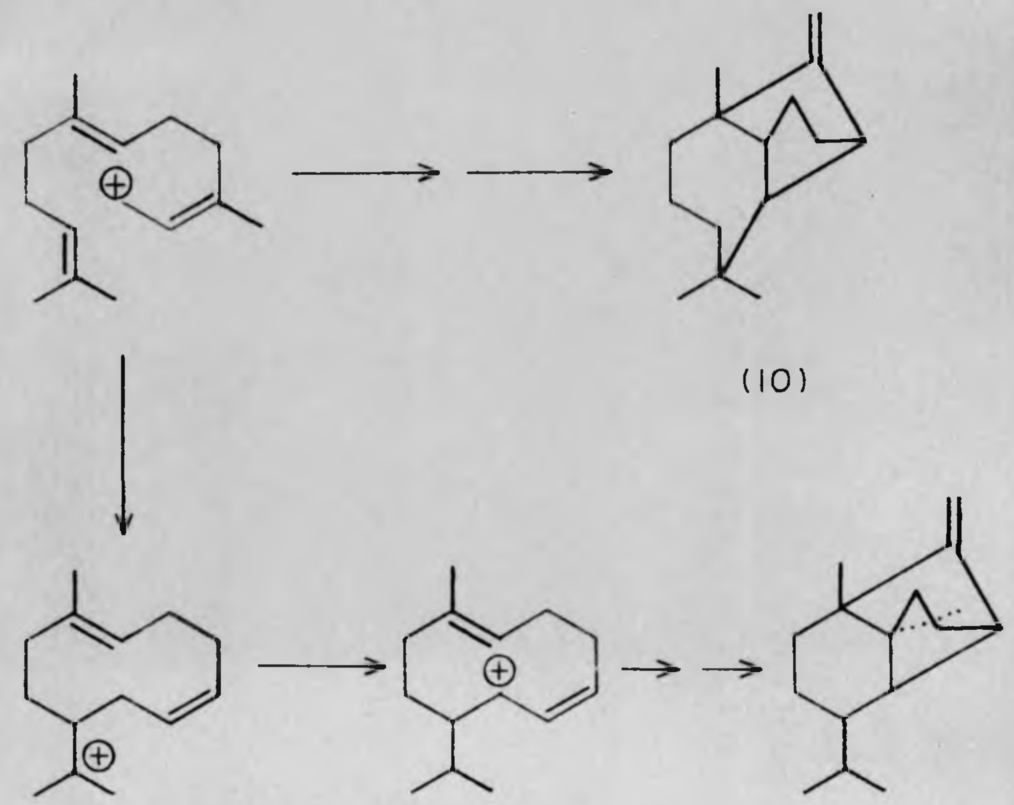


(8)

SCHEME 1

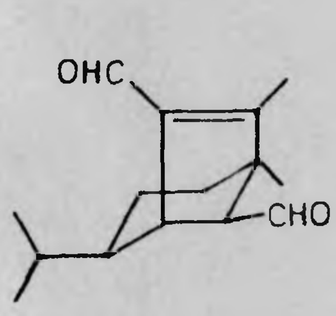


(10)

(9)

for longifolene (10) (Scheme 1). Oxidative cleavage at the dotted bond in (9) could then give rise to the dialdehyde (6). In a more recent communication de Mayo et al.[7c] have shown its stereochemistry as represented in (11).

Tadeonal,[9a] a component of the bitter principle of (Polygonum hydropiper) has the structure (12), since it could be converted into nor-drimenone (13) and drimanoic acid (14). Both nordrimenone (13) and drimanoic acid (14) have been prepared from a novel bicyclic sesquiterpenoid drimenol[9b] (15). Polygodial (16) isolated and characterised by Barnes et al.[10] has a similar iresane type carbon skeleton as ascribed to tadeonal (12) and drimenol (15).



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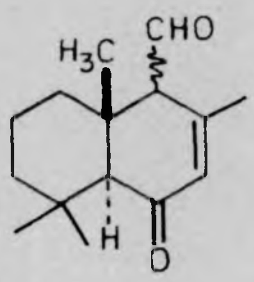

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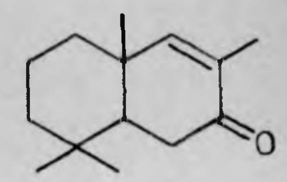

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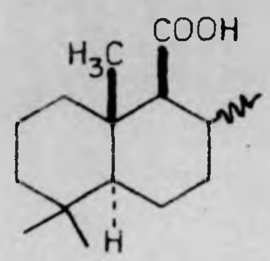

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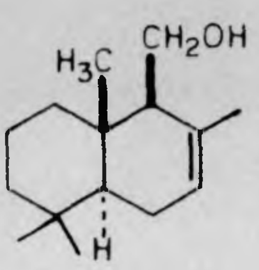

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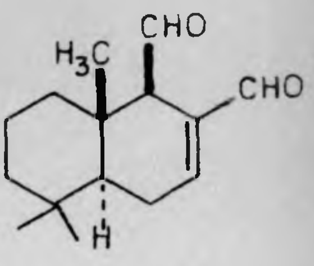
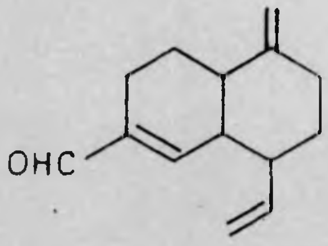
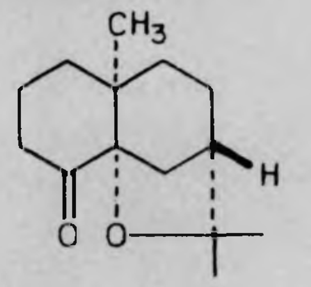


(16)

We have now isolated from North Indian vetiver oil (Vetiveria zizanioides, Linn.), a new C_{14} aldehyde which has been named by us as khusilal.[1] The isolation of any aldehydes has not been reported so far from any variety of vetiver oil. Khusilal possesses a novel C_{14} system which is not normally encountered among terpenoids, although a C_{14} ketone, norketoagarofuran, $C_{14}H_{18}O_2$ (17), has been isolated by Bhattacharyya et al.[11] from agarwood oil. An azulogenic lactone, mexicanin E, $C_{14}H_{16}O_3$ (18), has also been reported.[12] Evidences put forward in this part of the thesis show that khusilal is represented by the structure (1).



(1)



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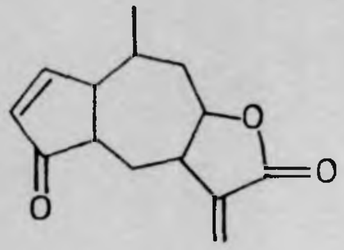


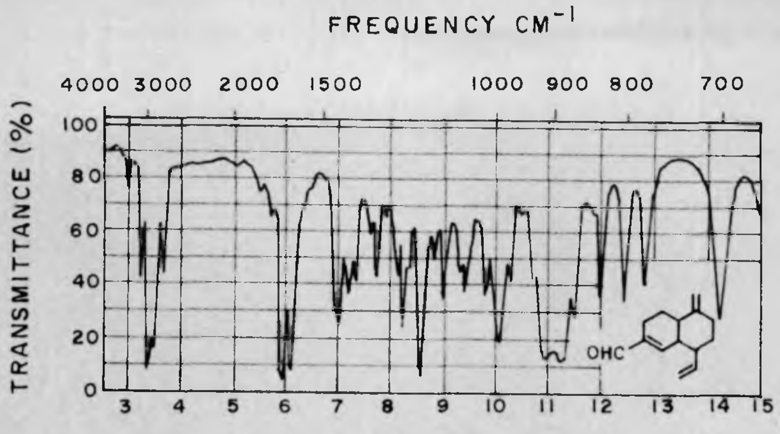
(18)

Khusilal (1) was obtained (isolation vide Chapter I, p. 17) from its crystalline semicarbazone, $C_{15}H_{21}ON_3$, m.p. 162° ($\lambda_{max.}$ 265 mμ, ϵ 28,850) by treatment with oxalic[13] acid as a highly laevorotatory colourless liquid in a pure form (VPC). This could be reconverted to the same semicarbazone (m.p. and mixed m.p. 162°) indicating that no change had taken place during these operations. Khusilal had the following properties, b.p. 115° (bath)/ 0.3 mm., $(\alpha)_D^{25}$ - 261°, n_D^{25} 1.5349. It analysed correctly for $C_{14}H_{18}O$; neutralisation equivalent of its crystalline acid, $C_{14}H_{18}O_2$ (Found: 219. Calc. 218.28). 2,4-Dinitrophenyl hydrazone, $C_{20}H_{22}O_4N_4$, deep red leaflets, m.p. 214° ($\lambda_{max.}^{CHCl_3}$ 378 mμ, ε 20,000); oxime, $C_{14}H_{19}ON$, white plates, m.p. 101-102° ($\lambda_{max.}$ 235 mμ, ε 18,270).

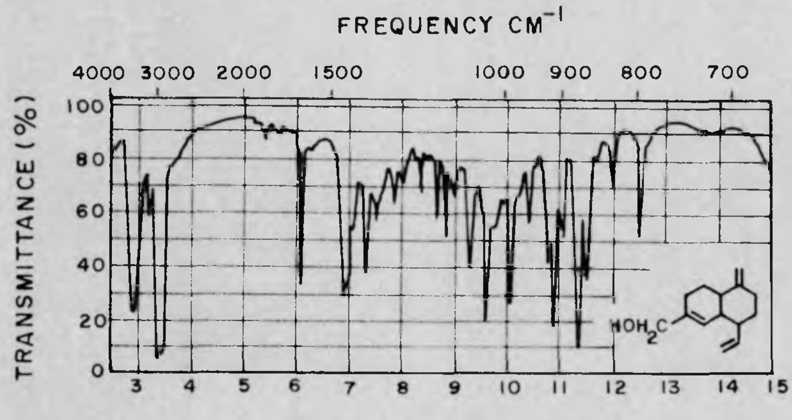
Nature of Unsaturation

The IR spectrum of khusilal (Fig. 4.1) showed bands at: 3080, 1634 and 892 due to methylenic double bond ($>C=CH_2$); 1818, 995 and 918 due to vinyl double bond ($-CH=CH_2$) and 840, 810 and 785 cm^{-1} due to trisubstituted ethylenic linkage. NMR spectrum of khusilal (Fig. 4.2) confirmed the presence of these double bonds, signals at 3.38 τ (singlet, $-C\underline{H}=C\diagup\!-CHO$); 4.5 - 4.9 τ (multiplet, $-CH=CH_2$) and 5.25 and 5.35 τ (doublet $>C=CH_2$). Reduction of khusilal with lithium aluminium hydride gave the corresponding crystalline alcohol khusilol, $C_{14}H_{20}O$ (19), m.p. 74°, $(\alpha)_D^{24}$ - 158°; IR spectrum (Fig. 4.1). NMR spectrum (Fig. 4.2) showed signals at

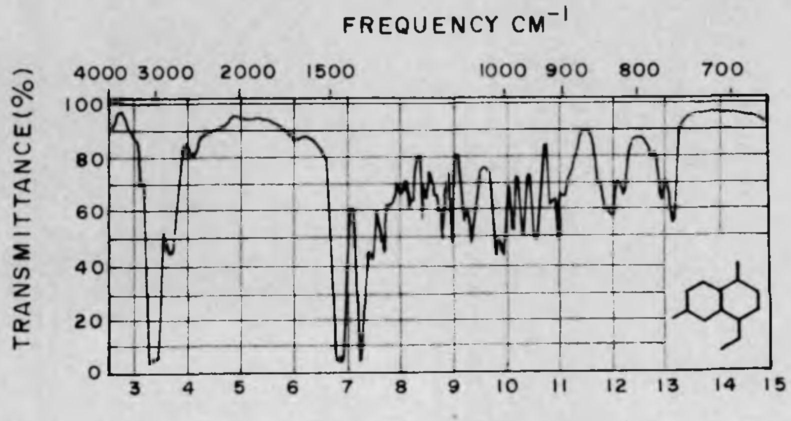
FIG. 4·1



IR SPECTRUM (LIQUID FILM) OF KHUSILAL 1

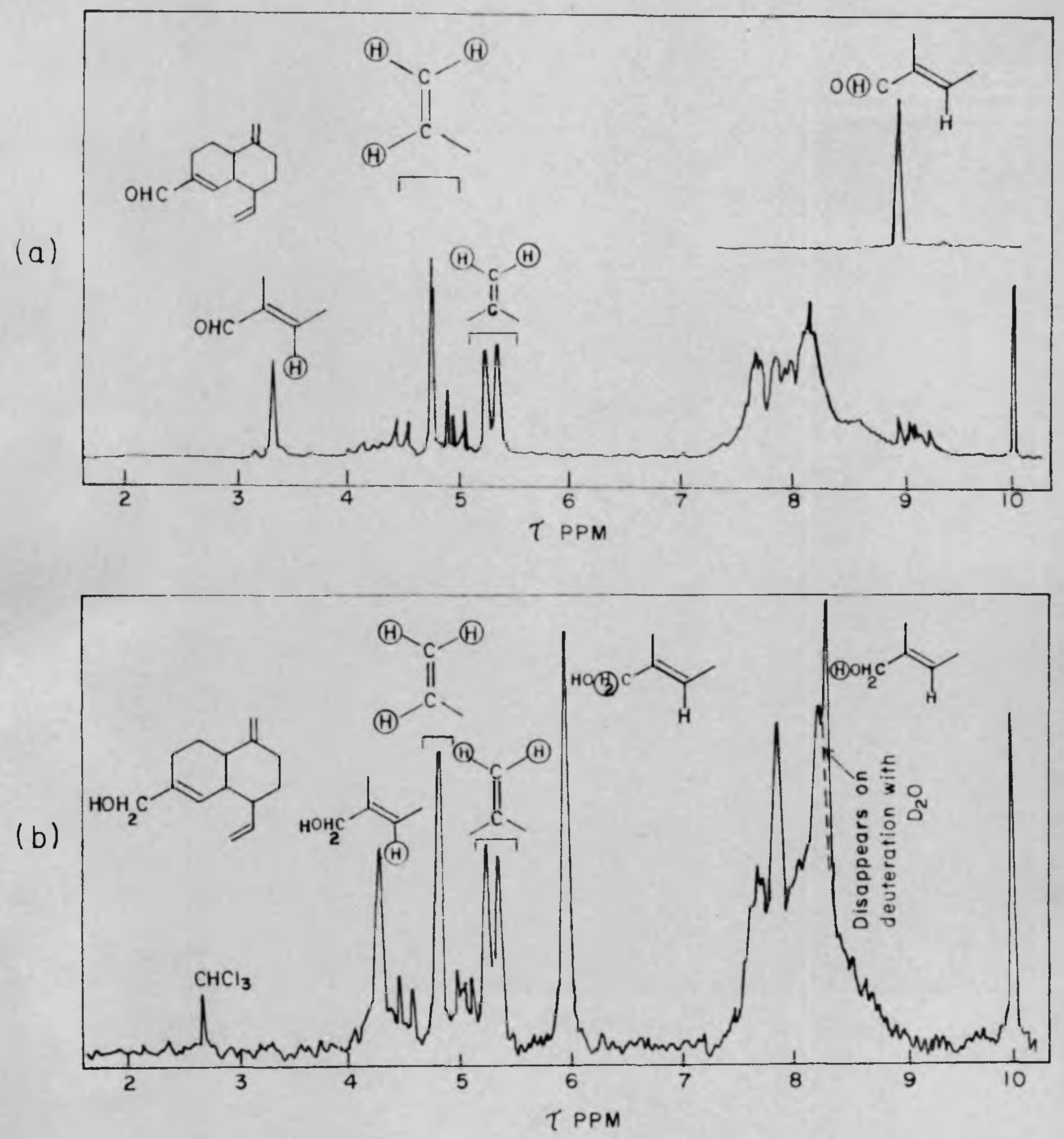


IR SPECTRUM (IN NUJOL) OF KHUSILOL 19



IR SPECTRUM (LIQUID FILM, 0·1 mm) OF HEXAHYDROKHUSILENE 21

FIG. 4.2

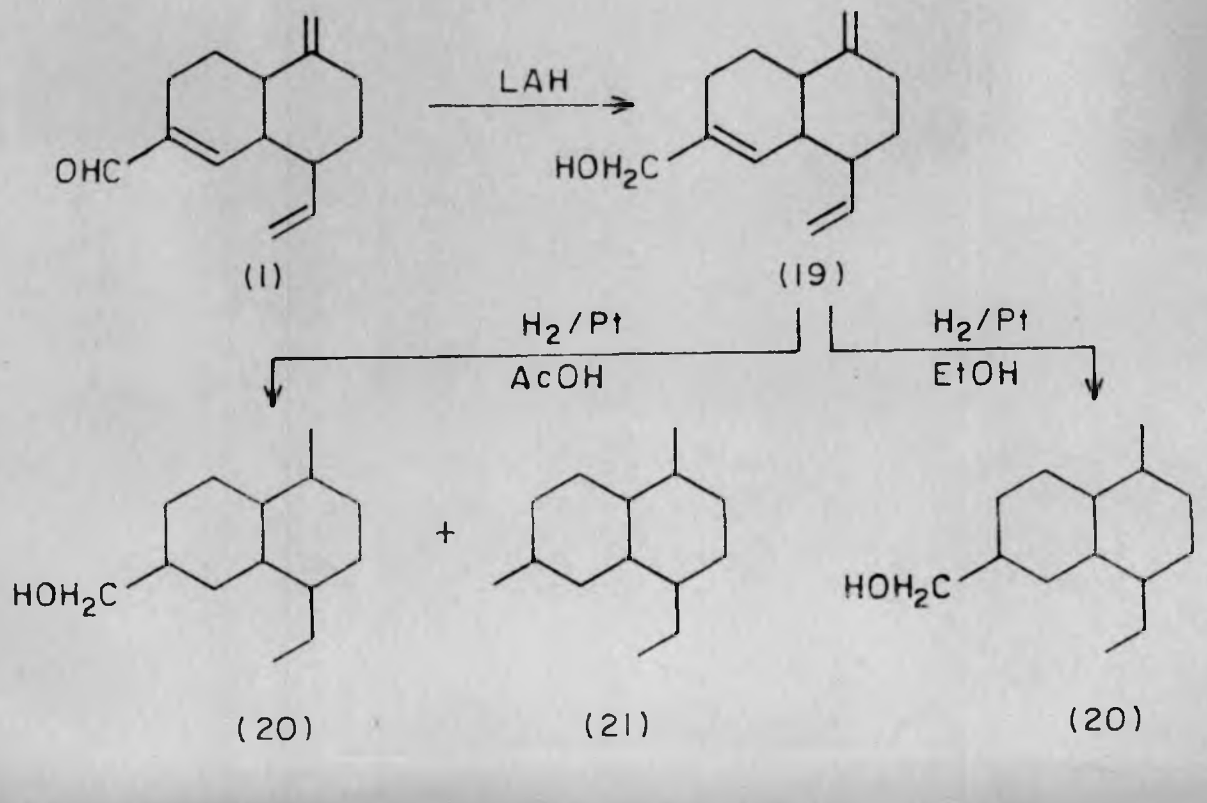


(a) NMR SPECTRUM OF KHUSILAL 1

(b) NMR SPECTRUM OF KHUSILOL 19

4.32 τ (singlet) -$\underline{H}$C=C-CH$_2$CH; 4.5-5 τ (multiplet) -CH=CH$_2$; 5.4 and 5.48 τ (doublet) >C=CH$_2$; 6.02 τ (singlet), -CH=C-C$\underline{H}_2$OH 8.36 τ (singlet) -CH=C-CH$_2$O$\underline{H}$. Khusilol did not show any UV absorption maximum, indicating absence of conjugation among the double bonds in khusilal.

