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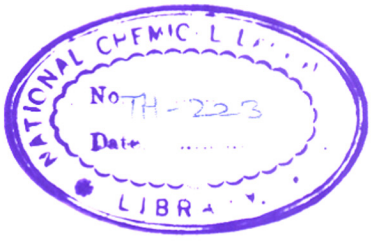
Prof W Cocker
(Dublin)
(Orlando)

SYNTHETIC STUDIES TOWARDS SESQUITERPENES

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



by

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JUNE 1977

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TO MY PARENTS

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C O N T E N T S

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

The author is grateful to Dr. S.N. Kulkarni, Scientist and Project Leader, National Chemical Laboratory, Poona, for suggesting the problem and for his constant and able guidance throughout the course of this investigation. He also thanks the senior colleagues in the Department, particularly Drs. K.G. Gore, B.V. Bapat, G.D. Joshi and Ms. A.B. Sahsrabudhe and K.V. Kale for their help and cooperation.

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He is also grateful to the Director, National Chemical Laboratory, Poona, for permitting to present this work in the form of a thesis; and to the C.S.I.R., New Delhi, for the financial assistance.

V. K. BELAVADI

POONA
June 1977.

SAN/

GENERAL REMARKS

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

(2) Optical rotations are measured in chloroform solution using sodium light (5893 A) as the source on Perkin-Elmer 141 polarimeter. Concentrations are expressed in gms/100 ml. of the solution.

(3) Figure numbers, chart numbers etc. given in each chapter refer only to that particular chapter.

(4) NMR spectra are recorded in carbon tetrachloride solution, using tetramethyl silane as the internal standard on a T-60 Varian instrument and all the chemical shifts are expressed in δ units.

(5) The UV spectra are recorded in methanol on a Perkin-Elmer 350 spectrophotometer.

(6) The IR spectra of liquids are recorded as smears and of solids as nujol mulls on a Perkin-Elmer infrared spectrophotometer model 221, with sodium chloride optics.

(7) Mass spectra was recorded on a CEC-2-110 B double focussing spectrometer using direct inlet system.

(8) GLC was run on an AIMIL-NCL dual column gas chromatograph, using hydrogen as the carrier gas.

(9) The list of references pertaining to each chapter is given at the end of that chapter.

INTRODUCTION

A BRIEF REVIEW OF TOTAL SYNTHESES AND BIOGENESIS OF CADALENE TYPE OF SESQUITERPENES

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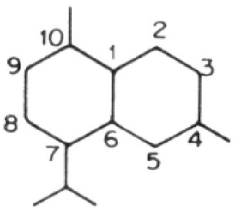
The group of naturally occurring compounds containing 15 carbon atoms and derivable from mevalonic acid *via* farnesyl pyrophosphate (FPP) are grouped under sesquiterpenes. They offer a truly remarkable variety of structural goals to synthetic chemist. Within this, rather restricted class of organic compounds one finds substances ranging from common to the exotic.[1] Various sesquiterpenes are known, which contain three, four, five, six, seven, nine, ten and eleven carbon atom rings. A high degree of stereochemical subtlety is encountered as members of the class are known, which possess as many as eight asymmetric centres. Because of this wide diversity of structural types, both structural and stereochemical, the sesquiterpene field is an excellent arena for testing and refining of new synthetic methods and concepts.

The fairly large number of sesquiterpenes, which possess the basic carbon skeleton 1 ('cadalene' skeleton) have by convention been divided into four classes or subgroups, differing only in the relative stereochemistry at C_1, C_6 and C_7. Thus the cadinane type (2) and bulgarene type (3) sesquiterpenes possess a *trans*-fused six-membered rings and differ only in the relative stereochemistry at C_7 (stereochemical orientation of the isopropyl group or the related side chain). On the other hand in muurolane (4) and amorphanes (5) the decalin system is *cis*-fused. Again these two types differ in the relative stereochemistry at C_7.

The four sesquiterpenoid classes mentioned above are mainly constituted of olefinic hydrocarbons and alcohols. Recently, compounds

CHART I



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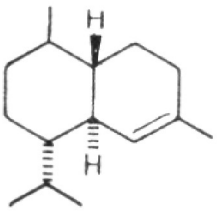

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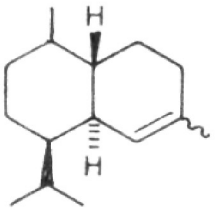

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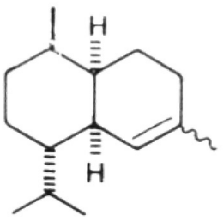

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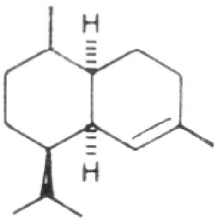

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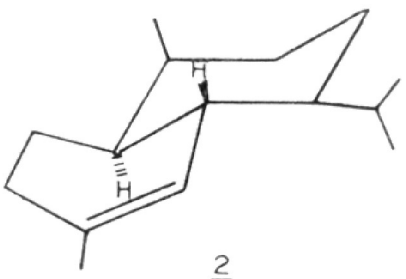

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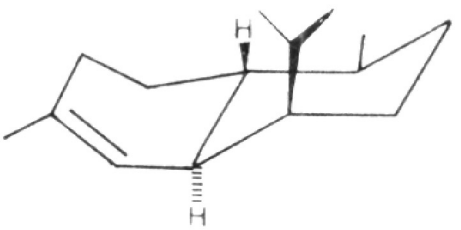

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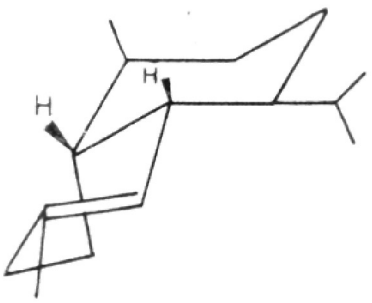

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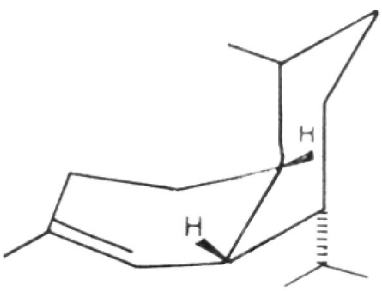

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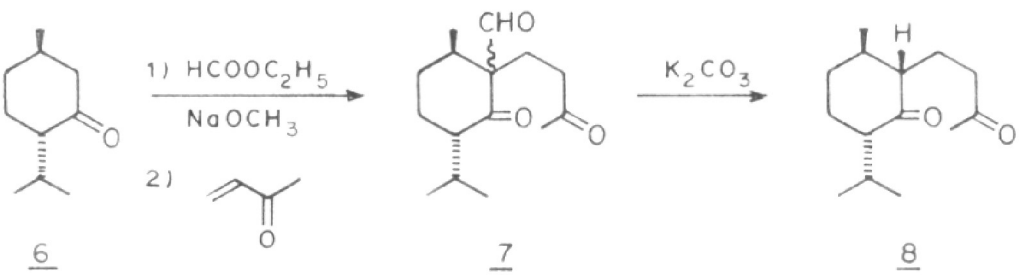
of this class with a -NC, -NHCHO and -NCS grouping have also been reported[2] to occur naturally in 'Halichondria' species. Structurally speaking many of the individual members of this class are very closely related and often differ from one another, only in the position of an olefinic double bond and/or in a diastereomeric sense. Because of this, it has been often difficult to separate mixtures of these types of compounds into individual components and the structural and stereochemical elucidation of cadinane and related sesquiterpenes was in the past often carried out with impure materials. Consequently the chemical literature dealing with this class of compounds contains many conflicting and erroneous reports. A classical and perhaps extreme example of this involves the naturally occurring olefinic alcohol, δ-cadinol. Since its isolation in 1922, no fewer than seven different proposals have been put forward regarding the structure and stereochemistry of this compound; the latest[3] being that δ-cadinol is in fact a muurolene derivative. However, with the advent of innumerable modern and sophisticated techniques, at least many of the old errors are in the process of being rectified. A few among these techniques like ORD, CD, high resolution mass spectra, INDOR technique etc. have been widely used to ascertain the structure and stereochemistry. X-ray diffraction too has lately invaded the area of natural products.

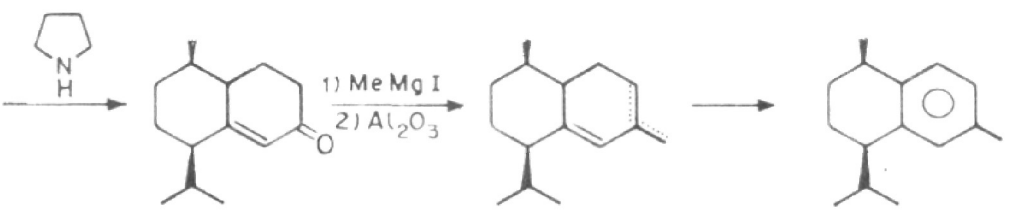
Up to the present time relatively little work has been reported concerning the synthesis of cadinane and related sesquiterpenoids. Only a few of the many naturally occurring compounds of this

CHART II

Scheme I



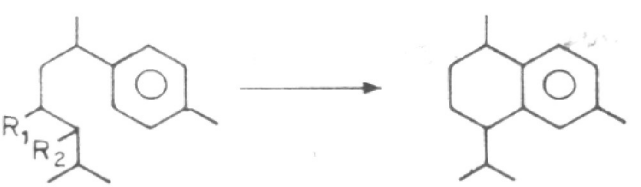
6 7 8



9 10 11

Scheme II

12, $R_1 = OH$, $R_2 = H$
13, $R_1 = H$, $R_2 = OH$



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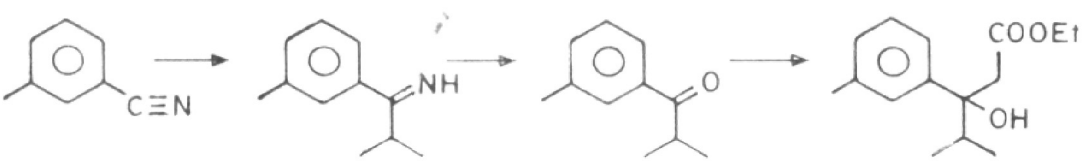
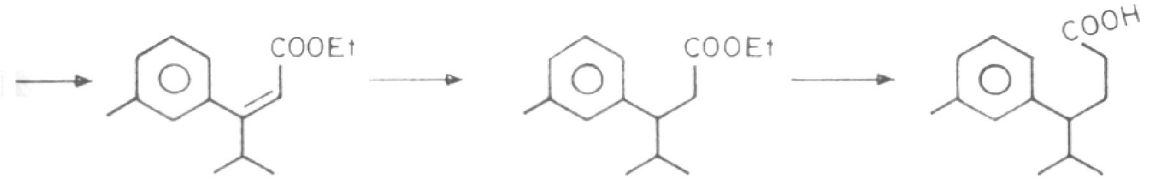
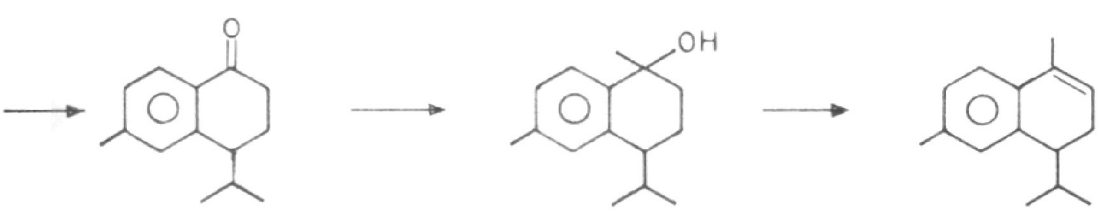


15 16 17 18



19 20 21



22 23 24

class have been synthesised. In this chapter we document various approaches made towards the synthesis of these skeletons. A wide variety of transformation within the subgroup as well as interconversion from one subgroup to the other are known. We will document only those transformations, which are biogenetically significant.

Calamenene

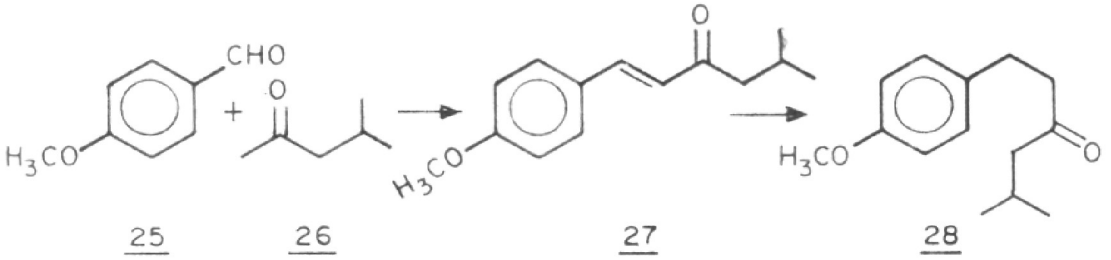
The Ladwa-Joshi-Kulkarni synthesis of (+) calamenene[4] the optical antipode of the more commonly occurring terpene is outlined in scheme I. (-) Menthone (6) was converted into diketoaldehyde (7) by the method of Corey and Nozoe. Deformylation of (7) with aqueous potassium carbonate gave dione (8) which was cyclised with pyrrolidine to enone (9). Compound (9) was methylated and dehydrated affording a mixture of diones (10). Selenium dehydrogenation of this mixture gave (+) calamenene in 80% yield. This compound (11) was earlier[4] assigned trans-structure, but later revised to cis based on a number of data.[5] The discussion on this subject is deferred to the next chapter. Calamenene has also been synthesised by cyclisation of compounds 12 and 13.[6,7] The cyclisations were induced by polyphosphoric acid (PPA).

(+)∝-Calcorene (24)

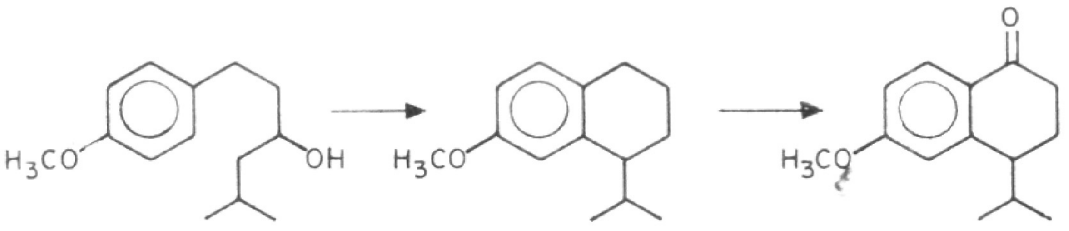
The only synthesis of (+) ∝-calacorene (24) reported[6] is depicted in scheme II. Meta-tolyl isopropyl ketone (17) is obtained from 15, via imine (16).[8] Condensation with ethyl chloroacetate in presence of magnesium[9] gave 18 which was dehydrated in presence of

CHART III

Cheme III

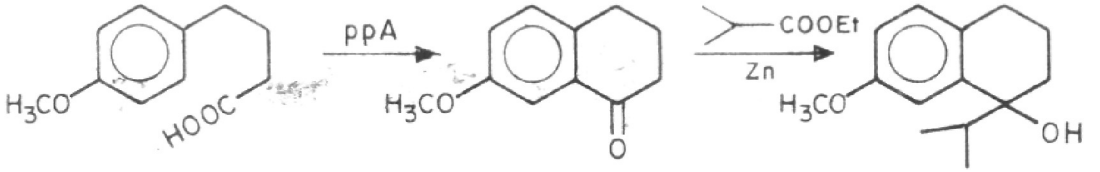


25 26 27 28

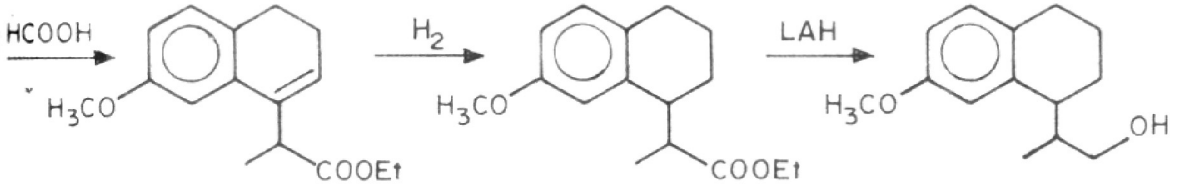


29 30 31

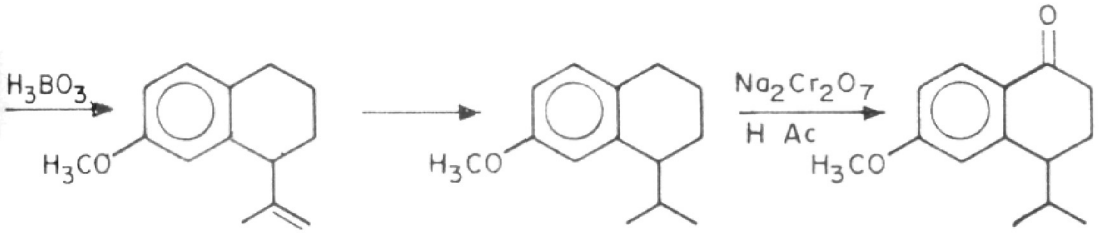
Scheme IV



32 33 34



35 36 37



38 30 31

p-toluene sulfonic acid to 19. This on hydrogenation gave 20; 20 on reduction, followed by bromination (PBr_3) and carbonotation of the organomagnesium derivative of bromide gave the acid 21. PPA cyclisation of 21 gave tetralone 22, which on reaction with methyl magnesium iodide, and dehydration of 23 (phosphoric acid) gave (+) α-calacorene (24).

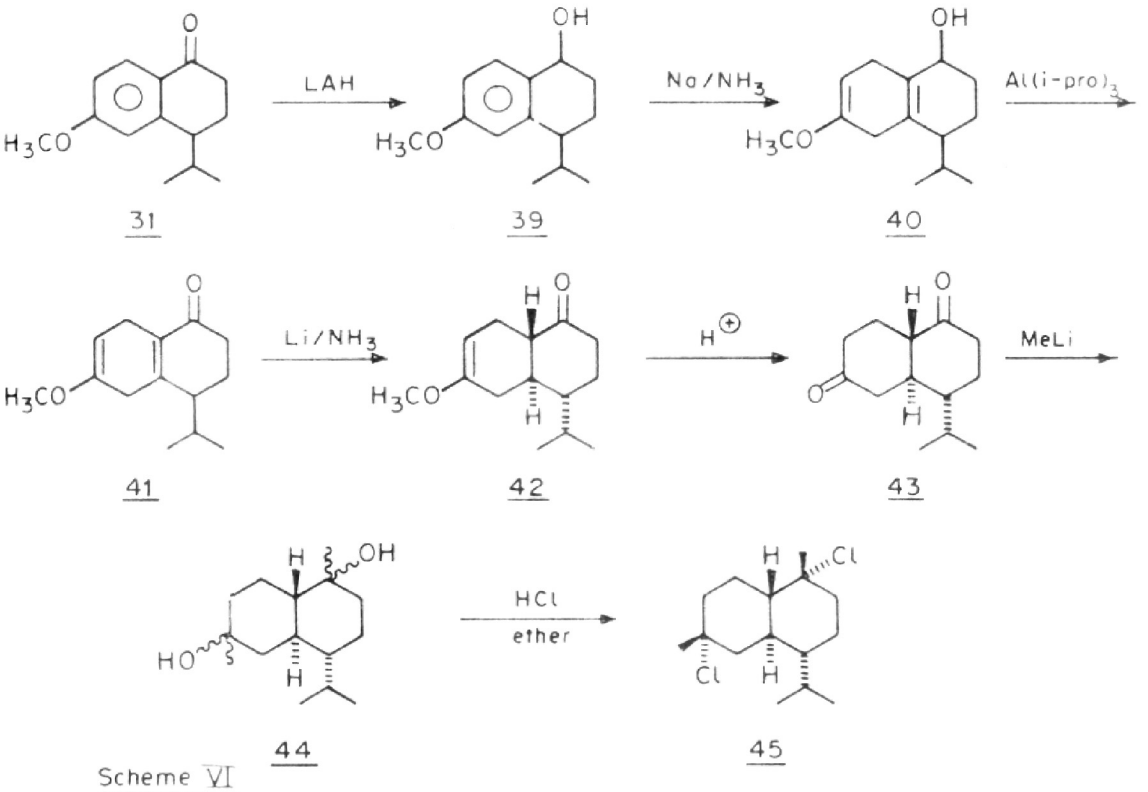
Cadinene dihydrochloride

The first total synthesis of (±) cadinene dihydrochloride was reported in 1960 by Rao et al.[10,11] The starting ketone, 4-isopropyl-6-methoxy-1-tetralone (31) has been previously synthesised by two different routes[12,13] as shown in scheme III and IV. Although the latter synthesis is more lengthy, it is reported[13] that tetralone (31) may be obtained in 45% yield based on acid (32).

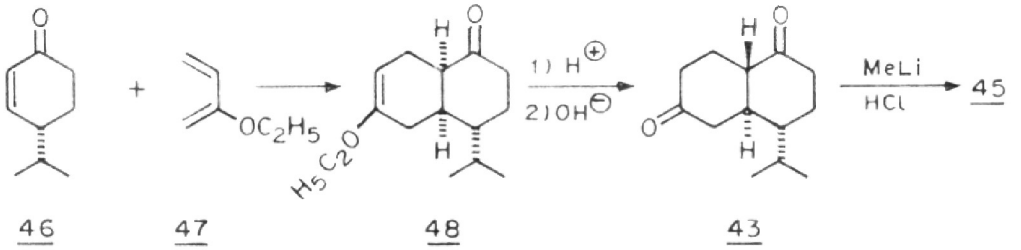
For the synthesis of (±) cadinene dihydrochloride (scheme V) the Bangalore group, first reduced the tetralone (31) to the secondary alcohol (39). Birch reduction of 39 afforded 40 which was submitted to Oppenauer oxidation to obtain enone (41). Lithium-liquid ammonia reduction of 41 gave 42 which was hydrolysed to diketone 43. Compound 43 with excess methyl lithium furnished the diol 44, which reacted with HCl in ether to give crystalline (±)-cadinene dihydrochloride (45), identical in all respects with the one obtained from (+) cadinene. The stereochemistry of the three centres in the crucial intermediate 43 is established in the metal ammonia reduction of 41. Mechanistic considerations,[14] predict that the more stable product 42 will be formed predominantly. In any event the diketone 43 was identical

CHART IV

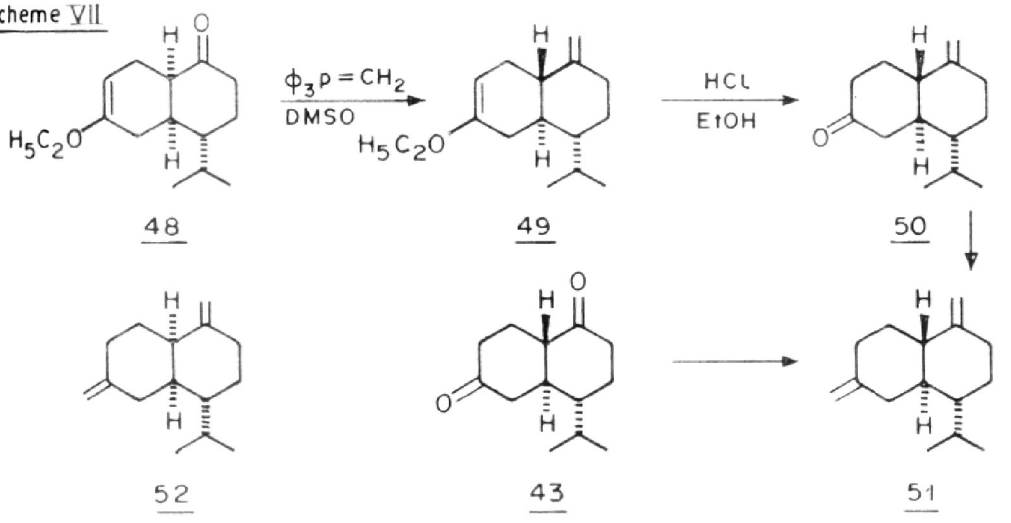
Scheme V



Scheme VI



Scheme VII



by IR spectroscopy with a sample of laevo-rotatory diketone obtained by degradation of ε-muurolene by Herout.[15] The second synthesis of (±) cadinene dihydrochloride by Soffer,[16,17] utilised somewhat a direct approach (scheme VI). Cryptone (46) on Diels-Alder reaction with 2-ethoxy butadiene (47) gave the anti-cis-enol ether (48), which upon hydrolysis and epimerisation with alkali gave as the main product (unspecified yield) anti-trans-diketone (43). The steric course of this reaction is critically controlled in the first step when the dienophile is attacked from the side of the molecule, opposite the bulky isopropyl group (equatorial). Diketone 43 was first converted by methyl lithium and then by HCl to (±) cadinene dihydrochloride (45).

The enol ether (48) is a very important synthetic intermediate. This has been successfully utilised for the synthesis of ε-cadinene[18] and γ_2-cadinene.[20]

(+) ε -Cadinene

The term ε-cadinene was erroneously applied to structure 52, Westfelt[19] showed that compound 52 in fact possesses a cis-ring junction and found that under traditional hydrochlorination conditions, compound 52 yields (-) cadinene dihydrochloride. However, the ring juncture point adjacent to the carbonyl group in 43 is epimerisable, ozonolytic degradation of 52 can still yield 43.

For the synthesis of ε-cadinene[18] (Scheme VII) octalone 48 was treated with methylene triphenyl phosphorane in DMSO to get the trans

methylene octalin 49, as shown by CD measurements. The Wittig reaction of *cis*-octalone enol ether (48) proceeds even under mildest conditions required for these reactions with inversion of configuration at C-1 bridge-head position. In these cases the addition reactions do not take normal course. The reaction of 48 with methylene triphenyl phosphorane presumably involves a fast reversible enolisation, followed by addition to give product 49. As one can visualise the reaction eliminates the need for a separate epimerisation step in the synthesis of trans decalin.

Acidic hydrolysis of 49 gave the methylene decalone 50, which was again submitted to Wittig reaction to obtain (+)ε-cadinene (51). Alternatively (51) can be obtained by direct bis-methylenation of dione 43.

(-)γ_2-Cadinene

The methylene octalone (50) has also been used for the synthesis of (-)-γ_2-cadinene by Soffer.[20] (Scheme VIII). The methylene decalone(50) was converted with excess methyl lithium to a mixture of tertiary alcohol (53) in which the axial epimer was expected to predominate. It has been pointed out that in addition reaction between methyl lithium and substituted cyclohexanones, the alkyl lithium reagent approaches preferentially from the least hindered equatorial side of the ketone group.[21] In accord with this, the crude carbinol (53) on treatment with thionyl chloride in pyridine gave (-)γ_2-cadinene (54). The formation of double bond at C_3-C_4 position of the trans-decalin system, in preference to the C_4-C_5 position has been explained in terms of hyper-conjugative[23]

and steric[22] effects.* A second total synthesis of (+)γ_2-cadinene (54) has been reported by Kelly,[24] which is along similar lines to that of Soffer. This is depicted in scheme IX. The keto enol ether (42) which was previously[11] obtained, as a liquid, was obtained as a solid. The fact that it remained unchanged after submitting to equilibrating conditions was a proof to the assigned stereochemistry. Reduction of 42 with LAH gave the alcohol 55 in 73% yield. Treatment of 55 with dilute methanolic solution of oxalic acid gave keto-alcohol 56 (95%). A Grignard reaction with methylmagnesium bromide converted 56 into a mixture of epimeric diols 57, one of which was obtained in 40% yield as a crystalline solid. Selective dehydration of 57 under mild conditions afforded the olefin 58. Oxidation of the olefin with Sarett reagent gave the enone 59, which was unchanged on submission to equilli-brating conditions. The enone 59 on Wittig reaction gave (+)γ_2-cadinene (54) in 90% yield.

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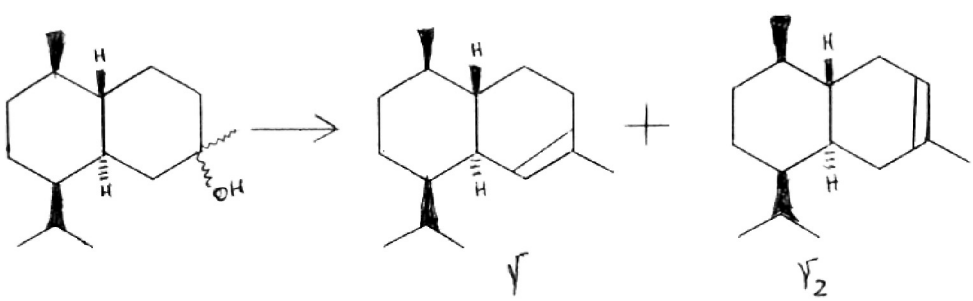
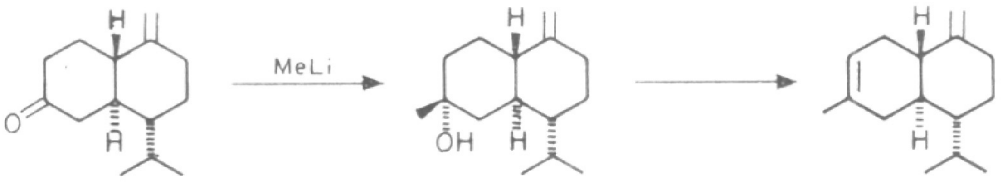
* This explanation did not however hold good during our synthesis of dihydrobulgarenes (see Chapter II). A mixture of both dihydro-γ-bulgarene and the corresponding γ_2-isomer was obtained on dehydration of the carbinol with acid. (Ratio γ; γ_2, 55:45).



γ γ_2

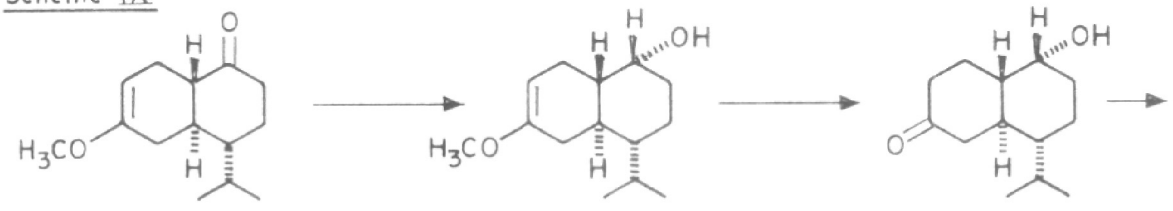
CHART V

Scheme VIII

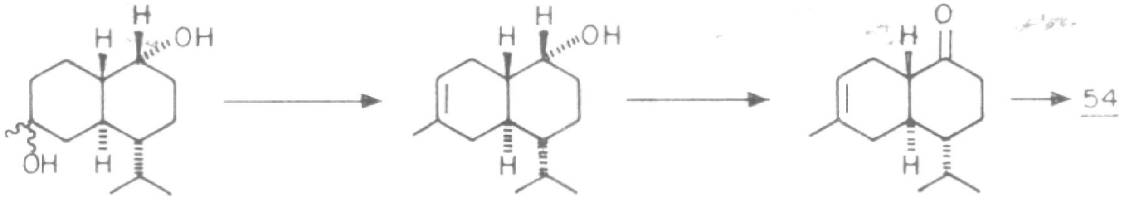


50 53 54

Scheme IX

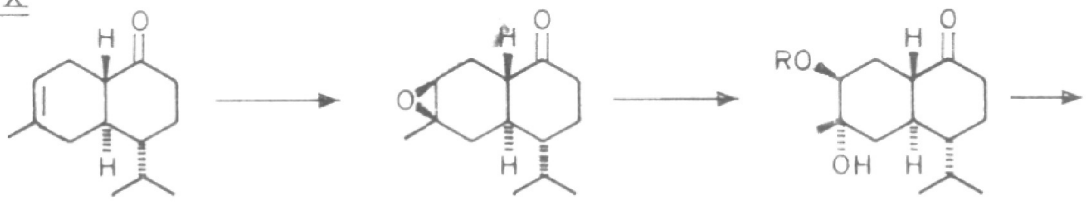


42 55 56

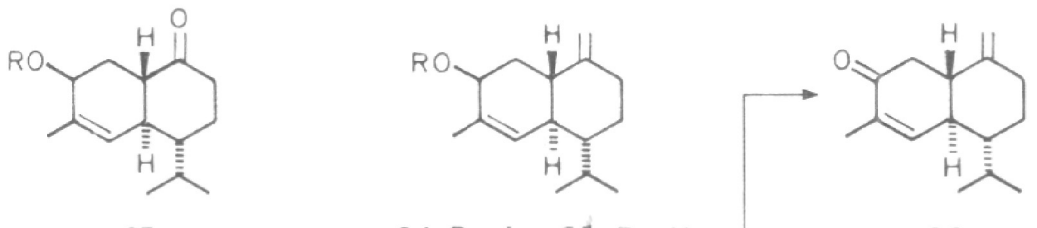


57 58 59 → 54

Scheme X



59 60 61, R = H; 62, R = Ac



63 64, R = Ac; 65, R = H 66

68 67

Synthesis of khusinol (old structure)

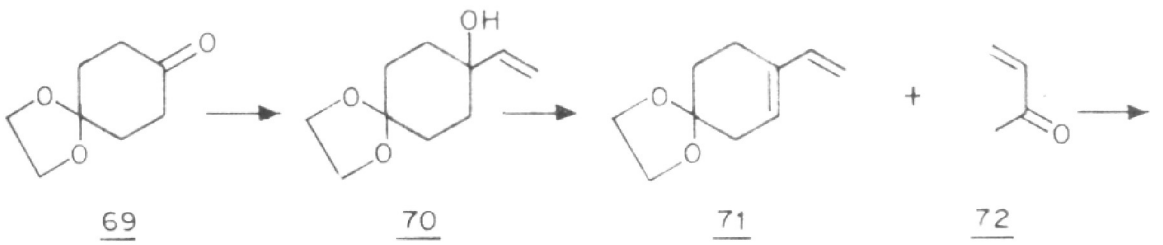
The enone (59) has also been used for the synthesis of khusinol (67) thereby confirming the revised structure (68) (scheme V).

Structure 67 for khusinol was adduced from chemical evidences.[26] More recently, however, the structure has been revised to 68 based on further chemical evidence and high resolution NMR.[27]

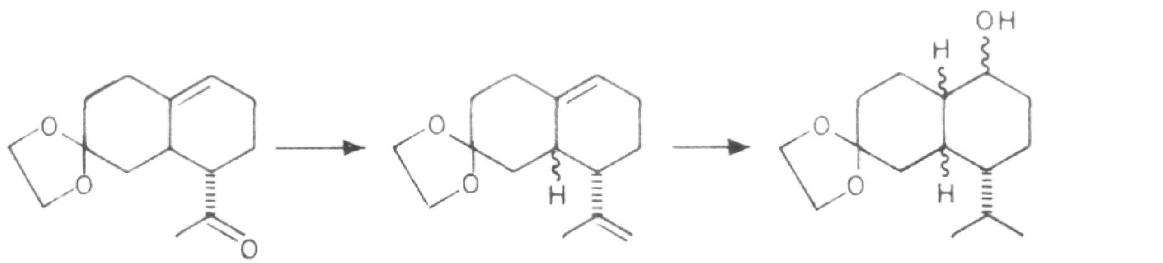
For the synthesis[25] of 67, the enone (59) was converted into the crystalline epoxide 60 by treatment with m-chloroperbenzoic acid. Hydrolysis of the epoxide afforded the crystalline diaxially oriented diol, 61. Acetylation of the latter and treatment of the resulting monoacetate (62) with phosphorous oxychloride gave the olefin (63). The fact that the NMR signal for vinylic proton in 63, appeared as singlet is proof that the double bond was introduced in the assigned position. The acetate was converted to the diene 64, through a modified Wittig reaction. As we have observed during our preceeding discussion decalones and octalones having the bridge-head position adjacent to the keto group undergo epimerisation during Wittig reaction (see refs. 28 and 29). This phenomenon has been observed in cis-fused compounds, naturally to give the more stable trans-product. The possibility of this type of epimerisation occurring in trans-fused decalones is theoretically not expected from stability point of the resulting cis product. In fact in case of 63, no cis-fused diene was formed as was evident from the NMR spectrum of the diene. The signal at 5.83 for the vinylic proton at C-5 appeared as a singlet. Reduction of the acetate (64) with LAH afforded the alcohol 65, which is the C_3 epimer of the desired compound (67). In order to get the

CHART VI

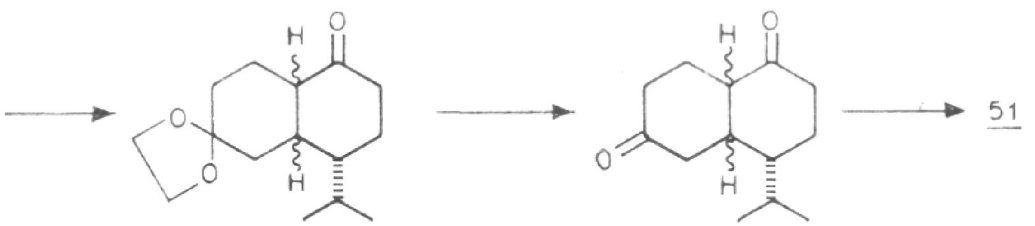
Scheme XI



69 70 71 72

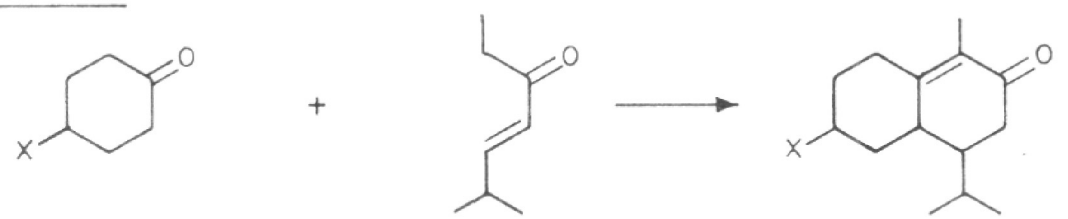


73 74 75

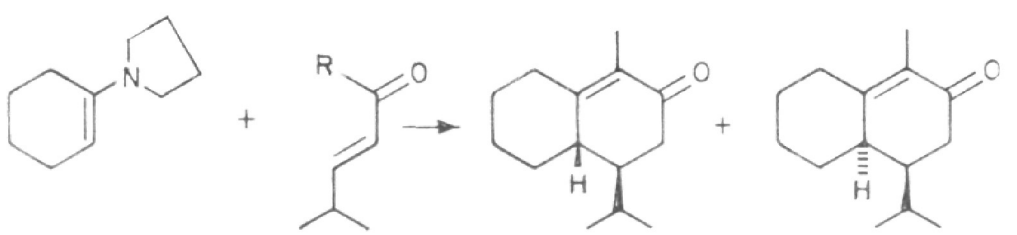


76 77 51

Scheme XII



78 79 80



81 82 83 84

desired compound with a α-hydroxyl function, 65 was oxidised with managanese dioxide to get α,β-unsaturated ketone 66. This on reduction with LAH gave 67 as a crystalline solid. The NMR signal of the C_3 proton was broadened by 13 Hz (HW) as a result of transformation from quasiaxial hydroxyl to quasi-equatorial hydroxyl (65 → 67). The synthetic compound did not agree with an authentic sample of khusinol (68).

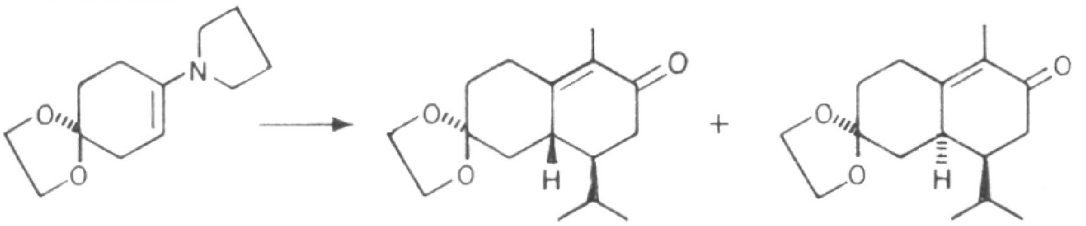
dl-Trans-δ-cadinene (Vig's approach)

A more recent application of Diels Alder reaction to the synthesis of dl-trans-δ-cadinene by Vig et al.[30] is outlined in Scheme XI. 4,4-Ethylenedioxy-1-vinyl cyclohexanol (70) was prepared by using ketal-ketone (69) and vinyl magnesium bromide. On dehydration with $POCl_3$ / pyridine, diene 71 was obtained, which on Diels-Alder reaction with MVK gave decalone 73. Orientation of the isopropyl group in 73 was fixed to equatorial position by using the method of Immer.[31] On Wittig reaction 73 gave 74 which on catalytic hydrogenation (1 mole of H_2), followed by hydroboration gave the alcohol 75, which was oxidised to ketone 76. Deketalisation gave the diketone 77, which was identical with diketone (43) obtained previously.[6] On Wittig reaction, the diketone gave dl-trans-δ-cadinene. No comparision with an authentic sample was made. Stereochemical ambiguities exist in this synthesis, since δ-bulgarene and δ-cadinene cannot be distinguished by ordinary means.

ε-Cadinene (Pier's approach)

A new approach towards the synthesis of cadinane and amorphane type of sesquiterpenoids hasbeen described by Piers.[39] This involves the

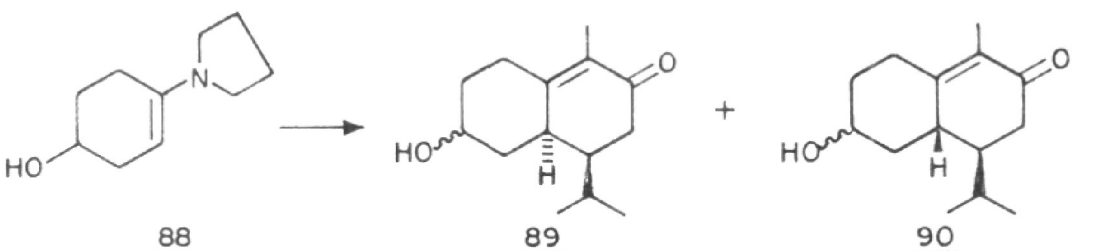
Scheme XIII



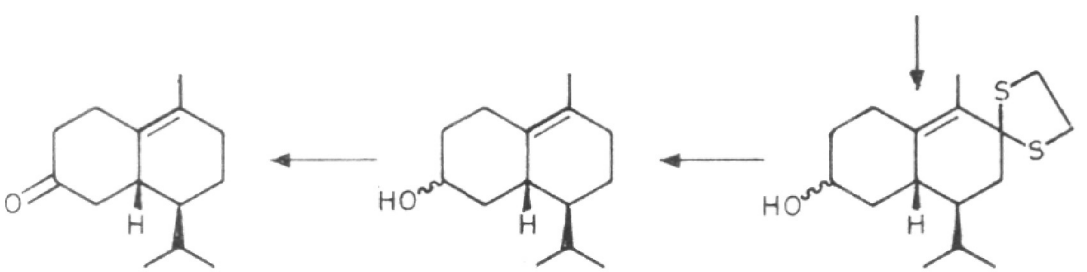
85 86 87

85(a) 88(a)

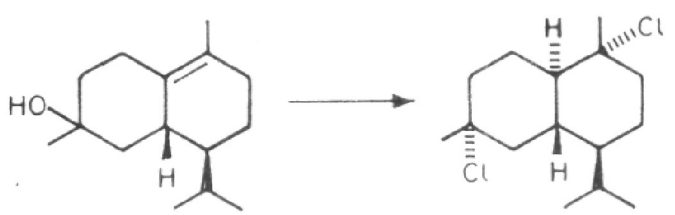
Scheme XIV



88 89 90



93 92 91



94 45

annelation of substituted cyclohexane derivatives (78) with (E)-2-methyl-3-hepten-5-one (79). Success of the reaction would give in one step 14 of the 15 carbon atoms necessary for the cadinanes and for related sesquiterpenoids. An appropriate functional group at C-4 (X) in the annelation product would then presumably allow for the introduction of the final required carbon atom.

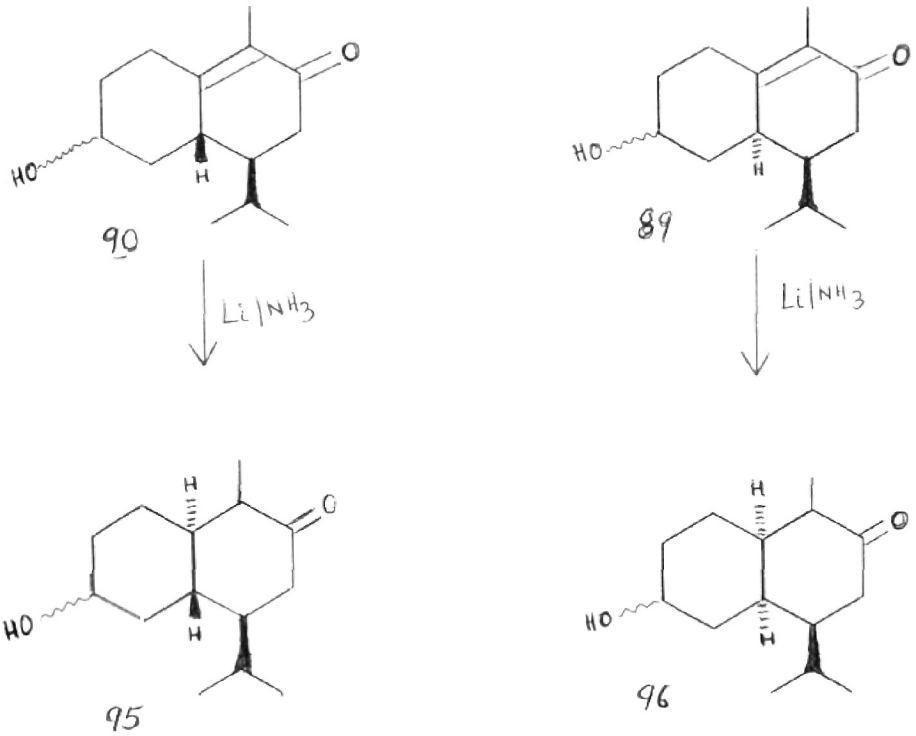
Attempted annelation of cyclohexanone, 2-methylcyclohexanone and 2-hydroxymethylene cyclohexanone with heptenone 79 using a variety of bases and reaction conditions proved unsuccessful. However, when pyrrolidine enamine of cyclohexanone (81) was allowed to react under carefully controlled conditions, the corresponding annelated product was formed in 83% yield as an epimeric mixture of 83 and 84 in the ratio of 7:3 (scheme XII). On the basis of conformational analysis octalone 83 containing an equatorially oriented isopropyl group, is expected to be more stable than octanone 84, containing an axially oriented isopropyl group. This was found to be the case by carrying out INDOR studies on hydrogenated products of 83 and 84.

