Synthetic Studies in Terpenes and Chemical Investigation of "Viola Odorata"

A Thesis
Submitted to
THE UNIVERSITY OF POONA
For
The Degree of
DOCTOR OF PHILOSOPHY
(in Chemistry)

By
PUNDLEEK HONNOSA LADWA, M. Sc.

Division of Organic Synthesis
NATIONAL CHEMICAL LABORATORY
POONA (INDIA)

1968

A C K N O W L E D G M E N T

I take this opportunity to express my sincere gratitude to Dr. S.N.Kulkarni, Ph.D.(Karnatak), Ph.D.(Exeter), under whose able guidance the work presented in the thesis has been carried out.

I am grateful to Drs. N.L. Dutta, S.S. Welankiwar and G.D. Joshi for helpful suggestions and keen interest in this work. Assistance received from microanalytical and spectroscopic sections is gratefully acknowledged. I also wish to express my sincere thanks to all my colleagues in the Department for their help and cheerful co-operation.

I am thankful to the Director, National Chemical Laboratory, Poona, for permitting me to submit this work in the form of a thesis.

(P.H. Ladwa)

November 1968

****

C O N T E N T S

****

INTRODUCTION

Essential oils, in a broad sense, may be defined as odorous volatile bodies of an oily nature extracted almost exclusively from vegetable sources. They are generally liquid, some times solid or semi-solid. The chemistry of essential oils is one of the oldest branches of organic chemistry and has contributed markedly to chemistry in general. Industry of essential oil is diversified; hence it is justified to mention that many of these natural isolates are used not only as perfumes and flavour materials, but also as intermediates as building-blocks, in the preparation of variety of products, such as aromatics, pharmaceuticals, household products and many others. This industry employs some of the most advanced chemical research and production techniques.

The result of these efforts serves the mankind to satisfy many of its demands, probably best described as 'part of our civilisation'. Essential oils are mainly composed of terpenoids with few exceptions like the oil of mustard, onion and garlic which contain sulphur compounds and some flower oils, which have benzenoid bodies. 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 proposed 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.

Terpenes are classified in six different classes which is generally based upon the molecular formula $(C_5H_8)_n$ where n is used as a basis for classification. The classes are (i) monoterpenes, $C_{10}H_{16}$; (ii) sesquiterpenes, $C_{15}H_{24}$; (iii) diterpene, $C_{20}H_{32}$; (iv) triterpenes, $C_{30}H_{48}$; (v) tetraterpenes, $C_{40}H_{64}$ (these are carotenoids); (vi) polyterpenes $(C_5H_8)_n$. The term terpene was originally reserved for the hydrocarbons of molecular formula $C_{10}H_{16}$, but by common usage, the term now includes all compounds of the formula $(C_5H_8)_n$.

The earlier methods for structure determination of terpenes have not been very successful, as the degradation products are often too complex to admit the separation and identification or are else too simple to throw any light on the original molecule. The most profitable researches centre around the newer methods of organic chemistry. Amongst such newer methods is the hydroboration-oxidation reaction which has been now extensively used in structure determination of organic compounds.

Similarly Robinson annelation reaction or its modification i.e. using substituted vinyl ketones has been used extensively to build up cyclohexane system and it has become the standard practice in syntheses of steroids and terpenoids to use this reaction. Recently lead tetraacetate has been used extensively in introducing functional group when it is not normally possible by other methods. For example in the steroid field, the C_{19} methyl group has been converted to $-CH_2OH$ or -COOH group which is not normally possible by other reactions. This along with photochemical reaction has revolutionised the steroid field. Lead tetraacetate is also useful in introducing an acetoxy group at the α-position. Still now, Grignard reaction has got importance in synthesising various terpenes like ($\pm$) curcumene, α-santalene, (-) zingiberene etc.

Lastly, the synthesis of an optically active natural product starting with an optically active compound of known stereochemistry is always a fascinating problem. One has to be extremely cautious for ascertaining the optical purity in each and every step. The rotation of the resulting compound gives some time the clue as regards its stereochemistry. Various physical methods have proved quite useful in the terpene field in general. Infrared, ultraviolet, mass and NMR spectroscopy have been used extensively.

Gas liquid chromatography and thin layer chromatography have helped the organic chemist to a great extent to check the purity of isolated products. A further impetus has been given to the organic chemist by the measurement of optical rotatory dispersion and circular dichroism measurements, which have now become the standard practice in structural determination. Mass spectrum also has been used extensively not only in determining the molecular weight but fragmentation pattern is of immense help in structural determination.

Keeping in view the above facts, we started with the work on hydroboration-oxidation reaction studies of carvone and its derivatives, the results of which have been described in detail in the first Chapter of the thesis. The main aim of these investigations was to study the hydroboration-oxidation reaction of monocyclic terpenes containing functional groups (carvone and its derivatives) and the stereochemistry of the new asymmetric centre created in such study will be of great help in choosing the starting compounds for synthesising the optically active terpenes viz. zingiberene, canarone etc. Carvone, dihydrocarvone, carvotanacetone and carveol were subjected to hydroboration (O) reaction, using diborane as hydroborating reagent.

The probable mechanisms for the formation of various products along with their stereochemistry have been discussed. Carveolacetate and carvotan-acetoneacetol were subjected for selective hydroboration using disiamylborane. 'Part B' describes the various methods for the chain extension of the side chain of (+) p-menthane-6-en-9-ol (hydroboration product of (+)-limonene) to the derivatives of natural compounds whose stereochemistry has been well established. These transformations helped to determine the stereochemistry of the new asymmetric centre created in (+)-p-menthane -6-en-9-ol and will be the important factor in determining the suitable starting compound for the ultimate synthesis of natural zingiberene.

Second Chapter deals with the synthesis of optically active (+)-calamenene and 8α-hydroxy-eudesm-7-(11)-en-13-oic acid starting from (-)-menthone and dihydroeudesmol respectively. The total synthesis of (+)-calamenene established the stereochemistry and absolute configuration of naturally occurring calamenenes. The synthesis of 8-α-hydroxy-eudesm-8-(11)-en-13-oic acid (butenoid), established the stereochemistry of atractylone and lindestrene at all the centres.

Third Chapter describes the chemical investigation of dry leaves of viola-odorata. The leaves after extraction with petroleum ether and careful chromatography furnished β-sitosterol, Friedelin, a straight chain alcohol along with waxy material.

GENERAL REMARKS

1. All the figure numbers, chart numbers, structure numbers and references in a chapter refer to that particular chapter only.

2. All melting points and boiling points are uncorrected and recorded on centigrade scale.

3. Optical rotations were taken in chloroform solutions unless otherwise mentioned and sodium light (5893 $\mathring{A}$) was used as the source. Concentrations are expressed in g/100 ml. of solution.

4. Light petroleum refers to the fraction boiling between the range (60-80°).

5. Ether extracts after washings were dried over anhydrous sodium sulphate.

6. Neutral alumina used for column chromatography was prepared from commercial alumina (100-230 mesh) bya washing with dilute nitric acid and activating to grade I by heating at 450-460° for 6 to 8 hr. Suitable grades were then prepared by addition of appropriate amounts of water and homogenising over a roller mill for 6 hr.

7. Silicic acid used for column chromatography was activated at 125-150° for 5 hr.

8. TLC was run over glass plates coated with a mixture of silicic acid and plaster of Paris (85:15; 200 mesh) and activated at 120° for 2 hr.

9. Infrared spectra were recorded (unless otherwise mentioned) as liquid film or in nujol suspension on Perkin Elmer Spectrophotometer (models 137B, 137E and 221) with sodium chloride optics.

10. Ultraviolet spectra were taken in 95% spectroscopic alcohol on Beckman ratio recording spectrophotometer, Model DK-2 and on Perkin-Elmer spectrometer Model 350.

11. NMR spectra were taken in 10% solutions in carbon tetrachloride or deuterochloroform on a Varian Associates A-60 spectrometer with tetramethyl silane as the internal standard; the signals (chemical shifts) are measured in δ values.

12. GLC analyses were carried out using hydrogen under pressure as the carrier gas on modified Griffin GLC apparatus, MK IIA with polyester column.

Chapter I

Hydroboration - Oxidation Studies of Monoterpenes

Part A

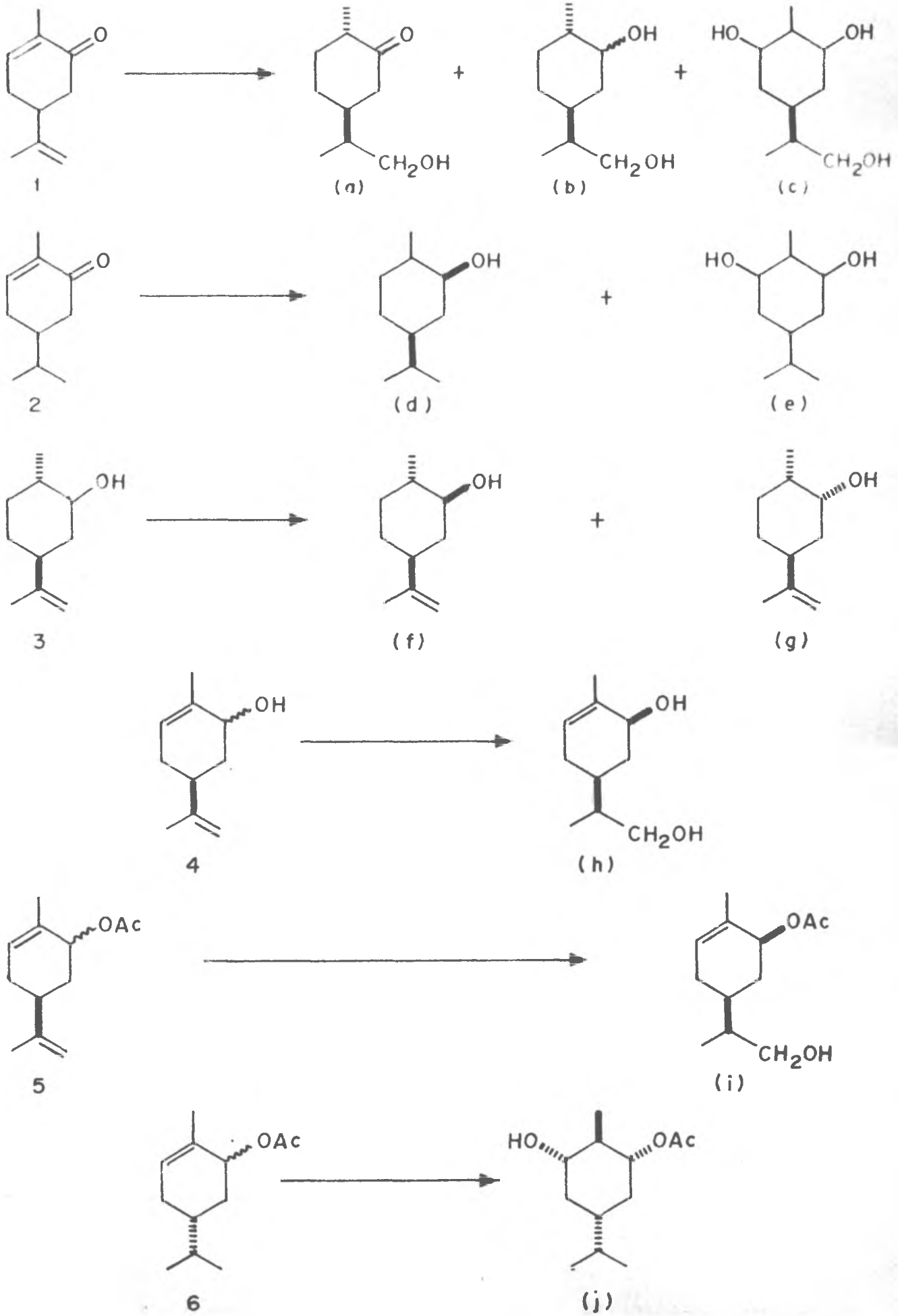
Hydroboration - Oxidation Studies of Carvone and its Derivatives

S U M M A R Y

This Chapter describes the hydroboration-oxidation reaction studies of carvone and its derivatives, using diborane and disiamyl-borane as hydroborating agents. The following table gives a brief survey of the various results.

Table

No.	Compound	Hydroborating reagent	Products
1	(+)-Carvone	Diborane	a) trans-p-menthane-2-keto-9-ol
			b) trans-p-menthane-2,9-diol
			c) p-menthane-2,6,9-triol
2	(+)-Carvotan-acetone	"	d) cis-carvotanacetol
			e) p-menthane-2,6-diol
3	(-) Dihydrocarvone	"	f) cis-dihydrocarveol
			g) trans-dihydrocarveol
4	(+) Carveol	"	h) p-menthane-6-ene-2,9-diol
5	(+) Carveolacetate	Disiamyl-borane	i) p-menthane-6-ene-2-acetate-9-ol
6	(-) Carvotanacetol-acetate	"	j) p-menthane-2-acetate-6-ol


O
CH2OH
(a)
OH
(b)
HO
OH
(c)
1
2
(d)
(e)
3
(f)
(g)
4
(h)
OAc
5
(i)
6
(j)

The present Chapter describes the hydroboration-oxidation reaction of carvone and its derivatives. This investigation was initiated as a part of an initial study to examine the products formed in the hydroboration (0) of mono and sesquiterpenes, containing functional groups. This became necessary because of our interest in using this reaction in the synthesis of naturally occurring compounds belonging to these series. Therefore a summary of this reaction as applied to (1) olefins (2) olefins containing other functional groups has been given below.

General survey of the reaction

Hydroboration-oxidation reaction was first discovered by H.C. Brown and Subbarao[1,2], when they were studying the enhance reducing power of sodium borohydride under the influence of aluminium chloride on ethyl oleate. They observed that, ethyl oleate consumed 3 moles of hydride as against two moles required for ester reduction. They found that, the extra one mole required was due to the reduction of double bond or in other words they found that the double bond can be reduced and an alcohol can be obtained. Once this was realised, they applied this hydroboration-oxidation reaction to various types of olefins. The earlier reaction of sodium borohydride-aluminium chloride was then replaced by diborane gas

which can be easily generated by the action of boron trifluoride etherate on sodium borohydride in diglyme. Although diborane gas was discovered long back, enhanced reducing power of this was recognised by Brown et al., who showed its effectiveness in presence of solvents containing ether linkage. Otherwise the reduction of this gas was very slow and thus, discourage the previous workers in using this gas.

Hydroboration involves the addition of boron-hydrogen bond to the carbon-carbon multiple bond[1,2] providing a new convenient route to the corresponding organoboranes, thus, making them readily available as

$$H_2C = CH_2 + HBH_2 \longrightarrow H_3C - CH_2 - BH_2$$

intermediates in organic synthesis. These organoboranes undergo rapid and quantitative oxidation with alkaline hydrogen peroxide to furnish the alcohols.

$$H_3C - CH_2 - BH_2 + H_2O_2 \xrightarrow{-OH^-} H_3C - CH_2 - OH + HOBH_2$$

The general chemical equation of hydroboration can be given as

$$12\ RCH = CH_2 + 3NaBH_4 + 4\ BF_3{:}O(C_2H_5)_2 \longrightarrow 4\ (RCH_2 - CH_2)_3B + 3NaBF_3 + 4(C_2H_5)O$$

The compound is treated with sodium borohydride and borontrifluoride etherate in appropriate solvents. These solvents do not interfere when the oxidation of

organoborane with alkaline hydrogen peroxide is carried out. So, the hydroboration reaction (O) can be performed without isolating the organoboranes. This reaction occures with retention of configuration and there is no carbon-skeleton rearrengements that occasionally accompany other hydration procedures.

Initially, the reaction got much significance in the field of olefins, dienes and acetylenes as one of the most important synthetic tool for the anti-Markownikoff cis-hydretion of double bonds. It was then extended to hydroborate the double bonds of olefins, containing other functional groups such as acid chlorides, esters, alcohols and nitro compounds[3,4].

Apart from diborane gas, as a hydroborating agent, selective hydroborating reagents such as bis-(3-methyl-2-butyl) borane[5-7], thexylborane[8], diisocamphenyl-borane[9-11] were developed, when synthetic chemist was faced with problem of two or more reactive sites within a single molecule.

A more recent development in this field is hydro-boration-carbonylation-oxidation of olefins to provide a synthetic route to tertiary alcohols, secondary alcohols and keontes characteristic of many types of synthesis involving the reactive Grignard reagent. This aspect will be discussed at the end.

Hydroboration of olefins

As mentioned previously, organoboranes are readily converted into the corresponding alcohols by oxidation with alkaline hydrogen peroxide and this reaction is quantitative, placing a hydroxyl group in precise position, previously occupied by the boron atom. Accordingly, a detailed study of the various structural types was undertaken by Brown et al. utilising the hydrogen peroxide oxidation of the organoboranes to establish the orientation[12].

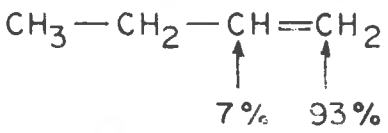
1. Terminal olefins

$RCH=CH_2$, gave predominantly addition of the boron atom to the terminal carbon atom (93.94%), which established the anti-Markownikoff direction of addition in most of the cases. For example, 1-butene and 1-hexene gave predominantly 93% and 94% of primary alcohols (Chart I). Branching of the alkyl groups adjacent to the double bond did not influence the direction of addition. Thus 3-methyl-1-butene, 3,3-dimethyl-1-butene and 4,4-dimethyl-1-pentene gave the same distribution (Chart I). But in the case of disubstituted terminal olefins the directive effect was overwhelming. For example, 2-methyl-1-butene gave 99% of primary alkylborane (Chart I). The fact that ethylene, isopropyl ethylene and t-butylene gave 93%, 94% and 94% respectively of primary alcohols, clearly showed that, the increase in the bulk of alkyl

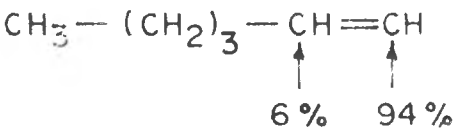
CHART - I.

DIRECTIVE EFFECTS

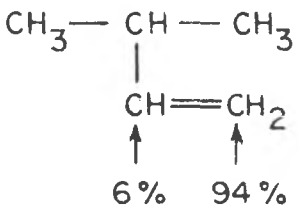
TERMINAL OLEFINS



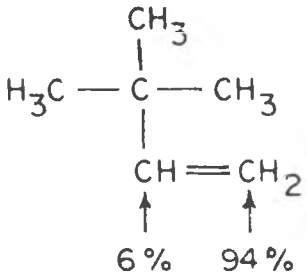
1 – BUTENE



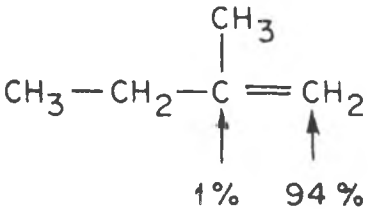
1 – HEXANE



3 – METHYL – 1 – BUTENE

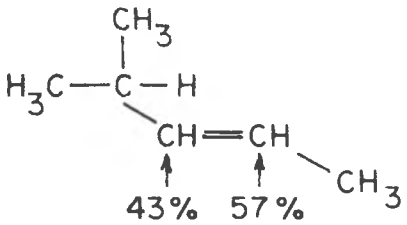


3,3 – DIMETHYL – 1 – BUTENE

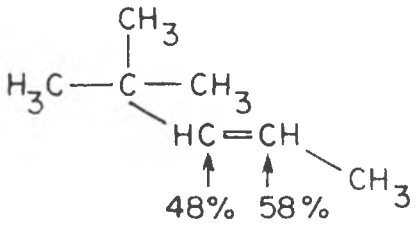


2 – METHYL – 1 – BUTENE

DISUBSTITUTED OLEFINS

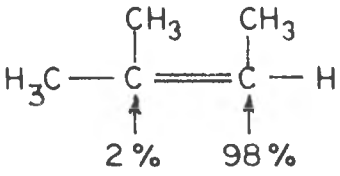


TRANS – 4 – METHYL – 2 – PENTENE

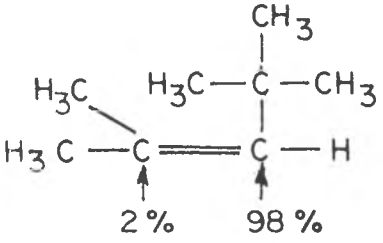


TRANS – 4 ,4 – DIMETHYL – 2 – PENTENE

TRISUBSTITUTED OLEFINS



2 – METHYL – 2 – BUTENE



2, 4, 4 – TRIMETHYL – 2 – PENTENE

group attached to double bond does not influence the direction of addition. These facts argue against the steric control of the direction of addition.

2. Dialkyl ethylenes

RCH=CHR', such as 2-pentene, 2-hexene undergo addition to place the boron atom in approximately equal amounts on the two carbon atoms. It was even true for molecules such as trans-4-methyl-2-pentene and trans-4,4-dimethyl-pentene, where the two alkyl groups differ markedly in the steric requirements (Chart I).

3. Trisubstituted olefins

R_2C=CHR. In the case of 2-methyl-2-butene and 2,4,4-trimethyl-2-petene, boron atom added predominantly at the less hindered ethylenic atom (Chart I).

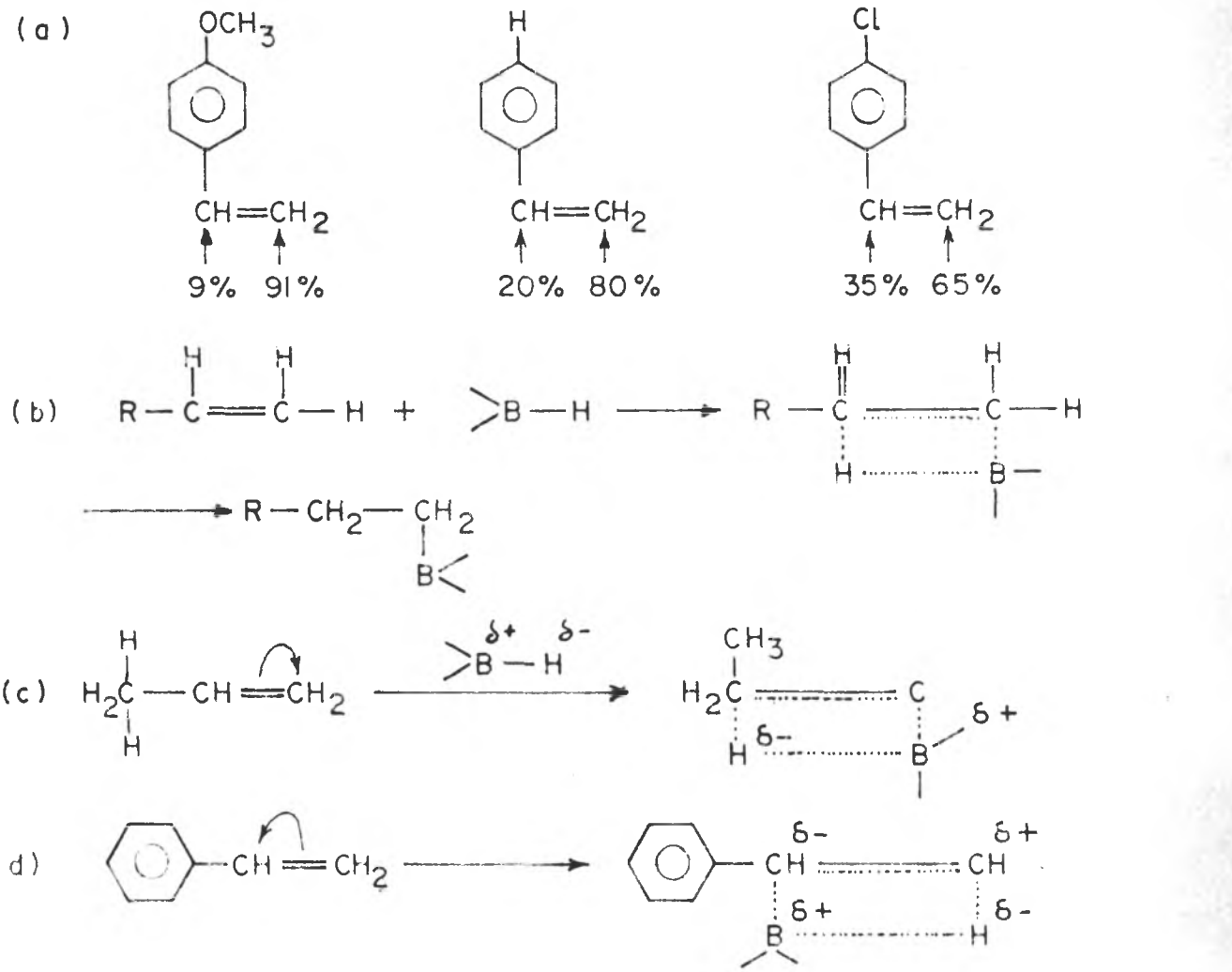
Mechanism

From these results it was concluded that the electronic influence play an important role rather than steric effect in controlling the direction of addition of the boron-hydrogen bond to the double bond. This conclusion was further confirmed by the marked influence exerted by para substituents in the styrene molecule (Chart IIa).

The addition of diborane to cyclic olefins and acetylenic occures cleanly to give cis compounds. Consequently it appeared that addition must involve a four-centre transition state (Chart II,b). The boron-

CHART – II

MECHANISM



hydrogen bond is presumably polarised, the hydrogen having some hydride character. The addition of the boron atom to the terminal position is then understood on the basis of electronic shift, generally assumed in order to account for the normal ionic addition to propylene (Chart II, c). In the case of styrene, similar arguments can be made to account for the observed preference of the boron atom fro terminal position. It is generally recognised that a phenyl group can supply electrons to an electron deficient centre or serve as sink. This provided a simple explanation for the increased substitution in the α position observed in styrene (Chart II, d). So it was concluded that anti-Markownikoff addition observed in hydroboration is primarily the result of the hydridic polarisation of the boron-hydrogen bond.

Isomerisation of organoboranes[13,14]

One of the most interesting and promising aspect of organoborane chemistry is the ready isomerisation of organoboranes at moderate temperature, thus providing a synthetic route to primary organoboranes derived from internal olefins. The small quantities of excess of diborane produced in the hydroboration stage markedly catalyses the isomerisation. For example, tri-n-hexylborane gave 1-hexylborane (Chart II, B1). In isomerisation, the boron atom migrates to the least

hinder position in the molecule. The mechanism of the isomerisation reaction appears to involve a partial dissociation of the organoborane into olefin and the boron-hydrogen bond, followed by readdition. The process occures repeatedly, until the boron atom ends up at the least hindered position of the molecule, thereby yielding the most stable of the organoboranes derivable from the particular alkyl group used (Chart II, B2).

It is evident from this mechanism that, the presence of another olefin in the reaction mixture of similar or greater reactivity should cause it to participate, freeing a corresponding number of molecules of the original olefin used to form the organoborane[13,15,16]. Such displacement reaction would lead to an equilibrium mixture of all possible organoboranes. Such equilibrium (Chart II, B3) could be driven toward completion (1) by using a large concentration of the displacing olefin, (2) by distilling the more volatile olefin out of the reaction mixture, and (3) by using an olefin that form a very stable organoborane viz. tri-n-pentyl-borane was heated with 1-decene. A good yield of 1-sentene was obtained and tri-n-decylborane was identified.

$$3n\text{-}C_8H_{17}CH=CH_2 + (n\text{-}C_5H_{11})_3B \xrightarrow[DG]{160^\circ}$$

$$3n\text{-}C_3H_7CH=CH_2\uparrow + (n\text{-}C_{10}H_{21})_3B$$

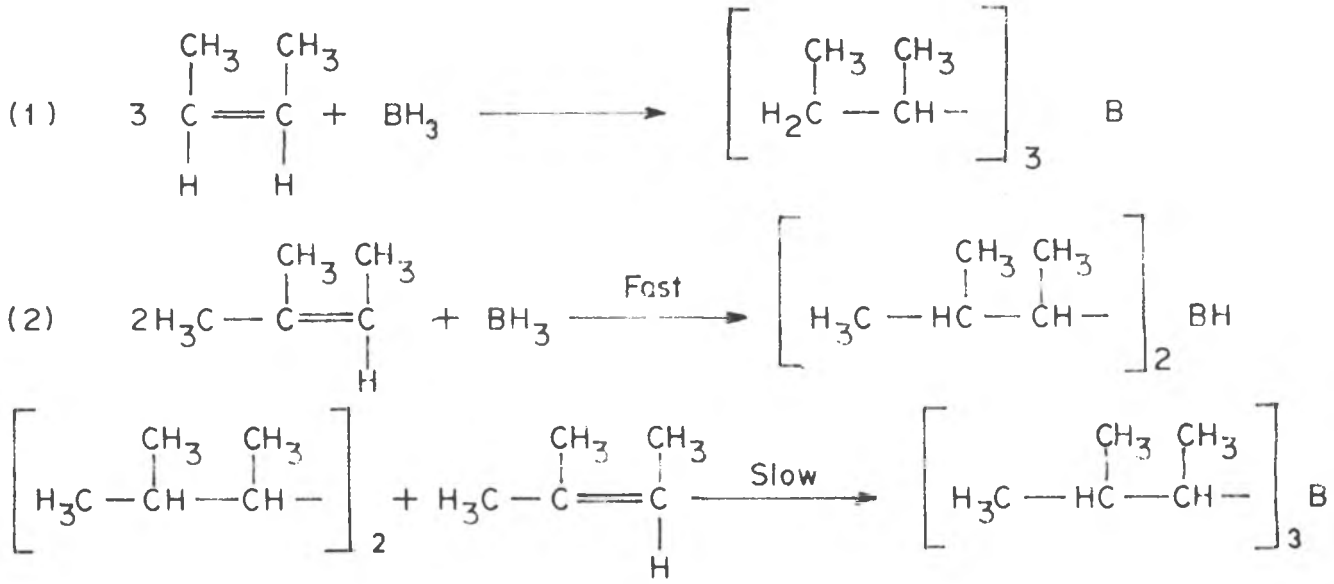
Selective hydroboration of olefins with disiamylborane[5-7,17]

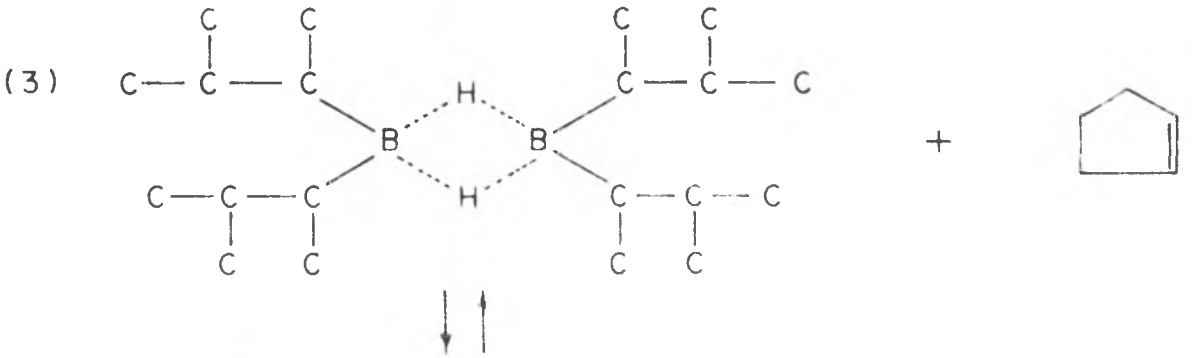
Simple olefins commenly utilised all the hydrogen atoms of diborane and formed the trialkyl borane (Chart III, 1). However, highly substituted olefins, such as 2-methy-2-butene utilised only two of the three hydrogen atoms of the borane group forming dialkyl borane (Chart III, 2). Further reaction to the trialkyl borane stage being relatively slow (Chart III, 2). The slowness of the last stage, in contrast to the high speed with which other olefins form the trialkyl boranes, is presumably a result of large steric requirements of the intermediate dialkylborane. It appeared therefore, that, this disiamylborane might exhibit an enhanced sensitivity to the steric requirements of the substitution on double bond.

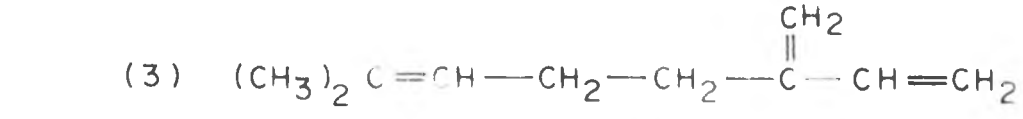
Both molecular-weight determination and infrared examination revealed that disiamylborane exists as dimer. It can be represented as in (Chart III, 3). This reagent has been successfully utilised for hydroboration of alkenes. The rate of utilisation of this reagent by terminal olefins, disubstituted olefins and trisubstituted olefins is different and it is in the order of terminal > disubstituted > trisubstituted olefins. The difference in the reactivity of various olefin structures permitted

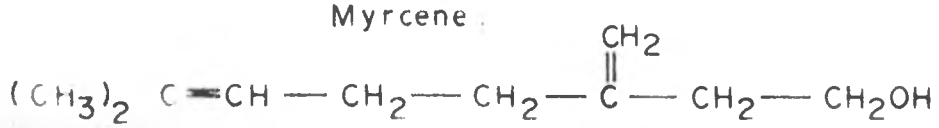
CHART III.

SELECTIVE HYDROBORATION BY DISIAMYLBORANE









a variety of selective hydroboration reaction, and comparative hydroboration were carried out for such selectivity reactions. For example a mixture of 1-pentene and 2-pentene gave mainly 1-pentanol leaving behind 99% of 2-pentene. The information developed on the effect of structure on reaction was utilised to predict the point of attack in a molecule containing two or more double bonds. For example, dienes, like vinylcyclohexenene, d-limonene and myrcene were hydroborated without attack on less reactive double bond (Chart III, 4).

Asymmetric hydroboration with diisopinocampheylborane[18]

Hydroboration of optically active ∝-pinene gave a optical active dialkyl borane, known as diisocompheylborane, $(\alpha)_D$ - 37.1°. This optically inactive diborane was subjected to hydroborate suitable olefin derivatives in order to examine the possibility of achieving as asymmetric synthesis of an optically active organoborane, as well as of alcohol derivable by oxidation. The results proved astounding. Thus cis-2-butene gave 2-butenol in 90% yield, $(\alpha)_D$ - 11.8° (87% pure) cis-3-hexene yielded 3-hexanol $(\alpha)_D$ - 6.5° (83% pure). The reagent react very sluggishly with trans olefins. These results indicated that a boron atom at the asymmetric centre is capable of maintaining asymmetry withoug significant recemisation.

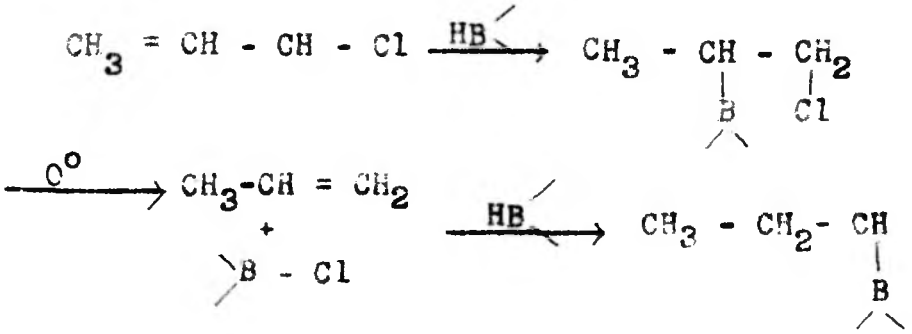
Hydroboration of olefins containing other functional groups

Extension of the reaction to functional derivatives of olefins is complicated by the reduction of many functional groups by diborane. The hydroboration of carbon-carbon double or triple bond is so rapid that they can frequently be converted to organoborane in excellent yield in the presence of such functions as acid chlorides, esters or nitro groups[3,4]. In some cases a group is reduced very rapidly, such as the carboxy group. Numerous alcohols have been hydroborated especially steriod alcohols.

Hydroboration of allyl derivatives[19]

The introduction of electron withdrawing functional groups at the allyl position brings about a marked increase in the addition of boron to the secondary carbon atom of the double bond. Thus in the hydroboration of allyl tosylate and allyl chloride, 45% and 40% respectively of the boron added to the non terminal position. It has also been observed in both allyl chloride and allyltosylate the addition of boron to the non terminal position accompanied by a spontaneous elimination of boron and the substituent in the β-position. The resulting olefin then underwent further

hydroboration.



The use of disiamylborane as the hydroborating agent for allyl compound results, as anticipated, in almost exclusive addition to the terminal carbon atom. Evidently the role of electronic effect of the substituent in directing the boron to the nonterminal is largely nullified by the large steric effect of the substituents. The use of disiamylborane provides a useful general method for the preparation of the alcohols of the allyl derivatives. It was found that the elimination reaction is faster than the hydroboration stage with diborane gas. But disiamylborane avoids many of the complications observed with diborane. The reduction of the functional group is not a factor here. Allyl benzoates, acetates, alcohols, borates, ethylethers, phenylethers were subjected to hydroboration (straight chain compounds).

In contrast to the corresponding allylic derivatives which lead to the formation of thermally unstable organoboranes that eliminate rapidly, the

3-butenyl derivative (CH_2=CH-CH_2-CH-X), yielded stable organoboranes, which can be readily oxidised to alcohols[20]. (Here X represents Me, OMe, OPh, OH, OAc, Cl, NH_2 and COOR etc.). They underwent no secondary reactions i.e. boron added to terminal carbon atom only and there was no elimination of functional groups.

It has been observed in the case of 3-butenyl (crotyl) derivatives (CH_3-CH = CH - CH_2-X)[21], a marked enhancement in the addition of the boron to the β-position, with an accompanying marked reduction in the formation of γ-derivative as compared with allyl derivatives (thus crotyl chloride yielded essentially 100% addition of boron to the β-position, as compared to a 40% β and 60% γ-distribution realised with allyl chloride under the same condition). But in the case of chloride and acetates, hydroboration accompanied with spontaneous elimination at 0°.

$$CH_3\text{-}CH = CH\text{-}CH_2\text{-}Cl \xrightarrow{HB} CH_3\text{-}CH_2\text{-}CH(B)\text{-}CH_2\text{-}Cl$$

$$\longrightarrow CH_3\text{-}CH_2\text{-}CH = CH_2 \xrightarrow{HB} CH_3\text{-}CH_2CH_2\text{-}CH_2(B) \quad (+ B\text{-}Cl)$$

Hydroboration of vinyl derivatives[22]

The hydroboration of $C_\beta = C_\alpha HX$ can proceed to place the boron on the α and β position. In the case of isobutenyl chloride, hydroboration proceeded to

place the boron atom predominantly on the carbon atom (α) holding the chlorine substituent.

$$(CH_3)_2C = CH\text{-}Cl \xrightarrow{BH_3} (CH_3)_2CH\text{-}\underset{\displaystyle B}{CH}\text{-}Cl$$

This accounts for the marked difference in the behaviour of the system, as compared to isopropenyl-acetate (chloride) and crotonylacetate (chloride), which hydroborate to form β-boron derivatives.

Introduction of functional groups through hydroboration of olefins (hydroboration-carbonylation oxidation)

This provides a synthetic route to tertiary alcohols, secondary alcohols, ketones, aldehydes by the use of carbonmonoxide with suitable conditions, which are otherwise normally involving the reactive Grignard reagent. Carbonmonoxide at atmospheric pressure readily reacted at 100-125° with the allylborane, synthesised in situ in diglyme solution, to provide a convenient route to the corresponding trialkylcarbinols[23].

$$\xrightarrow{BH_3} (C_6H_{11})_3B \xrightarrow[100^\circ]{CO} \xrightarrow[NaOH]{H_2O_2} (C_6H_{11})_3COH$$

Addition of small quantities of water to the reaction mixture inhibits the migration of the third alkyl group from boron to carbon. Consequently oxidation of the organoborane intermediate obtained in the presence of

water produced the corresponding dialkyl ketone[24].

$$R_3B + CO \xrightarrow{H_2O} [(OH)HB\text{-}CR_2(OH)] \xrightarrow[NaOH]{H_2O_2} R_2CO$$

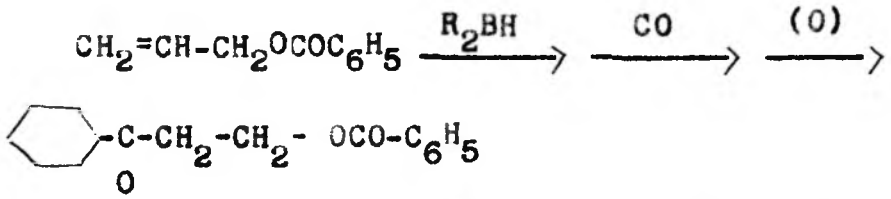
Carbonylation of organoborenes can be also achieved smoothly by using carbonmonoxide, trialkylborane in presence of little alkali borohydride[25]

$$R_3B + CO \xrightarrow[45^\circ]{NaBH_4} \xrightarrow{DG.KOH} R\text{-}CH_2\text{-}OH$$

The reaction can be controlled to achieve the transfer of one alkyl group from boron to carbon, when hydrolysis of the reaction intermediate was done with ethanolic potassium hydroxide giving a homologate alcohol. However, whereas the use of Grignard reagent is necessarily restricted to the use of building blocks which do not contain reactive substituents, the hydroboration carbonylation-oxidation is capable of utilising building blocks containing a wide variety of reactive functional groups.

Dicyclohexylborane was used as a reagent to react with a number of olefins containing a variety of functional groups. Carbonylation of the resulting organoborane in the presence of water yielded a functionally substituted cyclohexylmonoalkyl ketone, provided, substituent does not interfere with desired

reaction .



R_2BH = dicyclohexylborane

Aim of the present investigation

It is evident from the literature survey that very few compounds containing functional groups have been subjected to hydroboration (O) reaction particularly, in the field of terpenes. Hence, the hydroboration (O) reaction study of monoterpenes and sesquiterpenes containing functional groups was initiated in this laboratory. Besides, such a study was required in connection with the synthesis of optically active canarone and optically active zingiberene (Part II). The stereochemistry of the new asymmetric centre created in such a study will be greatly helpful in choosing the starting material for synthesising the above said compounds.

As a model study, the hydroboration (O) of carvone and its derivatives was undertaken. It is known that diborane gas is a reducing agent and reduces many functional groups. Being a strong Lewis acid, it is expected to attack at the highest electron density centres. Thus diborane reduces aldehydes and ketones of both aliphatic and aromatic series rapidly at room temperature.

$$2\ RCHO + BH_3 \longrightarrow (RCH_2O)_2BH$$

The following tables gives the action of diborane

on various types of groups.

Acid chlorides	..	No reaction
Lactone	..	Glycol
Oxide	..	Alcohol
Ester	..	Alcohol
Carboxylic acid	..	Alcohol (fast)
Nitrile	..	Amine
Nitro	..	No reaction
Olefin	..	Organoborane

As already mentioned, diborane adds at the olefinic double bond through a four centred transition state and therefore is a *cis* addition, and further the diborane adds at the highest electron density centres and the addition is against Markownikoff's rule. It is also discussed previously that, the Markownikoff's rule is followed in cases of allyl chlorides, esters, borates, benzoates etc. The present study, which is of preliminary nature throws further light on the use of hydroboration (O) reaction on the above findings.

Present work

In the present study, the action of diborane gas on carvone, carvotanacetone, dihydrocarvone, carveol and selective hydroboration of carveolacetate and carvotan-acetolacetate by disiamylborane, has been studied.

Hydroboration (0) of (+)-carvone (Chart II)

(+)-Carvone (I) is a monocyclic terpene ketone, having two double bonds, one of them being conjugated with keto group. Naturally, hydroboration (0) of carvone is of special interest as it has three possible sites of attack by diborane. Carvone (I) was dissolved in tetrahydrofuran and excess of diborane gas produced by adding sodium borohydride in diglyme, was bubled through at 0°. Then it was left overnight at room temperature and oxidised with alkaline hydrogen peroxide at 20-30°. The crude product so obtained was passed through alumina column (Gr.III) and eluted with petroleum ether, benzene, and alcohol and ether successively. Then each fraction was subjected for chemical investigation.

1. Benzene fraction (Isolation of p-menthane-2-keto-9-ol, II).

This fraction was found to be pure by TLC analysis. It has b.p. 150°(bath)/0.3 mm and $(\alpha)_D$ - 15.7°. It analysed for $C_{10}H_{18}O$. It formed a semicarbazone, m.p. 145°; 3:5-dinitrobenzoate, m.p. 115°. IR spectrum (NO 8) showed bands at 3350 cm^{-1} (for hydroxyl group) and 1709 cm^{-1} (for keto group). It did not show unsaturation in the region at 1660 cm^{-1} and 810 cm^{-1}. There was no absorption in UV spectrum. NMR spectrum showed a doublet (2H) centred at 3.41δ (J, 6 cps) due to proton attached

to alcohol group. Two doublets, one (3H) centred at 0.896 (J, 6 cps) due to a methyl group likely to be adjacent to alcoholic group and second doublet (3H) centred at 0.956 (J, 6 cps) due to methyl group adjacent to keto group.

All these results indicated that it is a saturated keto alcohol. The position of the keto group and alcohol group were determined as follows.

