TERPENOIDS

A

THESIS

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by

C·S·NARAYANAN , M.Sc.

ESSENTIAL OILS DIVISION

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C O N T E N T S

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INTRODUCTION

The tremendous development achieved in the application of physical methods in structural investigations in recent years has given considerable impetus to the study of natural products of animal and vegetable origin. The importance of "essential oils" in perfumery and indigenous medicine cannot be over emphasised and it has become one of the important fields of organic chemistry.

"Essential oils" derive their name from the belief that they represent the odour and flavour of the botanical species to which they belong. An absolutely scientific definition of 'essential oils' is not possible. They may be defined as the volatile odoriferous constituents of an oily nature obtained almost exclusively from vegetable sources. They are generally liquids (sometimes solids or semi-solids) at ordinary temperatures and volatile without decomposition.[1] The function of these oils in the plant cannot be ascertained with certainty, but it is assumed that in flowers they aid the natural selection by attracting and repelling certain insects, and in the roots, stems and leaves, they keep the parasites away. The oleoresinous exudations in the tree trunks, when wounded, may function as a seal against the loss of sap and as a protection against diseases.

With very few exceptions like oil of mustard, onion and garlic which contain sulphur compounds and some flower oils, which have benzenoid bodies, essential oils are mainly composed of terpenoids. The present knowledge of the chemistry of terpenoids is chiefly due to the pioneering work carried out by Wallach, Semmler, Simonsen, Ruzicka and others. In 1887, Wallach propounded the isoprene rule according to which terpenes are formed from two or more isoprene units arranged head to tail. It is interesting to note that only very few cases have been observed so far where this generalisation does not hold good.

Any general introduction to the chemistry of terpene compounds has been avoided for the sake of brevity and especially, since a large number of monographs and reviews have appeared in recent years.[2]

India is endowed with an abundance of diversified flora due to her geographic position and the resulting climatic conditions. The production and utilisation of aromatic essences goes back to centuries in this sub-continent.

Systematic investigation of essential oils of India was taken up in the National Chemical Laboratory, Poona, a decade ago. Since then a large number of aromatic extracts of indigenous plants have been thoroughly examined.

Present knowledge of the composition of valerian root oil

Valeriana officinalis, the true Continental valerian and to a lesser extent *Valeriana wallichi*, the Indian valerian have been employed in the indigenous as well as alopathic system of medicine as an antispasmodic and, stimulant.[3,4] Of these two varieties, the *Valeriana officinalis* has been studied thoroughly by many workers,[5-7] whereas the investigations carried out so far on the oil of *Valeriana wallichi*[8-10] have been of a preliminary nature. Hence, a critical examination of the oil of Indian valerian root was thought to be desirable.

Stoll and coworkers[6,7] isolated several known and unknown compounds from the oil of '*Valeriana officinalis*'. They include, valeranone, maaliol, hesperitinic acid, valerinic acid,[7] bornyl acetate, l-myrtenol, l-myrtenol isovalerate, β-sitosterol, behenic acid, a ketone of molecular formula, $C_{15}H_{22}O$, viz. valerenone, acetyl valerenolic acid, and four isomeric sesquiterpene hydrocarbons of molecular formula, $C_{15}H_{24}$ named α,β,γ and δ valenes.

The results of the study on the neutral substances present in the roots of *Valeriana officinalis* carried out by Sorm and coworkers[8] agree with those of Stoll *et al.*, in the identification of valeranone, l-myrtenol isovalerate,

l-borneol acetate, β-sitosterol and maaliol. Their results differ considerably, especially, as far as the nature of sesquiterpenoid hydrocarbons and the sesquiterpenoid carbonyl derivatives. They have reported that the ∝-valene obtained by Stoll and coworkers is identical with β-elemene. The Czech workers isolated β-bisabolene, ar-curcumene, β-sitosterol stearate, borneol isovalerate and ledol. They also reported the presence of an ∝,β-unsaturated aldehyde of molecular formula, $C_{15}H_{22}O$, a keto alcohol m.p.116-118°, two compounds probably hydroxylactones of m.p. 110 and 108.5°, a substance apparently identical with ∝-kessyl alcohol. The differences observed in the composition of the oils examined by Stoll *et al* and Sorm *et al* might be due to a different variety of the plant investigated or else to the different climatic conditions under which the plant was grown.

The examination of the valerian root oil of the Indian variety viz. *Valeriana wallichi* has been of a preliminary nature[8-11] and hence, very little is known about the chemical composition of the oil.

PRESENT INVESTIGATION

Indian valerian (Valeriana wallichi D.C.) is a small herbaceous plant[3] confined to the temperate Himalayas between the altitudes of 7000-10,000 ft. It yields a dull yellowish brown subcylindrical horizontal rhizome, about 2-8 cm long with a stock of fibrous roots, which often appear separated from the stalk. The pieces of the rhizomes are connected by short stolons about 2.5-4 cm long. The odour of this is more pungent and the taste more camphoraceous than that of the Continental variety. The oil obtained from the root is employed in medicine as a sedative, but the composition of the oil, as yet, is comparatively little known.

There are two types of valerian roots available in India viz. (i) valerian roots with rootlets and (ii) valerian roots without rootlets. Oils obtained from different samples of valerian root of both the types collected from different areas in the Himalayan belt have been examined separately in this laboratory. The results of the samples analysed by the author are incorporated in this thesis.

With a view to examine the oil of Valeriana wallichi DC more critically, the roots of this plant were extracted with light petroleum at low temperature, following the method developed in this laboratory for the extraction of costus root oil,[12] and the concentrated extract was resolved into acidic and neutral portions.

Employing a combination of fractional distillation and elaborate column chromatography, along with GLC analysis, several compounds were isolated and characterised. Among them mention must be made to the new sesquiterpene hydrocarbon, β-bergamotene[13,14] which is an isoprenologue of β-pinene, valeranone, hydroxy valeranone and its acetyl derivative.[15,16]

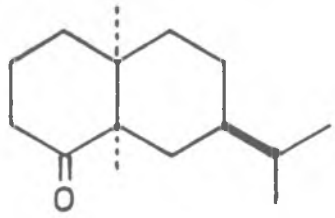
The first chapter of the thesis deals with the isolation and characterisation of the components of the neutral and acidic portions of the valerian root oil. These include ar-curcumene, α,β,γ-patchoulenes, patchouli alcohol, β-sitosterol, valeranone, maalioxide, maaliol from the neutral portion and formic, propionic, butyric, isovaleric, β-methyl valeric, palmitic acids and isovaleryl ester of α-hydroxy isovaleric acid along with some unidentified acids from the acidic portions of the oil.

The stereochemistry of the sesquiterpene ketone valeranone (I) has been the subject of much discussion

and controversy.[17-19]

Recently the Japanese workers[20] isolated valeranone and hydroxy valeranone (Ia) from the Japanese valerian root oil and proved the absolute stereochemistry of valeranone as (I) by degrading valeranone to the ∝,β-unsaturated ketoester (II) and proving its enantiomeric nature with a similar compound (III) obtained from β-eudesmol. Similar degradative experiments have been carried out by the author using maaliol, β-eudesmol and santonin without prior knowledge of the earlier publication. Two A ring ketones derived from valeranone with keto group at carbon atom 3 (IV) and carbon atom 2 (V) have also been prepared from valeranone by a series of reactions and their ORD curves studied with a view to throw light on the stereochemistry of valeranone. These results are presented in Chapter II.

The new sesquiterpene hydrocarbon, β-bergamotene[13,14] (VI) has been recently isolated from the valerian root oil of Indian variety viz. valeriana wallichi D.C. in this laboratory. Cis-norbergamotinic acid[22] (VII) an important intermediate required for the synthesis of ∝- and β-bergamotenes has been synthesised. Methyl heptenone on condensation with ethyl cyanoacetate in the presence of



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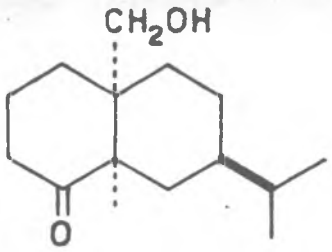

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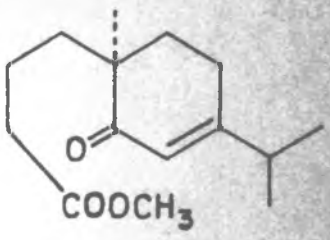

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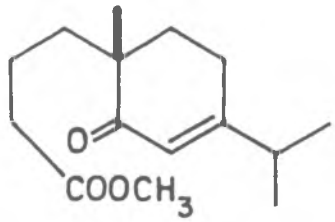

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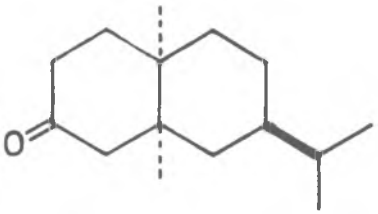

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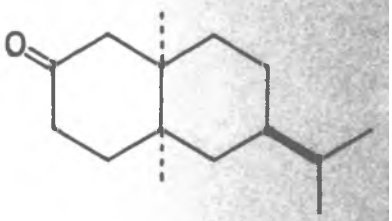

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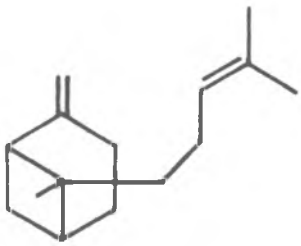

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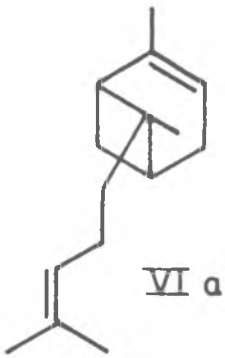

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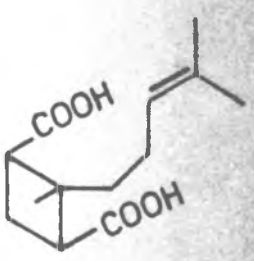

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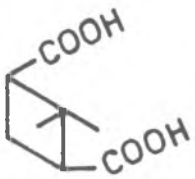

VIII

IX

X

ethanolic ammonia gave the Guareschi's imide. The cyclobutane ring was introduced by refluxing the sodium salt of Guareschi's imide in methanolic solution with methylene iodide. The cyclised Guareschi's imide was hydrolysed to give the tetra-carboxylic acid. The latter on decarboxylation gave a mixture of cis- and trans- norbergamotinic acids. To obtain pure cis-norbergamotinic acid, the mixture of acids was heated with acetic anhydride. The anhydride thus obtained on hydrolysis with water gave cis-norbergamotinic acid, which is a key material for the total synthesis of bergamotenes. These results are described in Chapter III.

The rare hydrocarbon, β-bergamotene (VI) is an isoprenologue of β-pinene (X). Its corresponding ∝-analogue viz. ∝-bergamotene (VIa) has been previously obtained by Sorm from bergamot oil.[14] Since then the isolation of ∝-bergamotene from two different sources has been reported.[14] In order to pave the way for the total synthesis of the above hydrocarbon, the synthesis of a model compound pinene was carried out.

Synthesis of cis-norpinic acid (VIII) has been reported by earlier workers.[23,24] Norpinic acid was synthesised following their methods. Pinic acid was obtained in practical amounts by the hypobromite oxidation of pinonic acid. The diethyl ester of pinic

acid on acyloin condensation gave a mixture of acyloins. The tosylate of the acyloin on reduction with $LiAlH_4$ gave the alcohol which on oxidation gave the ketone norpinone. α-Pinene (IX) was obtained from nopinone. The above synthesis and related results are described in Chapter IV.

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Note In this thesis, liberal use of ultraviolet, infrared and nuclear magnetic resonance spectra and rotatory dispersion studies has been made. At all stages, products according to specific requirements, were subjected to vapour phase chromatography and elaborate column chromatography using different grades of alkaline and neutral alumina.

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GENERAL REMARKS

1. The melting points and boiling points are uncorrected. The boiling points unless otherwise stated, correspond to bath temperatures.

2. All temperatures are recorded on centigrade scale.

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

4. The ultraviolet spectra were determined in 95% ethanol solution with a ratio recording Beckman DK-2 spectrophotometer.

5. The infrared spectra were recorded as a liquid film or in nujol suspension on a Perkin-Elmer Modol No. 137B infracord spectrophotometer.

6. The NMR spectra were measured in carbon tetrachloride solution using TMS as internal standard on a Varian Model spectrometer at 60 mc/s.

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

8. To ensure reliability, VPC analyses were carried out using atleast two stationary phases, employing a Perkin-Elmer Model A-350B, Aerograph and a Griffin MK-II model with hydrogen as carrier gas.

9. The numbers I, II, etc. given to structures and 1,2, etc. given to schemes in each chapter of the thesis refer only to that particular part.

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CHAPTER I

COMPONENTS OF INDIAN VALERIAN ROOT OIL

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SUMMARY

Indian valerian root oil obtained from the roots of the plant Valeriana wallichi is composed of a large number of constituents. Employing a combination of fractional distillation and elaborate column chromatography along with GLC analysis, several compounds were isolated and characterised. These include ar-curcumene ∝,β,γ-patchoulenes, patchouli alcohol, β-sitosterol, valeranone, maalioxide, maaliol, two unidentified hydrocarbons of molecular formulae $C_{15}H_{24}$ and $C_{15}H_{30}$, a compound suspected to be a sesquiterpene oxide from the neutral portion and formic, propionic, butyric, isovaleric, β-methyl valeric, palmitic acids and isovaleryl ester of ∝-hydroxy isovaleric acid along with some unidentified acids from the acidic portions of the oil.

Indian valerian, Valeriana wallichi D.C. (Family - Valerianaceae), is a pubescent perrennial herb growing wildly in the temperate Himalayas from Kashmir to Bhutan at altitudes of 4000-10000 ft. It also grows abundantly in the Khasia Hills at altitudes of 4000-6000 ft. The Indian valerian is commonly known as Mushakbala or Tagara. In India, the rhizomes and roots are used extensively in indigenous medicine, in perfumery, as an incense and as a flavouring agent for tobacco. Indian valerian closely resembles the continental variety of valerian viz. Valeriana officinalis Linn. (Family - Valerianaceae) in its properties and uses, and its volatile oil has a depressent effect upon the central nervous system.

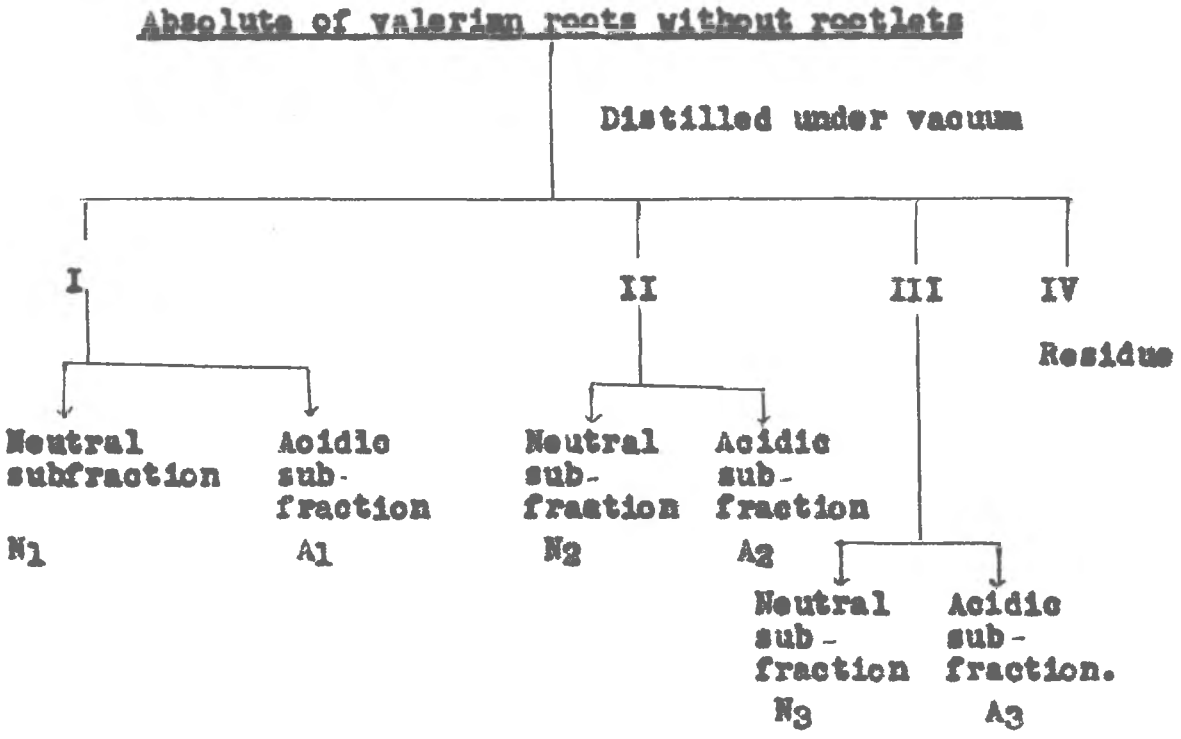
While the components of the roots of the continental variety of valerian (Valeriana officinalis) have been studied systematically,[1-3] very little is known about the constituents of the Indian variety (Valeriana wallichi D.C.). Most of the work carried out so far is limited to the physicochemical properties of the oil, general classification of the constituents which had only been obtained in impure form.[4-7]

There are two types of valerian roots available in India viz. (i) valerian roots with rootlets and (ii)

valerian roots without rootlets. Oil of different samples of valerian root from different areas in the Himalayan belt has been examined separately in this laboratory. The results of analysis of two of the samples examined by the author are incorporated in this thesis.

Based on the experience on costus root oil,[8] the constituents of the roots were collected by low temperature solvent extraction procedure generally employed for isolation of terpenic constituents.

The powdered roots (variety - valerian roots without rootlets), were thoroughly extracted with light petroleum (40-60°) at room temperature. The solvent was removed *in vacuo* at a bath temperature of 40° and the resulting thick extractive was taken up in alcohol. On prolonged cooling of the alcoholic solution at 0° a waxy material separated which was filtered off. The alcohol was then removed and the resulting absolute distilled *in vacuo*, initially using an rotary pump and finally a diffusion pump and separated into four main fractions as shown in the chart given below.



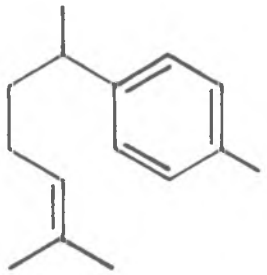
The first three fractions were separated into neutral and acidic subfractions. Investigation of fraction N_1 and N_3 has been done by my colleague K.S. Kulkarni. Fractions N_2 and A_2 were examined by me and the results presented in this thesis.

Investigation of subfraction N_2

The neutral subfraction N_2 was freed of any traces of acid present by treating it with a cold dilute solution of alkali. The neutral portion, free of acids was chromatographed over thirty fold grade III alumina. It was eluted with pet.ether, pet.ether-benzene (1:1), benzene, ether and ethyl alcohol respectively.

The pet.ether fraction on extensive chromatography in stages afforded a dextrorotatory aromatic hydrocarbon, having molecular formula, $C_{15}H_{22}$, $(\alpha)_D^{31}$ + 26.55° in a pure state. It was identified as ar-curcumene[9] (I) from its physical properties and comparative IR spectra. It was possible to isolate a saturated hydrocarbon of molecular formula, $C_{15}H_{30}$; n_D^{28} 1.4580; $(\alpha)_D^{28}$ - 0.4°, in a pure form, but due to paucity of material characterisation of the hydrocarbon could not be carried out (IR spectrum, Fig.1). Another hydrocarbon having the molecular formula, $C_{15}H_{24}$, n_D^{28} 1.4970, $(\alpha)_D^{28}$ - 8.63° was also isolated in small amounts. The IR spectrum (Fig. 2) of the hydrocarbon indicated the presence of an exocyclic double bond (1647, 888 cm^{-1}).

The infrared spectrum of the pet.ether-benzene fraction of the initial chromatography showed carbonyl and hydroxyl functions (bands at 1701, 1720 and 3450 cm^{-1}). The fraction readily formed a semicarbazone, $C_{16}H_{29}N_3O$, m.p. 205°. Decomposition of the semicarbazone with oxalic acid afforded a liquid ketone, $C_{15}H_{26}O$, its physical properties, n_D^{26} 1.4918, $(\alpha)_D^{28}$ - 54.5° and infrared spectrum indicated it to be identical with valeranone[10] (II). The melting point of the semicarbazone



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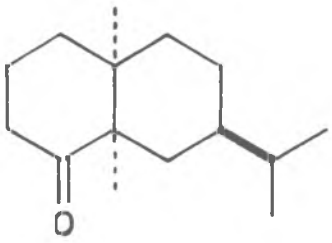

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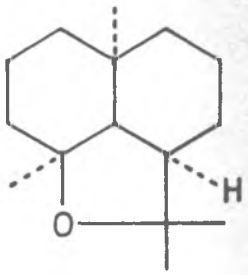

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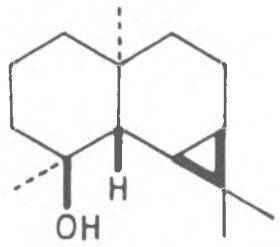

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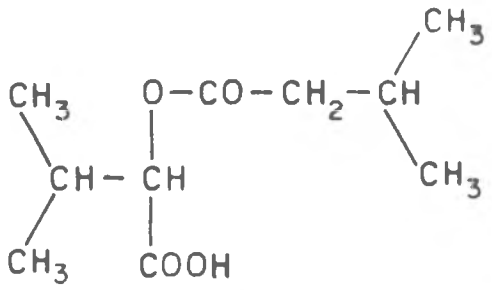

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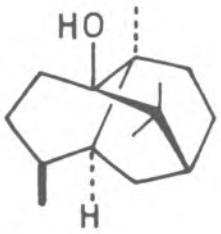

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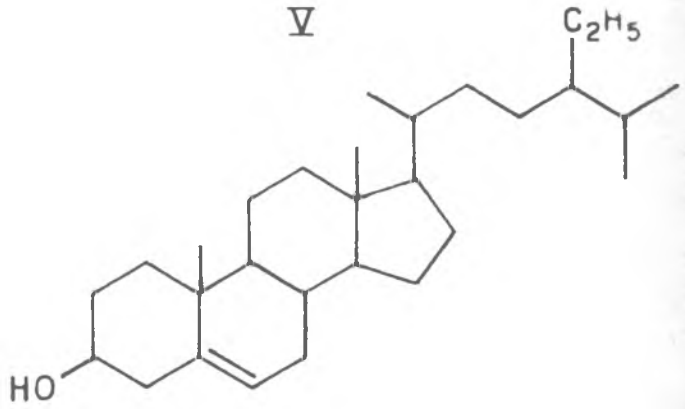

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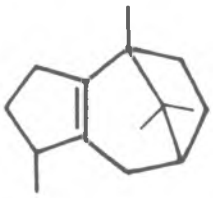
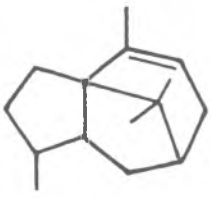
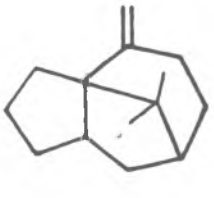


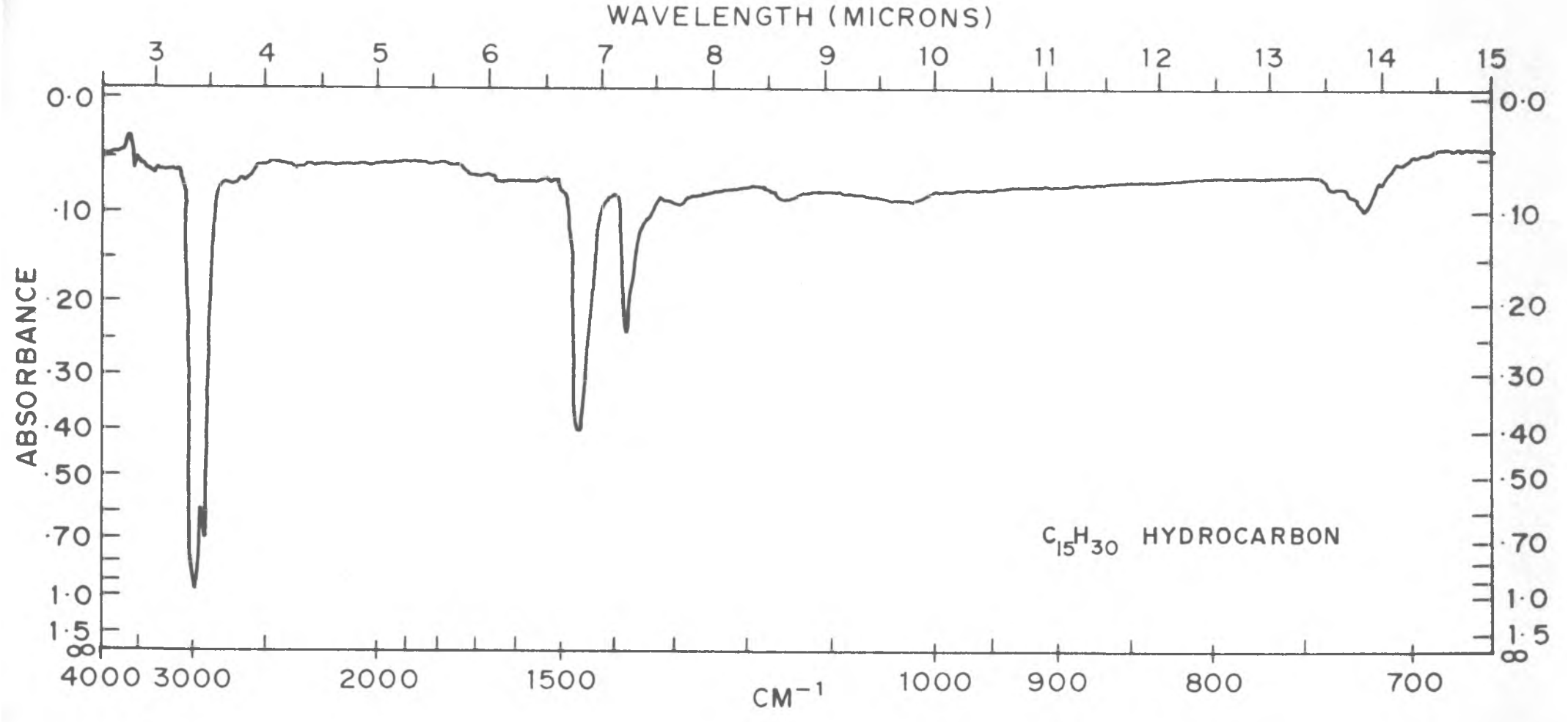
VIII



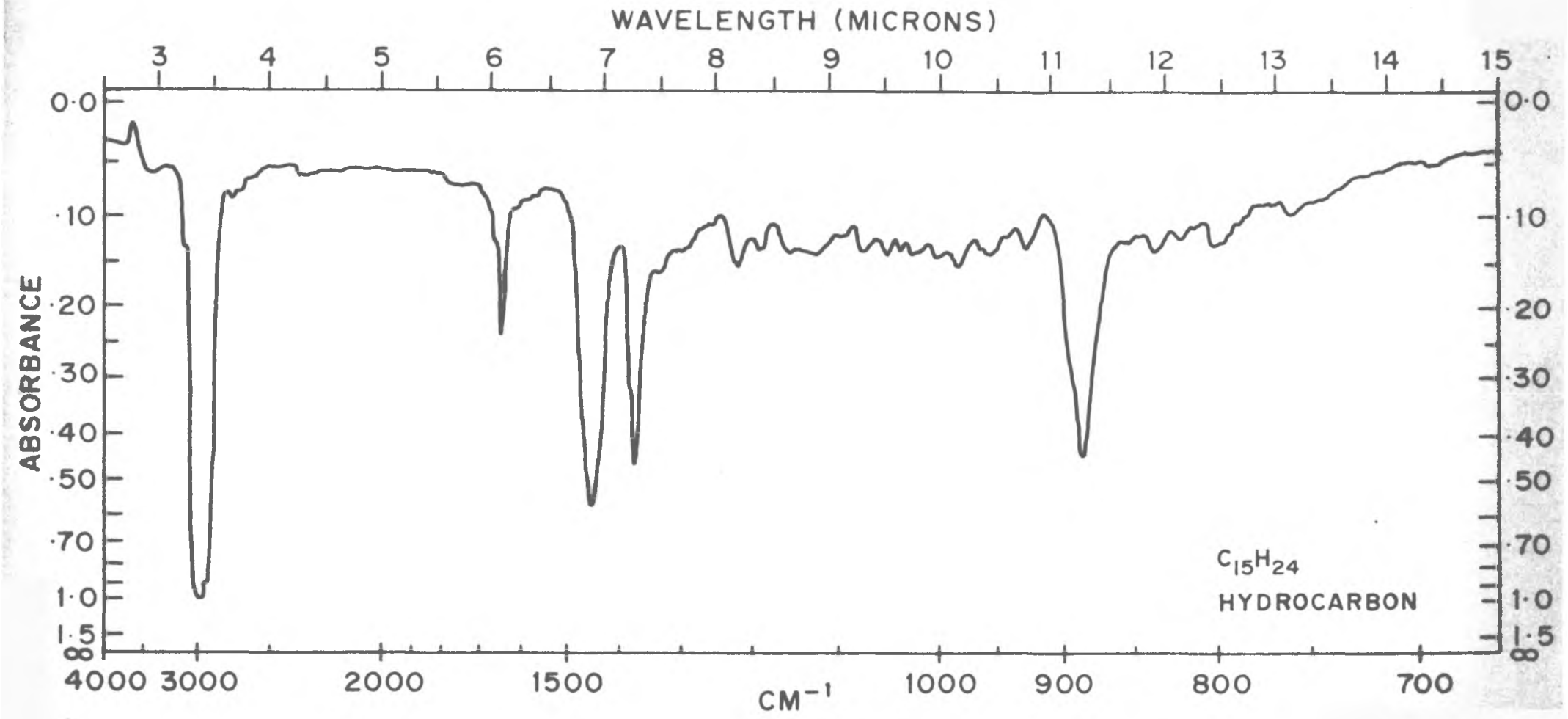
IX



X


WAVELENGTH (MICRONS)
3
4
5
6
7
8
9
10
11
12
13
14
15
0·0
·10
·20
·30
·40
·50
·70
1·0
1·5
∞
ABSORBANCE
$C_{15}H_{30}$ HYDROCARBON
4000
3000
2000
1500
1000
900
800
700
CM^{-1}

FIG·1


WAVELENGTH (MICRONS)
3
4
5
6
7
8
9
10
11
12
13
14
15
ABSORBANCE
0·0
·10
·20
·30
·40
·50
·70
1·0
1·5
∞
4000
3000
2000
1500
1000
900
800
700
CM⁻¹
C15H24
HYDROCARBON

FIG·2

on admixture with an authentic specimen of the semicarbazone of valeranone remained undepressed. The non-ketonic material obtained after the removal of valeranone as its semicarbazone, on repeated chromatography afforded a crystalline oxide, m.p.66°, identified as maali oxide (III), previously obtained by Buchi[11] by treatment of maaliol with iodine. This is probably the first instance of the occurrence of maali oxide in nature. The chromatography also yielded a crystalline alcohol, m.p. 104°, maaliol[11] (IV), characterised by its physical properties, mixed m.p. and comparative IR spectra. The only compound characterised from the benzene fraction was maaliol.

Investigation of the acidic subfraction A_2

The acidic subfraction A_2 was extensively analysed using paper and gas liquid chromatography. It was found to contain formic, propionic, butyric, isovaleric, β-methyl valeric and palmitic acids alongwith isovaleryl ester of D(-) α-hydroxyisovaleric acid[12] (V).

Investigation of valerian root oil with rootlets

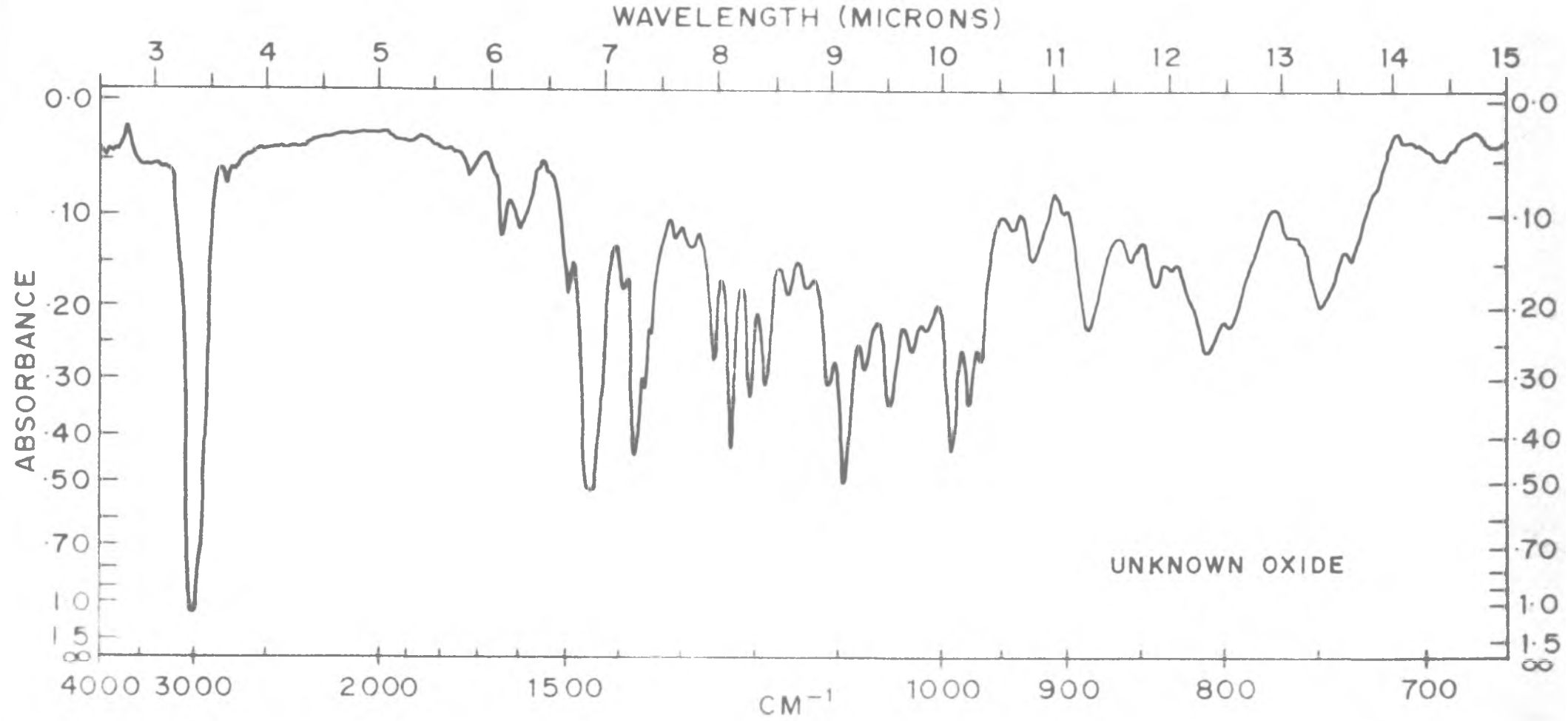
Valerian root oil with rootlets obtained by low temperature solvent extraction of the roots, was

investigated without resorting to fractional distillation. The dark viscous oil was separated into neutral and acid fractions using cold alkali solution.

The neutral portion of the oil was chromatographed through grade III alumina and it was eluted with pet.ether, ether and ethyl alcohol respectively.

The pet.ether fraction on extensive chromatography gave a mixture of hydrocarbons, which could not be separated into the individual constituents by column chromatography. It afforded a sesquiterpene compound, suspected to be an oxide from its IR spectrum (Fig. 3) in very small amounts. The chromatography also yielded a crystalline alcohol, m.p. 87°, identified as patchouli alcohol (VI)[13] from its physical properties, mixed m.p. and comparative IR spectra. This is the first instance of isolation of patchouli alcohol from valerian root oil. It also afforded a very high boiling ester, the alcoholic part of it was characterised as β-sitosterol[14] (VII). The mixed m.p. of the alcohol, m.p. 137° with an authentic sample of β-sitosterol remained undepressed.