Having found success in the annelation of cyclohexanone with heptenone (79), attention was diverted to the annelation of cyclohexanone derivative containing a substituent, suitable for the introduction of the last one carbon atom necessary for the synthesis of cadinane (or related sesquiterpenoids). The pyrrolidine enamine of 4,4 ethylene dioxy cyclohexane (85) was allowed to react with heptenone (79) under conditions similar to those used in the above condensation, but the annelated product (4:1 mixture) of octalones 86 and 87 was obtained in very poor yields (Scheme XIII).

It was felt that the ketal functionality with one of the carbon atoms necessarily axially oriented (85a) could be sterically interffering with the approach of the heptenone (79) to the β-carbon atom of the ring in enamine 85 (anti-parallel attack). However, this difficulty was circumvented by using the enamine of 4-hydroxycyclohexanone (88) which would presumably react with a conformation possessing an equatorially oriented hydroxyl group (88a). Condensation of 88 was realised after a number of variations. The annelation product was a mixture of hydroxyoctalones 90 and 89 in the ratio 7:3 (Scheme XIV).

The potential use of octalone (90) as an intermediate for the synthesis of cadinane type of sesquiterpenes is imminent. Octalone 90 was converted using ethane dithiol in presence of BF_3-etherate to the dithioketal (91). Desulfurisation of 91 with Ra/Ni gave the olefinic alcohol (92). Oxidation of 92 with chromium trioxide gave the keto-olefin (93) which in turn was converted by reaction with MeLi in ether to the tertiary alcohol (94). Treatment of the latter with anhydrous HCl in ether at 0° gave the racemic cadinene dihydrochloride (45). The enamine annelation approach to the synthesis of cadinane and/or related sesquiterpenoids as outlined above is attractive in terms of simplicity and efficiency. However, the general scheme does possess certain disadvantages. One of these is the production in the annelation reaction itself of diastereomeric products (90 and 89) which must be separated at an early stage of the overall synthetic sequence. The complication however is at least partially offset by the results obtained from the Lithium-liquid

ammonia reduction of the initially formed annelation products. The Li-liquid ammonia reduction of the initially formed-octalones (90 and 89) would produce a mixture of corresponding trans and cis fused decalones 95 and 96 (for detailed mechanistic consideration, see chapter II) .



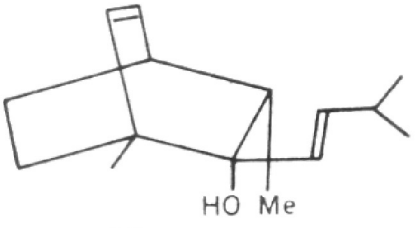
Separation at this stage, provides one with two distinct synthetic precursors, one potentially convertible into cadinane type and the other potentially convertible into amorphane type of sesquiterpenoids. The other problem of course is the regioselective introduction of the

CHART VIII

Scheme XV

97, R = H

98, R = Me



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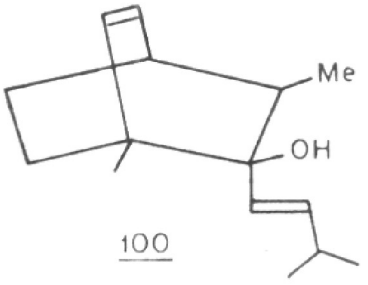

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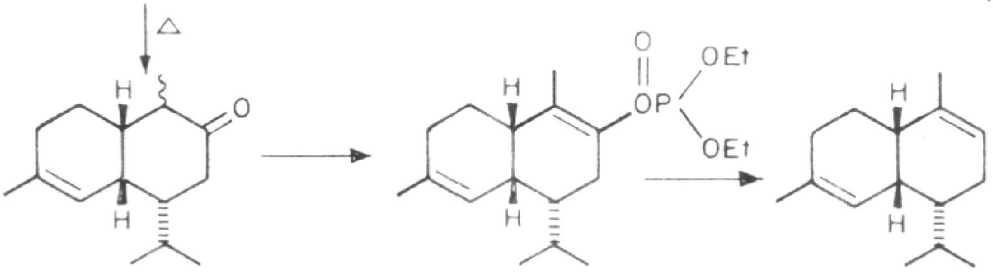
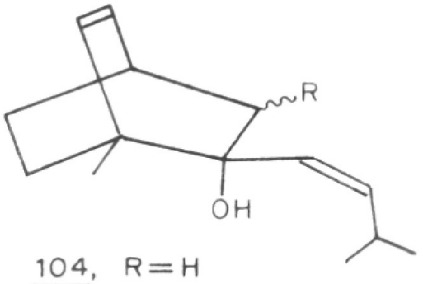
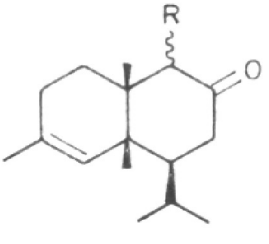


101 102 103



104, R = H

105, R = Me

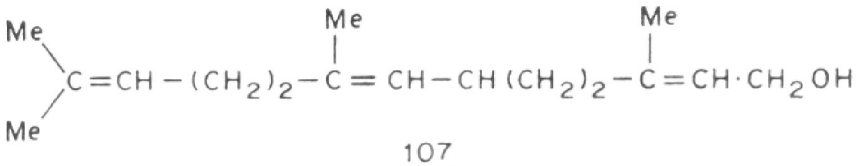


106

double bond into various positions of an appropriate synthetic intermediate to get the required cadinenes, like δ-cadinene and ω-cadinene.

Synthesis of α-amorphene using oxy-Cope rearrangements

The synthesis of α-amorphene[37] using oxy- Cope rearrangement has opened a new way for the syntheses of these class of sesquiterpenes (for details of this rearrangement, see refs. 32, 33, 34, 35 and 36). The synthesis(depicted in scheme XV) utilises the known[38] 1-methylbicyclo (2,2,2)oct-2-en-6-one (97) which was prepared from 1-methylcyclohexa, 1:3 diene by Diels-Alder reaction with α-chloroacrylonitrile, followed by the treatment of the 9:1 mixture of epimeric chloronitriles with ethanolic sodium sulfide. The hydroxymethylene derivative of 97 was converted into epimeric 98,(3:1, endo:exo) with methyl iodide in methanolic solution of sodium methoxide, followed by hydrolysis. A Grignard reaction between 98 and trans-3-methyl-but-1-enyl-bromide in THF afforded a 3:1 mixture of allylic alcohols 99 and 100; 99 when heated at 300° in vacuo for 1 hour, underwent the expected suprafacial (3,3) sigmatropic reaction to give ketone 101. The relative configuration at C-5 in 99 should have been retained during the oxy- Cope rearrangement and have given rise to an axial C-10 methyl in 101 as depicted, but 101 was recovered unchanged after treatment with methanolic solution of sodium methoxide. Ketone (101) was converted to the enol-phosphate(102) which on reduction with LAH (in ether:t-butyl alcohol, 1:1 mixture) gave (±)α-amorphene (103).



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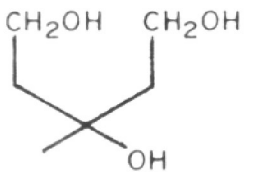

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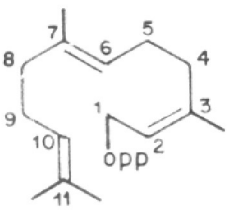

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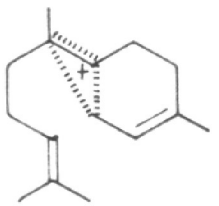

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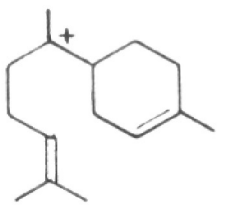

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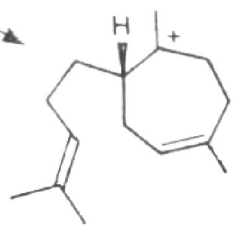

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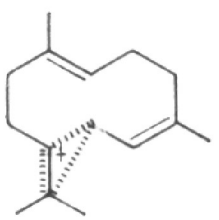

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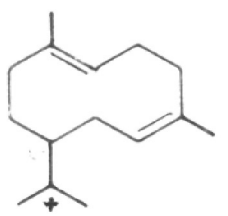

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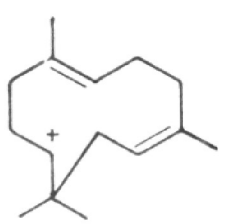
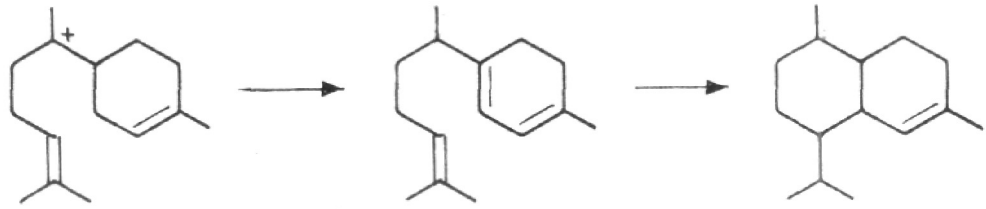


115

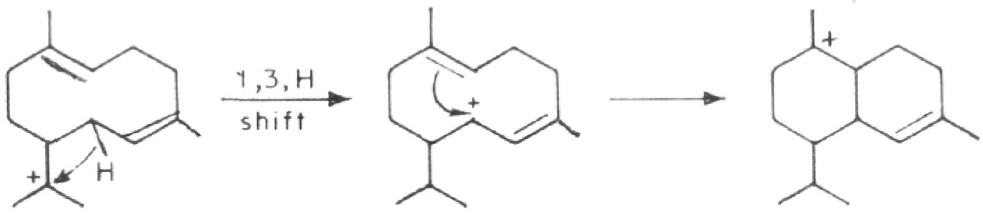
Chart IX (contd.)

Path (a)



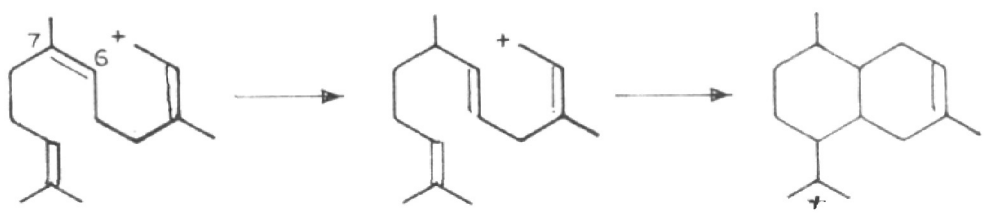
111 116 117

Path (b)



114 118 117

Path (c)



119 120 121

An interesting observation worth noting here is that the carbinol (104) with a cis-side chain did not furnish (+) ∝-munrolene as expected. Experiments with diethyl analogue (105) gave only aromatic compounds and no trace of octalone (106). It is noteworthy that there is considerable steric crowding between the olefinic bridge and the isopropyl group when the side chain of 105 (but not of 99) is forced to adopt a conformation favourable for a concerted rearrangement.

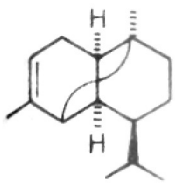
BIOGENESIS

The focal point of sesquiterpene biogenesis is the naturally occurring compound farnesol (107) whose formation from acetyl-Co-A via mevalonic acid (108) has been experimentally verified.[40] For the sake of simplicity the farnesyl unit is usually considered as having a trans-double bond with either a cis- or trans terminal double bond. It should be noted however that on occasion, the use of farnesyl precursor containing a cis central bond may be necessary to explain certain stereochemical features.

It can be seen that appropriate cyclisation of cation-III may lead to cadinane type of sesquiterpenoids (path a, chart IX). There are however two other possible ways for the formation of the carbon skeleton. One of them (path b) would involve an overall 1:3 hydride shift in cation 114, followed by ring closure, whereas the other (path c) would require cyclisation of a cis. $\Delta^{6,7}$ farnesyl precursor.

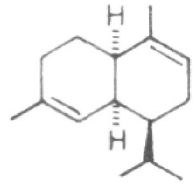
Hirose et al.[41] have proposed a biogenetic scheme based on transformation reaction of cubebene (128), ∝-ylangene (122) and ∝-copaene (134).

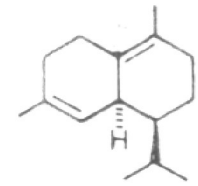
CHART X

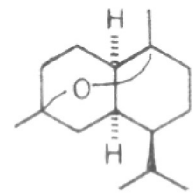


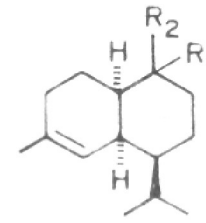
122

0·1 N
H_2SO_4

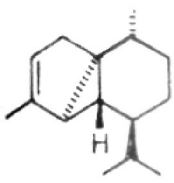


123 +  124 +



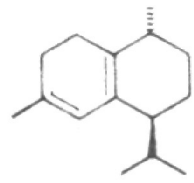
125 + 

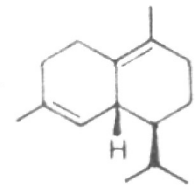
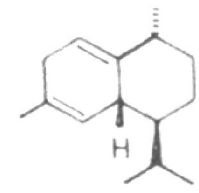
{ 126 R_1, α-Me, R_2, β-OH
{ 127 R_1, β-Me, R_2, α-OH

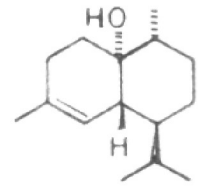
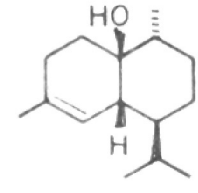


128

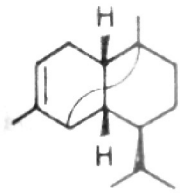
0·012N
HCl



129 +  130 +  131

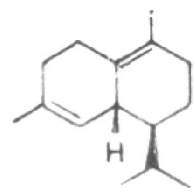
+  + 

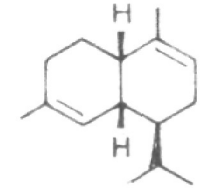
132 133

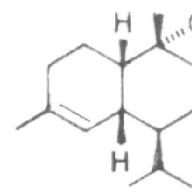


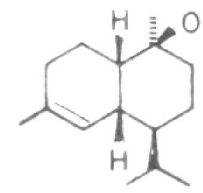
134

0·1N
H_2SO_4



130 +  135 +



136 +  137

These tricyclic hydrocarbons having a cyclopropane ring or a cyclobutane ring adjacent to a double bond in their molecule, were easily isomerised by dilute mineral acid to hydrocarbons of cadinane type. Chart X summarises these transformation products. These workers have made some interesting observations on sesquiterpene of cadalene skeleton.[41]
The three points which may be noted are:-

(1) There have been found to be no compounds in nature, which have a trans ring junction and a double bond at C9

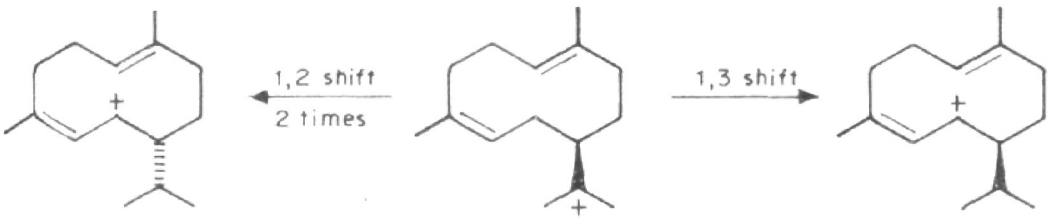
(2) Most commonly encountered alcohols, recently isolated have been proved to have a functional group on the right hand side of the cadalenic skeleton.

(3) As in the case of cubenol (132) and epi-cubenol (133) in "cubeb oil" and δ-cadinol (136) and τ-muurolol (137) in the oil of "Taiwanica cryptomerioides" epimeric pair of sesquiterpene alcohols often co-exist in one essential oil.

Based on these observations and above transformations, Hirose et al.[41] have postulated that anti-elimination of a hydrogen atom and SN^1 like attack of water molecule to carbonium ion are likely to be involved in the biogenesis of sesquiterpenes(see chart XI).

In the case of muurolane and amorphane group, the transition states (A) and (B) respectively that are responsible for the intermediate states in the isomerisation of α-copaene (134) and α-ylangene (122) respectively. Through the transition state (A), δ-cadinene, α and γ muurolene, and α-copaene will be formed by elimination of a hydrogen atom, whereas δ-cadinol and τ-muurolol may be formed by hydration.

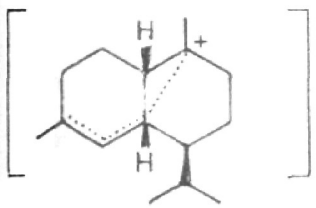
CHART XI



CATION. 3 CATION. 1 CATION. 2

CATION. 2

MURROLENE GROUP

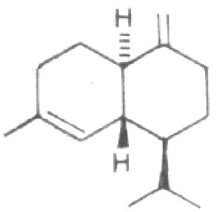


[A]

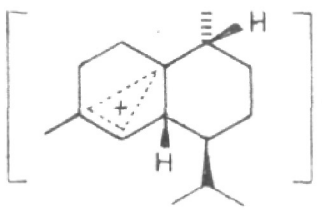
δ-cadinene
α-muurolene
γ-muurolene
δ-cadinol

τ-muurolol
α-copaene
β-copaene
etc.

CADINENE GROUP



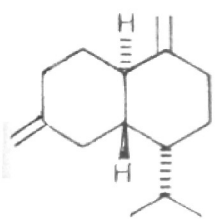
γ-cadinene
α-cadinol
τ-cadinol etc.



α-cubebene
β-cubebene
cubenol
epicubenol

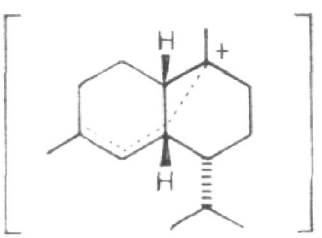
CATION. 3

BULGARENE GROUP



ε-bulgarene

AMORPHENE GROUP



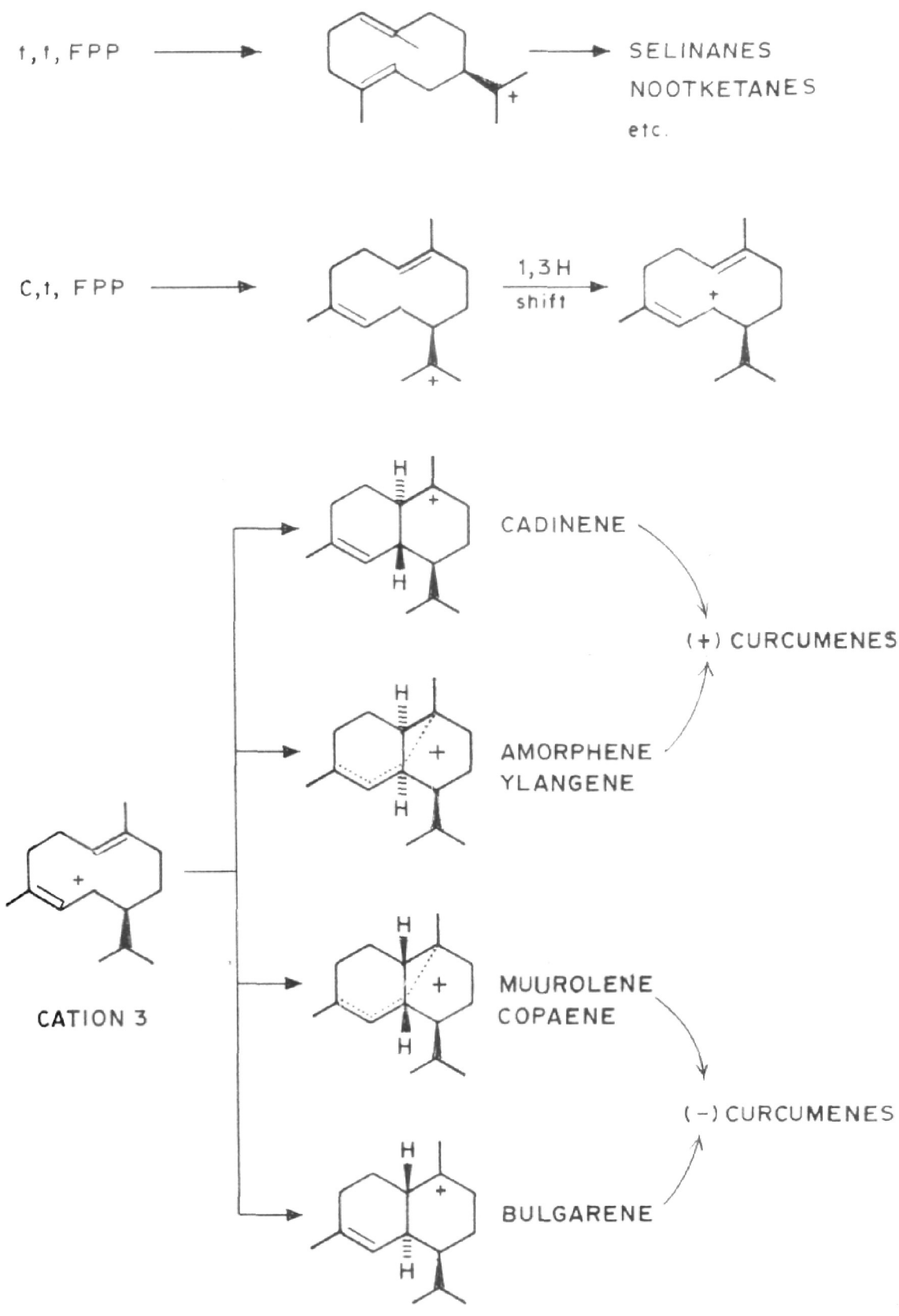
[B]

α-amorphene
δ-amorphene
α-ylangene
β-ylangene
etc.

Further, cubebene, cubenol and epi-cubenol will be formed from (A) via shift of the hydrogen atom from C_1 to C_{10}. Similarly the compounds of the amorphane group, α, δ and γ amorphene and α and β ylangene are to be formed via T.S.(B). As to the genesis of compounds having a trans ring junction, those of the cadinane and bulganane group, it is impossible to proceed through such T.S. as (A) or (B), and only hydrogen atom on C_{15} carbon atom seems to be allowed for elimination to form γ-type hydrocarbons.

The proposal of Herout described above of two 1:2 shift s from cyclodecadienyl cation (cation 1) to cation 3, which is the progenitor of trans ring compounds, like cadinanes and bulgaranes, has been eliminated by Andersen.[42] This modification is suggested by the number of absolute stereochemistry determinations in the literature and by the conviction that the 7-β-isopropyl group is the feature of singular importance in assessing the absolute configuration of a class of sesquiterpenes. These observations are that (-)α-copaene and (+)α-ylangene consistently co-occur in essential oils and that both (+)-ϵ-bulgarene and (-) γ-amorphene afford s-(+) isopropyl succinic acid (also obtained by cadinanes and muurolanes having a 7-β-isopropyl group) on vigorous oxidation. This modification strengthens the basis for an absolute configurational homogenity rule, since a single enzymatic cyclisation can account for all the sesquiterpene types, having a 7-β-isopropyl group.

CHART XII


t, t, FPP
SELINANES
NOOTKETANES
etc.
C, t, FPP
1,3 H
shift
CADINENE
(+) CURCUMENES
AMORPHENE
YLANGENE
CATION 3
MUUROLENE
COPAENE
(−) CURCUMENES
BULGARENE

In a later report[43] Andersen has summarised the biogenesis of cadalenic type of sesquiterpenoids. The scheme is depicted in Chart XII. Cation 3 could serve as the precursor of four stereochemical cadinanes and of both dextro and laevo rotatory curcumenes. Bulgarenes and muurolenes should afford the (-) curcumene, while the cadinenes and amorphenes should afford the (+) curcumene by a concerted fragmentation.

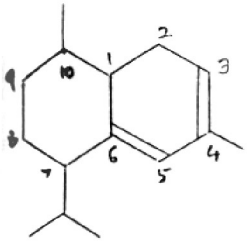
The observation of laevorotation of curcumenes in curcumene rich oil, requires that the fragmentation of bulgarenes and muurolenes, should be facile, relative to that of cadinenes and amorphenes. In the case of muurolene, the conformation has the favourable anti-parallel rearrangement at the fusion. The trans-fused bulgarenes have a axial isopropyl group and the fragmentation to (-) curcumene must be favoured (due to release of steric strain) even though the anti-parallel relationship cannot be achieved. Cadinene is necessarily in a unfavourable conformation and the favoured equatorial isopropyl conformer of amorphane also lacks the anti-parallel relationship, leading to facile fragmentation. However, another implication that curcumene rich oils ought to contain minor amounts of bulgarenes and perhaps muurolenes and copaenes has not been yet tested.

It must be finally admitted that any single species might well synthesise sesquiterpenes through a variety of unrelated or crossing routes, but only detailed examination of oil composition and experiments involving the incorporation of labelled materials will resolve this point. Until then, chemical reasoning must stand as the guiding principle in unravelling the sesquiterpene biogenesis.

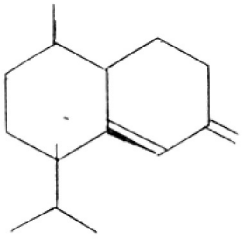
PRESENT INVESTIGATION

The thesis is divided into three chapters:

Chapter I: Stereospecific synthesis of (+) epizonarane. This work was undertaken as a continuation of our previous work on calamenenes. During the synthesis of calamenene[4,5] we had reported the formation of diene I and II prior to aromatisation.



I



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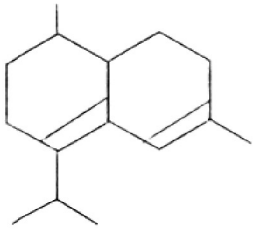

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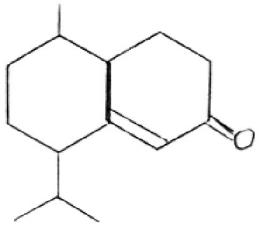


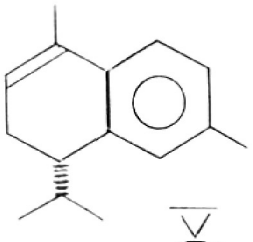
IV

However, a small percentage of another hydrocarbon in addition to I and II was indicated. Dienes I and II are highly susceptible to acids and are readily isomerised to a number of isomeric dienes.[44] In the NMR of spectrum of the diene mixture, a weak unresolved heptet (at τ 3.05) was noticed, but went unaccounted. It was later recognised that the naturally occurring heteroannular diene (III)[44] shows the same characteristic heptet centered at 3.05. Further the two heteroannular dienes (epizonarene and zonarene) can be readily distinguished by their IR and NMR spectra.[44] This prompted us to reinvestigate the dienes more elaborately, which led us to attempt the synthesis of one of the naturally occurring heteroannular dienes (depending on the stereochemistry of our intermediate compound). The stereospecificity during the synthesis

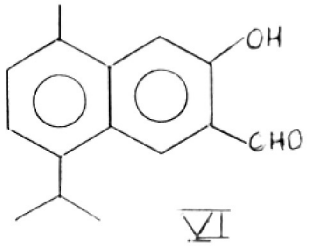
was achieved by selection of the proper synthetic route. This resulted in the stereospecific total synthesis of (+) epizonarene, which is described in this chapter.

Chapter II: The intermediate compound for the synthesis of (+) epizonarene is the ketone (IV). The synthesis of (+) epizonarene helped us to confirm the relative stereochemistry at C_1 and C_{10} of this compound (deduced earlier by us on the basis of CD curves). However, the stereochemistry of the isopropyl group remained to be established. Several erroneous reports regarding the stereochemistry of the isopropyl group in this ketone, prompted us to reinvestigate its structure in detail. This is described in the second chapter.

Chapter III: α-Calacorene (V) is a naturally occurring sesquiterpene. No synthesis of this compound was known when this work was started (lately it has been synthesised as described in the earlier part of this introduction).



V



VI

The present work was undertaken, envisaging the synthesis of V from carvotonacetone. Though the synthesis of this could not be achieved, the total synthesis of another natural product, 7-hydroxycadelenal (VI) has been achieved. The synthesis of this compound is described in Chapter III.

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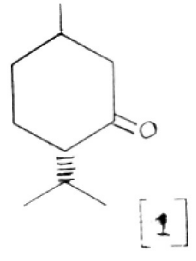
C H A P T E R - I

STEREOSPECIFIC TOTAL SYNTHESIS OF (+) EPIZONARENE

***

This chapter describes the stereospecific total synthesis of naturally occurring (+) ent-10-epizonarone, starting from l-menthone.

Mannich base (2) was prepared by using excess of l-menthone(1), dimethylammonium chloride, and paraformaldehyde. This on quaternisation with methyl iodide gave the quaternary salt (3). Treatment of (3) with sodium ethoxide in presence of ethylacetoacetate followed by basic hydrolysis gave the conjugated ketone (4). The crucial stereochemistry at C_1 (ring juncture) and C_{10} position was ascertained by circular dichroism data. (4) on Grignard reaction with methyl magnesium iodide followed by treatment with 33% sulfuric acid gave (+) epizonarene (5). A diene mixture (6) along with 5 was obtained when the acid treatment after Grignard reaction was totally avoided. A possible biogenetic scheme for 5 and zonarene is also discussed.



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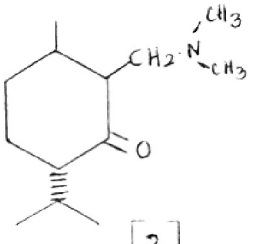

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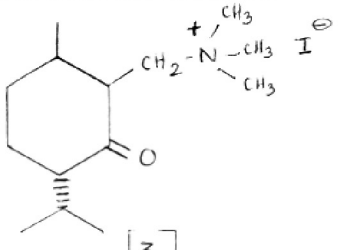

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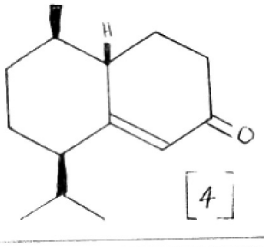

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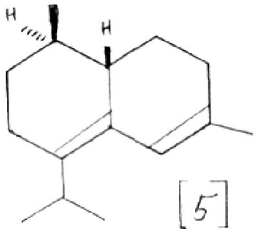

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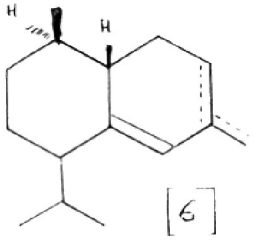


[6]

(-) Epizonarene, (+) epizonarene and (-) zonarene are new heteroannular dienes having a cadalene skeleton, encountered in a variety of essential oils and also as rearrangement products of a number of other sesquiterpenes. The first report[1] of their isolation came from the chemical examination of oil of brown sea-weed "Dictyopteris zonaroides". Subsequently their presence has been found in a number of other oils. In Canada (+) 5 and (-) 7 were first isolated from a sample of "Alpinia officinarium" oil. In Washington State (-) 5 and (-) 7 were found in Alaska cedar ("Chem aecyparis nootaktensis") and cade oil (Juniperus oxycedrus). Subsequent to this both the diasteromers have been found in "Zingiber officinale", 'Pelargonium graveolens, pimenta diocea, Eugenia caryophyllus and Laurus noblis. In addition both the isomers are encountered as products on acid treatment of various cadinene isomers. Following tables summarise the data concerning source,spectra,etc.

TABLE I(A)

Data for dienes 5 and 7 (obtained from natural sources)

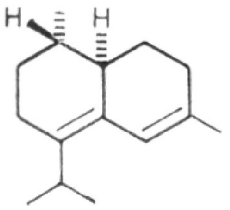
Source	PMR (δ in ppm) doublet $-CH_3$	$=C-H$;	$=C-CH_3$	λ 245-248	CD $\Delta\varepsilon$	α_D	Ref.No.
-5 Chamaccyparis nootktensis	3 Ca, 0.99	6.19	1.77	16,400	-15	-175	2
+5 Alpinia officinarium	0.97, 0.98, 1.00	6.22	1.75	12,000	+6.5	+ve	2
-7 Cade oil	0.79 2Ca, 0.96	6.20	1.74	10,800	-6.6	-140	2
-7 Alpinia officinarium	0.81, 0.95 0.96	6.27	1.76	13,000	-4.8	-Ve	2
-7 Dictyopteris Zonaroides	0.80 2 Ca 0.95	6.30	1.75	19,070	-Ve	-218	1

TABLE I(B)

Data for dienes 5 and 7 (obtained as transformation products)

Source	PMR (δ in ppm) doublet $-CH_3$;	=C-H;	$=C-CH_3$	UV λ 245-248	CD $\Delta\varepsilon$	α_D	Ref.No.
± 5 Farnesol & BF_3	3Ca,0.94;	6.10;	1.71	18,800	-	-	5
± 7 Farnesol & BF_3	0.78 2Ca; 0.99	6.10;	1.72	19,600	-	-	5
+5 (+) -Cadinene and H-COOH	3Ca; 0.99	6.20	1.76	17,800	+25	+ 95	2
+7 Preiso-calamandiol	0.80 2Ca 0.95	6.30	1.75	-	-	+322	7
-5 Guaiol and H_2SO_4	3Ca,0.99	6.19	1.77	13,000	-	-	6
+5 l-Menthone	3Ca 0.99	6.10	1.71	37,000	-	+240.2	-

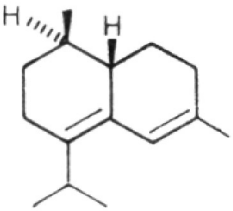
CHART I



(−) 10 Epizonarene

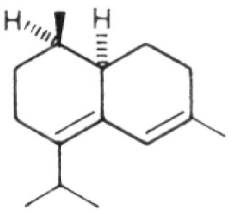
(−) 5

(−)10β,H muurola−4,6−diene



(+) Ent−10− Epizonarene

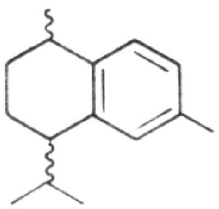
(+) 5



(−) Zonarene

(−) 7

(−)10 α, H muurola−4,6−diene



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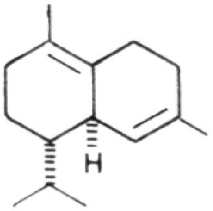

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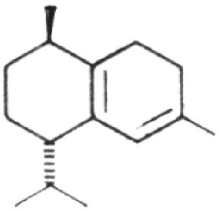

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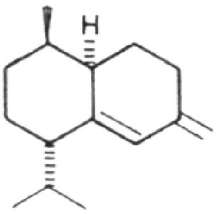
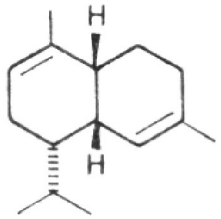


11



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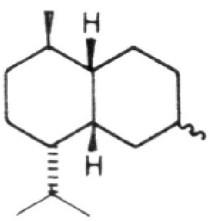
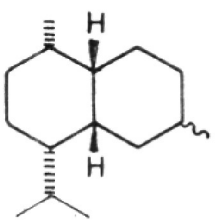


13

(+) 5

+



14

(−)7

Structure elucidation; Relative stereochemistry

The structure and relative stereochemistry, elucidation were accomplished by Andersen et al.[2] The cadalene skeleton was established by dehydrogenation with sulfur in triglyme at reflux temperature,[3] giving 90% cadalene from either diasteroismer. Using the new aromatisation technique,[4] diastereomeric calamenenes(8) were obtained from diene 5 and 7 in high yield. In case of (-) 5, the product was 59% cis and showed a positive ^1L_b band ($\Delta\varepsilon$ 278 = + 0.112). The cadalene skeleton was also suggested by the observation that dienes 5 and 7 result from isomerisation of known cadinenes as follows:

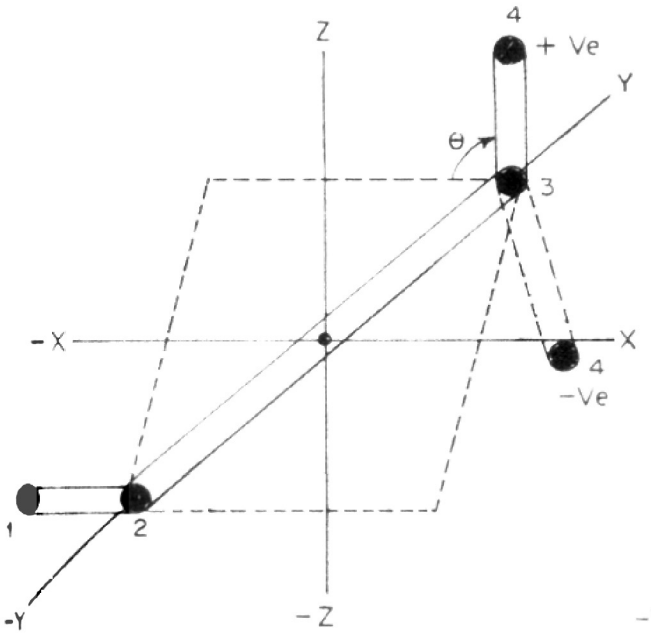
9 $\xrightarrow[100^\circ,\ 5\ \text{hrs.}]{\text{HCOOH}}$ + 5 (45% yield; 17% optical purity)

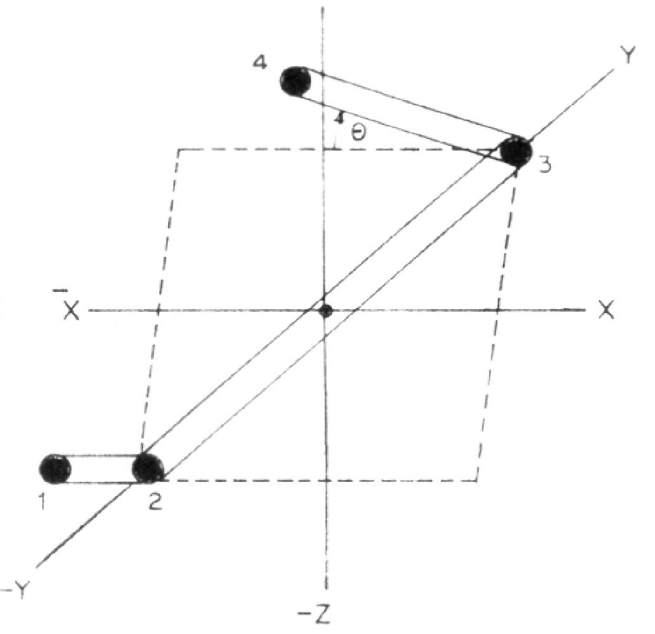
10 $\xrightarrow[80\%\ \text{aq.dioxane}\ 50^\circ,\ 1\ \text{hour}]{0.012\text{N HCl}}$ 10 (80%) + 7 (10%) + 8 (5%)

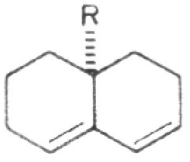
11 $\xrightarrow[80^\circ,\ 2\ \text{hrs.}]{0.012\text{N HCl}}$ 7 (8%) + 5 (59%) + 8 (13%)

With the skeleton established, the NMR data define the position of the double bonds; in particular the downfield hydrogen singlet must be in a internal butadiene, with a substantial peri effect. The cis, 1,10 hydrogen structure was assigned to isomer 7, based on the upfield position and the doublet methyl, reflecting the axial disposition of the group and its placement over the π orbitals of the diene. The assignment was

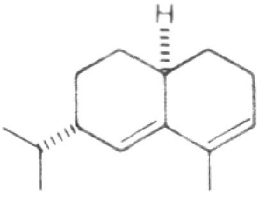
CHART II





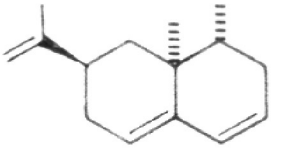


−Ve CD



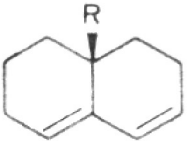
$\Delta\varepsilon_{239}$, −13

SELINA-3,5-DIENE

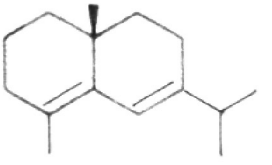


$\Delta\varepsilon_{232}$, −8

NOOTKATENE

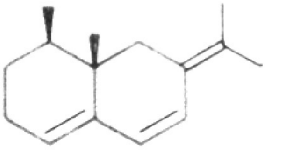


+ Ve CD

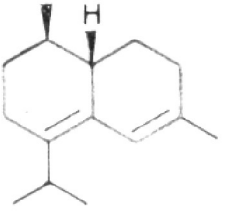


$\Delta\varepsilon_{244}$, +18·1

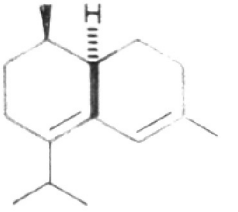
(+) 6-SELINENE



Δ_{266}, +10



$\Delta\varepsilon$, +6·5



$\Delta\varepsilon$, −4·8

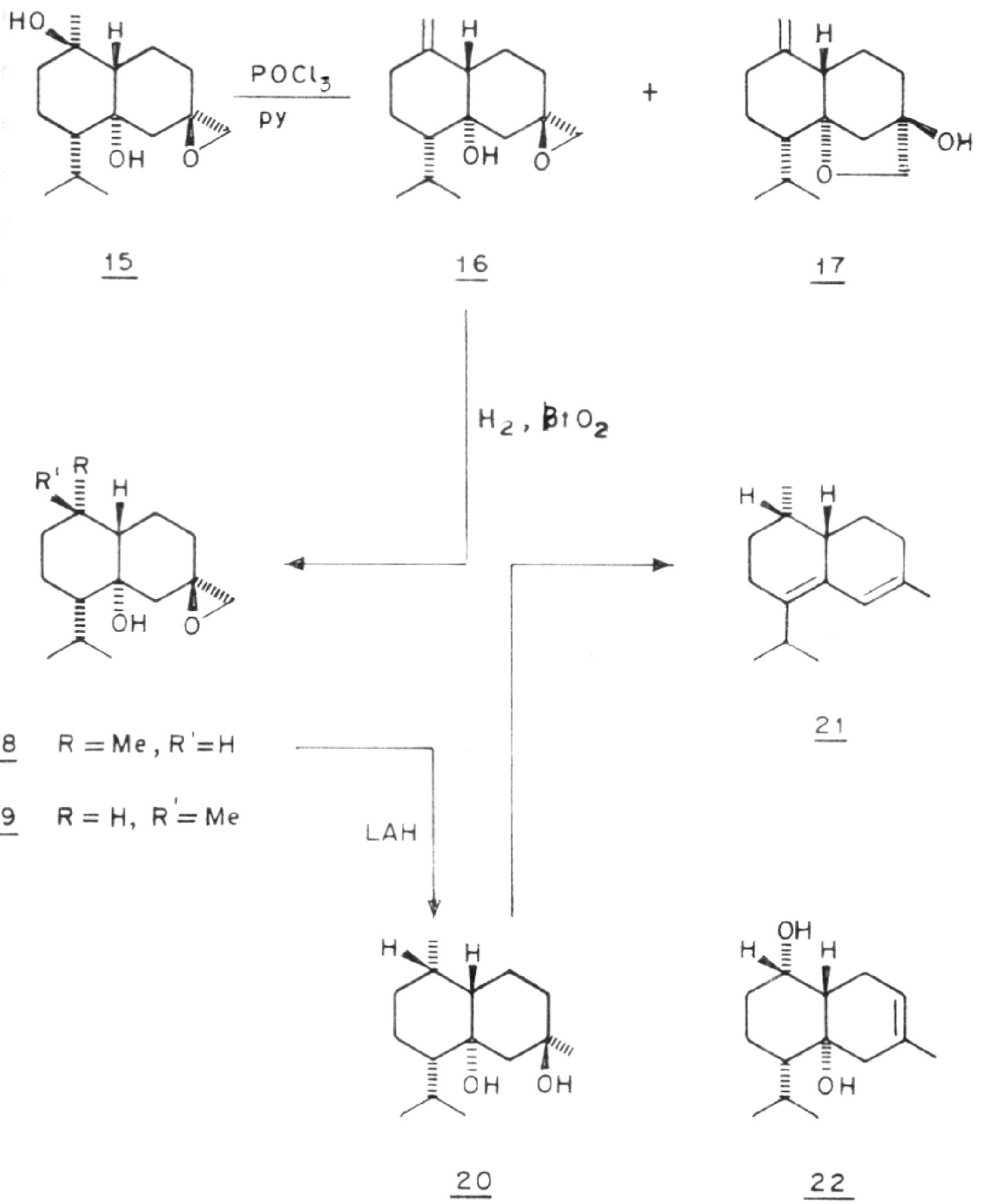
confirmed by hydrogenation product correlations, as shown in Chart 1. It was found that ∝-amorphene (12) (or zizanene, its enantiomer), diene 10 and diene 5 had one product in common, amorphane I (13). Conversely diene 7 had no products in common with diene 10, but did produce amorphane II (14). This establishes the relative stereochemistry at C_1 and C_{10} in the isomers.

Absolute Stereochemistry

It will be recognised that butadiene would be optically active, in any of its non planar forms, and that comparable disymmetric conformations, may be achieved permanently, when the conjugated moiety, is the part of a rigidly fixed ring system.[8] The contribution to the observed rotatory dispersion with such inherently disymmetric chromophore will usually outweigh any contribution associated with asymmetrically disposed alkyl groups. Hence the cotton effect observed in the vicinity of the diene absorption will be to a large extent reflection of the relative orientation of the double bonds of the chromophore,and therefore is, stereochemically significant. If the diene is oriented in such a way that, its carbon atoms 1, 2 and 3 (see figure in chart II) define a plane in a right handed coordinate system with carbon atoms 2 and 3 on the Y axis and carbon 1 in the negative X direction, the sign of the Cotton effect associated with UV absorption of lowest frequency is determined by the position of carbon atom 4 in the Z axis; it will be positive or negative respectively, if the coordinate of C-4 is positive or negative.

