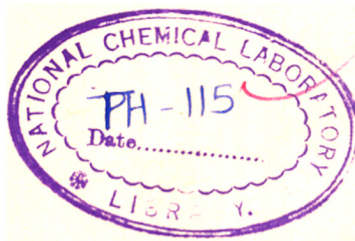


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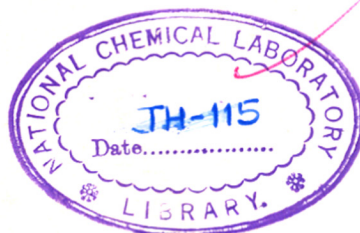
STUDIES IN SESQUITERPENES

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A THESIS
SUBMITTED TO THE
UNIVERSITY OF POONA
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN
(CHEMISTRY)

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C O N T E N T S

	Page
CHAPTER I	
BIOGENETIC-TYPE SYNTHESIS AND CONVERSIONS IN THE SESQUI- TERPENE SERIES	1 – 33
Introduction	1
General characteristics of The biogenetic-type synthesis .	1
Biogenesis of Terpenes	3
Biogenetic synthons	7
Cyclisation of farnesol and related Molecules	7
Further cyclisation of the-membered compounds	15
Further cyclisation of Bisabolane type	17
Further cyclisation of spiro-intermediates.	22
Summary	30
References	31
CHAPTER II	
β - HIMACHALENE OXIDE, ITS REACTIONS AND STEREOCHEMISTRY	34 – 94
Action of lithium-ethylene diamine on β - himachalene oxide and its stereochemistry	34
Lanthnide shift study and the conformation of β - himachalene β – oxide	44
Solvolysis of β -himachalene- β - epoxide	60
Discussion	76

	Page
Experimental	78
Summary	90
References	91
CHAPTER III	
HYDROBORATION OF – HIMACHALENE AND SOLVOLYSIS OF β -HIMACHALOL p-NITROBENZOATE	95 – 116
Attempted preparation of epi-himachalol from β -himachalene	95
Solvolysis of himachalol p-nitrobenzoate	107
Experimental	109
Summary	115
References	116
CHAPTER IV	
TOWARDS SYNTHESIS OF ALLOHIMACHALOL	117 – 203
Route one	118
Route Two	126
Route Three	127
Route Four	150
Method I	155
Method II	157
Method III	157
Experimental	165
Summary	199
References	200
ACKNOWLEDGEMENTS	204

CHAPTER I

**BIOGENETIC - TYPE SYNTHESIS AND CONVERSIONS IN THE
SESQUITERPENE SERIES - A REVIEW**

BIOGENETIC-TYPE SYNTHESIS AND CONVERSIONS IN THE SESQUITERPENE SERIES

INTRODUCTION

Efforts directed toward the synthesis of naturally occurring compounds have followed two kinds of pathways. The first and for many years the major road travelled was that of total synthesis¹⁻⁴. The alternate approach less explored until recent years has been the path of biogenetic-type synthesis^{5,6}. The present introduction attempts to describe developments in the latter direction in the sesquiterpene area which have been reported.

Biogenetic-type synthesis⁷ was defined as an organic synthesis designed to follow in at least its major aspects, biogenetic pathways proved or presumed to be used in the natural construction of the end product. The term biogenetic type is meant to refer to a synthesis which includes reactions patterned after those which occur in enzymatic systems but employing non-biological substrate and often vastly different reaction conditions from biological ones.

General characteristics of the biogenetic-type synthesis

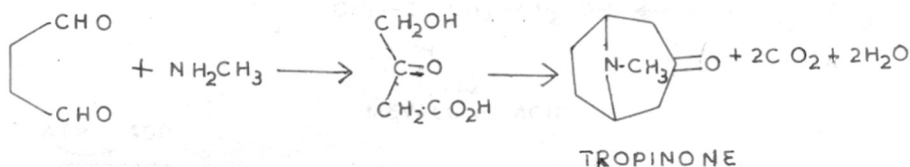
- (a) The biosynthetic route which serves as a model for the laboratory synthesis may be either experimentally based or hypothetical. In the latter instance a working knowledge of sound biochemical principles is presupposed, usually a single pathway will evolve

as the most logical.

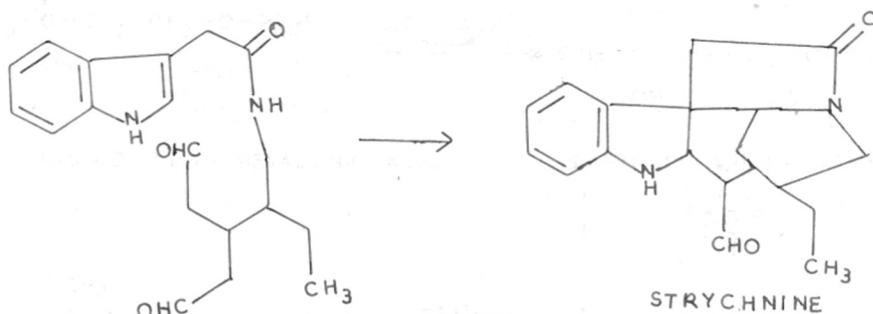
- (b) At least one reaction in the model biosynthesis will be outstanding i.e. the step is the focal point in the laboratory version.
- (c) The intermediate required for the execution of the critical step is usually prepared by synthetic operations. The key intermediate may possess the exact structure proposed in the biosynthetic scheme.
- (d) In the laboratory duplication of the key biological step, any conditions or reagents may be used. Choice in these matters are dictated by the purely chemical demands of the system: in some cases, mild conditions approximating the environment in the living cell will suffice; in others for want of enzyme influences, rather more drastic means will be employed. In the entire range of examples available, laboratory yields vary from nearly quantitative on the one hand to only a few percent on the other hand, in which cases practical considerations become secondary to theoretical success.
- (e) The key synthetic operations very likely fall near the end of the laboratory route, and if necessary routine means are employed to complete the synthesis.

Biogenetic-type syntheses often are neater, shorter, and more efficient than normal routes in which no attention is

paid to natural processes. The Robinson tropinone synthesis is an early, but still an excellent case in point; i.e.



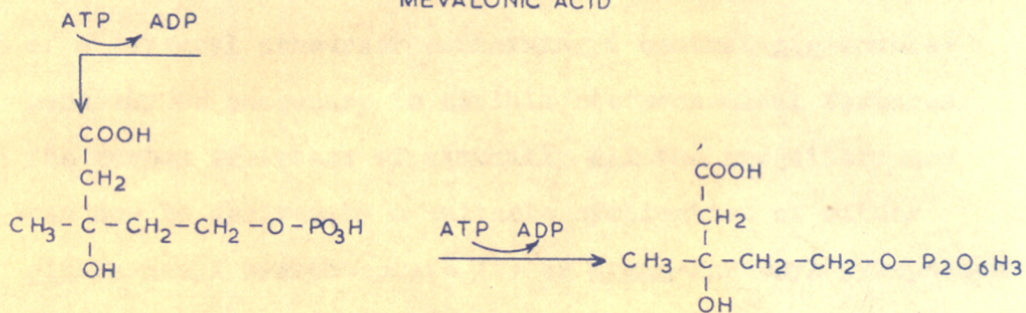
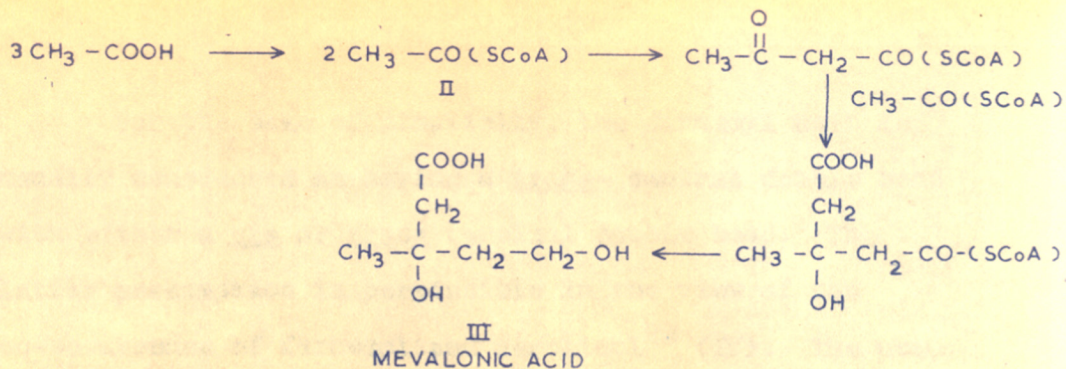
A direct method of constructing the complex strychnine skeleton summarised in the following scheme is another illustration.



Biogenesis of Terpenes ⁸⁻¹⁴

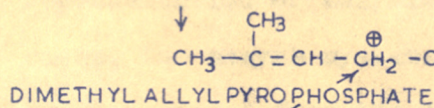
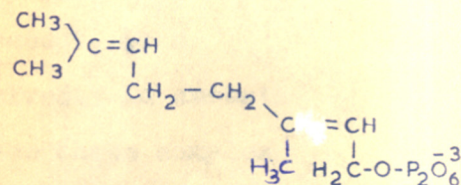
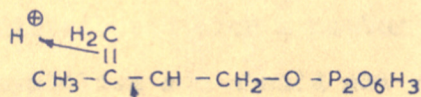
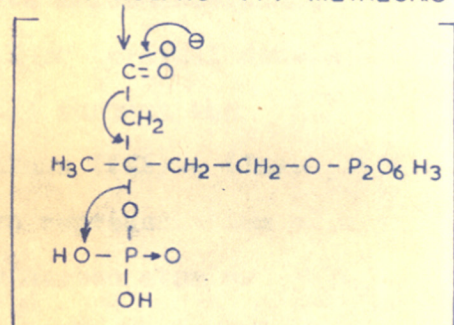
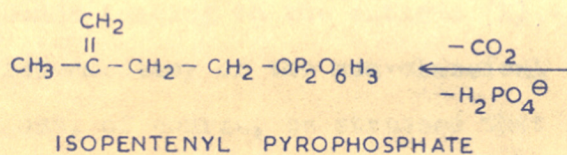
Over the years, the terpenoids have provided a host of challenging problems for the organic chemists. The resultant wide range of acyclic, monocyclic and fused ring structures was brilliantly rationalised in terms of the Biogenetic Isoprene Rules. Hendrickson¹⁷ in 1959 applied the principles embodied in this rule to a biogenetic correlation of certain sesquiterpenes.

The focal point of sesquiterpene biogenesis is the naturally occurring compound farnesol (I) whose formation from acetyl CoA (II), via mevalonic acid¹⁸ (III) has found experimental verification¹⁹⁻²¹ (Table 1).



5 - PHOSPHO - (+) - MEVALONIC ACID

5 - PYROPHOSPHO - (+) - MEVALONIC ACID



GERANYL PYROPHOSPHATE

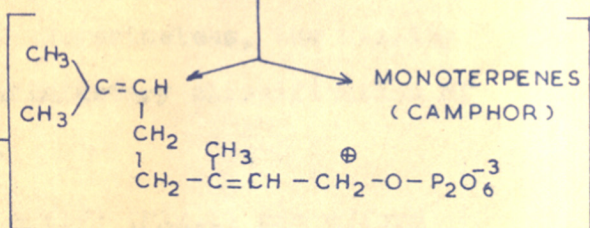
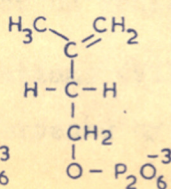
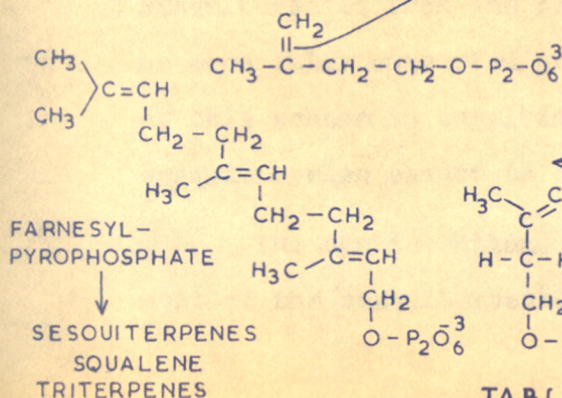


TABLE - I

BIOGENESIS OF TERPENES AFTER CORNFORTH ET. AL. & LYNEN ET. AL.

For the sake of simplicity, the farnesyl unit is usually considered as having a trans- central double bond with either a cis or trans terminal double bond. The latter presumption is permissible in the view of the co-occurrence of farnesyl and nerolidol²² (IV). The use of a farnesyl precursor containing a central cis-double bond may be necessary to explain stereochemical features. The carbon skeletons of virtually all the sesquiterpenes can now be derived by a suitable cyclisation of either cis-farnesyl pyrophosphate (V) or trans-farnesyl pyrophosphate (VI). The initial step in these cyclisations is envisaged (Fig.1) as removal of the pyrophosphate anion accompanied by participation of either the central or terminal double bonds leading to the cations (X) - (XV) through the intermediacy of the non-classical cations (VII) - (IX). It must, of course, be stressed that such representation of a formal charge, either on a particular carbon atom or distributed over a number of atoms, is only a convenient symbolism and should not be taken, at present, as a representation of enzymic processes involved. In certain cases, the enzyme systems may well produce these complex sesquiterpenes from the pyrophosphate precursor by a partially or even fully concerted process. Nevertheless, the utility of this scheme in supplying a satisfactory classification of sesquiterpenes cannot be denied.

The cyclic cations (VII) - (XV) (Fig.1) can afford most of the sesquiterpenes by processes such as 1,2 or 1,3

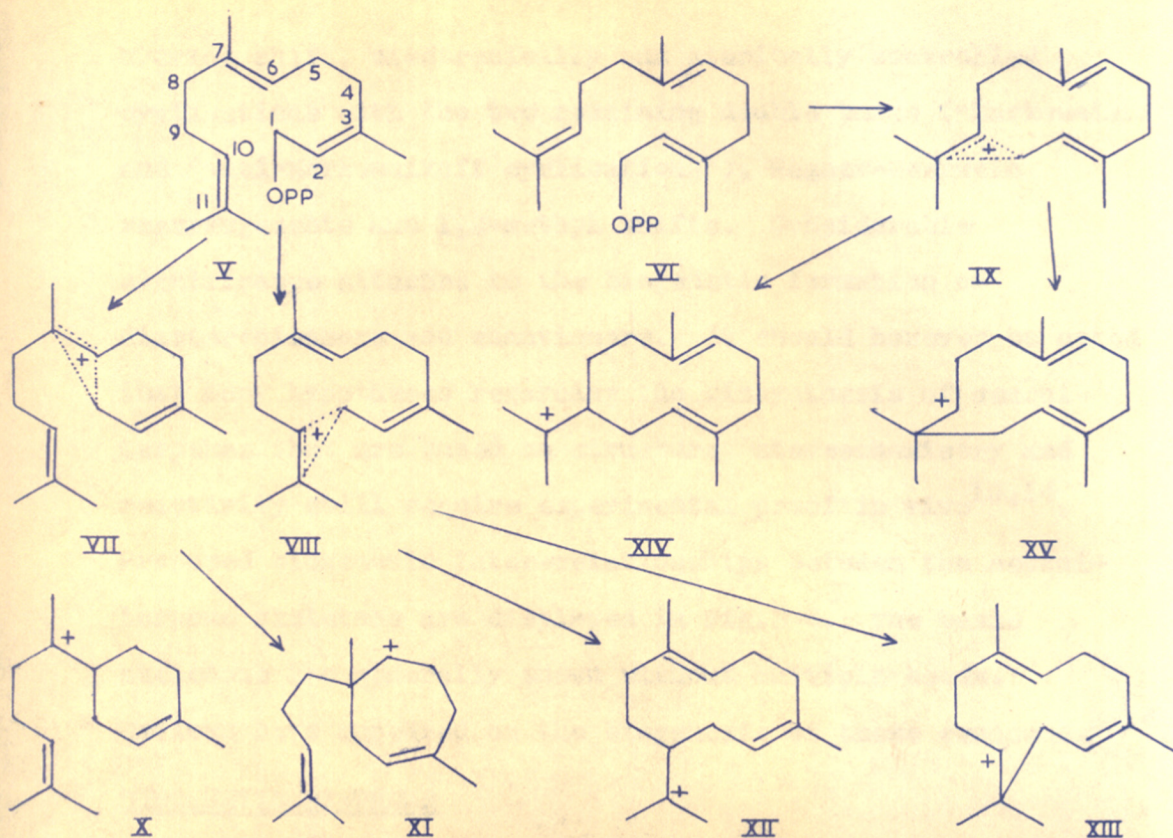


FIG-1 TRANSFORMATION OF CIS- AND TRANS-FARNESYL PYROPHOSPHATES

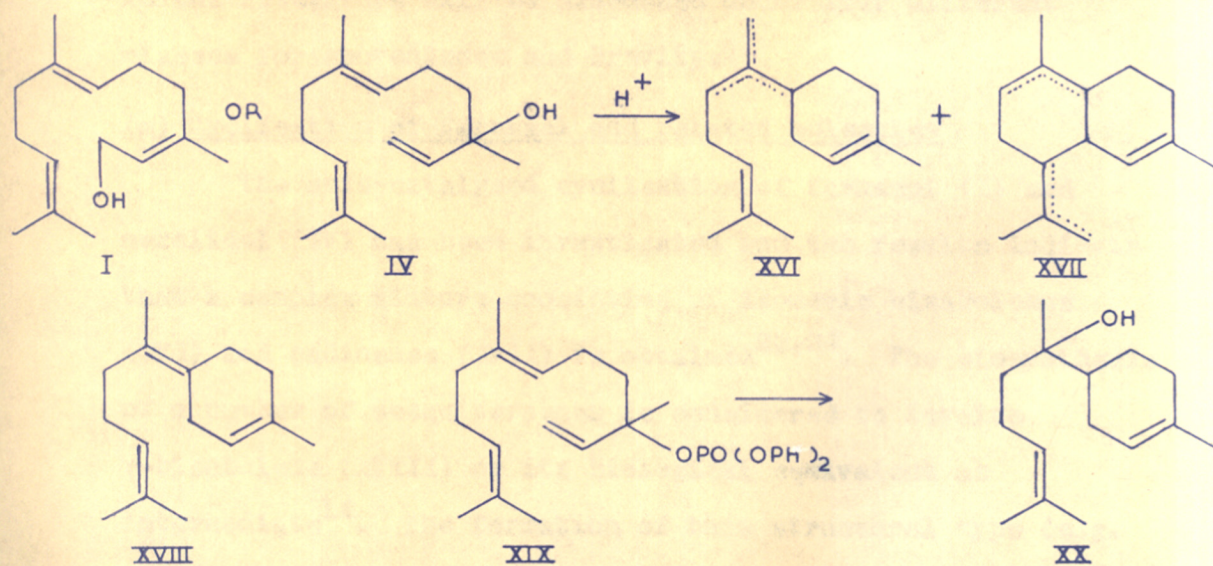


FIG-2 CYCLISATION OF FARNESOL & NEROLIDOL PYROPHOSPHATE

hydride shift, electronically and sterically controlled cyclisations with the two remaining double bonds ("Markownikoff" and "anti-Markownikoff cyclisations"), Wagner-Meerwein rearrangements and 1,2-methyl shifts. Considerable significance attaches to the biogenetic formation of diastereoisomers and enantiomers. It should however be noted that many hypotheses regarding the biosynthesis of sesquiterpenes that are based on structure, stereochemistry and reactivity still require experimental proof *in vivo*^{10,14}. Proposed biogenetic inter-relationships between the sesquiterpene skeletons are displayed in Fig.3-5. The basic skeletons are generally shown without multiple bonds. Reviews have appeared on the biogenesis of these compounds⁸⁻¹⁴.

BIOGENETIC SYNTHONS

Biogenetic-type synthesis of sesquiterpenes reported in the literature will be discussed under four different classes for convenience and brevity.

(a) Cyclisation of farnesol and related molecules

The acid-catalysed cyclisation of farnesol (I) and nerolidol (IV) has been investigated and the results indicate that a complex mixture consisting of isomeric bisabolenes (XVI) and cadinenes (XVII) is obtained^{23,24}. The biosynthesis of a number of sesquiterpenes is considered to involve γ -bisabolene (XVIII) or its biological equivalent as intermediate¹⁴. The formation of this structural type (e.g. bisabolol (XX) from nerolidyl diphenyl phosphate (XIX) has

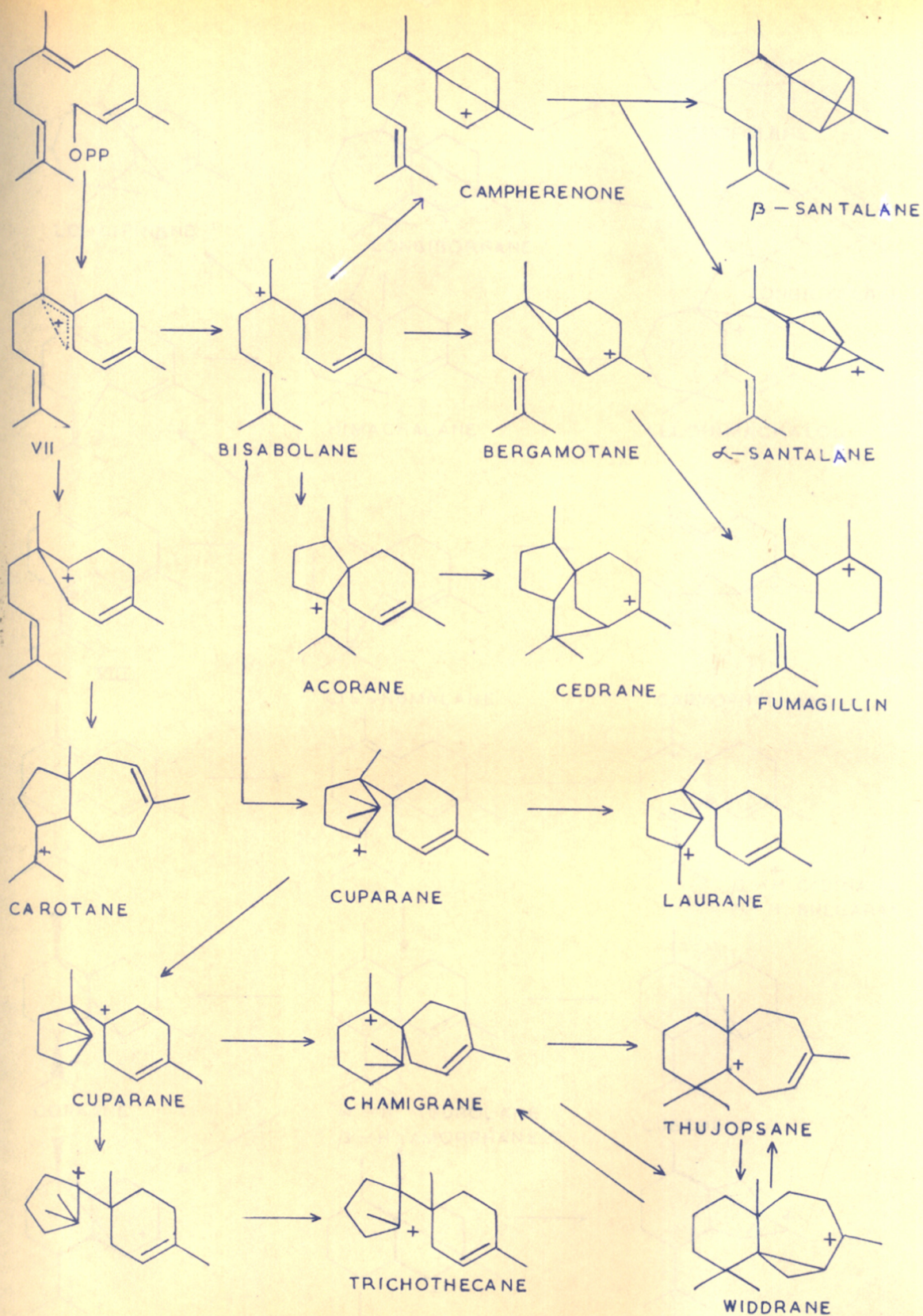


FIG - 3 BISABOLANE ACORANE WIDDRANE CEDRANE AND SANTALANE CLASS.

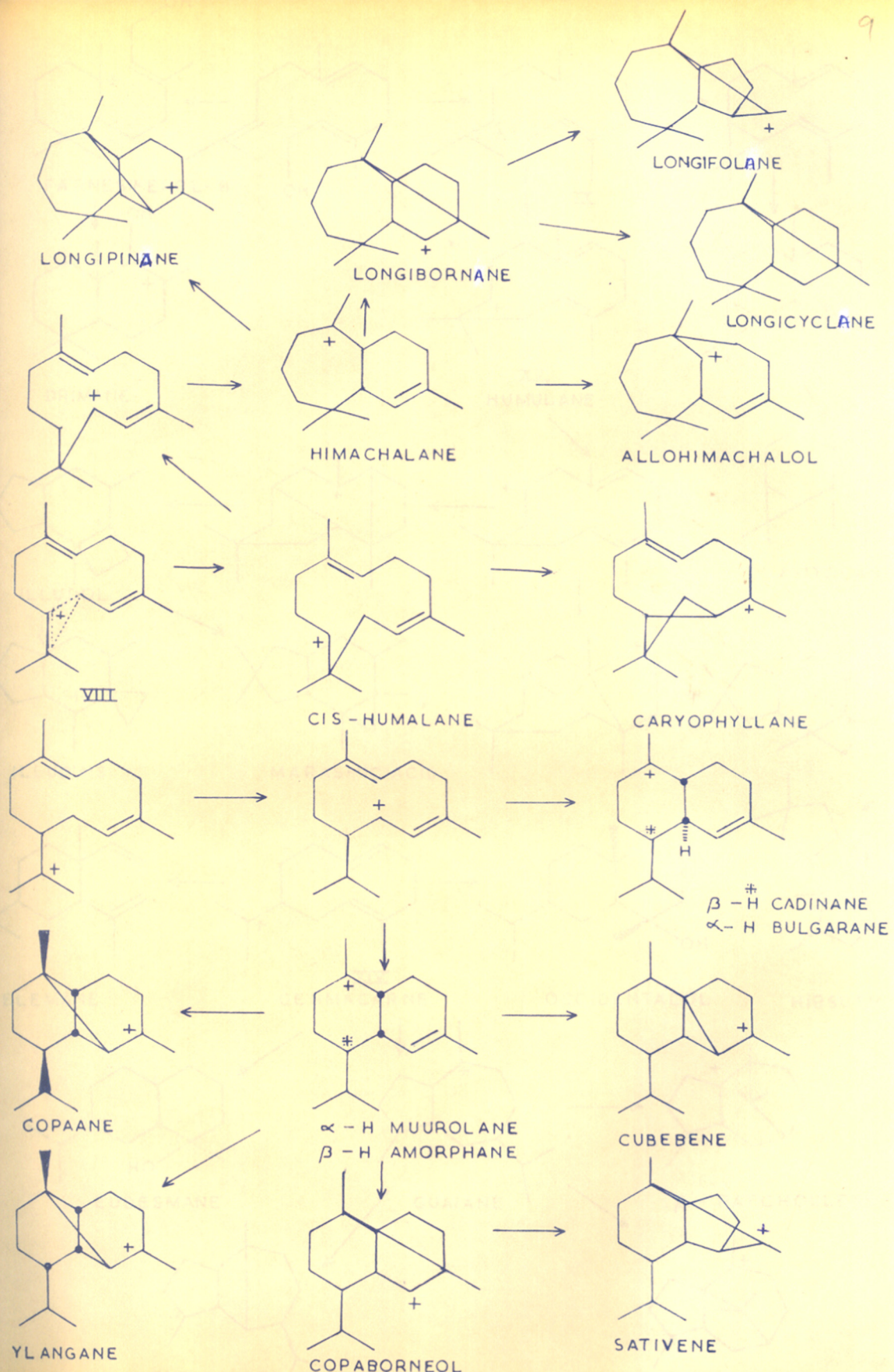


FIG-4 CARYOPHYLLANE HIMACHALANE LONGIPINANE COPAANE
YLANGANE HUMULANE & MUUROLANE CLASS

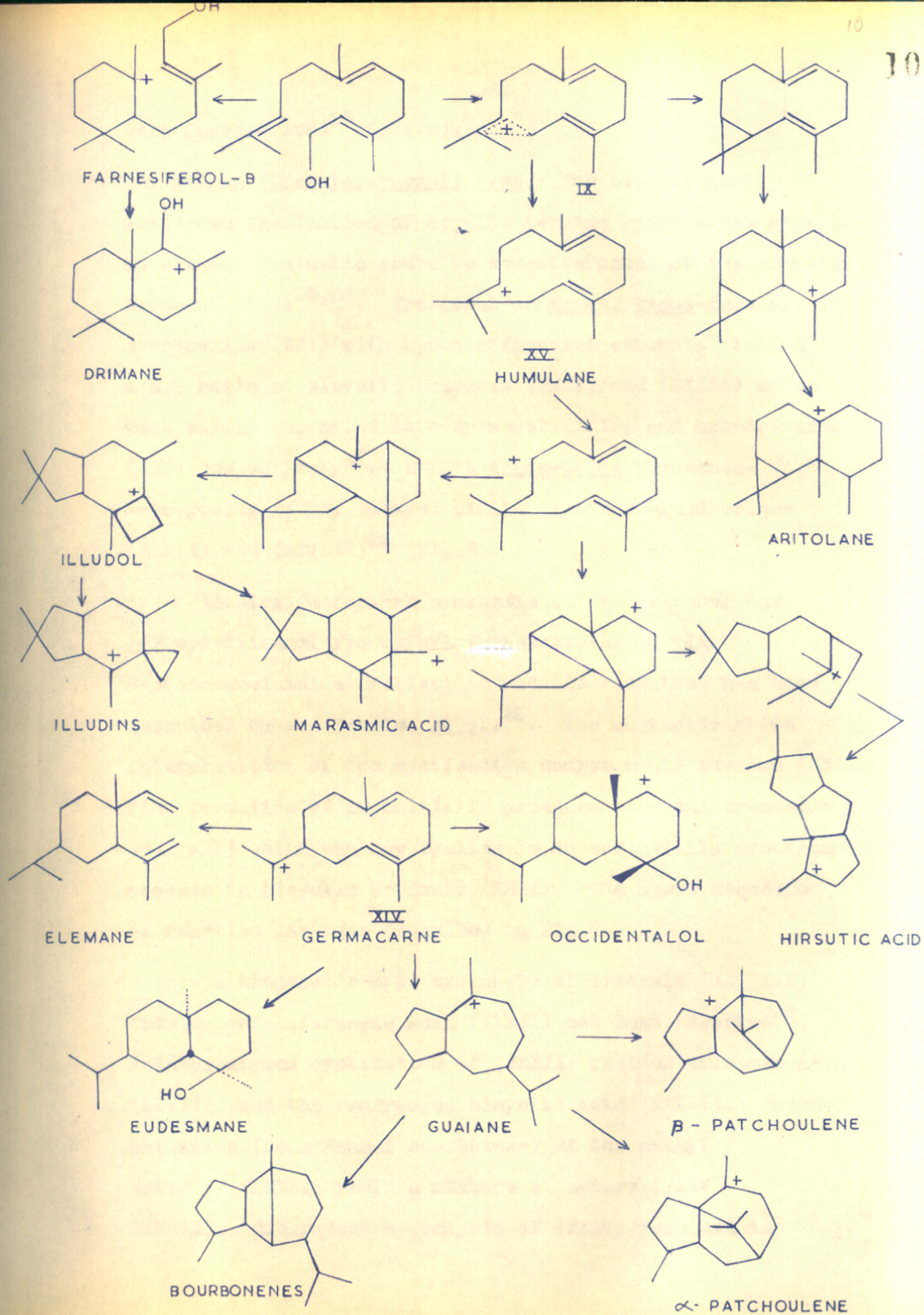


FIG-5 ILLUDIN ARISTOLANE DRIMANE GERMACRAENE & GUAIANE CLASS

been demonstrated²⁵ (Fig.2).

(1) Driman (bicyclofarnesol) type: The biogenetically patterned cyclisation of acyclic terpene epoxide has provided an elegant synthetic route to sesquiterpenes of the bicyclo-farnesol class^{25,26}. Treatment of trans, trans-farnesyl acetate monoepoxide (XXI) with borontrifluoride etherate yielded a 6:1 ratio of bicyclic acetates (XXII) and (XXIII) which were easily converted into drimenol (XXIV) and *epi*-drimenol (XXV) respectively²⁷. Methyl trans-trans farnesate-monoepoxide (XXVI) behaved similarly and yielded esters (XXVII) and (XXVIII)²⁶ (Fig.6).

A straightforward synthesis of (+) drimenol and (+) *epi*-drimenol from methyl farnesate (XXIX) via N-bromosuccinimide cyclisation and LAH reduction has been described by van Tamelen et al.²⁸. The most attractive interpretation of the cyclisation course would involve (XXIX) ring formation of an initially produced terminal bromonium ion (XXX) which can now cyclise in an essentially synchronous process to bicyclic products (XXXI). The above sequence of reaction has been described in Fig.6.

A biogenetic-type synthesis of drimenin (XXXVIII) from monocyclofarnesic acid (XXXII) has been reported²⁹. Acid-catalysed cyclisation of (XXXII) yielded drimenic acid (XXXIII) and the rearranged bicyclic acid (XXXIV). Photo-oxidation (Rose Bengal sensitiser) of the methyl ester of (XXXII) yield a mixture of esters (XXXV - XXXVII). Subsequent hydrolysis of (XXXV) resulted in

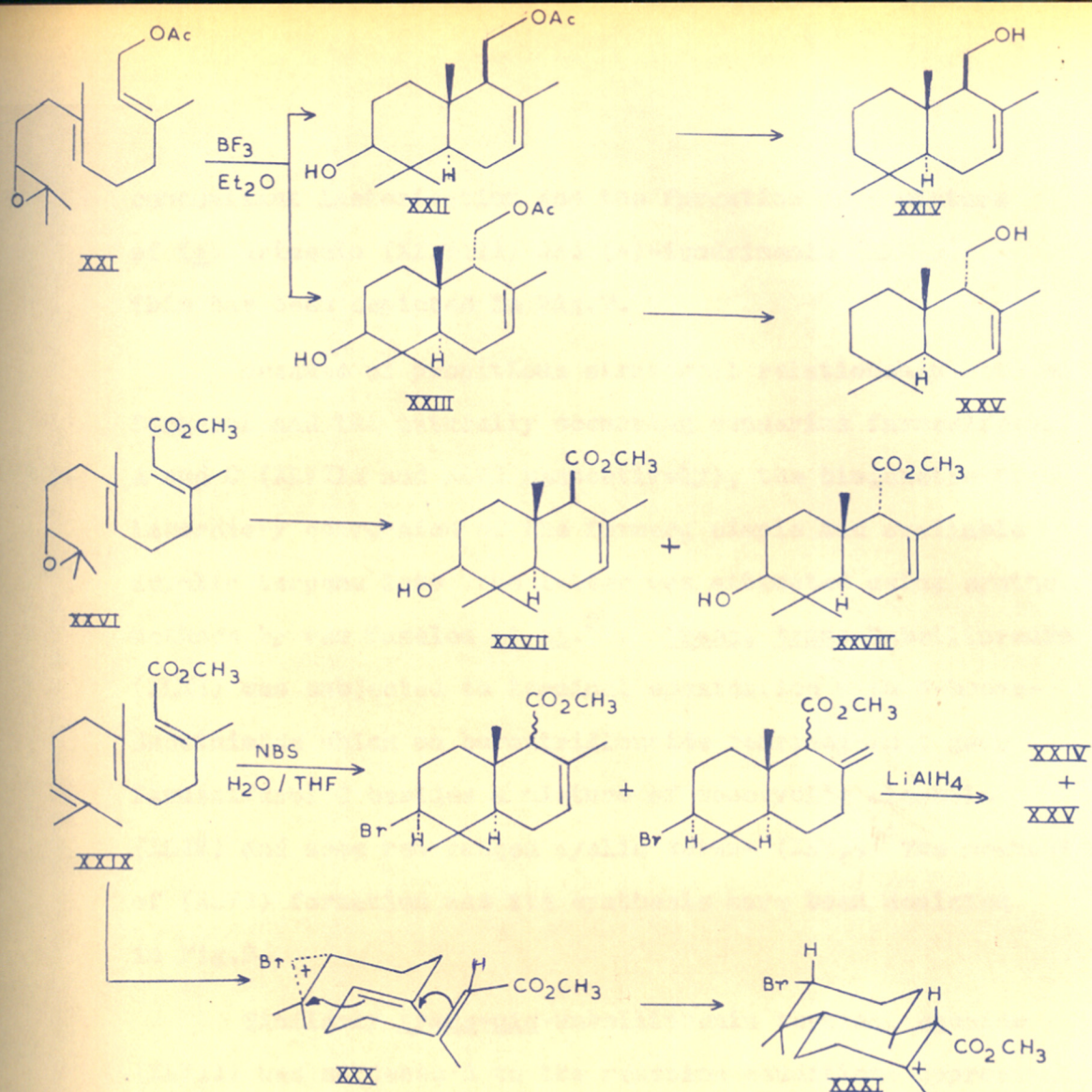


FIG.6 SYNTHESIS OF DRIMENOL AND EPI- DRIMENOL

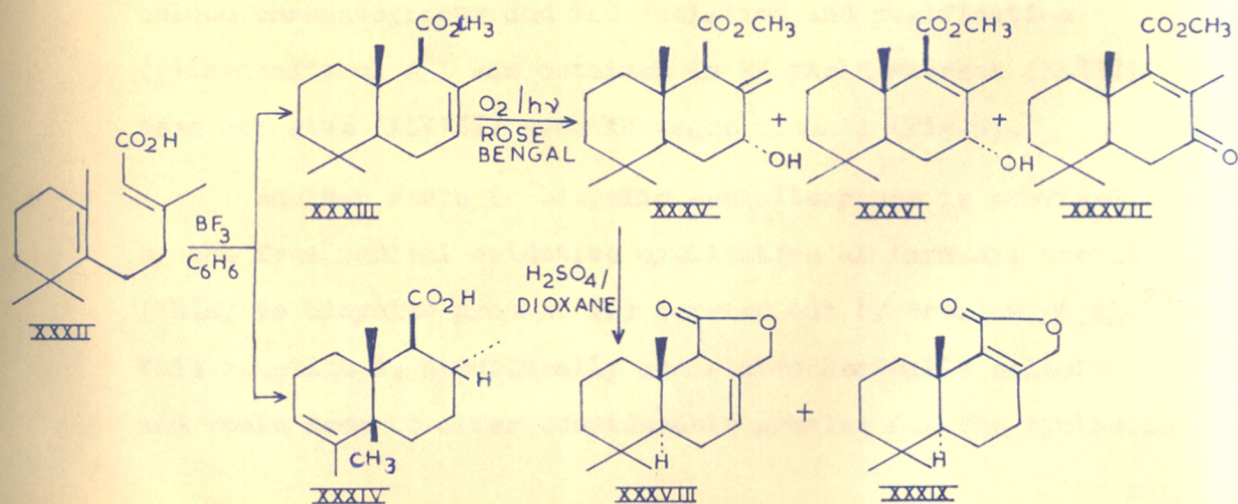


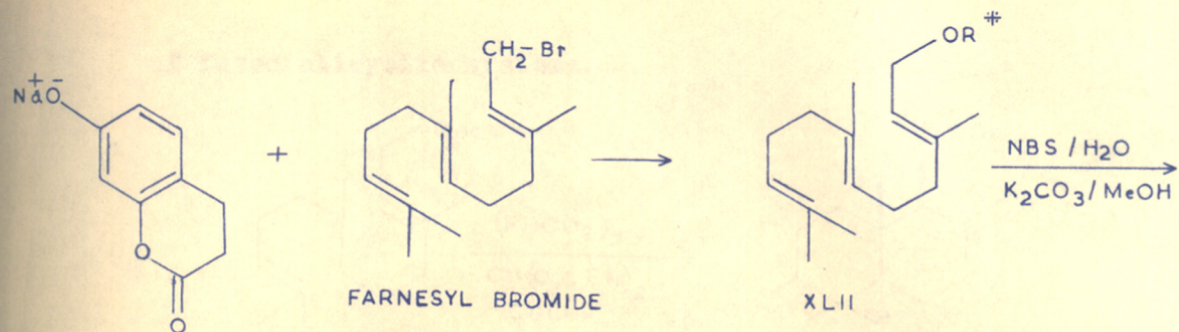
FIG.7 SYNTHESIS OF (±)-DRIMENIN AND (±)-ISODRIMENIN

concomitant lactonisation and the formation of a mixture of (+) drimenin (XXXVIII) and (+)-isodrimenin (XXXIX). This has been depicted in Fig.7.

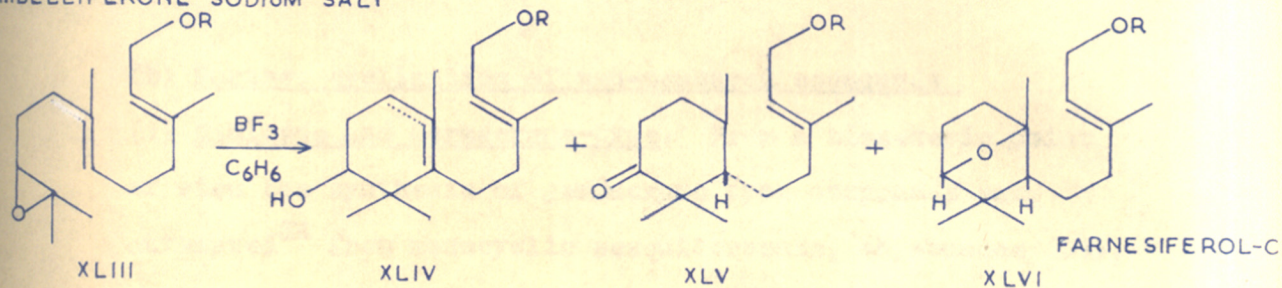
Because of propitious structural relationship between farnesol and the naturally occurring coumarins farnesiferol A and C (XLVIII and XLVI respectively), the biogenetic-type laboratory conversion of the former, simple and available acyclic terpene into the latter was attempted using synthetic methods by van Tamelen *et al.*³⁰. trans, trans-Umbelliprenin (XLII) was subjected to terminal epoxidation with N-bromo-succinimide which on borontrifluoride rearrangement gave farnesiferol C besides a mixture of monocyclic alcohols (XLIV) and some rearranged cyclic ketone (XLV). The mechanism of (XLVI) formation and its synthesis have been depicted in Fig.8.

Similarly trans-cis-umbelliprenin terminal epoxide (XLVII) was subjected to the reaction conditions approximately those described above for the cyclisation of (XLIII). After column chromatography and TLC isolation and purification (+)farnesiferol A²⁵ was obtained in 2% yield whereas (XLIII) does not give (XLVIII) even in trace amounts (Fig.8).

Another route to bicyclic sesquiterpenes is provided by the free radical oxidative cyclisation of farnesyl acetate (XLIX) to bicyclic product (L) carried out by Breslow *et al.*³¹. This reaction is structurally and stereochemically selective and would seem to offer considerable promise for the synthesis



UMBELLIFERONE SODIUM SALT



MECHANISM OF XLVI FORMATION

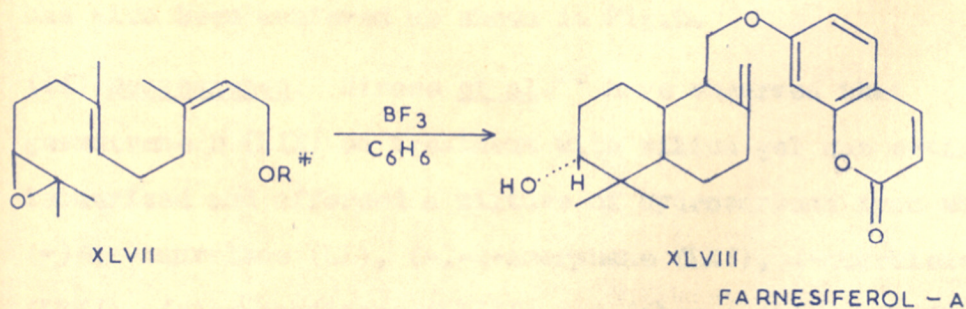
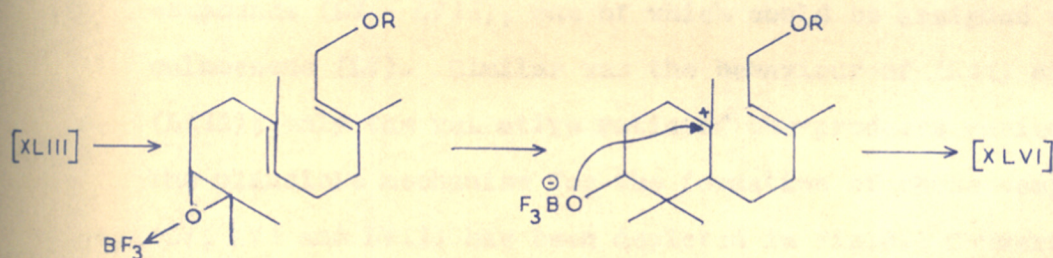
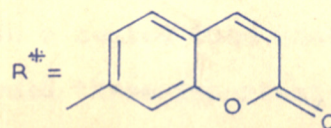
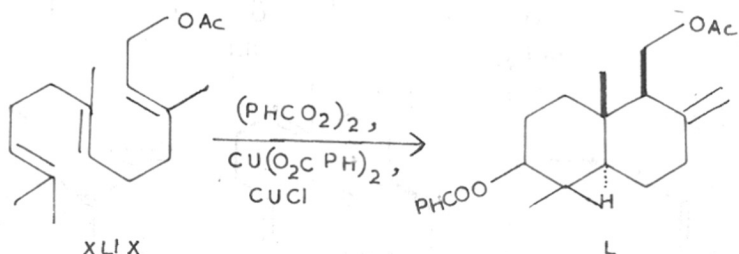


FIG-8 SYNTHESIS OF FARNESIFEROL-A AND FARNESIFEROL-C

of fused alicyclic systems.



(b) Further cyclisation of ten-membered compounds

(i) Cadinene and Germacrane-type: From a biogenetic point of view the synthesis of germacrane type compounds was attempted³² from monocyclic sesquiterpenes, shyobunone (LI), epi-shyobunone (LII) and iso-shyobunone (LIII) as well as isocalamendiol (LIV). When heated in a sealed tube under various conditions, shyobunone afforded three important compounds (LV - LVII), one of which could be assigned as calamenene (LV). Similar was the behaviour of (LII) and (LIII); only the relative ratio of the products varied. The plausible mechanism for the formation of these compounds (LV, LVI and LVII) has been depicted in Fig.9. Conversion of isocalamendiol into a new germacrane type compound (LVIII) has also been achieved as shown in Fig.9.

(ii) Bourbonenes. Hirose *et al.*³³ have observed that germacrene D (LIX) on treatment with silica gel was entirely isomerized and afforded a mixture of hydrocarbons from which (+)- γ -muurolene (LX), (-)- α -amorphene (LXI), α -muurolene (LXII), (+)- δ -cadinene (LXIII) and (+)- γ -cadinene (LXIV), were isolated as main products. The authors wish to stress

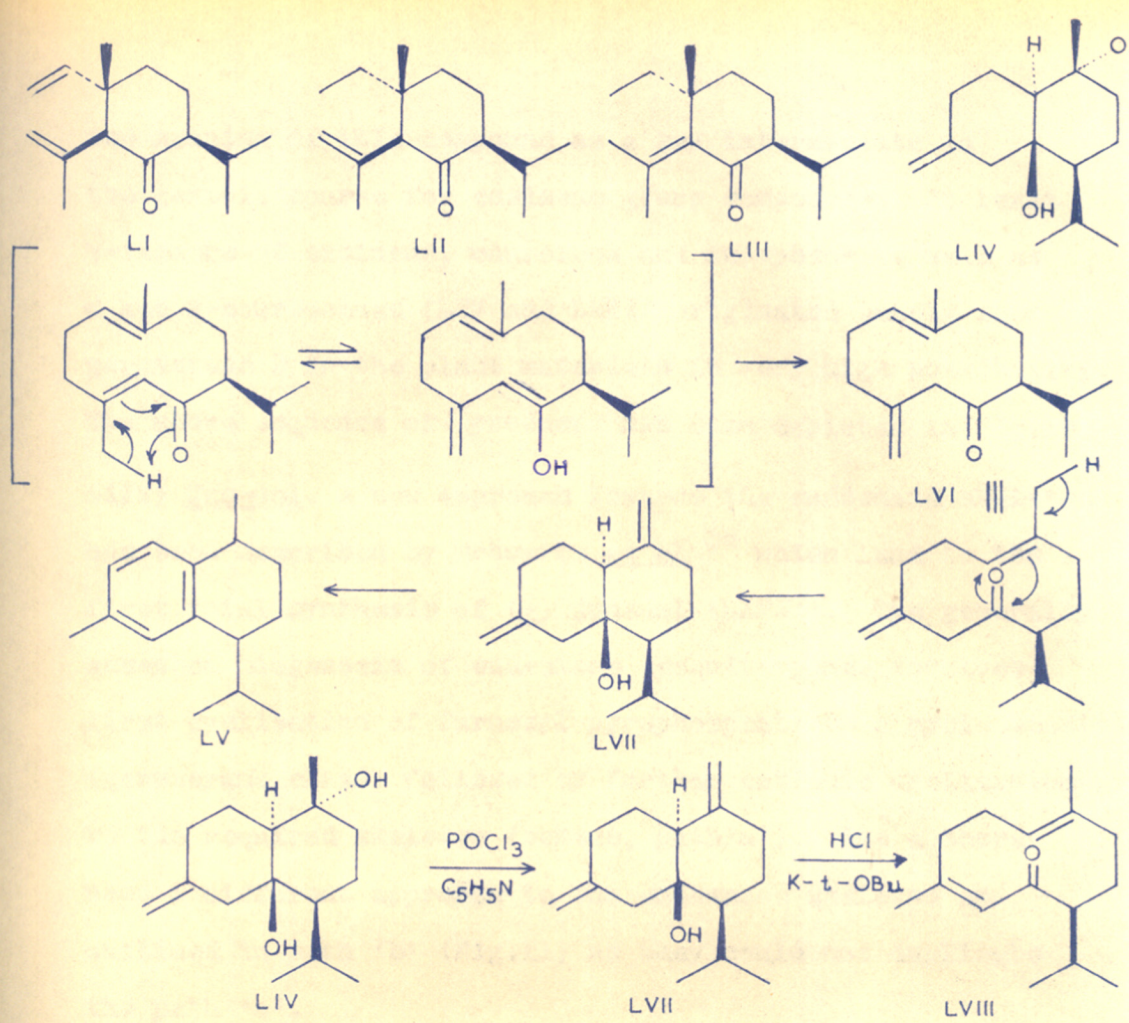


FIG.9 SYNTHESIS OF CADINENE AND GERMACRANE TYPE

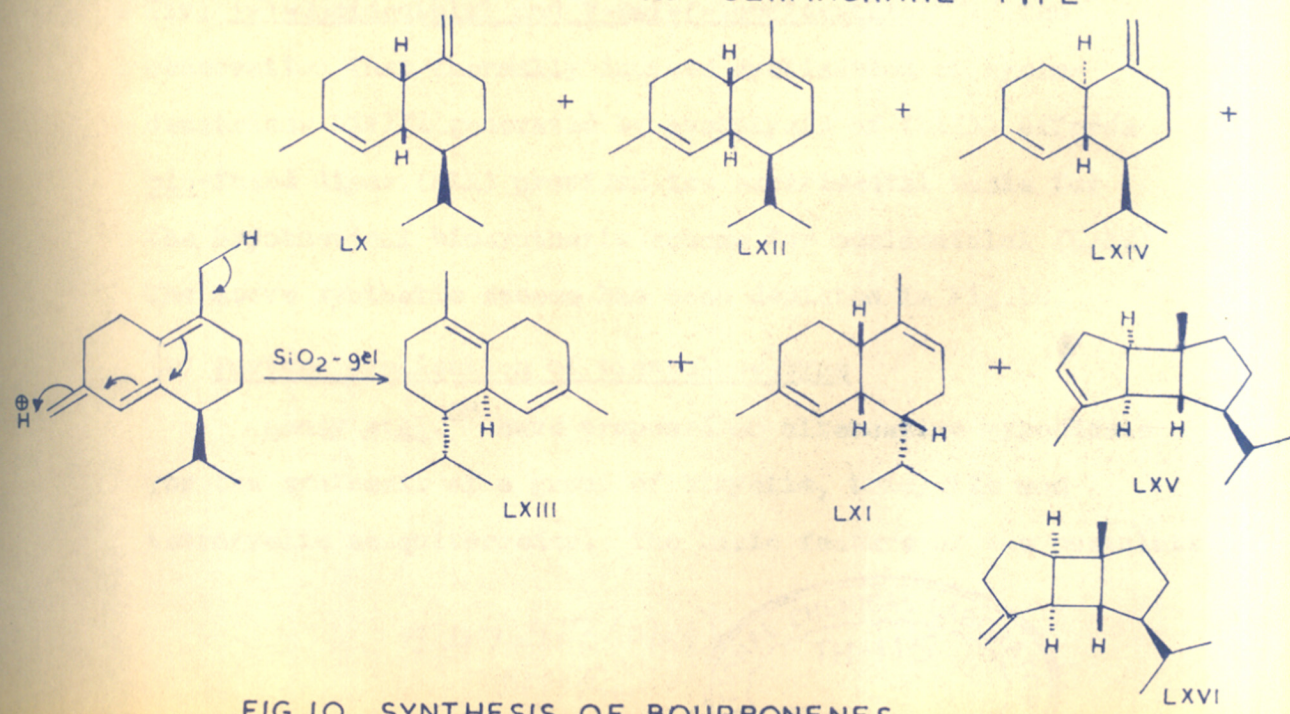


FIG.10 SYNTHESIS OF BOURBONENES

the meaning of this compound as a key intermediate in the genetic course for cadinene group compounds. At least γ -isomers of cadinene, muurolene and amorphene as well as α and β -bourbonenes (LXV and LXVI) originated solely from germacrene D in the plant materials in very high possibility. The above sequence of products has been depicted in Fig.10.

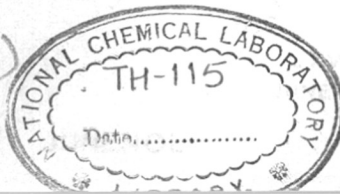
(iii) Junenol. A new approach towards the eudesmane skeleton has been described by Schwartz et al.³⁴ which lead to the first total synthesis of (+) junenol (LXVII). The generally accepted biogenesis of eudesmane sesquiterpenes involves first cyclisation of farnesyl pyrophosphate to a cyclodecadiene (germacrane class) followed by further cationic cyclisation to the required skeleton (scheme, path'a'). The authors used a different approach to the eudesmane skeleton as outlined in path 'b' (Fig.11) as they could not duplicate the path 'a'.

(iv) (+)-Occidentalol and 7-epi-(-)-occidentalol³⁵. The observation that thermally induced cyclisation of cyclo-decatriene LXVIII generated by photolysis of (LXIX) affords cis-fused diene (LXX) provided the experimental basis for the hypothetical biosynthetic scheme for occidentalol (LXXI). The above synthetic scheme has been depicted in Fig.12.

(c) Further cyclisation of bisabolane type

Money et al.³⁶ have proposed an alternative hypothesis for the synthesis of a group of bicyclic, tricyclic and tetracyclic sesquiterpenes. The basic feature of the postulate

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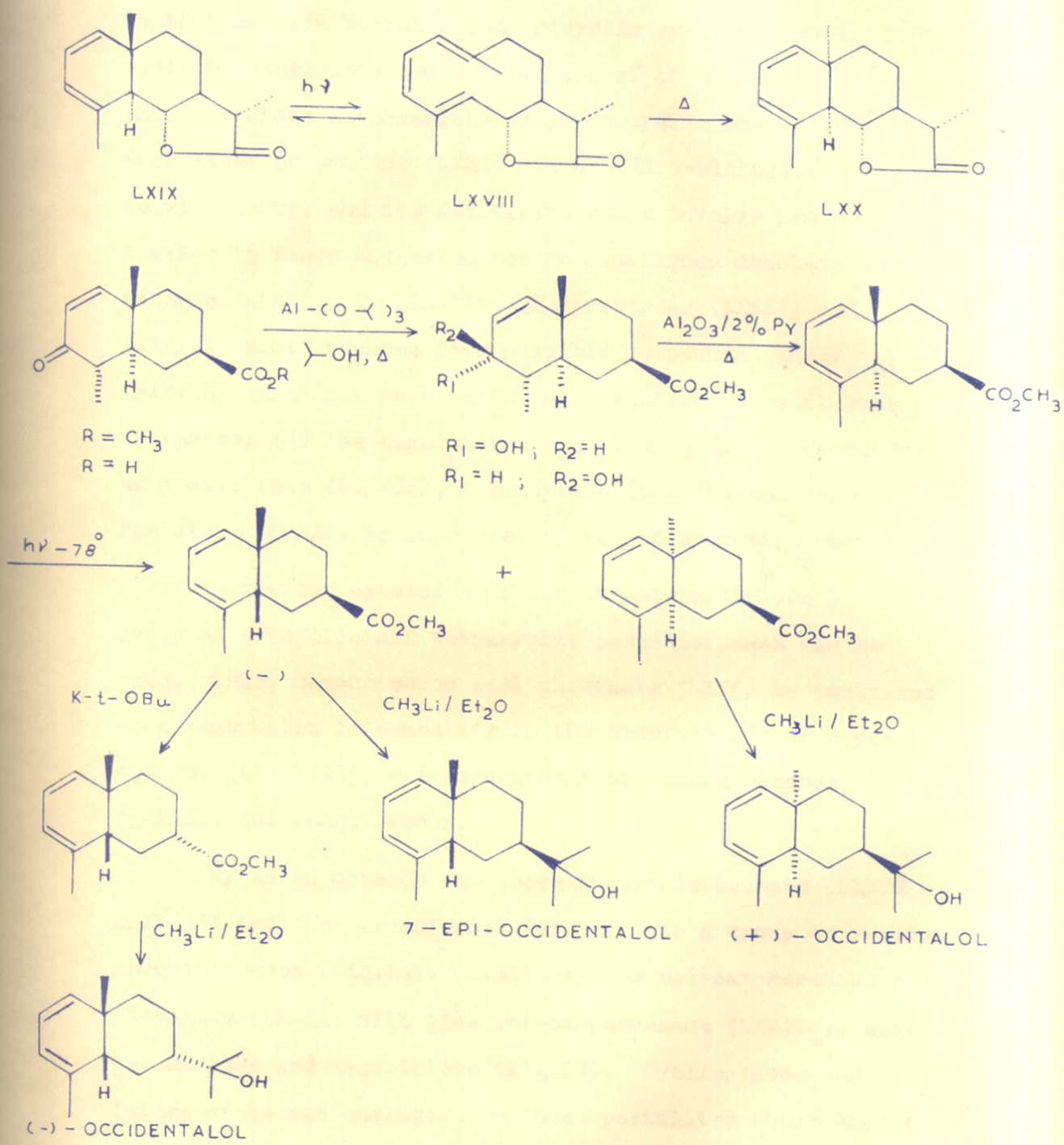


FIG-12 SYNTHESIS OF (+)-OCCIDENTALOL AND 7-EPI-(-)-OCCIDENTALOL

is that certain bicyclic and tricyclic sesquiterpenes could be constructed by cyclisation of an appropriate enol phosphate intermediate or a monocyclic enol ester, enol ether or enamine (LXXII and LXXIII; Z-biological leaving group) and its derivative could involve processes similar to those suggested for the analogous monoterpene intermediate³⁷. Cyclisation of structures (LXXII) and (LXXIII) could produce four possible compounds (LXXIV_{a-d}) (Fig.13) which may be regarded as sesquiterpene analogues of camphor and the expectation that they could be precursors of β -santalene (LXXXII), α -santalene (LXXXIV) and epi- β -santalene (LXXXV) is supported by recent synthetic work³⁸.

A further extension of the theme to include a group of tricyclic and tetracyclic sesquiterpenes can be made. Thus, campherenone enol phosphate (LXXV) is envisaged as a reasonable intermediate in the biosynthesis of copacamphor (LXXXVIII), epi-copacamphor or (ylangocamphor) (LXXXIX) and longicamphor.

