STUDIES IN SESQUITERPENES

(NOVEL REACTIONS OF LONGIFOLENE)

A THESIS

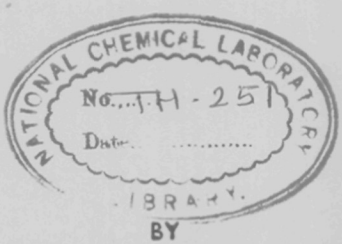
SUBMITTED TO THE

UNIVERSITY OF POONA

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)



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(NATURAL PRODUCTS)

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POONA - 411 008 (INDIA)

AUGUST 1979

COMPUTERISED

—TO MY PARENTS—

C O N T E N T S

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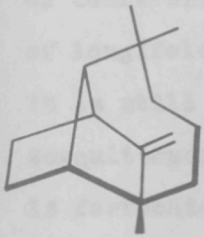
Finally, I wish to place my thanks on record, to the Director, National Chemical Laboratory, Pune 8, for permitting me to submit this work in the form of thesis.

August 1979 (R.P. DESHPANDE)

P R E F A C E

THIS THESIS highlights some novel reactions of longifolene 1 - an ace in the sesquiterpene sub-group of the major isoprenoid field of organic Natural Products. Speaking of Sesquiterpenoids, Barton[1] and de Mayo (1957) have said, "If no other type of organic compound were known, organic chemistry would still be a rich and varied field for investigation". After a lapse of two decades and more, this statement appears as valid as when it was first made.

Since its isolation (Simonsen, 1920) from the Indian turpentine oil from Chir pine - Pinus longifolia Roxb. (Hindi: Chir), the chemistry of longifolene has been an inspiration to the creative endeavours of the organic chemist. For a compound incorporating a lone functionality - a pendent exo-methylene group on a bicyclo [2.2.1]heptane-based tricyclic bridged system - longifolene 1 displays spectacular molecular agility. For sheer graceful, if complex, skeletal acrobatics (in terms of deep-seated multiple rearrangements/transannular reactions) longifolene[2] is unrivalled in Sesquiterpene chemistry, with perhaps the possible exception of caryophyllene 2 - an extremely minor constituent, also



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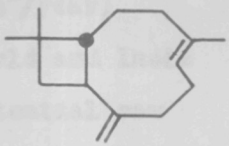

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present in P. longifolia.

Terpene chemicals industry in India is almost exclusively dependent on Indian turpentine oil (9000 tonnes[3]/year) as a raw material. The monoterpenes constitute the largest tonnage (α-pinene: 20-30%, 2300 tonnes; β-pinene: 5-10%, 550 tonnes; 3-carene: 55-65%, 5700 tonnes) of commercially important terpenes. The low yield (2-5%) of longifolene in Chir pine turpentine oil notwithstanding, it is still the highest tonnage (450 tonnes[3]/year) sesquiterpene available anywhere in the world and India is fortunately holding the key for this potential raw material. This one-time 'waste' material from Indian turpentine oil has exhilarated the organic chemist by its fascinating chemistry[2] and is now well on its way to provide him a terpene base for sophisticated items (in perfumery, pharmaceutical, plasticizer and related fields) for modern living. A large number of longifolene derivatives (the ketones and oxides, in particular) possess fragrant odours and commercial exploitation of these products in the perfumery industry has become a reality. The magic of the East has conjured up the most enchanting perfumes of the West.

From the purely academic, longifolene has already effected a breakthrough in the almost non-existent field

of sesquiterpene technology. Since India is in a dictating position for an enduring supply of longifolene, this substrate has a lot to commend to be considered as a hot favourite for intense exploration of its chemistry. The yet more new reactions of longifolene described in the present thesis, while adding on to the almost limitless chemistry[2] of the enigmatic sesquiterpene, it is hoped, may also provide useful pointers for enhancing the practical utility of this abundant raw material.

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PART - I
REACTIONS OF LONGIFOLANE - BASED HETERO ATOM RADICALS

CHAPTER - 1

HOFMANN-LÖEFFLER-FREYTAG REACTION: A NOVEL LONGIFOLANE-BASED TETRACYCLIC N-METHYL PYRROLIDINE

ABSTRACT

The low yield of 10% notwithstanding, it has been possible to trap the exotic longifolane-based tetracyclic N-methyl pyrrolidine 12 generated by the Hofmann-Löeffler-Freytag reaction on N-methyl-longifolamine 7.

HOFMANN-LÖFFLER-FREYTAG REACTION: A NOVEL LONGIFOLANE-BASED TETRACYCLIC N-METHYL PYRROLIDINE[1]

In continuation of our efforts aimed at the generation of suitably oriented heteroatom radicals (O,N) capable of procreating a heterocycle[2] *via* an intramolecular hydrogen abstraction in the rigid longifolane skeleton, this communication describes the Hofmann-Löeffler-Freytag reaction[3] for elaborating a novel longifolane-based tetracyclic N-methyl pyrrolidine.

The remarkable success of intramolecular hydrogen abstraction by the longifolane-based oxy radicals 1 (C-9H) and 2 (C-5H/C-3H) in the hypoiodite reaction[4] prompted us to generate and study the fate of the corresponding nitrogen radicals 3 / 4. The readily accessible pair of longifolic acids - endo epimer 5 / exo epimer 6, appeared attractive for the generation of the crucial longifolane-based secondary amines 7 / 8. The envisaged scheme consisted of: acid → acid chloride ($SOCl_2$) → 2° amide ($MeNH_2$) → 2° amine ($LiAlH_4$) → N-chloroamine (N-chlorosuccinimide) → N radical ($H_2SO_4/\triangle$) → pyrrolidine (base).

The N-methyl amide 9 (73% yield) was readily formed from the endo acid 5 but the isomeric amide 10 could not be

prepared by this method* since the exo acid 6 suffers facile epimerization[5] during reaction with $SOCl_2$. It was therefore expedient to utilize the epimeric mixture of acids (5 + 6), resulting from CrO_3-oxidation[6] of the parent longifolene, for preparation of the amide 9. $LiAlH_4$ reduction of the amide yielded the secondary amine 7 (58%). The N-chloroamine 11 was best generated by reaction of 7 with N-chlorosuccinimide in ether (28°/4 hr); the distinctive feature in the PMR of 11 was the deshielded N-Me singlet at 2.90 ppm and the absence of the upfield NH singlet at 0.45 ppm shown by 7. In the last step for the generation of the nitrogen radical 3, 11 was heated with 84% H_2SO_4 at 65°/0.5 hr (optimized) and the intermediate δ-haloamine was directly treated with aqueous NaOH. The expected N-methyl pyrrolidine 12 could be isolated but in a poor yield* (10%): m.p. 60°; M^+ 233 (base peak). IR (Nujol): NH absent; 1160, 1040 cm^{-1}. PMR(CCl_4): 2.39 ppm (s, 3H, N-Me) and 1.00 ppm (s, 9H, three tertiary methyls).

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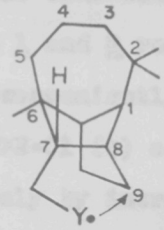
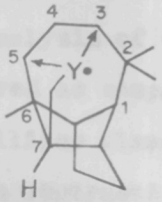
*Other methods of generating the amine 8 are under investigation.

*Intramolecularly cyclized products in the HLP reaction are generally formed in highly unpredictable yields (1 to 91%)[3], dictated by side reactions (dimerization and disproportionation).



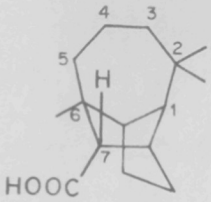
1: Y = O

3: Y = N–Me



2: Y = O

[4: Y = N–Me]



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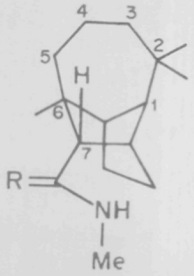
6: C–7 epimer

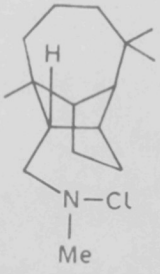


7: R = H, H

[8: 7 (C-7 epimer)]

9: R = O

[10: 8 (R = O)]



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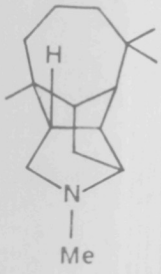

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Two conclusions can be drawn regarding the O and N radicals 1 and 2 respectively: (a) homolysis of -O-I can be more conveniently and easily achieved as compared to that of >N-Cl (b) oxygen radical stabilizes almost exclusively by intramolecular hydrogen abstraction producing the important, otherwise inaccessible tetrahydrofuran (cf 1) in >90% yield; this is in strong contrast when compared to the poor yield (ca 10%) of pyrrolidine (cf 3) from the nitrogen radical 2 in the HLF reaction.

EXPERIMENTAL

Melting and boiling points are uncorrected. Light petroleum refers to the fraction of b.p. 60-80°. All solvent extracts were dried over anhydrous Na_2SO_4. IR spectra were recorded on a Perkin-Elmer Inffacord model 137-E. PMR were measured on a Varian T-60 spectfometer with tetramethylsilane as internal standard. Mass spectra (MS) were obtained on a CEC spectrometer model 21-110B using an ionizing voltage of 70 eV and a direct inlet system.

N-Methyl longifolamide 3. The epimeric mixture of acids 5 and 6 (obtained by CrO_3-aq. H_2SO_4-AcOH oxidation[6] of longifolene; 23.6 g) and $SOCl_2$ (purified and freshly distilled, 22 ml) was refluxed on the waterbath for 3 hr (gas absorption trap), with frequent swirling. Excess $SOCl_2$ was then distilled off (water pump) and the residue distilled to furnish the acid chloride of 5 as a light yellow liquid b.p. 124°/1 mm (24.1 g, 96%).

Methylamine solution (38%; 200 ml) was taken in a 3-necked flask fitted with a stirrer, dropping funnel and condenser (connected to a gas absorption trap at the top). The flask was cooled in an ice-salt bath and the acid chloride (24.1 g) in dry benzene (150 ml) was added dropwise

to the stirred solution (0.5 hr). Stirring was continued for another 4 hr and the mixture left overnight at room temperature. The mixture was diluted with water (200 ml), the benzene layer was separated and the aqueous part further extracted with benzene (3 x 100 ml). The combined extracts were washed with 5% aq. KOH (3 x 150 ml) to remove any acid. The organic layer was washed with water, brine and dried. Removal of solvent gave the crude N-methylamide 2 which was recrystallised from light petroleum: colourless crystals m.p. 158-160° (18.0 g, 73%). IR (Nujol): 3100, 1645, 1550, 1530 cm^{-1}. PMR (CCl_4): 5.87 ppm (br.m, 1H, NHMe); 2.68 ppm (d, 3H, J = 6 Hz, H-NMe); 1.00, 0.95, 0.95 ppm (tertiary Me singlets). MS: m/e 243 (M^+, base peak). (Found: C, 77.09; H, 11.02; N, 5.35. $C_{16}H_{27}ON$ requires: C, 77.06; H, 10.91; N, 5.62%).

N-Methyl longifolamine 7. To a magnetically-stirred slurry of $LiAlH_4$ (7.5 g) in dry ether (250 ml) was added dropwise a solution of N-methyl longifolamide 2 (22.2 g) in dry ether (400 ml) at room temperature (anhydrous conditions). The mixture was stirred at ambient temperature (22 hr) and then gently refluxed (2 hr). The cooled reaction product was successively treated with H_2O (7.5 ml), 15% aq. NaOH (7.5 ml) and water (22.5 ml) while stirring for another 15 minutes. The grannular precipitate was filtered off and thoroughly

washed with more ether. The combined extracts were washed with brine, dried and the solvent removed. Distillation of the residue gave pure N-methyl longifolamine 7 as a colourless liquid: b.p. 142°/1 mm (12.3 g, 58%). IR (smear): 3150, 1650, 1140 cm^{-1}. PMR (CCl_4): 2.33 ppm (s, 3H, NMe); 1.00, 1.00, 0.80 ppm (three tertiary Me singlets); 0.45 ppm (s, 1H, NH). MS(m/e): 235 (M^+, base peak). (Found: C, 80.57; H, 12.34; N, 6.28. $C_{16}H_{29}N$ requires: C, 81.63; H, 12.42; N, 5.95%).

N-Methyl pyrrolidine 12. N-Methyl longifolamine 7 (6.11 g) in ether (120 ml) was treated with N-chlorosuccinimide (3.5 g) in ether (150 ml) and stirred at room temperature (4 hr). The mixture was washed with water (2 x 50 ml), dried and the solvent removed to furnish the N-chloroamine 11 as a liquid; TLC (10% EtOAc in C_6H_6); single spot. PMR (CCl_4): N-Me singlet at 2.30 ppm; NH singlet (at 0.45 ppm) of 7 was absent.

The above N-chloroamine (6.5 g) was stirred with 84% H_2SO_4 (20.8 ml) in an oil bath at 65° (30 minutes). The mixture was cooled, treated with 50% aq. NaOH (120 ml) till it was strongly alkaline and stirred at room temperature (30 minutes). Dilution with water (200 ml), extraction with $CHCl_3$, washing with water, drying and removal of solvent

gave a colourless liquid b.p. 145°/0.8 mm (1.74 g.). GLC indicated it to be a mixture of the cyclized compound 12 (RRT, 1.00) and the amine 7 (RRT, 1.29). The material was taken up in $CHCl_3$ (100 ml) and washed with 1:1 HCl (3 x 20 ml) to remove the more basic amine 7. The organic solution was washed with water, dried and the solvent removed to furnish the pure pyrrolidine 12 obtained by distillation of the ether-soluble part: colourless liquid, b.p. 150° (bath)/0.6 mm, m.p. 58-60° (0.63 g, 10%). (Found: C, 81.94; H, 11.72; N, 5.88. $C_{16}H_{27}N$ requires: C, 82.34; H, 11.68; N, 6.00%).

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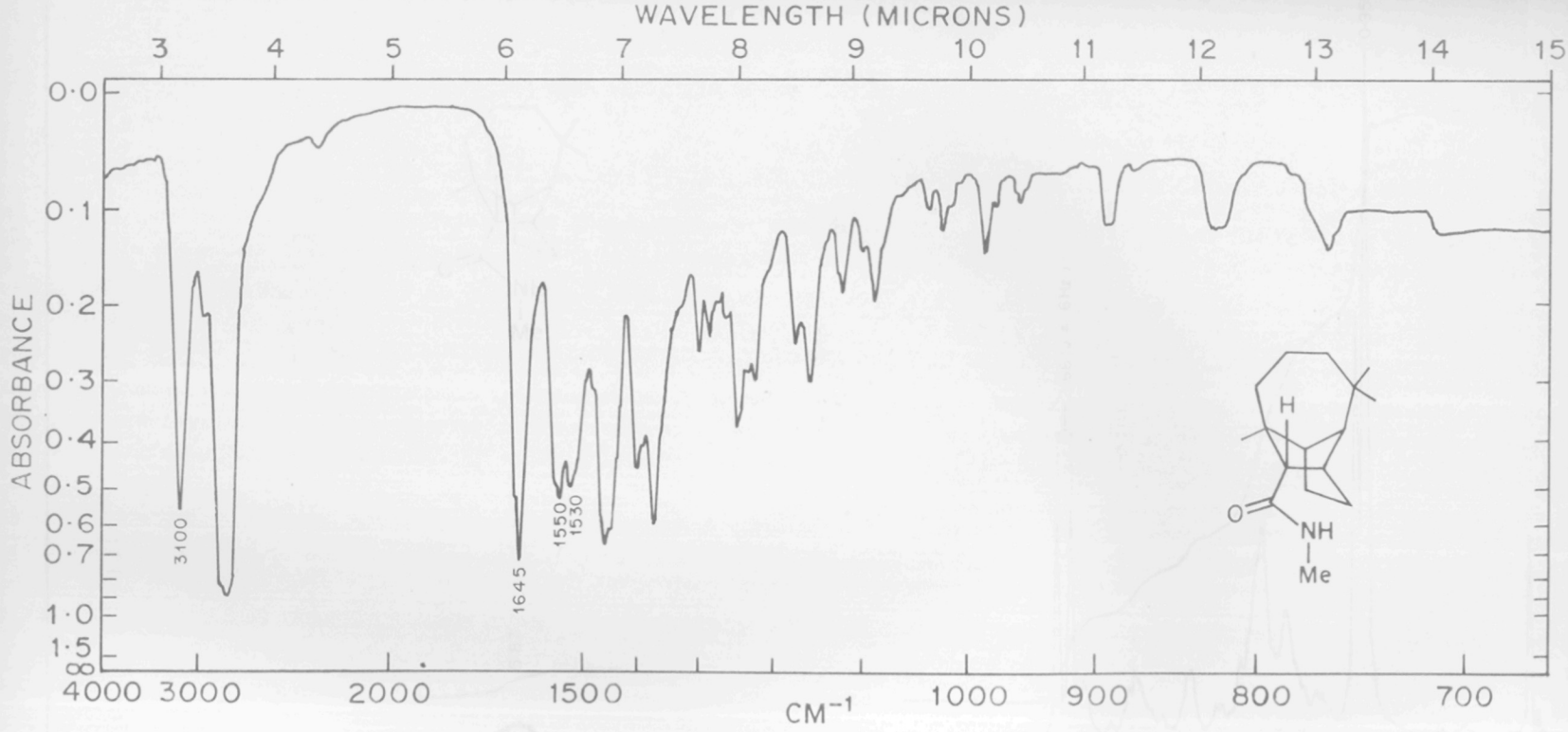