CHART III

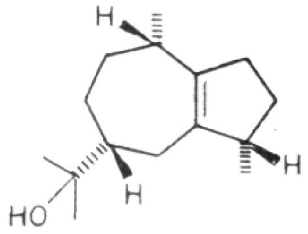
Scheme I



For convenience with models, the rule can be related in the following way: If the model of the diene is held in such a way that the double bond to its left defines a horizontal plane, the double bond pointing away from the observer, extends upwards or downwards respectively. Consequently the rotational contribution of the singlet transition of lowest energy is positive or negative, depending on the relative orientation of C-4 with respect to planes of carbon 1, 2 and 3. The application of this "Transoid diene chirality rule" to a number of heteroannular dienes is shown in chart II, together with the observed sign of Cotton effect. On this basis the absolute configuration of Zonarene and epizonarene is justified. In case of epizonarene the assignment has been confirmed by ORD comparison of amorphane I (13) isolated from hydrogenation product of zizanene and (+) epizonarene (from formic acid treatment of (±) δ-cadinene).

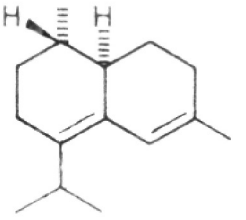
The described stereostructure was also independently confirmed by another group[7] through a transformation from preisocalamendiol (which hasbeen synthesised from l-santonin). The epoxy diol (15) was obtained from isocalamendiol as an acid catalysed cyclisation product of preisocalamendiol, The absolute configuration of which hasbeen already established. Further treatment of 15 with $POCl_3$/pyridine afforded the known dehydration product 16 and ahydroxy olefin 17 (scheme I). Catalytic hydrogenation of 16 on PtO_2/AcOEt afforded a mixture of two dihydrocompounds (18 and 19). On the basis of PMR spectrum, the newly formed methyl group in the product 18 must be an axial

Scheme II

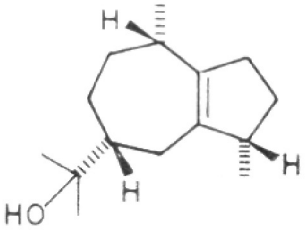


23

H_2SO_4
$0° - 5°$

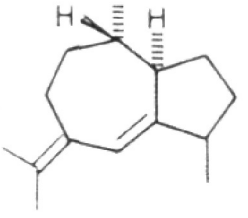


(−) 5



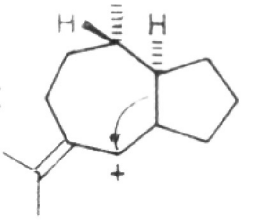
23

H^+

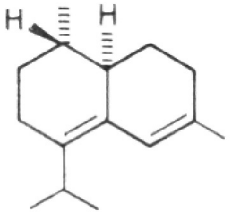


24

H^+

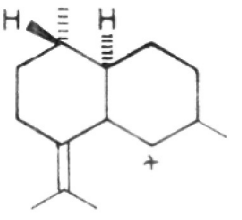


25



(−) 5

Na_2CO_3
$0° - 5°$



26

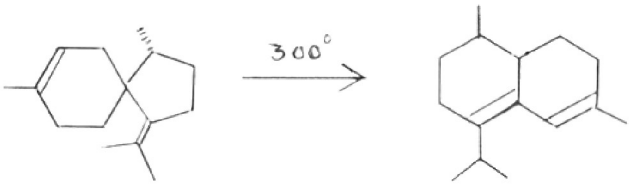
configuration (1.05 ppm) whereas the corresponding methyl group in 19 must be equatorial (0.87 ppm). When treated with LAH in ether, 18 was converted to the corresponding diol. Finally action of $POCl_3$/pyridine on 20 converted it to a mixture of two dehydration products 21 and 22. 21 was found to be completely identical with zonarene (except for sign of rotation) as shown by comparison of GLC and IR spectrum of authentic zonarene. In conclusion therefore the stereostructure of zonarene including absolute configuration can be represented as 21.

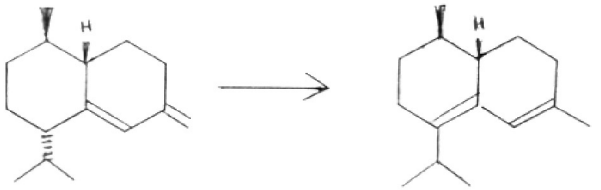
Epizonarene from Guaiol

Recently Mehta et al.[6] have obtained (+) epizonarene from guaiol (scheme II). When a solution of guaiol (23) in CH_2Cl_2 was dispersed in conc. H_2SO_4 at 0-5°, a clear orange solution was obtained. Quenching of this solution in iced aqueous sodium carbonate led to 80-90% recovery of an olefinic mixture from which the major component (5) was obtained in pure form ($AgNO_3$ - SiO_2 column) in 40% yield. The rest of the olefinic mixture consisted of various guaines. The natural identity of 5 and epizonarene was established by direct spectral comparison.

A reasonable interpretation of this transformation is depicted in scheme II. It involves an initial isomerisation of guaiol (23) to the guaine isomer (24) followed by protonation to 25. This is followed by alkyl migration to form 26, which subsequently isomerises to 5. The authors feel that this facile conversion of 23 to 5 is biogenetically significant, considering the fact that guaiene and Cadalene skeleton are abundantly distributed in nature and derived from farnesyl pyrophosphate by independent pathways.

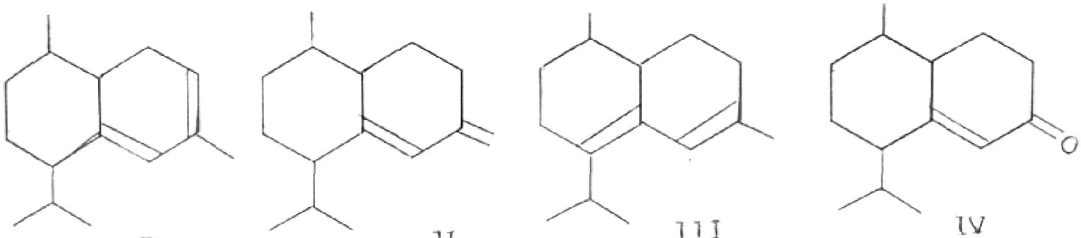
In passing it should be mentioned that zonarenes are also obtained as thermal rearrangement products of and β alaskenes,[9] and epizonarene is obtained from bicyclosesquiphellandrene, by treatment of acid.[10]





PRESENT INVESTIGATION

The present investigation was in fact undertaken as a continuation of our previous work on calamenenes. During the synthesis of (+) calamenene,[11] we had reported the formation of two diene I and II in approximately 50:50 ratio, when the Grignard reaction was done on the intermediate ketone(IV).



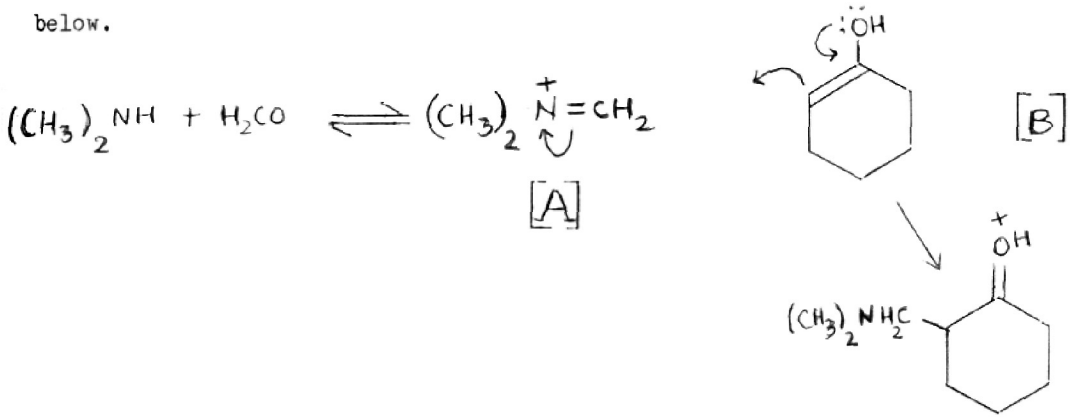
I II III IV

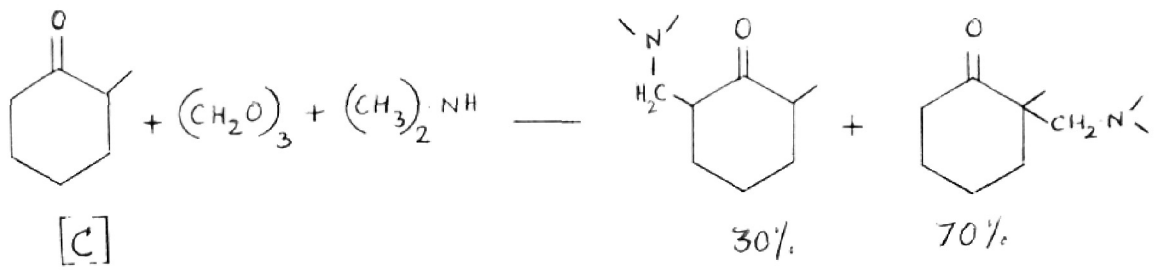
In the NMR spectrum of the diene mixture (I and II) a unresolved multiplet at 3.05 was noticed, but this went unaccounted. Later it was found that compounds with a heteroannular diene structure (III), which were isolated first during 1972 from natural sources possess this typical heptet at 3.05.[1,2] Further, the fact that compounds like I and II are readily isomerised,[10] in presence of acids to heteroannular diene (III), gave rise to the speculation that III may be produced from the conjugated ketone (IV) during Grignard reaction. So attempts were directed in this direction to get compound III in pure form, which would constitute a total synthesis.

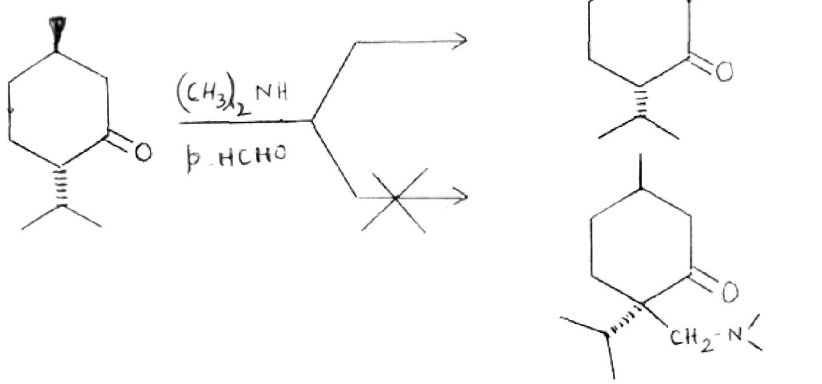
Once the synthesis of these naturally occurring heteroannular dienes was visualised, the next problem was to get the optically pure natural product (either zonarene or epizonarene). This requires the synthesis of a pure intermediate ketone (IV). The earlier route[11] through Michael addition of methyl vinyl ketone gives a epimeric mixture of the intermediate ketone and also this route is not advantageous because of the formation of spiro compound.[12] However, the same intermediate ketone (IV) was reported as a solid in literature.[13] This prompted us to explore this new route and the synthesis of pure ketone (IV) was realised. The crucial stereochemistry at C-1 and C-10 was assigned by CD curves (discussed in second chapter) and the synthesis of pure (+) epizonarone was achieved.

l-Menthol on oxidation with Jone's reagent gave l-menthone. A GLC pure sample of l-menthone (α_D 26.12°) was used for further reactions. The stereochemistry of l-menthone has been unambiguously fixed as 1,l-menthone was converted to the Mannich base (2) by refluxing a mixture of l-menthone, dimethylammonium chloride and paraformaldehyde in presence of a drop of HCl (0.2 ml) and ethanol. We modified the literature[14] procedure by using dimethyl ammonium chloride, instead of the diethyl analogue. The former was found to be better with respect to yield and reaction time (the yield of 62% of Mannich base when diethyl amine hydrochloride is used is improved to 88% when dimethyl compound is used). The Mannich base (2) has b.p. 104-105°/4.5 mm. and the pure distilled sample had a rotation of -38.90°(neat), and gave the correct elemental analysis.

Under the usual slightly acidic conditions, the mechanism of the Mannich reaction[15] is believed to involve electrophilic attack by the iminium salt (A) on enol (B) of the active methylene compound as shown below.







The consequence of the foregoing mechanistic scheme is the expectation, that unsymmetrical ketones (like 2-methylcyclohexanone, menthone, etc.) react predominantly at the more substituted position (alpha position), corresponding to the more stable enol form. Although early studies provided examples that appeared contrary to this expectation, reinvestigation[16] has shown that Mannich reaction products from unsymmetrical ketones such as (C) to be predominantly those that result from the attack at the more highly substituted position. In case of l-menthone however steric factors supersede the electronic factors; no products, which would be possible by the attack of the iminium ion at the more highly substituted poition (isopropyl group bearing carbon) were isolated during the reaction. This is expected since a large group, such as the isopropyl would sterically hinder the approach of the iminium ion in the transition state. The reaction thus is controlled by steric factors, rather than by electronic factors which would otherwise favour a more stable enol intermediate.

The Mannich base (2) was treated with methyl iodide to get the quarternary salt (3), which was set aside at room temperature overnight. The salt (3) was then condensed with ethyl acetoacetate in presence of sodium ethoxide, followed by hydrolysis with 50% KOH. The final product was obtained as a gummy liquid. This was chromatographed over a column of alumina (Gr. III, 1:10 ratio) and the chromatographed sample distilled at 125°/2.5 mm.(bath 180°) 40 gms. of the distilled mass was then dissolved in 250 ml. of anhydrous pet.ether and cooled at -20° for 3 days.

The conjugated ketone (4) separated out as a crystalline solid, m.p. 69°, semicarbazone, m.p. 158-159°. IR spectrum (Fig. 2-1) showed bands at 1681 ($\rangle C=O$) and 1613 ($=C-C$) cm^{-1}. PMR spectrum (Fig.2-2) showed C-10 methyl as a doublet at δ 0.9 (J~6 cps), C-7, isopropyl at 0.98 (J~6 cps) and the vinylic proton at δ 5.66 (sharp singlet, HW, 2 cps), thus showing an α-proton to the carbonyl group. Mass spectrum, M+ 206, α_D^{25} - 3 ($CHCl_3$), λ_{max}^{MeOH} 240 nm (ε, 26,100), CD (Fig. 2-3), $\Delta\varepsilon_{230}$ + 3.85, $\Delta\varepsilon_{315}$ -0.3 (MeOH). GLC analysis of the sample showed ≥.99° purity on various columns (carbowax, S.E. 30, polyester and QF_1 columns). TLC showed a single spot. It did not form a solid p-toluene sulfonyl hydrazone derivative, but only gave a gummy material.

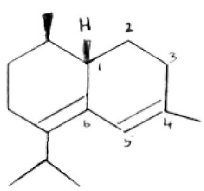
Having successfully isolated the intermediate ketone (4) in pure form, we recorded the circular dichroism curves of this compound (Fig. 2-3). The observed sign of Cotton effect indicated the required β stereochemistry at C-1, (for detailed discussion of CD, see chapter II).

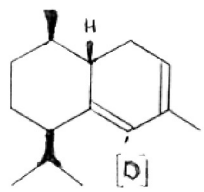
The solid ketone (4) on reaction with 1 mole of methyl magnesium iodide, in presence of a trace of iodine, followed by careful treatment with 33% sulfuric acid gave a hydrocarbon ($C_{15}H_{24}$). GLC analysis on carbowax and polyester columns, showed it to be a single compound. Its NMR spectrum (Fig. 2-3) was identical with that of epizonarene, especially the methyl signals at δ 0.99 (d, 3 Me) and a heptet centered at δ 3.05, which is typical of zonarenes. IR spectrum of the distilled sample (b.p. 105-110°/2.5 mm.(bath temp.) helped to distinguish the two

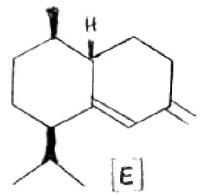
diastereomers (epizonarene and zonarene). The IR spectrum of our sample (Fig. 2-4) was superimposable on the authentic[2] IR spectrum of epizonarene and clearly differentiated our compound from zonarene. The purity of epizonarene was also evident, from the PMR spectrum of our compound (Fig.2-3), where the methyl signals at δ 0.80, due to zonarene are absent. The sample had the expected sign of rotation (+ 240.2). UV spectrum(Fig.2-5) λ_{max}^{MeOH} 245 nm (ε, 37,100) indicated a high purity.

Once the fact that acid treatment of the Grignard reaction product gave (+) epizonarene was revealed, we were tempted to carry out the reaction without using any acid. When the reaction was carried out and acid treatment totally avoided during all stages of work up, the product contained (+) epizonarene as the major product and a mixture of homoannular diene (D) and heteroannular diene (E), as judged by NMR spectrum (Fig.2-6) and GLC analysis on carbowax column (174°). These dienes can be readily recognised by chemical shifts of the olefinic protons in PMR[3] as follows:

DIENE ⟶







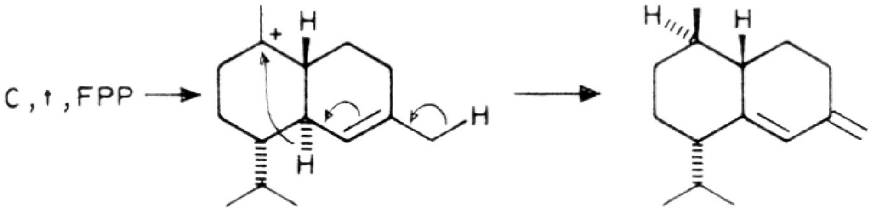
Chemical shift of protons (δ ppm)				
	C_3	-	5.82(bs)	-
	C_4	1.71(3H)	1.70(3H)	4.61(2H)
	C_5	6.10(s)	6.12(s)	5.40(s)

The mixture of these dienes are highly sensitive to acids. Attempts to get the diene (D) or (E) in pure form were not successful, since chromatography over alumina (neutral) or silicic acid isomerises the diene to epizonarene. In several experiments carried out carefully, we were able to get the diene (D), as a major compound (as indicated by PMR spectrum), but it gradually isomerised to epizonarene. During the experiments, the PMR recorded at regular intervals, indicated the disappearance of peak at 5.81 (broad singlet due to C_3 proton of diene D) and gradual appearance of the heptet at 3.05 (due to epizonarene).

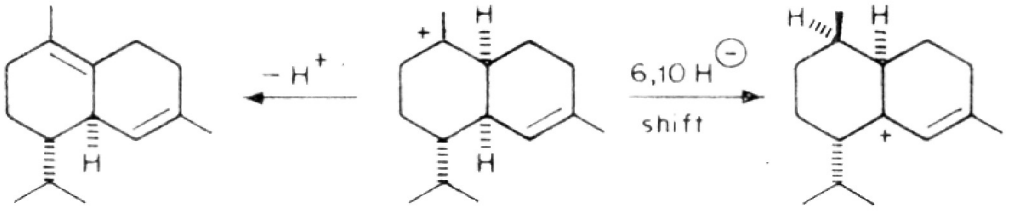
Our intermediate ketone (4) has a axially oriented isopropyl group at C-7 as is revealed by our investigation in the later part of this work (chapter II). The ready formation of epizonarene from this ketone (4) and the facile isomerisation of dienes (D) and (E) to epizonarene seem to be related to the stereochemical orientation of the isopropyl group at C-7. The formation of epizonarene with a heteroannular diene system, is highly favoured because in the process the bulky group at C-7 (isopropyl) is pushed from somewhat a unfavourable axial position to a planar form, on introduction the double bond between C_6-C_7 carbon atoms. Equatorial protons are not normally as vulnerable to enolisation as axial ones. In ketone 4, the enolisation can occur either across C_1-C_6 or C_6-C_7 carbon atoms, in the former case an axial proton (at C_1) has to be lost and in the latter case an equatorial proton (at C-7) has to be lost. The tendancy of these protons to participate in the enolisation seems to rest more with the C-7 proton, to which the above explanation appears reasonable. The biogenetic significance of this important observation is described below.

CHART IV

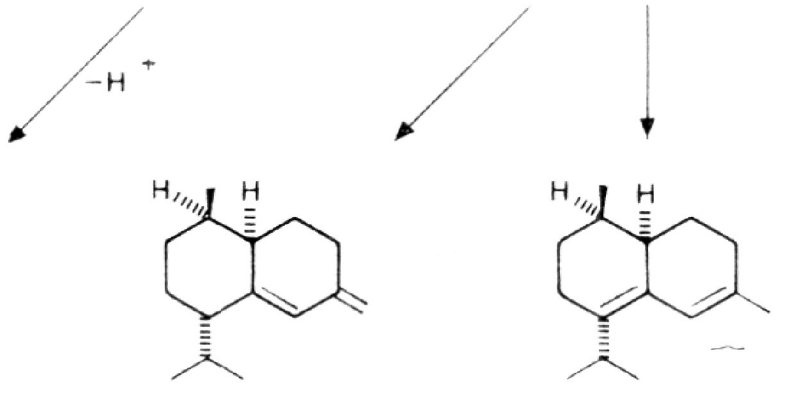
Scheme III



27 28



30 29 31



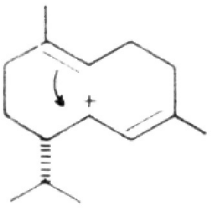
32 33 7

Biogenesis of Zonarene and Epizonarene

A possible biogenetic pathway has been suggested by Bhatwadekar et al.[17] for 1-epibicyclosesquiphellandrene (28). A stereospecific 1,3-hydride shift as shown in scheme III is suggested. Although not reported yet, the authors anticipate the presence of 1-epizonarene in the oil of 'O-basilicum' in which 1-epibicyclosesquiphellandrene occurs.[10] As per the scheme suggested by these authors, the biogenesis of zonarene and epibicyclosesquiphellandrene seem to involve a 1,3-hydride shift. A hypothetical biogenetic scheme which can account for the various constituents of 'cubeb oil' satisfying the assigned stereochemical details is postulated (scheme III). This postulate has been used to account for the cooccurrence of δ-cadinene (30) and a heteroannular diene (zonarene?) in 'cubeb oil'.[18]

A possible modification of this scheme, in which the stereochemical orientation of the isopropyl group is believed to be of singular importance is suggested by us (scheme IV). Whereas 1-epibicyclosesquiphellandrene (28) is derivable from cation 35 (precursor of cadinenes), zonarene and epizonarene are derivable from cation 29 and 37 respectively. Of the two competing reactions shown below (path A and path B), path A is favoured in case of cation 35, but path B is favoured in case of cations 29 and 37. Cation 29 and cation 37 are precursors of muurolene and bulgarene type of compounds respectively. Literature survey shows a relatively wide occurrence of muurolene type of sesquiterpenes as compared to the bulgarene type (hardly two bulgarene hydrocarbons are reported[19] to

Scheme IV



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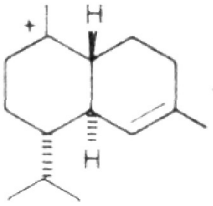
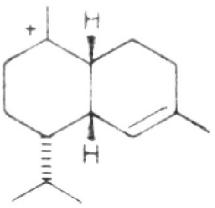


BIOCYCLOSESQUIPHELLANDRENE

35

CADINENES



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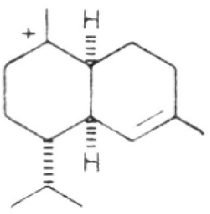
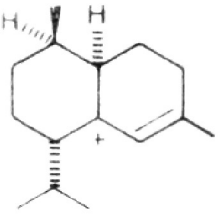
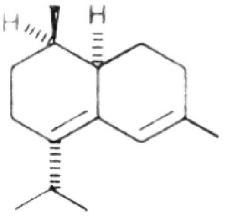
AMORPHENES



6,10 shift



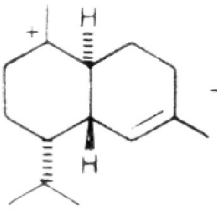


29

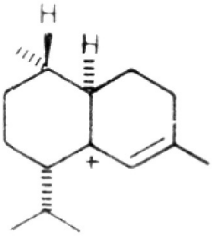
MUUROLENES

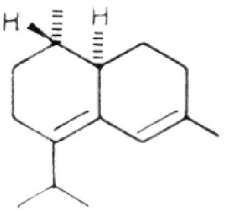
38

7



6,10 shift





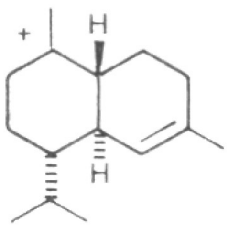
37

BULGARENES

39

5

Scheme V

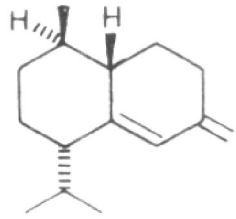


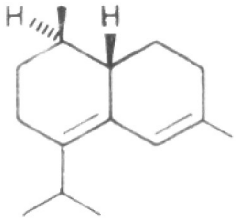
CATION 35

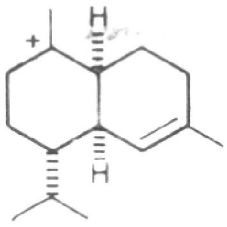
PATH

A

B





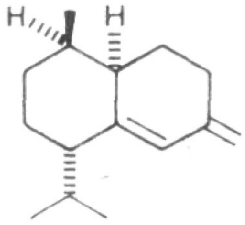


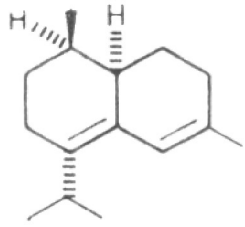
CATION 29

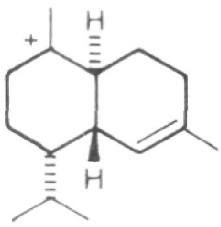
PATH

A

B





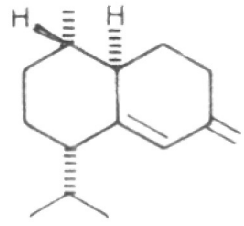


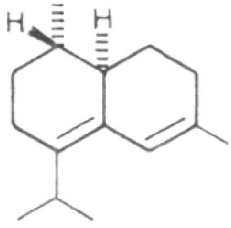
CATION 37

PATH

A

B





occur naturally so far). Both the cations 29 and 37 have an unfavourable axial orientation of the isopropyl group, and therefore, are expected to favour path B, leading to zonarene and epizonarene. Cation 29 however has a favourable anti-parallel relationship at the ring fusion,[20] and therefore the conversion of cation 37 to epizonarene may be more facile than that of cation 29 to zonarene. We anticipate the presence of bulgarene hydrocarbons in oils rich in epizonarene and muurolene hydrocarbons in oils rich in zonarene, on the basis of this postulate.

The position of double bonds in these cadalene sesquiterpenes argues against their production from germacrenes as is the usual case for cadinene, muurolenes, etc.[21] They probably represent the cyclisation products of bisabolenes and curcumenes, when they are true natural products.[2] In other cases they likely result from isomerisation of normal cadinenes under the oil isolating conditions. It is worth noting that the two isomers from 'Alpinio officinarium' retain the same absolute stereochemistry at C-10. Curiously Alaska-Cedar produces (-) epizonarene (10 α-CH_3 isomer) even though its oil is rich in (-) curcumenes (β-CH_3 series) and (-) calamene[22] (10 β-CH_3). In fact the only correlation of β-CH_3 stereochemistry in this oil is (-) epizonarene and β-alaskene which elute as a single peak on gas chromatography.[2] The variable optical purity of these dienes in nature is not unexpected, considering the multiple pathways in which they could be produced in any particular plant oil.

EXPERIMENTAL PART

Oxidation of l-menthol to l-menthone (1)

l-Menthol (200 g) (α_D - 46°) was dissolved in about 250 ml. of acetone and Jone's reagent was added dropwise, while cooling the reaction flask. The reaction mixture was kept for an hour, after addition is complete and then poured into 1 lit. of water. Extraction with ether (200 x 3 ml) followed by thorough washing with water and bicarbonate, followed by removal of the solvent furnished the crude ketone (166 g). It was distilled at 100°/20 mm., α_D - 26.12°(neat). Analysed for C, 77.58; H, 11.58. $C_{10}H_{18}O$ requires C, 77.86; H, 11.76%. GLC on carbowax column at 100° showed it to be homogeneous.

Preparation of Mannich base (2) from l-menthone (1)

l-Menthone (123.2 g.) (0.8 moles), dimethylammonium chloride (40.5 g) (0.5 moles), paraformaldehyde (32 g) (0.1 mole) and 2 ml. of conc. HCl in 160 ml. of ethanol were refluxed on a water bath for 10 hours. At the end of 10 hours, all the alcohol was removed and the reaction mixture cooled, when the amine hydrochloride crystallises out. It was dissolved in about 100 ml. of water and thoroughly shaken with ether (200 ml) to remove the unreacted ketone. Aqueous layer is then strongly basified with 50% KOH solution and then saturated with potassium bicarbonate. The amine separates out as a dark red compound, which is taken in ether. Usual work up gave the crude Mannich base (2) (77 g). Distillation at 121°/0.1 mm. (bath 150°) afforded 74 g. of the pure compound. α_D - 35.36°(neat). IR spectrum

(liquid film): bands at 1375, 1470 and 1730 cm^{-1}. Analysed for C, 75.83; H, 12.30; N, 5.94. $C_{13}H_{25}ON$ requires C, 75.30; H, 12.10; N, 5.85%.

Preparation of the quaternary salt (3) from Mannich base (2)

Amine (2) (74 g) was dissolved in about 50 ml. of absolute alcohol and 75 g. of methyl iodide (1.5 moles) was carefully added to the flask with vigorous shaking. An exothermic reaction ensures and the formation ofquaternary salt is indicated by appearance of turbidity. The mixture was loosely stoppered and allowed to settle overnight at room temp.

Preparation of the conjugated ketone (4)

Freshly cut pieces of sodium (7.36 g) were placed in a flask with a condenser and a dropping funnel; 120 ml. of super dry alcohol was allowed to run down slowly while cooling the reaction flask. When all the sodium was reacted, 41.6 ml. of freshly distilled ethylacetoacetate was added. To the reaction mixture, the methiodide in a little anhydrous ethanol (25 ml) is slowly added with vigorous stirring and the reaction allowed to settle overnight. It is then refluxed on a steam bath for 6 hours.The reaction mixture is then thoroughly cooled and 50% KOH (26 ml) was added, followed by 25 ml. of ethanol. The solution is further refluxed for 3 hours. Reaction mixture is then cooled, diluted with water (40 ml) and extracted with ether. Usuaal work up gave a gummy dark red mass (42.3 g).

Isolation of solid ketone (4)

The entire quantity of the crude compound (42.3 g) was dissolved in 250 ml. of dry pet.ether and cooled at -20° for 56 hours, when the ketone

separated out as a yellow coloured solid. It was filtered off and washed with cold pet.ether (5°) till the yellow tinge adhering to the crystals disappears; 21.5 g. of pure material was then obtained in the first crop, and a further quantity (16.86 g.) was obtained by repeated cooling of the mother liquor of each filtration.

An alternative procedure was followed for fractions of the crude compound, which did not readily yield the crystals; 5 g. of the crude material was passed over silica gel (100 g., 1:20 ratio) and eluted successively with pet.ether, pet.ether-benzene (50:50) and benzene. Of the eleven benzene fractions (10 ml. each) collected, fractions V→ IX gave the crystalline ketone. TLC (pet.ether + 10% ethyl acetate) showed a single spot. GLC single peak (S.E. 30 column, 186° and polyester column, 210°), m.p. 69°; mass spectrum, M+ peak, 206.

IR spectrum (Fig. 2-1): Bands at 1681 and 1613 cm^{-1}

NMR spectrum in δ ppm (Fig. 2-2)

Solvent	C_{10}-methyl	C_7-isopropyl	C_5-vinylic proton
CCl_4	0.90(d; J~6 cps)	0.98(d; J~6 cps)	5.75 (ss; HW, 2 cps)
Pyridine	0.86(d), 0.76	0.86 & [illegible]	5.83 (s)
Benzene	0.79; [illegible]	0.89(d)	5.76 (ss)

CD $\Delta\varepsilon_{230}$ + 3.5, $\Delta\varepsilon_{315}$ - 0.3 (MeOH).

λ_{max}^{MeOH} 240 nm (ε, 26,100).

Semicarbazone, m.p. 158-59° (Analyses for N, 15.90%. $C_{15}H_{25}ON_3$ requires N, 15.97%).

Conversion of conjugated (4) to epizonarene (5)

Grignard reagent was prepared from 1 g. of magnesium (Riedel make, specific for Grignard reactions) and 8 g. of methyl iodide in anhydrous ether. 1.5 g. of ketone (4) dissolved in 10 ml. of anhydrous ether was added dropwise to the Grignard reagent cooled to 0-5° over a period of 15 minutes. The reaction mixture is then allowed to stir overnight at room temperature. The reaction mixture is then allowed to stir overnight at room temperature. The complex is then broken up by ice cooled solution of ammonium chloride (10%). It was then extracted with ether (30 ml). The ethereal layer is then shaken with sulfuric acid (A.R. Grade, 33% aqueous solution) for about 30 seconds, followed by washing with aqueous bicarbonate (10%). Usual work up gave the crude compound (1.21 g) which was chromatographed over a short column of alumina (Gr.I, 10 g.) and pet.ether elutions were collected. Evaporation of the solvent, followed by distillation over sodium (b.p. 105-110°/2.5 mm., bath) gave 0.987 g. of pure hydrocarbon. GLC run on carbowax column at 170° showed a single peak ($\geq$ 99%).

IR spectrum (Fig. 2.4). Bands at 840, 864, 950, 971, 1112, 1250, 1610 and 1645 cm^{-1}. (superimposable on the IR spectrum of authentic epizonarene).

NMR spectrum (CCl_4, Fig. 2.3) 0.99 (d, 3Mc, J~6 cps); 3.05 (heptet, 1H); 6.10 (ss, 1H); 1.71 (s, 1 Me).

α_D + 240.2 (in $CHCl_3$), UV spectrum (Fig. 2-5) λ_{max}^{MeOH} 246 nm (ε, 30,100).

Mass spectrum, M+ peak, 204.

Grignard reaction without acid washing

In a different set of experiments the acid washing of the ethereal layer was totally avoided. GLC (carbowax column, 174°) showed three peaks. One of the major peaks corresponds to (+) epizonarene. The mixture of dienes (6) was assigned appropriate structure based on the NMR spectrum (Fig. 2-6), as discussed under discussion part.

The mixture of dienes (0.410 g) on treatment with 33% sulfuric acid (3 ml) in ethereal solution were converted to (+) epizonarene as judged by GLC analysis ($\geq$ 95% conversion).

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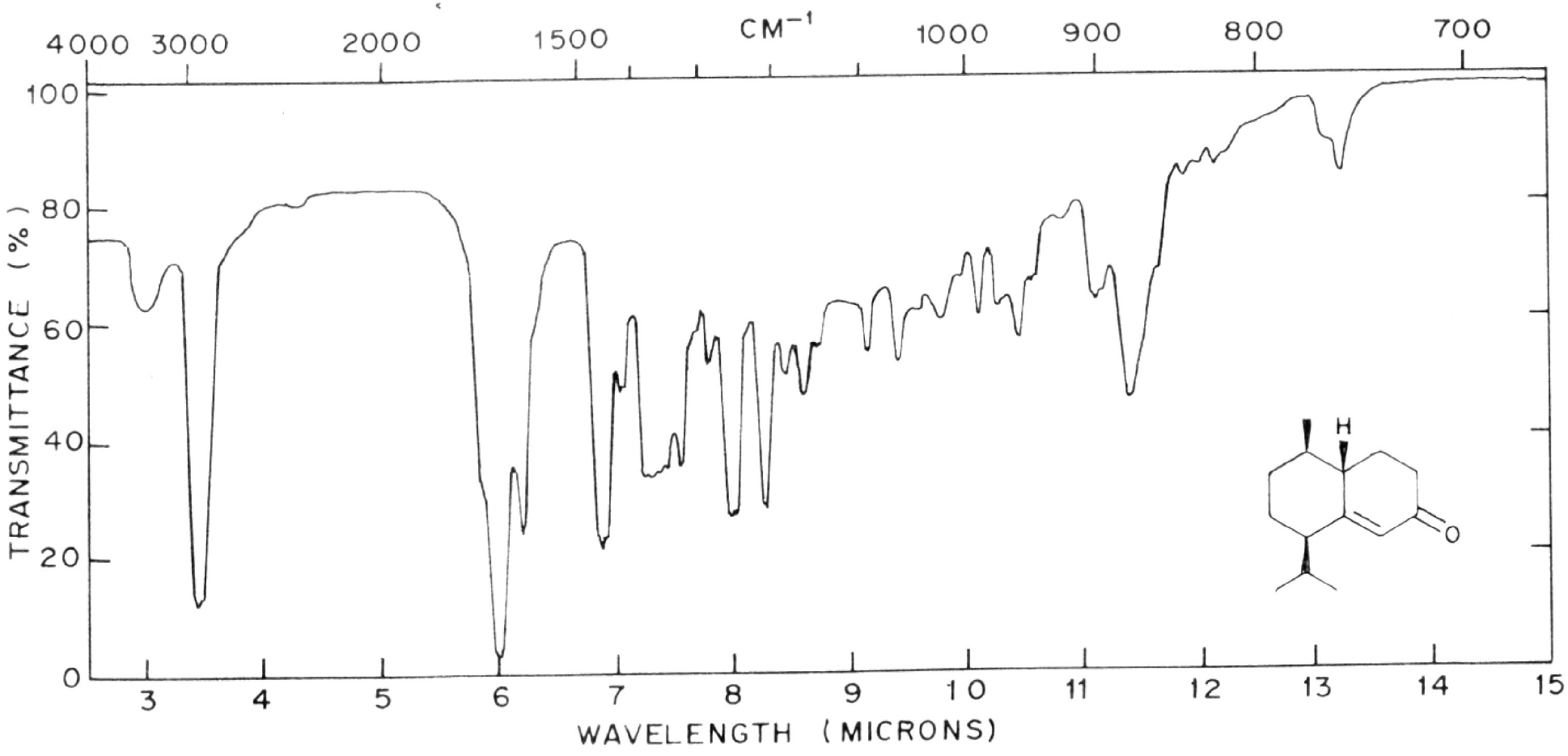


FIG - (2-1). IR SPECTRUM OF CONJUJATED KETONE (4)

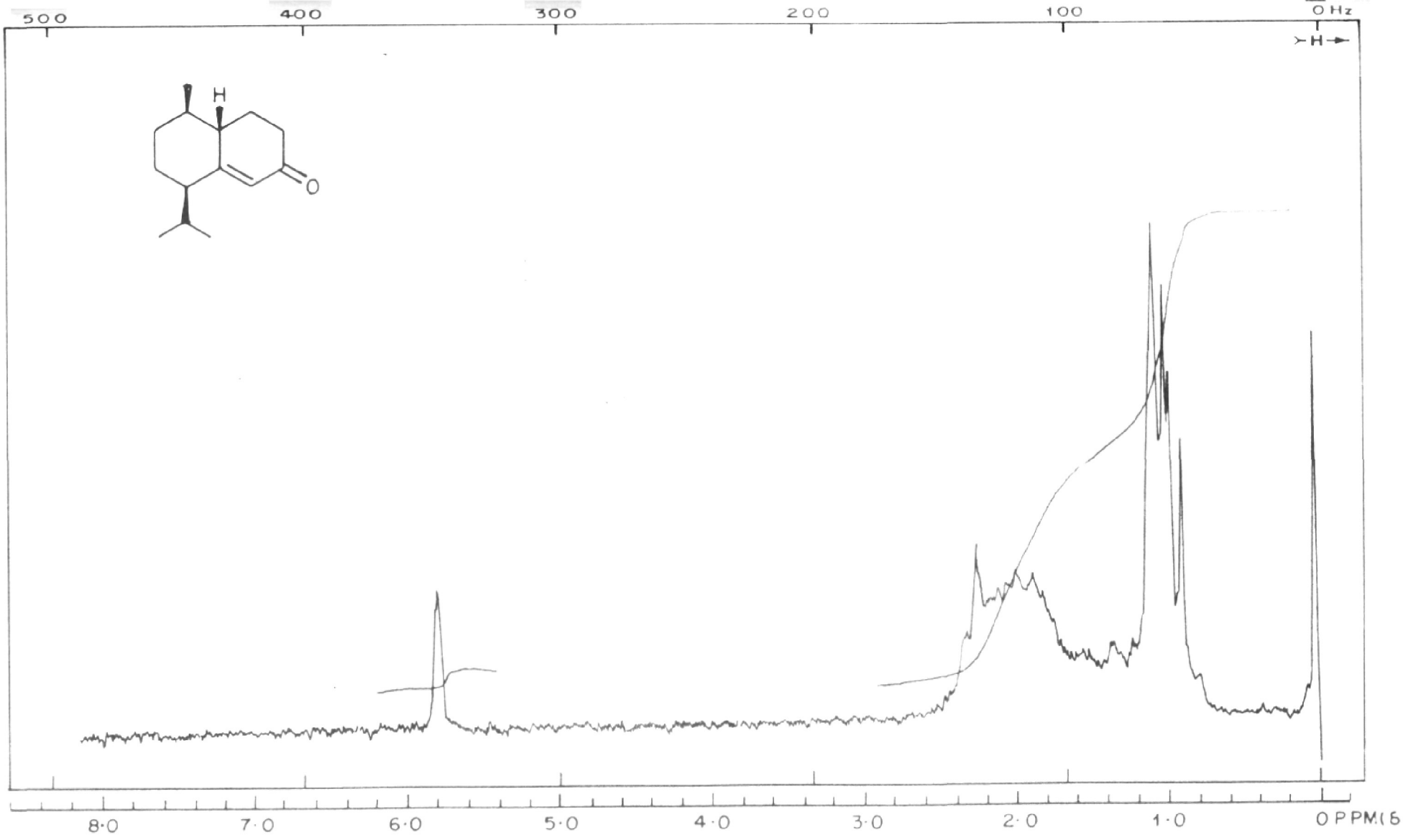


FIG. (2·2). NMR SPECTRUM OF CONJ. KET. (SOLID)

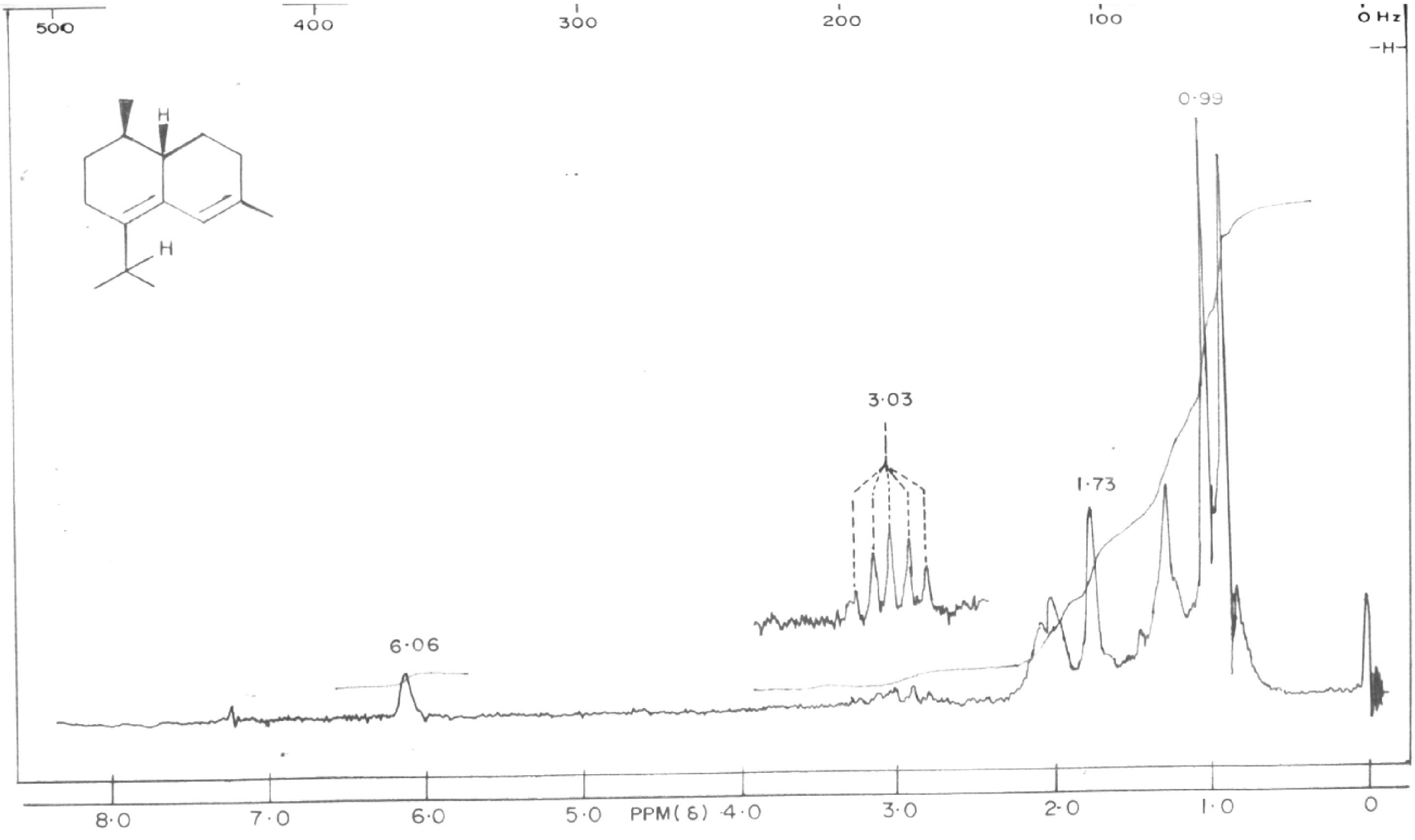


FIG. 2·3. NMR SPECTRUM OF (+) EPIZONARENE (5)

