SYNTHETIC STUDIES ON TERPENOIDS

A Thesis submitted to the
UNIVERSITY OF POONA

for the degree of
DOCTOR OF PHILOSOPHY
IN CHEMISTRY

by
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National Chemical Laboratory
Poona 411 008

May 30 , 1977

(A.S. Khanra)

C O N T E N T S

PART I

Pyrethroids

PART II

Insect Juvenile Hormone
&
their synthetic analogues

PART III

Cyclic Juvenoids

PART - I

PYRETHROIDS

CHAPTER I

I N T R O D U C T I O N

PART I

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PYRETHROIDS

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CHAPTER I

A. INTRODUCTION :

'Pyrethrum' represents[1] the dried flowers of Chrysanthemum cinerariaefolium, viz. (family compositae), a herbaceous perennial indigenous to Montenegro, Dalmatia and the adjacent coastal islands and also in Japan, Germany and Great Britain. The powdered flowers have long been used as an insecticide under the name 'Polvere de Pulisi'. The insecticidal properties of pyrethrum flowers are due to pyrethrins, cinerins and jasmolins. These are the esters of "Pyrethrum acids" (chrysanthemum monocarboxylic acid and chrysanthemum dicarboxylic acid).

Dalmatia (Yugoslavia) appears to be the first place in the history of Pyrethrum industry. It was introduced into Europe in 1828, in United States in 1855 and then in Japan (1884), Africa and South America. Japan was the main producer of Pyrethrum flowers before World War-II, then in 1939 Kenyan industry became the main supplier. The reason may be due to the higher content of the active ingredients in African flowers, about 1.3%,

compared to the flowers of Japanese origin, 0.9%. Pyrethrum flowers are also cultivated in Tanzania, Uganda, Congo and Ecuador.

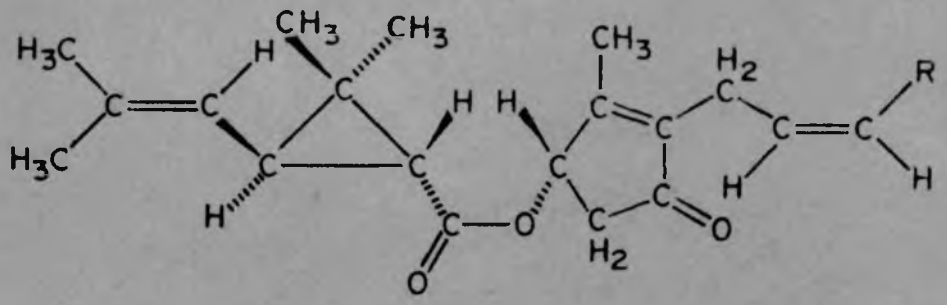
The flowers are collected during their full bloom because of the highest concentration of the active ingredients at this time, dried and extracted with an organic solvent. Resins and pigments are removed from the extract by liquid-liquid partition and a viscous residue with pyrethrin concentration $>90\%$ can be obtained[2].

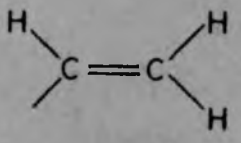
The active ingredients in the pyrathrum flowers are commonly known as 'Pyrethrins'. They are considered to be harmless to mammals and plants while being very toxic to insects. They induce a rapid paralytic action on insects commonly referred to as 'Knock down' and, therefore experience a great demand for their domestic use as insecticidal agents.

B. Chemistry of Pyrethrins :

The first detailed chemical investigations of the insecticidal ingredients of Pyrethrum flowers were reported by Japanese chemist, Fujitani[3] in 1909 followed by Staudinger and Ruzicka[4]. The absolute configurations of the pyrethrum acids were reported in 1954 by Crombie and Harper[5]. It has now been established[6] that pyrethrum extract

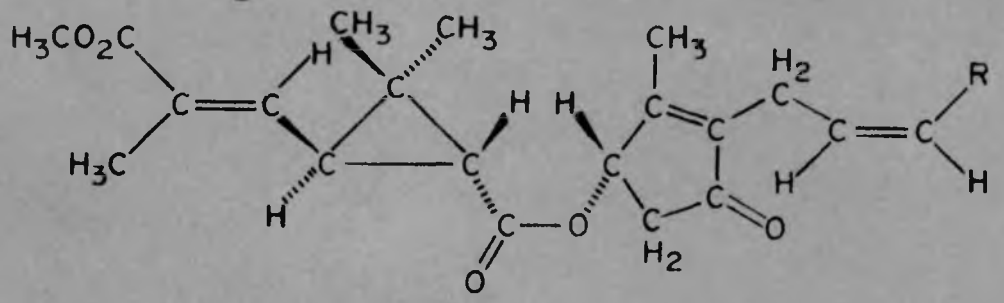
TABLE 1

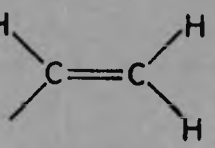


PYRETHRIN I, R =  (1)

JASMOLIN I, R = $-CH_2CH_3$ (2)

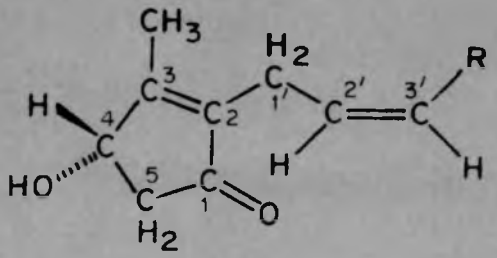
CINERIN I, R = $-CH_3$ (3)

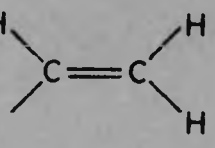


PYRETHRIN II, R =  (4)

JASMOLIN II, R = $-CH_2CH_3$ (5)

CINERIN II, R = $-CH_3$ (6)

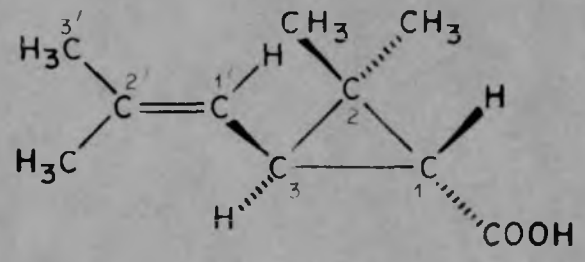


(+) −PYRETHROLONE, R =  (7)

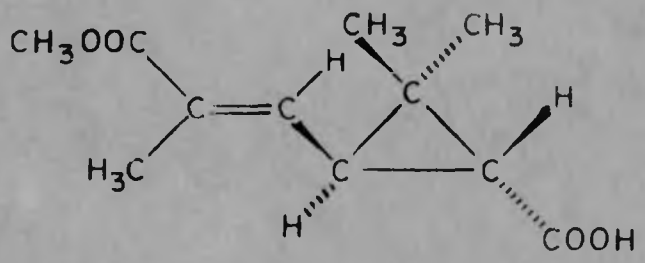
JASMOLONE, R = $-CH_2CH_3$ (8)

(+) −CINEROLONE, R = $-CH_3$ (9)

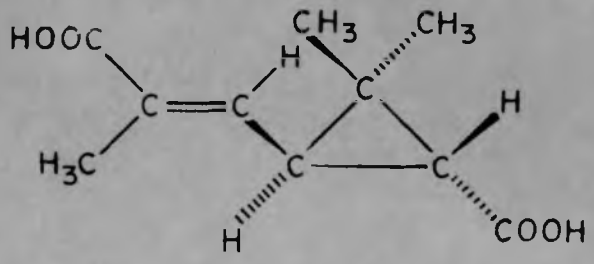
TABLE 2



(+) – TRANS – CHRYSANTHEMIC ACID (10)

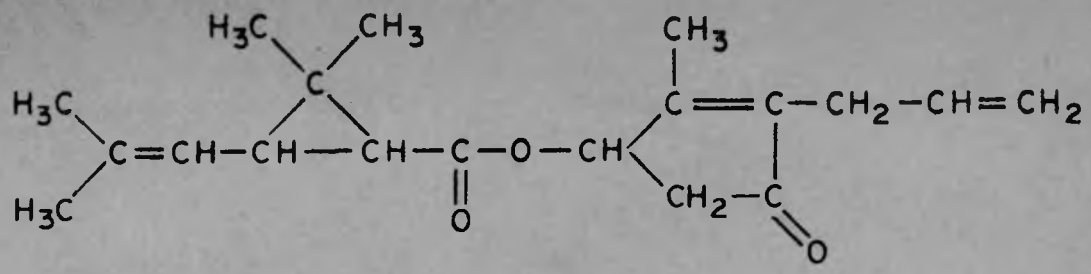


(+) – TRANS – PYRETHRIC ACID (11)

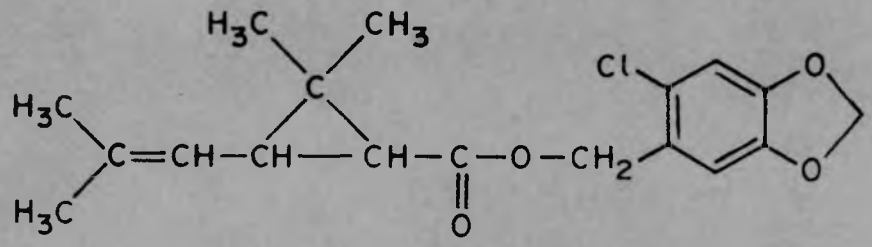


(+) – TRANS – CHRYSANTHEMUM DICARBOXYLIC ACID (12)

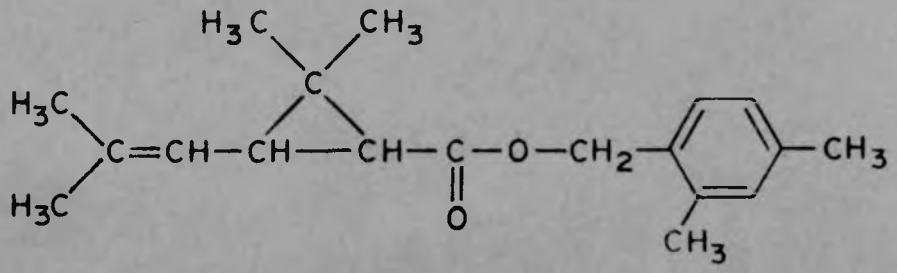
TABLE 3



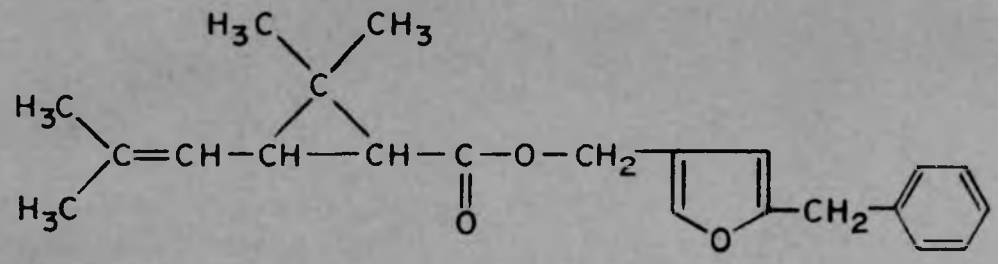
ALLETHRIN (13)



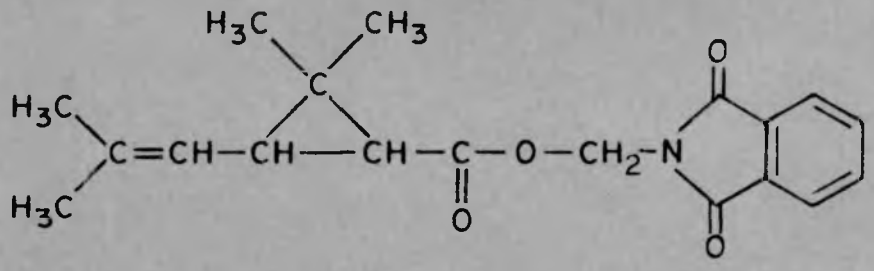
BARTHRIN (14)



DIMETHRIN (15)



5-BENZYL-3-FURYLMETHYL (+)-TRANS-
CHRYSANTHEMATE (16)



N-(PHTHALIMIDO) METHYL DL-CIS-TRANS-
CHRYSANTHEMATE (17)

contains at least six structurally related insecticidal esters (1-6) designated as 'Rethrins' by Harper[6a]. The corresponding ketols are collectively referred to as 'Rethrolones'. Their formulae are given in Table 1.

Pyrethrins are more toxic than the corresponding Jasmolins and Cinerins[7]. Pyrethrin II and Cinerin II show greater 'knock down' than the corresponding I compounds[8]. The toxicity of Jasmolin I and Cinerin I are almost equal to that of the corresponding II compounds respectively[9].

C. Pyrethroids from Chrysanthemic acid :

Schechter et al[10] prepared an ester of chrysanthemic acid by reacting with allyl-rethrolone or allethrolone. The ester known as 'allethrin' (13) is highly effective to housefly compared to natural pyrethrins and is now being produced commercially[11]. The same authors observed that there is a marked difference in toxicity of the stereo-isomers of allethrin and out of the eight isomers of allethrin obtained by esterifying optically resolved (+)- and (-)-allethrolone with (+) and (-)-trans-chrysanthemic acid and (+) and (-)-cis-chrysanthemic acids, only the (+)-alcohol ester of the (+)-trans-acid which has the same absolute configuration as natural pyrethrins exhibits the highest toxicity.

TABLE 3a

Insecticidal activity of the isomers of Allethrin

Alcohol Allethronyl	Acid chrysanthemate	Relative toxicity to Musca domestica L.
(+)	(+)-trans	100
(+)	(-)-trans	4
(-)	(+)-trans	17
(-)	(-)-trans	0.7
(+)	(+)-cis	83
(+)	(-)-cis	5
(-)	(+)-cis	10
(-)	(-)-cis	1.7

Many other rethrins[13] have also been synthesized and biologically tested. Several Benzyl[14], Furylmethyl[15] and Imidomethyl chrysanthemates[16] are also known to be active. Barthrin (14) Dimethrin (15)[14b,c] and several alkenyl benzyl compounds[14d,17] are known to be very insecticidal amongst benzyl chrysanthemates. 5-Benzyl-3-furylcarbinol was found to be most affective[15] alcoholic component whose (+)-trans-chrysanthemate is 54 times as toxic to houseflies as natural pyrethrins. Monothiophthalimidomethyl chrysanthemate was also found to exhibit a remarkable toxicity to houseflies[15]. All these compounds are actually far more toxic than natural pyrethrins but they are inferior to natural pyrethrins in paralytic action.

D. Mode of action of Pyrethroids :

Lauger et al[18] consider that the cyclopropane ring, the methyl, dimethyl ethylene and allene groups are the toxic components (toxaphore) in the pyrethrin which are responsible for the lipid solubility in the insect metabolism.

Hurst[19] believes that the knock-down phase is accompanied by the block of oxidase action and the irreversible increase in the phenoloxidase activity causing the displacement of protective lipids and accumulation of toxic quinoid metabolites in the blood and tissues.

The characteristic rapid paralytic effect of pyrethrins are due to its action on the insects central nervous system. Pyrethrin can stimulate the nerve membrane producing repetitive discharges and blocking the nerve conduction. It has been reported[20] that a neuroactive toxin is released from the nerves of the cockroaches when pyrethrin is applied thereby causing further stimulation followed by paralysis.

E. Biosynthesis of Pyrethrins :

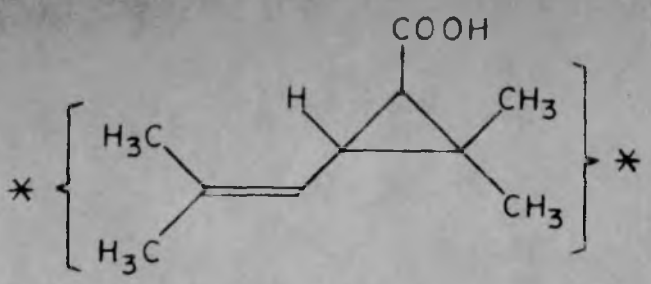
The biochemical process by which six 'Pyrethrins' are synthesised in pyrethrum plant have been recently studied. By applying (±)-2-^{14}C-mevalonic acid (20) to the flowers of chrysanthemum cinerariaefolium, Thain et al[21] observed

that the ^{14}C-labelled carbon atoms were incorporated into a C-methyl of the cyclopropane ring both in the case of chrysanthemic acid (18) and chrysanthemum dicarboxylic acid (19). The another ^{14}C labelled carbon atom was incorporated into a side chain terminal C-methyl of the f former but to the side chain terminal carboxylic group of the later (Table 4). They also observed that the 1-^{14}C-mevalonic acid was incorporated into neither pyrethrin I nor pyrethrin II. On the basis of these observations Godin et al[22] consider that the acid moiety of pyrethrins is derived biogenetically from mevalonic acid, two isoprene units fused in an unusual manner 'middle to tail' condensation. The incorporation of 2-^{14}C-mevalonic acid into the alcohol moiety of pyrethrins was not observed. The relative incorporation of 2-^{14}C-acetate into pyrathric acid and pyrethrolone have been investigated by Crowley et al[21e]. They proposed that the acid moiety of pyrethrins is biosynthetically formed via the acetate-mevalonate route and the alcohol moiety via the acetate route.

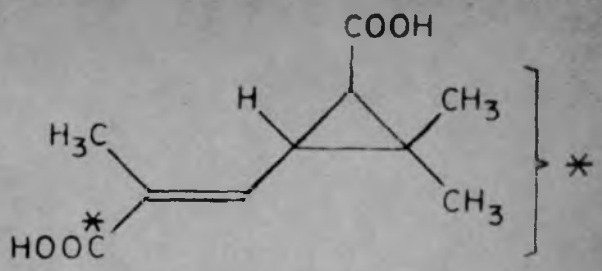
From the results of feeding experiments with L-(Me-^{14}C)-methionine, Godin et al[22] suggested that the methyl group in the ester of pyrethrin II is derived from S-methyl group of L-methionine.

In insect and mammals pyrethrin I is oxidised at the terminal methyl to give c-demethylpyrethrin II which may also occur in plants.

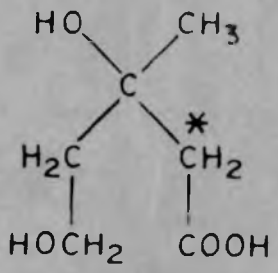
TABLE 4



(18)

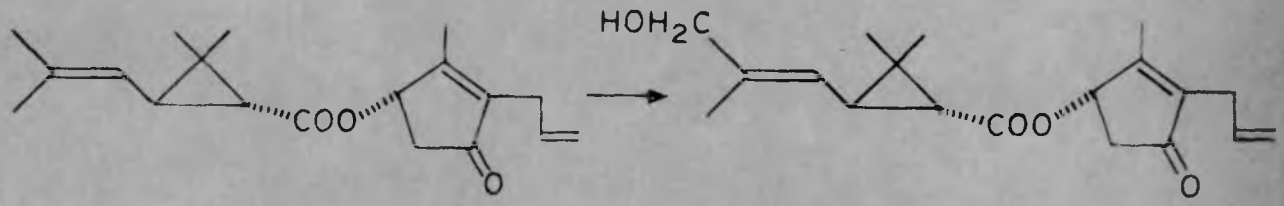


(19)



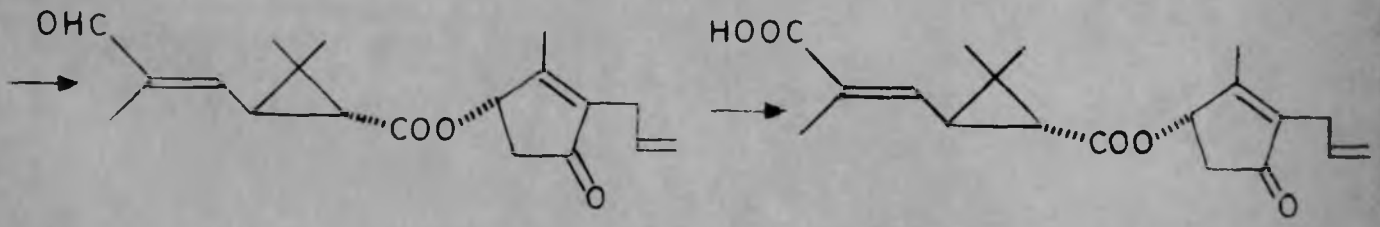
(20)

TABLE 5



(+)-TRANS-(+)-ALLETHRIN (21)

ω_1-HYDROXYALLETHRIN (22)

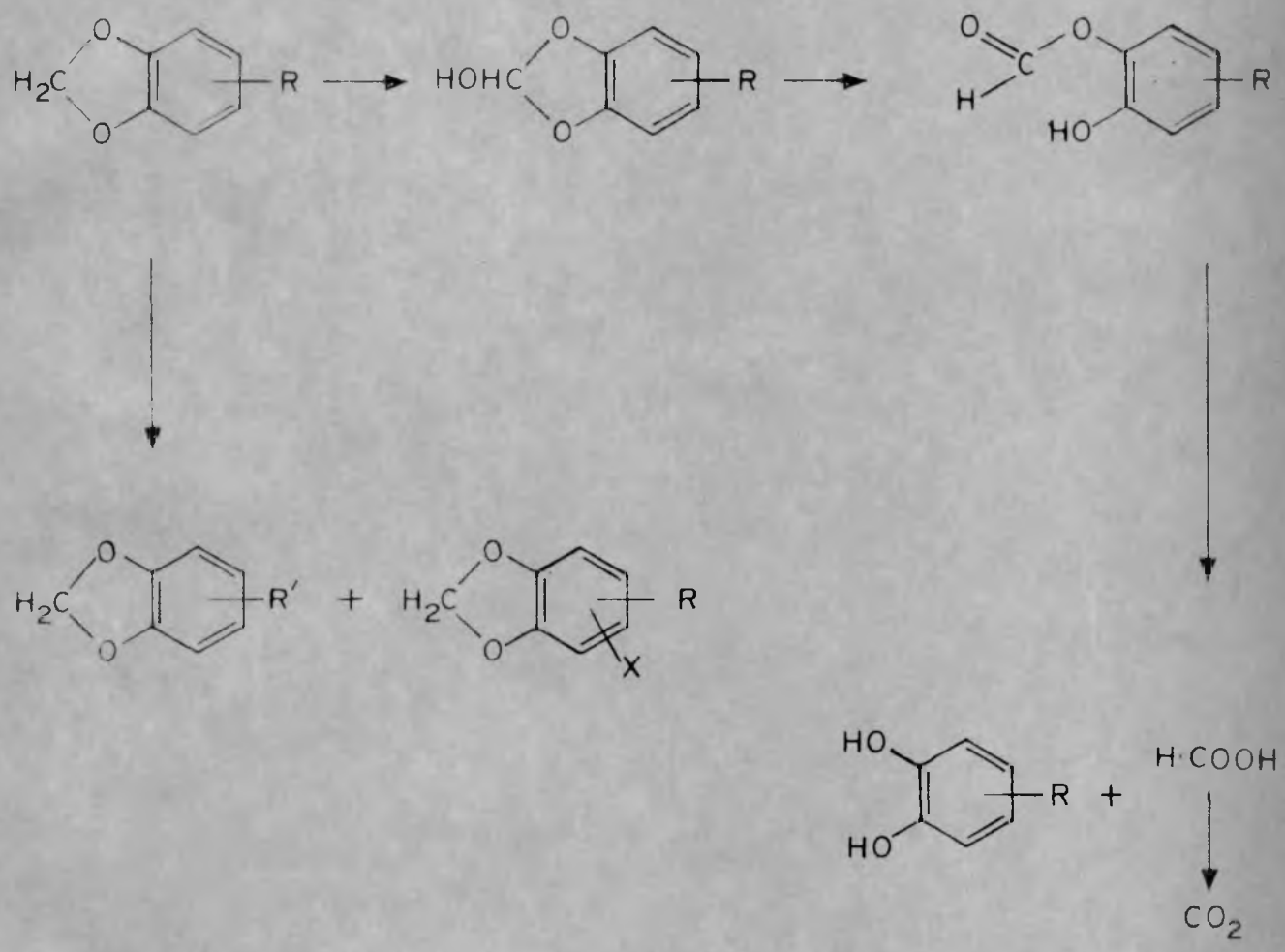


ω_1-OXOALLETHRIN (23)

ALLETHRIN-ω_1-OIC ACID (24)

METABOLISM OF ALLETHRIN

TABLE 6



R' DESIGNATES MODIFICATION OF THE RING SUBSTITUENT AND X DESIGNATES THE INTRODUCTION OF THE ADDITIONAL GROUP THROUGH HYDROXYLATION

F. Metabolism and Synergism :

From the studies of mechanism of metabolism[23] using fly abdomen homogenates and $NADPH_2$ as a metabolising system, it has been established[24] that one of the methyl groups in the isobutenyl side chain of pyrethrin is hydroxylated and then converted to a carboxylic acid via an aldehyde.

Such hydroxylation is also known in the case of Pyrethrin I, Dimethrin and Phthalthrin[24] and is a very common phenomenon in biological systems which is being regarded as a function of the microsomal fraction of cells.

Synergists play an important role in increasing the potency of pyrethroids by inhibiting detoxification in vivo. Methylenedioxy phenyl compounds are well-known synergists which can serve as substituents for pyrethroids in the enzyme system and can inhibit the pyrethroid metabolism[24] as shown in Table 6.

Experiments with Calandra granaria with piperonyl butoxide as synergist, it has been observed that[25] the pyrethrin effect increases to 4.6 fold for the susceptible strain and to 37 fold for resistant strain. In case of flies pyrethrins are more active at low temperature whereas such negative temperature coefficient diminishes in presence of piperonyl butoxide[26]. These are evidently

due to the inhibition of pyrethrin metabolism in presence of the synergist. Cinerin I which is less insecticidal than Pyrethrin I becomes equally potent in presence of sesamex. The same is true in case of Cinerin II and Pyrethrin II.

CHAPTER II

A new synthesis of (+)-*trans*-chrysanthemic acid from (+)-Car-3-ene.

CHAPTER II

A New Synthesis of (+)-trans-Chrysanthemic Acid from (+)-Car-3-ene.

A. Present scheme and work :

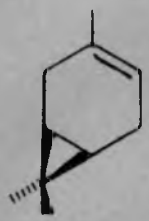
In our earlier discussion, we have mentioned that the (+)-trans-chrysanthemic acid is the essential component of naturally occuring pyrothrins and their synthetic analogues. Recently, Punja et al[27] have also reported that the alkyl and phenyl esters of both cis and trans-chrysanthemic acids possess a high order of insect juvenile hormone activity. Our present scheme involves a new synthesis of (+)-trans-chrysanthemic acid starting from (+)-Car-3-ene which is abundant in Indian turpentine oil (Pinus longifolia Roxb.).

The preferential boat conformation of car-3-ene (Table 7) has been established[26] on the following grounds:

i) In the alternative conformation viz., in the inverted boat form the cyclopropane protons are eclipsed with the α-H-atoms at C_2 and C_5 as well as a severe non-bonded interaction between bow and stern β H-atoms at C_2 and C_5 experienced by the C_8- methyl protons which are absent in the boat conformation.

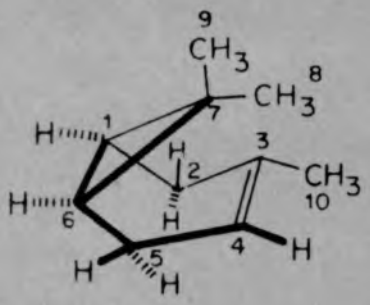
ii) The agreements with the results obtained in the study of NMR spectra of car-3-ene at various temperatures

TABLE 7

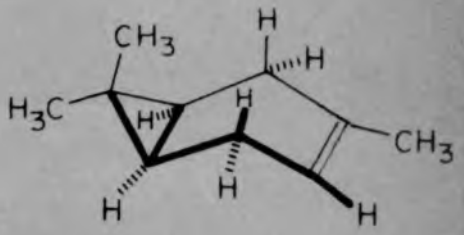


CAR-3-ENE

(I)



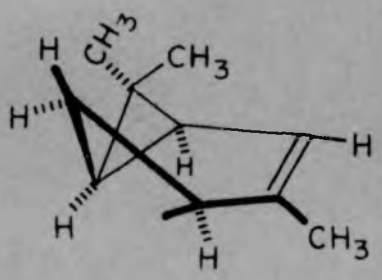
BOAT



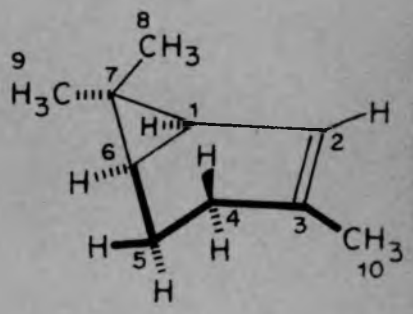
INVERTED BOAT

CAR-2-ENE

(I A)



PARTIAL BOAT



PARTIAL INVERTED BOAT

as well as from the free energy difference and the conformational equilibrium constant between the boat and the inverted boat conformations.

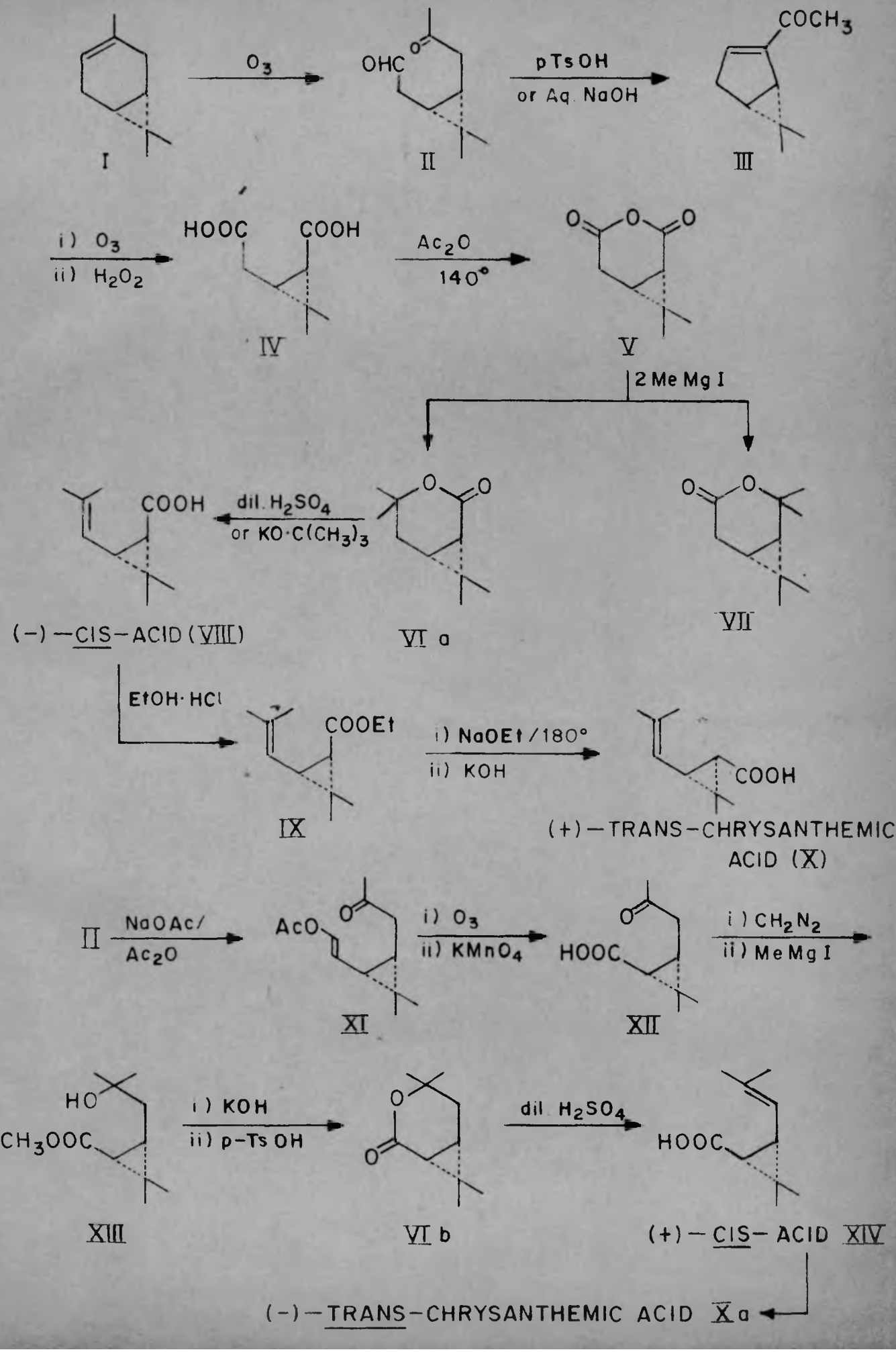
iii) The chemical shift difference between 8- and 9-methyl groups of Car-3-ene is larger than in Car-2-ene followed from the anisotropic effect of the double bond.

iv) In case of Car-2-ene the severe non-bonded interaction between the 8-methyl and the 3 β-H (separation being 0.2^{o} A) makes the partial inverted boat conformation unfavourable and therefore, the alternative partial boat form will be the possible conformation.

v) The rate of epoxidation and hydroboration is faster in case of Car-2-ene in contrast to Car-3-ene. This is because of the severe interaction experienced in the transition state (being cis addition and, therefore, the reagent should approach from the bottom side of the molecule) between the 8-methyl, 4H and 10-methyl groups in the boat conformations of Car-3-ene, whereas such interactions are not so prominent in either boat conformations of Car-2-ene as well as in the inverted boat form of Car-3-ene.

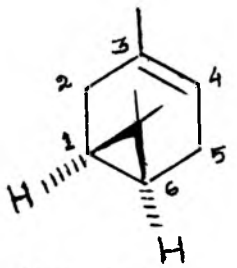
The first stereospecific synthesis of optically pure (+)-trans-chrysanthemic acid from (+)-Car-3-ene was reported by Matsui et al[29] via series of reactions as shown in Table 8.

TABLE 8

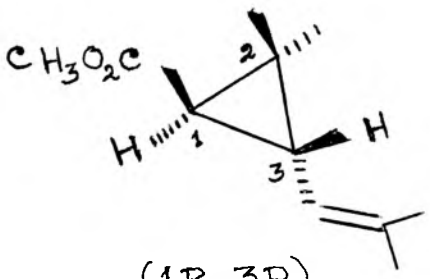

I
O_3
OHC
II
pTsOH
or Aq. NaOH
$COCH_3$
III
i) O_3
ii) H_2O_2
HOOC
COOH
IV
Ac_2O
140°
V
2 Me Mg I
COOH
dil. H_2SO_4
or $KO{\cdot}C(CH_3)_3$
(−)−CIS−ACID (VIII)
VI a
VII
EtOH·HCl
COOEt
IX
i) NaOEt / 180°
ii) KOH
COOH
(+)−TRANS−CHRYSANTHEMIC ACID (X)
II
NaOAc/
Ac_2O
AcO
XI
i) O_3
ii) $KMnO_4$
HOOC
XII
i) CH_2N_2
ii) Me Mg I
HO
CH_3OOC
XIII
i) KOH
ii) p-Ts OH
VI b
dil. H_2SO_4
HOOC
(+)−CIS− ACID XIV
(−)−TRANS−CHRYSANTHEMIC ACID Xa

The key-intermediate for this synthesis is the (+)-cis-homocaronic acid (IV). The Grignard reaction on the anhydride of (IV) gives the desired intermediate, (-)-dihydro-chrysanthemolactone (VIa) along with the isomeric lactone (VII) which are difficult to separate and the overall yields are low (≈ 2%). More recently, Cooker et al[30] have described an alternative route for the synthesis of (+)-trans-chrysanthemic acid via. the same intermediate (IV).

The absolute configuration of (+)-Car-3-ene (I) is 1 S, 6 R[39] and that of natural (+)-trans-chrysanthemic acid (X) has been established as 1 R, 3 R[37] from which it is clear that the C_3-chiral centre of X has the same absolute configuration as C_6 of I.



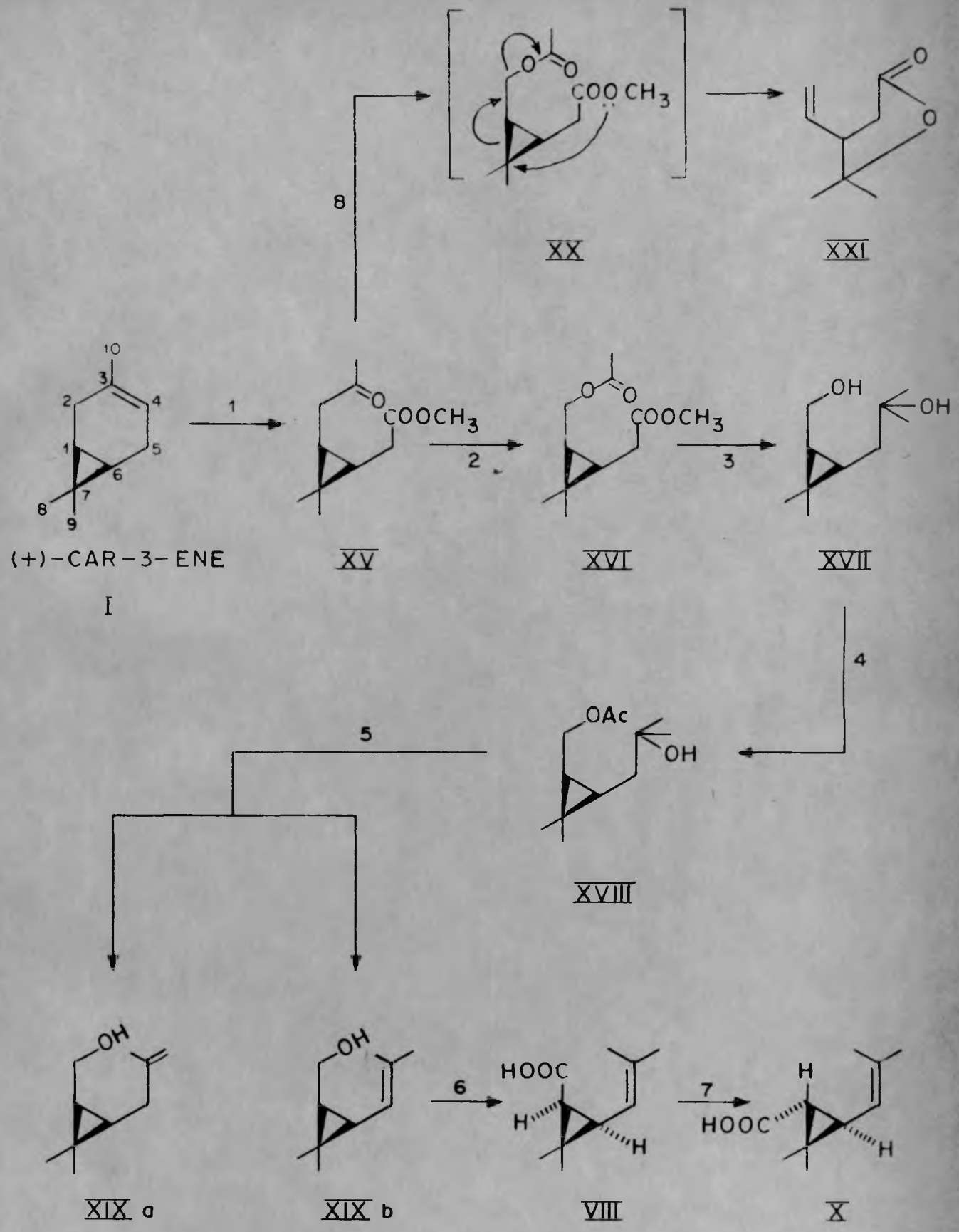
(1S, 6R)
I



(1R, 3R)
X

Considering the stereochemistry of (+)-trans-chrysanthemic acid (X) an obvious synthetic approach should be the oxidation of C_2-carbon atom of (+)-Car-3-ene (I)

TABLE 9



Reagents: (1) O_3, Jones reagents, CH_2N_2 (2) Permaleic acid (3) MeMg I (4) Ac_2O-Py (5) $POCl_3$-Py, NaOH-CH_3OH (6) CrO_3-Py (7) EtOH-H^+, NaOEt, NaOH, H^+ (8) BF_3-Et_2O, 90 % H_2O_2

to the -COOH group of (X). Oxidation of C_5-atom of (I) to -COOH group leads[29] to the enantiomorph of (X), the esters of which have no insecticidal activity.

In line with the above reasoning, we described a new improved and efficient synthesis[31] of (+)-trans-chrysanthemic acid starting from (+)-Car-3-ene with an overall yield of 35%. The synthetic route employed is shown in Table 9.

A very similar route for the synthesis of (X) was also reported later by Sobti and Sukh Dev[32].

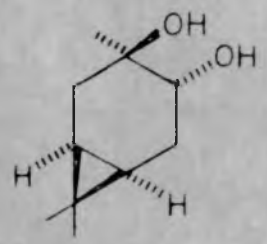
The present scheme[40] for the synthesis of (+)-(1R, 3R)-trans-chrysanthemic acid involves an alternative new route for the conversion of C_6 of I into C_3 of X.

B. Results and discussion :

The treatment of (+)-Car-3-ene with performic acid gives a diol, (+)-trans-3,4-carane diol (XXIIa), m.p. 69-70° (Crystallized from pet. ether (40-60°)), $(C_{10}H_{18}O_2)_2.H_2O$. The trans-conformation of the diol has been confirmed by its NMR spectrum which exhibited signals ( ) at 0.7 (2H, m, cyclopropyl protons); 0.97 (6H, CH_3-8 and -9); 1.17 (3H, s, CH_3-10); 3.27 (1H, m, CHOH).

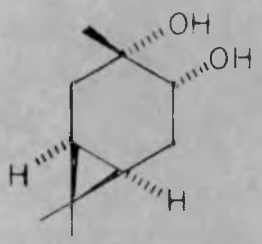
In the trans-diol both the -8 and -9 methyl groups experience the same magnetic field, the chemical shift difference being zero, whereas in the cis-diol (Fig. 4), the

TABLE 10



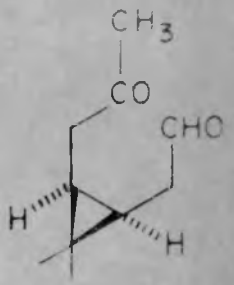
TRANS-3,4-CARANE-

DIOL XXII a

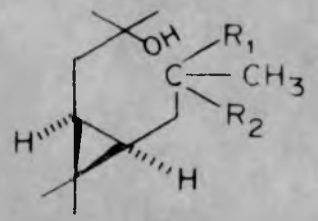


CIS-3,4-CARANE-

DIOL XXII b

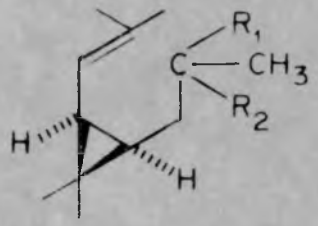


II

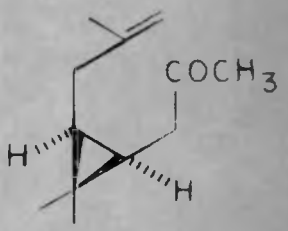


XXIII $R_1 = H, R_2 = OH$

XXIV $R_1, R_2 = O$

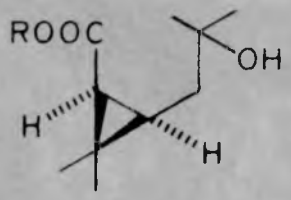


XXV a $R_1, R_2 = O$



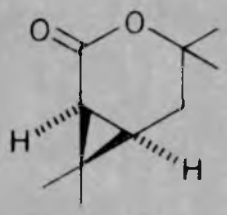
XXV b

XXVI $R_1 = CH_3, R_2 = OH$

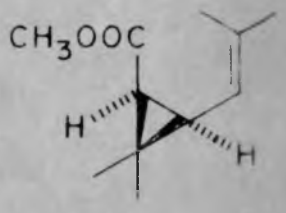


XXVII a, R = H

XXVII b, $R = CH_3$



XXVIII



XXIX

chemical shift difference between -8 and -9 methyl groups being 0.12 δ . The NMR spectrum of (+)-cis-3,4-carane-diol (XXIIb) has been reported by Kropp[33]. The authentic sample of the cis-diol was prepared by reaction of Osmium tetroxide on (+)-Car-3-ene as described by the author.

The trans configuration of 3,4-carane-diol obtained by the acidic hydrolysis of the 'α-epoxide' has been confirmed[34,35] by a number of properties e.g. its resistance to cleavage by lead tetraacetate, its ready convertion to the epimeric β-epoxide. Its proclivity of forming hydrate is also known[34b]. The (+)-trans-3,4-carane-diol obtained by the above performic acid reaction looses its crystalline character on slight warming with benzene, the residue melting at 87-88° (reported[35] m.p. of the trans-diol is 88-89°C) and when crystallized from ligroine changes its melting point to 88-89° with the loss of hydrated water molecules during crystallization.

The diol was cleaved by metaperiodate giving the keto-aldehyde (II) b.p. 85-87°/1.5 mm; ν_{max} 1725 (carbonyl), which on treatment with Me Mg I gave the diol (XXIII), b.p. 150°(bath)/0.5 mm. The IR spectrum of the diol (XXIII) displayed a strong hydroxyl absorption at 3250 cm^{-1}. The NMR spectrum exhibited signals (δ) at 0.53 (2H, m, cyclopropyl protons), 0.87 and 1.03 (3H each, $C(CH_3)_2$), 1.17 (3H, CH_3 protons), 3.73 (3H, CHOH and OH).

The secondary alcoholic group of XXIII was oxidised using Jones reagent to give the hydroxy ketone (XXIV) in almost quantitative yield. Its IR spectrum showed carbonyl absorption at 1695 cm^{-1}. NMR spectrum exhibited signals (δ) at 0.7 (2H, m, cyclopropyl protons); 0.87 and 1.10 (3H each, Me's on cyclopropane ring); 1.17 (6H, CH_3 protons); 1.33 (2H, q, J = 6 Hz, CH_2 protons); 2.10 (3H, s, $-COCH_3$); 2.30 (2H, t, J = 6 Hz, CH_2 protons adjacent to carbonyl function).

Dehydration of XXIV with $POCl_3$-pyridine gave an isomeric mixture of unsaturated ketones XXVa and XXVb in an approximate ratio of 3:1. The mixture was separated on $AgNO_3$-silica gel column using pet. ether (40-60°)-Chloroform mixture as eluent. Infrared absorption of the compound XXVa at 1725 and 1625 cm^{-1} corresponds to carbonyl and unsaturation respectively. Its NMR spectrum revealed signals at 0.93 and 1.17 (3H each, Me's on cyclopropane ring); 1.70 and 1.76 (3H each, $C = C(CH_3)_2$); 2.07 (3H, s, $COCH_3$); 2.27 (2H, t, J = 7 Hz, CH_2 protons); 4.76 (1H, broad, J = 8 Hz, proton on Sp^2 carbon). Compound XXVb exhibited carbonyl absorption at 1700 cm^{-1} and unsaturation at 1638 and 885 cm^{-1}. Its NMR spectrum displayed signals at 0.7 (2H, m, cyclopropyl protons); 0.86 and 1.10 (3H each, $C(CH_3)_2$); 1.70 (3H, s, CH_3 protons on double bond); 2.08 (3H, s, $COCH_3$); 2.27 (2H, t, J = 6 Hz, CH_2 protons adjacent to carbonyl function);

4.66 (2H, bs, C = CH_2).

Treatment of XXVa with MeMgI gave the unsaturated alcohol XXVI in quantitative yield $(\alpha)_D^{30}$ = + 30 (C, 2.1%, $CHCl_3$) b.p. 130-5° (bath)/5 mm. The infrared absorption spectrum of the compound at 3350, 1665 and 1380 cm^{-1} corresponds to hydroxyl, unsaturation and cyclopropane ring system respectively. Its NMR spectrum exhibited signals at 0.7 (2H, cyclopropyl protons); 0.90 and 1.13 (3H each, Me's on cyclopropane ring); 1.17 (6H, CH_3 protons); 1.70 and 1.73 (^{3}H each, C = $C(CH_3)_2$); 3.60 (1H, s, OH); 4.76 (1H, broad d, J = 8 Hz, proton on Sp^2 carbon).

Cleavage of the double bond of XXVI by ozonolysis and oxidative work up gave the hydroxy-acid XXVIIa, which on treatment with diazomethane gave the hydroxy-ester XXVIIb, b.p. 105° (bath)/3.5 mm, $(\alpha)_D^{30}$ = + 16.2 (C, 2.75%, $CHCl_3$). Its IR spectrum displayed absorption at 3450 cm^{-1} (OH), 1725 cm^{-1} ($COOCH_3$) and 1380 cm^{-1} (cyclopropane ring system). The NMR spectrum showed signals at 1.17 (6H, Me's on cyclopropane ring); 1.20 (6H, CH_3 protons); 1.40 (2H, d, J = 7 Hz, CH_2 protons); 3.60 (3H, s, $COOCH_3$); 4.33 (1H, s, OH). Compound XXVIIb on treatment with $POCl_3$-pyridine gave methyl (-)-cis-chrysanthemate XXIX, b.p. 85° (bath)/10 mm. $(\alpha)_D^{27}$ = -30° (C, 1.6%, $CHCl_3$). The NMR spectrum of XXIX was identical with that methyl (±)-cis-chrysanthemate reported by Bramwell[36] et al.

The hydroxy acid XXVIIa when treated with the

dehydrating agent N,N'-dicyclohexyl-carbodiimide in dry methylene chloride furnished the known[29,32] expected (-)-dihydrochrysanthemolactone XXVIII in good yield, m.p. 83-84°, $(\alpha)_D^{25}$ = -71° (C, 1.9%, $CHCl_3$); its infrared absorpti at 1720 cm^{-1} corresponds to δ-lactone. The NMR spectrum exhibited signals at 1.03 and 1.20 (3H each, Me's on cyclopropane ring); 1.27 and 1.37 (3H each, -O-CMe_2); 1.65 (2H, d, J = 4 Hz, CH_2 protons).

Synthesis of (+)-trans-chrysanthemic acid from the (-)-cis-isomer or its methyl ester has been reported[29] in literature. It can also be obtained conveniently from the lactone XXVIII according to the method described by Matsui et al[29] and later modified by Sobti and Sukh Dev[32].

C. Experimental procedure :

Trans-3,4-Carane-diol (XXIIa) : To (+)-Car-3-ene (204 g, 1.5 moles) in 92% formic acid (325 ml, 6.25 moles) was added hydrogen peroxide (200 ml, 30%, 1.75 moles) slowly with vigorous stirring, maintaining the temperature at 40° throughout the reaction (6 hr), the reaction mixture was kept overnight. The mixture was treated with aq. caustic soda (300 ml, 40%) to neutralise the acid. The hydroxy formoxy derivative separated as a viscous oil. Any dissolved hydroxy-formoxy derivative was extracted with ether and ether evaporated. The combined hydroxy formoxy derivative (250 g) was hydrolysed with aq. caustic soda (200 ml, 20%) to get the diol (126 g, 60%), which crystallised

from pet. ether (40-60°), m.p. 69-70°; $(\alpha)_D^{30}$ = +13.1° (C, 5%, acetone). (Found : C, 67.24; H, 10.63. $(C_{10}H_{18}O_2)_2 \cdot H_2O$ requires C, 67.00; H, 10.63%).

The diol was further crystallized from ligroin, m.p. 88-89°. (Found : C, 70.66; H, 10.77; M^+ 170. $C_{10}H_{18}O_2$ requires C, 70.54; H, 10.66%; mol. wt. 170.24. ν_{max}^{Nujol} 3250, 2900, 1460, 1375, 1060, 945, 815 cm^{-1}; NMR ($CHCl_3$,) 0.7 (2H, m, cyclopropyl protons); 0.97 (6H, s, $C(CH_3)_2$); 1.17 (3H, s, CH_3 protons); 1.72 to 2.23 (4H, CH_2 protons); 3.27 (1H, q, CHOH) and 3.62 (2H, OH protons).

3,3-Dimethyl-2-(2'-oxopropyl)-1-acetaldehydecyclopropane (II)

To 3,4-Carane-diol (30 g, 0.18 mole) in acetone (150 ml) and water (100 ml) was added potassium metaperiodate (50 g, 0.22 mole) portionwise during 2 hr with efficient stirring. The ppt. was filtered and washed thoroughly with ether. Acetone was removed from the filtrate by distillation. The aqueous portion was extracted with ether. The combined ethereal solution was washed with water, dried (Na_2SO_4) and evaporated to get the keto-aldehyde (II) (25 g, 83%), b.p. 85-87°/1.5 mm. (Found : C, 70.92; H, 9.45; M^+ 168. $C_{10}H_{16}O_2$ requires C, 71.39; H, 9.59%; mol. wt. 168.23); ν_{max} 3000, 1725, 1375, 1175, 955 cm^{-1}. NMR (CCl_4, δ) : 0.87 (2H, m, cyclopropyl protons); 0.91, 1.12 (3H each, s,s, $C(CH_3)_2$); 2.03 (3H, s, CH_3CO) and 2.27 (4H, CH_2 protons).

3,3-Dimethyl-2-(2'-hydroxy-2'-methyl-n-propyl) -1-(2'-hydroxy-n-propyl)-cyclopropane (XXIII) :

To dry magnesium turnings (3 g, 0.12 mole), dry ether (75 ml) and dry methyl iodide (0.5 g) was added gradually methyl iodide (17 g, 0.12 mole) with stirring. After 15-20 min, when all magnesium was dissolved, a solution of keto-aldehyde (II, 5 g, 0.036 mole) in ether (50 ml) was added dropwise; stirring was continued for another 30 min. The solution was refluxed for 15 min and then cooled. The reaction mixture was poured into an ice cold solution of NH_4Cl (50 g) in water (200 ml) and stirred for 15-20 min. The ether layer was separated and washed with water, dried (Na_2SO_4) and evaporated to get the compound (XXIII) (4.9 g, 70%) as a colourless viscous liquid, b.p. 150° (bath)/0.5 mm. (Found : C, 72.01; H, 12.10; M^+ 200. $C_{12}H_{24}O_2$ requires C, 71.95; H, 12.08%; mol. wt. 200.31; ν_{max} 3250, 2900, 1450, 1380, 965, 880 cm^{-1}. NMR (CCl_4, δ) : 0.53 (2H, m, cyclopropyl protons); 0.87 and 1.03 (3H each, $C(CH_3)_2$), 1.17 (9H, CH_3 protons), 3.73 (3H, OH and CHOH).

3,3-Dimethyl-2-(2'-hydroxy-2'-methyl-n-propyl) -1-(2'-oxopropyl) cyclopropane (XXIV) :

A solution of the diol (XXIII, 2 g) in acetone (15 ml) was cooled to 0-5°. Jones reagent (8 ml) was then added dropwise with vigorous stirring. The mass was left

at 0° for 1 hr and then diluted with ice cold water (50 ml) and extracted with ether (3 x 50 ml). The ether extract was washed successively with water, saturated aq. $NaHCO_3$, again with water and finally with brine and dried (Na_2SO_4). Removal of ether followed by distillation gave XXIV as a colourless liquid (1.9 g, 95%); b.p. 120° (bath)/1.5 mm; $(\alpha)_D^{30}$ = +41° (C, 1.92%, $CHCl_3$). (Found : C, 72.61, H, 11.12; M^+ 196. $C_{12}H_{22}O_2$ requires C, 72.68; H, 11.18%; mol. wt. 198.30). ν_{max} 3334, 2900, 1695, 1450, 1375, 910 cm^{-1}. NMR (CCl_4, δ) : 0.7 (2H, m, cyclopropyl protons); 0.87 and 1.10 (3H each, Me's on cyclopropane ring); 1.17 (6H, CH_3-protons); 1.33 (2H, d, J = 6 Hz, CH_2 protons); 2.10 (3H, s, $-COCH_3$); 2.30 (2H, d, J = 6 Hz, CH_2 protons adjacent to carbonyl function).

<u>2,2-Dimethyl-2-(2'-methyl-prop-1'-enyl)-1-(2'-oxopropyl) -cyclopropane (XXVa) and 2,2-dimethyl-2-(2'-methyl-prop-2'-enyl)-1-(2'-oxopropyl) cyclopropane (XXVb)</u> :

To an ice-cold solution of XXIV (1.5 g) dropwise in pyridine (10 ml) was added $POCl_3$ (2 g) dropwise during 15 min with constant cooling and shaking. The reaction mixture was left overnight at 0°, poured into ice-water and extracted with ether. The ether extract was washed successively with cold dil. HCl, saturated aq. $NaHCO_3$, water, brine and dried (Na_2SO_4). Ether was evaporated to get the residue which was chromatographed over $AgNO_3$-silica gel

(1:6 g, 50 g). The earlier fractions eluted with pet. ether (40-60°)-chloroform (1:1) furnished pure unsaturated ketone (XXVa, 1.02 g, 71%) which was distilled as a colourless liquid; b.p. 125° (bath)/2.5 mm; $(\alpha)_D^{30}$ = +77.8° (C, 2.4%, $CHCl_3$) (Found : C, 79.91; H, 11.13. $C_{12}H_{20}O$ requires C, 79.94; H, 11.18%). ν_{max} 2950, 1725, 1625, 1450, 1375, 1162, 985 cm^{-1}; NMR (CCl_4, δ) : 0.93 and 1.17 (3H each s,s, $C(CH_3)_2$); 1.70 and 1.76 (3H each, C = $C(CH_3)_2$); 2.07 (3H, s, $-COCH_3$); 2.27 (2H, d, J = 7 Hz, CH_2 protons); 4.76 (1H, broad d, J = 8 Hz; vinyl proton).