The ether fraction on elaborate column chromatography afforded a mixture of three sesquiterpene hydrocarbons. A $C_{15}H_{24}$ hydrocarbon isolated in a pure state from the mixture of hydrocarbons was characterised as


WAVELENGTH (MICRONS)
3
4
5
6
7
8
9
10
11
12
13
14
15
ABSORBANCE
0·0
·10
·20
·30
·40
·50
·70
1·0
1·5
∞
UNKNOWN OXIDE
4000
3000
2000
1500
1000
900
800
700
CM⁻¹

FIG·3

β-patchoulene[13] (VIII) from its IR spectrum, NMR and physical properties. The immediate fractions succeeding β-patchoulene were constituted of ∝ (IX), β (VIII) and γ (X) patchoulenes as confirmed through comparative GLC analysis with mixture of patchoulenes prepared from patchouli alcohol. The isolation of patchoulenes from this fraction was unexpected. The occurrence of these hydrocarbons in this fraction might be due to dehydration of patchouli alcohol during chromatography. The ether fraction also afforded a crystalline solid melting at 137°. It was characterised as β-sitosterol (VII) from its physical properties, mixed m.p. and IR spectrum. The chromatography also afforded a crystalline solid melting at 104°, identified as maaliol (IV) from its physical properties and mixed m.p. with an authentic sample of maaliol. Substantial amounts of patchouli alcohol were also isolated from the ether fraction.

The analysis of the acidic portions of the valerian root oil with rootlets showed it to contain large amounts of isovaleric acid and β-methyl valeric acid.

E X P E R I M E N T A L

Extraction of the valerian root oil

To the powdered roots (valerian roots without rootlets; 36.5 kg), light petroleum (40-60°; 90 l.) was added and the mixture stirred by a spark proof motor stirrer for 2 hrs. After standing (15 min), the extract was filtered. This operation was repeated twice with 55 l. light petroleum each time. From the combined filtrates, the solvent was removed at 40° (reduced press.), 73 kg. of roots gave 1.75 kg. of extractive.

The entire extractive was dissolved in ethanol (10 l) and the solution kept at 0° for 24 hrs. The wax that separated was filtered and washed with ice cold ethanol. The combined filtrates and washings were kept at 0° again for 24 hrs. and wax removed as before. From the final filtrate ethanol was removed (reduced press) at 60°. The absolute obtained was 1.5 kg.

Fractionation of the oil

Fractionation was done in small lots and appropriate fractions were combined. Each fraction was dissolved in ether and separated into neutral and acidic fractions by treatment with 10% NaOH followed by the usual operations to give the acidic fraction. The results are shown in Chart I.

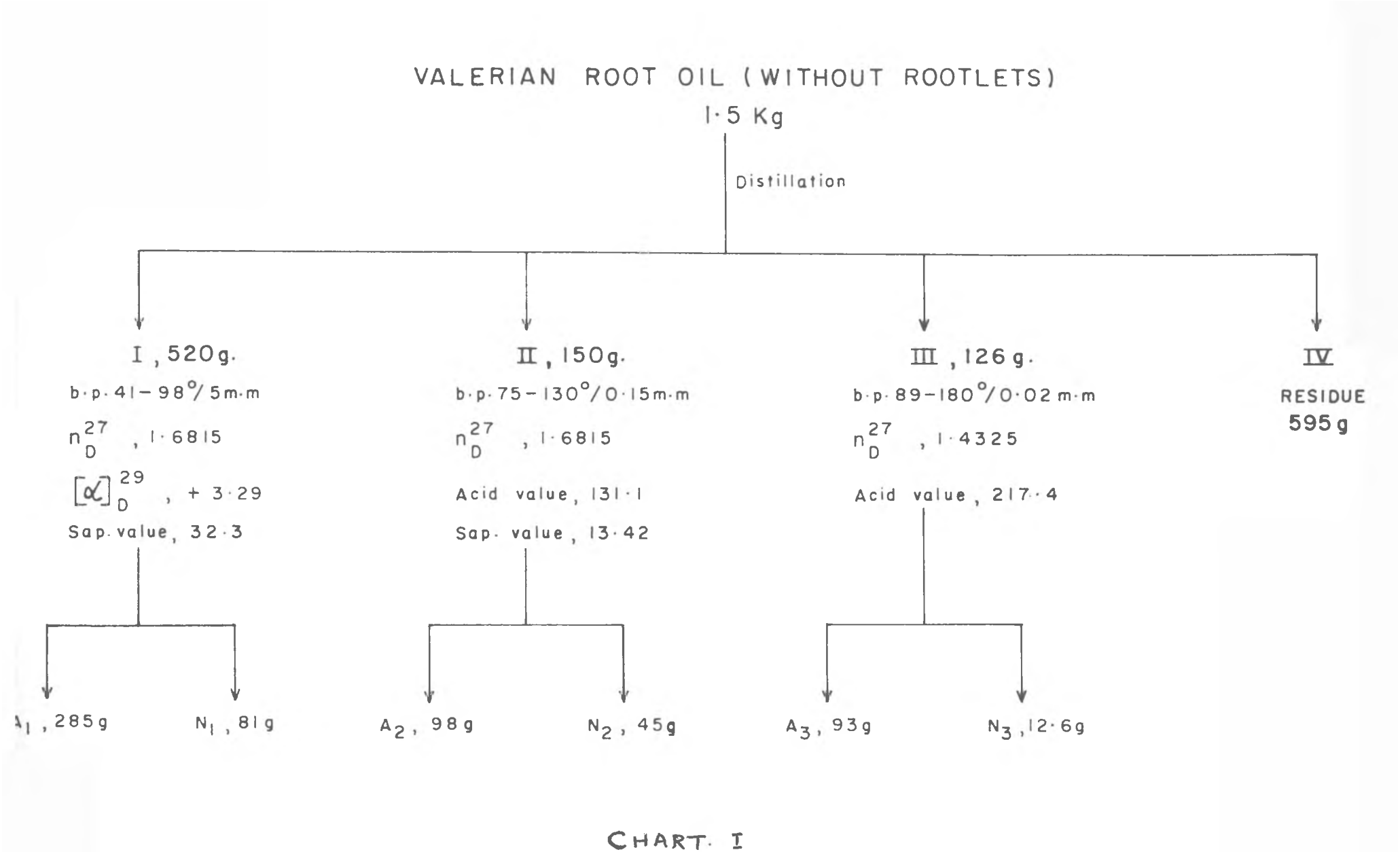

VALERIAN ROOT OIL (WITHOUT ROOTLETS)
1·5 Kg
Distillation
I , 520g.
b·p. 41–98°/5m·m
n_D^{27} , 1·6815
$[\alpha]_D^{29}$, + 3·29
Sap. value, 32·3
II , 150g.
b·p. 75–130°/0·15m·m
n_D^{27} , 1·6815
Acid value, 131·1
Sap. value, 13·42
III , 126 g.
b·p. 89–180°/0·02 m·m
n_D^{27} , 1·4325
Acid value, 217·4
IV
RESIDUE
595 g
A_1 , 285g
N_1 , 81g
A_2 , 98g
N_2 , 45g
A_3 , 93g
N_3 , 12·6g

CHART. I

Investigation of neutral fraction N2 of Chart I

The neutral portion of the II fraction (45 g) was taken in pet.ether (60-80°; 250 ml) and washed with a 5% solution of potassium hydroxide (50 ml) to remove any traces of acid. The potassium hydroxide solution was extracted twice with pet.ether (100 ml). The pet. ether extracts were combined together and washed free of alkali with water. The solvent was distilled off to get the neutral portion (43 g). The alkaline solution was acidified to congo red with dil. HCl (10%) and the liberated acids were extracted with ether. The ether extract was washed free of mineral acid and the solvent was distilled off to get the acids (1.5 g).

The neutral portion (43 g) was chromatographed through a column containing gr.III alumina (1.2 kg). The results are given in Table I.

It was possible to isolate three hydrocarbons in a pure state by elaborate column chromatography of the pet.ether fractions of Table I.

TABLE I

Fr.	Eluent volume (ml)	Weight (g)	$n_D^{21.5}$	$(\alpha)_D^{22}$ $CHCl_3$
	Pet.ether (60-80°)			
1	50	0.1990	1.4821	-
2	"	0.7858	1.4878	-3.10°
3	"	2.0185	1.4907	
4.	"	2.6913	1.4940	
5	"	3.5551	1.4970	
6	"	2.6931	1.5003	-12.46°
7	"	1.9107	1.4951	
8	"	1.5420	1.5051	
9	"	1.0817	1.5038	-8.54°
10	100	1.6259	1.5160	
11	200	0.7463	1.5440	-1.43°
12	400	0.8628		
	Pet.ether-benzene (1:1)			
13	100	1.5627	1.4768	
14	"	1.7998	1.4850	
15	"	1.6015	1.4890	-16.34°
16	"	1.3522	1.4912	
17	200	1.6258	1.4909	
18	"	0.4503	1.4949	-17.36°
19	"	0.8227	1.4973	
20	400	0.9203	1.4990	

Table I Contd.

Fr.	Eluent (ml)	Weight (g)	$n_D^{21.5^\circ}$	$(\alpha)_D^{22}$ $CHCl_3$
	Benzene			
21	100	1.2146	1.5022	-47.33°
22	200	0.6457	1.5010	
23	400	1.5251	1.4962	
24	800	2.2581	1.5042	+20.11°
	Ether			
25	200	1.9680	1.5120	
26	"	1.9658	1.5082	
27	"	1.3013	1.5120	+13.11°
28	800	1.1506		
	Alcohol			
29	700	0.5761		

Isolation of ar-curcumene (I)

An aromatic hydrocarbon of molecular formula, $C_{15}H_{22}$ was isolated in a pure state. The relevant details of the chromatography are given in Table II.

T A B L E II

Amount of hydrocarbon = 4.0453 g.

Grade I alumina = 400 g.

Fr.	Eluent volume (ml)	Weight (g)	$n_D^{30.5}$	$(\alpha)_D^{30}$ $CHCl_3$
1	Pet.ether, 10	0.1021	1.4960	
2	"	0.0778		+32.03°
3	"	0.1076	1.4980	
4	"	0.0607		
5	"	0.0741	1.4990	+38.47°
6	"	0.0716		
7	"	0.1568	1.4990	
8	"	0.0852		
9	"	0.0643	1.5000	
10	"	0.0722		
11	"	0.0733	1.5005	
12	"	0.0845		+37.51°
13	"	0.0722	1.5005	
14	"	0.1104		
15	20	0.1563	1.5005	+32.03°
16	40	0.0630		
17	80	0.1071	1.5005	
18	"	0.1691		+12.95°
19	"	0.0880	1.5000	
20	Benzene 200	0.2599		

Fractions 2-15 of Table II were combined together and distilled over sodium,

b.p. 98°/2 mm., n_D^{29} 1.5000;

$(\alpha)_D^{31}$ + 36.56° (c, 2.7).

Analysis

Found: C, 88.94; H, 11.2.

$C_{15}H_{22}$ requires: C, 89.04; H, 10.96%.

IR spectrum shows bands at: 2725, 1887, 1782, 1639, 1511, 1302, 1211, 1182, 1151, 1110, 1047, 1020, 986, 890, 817, 768, 735, 723 cm^{-1}.

UV spectrum:

$\lambda_{max.}$ 265 mμ (log ε 2.8097)

273 mμ (log ε 2.6949)

267 mμ (log ε 2.7618).

The IR spectrum and physical properties of the hydrocarbon were found to be comparable with those of ar-curcumene.

Isolation of saturated hydrocarbon, $C_{15}H_{30}$

The chromatography also yielded a saturated hydrocarbon of molecular formula, $C_{15}H_{30}$, the characterisation of which could not be done due to paucity of material. The hydrocarbon obtained by chromatography (200 mg) was taken in pet.ether (20 ml) and treated with oleum (1 ml).

The pet.ether layer was washed free of acid, the solvent was removed. The material (150 mg) obtained was distilled over sodium, b.p.130°/2 mm., n_D^{28} 1.4590; $(\alpha)_D^{28}$ -0.4 (c,1.0).

Analysis

Found: C, 85.95; H, 14.60.

$C_{15}H_{30}$ requires: C, 85.63; H, 14.37%.

IR spectrum (Fig. 1) shows bands at: 2924, 2849, 1471, 1383, 1374, 723 cm^{-1}.

Isolation of hydrocarbon, $C_{15}H_{24}$

The hydrocarbon (2.1 g) on chromatography through hundred fold gr.I alumina (210 g) afforded a hydrocarbon of molecular formula, $C_{15}H_{24}$. The relevant details of the chromatography are given in Table III.

Fractions 7 to 9 of Table III were combined together and distilled over sodium:

b.p.110°/1 mm., $n_D^{28.5}$ 1.4970; $(\alpha)_D^{28}$ -8.63° (c, 1.5).

Analysis

Found: C, 88.24; H, 11.92.

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

IR spectrum (Fig. 2) shows bands at 1647, 1222, 1193, 1075, 986, 889, 840, 819, 805 cm^{-1}.

T A B L E III

Weight of hydrocarbon 2.1 g.

Grade I alumina 210 g.

Fr.	Eluent volume (ml)	Weight (g)	n_D^{28}	$(\alpha)_D^{28}$
1	Pet.ether, 10	0.1031	1.4770	-22.54°
2	5	0.0376	1.4875	
3	"	0.0911		-16.29°
4	"	0.0849	1.4885	
5	"	0.0949	1.4885	
6	"	0.0590	1.4885	
7	"	0.0800	1.4935	-8.64°
8	"	0.0720	1.4935	-8.52°
9	"	0.1301		-8.43°
10	20	0.0731	1.4940	
11	"	0.0821		
12	100	0.1080	1.4940	

Isolation of valeranone (II)

A study of the IR spectra of the pet.ether-benzene fractions of Table I showed the presence of ester, hydroxyl and ketonic functions (bands at: 3510, 1730, 1701 cm^{-1}). Fractions 13 to 20 were combined together (2.3 g) dissolved

in 80 ml. of ethyl alcohol. To it was added a solution of semicarbazide hydrochloride (10 g) and sodium acetate (15 g) dissolved in the minimum amount of water. The mixture was kept overnight. The semicarbazone was collected and washed with water. The non-ketonic material was removed by washing it with pet.ether. The semicarbazone obtained was crystallised from ethyl alcohol in the form of needles (1.8 g), m.p.205°.

Analysis

Found: C, 68.75; H,10.47; N,14.64.

$C_{16}H_{29}N_3O$ requires: C, 68.77; H,10.46; N,15.04%.

Semicarbazone (0.7 g) was treated with oxalic acid (1.5 g) in 20 ml. of 50% alcohol and refluxed on a water bath for 1 1/2 hr. The reaction mixture was poured in water, extracted with pet.ether 3 times (3X30 ml). The pet.ether extract was washed free of oxalic acid with water, dried and the solvent removed. The ketone obtained (400 mg) was distilled:

b.p.123°/2 mm., n_D^{26} 1.4917; $(\alpha)_D^{28}$ -54.5° (c, 2.1).

Analysis

Found: C, 81.45; H, 13.34.

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

IR spectrum showed bands at: 1695, 1314, 1242, 1152, 1044, 938, 925, 840 cm^{-1}. m.p. of 2,4-dinitrophenylhydrazone, 102.5°.

The IR spectrum was found to be superimposable with the IR spectrum of valeranone. The mixed m.p. of the semicarbazone with an authentic sample of the semicarbazone of valeranone remained undepressed.*

A comparison of the physical constants of valeranone obtained from different sources is given in Table IV.

TABLE IV

Source	Valeriana officinalis	Nardostachys jatamansi	Valeriana wallichi
n_D	n_D^{20} 1.4944	n_D^{30} 1.488	n_D^{26} 1.4917
$(\alpha)_D$	$(\alpha)_D^{20}$ -43°	$(\alpha)_D^{30}$ -40.1°	$(\alpha)_D^{28}$ -54.5°
Semicarbazone m. p.	205-207°	206-208°	205°
2:4-dinitro-phenyl hydrazone	99-100°	101°	102.5°

The mother liquor after the filtration of the semicarbazone of valeranone was extracted with ether and the extract washed free of mineral salts. The solvent was distilled off and the material obtained was

* We are thankful to Professor T.R. Govindachari for supplying us with an authentic specimen of the semicarbazone of valeranone.

chromatographed through grade II alumina (ratio 1:15). It was eluted with pet.ether, benzene and ether respectively.

Pet.ether fractions gave 3.5 g.

Benzene fraction gave 1.5 g.

Ether fraction gave 2.5 g. of the semicarbazone of valeranone.

Isolation of Maalioxide (III)

The pet.ether fraction (3.5 g) of the above chromatography was rechromatographed through grade II alumina (1:30; 105 g) and 8 fractions were collected. Fraction 5 crystallised. The solid was filtered off and sublimed, m.p. 66°; $(\alpha)_D^{27}$ + 33.28° (c, 4.0).

Analysis

Found: C, 81.46; H, 11.80.

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

IR spectrum shows bands at: 1455, 1377, 1357, 1309, 1235, 1190, 1149, 1130, 1105, 1050, 980, 951, 847, 819, 787 and 776 cm^{-1}.

The IR spectrum of this solid was found to be identical with the IR spectrum of maalioxide. Mixed melting point with an authentic sample of maalioxide remained undepressed.

The other fractions of this chromatography contains an ester, probably an acetate from the IR spectra, which could not be obtained in pure form.

Isolation of maaliol(IV)

The benzene fraction (1.6 g) of the chromatography of the non-ketonic material after removal of valeranone semicarbazone, on chromatography through gr.III alumina (1:30; 48 g) gave a solid compound melting at 104°; $(\alpha)_D^{270}$ + 38.7° (c, 4.0).

Analysis

Found: C, 81.08; H, 11.87.

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

IR spectrum shows bands at: 3621, 1377, 1337, 1330, 1302, 1267, 1176, 1105, 1047, 1016, 975, 938, 919, 902, 884, 873, 836, 799, 753 cm^{-1}.

The IR spectrum of the solid was found to be identical with the IR spectrum of maaliol. Mixed m.p. of the solid with an authentic specimen of maaliol remained undepressed.

On analysis the benzene fraction of Table I was found to contain maaliol, valeranone and some unidentified compounds.

Investigation of acidic subfraction Ag of Chart I

The acidic fraction Ag of Chart I (98 g) was treated with ice cold 20% potassium hydroxide solution

till it was alkaline. It was extracted with ether to remove any trace of neutral material. The ether extracts were washed free of alkali and the solvent was removed to get the neutral material (15.8 g). The alkaline solution was acidified with 10% HCl in ice cold conditions. It was extracted four times with ether. The ether extracts were combined together and it was washed free of mineral acid with water. The solvent was removed to get the acids (54 g).

The acidified water (800 ml) after the extraction of the acids was steam distilled and 400 ml. of the distillate were collected. This was neutralised with ammonium hydroxide and the solution was evaporated in a china dish. The paper chromatography of the residue indicated the presence of formic, propionic, butyric and isovaleric acids.

Fractionation of the acids

The mixture of ether extracted acids (54 g) was fractionated in a Tower's column. The results are given in Table V.

The paper chromatography of the fractions was done in a system of butanol, ethyl alcohol, water and liquor ammonia (40:10:40 + 4 ml ammonia).

TABLE V

Fr.	B.P.	Pressure (mm)	Weight (g)	n_D^{24}	R_f	Eq. wt.
1	60-62	1.0	5.4256	1.4045	0.61	104.2
2	62-64	0.8	5.8720	1.4070	0.61,0.68	106.7
3	64-68	0.8	2.8563	1.4180	0.60,0.68	113.4
4	88-108	0.4	2.1831	1.4359	0.60,0.61 0.68,0.76	131.2
5	108-110	0.4	8.2261	1.4310	0.78	188.8
6	110-111	0.4	7.1407	1.4335	0.78	197.9
7	112-116	0.4	6.3054	1.4335	0.78	189.2
8	116-120	0.35	2.5506	1.4335	0.78	170.2
9	Residue					

[The paper chromatography of the fractions was done in a system of butanol, ethyl alcohol, water and liquor ammonia (40:10:40+4 ml. ammonia).]

Fractions 1-3 of Table V were composed of isovaleric and β-methyl valeric acids and confirmed through comparative paper chromatography and GLC analysis.

Fraction 4 of Table V consisted of isovaleric, β-methyl valeric acids and two new acids (R_f values 0.50 and 0.78).

Isolation of isovaleryl ester of D(-) α-hydroxy isovaleric acid (V)

Fractions 5-8 of Table V showed one spot on paper chromatography, R_f value 0.78.

Fraction 5 had the following physical properties, n_D^{24} 1.4335; $(\alpha)_D^{23}$ + 18.10°.

IR spectrum showed bands at: 1727, 1425, 1389, 1294, 1244, 1183, 1124, 1095, 925, 885, 837, 750 cm^{-1}.

Analysis

Found: C, 58.83; H, 9.32.

$C_{10}H_{18}O_4$ requires: C, 59.38; H, 8.97%.

The methyl ester of the acid (1 g) was prepared using diazomethane in the usual manner.

Properties of methyl ester:-

b.p. 72°/1 mm., n_D^{24} 1.4310; $(\alpha)_D^{23}$ + 16.31°.

Analysis

Found: C, 61.42; H, 9.49.

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

The acid (1.8 g) was heated under reflux with 1N NaOH (30 ml) on a water bath for 4 hr. Spots from this hydrolysis mixture were taken every half hour to know the progress of the hydrolysis. It was found by paper chromatography that the compound was hydrolysed completely during the first hour only, as indicated by the disappearance of the spot of R_f 0.72 and the appearance of two spots of R_f values 0.53 and 0.41. After 4 hr. the solution was cooled and extracted with ether. From the ether extract no neutral material was obtained. The alkaline solution was neutralised exactly by the addition of 0.932 N HCl (33 ml) and extracted thoroughly with ether. The aqueous layer was saturated with NaCl and again extracted thoroughly with ether. The ethereal extracts were combined, dried and the solvent was removed. The residue weighed 1.80 g. Chromatography of the ammonium salts showed only two spots, R_f 0.41 and 0.53. The residue was distilled under reduced pressure. Two fractions were collected.

First fraction. b.p.92-96°/36 mm.
Colourless liquid. Weight 0.76 g.
Equivalent weight: 104.2.

IR spectrum of Fraction I agrees with isovaleric acid.

Analysis

Found: C, 59.14; H, 10.34.

$C_5H_{10}O_2$ requires: C, 58.8; H, 9.87%.

Eq.wt. 102.13.

From chromatographic behaviour (GLC), IR spectrum and equivalent weight the compound was found to be isovaleric acid.

Second fraction: b.p. 138-142°/30 mm. Weight 0.73 g. Colourless syrupy liquid which slowly solidifies. It was purified by sublimation, m.p. 62-63°; $(\alpha)_D^{27}$ - 15°. Equivalent weight 122.5.

Analysis

Found: C, 50.5; H, 8.7.

$C_5H_{10}O_3$ requires: C, 50.83; H, 8.53%.

Eq. wt. 118.13.

The IR spectrum of the compound was identical with that of (-) α-hydroxy isovaleric acid given in literature.*

From the above evidences the parent compound was identified as the isovaleryl ester of D(-) α-hydroxy isovaleric acid.

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* Vinng and Taber, Can.J.Chem., 1955, 35,110.

Isolation of palmitic acid

The solid obtained by the distillation of residue 9 of Table V on crystallisation from pet.ether gave a solid melting at 62.8°.

Analysis

Found: C, 75.43; H, 12.20.

$C_{16}H_{32}O_2$ requires: C, 74.94; H, 12.58%.

The mixed melting point of the solid with an authentic sample of palmitic acid remained undepressed.

Investigation of valerian root oil with rootlets

Valerian root oil from roots with rootlets (2.12 kg) was separated into neutral and acidic fractions. The processing was done in five batches. A typical procedure followed is given below.

The oil taken for processing was very dark in colour. The oil (500 g) was taken in pet.ether (2 l) in a 5L separating funnel (the oil was completely miscible with pet.ether) and treated with 20% sodium hydroxide solution (900 ml) in ice cold conditions. The contents of the separating funnel were shaken thoroughly and it was allowed to separate. The pet.ether layer was separated. The alkaline solution was extracted three times with 500 ml. lots of pet.ether and finally it was extracted with 500 ml.

of ether. The extracts were combined together and it was washed free of alkali with water. The solvent was distilled off and the neutral material obtained (195 g) was kept in a freeze. The alkaline solution was acidified with 20% ice cold sulphuric acid and it was extracted with pet.ether in a 5L separating funnel. During acidification some solid separated which was insoluble in pet.ether. The pet.ether layer was separated. The acidic solution with solids was filtered and the filtrate was extracted with pet.ether and ether respectively. The combined extracts was washed free of mineral acid with water. The solvent was distilled off to get the acids (111 g) insoluble solid material obtained (176 g).

Valerian root oil (2.12 kg) was thus separated into neutral and acidic fractions.

Total wt. of neutral fraction - 780 g.
Total wt. of acid fraction - 445 g.
Total solid - 780 g.

Analysis of neutral portion of valerian roots with rootlets

The neutral fraction (780 g) was coloured dark green. A portion of the neutral fraction (50 g) was distilled under vacuum at a bath temperature of 130-70°/ 1.5-2 mm. and divided into two fraction.

Distillate 13 g. ; Residue 36 g.

It was thus observed that the neutral oil contained very high boiling constituents; hence the distillation of the oil was abandoned.

The neutral fraction was then chromatographed over thirty fold gr.III alumina in batches. It was eluted with pet.ether, ether and ethyl alcohol respectively. The final results are given in Table VI.

The pet.ether elute (137 g) of Table VI was chromatographed through gr.II alumina (ratio 1:30, 4 kg). The results are given in Table VII.

T A B L E VI

Wt. of neutral portion: 400 g. Alumina gr.III 12 kg.

	Fraction	Volume (L)	Weight (g)	Colour
1	Pet.ether	35	137	Reddish yellow
2	Ether	32	129	Dark green
3	Ethyl alcohol	20	13	Brownish black.

T A B L E VII

Fr.	Eluent volume (ml)	Weight (g)	Remarks
	Pet.ether		
1	250	5.9437	6 minor peaks of monoterpenes and 4 peaks of sesquiterpenes by GLC analysis.
2	"	12.5188	
3	"	11.3003	
4	"	7.6586	
5	"	4.5120	
6	"	6.2322	
7	1500	6.8101	
7a	1000	traces	
	Benzene		
8	250	4.9950	All the fractions were coloured deep reddish yellow.
9	"	5.3535	
10	"	5.2230	
11	"	4.0017	
12	"	4.1960	
13	"	2.8105	
14	2 L.	20.1773	
15	Ether, 1 L.	9.2921	
16	" 1 L.	11.8412	
	2 L.	traces	

The IR spectra of the pet.ether fractions of Table VII did not show any functional groups indicating the presence of hydrocarbons only. The pet.ether fractions were combined together (55 g) and it was distilled to effect a separation of the monoterpenes and sesquiterpenes.

Monoterpene hydrocarbons 4.2 g., b.p.110°/10 mm.

Sesquiterpene hydrocarbons 50 g., (as residue).

The sesquiterpene fraction of the hydrocarbon on GLC analysis showed 4 major peaks. Extensive column chromatography of the hydrocarbon mixture over hundred fold gr.I alumina failed to give the individual components in a pure state.

Isolation of patchouli alcohol (VI)

Fraction 15 of Table VII solidified. The solid was crystallised from pet.ether and sublimed, m.p. 57°, $(\alpha)_D^{26}$ - 121.8° (c, 0.8).

Analysis

Found: C, 81.0; H, 11.7.

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

IR spectrum showed bands at: 3621, 1379, 1368, 1323, 1272, 1211, 1179, 1172, 1149, 1100, 1047, 1038, 1006, 996, 981, 964, 927, 887, 854, 815, 775, 734 cm^{-1}.

The IR spectrum of the solid was found to be identical with the IR spectrum of patchouli alcohol. Mixed melting point of the solid with an authentic sample of patchouli alcohol remained undepressed.+

A study of the IR spectra of the benzene fractions 8-14 of Table VII showed it to contain esters and alcohols (absorptions at 1742 cm^{-1} and 3521 cm^{-1}). The benzene fractions were combined together and chromatographed through grade II alumina (ratio 1:30). The eresults are given in Table VIII.

The pet.ether fractions 1-16 of Table VIII were combined together (12.5 g) and distilled under vacuum.

Distillate 1.1 g., b.p.105-115°/3 mm.

The residue (11 g) was found to be undistillable.

Isolation of a sesquiterpene oxide

The distilled ester (1.1 g) on extensive chromatography afforded a sesquiterpene compound suspected to be an oxide from its IR spectrum in very small amounts (25 mg). IR spectrum (Fig.3) of the compound showed bands at: 1645(w), 1608(w), 1626,1404, 1362, 1353, 1235, 1211, 1190, 1087, 1050, 995, 978, 925 887, 842, 811, 798, 780 cm^{-1}.

+ We are thankful to Dr. Sukh Dev for supplying us with an authentic sample of patchouli alcohol.

T A B L E VIII

Fraction	Eluent volume (ml)	Weight (g)	Nature of compound	IR data
1	Pet.ether,60	0.9017		
2	60	1.2913	Deep	Fractions 1-16
3	"	1.2543	yellow	shows an absorption
4	"	0.8052	viscous	at 1742 cm-1 indicating
5	"	0.8213	liquid	the presence of ester.
6	"	0.5844		
7	"	0.6180		
8	"	0.3200		
9	"	0.3576		
10	"	0.7217		
11	"	0.3130		
12	"	0.6399		
13	"	0.7696		
14	200	1.0913		
15	"	1.5793		
16	500	1.2674		
17	Benzene, 50	2.2725	Reddish	Fractions 17-27
18	50	2.5706	yellow	shows a hydroxyl
19	"	2.2130		function (3521 cm-1)
20	"	2.2374		
21	"	2.9005		

Table VIII contd.

22	Benzene, 50	2.4002
23	"	2.1811
24	"	1.8028
25	250	9.3172
26	"	5.0697
27	1 L. Ether	3.5916
28	1 L.	3.5521

Isolation of β-sitosterol esters

The residue (11 g) after distillation of the lower boiling esters was coloured deep red. It was taken in 150 ml of ethyl alcohol and 2 g. of activated charcoal was added. The mixture was refluxed on a water bath for 3 hr. The mixture was filtered. The solid residue on the funnel was washed with hot ethyl alcohol several times. The washings were mixed with the filtrate and the solvent was removed. The material obtained was a very viscous liquid, pale yellow in colour. TLC analysis of this compound showed one spot.

This compound (8 g) was refluxed with 5% alcoholic KOH (50 ml) on a water bath for 2 hr. The reaction mixture was extracted with ether (50 ml), three times. The combined ether extracts was washed free of alkali with water, dried and the solvent was removed. The neutral portion (5.5 g) solidified. It crystallised from acetone-alcohol (1:1) in needles, m.p. 137°, $(\alpha)_D^{25}$ - 27.5°.

Analysis

Found: C, 84.12; H, 12.03.

$C_{29}H_{50}O$ requires: C, 83.99; H, 12.15%.

IR spectrum showed bands at; 3472, 3311, 1193, 1136, 1066, 1055, 975, 950, 920, 885, 840, 803 cm^{-1}. The IR spectrum of this solid was found to be identical with the IR spectrum of β-sitosterol. Mixed melting point of the solid with an authentic specimen of β-sitosterol remained undepressed.

The acidic part (2 g) of the ester on TLC analysis showed 3 spots indicating the presence of three acids, which could not be characterised.

The analysis of the benzene and ether fractions of Table VIII showed them to contain patchouli alcohol only.

Decolourisation of ether fractions of Table VI

The ether eluate (129 g) of Table VI was taken in pet.ether (1 l) and treated with activated charcoal (30 g). The mixture was refluxed for 5 hr., filtered and the charcoal thoroughly washed with hot pet.ether. The washings were combined with the filtrate and the solvent was distilled off to get the material (116 g). The material was coloured deep red.

The decolourised ether fraction (75 g) was chromatographed through gr.III alumina (1:30, 2.25 kg). The results of the chromatography are given in Table IX.

Isolation of β-patchoulene (VIII)

The IR spectra of fractions 1 and 2 of Table IX indicated the presence of hydrocarbons. GLC analysis of the fractions showed 3 peaks each. The fractions 1 and 2 were combined together (5.5 g) and chromatographed through gr.I alumina (ratio 1:150, 826 g). The results of the chromatography are given in Table X.

Fraction 1 of Table X was distilled over sodium, b.p.110° (bath)/2 mm., n_D^{26} 1.4940; $(\alpha)_D^{25}$ - 17.49°.

Analysis

Found: C, 87.86; H, 11.71.

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

TABLE IX

Fraction	Eluent volume(ml)	Weight (g)	Remark
1	Pet.ether,200	2.7291	
2	"	3.7757	
3.	Benzene, 200	9.2139	Fractions 3 - 9 are coloured deep yellow.
4	"	10.2008	
5	"	5.7376	
6	"	3.0887	
7	"	1.4537	
8	"	0.5475	
9	2 L.	3.5684	
10	Ether, 200	8.2939	
11	"	5.9532	
12	"	1.4769	Yellow solid
13	"	1.5745	
14	"	1.1376	
15	1 L.	traces	

TABLE X

Fraction	Eluent volume (ml)	Weight (g)	GLC analysis
1	Pet.ether, 10	0.4125	1 peak
2	"	0.4016	2 peaks 95:5
3	"	0.3921	2 peaks
4	"	0.4927	
5	"	0.4172	
6	"	0.3782	2 peaks
7	"	0.3812	2 peaks
8	"	0.3615	2 peaks
9	"	0.3851	
10	"	0.3321	3 peaks
11	"	0.3621	
12	"	0.3670	3 peaks
13	"	0.2470	
14	"	0.1712	3 peaks.

IR spectrum showed bands at: 1383, 1364, 1323, 1295, 1192, 1182, 1120, 1109, 1050, 990, 962, 943, 929, 911, 880, 811, 785, 744 cm^{-1}.

NMR signals at: 9.125, 9.1, 9.04, 8.75, 8.37, 8.23 and 7.82 τ.

The hydrocarbon gave a positive tetranitromethane test. The IR and NMR spectra confirmed its identity with β-patchoulene.

α,β and γ-Patchoulenes (IX, VIII, X)

Fractions 2-13 of Table X were constituted of α,β and γ-patchoulenes confirmed through comparative GLC analysis with mixture of patchoulenes prepared from patchouli alcohol.

Isolation of β-sitosterol (VII)

The ether fractions 13-15 of Table IX on crystallisation from ethyl alcohol-acetone mixture(1:1) gave fine needles of a compound melting at 137°; $(\alpha)_D^{26}$ - 29.2°.

Analysis

Found: C, 84.08; H, 12.1.

$C_{29}H_{50}O$ requires: C, 83.99; H, 12.15%.

IR spectrum showed bands at: 3472, 3311, 1193, 1136, 1066, 1055, 975, 950, 922, 885, 840 and 803 cm^{-1} and was identical with that of β-sitosterol.

The mixed melting point of the solid with an authentic sample of β-sitosterol remained undepressed.

Isolation of maaliol (IV)

Fractions 10 and 11 of Table X were treated with 90% methyl alcohol. β-sitosterol separated out. It was filtered off and the filtrate concentrated. The process

was repeated to remove β-sitosterol completely. The material so obtained on chromatography afforded a solid compound melting at 104°, $(\alpha)_D^{27}$ + 37.6°(c, 3.0).

Analysis

Found: C, 81.06; H, 11.82.

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

IR spectrum showed bands at: 3621, 1377, 1337, 1320, 1307, 1267, 1176, 1105, 1047, 1016, 975, 938, 919, 902, 884, 873, 836, 799, 753 cm^{-1}.

IR spectrum of the solid was found to be identical with the IR spectrum of maaliol. The melting point of the solid on admixture with an authentic sample of maaliol remained undepressed.

The benzene fractions 3-9 of Table X was found to contain mainly patchouli alcohol and maaliol.

Investigation of the acids of valerian root oil with rootlets

The acidic fraction (445 g) of the valerian root oil with rootlets, obtained during the initial separation of the oil into neutral and acidic fractions, was distilled to get the lower boiling acids (b.p. 110-140°/35-50 mm, 225 g). The distillate constituted of isovaleric acid only, confirmed through comparative paper chromatography and GLC analysis. The residue of

the above distillation was steam distilled to remove the lower boiling acids. Steam distilled acid obtained (82 g) was found to contain isovaleric and β-methyl valeric acids only. The residue after the steam distillation was worked out and distilled under high vacuum.

Fraction	b . p .	Weight
1	140-70°/0.8 mm.	46 g.
2	150-70°/0.02 mm.	24 g.
3	Residue	42 g.

The component acids of the above fractions could not be characterised so far.