FIG. 1. IR SPECTRUM OF N-METHYL LONGIFOLAMIDE 9

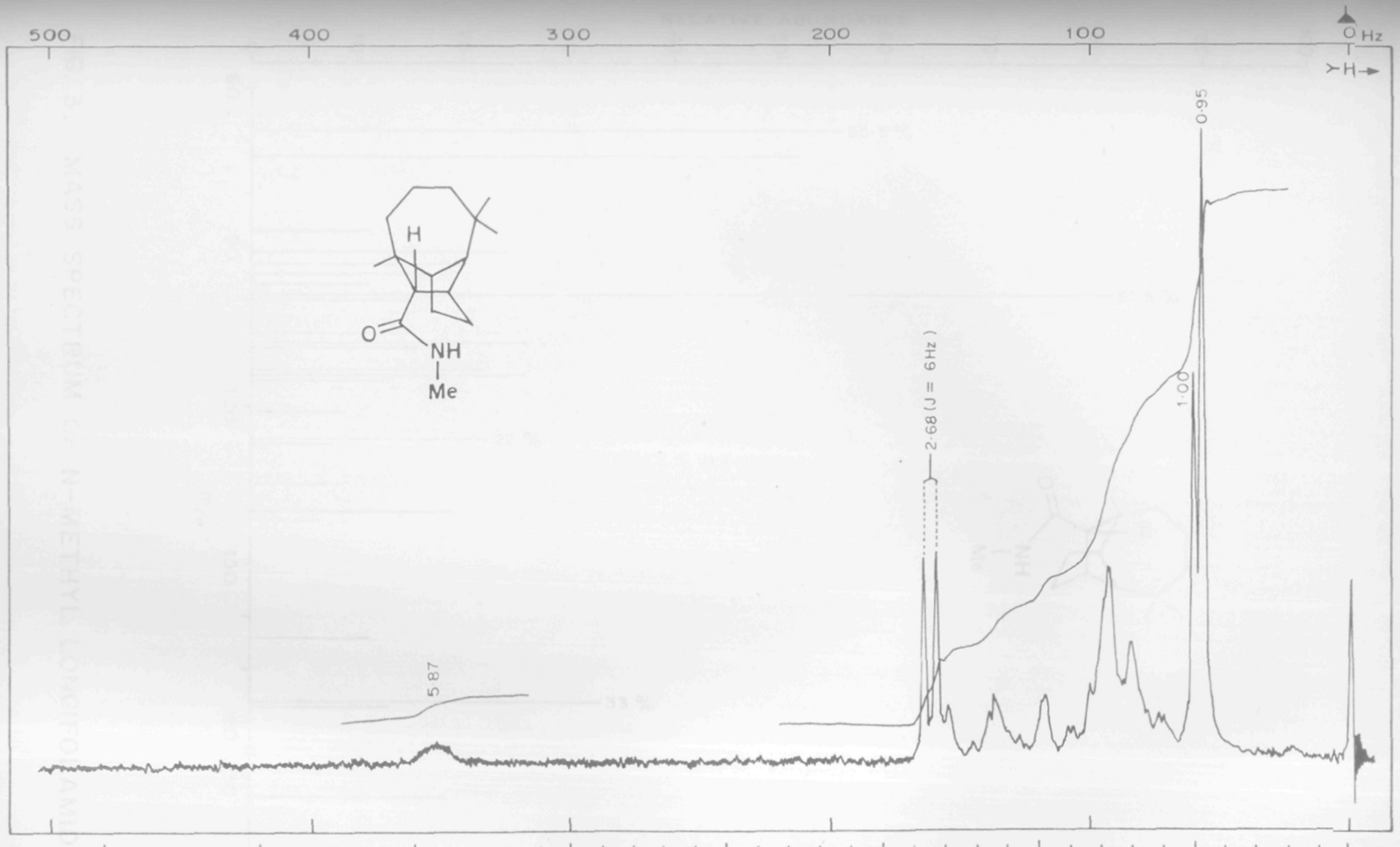


FIG. 2. PMR SPECTRUM OF N-METHYL LONGIFOLAMIDE 9

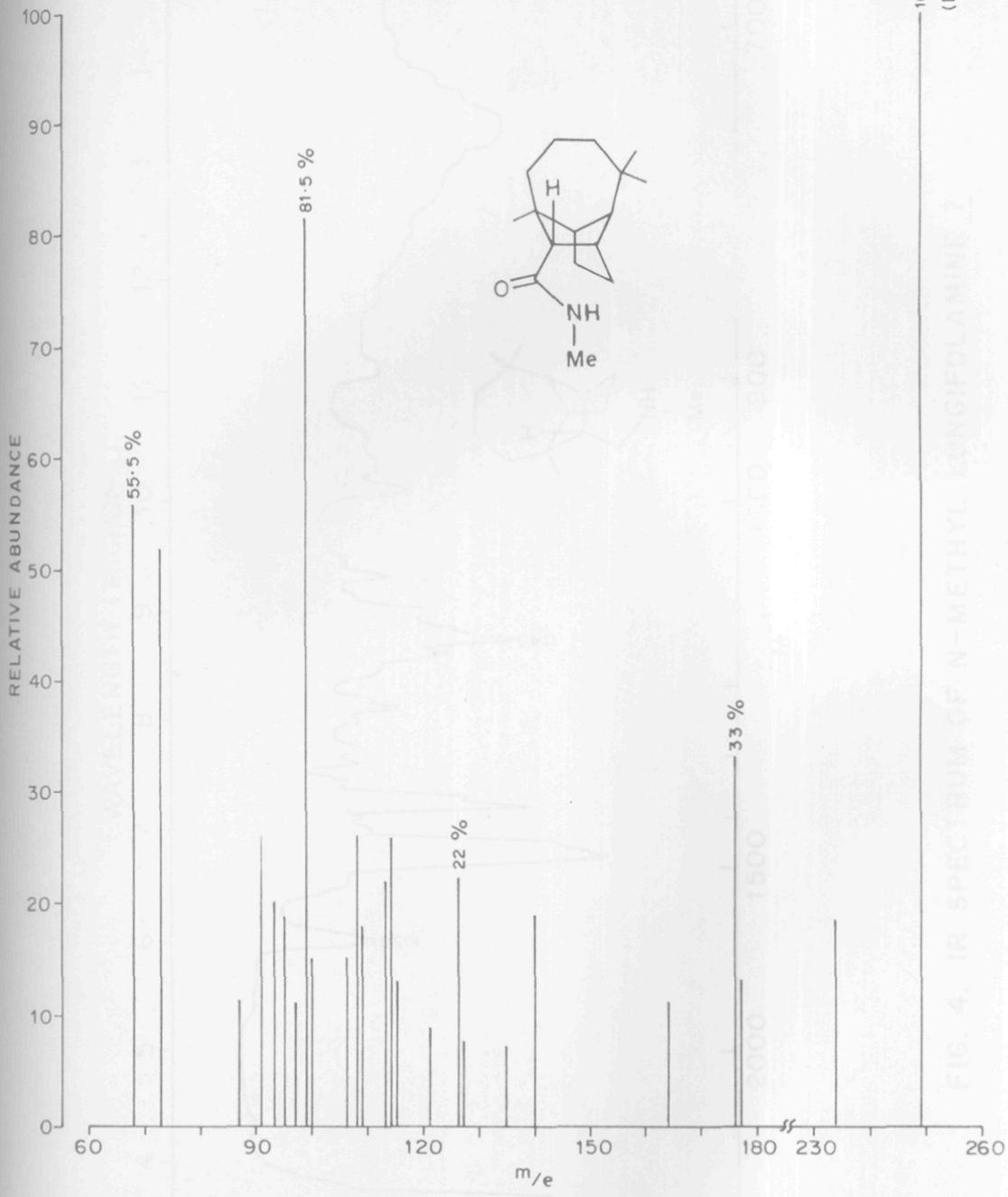


FIG. 3. MASS SPECTRUM OF N-METHYL LONGIFOLAMIDE 9

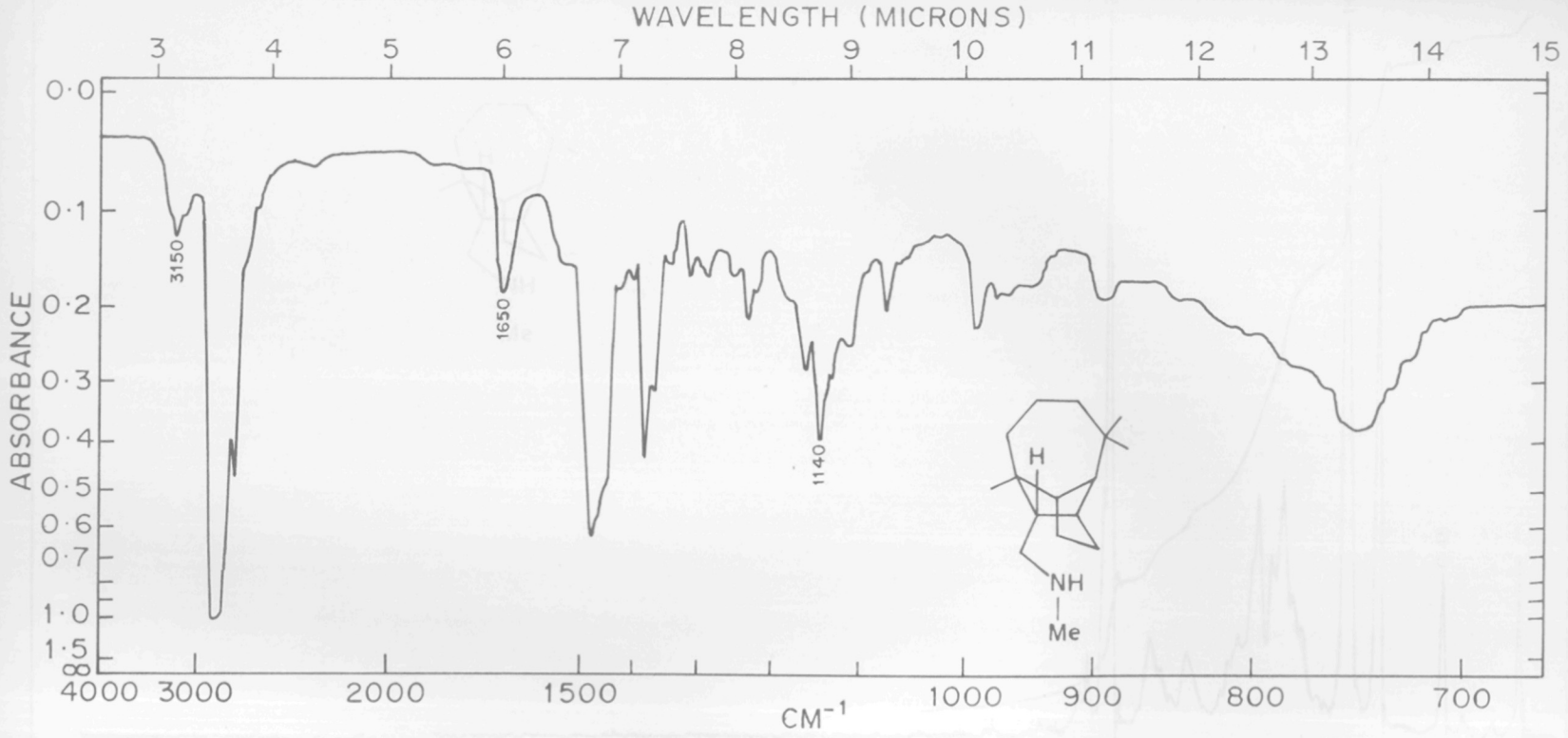


FIG. 4. IR SPECTRUM OF N-METHYL LONGIFOLAMINE 7

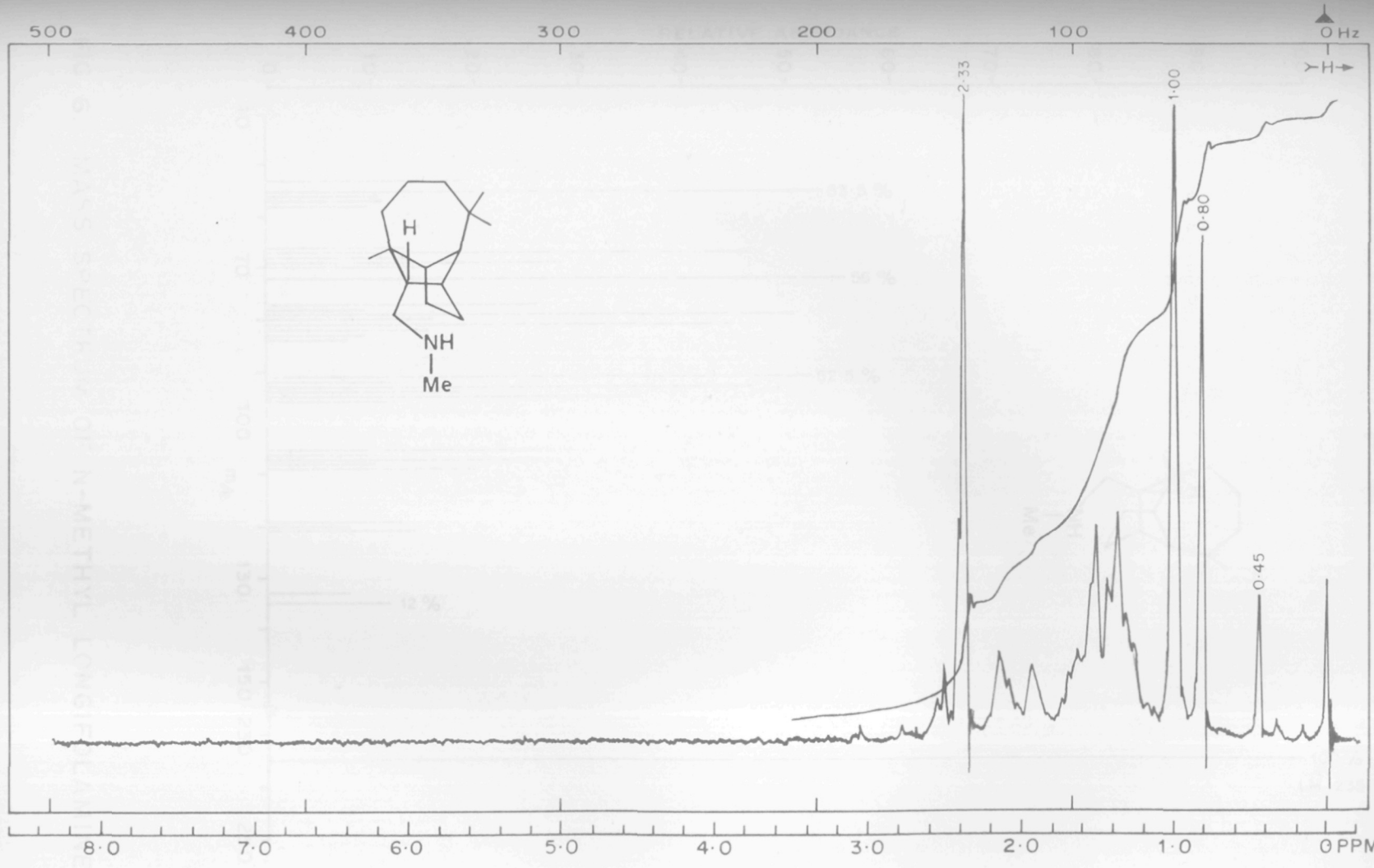


FIG. 5. PMR SPECTRUM OF N-METHYL LONGIFOLAMINE 7

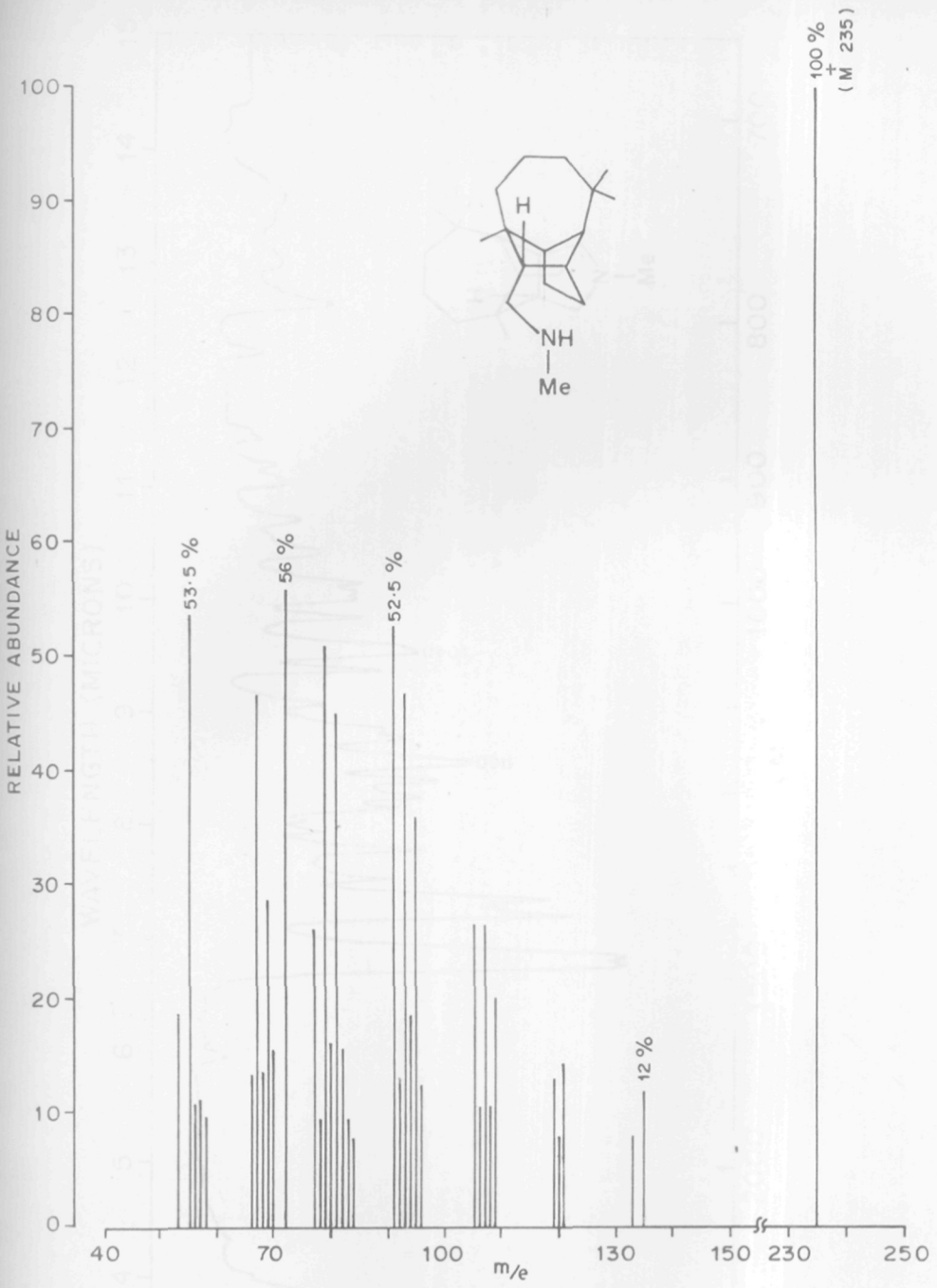


FIG. 6. MASS SPECTRUM OF N-METHYL LONGIFOLAMINE 7

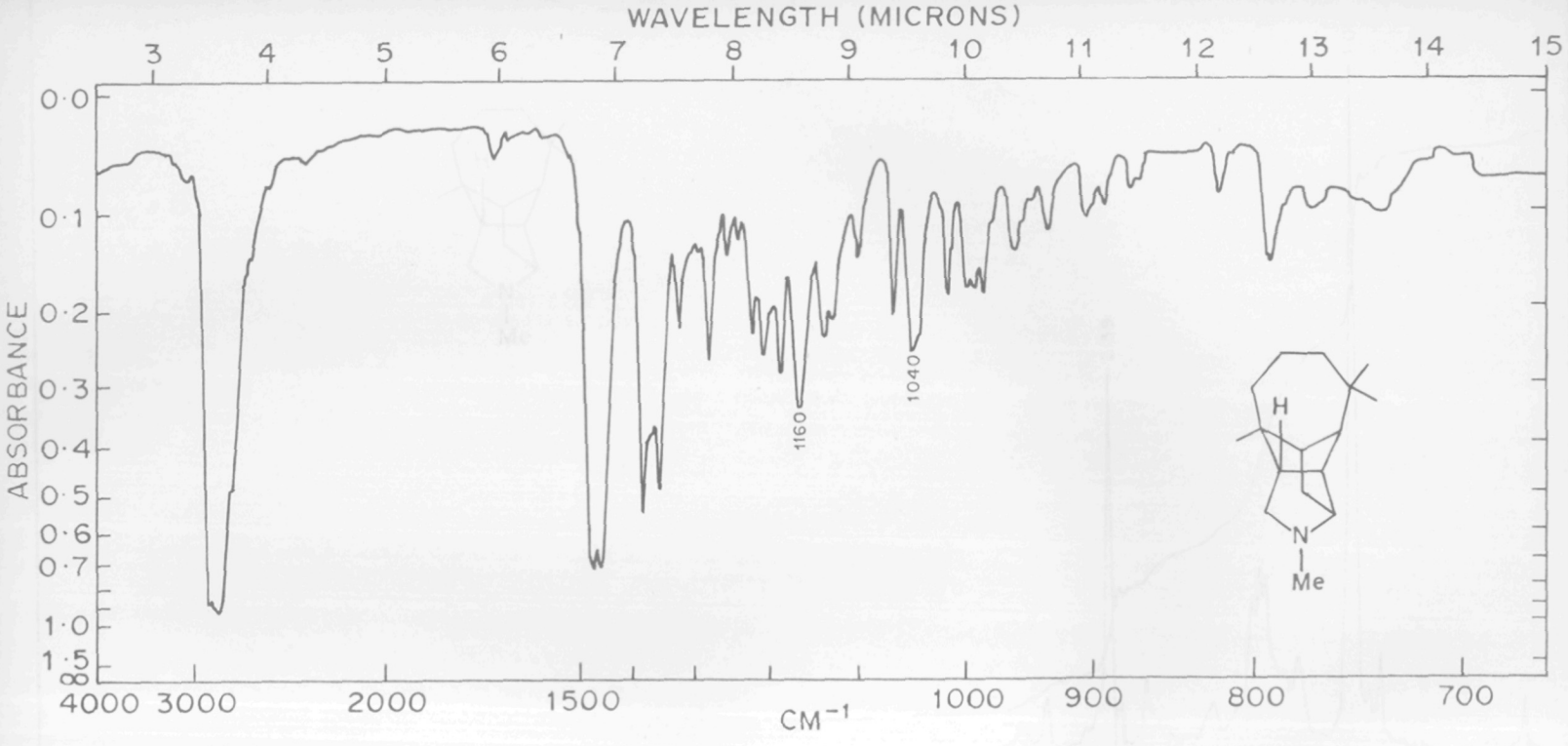


FIG. 7. IR SPECTRUM OF N-METHYL PYRROLIDINE 12

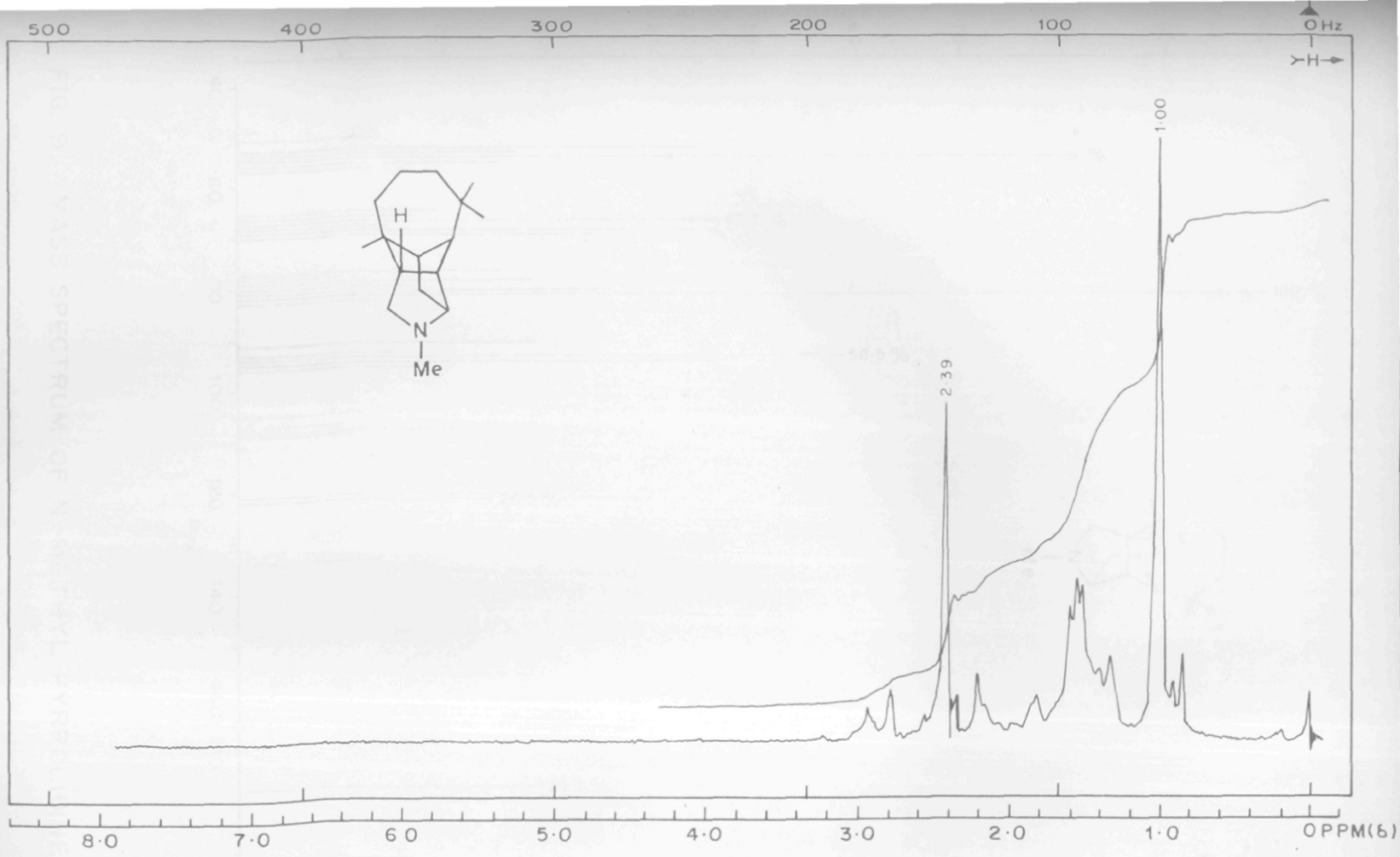


FIG. 8. PMR SPECTRUM OF N-METHYL PYRROLIDINE 12

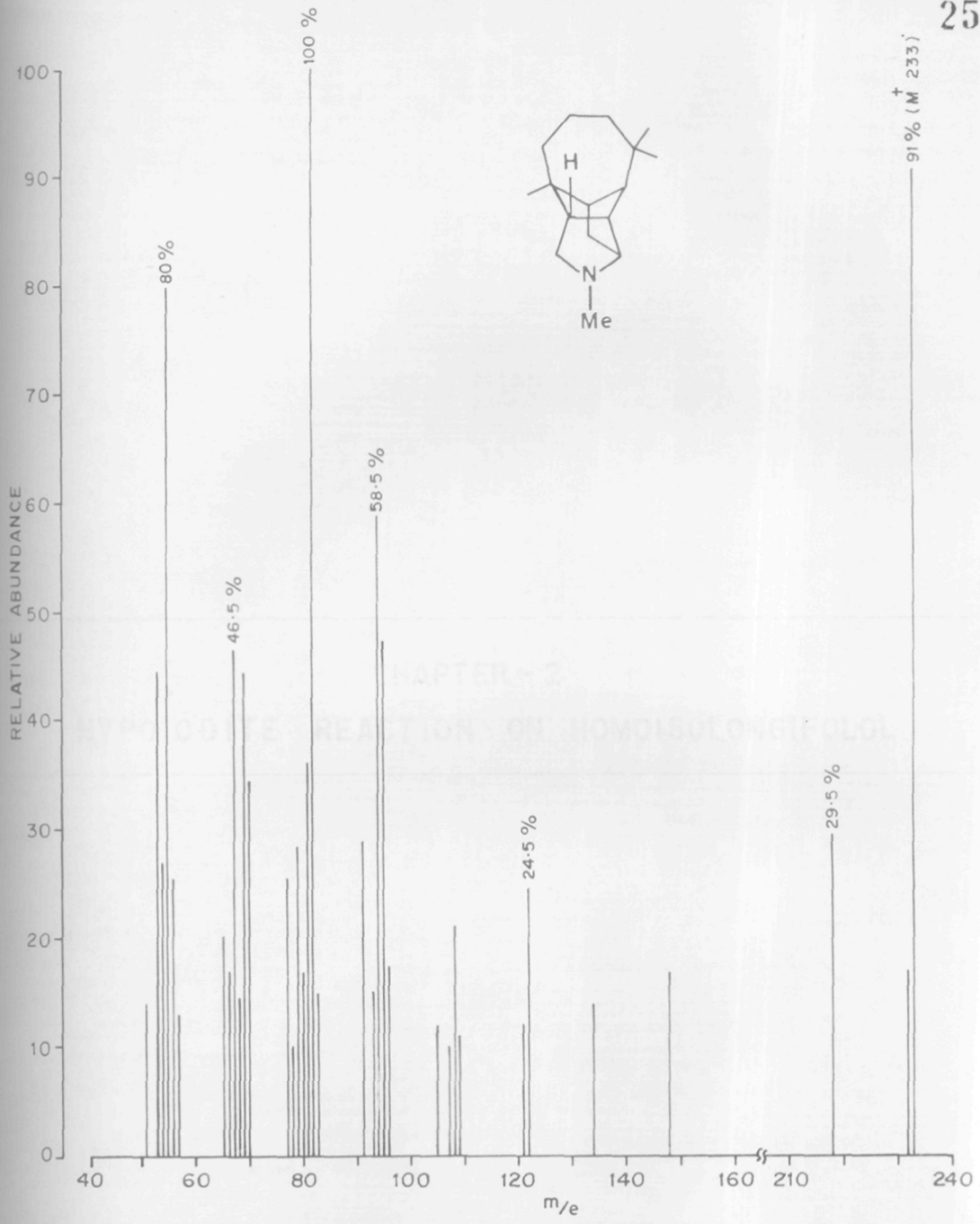


FIG. 9. MASS SPECTRUM OF N-METHYL PYRROLIDINE 12

CHAPTER-2

HYPOIODITE REACTION ON HOMOISOLONGIFOLOL

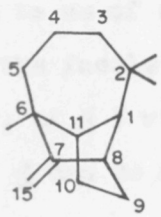
ABSTRACT

The hypoiodite reaction on homoisolongifolol 4, generated by the Arndt-Eistert homologation/$LiAlH_4$ reduction sequence on isolongifolic acid 5, has been studied: there was no evidence of any pyran formation although this oxidative cyclization pathway appeared quite facile for the oxy radical, by examination of a framework molecular model of 4. The product outcome of this sluggish reaction was nothing more than a partial conversion of 4 to its acetate 10.

HYPOIODITE REACTION ON HOMOISOLONGIFOLOL

Intramolecular hydrogen abstraction by oxygen and nitrogen free radicals constitutes an important method[1] for the generation of oxygen and nitrogen heterocycles. The success of this hydrogen abstraction process by the heteroatom radical, however, depends upon the relative orientation of the oxygen/nitrogen radical and the hydrogen to be abstracted and also on the rigidity of the system. The optimal spatial relations are best achieved in the case of a 1,5-hydrogen transfer and this explains the ease of formation of tetrahydrofuran/pyrrolidine compounds. But if this spatial orientation of the centres involved can be obtained otherwise, that internal hydrogen transfer occurs quite readily; a 1,6-hydrogen transfer in which a pyran ring is formed has been reported by Kashman and Benary[2].

It has been recently shown by us that the oxy radicals generated by the hypoiodite reaction [$Pb(OAc)_4$-I_2] on the epimeric pair of alcohols derived from longifolene 1 viz. isolongifolol (endo, cf 2) and longifolol (exo, cf 3) nicely functionalize strategic nonactivated sites: tetrahydrofuran (95%, cf. 2) in the case of isolongifolol[3];



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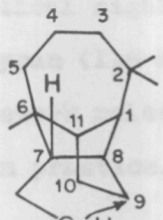

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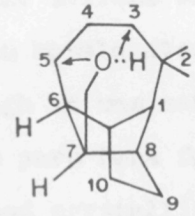

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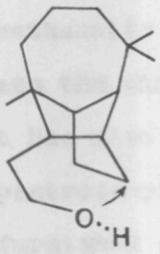

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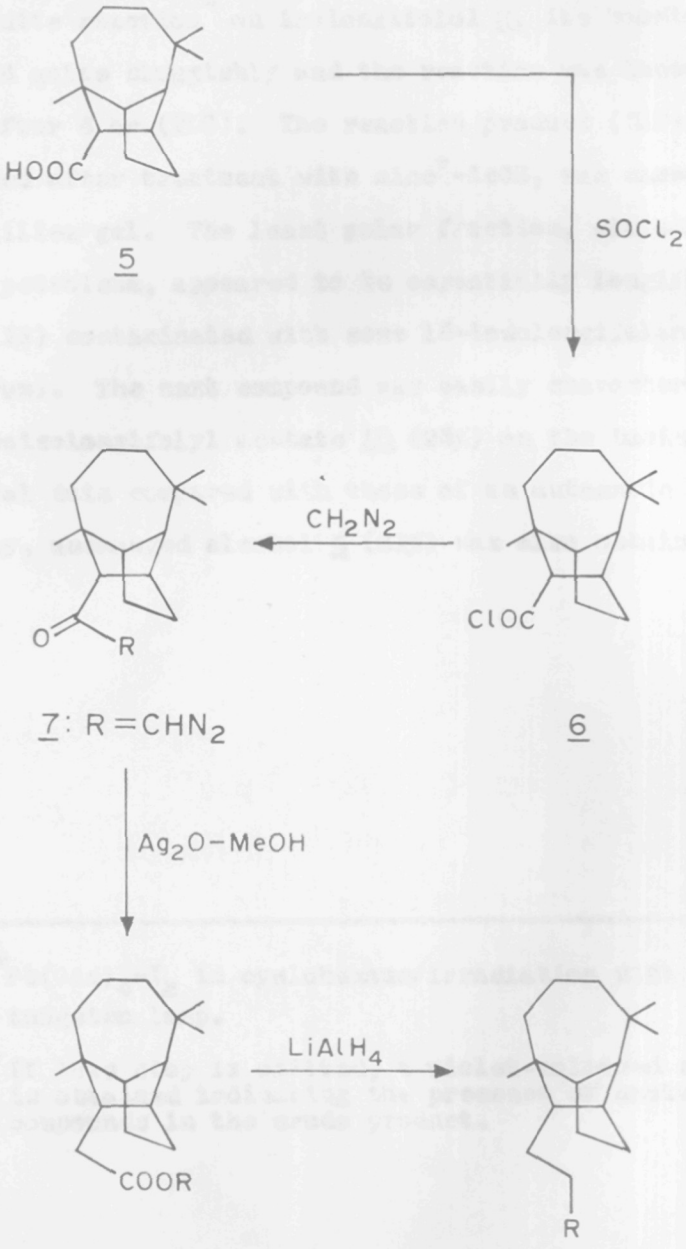
5-ring oxide and the unique 7-ring oxide (1:1) in the case of longifolol[4] (80%, cf 3). As an interesting offshoot of the above work, the generation and study of the fate of the oxy radical from homoisolongifolol 4 appeared to us of considerable theoretical significance: whether the facile formation of the pyran (1,6-hydrogen transfer, cf 4) visualized by a framework molecular model of 4 can be actually realized in practice.

The transformation of isolongifolic acid 5 into homoisolongifolol 4 via the Arndt-Eistert reaction[5]/$LiAlH_4$ reduction sequence is depicted in Scheme I. In the Wolff rearrangement of the diazoketone 7, initiated by Ag^+, reaction of the resulting ketene with water as the protonic solvent was quite unsatisfactory but gave the desired homologated ester 8 (71%) in methanolic medium. Although it was not necessary to isolate the diazoketone 7 in the pure form for the next step, it has also been obtained crystalline (m.p. 68°) and spectroscopically characterised. Base hydrolysis of 8 furnished pure homoisolongifolic acid 9 (m.p. 120°) and the slight contamination of the chloroketone 7 (R = CH_2Cl) (PMR) in the ester 8 was thus eliminated. Re-esterification of 9 with diazomethane followed by reduction with $LiAlH_4$ afforded homoisolongifolol 4 (89%).

SCHEME I


HOOC
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SOCl2
CH2N2
ClOC
6
O
R
7: R=CHN2
Ag2O-MeOH
LiAlH4
COOR
R
8: R=Me
9: R=H
4: R=OH
10: R=OAc

Under the optimized experimental conditions of the hypoiodite reaction* on isolongifolol 2, its homologue 4 behaved quite sluggishly and the reaction was incomplete even after 6 hr (TLC). The reaction product (TLC: 3 spots), obtained after treatment with zinc+-AcOH, was chromatographed over silica gel. The least polar fraction, eluted with light petroleum, appeared to be essentially longifolane (PMR, IR) contaminated with some 15-iodolongifolane (mass spectrum). The next compound was easily characterized as homoisolongifolyl acetate 10 (25%) on the basis of its spectral data compared with those of an authentic sample. Finally, unchanged alcohol 4 (21%) was also obtained.

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*$Pb(OAc)_4$-I_2 in cyclohexane/irradiation with a 250W tungsten lamp.

+If this step is omitted, a violet-coloured distillate is obtained indicating the presence of unstable iodo compounds in the crude product.

EXPERIMENTAL

Recorded temperatures are uncorrected. Light-petroleum refers to essentially hexane fraction, b.p. 63°. Solvent extracts were dried over anhydrous Na_2SO_4. Optical rotations were taken in $CHCl_3$ at 26°.

IR spectra were recorded on a Perkin-Elmer Infracord model 137E. PMR spectra were taken on a Varian T-60 spectrometer with TMS as internal standard. Mass spectra (MS) were obtained on a CEC spectrometer model 21-110B using an ionizing voltage of 70 eV and a direct inlet system.

TLC was carried out on silica gel layers (0.2 mm) containing 15% gypsum; visualization was done by spraying with conc. H_2SO_4 and charring at 120° in an oven.

Acid Chloride 6

This was prepared from longifolic acid 5 (epimeric mixture) by the action of $SOCl_2$ as described[6] earlier.

Diazoketone 7

A cold solution of the acid chloride 6 (10.9 g) in dry ether (50 ml) was added dropwise to a magnetically stirred ethereal solution of CH_2N_2 (5.4 g of CH_2N_2 in 200 ml of dry ether), cooled in an ice-bath. After the addition (1 hr), the mixture was kept at room temperature

(2 hr) and the solvent removed from a waterbath at 50°/50 mm. The crude solid (11.0 g) was recrystallised from light petroleum to furnish pale yellow needles of the diazoketone 7: m.p. 67-68°. IR (Nujol): 2100 (v.s) 1650, 840, 830, 790 cm^{-1}. PMR(CCl_4): 4.90 ppm (s, 1H, O=C-C<u>H</u>N_2); 1.03; 1.00, 1.00 ppm (three tertiary methyl singlets). MS (m/e): 260 (M^+). (Found: C, 73.48; H, 9.47; N, 9.11. $C_{16}H_{24}ON_2$ requires: C, 73.80; H, 9.29; N, 10.76%).

Methyl homoisolongifolate 8 and homoisolongifolic acid 9.

A slurry of Ag_2O [freshly prepared from $AgNO_3$ (4 g) in water (20 ml) and NaOH pellets (4 g) in water (40 ml)] in dry MeOH (50 ml) was added portionwise (in 3 lots) to a hot (50°), stirred solution of the crude diazoketone 7 (24.5 g) in dry MeOH (300 ml); after each addition of Ag_2O there was a brisk evolution of N_2. After refluxing for 0.5 hr the mixture was filtered (fluted filter), the filtrate taken to dryness and the residue distilled: b.p. 130°/0.7 mm (18.7 g); methyl ester 8 slightly contaminated with the chloroketone [illegible]. PMR (CCl_4): 3.57 ppm (q, J ≈ 22 Hz, O=C.C<u>H</u>$_2$Cl) superimposed on COO<u>Me</u> singlet (3.57 ppm).

The above ester (18.5 g) was hydrolysed by refluxing with 20% aq. methanolic KOH (100 ml) for 18 hr. The mixture was diluted with water (300 ml) and extracted with

EtOAc (100 ml x 3) to remove all neutral material. The aqueous alkaline portion was acidified with conc. HCl (Congo red), extracted with EtOAc (100 ml x 3), washed with water, brine, dried and the solvent removed. The crude solid (10 g, 57%), on recrystallisation from acetonitrile furnished colourless crystals of homoisolongifolic acid, m.p. 119-120°; $[\alpha]_D$ -188° (c = 0.5%). IR(Nujol): 3000, 2600, 1700, 1420, 1320, 1200 cm^{-1}. PMR (CCl_4): 1.03, 1.03, 0.80 ppm (three tertiary Me singlets). MS (m/e): 250 (M^+). (Found: C, 77.28; H, 10.63. $C_{16}H_{26}O_2$ requires: C, 76.75; H, 10.47%).

Methyl homoisolongifolate 8 (pure) was prepared by esterification of the acid 3 with a solution of CH_2N_2 in ether: colourless liquid, b.p. 135°/0.8 mm. IR(smear): 1740, 1180 cm^{-1}. PMR (CCl_4): 3.57 ppm (s, 3H, COOMe); 1.02, 1.02, 0.78 ppm (three tertiary Me singlets). MS (m/e): 264 (M^+, base peak). (Found: C, 77.11; H, 10.66. $C_{17}H_{28}O_2$ requires: C, 77.22; H, 10.67%).

Homoisolongifolol 4

Pure methyl homoisolongifolate 8 (5.9 g) in dry ether (60 ml) was added dropwise, to a stirred slurry of $LiAlH_4$ (2.0 g) in dry ether (200 ml) at room temperature (anhydrous conditions). After stirring overnight the mixture was refluxed for 2 hr for completion of reaction

(TLC). The mixture was cooled, treated successively with ice water (2 ml), 15% aq. NaOH (2 ml), water (6 ml) and stirred for 15 minutes. The grannular precipitate was filtered off, washed thoroughly with more ether, the filtrate taken to dryness and the residue was distilled to furnish pure homoisolongifolol **4**: colourless liquid, b.p. 130°/0.8 mm (4.6 g, 89%); $[\alpha]_D$ +83.35° (c = 0.6%). IR(smear): 3200, 1080, 1060, 1040, 895 cm^{-1}. PMR (CCl_4): 3.40 ppm (t, 2H, $CH_2\underline{CH_2}OH$, J = 7 Hz); 1.03, 0.98 , 0.83 ppm (three tertiary Me singlets). MS (m/e): 236 (M^+). (Found: C, 80.84; H, 12.00. $C_{16}H_{28}O$ requires: C, 81.29; H, 11.94%).

Hypoiodite reaction on homoisolongifolol **4**: Homoisolongifolyl acetate **10**.

A mixture of homoisolongifolol **4** (2.21 g), I_2 (1.30 g) and Pb $(OAc)_4$ (freshly prepared, 6.00 g) in cyclohexane (purified, 50 ml) was stirred and refluxed under irradiation from a 250 W-tungsten lamp (N_2 atmosphere, anhydrous conditions). After 6 hr, excess of the reagent was destroyed by adding ethanediol (1.5 ml). The organic layer was separated, the inorganic residue washed thoroughly with more cyclohexane (3 x 50 ml) and the combined extracts taken to dryness. The crude product was treated with zinc dust (1.2 g), gl. AcOH (12 ml) and heated on the water bath (2 hr). The mixture was poured into water,

extracted with light petroleum (3 x 100 ml), washed successively with 5% aq. Na_2CO_3, water, brine, dried and the residue distilled: colourless liquid (1.7 g); TLC: 3 spots. This mixture was chromatographed on silica gel/IIA (50 g, 55 cm x 1.8 cm) with TLC monitoring: Fr.1, light petroleum, 50 ml x 3; Fr.2, light petroleum-C_6H_6 (1:1), 50 ml x 3, pure; Fr.3, 5% MeOH in C_6H_6, 50 ml x 3, pure.

Fr.1: Colourless liquid, b.p. 100° (bath)/0.9 mm (0.16 g); essentially longifolane (PMR, IR) + iodo derivative (mass spectrum).

Fr.2: Homoisolongifolyl acetate 10, colourless liquid b.p. 150°(bath)/0.9 mm (0.71 g, 25%). IR (smear): 1740, 1250 cm^{-1}. PMR (CCl_4): 3.90 ppm (t, 2H, $CH_2.CH_2OAc$, J = 7 Hz); 1.98 ppm (s, 3H, $OCOCH_3$); 1.03, 0.96, 0.82 ppm (three tertiary Me singlets). MS (m/e): 278 (M^+); 218 (M-AcOH, base peak). (Found: C, 76.96; H, 10.71. $C_{18}H_{30}O_2$ requires: C, 77.65; H, 10.86%).

Fr.3: Homoisolongifolol 4 (0.5 g, 21%) identified by IR, PMR.

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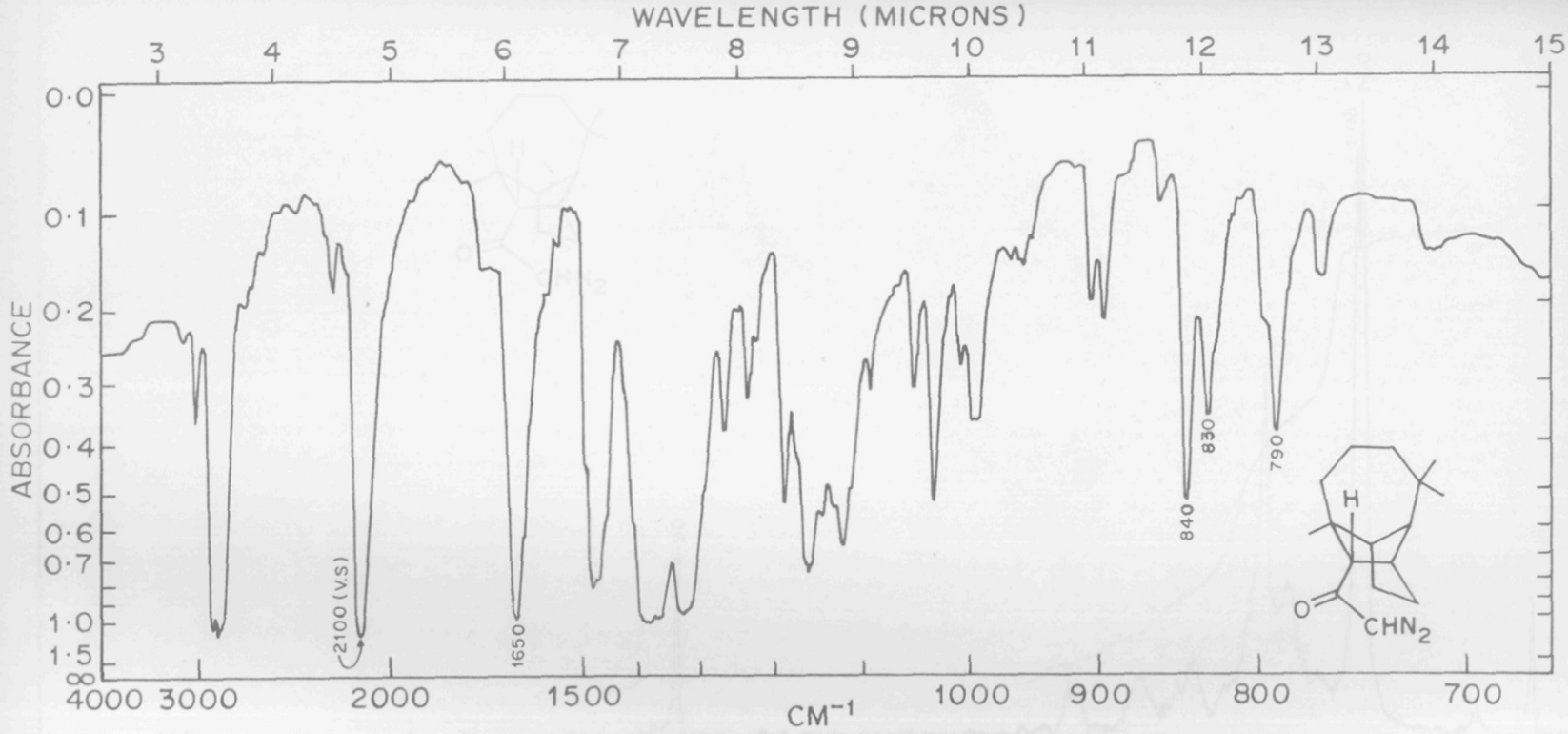