The later fractions of the chromatograph furnished pure isomeric unsaturated ketone (XXVb; 0.35 g, 25%) which was distilled to give a colourless liquid; b.p. 120° (bath)/2.5 mm; $(\alpha)_D^{30}$ = +4.6° (C, 4.7%, $CHCl_3$) (Found : C, 79.85; H, 11.14. $C_{12}H_{20}O$ requires C, 79.94; H, 11.18%). ν_{max} 2900, 1700, 1638, 1435, 1375, 1160, 885 cm^{-1}. NMR (CCl_4, δ) : 0.7 (2H, m, cyclopropyl protons); 0.86 and 1.10 (3H each, s,s, $C(CH_3)_2$); 1.70 (3H, s, CH_3 protons on double bond); 1.87 (2H, d, J = 6 Hz, CH_2 protons adjacent to double bond); 2.03 (3H, s, $COCH_3$); 2.27 (2H, d, J = 6 Hz, CH_2-protons adjacent to carbonyl function); 4.66 (2H, bs, C = CH_2).

<u>3,3-Dimethyl-2-(2'-methyl-prop-1'-enyl)-1-(2'-hydroxy-2'-methyl-n-propyl) cycloprepane (XXVI)</u> :

To a stirred solution of methyl magnesium iodide (prepared from 2.8 g of methyl iodide and 0.8 g of activated

magnesium) in dry ether (25 ml) was added dropwise in a solution of the unsaturated ketone (XXVa, 0.9 g) in dry ether (10 ml) during 15 min. After stirring the mixture for 30 min at room temperature, it was refluxed for 15 min, cooled and decomposed by pouring into an ice-cold saturated aq. NH_4Cl (50 ml) and the resulting solution extracted with ether (3 x 50 ml). Evaporation of the solvent afforded the expected unsaturated hydroxy compound (XXVI; 0.89 g, 92%) as a colourless liquid; b.p. 130° (bath)/1.5 mm; $(\alpha)_D^{30}$ = +30° (C, 2.1%, $CHCl_3$) (Found : C, 79.50; H, 12.26; M^+ 196. $C_{13}H_{24}O$ requires C, 79.53; H, 12.32%; mol. wt. 196.32). ν_{max} 3350, 2900, 1650, 1465, 1380, 1150, 915, 850 cm^{-1}. NMR (CCl_4, δ) : 0.7 (2H, cyclopropyl protons); 0.90 and 1.13 (3H each, s,s, Me's on cyclopropane ring); 1.17 (6H, s, CH_3 protons); 1.70 and 1.73 (3H each, C = $C(CH_3)_2$); 2.60 (1H, s, OH); 4.76 (1H, broad d, J = 8 Hz; vinyl proton).

<u>Methyl 3,3-dimethyl-1-(2'-hydroxy-2'-methyl-n-propyl) -cyclopropane-2-carboxylate (XXVIIb)</u> :

Compound XXVI (0.5 g) was dissolved in dry ethyl acetate (25 ml), cooled to -10° and treated with a gentle stream of ozonized oxygen for 10 min. The solvent was distilled off and the crude ozonide taken in acetone (10 ml), cooled to 0° and treated with Jone's reagent (3 ml). The product was worked up as usual to get the hydroxy acid

(XXVIIa) which on treatment with diazomethane afforded the hydroxy ester (XXVIIb; 0.41 g, 80%) as a colourless liquid, b.p. 105° (bath)/3.5 mm, $(\alpha)_D^{30}$ = +16.2° (C, 2.75%, $CHCl_3$). (Found : C, 65.93; H, 10.10; M^+ 200. $C_{11}H_{20}O_3$ requires C, 65.97; H, 10.07; mol. wt. 200.27). ν_{max} 3450, 2950, 1725, 1440, 1380, 1225, 1175, 885 cm^{-1}. NMR ($CDCl_3$, δ) : 1.17 (6H, Me's on cyclopropane ring); 1.20 (6H, CH_3 protons); 1.40 (2H, d, J = 7 Hz, CH_2 protons); 3.60 (3H, s, $COOCH_3$); 4.33 (1H, bs, OH).

(-)-Dihydrochrysanthemolactone (XXVIII) :

To a stirred solution of N,N'-dicyclohexylcarbodiimide (0.208 g, 0.001 mole) in dry methylene chloride (5 ml), cooled in an ice-bath, was added in one portion a solution of the hydroxy acid (XXVIIa, 0.185 g, 0.001 mole) in methylene chloride (2 ml). The stirring was continued for 1.5 hr at 0° and then for 1.5 hr at room temperature. The precipitated N,N'-dicyclohexyl urea was filtered out and washed with methylene chloride (4 ml). The filtrate was washed with cold saturated aq. $NaHCO_3$ (2 x 5 ml), then with cold water and dried (Na_2SO_4). Filtration and evaporation of the solvent left a semisolid mass (0.15 g) which was chromatographed over silica gel. Elution with a mixture of pet. ether (40-60°) and chloroform (3:1) afforded a crystalline mass (0.11 g, 63%) which was identified as (-)-dihydro chrysanthemolactone, m.p. 83-84°,

$(\alpha)_D^{25} = -71^\circ$ (C, 1.9%, $CHCl_3$). (Lit.[32] m.p. 83-84°; $(\alpha)_D^{20} = -77.24^\circ$ (C, 4.35%, $CHCl_3$)). (Found : C, 71.35; H, 9.61; M^+ 168. $C_{10}H_{16}O_2$ requires C, 71.39; H, 9.59%; mol. wt. 168.23).

ν_{max} 2950, 1720, 1380, 1275, 1105, 960, 835 cm^{-1}.

NMR (CCl_4, δ) : 1.08 and 1.20 (3H each, s,s, Me's on cyclopropane ring); 1.27 and 1.37 (3H each, s,s, $-O-CMe_2$); 1.65 (2H, d, J = 4 Hz; CH_2 prptons).

Methyl (-)-cis-chrysanthemate (XXIX) :

The hydroxy ester (XXVIIb, 0.5 g) in pyridine (3 ml) was treated with $POCl_3$ (0.75 g) at 0°. The reaction mixture was left overnight at 0°, poured into ice-cold water, worked up in the usual manner and chromatographed over $AgNO_3$ - silica gel (1:6). By eluting with a mixture of pet. ether (40-60°) - chloroform (3:1), pure methyl (-)-cis-chrysanthemate (0.3 g, 65%) was obtained as a colourless liquid, b.p. 85° (bath)/10 mm; $(\alpha)_D^{27} = -30^\circ$ (C, 1.5% $CHCl_3$) (Found : C, 72.81; H, 9.94. $C_{11}H_{18}O_2$ requires C, 72.49; H, 9.96%).

ν_{max} 2950, 1725, 1380, 1190, 1135 cm^{-1}.

NMR (CCl_4, δ) : 1.21 and 1.24 (3H each, s,s, Me's on cyclopropane ring); 1.70 and 1.75 (3H each, Me's on double bond); 3.60 (3H, s, $-COOCH_3$); 5.33 (1H, d, J = 8 Hz, Vinyl proton).

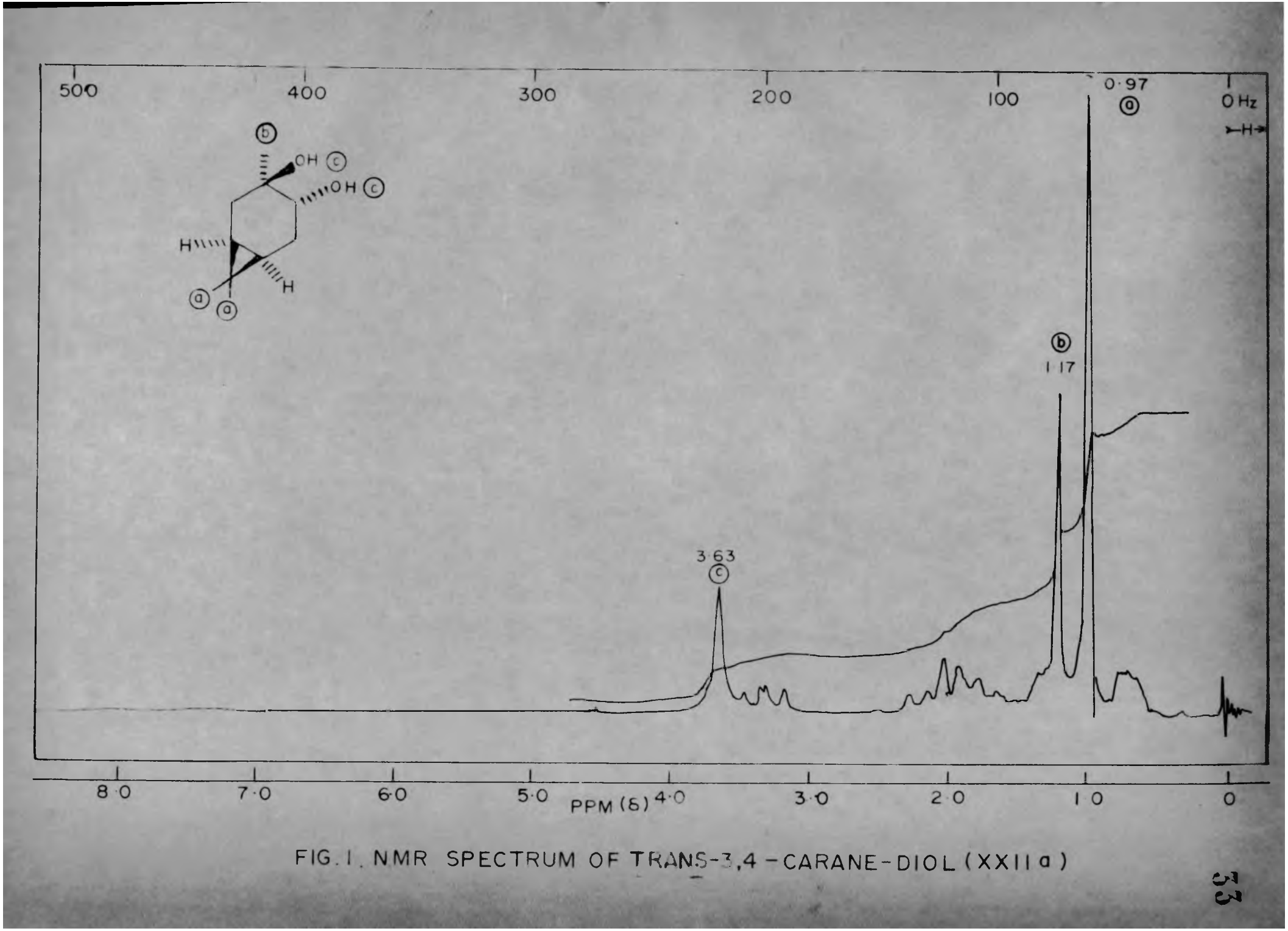


FIG. I. NMR SPECTRUM OF TRANS-3,4-CARANE-DIOL (XXIIa)

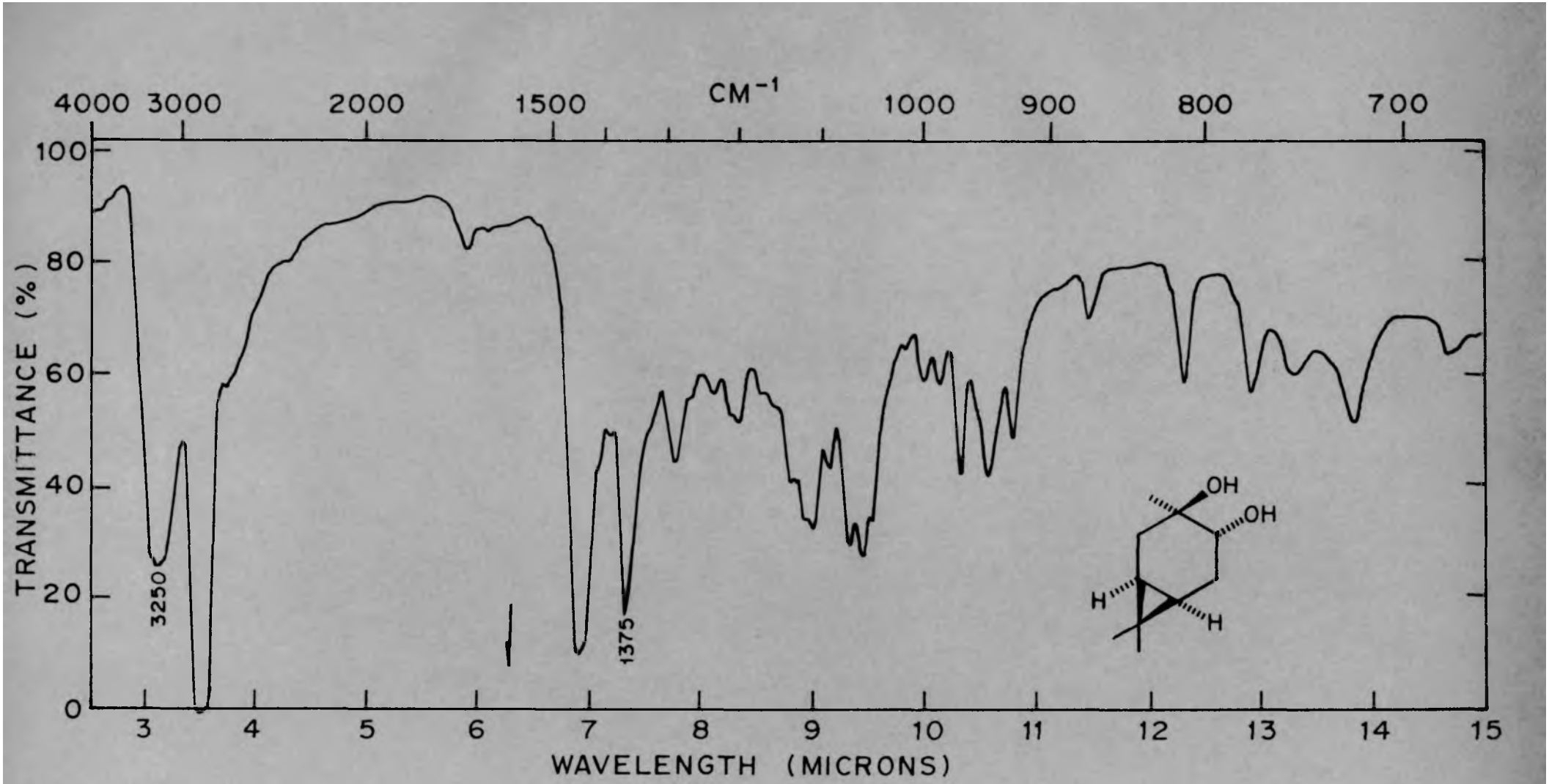


FIG. 2. IR SPECTRUM OF (+) TRANS-3,4-CARANE DIOL (XXII a)

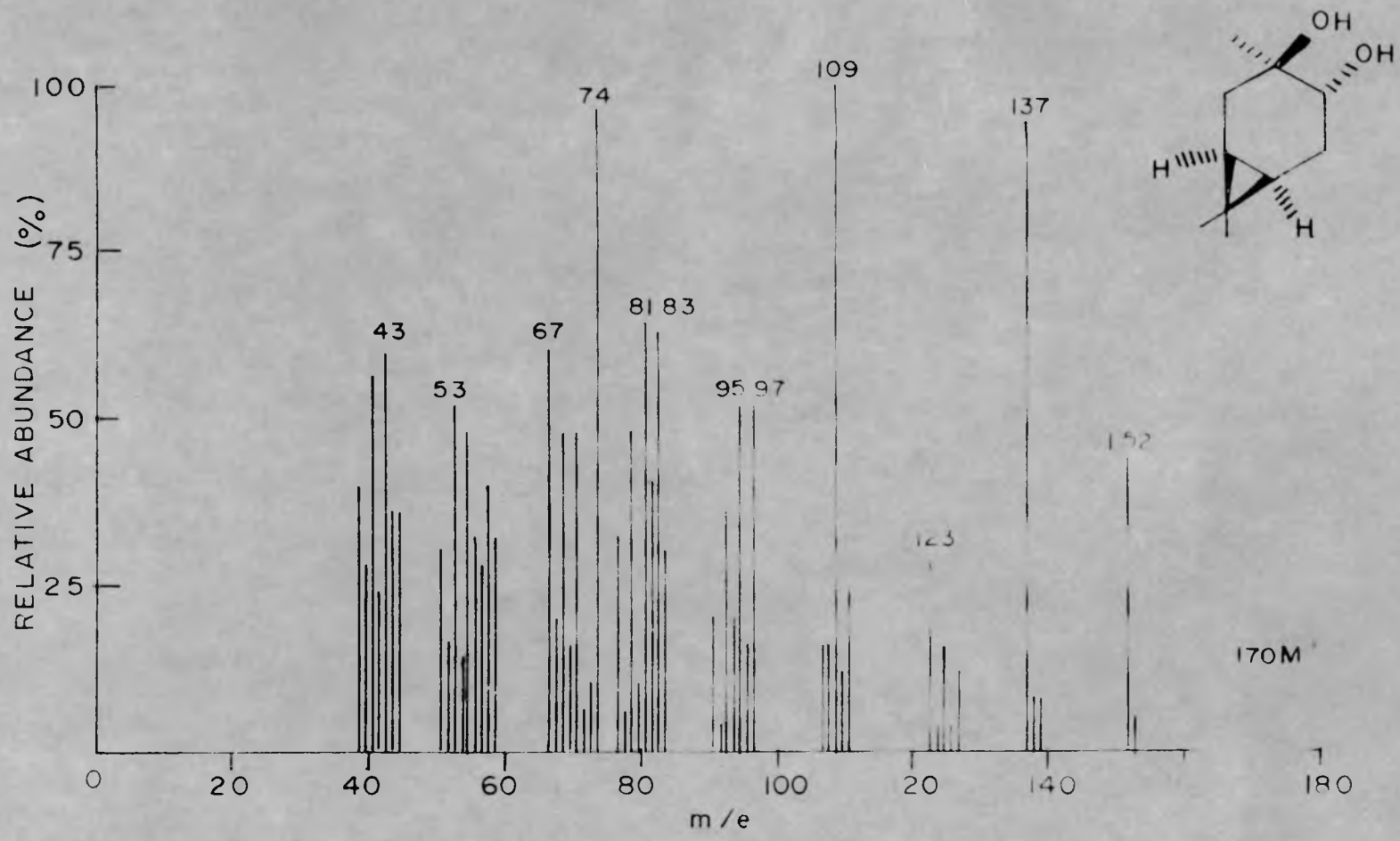


FIG. 3_MASS SPECTRUM OF (+) - tran 3,4- CAR A (XXIIa)

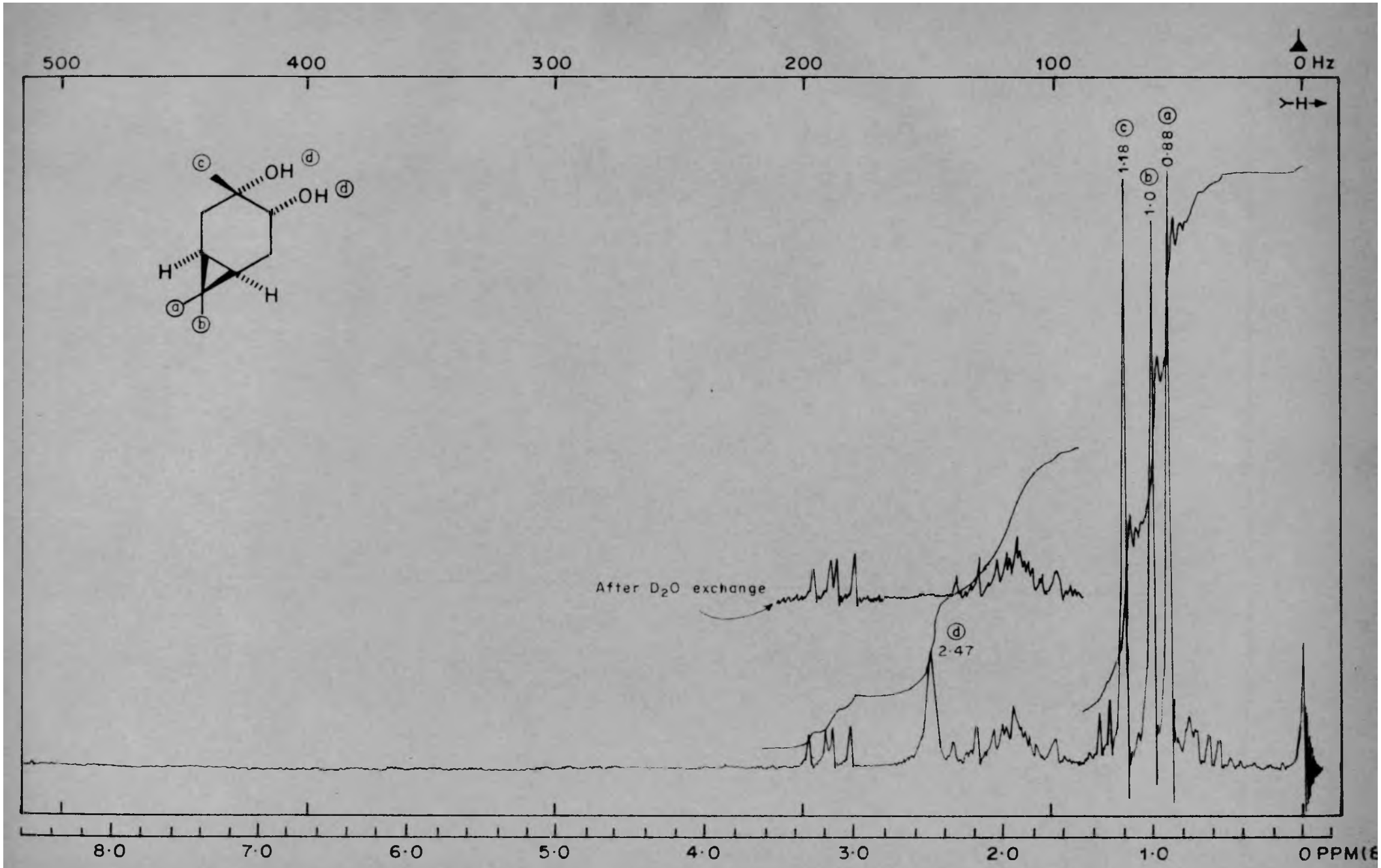


FIG. 4. NMR SPECTRUM OF CIS-3,4-CARANE-DIOL (XXII b)

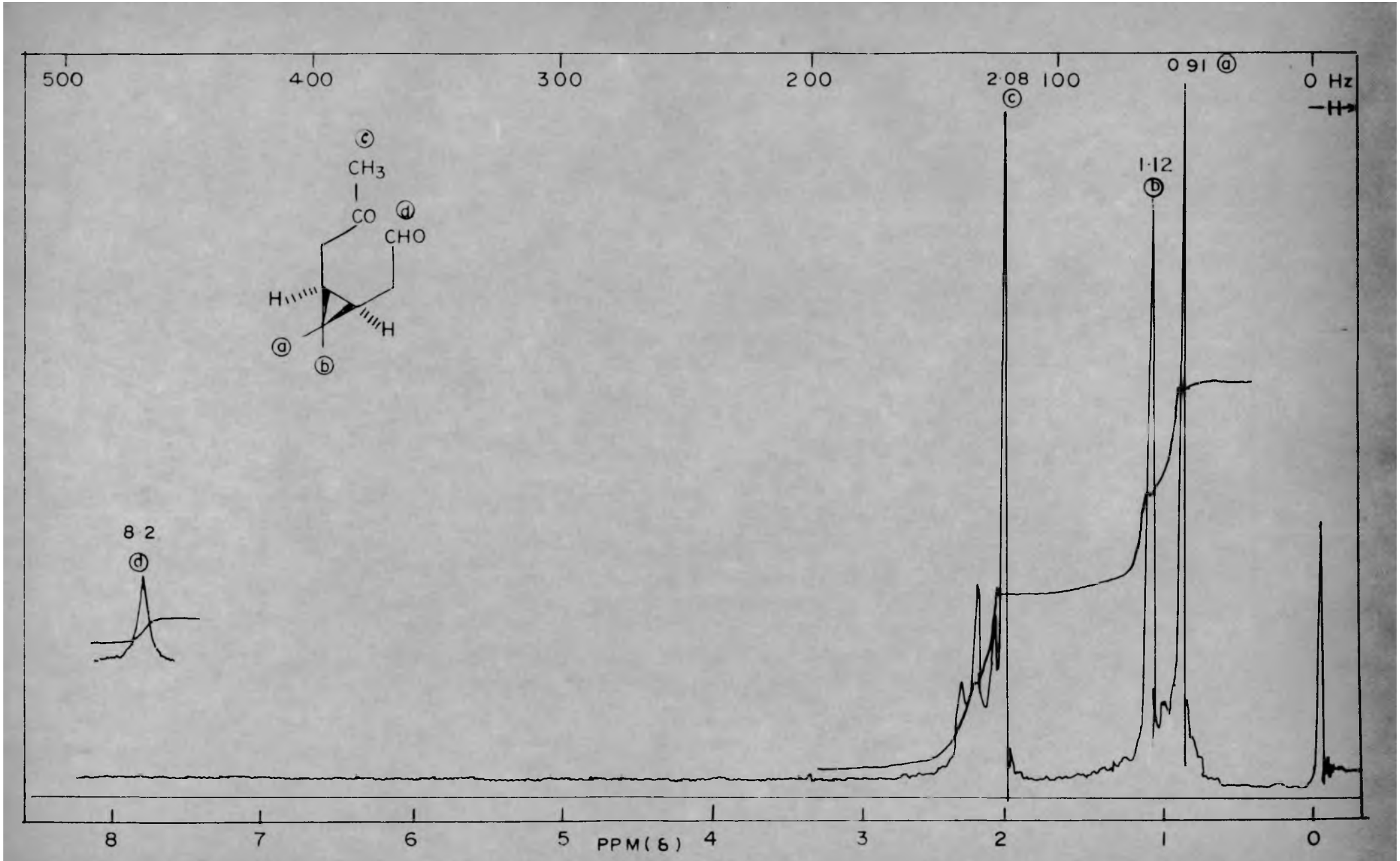


FIG. 5. NMR SPECTRUM OF 3,3-DIMETHYL-2-(2'-OXOPROPYL)-1-ACETALDEHYDE CYCLOPROPANE (II)

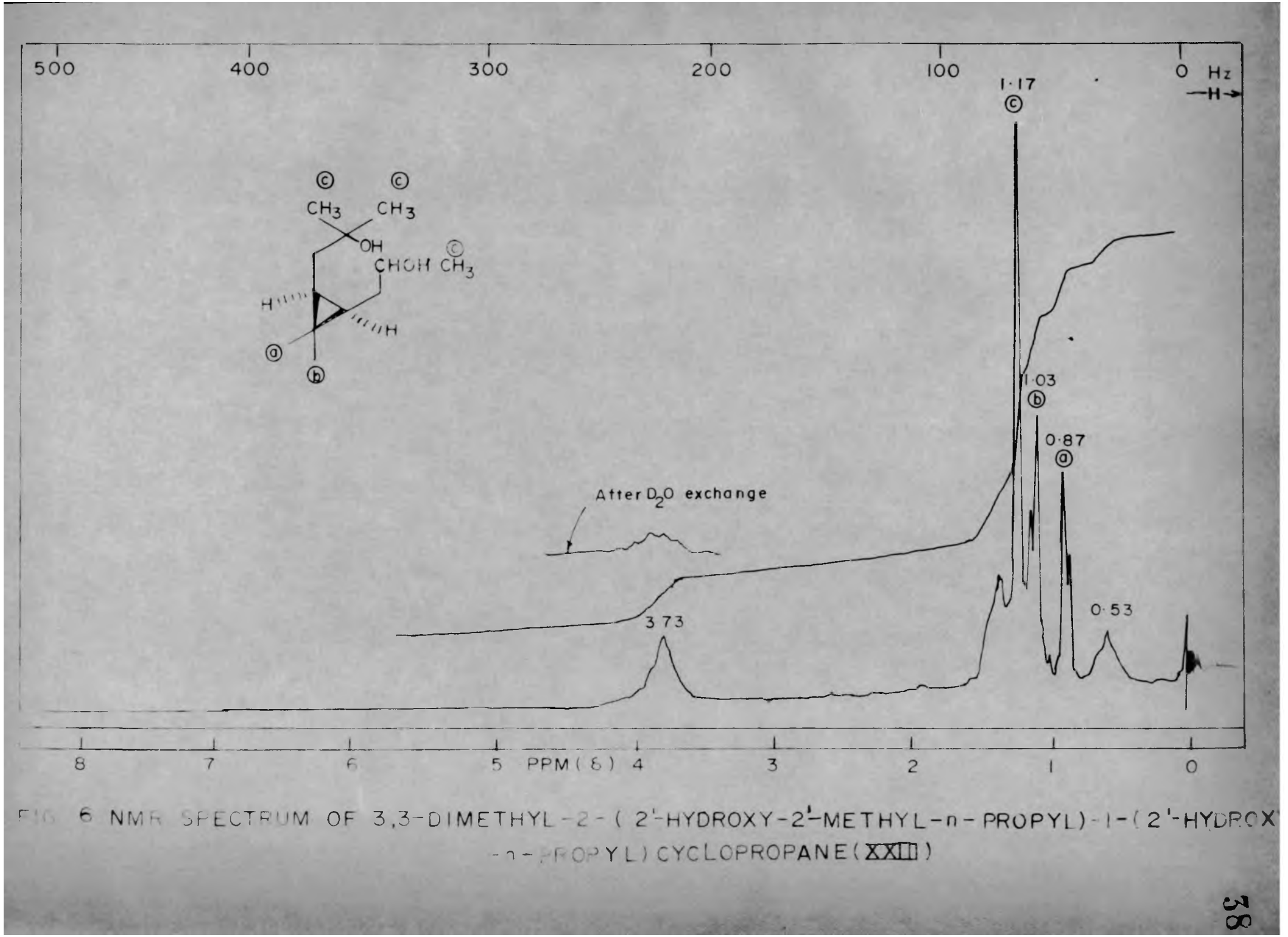


FIG 6 NMR SPECTRUM OF 3,3-DIMETHYL-2-(2'-HYDROXY-2'-METHYL-n-PROPYL)-1-(2'-HYDROXY-n-PROPYL) CYCLOPROPANE (XXIII)

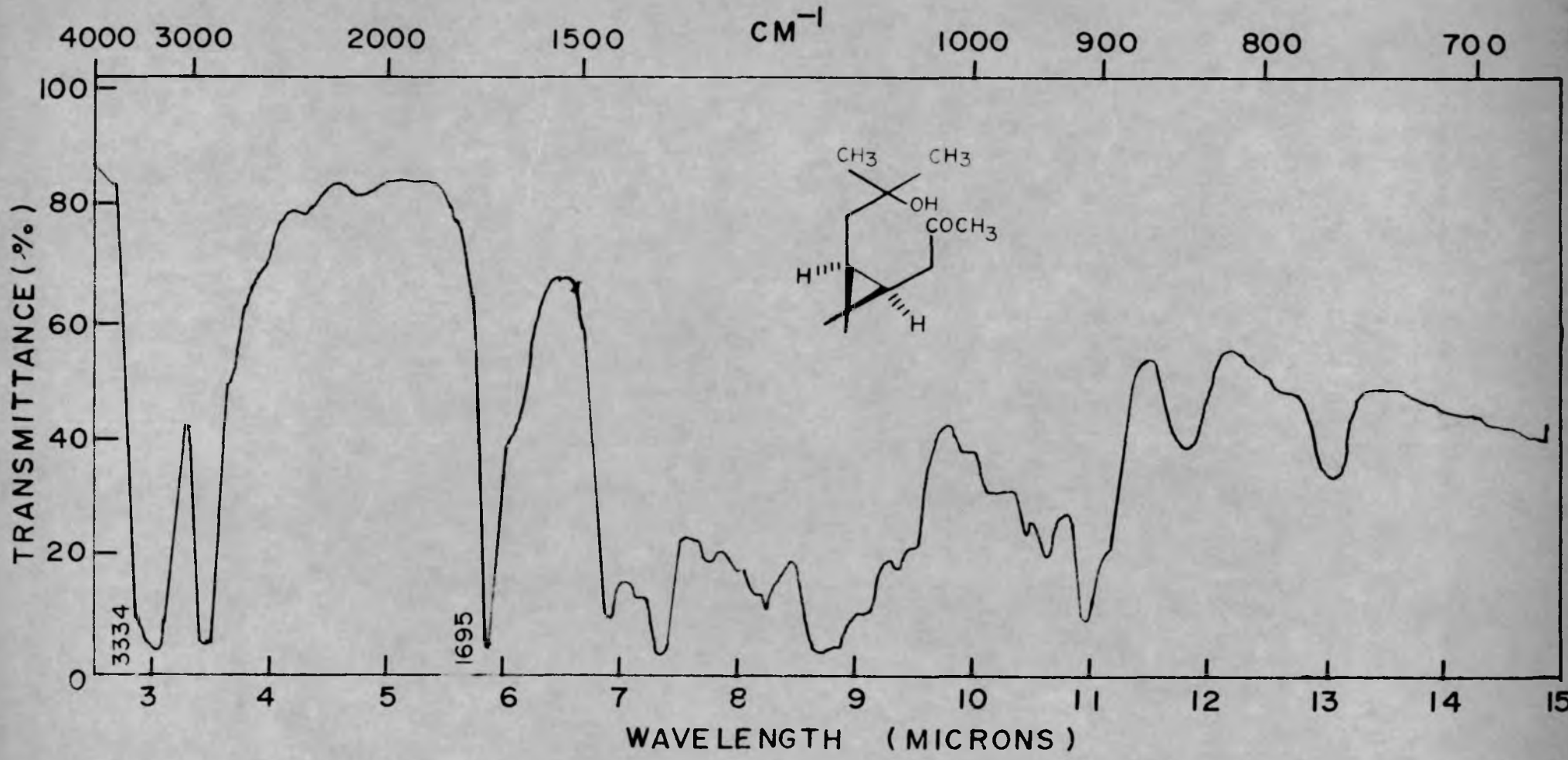


FIG. 7. IR SPECTRUM OF 3,3-DIMETHYL-2-(2'-HYDROXY-2'-METHYL-n-PROPYL)-1-(2'-OXOPROPYL)CYCLOPROPANE (XXIV)

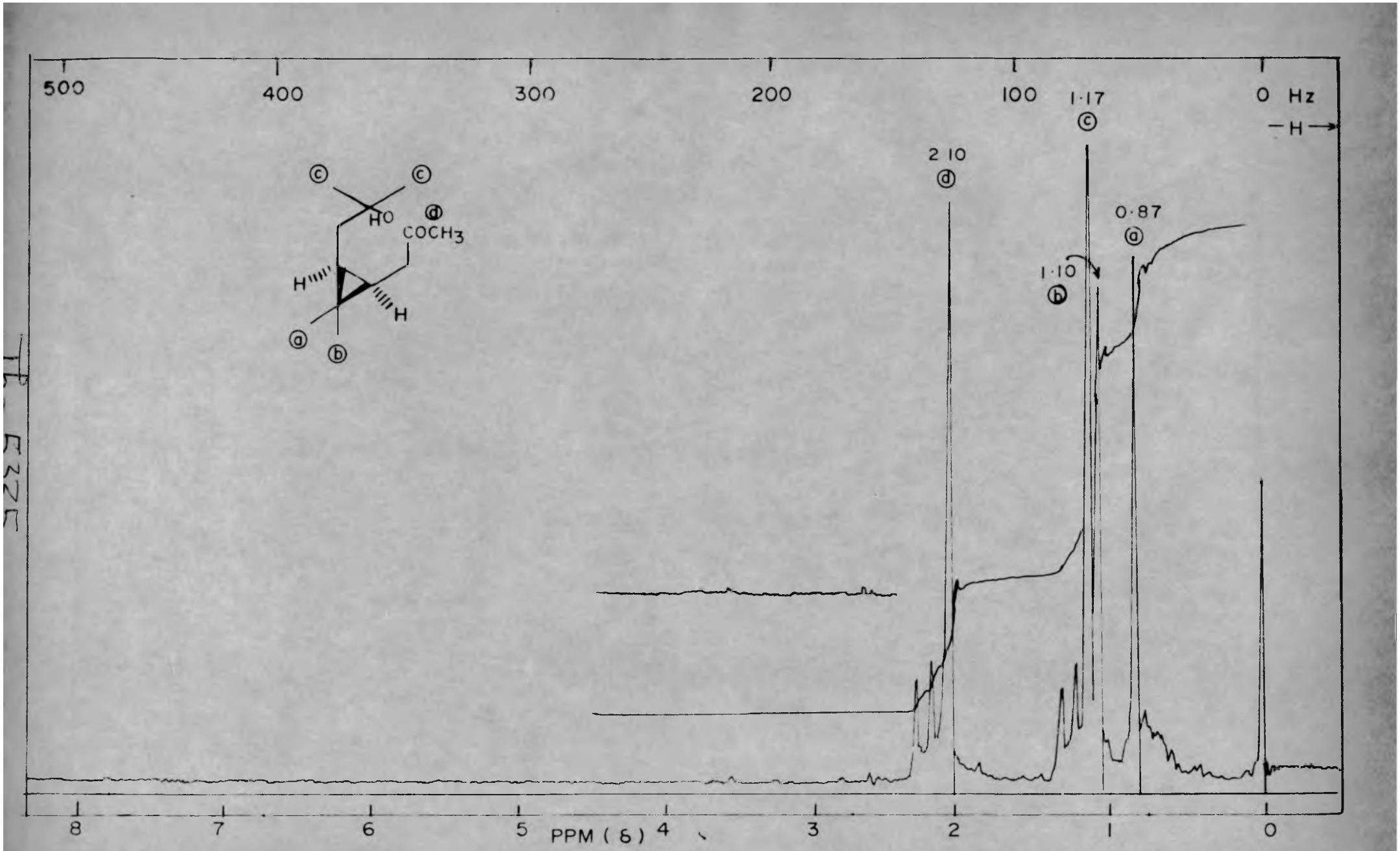


FIG. 8. NMR SPECTRUM OF 3,3-DIMETHYL-2-(2'-HYDROXY-2'-METHYL-n-PROPYL)-1-(2'-OXOPROPYL CYCLOPROPANE (XXIV)

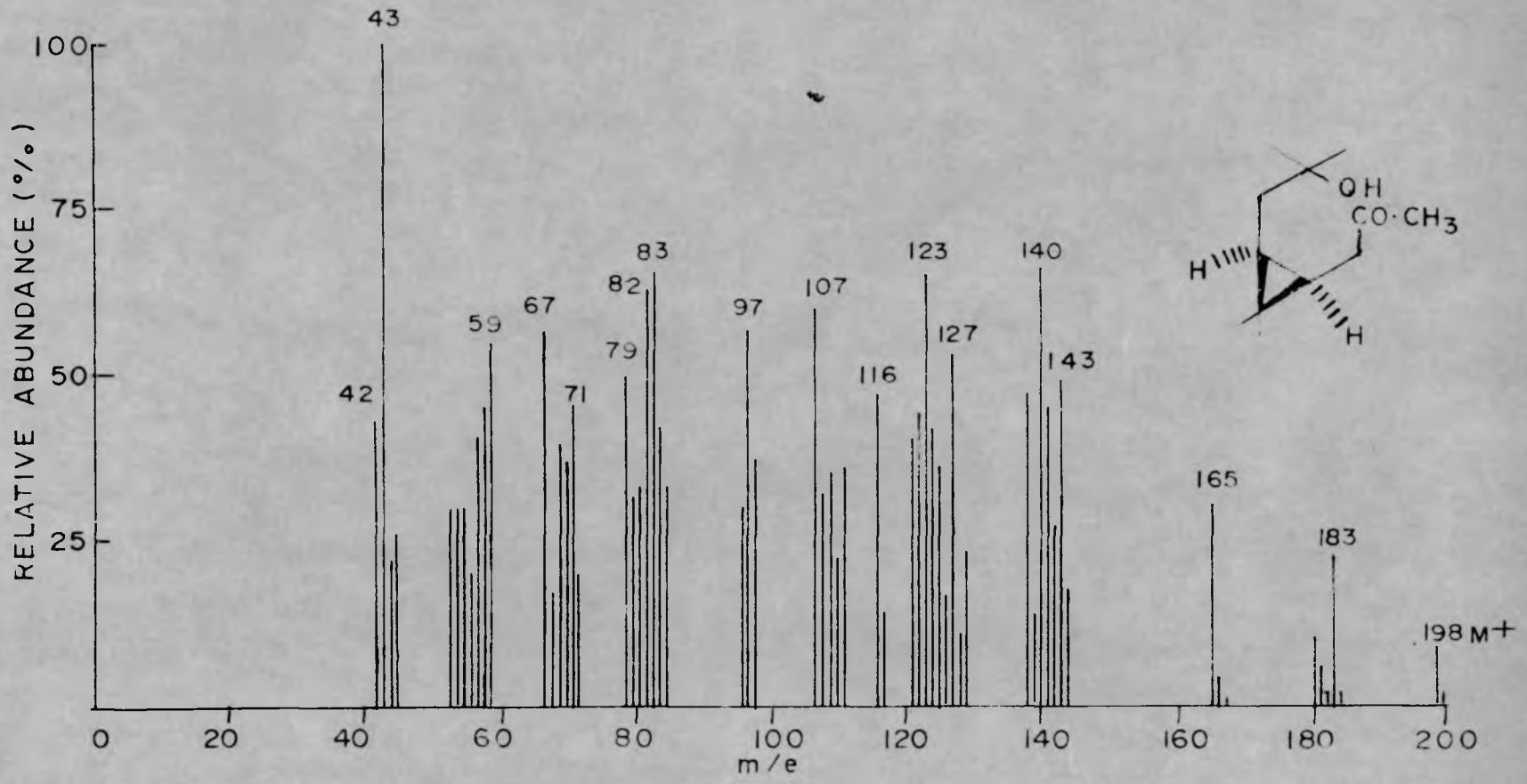


FIG. 9. MASS SPECTRUM OF 3,3-DIMETHYL-2-(2'-HYDROXY-2'-METHYL-n-PROPYL)-1-(2'-OXOPROPYL) CYCLOPROPANE (XXIV)

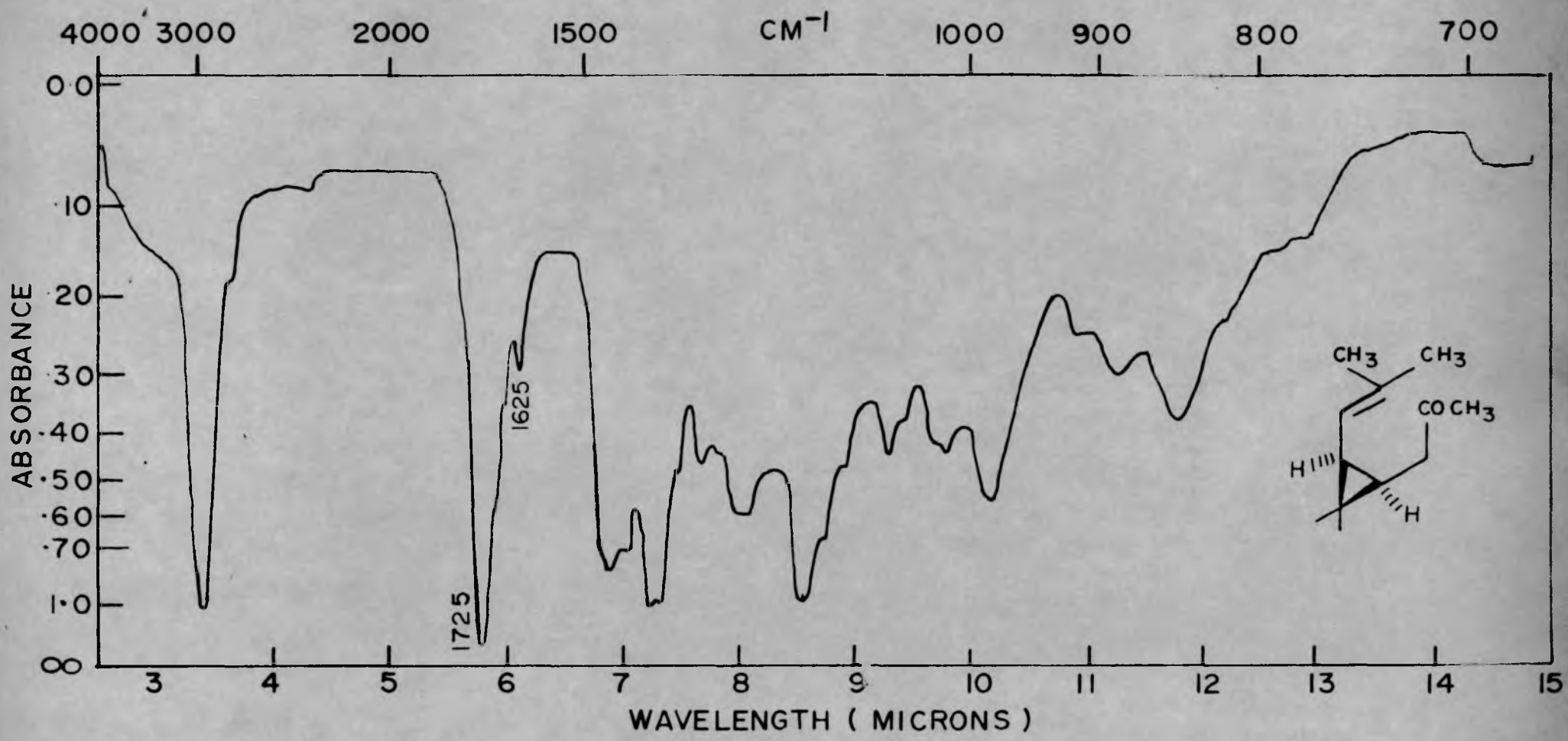


FIG. 10. IR SPECTRUM OF 3,3-DIMETHYL-2(2'-METHYL-PROP-1'-ENYL)-1-(2'-OXOPROPYL) CYCLOPROPANE (XXVa)

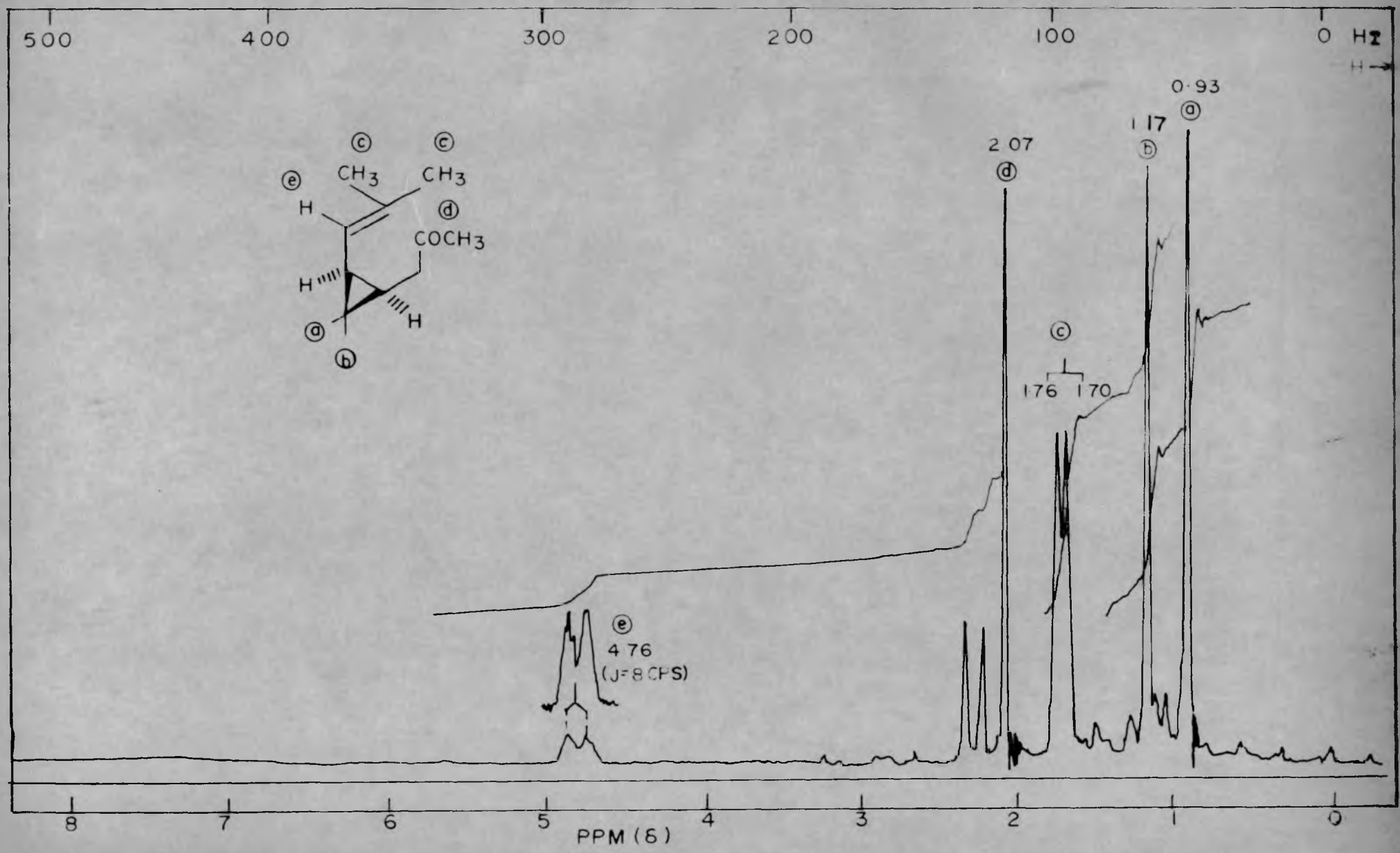


FIG 11. NMR SPECTRUM OF 3,3-DIMETHYL-2-(2'-METHYL-PROP-1'-ENYL)-1-(2'-OXOPROPYL) CYCLOPROPANE (XXVa)

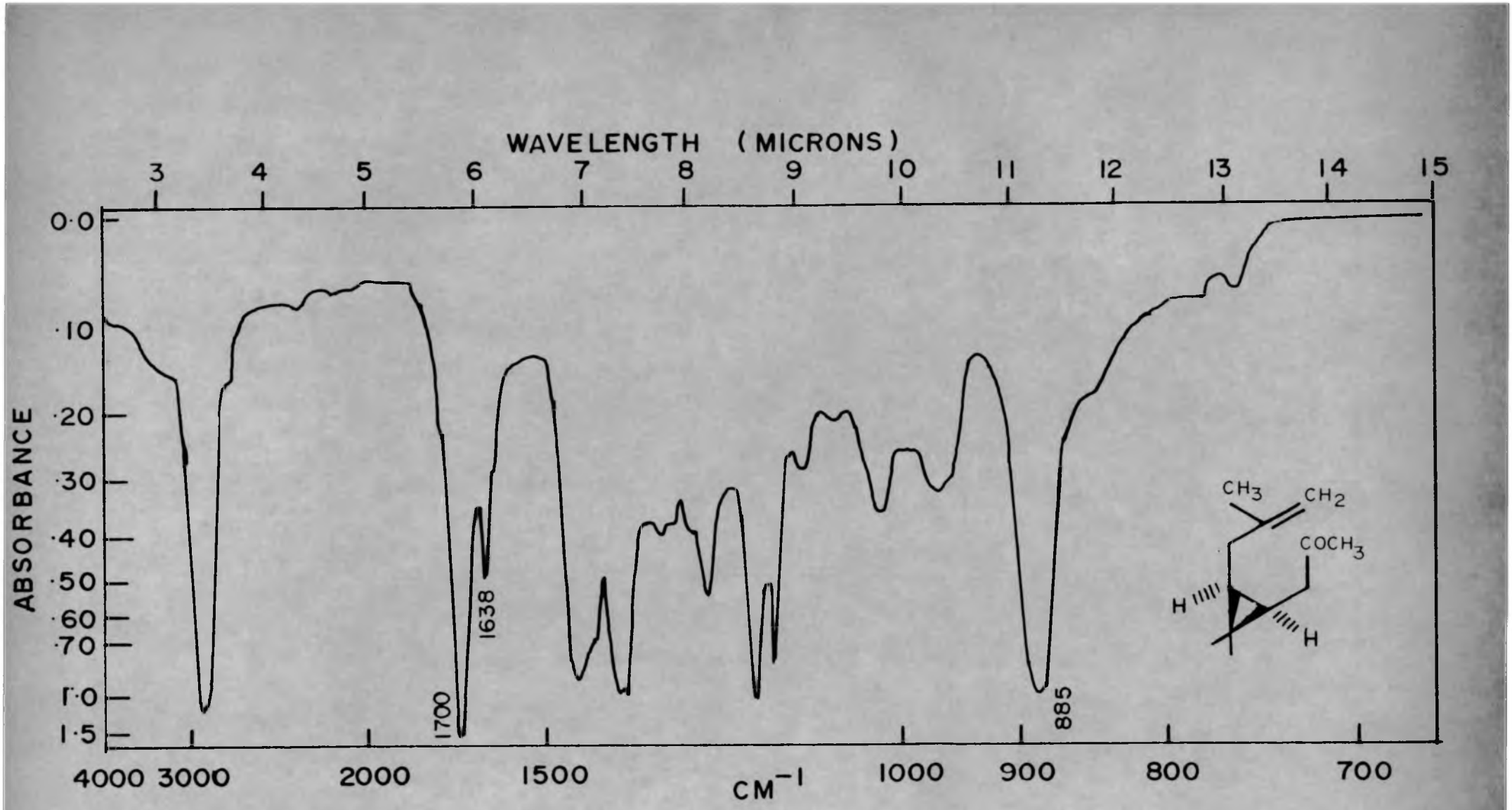


FIG. 12. IR SPECTRUM OF 3,3-DIMETHYL-2-(2'-METHYL-PROP-2'-ENYL)-1-(2'-OXOPROPYL CYCLOPROPANE (XXVb)

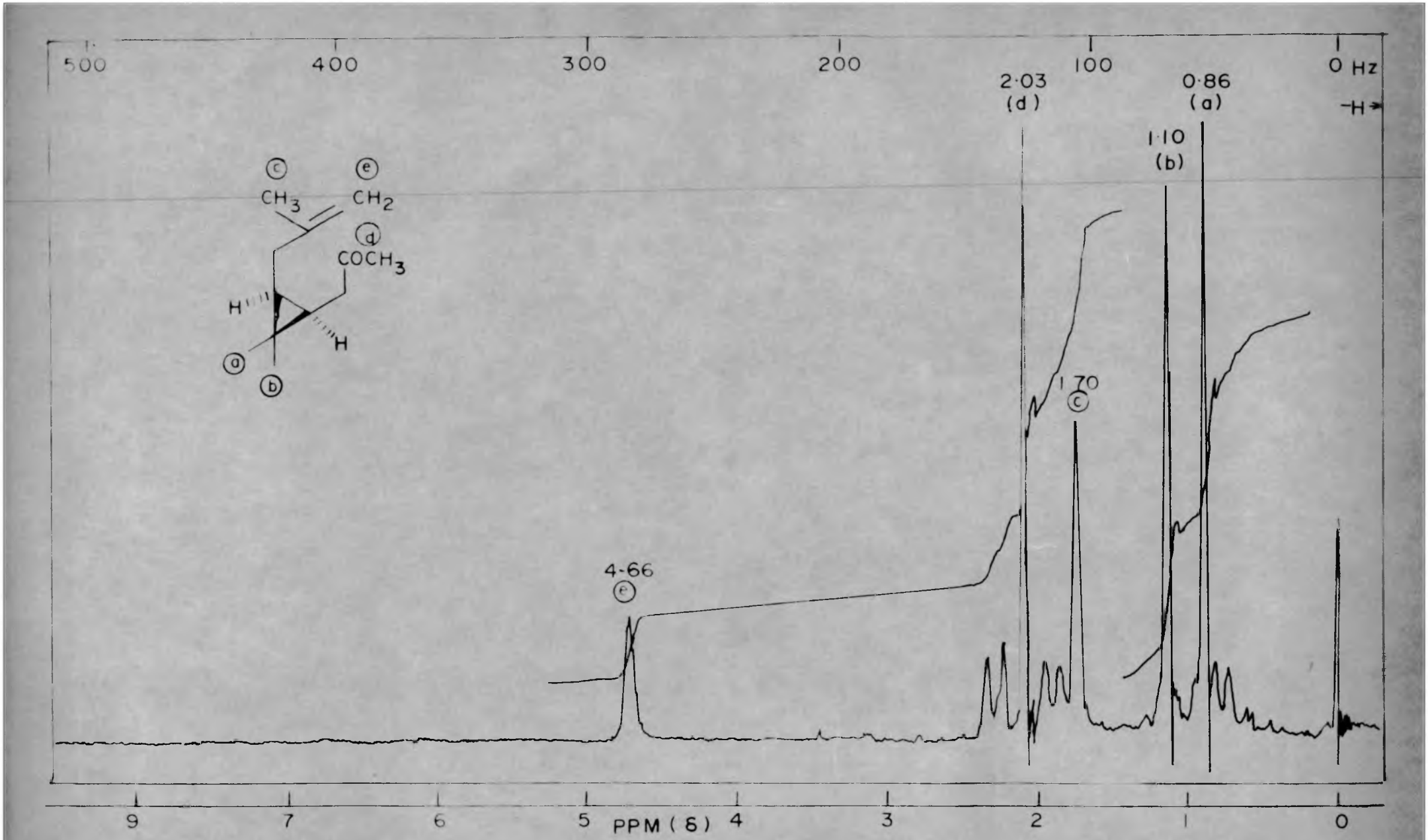


FIG 13. NMR SPECTRUM OF 3,3-DIMETHYL-2-(2'-METHYL-PROP-2'-ENYL)-1-(2'-OXOPROPYL CYCLOPROPANE (~~XXV~~ b)