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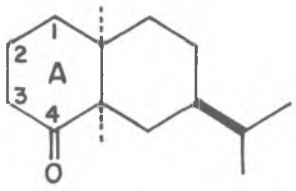
C H A P T E R II

ON THE STEREOCHEMISTRY OF VALERANONE

**

SUMMARY

The stereochemistry of the sesquiterpene ketone, valeranone, has been proved as shown below by Takemoto *et al*. by a series of degradation reactions of valeranone and β-eudesmol. Similar degradative experiments have been carried out by the author using maaliol, santonin and β-eudesmol without prior knowledge of the earlier publication by the Japanese workers. Two A-ring ketones derived from valeranone with keto group at carbon atom 2 and carbon atom 3 have also been prepared from valeranone by a series of reactions and their ORD curves studied with a view to throw light on the stereochemistry of valeranone.



The sesquiterpene ketone, valeranone, was isolated first by Stoll and co-workers[1] from the roots of European valerian. It has been encountered since then in a number of valerianaceous species, e.g. an Indian nard[2], viz. Nardostachys jatamansi, Indian valerian root oil[3] and Japanese valerian root.[4] Govindachari and co-workers isolated a sesquiterpene ketone from the oil of the roots of jatamansi (Nardostachys jatamansi) and named it jatamansone.[5] It was proved later that jatamansone and valeranone were identical.

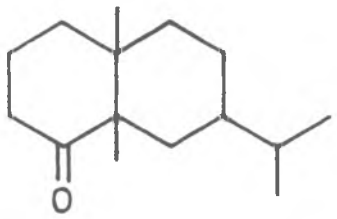
The structural investigations of valeranone were initiated by Govindachari. It was followed by Krepinsky et al. who proposed two alternative formulae, (I) and (II).[6] The Indian workers proposed structure (III).[7] On the basis of this skeleton and the fact that they obtained (-) carvomenthone (IV) as a degradation product of jatamansone, Djerassi and co-workers suggested the absolute configuration of jatamansone (valeranone) as (V)[8] by optical rotatory dispersion studies of dibromo-jatamansone (VI) applying the axial α-haloketone rule.

The Czechoslovakian workers[9] reinvestigated the main series of reactions of the Indian authors

and pointed out that the dehydrobromination product of monobromojatamansic anhydride did not give (-) carvomenthone and they proposed the gross structural formula I for valeranone. The Czech workers further advanced the absolute configuration of valeranone as (VII) by the application of the extended lactone rule and by the X-ray analysis of the brominated anhydride of seco nor-valeranoic acid (VIII).[10] Subsequently the Japanese workers isolated valeranone and hydroxy valeranone from the oil of Japanese valerian root. They established the stereochemistry of valeranone as (IX) by a series of degradation reactions.[11] They prepared the α,β-unsaturated keteester (X) from valeranone and the corresponding α,β-unsaturated keto ester (XI) from β-eudesmol (XII) and proved the enantiomeric nature of these two compounds by monochromatic rotations. The reaction sequences carried out by them are shown in Schemes 1 and 2.

The relative stereochemistry of the centres in the molecule of valeranone is fixed without doubt as VII or IX by X-ray work and also by other evidences.

Prior to the publication by the Japanese workers, no convincing evidence could be presented regarding the absolute stereochemistry of valeranone.[11] The difficulty arises from the fact that valeranone is a cis-decalone



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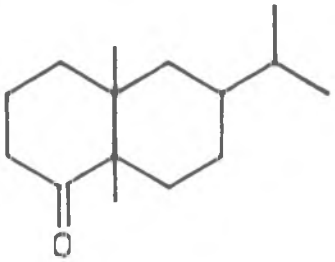

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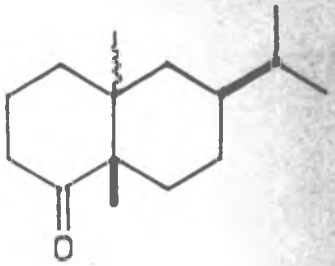

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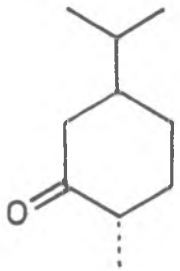

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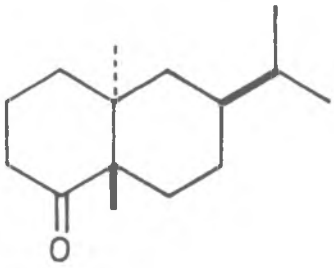

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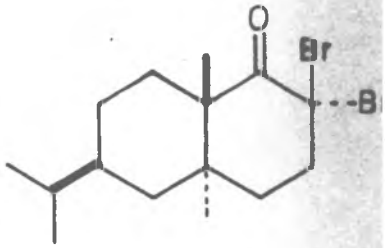

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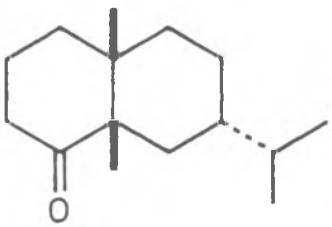

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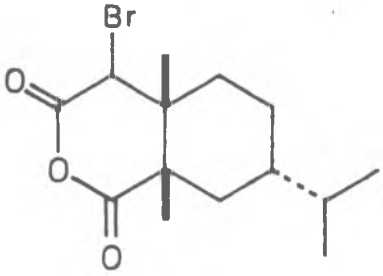

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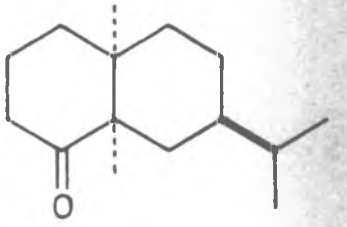

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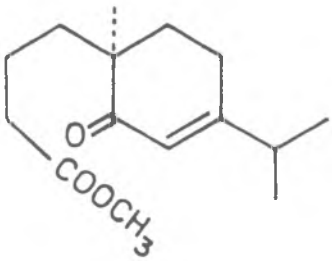

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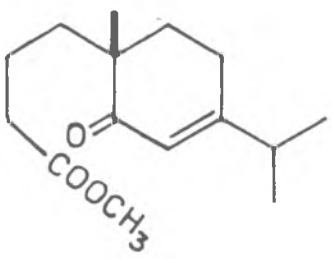

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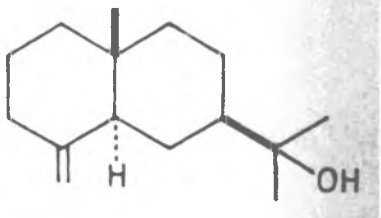
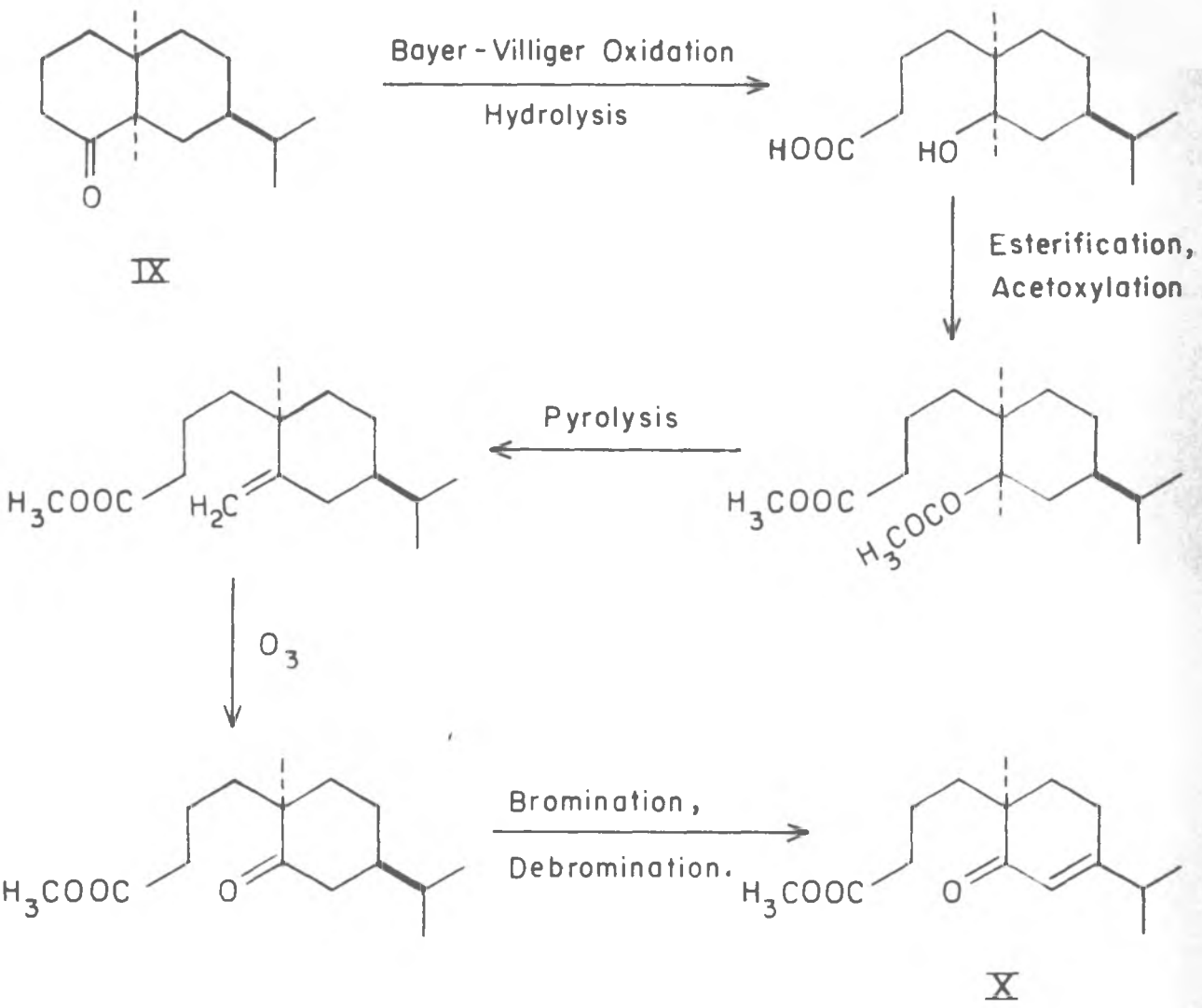


XII

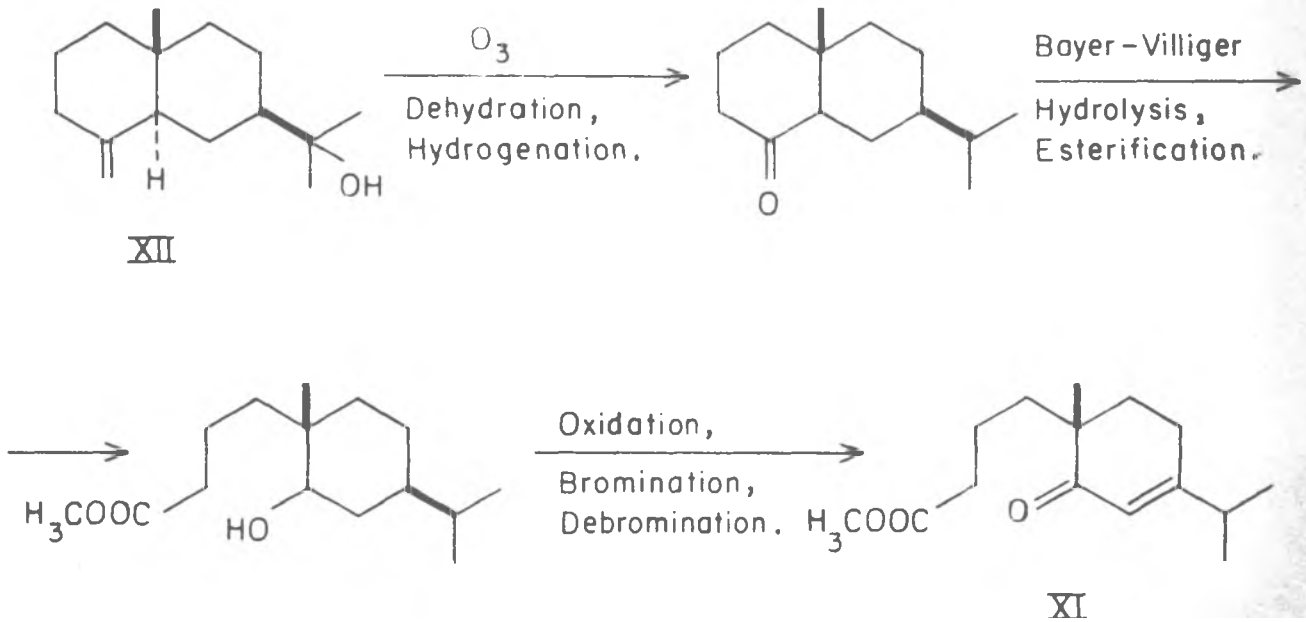
SCHEME No. 1



IX

X

SCHEME No 2



XII

XI

which can always take up one of two possible two chair conformations; this makes the application of physical methods such as optical rotatory dispersion ambiguous. The compound is unusual in having angular methyl groups at both the ring junctions between the two rings A and B. For this reason, no easily accessible reference compounds are available to which the compound can be correlated. Recently W .Klyne has reported the optical rotatory dispersion curves of steroids having methyl groups at both the A/B ring junctions.[12]

In the National Chemical Laboratory, Poona, India, Bhattacharyya et al. have also isolated hydroxy valeranone along with valeranone from Indian valerian root oil and have independently examined their structures. Some of these results have been published.[13] A joint paper has also been published with W. Klyne and Sorm et al regarding the absolute stereochemistry of valeranone.[13] In the course of this, a series of degradation reactions were also simultaneously carried out by the present author independently using maaliol (XIII), α-santonin (XXIII) and β-eudesmol (XII). Mainly because of the limited availability of the key raw materials the series of reactions could not be brought to the logical conclusions. The results have also lost some of their

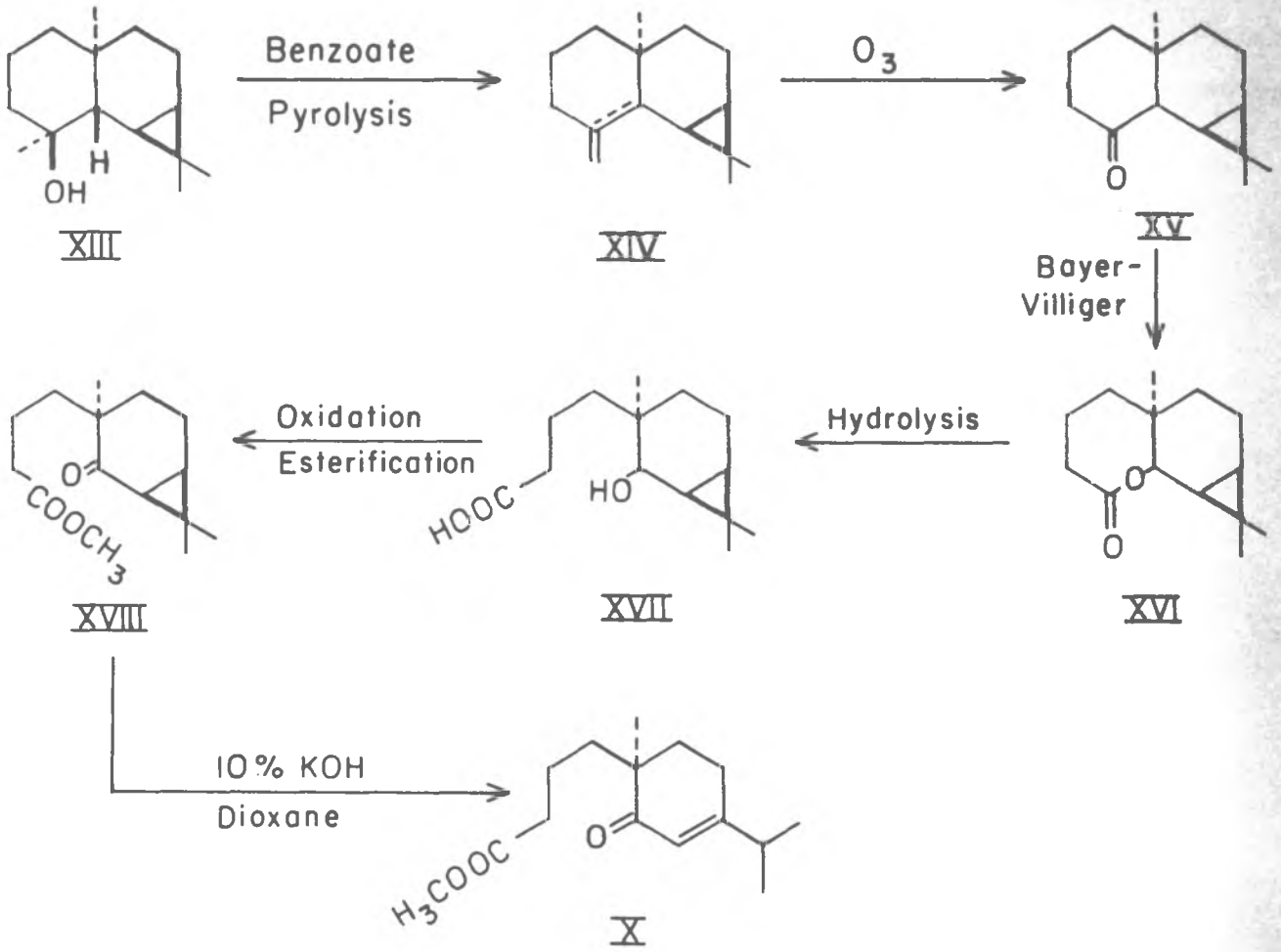
original significance because of the Japanese publication.[11] They are however presented in this chapter.

In Schemes 3 and 4, reactions carried out with maaliol (XIII) are shown. In Schemes 5 and 6, reactions carried out with α-santonin (XXIII) and β-eudesmol(XII) are represented.

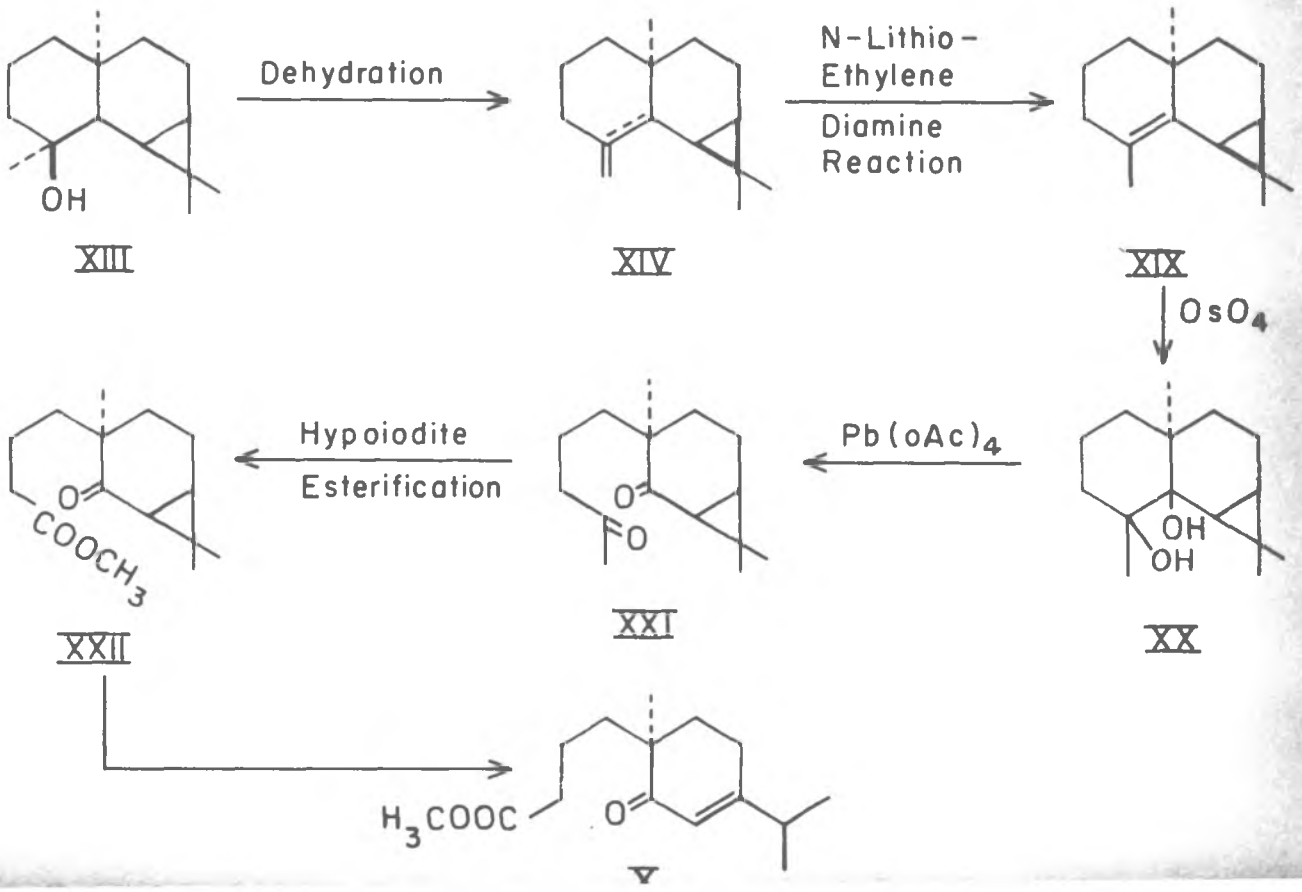
In Scheme 3, following essentially the procedure of Buchi[14] maaliol (XIII) was converted to its benzoate and pyrolysed to get the mixture of hydrocarbons (XIV). The hydrocarbon mixture was ozonolysed and the norketone (XV) obtained on Bayer-Villiger oxidation gave the lactone (XVI). The lactone was hydrolysed to get the hydroxy acid (XVII). It was oxidised and esterified to the ketoester (XVIII). The cyclopropane ring in the ketoester (XVIII) however could not be effectively isomerised by refluxing it with 10% potassium hydroxide solution in dioxane according to the procedure described in the literature.[14] Since maaliol is a rare terpenic alcohol only limited quantities of which were available at our disposal, we were compelled to leave this series of reactions at the penultimate stage.

In Scheme 4, maaliol was dehydrated with thionyl chloride in pyridine to get the hydrocarbon mixture (XIV). The mixture of hydrocarbons was subjected to isomerisation

SCHEME No. 3



SCHEME No 4

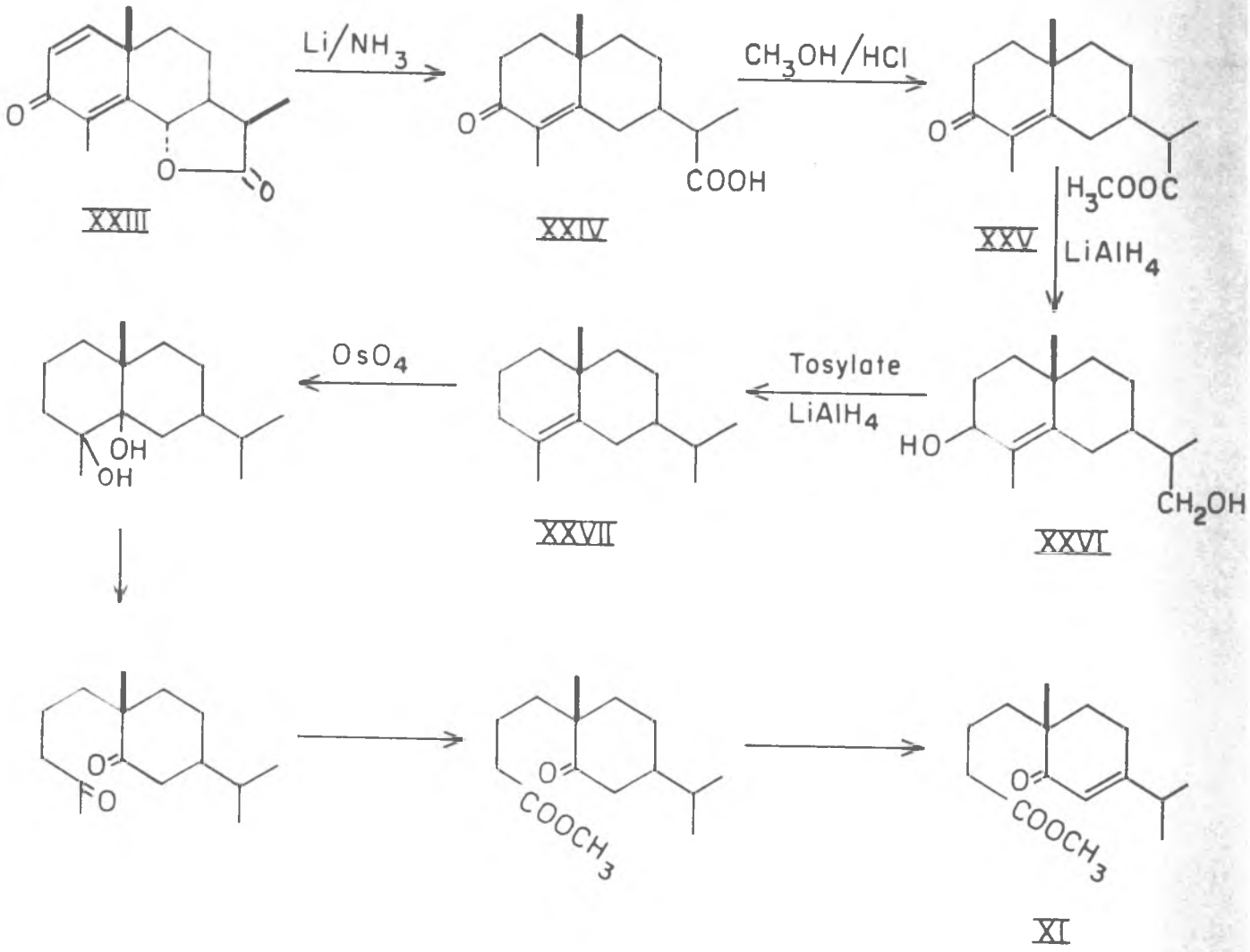


with lithioethylene diamine[15] whereby the exocyclic double bond of the hydrocarbon migrated into the ring to give β-maaliene (XIX). Osmium tetroxide oxidation[14] of (XIX) afforded the crystalline diol (XX) which was oxidised to the diketone (XXI) with lead tetraacetate. Hypoiodite oxidation of the diketone (XXI) gave the ketoester (XXII) in poor yields. The sequence of reactions was also not further pursued because of the same reasons mentioned earlier.

In Scheme 5, (-) α-santonin (XXIII) on Birch-reduction gave the unsaturated ketoacid (XXIV). The methyl ester (XXV) of the unsaturated keto acid was prepared. Reduction of (XXV) with lithium aluminium hydride afforded the diol (XXVI), the tosylate of which on reduction with lithium aluminium hydride gave the hydrocarbon (XXVII). The hydrocarbon, however, did not react with osmium tetroxide to give the desired diol. It appeared that during the reduction of the unsaturated keto ester with lithium aluminium hydride the double bond was also simultaneously reduced. The hydrocarbon was found to be saturated. This line also was not pursued further.

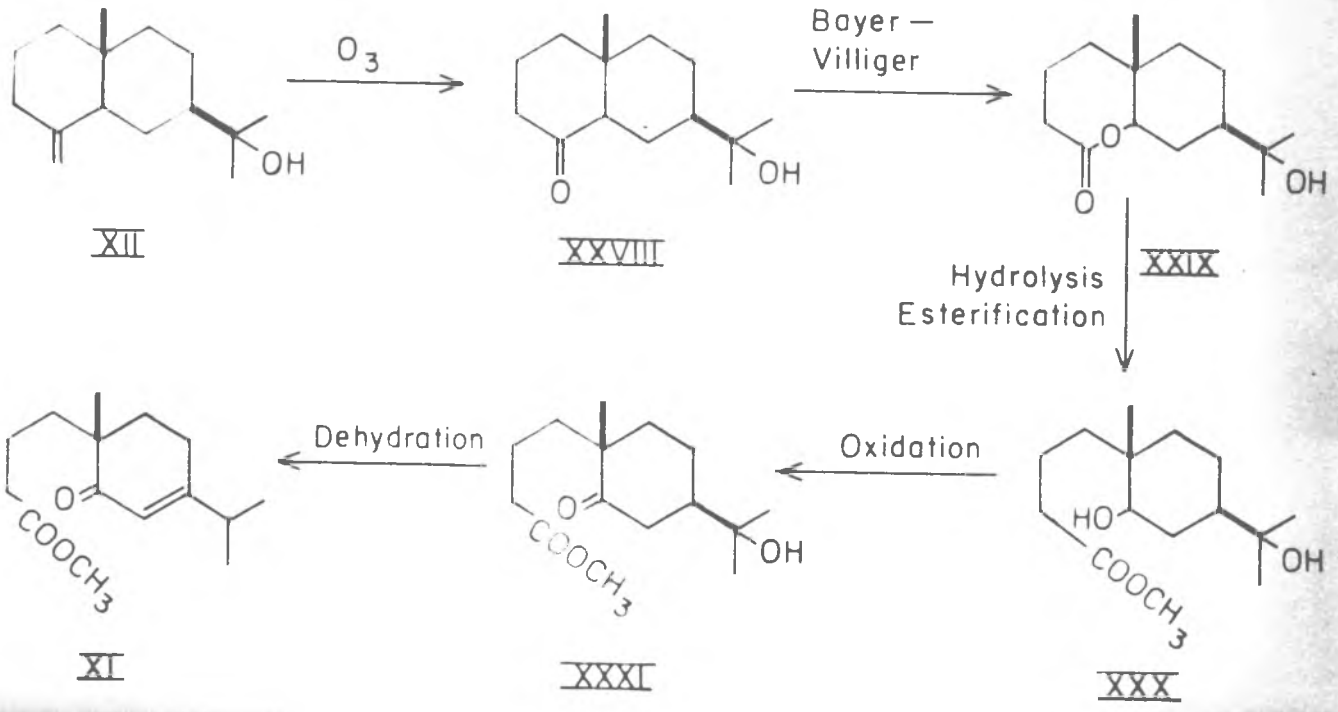
In Scheme 6, β-eudesmol (XII) was put for ozonolysis to get the keto-alcohol (XXVIII). Bayer-

SCHEME No. 5



XXIII XXIV XXV XXVII XXVI XI

SCHEME No 6



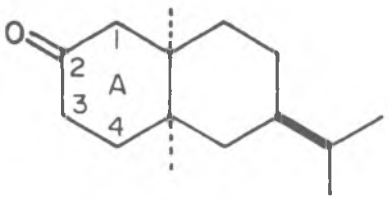
XII XXVIII XXIX XXX XXXI XI

Villiger oxidation of the keto-alcohol afforded the hydroxy lactone (XXIX), which on hydrolysis and esterification gave the diol ester (XXX). Oxidation of (XXX) afforded the hydroxy keto ester (XXXI). Dehydration of this compound with p-toluene sulphonic acid in toluene did not give the desired product (XI) and the product could not be fully characterised.

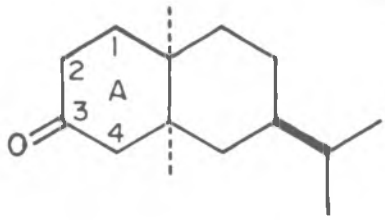
After the series of reactions we diverted our attention to convert valeranone to the corresponding "A ring ketones" with ketogroup at carbon atom 2 (XXXII) and carbon atom 3 (XXXIII) respectively with a view to study their optical rotatory dispersion. These conversions could be successfully carried out in good yields. Both the ketones could be obtained in pure form via the crystallisation of the semicarbazones. These results are also described in this chapter.

Since optical rotatory dispersion has been widely applied in the case of valeranone, it is felt that a brief review on the subject would not be out of place.

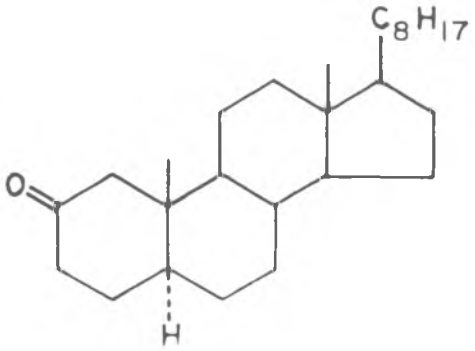
Optical rotation has been used for a long time as a criterion for purity, proof of identity, for the determination of enantiomeric nature and to some extent as an indication of the position of a functional group or of the relative configuration of different asymmetric centres in a molecule.



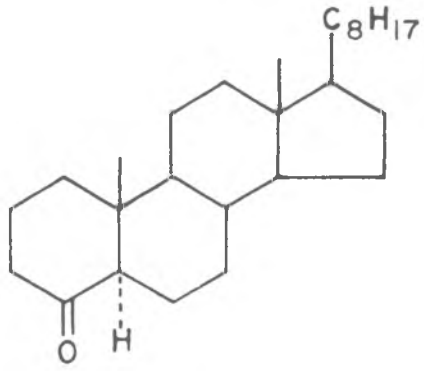
XXXII



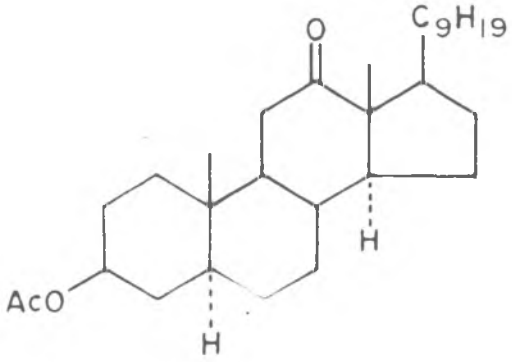
XXXIII



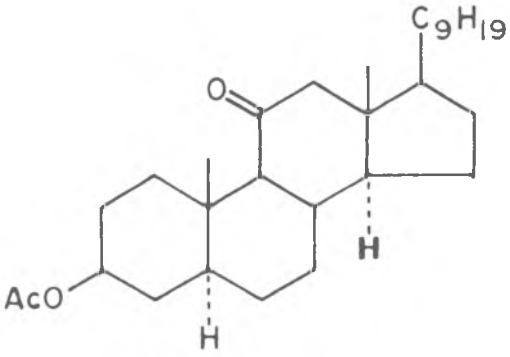
XXXIV



XXXV



XXXVI



XXXVII

"Optical rotation is equivalent to circular birefrigence and occurs when a substance transmits the left and right hand components of a beam of circularly polarised light with unequal velocity. If these components are absorbed unequally, the optical rotation will vary with wavelength, and classical equations have been proposed to express this. The variation of specific rotation with wavelength becomes greater as the absorption band is approached, and, as it is traversed, a Cotton effect may be observed, the optical rotation changing rapidly in magnitude and sign.[16] This arises when the vibrating electric moment associated with the optical absorption band has non-parallel coplanar components in separate parts of the molecule. The anisotropy is high when the absorption co-effisient is low and this makes the phenomenon sensitive to structural changes which, in general, affect a weak absorption band more than a strong one. The variation of optical rotation with wavelength is described by a plain curve, a single Cotton curve or a multiple Cotton curve when several absorption bands are effective."[16]

The classical work of Djerassi[16] and co-workers in this field of ORD has clearly shown that the characteristics of these curves are remarkably sensitive to

structural factors, such as the proximity of the absorption group to any asymmetric centre or conformational differences.

Previously, the rotatory dispersion measurements were carried out by photographic methods, which were laborious. In 1963, photoelectric spectropolarimeters were commercially available which allowed rapid measurements of RD and were also comparatively simple to operate. The present spectropolarimeter available permits determination of RD in the region of 7000-2500 A°. RD curves are of two types in general (i) plain curves and (ii) anomalous curves.

Plain curves, depending upon whether they rise or fall towards shorter wavelength, are of two types, namely positive and negative. A plain curve is to be expected for compounds, which do not absorb light with in the expected region of the range of wavelengths measured.

Anomalous curves are of two types viz. (i) single Cotton effect curve, and (ii) multiple cotton effect curve. Single Cotton effect curve is one with a geometrical maximum and minimum, which are called peaks and troughs respectively; the multiple cotton effect curves have two or more peaks and a corresponding number of troughs. A positive Cotton curve is one in

which the peak occurs at a larger wavelength and in a negative cotton curve, the trough is found at the larger wavelength. The vertical distance between the peak and trough is termed the amplitude (a).