The keto-alcohol (II) was converted to its tosylate (V) by treating with p-toluene sulphonyl-chloride in pyridine. The crude tosylate (V) showed bands at 1718 cm^{-1}, 1600 cm^{-1} and a broad band between 990 cm^{-1} to 925 cm^{-1}. When it was reduced with LAH, an alcohol (VI) was obtained. The crude alcohol (VI) when subjected to oxidation by Jones reagent gave tetra-hydrocarvone (VII). It has b.p. 218° and $(\alpha)_D$ - 16.6° [lit. $(\alpha)_D$ - 18.7°][26]. It showed identical retention time with authentic sample of tetrahydrocarvone in GLC analysis. Its IR spectrum (Not) showed bands at 1709 cm^{-1} (for keto group). This definitely established that the keto group is at C_2-position. In order to find the position of the alcohol group, the keto-alcohol (II) was oxidised, when keto acid (VIII) was obtained. This acid was converted to its methylester by treating with diazomethane in ether. It has b.p. 125-130°(bath)/0.5 mm and $(\alpha)_D$ - 10.2°. GLC analysis showed it to be a single

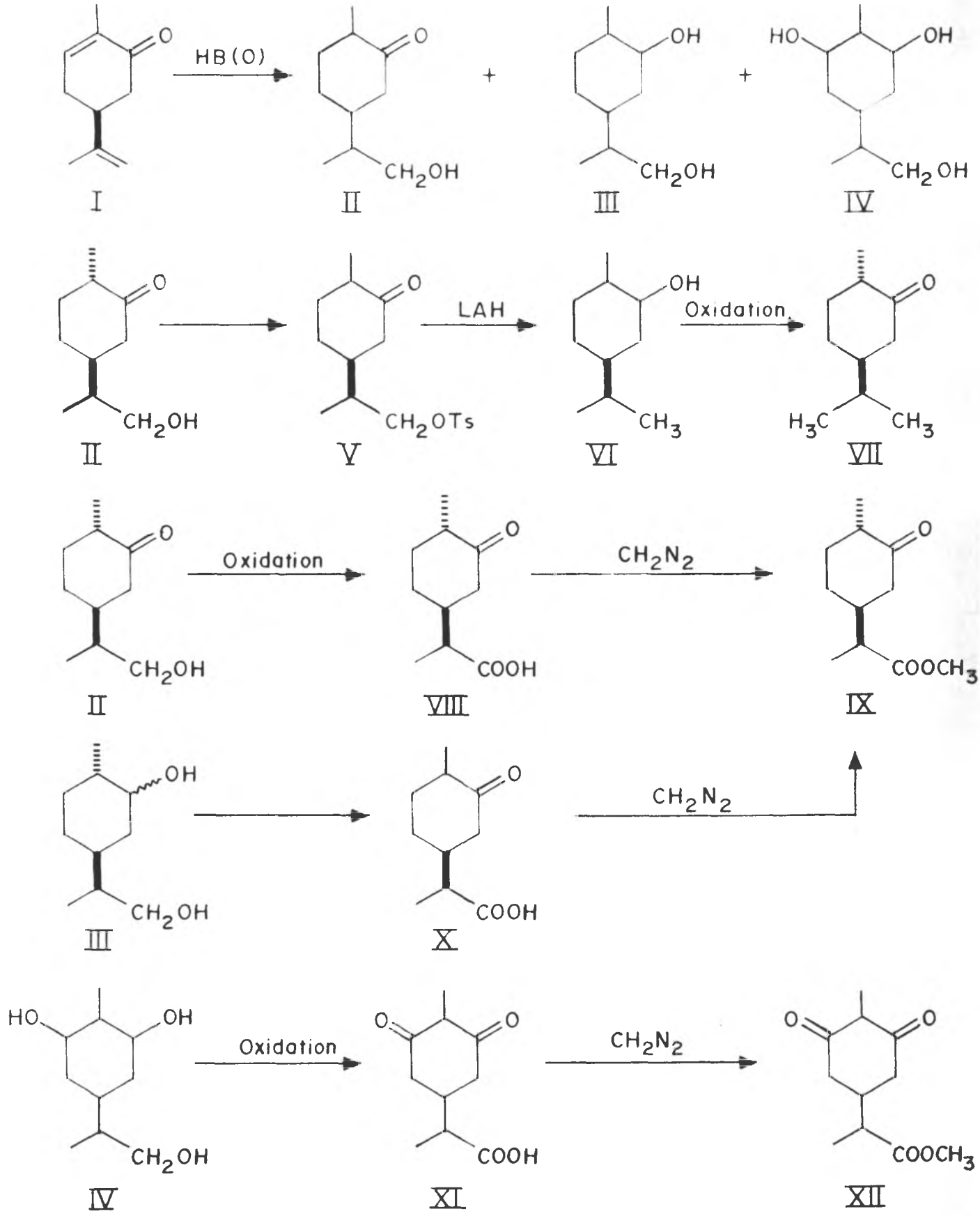
compound. The same compound has been prepared from hydrogenation of epoxide of dihydrocarvone by Raney nickel, which has rotation $(\alpha)_D$ - 10.3[27]. Thus, this keto-alcohol (II) is <u>trans</u>-p-menthane-2-keto-9-ol.

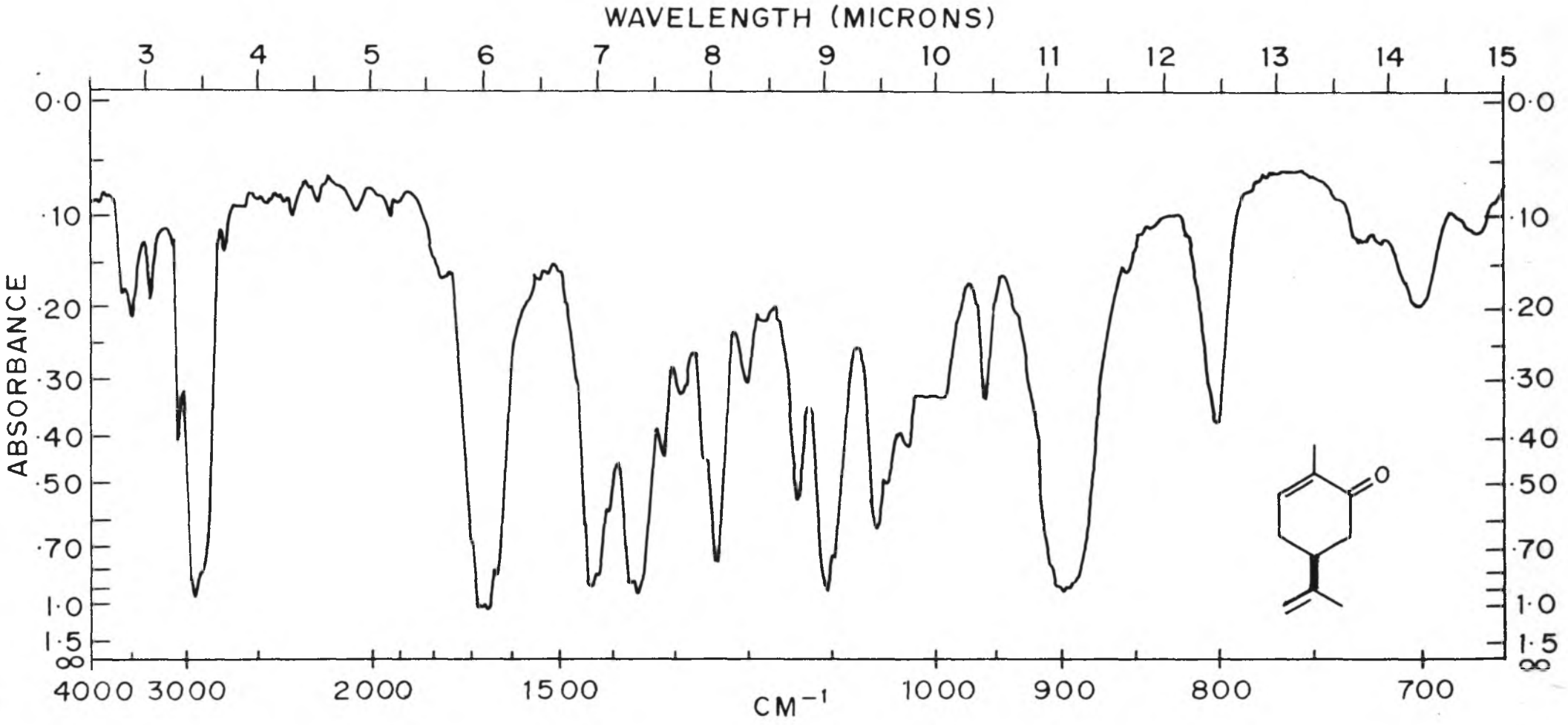
<u>Ether fraction</u> (Isolation of p-menthane 2,9-diol, IIIa + IIIb).

The compound isolated from benzene fraction was found to be pure by TLC analysis. It has b.p. 190°(bath)/0.3 mm and $(\alpha)_D$ + 10.5°. Elemental analysis showed it to have the molecular formula $C_{10}H_{20}O_2$. IR spectrum showed no unsaturation and indicated a hydroxyl absorption at 3400 cm^{-1}. In the NMR spectrum it showed a broad band at 3.75δ (HW ~15 cps, C<u>H</u>OH) and comparatively sharper singlet at 4.65δ (HW 5 cps, C<u>H</u>OH), both accounting for one proton and thus showing that it is a mixture of two secondary alcohols. Further it showed a doublet (2H) centred at 3.48δ (C<u>H</u>$_2$OH; J, 6 cps). The nature of the alcohol was proved by subjecting the diol (III) to oxidation by Jones reagent (Chart IV), when a keto-acid (X) was obtained. This acid (X) was further converted to p-menthane-2-keto-9-methylester (IX), by treating it with diazomethane in ether. It has b.p. 125-130°(bath)/0.5 mm; $(\alpha)_D$ - 10.1°. The p-menthane-2-keto-9-methyl esters obtained from p-menthane-2-keto-9-ol (II) and

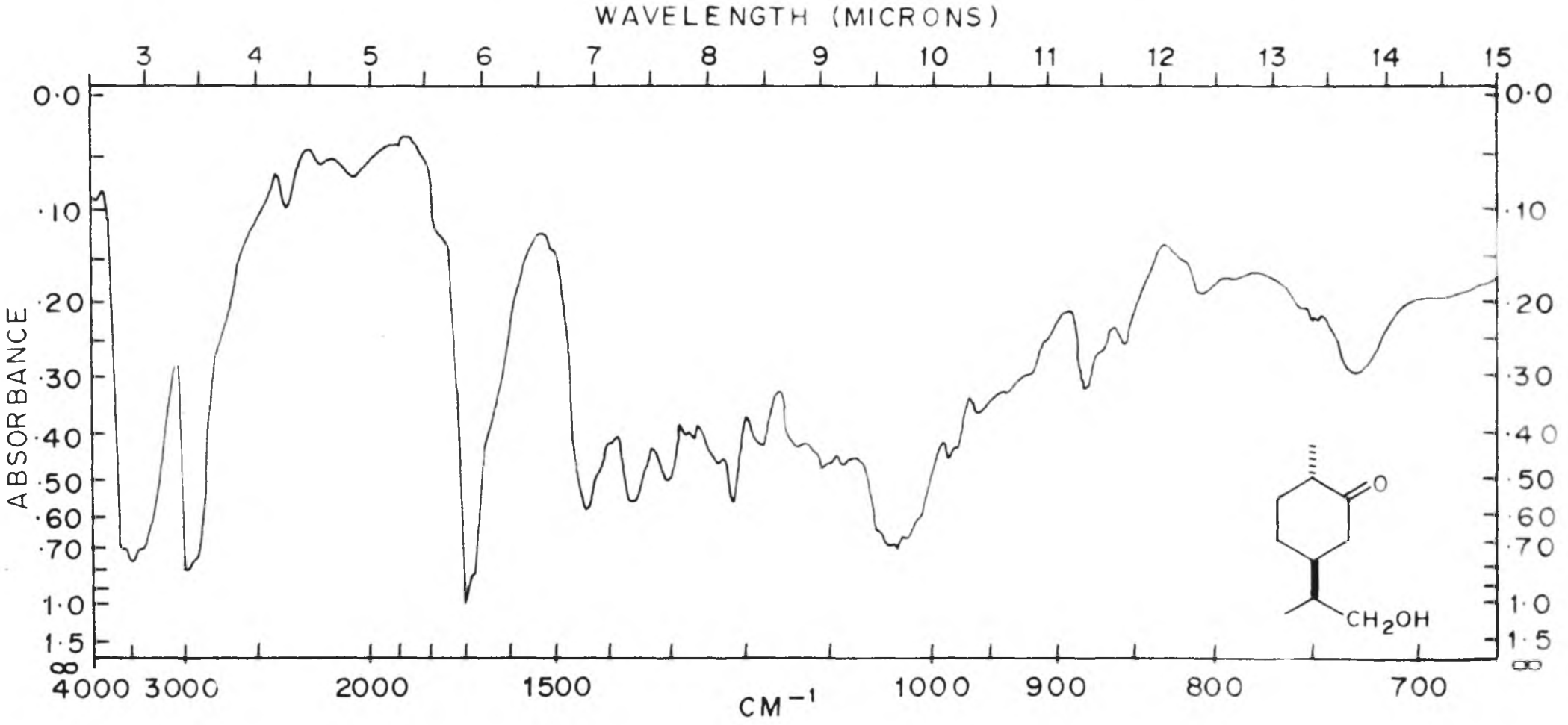
CHART IV

HYDROBORATION (O) OF CARVONE

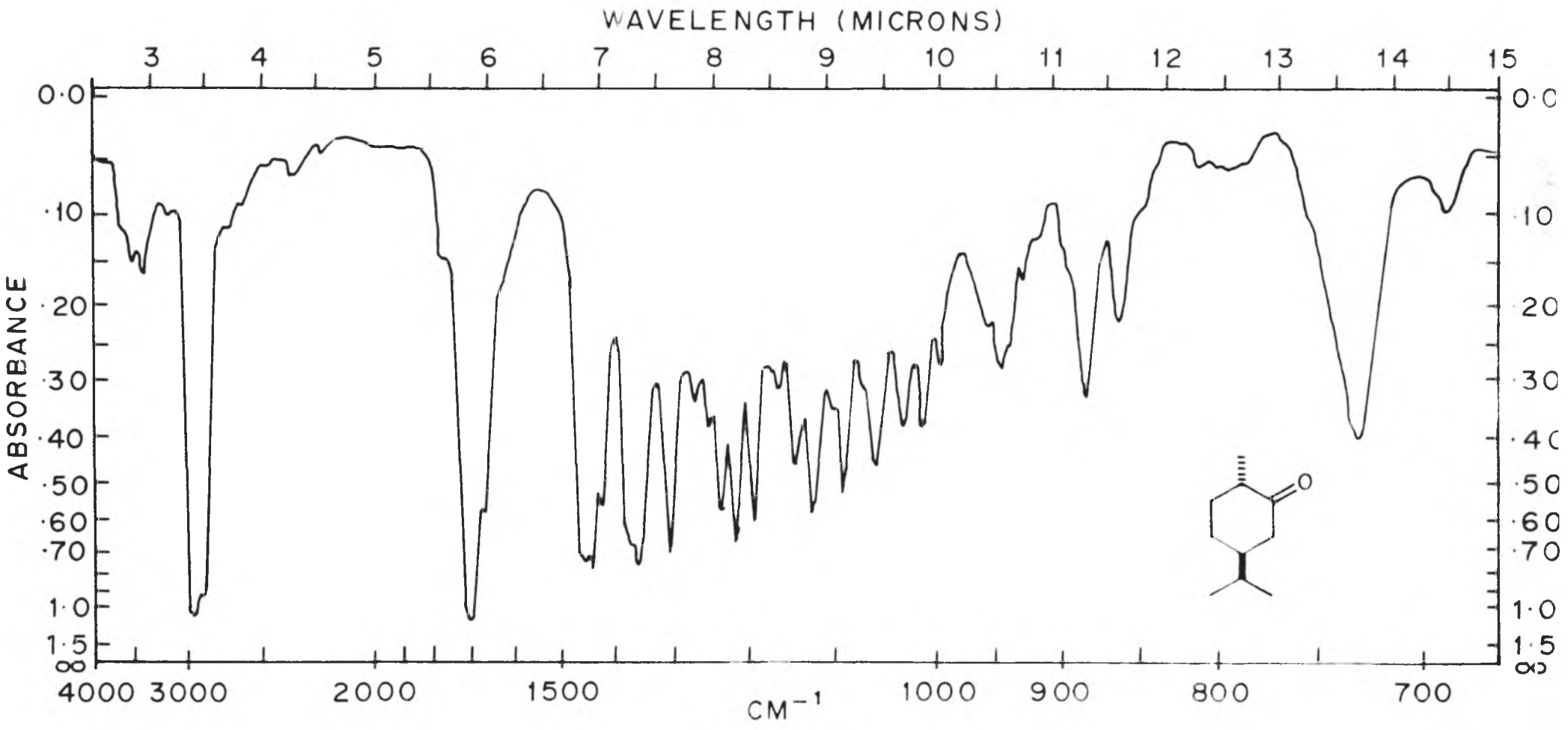




IR SPECTRUM (LIQUID FILM) No. 1.



IR SPECTRUM (LIQUID FILM) NO. 8.



IR SPECTRUM (LIQUID FILM) NO. 9.

diol (III) were identical with respect to IR spectrum and GLC analysis also. Hence, this diol can be represented as a mixture of (IIIa and IIIb). If one assumes that C_8 asymmetric centre contributes very little for rotation (since p-menthane-9-ol has rotation), then it is easy to calculate the percentage of two alcohols (IIIa and IIIb). (+)-Carvomenthol has rotation + 26.35° and (-)-isocarvomenthol has rotation -17.72°. This gives the mixture IIIa and IIIb in the ratio of roughly 65:35. The relative integration ratio of the protons attached to secondary alcohol groups roughly points to the correctness of the above conclusion.

Alcohol fraction (Isolation of p-menthane-2,6,9-triol, IV)

The compound was found to be pure by TLC analysis. It has b.p. 210°(bath)/0.3 mm. Elemental analysis showed it to have the molecular formula $C_{10}H_{20}O_3$. The IR spectrum showed band at 3450 cm^{-1} (for hydroxyl group). It was oxidised to an acid (XI), using Jones reagent and was converted further, to its methyl ester (XII) by treating it with diazomethane in ether. The elemental analysis indicated molecular formula $C_{11}H_{16}O_4$, thus showing that it is a diketo ester. Hence this compound can be represented as in (IV).

Hydroboration (O) of carvotanacetone (XV) (Chart V)

The unusual formation of p-menthane 2-keto-9-ol when carvone was subjected to hydroboration (O), prompted

us to carry out the hydroboration (O) of carvotanacetone (XV), similarly as done in the case of carvone (I) by passing through excess of diborane gas. The crude product was passed through the alumina (Gr.I) column.

Petroleum ether fraction

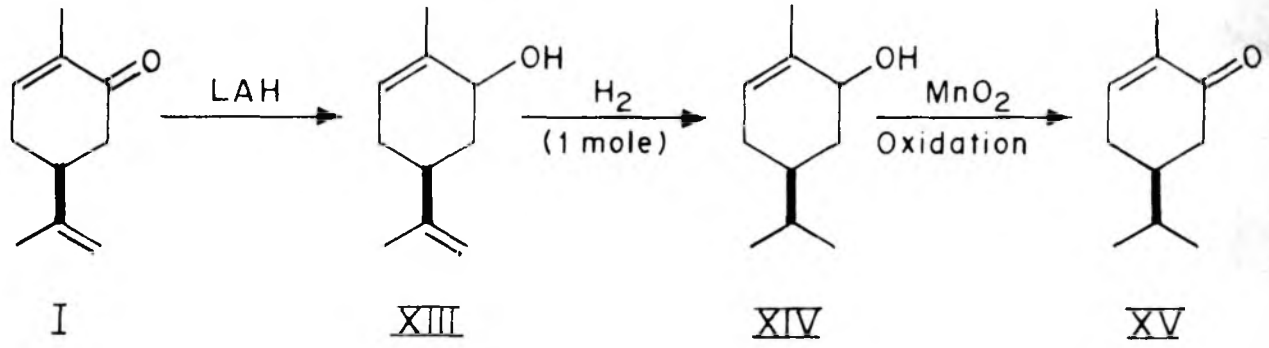
The fraction was found to contain two compounds by GLC analysis. The IR spectrum indicated a less intense hydroxyl absorption. One of the major compound corresponded to the unreacted carvotanacetone; the other compound (8%) agreed with tetrahydrocarveol as adjudged by comparative GLC analysis.

Ether fraction (Isolation of cis-carvotanacetol, XVI)

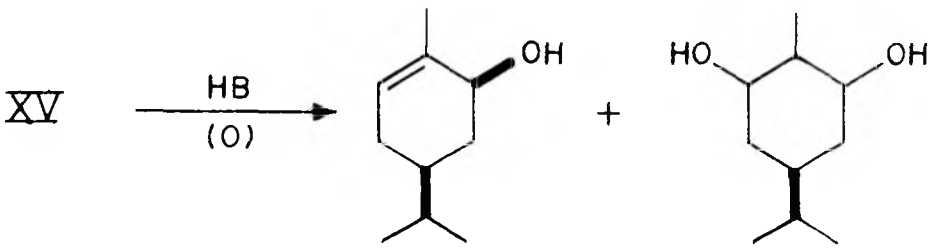
This fraction was found to be pure by GLC analysis. It has b.p. 120°(bath)/10 mm and $(\alpha)_D$ + 51°. The IR spectrum$^{(NC4)}$ showed bands at 3400 cm^{-1} (for hydroxyl group) and 813 cm^{-1} (for trisubstituted double bond). The NMR spectrum showed a broad singlet (1H) centred at 5.36δ (trisubstituted double bond); a broad singlet (1H, H.W.~15 cps) centred at 4.05δ (CHOH), showing allylic equatorial hydroxyl group. Further it showed a singlet (3H) at 1.72δ (methyl on a double bond) and a doublet (6H) at 0.88δ (J, 5 cps). From its optical rotation and NMR data, it is evident that it is a pure cis-carvotanacetol.

CHART V

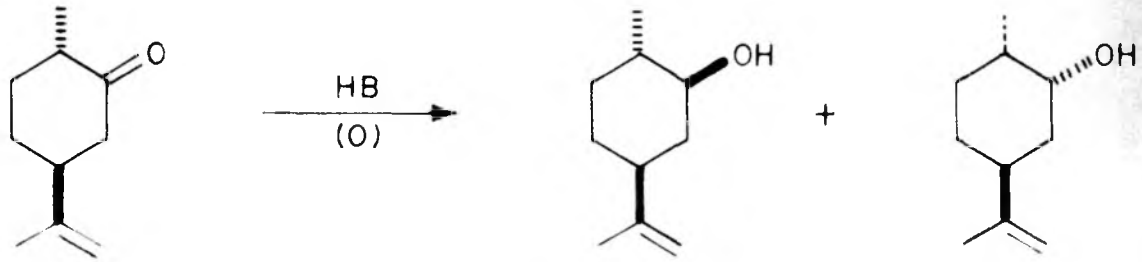
HYDROBORATION (O) OF CARVOTANACETON CARVEOL AND DIHYDROCARVEOL



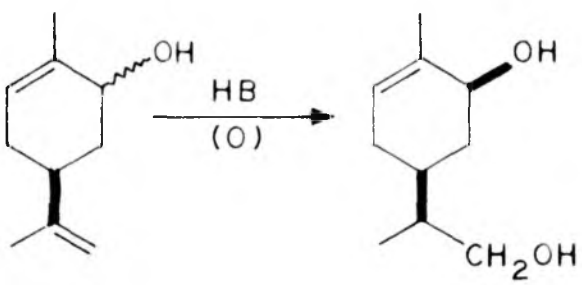
I XIII XIV XV



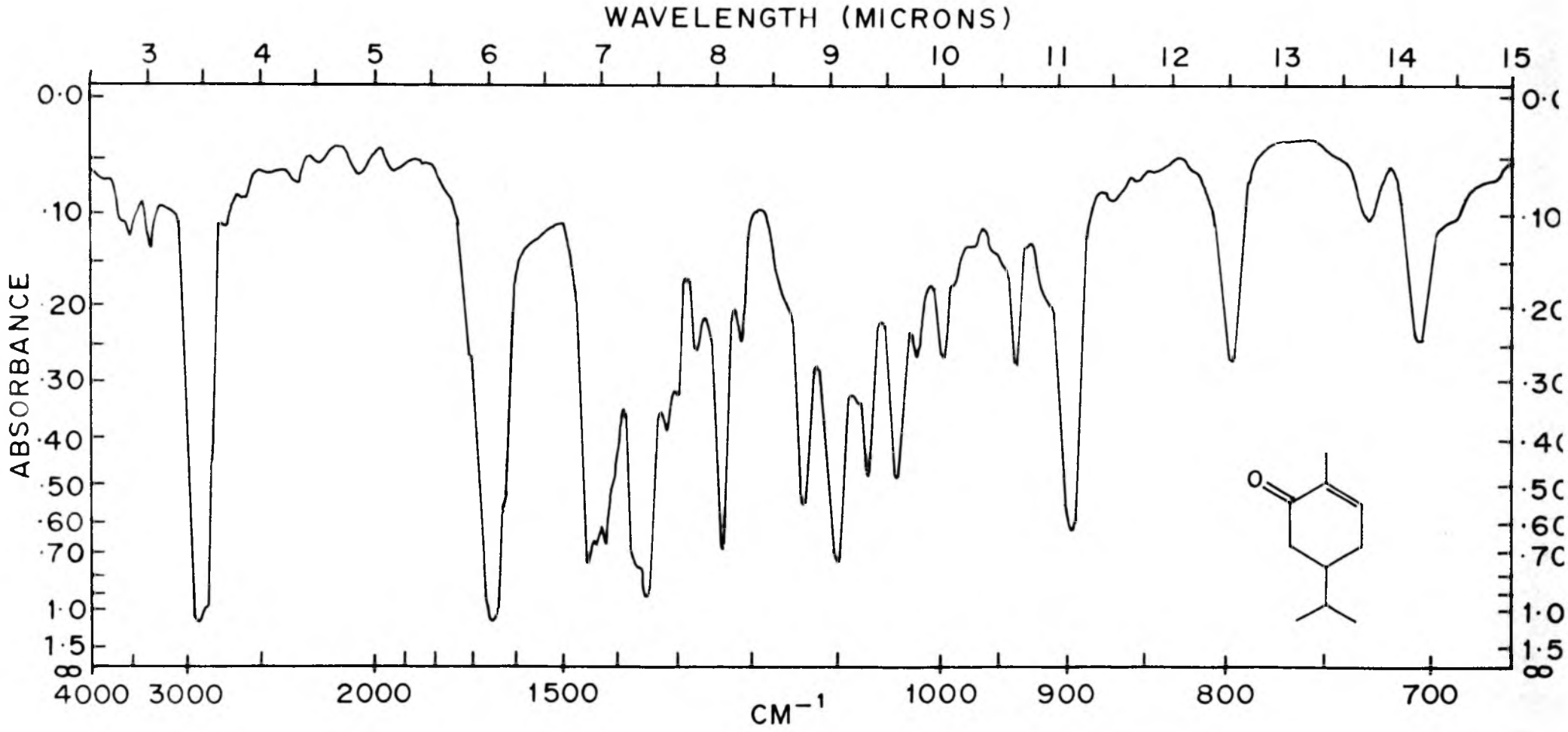
XVI XVII



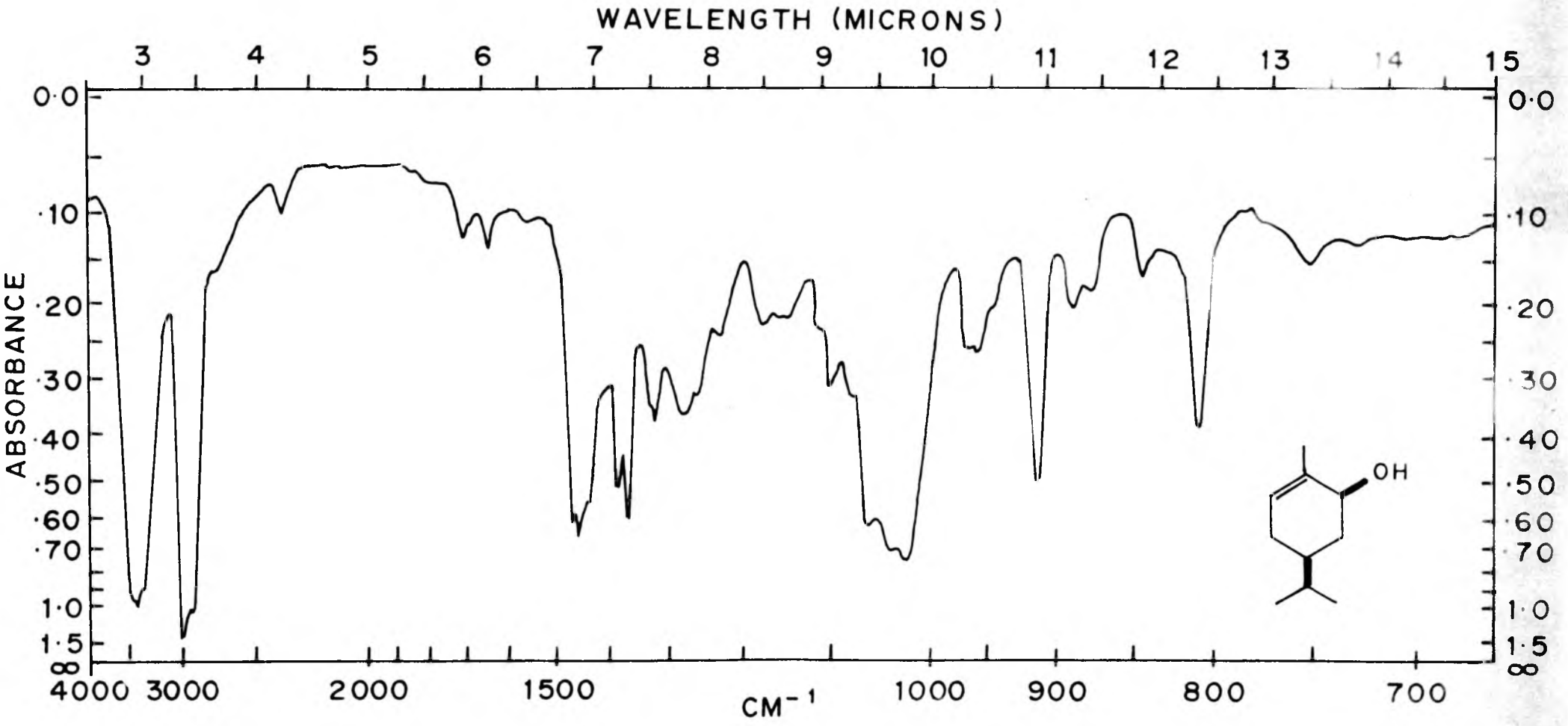
XVIII XIX XX



XIII XXI



IR SPECTRUM (LIQUID FILM) NO. 7.



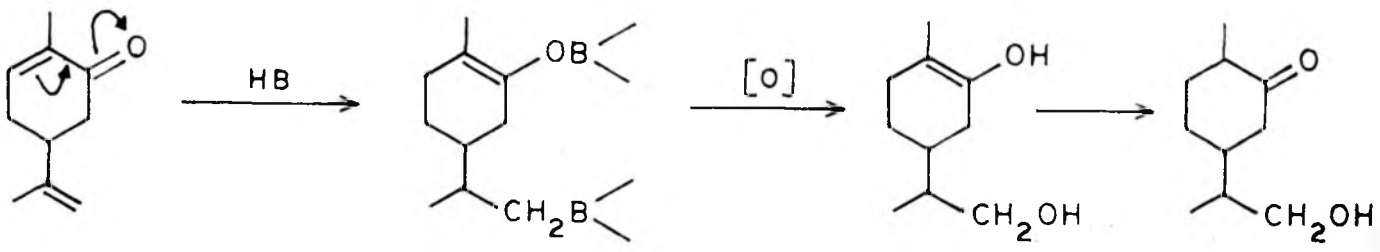
IR SPECTRUM (LIQUID FILM) NO. 4 .

Alcohol fraction (Isolation of p-menthane-2,6-diol, XVII)

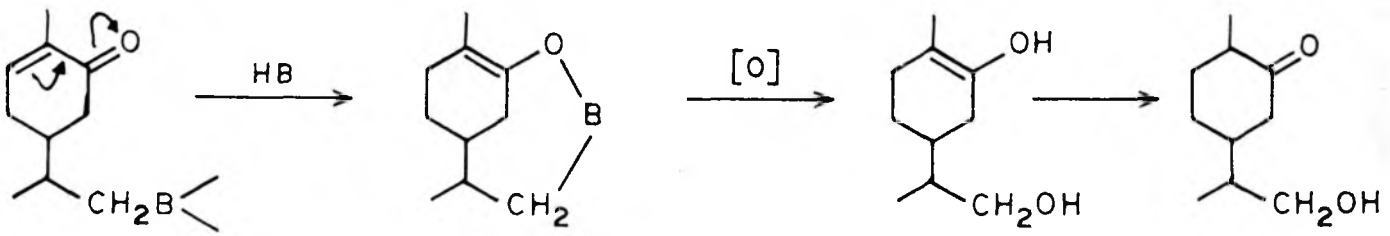
This fraction furnished a solid compound, which was crystallised from pet.ether and ether mixture. It has m.p. 109° and $(\alpha)_D \pm 0$. IR spectrum showed bands at 3400 cm^{-1} (for hydroxyl group). Elemental analysis indicated the molecular formula $C_{10}H_{20}O_2$. These results indicated that it must be p-menthane-2, 6-diol (XVII). Because it has zero rotation, it is quite likely that, both the alcohol groups may be cis oriented.

Discussion of the above results

In the case of carvone the formation of three compounds seems to be interesting. It is quite clear that the different mechanisms must be operating in all the three cases, since there are three reactive centres and that it contains an α,β-unsaturated ketone system. If one assumes that the boron atom attacks at the highest electron density centre, the following mechanism seems to explain very well for the formation of p-menthane 2-keto-9-ol.



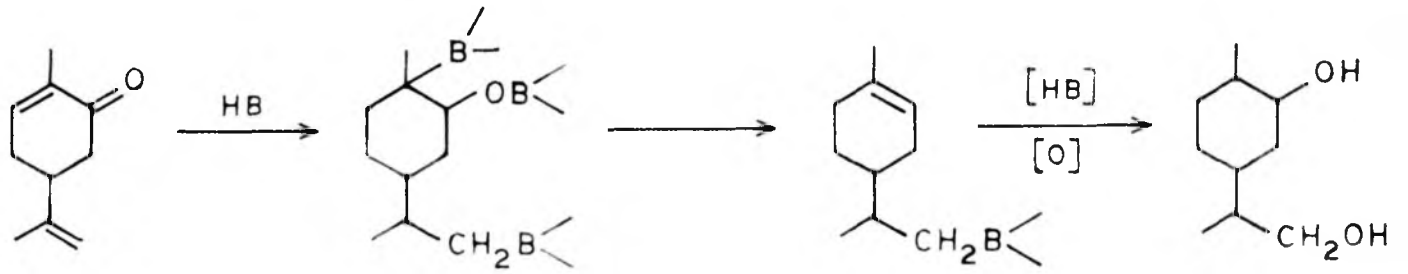
But this mechanism fails to explain when applied to carvotanacetone, as tetrahydrocarvone was not obtained. The difference in behaviour is not understood. But it seems that the isolated double bond is playing some part. If this is so, one can put an alternative mechanism as shown in below chart.



This mechanism explains better for the formation of p-methane-2-keto-9-ol. However, in the case of carvotanacetone, this mechanism may not be operating due to the absence of an isolated double bond and hence gave a mixture of carvotanacetol and p-menthane-2-6-diol. However it is interesting to note that carvotanacetol obtained is pure <u>cis</u>-carvotanacetol and diol has no optical rotation. The correctness of the mechanism is still to be investigated.

As regards, the formation of p-menthane-2,9-diol, which formed in about 7% yield, one can explain by the

observation of Brown et al. that the addition of boron takes place according to Markownikoff's rule in the case of allyl derivative to certain extent, when diborane gas is used as hydroborating agent. If that is so, one could expect the boron atom to be attached to the C_1-methyl group, followed by elimination of borate group and finally rehydroboration to get p-menthane-2, 9-diol (see below chart).



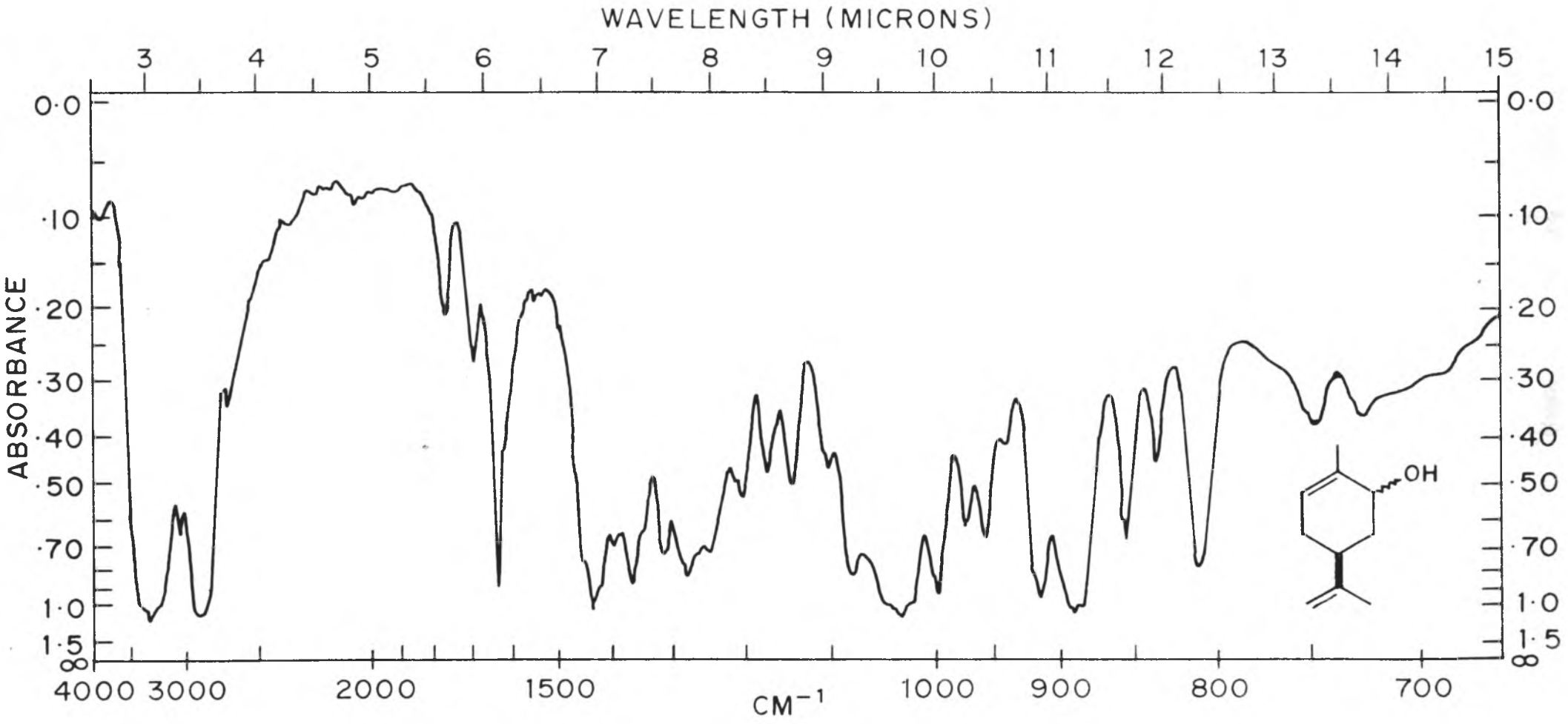
This means, that in the case of carvotanacetone one should get small percentage of tetrahydrocarveol. This indeed seemed to be the case, as GLC of the unreacted carvotanacetone fraction indicated 8% of the tetrahydrocarveol in the mixture.

The formation of triol, in the case of carvone and diol, in the case of carvotanacetone can be easily explained if diborane attacks all the olefinic centres along with reduction of carbonyl group.

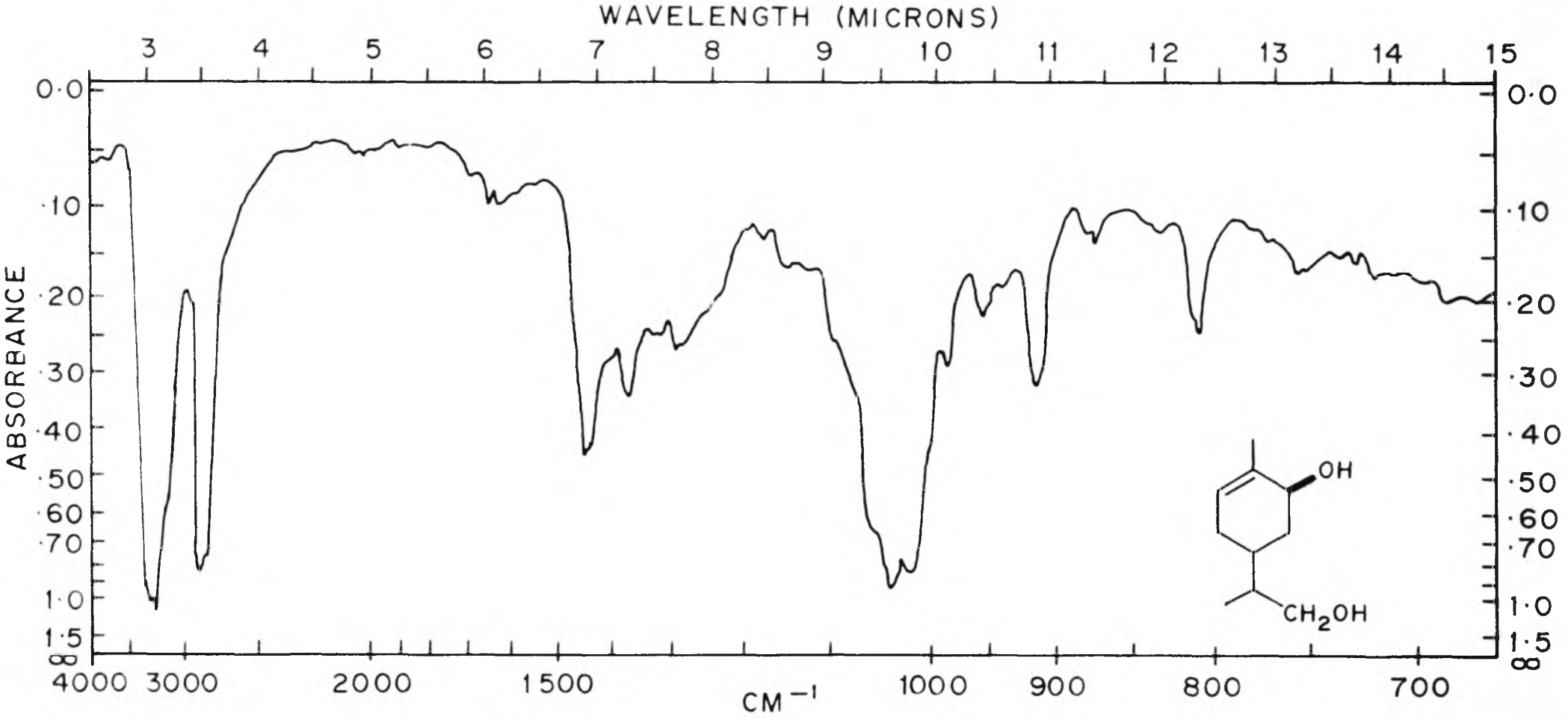
The above discussion indicates that the methylenic double bond does influence the formation of different products in the case of carvone. This prompted us to investigate the hydroboration (O) of carveol and dihydrocarvone both of which contains methylenic double bond.

Hydroboration of carveol (XIII) (Chart V

Hydroboration (O) of carveol /XIII, $(\alpha)_D$ + 41°/, was carried out using excess of diborane gas in tetrahydrofuran. The crude reaction product was chromatographed over alumina (Gr. III). Benzene fraction gave unreacted carveol. The latter ether fraction and alcohol fraction gave/a alcohol. It has b.p. 140-150°(bath)/0.5 mm and $(\alpha)_D$ + 27.7°. Elemental analysis indicated molecular formula $C_{10}H_{18}O_2$. IR spectrum showed absorption for hydroxy group at 3350 cm^{-1}. NMR spectrum showed a broad signal (1H) at 4.11δ (C<u>H</u>OH; HW ~15 cps). And hence this allylic hydroxyl group has β-equatorial configuration. A broad doublet (2H) at 3.55δ (C<u>H</u>$_2$OH; J, 6 cps). NMR spectrum further showed a broad signal (1H) at 5.5δ (trisubstituted double bond) and a singlet (3H) at 1.75δ (methyl on a double bond). It also showed a doublet (3H) centred at 0.91δ (J, 6 cps). Based on elemental analysis and NMR spectral data, it has been assigned the configuration as in (XXI).