FIG. 1. IR SPECTRUM OF DIAZOKETONE 7

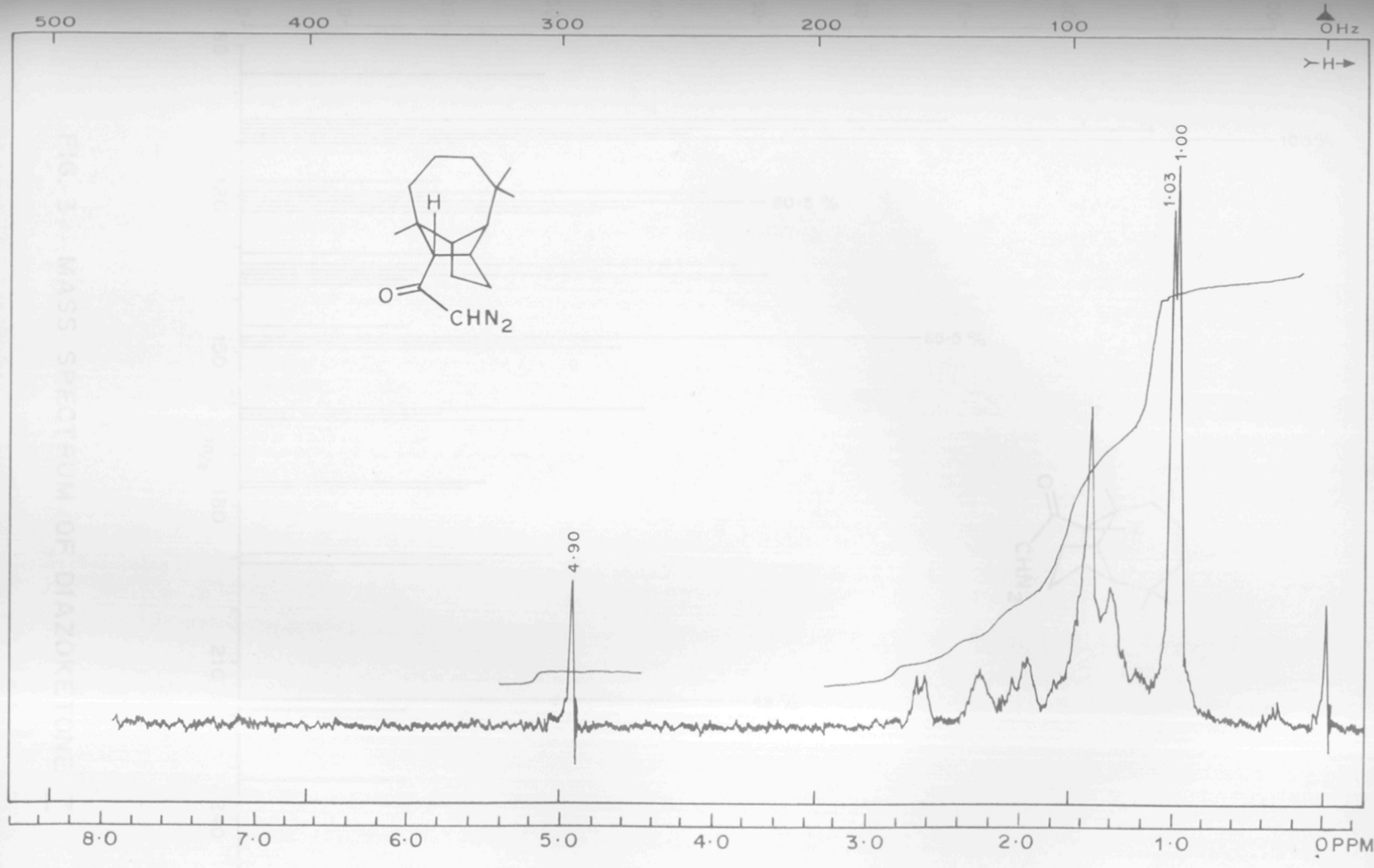


FIG. 2. PMR SPECTRUM OF DIAZOKETONE 7

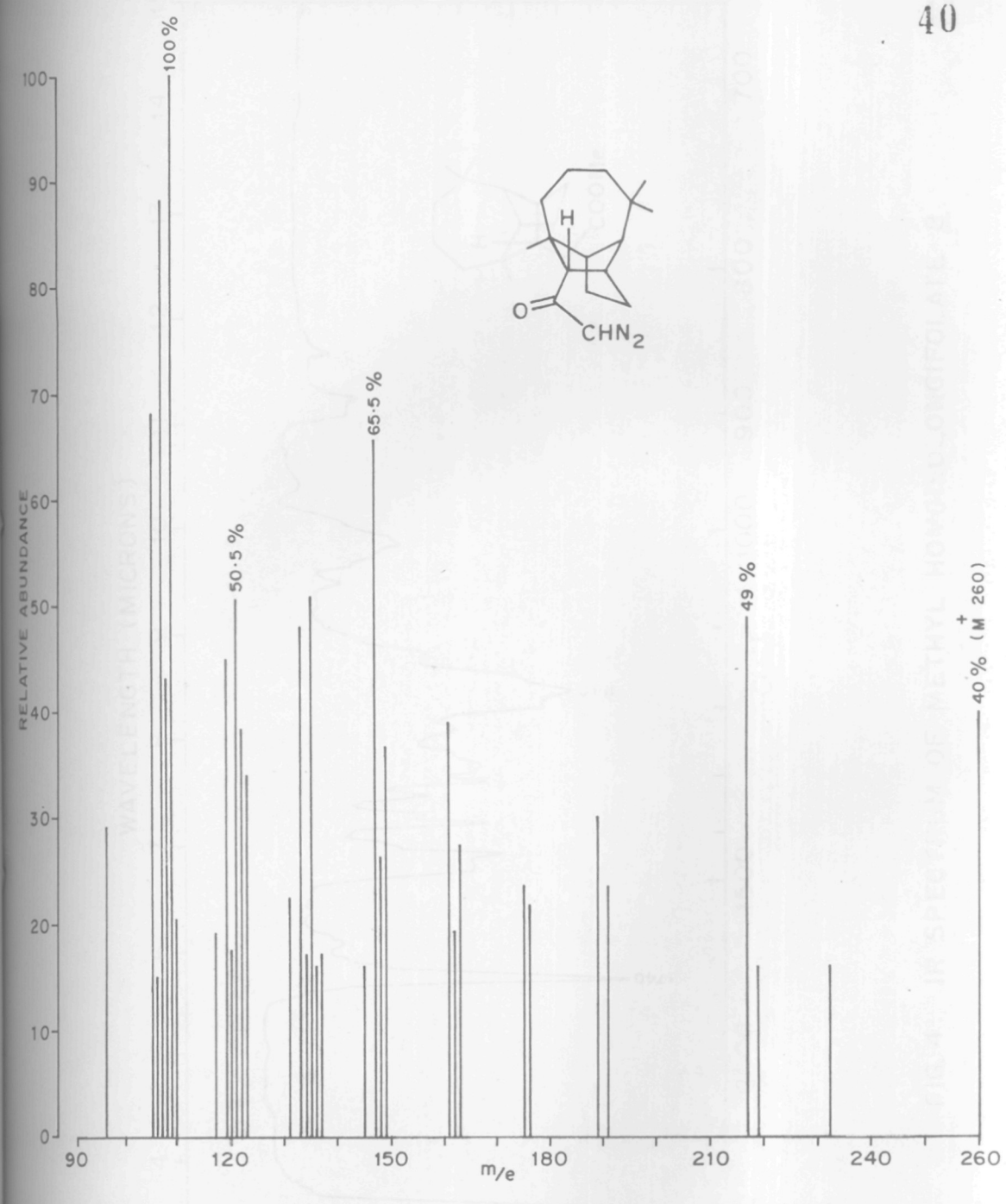


FIG. 3. MASS SPECTRUM OF DIAZOKETONE 7

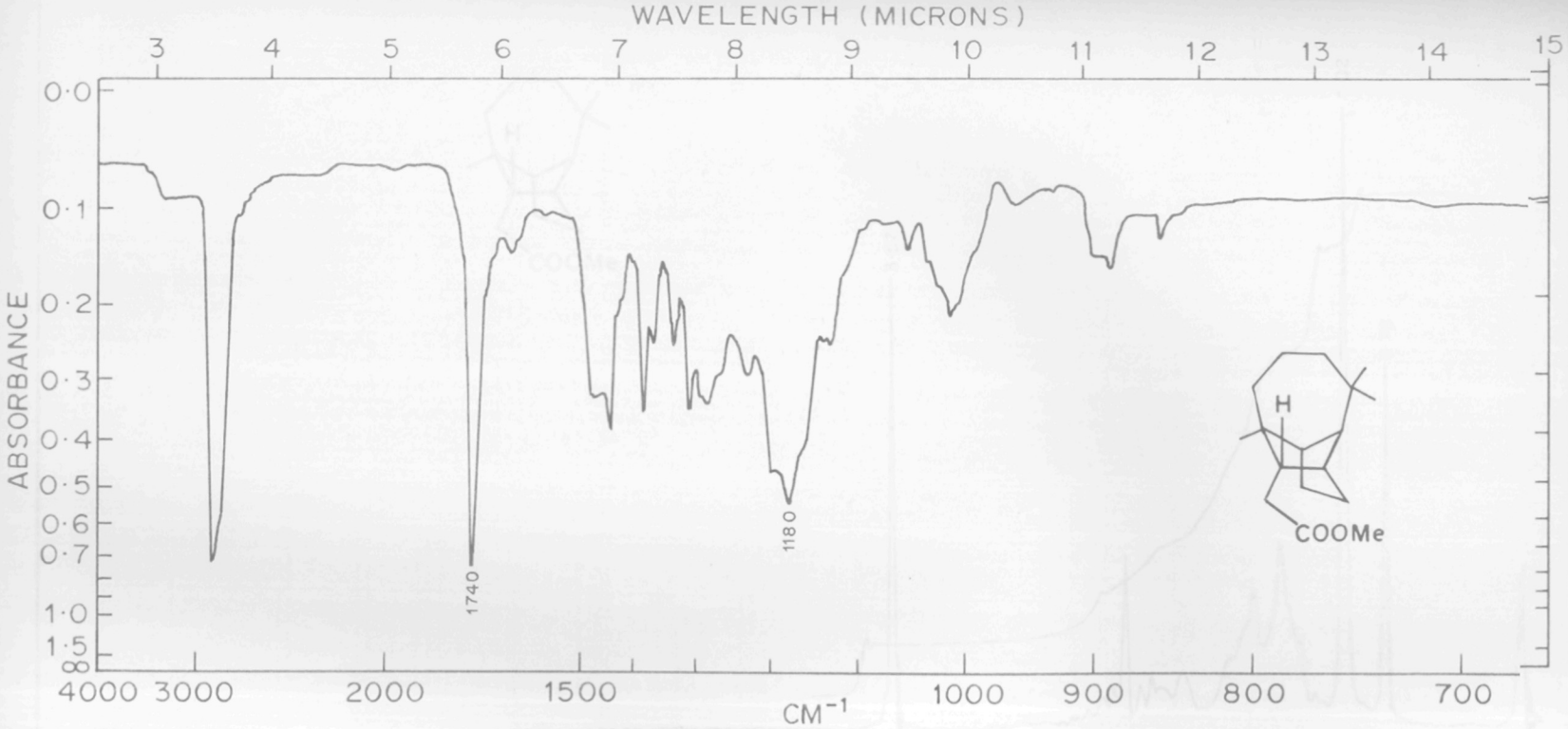


FIG. 4. IR SPECTRUM OF METHYL HOMOISOLONGIFOLATE 8

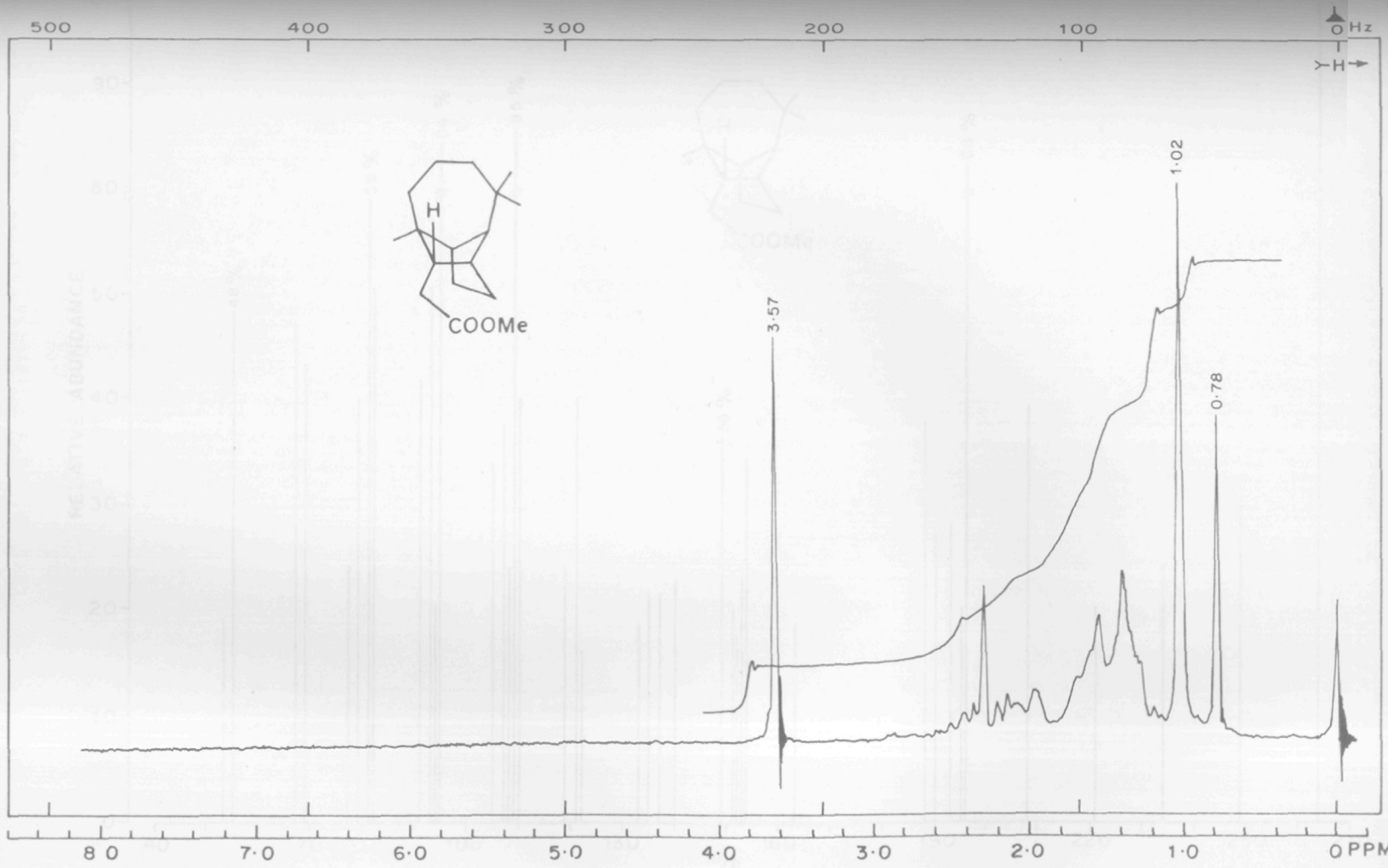


FIG. 5. PMR SPECTRUM OF METHYL HOMOISOLONGIFOLATE 8

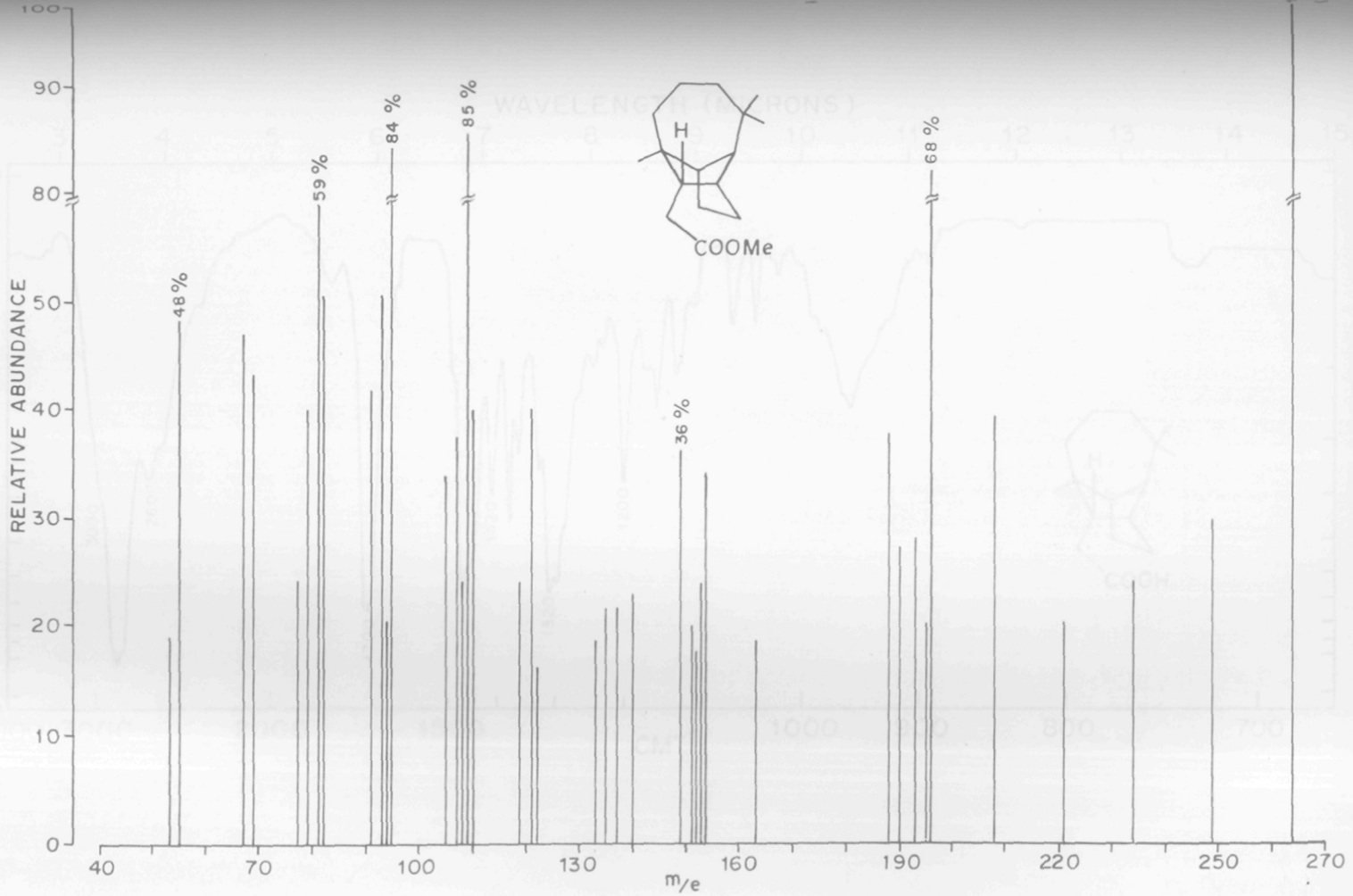


FIG. 6. MASS SPECTRUM OF METHYL HOMOISOLONGIFOLATE 8

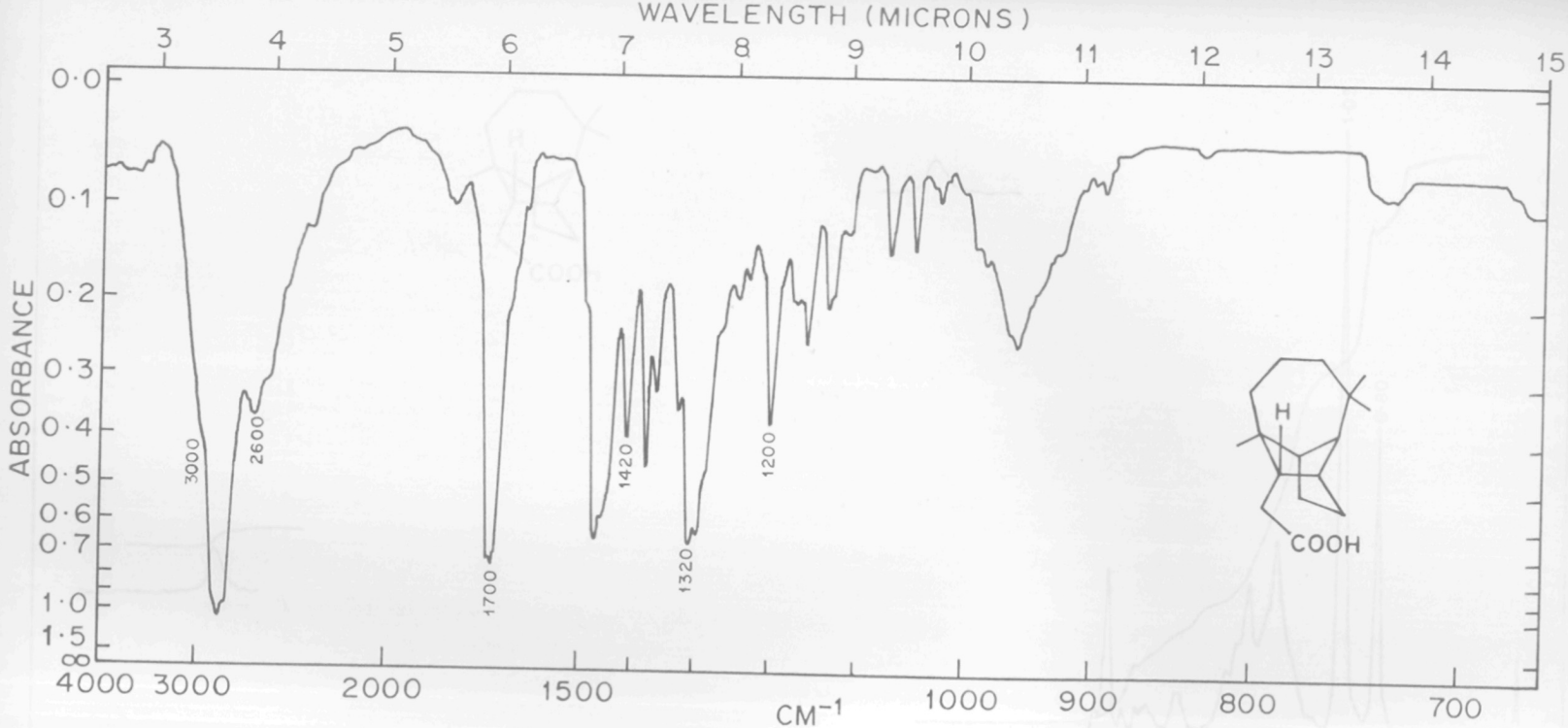


FIG. 7. IR SPECTRUM OF HOMOISOLONGIFOLIC ACID 9

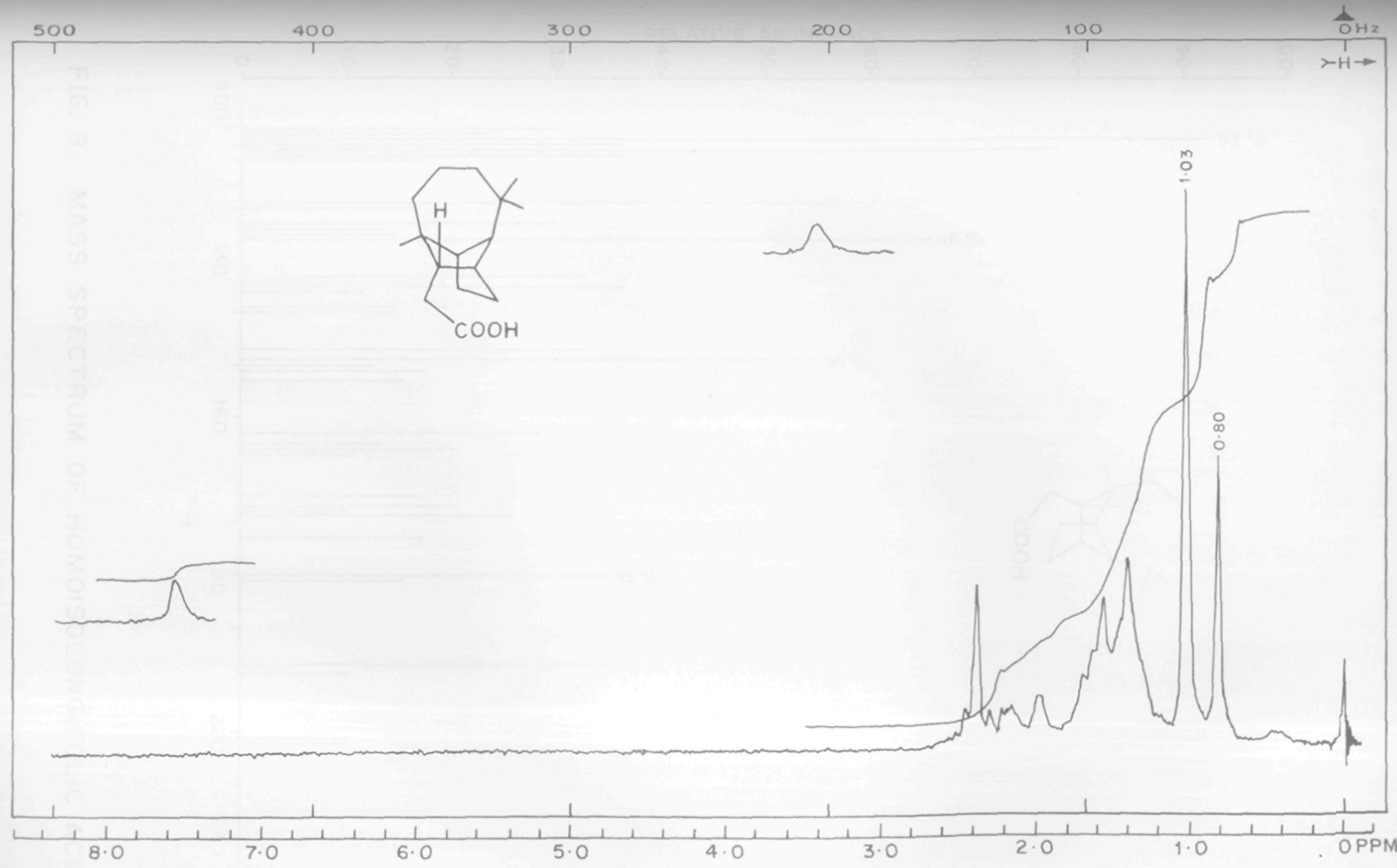


FIG. 8. PMR SPECTRUM OF HOMOISOLONGIFOLIC ACID 9

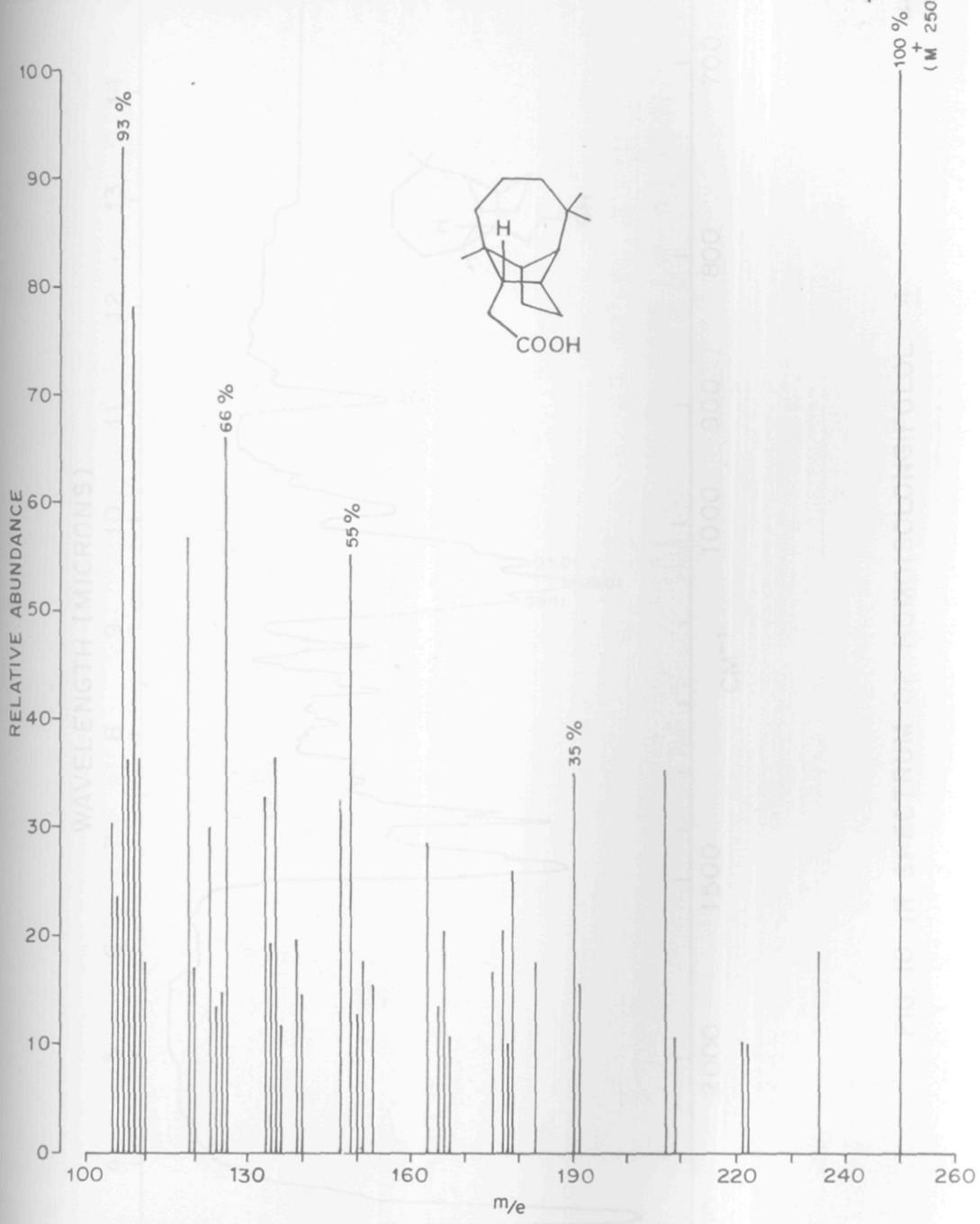


FIG. 9. MASS SPECTRUM OF HOMOISOLONGIFOLIC ACID 9

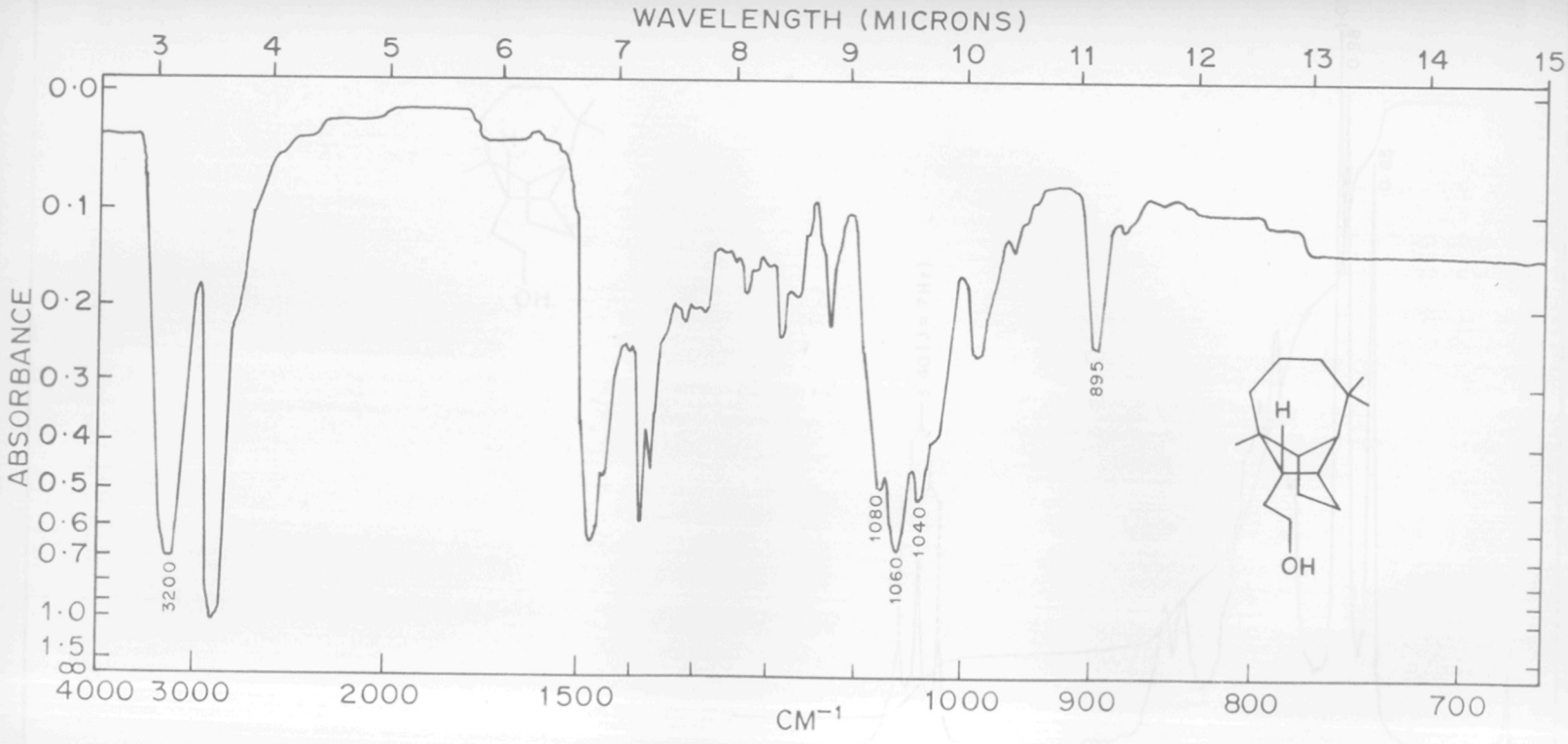


FIG. 10. IR SPECTRUM OF HOMOISOLONGIFOLOL 4

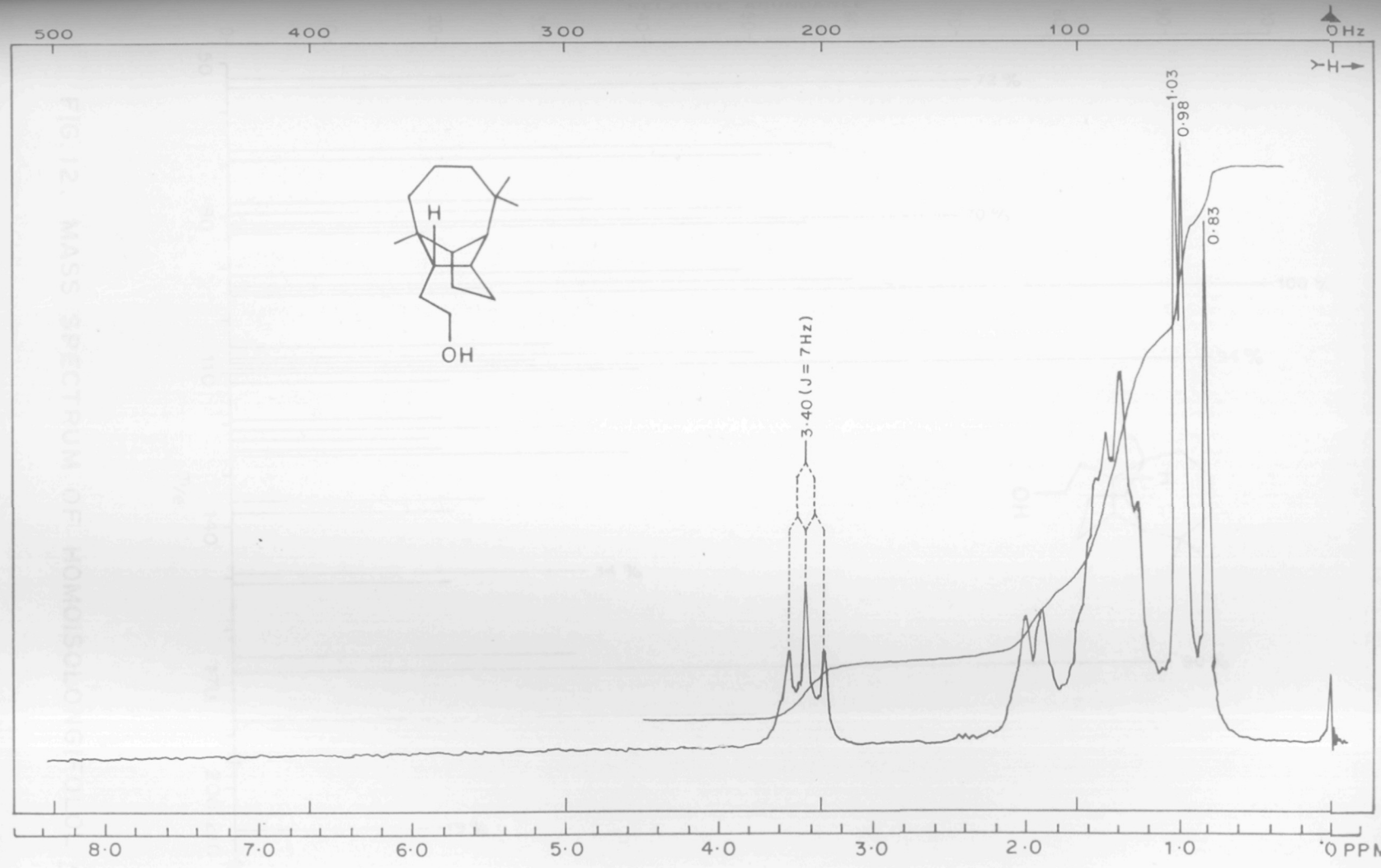


FIG. 11. PMR SPECTRUM OF HOMOISOLONGIFOLOL 4

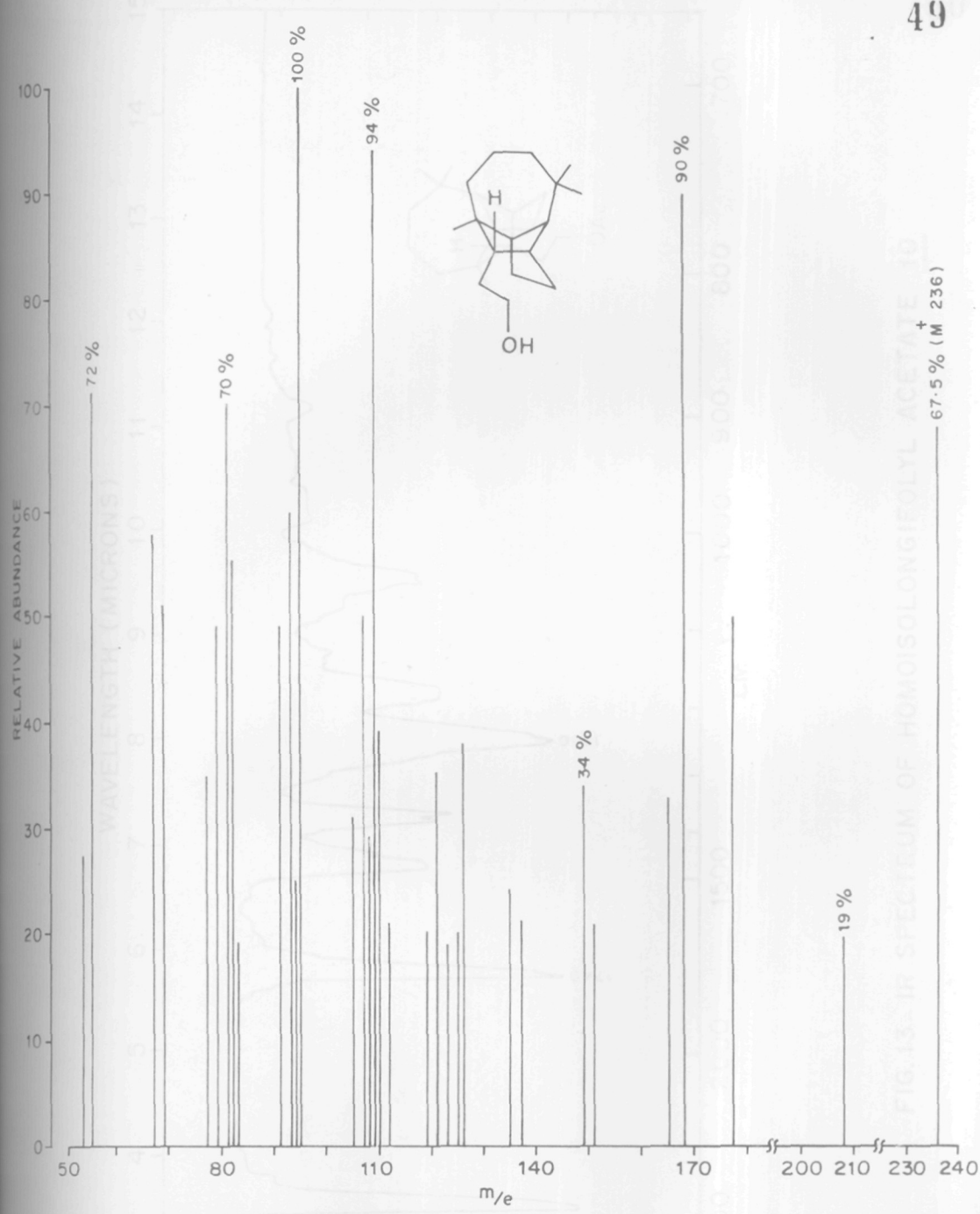


FIG. 12. MASS SPECTRUM OF HOMOISOLONGIFOLOL 4

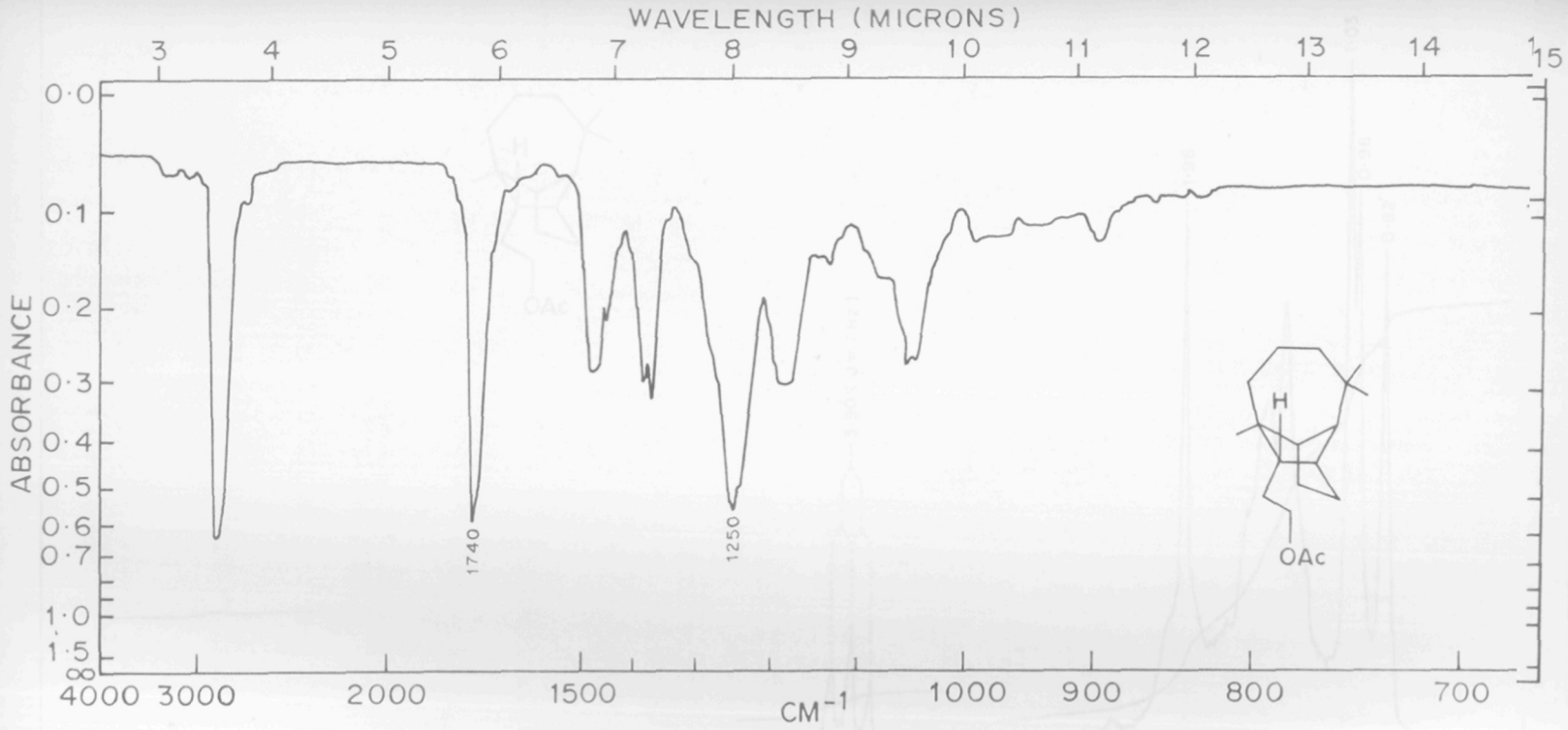


FIG. 13. IR SPECTRUM OF HOMOISOLONGIFOLYL ACETATE 10

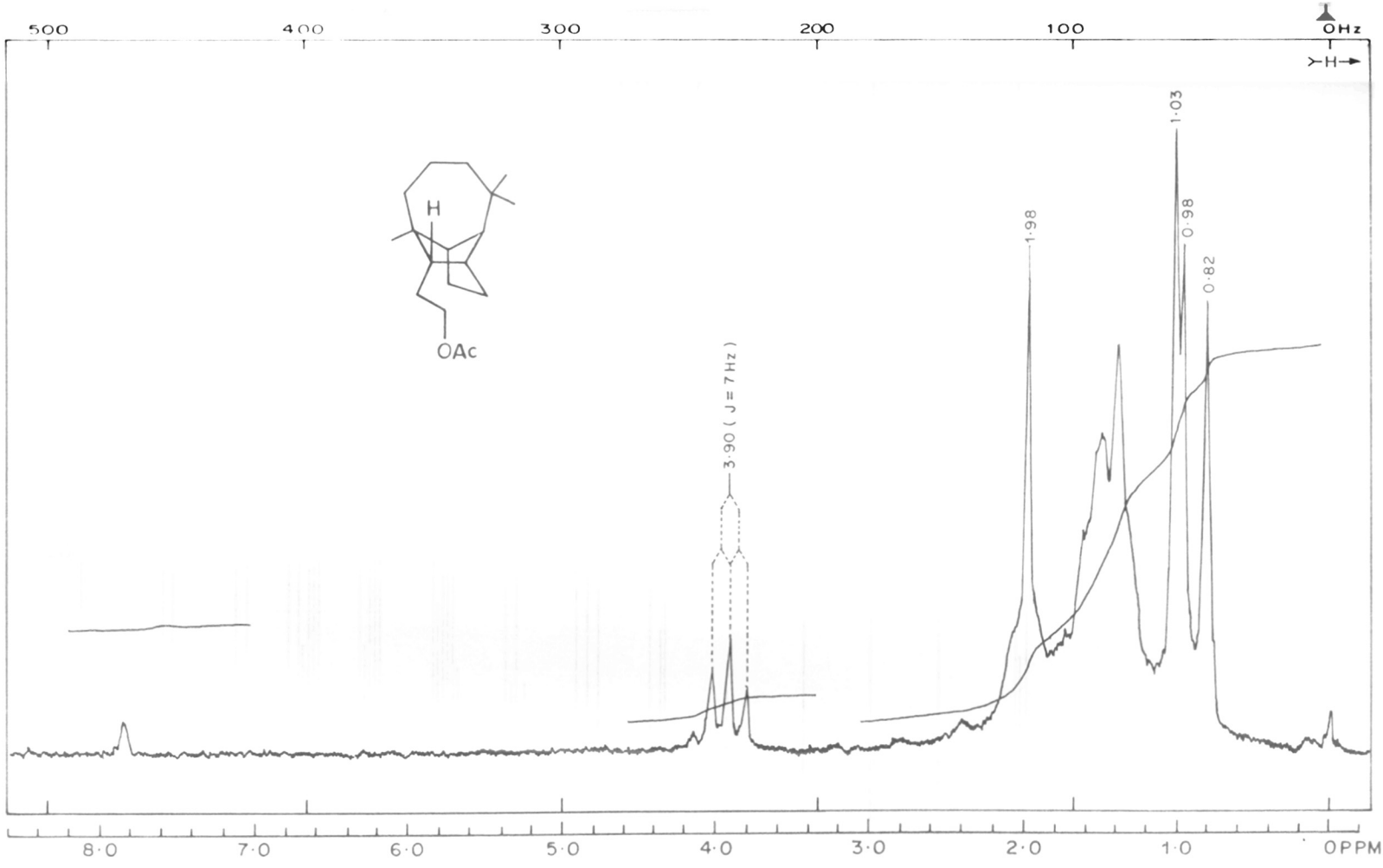


FIG. 14. PMR SPECTRUM OF HOMOISOLONGIFOLYL ACETATE 10

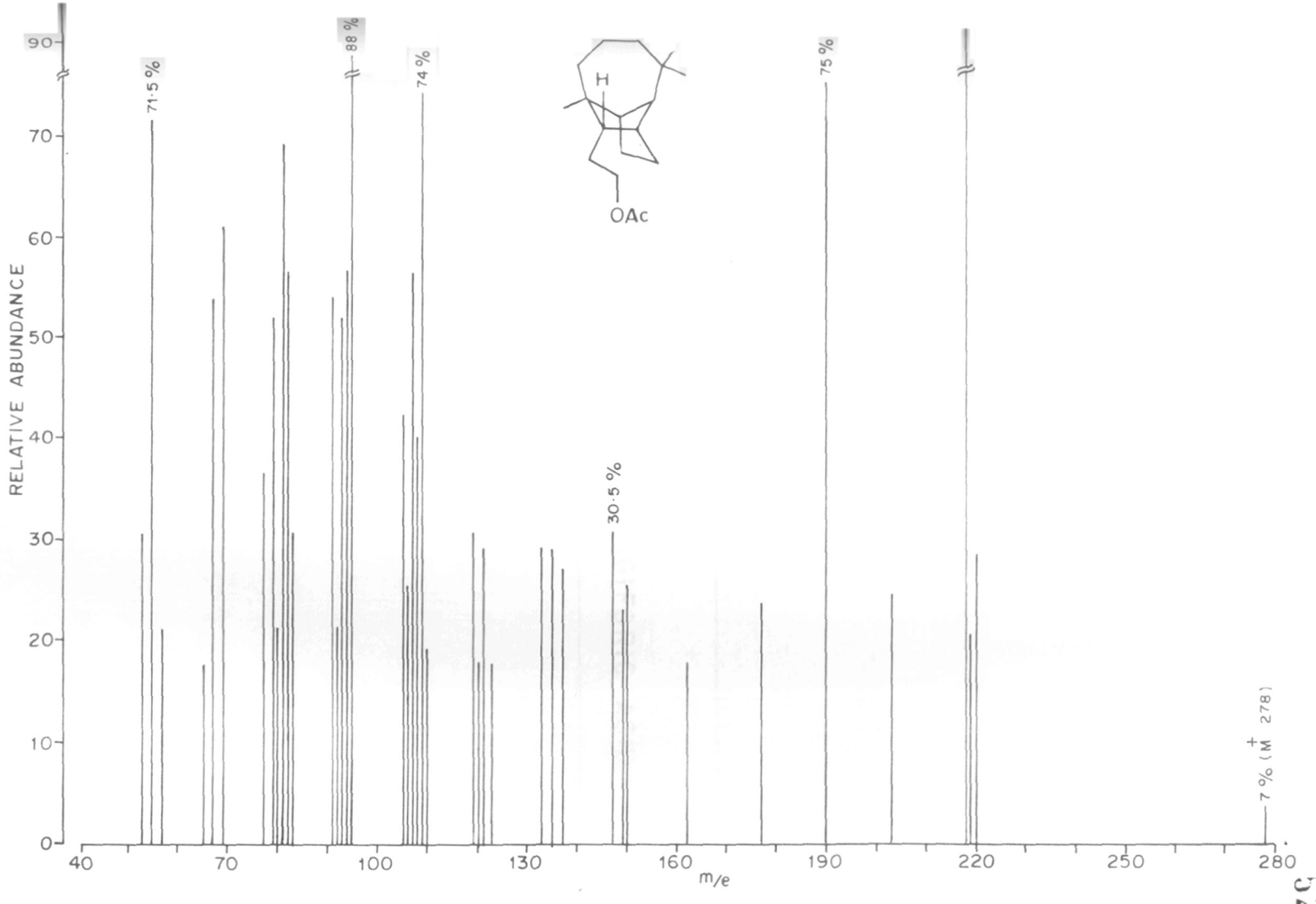


FIG. 15. MASS SPECTRUM OF HOMOISOLONGIFOLYL ACETATE 10

PART II

NOVEL REACTIONS OF α-LONGIFORIC ACID

CHAPTER –1

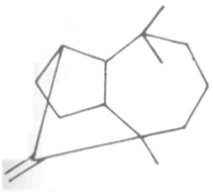
AN EFFICIENT PREPARATION OF α-LONGIFORIC ACID A cis-1,4-DICARBOXYLIC ACID FROM LONGIFOLENE

ABSTRACT

A convenient and efficient preparation of α-longiforic acid 4 from longifolene 1 via ω-bromo-longifolene 5 is described.

AN EFFICIENT PREPARATION OF α-LONGIFORIC ACID - A CIS-1,4-DICARBOXYLIC ACID FROM LONGIFOLENE

The imperative need for a practical preparative method for α-longiforic acid 4 - the vitally important 5,7-bicyclic cis-1,4-dicarboxylic acid from the tricyclic longifolene 1 - was increasingly felt during the course of our relentless efforts aimed at the transformation of 1 to an azulene. The existing method[2] (1 → 4 overall yield: 29%) consists of three steps including the crucial ring expansion reaction: 1 → longihomocamphenilone 2 (lead tetraacetate[2]/base) → longidione 3 (SeO_2) → 4 (alkaline H_2O_2). The large-scale preparation of α-bromolongifolene 5 in a near quantitative yield, by our recently described[3] simple expedient of bromination of 1 in pyridine, prompted us to exploit the vinylic bromide for the base-catalyzed ring expansion[4]. The t-BuOK-xylene reaction on 5 was conveniently and efficiently achieved, especially on large batches (0.5 mole), without the actual isolation of the alkoxide, as described in the experimental section. Since a test sample of the KOBu-product indicated it to be essentially the t-butyl enol ether (IR, PMR) of a ketone along with a minor amount of the ketone itself, the crude



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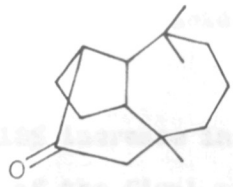

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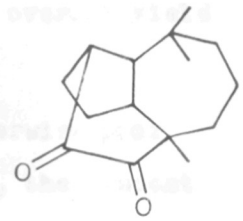

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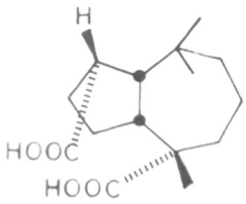

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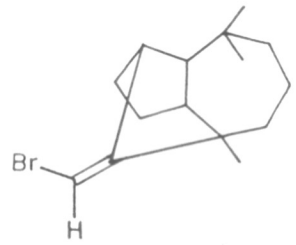

5

material was directly hydrolysed with 6% hydrogen chloride in methanol at reflux (24 hr). The resulting ketone was readily identified as essentially pure longihomocamphenilone[4] 2 (IR, PMR). Riley oxidation of 2 followed by cleavage of the α-diketone 3 with alkaline H_2O_2 in a precedented[2] manner furnished α-longiforic acid 4 in an overall yield of 43% (1 → 4).

Besides the 13% increase in the otherwise poor overall yield (29%) of the final product 4, the present method offers significant operational advantages. In particular, the somewhat tedious $Pb(OAc)_4$ reaction on longifolene, which also involves a fractional distillation to separate the unchanged hydrocarbon, is avoided.

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

Melting and boiling points are uncorrected. Light petroleum refers to the fraction b.p. 60-80° (essentially hexane). Solvent extracts were dried over anhydrous Na_2SO_4. IR spectra were recorded on a Perkin-Elmer Infracord model 137-E. PMR spectra were taken on a Varian T-60 spectrometer. Mass spectra were obtained on a CEC spectrometer model 21-110B using an ionizing voltage of 70 eV and a direct inlet system.

(E)-ω-Bromolongifolene 5

This was prepared[3] by bromination of longifolene (102 g, 0.5 mole) with pyridine perbromide: yield, 138 g (98%).

Longihomocamphenilone 2

Potassium (39 g, 1.0 g atom) was dissolved in dry t-BuOH (1 lit.) by heating under reflux in a 3-necked flask (anhydrous conditions). The t-KOBu solution was treated with ω-bromolongifolene 5 (139 g), refluxed for 10 minutes, and the butanol was removed completely on the waterbath/50 mm. Dry xylene (1 lit.) was added to the brown residue in the flask, stirred and refluxed for 24 hr. The mixture was cooled, water (500 ml) was added, the xylene layer was separated and the aqueous portion extracted with light petroleum (3 x 250 ml). The combined organic extracts were

washed with water, brine, dried and the solvents removed completely; last traces of xylene were removed at 120°/50 mm (oil bath). A test sample (2.0 g) was distilled to yield the t-butyl enol ether of 2 + minor amount of ketone 2 as a colourless liquid b.p. 145°/0.7 mm. IR(smear): 1700 (v.w.), 1650(s). PMR(CCl_4): 4.00 ppm (br s, olefinic H); 1.33 ppm (s, =C-O-C(Me)(Me)Me ; 1.03, 1.00, 0.92 ppm (tertiary Me singlets). MS (m/e): 276 (M^+; $C_{19}H_{32}O$).

The crude product was hydrolysed by refluxing with 6% hydrogen chloride in MeOH (1 lit.) for 24 hr. The mixture was diluted with water (1 lit.), extracted with light petroleum (3 x 500 ml), washed with water, brine, dried, the solvent removed and the residue distilled to furnish longihomocamphenilone 2 (essentially pure) as a colourless liquid b.p. 130°/0.9 mm (76 g, 69%). PMR(CCl_4): 2.03 ppm (s, O=CCH_2C-); tertiary Me singlets at 1.10, 1.00, 1.00 ppm; minor impurity of longi-isohomocamphenilone[4a] (s at 0.95 ppm). IR(smear): 1700, 1420 cm^{-1}.

Longidione 3

The ketone 2 (76 g) was oxidized with SeO_2 (50 g) in AcOH (500 ml) containing water (12 ml) at reflux (18 hr) essentially by the method described by Ourisson[2]. Longidione, b.p. 155-60°/0.9 mm (60 g, m.p. 90-91°) was obtained in 74% yield.

α-Longiforic acid 4

A mixture of longidione (60 g) in acetone (810 ml) and 2N NaOH (480 ml) was stirred and 30% H_2O_2 solution was added dropwise with occasional cooling of the reaction flask. After the addition was over (0.5 hr) the mixture was kept at room temperature for 2 hr and then concentrated to about half the volume on the water bath/50 mm. The mixture was diluted with water (300 ml), extracted with light petroleum to remove any neutral material and the aqueous part acidified with conc. HCl (Congo red). The crystalline solid was filtered off and recrystallised from EtOAc to furnish pure α-longiforic acid m.p. 235-36° (55 g, 80%).

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CHAPTER – 2

NOVEL LEAD TETRAACETATE OXIDATIVE DECARBOXYLATION OF THE HALF ESTERS OF α-AND β-LONGIFORIC ACIDS

ABSTRACT

The formation of the same olefinic ester 10 - normal for the tertiary half-ester 7 but abnormal for the secondary half-ester 6 of α-longiforic acid 2 (a cis 1,4-dicarboxylic acid from longifolene 1) - in the lead tetraacetate (LTA) oxidative decarboxylation reaction has been mechanistically rationalized on the basis of a unique ester participation pathway (cf 11). The normal behaviour of the secondary half-ester 9 from β-longiforic acid 3 (trans), in the Kochi reaction, provides experimental support for this hypothesis; the expected olefinic esters 13 / 14 formed in the reaction have been separated and spectroscopically characterized.

LEAD TETRAACETATE OXIDATIVE DECARBOXYLATION OF THE HALF-ESTERS OF α- AND β-LONGIFORIC ACIDS

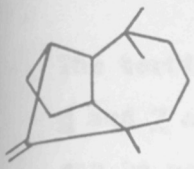
Lead tetraacetate oxidation of aliphatic and alicyclic carboxylic acids[1] generally leads to mixtures of alkenes, alkanes and acetate esters. However, in recent years, increased knowledge of the reaction mechanism has led to a measure of control allowing for optimization of specific products and the reaction is now of synthetic value. In the presence of copper (II)[2] acetate, the reaction is strongly oriented in favour of alkene formation.

While LTA treatment of carboxylic acids usually leads to decarboxylation, a number of useful oxidative cyclizations, involving the carboxyl group, have been observed, particularly when a suitable cyclization site, e.g. a double bond[3], is located nearby. The relative rates of decarboxylation of carboxylic acids is tertiary (100) > secondary (5) > primary (1) and hence selective monodecarboxylation to give lactones has been found possible with molecules containing different types[4] of carboxyl groups.

In a systematic approach to an azulene from longifolene 1 we had envisaged a novel Pb(IV)/Cu(II) oxidative bis decarboxylation strategy[5] on the secondary/

tertiary 1,4-dicarboxylic acids - α-longiforic acid (cis, 2) and its epimer, β-longiforic acid (trans, 3) - both readily accessible derivatives of 1. It was surmised that Cu(II) might accelerate decarboxylation of the secondary carboxyl in 2 / 3 to a rate comparable with that of the tertiary and hence minimize product formation from the monodecarboxylated species at the intermediate stage; independent oxidative decarboxylation of the two groups was then expected to generate azulenogenic dienes for the final dehydrogenation step. In practice, however, this bisdecarboxylation strategy proved quite unsatisfactory as a result of more effective lactone formation[5] in a competing reaction: 2 → 4 and 3 → 5. For by-passing this undesired lactone formation we envisaged[6] a step-wise LTA reaction on the secondary/tertiary half-ester 6 / 7. In this paper we describe an exotic ester participation which takes place in the Kochi reaction on the secondary half-ester 6.