The choice of solvent is determined by its transparency and solubility considerations. The much used solvents are dioxane and methanol. It is important to note that a change of solvent may give rise to some fundamental alterations, especially when the solute molecule is flexible and can exist in different solvents in different preferred conformations. 2-Chloro-5-methyl-cyclohexanone gives two different optical rotatory dispersion curves in methanol and in octane solution.[16]

Much work has been carried out with compounds containing a carbonyl group, since its intrinsic absorption coefficient is low, and the band lies in a convenient spectral region. Far more important work has been carried out with cyclic compounds and two general principles can be made.

(i) That enantiomorphs give mirror image Cotton effects and (ii) that similar stereochemical environments in the region of the carbonyl group lead to similar dispersion curves. The factors which affect the optical rotatory dispersion curve of ring ketones such as the

steroids are ring size, cis or trans fusion of rings, the relation of the carbonyl to the ring juncture, substituents at the junction or ∝- to the carbonyl group or other conformational effects. When the substituent is far removed from the carbonyl absorption group, its nature has very little effect upon the ORD curve. For example, in sapogenins and bile acids and other classes with different groups at C_{17} position of the steroid skeleton, the rotatory dispersion characteristics of the main A/B ring remain the same.

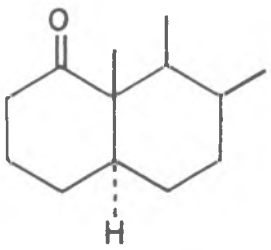
ORD curves help in determining the location of carbonyl groups in the A/B/C rings of steroids.

The ORD curves of cholestan-2-one (XXXIV) and 4-one (XXXV) differ in sign.[17]

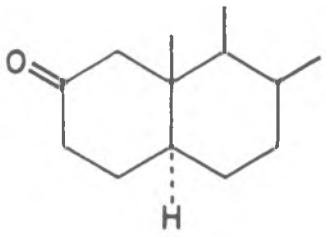
A difference of amplitude is observed with the acetates of ergostan-3β-ol-11-one (XXXVI) and Ergostan-3β-12-one (XXXVII).[18]

The ORD curves also give informations if more than one carbonyl group is present in a steroid.

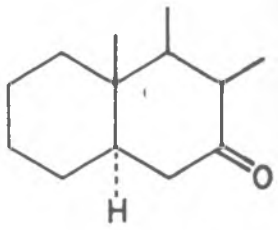
In the case of substituted decalones (XXXVIII to XLI) the ORD curve is mainly dependent upon the position of the carbonyl group in relation to the substituents.[19]



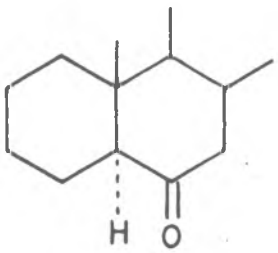
XXXVIII



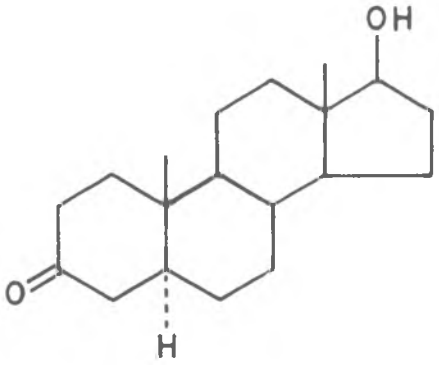
XXXIX



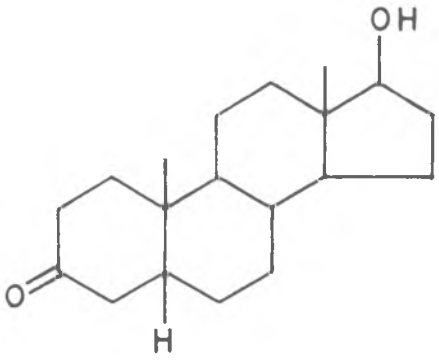
XL



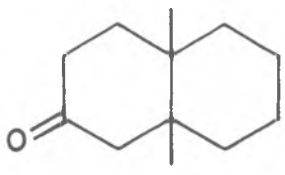
XLI



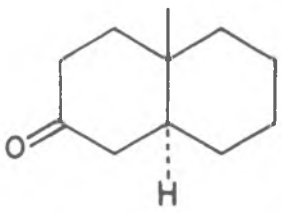
XLII



XLIII



XLIV



XLV

ORD is very valuable in sorting out the stereochemical conformational problems of cyclic systems, e.g. the 5α (XLII) and 5β (XLIII) isomers of androstan-17β-ol-3-one differ only in the A/B ring junction, but have different ORD curves.[20] Another example of cholestan-4-one and coprastan-4-one (5β-cholestan-4-one) have very different ORD curves.[21]

The cis- and trans- 10-methyl-2-decalones (XLIV and XLV), give ORD curves of opposite sign and correspond closely to those of 3-keto-5β- and 3-keto 5α-steroids respectively.[22]

Axial and equatorial hydroxyl groups adjacent to the carbonyl group in steroids shift the mid point of the cotton curves to longer and shorter wavelengths respectively.[23] Acetoxy groups have a similar effect, and, if axial lead to enhanced amplitudes. The effect of α-halogen atom is similar, and may even change the sign of the Cotton curve.[24]

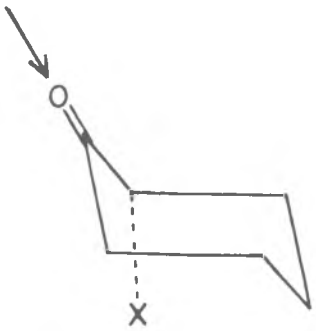
<u>Axial haloketone rule</u>.[25]

"This rule states that introduction of equatorial halogen in either of the positions adjacent to a cyclohexanone does not affect qualitatively the cotton effect of the parent ketone. On the other hand, axial halogen

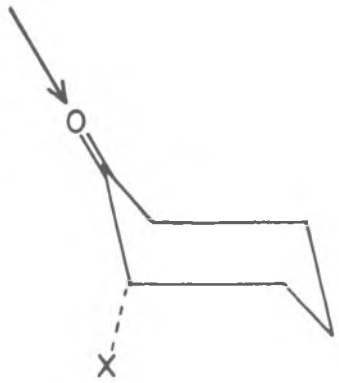
has a profound effect. First of all, the rotatory dispersion curve suffers a bathochromic shift with a concomitant increase in the amplitude of the Cotton effect. Secondly, the sign of the Cotton effect of such an α-halogenocyclohexanone (this applies to chlorine, bromine, and iodine, but not to axial fluorine where the opposite effect is noted) can be predicted in the following empirical manner. A model of the cyclohexanone ring is placed in such a manner that the carbonyl group occupies the head of the chair (or boat). By looking down the O=C axis as indicated by the arrow in Fig. (XLVI and XLVII) a cyclohexanone with an axial halogen atom on the left side of the observer will show a negative cotton effect, while a positive one will be observed if the halogen atom is situated on the right side.[25]"

The octant rule regarding rotatory dispersion curves of saturated ketones, has also been widely used[27-29] for configurational allotments to a wide range of compounds in which the carbonyl group is placed in a six-membered ring, including decalones, sesquiterpenes, diterpenes, steroids and triterpenoids.

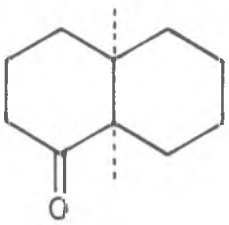
ORD has been able to show the existence of conformational equilibrium in a brominated cis-decalone.



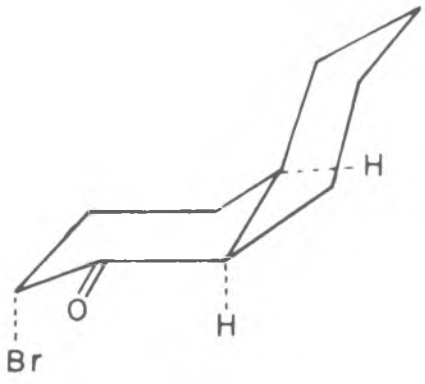
XLVI



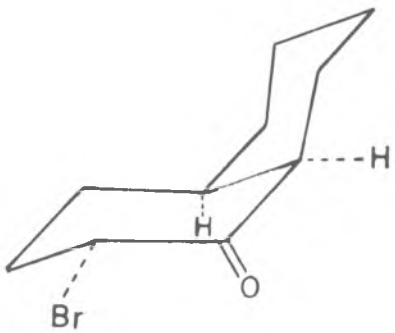
XLVII



XLVIII



XLIX



L

(-) Cis-1-decalone (XLVIII) was converted to the x axially oriented (-)-2-bromo-cis-1-decalone, whose strongly negative Cotton effect in iso-octane solution requires that the compound exist in the steroid conformation (XLIX). When the dispersion measurement was repeated in the polar solvent methanol, there occurred a reduction in amplitude which is only possible if a certain proportion of the non-steroid compound (L) with the equatorial bromine atom is formed.[30]

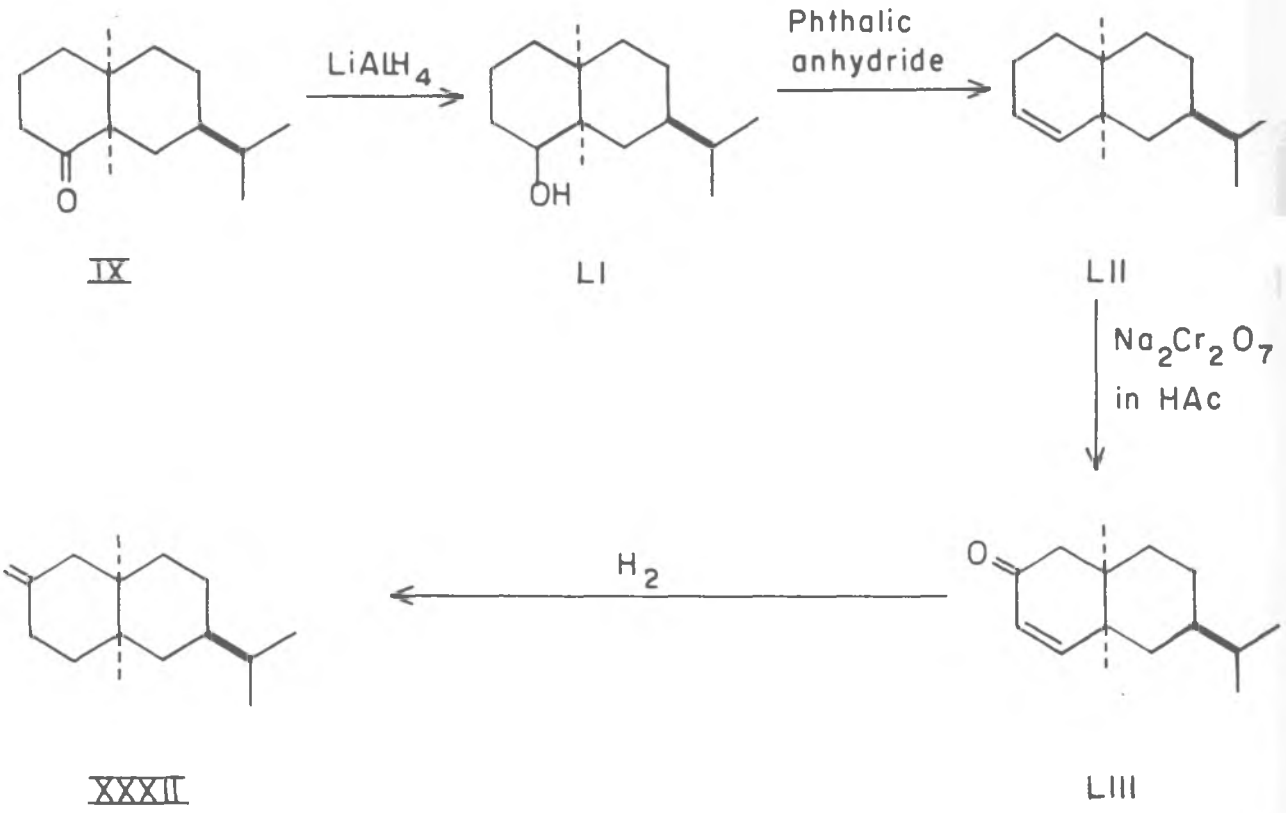
This phenomenon of optical rotatory dispersion has been widely used in solving stereochemical problems in steroids[31,32] and triterpenoids.[33,34]

In the present investigation the assigned configuration of valeranone (IX) is further supported through a study of the ORD curves of the ketones (XXXII and XXXIII) prepared from valeranone.

Transformation of valeranone to ketone XXXII

The ketone was prepared from valeranone as shown in Scheme 7. Valeranone on reduction with lithium aluminium hydride in dry ether, readily furnished valeranol (LI). The alcohol was purified by chromatography over gr.III neutral alumina and distilled in vacuum. IR spectrum of the alcohol showed bands at 3472 cm^{-1} for the hydroxyl group. Valeranol was

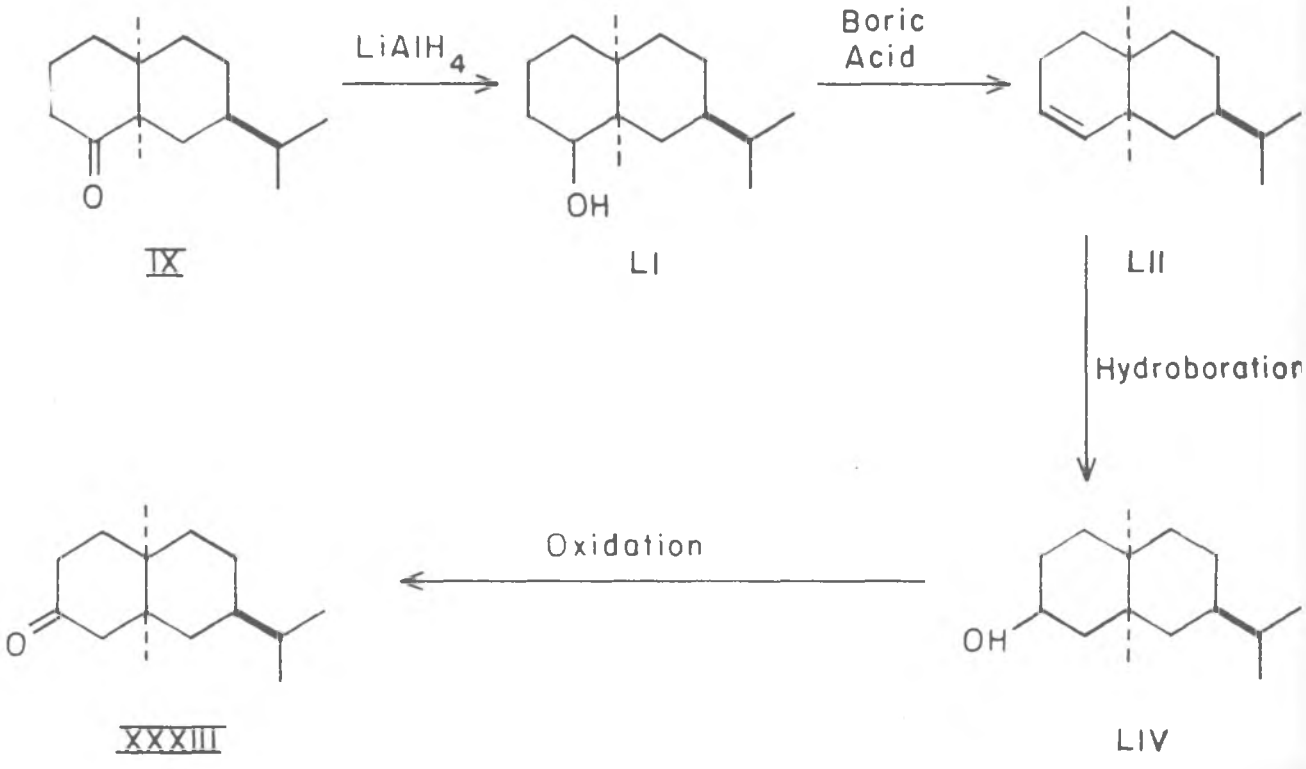
SCHEME No. 7



IX LI LII

LIII XXXII

SCHEME No 8



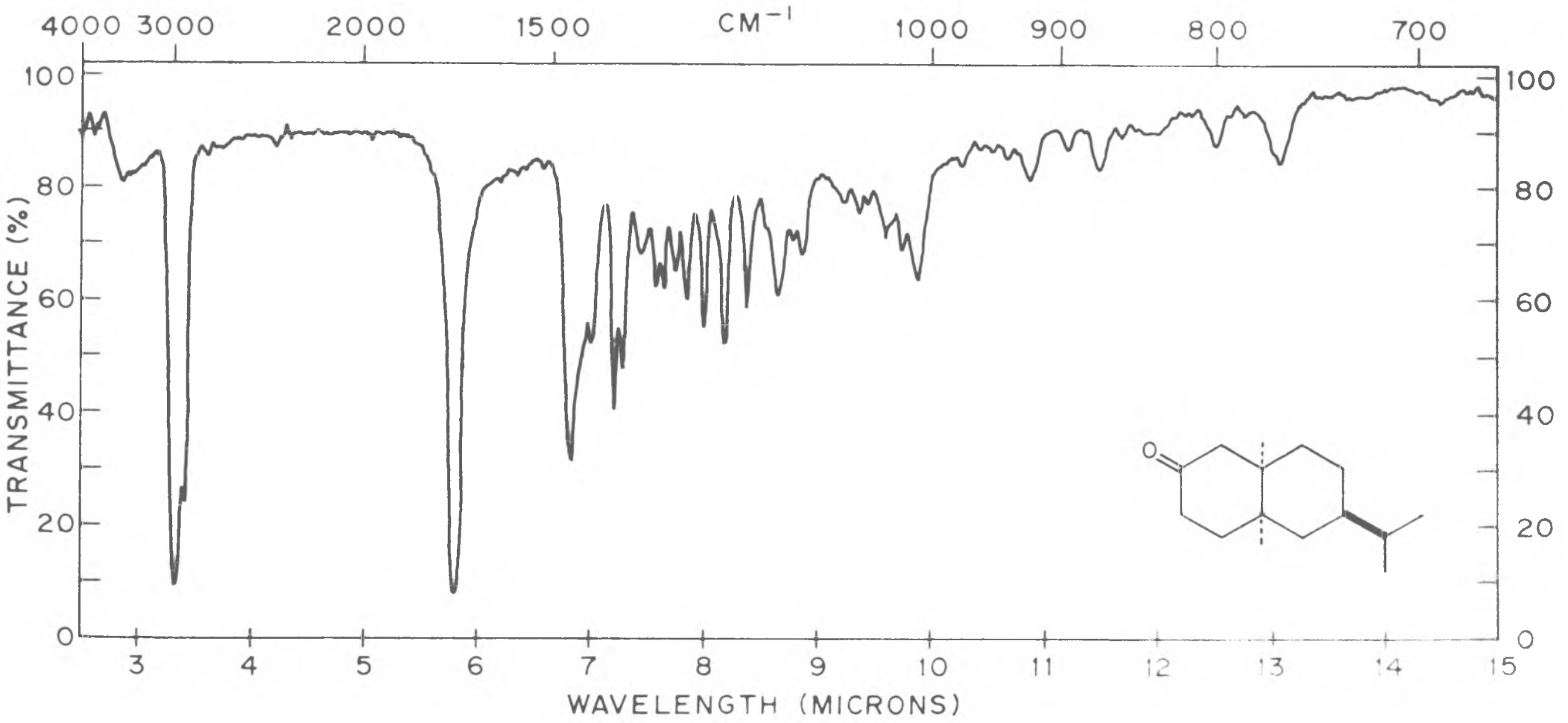
IX LI LII

LIV XXXIII

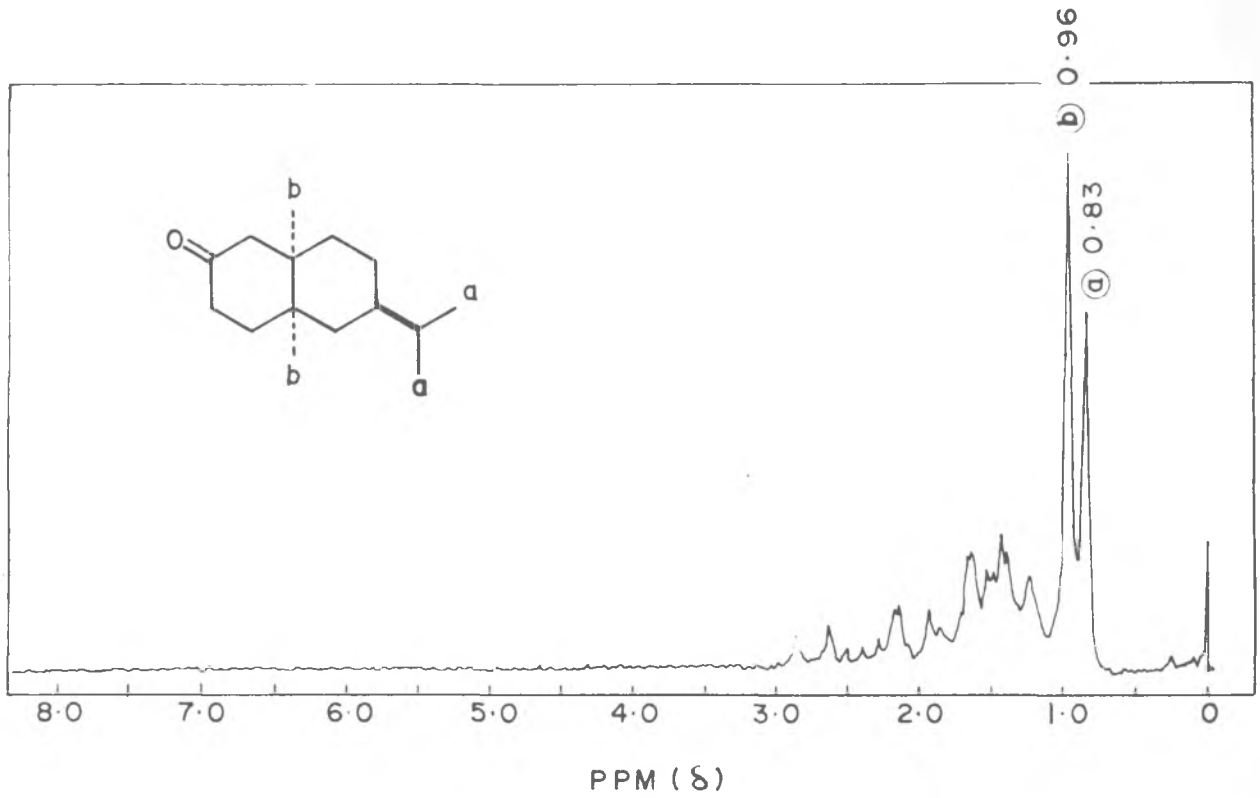
dehydrated by heating it with phthalic anhydride at 270-280° for 1 hr. and purified by chromatography to yield the hydrocarbon (LII) in good yield. It gave back valerane on hydrogenation indicating that there was no change of the basic skeleton during dehydration. The hydrocarbon was oxidised with sodium dichromate in glacial acetic acid and worked up to afford the unsaturated ketone (LIII). It was purified by chromatography and then through its semicarbazone which melted at 199-200°. The IR spectrum of the unsaturated ketone showed bands at 1650 cm^{-1} (C=O absorption in conjugation to a double bond) and characteristic ultraviolet spectrum. The unsaturated ketone was hydrogenated to the saturated ketone (XXXII) in ethanol in presence of Adams' catalyst. The purified ketone is a liquid. IR spectrum of the ketone (Fig. 4) showed carbonyl absorption at 1724 cm^{-1}. NMR spectrum of the ketone(Fig. 5) showed signals at 0.82 δ (6H) and 0.96 δ (6H) for the four methyl groups and signals at 2.12, 2.17, 2.61 and 2.86 δ (4H) for the four α-hydrogen atoms.

Transformation of valeranone to ketone (XXXIII)

The ketone (XXXIII) was prepared from valeranol(LI) as shown in Scheme 8. Valeranol was dehydrated by heating it with boric acid at 200° for 30 minutes. The product


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
O

FIG·4



FIG·5

was worked up as usual and the resulting hydrocarbon(LII) was distilled and purified by column chromatography. The hydrocarbon (LII) was subjected to hydroboration reaction by passing diborane through a solution of the hydrocarbon in tetrahydrofuran at 0°. The reaction was carried out under dry conditions in an atmosphere of nitrogen. Diborane was produced by treating sodium borohydride in diglyme with borontrifluoride. Nitrogen was used as the carrier gas. The reaction product was treated with alkaline hydrogen peroxide to decompose the boron complex. The alcohol (LIV) thus obtained was purified by column chromatography. IR spectrum of the alcohol showed hydroxyl absorption at 3485 cm^{-1}. The alcohol (LIV) was oxidised with 8N chromic acid (Jones reagent). The ketone (XXXIII) formed was purified through its semicarbazone which melted at $217-218^{\circ}$. The ketone (XXXIII) is a liquid, IR spectrum of the (Fig.6) ketone showed the carbonyl absorption at 1718 cm^{-1}.

The ORD curves of the two ketones (XXXII) and (XXXIII) were taken.

Ketone (XXXII)

The octant diagram of the ketone is represented as shown in (LV). It follows that this ketone should show a negative Cotton effect. The ORD curve (Fig. 7)

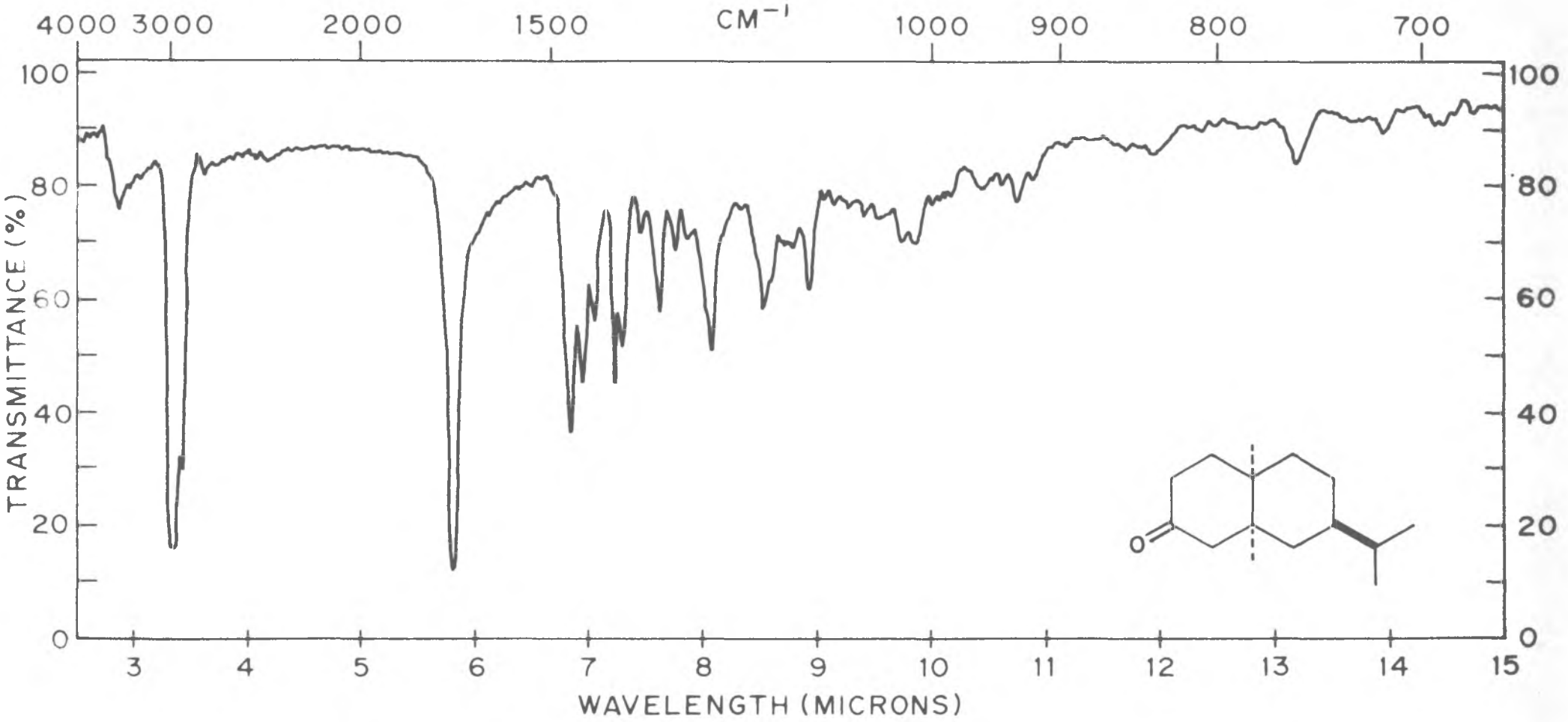
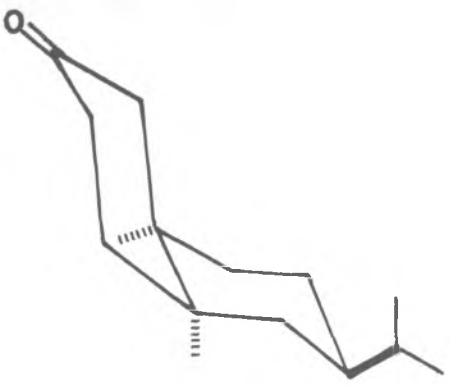

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
O

FIG. 6



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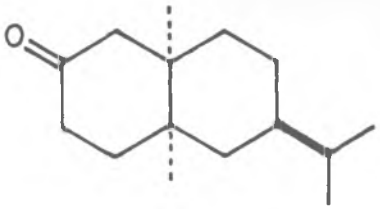
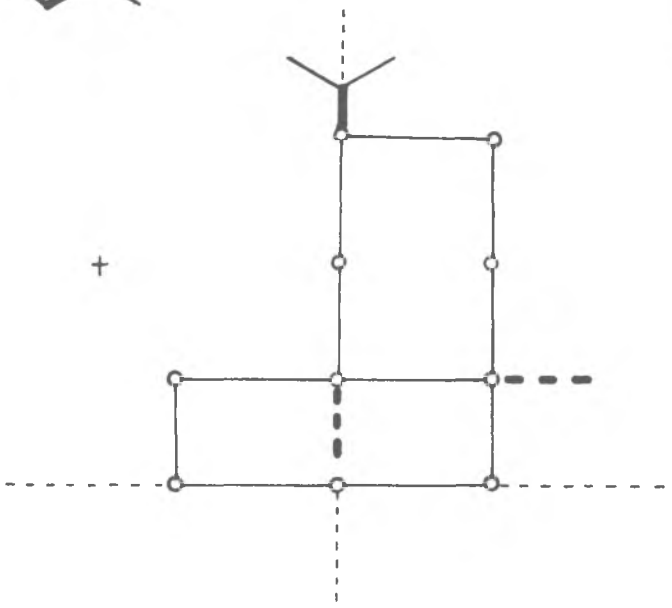
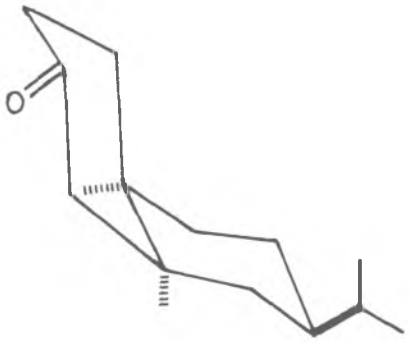


XXXII



LV



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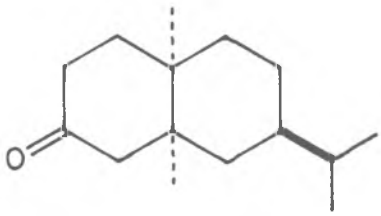
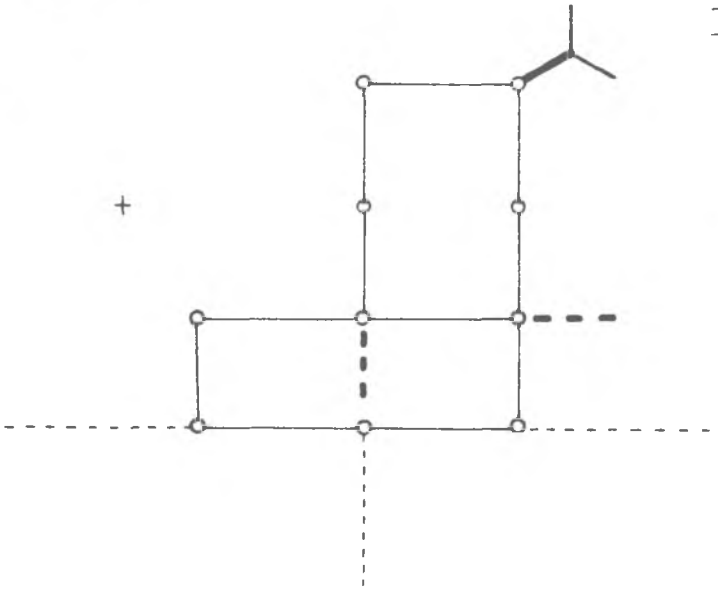


XXXIII



LVI

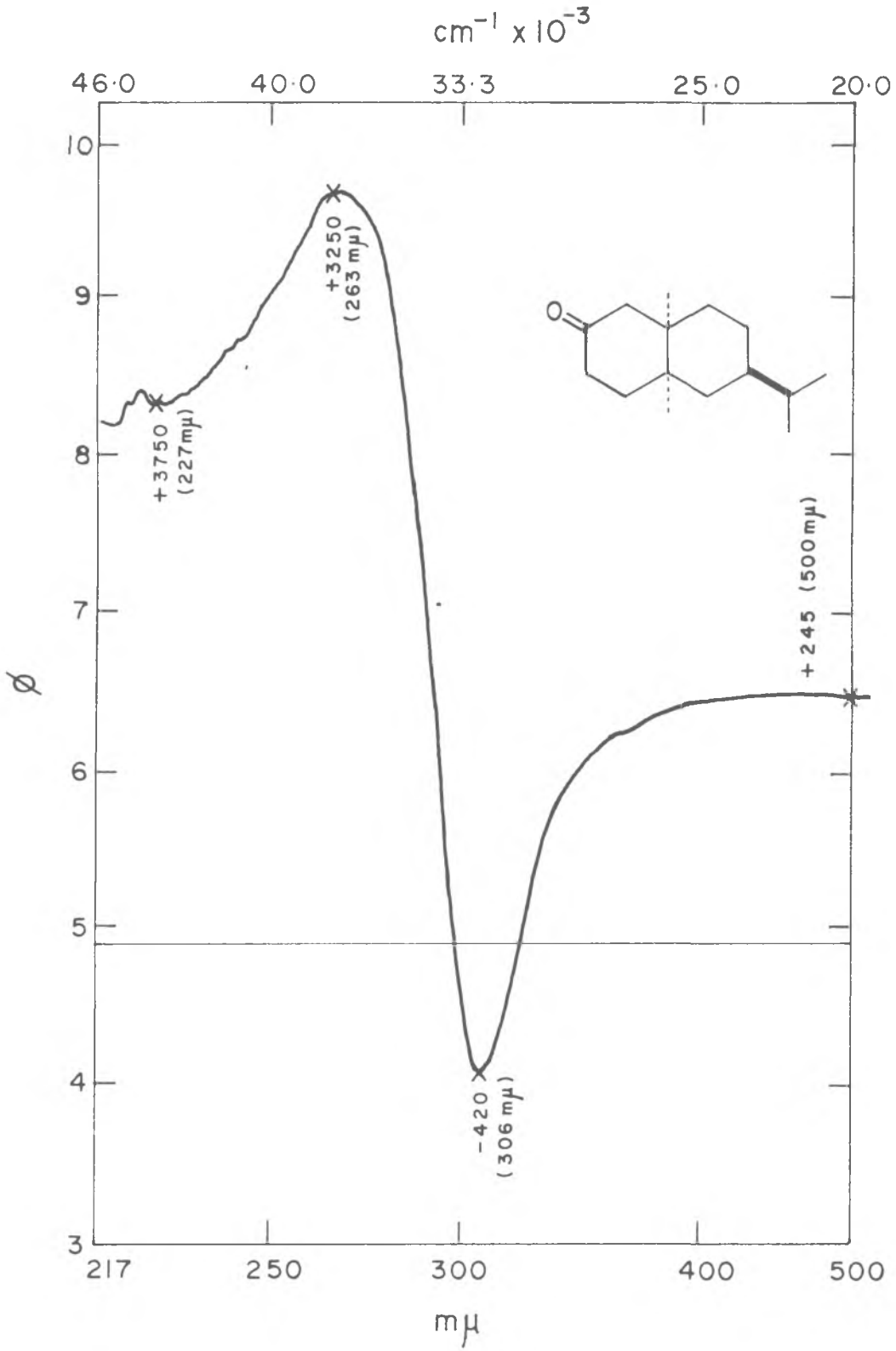
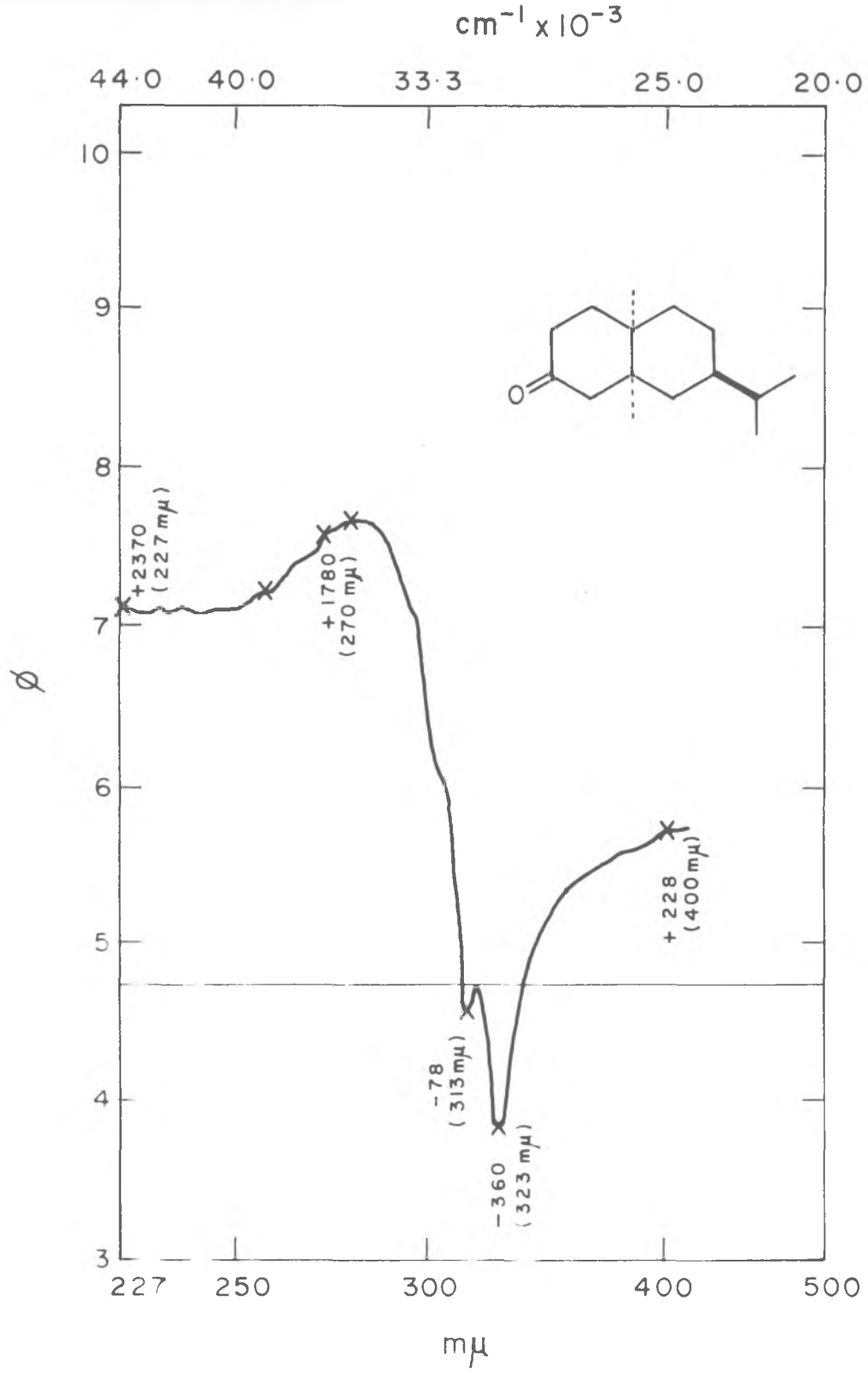

cm⁻¹ x 10⁻³
46·0
40·0
33·3
25·0
20·0
10
9
8
7
6
5
4
3
Ø
+3750 (227mμ)
+3250 (263 mμ)
-420 (306 mμ)
+245 (500 mμ)
O
217
250
300
400
500
mμ

FIG. 7


cm⁻¹ x 10⁻³
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40·0
33·3
25·0
20·0
10
9
8
7
6
5
4
3
Ø
+2370
(227 mμ)
+1780
(270 mμ)
-78
(313 mμ)
-360
(323 mμ)
+228
(400 mμ)
O
227
250
300
400
500
mμ

FIG. 8

of this ketone (XXXII) shows a negative Cotton effect. It has got an amplitude of -37, which fits the octant rule well.