IR SPECTRUM (LIQUID FILM) No. 3



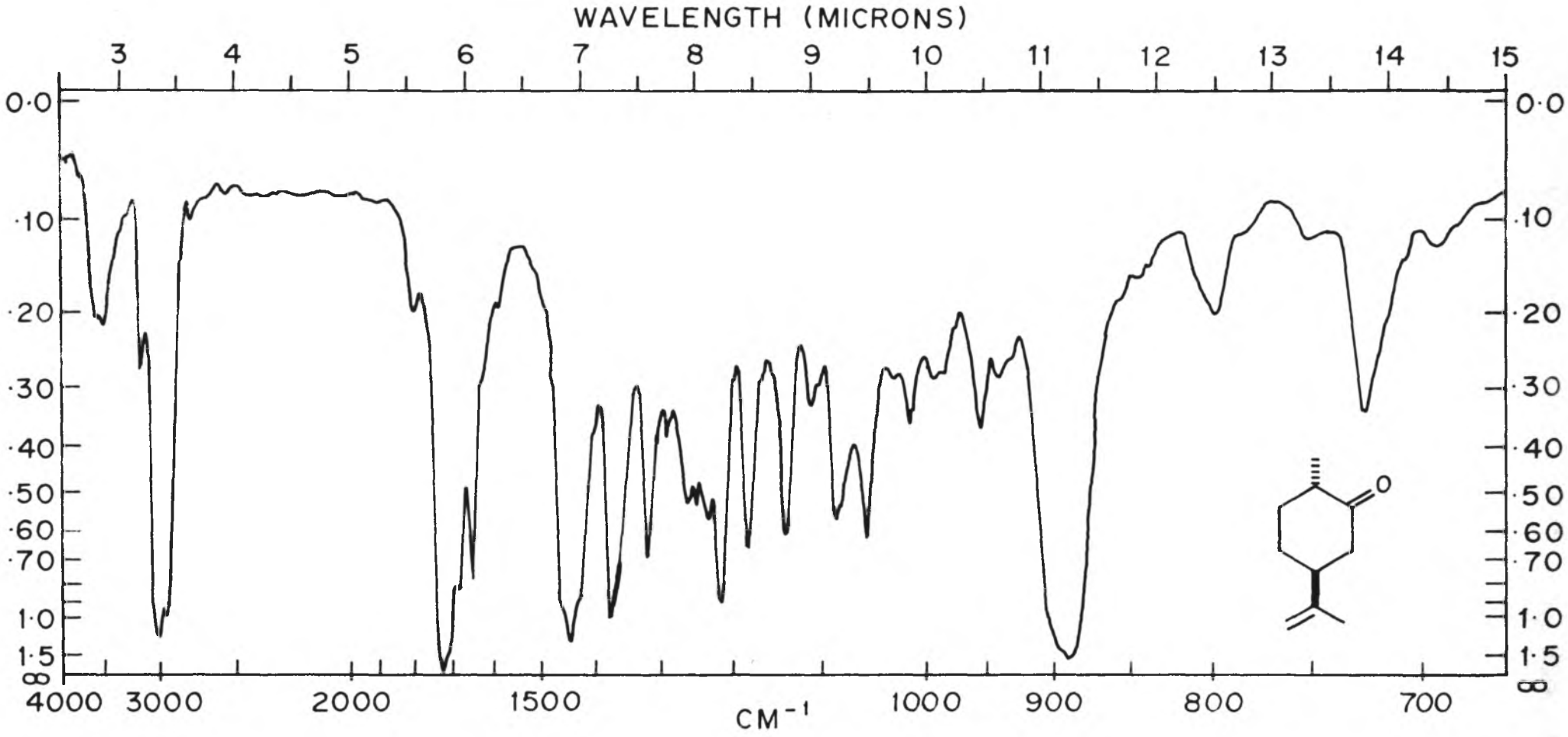
IR SPECTRUM (LIQUID FILM) NO. 11.

Hydroboration (O) of dihydrocarvone (XVIII) (Chart V)

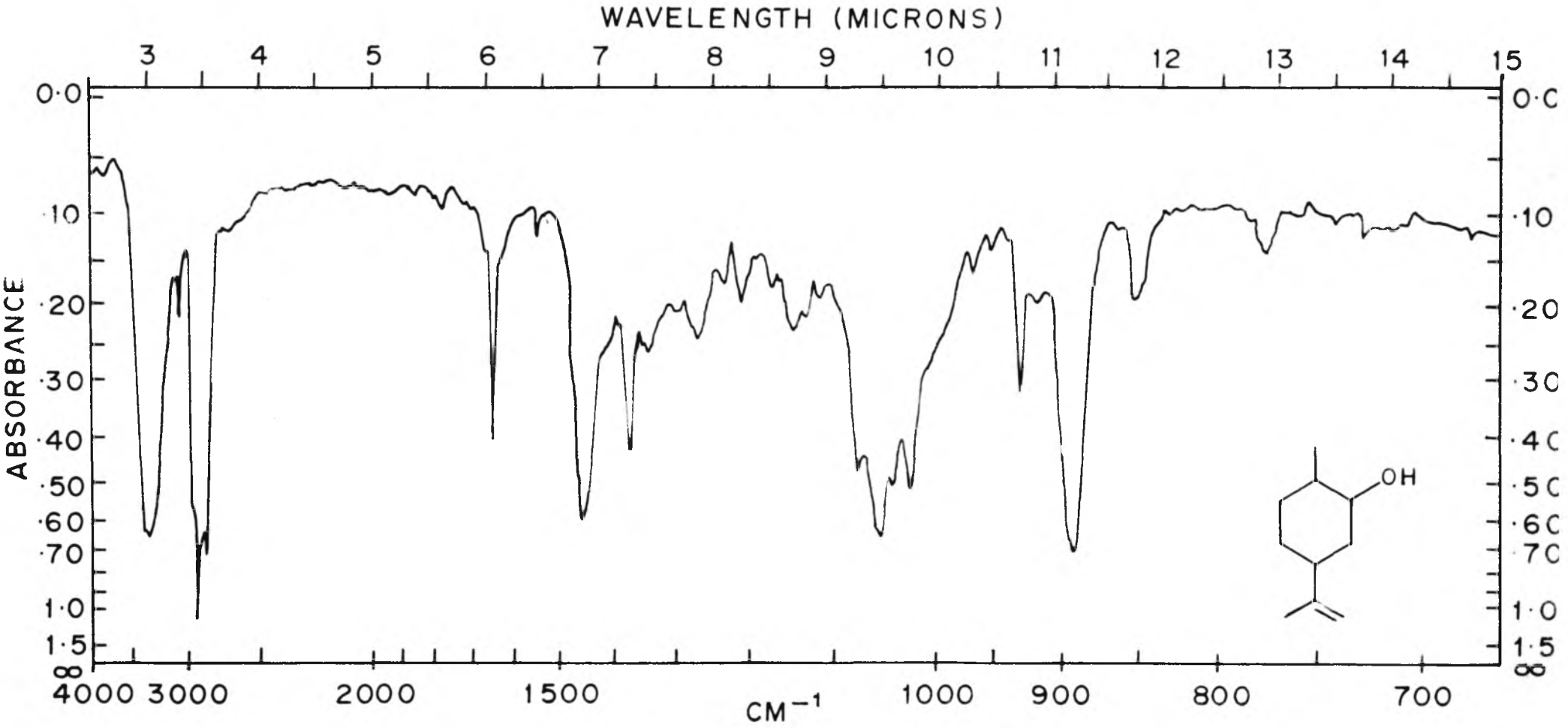
The crude product, obtained after hydroboration (O) of dihydrocarvone, $(\alpha)_D$ - 18.8°, using excess of diborane gas, was chromatographed over alumina (Gr. III). Petroleum ether fraction gave only unreacted dihydrocarvone (XVIII). Benzene fraction furnished a alcohol. GLC showed it to be a mixture of two isomers in the ratio of 83:17. It has b.p. 135°(bath)/20 mm and $(\alpha)_D$ + 17°. IR spectrum (Note 6) showed bands at 3350 cm^{-1} (for hydroxyl group) and 1639 cm^{-1}, 892 cm^{-1} (exocyclic double bond). Elemental analysis indicated the molecular formula $C_{10}H_{18}O$. It can be represented as a mixture of two isomers (XIX and XX) as adjudged by its total optical rotation and GLC analysis. It is interesting to note that the exomethylenic double bond remained unaffected, the reason for which is not quite clear.

Hydroboration (O) of carvotanacetol acetate (XXIII) (Chart VI)
(By disiamylborane)

Carvotanacetolacetate, $(\alpha)_D$ - 49°, (XXIII, 1 mol.) on hydroboration (O) with disiamylborane (2 mol.) gave mainly a alcohol acetate after chromatography over alumina (Gr. II). It is a solid compound, which can be crystallised from pet.ether and ether mixture, m.p. 97°C; $(\alpha)_D$ - 51°. Elemental analysis showed the molecular formula $C_{12}H_{22}O_3$. IR spectrum showed bands at 3330 cm^{-1} (hydroxyl group) and



IR SPECTRUM (LIQUID FILM) No. 2



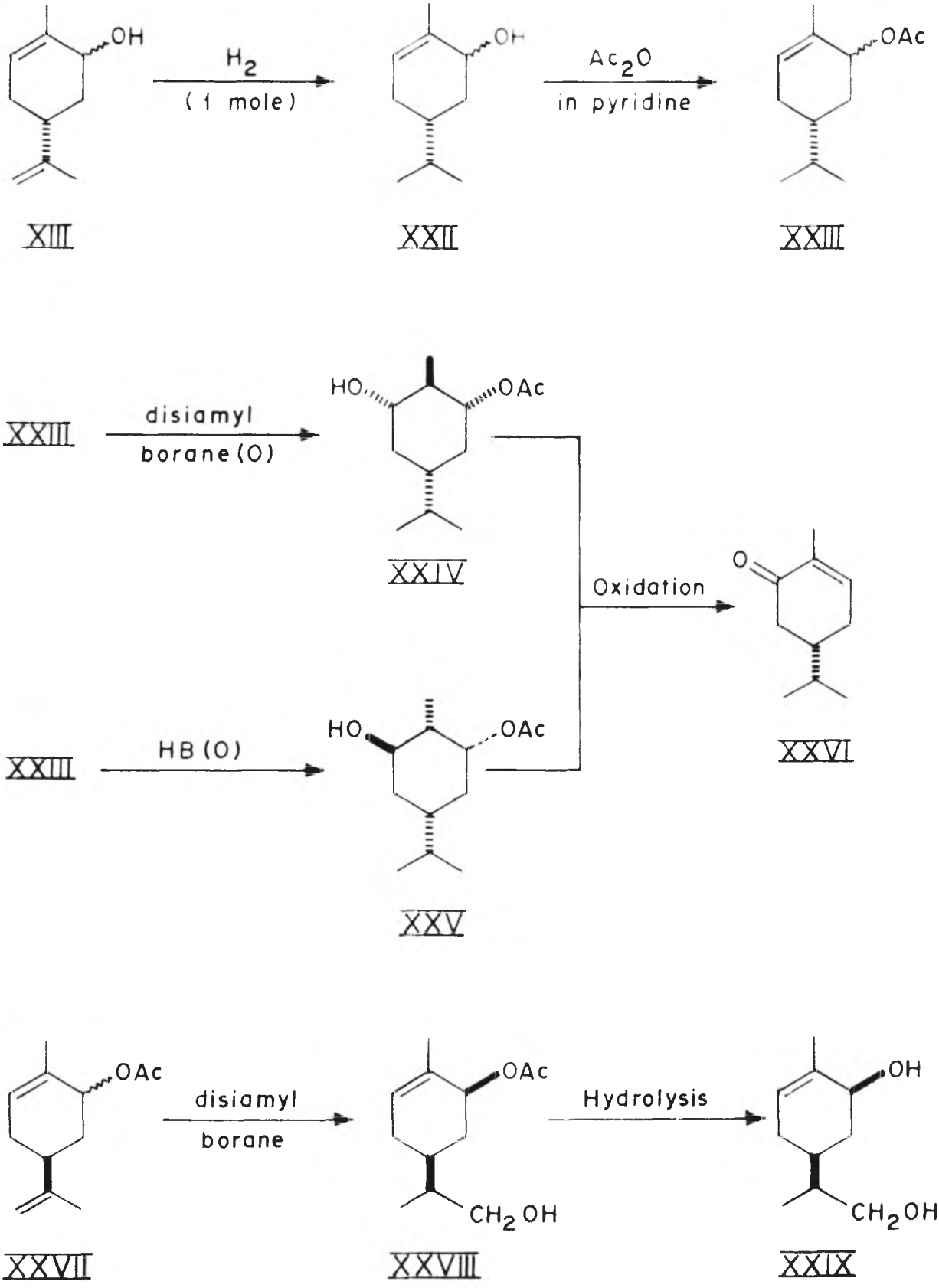
IR SPECTRUM (LIQUID FILM) NO. 10.

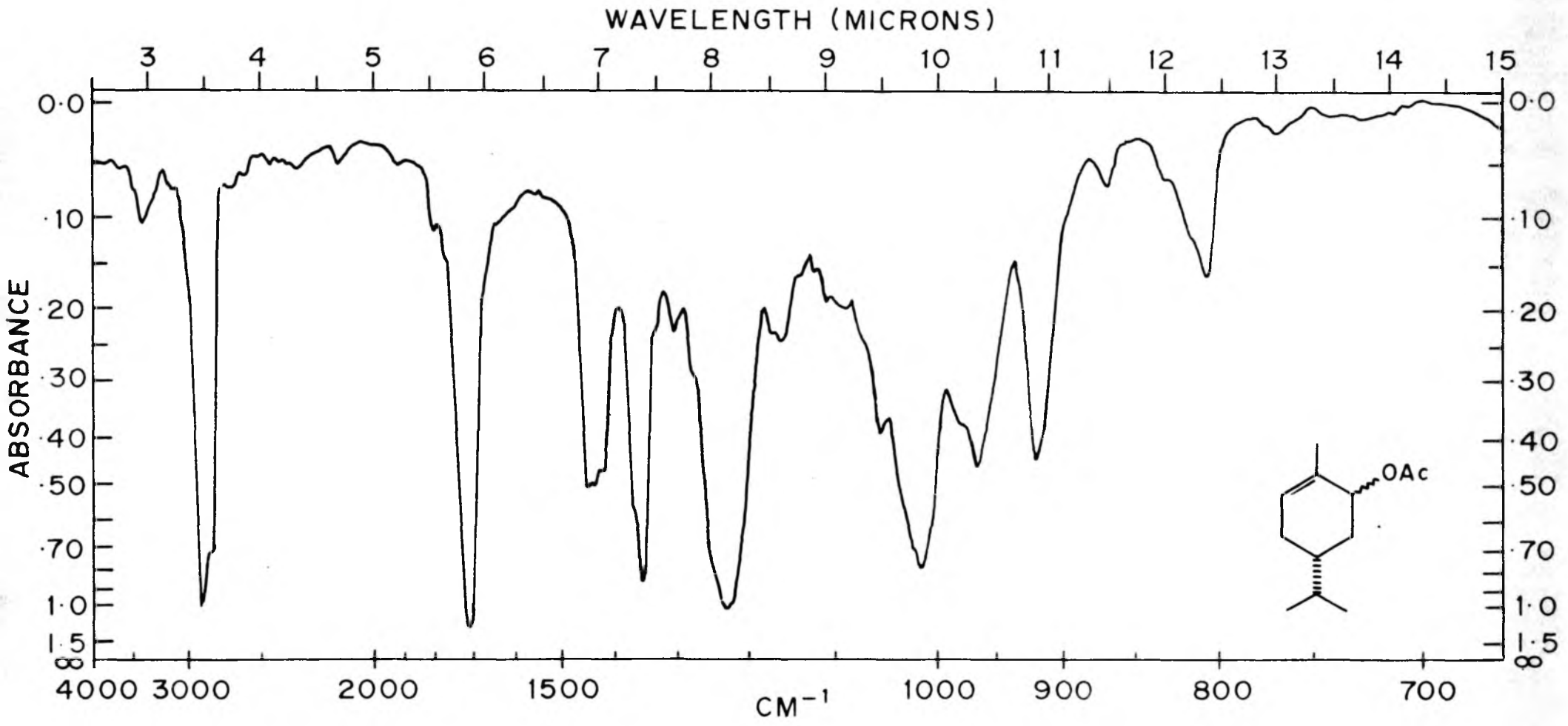
1724 cm^{-1} (for acetate group). NMR spectra showed a broad multiplet at 3.25 (CHOH, H.W. 15 cps), a singlet (3H) at 2.06 due to $-CO-CH_3$ grouping and a triplet (9H) centred at 0.955 (J, 6 cps)
Further, it is interesting to note that the acetate group at C_2 position has got α-equatorial configuration as proved by its NMR spectrum showing a broad multiplet (1H) at 4.336 (H.W. 15 cps), though the starting compound carvotanacetolacetate (XXIII) was a mixture of two isomers, cis and trans in the ratio of 10:1 respectively (roughly calculated from its optical rotation). Hence this alcohol-acetate can be represented as in (XXIV).

When the hydroboration (O) of carvotanacetol-acetate (XXIII) was carried out with diborane in situ, a mixture of cis (XXIV) and trans (XXV) epimeric alcohols were obtained in the ratio of 1:10 (see experimental). The trans isomer (XXV), has b.p. 125-130°(bath)/0.25 mm and $(\alpha)_D$ + 30°. The hydroxyl group in (XXV) was shown to be β-axial by its NMR spectrum (CHOH, a sharper multiplet at 3.875 H.W. 5 cps). Further it showed a singlet (3H) at 2.06 due to $-CO-CH_3$ group. These two isomers have superimposible IR spectrums. Further the acetate group at C_2-position in trans isomer (XXV) has also got α-equatorial configuration as proved by its NMR spectrum (CHOAC, broad multiplet, at 5.035, H.W. 15 cps).

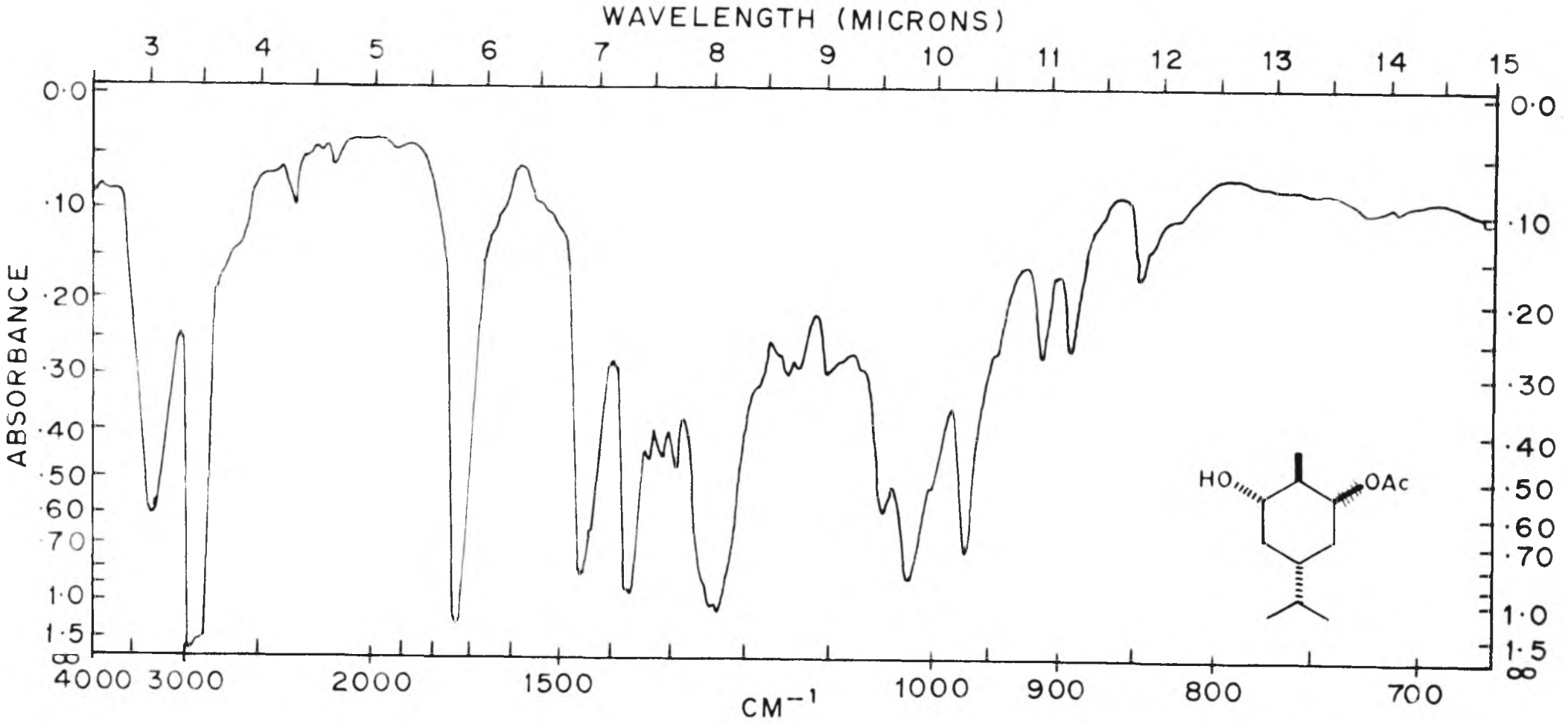
CHART VI

HYDROBORATION (O) OF CARVEOLACETATE AND CARVOTANACETOL ACETATE





IR SPECTRUM (LIQUID FILM) No. 5



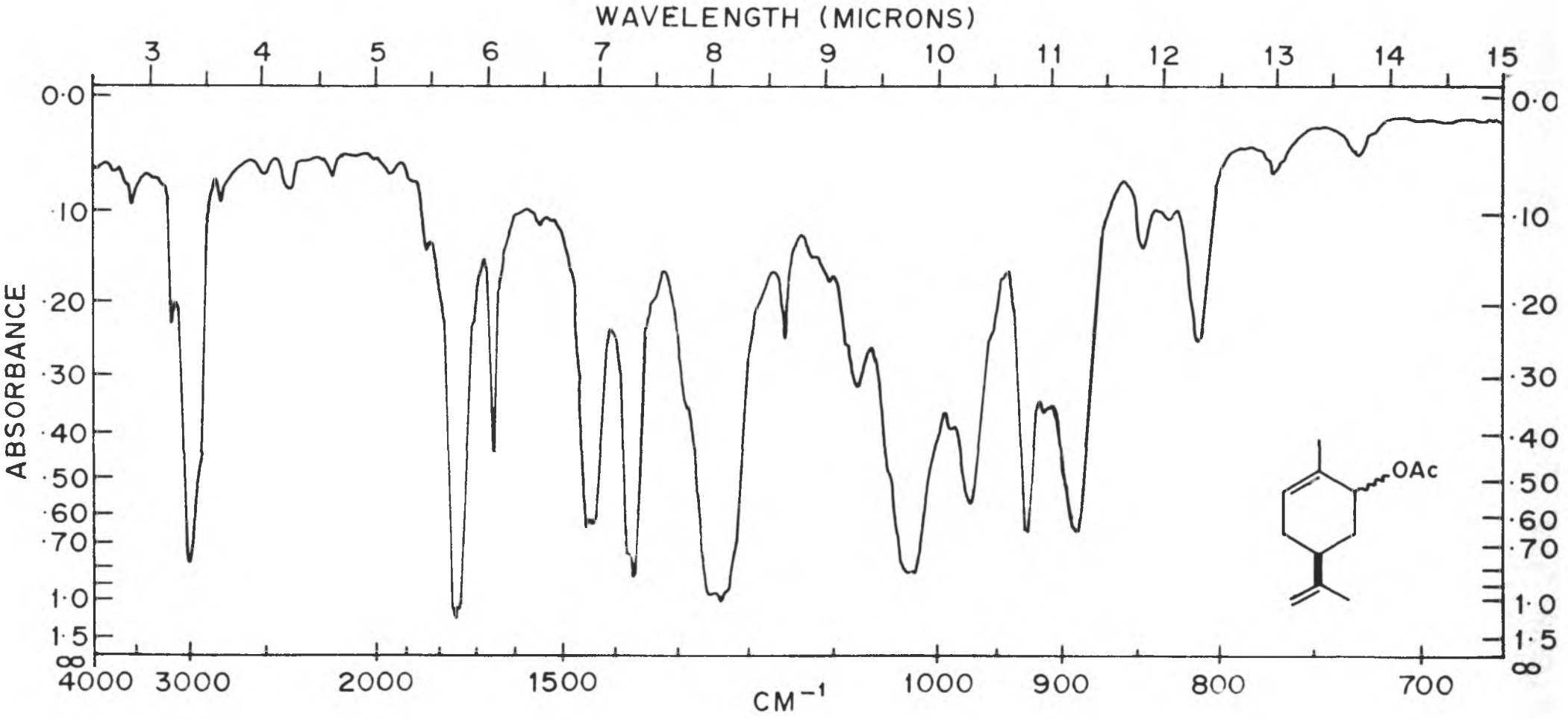
IR SPECTRUM (NUJOL) NO. 13.

(The shift of this proton in trans isomer (XXV) may be attributed to 1,3 diaxial interaction with the hydroxyl group at C_6). Hence this trans isomer can be represented as in (XXV).

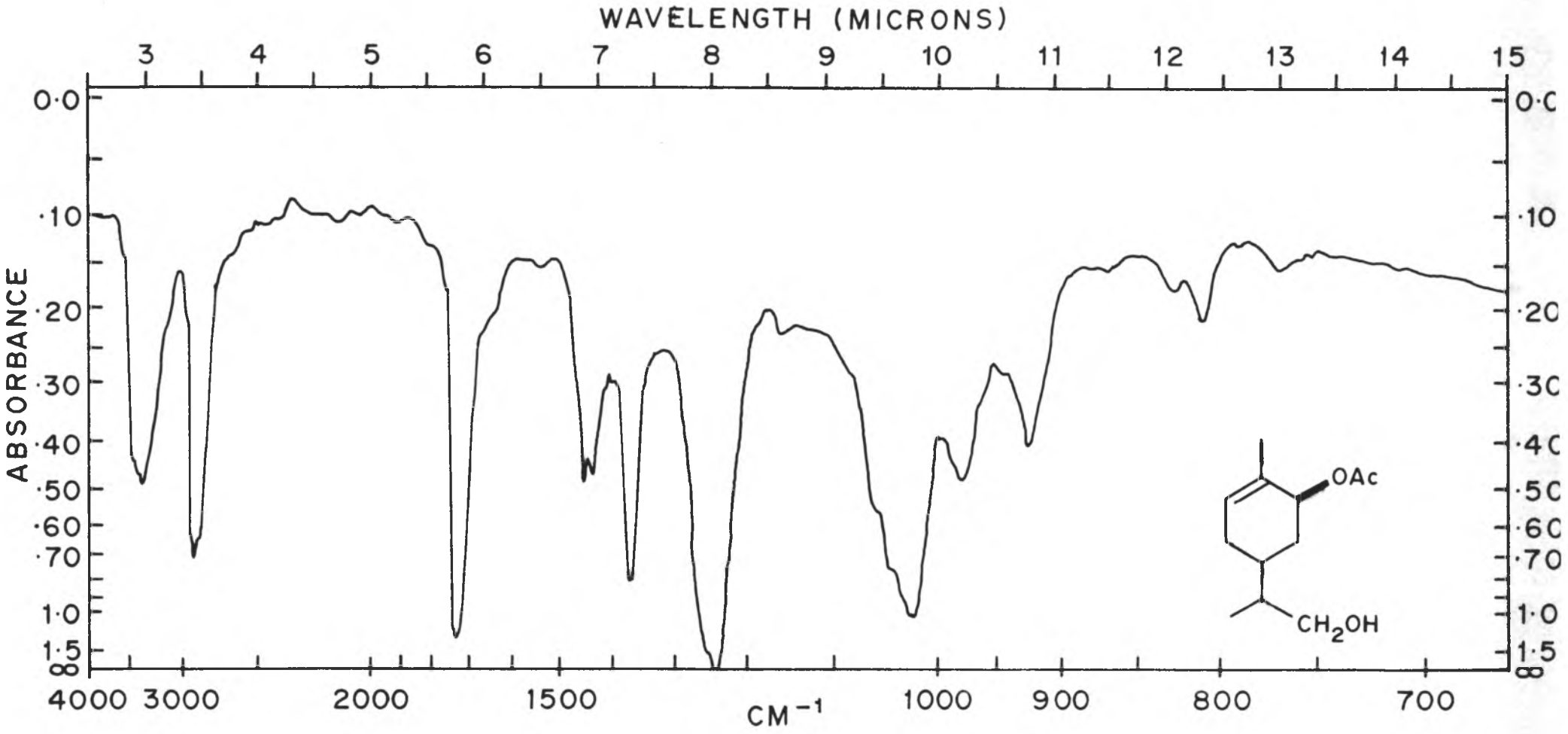
Both these isomers, or their mixture were converted to (+)-carvotanacetone (XXVI), $(\alpha)_D$ + 49.9°, when subjected to oxidation by Jones reagent. This is incidently a convenient method to change from one series to other.

Hydroboration of carveol acetate (XXVII) (chart VI)
(By disiamylborane)

Hydroboration of carveolacetate [XXVII, $(\alpha)_D$ + 59°] was carried out using disiamylborane as hydroborating agent. Only alcoholacetate along with some unreacted carveolacetate was obtained after usual chromatography of the crude reaction product over alumina (Gr. III). Alcohol-acetate came in benzene eluate. TLC analysis showed that it is a single compound. It has b.p. 160-165° (bath)/4 mm; $(\alpha)_D$ + 46°. Elemental analysis indicated the molecular formula $C_{12}H_{20}O_3$. The IR spectrum showed bands at 3450 cm^{-1} (for hydroxyl group), 1730 cm^{-1} and 1240 cm^{-1} (for acetate). NMR spectrum showed a singlet (3H) at 2.06 (acetyl group), a singlet (3H) at 1.76 (methyl on a double bond). Further it showed a doublet (3H) at 0.96 (J, 6.5 cps) and a broad doublet (2H) at 3.81δ (CH_2OH; J 6 cps). The allyl acetyl group at



IR SPECTRUM (LIQUID FILM) No. 6



IR SPECTRUM (LIQUID FILM) NO. 12.

C_2-position has β-equatorial configuration as proved by its NMR spectrum (CHOAC, broad multiplet at 5.13δ, H.W. ~ 15 cps). Further it showed a broad multiplet (1H) at 5.56 (trisubstituted double bond). All these results indicated that this compound is p-menthane-6-en-2-acetate-9-ol and can be represented as in (XXVIII).

This was further proved by hydrolysing it to p-menthane-6-en-2,9-diol with alcoholic potassium hydroxide. This diol was identical with the diol obtained by hydroboration of carveol, with respect to IR spectrum and optical rotation. It has b.p. 140-145°(bath)/0.5 mm and $(\alpha)_D$ + 29.8°.

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

Isolation of carvone (I) and dihydrocarvone (XVIII)

Dill oil (320 g) was vigorously stirred in a three necked flask provided with a condenser, a dropping funnel and a stirrer on the boiling water bath with sodium sulphite solution (370 g in 1300 mls of water and a few mls of phenolphthalein). The liberated alkali was neutralised from time to time by addition of requisite quantity of acetic acid. After the completion of reaction (one hour), as indicated by no further liberation of alkali, the contents of the flask were cooled, the oily upper layer separated and aqueous layer extracted with ether twice. The ether extract was mixed with the separated oil. The ethereal and aqueous solution treated separately as follows.

Aqueous solution (Isolation of carvone I)

Aqueous solution was steam distilled while a concentrated solution of alkali (150 g in 500 mls of water) was gradually added. The liberated carvone was collected in the distillate and separated, dried and distilled. Yield 96 gm. B.p. 104/11 mm; $(\alpha)_D$ + 55°. IR spectrum (1) showed bands at 3073, 2941, 1667, 1439, 1370, 1143, 1111, 1058, 961, 901 and 806 cm^{-1}. (Found: C, 79.68; H, 9.50; $C_{10}H_{14}O$ requires: C, 79.95; H, 9.39%).

Ether extract (Isolation of dihydrocarvone (XVIII)

160 g of oil obtained in above ether extract was subjected to fractional distillation. The results are summarised in the following tables.

Fr.No.	Pr/mm	b.p.	Weight (g)
1	20 mm	80-100°	60
2	2 mm	80-100°	20
3	2 mm	100-120°	12
4	2 mm	137°	15
5	2 mm	137°	18

Fr.No. 2 was further fractionated using a long fractionating column.

Fr.No.	Pr/mm	b.p.	Weight (g)
1	2 mm	80°	3.3
2	2 mm	90°	8
3	2 mm	100°	8

Fraction No. 2 (8 g) was converted to semicarbazone, using semicarbazide hydrochloride (8 g) and sodium acetate (12 g). The semicarbazone was crystallised in ethanol, yield 8 g. m.p. 202° (lit. m.p. 201-202°). The ketone was regenerated by decomposing with oxalic acid. Yield 5.5 g. b.p. 104°/18 mm; $(\alpha)_D$ - 18.8°.

(Found: C, 78.56; H, 10.37. $C_{10}H_{16}O$ requires C, 78.89; H, 10.59%). IR spectrum (2) showed bands at 3077, 2941, 1709, 1639, 1449, 1370, 1316, 1220, 1183, 1136, 1087, 1053 and 892 cm^{-1}.

Preparation of carveol(XIII)

A solution of carvone (I, 10 g) in dry ether was added to a stirred solution of lithium aluminium hydride (3.2 g) in dry ether during one hour at 0°C. The mixture was heated under reflux for 5 hrs. It was cooled in ice bath and was treated with water to decompose excess of LAH and left over night. The lithium aluminium complex so separated was dissolved in dilute hydrochloric acid, extracted with ether, dried and solvent evaporated to furnish carveol (8.6 g) b.p. 102°/10 mm. $(\alpha)_D$ + 41°. (Found: C, 78.98; H, 10.48. $C_{10}H_{16}O$ requires: C, 78.89; H, 10.59%). IR spectrum (3) showed bands at 3400, 2900, 1613, 1031 (broad), 917, 892, 854 and 813 cm^{-1}.

Preparation of carvotanacetolacetate (XXIII)

Carveol (XIII, 8 g) was dissolved in 50 ml of ethanol and Raney nickel (4.5 g) in ethanol (20 ml) was added to it. One mole of hydrogen was passed while stirring. Filtered and ethanol from filtrate was distilled off to give (7.5 g, XXIII). It has b.p. 100°/10 mm. IR spectrum showed bands at 3400,

2941, 1449, 1385, 1364, 1075 (broad) 917 and 813 cm^{-1}.

(7.4 g) of hydrogenated alcohol (XXIII) was dissolved in 25 ml of pyridine and 8 ml of acetic anhydride was added to it. Heated on the water bath for 2 hrs. After cooling, poured into ice cold water. Extracted with ether. Ether extract was washed with cold dilute hydrochloric acid and then with cold water. Dried over anhydrous sodium sulphate. Ether evaporated. After distillation 7.9 g of carvotanacetolacetate (XXIII) was obtained b.p. 106°/10 mm; $(\alpha)_D$ - 49°. (Found: C, 72.27; H, 10.52. $C_{10}H_{20}O_2$ requires: C, 73.43; H, 10.27%). IR spectrum showed bands at 2857, 1709, 1429, 1351, 1227, 1010, 917 and 806 cm^{-1}.

Preparation of carveol acetate (XXVII)

Carveol (10 g; $(\alpha)_D$ + 41 XIII) was dissolved in pyridine (30 ml) and acetic anhydride (10 ml). Heated on water bath for 2 hrs, then worked out according to the procedure followed in the case of preparation of acetate from carvotan-acetol-acetate. Yield 11.2 g, b.p. 108°/10 mm; $(\alpha)_D$ + 59°. (Found: C, 74.09; H, 9.25. $C_{12}H_{18}O_2$ requires C, 74.19; H, 9.34). IR spectrum showed bands at 2941, 1739, 1639, 1449, 1370, 1235, 925, 892 and 813 cm^{-1}.

Preparation of carvotanacetone (XV)

Carveol, $(\alpha)_D$ + 41°, (10 g, XIII), was hydrogenated to carvotanacetol by passing one mole of hydrogen gas. Carvotanacetol so obtained, was dissolved in 100 ml of dry petroleum ether and treated with neutral manganese dioxide (30 g). Then stirred for 1 hour at room temperature. Filtered. Petroleum ether from filtrate was distilled off. Yield 7.0 g. Chromatographed over neutral alumina (Gr. III).

Fr.No.	Solvent	Weight (g)
1	Pet.ether	4
2	Ether	2.6

Petroleum ether eluate furnished carvotanacetone, b.p. 96-7°/9 mm $(\alpha)_D$ + 52°. (Found: C, 78.46; H, 10.41%. $C_{10}H_{16}O$ requires: C, 78.89; H, 10.59%). IR spectrum (7) showed bands at 2899, 1667, 1351, 1333, 1250, 1136, 1093, 1070, 1047, 943, 909 and 809 cm^{-1}.

General procedure of hydroboration (O) by diborange gas

The generator consisted of a 250-ml conical flask equipped with a pressure equilized dropping funnel, an inlet for nitrogen, an outlet for the diborane gas and a magnetic stirrer. The diborane outlet was fitted with a T-tube, one end dipping into mecury bubler to serve as safety release valve. Another

remaining end of T tube was connected to gas absorption flask containing the compound dissolved in tetrahydrofuran. Polythenes tubes were used for connecting the glass apparatus with each other. The glass apparatuses were heated in oven at 110° and assembled when they were sufficiently hot . And whole system was cooled down to room temperature, while passing dry nitrogen gas. The diborane gas was generated by dropwise addition of sodium borohydride suspension in diglyme to the stirred boron trifluoride etherate in diglyme. The diborane gas so generated was bubbled into the compound - tetrahydrofuran solution at 0°. The container of the mixture was corked tightly and left overnight at room temperature. The container was cooled to 0° and excess of hyuride was destroyed by careful addition of ice cold water. The organoborane so formed was oxidised by simultaneous addition of sodium hydroxide (3N) and 30% hydrogen peroxide maintaining the temperature of the reaction mixture between 20-30°. Also the pH of the solution was maintained between 8-9. Left overnight. Extracted with ether. Ether extracts were washed with saturated sodium chloride and ether distilled off. The various compounds were isolated in pure forms, from reaction product by chromatography using neutral alumina.

Preparation of solvents

1. Diglyme: It was distilled between 155°-158°. Refluxed over sodium metal for 48 hours and distilled.

2. Tetrahydrofuran: It was distilled between 60-64°. Dried over potassium hydroxide pellets. Then the distilled tetrahydrofuran was refluxed with lithium aluminium hydride for six hours and distilled b.p.64°.

3. BF_3-etherate: Freshly distilled borontrifluoride etherate at room temperature was used.

Carvone (I)

(+)-Carvone (20 g, I), was subjected to hydroboration followed by alkaline hydrogen peroxide oxidation using sodium borohydride (7 g) dissolved in diglyme (100 ml) and boron trifluoride etherate (30 g) in diglyme (30 ml). Wt. of the product 16.7 g. TLC showed that it is a mixture of 3 compounds. Chromatographed over alumina (Gr. III, 320 g).

Fr.No.	Solvent	Wt. (g)
1	Pet.ether	-
2	Benzene	10.5
3	Ether	2.0
4	Alcohol	4.0

Benzene fraction (No. 2) (Isolation of ketoalcohol II)

10.5 g. of the compound obtained was rechromatographed over alumina (Gr. III, 210 g).

Fr.No.	Solvent	Wt.(g)
1'	5% (Pet.ether + ether)	0.200
2'	10% (Pet.ether + ether)	10.0

Fraction 2' (10 g) showed single spot on TLC analysis, b.p. 150°(bath)/0.3 mm; $(\alpha)_D$ + 15.7°. (Found: C, 69.97; H, 10.90. $C_{10}H_{18}O$ requires C, 70.54; H, 10.66%)
IR spectrum showed bands at 3450, 2941, 1709 and 1042 cm^{-1} (broad).
It formed a semicarbazone, m.p. 145° (Found: C, 58.02; H, 9.41%; N, 18.0%. $C_{11}H_{21}O_2N_3$ requires C, 58.12; H, 9.31; N, 18.49%). It also formed 3.5 dinitrobenzoate m.p. 115. (Found: C, 56.04; H, 5.53; N, 7.69%. $C_{17}H_{20}O_7N_2$ requires: C, 55.58; H, 5.4; N, 7.37%).

Alcohol fraction (No.4) (Isolation of triol, III).

The compound obtained thus was found to be pure by TLC analysis, b.p. 230° (bath)/0.3 mm. (Found: C, 63.76; H, 10.96%. $C_{10}H_{20}O_3$ requires C, 63.79; H, 10.71%). IR spectrum showed bands at 3450, 2941, 1449, 1370 and 1020 cm^{-1} (broad).

Ether fraction (No.3) (Isolation of diol, III)

The compound was found to be pure by TLC.

B.p. 190°(bath)/0.3 mm; $(\alpha)_D$ + 10.5. (Found: C, 69.46; H, 11.43. $C_{10}H_{20}O_2$ requires C, 69.72; H, 11.70%). IR spectrum showed bands at 3450, 2941, 1471, 1449, 1379 and 1031 (broad).

Conversion of p-menthane-2-keto-9-ol (II) to p-methane--2-keto-9-methyl ester

p-Menthane-2-keto-9-ol (II, 1 g) was dissolved in acetone and oxidised with Jones reagent. After one hour, poured into water (50 ml). Extracted with ether. Ether extracts were thoroughly washed with 10% aq. sodium-bicarbonate solution (25 ml x 2). Bicarbonate extracts were shaken with ether and then acidified with dil. HCl (1:1). Extracted with ether, washed with water, dried over sodium sulphate (anhydrous). p-Menthane-2-keto-9-carboxylic acid (0.70 g, VIII) was obtained after removal of the solvent. IR spectrum showed bands at 3125, 2941, 2703, 1718, 1449, 1379 and 1205 cm^{-1} (broad).

The crude acid (VIII) dissolved in dry ether and treated with diazomethane gas dissolved in ether sufficient to complete the esterification. After keeping the reaction mixture for one hour, was worked out by extracting with ether. Ether extracts were washed with water, dried over anhydrous sodium sulphate. Ether was evaporated. Chromatographed over alumina (Gr. II, 10 g). Pet.ether elution gave 0.500 g. b.p. 125-135°(bath)/0.5 mm; $(\alpha)_D$ - 10.2. (Found: C, 66.27; H, 9.05%. $C_{11}H_{18}O_3$

requires: C, 66.64; H, 9.15%). IR spectrum showed bands at 2941, 1709, 1449, 1250 - 1136 (broad), 1075, 1031, 980, 892, 854, 775, 763 and 735 cm^{-1}.

Conversion of p-menthane-2-keto-9-ol (II) to tetrahydrocarvone (VII)

1. Tosylation of p-menthane-2-keto-9-ol

p-Menthane-2-keto-9-ol (1 g) was dissolved in pyridine (10 ml) and p-toluenesulphonyl chloride was added. Kept at room temperature for 48 hours. Then poured into ice cold water. Acidified with cold sulphuric acid (10%) and extracted with ether. Ether extracts were washed with cold sulphuric acid (10%) and water successively. Dried over anhydrous sodium sulphate. Ether was evaporated. Yield-1 g. IR spectrum showed bands at 2941, 1718, 1600, 1471, 1370, 1190, 1176, 1099, 990-925 (broad), 840, 813 and 730 cm^{-1}.

2. LAH reduction of tosylate (V) to p-menthane-2-ol (VI)

p-Menthane-2-keto-9-tosylate (V, 1 g) dissolved in dry ether (20 ml) and added to a stirred solution of LAH (0.400 g) in ether (10 ml) at 0^{o}. Refluxed for 4 hours. Decomposed with water. Left overnight. Extracted with ether, washed with water and dried over anhydrous sodium sulphate. Evaporation of solvent gave the alcohol (VI, 0.500 g). IR spectrum showed bands at 3450 cm^{-1}.

3. Oxidation of p-menthane-2-ol (VI) to tetrahydrocarvone (VII)

p-Menthane-2-ol (VI, 0.400 g) was dissolved in

acetic anhydride and oxidised by Jones reagent. After usual working up furnished a crude product which was passed through alumina column (Gr. III). Petroleum ether elute gave tetrahydrocarvone (VII), b.p. 210°; $(\alpha)_D$ - 16.6°. (Found: C, 77.68; H, 11.57%. $C_{10}H_{18}O$ requires: C, 77.86; H, 11.76%). IR bands at 2941, 1709, 1471, 1379, 1370, 1366, 1235, 1220, 1198, 1149, 1136, 1093, 1064, 952, 885, 869 and 729 cm^{-1}.

Carvotanacetone (XV)

Carvotanacetone (3 g, XV) was hydroborated as usual using excess of diborane gas; produced from sodium borohydride (1.5 g) suspended in diglyme and BF_3-etherate (5 g) in diglyme. After the alkaline-hydrogen peroxide oxidation 2.8 g of the product was obtained which was chromatographed over neutral alumina (Gr. I, 60 g).

Fr.No.	Solvent	Wt. (g)
1	Pet.ether	0.800
2.	Benzene	-
3	Ether	1.6
4	Alcohol	0.300

Pet.ether eluate gave the unreacted carvotanacetone (XV).