By known methods the above tricyclic ketones (LXXVI - LXXVIII) could be transformed further into a group of related sesquiterpenes (Fig.14). Similarly the epi-campherenone enol phosphate (LXXIX) will give epi-campherenone (LXXIV_b), epi- β -santalene and α -santalene (Fig.14). Cyclisations and interconversions analogous to those postulated above have been carried out by Money *et al.*³⁶ from campherenone (LXXIV_c) and epi-campherenone (LXXIV_b). These two compounds were synthesised

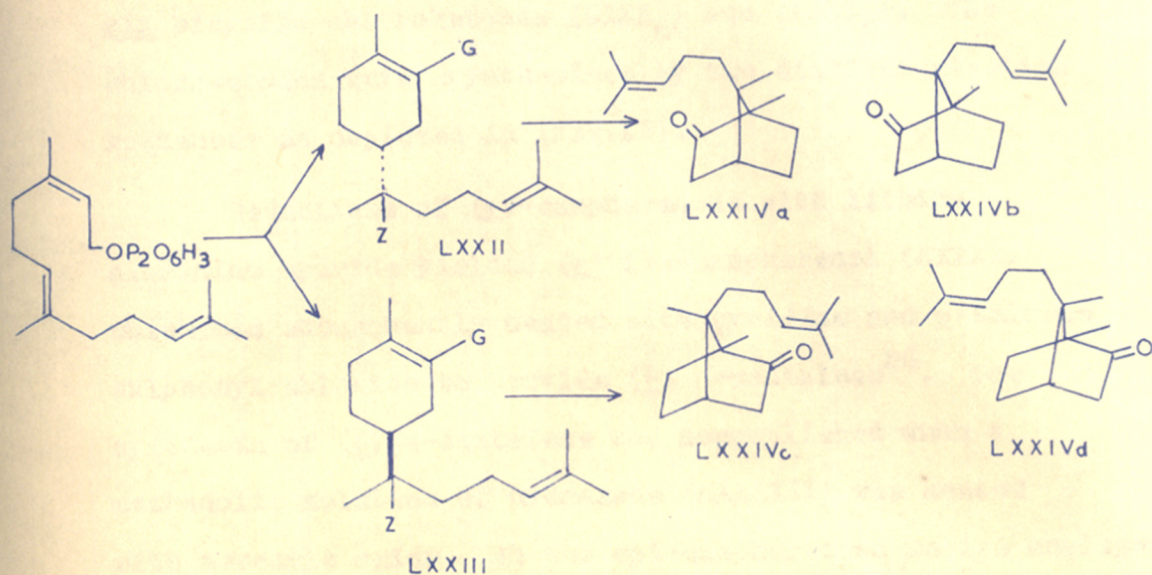


FIG. 13

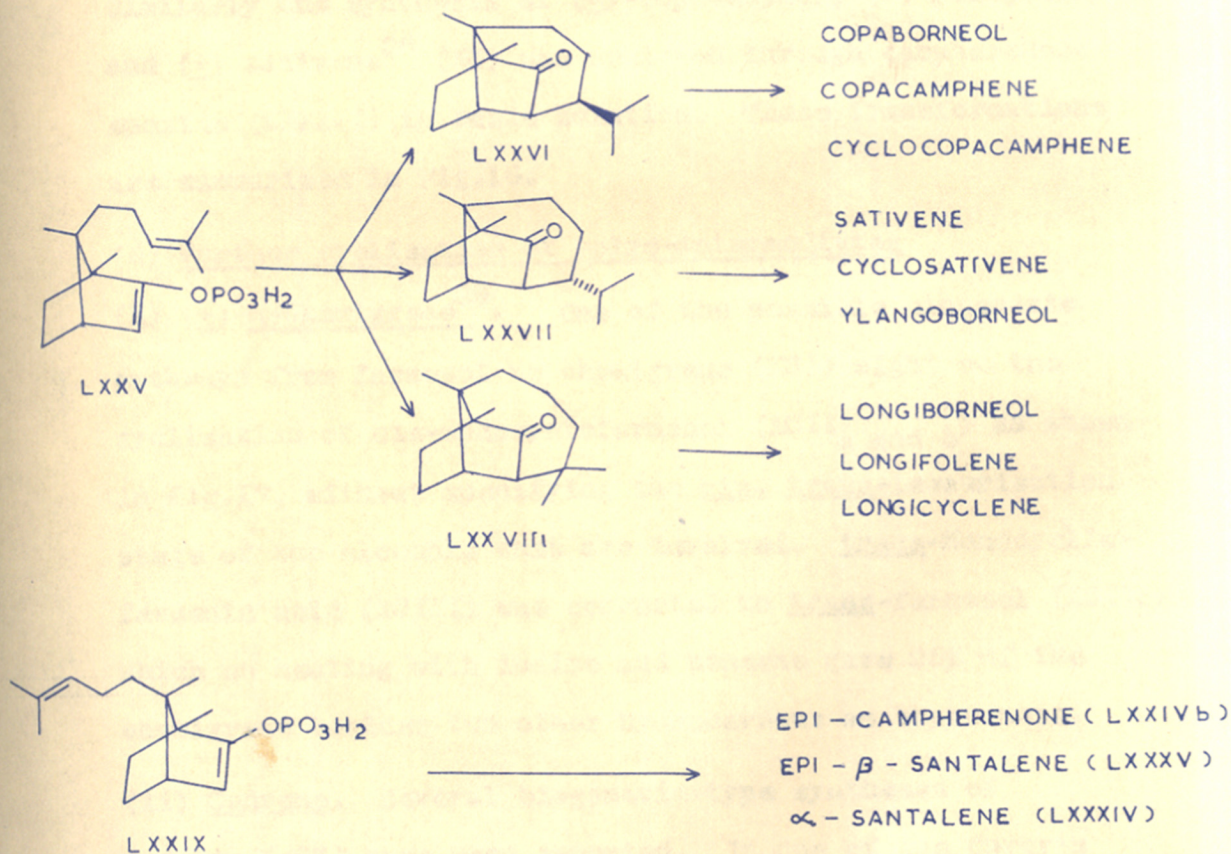


FIG. 14 TRANSFORMATION OF CAMPHERENONE AND EPI - CAMPHERENONE ENOL PHOSPHATES.

via bicyclic chloroketones (LXXX_a) and (LXXX_b). The chloroketones were synthesised by two distinct reaction sequences as depicted in (Fig.15).

Reductions of (+)-campherenone with lithium aluminium hydride yielded (+) iso-campherenol (LXXXI) which was subsequently heated with pyridine and p-toluene sulphonyl chloride to provide (+) β-santalene³⁶. The synthesis of (+)-α-santalene was accomplished when a methanolic solution of hydrazone (LXXXIII) was heated with mercuric oxide. In the epi-campherenone series analogous reactions yielded (+)-epi-β-santalene³⁶ and (+)-α-santalene. Similarly the synthesis of (+)-copacamphor, (+)-ylangocamphor and (+) sativene³⁶ (XC) was achieved through campherenone epoxide (LXXXVI) in basic solution. These transformations are summarised in Fig.16.

(d) Further cyclisation of spiro-intermediates

- (1) (+) α-Chamigrene³⁹. One of the possible biogenetic pathways from farnesol to chamigrene (XCI) might be the cyclisation of cis-monocyclofarnesol (XCII_a and b) as shown in Fig.17, without specifying the cis, trans-isomerisation stage of the alcohols that are involved. trans-Monocyclic-farnesic acid (XCIII) was converted to trans-farnesol (XCII_b) which on heating with iodine and benzene gave 25% of the chamigrene besides two other hydrocarbons as byproducts.
- (11) Cedrene. Several biogenetic-type syntheses of cedrene (XCV) have been reported. In one of the Corey's

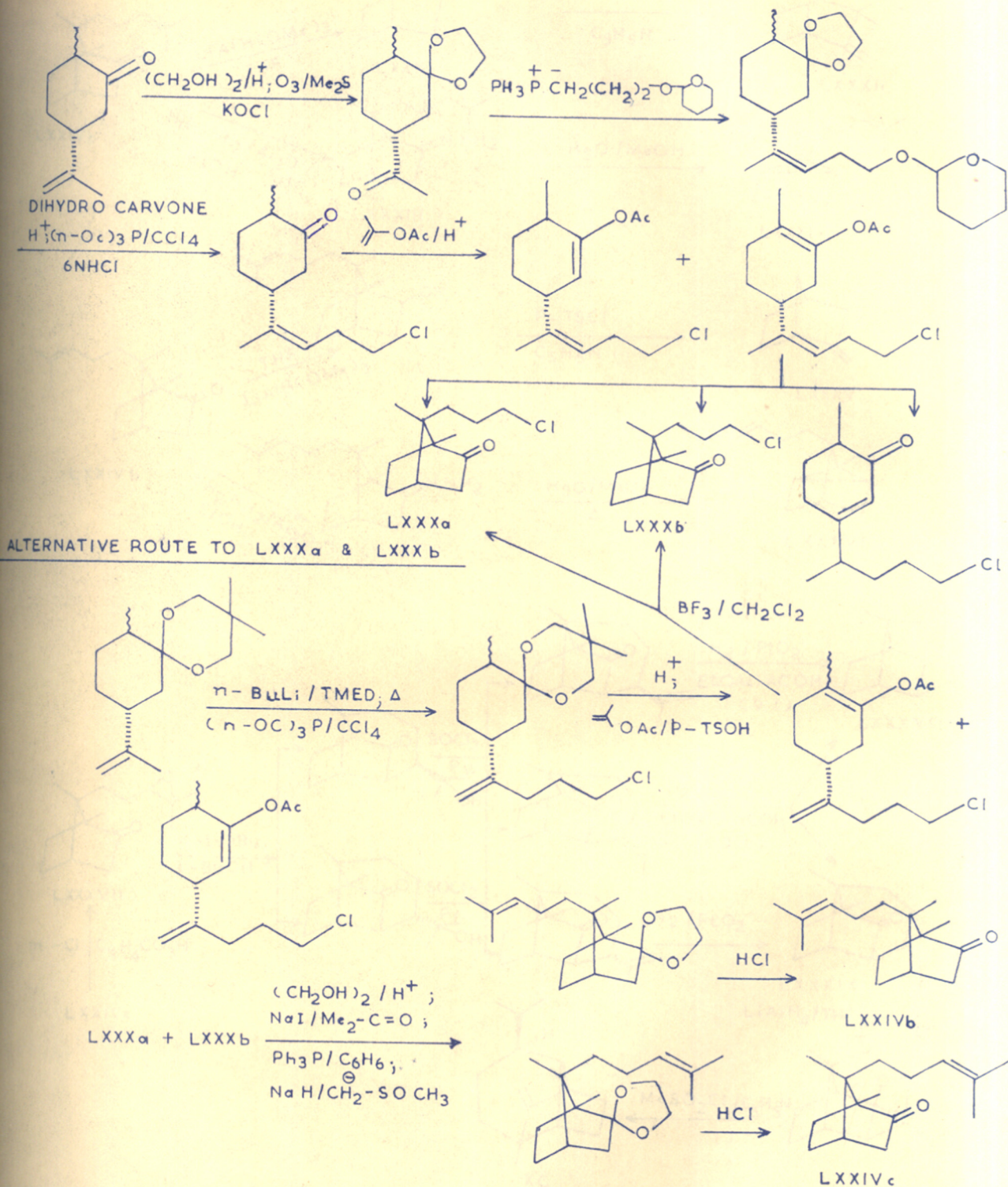


FIG - 15 SYNTHESIS OF CAMPHENONE & EPI-CAMPHENONE

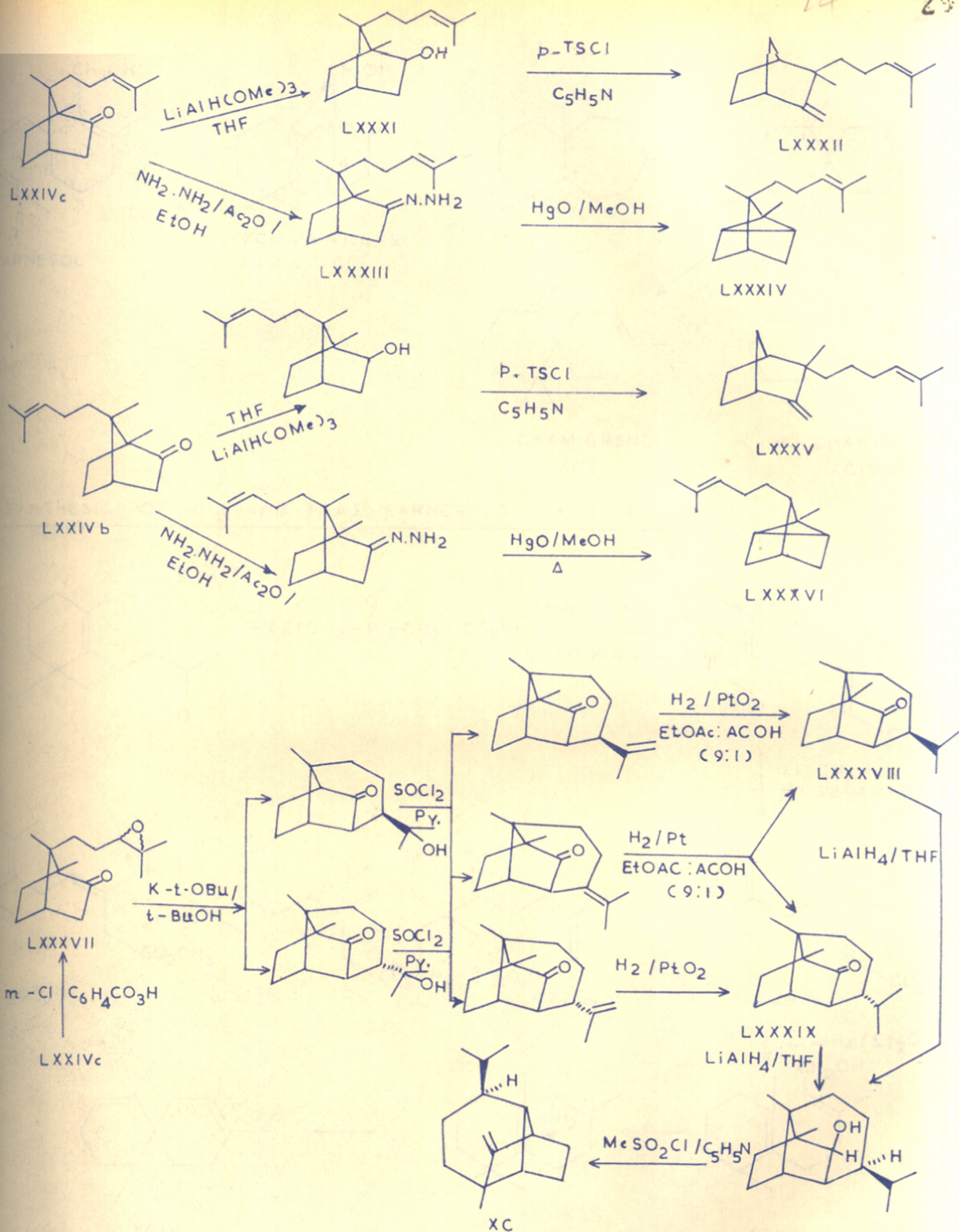
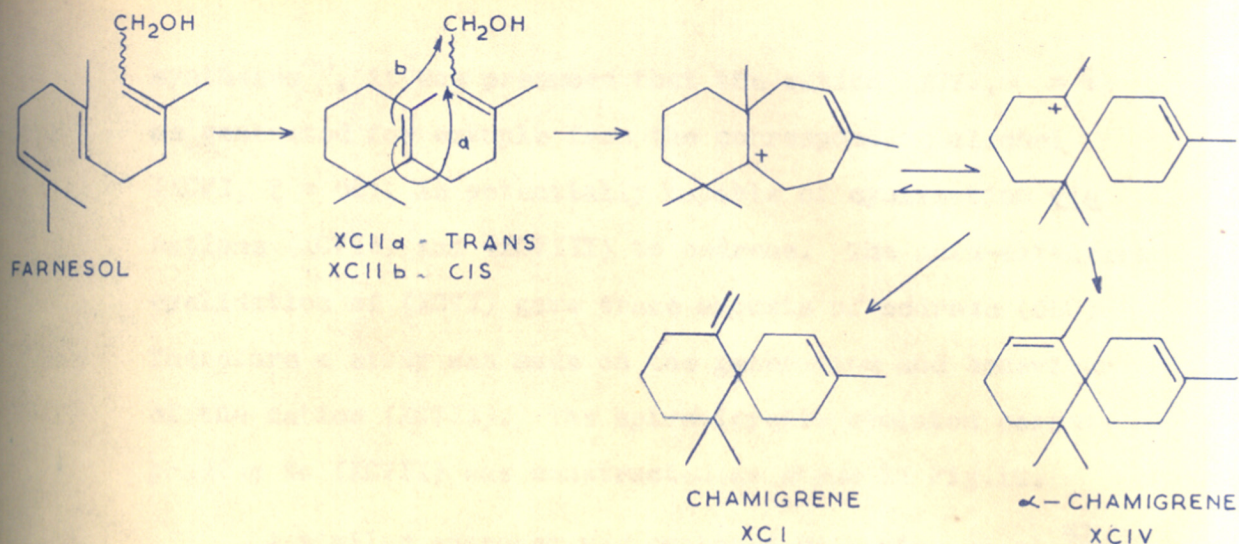


FIG. 16 TRANSFORMATION OF CAMPHENONE, EPI - CAMPHENONE AND CAMPHENONE EPOXIDE



SYNTHESIS OF CIS AND TRANS FARNESOLS XCIIa & b

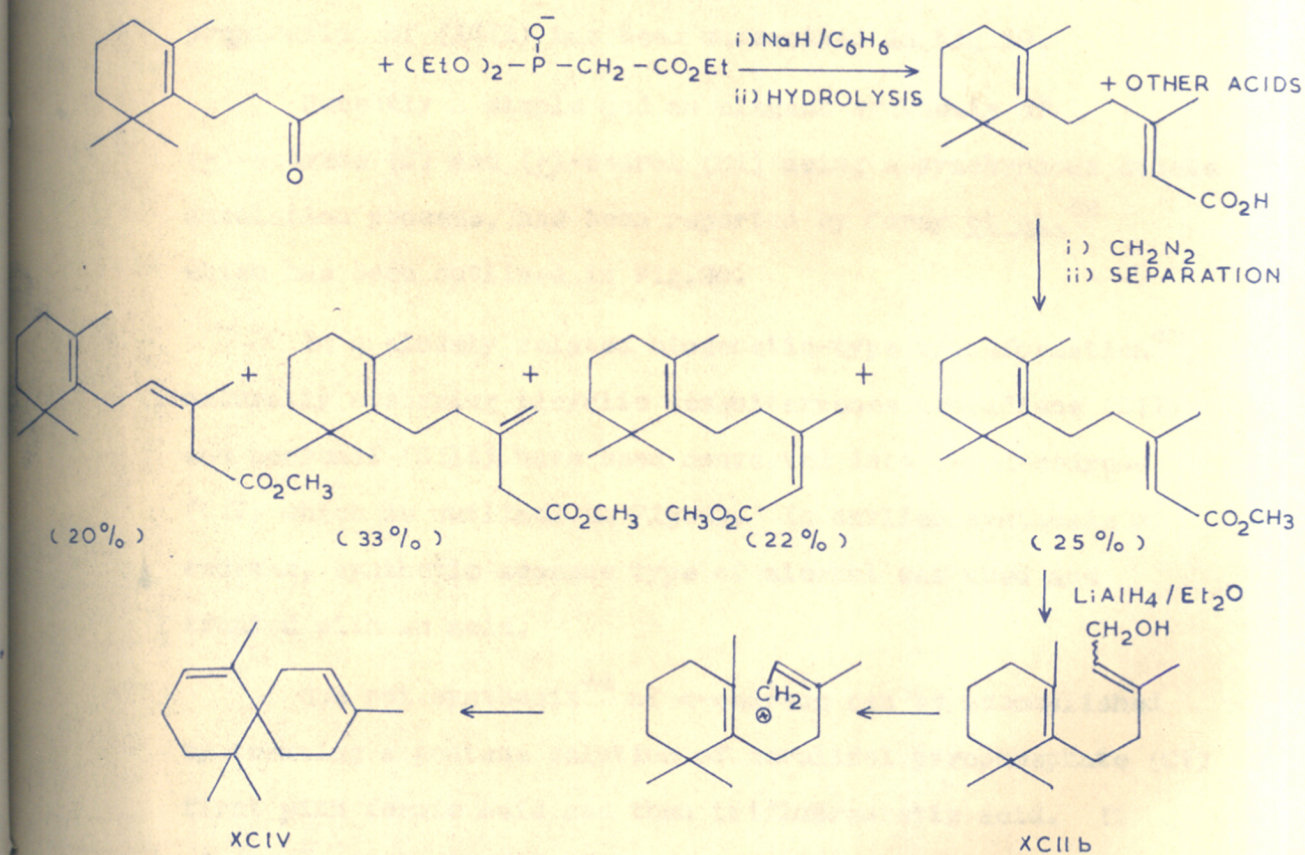


FIG-17 SYNTHESIS OF (±)- α -CHAMIGRENE

syntheses⁴⁰, it was presumed that the cation (XCVI, Y = +) as generated for example from the corresponding alcohol (XCVI, Y = OH), is potentially capable of cyclisation via cations (XCVII) and (XCVIII) to cedrene. The acid-catalysed cyclisation of (XCVI) gave trace amounts of cedrene (GLC). Therefore a study was made on the generation and behaviour of the cation (XCVII). The spirobicyclic skeleton corresponding to (XCVII) was constructed as shown in Fig.18.

A similar approach was employed by Lawton et al.⁴¹ who exposed the unsaturated alcohol (XCIX) to formic acid and obtained an approximately 80% yield of cedrene. The preparation of (XCIX) has been summarised in Fig.19.

Recently a simple and an elegant synthesis of (+)-cedrene (C) and (+)-cedrol (CI) using a synchronous double annulation process, has been reported by Corey et al.⁴² which has been outlined in Fig.20.

In a closely related biogenetic-type transformation⁴³, naturally occurring bicyclic sesquiterpenes acoradiene (CII) and acorenol (CIII) have been converted into (-) α -cedrene (CIV) which is outlined in Fig.21. In earlier synthesis of cedrene, synthetic acorane type of alcohol was used and treated with an acid.

One pot synthesis⁴⁴ of α -cedrene can be accomplished by treating a pentane solution of nerolidol pyrophosphate (CV) first with formic acid and then trifluoroacetic acid. It gives α -cedrene in 20% yield in less than two hours. The key

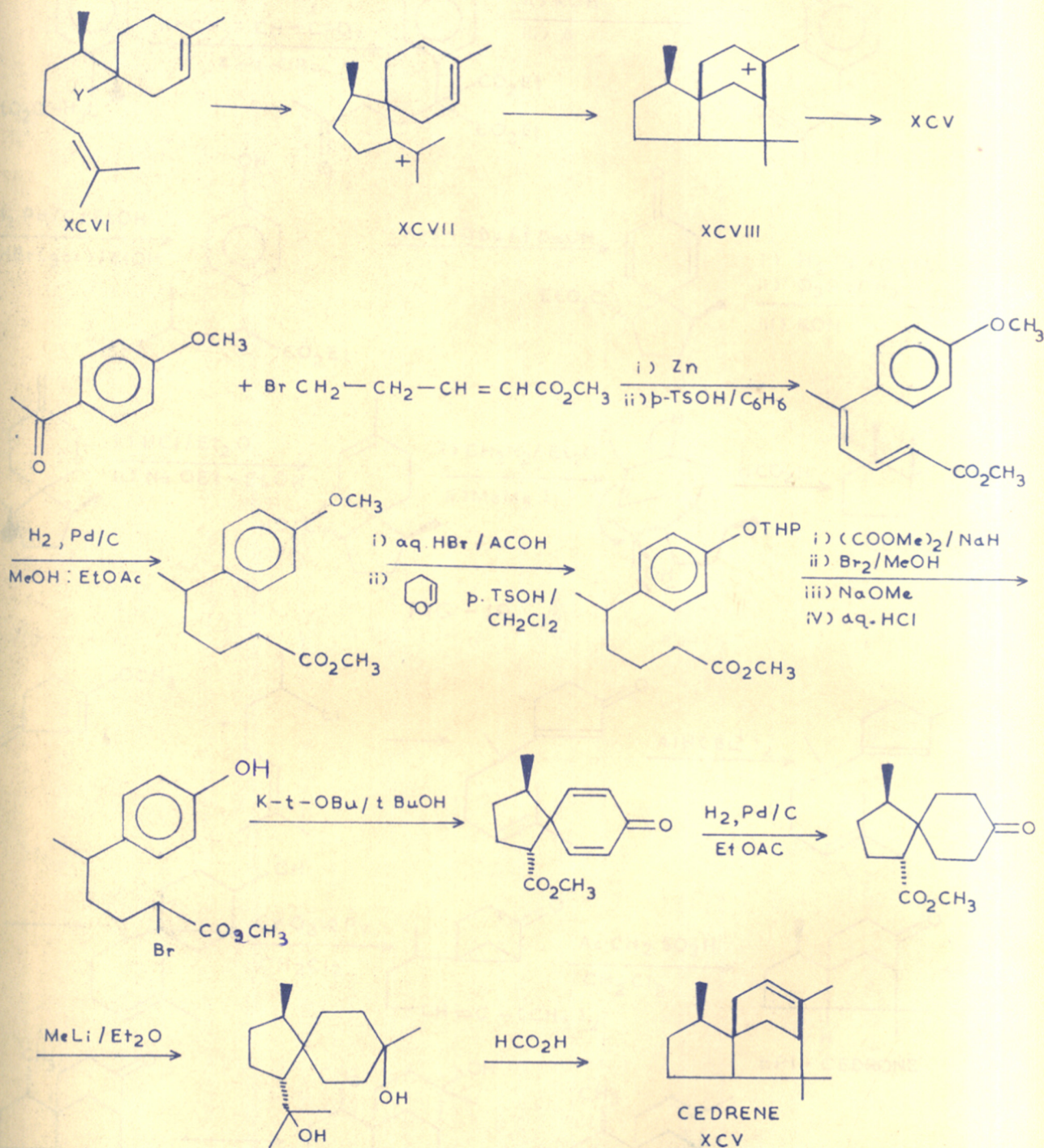


FIG. 18 SYNTHESIS OF CEDRENE

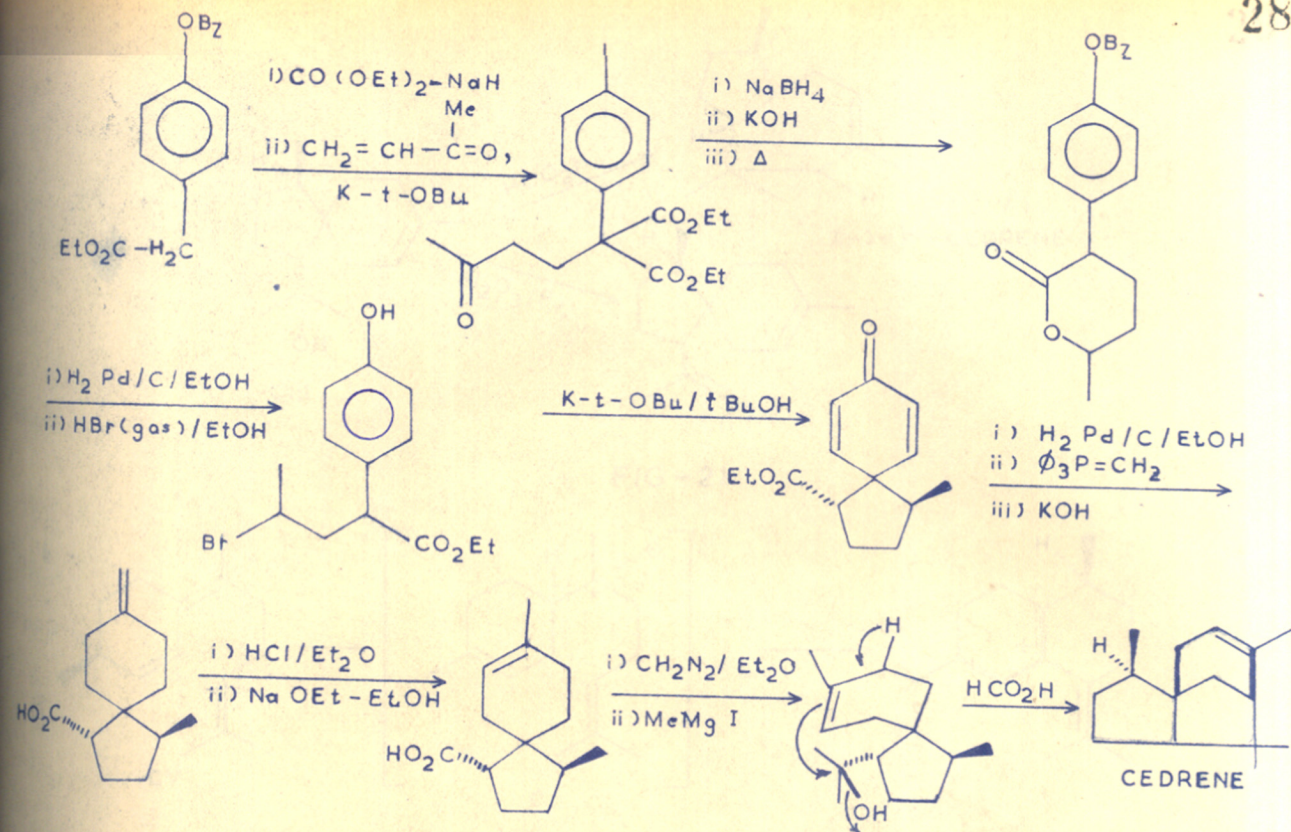


FIG - 19

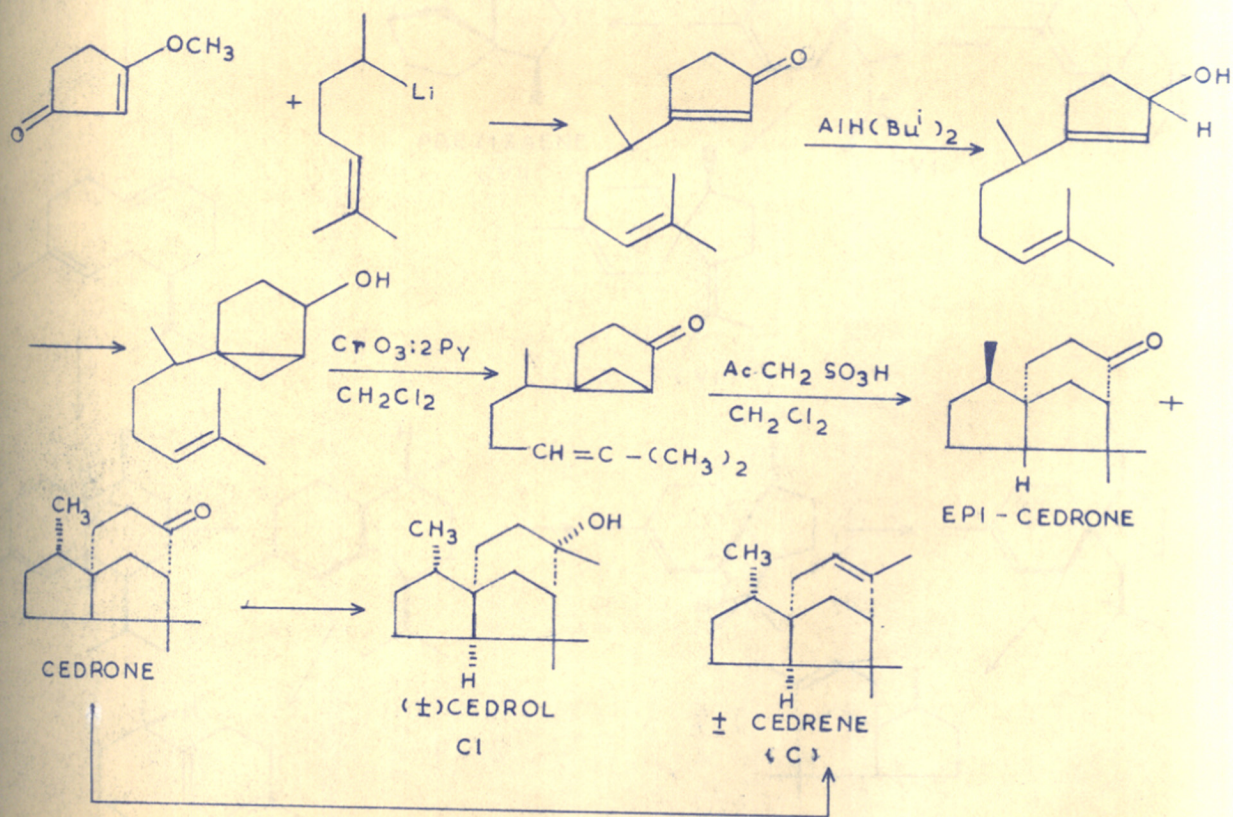


FIG - 20 SYNTHESIS OF CEDRENE

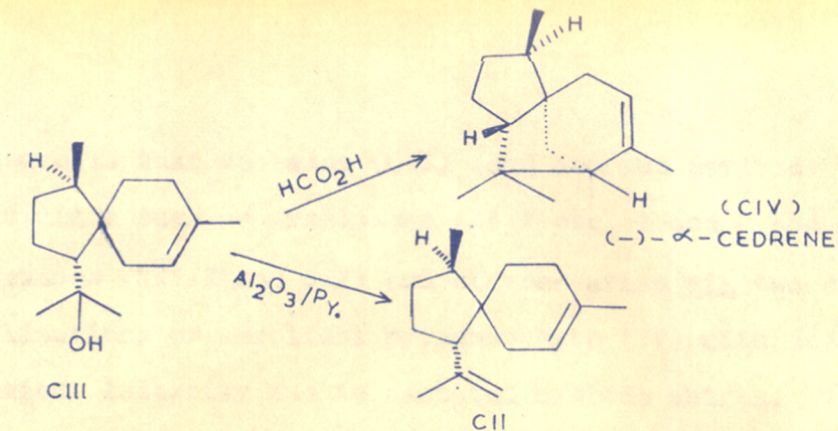


FIG - 21

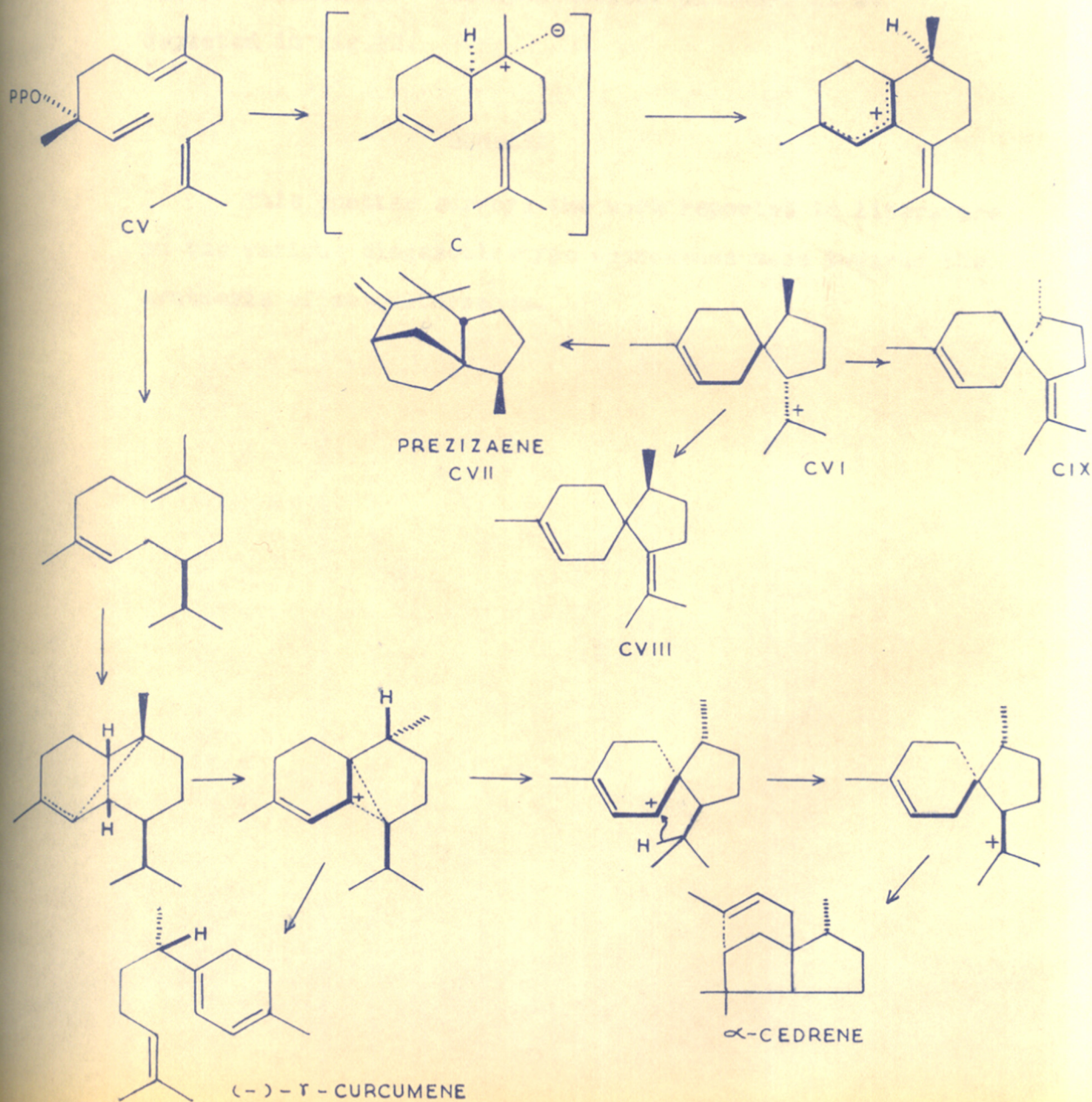


FIG-22 SYNTHESIS OF CEDRENE

feature is that acoranes (CVI) (and acorane derived tricyclics such as prezizaene (CVII) etc.) and β and α -alaskanes (CVIII and CIX) and cedrene arise via two distinct cyclisations of nerolidol pyrophosphate (CV) with stereochemical integrity due to assisted hydride shifts. Ion (c) represents an asymmetrically solvated or bound (+)-bisabolyl ion or bisabolol. The hypothetical pathways is as depicted in Fig.22.

SUMMARY

This Chapter surveys the work reported in literature on the various biogenetic-type approaches made towards the synthesis of sesquiterpenes.

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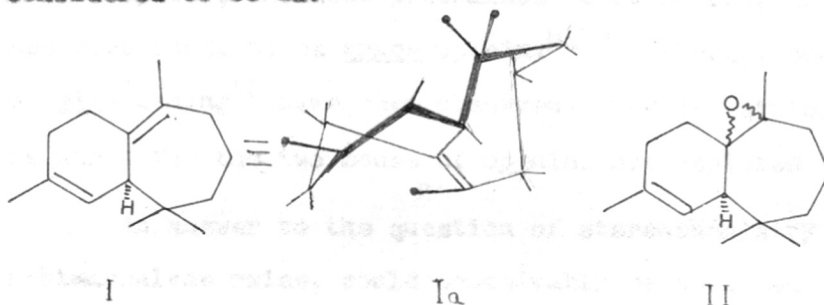
CHAPTER II

β - HIMACHALENE OXIDE, ITS REACTIONS AND STEREOCHEMISTRY

β-HIMACHALENE OXIDE, ITS REACTIONS AND STEREOCHEMISTRY

β-Himachalene (I)¹ on epoxidation² gives a mono-oxide, which has been shown to possess a gross structure II.

It has been suggested that this oxide has a stereochemistry III, essentially on the basis that the per acid will approach the hydrocarbon molecule from the less hindered (concave) *g*-face. This, of course, presupposes a preferred conformation for β-himachalene, which was considered to be Ia.



A careful analysis of the various conformations which the molecule of β-himachalene (I) can adopt, shows that the conformation Ia, may not be unique in terms of energy content. This reopens up the question of the stereochemistry of the oxide.

In this Chapter we have sought to answer this question and describe some of its reactions. These are briefly discussed below.

Action of Lithium-Ethylenediamine on β-Himachalene oxide and its stereochemistry

Opening of oxirane rings by a hydride attack has been extensively investigated³. Various reagents which have been employed are:

1. Lithium-aluminium hydride
2. Mixed hydrides⁴
3. Diborane⁵
4. Lithium-triethyl borohydride⁶
5. Lithium-liquid ammonia⁷
6. Lithium-ethylamine⁸ and
7. Lithium-ethylene diamine⁹ etc.

By far, the most predominant mode of ring cleavage has been found to be trans-opening^{8,10}, though, some cases of cis-opening¹¹ have been observed. The transition states required for the two modes of opening are depicted in Fig.1.

An answer to the question of stereochemistry of the β -himachalene oxide, could conceivably be obtained by studying the product(s) of hydride cleavage of this oxide. Fig.2 depicts the products possible from cleavage of the epoxide ring.

A perusal of Fig.2 will show that, depending upon the stereochemistry of the oxide ring, a unique compound is possible in each case: β -oxide (IV) giving rise to himachalol (VI)¹² by trans-opening^{8,10}, while α -oxide (III) can lead to epi-himachalol (V)¹³ by cis-cleavage¹¹. These compounds have been specially picked out for this discussion as both of these are known and have well-established stereochemistry.

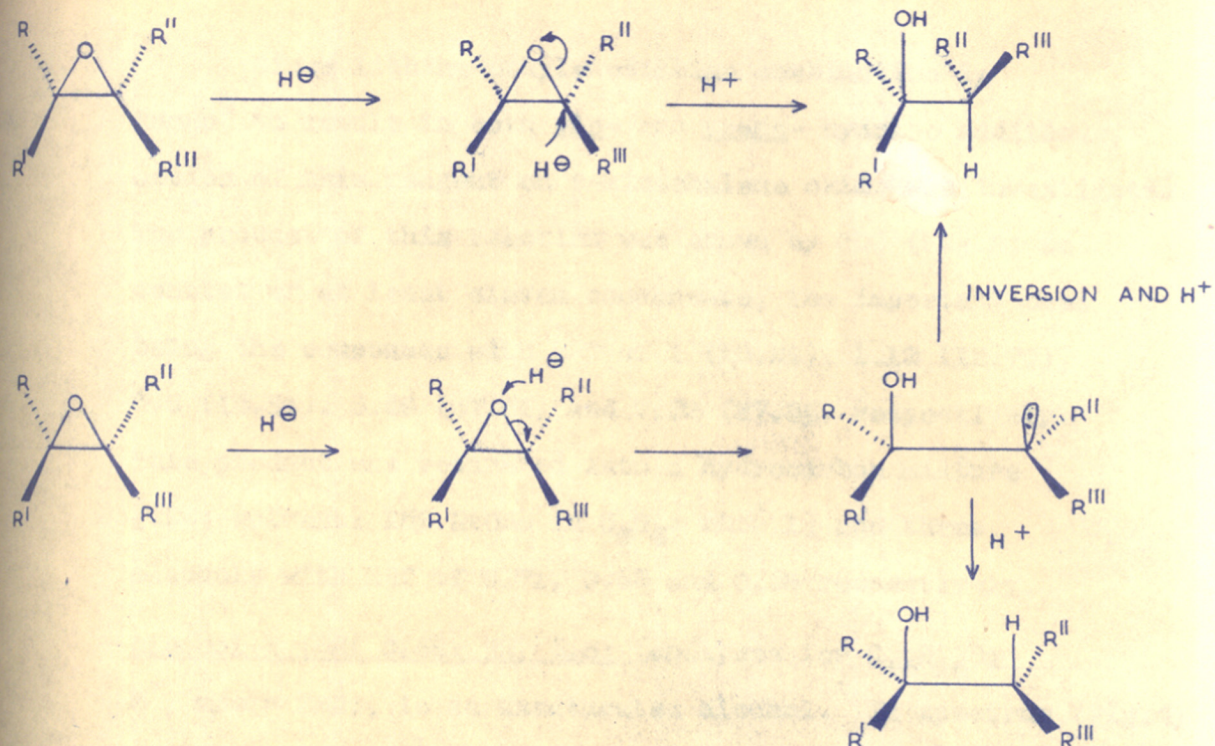


FIG. 1 - CIS- AND TRANS - MODES OF RING OPENING OF EPOXIDES

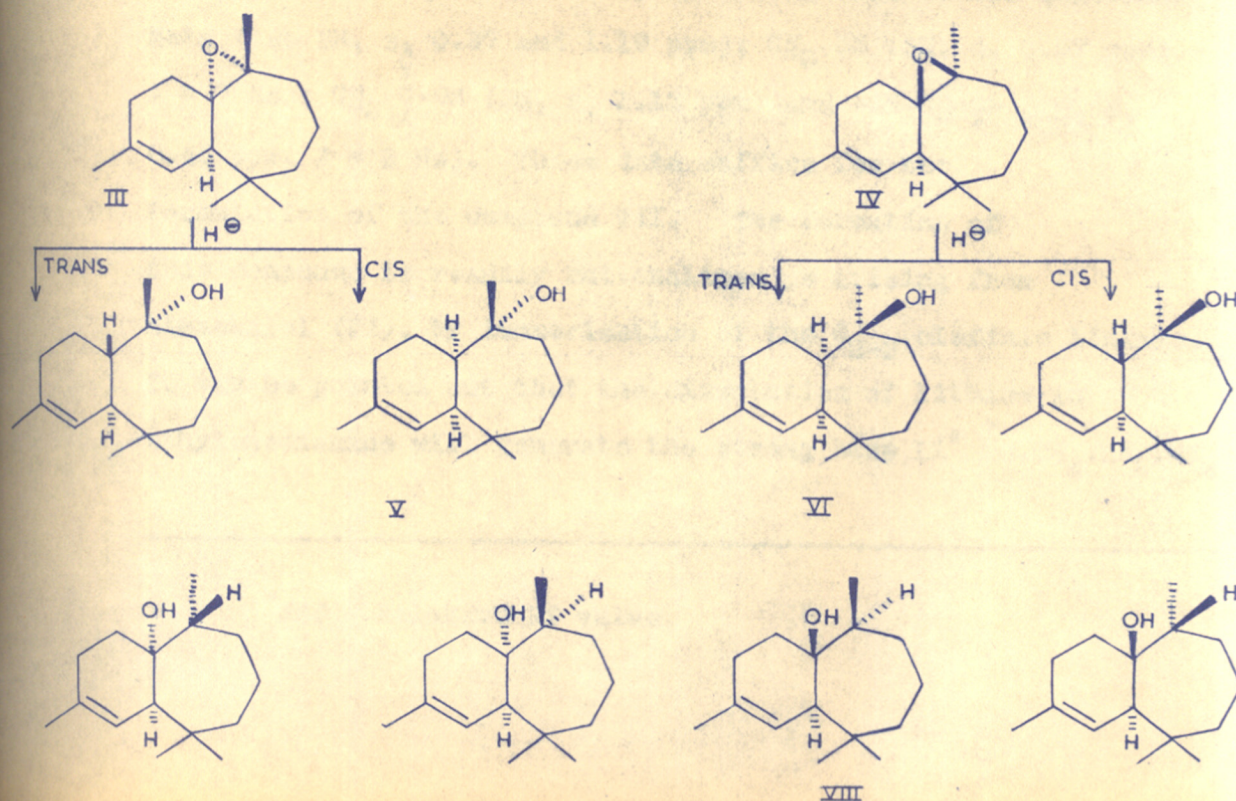


FIG. 2 - POSSIBLE PRODUCTS FROM THE CLEAVAGE OF β -HIMACHA-
LENE - α -OXIDE (III) AND β -OXIDE (IV)

Since lithium-ethylenediamine combination is known⁹ to result in both cis- and trans-hydride additions, action of this reagent on β -himachalene oxide was investigated. The product of this reaction was shown by GLC (Fig.3) to consist of at least eleven components, the important ones being the compounds with RRT of 1 (10.2%), 1.12 (12.7%), 5.6 (14.8%), 6.56 (27.8%) and 7.62 (27.3%) respectively. This product was separated into a hydrocarbon mixture [TLC; solvent: 15% EtOAc in C_6H_6 ; RRF* 1] and three alcohols with RRF of 0.71, 0.65 and 0.58 respectively.

Alcohol-1 (RRf 0.58; RRT 5.6) (analyses for $C_{15}H_{26}O$; M^+ , $m/e = 222$), is an unsaturated alcohol. IR spectrum (Fig.4): OH 3300, 1017 cm^{-1} ; $-C=CH-$ 1640, 910 and 864 cm^{-1} . It gives yellow colour with tetranitromethane (TNM). Its PMR spectrum (Fig.5) shows signals assignable to two quaternary Me's (two 3H, s, 0.97 and 1.10 ppm); CH_2-CH (3H, d, 0.97 ppm; $J = 7$ Hz); $CH_3-\overset{\overset{O}{|}}{\underset{\underset{C}{|}}{C}}-OH$ (3H, s, 1.13 ppm) and $-CH-CH=C-$ (1H, d, 5.46 ppm, $J = 3$ Hz). These data suffice for the formulation of the compound VII. The formation of this compound is readily rationalised as arising from himachalol (VI), by isomerisation of the C_{2-3} olefinic linkage. It may be pointed out that the dissolution of lithium in ethylenediamine will generate the strong base $Li^+ \bar{NH}.CH_2.CH_2.NH_2$

* RRF = Relative Rf value.

COLUMN: 20% DIETHYLENE GLYCOL
POLYSUCCINATE / CHROMOSORB W
TEMP. RISE 6°/MIN.
CHART SPEED (30" / HR)
FLOW RATE: 110 ML / MIN.
CARRIER GAS: H₂

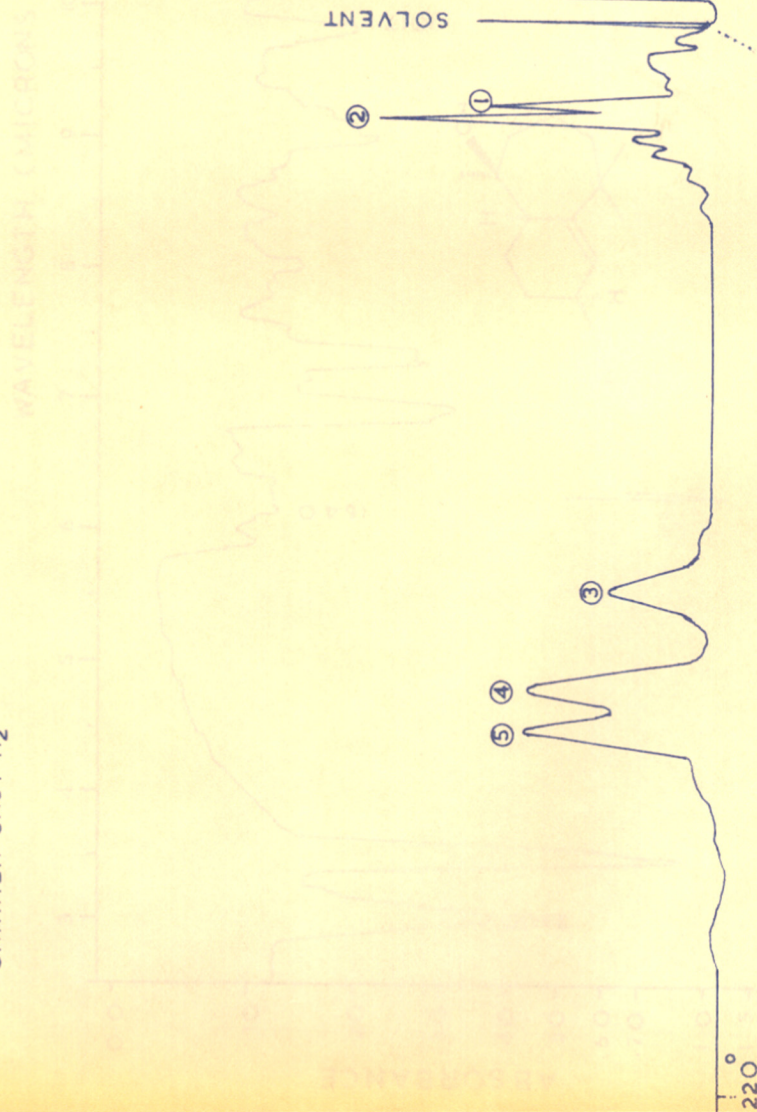


FIG. 3 PROGRAMMED GLC OF TOTAL PRODUCTS OF LITHIUM -
ETHYLENE DIAMINE CLEAVAGE OF β -HIMACHALENE
EPOXIDE

IDENTIFICATION: (1) COMPOUND (IX) (2) HIMACHALANE (X)
(3) 7 β - HYDROXY - HIMACHAL - 1 - EN - E (VII)
(4) 6 β - HYDROXY - 1 α - HIMACHAL - 2 - EN - E (VIII) (5) HIMACHALOL (VI)

COLUMN: 20% DIETHYLENE GLYCOL
POLYSUCCINATE / CHROMOSORB W
FLOW RATE: 70 ML / MIN.
CHART SPEED (30" / HR)
CARRIER GAS: H₂

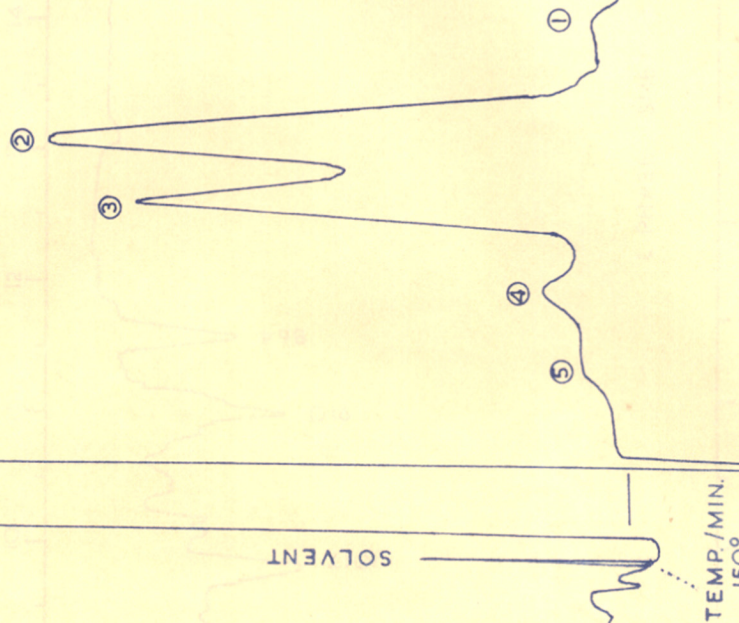


FIG. 8 GLC OF HYDROCARBON MIXTURE
OF LITHIUM ETHYLENE DIAMINE
CLEAVAGE OF β HIMACHALENE
EPOXIDE

IDENTIFICATION: (1) UNIDENTIFIED (2) HIMACHALANEX
(3) COMPOUND (IX) (4) UNIDENTIFIED (5) UNIDENTIFIED

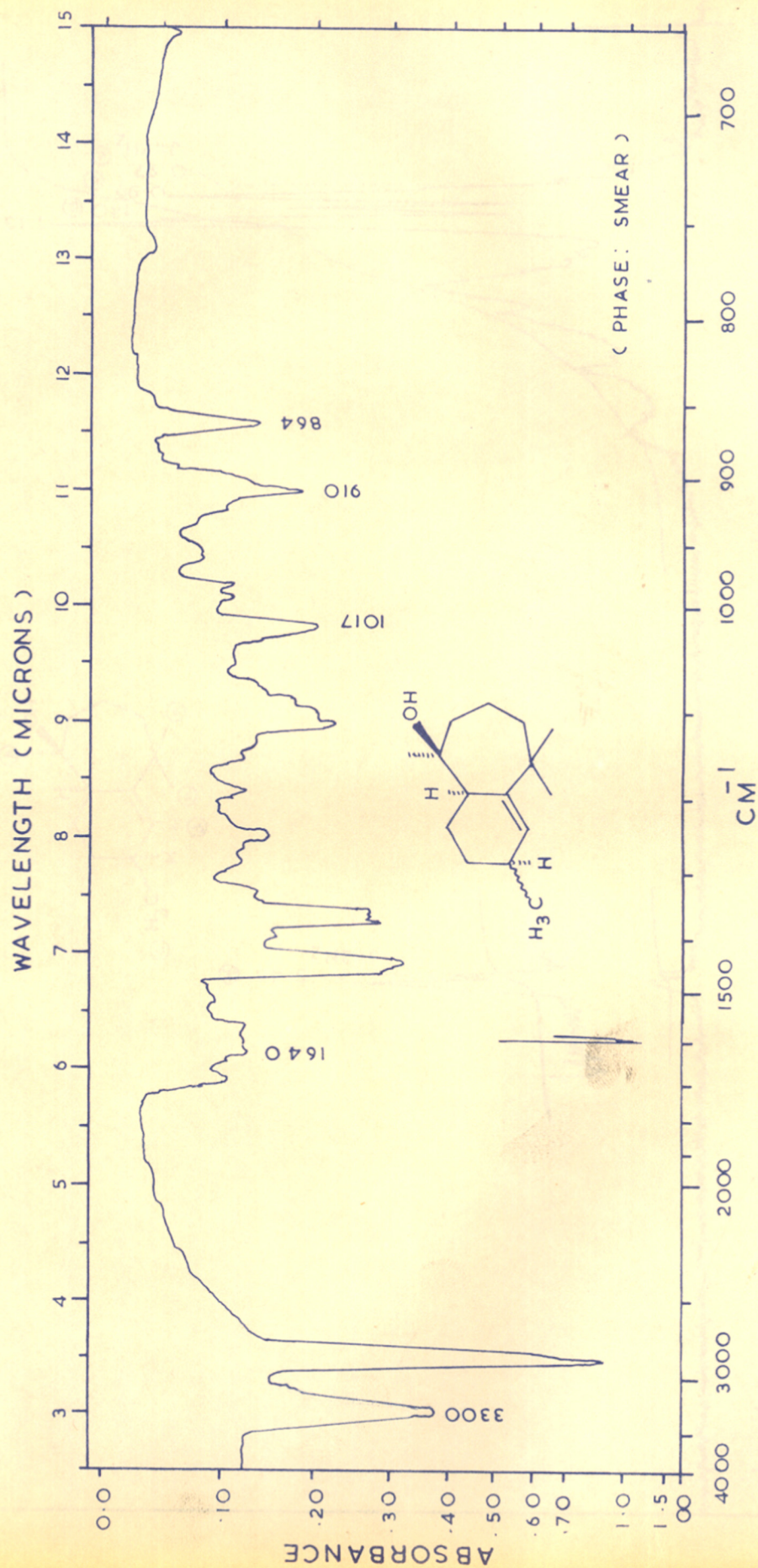
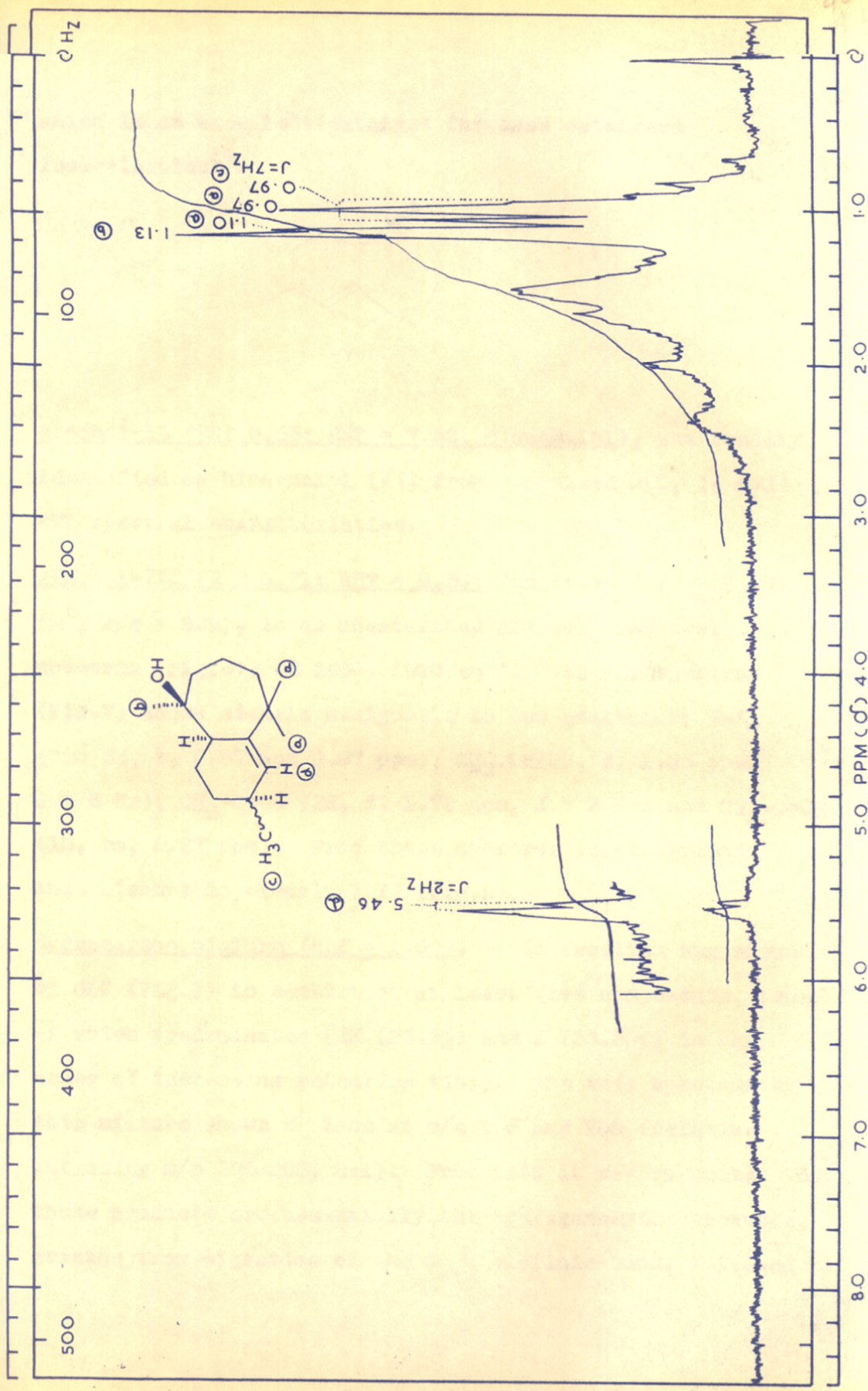
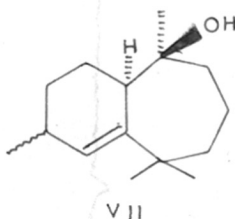
FIG.4 IR SPECTRUM OF ALCOHOL -1 (7β - HYDROXY - HIMACHAL -1-ENE , VII)

FIG.5 PMR SPECTRUM OF ALCOHOL -1 (7 β - HYDROXY - HIMACHAL -1-ENE, VII)



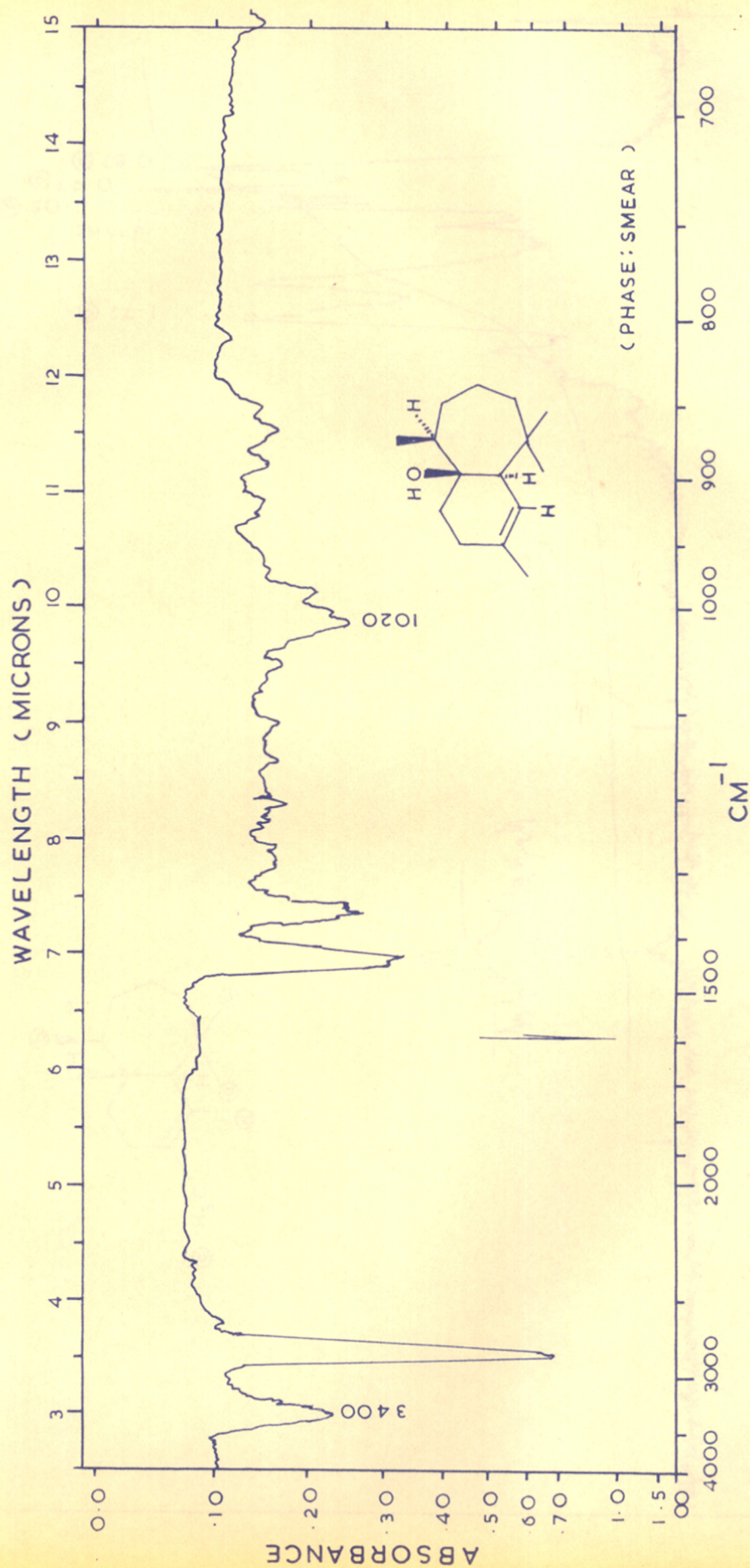
which is an excellent catalyst for base catalysed isomerisation¹⁴.