Catalytic hydrogenation confirmed the presence of three double bonds in khusilal. Khusilol in alcohol medium using Adams catalyst absorbed three moles hydrogen giving hexahydrokhusilol, $C_{14}H_{26}O$ (20). Catalytic reduction of khusilol in acetic acid medium using Adams catalyst consumed 3.6 moles of hydrogen due to hydrogenolysis of the allylic hydroxyl group. In agreement with this, the hydrogenation product gave a saturated hydrocarbon hexahydrokhusilene (khusilane) $C_{14}H_{26}$ (21), IR spectrum (Fig. 4.1) and the saturated alcohol

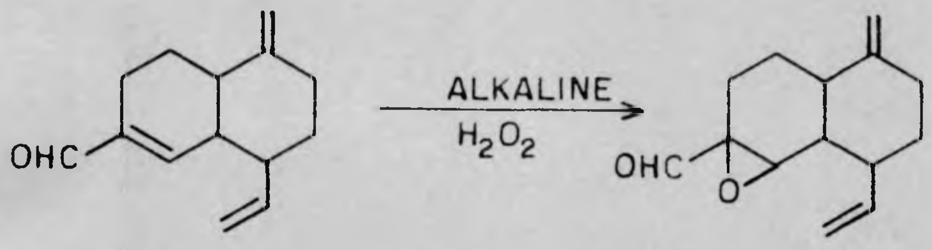


hexahydrokhusilol (20). The alcohol (20) did not show any end absorption around 210 mμ region indicating the absence of tetralkylated double bond, further supported by a negative tetranitromethane test. Neither khusilal nor khusilol showed the presence of methyl group on C.methyl determination.

Nature of oxygen function

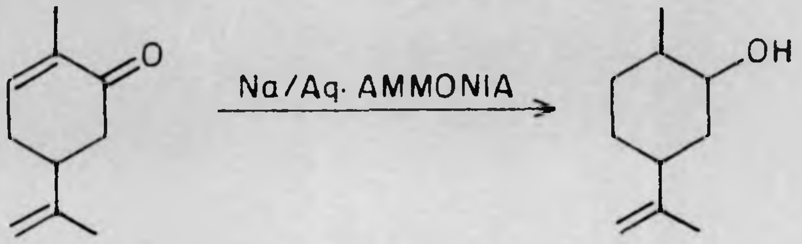
As shown by the molecular formula, $C_{14}H_{18}O$, khusilal contains one oxygen function. Its IR spectrum (Fig.4.1) shows bands at 2703 and 1678 cm-1 typical of an α,β- unsaturated aldehyde function. In confirmation with this fact khusilal gave positive tests with Fehling's solution and ammonical silver nitrate. The UV absorption spectra of khusilal ($\lambda_{max.}$ 232 mμ, ε12,320) confirmed the presence of a conjugated enone chromophore. NMR spectrum of khusilal further confirmed the aldehyde nature of the oxygen function which is in conjugation with one of the ethylenic linkages of khusilal, signal at 0.6 τ due to $(\text{-CH=}\overset{/}{\text{C}}\text{-C}\underline{\text{H}}\text{O})$.

To prove that the trisubstituted double bond is in conjugation with the aldehyde function, epoxy khusilal, $C_{14}H_{18}O_2$ (22), was prepared by treatment of khusilal with alkaline hydrogen peroxide.[14] The IR spectrum (2703 and 1724 cm-1) of the epoxy compound was characteristic of a saturated aldehyde function and lacked the characteristic UV absorption of a conjugated aldehyde. The epoxy aldehyde in its IR spectrum showed intense bands due to methylenic and vinyl double bonds while the bands ascribable to trisubstituted ethylenic linkage were absent. This fact was further confirmed by the reduction of khusilal with sodium in aqueous ammonia.



(1) (22)

In 1959, Hirro Ueda et al.[15] reported the reduction of terpenes with sodium in aqueous-ammonia. During the reduction of (-)-carvone (23) they found that the keto group and the double bond in conjugation with it are preferentially attacked, while the methylenic double bond of the isopropyl group remained uneffected affording (-)-dihydrocarveol (24).



(23) (24)

Reduction of khusilal according to this method afforded crystalline alcohol, dihydrokhusilol, $C_{14}H_{22}O$ (25), m.p. 72°, $(\alpha)_D^{24}$ - 30° and the aldehyde dihydrokhusilal, $C_{14}H_{20}O$ (26; IR bands at: 2710 and 1724 cm^{-1}; corresponding acid, $C_{14}H_{20}O_2$, 27; m.p. 101°; IR spectrum in nujol, Fig. 4.3; 2,4-dinitrophenyl hydrazone, $C_{20}H_{24}O_4N_4$, m.p. 174°). Dihydrokhusilal and dihydrokhusilol in their infrared spectra (Fig. 4.3) retained the bands due to methylenic and vinyl double bonds, the absorption due to trisubstituted double bond being absent. NMR spectrum of khusilal in further confirmation of this fact showed a signal at 3.38 τ due to the conjugated olefinic proton of the trisubstituted double bond $(-C\underline{H}=\overset{/}{C}-CHO)$.

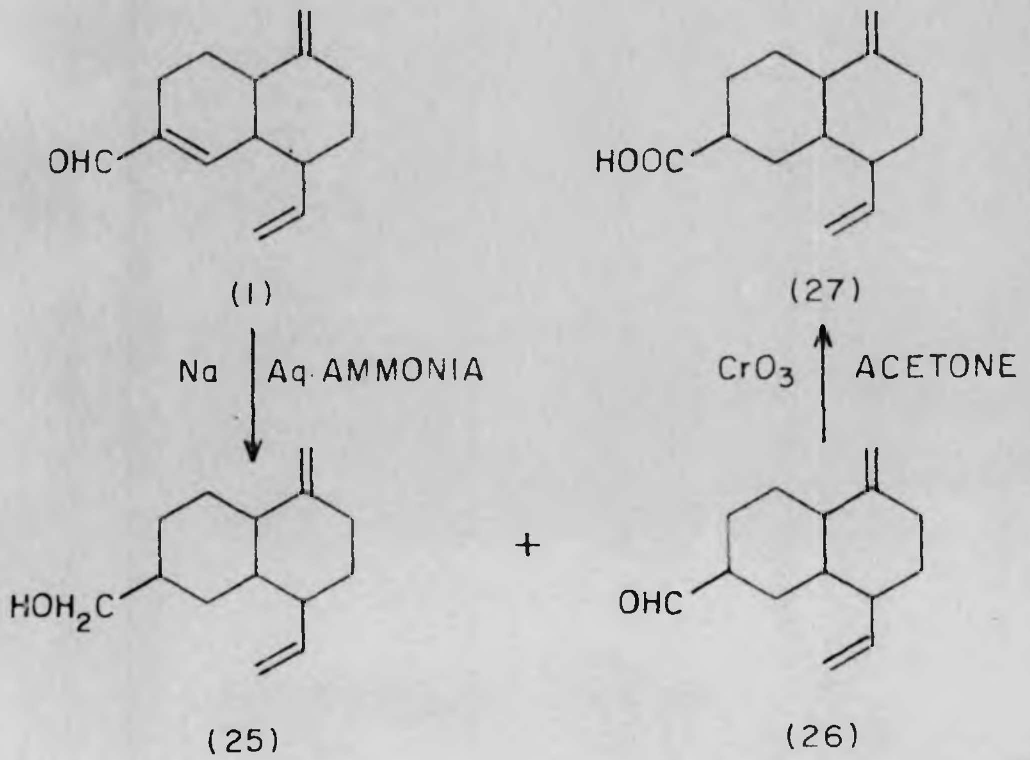
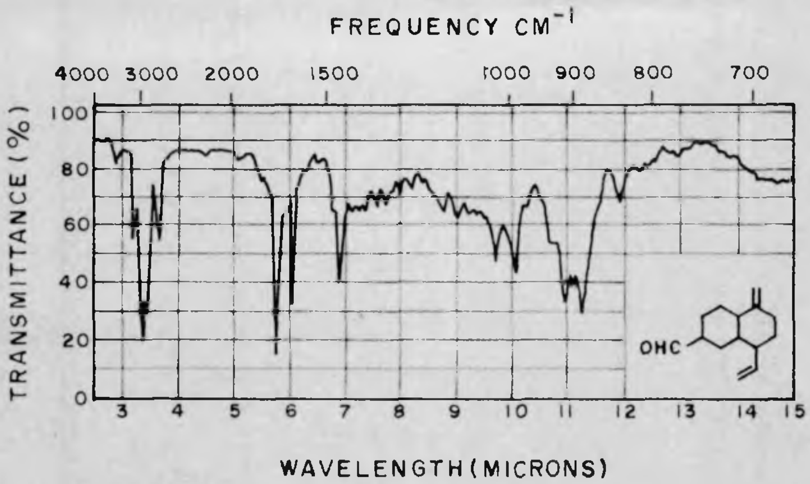
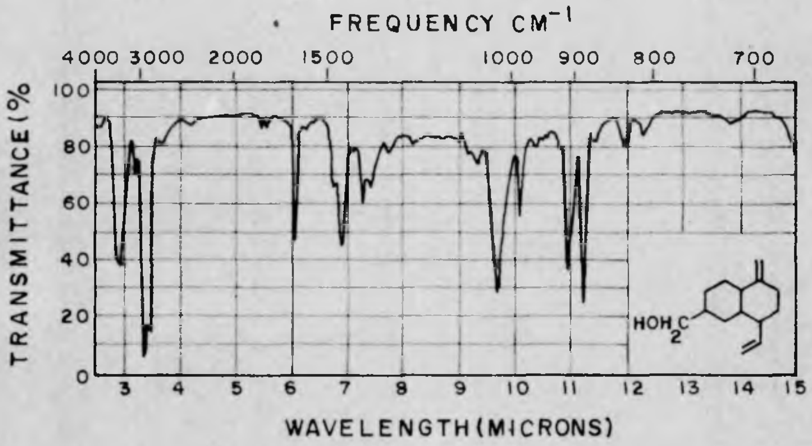


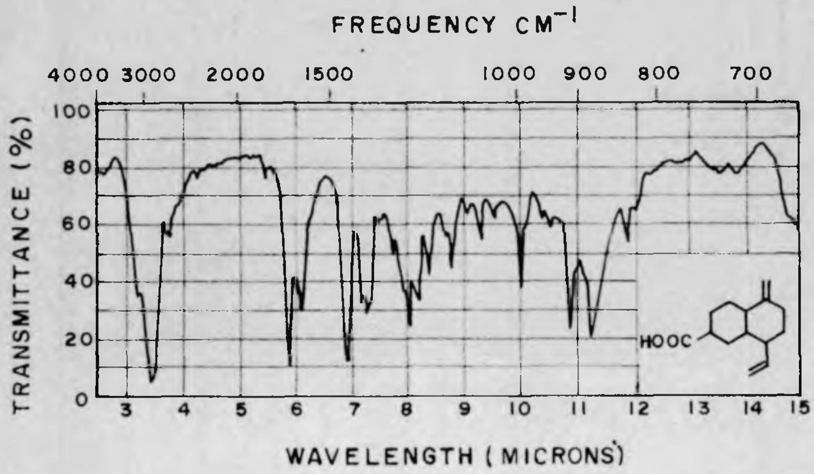
FIG.4.3



IR SPECTRUM (LIQUID FILM) OF DIHYDROKHUSILAL 26



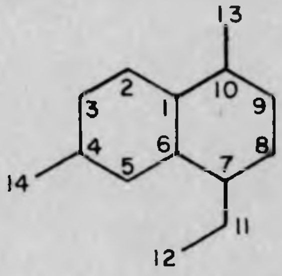
IR SPECTRUM (IN NUJOL) OF DIHYDROKHUSILOL 25



IR SPECTRUM (IN NUJOL) OF ACID 27

Nature of Carbon skeleton

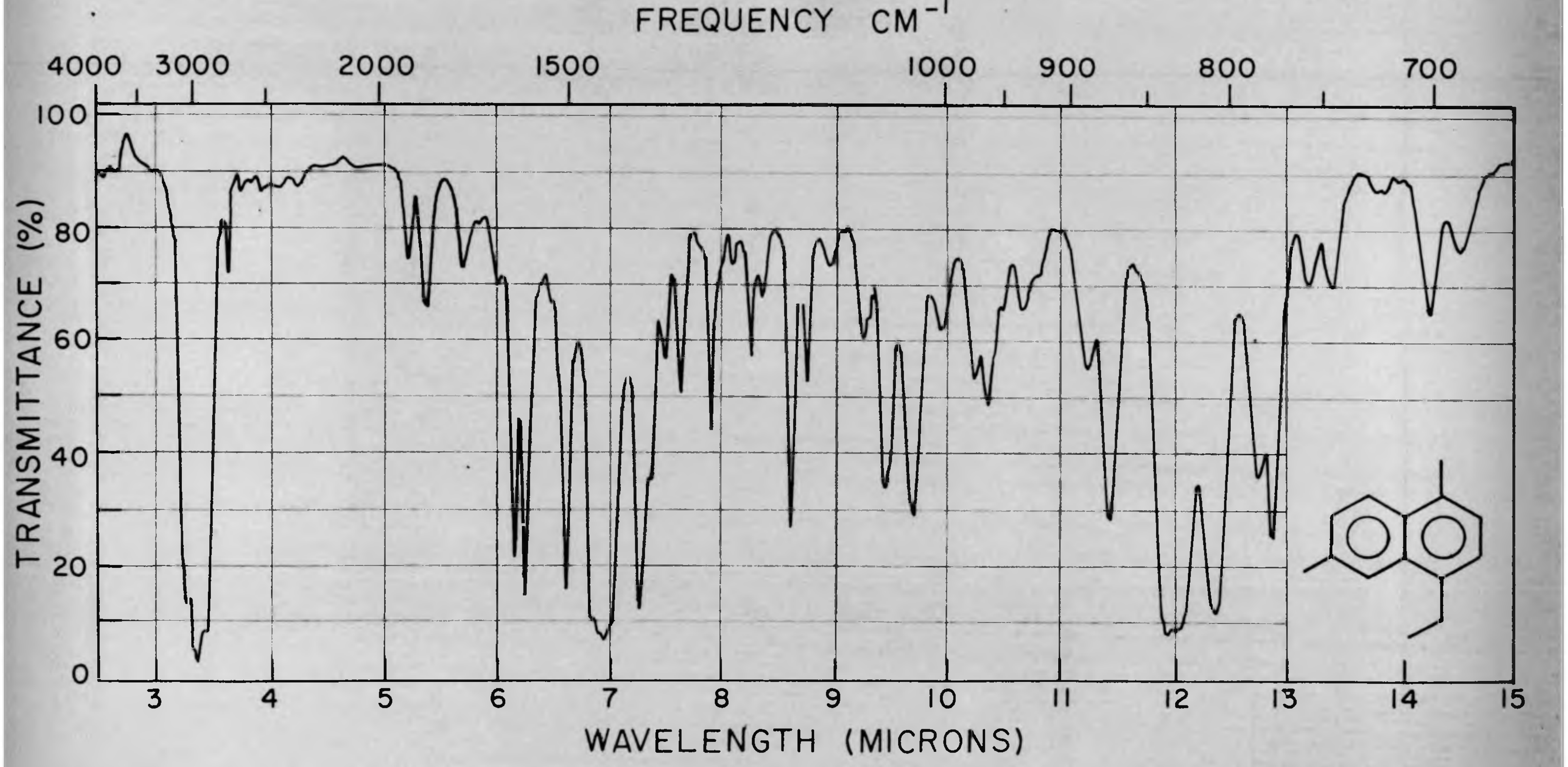
The gross structural feature of khusilal was detected by dehydrogenation experiments. Khusilol (19) on dehydrogenation with selenium at 290° in an atmosphere of nitrogen gave 1,6-dimethyl-4-ethyl naphthalene, $C_{14}H_{16}$ (28; IR spectrum Fig. 4.4) as the main product (90%, VPC) together with only a small amount of 1,6-dimethyl naphthalene (29). 1,6-Dimethyl-4-ethyl naphthalene was identified by gas chromatography with an authentic sample prepared earlier from khusol[16] (Ref. Chapter III, p.46) and by mixed m.p. of its TNB adduct with that of an authentic specimen. 1,6-Dimethyl-4-ethylnaphthalene was also obtained in high yields by the dehydrogenation of dihydrokhusilene, $C_{14}H_{22}$ (30) prepared via dihydrokhusilol(25) by tosylation and subsequent reduction with lithium aluminium hydride. This accounts for all the fourteen carbon atoms of khusilal and consequently its basic skeleton should be represented by (31).