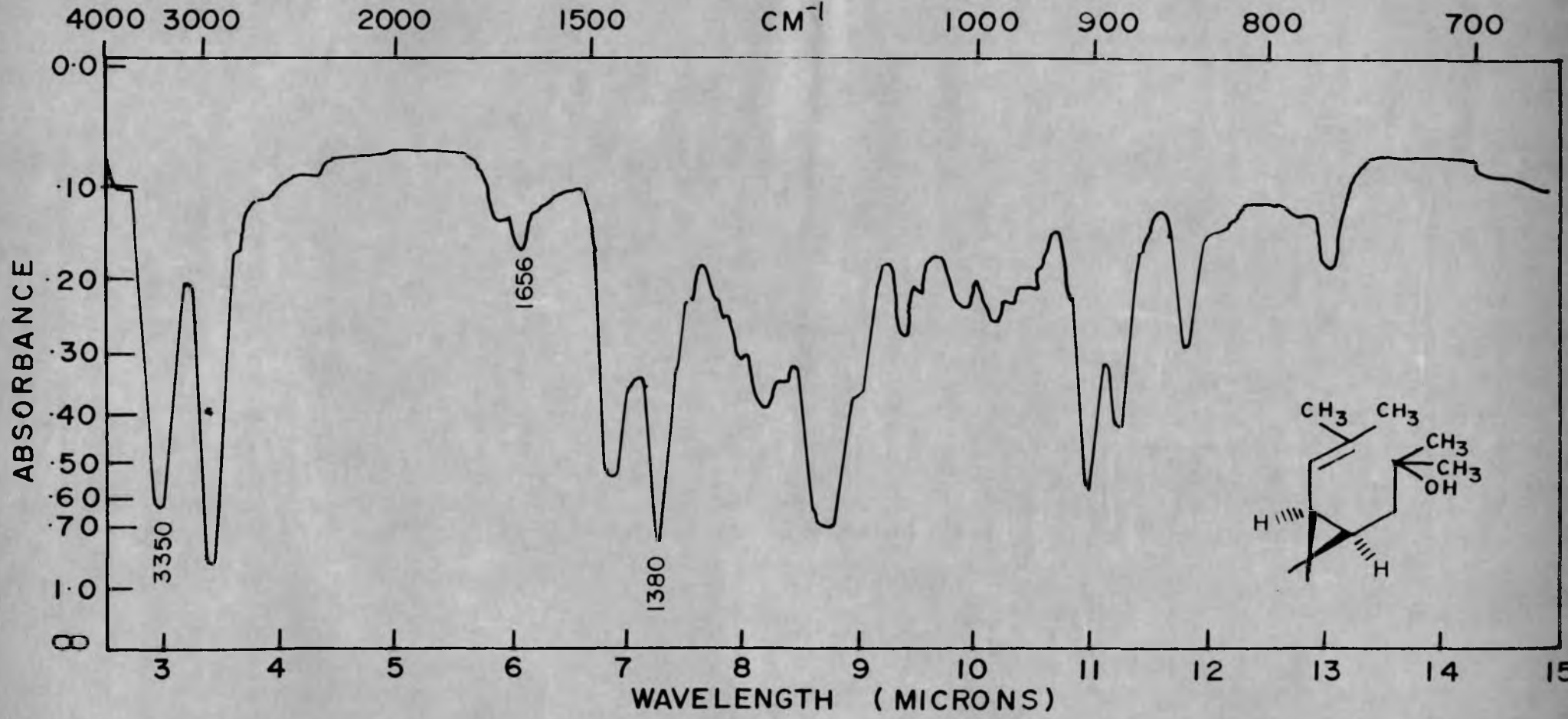


FIG.14.IR SPECTRUM OF 3,3-DIMETHYL-2-(2'-METHYL-PROP-1'-ENYL)-1-(2'-HYDROXY-2'-METHYL-n-PROPYL) CYCLOPROPANE (XXVI)

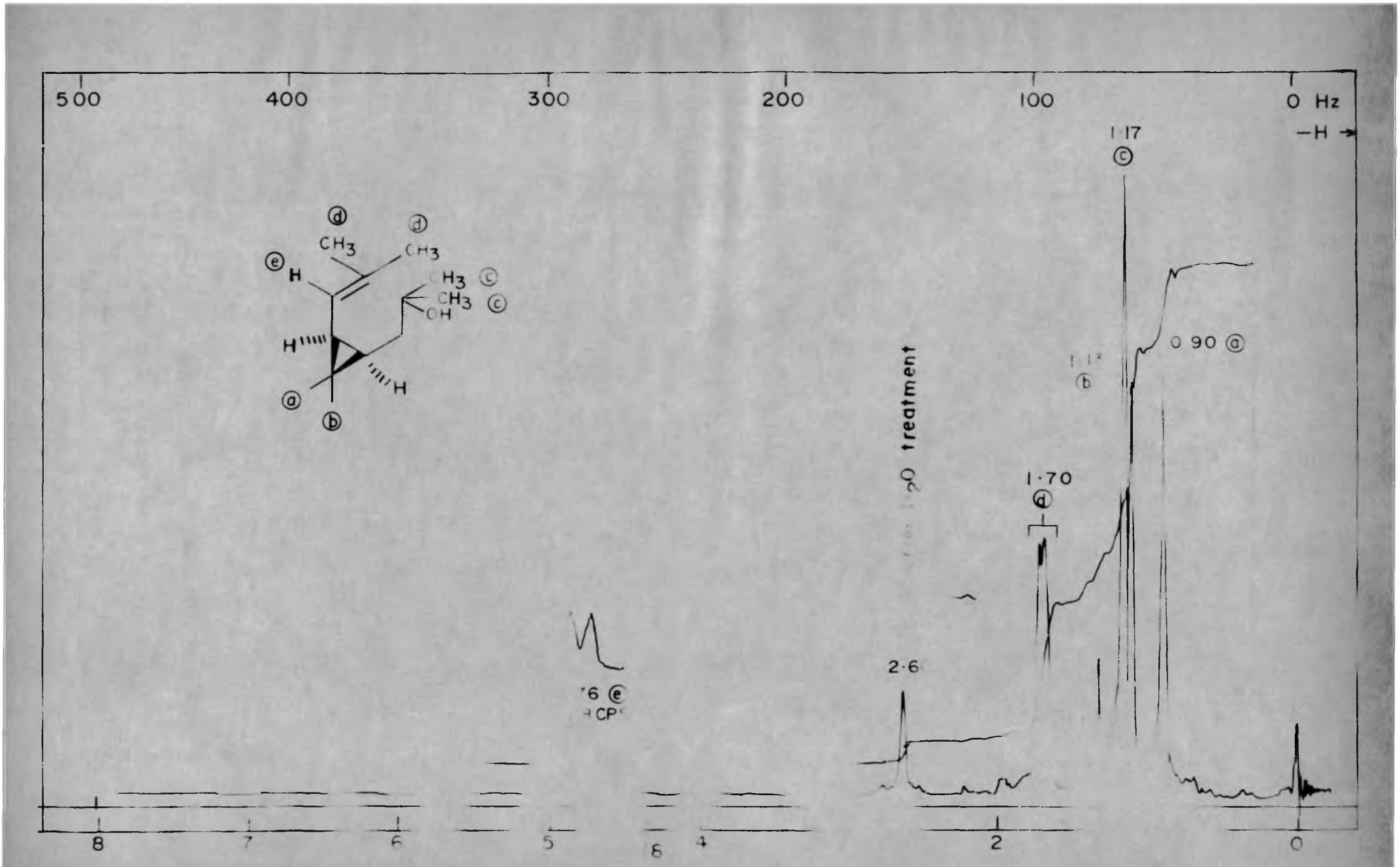


FIG.15 NMR SPECTRUM OF 3,3-DIMETHYL-PROPANE (XX).

2'-HYDROXY-2-METHYL-n-PROPANE (L)

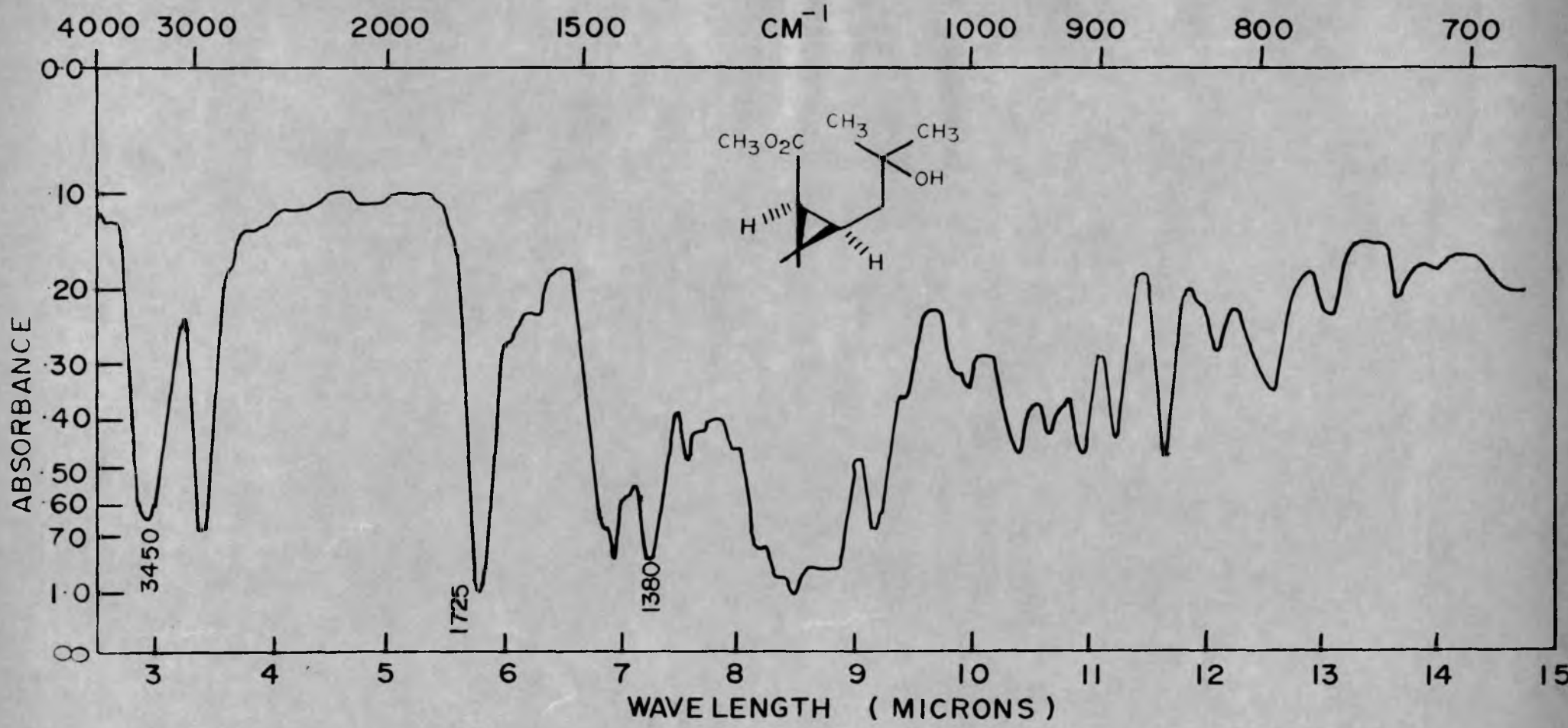


FIG.16. IR SPECTRUM OF METHYL 3,3-DIMETHYL-1-(2'-HYDROXY-2'-METHYL-n-PROPYL)-CYCLOPROPANE-2-CARBOXYLATE (XXVII b)

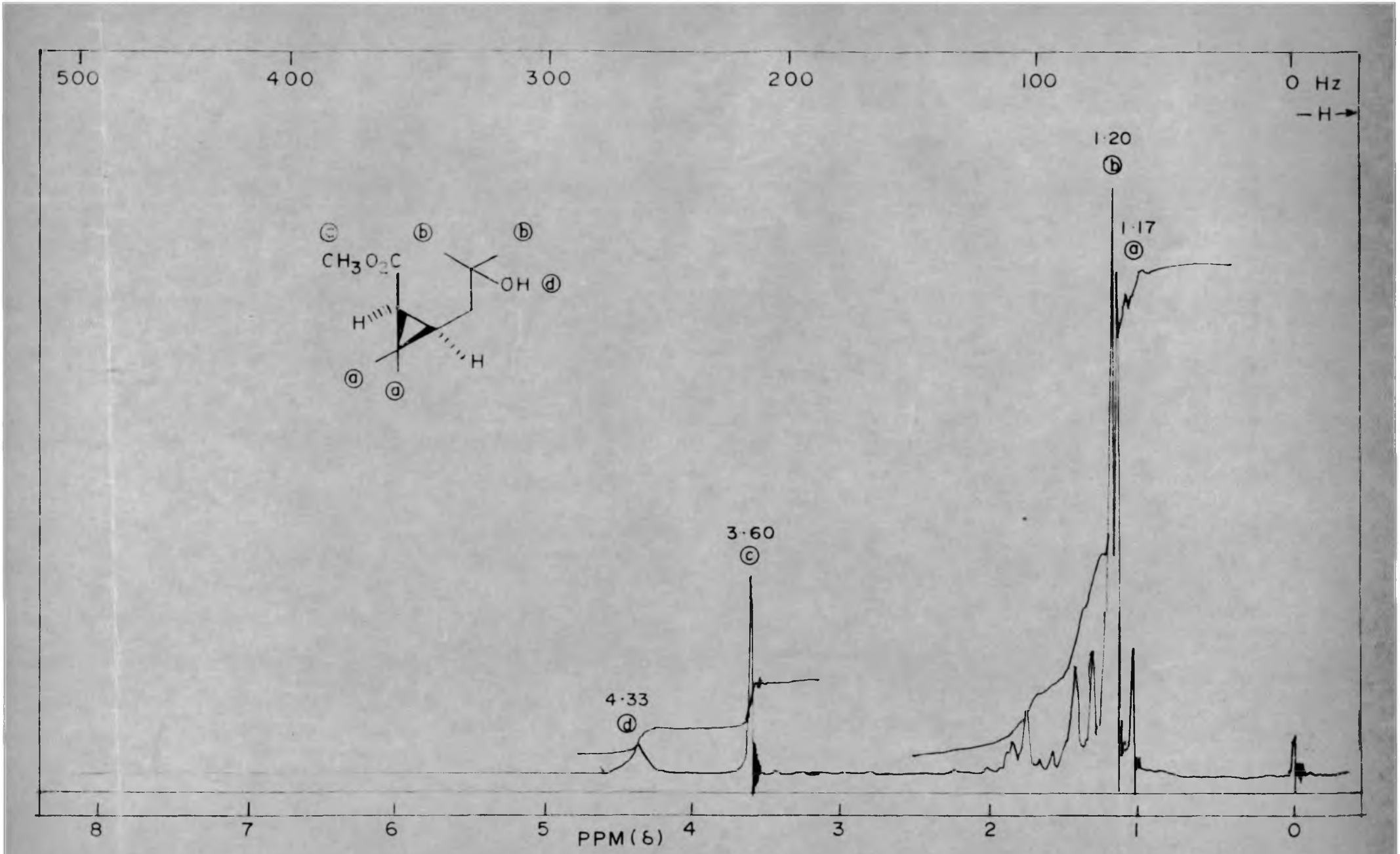


FIG.17. NMR SPECTRUM OF METHYL 3,3-DIMETHYL-1-(2'-HYDROXY-2'-METHYL-n-PROPYL) CYCLOPROPANE-2-CARBOXYLATE(~~XXVII~~ b)

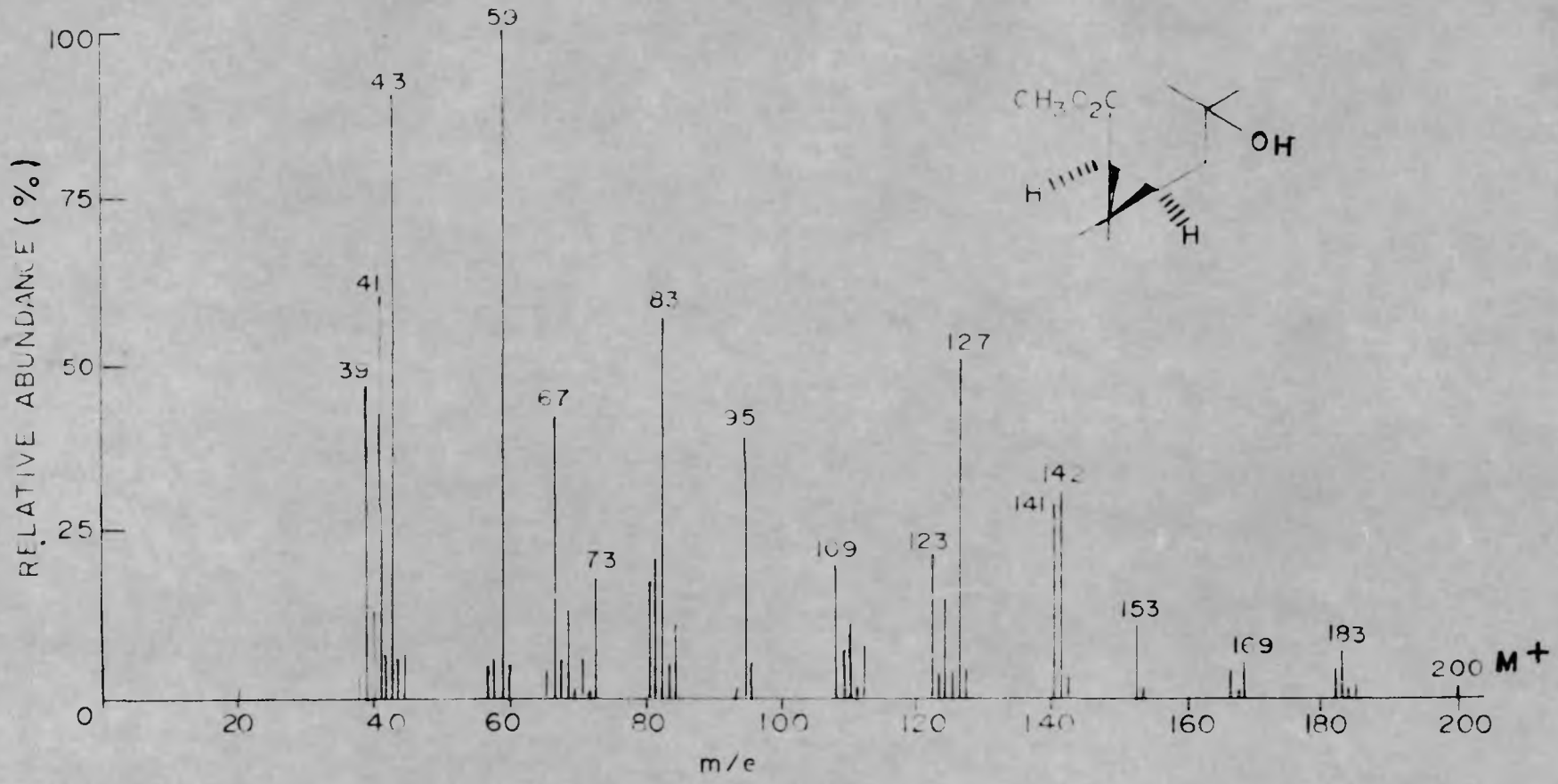


FIG 18. MASS SPECTRUM OF METHYL 3,3 DIMETHYL-1-(2'-HYDROXY-2' METHYL-n-PROPYL)-CYCLOPROPANE-2-CARBOXYLATE (XXVII b)

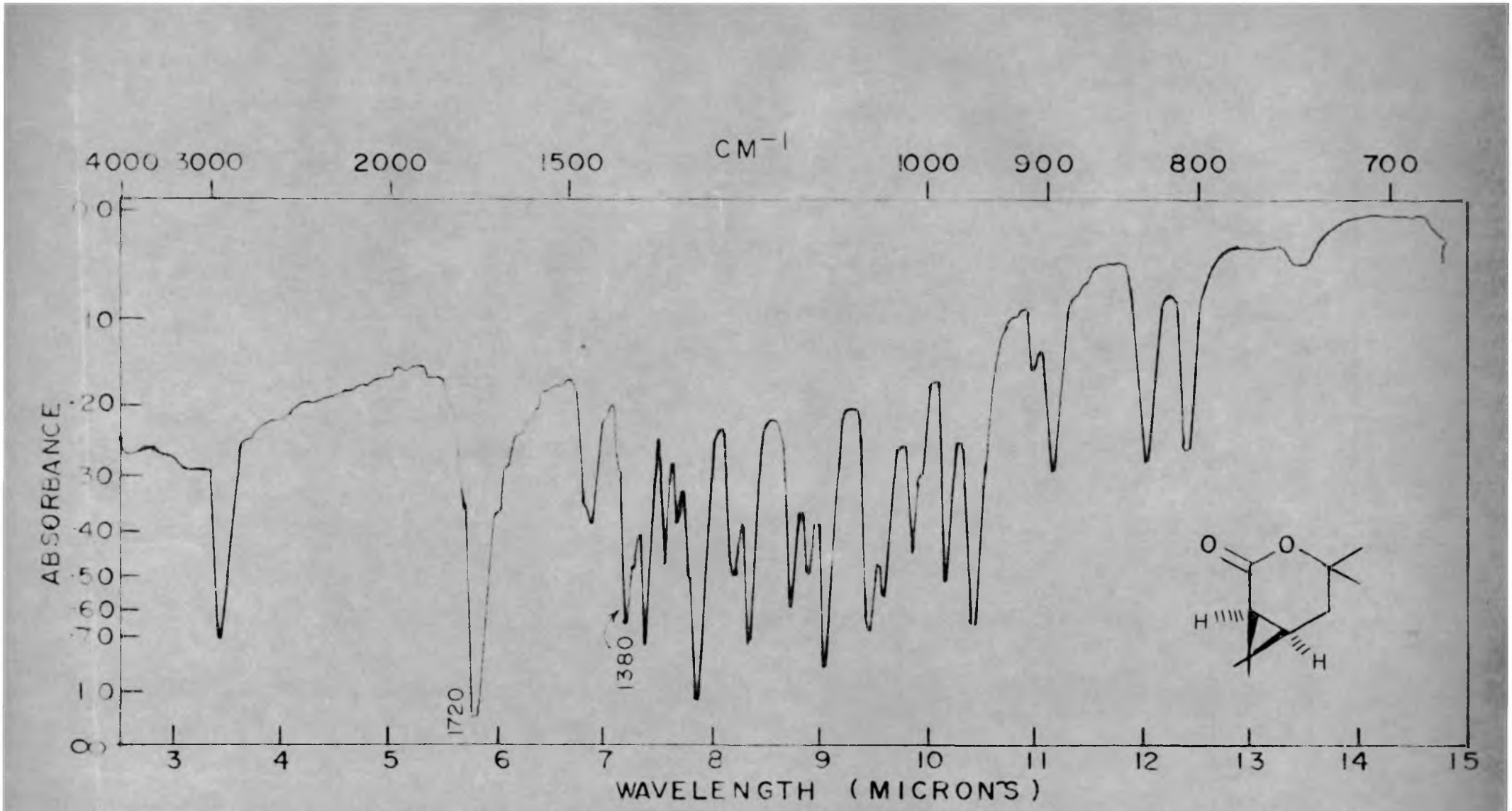


FIG 19. IR SPECTRUM OF (−) DIHYDROCHRYSANTHEMOLACTONE (XXVIII)

T5

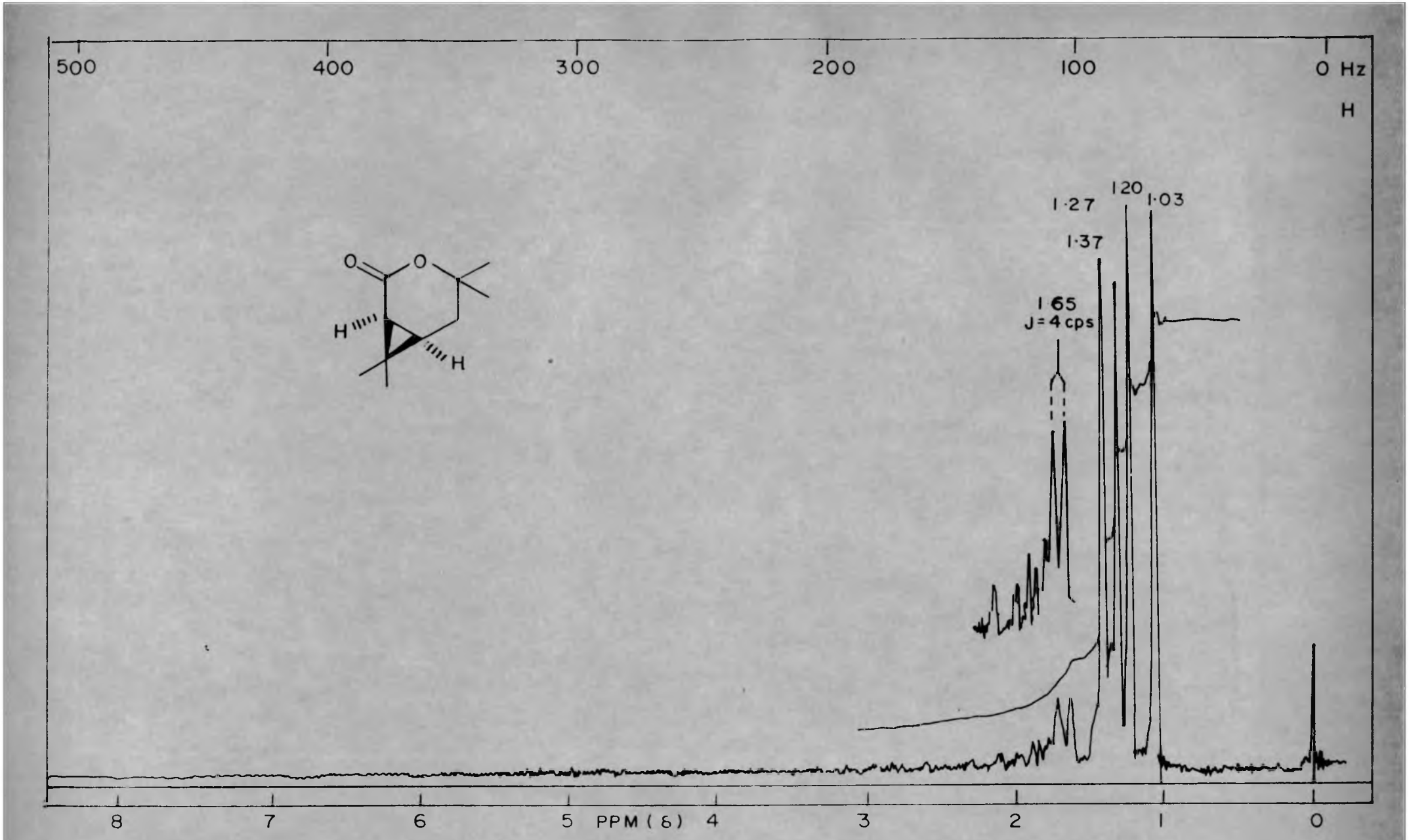


FIG. 20. NMR SPECTRUM OF (−)-DIHYDROCHRYSANTHEMOLACTONE (XXVIII)

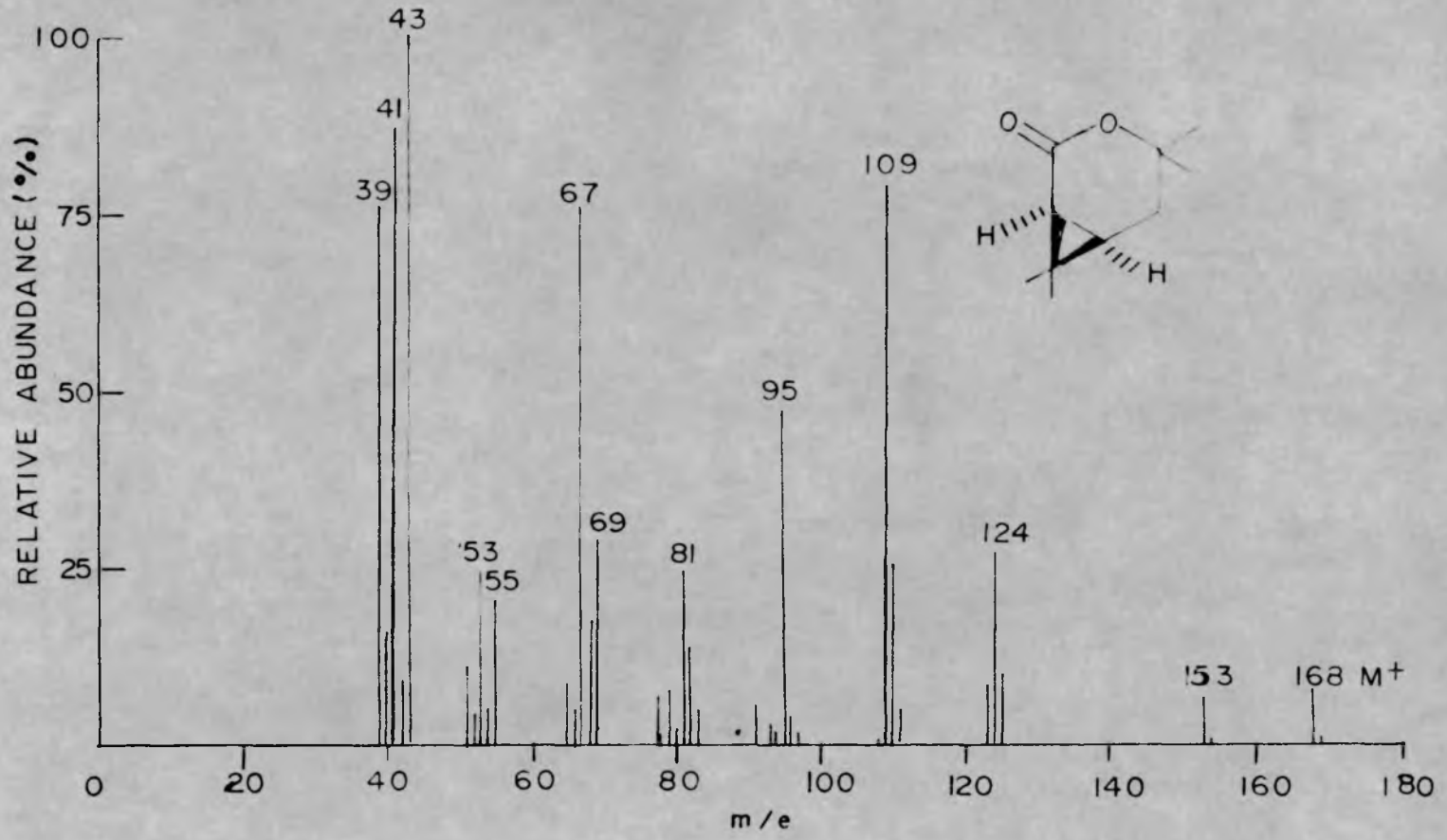


FIG. 21. MASS SPECTRUM OF (−)−DIHYDRO CHRYSANTHEMOLACTONE (XXVIII)

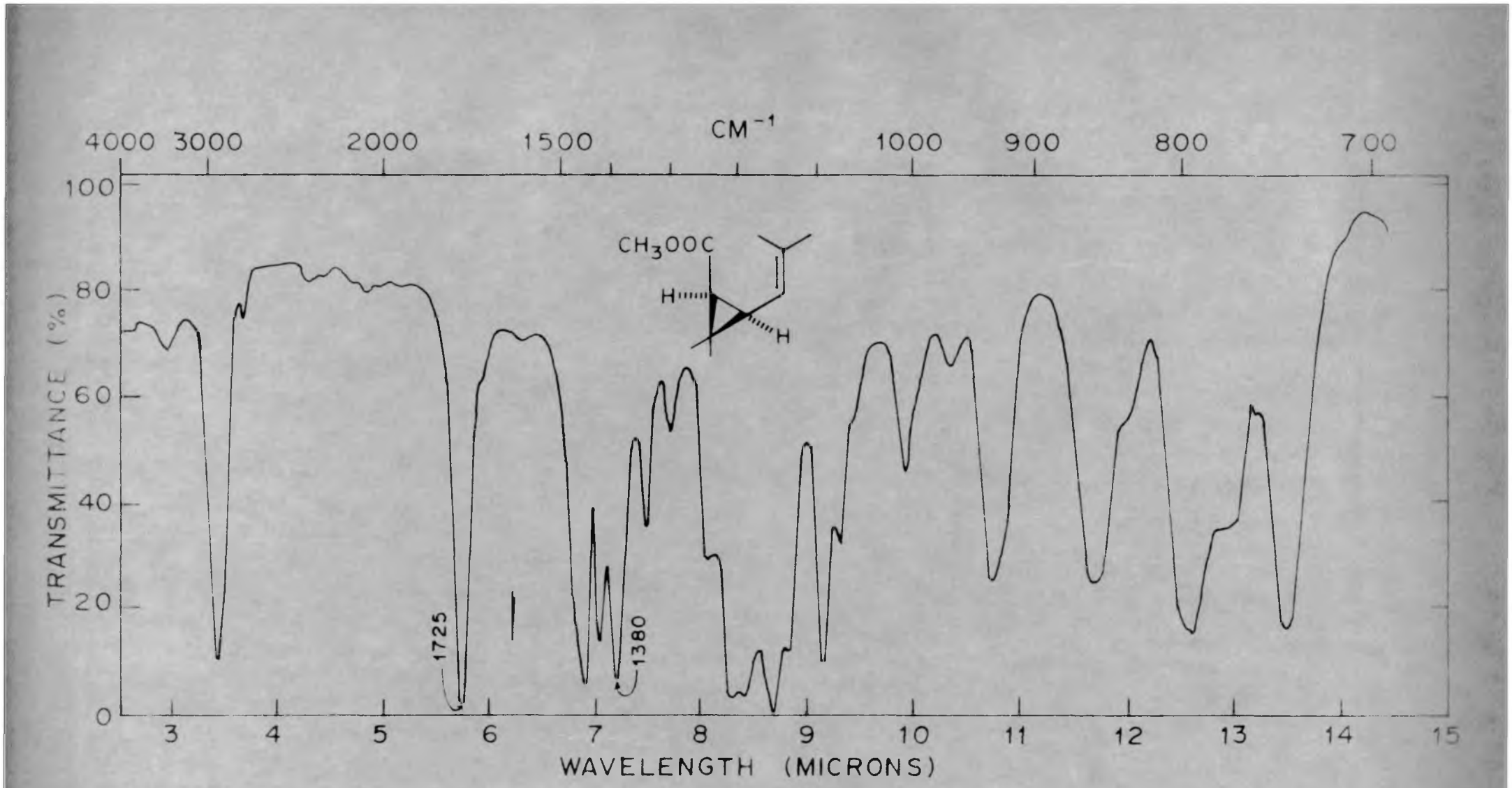


FIG. 22 IR SPECTRUM OF METHYL (-) - CIS - CHRYSANTHEMATE (XXIX)

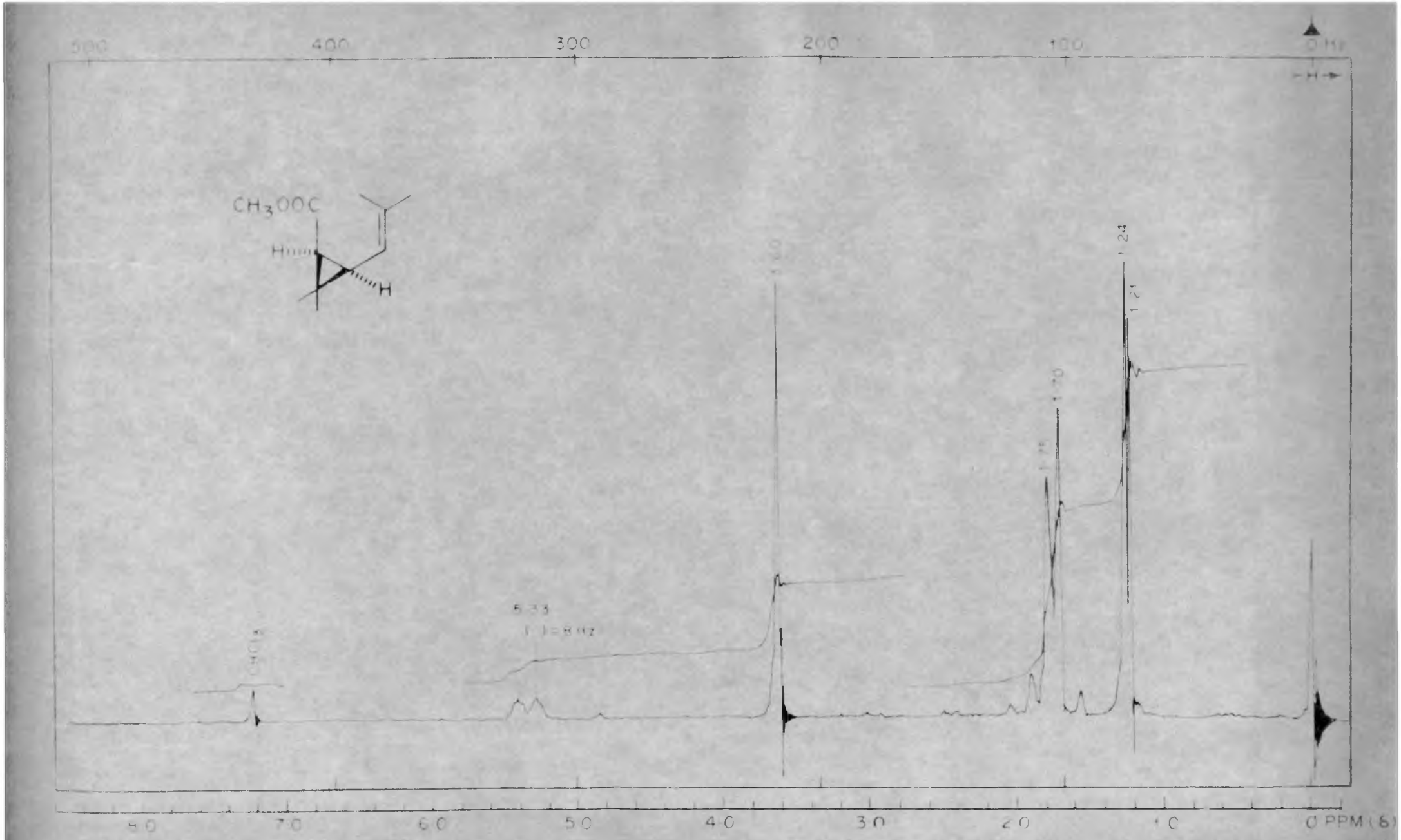


FIG 23 NMR SPECTRUM OF METHYL (-)-CIS-CHRYSANTHEMATE (XXIX)

CHAPTER III

A stereospecific synthesis of methyl (+)-trans-chrysanthemate from (+)-α-Pinene.

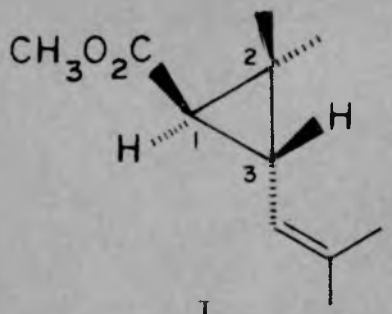
CHAPTER III

A STEREOSPECIFIC SYNTHESIS OF METHYL (+)-TRANS-CHRYSANTHEMATE FROM (+)-∝-PINENE

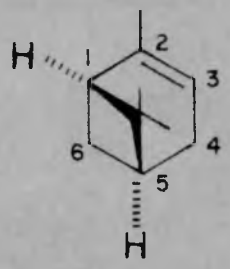
In the previous chapter we described a new synthesis of (+)-trans-chrysanthemic acid from (+)-(1 S, 6 R)-Car-3-ene (III). We now wish to describe[45] a stereospecific synthesis of the natural (+)-(1 R, 3 R)-trans-chrysanthemic acid methyl ester (I) from (+)-(1 R, 5 R)-∝-pinene (II) via. a Favorskii ring contraction of an appropriately substituted -bromocyclobutanone intermediate. The absolute configuration of I is well established[37] and a persual of the absolute structures of I, II[38] and III[39] as shown in the accompanying figures clearly indicates that the C-3 chiral centre of I has the same absolute configuration as C-5 of II and C-6 of III.

In our earlier syntheses[31,40] the C-6 of III became C-3 of I without epimerisation, thus maintaining the transition into the natural series. The present synthesis describes the conversion of C-5 of II into C-3 of I giving again the natural (+)-isomer.

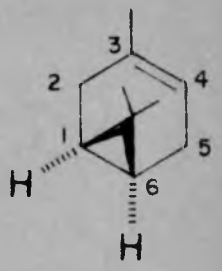
The acetoxy ester, methyl 2,2-dimethyl-3-acetoxy-cyclobutyl acetate (V), b.p. 120-5° (bath)/1.5 mm, $(\alpha)_D^{23}$ = -21.3°. (C, 1.53%, $CHCl_3$) was obtained by known methods[41]



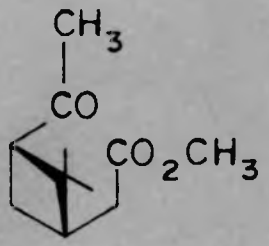
I



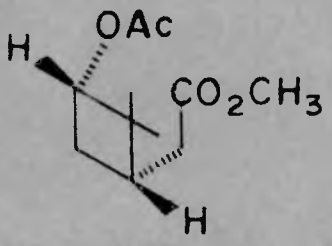
II



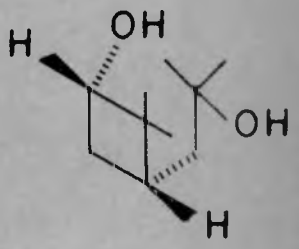
III



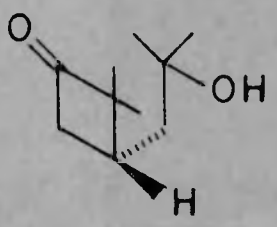
IV



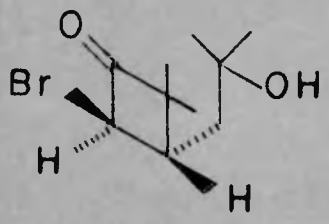
V



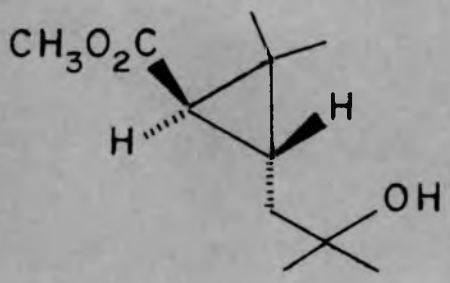
VI



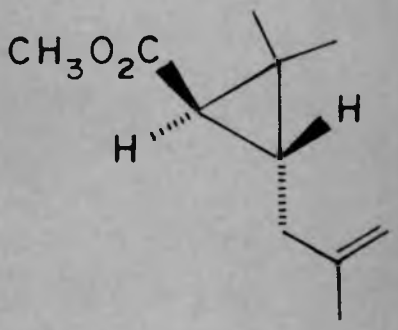
VII



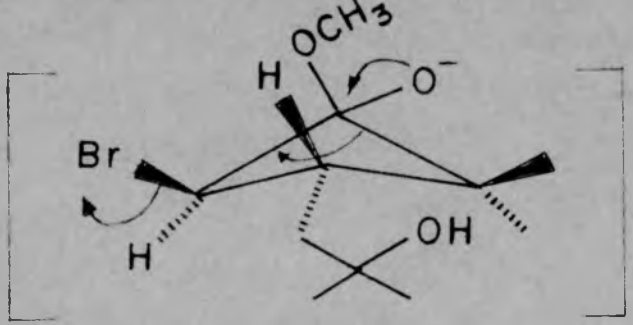
VIII



IX



X



VIII A

from II by ozonolysis, Baeyer-Villiger oxidation and esterification with diazomethane. Treatment of V with methyl magnesium iodide gave in 80% yield, the solid crystalline diol, 2,2-dimethyl-3-(2'-hydroxyisobutyl) cyclobutanol (VI), m.p. 70-72°, $(\alpha)_D^{23} = -6.9°$ (C, 1.4%, $CHCl_3$); IR : 3335 cm^{-1} (hydroxyl); NMR ($CDCl_3$), δ 0.9, 1.03 (s,s, 3H each, CH_3); 1.15 (s, 6H, $C(CH_3)_2$); 1.25 - 1.73 (m, 5H, CH_2, CH); 2.56 (2H, OH); 3.66 (m, 1H, CHOH).

Oxidation of VI with either chromium trioxide-pyridine or Jone's reagent gave the cyclobutanone derivative 2,2-dimethyl-3-(2'-hydroxyisobutyl) cyclobutanone (VII) in Ca 60% yield, b.p. 130-5° (bath)/1.5 mm; $(\alpha)_D^{23} = -24°$ (C, 2.5%, $CHCl_3$); IR : 3335 (hydroxyl); 1778 cm^{-1} (carbonyl). NMR (CCl_4) : δ 1.05, 1.15 (s,s, 3 H each, CH_3); 1.20 (s, 6H, $C(CH_3)_2$); 1.68 (d, 2H, J = 4 Hz, CH_2); 2.91 (m, 2H, $COCH_2$). Bromination[42] of VII with 1 equiv. of bromine in chloroform at room temp. for 30 min. gave the α-bromo-cyclobutanone derivative VIII as an unstable oil, IR 1785 cm^{-1}. The bromination was not very clean with some side products present due possibly to the presence of the free tertiary hydroxyl group. Crude VIII was, therefore, treated directly with powdered sodium methoxide (1 equiv.) in dry ether. The crude reaction product was chromatographed over silica gel (eluted with 1:1 mixture of pet. ether, b.p. 40-60° and chloroform) to furnish methyl 2,2-dimethyl-3-(2'-hydroxy-

isobutyl)-cyclopropane carboxylate IX, in 34% yield from VII, as a colourless liquid, b.p. 120-5° (bath)/3.5 mm, $(\alpha)_D^{21} = -10.66°$ (C, 3.75%, $CHCl_3$); IR - 3700 cm^{-1} (hydroxyl) NMR (CCl_4, δ) : 1.10 (s, 3H, CH_3); 1.13 (s, 9H, CH_3); 1.45 (d, J = 4 Hz, CH_2); 1.08 - 1.53 (2H, CH); 2.21 (bs, 1H, OH); 3.56 (s, 3H, $COOCH_3$). That IX had the carbomethoxy and hydroxybutyl side chain trans to each other was clear from a comparison of its NMR spectrum and GLC behaviour with the cis-isomer obtained from (+)-Car-3-ene (Chapter II). GLC of crude IX before chromatographic purification, showed no trace of the cis-isomer (with 5% carbowax 4000 on chromosorb at 180° and H_2 flow rate 70 ml/min IX has a retention time of 5.30 min whereas the cis-isomer elutes at 4.67 min.).

Since the semi-benzillic Favorskii ring contraction of α-bromo-cyclobutanones is known to proceed stereospecifically[43] via a reaction path way depicted in VIII-A the fact that only the trans-isomer IX was formed shows that bromination of VII was also stereospecific leading to the absolute configuration VIII. This was expected since Dreiding models show that the bulky tertiary hydroxybutyl side chain effectively blocks one side of the cyclobutanone ring in VII resulting in a steric preference of approach of the bromonium ion from the opposite side.

Finally, dehydration of IX with phosphorousoxychloride

in pyridine at 0° gave a 3:1 mixture of I and its exo-double bond isomer, methyl 2,2-dimethyl-3-(2'-methyl-2'-propenyl) cyclopropane carboxylate (X). The mixture was separated by chromatography over silver nitrate silica gel (1:6) (elution with 3:1 mixture of pet. ether, b.p. 40-60° and chloroform) to furnish pure-I, in 66% yield from IX, b.p. 95-100° (bath)/7 mm; $(\alpha)_D^{21}$ = +11.2° (C, 1.97%, $CHCl_3$) (Lit.[32] $(\alpha)_D^{27}$ = +13.27° (C, 3.13%, $CHCl_3$)). The product when compared with an authentic dl-trans-chrysanthemic acid methyl ester[44] gave superimposable NMR spectrum which fully agreed with the spectrum reported in literature[36] and had identical retention times in GLC (with 5% QF-1 on chromosorb at 86°, H_2 flow rate 60 ml/min; I and authentic dl-trans-isomer had retention time of 6.11 min., whereas authentic dl-cis-trans isomer[44] had retention time of 5.13 min.). No trace of the cis-isomer was found in I.

Experimental procedure :

Methyl (+)-pinonate (IV) :

(+)-α-Pinene (15 g) was dissolved in dry ethyl acetate (75 ml), cooled to -10° and treated with a stream of ozonized oxygen at the rate of 1.2 g of ozone per hr. till no more ozone was absorbed. The solvent was distilled off under reduced pressure and the crude ozonide taken in acetone (25 ml), cooled to 0° and slowly treated with Jone's

reagent (50 ml). The reaction mixture was allowed to stand at room temperature for 1 hr, then diluted with ice-water (150 ml) and extracted with ether. The keto-acid was separated from the ethereal solution in the form of its K-salt by extraction with aq. K_2CO_3 (15%, 150 ml). The aq. portion was acidified with cold dil. HCl and extracted with ether which was washed thoroughly with cold water, brine and dried. Ether was evaporated to get the keto-acid, which was esterified with diazomethane and then distilled to get the pure methyl pinonate (12.8 g, 58%), b.p. 120°/2.5 mm. $(\alpha)_D^{23}$ = +34.3° (C, 1.1%, $CHCl_3$). (Found : C, 66.53; H, 9.01. $C_{11}H_{18}O_3$ requires C, 66.64; H, 9.15%). ν_{max} 2900, 1720, 1685, 1425, 1015, 960, 885 cm^{-1}. NMR (CCl_4, δ) : 0.8 and 1.3 (3H each, s,s, $C(CH_3)_2$); 1.93 (3H, s, $COCH_3$); 2.23 (2H, d, J = 2 Hz, CH_2 protons adjacent to $COOCH_3$); 3.56 (3H, s, $COOCH_3$).

Methyl (-)-2,2-dimethyl-3-acetoxy cyclobutyl acetate (V) :

Methyl (+)-pinonate (15 g, 0.075 mole) was mixed with moist chloroform solution (125 ml) of perbenzoic acid (approx. 13.6 g, 0.1 mole) and the resulting solution was allowed to stand in dark at room temperature for 10 days with occational swirling. Free acid was removed from the chloroform solution by extraction with aq. K_2CO_3 (10%, 200 ml). The organic layer was then washed with water and dried ($MgSO_4$). Chloroform was distilled out from the solution and the residue was chromatographed through silica gel. The

acetate V was obtained (13.6 g, 84%) by eluting with a mixture of pet. ether (40-60°) and chloroform (3:2) and then distilled as colourless liquid, b.p. 120-5° (bath)/ 1.5 mm. $(\alpha)_D^{23}$ = -21.3° (C, 1.53%, $CHCl_3$). (Found : C, 61.57; H, 8.40; $C_{11}H_{18}O_4$ requires C, 61.66; H, 8.47%). ν_{max} 2900, 1736, 1437, 1370, 1234, 1045 cm^{-1}. NMR (CCl_4, δ) : 0.9 and 1.15 (3H each, s,s, $C(CH_3)_2$); 1.95 (3H, s, OAc); 2.21 (2H, m, CH_2 adjacent to $COOCH_3$); 3.56 (3H, s, $COOCH_3$); 4.53 (1H, m, $CHOAc$).

<u>2,2-Dimethyl-3-(2'-hydroxyisobutyl) cyclobutanol (VI)</u> :

To a stirred solution of methyl magnesium iodide (prepared from 28.4 g, 0.2 mole of methyl iodide and 5 g, 0.2 mole of activated magnesium) in dry ether (225 ml) was added dropwise a solution of the acetate V (10.7 g, 0.05 mole) in dry ether (50 ml) during 30 min. maintaining nitrogen atmosphere throughout the reaction. After stirring the mixture for 1 hr at room temperature, it was refluxed for half an hr, cooled and decomposed by pouring into an ice-cold saturated NH_4Cl (150 ml) and the resulting solution was extracted with ether (3 x 50 ml). The residue after removal of ether was chromatographed over silica-gel. By eluting with a mixture of pet. ether (40-60°) and chloroform (1:1) the diol VI was obtained as a colourless crystalline solid (6.9 g, 80%) which was recrystallized from pet. ether (40-60°), m.p. 70-72°, $(\alpha)_D^{23}$ = -6.9°

(C, 1.4%, $CHCl_3$) (Found : C, 69.68; H, 11.63. $C_{10}H_{20}O_2$ requires C, 69.72; H, 11.70%). m/e, 155 (M^+ - OH); 138 (M^+ - 2OH); ν_{max} 3335, 2900, 1465, 1375, 1138, 1065, 920 cm^{-1}; NMR ($CHCl_3$, δ) : 0.9 and 1.03 (3H each, s,s, CH_3 protons); 1.15 (6H, s, $C(CH_3)_2$); 1.25 - 1.73 (5H, m, CH_2,CH); 2.56 (2H, OH protons); 3.66 (1H, $C\underline{H}OH$).

2.2-Dimethyl-3-(2'-hydroxyisobutyl) cyclobutanone (VII) :

Anhydrous chromium trioxide (3 g, 0.03 mole) was added to a stirred solution of dry pyridine (4.74 g, 0.06 mole) in CH_2Cl_2 (75 ml). The deep burgandy solution was stirred for 30 min at room temperature, and a solution of the diol (VI, 1.72 g, 0.01 mole) in CH_2Cl_2 (5 ml) was added in one portion. Stirring was continued for 3 hr at room temperature and the solution decanted from the tarry black residue which was washed with ether (100 ml). The decanted CH_2Cl_2 solution was concentrated in vacuo; the residue taken up in ether and the combined ether solutions was washed successively with water, cold dil. HCl, aq. $NaHCO_3$ and finally with brine and dried (Na_2SO_4). The residue after removal of ether was chromatographed over silica gel. By eluting with a mixture of pet. ether (40-60°) and chloroform (7:3) the hydroxy-ketone VII (1.01 g, 60%) was obtained as a colourless liquid, b.p. 130-5° (bath)/1.5 mm. $(\alpha)_D^{23}$ = -24° (C, 2.5%, $CHCl_3$) (Found : C, 70.51; H, 10.58; $C_{10}H_{18}O_2$ requires C, 70.54; H, 10.66%).

ν_{max} 3336, 2850, 1778, 1465, 1375, 1165, 1065, 910 cm^{-1}.
NMR (CCl_4, δ) : 1.05 and 1.15 (3H each, CH_3 protons); 2.91 (2H, m, $COCH_2$); 1.20 [6H, $C(CH_3)_2$]; 1.68 (2H, d, J=4Hz, CH_2).

2,2-Dimethyl-3-(2'-hydroxyisobutyl)-4-bromocyclobutanone (VIII) :

To a stirred solution of the hydroxy-ketone VII (0.85 g, 0.005 mole) in dry $CHCl_3$ (15 ml) was added drop wise a solution of dry bromine (0.82 g, 0.005 mole) in $CHCl_3$ (5 ml) during 15 min at room temperature. Stirring was continued for another 30 min when bromine colour disappeared. The $CHCl_3$-solution was washed thoroughly with ice-cold water and dried (Na_2SO_4). Chloroform was distilled out in vacuo and the residue (0.86 g, corresponding infrared absorption at 1785 cm^{-1}, cyclobutanone) was used directly for the next reaction.