Alcohol-II (RRf 0.65; RRT = 7.62, Himachalol), was readily identified as himachalol (VI) from its mixed GLC, IR and PMR spectral characteristics.

Alcohol-III (RRf 0.71; RRT = 6.56) (analyses for $C_{15}H_{26}O$) (M^+ , $m/e = 222$), is an unsaturated alcohol (TMM test), IR spectrum (Fig.6): OH 3400, 1020 cm^{-1} . Its PMR spectrum (Fig.7) shows signals assignable to two quaternary Me's (two 3H, s, 0.87 and 0.97 ppm); CH_3-CH (3H, d, 1.05 ppm, $J = 6$ Hz); $CH_3-C=CH$ (3H, d, 1.72 ppm, $J = 2$ Hz) and $CH_3-C=CH$ (1H, bs, 5.37 ppm). From these spectral characteristics this alcohol is clearly VIII (Fig.2).

Hydrocarbon mixture (RRf = 1.00). This fraction was shown by GLC (Fig.8) to consist of at least five components, two of which predominated [IX (36.5%) and X (53.50%) in the order of increasing retention time]. The mass spectrum of this mixture shows M^+ ions at m/e 206 and 208 (relative intensity m/e 206:208, 2:1). From this it was suspected that these products are essentially the hydrogenolysis products, arising from migration of the C_{2-3} olefinic bond, followed

FIG.6 IR SPECTRUM OF 6 β - HYDROXY - 1 α - HIMACHAL - 2 - ENE (VIII)

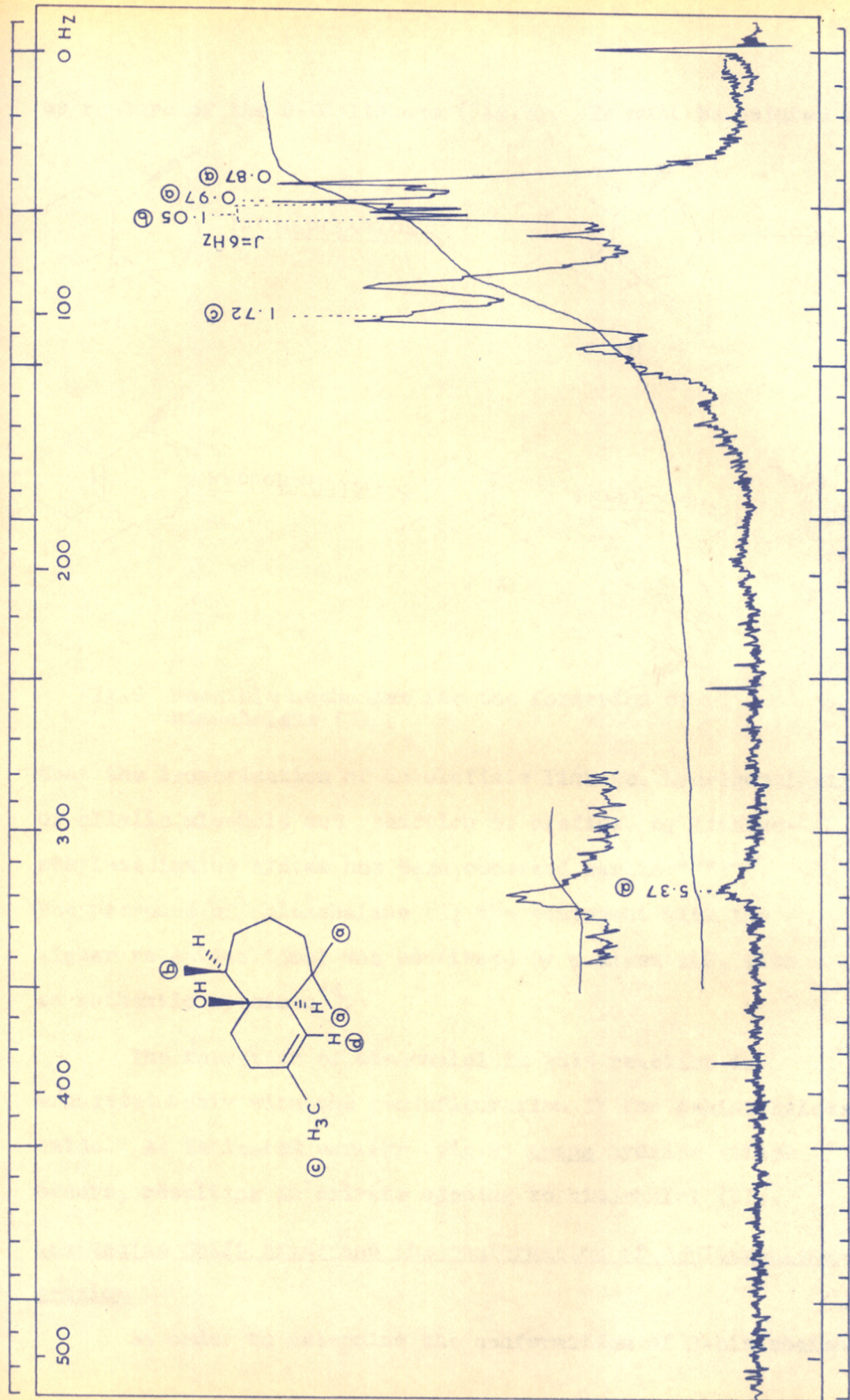


FIG.7 PMR SPECTRUM OF 6 β -HYDROXY-1 α -HIMACHAL-2-ENE (VIII)

by rupture of the C-OH linkage (Fig.9). It must be pointed out

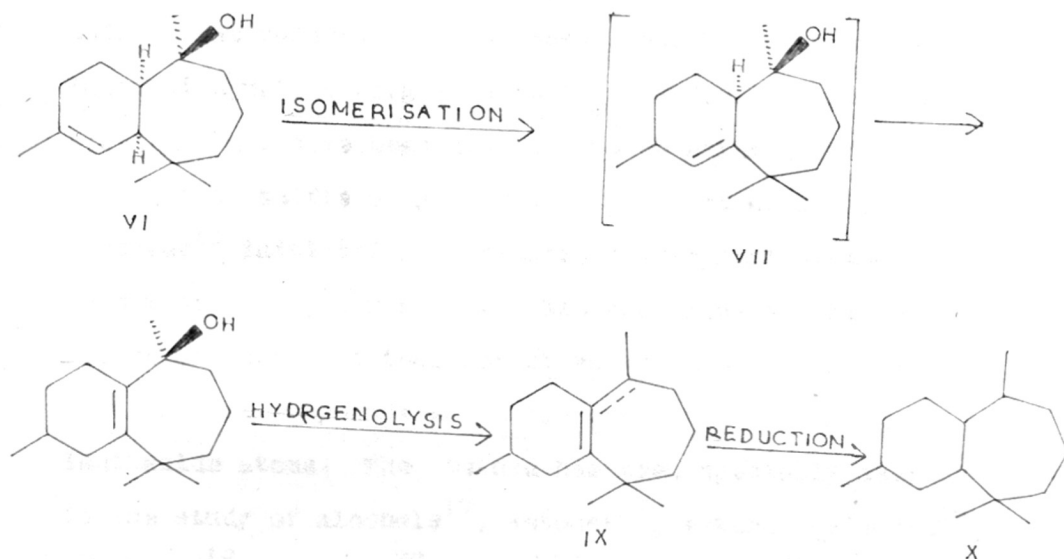


Fig.9 Possible mechanism for the formation of himachalane (X)

that the isomerisation of an olefinic linkage, hydrogenolysis of allylic alcohols and reduction of olefins by lithium-ethylenediamine system has been observed earlier^{14a,15}. The presence of himachalane (X; the component with the higher retention time) was confirmed by a mixed GLC, with an authentic specimen⁴⁴.

The formation of himachalol in this reaction is consistent only with the β -configuration IV for β -himachalene oxide. As indicated earlier (Fig.2) trans-hydride attack occurs, resulting in oxirane opening to himachalol (VI).

Lanthanide Shift Study and the conformation of α -himachalene- α -oxide

In order to determine the conformation of β -himachalene-

g-oxide (IV) a detailed study, involving PMR lanthanide shifts, was undertaken. In recent years, complexes of lanthanide metals [e.g.: $\text{Eu}(\text{DPM})_3 \cdot 2\text{Py}$] with suitable 1,3-diketones have been used to induce paramagnetic/diamagnetic shifts of protons. It was not until 1969 that Hinckley¹⁶ initiated a systematic development of this aspect of NMR spectroscopy. This technique has since become an important tool for structure and conformational studies¹⁷ of compounds which can co-ordinate with the lanthanide atoms. The method has been specially useful in the study of alcohols¹⁷, ketones¹⁷, esters, quinones¹⁸, aldehydes¹⁹, lactones²⁰, ethers²¹ and acetals²² etc.

The oxygen atom of the oxirane ring can also conceivably co-ordinate with europium and hence it should be possible to extract configurational/conformational information from such a study. However a survey of the pertinent literature shows that till todate only three cases* have been examined.

The configuration of the three epoxy insecticides²³, endrin (XI), dieldrin (XII), and phétoaldrin (XIII), have been fixed using the lanthanide induced shifts (LIS) produced

*As a matter of fact when this work was started, only two cases had been examined^{23,24}.

by tris-(2,2,6,6)-tetramethyl-3,5-heptanedione europium $[\text{Eu}(\text{DPM})_3]$ (Fig.10). Willcot et al.²⁴ used $\text{Eu}(\text{DPM})_3$ as a shift reagent to confirm the stereochemistry of the cyclo-octatetraene dimer- β -oxide (XIV) (Fig.10). The LIS data, coupled with PMR and Nuclear Overhauser effect (NOE) studies have been used very recently by Willcot et al.²⁵ to fix the configuration and conformation of 7-chloro-1,6-dibromo-3,7-dimethyl-3,4-epoxy-1-octene (XV), using $\text{Y-b}(\text{DPM})_3$ as a shift reagent (Fig.10).

In the above mentioned examples, $\text{Eu}(\text{DPM})_3$ was used for inducing downfield shifts while $\text{Y-b}(\text{DPM})_3$ was used for causing shifts to the higher field. In the lanthanide substrate complex, the interaction between paramagnetic metal ion and the nuclei of the substrate cause changes in the chemical shift of the nuclei. These shifts, which are considered to arise from a dipolar (pseudo contact) mechanism²⁶ are dependent on the distance (r), between the lanthanide ion nucleus and the specific proton and the angle (θ) subtended by the lanthanide ion and lanthanide ion substrate (Fig.11). Several formulae^{27,28} have been advanced to

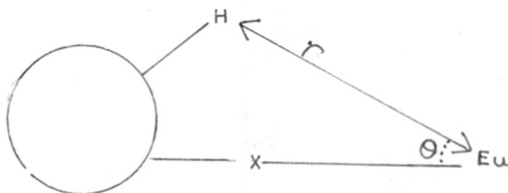
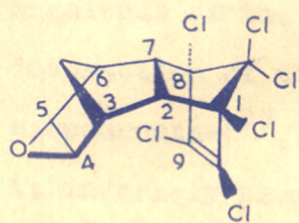
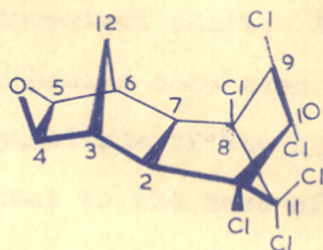


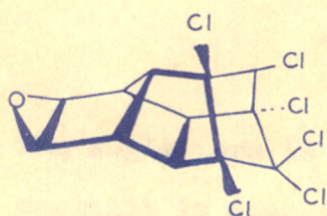
Fig.11 Geometrical variables which control the magnitude of the Induced Shifts.



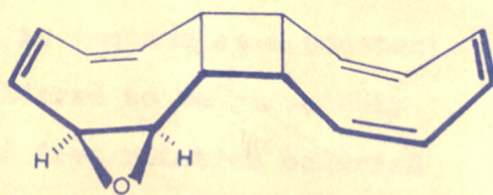
XI



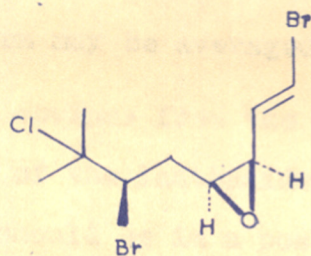
XII



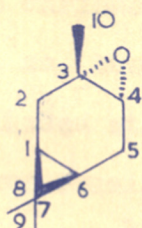
XIII



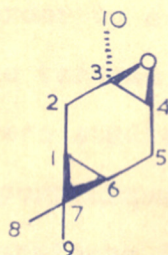
XIV



XV



XVI



XVII



XVIII

FIG. 10

calculate the magnitude of the shift. For our present purpose we have selected the McConnell-Robertson equation²⁹.

$$\Delta\delta = \chi \frac{(3 \cos^2\theta_i - 1)}{r^3} \quad \text{where } \Delta\delta, \text{ is the}$$

magnitude of the pseudocontact shift. Assuming the interaction of the lanthanide complexes is predominantly pseudocontact²⁶, the magnitude of the LIS of the i^{th} nucleus is inversely proportional to the cube of the average distance from the metal ion i.e.

$$\Delta\delta = b/r^3$$

where b , is assumed as a constant.

The angle term is frequently considered to be reasonably constant in many substrates and if free rotation occurred about the metalion-heteroatom bond of the labile complex, the angle term may be averaged out.

It is obvious from the above, that if one can fix the position of the lanthanide ion with respect to the oxirane oxygen, one should be in a position to say something definite about the geometry of the substrate by observing the shifts of the various protons. In order to ascertain that this is indeed so, the shifts for some terpene epoxides of well-established stereochemistry were studied. For this purpose, LIS were examined for 3 α ,4 α -epoxycarane (XVI)³⁰, 3 β ,4 β -epoxycarane (XVII)³¹ and 2 α ,3 α -epoxypinane (XVIII)³².

For this study we selected tris-1,1,1,2,2,3,3-hepta-fluoro-7,7-dimethyl octane-4,6-dionate europium [Eu(fod₃)]³³,

because firstly, it has higher solubility in CCl_4 and secondly, since it is a much stronger Lewis acid, it should induce more pronounced shifts of the epoxides, which are weaker bases.

A known weight of the $\text{Eu}(\text{fod})_3$ was added to each of these epoxides (0.0001 mole in 0.25 ml of dry CCl_4) and spectra were recorded for four different mole ratios (~ 0.25 mole to one mole) of $\text{Eu}(\text{fod})_3$ /epoxide. The shifts produced for all these epoxides (XVI - VIII) are given in Tables 1-3.

In trying to seek a correlation between the experimental LIS results and the calculated values, we have assumed the following:

1. The Eu-O bond has been taken to be $2.35^\circ \text{A}^{17c,34}$.
2. Of the two possible lobes on oxygen with which the metal ion could co-ordinate, we have selected the lobe which is away from the bulk of the molecule. This is reasonable on steric considerations.

3,4,4'-Epoxy-carane. From a consideration of models, it becomes obvious that there are three possible conformation of low energy, which must be considered. These conformations, A, B and C, are shown in Fig.12. By fixing the position of the Eu at a distance of 2.35 A° from the oxygen atom so as to avoid steric interactions, distances were measured for the readily identifiable signals (two tertiary methyls, epoxy-methyl and epoxy hydrogen) for all the three conformations A, B and C (Fig.12). A graph was plotted for the

TABLE 1 - 3 α ,4 α -EPOXYCARANE

Shift Reagent added (m.moles)	Position of upfield Me (ppm)	Position of downfield Me (ppm)	Position of	
			Epoxy Me (ppm)	Epoxy H (ppm)
	C ₈	C ₃	C ₃	C ₄
0.00	0.70	1.00	1.17	2.62
0.031	0.78	1.05	1.35	2.88
0.054	0.82	1.08	1.46	3.07
0.105	0.90	1.13	1.67	3.38
0.12	0.92	1.14	1.72	3.47
Max. shift induced ($\Delta\delta$, ppm)	0.22	0.14	0.55	0.85

TABLE 2 - 36,40-EPOXYCARAME

Shift Reagent added (m.mole)	Position of upfield Me (ppm)	Position of downfield Me (ppm)	Position of Epoxy Me (ppm)	Position of Epoxy-H (ppm)
	C ₈	C ₉	C ₃	C ₄
0.00	0.93	0.96	1.25	2.82
0.025	0.98	0.98	1.37	2.93
0.054	1.02	1.02	1.47	3.08
0.079	1.06	1.04	1.57	3.26
0.10	1.11	1.06	1.66	3.38
Max. shift induced ($\Delta\delta$, ppm)	0.18	0.10	0.41	0.56

TABLE 3 - 2 α ,3 α -EPOXYPIRANE

Shift Reagent added (m.mole)	Position of upfield Me (ppm)	Position of downfield Me (ppm)	Position of Epoxy Me (ppm)	Position of Epoxy-H (ppm)
	C ₉	C ₈	C ₃	C ₂
0.00	0.93	1.28	1.28	2.89
0.025	1.01	1.34	1.45	3.15
0.046	1.07	1.38	1.59	3.35
0.075	1.12	1.41	1.72	3.55
0.10	1.16	1.41	1.84	3.71
Max. shift induced ($\Delta\delta$, ppm)	0.23	0.13	0.56	0.82

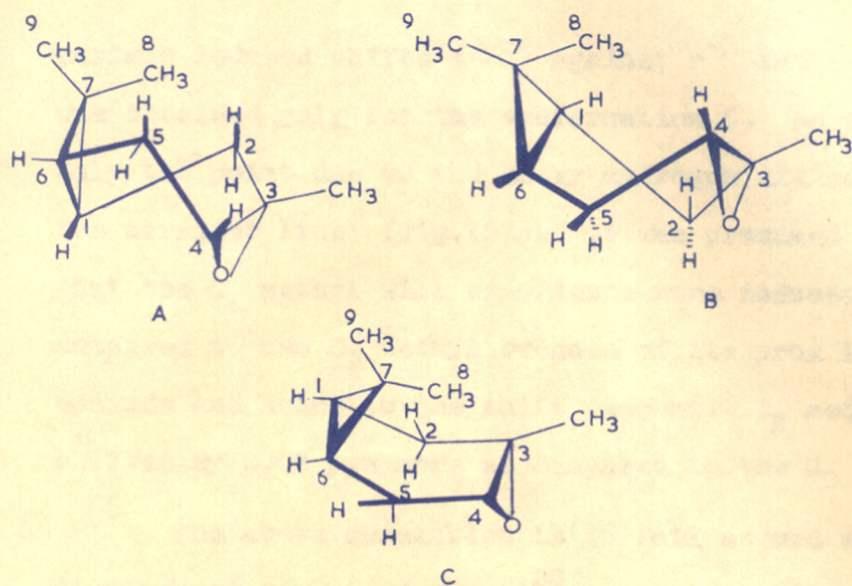


FIG.-12 CONFORMATIONS OF 3 α ,4 α -EPOXYCARANE

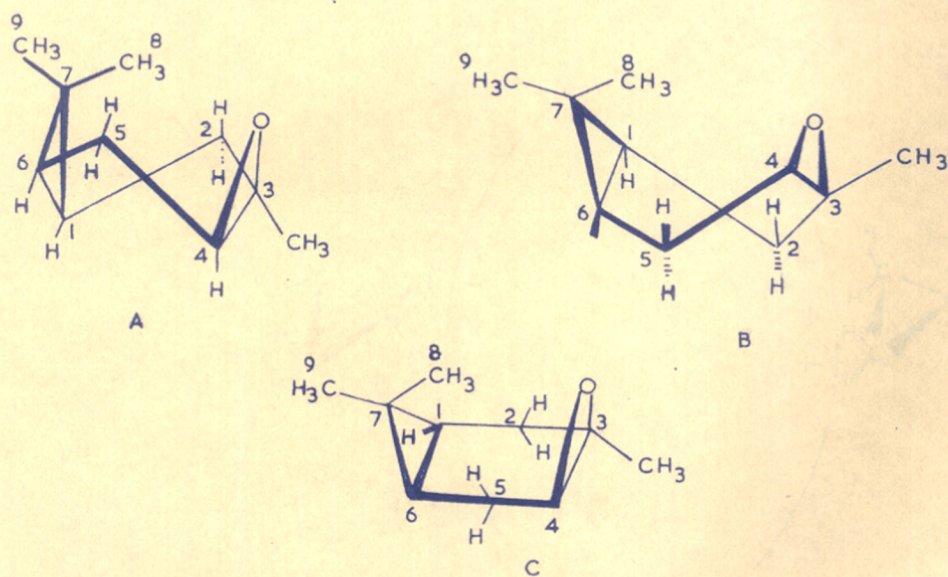


FIG.-15 CONFORMATIONS OF 3 β ,4 β -EPOXYCARANE

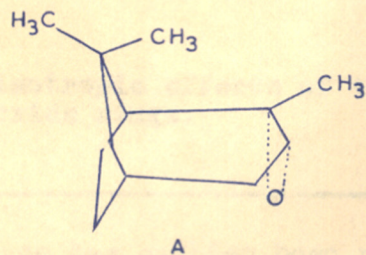


FIG.-16 CONFORMATION OF 2 α ,3 α -EPOXYPINANE

maximum induced shifts ($\Delta\delta$) against r^{-3} and a straight line¹⁶ was obtained only for the conformation C. As expected, only the point due to the epoxy hydrogen did not fall on the straight line* (Fig.13A). It was presumed (models) that the C₈ methyl will experience more induced shift as compared to the C₉ methyl because of its proximity to the epoxide and hence to the shift reagent. C₈ methyl is in fact shifted by 0.08 ppm more as compared to the C₉ methyl (Table 1).

The above conclusion is in full accord with the findings of Brown and Suzuki³⁰, who, by taking into consideration the anisotropy of the three membered ring³⁵ (Fig.14)/oxirane (Fig.14), have come to the same conclusion.

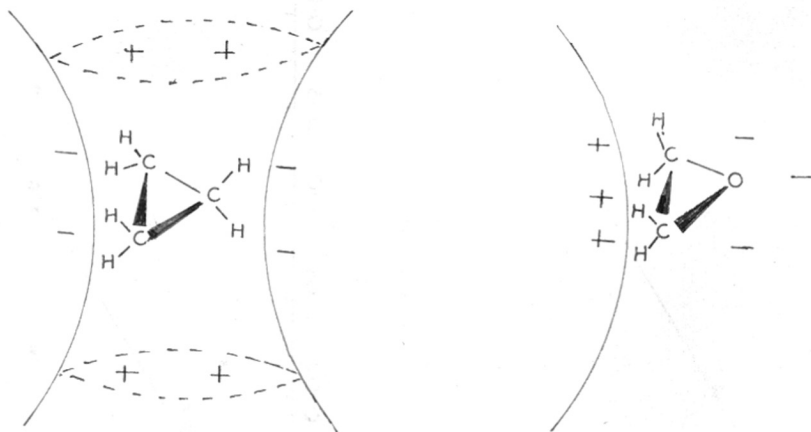


Fig.14 Anisotropic effects of the cyclopropane and epoxide rings.

*A similar case has earlier been reported by Keith²³.

3 α ,4 α -EPOXYCARANE
CONFORMATION A ●
CONFORMATION B ■
CONFORMATION C ▲

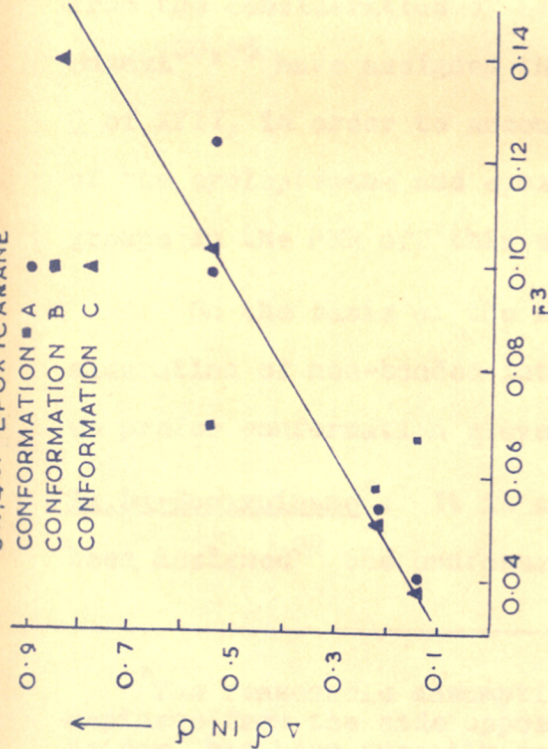


FIG. 13 A

2 α ,3 α -EPOXYPINANE
CONFORMATION A ●

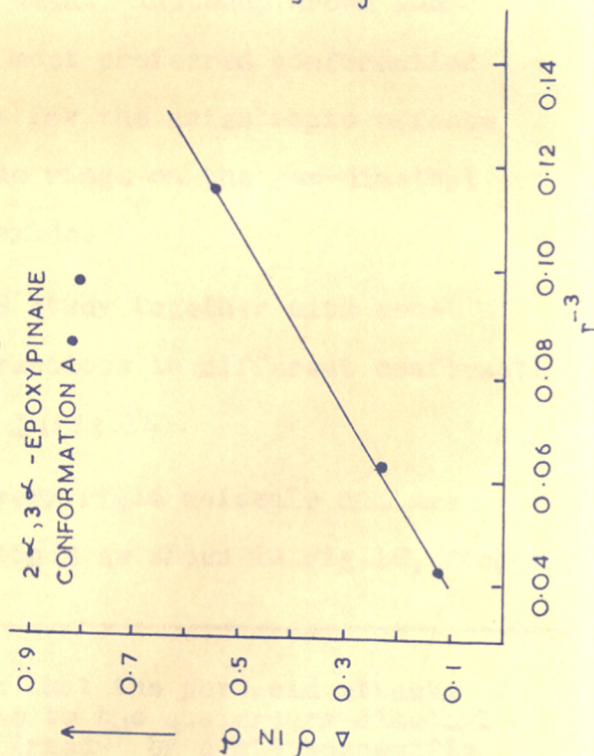


FIG. 13 C

3 β ,4 β -EPOXYCARANE
CONFORMATION A ●
CONFORMATION B ■
CONFORMATION C ▲

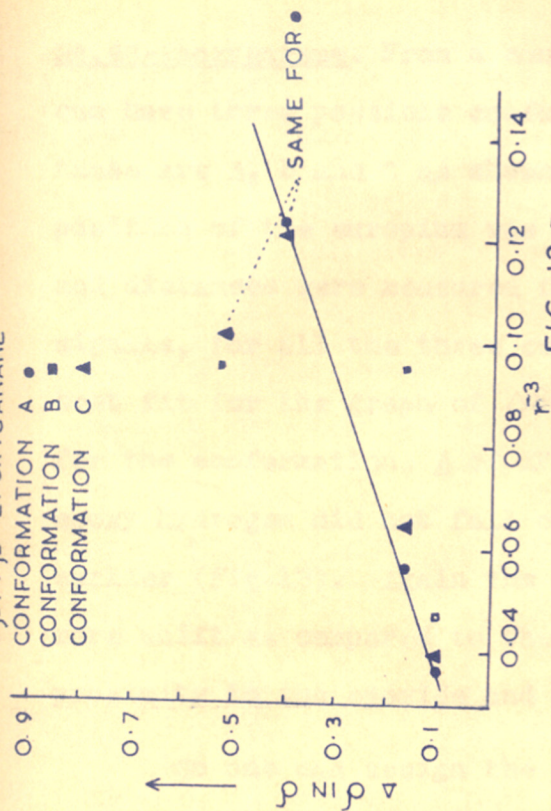


FIG. 13 B

β -HIMACHALENE- β -EPOXIDE
CONFORMATION A ▲
CONFORMATION B ●
CONFORMATION C ■

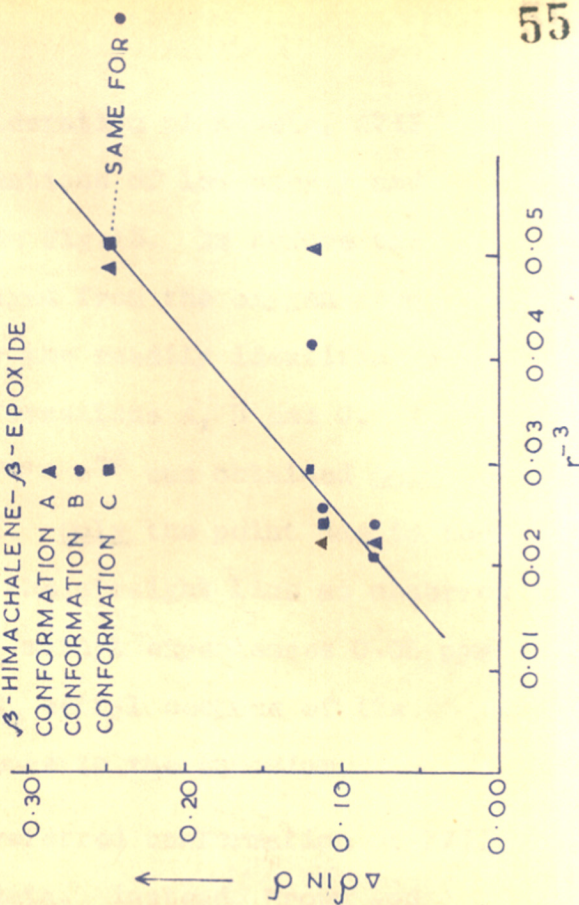


FIG. 18

3a,4a-Epoxy-carane. From a consideration of models, XVII can have three possible conformations of low energy and these are A, B and C as shown in Fig.15. As before the position of the europium was fixed from the oxygen atom, and distances were measured for the readily identifiable signals, for all the three conformations A, B and C. A best fit for the graph of $\Delta\delta$ vs r^{-3} was obtained only for the conformation A of XVII. Only the point due to the epoxy hydrogen did not fall on the straight line as observed earlier (Fig.13). Again the C_8 methyl experiences 0.08 ppm more shift as compared to the C_9 methyl because of its proximity to the epoxide and hence to the europium.

So one can assign the preferred conformation of XVII, from the consideration of LIS data. Instead, Brown and Suzuki^{30,36} have assigned the most preferred conformation C of XVII, in order to account for the anisotropic effects of the cyclopropane and epoxide rings on the gem-dimethyl groups in the PMR of this epoxide.

On the basis of the LIS study together with consideration of non-bonded interactions in different conformations we prefer conformation A over C (Fig.15).

2a,3a-Epoxy-pinane*. It is a very rigid molecule and has been assigned³² the conformation A as shown in Fig.16, from a

*The reasonable assumption that the per acid attacks α -pinene from the side opposite to the quaternary dimethyl bridge, has been recently confirmed³⁷ by a stereospecific synthesis of XVIII.

study of its hydrogenolysis products, using Raney nickel in presence of alkali. Again by fixing the position of the europium from the oxirane oxygen, and measuring the distances for easily identifiable protons as carried out earlier, a straight line was obtained for a plot of $\Delta\delta$ vs r^{-3} . As expected, only the point due to the epoxy hydrogen did not fall on the straight line (see Fig.13C).

Hence it is clear that the results obtained from the LIS data are consistent with the previous finding³².

β -Himachalene- α -oxide. After obtaining a successful linear correlation between the maximum induced shifts and the calculated distances for easily identifiable protons, for the above known terpene epoxides (XVI - XVIII), we extended the LIS study for determining the conformations of β -himachalene- α -oxide. The LIS shifts produced for IV are recorded in Table 4.

In order to calculate the distances between protons and the shift reagent molecular models for three different conformations A, B and C of β -himachalene- α -epoxide were constructed as shown in Fig.17. These conformations were chosen on the basis of minimum non-bonded interactions.

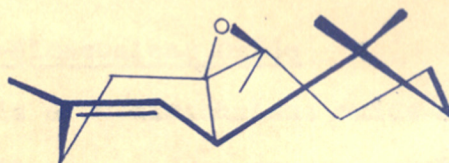
As before the position of the europium was fixed at a distance of 2.35 Å from one of the lone pairs of oxygen and the distances for easily identifiable protons were measured for all the three conformations of β -himachalene- α -oxide. The best fit for the plot of $\Delta\delta$ vs r^{-3} gives a

TABLE 4 - β -HIMACHALENE- β -OXIDE

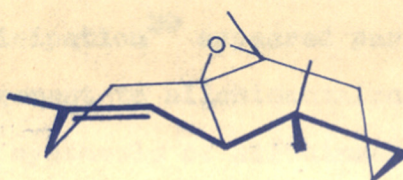
Shift Reagent added m.moles	Position of upfield Me (ppm)	Position of downfield Me (ppm)	Position of Epoxy Me (ppm)	Position of olefinic H (ppm)	
	C ₁₁	C ₁₂	C ₇	C ₂	
0.00	0.84	0.95	1.27	5.37	
0.026	0.87	0.97	1.34	5.39	
0.051	0.89	0.98	1.39	5.43	
0.073	0.92	1.02	1.45	5.46	
0.105	0.96	1.03	1.52	5.48	
Max. shift induced ($\Delta\delta$, ppm)	0.12	0.08	0.25	0.11	



C



A



B

FIG.17 CONFORMATIONS OF β - HIMACHALENE . β - OXIDE

straight line only for the conformation C, whereas the consideration of other conformations gave a considerably poorer correlation between the maximum induced shifts and the interatomic distances, as shown by the points on the graph depicted in Fig.18.

From this study, therefore it appears that β -himachalene- β -epoxide exists in conformation C (Fig.17).

Solvolysis of β -Himachalene Oxide

Solvolysis of β -himachalene oxide appeared to be of interest as it can lead to several skeletons depending upon the conformation(s) of the reacting molecule. These possibilities are shown in Fig.19.

Of the possibilities listed in Fig.19, the one leading to allohimachalone (XXIII)³⁸ and other one involving homoallylic participation³⁹ appeared particularly interesting. Whereas, rearrangement to allohimachalone would constitute a biogenic-type synthesis of allohimachalol³⁸ skeleton, the homoallylic participation would become possible only if the oxide reacts through a conformation such as A (Fig.20), in which the six-membered ring has a twist boat conformation, as only such a conformation permits overlap of the π -electrons with the vacant orbital at C₆ (see Fig.20).

In actual practice, it was found that the nature of the products depended heavily on the type of the reagent used. Thus sulphuric acid (0.16%)⁴⁰ in aqueous acetone at $\sim 29^\circ$, for 24 hrs under N₂, resulted essentially in a mixture

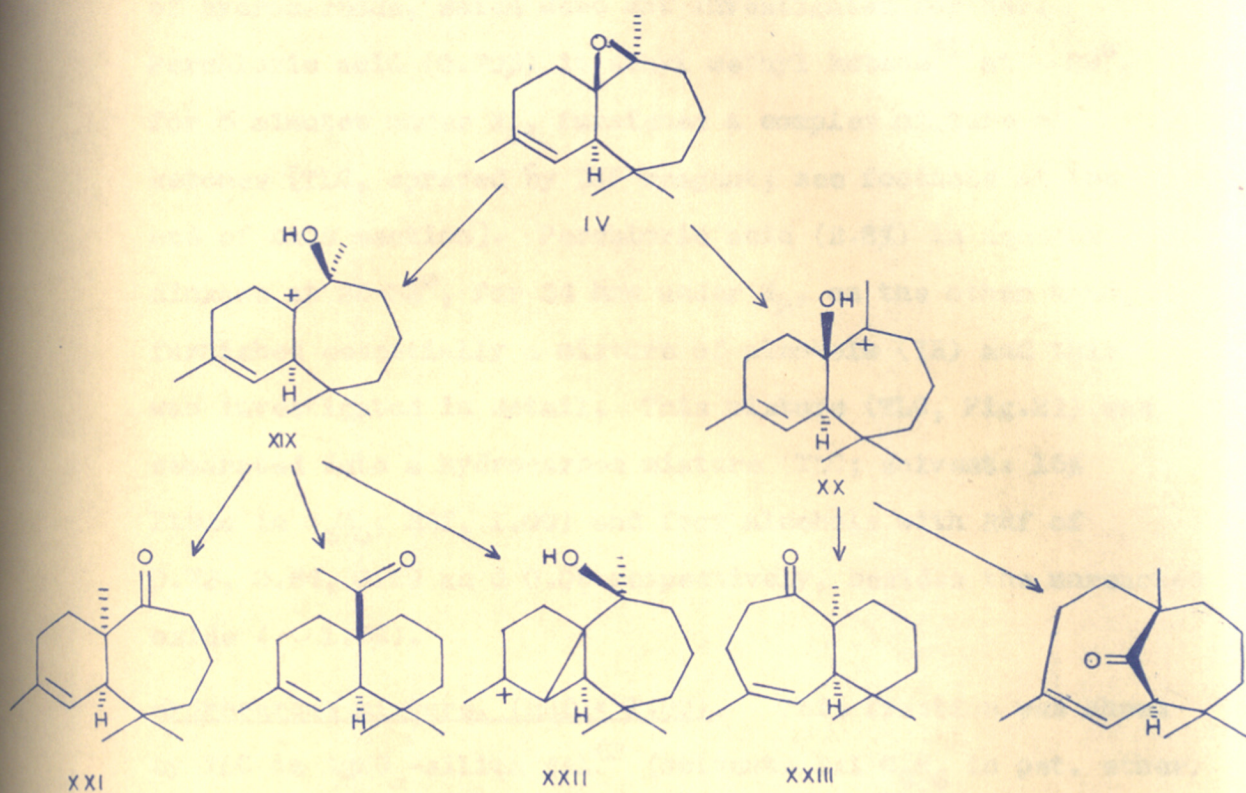


FIG.19 POSSIBLE SKELETONS FROM SOLVOLYSIS OF β -HIMACHALENE OXIDE

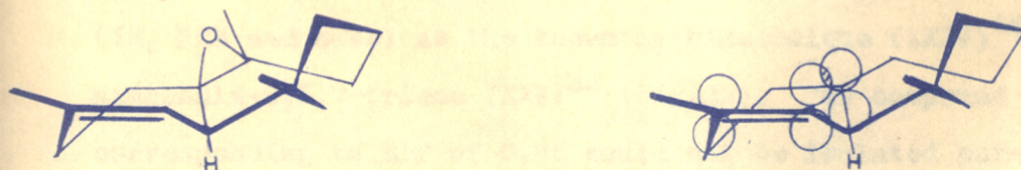


FIG.20 HOMOALLYLIC PARTICIPATION BY OVERLAP OF π -ORBITALS OF β -HIMACHALENE β -OXIDE

of hydrocarbons, which were not investigated further. Perchloric acid (0.70%) in ethyl methyl ketone⁴¹ at $\sim 29^\circ$, for 5 minutes under N_2 , furnished a complex mixture of ketones [TLC, sprayed by DNP reagent; see footnote at the end of this section]. Perchloric acid (2.8%) in aqueous dioxane at $25-33^\circ$, for 34 hrs under N_2 , on the other hand, furnished essentially a mixture of alcohols (IR) and this was investigated in detail. This mixture (TLC, Fig.21) was separated into a hydrocarbon mixture (TLC; solvent: 15% EtOAc in C_6H_6 ; Rrf, 1.00) and four alcohols with Rrf of 0.73, 0.64, 0.29 and 0.09 respectively, besides the unreacted oxide ($\sim 1.5\%$).

Hydrocarbon mixture. (Rrf = 1.00). This fraction was shown by TLC on $AgNO_3$ -silica gel⁴² (solvent: 1:1 C_6H_6 in pet. ether) to consist of three compounds having Rrf of 1.00, 0.71 and 0.25 respectively. The compounds having Rrf of 1.00 and 0.71 could be separated by inverted dry column chromatography⁴³ (IDCC) over $AgNO_3$ -silica gel (solvent: 1:1 C_6H_6 in pet. ether) and were readily identified from spectral characteristics (IR, PMR and mass) as the known ar-himachalene (XXIV)⁴⁴ and himachala-2,5,7-triene (XXV)^{2a} (Fig.22). The compound corresponding to Rrf of 0.25 could not be isolated pure.

Alcohol-I (Rrf, 0.73) was readily recognised as the known^{2a} allylic tertiary alcohol (XXVI) from its IR and PMR spectral characteristics.

Alcohol-II (Rrf, 0.64) (analyses for $C_{15}H_{24}O$; M^+ , $m/e = 220$)

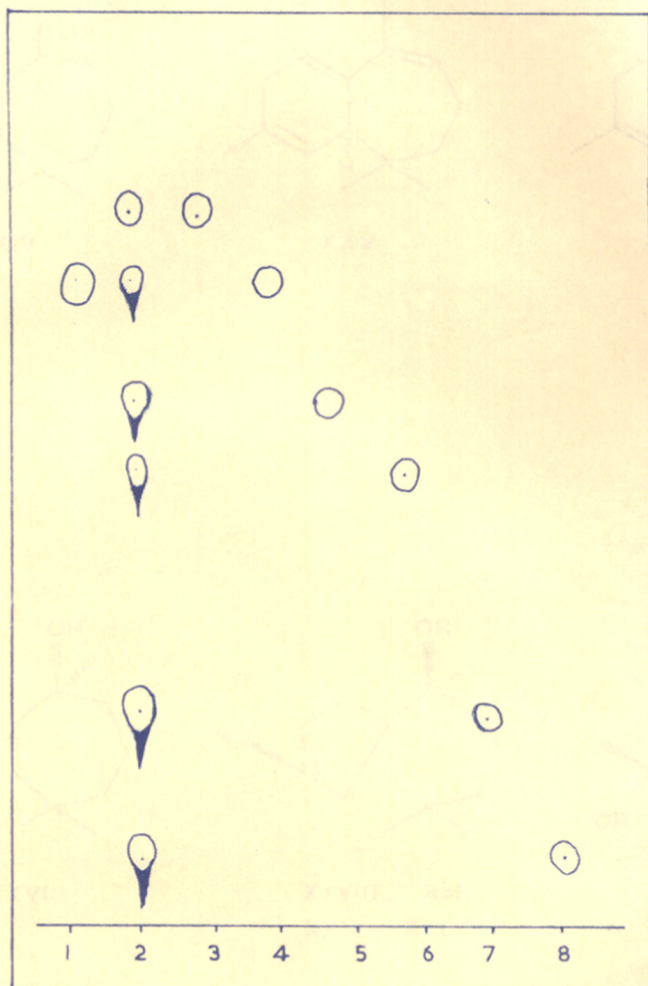
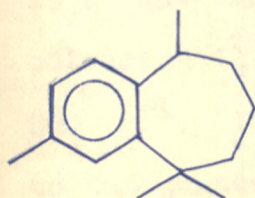
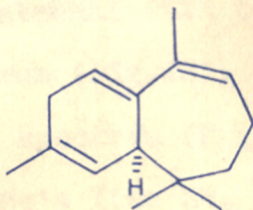


FIG. 21 THIN LAYER CHROMATOGRAPHY OF MIXTURE FROM β - HIMACHALENE EPOXIDE AND AQ, DIOXANE / PERCHLORIC ACID (SiO₂ PLATE; SOLVENT SYSTEM 15% EtOAc / C₆H₆)

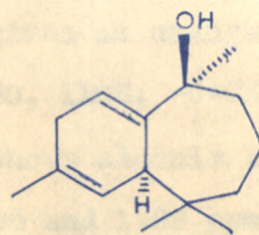
- | | |
|----------------------------------|-----------------------------------|
| 1) β - HIMACHALENE EPOXIDE | (2) REACTION MIXTURE |
| 3) HYDROCARBON MIXTURE | (4) β - HIMACHALENE EPOXIDE |
| 5) ALCOHOL - I (XXVI) | (6) ALCOHOL - II (XXVII) |
| 7) DIOL - I (XXVIII) | (8) DIOL - II (XXX) |



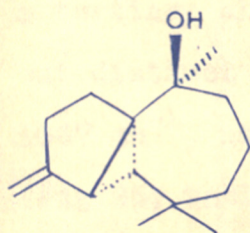
XXIV



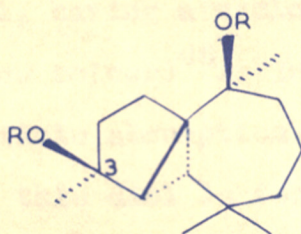
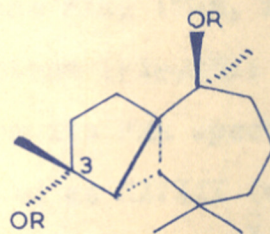
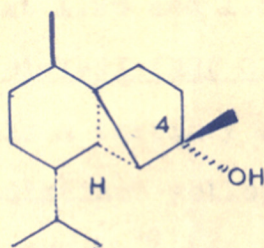
XXV



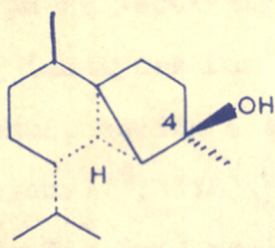
XXVI



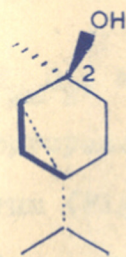
XXVII

XXVIII, R=H
XXIX, R=COHXXX, R=H
XXXI, R=COH

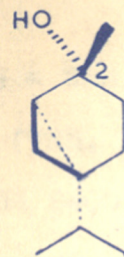
XXXII



XXXIII



XXXIV



XXXV

FIG.- 2 2

is an unsaturated alcohol (TNM test: gives an orange yellow colour). IR spectrum (Fig.23): OH 3350, 1106; -C=CH_2 1625, 880 cm^{-1} . Its PMR spectrum (Fig.24) shows signals assignable to two quaternary Me's (two 3H, s, 0.95 and 1.02 ppm); $\text{CH}_3\text{-}\overset{\text{C}}{\underset{\text{C}}{\text{C}}}\text{-OH}$ (3H, s, 1.23 ppm); one cyclopropane proton (1H, d, 0.53 ppm, $J = 4.5$ Hz) and -C=CH_2 (2H, s, 4.75 ppm). From these spectral data, this alcohol is clearly assigned structure XXVII. This is further supported by its UV absorption⁴⁵: app. $\lambda_{\text{max}}^{\text{EtOH}}$ 223 nm (ϵ , 2480).

Diol-I (RRf, 0.29) (analyses for $\text{C}_{15}\text{H}_{26}\text{O}_2$; M^+ , $m/e = 238$) is a tertiary alcohol, having a cyclopropane ring (TNM, faint but distinct yellow colour)⁴⁶. IR spectrum (Fig.25): OH 3390, 1047 cm^{-1} , no olefinic absorption. From its PMR spectrum (Fig.26; Table 5) this diol is formulated as XXVIII (vide infra). The presence of two groups of the type $\text{CH}_3\text{-}\overset{\text{C}}{\underset{\text{C}}{\text{C}}}\text{-OH}$ was confirmed by formylation⁴⁷; the PMR spectrum (Fig.27; Table 5) of the derived diformate (XXIX; two 1H, s, 7.71 and 7.78 ppm, assignable to OCHO protons) shows the expected deshielding⁴⁷ of the two methyl groups, which now resonate at 1.26 and 1.58 ppm respectively.

Diol-II (RRf 0.09) (analyses for $\text{C}_{15}\text{H}_{26}\text{O}_2$; M^+ , $m/e = 238$) is a tertiary alcohol, having a cyclopropane ring (TNM, faint distinct yellow colour)⁴⁶. IR spectrum (Fig.28) OH 3400, 1047 cm^{-1} and no double bond absorption. From its PMR spectrum (Fig.29, Table 5) this diol is clearly assigned structure XXX/XXVIII. Again, the presence of two groups of

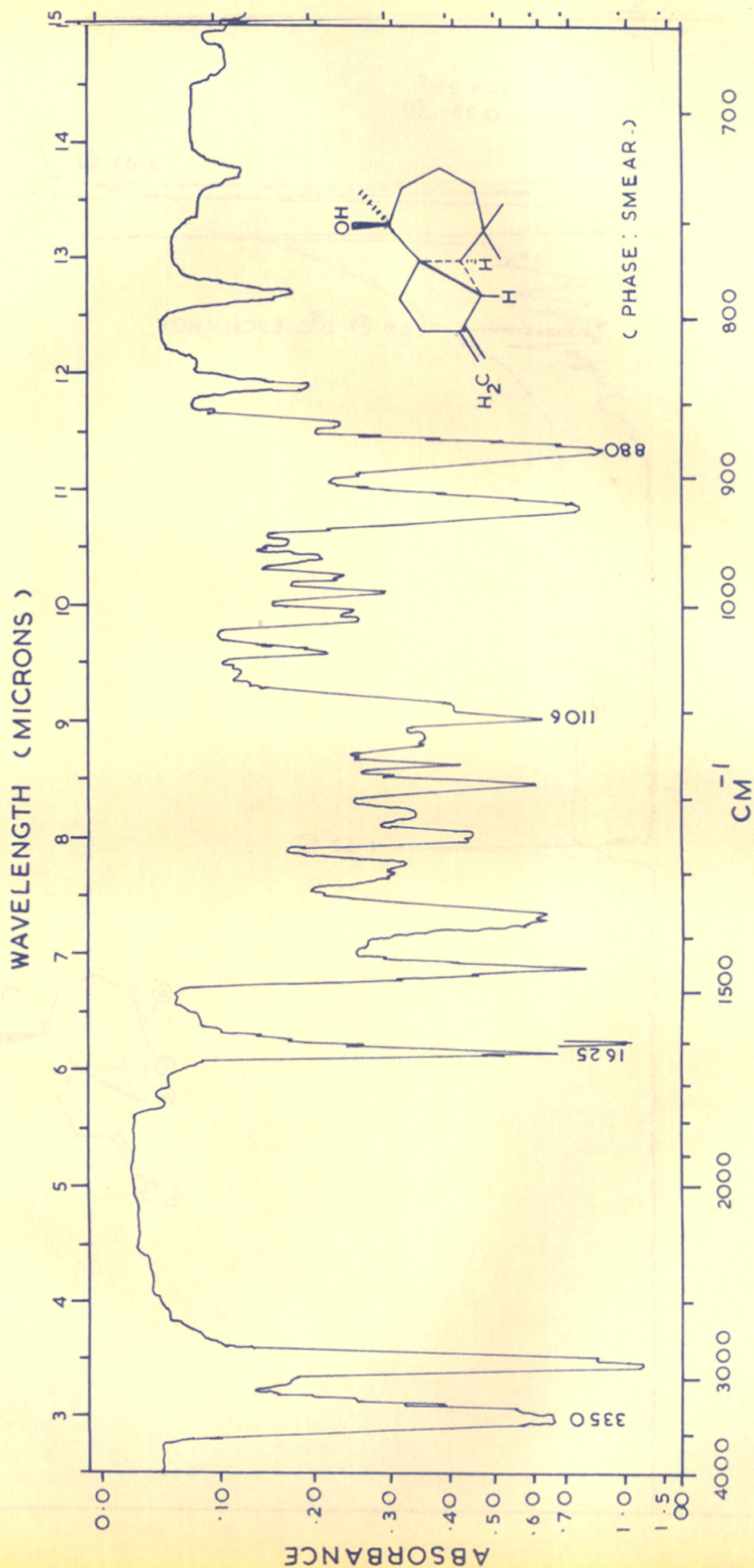


FIG.23 IR SPECTRUM OF 7 β - HYDROXY - 3,15 - DEHYDRO - 2,6 - CYCLOHIMACHALANE (XXVII)

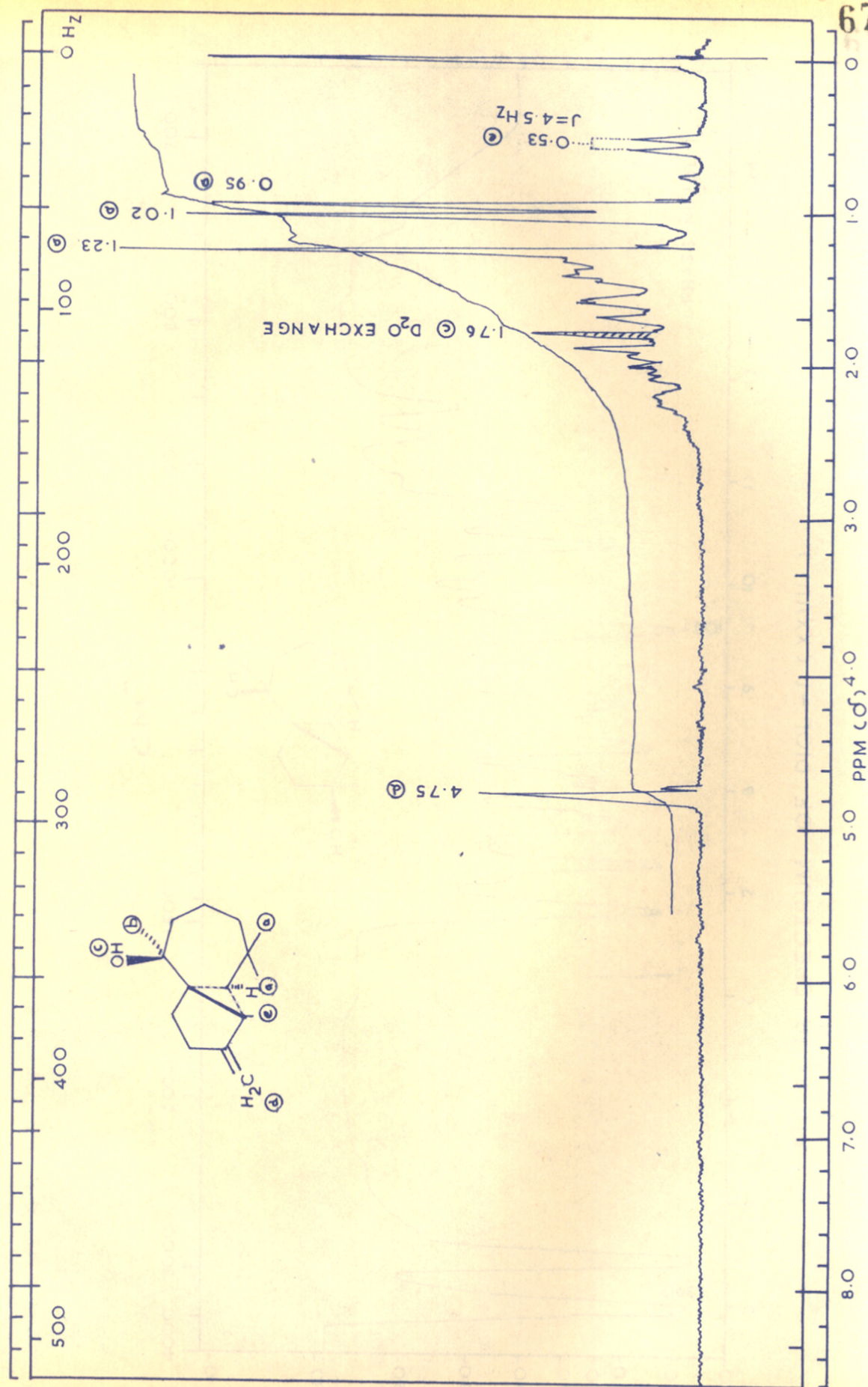


FIG. 24 PMR SPECTRUM OF 7 β -HYDROXY-3,15-DEHYDRO-2,6 - CYCLOHIMACHALANE (XXVII)

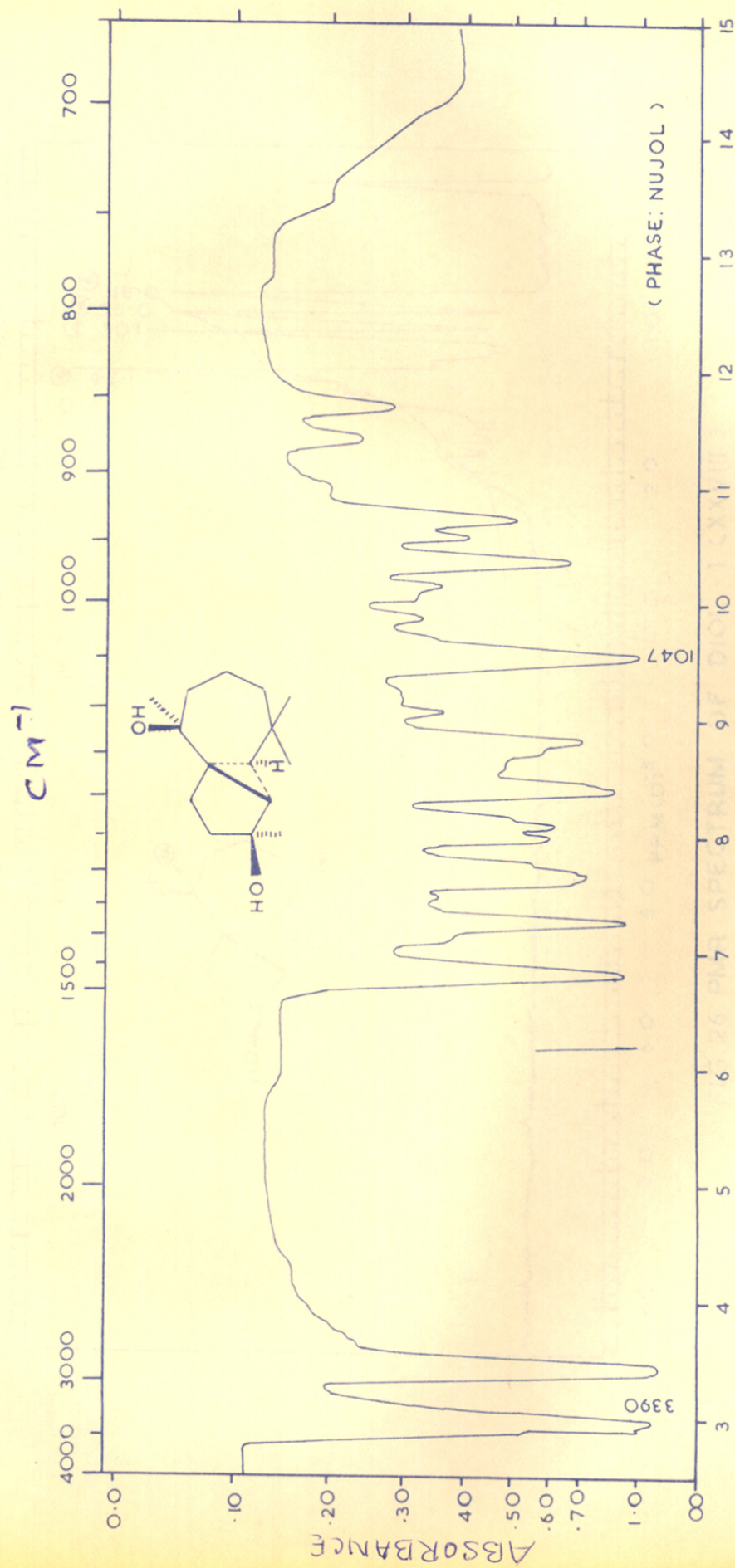


FIG.25 IR SPECTRUM OF DIOL -I (XXVIII)