Ketone (XXXIII)

The octant diagram of this ketone is shown in (LVI). In this case also the ketone should show a negative Cotton effect curve. The ORD curve of this ketone (Fig. 8) shows a negative Cotton effect. It indicates an amplitude of -28, which fits the octant rule well.

E X P E R I M E N T A L

Preparation of the benzoate of maaliol (XIII)

To maaliol (2.5 g) in pyridine (15 ml), benzoyl chloride (3.8 ml) was added while shaking and the mixture kept at the room temperature for 48 hr. and refluxed for 2 hr on a water bath. The reaction mixture was then poured into water, extracted with ether, the ether extract washed with dil. HCl, sodium carbonate solution and water, dried, solvent removed. The residue was chromatographed through gr.III alumina (25 g) and the benzoate was eluted with pet.ether and crystallised from the same solvent (3 g), m.p.103-104°.

IR spectrum of the benzoate showed bands at: 1695, 1585, 1278, 1255, 1147, 1110, 1087, 1055, 1015, 880, 711, 703 cm^{-1}.

Analysis

Found: C, 80.72; H, 8.92.

$C_{22}H_{30}O_2$ requires: C, 80.93; H, 9.26%.

Hydrocarbon XIV

The benzoate of maaliol (2.5 g) was pyrolysed at 200-210°/60 mm. in a pyrolysis flask till the liberation of benzoic acid was complete (20-30 mts.).

The pyrolysed product was taken in ether and washed free of benzoic acid with sodium carbonate solution (10%). The ether extract was washed free of alkali with water, dried, solvent removed and the residue chromatographed through gr.I alumina (30 g). The hydrocarbon (1.9 g) was eluted with pet.ether. GLC analysis showed 80:20 of γ-maaliene and β-maaliene, b.p.100°/0.3 mm.
IR spectrum of the hydrocarbon showed bands at: 1637, 1325, 1221, 1190, 1162, 1133, 1064, 1014, 980, 881, 858, 837, 801, 770 cm^{-1}.

Analysis

Found: C, 88.22; H, 11.62.

Calc. for $C_{15}H_{24}$ C, 88.16; H, 11.84%.

Norketone (XV) from hydrocarbon (XIV)

Hydrocarbon (1.7 g) in chloroform (20 ml) was ozonised at 0° till it was complete. The chloroform was removed and the ozonide was hydrolysed with water by heating on a water bath for 2 hr. The product was extracted with ether, dried and chromatographed through gr.II alumina (20 g). Any unreacted hydrocarbon was eluted with pet.ether. The ketone (1.2 g) was eluted with ether, b.p. 120°/0.35 mm.

D.N.P. of the norketone melted at 172°,

IR spectrum of nor-maaliona showed bands at: 1706, 1661(w), 1330, 1297, 1261, 1235, 1220, 1209, 1195, 1176, 1155, 1130, 1016, 1070, 1038, 1015, 944, 900, 825, 774, 745 cm^{-1}.

Analysis

Found: C, 81.3; H, 10.8.

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

Lactone XVI from normaaliona (XV)

To normaaliona (980 mg) in chloroform (50 ml) perbenzoic acid (900 mg) in chloroform and p-toluene sulphonic acid (10 mg) in benzene (25 ml) were added. The reaction mixture was allowed to stand for 7 hr. in freeze. The chloroform solution was extracted with 10% sodium carbonate solution, washed with water, dried and solvent removed.

IR spectrum showed bands at: 1764 and 1706 cm^{-1} showing it to be a mixture of lactone and ketone.

Hydrolysis of lactone (XVI) to hydroxycarboxylic acid(XVII)

The above product in dioxane (5 ml) and 10% sodium carbonate solution was heated under reflux for 3 hr. The solution was cooled, extracted with ether and acidified with a saturated solution of tartaric acid until the pH was 2-3. The insoluble organic material was taken up in

ether, washed with water, dried, solvent removed. The hydroxy acid was crystallised from pet.ether-ether mixture. The hydroxy acid (475 mg), melted at 119°. IR spectrum showed bands at: 3355, 2654, 1692, 1404, 1337, 1266, 1225, 1190, 1117, 1064, 1041, 985, 934, 907, 881, 846 cm^{-1}.

Analysis

Found: C, 70.20; H, 9.89.

Calc. for $C_{14}H_{24}O_3$: C, 69.95; H, 10.07%.

Ketoester (XVIII) from hydroxy acid (XVII)

The hydroxy acid (405 mg) in pyridine was added to pyridine-chromic oxide complex prepared by adding chromic oxide (1 g) to pyridine (18 ml), cooled to 10-15°. The reaction mixture was stirred for 17 hr. at 27°. The reaction product was poured into water, extracted, washed with dil. HCl, water, dried, solvent removed. The keto acid obtained was esterified with diazomethane as usual. The keto ester (300 mg) had a b.p.155°/0.5 mm.

IR spectrum showed bands at: 1738, 1692, 1225, 1250, 1220, 1190, 1170, 1112, 1011, 988, 959, 923, 888, 855, 797 cm^{-1}.

Analysis

Found: C, 71.21; H, 9.71.

Calc. for $C_{15}H_{24}O_3$: C,71.39; H, 9.59%.

Unsaturated ketoester (X) from ketoester (XVIII)

Ketoester (150 mg) was refluxed with 10% KOH (0.4 ml) and dioxane (1 ml) for 1/2 hr. The mixture was poured into water, extracted with ether, the ether extract washed with water, dried and the solvent removed. The residue did not show any absorption in the UV spectrum for the double bond in conjugation to a keto group. IR spectrum of the compound was different from that of the starting material. It could not be characterised due to small amounts.

The alkaline portion was acidified with dil. HCl, extracted with ether. The ether extract was washed free of acid, dried, the solvent removed. The residue in traces could not be characterised.

Hydrocarbon (XIV) from saaliol (XIII) via dehydration with thionyl chloride in pyridine

To a solution of the alcohol (1 g) in pyridine (10 ml), freshly distilled thionyl chloride (1.3 ml) in pyridine (10 ml) was added dropwise under cooling in an ice bath. After standing for 45 minutes at 0°, the excess reagent was destroyed with ice and the product extracted with ether. The ether extract was washed with dilute HCl, sodium carbonate solution, water, dried and the solvent removed. The residue was chromatographed through gr.I alumina (10 g.). The

hydrocarbon (900 mg) was eluted with pet.ether. GLC analysis showed it to be a mixture of γ- and β-maalienes in 55:45 proportions, b.p.100°/0.35 mm.

IR spectrum showed bands at: 1637, 1385, 1221, 1190, 1152, 1133, 1064, 1014, 950, 881, 858, 837, 801, 770 cm^{-1}.

Analysis

Found: C, 88.31; H, 11.75.

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

β-Maaliene (XIX) from hydrocarbon mixture (XIV)

The hydrocarbon mixture (850 mg) was added to a previously prepared N-lithioethylenediamine complex and refluxed for 6 hrs. with stirring in nitrogen atmosphere (the reagent was prepared by refluxing lithium in ethylene diamine in nitrogen atmosphere for 3 hr. The hydrogen formed during the reaction was removed by nitrogen). The reaction product was distilled to remove the ethylene diamine. The residue was poured into water, extracted with ether. The ether extract was washed with water, dried and the solvent removed. The residue was chromatographed through gr.I alumina (10 g). The hydrocarbon (750 mg) was eluted with ether. GLC analysis showed it to contain 95% of β-maaliene. It was purified by chromatography, b.p.100°/0.4 mm., $(\alpha)_D^{26}$ - 58.6° (c, 1.5).

IR spectrum showed bands at: 1335, 1235, 1163, 1143, 1073, 1021, 974, 959, 900, 859, 839, 797, 722, 745 cm^{-1}.

Analysis

Found: C, 87.91; H, 11.90.

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

β-Maali diol (XX) from β-maaliene (XIX)

To the hydrocarbon (600 mg) in pyridine (10 ml), a solution of osmium tetroxide (1 g) in pyridine (10 ml) was added slowly and with cooling (20°) and the mixture was allowed to stand for 11 days at 25° in the dark. The pyridine was removed under reduced pressure. A mixture of ethanol (30 ml) and benzene (30 ml) were added to the residue. Mannitol (10 g) and KOH (7 g) in water (20 ml) were added to the mixture and it was refluxed for 7 hrs. The mixture was allowed to cool, concentrated to 50 ml and it was extracted with ether, the ether extract washed with water, dried and the solvent removed. The solid residue was chromatographed through gr.II alumina (10 g). Pet.ether eluted the unreacted hydrocarbon. Pet. ether-benzene (1:1) eluted some oil. Ether eluted the solid diol. It was crystallised from pet.ether (275 mg), m.p. 92-93°.

IR spectrum showed bands at: 3401, 1340, 1319, 1282, 1202, 1178, 1163, 1117, 1047, 1030, 1015, 975, 930, 909, 883, 842, 790 cm^{-1}.

Analysis

Found: C, 75.36; H, 10.83.

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

Diketone (XXI) from β-maalidiol (XX)

To the diol (250 mg) in acetic acid (15 ml), lead tetraacetate (750 mg) in glacial acetic acid (15 ml) was added and the mixture was allowed to stand overnight at room temperature in the dark. The acetic acid was removed under reduced pressure. The residue was treated with pet.ether. The pet.ether extract was distilled to remove the solvent and the residue was chromatographed through gr.III alumina (10 g). Pet.ether eluted the diketone (174 mg), b.p.135°/0.01 mm.

IR spectrum showed bands at: 1706, 1684, 1404, 1321, 1248, 1218, 1163, 1130, 1011, 990, 955, 885, 798 cm^{-1}.

Analysis

Found: C, 76.38; H, 10.17.

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

Ketocarboxylic acid from diketone (XXI)

To a solution of the diketone (150 mg), in 0.8 ml of dioxane, 0.2 ml of water and 0.4 ml of 10% aqueous potassium hydroxide was added iodine potassium iodide solution till the reaction mixture was coloured

pale yellow. The reaction mixture was heated to 60° for 3 minutes. More iodine-potassium iodide solution was added until the yellow colour persisted. Water(2 ml) was added to the mixture and it was treated with sodium bisulphite (10%) solution, acidified, with hydrochloric acid, and extracted with ether. The ether extract was washed with water, dried and the solvent removed. The residue was taken up in ether and it was washed with sodium carbonate solution. The sodium carbonate solution was acidified with hydrochloric acid and extracted with ether. The extract was washed free of mineral acid, dried and solvent removed. The residue obtained (10 mg), in small amounts was not pursued further.

Unsaturated keto acid (XXIV) from (-) α-santonin(XXIII)

To liquid ammonia (2 L) was added with stirring lithium (3 g) during 2 hrs. To this a solution of santonin (10 g) in dry tetrahedrofuran (100 ml) was added. The reaction mixture was stirred for 3 hrs. and kept overnight, acidified with cold dilute sulphuric acid to congo red and the product was separated into acidic and neutral portions. The acidic portion (6 g) on crystallisation from acetone-hexane yielded the pure acid (XXIV; 4 g), m.p.123°.

IR spectrum showed bands at: 1709, 1661, 1608, 1448, 1417, 1377, 1351, 1232, 1179, 1084 and 1017 cm^{-1}.

Analysis

Found: C, 71.76; H, 8.94.

Calc. for $C_{16}H_{22}O_3$: C, 71.97; H, 8.86%.

Methylester (XXV) of the unsaturated keto acid

The acid (5 g) was taken in absolute methanol (50 ml) and dry HCl gas was passed through it for 2 hr. The reaction mixture was kept overnight. The reaction mixture was poured in water and extracted with ether. The ether extract was washed with sodium carbonate solution to remove any unreacted acid, washed with water, dried and the solvent removed. The residue was distilled (3.7 g), b.p.170°/0.08 mm.

IR spectrum of the methyl ester showed bands at: 1736, 1664, 1626, 1608, 1342, 1295, 1252, 1163, 1119, 1063, 1018, 1005, 872, 851, 832 cm^{-1}.

Analysis

Found: C, 72.43; H, 8.97.

Calc. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15%.

Diol (XXVI) from unsaturated keto ester (XXV)

To lithium aluminium hydride (1 g) in dry ether (30 ml) was added the unsaturated keto ester (2.5 g) in dry ether dropwise. The reaction mixture was cooled in an ice bath. After the addition, the reaction mixture was refluxed for 6 hrs. with stirring. The excess reagent was decomposed with moist ether at 0°. The reaction

mixture was taken in a separating funnel, washed with dilute HCl, water, dried and the solvent removed. The residue was a semisolid which was chromatographed through gr.III alumina (40 g). The diol (2.3 g) was eluted with ether and distilled, b.p.180-190°/0.08 mm.

IR spectrum showed bands at: 3425, 1295, 1220, 1202, 1117, 1070, 1028, 995, 933, 867, 832, 807 cm^{-1}.

Analysis

Found: C, 76.12; H, 11.04.

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

Tosylate of diol (XXVI)

To the diol (2 g) in pyridine (30 ml) was added p-toluene sulphonyl chloride (2.5 g). The mixture was thoroughly shaken and kept for 48 hr. at room temperature. The mixture was poured into water and extracted with ether. The ether extract was washed with dil. HCl, sodium carbonate solution, water, dried and the solvent removed. The tosylate (2.1 g), obtained was subjected to lithium aluminium hydride reduction.

IR spectrum of the tosylate of the diol showed bands at: 1590, 1299, 1188, 1170, 1117, 1095, 1018, 966, 936, 870, 841, 812 cm^{-1}.

Reduction of tosylate of diol to hydrocarbon(XXVII)

To lithium aluminium hydride (1 g) in dry ether (30 ml) was added the tosylate of the diol (2.1 g) in dry ether (25 ml). The reaction mixture was cooled with ice during the gradual addition of the material. After the addition the reaction mixture was refluxed for 8 hr. with stirring. The excess of reagent was decomposed with moist ether at 0°. The reaction mixture was taken in a separating funnel, washed with dil. HCl, water, dried, and the solvent removed. The residue was chromatographed through gr.I alumina (15 g). The hydrocarbon (1.5 g) was eluted with pet.ether, b.p. 105°/0.8 mm.

IR spectrum showed bands at: 1295, 1218, 1163, 1117, 1070, 1017, 998, 931, 846, 810 cm^{-1}.

Analysis

Found: C, 86.76; H, 13.15.

Calc. for $C_{16}H_{26}$: C, 87.30; H, 12.70%.

The hydrocarbon obtained was subjected to osmium tetroxide oxidation. The product obtained was found to be the starting material. Tetranitromethane test of the hydrocarbon was negative showing its saturated nature. Thus it appeared that the hydrocarbon was reduced during the lithium aluminium hydride reduction of the unsaturated ketoester (XXV).

Norketo alcohol (XXVIII) from β-eudesmol (XII)

β-Eudesmol (1 g) in chloroform (20 ml) was ozonised at 0° till the reaction was complete. The chloroform was distilled off and the ozonide obtained was hydrolysed by refluxing it with water for 2 hr. on a water bath. It was extracted with ether. The ether extract was dried, the solvent removed. The residue was chromatographed through gr.III alumina (20 g). The keto alcohol was eluted with ether. It was distilled (750 mg), b.p.150°/0.5 mm.

IR spectrum of nor keto alcohol showed bands at: 3460, 1701, 1282, 1261, 1198, 1147, 1122, 1104, 1093, 958 cm^{-1}.

Analysis

Found: C, 75.3; H, 10.41.

Calc. for $C_{14}H_{22}O_2$: C, 75.0; H, 10.71%.

Hydroxylactone (XXIX) from norketoalcohol (XXVIII)

To the norketoalcohol (700 mg) in chloroform (10 ml) perbenzoic acid (800 mg) in chloroform and p-toluene sulphonic acid (5 mg) in benzene (15 ml) were added. The reaction mixture was allowed to stand overnight in freeze. The chloroform solution was washed with sodium carbonate solution, water, dried and solvent removed. The IR spectrum showed it to be a mixture of the hydroxy lactone and the starting material, bands at: 1770, 1709 cm^{-1}.

Ester diol (XXX) from hydroxylactone (XXIX)

The above material (650 mg) was refluxed with 10% sodium carbonate solution (10 ml) for 3 hr. The solution was cooled, extracted with ether. The alkaline solution was acidified with dil. HCl and extracted with ether. The ether extract was washed free of mineral acid, dried and the solvent removed. The acid diol obtained was esterified using diazomethane in the usual manner. The ester diol (300 mg) obtained was put for oxidation.

Hydroxyketo ester (XXXI) from ester diol(XXX)

To the diol ester (300 mg) in acetone was added 8N chromic acid dropwise till the colour persisted. Ethanol (5 ml) was added to destroy the excess of chromic acid. The reaction mixture was poured into water, extracted with ether. The ether extract was washed free of acid with water, dried and the solvent removed. The residue was chromatographed through gr.III alumina (5 g). The residue was distilled (176 mg), b.p. 170°/0.01 mm.

IR spectrum showed bands at: 3545, 1742, 1721, 1279, 1202, 1183, 1176, 1135, 1050, 1030, 955, 869 cm^{-1}.

Analysis

Found: C, 67.14; H, 10.05.

Calc. for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69%.

Unsaturated ketoester (XI) from hydroxy ketoester(XXXI)

To the hydroxy ketoester (150 mg) in toluene (5 ml) was added p-toluene sulphonic acid (10 mg). The mixture was refluxed for 20 minutes on an oil bath. The reaction mixture cooled, taken up in ether, washed with sodium carbonate solution (1%), washed with water, dried, solvent removed. The residue was distilled, b.p.160°/1 mm. The IR spectrum did not show any conjugation of double bond with a carboxyl group, UV did not absorb at 235 mμ. The compound obtained could not be characterised. Because of paucity of material, the reactions were not further pursued.

Preparation of valeranol (LI)

Valeranone (3 g) in dry ether (25 ml) was added dropwise to an ice cold solution of dry ether (100 ml) containing lithium aluminium hydride (800 mg). After the addition, the reaction mixture was refluxed with stirring for 4 hr. The reaction mixture was cooled and the excess of the reagent was decomposed with moist ether. The ether solution was taken in a separating funnel, and washed with dilute hydrochloric acid, water, dried and the solvent removed. The residue was chromatographed over gr.III alumina (30 g). Any unreacted ketone was eluted with pet.ether. The alcohol was eluted with ether. The alcohol (2.9 g) was distilled, b.p.125-130°/3 mm. It is a colourless

liquid. IR spectrum of the alcohol showed bands at: 3472, 1385, 1370, 1330, 1253, 1220, 1195, 1178, 1105, 1025, 939, 925 and 829 cm^{-1}.

Analysis

Found: C, 80.45; H, 12.72.

Calc. for $C_{15}H_{28}O$: C, 80.30; H, 12.50%.

Hydrocarbon (LII) from valeranol (LI)

Valeranol (2.8 g) was heated with phthalic anhydride (3 g) at 270-280° for 1 hr. After cooling the reaction mixture was extracted with pet.ether and poured on a column of gr.I alumina (50 g). The fraction eluted with pet.ether afforded the hydrocarbon (1.8 g), b.p.125-130°/5 mm., n_D^{29} 1.4860. GLC analysis showed one peak. IR spectrum of the hydrocarbon showed bands at: 1650(w), 1332, 1290, 1266, 1208, 1163, 1124, 1099, 1085, 1026, 930, 888, 855, 818, 799, 770, 745, 708 cm^{-1}.

Analysis

Found: C, 87.06; H, 12.60.

Calc. for $C_{15}H_{28}$: C, 87.30; H, 12.70%.

Unsaturated ketone (LIII) from hydrocarbon (LII)

A solution of the hydrocarbon (1.7 g) and sodium dichromate (6 g) in glacial acetic acid (80 ml) was kept overnight at room temperature; then heated at 95-100° for 2 hr. on a water bath. Ethanol (3 ml) was

added to the hot solution to decompose the excess of dichromate and the resulting solution was diluted with water. The solution was extracted with ether, washed free of acid with water, dried and the solvent removed. The product (1.5 g) was chromatographed through gr.II alumina (80 g). The unreacted hydrocarbon was eluted with pet.ether. The unsaturated ketone (400 mg) was eluted with ether. The ether eluate was put for semicarbazone preparation and the semicarbazone obtained was crystallised from alcohol, dried. It had m.p. 199-200°.

Analysis

Found: N, 14.85.

$C_{16}H_{27}ON_3$ requires: N, 15.16%.

The semicarbazone was decomposed with oxalic acid in the usual manner. The ketone obtained (250 mg) had b.p.140°/3.5 mm. IR spectrum of the unsaturated ketone showed bands at: 1678, 1618, 1414, 1388, 1174, 1087, 1053, 1026, 980, 916, 878, 840, 818 and 776 cm^{-1}.

$\lambda_{max.}$ 235 mμ, log ε 3.7314.

Analysis

Found: C, 81.66; H, 10.82.

$C_{16}H_{24}O$ requires: C, 81.81; H, 10.91%.

Hydrogenation of unsaturated ketone (LIII) to ketone (XXXII)

The unsaturated ketone (240 mg) in ethanol (25 ml) was hydrogenated in the presence of pre-reduced Adams catalyst (20 mg) until no further absorption took place. The catalyst was separated by filtration and the solvent was removed. The product obtained was chromatographed through gr.II alumina (6 g) and the saturated ketone was eluted with pet.ether. The ketone had a b.p.140°/1.7 mm., n_D^{27} 1.4905.

IR spectrum (Fig. 4) of the ketone showed bands at: 1724, 1387, 1377, 1260, 1181, 940, 925 and 831 cm^{-1}.

Analysis

Found: C, 81.35; H, 12.06.

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

Hydrocarbon (LII) from valeranol (LI) (by boric acid)

Valeranol (2.3 g) was heated with boric acid (3 g) at 200° for 30 minutes. The product was distilled under reduced pressure. The distillate was taken up in ether, washed with aqueous potassium carbonate, washed free of alkali, dried and solvent removed. The residue (1.8 g) was chromatographed through gr.I alumina(30 g). The hydrocarbon (1.5 g) was eluted with pet.ether, b.p.125-130°/5 mm., n_D^{28} 1.4865. GLC analysis showed

one peak. IR spectrum of the hydrocarbon showed bands at: 1650(w), 1332, 1290, 1266, 1208, 1163, 1124, 1099, 1056, 1026, 930, 888, 855, 818, 799, 770, 745, 708 cm^{-1}.

Analysis

Found: C, 87.21; H, 12.75.

Calc. for $C_{18}H_{36}$: C, 87.30; H, 12.70%.

Alcohol (LIV) from hydrocarbon (LII)

Diborane produced by the gradual addition of sodium borohydride (2 g) in diglyme (50 ml) to boron-trifluoride (30 ml) was passed through an ice cold solution of the hydrocarbon (1.1 g) in tetrahydrofuran (25 ml) for 1 hr. The reaction was carried out under dry conditions and in an atmosphere of nitrogen, which acted as the carrier gas. The boron complex in tetra-hydrofuran was decomposed with alkaline hydrogen peroxide (10 ml of 50% KOH and 25 ml of H_2O_2). The product was extracted with ether, washed free of alkali, dried and solvent removed. The residue was chromatographed through gr.III alumina (30 g). It was eluted with pet.ether to remove any unreacted hydrocarbon. The alcohol (1 g) was eluted with ether. The alcohol on GLC analysis showed two alcohols in 90:10 proportions. The alcohol is a liquid b.p.140°/ 1.5 mm.

IR spectrum showed bands at: 3468, 1239, 1176, 1117, 1108, 1010, 929, 839, 786, 760 cm^{-1}.

Analysis

Found: C, 80.14; H, 12.40.

$C_{15}H_{28}O$ requires: C, 80.30; H, 12.80%.

Ketone (XXXIII) from alcohol (LIV)

To the alcohol (950 mg) in acetone 8N chromic acid was added drop by drop till there is an excess of chromic acid. The reaction mixture was diluted with water and extracted with ether. The ether extract was washed free of acid with water, dried and solvent removed. The residue was chromatographed through gr.II alumina (15 g). The ketone (850 mg) was eluted with pet.ether. On GLC analysis the ketone showed two peaks in 90:10 proportions. The minor peak was found to be valeranone by comparative GLC with an authentic sample of valeranone. The ketone was put for semicarbazone preparation. The semicarbazone obtained (1.1 g) was fractionally crystallised from alcohol. A semicarbazone of constant melting point at 217-218° was obtained.

Analysis

Found: N, 14.86.

$C_{16}H_{29}N_3O$ requires: N, 15.04%.

The semicarbazone (700 mg) was decomposed as usual with oxalic acid. The regenerated ketone had a b.p.135-140°/1.5 mm., n_D^{28} 1.4910.

IR spectrum (Fig.6) of the ketone showed bands at: 1718, 1439(w), 1418(w), 1312, 1239, 1175, 1117, 1078, 1010, 928, 840, 785, 759 cm^{-1}.

Analysis

Found: C, 81.26; H, 11.95.

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

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C H A P T E R III

SYNTHESIS OF C18-NORBERGAMOTINIC ACID

**

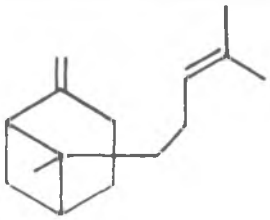
SUMMARY

The new sesquiterpene hydrocarbon, β-bergamotene has been recently isolated from the valerian root oil of Indian variety viz. Valeriana wallichi D.C. in this laboratory. Cis-norbergamotinic acid, an important intermediate required for the synthesis of α- and β-bergamotenes has been synthesised. Methyl heptenone on condensation with ethyl cyanoacetate in the presence of ethanolic ammonia gave the Guareschi's imide. The cyclobutane ring was introduced by refluxing the sodium salt of Guareschi's imide in methanolic solution with methylene iodide. The cyclised Guareschi's imide was hydrolysed to give the tetracarboxylic acid. The latter on decarboxylation gave a mixture of cis- and trans-norbergamotinic acids. To obtain pure cis-norbergamotinic acid, the mixture of acids was heated with acetic anhydride. The anhydride thus obtained on hydrolysis with water gave cis-norbergamotinic acid, which is a key material for the total synthesis of bergamotenes.

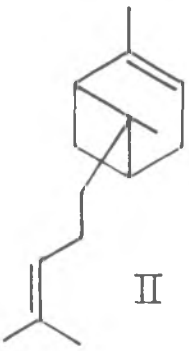
A new sesquiterpene hydrocarbon, β-bergamotene has been isolated recently from Indian valerian root oil in this Laboratory. Its structure has been established as (I) by the application of modern physical methods and chemical degradation to known products.[1] Its ∝-isomer, ∝-bergamotene (II) has been previously examined by Sorm et al and also by others.[2]

Cis-norbergamotinic acid (III) an important intermediate required for the total synthesis of ∝- and β- bergamotenes, has been synthesised. The laboratory scale experiments were standardised by the present author and the results are presented in this chapter. The synthesis is patterned in the lines used for the synthesis of cis- norpinic acid.[3] The route adopted for the synthesis of cis-norbergamotinic acid is represented in scheme I.