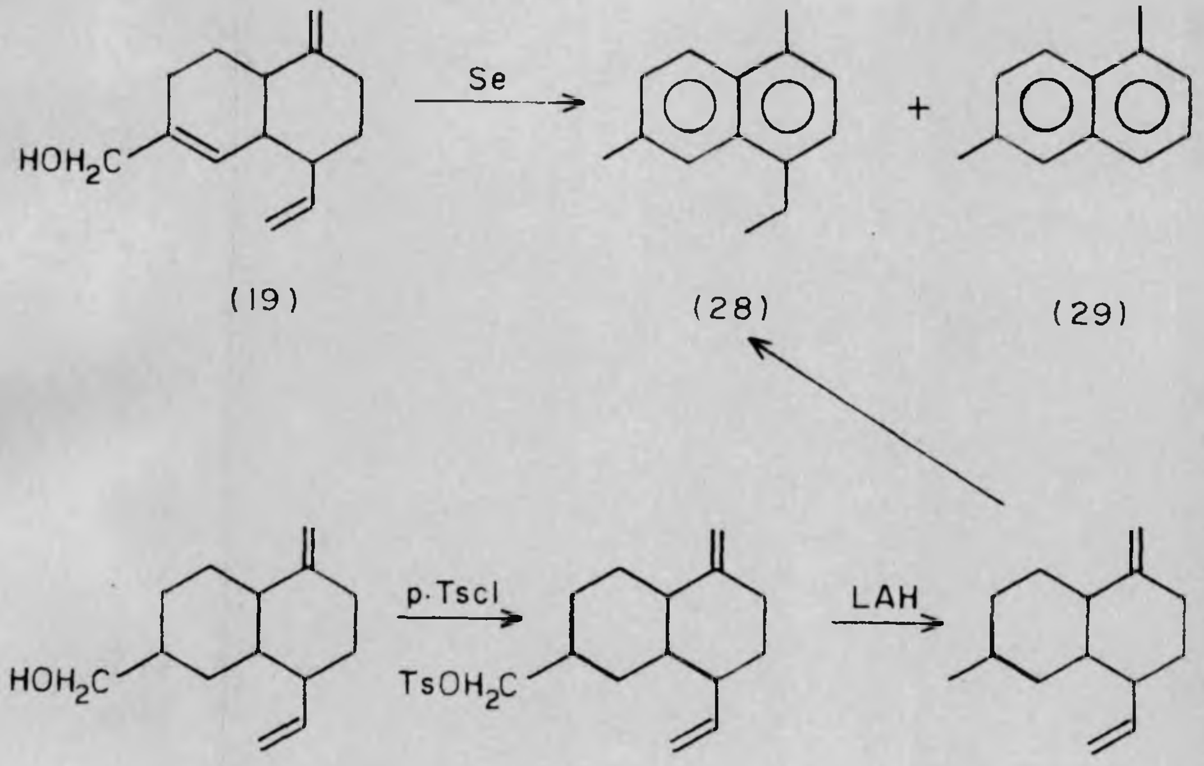
(31)

Position of unsaturation and the aldehyde function

The above results would suggest three possible structures (1, 32 and 33) for khusilal. The position of

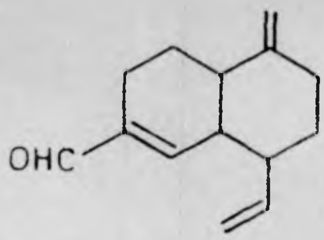


FIG·4·4 IR SPECTRUM (LIQUID FILM, 0·05 mm) OF 1,6-DIMETHYL-4-ETHYL NAPHTHALENE 2 vinyl double bond being fixed at C_{11} and C_{12}, the relative positions of the aldehydic carbonyl and exocyclic methylene group have been assigned on the basis of the formation of dehydrogenation products from the corresponding acid of khusilal.

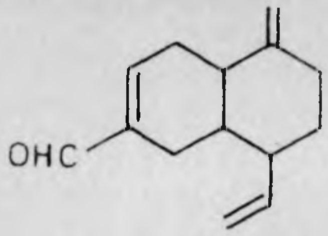


(19) (28) (29)

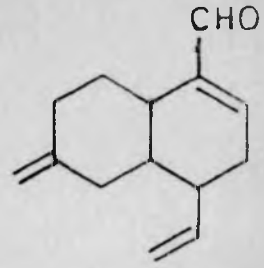
(25) (30)



(1)

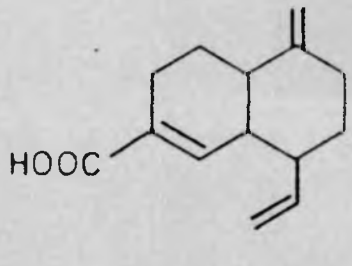


(32)



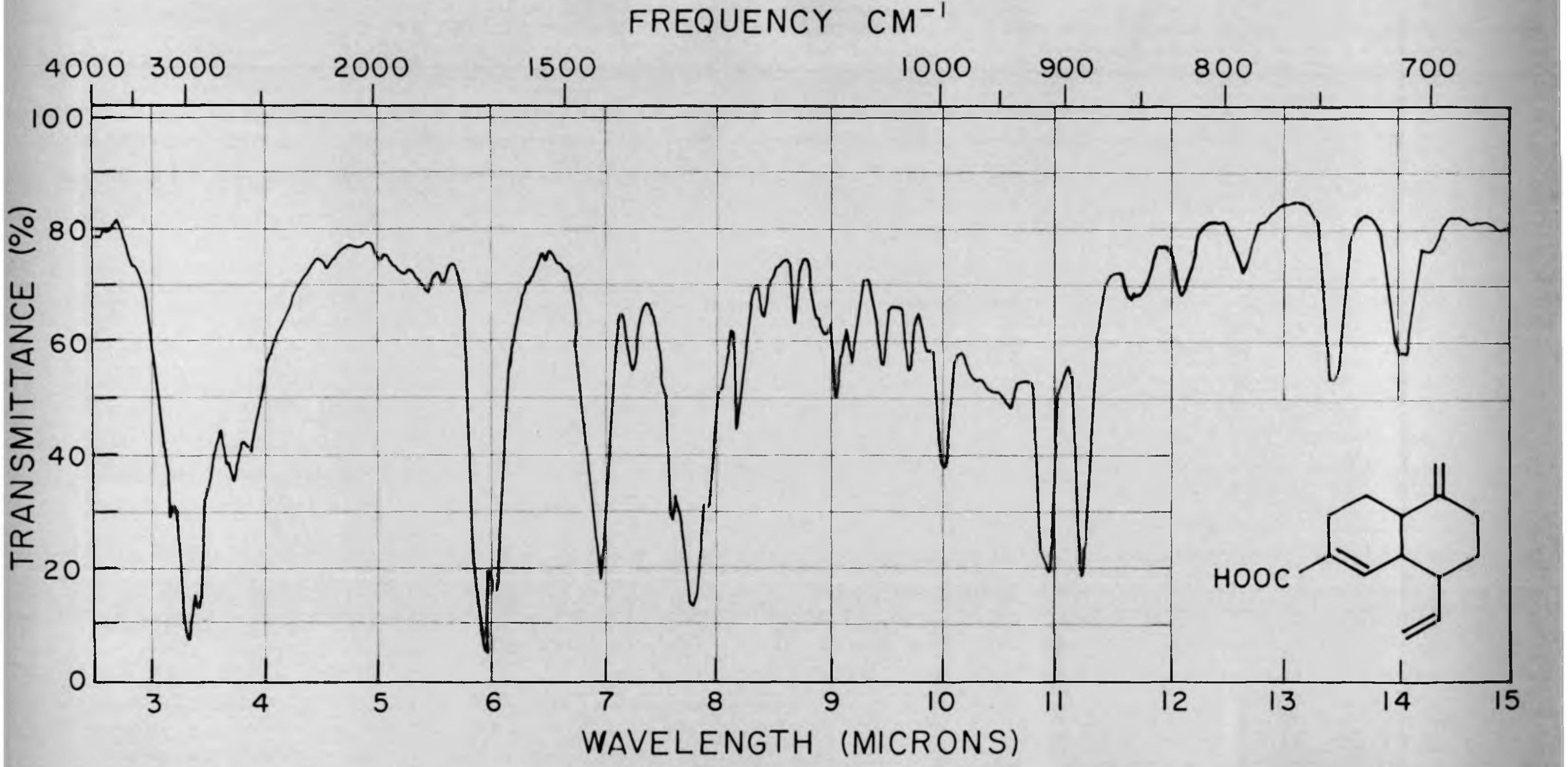
(33)

Oxidation of khusilal with alkaline silver oxide gave the corresponding crystalline α,β- unsaturated acid, $C_{14}H_{18}O_2$ (34, m.p.124°; IR spectrum Fig. 4.5; UV spectrum $\lambda_{max.}$ 215 mμ, ϵ 9,482) in low yields and this oxidation was not always reproducible. Similar observations have been recorded by other workers dealing with the oxidation of α,β- unsaturated aldehydes.

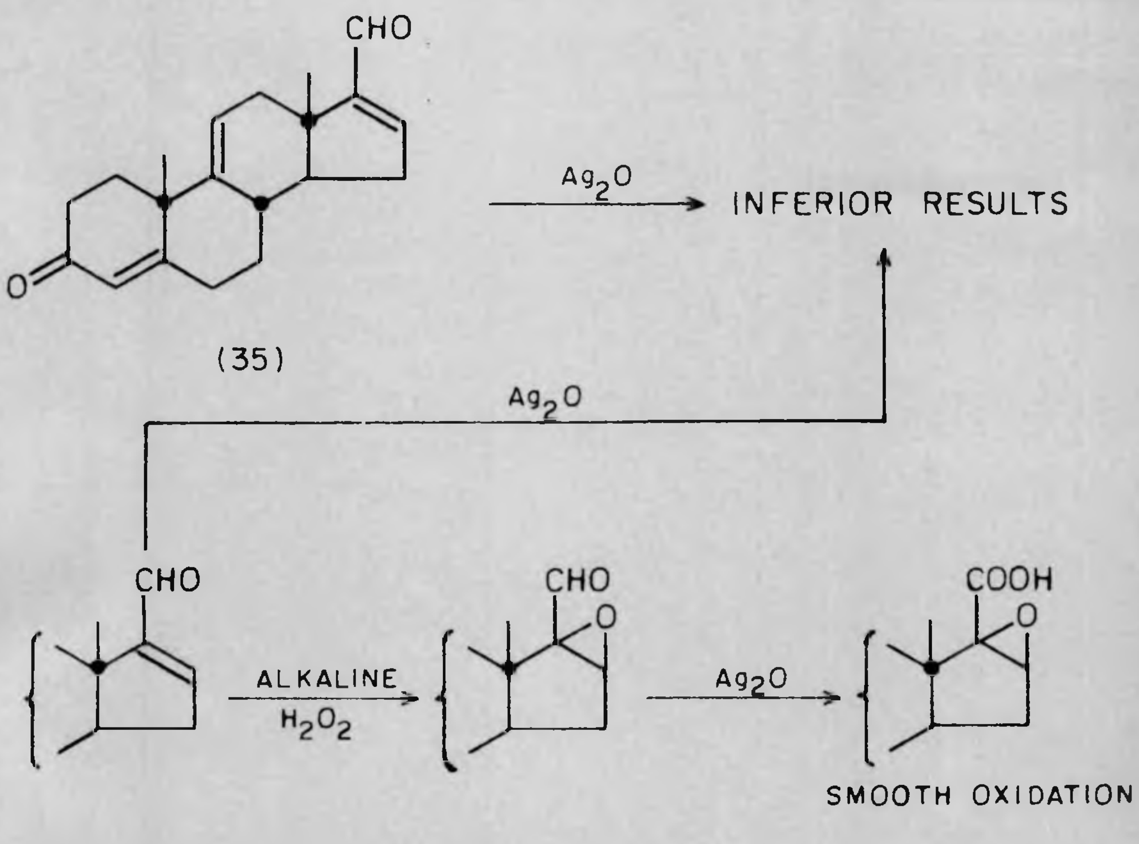


(34)

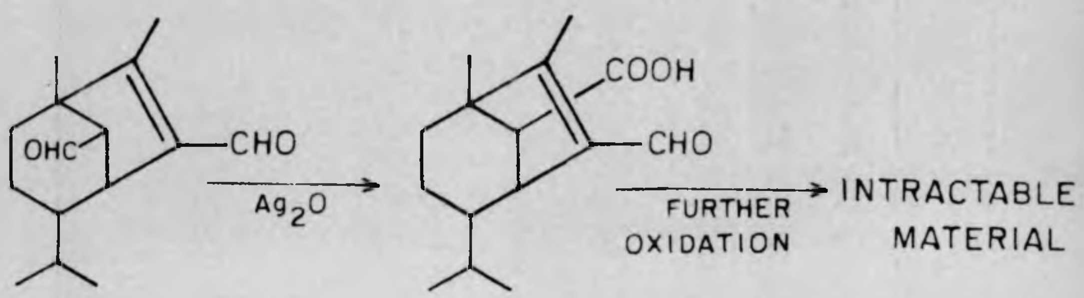
Woodward et al.[17] could not oxidise the α,β- unsaturated aldehyde (35) with neutral or alkaline silver oxide, Tollen's reagent, Fehling's solution or chromium trioxide in aqueous acetone. Similar difficulties were observed by Barkley et al.[18] during oxidation of a related α,β- unsaturated aldehyde (36) to its corresponding acid. When however conjugation was removed by preparing the corresponding epoxide (37), the epoxy acid (38) could be prepared by smooth oxidation of (37) with silver oxide. de Mayo et al. have reported the oxidation of helminthosphoral (6) with alkaline silver oxide to give the mono acid (39), without effecting the conjugated aldehyde function.[7] Their attempts for further oxidation only led them to intractable material. The open chain α,β- unsaturated aldehyde (40) has also been found



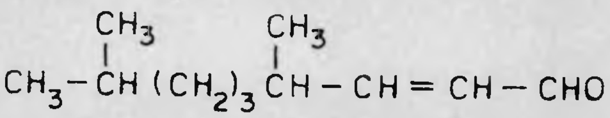
FIG·4·5 IR SPECTRUM (IN NUJOL) OF ACID 34 resistant[19] to oxidation with silver oxide, the corresponding acid has been prepared via its oxime (treatment with KOH and acidification).