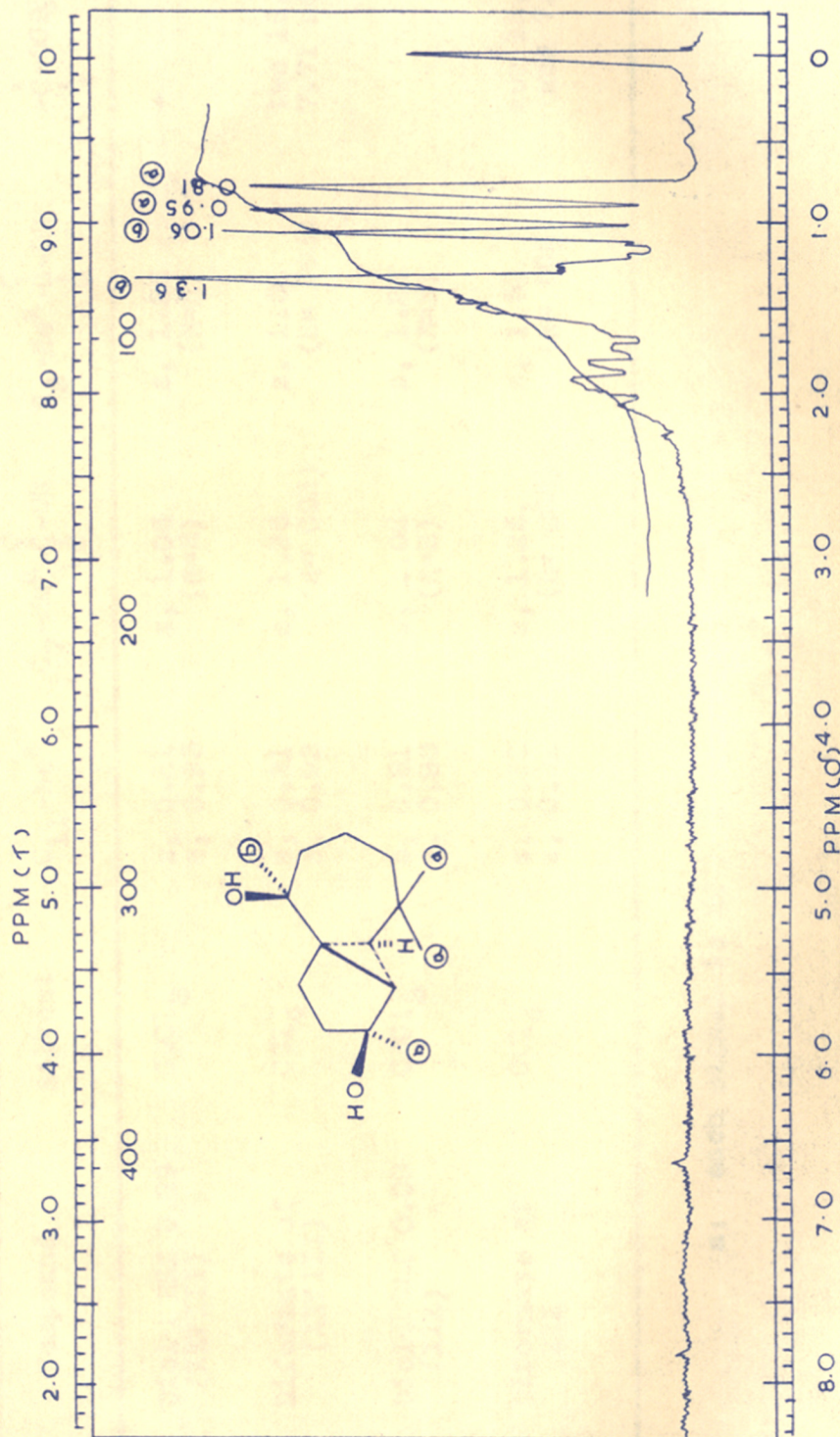


FIG.26 PMR SPECTRUM OF DIOL -I (XXVIII)

TABLE 5 - PMR SPECTRA OF EPIMERIC DIOLS AND THEIR
FORMATES
CHEMICAL SHIFT IN PPM

No.	Compound	Solvent	$C_{11}-Me^a$	$C_7-Me^a-\overset{\overset{C}{ }}{\underset{\underset{C}{ }}{C}}-OR$		$C_3-Me^a-\overset{\overset{C}{ }}{\underset{\underset{C}{ }}{C}}-OR$		$-C(=O)COH$
1	Diol-I RRF 0.29 (XXVIII)	$CDCl_3$	s, 0.81 s, 0.95	s, 1.06 (R=H)	s, 1.36 (R=H)	-	-	-
2	Diformate of (XXVIII)	CCl_4	s, 0.81 s, 0.93	s, 1.26 (R=COH)	s, 1.58 (R=COH)	two 1H, s, 7.71 and 7.78		
3	Diol-II RRF 0.09 (XXX)	$CDCl_3$	s, 0.81 s, 0.90	s, 1.06 (R=H)	s, 1.23 (R=H)			
4	Diformate of XXX	CCl_4	s, 0.88 s, 0.91	s, 1.25, (R=COH)	s, 1.50 (R=OCH)	two 1H, s, 7.73 and 7.81 ppm		

a: each signal is 3H

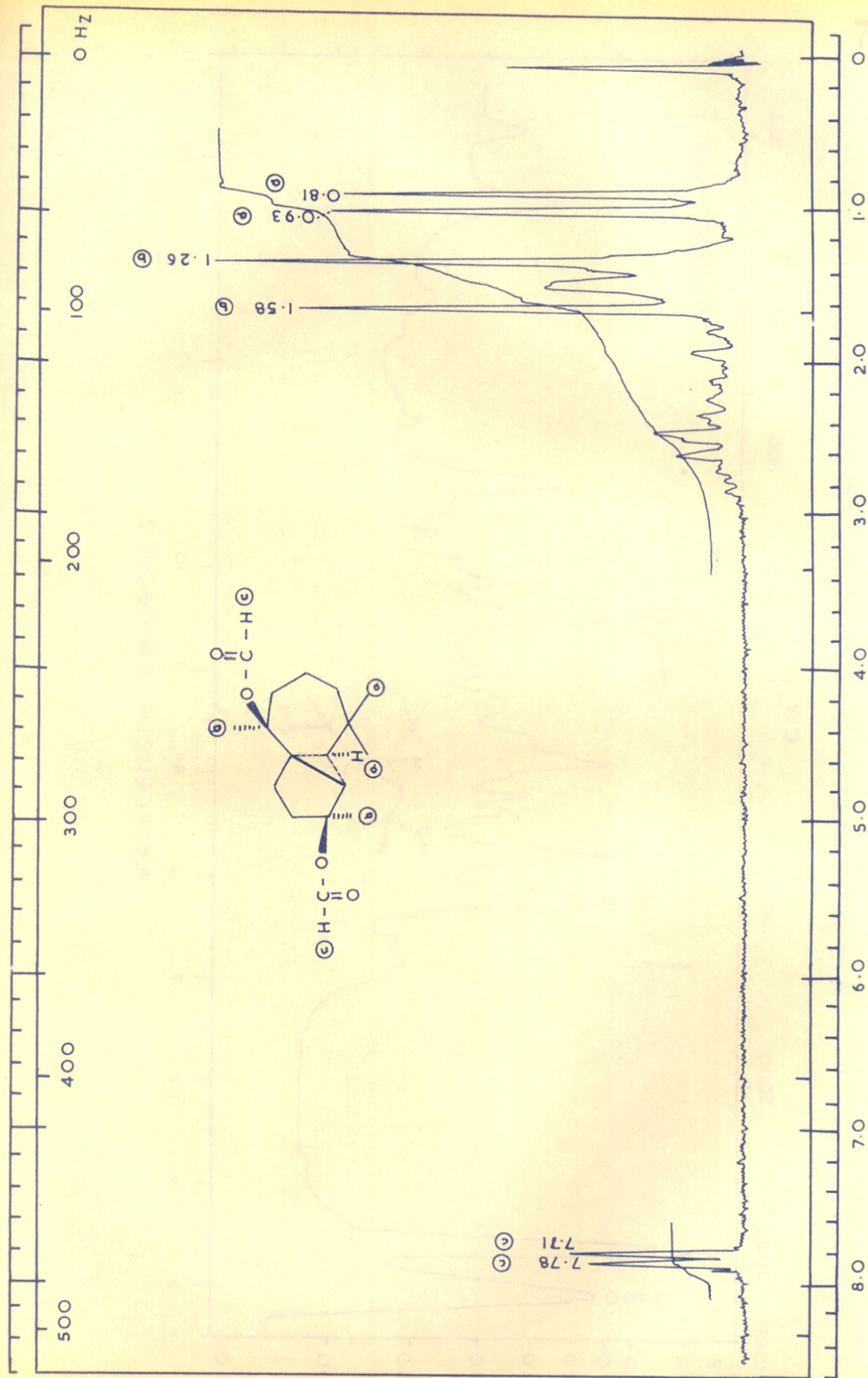


FIG. 27 PMR SPECTRUM OF THE FORMATE ESTER OF DIOL-I (XXIX)

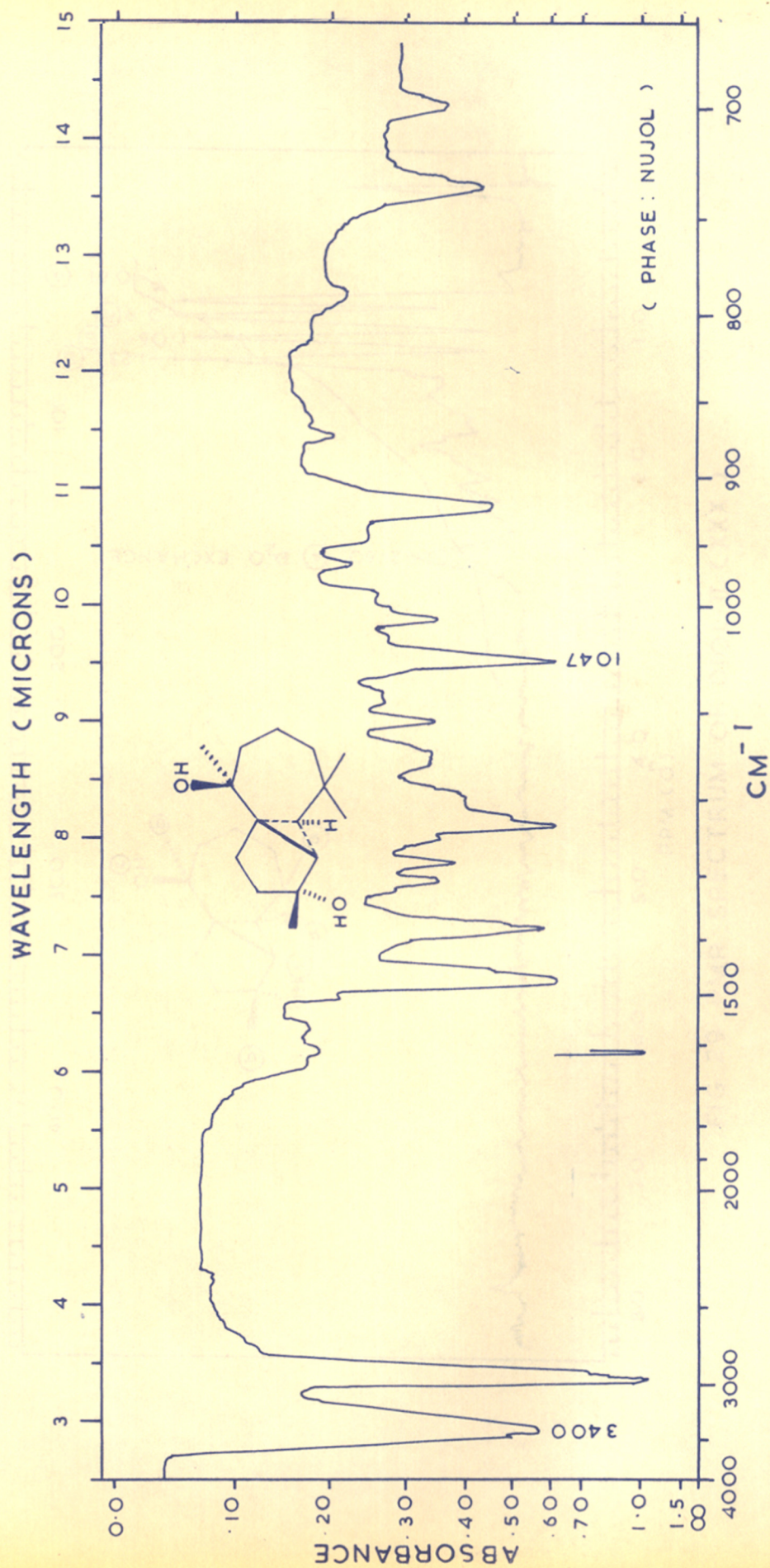


FIG.28 IR SPECTRUM OF DIOL-II (XXX)

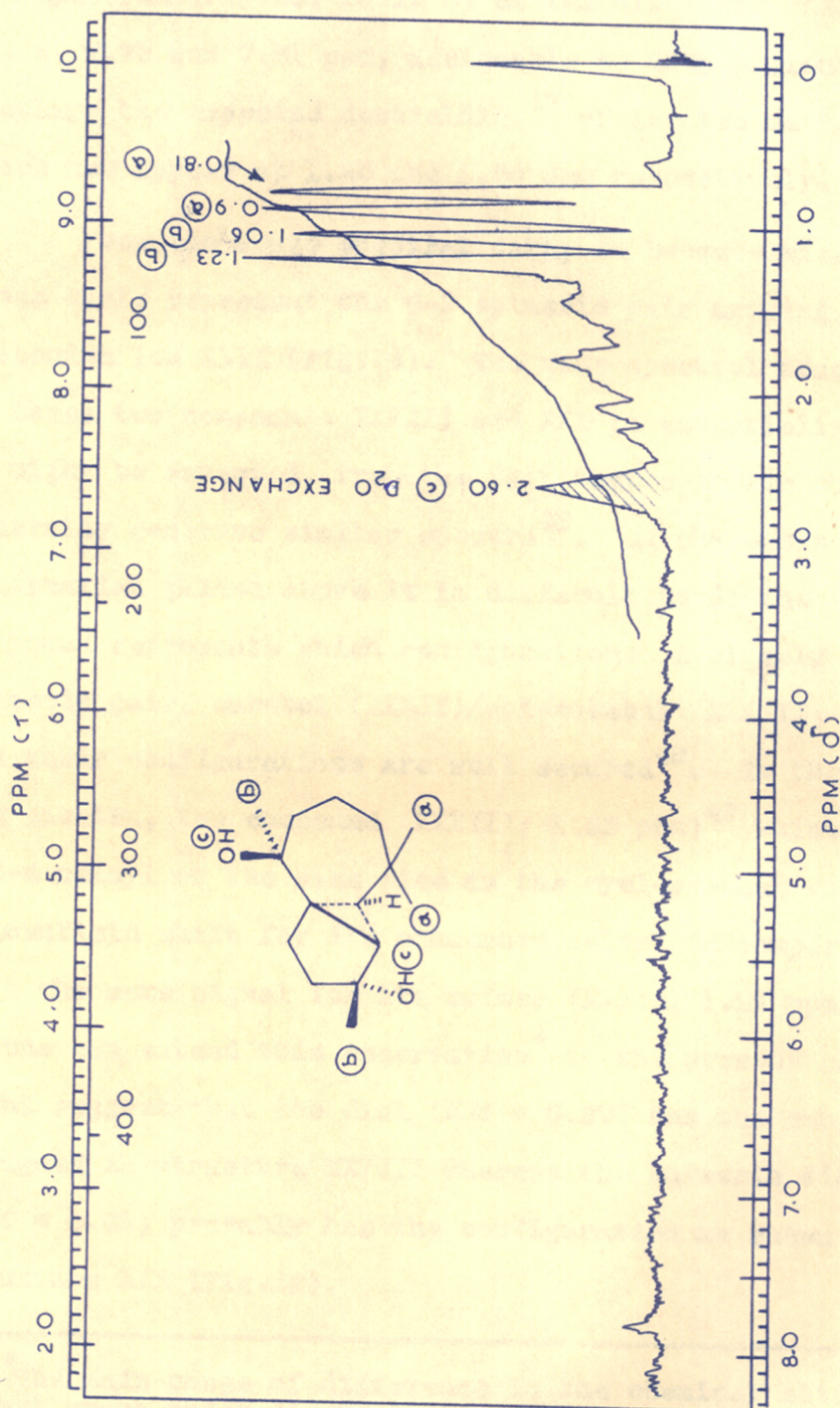


FIG.29 PMR SPECTRUM OF DIOL-II (XXX)

the type $\text{CH}_3-\overset{\text{C}}{\overset{\text{C}}{\text{C}}}-\text{OH}$ was corroborated by formylation⁴⁷; the PMR spectrum (Fig.30, Table 5) of the diformate (XXXI; two 1H, s, 7.73 and 7.81 ppm, assignable to OCOH protons) displays the expected deshielding⁴⁷ of the two methyl groups which now appear at 1.25 and 1.50 ppm respectively.

From the above spectral data, it becomes clear, that these diols represent the C-3 epimeric pair arising from the carbonium ion XXII (Fig.19). The mass spectral fragmentation of these two compounds XXVIII and XXX is essentially identical, as might be expected, from the fact that epimeric compounds generally generate similar spectra⁴⁸. On the basis of information gained above it is difficult to decide which compound represents which configuration. A closely related epimeric pair, cubebol (XXXII)/epi-cubebol (XXXIII; Fig.22) and their configurations are well secured⁴⁹. In their PMR spectra, the compound (XXXIII; 1.33 ppm)⁴⁹ which has a C-4 methyl on the same side as the cyclopropane ring shows a downfield shift for its concerned methyl in comparison with the same signal for its epimer (XXXII; 1.27 ppm)⁴⁹. If one can extend this observation* to the present case, one might suggest that the diol (RRf = 0.29) has the configuration assigned in structure XXVIII whereas the epimeric diol (RRf = 0.09) probably has the configuration as shown in structure XXX (Fig.22).

*The main cause of difference in the chemical shift of the methyl group under discussion in the epimeric pairs is not clear. Magnetic anisotropy of the cyclopropane ring³⁵ also does not appear to be the deciding factor since in the epimeric alcohols, cis-sabinene hydrate (XXXIV)⁵⁰ and trans-sabinene hydrate (XXXV)⁵⁰ (Fig.22); the methyl group at C-2, shows the same chemical shift and resonates at 1.30 ppm⁵⁰.

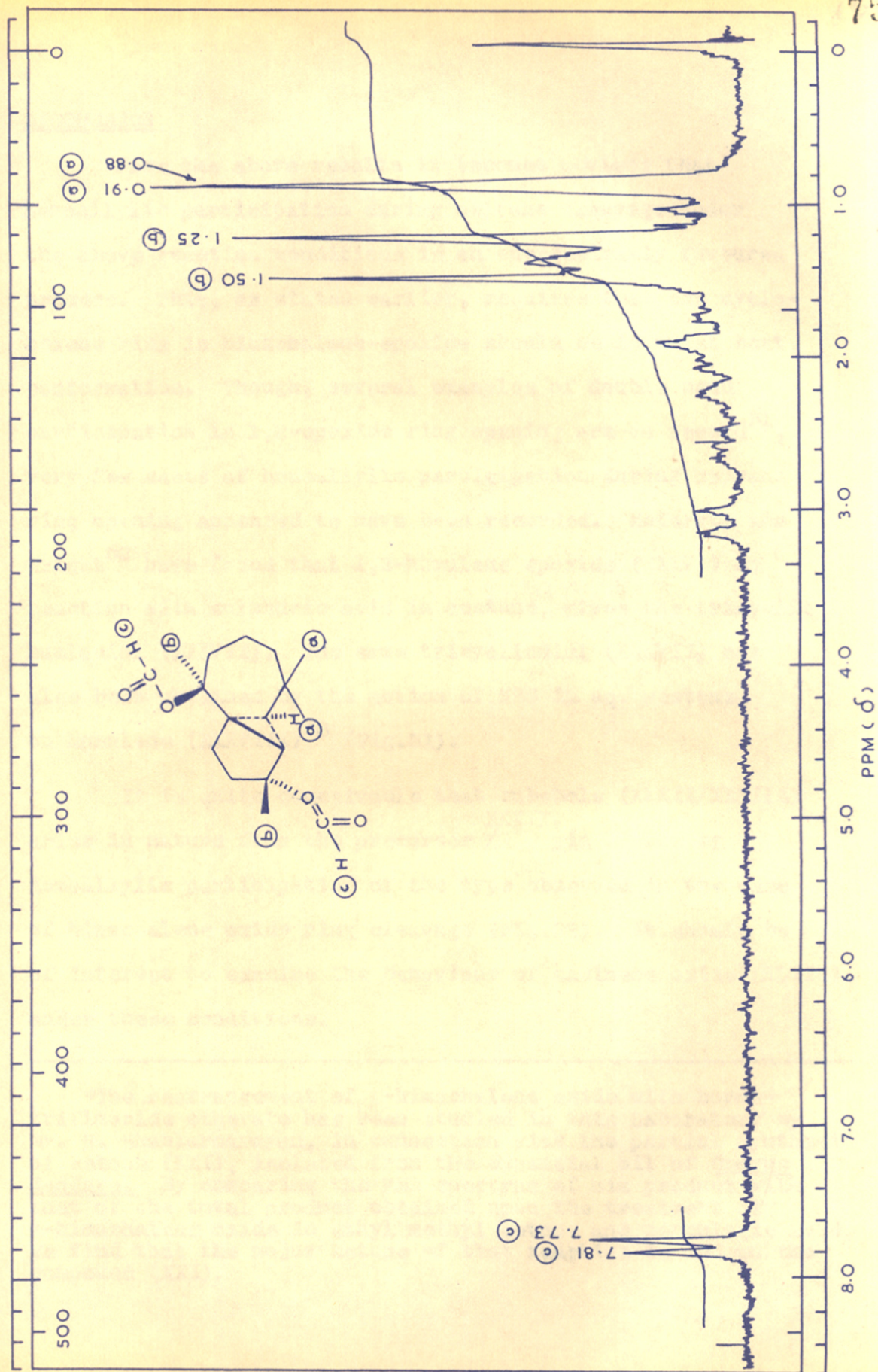


FIG.30 PMR SPECTRUM OF FORMATE ESTER OF DIOL -II (XXXI)

DISCUSSION

From the above results it becomes obvious that homoallylic participation during oxirane cleavage under the above reaction conditions is an energetically favoured process. This, as stated earlier, requires that the cyclohexene ring in himachalene-epoxide should be in twist boat conformation. Though, several examples of double bond participation in 1,2-epoxide ring opening are on record⁵¹, very few cases of homoallylic participation during oxirane ring opening appeared to have been recorded. McKervey and Wright⁵² have found that 1,2-humulene epoxide (XXXVI) on reaction with sulphuric acid in acetone, gives the tricyclic humladiol (XXXVII). The same tricyclicdiol (XXXVII) has also been obtained by the action of NBS in aq. acetone on humulene (XXXVIII)⁵³ (Fig.31).

It is quite conceivable that cubebol (XXXII/XXXIII) arise in nature from the precursor ^{XXXIX,} via XL-XLI by homoallylic participation of the type observed in the case of himachalene oxide ring cleavage (Fig.32). It should be of interest to examine the behaviour of cadinene oxide (XLIII) under these conditions.

*The rearrangement of β -himachalene oxide with boron-trifluoride etherate has been studied in this Laboratory by Mr. R. Shankarnarayan, in connection with the partial synthesis of ketone (XXI), isolated from the essential oil of Cedrus deodara. By comparing the PMR spectrum of his product with that of the total product obtained upon the treatment of β -himachalene oxide in ethyl methyl ketone and perchloric acid, we find that the major ketone of that reaction is indeed the compound (XXI).

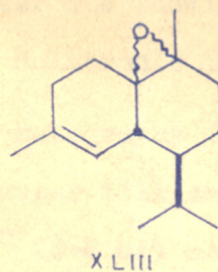
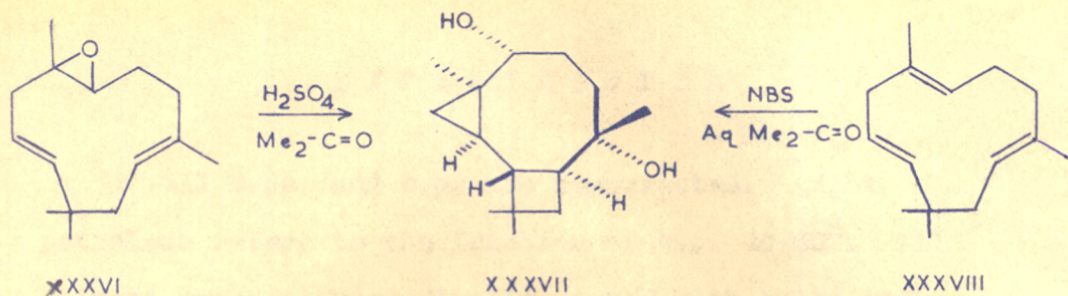


FIG. - 31

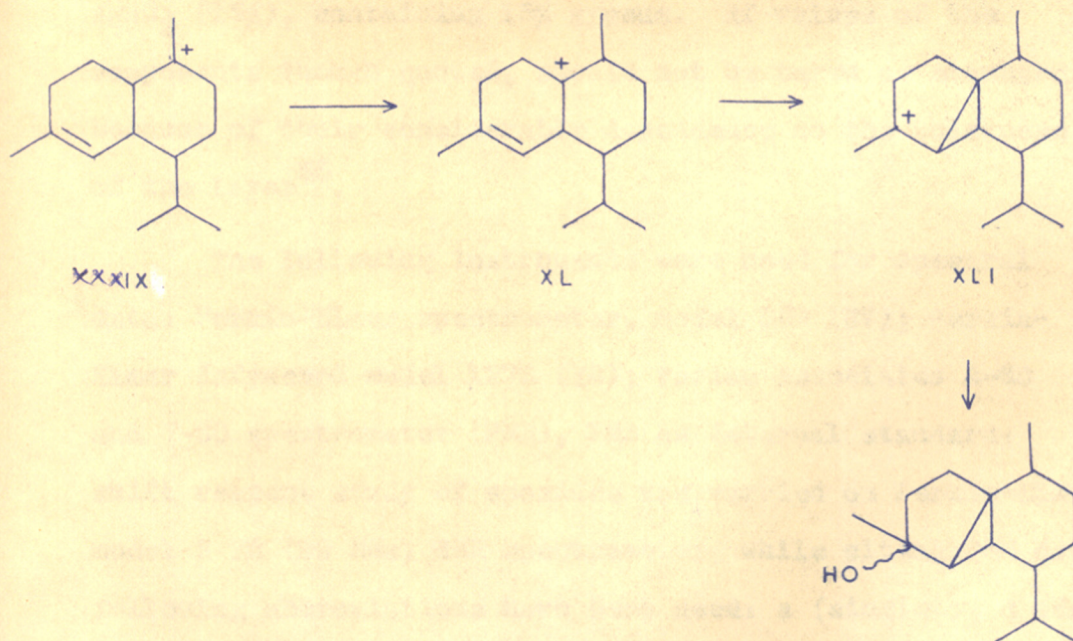


FIG.-32 POSSIBLE GENESIS OF CUBEBOLS

EXPERIMENTAL

All m.ps. and b.ps are uncorrected. Light petroleum refers to the fraction of b.p. 40-60°. All solvent extracts were finally washed with brine before drying over anhydrous Na_2SO_4 . Optical rotations were measured in CHCl_3 soln. (unless specified) on a Perkin-Elmer (Model 141) automatic polarimeter and Schmidt-Haensch Electronic Polarimeter model Polatron 1.

The silica gel for column chromatography (100-200 mesh) was washed with hot distilled water till sulphate-free, dried and activated at 125-130° (6-8 hr) and then standardised⁵⁴. AgNO_3 -impregnated silica gel was made by the method of Gupta and Dev⁴² and activated at 100-110° (4 hr). TLC were carried out on silica gel, silica gel- AgNO_3 (15%), containing 15% gypsum. Rf values of the components though quoted, should not be taken as standard because of their considerable dependence on the thickness of the layer⁵⁵.

The following instruments were used for spectral data: Perkin-Elmer spectrometer, model 350 (UV); Perkin-Elmer Infracord model 137E (IR); Varian Associates A-60 and T-60 spectrometer (PMR), TMS as internal standard; shift reagent study of epoxides was carried on Perkin-Elmer model R 32 (90 MHz) NMR spectrometer; while citing PMR data following abbreviations have been used: s (singlet), d (doublet),

t (triplet), q (quartet), m (multiplet) and b (broad); the chemical shift position given is that of the centre of signal. CEC Mass spectrometer, model 21-110B (Mass; 70 eV, direct inlet system). While summarising mass spectral data, besides the molecular ion, ten most abundant ions (above m/e 40) are given with their relative intensities.

Chromatographic separations were monitored by TLC. Spectral data (IR, UV, PMR and mass) for new compounds reported in this chapter have not been included here but are conveniently discussed at the appropriate places in the subsequent chapters.

GLC were carried out on 'Aerograph', model A-350-B using a 300 cm x 0.8 cm column (packed with 20% diethylene glycol polysuccinate on 60-80 mesh Chromosorb-W) for analytical chromatography, unless otherwise stated; H_2 was used as the carrier gas.

Action of Lithium-Ethylene diamine on α -Himachalene Oxide: To a 100 ml three-necked flask fitted with a septum inlet, magnetic bar, under N_2 was added β -himachalene epoxide (5.5 g, 0.025 mole) and dry ethylenediamine (30 ml). Lithium metal (4 g, 0.57 mole) was added slowly with vigorous stirring, till the blue colour persisted ($\sim$ 2 hr) while the temperature was kept at 55° . At the end reaction mixture was cooled and crushed ice was added to destroy excess reagent. The aqueous layer was saturated with NaCl and extracted with Et_2O (100 ml x 4), ether layer was washed

with H_2O (20 ml x 5), brine (25 ml x 2), dried and distilled to remove the solvent, furnishing 5.50 g of the reduced mixture. GLC (programming, Fig.3) indicated the presence of five major components having RRT of 1(10.2%), 1.12 (12.7%), 5.6 (14.8%), 6.56 (27.8%) and 7.6 (27.3%) respectively.

BROAD SEPARATION

The reduced mixture (5.5 g) was chromatographed on Al_2O_3 (500 g, grade III; 100 cm x 2.5 cm) with TLC and GLC monitoring:

TABLE 6

Fr.No.	Eluent	Vol. collected.	Wt.	Remarks
1	Pet. ether	200 ml	-	-
2	"	200 ml x2	0.4011 g	Hydrocarbon mixture
3	"	200 ml x2	-	-
4	15% C_6H_6 in pet. ether.	200 ml x10	2.4542 g	Corresponds to compounds having RRT of 6.56 and 7.6.
5	20% " "	200 ml x8	2.3035 g	Corresponds to compounds having RRT of 7.62 and 5.6.
6	30% " "	100 ml x5		
7	40% " "	100 ml x5		
8	50% " "	200 ml x3	0.2087 g	Corresponds to compounds with RRT of 5.6 + tailings of 7.6.
9	C_6H_6	200 ml x2		

Hydrocarbon mixture (RRf = 1.0): Fr.2 (Table 6, 0.4011 g) was distilled in a small bulb, b.p. 100° (bath)/0.7 mm. This fraction was shown by GLC (Fig.8) to consist of two major components having RRT of 1.0 (36.5%) and 1.18 (53.5%). The compound with higher retention time, was identified by mixed GLC as himachalane⁴⁴ (X). The compound with RRT 1.0 was suspected to be IX. The mass spectrum of this mixture shows M^{+} ions at m/e 206 and 208 (relative intensity m/e 206:208, 2:1), corresponding to the mol. weights of compounds IX and X. PMR of the mixture (CCl_4): shows signals assignable to two CH_3CH (two 3H, d, 0.83 and 0.88 ppm; $J = 8$ and 6 Hz respectively) and peaks at 1.5 and 1.7 ppm, the latter corresponding to a $Me-C=C$.

Alcohol-III (RRf, 0.71; RRT = 6.56; 6 α -hydroxy-1 α -himachal-2-ene (VIII): Fr.4 (Table 6, 2.4542 g). GLC [temp. 180° ; gas flow 60 ml/min.] showed it to be a mixture of two components having RRT of 6.56 and 7.6 and its TLC (solvent: 15% EtOAc/ C_6H_6), indicated it to be a mixture of two compounds corresponding to RRf of 0.71 and 0.65 respectively. The component having RRf Of 0.71 was isolated pure by chromatography of the mixture on Al_2O_3 (225 g, Grade III, 110 cm x 2 cm; solvent: 10% C_6H_6 in pet. ether), to furnish VIII (0.6506 g); b.p. 130° (bath)/0.5 mm; $[\alpha]_D +52.01^{\circ}$ (c, 2.48%). IR spectrum (Fig.6). PMR spectrum (Fig.7). Mass spectrum: m/e 222 (M^{+} , 47%), 119 (100%), 82 (73%), 55(69%), 109 (62%), 69 (58%), 95 (49%), 204 (47%), 111 (47%) and 93 (41%). (Found: C, 80.71; H, 12.27. $C_{15}H_{26}O$ requires: C,

81.02; H, 11.79%).

Fr.5 - Fr.7 (Table 6, 2.3035 g), GLC [temp. 180°; gas flow 60 ml/min] showed it to be a mixture of two components having RRT of 5.6 and 7.62 and TLC also (solvent: 15% EtOAc/C₆H₆), indicated it to be mixture of two compounds corresponding to RRF of 0.58 and 0.65 respectively. It was chromatographed on Al₂O₃ (250 g, Grade III, 100 cm x 2 cm) with TLC monitoring (solvent: 15% EtOAc in C₆H₆).

TABLE 7

Fr.No.	Eluent	Vol. collected	Wt.	Remarks
1	Pet. ether	200 ml x5	-	-
2	20% C ₆ H ₆ in pet.ether	200 ml x3	negligible	-
3	" "	150 ml x6	0.5045 g	Corresponds to RRF = 0.65
4	25% "	150 ml x6	0.4694 g	mixture
5	30% "	100 ml x4	0.9944	mixture
6	50% "	100 ml x5		
7	C ₆ H ₆	100 ml x3		

Alcohol-II, (RRF, 0.65; RRT = 7.62; Himachalol (VI):

Fr.3 (Table 7, 0.5045 g) was recrystallised from MeCN (-10°), m.p. 67-68° and identified as himachalol by mixed GLC and PMR spectrum (CCl₄): two quaternary Me's (two 3H, s, 0.81 and 0.96 ppm); CH₃-C-OH (3H, s, 1.18 ppm); CH₃-C=CH (3H, bs, 1.65 ppm)

and $\text{CH}_3\text{-C=CH}$ (1H, m, 5.5 ppm) [Lit.¹² m.p. 67-68°, PMR].

Alcohol-I (RRf, 0.58; RRT, 5.6: 7 α -hydroxyhimachal-1-ene (VII):

Fr.5 - Fr.7 (Table 7, 0.9944 g). TLC showed major compound with RRf 0.58 and traces of compounds having RRf 0.65.

This mixture was resolved by inverted dry column chromatography (IDCC)⁴³ on SiO_2 -gel (250 g, grade II, 25 cm x 4 cm; solvent: 10% EtOAc in C_6H_6) into a pure compound, having RRf of 0.58 and this was identified as VII, from its spectral characteristics. (0.423 g) was distilled, b.p.

140° (bath)/0.7 mm; $[\alpha]_D^{25} +8.172^\circ$ (c, 2.57%). IR spectrum

(Fig.4). PMR spectrum (Fig.5). Mass spectrum: m/e 222

(M^+ , 10%), 43 (100%), 95 (92%), 137 (85%), 41 (79%), 103 (77%), 127 (68%), 55 (49%), 69 (45%), 84 (44%) and 110 (41%).

(Found: C, 80.60; H, 11.99. $\text{C}_{15}\text{H}_{26}\text{O}$ requires: C, 81.02; H, 11.79%).

The terpene epoxides, 3 α ,4 α -epoxy carane (XVI)^{56,32}, 3 β , 4 β -epoxy-carane (XVII)³¹ and 2 α ,3 α -epoxy pinane (XVIII)^{57,32} used for shift reagent study were prepared according to the reported procedures.

β -Himachalene epoxide (IV).* In a 500 ml three necked, round bottomed flask equipped with a mechanical stirrer, a reflux condenser and a thermometer, EtOH (500 ml),

* Standard reaction conditions for its preparation were kindly supplied by Dr. S. Krishnappa of this Laboratory.

β -himachalene (20.4 g, 0.10 mole), 30% H_2O_2 (30 ml), 0.1M Na_2HPO_4 aq. (5 ml), and 0.5N NaOH aq. (8 ml) were added. The mixture was stirred at 55° for 4 hr while 0.5N NaOH aq. (32 ml) was added gradually. The mixture was cooled to room temperature and diluted with H_2O (200 ml) and extracted with CHCl_3 (50 ml x 3). The combined extract after washing with H_2O (15 ml x 2), brine (15 ml x 2) and drying was distilled to furnish 10 - 12% of the unreacted β -himachalene, b.p. $93-96^\circ/0.6$ mm, followed by 16.5 g (85%) of β -himachalene epoxide, based on the β -himachalene consumed b.p. $100-102^\circ/0.6$ mm. PMR (CCl_4): two quaternary Me's (two 3H, s, 0.85 and 0.95 ppm); $\text{C}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{Me}$ (3H, s, 1.28 ppm); $\text{CH}_3-\text{C}=\text{CH}-$ (3H, d, 1.75 ppm, $J = 1$ Hz) and $\text{CH}_3-\text{C}=\text{CH}-$ (1H, b hump, 5.33 ppm, $w_H = 9$ Hz). [Lit.^{2a}: b.p. $150^\circ/9$ mm, PMR].

Solvolysis of β -himachalene epoxide (IV)

(a) Aqueous acetone and sulphuric acid⁴⁰. β -Himachalene epoxide (0.540 g, 0.0025 mole), acetone (1.1 ml), H_2O (1.1 ml) and conc. H_2SO_4 acid (0.0160 g, 0.16%) were shaken together at $\sim 29^\circ$ for 24 hr under N_2 . TLC (solvent: 10% EtOAc in C_6H_6) indicated the formation of a hydrocarbon, which was not investigated further.

(b) Ethyl methyl ketone and Perchloric acid⁴¹. To the epoxide (0.1150 g, 0.0005 mole) taken in (1.8 ml) of ethyl methyl ketone was added perchloric acid (1.5%, 0.09 ml; of 60%). After stirring for 5 minutes, the reaction mixture was worked up,

to furnish a product which was distilled, b.p. 130-135° (bath)/0.1 mm. TLC (solvent: 10% EtOAc in C_6H_6 ; DNP sprayed) indicated it to be a complex mixture of ketones. Major ketone was identified as XXI, from the PMR spectra of the mixture, by comparison with authentic PMR* and its spectral data are reported here. IR: $C=O$ 1700 cm^{-1} . PMR (CCl_4): three quaternary Me's (three 3H, s, 0.75, 0.98 and 1.15 ppm); $CH_3-C=CH$ (3H, s, 1.80 ppm) and $CH_3.C=CH$ (1H, m, 5.53 ppm).

(c) Aqueous dioxane and perchloric acid. β -Himachalene epoxide (16 g, 0.078 mole), purified dioxane (53.5 ml), H_2O (12 ml) and perchloric acid (60%; 0.4700 g, 4.7%) were mixed together at 0° (ice/ H_2O) and then left aside at room temperature ($\sim 33^\circ$) for 34 hrs. The mixture was shaken from time to time and in the end the mixture became homogeneous. The reaction mixture was poured in H_2O (300 ml) and extracted with Et_2O (100 ml x 4), the ether extract was washed with H_2O (50 ml x 4), $NaHCO_3$ aq. (15 ml x 2), H_2O , brine, dried and distilled to remove the solvent furnishing 16 g of the crude product. TLC (solvent: 15% EtOAc in C_6H_6) indicated the presence of five compounds, with Rf of 1.00, 0.73, 0.64, 0.29 and 0.09 respectively, besides the unreacted oxide. (Fig.21).

*See foot-note at the end of the 'Discussion' of this Chapter.

The crude product (~ 16 g) was chromatographed on Al_2O_3 (grade III, 1700 g; 164 cm x 4.7 cm) with TLC monitoring (solvent: 15-20% EtOAc in C_6H_6).

TABLE 8

Fr.No.	Eluent	Vol. collected	Wt.	Remarks
1	Pet. ether	200 ml	-	-
2	"	600 ml x4	3.249 g	Corresponds to Rf = 1.00
3	"	600 ml	-	-
4	"	600 ml x5	0.5849 g	mixture
5	"	600 ml x7	0.2627 g	"
6	"	600 ml x6	0.1536 g	Unreacted oxide.
7	25% C_6H_6 in pet. ether.	600 ml x5		
8	50% "	600 ml x7	0.3711 g	Corresponds to Rf = 0.73
9	"	600 ml x6	0.5368 g	mixture of compounds Rf = 0.73 and 0.64
10	75% "	600 ml x2		
11	"	600 ml x13	0.7433 g	Corresponds to Rf = 0.64
12	C_6H_6	600 ml x2	-	-
13	"	600 ml x22	3.8549 g	Corresponds to Rf = 0.29
14	5% EtOAc in C_6H_6	600 ml x5		
15	10% " " "	600 ml x3		
16	15% " " "	600 ml x2		
17	" " " "	600 ml x4	0.8956 g	mixture
18	20% " " "	600 ml x1		
19	25% " " "	600 ml x21		
20	" " " "	600 ml x5	3.1149 g	Corresponds to Rf 0.09
	+5% MeOH			
21	MeOH	600 ml x2	1.6 g	-junk-

Ar-Himachalane (XXIV) and himachala-2,5,7-triene (XXV):

Fr.2 (Table 8, 3.249 g) was shown by TLC on 15% AgNO_3 -silica gel/IIA (solvent: 1:1 C_6H_6 in pet. ether) to consist of three compounds having RRF of 1.00, 0.71 and 0.25 respectively. This mixture was subjected to IDCC⁴³ (15%- AgNO_3 - SiO_2 gel/IIA, 500 g, 25 cm x 6.6; solvent: 1:1 C_6H_6 in pet. ether). The compound with RRF of 1.0 (0.3768 g) was distilled, b.p. 125-130° (bath)/2 mm and identified as XXIV, by comparison (IR, PMR) with an authentic specimen.⁴⁴

The compound with RRF of 0.71 (0.6468 g) was distilled, b.p. 140° (bath)/2 mm and identified as XXX by comparison (IR, PMR and mass) with the reported^{2a} spectral data.

The compound with RRF 0.25 got changed into XXIV and XXV during IDCC.

Alcohol-I (RRf, 0.73; 7 α -hydroxy-1 α -himachal-2,5-diene (XXVI):

Fr.8 (Table 8, 0.3711 g) was distilled, b.p. 130-140° (bath)/0.8 mm. IR (smear): OH 3420, 1075 cm^{-1} . PMR (CCl_4): two quaternary Me's (two 3H, s, 0.67 and 0.96 ppm); $\text{CH}_3-\overset{|}{\underset{|}{\text{C}}}-\text{OH}$ (3H, s, 1.19 ppm); $\text{CH}_3-\text{C}=\text{CH}$ (3H, bs, 1.78 ppm); $\text{H}_2\text{C}-\text{CH}=\text{C}-$ (1H, q, 6.21 ppm, $J_1 = 3$ and $J_2 = 2$ Hz); $\text{CH}_3-\text{C}=\text{CH}-$ (1H, m, 5.53 ppm); $-\text{C}=\text{CH}-\text{CH}_2-\text{C}=\text{C}-$ (2H, ill-resolved m, 2.51 ppm) and $-\overset{|}{\underset{|}{\text{C}}}-\text{OH}$ (1H, b hump, 3.80 ppm, disappears on D_2O exchange). From IR and PMR, it was identified as known^{2a} allylic tertiary alcohol [Lit.^{2a}: b.p. 150° (bath)/3 mm, IR and PMR].

Alcohol-II (RRf 0.64; 7 α -hydroxy-3(15)-dehydro-1 α -2,6-cyclohimachalane (XXVII): Fr.11 (Table 8, 0.7433 g) was distilled to give pure XXVII, b.p. 135° (bath)/0.7 mm, $[\alpha]_D +110.3$ (c, 1.43%); λ_{max}^{EtOH} 215 nm (ϵ 456). IR spectrum (Fig.23). PMR spectrum (Fig.24). Mass spectrum: m/e 220 (M^+ , 44%), 206 (100%), 41 (74%), 178 (68%), 43 (66%), 83 (58%), 92 (55%), 163 (44%), 122 (39%) and 106 (37%). (Found: C, 81.53; H, 10.76. $C_{15}H_{24}O$ requires: C, 81.76; H, 10.98%).

Diol-I (RRf 0.29; 7 α ,3 α -dihydroxy-1 α -2,6-cyclohimachalane (XXVIII): Fr.13-16 (Table 8, 3.8549 g), were pooled and crystallised from pet. ether to furnish flakes, m.p. 106-107°; $[\alpha]_D +8.3$ (c, 0.74%). IR spectrum (Fig.25). PMR spectrum (Fig.26). Mass spectrum: m/e 238 (M^+ , 1%), 109 (100%), 97 (44%), 125 (39%), 99 (33%), 124 (26%), 43 (22%) and 41 (17%). (Found: C, 75.58; H, 11.39. $C_{15}H_{26}O_2$ requires: C, 75.58; H, 11.00%).

Formate of (XXVIII). The above alcohol (0.1430 g) on treatment with acetic-formic anhydride⁵⁸ (1.8 ml) at 30°/16 hr after removal of excess of reagent under vacuum, followed by usual work up, furnished XXIX, b.p. 130-140° (bath)/0.2 mm. PMR spectrum (Fig.27) (Found: C, 69.00; H, 9.5. $C_{17}H_{26}O_4$ requires: C, 69.36; H, 8.9%).

Diol-II (RRf. 0.09; 7 α ,3 α -dihydroxy-1 α -2,6-cyclohimachalane (XXX): Fr.20 (Table 8, 3.1149 g) was crystallised from acetonitrile, m.p. 78-80°, $[\alpha]_D +102.7^\circ$ (c, 0.85%). IR

spectrum (Fig.28). PMR spectrum (Fig.29). Mass spectrum: m/e 238 (M^+ , 0.13%), 109 (100%), 97 (46%), 124 (33%), 99 (28%), 43 (19%) and 41 (14%). (Found: C, 74.82; H, 11.03. $C_{15}H_{26}O_2$ requires: C, 75.58; H, 11.00%).

Formate of (XXX). (0.1450 g) of the compound, XXX was treated with acetic-formic anhydride⁵⁸ (2 ml) at 30°/20 hr and after removal of excess of the reagent under vacuum, followed by usual work up, it furnished the required formate ester (0.1597 g), m.p. 79-81°C. PMR spectrum (Fig.30). (Found: C, 69.05; H, 9.05. $C_{15}H_{26}O_4$ requires: C, 69.36; H, 8.9%).

SUMMARY

The stereochemistry of the oxirane ring in β -himachalene epoxide is shown to possess a β -configuration. Lanthanide shift study has been used to assign the preferred conformations of known terpene epoxides. Products resulting from the homoallylic participation of double bond in the solvolysis of β -himachalene- β -oxide are described.

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CHAPTER III

HYDROBORATION OF β - HIMACHALENE AND SOLVOLYSIS
OF HIMACHALOL *p* - NITROBENZOATE

HYDROBORATION OF β -HIMACHALENE AND SOLVOLYSIS OF HIMACHALOL *p*-NITROBENZOATE

Solvolysis of allohimachalol tosylate (I) has been shown¹ to furnish a mixture of α -himachalene (II)², β -himachalene (III)², himachalol (III)³ and allohimachalol (V)¹/Fig.1. It was thought of interest to study the solvolysis of a suitable derivative of himachalol (IV) and epihimachalol (VI)⁴. It was envisaged that himachalol derivative (XIV) on solvolysis might give allohimachalol as one of the products which will constitute a biogenetic-type synthesis of allohimachalol (Fig.2). On the other hand epi-himachalol derivative can possibly lead to longiborane/longifolane skeletons⁵ (Fig.3). In the first instance, we thought of preparing epi-himachalol from β -himachalene. In the first part of this chapter, are described the attempts directed towards the synthesis of epi-himachalol while in the second part we describe the solvolysis of himachalol *p*-nitrobenzoate.

Attempted preparation of epihimachalol from β -himachalene

In the reaction of β -himachalene with per acid, it is known⁶ that fully substituted olefinic linkage is attacked preferentially. It was hoped that the hydroboration of β -himachalene with limited amount of diborane would generate olefinic alcohols, of which there would be at least some product development resulting from the

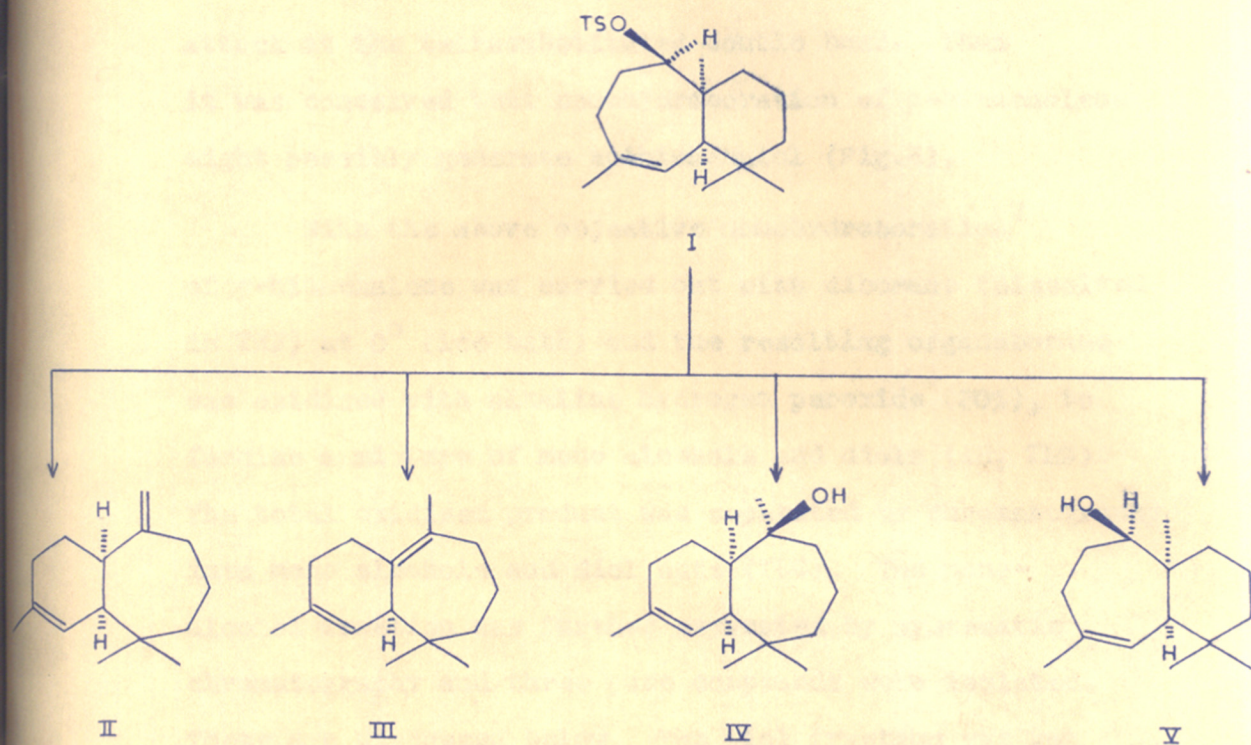


FIG. 1 SOLVOLYSIS PRODUCTS OF ALLOHIMACHALOL TOSYLATE (1)

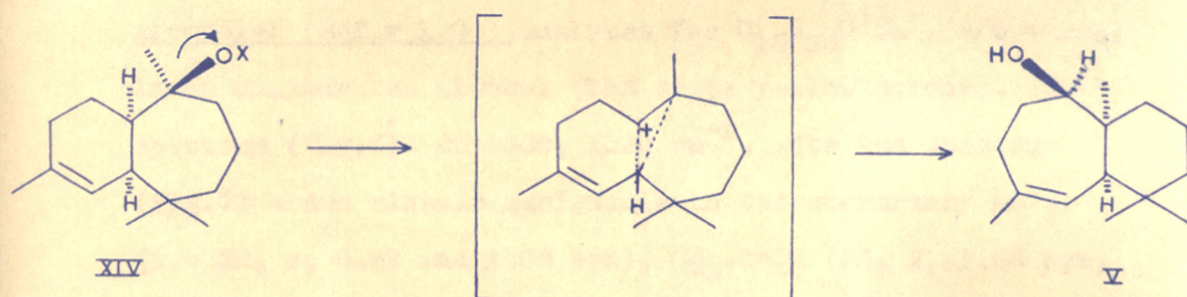


FIG. 2 POSSIBLE FORMATION OF ALLOHIMACHALOL FROM SOLVOLYSIS OF HIMACHALOL DERIVATIVE

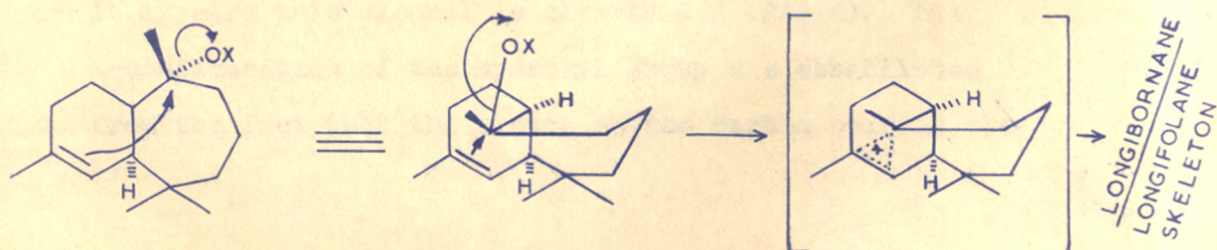


FIG. 3 - POSSIBLE PRODUCTS FROM SOLVOLYSIS OF EPI-HIMACHALOL DERIVATIVE.

attack at the tetrasubstituted double bond. Thus it was conceived that monohydroboration of β -himachalene might possibly generate epihimachalol (Fig.4).

With the above objective monohydroboration⁷ of β -himachalene was carried out with diborane (dissolved in THF) at 0° (ice bath) and the resulting organoborane was oxidised with alkaline hydrogen peroxide (30%), to furnish a mixture of mono alcohols and diols (IR, TLC). The total oxidised product was separated by chromatography into mono alcohols and diol cuts (TLC). The mono-alcohol fraction was further separated by systematic chromatography and three pure compounds were isolated. These are discussed below. The diol fraction was not investigated.