Methyl trans-2,2-dimethyl-3-(2'-hydroxyisobutyl) cyclopropanecarboxylate (IX) :

A solution of the bromo compound VIII (0.61 g) in dry ether (5 ml) was added to a stirred suspension of dry sodium methoxide (0.2 g) in dry ether (25 ml). After stirring for 1.5 hr, water was added to the reaction mixture and extracted with ether. The ether solution was washed throughly with water, brine and dried (Na_2SO_4). Ether was evaporated from the solution and the residue was chromatographed over silica gel. By eluting with a mixture of pet. ether (40-60°) and chloroform (1:1) the hydroxy-

ester VIII was obtained (0.16 g, 34%), colourless liquid, b.p. 120-5°(bath)/3.5 mm. $(\alpha)_D^{21}$ = -10.66° (C, 3.75%, $CHCl_3$); (Found : C, 65.94; H, 9.98. $C_{11}H_{20}O_3$ requires C, 65.97; H, 10.07%). m/e, 185 (M^+-CH_3); 182 (M^+-H_2O); 123 ($M^+-H_2O-COOCH_3$); (Mol. wt. 200.27). ν_{max} 3700, 3000, 1725, 1440, 1380, 1280, 1170, 1115, 855 cm^{-1}. NMR (CCl_4, δ) : 1.10 (3H, s, CH_3); 1.13 (9H, s, CH_3 protons); 1.45 (2H, d, J = 4 Hz, CH_2 proton); 1.08 - 1.53 (2H, CH); 2.21 (1H, OH); 3.56 (3H, s, $COOCH_3$).

Methyl (+)-trans-chrysanthemate :

The hydroxy-ester IX (0.27 g) in pyridine (1.6 ml) was treated with $POCl_3$ (0.41 g) at 0°. The reaction mixture was left overnight at 0°, poured into ice-cold water, worked up in usual manner and chromatographed over $AgNO_3$-silica gel (1:6). By eluting with a mixture of pet. ether (40-60°) and chloroform (3:1) pure methyl (+)-trans-chrysanthemate (0.16 g, 66%) was obtained as a colourless liquid, b.p. 95-100°(bath)/7 mm. $(\alpha)_D^{21}$ = +11.2° (C, 1.97%, $CHCl_3$); (Lit.[32] - $(\alpha)_D^{27}$ = +13.27° (C, 3.18%)). (Found : C, 72.47; H, 9.93; M^+ 182. $C_{11}H_{18}O_2$ requires C, 72.49; H, 9.96%; Mol. wt. 182.25). ν_{max} 1730 cm^{-1} ($COOCH_3$). NMR (CCl_4, δ) : 1.12 and 1.23 (3H each, s,s, $C(CH_3)_2$); 1.32 (1H, cyclopropyl proton); 1.70 (6H, s, $C=C(CH_3)_2$); 1.95 (1H, d,d, cyclopropyl proton); 3.60 (3H, s, $COOCH_3$); 4.23 (1H, dm, C = CH).

Gas liquid chromatographic analysis of -

1) Methyl (+)-pinonate (A) and methyl 2,2-dimethyl-3-acetoxy-cyclobutyl acetate (B) obtained from (+)-α-Pinene (Fig.36);

2) Cis (C) and trans (D) -isomers of methyl 2,2-dimethyl -3-(2'-hydroxyisobutyl) cyclopropane-carboxylate obtained from (+)-car-3-ene and from (+)-α-pinene respectively (Fig. 37); and

3) Cis (E) and trans (F) isomers of (±)-methyl chrysanthemate (authentic samples) and the (+)-trans-methyl chrysanthemate obtained from (+)-α- pinene (Fig. 38) -

were carried out under the following parameters of the instruments :

AIMIL-NCL Dual Column Gas Chromatograph

S. No.70020

	Parameters	For compounds A & B	For compounds C & D	For compounds E & F
i)	Column length	6'	6'	6'
ii)	Wt. of the substrate	QF-1 0.35 gm	Carbowax 0.70 gm	QF-1 0.35 gm
iii)	Carrier gas (H_2) flow rate	70 ml/min	70 ml/min	60 ml/min.
iv)	Temp. of the column	130°	180°	86°
v)	Temp. of injection block.	160°	200°	180°
vi)	Temp. of detector	250°	250°	300°
vii)	Inlet pressure	5 lbs.	10 lbs.	-

	Parameters	For compounds A & B	For compounds C & D	For compounds E & F
viii)	Bridge current (in mA)	140	140	140
ix)	Attenuation	4	4	2
x)	Sample size (μl)	1.0 to 3.0	1.0 to 3.0	1.0 to 3.0
xi)	Chart speed	1200 mm/hr	600 mm/hr	457 mm/hr

Retention times were recorded in the usual manner and the data for the above compounds are as follows :

Retention time Tr (min)	Compounds					
	A	B	C	D	E	F
	Fig. 36		Fig. 37		Fig. 38	
	2.15	1.45	4.67	5.3	5.13	6.11

Acknowledgement :

We thank Dr. H. Yoshioka of Sumitomo Chemical Co., Japan, for authentic samples of dl-*cis* and dl-*trans*-chrysanthemic acid and their IR and NMR spectra.

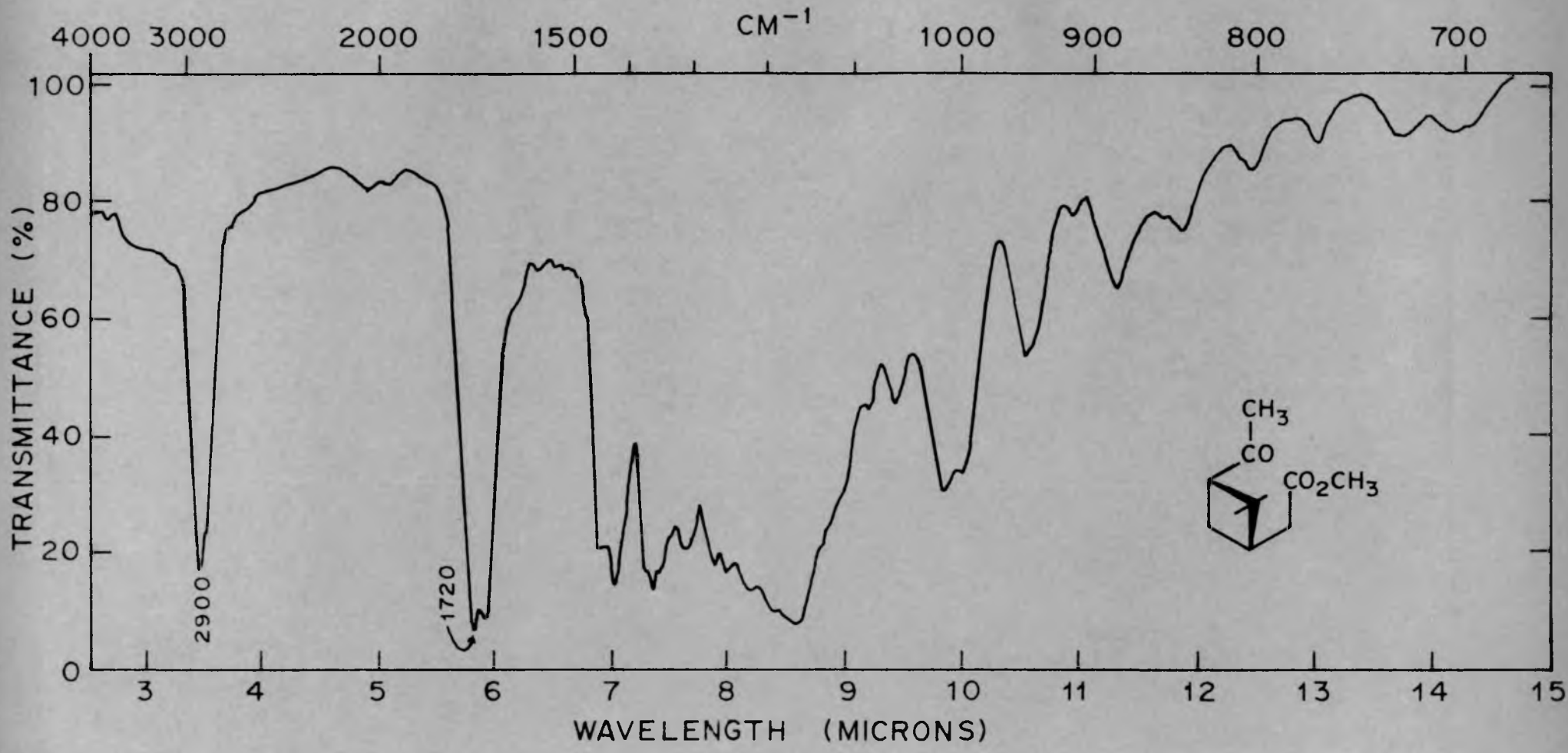


FIG. 24. IR SPECTRUM OF METHYL (+)-PINONATE (IV)

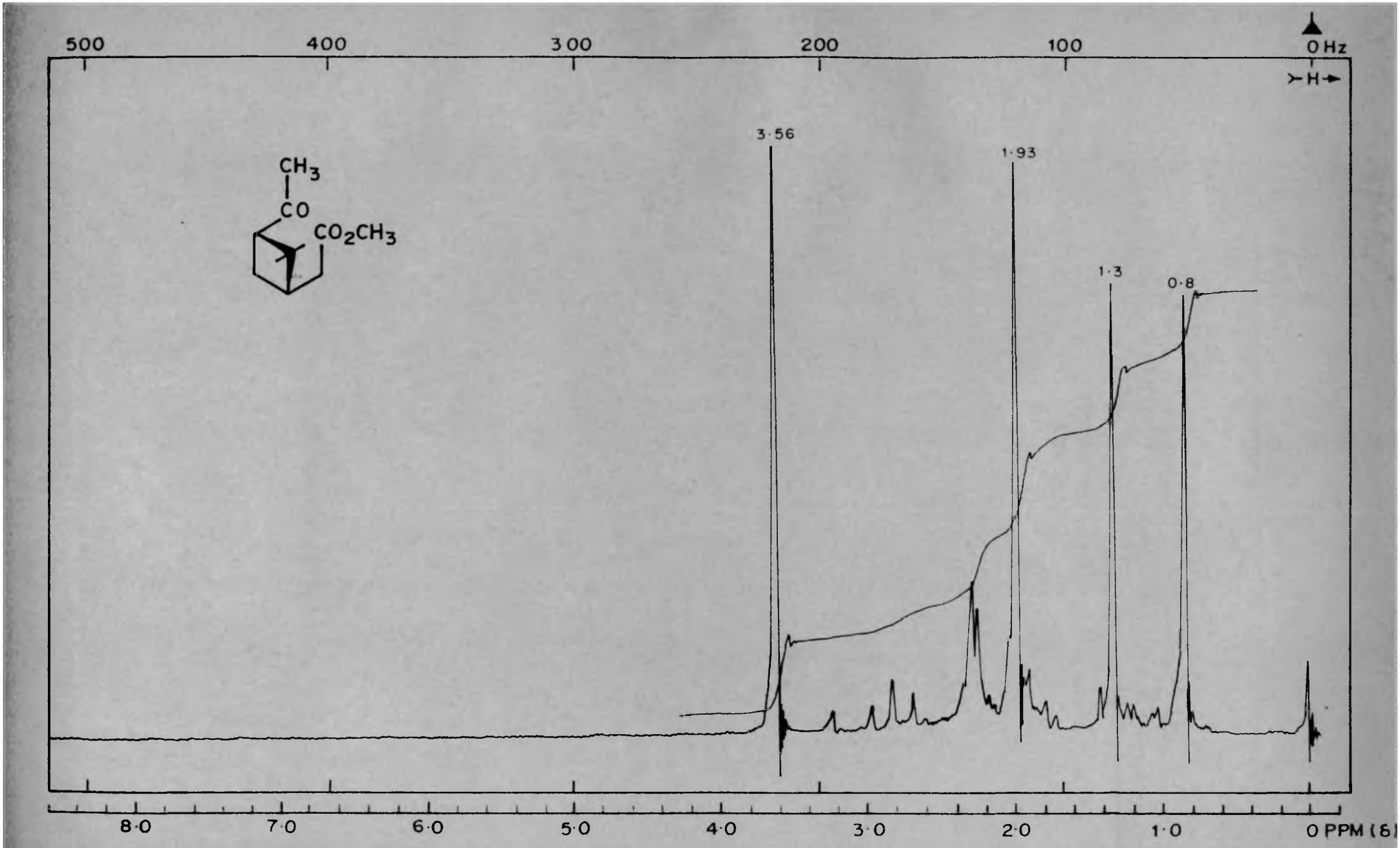


FIG. 25. NMR SPECTRUM OF METHYL (+)– PINONATE (IV)

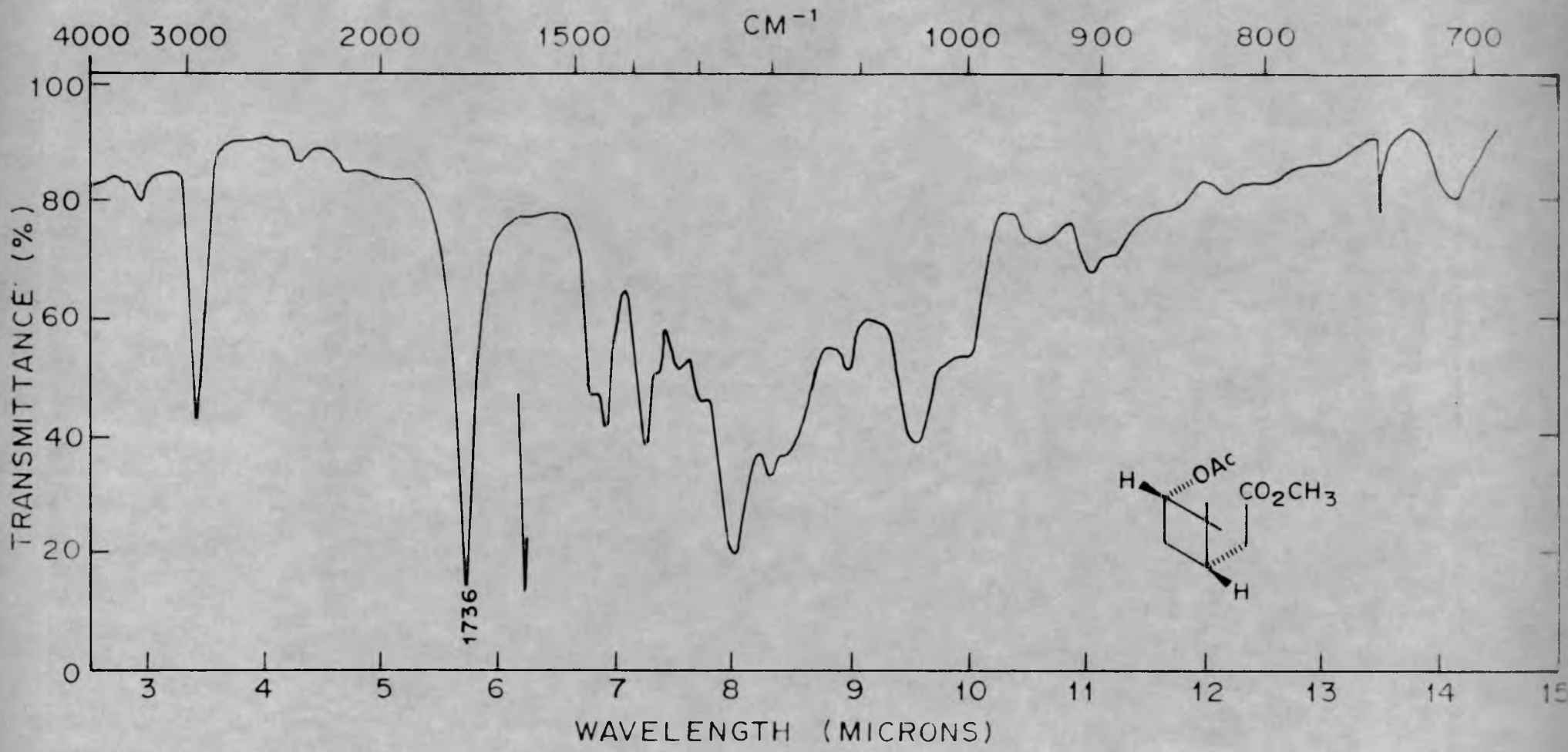


FIG. 26. IR SPECTRUM OF METHYL (−) 2,2-DIMETHYL-3-ACETOXY-CYCLOBUTYL ACETATE (V)

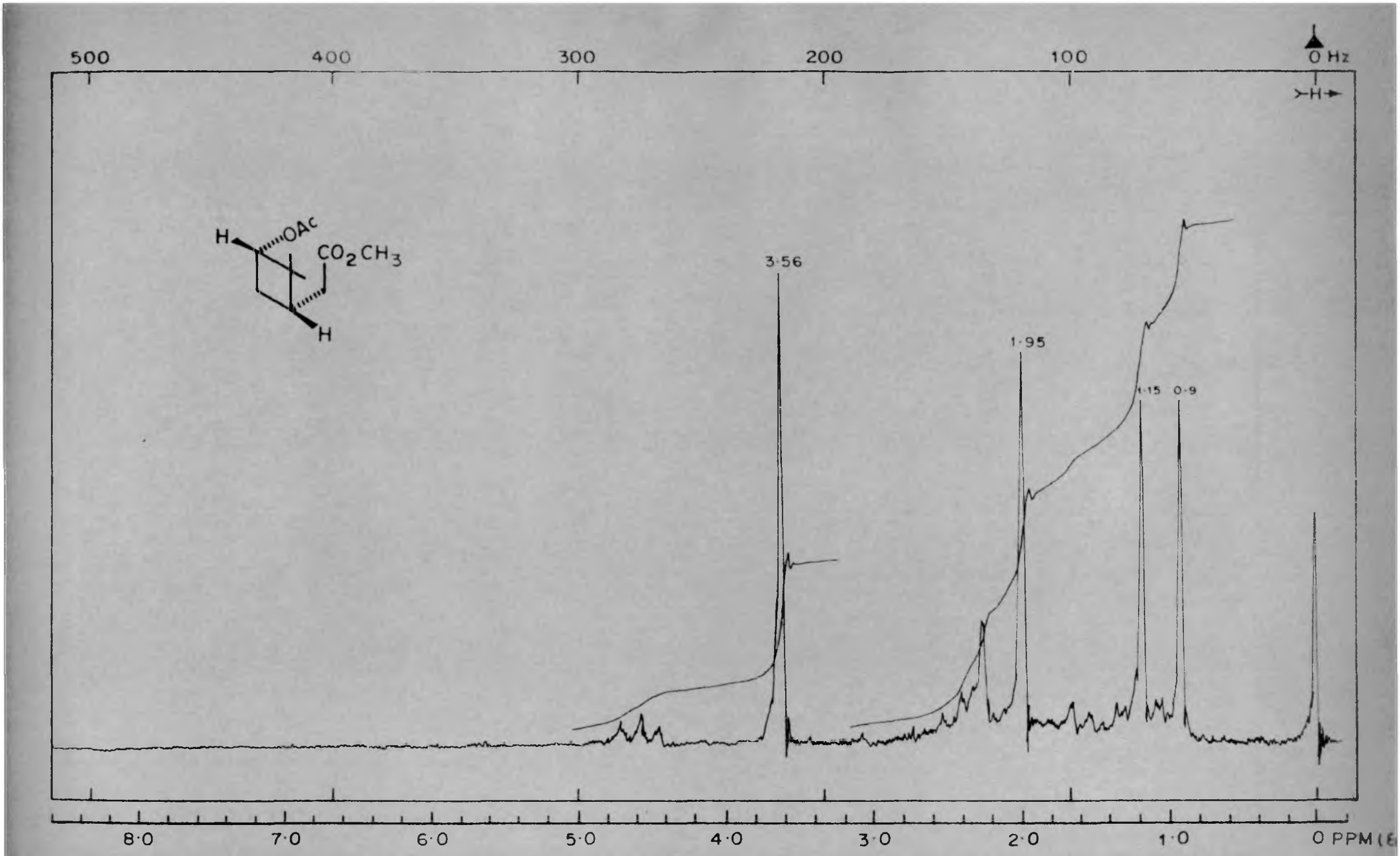


FIG. 27. NMR SPECTRUM OF METHYL (−) 2,2-DIMETHYL-3-ACETOXY-CYCLOBUTYL ACETATE (V)

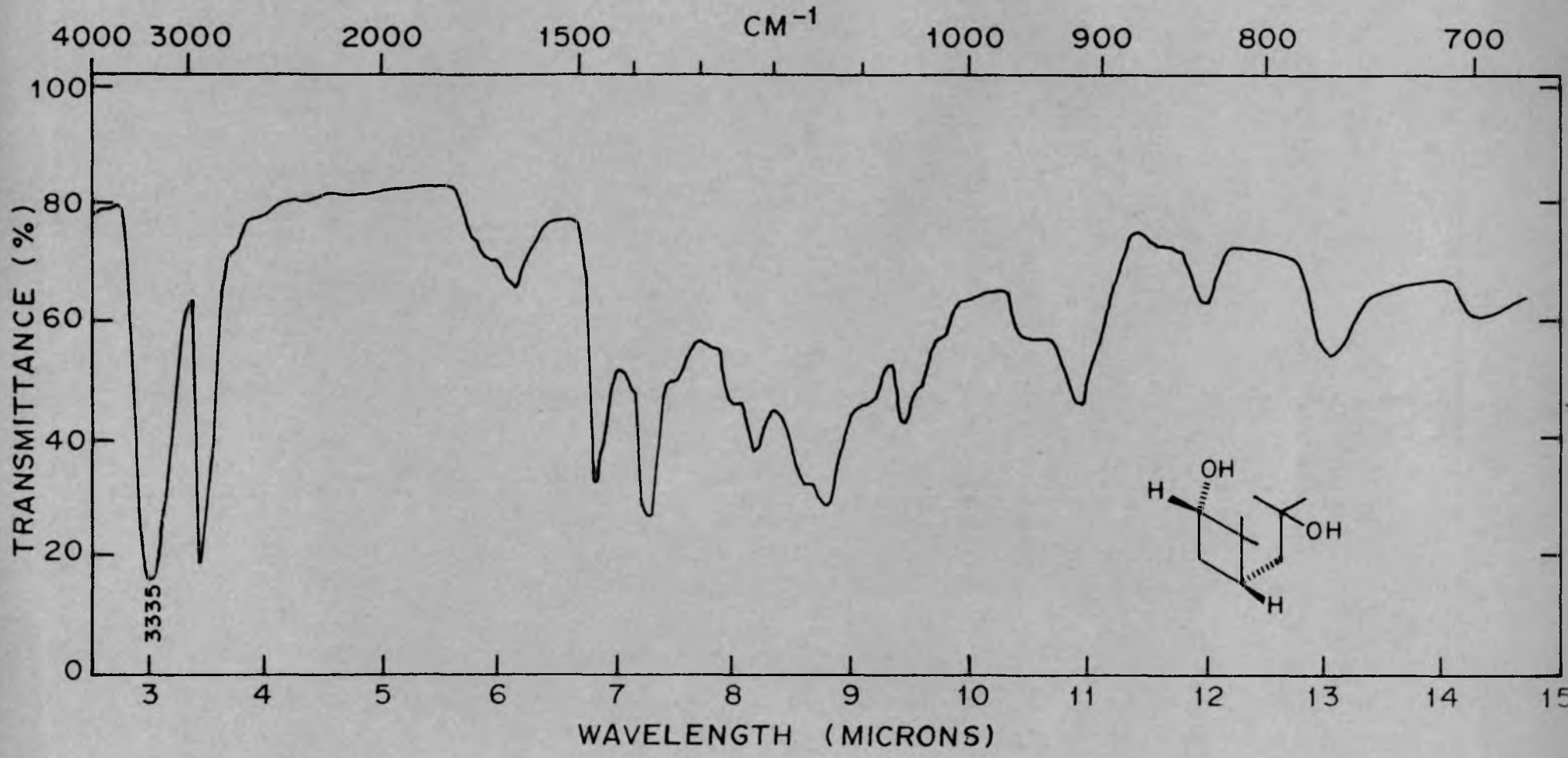


FIG. 28. IR SPECTRUM OF 2,2-DIMETHYL-3-(2'-HYDROXYISOBUTYL) CYCLOBUTANOL (VI)

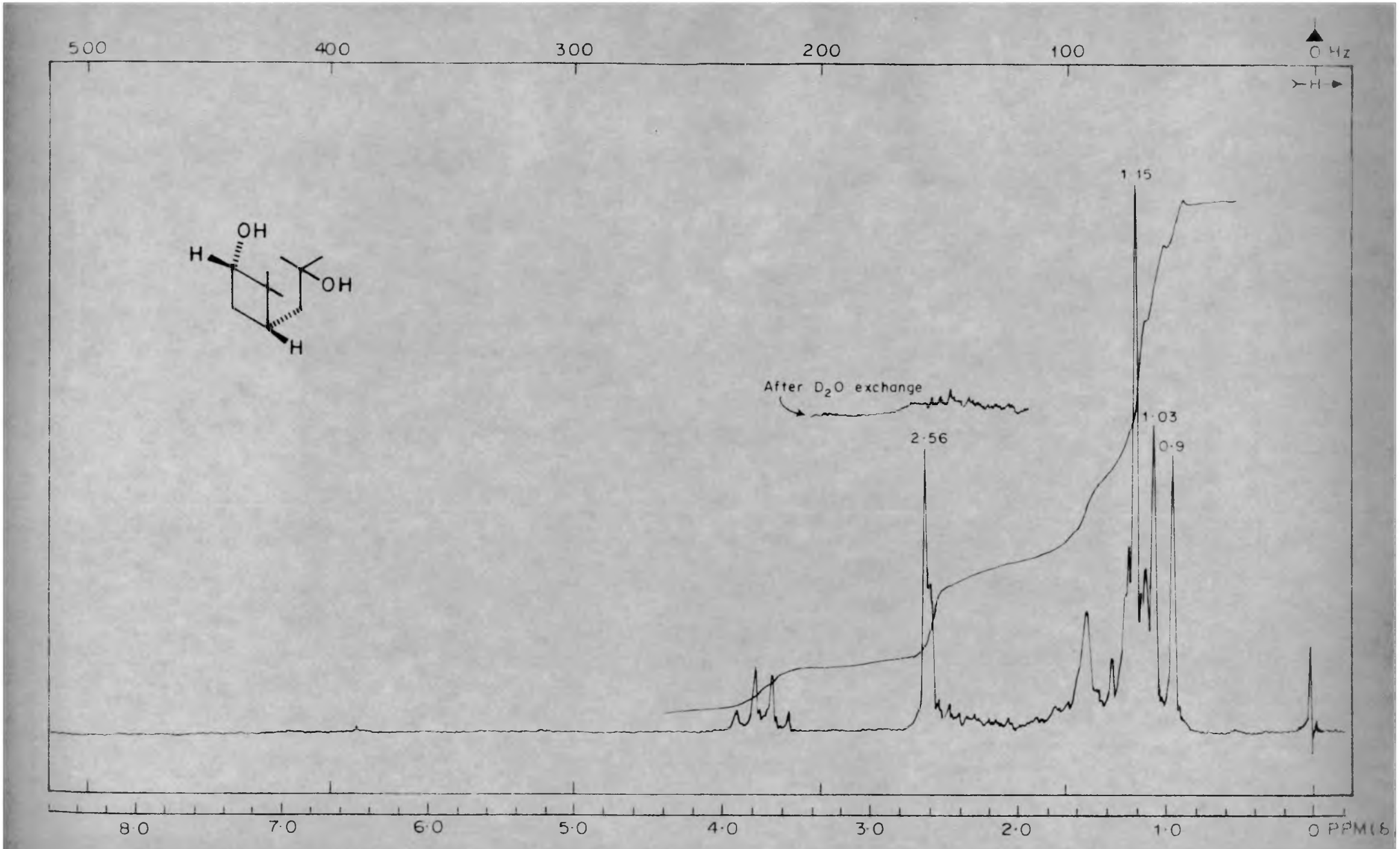


FIG. 29. NMR SPECTRUM OF 2,2-DIMETHYL-3-(2'-HYDROXYISOBUTYL) CYCLOBUTANOL (VI)

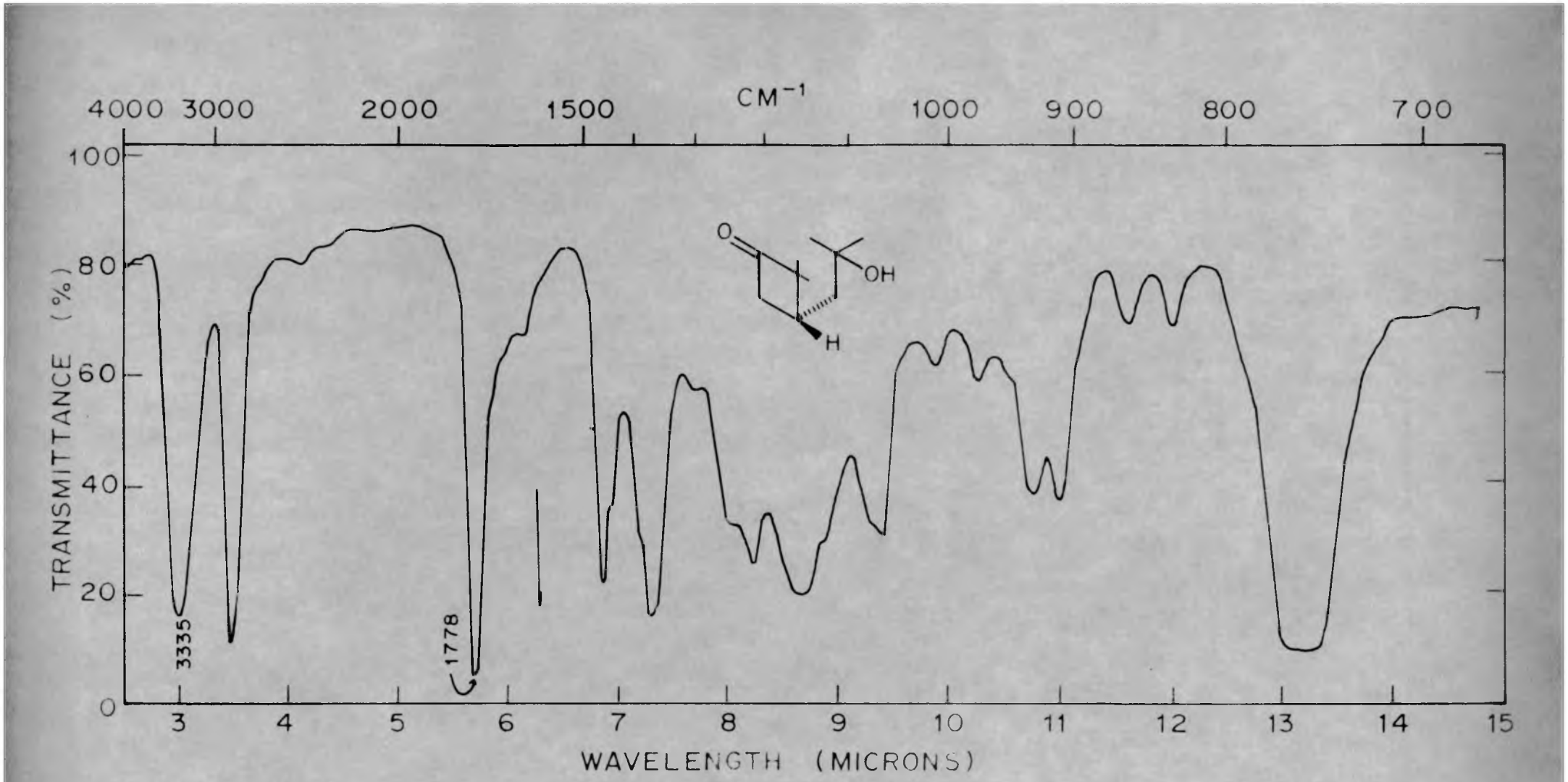


FIG. 30. IR SPECTRUM OF 2,2-DIMETHYL-3-(2'-HYDROXYISOBUTYL) CYCLOBUTANONE (VII)

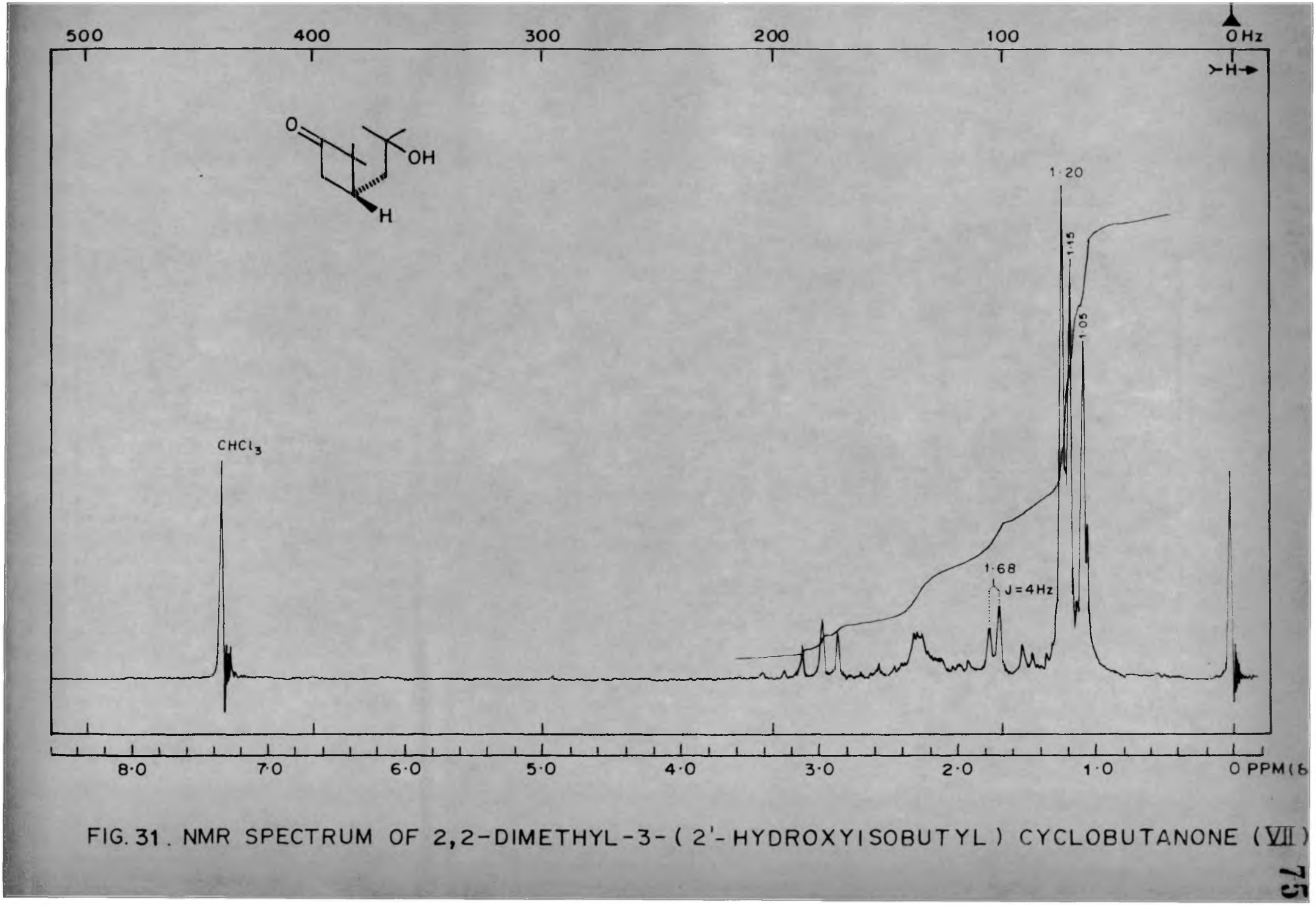


FIG. 31. NMR SPECTRUM OF 2,2-DIMETHYL-3-(2'-HYDROXYISOBUTYL) CYCLOBUTANONE (VII)

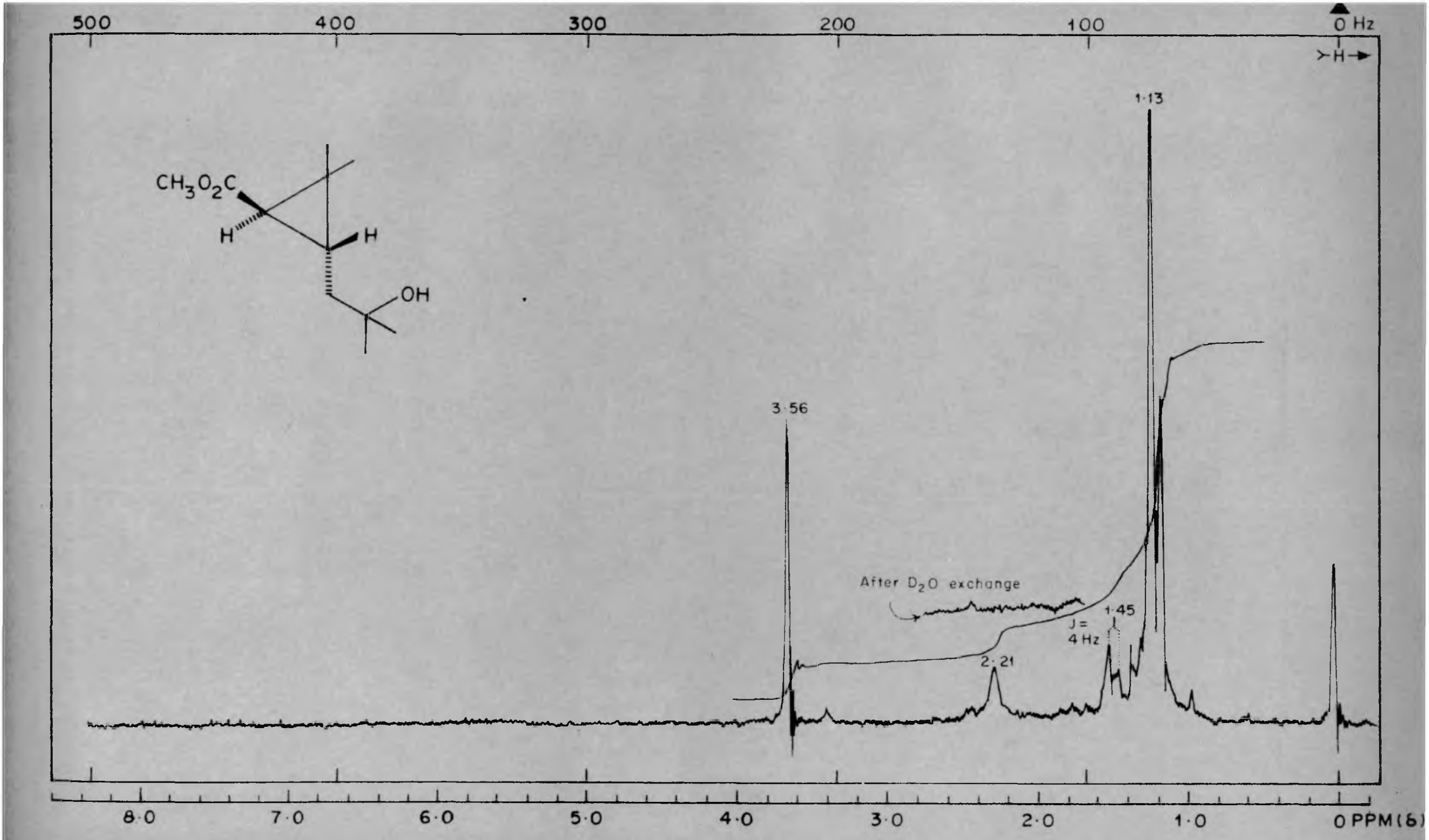


FIG. 32. NMR SPECTRUM OF METHYL 2,2-DIMETHYL-3-(2'-HYDROXYISOBUTYL) CYCLOPROPANECARBOXYLATE (IX)

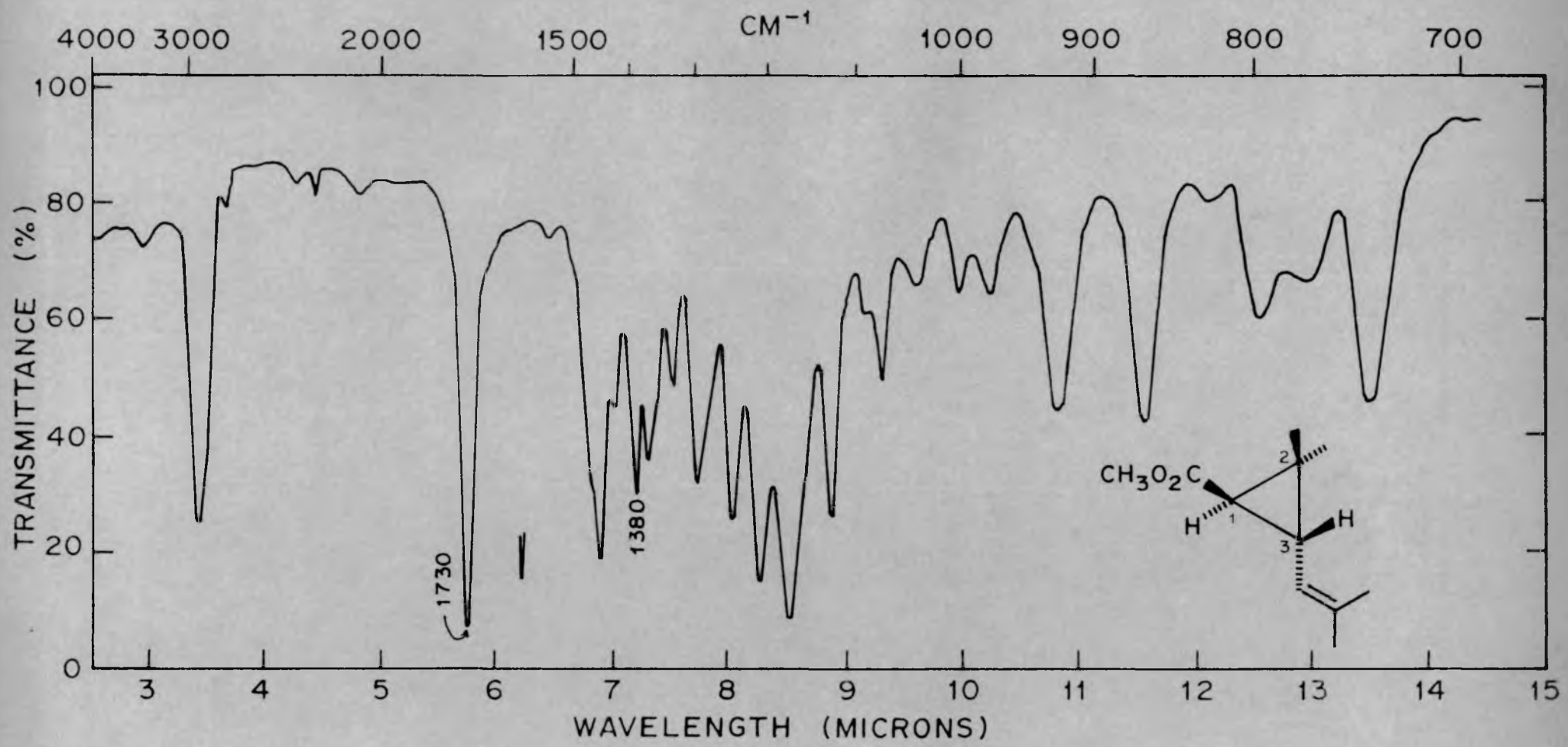


FIG. 33. IR SPECTRUM OF METHYL (+)-TRANS-CHRYSANTHEMATE (I)

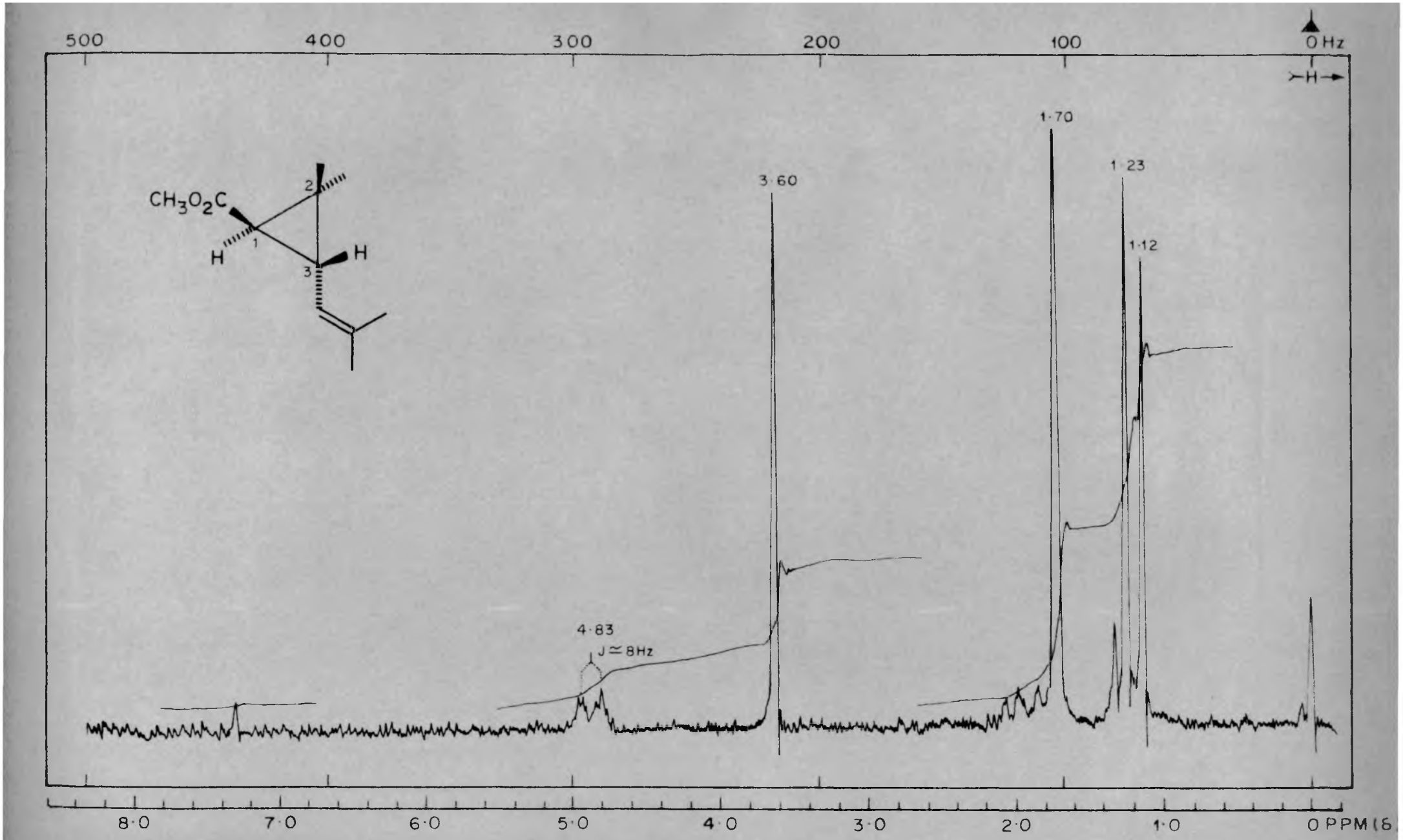


FIG. 34. NMR SPECTRUM OF METHYL (+) TRANS-CHRYSANTHEMATE (I)

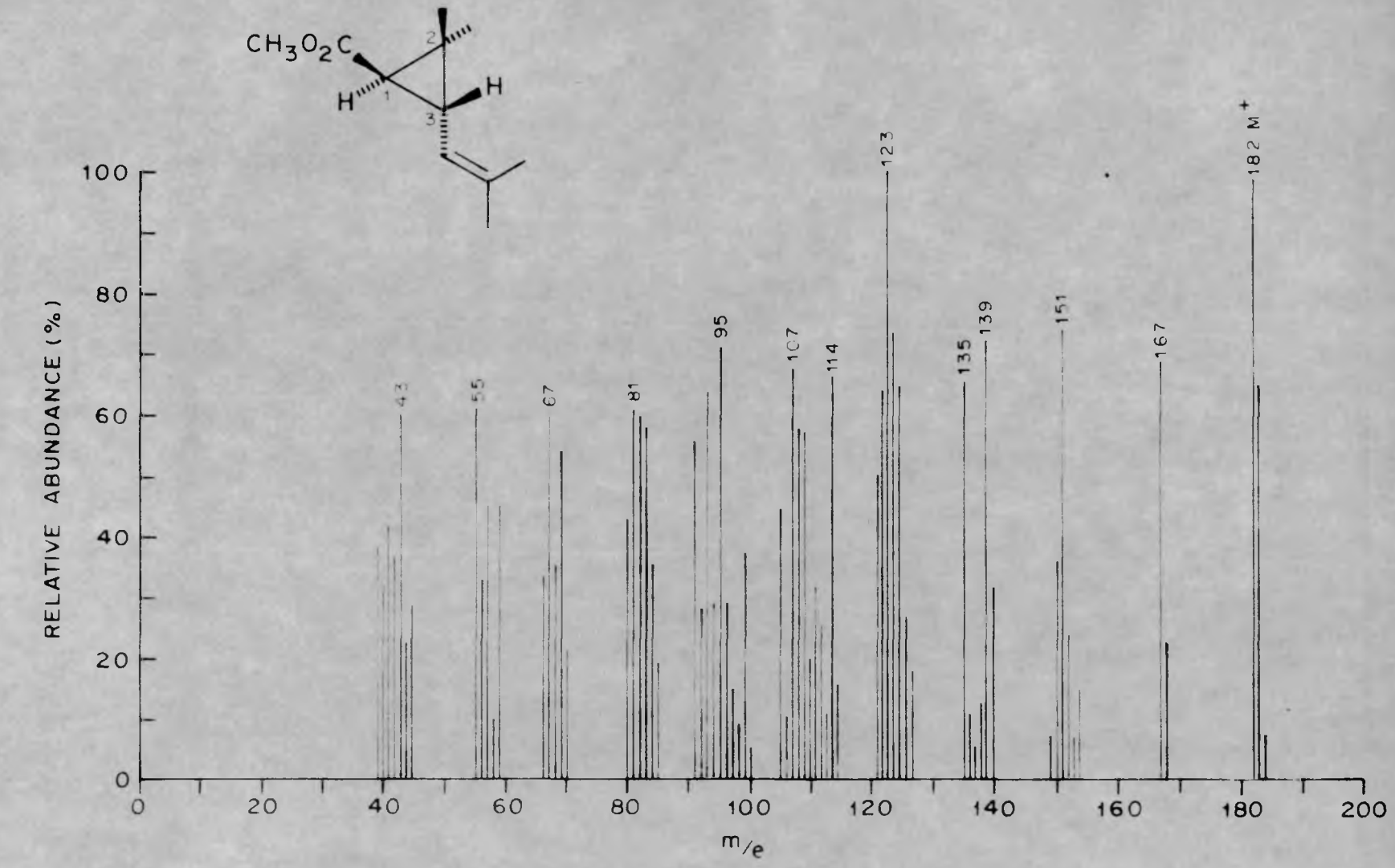


FIG. 35. MASS SPECTRUM OF METHYL (+)-TRANS-CHRYSANTHEMATE (I)

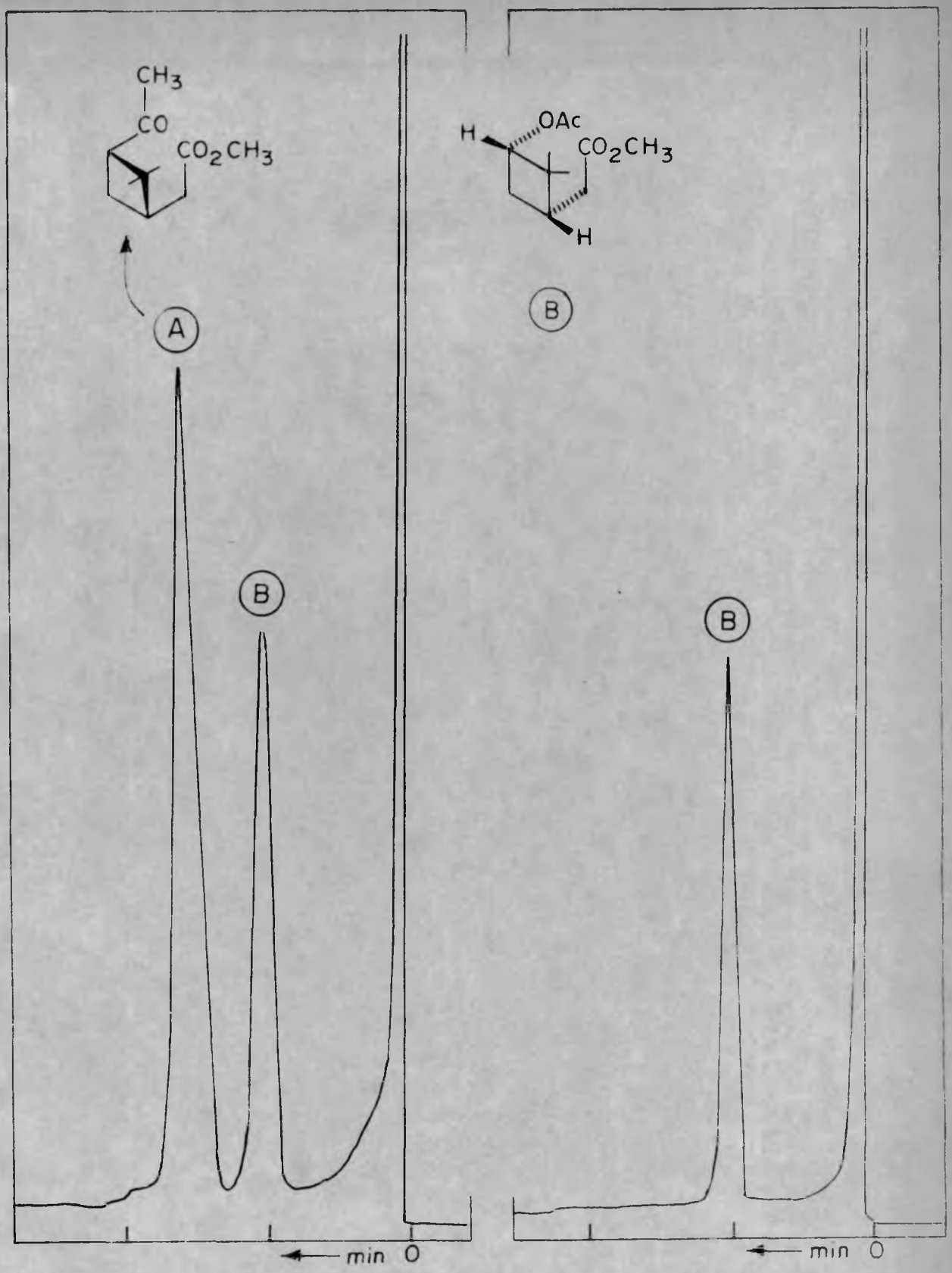


FIG. 36. GLC ANALYSIS OF METHYL (+)-PINONATE (A) and METHYL 2,2-DIMETHYL-3-ACETOXY CYCLOBUTYL ACETATE (B)

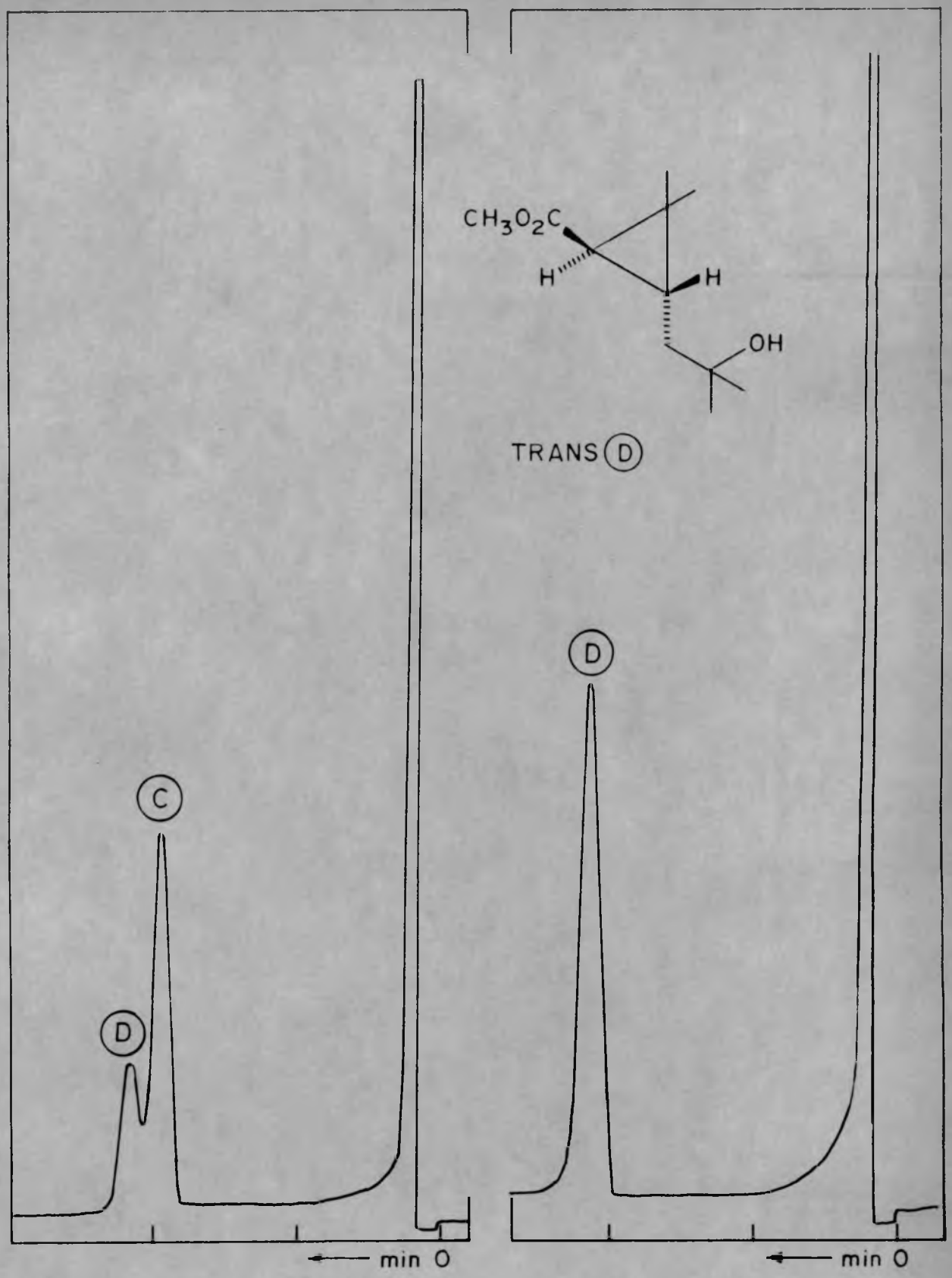


FIG. 37. GLC ANALYSIS OF CIS (C) and TRANS (D) METHYL 2,2-DIMETHYL-3-(2'-HYDROXYISOBUTYL) CYCLOPROPANE CARBOXYLATE

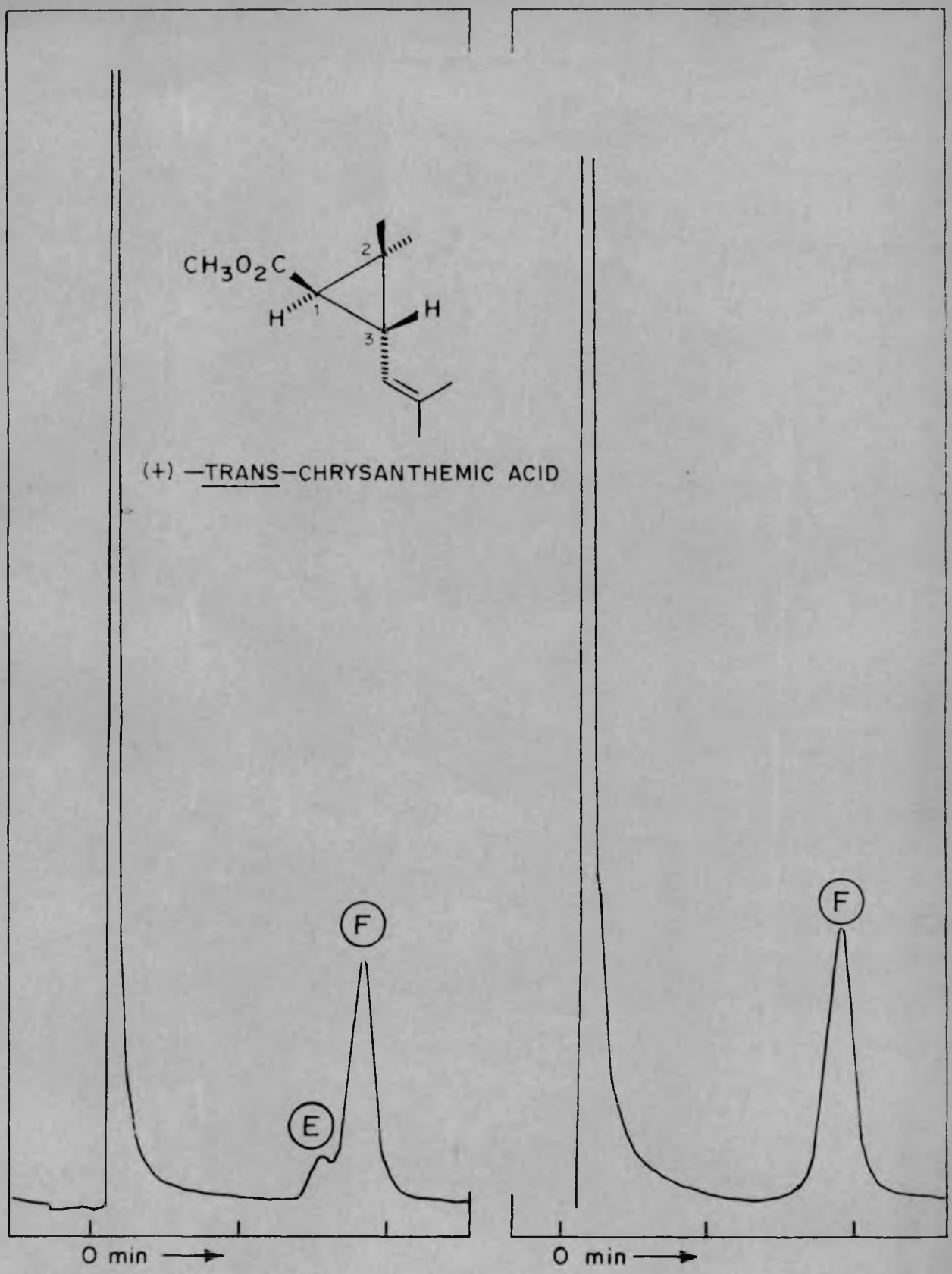


FIG. 38. GLC ANALYSIS OF CIS (E) and TRANS (F) CHRYSANTHEMIC ACIDS

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PART – II

INSECT JUVENILE HORMONE & THEIR SYNTHETIC ANALOGUES

CHAPTER I

I N T R O D U C T I O N

PART II

Insect Juvenile Hormone

CHAPTER - I

A) Introduction

The usual method of controlling insect pests by application of pesticides suffers from a serious drawback in that they are toxic not only to other insects and domestic animals but also to human beings. These pesticides can pollute the environment and many of them possess a residual effect. Moreover, insects have been observed to develop a remarkable resistance to pesticides by their frequest use.