Ether fraction (No.3)

Found to be a single compound by TLC and GLC analysis. It was proved to be cis-carvotanacetol (XVI)

b.p. 120 (bath)/10 mm; $(\alpha)_D$ + 51° (Found: C, 77.47; H, 11.81%. $C_{10}H_{18}O$ requires: C, 77.86; H, 11.76). IR spectrum (4) showed bands at 3400, 2941, 1449, 1385, 1364, 1075 (broad), 917 and 813 cm^{-1}.

Alcohol fraction (No.4) furnished a solid diol (XVII) m.p. 110°C; $(\alpha)_D$ ± 0. (Found: C, 69.46; H, 11.80%. $C_{10}H_{20}O_2$ requires: C, 69.72; H, 10.70%). IR spectrum showed bands at 3400, 1477, 1370,1124, 1064, 1020, 892 and 847 cm^{-1}.

Dihydrocarvone (XVIII)

Dihydrocarvone (XVIII, 5 g) was hydroborated using sodium borohydride (2.8 g) and BF_3-etherate (12 g). After oxidation of the borane complex with alkaline hydrogen peroxide, 4.2 g compound was obtained. Chromatographed over alumina (Gr. III, 80 g).

Fr.No.	Solvent	Wt. (g)
1	Pet.ether	1.2
2	Benzene	2.8

Pet.ether fraction gave unreacted dihydrocarvone (XVIII).

Benzene fraction (No.2) Furnished a mixture of dihydrocarveols (XIX and XX). It has b.p.135°(bath)/20 mm; $(\alpha)_D$ + 17°. (Found: C, 77.67; H, 11.5%. $C_{10}H_{18}O$ requires C, 77.86; H, 41.76%). It is a mixture of two isomers in the ratio of 83:17 as adjudged by its GLC analysis

and optical rotation. IR spectrum showed bands at 3350, 2874, 1639, 1471, 1376, 1053, 1020, 934 and 892 cm^{-1}.

Carveol (XIII)

Carveol (XIII, 5 g) was hydroborated with sodiumborohydride (2.5 g) and BF_3-etherate (12 g) as was done in carvone. Alkaline hydrogen peroxide oxidation of the organoborane furnished 4.0 g of product. TLC showed it to be a mixture three compounds. Chromatographed over alumina (Gr. III, 80 g).

Fr.No.	Solvent	Wt.(g)
1	Pet.ether	-
2	Benzene	0.600
3	Ether (1)	0.800
4	Ether (2)	0.600
5	Alcohol	1.7

Benzene fraction (No.2)

It was found to be unreacted carveol (XIII).

Ether elutes (1) and (2) were found to contain two compounds as shown by TLC analysis, more polar being in major amount.

Alcohol fraction

This furnished a compound similar to the major compound obtained in ether fraction. It was found to be

pure by TLC analysis b.p. 140-150°(bath)/0.5 mm: $(\alpha)_D$ + 27.7°. (Found: C, 70.23; H, 11.69%. $C_{10}H_{18}O_2$ requires: C, 70.54; H, 11.76%). IR spectrum showed bands at 3300 and 1042 cm^{-1} (broad).

Preparation of bis-(3-methyl-2-butyl)borane

2-Methyl-2-butene (6 g) was taken in tetrahydrofuran (40 ml) and hydroborated as usual by bubling diborane gas produced by adding sodium borohydride (1.6 g) in diglyme to the stirring solution of boron-trifluoride etherate (10 g) in diglyme for one hr. at 0°C. Kept overnight at 0-5° in nitrogen atmosphere. Bis-(3-methyl-2-butyl) borane, thus obtained was used further for hydroboration of carveolacetate and carvotanacetolacetate.

Carveolacetate (XXVII)

Carveolacetate (4 g) in tetrahydrofuran (20 ml) was added drop by drop to the cooled solution of disiamyl borane prepared above, while stirring the solution magnetically. The reaction mixture was further stirred for 3 hrs. at room temperature. Organoborane wax oxidised by alkaline hydrogen peroxide. Left overnight. Organic layer separated. Aqueous layer was extracted with ether. Combined organic layer was then washed with saturated sodium chloride solution. Dried over anhydrous sodium sulphate. 3.3 g of the compound was obtained after evaporation of solvent. TLC analysis

showed it to be a mixture of two compounds and one of them corresponded to the unreacted carveolacetate. Chromatographed over alumina (Gr. III, 80 g). Pet.ether elute furnished the starting material (0.800 g) XXVIII).

p-Menthane-2-acetate-6-ene-9-ol came in benzene eluate (2.4 g XXVIII) b.p. 160-65°(bath)/4 mm; $(\alpha)_D$ + 43°. (Found: C, 68.10; H, 9.84%. $C_{12}H_{20}O_3$ requires C, 67.89; H, 9.50%). IR spectrum (12) showed bands at 3450, 2900, 1730, 1240 and 1025 cm^{-1}.

Hydrolysis of p-menthane-6-ene-2-acetate-9-ol (XXVIII) to p-menthane-6-ene-2,9-ol (XXIX)

p-Menthane-6-ene-2-acetate-9-ol (1 g) was hydrolysed by refluxing with alcoholic potassium hydroxide (1 g KOH in 40 ml alcohol) for 5 hrs. Cooled, poured into ice cold water. Extracted with ether. Ethereal extracts were washed with water. Dried over anhydrous sodium sulphate. Ether distilled off. The diol so obtained (XXIX) has b.p. 140-50 (bath)/0.5 mm.; $(\alpha)_D$ + 29.8°.

Carvotanacetol acetate (XXIII)

Disiamylborane in tetrahydrofuran was prepared by using sodium borohydride (0.800 g), BF_3-etherate (5 g) in diglyme and 2-methyl 2-butene (3 g). To this reagent carvotanacetolacetate (2 g) was added and resulting organoborane was oxidised by alkaline hydrogen

peroxide.yield 1.8 g. Chromatographed over alumina (Gr. II, 40 g).

Fr.No.	Solvent	Wt.(g)
1	Pet.ether	0.200
2	20%(Pet.ether + ether)	1.49
3	Ether	0.180

Petroleum ether fraction gave unreacted carvotanacetol. 20% (pet.ether + ether) fraction (No.2) furnished a solid, p-menthane-2-acetate-6-ol (XXIV), crystallised from pet.ether and ether mixture. m.p. 97°C; $(\alpha)_D$ - 51°. (Found: C, 66.83; H, 10.32%. $C_{12}H_{22}O_3$ requires: C, 67.25; H, 10.35%). IR spectrum (13) showed bands at 3330, 2941, 1724, 1250, 1053, 1026, 980, 917 and 892 cm^{-1}.

Hydroboration of carvotanacetolacetate (XXIII) with diborane gas in situ

To a well stirred suspension of sodium-borohydride (0.5 g) in diglyme (15 ml) and carvotanacetolacetate (6 g) in diglyme (15 ml), was added BF_3-etherate (2.1 g) over a period of half an hour, while temperature was maintained at 25°C. The flask was kept for 3 hrs. at room temperature. Excess hydride was then decomposed by careful dropwise addition of water. The organoborane was oxidised at 30-35°C by the immediate addition of

3N sodiumhydroxide (5 ml) followed by the dropwise addition of 30% hydrogen peroxide (5 ml). The reaction mixture was left for 1 hour at room temperature and was extracted with ether. Organic layer washed with ice cold water to remove diglyme and dried over sodium sulphate (anhydrous). The weight of the product after removal of solvent was 5.06 gm. TLC analysis showed four spots. Chromatographed over alumina (Gr. II, 100 g).

Fr.No.	Solvent	Wt. (g)
1	Pet.ether	-
2	(10%) Pet.ether-ether (25 ml)	
	i) "	1.65
	ii) "	0.35
	iii) "	0.35
	iv) "	0.20
	v) "	0.190
3	20% pet.ether + ether	0.100
4	Ether	1.4

10% (Pet.ether + ether) fraction (No.2)

Fr.No. 2(i) was purely unreacted material carvotanacetolacetate. Fr.No.2 (ii and iii) were mixture of unreacted material and another compound. This fraction was not investigated further. Fr. No. 2 (IV and V) and

Fr. No. 3, 20% (pet. ether + ether fractions) were combined. Solvent was removed to furnish a solid compound, which was crystallised from mixture of pet.ether and ether. Yield 120 g. This compound was found to be identical with cis-p-menthane-2-acetate-6-ol (XXIV).

Ether fraction: Furnished trans-p-menthane-2-acetate-6-ol (XXV), b.p. 125-30° (bath)/0.25 mm; $(\alpha)_D$ + 30°. (Found: C, 66.97; H, 10.23%. $C_{12}H_{22}O_3$ requires C, 66,25; H, 10.35%) IR spectrum was superimposible with the IR spectrum of cis-p-menthane-2-acetate-6-ol (XXIV, No. 13).

Oxidation of p-menthane-2-acetate-6-ol to carvotanacetone (XXVI)

p-Menthane-2-acetate-6-ol (1 g) was dissolved in acetone and oxidised by Jones reagent at 0°C. After 5 minutes it was worked as usual by extracting with ether. Yield 0.905 g. Chromatographed over alumina (Gr. III, 20 g). Petroleum ether eluate furnished 0.500g of carvotanacetone (XXVI) b.p. 96-97°/9 mm $(\alpha)_D$ + 49°. (Found: C, 78.48; H, 10.45%. $C_{10}H_{16}O$ requires: C, 78.89; H, 10.59%). IR spectrum was superimposible with the IR spectrum of authentic carvotanacetone.

REFERENCES

1. H.C. Brown and B.C. Subba Rao, J.Am.Chem.Soc., 5694, 78 (1964).

2. ibid., 6423, 81 (1959).

3a. ibid. 681, 82 (1960).

3b. H.C. Brown and Korytnyk, ibid., 3866, 82 (1960).

4. H.C. Brown and Bigley, ibid., 486, 83 (1961).

5. H.C. Brown and G. Zweifel, ibid., 1241, 83 (1961).

6. H.C. Brown and A.W. Moerkofer, ibid., 3417, 83 (1961).

7. G. Zweifel, K. Sagase and H.C. Brown, ibid., 190, 84 (1962).

8. H.C. Brown and G. Zweifel, ibid., 2066, 85 (1963).

9. H.C. Brown, N.R. Ayyangar and G. Zweifel, ibid., 397, 86 (1964).

10. ibid., 1071, 86 (1964).

11. G. Zweifel, N.R. Ayyangar and Muneketar, ibid., 1076, 86 (1964).

12. H.C. Brown and G. Zweifel, ibid.. 4708, 82 (1960).

13. H.C. Brown and B.C. Subba Rao, J.Org.Chem., 1136, 22 (1957).

14. G.F. Hennion, P.A. McCusker, E.C. Ashby and A.J. Rutkowski, J.Am.Chem.Soc., 5190, 79 (1957).

15. R. Koster, Ann., 6118, 31 (1958).

16. H.C. Brown and M.V. Bhatt, J.Am.Chem.Soc., 2074, 82 (1960).

17. H.C. Brown and G. Zweifel, ibid., 3222, 82 (1960).

18. Ibid., 486, 83 (1961).

19. H.C. Brown and K.A. Keblys, ibid., 1791 and 1795 86 (1964).

20. H.C. Brown and M.K. Unni, Ibid., 2902, 90 (1962).

21. H.C. Brown and K.M. Gallivan Jr. Ibid., 2909, 90 (1968).

22. H.C. Brown and R.L. Sharp, Ibid., 2915, 90 (1968).

23. H.C. Brown and M.W. Rathke, Ibid., 2737, 89 (1967).

24. Ibid., 2739, 89 (1967).

25. Ibid., 2740, 89 (1967).

26. W.F. Newhall, J.Org.Chem. 275, 23 (1958).

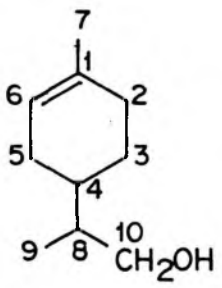
27. [illegible].R. Clemo and F.J. Mcquillin, J.Chem.Soc., 3839 (1952).

Part B

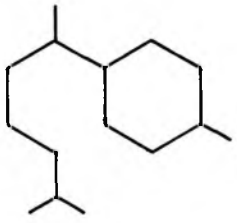
Stereochemistry of Hydroboration - Oxidation Product of limonene

S U M M A R Y

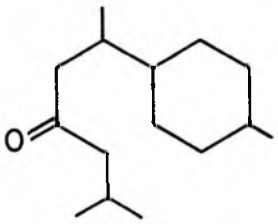
This Chapter (Part B) describes the different methods used to extend the side-chain of (+)-p-menthane-6-en-9-ol (1) (hydroboration product of (+) limonene) to hexahydrozingiberene (2), hexahydroturmerone (3) and β-(4-methyl cyclohexyl) butanoic acid (4) in order to establish the stereochemistry of the methyl group at C_8-position.



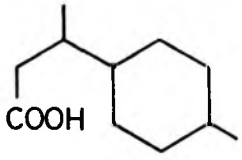
1



2



3



4

The present investigation was undertaken with a view to study the methods which can be utilised for the synthesis of natural zingiberene.

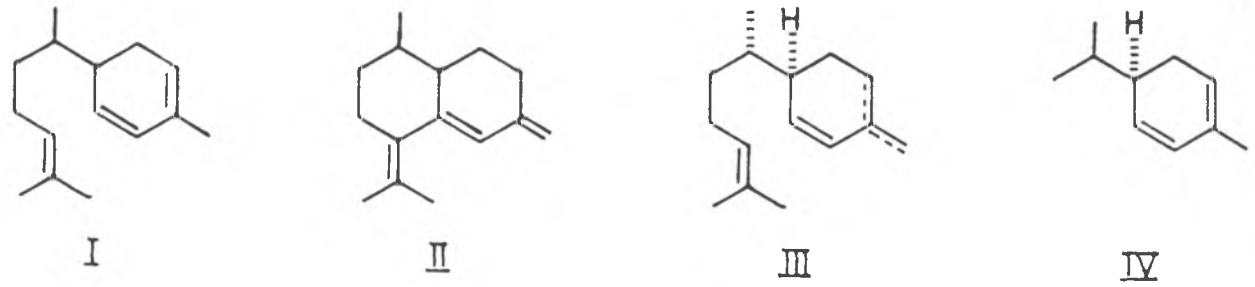
The monocyclic sesquiterpene zingiberene isolated from '<u>zingiber officinale</u>' has been assigned the structure (I). Natural zingiberene is a mixture of two compounds (I) and (II). Two syntheses of (±)-zingiberene have been reported in literature[2,3]. Its absolute configuration has been arrived at by Arigoni and Jeger[4] and by Mills[5]. The carbon at C_6 has been assigned S configuration by comparison of the rotation of 2,6-dimethyl-octa-2,7-diene (Va), obtainable by the pyrolysis of dimethyl acetylene-dicarboxylate adduct of zingiberene, with the one obtained from citronellal (Vb). The rotations were found to be of the opposite sign. Mills on the other hand, fixed the other asymmetric centre by comparing the molecular rotation with that of α-phellandrene. On the basis of this, the complete stereochemistry of the natural zingiberene may be represented as in (III). The optical rotation of zingiberene is represented as the sum of contribution due to each of these two asymmetric centres, the major contribution to the rotation of zingiberene is due to α-phellandrene part (M_D - 241°), which can be represented by (IV).

Some time back, as a model study, Joshi et al.[6], reported the synthesis of (-)-zingiberene starting with (+)-citronellal. The reaction seaquences used are shown in Chart I.

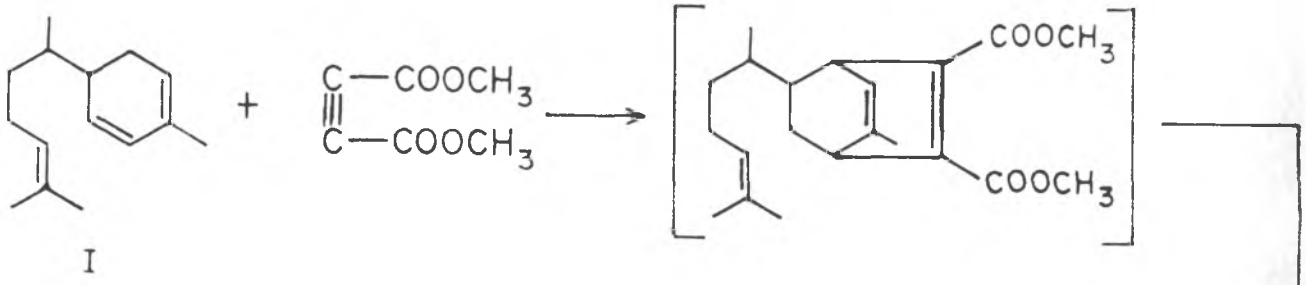
Citronellal (V, $(\alpha)_D$ + 8.5°) was condensed with piperidine in the presence of anhydrous potassium carbonate to obtain the enamine (VI). This when treated with methyl vinyl ketone followed by heating with acetic acid yielded an α,β-unsaturated ketone (VII), α,β-unsaturated ketone (VII), on treatment with methyl magnesium iodide furnished tertiary alcohol (VIII). This carbinol on further hydrogenation with oxalic acid solution gave (-)-zingiberene [X], $(\alpha)_D$ - 49°]. In this synthetic zingiberene, since a new asymmetric centre has been created by the enamine method, it should give an epimeric mixture at this centre. Based on the rotation of synthetic zingiberene Joshi et al. suggested that, it has the preponderance of R isomer at this centre. It, therefore, seems not possible using the experimental conditions used in their work, to obtain natural zingiberene using (-) citronellal, since one would end up with (+) zingiberene.

The present investigation was therefore undertaken in order to circumvent the above shortcomings. For example, in the above synthesis they started with a compound having fixed stereochemistry of the side chain

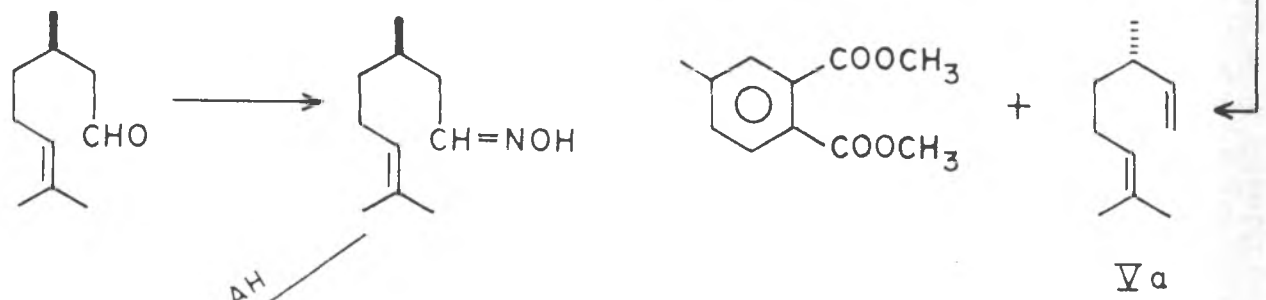
CHART I



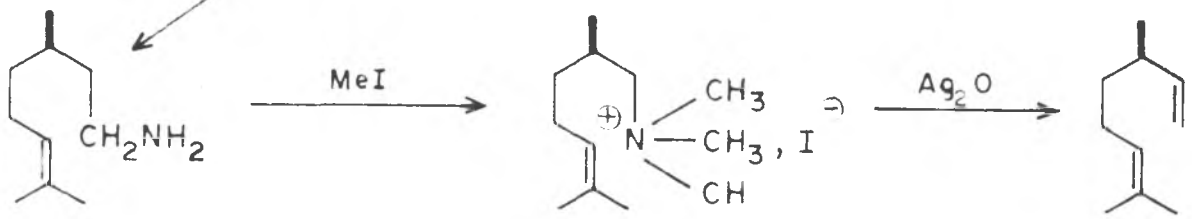
I II III IV



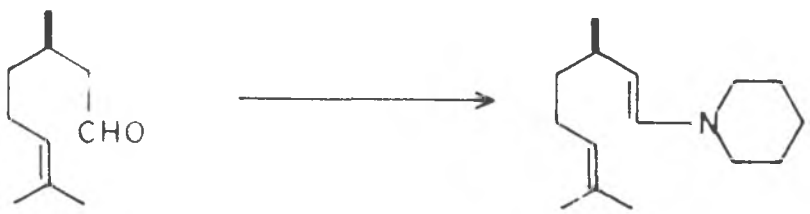
I



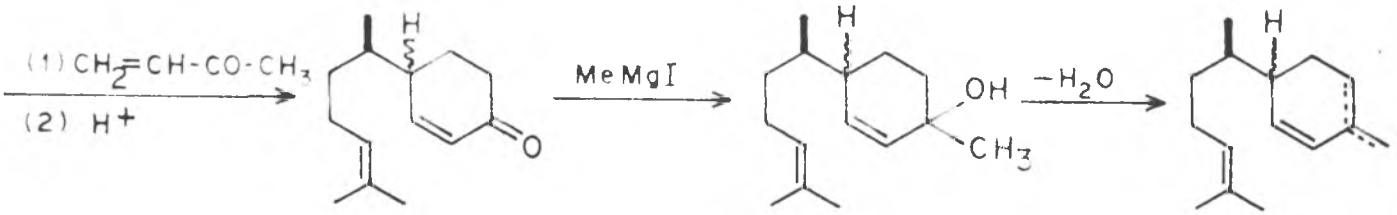
Va



Vb



VI VII



VIII IX X

and then built the ring system consisting of the α-phellandrene part. In the present work it is aimed to start with the phellandrene part (i.e. cyclohexane ring) and then see whether it is possible to introduce the side-chain with the right stereochemistry of the methyl group at C_6-position.

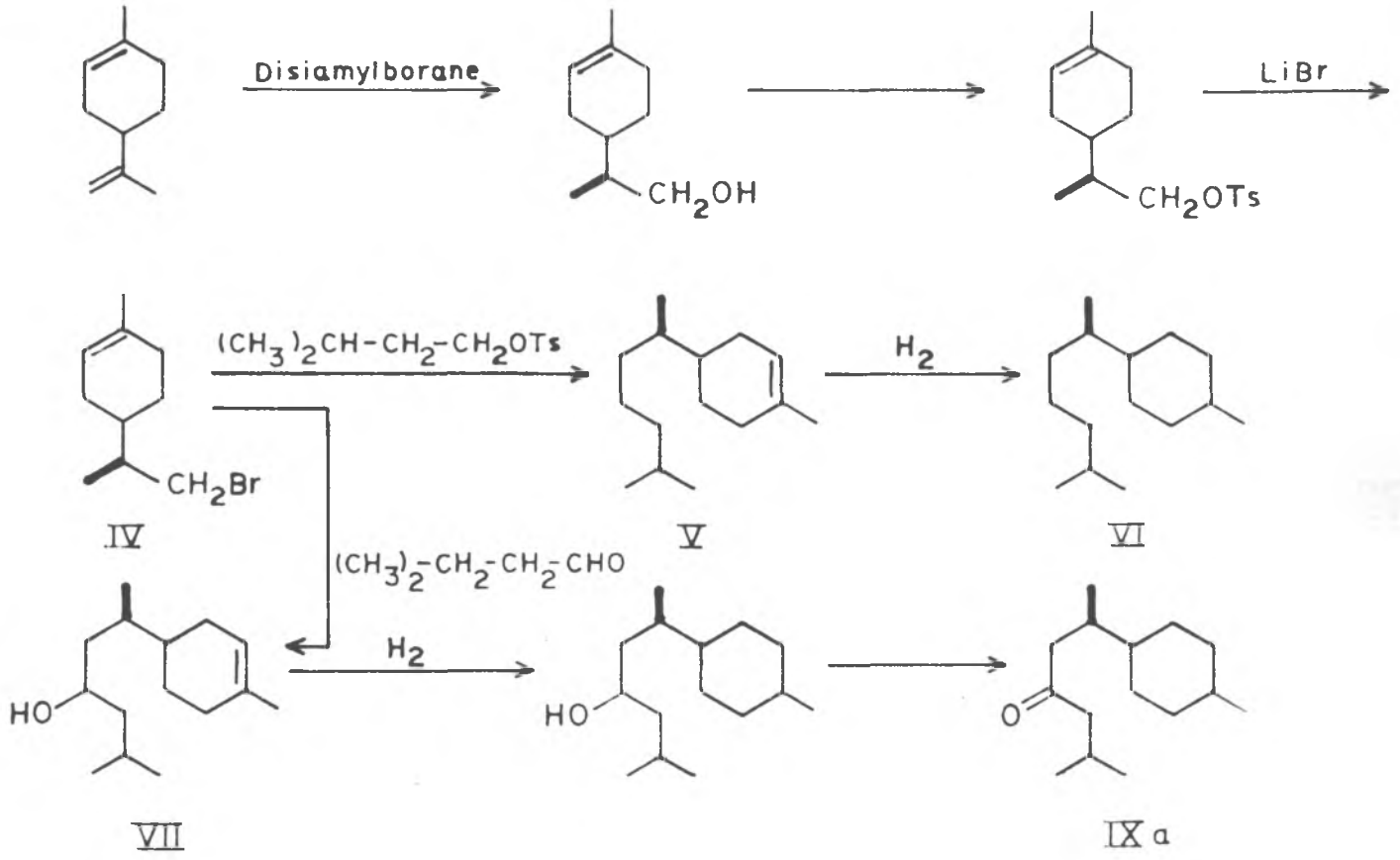
In order to achieve the above objectives, limonene was chosen as a model compound. The hydroboration (O) of limonene by disiamylborane as done by Brown et al. will give p-menthane-6-ene-9-ol (II, Chart II). It is then hoped that the stereochemistry of the new asymmetric centre thus created will be the important factor in determining a suitable starting compound for the ultimate synthesis of natural zingiberene. So the aim of the present work is to determine the stereochemistry of this alcohol and develop methods if possible for the extension of the chain.

Present work (Chart II)

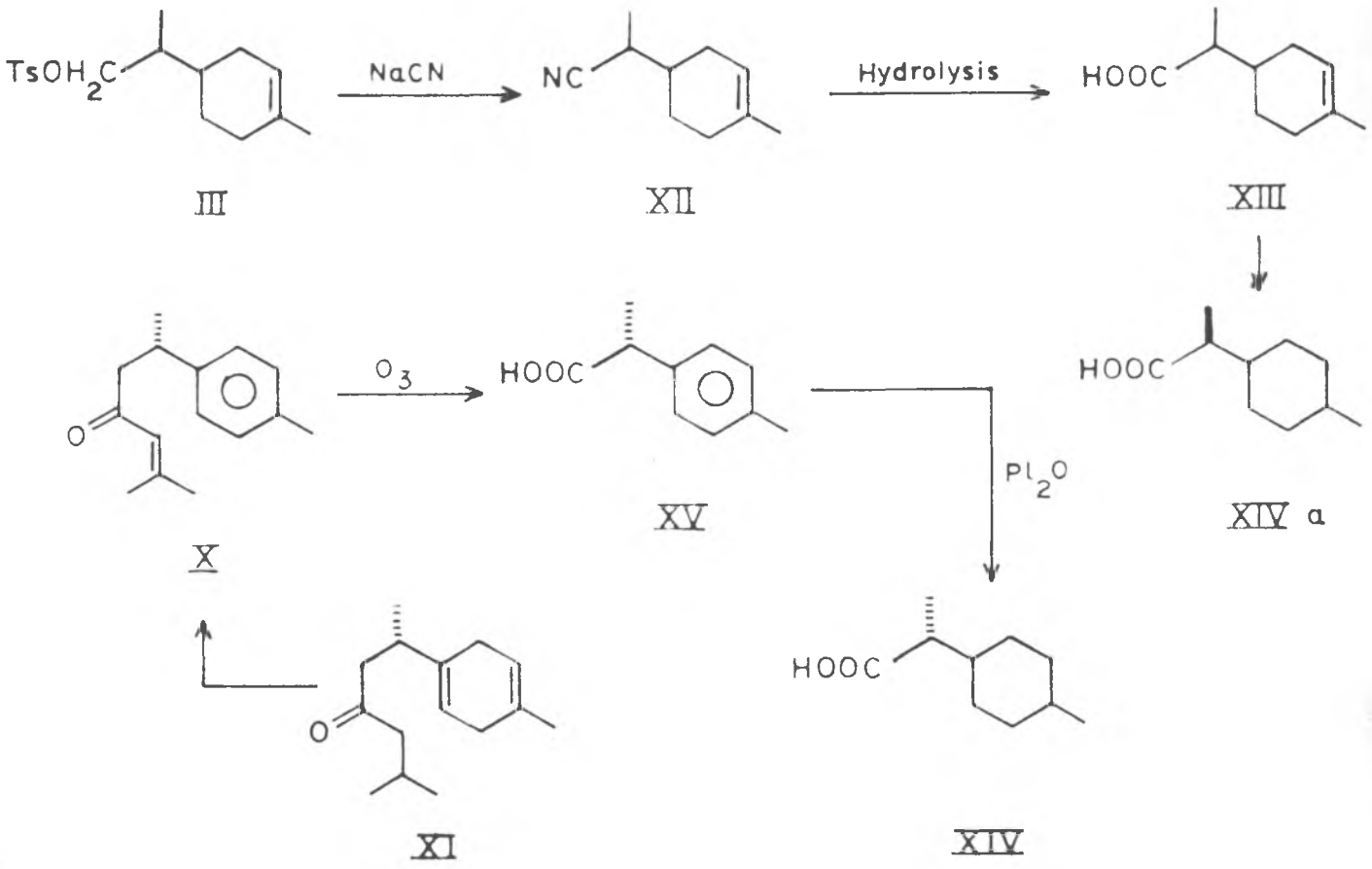
One of the earliest attempt made to determine the stereochemistry of the methyl group is to convert (+) p-menthane-6-ene-9-ol (II) to hexahydrozingiberene [VI, $(\alpha)_D$ - 10°]. (+) Limonene [I, $(\alpha)_D$ + 123°] on hydroboration with disiamylborane according to the method of Brown et al.,[12] furnished (+) p-menthane-6-ene-9-ol (II) in excellent yield; $(\alpha)_D$ + 96°. GLC analysis showed it to be a single compound. The chain extension of

CHART II

SYNTHESIS OF HEXAHYDROZENGIBERENE AND HEXAHYDROTURMERONE



SYNTHESIS OF α-(4-METHYL CYCLOHEXYL) PROPOINIC ACID



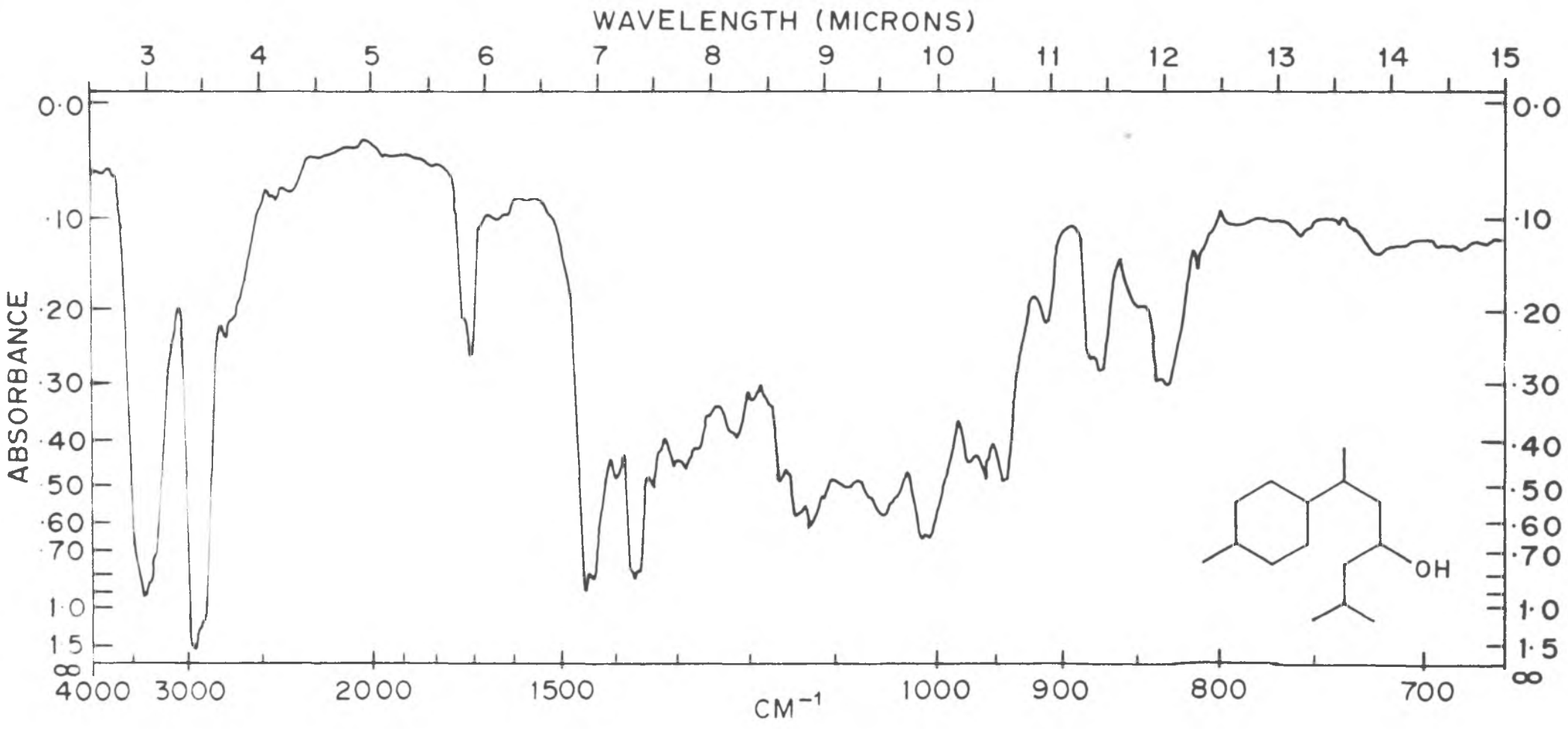
(+) p-menthane-6-en-9-ol (II) to hexahydro-zingiberene was attempted according to the method used by Rao et al.[8] in synthesising (±)-α-curcumene. This method consists in reacting p-tolyl magnesium bromide with p-toluenesulphonate of methylheptanol. Thus, in the present work, p-menthane-6-ene-9-tosylate (III) was prepared by treating (+) p-menthane-6-en-9-ol (II) with p-toluene sulphonyl chloride in pyridine. The crude tosylate (III) showed IR bands at 1600 cm^{-1} and 970 cm^{-1} (for tosylate group). The crude tosylate was dissolved in acetone containing excess of lithium bromide and refluxed on the water bath for 3 hours. After usual working up (+) p-menthane-6-en 9-bromide (IV) was obtained. It has b.p.120-125°(bath)/ 5 mm and $(\alpha)_D$ + 100.2°. p-Menthane-6-en-9-magnesium bromide was condensed with isoamyl tosylate and the reaction product after working up was chromatographed over alumina (Gr. I). The petroleum ether eluate furnished mainly a compoundhaving M^+ 274, obviously a dimer formed as a Wurtz reaction product from p-menthane-6-en-9-bromide, instead of tetrahydrozingiberene (V). To avoid the formation of the dimer, p-menthane-6-en-9-tosylate (III), was added to isoamyl magnesium bromide. The GLC analysis of the reaction product showed it to be a mixture of at least four compounds, the separation of which was not possible. Moreover the percentage of hydrocarbons formed was very poor.

Some more efforts were made to get tetrahydrozingiberene. For example, the Grignard reaction was carried out by reverse addition viz. the isoamyl magnesium bromide was added to p-menthane-6-en-9-tosylate (III) at 0° in nitrogen atmosphere. The crude product thus obtained was passed through silver nitrate impregnated silicic acid (10%). The petroleum ether eluate showed minimum three compounds as shown by silver nitrate impregnated TLC analysis; the separation of which was found to be difficult and the percentage of the hydrocarbons formed was also poor.

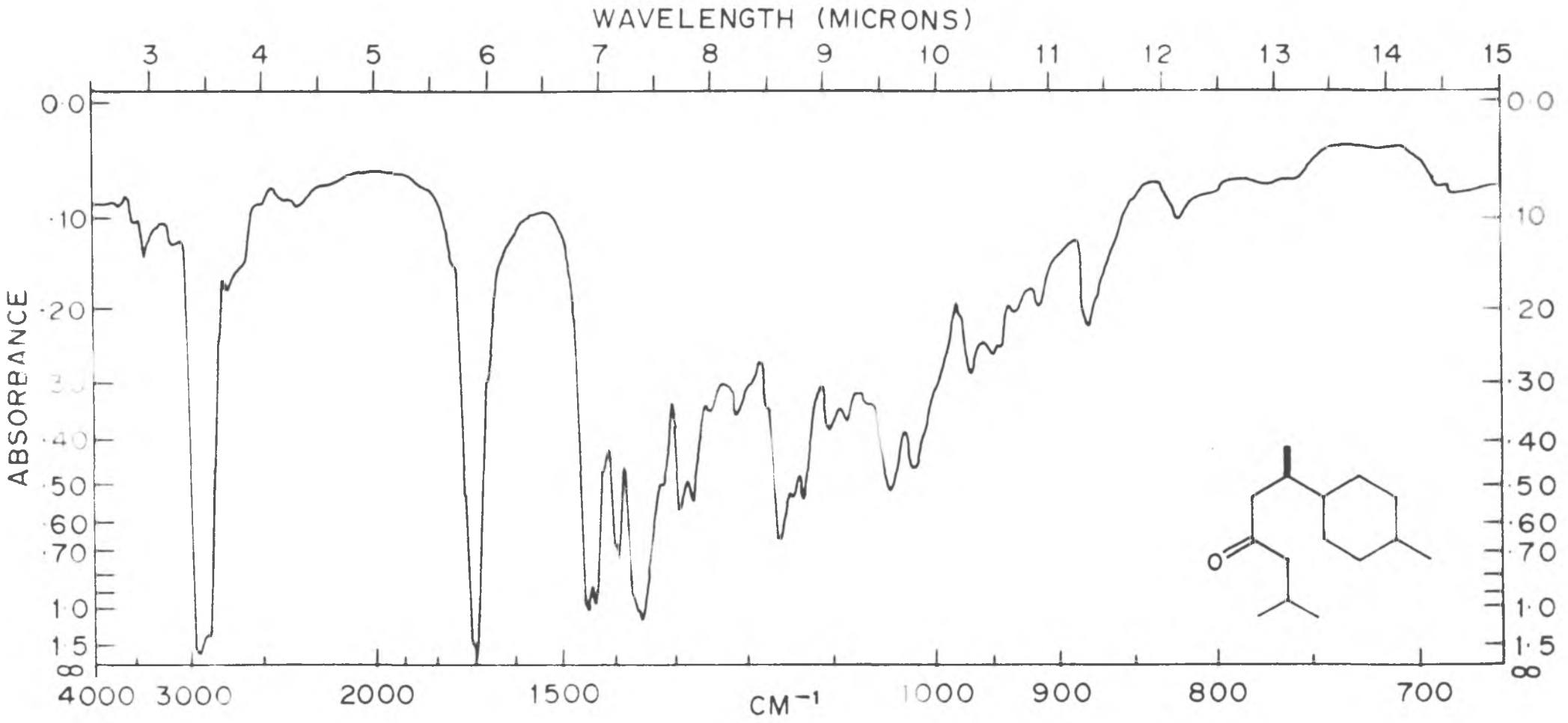
Having failed to correlate (+) p-menthane-6-en-9-ol (II) to tetrahydrozingiberene attempts were made to correlate it to hexahydroturmerone (IXb, octahydro-ar-turmerone). (-)-Turmerone (XI) has been correlated to (+)-ar-turmerone (X) and its stereochemistry has been well established[13]. It has the stereochemistry as depicted in (X). The complete saturated product of turmerone (XI) is hexahydroturmerone (IXb).

Synthesis of hexahydroturmerone (Chart II)

Following the method of Mukherjee et al.[10] of synthesising (±)-zingiberene (old structure) a carbinol (VII) was synthesised by the reaction between p-menthane-6-en-9-magnesium bromide (IV) and isovaleraldehyde. It afforded only 5% of the carbinol (VII), which can be separated easily from the reaction mixture by



IR SPECTRUM (LIQUID FILM) No. 1



IR SPECTRUM (LIQUID FILM) No. 2

chromatography. The alcohol, thus formed showed IR bands at 3390 cm^{-1} (for hydroxyl group) and 800 cm^{-1} (trisubstituted double bond). It has b.p. 135°(bath)/0.5 mm. The alcohol (VII) was hydrogenated by Adams catalyst in ethanol. The hydrogenated alcohol (VIII) did not show any absorption at 800 cm^{-1} in its IR spectrum.(NC-1) The crude hydrogenated alcohol (VIII) was further subjected to oxidation, using Jones reagent, to furnish hexahydroturmerone (IXa). It has b.p. 120°(bath)/0.5 mm and $(\alpha)_D$ + 1.3°. It was found to be single compound by GLC analysis. IR spectrum showed band at 1703 cm^{-1} (for keto group).

Complete hydrogenation of (-) turmerone (XI), using Adam's catalyst, followed by oxidation of the resulting alcohol, furnished hexahydroturmerone whose stereochemistry can be represented as in (IXb). It has b.p. 120°(bath)/0.5 mm and $(\alpha)_D$ - 1.5°. It was found to be pure by GLC analysis and has the same retention time as that of hexahydroturmerone (IXa) in GLC analysis.

Evidently, both (IXa and IXb) are epimers having opposite optical rotation and hence the methyl group at C_8 in (+) p-menthane-6-en-9-ol (II) can be represented as in II and therefore has the $\overset{S}{R}$ configuration.

Most of the other fractions obtained by the chromatography of the above Grignard product showed both alcohol and keto groups absorption in their IR spectra

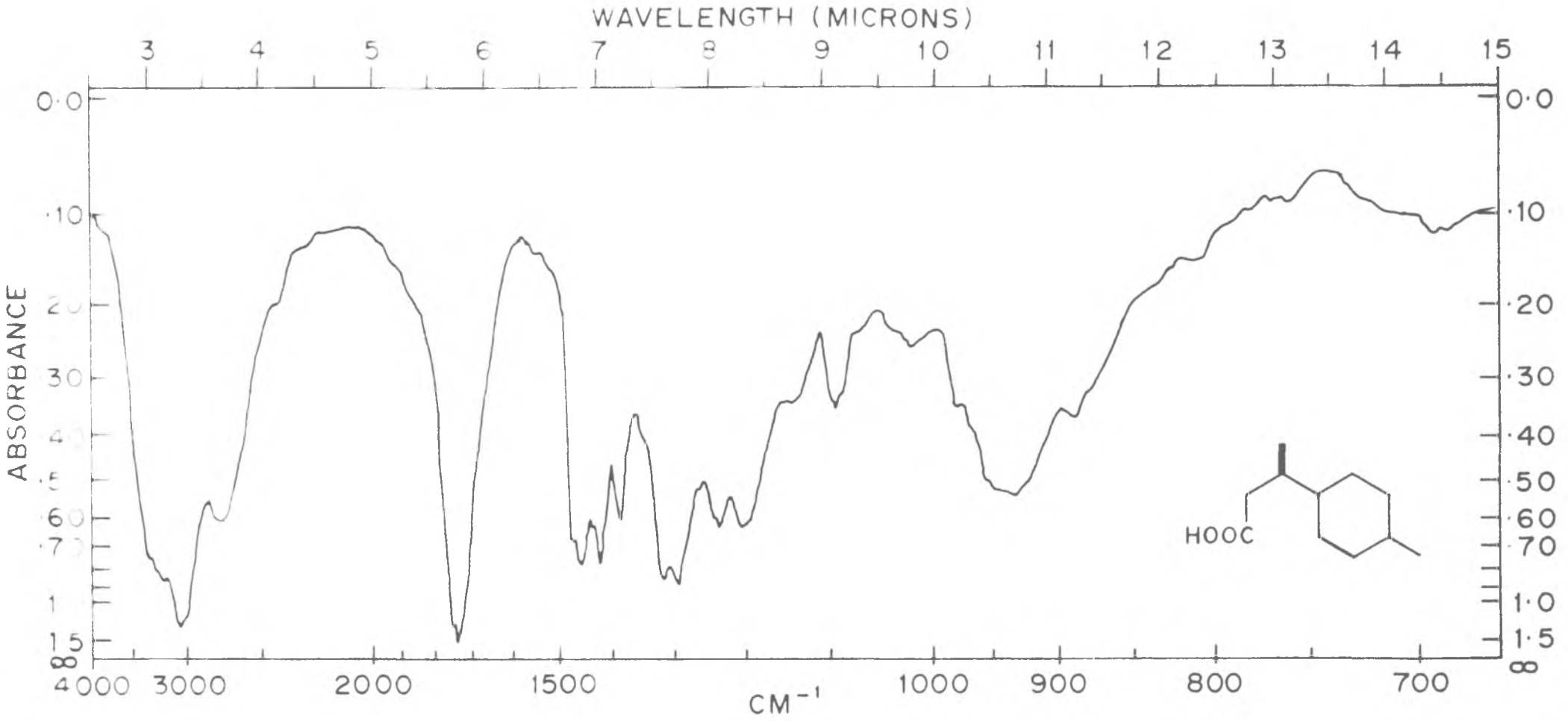
Probably aldol condensation of isovaleraldehyde might have taken place. These fractions were not further investigated.