Alcohol-1 (RRf = 1.00), analyses for $C_{15}H_{26}O$ (M^+ , $m/e = 222$) is an unsaturated alcohol (TNM test: yellow colour). IR spectrum (Fig.6): OH 3300, 1030 cm^{-1} . Its PMR spectrum (Fig.7) shows signals assignable to two quaternary Me's (two 3H, s, 0.82 and 1.05 ppm); $CH_3.C=CH$ (3H, d, 1.66 ppm, $J = 1$ Hz); $CH_3.CH$ (3H, d, 1.06 ppm, $J = 8$ Hz); $HOCH-CH-C\equiv C-$ (1H, d, 2.3 ppm, $J = 8$ Hz) and $-CH-CH(OH)-CH-$ (1H, t, 3.28 ppm, $J_1 = 9$ Hz; $J_2 = 8$ Hz). From spectral characteristics, it appears this alcohol is clearly VII (Fig.5). The α -configuration of the hydroxyl group was established from the fact that the proton on the carbon bearing the

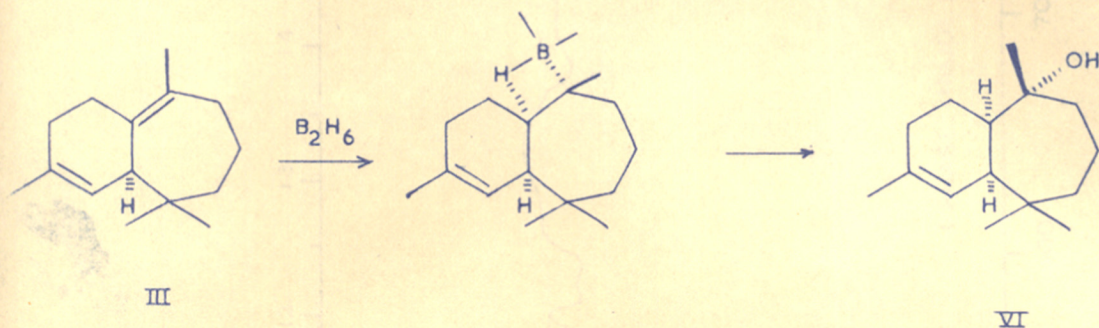


FIG. 4 - PREPARATION OF EPI-HIMACHALOL VIA HYDROBORATION OF β -HIMACHALENE

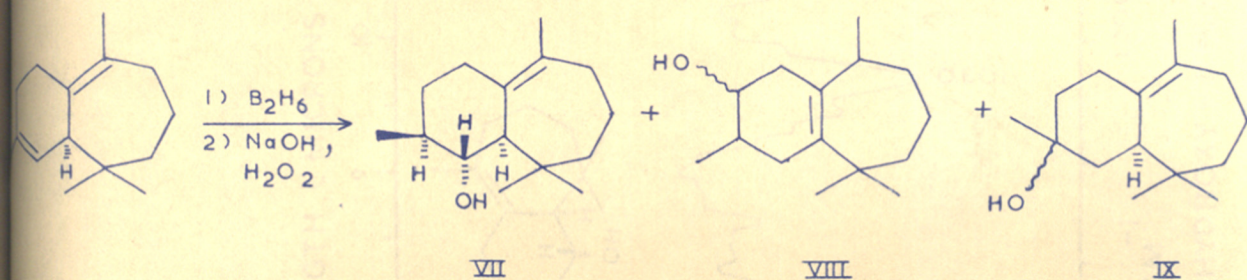


FIG. 5 - MONOALCOHOLS FROM THE MONOHYDROBORATION OF β -HIMACHALENE

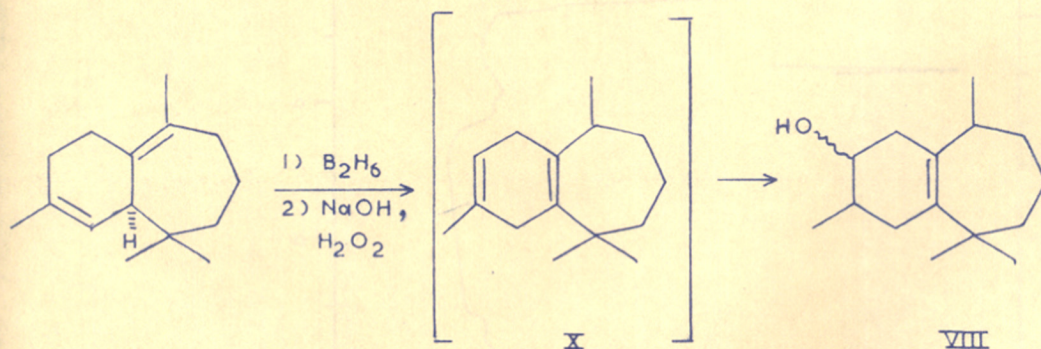


FIG. 10 - POSSIBLE FORMATION OF ALCOHOL - III (VIII) VIA X

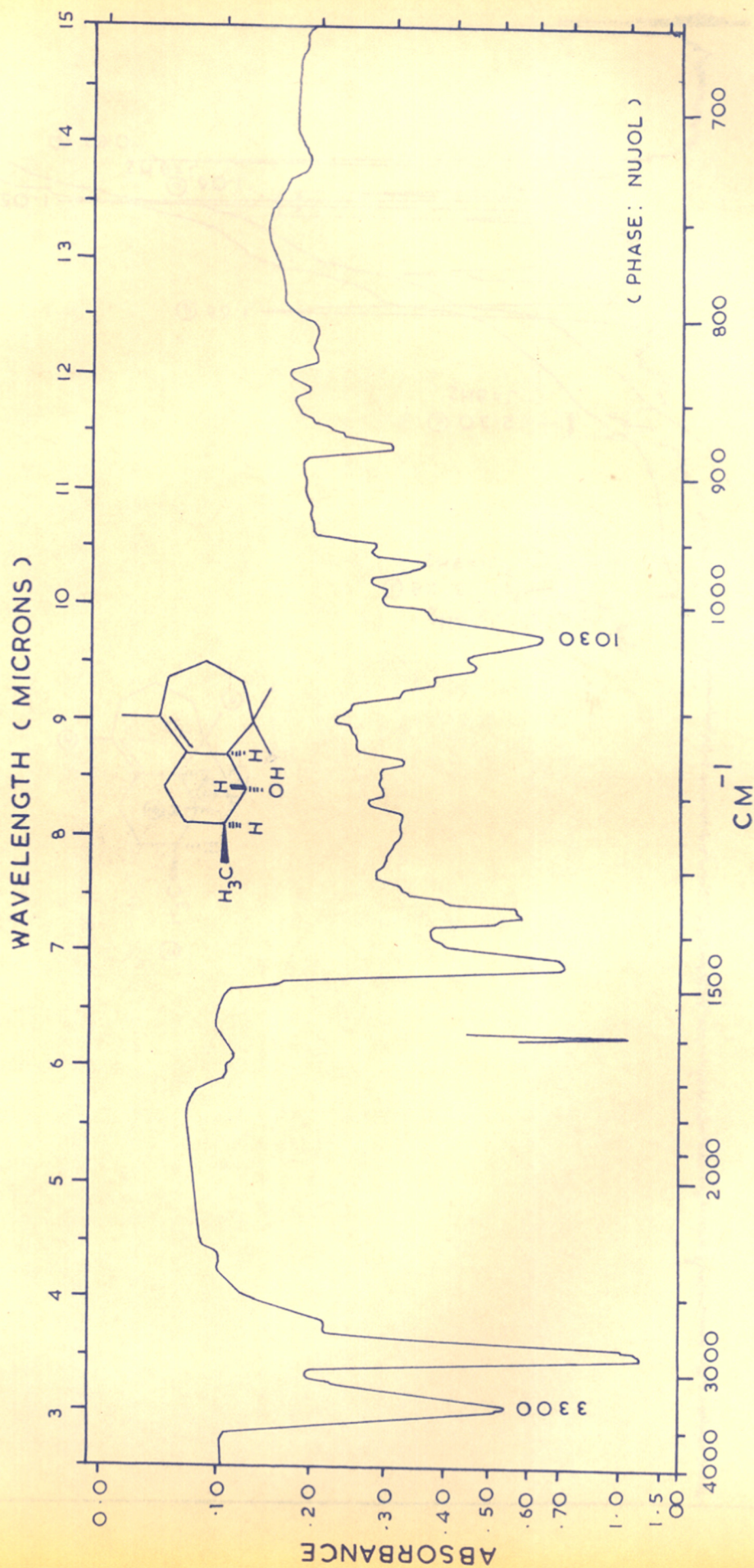


FIG. 6 IR SPECTRUM OF 2 α -HYDROXY - 1 α - HIMACHAL - 6 - ENE (VII)

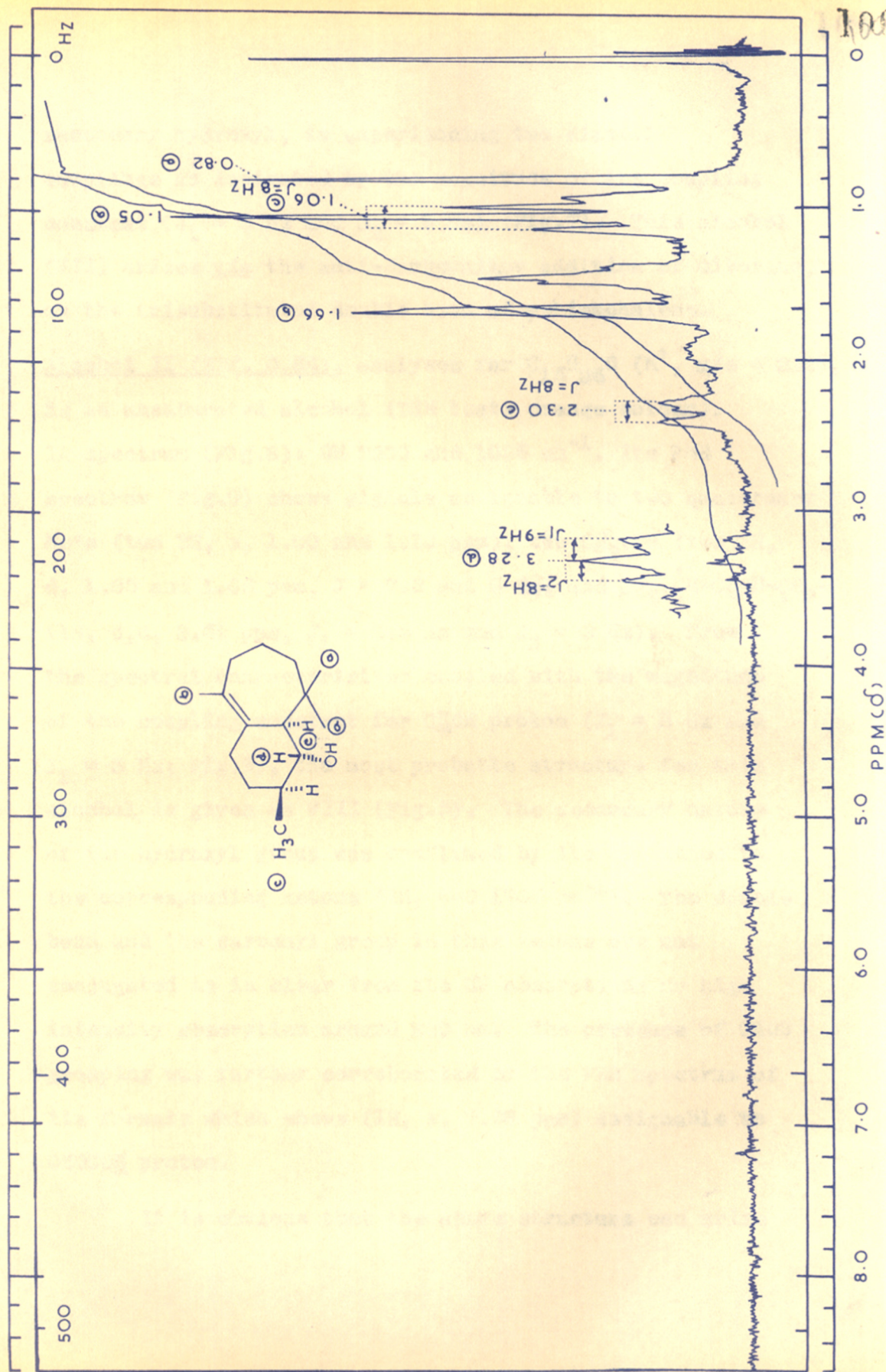


FIG.7 PMR SPECTRUM OF 2 α -HYDROXY -10 α -HIMACHAL -6-ENE (VII)

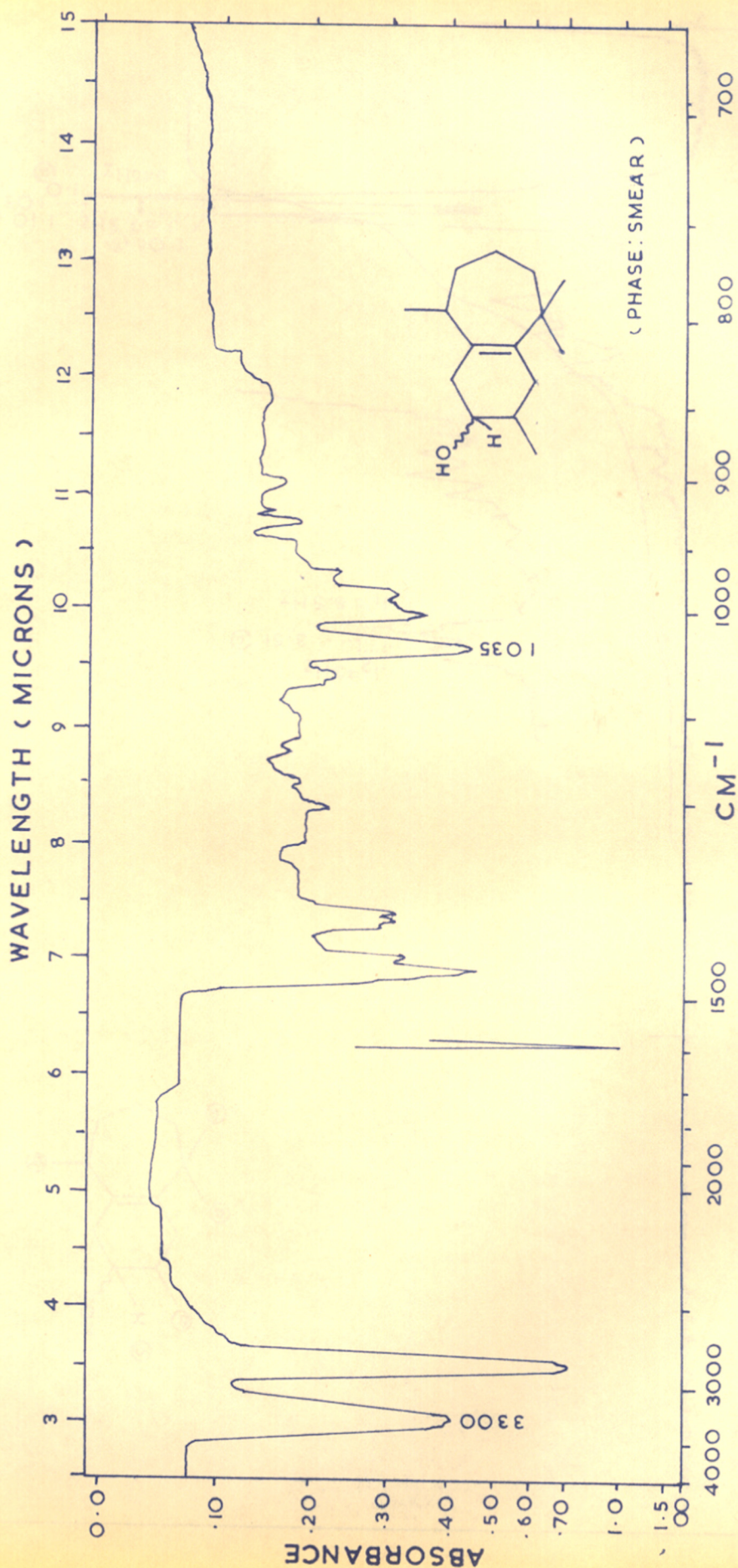
secondary hydroxyl, is experiencing two diaxial couplings as indicated by the magnitude of its coupling constant ($J_1 = 9$ Hz and $J_2 = 8$ Hz) (Fig.7). This alcohol (VII) arises via the anti-Markovnikov addition of diborane, on the trisubstituted double bond of β -himachalene.

Alcohol II (Rrf. 0.84), analyses for $C_{15}H_{26}O$ (M^+ , $m/e = 222$), is an unsaturated alcohol (TNM test: orange colour).

IR spectrum (Fig.8): OH 3300 and 1035 cm^{-1} . Its PMR spectrum (Fig.9) shows signals assignable to two quaternary Me's (two 3H, s, 1.00 and 1.10 ppm); two $\underline{CH}_3$.CH (two 3H, d, 1.05 and 1.06 ppm, $J = 7.5$ and 6 Hz) and $\underline{CH}_3$. $\overset{|}{\underset{|}{CH}}$ - $\underline{CHOH}$ - $\overset{|}{\underset{|}{CH_2}}$ - (1H, d,d, 3.51 ppm, $J_1 = 8.5$ Hz and $J_2 = 3$ Hz). From the spectral characteristics coupled with the magnitude of the coupling constant for $\underline{CHOH}$ proton ($J_1 = 8$ Hz and $J_2 = 3$ Hz; Fig.9), the most probable structure for this alcohol is given as VIII (Fig.5). The secondary nature of the hydroxyl group was confirmed by its oxidation to the corresponding ketone (IR, $C=O$ 1705 cm^{-1}). The double bond and the carbonyl group in this ketone are not conjugated as is clear from its UV absorption: no high intensity absorption around 220 nm. The presence of $\underline{CHOH}$ grouping was further corroborated by the PMR spectrum of its formate which shows (1H, s, 7.98 ppm) assignable to $\underline{CHOCOH}$ proton.

It is obvious that the above structure can arise

102
FIG.8 IR SPECTRUM OF 4-HYDROXY-HIMACHAL-I(6)-ENE. (VIII)



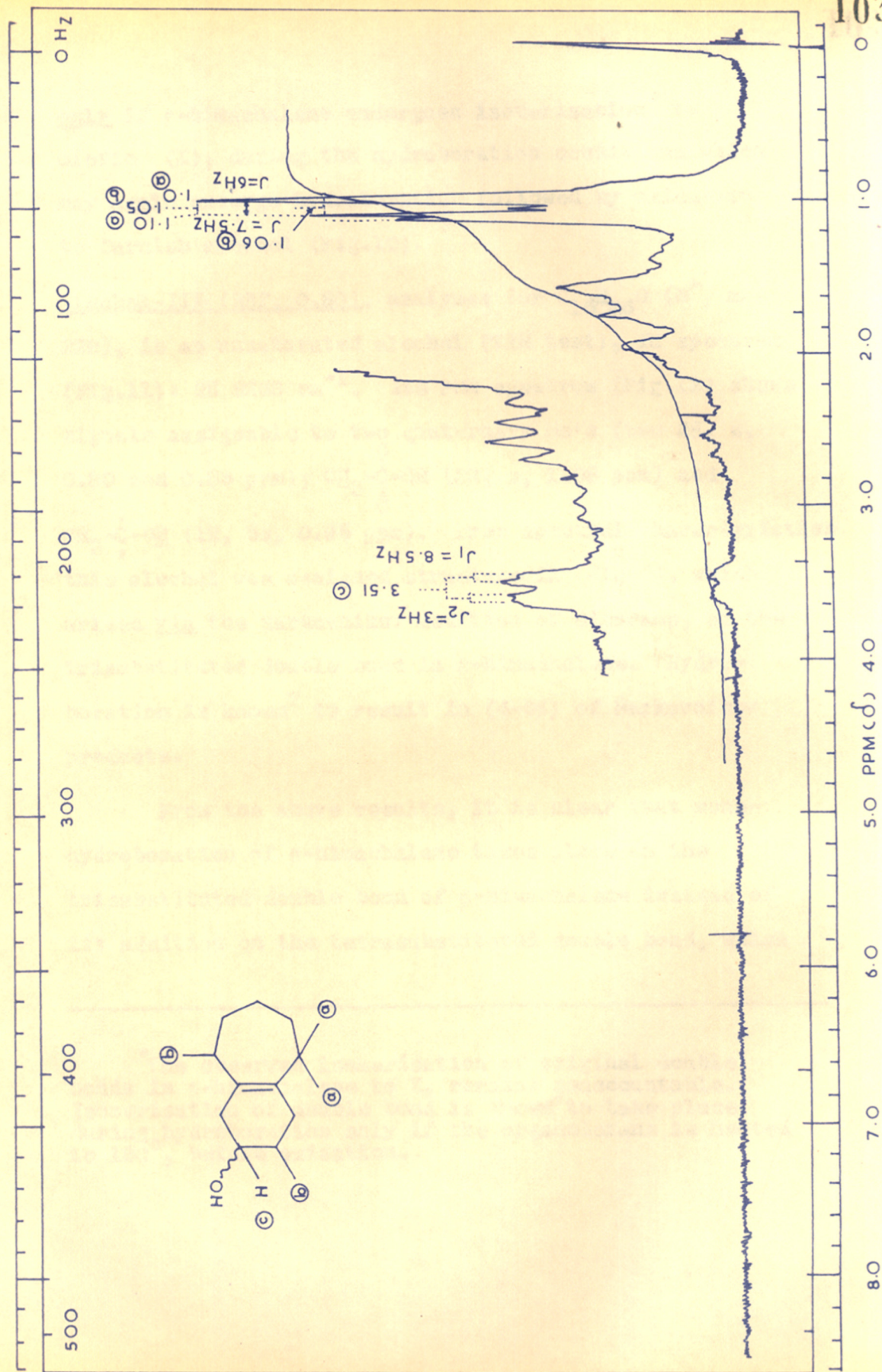


FIG. 9 PMR SPECTRUM OF 4-HYDROXY HIMACHAL-1-(6)-ENE (VIII)

only if β -himachalene undergoes isomerisation* to olefin (X), during the hydroboration conditions which may again undergo hydroboration followed by oxidation to furnish alcohol (Fig.10).

Alcohol-III (RRf, 0.80), analyses for $C_{15}H_{26}O$ (M^+ , m/e 222), is an unsaturated alcohol (TMM test), IR spectrum (Fig.11): OH 3268 cm^{-1} . Its PMR spectrum (Fig.12) shows signals assignable to two quaternary Me's (two 3H, s, 0.80 and 0.85 ppm); $\text{CH}_3-\overset{\text{C}}{\underset{\text{C}}{\text{C}}}-\text{OH}$ (3H, s, 1.08 ppm) and $\text{CH}_3-\overset{\text{C}}{\underset{\text{C}}{\text{C}}}-\text{OH}$ (1H, bs, 0.95 ppm). From spectral characteristics this alcohol was assigned structure IX (Fig.5), which arises via the Markovnikov addition of diborane, on the trisubstituted double bond in β -himachalene. Hydroboration is known⁷ to result in (4-6%) of Markovnikov products.

From the above results, it is clear that monohydroboration of β -himachalene takes place on the trisubstituted double bond of β -himachalene instead of its addition on the tetrasubstituted double bond, which

*The observed isomerisation of original double bonds in β -himachalene to X, remains unaccountable. Isomerisation of double bond is known⁸ to take place during hydroboration only if the organoborane is heated to 160° , before oxidation.

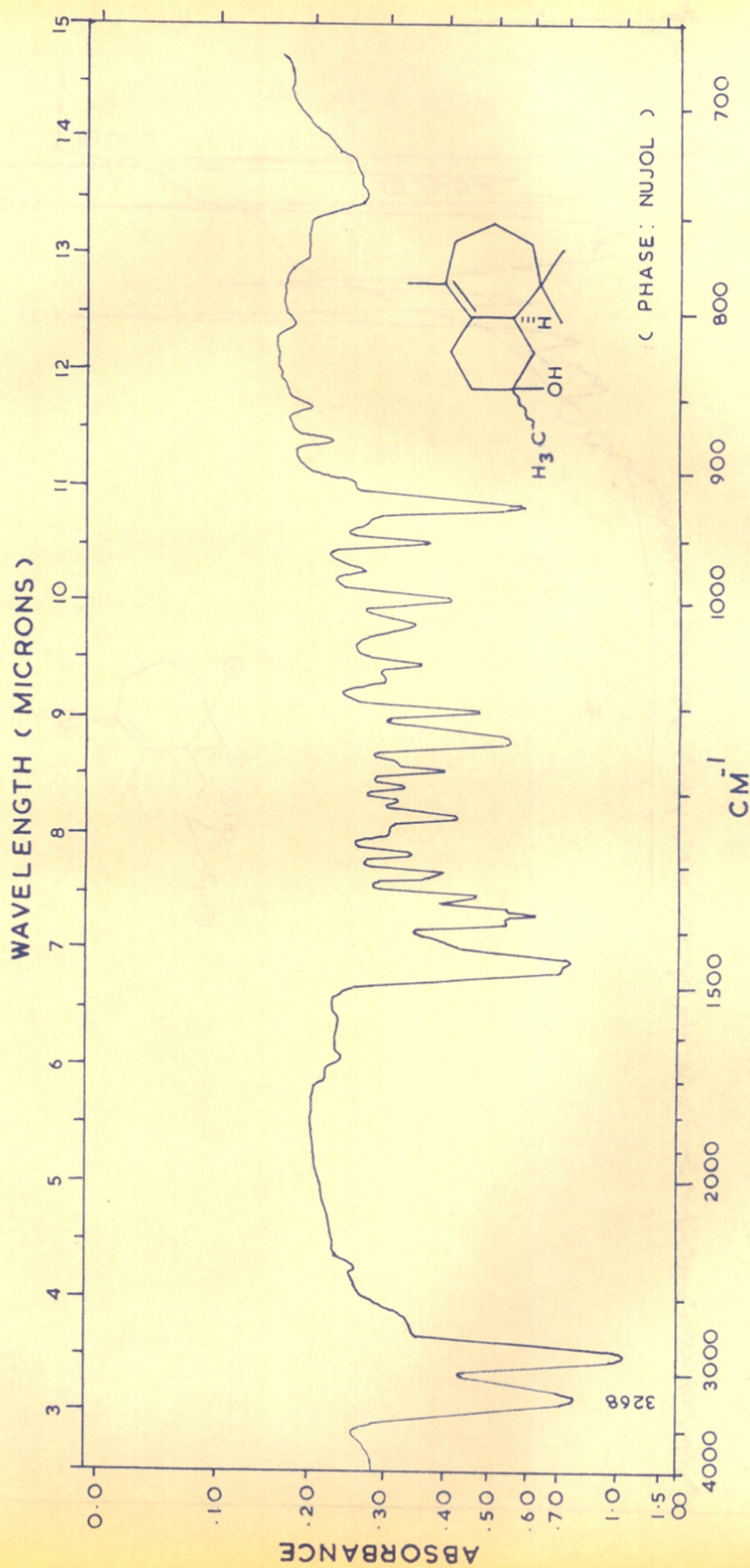


FIG. 11 IR SPECTRUM OF 3-HYDROXY - 1 α - HIMACHAL - 6 - ENE (IX)

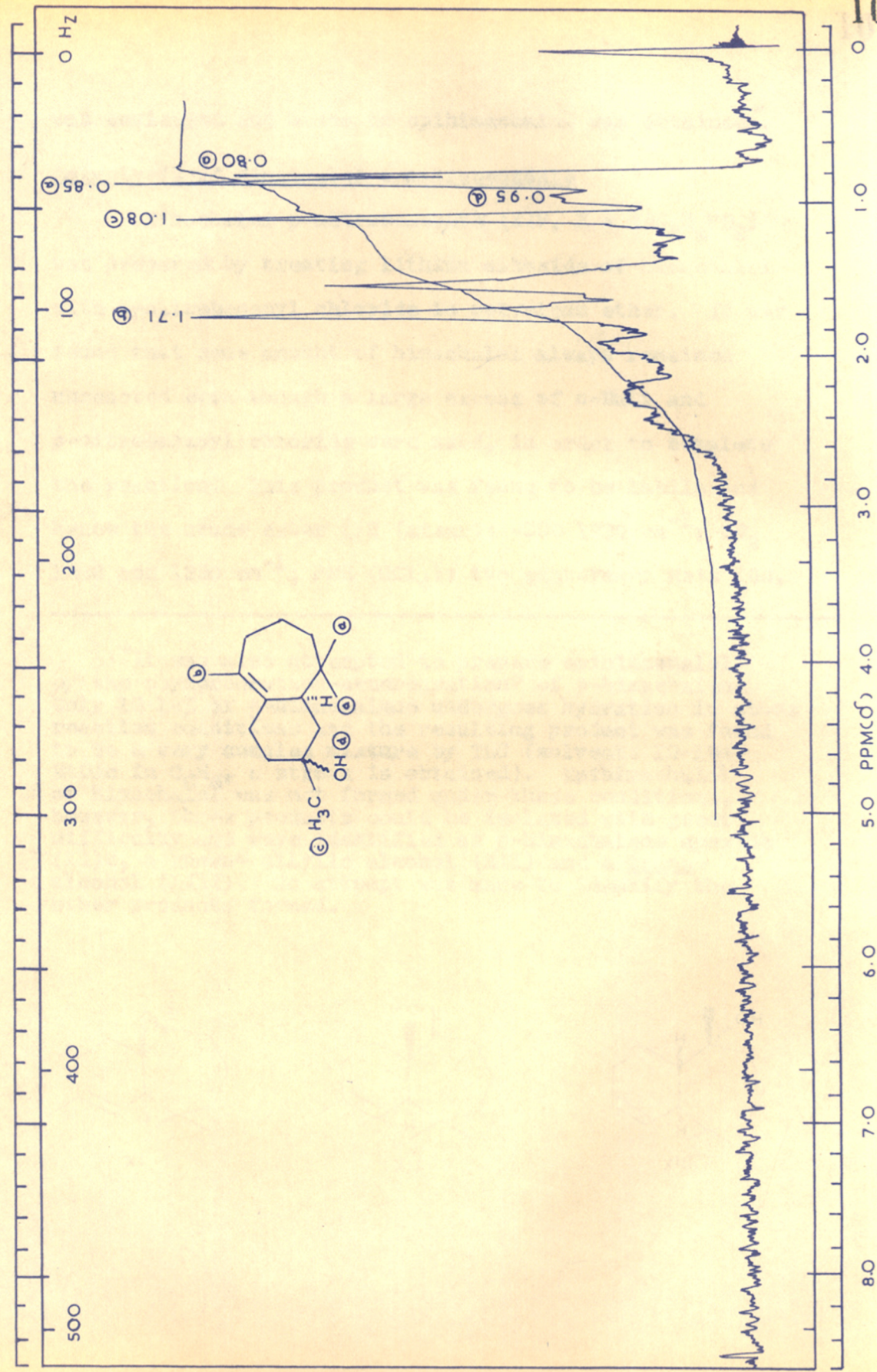


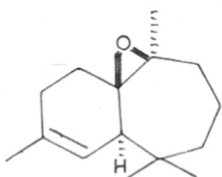
FIG.12 PMR SPECTRUM OF 3-HYDROXY-1,8-HIMACHAL-6-ENE (IX)

was envisaged and hence no epihimachalol was obtained*.

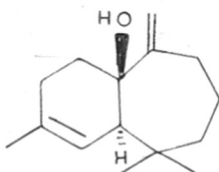
Solvolysis of Himachalol p-nitrobenzoate

Himachalol p-nitrobenzoate (XIV, $X = \text{COC}_6\text{H}_4\text{NO}_2$) was prepared by treating lithium alkoxide of himachalol with p-nitrobenzoyl chloride in petroleum ether. It was found that some amount of himachalol always remained unreacted even though a large excess of n-BuLi and p-nitrobenzoyl chloride were used, in order to complete the reaction. This product was found to be labile and hence the crude ester [IR (smear): $-\text{COO}$ 1720 cm^{-1} ; NO_2 1528 and 1350 cm^{-1} ; PMR (CCl_4): two quaternary Me's (6H,

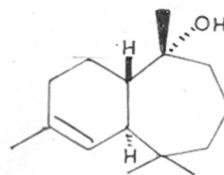
*It was also attempted to prepare epihimachalol by the oxymercuration-demercuration⁹ of β -himachalene. Only 10-12% of β -himachalene undergoes hydration in above reaction conditions and the resulting product was found to be a very complex mixture by TLC (solvent: 10-15% EtOAc in C_6H_6 , a streak is obtained). Epihimachalol or himachalol was not formed under these conditions, however, three products could be isolated with great difficulty and were identified as β -himachalene epoxide (XI)⁶, a known⁶ allylic alcohol (XII) and a trans-alcohol (XIII). No attempt was made to identify the other products formed.



XI



XII



XIII

s, 0.93 ppm); $\text{CH}_3\text{-OCOC}_6\text{H}_4\text{NO}_2$ (3H, s, 1.73 ppm); $\text{CH}_3\text{-C=CH-CH}$, ill-defined d, 5.58 ppm, $J = 4.5$ Hz and $\text{-OCO C}_6\text{H}_4\text{NO}_2$ (4H, q, 8.24 ppm); these bonds have been selected from the IR and PMR of the crude ester] was subjected to solvolysis with 80% aq. acetone at $70\text{-}80^\circ$. This furnished a hydrocarbon mixture.

This hydrocarbon mixture was shown to consist of only two components (7.5 : 92.5) by GLC; the components were found to be α -himachalene (II)² and β -himachalene (III)² from their retention times, IR and PMR and this was confirmed by the study of specific rotation and IR and comparing with those of a mixture of the same composition prepared from authentic samples of pure α and β -himachalenes. Thus in this reaction, a simple elimination rather than rearrangement took place, unlike the case of allohimachalol tosylate (I).

EXPERIMENTAL

For general remarks, see p. 78 . Analytical GLC were recorded on Hewlett-Packard 5700A gas chromatograph (column: 180 cm x 3 mm; 3% carbowax on chromosorb W 60-80; H_2 as carrier gas).

Monohydroboration of β -himachalene (III): In a dry flask (250 ml), equipped with septum inlet, pressure equalizing dropping funnel and a magnetic stirrer, under a positive N_2 pressure dry THF (25 ml) and (10.2, 0.05 mole) of β -himachalene were taken and cooled to 0° (ice- H_2O bath). Hydroboration was achieved by the dropwise addition of (29 ml, 0.4590 g; 0.0166 mole) of 1M solution of diborane in THF. The solution was stirred for 30 minutes at 0° and 15 hr at room temperature ($\sim 30^\circ$). (10 ml) of H_2O was then added very slowly and cautiously to destroy excess of diborane, followed by (50 ml) of 1M NaOH and (50 ml) of 30% H_2O_2 and stirred for two hr. The reaction mixture was poured into (300 ml) of H_2O and saturated with NaCl. The organic layer was separated from the aqueous layer, the aqueous layer extracted with Et_2O (100 ml x 4), washed with H_2O (30 ml x 3), brine (30 ml x 3), dried and the solvent distilled off to give 12.7 g of the hydroboration mixture. TLC (solvent: 15% $EtOAc$ in C_6H_6) indicated the presence of some very polar compounds besides unreacted β -himachalene and mono-alcohols.

BROAD SEPARATION

The hydroboration mixture (11.78 g) was chromatographed on alumina (grade III, 350 g; 43 cm x 3.5 cm) with TLC (solvent: 15% EtOAc in C_6H_6) monitoring.

TABLE 1

Fr.No.	Eluent	Vol. collected	Wt.	Remarks
1	Pet. ether	400 ml	-	-
2	" "	300ml x2	2.80 g	β -himachalene
3	10% C_6H_6 in pet. ether	300ml x8	5.1840g	Corresponds to mixture of mono-alcohols.
4	C_6H_6	400ml x8		
5	5% MeOH in C_6H_6	400ml x6	2.8488g	Corresponds to mixture of diols.

Fr.2 (Table 1, 2.80 g), was distilled to give pure β -himachalene (1.8434 g); b.p. $107^\circ/1.5$ mm and was further identified by TLC and PMR [Lit.²: b.p. $121-122^\circ/4$ mm, PMR].

Fr.5 (Table 1, 2.8488 g), TLC (solvent 15% EtOAc in C_6H_6) indicated the presence of most polar compounds, probably diols which were not investigated further.

Chromatography of mono-alcohols. Fr.3 - Fr.4 (Table 1, 5.184 g), TLC (solvent 15% EtOAc in C_6H_6) indicated the presence of three alcohols, corresponding to R_F of 1.00, 0.84 and 0.80 respectively. This mixture (5.00 g) was

chromatographed on Al_2O_3 (grade III, 500 g; 109 cm x 2.5 cm) with TLC monitoring.

TABLE 2

Fr.No.	Eluent	Vol. collected	Wt.	Remarks
1	Pet. ether	500 ml	0.0578 g	Unreacted β -himachalene
2	10% C_6H_6 in pet. ether	100ml x3	-	-
3	" "	75ml x3	0.1584 g	Mixture β -himachalene + compound of Rrf = 1.00.
4	" "	100ml x14	0.8399 g	Corresponds to pure compound of Rrf = 1.00
5	10% C_6H_6 in pet. ether	100ml x12	0.8609 g	Mixture of compounds with Rrf = 1.00 and 0.84
6	" "	100ml x5	0.3628 g	Compound with Rrf = 0.84
7	" "	100ml x5	0.5301 g	Mixture of compounds with Rrf = 0.84 and 0.80
8	" "	100ml x15	1.1698 g	Major (0.80) + traces of compound (Rrf = 0.84)
9	15% " "	100ml x7		
10	C_6H_6	100ml x2	-	-

Alcohol-I [Rrf, 1.00; 2 α -hydroxy-1 α -himachal-6-ene (VII)]:

Fr. 4 (Table 2, 0.8399 g), was distilled to give pure VII,

b.p. 140° (bath)/0.4 mm which became solid on keeping, $[\alpha]_D +9.5^{\circ}$ (c, 2.02%). IR spectrum (Fig.6). PMR spectrum (Fig.7). Mass spectrum: m/e 222 (M^+ , 71%), 41 (100%), 82 (87%), 135 (79%), 111 (64%), 55 (59%), 43 (55%), 109 (45%), 95 (45%) and 93 (43%). (Found: C, 81.17; H, 11.82. $C_{15}H_{26}O$ requires: C, 81.02; H, 11.79%).

Alcohol-II [RRf, 0.84; 4-hydroxyhimachal-1(6)-ene (VIII)].

Ex.6 (Table 2, 0.3628 g), was distilled to give pure VIII, b.p. $130-135^{\circ}$ (bath)/0.7 mm; $[\alpha]_D -147.6$ (c, 1.97%). IR spectrum (Fig.8). PMR spectrum (Fig.9). Mass spectrum: m/e 222 (M^+ , 86%), 41 (100%), 161 (95%), 189 (78%), 55 (67%), 81 (64%), 153 (59%), 148 (48%) and 105 (44%). [Found: C, 80.91; H, 11.73. $C_{15}H_{26}O$ requires: C, 81.02; H, 11.79%].

Jones oxidation of (VIII): (0.2040 g) of this alcohol was taken up in (25 ml) of dry Et_2O and treated with (1.2 ml) of Jones reagent¹⁰ [stock solution: CrO_3 (133 g), conc. H_2SO_4 (115 ml), H_2O (385 ml)] at $(0-5^{\circ}C)$ and stirred for 2.5 hrs. After usual work up (0.200 g) of the corresponding ketone was obtained which was distilled; b.p. $130-135^{\circ}$ (bath)/0.3 mm; TNN test: +ve. UV absorption: λ_{max}^{EtOH} 214 and 245 nm (ϵ 180.7 and 110.5).

Formate of (VIII): The above alcohol (0.190 g) on treatment with acetic-formic anhydride¹¹ (2 ml) at 30° /12 hr (N_2), furnished (0.211 g) of the required formate, after usual work up. b.p. 115° (bath)/0.5 mm. Mass spectrum: m/e 250 (M^+ , 8%), 204 (100%), 176 (85%), 55 (76%), 105 (75%),

91 (72%), 161 (66%), 43 (53%), 119 (48%) and 79 (48%).

Fr.8 - Fr.9 (Table 2, 1.1698 g), TLC (solvent: 15% EtOAc in C_6H_6) indicated it to be mixture of two compounds with RRF of 0.84 (minor) and 0.80 (major). The major compound was isolated pure by inverted dry column chromatography¹² on SiO_2 -gel (250 g, 25 cm x 4.7 cm; solvent: 15% EtOAc in C_6H_6).

Alcohol-III [RRF, 0.80; 3-hydroxy-1 α -himachal-6-ene (IX)]:

The major compound, isolated from above IDCC was crystallised from MeCN to give silky crystals, m.p. 125-126°, $[\alpha]_D^{25} +14.6^\circ$ (c, 1.24%). IR spectrum (Fig.11). PMR spectrum (Fig.12). Mass spectrum: m/e 222 (M^+ , 48%), 135 (100%), 93 (83%), 41 (65%), 42 (52%), 55 (45%), 79 (43%), 148 (42%), 122 (41%), 95 (38%) and 107 (35%). (Found: C, 80.37; H, 11.7. $C_{15}H_{26}O$ requires: C, 81.02; H, 11.79%).

Himachalol p-nitrobenzoate (XIV, X = $COOC_6H_4NO_2$): In a flame dried flask, flushed with N_2 , were taken dry pet. ether (6 ml), himachalol (0.2336 g, 0.001 mole) and (1.4 ml) of n-BuLi solution¹³ (0.096 g; 0.0015 mole) and the mixture stirred at room temperature (29°) for 1 hr. To this solution was added an ethereal solution of p-nitrobenzoyl chloride, through a septum and the mixture stirred for 2 hr/29°. The solution was separated from the precipitated lithium chloride and the crude product (0.2630g), was recovered from the filtrate and used as such for solvolysis.

Solvolysis of himachalol p-nitrobenzoate: To the freshly prepared crude himachalol p-nitrobenzoate (0.2630 g) in acetone (2 ml), H_2O (8 ml) was added and the reaction mixture was stirred under N_2 at $70-80^\circ$ for 42 hr. The solid separated was filtered off and the aq. phase extracted with pet. ether (25 ml x 3). Pet. ether extract was washed with $NaHCO_3$, H_2O , brine, dried and freed from the solvent to give a product, which was identified as follows.

α - and β -Himachalene. The above product was found to be a hydrocarbon (TLC) which was filtered through a small alumina column (Grade II, 20 g; 20 cm x 1 cm) using pet. ether for elution. (0.0910 g) of hydrocarbon was obtained and distilled. b.p. $110-120^\circ$ (bath)/1 mm, $[\alpha]_D +155.8$ (c, 0.38%). GLC (temp. 130° ; gas flow 60 ml/min] showed it to consist of two components in the percentages of 7.5 : 92.5 and having RRT 1.1 and 1.3 respectively, and these were identified (IR, PMR) as α and β -himachalenes respectively.

SUMMARY

Monohydroboration of β -himachalene has been studied with a view to prepare epi-himachalol. Solvolysis of himachalol p-nitrobenzoate gives α and β - himachalenes.

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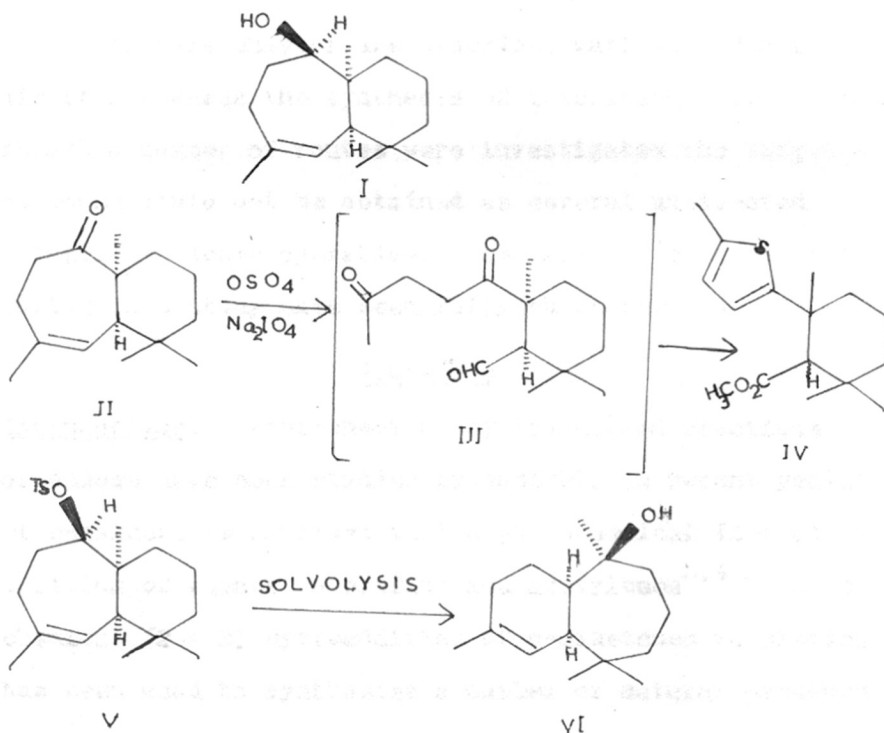
CHAPTER IV

TOWARDS SYNTHESIS OF ALLOHIMACHALOL

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Allohimachalol (I) is a sesquiterpene alcohol which is present to the extent of 4% in the essential oil of Cedrus deodara Loud. Its structure and stereochemistry have been proposed on the basis of its spectroscopic and degradative data and solvolytic reactions¹. Some important chemical evidence for the structure I is briefly given below.

On pyridine-chromic acid oxidation, allohimachalol yields an unsaturated ketone, allohimachalone (II) and its structure was established by its degradation to the



thiophene derivative (IV) via (III). Solvolysis of allohimachalol tosylate (V) gives himachalol (VI), a compound with established² absolute stereochemistry, as one of the products of solvolysis. The absolute stereochemistry of allohimachalol has been deduced from the mechanistic requirements of this transformation. In Wagner-Meerwein rearrangement of this type, the migrating bond and the leaving group have antiparallel geometry and the rearrangement proceeds in a well-defined stereochemical sense, inversion occurring both at the migration terminus and at the migration origin. Based on these considerations, structure I has been considered most likely, for allohimachalol.

In this chapter are described various attempts directed towards the synthesis of allohimachalol. However, though a number of routes were investigated the targetted compound could not be obtained as several unexpected situations became operative. The various compounds obtained during this study have been fully characterised.

Route One

Introduction: Photochemical cycloaddition reactions of enones have been studied extensively in recent years³. Of considerable interest is the photochemical (2 + 2) cycloaddition of enones to olefins and acetylenes^{3,4}. Photochemical (2 + 2) cycloaddition of β -diketones to olefins has been used to synthesise a number of natural products

e.g. caryophyllene⁵, bourbonenes⁶, β -himachalene⁷, artisine⁸ and loganin⁹ etc.

Present Work: A scheme involving the photochemical (2 + 2) cycloaddition of 1,3,3-trimethyl cyclohex-1-ene¹⁰ (VII) and 1,3-cyclopentadione¹¹ (VIII, R = H) was planned as depicted in Fig.1 The reaction of VII and VIII could, in principle, lead to two modes of union, IX and X, aside from the other stereochemical possibilities implied by each of these structures. It was expected that the hydroxy ketone (X) would dealdolize under mild alkaline conditions to furnish 1,5-diketone (XI) which could conceivably be converted into allohimachalol.

1,3,3-Trimethyl cyclohex-1-ene (VII): Since no efficient method was available for the preparation of (VII) and the reported^{10,12} procedures are lengthy and give poor yields of VII, a new route for its synthesis (Fig.2) involving the pyrolysis of 1,3,3-trimethyl cyclohexyl-2-acetate (XV) was planned. Since pyrolysis¹³ of acetates involve a six-membered transition state to give olefin, it is important that the acetate group and the hydrogen on adjacent C₁ in XV should be cis-oriented. The compound (XV) was prepared as follows.

1,3,3-Trimethyl cyclohexanone (XIII) was prepared by the methylation of 2-carboethoxy cyclohexanone¹⁴ (XII) as reported by Weinheimer et al.¹⁵. Reduction of XIII with

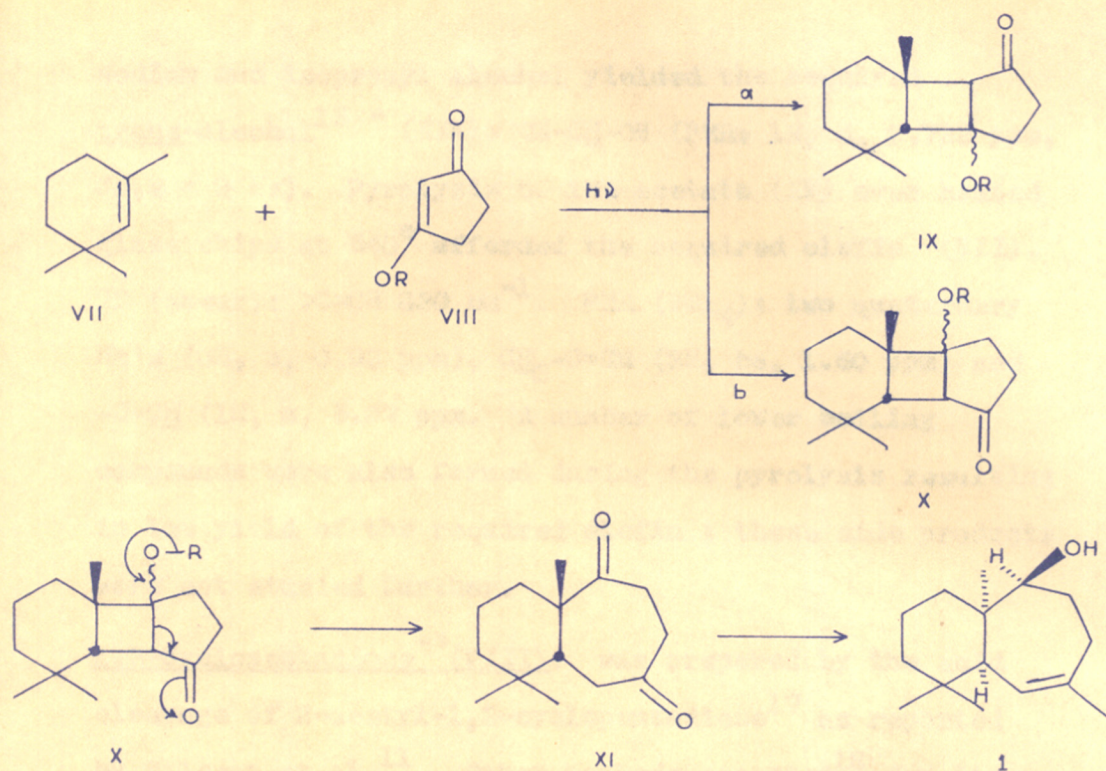
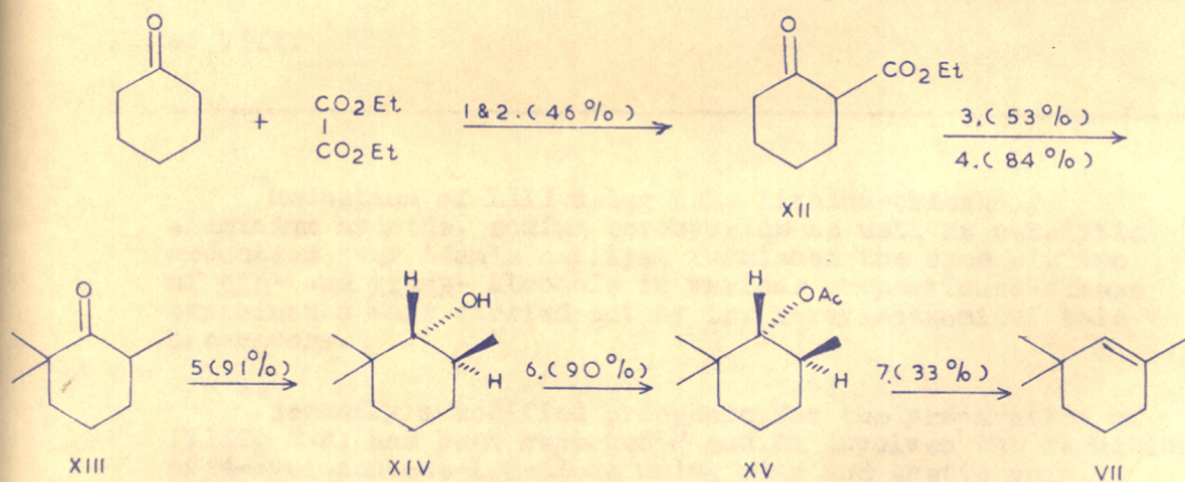


FIG. 1 ROUTE ONE FOR THE SYNTHESIS OF ALLOHIMACHALOL (1)



REAGENTS.

1) NaOEt, EtOH

(2) GLASS, Δ

3) NaH, CH₃I

(4) CONG. HCl, ACOH

5) Na, $\text{CH}_2=\text{CH}-\text{OH}$ (6) Ac₂O, C₅H₅N

7) Δ (540°)

FIG. 2 SYNTHESIS OF 1,3,3-TRIMETHYLCYCLOHEX-1-ENE (VII)

sodium and isopropyl alcohol yielded the required trans-alcohol¹⁶ * (XIV): $\text{CH}-\underline{\text{CH}}-\text{OH}$ (PMR: 1H, d, 2.723 ppm, $J_{a,a} = 9$ Hz). Pyrolysis of its acetate (XV) over heated glass chips at 540° afforded the required olefin (VII). IR (smear): >C=CH 830 cm^{-1} . PMR (CCl_4): two quaternary Me's (6H, s, 0.93 ppm), $\underline{\text{CH}}_3-\text{C=CH}$ (3H, bs, 1.60 ppm) and $-\text{C=CH}$ (1H, m, 5.07 ppm). A number of lower boiling compounds were also formed during the pyrolysis resulting in low yield of the required olefin; these side products were not studied further.

1,3-Cyclopentadione^{**} (VIII): was prepared by the acid cleavage of 2-acetyl-1,3-cyclopentadione¹⁷ as reported by Nilsson et al.¹¹. Other methods reported¹⁸ for its preparation involve large number of steps giving poor yields of VIII.

*Reduction of XIII using LAH, lithium-triethoxy aluminium hydride, sodium borohydride as well as catalytic reduction over Adam's catalyst furnished the same mixture of cis- and trans- alcohols in various proportions. (These experiments were carried out by Dr. Narayanaswami of this Laboratory.

**Recently a modified procedure for the preparation of (VIII, R=H) has been reported¹⁹ and it involves the reduction of 4-cyclopentene-1,3-dione using zinc and acetic acid.

Photo-reaction: Irradiation of 1,3,3-trimethyl cyclohex-1-ene and 1,3-cyclopentadione was carried out in dioxane using a pyrex filter. The dione was found to be insoluble in dioxane but still irradiation was carried out with the hope that as the photochemical cycloaddition will proceed, it will go into solution. Even after 5 hrs of irradiation, (VIII) remained insoluble. The irradiated mixture was worked up and the product distilled under high vacuum through a short path still, in order to screen if any desired product (X, R=H) was formed. No trace of the desired product (X, R=H) could be isolated as revealed by its (IR, TLC).

Assuming that the above irradiation did not yield the desired adduct (X, R=H) because of VIII being insoluble, it was envisaged that this problem can be circumvented by using 1,3-cyclopentadione enol acetate⁷ (VIII, R=Ac) which is readily soluble. However, enol acetate (VIII, R=Ac) was found to be easily hydrolysable and as an alternative 1,3-cyclopentadione enol methyl ether²⁰ (VIII, R=Me), which is also readily soluble under the reaction conditions, was prepared and used for cycloaddition reaction.

Irradiation of (VII) and (VIII, R=Me) was carried out in a mixture of cyclohexane and dioxane, under the same conditions used earlier. The reaction was monitored by TLC and the irradiation was continued for 37 hrs. After usual work up, the crude product was chromatographed over silica gel,

in order to isolate, any photochemical adduct (IX/X, R=Me), if formed. Besides, unreacted olefin (VII) and enol methyl ether (VIII, R=Me), trace quantities of a polar compound was isolated which did not possess the spectral characteristics expected of the photo-adduct (X, R=Me).

The above results suggested that steric hindrance may be playing a role. In all enone photo-annulations³, the reactive species are triplets of cyclic enone having energies in the 70 K.cal/mole region. This triplet energy of the enone is quenched on the olefin to furnish the photochemical adduct. This quenching could not take place presumably because the olefine (VII) may be sterically hindered for this type of reaction. Hence a modified route was planned.

For this 2-acetyl-1,3,3-trimethyl cyclohex-1-ene²¹ (XVI) was chosen as the enone and cyclopentene (XVII) as the olefine. It was presumed that photochemical cyclo-addition of XVI and XVII, will result in the formation of XVIII, as one of the photo adducts. Baeyer-Villiger oxidation of the photo-adduct (XVIII) will furnish XIX which could conceivably be converted into allohimachalol via (XX - XXII) (Fig.3).

2-Acetyl-1,3,3-trimethyl cyclohex-1-ene(XVI): was prepared by the acid-catalysed hydration of 2-ethynyl-1,3,3-trimethyl

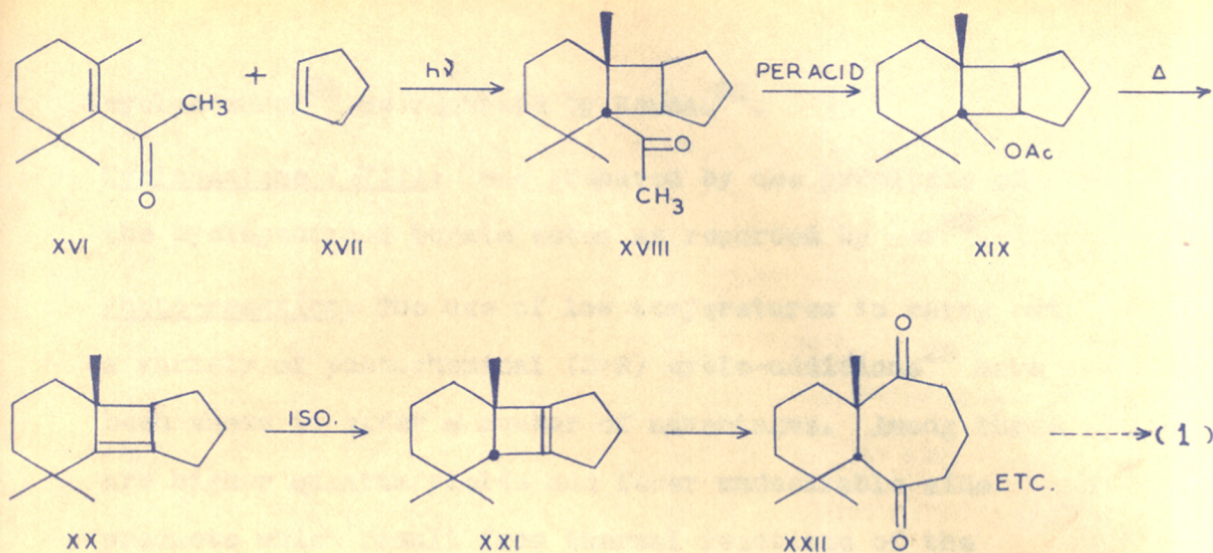


FIG. 3 MODIFIED ROUTE ONE FOR THE SYNTHESIS OF ALLOHIMACHALOL

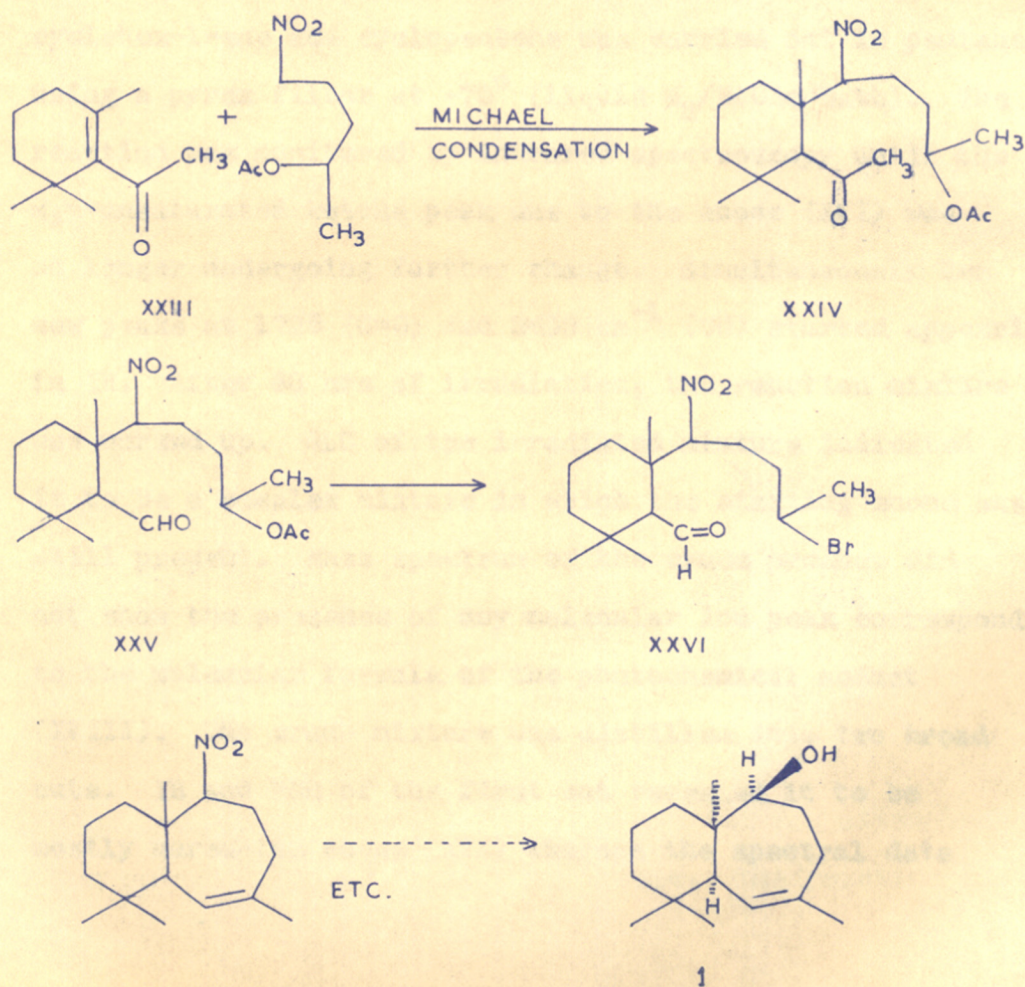


FIG. 4 ROUTE TWO FOR THE SYNTHESIS OF ALLOHIMACHALOL

cyclohexanol⁵¹ as reported by Newman²¹.

Cyclopentene (XII): was prepared by the pyrolysis of the cyclopentanol borate ester as reported by Dev²².

Photo-reaction. The use of low temperatures to carry out a variety of photochemical (2+2) cyclo-additions²³ have been shown to offer a number of advantages. Among these are higher quantum yields and fewer undesirable side products which result from thermal reactions of the photo-adduct.

So the irradiation of 2-acetyl-1,3,3-trimethyl cyclohex-1-ene and cyclopentene was carried out in pentane using a pyrex filter at -70° (liquid N_2 /EtOAc bath). The reaction was monitored by infrared spectroscopy until the α,β -unsaturated ketone peak due to the enone (XVI) was no longer undergoing further change. Simultaneously two new peaks at 1725 ($C=O$) and 3400 cm^{-1} (OH) started appearing in IR. After 60 hrs of irradiation, the reaction mixture was worked up. GLC of the irradiated mixture indicated it to be a complex mixture in which the starting enone was still present. Mass spectrum of the crude product did not show the presence of any molecular ion peak corresponding to the molecular formula of the photochemical adduct (XVIII). The crude mixture was distilled into two broad cuts. IR and PMR of the first cut revealed it to be mostly unreacted enone (XVI) whereas the spectral data

(IR and PMR) of the second cut indicated the presence of compounds possessing a keto and hydroxyl groups respectively.

The second cut was chromatographed over SiO_2 -gel, in order to isolate any of the above compounds and the photo-adduct (XVIII), if formed. Systematic chromatography furnished five TLC pure compounds but their PMR and IR spectra revealed them to be mixtures of compounds possessing a keto as well as hydroxyl groups. Mass spectra of these compounds were devoid of the molecular ion peak required for (XVIII). No further attempt was made to separate and identify them.

Route Two

Concurrent with the above route utilising XVI, a non-photochemical route involving Michael addition of 5-nitropentanol-2-acetate²⁴ (XXIII) to XVI was also investigated (Fig.4). It was envisaged that the Michael adduct (XXIV) could be converted into its corresponding aldehyde (XXV), its internal Wittig reaction²⁵ with the bromide (XXVI) will lead to (XXVII), which could conceivably be elaborated to allohimachalol.

5-Nitropentanol-2-acetate (XXIII): was prepared from 5-nitro-2-pentanone as reported by Zeldin et al.²⁴.

Michael addition. Reaction of XVI and XXIII was attempted using potassium tert-butoxide as a base. The reaction was

followed by TLC. Even after stirring and keeping the reaction mixture at room temperature (31°) for 100 hrs not much change in the reactants was observed. However, the reaction was worked up and the crude mixture distilled. IR and PMR of the distillate revealed it to be mixture of XVI and XXIII only. No trace of the Michael adduct (XXIV) was formed. This reaction might not have proceeded since the enone (XVI) may be a bad Michael acceptor because of steric reasons²⁶.

Route Three

In view of the difficulties encountered in our earlier synthetic routes, we planned a new route for the synthesis of allohimachalol, keeping steric factors, as far as possible under control. As the key reaction, we chose intramolecular acylation of XXVIII to XXIX. This product (XXIX) could conceivably be elaborated into I (Fig.5). Analogous cyclisation has already been achieved successfully by Sobti and Dev²⁷, for the synthesis of isolongifolene. So a route for the construction of a model compound was planned and carried out (Fig.6).