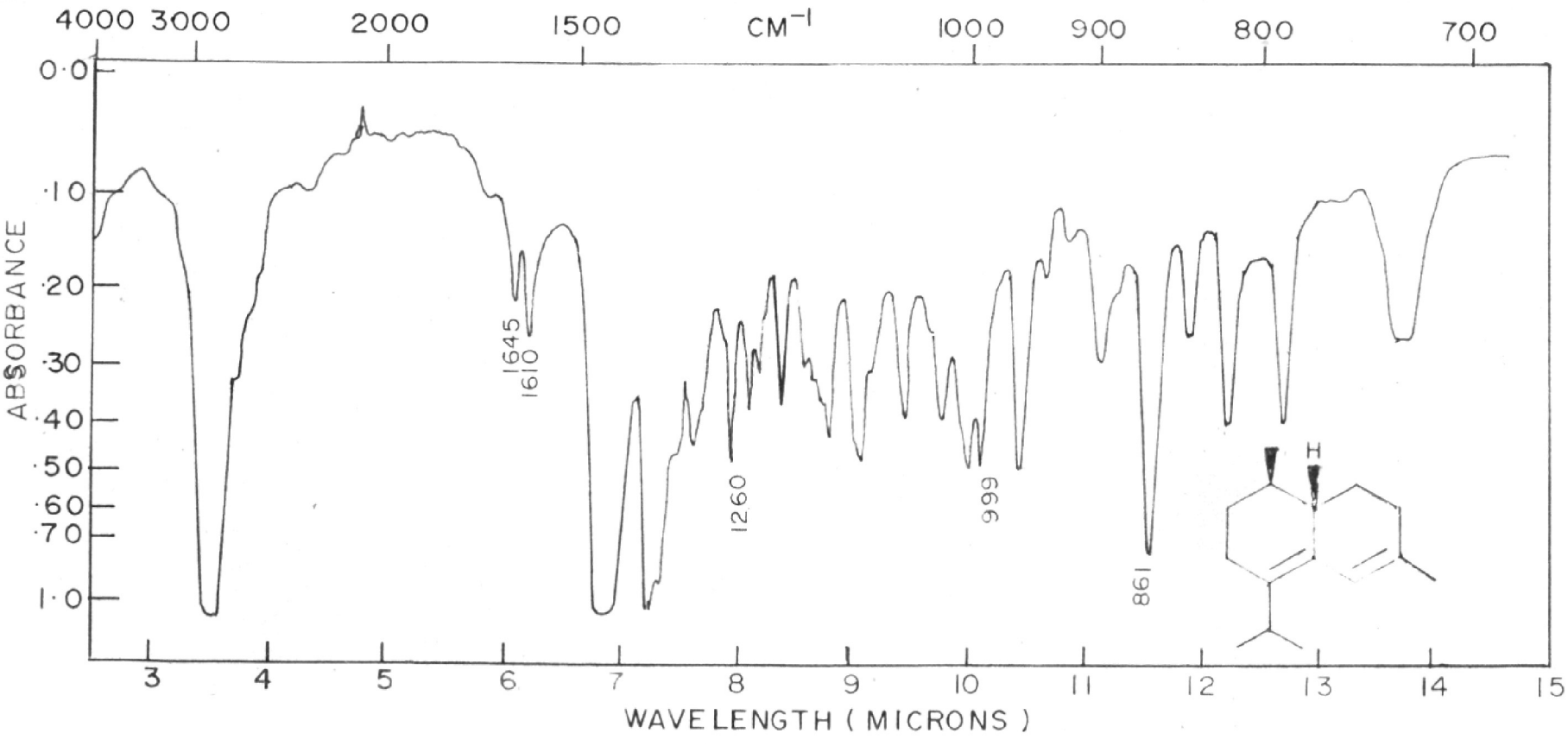


FIG. 2·4. IR SPECTRUM OF (+) EPIZONARENE

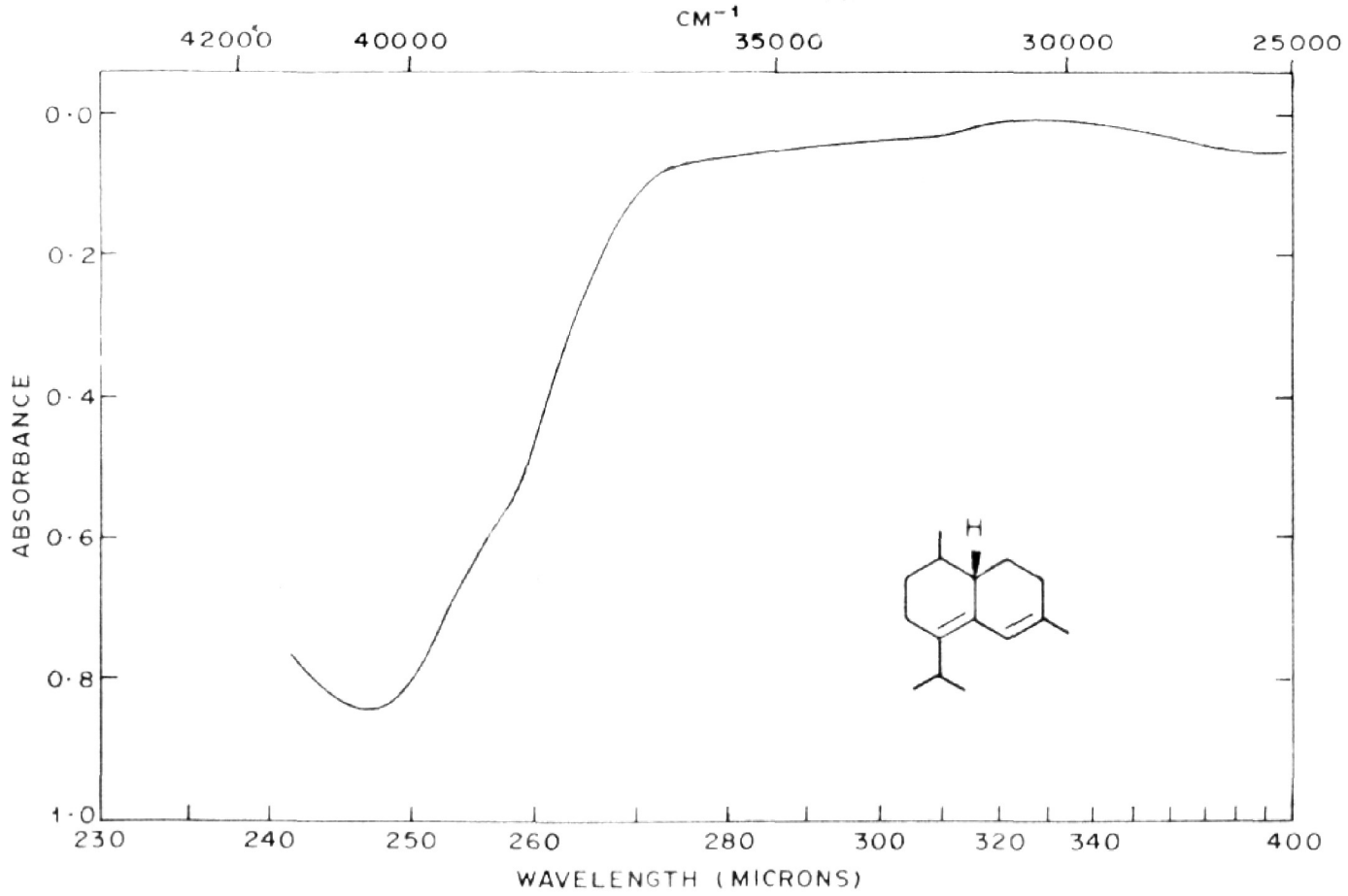


FIG. (2-5) UV SPECTRUM OF (+) EPIZONARENE

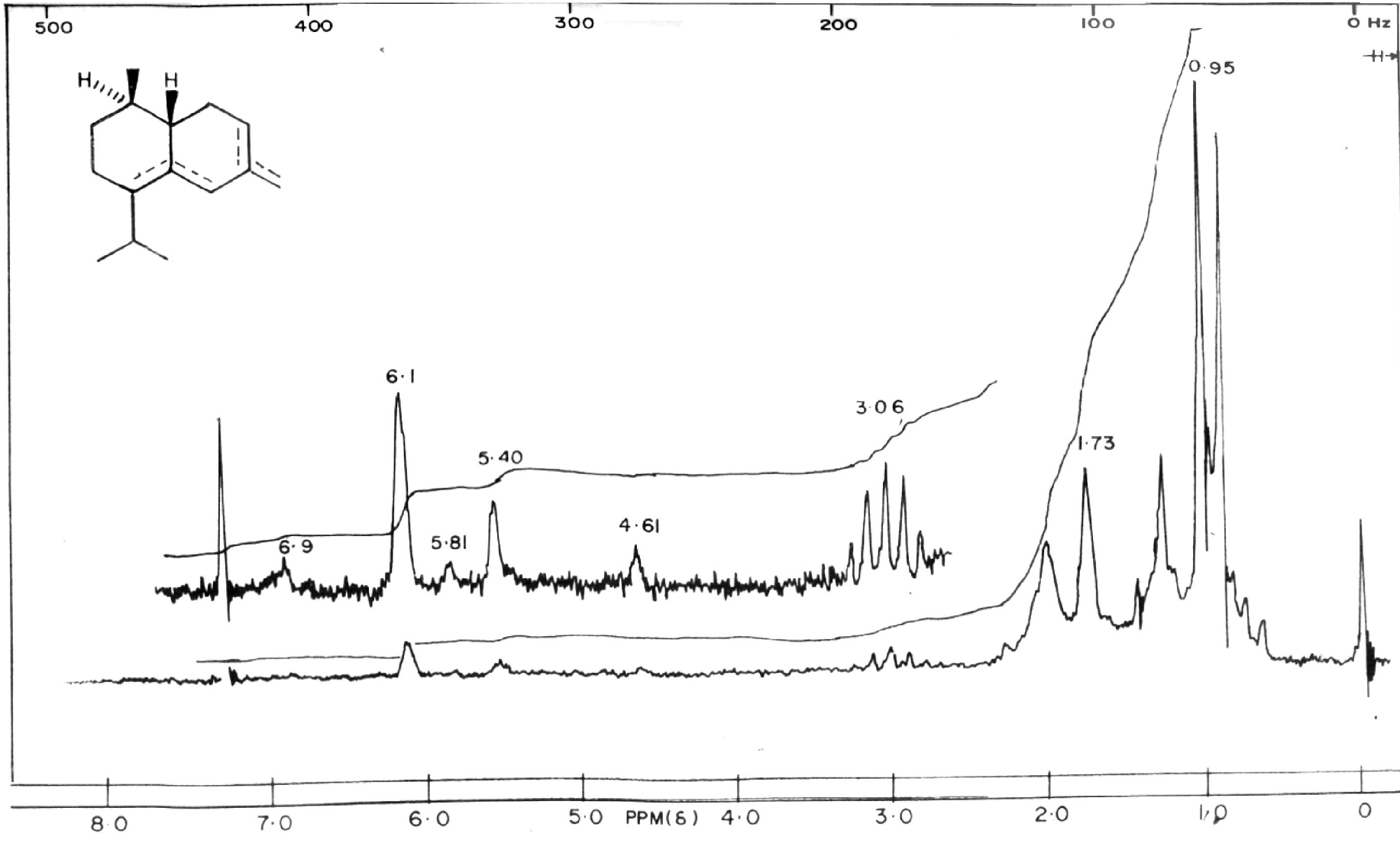


FIG. 2·6. NMR SPECTRUM OF DIENE MIXTURE (5+6)

C H A P T E R - II

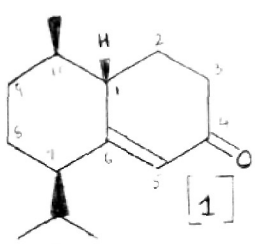
STEREOCHEMISTRY OF THE ISOPROPYL GROUP

***

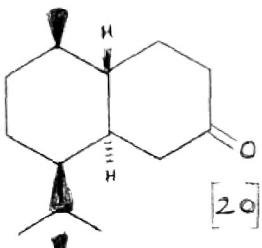
SUMMARY

This chapter describes the detailed studies undertaken to elucidate the stereochemistry of the conjugated ketone 1. During the course of this investigation, two ketones were prepared and both were studied separately.

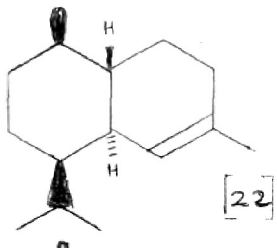
Firstly, the ketone (1) obtained as a solid was assigned the stereochemistry as shown in 1, based on its conversion to epizonarene, and dihydro compounds (dihydrobulgarenes) 22 and 23 and to the tetrahydro compound 28 (tetrahydrobulgarene). The CD data of 1 as well as its hydrogenation product (20) helped us to confirm the assigned stereochemistry.



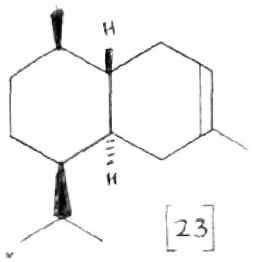
[1]



[20]



[22]



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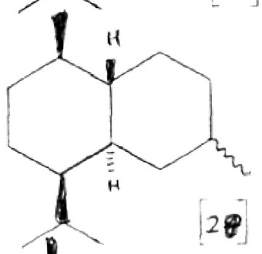
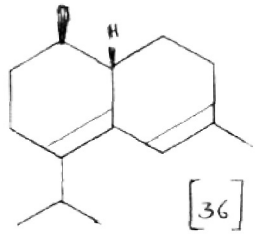
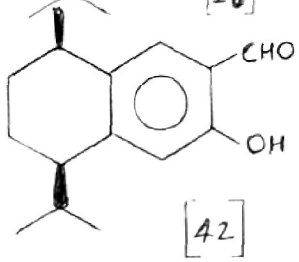


[28]

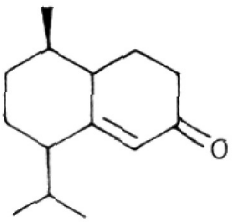


[36]



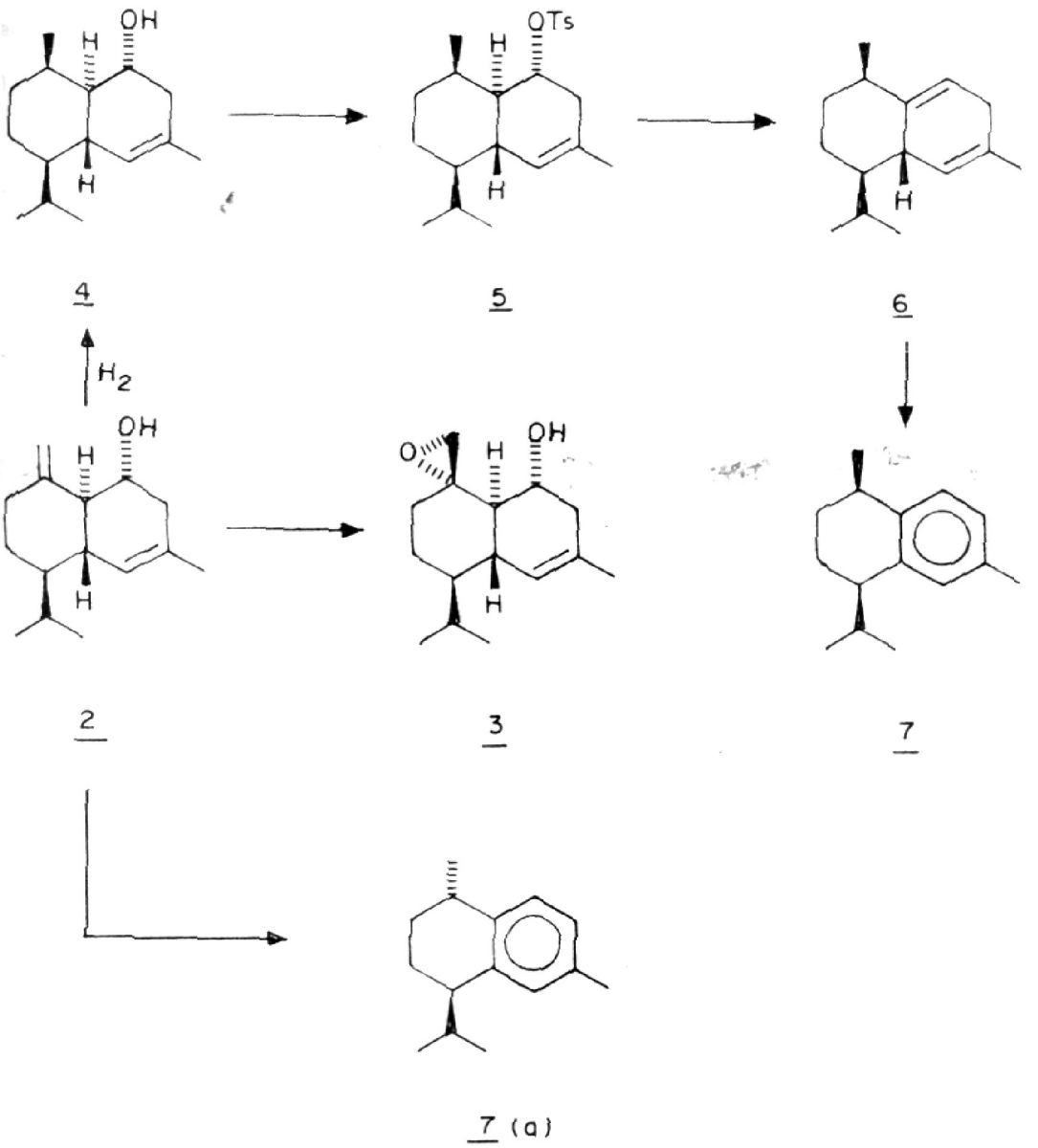
[42]

CHART I



1

Scheme I



4 5 6

H_2

2 3 7

7 (a)

A second form of the same ketone (1) was also encountered, and based on its conversion to epizonarene and zonarene and also by the synthesis of its enol acetate (36) and compound (42), the stereochemistry at various centres was ascertained. The difference between the two forms of ketone is discussed at the end of the chapter.

Conjugated ketone (1) is a very useful intermediate for the syntheses of a number of naturally occurring compounds. An obvious requirement for using this ketone, as a potential intermediate, is the elucidation of its stereochemistry, at all the centres (C_1, C_7 and C_{10} positions). Once this is accomplished, the ketone can then be used for the syntheses of any one of the cadinanes, muurolanes, amorphanes or bulgaranes. As will be evident, later, the elucidation of the stereochemistry of the C_7 isopropyl group is a tough problem. Absence of genuine chemical methods and the flexibility of the decalin system are two reasons for this difficulty. In case of compound I, the purity of the compound itself was a problem, though this is of secondary nature, since compromise may be made when dealing with a mixture of diastereomers.

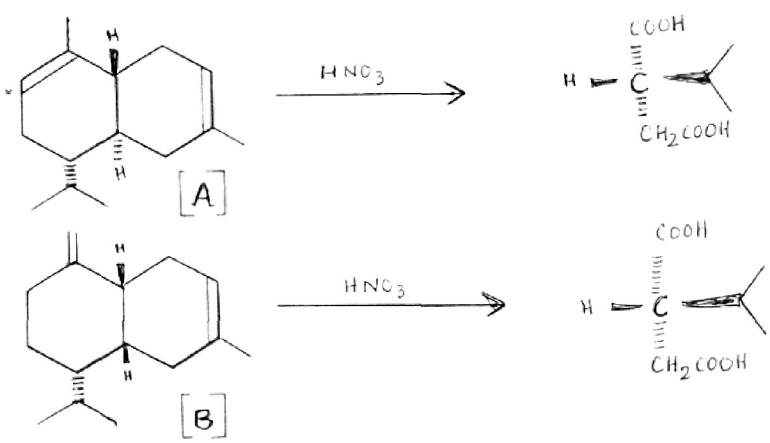
Though the presence of isopropyl group in sesquiterpene chemistry is a very conspicuous feature, relatively little work is done regarding the elucidation of stereochemistry of the isopropyl group. One of the reasons may be that the bulkiness of the group has naturally led to the assumption that it assumes an equatorial conformation,[1] in accordance with the fundamentals of conformational analysis. This

simple rule, as we shall see later, no longer holds good in the case of compound 1, where unfavourable factors, force the isopropyl group to assume an axial orientation.

Methods available for determining isopropyl stereochemistry

Two widely different methods are so far known to determine the stereochemistry of the isopropyl group in cadalene type of sesquiterpenes. One of them is based on purely chemical means and the other purely on physical means, but both of them establish absolute stereochemistry without any ambiguity.

The unambiguous absolute configuration of compounds based on chemical proof is by oxidative degradation of the sesquiterpenes by conc. nitric acid to the corresponding isopropyl succinic acid. The existence of four diastereomeric series of cadalenic type of sesquiterpenes (cadinanes, muurolanes, amorphanes and bulgaranes) has been proved based on these considerations.[2-5] Thus for example, β-cadinene(A) gives S(+) isopropyl succinic acid,[3] and (-) r_2 amorphane (B) gives S(+) isopropyl succinic acid.



Similarly the absolute configuration of muurolenes[4] and bulgarenes[6] has been established.

The second method based on physical means is by X-ray diffraction of dihydrochlorides of these compounds. This technique has been used in case of (-) cadinene dihydrochloride[2] and bulgarene hydrochloride.[6] The immediate disadvantage of this method becomes clear when one recognises the fact that this method cannot be used in case of compounds which do not form a solid dihydrochlorides (for example compounds of amorphene series).

The classification of the cadalenic type of sesquiterpenes into four groups (cadinanes, muurolanes, amorphanes and bulgaranes) is based on the nature of the ring juncture (C_1 and C_6 stereochemistry) and on C_7 stereochemistry. From this point of view, the elucidation of the stereochemistry of C_7 isopropyl group in our ketone 1 is of importance. This compound can be used for the synthesis of a number of naturally occurring compounds like calamenene, zonarene, epizonarene, bicyclosesquiphellandrene, etc. and the elucidation of the stereochemistry of this ketone may have far reaching consequences. In addition to this, certain erroneous reports in the literature concerning the stereochemistry of this compound led us to take the reinvestigation.

The synthesis of (+) cis calamenene by us through the conjugated ketone 1 was the main reason to take up the reinvestigation of compound 1. Starting from l-menthone, which has a trans-stereochemistry, we expected to end in trans-calamenene; in fact the (+) calamenene synthesised by us was assigned a trans structure in our preliminary publication.[7] This was however revised to cis based on a number of considerations.[8]

The first clue to the cis stereochemistry of our compound was obtained on comparing the rotation of (-) calamenene obtained from 7-hydroxy-calamenene by Rowe et al.* Our synthetic sample had α_D + 42° and calamenene of Rowe had α_D - 42°. The isopropyl group was assigned an 'S' configuration by these workers.[9] The NMR spectrum of this compound agreed with ours (especially the major peaks at 43, 50, 58 and 65 cps). This suggested that our compound must have the isopropyl in 'R' configuration (B-isopropyl). Since we started from l-menthone with a β-methyl group (R configuration) our calamenene must contain cis isomer (7) as the major compound.

The second clue to the change in stereochemistry of the isopropyl group was indicated by the half width of the C_5-olefinic proton (NMR) in compound 1. C_5-proton can couple with two allylic protons, one at C_1 and the other at C_7. Coupling with C_1 would produce a singlet for C_5 with a half width of 2 cps (approx.). A further coupling with C_7 proton (possible only if it is axial and makes an dihydral angle close to 90° with the C_5 proton) would broaden this signal to 4.3 cps.[10] The observed half width of 2 cps in our compound indicated virtually no allylic coupling between C_5 and C_7 protons (dihedral angle, almost zero). In other words, the isopropyl group must assume an axial (β, in view of the above observation) orientation in ketone 1.

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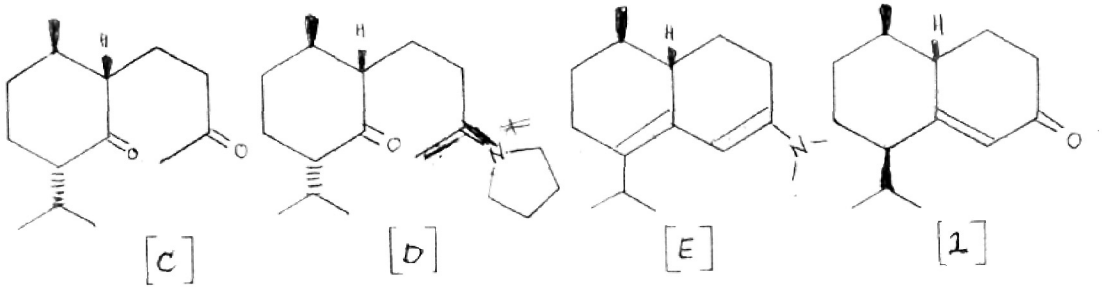
* We are grateful to Prof. J.W. Rowe, Forest Products Laboratory, Madison, Wisconsin, for sending a copy of the manuscript of his paper prior to publication.[9]

The change in stereochemistry from α-equatorial in l-menthone to β-axial in ketone 1 was initially baffling, but a reasonable explanation can be put forward at this stage. This change in stereochemistry might have taken place during the formation of unsaturated ketone (1) from the open chain ketone (c), followed by protonation with acid.



[C] [D] [E] [1]

The change in stereochemistry is attributed to the allylic strain,[11] one should expect between the C_5 proton and the C_7 isopropyl group, if the latter is in a α-equatorial configuration. The β-axial stereochemistry for the isopropyl is especially favoured, since protonation occurs from α side in (E); β-protonation would give a compound having an equatorial isopropyl group, which will introduce a non-bonded interaction with the C_5 olefinic proton.

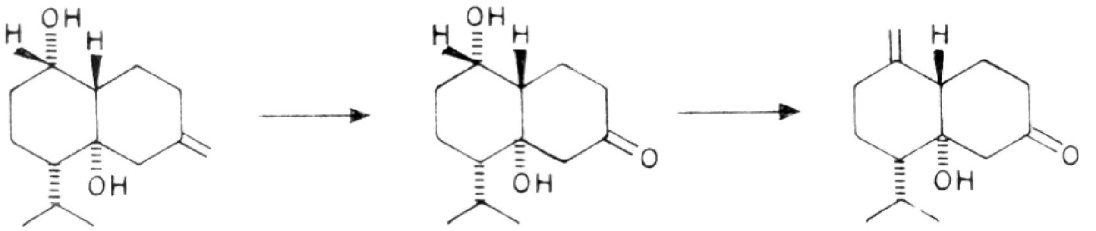
These arguments were amply supported by synthesis of (+) calamenene (of α_D + 37.5°) from dihydrokhusinol[12] (Chart 1). Dihydrokhusinol (4) is obtained from khusinol (2) by catalytic hydrogenation, and hence the relative stereochemistry in 4 at C_7 and C_{10} must be cis. The explanation for the hydrogenation of khusinol (2) occurring from

β-side may be obtained by the nature of epoxidation of 2. Khusinol(2) on epoxidation with perchlorobenzoic acid gives monoepoxide (3).[13] It follows from this that hydrogenation of 2 must also occur from the same side as epoxidation. Further, the conversion of dihydrokhusinol (4) to (+) calamenene (7) through tosylation to 5, followed by solvolysis in pyridine and dehydrogenation, should involve no inversion at C_{10} or C_7. Thus the calamenene obtained by this method was anticipated to be cis. This was indeed found to be the case, as the NMR signals of this compound agreed very well with ours. (+) Calamenene (7a) obtained from khusinol (2)[14] has α_D of + 82° and the four signals in the NMR of this compound agreed with the satellite peaks of our synthetic calamenene, (40, 47, 53 and 65 cos). As also natural calemenene[15] with α_D - 80°, had a similar pattern in the NMR spectrum. These satellite peaks correspond to the impurity of trans isomer in our synthetic calamenene. On the basis of rotations of pure trans (α_D-80°) and pure cis (α_D + 35°5(± 2) calamenenes we calculated the ratio of cis-trans calamenenes in our synthetic compound. It turned out to be a 80:20 mixture with a rotation of + [illegible].460°

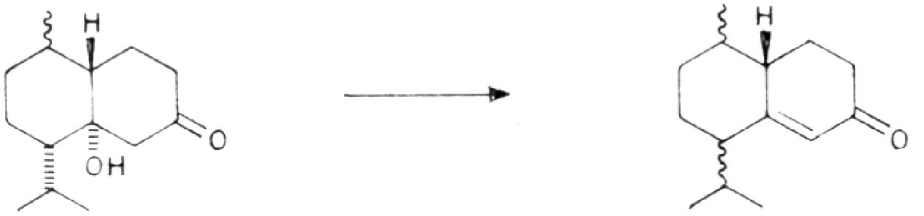
The outcome of all these findings can be summarised in a way to make it useful for future stereochemical elucidations. The stereochemistry of the natural calamenenes can be determined by the NMR signals and their optical rotation helps us to determine the ratio of trans-cis mixture. The pure (-) trans compound gives NMR signals at 40, 47, 56, and 63 cps and has α_D - 80° and the pure (+) cis-compound gives signals

CHART II

Scheme II

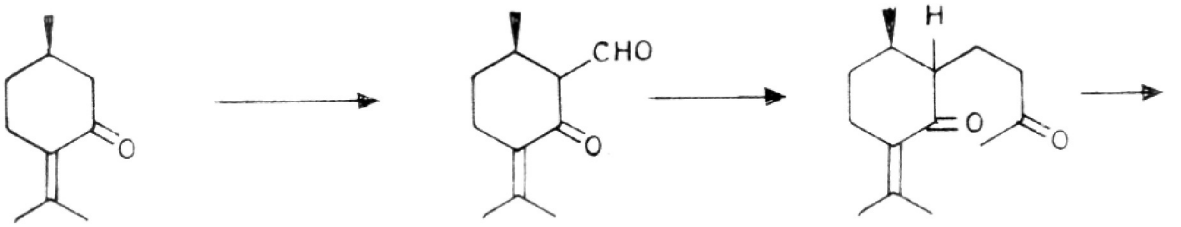


8 9 10

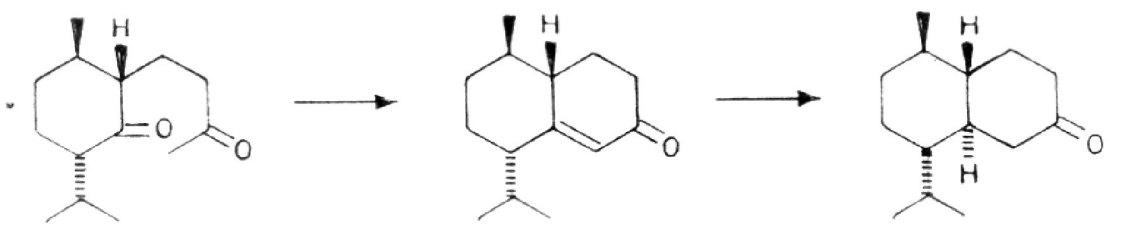


11 12

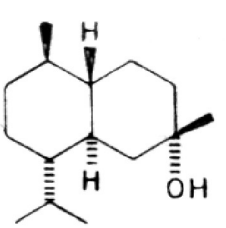
Scheme III



13 14 15



16 17 18



19

at 43, 50, 58 and 65 cps,and has α_D + 37°. Andersen et al.[16] have independently arrived at the same conclusion by a more elaborate study, through ORD measurements.

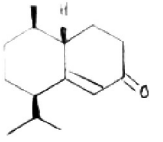
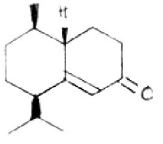
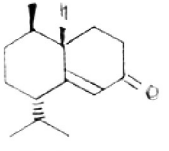
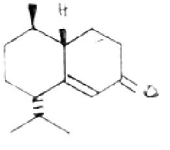
It was therefore our intention to reinvestigate the conjugated ketone (1) and to confirm our original findings. It would be appropriate at this stage to make a brief mention of the literature dealing with this ketone. This is summarised in the chart.

The first synthesis of this ketone through Mannich reaction[17] on l-menthone does not report of any detailed studies regarding the compound. The second synthesis[18] is on closely similar lines to the first, except that diethylammonium chloride is used instead of morpholine hydrochloride in the Mannich reaction. The ketone obtained is a liquid and no stereochemistry is discussed.

In the third report[19] the ketone is obtained as a degradation product of isocalamendiol. The transformation is depicted in scheme II. Isocalamendiol (8) on ozonolysis gave a ketone (9). Further treatment of 9 with $POCl_3$ - pyridine at room temperature gave dehydroketone 10. Catalytic hydrogenation of 10 over PtO_2 gave dihydroketone (11), which on refluxing with sodium methoxide and methanol gave the $\alpha:\beta$-unsaturated ketone (12). These workers have established the absolute configuration of isocalamendiol as 8 in their later report,[20] assigning an equatorial configuration for the isopropyl group in compound 8, but no comments are made regarding the stereochemistry of the isopropyl group in the ketone(12) The NMR* of 12 agreed with the NMR of one of our ketones.[7] (see later).

* We thank Prof.Yamamura for kindly sending us the NMR of this compound for comparison.

PHYSICO CHEMICAL DATA OF THE CONJUGATED KETONE

Source	Purity	Rotation α_D	PMR spectrum (δ ppm) C_{10} Me & C_7 isopr.	PMR spectrum (δ ppm) C_5 proton	UV λ_{max}.	Proposed structure	Ref. No.
Menthone & morpholine hydrochloride.	Solid m.p.69°	-	-	-	-	~~17~~	17
Menthone & Michael addition of MVK	Liquid mixture	-42°	0.78(d) 0.98	5.84 HW or 2 cps.	242 nm.		7
Menthone & diethyl amine hydrochloride.	Liquid	-	-	-	-		18
Menthone and dimethylamine hydrochloride	Solid m.p.68°	-3°	0.98(d)	5.66 HW 2 cps	240 nm.		Present investigation
Preisocalamendiol	Liquid	-	0.78(d) 0.98	5.84 HW 2 cps	-		19
Isopulegone & Michael addition of MVK	-	-	θ	-			21
(+) Menthone & Michael addition of MVK.	-						22

The fourth report[21] of synthesis of this unsaturated ketone, starting from pulegone (13) is depicted in scheme III. The stereochemical assignment of the isopropyl group is wrongly done, as will be evident from the discussion in the later part of this chapter.

Recently Vig et al.[22] have synthesised this ketone by the same route as ours.[7] (Michael addition through methyl vinyl ketone). However, stereochemical inconsistencies are possible in their report. The discussion of this also is deferred to the later part.

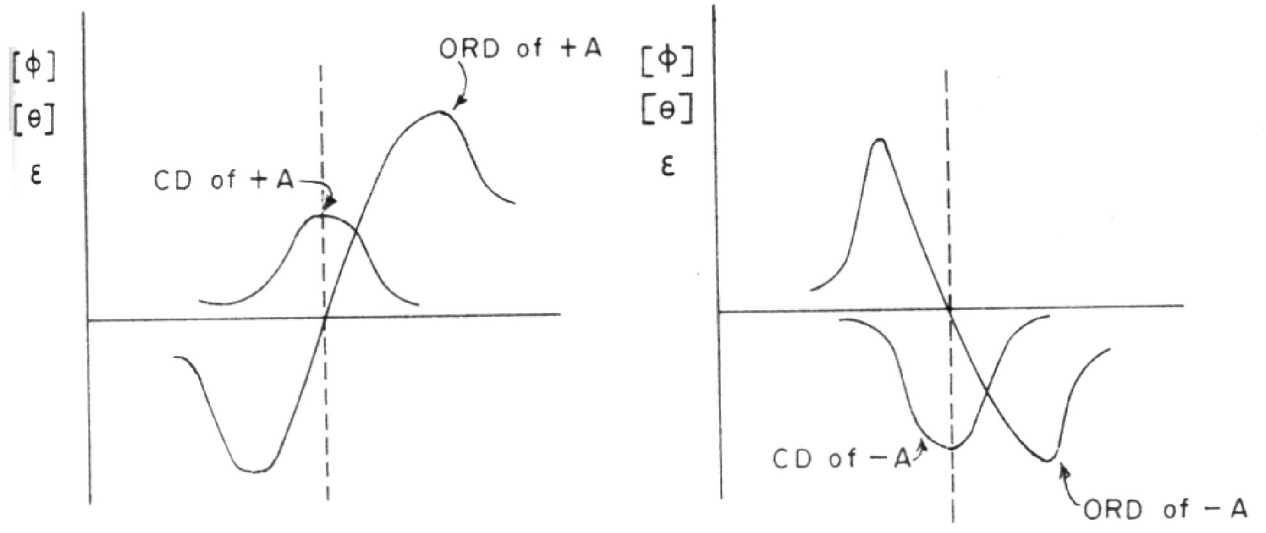
PRESENT INVESTIGATION

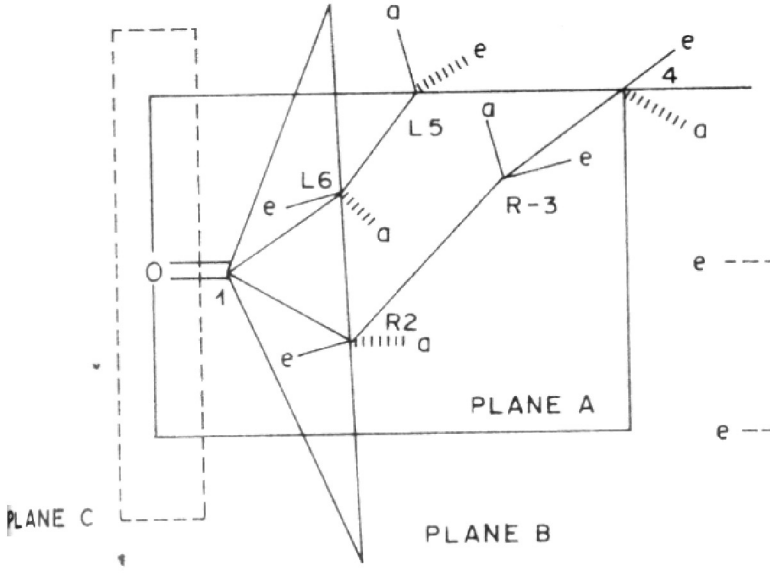
The synthesis of the conjugated ketone is already described in the first chapter. However, some points have to be made clear, before proceeding with the discussion of our findings. Out of twelve experiments to prepare the conjugated ketone (1) we were able to isolate it as a crystalline solid only twice; the rest of the time it was obtained as a liquid, which could not be induced to crystallise. The solid seems to be unstable, isomerising slowly from solid form to a liquid form. The liquid compound on the other hand is quite stable. Apart from this difference in physical state, the two ketones (designated henceforth as solid and liquid ketones) have two more important differences. They differ in their NMR spectrum (especially C_{10} methyl signal) and also in the magnitude of their rotations. The solid (α_D - 3°) shows the C_{10} methyl in NMR at 0.99(d) and isopropyl at 0.98(d) and C_5 proton at 5.66 (ss, HW, 2 cps). The liquid ketone (α_D - 60°) has the C_{10} methyl at 0.77(d), isopropyl at 0.98(d), 1.03(d), and C_5 proton at 5.70 (ss, HW, 2 cps). This difference prompted us to study the two ketones separately.

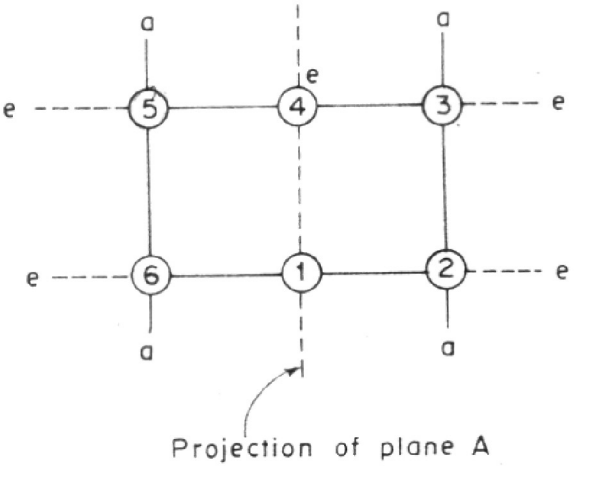
SOLID KETONE

C_1 and C_{10} stereochemistry. The C_1 and C_{10} stereochemistry of the solid conjugated ketone was decisively established as 'B' on the basis of its conversion to (+) epizonarene (see first chapter) and also by circular dichroism data. Since we are dealing with the CD data in this chapter, a brief discussion of this subject follows:

CHART III


[ϕ]
[θ]
ε
ORD of +A
CD of +A
[ϕ]
[θ]
ε
CD of −A
ORD of −A


a
e
e
4
L5
a
e
L6
e
a
R-3
O
1
R2
e
a
PLANE A
PLANE C
PLANE B


a
a
e
e
5
4
3
e
e
6
1
2
e
a
a
Projection of plane A

The chiro-optical techniques, optical rotatory dispersion (ORD) and circular dichroism (CD) have now been used by organic chemists for about twenty years. These techniques measure the interaction of the polarised light with a disymmetric medium; ORD arises from difference in refraction and CD from the difference in absorption by the medium for right and left circularly polarised light.[23]

The figure in chart III shows the relationship between the absorption band and ORD/CD of an imaginary compound A. The Cotton effect in the CD curve of +A has a single positive maximum at appropriately the same wavelength as the maximum of the UV absorption hand, while in the ORD curve, the Cotton effect shows two extrema, one positive (peak) and one negative (trough); in an ideal case, the wavelength of the midpoint of the ORD curve, coincides with the wavelength of the CD and UV maxima. For the enatiomeric compound the sign of the Cotton effect is necessarily reversed. ORD results are expressed in units of molecular rotation (ϕ) defined by $(\phi) = M \times 10^{-2}[\alpha]$ where M is the molecular weight and (α) the specific rotation at a given wavelength. The amplitude 'a' which is a convenient measure of the magnitude of the Cotton effect, is the difference between the molecular rotation at the extremum of longer wavelength $(\phi)_1$ and the molecular rotation at the extremum of shorter wavelength $(\phi)_2$, divided by 100 for convenience. Thus,

$$a = \frac{\left([\phi]_1 - [\phi]_2\right)}{100} = \left([\phi]_1 - [\phi]_2\right) \times 10^{-2}$$

For CD, two units are in common use, the differential absorption, $\Delta\varepsilon = (E_L - E_R)$ and (θ), molecular eliplicity. These two are related by the relation

$$[\theta] = 3300.\Delta\varepsilon$$

In our work we have used the differential absorption units $(\Delta\varepsilon)$.

Carbonyl Chromophores

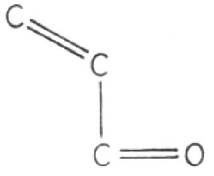
The study of the carbonyl chromophores by various distinguished workers, culminated in the octant rule,[24] which summarises the relationship between the absolute configuration and conformation of the asymmetric environment of the carbonyl $n \rightarrow \pi^*$ transition and the sign and semi-quantitatively, the intensity of the Cotton effect. The relative importance of the octant rule which is summarised below, may be attributed first to the accessibility of $n \rightarrow \pi^*$ transition of approximately 290 nm. to the earliest spectrophotometers; second to the very extensive data available for ketones and third to the comparitive simplicity of the carbonyl chromophore, whose two symmetry planes are necessarily the two regional boundaries in the octant rule.

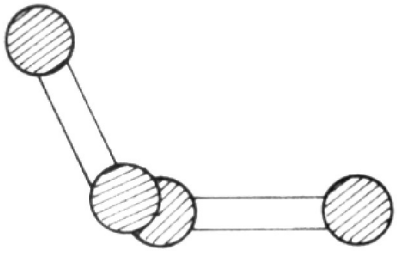
The carbonyl chromophore being the reference point, a cyclohexanone can be divided into eight octants, by means of three mutually perpendicular planes. These are the nodal and the symmetry planes of the orbitals involved in the $n \rightarrow \pi^*$ transition, associated with the absorption of the carbonyl chromophore. The cyclohexanone is used as an example only because it is easy to discuss. However, the same concept is applicable to any ring system or a side chain carrying a carbonyl chromophore.

As shown in Figure (chart III) the plane A is vertical passing through C_1 and C_4. The only substituents in this plane are the ones attached to C_4. The horizontal plane consists of carbon atoms bearing the carbonyl group (C_1) and its adjacent carbon atoms; C_2 to the right called R-2 and C_6 to the left called L-6. The equatorially oriented substituents, attached to these carbon atoms, C_2 and C_6, lie in the nodal plane B; planes A and B, provide four octants, 'back octants'. A third plane 'C' perpendicular to plane 'A' and dissecting the oxygen-carbon bond, produces four additional octants, called 'front-octants'. The four back-octants, defined by planes A and B are the most important ones, for practical application.

The octant rule states that the substituents lying in plane A and B make no contribution to the Cotton effect associated with carbonyl. Indeed a substituent, which is in one of the symmetry planes does not appear unsymmetrical to the carbonyl chromophore. This includes the equatorial substituents on carbon atoms C_2 and C_6, provided that they are exactly in the plane and both substituents on carbon C_4. Furthermore, the atoms or groups of atoms situated in an axial configuration on C-2 (lower right octant) as well as the axial and equatorial substituents on C_5 (upper left octant) make a positive contribution to the Cotton effect. Finally the substituents situated in an axial configuration on carbon C_6 (lower left octant) as well as the axial and equatorial substituents on carbon 3 produce negative Cotton effect.