Efforts were under way to find out some new chemicals which should be highly specific to the insects to be treated, should be non-toxic to other insects and human beings and the insects should not develop resistance to these new chemicals. Success in achieving this goal developed with the knowledge of biological, biochemical and behavioral differences which set insects apart from other animals. Historically the fact that harmful insect species can be controlled with their own hormones begins with Williams[1a] who was the first to observe that the lipid extracts from abdomens of adult male cecropia moths could oppose or prevent the metamorphosis of immature insects. The substance responsible for the failure of the

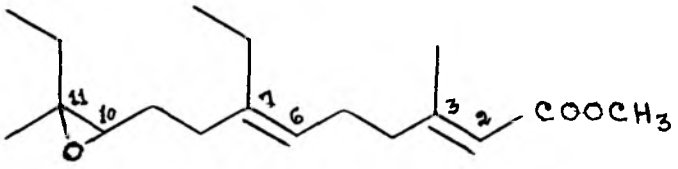
reappearance of any trace of larval characteristics was the Juvenile hormone. It was further confirmed by Wigglesworth[2] that the active hormonal compounds were able to penetrate the unbroken cuticle of insects to produce sufficient morphogenetic damage to preclude normal metamorphosis. The result was an insect of a pupal-adult mixture which is less viable and as a result soon dies without completing its further development.

It was soon confirmed[3-6] that the lipid extracts from thymus, human placenta, various other vertebrate organs, even from ordinary heavy cream and also the extracts from adrenal cortex of vertebrates from crustaceans, from almost all phyla of animals, hydroids to vertebrates, from micro-organisms, and plants possess a variable amount of juvenile hormone active substances.

B. Chemistry of insect Juvenile Hormone

It was observed by Williams[1(a-e)] in 1956 that the abdomens of the males of large butterflies, Hyalophora cecropia and Samia cinthia, contain an unusually large amount of the juvenile hormone which he extracted as 'Cecropia oil'. Efforts were under way for the preparation of purified extracts[7-9]. By employing extraction with methanol and by the application of chromatographic techniques Williams and Law[10] obtained a fraction with at least 50,000 times higher activity than the initial cecropia oil. Finally Roller et al.[11,12] were able to isolate the pure form of the juvenile hormone from cecropia oil

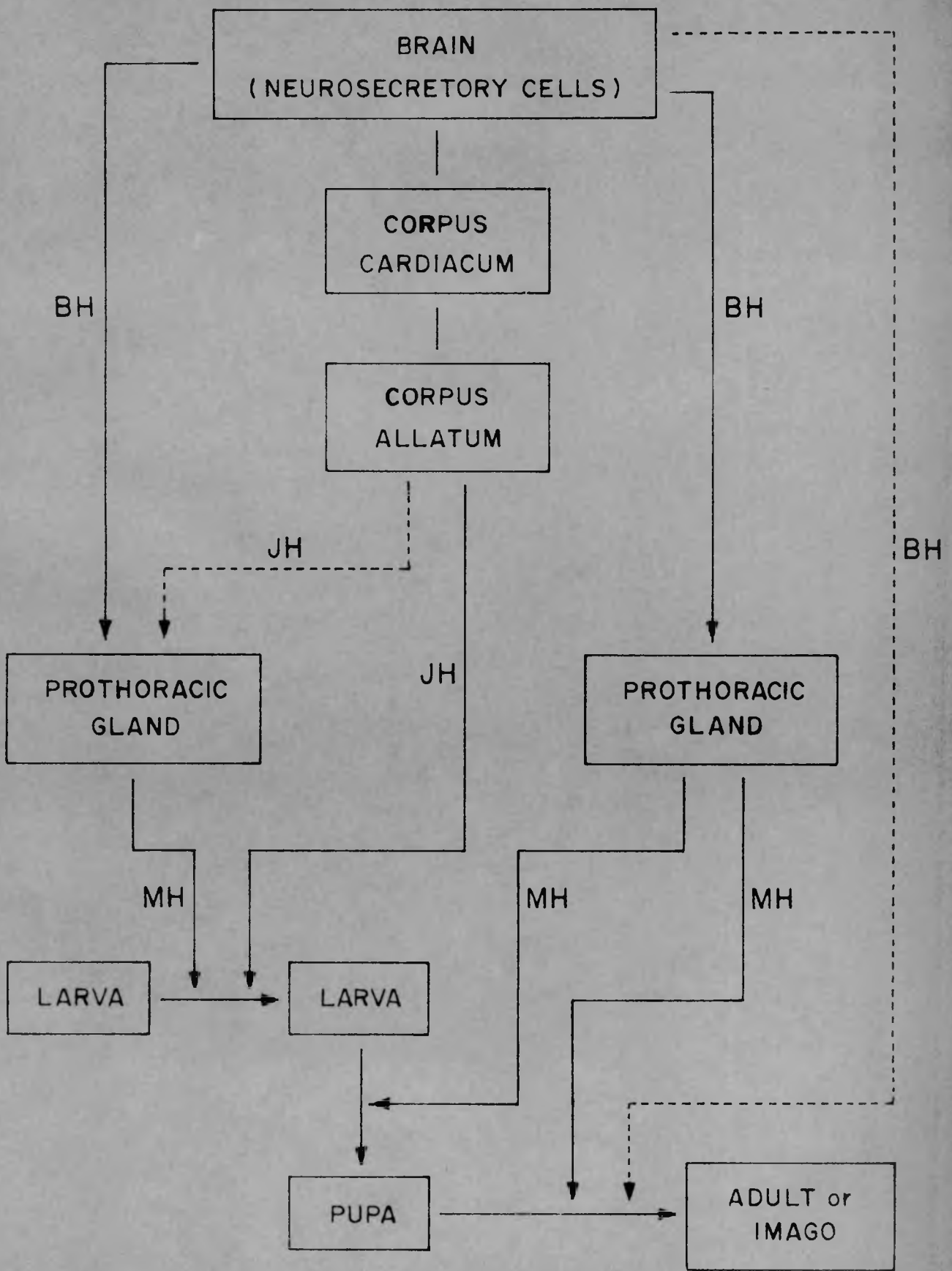
by an improved method of molecular distillation[13]. The pure juvenile hormone had an activity of 2,6 x 10^6 'tenebrio' units per microlitre compared to an activity of 25 'tenebrio' units of the initial unpurified cecropia oil. The compound responsible for this juvenile hormone activity was identified[14,15] as methyl 10,11-epoxy-7-ethyl-3,11-dimethyl-tridecan-2,6-dienoate (I) with trans-configuration of the substituents at the 2,3-double bond[16-17].



(I)

The first synthesis of racemic juvenile hormone was reported by Roller et al.[18,19]. Comparison of the biological activities of the natural juvenile hormone and the synthetic specimens of the eight isomers of the hormone[16] showed that synthetic methyl (±)-trans, trans, cis-10,11-epoxy-7-ethyl-3, 11-dimethyl-tridecan-2,6-dienoate (I) has the same activity as the natural hormone[16,17]. The remaining isomers were less active. In 1968, a second juvenile hormone (II) of small percentage (13-20%) in cecropia oil was isolated by Mayer et al.[20,2] This compound differs from I by the presence of a methyl instead of an ethyl group at C_7. It is believed that the second hormone is a precursor in the biosynthesis of I.

FLOWSHEET 12



A stereospecific synthesis of juvenile hormone was achieved by Corey et al.[23] in 1968. Several other methods for the synthesis of the hormone have also been described in literature[24-27].

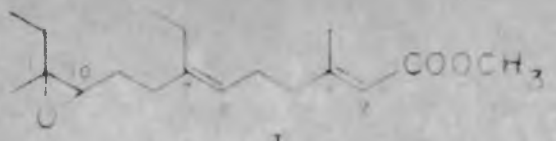
C. Role of Insect Juvenile Hormone for their Control of moulting and metamorphosis

Three hormones play vital roles in the regulation of insect post-embryonic development[28-30] e.g. Brain hormone (BH), Juvenile hormone (JH) and the Moulting hormone (MH). Hormonal control of insect development may be represented as shown in flow-sheet 12.

The development and growth of larva is accompanied by moulting. Larval moults are initiated by a secretion of the polypeptide hormone from the neurosecretory cells of the brain. This is also known as the activating hormone since one of its main function is to stimulate the activity of the prothoracic glands, which produce the moulting hormone or ecdysone. And the corpora allata secrete the juvenile hormone, the concentration of which varies in the different stages of insect development. Thus it is absent in the embryonic period appears in the moulting stage and slowly disappears in the pupal moulting. Moulting of the imago takes place only in the relative absence of the juvenile hormone. Therefore the treatment of the pupa with juvenile hormone leads to additional moulting and the appearance of giant forms which are evidently

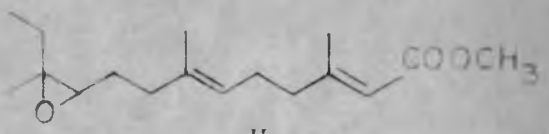
CHART-13

1. CECROPIA JUVENILE HORMONE



I

CECROPIA C_{18} JUVENILE HORMONE



II

CECROPIA C_{17} JUVENILE HORMONE

2. FARNESOL AND ITS DERIVATIVES

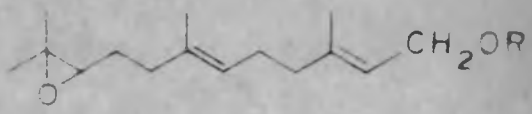
III

FARNESOL

IV

V

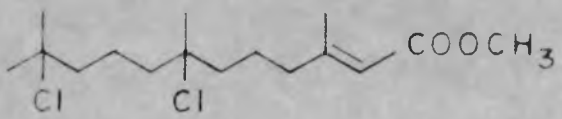
VII



VI a, R = H

VI b, R = Me

VIII

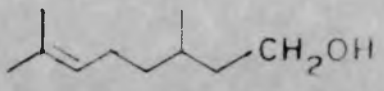


IX

METHYL TRANS-7,11-DICHLOROFARNESENATE

X

GERANIOL



XI

CITRONELLOL

XII

TETRAHYDROGERANIOL

non-viable[31,32]. Juvenile hormone again begins to be produced in the adult insects and it is necessary for yolk formation in the female and for full activity of the accessory glands in the male[33]. It has been suggested that the juvenile hormone controls ovarian and egg development by control of protein metabolism[34]. Juvenile hormone can also activate the prothoracic glands which produce ecdysone[35,36].

D. Natural and synthetic analogues of juvenile hormone

1. Farnesol and its derivatives: Much attention was diverted towards the field of terpenoid chemistry for the synthesis of juvenoids when Schmialek[37(a-c)] isolated the well-known sesquiterpenoid alcohol, Farnesol (III) from the Tenebrio excrements and yeasts. He observed[37c] that among various terpene derivatives the farnesyl methyl ether (IV) and farnesyl diethylamine (V) were considerably more active than farnesol and the ethyl ether of farnesol was nearly twice as active as that of methyl ether. Wigglesworth[38] also confirmed their activity on the bug Rhodnius prolixus. Farnesyl methyl ether is also being used as the test substance in several physiological assays. 10,11-Epoxy-farnesol (VIa) and 10,11-epoxy-farnesyl-methyl-ether (VIb) are also shown to be physiologically active[39]. Several saturated straight chain alcohols and their methyl ethers were prepared and tested by Bowers et al.[40] They found that dodecanol and dodecyl methyl ether (VII) with similar carbon skeleton as farnesol were exceptionally active. Even saturated hexahydrofarnesol (VIII)

possessed some activity.

2. Law-Williams hydrochlorination reaction mixture

Law et al.[41] described a reaction mixture prepared by treatment of an anhydrous ethanolic solution of farnesenic acid with hydrogen chloride. The mixture known as Law-Williams reaction mixture was shown to possess a high juvenile hormone activity on certain insects. The most active component with higher activity on certain Hemiptera was identified by Romaniuk et al.[42] as methyl trans 7,11-dichlorofarnesenate (IX). They observed that even a nanogram level dosage of this compound was sufficient to prevent normal morphogenesis in Pyrrhocoris. This compound was extensively used in studies on female sterility, ovicidal effects and inhibition of metamorphosis by juvenoids.

3. Geraniol and its derivatives: Compared to farnesol geraniol (X) and its lower ethers do not exhibit any juvenile activity[43,37c]. But a series of derivatives of geraniol (X), citronellol (XI) and tetrahydrogeraniol (XII) are known which are active on some bugs[44].

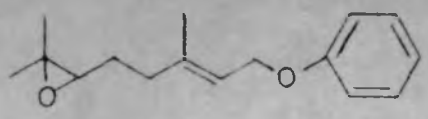
Important aromatic derivatives of Geraniol with JH-activity

(a) Derivatives of Benzoic acid and Acetophenone

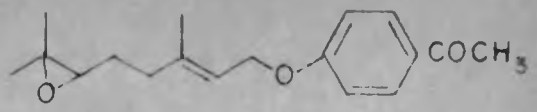
The epoxide of geranyl phenyl ether (XIII) and the analogous ether derived from p-hydroxyacetophenone (XIV) prepared by Bowers[45] were found to be less active on hemipteran

CHART - 13 (Contd)

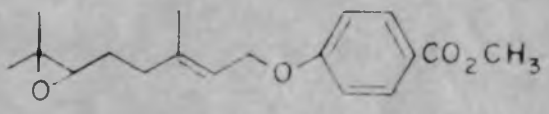
3 DERIVATIVES OF BENZOIC ACID AND ACETOPHENONE



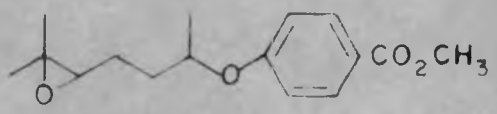
XIII



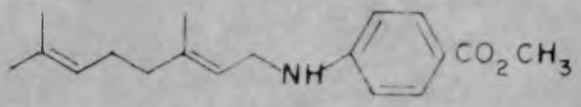
XIV



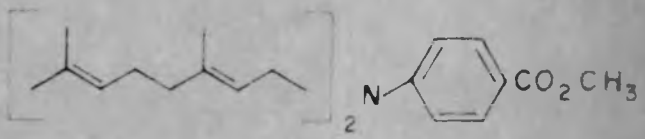
XV



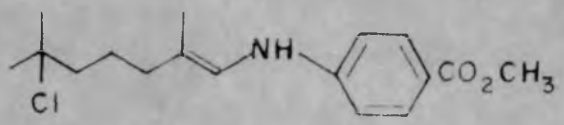
XVI



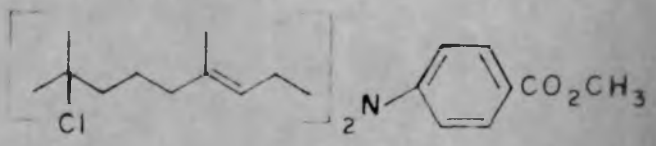
XVII



XVIII

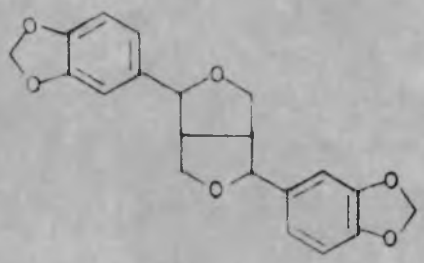


XIX

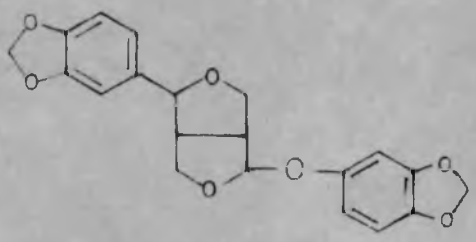


XX

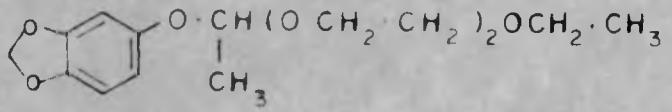
4. PHENYL ETHERS



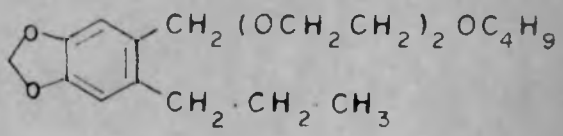
XXI SESAMINE



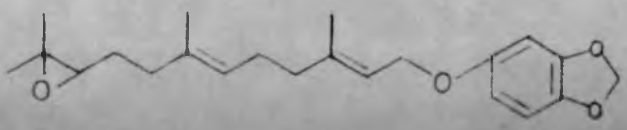
XXII SESAMOLINE



XXIII SESOXANE



XXIV PIPERONYL BUTOXIDE



XXV

Oncopeltus fasciatus and on Tenebrio molitor[46], while methyl p-(trans-6,7-epoxy-3,7-dimethyl-2-octenyloxy)-benzoate (XV), the geranyl ether epoxide from methyl p-hydroxy benzoate was found to possess a remarkable activity on Oncopeltus fasciatus. The JH-activity of similar ethers derived from p-hydroxy-benzoic acid was further investigated by Romanuk et al.[47] Methyl p-(4,5-epoxy-1,5-dimethyl-hexyloxy) benzoate (XVI) exhibited a high activity on hemipteran Lygaeus equestris.

All these ethers were usually prepared by alkylation of the hydroxylic groups of the corresponding phenols with the terpenoid bromide in presence of a base following epoxidation with m-chloroperbenzoic acid. Several p-amino-benzoic acid derivatives were found to be active[48] on some hemipteran species. Alkylation of the p-amino-benzoic esters with geranyl bromide in presence of pyridine usually afforded a mixture of mono (XVII) and dialkyl (XVIII) derivatives which were separated by chromatography. Addition of hydrogen chloride to these esters led to the corresponding chloro derivatives (XIX, XX). All these compounds exhibited a high JH-activity on hemipterans of the family Pyrrhocoridae but were found to be inactive on other insect species. The chloro and the epoxy-compounds were shown to possess the highest biological activity.

b) Phenyl Ethers and Aniline derivatives

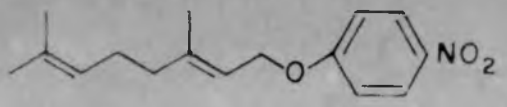
The presence of a methylene-dioxy group is known[45,46] to potentiate the JH-activity. The methylene-dioxy groups attached to an aromatic nucleus is very common in some natural

and synthetic synergists of pyrethrum and carbamate insecticides. Some synthetic components e.g. sesoxane (XXIII), piperonyl butoxide (XXIV) are known to be more active than the natural components of sesame oil, sesamine (XXI) and sesamoline (XXII). They are also known to mimic juvenile hormone in the case of mealworm Tenebrio molitor and the milkweed bug Oncopeltus fasciatus. The monoepoxide (XXV) of the piperonyl farnesyl ether prepared by Bowers[48] from piperonyl alcohol and farnesyl chloride in presence of potassium t-butoxide in dimethoxyethane followed by epoxidation was found to be highly active on the milk weed bug Oncopeltus fasciatus[48]. Several other aromatic ethers derived from 3,4-methylene dioxy phenol with definite biological activity have also been reported by Bowers[49]. Some analogous compounds[48a] derived from 3,4-methylene dioxy aniline are also known to be active on hemipterans Pyrrhocoridae, T. molitor and the South American hemipteran Triatoma infestans.

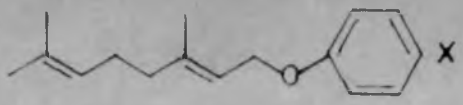
(e) Derivatives of Nitrophenols, Halophenols and Nitroanilines:

Geranyl p-nitrophenyl ether (XXVI) and Geranyl p-halophenyl ethers (XXIXa,b) were found to be active[50,51] on hemipterans and Tenebrio molitor. These compounds were prepared by condensation of sodium p-nitrophenoxide or sodium p-halophenoxide with geranyl bromide in dimethylformamide. The corresponding trans 6,7-monoepoxides (XXVII, XXXa,b) were far more active specially on hemipteran Graphosoma italicum. The geranyl ethers derived from o-nitrophenol and m-nitrophenol

4. DERIVATIVES OF NITROPHENOLS, HALOPHENOLS AND NITROANILINES

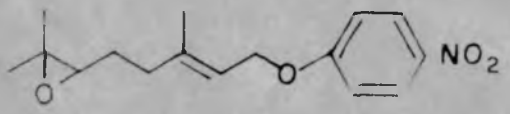


XXVI

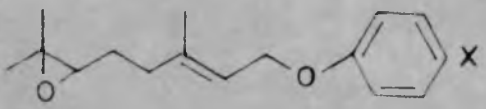


XXIX a, X = Cl

XXIX b, X = Br

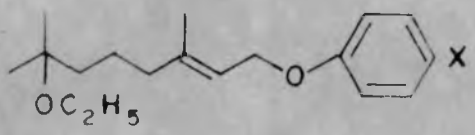


XXVII



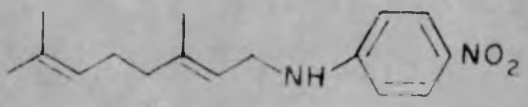
XXX a, X = Cl

XXX b, X = Br

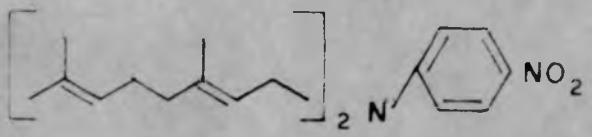


XXVIII a, X = Cl

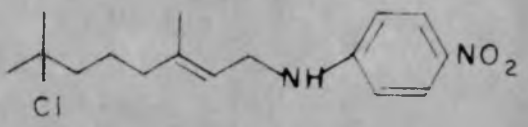
XXVIII b, X = Br



XXXI a

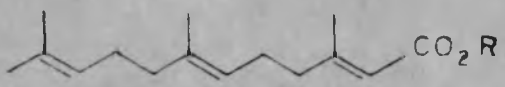


XXXI b



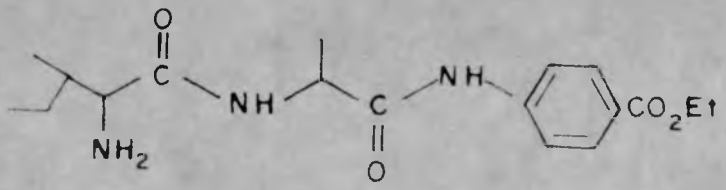
XXXI c

5. FARNESOIC ACID DERIVATIVES

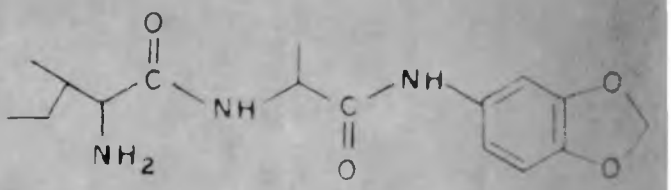


XXXII R = Me , R = Et

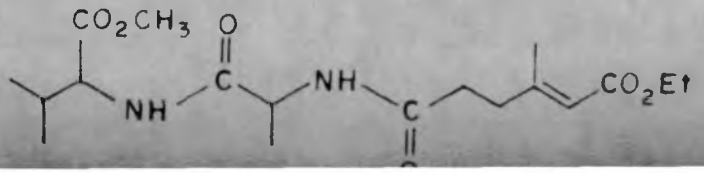
6. PEPTIDE DERIVATIVES



XXXIII



XXXIV



XXXV

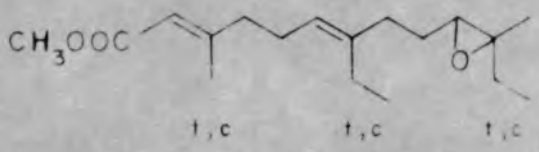
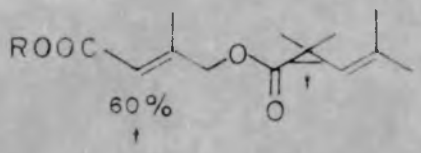
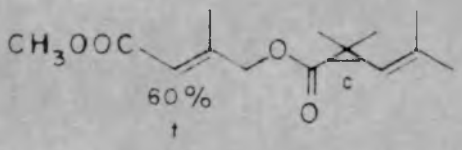
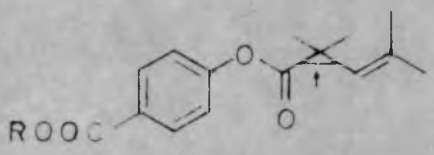
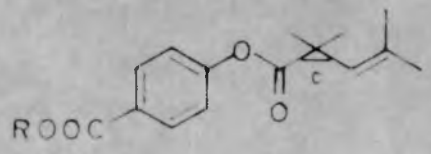
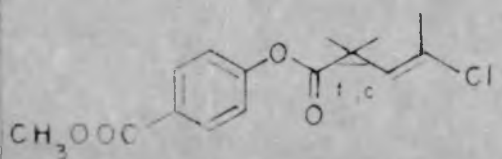
were found to be completely inactive[50]. The ethoxy derivatives (XXVIII) were also highly active on Graphosoma italicum and Coleoptera.

Alkylation[52] of p-nitroaniline with geranyl bromide gave a mixture of p-N-geranyl aminonitrobenzene and p-N,N-digeranyl-amino nitrobenzene (XXXIa,b). Addition of hydrogen chloride led to p-N-(7-chloro-3,7-dimethyl-2-octenyl-amino) nitro-benzene (XXXIc) which showed the highest JH-activity on hemi-pterans of the family pyrrhocoridae.

4. Farnesoic acid and derivatives: The JH-activity of the free farnesoic acid is negligible[42b]. But its methyl and ethyl esters are considerably active. Several farnesoic acid derivatives with a double bond at the position α,β- with respect to the carbonyl group were found to be remarkably active on some beetle species but are much less active on bugs[53]. The presence of the oxirane ring in the molecule of juvenoids plays a very important role. The 6,7-epoxy and 10,11-epoxy derivatives of methyl trans-trans-farnesoate(XXXII, R=Me) have been reported by Bowers et al.[39]

5. Peptide derivatives: The first peptide juvenile hormone like compounds were prepared by Zaoral and Slama[54]. Thus, ethyl L-isoleucyl-L-alanyl-p-aminobenzoate (XXXIII) showed a relatively high activity on the hemipterans. Pyrrhocoris apterus (0.5 μg per specimen) and Lygaeus cingulatus (0.5 μg). On the other

TABLE 14 EFFECT OF CHRYSANTHEMIC ACID ESTERS ON DYSDERCUS FASCIATUS

POUND NO	STRUCTURE AND ISOMERISM (t = trans, c = cis)		D^{50} ADULT DEFORMITY (mg)	D^{50} ADULT STERILITY (mg)
1			0·05 – 1	0·02 – 0·04
2		$R = CH_3$	0·01	0·01
		$R = C_2H_5$	0·1	0·05
3			0·01	0·01
4		$R = CH_3$	0·1 – 0·5	0·05 – 0·1
		$R = C_2H_5$	1 – 5	0·1 – 0·5
5		$R = CH_3$	0·1 – 0·5	0·1
		$R = C_2H_5$	1	0·1
6			0·01 – 0·05	0·01 – 0·05

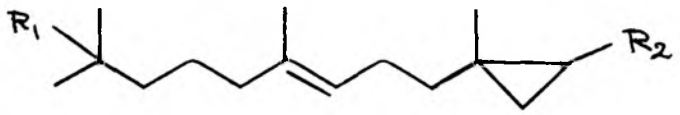
hand the peptide analogue (XXXV) of farnesoic acid was completely inactive. The derivative (XXXIV) of 3,4-methylene-dioxy aniline was weakly active.

Later on, numerous peptide derivatives of alkyl p-amino-benzoates and others were prepared by Poduska et al.[55]

6. Cyclopropane derivatives as insect juvenile hormone mimics

Punja et al.[56] in 1973 discovered that the alkyl and aromatic esters of chrysanthemic acid possess a high order of juvenile hormone activity. They prepared the esters of both cis and trans chrysanthemic acid and tested their JH activity on various insects. Some of these esters and their JH-activity are shown in Table 14.

Very recently Kocor et al.[58] have reported that the modified JH-analogues XXXVI(a-d) where a double bond at C_2-position have been replaced by a cyclopropane ring also exhibit hormonal activity against Pyrrhocoris apterus.



XXXVI a $R_1 = OMe$, $R_2 = CO_2Et$

b $R_1 = OMe$, $R_2 = CO_2$ i-Pr

c $R_1 = OEt$, $R_2 = CO_2Et$

d $R_1 = OEt$, $R_2 = CO_2$ i-Pr

7. Cyclic juvenoids: Cyclic juvenoids e.g. methyl ester of todomatuic acid and the aromatic juvabione analogues have been described in Part III.

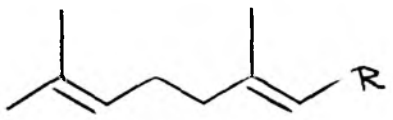
CHAPTER II

Insect Juvenile Hormone analogues : Synthesis of substituted terpenoids bearing a cyclopropane ring.

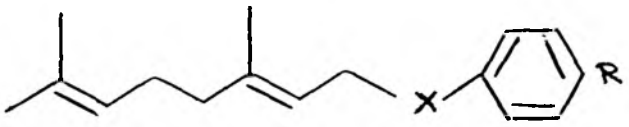
CHAPTER II

A. Present scheme and work:

Various synthetic juvenile hormone analogues are currently being synthesized and tested in different laboratories around the world, as part of a programme for the integrated plant protection measures by controlling insects by hormonal action. From the earlier discussion it is evident that the straight chain monoterpenes (A) where R is an alkoxy carbonyl, alkoxy methyl or hydroxy methyl group have very little or no JH-activity[53a]. But hormonal activity can be induced by forming their aliphatic and aromatic ethers, thio-ethers and amines (B).



A



B

X = O, S, NH

R = $-COOCH_3$
$-OCH_3$
$-COCH_3$
$-NO_2$
$-Cl, Br$
$-SO_2NH_2$ etc.

These JH-analogues are known to be very active on various Exopterygote and Endopterygote insects[46]. Introduction of

substituents such as halogens or epoxy groups at the end of the chain of farnesol and farnesenic acid ester derivatives are also known to enhance the JH-activity of the compounds[16,42].

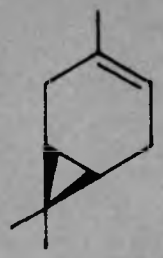
Our approach to the synthesis of JH-analogues is based on the concept that a cyclopropane ring could be substituted for a double bond in the terpenoid chain. The present work involves the synthesis of several intermediates along with the synthesis of a few JH-analogues. (+)-Car-3-ene which is abundant in Indian turpentine oil contains a cyclopropane ring and is the starting material for our syntheses.[57]

B. Results and discussion:

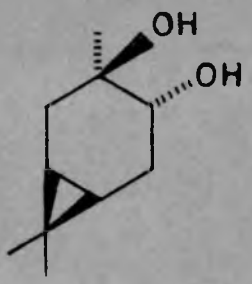
The keto-aldehyde (III) on treatment with EtMgI and MeMgI produced the diols IVa and IVb respectively. The physical and spectral properties of the diol IVb has been described in Chapter II of Part I. The diol IVa was readily crystallised from pet.ether (40-60°) to give colourless crystals m.p.95°. Its IR spectrum displayed a strong hydroxyl absorption at 3360 cm^{-1} The NMR spectrum exhibited signals (δ) at 0.5 (2H, m, cyclopropyl protons); 0.83 [6H, $C(CH_3)_2$]; 1.03 to 1.06 (9H, CH_3 protons); 1.26 to 1.66 (8H, CH_2 protons) and 3.5 (1H, m, CHOH).

The diol IVa on treatment with benzoyl chloride in pyridine formed the benzoyl derivative (VIa), b.p. 150°(bath)/ 0.5 mm. The compound showed absorption in IR at 3500 cm^{-1} (hydroxyl), 1725 cm^{-1} (carbonyl), 1450 cm^{-1} (aromatic) and the NMR showed signals (δ) at 0.9 (6H, Me's on cyclopropane ring);

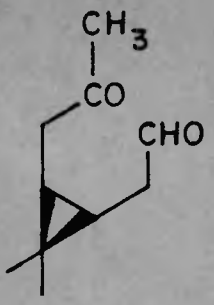
CHART - 15



I



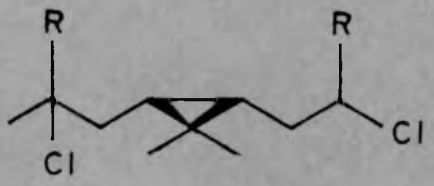
II



III

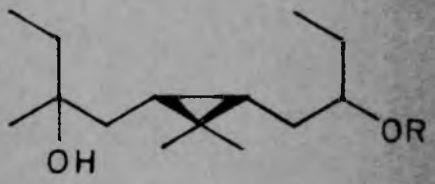
IV a, R = Et

IV b, R = Me



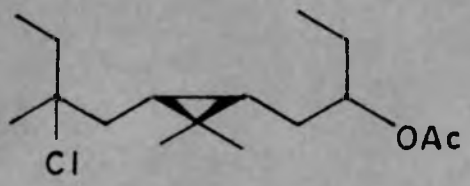
V a, R = Et

V b, R = Me

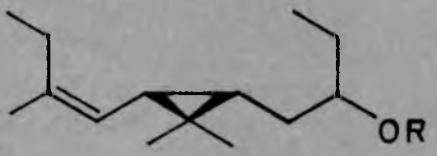


VI a, R = COC_6H_5

VI b, R = $COCH_3$



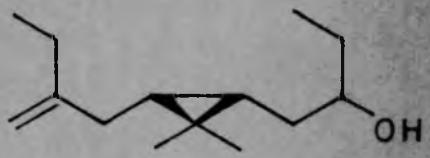
VII



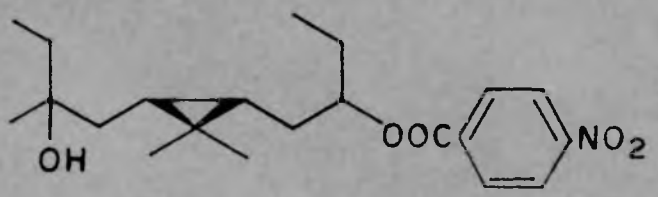
VIII a, R = H

VIII b, R = $COCH_3$

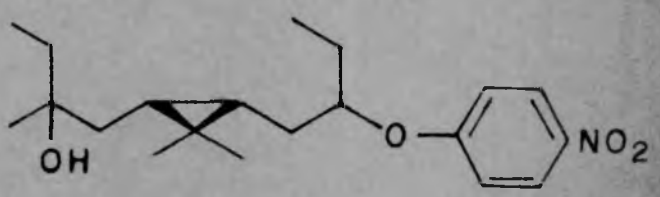
IX, R = Cl



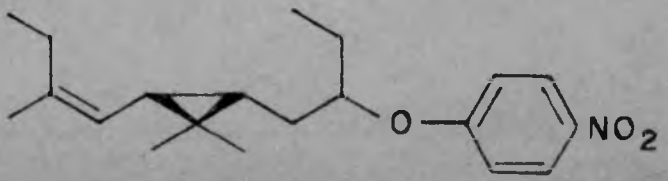
VIII c



X



XI



XII

1 to 1.2 (9H, CH_3 protons); 1.2 to 1.6 (8H, CH_2 protons) and 7.2 to 8.1 (5H, aromatic protons). The diol IVa on similar treatment with acetic anhydride in pyridine formed the hydroxy acetate VIb. Its IR showed absorption at 3600 cm^{-1} (hydroxyl); 1750 cm^{-1} (acetate). The NMR spectrum exhibited signals at 0.5 (2H, m, cyclopropyl protons); 0.88 [6H, $C(CH_3)_2$]; 1.03 to 1.1 (9H, CH_3 protons); 1.20 to 1.67 (8H, CH_2 protons); 2.00 (-OAc protons) and 4.8 (1H, m, CH OAc).

The diols IVa and IVb when treated with equimolar proportion of $POCl_3$/Pyridine gave the dichloro compounds Va and Vb respectively. The hydroxy acetate VIb on similar treatment with $POCl_3$/Pyridine gave the chloro-acetate VII. Compound VII when treated with ethanolic sodium ethoxide gave mainly the unsaturated hydroxy compound VIIIa in about 75% yield. About 10-15% of the isomeric alcohol VIIIc was also isolated.

The diol IVa was condensed with p-nitrobenzoic acid and p-nitrophenol in presence of p-toluene-sulphonyl chloride in pyridine to yield the corresponding p-nitrobenzoate X and p-nitrophenyl ether XI respectively. Under these conditions the tosylate of the secondary alcohol was formed in situ which underwent nucleophilic displacement by the p-nitrobenzoate and p-nitrophenolate ions.

The IR spectrum of the compound X displayed absorption at 3500 (hydroxyl), 1725 (benzoate), 1375 (cyclopropane ring system), 1500 and 750 cm^{-1} (aromatic). Compound XI showed absorption in IR at 3300 (hydroxyl), 1500 and 755 cm^{-1} (aromatic).

Its NMR spectrum exhibited signals at 0.6 (2H, m, cyclopropyl protons); 0.87 (6H, C $(CH_3)_2$); 1.03 to 1.17 (9H, CH_3 protons); 1.2 to 1.6 (8H, CH_2 protons); 3.6 (1H, m, CHOAr); 5.1 (1H, OH); 6.8 and 7.97 (2H, d; 2H, d, aromatic protons).

The unsaturated alcohol VIIIa was also condensed with p-nitrophenol to form the p-nitrophenyl ether XII. Its IR absorption at 1500 and 760 cm^{-1} corresponds to aromatic system. Its NMR spectrum exhibited signals (δ) at 0.6 (2H, m, cyclopropyl protons); 0.9 (6H, $C(CH_3)_2$); 1.0 (6H, CH_3 protons); 1.2 to 1.6 (6H, CH_2 protons); 1.8 (3H, CH_3 protons on double bond); 3.6 (1H, m, CHOAr); 5.19 (1H, bd, δ = CH); 6.8 and 8 (2H, d; 2H, d aromatic protons).

The compounds VIa, X, XI and XII were tested on freshly moulted fifth instar nymps of red cotton bug Dysdercus koenigii by topical application. Hormone activity was assayed on the basis of wing deformities of the moulted adultoids. It was observed that at a dose level of 10 µg/Nymph, compound XI showed JH-activity, comparable to farnesyl methy ether. Compounds VIa, X and XII showed weak JH-activity under these conditions.

C. Experimental procedure

Trans 3,4-Carane-diol (II): Trans 3,4-carane-diol was prepared from (+)-car-3-ene by reaction with performic acid as described in Chapter II of Part I.

2,2-Dimethyl-2-(2'-oxopropyl)-1-acetaldehydecyclopropane (III)

The keto-aldehyde III also has been described in Chapter II of Part I.

3,3-Dimethyl-2a(2'-hydroxy-2'-methyl-4-butyl)-1-(2'-hydroxy-4-butyl)cyclopropane (IVa)

To dry magnesium turnings (3 g, 0.12 mole), dry ether (75 ml) and dry ethyl bromide (0.5 g) was added gradually ethyl bromide (12 g, 0.9 mole) with stirring. After 15-20 min., when all magnesium was dissolved, a solution of keto-aldehyde (III, 5.04 g, 0.036 mole) in ether (50 ml) was added dropwise; stirring was continued for another 30 min. The solution was refluxed for 15 min. and then cooled. The reaction mixture was poured into an ice-cold solution of NH_4Cl (50 g) in water (200 ml) and stirred for 15-20 min. The ether layer was separated and washed with water dried (Na_2SO_4) and evaporated to get the compound (IVa), which was crystallized from pet.ether (40-60°) as colourless crystals (5 g, 62%), m.p.98° (Found: C, 73.74; H, 12.12; M^+ 228. $C_{14}H_{28}O_2$ requires C, 73.63; H, 12.36; mol.wt 228.36; ν_{max}^{Nujol} 3350, 2900, 1450, 1376, 1025, 930, 880 cm^{-1}; NMR (CCl_4,δ): 0.5 (2H, m, cyclopropyl protons); 0.83 [6H, $C(CH_3)_2$]; 1.03 to 1.06 (9H, CH_3

protons); 1.26 to 1.66 (8H, CH_2 protons) and 3.5 (1H, m, CHOH).

2,3-Dimethyl-2-(2'-hydroxy-2'-methyl-n-propyl)-1-(2'-hydroxy-n-propyl) cyclopropane (IVb) - The keto-aldehyde (III, 5 g, 0.036 mole) was treated in a similar manner with methyl magnesium iodide to get the diol (IVb) (4.9 g, 70%) as a colourless viscous liquid, b.p. 150°(bath)/0.5 mm (Found: C, 72.01; H, 12.10; M^+ 200. $C_{12}H_{24}O_2$ requires C, 71.96; H, 12.08%; Mol.wt. 200.31); ν_{max}^{Nujol} 3250, 2900, 1450, 1380, 965, 880 cm^{-1}.

3,3-Dimethyl-2-(2'-chloro-2'-methyl-n-butyl)-1-(2'-chloro-n-butyl) cyclopropane (Va) - The diol (IVa, 0.23 g, 0.001 mole) was dissolved in pyridine (2 ml) and treated with $POCl_3$ (0.2 g, 0.0013 mole) at 0°C and kept overnight. The reaction mixture was poured into ice-water and extracted with ether. The ether extract was successively washed with cold dil. HCl (2%, 50 ml), sat. $NaHCO_3$ and cold water and dried (Na_2SO_4). The solvent was evaporated to get the dichloro-compound (Va) (0.22 g, 85%) as a colourless liquid; b.p. 140-45°(bath)/1 mm. (Found: C, 63.66; H, 9.10; M^+ 265. $C_{14}H_{26}Cl_2$ requires C, 63.39; H, 9.18%; mol.wt. 265).

3,3-Dimethyl-2-(2'-chloro-2'-methyl-n-propyl)-1-(2'-chloro-n-propyl) cyclopropane (Vb) - The diol (IVb, 0.2 g, 0.001 mole) in pyridine (2 ml) was treated similarly with $POCl_3$ (0.2 g, 0.0013 mole) to get the dichloro-compound (Vb) (0.21 g, 91%) as colourless liquid; b.p. 136-40°(bath)/1 mm (Found: C, 61.12; H, 9.35; M^+ 236, 238, 240. $C_{12}H_{22}Cl_2$ requires C, 60.76;

H, 9.28%; mol. wt. 237).

3,3-Dimethyl-2-(2'-hydroxy-2'-methyl-n-butyl)-1-n-butyl-2'-benzoyloxy) cyclopropane (VIa) - The diol (IVa, 0.23 g, 0.001 mole) in pyridine was treated with benzoyl chloride (0.15 g, 0.001 mole) and kept overnight. The mass was poured into ice-water and extracted with ether. The ether extract was successively washed with cold dil. HCl (2%, 50 ml), sat. $NaHCO_3$ and cold water and dried (Na_2SO_4). After removal of ether the product was distilled to give a colourless viscous liquid (0.25 g, 75%), b.p. 150°(bath)/0.5 mm. (Found: C, 76.89; H, 9.54; M^+ 332. $C_{21}H_{32}O_3$ requires C, 76.86; H, 9.70%; mol. wt. 332.47); ν_{max}^{neat} 3500, 2900, 1725, 1600, 1450, 1380, 1050, 930, 790, 715 cm^{-1} NMR (CCl_4, δ): 0.6 (2H, m, cyclopropyl protons; 0.9 (6H, $C(CH_3)_2$); 1 to 1.2 (9H, CH_3 protons); 1.2 to 1.6 (8H, CH_2 protons); 7.2 to 8.1 (5H, aromatic protons).

3,3-Dimethyl-2-(2'-hydroxy-2'-methyl-n-butyl)-1-(n-butyl-2'-acetyloxy) cyclopropane (VIb) - The diol (IVa, 0.23 g, 0.001 mole) in pyridine (2 ml) was treated similarly with acetic anhydride (0.15 g, 0.0014 mole) to get the mono-acetyl derivative (VIb) (0.23 g, 92%) as a colourless viscous liquid, b.p. 145°(bath)/ 0.5 mm (Found: C, 71.30; H, 10.73; M^+ 270. $C_{16}H_{30}O_3$ requires C, 71.07; H, 11.18%, mol. wt. 270.40); ν_{max}^{neat} 3600, 3000, 1750, 1475, 1380, 970, 890 cm^{-1}.

NMR (CCl_4, δ): 0.6 (2H, m, cyclopropyl protons); 0.88 (6H, $C(CH_3)_2$); 1.08 to 1.1 (9H, CH_3 protons); 1.20 to 1.67 (8H, CH_2 protons); 2.00 (OAc protons); and 4.8 (1H, m, CHOAc).

3,3-Dimethyl-2-(2'-chloro-2'-methyl-n-butyl)-1-(n-butyl-2'-acetyloxy) cyclopropane (VII) - The mono-acetyl derivative (VIb, 0.27 g, 0.001 mole) in pyridine (2 ml) was treated with $POCl_3$ (0.2 g, 0.0013 mole) to get the chloro-acetyl derivative (VII) as colourless viscous liquid (0.25 g, 89%); b.p.140°(bath)/0.5 mm (Found: C, 66.40; H, 10.00; Cl, 12.25; M^+ 288, 290. $C_{16}H_{29}O_2Cl$ requires C, 66.55; H, 10.05; Cl, 12.35%; mol.wt. 288.5).

3,3-Dimethyl-2-(2'-methyl-but-1'-enyl)-1-(2'-hydroxy-n-butyl) cyclopropane (VIIIa) and 3,3-Dimethyl-2-(2'-methyl-but-2'-enyl)-1-(2'-hydroxy-n-butyl) cyclopropane (VIIIa) - The chloro-acetyl derivative (VII, 0.58 g, 0.002 mole) in anhyd. EtOH (5 ml) was added to a solution of sodium ethoxide in ethanol (0.46 g, 0.02 mole of sodium in 3 ml of anhyd. ethanol). The mixture was warmed for 15-20 min., cooled, diluted with water and extracted with ether. The ether extract was washed with water, brine and dried (Na_2SO_4). The ether solution was concentrated and the residue was chromatographed over $AgNO_3$-silica gel (1:6, 15 gm). The earlier fractions eluted with pet.ether (40-60°)-chloroform mixture (1:1) furnished pure unsaturated hydroxy compound (VIIIa, 0.30 g, 75%) as colourless liquid, b.p. 135-40°(bath)/0.5 mm (Found: C, 79.89; H, 12.49; M^+ 210 $C_{14}H_{26}O$ requires C, 79.93; H, 12.46% mol. wt. 210).

ν_{max} 3350, 2900, 1675, 1475, 1375, 1025, 805 cm^{-1}.

NMR(CCl_4, δ): 0.5 (2H, m, cyclopropyl protons); 0.9 (6H, $C(CH_3)_2$); 1.06 to 1.10 (6H, CH_3 protons); 1.17 to 1.57

(4H, CH_2 protons); 1.63 (3H, CH_3 protons on double bond); 1.8 (2H, m, allylic CH_2); 3.47 (1H, m, CHOH) and 5.15 (1H, bd, C = CH).

The later fractions of the chromatograph furnished pure isomeric unsaturated alcohol (VIIIc, 0.068 g, 14%) b.p.138°(bath)/0.5 mm. (Found C, 79.87; H, 12.43; $C_{14}H_{26}O$ requires C, 79.93; H, 12.46%). ν_{max} 3400, 2900, 1638, 1330, 855 cm^{-1}. NMR (CCl_4,δ) 0.63 (2H, m, cyclopropyl protons); 0.86 [6H, $C(CH_3)_2$]; 1.03 to 1.10 (6H, CH_3 protons); 1.17 to 1.60 (4H, CH_2 protons); 1.93 (2H, m, allylic CH_2), 2.66 (1H, OH); 3.47 (1H, m, CHOH), 4.70 (2H, bs, C = CH_2).

<u>3,3-Dimethyl-2-(2'-methyl-but-1'-enyl)-1-(n-butyl-2'-acetyloxy) cyclopropane (VIIIb)</u> - The unsaturated hydroxy compound (VIIIa, 0.22 g, 0.001 mole) in pyridine (2 ml) was treated with acetic anhydride (0.21 g, 0.002 mole) and left overnight at room temp. The mass was poured into ice-water and extracted with ether. The ether extract was successively washed with cold dil. HCl (2%, 50 ml), sat. $NaHCO_3$ and cold water and dried (Na_2SO_4). After removal of ether the product was distilled to give a colourless liquid (0.18 g, 75%), b.p. 130-5°(bath)/1.5 mm. (Found: C, 76.0%; H, 11.11; $C_{16}H_{28}O_2$ requires C, 76.14; H, 11.18%). ν_{max} 2900, 1725, 1640, 1450, 1375, 1248, 1050, 965, 895, 850 cm^{-1}.

NMR (CCl_4, δ) 0.6 (2H, m, cyclopropyl protons); 0.9 [6H, $C(CH_3)_2$]; 1.03 (6H, CH_3 protons); 1.63 (3H, CH_3 protons

on double bond); 1.97 (3H, $OCOCH_3$); 4.70 (1H, m, CHOAc), 5.17 (1H, bd, C = CH).

3,3-Dimethyl-2-(2'-methyl-but-1'-enyl)-1-(2'-chloro-n-butyl) cyclopropane (IX) - The unsaturated alcohol (VIIIa, 0.21 g, 0.001 mole) in pyridine (2 ml) was treated with $POCl_3$ (0.2 g, 0.0013 mole) to get the chloro-derivative (IX) as colourless liquid (0.19 g, 82%); b.p. 135-40°(bath)/1.5 mm. (Found: C, 73.41; H, 10.51; M^+ 228, 230. $C_{14}H_{25}Cl$ requires C, 73.52; H, 10.94%; mol. wt. 228.8).