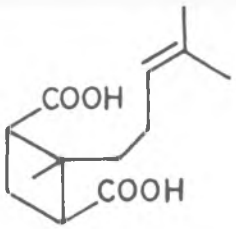
Methyl heptenone on condensation with ethyl cyanoacetate in the presence of ethanolic ammonia gave the Guareschi's imide (IV) (2,4-dicyano-3-methyl-3-(2-methyl-Δ^2-pentene) glutarimide) which was crystallised from ethanol or isopropyl alcohol in 68% yields. The imide (IV) melted at 190°. The IR spectrum of the imide (Fig. 9) showed bands at 3236 (bonded amide- NH absorption; compounds containing the group CO-NH-CO);



I

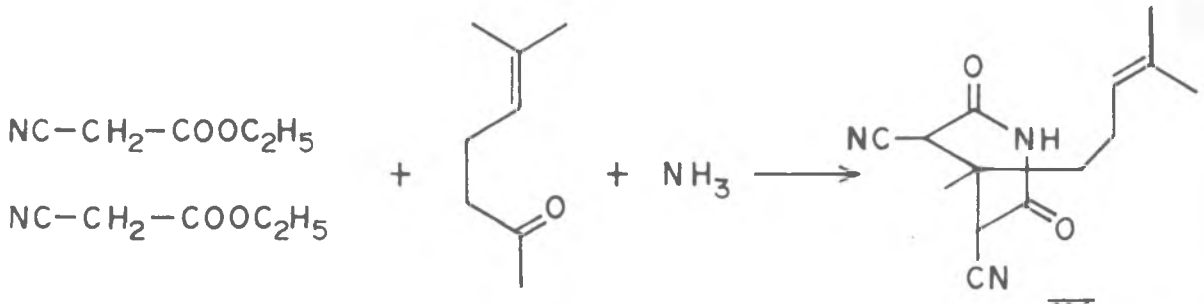


II

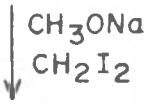


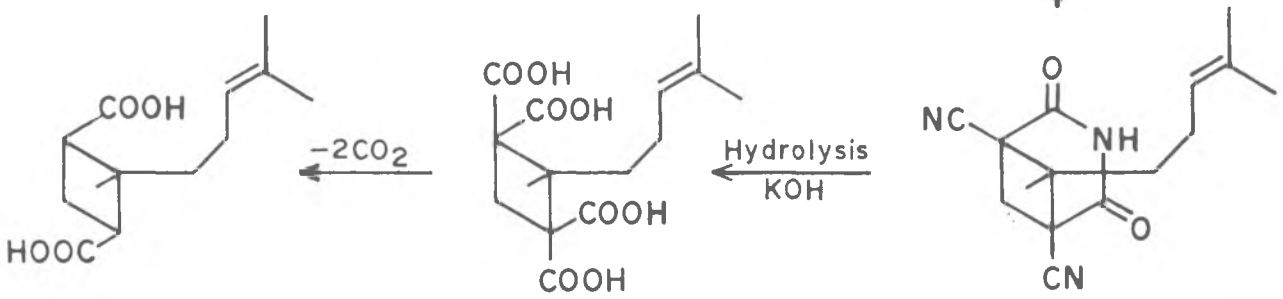
III

SCHEME No. I

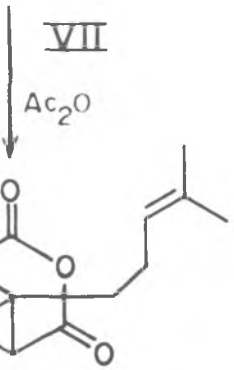


IV

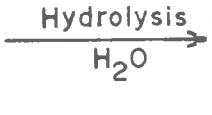


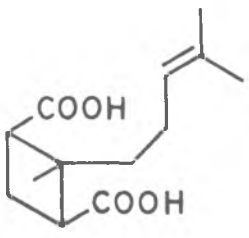


V VI VII



VIII



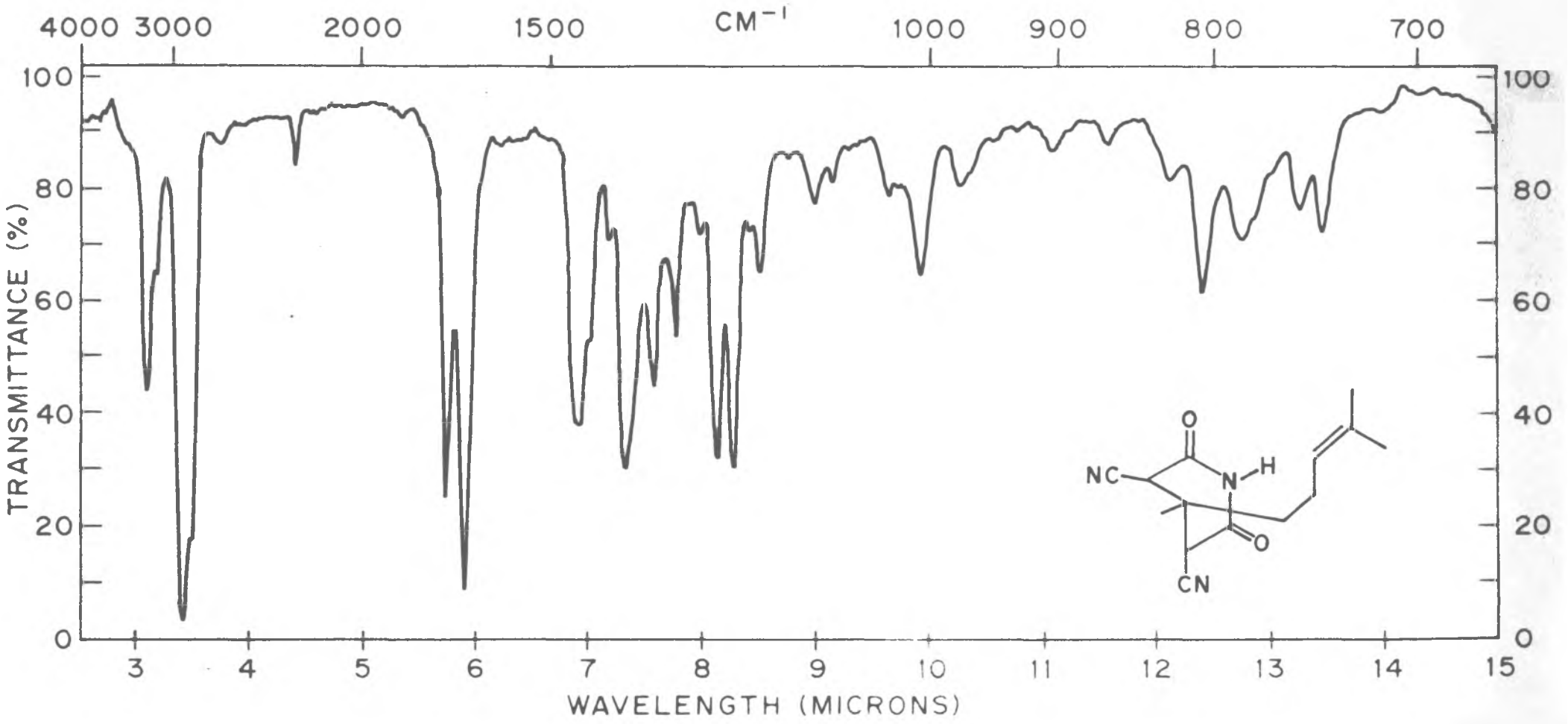


III

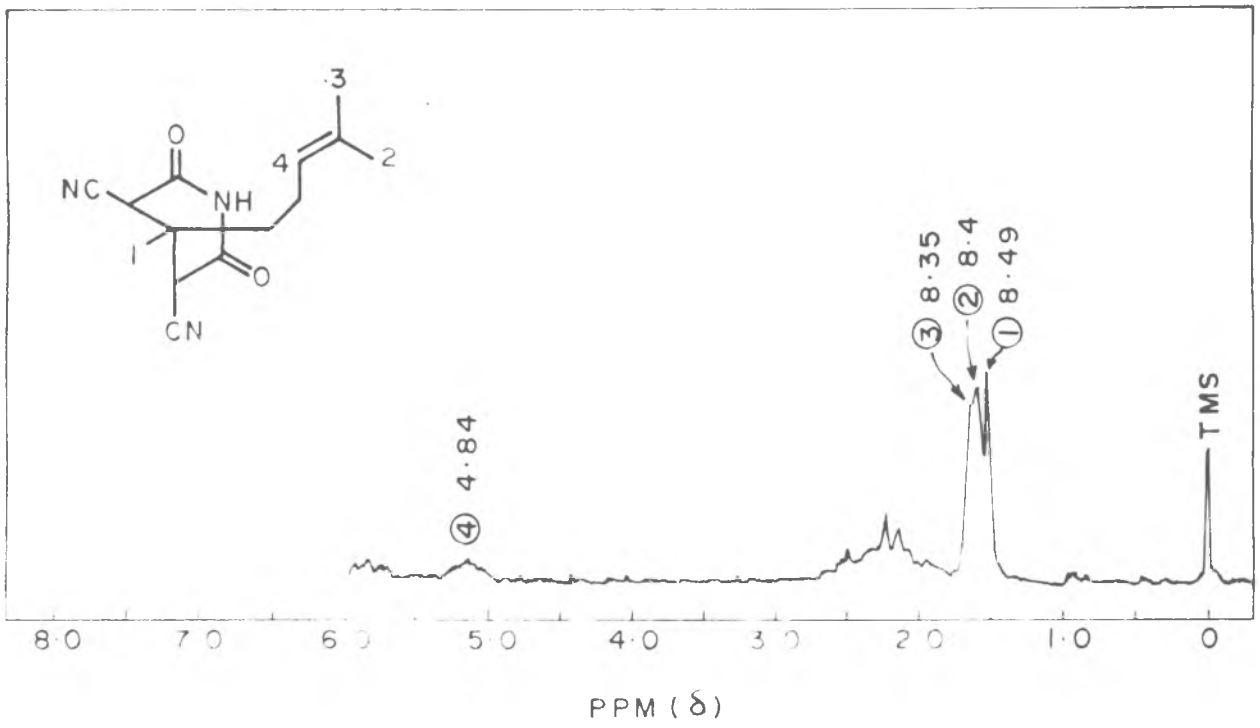
2268 (-C≡N stretching vibration); 1739, 1695 (CO-NH-CO absorption) and 828 cm^{-1} (a trisubstituted double bond in the form of an isopropylidene group - peak at 1366 cm^{-1}).

NMR spectrum of imide (IV) (Fig.10) showed the presence of one vinyl proton (signal at 4.84 τ (1H) C=CH-); two methyl groups on a double bond (signals at 8.4 and 8.35 τ (6H) $\frac{CH_3}{CH_3}>C=$) and one quarternary methyl group (singlet at 8.49 τ (3H) $\geqslant C-CH_3$). The standard compound, acetone guaresehimide (IX) showed a signal at 8.51 τ (6H) representing the two quarternary methyl groups.

The cyclobutane ring was introduced in the imide IV by refluxing its sodium salt in methanolic solution with methylene iodide. Acidification then gave (V) (crude m.p.152°) which on crystallisation from isopropyl alcohol or ethanol showed a constant m.p.178° (yield 87%). The IR spectrum (Fig.11) of this compound showed absorption bands at 3278 (>NH stretching vibration), 2252 (-C≡N), 1745, 1715 (>C=O), 834 (>C=CH-) and 1366 cm^{-1} ($\frac{CH_3}{CH_3}>C=CH$). A strong peak at 1136 cm^{-1} has appeared in the cyclised imide V which might be attributed to the inclusion of cyclobutane ring in the imide (IV). Bands at 895, 878 cm^{-1} can be attributed to the presence of a cyclobutane ring in the molecule.


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
O
NC
N
H
O
CN

FIG·9


3
2
4
NC
NH
1
CN
O
O
④ 4·84
③ 8·35
② 8·4
① 8·49
TMS
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)

FIG·10

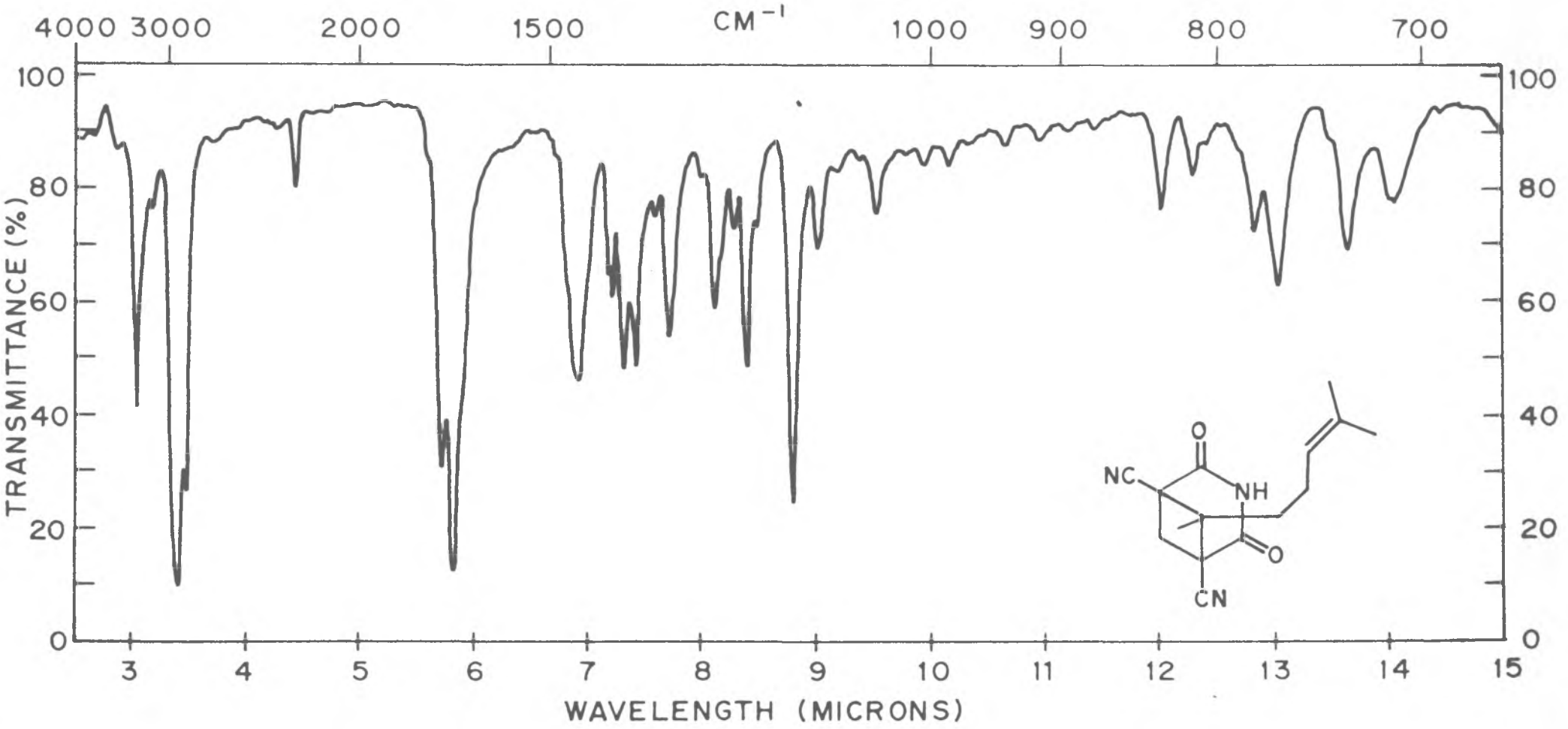
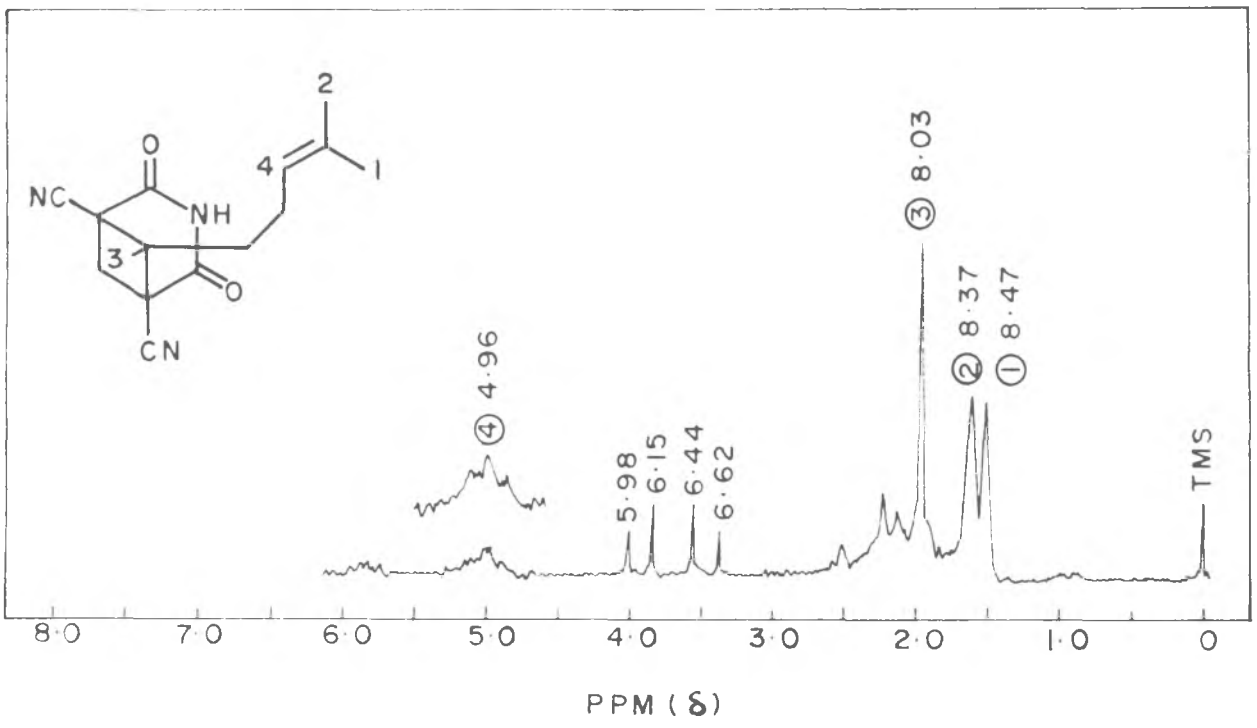

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
NC
NH
O
O
CN

FIG. II

NMR spectrum (Fig.12) of the cyclised imide (V) indicated the presence of one vinyl proton (signal at 4.96 τ(1H) >C=CH), two methyl groups on a double bond (signals at 8.47 and 8.37 τ(6H) and one quarternary methyl group (singlet at 8.03 τ(3H). The NMR spectrum also gives a typical quartet at 5.98, 6.15, 6.44 and 6.62 τ(2H) which is almost identical with a similar quartet (6.0, 6.18, 6.5; 6.68 τ(2H) observed in the case of the cyclised acetone guareschimide (X) (Fig.13). The cyclised imide V shows a signal at 8.03 τ for a quarternary methyl which indicates that the stereochemistry of (V) is as shown in (Va). The corresponding imide (X) in the pinane series shows signals at 8.13 and 8.7 τ for the two quarternary methyl groups. The absence of signal at 8.7 τ in V indicates that only one compound is formed and that too has the stereochemistry as shown in Va.

The cyclised imide (V) was hydrolysed by refluxing gently with aqueous potassium hydroxide (10%, 10 moles, 12 hr) and worked up as usual to yield the malonic acid derivative (VI) in 30% yields, alongwith products of partial decarboxylation, as revealed by the nitrogen analysis of cyclohexylamine salt. The IR spectrum of VI showed bands at 1709, 1368 and 832 cm^{-1}.

Decarboxylation of the malonic acid derivative VI was done by heating it at 180-185° for 30 minutes. The


2
O
4
1
NC
NH
3
O
CN
④ 4·96
5·98
6·15
6·44
6·62
③ 8·03
② 8·37
① 8·47
TMS
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)

FIG·12

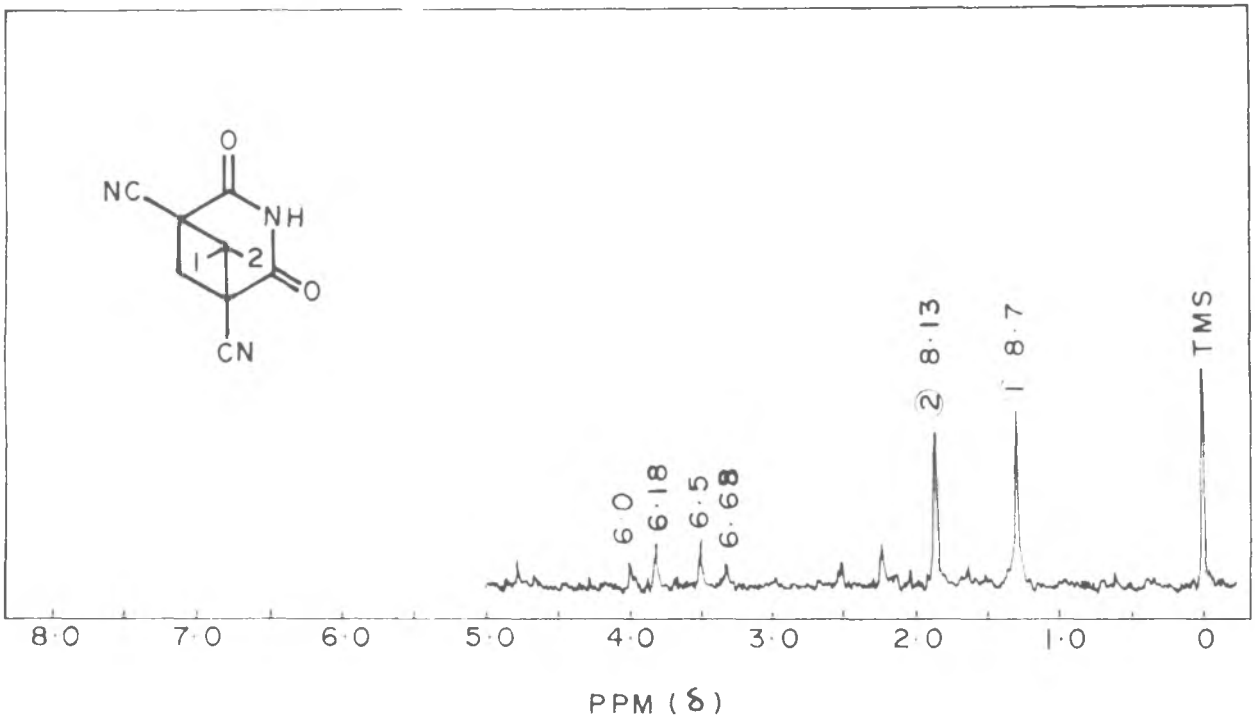
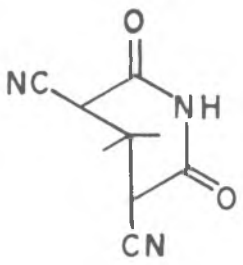
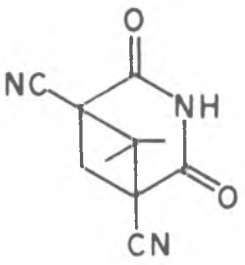

O
NC
NH
1
2
O
CN
6·0
6·18
6·5
6·68
2 8·13
1 8·7
TMS
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)

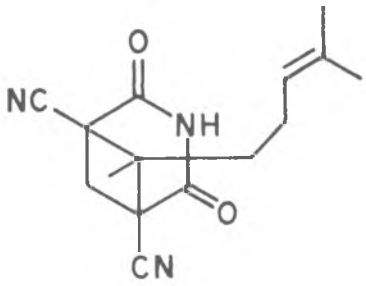
FIG. 13



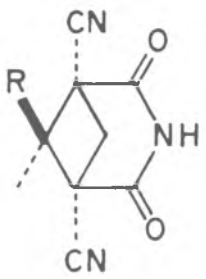
IX



X

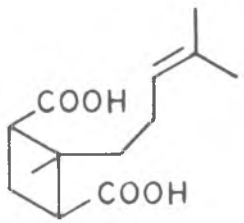


V

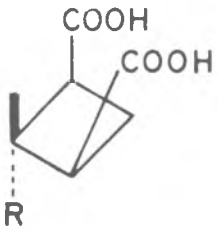


R = $\begin{matrix} CH_3 \\ \diagdown \\ \quad C = CH - CH_2 - CH_2 - \\ \diagup \\ CH_3 \end{matrix}$

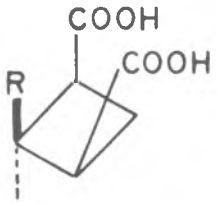
V a



III



III a



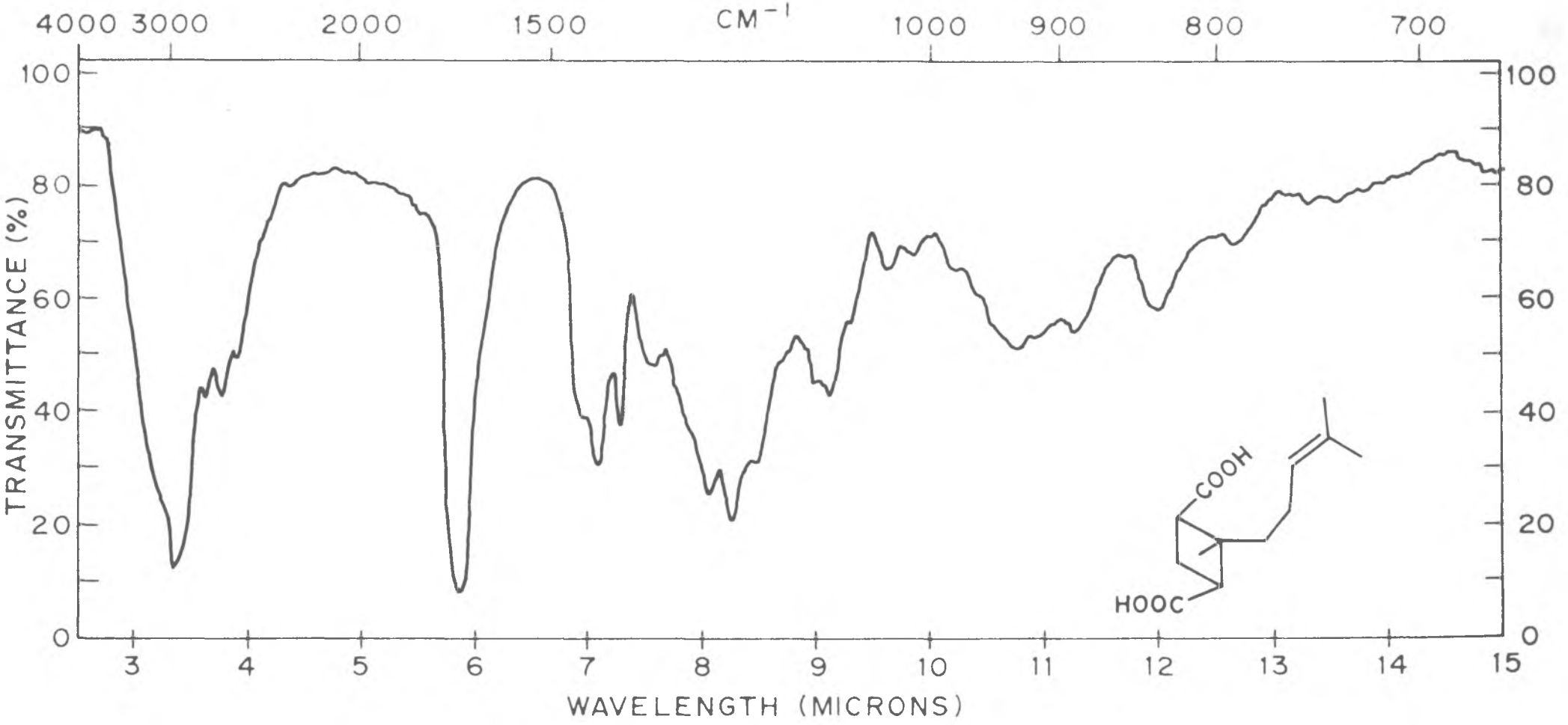
R = $\begin{matrix} CH_3 \\ \diagdown \\ \quad C = CH - CH_2 - CH_2 - \\ \diagup \\ CH_3 \end{matrix}$

III b

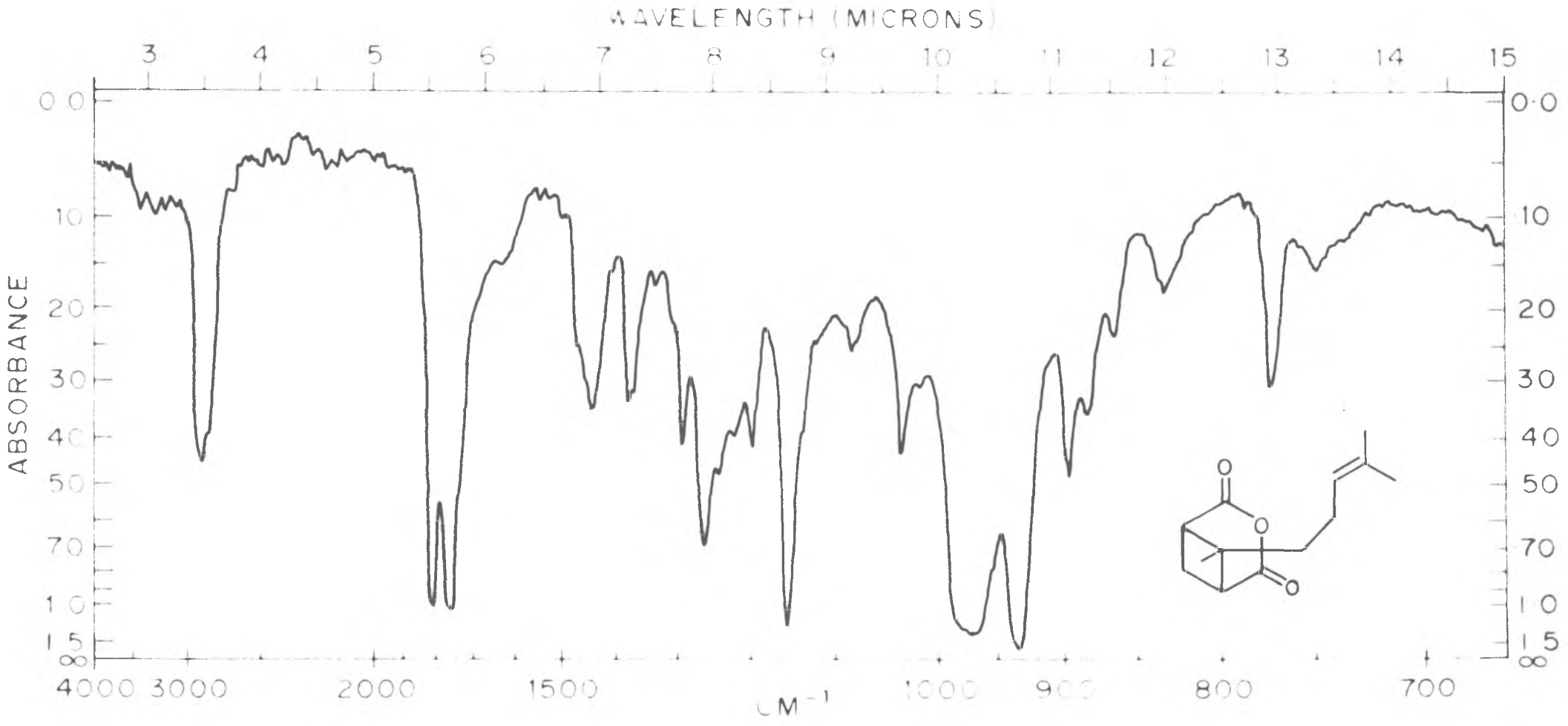
resulting product in the form of a semisolid, should be essentially a mixture of cis- and trans-dicarboxylic acids (III and VII). Yield was quantitative. Attempt to obtain an isomerically pure dicarboxylic acid via the crystalline cyclohexylamine salt (m.p.168°) did not give the desired results. IR spectrum (Fig.14) showed bands at 1709 (>C=O of the -COOH), 832 cm^{-1} (>C=CH).

Following the procedure adopted in the case of norpinic acid, the mixture of the dicarboxylic acids was heated with acetic anhydride (3 ml for 1 g) at 180-200° for 5 hr in a sealed tube. The anhydride(VIII) (yield 55.8%) thus obtained was distilled, b.p.175°(bath)/ 5 mm. It is a pale yellow viscous liquid. IR spectrum of the anhydride (Fig.15) showed bands at 1818, 1770 (>C=O absorption), 1266 (-C-O-C stretching vibration), 834 cm^{-1} (>C=CH-). It also showed strong bands at 1160, 978 and 948 cm^{-1}.

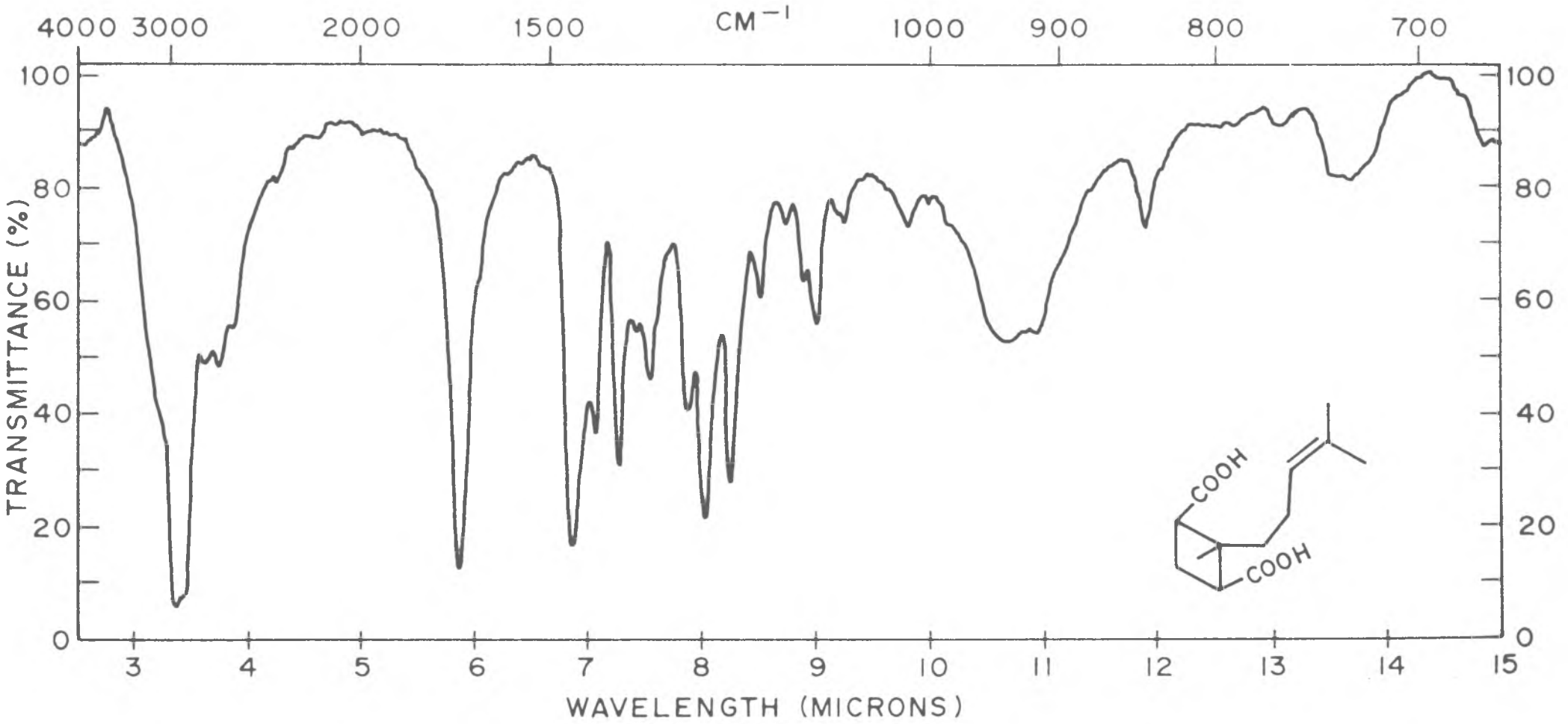
The anhydride (VIII)was hydrolysed by heating with water and the product obtained (yield, quantitative) was crystallised from pet.ether-ether mixture. The cis-norbergamotinic acid (III) crystallised as a colourless solid melting at 168°. IR spectrum (Fig.16) showed bands at 1706 (>C=O of -COOH), 832 cm^{-1} (>C=CH). The dimethyl ester of the cis- acid (III) was prepared


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
COOH
HOOC

FIG·14


WAVELENGTH (MICRONS)
3
4
5
6
7
8
9
10
11
12
13
14
15
0·0
10
20
30
40
50
70
1·0
1·5
∞
ABSORBANCE
4000
3000
2000
1500
1000
900
800
700
CM⁻¹
O
O
O
O

FIG·15


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
COOH
COOH

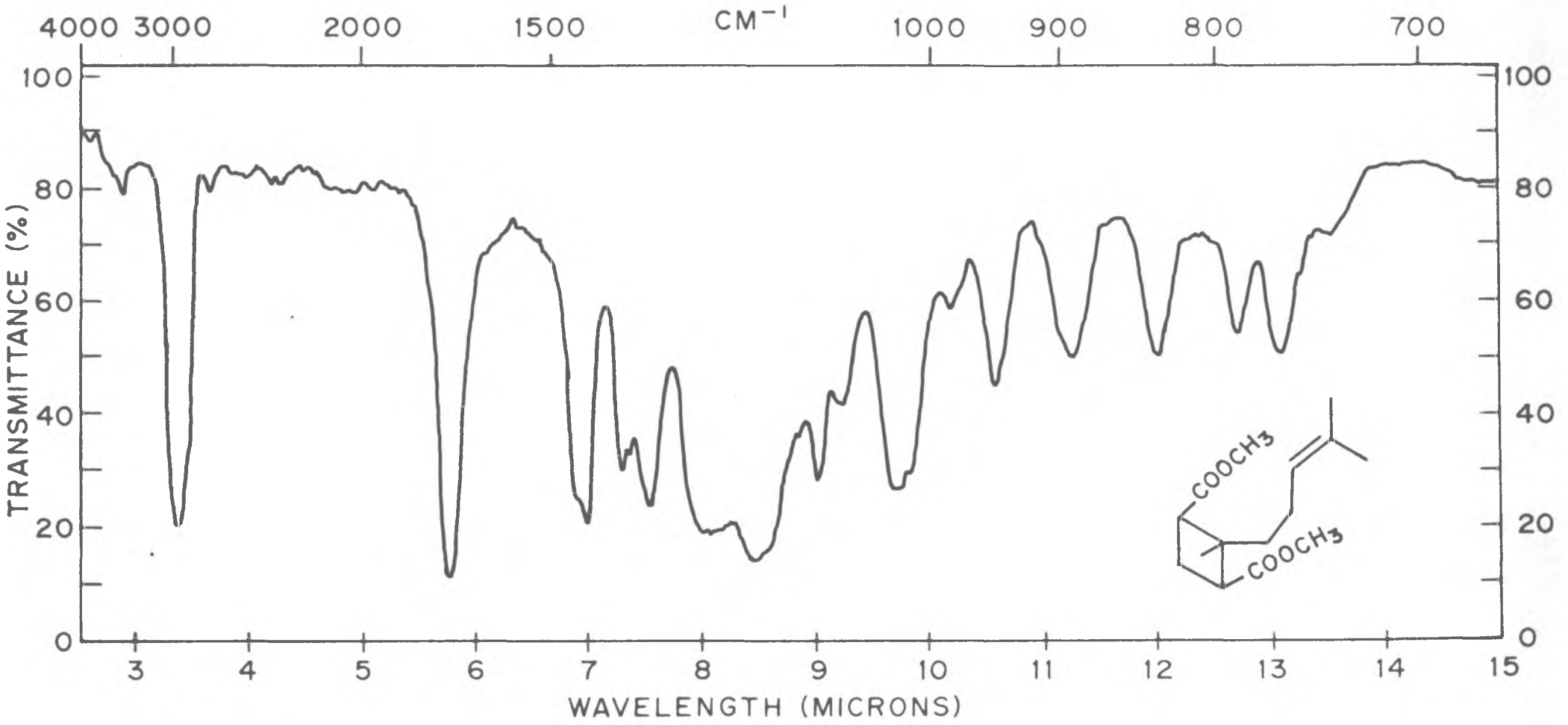
FIG·16

by treatment with diazomethane. The IR spectrum (Fig.17) of the dimethyl ester showed bands at: 1733 (>C=O of ester), 1255 (C-O- of ester), 832 cm^{-1} (>C=CH).

The NMR spectrum of the dimethyl ester (Fig.18) in CCl_4 indicated the presence of a vinyl proton (signal at 4.92 τ (1H), >C=CH), two methyl groups on a double bond (signals at 8.37, 8.32 τ (6H) and one quarternary methyl group (singlet at 9.07 τ (3H).

The NMR spectrum of the dimethyl ester of cis-norpinic acid (Fig.19) is comparable to the NMR spectrum of the dimethyl ester of cis- norbergamotinic acid.