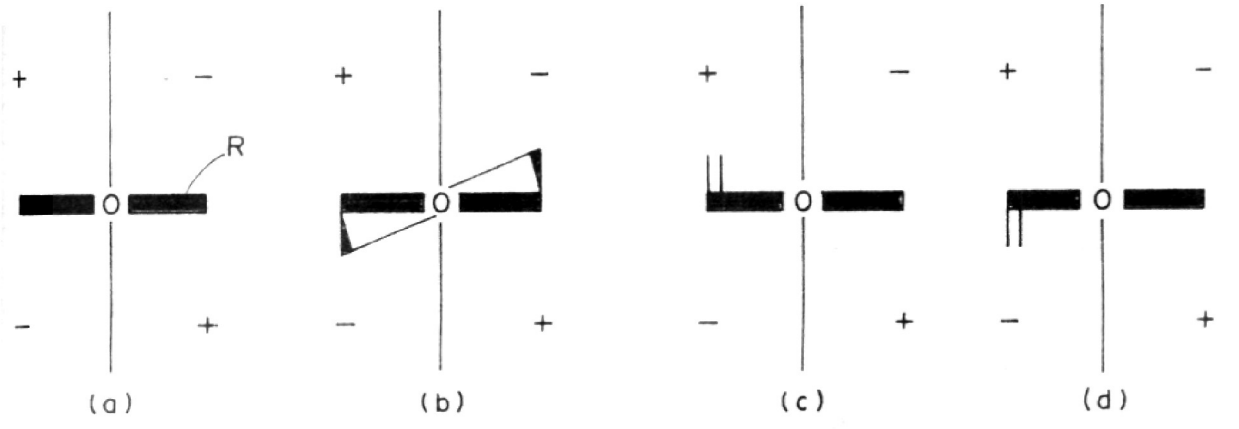
CHART IV

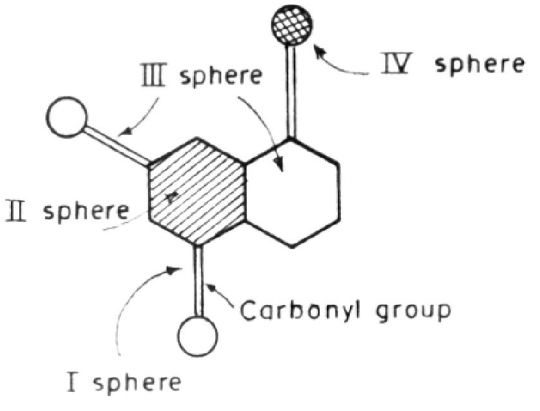




$n \rightarrow \pi^*$
R – band
– CE

$\pi \rightarrow \pi^*$
K – band
+ CE



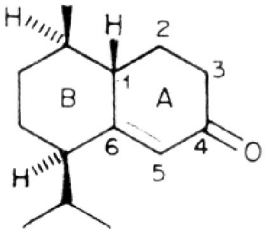


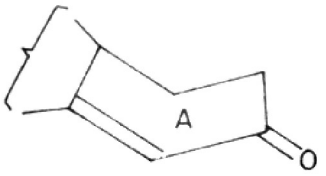
$\alpha:\beta$-Unsaturated Ketones

A fairly good amount of work has been done on CD of $\alpha:\beta$-unsaturated ketones.[25,26] $\alpha:\beta$ -Unsaturated ketones show two bands in the accessible region of UV modern spectrophotometers, one at about 350 nm, which is due to an $n \rightarrow \pi^*$ transition (R-band) and another between 230 nm and 260 nm, coming from $\pi \rightarrow \pi^*$ transition (K-band), In chiral molecules both are optically active and give rise to simple or complex Cotton effects. In 1962 a rule was proposed for correlating the chirality of a non-planar transoid-enone system with the sign of Cotton effect of the K band. Similarly another one has been proposed for the R band.

The above mentioned correlation between the chirality of a transoid-enone chromophore and sign of the Cotton effect can be derived from a very pictorial treatment of this $n \rightarrow \pi^*$ transition. For this it is useful to make a list of the more important rules for ketones, as is done in Figure (a,b,c and d in chart IV) in such a way as to depict a configuration always giving rise to negative $n \rightarrow \pi^*$ Cotton effect. The ring in to which the carbonyl is incorporated twisted, as in most cyclophentanones and cyclohexanones with the $\rangle C=O$ in the point, the chirality of the twist determines the sign of the Cotton effect (b). All these rules are understood if one divides the molecule into spheres and postulates that the nearest sphere to the chromophore which becomes disymmetric determines the sign and to a great extent the magnitude of the Cotton effect. If the first and the second spheres of a ketone are

CHART V





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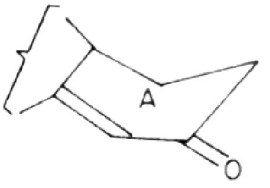
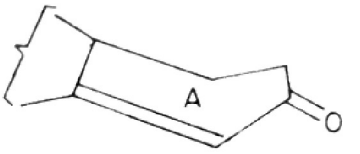
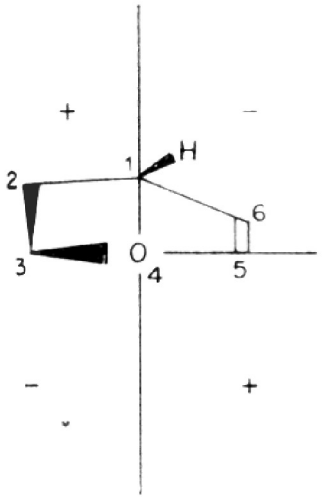
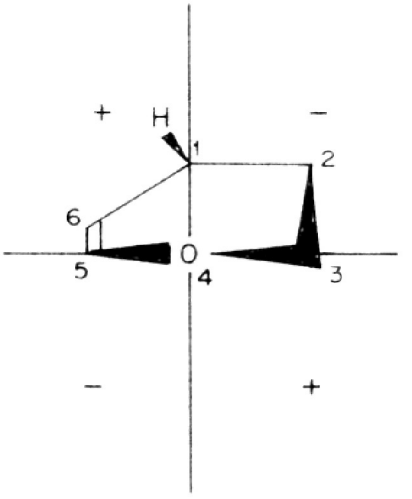


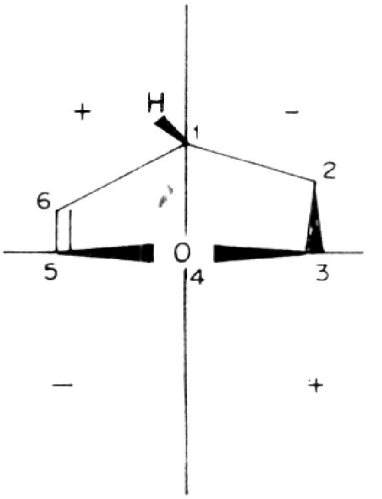
II



III







SIGN OF COTTON EFFECT (R. BAND) →	− Ve	+ Ve	+ Ve

symmetric (chair or a C_{2v} boat cyclohexanone ring) and only in these cases, the normal octant rule is valid. Let us apply these considerations to our solid ketone.

Circular dichroism of solid conjugated ketone

The ring A of this compound can adopt any one of the three conformations, two half chairs and one half boat (Boat can mean any one of the possible conformations of the cyclohexanone ring. The classical boat is referred to by indicating its C_{2v} symmetry). The observed Cotton effect of our ketone are as follows:

K band $\Delta\varepsilon_{230}$ + 3.5

R band $\Delta\varepsilon_{315}$ - 0.3

From the molecular models it is clear that the entire third sphere falls in the upper right octant in case of I (-ve Cotton effect) and in upper left octant in case of II (+ve Cotton effect). This is the sphere which contributes most to the observed Cotton effect. The orientation of the isopropyl group which constitutes the IVth sphere is irrelevant, because in either conformation (α or β) the sign of Cotton effect remains the same. The assigned stereochemistry at C_1 and C_{10} is thus in agreement with the sign of the observed Cotton effect of the R band.*

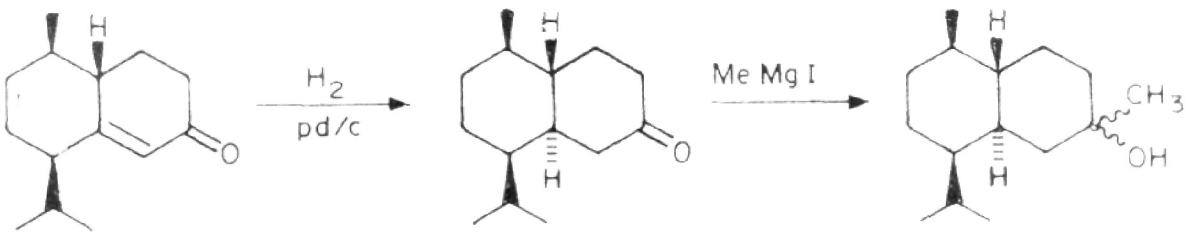
* It should be noted that in assigning the stereochemistry at C_1 position on the basis of R band Cotton effect, the ring 'A' is assumed to have a half chair conformation. The half boat is unfavourable from strain point of view.

Catalytic Hydrogenation

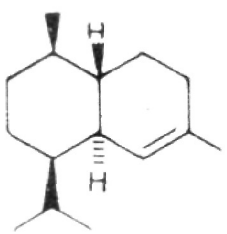
The circular dichroism curves of the solid ketone do not help us in determining the stereochemistry of the conjugated ketone at C_7. The determination of the stereochemistry through catalytic hydrogenation followed by preparation and subsequent separation of the dihydrocompounds (22 and 23) is described below.

Both the ease and stereochemical course of catalytic hydrogegenation of α,β-unsaturated ketones are influenced by the nature of the solvent and by the presence of acid or base in the reaction mixture.[27] The interpretation of results from the hydrogenation of conjugated ketones, is further complicated by the possibility that the conjugated ketone may isomerise to the unconjugated ketone during hydrogenation. The increased amount of trans-fused product obtained by the hydrogenation of the enone in basic solution has been suggested to arise from the hydrogenation of relatively planar enolate anion present in the solution.[28] In acidic solution (pH $\ll$ 2) the O-protonated derivative of the enone is thought to be the species reduced most rapidly.

In order to overcome the difficulties, which arise in predicting the stereochemical outcome of catalytic hydrogenation, when acids or bases are used, we carried out the hydrogenation in neutral medium (pH 7). Under these conditions, we expected the stereochemical course to be determined by the orientation of the isopropyl group at C7 in the conjugated ketone. We assumed a β-quasiaxial configuration for the isopropyl group based onhalf width of C_5 olefinic proton in the



20 + 21 $-H_2O$



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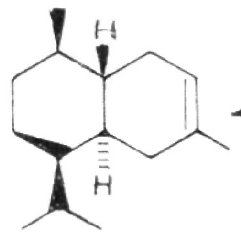
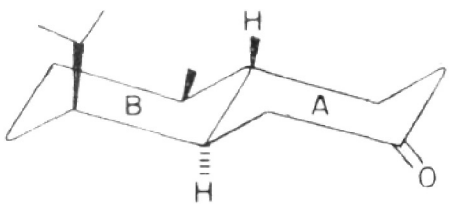
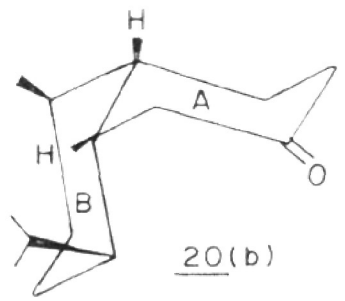


23



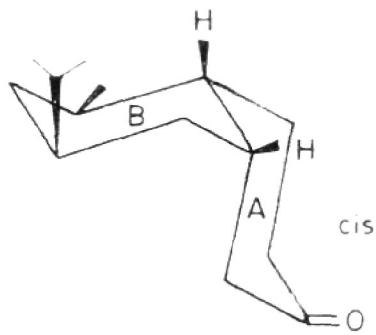
20 (a)

trans (– Ve CD)

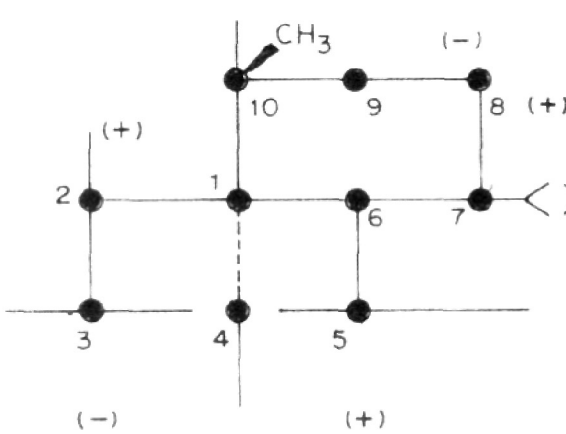


20(b)

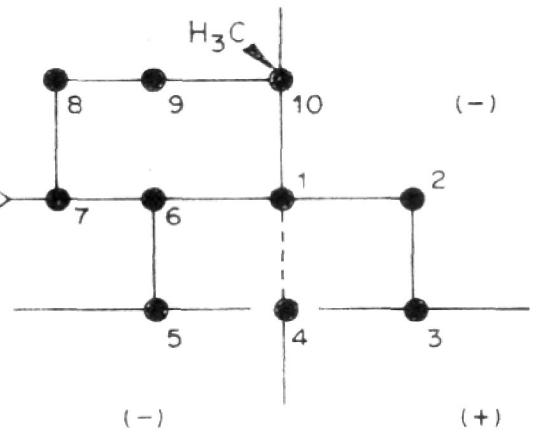
cis – steroidal (– Ve CD)



cis – non steroidal (+ Ve CD)



Octant diagram for trans and cis – steroidal decalones



Octant diagram for cis – non – steroidal decalone

conjugated ketone. It is expected that the hydrogenation should occur from the least hindered α-side of the molecule (steric approach control). Hydrogenation of conjugated ketone over palladium charcoal (10%) in ethanol at room temperature and atmospheric pressure gave a saturated ketone (20). Ketone 20, was homogeneous on GLC (polyester column, 200°). IR spectrum (Fig.3.1) showed bands at 1730 cm-1 (>C=O) thus indicating the absence of conjugation. NMR* showed the C_{10} methyl at δ 0.90 as doublet and the disappearance of signal at 5.75 (Fig.3.2). The distilled sample (126°/3 mm) had α_D -58.30°(neat). It showed a negative Cotton effect in CD. $\Delta\varepsilon_{285}$. -0.3 (MeOH).

From octant diagrams (see chart VI) one can see that both trans-decalone (20a) and cis-decalone (20b) with a steroidal conformation (C_1 proton axial and C_6 proton equatorial) can give rise to -ve Cotton effect, whereas the cis-decalone (20c) with a non-steroidal conformation (C_1 proton equatorial and C_6 proton axial) can give rise to +Ve Cotton effect. The observed value of -0.3, reduces our problem to consideration of only two possibilities (20a or 20b). The decision between the two structures 20a and 20b was done on the basis of the following experiments:

Decalone (20) on reaction with methyl magnesium iodide gave a tertiary alcohol 21. IR spectrum (Fig.3-3) showed bands at 3330 cm^{-1}

---

* The doublet at δ 0.90 for the C_{10} methyl might suggest an axial nature for C_{10} methyl and a boat like conformation for ring 'B' in ketone 20. The flexibility of the decalone system does not permit us to suggest the exact geometry of ring 'B'. Since the nature of 'B' ring has no consequence on our future discussion, it is treated as a perfect half chair.

and 1160 cm^{-1} assignable to the tertiary alcoholic function. The 3β alcohol was dehydrated using a 50:50 mixture of conc. H_2SO_4 and glacial acetic acid, at room temperature in about 2 hours. Usual work up of the reaction mixture gave a hydrocarbon. TLC on silica gel impregnated with silver nitrate (15%) showed two spots. GLC on QF_1 column at 160°, showed two peaks in the ratio of 55:45, the less polar compound being more. Separation of the two hydrocarbons required two careful chromatography over a column of silica gel impregnated with $AgNO_3$ (15%). First fractionation gave several fractions, which were mixtures, but containing more percentage of one component (more polar compound corresponding to 45% peak in GLC). These fractions were properly combined and rechromatographed using a narrower column of longer length. By this combined operation the two hydrocarbons were separated in pure form as well as was evident by GLC on a polyester column at 100°.

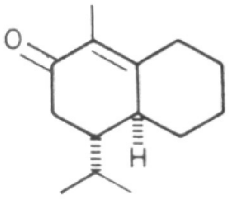
The two hydrocarbons being thus obtained in pure form, the NMR spectrum distinguished the two hydrocarbons as regards the position of the double bond. The NMR spectrum of the two hydrocarbons (Figs.3-4 and 3-5) differ in the nature of the olefinic proton. One of the hydrocarbons, (more polar on GLC) shows the olefinic proton at δ 5.16 as a broad singlet (HW 12 cps). This compound, therefore, must have the double bond at C_3-C_4 position (Δ^2 position), since one of the protons at C_2 is disposed at a proper angle to couple with the olefinic proton at C_3. The structure 23 for the more polar compound was further confirmed by

comparison of IR spectra of a number of compounds having the double bond at the γ_2-position. These compounds give a characteristic[29] peak at 1720 cm^{-1} (Fig. 3-6).

The less polar compound differs from 23 in having a sharp singlet at 5.16 (HW, 6 cps). This simply means that the olefinic proton should virtually have no vicinal coupling. The ideal structure that would account for this is 22 with a transfusion of the rings, where the dihedral angle between C_5 and C_6 protons is close to 90°. On the basis of this, we can also rule out the alternative structure (20b) having cis-fused rings with a steroidal conformation (the possibility which arose as a consequence of negative CD). In this cis-configuration i.e. compounds having a muurolane skeleton, the dihedral angle between C_5 and C_6 is small and a significant vicinal coupling is observed.[30,31] The assigned γ-position for the double bond between C_4-C_5 was also confirmed by the IR spectrum (Figs.3-7) which shows the characteristic[32] peak at 1650 cm^{-1}.

In effect, the outcome of these observations can be used to assign the stereochemistry of the isopropyl group. The trans-fusion of the rings in 20, 22 and 23 indicates that the hydrogenation has occurred from the less hindered α-side of the molecule. The isopropyl group is known to play a remarkable role in determining the stereochemistry of the products obtained by metal-ammonia reductions of octalones.[33] Piers et al. subjected ketones 24 and 25 to lithium liquid ammonia reduction and

CHART VII



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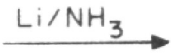

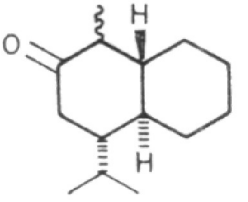

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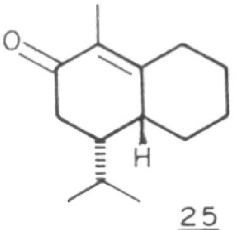

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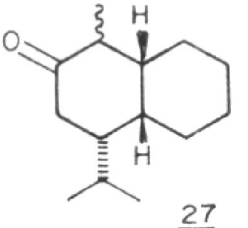

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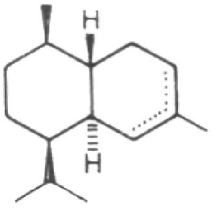
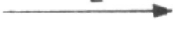
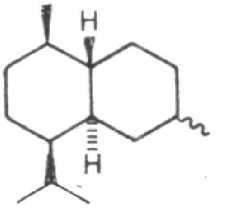


22 + 23





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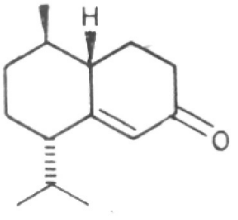

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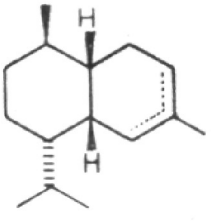

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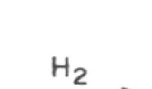

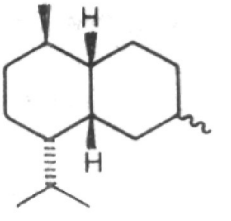

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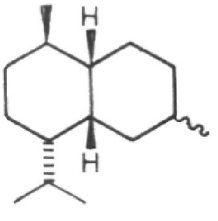

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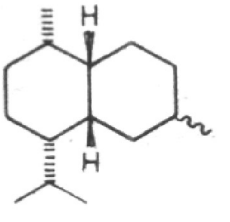


32

obtained decalones 26 and 27 respectively. Detailed investigation through INDOR studies, indicated that the compound 24 with an equatorially oriented isopropyl group gave the expected trans ketone 26, the other ketone 25, with an axially oriented isopropyl group, gave the unexpected cis compound (27). Furthermore, the hydrogenation of compound 25 over palladium on charcoal afforded in each case a high yield ($\geq$ 95%) of the corresponding cis fused decalone (27). It is well-known that alkali-metal ammonia reduction of simply substituted octalones generally affords in each case a high proportion of the trans fused decalone[34]. Therefore the stereoslective formation of the cis fused decalone (27) from Li-liquid ammonia reduction of 26 though surprising, clearly indicates that the presence of an axially oriented isopropyl group at C_7 position, can exert a profound effect on stereochemical outcome of reduction. From the above observation of Piers et al., it is reasonable to say that the stereochemical outcome of the hydrogenation of octalones 24 and 25, either by Li-liquid ammonia or by catalytic method, is necessarily controlled by the isopropyl group at C_7.

It is therefore clear that Lithium liquid ammonia reduction of our ketone 1 (with a β-axial isopropyl group at C_7) must also give the trans-compound 20. This indeed is the case as reported in literature.[21] These workers have reduced the conjugated ketone (17) obtained from pulegone with Lithium-Liquid ammonia to get the trans-ketone (18), as was found by ORD curves. This report, however, assigns a wrong stereochemistry to the isopropyl group at C_7 (equatorial orientation).

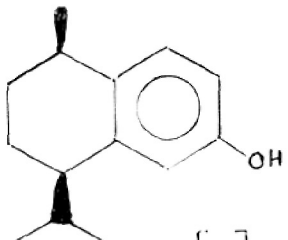
The structure 17 given for the conjugated ketone can be disapproved on the basis of its reduction by lithium-liquid ammonia to the trans isomer. In terms of the qualitative explanation of the proposals as originally given by Robinson,[35] the compound 17 with an α-oriented isopropyl group should afford the cis-decalone.(In these considerations, the isopropyl group should be treated as having an α-axial orientation, since α-equatorial-conformation results in non-bonded interaction with C_5-proton). Molecular model examinations, suggest that the effect of C_7-axial substituent in conjugated ketone 1, on the stereochemical outcome of lithium-ammonia reduction is much more pronounced than the effect of C_7 substituent in ketone 25. The error in assigning the stereochemistry of the isopropyl group may possibly be due to the assumption that lithium ammonia reduction always gives predominantly the trans-fused decalone. Moreover, the change in stereochemistry from α-equatorial in the diketone 16 to β-axial in ketone 17, which occurs during the cyclisation is ignored here.(The reasons discussed earlier). These authors report the synthesis of dihydrocadinol (19) from ketone (18). The tertiary alcohol is in fact dihydrobulgarinol (21) synthesised by us from20.

In order to decisively prove our assumption we converted the mixture of dihydrocompounds (22 and 23) to the tetrahydro compound 28, by hydrogenation over Adam's catalyst at room temperature. The tetrahydro compound (28) did not agree with tetrahydroamorphane (31),

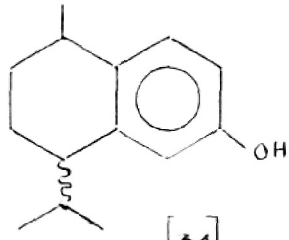
as was evident by comparison with an authentic infrared spectrum.[36] If the α-stereochemistry of the isopropyl group were correct, one would end up with 31, as shown in the hypothetical scheme in chart.

Direct aromatisation of the solid ketone

From our own observation,[8] and also from literature[16], it was clear that in bicyclic compounds of the type 1, the relative stereochemistry at C_7 and C_{10} can be determined by aromatisation of the 'A' ring. The NMR chemical shifts of the isopropyl group then appear at different positions for cis and trans compounds. When the ring A aromatic compound with C_7-isopropyl group in α or β -configuration shows four lines (a pair of doublets), when the ring 'A' aromatic compound is comprised of both the diastereomers, one would get eight lines (4 each for cis and trans). In our solid ketone, the C_{10} methyl has a β-configuration, which has been proved beyond ambuguity by the synthesis of (+) epizonarene, and by measurement of CD curves. It was with this intention that an attempt was made to aromatise our solid ketone (1) to the corresponding phenol (33).



[33]



[34]

Aromatisation of conjugated ketones by N-bromosuccinamide (NBS) are known in literature.[37] Our conjugated ketone was a solid and so we assumed it to be optically pure (isopropyl in either α or β configuration). From hydrogenation studies discussed before, we assigned an β-axial configuration to the isopropyl group, and so we expected to get the cis-phenol (33) on aromatisation of our solid ketone. On aromatisation of the solid ketone, with NBS in presence of a photo-flood lamp, a phenol was obtained, which was racemic at C_7 as was evident by NMR (Fig. 3-8). This unexpected racemisation may be due to initial allylic bromination, dehydrobromination, followed by aromatisation. Changes in stereochemistry at the ring juncture are known in literature.[38] Therefore, this attempt to confirm the assigned stereochemistry was unsuccesful.

LIQUID KETONE

The liquid ketone was obtained by the same route as the solid ketone, but it was not possible to induce this compound to crystallise. However, its NMR spectrum (see discussion later) and magnitude of rotation were different from that of solid ketone. The liquid ketone was found to be similar to the one obtained from l-menthone by Ladwa et al.[7] and also to the one obtained from preisocalamendiol.[19] (NMR spectrum comparisons). Recently, Vig et al.[22] have synthesised the same ketone in the course of their synthesis of epibicyclosesquiphellandrene. A wrong stereochemistry was assigned by them, which is revised (see later).

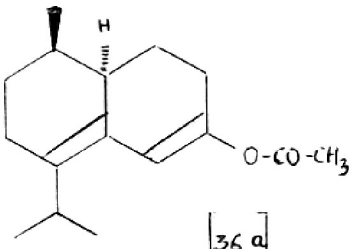
The pure distilled sample of conjugated ketone (b.p. 123°/2.5 mm) was once chromatographed over a column of silica gel (ratio 1:20) and benzene fractions containing the TLC-pure ketone were obtained. However, all the TLC-pure fractions were found to be mixture of two epimers, when analysed on GC-MS (column, S.E. 30, temp. 180°, M+ peak for both components on GC, 206) in the ratio of 85:15. A number of methods were tried to purify the epimeric mixture, but without success. The investigations were therefore carried out on the liquid conjugated ketone, about the identity of the major compound in the epimeric mixture.

IR spectrum of this ketone showed bands at 1681 and 1613 cm^{-1}. NMR spectrum (Fig. 3-9) showed C_{10} methyl signals at 0.77 as a clear doublet ($J \sim 6$ cps), isopropyl as a pair of doublets at 0.98 ($J \sim 6$ cps), and the vinylic proton, α to the carbonyl group at 5.68 as a sharp singlet (HW 2 cps). This ketone did form a crystalline semicarbazone (m.p. 147°), but did not form a p-toluene sulfonyl hydrazide derivative. The stereochemistry of the major compound in this epimeric mixture was deduced on the basis of experiments described below.

Preparation of the enol-acetate and regeneration of the ketone

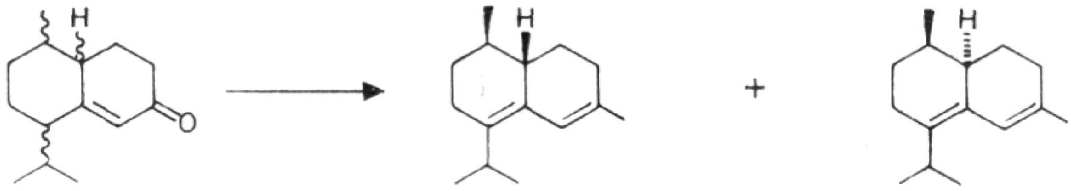
The preparation of the enol acetate (36) from the liquid ketone had two advantages. Firstly the stereochemistry at the C_1 position could be ascertained by the sign of the rotation of the enol-acetate. Secondly, it was found that on regeneration of the ketone from the enol-acetate(36), a pure form of ketone was obtained in which the minor epimer was found to be absent.

The enol-acetate was prepared by heating the ketone with acetic-anhydride and p-toluene sulfonic acid monohydrate. The resulting crude enol acetate showed two distincts spots on TLC (pet.ether + 30% ethyl acetate). The mixture was passed over silica gel (ratio, 1:20) and pet. ether:ether (10:1) fractions were collected. The TLC pure compound was distilled at $140^{\circ}/5$ mm(bath). It had α_D + 105.4 ($CHCl_3$). The positive rotation of the enol-acetate indicated β-stereochemistry at the ring juncture (C_1). The sign of rotation would have been negative if C_1 stereochemistry was α. UV spectrum showed λ_{max}^{MeOH} 246 nm (ε, 16,900). The NMR spectrum of the enol acetate 36 is interesting. It showed (Fig.3-10) the methyls at 0.98 (d, 3 Me) and the O-CO-CH_3 proton as a singlet at 2.06 and the C_5 olefinic proton as a singlet at 6.03. The heptet centered at 2.83 is typical of the heteroannular diene system with a isopropyl group on one of the double bonds, as in 36. The most conspicuous feature of the NMR spectrum is the absence of doublet at 0.77 which arises due to the other epimer 36 (a).

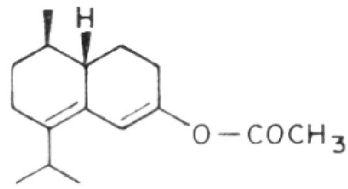


[36 a]

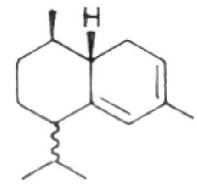
Scheme III



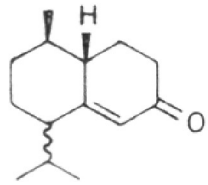
35 37 38



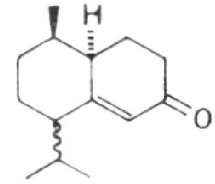
36



37(a)

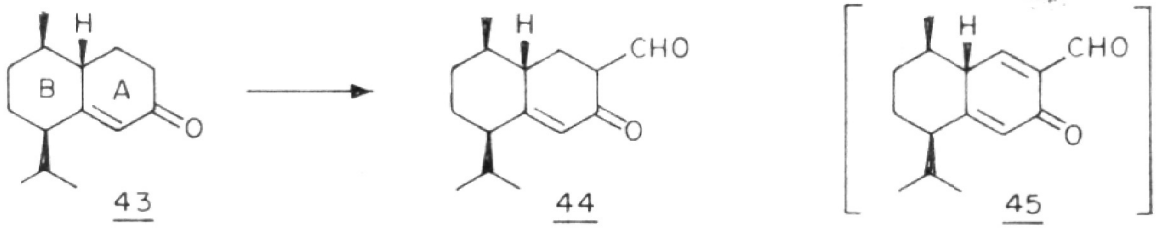


39

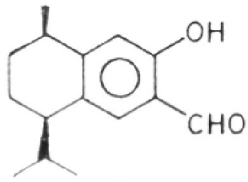


40

Scheme IV



43 44 45



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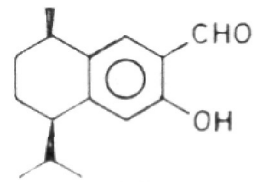
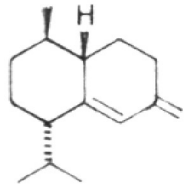
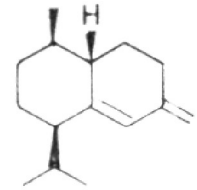


42



46



47

The spectrum of 36 is similar to that of epizonarene with the doublet due to 36(a) at 0.77 (as found in zonarene) being absent.

Regeneration of the ketone was done by heating the enol acetate (36) under reflux with sodium bicarbonate in methanol.[39] The product obtained after usual work up, showed IR $\tilde{\nu}$ bands at 1681 and 1613 cm^{-1}, thus showing the formation of the ketone. The purified sample (alumina chromatography) was found to be identical in all respects with the major component in the original epimeric mixture (NMR and GLC).

Relative Stereochemistry at C_1 and C_{10}

In order to determine the relative stereochemistry at C_1 and C_{10} of the major compound in the liquidketone, the latter was converted into a mixture of epizonarene (37) and zonarene (38). Grignard reaction of the liquid ketone followed by treatment with 33% sulfuric acid (as described in the previous chapter) gave a hydrocarbon. Its NMR spectrum showed (Fig. 3-11) signals at 0.77 to 0.99 (3Me), 1.71 (S, 1Me), 5.53 (S, 1H) and 6.00 (S, 1H) in addition to traces of the heteroannular dienes 37 and 38. This may be due to diene 37(a). However, this compound on chromatography over a column of alumina* impregnated with 15% silver nitrate, gave a mixture of epizonarene (37) and zonarene (38) in the ratio of 87:13 as judged by the relative area measurement of NMR signals of C_{10} methyl in epizonarene (37) and zonarene (38) at 0.99 and 0.77 respectively (Fig. 3-12). The IR spectrum was in agreement with this, as the characteristic peaks [36] of both 37 and 38 were found to be present.

* Silic acid-$AgNO_3$ chromatography gave a complicated mixture of hydrocarbons.

UV of the mixture showed λ_{max}^{MeOH} 246 nm. From these observations, it was concluded that the major compound in the epimeric mixture must have the relative stereochemistry at C_1 and C_{10} as shown in 39. This accounts for the formation of epizonarene in 87% ratio. The minor epimer may be 40, since it can account for the formation of 13% of zonarene (38).

Stereochemistry of the Isopropyl Group

As already mentioned, in compounds of the conjugated ketone type, the relative stereochemistry at C_7 and C_{10} can be determined by aromatising the 'A' ring. The chemical shift of the isopropyl group then appears at different regions for the cis and trans compounds.[8,16]

7-Hydroxycalamenenal (41) is a naturally occurring compound isolated by Rowe et al.[40] The relative stereochemistry at C_7 and C_{10} for this compound has been established as cis by converting it to cis-calamenene.[9] We decided to convert our liquid ketone to a compound similar to the naturally occurring 7-hydroxycalamenenal. In order to achieve this, the liquid ketone was converted to its C_3-formyl derivative (44) by reacting the ketone with ethyl formate in presence of sodium methoxide. The hydroxymethylene derivative (44) was then taken out by strong alkali and alkaline layer acidified with 1:1 HCl to pH 6. Usual work up gave the formyl derivative. The crude compound, as such was used for dehydrogenation. The compound 44 was dehydrogenated with DDQ (1 mole) in dioxane at reflux temperature.

The crude phenol thus obtained was purified by column chromatography over silica gel; benzene elutions gave the pure phenol (42). TLC showed a single spot. IR spectrum (Fig.3-13)showed bands at 1724, 1629, 1664 and 1572 cm^{-1}. The NMR (Fig.3-14) spectrum of this sample agreed very well with the NMR of 7-hydroxycalamenenal.[40] Our compound (42) showed signals for the isopropyl group at 0.80, 0.90, 1.06 and 1.16 (a pair of doublets) and satellite peaks at 0.73, 0.83, 1.00 and 1.10. From these signals, the relative percentage of cis:trans may be about 85:15, corresponding to the original mixture in the starting ketone. The C_2 and C_5 aromatic protons appear as singlets at 6.56 and 7.03 respectively. The aromatic -CHO- appears at 9.56 (singlet) and the OH appears at 10.30 (singlet). From these results, the stereochemistry of the isopropyl group in the major compound of the epimeric mixture, must be as represented in 43 (β-isopropyl).

Discussion of the NMR spectrum of the two ketones

It is already indicated that the two ketones were studied separately as they differed in the nature of the NMR spectrum and also in the magnitude of rotation. In both the ketones, the C-5 olefinic probon has a half width of 2 cps, which requires that the isopropyl group in both the ketones must have axial orientation (either α or β), because a half width of 4.3 cps would have been observed if the isopropyl group were in a equatorial conformation. A similar situation is seen in 6-α-substituted Δ^4-3-ketones in 19- nor-steroids.[10]

A careful examination of the NMR spectrum of the two ketones, showed that they differed only in the chemical shifts of the C_{10}-methyl signal. The C_{10}-methyl group in solid ketone is deshielded by about 0.21 ppm as compared to the liquid ketone. In solid ketone, the C_{10}-methyl signal appears at 0.98 as a doublet ($J \sim 6$ cps) almost buried under the isopropyl signals (0.98), whereas in the liquid ketone it appears separately as a clear doublet at 0.77 ($J \sim 6$ cps). The deshielding of the C_{10}-methyl signal in solid may be explained, if ring 'B' in solid ketone is assumed to have a 'twisted boat' conformation, where the C_{10} methyl assumes an β-axial orientation and falls in plane of the C_4-carbonyl. The consequence of the C_{10} methyl and the relatively bulky isopropyl group on ring 'B' assuming a β-axial configuration is to flatten the ring somewhat. The non-bonded interactions between the two axial groups is thus minimised. It is interesting to note that even in this flattened form, the angle between C_5 and C_7 protons is still very small, thus accounting for the observed value of half width of C_5 olefinic proton.

This assumption of twisted boat conformation for the 'B' ring is useful, since it can be extended to rule out one of the two conceivable configurations (α-axial) for the isopropyl group. Molecular model examination shows that if the C_{10}-methyl is to assume a β-axial orientation on a twisted 'B' ring, the isopropyl group cannot assume an α-axial orientation; it must then assume a β-equatorial configuration, which is ruled out on the basis of half width of C_5-olefinic proton.

The configuration of the C_7-isopropyl group must therefore be -axial as is also suggested by other data, discussed previously.

In the liquid ketone, the ring 'B' has a normal chair form, with the C_{10}-methyl in a β-equatorial configuration. This difference in conformation between the two ketones is reflected in their stability: the solid ketone is unstable as compared to the liquid form. Further, since both the ketones have a axially oriented isopropyl group, they are readily converted on Grignard reaction to epizonarene with a heteroannular diene system, thus relieving the strain due to the axial isopropyl group.

Comments on the recent synthesis of 1-epibicyclosesquiphellandrene

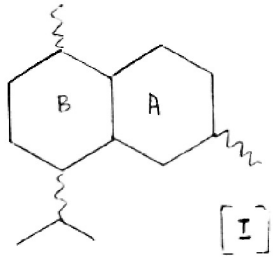
In view of our findings on the liquid conjugated ketone, the recent synthesis of 1-epibicyclosesquiphellandrene (46) by Vig et al.[22] is doubtful, especially as regards the stereochemistry of the isopropyl group. These workers have synthesised the conjugated ketone by the same route, as we followed during synthesis of (+) calamenene.[7] However, these authors have not taken into consideration our later report,[8] in which we had suggested a revised structure for the conjugated ketone. We did not attempt the synthesis of 46, since our intermediate ketone did not have the required stereochemistry at C_7 position. However, after the report of synthesis of 46 by Vig et al.[22] from our ketone, we decided to reinvestigate our results by converting the liquid ketone to compound 47 and show that it does not correspond to naturally occurring compound 46. Although several attempts have been made to convert the liquid ketone to compound 47 by Wittig reaction, only the starting ketone was recovered back in all cases. The reason for the failure of the Wittig reaction is not clear.

C O N C L U S I O N

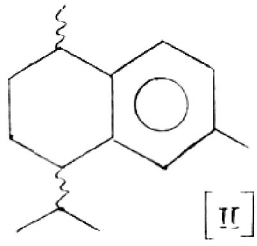
In conclusion it can be said that conjugated ketone 1 can serve as an ideal intermediate for the syntheses of bulgarene type of compounds. Bulgarene compounds have evaded isolation at present, but their isolation in future may not be ruled out. An obvious limitation is the purity of the intermediate ketone, which is normally obtained as a 85:15 epimeric mixture, but this difficulty can be overcome by the purification of the epimeric mixture through enol-acetate derivative. The regeneration of the enol-acetate after separation, provides us with two distinct ketones. From synthetic point of view it is clear that the minor component (15%) must also serve as a potential intermediate for the syntheses of other classes of cadalenic sesquiterpenes.

In the beginning of this chapter it was pointed out that there is hardly the chemical method for determining the absolute stereochemistry of the isopropyl group in cadalenic sesquiterpenes (oxidative degradation by conc.nitric acid). Our experience (during the synthesis and elucidation of stereochemistry of calamenenes) in the past and during the present investigation may be fruitfully used in future for elucidating the stereochemistry of the isopropyl group. The method suggested depends on aromatising ring 'A' in I to the corresponding aromatic compound II.

From the NMR signals of the isopropyl group, one can determine the cis:trans ratio of C_{10} and C_7 positions. Optical rotation of II further helps in elucidating the absolute stereochemistry.



[I]



[II]

In order to evolve this into a general method for determining the stereochemistry of the isopropyl group in cadalenic sesquiterpenes, it is necessary to find easier aromatisation techniques, so that any cadalenic compound with a variety of functionality on either ring may be converted to the corresponding aromatic compound. Elaborate studies in this direction are in progress.

EXPERIMENTAL

Catalytic Hydrogenation of Conjugated Ketone (1)

Solid ketone (1) (4.12 g) was dissolved in 50 ml. of absolute alcohol and hydrogenated over palladium on charcoal (10%) at atmospheric pressure (712.5 mm. of Hg) and room temperature (23°). The absorption of H_2 gas stopped, when 529 ml of H_2 were absorbed (in about 4-5 hours). The solution was then filtered and alcohol removed. The crude product (4.01 g) on TLC (pet.ether + 10% ethyl acetate) showed almost 95% purity. It was chromatographed over a column of alumina (Gr.II, 120 g) and following elutions were done (fractions of 8 ml. were collected).

Fr. No.	Weight(g)	TLC	GLC*	IR spectrum	Remarks
Pet.ether					
I	0.616				
II	0.111				
III	1.038	pure	99%	1730 cm^{-1}	Pure ketone (20)
IV	0.816				
V	1.189				
VI	0.316				

* Column used, polyester, temp. 210°

Fractions III to VI were combined and distilled at 123°/3 mm., α_D -58.30(neat).

IR spectrum (Fig.3-1) 1730, 1450, 1375 cm^{-1}

NMR spectrum (Fig. 3-2) 0.90, 0.95-0.97 (d, 3H)

CD $\Delta\varepsilon_{285}$ -0.3 (MeOH)

Analysis. C, 81.20; H, 11.63. $C_{14}H_{24}O$ requires C, 80.76;H,11.53%.

Grignard reaction of ketone (20)

Grignard reagent was prepared from magnesium (2 g), methyl iodide (16 g) in anhydrous ether. 2.294 g. of pure ketone (20) dissolved in 25 ml. of dry ether is added dropwise to the stirred Grignard complex at 0-5°. The reaction mixture is then allowed to stand overnight. The complex is then broken up by ice-cooled solution of ammonium chloride(10%). The ether extraction of the reaction mixture followed by water and brine washing gave crude alcohol (21) (2.016 g). Distillation at 120°/2.5 mm. afforded the pure compound.

IR spectrum (Fig. 3-3). 3330, 1450, 1375 and 1270 cm^{-1}. Compound analyses for C, 80.12; H, 12.56. $C_{15}H_{28}O$ requires C, 80.37 and H, 12.50%.

Dehydration of the tertiary alcohol (21)

Tertiary alcohol (21) (2.016 g) was gently shaken with a mixture of conc. sulfuric acid and glacial acetic acid (50:50) for 5 min. It was then carefully diluted with water and extracted with ether. Ethereal layer was washed with bicarbonate (40%) and water. Drying of the ethereal layer (anhydrous Na_2SO_4) and evaporation of the solvent gave 1.90 g. of the product. GLC analysis of the crude product on QF_1 column at 160°, showed a mixture of two compounds (ratio 55:45). TLC on silica gel-$AgNO_3$ plate (15%) showed two distinct spots.

IR spectrum showed bands at 1650, 1770, 1450 and 1375 cm^{-1}.

Purification of the hydrocarbon mixture

The mixture of hydrocarbon (1 g) was passed over 30 g. of silica gel impregnated with 15% silver nitrate and eluted with pet. ether. Fractions of 10 ml. were collected and analysed on GLC.

Fr.No.	Wt.in (g)	GLC*	Remarks
Pet.ether			
I			
II			
III	0.613	mixture	A mixture of hydrocarbons 22 and 23.
IV			
V			
VI			
VII	0.216	pure single peak 95%	Pure compound (23)
VIII			

*Column used, polyester, temp. 100°

A second chromatography of the combined fractions (I to VI) furnished the GLC pure compound corresponding to the first peak in the mixture, in the first two fractions. Both the samples were separately distilled at 128°/2.5 mm.(bath) and the data related to them is given below.

Fractions I and II corresponding to compound 22.

IR spectrum (Fig.3-7) characteristic peak at 1650 cm^{-1}(weak). -isomer 1450, 1375 cm^{-1}.

NMR spectrum (Fig.3-5) 0.95-0.97 (m, 9H), 1.61 (s, 3H), 5.13 (singlet; HW 6 cps, 1H).

α_D + 14.29°($CHCl_3$).

Fraction (VII) and (VIII) corresponding to compound 23.

IR spectrum (Fig.3-6). Characteristic peak at 1720 cm^{-1}(weak), γ_2-isomer 1450, 1375 cm^{-1}.

NMR spectrum(Fig.3-4) 0.95-0.97 (m,9H), 1.61 (s,3H), 5.13 (broad singlet, HW 12 cps, 1H).

α_D + 65.20°($CHCl_3$).

Hydrogenation of the hydrocarbon mixture (22 and 23)

The hydrocarbon mixture (0.356 g) of γ-isomer (22) and γ_2-isomer (23) was dissolved in 20 ml. of alcohol and hydrogenated over Adam's catalyst. Absorption of hydrogen stopped in about 20 minutes. On filtration and removal of the solvent, the crude product (0.289 g) was distilled (130°/5 mm.) α_D -48.28°($CHCl_3$). The IR spectrum of this sample did not agree with that of tetrahydroamorphane, especially in the fingerprint region.

Aromatisation of the solid ketone using N-bromosuccinimide (NBS)

Freshly crystallised NBS (0.356 g) (0.002 moles) was crushed under dry carbon tetrachloride (10 ml) and 0.412 g. of the ketone (0.002 mole) was added to it and the system flashed with nitrogen gas. The mixture was then refluxed on a steam bath for 3 minutes, and exposed to light from a photoflood lamp for about 3 to 5 minutes. The mixture became colourless. The exposure was for a few minutes more and refluxing carried out for further five minutes. The mixture was cooled and extracted with ether and washed with bicarbonate (10%). Removal of the solvent afforded a crude gummy material (0.286 g). TLC (pet.ether + 50% ethyl acetate) indicated the presence of about 10% starting ketone.

Purification was attempted by dissolving the crude compound in 20 ml. of ether and extracted with 10% NaOH (5 x 3 ml). The combined alkaline layer was then acidified with dilute HCl. The phenolic compound failed to come in the alkaline layer. Purification was finally done by column chromatography over 30 g. of silica gel. Initial benzene fractions gave TLC pure phenol.

NMR spectrum (Fig. 3-8) showed the isopropyl signals at 40, 44, 48, 52, 56, 60, 64 and 68 Hzs.

The compound analysed for C, 82.29; H, 10.87. $C_{14}H_{20}O$ requires C, 82.35; H, 10.80%.

Preparation of the Liquid Conjugated Ketone

A similar procedure as described under the preparation of solid ketone was followed. The final product could not be induced to crystallise at -30 to -40°. TLC showed single spot (pet.ether + 10% ethyl acetate). GLC on S.E. 30. Column at 186° showed two peaks (ratio 85:15). Distillation at 123°/2.5 mm. gave the pure compound, α_D-60°(neat).

IR spectrum showed bands at 1681 and 1613 cm^{-1} .