The starting material chosen was the C₁₂-aldehyde (XXX) previously prepared by Büchi *et al.*²⁸. Wittig reaction of the C₁₂-aldehyde with carbethoxy methylene triphenylphosphorane²⁹ furnished the Wittig product (XXXI) in 90% yield. IR (Fig.7): α,β -unsaturated COOEt

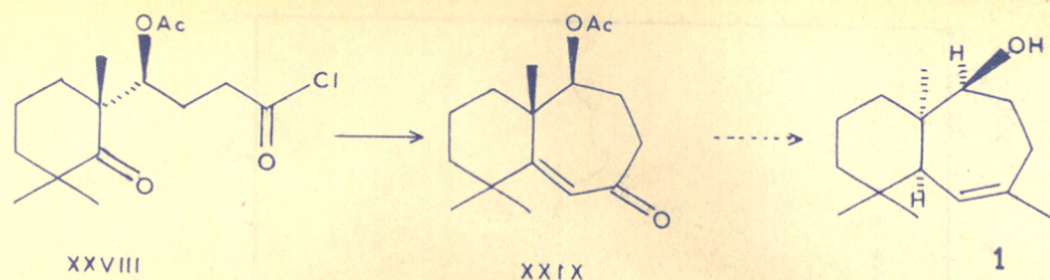
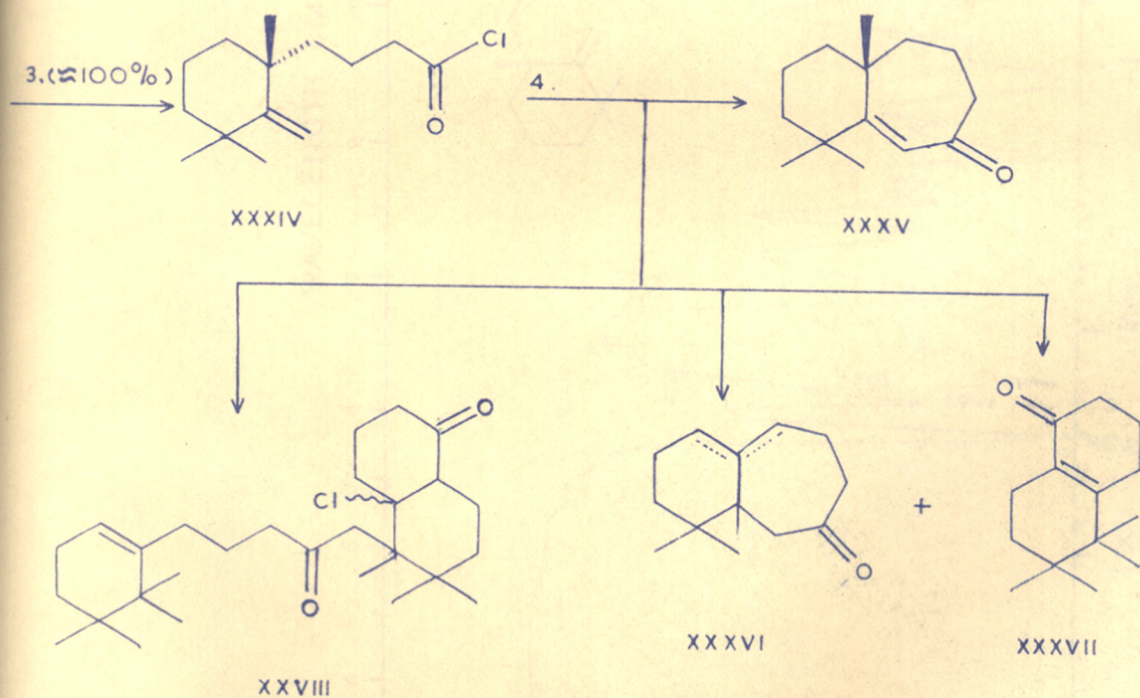
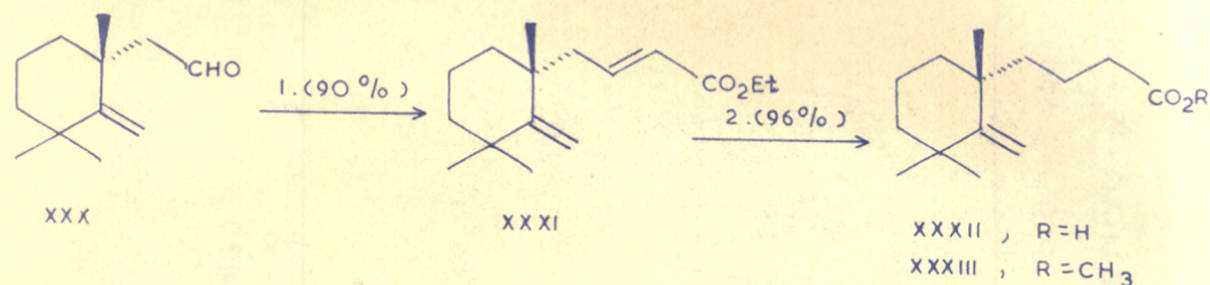


FIG.-5 ROUTE THREE FOR THE SYNTHESIS OF ALLOHIMACHALOL



REAGENTS. 1) $\text{Ph}_3\text{P}=\text{CH} \cdot \text{CO}_2\text{Et}$, C_6H_6 (2) $\text{Ni}-\text{Al}$, NaOH ,
3) $(\text{COCl})_2$, $\text{C}_5\text{H}_5\text{N}$, C_6H_6 (4) $\text{SnCl}_4 \cdot \text{CS}_2$

FIG.-6 ROUTE FOR THE SYNTHESIS OF THE MODEL COMPOUND(XXXIV)

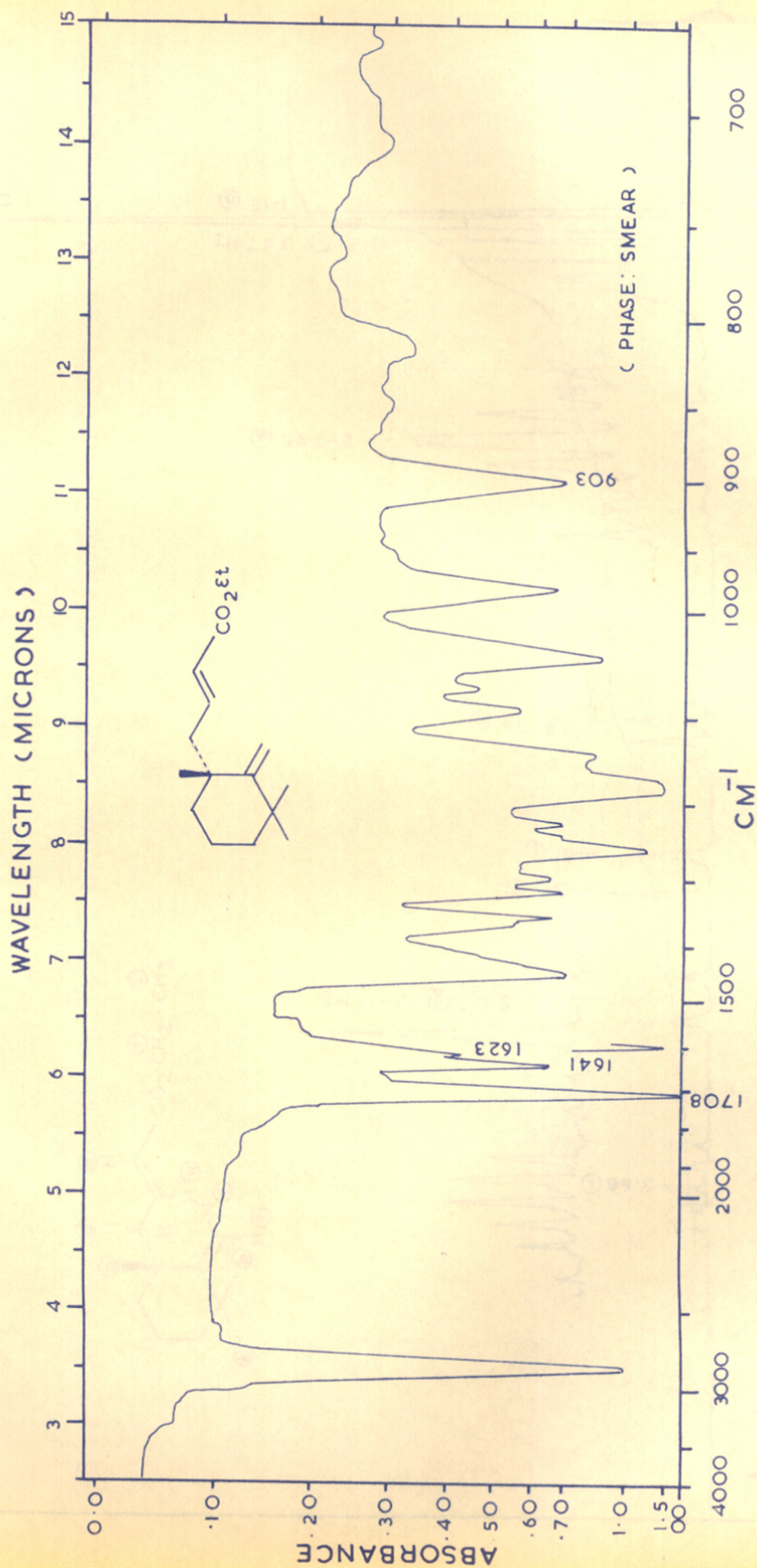


FIG. 7 IR SPECTRUM OF ETHYL 4 [1-c 1,3,3 - TRIMETHYL - 2 - METHYLENE CYCLOHEXYL)] - CROTONATE (XXXI)

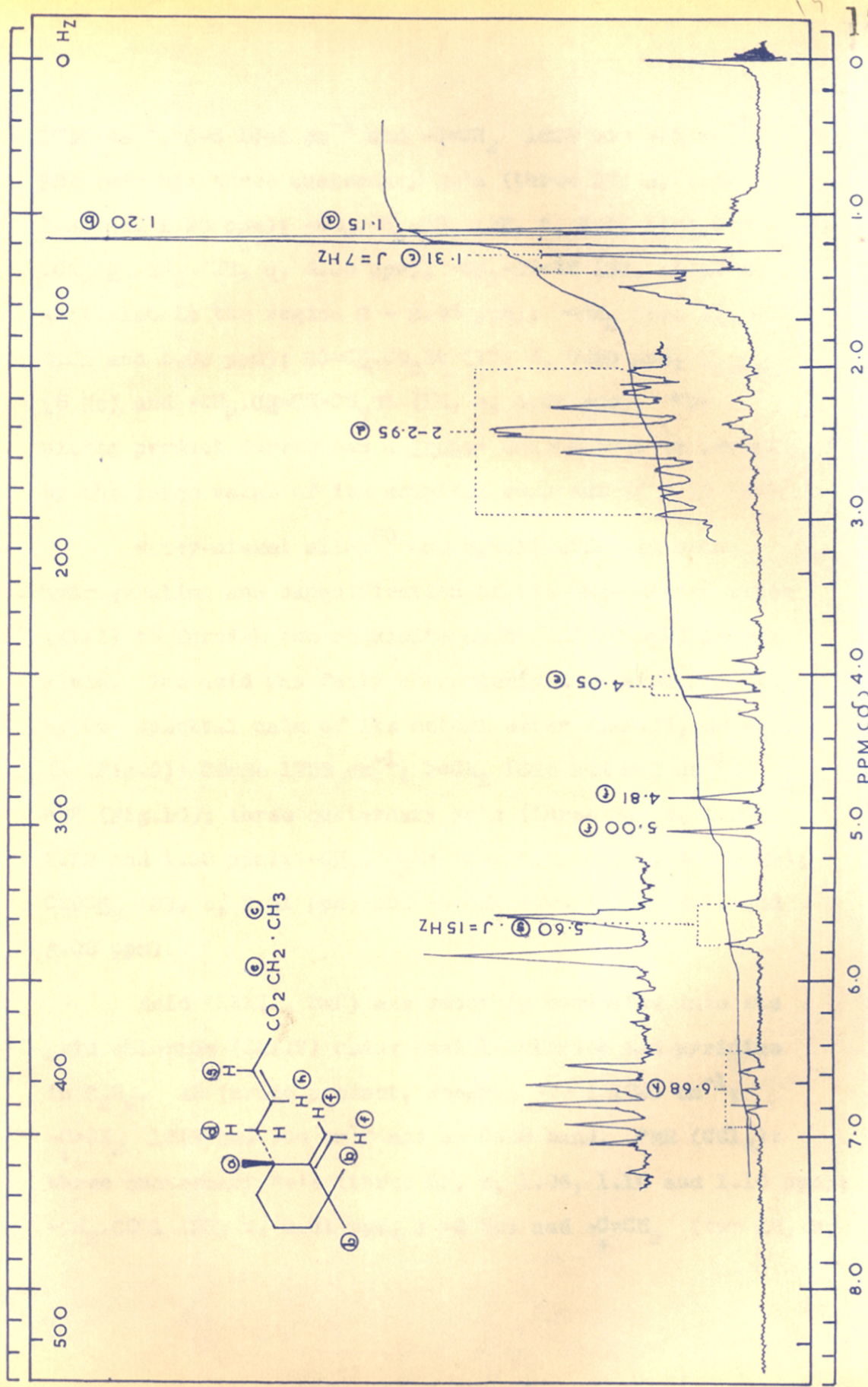


FIG. 8 PMR SPECTRUM OF ETHYL 4 [1-C1,3,3-TRIMETHYL-2-METHYLENE CYCLOHEXYL]-CROTONATE (XXXI)

1708 cm^{-1} ; $\text{C}=\text{C}$ 1641 cm^{-1} and $-\text{C}=\text{CH}_2$ 1623 and 903 cm^{-1} .
 PMR (Fig.8): three quaternary Me's (three 3H, s, 1.15, 1.20 and 1.20 ppm); $-\text{CO}_2\text{CH}_2\text{CH}_3$ (3H, t, 1.31 ppm; $J = 7$ Hz); $-\text{CO}_2\text{CH}_2\text{CH}_3$ (2H, q, 4.05 ppm); $-\text{CH}_2-\text{CH}=\text{CH}$ (2H, complex multiplet in the region 2 - 2.95 ppm); $>=\text{CH}_2$ (two 1H, s, 4.81 and 5.00 ppm); $\text{HC}=\text{CH}\text{CO}_2\text{Et}$ (1H, d, 5.60 ppm, $J_{\text{trans}} 15$ Hz) and $-\text{CH}_2\text{CH}=\text{CH}\text{CO}_2\text{Et}$ (1H, m, 6.68 ppm). The Wittig product formed has a trans- double bond as revealed by the large value of its coupling constant ($J = 15$ Hz).

Raney-nickel alloy³⁰ and alkali effected both hydrogenation and saponification of the unsaturated ester (XXXI) to furnish the requisite acid (XXXII, $\text{R}=\text{H}$) in 96% yield. The acid was fully characterised as such and also by the spectral data of its methyl ester (XXXIII, $\text{R}=\text{CH}_3$).
 IR (Fig.9): COOMe 1733 cm^{-1} ; $>=\text{CH}_2$ 1624 and 903 cm^{-1} .
 PMR (Fig.10): three quaternary Me's (three 3H, s, 1.06, 1.33 and 1.33 ppm); $-\text{CH}_2\text{CO}_2\text{Me}$ (3H, t, 2.2 ppm; $J = 6$ Hz); COOCH_2 (3H, s, 3.61 ppm) and $-\text{C}=\text{CH}_2$ (two 1H, s, 4.81 and 5.03 ppm).

Acid (XXXII, $\text{R}=\text{H}$) was smoothly converted into its acid chloride (XXXIV) using oxalyl chloride and pyridine in C_6H_6 . IR (crude product, smear): $-\text{COCl}$ 1780 cm^{-1} ; $-\text{C}=\text{CH}_2$ 1619 and 904 cm^{-1} and no COOH band. PMR (CCl_4): three quaternary Me's (three 3H, s, 1.06, 1.10 and 1.10 ppm); $-\text{CH}_2\text{COCl}$ (2H, t, 2.81 ppm, $J = 6$ Hz) and $-\text{C}=\text{CH}_2$ (two 1H, s,

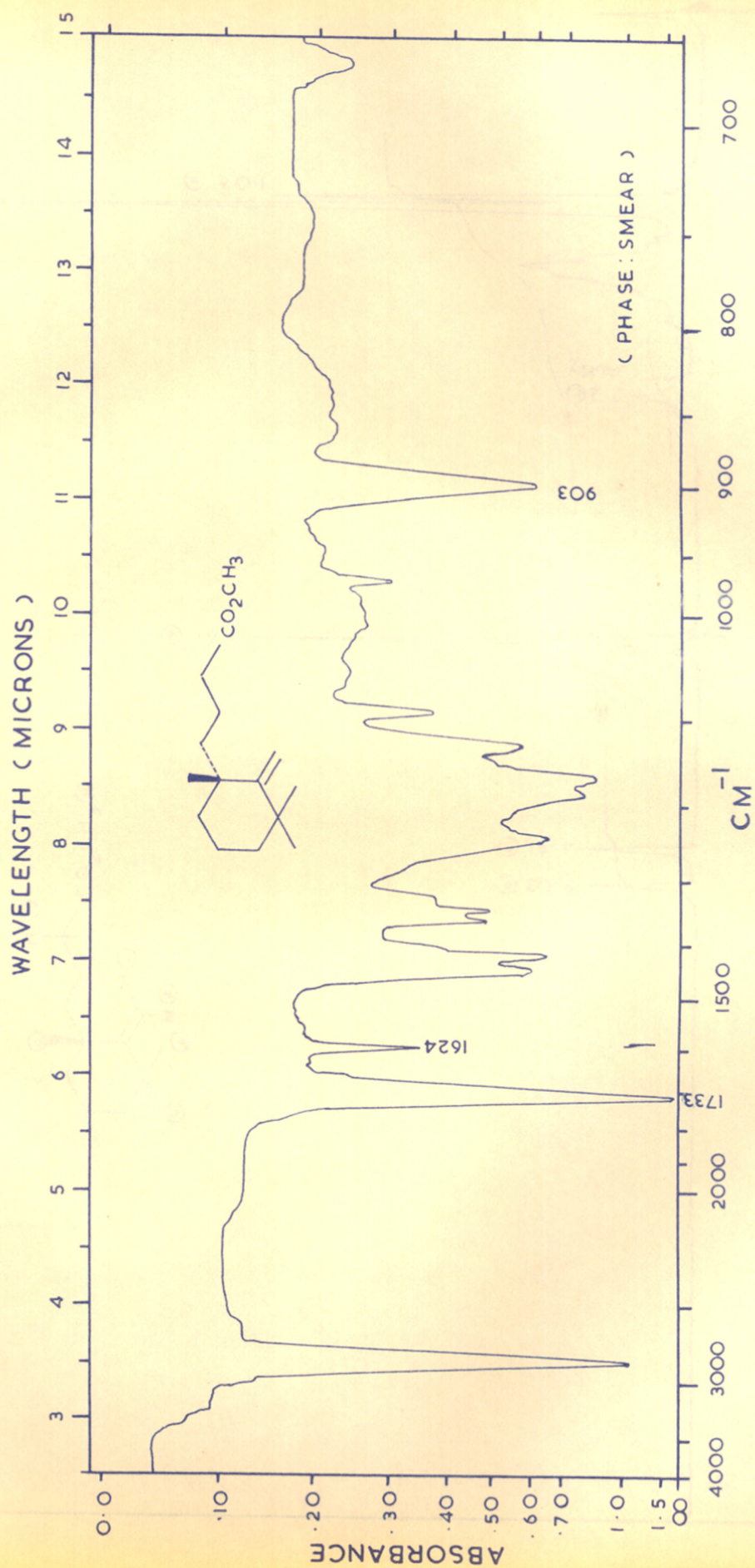


FIG.9 IR SPECTRUM OF 4 [1-(1,3,3-TRIMETHYL-2-METHYLENE -
CYCLOHEXYL)]-BUTANOATE (XXXIII, R=CH₃)

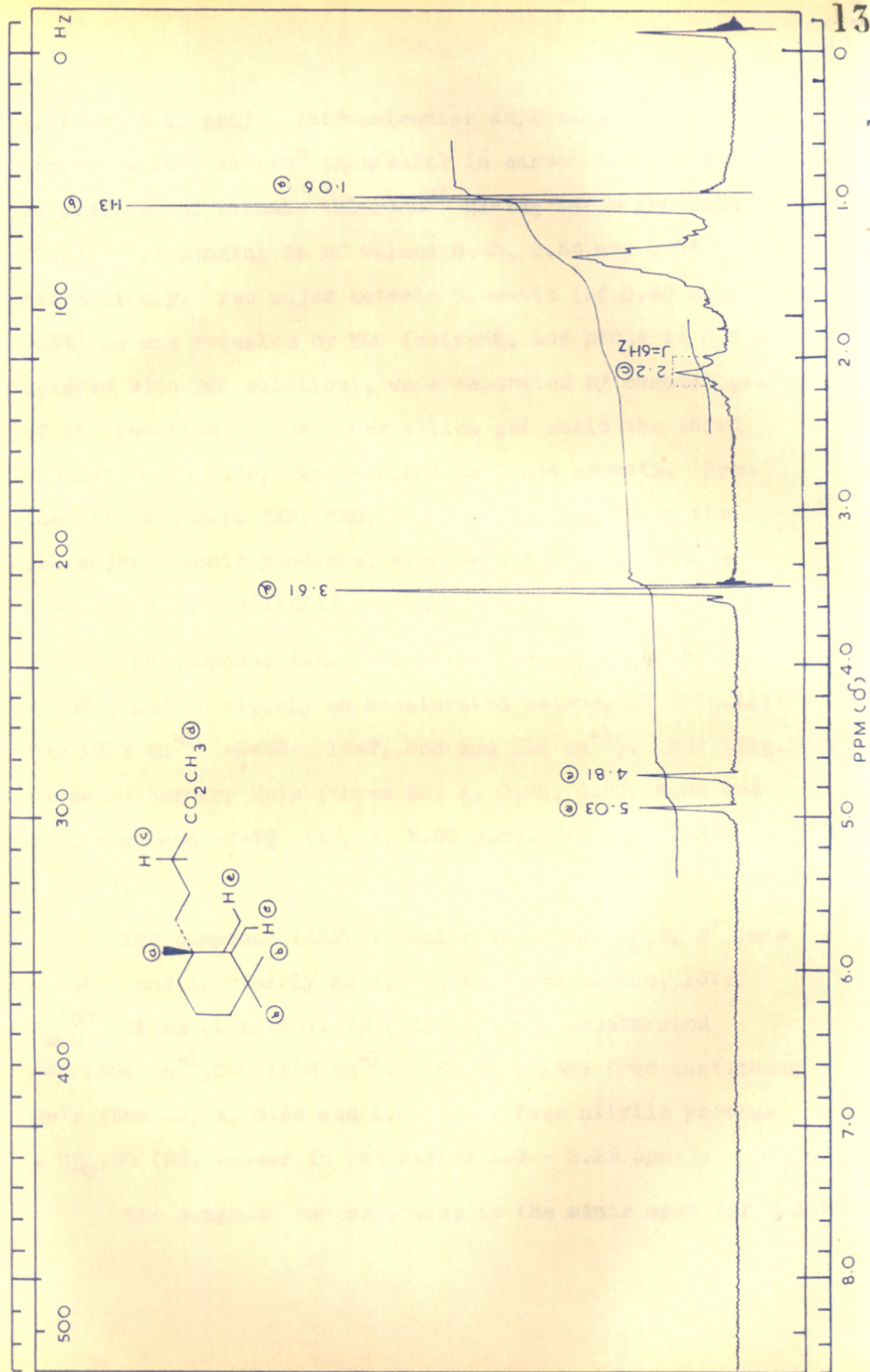


FIG.10 PMR SPECTRUM OF 4 [1-(1,3,3-TRIMETHYL-2-METHYLENE - CYCLOHEXYL)]-
BUTANOATE (XXXIII, R=CH₃)

4.81 and 5.03 ppm). Intramolecular acylation of XXXIV proceeded well at -10° (ice/salt) in carbon disulphide in presence of stannic chloride³¹ giving three products (TLC) corresponding to Rf values 0.45, 0.54 and 0.75 respectively. Two major ketonic products (Rf 0.45 and 0.54) as was revealed by TLC (solvent: 10% EtOAc in C_6H_6), sprayed with DNP solution), were separated by chromatography of the reaction mixture over silica gel while the third product (Rf = 0.75) was isolated in trace amounts. From the spectral data (IR, PMR, Mass) it is clear that the two major ketonic products, corresponding to Rf values 0.45 and 0.54 are XXXVII and XXXVI.

The compound (XXXVI) analyses for $C_{14}H_{22}O$, M^+ (m/e = 206), and is clearly an unsaturated ketone, IR (Fig.11): $C=O$ 1712 cm^{-1} ; $-C=CH-$ $1647, 838$ and 818 cm^{-1} . PMR (Fig.12): three quaternary Me's (three 3H, s, 0.92, 0.92, 0.92 and 0.98 ppm) and $-C=CH-$ (1H, m, 5.38 ppm). UV: λ_{max}^{EtOH} 211 nm (ϵ 1260).

The compound (XXXVII) analyses for $C_{14}H_{22}O$, M^+ (m/e = 206), and is clearly an α,β -unsaturated ketone, [UV: λ_{max}^{EtOH} 248 nm (ϵ 11460). IR (Fig.13): α,β -unsaturated $C=O$ 1658 cm^{-1} , $C=C$ 1618 cm^{-1} . PMR (Fig.14): four quaternary Me's (two 6H, s, 0.86 and 1.01 ppm); four allylic protons + $CH_2.CO$ (6H, appear in the region 1.9 - 2.35 ppm)].

The compound corresponding to the minor spot (Rf = 0.75),

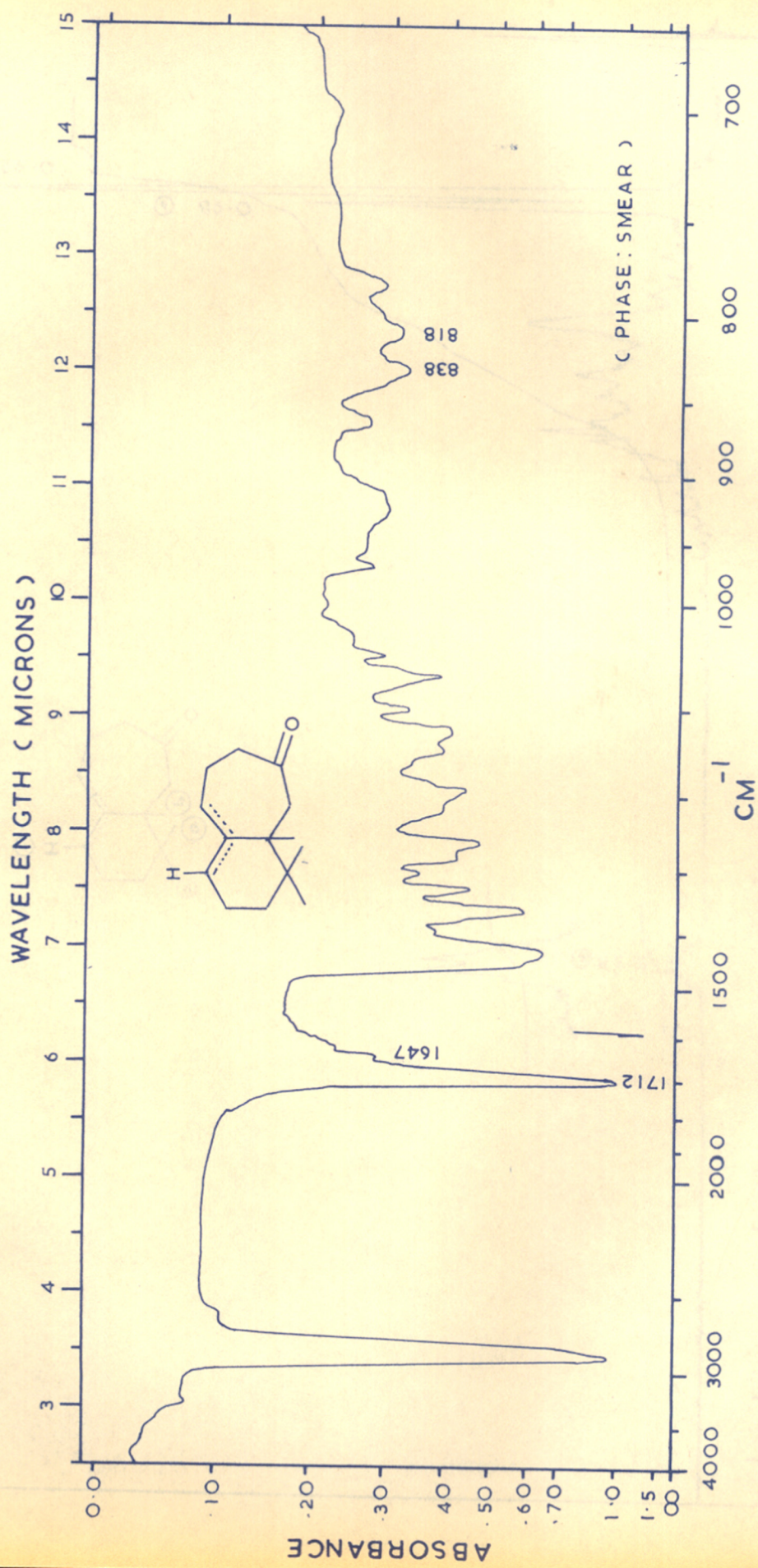


FIG.11 IR SPECTRUM OF 1,2,2 -TRIMETHYL BICYCLO (5,4,0) -UNDEC -5OR (6) -ENE -10 - ONE (XXXVI)

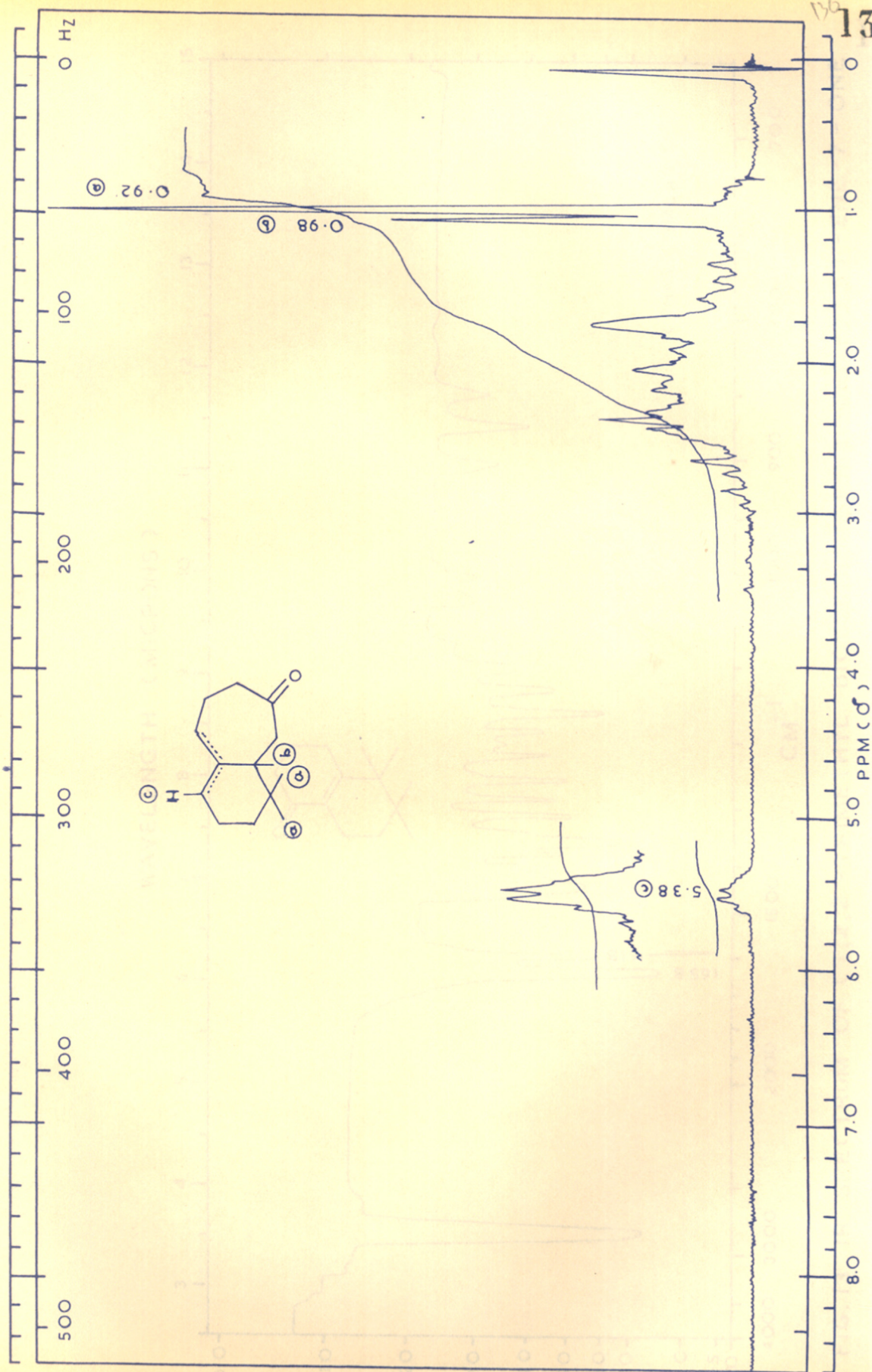


FIG.12 PMR SPECTRUM OF 1,2,2-TRIMETHYL BICYCLO (5,4,0) -UNDEC -5OR (6) -ENE -
IO -ONE (XXXVI)

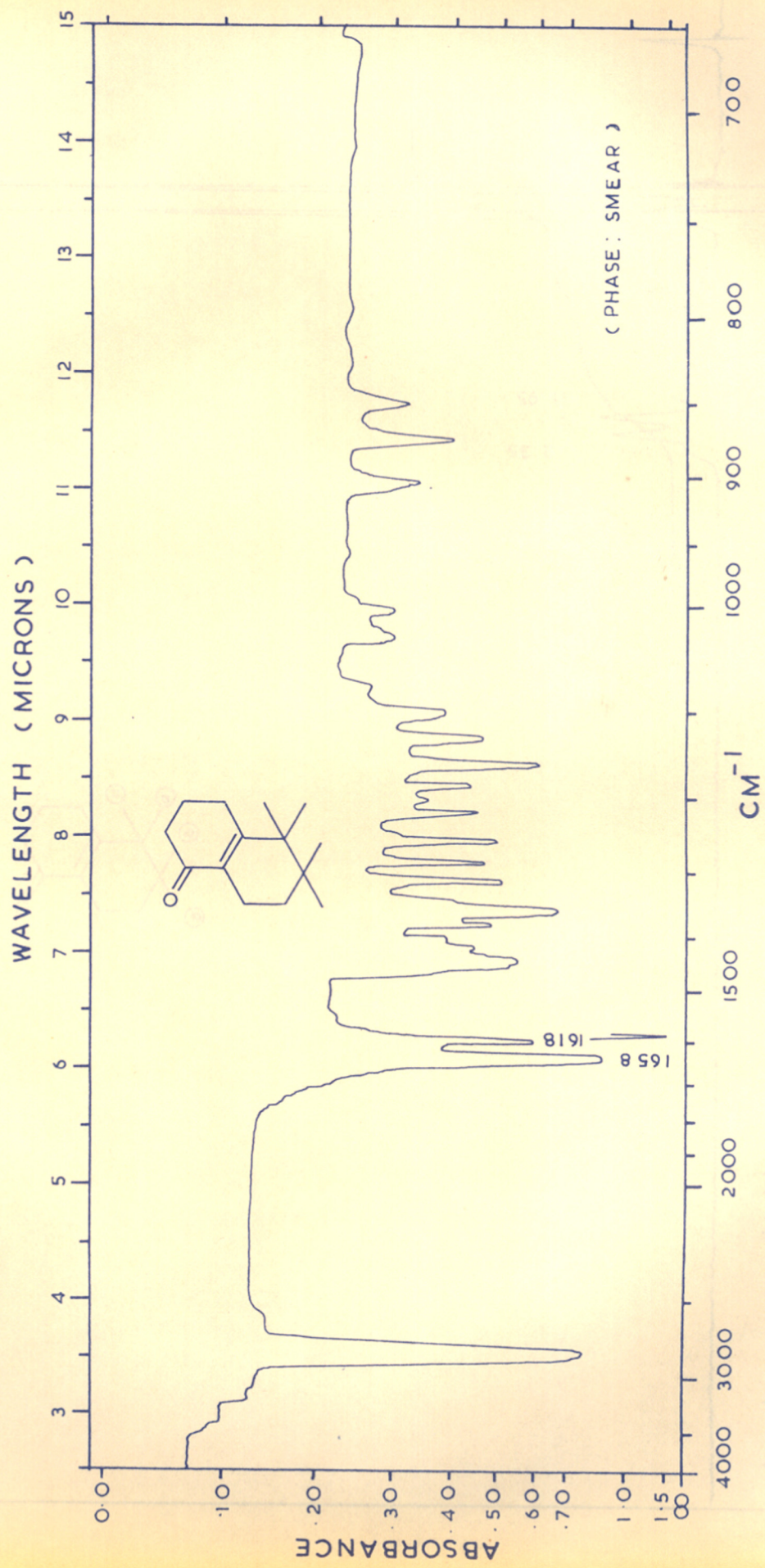


FIG. 13 IR SPECTRUM OF (1,2,2 - TRIMETHYL BICYCLO (4,4,0) - DEC - 1 (6) - ENE - 7 - ONE
(XXVII)

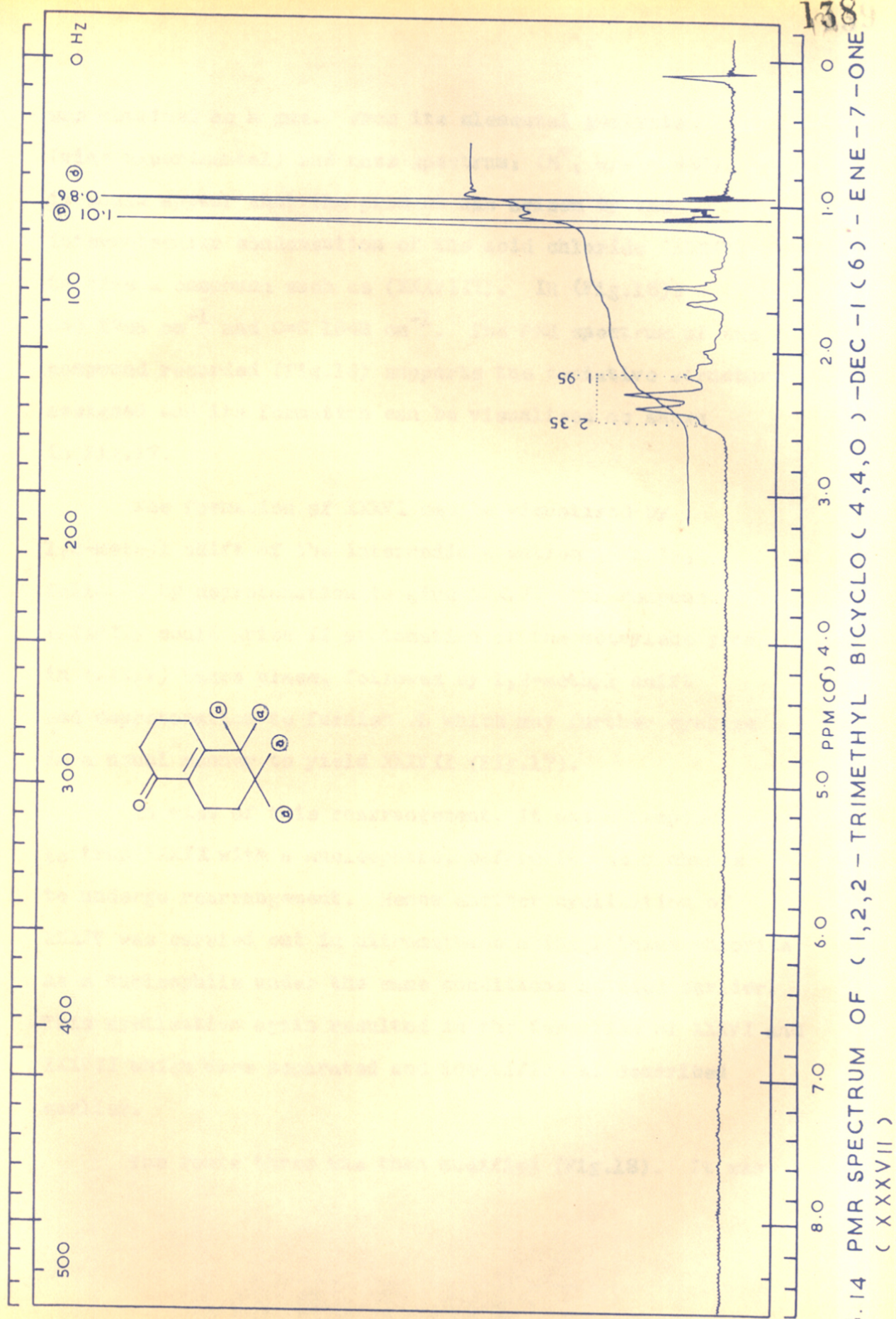


FIG. 14 PMR SPECTRUM OF (1,2,2 - TRIMETHYL BICYCLO (4,4,0) - DEC - 1 (6) - ENE - 7 - ONE)
(XXXVII)

was obtained as a gum. From its elemental analysis (vide Experimental) and mass spectrum: (M^+ , $m/e = 448$), it would appear that the product has arisen by the intermolecular condensation of the acid chloride (XXXIV) to give a compound such as (XXXVIII). IR (Fig.15): $C=O$ 1728 cm^{-1} and $C=C$ 1642 cm^{-1} . The PMR spectrum of the compound recorded (Fig.16) supports the tentative structure assigned and its formation can be visualised as shown in Fig.17.

The formation of XXXVI can be visualised by 1,2-methyl shift of the intermediate cation (XXXIX), followed by deprotonation to give XXXVI. The compound (XXXVII) could arise if protonation of the methylene group in (XXXIV) takes place, followed by 1,2-methyl shift and deprotonation to furnish XL which may further cyclise in a usual manner to yield XXXVII (Fig.17).

In view of this rearrangement, it was attempted to trap XXXIX with a nucleophile, before it has a chance to undergo rearrangement. Hence another cyclisation of XXXIV was carried out in nitromethane using lithium chloride as a nucleophile under the same conditions as used earlier. This cyclisation again resulted in the formation of XXXVI and XXXVII which were separated and identified as described earlier.

The route three was then modified (Fig.18). It was

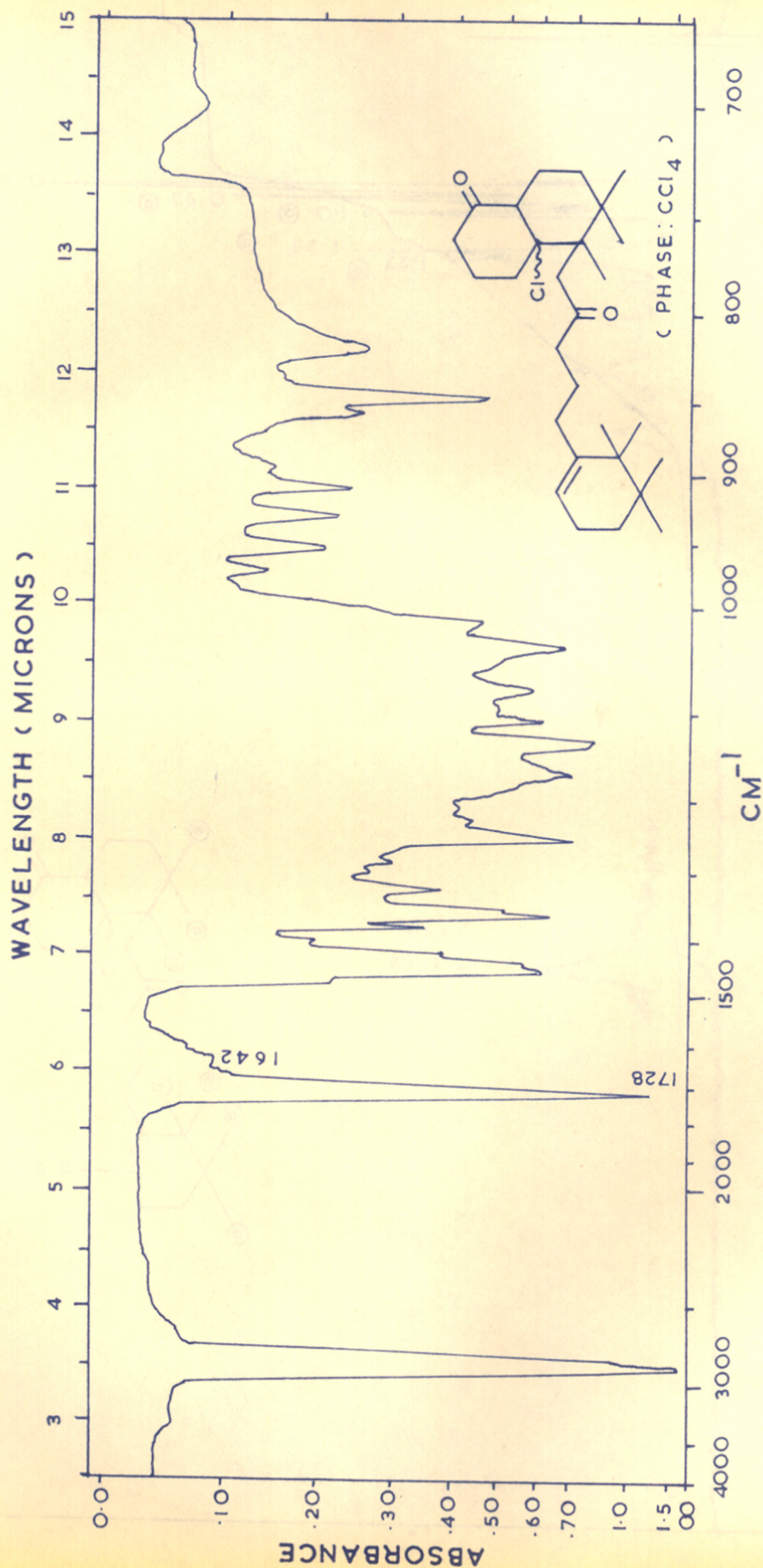


FIG. 15 IR SPECTRUM OF MINOR COMPOUND (XXXV)

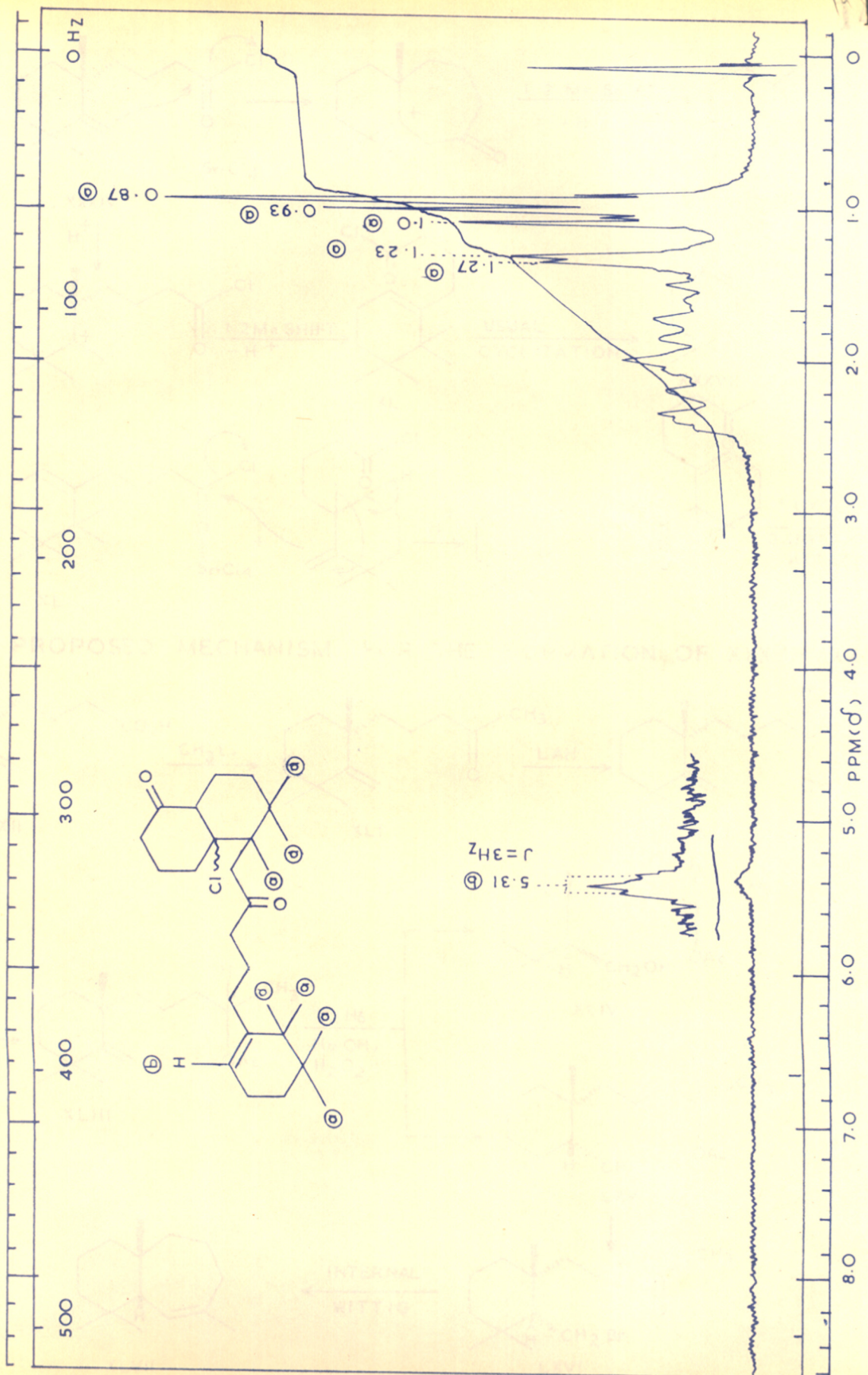


FIG.16 PMR SPECTRUM OF MINOR COMPOUND (XXXVIII)

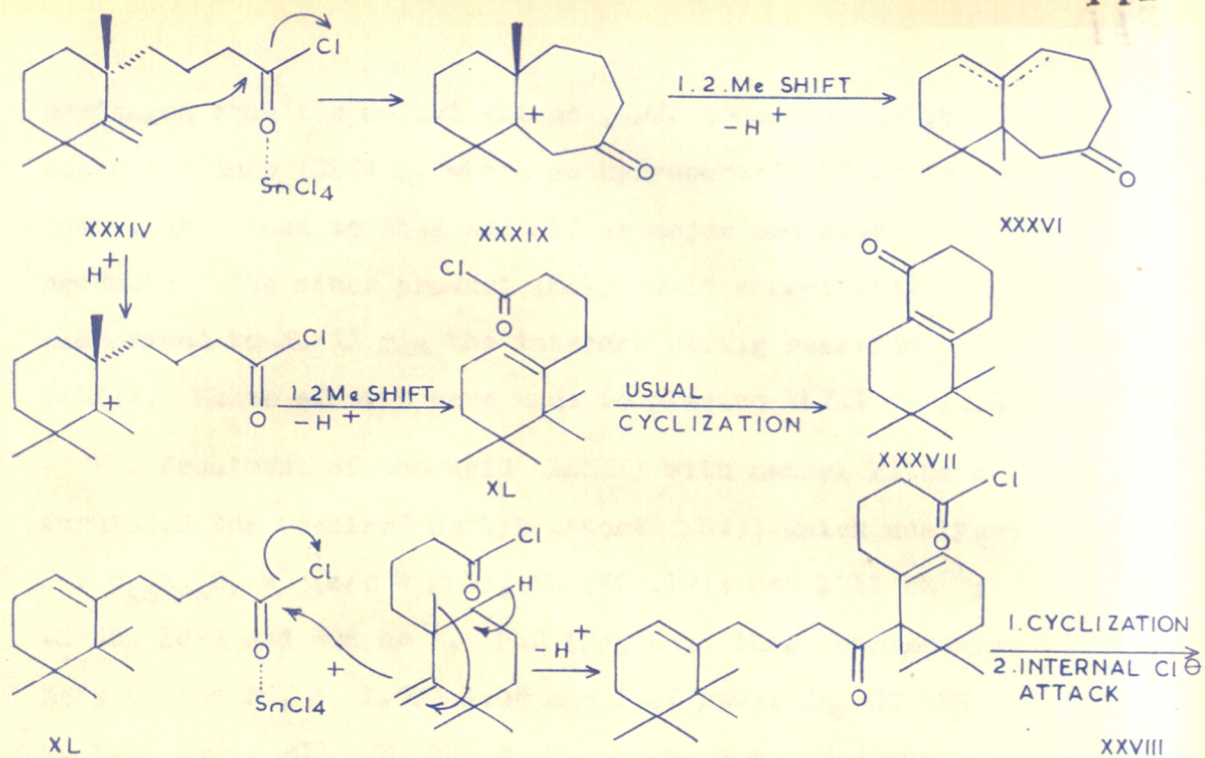


FIG. 17 PROPOSED MECHANISM FOR THE FORMATION OF XXXVI-XXXVIII

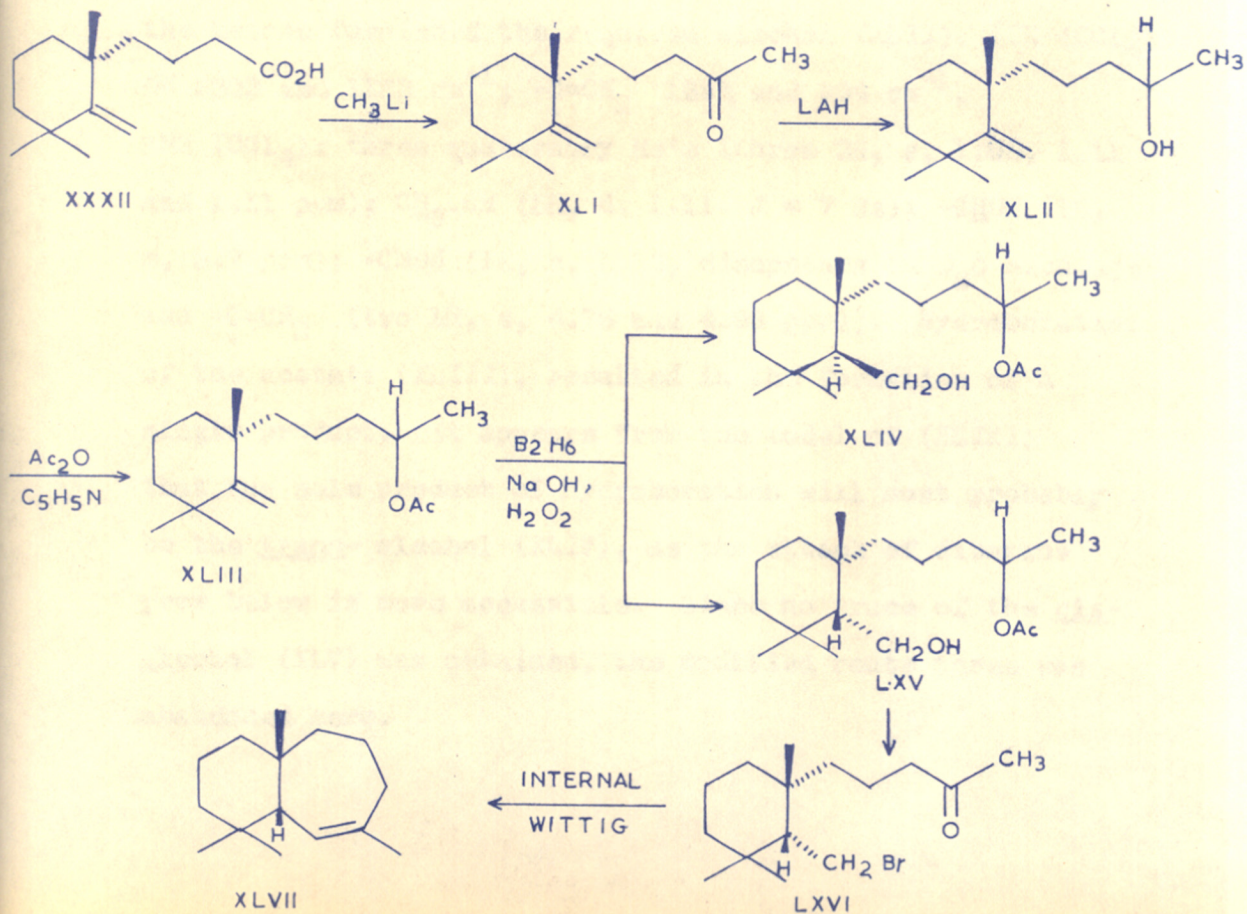


FIG. 18 MODIFIED ROUTE THREE FOR SYNTHESIS OF XLVII

envisaged that the methyl ketone (XLI) could be easily converted into (XLI³²), which on hydroboration³² could conceivably lead to XLIV and XLV as major and minor products. The minor product (XLV) could conceivably be elaborated to XLVII via the internal Wittig reaction²⁵ of (XLVI). Hence efforts were made to prepare XLI³² (Fig.18).

Treatment of the acid (XXXII) with methyl lithium furnished the required methyl ketone (XLI), which analyses for $C_{15}H_{26}O$, M^+ ($m/e = 222$), IR (Fig.19): $C=O$ 1711 cm^{-1} ; $-C=CH_2$ 1621 and 908 cm^{-1} . PMR (Fig.20): three quaternary Me's (three 3H, s, 1.02, 1.05 and 1.05 ppm); CH_3CO (3H, s, 1.98 ppm); $-CH_2-CO$ (2H, t, 2.25 ppm, $J = 6\text{ Hz}$) and $-C=CH_2$ (two 1H, s, 4.73 and 4.95 ppm). LAH reduction of the ketone furnished the required alcohol (XLII). [IR (CCl_4): OH 3303 and 1123 cm^{-1} ; $-C=CH_2$ 1621 and 904 cm^{-1} . PMR (CCl_4): three quaternary Me's (three 3H, s, 1.05, 1.11 and 1.11 ppm); CH_3CH (3H, d, 1.11, $J = 7\text{ Hz}$); $-CHOH$ (1H, m, 3.7 ppm); $-CHOH$ (1H, s, 1.33, disappears on D_2O exchange) and $-C=CH_2$ (two 1H, s, 4.76 and 4.98 ppm)]. Hydroboration of the acetate (XLI³²), resulted in the formation of a single product. It appears from the model of (XLI³²) that the sole product of hydroboration will most probably be the trans- alcohol (XLIV), as the attack of diborane from below is more accessible. Since no trace of the cis-alcohol (XLV) was obtained, the modified route three was abandoned here.