3,3-Dimethyl-2-(2'-hydroxy-2'-methyl-n-butyl)-1-(n-butyl-2'-p-nitrobenzoyloxy) cyclopropane (X)

A mixture of the diol (IVa, 0.114 g, 0.005 mole), p-nitrobenzoic acid (0.0835 g, 0.005 mole)and p-toluene-sulphonyl chloride (0.095 g, 0.005 mole) in pyridine (4 ml) was heated at 100° for 12 hr. The product was diluted with water and extracted with ether. The ethereal layer was washed successively with dil. HCl (2%), sat. $NaHCO_3$, water and brine and dried (Na_2SO_4). Ether was evaporated and the residue distilled to get the p-nitrobenzoate (X) (0.15 g, 78%) as pale yellow viscous liquid; b.p. 155°(bath)/1 mm. (Found: C, 66.55; H, 8.14; N, 3.69. $C_{21}H_{31}O_5N$ requires C, 66.82; H, 8.28; N, 3.71%); ν_{max}^{neat} 3500, 1725, 1500, 1375, 750 cm^{-1}. NMR ($CHCl_3$ δ): 0.6 (2H, m, cyclopropyl protons); 0.9 [6H, $C(CH_3)_2$]; 1 to 1.2 (9H, CH_3 protons); 1.2 to 1.6 (8H, CH_2 protons); and 2 (1H, s, OH).

2,2-Dimethyl-3-(2'-hydroxy-2'-methyl-n-butyl)-1-(2'-p-nitrophenyloxy-n-butyl) cyclopropane (XI)

A mixture of the diol (IVa) (0.114 g, 0.005 mole), p-nitrophenol (0.0695 g, 0.005 mole), p-toluene sulphonyl chloride (0.095 g, 0.005 mole) in pyridine (4 ml) was heated at 100° for 12 hr. The product was diluted with water and extracted with ether. The ethereal layer was washed successively with dil. HCl (2%), sat. $NaHCO_3$, water and brine and dried (Na_2SO_4). The ether was evaporated and the residue was chromatographed over silica gel. By eluting with a mixture of ether and pet.ether (1:4) a residue was obtained (0.14 g, 84%) which was identified as compound (XI); pale yellow viscous liquid, b.p.142°(bath)/0.5 mm (Found: C, 68.86; H, 9.01; N, 4.00. $C_{20}H_{31}O_4N$ requires C, 68.74; H, 8.94; N, 4.01%); ν_{max} 3600, 1600, 1375, 1112, 765 cm^{-1}. NMR (CCl_4, δ): 0.6 (2H, m, cyclopropyl protons); 0.87 (6H, $C(CH_3)_2$); 1.03 to 1.17 (9H, CH_3 protons); 1.2 to 1.6 (8H, CH_2 protons); 3.6 (1H, m, CH proton); 5.1 (1H, OH); 6.8 and 7.97 (2H, d; 2H, d, aromatic protons).

2,2-Dimethyl-3-(2'-methyl-but-1'-enyl)-1-(2'-p-nitrophenyloxy-n-butyl) cyclopropane (XII)

A mixture of the unsaturated alcohol (VIIIa, 0.105 g, 0.005 mole), p-nitrophenol (0.0695 g, 0.005 mole), p-toluene-sulphonyl chloride (0.095 g, 0.005 mole) in pyridine (4 ml) was heated at 100° for 14 hr. The product was diluted with water

and extracted with ether. The ethereal layer was washed successively with dil. HCl (2%), sat. $NaHCO_3$, water brine and dried (Na_2SO_4). The ether was evaporated and the residue chromatographed over silica gel. By eluting with ether-pet. ether mixture (1:4) a residue was obtained (0.12 g, 7%) which was identified as compound (XII); pale yellow viscous liquid; b.p. 145° (bath)/0.5 mm. (Found: C, 72.57; H, 9.02; N, 4.21. $C_{20}H_{29}O_3N$ requires C, 72.47; H, 8.82; N, 4.23%); ν_{max} 2900, 1500, 1375, 1112, 950, 760 cm^{-1}.

NMR(CCl_4, δ): 0.6 (2H, m, cyclopropyl protons); 0.9 (6H, $C(CH_3)_2$); 1.0 (6H, CH_3 protons); 1.2 to 1.6 (6H, CH_2 protons); 1.8 (3H, CH_3 protons adjacent to double bond); 3.6 (1H, m, CHOAr); 5.19 (1H, bd, C=CH) 6.8 and 8 (2H, d, 2H, 4, aromatic protons).

Acknowledgement

The authors are grateful to Dr. M.S. Chaddha and his colleagues of BARC, Bombay, for the screening of compounds for juvenile hormone activity.

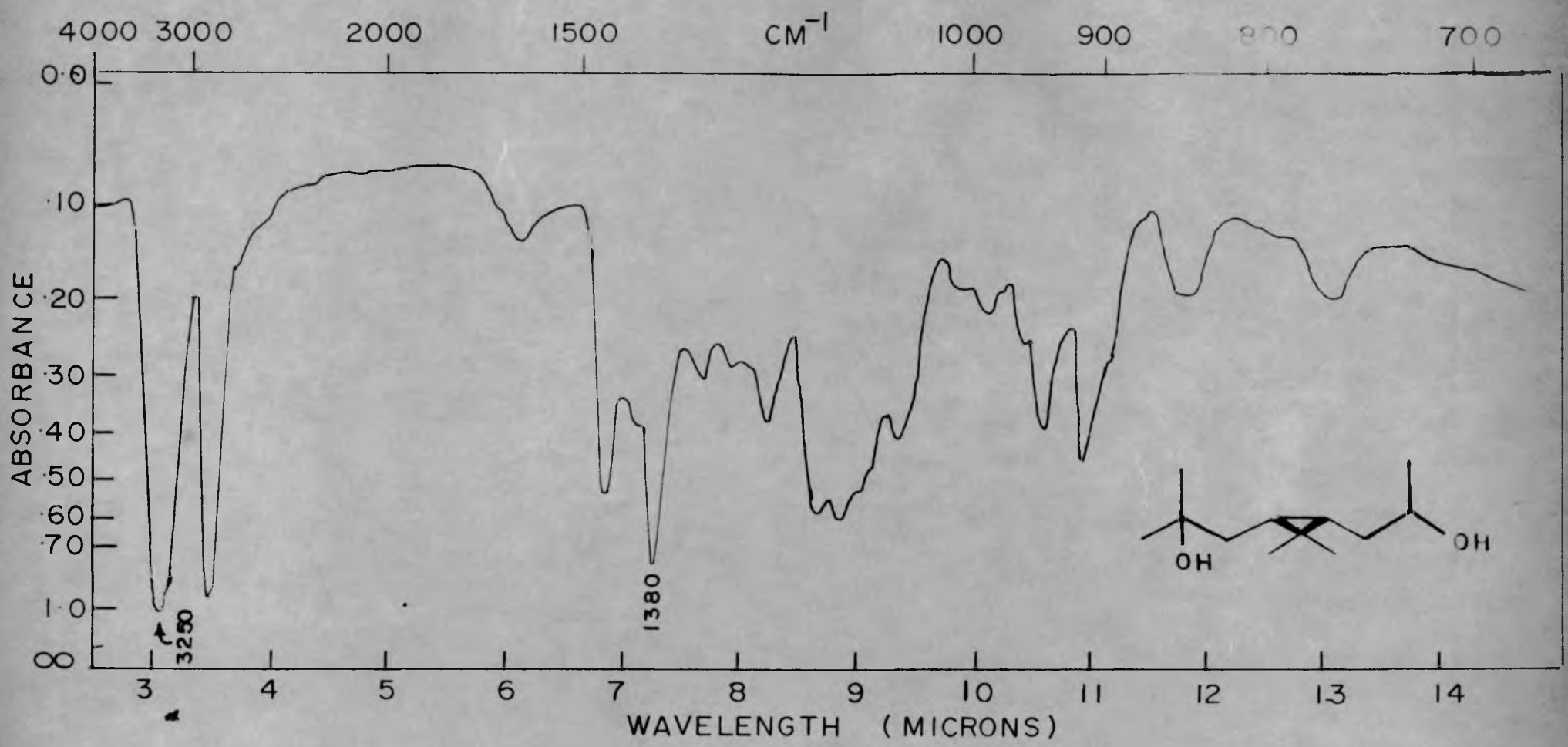


FIG. 39 IR SPECTRUM OF 3,3-DIMETHYL-2-(2'-HYDROXY-2'-METHYL-n-PROPYL)-1-(2'-HYDROXY-n-PROPYL)-CYCLOPROPANE (IVb)

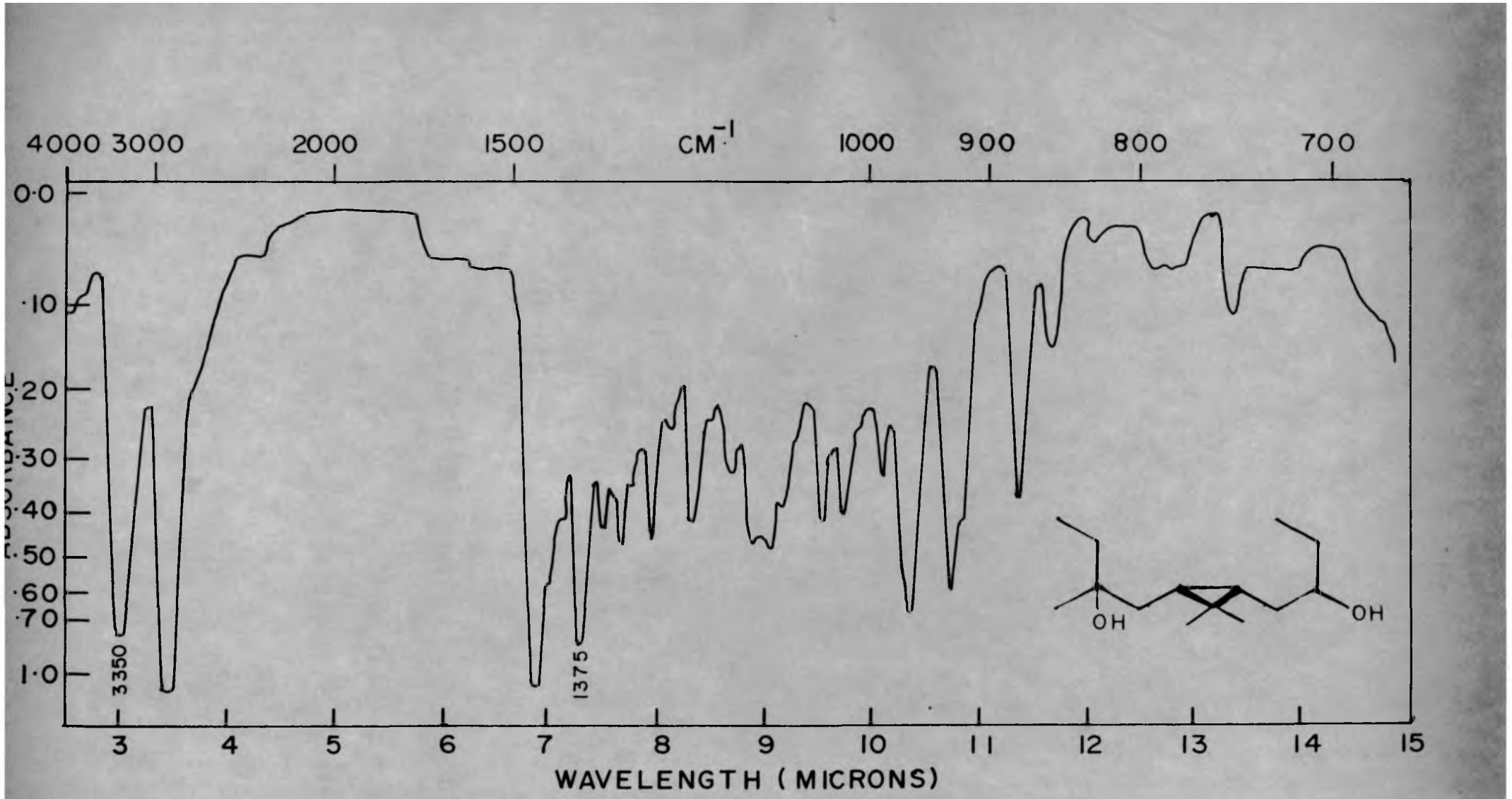


FIG 40. IR SPECTRUM OF 3,3-DIMETHYL-2-(2'-HYDROXY-2'-METHYL-n-BUTYL)-1-(2'-HYDRO
-n-BUTYL) CYCLOPROPANE (IVa)

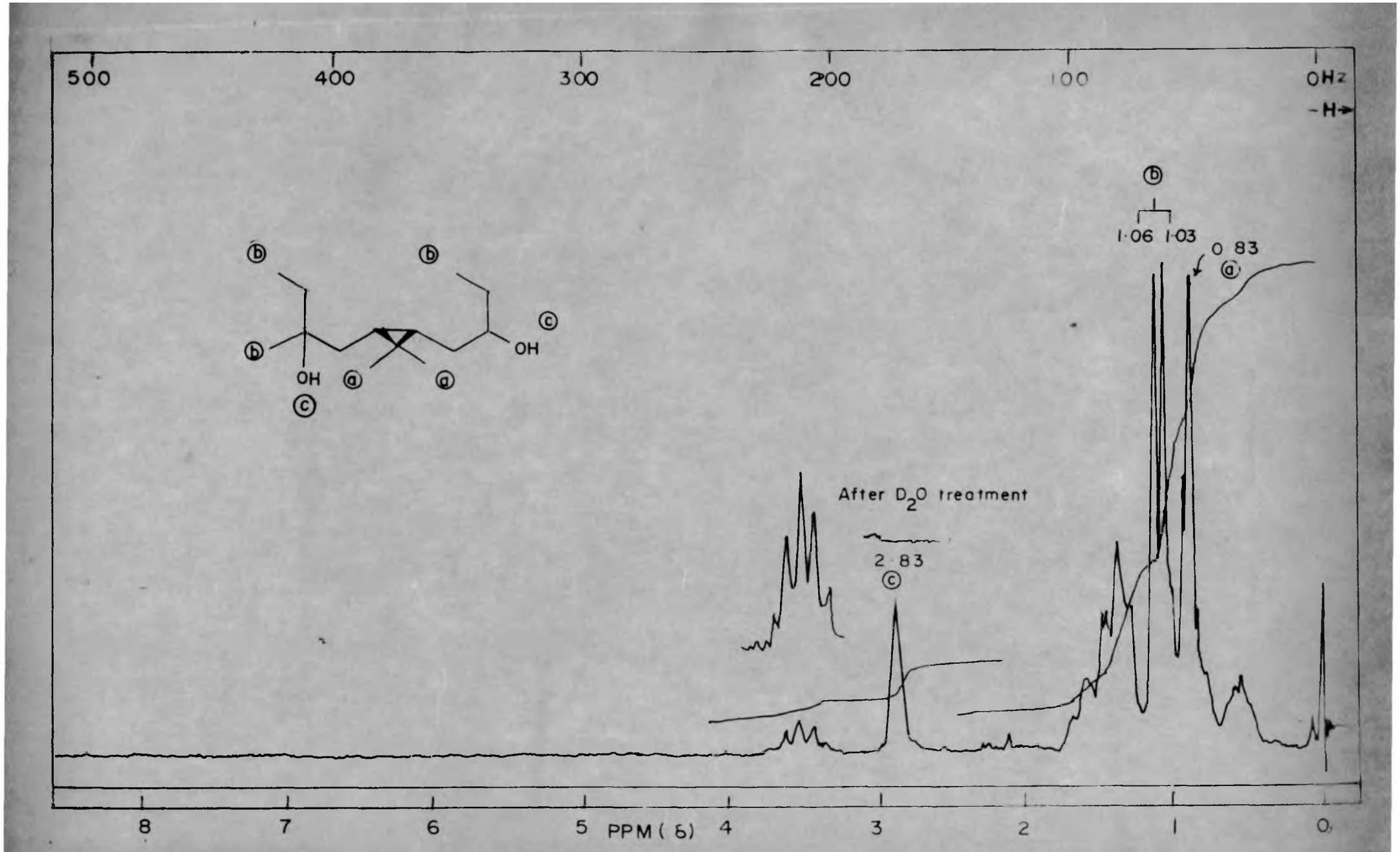


FIG. 41. NMR SPECTRUM OF 3,3-DIMETHYL-2(2'-HYDROXY-2'-METHYL-n-BUTYL)-1-(2'-HYDROXY-BUTYL) CYCLOPROPANE (IV a)

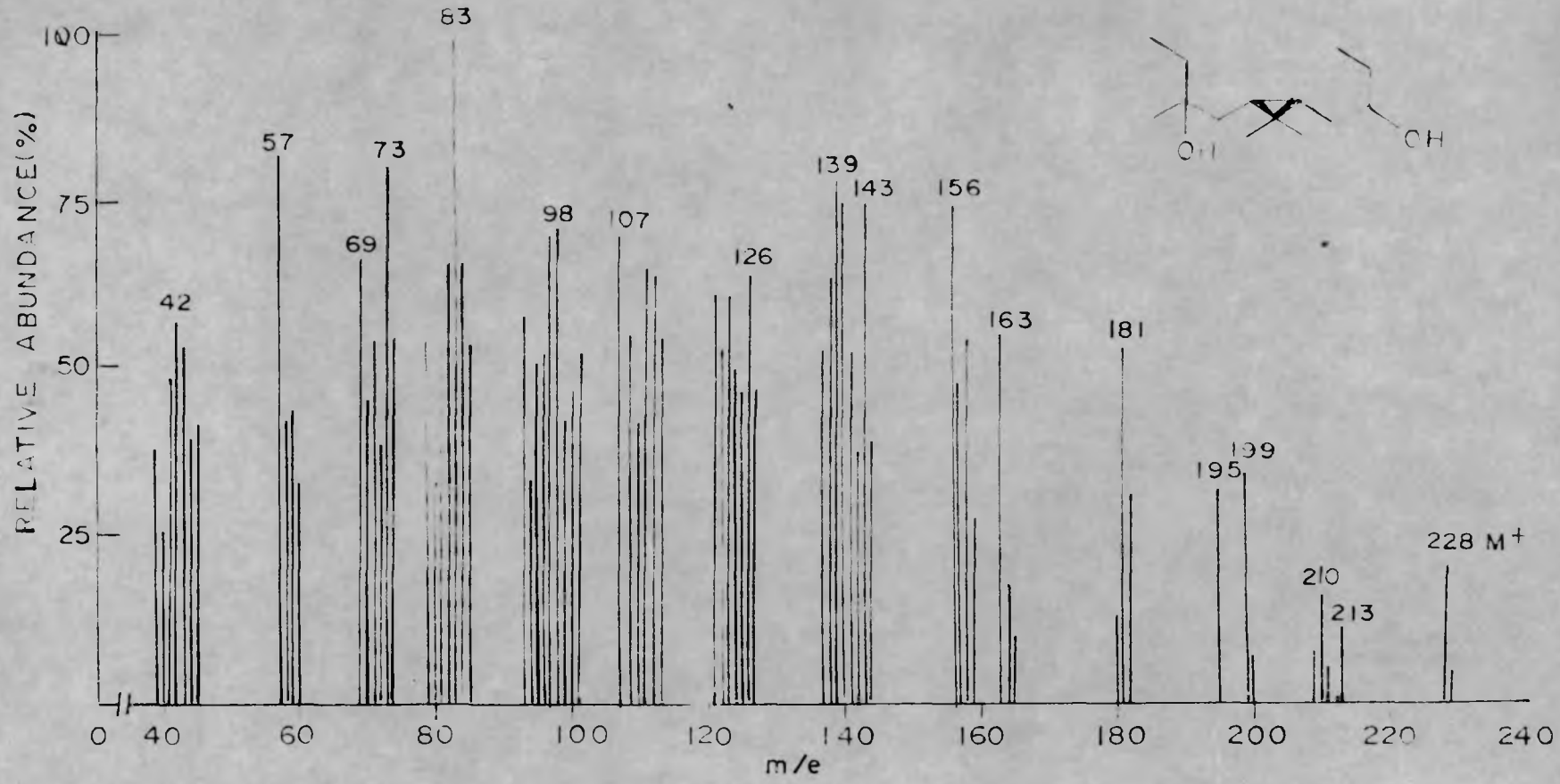


FIG. 42 MASS SPECTRUM OF 3,3-DIMETHYL-2-(2'-HYDROXY-2'-METHYL-n-BUTYL)-1-(2'-HYDROXY-n-BUTYL) CYCLOPROPANE (IV a)

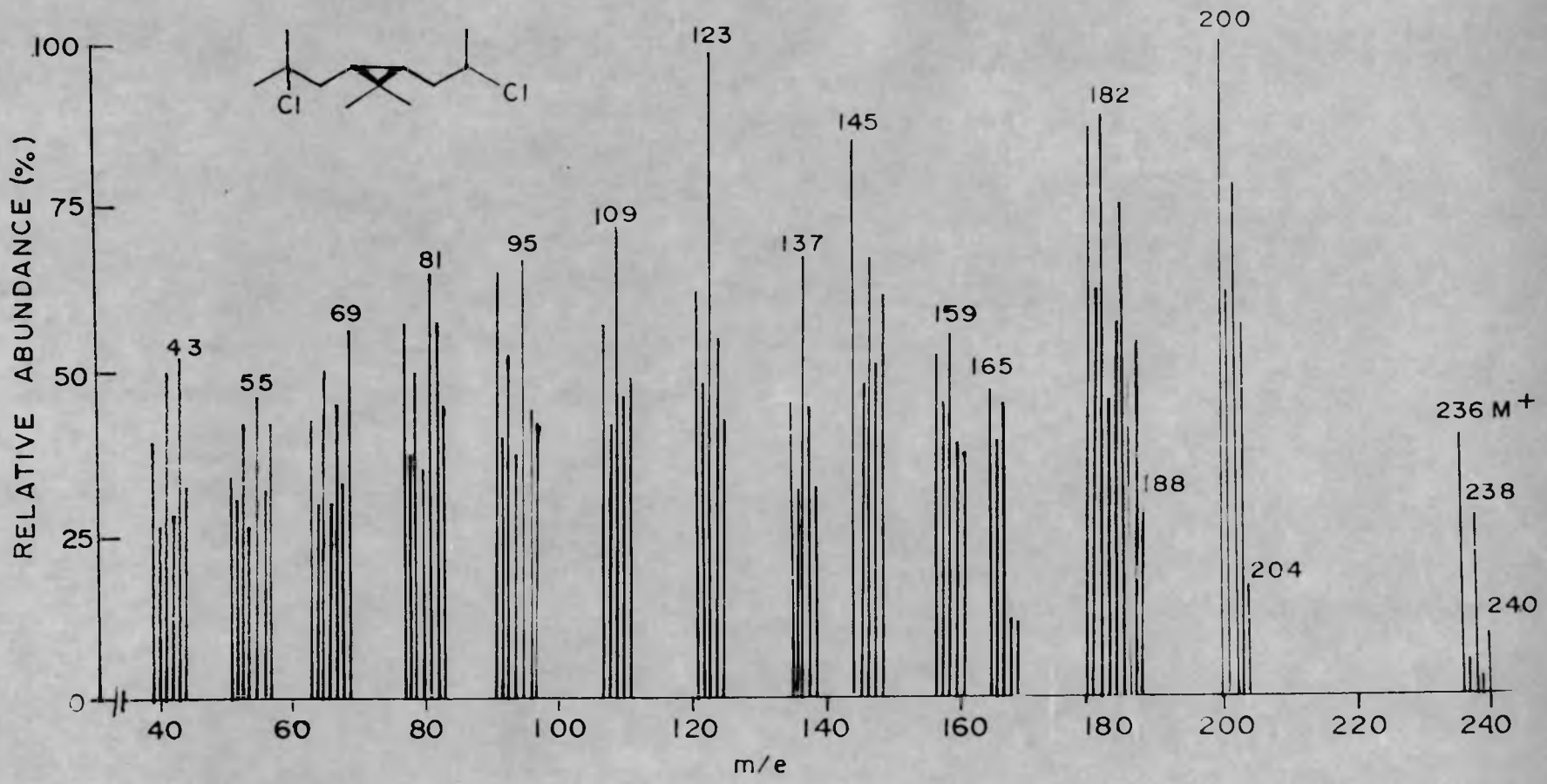


FIG 43. MASS SPECTRUM OF 3,3-DIMETHYL-2-(2'-CHLORO-2'-METHYL-n-PROPYL)-1-(2'-CHLORO-n-PROPYL) CYCLOPROPANE (Vb)

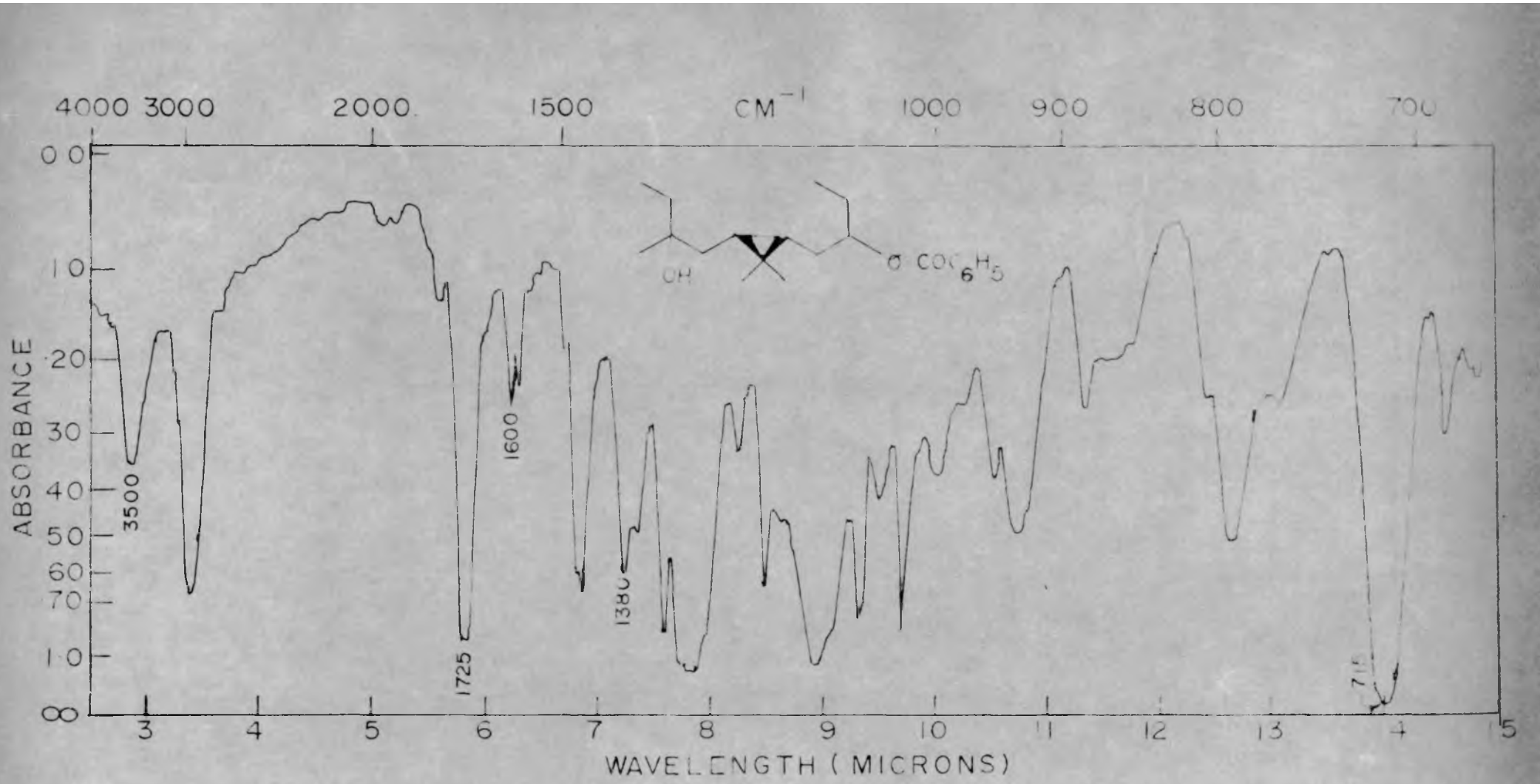


FIG. 44 IR SPECTRUM OF 3,3-DIMETHYL-2-(2'-HYDROXY-2'-METHYL-n-BUTYL)-1-(n-BUTYL-2'-BENZOYLOXY)CYCLOPROPANE(XIIa)

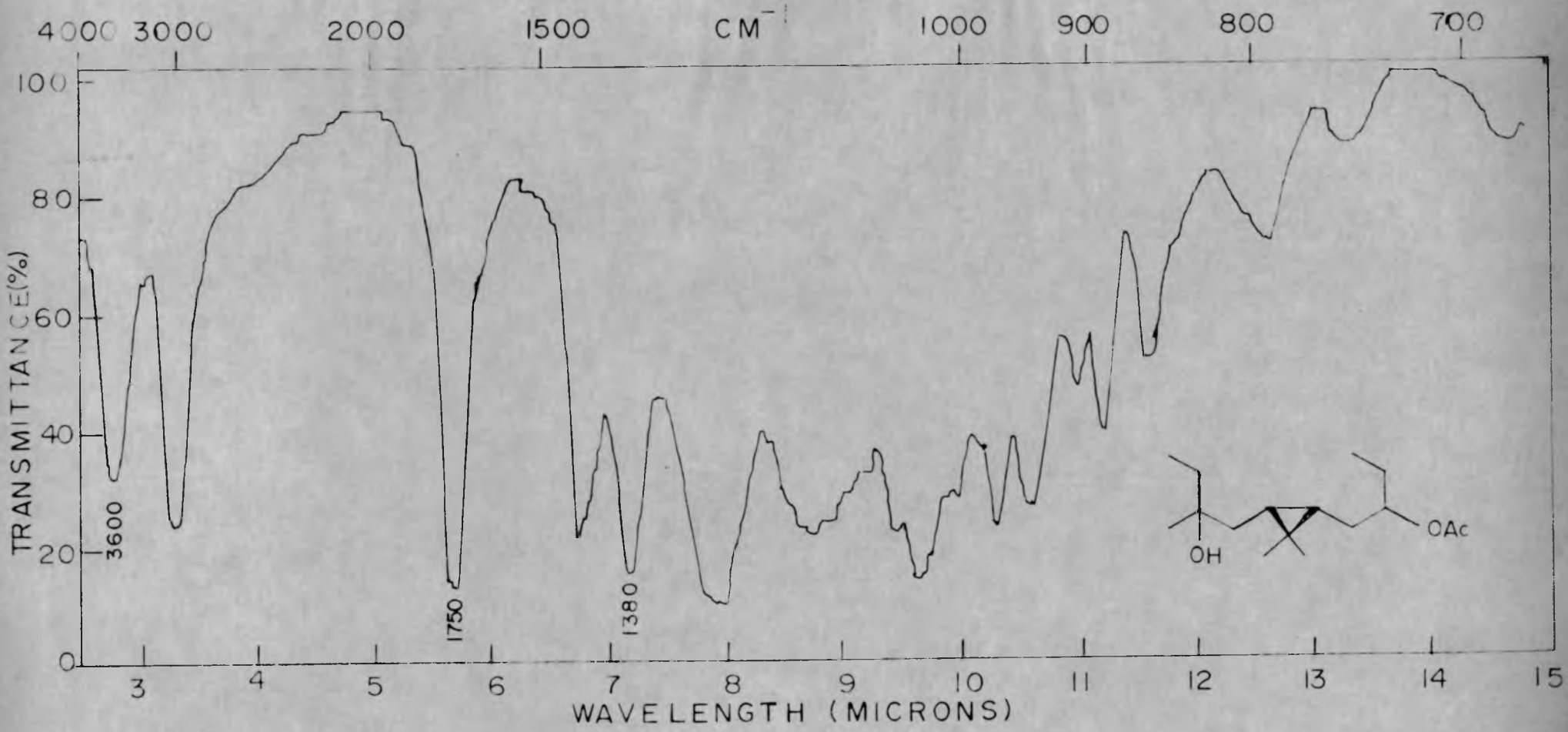


FIG 45. IR SPECTRUM OF 3,3-DIMETHYL-2-(2'-HYDROXY-2'-METHYL-n-BUTYL)-1(n-BUTYL-2'-ACETYLOXY)CYCLOPROPANE (VIb)

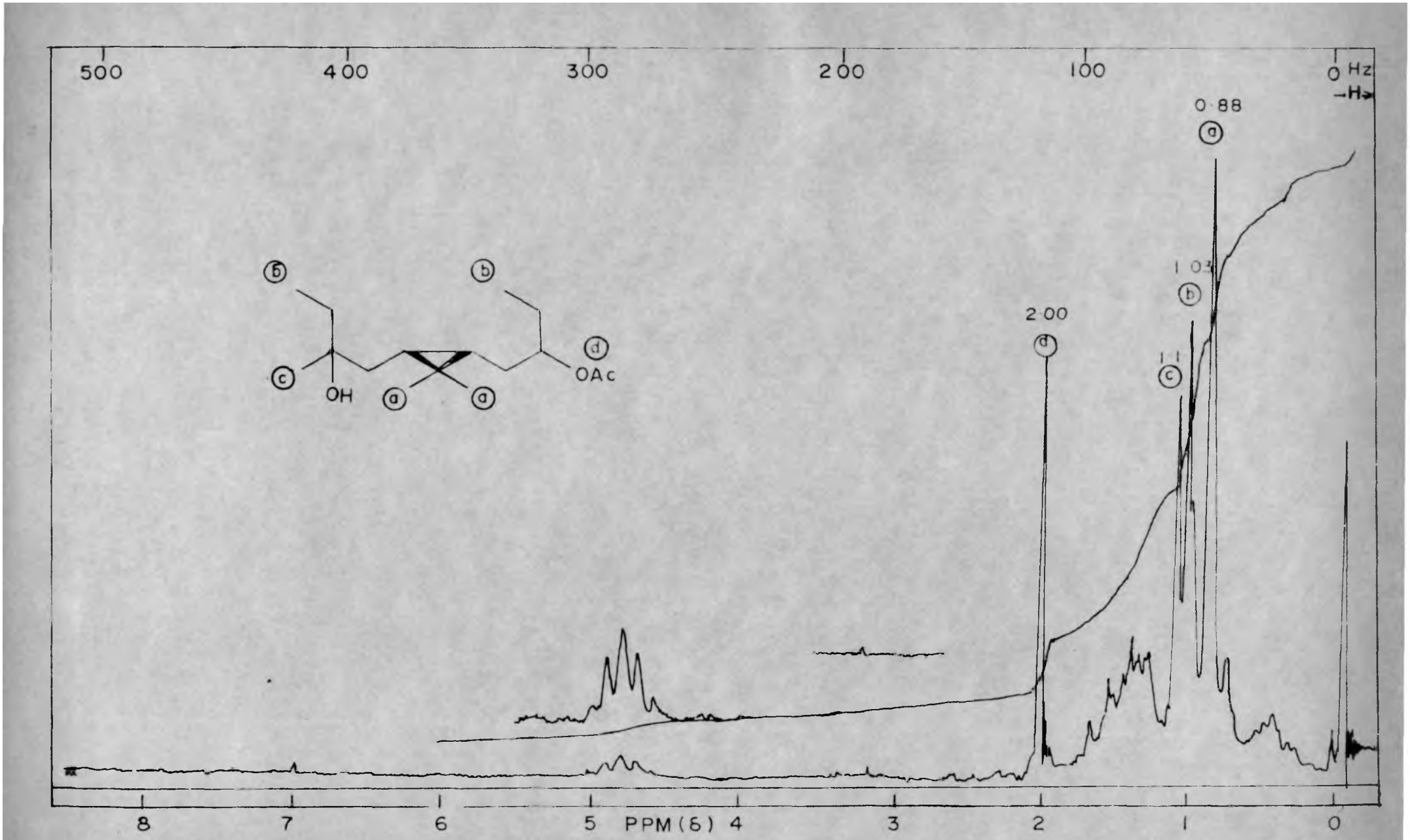


FIG 46 NMR SPECTRUM OF 3,3-DIMETHYL-2-(2'-HYDROXY-2'-METHYL-n-BUTYL)-1-(n-BUTYL-2'-ACETYLOXY) CYCLOPROPANE (VIb)

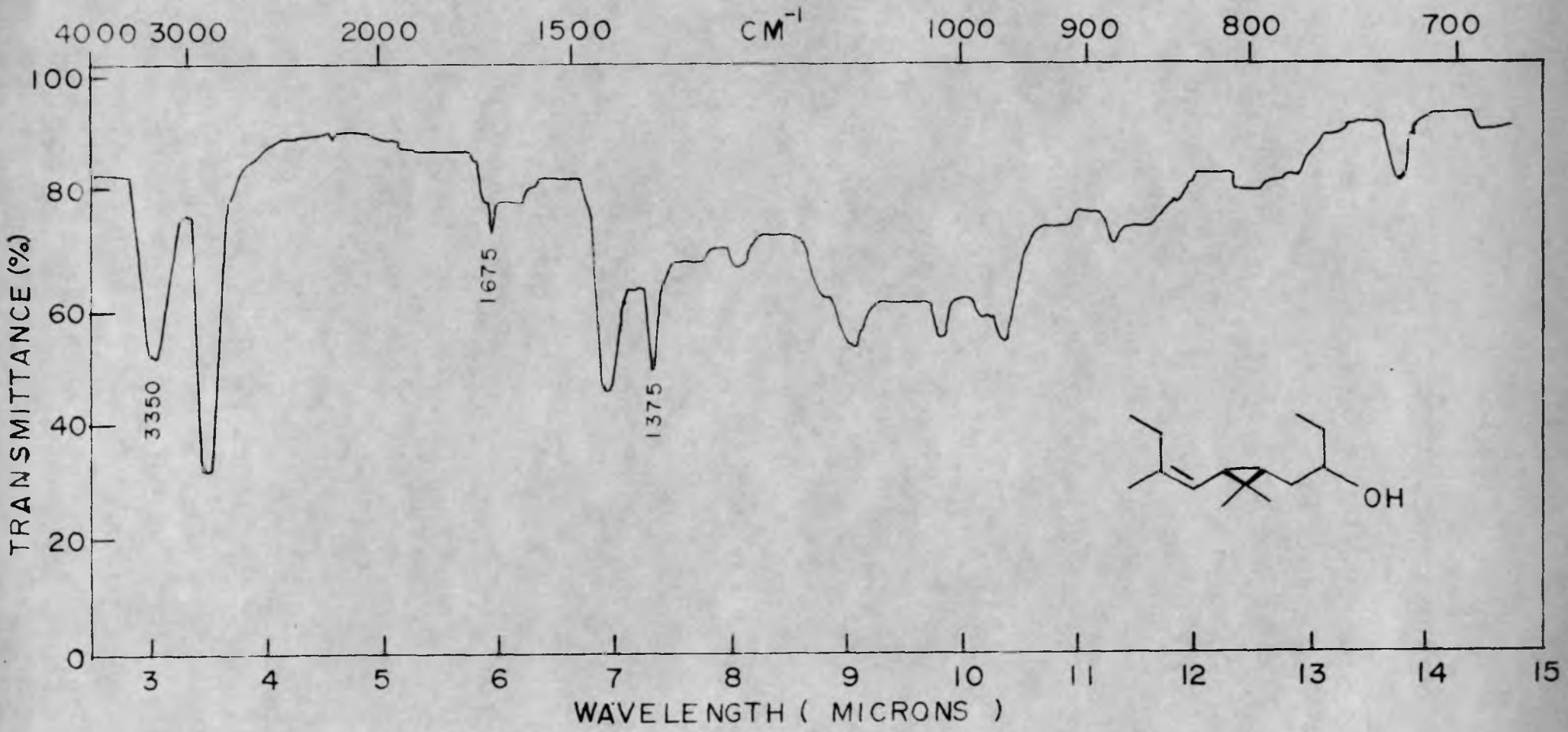


FIG 47. I R SPECTRUM OF 3, 3 – DIMETHYL – 2 – (2' – METHYL – BUT – 1' – ENYL) – 1 – (2' – HYDROXY – n – BUTYL) CYCLOPROPANE (VIIIa)

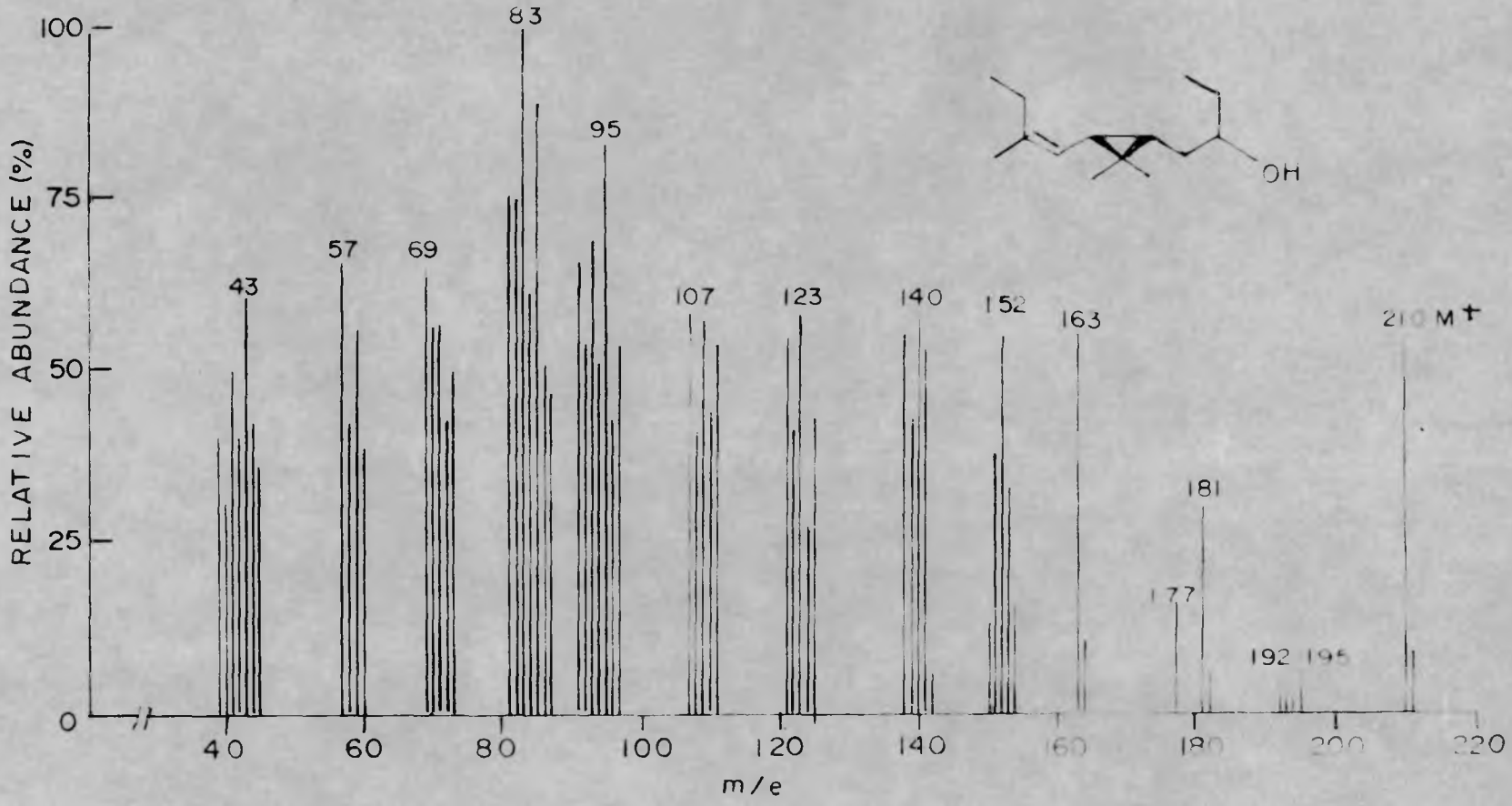


FIG 48. MASS SPECTRUM OF 3,3-DIMETHYL-2-(2'-METHYL-BUT-1'-ENYL)-1-(2'-HYDROXY-n-BUTYL) CYCLOPROPANE (VIIIa)

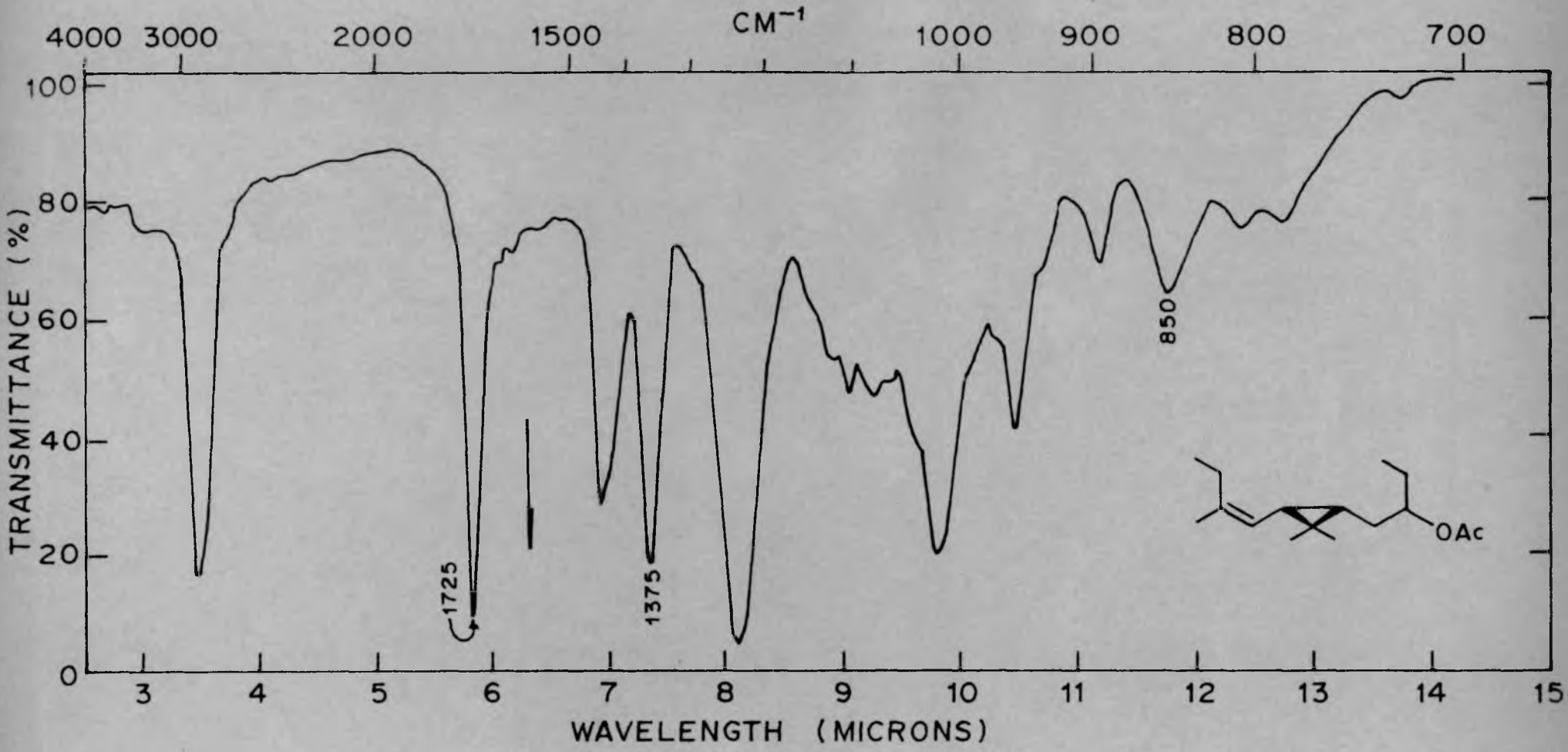


FIG. 49 IR SPECTRUM OF 3,3-DIMETHYL-2(2'-METHYL-BUT-1'-ENYL)-1-(n-BUTYL-2'-ACETYLOXY) CYCLOPROPANE (VIII b)

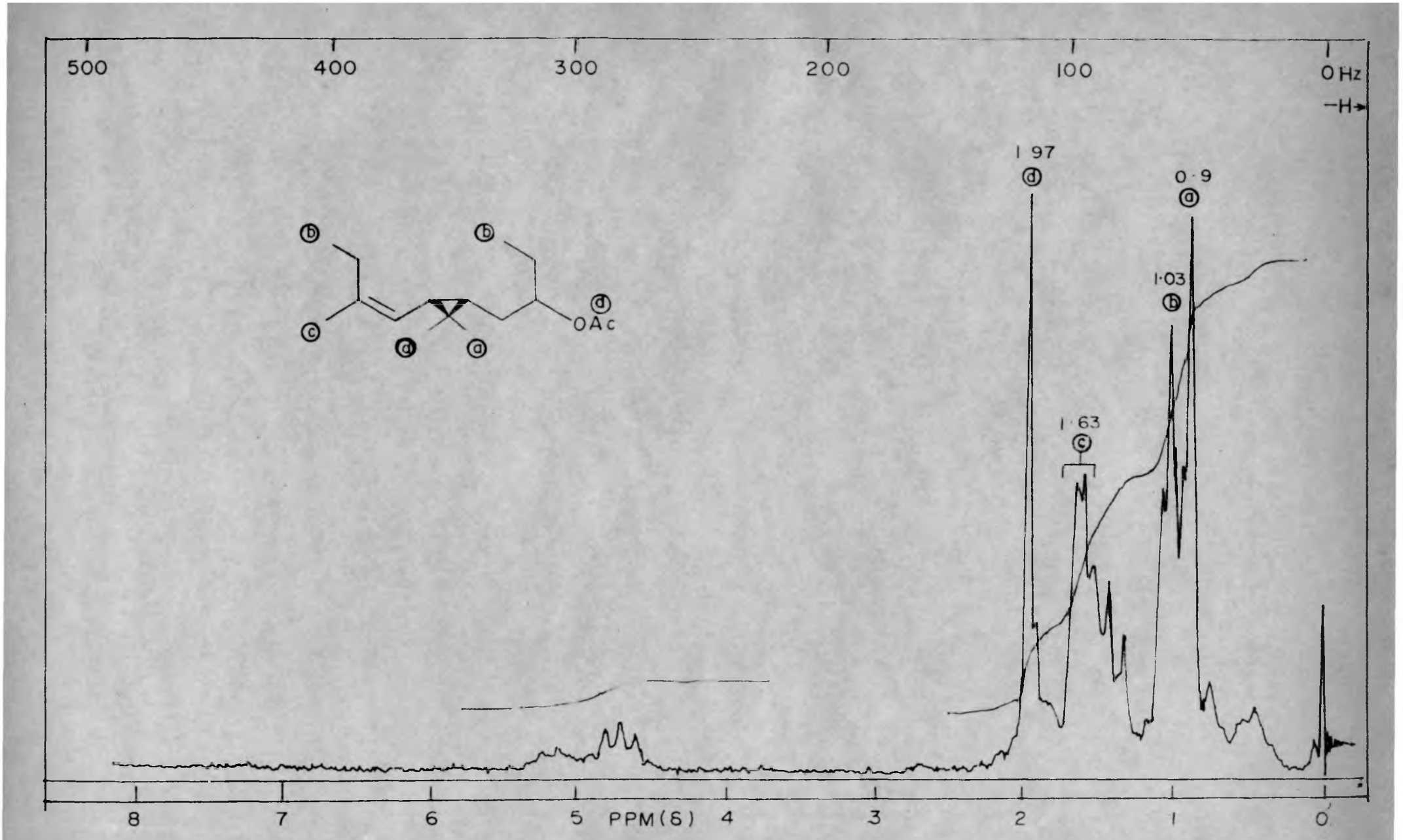


FIG 50 NMR SPECTRUM OF 3,3-DIMETHYL-2-(2'-METHYL-BUT-1'-ENYL)-1-(n-BUTYL-2'-ACETYLOXY) CYCLOPROPANE (VIIIb)

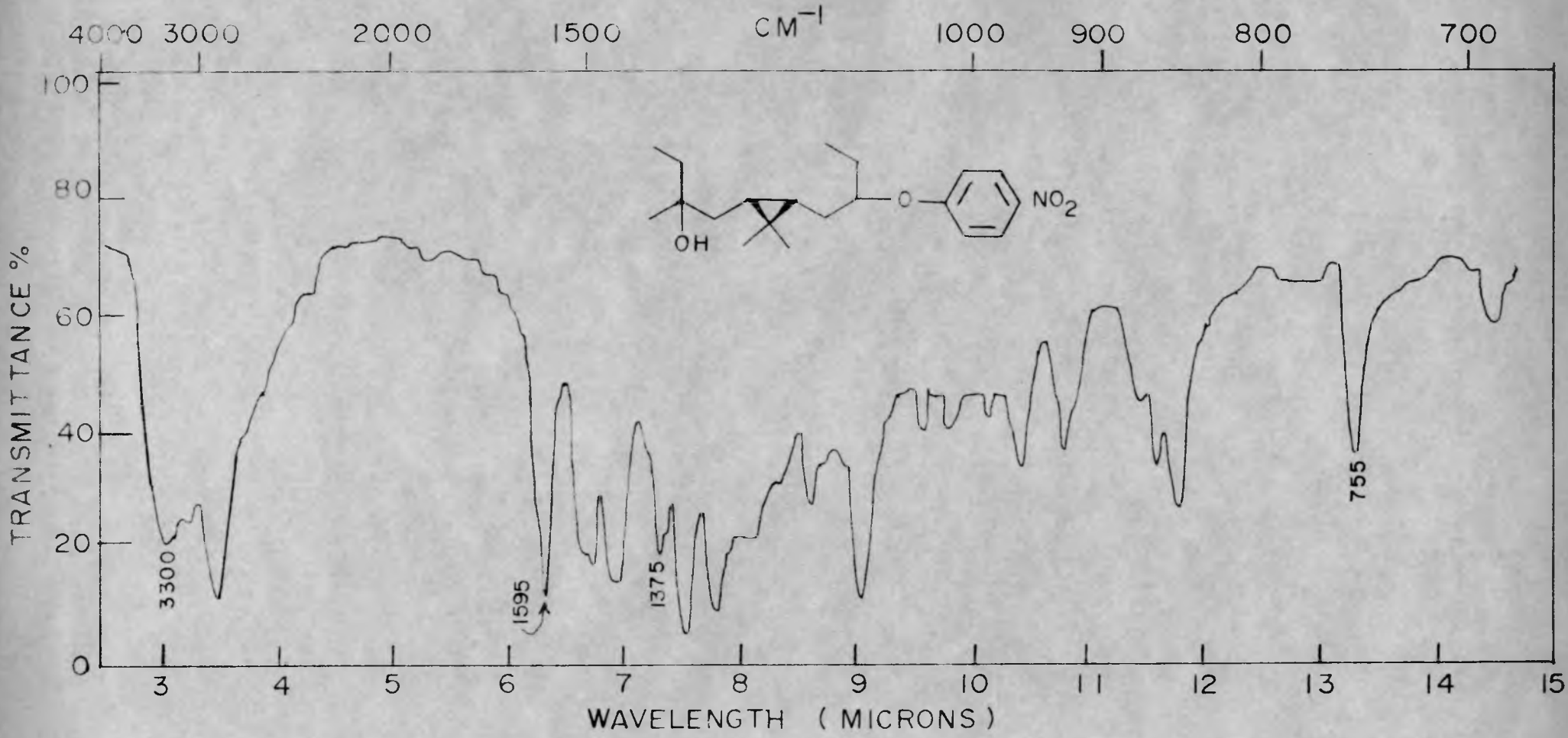


FIG. 51. IR SPECTRUM OF 3,3-DIMETHYL-2-(2'-HYDROXY-2'-METHYL-n-BUTYL)-1-(2'-p-NITROPHENYLOXY-n-BUTYL) CYCLOPROPANE (XI)

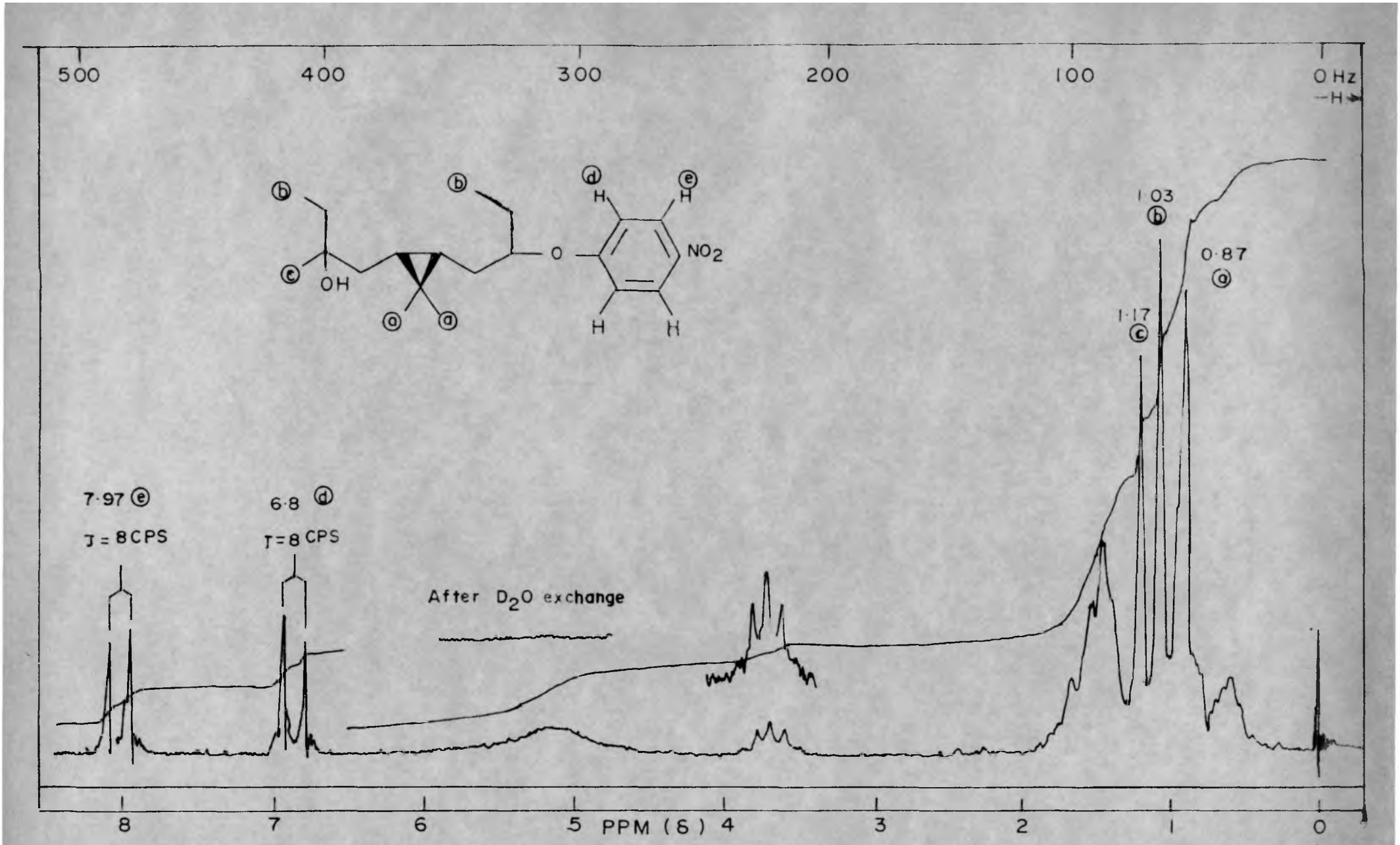


FIG. 52 NMR SPECTRUM OF 3,3-DIMETHYL-2-(2'-HYDROXY-2'-METHYL-n-BUTYL)-1-(2'-p-NITRO PHENYLOXY -n- BUTYL) CYCLOPROPANE (XI)

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PART - III

CYCLIC JUVENOIDS

CHAPTER I

I N T R O D U C T I O N

PART III

Cyclic Juvenoids

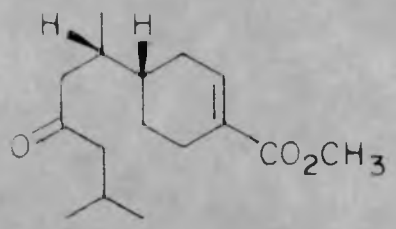
CHAPTER I

Introduction:

The wood of Canadian Balsam fir (Abies balsamea) contains factors exhibiting a high JH-activity specially on the bug Pyrrhocoris apterus. This was due to the discovery of Slama[1] in 1965 who observed that the larvae of the above hemipteran bug failed to metamorphose into adults when they came into contact with the papers manufactured from the above balsam fir. The active compound in the 'paper factor' was identified as (+)-juvabione, the methyl ester of todomatuic acid (Ia) by Bowers et al.[2] and also by Cerny et al.[3] independently. The latter authors also isolated another more active factor, dehydrojuvabione (II) from a slovak fir.