(36) (37) (38)



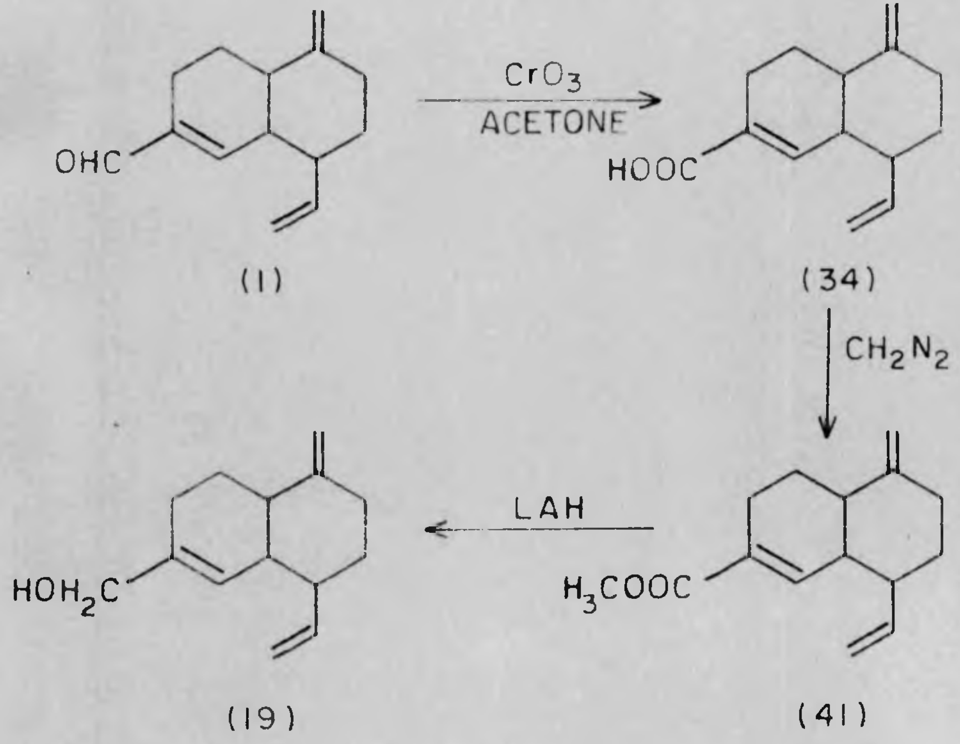
(6) (39)



$$CH_3-\overset{CH_3}{\overset{|}{C}H}(CH_2)_3\overset{CH_3}{\overset{|}{C}H}-CH=CH-CHO$$

(40)

The acid (34) in the present case could however be prepared in high yields by oxidation of khusilal with chromic acid in acetone,[20] as reported by Bladon *et al.*,[21] no attack on the double bonds was observed and the acid was identical in all respects with the acid prepared by silver oxide oxidation of khusilal. Its methyl ester, $C_{15}H_{20}O_2$ (41; IR spectrum Fig. 4.6; $\lambda_{max.}$ 217 mμ, ϵ 10,500) could be reconverted to the crystalline alcohol khusilol (19), on reduction with lithium aluminium hydride.



The crystalline acid on dehydrogenation with selenium gave two main dehydrogenation products, 1-methyl 4-ethyl naphthalene (42) and 1,6-dimethyl-4-

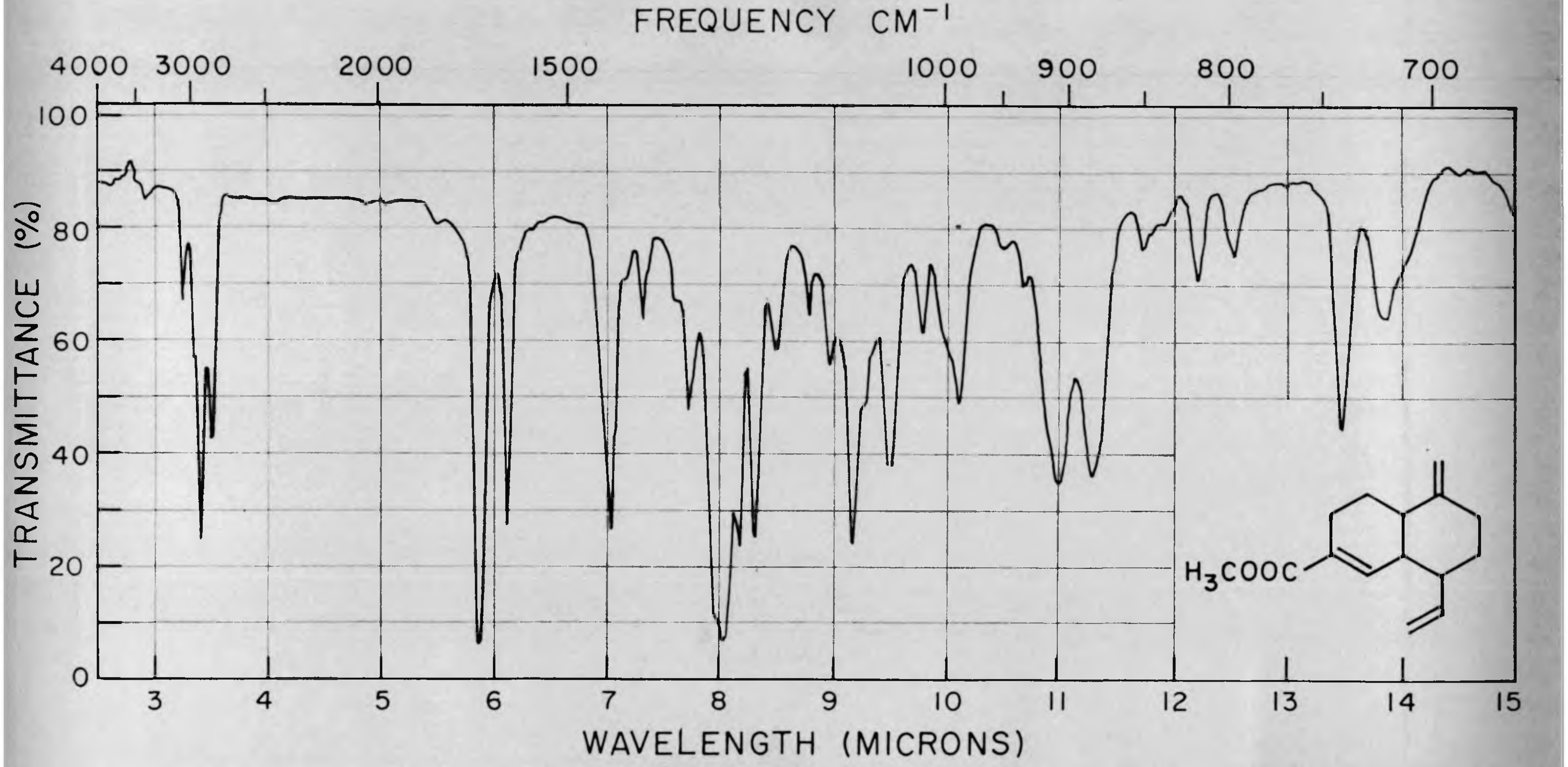
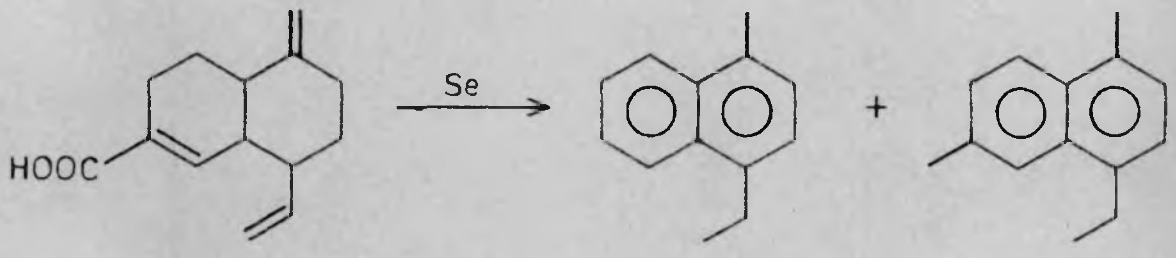


FIG.4.6 IR SPECTRUM (LIQUID FILM) OF METHYL ESTER 41

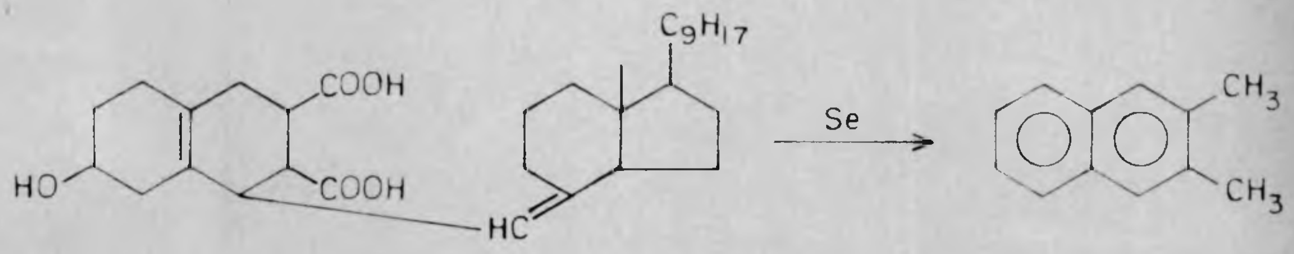
ethyl naphthalene (28) in the ratio (3:2) (on the basis of VPC with authentic samples). The formation of 1-methyl-4-ethyl naphthalene (42) on dehydrogenation of the acid (34) shows that the aldehyde group in khusilal is present at position 4 of structure (31), which eliminates structure (33) for consideration.



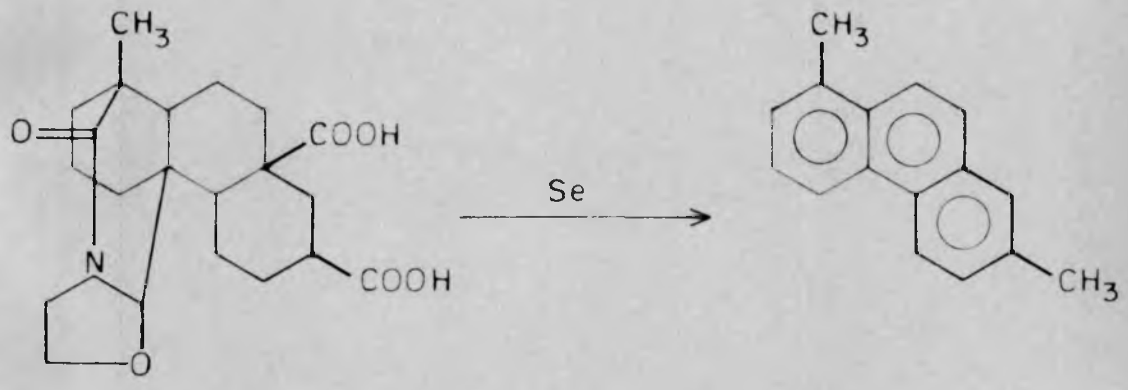
(34) (42) (28)

Production of 1,6-dimethyl-4-ethyl naphthalene (28) indicates that its 4-methyl group is formed by the reduction of the carboxyl group at that position by the reducing medium of selenium dehydrogenation. Reduction of carboxyl to methyl groups under such conditions has already been recorded. Windaus *et al.*[22] obtained 2,3-dimethyl naphthalene (44) by the dehydrogenation of (43) with selenium. Wiesner *et al.*[23] were able to show convincingly that during dehydrogenation one of the carboxyls of oxoveatchine (45) is in fact a precursor of a methyl group in pimanthrene (46).

During the dehydrogenation of the acid (34), khusilol (19), and dihydrokhusilene (30), in addition to the other products reported, 1,6-dimethyl naphthalene (29) in small amounts was invariably formed in each case, evidently due to the loss of ethyl group from the system during aromatisation. A number of cases mentioned in



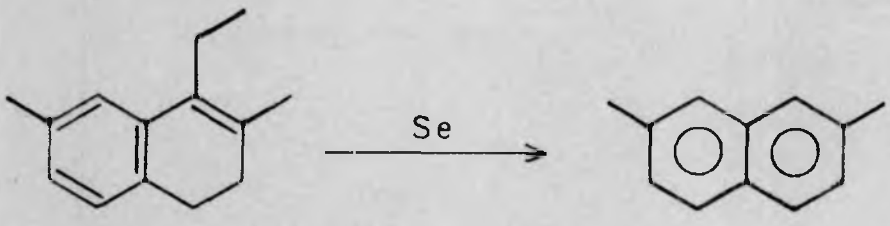
(43) (44)



(45) (46)

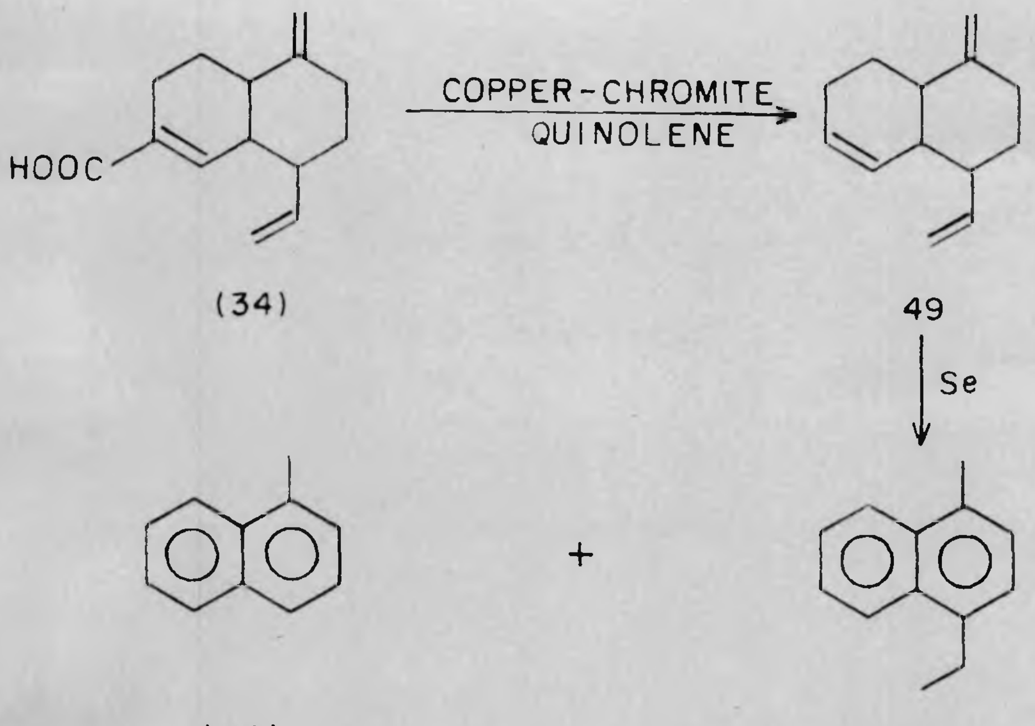
literature show that non-angular alkyl groups get eliminated during aromatisation reactions.[24,25] Ruzicka <u>et al</u>.[25] showed that 1, ethyl-3,4-dihydro-2,7-dimethyl naphthalene (47) during treatment with selenium at 300° is partly converted to 2,7-dimethyl naphthalene(48).

Loss of non-angular ethyl groups from naphthalenic systems when dehydrogenated with selenium have been described by Cocker et al.[25]

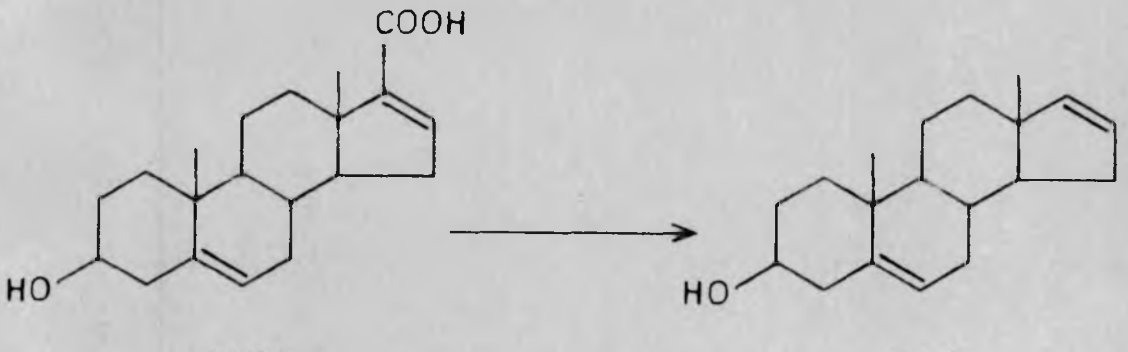


(47) (48)

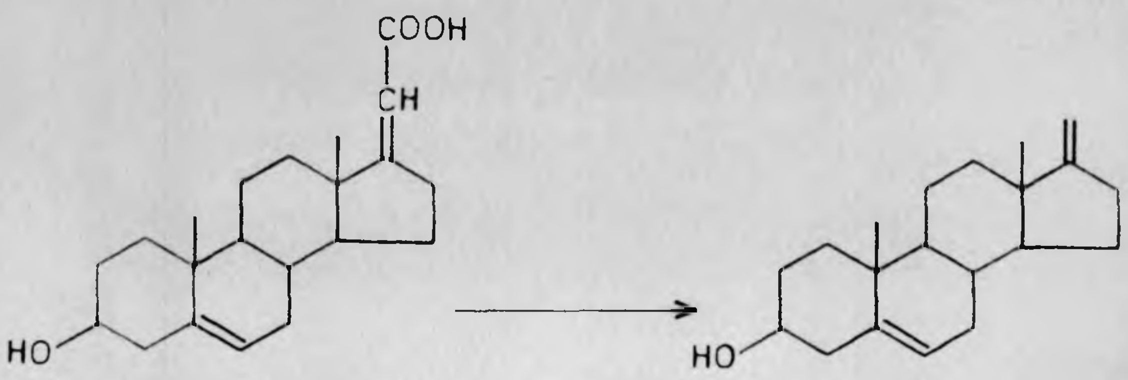
Hydrocarbon (49) was prepared in a state of 80% purity (VPC analysis) by the decarboxylation of the acid (34) by the method of Rosenkranz et al.[26] Infrared spectrum of this hydrocarbon showed the presence of aromatic impurities. Rosenkranz et al. have reported the decarboxylation of the α,β-unsaturated acid (50) in boiling quinoline in the presence of copper chromite catalyst. The compound (51) was obtained in 70% yield without any rearrangement during this decarboxylation similarly the unsaturated acid (52) yielded the expected compound (53) on decarboxylation. The hydrocarbon (49) on dehydrogenation with selenium at 290° gave the expected 1-methyl-4-ethyl naphthalene (42, 60%) and partly lost the ethyl group in the process to yield in addition 1-methyl naphthalene (54, 25%) as well (on the basis of VPC analysis with authentic samples).