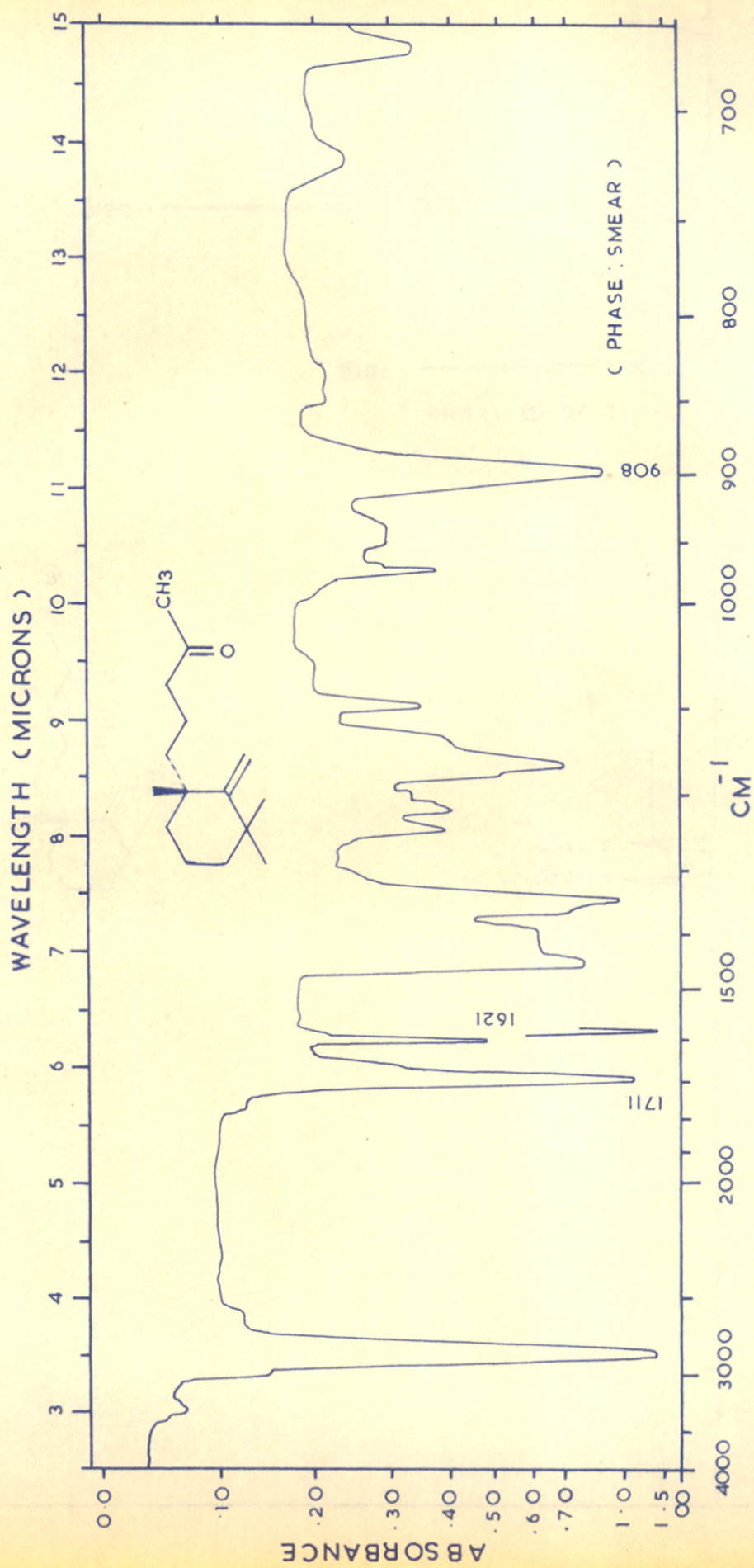


FIG.19 IR SPECTRUM OF 5[1-(1,3,3-TRIMETHYL-2-METHYLENE CYCLOHEXYL)-2-PENTANONE (XLI)]

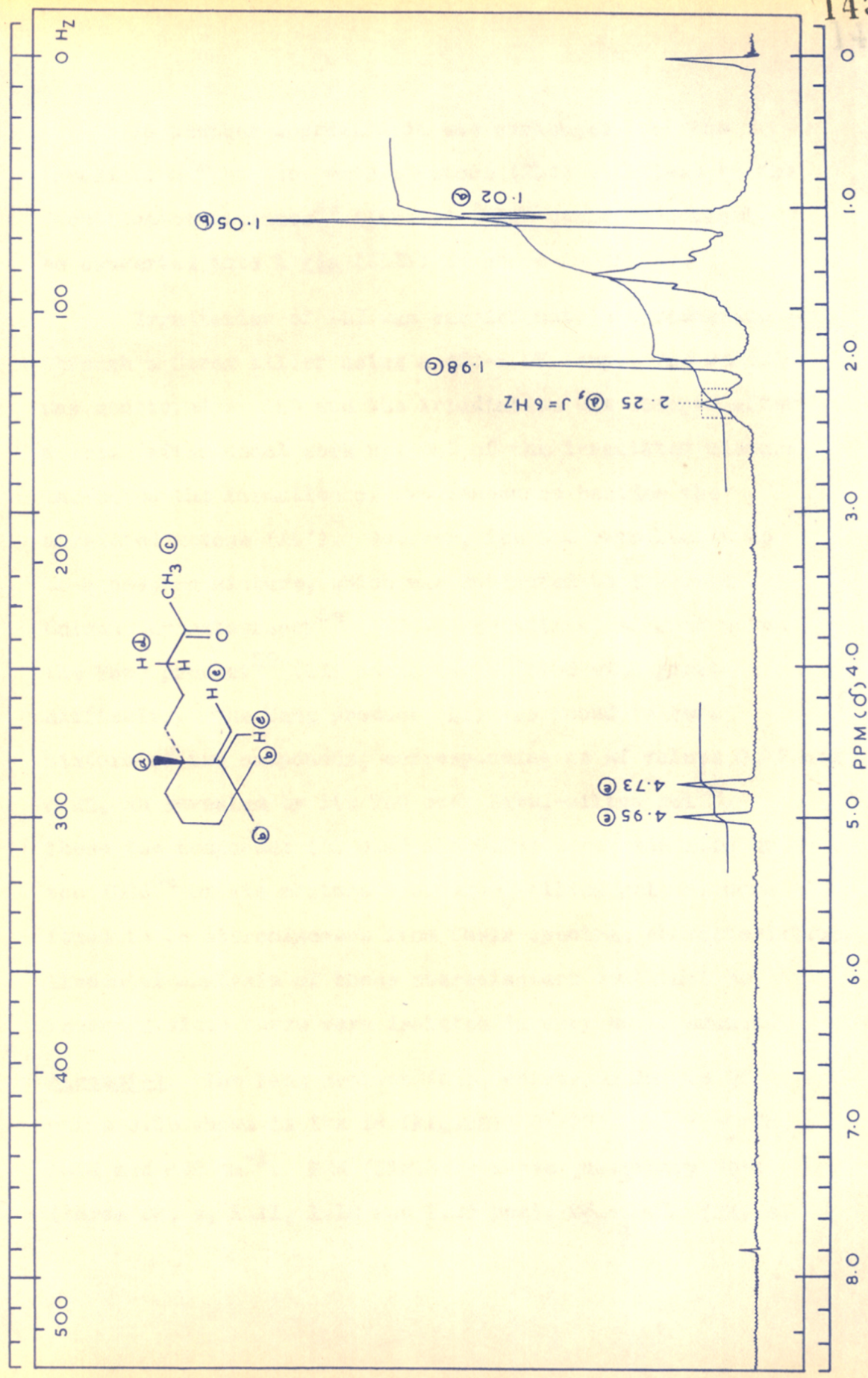


FIG.20 PMR SPECTRUM OF 5 [1 - (1,3,3-TRIMETHYL - 2 - METHYLENE CYCLOHEXYL) - 2 - METHYLENE CYCLOHEXYL] - 2 - PENTANONE (XLI)

In another approach, it was envisaged that the irradiation³³ of the methyl ketone (XLI) will lead to the formation of oxetanes³⁴ (XLVIII) which could conceivably be converted into L via (XLIX) as shown in Fig.21.

Irradiation of XLI was carried out in cyclohexane through a Correx filter using a 450-W UV lamp. The reaction was monitored by TLC and the irradiation was stopped after 8 hrs. After usual work up, TLC of the irradiated mixture indicated the formation of two compounds besides the unreacted ketone (XLI). However, its GLC revealed it to be a complex mixture, which was subjected to Inverted Dry Column Chromatography⁵⁴ (IDCC) over silica gel from which the Yang product³³ (LI) could be isolated with great difficulty. The Yang product (LI) was found to be a mixture of two compounds, corresponding to Rf values 0.25 and 0.22, as revealed by its TLC over AgNO₃-silica gel⁵⁵. These two compounds (Rf 0.25 and 0.22) were separated by the IDCC⁵⁴ of its mixture over AgNO₃-silica gel and were found to be stereoisomers from their spectral characteristics. Elemental analysis of these stereoisomers could not be recorded since these were isolated in very small amounts.

Alcohol-I. The Yang product (LI), corresponding to Rf value 0.25 shows in its IR (Fig.22): OH 3300 cm⁻¹; -C=CH₂ 1618 and 898 cm⁻¹. PMR (Fig.23): three quaternary Me's (three 3H, s, 1.11, 1.12 and 1.20 ppm); $\text{CH}_3-\overset{\text{C}}{\underset{\text{C}}{\text{C}}}-\text{OH}$ (3H, s,

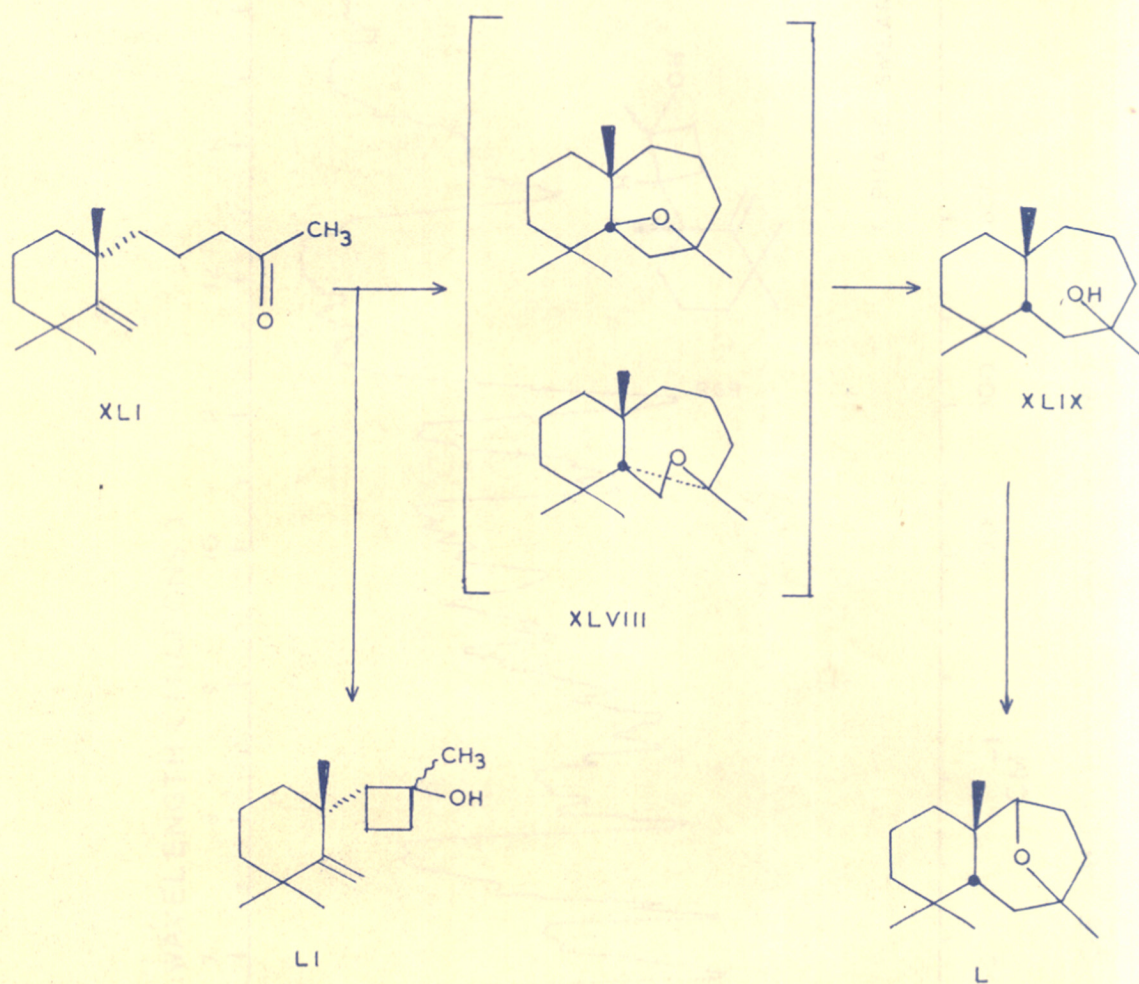


FIG. 21 MODIFIED ROUTE THREE FOR THE SYNTHESIS OF (L)

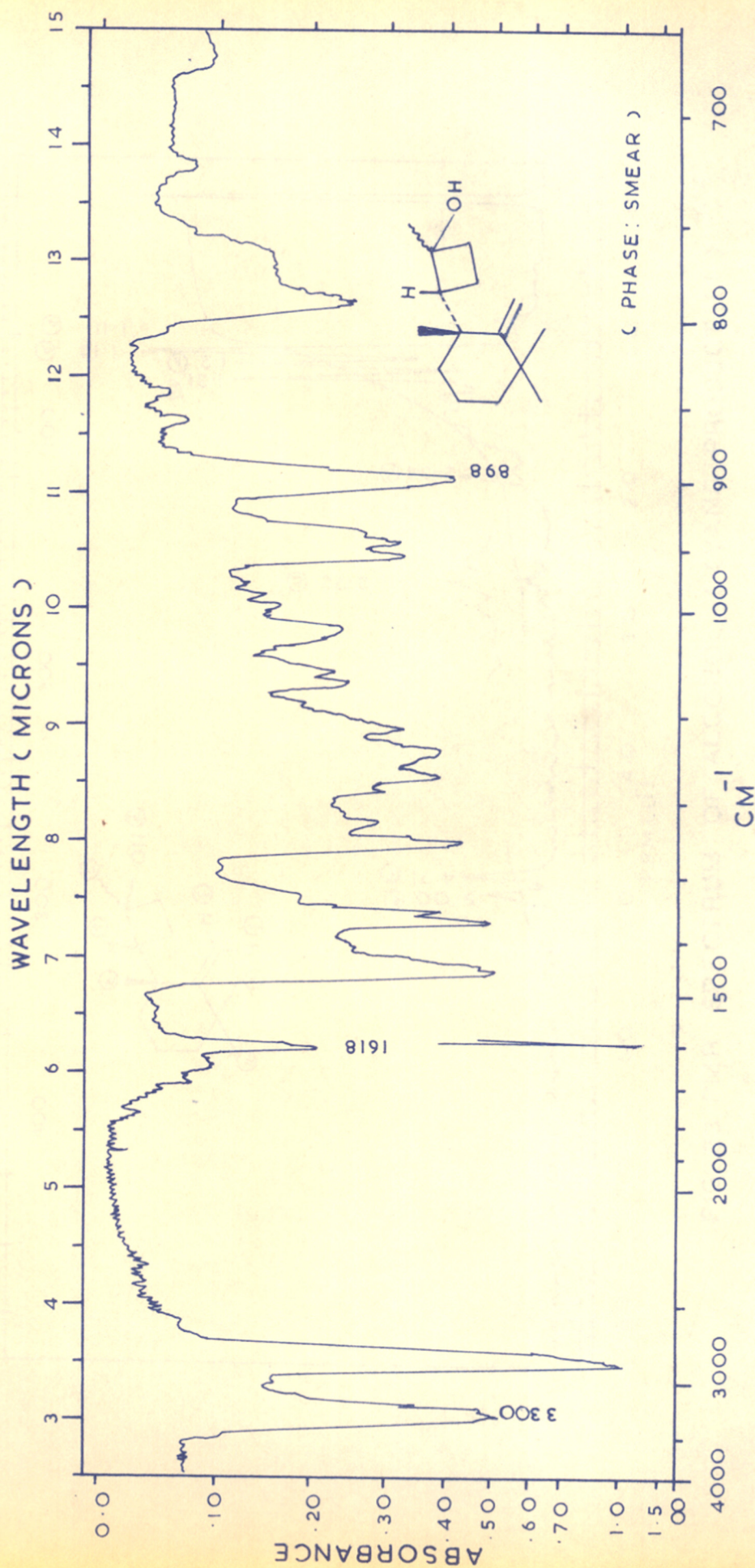


FIG. 22 IR SPECTRUM OF ALCOHOL-1 (YANG PRODUCT, LI)

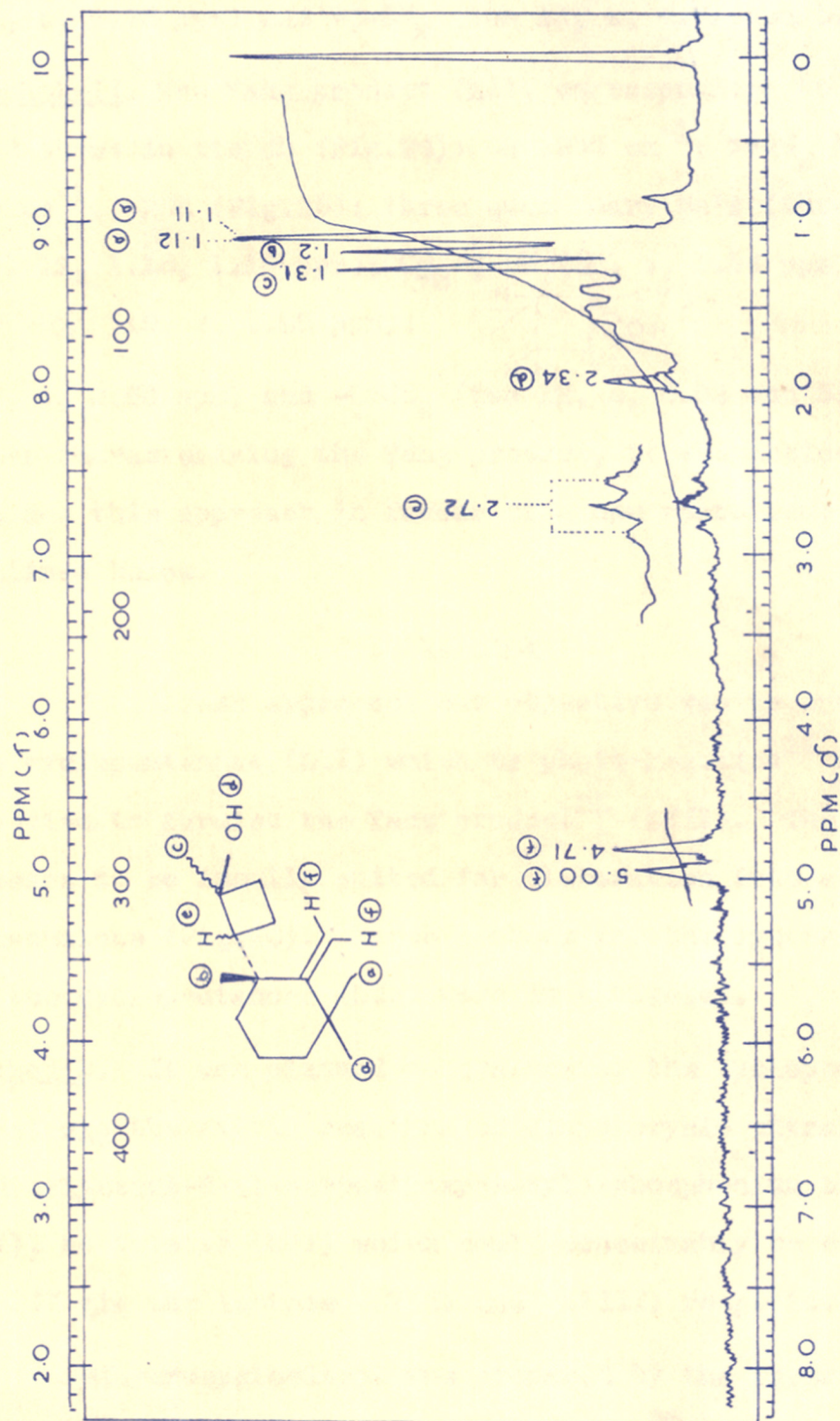
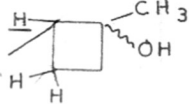
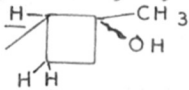


FIG. 23 PMR SPECTRUM OF ALCOHOL -1 (YANG PRODUCT, LI)

1.31 ppm); $\text{CH}_3\text{-}\overset{\text{C}}{\underset{\text{C}}{\text{C}}}\text{-OH}$ (1H, s, 2.34 ppm);  (1H, t, 2.75 ppm) and -C=CH_2 (two 1H, s, 4.71 and 5.0 ppm).

Alcohol-II. The Yang product (LI), corresponding to Rf value 0.22 shows in its IR (Fig.24): OH 3300 cm^{-1} ; >CH_2 1618 and 900 cm^{-1} . PMR (Fig.25): three quaternary Me's (three 3H, s, 1.12, 1.15, 1.17 ppm); $\text{CH}_3\text{-}\overset{\text{C}}{\underset{\text{C}}{\text{C}}}\text{-OH}$ (3H, s, 1.34 ppm); $\text{Me-}\overset{\text{C}}{\underset{\text{C}}{\text{C}}}\text{-OH}$ (1H, s, 1.88 ppm);  (1H, t, 2.68 ppm) and -C=CH_2 (two 1H, s, 5.03 and 5.11 ppm).

After characterising the Yang product, it was decided to abandon this approach in favour of a new route four as outlined below.

Route Four

In a fresh approach, our objective was to synthesise the cyclopentanone (LII) which by photo-reaction³³ was expected to furnish the Yang product³³ (LIII). The latter appears to be ideally suited for elaboration into allo-himachalone (Fig.26). Three methods for the synthesis of the cyclopentanone (LII) were investigated.

Method 1. It was planned to synthesise the cyclopentanone (LII) via the Wittig reaction of dihydrocyclo citral³⁵ (LIV) and triphenyl-4-(1-carboethoxypentyl)-phosphonium bromide (LV), to furnish (LVI) which could conceivably be converted to LII via the lactone (LVII) and (LVIII) respectively (Fig.27)..

Dihydrocyclocitral was prepared by the reported catalytic hydrogenation of β -cyclocitral³⁶ over Pd and BaCO_3 .

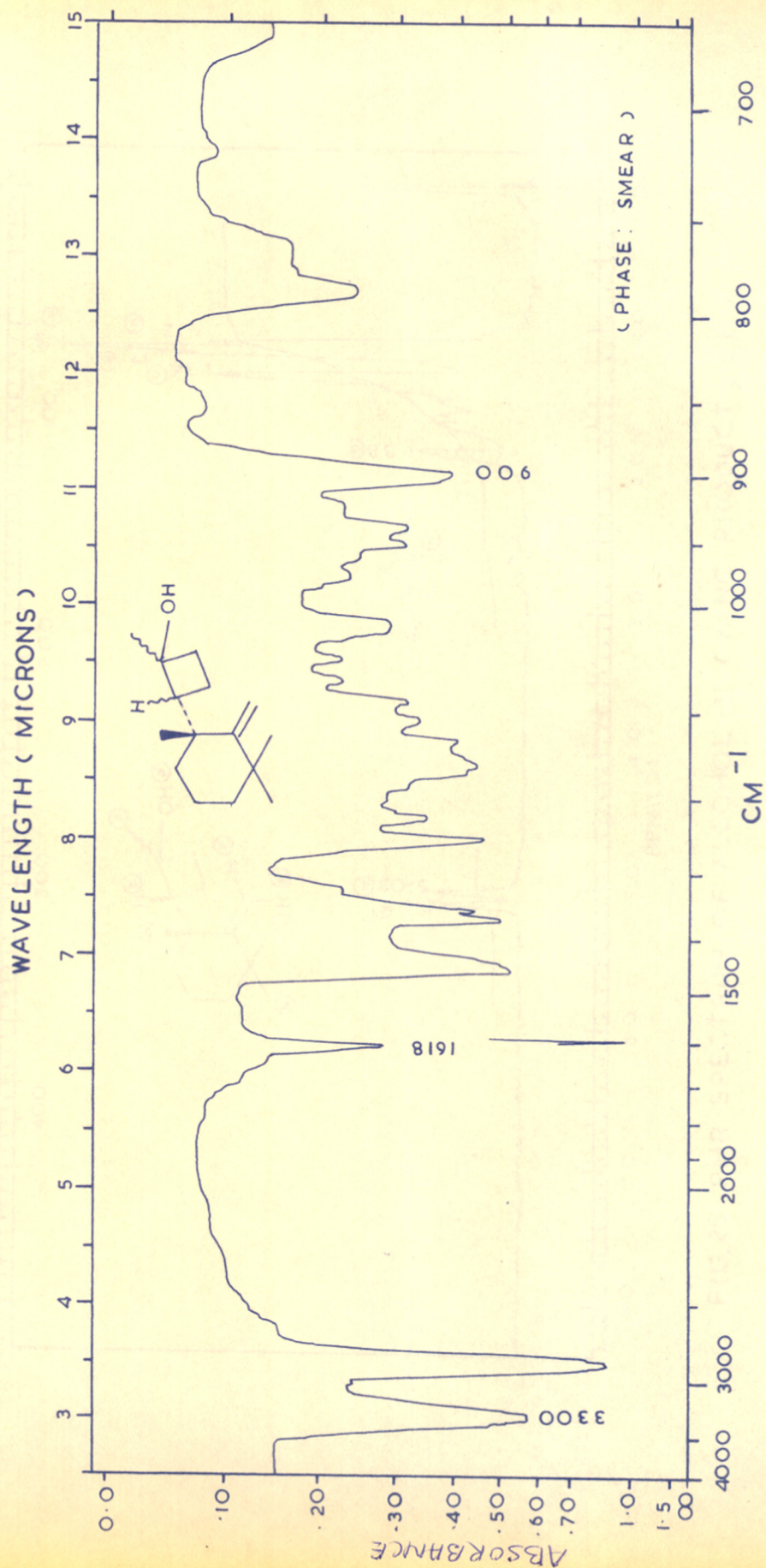
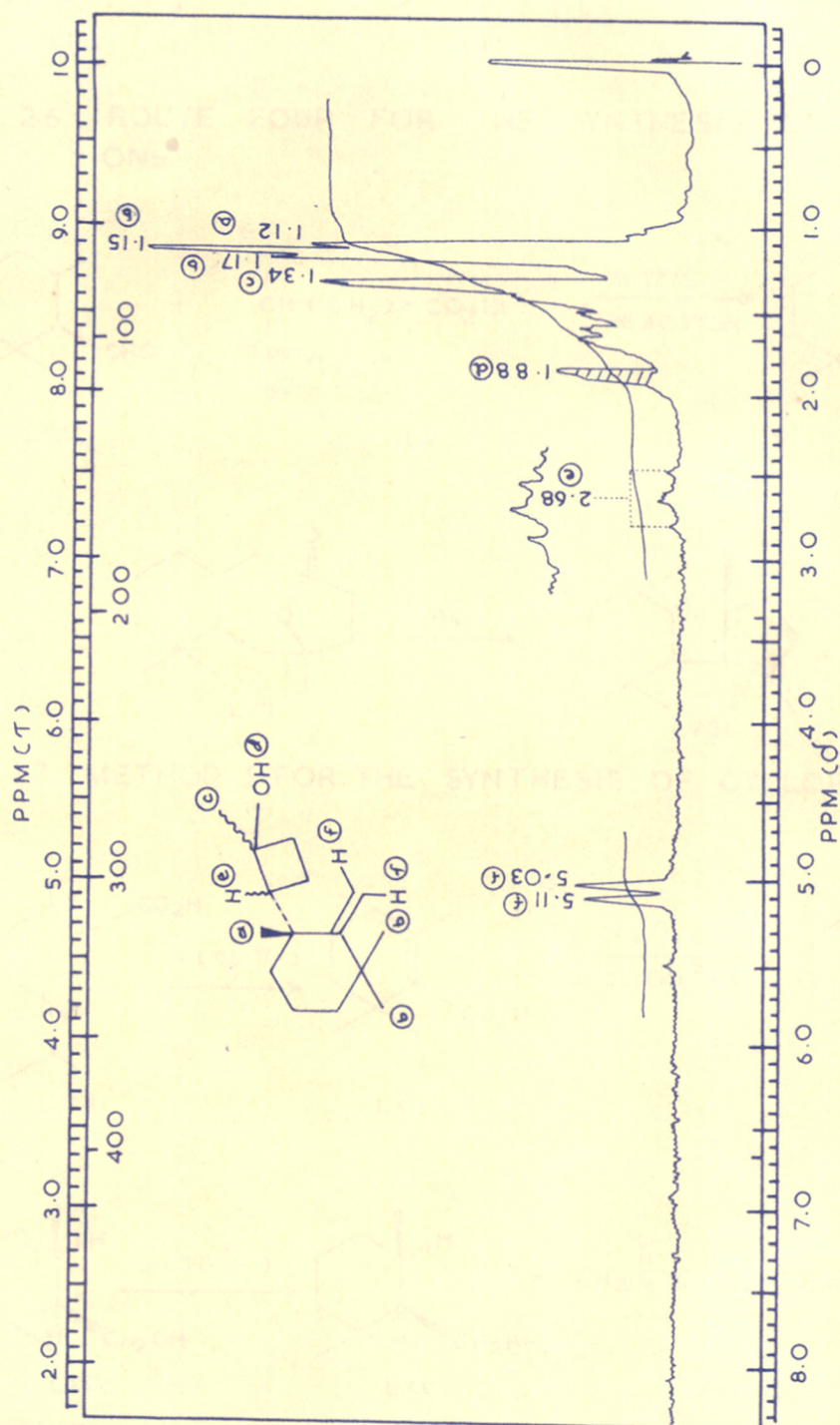


FIG.24 IR SPECTRUM OF ALCOHOL-II (YANG PRODUCT; LI)

FIG.25 PMR SPECTRUM OF ALCOHOL-II (YANG PRODUCT₃ LI)

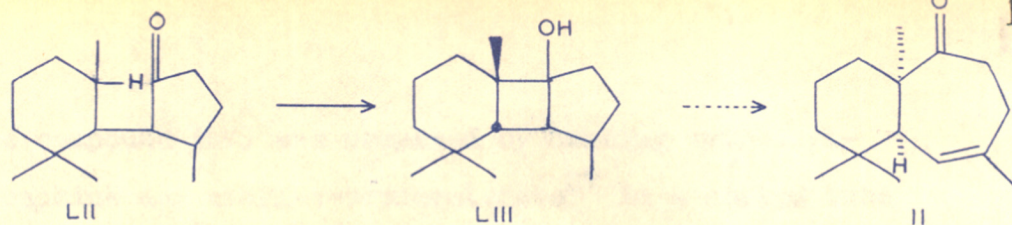


FIG. 26 ROUTE FOUR FOR THE SYNTHESIS OF ALLOHIMACHAL-ONE

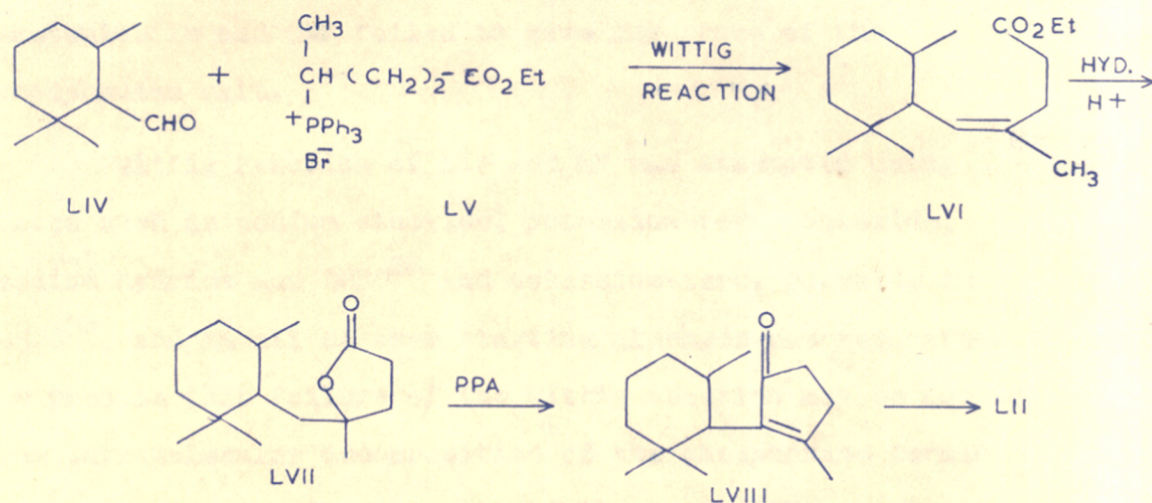
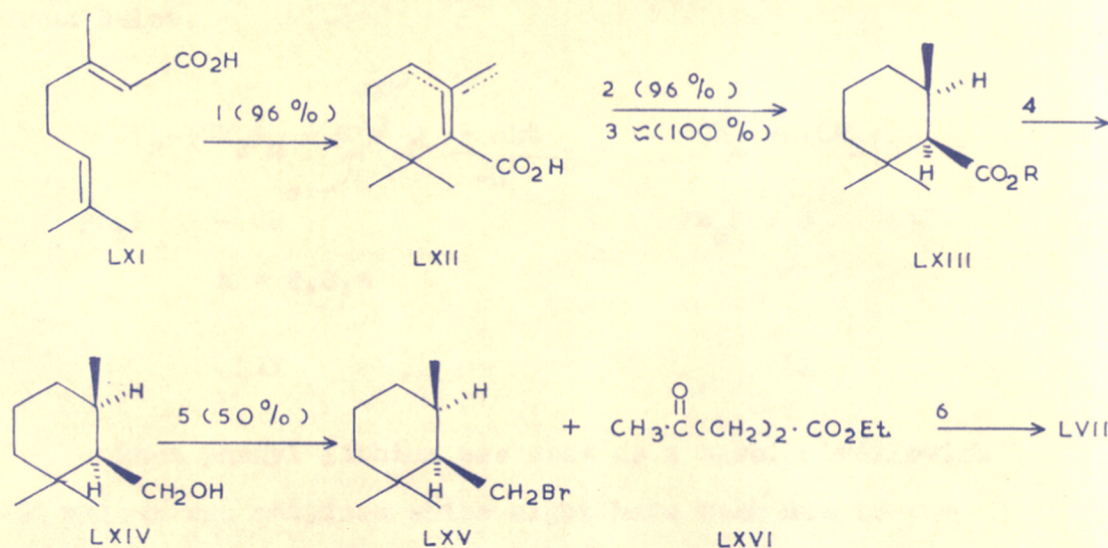


FIG. 27 METHOD 1 FOR THE SYNTHESIS OF CYCLOPENTANONE (LII)

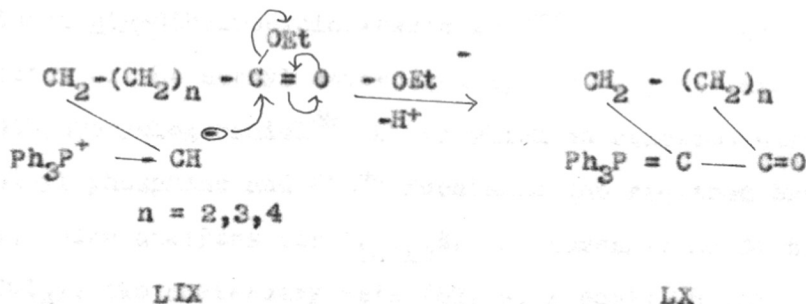


REAGENTS. 1) $\text{CH}_3\text{OSO}_2\text{H}$, CH_3NO_2 ; (2) 5% Rh/C , H_2 ;
 3) CH_2N_2 (4) LiAlH_4
 5) Ph_3P , NBS , C_6H_6 (6) Mg

FIG. 28 METHOD II FOR THE SYNTHESIS OF CYCLOPENTANONE (LII)

The compound (LV) was prepared by heating triphenylphosphine and ethyl- γ -bromovalerate³⁷ in a sealed tube at 120° for 15-20 hrs. The phosphonium salt (LV) correctly analysed with its formula. The attempted preparation of LV in various solvents such as benzene, xylene, nitromethane, acetonitrile and DMF failed to give any trace of the phosphonium salt.

Wittig reaction of LIV and LV was attempted using bases such as sodium ethoxide, potassium-tert. butoxide, sodium hydride and DMSO³⁸ and potassium-tert. butoxide in DMSO³⁹, and in all of them starting aldehyde was recovered. We presume that failure of the Wittig reaction may be due to the intramolecular decomposition of the phosphorane formed in the reaction. Phosphoranes of the type (LIX) are known to decompose via intramolecular reaction to furnish LX as shown below.



When phenyl lithium was used as a base, a yellowish red colour was obtained which might have been due to the phosphorane of (LV) and its reaction with dihydrocyclocitral

did not furnish the required product (LVI), as revealed by IR and PMR of the reaction product. No further attempt was made to characterise it.

Method II. In another approach (Fig.28), it was envisaged that the Grignard reaction of dihydrocyclogeranyl bromide (LW) and ethyl levulinate (LXVI) will result in the formation of the lactone (LVII), which could conceivably be converted into the cyclopentanone (LII) as described earlier.

Methods reported^{41a-c} for cyclisation of geranic acid^{41a} (LXI) are cumbersome and involve mixture of inorganic acids. We have found that methane-sulphonic acid in nitromethane effects the cyclisation of geranic acid at room temperature and furnishes a mixture of α,β - and allocyclogeranic acids (LXII) in almost quantitative yield. As soon as the cyclisation is complete, LXII is thrown out as a solid. Catalytic hydrogenation of LXII over 5% Rh/C furnished cis-dihydrocyclogeranic acid⁴² (LXIII, R=H). LAH reduction of the methyl ester (LXIII, R = CH₃) yielded cis-dihydrocyclogeraniol⁴² (LXIV) which on reaction with triphenyl phosphine and NBS⁴³ furnished the required bromide (LXV), which analyses for C₁₀H₁₉Br. IR (smear): no OH bond. PMR(CCl₄): two quaternary Me's (6H, s, 1 ppm); CH₃.CH (3H, d, 0.97 ppm, J = 7 Hz) and CH₂Br (2H, m, 3.4 ppm). Various other reagents (Table 1) used for converting alcohol (LXIV) into its corresponding bromide, either resulted in complete loss of the material or rearranged products were formed.

No attempt was made to identify the products formed.

TABLE 1

Sl.No.	Compound used	Reagents used	Results
1	LXIV	PBr_3 , EtO ²	Loss of material
2	"	PBr_3 , $\text{C}_5\text{H}_5\text{N}$, C_6H_6 ⁴⁴	"
3	"	HBr , H_2SO_4 ⁴⁵	Polymerisation occurred.
4	"	Ph_3P , Br_2 , DMF ⁴⁶	
5	"	p-TsCl (5 H_5N and NaBr , Me_2CO , reflux ⁴⁷).	Tosylate of LXIV. Mixture of olefins formed (PMR).
6	"	NBS , Ph_3P ⁴³	Required bromide (LXV).

Attempted Grignard reaction of the bromide (LXV) and ethyl levulinate did not take place presumably because magnesium failed to react with the bromide (LXV) and to furnish the corresponding Grignard reagent. This reaction was attempted twice, without any success, by changing the solvent as well as the temperature and in both cases starting materials were recovered.

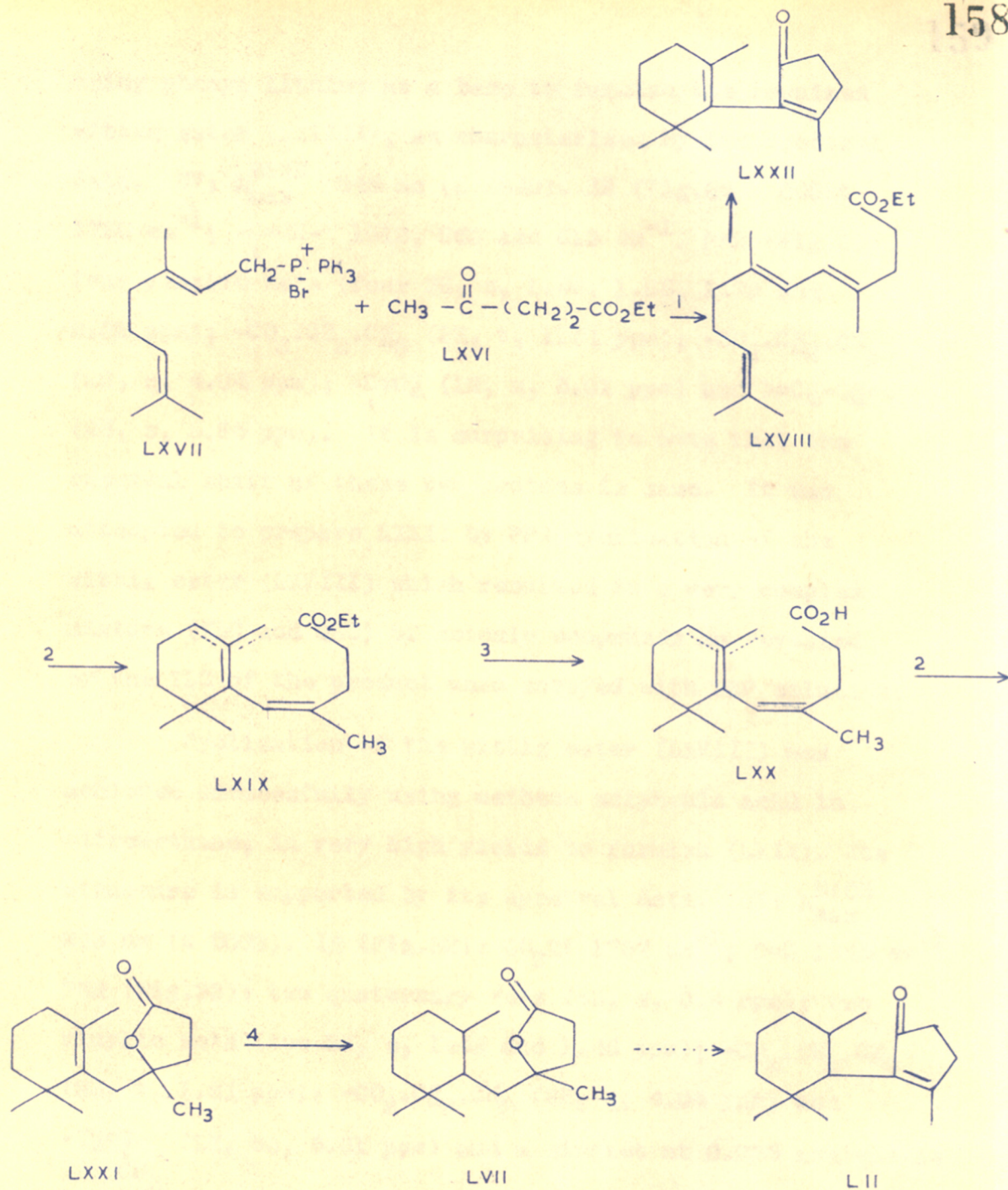
In view of the above obstacle, it was envisaged to prepare the triphenyl phosphonium salt of LXV and then to carry out its Wittig reaction with ethyl levulinate which will furnish (LVI) and this could conceivably be converted

into the cyclopentanone (LII) as shown in Fig.27. No trace of the phosphonium salt of LXV could be obtained under the variety of conditions used. We presume that failure of the above two reactions could be attributed to the steric hindrance caused by the three (ring) methyls of LXV. The steric hindrance in this system is also reflected by the failure of dihydrocyclogeranyl acid chloride (LXIII, OR=Cl) to react with a small molecule such as diazomethane*. This reaction was attempted with the aim to prepare homo-dihydrocyclogeranic acid which could conceivably be used to prepare the cyclopentanone (LII). So this method was abandoned in favour of a new approach as outlined in method III.

Method III. This approach was designed bearing in mind that the six-membered ring of the cyclopentanone (LII) should be constructed at a later stage in the synthesis so that steric problems encountered earlier are avoided. For this reason geraniol was chosen as the starting material and it could be elaborated to LII as shown in Fig.29.

Triphenyl geranyl phosphonium bromide⁴⁹ (LXVII) undergoes a smooth Wittig reaction with ethyl levulinate

*The acid chlorides of two hindered acids have been found to resist the action of diazomethane; these are the acid chlorides of the acid ester of homocamphoric acid⁴⁸ in which the acid chloride group is attached to a tertiary carbon atom and mesitoyl chloride⁴⁸.



REAGENTS. 1) PhLi , Et_2O ; 2) $\text{CH}_3\text{OSO}_2\text{H}$, CH_3NO_2 ;
 3) KOH , MeOH 4) Cat. H_2
 5) PPA

FIG. 29 METHOD III FOR THE SYNTHESIS OF CYCLOPENTANONE (LII)

using phenyl lithium as a base to furnish the required Wittig ester (LXVIII), as characterised by its spectral data. UV: $\lambda_{\text{max}}^{\text{EtOH}}$ 246 nm (ϵ 2640). IR (Fig.30): COOEt 1730 cm^{-1} ; $-\text{C}=\text{CH}-$ 1612 , 863 and 813 cm^{-1} . PMR (Fig.31): four vinylic Me's (four 3H, s, 1.59, 1.65, 1.70 and 2.32 ppm); $-\text{CO}_2\cdot\text{CH}_2\cdot\text{CH}_3$ (3H, t, 1.21 ppm); $-\text{CO}_2\cdot\text{CH}_2\cdot\text{CH}_3$ (2H, q, 4.04 ppm); $-\text{C}=\text{CH}-$ (1H, m, 5.01 ppm) and $>=\text{CH}-\text{CH}=<$ (2H, s, 5.85 ppm). It is surprising to note that the chemical shift of these two protons is same. It was attempted to prepare LXXII by PPA cyclisation of the Wittig ester (LXVIII) which resulted in a very complex mixture (TLC and GLC) of ketonic compounds as revealed by the TLC of the product when sprayed with DNP solution.

Cyclisation of the Wittig ester (LXVIII) was achieved successfully using methane sulphonic acid in nitromethane, in very high yields to furnish (LXIX). Its structure is supported by its spectral data. UV: $\lambda_{\text{max}}^{\text{EtOH}}$ 218 nm (ϵ 5003). IR (Fig.32): CO_2Et 1737 cm^{-1} ; $\text{C}=\text{C}$ 1645 cm^{-1} . PMR (Fig.33): two quaternary Me's (6H, s, 0.9 ppm); two vinylic Me's (two 3H, s, 1.42 and 1.46 ppm); $-\text{CO}_2\cdot\text{CH}_2\cdot\text{CH}_3$ (2H, t, 1.21 ppm); $-\text{CO}_2\cdot\text{CH}_2\cdot\text{CH}_3$ (2H, q, 4.04 ppm) and $-\text{CH}=\text{C}-$ (1H, bs, 5.61 ppm) and a singlet at 0.235 assignable to allylic protons (4H).

The cyclised ester (LXIX) on hydrolysis with methanolic potassium hydroxide furnished the corresponding acid (LXX), identified fully by its IR and PMR. The acid

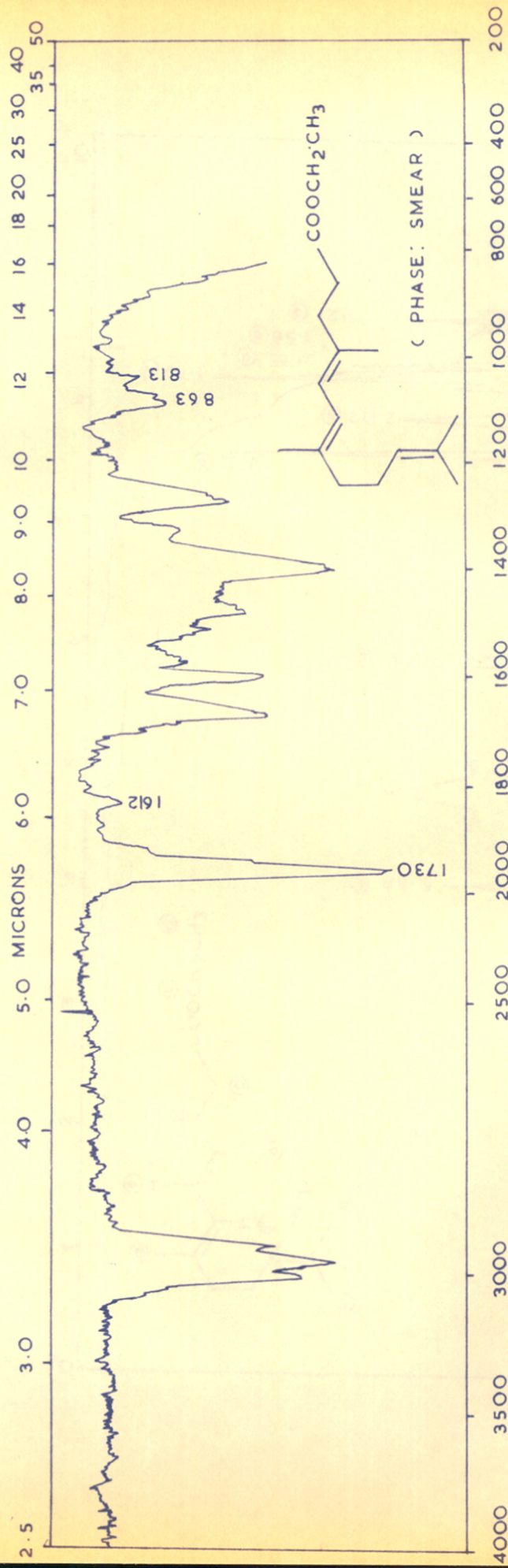


FIG. 30 IR SPECTRUM OF ETHYL 4,7,11 - TRIMETHYL DODECA - 4,6,10 - TRIEN - OATE (LXVIII)

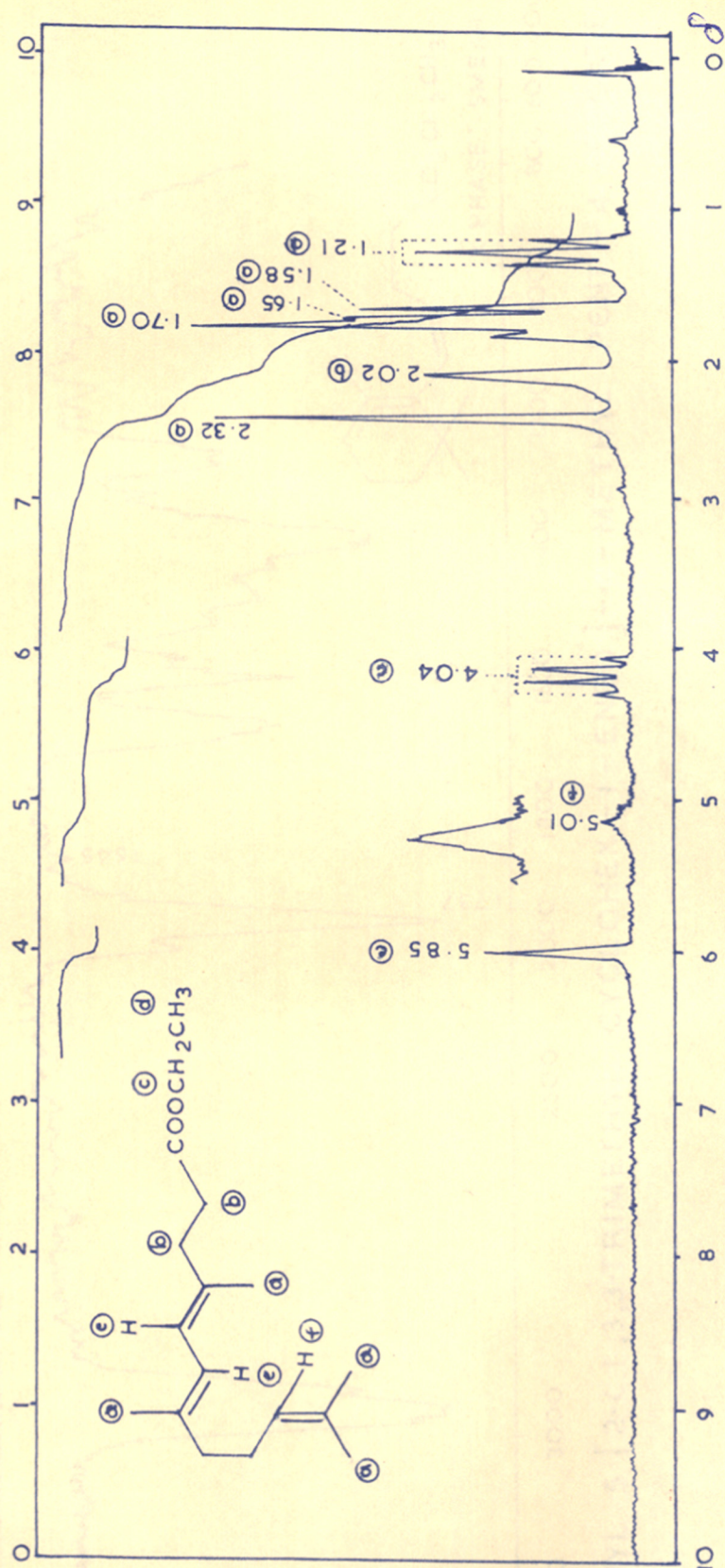


FIG.31 PMR SPECTRUM OF ETHYL 4,7,11 - TRIMETHYL DODECA - 4,6,10 - TRIEN-OATE (LXVIII)

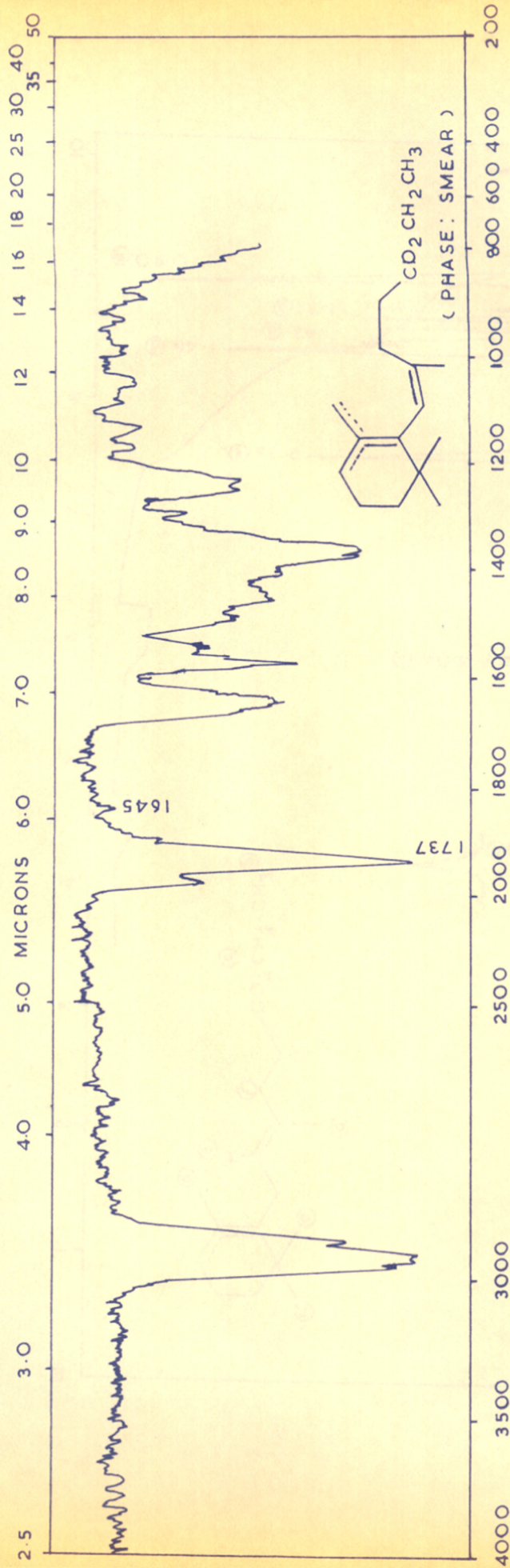


FIG.32 ETHYL 5 [2-(1,3,3,3-TRIMETHYL CYCLOHEX - 1 - ENE)] - 4 - METHYL PENT - 4 - ENOATE (LXIX)

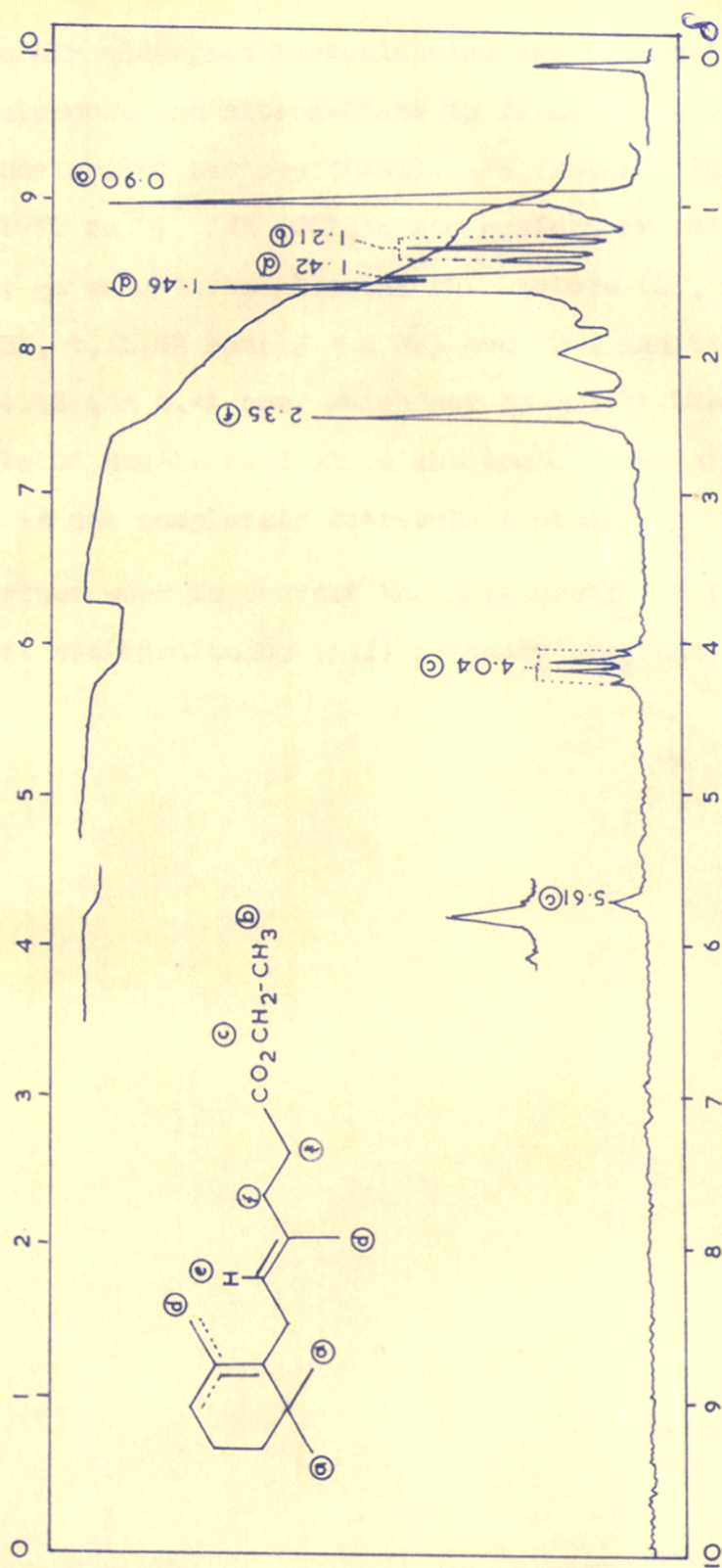


FIG.33 ETHYL 5 [2 -(1,3,3-TRIMETHYL CYCLOHEX -1-ENE)] -4 -METHYL PENT -
- 4 -ENOATE (LXIX)

(LXX) smoothly undergoes lactonisation again by using methane sulphonic and nitromethane to furnish the corresponding unsaturated lactone (LXXI). IR (smear): lactone 1770 and 1777 cm^{-1} . PMR (CCl_4): two quaternary Me's (6H, s, 1.01 ppm); Me on a carbon bearing the lactone (3H, s, 1.34 ppm); $\text{CH}_3\text{C}=\text{C}$ (3H, t, 1.62 ppm; $J = 2 \text{ Hz}$) and some additional peaks at 0.88 and 5.41 ppm, which may be due to the isomeric trisubstituted double bond since the double bond present in (LXXI) is not completely tetrasubstituted.

Further work to convert the unsaturated lactone (LXXI) into cyclopentanone (LII) is under progress.

EXPERIMENTAL

For general remarks, see p. 78.

Analytical GLC were carried out on 'Aerograph' model A-350-B using a 300 cm x 0.8 cm column (packed with 30% diethylene glycol polysuccinate on 30 - 60 mesh chromosorb W); H_2 was used as the carrier gas.

The following instruments were used for recording spectral data of the compounds prepared in the route four: Perkin-Elmer model R 32 (90 MHz) NMR spectrometer, Perkin-Elmer Infrared spectrophotometer, model 267.

1,3,3-Trimethyl cyclohexanone (XIII)

2-Carboethoxy cyclohexanone¹⁴: Cyclohexanone (98 g, 1 mole) on condensation with diethyl oxalate (146 g, 1 mole), using NaOEt (prepared from 23 g of Na and (300 ml) of EtOH), furnished (91 g) of the glyoxalate, which on pyrolysis with (0.5 g) of soft glass and trace of iron, yielded 2-carboethoxy cyclohexanone (78 g, 46%) b.p. 142-144°/50-60 mm [Lit.¹⁴ b.p. 159-60°/100 mm].

2-Carboethoxy-1,3,3-trimethyl cyclohexanone¹⁵: 2-Carboethoxycyclohexanone (18.7 g, 0.11 mole), NaH (27 g, 50% dispersion in oil), CH_3I (79 g) and dry C_6H_6 (70 ml) on refluxing under H_2 , for 40 hrs furnished (12.12 g, 53%) of 2-carboethoxy-1,3,3-trimethylcyclohexanone b.p. 90°/7 mm [Lit.¹⁵ b.p. 118-120°/15 mm].

1,3,3-Trimethyl cyclohexanone (XIII): 2-Carboethoxy-1,3,3-

trimethyl cyclohexanone (12.12 g) was subjected to hydrolysis and decarboxylation⁵⁰ using a mixture of AcOH (24 ml) and conc. HCl (60 ml) and refluxed the resulting mixture for 64 hrs. The solution was cooled, diluted with H₂O (200 ml), extracted with pet. ether (30 ml x 4), washed with NaHCO₃, H₂O, brine, dried and distilled to furnish (10.3 g, 84.4%) of (XIII) b.p. 87°/13 mm. IR(smear): C=O 1700 cm⁻¹. PMR (CCl₄): two quaternary Me's (two 3H, s, 1.0 and 1.15 ppm) and CH₃.CH (3H, d, 0.95, J = 6 Hz) [Lit.¹⁵ b.p. 176.5 - 178°].

1,3,3-Trimethyl cyclohexanol (XIV): In a three necked flask, Na (8.4 g) was covered with dry toluene (50 ml). This was heated in an oil bath (120-130°) till the Na melted and with vigorous stirring a mixture of (XIII) and isopropyl alcohol (24 ml) was introduced during 15 minutes, toluene (20 ml) was used to wash in the last traces of ketone-alcohol mixture. The reaction mixture was stirred and refluxed (N₂) till all the Na disappeared (~ 2 hrs). After usual work up and distillation furnished the required product (15.2 g, 91%) b.p. 92-94°/35 mm. IR(smear): OH 3400 and 1030 cm⁻¹. PMR (CCl₄): two quaternary Me's (two 3H, s, 0.86 and 0.97 ppm), Me.CH (3H, d, 0.96 ppm, J = 5.5 Hz); -HC-CHOH (1H, d, 2.723 ppm, J_{a,a} = 9 Hz) and -CHOH (1H, m, 1.78 ppm, disappears on D₂O exchange) [Lit.¹⁶; m.p. 54°].