As an additional proof, (+)-p-menthane-6-en-9-ol (LI) was converted to β-(4-methyl cyclohexyl)-butanoic acid (XIVa). The same acid was obtained by degradation of ar-turmerone (X). This gives further proof for the stereochemistry of (+) p-menthane-6-en-9-ol. This has been done as follows.

Conversion of (+) p-menthane-6-en-9-ol (II) to β-(4-methyl cyclohexyl) butanoic acid XIVa) (chart II)

(+)-p-Menthane-6-en-9-tosylate (II) was converted to (+)-p-menthane-6-en-9-nitrile (XII), by refluxing in dimethyl sulphoxide containing sodium cynide. GLC analysis showed it to be single compound. It has b.p. 140-145°(bath)/10 mm and $(\alpha)_D$ + 75°. (+)-p-Menthane-6-en-9-carboxylic acid (XIII) was obtained by the hydrolysis of (+)-p-menthane-6-en-9-nitrile (XII) with sodium hydroxide in dimethyl sulphoxide. It has b.p. 150-155°(bath)/1 mm and $(\alpha)_D$ + 85.6°. IR spectrum showed bands at 943 cm^{-1} (broad) and 800 cm^{-1}.

Hydrogenation of p-menthane-6-en-9-carboxylic acid (XIII) with Adams catalyst in ethanol furnished β-(4-methyl cyclohexyl) butanoic acid (XIVa). It has b.p. 140-145° (bath)/1 mm and $(\alpha)_D$ + 2.4°. IR spectrum showed bands at 2703 cm^{-1}, 943 cm^{-1} (broad).

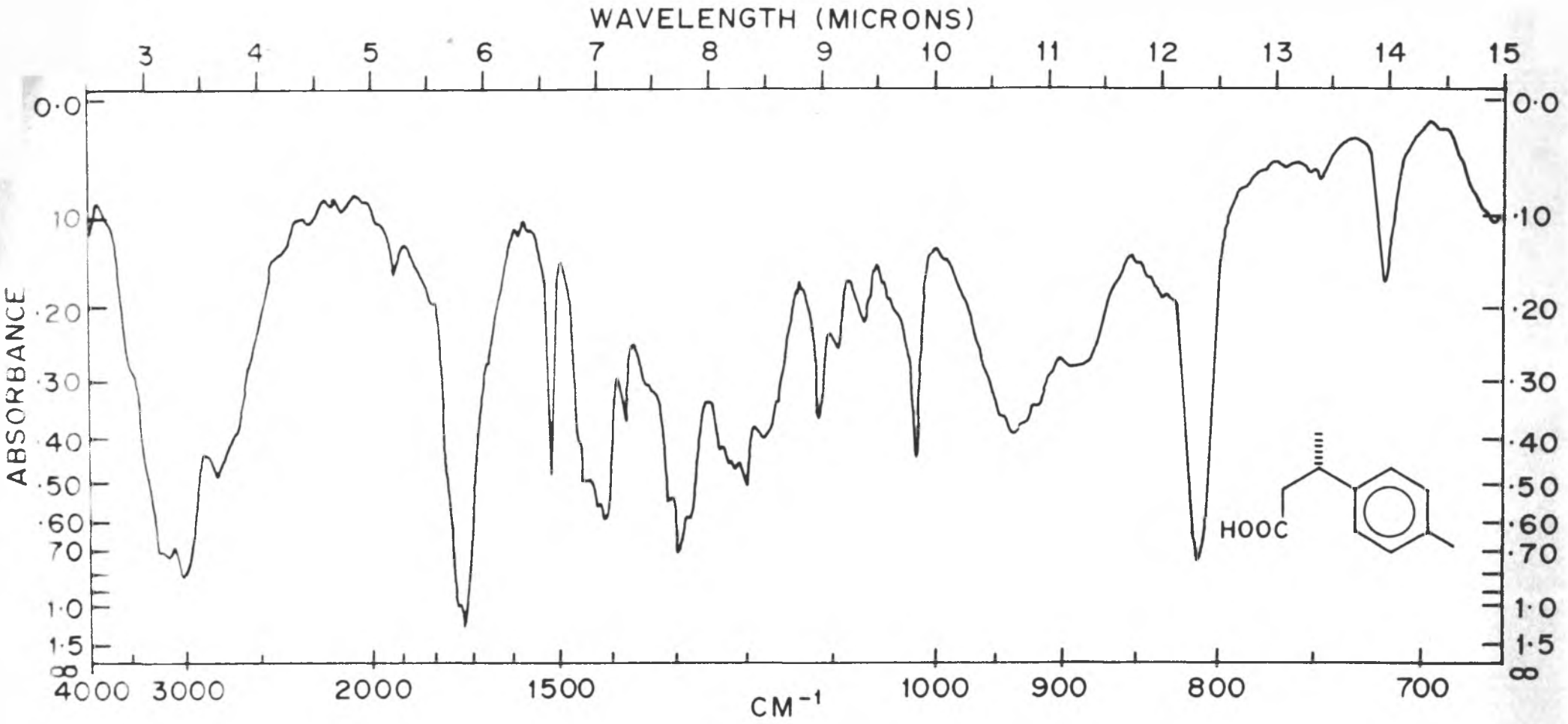


IR SPECTRUM (LIQUID FILM) No. 3

Conversion of ar-turmerone (X) to β-(4-methyl cyclohexyl) butanoic acid (XIVb)

Ozonolysis of (+) ar-turmerone[13] [b.p.140°(bath)/1 mm; $(\alpha)_D$ + 55.8°] in ethyl acetate furnished the acid (+) β-p-tolyl butanoic acid (XV) and was purified through its s-benzyl-isothiouronium salt (m.p. 155°). The acid has b.p. 145-150°(bath)/1 mm and $(\alpha)_D$ + 49.9°. IR spectrum showed bands at 2703 cm^{-1}, 1515 cm^{-1} and 942 cm^{-1} (broad). Hydrogenation of the acid (XV) by Adams catalyst in acetic acid furnished completely saturated acid; β-(4-methyl cyclohexyl)-butanoic acid (XIVb). It has b.p. 140°(bath)/1 mm and $(\alpha)_D$ - 2.4°. IR spectrum of the acids (XIVa and XIVb) are superimposible. It is evident from the optical rotations of two acids (XIVa) and (XIVb) that, they are epimers at C_8-position. Hence the C_8-methyl in (+)-p-menthane-6-en-9-ol (II) has S configuration as the methyl group at C_6-position in ar-turmerone has been assigned as S configuration[13].

Based on these results, the total synthesis of natural zingiberene has now been undertaken.



IR SPECTRUM (LIQUID FILM) No. 4

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

Preparation of p-menthane-6-en-9-ol (II) from limonene (I)

In a 500 ml flask, equipped with a condenser thermometer and a pressure equilibrated dropping funnel, were placed diglyme (80 ml), 2-methyl-2butene (23.1 g) in diglyme (20 ml) and sodium borohydride (4.7 g). The flask was immersed in ice bath and boron trifluoride etherate (23.5 g) was added dropwise to the well stirred reaction mixture over a period of 30 minutes. The reaction mixture was permitted to remain an additional 15 hours at 0-5°, then used for the hydroboration of limonene. To the above disiamylborane reagent was added limonene ⁄20.5 g: $(\alpha)_D$ + 124°7 over a period of 5 minutes. The stirring was continued for 3 hours at room temperature. The reaction mixture was oxidised by alkaline hydrogen peroxide, 3N sodium hydroxide (50 ml) followed by 30% hydrogen peroxide (50 ml). The alcohol was obtained after usual extraction of the reaction mixture with ether. The crude product, after chromatography over alumina (Gr. II, 200 g), and distillation furnished p-menthane-6-en-9-ol (II, 16.0 g); b.p. 135°/10 mm; $(\alpha)_D$ + 96. (Found: C, 77.54: H, 11.82%. $C_{10}H_{18}O$ requires: C, 77.86; H, 11.76%).

IR spectrum showed bands at 3400, 2924, 1449, 1385,

1042, 921 and 800 cm^{-1}.

Tosylation of p-menthane-6-en-9-ol (II)

p-menthane-6-en-9-ol (6 g, II) was dissolved in pyridine (30 ml) and p-toluenesulphonychloride (7.3 g) was added. Left over night at room temperature. Poured into ice cold water (100 ml). Acidified with cold 1N sulphuric acid. Extracted with ether. The ethereal extracts were washed successively with cold 1N sulphuric acid, water and dried over anhydrous sodium sulphate. After evaporation of the solvent, p-menthane-6-ene-9-tosylate (III, 8 g) was obtained. IR spectrum showed bands at 2941, 1600, 1449, 1370, 1190, 1099, 970 (broad), 851 and 813 cm^{-1}.

Preparation of p-menthane-6-en-9-bromide (IV)

p-Menthane-6-en-9-tosylate (III, 7.8 g) was dissolved in anhydrous acetone and lithiumbromide (20 g) dissolved in acetone (30 ml) was added to it. The mixture was stirred and refluxed for 90 minutes. After cooling, a solid at once separated. The acetone was separated by decantation and the residue was dissolved in water. The organic layer was separated and the aqueous layer was extracted twice with petroleum ether. The combined organic layers along with above acetone solution were dried over anhydrous sodium sulphate and solvent removed. It was chromatographed over alumina (Gr. II). Petroleum

ether eluate gave p-menthane-6-en-9-bromide (IV, 4.8 g). GLC analysis showed it to be a single compound, b.p. 120-125°(bath)/5 mm and $(\alpha)_D$ + 100.2°. (Found: C, 55.3; H, 8.3, Br, 36.0 %. $C_{10}H_{17}Br$ requires: C, 55.2; H, 8.0; Br, 36.8%).

Condensation of (+) p-menthane-6-ene9-magnesium bromide with isovaleraldehyde

Undistilled but well dried p-menthane-6-en-9-bromide (IV) was used for Grignard reaction. Grignard reagent was prepared from magnesium (1 g) and p-menthane-6-en-9-bromide (IV, 4.7 g) in ether. To the freezing mixture of Grignard solution, isovalaraldehyde (isoamyl aldehyde) (7 g) in ether (10 ml) was added slowly with mechanical stirring. The reaction mixture was kept in the ice bath for 1/2 hour, then overnight at room temperature. It was then refluxed for 1-1/2 hours, cooled in the ice bath and ice cold ammonium chloride was added to decompose the complex. It was extracted with ether and the ether extract was washed with water, dried over anhydrous sodium sulphate. On removal of the solvent, crude product (7.0 g) was obtained. TLC showed it to be a mixture of four compounds. It was chromatographed over alumina (Gr.II, 150 g).

Fr.No.	Solvent	Wt.(g)
1	Pet.ether	2.5
2	50% (pet.ether + benzene)	1.0
3	Benzene	1.0
4	Ether	4.0

Fraction 1 was found to be the unreacted bromide (IV). Fraction 2 was found to be a mixture of the unreacted bromide and carbinol (VII).

Benzene fraction (Isolation of alcohol, VII)

TLC showed it to be a mixture of two compounds, one being in major amount. It was rechromatographed over alumina (Gr.II, 20 g) and following fractions were collected using different solvents (10 ml each) (1) Pet.ether (2) 5% (pet.ether + ether) (3) 10% (pet. ether + ether) (4) 20% (pet.ether + ether) (5) 40% pet. ether + ether (6) ether. TLC analysis showed that only pet.ether and 5% (pet.ether + ether) fractions contained only one compound and showed hydroxyl band in the IR spectrum. Hence they were mixed and distilled b.p. 135°(bath)/2 mm. (Found: C, 80.6: H, 12.08%. $C_{15}H_{28}O$ requires C, 80.29; H, 12.58%). IR spectrum showed bands at 3390, 1695, 1449, 1370, 1015, 888, 840 and 800 cm^{-1}.

Ether fraction

IR spectrum showed absorption for alcohol and keto groups and further found to be a mixture of two compounds. This was not further investigated.

Hydrogenation of alcohol (VII)

The carbinol (VII, 0.200 g) was dissolved in ethanol (10 ml) and hydrogenation was affected by Adams catalyst. The catalyst was removed by filtration and ethanol removed. The crude hydrogenation product (VIII),

showed no absorption at 800 cm^{-1} (trisubstituted double bond). It has b.p.130-135°(bath)/2 mm (Found: C, 79.38; H, 13.06%. $C_{15}H_{30}O$ requires: C, 79.57; H, 13.36%).

Oxidation of alcohol (VIII) to hexahydroturmerone (IXa)

The crude alcohol (VIII) obtained above was dissolved in acetone (10 ml) and oxidised with Jones reagent. After the usual extraction with ether, washing the ethereal extracts with water and finally evaporating the solvent, furnished hexahydroturmerone (0.184 g, IXa). It was found to be single compound by GLC analysis. It has b.p. 120-122°(bath)/0.5 mm; $(\alpha)_D$ + 1.3°*. (Found: C, 80.44; H, 12.15%. $C_{15}H_{28}O$ requires: C, 80.29; H, 12.58%). IR spectrum showed bands at 2924, 1703, 1449, 1439, 1399, 1361, 1299, 1282, 1163, 1053, 1026 and 897 cm^{-1}.

Preparation of p-menthane-6-en-9-nitrile (XII)

p-Menthane-6-en-9-tosylate (4.1 g) was dissolved in dimethyl sulphoxide containing sodium-cynide (1.2 g). The mixture was refluxed for six hours in the oil bath, cooled and poured into water (100 ml). It was extracted with ether and the ethereal layer washed with water and dried over anhydrous sodium sulphate. After evaporation of the solvent, the crude product (1.9 g)

*Optical rotations have been determined by using automatic polarimeter instrument.

was chromatographed over alumina (Gr. III, 40 g). Petroleum ether eluate furnished p-menthane-6-en-9-nitrile (XII). GLC analysis showed it to be single compound. It has b.p. 140-145°(bath)/10 mm and $(\alpha)_D$ + 75° (Found: C, 82.13; H, 9.5, N, 8.1%. $C_{11}H_{17}N$ requires C, 82.2; H, 9.3; N, 8.5%).

Preparation of p-menthane-6-en-9-carboxylic acid (XIII)

To p-Menthane-6-en-9-nitrile (XII, 1.0 g) dissolved in dimethylsulphoxide, sodium hydroxide (1 g) in water (10 ml) was added and the mixture was refluxed for 48 hours. Cooled and diluted with water (100 ml). It was extracted with ether and the ethereal layer was washed with water and dried over anhydrous sodium sulphate. Evaporation of the solvent furnished a solid compound and was found to be amide. Aqueous layer was acidified with dil. hydrochloric acid, extracted with ether and ethereal layer was washed with water and dried over anhydrous sodium sulphate. Solvent removal gave p-menthane-6-en-9-carboxylic acid (XIII, 0.35). It has b.p. 150-155°(bath)/1 mm and $(\alpha)_D$ + 85.6°. (Found: C, 72.09; H, 10.14%. $C_{11}H_{18}O_2$ requires: C, 72.49; H, 9.96. IR spectrum showed bands at 3175, 3012, 2703, 1724, 1449, 1429, 1389, 1316, 1299, 943 (broad) and 800 cm^{-1}.

Hydrogenation of p-menthane-6-en-9-carboxylic acid (XIII)

p-Menthane-6-en-9-carboxylic acid (XIII, 0.300g) was dissolved in ethanol (10 ml) and hydrogenated over Adams catalyst (30 mg). After usual working up, β-(4-methyl-cyclohexyl) butanoic acid (XIVb) was obtained. It has b.p.140-145°(bath)/1 mm and $(\alpha)_D$ + 2.4°. (Found: C, 71.52; H, 10.83%. $C_{11}H_{20}O_2$ requires: C, 71.69; H, 10.95%).
IR spectrum showed bands at 3175, 3012, 2703, 1724, 1449, 1429, 1389, 1316, 1299, and 943 (broad) cm^{-1}.

Ozonolysis of ar-turmerone

Freshly distilled ar-turmerone [1.5 g $(\alpha)_D$ + 55.8°] was dissolved in ethylacetate (30 ml) and ozonised at 5-10°. To the ozonised solution 30% hydrogen peroxide (2 ml) and dil.acetic acid (5 ml) were added and the mixture was kept overnight. Extracted with ether. The ethereal layer was washed with aqueous sodium bicarbonate solution and then with water. The aqueous sodium carbonate extract was acidified with dil.hydrochloric acid and was extracted with ether and ethereal layer was washed with water. Evaporation of the solvent furnished (β-p-tolyl-butanoic acid (XV, 0.5 g) and was purified through its s-benzylisothiouronium salt. It was crystallised from ethanol, m.p. 155-156°. (Found: C, 66.22; H, 7.33; N, 8.37%. $C_{19}H_{24}N_2SO_2$ requires

C, 66.22; H, 7.02; N, 8.13%).

A mixture of the above s-benzylisothiouronium salt (0.6 g), ether (20 ml) and hydrochloric acid (1N, 10 ml) was stirred at room temperature for 1 hr. The ethereal layer was washed with water, dried over anhydrous sodium sulphate. Evaporation of the solvent furnished (+) β-p-tolyl-butanoic acid (XV, 0.22 g). It has b.p. 145-150°(bath)/1 mm and $(\alpha)_D$ + 49.9°. (Found: C, 74.01; H, 7.84%. $C_{11}H_{14}O_2$ requires: C, 74.13; H, H, 7.92). IR spectrum showed bands at 3077, 2941, 2703, 1701, 1515, 1408, 1297, 1111, 1020, 943 (broad) and 823 cm^{-1}.

Hydrogenation of β-p-tolyl-butanoic acid
(Preparation of (-) β-(4-methyl-cyclohexyl) butanoic acid, XIVb)

β-p-Tolyl-butanoic acid (XV) was dissolved in acetic acid (10 ml) and hydrogenation was carried out using Adams catalyst (70 mg). It was filtered and filterate diluted with water and extracted with ether. Ethereal layer was thoroughly washed with water and dried over anhydrous sodium sulphate. The residue after evaporation of ether was dried over phosphorous pentoxide and potassium hydroxide pellets in a vacuum desicator. It has b.p.140°(bath)/1 mm and $(\alpha)_D$ - 2.4°. Found: C, 71.42; H, 10.62% $C_{11}H_{20}O_2$ requires C, 71.69; H, 10.94%). IR spectrum showed bands at 3175, 3012, 2703, 1724, 1449, 1429, 1389, 1316, 1294 and 943 (broad).

REFERENCES

1. A. Eischenmoser and H. Schinz, Helv.Chim.Acta., 171, 33 (1950).

2. S.M. Mukherji and N.K. Bhattacharyya, J.Am.Chem.Soc., 4698, 75 (1953).

3. A.J. Birch and S.M. Mukherji, J.Chem.Soc., 2531 (1949).

4. D. Arigoni and O. Jeger, Helv.Chim.Soc. 881, 37 (1954).

5. J.A. Mills, J.Chem.Soc., 127, 6, (1968).

6. G.D. Joshi and S.N. Kulkarni, Indian J.Chem., 127, 6 (1968).

7. J. Kenyon, H. Phillips and V.P. Pittman, J.Chem.Soc. 1072 (1935).

8. A.S. Rao, Indian J.Chem., 419, 3 (1965).

9. E.J. Corey, S.W. Chow and R.A. Scherer, J.Am.Chem.Soc., 5773 (1957).

10. S.M. Mukherjee, J.Ind.Chem.Soc., 155, 25 (1943).

11. T.W. Gibson and W.F. Erman, Tetrahedron Letters, 905, No.10 (1967).

12. H.C. Brown and G. Zweifel, J.Am.Chem.Soc., 1245, 83 (1961).

13. V.K. Honwad and A.S. Rao, Tetrahedron, 2921, 20 (1964).

Chapter II

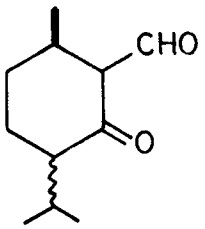
Synthetic Studies in Sesquiterpenes

Part A

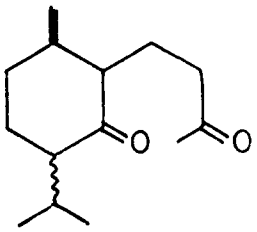
Synthesis of (+) - Calamenene

SUMMARY

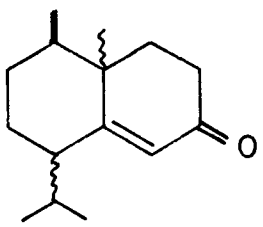
Starting from (-)-menthone, optically active (+)-calamenene has been synthesised. The reaction involves the condensation of hydroxymethylene derivative of menthone (1) with methyl vinyl ketone to yield diketo-aldehyde, which on deformylation yields diketone (2). This on heating with pyrolidine (azeotropically) gives readily the α,β-unsaturated ketone (3). The ketone (3) on reaction with methyl magnesium iodide followed by dehydration furnishes the diene (4) which on simple air oxidation gave (+)-calamenene (5).



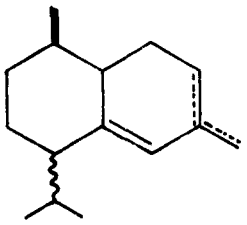
1



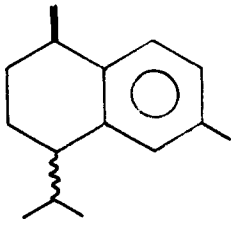
2



3



4



5

Calamenene is a naturally occurring hydrocarbon belonging to cadalene series, containing aromatic nucleus. It was first obtained as a dehydration product from calameone (III), a sesquiterpene ditertiary alcohol ($C_{15}H_{26}O_2$), isolated from sweet flag oil (Chart IA). The dehydrated compound ($C_{15}H_{22}$ $(\alpha)_D$ - 6°) was termed as calamenene and was given the structure (II) by Treibs[1], which exhibited all the properties of an aromatic hydrocarbon. This was considered to be 1,6-dimethyl-4-isopropyl-5,6,7,8-tetrahydronaphthalene (II). To explain this Treibs assumed that during dehydration of calameone by boiling with 100% formic acid, both the hyuroxyl group were removed and the double bond present in ring B, migrated to ring A. This was criticised by Sorm et al.[2] on the ground that Treibs did not consider the other possibility of forming compound (I) and therefore, synthesised both compound (I) and (II) by unambiguous synthesis. He showed that the IR of the natural calamenene agreed with the compound(I)rather than (II). This therefore constitutes the first synthetic proof of the structure of calamenene.

Natural occurrence of calamenene

Calamenene occurs in nature mainly in the (-)-form. It has been isolated from many natural sources. The following table, lists only those, whose rotations

are given, since this is important for our future discussion.

Table I

No.	Source	Optical rotation	Reference
1	Cedrela toona Roxb	-68°, -80°	3,4
2	The berries of Piper Cubeba L (Cubebs)	-50.6°	5
3	Heart wood of Juniperus foestidissima	-46°	6
4	Extracts from the fresh and fungus infested wood of pinus silverstrist	-23°	7
5	Essentials of Kusunoki (Cinnamomum camphor)	-44°	8
6	Oil of Amorpha frouticasa	-33.6°	9
7	Wood of Cryptomeria Japonica	-67°	10

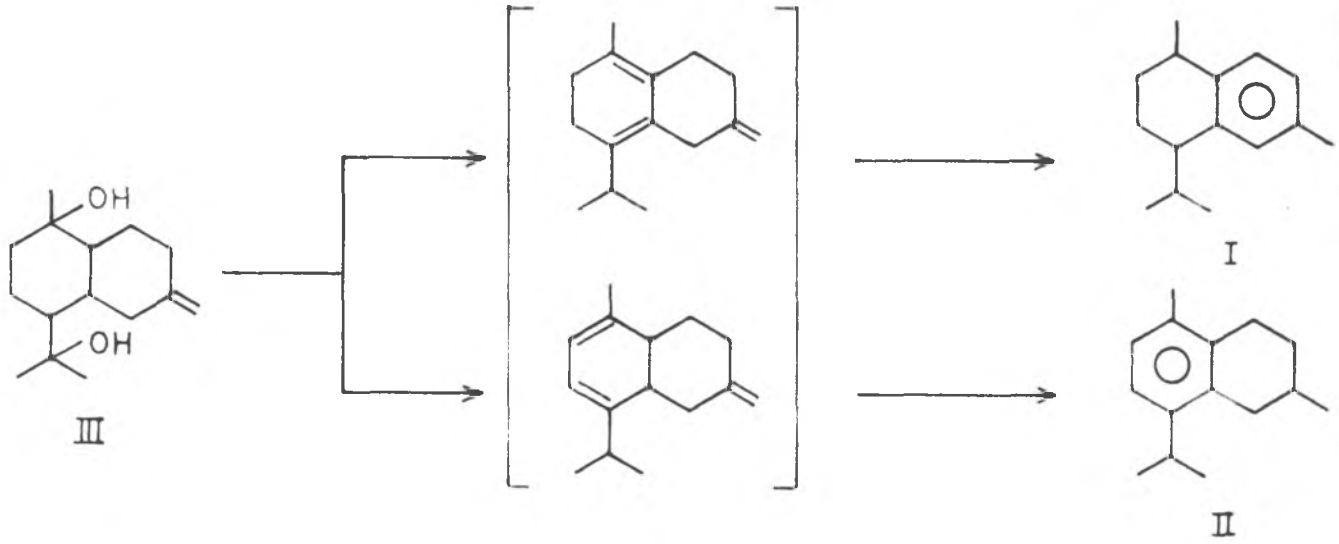
As seen from the above table that, the rotation differ widely and it seems that some of them may be pure compounds having 1,4 *cis* and 1,4 *trans* stereochemistry: while others may be obviously mixture of both these compounds. However the stereochemistry of these compounds are not established.

Total synthesis of (±) calamenene

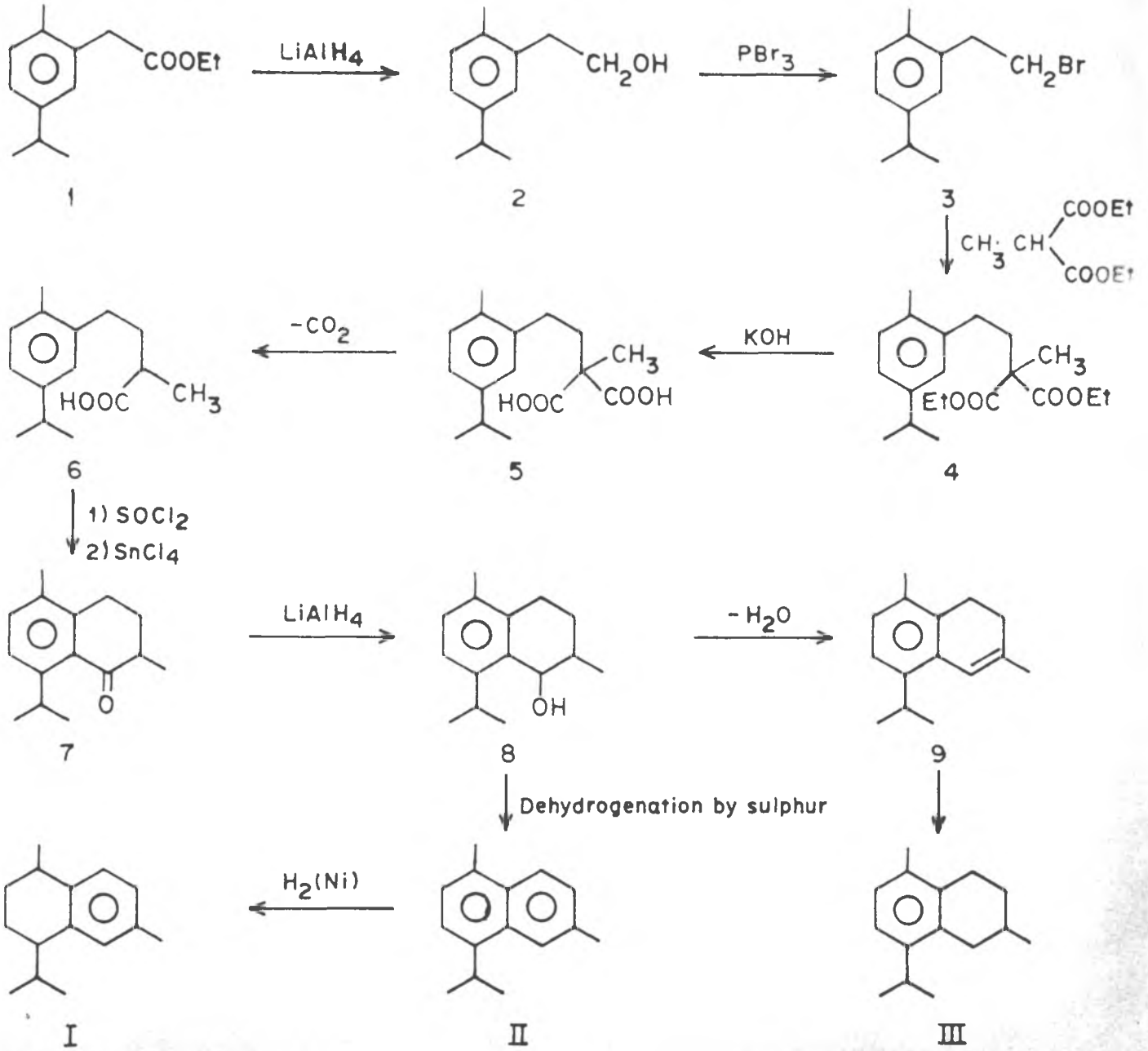
As pointed out, the first synthesis of (±) calamenene has been reported by sorm et al.[2] This has been

CHART I

(A) TRANSFORMATION OF CALEMEONE TO CALAMENENE



(B) SYNTHESIS OF 1,6-DIMETHYL-4-ISOPROPYL-5,6,7,8-TETRAHYDRONAPHTHALEN



summerised in Chart IB.

The key intermediate in the above synthesis is the carboxylic acid (6), which has been synthesised from the ethylester of carvacrylacetic acid. This carboxylic acid was converted through its acid chloride to the ketone (7). Lithium aluminium hydride reduction gave a mixture of two epimeric alcohols(8). The alcohol mixture on dehydration with potassium hydrogen sulphate followed by hydrogenation over platinum furnished compound (III). On the other hand dehydrogenation of (8) by sulphur followed by selective hydrogenation gave calamenene (I), whose IR spectra was identical with the IR spectra of natural calamenene.

Calamenene obtained from other natural compounds

1. From calameone

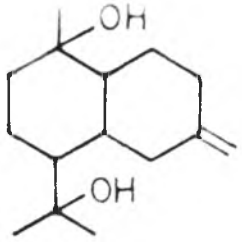
As described earlier (Chart IA), calameone (III, isolated from sweet flag oil) on dehydration with 100% formic acid gave calamenene, $(\alpha)_D$ - 6°.

2. From khusinol

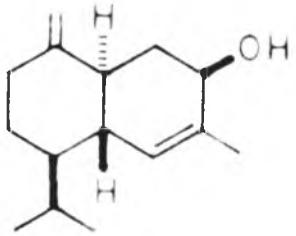
Khusinol is a sesquiterpene alcohol, isolated from vetiver oil. By chemical degredation and spectral data along with conversion to (+) cadalene dihydrochloride, it has been given the structure and stereochemistry as (IV, Chart IIA)[11]. This when treated with BF_3-etherate gave (+) calamenene, $(\alpha)_D$ + 82°, as one of the products[12]. Formation of this has been explained by "Dienone-benzene"

CHART II

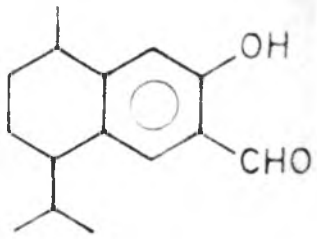
(A)



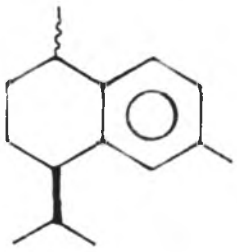
III



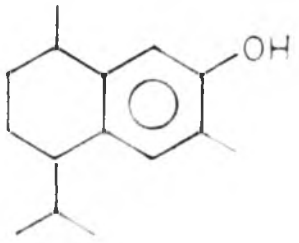
IV



VI

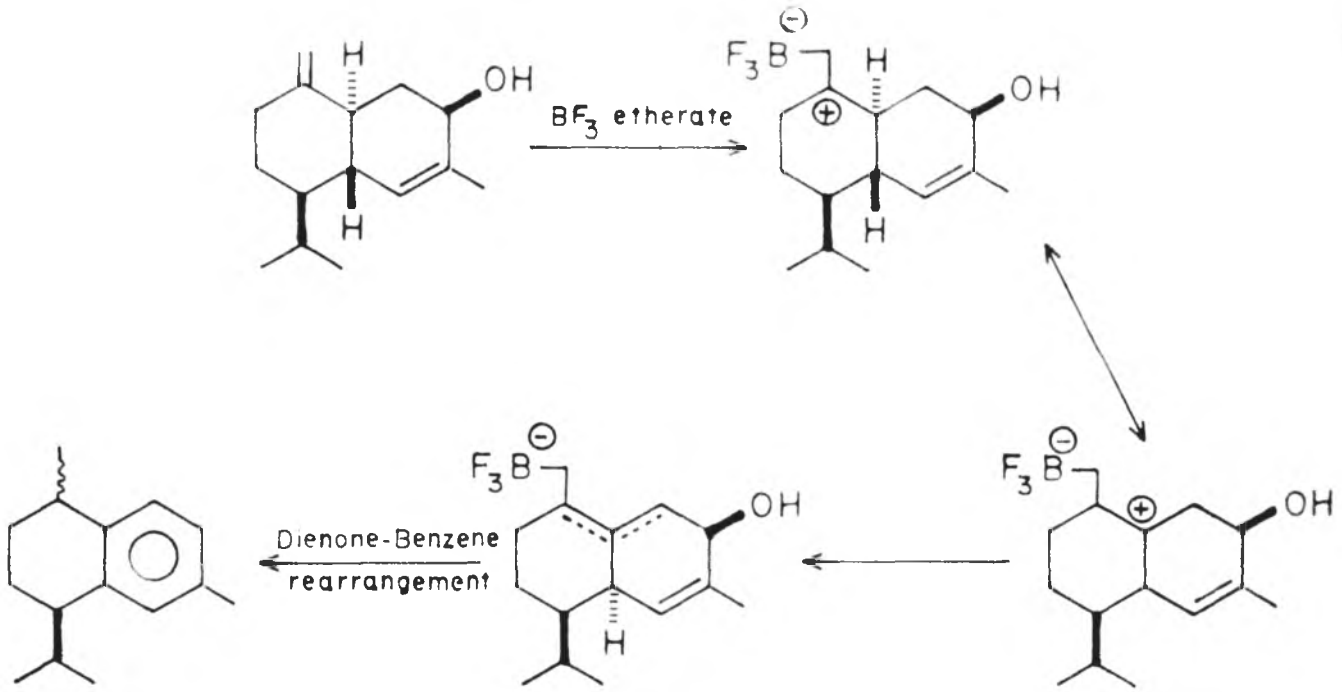


V



VII

(B) MECHANISM OF BF_3 ETHERATE REARRANGEMENT OF KHUSINOL TO (+)-CALAMENENE



type rearrangement (Chart IIB)[12]. This transformation gives some clue as regards the stereochemistry of C_4-isopropyl in (+) calamenene as in (V).

3. From 7-hydroxy calamenenal[13]

This compound was isolated from the yellow wood of slippery elm and has the structure (VI). Hydrogenation of 7-hydroxy calamenal (VI), gave 7-hydroxy calamenene (VII), $(\alpha)_D$ -30°. This has been converted to the oily calamenene (I) by formation of the phenyltetrazoyl ether followed by hydrogenation. It has $(\alpha)_D$ - 47°.

Aim of the present investigation

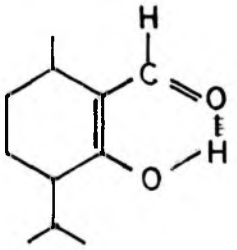
As can be seen from the previous discussion that, the stereochemistry of the natural calamenene has not been established so far. Besides, the rotations reported for calamenene isolated from different natural sources, differ so widely that, it becomes very difficult to decide which of these are pure compounds. Since, it contains two asymmetric centres, there are four isomers possible. Therefore, the present synthesis has been undertaken, which will throw some light on its stereochemistry. Further the method developed for building the cadalene systems will be helpful in synthesising the various cadanenes, several of which are naturally occurring.

Present synthesis

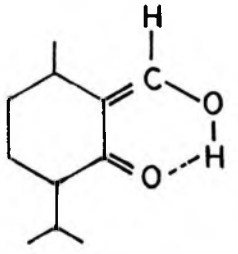
There was only one clue known, regarding the stereo-

chemistry of C_4-isopropyl group in (+) calamenene $(\alpha)_D$ + 82° (which has been obtained from khusinol (IV) of known obsolute stereochemistry) before the present synthesis of (+) calamenene undertaken. It has the stereoformula V, wherein the stereochemistry of C_1-methyl is not known. There was also available the NMR datas of the various calamenenes, isolated elsewhere along with (+) calamenene, $(\alpha)_D$ + 82° and (-) calamenene, $(\alpha)_D$ - 80°, as well as calamenene $(\alpha)_D$ + 0.82° obtained from lithio ethylene diamine reaction on khusinol[14].

In the present synthesis (-) menthone was used as the starting material, where in the stereochemistry of C_1-methyl is known. The various reaction sequences are given in the Chart III. Natural (-) menthol on oxidation with Jones' reagent gave menthone and isomenthone in the ratio of about 80:20. (-) Menthone (Chart III, VIII) condensed with ethyl formate in the presence of sodium ethoxide to give the hydroxymethylene derivative[15] (IX), b.p. 110°/12 mm. The NMR spectra of (IX) showed a one proton resonance at 8.66δ. The above signal corresponds to about 78% of form a and 22% of form b[16].



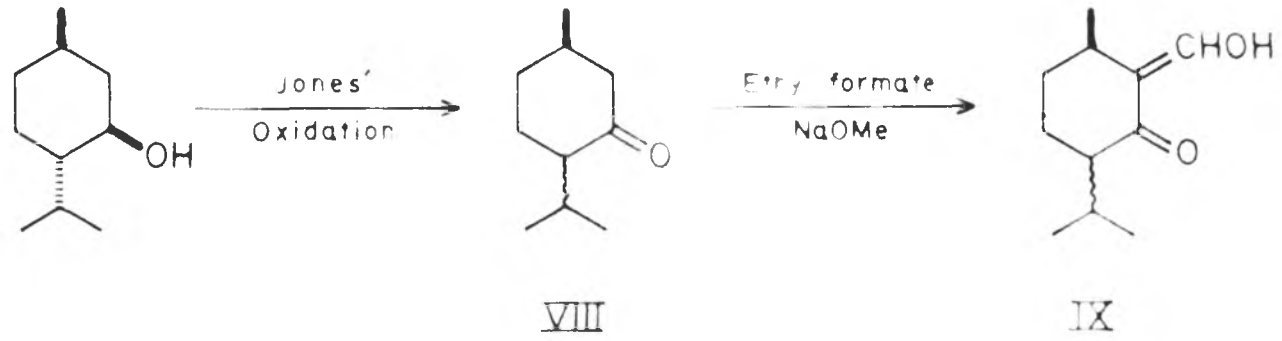
a



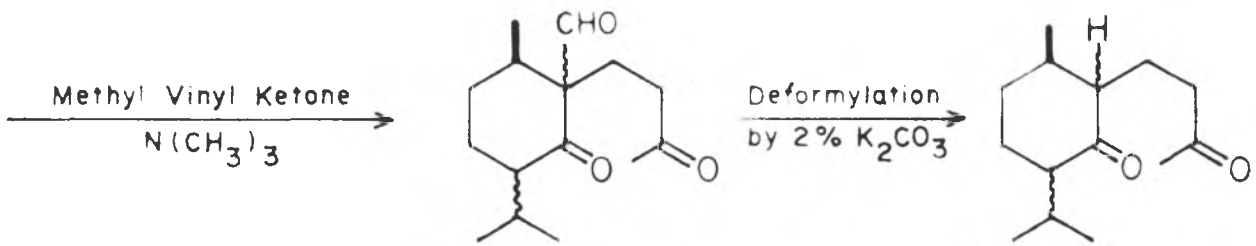
b

CHART III

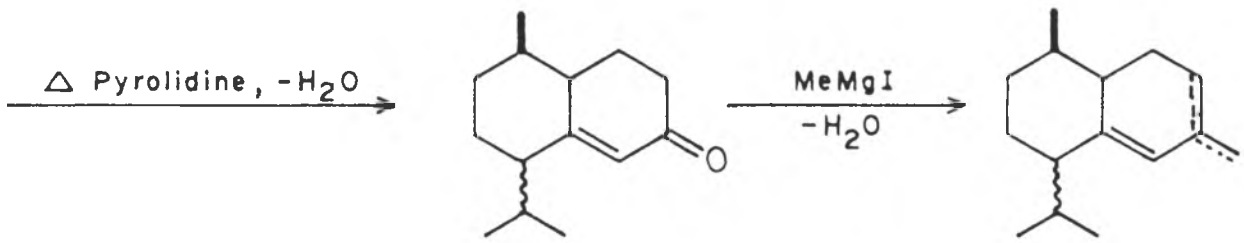
SYNTHESIS OF (+) CALAMENENE



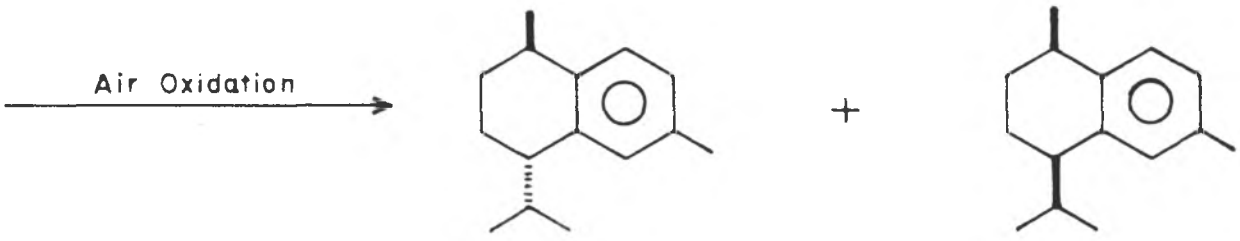
VIII IX



X XI



XII XIII



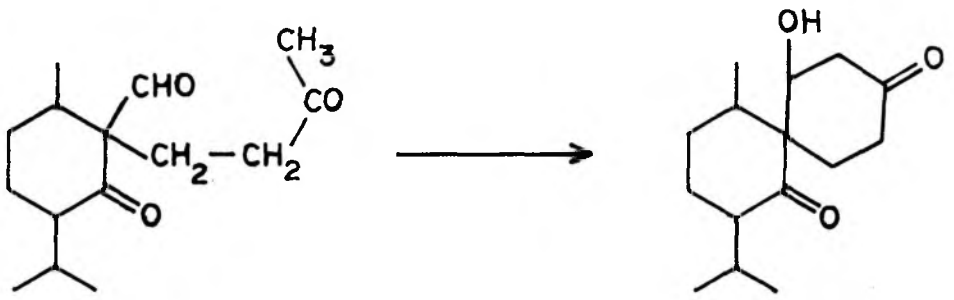
XIV XV

The proton of the enolic OH appeared at 14.7δ which disappeared after D_2O exchange. Besides, it showed C_1-methyl as a doublet at 0.85δ (J, 7 cps); C_4-isopropyl as a triplet at 1.05 δ (J, 7 cps); a multiplet between 2.05 to 2.80δ for allylic protons (2H). The hydroxymethylene derivative on condensation with methylvinylketone in presence of trimethylamine readily furnished crude diketo aldehyde (X), which was used as such for further reaction. The NMR spectrum of this crude diketoaldehyde (X) showed two signals of almost equal intensity at 2.37δ and 2.42δ due to $-COCH_3$ grouping and the CHC proton also appeared as doublet of equal intensity at 9.05δ and 9.15δ. This therefore suggests that, the diketoaldehyde is a mixture of two compounds, in which the $-CH_2-CH_2-CO-CH_3$ grouping has a α or β conformation.