(34) 49 (54) (42)

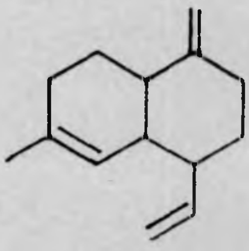


(50) (51)

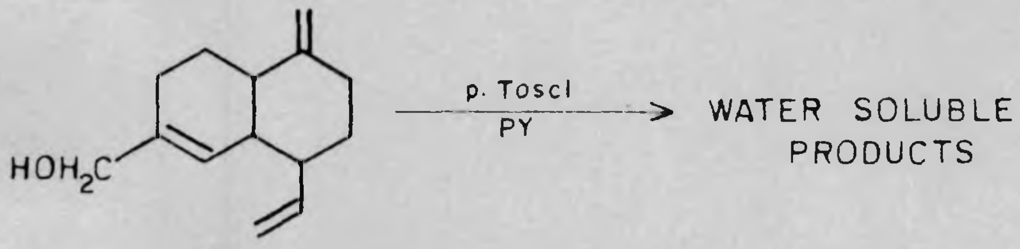


(52) (53)

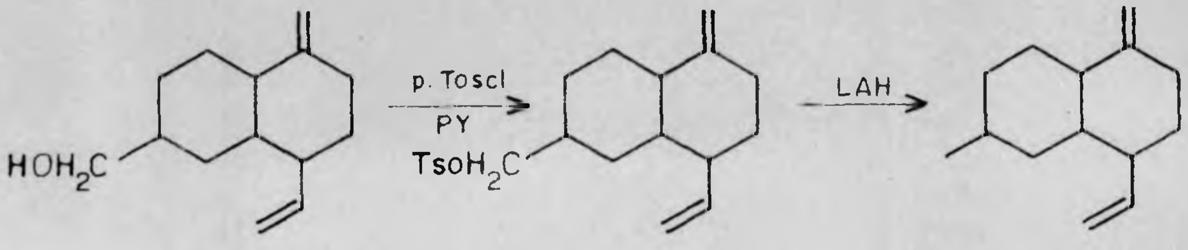
To prepare the parent hydrocarbon khusilene (55), khusilol (19) was tosylated at room temperature. It is interesting to note that after working up as usual, neither the tosylate nor the starting material could be isolated, but only water soluble products were formed. Similar behaviour has been observed with several other primary allylic alcohols in our laboratory. The dihydrokhusilol (25), however, can be converted to its corresponding tosyl derivative (IR spectrum, Fig. 4.7) in quantitative yields which on reduction with lithium aluminium hydride gave the hydrocarbon dihydrokhusilene, $C_{14}H_{22}$ (30; IR spectrum Fig. 4.7) in a pure form (VPC). Subsequently semicarbazone of khusilal was



(55)

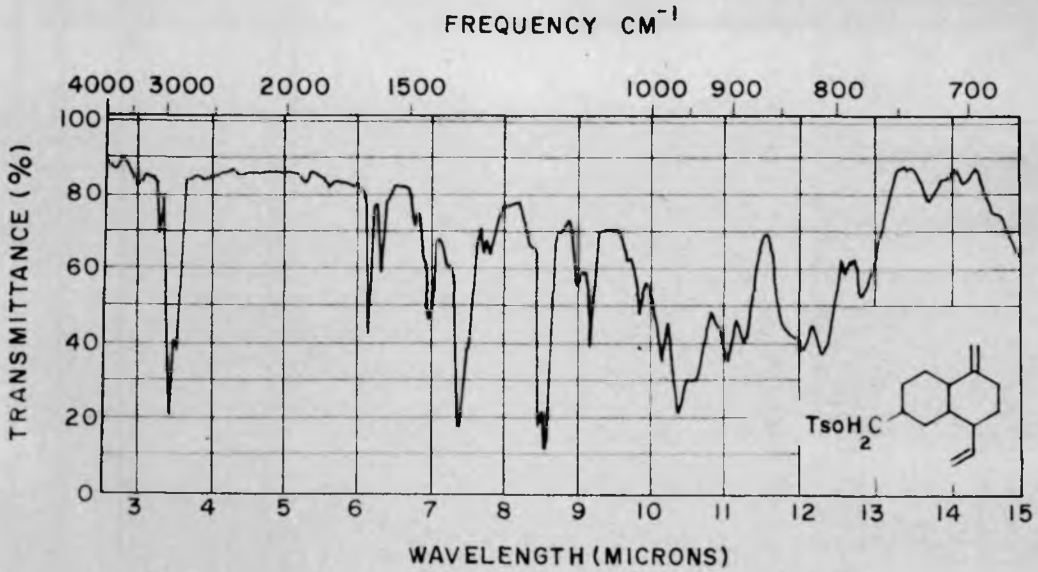


(19)

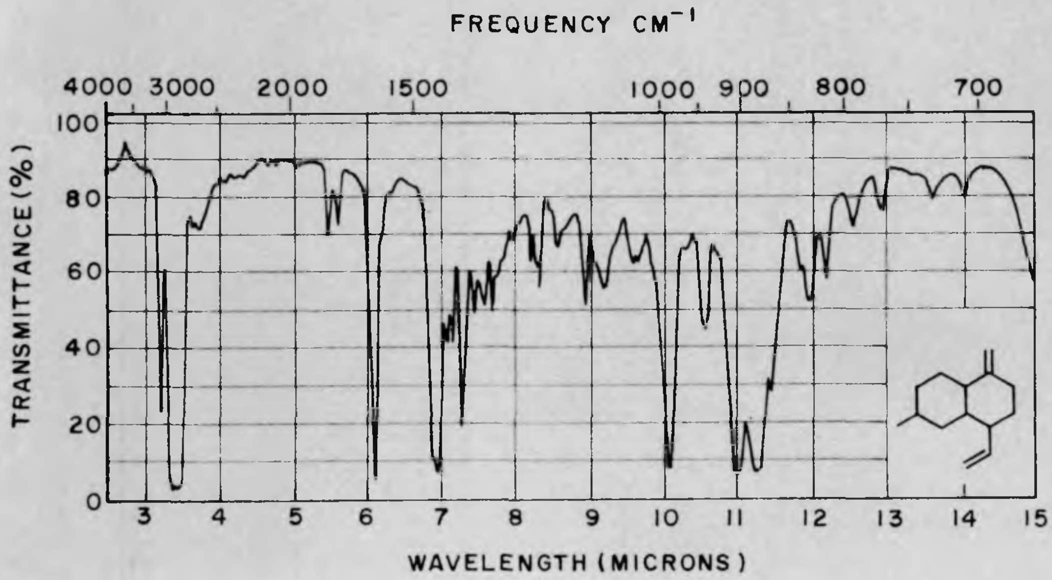


(25) (30)

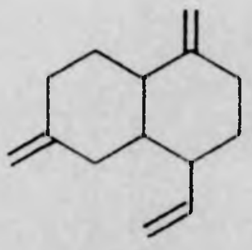
FIG. 4·7



IR SPECTRUM (LIQUID FILM) OF TOSYL DERIVATIVE OF DIHYDROKHUSILAL



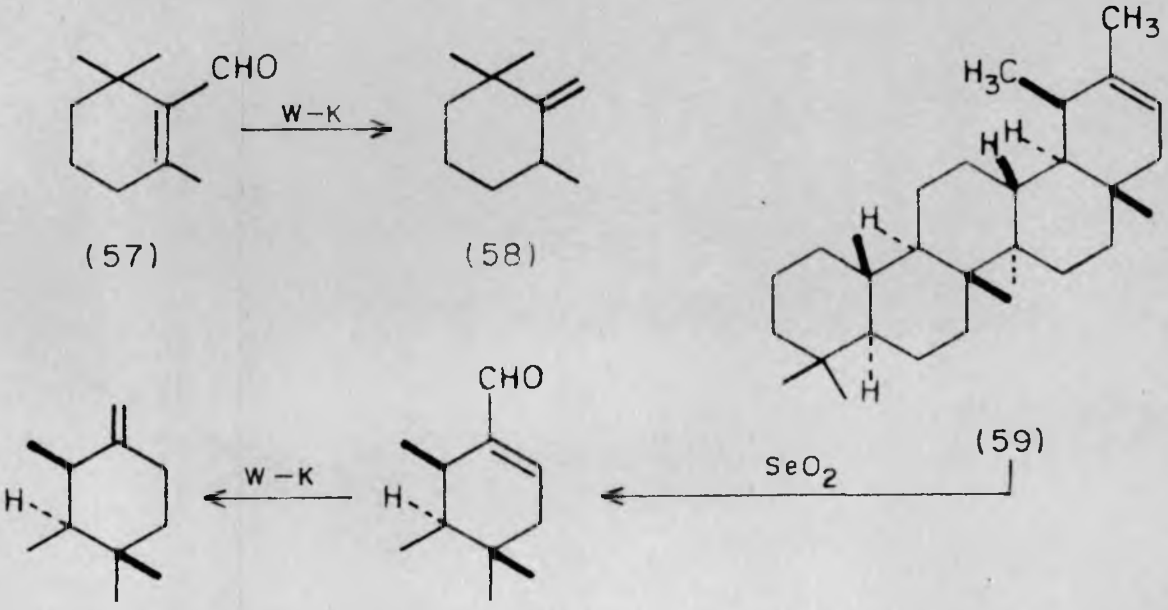
IR SPECTRUM (LIQUID FILM, 0·05 mm) OF DIHYDROKHUSILENE 30



(56)

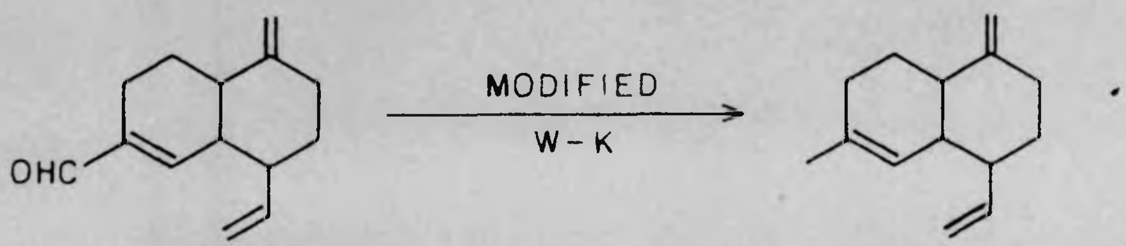
subjected to Wolff-Kishner reduction and the hydrocarbon (56) was obtained with expected double bond shift.[27-29] IR spectrum of this hydrocarbon (56) lacked the absorptions due to trisubstituted double bond. NMR spectrum showed signals at: 4.17 to 5.32τ (multiplet) due to $-CH=CH_2$; 5.48τ(singlet) due to two $>C=CH_2$ groups.

Lardelli and Jeger[27] had studied the Wolff-Kishner reduction of α,β-unsaturated aldehydes and ketones and found that the reduction is frequently accompanied by the shift in the position of double bond. Particular mention may be made of the reduction of β-cyclocitral (57) which gives the hydrocarbon (58). Wolff-Kishner reduction of the α,β- unsaturated aldehyde (60) prepared by the selenium dioxide oxidation of lupene-1 (59) is also accompanied by the double bond shift[27,28] to afford the hydrocarbon (61).



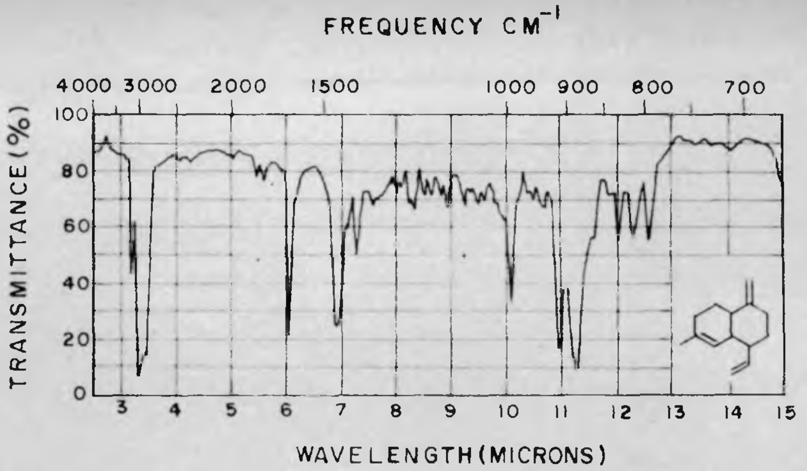
(57) (58) (59) (60) (61)

In a recent communication Grundon et al.[29] have shown that at lower temperatures potassium t-butoxide in toluene or dimethyl sulphoxide promotes the normal Wolff-Kishner reduction. This modified procedure when applied to the semicarbazone of khusilal gave the expected hydrocarbon khusilene, $C_{14}H_{20}$ (55; IR spectrum, Fig. 4.8). To ascertain the position of the trisubstituted double bond in khusilal, khusilene was converted to its monoepoxide (62) which on reduction with lithium aluminium hydride afforded a secondary alcohol[30] $C_{14}H_{22}O$ (63; IR spectrum Fig. 4.8). Reduction of the latter with palladium-charcoal in ethanol gave the corresponding tetrahydro derivative $C_{14}H_{26}O$ (64) which on oxidation furnished the ketone $C_{14}H_{24}O$ (65). The IR spectrum of this ketone (Fig. 4.8) showed an intense band at 1706 cm^{-1} for the carbonyl function on a six-membered ring, absorption in the vicinity of 1420 cm^{-1} due to a $-CO-CH_2$ - grouping being absent. This established structure (1) for khusilal.

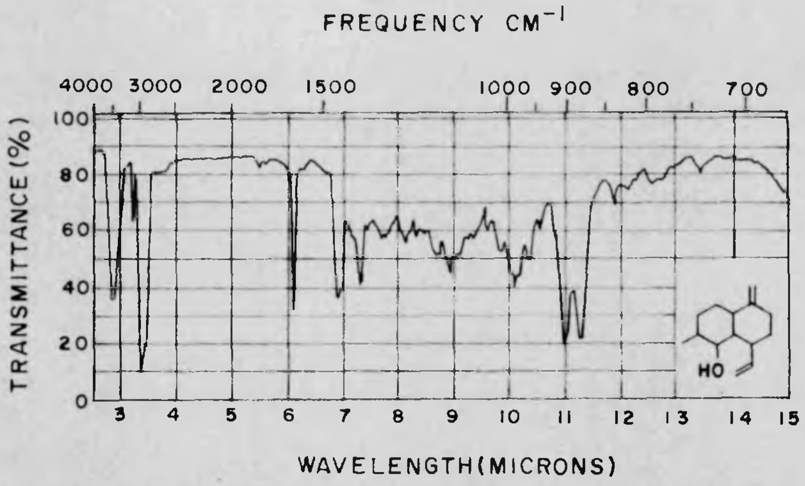


(1) (55)

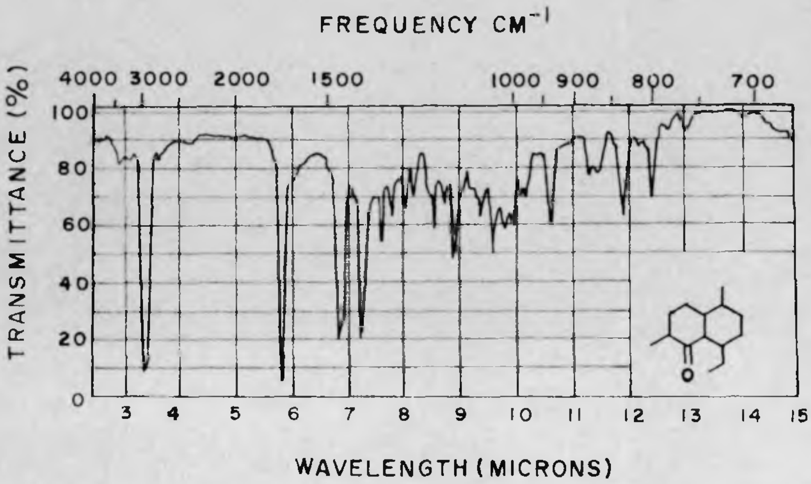
FIG·4·8



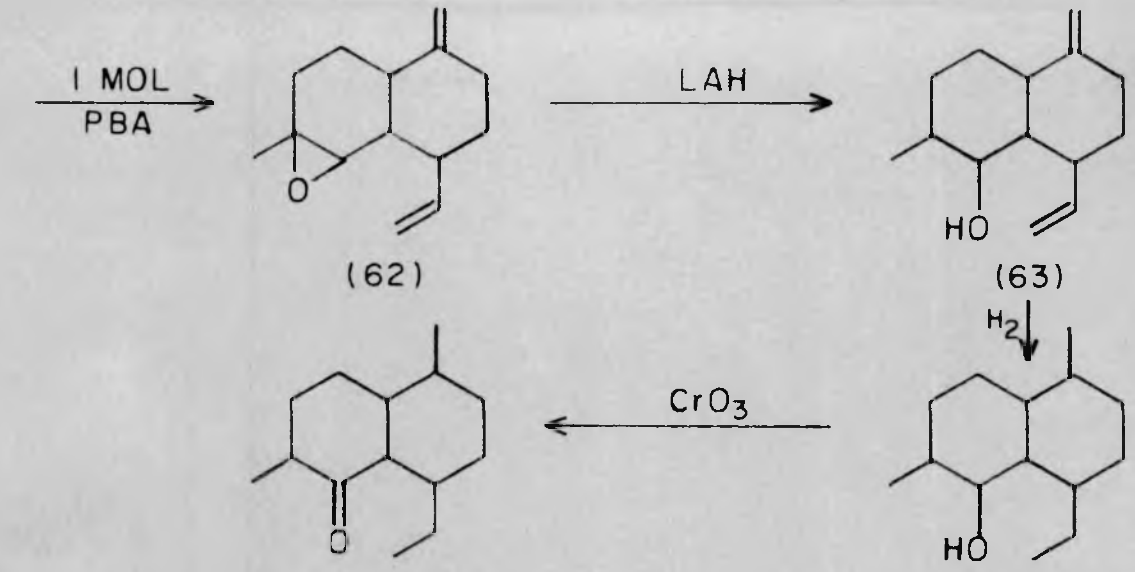
IR SPECTRUM (LIQUID FILM) OF KHUSILENE 55



IR SPECTRUM (LIQUID FILM) OF ALCOHOL 63

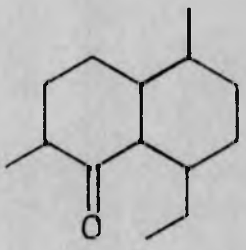


IR SPECTRUM (LIQUID FILM) OF KETONE 65

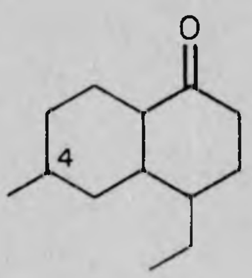


(62) (63) (65) (64)

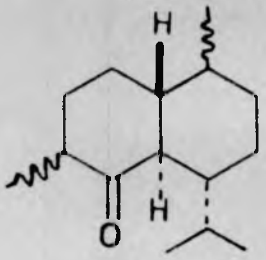
The stereochemistry of khusilal at ring juncture has been established on the basis of the ORD curves of the ketones (65) and (66) and their comparative study with the corresponding ketones (67) and (68) respectively.