There is the possibility of the formation of two anhydrides which on hydrolysis should give two cis-acids, (IIIa & IIIb). The NMR spectrum of the diester showed the methyl signal at 9.07 τ which indicates that the methyl group is not shielded and therefore should have the configuration (IIIb) since the corresponding dimethyl ester of cis-norpinic acid gives signals at 9.01 and 8.7 τ for the two quarternary methyl groups.


4000 3000
2000
1500
CM⁻¹
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)
COOCH3
COOCH3

FIG·17

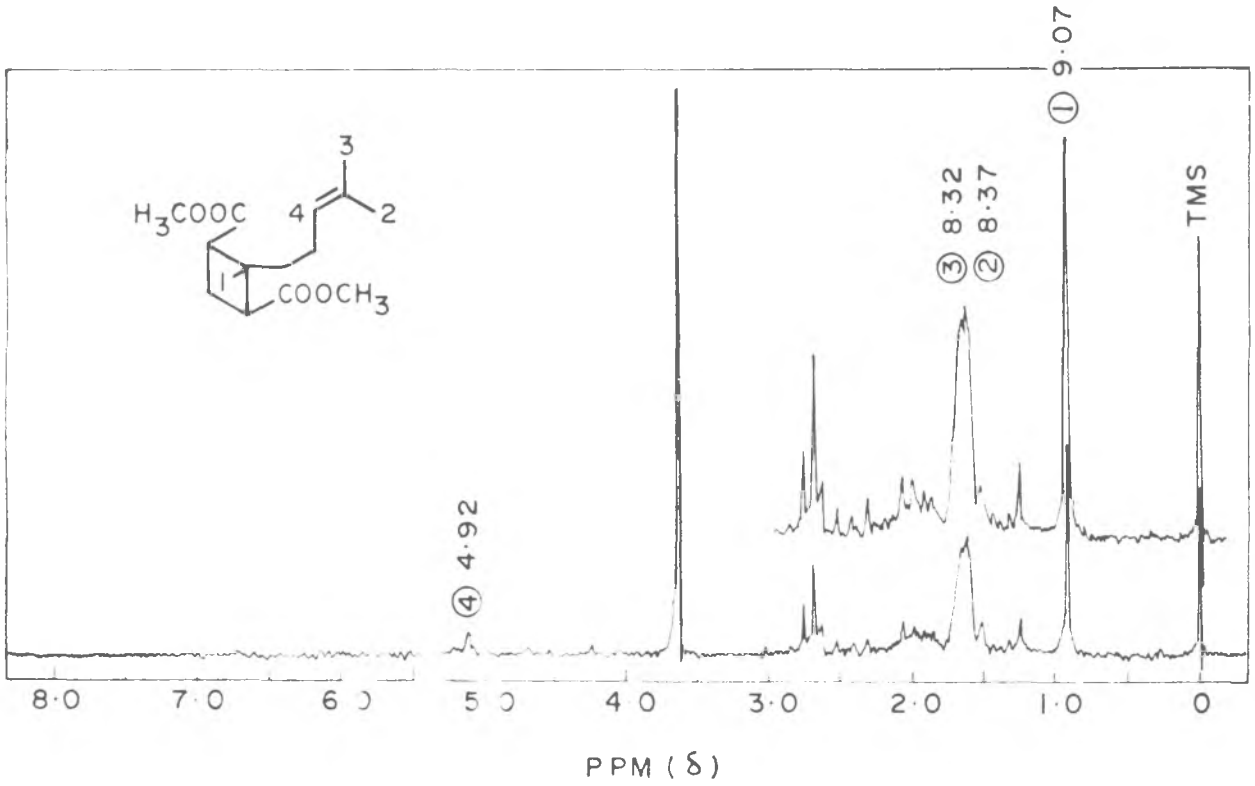

H3COOC
4
3
2
1
COOCH3
④ 4·92
③ 8·32
② 8·37
① 9·07
TMS
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0
PPM (δ)

FIG 8

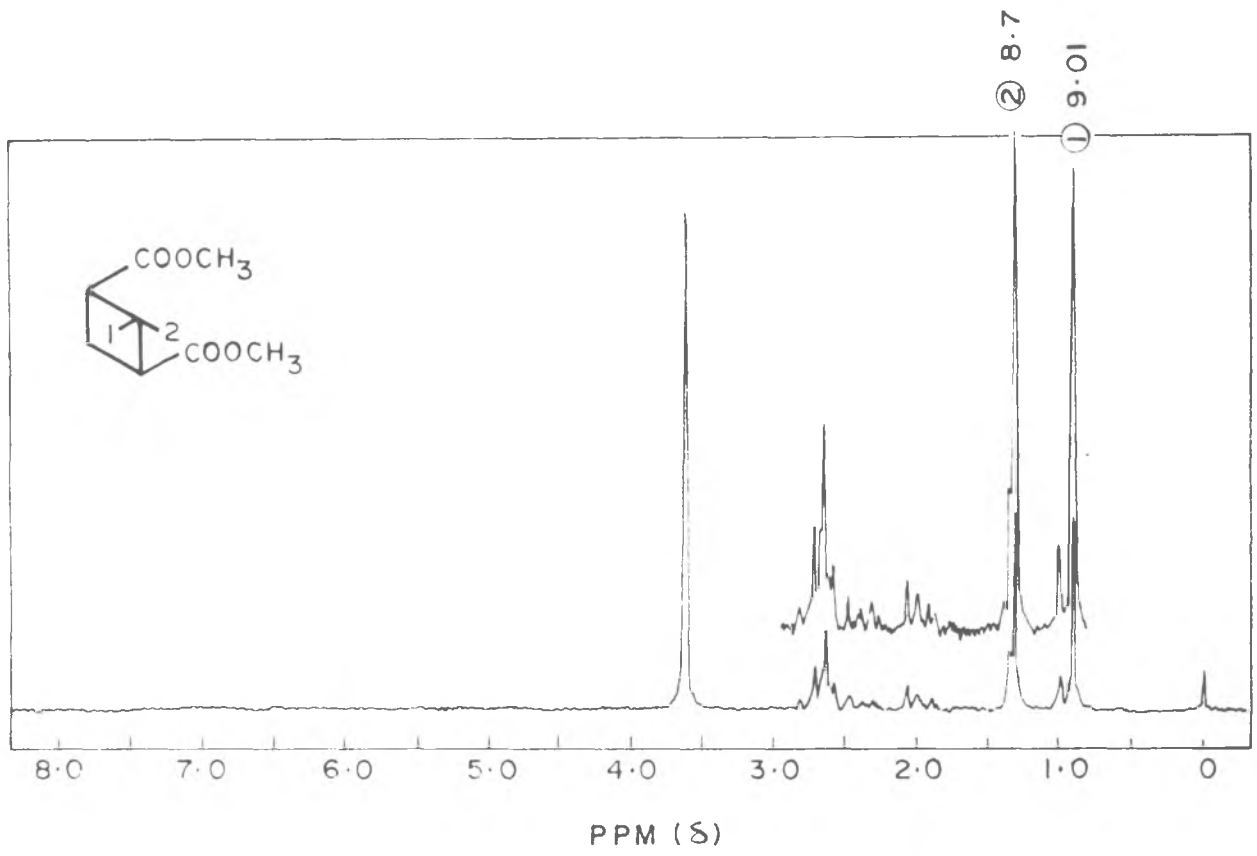


FIG. 19

E X P E R I M E N T A L

Methyl-heptenone guareschimide (IV)

(2,4-dicyano-3-methyl-3(2-methyl Δ^2-pentene) glutarimide.

To 125 ml. of ethyl alcohol kept at 0° ammonia was passed for 2 hr. Methyl heptenone (30 g) was mixed with ethylcyanoacetate (54 g) and the mixture was cooled and then added to the cold alcoholic ammonia solution. The solution became yellow in colour. The reaction mixture was kept in the freeze for 48 hr. The ammonium salt which precipitated as a solid was filtered. The residue washed with ether to remove any unreacted material. The residue was dissolved in the least amount of water (30 ml) and acidified with conc. HCl. The imide precipitated was filtered, washed free of acid with water, dried and crystallised from isopropyl alcohol in colourless needles (yield 35 g., 58%), m.p.190°.

Analysis

Found: C, 64.62; H,6.51; N,16.01.

$C_{14}H_{17}N_3O_2$ requires: C, 64.86; H,6.55; N,16.02%.

IR spectrum (Fig. 9) showed bands at: 3226, 2268, 1739, 1695, 1393, 1366, 1319, 1287, 1229, 1209, 1176, 1112, 975, 903, 865, 822, 805, 784, 753 and 743 cm^{-1}.

NMR spectrum showed signals at 4.84, 8.4, 8.35 and 8.49 τ.

Another batch was done with 40 g. of methyl heptenone under the same conditions. Yield of crystallised imide 42 g.

Condensation of methylheptenone Guareschimide (IV) with methylene iodide

Sodium metal (9.7 g) was dissolved in absolute methyl alcohol (100 ml) in a RB flask fitted with a reflux condenser and guard tube. The imide (35.2 g) was added to the above solution. The compound went into solution very quickly. It was refluxed on a water bath for 1/2 hr., CH_2I_2 (45 g) was added and the reaction mixture was refluxed for 4 1/2 hr. The reaction mixture was cooled and poured into a cold solution of nitric acid (10%, 400 ml). The compound precipitated was filtered, washed free of acid, with water. It was washed with a little amount of ether to remove any unreacted methylene iodide. The crude product melted at 165°. It was crystallised from isopropyl alcohol and dried. Yield of crystallised product 14 g. (37%), m.p.178°, colourless solid.

Analysis

Found: C, 65.91; H, 6.51; N,18.24.

$C_{15}H_{17}N_3O_2$ requires: C, 66.42; H, 6.27; N,15.49%.

IR spectrum (Fig.11) of the cyclised imide showed bands at: 3279, 2282, 1745, 1715, 1385, 1366, 1348, 1295, 1235, 1192, 1136, 1111, 1080, 988, 941, 916, 895, 878, 834, 817, 780, 768, 732, 712 cm^{-1}.

NMR spectrum (Fig.12) of the compound in pyridine showed signals at 4.96, 6.98, 6.15, 6.44, 6.62, 8.03, 8.37 and 8.47 τ.

Another batch of the condensation with 41 g. of methylheptenone guareschimide gave 18 g. of the crystallised cyclised imide (V) melting at 178°.

Hydrolysis of the cyclised methylheptenone guareschimide (V)

The cyclised imide (18 g) was dissolved in aqueous potassium hydroxide (10%, 400 ml) and the mixture was refluxed gently till ammonia ceases to evolve (120 hr). The reaction mixture was concentrated to 150 ml. It was transferred to a beaker and cooled thoroughly with ice. The reaction mixture was acidified with conc. HCl till it was just acidic to congo red. The acidified mixture was thoroughly extracted with ether (200 ml), three times. The acidified solution was made saturated with ammonium sulphate and again extracted with ether. The combined ether extract was distilled to get the tetracarboxylic acid. The compound obtained was a gum (6 g), yield 30%.

The cyclohexylamine salt of the tetracarboxylic acid (800 mg) was prepared, colourless solid, m.p.167°.

Analysis

Found: C,66.92; H,10.21; N,6.51.

$C_{39}H_{72}N_4O_8$ requires: C,64.64; H,9.94; N,7.73%.

IR spectrum of the tetracarboxylic acid showed bands at: 1709, 1368, 832 cm^{-1}.

Another batch of the hydrolysis of the cyclised imide (14 g) was carried out. Tetracarboxylic acid obtained, 4.5 g.

Decarboxylation of the tetracarboxylic acid (VI)

The tetracarboxylic acid (10 g) was taken in a 50 ml. RB flask with a reflux condenser and heated in an oil bath at 180-185° for 1/2 hr. The reaction product was taken in ether, dried, filtered and the solvent removed to get the dicarboxylic acid (7.2 g). The compound obtained was semi-solid (yield 98%). IR spectrum of the dicarboxylic acid (Fig.14) showed bands at: 1709, 1374, 1247, 1215, 1099, 1044, 981, 930, 892, 832, 790 cm^{-1}.

The cyclohexylamine salt of the dicarboxylic acid was prepared. The crystallised salt melted at 168°.

Analysis

Found: C,68.12; H,10.51; N,6.01.

$C_{28}H_{46}N_2O_4$ requires: C,68.49;H,10.50;N,6.3%.

Fractional crystallisation of the cyclohexylamine salt in methyl ethyl ketone and other solvents failed to give separation of salts of the cis- and trans acids.

Preparation of the anhydride (VIII)

The dicarboxylic acid (3 g) was taken in a Carius tube and acetic anhydride (10 ml) was added. The tube was sealed off and it was heated in Carius furnace at 185-200° for 5 hr. The tube was cooled. The acetic anhydride was removed and the product was distilled under vacuum, b.p.175°(bath)/0.5 mm.

The anhydride obtained (1.5 g., yield 55.5%) was a pale yellow viscous liquid.

Analysis

Found: C, 70.76; H, 8.57.

$C_{13}H_{18}O_3$ requires: C, 70.27; H, 8.10%.

IR spectrum of the anhydride (Fig. 15) showed bands at: 1818, 1770, 1383, 1372, 1299, 1266, 1202, 1160, 1087, 1038, 978, 940, 898, 885, 868, 834, 775 cm^{-1}.

Hydrolysis of the anhydride (VIII) to cis-norbergamotinic acid

The anhydride (1.4 g) was taken in dioxane (10 ml), 10 ml. of water was added and the mixture was heated on a water bath for 12 hr. The mixture was cooled and extracted with ether (20 ml) five times. The solution was made saturated with ammonium sulphate and it was again extracted with ether twice. The combined ether extract was dried and distilled to remove the solvent. The product obtained (1.35 g) was crystallised from pet.ether-ether mixture (1:1) as a colourless solid, m.p.155°.

Analysis

Found: C, 65.06; H, 8.41.

$C_{13}H_{20}O_4$ requires: C, 65.00; H, 8.33%.

IR spectrum of the solid (Fig.16) showed bands at: 1706, 1374, 1325, 1272, 1247, 1212, 1176, 1135, 1111, 1081, 1019, 945, 915, 840, 832, 766, 740, 730 cm^{-1}.

Preparation of the dimethylester of cis-norbergamotinic acid

The dimethylester of the cis- acid (100 mg) was prepared using diazomethane. The dimethyl ester obtained was distilled, b.p.155°(bath)/0.2 mm.

Analysis

Found: C, 67.03; H, 8.93.

$C_{15}H_{24}O_4$ requires: C, 67.16; H, 8.98%.

IR spectrum of the dimethyl ester (Fig.17) showed bands at: 1733, 1374, 1255, 1189, 1112, 1087, 1031, 1019, 989, 980, 890, 832, 789, 768, 741 cm^{-1}.

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3. C.A. Kerr, J.Am.Chem.Soc., 51, 614 (1929); C.W. Shoppee and J.L. Simonsen, J.S.C.I., 48, 730 (1929).

CHAPTER IV

NOPINONE, α- and β- PINENES FROM PINIC ACID

**

SUMMARY

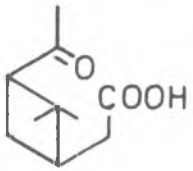
The rare hydrocarbon, β-bergamotene, is an isoprenologue of β-pinene. Its ∝- isomer, ∝-bergamotene, has been previously examined by Sorm from bergamot oil. Since then it has been encountered in a number of sources. In order to pave the way for the total synthesis of ∝- and β- bergamotenes, the synthesis of a model compound, pinene was carried out using pinic acid as the starting material. Pinic acid was obtained in good amounts by the hypobromite oxidation of pinonic acid. The diethyl ester of pinic acid on acyloin condensation gave a mixture of acyloins. The tosylate of the acyloin on reduction with lithium aluminium anhydride gave the alcohol, oxidation of which afforded nopinone. ∝-Pinene was obtained from nopinone.

Nopinone was converted to β-pinene.

The bicyclic monoterpenoid hydrocarbon ∝-pinene (I) is the most important member of the pinane group. It has been investigated thoroughly by earlier workers and the structure has been determined as I. ∝-Pinene is very widely distributed in nature and is present in the oils obtained from most conifers; it is the main constituent of turpentine, a substance which has been known for several centuries. The oxidation of ∝-pinene has been studied by, amongst others, Baeyer who showed that with permanganate two main products were obtained viz. pinonic (II) and pinoylformic acid (III). Hypobromite oxidation of pinonic acid gave a dicarboxylic acid, pinic acid (IV) which was brominated to (V) and converted to the hydroxy dicarboxylic acid (VI) with barium hydroxide. Lead dioxide oxidation of (VI) yielded the stable cis-norpinic acid (VII). The structure of cis-norpinic acid was confirmed by its elegant synthesis by C.A. Kerr[1] in 1929 and by C.W.Shoppe and J.L. Simonsen.[2] The route adopted by Kerr for the synthesis of cis-norpinic acid is shown in Scheme 1.

Two molecules of cyanacetic ester were condensed on to one molecule of acetone with ammonia to give the cyclic imide (VIII). Alkylation with methylene iodide constructed the cyclobutane ring (IX), hydrolysis and

I



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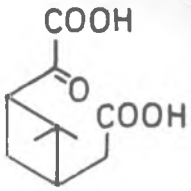

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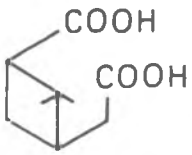

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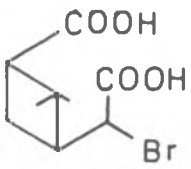
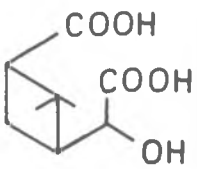
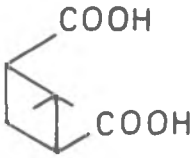


V

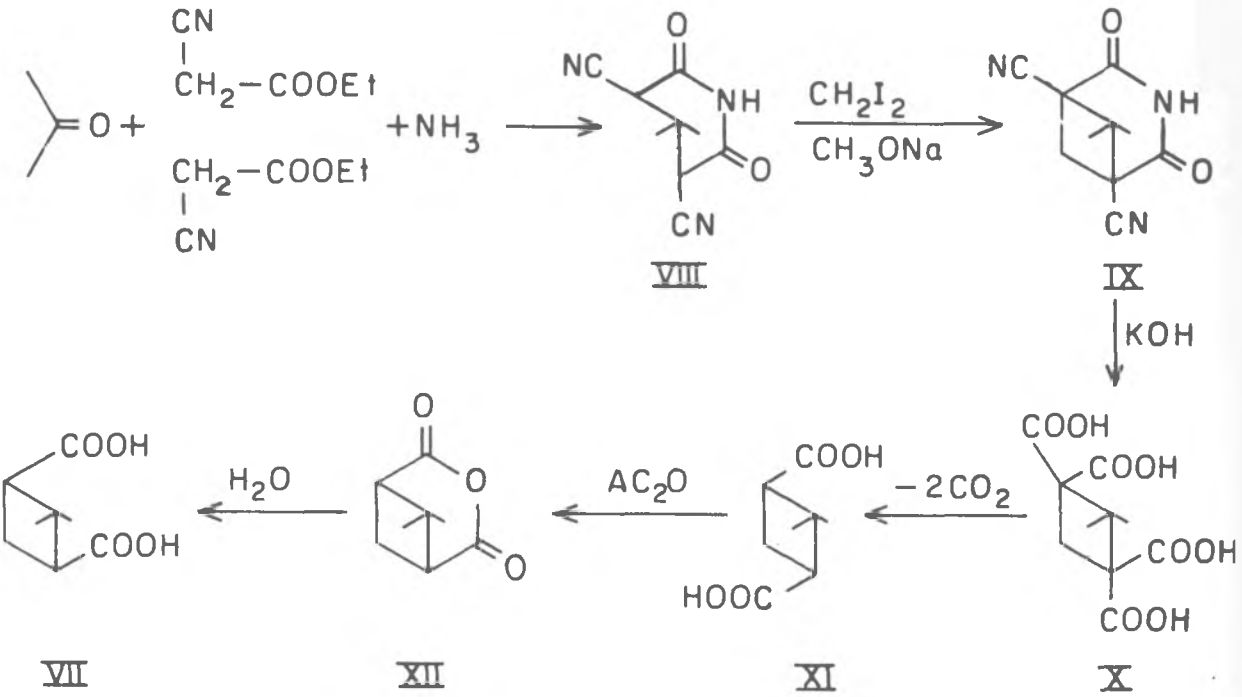


VI



VII

SCHEME No. 1



VIII IX X XI XII VII

decarboxylation of the intermediate malonic acid (X) then yielded a mixture of the cis- and trans-norpinic acid (XI) which was converted to cis-norpinic anhydride (XII), hydrolysis with water then gave the cis-norpinic acid (VII).

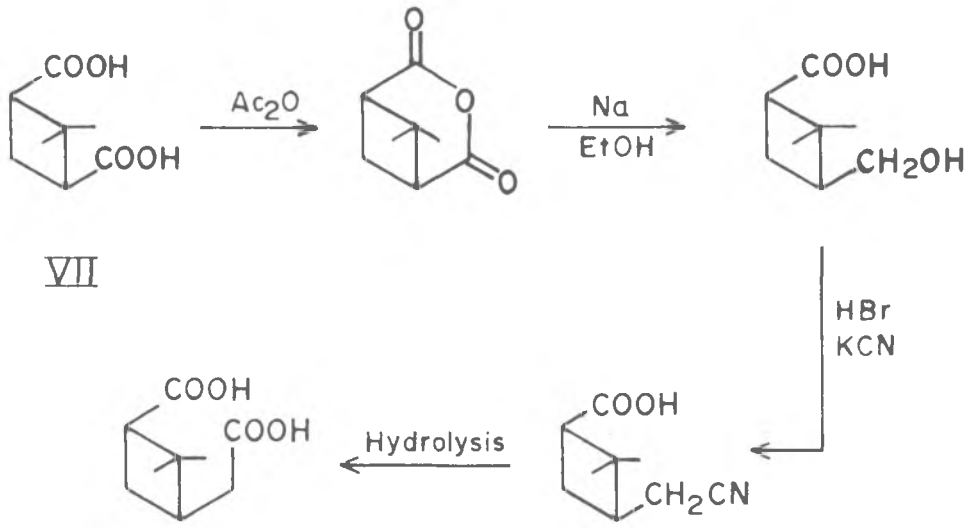
Although the direct synthesis of ∝-pinene has not been recorded, a number of syntheses by different workers leads from norpinic acid to the hydrocarbon. The cis-norpinic acid has been converted to pinonic acid, by Komppa[3] et al. in 1937. Guha et al. also achieved the synthesis of pinic[4] (IV) and pinonic[5] acids starting from norpinic acid as shown in Scheme 2.

Ruzicka[6] synthesised pinocamphone (XIII) from pinonic acid (II). Later starting from pinocamphone, he synthesised ∝- and ∂- pinenes (XIV).[6] The synthesis is represented in Scheme 3.

β-Pinene (XV) occurs with ∝-pinene in varying proportions. Its presence was inferred by Baeyer[7] when he obtained, during the oxidation of turpentine with permanganate, a small quantity of an acid, nopinic acid (XVI). Lead dioxide oxidation of (XVI) gave nopinone (XVII).

Nopinone was reconverted to β-pinene by Wallach[8] as shown in Scheme 4.

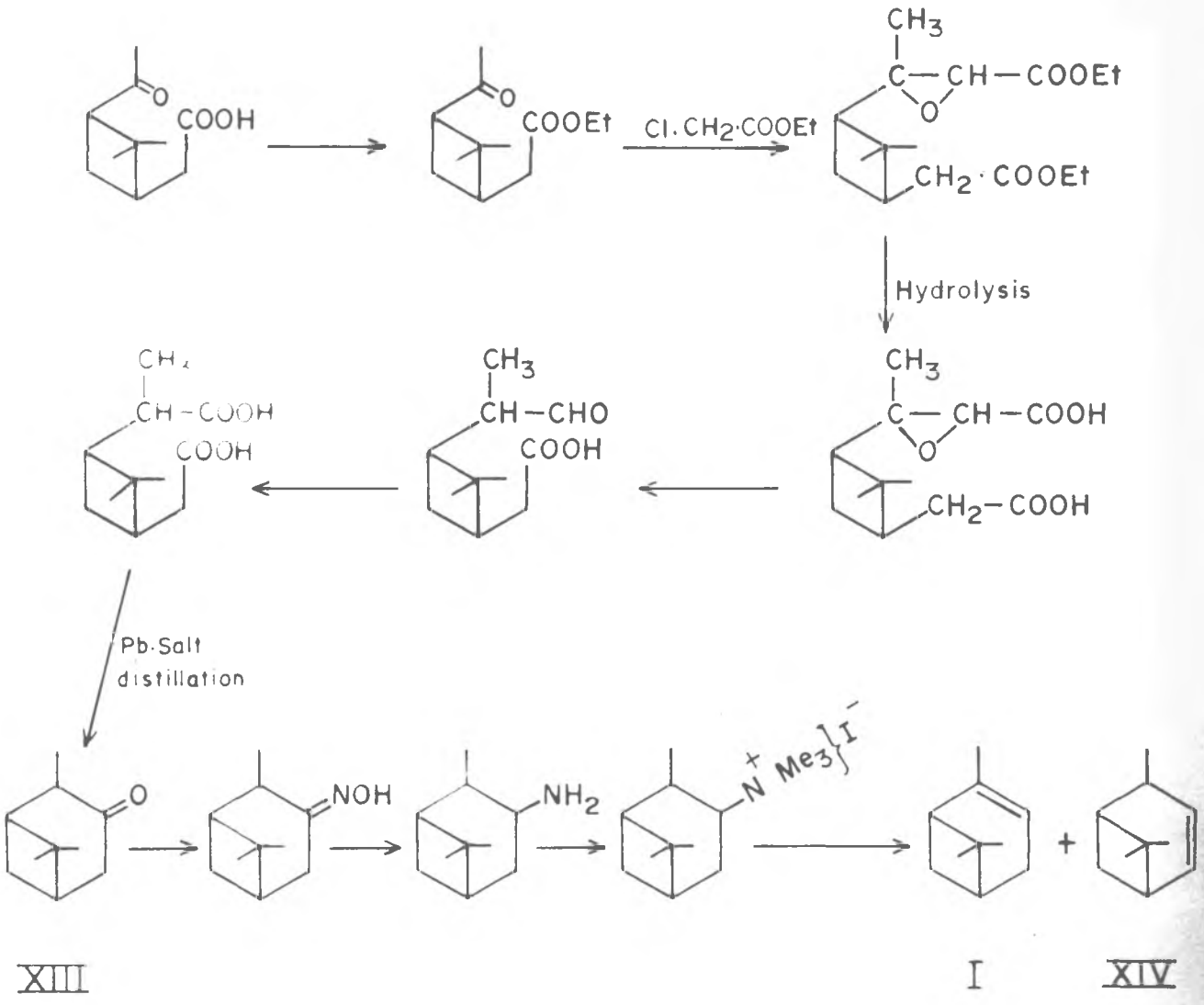
SCHEME No·2



VII

IV

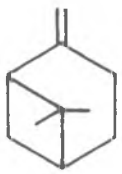
SCHEME No·3



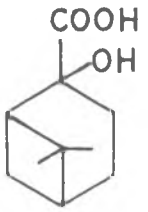
XIII

I

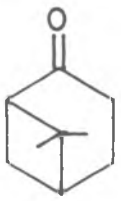
XIV



XV

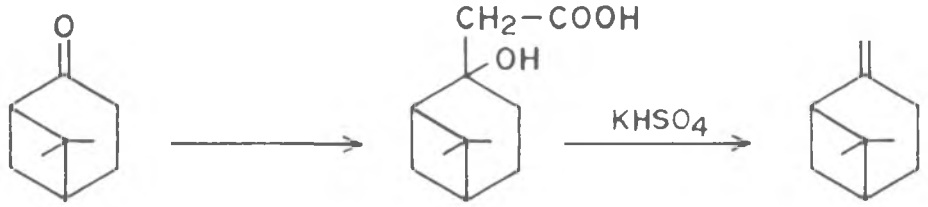


XVI

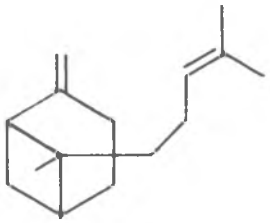


XVII

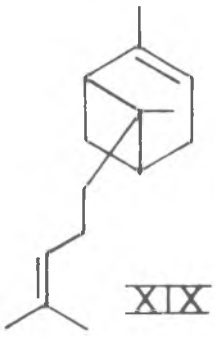
SCHEME No. 4



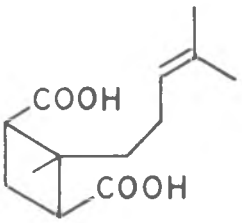
XVII XV



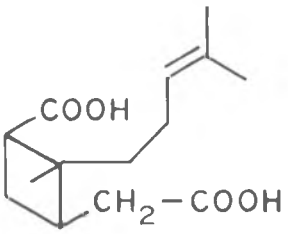
XVIII



XIX



XX



XXI

PRESENT INVESTIGATION

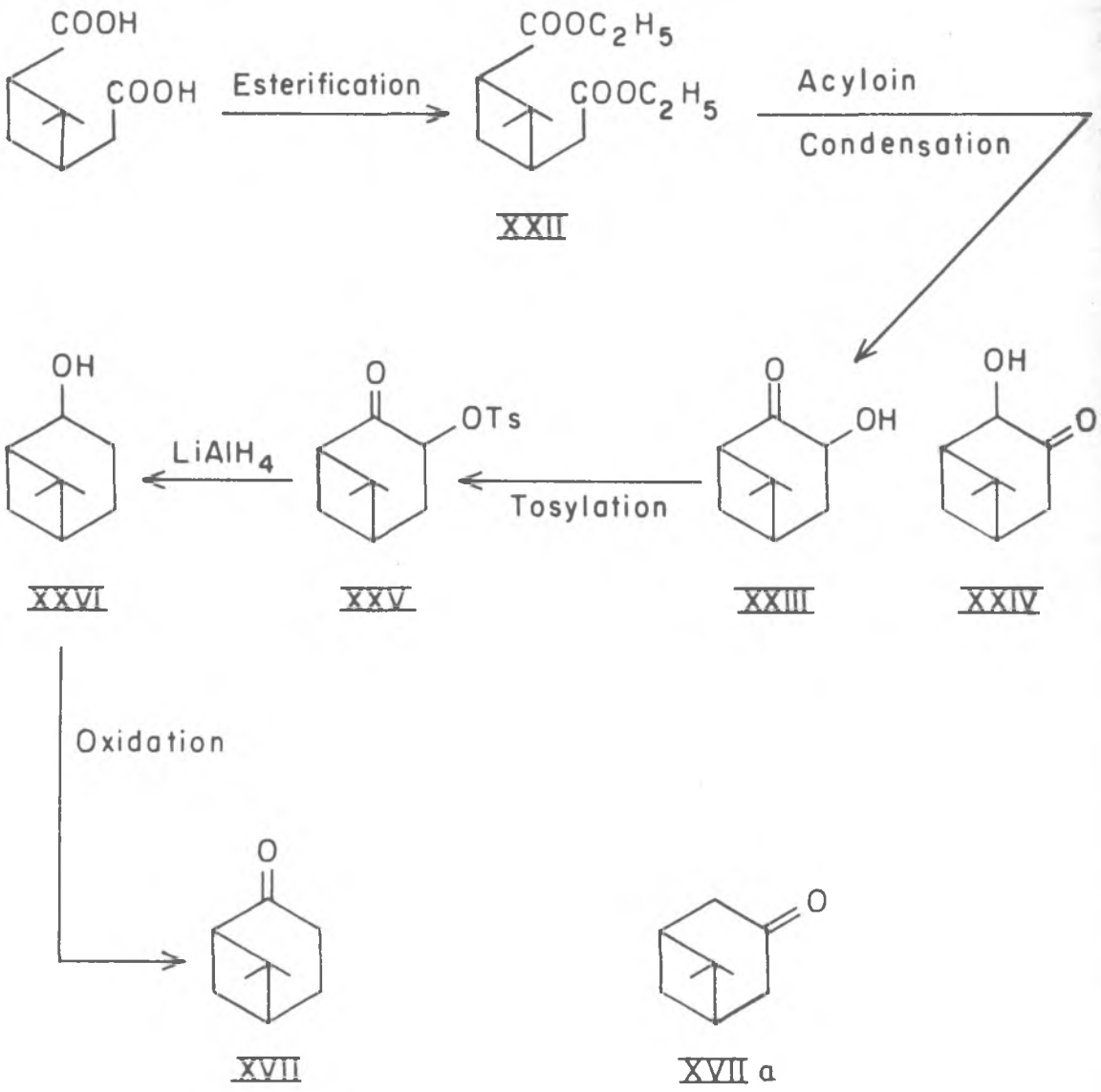
The rare hydrocarbon β-bergamotene[9] (XVIII) is an isoprenologue of β-pinene (XV). The corresponding ∝-isomer, ∝-bergamotene (XIX) has been found to occur in several sources.[10] A plan to synthesise these two hydrocarbons was visualised and a key intermediate cis-norbergamotinic acid (XX) was synthesised from methyl heptenone. The details of this synthesis have been described in Chapter III of this thesis.

Considering the difficulties involved in the synthesis of cis- norbergamotinic acid (XX) it was felt that though its conversion into the higher homologue bergamotinic acid (XXI) should be easy, subsequent conversion of the latter to the bergamotenes by adopting procedures employed in the case of pinenes would be beset with practical difficulties and it will be desirable to develop newer approaches.

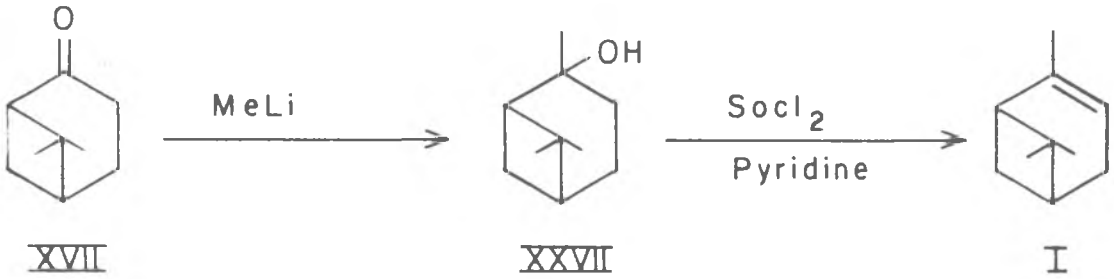
This has been done now and a new model synthesis of pinene developed from pinic acid (IV). Starting from pinic acid, nopinone was initially prepared as shown in Scheme 5.

Pinic acid (IV) required for the purpose was obtained in large amounts by the hypobromite oxidation

SCHEME No. 5



SCHEME No 6



of pinonic acid+ (II), which in its turn was obtained by oxidation of pinene.