NMR spectrum(Fig.3-9). 0.77 (d, J~6 cps, 3H) ; 0.98 (m,6H); 5.74 (ss, HW 2 cps, 1H).

GC:MS shows two distinct peaks on S~ 30, column at 180°, M+ for both the peaks 206 (ratio of the epimers 87:13).

Forms a solid semicarbazone, m.p. 147°. Did not form a solid p-toluene sulfonyl hydrazone derivative.

Preparation of the enol acetate (36) of liquid ketone

Liquid ketone (1 g) was heated at 90° with freshly distilled acetic anhydride (10 ml) and p-toluenesulfonic acid monohydrate (0.05 g) for 1 hour. The reaction mixture is then poured in about 50 ml. of water and extracted with ether. Usual work up gave the crude enol-acetate (0.869 g). TLC (pet.ether + 10% ethyl acetate) showed two spots. It was passed over a column of silicic acid (20 g., 1:20 ratio). Pet. ether:ether (10:1) fractions gave the pure enol-acetate as was evident by TLC.(pet.ether + 10% ethyl acetate). Distillation (140/5 mm. bath) gave 0.1 g. of pure material.

α_D + 105.4 ($CHCl_3$)

UV $\lambda_{max.}^{MeOH}$ 246 nm (ε, 16,900).

NMR spectrum (Fig. 3-10). 0.99 (d, 9H), 6.01 (S,1H), 2.83 (heptet, 1H), 2.06 (s, 3H).

Regeneration of the ketone from enol-acetate (36)

Enol acetate (36) (0.140 g.) was heated under reflux with sodium bicarbonate (0.280 g) in dry methanol (4 ml) for five minutes and the solution was then poured into 27 ml. of 1% acetic acid. Usual work up gave 0.118 g. of the crude material which was once filtered over a column of alumina (Gr.III, 10 g.). Pet.ether fractions afforded the pure ketone.

IR spectrum: 1681 cm^{-1} ($\diagdown$ C=O); 1613 cm^{-1} (double bond). The sample was identical with pure liquid ketone. GLC-showed a single peak indicating the absence of the minor component (15%) (column used S.E.30, 174°).

Conversion of the liquid ketone to a mixture of epizonarene (37) and zonarene (38)

The Grignard reaction was carried out in a similar way as described under the preparation of epizonarene. Acid washing (33%) of the ethereal layer gave a hydrocarbon (0.816 g). It was passed over a column of Gr.I alumina and eluted with pet.ether. Removal of the solvent 'in vacuo' gave a colourless liquid, whose NMR (Fig.3.11) showed signals at 0.77 to 0.99 (m, 9H); 1.71(s, 3H); 3.08(unresolved heptet); 5.53 (s, 1H), 6.01 (s, 1H,trace). This may be due to hydrocarbon 37(a).

However this hydrocarbon (37a) on chromatography over a column of basic alumina impregnated with silver nitrate gave a mixture of zonarene and epizonarene. Analysis of this material on GLC (carbowax column, temp. 190°) showed two compounds in the ratio 87:13. The major peak corresponds with (+) epizonarene as shown when injected as a mixture with a pure sample of (+) epizonarene obtained previously. The minor component (13%) was shown to be zonarene (38) by NMR spectrum:

NMR, 0.99 (d, 3 Mc), corresponding to epizonarene (percentage calculated from integrated area, 83%); 0.77 (doublet) corresponding to zonarene (percentage calculated from integrated area 17%).

Preparation of the hydroxymethylene derivative (44) from liquid ketone

Sodium methoxide was prepared in a 250 ml. reaction flask, using 0.70 g. of sodium and dry methanol. This was suspended in 20 ml. of dry

benzene 2.22 g. of ethyl formate in 20 ml. of dry benzene was then added to this suspension and the reaction mixture then cooled to 0°. 2.06 g. of conjugated ketone in 15 ml. of dry benzene was slowly added by means of a dropping funnel. The whole operation was carried out under an atmosphere of N_2-gas with stirring of the reaction mixture. It is then set aside for 48 hours at room temperature. The benzene layer is then repeatedly shaken with ether (50 ml) to remove the unreacted materials. The alkaline layer is acidified with 1:HCl to pH 6. The hydroxymethylene derivative separates out which is taken in ether, dried and solvent evaporated to get the crude compound (1.03 g). Distilled at $158^{\circ}/3$ mm.(bath). This compound as such was used for dehydrogenation.

Dehydrogenation of hydroxymethylene compound 44 to 42

Hydroxymethylene derivative (44) (1.03 g) was refluxed in dry dioxane (12 ml) with 1 mole of DDQ on an isomantle for 3 hours. The solvent was then removed on a water bath and the crude phenol (0.616 g) was passed over 15 g. of silica gel. Benzene elution gave 0.344 g. of pure phenol as was evident by TLC (benzene).

IR spectrum (Fig. 3-13) 1724, 1629, 1664 and 1572 cm^{-1}.

NMR spectrum (Fig. 3-14). 0.80, 0.90, 1.06 and 1.16 (major peaks as pair of doublets, J 6 cps). Satellite peaks at 0.73, 0.83, 1.00 and 1.10 (relative ratio from peak area measurement 90% cis and 10% trans, 6.56 (s, 1H); 7.03 (s, 1H); 9.56(s,1H) and 10.30(s,1H).

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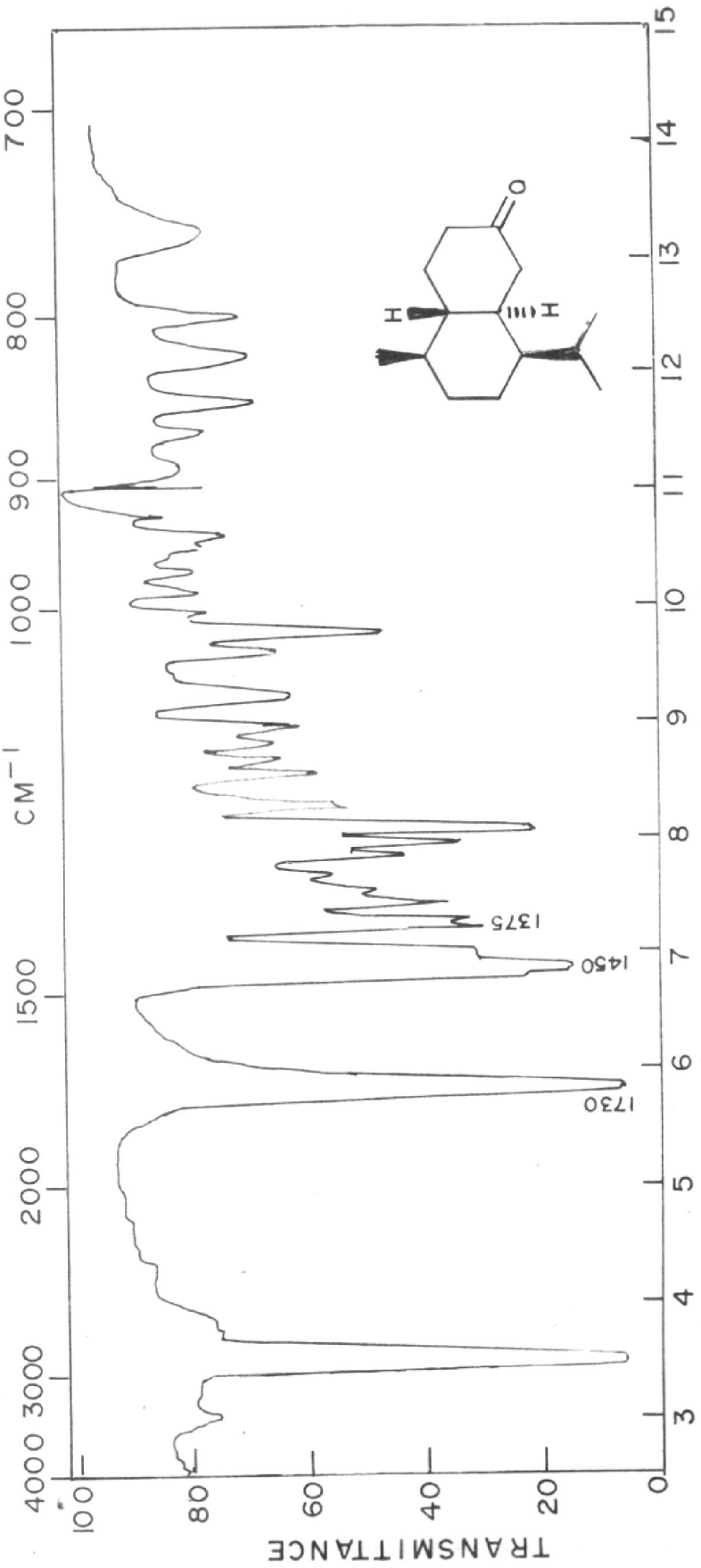


FIG. 3-1 IR SPECTRUM OF DECALONE(20)

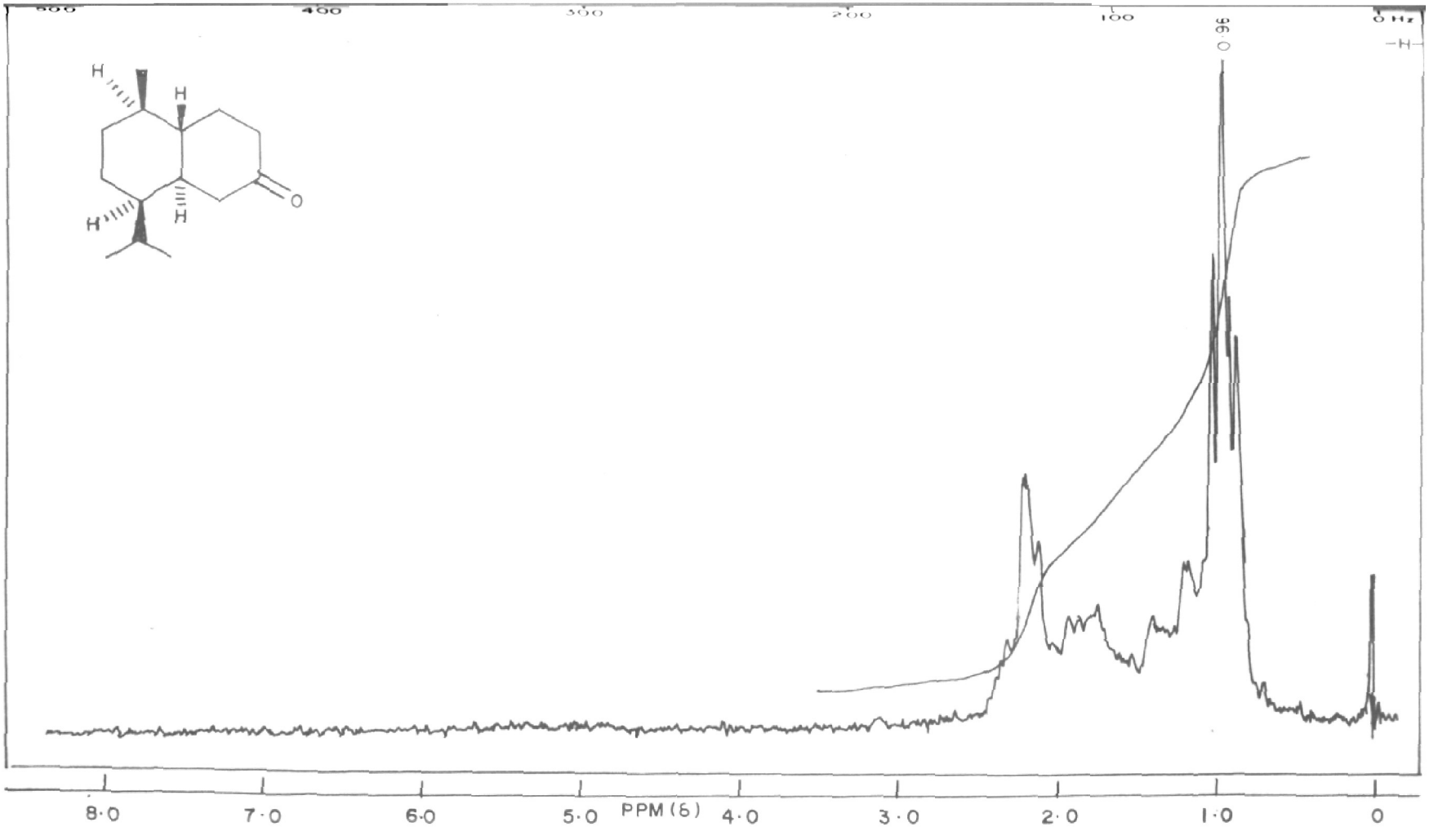


FIG. 3-2 NMR SPECTRUM OF DECALONE (20)

T-60

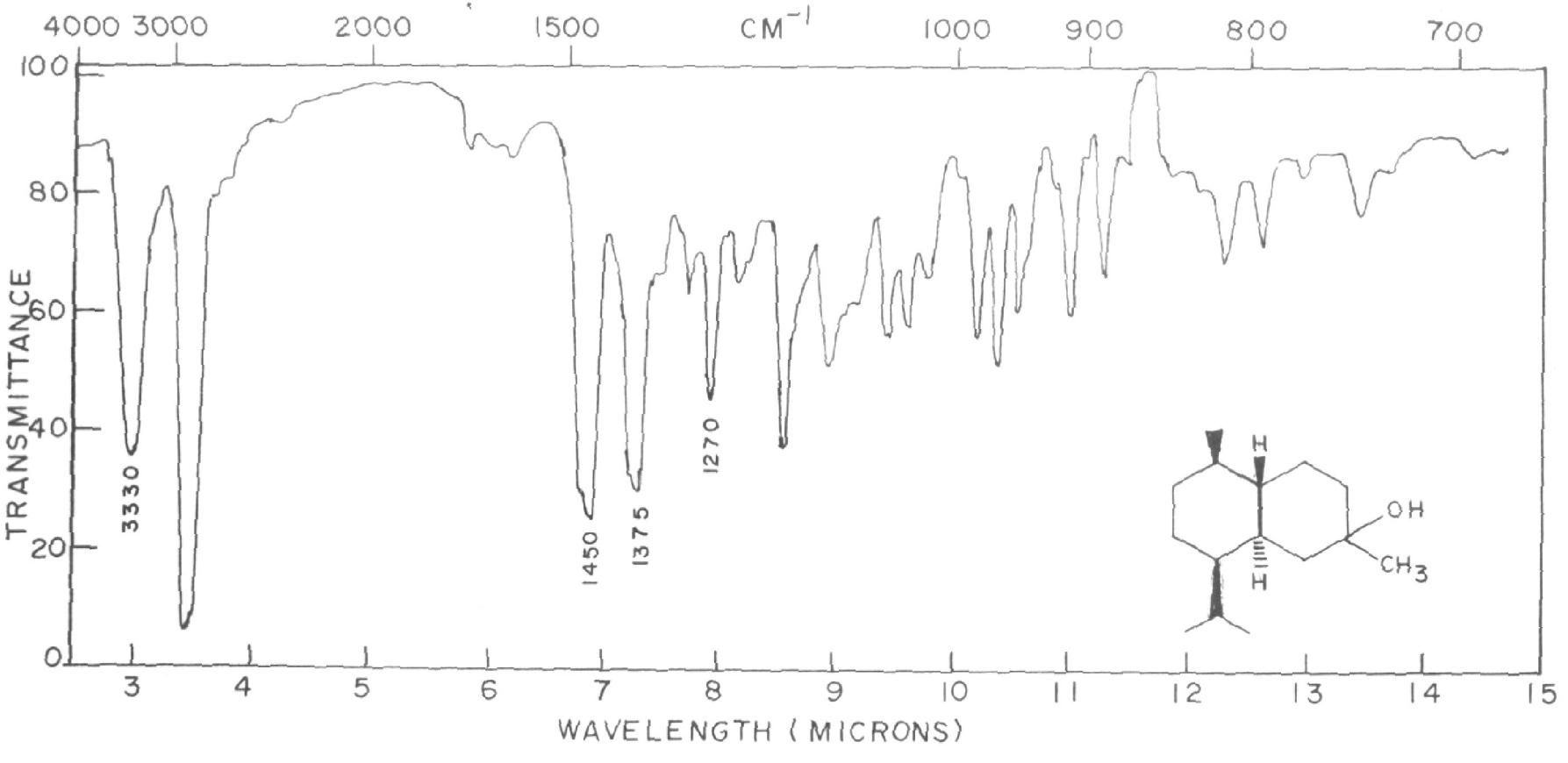


FIG. 3-3. IR SPECTRUM OF DIHYDRO BULGARINOL (21)

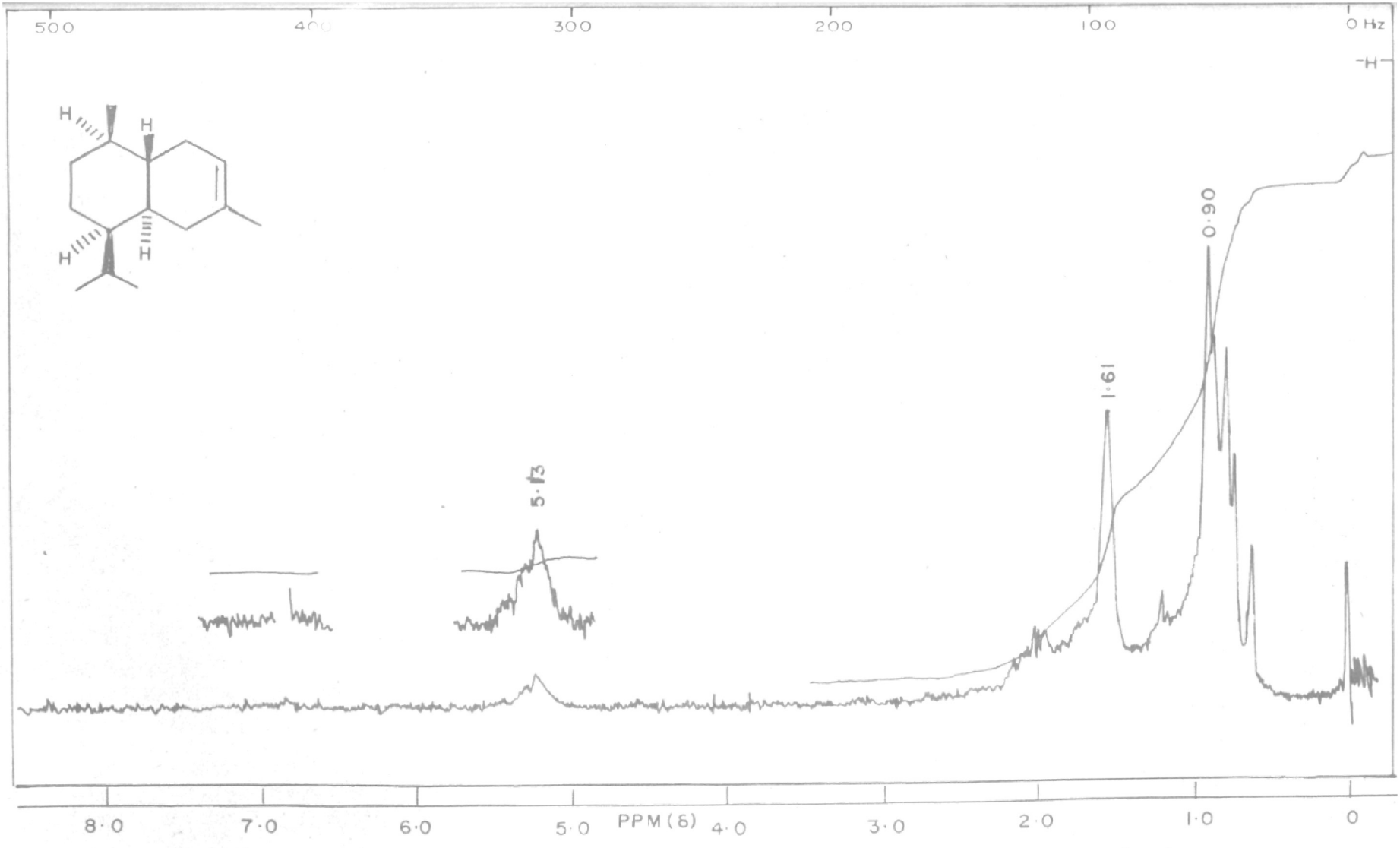


FIG.3·4 NMR SPECTRUM OF DIHYDRO-r_2-BULGARENE(23)

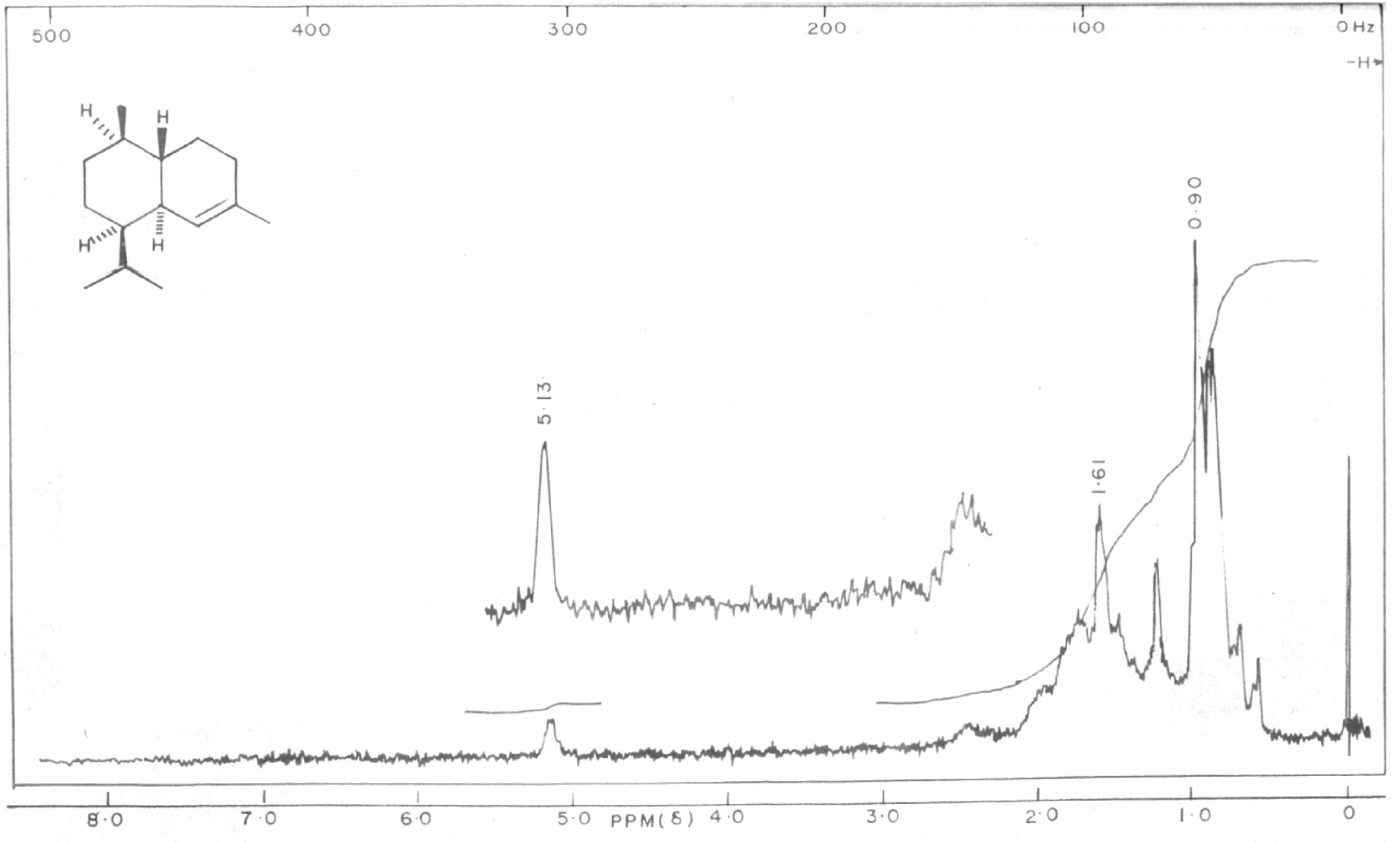


FIG 3·5.NMR SPECTRUM OF DIHYDRO-r-BULGARENE(22)

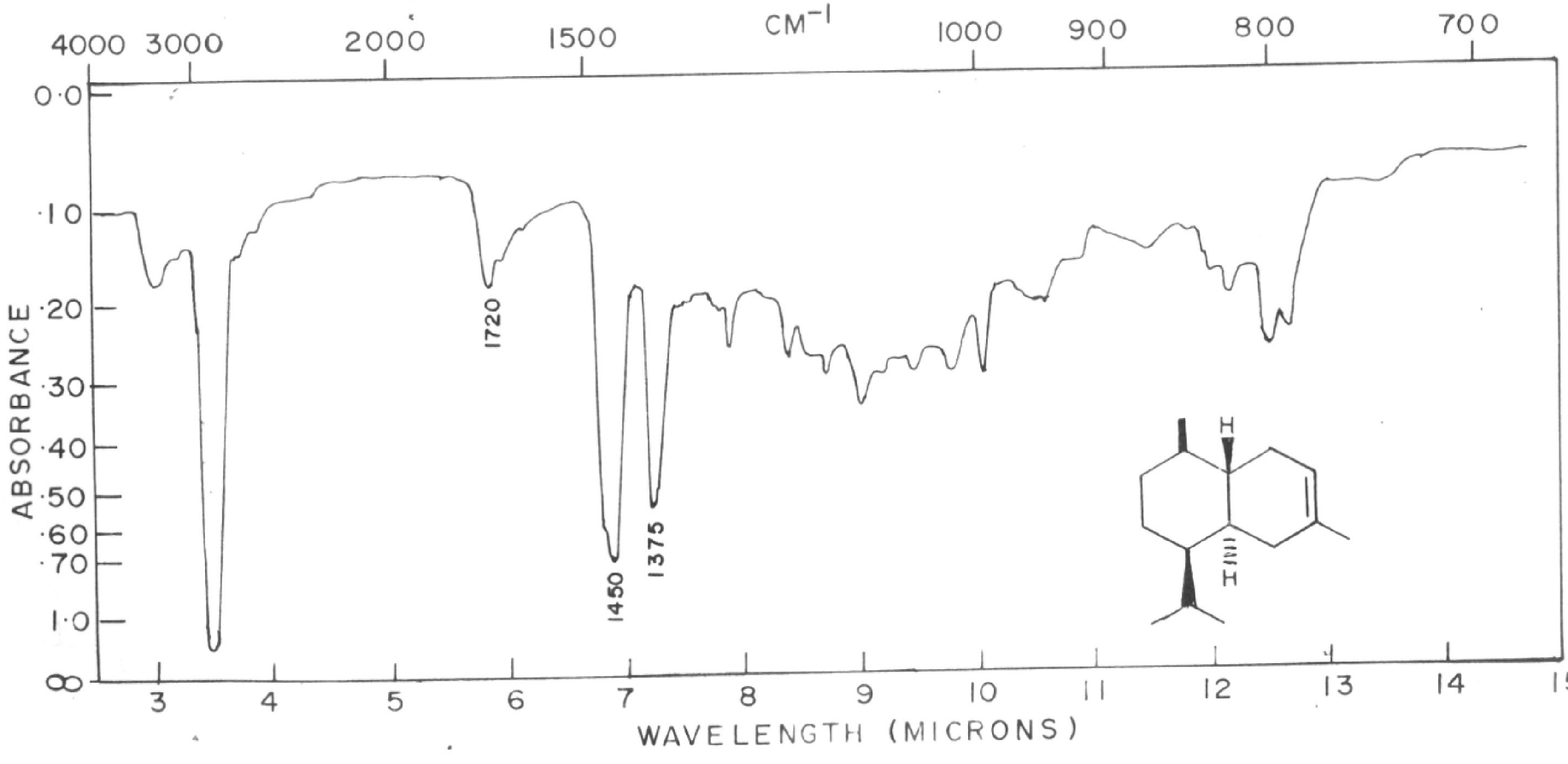


FIG.3-6 IR SPECTRUM OF DIHYDRO-r_2-BULGARENE(23)

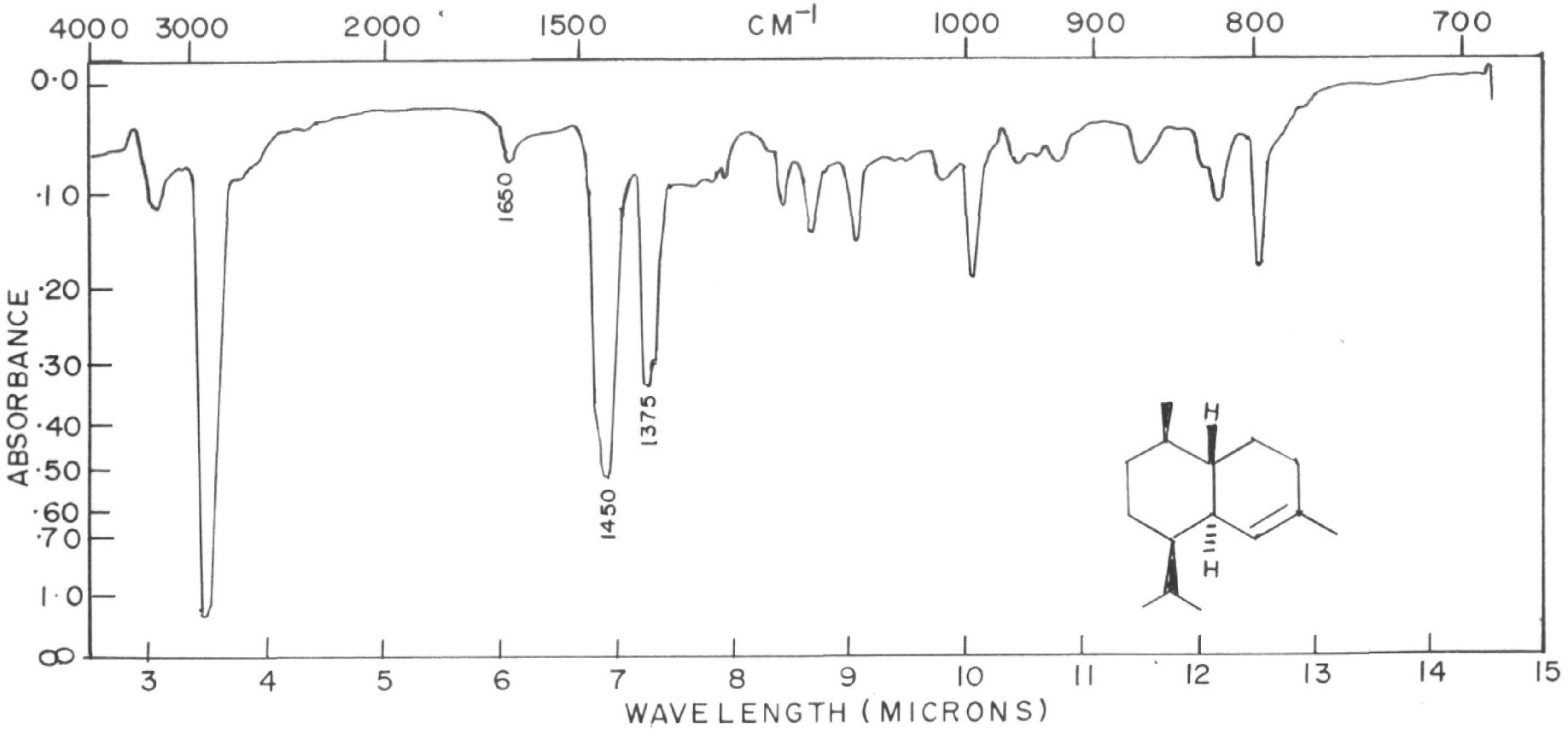


FIG. 3·7 IR SPECTRUM OF DIHYDRO-r-BULGARENE(22)

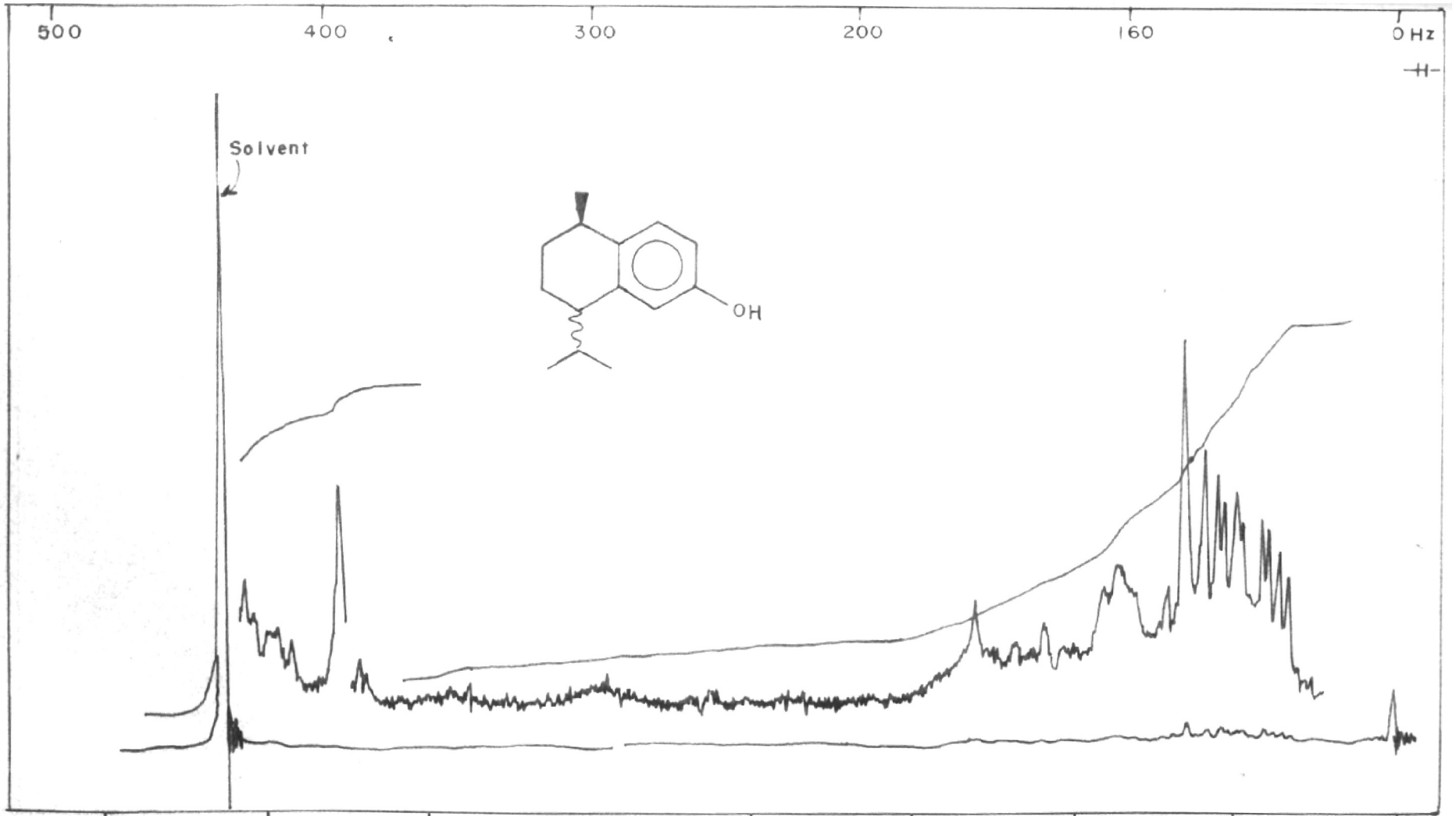


FIG. 3·8. NMR SPECTRUM OF PHENOL(34)

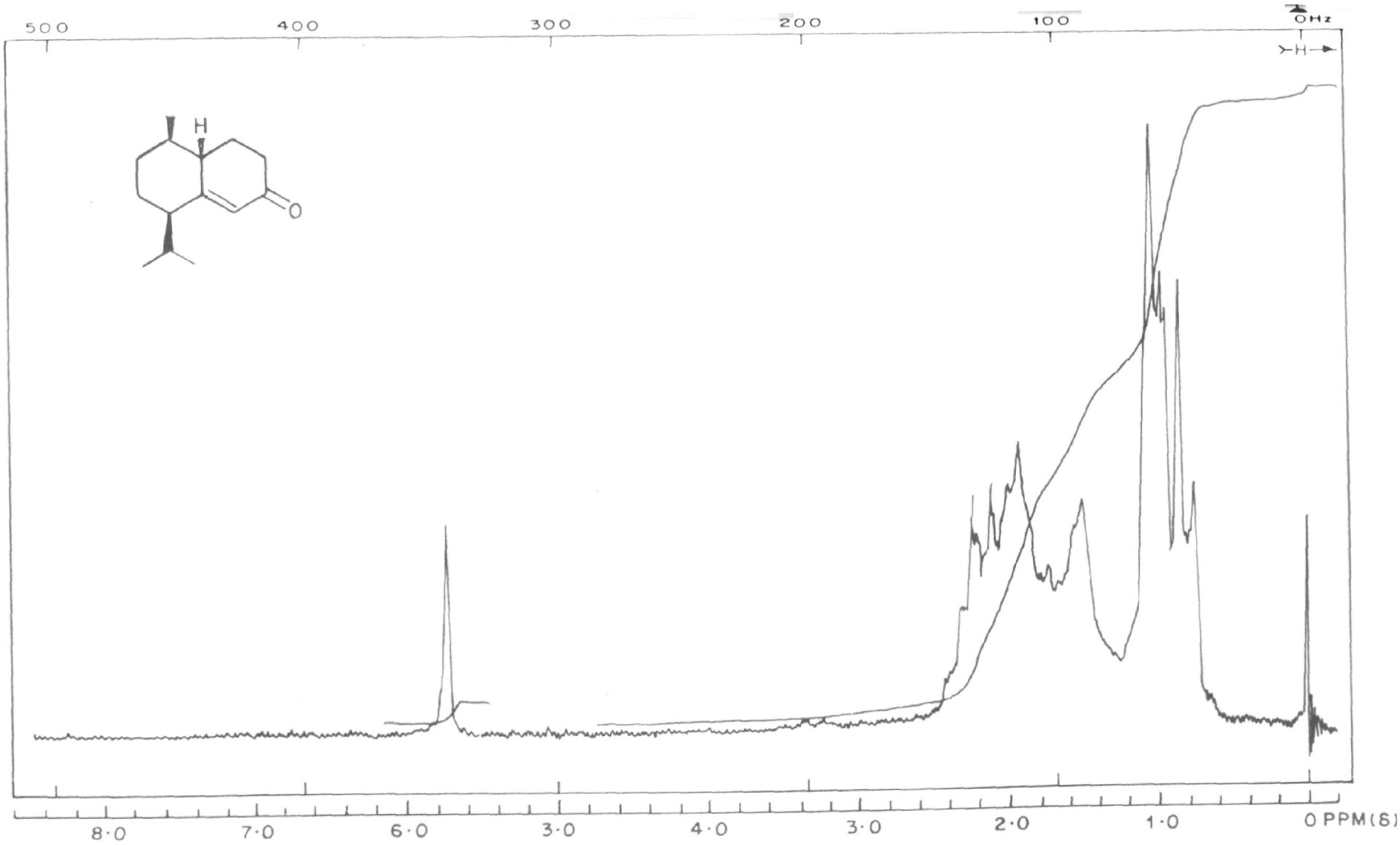


FIG. (3·9). NMR SPECTRUM OF CONJ. KET (LIQUID)

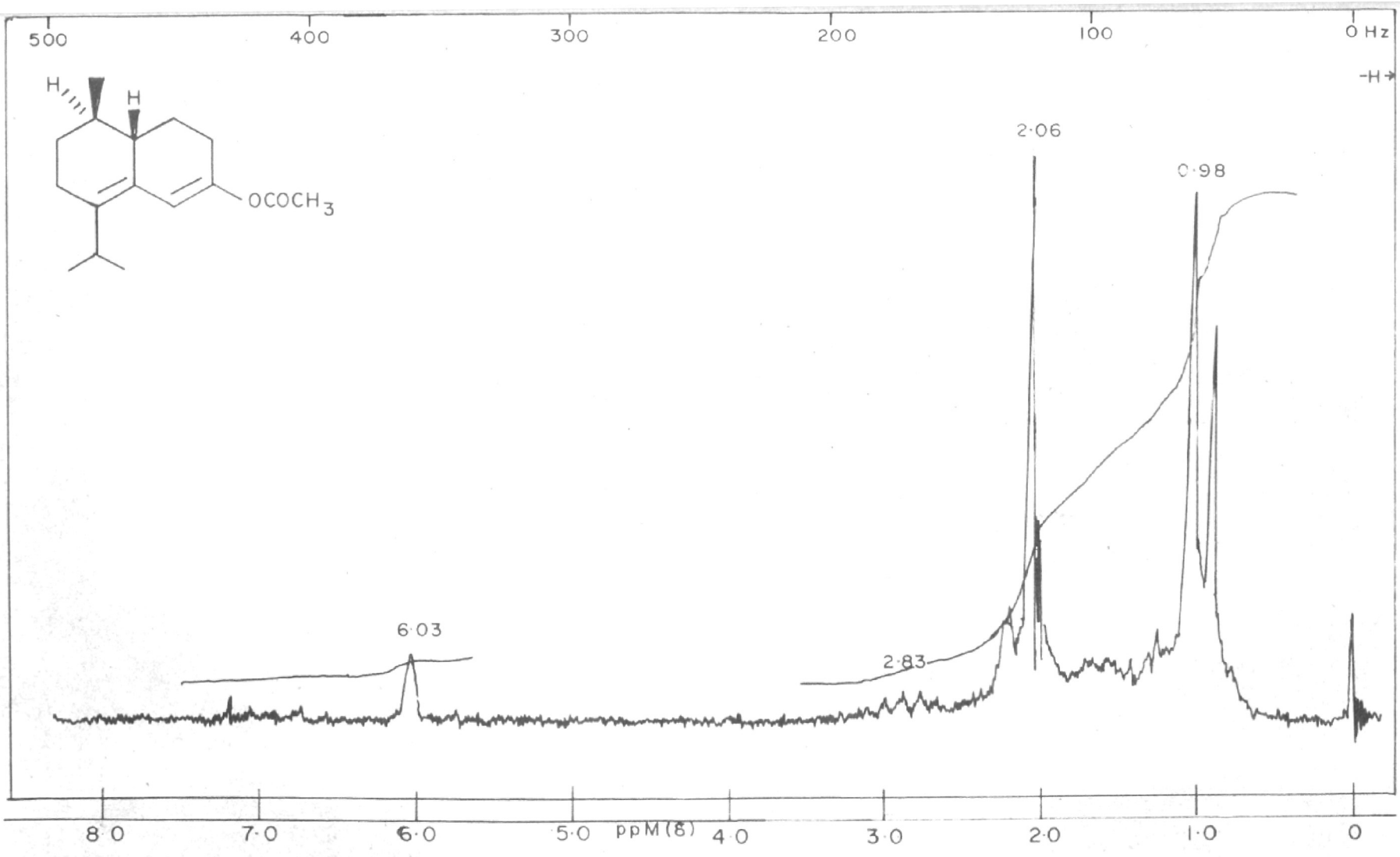


FIG.3·10. NMR SPECTRUM OF THE ENOL–ACETATE (36)

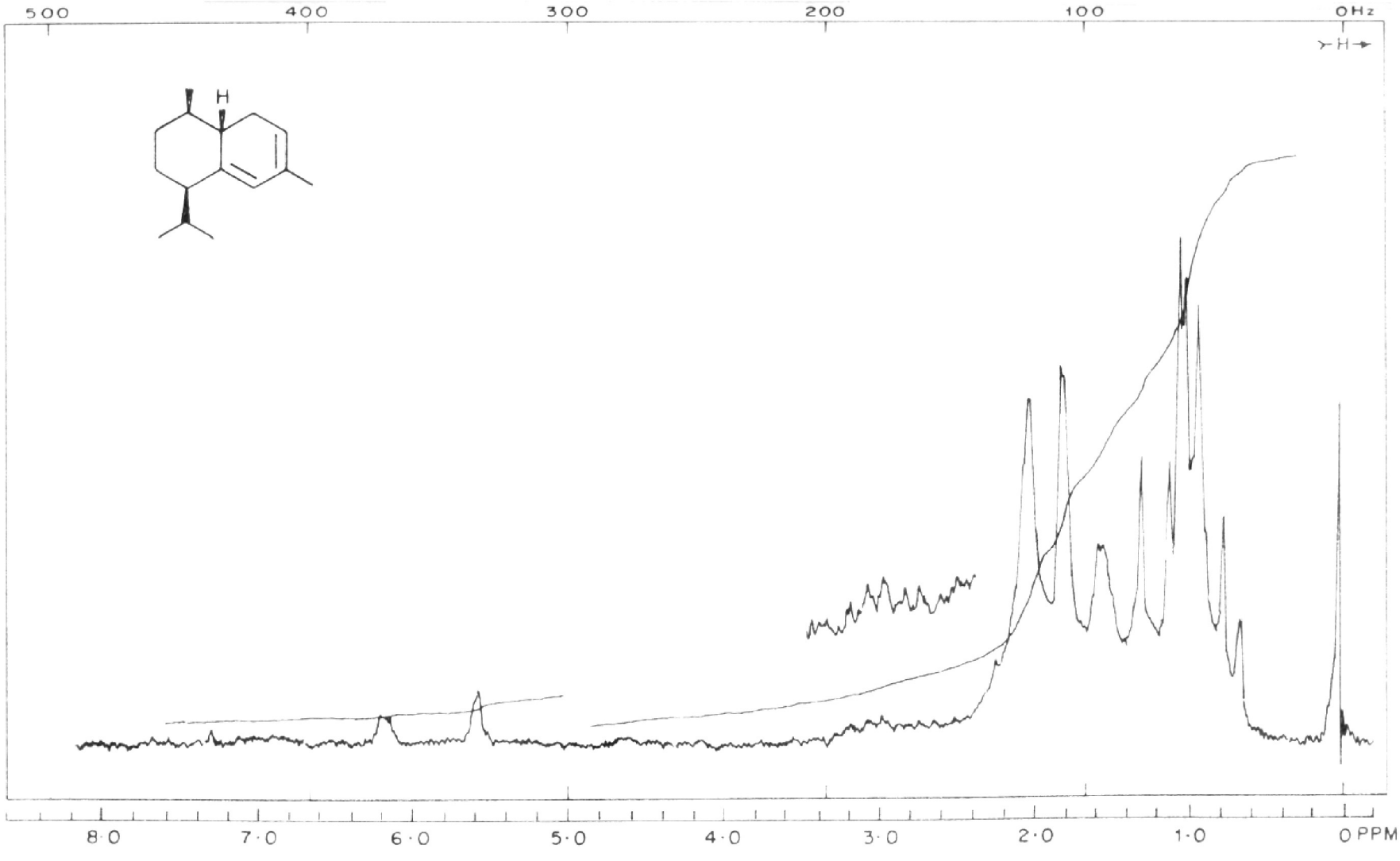


FIG. (3·11). NMR SPECTRUM OF DIENE (37a)