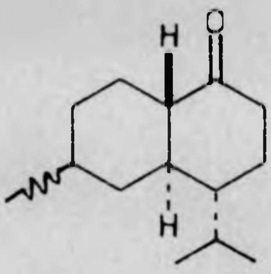
(65)



(66)

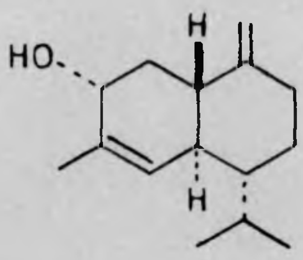


(67)

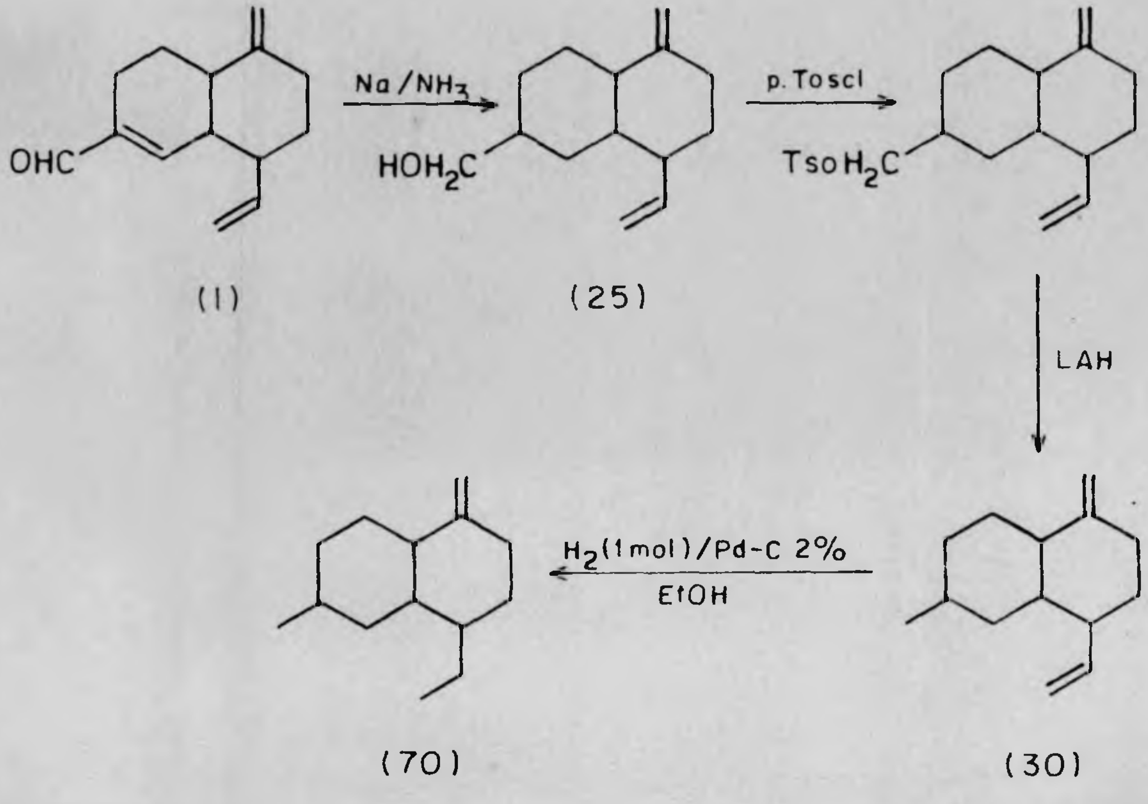


(68)

The ketones (67) and (68) have been prepared[31] from khusinol (69) of known absolute configuration. The ketone (66) was prepared from khusilal in the following way. Dihydrokhusilene (30) was hydrogenated in the presence of 2% palladium-charcoal catalyst and ethanol. The hydrogenation was stopped after the absorption of one mole of hydrogen to give the hydrocarbon, $C_{14}H_{24}$ (70). IR spectrum (Fig. 4.9) of this hydrocarbon showed the complete absence of absorption bands due to the vinyl double bond and showed strong absorption bands due to the presence of methylenic double bond.



(69)



The hydrocarbon (70) was oxidised with osmium tetroxide to the diol, $C_{14}H_{26}O_2$ (71); m.p. 130°; IR spectrum (Fig. 4.9). This diol on oxidation with lead tetracetate afforded the ketone, $C_{13}H_{22}O$ (66; semicarbazone, $C_{14}H_{25}ON_3$, m.p. 195°) which was also obtained by the ozonolysis of the hydrocarbon (70).

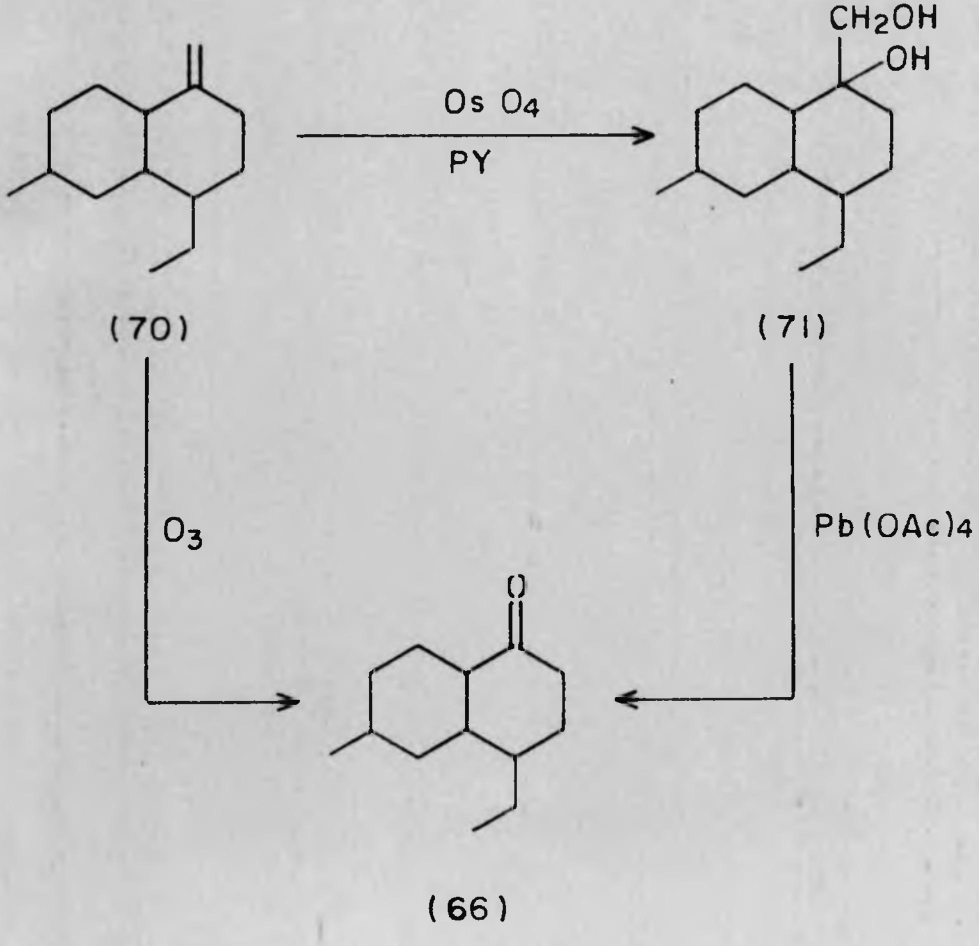
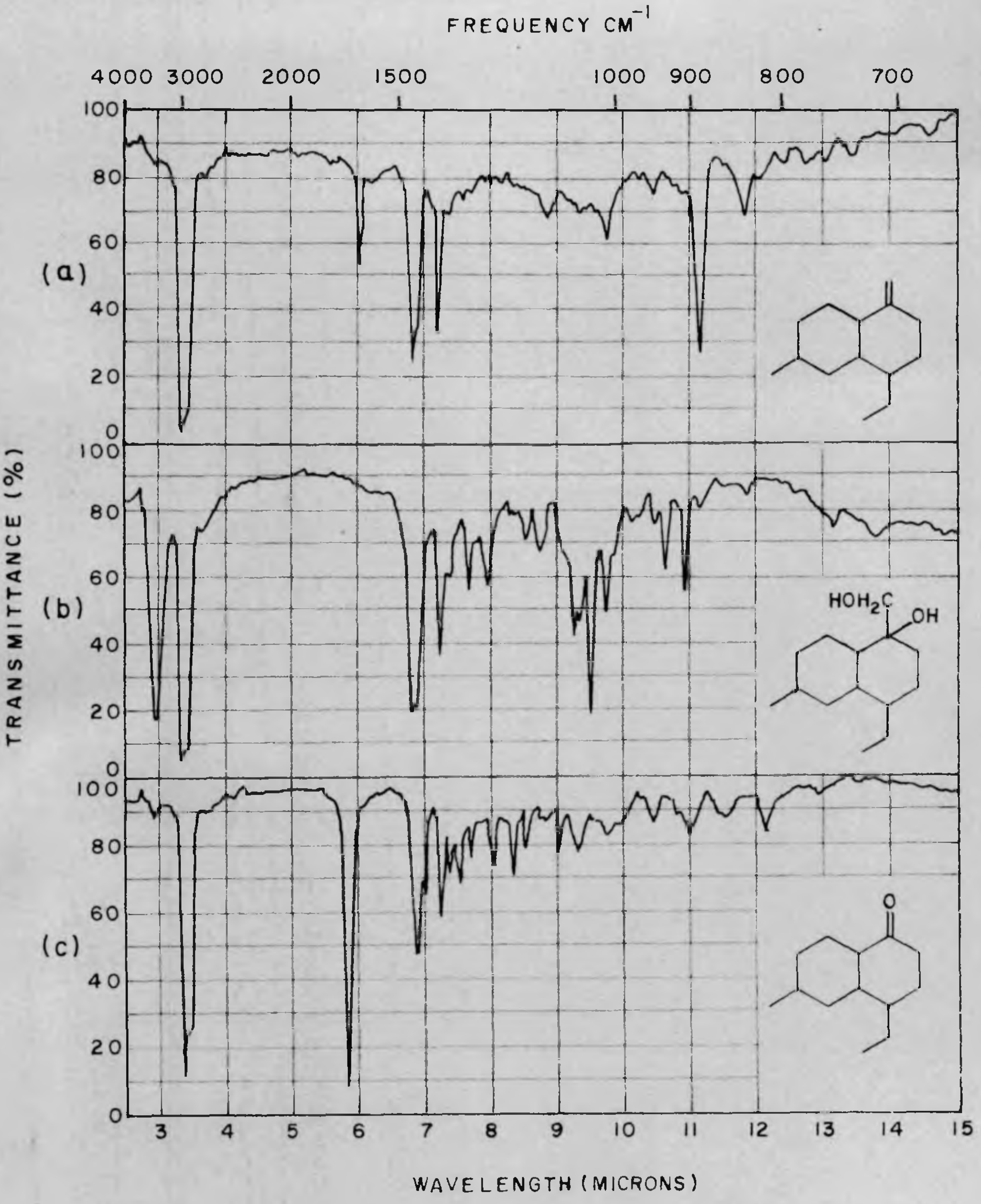


FIG. 4·9



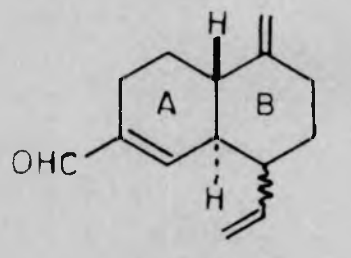
(a) IR SPECTRUM (LIQUID FILM) OF HYDROCARBON 70

(b) IR SPECTRUM (IN NUJOL) OF DIOL 71

(c) IR SPECTRUM (LIQUID FILM) OF KETONE 66

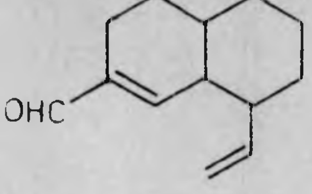
IR spectrum of the ketone (66) (Fig. 4.9) showed an intense band at 1712 cm^{-1} due to the carbonyl function on a six-membered ring and a band at 1429 cm^{-1} showed the presence of -CO-CH$_2$- grouping.

Ketone (66) showed a +ve cotton effect at 301 mμ which can be compared with the +ve cotton effect of the related ketone (68) (Fig.4.10) having the hydrogen atom, at C_1 to be β-oriented. The ketone (65) showed a -ve cotton effect indicating that hydrogen atom at C_6 is α-oriented, since a similar -ve cotton effect has been observed in the known ketone (67) (Fig. 4.11). Hence the A and B rings of khusilal are trans-fused and the partial stereochemistry of the molecule can be represented by (72).

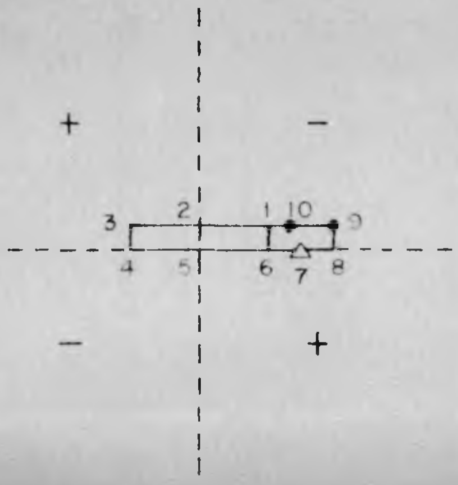


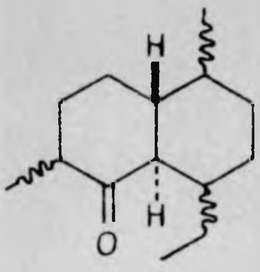
(72)

Application of octant rule further confirms the structure of khusilal as shown in (1), since the derived ketone (65) shows the expected -ve cotton effect.