The secondary half-ester 6 (m.p. 165°; 20% yield) was accessible with some difficulty by the partial esterification with 6% hydrogen chloride in methanol of α-longiforic acid[7] 2 while the tertiary half-ester 7 (m.p. 135°; 35%) was generated relatively more easily by the partial hydrolysis[7a] of dimethyl α-longiforate 8.



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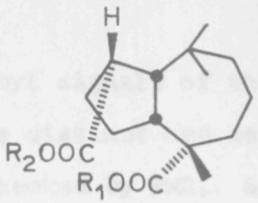
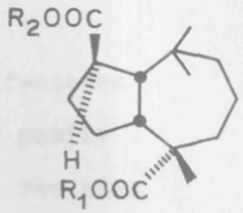


2: $R_1 = R_2 = H$



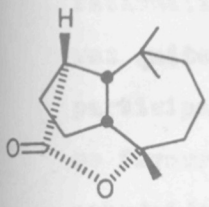
3: $R_1 = R_2 = H$

6: $R_1 = H$, $R_2 = Me$

9: $R_1 = H$, $R_2 = Me$

7: $R_1 = Me$, $R_2 = H$

8: $R_1 = R_2 = Me$



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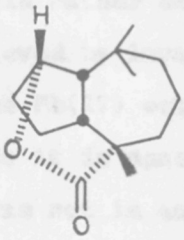

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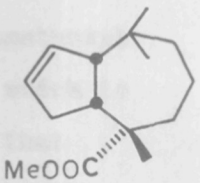

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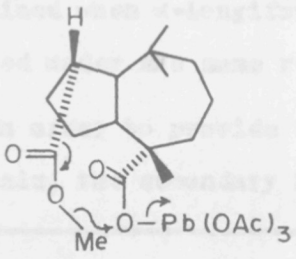

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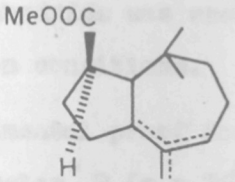

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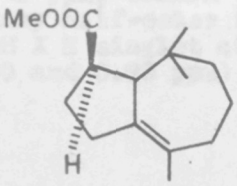

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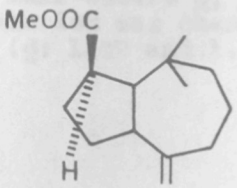

14

The tertiary methyl signals of the two half-esters 6 and 7 are quite distinct and hence their purity can be readily checked by PMR. LTA-Cu(II) reaction on the tertiary half-ester 7 generated the expected olefinic ester 10: PMR(CCl_4): three tertiary methyl singlets at 0.83, 0.87, 1.37 ppm; COOMe singlet at 3.53 ppm; broad (W_H = 5 Hz) unsymmetrical "singlet" at 5.70 ppm (2H, olefinic). Formation of the same olefinic ester 10 (GLC, IR, PMR) from the secondary half-ester 6 also, however, was quite unusual. Mechanistic rationalization of this rather bewildering observation was quite simply achieved by invoking a carbomethoxyl participation with the Pb(IV) ester function which is so favourably close to it in space (cf 11). That anhydride formation was not in any way involved in the anomalous LTA reaction on the half-ester 6 was ascertained when α-longiforic anhydride was recovered unscathed under the same reaction conditions.

In order to provide experimental proof for this hypothesis, the secondary half-ester* 9 (m.p.75°; 30%)

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*Prepared by the partial esterification method as before. Besides the downfield tertiary methyl singnal at ca. 1.40 ppm, common to all the half-esters 6, 7 and 9, the secondary half-ester from the 8-series was characterized by a 3H X 2 singlet at 0.95 ppm (6: 1.02 and 1.12 ppm; 7: 0.90 and 0.95 ppm).

from β-longiforic acid[8] 3 (carboxyl groups trans) was also subjected to the Kochi reaction[1] under the same conditions. No ester participation was theoretically possible in this case nor was it observed. A mixture of two of the three possible, normal olefinic esters (cf. 12) was obtained; chromatographic resolution over 15% $AgNO_3$-silica gel furnished the pure compounds 13 / 14. The olefinic ester 13 was characterized by a transparent 1600 - 1650 cm^{-1} region in the IR. PMR (CCl_4): two tertiary methyl singlets at 0.75, 0.80 ppm; one vinylic methyl singlet at 1.72 ppm and COOMe singlet at 3.60 ppm. The second unsaturated ester had spectral features clearly supporting the structure 14. IR(Nujol): 1620 and 895 cm^{-1} (exo methylene). PMR(CCl_4): two tertiary methyl singlets at 0.78, 0.87 ppm; COOMe singlet at 3.60 ppm; olefinic singlets at 4.58 and 4.62 ppm (2H, $>=CH_2$).

EXPERIMENTAL

Light petroleum refers to the fraction b.p. 60-80° (essentially hexane). All solvent extracts were dried over anhydrous Na_2SO_4. Rotations were taken in $CHCl_3$ (at 26°) on a Perkin-Elmer 141 spectropolarimeter (automatic). Recorded temperatures are uncorrected.

IR spectra were taken on a Perkin-Elmer Infracord model 137B. PMR spectra were recorded on a Varian T-60 spectrometer using tetramethylsilane as internal standard. Mass spectra (MS) were obtained on a CEC spectrometer model 21-110B using an ionising voltage of 70 eV and a direct inlet system.

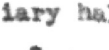
Partial esterification of α-longiforic acid 2: Secondary half-ester 6

α-Longiforic acid (10 g) and 6% hydrogen chloride in MeOH (100 ml) were refluxed on the waterbath for 1 hr. The mixture was taken to dryness and the residue was refluxed with light petroleum (100 ml) when some unchanged dicarboxylic acid (5.6 g) separated out and was removed by filtration. This material was subjected to partial esterification as before and some α-longiforic acid was again recovered. This process was repeated thrice and the light petroleum filtrates were combined and washed with 5% aq. $NaHCO_3$ to

remove traces of the diacid 2. The organic solution, after removal of the required half-ester by extraction with 5% KOH, gave the neutral dimethyl ester, m.p. 94-95° (1.84 g). The aq. alkaline part was acidified with conc. HCl, extracted with EtOAc (3 x 200 ml), washed with water, dried and the solvent removed. The crude product was recrystallised twice from light petroleum to furnish colourless of the secondary half-ester 6 m.p. 164-165° (2.03 g, 20%). IR(Nujol): 3050, 2610, 1700 (br, unresolved), 1240 cm^{-1}. PMR(CCl_4): 11.33 ppm (br s, COOH); 3.63 ppm (s, 3H, COOMe); 1.40 ppm (s, 3H $><^{COOH}_{Me}$); 1.12, 1.02 ppm (two tertiary Me singlets). MS(m/e): 282 (M^+, 2%); 264(6), 223(7), 200(25), 182(11), 177(17), 170(42), 154(32), 140(10), 101(100), 81(33), 70(69), 55(56). (Found: C, 68.00; H, 9.37. $C_{16}H_{26}O_4$ requires: C, 68.05; H, 9.98%).

Partial hydrolysis of dimethyl α-longiforate 8: Tertiary half-ester 7

Dimethyl α-longiforate 8 (10.8 g) was subjected to partial hydrolysis using N/10 aq. ethanolic KOH (360 ml) at 5° for 24 hr followed by heating at 80°/2 hr. The mixture was diluted with water (400 ml) and extracted with light petroleum (3 x 100 ml) which gave the unchanged diester (6.1 g). The aq.alkaline part was acidified with conc. HCl,

extracted with EtOAc (3 x 200 ml), washed with water, brine, dried and evaporated. The crude product, on recrystallization from light petroleum, furnished colourless crystals of the tertiary half-ester 7, m.p. 134-35° (3.6 g, 35%), $[\alpha]_D$ -59.20° (c, 0.5%). IR(Nujol): 3000-2600, 1730, 1700, 1260 cm^{-1}. PMR (CCl_4): 3.63 ppm (s, 3H, $COOCH_3$); 1.37 ppm (s, 3H, ); 0.95, 0.90 ppm (tertiary Me singlets). MS(m/e): 282 (M^+, 4%), 264(15), 223(29), 222(100), 200(29), 177(36), 154(29), 140(16), 107(36), 101(95), 96(36), 94(36), 82(55), 55(82).

(Found: C, 68.81; H, 9.35. $C_{16}H_{26}O_4$ requires: C, 68.05; H, 9.98%).

Pb(IV)/Cu(II) reaction on the tertiary half-ester 7: olefinic ester 10

The tertiary half-ester 7 (2.82 g) in dry benzene (90 ml) was treated with LTA (6.6 g), $Cu(OAc)_2$ (0.3 g), pyridine (0.3 ml) and stirred under reflux (4 hr). Ethane diol (3 ml) was added and stirred for 15 min. more. The benzene layer was separated, the inorganic residue was thoroughly washed with hot benzene and the combined extracts washed with 10% aq. KOH (2 x 50 ml), water, brine and dried. Removal of solvent and distillation gave the olefinic ester 10 as a colourless liquid, b.p. 130°/2 mm (1.99 g). IR(smear):

1730, 1600, 1240 cm^{-1}. PMR (CCl_4): tertiary Me singlets at 0.83, 0.87, 1.37 ppm; 3.53 ppm (s, COOMe); 5.70 ppm (br "singlet", 2H, olefinic).

Pb(IV)/Cu(II) reaction on the secondary half-ester 6: olefinic ester 10

The secondary half-ester 6 (2.82 g) was subjected to LTA oxidative decarboxylation exactly as described earlier for the tertiary half-ester 7. The isolated product (1.5 g) was identified as the olefinic ester 10 by a comparison of its spectral data (IR, PMR and Mass) with the authentic sample.

Partial esterification of α-longiforic acid 3: Secondary half-ester 9

α-Longiforic acid (10 g) was refluxed with 6% hydrogen chloride in methanol (100 ml) for 1 hr. The mixture was taken to dryness on the waterbath/water pump, the residue taken up in light petroleum (200 ml) and extracted with 5% aq. KOH (3 x 100 ml). The aq. alkaline layer was acidified with conc. HCl (Congo red), extracted with EtOAc (3 x 100 ml), washed with water, brine, dried and the solvent removed. Distillation of the crude product gave the pure secondary half-ester 9, b.p. 210°/0.7 mm, m.p. 74-75° (2.9 g, 27%); $[\alpha]_D$ -70.3° (c, 0.6%). IR(Nujol): 3000, 2600, 1700 (br,

unresolved). PMR(CCl_4): 11.60 ppm (br.s, COO<u>H</u>), 3.63 ppm (<u>s</u>, 3H, COOMe); 1.45 ppm (<u>s</u>, 3H, ); 0.95, 0.95 ppm (two tertiary Me singlets). MS(m/e): 282 (M^+ 61%); 237(19), 236(100), 201(8), 182(8), 154(9), 107(18), 93(16), 87(18), 67(27), 55(27). (Found: C, 68.70; H, 9.63. $C_{16}H_{26}O_4$ requires: C, 68.05; H, 9.98%).

<u>Pb(IV)/Cu(II) reaction on the 8-secondary half-ester 9: olefinic esters 13 and 14</u>

The 8-secondary half-ester <u>9</u> (2.82 g), when subjected to the LTA reaction under Kochi conditions as described for the half-ester <u>7</u> gave a neutral material (1.8 g) which was chromatographed over 15% $AgNO_3$-silica gel (60 g, 65 cm x 1.5 cm) with TLC-monitoring: Fr.1, 20% C_6H_6 in light petroleum, 4 x 200 ml, pure. Fr.2, 50% C_6H_6 in light petfoleum, 3 x 200 ml, pure.

Fr.1 was distilled to furnish the olefinic ester <u>13</u> as a colourless liquid, b.p. 125°(bath)/0.7 mm (0.49 g); $[\alpha]_D$ -14.89° (<u>c</u>, 0.45%). IR(smear): 1600-1650 cm^{-1} region transparent. PMR(CCl_4): 3.60 ppm(<u>s</u>, 3H, COOMe); 1.72 ppm (<u>s</u>, 3H, vinylic Me); 0.80, 0.75 ppm (two tertiary Me singlets). MS(m/e): 236 (M^+ 92%); 205(15), 177(43), 176(33), 167(29), 135(24), 107 (100), 91(26), 83(77). (Found: C, 76.27; H, 10.35. $C_{15}H_{24}O_2$ requires: C, 76.22; H, 10.24%).

Fr.2, on distillation gave the olefinic ester <u>14</u>,

b.p. 125°(bath)/0.7 mm (0.12 g); $[\alpha]_D$ -49.38° (c, 0.5%). IR(smear): 1620, 895 (exo methylene). PMR(CCl_4): 0.78, 0.87 ppm (two tertiary Me singlets); 3.60 ppm (s, 3H, COOMe); 4.58, 4.62 ppm (1H singlets, $>=CH_2$). MS (m/e): 236 (M^+ 50%); 205(19), 177(37), 176(68), 167(28), 161(44), 133(25), 121(28), 109(31), 107(93), 91(41), 82(100), 79(38), 67(44). (Found: C, 75.66; H, 10.28. $C_{15}H_{24}O_2$ requires: C, 76.22; H, 10.24%).