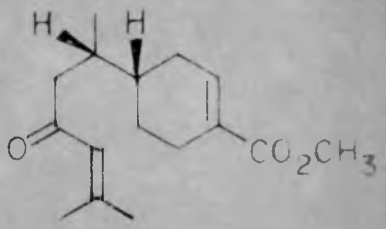
Recently Manville[4] has isolated the epimeric mixtures of juvabiol (A) and isojuvabiol (B) and also the dehydro-juvabiol (C) from the North American Abies balsamea (L). Mill.trees and reported that these juvabione related alcohols are insect juvenile hormone analogues with selective action typical of juvabione Ia and dehydrojuvabione II. The original 'paper factor' is therefore not due to a mixture of Ia and II only, the corresponding alcohols also play an important role in this factor.

CHART-16



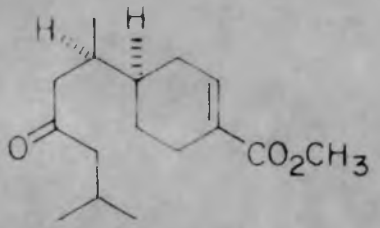
I a

(+) — JUVABIONE



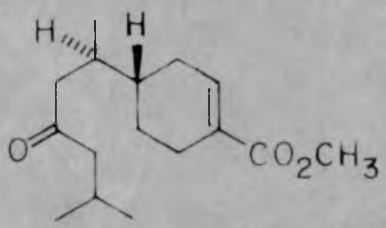
II

DEHYDROJUVABIONE



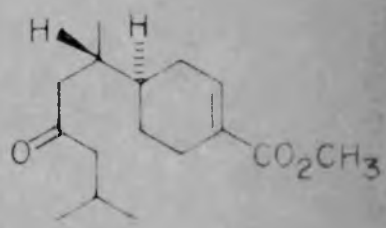
I b

(-) — JUVABIONE



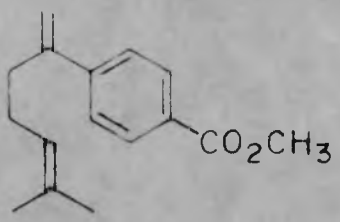
I c

(+) — EPIJUVABIONE



I d

(-) — EPIJUVABIONE



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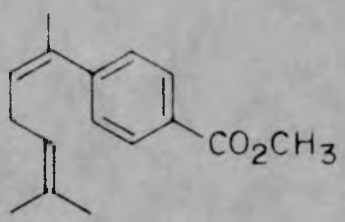

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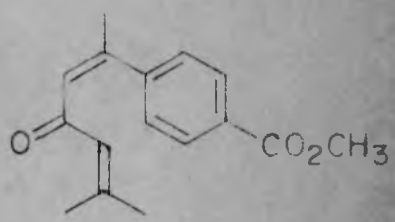
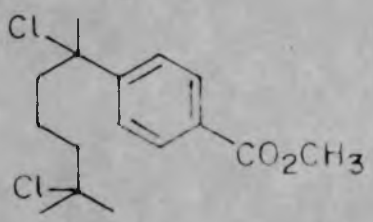
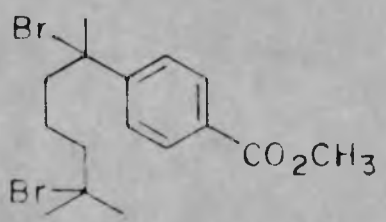


V



VI



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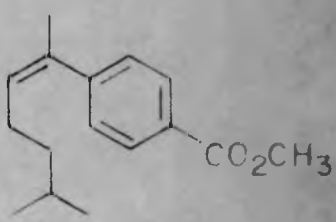

VIII

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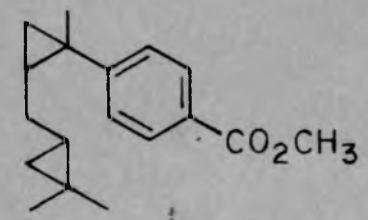

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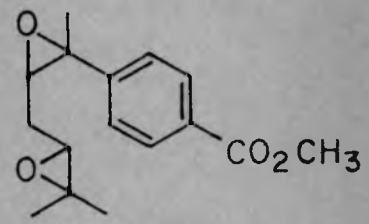
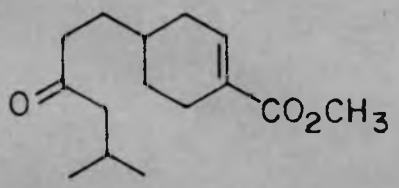
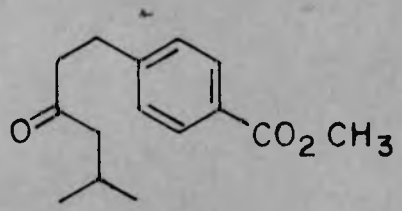


X



XI



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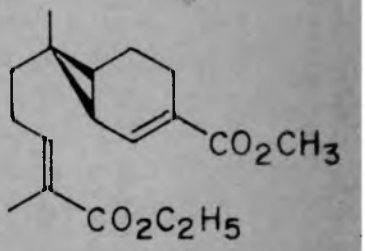

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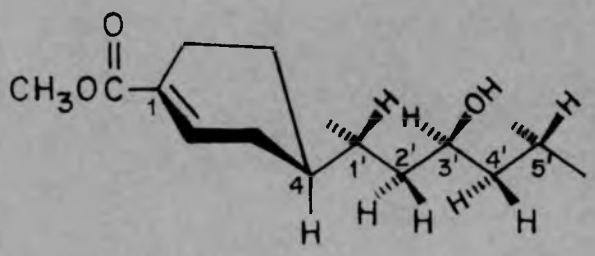
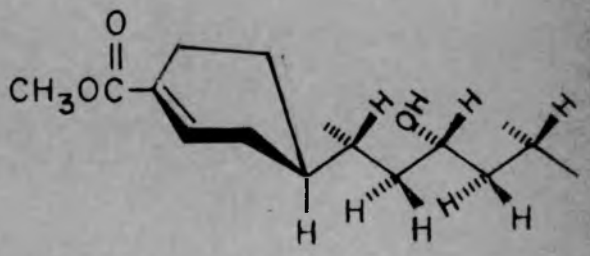


A



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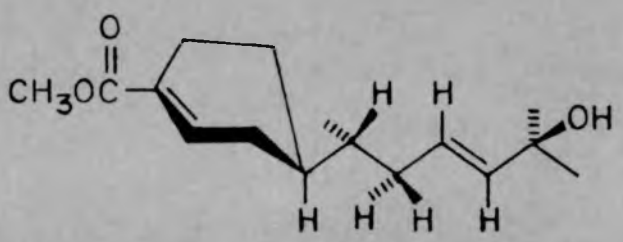


C

The first synthesis of racemic (+)-juvabione was reported by Mori and Matsui[5] with the use of p-methoxy-acetophenone as the starting material. The synthesis of racemic juvabione and dehydro-juvabione was also reported by Ayyar & Krishna Rao[6]. The first stereo-specific synthesis was attempted by Birch et al.[7] Bowden et al.[8] have described a stereospecific synthesis of (+)-juvabione and have suggested that out of the four theoretically possible isomers of juvabione, the naturally occurring (+)-juvabione has an absolute configuration R at position 4 of the menthane skeleton and absolute configuration S at position 8 of the same system. The starting material for his synthesis was with R(+)-Limonene on one hand and S(-)-Limonene on the other with known absolute configuration. The enantiomeric (-)-juvabione (Ib) and (-)-epijuvabione (Id) with configuration at the optically active centers as S,R and S,S respectively were prepared from S(-)-Limonene.

It is noteworthy that the biological activities of optical isomers of juvabione on Pyrrhocoris apterus and Dysdercus Cingulatus differ only to a negligible extent as observed by Slama[9].

The first juvabione and dehydrojuvabione analogues of the aromatic series were prepared by Buchy and Sorm[10] starting from p-bromobenzyl alcohol. The compounds III-X also been reported by the same authors. Compounds III and IV exhibited a relatively high biological activity especially on the hemipterans of the family Pyrrhocoridae. Compounds VI and VII

showed high biological activity on the hemipteran Dysdercus cingulatus. Compound IX showed higher biological activity than the analogous diepoxide X. Compound VIII exhibited lower activity.

The synthesis of aromatic juvabione analogues have also been described by Ayyar and Krishna Rao[6].

(±)-Demethyljuvabione (XI) and demethyl-ar-juvabione (XII) synthesised by Mori et al.[11] also proved to be the most active substance. Compound (XIII) synthesized by Mori and Matsui[12] also exhibited JH-activity on the hemipteran Pyrrhocoris apterus.

CHAPTER II

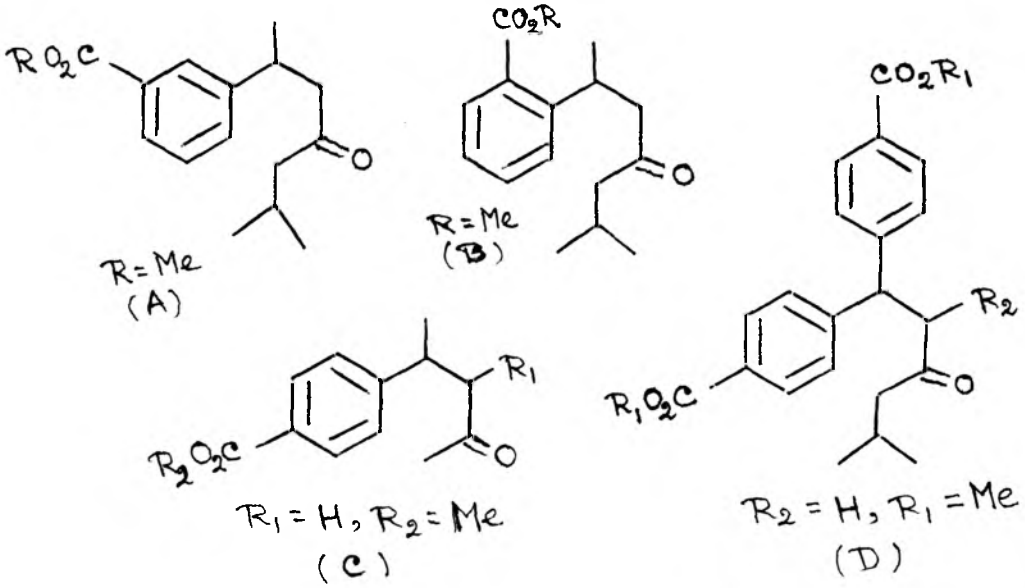
Juvabione analogues: Synthesis of substituted terpenoids bearing a cyclopropane ring

CHAPTER II

Insect Juvabione Analogues: Synthesis of Substituted Terpenoids Bearing a Cyclopropane Ring

A. Present scheme and work

Meno and Krishna Rao[13] have reported some aromatic juvabione analogues with varied position of the ester group in the aromatic ring. These compounds still exhibit JH-activity (e.g. A & B). Even the JH-analogues without the presence of isopropyl group in the side chain (e.g. C) and also the compound containing two aromatic nuclei in the molecule (e.g. D) are also active.



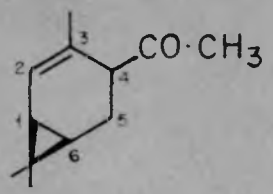
The foregoing data thus clearly indicates that a variety of structures based on a substituted six-membered ring, either olefinic or aromatic, together with an attached side

chain, exhibit JH-activity. It was therefore of interest to synthesize a few other novel structures to study the structure activity relationship further. The present synthesis of juvabione analogues is based on the replacement of the substituted cyclohexene or aromatic nucleus with Car-2-ene nucleus.

B. Results and discussion:

4-(1-Hydroxy-1-methyl-2-carbethoxy ethyl)-car-2-ene (II) was obtained by Reformatsky reaction on (+) 4-acetyl-car-2-ene (I)[14] using zinc and ethyl bromo-acetate. Its IR spectrum showed absorption at 3700 cm^{-1} (hydroxyl), 1725 cm^{-1} (ester carbonyl), 1375 cm^{-1} (cyclopropane ring system). The NMR spectrum exhibited signals (δ) at 0.8 (2H, m, cyclopropyl protons); 0.83 [6H, $C(CH_3)_2$]; 1.03 (3H, s, Me-on tertiary centre); 1.27 (3H, OCH_2Me); 1.8 (3H, bs, C = CMe); 4.06 to 4.26 (2H, q, OCH_2); 5.53 (1H, olefinic proton). The hydroxy ester (II) on treatment with $POCl_3$-pyridine gave 4-(2-carbethoxy-1-methyl vinyl) car-2-ene (IV), b.p. 125°(bath)/2 mm. Its IR spectrum displayed ester carbonyl absorption at 1750 cm^{-1} and unsaturation at 1650 cm^{-1}. Its UV-absorptions are consistent with the typical of an α,β-unsaturated ester, [λ_{max} 224 nm (ε, 14,050)]. Its NMR spectrum showed signals (δ) at 0.83 (2H, m, cyclopropyl protons); 0.86 and 1.06 [6H, $C(CH_3)_2$]; 1.26 (3H, t, OCH_2Me); 1.56 and 1.8 (3H each, Me's on double bonds); 3.8 to 4.33 (2H, q, OCH_2 protons); 5.56 (2H, olefinic

CHART - 17



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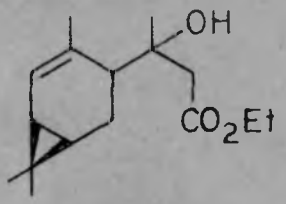

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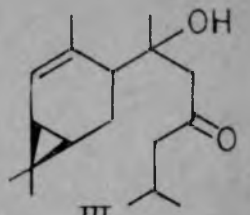

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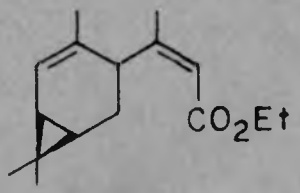

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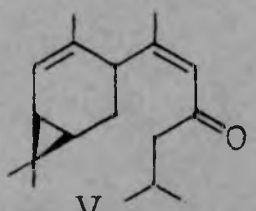

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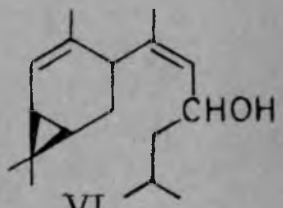

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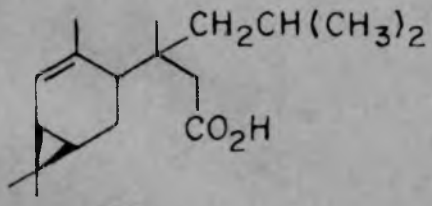

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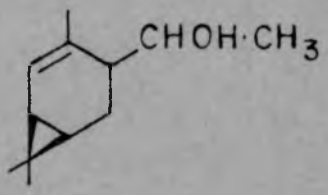

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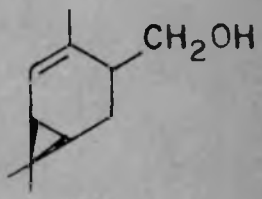

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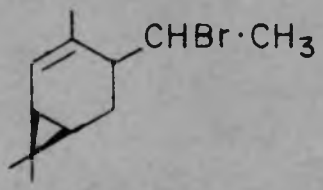

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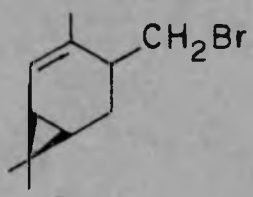

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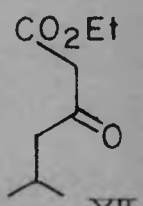

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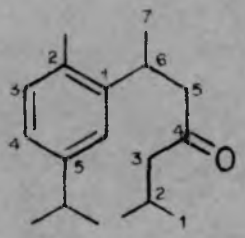
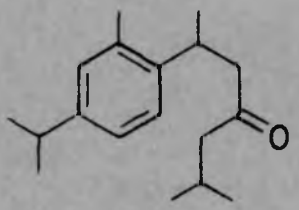


67%

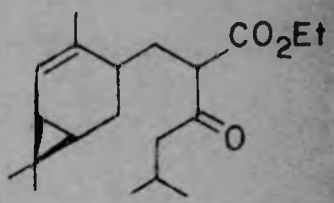
XIII a

+



33%

XIII b



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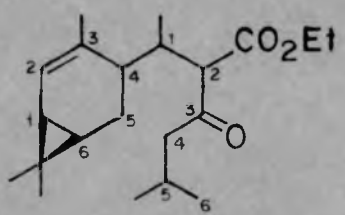
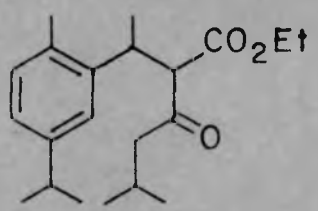
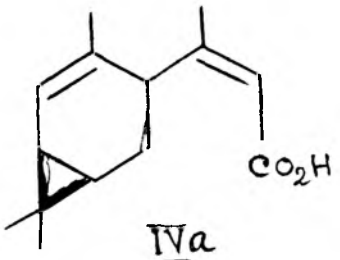


XV



XVI

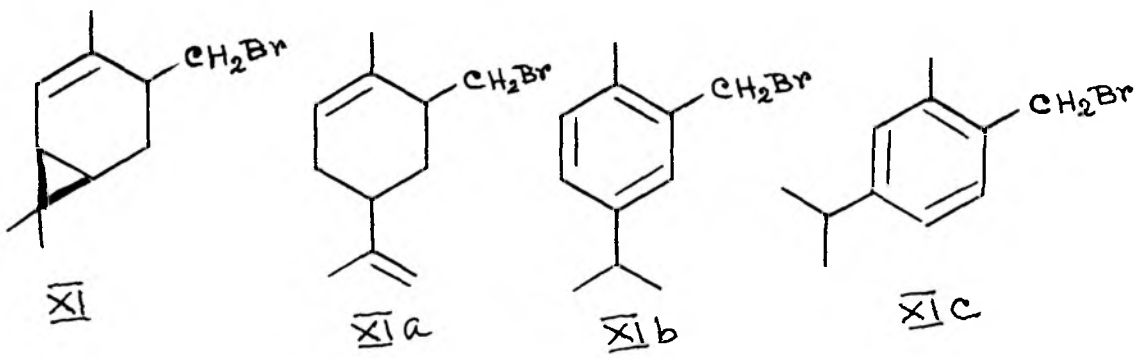
protons). Compounds II and IV were subjected to Grignard reaction using isobutyl magnesium bromide to obtain 4-(1,5-dimethyl-1-hydroxy-3-oxo-hexyl) car-2-ene (III) and 4-(1,5-dimethyl-3-oxo-hex-1-enyl) car-2-ene (V) respectively. Compound III exhibited IR-absorption at 3450 cm^{-1} (hydroxyl); 1725 (carbonyl). Its NMR spectrum showed signals (δ) at 1.0 (6H, CH_3 protons on cyclopropane ring; 1.33 (6H, CH_3 protons on isopropyl side chain); 2.13 (4H, CH_2 protons adjacent to carbonyl function); 5.73 (1H, olefinic proton). The IR spectrum of the compound V displayed carbonyl absorption at 1716 cm^{-1} and unsaturation at 1650 cm^{-1}. Its NMR spectrum revealed signals at 0.86 (6H, $C(CH_3)_2$; 1.00 and 1.06 (6H, Me's on isopropyl side chain) 1.56 and 1.80 (Me's on double bond); 2.17 (2H, m, ($COCH_2$) 5.1 and 5.47 (2H, olefinic protons). The compound V on treatment with $LiAlH_4$ produced 4-(1,5-dimethyl-3-hydroxy-hex-1-enyl)-car-2-ene (VI).



IVa

The unsaturated acid IVa obtained by hydrolysis of IV when treated with isobutyl lithium gave mainly the compound VII, 4-(1-isobutyl-1-methyl-2-carboxy ethyl)car-2-ene. No detectable amount of the α,β-unsaturated ketone V was isolated.

(+)-2-Carene-4α-methanol (IX) and the $NaBH_4$ reduction product of (+)4α-acetyl-car-2-ene, 4-1'-hydroxy-ethyl-car-2-ene (VIII) were converted into the corresponding bromo compounds on treatment with equimolar proportions of PBr_3-pyridine in benzene. The IR absorption of 4-bromo-methyl-car-2-ene (XI) at 1650 and 1380 cm^{-1} corresponds to unsaturation and cyclopropane ring system respectively. Its NMR spectrum revealed signals at 0.86 and 1.06 (3H each, s,s, Me's on cyclopropane ring); 1.7 (3H, bs, Me on double bond); 3.86 (2H, m, CH_2Br); 5.37 (1H, olefinic proton). The NMR spectrum of the bromo compound X exhibited signals at 0.8 and 1.0 (3H each s,s, Me's on cyclopropane ring); 1.26 (3H, CH_3 protons); 1.7 (3H, bs, Me on double bond); 4.66 (1H, m, CHBr); 5.45 (1H, olefinic proton). The bromo compound XI on passing through a silica gel column (pet.ether-chloroform mixture (3:1) as eluent) at room temp. rearranged mainly to the compound XIa by an acid-catalysed ring opening of the vinyl cyclopropane system, together with small amounts of XIb, XIc and the unchanged XI on the basis of the NMR spectrum.(Fig. 66).



XI XIa XIb XIc

The bromo-compound X when condensed with ethyl-3-oxo-5-methyl-hexanoate (XII) in presence of sodium ethoxide in ethanol gave mainly a mixture of the ketone XIIIa and its isomer XIIIb. Decarboxylation of the β-keto-ester and the aromatization of the car-2-ene nucleus occurred simultaneously under the reaction condition. The isomeric mixture was not separated. The NMR signals (δ) (Fig. 68) at 1.16, 1.27 (isopropyl), 2.30 (CH_3 on aromatic ring) and 6.87 (aromatic protons) are characteristics of meta and para cymene derivatives. The corresponding methyl signals from the isopropyl group on the aromatic ring of one isomer tends to merge with those from the other isomer at 1.16 and 1.27 δ respectively and it appears from the ratio of the intensity of the corresponding signals at these positions that the two isomers are present in the ratio of 2:1 approximately. But which isomer is predominating in this case and the mechanism of their formation is still a subject of further investigation.

A base-catalysed aromatization of (+)-car-3-one with N-lithioethylenediamine has been reported by Tyagi et al.[15] when a mixture of m and p-cymene in approximately equal proportions was obtained.

When the above condensation was carried out in presence of dry powdered sodium ethoxide in dry ether the main product isolated was 4-(2-carbethoxy-1,5-dimethyl-3-oxo-hexyl)-car-2-ene (XV). Another compound 2-methyl-5-carbethoxy-6(5-isopropyl-2-methyl phenyl) heptan-4-one (XVI) ~~of about 25%~~ probably with its m-isomer was also isolated.

from the reaction mixture. The keto-ester XIV was obtained by the similar reaction from the bromo compound XI.

The compounds III, V, XIV, XV and XVI were tested against freshly moulted fifth instar larvae of Dysdercus koenigii at a dose level of 10 µg/insect. This dose level was used as a diagnostic one for determining the presence or absence of JH-activity of the compounds. The compounds tested showed no JH-activity at the above dose level. Compound XVI when tested against fourth instar larvae of Aedes aegypti exhibited acute toxicity of the order of 100% at the maximum dose of 100 ppm but no JH-activity was exhibited at this or lower dosages.

C. Experimental Procedure:

4-(1-Hydroxy-1-methyl-2-carbethoxy-ethyl)-car-2-ene (II)

A solution of ethyl-bromoacetate (2.7 g, 0.015 mole) and (+)-4-acetyl-car-2-ene (I, 1.06 g, 0.006 mole) in dry benzene (15 ml) and absolute ether (5 ml) was slowly added to a mixture of freshly sandpapered zinc foil (1 g, 0.015 g. atom) in the form of narrow strips and dry benzene (5 ml) and dry ether (5 ml) during 20 min. maintaining nitrogen atmosphere. The reaction mixture was then refluxed for 3 hr, cooled and hydrolysed by addition of cold saturated ammonium chloride solution (50 ml) under vigorous stirring. The benzene solution was washed with cold saturated ammonium chloride solution (2 x 25 ml) and then with water (2 x 25 ml). The aqueous part was extracted with ether (2 x 25 ml) and the combined benzene and ether solutions were dried (Na_2SO_4) and filtered. The solvent was distilled off and the residue was chromatographed over silica gel. By eluting with a mixture of pet.ether (40-60°) and chloroform (3:1) compound II (0.79 g, 49%) was obtained as a colourless liquid, b.p. 120°(bath)/1.5 mm. (Found: C, 72.09; H, 9.79; M^+ 266 $C_{16}H_{26}O_3$ requires C, 72.14; H, 9.84; Mol.wt. 266.37) ν_{max} 3700, 2900, 1725, 1650, 1475, 1375, 1200, 1035 cm^{-1}. NMR (CCl_4, δ): 0.8 (2H, m, cyclopropyl protons); 0.83 [6H, $C(CH_3)_2$]; 1.03 (3H, s, Me on tertiary centre); 1.27 (3H, m, OCH_2Me); 1.8 (3H, s, $C=CHMe$); 1.83 to 2.36 (4H, CH_2 protons); 4.06 to 4.26 (2H, m, OCH_2); 5.53 (1H, olefinic proton).

4-(2-Carbethoxy-1-methyl vinyl)-car-2-ene (IV)

To an ice cold solution of hydroxy ester (II, 2.5 g) in pyridine (10 ml) was added phosphorous oxychloride (3 g) dropwise during 15 min with constant cooling and shaking. The reaction mixture was left overnight at 0°, poured into ice-water and extracted with ether. The ether extract was washed successively with cold dil. HCl, sat. $NaHCO_3$, water, brine and dried (Na_2SO_4). Ether was evaporated to get the residue (2.37 g) which was chromatgraphed over silica gel. By eluting with a mixture of pet.ether (40-60°) and chloroform (9:1) pure unsaturated ester (IVa, 0.87 g, 37%) was obtained as a colourless liquid b.p. 125°(bath)/2 mm. (Found: C, 77.33; H, 9.71; M^+ 248 $C_{16}H_{24}O_2$ requires C, 77.37; H, 9.74; Mol. wt. 248.36) ν_{max} 2950, 1750, 1650, 1470, 1375, 1145, 875 cm^{-1}. NMR (CCl_4, δ): 0.83 (2H, m, cyclopropyl protons); 0.86 and 1.06 (6H, $C(CH_3)_2$); 1.26 (3H, t, $OCH_2\underline{Me}$); 1.56 and 1.8 (3H each, Me's on double bond); 3.8 to 4.23 (2H, q, OCH_2 protons); 5.56 (2H, olefinic proton).

4-(1,5-Dimethyl-1-hydroxy-3-oxo-hexyl)-car-2-ene (III)

To a stirred solution of iso-butyl magnesium bromide (prepared from 1 g, 0.006 mole of isobutylbromide and 0.15 g, 0.006 mole of activated magnesium) in dry ether (25 ml) was added dropwise a solution of hydroxy ester (II, 1.32 g, 0.005 mole) in dry ether during 15 min maintaining nitrogen atmosphere throughout the reaction. After stirring the

mixture for half an hr at room temperature it was refluxed for 20 min, cooled and decomposed by pouring into an ice cold sat NH_4Cl (50 ml) and the resulting solution was extracted with ether (3 x 25 ml). Ether was evaporated to get the residue which was chromatographed over silica gel. By eluting with a mixture of pet.ether (40-60°) and chloroform (8:2) compound III (0.42 g, 35%) was obtained as a colourless liquid; b.p. 130°(bath)/2 mm. (Found: C, 77.59; H, 10.83; M^+ 278. $C_{18}H_{30}O_2$ requires C, 77.65; H, 10.86; Mol.wt. 278.42) ν_{max} 3450, 2900, 1725, 1375, 1030, 800, 755 cm^{-1}.

NMR (CCl_4,δ): 1.0 [6H, $C(CH_3)_2$]; 1.33 (6H, Me's on isopropyl side chain; 1.6 (2H, m, CH_2 protons); 2.13 (4H, CH_2 adjacent to carbonyl function); 5.73 (1H, olefinic proton).

~~4-(1,5-dimethyl-3-c-c-hex-1-enyl)-but-2-ene (V)~~

The ~~xxxxx~~ unsaturated ester (IV, 0.5 g, 0.002 mole) was treated similarly with isopropyl magnesium bromide (prepared from 0.079 g, 0.003 mole of magnesium and 0.4 g, 0.003 mole of isopropyl bromide) and working as usual afforded a liquid which was chromatographed over silica gel. By eluting with a mixture of pet. ether (40-60°) and chloroform (8:2) compound V (0.19 g, 37%) was obtained as a colourless liquid, b.p.130-5°(bath)/2 mm. (Found: C, 82.88; H, 10.78; M^+ 260. $C_{18}H_{28}O$ requires C, 83.02; H, 10.84; Mol.wt. 260.40). ν_{max} 2900, 1716, 1650, 1435, 1375, 1216, 1140, 1040, 865 cm^{-1}. NMR(CCl_4, δ): 0.86 [6H, Me's on cyclopropane ring]; 1.00 and 1.06 (6H, Me's on isopropyl); 1.56 and 1.80 (3H each, Me's

on double bond); 2.17 (2H, m, $COCH_2$); 5.1 and 5.47 (2H, olefinic protons).

4-(1,5-Dimethyl-5-hydroxy-hexyl)-car-3-ene (VI)

A solution of the unsaturated ketone V (0.18 g, 0.0005 mole) in ether (5 ml) was added dropwise with constant stirring to a suspension of lithium aluminium hydride (0.16 g, 0.0043 mole) in ether (10 ml). Ether was refluxed for 15 min, cooled and the complex was hydrolysed by cautious addition of water (15 ml). The ether layer was separated and the aqueous layer was extracted with ether (2 x 25 ml). The combined ether solution was evaporated and the residue was distilled to get the compound VI (0.11 g, 84%), b.p.132-5° (bath)/2 mm. (Found: C, 82.36; H, 11.48; M^+ 262. $C_{19}H_{30}O$ requires C, 82.33; H, 11.68; Mol.wt. 262.42). ν_{max} 3350, 1650, 1465, 1375, 1020, 835 cm^{-1}. NMR (CCl_4, δ): 0.7 to 0.8 (2H, m, cyclopropyl protons); 0.83 (6H, $C(CH_3)_2$); 1.07 and 1.08 (6H, Me's on isopropyl side chain); 1.33 (4H, CH_2 protons); 1.6 (6H, Me's on double bond); 5.0 and 5.46 (1H each, olefinic protons)

4-(1-Isobutyl-1-methyl-2-carboxy ethyl) car-3-ene (VII)

A solution of isobutyl lithium in tetrahydrofuran (THF) was prepared by dropwise addition of isobutyl bromide (1.37 g, 0.01 mole) to a stirred suspension of metallic lithium (0.2 g, 0.028 mole) in dry THF (10 ml) and continuous stirring

for 4 hr. A solution of the unsaturated acid, 3-(4'-car-2'-enyl)-2-enyl butyric acid (obtained by hydrolysis of IV by methanolic KOH) (0.22 g, 0.001 mole) in THF (5 ml) was then slowly added to the above solution. The mixture was stirred at room temperature for 1 hr and then at 45-50° for half an hr and decomposed with cold sat. NH_4Cl (25 ml). The organic layer was separated and the aqueous layer was extracted with ether (2 x 25 ml). The combined ether and THF solution was dried (Na_2SO_4) and evaporated to get the residue which was chromatographed over silica gel. By eluting with a mixture of pet.ether and chloroform (1:1) compound VII (0.18 g, 64%) was obtained as a colourless liquid, (b.p. of the methyl ester, 130°(bath)/2 mm) ν_{max} 3050, 1675, 1625, 1375, 1145, 965 cm^{-1}. NMR (CCl_4, δ): 0.87 ($6H_s$, Me's on cyclopropane ring); 0.95 ($6H_s$, $CHMe_2$); 1.06 ($3H_s$, CH_3 proton on tertiary centre); 1.60 ($3H_s$, CH_3 protons on double bond); 3.61 ($2H_t$, CH_2 protons adjacent to carboxyl group); 5.63 ($1H_t$, olefinic proton).

4-(1'-hydroxyethyl)-car-2-ene (VIII)

A solution of 4'-acetyl-car-2-ene (I, 1.6 g) in methanol (20 ml) was stirred with $NaBH_4$ (1.5 g) at 0° for 3 hr. The mixture was diluted with ice-water, acidified with cold dil.HCl and extracted with ether. The washed and dried (Na_2SO_4) extract was evaporated and the residue was distilled to get the hydroxy compound VIII (1.3 g, 80%), b.p. 130-5°(bath)/2 mm.

(Found: C, 79.83; H, 11.09. $C_{12}H_{20}O$ requires C, 79.94; H, 11.18%).

ν_{max} 3250, 2850, 1450, 1375, 1075, 900 cm^{-1}.

NMR (CCl_4, δ): 0.86 and 1.06 (3H each, s,s, Me's on cyclopropane ring); 1.13 (3H, d, CH_3 protons); 1.7 (3H, CH_3 protons on double bond); 3.83 (1H, m, CHOH); 5.42 (1H, olefinic proton).

4α,1'α-Bromomethyl-car-2-ene (X) - To an ice-cold solution of the alcohol VIII (0.9 g, 0.005 mole) and pyridine (0.4 g, 0.005 mole) in dry benzene (25 ml) was added PBr_3 (1.4 g, 0.0051 mole) dropwise with stirring during 10 min. Stirring was continued for 1 hr. and the solution was left overnight at room temperature. The reaction mixture was then poured into ice-water and extracted with benzene. The benzene extract was washed successively with cold dil. HCl, water, brine and dried ($MgSO_4$). Benzene was distilled off from the solution and the residue was directly used for the next reaction.

ν_{max} 2950, 1475, 1385, 1250, 825 cm^{-1}. NMR (CCl_4, δ): 0.8 and 1.0 (3H each, s,s, Me's on cyclopropane ring); 1.26 (3H, CH_3 protons); 1.7 (3H, bs, CH_3 protons on double bond), 4.06 (1H, m, CHBr); 5.45 (1H, olefinic proton).

4α-Bromo-methyl-car-2-ene (XI)

A solution of (+)-2-carene-4α-methanol (IX, 1.6 g, 0.01 mole) and pyridine (1 g, 0.012 mole) in dry benzene (50 ml) ecoled to 0° was treated similarly with PBr_3 (2.8 g, 0.01 mole).

The residue after working up as above was directly used for the next reaction. ν_{max} 2900, 1650, 1470, 1380, 1267, 825 cm^{-1}. NMR(CCl_4,δ): 0.86 and 1.06 (3H each, s,s, Me's on cyclopropane ring); 1.7 (3H, bs, CH_3 protons on double bond); 3.86 (2H, m, CH_2Br); 5.37 (1H, olefinic proton).

2-Methyl-6-(5-isopropyl-2-methyl phenyl) heptan-4-one (XIIIa) and 2-methyl-6(4-isopropyl-2-methyl phenyl) heptan-4-one (XIIIb)

A solution of sodium ethoxide prepared by dissolving sodium (0.15 g, 0.0065 mole) in ethanol (3 ml) was cooled to 0° and ethyl -3-oxo-5-methyl-hexanoate (XII, 0.96 g, 0.005 mole) was added. After stirring the mixture for half an hr. 4-1'-bromo-ethyl-car-2-ene (X, 1.2 g, 0.005 mole approx) in ethanol (2 ml) was added in one portion and the stirring continued for 3 hr.

Ethanol was distilled off and the reaction mixture was diluted with water and extracted with ether. The ether solution was washed with water, brine and dried (Na_2SO_4). After evaporation of ether the residue was chromatographed through silica gel. By eluting with a mixture of pet.ether (40-60°) and chloroform (10:1) a fraction was obtained (0.7 g) which was found to be a mixture of XIIIa (66.7%) and XIIIb (33.3%) on the basis of NMR spectrum. b.p. 125-135°(bath)/2.5 mm. (Found: C, 83.89; H, 10.90; M^+ 260; $C_{18}H_{28}O$ requires C, 83.02; H, 10.84; Mol.wt. 260.40). ν_{max} 2850, 1700, 1617, 1500, 1465, 1367, 1062, 825, 736 cm^{-1}.

NMR(CCl_4,δ): 0.76 to 0.95 (9H, CH_3 protons); 1.16 and 1.27 (3H each, s,s $CH(CH_3)_2$ on the aromatic ring); 2.07 (4H, m, $COCH_2$); 2.30 (3H, s, CH_3 on aromatic ring); 6.87 (3H, bs, aromatic protons).

4-(2-Carbethoxy-3-oxo-5-methyl hexyl) car-2-ene (XIV)

A solution of ethyl-3-oxo-5-methyl-hexanoate (XII, 0.86 g, 0.005 mole) in dry ether (5 ml) was added to a stirred suspension of powdered sodium ethoxide (0.35 g, 0.0051 mole) in dry ether (25 ml). The mixture was stirred for 15 min. at room temperature and then added a solution of 4-bromo-methyl-car-2-ene (XI, 1.14 g, 0.005 mole approx) in dry ether (10 ml). Stirring was continued for 12 hr, then water was added to the reaction mixture and the organic layer was extracted with ether. The ether solution after drying (Na_2SO_4) was evaporated and the residue was chromatographed through silica-gel. By eluting with a mixture of pet.ether (40-60°) and chloroform (4:1) a fraction was obtained which was identified as compound XIV. (0.93 g, 58%). (Found: C, 74.88; H, 9.95; $C_{20}H_{32}O_3$ requires C, 74.96; H, 10.06%). ν_{max} 2950, 1765, 1725, 1625, 1475, 1380, 1225, 1163, 1062, 895 cm^{-1}.

NMR (CCl_4, δ): 0.83 (6H, Me's on cyclopropane ring); 0.93 and 1.03 (3H each, CH_3 protons); 1.70 (3H, bs, methyl on double bond); 2.16 (2H, m, $COCH_2$); 4.0 (2H, q, OCH_2); 5.43 (1H, olefinic proton).

4-(2-Carbethoxy-1,5-dimethyl-3-oxo-hexyl) car-2-ene (XV) and 2-methyl-5-carbethoxy-6 (5-isopropyl-2-methyl phenyl)-hexan-4-one (XVI)

A solution of ethyl-3-oxo-6-methyl hexanoate (XII, 0.86 g, 0.005 mole) in dry ether (5 ml) was added to a stirred suspension of powdered sodium ethoxide (0.36 g, 0.005 mole) in dry ether (25 ml). The mixture was stirred for 15 min. at room temperature and then added a solution of 4,1'-bromo-ethyl-car-2-ene (X, 1.21 g, 0.005 mole approx) in dry ether (10 ml). Stirring was continued for 12 hr, then water was added to the reaction mixture and the organic layer was extracted with ether. The ether solution after drying (Na_2SO_4) was concentrated and the residue was chromatographed over silica-gel. The earlier fractions by eluting with a mixture of pet.ether (40-60°) and chloroform (9:1) gave the aromatic compound XVI (0.33 g, 24%). (Found: C, 75.79; H, 9.88. $C_{21}H_{32}O_3$ requires C, 75.86; H, 9.70%). ν_{max} 2850, 1750, 1725, 1610, 1500, 1425, 1235, 825 cm^{-1}.

NMR(CCl_4; δ) 0.87 to 0.96 (9H, CH_3 protons), 1.15, 1.27 (6H, $CH(CH_3)_2$ on aromatic ring); 2.32 (3H, CH_3 on aromatic ring); 4.17 (2H, q, OCH_2 protons), 6.73 to 7.3 (3H, m, aromatic protons).

The later fractions of the chromatograph by eluting with pet.ether (40-60°)-chloroform mixture (4:1) gave pure keto-ester XV (0.76 g, 46%). (Found: C, 75.35; H, 10.12, $C_{21}H_{34}O_3$ requires C, 75.40; H, 10.25%). ν_{max} 2900, 1750, 1725, 1475, 1380, 1055, 910 cm^{-1}.

NMR(CCl_4,δ) 0.83 (6H, Me's on cyclopropane ring), 0.96 to 1.03 (6H, CH_2 protons); 1.27 (3H, t, OCH_2CH_3), 1.68 (3H, bs, CH_3 protons on double bond); 4.15 (2H, q, OCH_2 proton); 5.45 (1H, olefinic proton)

Acknowledgement

We are thankful to Dr. R.N. Sharma, Entomologist, NCL and the Entomology group of NCL for bioassaying the compounds for JH-activity.

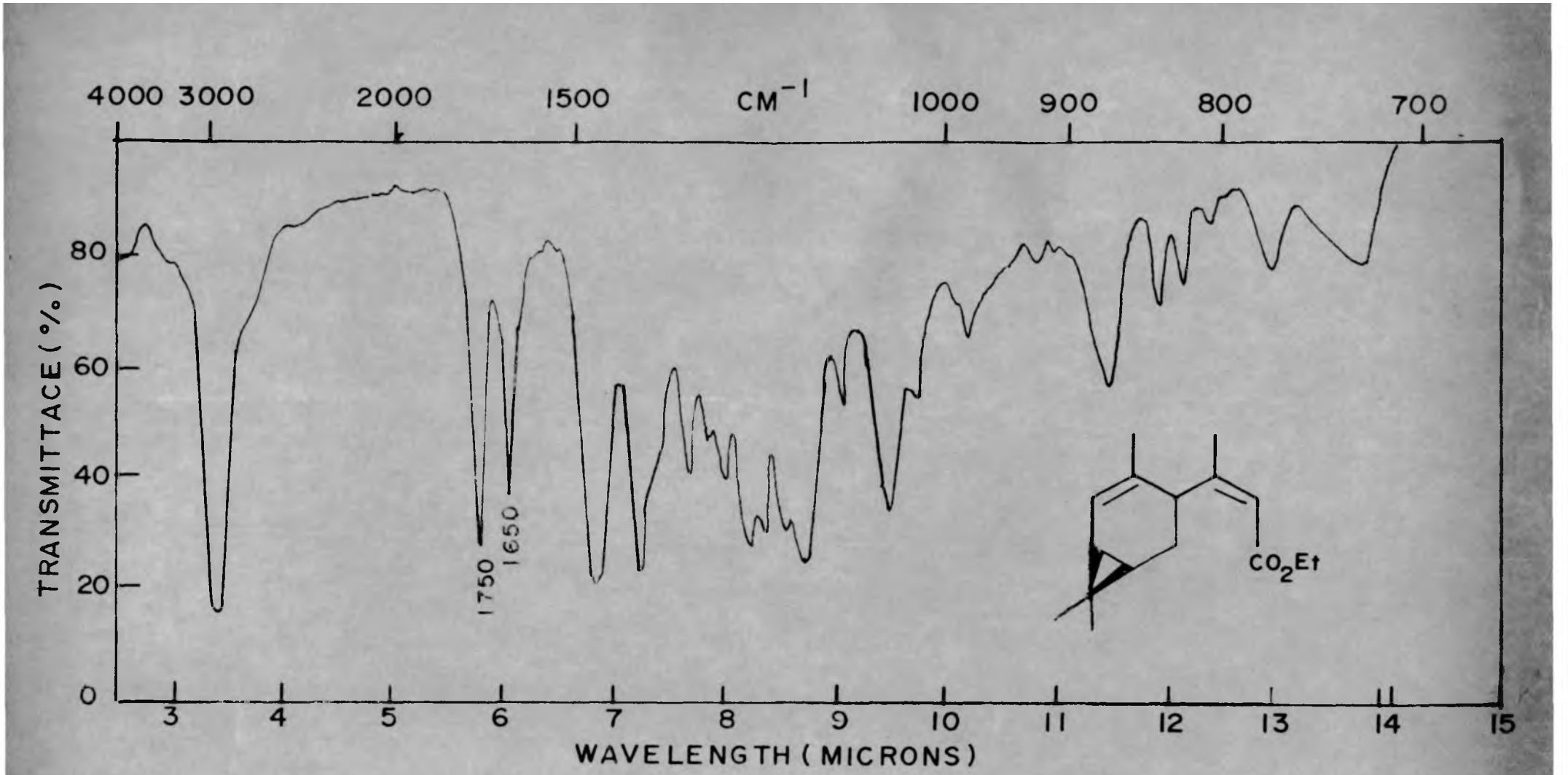


FIG. 53. IR SPECTRUM OF 4(2-CARBETHOXY-1-METHYL VINYL)CAR-2-ENE(IV)

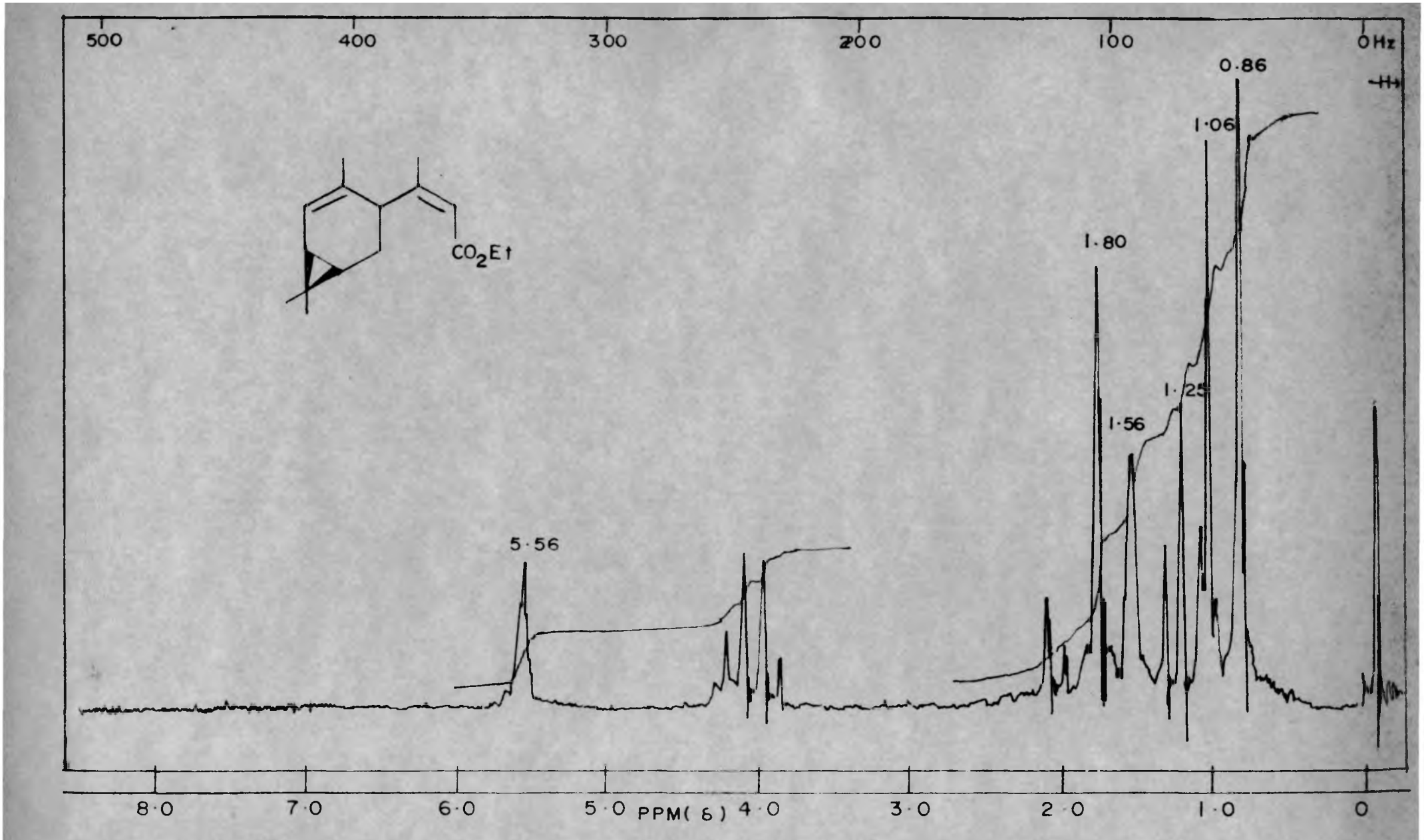


FIG.54. NMR SPECTRUM OF 4-(2-CARBETHOXY-1-METHYL VINYL) CAR-2-ENE (IV)

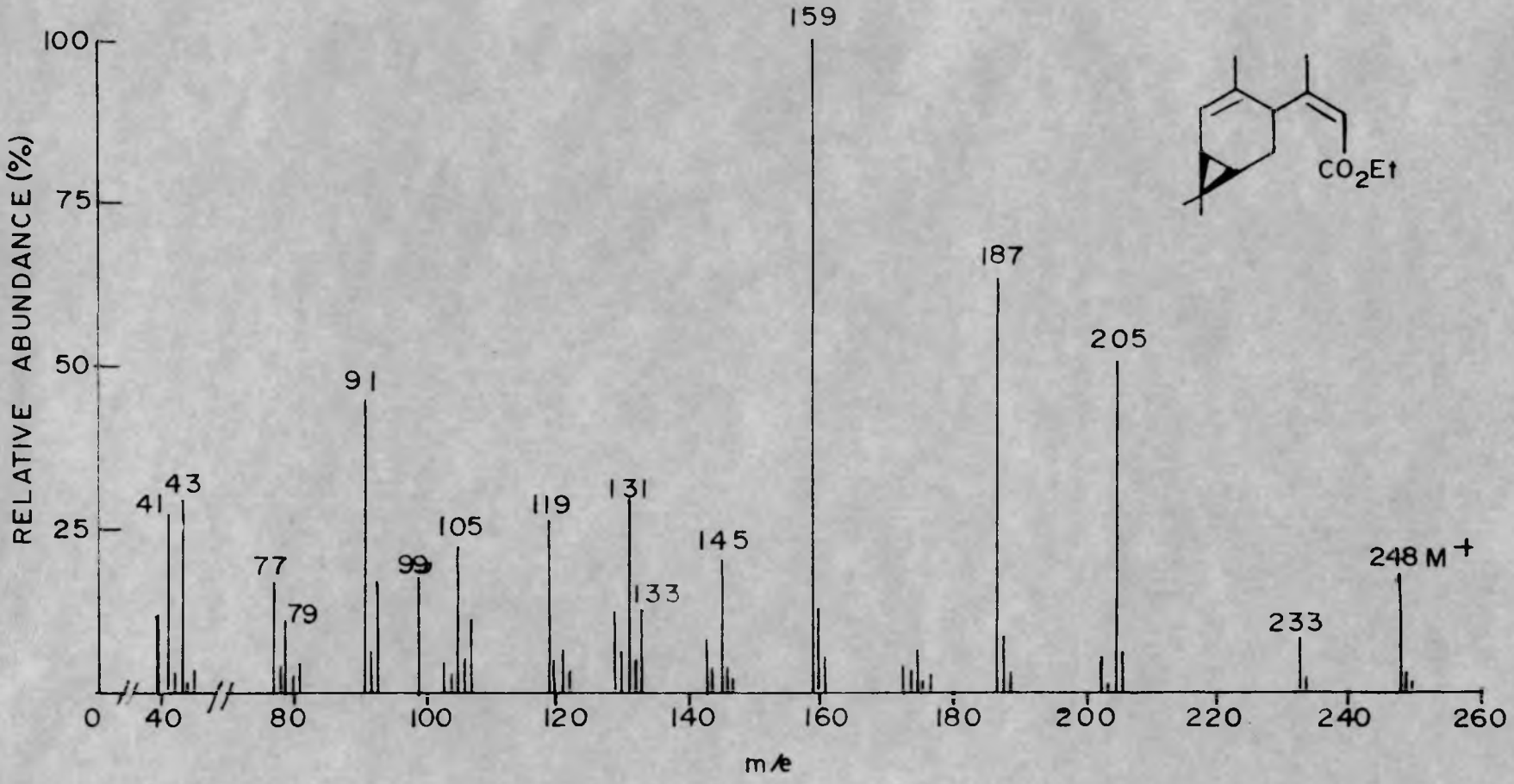


FIG.55. MASS SPECTRUM OF 4-(2-CARBETHOXY-1-METHYL VINYL) CAR-2-ENE(IV)