1,3,3-Trimethyl cyclohexyl acetate (XV): 1,3,3-trimethyl-

cyclohexanol (15.2 g) was mixed with Ac_2O (18.1 ml) and pyridine (1.8 g) and left aside for 24 hrs at 30°C . The mixture was poured on crushed ice (280 g) to decompose excess of Ac_2O . The aqueous solution was extracted with pet. ether (100 ml x 3), washed with HCl (1N, 20 ml x 3), saturated NaHCO_3 (30 ml x 3), H_2O (20 ml x 3), brine (50 ml x 3), dried and the solvent was stripped off and distilled to give the acetate (17.6 g, 90%). b.p. $110-111^\circ/40$ mm. IR (smear): AcO 1740 and 1240 cm^{-1} . PMR (CCl_4): two quaternary Me's (two 3H, s, 0.85 and 0.91 ppm); Me-CH- (3H, d, 0.8 ppm, $J = 6.5$ Hz); Me-COO (3H, s, 2.03 ppm) and $-\text{CH-CH-OAc}$ (1H, d, 4.55 ppm; $J_{a,a} = 10$ Hz).

1,3,3-Trimethyl-cyclohex-1-ene (VII): A pyrex tube (45 cm, ID 1.5 cm) with a narrow end was filled with broken glass chips to a length of (35 cm) and the packed portion of the column was heated by coils wound round an outer tube, the required temperature was regulated with a variac. The acetate (XV, 16.5 g) was added dropwise (one drop/35 sec) to the heated column (540°C) with an inert atmosphere (N_2) being maintained and under a mild suction (600 mm). The acetate decomposed with a white cloud formation and the resulting product was allowed to drip into a receiver (containing some glass wool), connected to two traps (cooled to -10°C by ice/salt), containing pet. ether. After the pyrolysis, the tube was allowed to cool to about 100°C and pet. ether (50 ml) was let in as a chaser to remove last traces of the material. The pet. ether solutions were combined

washed with NaHCO_3 (15 ml x 3). H_2O (20 ml x 3), brine (25 ml x 3) and dried. The solvent was distilled (column) and the residue (10.7 g) was subjected to spinning band distillation, which furnished (3.9 g) of the required olefin (GLC pure), b.p. $133^\circ/710$ mm; [Lit.¹⁰: b.p. $137^\circ/760$ mm].

A number of lower boiling compounds were also obtained which were rejected.

1,3-Cyclopentadione (VIII, R=H):

2-Acetyl-1,3-cyclopentadione¹⁷: Succinic anhydride (10 g, 0.1 mole), isopropenyl acetate (10 g, 0.1 mole), anhyd. AlCl_3 (20.5 g, 0.2 mole) in dichloroethane (100 ml), furnished 3.183 g (25%) of 2-acetyl-1,3-cyclopentadione m.p. $70-71^\circ$. (Found: C, 60.05; H, 5.88. $\text{C}_7\text{H}_8\text{O}_3$ requires: C, 60.00; H, 5.8%). [Lit.¹⁷: m.p. $69-71^\circ$; analysis].

1,3-Cyclopentadione (VIII, R=H): 2-Acetyl-1,3-cyclopentadione (0.5 g) on acid cleavage with HCl (50M, 2M), furnished 0.28 g of (VIII, R=H), recrystallised from EtOAc, m.p. $152-154^\circ\text{C}$ (Found: C, 61.67; H, 6.76. $\text{C}_5\text{H}_6\text{O}_2$ requires: C, 61.22; H, 6.12%). [Lit.¹¹ m.p. $152-154^\circ$; analysis].

1,3-Cyclopentadione enol acetate⁷ (VIII, R=Ac): Into

1,3-cyclopentadione (1 g) in 100 ml of dry Et_2O , was passed ketene gas which furnished 0.8085 g of (VIII, R = Ac) as an oil. b.p. $112^\circ/2$ mm. IR (smear): 1790, 1702 and 1601 cm^{-1} . PMR (CCl_4): $\text{CH}_3\text{-COO}$ (3H, s, 2.26 ppm) and CH=C.OAc (1H, t, 6.08 ppm, J = 1.5 Hz). [Lit.⁷: IR, PMR].

1,3-Cyclopentadione enol methyl ether²⁰ (VIII, R=Me): 1,3-Cyclopentadione (0.5 g) on reaction with diazomethane solution furnished a solid (VIII, R = Me), m.p. 51-53°C. IR (CCl₄): 1710, 1695 and 1601 cm⁻¹. PMR (CCl₄): CH₃O (3H, s, 3.86 ppm), Me=CH-C=O (1H, unresolved t, 5.26 ppm, J = 1 Hz) and 2 allylic-CH₂ (4H, m, 2.2 - 2.9 ppm).

Photo-reaction: 1,3,3-Trimethyl cyclohex-1-ene (0.62 g, 0.005 mole) and 1,3-cyclopentadione (0.49 g, 0.005 mole) were taken in dioxane and irradiated through a pyrex filter using a 200-W UV lamp and under nitrogen bubbling to keep the solution stirring. After 5 hrs of irradiation the reaction was worked up. The excess of dioxane was distilled off while its last traces were removed under suction (50 mm). The residual product was distilled in a short path still and following two cuts were made.

1st cut, b.p. 46°/0.5 mm, (0.104 g)

2nd cut, b.p. 110-120°(bath)/0.5 mm, (0.064 g)

IR and TLC of these cuts revealed the presence of 1,3-diketone (VIII, R = H) mostly. No trace of the adduct was formed.

Irradiation of (VII) and 1,3-cyclopentadione-enol methyl ether (VIII, R = Me): (VII, 1.25 g; 0.001 mole) and (VIII, R = Me; 1.12 g; 0.001 mole) were taken in a mixture of cyclohexane and dioxane (30 ml, 1:1) and was irradiated through a pyrex filter using the same conditions as used earlier. The reaction was monitored by TLC of the aliquot withdrawn after every one hour. The reaction mixture was

worked up after 37 hrs of irradiation. TLC (solvent: 5% EtOAc in C_6H_6) indicated the presence of a polar compound besides the unreacted (VIII, R=Me). The reaction product was chromatographed on SiO_2 -gel/Iib (70 g, 4.4 cm x 1.5 cm) using increasing amounts of C_6H_6 in pet. ether and with TLC monitoring.

TABLE 2

Fr.No.	Eluent	Vol. collected	Wt.	Remarks
1	Pet. ether	200 ml x2	0.5702	Recover (VII)
2	" "	200 ml x8	0.712 g	Recovered (VIII, R=Me)
3	10% C_6H_6 in pet. ether	200 ml x3	negligible	-
4	50% " "	200 ml x3	-	-
5	C_6H_6	200 ml x2	-	-
6	10% EtOAc in C_6H_6	200 ml x5	37 mg	Polar spot (TLC)
7	20% EtOAc "	200 ml x2	-	rejected
8	50% " "	200 ml x2	-	
9	MeOH		-	junk

Fr. 6 (Table 2, 37 mg) - PMR and mass spectrum did not possess the spectral characteristics expected of the photoadduct (X, R=Me).

2-Acetyl-1,3,3-trimethyl cyclohex-1-ene (XI):

2-Ethynyl-1,3,3-trimethyl cyclohexanol⁵¹: 1,3,3-Trimethyl-cyclohexanone (7 g, 0.05 mole) on reaction with sodium acetylide (0.05 mole, prepared from Na (1.65 g, 0.05 mole) and 200 ml of liquid NH_3 and passing acetylene gas), furnished 7.4 g (87%) of 2-ethynyl-1,3,3-trimethylcyclohexanol. b.p. $103-105^\circ/25$ mm. IR(smear): OH 3480 and 1030 cm^{-1} ; $\text{C}\equiv\text{CH}$ 3300 and 2100 cm^{-1} . PMR (CCl_4): two quaternary Me's (two 3H, s, 0.97, 1.06 ppm); $\text{CH}_3\text{-CH}$ (3H, d, 1.03 ppm, $J = 7$ Hz); -OH (1H, bs, 1.82 ppm, D_2O exchange) and $\text{C}\equiv\text{CH}$ (1H, s, 2.36 ppm). [Lit.⁵¹: b.p. $93^\circ/13-14$ mm].

2-Acetyl-1,3,3-trimethyl cyclohex-1-ene: A stirred mixture of (20 g) of 2-ethynyl-1,3,3-trimethylcyclohexanol, AcOH (80 ml), H_2O (9 ml) and Dowex-50 (12 g) resin was held at reflux for 90 minutes. Worked up as usual and distilled to furnish 14.16 g (71%) of (XVI). b.p. $102-104^\circ/25$ mm, n_D^{27} 1.480. IR (smear): α,β -unsaturated $\text{C}=\text{O}$ 1695 cm^{-1} and $\text{C}=\text{C}$ 1650 cm^{-1} . PMR (CCl_4): two quaternary Me's (6H, s, 1.05 ppm); $\text{CH}_3\text{-C}=\text{C}$ (3H, s, 1.56 ppm) and $\text{CH}_3\text{-CO}$ (3H, s, 2.18 ppm). (Lit.²¹: b.p. $110-111^\circ/21$ mm, IR).

Cyclopentene (XVII): Cyclopentanol borate ester (prepared from cyclopentanol (43 g, 0.5 mole) and boric acid (31 g, 0.5 mole), toluene (50 ml) and removed H_2O azeotropically) on pyrolysis at $215-225^\circ$, furnished (30 g, 88%) of (XVII). b.p. $40-41^\circ/710$ mm.

Irradiation of 2-acetyl-1,3,3-trimethyl cyclohex-1-ene (XVI) and cyclopentene (XVII). (XVI; 4 g, 0.035 mole) and cyclo-

pentene (23.4 g, 0.375 mole) were taken in 130 ml of pentane. The quartz reactor was cooled to -70° (EtOAc/liq. N_2), H_2O and glycol (1:1) mixture was circulated through the immersion well. The reaction mixture was irradiated for (80 hrs) through a pyrex filter, using a 200 W UV lamp while the reaction was monitored by IR. The reaction was stopped when the enone band due to (XVI) was not undergoing further change. After usual work up, the reaction mixture was distilled into two broad cuts.

1st cut, b.p. $70-80^{\circ}/1.5$ mm (3.0609 g) - consisted of mostly starting materials as shown by its TLC and IR and hence was discarded.

2nd cut, b.p. $81-106^{\circ}/1$ mm (0.7302 g). TLC (solvent: 10% EtOAc in C_6H_6) revealed it to be complex mixture. The product (1.0874 g) from one such experiment was chromatographed on SiO_2 -gel/IIb (70 g, 44 cm x 1.5 cm) with TLC monitoring.

TABLE 3

Fr.No.	Eluent	Vol. collected	Wt.	Remarks
1	Pet. ether	100 ml x2	0.0568 g	-
2	50% C_6H_6 in pet. ether	150 ml	0.0323 g	Recovered (XVI)
3	75% " "	100 ml	0.2151 g	TLC pure
4	" " "	50 ml x4	0.0763 g	"

....contd.

TABLE 3 (Contd)

Fr.No.	Eluent	Vol. collected	Wt.	Remarks
5	85% C ₆ H ₆ in pet. ether	50 ml x5	0.1566 g	TLC pure
6	C ₆ H ₆	50 ml x2	0.1329 g	Complex mixture (TLC)
7	2% EtOAc in C ₆ H ₆	50 ml x2		
8	4% " " "	50 ml x2		
9	8% " " "	50 ml x2		
10	10% " " "	50 ml x3	0.0862 g	TLC pure
	15% " " "	50 ml x1		
11	" " " "	50 ml x4	0.0045 g	Rejected
12	20% " " "	50 ml x3		
13	MeOH			junk.

Fr.3 - Fr.5 and Fr.10 (Table 3): were found to be mixture of compounds containing a keto as well as hydroxyl groups, as shown by their IR, PMR. So no further attempt was made to identify them.

Nitropentanol-2-acetate (XXIII)

5-Nitro-2-pentanone²⁴: Methyl vinyl ketone (8.24 g, 0.1 mole), nitromethane (61 g, 1.0 mole), Et₂O (100 ml) on reaction with benzyl trimethyl ammonium hydroxide (Triton B, 0.7 ml), furnished 6.9 (60%) of 5-nitro-2-pentanone b.p. 117-120°/10 mm. IR (smear): C=O 1710 cm⁻¹; NO₂ 1552 cm⁻¹. PMR (CCl₄): CH₃.CO (3H, s, 2.15 ppm) and -CH₂.NO₂ (2H, t, 4.37 ppm; J = 6 Hz) [Lit.²⁴: b.p. 117-120°/10 mm and IR].

5-Nitro-2-Pentanol²⁴: 5-Nitro-2-pentanone (6.5 g, 0.0565 mole) on reduction with NaBH_4 (0.8820 g, 0.0174 mole) in H_2O (17 ml) containing a drop of conc. NaOH , furnished 5-nitro-2-pentanol (2.2838 g, 53.2%), b.p. $90-96^\circ/1.5$ mm. IR (smear): OH 3400 cm^{-1} ; NO_2 1555 cm^{-1} . PMR (CCl_4): $\text{CH}_3\text{-CH}$ (3H, d, 1.23 ppm, $J = 7$ Hz); $\text{CH}_3\text{-CHOH}$ (1H, q, 3.83 ppm); CHOH (1H, s, 1.67 ppm, undergoes D_2O exchange) and $\text{CH}_2\text{-CH}_2\text{-NO}_2$ (2H, t, 4.4 ppm, $J = 7$ Hz). [Lit.²⁴: b.p. $87-88^\circ/1$ mm and IR].

5-Nitropentanol-2-acetate: 5-Nitro-2-pentanol (3 g) on exposure to Ac_2O (3.57 ml) and pyridine (0.357 ml) at room temperature for 24 hrs, furnished 3.2949 (73.5%) of the 5-nitropentanol-2-acetate b.p. $111^\circ/2.5$ mm. IR(smear): -OAc 1745 and 1250 cm^{-1} ; NO_2 1555 cm^{-1} . PMR (CCl_4): $\text{CH}_3\text{-CH}$ (3H, d, 1.23 ppm, $J = 7$ Hz); -O-C(=O)-CH_3 (3H, s, 1.98 ppm), $\text{CH}_3\text{-CH-OAc}$ (1H, q, 4.83 ppm) and $\text{-CH}_2\text{-CH}_2\text{-NO}_2$ (2H, t, 4.3 ppm, $J = 6$ Hz). [Lit.²⁴: b.p. $87-90^\circ/1$ mm, IR].

Michael Addition of (XVI) and (XXII): A solution of the K-salt of (XXIII) (from (XXIII), 820 mg, 0.0045 mole, K-metal 80 mg) in $t\text{-BuOH}$ (5 ml) was added to a solution of the enone (XVI, 498 mg, 0.003 mole) in $t\text{-BuOH}$ (5 ml). The reaction was allowed to stand at room temperature (31°) for 100 hrs. The reaction was monitored by TLC (solvent: 10% EtOAc in C_6H_6). TLC indicated not much change in the starting materials. The reaction was stopped and worked up. The solution was neutralized with 10% AcOH (2 ml) and excess H_2O was added, the organic material was taken up in CH_2Cl_2

(200 ml), washed with 10% NaHCO_3 (10 ml), H_2O (20 ml x 3), brine (25 ml x 2), dried and stripped off solvent to furnish the crude product (0.8769 g) which was distilled, b.p. 130-140° (bath)/1.5 mm. IR and PMR of the reaction product revealed the presence of peaks due to the unreacted enone (XVI) and (XXII) and no trace of the required adduct (XXIV) was obtained.

1,3,3-Trimethyl-2-methylene cyclohexyl acetaldehyde (XXX):

α -Cyclocitral^{35,36}: Citral anil (prepared from citral (76 g, 0.5 mole) and aniline (46.5 g, 0.5 mole) on cyclization⁵² with conc. H_2SO_4 acid (500 ml) at -20° (liq. N_2 /EtOAc bath), furnished a mixture of α and β -cyclocitrals (57 g, 75%) b.p. 80-105°/12 mm. 55 g of α - and β -cyclocitrals were isomerised using 8% KOH solution (200 ml) in 80% alcohol, at -5°, for 15 hr (N_2) to give β -cyclocitral (51 g, 93%), b.p. 92-93°/11 mm. [Lit.³⁵: b.p. 89-97°/9 mm or 93°/12 mm].

β -Cyclogeraniol²⁸ *: β -Cyclocitral (87 g, 0.53 mole) on reduction with NaBH_4 in a mixture of EtOH and isopropyl alcohol (150 ml, 1:1), furnished β -cyclogeraniol (77 g, 91%), b.p.

* β -Cyclogeraniol is highly acid and heat sensitized and decomposes to yield 2,4,4-trimethyl-3-methylene cyclohex-1-ene b.p. 52°/8 mm; identified by IR and PMR. IR (smear): $\text{C}=\text{C}$ 1650, 1601 and 840 cm^{-1} ; $-\text{C}=\text{CH}_2$ 890 cm^{-1} . PMR (CCl_4): two quaternary Me's (6H, s, 1.05 ppm); $\text{CH}_2=\text{C}$ (3H, t, 1.78 ppm, $J = 1.5$ Hz); $-\text{C}=\text{CH}_2$ (2H, d, 4.87 ppm) and $\text{CH}_3-\text{C}=\text{CH}-$ (1H, m, 5.58). [Lit.⁵³: b.p. 100-103°/100 mm; IR and PMR].

100-102°/10 mm. IR (smear): OH 3300 cm^{-1} ; C=C 1650 cm^{-1} . PMR (CCl_4): two quaternary Me's (6H, s, 1.01 ppm); $\text{CH}_3\text{-C=C}$ (3H, s, 1.71 ppm), CH_2OH (2H, s, 3.95 ppm) and CH_2OH (1H, s, 1.63 ppm, D_2O exchange) [Lit.²⁸: b.p. 101-103°/10 mm, IR, PMR].

β -Cyclogeranyl vinyl ether²⁸: β -Cyclogeraniol (28.6 g, 0.1588 mole), Hg (OAc)₂ (1.54 g, 0.0044 mole) and ethyl vinyl ether (750 ml) on refluxing for 34 hrs, furnished a product, which on chromatographic separation over $\text{Al}_2\text{O}_3/\text{III}$ (860 g, 100 cm x 3.5 cm), furnished (17 g, 49%) of the β -cyclogeranyl vinyl ether, while (50%) of the β -cyclogeraniol was recovered. b.p. 86°/6 mm. IR (smear): 1650, 1620, 1320, 1200, 1050, 980 and 815 cm^{-1} . PMR (CCl_4): two quaternary Me's (6H, s, 0.96 ppm), $\text{CH}_3\text{C=C}$ (3H, s, 1.61 ppm); $-\text{CH}=\text{CH}_2$ (2H, m, 3.91 ppm); $\text{HC}=\text{CH}_2$ (1H, q, 6.27 ppm) and $-\text{CH}_2\text{-O}$ (2H, s, 3.96 ppm). [Lit.²⁸: b.p. 99-102°/15 mm, IR and PMR].

1,3,3-Trimethyl-2-methylene cyclohexylacetaldehyde (XXX):

β -Cyclogeranyl vinyl ether (10 g, 0.055 mole) was pyrolysed at 336° (N_2) to furnish 8.65 g (86%) of the required aldehyde (XXX). b.p. 110-113°/11 mm. IR (smear): CHO 2700 and 1720 cm^{-1} ; $>=\text{CH}_2$ 3100, 1625 and 908 cm^{-1} . PMR (CCl_4): three quaternary Me's (three 3H, s, 1.18, 1.18 and 1.27 ppm); $\text{CH}_2\text{.CHO}$ (2H, d, d, 2.6 ppm, $J_1 = 3$ and $J_2 = 9$ Hz); $-\text{CH}_2\text{.CHO}$ (1H, t, 9.63 ppm, $J = 3$ Hz) and $\text{C}=\text{CH}_2$ (1H, two s, 4.87 and 5.03 ppm). [Lit.²⁸: b.p. 111-115°/13 mm, IR and PMR].

Ethyl 4 [1-(1,3,3-trimethyl-2-methylene cyclohexyl)]-crotonate (XXXI): 1,3,3-Trimethyl-2-methylene cyclohexyl acetaldehyde (18 g, 0.1 mole) and carboethoxy methylene triphenyl phosphorane²⁹ (38.3 g, 0.11 mole) were taken in 500 ml of dry C_6H_6 and refluxed under N_2 for 12 hrs on steam bath ($100^\circ C$). The reaction mixture was cooled and solvent was flashed off. $Ph_3P=O$ separated was filtered off and washed with pet. ether (500 ml). The filtrate after washing with H_2O , brine was dried and distilled into two fractions. Fr.1 (lower boiling) b.p. $50-110^\circ/1$ mm, 0.216 g, was discarded. Fr.2 b.p. $120-125^\circ/1.2$ mm (22.5 g, 90%) was the required product. IR (Fig.7). PMR (Fig.8). Mass spectrum: important ions at m/e 250 (M^+ 3%), 137 (100%), 41 (95%), 95 (90%), 81 (58%), 55 (43%), 91 (37%), 53 (34%), 79 (29%), 77 (28%) and 67 (28%). (Found: C, 77.12; H, 10.55. $C_{16}H_{26}O_2$ requires: C, 76.75; H, 10.47%).

4[1-(1,3,3-Trimethyl-2-methylene cyclohexyl)]-Butanoic acid (XXXII): To 400 cc of H_2O was added pellets of NaOH (65 g) in one lot and stirred for a minute to effect solution. The unsaturated ester (XXXI, 20.9 g; 0.084 mole) was added, followed by 5-10 cc of EtOH, used to wash the last traces of the ester. With vigorous stirring the Ni-Al alloy³⁰ (20.9 g) was then added in small lots during 2 hrs. (there should not be much foaming, the second addition of the alloy was made only after the brisk reaction due to the previous lot had subsided). Finally the reaction mixture was heated

(90-95°) and stirred for 2 hrs and after cooling, diluted with H₂O (200 ml). The residual Ni (pyrophoric) was removed by filtration and washed with H₂O (100 ml). The combined filtrate and washings were cautiously introduced portionwise, with mixing, into warm dilute H₂SO₄ (150 ml), (conc. H₂SO₄ (90 ml) + H₂O (130 ml). The acidic solution was diluted with 1 litre of H₂O and the aq. solution extracted with Et₂O (500 ml x 4), washed with H₂O (50 ml x 4), brine (100 ml x 2), dried and solvent stripped off to furnish the crude acid which was distilled to (XXXII) in 96.5% yield. b.p. 136°/0.5 mm. The acid solidified on cooling m.p. of the crystallised acid (MeCN) 76-77°. IR (Nujol): COOH 2670 and 1700 cm⁻¹; -C=CH₂ 1621 and 904 cm⁻¹. PMR (CCl₄): three quaternary Me's (three 3H, s, 1.06, 1.10 and 1.10 ppm). -CH₂-CH₂.CO₂H (2H, t (ill-defined) 2.26 ppm); -C=CH₂ (two 1H, s, 4.81 and 5.01 ppm) and -COOH (1H, m, 10.7 ppm). The acid formed was confirmed by making its methyl ester (XXXIII).

Methyl 4[1-(1,3,3-trimethyl-2-methylene cyclohexyl)]

Butanoate (XXIII): The above acid (108 mg, 0.0005 mole) was esterified with CH₃N₂ in situ. After usual work up and distillation, it furnished the methyl ester (XXIII).

b.p. 110-115° (bath)/0.5 mm. IR (Fig.9). PMR (Fig.10).

Mass spectrum: important ions at m/e 238 (M⁺ 2%), 138 (100%), 137 (81%), 123 (77%), 95 (62%), 41 (54%), 81 (45%), 55 (33%), 82 (25%), 69 (24%) and 67 (22%). (Found: C, 76.42; H, 11.0.

C₁₅H₂₆O₂ requires: C, 75.58; H, 11.00%).

Cyclisation of 4[1-(1,3,3-trimethyl-2-methylene cyclohexyl)] butanoyl chloride (XXXIV):

To a solution of acid (XXXII, 1 g) in dry C_6H_6 (15 ml) was added two drops of pyridine solution (10 drops of pyridine in 1 ml of C_6H_6). This was cooled to 0° and a C_6H_6 solution of oxalyl chloride (2 ml in 10 ml of C_6H_6) was added. These additions were done in N_2 atmosphere. After 0.5 hr at 0° , the reaction mixture was allowed to stand at room temperature (28°) for 3 hrs. It was next gently warmed on a steam bath for 5 minutes and the solvent removed under suction (30 mm). The crude acid chloride thus obtained was identified by its IR and PMR.

The crude acid chloride, thus obtained, was taken up in CS_2 (20 ml, dried over P_2O_5 and distilled) and added to a solution of $SnCl_4$ in CS_2 (0.12 ml of freshly distilled $SnCl_4$ diluted with 10 ml of dry CS_2) at -10° (ice-salt). The reaction mixture was allowed to attain room temperature (28°) during 17 hrs, after which (50 ml) H_2O was added and the organic phase taken up in Et_2O 150 ml (50 ml x 3), washed with 10% $NaHCO_3$ (5 ml x 3), H_2O (10 ml x 3), brine (10 ml x 3) and dried. Solvent was flashed off to give a crude product 0.9533 g. Its TLC (solvent 10% $EtOAc$ in C_6H_6) indicated two spots, (yellow and red) when sprayed with DNP solution, corresponding to compounds (XXXVI) and (XXXVII). When DNP sprayed plate was charred, one more faint spot appeared at 0.75 Rf value.

The crude product was distilled to give (0.5678 g) of the mixture and 0.369 g of the residue was left (rejected). b.p. 130-140° (bath)/0.2 mm, [GLC: 200°, flow rate 70 ml/min] also indicated to be a mixture of two compounds.

Chromatography of the reaction mixture: (0.567 g) of the distilled mixture was chromatographed on SiO₂-gel/IIb (70 g, 60 cm x 1.7 cm) and monitored by TLC. The column was loaded in C₆H₆ and eluted with C₆H₆.

TABLE 4

Fr.No.	Eluent	Vol. collected	Wt.	Remarks
1	C ₆ H ₆	30 ml	-	-
2	"	30 ml x2	0.032 g	Corresponds to compound with Rf 0.75 (XXXVIII)
3	"	50 ml x1	-	-
4	"	25 ml x8	0.194 g	Compound (XXXVI)
5	"	30 ml x2	-	Mixture of compounds (XXXVI) and (XXXVII)
6	"	30 ml x2	0.246 g	Compound (XXXVII)
7	"	150 ml x5		

Minor Compound (XXXVIII)

Fr.2 (Table 4, 0.032 g) was distilled in a small bulb b.p. 200-210° (bath)/0.1 mm. IR (Fig.15). PMR (Fig.16). Mass

spectrum: important ions at m/e 448 (M^+ 3%), 189 (100%), 223 (50%), 96 (38%), 69 (37%), 55 (36%), 161 (35%), 57 (33%), 95 (32%), 107 (26%), 91 (24%), 224 (23%). (Found: C, 72.71; H, 10.06. $C_{28}H_{45}O_2Cl$ requires: C, 74.99; H, 10.04%).

1,2,2-Trimethyl bicyclo (5,4,0)-undec-5 or 6-ene-10-one (XXXVI):

Fr.4 (Table 4, 0.194 g) was distilled to furnish pure (XXXVI), b.p. 115-120° (bath)/0.2 mm. IR (Fig.11). PMR (Fig.12). Mass spectrum: important ions at m/e 206 (M^+ 100%), 150 (78%), 121 (74%), 79 (54%), 41 (54%), 107 (48%), 173 (45%), 55 (39%), 122 (35%) and 96 (34%). (Found: C, 80.83; H, 10.64. $C_{14}H_{22}O$ requires: C, 81.50; H, 10.75%).

2,2,3,3-Tetramethyl bicyclo (4,4,0)-dec-1(6)-ene-7-one (XXXVII):

Fr.6-7 (Table 4, 0.246 g) was distilled to give pure (XXXVII) b.p. 110°(bath)/0.2 mm. IR (Fig.13). PMR (Fig.14). Mass spectrum: important ions at m/e 206 (M^+ 90%), 150 (100%), 135 (38%), 41 (35%), 149 (34%), 163 (31%), 191 (30%), 107 (29%), 55 (24%) and 79 (21%). (Found: C, 80.65; H, 11.01. $C_{14}H_{22}O$ requires: C, 81.50; H, 10.75%).

Cyclisation of (XXXIV) with $SnCl_4$ in nitromethane and

lithium chloride: 400 mg of the acid (XXXII) was converted into its acid chloride as above and taken up in (8 ml) of dry CH_3NO_2 and added under N_2 to 12 ml of $SnCl_4$ solution (0.12 ml of $SnCl_4$ in 10 ml of CH_3NO_2 , 4 ml of this solution + 8 ml of CH_3NO_2 was used for the reaction) at -10° (ice/salt). LiCl (0.739 g, 10 moles excess) was also added to the above solution. The reaction mixture was

allowed to attain room temperature (28°) during 18 hrs. After usual work up, TLC (solvent: 10% EtOAc in C_6H_6) of the crude product, revealed two spots (yellow and red) when sprayed with DNP solution, which were separated and identified as (XXXVI) and (XXXVII) from their spectral data.

5 [1-(1,3,3-trimethyl-2-methylene cyclohexyl)]-pent-2-one (XLI):

To a stirred solution of the acid (XXXII, 10.95 g, 0.049 mole) in dry ether (200 ml) was introduced slowly (15 min) an ethereal solution of MeLi (2.65 g, 0.12 mole of 0.9M solution). Stirring was continued for another 1 hr under (N_2). Excess of MeLi was destroyed by adding (10 ml) of dry acetone, followed by (400 ml) of H_2O . The aqueous solution was extracted with Et_2O (100 ml x 3), washed with H_2O (25 ml x 3), brine (25 ml x 2), dried and solvent flashed off to yield the crude product (12 g). TLC (solvent: 10% EtOAc in C_6H_6), indicated the presence of a polar impurity, besides the required ketone (DNP). It was chromatographed over SiO_2 -gel/IIB (250 g, 110 cm x 25 cm) and eluted with increasing amounts of C_6H_6 in pet. ether. A fraction (7.5 g) eluted with 15% C_6H_6 in pet. ether was distilled to give pure (XLI), b.p. $104^{\circ}/0.7$ mm. IR (Fig.19). PMR (Fig.20). Mass spectrum: important ions at m/e 222 (M^+ 2%), 43 (100%), 41 (51%), 138 (28%), 39 (26%), 95 (25%), 81 (22%), 123 (20%), 137 (19%) and 55 (18%). (Found: C, 81.08; H, 11.82. $C_{15}H_{26}O$ requires: C, 81.02; H, 11.79%).

5 [1-(1,3,3-trimethyl-2-methylene cyclohexyl)]-2-Methyl-

2-Pentanol: 50% C_6H_6 in pet. ether eluted the polar compound

(2.5336 g) which was identified by its IR and PMR as 5[1-(1,3,3-trimethyl-2-methylene cyclohexyl)]-2-Methyl-2-pentanol. [IR(smear): OH 3206 cm^{-1} ; $-\text{C}=\text{CH}_2$ 1619 and 905 cm^{-1} . PMR (CCl_4): three quaternary Me's (three 3H, s, 1.06, 1.13, 1.15 ppm); 2. $\text{CH}_3-\overset{\text{OH}}{\underset{|}{\text{C}}}-\text{CH}_3$ (6H, s, 1.15 ppm) and $-\text{C}=\text{CH}_2$ (two 1H, s, 4.78, 5.0 ppm)].

5-[1-(1,3,3-Trimethyl-2-methylene cyclohexyl)]-Pentanol (XLII):

A solution containing (1 g, 0.0045 mole) of the methyl ketone (XLI) and (0.209 g, 0.0055 mole) LAH in 10 ml of ether was stirred at room temperature for 2 hrs. The solution was processed in the standard manner giving 0.952 g (95%) of the required alcohol (XLII) b.p. 130-140° (bath)/0.8 mm. (Found: C, 80.54; H, 12.41. $\text{C}_{15}\text{H}_{28}\text{O}$ requires: C, 80.29; H, 12.58%).

5[1-(1,3,3-Trimethyl-2-methylene cyclohexyl)]-Pentane-

2-acetate (XLIII): 800 mg of the above alcohol was added to 6 ml (1.2 m.mol) of dry Ac_2O containing 2 drops of dry pyridine. The mixture was left aside for 24 hrs at room temp. After usual work up distillation yielded the required acetate [(0.847 mg, (88%), b.p. 140-150°(bath)/0.4 mm]. IR(smear): ACO 1740 and 1240 cm^{-1} ; $-\text{C}=\text{CH}_2$ 1620 and 902 cm^{-1} . PMR (CCl_4): three quaternary Me's (three 3H, s, 1.07, 1.13 and 1.13 ppm); $\text{CH}_3\text{-CH-}$ (3H, d, 1.17 ppm, $J = 7$ Hz); $-\text{OCOCH}_3$ (3H, s, 1.97 ppm); $-\text{CH-OAc}$ (1H, m, 4.80 ppm, hidden under one of the peaks due to $-\text{C}=\text{CH}_2$) and $-\text{C}=\text{CH}_2$ (two 1H, s, 4.8 and 5.03 ppm). (Found: C, 77.00; H, 11.48. $\text{C}_{17}\text{H}_{30}\text{O}_2$ requires: C, 76.64; H, 11.38%).

5[1-(1,3,3-Trimethyl-2-hydroxy methyl cyclohexyl)]-Pentane-2-acetate (XLV): 532 mg (0.002 mole) of (XLIII) was taken up in (10 ml) of dry THF. Hydroboration was achieved by the dropwise addition of 4 ml of 0.64M solution of diborane (0.0025 mole) in THF at 0°. The solution was stirred under (N₂) for 30 minutes at 0° and for 30 minutes at room temperature (28°). Excess of diborane was decomposed by adding (1 ml) of MeOH. The organoborane was oxidised at (28°) by the addition of 2M NaOH (2 ml), followed by 2 ml (30% H₂O₂). The reaction mixture was stirred at room temperature (28°) for 2 hrs and worked up to furnish the required alcohol, which was distilled in a bulb b.p. 180° (bath)/0.5 mm.

Alcohol-I and -II Yang product (LI) 4[1-(1,3,3-trimethyl-2-methylene cyclohexyl)]-methyl cyclobutan-1-ol]: Methyl ketone (XLI) (0.992 g, 0.0047 mole) was taken in cyclohexane (50 ml) and irradiated through a Corex filter, with a 450 W UV lamp, while N₂ gas was bubbled in order to stir the solution. The reaction was monitored by TLC. The reaction mixture was irradiated for 8 hrs and the solvent was removed through a column under mild suction (350 mm) at 50°, to furnish 0.981 g of the reaction product. TLC (solvent: 10% EtOAc in C₆H₆) revealed it to be mixture of at least three major compounds corresponding to R_f values of 0.65, 0.44 and 0.31 respectively.

880 mg of the reaction mixture was resolved by IDCC⁵⁴ (SiO₂ gel; 225 g, 40 cm x 3.5 cm; solvent: 10% EtOAc

in C_6H_6) into four fractions as follows:

Fr.1 (0.1684 g) - TLC corresponding to the compound with
Rf value 0.31.

Fr.2 (0.1023 g) - TLC - mixture of compounds with Rf values
0.31 and 0.44.

Fr.3 (0.1844 g) - TLC - mixture of compounds with Rf values
0.44 and 0.65.

Fr.4 (0.1865 g) - TLC - corresponds to compound with Rf value
0.65 [GLC: (175°, flow rate 70 ml/min.)
mixture of at least 6 components]. This
fraction was rejected.

Fr.1 (0.1684 g), was distilled b.p. 120-125° (bath)/0.3 mm.
TLC (solvent: 10% EtOAc in C_6H_6) on $AgNO_3-SiO_2$ gel⁵⁵ revealed
it to be a mixture of two compounds, corresponding to Rf values
0.22 and 0.25. 190 mg of the mixture (22 mg obtained from earlier
chromatography) was resolved by IDCC⁵⁴ ($AgNO_3-SiO_2$ -gel, 75 g,
25 cm x 2.5 cm; solvent: 10% EtOAc in C_6H_6). Of the two
compounds (Rf 0.25 and 0.22) isolated the faster moving
[0.0454 g, Rf = 0.25; Alcohol-I Yang product (LI)]: had
b.p. 125°(bath)/0.5 mm. IR (Fig.22). PMR (Fig.23). Mass
spectrum: important ions at m/e 222 (M^+ 4%), 43 (100%),
41 (83%), 149 (75%), 95 (70%), 123 (67%), 93 (50%), 81 (50%),
55 (45%), 107 (41%) and 121 (38%).

Alcohol-II: 4-[1-(1,3,3-Trimethyl-2-methylene cyclohexyl)]-1-methyl cyclobutan-1-ol (LI): The slower moving compound
[0.0418 g, Rf 0.22; Yang product (LI)]: had b.p. 125°(bath)/0.5 mm

IR (Fig.24). PMR (Fig.25). Mass spectrum: important ions at m/e 222 (M^+ 3%), 95 (100%), 41 (91%), 43 (87%), 123 (84%), 149 (81%), 81 (76%), 55 (76%), 93 (61%) and 79 (61%).

Fr.2 and Fr.3 (0.2867 g) were distilled, b.p. 110-130° (bath)/0.7 mm. TLC (solvent: 10% EtOAc in C_6H_6) indicated it to be mostly the starting ketone. IR and PMR revealed it to be mixture of compounds. TLC (solvent: 10% EtOAc in C_6H_6) on $AgClO_4-SiO_2$ -gel, resolved it into three compounds. Twice it was attempted to separate the mixture by IDCC ($AgClO_4-SiO_2$ -gel⁵⁶, 150 g, 40 cm x 2.5 cm; solvent: 10% EtOAc in C_6H_6) without any success and finally this separation was abandoned.

Dihydrocyclocitral (LIV). β -Cyclocitral (9 g, 0.06 mole) in EtOH (150 ml) consumed (0.9 mole) of H_2 at 27°/715 mm over presaturated 5% Pd/BaCO₃ (1.78 g). Distillation of the hydrogenated product furnished 7.2 g of (LIV) b.p. 81-84°-85°/11-12 mm. IR(smear): CHO 2875, 2720 and 1724 cm^{-1} . PMR (CCl_4): two quaternary Me's (two 3H, s, 0.93 and 1.01 ppm); $\underline{CH}_3$.CH (3H, d, 0.91 ppm, $J = 7$ Hz) and -CH. $\underline{CH}_2$ O (1H, d, 9.76 ppm, $J = 4$ Hz, another doublet at 10.06 ppm, $J = 5$ Hz) [Lit.³⁵: b.p. 81°/12 mm, IR⁵⁸].

Triphenyl-4(1-Carbethoxy pentyl)-phosphonium bromide (LV):

Ethyl- γ -bromo valerate: γ -Valerolactone (15 g) in absolute EtOH (28 ml) was cleaved by passing dry HBr gas³⁷ [(generated from (60 g) of dry teralin and liquid Br₂ (2 ml)],

at 0°C. This alcoholic solution, after keeping at 0°C for 24 hrs, furnished 10.9 g of the ethyl-γ-bromo-valerate. b.p. 110-112°/35 mm. IR(smear): COOEt 1730 cm^{-1} . PMR (CCl_4): $\text{CH}_3\text{-CH}$ (3H, d, 1.76 ppm, $J = 7$ Hz), $\text{CH}_2\text{-CHBr}$ (1H, q, 4.09 ppm); $-\text{COOCH}_2\text{-CH}_3$ (2H, q, 4.09 ppm) and $-\text{COOCH}_2\text{-CH}_3$ (3H, t, 1.26 ppm) [lit.³⁷: b.p. 104/22 mm, IR and PMR].

Triphenyl-4(1-carbethoxy pentyl)-phosphonium bromide (IV):

(a) Ph_3P (0.131 g, 0.0005 mole) was dissolved in (10 ml) of dry C_6H_6 , ethyl-γ-bromo valerate³⁷ (0.110 g, 0.0005 mole) in 2 ml of C_6H_6 was added slowly and stirred the reaction mixture for 24 hrs. No solid separated even when the mixture was refluxed for 12 hrs. In another experiment, C_6H_6 was replaced by xylene, but no trace of salt was obtained even when the mixture was refluxed for 4 days.

(b) Using Nitromethane or DMF: Ph_3P (0.131 g, 0.0005 mole) and ethyl γ-bromo valerate (0.110 g, 0.005 mole) were stirred and refluxed in dry DMF (10 ml) for 3 days. No salt was formed. Similarly when $\text{CH}_3\text{-NO}_2$ was used instead of DMF, no phosphonium salt was obtained.

(c) Direct Heating in sealed tube: Ph_3P (7.8 g, 0.031 mole) and ethyl-γ-bromo valerate (6.7 g, 0.031 mole) were heated together in a sealed tube at 120-130° for 14-16 hrs. The solid separated was washed with Et_2O and C_6H_6 , to furnish the required phosphonium salt (10.5 g, 73%). Crystallised from EtOH and Et_2O m.p. 186°. (Found: C, 64.53; H, 5.15. $\text{C}_{25}\text{H}_{28}\text{O}_2\text{PBr}$ requires: C, 63.7; H, 5.94%).

Attempted Wittig reaction of dihydrocyclocitral (LIV) and triphenyl-4-(1-carboethoxy phenyl)-phosphonium bromide (LV): Various bases employed for Wittig reaction are listed in the Table (5). No further attempt was made to identify the abnormal product if formed.

Dihydro cyclogeranyl bromide (LXV)

Geranic acid (LXI)^{41a}: Citral (40 g, 0.263 mole) on Ag_2O (90 g, 0.4 mole) oxidation in (200 ml) of H_2O , furnished 41.5 g (94%) of geranic acid b.p. 112-116°/0.7-0.8 mm. IR (smear): 2730-2560 and 1760 cm^{-1} ; >C=CH 1660, and 860 cm^{-1} . PMR (CCl_4): three vinylic Me's (two 3H, s, 1.61, 1.68 and 3H, d, 2.16 ppm, $J = 1.5$ Hz); $\text{Me}-\underset{\text{Me}}{\text{C}}=\text{CH}-$ (1H, m, 5.03 ppm); $-\text{C}=\text{CH}_2\cdot\text{CO}_2\text{H}$ (1H, s, 5.68 ppm) and CO_2H (1H, bs, 11.26 ppm). [Lit.^{41a}: b.p. 153°/13 mm, PMR⁵⁸].

Cyclogeranic acids (LXII). Geranic acid (30 g, 0.18 mole) was taken up in dry CH_3NO_2 (75 ml). MeSO_3H (3 g in 25 ml CH_3NO_2) acid solution was added slowly (0.5 hr) and the mixture allowed to stir at room temperature (28° for 5.5 hrs, when solid cyclogeranic acid separated out. Excess of CH_3NO_2 was flashed off, the concentrate was taken up in Et_2O (100 ml), washed with H_2O (10 ml x 3), brine (10 ml x 2) dried and the solvent distilled off to furnish a crude mixture of cyclogeranic acids (28.6 g, 96%) as revealed by its PMR. b.p. 85-96-98°/0.7 mm. IR (Nujol): COOH 2640, 1760 cm^{-1} ; $=\text{CH}_2$ 896 (w) cm^{-1} ; >CH 870 (w) cm^{-1} . PMR (CCl_4): quaternary Me's (three 3H, s, 0.96, 1.01, 1.15 ppm);

TABLE 5

Sl.No.	Aldehyde used (LIV)	Phosphonium salt (LV)	Base and reaction conditions used.	Results
1	(0.200 g, 0.00133 mole)	(1.6797 g, 0.0038 mole)	K-t-OBu (0.784 g, 0.007 moles) was freshly prepared in THF, (N ₂). The reaction mixture was stirred and refluxed for 48 hrs. TLC (solvent: C ₆ H ₆) indicated starting compound, when sprayed with DNP solution.	No reaction.
2	(0.400 g, 0.00266 mole)	(1.4483 g, 0.003 mole)	K-t-OBu (0.336 g, 0.003 mole), (10 ml) of dry DMSO (freshly distilled over CaH ₂), stirred for 15 hrs at room temp. (28°). TLC indicated no starting aldehyde. After usual work up, PMR, IR and mass was recorded.	No Wittig product was formed. No attempt was made to identify the product formed.
3	(0.200 g, 0.0013 mole)	(0.942 g, 0.002 mole)	Methyl sulfinyl carbanion (0.002 mole) was prepared as reported ³⁸ DMSO (15 ml), Heated for 8 hrs at 60°. After usual work up, TLC (solvent: C ₆ H ₆) indicated the presence of starting aldehyde only.	No reaction.
4	(0.500 g, 0.00325 mole)	(1.884 g, 0.004 mole)	Phenyl Lithium (0.420 g, 0.0045 moles) was added to a stirred solution of salt in Et ₂ O (40 ml), stir at -10° (ice-salt) for 45 mins. and added the aldehyde. Phosphorane colour disappeared (1.5 hr). TLC (1:1 C ₆ H ₆ in pet. ether) indicated no starting aldehyde. After usual work up, IR, PMR and mass of the distilled compound was recorded.	No Wittig product was formed. No attempt was made to assign the structure of the compound formed.

$\text{CH}_3\text{-C=CH-}$ (3H, s, 1.71 ppm); $\text{CH}_3\text{-C=C-}$ (3H, s, 2.0 ppm) and $\text{CH}_3\text{-C=CH}$ (1H, bs, 5.55 ppm) and traces of -C=CH_2 , weak, peaks in the region 4.66 - 4.83 ppm).

cis-Dihydrocyclogeranic acid⁴² (LXIII, R=H): Mixture of cyclogeranic acids (15.1 g) was hydrogenated in gl. AcOH (120 ml), over presaturated 5% Rd/C catalyst (1.5495 g) which consumed 2.32 liters of H_2 at $28^\circ/715$ mm (~1 equiv.) during 13 hrs. Usual work up and distillation afforded the required acid (14.57 g, (96%) b.p. $115^\circ/1.6 - 2$ mm.

IR(Nujol): COOH 2750, 2680 and 1780 (b) cm^{-1} .

PMR (CCl_4): two quaternary Me's (two 3H, s, 1.02 and 1.04 ppm); $\text{CH}_3\text{-CH-}$ (3H, d, 0.96 ppm, $J = 7$ Hz); $\text{-CH-CH}_2\text{CO}_2\text{H}$ (1H, d, 2.24 ppm, $J_{\text{a,e}} = 5$ Hz) and COOH (1H, bs, 10.58 ppm) [Lit.⁴² m.p. $71-2^\circ$, IR⁵⁹].

cis-Dihydrocyclogeraniol (LXIV)⁴²: was prepared by the reported LAH (12 g, 0.16 mole, 54% active) reduction of dihydro cyclo-methylgeranate (11.3 g, 0.61 mm) to the required cis-alcohol (8.437 g, 88%) b.p. $62^\circ/2.5$ mm. IR (smear): OH 3380 and 1020 cm^{-1} . PMR (CCl_4): two quaternary Me's (6H, s, 1.03 ppm); $\text{CH}_3\text{-CH-}$ (3H, d, 0.96 ppm, $J = 8$ Hz); $\text{-CH-CH}_2\text{OH}$ (2H, d, 3.61 ppm, $J = 4$ Hz) and $\text{-CH}_2\text{-OH}$ (1H, s, 3.55 ppm, D_2O exchange) [Lit.⁴²: b.p. $100-2^\circ/11$ mm, IR⁵⁹].

Dihydro cyclogeranyl bromide (LXV): Its preparation was attempted using five different reagents, which did not yield the required product (LXV). Details of these experiments won't be described and the literature methods were followed.

Finally the required bromide (LXV) was obtained using NBS and β_3P .

(a) Using PBr_3 , Et_2O : Dihydrocyclogeraniol (0.506 g, 0.003 mole) in (10 ml) of dry Et_2O , cooled $0^\circ C$ (ice bath) and added a solution of PBr_3 (0.864 g, 0.0032 mole, in 10 ml of Et_2O) with stirring. The reaction mixture did not show the presence of any non-polar compound (TLC) even when the mixture was stirred for 16 hrs at room temperature (28°). After usual work up, the starting alcohol (LXIV) was also not recovered.

(b) Using PBr_3 , C_6H_6 and pyridine⁴⁴: Dihydrocyclogeraniol (0.154 g, 0.001 mole) in (5 ml) of dry C_6H_6 , a drop of pyridine was added and chilled in ice/salt bath. A solution of PBr_3 (0.100 g, 0.00034 mole, in 2 ml of dry C_6H_6) was added slowly (N_2) and with stirring. It was allowed to attain room temperature (28°) and left for 10 hrs. TLC (solvent C_6H_6) revealed no non-polar compound and hence the reaction was abandoned without work up.

(c) Using 48% HBr, H_2SO_4 acid⁴⁵: (0.480 g, 0.003 mole) of the alcohol (LXIV) was added to a mixture of HBr (48%, 1.05 g, 0.006 mole) and (0.18 ml) of conc. H_2SO_4 acid and refluxed the mixture for 1 hr. TLC (solvent: C_6H_6) indicated no starting material. After usual work up, a dark colour compound was obtained which could not be distilled.

(d) Using Br_2 , Ph_3P and DMF⁴⁶: To a stirred solution of

dihydro cyclogeraniol (0.1000 g, 0.00064 mole) in dry DMF (3 ml), Ph_3P (0.196 g, 0.00075 mole) was added a solution of Br_2 (0.120 g, 0.0384 mole, in 1 ml of DMF) under (N_2), no orange colour was formed so 0.03 ml of Br_2 was added again to get an orange tinge. The reaction temperature was not allowed to increase more than 55° . After usual work up, the starting alcohol (LXIV) was recovered as indicated by TLC.

(e) Via tosylate and refluxing with LiBr and Me_2CO ⁴⁷:

(100 mg, 0.00064 mole) of the alcohol was converted into its tosylate, using (2 ml) of pyridine and (0.214 g, 0.00128 mole) of tosyl chloride. The tosylate was identified by its PMR (CCl_4): two quaternary Me's (two 3H, s, 0.90 and 0.96 ppm), $\text{CH}_2\text{-CH}$ (3H, d, 0.84 ppm, $J = 7$ Hz), $\text{CH}_3\text{-C}_6\text{H}_4$ (3H, s, 2.46 ppm), $\text{-CH}_2\text{-OTs}$ (2H, d, 2.46 ppm, $J = 4$ Hz) and $\text{CH}_3\text{-C}_6\text{H}_4\text{-}$ (4H, q, 6.81 - 7.70 ppm).

Tosylate (0.14 g) in (10 ml) of dry Me_2CO , 1.2 g of LiBr was refluxed on H_2O bath for 22hrs. After usual work up, a black coloured product was obtained which was filtered through a small alumina (10 g) column and eluted with pet. ether to give a non-polar compound which was found to be a mixture of olefins as indicated by PMR. No attempt was made to identify them.

(f) Using NBS, P_2S_5 and C_6H_6 ⁴⁸: To a mixture of (LXIV, 32 g, 0.1 mole), Ph_3P (36.2 g, 0.1 mole); (100 ml) of dry C_6H_6 in 250 ml three necked flask, fitted with a reflux

condenser and a mechanical stirrer was added (17.8 g, 0.1 mole) of NBS very slowly and with continuous stirring (2 hrs for addition of NBS) under N_2 . After 2 hrs of refluxing during the addition of NBS, it was cooled and filtered. Solvent was flashed off to furnish the crude bromide containing some Ph_3PO . It was filtered through a SiO_2 -gel/IIb (200 g) column and pet. ether eluted 11g. of the required bromide, b.p. $65-75^\circ/2-5$ mm, IR (smear) no OH band. PMR (CCl_4): two quaternary Me's (6H, s, 1.00 ppm); CH_3-CH (3H, d, 0.97 ppm, $J = 7$ Hz) and $CH-CH_2-Br$ (2H, complex multiplet centered at 3.4 ppm). Mass spectrum: m/e 220 (Found: C, 55.49; H, 8.13 and Br 37.30. $C_{10}H_{19}Br$ requires: C, 54.8; H, 8.58 and Br, 36.53%).

Attempted Grignard reaction of *cis*- dihydrocyclogeranyl bromide (LIV) and ethyl levulinate (LXVI): Mg (.12 g, 0.005 mole) was covered with (20 ml) of dry Et_2O and a crystal of iodine was added, followed by dihydro cyclogeranyl bromide (1.095 g, 0.005 mole) in 10 ml of dry Et_2O . The solution was stirred and refluxed for 4 hrs (N_2). No Grignard reagent formation was observed. To the above solution was added C_6H_6 (dry, 30 ml) and the whole mixture was stirred and refluxed for 36 hrs to effect the preparation of Grignard reagent. The Grignard reagent was transferred under (N_2) into a dropping funnel although some unreacted Mg was left. This was added to ethyl levulinate (0.653 g, 0.0045 mole) in (15 ml) of dry C_6H_6 . Cooled to $-5 - 0^\circ$ (ice/salt), in about one hour.

The reaction mixture was stirred under (N_2) for 2 hrs and then at room temperature (28°) for 16 hrs. The Grignard complex was decomposed with dil. H_2SO_4 . The organic layer was separated and the aqueous phase was extracted with Et_2O (40 ml x 3), washed with 5% $NaHCO_3$, H_2O , brine dried and solvent stripped off to furnish the crude product (1.742 g). TLC (solvent: 10% $EtOAc$ in C_6H_6) revealed the presence of both the starting materials indicating that no reaction had taken place. The product was chromatographed over SiO_2 -gel/IIb (75 g, 50 cm x 1.2 cm) recovering both the starting materials.

Attempts to prepare diazoketone of (LXIII, R=H): *Cis*-dihydro-cyclogeranic acid (1.5 g) was taken up in (25 ml) of dry C_6H_6 containing two drops of pyridine, cooled to 0° and added (2 ml) of $(COCl)_2$ taken in 15 ml of dry C_6H_6 . The reaction mixture was left at room temperature (32°) for 10 hrs and the solvent was flashed off to give crude acid chloride (LXIII, R=Cl, 1.09 g). IR (smear): $C=O$ 1790 cm^{-1} . PMR (CCl_4): two quaternary Me's (6H, s, 1.00 ppm); $CH_3\cdot CH$ - (3H, d, 0.96 ppm, $J = 7\text{ Hz}$) and no acid proton.

To the above acid chloride, in (15 ml) of dry Et_2O , was added an ethereal solution of CH_2N_2 , with swirling at 0° (ice bath). After 3 hrs of stirring, a little sample was withdrawn for checking its IR. No diazoketone band at 2100 cm^{-1} was present, indicating that no reaction had

taken place. Stirring was continued for 14 hrs more and the solvent was flashed off under suction (50 mm) at room temperature to give reaction product. IR of the crude product (smear): -COCl 1790 cm^{-1} , no $\text{CH=N=N}^{\ast-}$ band.

Triphenyl geranyl phosphonium bromide (LXVII):

Geranyl bromide: Geraniol (6.6244 g, 0.043 mole) in dry Et_2O (25 ml) was cooled to -10° (ice/salt) and a solution of freshly distilled PBr_3 (1.5 ml, 0.045 mole) in 10 ml of Et_2O was added in 0.5 hr. The reaction mixture was allowed to stir at room temperature (32°C) for 45 minutes. The product was poured on crushed ice, extracted with Et_2O (50 ml x 3), washed with 5% NaHCO_3 (5 ml x 3), H_2O (20 ml x 3), brine (4 ml x 2), dried and the solvent flashed off to furnish 9.3386 ($\sim 100\%$) of the geranyl bromide. IR (crude product, smear): no OH band. PMR (CCl_4): three $\text{CH}_3\text{-C=C}$ (three 3H, s, 1.61, 1.69 and 1.75 ppm); two, $\text{CH}_2\text{-C=C}$ (4H, d, 2.06 ppm, $J = 3\text{ Hz}$); $\text{-C=CH}_2\text{-Br}$ (2H, d, 3.95 ppm, $J = 9\text{ Hz}$), two, -C=CH-CH_2 (2H, t, 5.51 ppm) and -C=CH-CH_2 (1H, m, 5.06 ppm).

Triphenyl geranyl phosphonium bromide (LXVII): Geranyl bromide (crude product, 9.338 g, 0.043 mole) was added during 0.5 hr, to Ph_3P (11.268 g, 0.043 mole) and allowed to stir at room temperature (32°C) for 64 hrs. The solid precipitated was filtered, washed with C_6H_6 , pet. ether and dried under vacuum to furnish (LXII; 17 g) m.p. $170-3^\circ$ [lit.⁴⁹ m.p. $171-73^\circ$].

Ethyl 4,7,11-trimethyl dodeca-4,6,10-trien-oate (LXVIII):

To a stirred suspension of triphenyl geranyl phosphonium bromide (4.79 g, 0.0124 mole) in (60 ml) of dry Et_2O was added (11 ml) of the ethereal solution of PhLi (1.512 g, 0.015 mole) through a septum. Blood red coloured phosphorane formed was stirred at ice- H_2O bath for one hour. Ethyl levulinate (1.696 g, 0.0124 mole) was added slowly under (N_2). Red colour due to the phosphorane disappeared in 10 minutes and the mixture was stirred for another 45 minutes. $\text{Ph}_3\text{P}=\text{O}$ -formed was filtered off and washed with Et_2O . The total filtrate was washed with H_2O (10 ml x 3), brine (15 ml x 3), dried and solvent stripped off, to furnish the crude Wittig product (2.34 g). Distillation afforded 1.315 g of the pure Wittig product besides 0.18 g of the lower boiling fraction. Some residue was left in the distillation flask. b.p. $123^\circ/1$ mm. Analytical sample was prepared by filtration of the Wittig product through a small column of Al_2O_3 (20 g) and eluting with pet. ether. IR (Fig.30). PMR (Fig.31). Mass spectrum: important ions at m/e 264 (M^+ 8%), 99 (100%), 43 (33%), 41 (30%), 154 (56%), 91 (55%), 107 (48%), 77 (45%), 69 (40%), 149 (38%) (Found: C, 77.32; H, 10.10. $\text{C}_{17}\text{H}_{28}\text{O}_2$ requires: C, 77.22; H, 10.67%).

Ethyl 5 [2-(1,3,3-trimethyl cyclohex-1-ene)]-4-methyl pent-4-oate (LXVIII). (3.4, 0.0134 mole) of the Wittig product

(LXVIII) was taken in (10 ml) of dry CH_3NO_2 . To this a solution

of MeSO_3H (0.400 g) in (5 ml) of CH_3NO_2 , was added with stirring at room temperature (32°). The dark coloured solution was stirred for 1.5 hr. CH_3NO_2 was flashed off and the concentrate was taken up in Et_2O (100 ml) washed with 5% NaHCO_3 (5 ml x 2), H_2O (10 ml x 2), brine (10 ml x 2) and dried. Et_2O was stripped off and the concentrate distilled to yield 2.8328 g of the cyclised product. b.p. $135^\circ/1$ mm. IR (Fig.32). PMR (Fig.33). Mass spectrum: important ions at m/e 264 (M^+ 65%), 208 (100%), 161 (54%), 203 (25%), 175 (20%), 249 (20%), 108 (14%), 209 (13%), 219 (13%) and 43 (12%). (Found: C, 77.65; H, 10.64. $\text{C}_{17}\text{H}_{28}\text{O}_2$ requires: C, 77.22; H, 10.67%).

5[2-(1,3,3-Trimethyl cyclohex-1-ene)]-4-Methyl pent-4-enoic acid (LXX): (2.6287 g) of the cyclised ester (LXIX) was added to (6 g) of KOH dissolved in (30 ml) of EtOH. The mixture was refluxed over steam bath for 2.5 hr under (N_2). The reaction mixture was cooled and acidified with 2N HCl to regenerate the acid. Aqueous solution was extracted with Et_2O (30 ml x 3), washed with brine (10 ml x 2), dried and the solvent flashed off to furnish 2.17 g of the acid after distillation b.p. $160-165^\circ$ (bath)/1 mm. IR(smear): COOH 2680 and 1710 cm^{-1} . PMR (CCl_4): two quaternary Me's (two 3H, s, 0.92 and 0.94 ppm); two $\text{CH}_3\text{-C=C}$ (two 3H, s, 1.51 and 1.50 ppm); HC=C- (1H, m, 5.7 ppm); COOH (1H, broad m, 9.7 ppm) and a broad singlet at 2.45 ppm (4H).

α -Cyclogeranyl- γ -valerolactone (LXXI): 2 g of the unsaturated acid (LXX) was taken up in (10 ml) of nitromethane and a

solution methanesulphonic acid (1 g/5 ml of CH_3NO_2) was added slowly and stirred under (N_2) for 1.5 hr at room temperature (32°). Excess of CH_3NO_2 was distilled off and the crude product taken up in Et_2O (60 ml), washed with 5% NaHCO_3 (10 ml x 3), to recover the unreacted acid. The neutral Et_2O extract was washed with H_2O (10 ml x 3), brine (15 ml x 2), dried and the solvent removed to give a crude product which was distilled to furnish 1.48 g of the required lactone (LXXD) b.p. $160-165^\circ$ (bath)/1 mm.

SUMMARY

Four different routes towards the synthesis of allohimachalol have been investigated. However, allohimachalol could not be synthesised, instead abnormal products were obtained which were fully identified.

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