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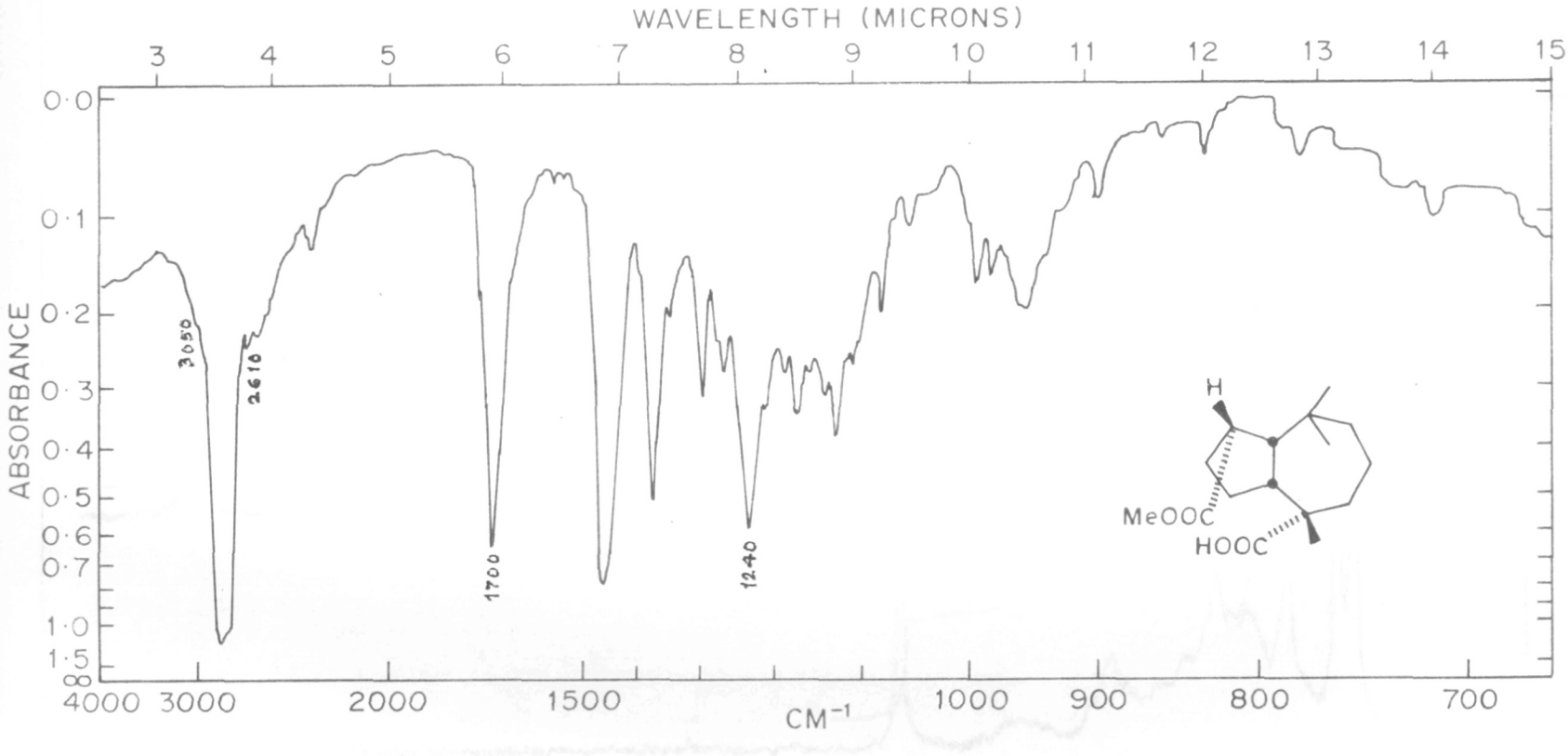

FIG. 1. IR SPECTRUM OF α-SECONDARY HALF ESTER 6

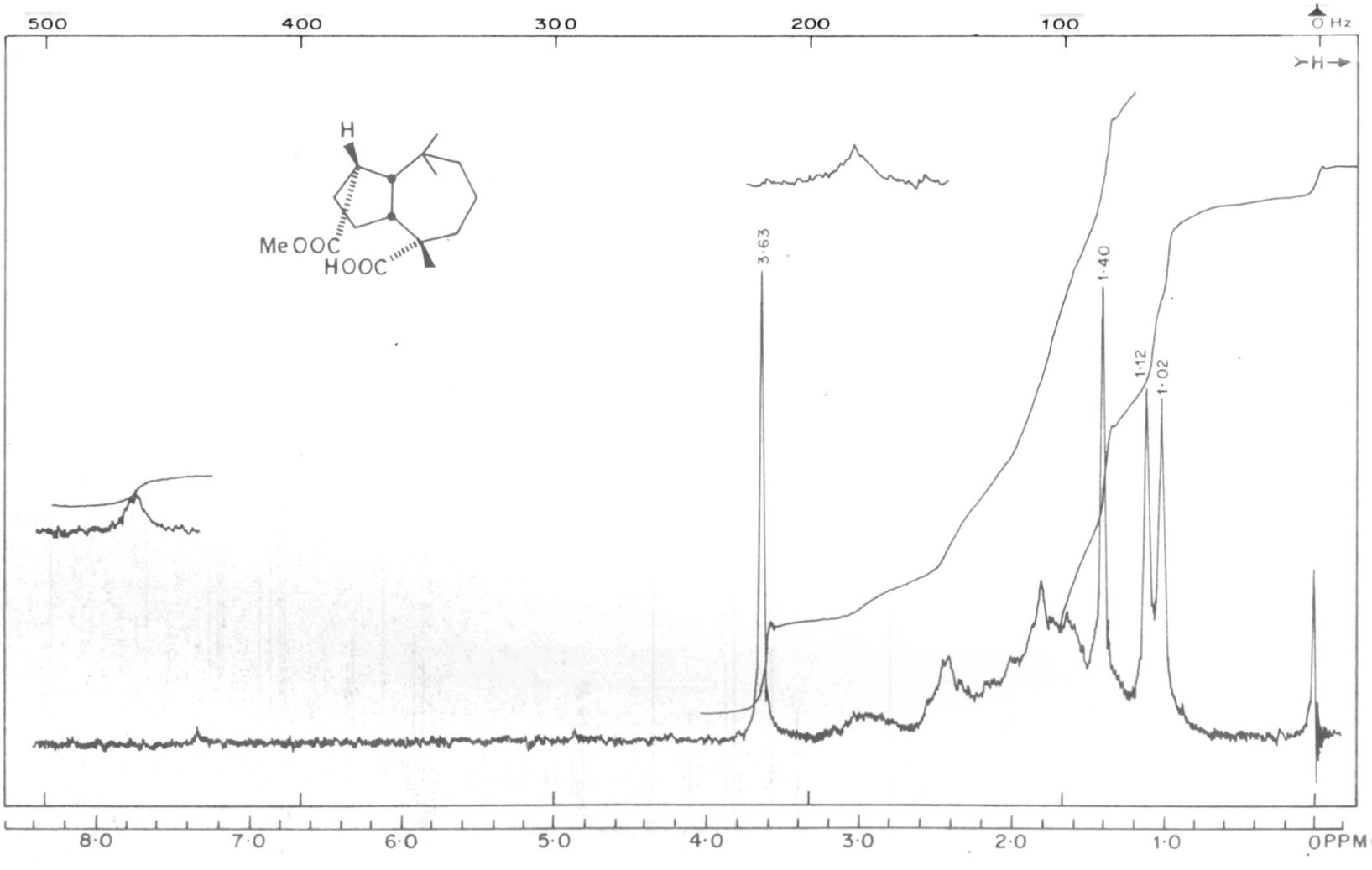

FIG. 2. PMR SPECTRUM OF α-SECONDARY HALF ESTER 6

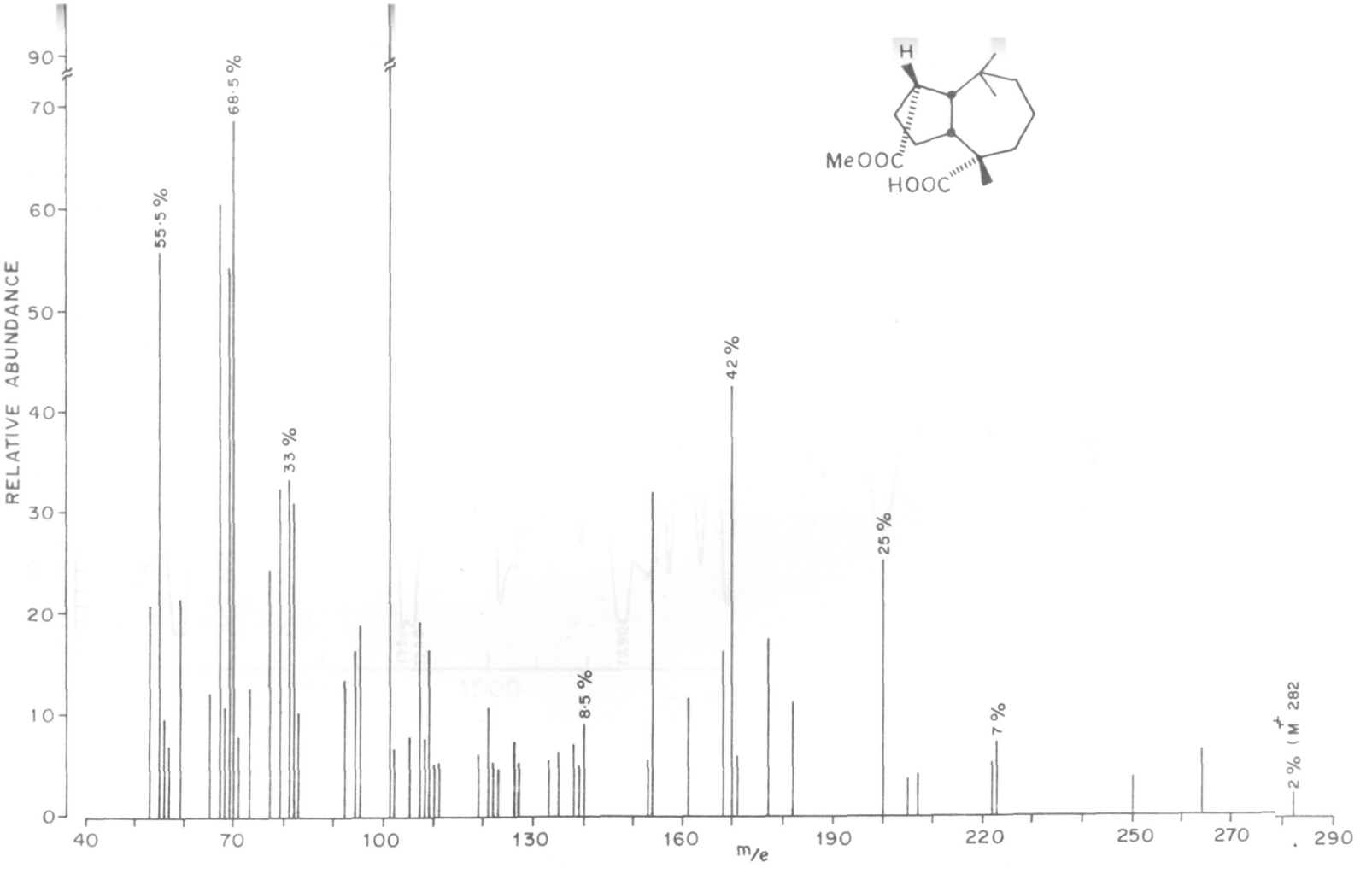

FIG. 3. MASS SPECTRUM OF α-SECONDARY HALF ESTER 6

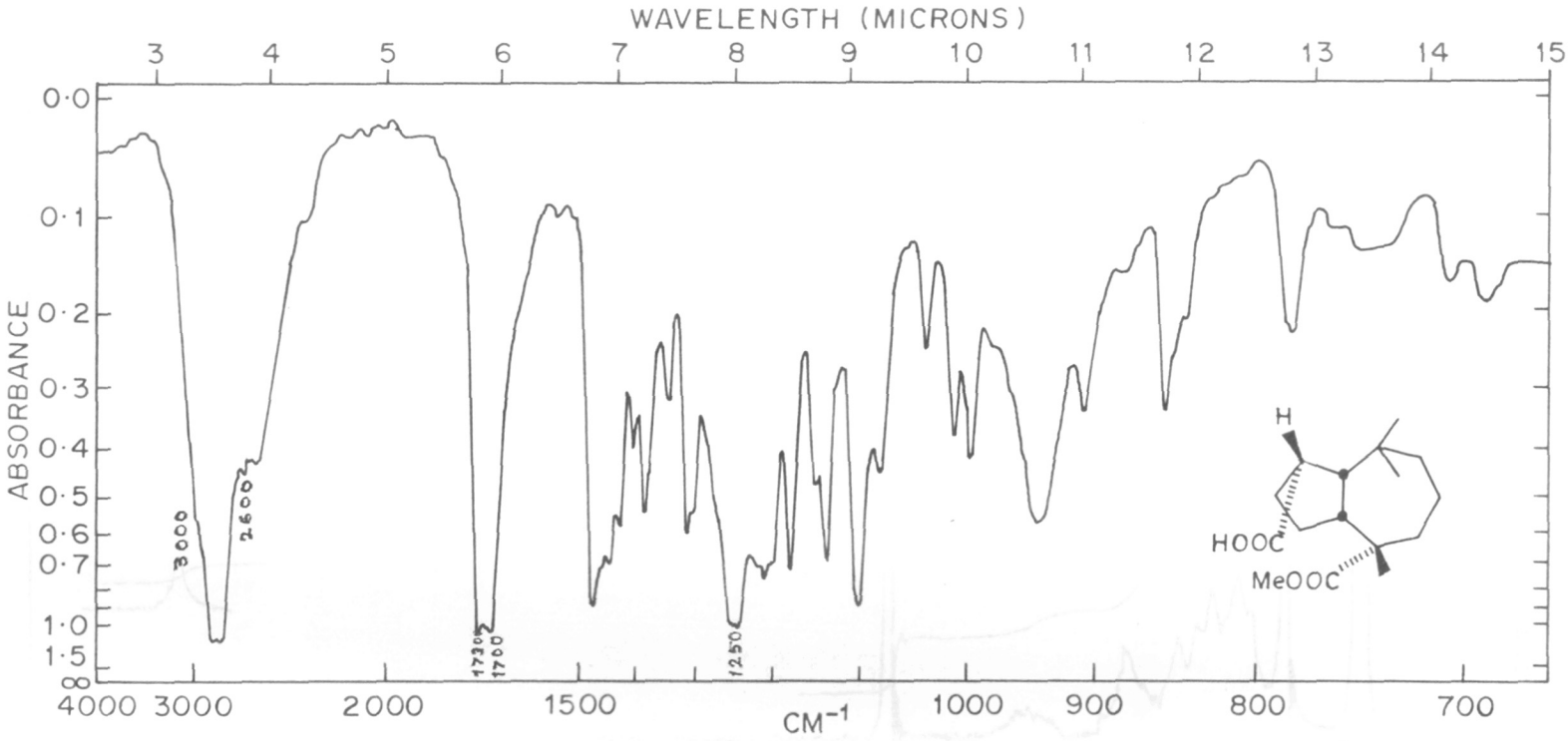

FIG. 4. IR SPECTRUM OF α-TERTIARY HALF ESTER 7

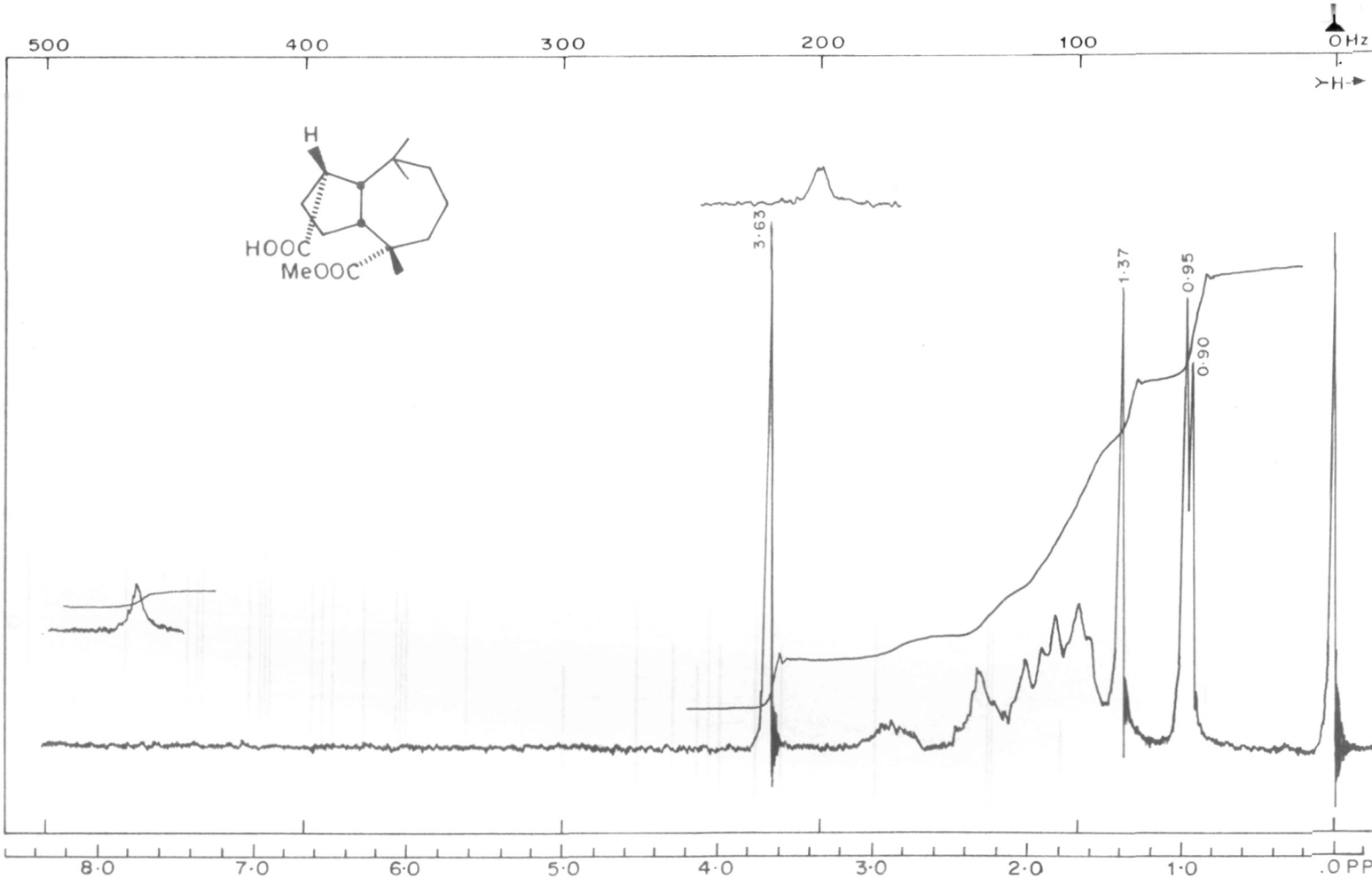

FIG. 5. PMR SPECTRUM OF α-TERTIARY HALF ESTER 7

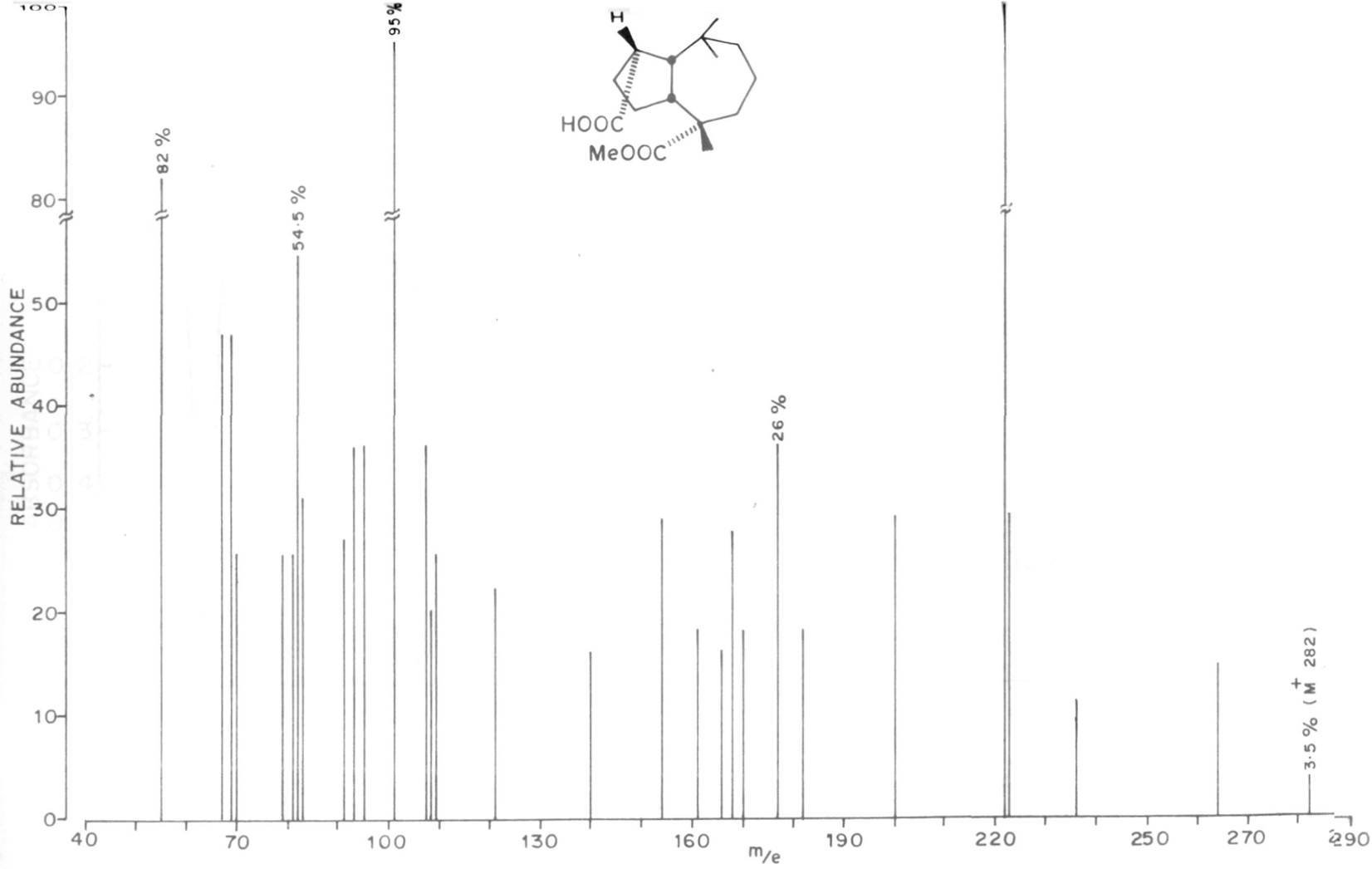

FIG. 6. MASS SPECTRUM OF α-TERTIARY HALF ESTER 7

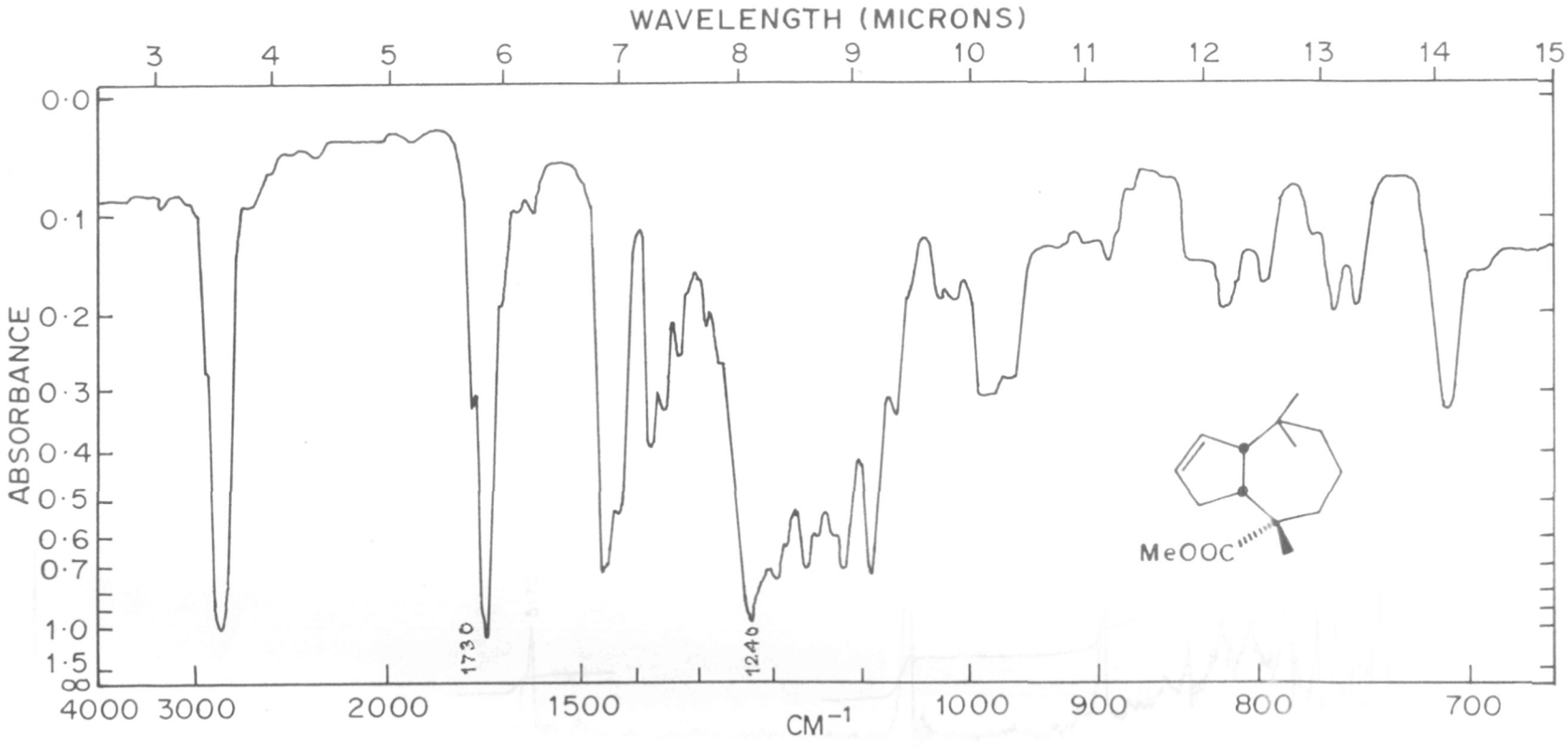

FIG. 7. IR SPECTRUM OF α-OLEFINIC ESTER 10

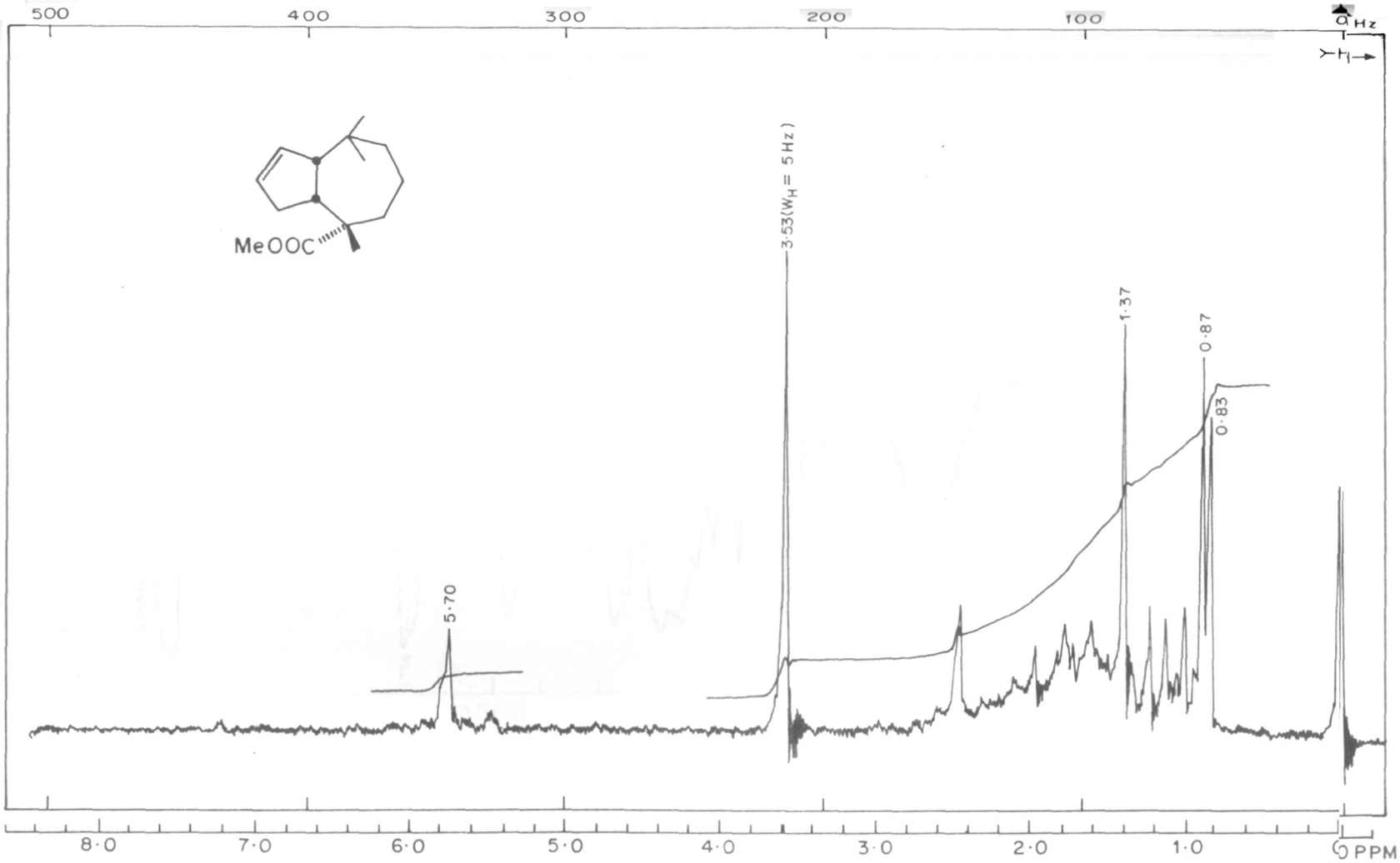

FIG. 8. PMR SPECTRUM OF α-OLEFINIC ESTER 10

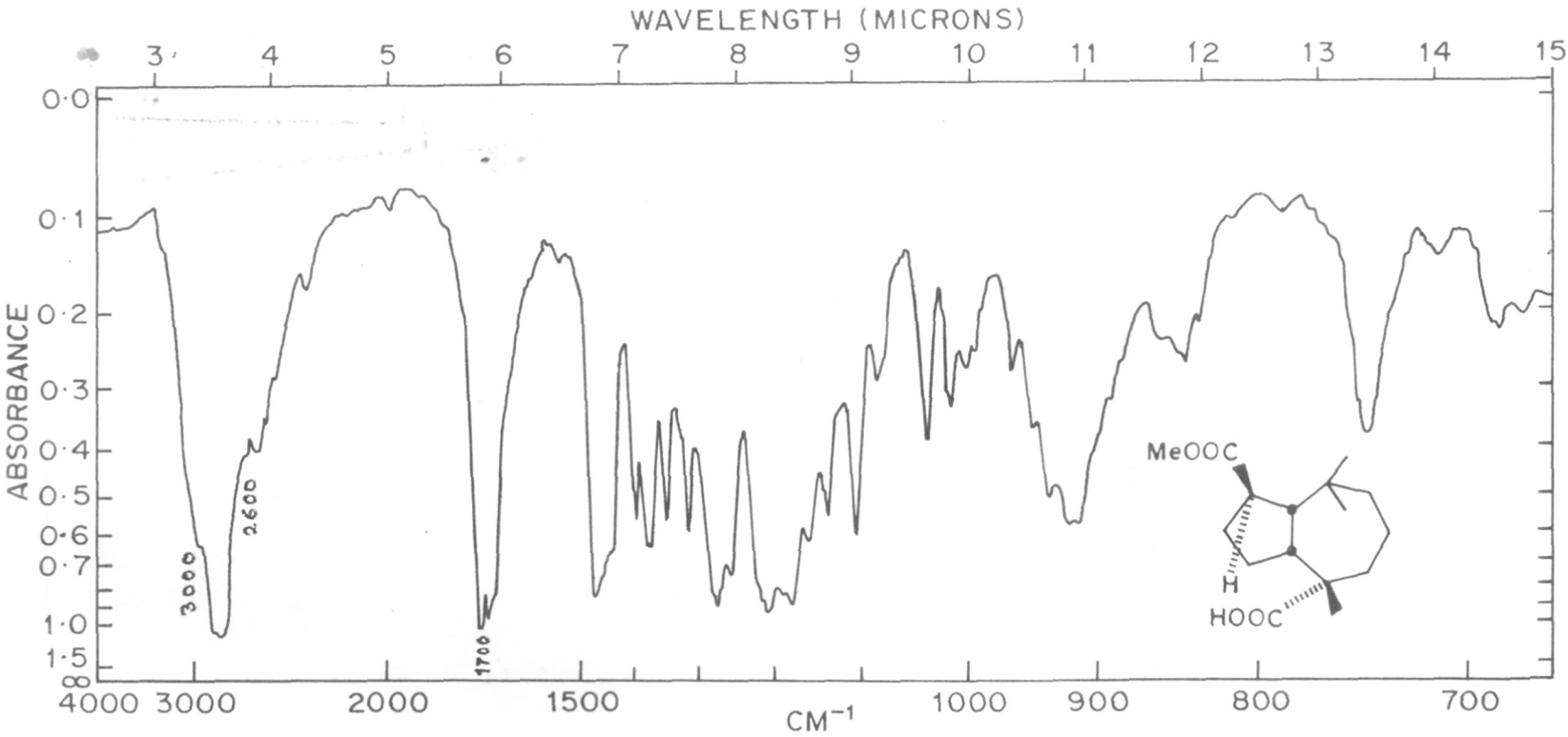

FIG. 9. IR SPECTRUM OF β-SECONDARY HALF ESTER 9

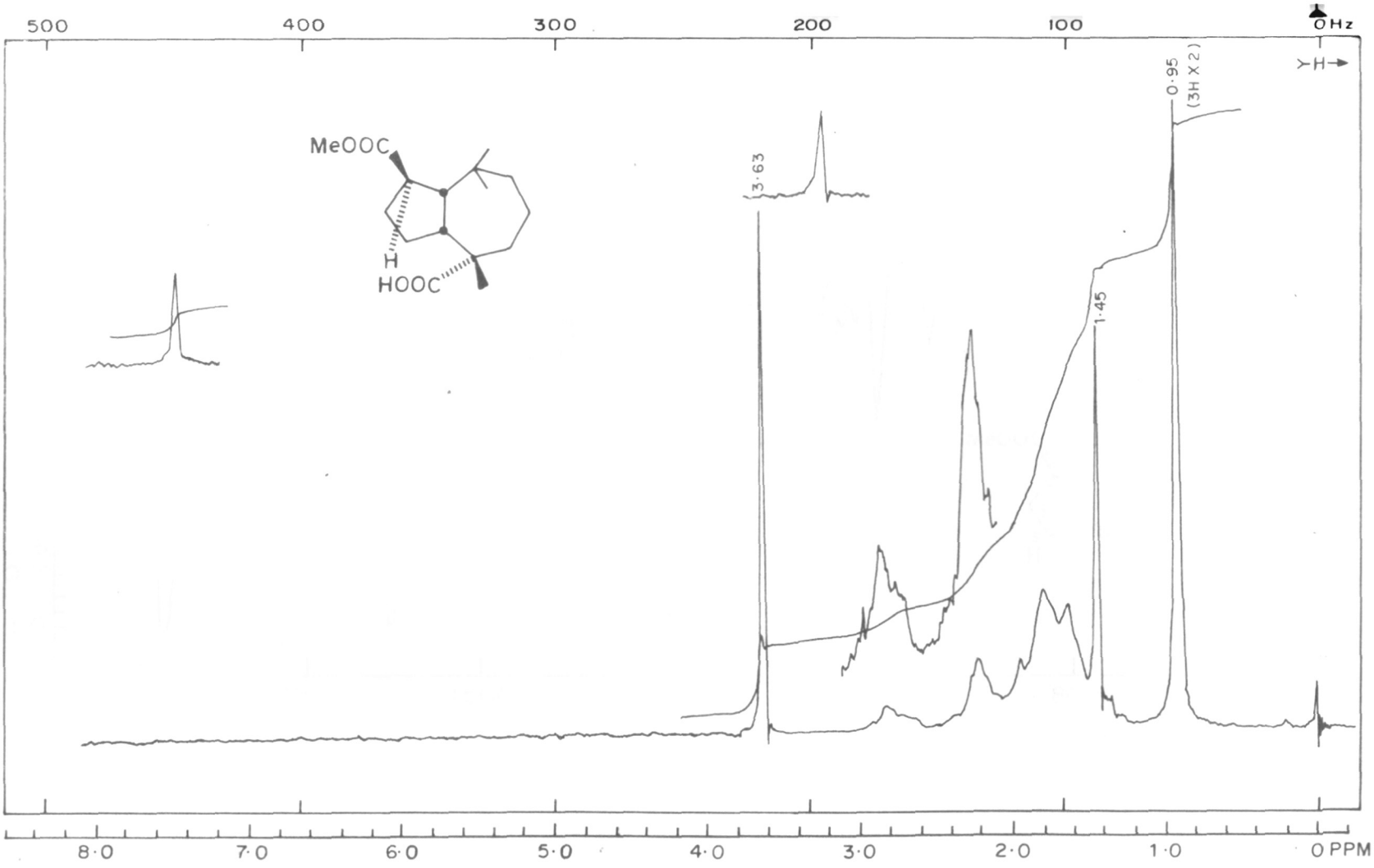

FIG. 10. PMR SPECTRUM OF β-SECONDARY HALF ESTER 9

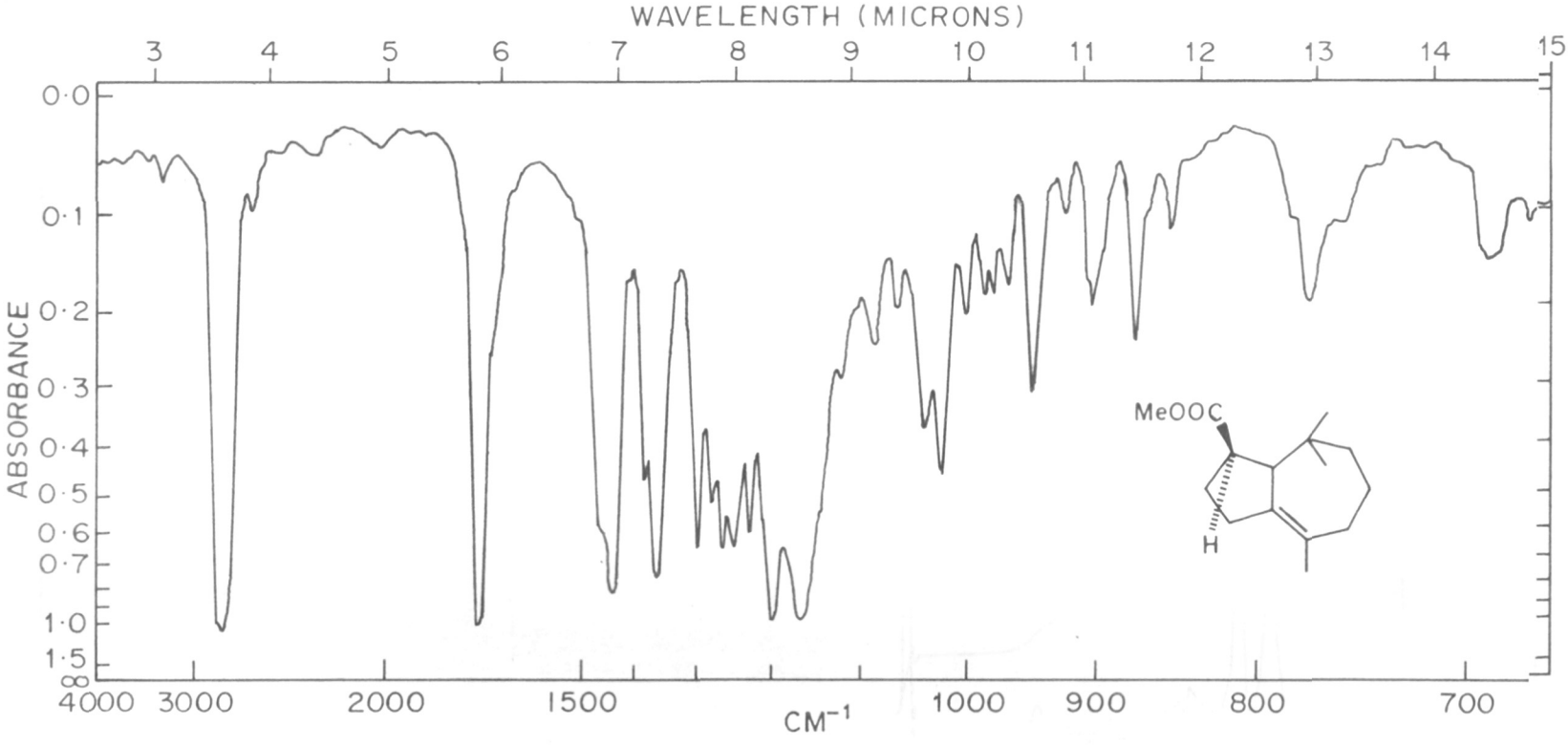

FIG. 11. IR SPECTRUM OF β-OLEFINIC ESTER-I (13)