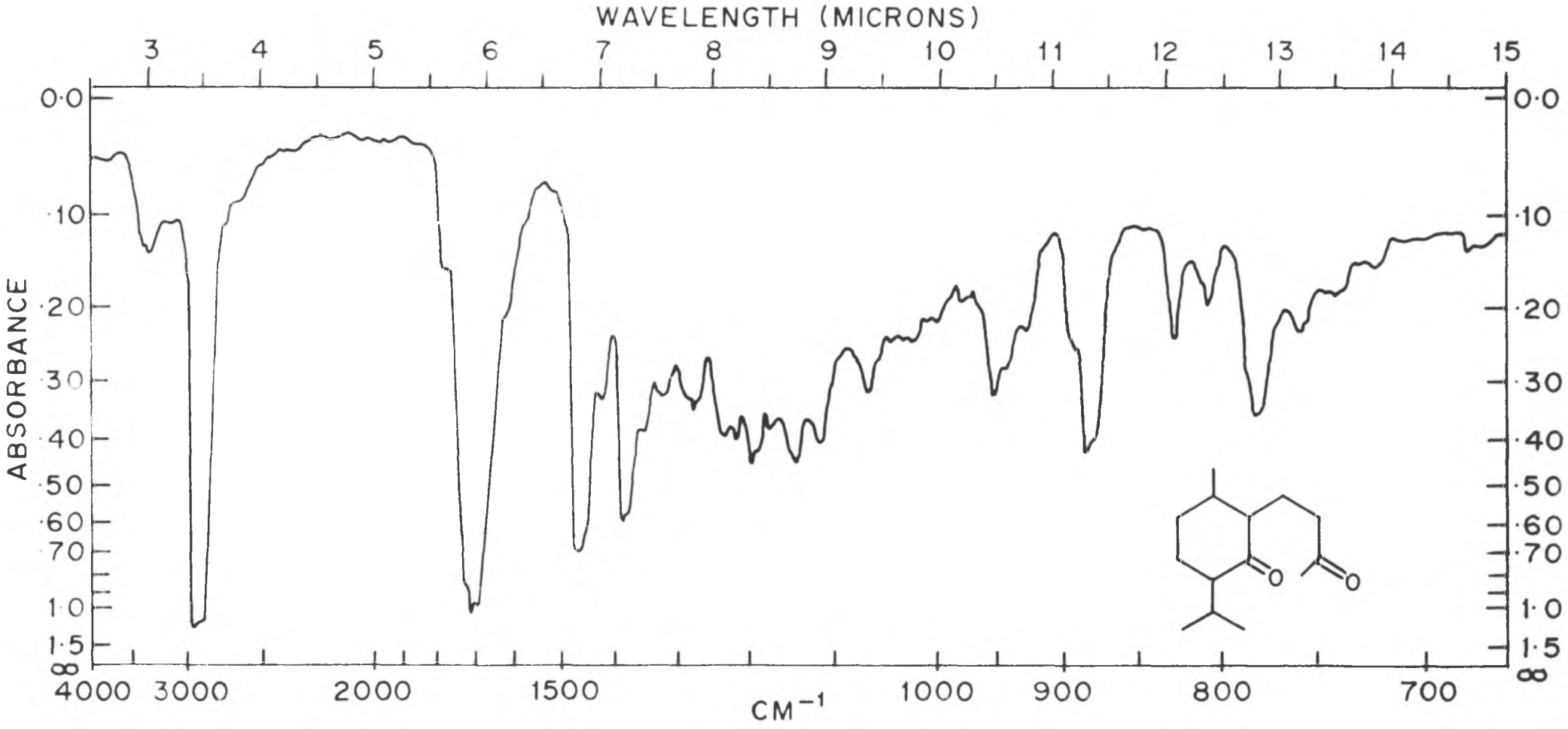
The diketoaldehyde (X) was then deformylated by refluxing with 2% ethanolic potassium carbonate. After working out, the diketone was passed through grade III alumina and eluted with petroleum ether. It has b.p. 180-90°(bath)/2 mm; monosemicarbazone: m.p. 205°. The NMR spectrum of this compound showed a singlet at 2.07δ due $-COCH_3$ grouping and showed no formyl proton. It has $(\alpha)_D$ - 49.4°.

During the above chromatography after removing the diketone (XI) by petroleum ether, another compound was eluted by ether. This has m.p. 126°C and analysed well

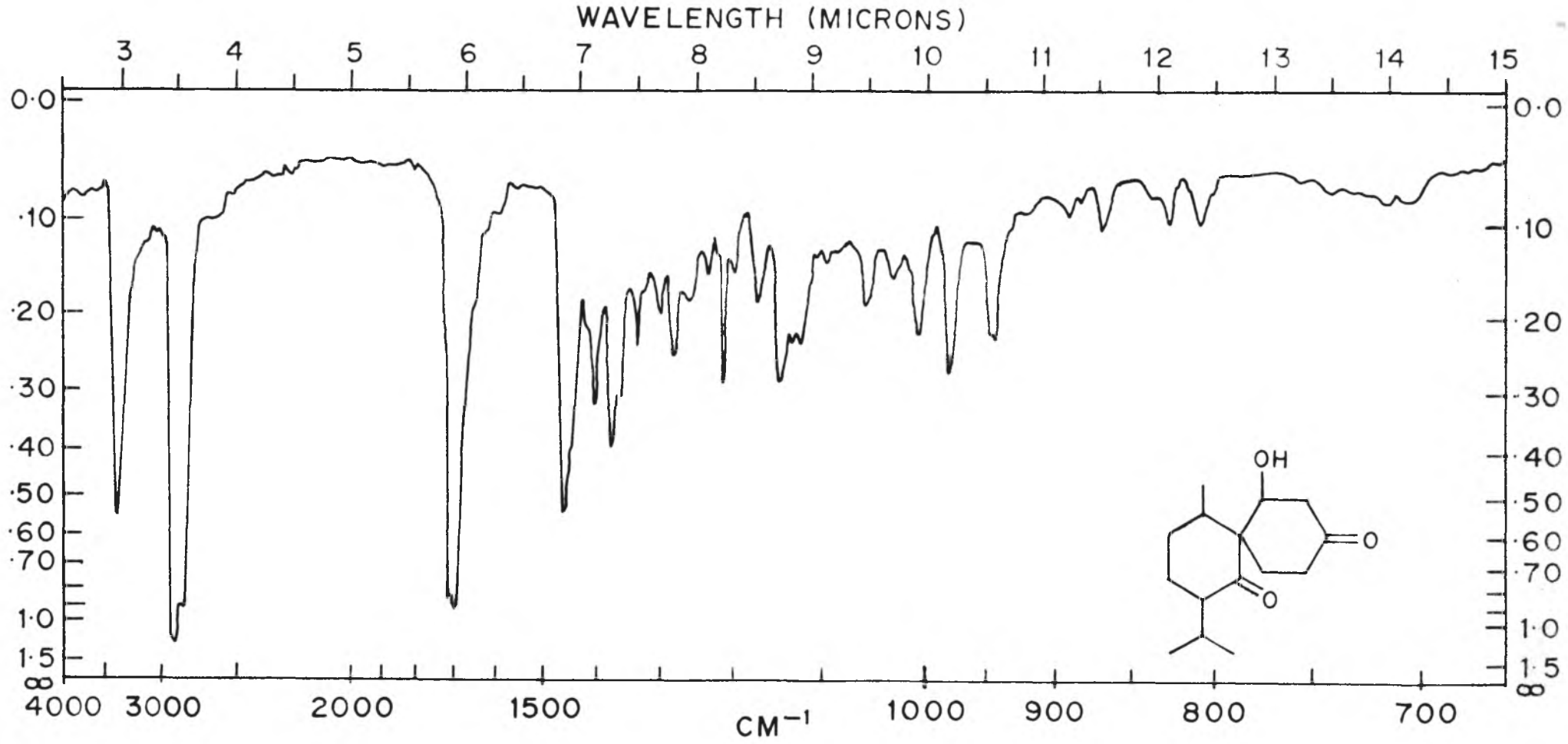
for $C_{15}H_{24}O_3$. The molecular formula is further confirmed by mass spectrum, M^+ 252. The NMR spectrum showed a somewhat sharper multiplet at 4.41δ (C<u>H</u>OH, H.W. 6.5 cps). IR spectrum showed bands at 3400 cm^{-1} (for hydroxyl) and 1709 cm^{-1} (for carbonyl). The following structure (XVI) has been tentatively assigned to it and the formation of this can be explained as a base catalysed cyclisation with the aldehyde.



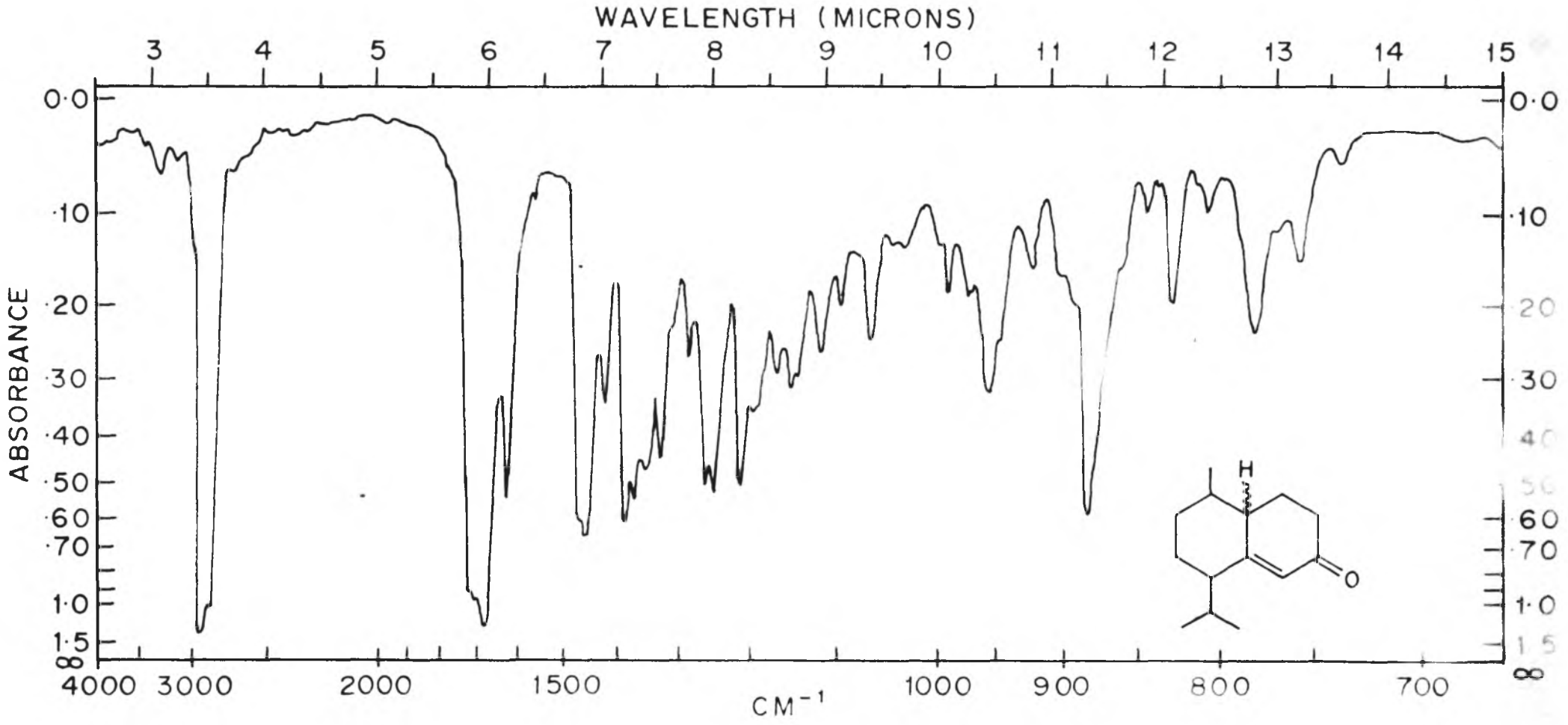
The base catalysed cyclisation might have taken place during the condensation of hydroxymethylene derivative (IX) with methylvinyl ketone in presence of trimethylamine. This is indeed found to be the case, because the same compound can be isolated from diketoaldehyde reaction mixture, by treating with excess of petroleum ether. Further investigation of its structure is in progress.



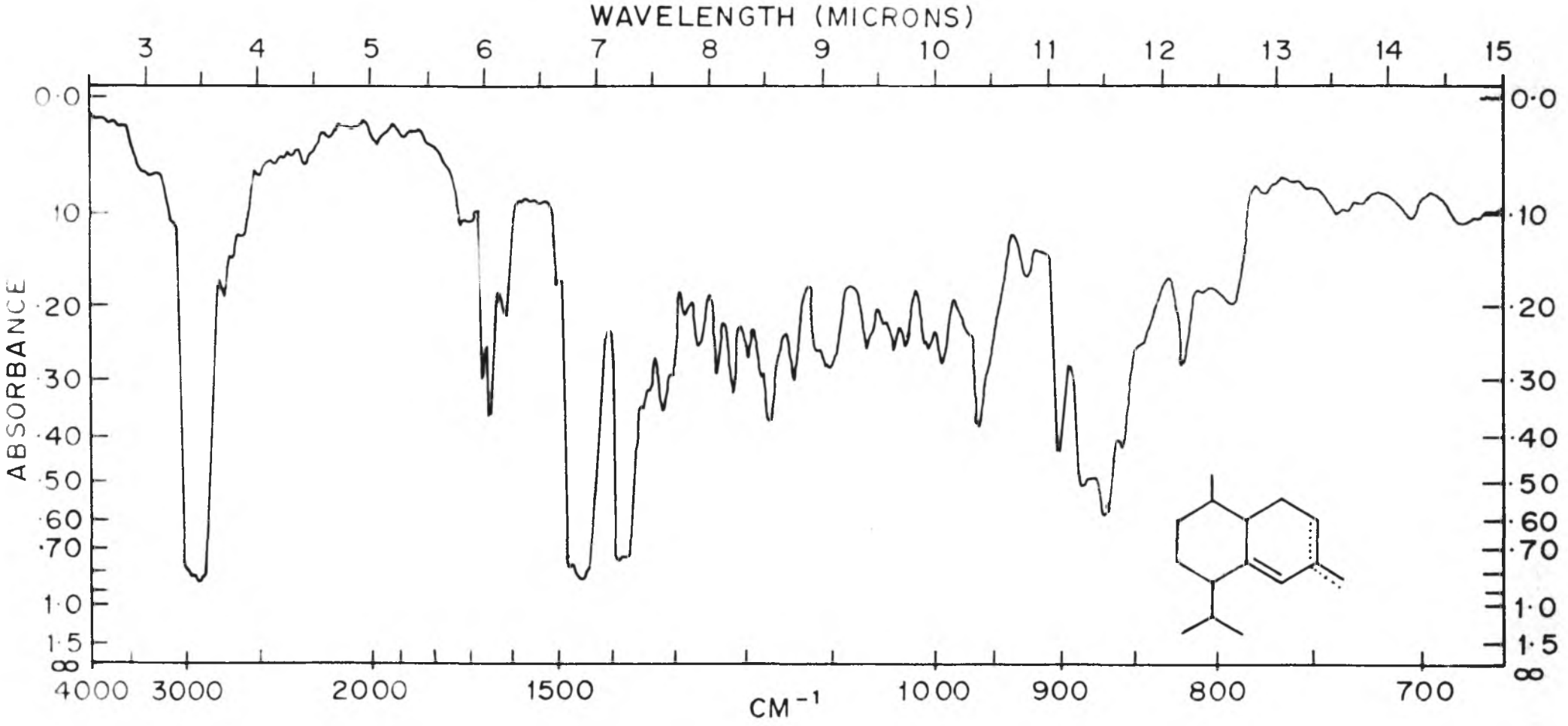
IR SPECTRUM (LIQUID FILM) No. 1.



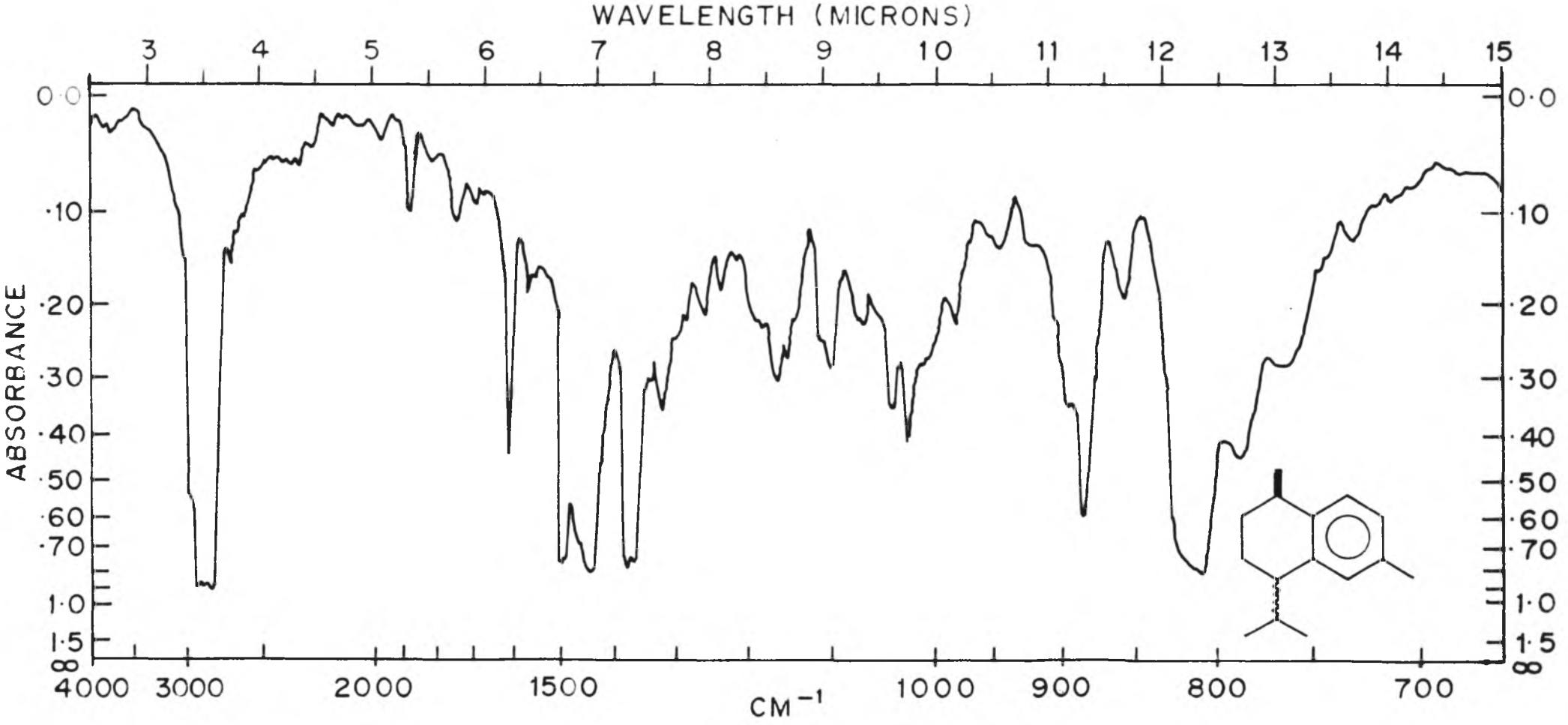
IR SPECTRUM (NUJOL) No. 2.



IR SPECTRUM (LIQUID FILM) No. 3.



IR SPECTRUM (LIQUID CELL, 0·05 mm.) No. 4.



IR SPECTRUM (LIQUID CELL, 0·05 mm.) No. 5.

The diketone (XI) on heating with one mole of pyrolidine azeotropically, furnished readily the α,β-unsaturated ketone (XII), which was first purified by passing through grade III alumina and eluting with petroleum ether and benzene mixture. It was then converted to its semicarbazone, crystallised once from alcohol, m.p. 140°C. This on regeneration on decomposition with oxalic acid furnished the pure α,β-unsaturated ketone (XII); b.p. 150-55° bath/1 mm; $(\alpha)_D$ - 44.2; λ_{max}^{EtOH} 242 (log ϵ, 4.17); $IR_{\lambda}^{(Nujol)}$ bands at 1681 cm^{-1} (conjugated ketone) and 1613 cm^{-1} (conjugated trisubstituted double bond). The NMR spectrum showed a singlet at 5.75δ, thus, showing an α-proton to carbonyl. The α,β-unsaturated ketone was then treated with MeMgI, wherein the Grignard reaction was initiated by iodine. It was worked up (see experimental) and passed through alumina (grade I), the diene obtained in pet.ether eluate. GLC analysis showed it to be 50:50 mixture of two compounds, most probably of homoannular and heteroannular dienes. This was found to be the case as by 'e' values in UV analysis. In the UV spectrum, it showed. λ_{max}^{EtOH} at 242 (ϵ, 11650) and 268 (ϵ, 3480). $(\alpha)_D$ + 64.5 The IR spectrum$_{\lambda}^{(Neat)}$ showed bands at 1667 cm^{-1} (for conjugated diene) and 1639 cm^{-1} (for methylenic double bond). The diene showed a tendency of aromatising slowly, when kept. Thus, the NMR spectrum

of the diene always showed the aromatic protons at 6.86δ. Further, the diene showed four broad bands at 4.58δ, 5.55δ (for protons present in heteroannular diene) and 5.8δ, 6.12δ (for protons present in homo-annular diene). There is also a broad singlet at 1.76δ due to a methyl group on a double bond.

In order to convert the diene (XIII) to calamenene, oxidation was carried out using selenium dioxide in acetic acid. After working it out and passing through grade I alumina, it showed the presence of two compounds in 50:50 ratio by GLC analysis in which the first peak agreed with natural calamenene. It was further purified by passing through silver nitrate impregnated silicic acid (10%) and the pet.ether eluate was found to contain two compounds in the ratio of 60:40 in which 60% (first peak) corresponded to the natural calamenene as shown by comparative GLC analysis. The separation of these was however found to be tedious and even then, the separation was incomplete. However, it was observed that after keeping the diene for longer time (10°C), some part of it aromatised and this aromatised compound was found to be identical with calamenene by comparative GLC analysis. The diene was therefore chromatographed over 10% silver nitrate impregnated silicic acid, three times to obtain pure calamenene free from the diene, b.p. 150-55°(bath)/3 mm.

It showed single peak in GLC analysis; $(\alpha)_D$ + 42°; IR bands at 1613 cm^{-1} and 838 cm^{-1} (for aromatic ring).

Discussion of the results

Since we have started with (-) menthone of $(\alpha)_D$ - 16.7°, one should expect a mixture of calamenenes (XIV) and (XV). It is very difficult to ascertain the % of th se compounds by GLC or TLC analysis as they showed a single component. It is also not possible to determine the percentage of these compounds, based mainly on optical rotation, since the optical rotation values in literature differ so widely and that too, the stereochemistry of these are not known. However, the NMR spectrum is of some use in this case. As already mentioned, we have the NMR spectrum of (+) calamenene, $(\alpha)_D$ + 82°; (-) calamenene, $(\alpha)_D$ - 80°; the calamenene obtained by lithioethyldiamine reaction on khusinol $(\alpha)_D$ + 0.82. For a thorough study we give the NMR spectrum data of the some calamenenes.

Table II

Nuclear magnetic resonance spectra for calamenenes

Functional group	Compounds			
	1	2	3	4
	δ value of hydrogen on naphthalene nucleus			
$\begin{matrix} & CH_3 \\ C & \\ H & CH_3 \end{matrix}$	0.73 (3H, d, J 7 c/s)	0.69 (3H, d, J 7 c/s)	0.78* (3H, d, J, 7 c/s)	0.77* (3H, d, J 7 c/s)
	0.98 (3H, d, J 7 c/s)	0.94 (3H, d, J 7 c/s)	1.02* (3H, d, J 7 c/s)	1.03 (3H, d, J 7 c/s)
$\begin{matrix} \\ CH\text{-}\underline{CH_3} \\ \\ \end{matrix}$	1.23 (3H, d, J 7 c/s)	1.23 (3H, d, J 7 c/s)	1.24 (3H, d, J 7 c/s)	1.23 (3H, d, 7 7 c/s)
$\phi\text{-}\underline{CH_3}$	2.24 (3H, s)	2.28 (3H, s)	2.28 (3H, s)	2.25 (3H, s)
Aromatic Protons	6.86 (3H, bm)	6.95 (3H, bm)	7.0 (bs) 6.94 (d)** (J 8 c/s) 7.04 (d)** (J 8 c/s)	6.87 (3H, bm)

bm = broad multiplet
bs = broad singlet
d = doublet
s = singlet

* other peaks also present
** assignment uncertain

(1) From Cedrela toona Roxb[2]
(2) Obtained from khusinol[8]
(3) From 7-hydroxy calamenene[9]
(4) Synthetic compound from (-) methone

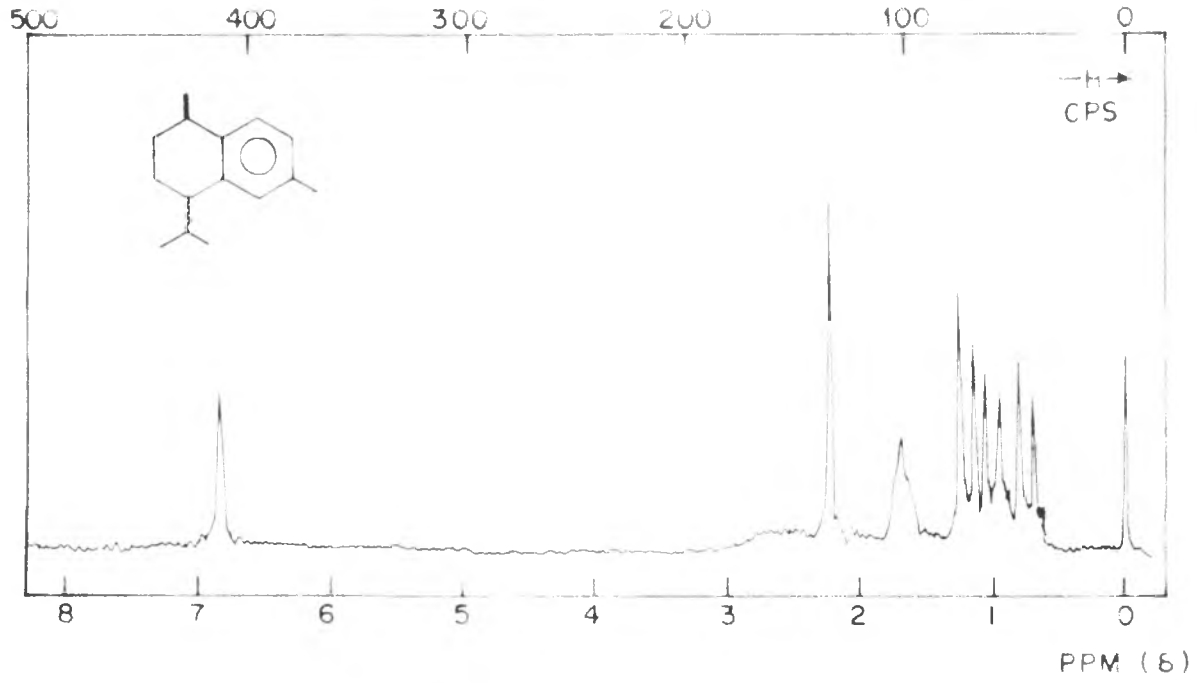
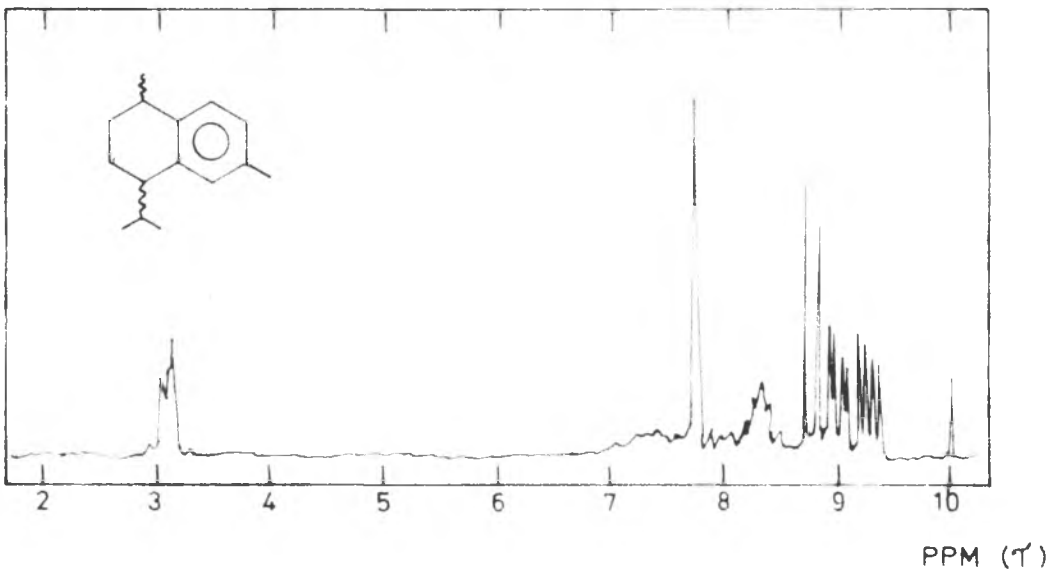


FIG. 1 NMR SPECTRUM OF CALAMENENE $(\alpha)_D$ + 42°



NMR SPECTRUM OF CALAMENENE $(\alpha)_D$ + 0·85°

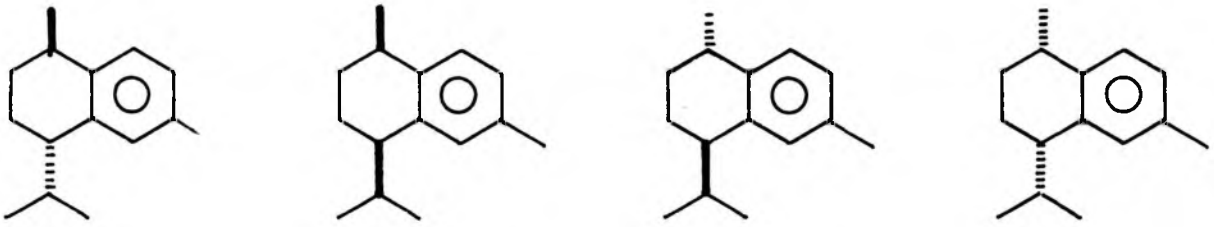
Discussion of the NMR results

As seen from the above table that, the isopropyl signals of the various calamenene differ slightly. The NMR spectrum of calamenene $(\alpha)_D$ + 0.82° clearly shows this difference since, it showed 8 signals due to the isopropyl group. A pure trans or cis isomer shows only 4 lines in the isopropyl region. This therefore, means that, one can distinguish between two isomers (cis or trans) with the help of NMR spectrum. The NMR spectrum of our synthetic (+) calamenene showed 4 signals centred at 0.776 and 1.036 with satellite signals at 0.715 and 0.986. The relative integrated area shows that, it is a mixture of two isomers roughly in a 80:20 ratio. However the NMR spectrum of (1) and (2), which have equal and opposite rotations, showed identical signals in the isopropyl region but whose signals more closely resembled to the satellite peaks of our synthetic calamenene. On the other hand, major peaks of our synthetic calamenene agreed more closely to the compound (3). Obviously, compound (3) also contained other signals too in that region, which certainly indicates that it (3) is a mixture in which, the major compound corresponds to our major compound but must be having equal and opposite rotation. Therefore, based on NMR data, we conclude that, our compound is a mixture of two isomers in a ratio of 80:20 and the signals

correspond to the signals of compound (3). On the other hand compound (1) and (2) have equal and opposite rotation, whose NMR signals correspond to the satellite peaks of our synthetic compound. Therefore (1) and (2) have opposite stereochemistry to that of the major compound present in the present synthesis.

Absolute stereochemistry

Since calamenene contains two asymmetric centres, it must exist in four isomeric forms as shown below.



XIV XV XVI XVII

As we started with (-) menthone, containing more than 80% of trans compound, it was expected that synthetic (+) calamenene must also contain 80% of trans compound. Therefore we assign the trans stereochemistry (XIV) to the major compound (80%) and cis stereochemistry (XV) to the minor compound (20%). This therefore gives the stereochemistry of natural (-) calamenene of $(\alpha)_D$ - 80°

as (XVII) and (+)-calamenene of $(\alpha)_D$ + 82° as (XV). (-) Calamenene of $(\alpha)_D$ - 47°, which has rotation almost opposite and equal to our synthetic mixture of $(\alpha)_D$ + 42°, must therefore be epimeric mixture of (XVI) and (XVII) containing 80% of the major compound (XVI). This therefore gives the rotation of (XIV) as + 35°.

EXPERIMENTAL

Oxidation of menthol to menthone VIII

50 g of menthol, $(\alpha)_D$ - 46°, was dissolved in 50 ml of acetone and Jones reagent was added dropwise to it, while cooling the solution. It was kept for one hour after the addition and poured into water (250 ml). It was extracted repeatedly with ether. Ether extracts were washed with dil. aqueous sodium bicarbonate and then with water. After drying and evaporating the solvent, the crude ketone (37 g) was distilled b.p. 100°C/20 mm; $(\alpha)_D$ - 16.7° (Found: C, 77.58; H, 11.58; $C_{10}H_{18}O$ requires C, 77.86; H, 11.76%).

Preparation of hydroxymethylene derivative of menthone (IX)

A suspension of dry powdered sodium methoxide (from 12 g of sodium) in dry benzene (100 ml) was treated with a solution of ethylformate (40 g) in benzene (100 ml) and the mixture cooled externally with ice. (-) Menthone (25 g, VIII), in benzene (50 ml) was added and the mixture allowed to stand for 48 hours at room temperature. The entire operation was carried out in nitrogen atmosphere and with mechanical stirring of the reaction mixture. Water (100 ml) was then added and the benzene layer repeatedly shaken with 5% aqueous sodium hydroxide (25 ml x 3). The combined aqueous

portions were shaken with ether, aqueous layer acidified with HCl (1:1) to pH 6 and the product taken in-to ether and dried over anhydrous sodium sulphate. After removal of the solvent, it was distilled at 110°/12 mm; yield 15 g.

Condensation of hydroxy methylene derivative (IX) with methylvinyl ketone

Preparation of diketoaldehyde (X)

To a mixture of hydroxymethylene derivative (IX 19 g) and freshly distilled methylvinyl ketone (25 g) was added trimethylamine (15 g) with stirring and cooling. The reaction mixture was cooled in ice bath for 1 hr and then allowed to stand at 25° for three days, after which, the unreacted methylvinyl ketone and trimethylamine were removed by distillation under reduced pressure and residue was dissolved in ether. The ethereal solution was washed successively with dilute HCl, dil.aqueous sodium hydroxide, water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave (24 g) crude product and used as such for further reaction.

Deformylation: preparation of diketone (XI)

To a solution of the diketoaldehyde (XI, 24 g) in 500 ml of ethanol was added a solution of 2% potassium carbonate solution (12 ml). The reaction mixture was heated at reflux for 24 hours under nitrogen atmosphere.

The solvent was removed under reduced pressure and the residue was dissolved in ether. The ether solution was washed with water, dried and evaporated to give a crude product, which was passed through alumina (Gr. III, 60 g) column. Pet.ether elute gave (20 g) compound. Distillation at 180-90°(bath)/2 mm afforded only (12 g) compound, $(\alpha)_D$ + 49.4°
(Found: C, 68.01; H, 7.74%. $C_{15}H_{24}O$ requires: C, 68.16; H, 7.63%). IR spectra (No.1) showed bands at 1700; 1476, 1389, 952, 896, 833, 813 and 787 cm^{-1}. It formed monosemicarbazone, m.p. 205°C. (Found: N, 15.1; $C_{15}H_{27}O_2N_3$ requires N, 14.93%).

To the above undistilled material (6.6 g), dry petroleum ether was added and a solid compound (XVI) separated after cooling it. Solid compound was separated by filteration and crystallised from petroleum ether and ether mixture; yield 1.6 g; m.p. 126°; $\alpha_D \pm 0$;
(Found: C, 71.44; H, 9.58; $C_{15}H_{24}O_4$ requires C, 71.39; H, 9.95%).

IR spectrum (No.2) showed bands at 3400 cm^{-1} 2900 cm^{-1} 1709 and 1695 cm^{-1}. Filtrate from the above filtration gave the same diketone (XI 4.7 g) after removal of the solvent.

Ether elute of the above chromatography furnished the solid compound (XVI).

Cyclisation of diketone (XI) to conjugated ketone (XII)

A mixture of pyridine (3 ml) and diketone (9 g) in benzene (500 ml) was refluxed for 24 hours using Dean Starks phase separating head. One mol water was collected. The mixture was cooled. A buffer solution made up of acetic acid (5 ml), water (5 ml) and sodium acetate (2.5 g) was then added to the cooled reaction mixture. Refluxing continued for another 4 hours separation of the two layer, extraction of the aqueous layer with benzene and washing the combined extracts with 10% hydrochloric acid and then with aqueous sodium carbonate gave (8 g) of the crude product. It was chromatographed over alumina (Gr.III, 160 g).

Fr.No.	Solvent	TLC spots	Wt. g
	Pet.ether (20 ml each)		
1	"	one	
2	"	"	
3	"	"	0.600
4	"	"	
5	"	"	
6	"	two	
7	"	"	Negligible
8	"	"	
9	"	one	0.600
10	"	one	0.300
	Pet.ether Benzene (50%)		
11	150 ml	one	2.4
12	100 ml	one	0.600
13	Benzene	two	0.300
14	Ether	two	0.300

Only fraction No.11 was found to be very pure by TLC analysis, b.p. 150°(bath)/1 mm; $(\alpha)_D$ - 28.1°; λ^{EtOH}_{max} 242 (ε, 11000). Further purification was done by preparation of its semicarbazone derivative. It was crystallised once from ethanol, m.p. 140°C. (Found: N, 15.64; $C_{15}H_{25}ON_3$ requires N, 15.96%). The α,β-unsaturated ketone was regenerated by decomposition with oxalic acid. The conjugated ketone (1.2 g) was distilled b.p. 155° bath/1 mm; $(\alpha)_D$ - 44.2° λ^{EtOH}_{max} 242 (ε, 15400); (Found: C, 81.45; H, 10.69. $C_{14}H_{22}O$ requires C, 81.50; H, 10.75%). IR spectrum showed bands at 2899, 1667, 1613, 1418, 1379, 1325, 1266, 1250, 1212, 1117, 1053, 957, 885, 836, 792 and 766 cm^{-1}.

Preparation of diene (XIII)

Grignard reagent was prepared from magnesium (1 g) and methyl iodide (3 g) and anhydrous ether (25 ml) (a little iodine added for activation of magnesium turnings). To the freezing mixture of Grignard solution the ketone (XII) dissolved in anhydrous ether (25 ml) was added slowly with mechanical stirring. The reaction mixture was kept in ice bath for 1/2 hour, then overnight at room temperature. It was cooled in ice bath and solid ammonium chloride added slowly to decompose the complex. It was extracted with ether, the ethereal layer washed with cold dil. sulphuric acid, aqueous

sodium bicarbonate, water and dried over anhydrous sodium sulphate. The residue (0.950 g) was obtained after removal of the solvent. It was chromatographed over alumina (Gr.I, 20 g). Pet.ether eluate furnished the hydrocarbon (0.800 g). It was distilled over sodium b.p. 160°(bath)/ 5 mm; α_D + 64.5°; (Found: C, 89.02; H, 9.5; $C_{15}H_{24}$ requires C, 89.2; H, 9.8%). GLC showed it to be a mixture of two components (50:50); UV spectrum ; λ_{max}^{EtOH} 242, 268 (ε, 11650, 3480). IR spectrum showed bands at 2899, 1689, 1653, 1466, 1389, 975, 909, 894 and 883 cm^{-1}.

dioxide

Selenium oxidation of diene (XIII) to (+) calamenene

A solution of 0.200 g of diene (XIII) in acetic acid (10 ml) was refluxed with freshly sublimed selenium dioxide (0.085 g) for 5 hours in a current of nitrogen. After filteration of selenium it was poured into water and extracted with ether. The ether extract was thoroughly washed with water and dried over anhydrous sodium sulphate. The reddish coloured crude product was filtered through a short column of alumina (Gr. I) and eluted with pet.ether. It has b.p. 150-55(bath)/3 mm. GLC showed it to be a mixture of two compounds (50:50). It was then rechromatographed over silvernitrate impregnated silicic acid (10%, 5 g). Pet.ether fractions were collected. Even after laborious collection of

fractions it was not possible to separate these compounds. Only we achieved to get a mixture of these compounds in 60:40 ratio. GLC analysis showed that peak corresponding to 60% belongs to natural calamenene. One can however get pure calamenene by repeated chromatography over silver nitrate impregnated silica gel. However, the following method seems to be better.

Air oxidation

The diene (XIII, 120 g) was kept for nearly two months at (10°C), in order to affect air oxidation. Chromatographed over silver nitrate impregnated silicic acid (10%, 5 g) and petroleum ether fractions were collected. Like this, chromatography was repeated for three times to get rid of diene. The petroleum ether eluate of the final chromatography showed one peak in GLC analysis. b.p. 155°(bath)/3 mm; $(\alpha)_D$ + 42°. (Found: C, 89.3; H, 10.02; $C_{15}H_{22}$ requires C, 89.1; H, 9.9%). IR spectrum showed bands at 1901, 1748, 1613, 1493, 1449, 1163, 1111, 1042, 892, 833 and 769 cm^{-1}.

REFERENCES

1. W. Treibs, Ber., 530, 82 (1949).

2. V. Herout, F. Sorm and Veres, Coll.Czech.Chem. Comm., 106, 18 (1953).

3. P. De Mayo, R.E. Williams, G. Buchi and S.H. Pearlhelier, Tetrahedron, 619, 21 (1965).

4. B.A. Nagasampagi, Ph.D. Thesis, Poona University, page 151 (1965).

5. F.Vonasek, V. Herout and F. Sorm, Coll.Czech.Chem.Comm. 919, 25

6. J. Runenberg, Acta.Chem.Scand. 721, 15

7. L. Westfelt, ibid, 284, 20

8. S. Hayashi, N. Hayashi, K. Yano, M. Okano and T. Matsura, Bull.Chem.Soc. Japan, 234, 41 (1968).

9. O. Motl, M. Romanuk and V. Herout, Collection, 2025, 31 (1966).

10. S. Nagahawa, Bull.Chem.Soc.Japan, 1029, 37 (1964).

11. A.S. Rao, K.L. Surve, K.K. Chakravarthi and S.C. Bhattacharyya, Tetrahedron, 233, 19 (1963).

12. G.K. Trevadi, A.D. Wagh, S.K. Paknikar, K.K. Chakravarthi and S.C. Bhattacharyya, ibid., 1641, 22 (1966).

13. M. Frachebond, J.W. Rowe, R.W. Scott, S.M. Panega, A.J. Buhl and J.K. Todd, Forest Products Journal 37, 13 (1968).

14. B.N. Joshi, R. Seshadri, K.K. Chakravarthi and S.C. Bhattacharyya, Tetrahedron, 2911, 20 (1964).

15. E.J. Corey and S. Nozoe, J.Am.Chem. Soc., 5723, 87(24) (1965).

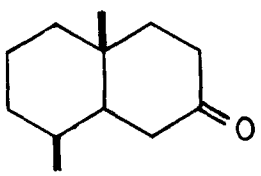
16. Application of NMR spectroscopy in organic chemistry by N.S. Bhacca and D.H. Williams, 1964.

Part B

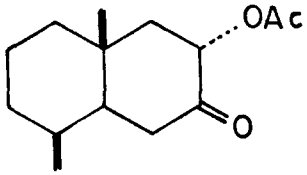
Transformation Products of Eudesmol
Synthesis of Lactone of
8 – α – hydroxy eudesm – 7 (11)–ene - 13 - oic acid

SUMMARY

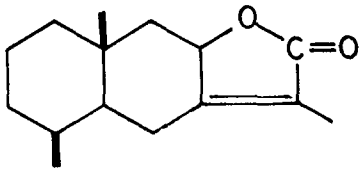
Starting from dihydroeudesmol, 8∝-hydroxy-eudesm-8-(11)-en-13-oic acid has been synthesised. The reaction scheme involves the action of lead tetraacetate on trans-4,10-dimethyl decalene-7-one (1) to give trans-4,10-dimethyl decalene-7-one 8-(∝)-acetate (2), which on Reformatsky reaction with ∝-bromopropoinic ester, followed by hydrolysis and dehydration, gives the 8∝-hydroxy-eudesm-8-(11)-en-13-oic acid (3).