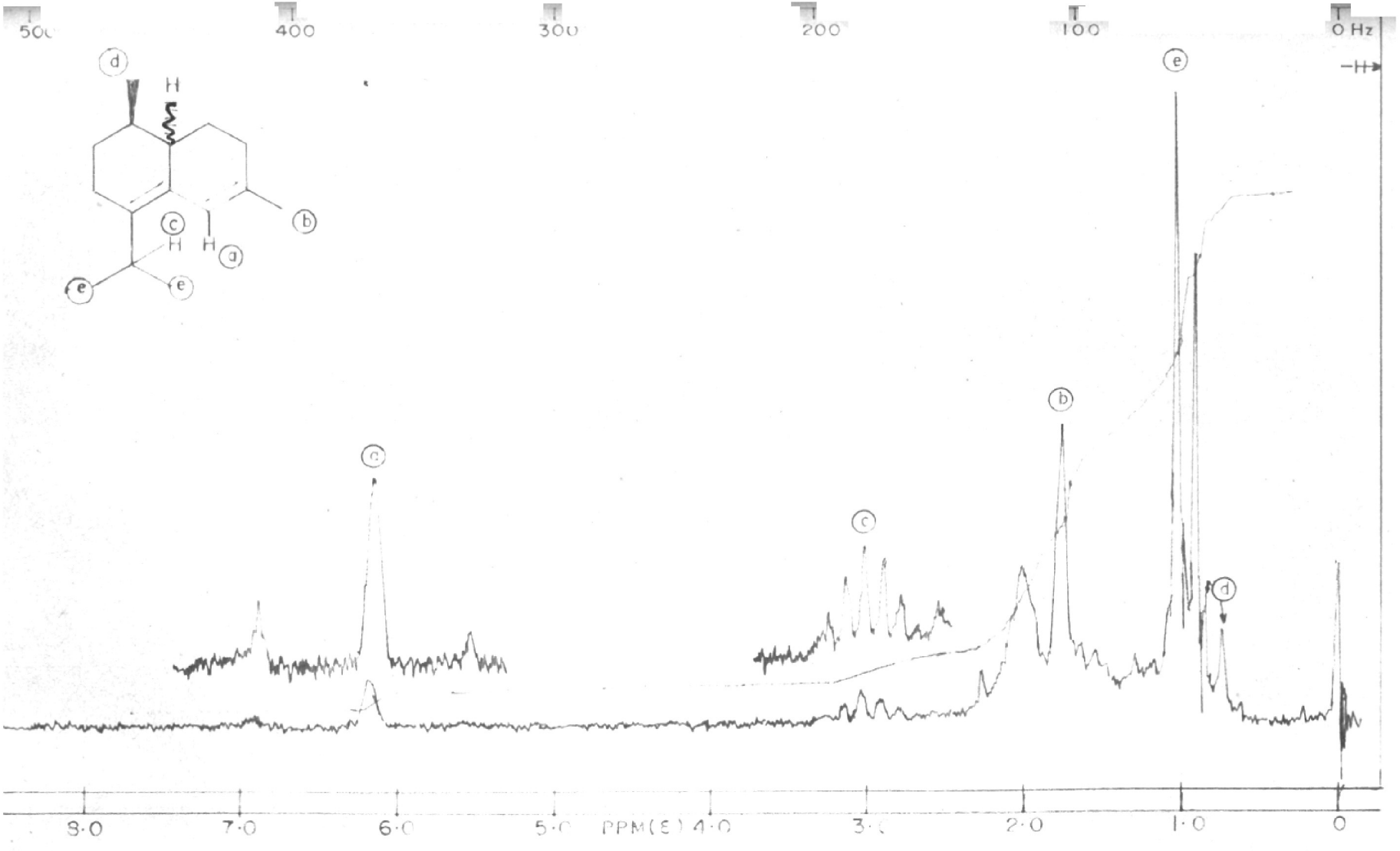


FIG. 3·12 . NMR SPECTRUM OF EPIZONARENE AND ZONARENE (85:15)

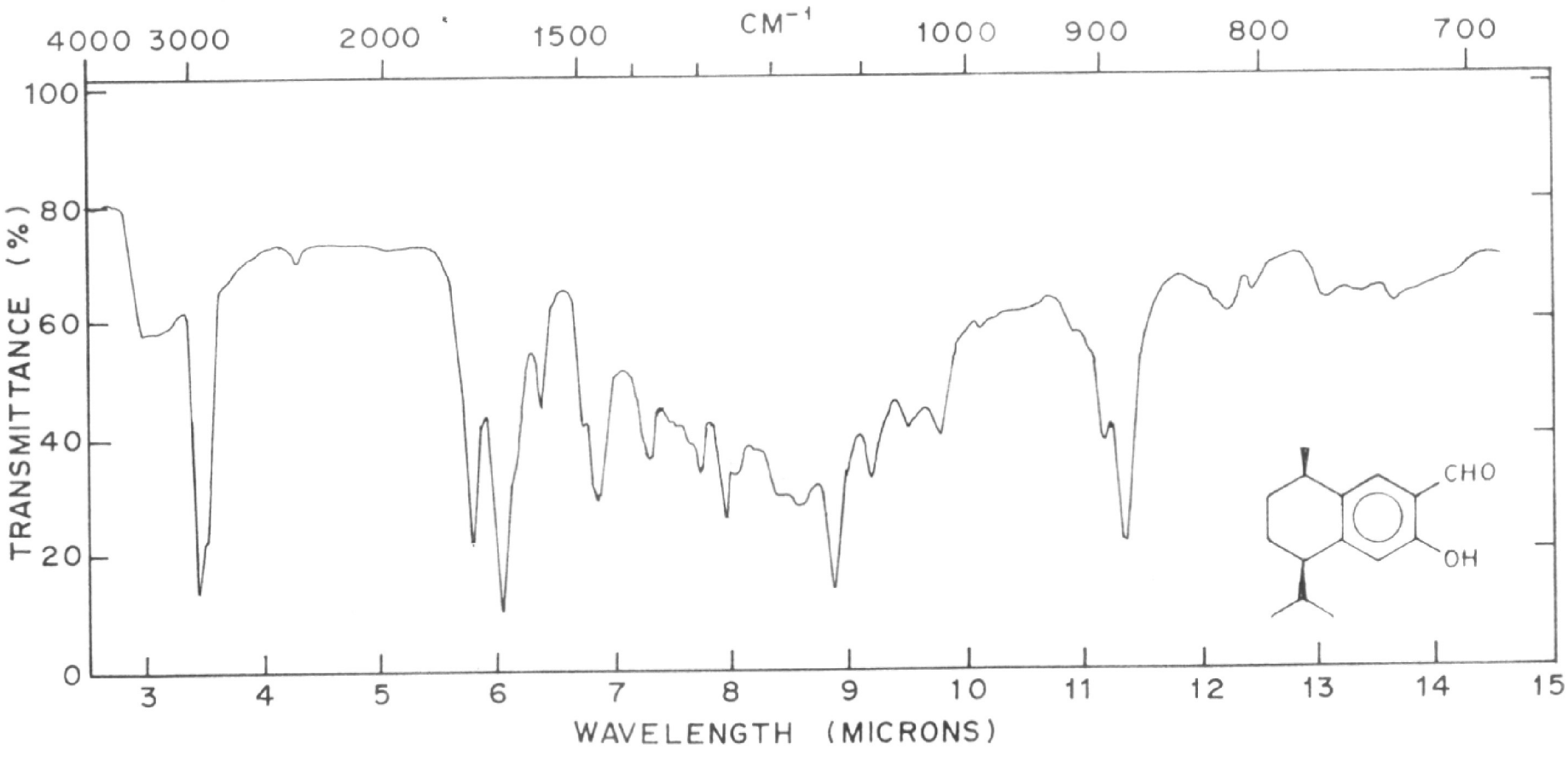


FIG-(3-13). IR SPECTRUM OF 4-HYDROXY-3-NAPHTHALDEHYDE DERIV (42)

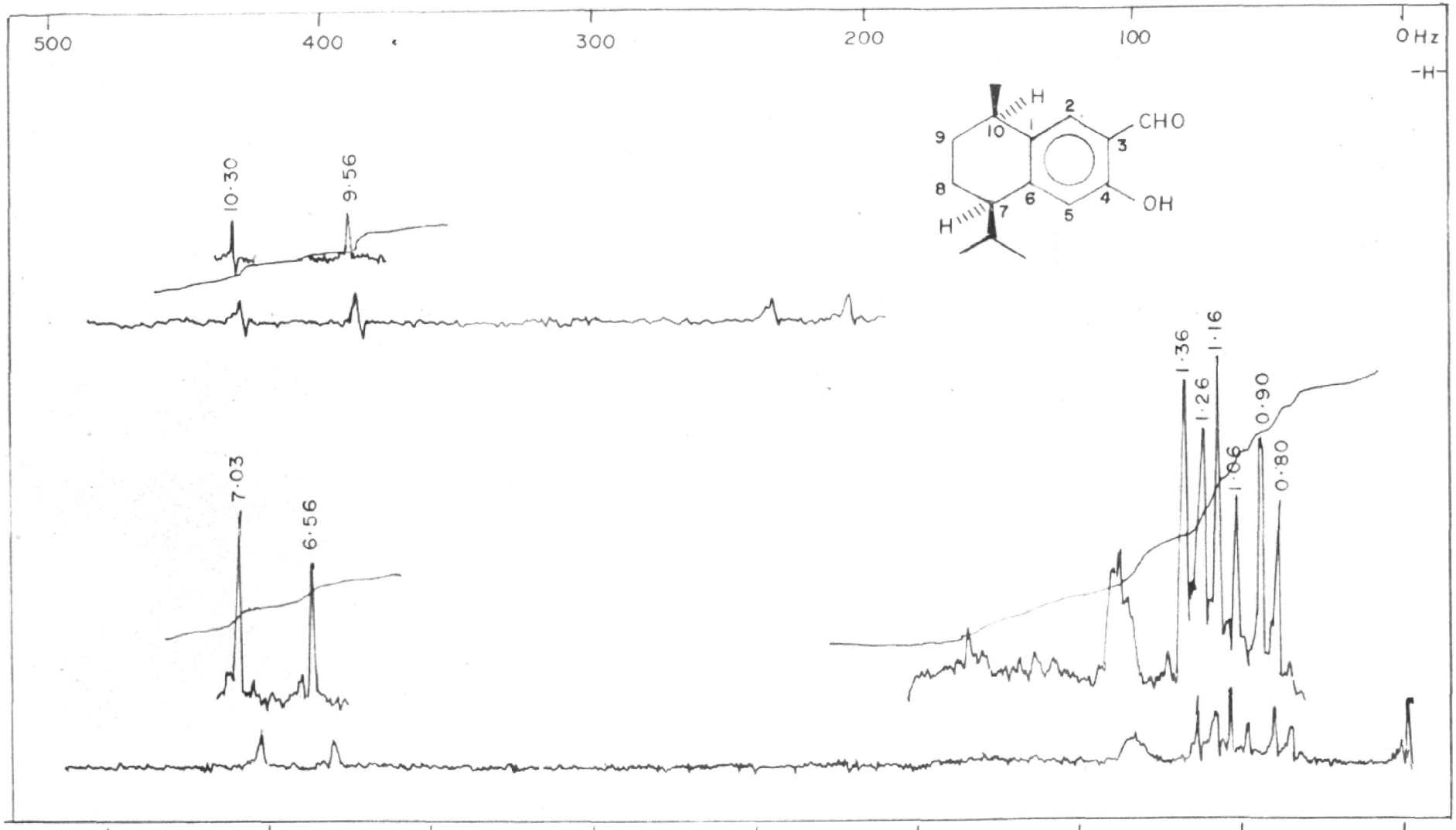


FIG. 3·14. NMR SPECTRUM OF 4-HYDROXY-3-NAPHTHALDEHYDE DERIV.(42)

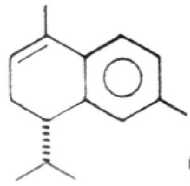
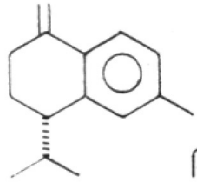
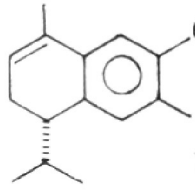
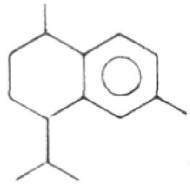
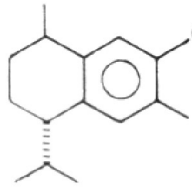
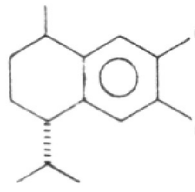
C H A P T E R - III

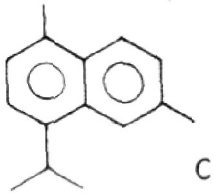
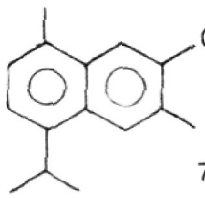
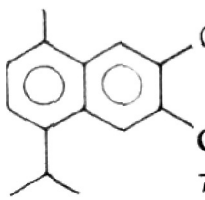
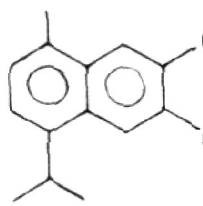
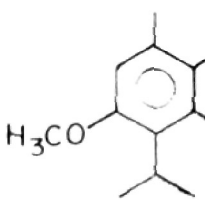
TOTAL SYNTHESIS OF 7-HYDROXYCADELENAL

***

LIST OF NATURALLY OCCURING COMPOUNDS HAVING A CADALENE SKELETON

—1—

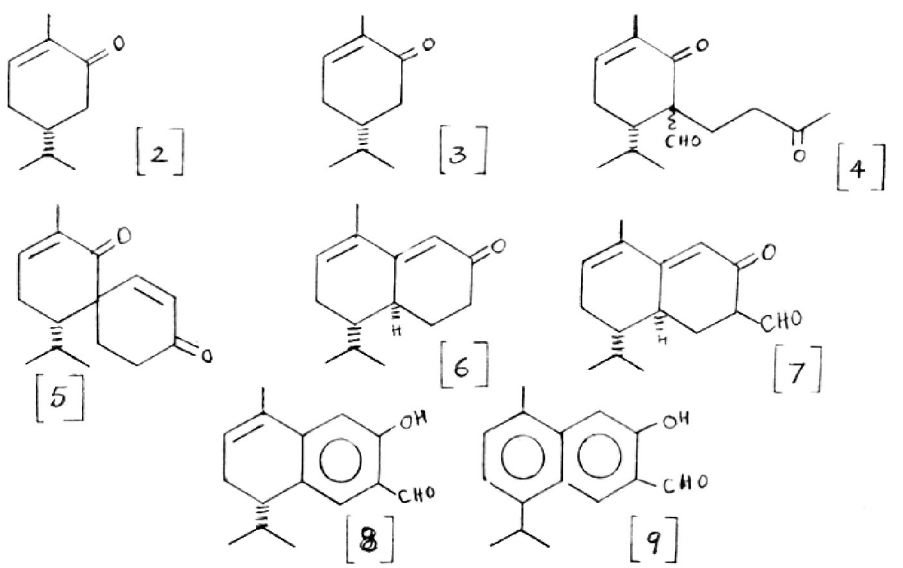
STRUCTURE	α_D	REFERENCE NUMBER
 α–Calacorene	+52°	1
 β–Calacorene	+50	2
 7–OH, Calacorene	–	3
 Calamenene	–	4 5
 7, OH–Calamenene	–30°	6
 7,OH–Calamenenal		7

STRUCTURE	α_D	REFERENCE NUMBER
 Cadalene	–	8
 7, OH – Cadalene	–	9
 7 – OH, Cadelenal	–	7
	–	10
 7, OH, 3 – OMe – Cadelenal	–	7

SUMMARY

Naturally occurring 7-hydroxycadelenal (9) has been synthesised starting from (-) carvotonacetone (2).

Carvotonacetone (2) on formylation gave the formyl derivative (3) which on condensation with methyl vinyl ketone, followed by deformylation using 2% potassium carbonate gave a mixture of two compounds 5 and 6. They were separated and characterised. 6 on formylation gave 7, which was dehydrogenated to a mixture of 8 and 9, using DDQ. The ratio of 8:9 was found to be roughly 75:25 by NMR spectrum. This mixture on dehydrogenation with palladised charcoal gave 9. The purified sample was identical with naturally occurring 7-hydroxycadelenal in all respects (TLC, IR, NMR and mixed m.p.).



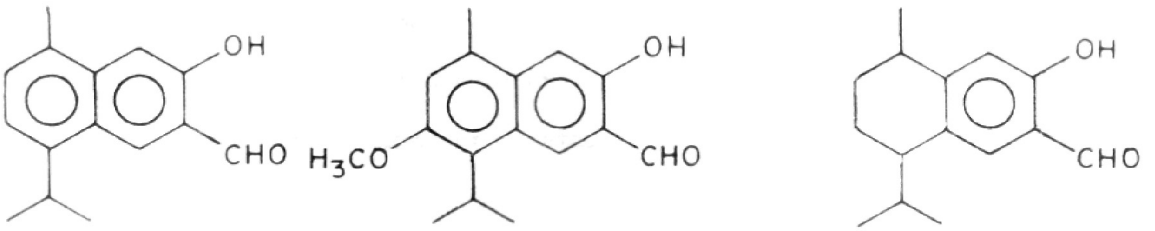
[2] [3] [4] [5] [6] [7] [8] [9]

Occurrence

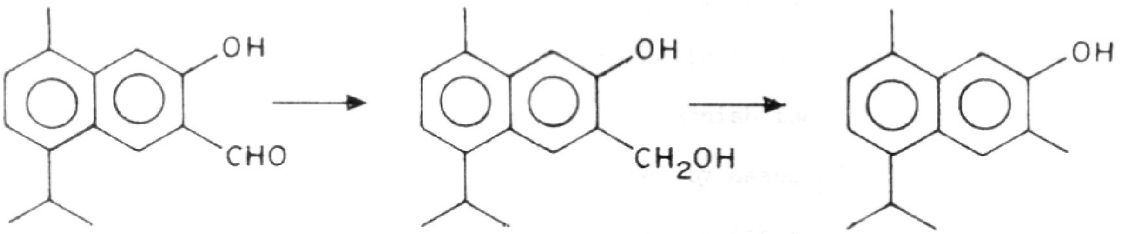
7-Hydroxycadelenal (9) occurs in nature along with three other related sesquiterpenes in the yellow heartwood of Ulmus rubra Mahl.[1] It was obtained as brilliant yellow compound from the benzene extracts of the wood. It had m.p. 88° and was shown by mass spectrum and analysis to be $C_{15}H_{16}O_2$. It gave positive Fehling's and Tollen's test and turned intense green with ferric chloride; gave a dark purple iodophenol when treated with nitrous acid and weakly fluorescent. Its UV absorption ($\lambda^{max}_{isooctane}$ 221, 256, 266, 303, 314 and 397 nm; log ε 4.44, 4.58, 4.59, 3.98, 4.03 respectively) was very similar to that of 3-hydroxy-2-naphthaldehyde, but displaced somewhat to longer wavelengths. In alcohol the UV showed a bathochromic shift of about 15 nm on addition of sodium acetate or aluminium chloride. The IR spectrum (νCCl_4 max. 3247 (hydrogen bonded phenol), 2700 and 1664 cm^{-1} (aldehyde) also was similar to that of 3-hydroxy-2-naphthaldehyde. The NMR spectrum strongly indicated structure 9 for the compound. This has the sesquiterpene skeleton of cadalene. The intense colour is due to the equillibrium $9 \rightleftharpoons 9a$.

Derivatives of 9a, were prepared including its phenyl hydrazone (m.p. 186°), N:N-dimethyl p-phenylene diamine anil, acetate and carboxymethyl ether. In all cases, the spectral properties showed them to be derived from the normal form 9 rather than from

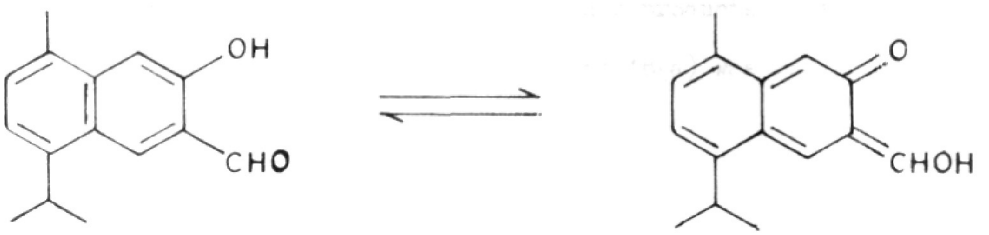
CHART I



9 10 11



9 12 13



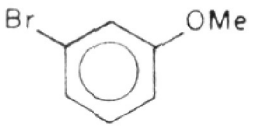
9 9a

9a. The structure 9 was further supported by sodium borohydride reduction to the corresponding diol (12) and proved by conversion to the known 7-hydroxycadalene (13). The Huang-Minlon modification of Wolff-Kishner reduction of 9 gave only a very low yield of 13, the diazine being the major product. Catalytic hydrogenation of 9 yielded 13, but of low purity.

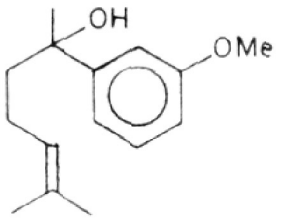
Synthesis

The first and the only synthesis of 7-hydroxycadelenal (9) has been reported by Rao et al.[3] Their scheme is represented in Chart II. Grignard reaction of m-bromoanisole (14) gave a mixture of carbinol (15) and its dehydration product (16). Catalytic hydrogenolysis/hydrogenation (10% Pd/C or PtO_2 in acetic acid containing perchloric acid) of this mixture failed to furnish the desired compound (17). However, reduction to 17 was achieved by means of lithium in moist ammonia. The PPA cyclisation of 17 to 7-methoxy tetralin(18a) was patterned after similar successful results achieved previously,[4] with monocyclic carbinol precursors, and experience in the cyclisation of ar-curcumene to calamenene.[5] However, since the unsymmetrical substitution of the ring in 17 and the more stable tertiary cationic site of the side chain, does not preclude other products of cyclisation (19 to 21) besides 18a. However, structure of 18(a) was established by an alternate synthesis.

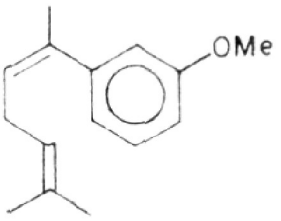
CHART II



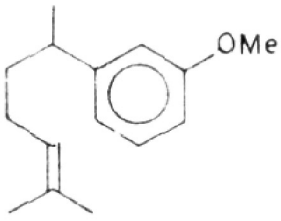
14



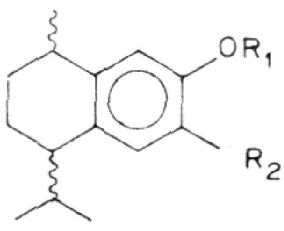
15



16



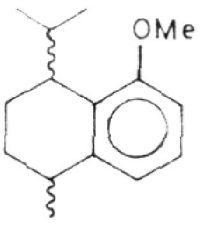
17



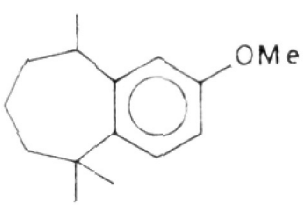
18a $R_1 = Me$, $R_2 = H$

18b $R_1 = Me$, $R_2 = CHO$

18c $R_1 = Me$,
$R_2 = CH=N\cdot NH-CO\cdot NH_2$



19



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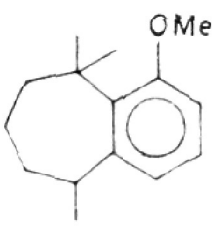

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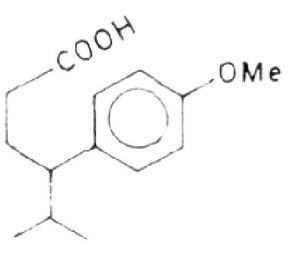

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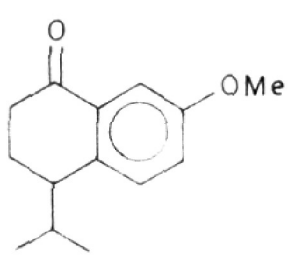

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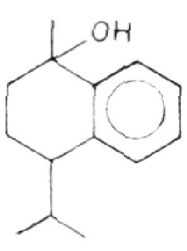

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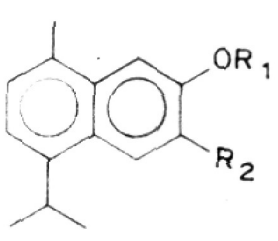


25a $R_1 = Me$,
$R_2 = CH=N\cdot NH-CO\cdot NH_2$

25b $R_1 = H$, $R_2 = CHO$

4-(p-anisyl)-5-Methyl hexanoic acid (22) obtained by the inverse Grignard reaction[6] of isopropyl magnesium iodide to methyl-3 (p-anisoyl) propionate followed by hydrogenation was cyclised by PPA under mild conditions to tetralone (23). Reaction of 23 with methyl lithium and hydrogenolysis of the resulting carbinol (24) gave the corresponding 7-methoxy tetralin (18a), which was identical with (18(a) prepared previously. The IR spectrum of the two samples agreed favourably except for some minor differences. Minor differences in the spectra in the fingerprint region may be due to existence of minor amounts of other possible cyclic isomers (19 to 21) in the product obtained by former route and a likely higher ratio of cis/trans of 18a as a result of catalytic hydrogenation in the product from the latter synthesis.

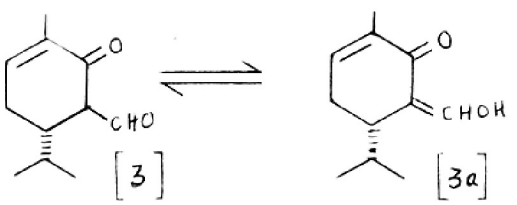
The methoxy-tetralin from both the routes on formylation by Vilsmier reaction[7] gave identical 7-methoxycalamenal (18b) isolated as the sparingly soluble semicarbazone (18c).

Dehydrogenation of 18c with DDQ gave the product 25a as a crystalline product. From the semicarbazone (25a) the crystalline 7-methoxycalamenal was regenerated. Its demethylation with pyridine hydrochloride, furnished 7-hydroxycadelenal (25b) as yellow needles.

PRESENT INVESTIGATION

7-Hydroxycadalenal (9) was synthesised starting from (-) carvotonacetone (2), which is distinct from the synthesis described above. The intermediate conjugated ketone was obtained by two different routes. The ketone obtained by the Michael addition of methyl vinyl ketone on carvotonacetone was used for further synthesis.

Carvone (α_D -59.40°) was hydrogenated over Adam's catalyst for 15 hours. IR spectrum of the crude product showed the presence of both carvotonacetone (1667 cm^{-1} conj.ket.) and carvomenthone (1730 cm^{-1} $>C=O$). The crude mixture was distilled on a spinning band column and carvotonacetone (2) boiling in the range of 107-110° was collected. A GLC pure sample of carvotonacetone (α_D - 54.66°) was formylated according to the procedure of Corey and Nozoe.[8] The crude hydroxymethylene derivative (3) was distilled at 116-118°/3 mm. (bath 140°). The IR spectrum (Fig.4-1) showed bands at 3340, 1650 and 1667 cm^{-1}. NMR spectrum (Fig .4-2) showed a pair of doublets for the isopropyl group at 0.85, and methyl on a double bond at 1.83 (singlet) and the β-proton to the carbonyl group at 6.40 as a broad singlet. The aldehyde proton appears at 7.43 as a singlet. From the NMR spectrum, it is clear that the compound exists predominantly in form 3 rather than 3a.

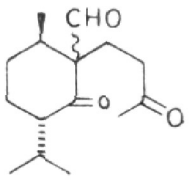


[3] [3a]

The hydroxymethylene derivative (3) was condensed with freshly distilled methyl vinyl ketone in presence of triethylamine under an atmosphere of N_2 gas. The crude diketoaldehyde (4) was distilled at 136°/3 mm.(bath 160°). Its NMR spectrum (Fig.4-3) shows a pair of doublets at 0.86 (isopropyl) and a singlet at 1.76 (methyl on double bond). The newly introduced $-CO-CH_3$ grouping appears as a doublet of unequal intensity at 2.03 and 2.20. This therefore suggests that the diketoaldehyde is a mixture of two compounds, in which the $-CH_2-CH_2-CO-CH_3$ grouping has a α or β -conformation. In addition to these peaks the compound showsthe β-proton at 6.73 (bs) and the aldehyde proton at 9.96 (ss). The deformylation of 4 was carried out by using 2% potassium carbonate. TLC of the resulting product showed three compounds in unequal amounts. The two major compounds were separated by column chromatography over silica gel.

The more polar compound was obtained from the last chromatographic fractions of pet.ether + 10% ether elutions. The sample was found to be TLC pure and the distilled compound (b.p. 150-155°/2.5 mm.) showed a single peak on GLC (carbowax column, 190°). Mass spectral analysis showed the molecular weight to be 232 (M+). The IR spectrum (Fig.4-4) show3d bands at 1634, 1590, 1450, 1375, 910 and 865 cm^{-1}. It had λ_{max}^{MeOH} 239 nm (ε, 10,600) in the UV spectrum. The possible structure 5 for this compound was confirmed by the NMR spectrum (Fig.4-5). It showed a multiplet at 0.73→0.93 (isopropyl), singlet at 1.71 (methyl

CHART III



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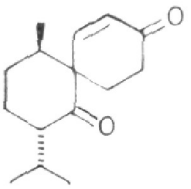

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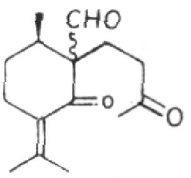

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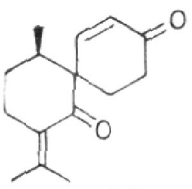

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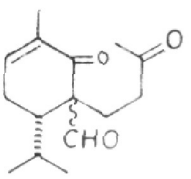

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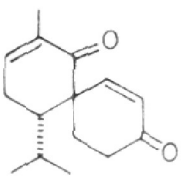

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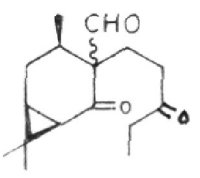

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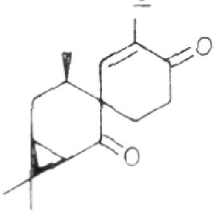

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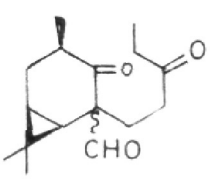

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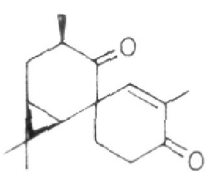

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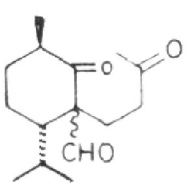

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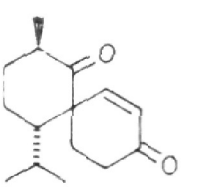


36

on a double bond) and a pair of doublets, one centered at 5.93 (J ~10 cps) and another centered at 7.03 (J~ 10 cps), assignable to the α and β protons of a cyclohexenone system with no allylic coupling (The characteristic[9,10] coupling constant in such systems is 9.6 Hz). The β-proton of the original carvotonacetone system appears at 6.66 as a broad singlet.

The formation of spiro compounds during Michael addition was first observed by Ladwa et al.[11,12] Subsequently many workers have reported the formation of spiro compounds during the Michael additions (see ref. nos. 9 to 14). Some of these spiroketones(23-36) formed from the corresponding diketoaldehydes of menthone (27), pulegone (29), cis-Caran-5-one (31), cis-Caran-4-one (33) are shown in the chart III. The formation of spiro compound (5) from carvotonacetone (2) was thus not unexpected. It is interesting to note that the diketoaldehyde (35) derived from carvomenthone did not furnish the expected spiro compound (36), as was evident by the NMR of the product during our investigation. The same diketoaldehyde(35) has been used for the synthesis of Helminthosporal by Corey et al.,[15] and no spiro compound is reported by them.

The extended conjugated ketone (6) was obtained in the initial fractions of pet.ether + 10% ether elution of the crude deformylated product. TLC showed a single spot and GLC on QF_1 column at 210°, showed more than 90% purity. The crude compound was distilled at

148-150°/3 mm. The UV spectrum showed λ_{max}^{MeOH} 285 nm (ε,12,580) indicating extended conjugation (expected value 287 nm), α_D - 25.36° ($CHCl_3$). The NMR spectrum (Fig.4-6) shows the isopropyl group as a multiplet at 0.93 and the methyl on a double bond at 1.86 (singlet). The α-proton to the carbonyl appears at 5.80 and the δ-proton appears at 6.10 as a very broad singlet.

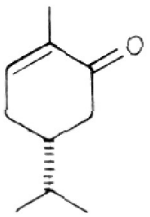
The IR spectrum (Fig.4-7) of 6 showed bands at 1667, 1634 and 1592 cm^{-1} which are all in agreement with the expected structure (6), but a band 1704 cm^{-1} could not be accounted for. Several attempts through column chromatography were made to get rid of this unwanted band, but without success. It was however observed that Marshall et al.[16] were encountered with a similar difficulty during their synthesis of a similar extended conjugated ketone.

The observed low ε value in the uv spectrum (when compared with ε-value of analogous systems) and the unwanted impurity in the IR (1704 cm^{-1} peak) of ketone 6, prompted us to attempt the preparation of the same compound by a different route. Further, the above method gave a very low yield of ketone 6, because of formation of spiro compound (5).

Second route for the synthesis of ketone (6)

The scheme followed is shown in chart IV. Carvotanacetone (2) on Mannich reaction[17] with dimethylammonium chloride and paraformaldehyde

CHART IV



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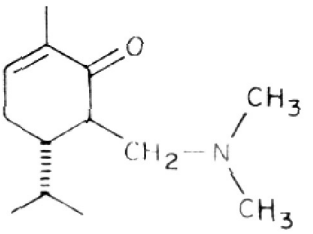

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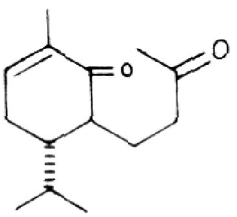

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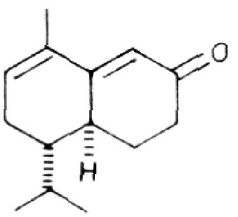

6

gave the Mannich base (37) in 75% yield, b.p. 100°/2.5 mm.(bath 130°). The NMR spectrum (Fig. 4-8) showed the isopropyl at 0.80 (doublet), the two methyls on the nitrogen atom at 2.18 (singlet), methyl on a double bond at 1.70 (singlet) and the β-proton at 6.40 (broad singlet). The presence of the conjugated ketone system in the Mannich base (37) was confirmed by UV spectrum λ_{max}^{MeOH} 240 nm (ε, 16,780). The Mannich base 37 was quaternised with methyl iodide and was condensed with ethyl acetoacetate in presence of sodium ethoxide. Subsequent hydrolysis with potassium hydroxide gave a mixture of diketone (38) and ketone (6), as was evident by TLC and NMR. Cyclisation was finally achieved by sodium ethoxide. The extended conjugated ketone (6) showed a single spot on TLC, but GLC analysis on QF_1 column at 200° showed the presence of an epimeric mixture in the ratio of 60:40 (epimeric probably at the ring juncture). Its UV showed λ_{max}^{MeCH} 285 nm (ε, 9060). A comparison of this sample with the ketone obtained by the first route was done on GLC (QF_1 column, 200°). The major peak (60%) in the epimeric mixture agreed with the ketone obtained by previous method. The NMR spectrum of the two samples were superimposable, and the IR spectrum again showed the same impurity (1704 cm^{-1} peak). It was therefore not possible to get a 100% pure sample of ketone (6), but further conversion to 7-hydroxycadelenal (9) was carried out using the ketone obtained by the first route.

Conversion of extended conjugated ketone to 7-hydroxycadelenal

The extended conjugated ketone (6) was formylated using ethyl formate in presence of sodium methoxide to compound 7. This compound was taken out in 10% alkaline layer by extraction followed by acidification using 1:1 HCl to pH 6. The crude compound (7) was used as such for dehydrogenation.

The hydroxymethylene derivative (7) on refluxing with 2:3 dicyano, 5:6 dichloroquinone (DDQ) in dioxane (dry)[18] for 3 hours under an atmosphere of N_2 gas, followed by usual work up gave the crude compound. TLC showed two spots. The NMR spectrum (Fig.4-9) showed it to be a mixture of compounds 8 and 9. The ratio of 8:9 was found to be 75:25 as judged by the relative area of the signals of C_7 phenolic proton at 10.8(s) and the C_6 aldehyde proton at 9.7(s) of compound 8, with that of 9 which has the C_7 phenolic proton at 10.2(s) and C_6 aldehydic proton at 10.1(s). This was further confirmed by relative area measurement of C_1 methyl signal of 8 at 2.07(s) and C_1 methyl signal of 9 at 2.60(s). No attempt was made to separate the two compounds but the mixture was as such dehydrogenated over palladised charcoal (10%) at 160° on an air bath (6 hours). Usual work up and elution with pet.ether over silica gel afforded brilliant yellow needles having m.p. 87° (lit.[88°]). TLC showed the compound to be very pure. The IR spectrum (Fig.4-10) showed bands at 3274 (hydrogen bonded phenol), 2700 and 1664 cm^{-1} (aldehyde). The spectrum

was superimposable on the authentic IR spectrum. Mixed m.p. measurements with an authentic sample of 7-hydroxycadelenal did not show any depression. The NMR spectrum (Fig.4-11) shows the chemical shift of each proton as follows:

C_1-methyl-2.60(s); C_2-H, 7.33(d, J~7 cps); C_3-H, 7.20 (d, J~7 cps); C_5-H, 8.33(s); C_6-aldehyde proton, 10.1(s); C_7-phenolic proton, 10.2(s); C_8-H, 7.36(s); C_9-H, 3.66 (heptet); C_{10} and C_{11} methyls 1.40 (d, , J~7 cps).

A comparison of the NMR of the synthetic sample (recorded in CCl_4) with the NMR of the authentic sample (recorded in $CDCl_3$) gave rise to a slight confusion in assigning the signals of C_7-phenolic and C_6 aldehydic protons in our NMR. The literature[1] reported the signals of C_7 phenolic proton at 10.30 and C_6-aldehydic proton at 10.05, whereas in our spectrum they appeared at 10.2 and 10.1 respectively. It was later recognised that the solvent used for recording the spectrum was responsible for the observed shift of the signals. The NMR of the authentic sample* recorded in CCl_4 on our instrument was superimposable on the NMR spectrum of the synthetic sample.

The chemical shift of the protons of the phenolic and aldehyde group may be due to the equilibrium $9 \rightleftharpoons 9a$. A slight change in the polarity of the solvent may shift the normal equilibrium. The presence of trace amounts of hydrochloric acid in the recording solvent is expected to induce such shifts.

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* We thank Prof. J.W. Rowe, Forest Products Laboratory, Madison, Wisconsin, for useful discussion and a generous sample of 7-hydroxycadelenal.

EXPERIMENTAL PART

Preparation of carvotonacetone from carvone

(-) Carvone (α_D -59.40) (75 g) in dry alcohol (250 ml) was hydrogenated over 0.500 g. of Adam's catalyst at room temperature, and atmospheric pressure. Hydrogenation was stopped after 16 hours and the crude product showed the presence of both carvotonacetone (1667 cm^{-1}) and carvomenthone (1730 cm^{-1}). The crude mixture was distilled on a spinning band column at 15 mm. of Hg, maintaining the reflux ratio of 1:40 throughout the distillation. Initial fractions boiling at 95° furnished carvomenthone of 95% purity (GLC on S.E.30 column at 130°). Total weight 15.67 g. The later fractions boiling at 107-110° gave carvotonacetone (2) of ≥ 99% purity. Total weight 40.86 g. The intermediate fractions (97° to 105°) contained mixtures of both compounents in various proportions(GLC).

Preparation of extended conjugated ketone

Route 1:

Preparation of hydroxymethylene derivative(3) of carvotonacetone(2)

A suspension of dry sodium methoxide (prepared previously in a 3-necked flask from 4 g. of sodium and dry methanol) in 20 ml. of dry benzene was treated with 20 g. of ethyl formate in 20 ml. of dry benzene. The mixture was cooled under ice. 7.6 g. of pure carvotonacetone was added dropwise. The whole reaction was carried out under an atmosphere of N_2 gas and with mechanical stirring of

the reaction mixture. After 48 hours, about 20 ml. of water was added to the reaction mixture and the benzene layer repeatedly shaken with 5% NaOH solution (12 x 3 ml). The alkaline layer was then shaken with ether to remove the unreacted ketone. The aqueous layer on acidification with 1:1 HCl (pH 6) gave the formyl derivative(3). The crude product (5.30 g) was distilled at 116-118°/3 mm.(bath 140°) yield of pure compound, 5.16 g.

IR spectrum (Fig. 4-1), bands at 3340, 1650, 1450, 1375 cm^{-1}.

NMR spectrum (Fig. 4-2). 0.82, 6.95, (pair of doublets, 6H); 1.83 (s,3H); 6.40 (bs, 1H); 7.43 (ss, 1H).

Condensation of hydroxymethylene derivative (3) with methyl vinyl ketone

Triethylamine (4 g) was added to an ice coold mixture of hydroxymethylene derivative (3, 5.16 g) and freshly distilled methyl-vinyl ketone (8.5 ml). The reaction mixture was stirred at room temperature and under an atmosphere of N_2 gas for 3 days. Excess of triethylamine and methyl vinyl ketone were then removed 'in vacuo'. Extraction with ether (25 ml) followed by washing with dilute HCl, dilute NaOH, water and removal of the solvent gave 3.11 g. of crude compound. Distilled at 136°/3 mm.(bath 160°).

TLC (pet.ether + 50% ethyl acetate) shows a single spot.

NMR spectrum (Fig. 4-3). 0.86 (pair of doublets, 6H); 1.76 (s, 3H); 2.01 (d, 3H*; 6.73 (very bs; 1H) 9.96(ss,1H).

Deformylation of diketoaldehyde (4) with 2% potassium carbonate

Diketoaldehyde (4) (3.06 g) was refluxed with 2% potassium carbonate solution in 12 ml. of ethanol under an atmosphere of N2 gas, over a steam bath for 24 hours. Removal of the solvent followed by extraction with ether (25 ml) afforded the crude (2.81 g) material. TLC (pet.ether + 50% ethyl acetate) of the crude showed three spots. The crude compound was passed over a column of silica gel (40 g), and eluted with pet.ether, followed by pet.ether + 10% ether. The initial fractions of pet.ether + 10% ether elution gave the extended conjugated ketone (6, 0.216 g.). Distilled at 148-150°/2.5 mm. TLC (pet.ether + 10% ethyl acetate); single spot. GLC on QF_1 column at 200° showed 90% purity.

IR spectrum (Fig.4-7) 1667, 1634, 1592, 1450 and 1375 cm^{-1}.

An unidentified peak at 1704 cm^{-1}.

UV spectrum, λ_{max}^{MeOH} 285 nm, ε 12,580, α_D - 25.36° ($CHCl_3$).

NMR (Fig.4-6). 0.93 (m,6H); 1.86 (s, 3H); 5.80 (s, 1H), 6.10 (bs, 1H). The spiro compound (5) was obtained from last chromatographic fractions of pet.ether + 10% pet.ether elutions. Distillation at 150-155°/3 mm. afforded 0.299 g. of pure compound (5). TLC (pet.ether + 10% ethyl acetate) showed a single spot. GLC on carbowax column at 190° showed a single peak.

IR spectrum (Fig.4-4) 1634, 1590, 1450, 1375, 910, 865 cm^{-1}.

NMR spectrum (Fig.4-5) 0.73-0.93 (m,6H); 1.71(s,3H); 5.93 (d, J~10 cps),1H); 7.03 (d,J~10 cps, 1H); 6.66(bs,1H).

Mass spectrum. Molecular weight 232 (M+).

UV spectrum λ_{max}^{MeOH} 239 nm, (ε, 10,600).

Route II

Preparation of Mannich base (37) from carvotonacetone (2)

Carvotonacetone (0.2 moles; 30.4 g.), dimethylaminehydrochloride (0.3 moles; 24.4 g.), paraformaldehyde (8 g.) and absolute alcohol(60 ml) in presence of 2 ml. of conc. HCl are refluxed on a steam bath for 8 hours. Most of the solvent was then removed and the solid mass dissolved in about 50 ml. of water and extracted with ether (50 ml). The aqueous layer was then made alkaline by addition of KOH (30 g) in water(15 ml). The solution was then saturated with potassium carbonate. It was then extracted with ether (75 x 2 ml). The combined ethereal layer was thoroughly washed to remove the excess alkali. Evaporation of the solvent furnished 32.5 g. of Mannich base (37), b.p. 100/2.5 mm. (bath 130-135°) (yield 75%).

NMR (Fig.4-8) 0.88, 0.92 (d, 6H); 1.70(s,3H); 2.20(s,6H); 6.40 (bs, 1H).

Microanalysis. Found: C, 76.16; H, 11.00; N, 5.812.

$C_{10}H_{23}O_2$ requires C, 76.33; H, 11.00; N, 5.896%.

Preparation of quaternary salt

Methyl iodide (12 ml) was catiously added to 31.4 g. of Mannich base (37) in16 ml. of anhydrous ethanol. A vigorous reaction ensues with the formation of quaternary salt. This was allowed to settle down at room temperature for 20 hours.