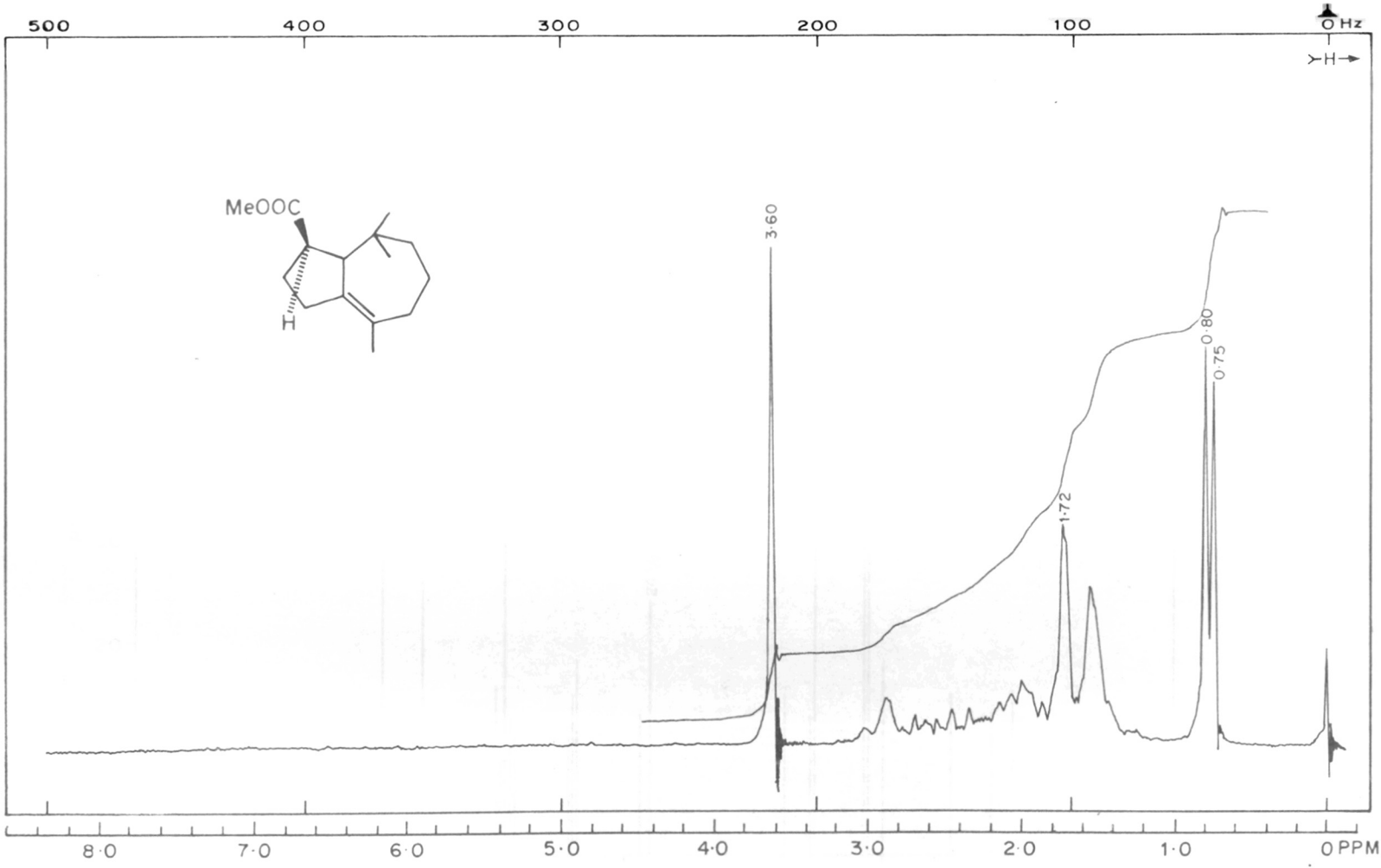

FIG. 12. PMR SPECTRUM OF β-OLEFINIC ESTER-I (13)

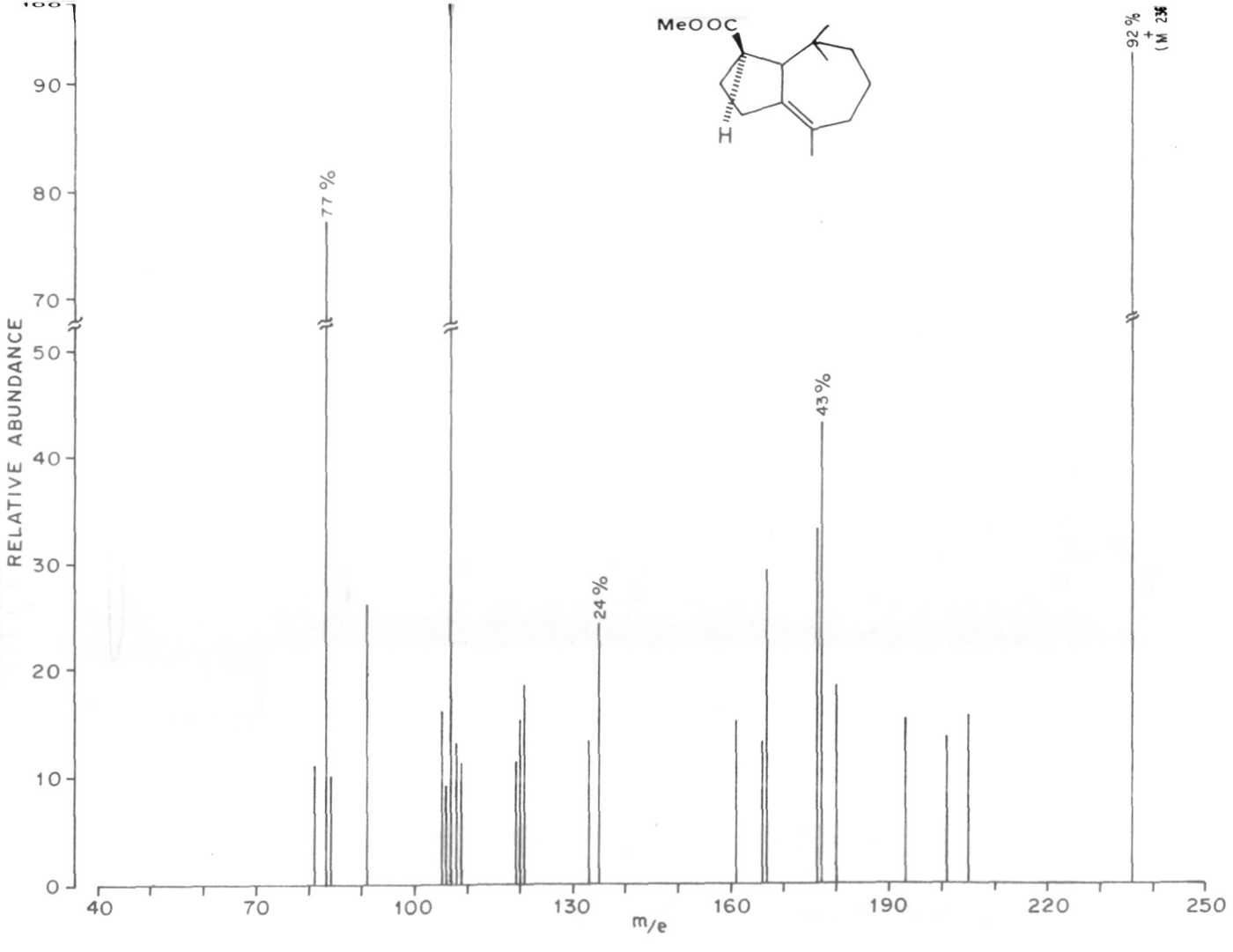

FIG. 13. MASS SPECTRUM OF β-OLEFINIC ESTER - I (13)

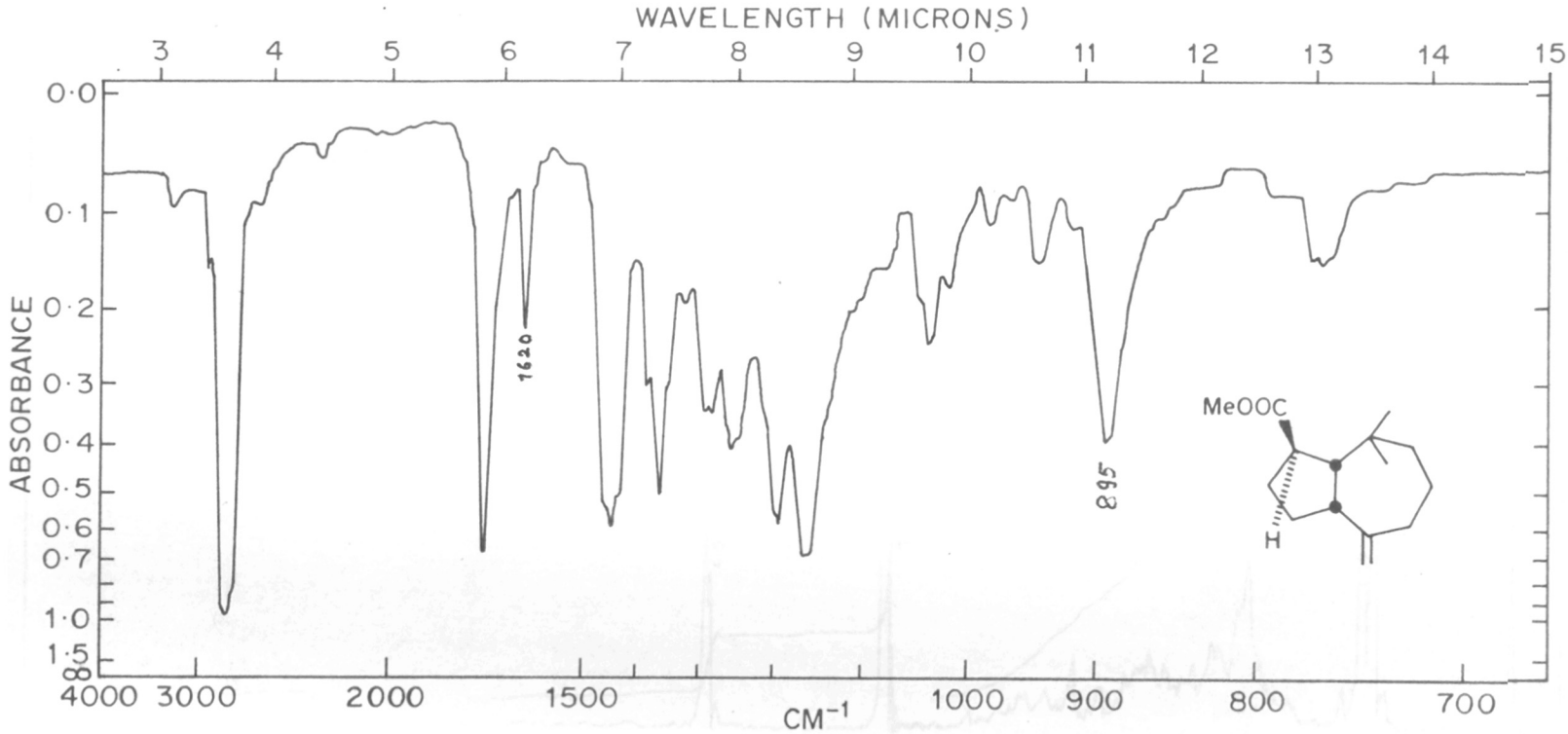

FIG. 14. IR SPECTRUM OF β-OLEFINIC ESTER-II (14)

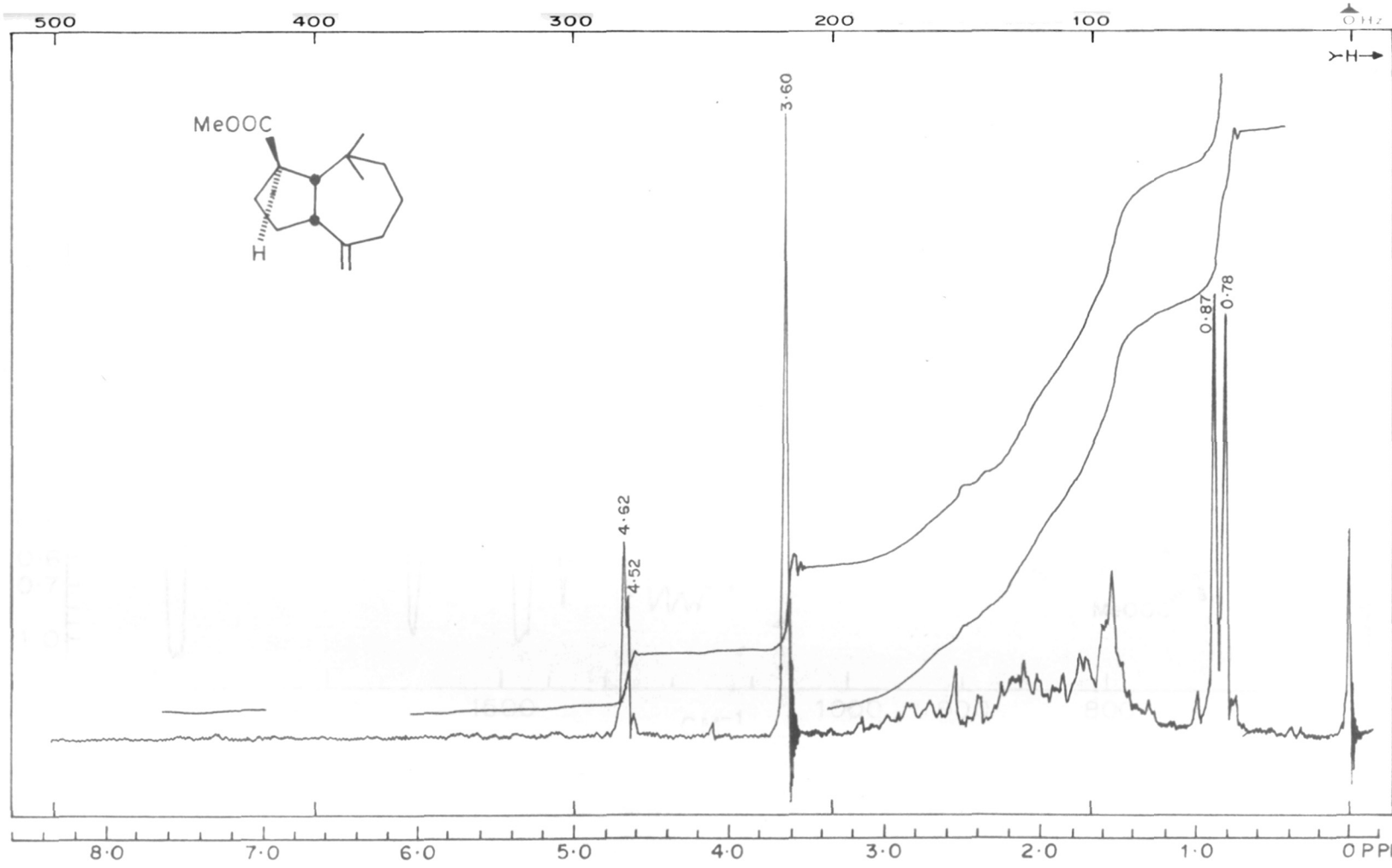

FIG. 15. PMR SPECTRUM OF β-OLEFINIC ESTER-II (14)

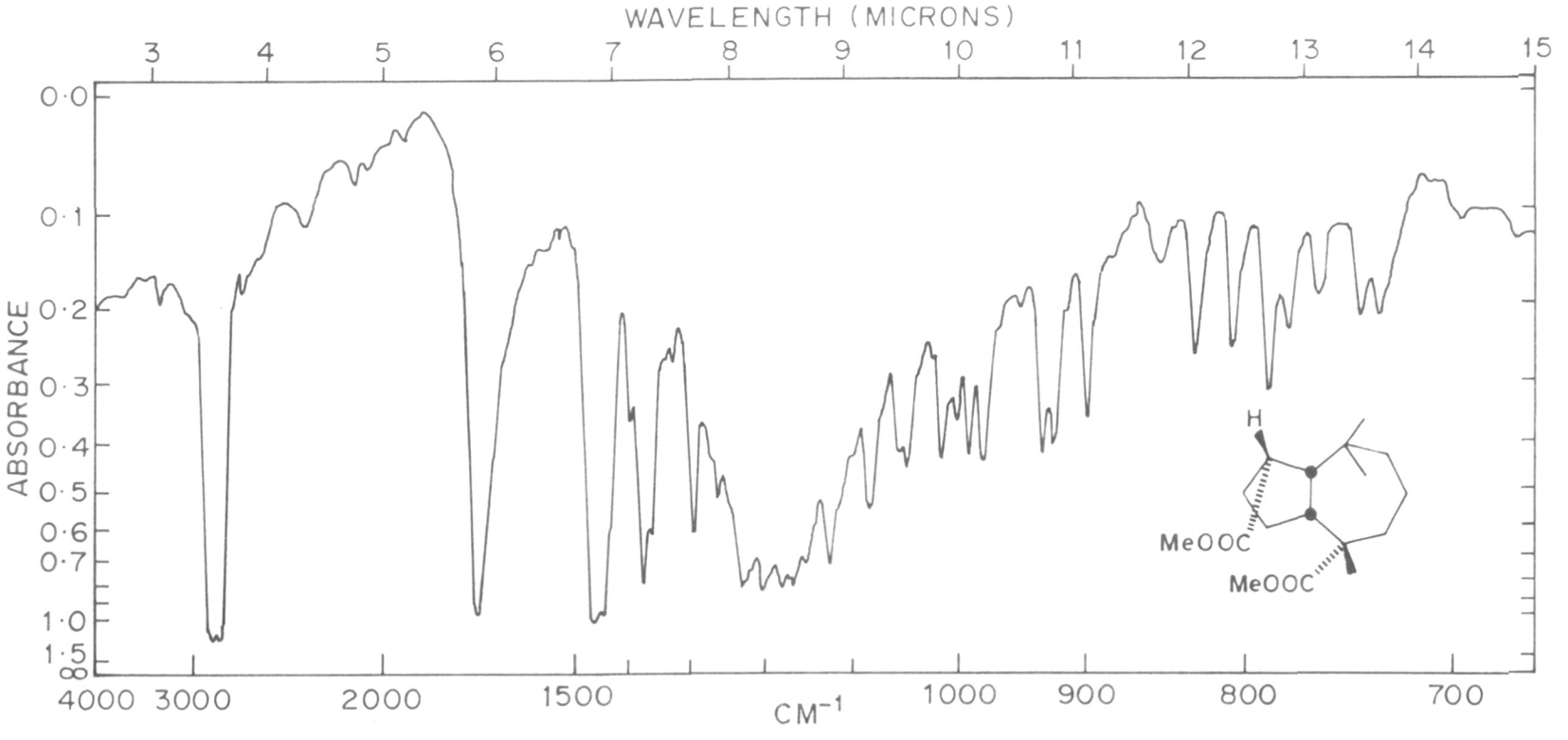

FIG. 16. IR SPECTRUM OF DIMETHYL α-LONGIFORATE 8

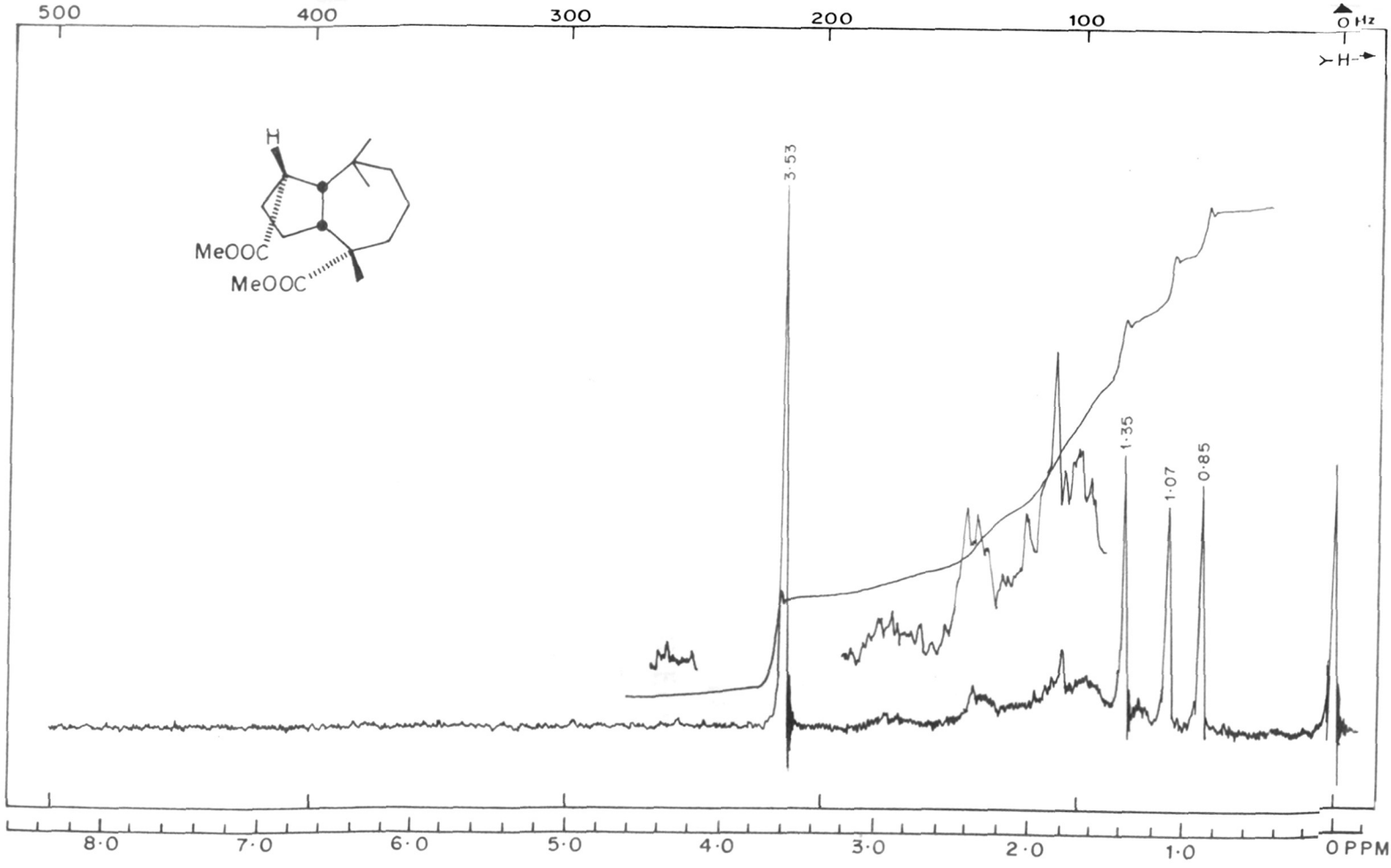

FIG. 17. PMR SPECTRUM OF DIMETHYL α-LONGIFORATE 8

CHAPTER – 3

TRANSFORMATION OF LONGIFOLENE TO THE ELUSIVE, NEW 4,5,8 – TRIMETHYL AZULENE

ABSTRACT

The long-cherished goal - longifolene → azulene transformation - has been achieved in a final, unexceptionable, systematic degradation which involves the step-wise Pb(IV)-oxidative decarboxylation strategy on α-longiforic acid 3 - a key 5,7-bicyclic derivative of the tricyclic longifolene 1. The resulting azulenogenic diene substrate 4, on vapour phase dehydrogenation over 30% Pd-C catalyst at 500°, generated a new azulene characterized as 4,5,8-trimethyl azulene 9, by PMR. Furthermore, the mixture 4 has been resolved by $AgNO_3$-SiO_2 chromatography to yield the pure dienes 7 and 8.

4,5,8-TRIMETHYL AZULENE - THE ELUSIVE, NEW AZULENE FROM LONGIFOLENE

The systematic generation of azulene as an irrefutable chemical proof of the built-in 5,7-bicyclic framework (cf 1a) camouflaged in the bridged tricyclic structure 1 of longifolene has been a long-cherished but unrealized goal. We now describe a rational procreation of the elusive azulene from the key bicyclic olefinic acid 2, accessible from α-longiforic acid 3 - the well-characterized perhydroazulene-based 1,4-dicarboxylic acid derivable from longifolene 1.

In a critical approach to an azulene from α-longiforic acid* 3 we envisaged a highly superior azulenogenic diene+ substrate of the type 4 - free from superfluous carboxyl groups and incorporating at least two sites of unsaturation (compare 3) - for the final

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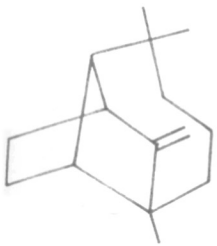
*Direct dehydrogenation of α-longiforic acid has been reported earlier:
(a) Formation of a trace amount (unspecified yield) of 4,8-dimethyl azulene 10[2].
(b) Formation of a mixture of indanes[3].

+Attempted generation of azulene from an azulenogenic monoene resulted only in a dimethyl naphthalene[4].



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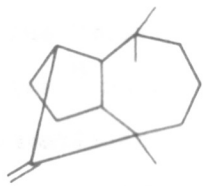

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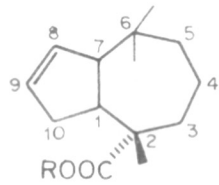

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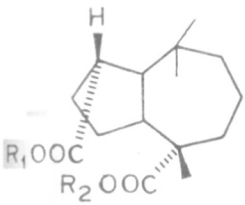
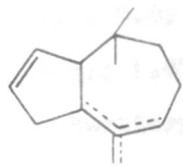
6: R = Me



3: $R_1 = R_2 = H$

5: $R_1 = H$, $R_2 = Me$



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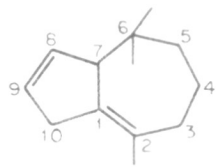

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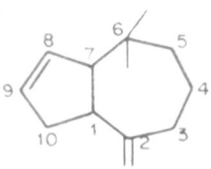

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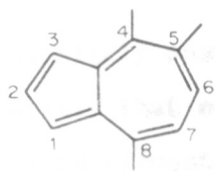

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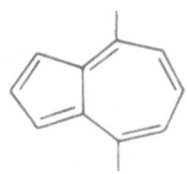

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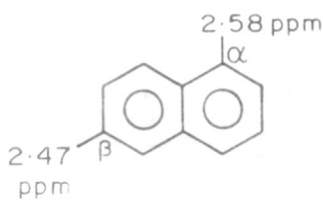

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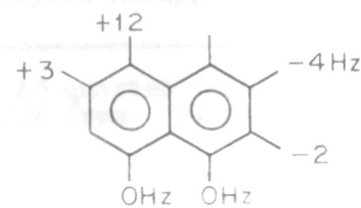

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dehydrogenation step. The Pb(IV)/Cu(II) oxidative bisdecarboxylation strategy[5] on 3 for directly generating 4 having proved quite unsatisfactory, we next contemplated a stepwise lead tetraacetate (LTA) reaction on the tertiary half ester. The transformation 3 → 5 and oxidative decarboxylation of 5 → 6 has been described recently[6]. Base hydrolysis of 6 gave the crucial olefinic acid 2: $C_{14}H_{22}O_2$ (M^+ 222). PMR(CCl_4): 5.80 ppm (AB pseudo* singlet, W_H = 6 Hz, 2H, HC=CH); 1.47 ppm (s, 3H, Me-C-COOH); 0.90, 0.87 ppm (tertiary Me singlets). Refluxing the olefinic acid 2 with LTA in benzene (Kochi[7] conditions/4 hr) smoothly furnished the expected mixture of dienes (64%), readily separable by chromatography over 15% $AgNO_3$-SiO_2 gel into two pure compounds 7 and 8 (approx. 1:1).

Diene 7 (M^+ 176) is highly unstable and absorbs atmospheric oxygen so rapidly that even a freshly prepared sample failed to give a good elemental analysis. IR(smear): 3010, 1620, 775, 705 cm^{-1}. PMR(CCl_4): 5.77 ppm (AB pseudo* singlet, 2H, HC=CH); 3.17 ppm (br,s, 1H, diallylic methine), 2.87 ppm (br s, 2H, diallylic methylene);

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*Actually a badly degenerated AB quartet (endocyclic disubstituted double bond) resulting from δ/J ratio being very small.

1.70 ppm (s, vinylic methyl); 0.92, 0.65 ppm (two tertiary methyl singlets).

Diene 8 (M^+ 176) - IR(smear): 3010, 1640, 895 cm^{-1}. PMR (CCl_4): 5.75 ppm (AB pseudo* singlet, 2H, HC=CH); 4.62 ppm (d, 2H, $J \approx 2$ Hz, $>=CH_2$); 0.92, 0.85 ppm (two tertiary methyl singlets).

In the final decisive step, two mutually-conflicting factors - the imperative need for a relatively high dehydrogenation temperature (for expelling a recalcitrant methyl from the gem dimethyl group in 7 / 8) versus prevention/minimization of the offensive azulene → naphthalene rearrangement inevitably fostered under these forcing conditions - were reconciled to the best possible extent in practice by performing the reaction in the vapour phase[8] (minimum contact time!) at 500° over 30% Pd-C catalyst dispersed on pyrex glass pieces. At 450° there was no evidence of any azulene formation. The dehydrogenation product resulting from the dienes mixture 7 / 8 was processed for azulene by Sherndal's method to furnish a deep blue-violet oil in 3-4% yield. [The H_3PO_4-insoluble product (60%) - a complex mixture of alkyl naphthalene, tetralin etc. (PMR) was not investigated further]. The three aromatic singlets in the PMR

spectrum of the product at 2.90, 2.82 and 2.58 ppm (approx. intensity ratio 1.5:1:1) could be rationalized only on the basis of a mixture of 4,5,8-trimethyl azulene [major; in pure 9 intensities of the three methyl signals at 2.90, 2.82 and 2.58 ppm (vide infra) should be equal] and 4,8-dimethyl azulene (minor; in pure 10 only one singlet at 2.90 ppm (3H x 2) should be expected). Formation of both 9 and 10 are theoretically conceivable: aromatization of ring systems containing quaternary carbon atoms takes place by loss[9] of one of the alkyl groups and/or its migration[9] to a nearby atom. The azulene mixture (only 115 mg) was fractionated by complex formation with TNB in EtOH. The azulene regenerated from the bronze crystals of the adduct (m.p. 169-70°)* was still a mixture but considerably enriched in the dimethyl azulene 10 (the intensity of the most downfield aromatic singlet at 2.90 ppm had considerably increased; the intensity ratio was now approx. 2.5:1:1). The mother liquor of TNB adduct, after passage through a column of alumina as before, also gave an azulene (blue-violet). A PMR scrutiny of this product surprisingly

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*Further recrystallization did not raise the m.p. [TNB adduct of 4,8-dimethyl azulene, m.p. 179-80° [10]].

indicated it to be pure (three aromatic methyl singlets of equal intensity). The substitution pattern of the now meagre (25 mg) azulene could be derived by application of the methylnaphthalene-PMR rules[11] (vide infra) and the compound characterized as the hitherto unknown 4,5,8-trimethyl azulene 9 - $C_{13}H_{14}$ (M^+ 170); PMR(CCl_4): 3H singlets at 2.90* ppm (α-methyl at C-8), 2.82 ppm (α-methyl at C-4), 2.58 ppm (β-methyl at C-5); 6.77 to 8.07 ppm (aromatic, 5H). The position of the aromatic methyl signal is governed not only by its position (α or β) on the nucleus but also by the disposition of the neighbouring methyl group. In the case of methylnaphthalenes the rules have been summarized[11] as in 11 and 12.

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*PMR (CCl_4) of 4,7-dimethylazulene[11]: 2.86 ppm (α-methyl at C-4) and 2.63 ppm (β-methyl at C-7).

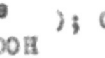
EXPERIMENTAL

Light petroleum refers to the fraction b.p. 60-80° (essentially hexane). All solvent extracts were dried over anhydrous Na_2SO_4. Rotations were taken in $CHCl_3$ (at 26°) on a Perkin-Elmer 141 spectropolarimeter (automatic). Recorded temperatures are uncorrected.