1



2

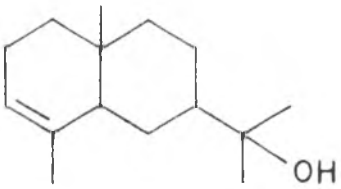


3

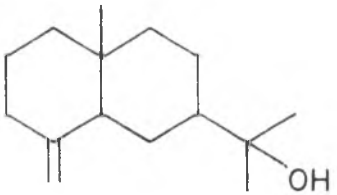
The structure of eudesmol (α and β) (Chart I)

Eudesmol, $C_{15}H_{26}O$, a bicyclic sesquiterpenic alcohol was first isolated by Baker and Smith[1a] from the oil derived from Eucalyptus piperita[1b]. It has also been found to occur in various other eucalyptus oils. It has m.p. 82-83° and $(\alpha)_D$ + 31.3°. Previously it was considered to be an oxide having the formula $C_{10}H_{16}O$, by Smith[1a], which was later found to be incorrect. Eudesmol is an alcohol, having the formula $C_{15}H_{26}O$, and containing one ethylenic linkage. This was confirmed by Semmelar and Tobias[2]. Acetylation of eudesmol gave eudesmol acetate, b.p.165-170°/11 mm., $(\alpha)_D$ + 31°. Catalytical hydrogenation furnished dihydro-eudesmol, $C_{15}H_{20}O$ m.p. 84-85°. Eudesmol gave eudalene on dehydrogenation with sulphur; thus proving the relative position of fourteen of the fifteen carbon atoms present in the alcohol[3a]. The nature of the ethylenic linkage in eudesmol was proved by preparing the dihydrochloride, by treating with hydrogen chloride, either in acetic acid, or ether solution. The dihydro-chloride, m.p. 74-75°, $(\alpha)_D$ + 20°, was identical with selinene dihydrochloride, described by Schimmel and Co.[3b] This suggests that eudesmol may be represented by (I), (II) or (III). The position of the alcoholic group was determined by carrying out hydrogenation of eudesmol to

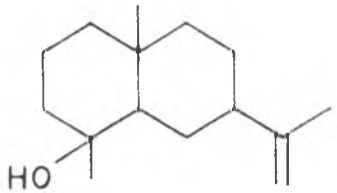
CHART I



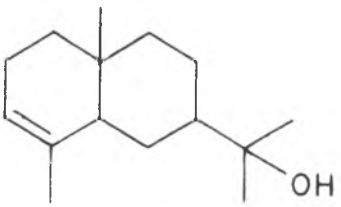
I



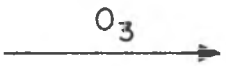
II

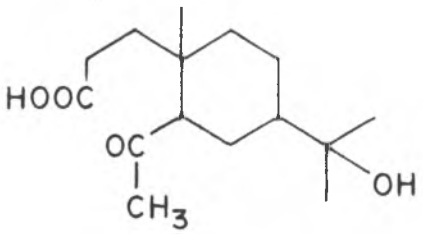


III

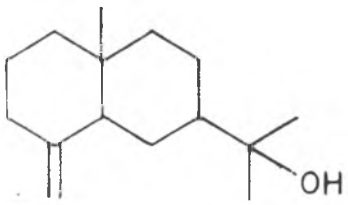


I

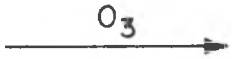


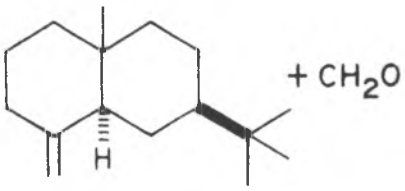


IV

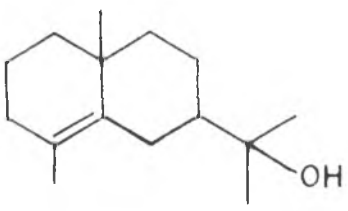


II





V



VI

dihydroeudesmol. The dihydro compound on treatment with hydrogen chloride, followed by dehydrohalogenation, furnished dihydroeudesmene, which on ozonolysis, yielded 3-acetyl-5,9-dimethyldecalin, with the elimination of one carbon atom. These results can be explained only if eudesmol is represented by (I) or (II). Finally these observations were confirmed by carrying out ozonolysis experiment. Eudesmol (I), on ozonolysis, gave two products: (A) hydroxy keto acid (IV) and (13) hydroxy ketone (V). The characterisation of these two products confirmed that eudesmol is a mixture of double bond isomers namely α-eudesmol (I) and β-eudesmol (II). Mcquillin[4] in 1956 succeeded in the isolation of a third isomer, γ-eudesmol (VI), from the natural source.

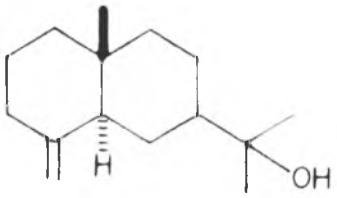
Absolute configuration of eudesmol (Chart II)

Configuration at C_{10} and C_5

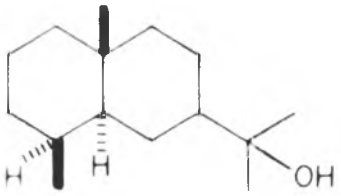
Ruzicka et al.[5], through comparative molecular refraction studies considered that selinenes belong to cis rather than trans decaline types. This was further supported by Plattener and co-workers[6]. Later Barton[7] reinterpreted the results of Plattner et al. and arrived at the conclusion that they belonged to trans-decaline system. Accordingly if β-eudesmol is represented as (II), then dihydroeudesmol should be represented as (VII). Further, they proved that the acid obtained by Plattner et al.[6]

CHART II

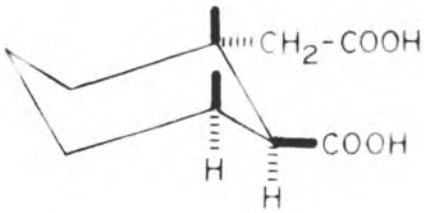
ABSOLUTE CONFIGURATION OF EUDESMOL



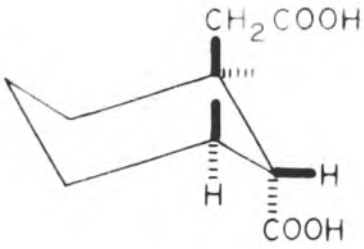
I



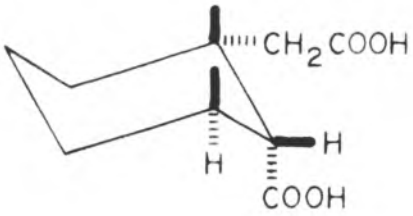
VII



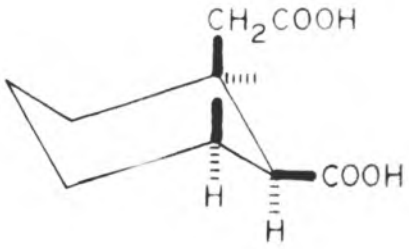
VIII



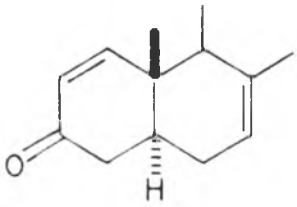
IX



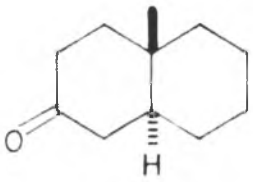
X



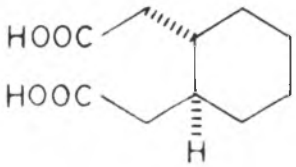
XI



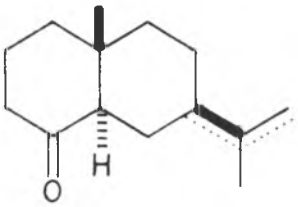
XII



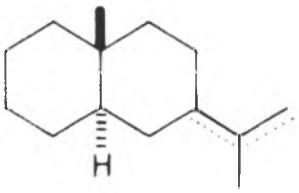
XIII



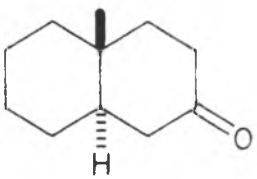
XIV



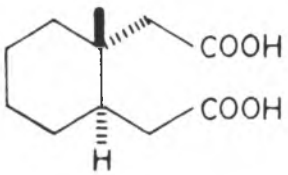
XV



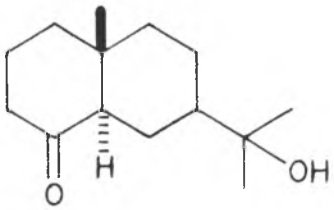
XVI



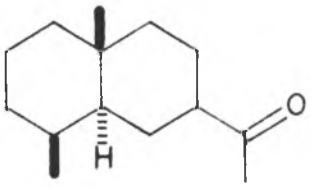
XVII



XVIII



XIX



XX

must have either conformation (VIII) or (IX). In both the cases, isomerisation of the secondary carbonyl would give, more stable conformation (X) or (XI).

Thus the evidences about cis fusion rings, as suggested by Plattner, Furst and Hellerbeck are found to be more favourable for the trans fusion rings.

Klyne[8], in 1953, came to the same conclusion by comparing the molecular rotational differences for the pairs of α-eudesmol/dihydroeudesmol and α-selinene/tetrahydroselinene with Δ^3-cholestene/cholestane.

Later, Woodward[9] and co-workers by a direct stereochemical correlation of β-eudesmol, with steroids, established that the angular methyl group at C_{10} in eudesmol is β-oriented. They prepared two reference compounds, viz. the trans-9-methyl, 3-decalone (XIII) and a dicarboxylic acid (XIV) from a laevorotary bicyclic ketone (XII), a compound derived from the natural steroids. Further, they prepared an unsaturated ketone (XV) from β-eudesmol (II) by ozonisation followed by dehydration which on Wolf-Kishner reduction gave an unsaturated hydrocarbon (XVI), chromic acid oxidation of which furnished trans-9-methyl-3-decalone (XVII) and a diacid (XVIII). The IR spectrum of the diacid (XVIII) was identical with that of acid (XIV). The ketone (XVII) and the diacid (XVIII), prepared from β-eudesmol are the enantiomers of (XIII) and (XIV), thus suggesting the

β-configuration for the C_{10} methyl group in eudesmol.

Further evidence to the trans ring juncture has come from Birch and Mostyn[10], wherein they have prepared a keto alcohol (XIX) by oxidation of β-eudesmol (II), which was found to be stable to acids or alkali.

Configuration at C_7

Dihydroeudesmol (VII) was converted to the ketone (XX) in two steps. The ketone so obtained was unaffected by alkali[9] indicating the C_7 hydroxy isopropyl group in the stable equatorial configuration. Also it should be β, since the ring juncture is trans with β-C_{10} methyl.

The final confirmation of the structure of β-eudesmol (II) came from the stereospecific synthesis of β-eudesmol[11a,b] and γ-eudesmol have been reported[12,13].

Most of the natural products belonging to eudesmol group have been converted to the derivatives of eudesmol There are, however, very few examples reported in the literature, where eudesmol or its derivatives have been related to the natural products or their derivatives. A brief resume of such correlations is given below, (Chart III).

Transformation of eudesmol (Chart III)

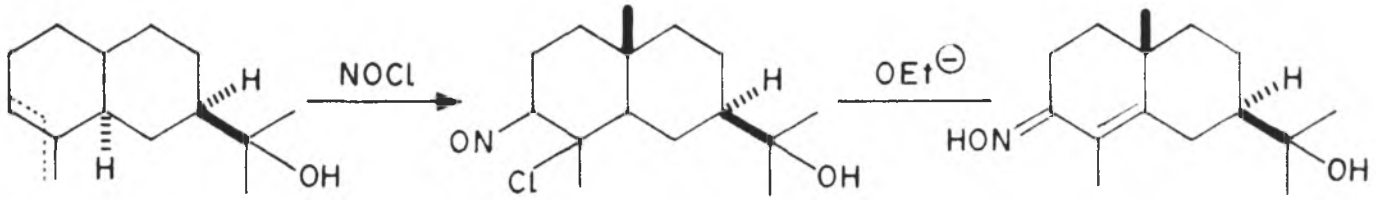
(A) Eudesmol to carissone and cyperone

In eudesmol series Ayer and Taylor[14] have synthesised carissone by treating eudesmol mixture (α and β) with

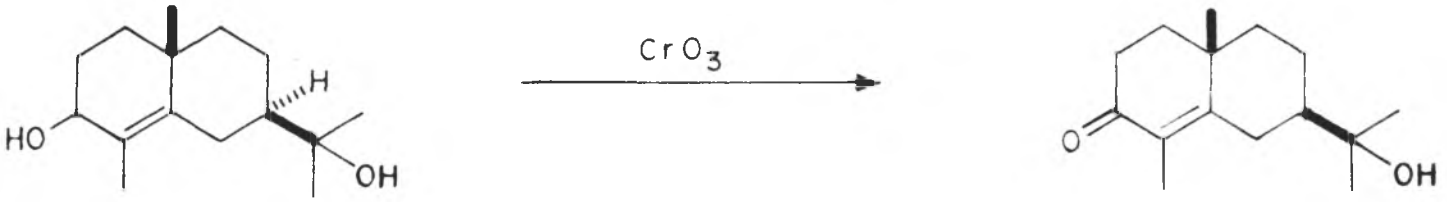
CHART III

TRANSFORMATION OF EUDESMOL

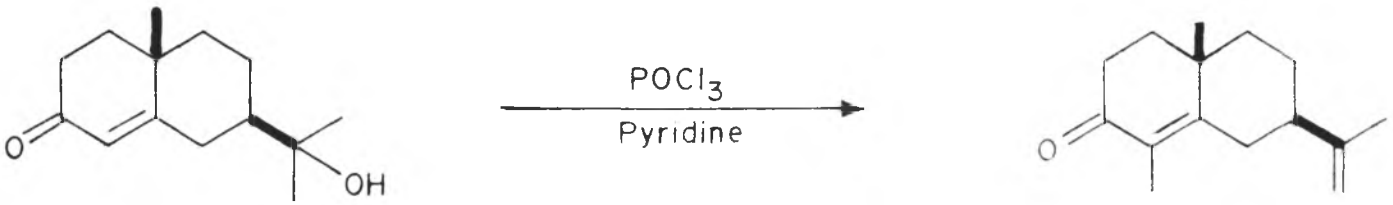
(A) EUDESMOL TO CARISSONE AND CYPERONE



I + II

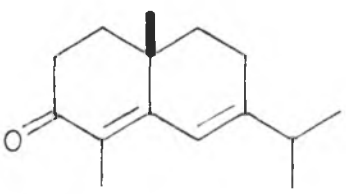


XXI



XXII

or



XXIII

nitrosyl chloride. The nitrosyl chloride was dehydrochlorinated, with sodium ethoxide to the oxime of carissone, which was obtained as an oil. Conversion of the oxime to the corresponding 2,4-dinitrophenylhydrazone, however, gave a crystalline product identical with carissone-2-4-dinitrophylhydroazone, from which carissone (XXI) was obtained by reaction with pyruvic acid. Carissone itself was obtained when eudesmol was subjected to successive oxidations with selenium dioxide and chromium trioxide as shown by Barton[15] et al., that carissone can be dehydrated to give either α-cyperone (XXII) or β-cyperone (XXIII).

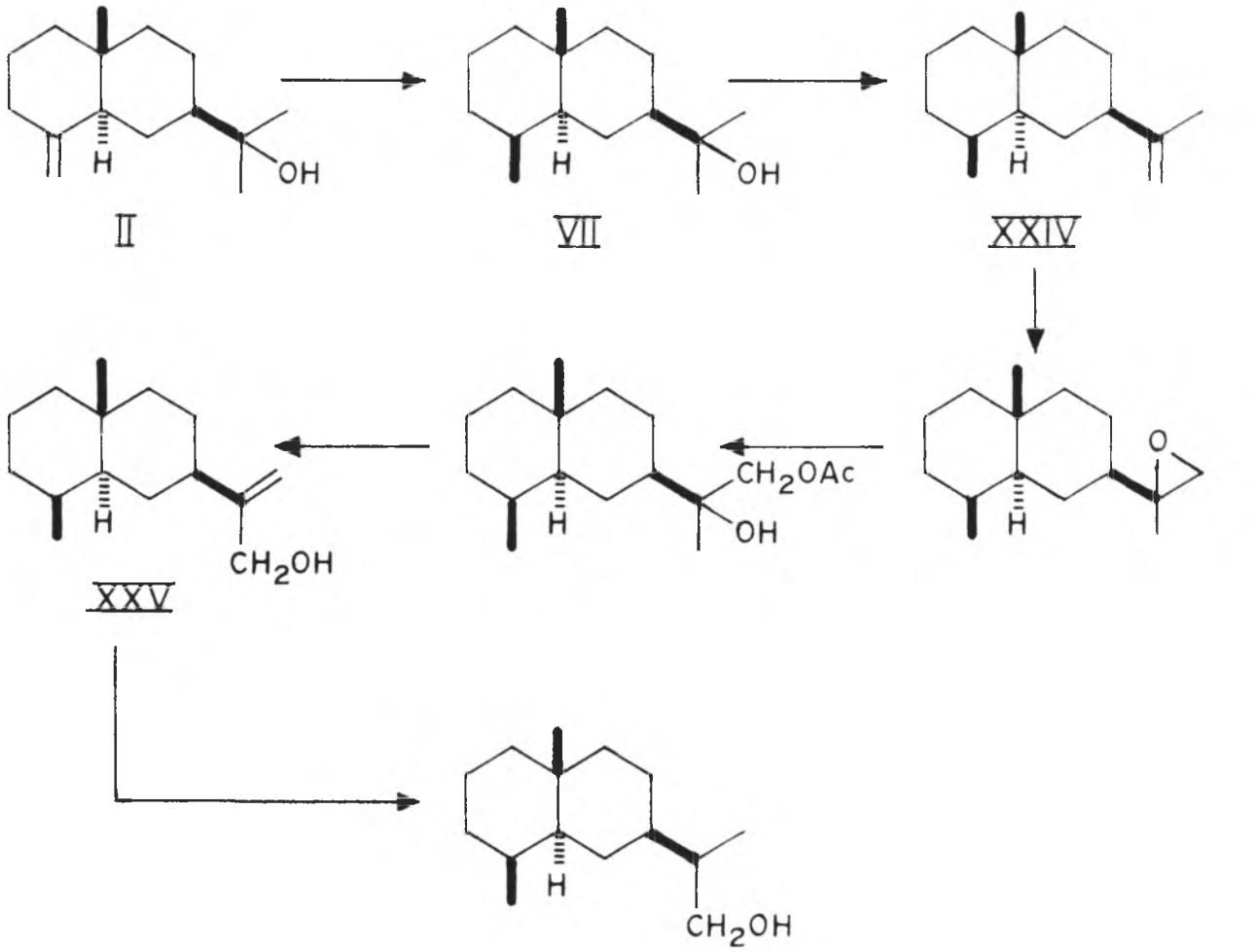
(B) Eudesmol to dihydrocostol, tetrahydrocostol, tetrahydrocostic acid and santonolide 'c'

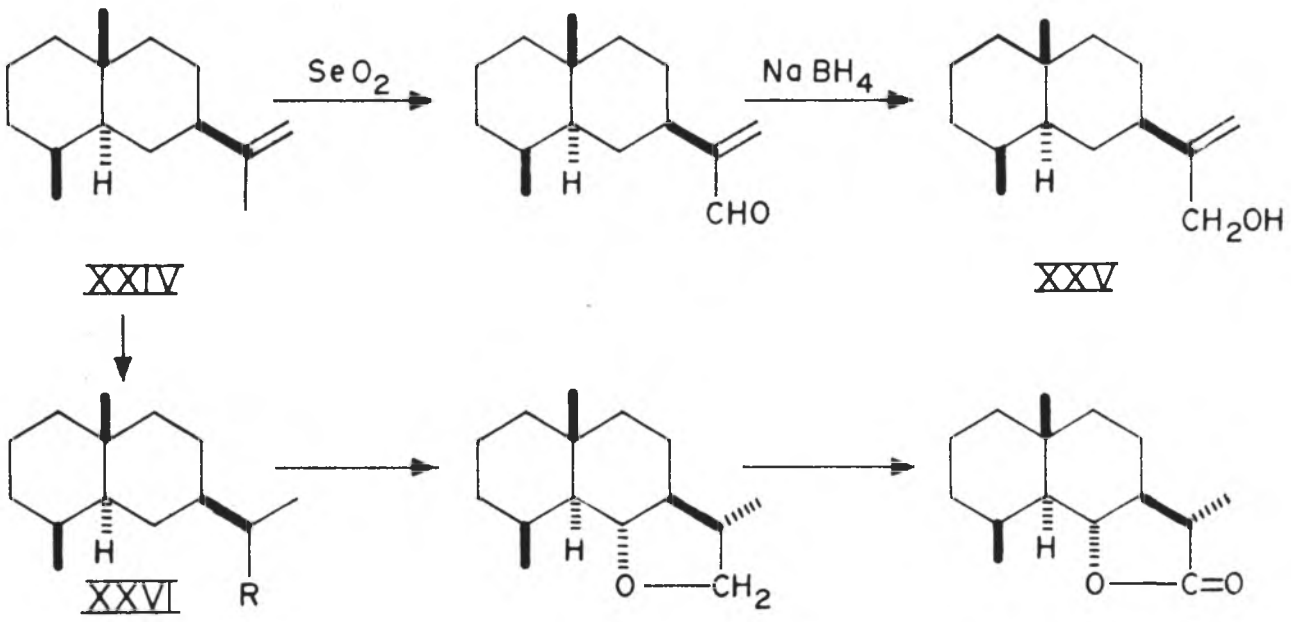
The above conversions have been reported in this laboratory by Battacharyya and co-workers[16,17,18].

Dihydroeudesmol (VII) on pyrolysis via its benzoate, gave dihydro-β-selinene (XXIV). Its epoxy derivative was converted to the epoxy hydroxy acetate on treatment with acetic acid. The benzoate of the hydroxy acetate on pyrolysis followed by saponification afforded dihydrocostol (XXV), which is further converted to tetrahydrocostol (XXVIa) by hydrogenation. On the other hand, Kadival et al.[17] obtained dihydrocostol (XXV) by selinium dioxide oxidation of dihydro-β-selenine (XXIV), followed by reduction with sodium borohydride.

CHART III (Contd.)

(B) EUDESMOL TO DIHYDROCOSTOL, TETRAHYDROCOSTOL TETRAHYDROCOSTIC ACID AND SANTONOLIDE 'C'





(a) R=CH_2OH, (b) R=CHO

(c) R=COOH

They have also prepared[18] tetrahydrocostol (XXVIa) via hydroboration oxidation of dihydro-β-selinene (XXIV), and converted it to tetrahydrocostal (XXVIa) and tetrahydrocostic acid (XXVIc), with Jones reagent. This conversion independently established the structure and stereochemistry of costic acid and costol; the natural products isolated from costus root oil in our laboratory[19].

Lead tetraacetate oxidation of tetrahydrocostol (XXVIa) in benzene medium, furnished an oxide, which on chromic acid oxidation, gave santanolide 'c'[18] (XXVII), as one of the products, which is a key compound for establishing the stereochemistry of many selinanic compounds.

(C) Eudesmol to cryptomeridiol

β-Eudesmol (II) has been converted[20] to the epoxide (XXVIII), by monoperphthalic acid, which on reduction with lithium aluminium hydride, gave cryptomeridiol (eudesm 4,11-diol) (XXIX).

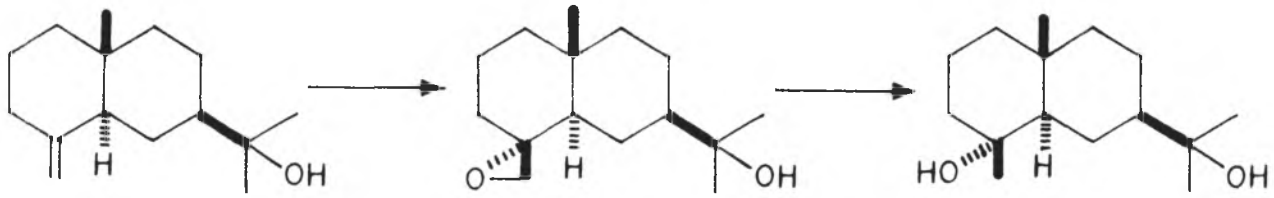
(D) Eudesmol to tetrahydroalantalactone and dihydrojunenone

Conversion of eudesmol to tetrahydroalantalactone and dihydrojunenone has been reported by Joshi et al. in this laboratory[18].

Dihydroeudesmol (VII), a hydrogenation product of eudesmol (I) and (II), on dehydration with perchloric

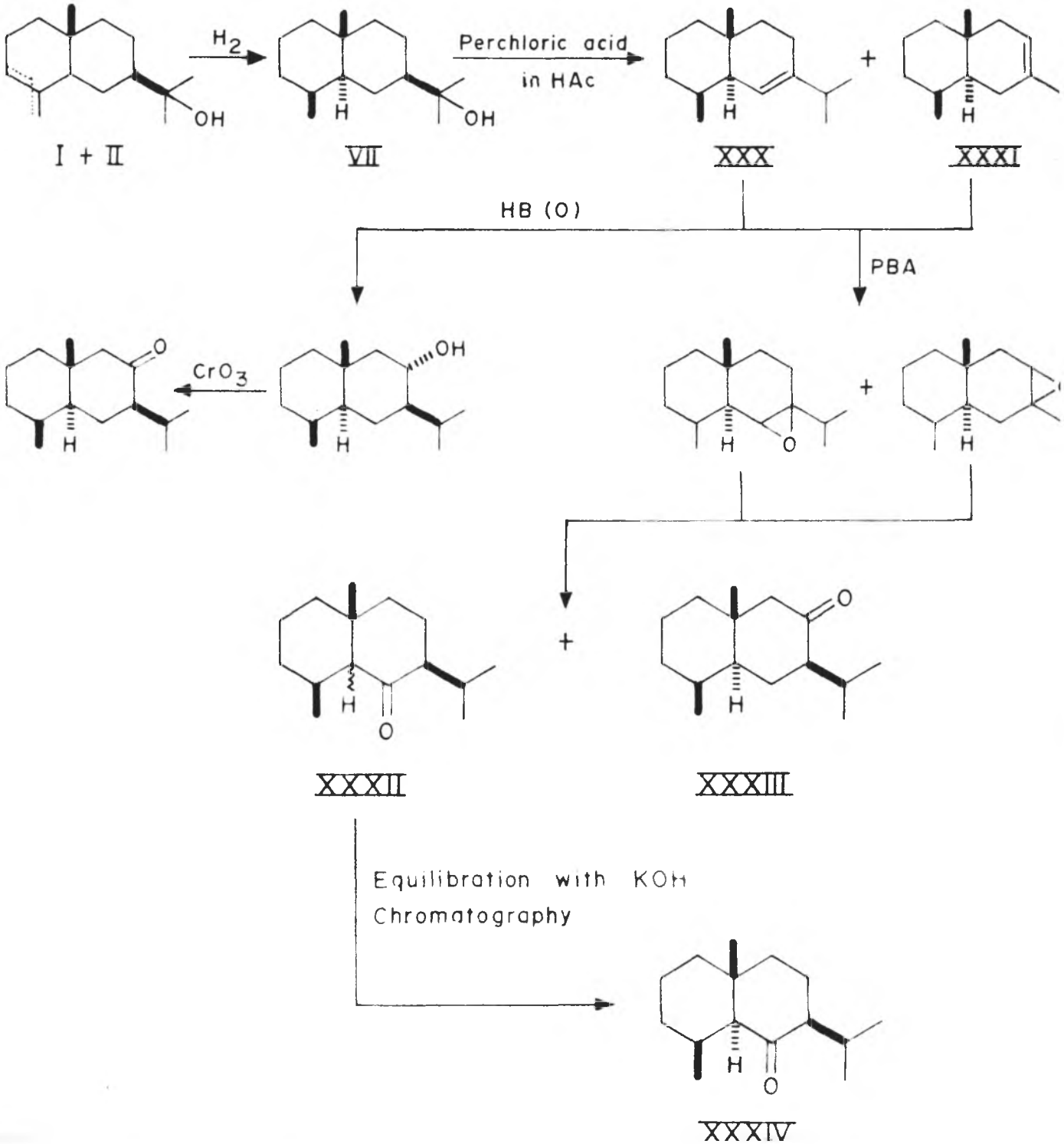
CHART III (Contd.)

(C) EUDESMOL TO CRYPTOMERIDIOL (EUDESMAN-4-11-DIOL)



XXVIII XXIX

(D) EUDESMOL TO TETRAHYDRO-ALANTA-LACTONE AND DIHYDROJUNENONE



I + II VII XXX XXXI

XXXII XXXIII

XXXIV

acid, in acetic acid, resulted in a mixture of hydrocarbon (XXX) and (XXXI). Epoxidation and borontrifluoride treatment gave a mixture of ketones (XXXII) and (XXXIII), which were separated by formation of semicarbazone of (XXXIII). Equilibration of the mixture of the ketones with alkali, followed by intensive chromatography, as described by Theobald[21] gave pure (+)-dihydrojunenone (XXXIV). Further, Theobald[21] converted dihydrojunenone to dihydrojunenol, a derivative of the natural product junenol.

The ketone (XXXIII) was also obtained by hydroboration-oxidation of hydrocarbon (XXXI), followed by oxidation with Jones reagent. This was reduced with LAH to obtain β-hydroxy-eudesman (XXXV). The β-alcohol, (XXXV) on treatment with lead tetraacetate in benzene, gave mixture of oxides (XXXVI) and (XXXVII), which on chromic acid oxidation gave a mixture of lactones (XXXVIII) and (XXXIX) from which tetrahydroalantalactone (XXXIX) was separated by chromatography.

(E) Eudesmol to Neo-intermedeol[22]

Ozonolysis of β-eudesmol in ethylacetate gave the ketoalcohol (XL), which was converted to the keto-acetate (XLI). Pyrolysis of (XLI) at 400°C gave the unsaturated ketone (XLII), which on treatment with methylmagnesium iodide gave neo-intermedeol (XLIII) identical in all respect with natural compound.

(F) Eudesmol to selin-11-en-4α-ol[23] and junicamphor

Selin-11-en-4α-ol (XLVI) is a enantiomer of junipher camphor (XLVII) and has been synthesised by Chetty et al.[24], starting with eudesmol mixture (I + II). Mixture of two epoxides (XLIV) and (XLV) were obtained, by heating eudesmol mixture with m-chloroperbenzoic acid and dehydrating with phosphorous oxychloride in pyridine in the ratio of 1:1. Reduction of the mixture of these epoxides with LAH, followed by chromatography gave a 1:1 ratio selin-11-en-4α-ol (XLVI) and junicamphor (XLVII). Selin-11-en-4α-ol (XLVI) was identical in all respect to the naturally occurring active selin-11-en-4α-ol. Synthetic junicamphor was identical to (±)-junicamphor (except optical rotation). Synthetic one gave (-) plane ORD curve whereas natural gave (+) plane ORD. Thus they are enantiomorphic to each other. The transformation definitely established that the ring juncture is trans and not cis as originally given by Bhattacharyya.

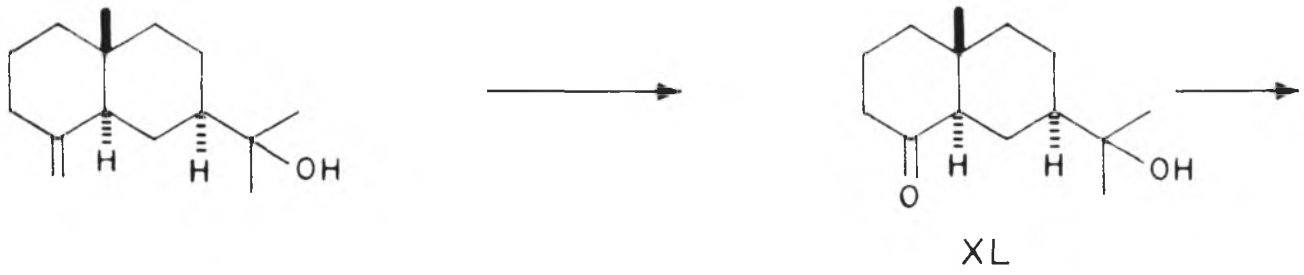
Eudesmol to isomeric tetrahydroalantalactone

This lactone is related to atractylon[25] a natural compound isolated from the rihizome of Manchurian atractylodes and rihizomes of A. Joponica, as shown in (Chart III).

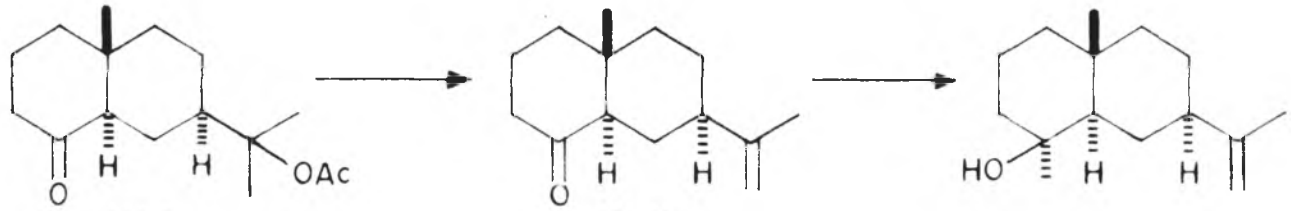
Atractalyon (XLVIII) on autooxidation gave two products (XLIX) and (XLX). The product (XLIX) on

CHART III (Contd.)

EUDESMOL TO NEO-INTERMEDOL

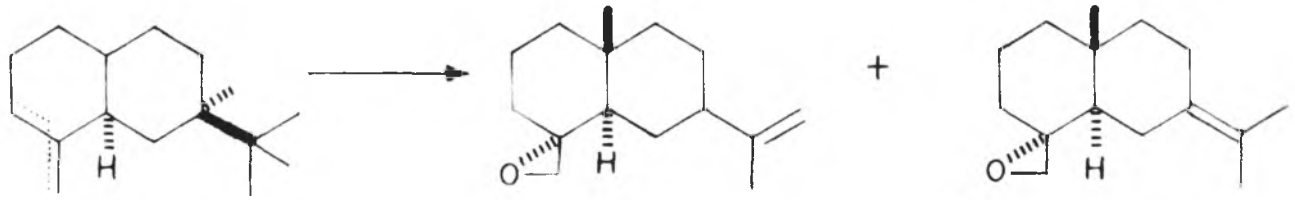


XL

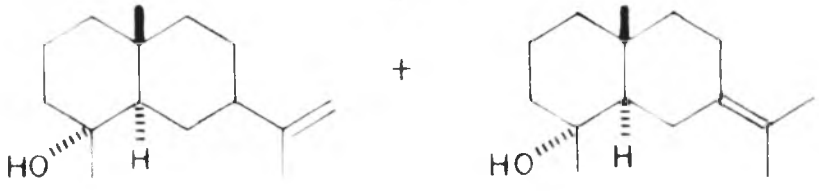


XLI XLII XLIII

EUDESMOL TO SELIN-11-EN-4α-OL AND JUNICAMPHOR



I + II XLIV XLV



XLVI XLVII

CHART III (Contd.)

ATRACTYLONE TO ISOMERIC TETRAHYDROALANTALACTONE

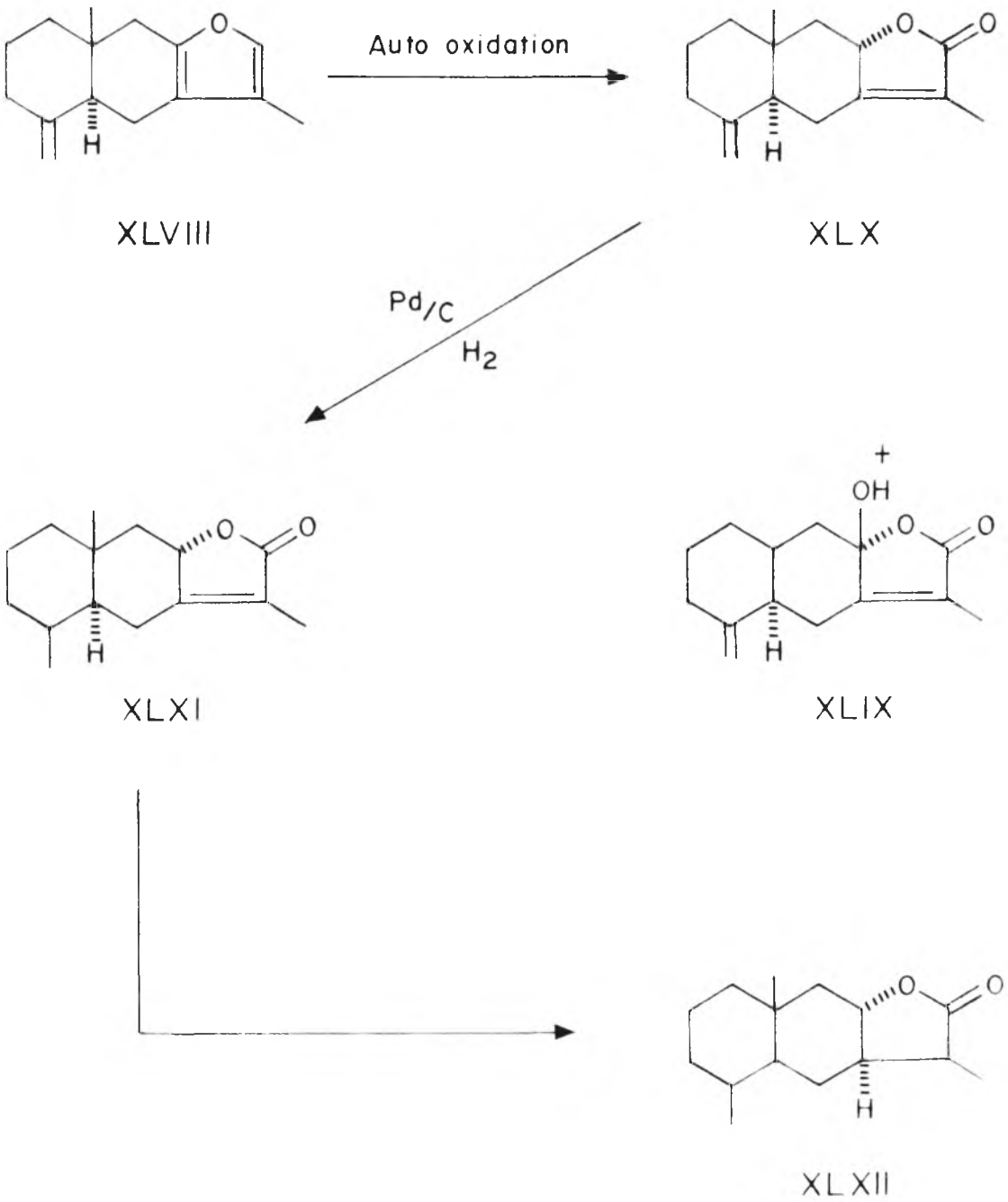


CHART III (Contd.)

SYNTHESIS OF ISOMERIC TETRAHYDROALANTALACTONE

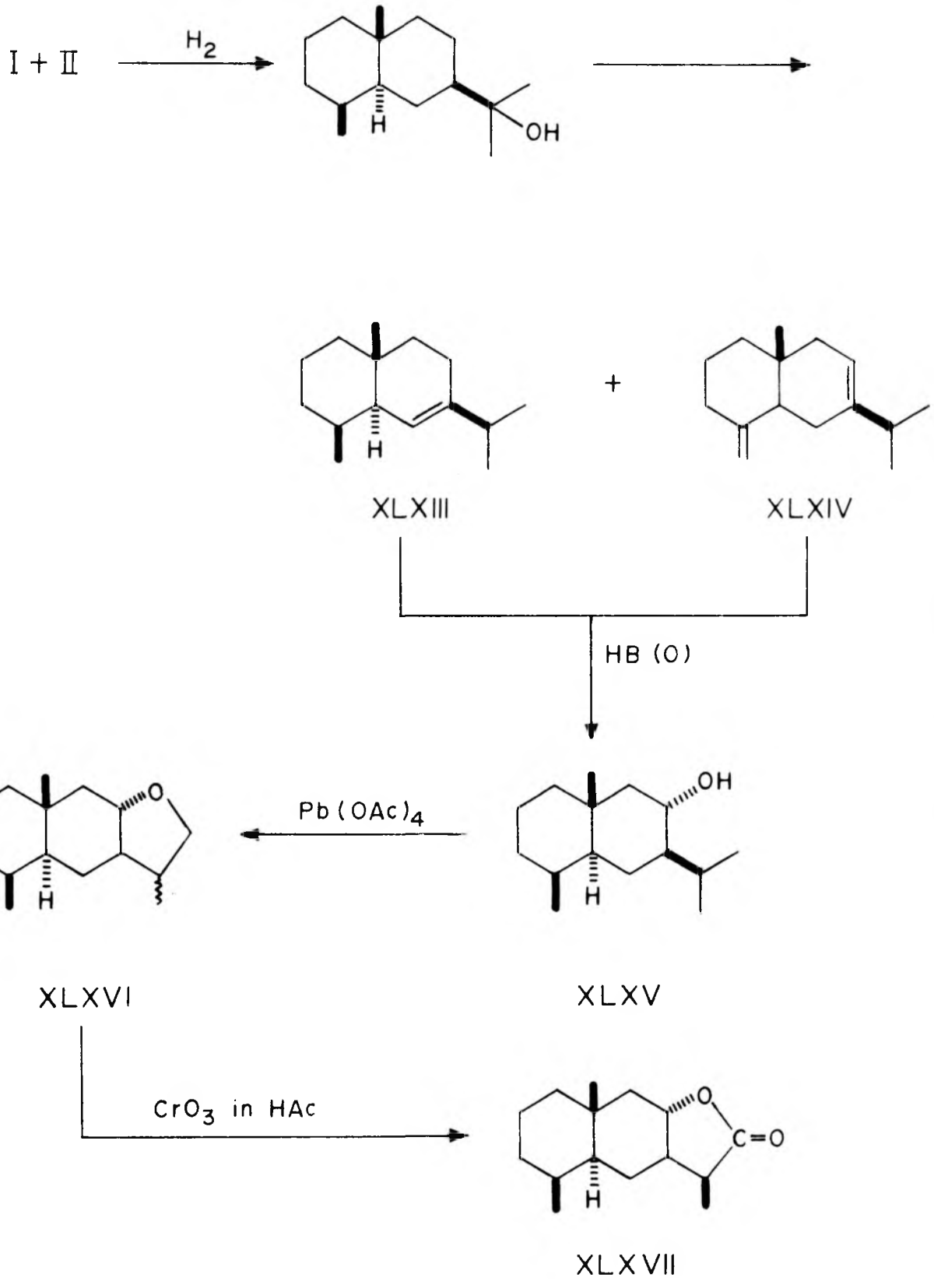
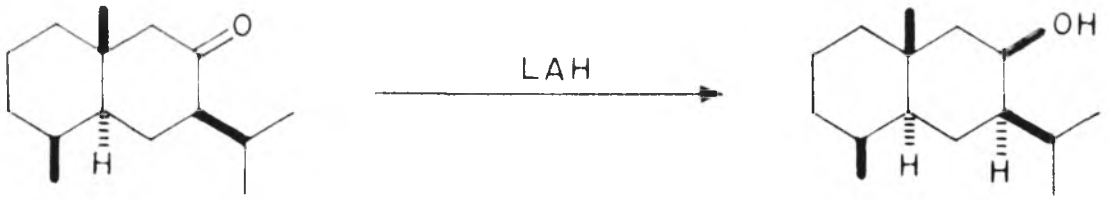
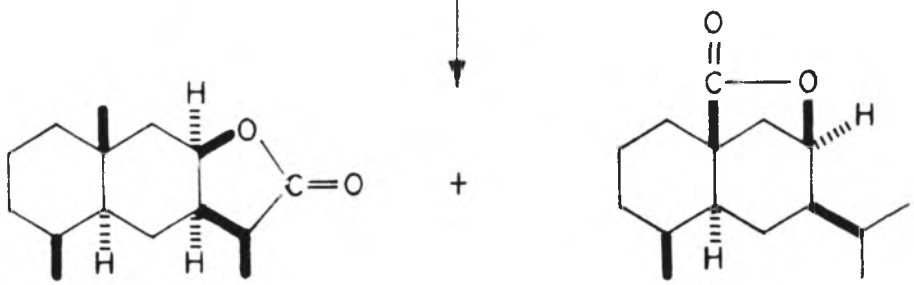


CHART III (Contd)



XXXIII XXXIV

XXXVI XXXVII



XXXIX XXXVIII

hydrogenation with 5% Pd/C gave (XLXI). This on reduction gave isomeric tetrahydroalantalactone (XLXII). The synthesis of above lactone starting from santonin and tetrahydroalantalactone has been reported by Cocker et al.[26] and Tsuda et al.[27] respectively. This isomeric lactone has been synthesised recently in our laboratory by Welankiwar et al.[28], following the procedure of Joshi et al.[18]

Dihydroeudesmol (VII), was dehydrated with perchloric acid in acetic acid. A mixture of unsaturated hydrocarbons (XLXIII) and (XLXIV), were obtained, which of hydroboration-oxidation gave 8α-hydroxy eudesman (XLXV). On subjecting this alcohol (XLXV) to lead tetraacetate oxidation, an oxide mixture (XLXVI) was obtained. When the mixture as such was subjected to oxidation with chromic acid in acetic acid gave two compounds on the lactone (XLXVII) was obtained as gum by chromatography over silicic acid. This lactone did not solidify inspite of the attempts confirming the observation of Cocker[26]. But the optical rotation was in agreement with rotation given by Tsuda[27], who obtained the same lactone in solid form, m.p. 77-78°.

Aim of the present investigation

As mentioned above isomeric tetrahydro alantalactone (XLXVII) was synthesised by Welankiwar et al.[28] in order to correlate it to the natural products atractylon and this lactone was obtained as a gum in agreement with the results of Cocker et al.[26] and the IR spectrum and rotation agreeing with that of Tsuda et al.[27] Attempts to get this lactone in crystalline form was however unsuccessful. So it was inferred by Welankiwar et al. from the NMR spectrum in two solvents viz. carbon tetrachloride and benzene, that it may be epimeric mixture at C_{11}. Since we could not get an authentic sample of this lactone for comparative studies (particularly NMR study to ascertain the stereochemistry of C_{11}-methyl group), we undertook the synthesis of the lactone of 8α-hydroxy-8-(11)-ene-13-oic acid (butenoid) whose stereochemistry is as depicted in (XLX)[25] and whose reduction product with sodium and amalgum has been reported to give lactone (XLXII, Chart III or Chart IV) having m.p. 108-9°C. Further our continued interest in correlating natural products belonging to eudesman group, starting from eudesmol to derivatives derived from natural products prompted us to synthesise this compound, which is related to atractylone; thus giving another route for establishing the stereochemistry of butenoid and its correlation with atractylone.