(1)





(65)

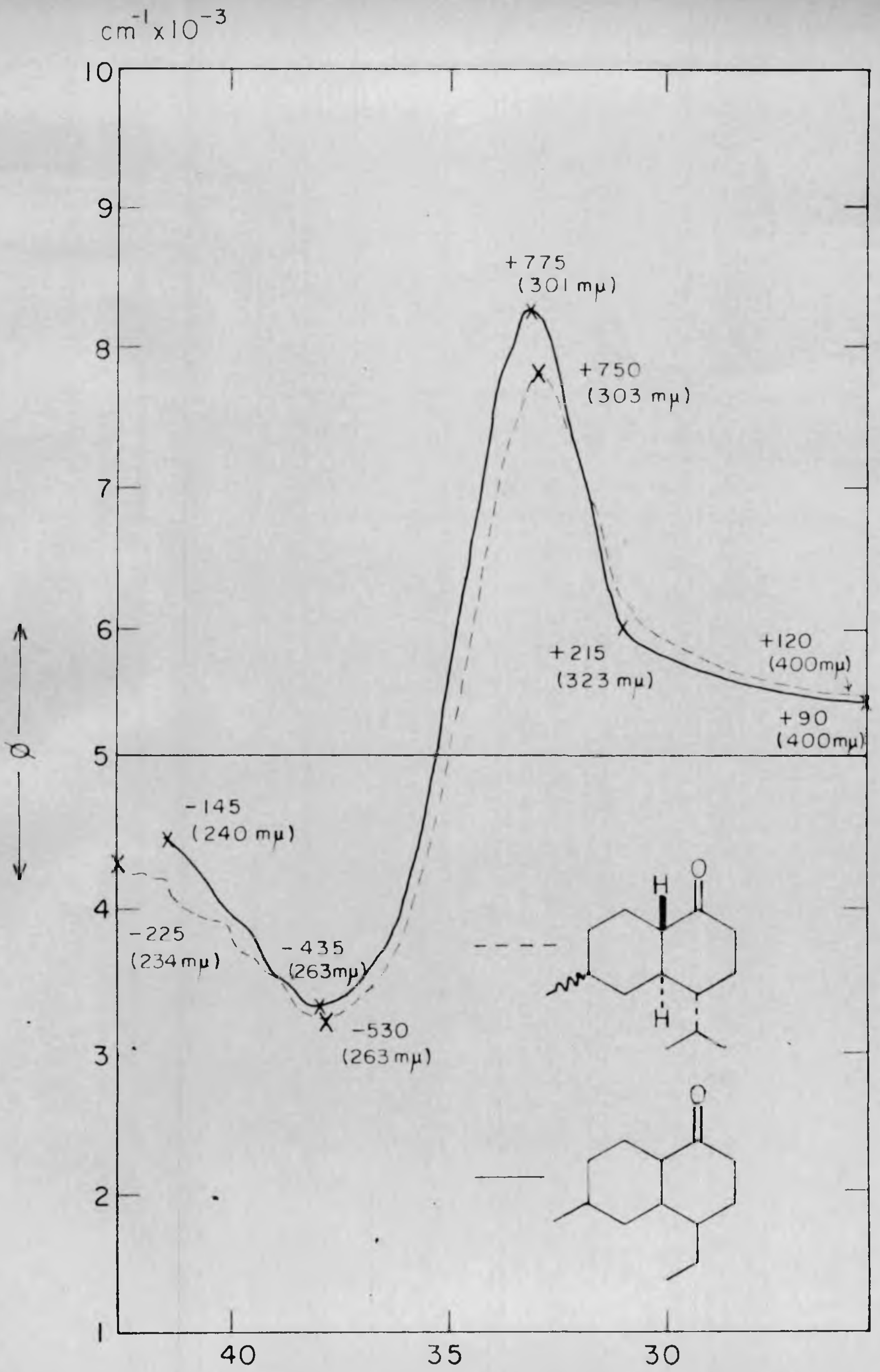

cm⁻¹x10⁻³
10
9
8
7
6
5
4
3
2
1
ϕ
40
35
30
+775
(301 mμ)
+750
(303 mμ)
+215
(323 mμ)
+120
(400mμ)
+90
(400mμ)
-145
(240 mμ)
-225
(234mμ)
-435
(263mμ)
-530
(263mμ)
H
O
H
O

FIG. 4·10

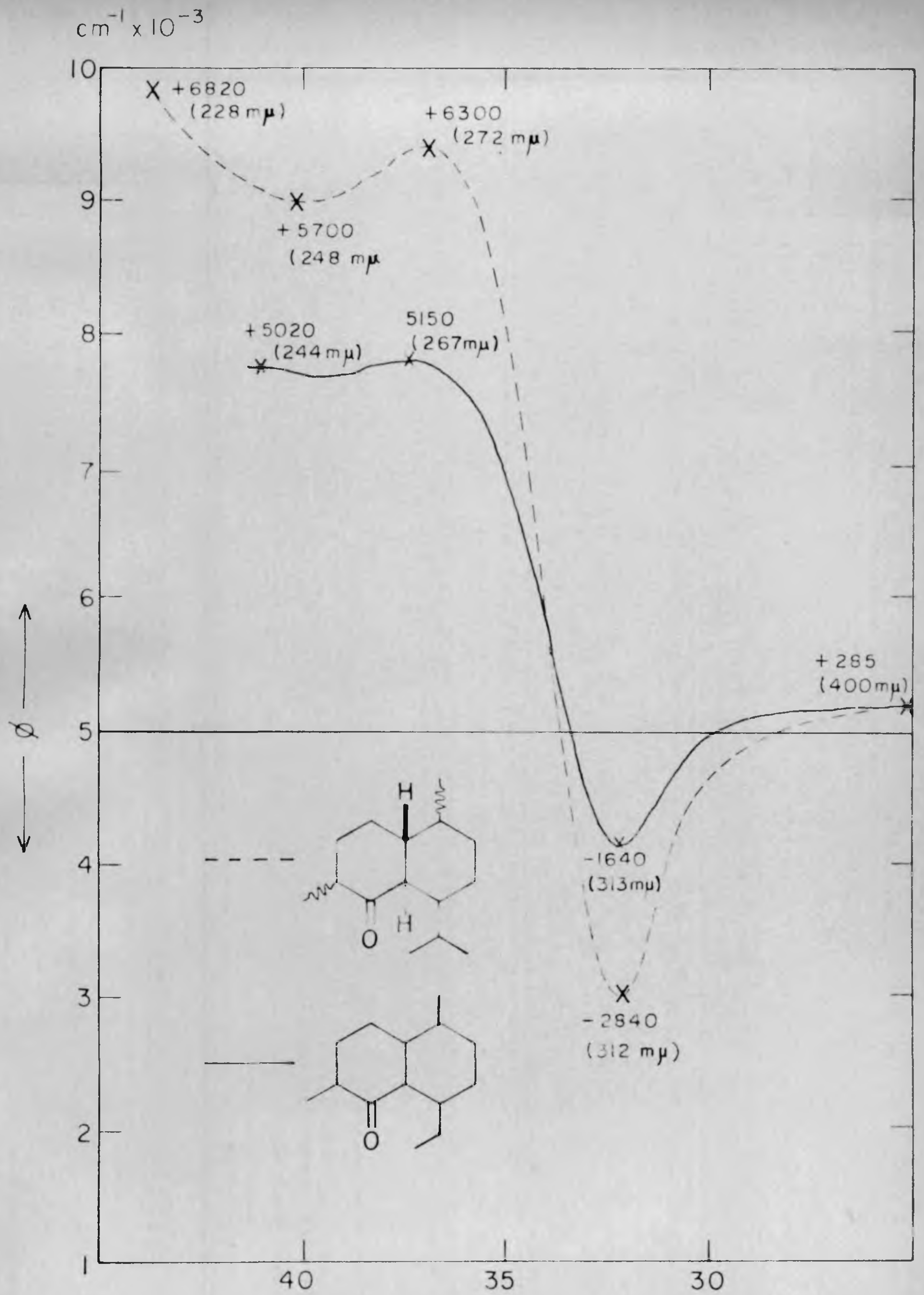
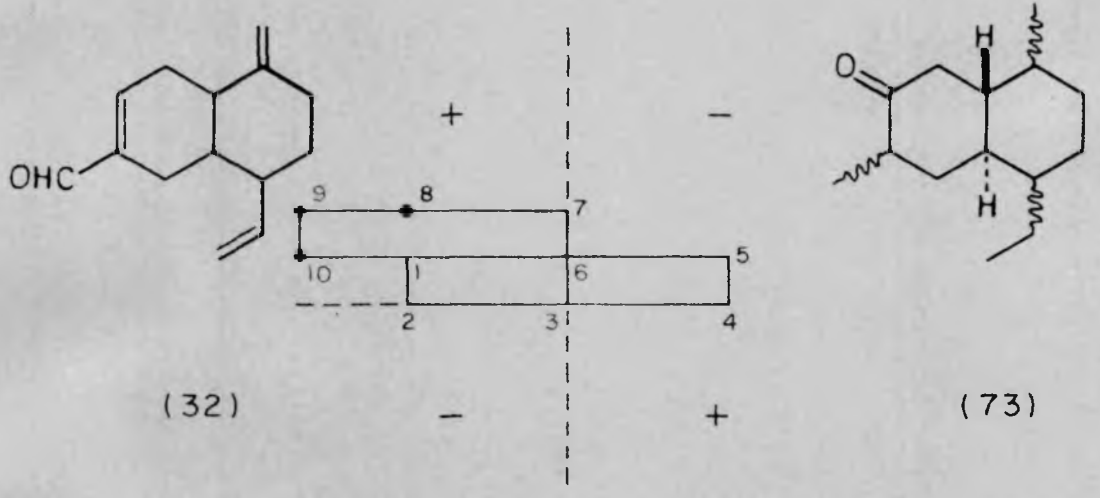

cm^{-1} x 10^{-3}
10
9
8
7
6
5
4
3
2
1
40
35
30
φ
+6820 (228 mμ)
+5700 (248 mμ
+6300 (272 mμ)
+5020 (244mμ)
5150 (267mμ)
+285 (400mμ)
-1640 (313mμ)
-2840 (312 mμ)
H
H
O
O

FIG. 4·11

Structure (32) for khusilal is ruled out on the basis of octant rule since the derived ketone (73) would have instead shown a +ve cotton effect (provided other asymmetric centres C_1 and C_6 do not change, irrespective of the orientation of the C_4 methyl group).



(32)

(73)

EXPERIMENTAL

Khusilal had b.p. 115°(bath)/0.3 mm., $(\alpha)^{25}_{D}$ - 261°, (c, 9.7), n^{25}_{D} 1.5349 (Found: C, 83.18; H, 9.04. $C_{14}H_{18}O$ requires: C, 83.12; H, 8.97%). It shows a single peak on VPC analysis.

Neutralisation equivalent of its crystalline acid, $C_{14}H_{18}O_2$ (34) (Found: 219. Calc: 218.28). IR spectrum (Fig. 4.1) bands at: 2703, 1678, 3060, 1634, 892, 1818, 995, 918, 840, 810, 785 and 704 cm-1. UV spectrum: $\lambda_{max.}$ 232 mμ, ϵ 13,320. NMR spectrum (Fig. 4.2). Signals at: 0.6 τ (singlet) $-CH=C-\acute{C}\,\underline{H}O$, 3.38 τ (singlet) $-C\underline{H}=\acute{C}-CHO$, 4.5 - 4.9 τ (multiplet) $-CH=CH_2$, 5.25 and 5.35 τ (doublet) $>C=CH_2$.

Oxime of khusilal

Khusilal (1 g) was refluxed for 1/2 hr with a mixture of pyridine (1 ml), ethanol (12 ml, 95%) and hydroxylamine hydrochloride (0.5 g) It was crystallised from pet.ether to furnish white plates, m.p. 101-102° (Found: N, 6.73; $C_{14}H_{19}ON$ requires N, 6.45%). UV spectrum: $\lambda_{max.}$ 235 mμ, ϵ 18,270.

2,4-Dinitrophenylhydrazone of khusilal

To a hot solution of khusilal (0.5 g) in ethanol (15 ml) a solution of 2,4-dinitrophenylhydrazine in ethanol acetic acid mixture was added. The solution, after heating on a water bath for 10 min. was cooled and the derivative crystallised from ethanol-chloroform mixture in the form of deep red leaflets, m.p. 214° (Found: N, 14.17. $C_{20}H_{22}O_4N_4$ requires: N, 14.65%). UV spectrum: $\lambda_{max.}^{CHCl_3}$ 378 mμ, ε 20,000.

<u>Khusilol</u> (19).

A solution of khusilal (5 g) in dry ether (50 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (1.5 g) in dry ether (500 ml). The mixture was stirred at room temperature for 10 hr. under reflux and then the excess of reagent was decomposed by addition of water (30 ml) followed by cold dilute hydrochloric acid. After extraction with ether the product crystallised from pet.ether as long, white, silky needles (4.8 g), m.p. 75°, $(\alpha)_D^{26}$ - 158° (c, 2) (Found: C, 82.45; H, 9.97. $C_{14}H_{20}O$ requires: C, 82.30; H, 9.87%).

IR spectrum in nujol (Fig. 4.1) bands at: 3400, 3088, 1639, 1042, 990, 917, 885, 833 and 795 cm-1. No characteristic UV absorption. NMR spectrum (Fig. 4.2) signals at: 4.32 τ (singlet) $-\underline{H}\ C{=}\overset{\diagup}{C}{-}CH_2OH$, 4.5-5 τ (multiplet) $-CH{=}CH_2$, 5.4 and 5.48 τ (doublet) $>C{=}CH_2$, 6.02 τ (singlet) $-CH{=}\overset{\diagup}{C}{-}C\ \underline{H_2}OH$, 8.36 τ (singlet) $-CH{=}\overset{\diagup}{C}{-}CH_2O\underline{H}$.

Hexahydrokhusilol (20) and hexahydrokhusilene (21).

(i) A solution of khusilol (19, 1.1 g) in acetic acid (50 ml) was hydrogenated in presence of pre-reduced Adams catalyst (140 mg). Hydrogen absorbed (512 ml at 31° and 716 mm, 18 hr) corresponded to 3.6 moles hydrogen. Catalyst was filtered off and acetic acid was removed in vacuo on a steam bath. The residue was chromatographed over alumina (grade II, 40 g) and eluted with pet.ether (150 ml) to yield the hydrocarbon hexahydrokhusilene (21, 0.59 g), b.p. 103°(bath)/3 mm., $(\alpha)_D^{30}$ + 44° (c, 3), n_D^{30} 1.4761. (Found: C, 86.2; H, 13.8. $C_{14}H_{26}$ requires: C, 86.51; H, 13.49%). IR spectrum in liquid cell 0.1 mm (Fig. 4.1). NMR spectrum signals at: 9.01, 9.11 and 9.2 τ (overlapping) two $-CH-CH_3$ groups and one $-CH_2-CH_3$ group. Ether eluted the alcohol hexahydrokhusilol (20, 0.38 g), b.p.130°(bath)/ 0.9 mm., $(\alpha)_D^{27}$ + 44° (c, 1.4), n_D^{27} 1.4965. (Found: C, 80.09; H, 12.41. $C_{14}H_{26}O$ requires: C, 79.93; H, 12.46%). UV spectrum: no end absorption around 210 mμ; no colouration with tetranitromethane.

(ii) A solution of khusilol (0.6 g) in ethanol(20 ml) was hydrogenated in the presence of Adams catalyst (10 mg). The hydrogen absorbed (231 ml at 24° and 712 mm, 16 hr) corresponded to 3 moles hydrogen. The product (0.55 g) was identical with hexahydrokhusilol (20).

Epoxy khusilal (22)

To a solution of khusilal (1 g) in methanol(65 ml) at 0-5^{o} was added a solution of 4 N sodium hydroxide (2 ml) and hydrogen peroxide (4 ml, 30%). The mixture was then kept at 5^{o} for 16 hr. The mixture was poured into water (250 ml) and the epoxide isolated by chloroform extraction. Chloroform layer was washed repeatedly with water and dried. Solvent was evaporated and the product chromatographed over alumina (grade III, 30 g) and eluted with pet.ether:benzene (1:2) to yield the epoxide (0.6 g), b.p.130^{o}(bath)/0.8 mm. (Found: C, 77.18; H, 8.66. $C_{14}H_{18}O_2$ requires: C, 77.03; H, 8.31%). IR bands at: 3096, 2703 (w), 1724, 1639, 990, 915, 890 and 842 cm-1; no characteristic UV absorption.

Dihydrokhusilol (25) and dihydrokhusilal (26)

To a mixture of khusilal (8 g) in benzene (20 ml) and aqueous ammonia (20 ml, d 0.8) at -2^{o} was added sodium (7 g) in the form of a thin wire in small portions with stirring. During the addition the temp. was kept below 0^{o} in an ice-salt bath. After the addition of half of the sodium in 1 hr., additional amounts of benzene (15 ml) and aqueous ammonia (30 ml) were added. After all the sodium had been added in 2 hr. stirring was continued for another 2 hr. The organic phase was extracted with ether (300 ml) and washed with cold dilute hydrochloric acid (5%) and then with water till free from acid. It was dried and on evaporation of the solvent, the product (8 g) was isolated. It was chromatographed over alumina (grade II, 320 g). (i) Elution of the column with pet. ether-benzene (1:1, 300 ml) gave (1 g) dihydrokhusilal (26), b.p.110°(bath)/0.5 mm. (Found: C, 82.24; H, 9.47. $C_{14}H_{20}O$ requires: C, 82.30; H, 9.87%). IR spectrum (Fig. 4.3) bands at: 3095, 2710, 1724, 1642, 998, 915, and 892 cm-1; no UV absorption.

2,4-Dinitrophenylhydrazone of dihydrokhusilal.

It was crystallised from ethanol-chloroform mixture in the form of deep yellow leaflets, m.p. 174° (Found: N, 14.50. $C_{20}H_{24}O_4N_4$ requires: N, 14.58%).

Acid (27)

It was prepared by the oxidation of dihydrokhusilal with chromic acid in acetone, crystallised from pet.ether, m.p. 101° (Found: C, 76.47; H, 9.20. $C_{14}H_{20}O_2$ requires: C, 76.32; H, 9.15%). IR spectrum in nujol (Fig. 4.3) bands at: 3077, 1706, 1639, 1000, 917 and 892 cm-1.