IR spectra were taken on a Perkin-Elmer Infracord model 137E. PMR spectra were recorded on a Varian T-60 spectrometer using tetramethylsilane as internal standard. Mass spectra (MS) were obtained on a CEC spectrometer model 21-110B using an ionizing voltage of 70 eV and a direct inlet system.

Pb(IV)/Cu(II) reaction on the tertiary half ester 5: 2,6,6-Trimethyl-2-carboxy-bicyclo[5.3.0]dec-8-ene 2

The dimethyl ester (62.3 g) of α-longiforic acid 3 was subjected to partial hydrolysis by N/10 aqueous ethanolic KOH (2.1 l) at 5°/24 hr and then at 80°/2 hr. The mixture was diluted with water (1.5 l) and extracted with light petroleum (3 x 500 ml) which gave the unchanged diester (30.6 g). The aqueous alkaline part was acidified with conc. HCl, extracted with $CHCl_3$ (3 x 500 ml), washed with water, brine, dried and evaporated. The crude product

was recrystallized from light petroleum to furnish colourless needles of the tertiary half-ester 5, m.p. 134-35° (25.8 g). $[\alpha]_D$ -59.20° (c = 0.5%). IR (Nujol): 3000-2600, 1730, 1700, 1250 cm^{-1}. PMR (CCl_4): 3.63 ppm (s, 3H, $COOCH_3$); 1.37 ppm (s, ); 0.95, 0.90 ppm (tertiary Me singlets). MS (m/e): 282 (M^+). (Found: C, 68.81; H, 9.35. $C_{16}H_{26}O_4$ requires: C, 68.05; H, 9.98%).

The 3°-half ester 5 (62.0 g) in dry benzene (1.5 l) was treated with LTA (130.0 g), $Cu(OAc)_2$ (6.6 g), pyridine (6.6 ml) and stirred under reflux for 4 hr. Ethylene glycol (10 ml) was added and stirred for another 15 min.; the benzene layer was separated, the inorganic residue was thoroughly washed with hot benzene and the combined extracts washed with 10% aq. KOH (2 x 200 ml), water, brine and dried. Removal of solvent and distillation gave the olefinic ester 6 (slightly impure) as a colourless liquid, b.p. 125-130°/2 mm (56.2 g). IR(smear): 1730, 1600, 1240 cm^{-1}. PMR (CCl_4): three tertiary Me singlets at 0.83, 0.87, 1.37 ppm (impurity singlets at 0.98, 1.10, 1.20 ppm); 3.53 ppm (s, COOMe); 5.70 ppm (olefinic H).

The olefinic ester 6 (57.0 g) was hydrolysed by refluxing it for 24 hr with 30% aq. ethanolic KOH (200 ml). The mixture was concentrated to about half (water bath/

water pump), diluted with water (400 ml) and extracted with $CHCl_3$ (2 x 200 ml) to remove the unchanged ester (5.3 g). The aqueous alkaline part was acidified with conc. HCl, extracted with $CHCl_3$ (3 x 250 ml), washed with water, brine, dried and the solvent removed. The crude product was recrystallised from MeCN to furnish colourless prisms of the olefinic acid 2, m.p. 101-102° (26.3 g, 50%). IR (Nujol): 2550-3000, 1700, 1280 cm^{-1}. PMR(CCl_4): 5.80 ppm (AB pseudo singlet, W_H = 6 Hz, 2H, HC=CH); 1.47 ppm (s, 3H ); 0.90, 0.87 ppm (tertiary Me singlets). MS (m/e): 222 (M^+, 13%), 151(43), 140(25), 107(26), 91(43), 87(68), 77(34), 70(100), 67(24), 55(38). (Found: C, 74.97; H, 10.39. $C_{14}H_{22}O_2$ requires: C, 75.63; H, 9.97%).

Pb(IV)/Cu(II) reaction on the olefinic acid 2: 2,6,6-Trimethyl-bicyclo]5.3.0]deca-1,8-diene 7 and 6,6-dimethyl-2-methylene-bicyclo[5.3.0]dec-8-ene 8.

A mixture of the olefinic acid 2 (25.0 g), dry benzene (1.2 litres), LTA (53.2 g), $Cu(OAc)_2$ (3.7 g) and pyridine (3.7 ml) was stirred under reflux (4 hr) in an oil bath. Ethane diol (24 ml) was added and the stirring continued for another 15 min. to destroy excess of LTA. The benzene layer was decanted off and the inorganic residue thoroughly washed with hot benzene (4 x 50 ml). The organic

layer was washed with 10% aq. KOH, water, brine, dried and the solvent removed. The crude product was carefully fractionated (8" vigreux column) to yield the major hydrocarbon fraction b.p. 120-25°/1 mm (12.3 g, 64%) showing two spots on $AgNO_3$-TLC [the higher boiling fraction (1.7 g) was a mixture of oxygenated products (TLC, IR/PMR) and was not investigated].

The hydrocarbon mixture (10 g) was chromatographed on 15% $AgNO_3$-SiO_2 gel (30 g, 46 cm x 1.5 cm) with TLC monitoring: Fr.1, light petroleum, 2 x 100 ml, pure. Fr.2, C_6H_6, 2 x 100 ml, pure.

Fr.1 on distillation gave the diene 7 as a colourless liquid b.p. 90° (bath)/0.8 mm (0.3 g). IR(smear): 3010, 1620, 775, 705 cm^{-1}. PMR (CCl_4): 5.77 ppm (AB pseudo singlet, 2H, HC=CH); 3.17 ppm (br s, 1H, diallylic methine), 2.87 ppm (br s, 2H, diallylic methylene); 1.70 ppm (s, vinylic Me); 0.92, 0.65 ppm (two tertiary Me singlets). MS (m/e): 176 (M^+ 88%), 161(31), 120(35), 107(50), 106(100), 91(81), 77(50), 55(56). (Found: C, 87.14; H, 11.72. $C_{13}H_{20}$ requires: C, 88.56; H, 11.44%).

Fr.2 was distilled to yield the diene 8 as a colourless liquid b.p. 90° (bath)/0.8 mm (0.25 g). IR(smear): 3010, 1640, 895 cm^{-1}. PMR(CCl_4): 5.75 ppm ('singlet' 2H, HC=CH);

4.62 ppm (d, 2H, J = 2 Hz, >=C$\underline{H}_2$); 0.92, 0.85 ppm (two tertiary Me singlets). MS (m/e): 176 (M^+ 14%), 161(100), 136(23), 121(15), 107(26), 97(44), 94(50), 81(23), 80(33), 66(40). (Found: C, 88.93; H, 11.60. $C_{13}H_{20}$ requires: C, 88.56; H, 11.44%).

Vapour phase dehydrogenation of dienes mixture 4: 4,5,8-Trimethylazulene 3

A vertical pyrex glass tube (48 cm x 2 cm) packed with the catalyst (4.0 g of 30% Pd-C dispersed on nearly uniform pieces of crushed pyrex glass) was enclosed in an electrically heated furnace. The latter consisted of a pyrex glass tube (50 cm x 5 cm), on which Nichrome wire was carefully wound along the length of the tube (the heating being controlled by a 'variac') and snugly fitted into an outer glass tube (50 cm x 7 cm). The dehydrogenation tube was equipped with a pressure-equalizer type addition funnel (capillary bore stopcock) at the top and a receiver [with side arm, containing light petroleum (20 ml)] at the bottom, which was cooled in an ice-salt bath. The temp. of the furnace was adjusted at 500 $\pm$ 5° and the diene mixture (5.6 g) was added dropwise (6 drops/min.) into the dehydrogenation tube (atmosphere of O_2-free N_2) with very mild suction (650 mm) at the receiver end. When the addition was over, the column was cooled to room temp. and washed with light petroleum

(3 x 25 ml). The deep violet-blue pyrolysate solution and the washings were combined and fractionated for azulene by extraction with 85% H_3PO_4 (4 x 20 ml). [The light petroleum soluble part (3.1 g, 55%) was a complex mixture (TLC, PMR) and was not investigated].

The H_3PO_4-soluble part was diluted with ice water (100 ml), extracted with light petroleum, washed with water, brine, dried and the solvent removed. Distillation of the residue gave a deep blue-violet oil b.p. 120° (bath)/0.8 mm (0.115 g). PMR (CCl_4): three aromatic methyl singlets at 2.90, 2.82 and 2.58 ppm (approx. intensity ratio 1.5:1:1).

Purification of 4,5,8-trimethylazulene 9 via TNB adduct.

The azulene (0.115 g) in EtOH (5 ml) was reacted with TNB reagent (0.15 g) in hot EtOH (5 ml) and kept at room temp. for 1 hr. The bronze crystals of the adduct had m.p. 169-70° (0.087 g) which remained unchanged upon recrystallisation from EtOH (Lit.[10]: TNB adduct of 4,8-dimethylazulene, m.p. 179-80°). The adduct (0.087 g) dissolved in benzene (3 ml) was applied to a short column of Al_2O_3 (neutral/I) and eluted with light petroleum. The regenerated azulene was distilled to yield a deep violet-blue oil. PMR (CCl_4): aromatic methyl singlets at 2.90, 2.82, 2.58 ppm (approx. intensity ratio 2.5:1:1).

The mother liquor of TNB adduct was adsorbed on Al_2O_3 (25 cm x 1.5 cm) and eluted with light petroleum to furnish, after distillation in a bulb-tube, pure 4,5,8-trimethylazulene 9 as a deep violet-blue oil (0.025 g). PMR (CCl_4): 3H singlets at 2.90 ppm (α-methyl at C-8), 2.82 ppm (α-methyl at C-4), 2.58 ppm (β-methyl at C-5); 6.77 to 8.07 ppm (aromatic, 5H). MS (m/e): 170 (M^+ 27%), 154(37), 161 (54), 128 (17), 115(20). (Found: C, 91.84; H, 8.47. $C_{13}H_{14}$ requires: C, 91.71; H, 8.29%).

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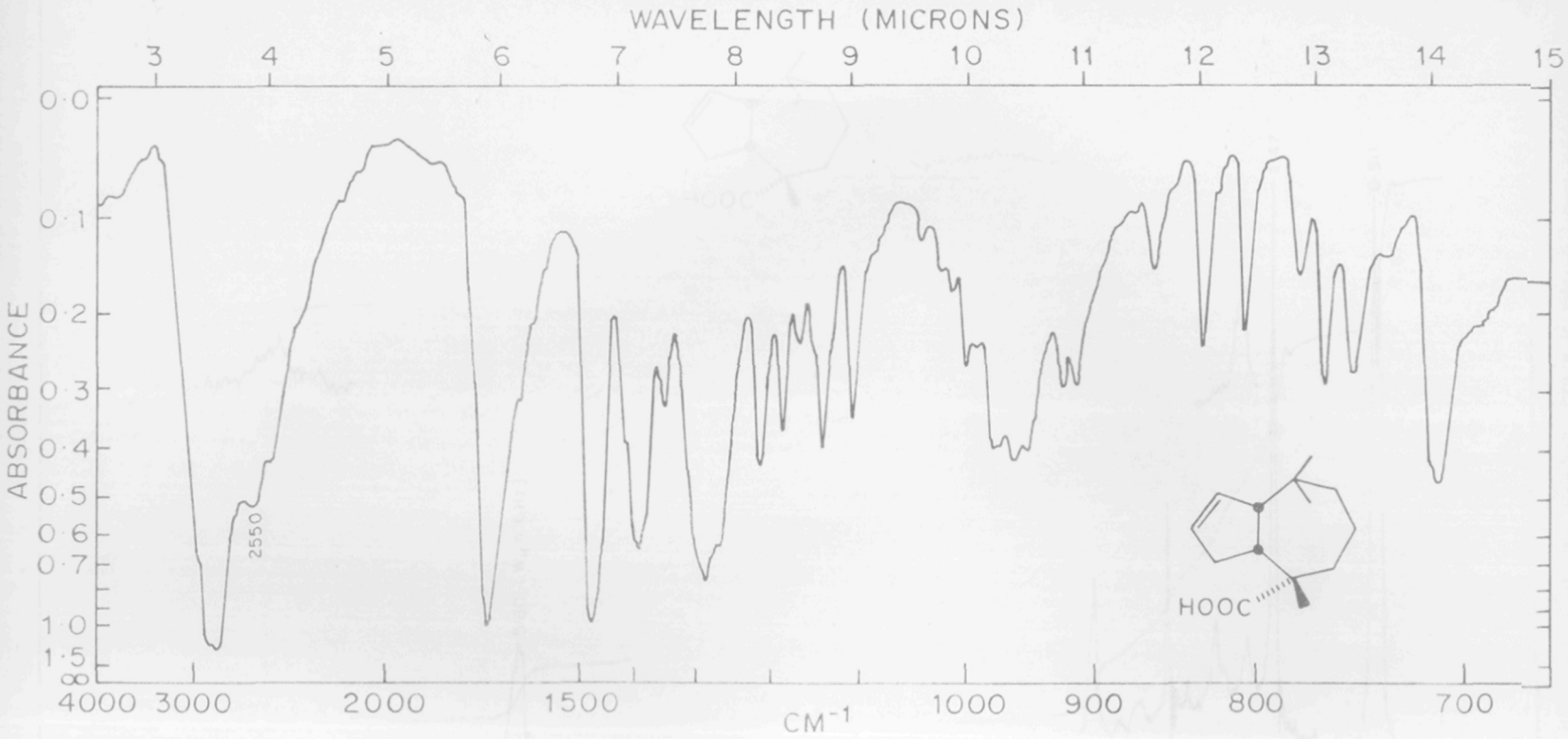