Present Synthesis

Synthesis of 8α-hydroxy-eudesm-7-(11)-en-13-oic acid (Chart IV)

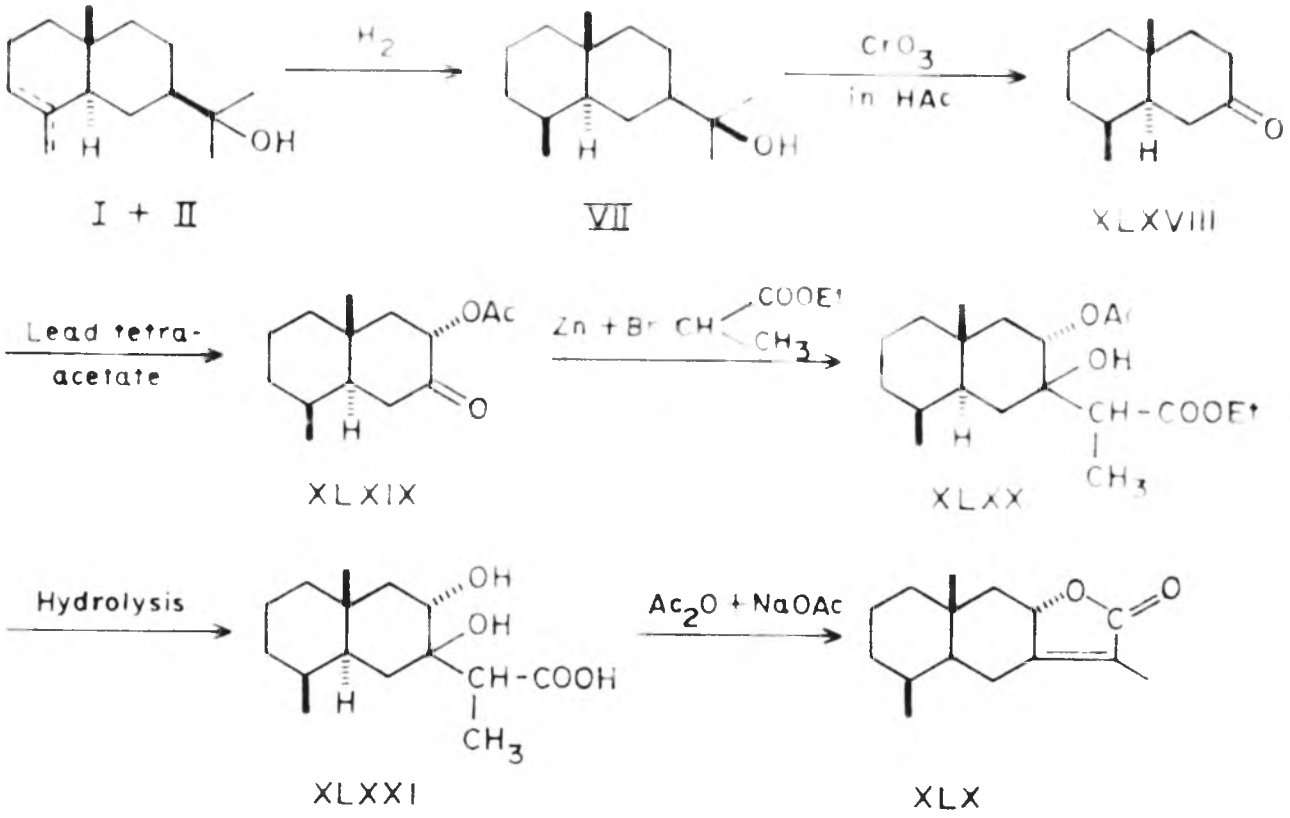
Dihydroeudesmol (VII) was oxidised with chromic acid in acetic acid to the trans 4-10-dimethyl-decalene-7-one (XLXVIII), according to the method of Ruzicka et al.[29] The IR spectrum (No. 1) indicated bands at 1724 cm^{-1} for a cyclohexanone system. It was purified through its semicarbazone derivative (m.p.220°C). It has b.p. 140-50°/3 mm and showed a single component by GLC and TLC analysis; $\alpha_D \pm 0$.

It has been reported that (see Chart IV), the reduction of keto-acid (XLXXIV) with sodium and isopropyl alcohol gives a hydroxy acid (XLXXV) in addition to a small amount of isomeric tetrahydroalantalactone (XLXII, m.p. 108-109), along with the product obtained previously by the sodium-amalgum reduction of butenoid[30]. Such reduction affords predominantly equitorial hydroxyls. This proves that the stereochemistry of butenoid is as represented in (XLX). This can also be proved by the fact that atractylon slowly auto-oxidised (Chart III) to give two compounds (XLX AND XLIX), and dihydro-derivative of (XLX) was prepared and compared with butenoid[31]. Since Tanabe[31] has shown that reduction of the lactone (XLXI) gave the saturated lactone of stereo-formula (XLXII), the orientation of C_8-hydrogen in the product (XLX) is β-oriented.

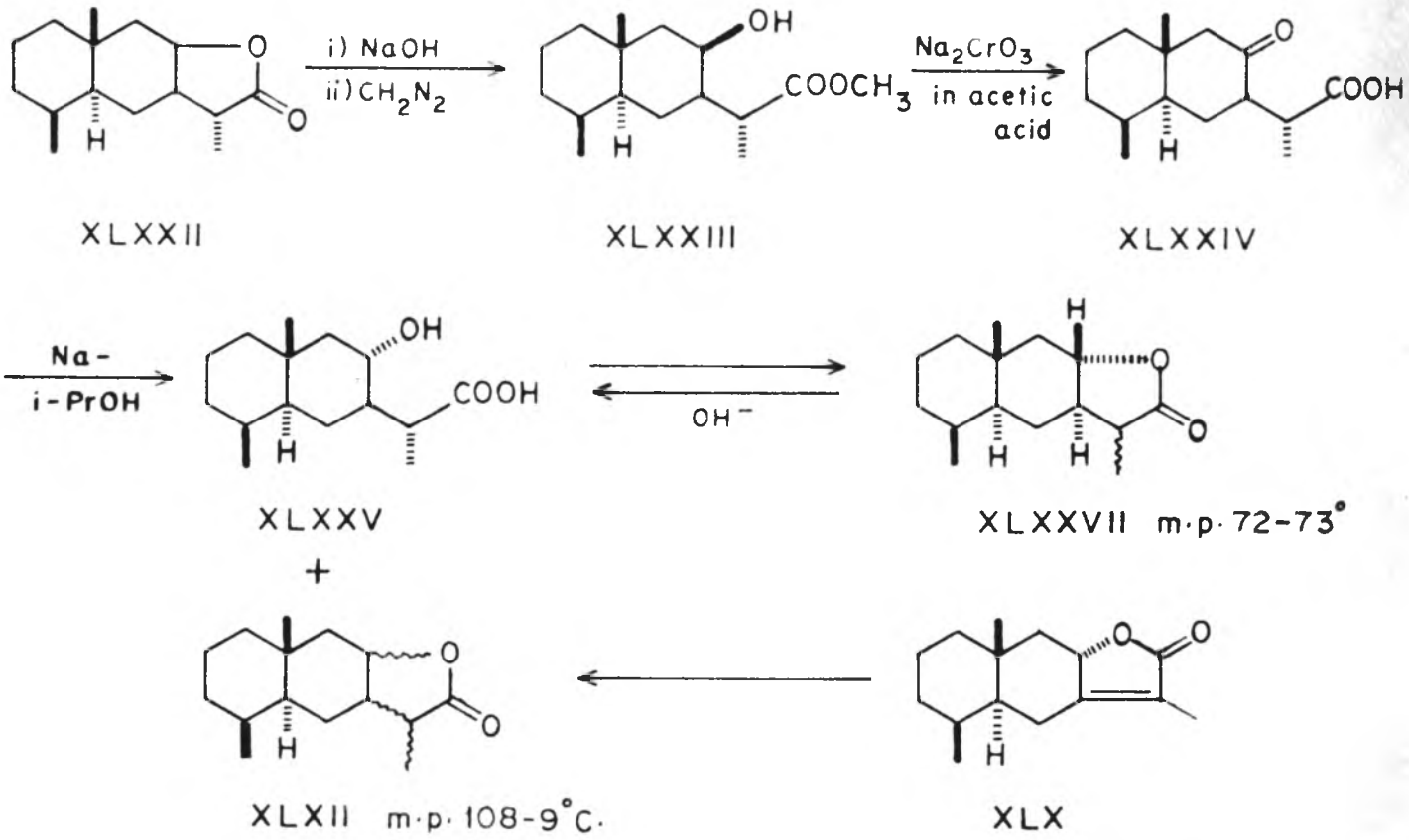
So it is necessary to introduce α-hydroxyl group

CHART IV

SYNTHESIS OF LACTONE OF 8 α-HYDROXYEUDESM-8-(11)-EN-OIC ACID



SYNTHESIS OF ISOMERIC TETRAHYDROALANTALACTONE

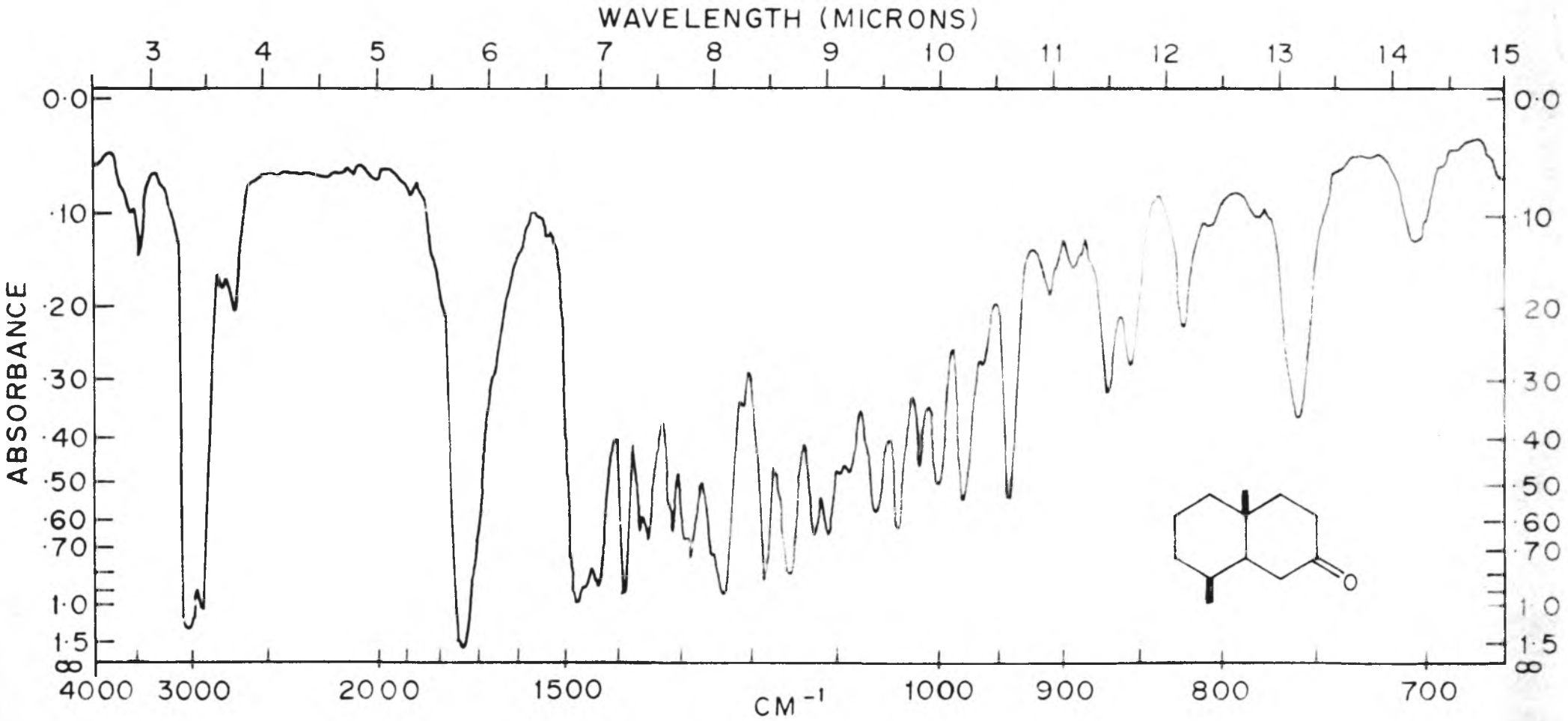


at C_8-position in the keto compound (XLXVII, Chart IV). This can be achieved in two ways.

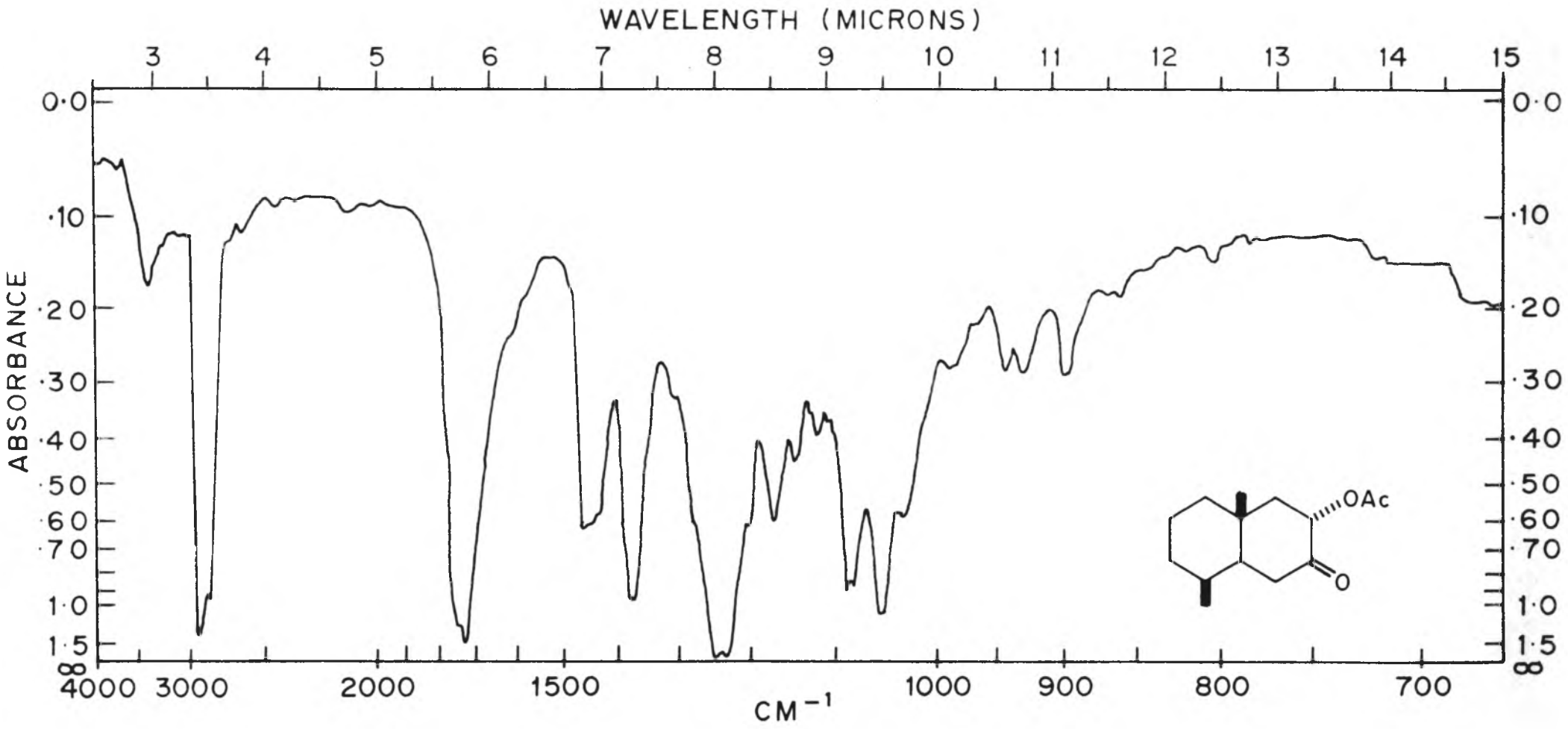
1. Treating the ketone with isophenylacetate to get enolic acetate. Epoxide of this is treated with BF_3-etherate to get α-ketoacetate[33].

2. Treating the ketone with lead tetraacetate in acetic acid[32].

In the present synthesis we followed the second method for the preparation of the desired keto-acetate. The ketone (XLXVIII), when treated with leadtetraacetate in acetic acid for 20 hours gave the ketoacetate (XLXIX), which was separated from the material by fractional distillation and fraction between 140-50°/0.5 mm was collected and found to be pure compared by GLC and TLC analysis; $(\alpha)_D$ - 32.7°. The stereochemistry of the resulting ketoacetate has been assigned as in (XLXIX) based mainly on NMR (No.1) data[34]. The NMR spectrum of the ketoacetate showed a clear quartet centred at 5.22δ with J_{8aa} = 12.5 cps and J_{8ae} = 7 cps, which clearly indicates that it has the stereochemistry as depicted in (XLXIX) i.e. α-acetoxy ketone.
(If keto acetate has β-acetoxy group, then it should have shown a quartet with J_{8aa} = 9.5 cos and J_{8ae} = 7.4 cps. If at all some percentage of β-acetoxy ketone is formed it will be converted to α-acetoxyketone by heating with acetic acid for prolonged time. This has



IR SPECTRUM (LIQUID FILM) No. 1.



IR SPECTRUM (LIQUID FILM) No. 2.

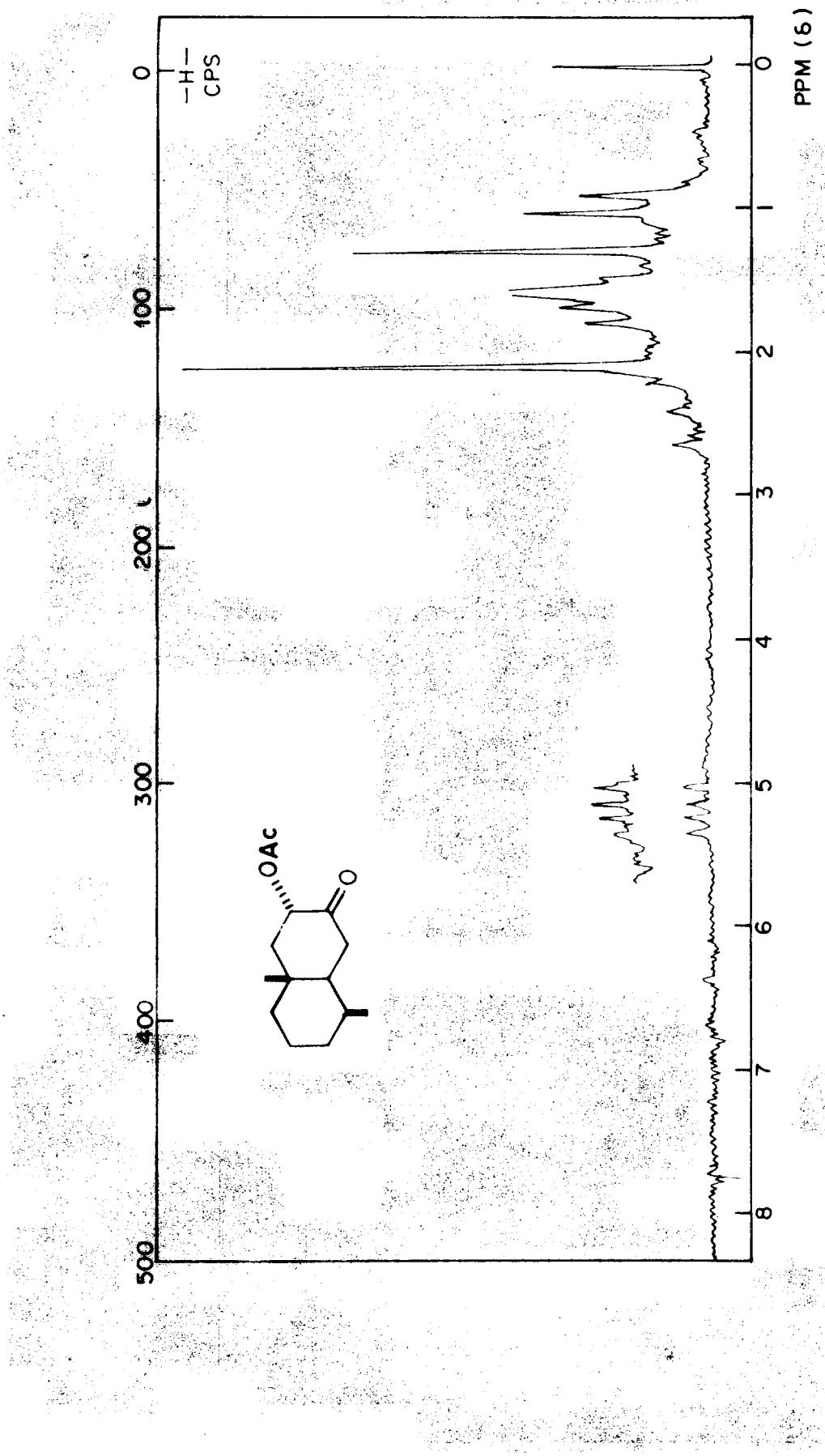
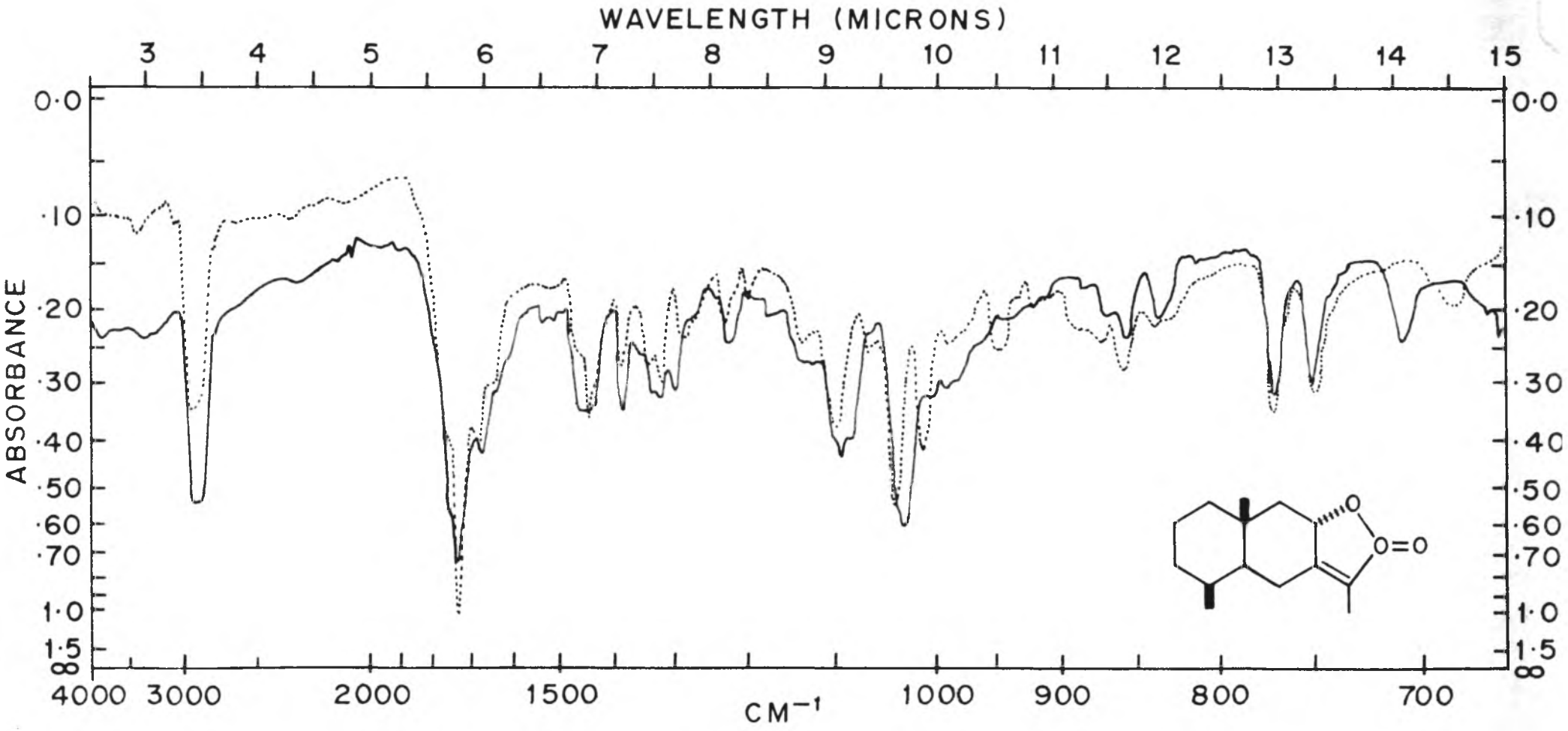


FIG. 1. NMR SPECTRUM OF TRANS-4,10-DIMETHYL DECALENE-7-ONE-8-(α)-ACETATE.



IR SPECTRUM (KBr. PELLET) No. 3.

been demonstrated by Sondheimer et al.[32,35] in the case of steroids).

Further, it showed C_{10}-methyl as a singlet at 1.27δ and C_4-methyl as a doublet at 0.94δ (J, 7 cps) and another singlet at 2.07δ due to acetyl grouping. The ketoacetate is then subjected to Reformatsky reaction with α-bromopropoinic ester to give the hydroxy ester (XLXX), which was then hydrolysed, dehydrated and cyclised with sodium acetate and acetic anhydride. The crude butenoide (XLX), so obtained showed two spots in TLC analysis. It was passed over silicic acid to obtain the pure lactone. This was further purified by crystallisation from petroleum ether, m.p.110-11°, $(\alpha)_D$ + 132°; λ_{max}^{EtOH} 221 (log ε, 4.3) (Lit. $(\alpha)_D$+ 130.8°, m.p. 113-14°). It showed IR bands at 1724 cm^{-1} and 1667 cm^{-1}. It showed no depression in melting point with authentic sample and has superimposible IR spectrum with the same.

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

Purification of eudesmol (I and II)

Commercial eudesmol (550 gms) (Plainer Ltd., N.S.W., Australia, isolated from the essential oil of Neocalliotropsis araucariordes) was fractionally distilled at 0.7 mm pressure through a high efficiency packed column and the results are recorded in table below.

Fr.	B.P./0.7 mm	Wt.(gms)	Remarks
1	110°	33.6	Oily liquid
2	"	43.3	"
3	"	42.6	"
4	"	28.1	Solidified after 48 hrs.
5	"	21.4	"
6	121°	25.3	Solidified after 12 hrs.
7	"	25.1	"
8	"	23.7	"
9	"	26.0	"
10	"	15.6	"
11	"	23.2	Solidified immediately
12	"	26.1	"
13	"	23.1	"
14	"	22	Solidified after 12 hrs.
15	126	23.8	Mobile liquid
16	"	16.9	"

Fractions 8,9,10,11 and 12 were mixed and crystallisation from dry acetone furnished eudesmol, (40 g. α and β isomer) m.p. 70-70.5, α_D + 35°, GLC analysis indicated it to be composed of 25% of α-isomer and 75% of the β-isomer.

Hydrogenation of eudesmols to dihydroeudesmol (VII)

The eudesmol mixture (33 g) was hydrogenated in the presence of Raney nickel catalyst (15 g) and alcohol (350 ml) at 1000 atoms/100° for 12 hrs. Usual working up, furnished dihydroeudesmol (VII), which was distilled at 121°/0.5 mm (31.4 g), m.p. 84-85°, α_D + 18.6°. GLC analysis showed it to be composed of single component.

Conversion of dihydroeudesmol (VII) to trans-4-10-dimethyl decalene-7-one (XLXVIII)

Dihydroeudesmol (VII) in acetic acid (80 ml) was heated to 75°C and a solution of chromic acid (13.5 g) in water (80 ml) and acetic acid (160 ml) was added to it with stirring during one hour. A drop of sulphuric acid was added before the start of the reaction. The reaction mixture was heated for two hrs. Excess of chromic acid was removed by adding methyl alcohol. After dilution with water (1000 ml), the mixture was extracted with ether and the ethereal extract was washed successively with aqueous sodium bicarbonate solution, dilute acid and water. The removal of the solvent furnished a crude product. It was chromatographed over Gr. III alumina. Elution with petroleum ether furnished the crude ketone (XLXVIII), which was further converted to its semicarbazone, m.p. 220°. Lit. m.p.222°C; (Found: C, 66.43; H, 9.98; N, 17.55. $C_{13}H_{23}N_3O$ requires

C, 65.78; H, 9.77 and N, 17.72%). The ketone (XLXVIII) was then regenerated by decomposition of semicarbazone with oxalic acid. The ketone (XLXVIII), thus obtained was distilled at 140-150°/3 mm; yield 3.5 g. TLC and GLC analysis showed it to be a single component; $\alpha_D \pm 0$ (Found: C, 80.09; H, 11.36; $C_{12}H_{22}O$ requires C, 80; H, 11.11%). IR spectrum (No.1) showed bands at 2941, 1724, 1390, 943, 877, 870 and 769 cm^{-1}.

Action of lead tetraacetate on ketone (XLXVIII) Formation of ketoacetate (XLXIX)

The ketone (XLXVIII, 3.3 g) was heated to reflux with lead tetraacetate (2 g) in glacial acetic acid (300 ml) for 20 hrs in an oil bath. After cooling, the acetic acid was mostly distilled under reduced pressure and the residue was mixed with aqueous sodium bicarbonate and extracted with ether. After the removal of the insoluble material by filteration, the extract was again washed with aqueous bicarbonate, then with water and dried over anhydrous sodium sulphate. Evaporation of ether left crude ketoacetate (XLXI 3.1 g). It was fractionally distilled and the fraction distilled at 140-150°C/0.5 mm (1.8 g) was collected, $(\alpha)_D$ - 32.75 (C, 1.32), GLC showed to be a single compound (Found: C, 69.97; H, 9.28; $C_{14}H_{22}O_3$ requires C, 70.6; H, 9.25%. IR spectrum (No.2) showed bands at 2920, 1730, 1240 and 1055 cm^{-1}.

Conversion of ketoacetate (XLXIX) to hydroxy ester by Reformatsky reaction

Zinc wool (1 g) was taken in three necked flask, fitted with mechanical stirrer, reflux condenser and a dropping funnel. Solution of α-bromopropoinic ester (3 ml) and the ketoacetate (XLXIX, 1.20 g) in dry benzene (5 ml) and dry ether (2 ml) was taken in a dropping funnel. First solution (2 ml) was added and the flask was warmed till reaction started. After that stirring was started and the remaining solution was added dropwise during 30 minutes. The reaction mixture was further stirred for 1 hour and then cooled to 0°C. The excess of zinc was removed by careful addition of cold dilute sulphuric acid. The reaction mixture was then extracted thrice with ether, the extract was washed with water, dried over anhydrous sodium sulphate and solvent removed. The crude hydroxy ester weighed 1.5 g.

Hydrolysis of hydroxy ester (XLXX) to hydroxy acid (XLXXI)

The crude hydroxy ester (XLXX, 1.3 g) was refluxed with alcoholic potassium hydroxide (20 ml. 10%) for 6 hrs. Most of the alcohol was removed by distillation and then the product was dissolved in water and then extracted twice with ether. The aqueous extract was acidified with dilute acid, extracted with ether, washed with little water, dried and solvent removed. The crude hydroxy acid weighed 0.8 g.

Cyclisation of hydroxy acid to lactone (XLX)

The crude acid (0.7 g) was refluxed with acetic anhyaride (8 ml) and fused sodium acetate (1 g) for 4 hrs. The reaction mixture was cooled, powdered in water (50 ml) and extracted with ether. The ether extract was washed several times with aqueous sodium bicarbonate, water and dried over anhydrous sodium sulphate and solvent removed. The crude product (560 mg) was saponified by refluxing with 10% ethanolic potassium hydroxide (20 ml). The alcohol was removed by distillation and the residue was diluted with water (20 ml) and extracted with ether to remove other impurities. The aqueous solution was acidified with acetic acid and heated on water bath for 1 hr. It was then cooled, diluted with water (50 ml) and extracted with ether. The ethereal extract was successively washed with water, aqueous sodium bicarbonate, water and dried over anhydrous sodium sulphate. Solvent removed. The product weighed 142 mg. It showed two spots on TLC. Hence it was chromatographed over silicic acid (10 g). The less polar product was removed by eluting the column with the mixture of petroleum ether and benzene (1:1) and then it was eluted with benzene in 6 portions of 10 ml each; fractions 2-6 were essentially a single component as shown by TLC and hence they were mixed. Removal of the solvent gave pure lactone (XLXI) as a thick liquid

which solidified after 2 hours. It was then crystallised from petroleum ether to colourless crystalline solid (42 mg). $(\alpha)_D$ + 132° (Lit. α_D + 130.8°), m.p. 110-11°C. (lit. m.p. 113-14°C). (Found C, 76.52; H, 9.38; $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46%). IR spectrum (No.3) showed bands at 3357, 1730, 1667, 1093 and 1031 cm^{-1} and it was superimposible with that of an authentic sample. There is no depression in mixed melting point.

REFERENCES

1. Baker and Smith, J.Proc.Roy.Soc. New South Wales, 1897, 31 (1896).

2. Semmelar and Tobias, Ber., 2026, 46 (1913).

3. L. Ruzicka, Meyer and Mingazzim, Helv.Chim.Acta., 362, 5 (1922).
   L. Ruzicka, Wind and Boolnass, ibid., 1132, 14 (1931).

4. F.J. Mcquillin and J.D. Parrach, J.Chem.Soc., 2973 (1956).

5. L. Ruzicka, D.R. Kochas and A.H. Wind, Helv.Chim.Acta., 1171, 14 (1931).

6. Pl.A. Plattner, A. Furst and J. Hellerback, Helv.Chim.Acta., 2158, 30 (1947).

7. D.H.R. Barton, Chem. and Ind., 664 (1953).

8. W. Klyne, J.Chem.Soc., 3080 (1953).

9. B. Riniker, J. Kolvoda, D. Arigoni, A. Furst, O. Jeger, A.M. Gold and R.R. Woodward, J.Am.Chem.Soc., 313, 76 (1954).

10. A.J. Birch and K.M.C. Mostyn, Aust.J.Chem., 301, 7 (1954).

11a J.A. Marshall and M.T. Pike, Tetrahedron Letters, 2107, 35 (1965).

11b R.P. Houghton, D.C. Humber and A.R. Pinder, Tetrahedron Letters, 353, 3 (1966).

12. D.C. Humber and A.R. Pinder, ibid., 4985, 41 (1966).

13. J.A. Marshall and M.T. Pike, ibid., 4989, 41 (1966).

14. W.A. Ayer and W.I. Taylor, J.Chem.Soc., 3027 (1955).

15. D.H.R. Barton and E.J. Tarliton, ibid., 3492 (1954).

16. K.R. Verma and S.C. Bhattacharyya, Tetrahedron, 2927, 20 (1964).

17. M.V. Kadival, V.M. Sathe, K.K. Chakravarthi and S.C. Bhattacharyya, Ind.J.Chem., 393, No.9, 4, (1966).

18. G.D. Joshi, M.V. Kadival, S.N. Kulkarni and S.C. Bhattacharyya, Tetrahedron, 1985, 23 (1967).

19. A.C. Bawdekar and G.R. Kelkar, ibid., 1521, 21 (1965).

20. M. Sumimoto, Chem. and Ind., 780 (1963).

21. D.W. Theobald, Tetrahedron, 2593, 20 (1964)

22. V.B. Zalkov, A.M. Shaligram and L.H. Zalkov, Chem. and Ind. 194 (1964).

23. R.E. Corbett and R.A.J. Smith, Tetrahedron Letters, 1009 (1967).

24. G.L. Chetty, V.B. Zalkov and L.H. Zalkov, Tetrahedron Letters, 3223, 28 (1968).

25. H. Hikino, Y. Hikino and I. Yosioka, Chemical and Pharm.Bull., 755, 12 (1964).

26. W. Cocker, T.B.H. McMurry and L.O. Hopkins, J.Chem.Soc., 1998 (1959).

27. K. Tsuda and K. Tanabe, J.Am.Chem.Soc. 5721, 79 (1957).

28. S.S. Welankiwar, Ph.D. Thesis, page 32 (1967).

29. L. Rujick, A.Pl. Plattner and A. Furst, Helv.Chim.Acta., 1370, 25 (1942).

30. H. Matsumura, I. Iwai and Eizi, J.Pharm.Soc. Japan, 738, 74 (1954).

31. ibid., 1209, 74 (1959).

32. F. Sondheimer, S. Kaufmann, S. Romo, H. Martinez and G. Rosenkranz, J.Am.Chem.Soc., 75, 4712 (1953).

33. H.B. Henbest, D.N. Jones and G.P. Slater, J.Chem. Soc., 4472 (1961).

34. K.L. Williamson and J.W. Johnson, J.Am.Chem.Soc., 4623, 83 (1961).

35. J. Harran, G. Rosenkranz and F. Sondheimer, J.Am.Chem.Soc., 5531, 76 (1954).

Chapter III

Chemical Investigation of Leaves of Viola - Odorata

The chemical investigation of leaves of "Viola odorata Linn" was undertaken as a part of the chemical investigation of the plants used in indigenous system of medicine. Viola odorata (Hindi - Banafsha) is found in Kashmir and many hill stations (5000-6000'). The flowers, petals and roots of the plant have been used in indigenous system of medicine.[1]

Plant - Antipyretic, diaphoretic, febifuge.

Flowers - Emollient, demulcent, used in biliousness and lung troubles.

Petals - Made into a syrup used as a remedy for infantile disorders.

Root - Emetic.

The roots have been shown by early workers to contain traces of alkaloids[2] and saponin[3]. The leaves, blossoms contain methyl salicylate in the form of glucoside[3]. The dry plant material has been shown to contain odoratine, an active principle of plant, later shown to be triacetonamine, probably formed by the catalysed action of some components of the plants[5] on extracting solvents. These workers however failed to isolate any triterpene from the plant.

The extract of the dried and powdered leaves with petroleum ether at room temperature, was carefully chromatographed over alumina (Gr. II). Elution with

petroleum ether provided waxy material along with a mixture of six hydrocarbons (GLC analysis). Further elutionwith a mixture of petroleum ether and benzene (1:1) in the above chromatography furnished a solid compound, which was crystallised from petroleum ether as colourless silky needles, m.p. 258-60°, $(\alpha)_D$ - 28° (Found: C, 84.76; H, 11.42%. $C_{30}H_{50}O$ requires C, 84.44; H, 11.81%). IR spectrum showed band at 1725 cm^{-1} (six membered ketone). This compound was converted to the corresponding alcohol according to the procedure of Drake and Campbell[6] (sodium + amyl alcohol reduction), which was crystallised from ethyl acetate as plates. TLC analysis showed it to be single compound, m.p. 299-302°. (Found: C, 83.72; H, 12.1%. $C_{30}H_{52}O$ requires: C, 84.03; H, 12.23%). The oxime derivative of the ketone was also prepared and was crystallised from benzene-ethyl acetate mixture (2:1) as hexagonal plates, m.p. 290-294°. (Found: N, 3.23%. $C_{30}H_{51}ON$ requires: N, 3.71%).

From all these properties, the substance appears to be identical with Friedelin[8] (not compared with authentic sample as the same was not readily available).

Further elution with petroleum ether-benzene mixture (1:1) furnished a solid, crystallised from petroleum ether. TLC showed it to be single compound, m.p.85° (Found: C, 82.35; H, 14.39%. $C_{33}H_{70}O$ requires: C, 82.04;

H, 14.69%). It has a absorption at 3300 cm^{-1} in its IR spectrum characteristic of hydroxyl group. This compound was not further investigated.

Benzene elution of the above chromatography, provided a solid, crystallised from methanol, m.p. 136-138° $(\alpha)_D$ - 27.5° giving all test for sterols (Found: C, 84.1; H, 12.50%. $C_{29}H_{50}O$ requires: C, 83.99; H, 12.15%). It has a superimposible IR spectrum and there is no depression in the mixed melting point with authentic sample of β-sitosterol. The same was proved by preparing its acetate, which was crystallised from ethanol, m.p. 120° $(\alpha)_D$ - 38°. The ethanol extract of the leaves did not furnish any alkaloids or saponins.

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

Extraction

The dried and powdered leaves of viola odorata (3 kg) were introduced in a 5 litre flat bottom bottle having a stop-cock. Then it was filled with pet.ether. After keeping it for 3 days, the solvent was removed by opening the stop-cock. Last traces of the solvent were removed by applying suction. Solvent was distilled off. This process was repeated thrice to complete the extraction. The total weight of the extract after removal of the solvent was 40 g. The extract was dark green coloured. The thin layer chromatography showed the presence of at least seven compounds.

The extract (4 g) was chromatographed over alumina (Gr. II, 120 g).

Fr.No.	Solvent 20-25 ml frs.	TLC Spots	State	Wt. (g)	TLC system
1	Pet.ether	3	semisolid	0.785	Petroleum ether
2	"	2	"		
3-10	"	2	"	0.915	
1-4	Pet.ether + Benzene (10:1)	2	solid	0.035	Pet.ether + ethyl acetate (8:1)
1	Benzene + pet. ether (1:1)	1	solid	Negligible	
2-3	"	2	"	0.040	Pet.ether + ethyl acetate (8:1)
4-6	"	2	"	0.020	
7-10	"	2	liquid	0.020	
14-17	"	1	solid	0.050	
19-22	"	2	solid	0.005	
1-6	Benzene	1	liquid	0.045	
7-9	"	1	"	0.015	
10-11	"	1	solid	0.030	
12-16	"	1	solid		

Further elution of the above alumina column with ether and alcohol did not furnish any compounds.

Benzene + pet.ether fraction (1:1) (Isolation of Friedelin)

Fractions No.1 and 3 were mixed and solvent was removed to furnish a yellow solid, which was crystallised from pet. ether (two times) as colourless silky needles. TLC showed it to be a single compound. It has m.p. 258-60° and $(\alpha)_D$ - 28°. (Found: C, 84.4; H, 11.42%. $C_{30}H_{50}O$ requires: C, 84.4; H, 11.7%). IR spectrum showed bands at 2941, 1725, 1485, 1385, 1110 and 1080 cm^{-1}.

Reduction of Friedelin

Friedelin (0.010 g) was dissolved in amyl alcohol (1 ml) and sodium (0.020 g) was added to it. Refluxing was continued until all the sodium was dissolved. The solvent was removed and the residue was dissolved in little ether and washed with little water. Ether distilled off. The residue was crystallised from ethyl-acetate as plates. TLC showed it to be different from Friedelin and further showed it to be a single compound, m.p. 299-302 (Found: C, 83.72; H, 12.01%. $C_{30}H_{52}O$ requires: C, 84.03; H, 12.33%).

Preparation of the oxime of Friedelin

Friedelin (0.020 g) was dissolved in ethanol and hydroxylamine hydrochloride (0.020 g) dissolved in

ethanol was added. Potassium hydroxide (1 pellet) dissolved in ethanol was added to the above mixture and refluxed for one hour. Cooled and poured into ice cold water. The resulting solution was made acidic with sulphuric acid (1:1) and the product was extracted with ether. The ethereal layer was washed with little water. Dried and the solvent removed. The residue was crystallised from benzene-ethylacetate mixture (1:1) as hexagonal plates m.p. 290-294° (Found: N, 223%. $C_{30}H_{51}ON$ requires N, 3.17%).

Pet.ether + benzene fraction (1:1)
(Isolation of straight chain alcohol)

Fraction Nos.14-17 were mixed and solvent was removed to furnish a coloured solid compound. The solid compound thus obtained was crystallised twice from pet. ether m.p. 85°. (Found: C, 82.35; H, 14.39%. $C_{33}H_{70}O$ requires: C, 82.04; H, 14.69%). IR spectrum showed bands at 3300, 2900, 1380, 1130, 1080, 1070, 775 and 750 cm^{-1}.

Benzene fraction (isolation of β-sitosterol)

Fractions Nos.12-16 were combined and solvent was distilled off to furnish a coloured solid compound. This was crystallised from methanol twice. TLC indicated single spot, m.p. 136-138°; α_D - 27.5°. (Found: C, 84.02; H, 12.08%. $C_{29}H_{50}O$ requires C, 83.99; H, 12.15%). There was no depression in the melting point with authentic

sample of β-sitosterol. IR spectrum showed bands at 3472, 1193, 1136, 1060, 1055, 975, 960, 920, 885, 840 and 803 cm^{-1}. The acetate derivative was prepared using acetic anhydride in pyridine. It was crystallised from ethanol. It has m.p. 120° and $(\alpha)_D$ - 38°.

REFERENCES

1. R.N. Chopra, S.L. Nayal and I.C. Chopra, Glossary of Indian Medicinal Plants, page No.255.

2. O. Linde, Apoth.Ztg., 34, 37-38 (1919).

3. L. Kroeber, Pharmazie, 85-90 (1946).

4. I. Frenclowa, Acta.Polon.Pharm., 18, 187-95 (1961).

5. I. Frenclowa, Acta.Polon.Pharm., 21(2) 145-8 (1964).

6. N.L. Drake and W.P. Campbell, J.Amer.Chem.Soc., 58, 1381 (1936).

7. N.L. Drake and S.A. Shrader, J.Amer.Chem.Soc., 57, 1855 (1935).

8. N.L. Drake and R.P. Jacobson, J.Amer.Chem.Soc., 57, 1570 (1935).