(ii) Elution with ether (400 ml) gave the alcohol, dihydrokhusilol (25) (6.5 g), b.p.132°(bath)/0.25 mm., n_D^{30} 1.5180, $(\alpha)_D^{30}$ - 30° (c, 1.3) (Found: C, 81.72; H, 10.73. $C_{14}H_{22}O$ requires: C, 81.50; H, 10.75%). This fraction solidified on standing at room temp. and was crystallised from pet.ether to yield white silky needles, m.p. 72°. IR spectrum in nujol (Fig. 4.3) bands at: 3400, 3088, 1639, 1031, 990, 910 and 890 cm-1.

Dehydrogenation of khusilol with Se.

Khusilol (0.4 g) was mixed with selenium (0.8 g) and heated in nitrogen atm. at 290° for 18 hr. The product in pet.ether was chromatographed over alumina (grade I, 20 g). The pet.ether eluate (0.23 g) on VPC analysis showed the presence of 1,6-dimethyl-4-ethylnaphthalene (28) to the extent of 90% with small amounts of 1,6-dimethyl-naphthalene (29). 1,6-Dimethyl-4-ethyl-naphthalene was isolated from the mixture in a pure form via its TNB derivative, m.p. 135° undepressed on admixture with an authentic specimen (Found: N, 10.63. $C_{20}H_{19}O_6N_3$ requires: N, 10.58%). An analytical sample of 1,6-dimethyl-4-ethyl-naphthalene had b.p. 128° (bath)/ 2 mm. (Found: C, 91.33; H, 8.63. $C_{14}H_{16}$ requires C, 91 25; H, 8.75%). IR spectrum in liquid cell 0.05 mm (Fig. 4.4).

NMR spectrum: 1,6-dimethyl-4-ethyl naphthalene.

Signals at	Multiplicity	No. of protons	Assignment
2.13	doublet	one	H_8
2.21	singlet	one	H_5
2.74	doublet-doublet	one	H_7
2.89	singlet	two	H_2 & H_3
6.99	quadruplet	two	$Ar\text{-}CH_2\text{-}$
7.4	singlet	three	$1\text{-}CH_3$
7.48	singlet	three	$6\text{-}CH_3$
8.67	singlet	three	$4\text{-}CH_2\text{-}CH_3$

Acid (34) from khusilal

Oxidation with alkaline silver oxide.

(i) To a cold solution of khusilal (0.6 g) and powdered silver nitrate (1.2 g) in ethanol was added dropwise a solution of sodium hydroxide (0.8 g) in aqueous ethanol (20 ml) with stirring. After 24 hr. at room temp. (27°) the mixture was diluted with water and acidified with cold dilute hydrochloric acid. It was extracted with ether and the ethereal solution washed with cold water and dried. After removal of the solvent, the acid (34, 0.10 g), crystallised from pet.ether, m.p. 124°, $(\alpha)_D^{24}$ - 198° (c, 2).

(Found: C, 77.11; H, 8.55; eq. wt. 219. $C_{14}H_{18}O_2$ requires: C, 77.03; H, 8.31%; eq. wt. 218.28). IR spectrum in nujol (Fig. 4.5) bands at: 3077, 1675, 1639, 988, 910, 892, 830 and 791 cm-1. UV spectrum: $\lambda_{max.}$ 215 mμ, ε 9,482.

(ii) <u>Oxidation with chromic acid in acetone</u>.

The chromic acid solution (Ca. 8 N) used as the oxidising agent was prepared by dissolving pure chromium trioxide (66.7 g) in water, adding concentrated sulphuric acid (53.3 ml) and diluting the mixture with water to 250 ml. To a solution of khusilal (6 g) in dry acetone (400 ml), chromic acid solution was added drop by drop at room temp. (26°) in 8 hrs. till the solution retained the reddish colour of the oxidising reagent. The mixture was diluted with water (300 ml) and the reaction product isolated with ether, solvent was evaporated and the product (5.8 g) treated with saturated aqueous solution of sodium carbonate. It was extracted with ether (250 ml) to remove unreacted khusilal (1.2 g). The sodium carbonate solution was acidified with cold dilute hydrochloric acid. It was extracted with ether and the ethereal solution washed repeatedly with cold water and dried. After removal of the solvent, the acid (34, 4.2 g) crystallised from pet.ether, m.p.124° $(\alpha)_D^{24}$ - 200° (c, 1.2). The mixed m.p. with the sample prepared by silver oxide oxidation of khusilal remained undepressed and their IR and UV spectra were identical.

Methyl ester (41) of acid (34)

The acid (0.47 g) in dry ether was converted to its methyl ester (diazomethane) and chromatographed over alumina (grade II, 30 g) and eluted with pet.ether:benzene mixture (1:1) and distilled, b.p.130° (bath)/0.5 mm. (Found: C, 78.00; H, 8.86. $C_{15}H_{20}O_2$ requires: C, 77.55; H, 8.68%). IR spectrum (Fig. 4.6) bands at: 3077, 1698, 1639, 1248, 990, 917, 892, 826 and 800 cm-1. UV spectrum: $\lambda_{max.}$ 217 mμ, ε 10,500.

Reduction of the methyl ester with lithium aluminium hydride gave the crystalline alcohol khusilol (19), m.p. and mixed m.p. 75°.

Dehydrogenation of the acid (34) with selenium.

The crystalline acid (2 g) was mixed with selenium (5 g) and heated in nitrogen atm. at 300° for 17 hr. The reaction mixture in pet.ether was filtered through alumina (grade I, 50 g). The product (0.7 g) on VPC analysis showed the presence of essentially two products, 1-methyl-4-ethyl-naphthalene (42) and 1,6-dimethyl-4-ethyl naphthalene (28) in the ratio (3:2).

Decarboxylation of the acid (34)

A solution of the crystalline acid (34, 0.5 g) in freshly distilled quinolene (5 ml) was refluxed with copper chromite (0.15 g) for 6 hr., water was then added and the product was extracted with ether. The extract was washed with dilute hydrochloric acid, made neutral and dried. It was then chromatographed over alumina (10 g, grade I) to give the hydrocarbon (49, [illegible]) in a state of 80% purity (VPC). IR spectrum showed bands at: 1525 and 1625 cm-^{1} due to aromatic impurities, 1670 and 892 due to methylenic double bond, 1000 and 915 due to vinyl double bond and at 725 cm-1 due to (-CH=CH-, cis).

Dehydrogenation of the hydrocarbon (49) with Se

Hydrocarbon (49, [illegible] g) was mixed with selenium (0.3 g) and heated in nitrogen atm. at 300° for 13 hr. The product in pet.ether was filtered through alumina (grade I, 10 g) which on VPC analysis showed the presence of mainly 1-methyl-4-ethyl naphthalene (42, 60%) and 1-methyl [illegible] (54, 25%).

Tosylation of dihydrokhusilol (25)

A mixture of dihydro-khusilol (5 g) in dry pyridine (30 ml) and freshly crystallised p-toluene sulphonyl chloride (6.5 g) in dry pyridine (60 ml) was kept at room temp (25°) for 50 hr. It was poured into crushed ice, taken up in ether and the ether layer washed successively with cold, dilute hydrochloric acid, sodium bicarbonate solution and finally with water and dried. After the removal of the solvent the tosylate (6.4 [illegible] as isolated. The IR spectrum (Fig. 4.7) showed absence of absorption in the vicinity of (3400 cm-1) and showed intense bands due to tosyl group (1600, 1485, 1176 and 1100 cm-1).

Dihydrokhusilene (30)

The tosyl derivative (5 g) in dry ether (20 ml) was added dropwise in 1 hr to a slurry of powdered lithium aluminium hydride (2 g) in dry ether (20 ml) at 0° with stirring. The contents were then refluxed for 18 hr., the mixture decomposed with water (20 ml) and worked up to afford dihydrokhusilene (2.4 g) which was chromatographed over alumina (grade I, 100 g) and distilled over sodium, b.p. 100°(bath)/0.8 mm., $(\alpha)_D^{27}$ - 22° (c, 2), n_D^{30} 1.4980 (Found: C, 87.80; H, 11.90. $C_{14}H_{22}$ requires: C, 88.35; H, 11.65%); (single peak in VPC); IR spectrum in liquid cell 0.05 mm. (Fig. 4.7) bands at: 3085, 1820, 1642, 995, 910 and 892 cm-1. NMR spectrum: signals at: 4.25 to 5.3τ (multiplet) $-CH=CH_2$, 5.45 and 5.52τ (doublet) $>C=CH_2$, 9.07τ (doublet, J=1 7 cps) $-\acute{C}H-CH_3$.

Hydrocarbon (56) by Wolff-Kishner reduction of the semicarbazone of khusilal.

A mixture of the semicarbazone (1.7 g) diethylene glycol (30 ml) and potassium hydroxide pellets (2 g) was heated at 100° for 2 hr. in an atm. of nitrogen. Water from the reaction mixture was removed by raising the temperature gradually to 195° and then heating continued at 200° for 5 hr. The reaction product was diluted with water (100 ml), neutralised with cold dilute hydrochloric acid and extracted with ether. The extract was made neutral, dried and evaporated. The product (1.5 g) was chromatographed over alumina (grade I, 50 g) giving the hydrocarbon (56, 0.4 g) contaminated with slight aromatic impurities (UV spectrum: $\lambda_{max.}$ 246, 252, 257, 263 mμ; ϵ 650, 900, 850, 600). It was rechromatographed over alumina (grade I, 70 g), eluted with pet.ether and 6 X 20 ml fractions were collected. Considering the UV spectra and VPC analysis fractions 2 to 4 were essentially pure. These were combined (0.21 g) and constituted the hydrocarbon (56), b.p.120° (bath)/4 mm., $(\alpha)_D^{26}$ - 84° (c, 1.1), n_D^{26} 1.5140. (Found: C, 89.5; H, 10.8. $C_{14}H_{20}$ requires: C, 89.29; H, 10.70%). IR spectrum bands at: 3085, 1639, 998, 910 and 892 cm^{-1}. NMR spectrum signals at: 4.17 to 5.32 τ (multiplet) $-CH=CH_2$, 5.48 τ (singlet) two $>C=CH_2$ groups.

Khusilene (55) by modified Wolff-Kishner reduction

A mixture of khusilal semicarbazone (10 g), toluene (250 ml) and potassium t-butoxide (5 g) was heated under reflux 50 hr. After usual decomposition with water, the toluene layer was separated and the aqueous layer was extracted several times with ether. The combined ether and toluene solutions were washed several times with water and dried. Removal of the solvent gave a brown liquid (9 g). It was filtered through alumina (grade I, 450 g) and eluted with pet.ether (500 ml). The hydrocarbon (55, 5 g) was obtained in a state of 90% purity on the basis of VPC analysis. IR spectrum showed the presence of aromatic impurities. It was chromatographed over alumina (grade I, 500 g) and 5 X 100 ml pet.ether fractions were collected. Considering the spectroscopic data, together with VPC analysis fractions 4 and 5 consisted of almost pure khusilene (1.8 g), b.p. 100°(bath)/0.6 mm. $(\alpha)_D^{27}$ -102° (c, 2.4), n_D^{31} 1.5110. (Found: C, 89.30; H, 10.9. $C_{14}H_{20}$ requires: C, 89.29; H, 10.71%). IR spectrum (Fig. 4.8) bands at: 3085, 1820, 1642, 998, 910, 892, 833, 815, and 795 cm^{-1}. NMR spectrum signals at: 4.17 to 5.25τ(multiplet) $-CH=CR_1R_2$ and $-CH=CH_2$; 5.4 and 5.48 τ (doublet) $>C=CH_2$, 8.36 τ (singlet) $>C=\overset{\diagup}{C}-CH_3$.

Alcohol (63)

Fractions (1 to 3) from above experiment gave hydrocarbon (2.6 g) which was treated in chloroform solution (150 ml) with perbenzoic acid in chloroform (30 ml, 0.8108 N) at 0° for 16 hr. Chloroform solution was washed with sodium bicarbonate solution, water and dried. Evaporation of the solvent gave crude epoxide (62, 2.6 g). The ethereal solution of epoxide (10 ml) was added dropwise to a well dispersed suspension of lithium aluminium hydride (1.5 g) in ether (30 ml) and the reaction mixture was refluxed for 10 hr. The reaction mixture after working up gave the crude product (2.35 g) which was chromatographed over alumina (grade II, 60 g) and eluted with pet.ether (500 ml) to yield the unreacted hydrocarbon (0.49 g). The alcohol (63, 1.5 g) was obtained by eluting the column with ether (400 ml), b.p.125°(bath)/ 0.6 mm., $(\alpha)_D^{24}$ - 17° (c, 3) (Found: C, 81.14; H, 10.7. $C_{14}H_{22}O$ requires: C, 81.50; H, 10.75%). IR spectrum (Fig. 4.8) bands at: 3400, 3080, 1820, 1634, 990, 909 and 887 cm-1.

Ketone (65)

The alcohol (63, 1.6 g) was hydrogenated in the presence of palladised-charcoal (1 g, 5%) in ethanol (30 ml) at 24° and 713 mm, the absorption of 1.9 moles hydrogen was complete in 4 hr. The product (1.5 g) was purified by chromatography over alumina (grade II, 50 g) and eluting the column with benzene-ether (1:2, 500 ml), the alcohol (64, 1.39) was obtained b.p.120°(bath)/0.6 mm. (Found: C, 79.50; H, 12.30. $C_{14}H_{26}O$ requires: C, 79.93; H, 12.46%).

Alcohol (64, 1 g) in acetone (150 ml) was treated with chromic acid solution in acetone (6 ml). The reaction mixture was allowed to stand at room temp. for 1/2 hr. After working up in the customary manner, the product was chromatographed over alumina (grade III, 30 g) and eluted with pet.ether to give the ketone (65, 0.49 g), b.p.115° (bath)/0.5 mm., $(\alpha)_D^{23}$ + 39° (c, 1) (Found: C, 80.31; H, 11.77. $C_{14}H_{24}O$ requires: C, 80.71; H, 11.61%). IR spectrum (Fig. 4.8) band at 1706 cm-1.

Hydrocarbon (70)

A solution of dihydrokhusilene (30, 1.2456 g) in ethanol (50 ml) was hydrogenated in the presence of 2% palladium-charcoal catalyst (0.35 g). The hydrogen absorbed (169 ml at 23° and 714 mm in 4 hr) corresponded to one mole of hydrogen. The hydrogen was stopped at this stage. The product was chromatographed over alumina (50 g, grade I), eluted with pet ether and 6 X 20 ml fractions were collected. On the basis of VPC analysis fractions 1 to 4 were pure. These were combined (0.8 g) and constituted the hydrocarbon (70), b.p. 90° (bath)/0.7 mm., $(\alpha)_D^{25}$ + 59° (c, 2), n_D^{26} 1.5140. (Found: C, 87.18; H, 12.45. $C_{14}H_{24}$ requires: C, 87.42; H, 12.58%). IR spectrum (Fig.4.9) showed the complete absence of absorptions due to vinyl double bond and showed intense absorption bands due to an exocyclic double bond.

Oxidation of the hydrocarbon (70) with osmium tetroxide, diol (71)

A solution of the hydrocarbon (70, 0.8 g) in dry pyridine was added drop by drop with cooling to a solution of osmium tetroxide (1 g) in pyridine (10 ml). The mixture was allowed to stand at room temp. for 25 days (22-27°). Most of the pyridine was removed in vacuo and the brown residue was taken up in a mixture of benzene (25 ml) and ethanol (22 ml) to which was added mannitol (14 g) and a solution of potassium hydroxide (14 g) in a mixture of water (35 ml) and ethanol (80 ml). The mixture was heated under reflux for 6 hr., allowed to cool to room temperature and concentrated in vacuo to half its volume. It was extracted with ether and the extract was washed with water and dried. Removal of the solvent gave the solid diol which was recrystallised from pet.ether benzene mixture (0.5 g), m.p.130° (Found: C, 74.30; H, 11.54. $C_{14}H_{26}O_2$ requires: C, 74.28; H, 11.58%). IR spectrum in nujol (Fig. 4.9) showed bands at 3400 cm-1 due to hydroxyl groups and at 1040 cm-1 due to the primary hydroxyl group.

Ketone (66)

Diol (71, 100 mg) in acetic acid (5 ml) was oxidised with lead tetracetate (200 mg) in acetic acid (5 ml). The mixture was kept at room temp. (27°) for

14 hr. It was poured into water and the organic material extracted with ether. Extract was made neutral and dried. Removal of the solvent gave the ketone (66) contaminated with small amounts of acetate impurities. It was purified through its crystalline semicarbazone, $C_{14}H_{25}ON_3$, m.p. 195° (Found: N, 16.58; $C_{14}H_{25}ON_3$ requires: N, 16.72%). This semicarbazone on treatment with oxalic acid as described earlier (p. 19) afforded the ketone (66). IR spectrum (Fig. 4.9) showed an intense band at 1712 cm^{-1}, due to the carbonyl function on a six-membered ring and at 1429 cm-1 due to $-CO-CH_2-$ grouping.

Ozonolysis of the hydrocarbon (70) also afforded the same ketone. An analytical sample of the ketone (66) had b.p. 100-102° (bath)/0.2 mm. (Found: C, 80.48; H, 11.38. $C_{13}H_{22}O$ requires: C, 80.35; H, 11.41%).

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