Condensation with ethyl acetoacetate

Freshly cut sodium (3.68 g) was placed in a 2-necked flask, fitted with a dropping funnel and a condenser. 64 ml. of super dry alcohol was allowed to run slowly. When all the sodium had reacted, 20.8 ml. of freshly distilled ethyl acetoacetate was added. The quaternary salt prepared previously, is taken in a little anhydrous ethanol and added to the reaction mixture, and allowed to settle overnight. It is then vigorously refluxed on a water bath for 8 hrs. It was cooled and 18 g. of KOH in 30 ml. of water was added and the resulting solution further refluxed for 3 hours. Removal of the solvent and the usual work up gave 13.26 g. of dark brown compound. TLC (pet.ether + 50% ethyl acetate) showed two spots, with very little difference in their R_f values.

It showed IR bands at 1740, 1667, 1450, 1375, 890 cm^{-1}.

NMR spectrum showed signals at 0.87 (m,6H); 1.87(s,3H); 6.09(bs,1H); 5.8(ss,1H), 2.03(d,3H).

Cyclisation with sodium ethoxide

The crude material (12.1 g.; a mixture of 38 and 6) was refluxed in ethanol with sodium ethoxide for 6 hours. Usual work up gave 11.12 g. of crude ketone. A part of it (4.0 g.) was passed over a column of Gr.III alumina (40 g). Pet.ether elutions gave 2.36 g. of the ketone (6). Distillation at 150-155°/3 nm. gave the pure ketone. TLC (pet.ether + 10% ethyl acetate) showed a single spot.

GLC on QF_1 column at 200° shows two peaks (60:40 ratio). The major peak corresponds with the ketone obtained by earlier route.

UV λ_{max}^{MeOH} 285 nm (ε, 9,060).

IR spectrum. 1667, 1634, 1592, 1450, 1375 cm^{-1}

(unidentified peak at 1704 cm^{-1}).

NMR 0.93(m,6H); 1.86(s,3H); 5.80(s,1H);6.10(bs,1H).

Conversion of extended conjugated ketone to 7-hydroxycadelenal (9)

Preparation of hydroxymethylene derivative of ketone (6).

A suspension of sodium methoxide was prepared using 1.15 g. of sodium and dry methanol in a 3-necked flask. It was thoroughly dried under vacuum and 3.70 g. ethyl formate in10 ml. of dry benzene was added to it. 2.05 g. of ketone (6) in 10 ml. of dry benzene was slowly added to it. The entire operation was carried out under an atmosphere of N_2 gas and with stirring. At the end of 48 hours, the reaction mixture was extracted with 10% NaOH solution (10 x 2 ml). The alkaline layer was once extracted with ether (25 ml) to remove the unreacted ketone. The aqueous layer was then acidified with 1:1 HCl to pH 6. It was thoroughly cooled and extracted with ether (30 x 3 ml). Evaporation of the solvent gave a gummy mass (1-16 g). This compound was used as such for dehydrogenation.

Dehydrogenation of hydroxymethylene derivative (7) using DDQ

Hydroxymethylene derivative (7) (1.16 g) was refluxed in dry dioxane with DDQ (1 mole) under an atmosphere of N_2 gas. The reaction

mixture was then drowned in water (15 ml) and extracted with ether. Usual work up gave a yellow liquid (0.816 g). TLC (benzene + 10% ethyl acetate) showed two spots. The NMR spectrum (Fig.4-9) of the crude showed a mixture of compound 8 and 9 in the ratio of 75:25 respectively. The mixture showed signals at 0.93(m), 1.40(d),2.03(s), 2.60(s), 5.98.

Peaks used for relative area measurement

Compound (8) 9.70 (s,1H); 10.8(s,1H);2.03(s,3H) 75%

Compound (9) 10.20(s,1H); 10.1(s,1H); 2.60(s,1H) 25%

Aromatisation with palladised charcoal

The above mixture (0.100 g) was heated with 10% palladium charcoal at 160° in an air bath for 6 hours. The compound was then taken out in pet.ether by warming. Removal of the solvent after filtering off the catalyst gave a solid yellow mass. It was passed over a column of silica gel. Elution with pet.ether + 30% ether afforded brilliant yellow needles of 7-hydroxycadelenal (9). TLC (benzene) single spot, m.p. 87-88°. A mixed m.p. measurement with an authentic sample did not show any depression.

IR spectrum. 3247(hydrogen bonded phenol), 2700 and 1664 cm^{-1}. (Fig.4-10). Superimposable on the IR spectrum of the authentic sample.

NMR(Fig.4-11): 1.40(d, J~7 cps); 2.60(s,3H);3.66(heptet,1H); 7.20(d, J~7 cps, 1H); 7.33(d, J~7 cps, 1H); 7.36(s,1H); 8.33(s,1H); 10.1(s,1H);10.2)s,1H). Identical with the NMR spectrum of the authentic sample recorded in CCl_4.

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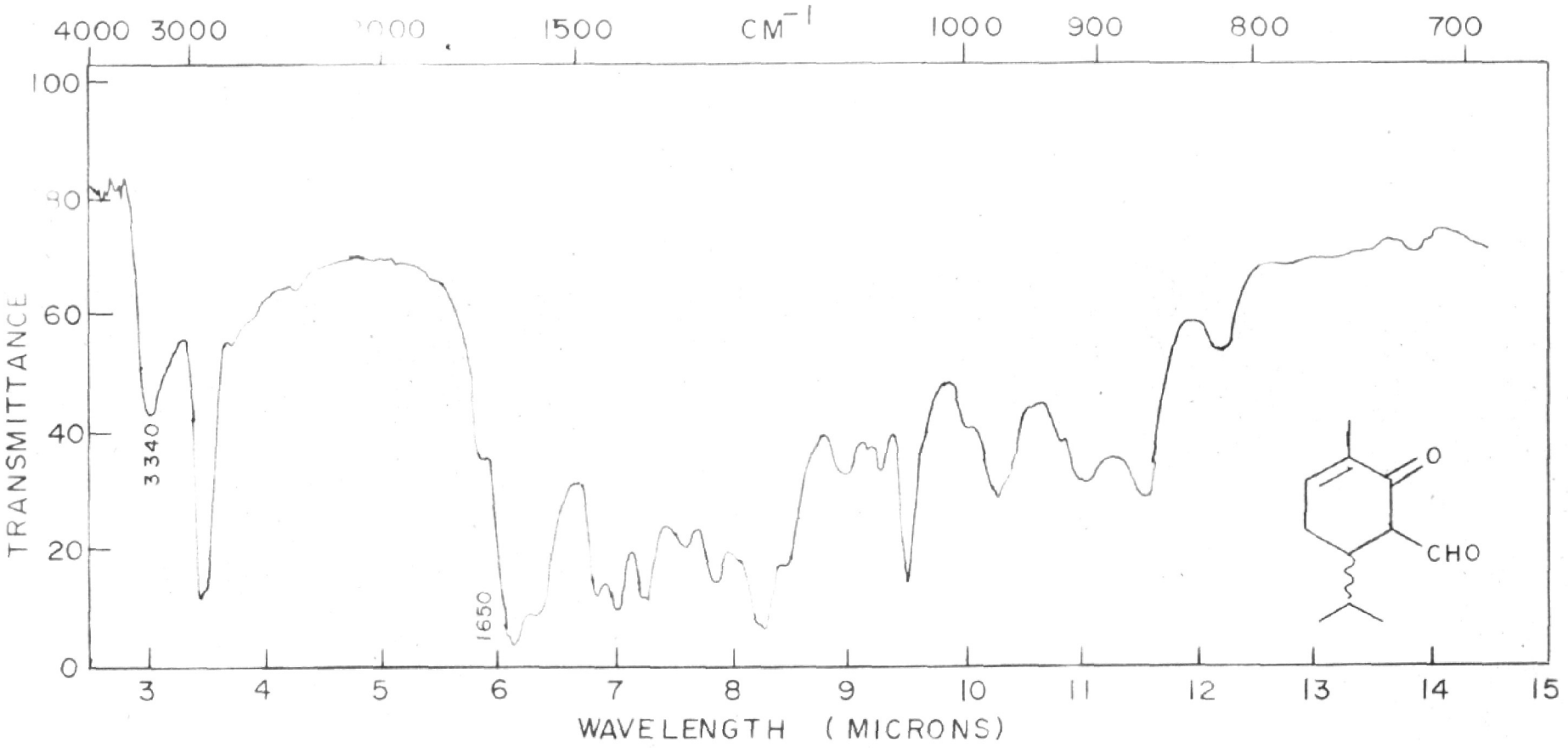

FIG. 4·1 . IR SPECTRUM OF HYDROXYMETHYLENE DERIV.(3)

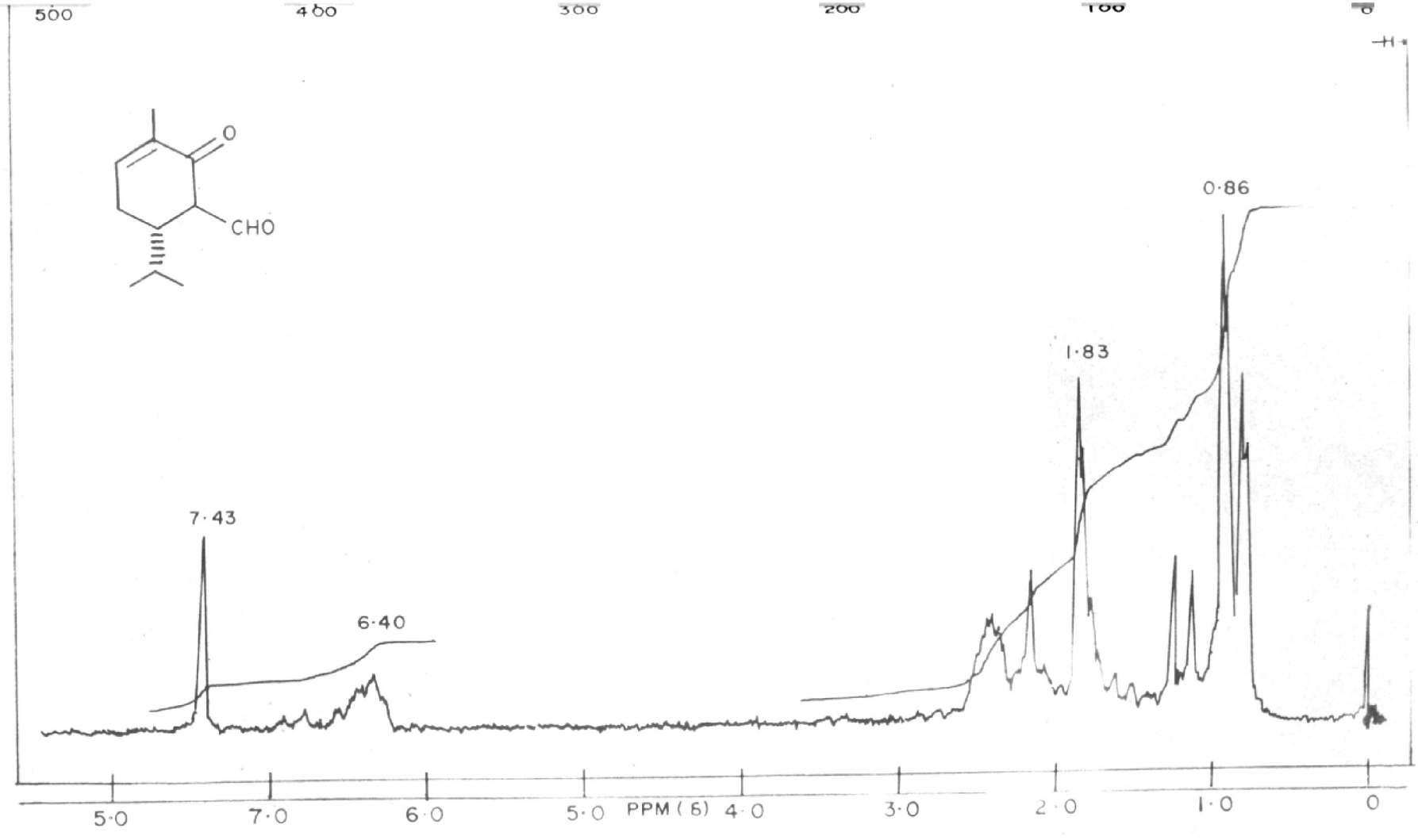

FIG. 4·2. NMR SPECTRUM OF HYDROXYMETHYLENE DERIV. (3)

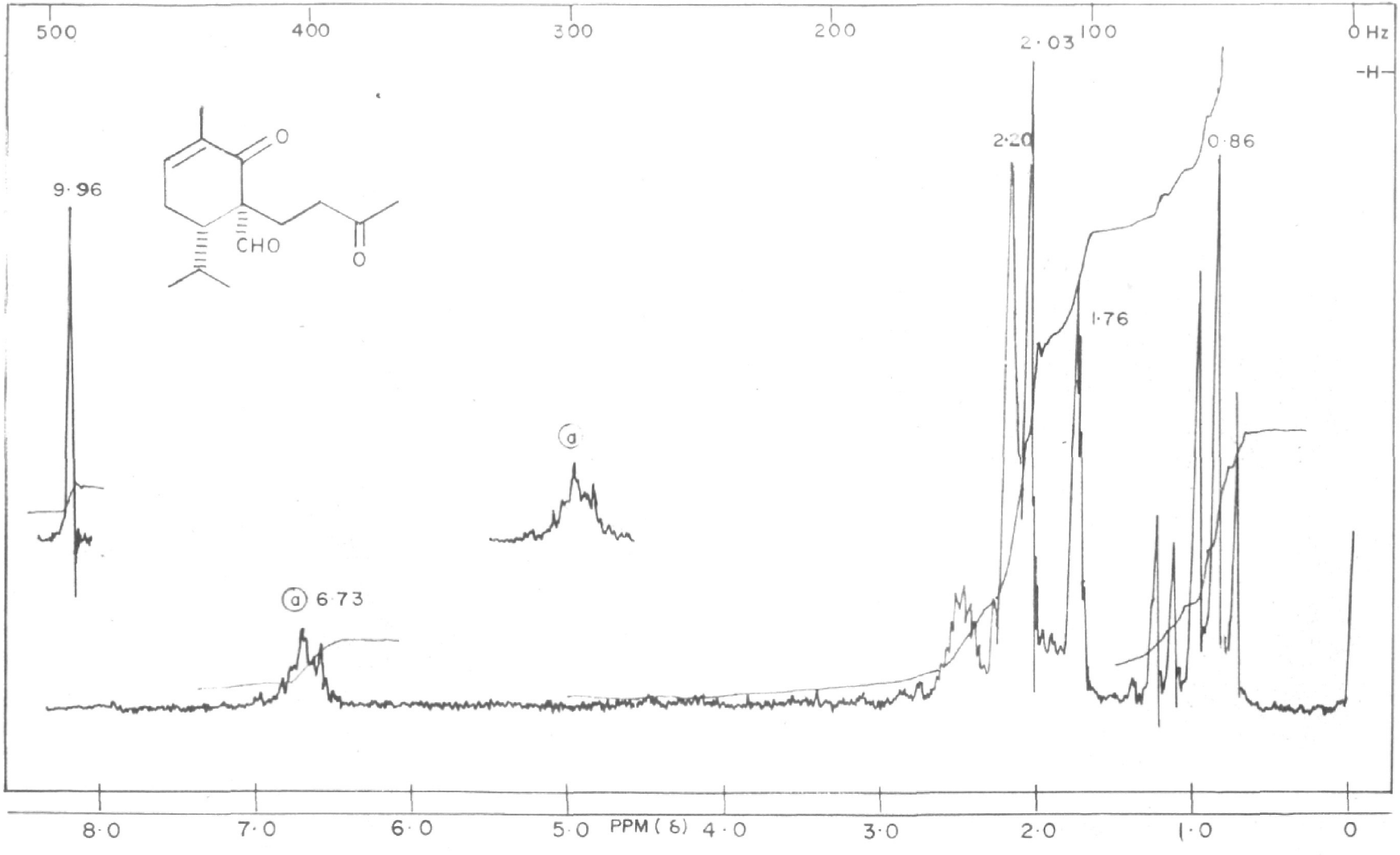

FIG. 4.3. NMR SPECTRUM OF DIKETOALDEHYDE(4)

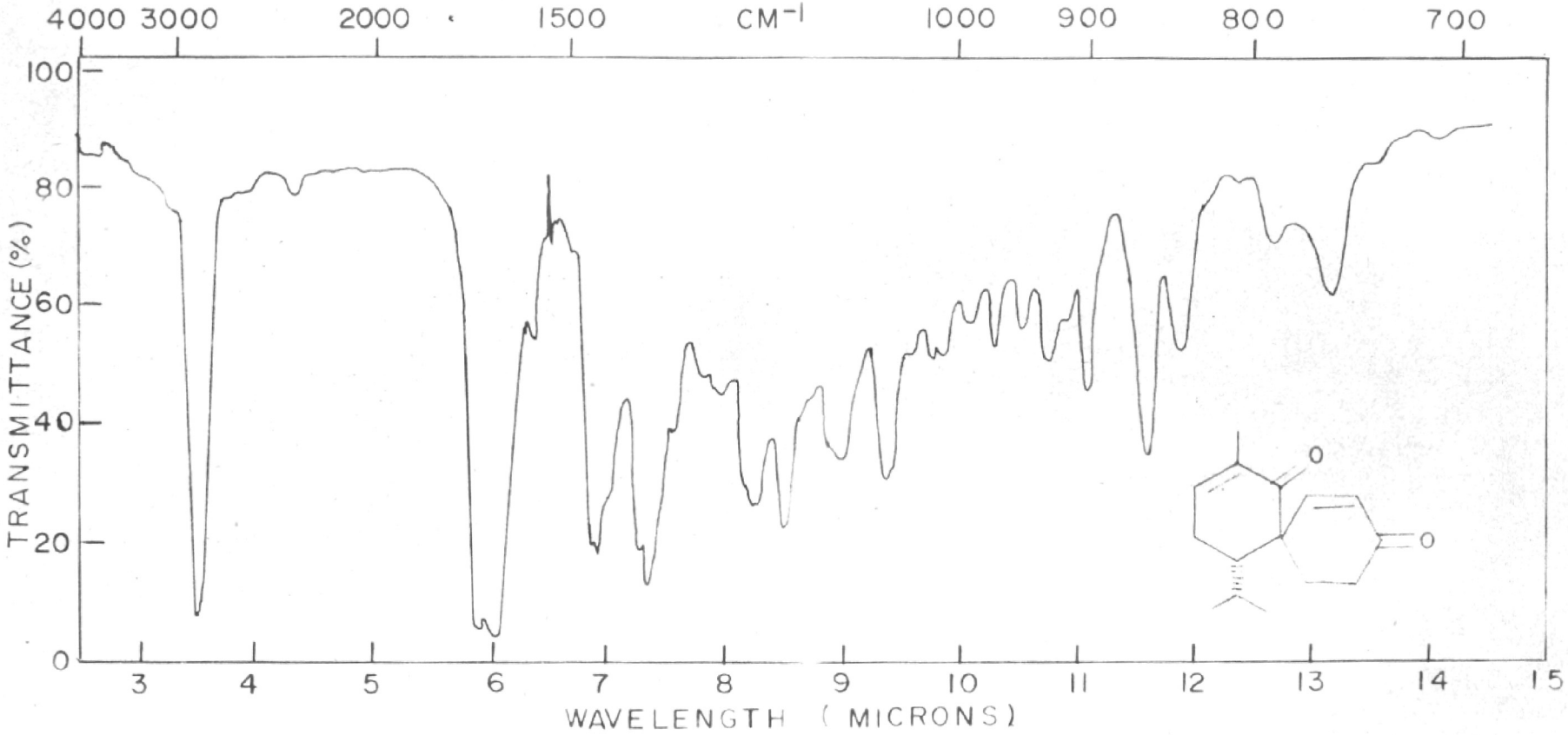

FIG. 4·4. IR SPECTRUM OF SPIROKETONE (5)

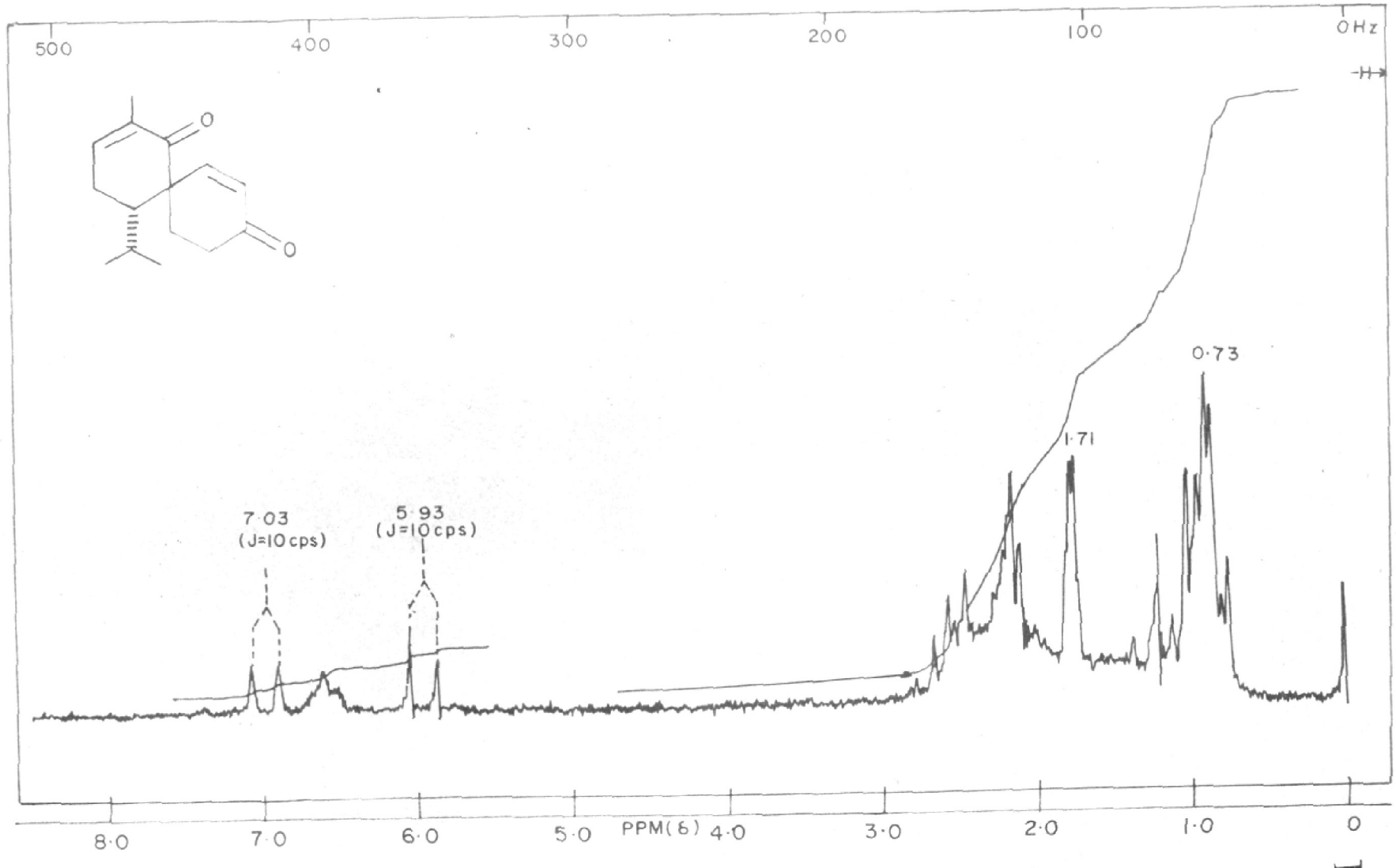

FIG. 4·5. NMR SPECTRUM OF SPIROKETONE(5)

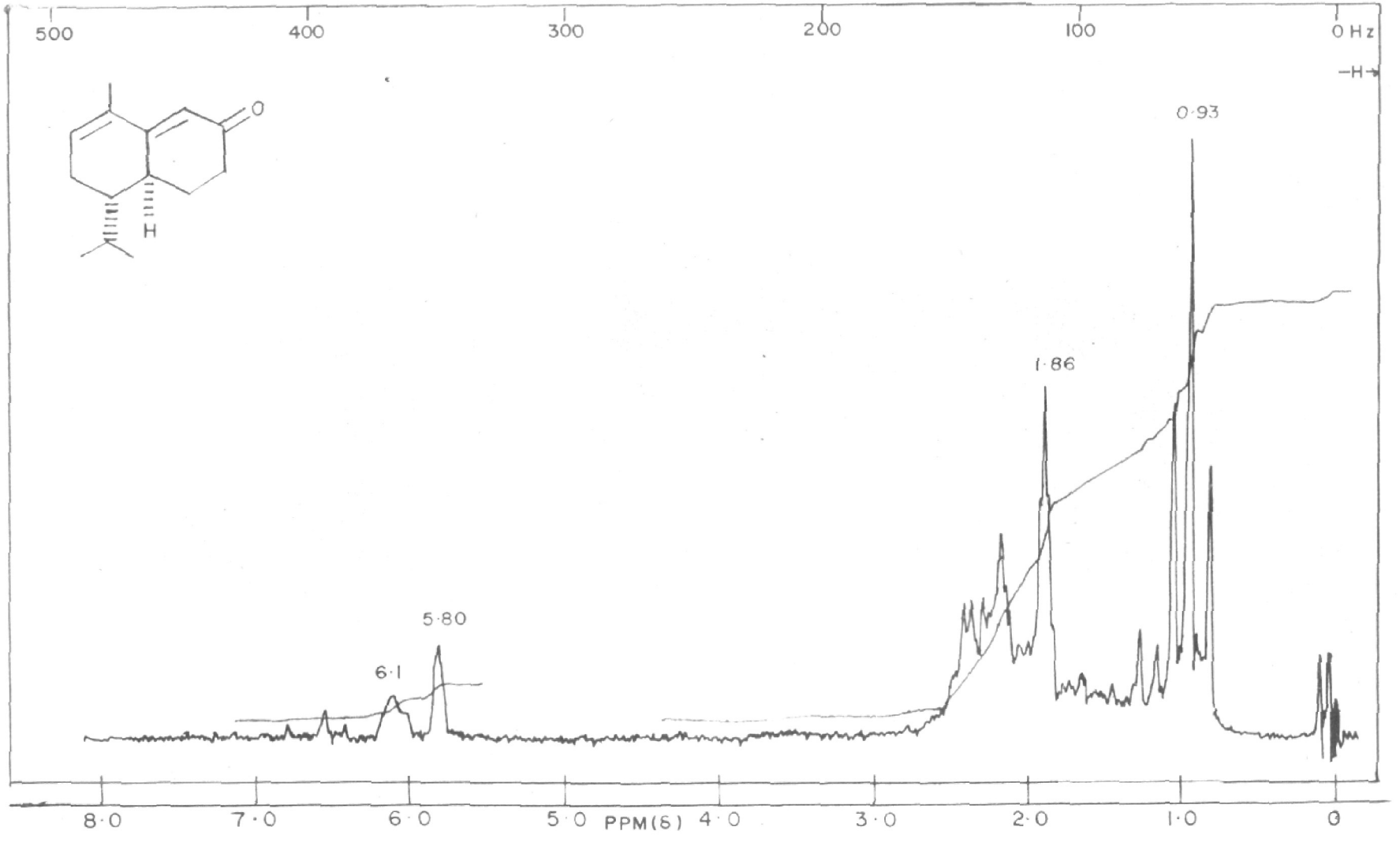

FIG. 4·6. NMR SPECTRUM OF KETONE (6). [ROUTE-I]

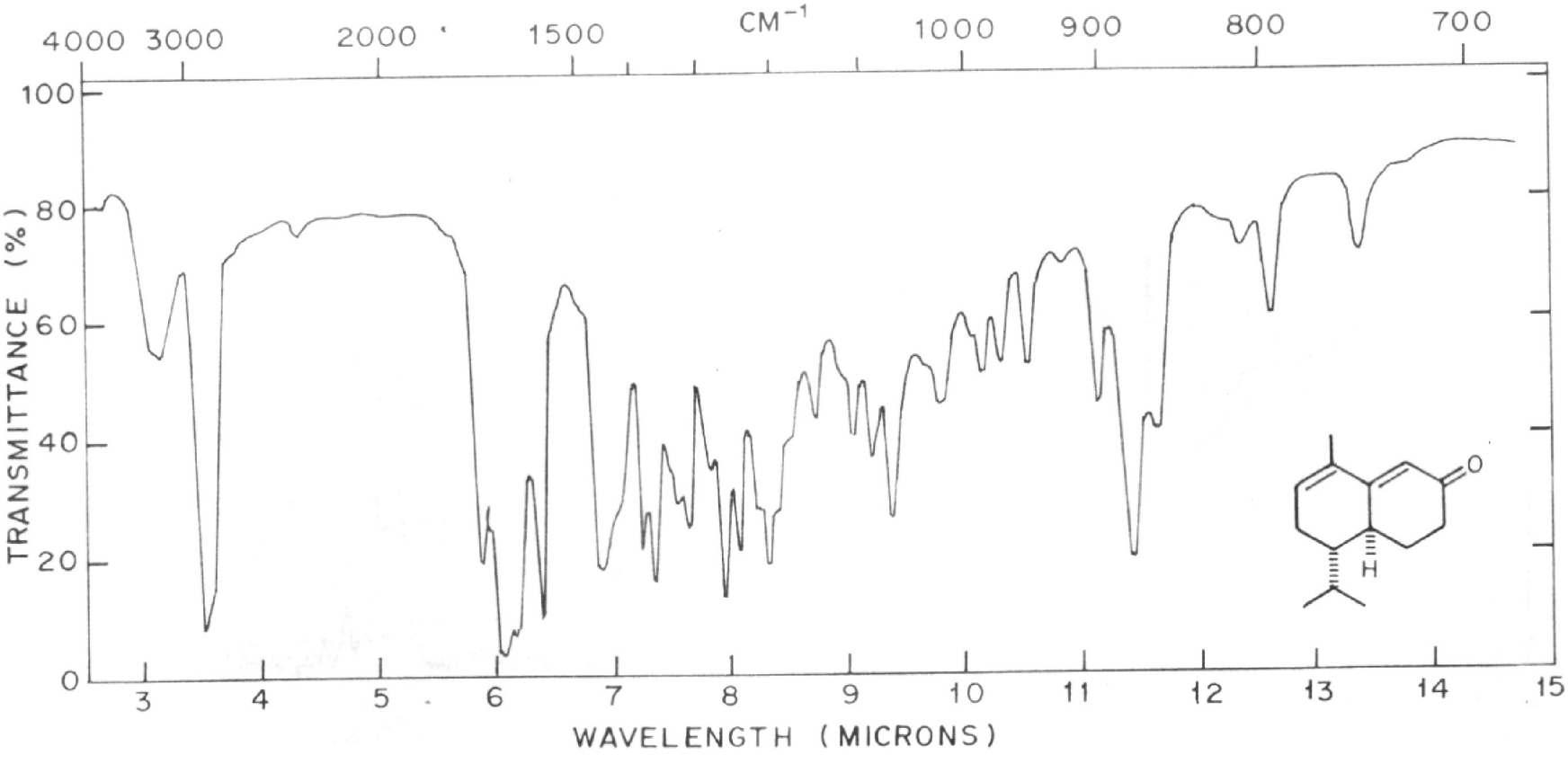

FIG. (4-7) IR SPECTRUM OF EXTENDED CONJ. KETONE (6)

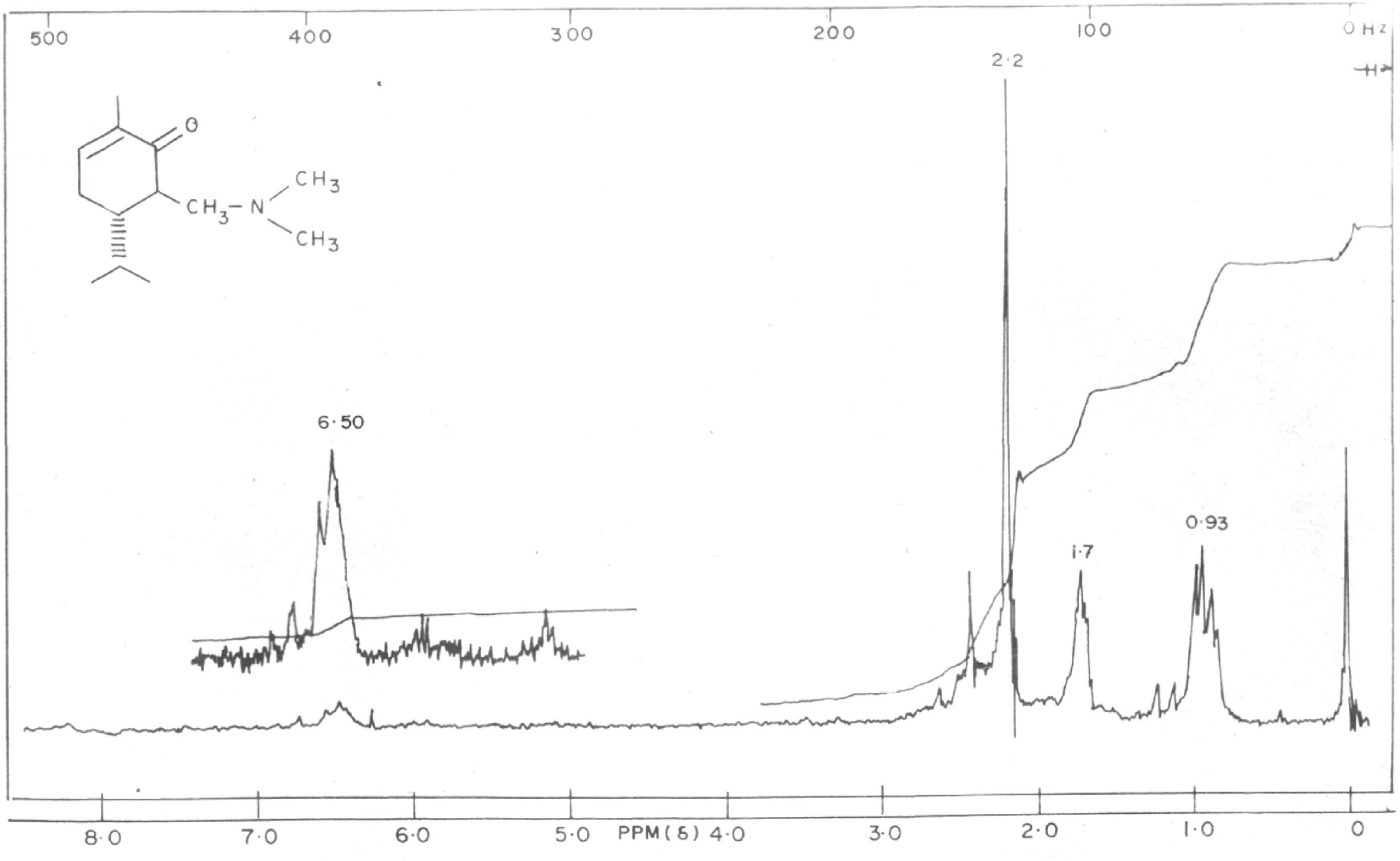

FIG. 4·8. NMR SPECTRUM OF MANNICH BASE (37)

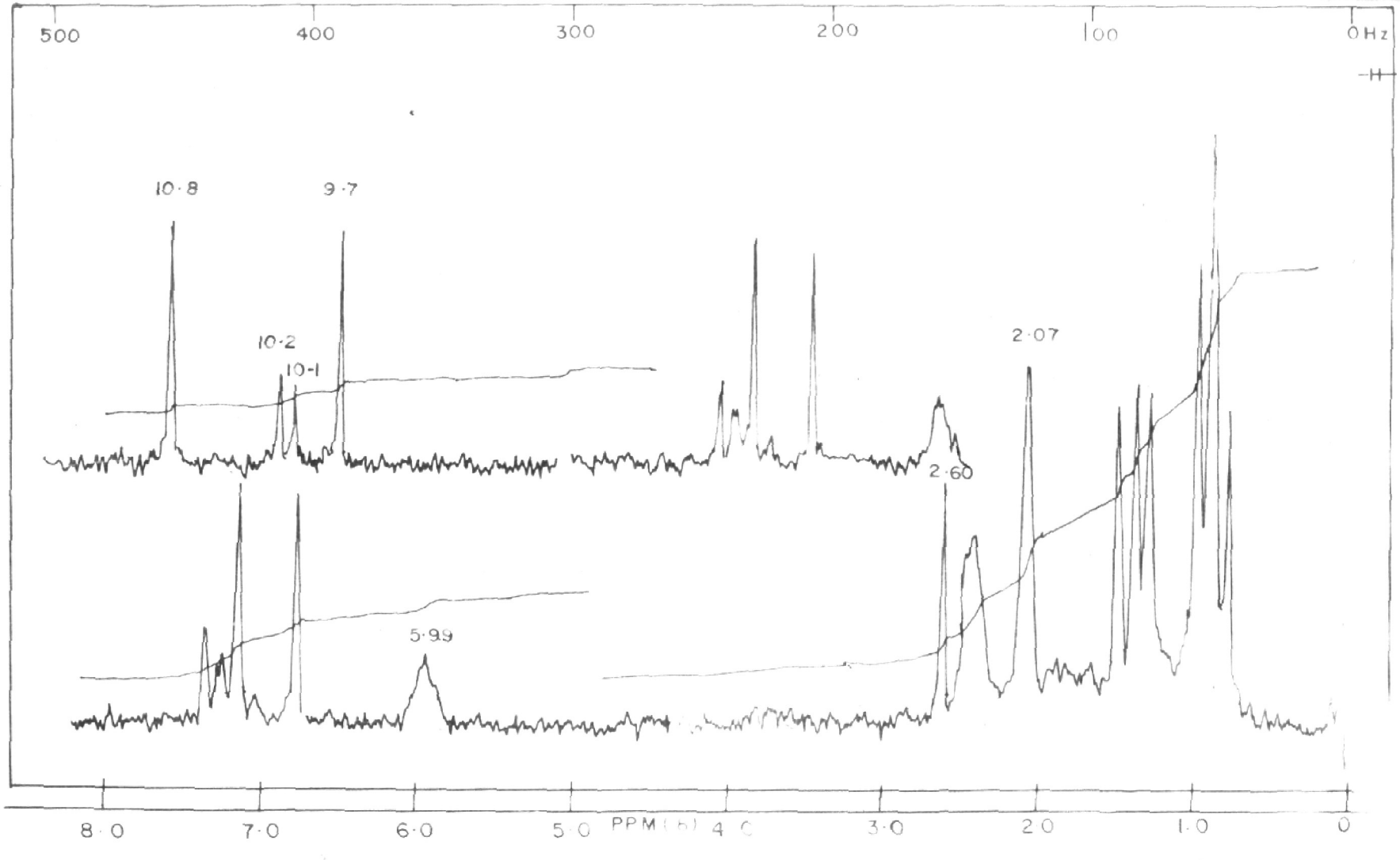

FIG. 4·9. NMR SPECTRUM OF MIXTURE OF 8 AND 9 (75:25)

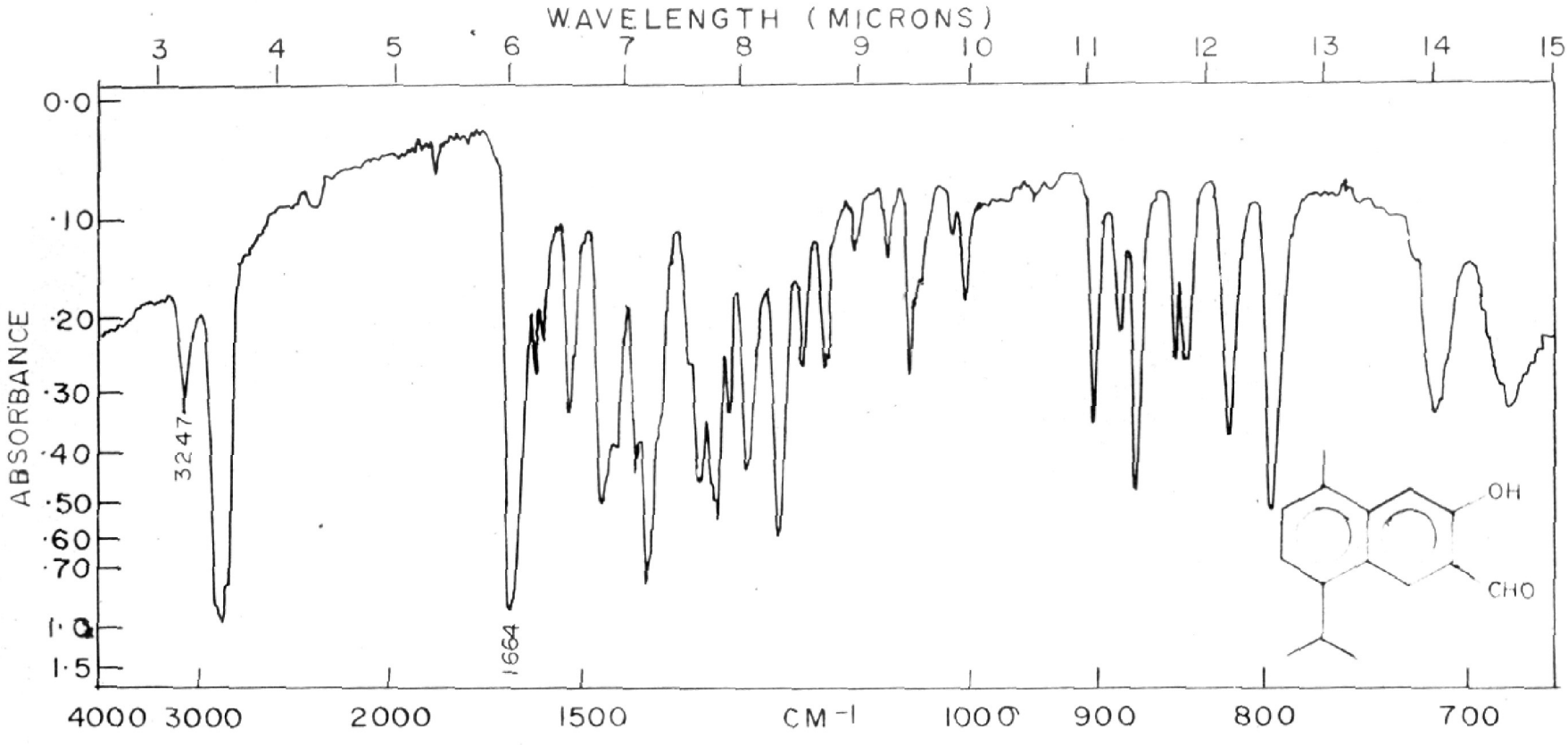

FIG. 4·10. IR SPECTRUM OF 7-OH-CADELENAL (9)

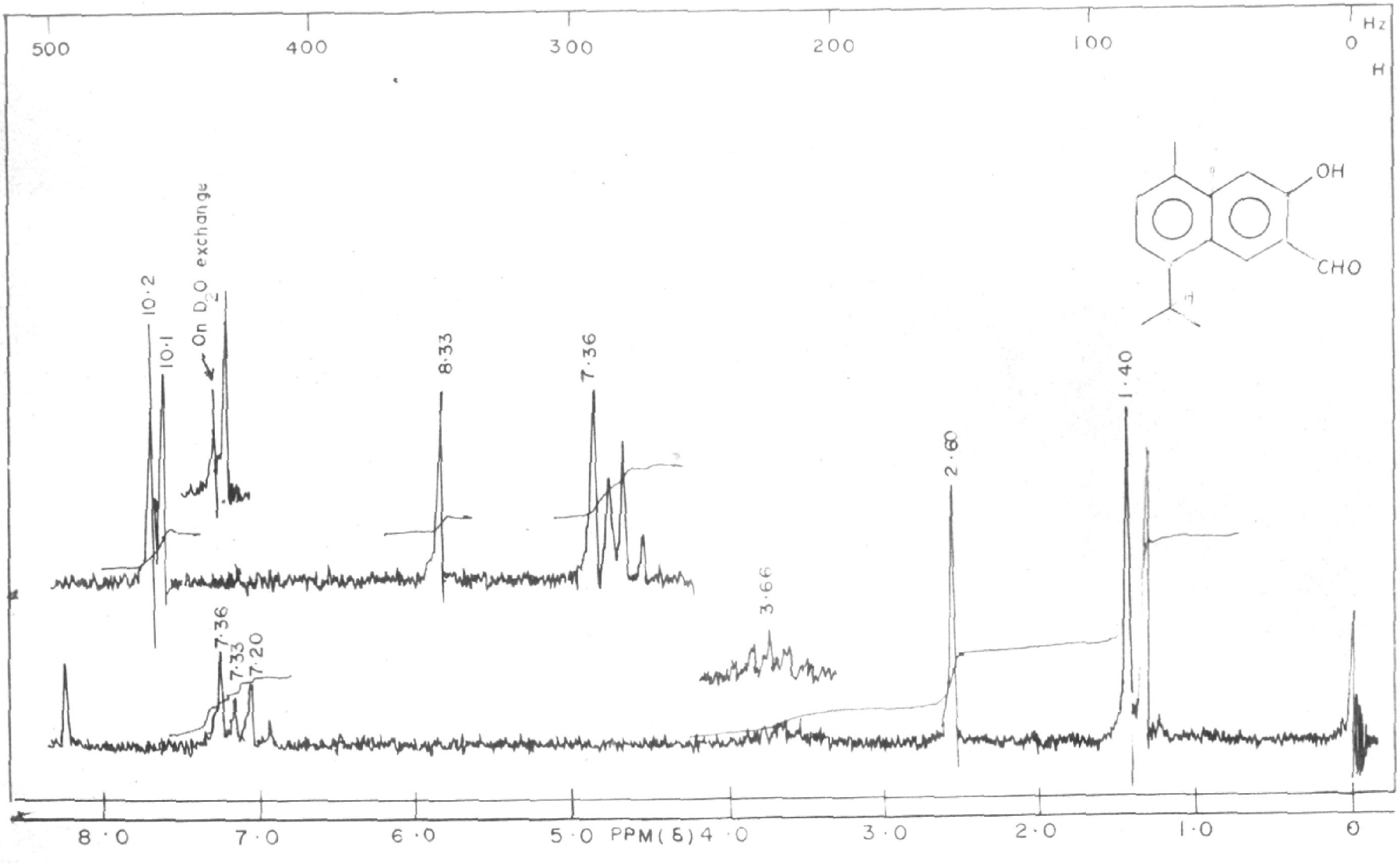

FIG. 4·11. NMR SPECTRUM OF 7-OH-CADELENAL(9) [CCl_4]