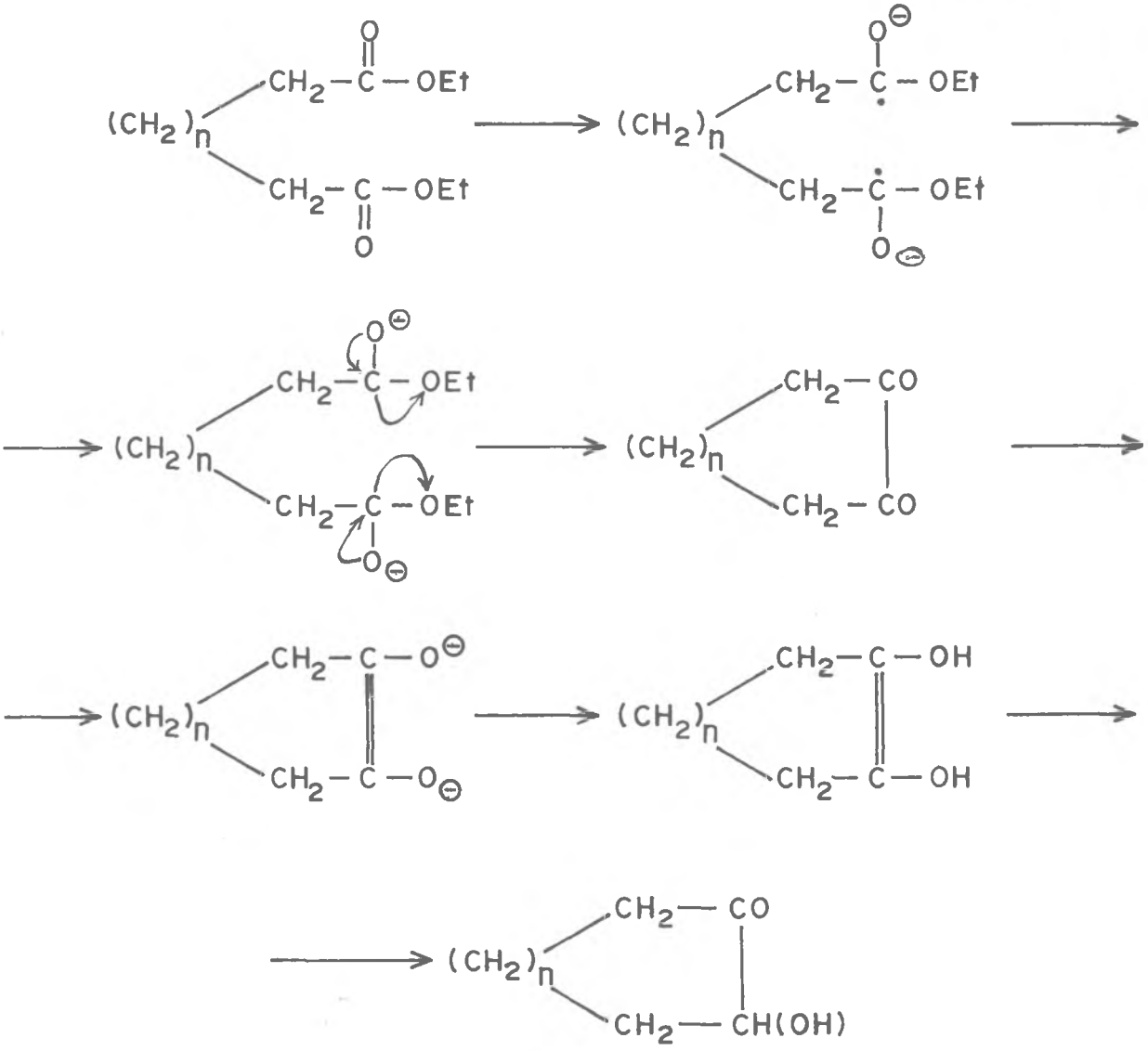
Acyloin condensation

Hansley[11] found that α,ω-dicarboxylic esters, on treatment with finely divided sodium in hot xylene gave cyclic acyloins. Prelog[12] and Stoll[13] applied this procedure independently and simultaneously for the preparation of higher membered cyclic acyloins with surprisingly good results. The process involved vigorous stirring of a solution of the ester of a α,ω-dicarboxylic acid in hot xylene with molten sodium. An intramolecular acyloin condensation takes place to give cyclic α-hydroxy ketone. It is important that the reaction be carried out in the absence of any free alcohol or oxygen.

In this process two electrophilic carbon atoms at the ends of the chain of the diester are first absorbed by the electron covered surface of the molten sodium. So far as chain flexibility allows, the electrophilic residue can slide over the metal surface to approach each other. The energy required for the process is less than that required for splitting the molecules off the surface; the collissions of absorbed molecule

+ Pinonic acid was donated by the Naval Stores Research Station, Fla, U.S.A.

with other molecules lead to close proximity of the two terminal carbon atoms and finally to the ring closure.



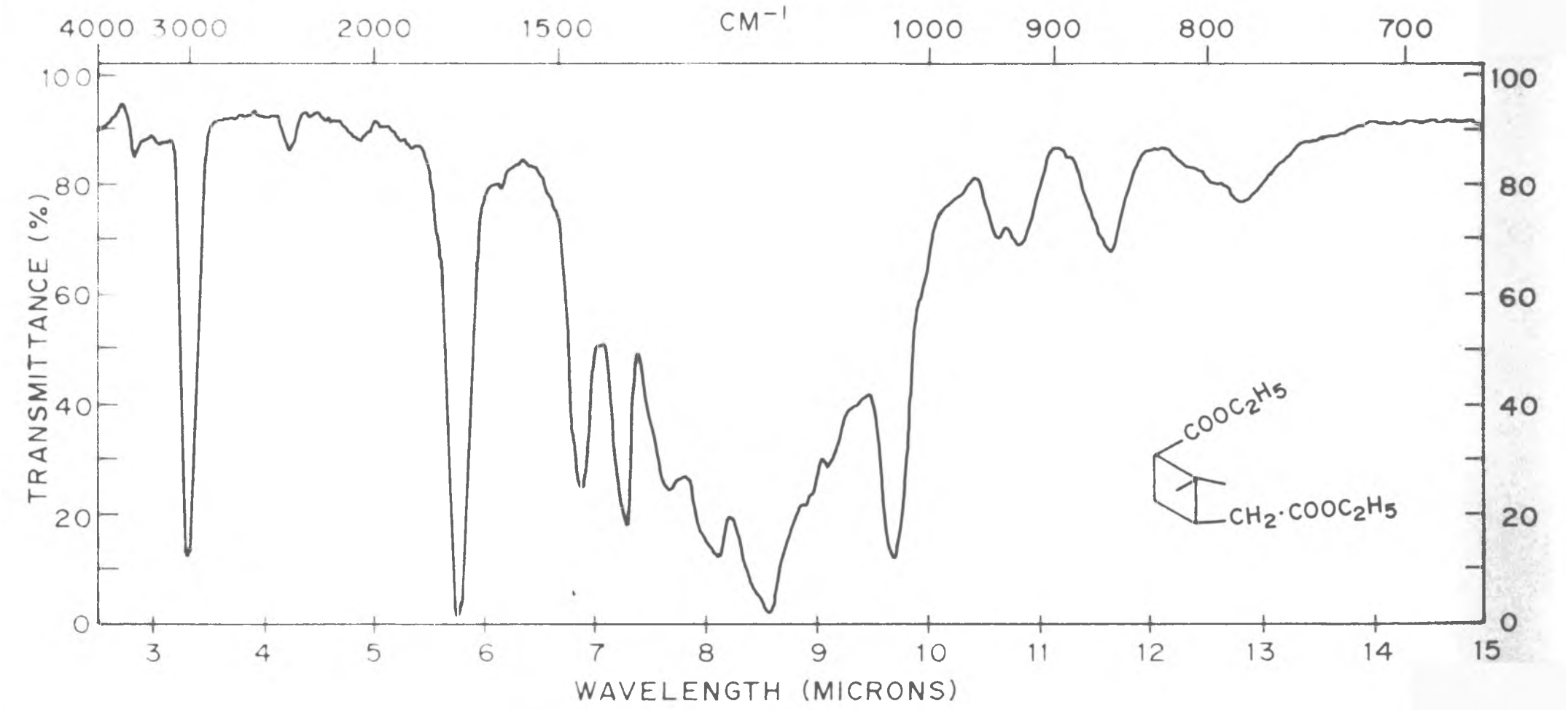
After the ring closure the molecule no longer possesses electrophilic centres and is therefore no longer bound to the surface. This method proved to be extremely useful in the synthesis of medium and large

ring compounds. This reaction did not require high dilution conditions and afforded the cyclic ketone containing the same number of carbon atoms as the starting dicarboxylic acid, which no other hitherto known method was able to furnish. Further by this method even 2-substituted dicarboxylic esters could be cyclised.

The diethyl ester of pinic acid was prepared by the azeotropic method. It is a colourless liquid boiling at 120°/3 mm. The IR spectrum of the diethyl ester (Fig. 20) showed bands at: 1724 (C=O stretching vibration) and 1170 cm^{-1} (C-O stretching vibration).

Acyloin condensation of the diethyl ester of pinic acid (XXII) in xylene in the presence of molecular sodium and potassium metals yielded the acyloin(XXIII). The distilled acyloin obtained is coloured yellow. The acyloin was purified by column chromatography. The acyloin thus obtained was found to be composed of two compounds by GLC analysis in 60:40 proportion viz. XXIII and XXIV. The IR spectrum of the acyloin (Fig.21) showed absorptions at 3546 (hydroxyl), 1733 cm^{-1} (C=O).

Treatment of the acyloin with p-toluene sulphonyl chloride in pyridine yielded the tosylate derivative XXV which was reduced with lithium aluminium hydride to get


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
COOC2H5
CH2·COOC2H5

FIG·20

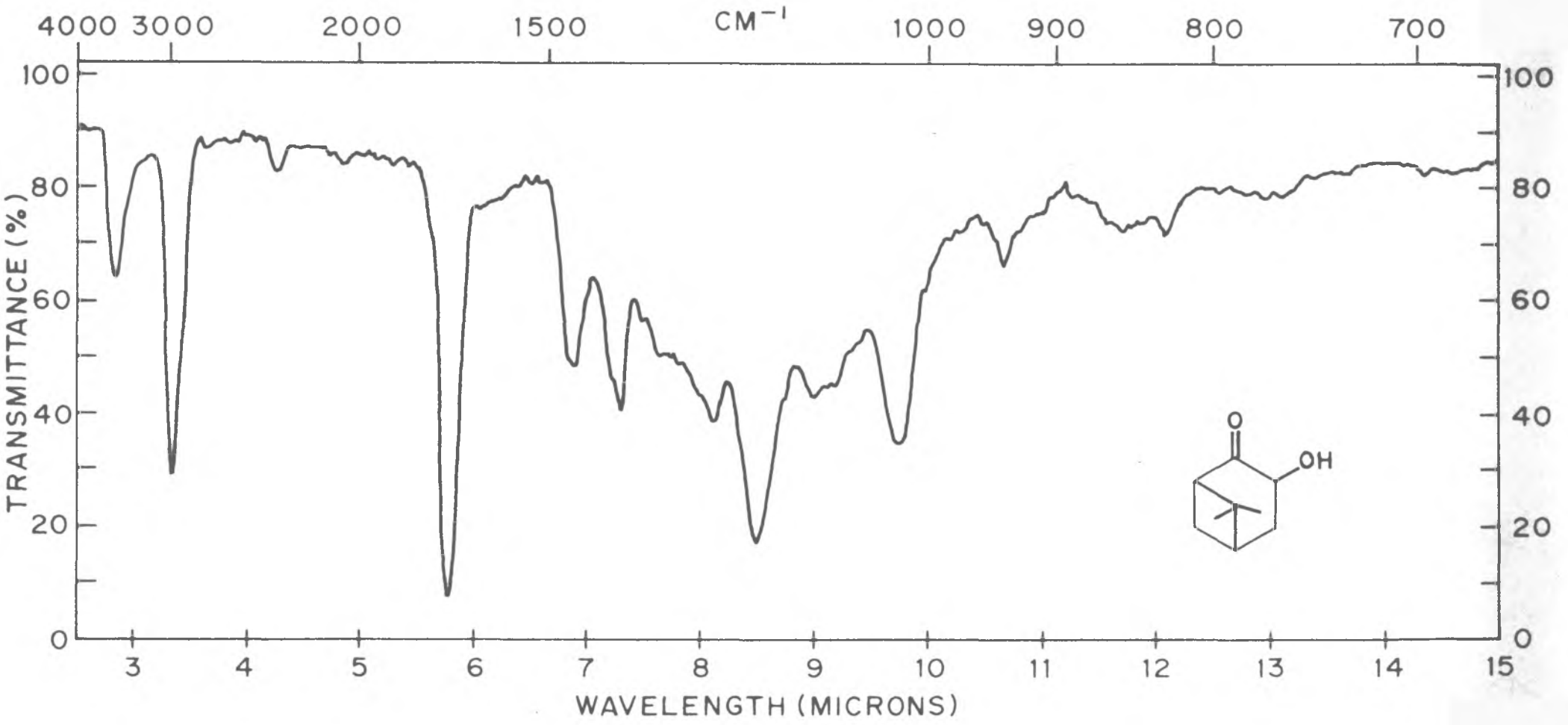

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
O
OH

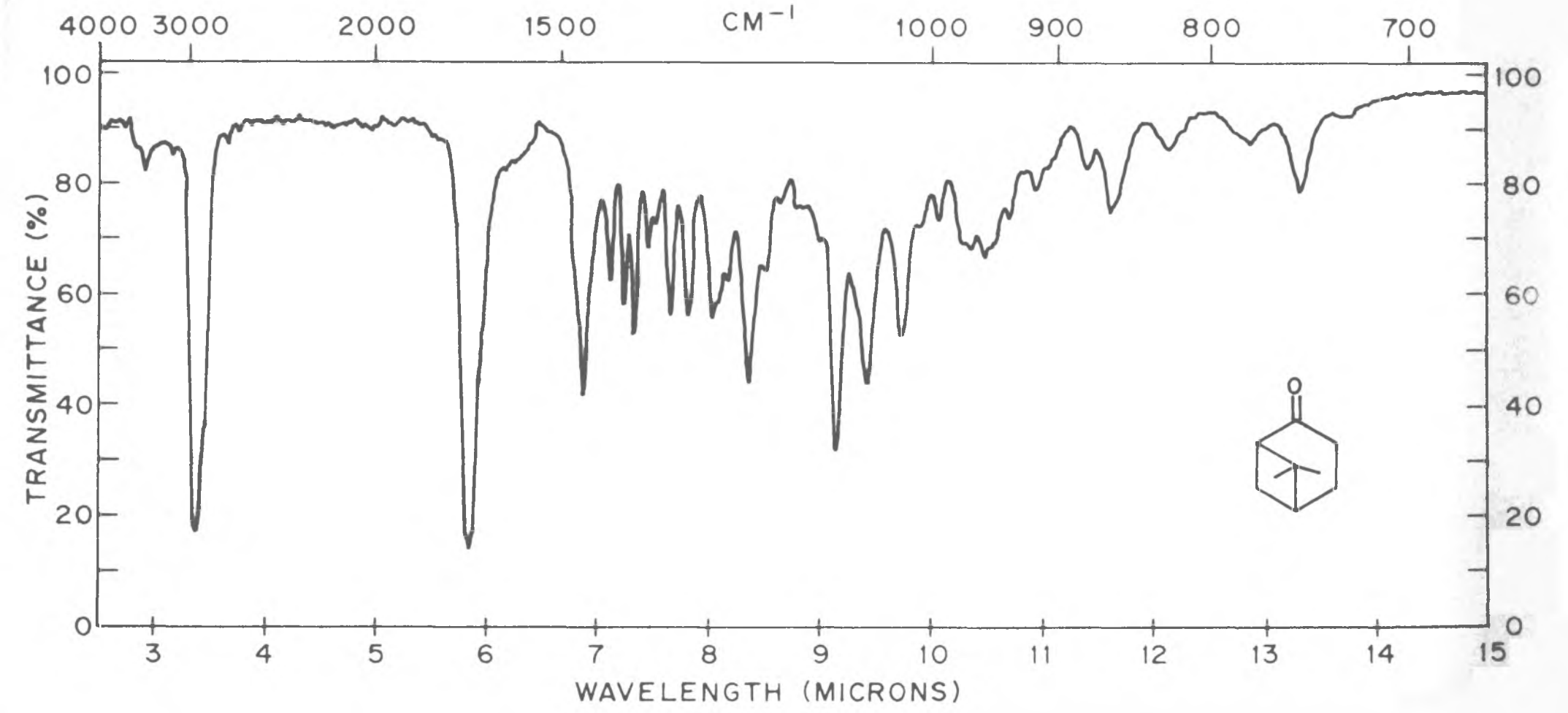
FIG. 21

the alcohols XXVI which on oxidation with Jones reagent yielded the ketones[14] XVII, XVIIa. The ketone obtained was found to contain 60% nopinone as confirmed by GLC analysis with an authentic specimen of nopinone obtained by ozonolysis of β-pinene. The product formed a mixture of semicarbazones from which a semicarbazone melting at 188° could be separated by fractional crystallisation. Mixed melting point of the semicarbazone with an authentic specimen of the semicarbazone of nopinone remained undepressed. The IR spectrum of nopinone (Fig.22) showed a band at 1709 cm^{-1} for the carbonyl absorption.

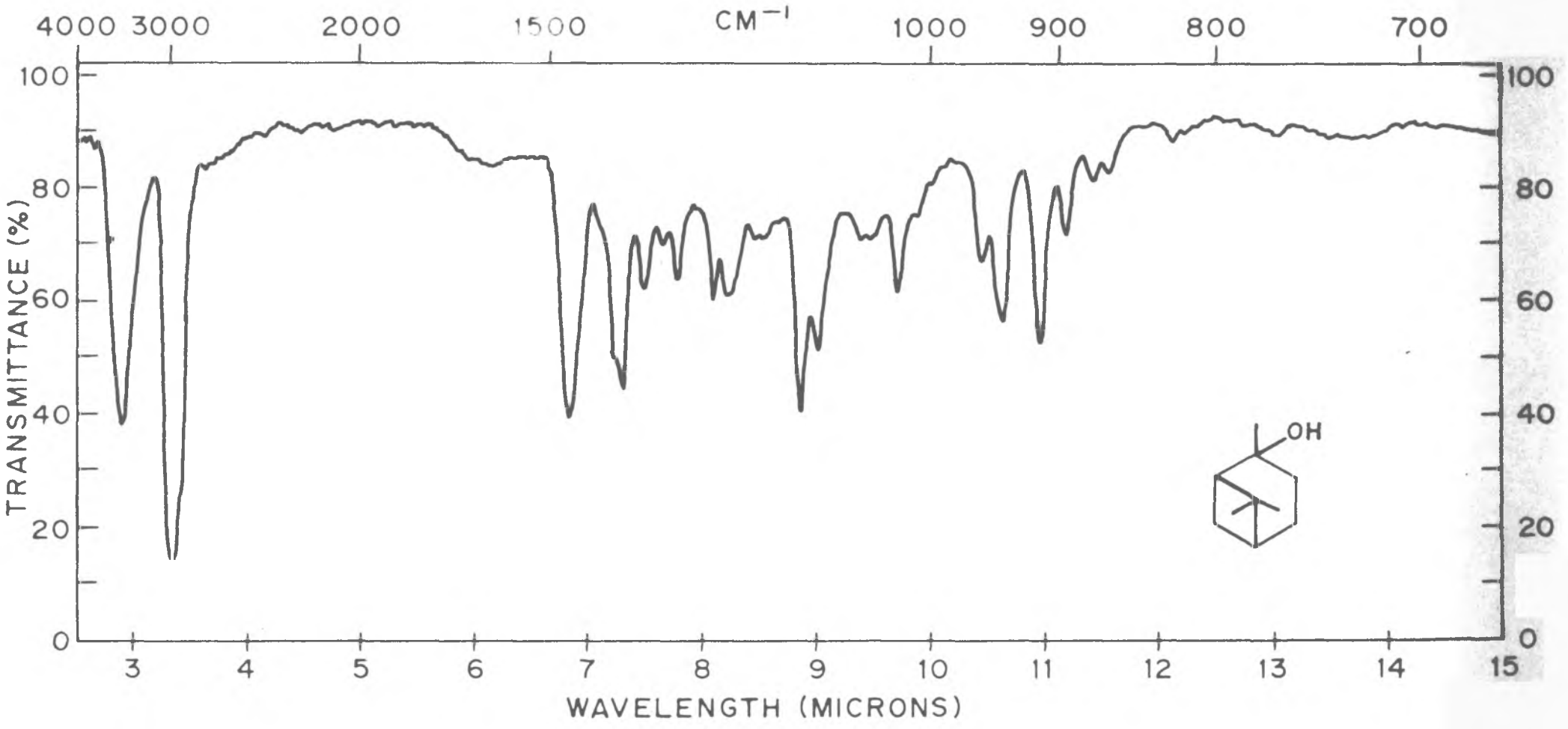
<u>α-Pinene from nopinone</u>

α-Pinene was synthesised from nopinone (XVII) by the method shown in Scheme 6.

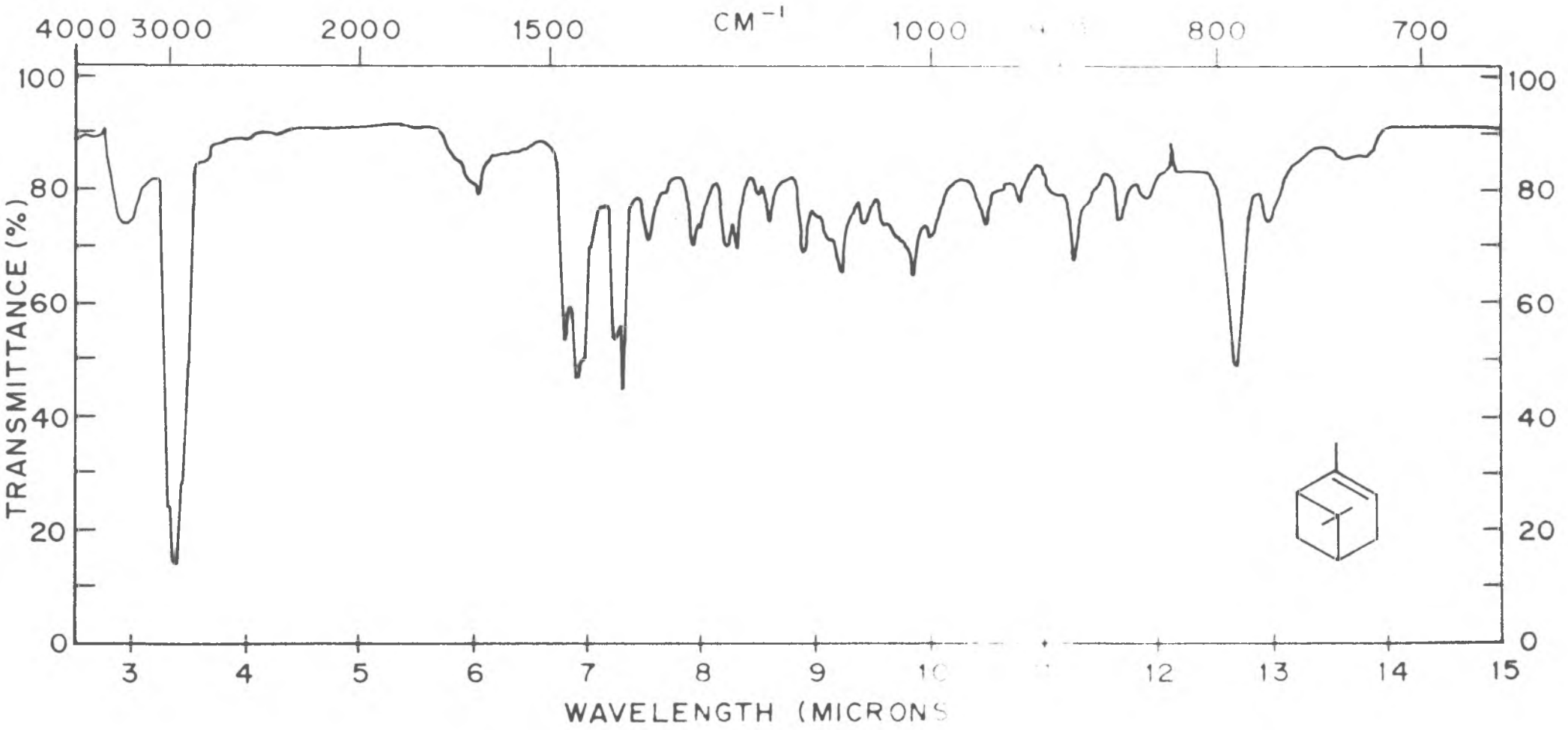
Nopinone was obtained in good amounts by the ozonolysis of β-pinene. Reaction of nopinone with methyl lithium afforded the tertiary alcohol (XXVII). IR spectrum (Fig.23) of the alcohol (XXVII) showed bands at: 3448, 1130 cm^{-1} (hydroxyl function). It is a solid melting at 47-48°. Dehydration of this alcohol (XXVII) with thionyl chloride in pyridine afforded α-pinene as one of the dehydration products. This was confirmed by GLC analysis with an authentic specimen of α-pinene. The dehydrated product on chromatography afforded a fraction containing α-pinene in a pure state.


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
O

FIG·22


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
OH

FIG·23


4000 3000
2000
1500
CM⁻¹
1000
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
12
13
14
15
WAVELENGTH (MICRONS

FIG·24

IR spectrum of the hydrocarbon (Fig.24) obtained was superimposable with that of ∝-pinene.

Based on these model reactions, synthesis of ∝- and β- bergamotenes (XIX and XVIII) from cis-norbergamotinic acid (XX) has been now taken in hand.

β-Pinene (XV) from nopinone (XVII)

β-Pinene was synthesised from nopinone by Wittig reaction.[15] Nopinone was treated with methylene triphenyl phosphorane in benzene solution and the resultant product on working up yielded β-pinene in 30% yield. This was confirmed by GLC analysis with an authentic sample of β-pinene. IR spectrum of the hydrocarbon obtained was superimposable with that of β-pinene.

E X P E R I M E N T A L

Preparation of pinic acid (IV)

Pinonic acid (5 g) dissolved in aqueous sodium hydroxide was added in one portion to a sodium hypobromite solution made by adding slowly bromine (20 g) to a cold solution of sodium hydroxide (15 g) in water (150 ml). Bromoform separated after a short time. A little more sodium hydroxide was added and the mixture was allowed to stand for 1 hr. The reaction mixture was then poured into a cold solution of bisulphite and dilute sulphuric acid. The heavy layer of bromoform was separated and the aqueous solution was saturated with ammonium sulphate and thoroughly extracted with ether. The solvent was distilled off and pinic acid was obtained as a thick oil (5.5 g).

IR spectrum of pinic acid showed bands at: 1701, 1427, 1370, 1282, 1248, 1205, 1047, 940, 880, 840, and 737 cm^{-1}.

Another batch of pinonic acid (50 g) was oxidised in the above manner and pinic acid (54.5 g) was obtained in good yield.

Preparation of pinic acid diethylester (XXII)

In a one lit. RB flask pinic acid (55 g) was taken in dry benzene (600 ml). Absolute ethyl alcohol (60 ml)

and one ml. conc. H_2SO_4 were added. The flask containing the reaction mixture was connected with an azeotropic apparatus and refluxed on a water bath till water ceased to form (36 hrs). The reaction mixture was taken in a separating funnel and washed free of the mineral acid with water. The benzene solution was washed with a dilute solution of sodium carbonate to remove unreacted pinic acid, washed with water, dried and benzene removed. The residue thus obtained was distilled under vacuum, yield 64.5 g., b.p.120°/3 mm.

The diethyl ester of pinic acid is a colourless liquid.

Analysis

Found: C, 64.10; H, 9.04.

$C_{13}H_{22}O_4$ requires: C, 64.4; H, 9.08%.

Acyloin condensation

Sodium dry xylene (3.5 L) was taken in a 5 L. three necked flask fitted with a reflux condenser, a powerful stirrer and a dropping funnel. The flask was fitted in a heating mantle. Oxygen-free* nitrogen was passed through the flask. Metallic sodium (15 g) and

* Nitrogen was purified by passing it through traps containing alkaline pyrogallol, conc. H_2SO_4, and a red hot furnace containing Cu turnings.

metallic potassium (15 g) were added to the xylene and the mixture was heated to reflux xylene. A portion of xylene (100 ml) was distilled off. The stirring was started to convert the molten mixture of sodium and potassium into very fine particles. The diethyl ester of pinic acid (61 g) in xylene was added in 2 hr. to the reaction mixture. The whole reaction was carried out under very dry conditions. After the complete addition, the reaction mixture was stirred for 1/2 hr. more. The reaction mixture was cooled to room temperature and then with ice. Alcohol was added dropwise to decompose the alkali metals. The reaction mixture was acidified with conc. HCl. The product in xylene was washed free of acid with water. The xylene was removed in an atmosphere of nitrogen under reduced pressure. The product obtained was distilled under high vacuum (20 g), b.p. 120°/2.5 mm.

The product was found to be a mixture of the diester and acyloin. The acyloin was separated by chromatography over gr.II alumina (1:10). The diester was eluted with pet.ether. The acyloin was eluted with ether (4 g). It was distilled under high vacuum. It is a pale yellow viscous liquid, b.p.115°/2 mm.

GLC analysis of the acyloin showed it to contain 2 peaks in the ratio 60:40.

Analysis

Found: C, 69.61; H, 9.34.

$C_9H_{14}O_2$ requires: C, 70.12; H, 9.09%.

The IR spectrum of the acyloin showed bands at: 3455, 1733, 1372, 1239, 1182, 1114, 1030, 940, 885, 830 cm^{-1}.

Preparation of the tosylate of the acyloin (XXV)

The acyloin (800 mg) was dissolved in pyridine (15 ml) and crystallised p-toluene sulphonyl chloride (1.2 g) was added to the mixture. The reaction mixture was kept for 48 hours at room temperature, poured in water and extracted with ether. It was washed with sodium carbonate solution and dilute hydrochloric acid to remove the p-toluene sulphonic acid and pyridine respectively. It was washed free of acid with water. The extract was dried and the solvent was distilled off. The tosylate (XXV) obtained was a liquid (1.1 g).

IR spectrum of the tosylate showed bands at: 1730, 1595, 1368, 1335, 1300, 1188, 1176, 1117, 1094, 1031, 989, 969, 940, 868, 814 and 788 cm^{-1}.

Reduction of tosylate (XXV) with $LiAlH_4$

The tosylate of acyloin (1.1 g) was added drop by drop to an ice cold solution of dry ether (100 ml)

containing lithium aluminium hydride (0.8 g). The reaction mixture was refluxed for 6 hrs. under dry conditions. The reaction mixture was cooled with ice and the excess lithium aluminium hydride was decomposed with moist ether followed by water. The product was taken in a separating funnel and washed with very dilute HCl. The ether extract was washed free of acid and the solvent was removed. The product obtained was a liquid (750 mg), b.p.110°/2 mm.

IR spectrum of the alcohol obtained showed bands at: 3425, 1453, 1379, 1366, 1266, 1242, 1117, 1053, 1012, 981, 924, 888, 841 and 811 cm^{-1}.

Analysis

Found: C, 76.82; H, 10.2.

$C_9H_{16}O$ requires: C, 77.14; H, 10.14%.

Oxidation of the alcohol (XXVI)

The secondary alcohol obtained by the reduction of the tosylate of the acyloin (650 mg) was taken in acetone and Jones reagent was added drop by drop while cooling, till the mixture showed an excess of chromic acid. The reaction mixture was poured into water, extracted with ether, the ether extract washed free of acid with water, and the solvent removed. The product was

chromatographed through gr.II neutral alumina. The ketone was eluted with pet.ether (250 mg). The ketone obtained on GLC analysis showed two peaks in 60:40 proportions. The mixture of ketones was found to contain 60% of nopinone by comparative GLC analysis with an authentic sample of nopinone prepared by ozonolysis of β-pinene. The mixture was put for semicarbazone preparation. The semicarbazone obtained had a m.p. of 180-200°. The semicarbazone was fractionally crystallised from alcohol three times. A semicarbazone, m.p. 185-186°, was obtained. Mixed m.p. of this semicarbazone with an authentic specimen of the semicarbazone of nopinone remained undepressed. The semicarbazone of m.p. 185-186° (40 mg) was cleaved with oxalic acid and the regenerated ketone was found to be identical with nopinone by IR and GLC analysis. IR spectrum of the ketone showed bands at: 1709, 1408, 1368, 1346, 1311, 1282, 1250, 1096, 1063, 1030, 970, 954, 940, 915, 880, 872 and 752 cm^{-1}.

It is a colourless liquid, b.p.85°/ 2.5 mm.

Analysis

Found: C, 77.90; H, 9.91.

Calc. for $C_9H_{14}O$: C, 78.11; H, 10.14%.

Nopinone from β-pinene

β-Pinene (15 g) was ozonised at 0° in chloroform (75 ml) for 4 hrs. The ozonide after removing the solvent

was decomposed by boiling with water for 2 hr. The product was extracted with ether; the solvent was removed and the residue was chromatographed over gr.II neutral alumina (300 mg). Any unreacted hydrocarbon was eluted with pet.ether. The ketone was eluted with pet.ether-benzene mixture. The ketone obtained (13 g) was distilled, b.p.87°/7 mm. GLC analysis showed only one peak indicating its purity.

IR spectrum of the ketone showed bands at: 1709, 1368, 1346, 1311, 1283, 1250, 1096, 1063, 1030, 970, 954, 940, 880, 873 and 782 cm^{-1}.

Analysis

Found: C, 77.95; H, 10.10.

Calc. for $C_9H_{14}O$: C, 78.11; H, 10.14%.

Tertiary alcohol (XXVII) from nopinone (XVII)

Nopinone (5g) in dry ether (30 ml) was added dropwise with stirring to a cooled (0°) solution of methyl lithium reagent prepared from lithium (1.2 g), dry ether (150 ml) and methyl iodide (20 g). The reaction mixture was allowed to be stirred for 30 min. and the excess reagent was decomposed with water. The product was extracted with ether; the ether extract was washed with a very dilute solution of HCl to remove the

lithium hydroxide as its chloride. The ether extract was washed free of acid; the solvent was removed. The residue was chromatographed over gr.III alumina (75 g), eluted with pet.ether to remove the unreacted ketone. The alcohol was eluted with ether. The alcohol obtained was liquid which solidified (3.5 g). The solid alcohol obtained was purified by sublimation. It melted at 47-48°. IR spectrum of the compound showed bands at: 3448, 1387, 1370, 1337, 1312, 1289, 1238, 1220, 1183, 1130, 1111, 988, 940, 912, 893, 876, 865 and 826 cm^{-1}.

Analysis

Found: C, 77.64; H, 11.4.

$C_{10}H_{18}O$ requires: C, 77.92; H, 11.68%.

<u>α-Pinene from tertiary alcohol</u> (XXVII)

The tertiary alcohol (3 g) was taken in pyridine (30 ml) and cooled with ice. Thionyl chloride (5 ml) was added drop by drop and the reaction mixture was allowed to stand at 0° for 30 minutes. The excess of the reagent was decomposed by adding small pieces of ice. The reaction mixture was poured into water and it was extracted with ether. The ether extract was washed with dilute HCl to remove the pyridine, then was washed with

sodium carbonate solution. Finally it was washed free of any alkali. The extract was dried with anhydrous sodium sulphate and the solvent was removed. The residue (3.8 g) was chromatographed through gr.I neutral alumina (30 g). The hydrocarbon (2 g) was eluted with pet.ether. GLC analysis of the hydrocarbon showed it to contain ∝-pinene as the main constituent alongwith small quantities of other hydrocarbons. The hydrocarbon mixture (2 g) was rechromatographed over gr.I alumina (100 g) and eluted with pet.ether. The initial fractions contained pure ∝-pinene confirmed through GLC analysis with an authentic specimen of ∝-pinene. ∝-Pinene obtained (0.8 g), had a b.p. of 90°/4 mm., $(\alpha)_D^{29}$ - 34.5°. IR spectrum of the hydrocarbon showed bands at: 1639, 1473, 1449, 1385, 1370, 1336, 1266, 1220, 1205, 1166, 1136, 1087, 1017, 957, 889, 861 and 790 cm^{-1}.

Analysis

Found: C, 87.94; H, 11.5.

$C_{10}H_{16}$ requires: C, 88.23; H, 11.76%.

β-Pinene (XV) from nopinone (XVII)

Preparation of triphenyl methylphosphonium iodide.

Triphenyl phosphine (7 g) was dissolved in dry benzene (50 ml). To this was added methyl iodide (5.5 g) over 30 minutes. The gradual precipitation of triphenyl methyl phosphonium iodide insoluble in the medium was observed. The reaction was complete after 12 hr. The phosphonium salt was suction filtered and washed with a small amount of anhydrous benzene. The product was obtained in a yield of 10 g., m.p. 176°.

Preparation of methylene triphenylphosphorane

In a 500 ml. flask equipped with mechanical stirrer, reflux condenser were placed triphenyl methyl phosphonium iodide (10 g) and anhydrous benzene (250 ml). To this was added sodium amide (1 g) over a few minutes and the stirring was started. The entire preparation was effected under an atmosphere of nitrogen. The temperature of the suspension was slowly raised to the reflux temperature of benzene and the NH_3 evolving during the reaction was entrained by the nitrogen stream toward an absorber flask. The reaction was complete after 6 hr. of refluxing. The reaction mixture comprises of two phases, the first phase consisting of sodium iodide, the second phase being

the benzene phosphorane solution. The contents of the flask was cooled to room temperature.

Nopinone (6 g) in dry benzene (25 ml) was added to the above reaction mixture in 15 minutes. The contents of the flask was stirred for 15 hr. at room temperature and then refluxed for 6 hr. The reaction mixture was cooled. The benzene solution was washed until it was neutral, dried and the solvent removed. The residue was triturated with pet.ether. The pet.ether extracts were combined together and the solvent removed. The residue was chromatographed through gr.I alumina (100 g). The hydrocarbon (1.8 g) was eluted with pet.ether, b.p. 80°/4.5 mm., n_D^{26} 1.4715; $(\alpha)_D^{26}$ - 20.4°.

Analysis

Found: C, 87.14; H, 11.85.

Calc. for $C_{10}H_{16}$: C, 88.23; H, 11.76%.

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