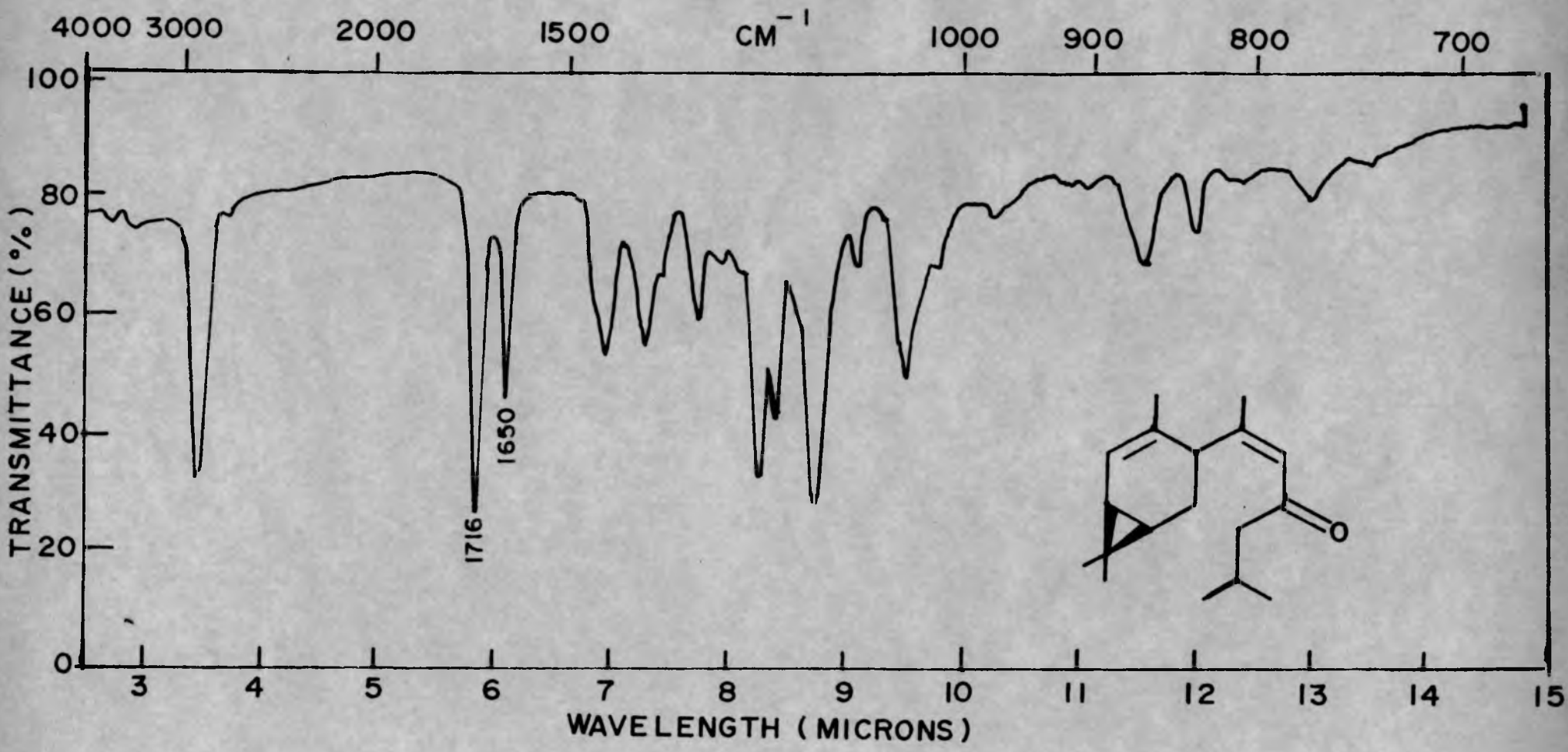


FIG. 56. I R SPECTRUM OF 4-(1,5 DIMETHYL-3-OXO-HEX-1-ENYL) CAR-2-ENE. (V)

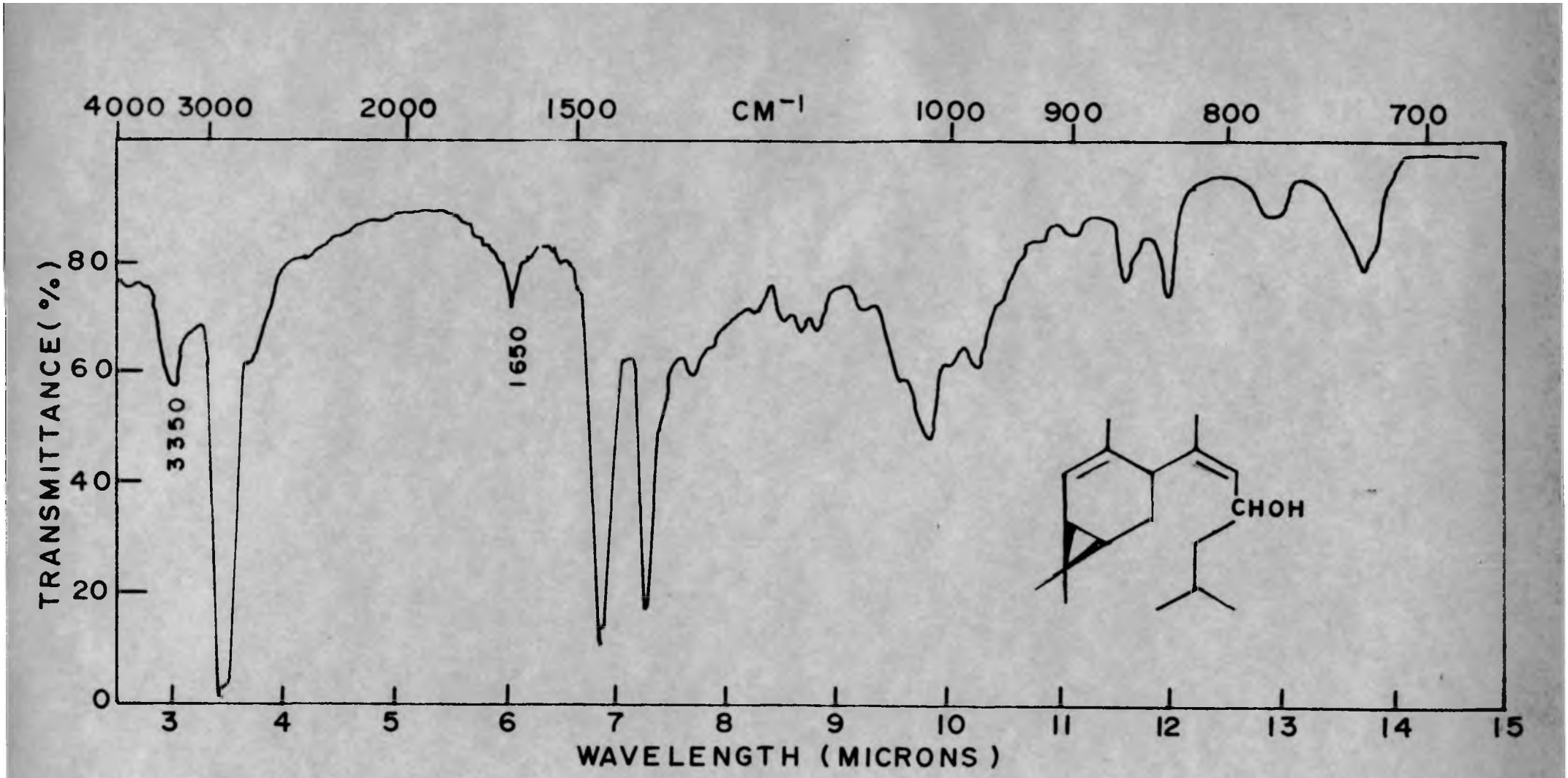


FIG. 57. IR SPECTRUM OF 4-(1,5-DIMETHYL-3-HYDROXY-HEX-1-ENYL) CAR-2-ENE(V)

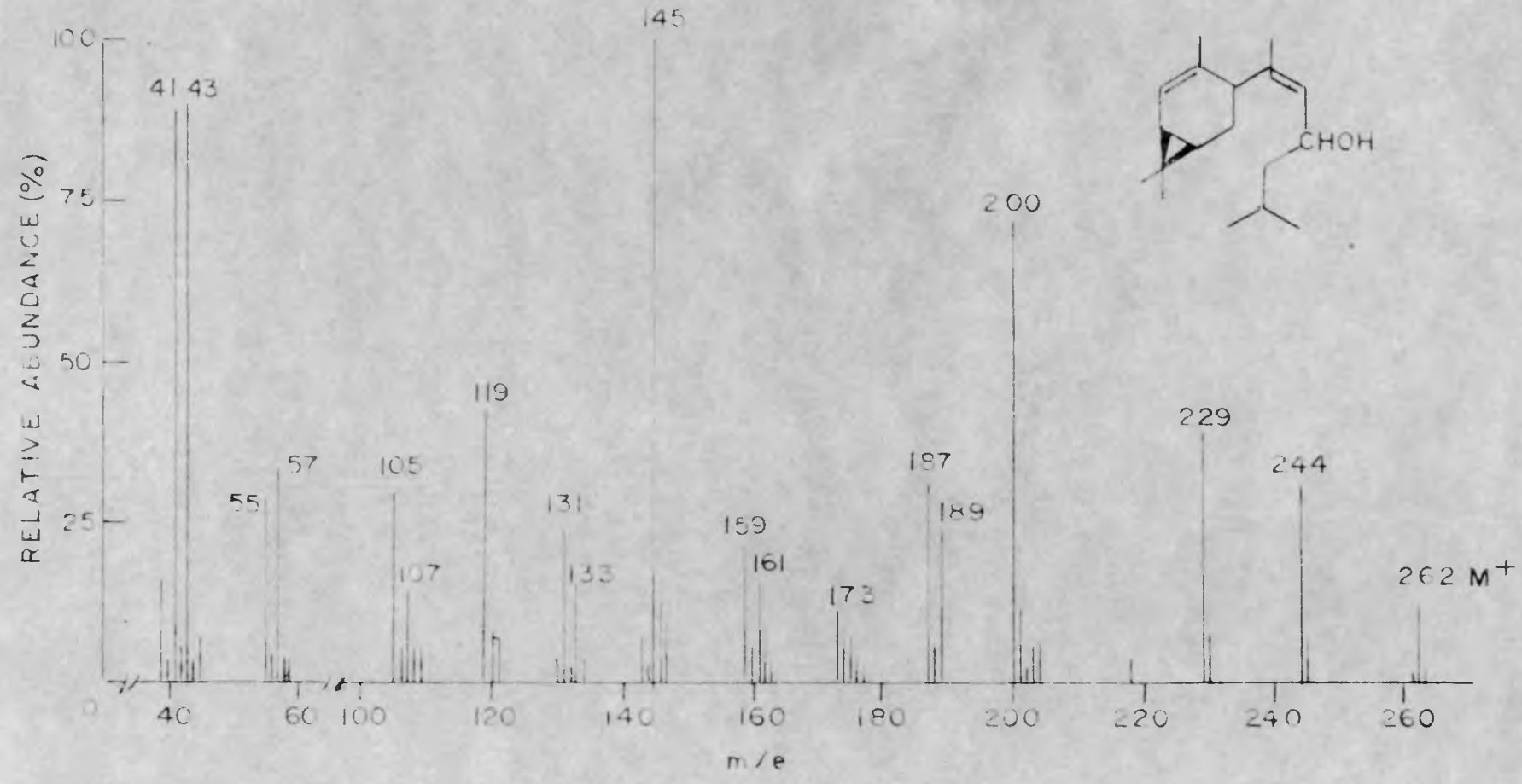


FIG 58 MASS SPECTRUM OF 4-(1,5-DIMETHYL-3-HYDROXY-HEX-1-ENYL) CAR-2-ENE (VI)

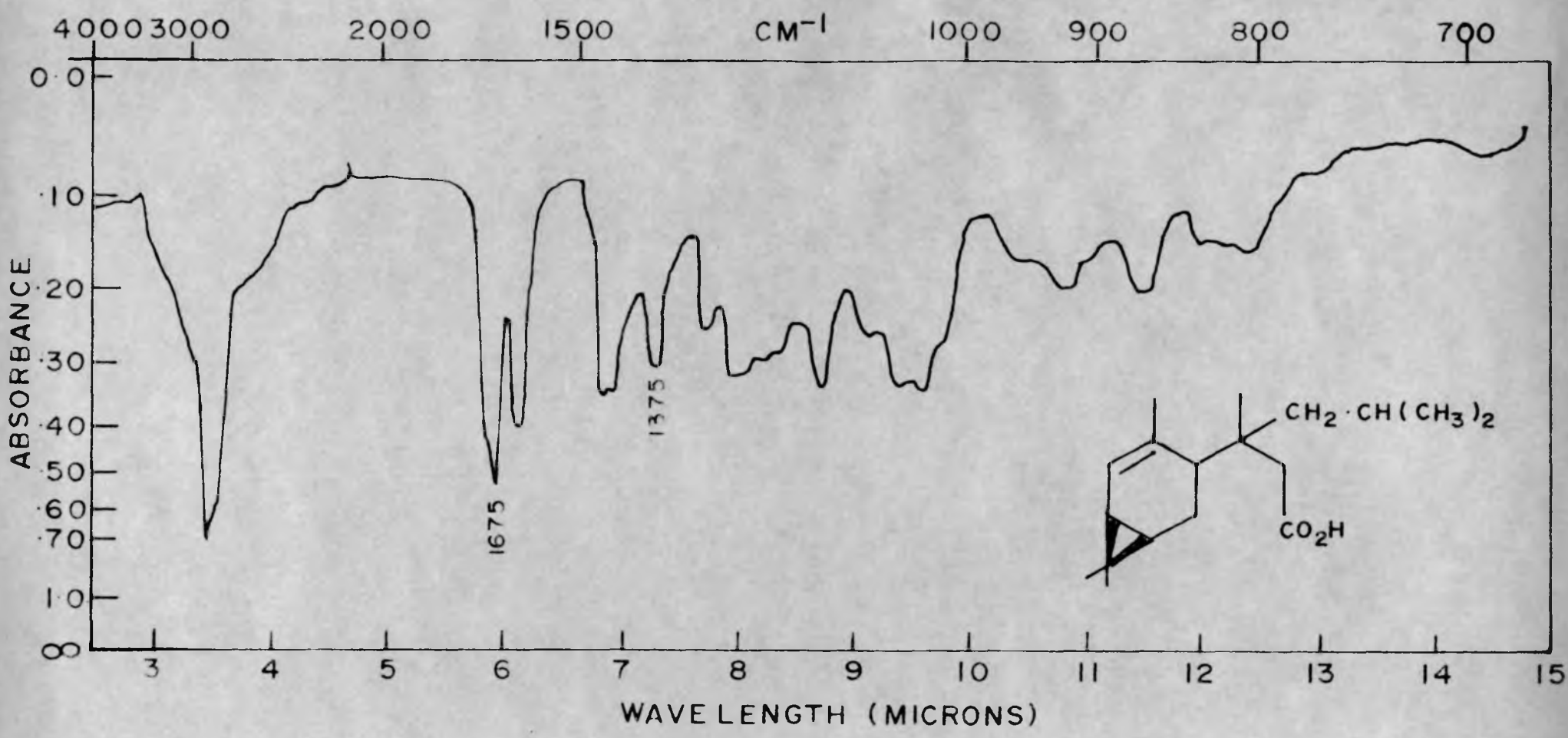


FIG 59 IR SPECTRUM OF 4-(1-ISOBUTYL-1-METHYL-2-CARBOXY ETHYL) CAR-2-ENE(VII

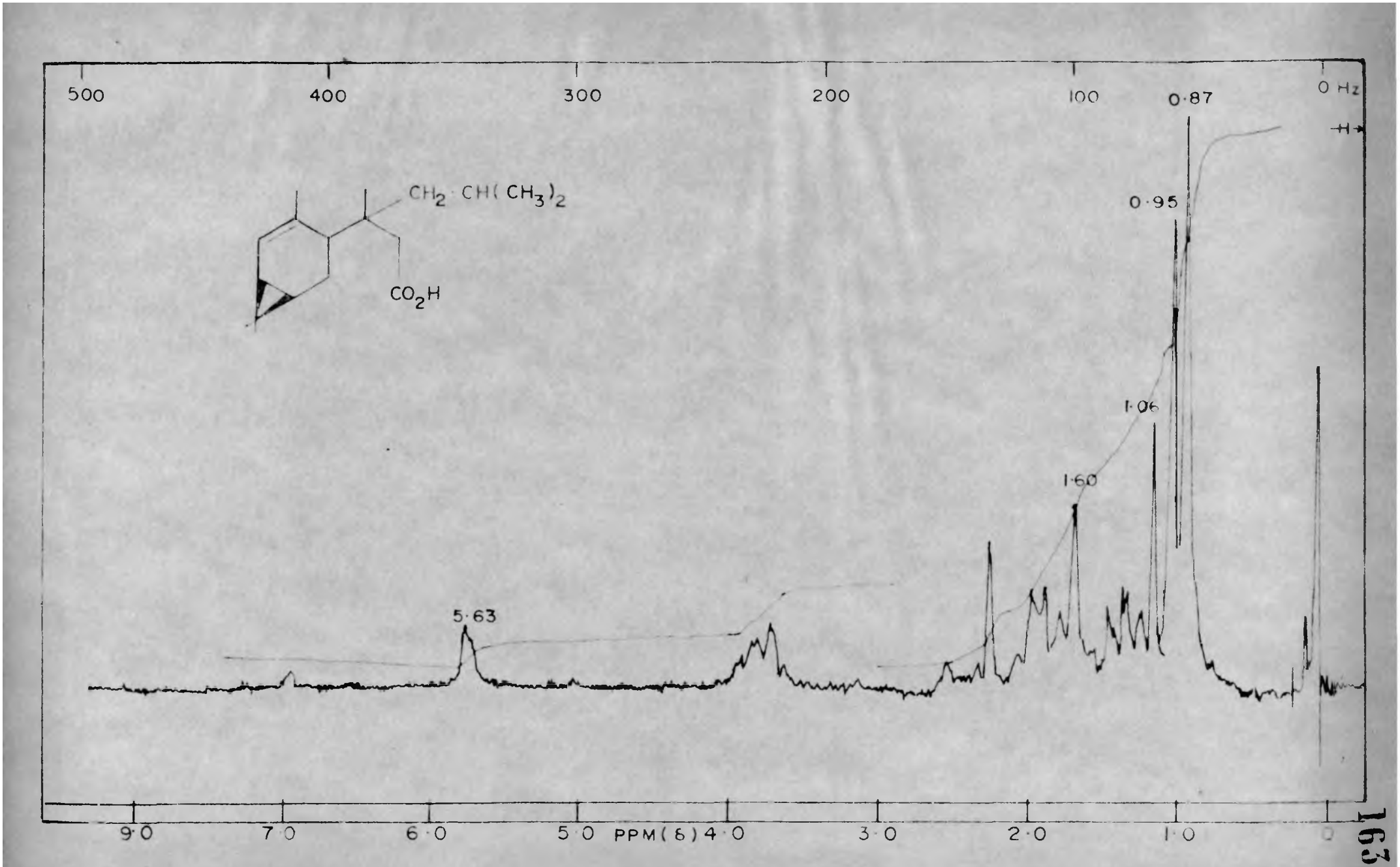


FIG. 60. NMR SPECTRUM OF 4-(1-ISOBUTYL-1-METHYL-2-CARBOXY ETHYL)CAR-2-ENE (VII)

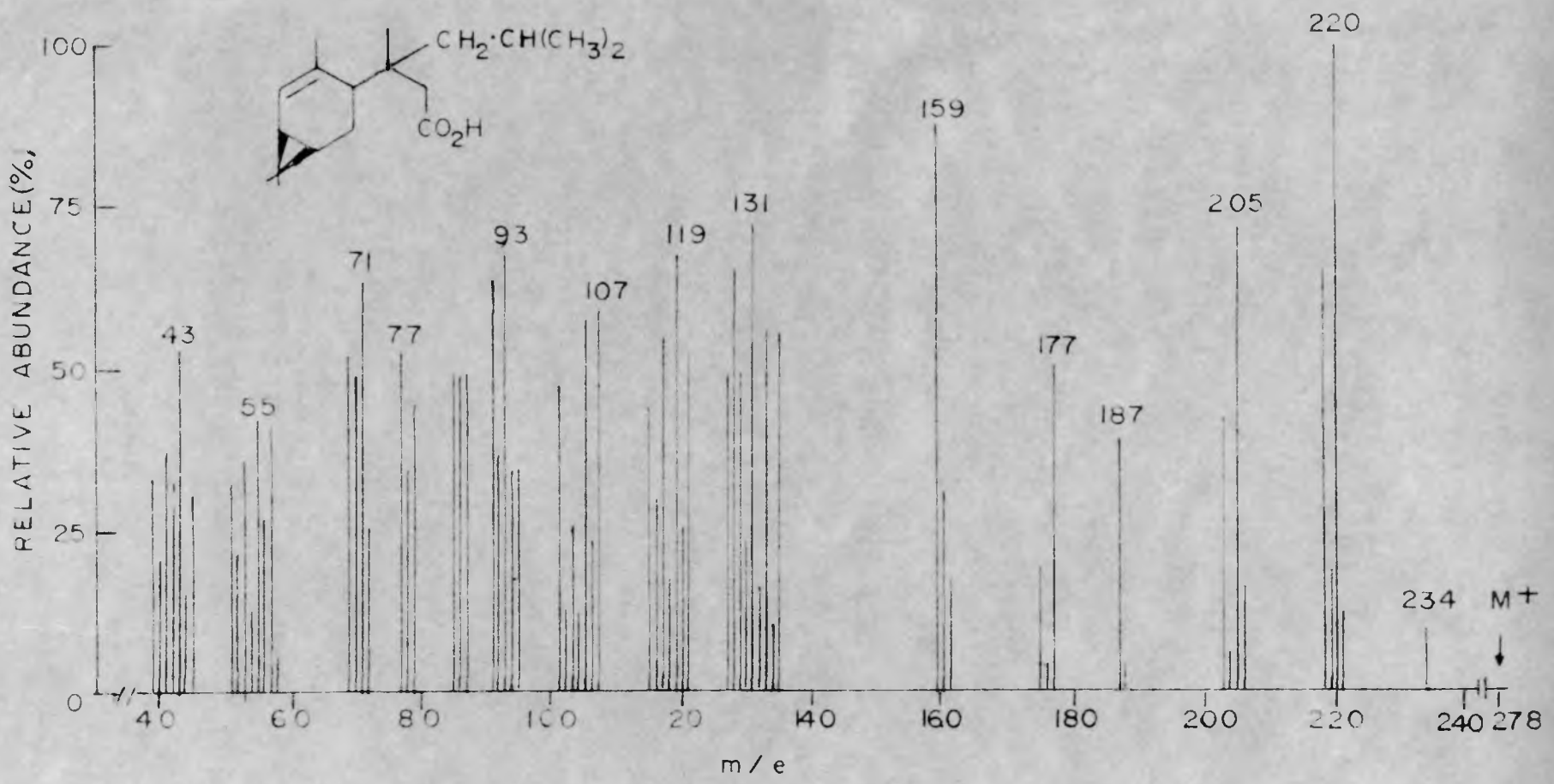


FIG 61 MASS SPECTRUM OF 4-(1-ISOBUTYL-1-METHYL-2-CARBOXY ETHYL) CAR-2-ENE (VII)

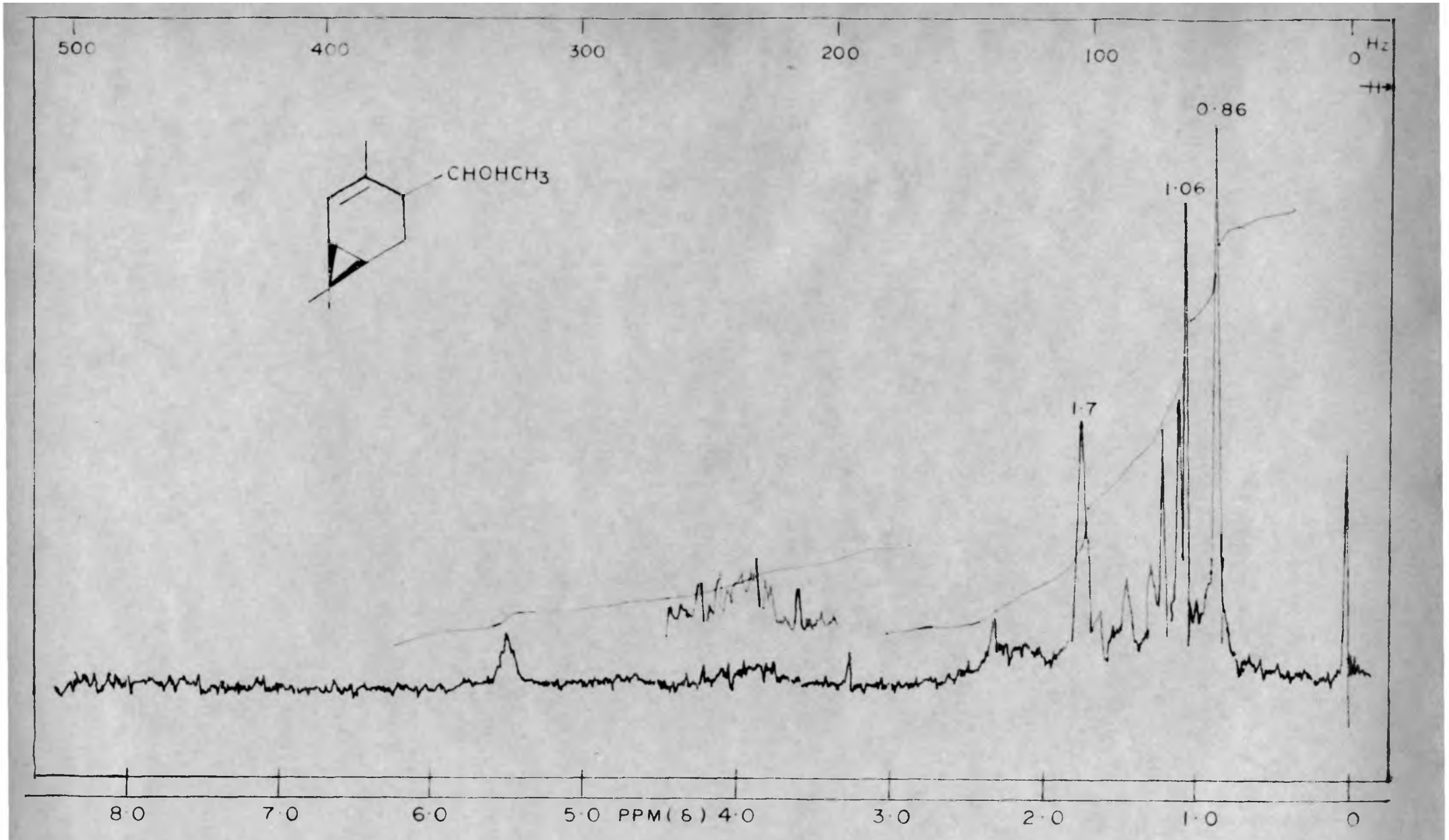


FIG. 62. NMR SPECTRUM OF 4-1'-HYDROXY ETHYL CAR-2-ENE (VIII)

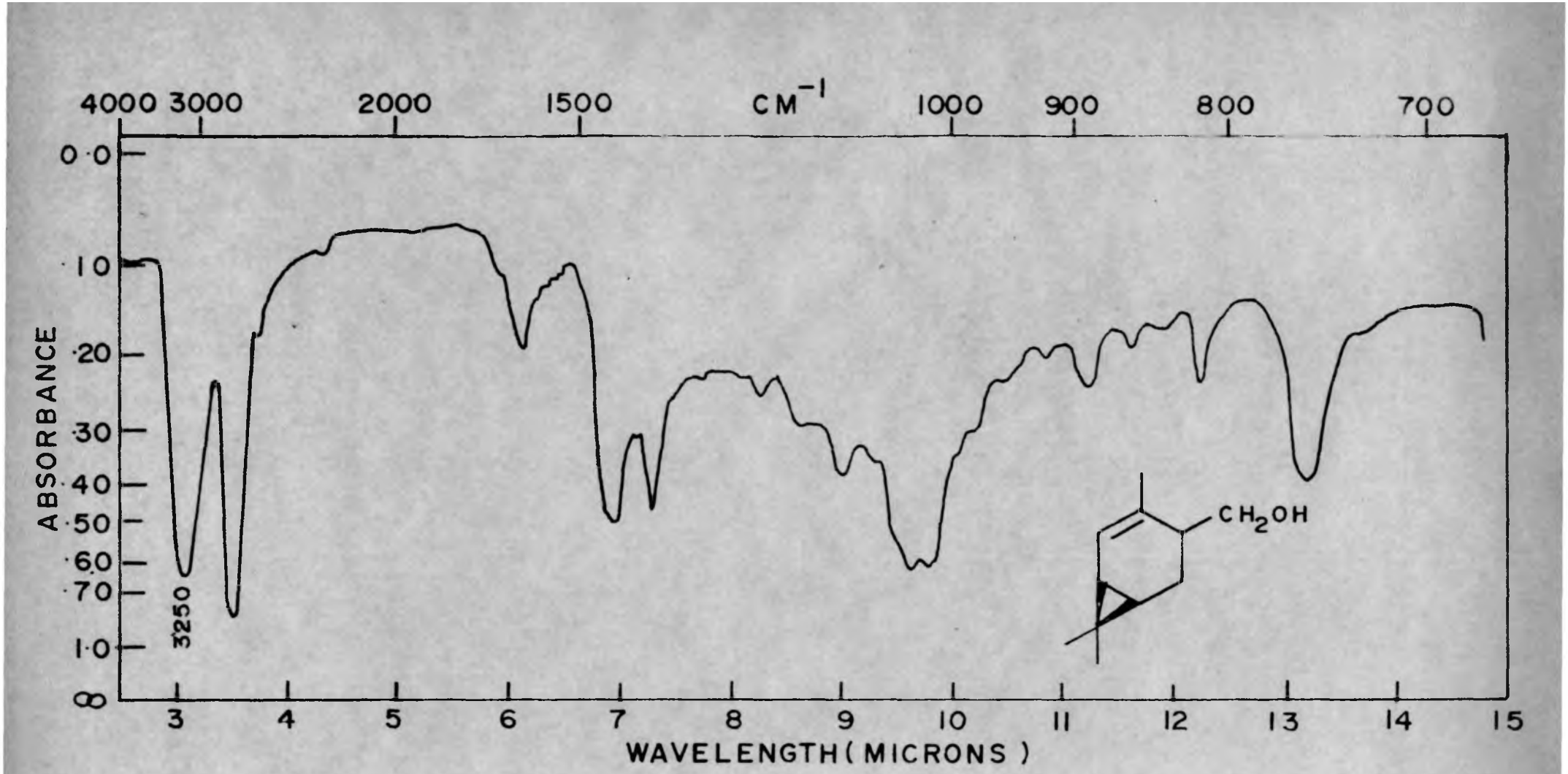


FIG. 63. IR SPECTRUM OF (+)-2-CARENE-4α-METHANOL (IX)

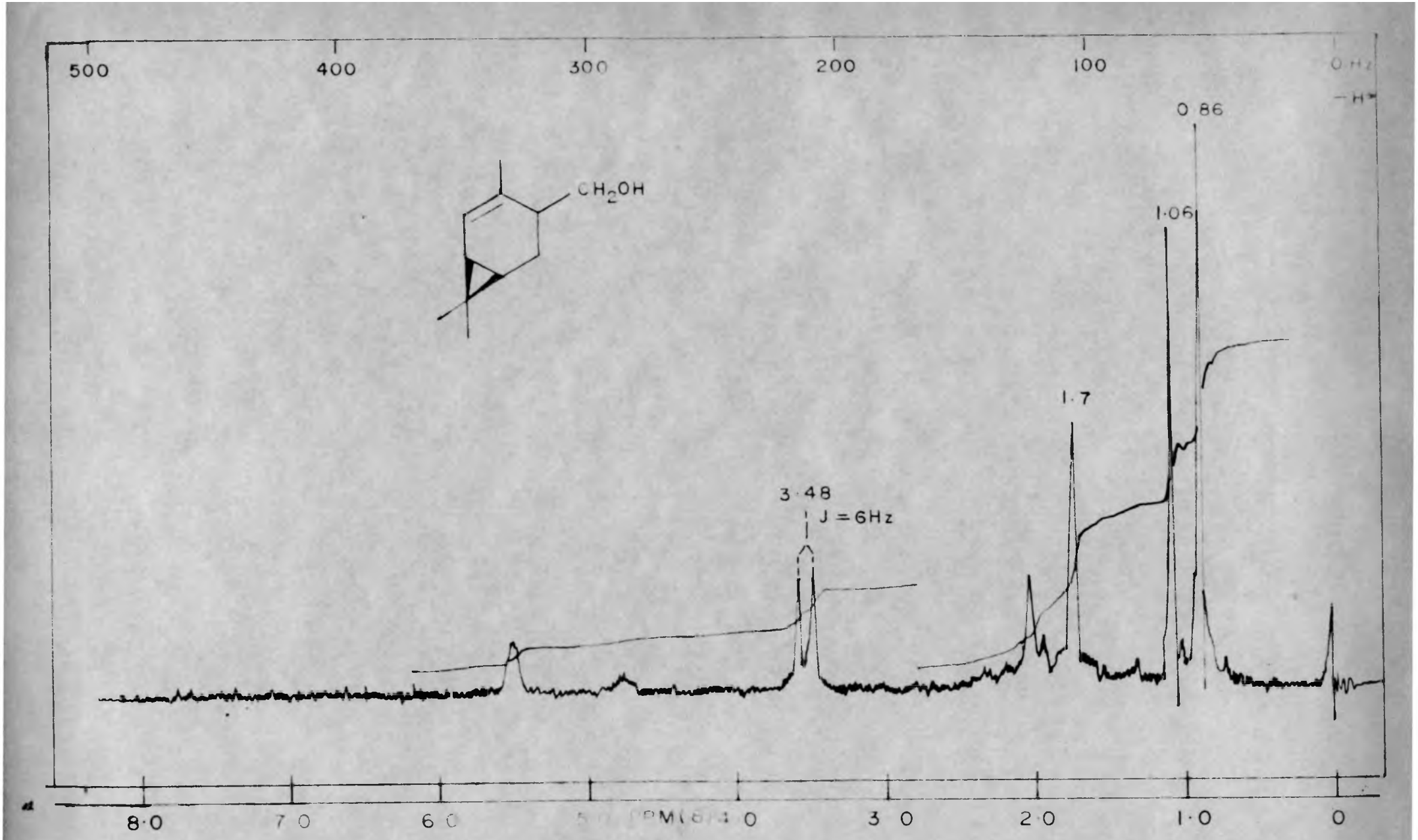


FIG 64. NMR SPECTRUM OF (+)-2-CARENE-4α-METHANOL (IX)

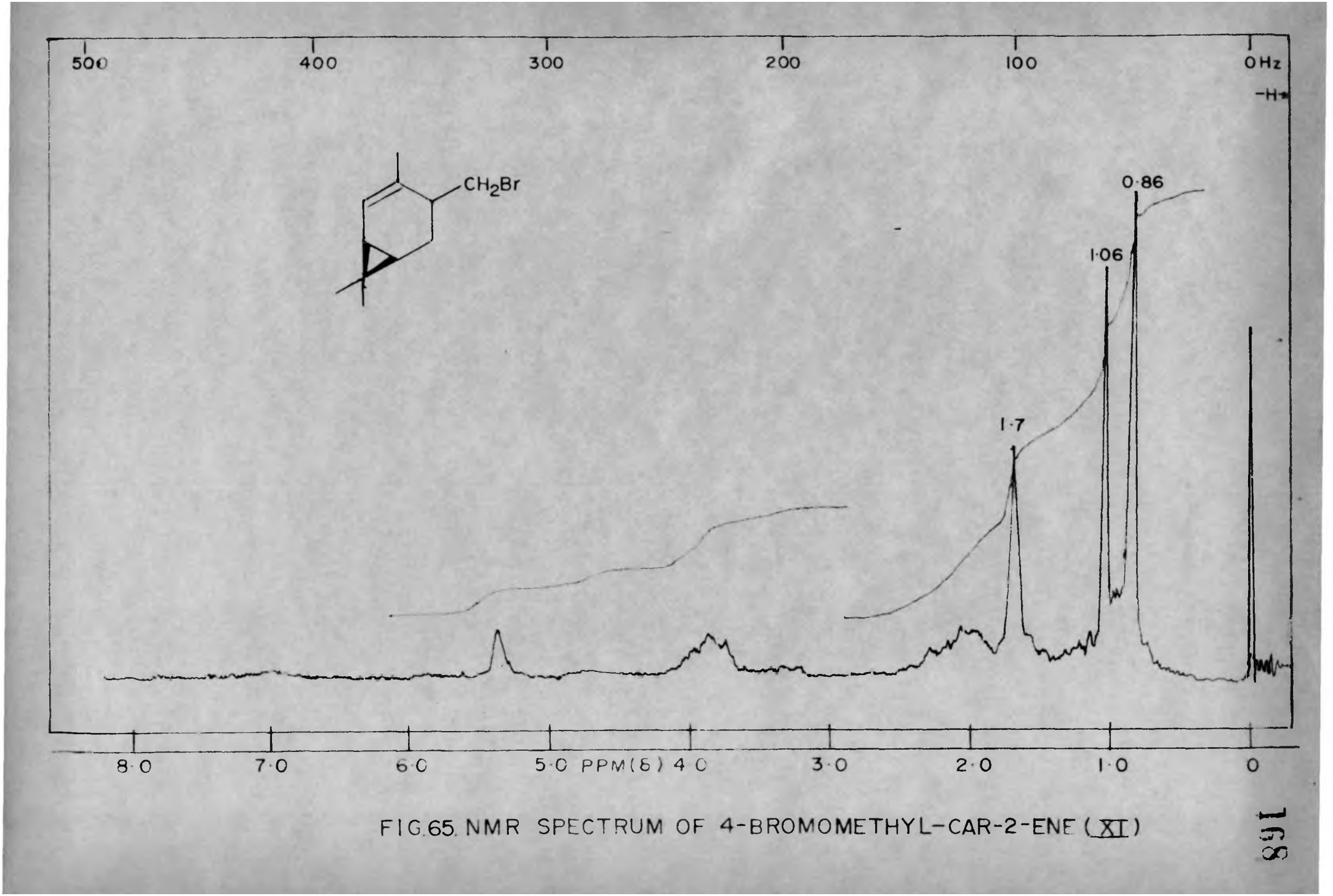


FIG.65. NMR SPECTRUM OF 4-BROMOMETHYL-CAR-2-ENE (XI)

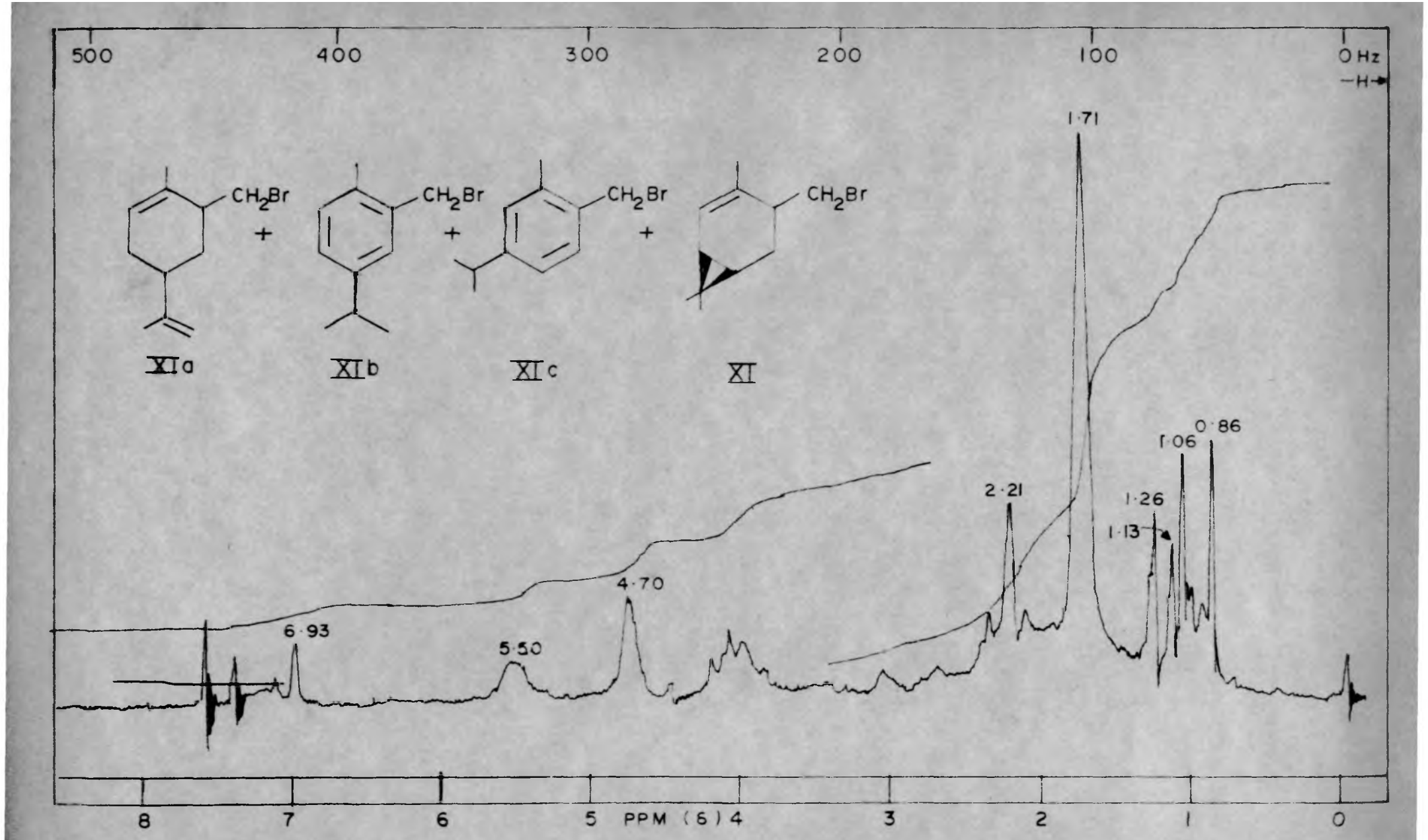


FIG.66. NMR SPECTRUM OF THE MIXTURE OF REARRANGEMENT PRODUCTS FROM 4-BROMOMETHYL CAR-2-ENE(XI) ON SILICA GEL COLUMN AT ROOM TEMPERATURE

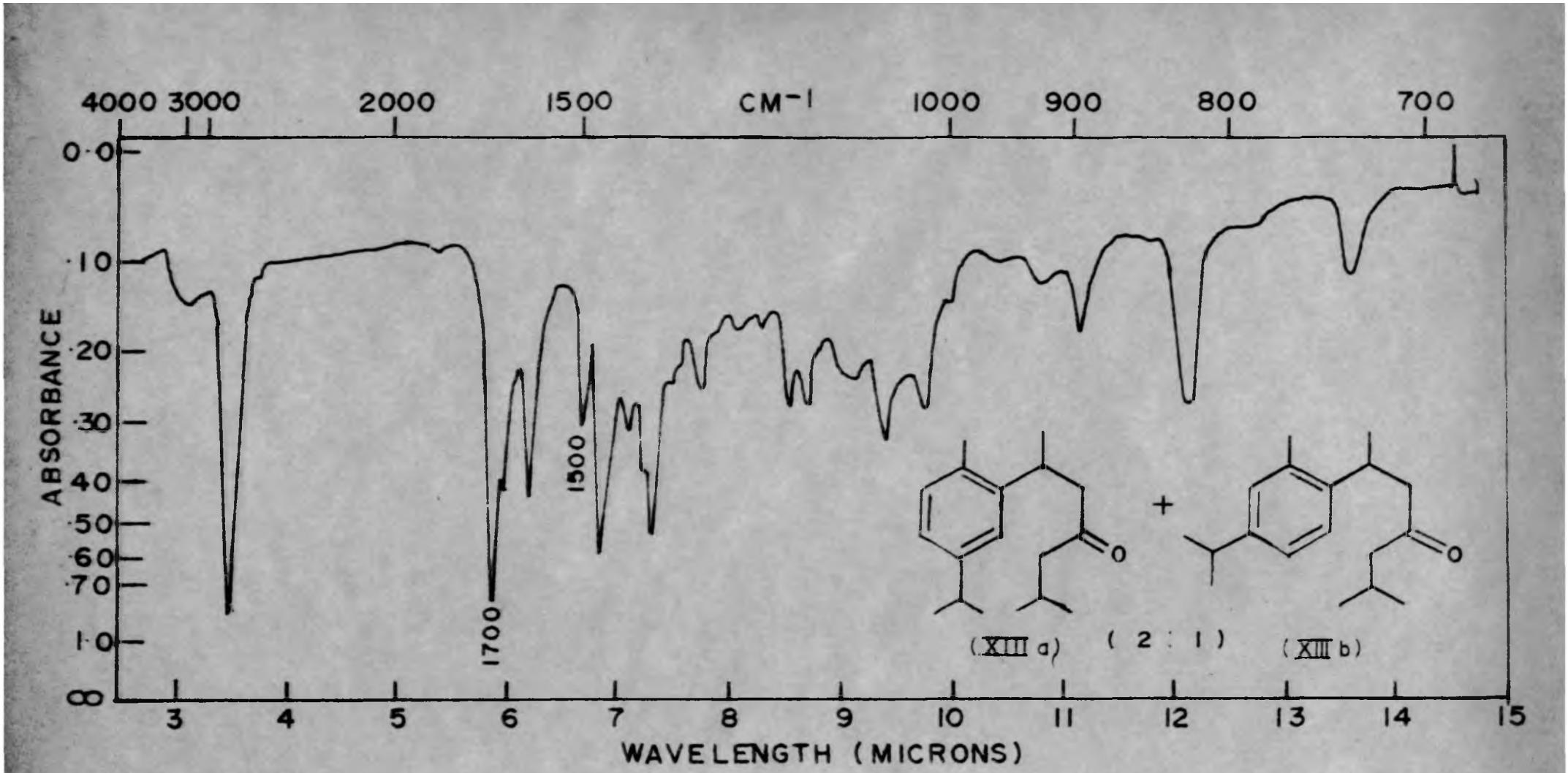


FIG.67. IR SPECTRUM OF 2-METHYL-6(5-ISOPROPYL-2-METHYL PHENYL)-HEPTAN-4-ONE WITH ITS ISOMERIC MIXTURE

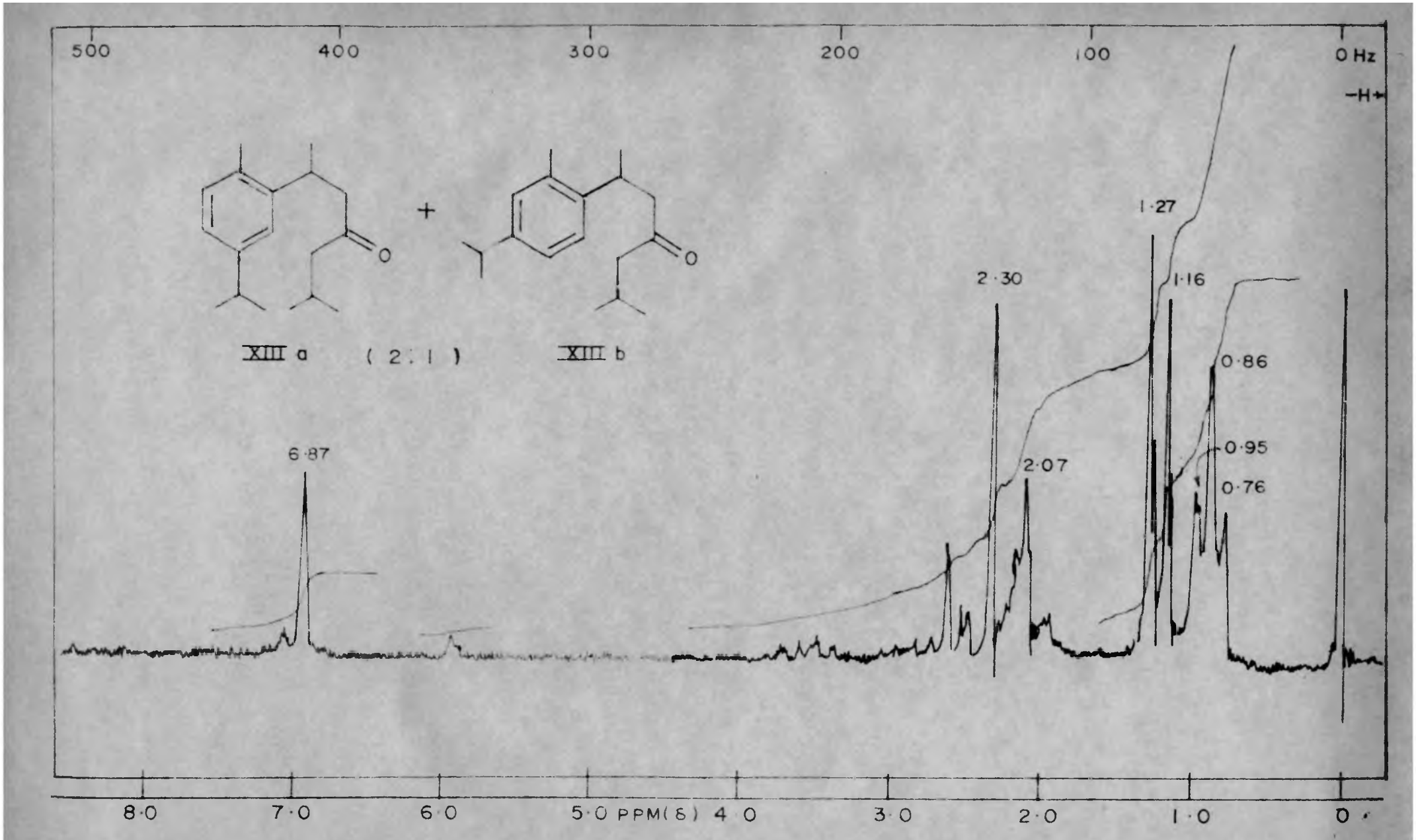


FIG. 68 NMR SPECTRUM OF 2-METHYL-6-(5-ISOPROPYL-2-METHYL PHENYL)-HEPTAN-4-ONE (XIIIa) WITH ITS ISOMERIC MIXTURE (XIIIb)

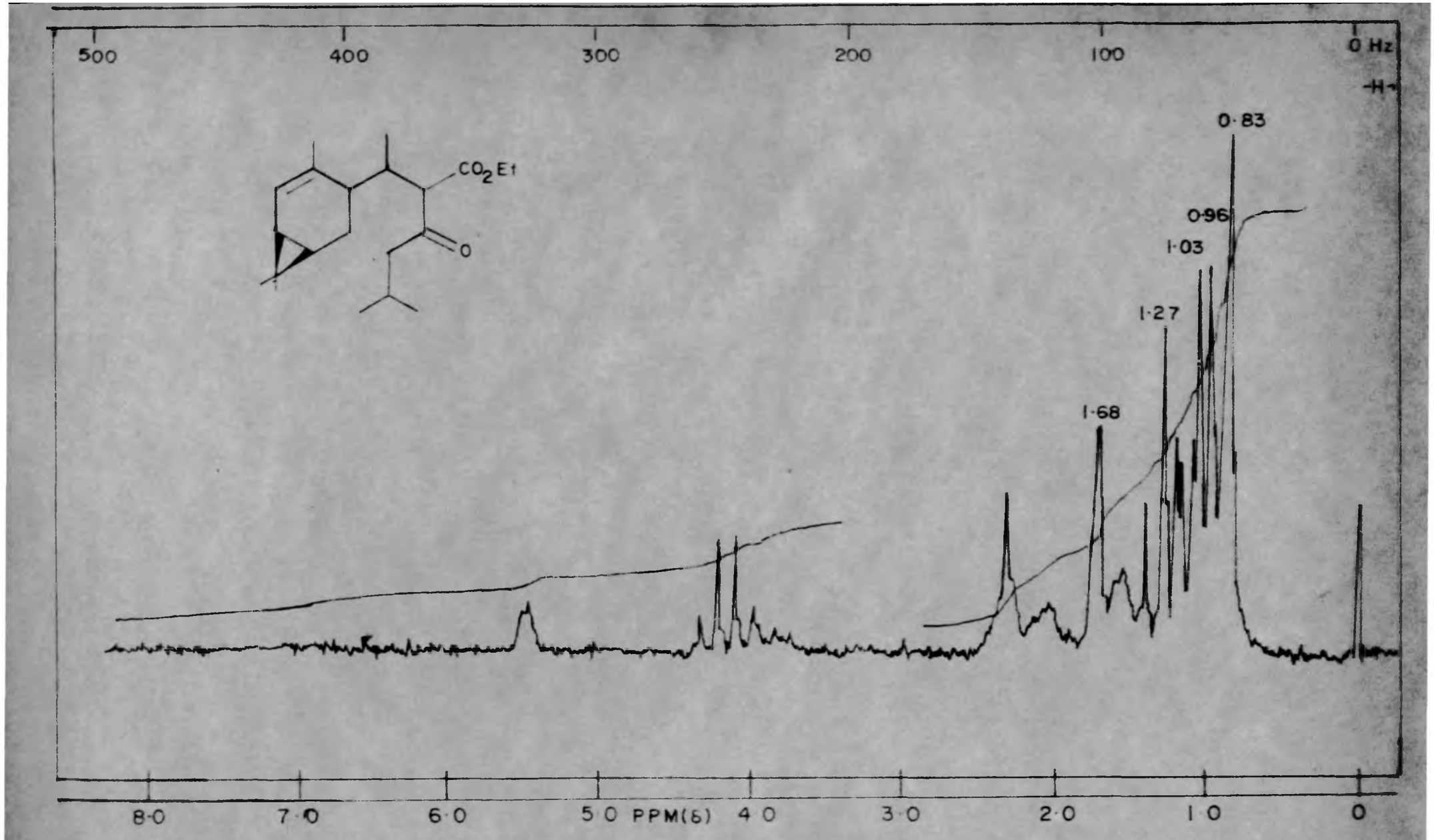


FIG.69 NMR SPECTRUM OF 4-(2-CARBETHOXY-1,5-DIMETHYL-3-OXO-HEXYL) CAR-2-ENE (XV)

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SUMMARY

The thesis entitled 'Synthetic studies on terpenoids' is divided into three parts.

Part I

This part is divided into three chapters as follows:

Chapter I - Introduction to the present work on (+)-trans-chrysanthemic acid

A brief history and chemistry of Pyrethrins[1] have been described in this Chapter.

Chapter II - A new synthesis of (+) trans-chrysanthemic acid from (+)-car-3-ene

This chapter describes a new synthesis[2] of (+)-trans-chrysanthemic acid, the essential component of naturally occurring Pyrethrins and their synthetic analogues e.g. allethrin, phthalthrin etc. which are well known for their high insecticidal activity with low mammalian toxicity. A new route for the synthesis of (-)-dihydrochrysanthemolactone and methyl (-)-cis-chrysanthemate[3] starting from (+)-car-3-ene is being recorded in this chapter.

Chapter III- A stereospecific synthesis of methyl (+)-trans chrysanthemate from (+)-α-pinene

A stereospecific synthesis[4] of natural (+)- (1R, 3R)-trans-chrysanthemic acid methyl ester from (+)-(1R, 5R)-α-pinene via a Favorskii ring contraction of an appropriately

substituted α-bromocyclobutanone intermediate has been reported in this chapter.

Both (+)-car-3-ene and (+)-α-pinene are abundant in Indian turpentine oil.

Part II

This part is divided into Chapter I and II.

Chapter I - A brief histroy and chemistry of juvenoids[5] have been described in this chapter.

Chapter II - Insect juvenile hormone analogues: Synthesis of substituted terpenoids bearing a cyclopropane ring

Various synthetic juvenile hormone analogues are currently being synthesised and tested in different laboratories around the world, as part of a programme for the integrated plant protection measures by controlling insects by hormonal action. In view of this several substituted terpenoids bearing ~~being~~ a cyclopropane ring have been synthesised[6] from (+)-car-3-ene and are reported in this chapter. The juvenile hormone activity from one of the compound 3,3-dimethyl-2-(2'-hydroxy-2'-methyl-n-butyl)-1-(2'-p-nitrophenyloxy-n-butyl) cyclopropane has been recorded.

Part III

Cyclic juvenoids e.g. methyl ester of todomatuic acid[7], its aromatic analogues[8] and Juvabiols[9] are of increasing interest for their high juvenile hormone activity. The present syntheses of juvabione analogues are based on the replacement

of the substituted cyclohexene or aromatic nucleus in juvabione with oar-2-one nucleus which are described in this part. The remarkable acute toxicity of the order of 100% at the maximum dose of 100 ppm from one of the compound 2-methyl-5-carboethoxy-6-(5-isopropyl-2-methyl-phenyl)-heptan-4-one is being recorded in this chapter.

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3. See also:
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Corrigenda and notes

1.p.137, The correct assignment for the absolute configuration of (+)-juvabione should be R,R as described by Manville, Canadian J. Chem. 53, 1579 (1975) and not R,S as postulated by Cerny et al. (Ref. 3, p. 173).

2.p.22; Theoretically, diastereoisomers are possible for the compounds XXIII (= IVb, p.104) and IVa, p.104. No attempt was made to separate them. Similarly, compounds I-XVI on page 140 are also possibly isomeric mixtures. Separation and assignment of the stereochemistry for these compounds were not studied in details since the main interest lay in testing the gross structures of the compounds for their JH-activity. In compounds IV-VI p.140 the geometry of the side chain is not known even though z-geometry is shown in the figures.

3. p.20, line 2, enantiomorph should be read as enantiomer.

4. Assignment for the cyclopropyl methyl frequencies in the NMR spectrum of compounds IVa-XII, p.105. Although the cyclopropyl methyl proton for (+)-trans-3,4-carane-diol have the same resonance frequency (fig.1, p.33), examination of the NMR spectrum of the diol IVb (fig.6, p.38) shows that the signals for the cyclopropyl methyl protons appear separately at 0.87 and 1.036. Likewise, the cyclopropyl methyl proton signals for the compounds IVa-XII must also have appeared at approx. 0.87 and 1.036 separately which must have merged with the other methyl signals.