FIG. 1. IR SPECTRUM OF α-OLEFINIC ACID 2

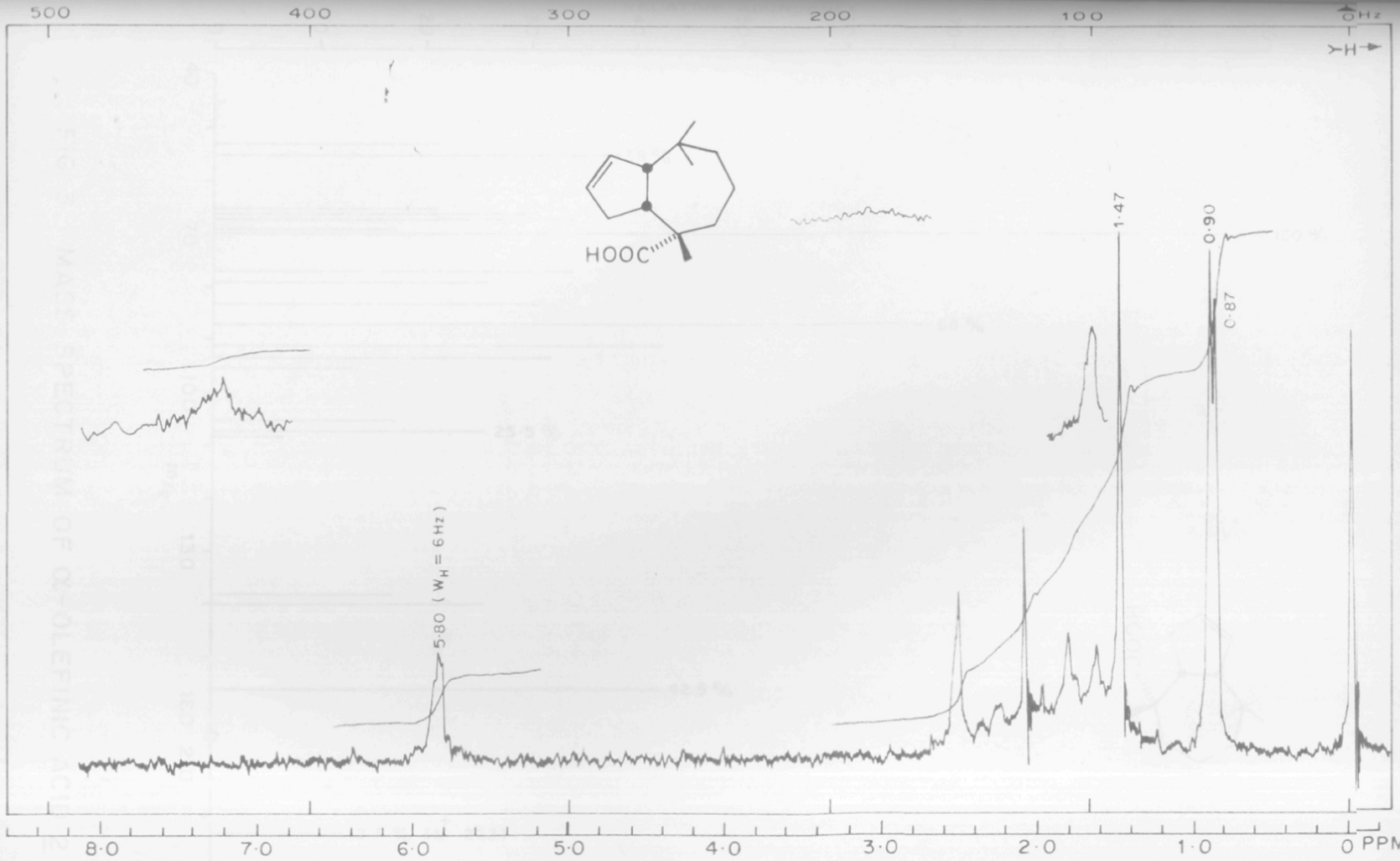


FIG. 2. PMR SPECTRUM OF α-OLEFINIC ACID 2

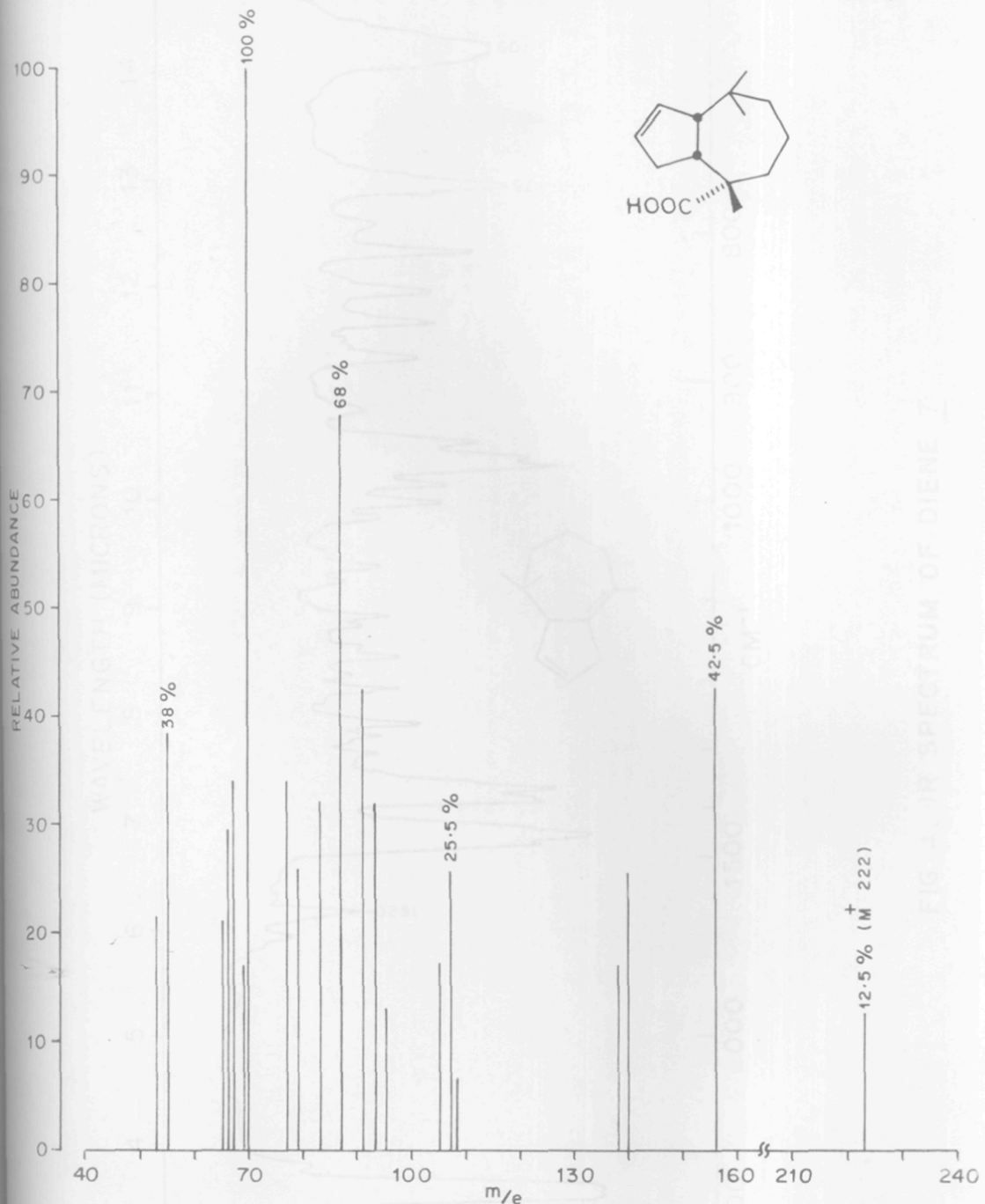


FIG. 3. MASS SPECTRUM OF α-OLEFINIC ACID 2

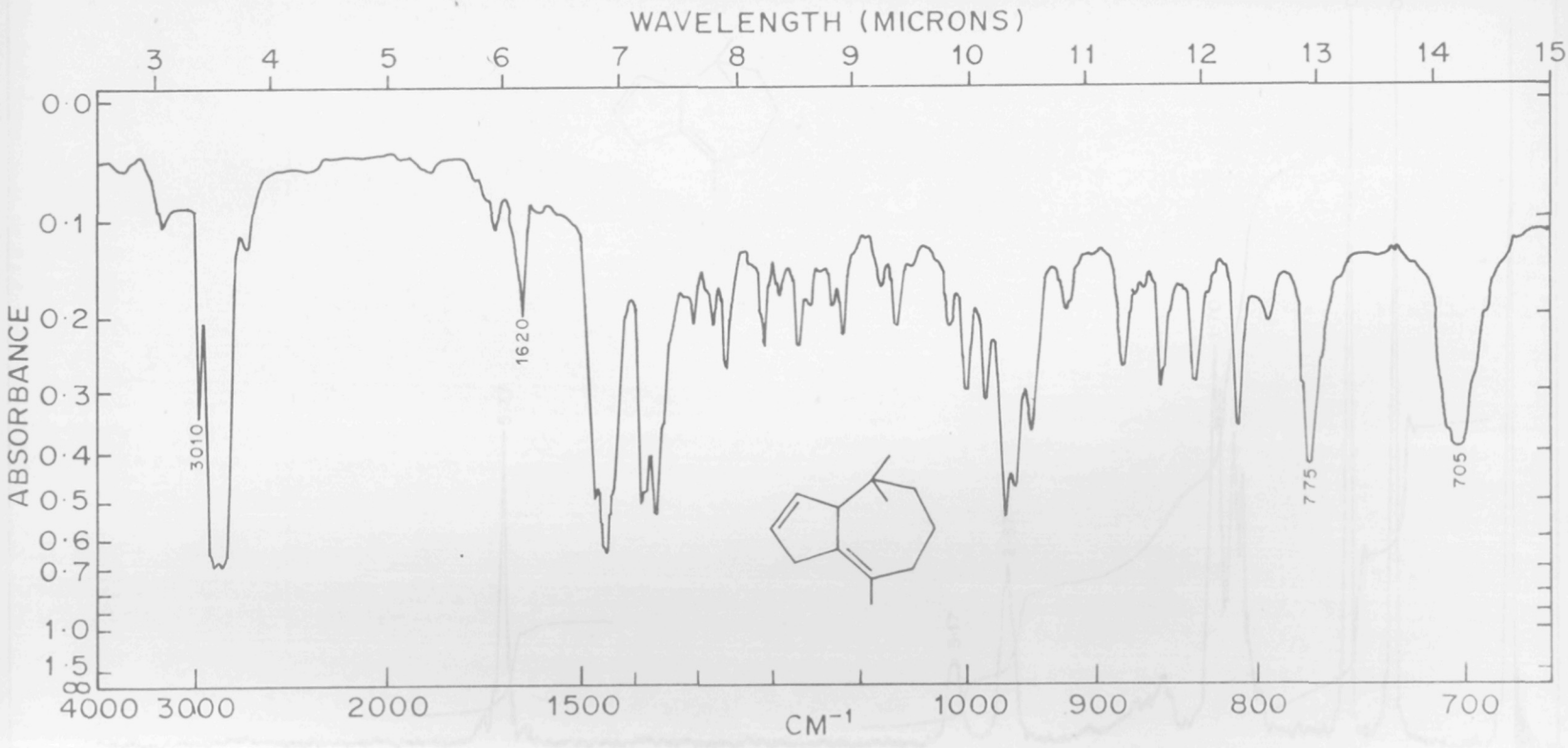


FIG. 4. IR SPECTRUM OF DIENE 7

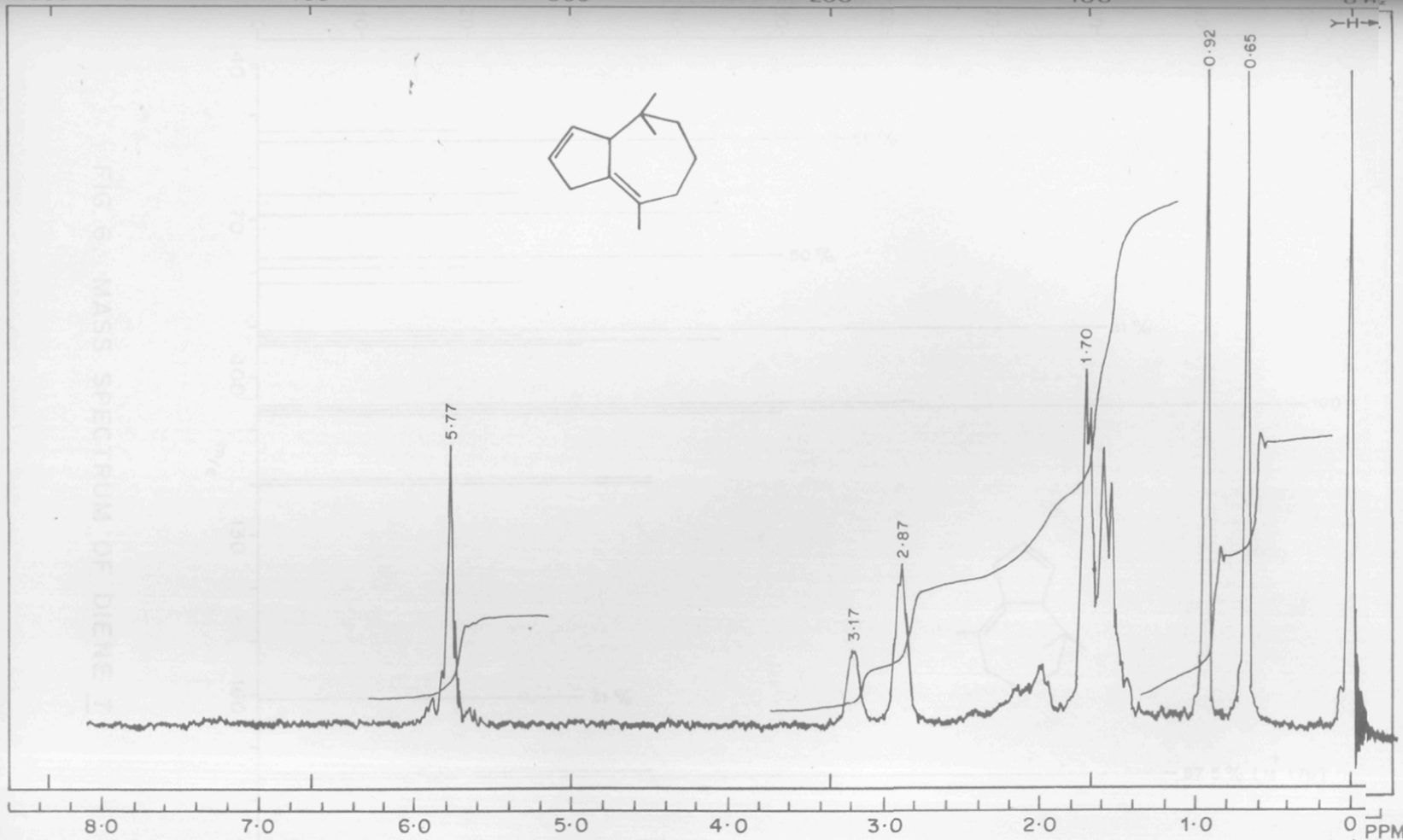


FIG. 5. PMR SPECTRUM OF DIENE 7

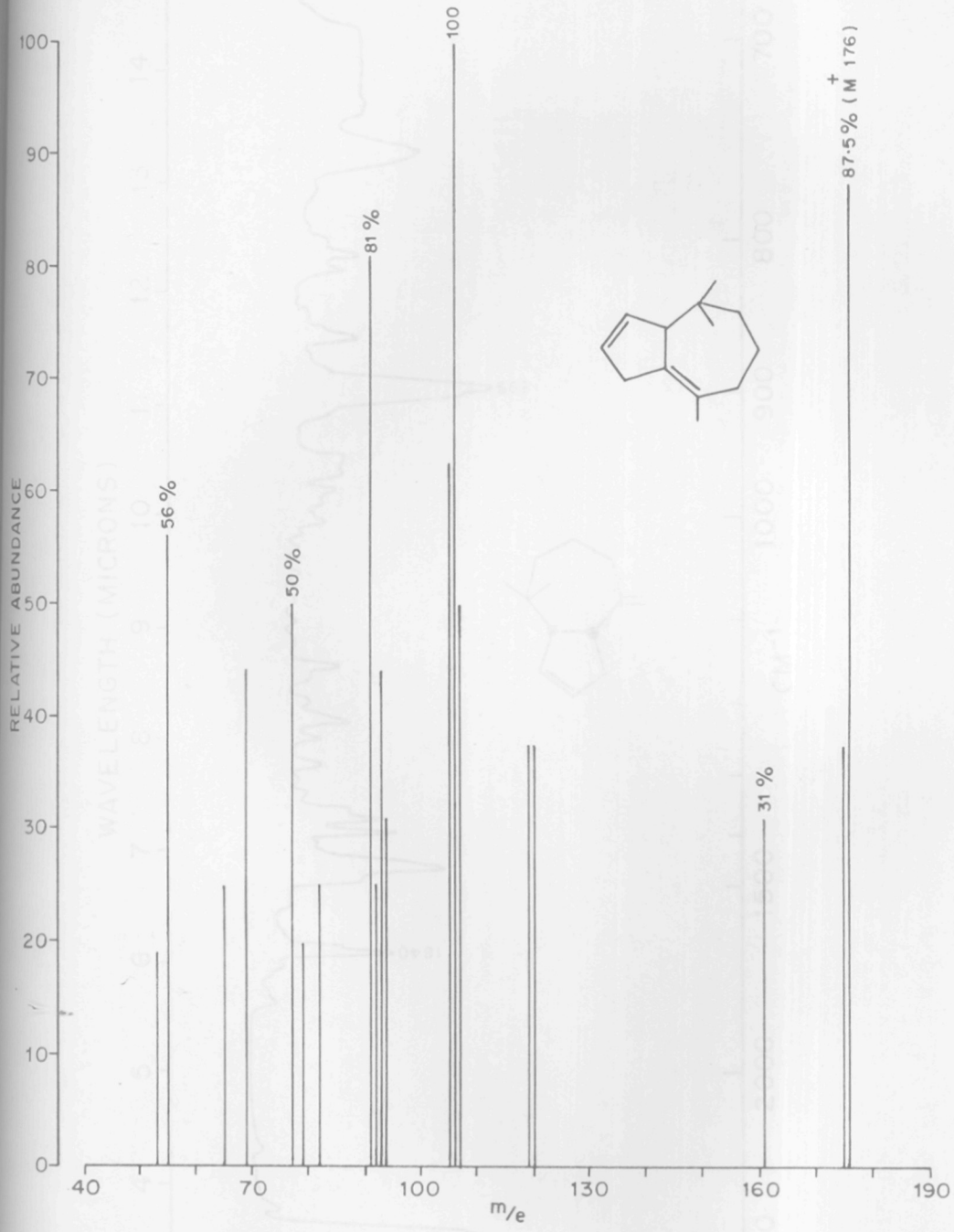


FIG. 6. MASS SPECTRUM OF DIENE 7

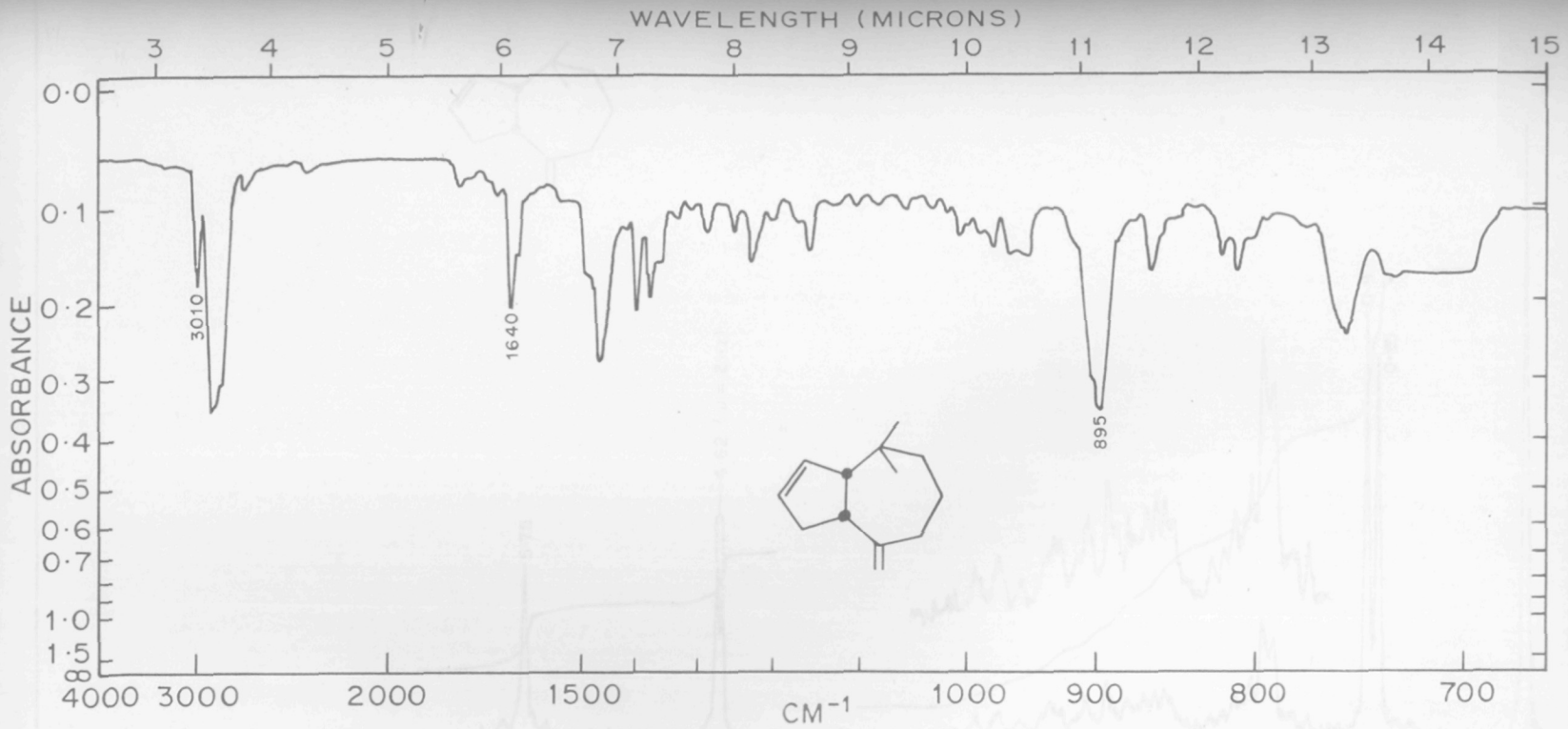


FIG. 7. IR SPECTRUM OF DIENE 8

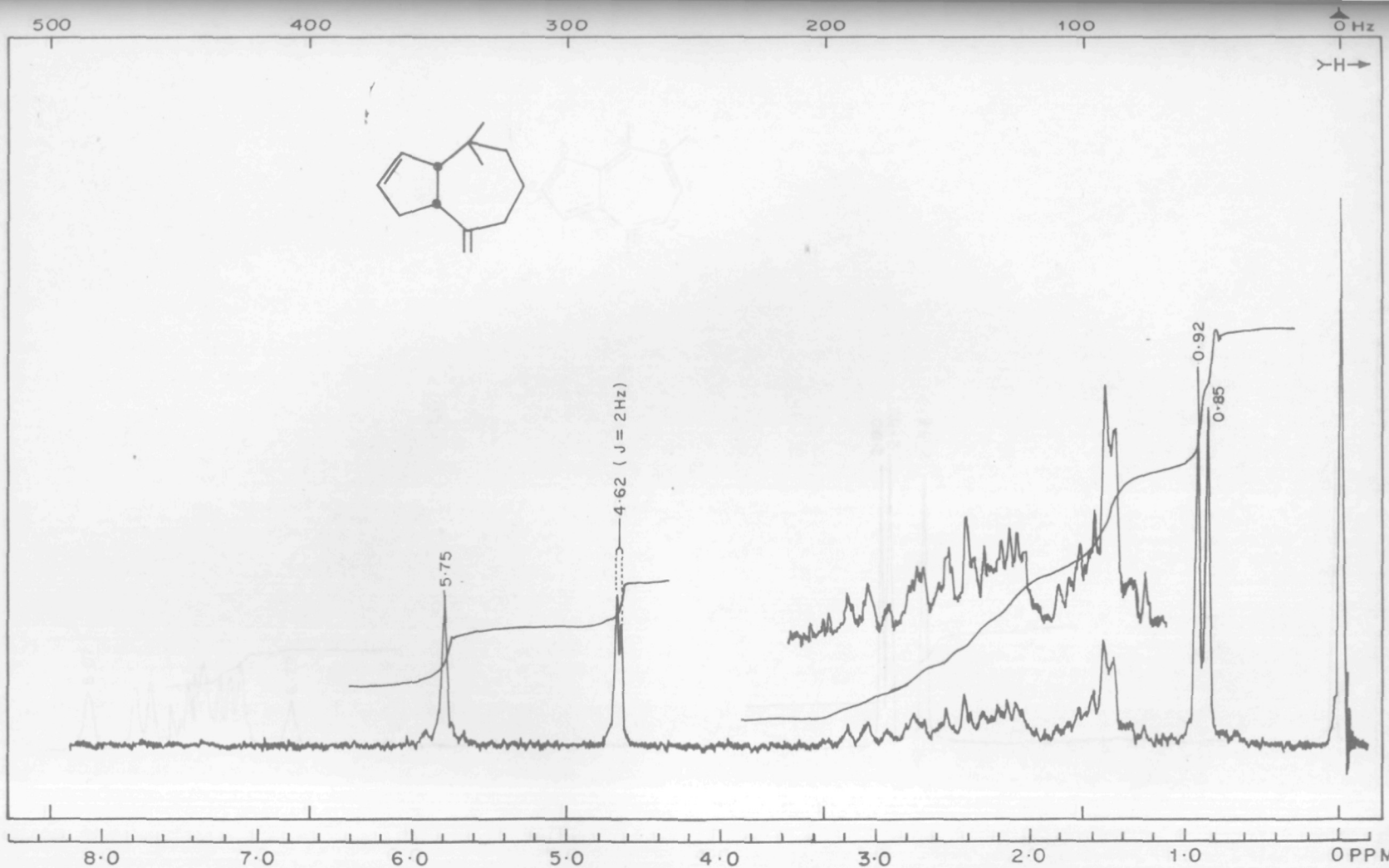


FIG. 8. PMR SPECTRUM OF DIENE 8

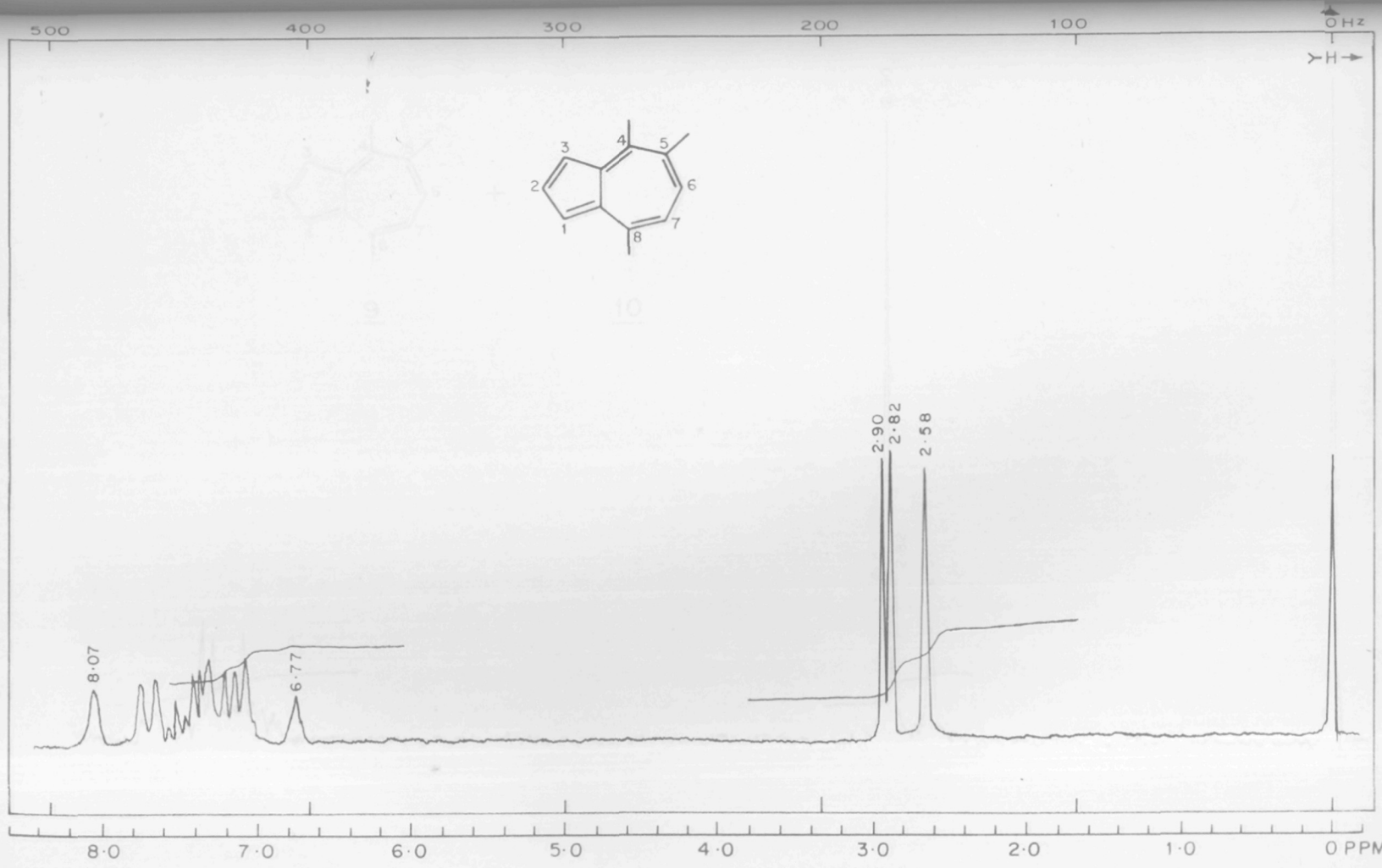
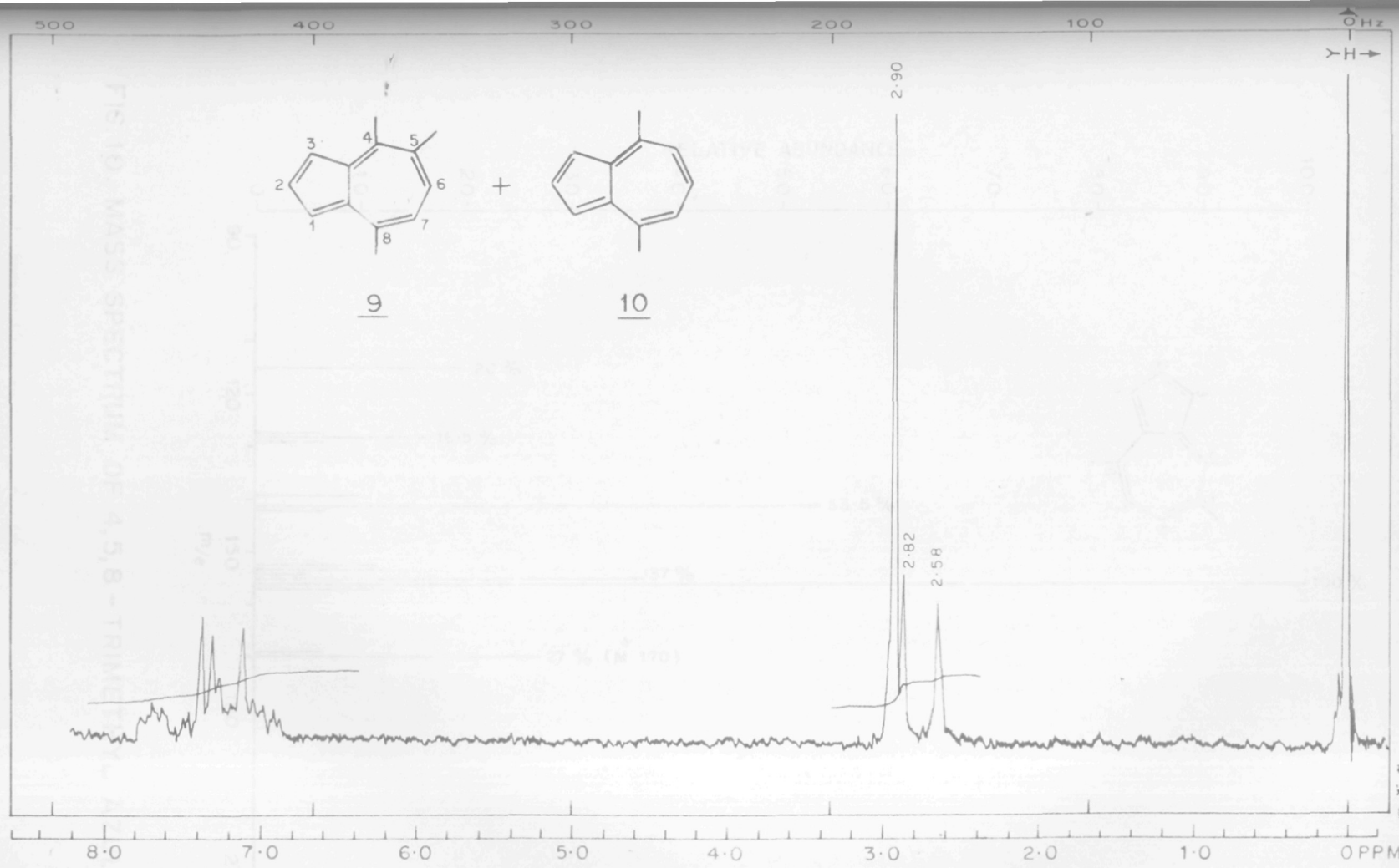


FIG. 9(a). PMR SPECTRUM OF 4,5,8-TRIMETHYL AZULENE 9



9 + 10

FIG. 9(b). PMR SPECTRUM OF AZULENE REGENERATED FROM TNB ADDUCT (m.p. 169–170°)[9+10]

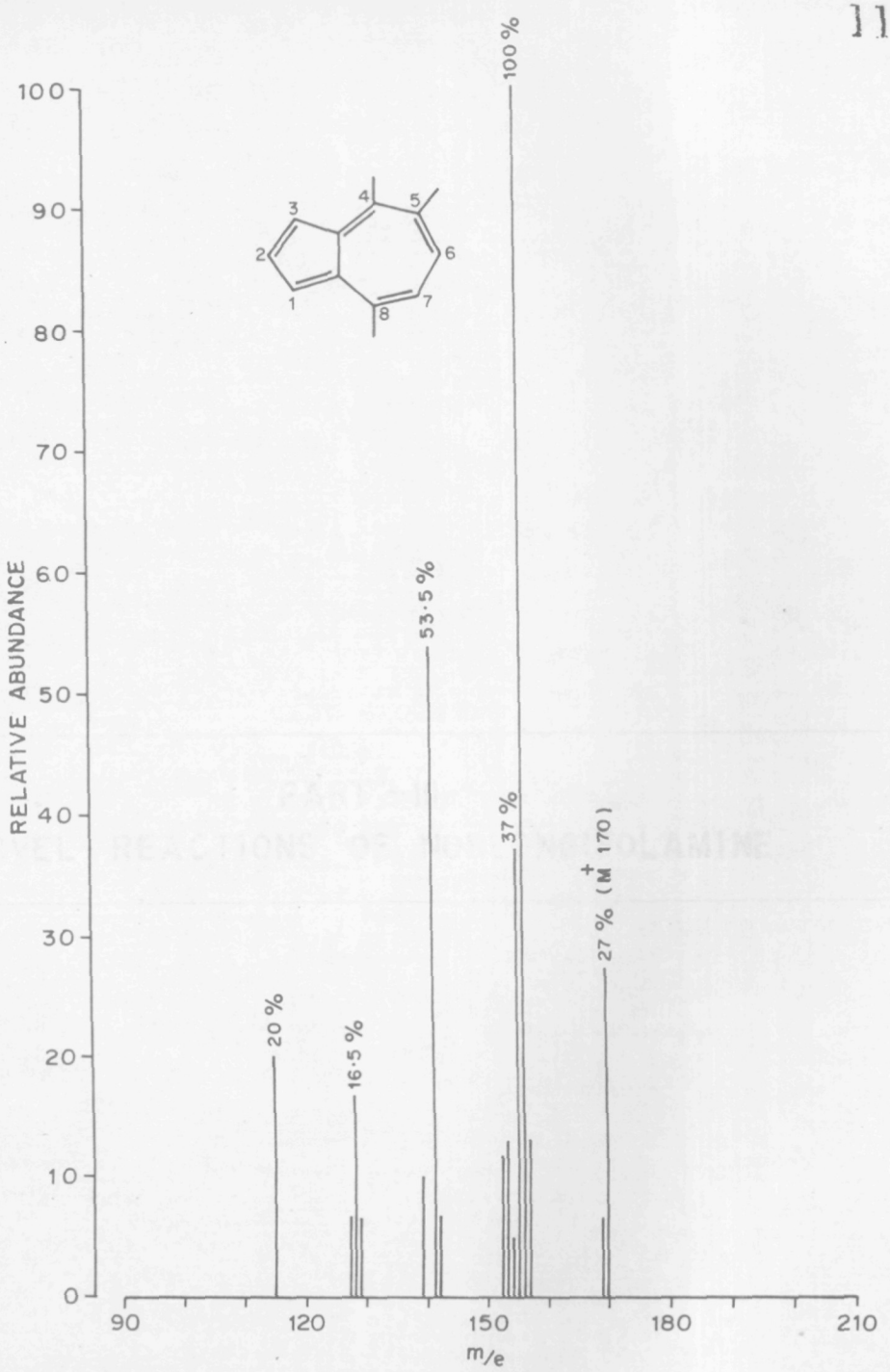


FIG. 10. MASS SPECTRUM OF 4,5,8 - TRIMETHYL AZULENE 9

PART - III

NOVEL REACTIONS OF NORLONGIFOLAMINE

CHAPTER - 1

NOVEL CYCLOPROPANATION DURING THE HOFMANN ELIMINATION REACTION ON NORLONGIFOLAMINE: FORMATION OF NORLONGICYCLENE

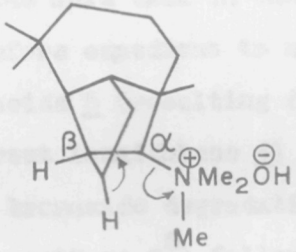
ABSTRACT

Pyrolysis of the quaternary base 1, from the bridged tricyclic norlongifolamine 9 (in which a β-hydrogen is available but is sterically constrained for the Hofmann elimination), has been shown to undergo a novel cyclopropanation reaction to generate norlongicyclene 12 - at least to the extent of 7%; a reversal to the dimethylamine 10 (93%), by the loss of elements of CH_3OH, constitutes the major pathway. Facile epimerization takes place during the $SOCl_2$ reaction with the exo epimer 2 of longifolic acid resulting in the isolation of the acid chloride of the more stable endo epimer.

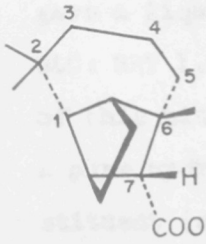
NOVEL CYCLOPROPANATION DURING THE HOFMANN ELIMINATION REACTION ON NORLONGIFOLAMINE: FORMATION OF NORLONGICYCLENE

Pyrolysis of a quaternary ammonium hydroxide leads to elimination if a β-hydrogen is available, the hydroxide acting as a base for the elimination: the Hofmann elimination reaction[1]. The mechanism usually, though not always, follows the E2 pattern[1]. The application of the Hofmann elimination reaction to the quaternary base 1, derived from the bridged tricyclic norlongifolamine 2, in which a β-hydrogen is available but is sterically constrained for elimination (since this would lead to a bridgehead sp^2 carbon), appeared to be of some theoretical interest and the results of our investigation are described in this communication.

The most convenient way of preparing the crucial norlongifolamine 2 appeared to be via the Hofmann bromamide[2] route as indicated in Chart I; the starting amide was easily available by reaction of the acid chloride in benzene[3] with aqueous ammonia. The amide prepared from the pure exo epimer 3 of the acid, however, turned out to be identical with the amide generated from the endo epimer 4. It was apparent that an epimerization was

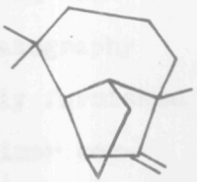


1



2: C–7 exo epimer

3: C–7 endo epimer



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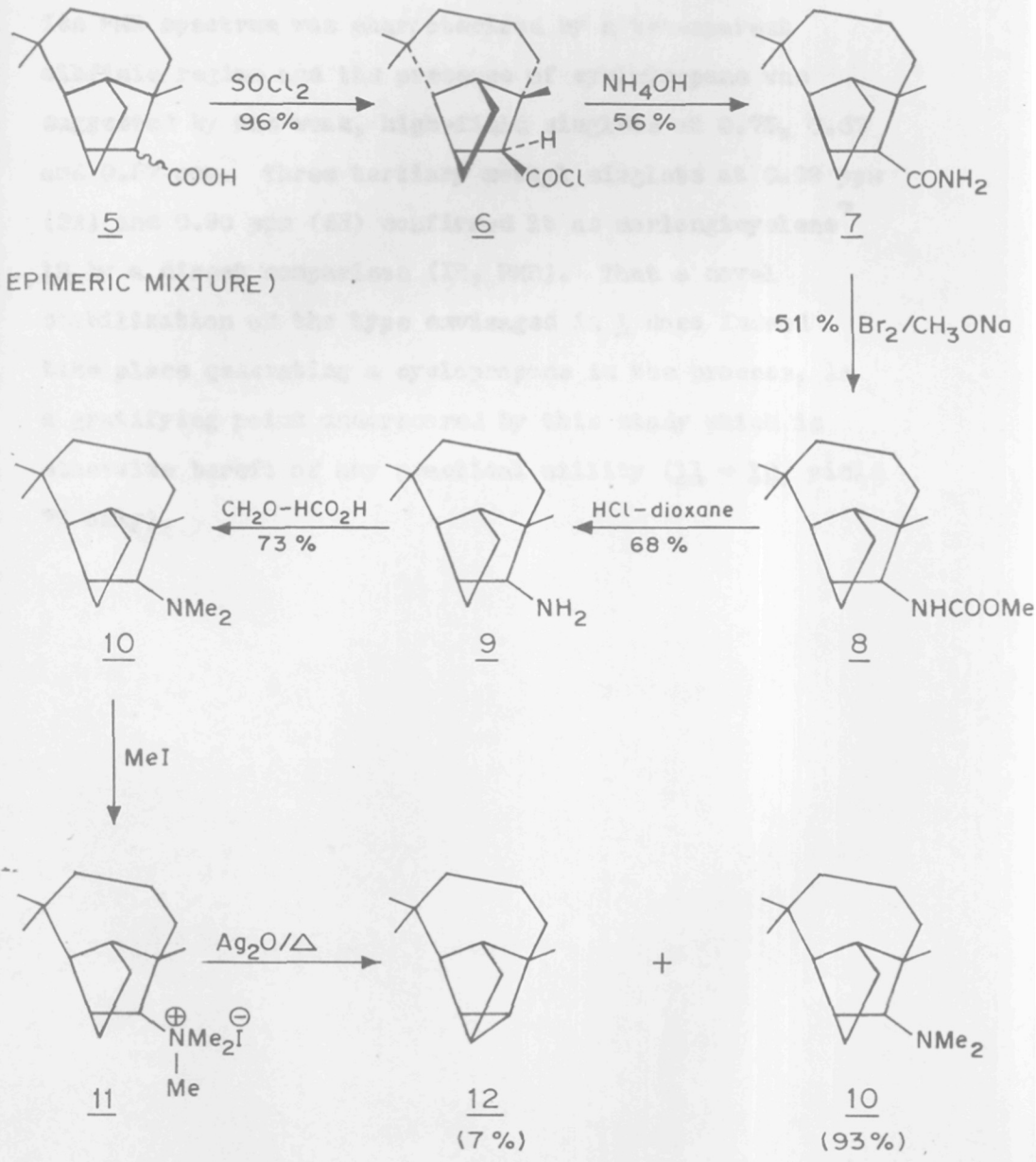
involved in the $SOCl_2$ reaction with the exo acid 2: treatment of the acid chloride with aq. KOH resulted in the isolation of the acid back in the epimerized form 3. It was therefore expedient to utilize the epimeric mixture of acids 5 (resulting from CrO_3-oxidation[4] of the parent longifolene 4) for preparation of the amide 7. The bromamide degradation of 7 to the amine 9 (via the urethane 8[5]) followed by the Eschweiler-Clarke methylation[6] (CH_2O/HCO_2H) gave the dimethylamine 10 which was quaternized with methyl iodide to the beautifully crystalline methiodide 11. Treatment of 11 with silver oxide in aqueous methanol, followed by pyrolysis of the quaternary ammonium hydroxide, gave a liquid product which showed two peaks in its GLC: RRT 1.00 (7%) and RRT 2.43 (93%); chromatography of this binary mixture over silica gel readily furnished a pure hydrocarbon (GLC, $AgNO_3$-TLC) as the minor constituent (eluted with light petroleum) while the more polar major compound (which still contained nitrogen) was identified as the starting dimethylamine 10 (IR, PMR).

Taking the stereoelectronic factors disposed in the quaternary base 1 into consideration, the major product outcome 1 → 10 (93%) is quite reasonable, if disappointing. Of considerable theoretical interest,

CHART I

HOFMANN ELIMINATION REACTION ON NORLONGIFOLAMINE 9



however, was the structure of the hydrocarbon ($C_{14}H_{22}$, M^+ 190), notwithstanding its poor yield (only 7%). Its PMR spectrum was characterized by a transparent olefinic region and the presence of cyclopropane was suggested by the weak, high-field singlets at 0.73, 0.67 and 0.57 ppm. Three tertiary methyl singlets at 0.98 ppm (3H) and 0.90 ppm (6H) confirmed it as norlongicyclene[7] 12 by a direct comparison (IR, PMR). That a novel stabilization of the type envisaged in 1 does indeed take place generating a cyclopropane in the process, is a gratifying point underscored by this study which is otherwise bereft of any practical utility (11 → 12, yield 7% only).

EXPERIMENTAL

Light petroleum refers to the fraction b.p. 60-80° (essentially hexane). All solvent extracts were dried over anhydrous Na_2SO_4. Rotations were measured in $CHCl_3$ (at 26°) on a Perkin-Elmer 141 spectropolarimeter (automatic). M.p's and b.p's are uncorrected.

IR spectra were recorded as smears (liquids) or Nujol mulls (solids) on a Perkin-Elmer Infracord model 137-E. PMR spectra were measured in 10-20% CCl_4 soln. on a Varian T-60 spectrometer using tetramethylsilane as internal standard. Mass spectra (MS) were obtained on a CEC spectrometer model 21-110B using an ionizing voltage of 70 eV and a direct inlet system.

TLC was carried out on silica gel or $AgNO_3$-silica gel layers (0.2 mm) containing 15% gypsum; visualization was done by spraying with conc. H_2SO_4 and heating the plates in an oven at 120°.

Analytical GLC was carried out on an Aerograph model A-350-B using 150 cm x 0.6 cm aluminium column packed with 20% FFAP on Chromosorb W (60-80 mesh) with H_2 as carrier gas.

Longifolic acids 5. This was prepared by the CrO_3-aqueous H_2SO_4-AcOH oxidation of longifolene as described[4] by Nayak and Dev.

Acid chloride 6. A mixture of the acids 5 (25.6 g) and $SOCl_2$ (freshly distilled, 22 ml) was refluxed on the waterbath for 3 hr (gas absorption trap), with frequent swirling. Excess $SOCl_2$ was then distilled off (water pump) and the residue distilled to furnish the acid chloride 6: pale yellow liquid b.p. 124°/1 mm (24.1 g, 96%). PMR(CCl_4): 3.33 ppm (d, 1H, HC.CHCOCl); 1.13, 1.03, 1.00 ppm (3 tertiary Me singlets).

Longifolamide 7. Aq. ammonia (28%, 200 ml) was taken in a 3-necked flask fitted with a stirrer, dropping funnel and condenser (connected to a gas absorption trap at the top). The flask was cooled in an ice-salt bath and the acid chloride (freshly prepared, 24.1 g) in dry benzene (150 ml) was added dropwise to the stirred solution (0.5 hr). Stirring was continued for another 4 hr and the mixture left overnight at room temperature. The mixture was diluted with water (200 ml), the benzene layer separated and the aqueous part further extracted with benzene (100 ml x 3). The combined extracts were washed with 5% aq. KOH (150 ml x 3) to remove any acid. The organic layer was washed with water,

brine and dried. The solid, obtained after removal of solvent, was recrystallised from light petroleum to furnish colourless needles of longifolamide 7, m.p. 106-107° (13 g, 56%); $[\alpha]_D$ -31.7° (c, 0.75%). IR (Nujol): 3200, 3100, 1650, 1600 cm^{-1}. PMR(CCl_4): 5.83 to 6.78 ppm (very br, 2H, $CONH_2$); tertiary Me singlets at 0.98 (3H) and 1.02 ppm (6H). MS: m/e 235 (M^+, base peak). (Found: C, 75.70; H, 10.51; N, 5.36. $C_{15}H_{25}ON$ requires: C, 76.54; H, 10.71; N, 5.95%).

Urethane 8. To a soln. of NaOMe [prepared from Na (0.46 g) in dry MeOH (30 ml)] was added longifolamide 7 (2.35 g) in dry MeOH (10 ml). The mixture was cooled to below 5° in ice water and Br_2 (6.6 ml) was added dropwise, with stirring. After 20 minutes the mixture was refluxed on the water bath (3 hr), cooled and poured into ice water. The semi-solid material was extracted with EtOAc (3 x 100 ml), washed with water, brine and dried. Removal of solvent gave the crude urethane containing some unchanged amide (TLC). Chromatography over SiO_2 gel/IIa (60 g) and elution with C_6H_6 gave the pure urethane (faster moving): b.p. 140°/0.9 mm, colourless liquid, solidifies slowly m.p. 65-66° (1.36 g, 51%). IR(Nujol): 3200, 1720, 1250, 1050 cm^{-1}. PMR(CCl_4): 4.77 ppm (br, 1H, HC-NH); 4.17, 4.00 ppm (dd, 1H,

HC,CH.NH); 3.60 ppm (s, 3H, $COOCH_3$); 1.05 ppm (s, 6H, 2 x tert Me); 0.78 ppm (s, 3H, tert Me). MS: m/e 265 (M^+, base peak). (Found: C, 73.24; H, 10.34; N, 4.97. $C_{16}H_{27}O_2N$ requires: C, 72.41; H, 10.26; N, 5.06%).

Norlongifolamine 9. A mixture of the urethane 8 (8.1 g), purified dioxane (peroxide-free, 60 ml) and 37% hydrochloric acid (115 ml) was refluxed (N_2-atmos, 48 hr). The mixture was cooled, diluted with water (200 ml) and extracted with benzene (100 ml x 2) to remove the unchanged urethane (2.6 g). The acidic aq. solution was basified with 20% aq. KOH (300 ml), extracted with ether (200 ml x 3), washed with water, brine and dried. Removal of solvent followed by distillation of the residue gave the pure amine 9: colourless liquid b.p. 150°/0.9 mm (4.2 g, 68%); $[\alpha]_D$ -47.50° (c, 0.40%). IR (smear): 3200, 1660, 1600 cm^{-1}. PMR(CCl_4): 3.25 ppm (d, 1H, HC.CHNH$_2$, J = 4 Hz); 1.03 ppm (s, 6H, 2 x tert Me), 0.77 ppm (s, 3H, tert Me). MS: m/e 207 (M^+). (Found: C, 80.93; H, 12.09; N, 6.32. $C_{14}H_{25}N$ requires: C, 81.09; H, 12.15; N, 6.76%).

N,N-Dimethyl norlongifolamine 10. A mixture of the amine 9 (8.2 g), formaldehyde soln. (35%, 30 ml) and formic acid (99%, 20 ml) was refluxed for 15 hr. The

mixture was cooled, diluted with water and basified with 10% aq. KOH soln. Extraction with ether (100 ml x 3), washing with water, brine, removal of solvent and distillation of the residue gave the dimethylamine 10: colourless liquid, b.p. 145°/0.8 mm (6.85 g, 73%); $[\alpha]_D$ -41.3° (c, 1.65%). IR (smear): 2650, 1060, 1040, 905 cm^{-1}. PMR (CCl_4): 2.07 ppm (s, 6H, NMe_2); 1.00 ppm (s, 6H, 2 x tert Me), 0.97 ppm (s, 3H, tert Me). MS: m/e 235 (M^+). (Found: C, 81.87; H, 12.43; N, 5.84. $C_{16}H_{29}N$ requires: C, 81.63; H, 12.42; N, 5.95%).

The methiodide 11 was prepared by treating the dimethylamine 10 (1.5 g) in dry methyl ethyl ketone (6 ml) with excess of MeI (5 ml) and refluxing for 3 hr. On removal of the solvent the crude methiodide was obtained which was recrystallized from acetone: white solid m.p. 260-61°. (Found: C, 53.36; H, 8.64; N, 3.14; I, 33.14. $C_{17}H_{32}NI$ requires: C, 54.12; H, 8.48; N, 3.80; I, 33.69%).

"Hofmann Elimination": Isolation of Norlongicyclene 12 and NN-dimethyl norlongifolamine 10. A mixture of the methiodide 11 (8.0 g), Ag_2O [freshly prepared by the addition of a soln. of $AgNO_3$ (8.0 g) in water (65 ml) to a soln. of NaOH (3.2 g) in water (10 ml)], water (90 ml) and MeOH (9 ml) was stirred at 30° for 3 hr. The precipitate was filtered, washed thoroughly with water and the combined

filtrates taken to dryness on the water bath/40 mm. The residue was transferred to another small distillation flask and pyrolysed [oil bath (230°)/45 mm]; the collected distillate was taken up in light petroleum (100 ml) and washed successively with 6N HCl (10 ml x 2), 5% aq. Na_2CO_3 and water. After drying and removal of solvent, the residue was distilled at 145°(bath)/0.8 mm (2.63 g); GLC showed two peaks at RRT 1.00 (7%) and RRT 2.43 (93%). The mixture was chromatographed on SiO_2 gel/IIa (90 g, 84 x 2 cm). Elution with light petroleum gave a pure (GLC, $AgNO_3$-TLC) hydrocarbon [b.p. 90°(bath)/0.9 mm, 0.17 g] identified as norlongicyclene 12 (IR, PMR). Elution with 5% MeOH-EtOAc followed by distillation of the residue gave a pure compound b.p. 145°(bath)/0.9 mm (2.0 g) identified as the dimethylamine 10 (IR, PMR).

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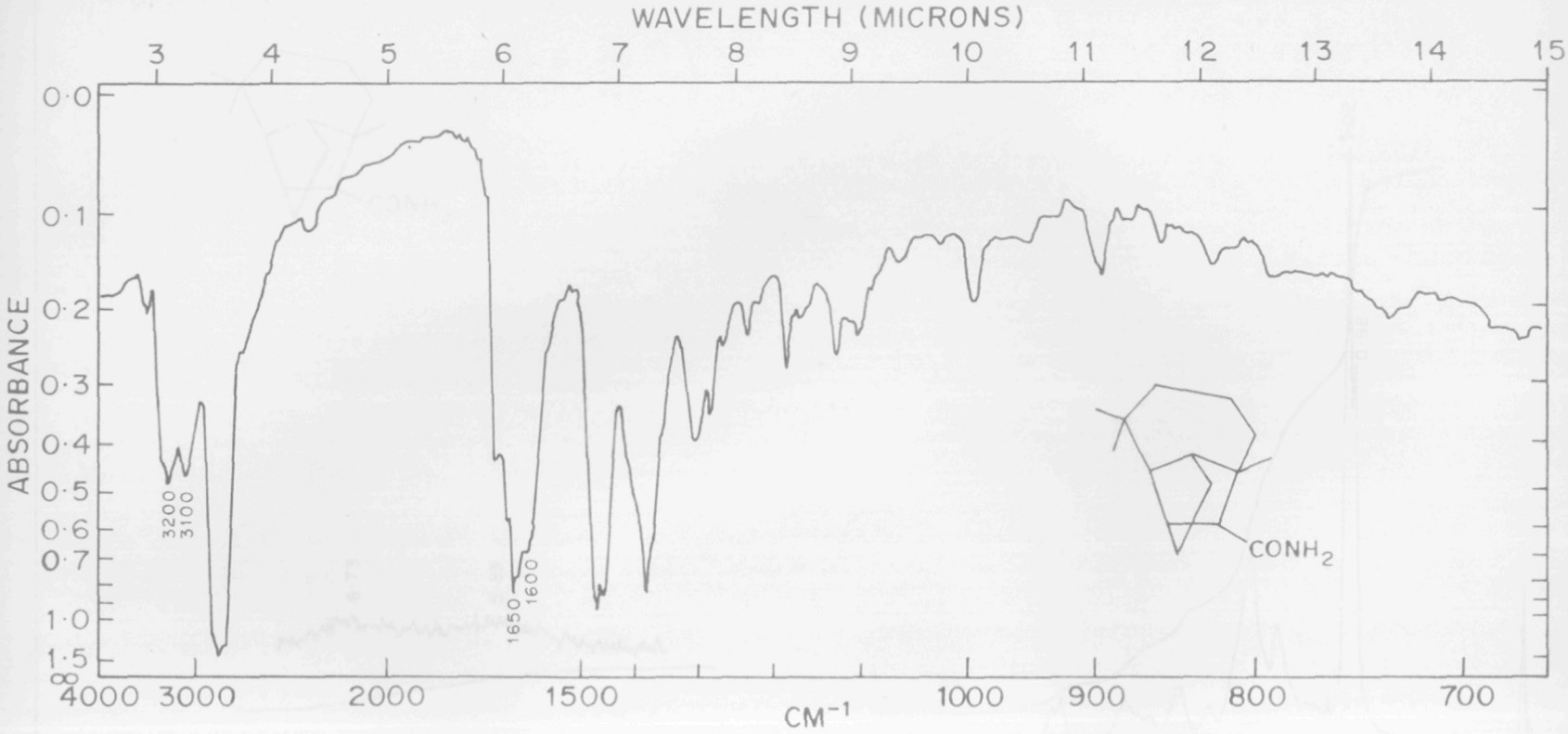


FIG. 1. IR SPECTRUM OF LONGIFOLAMIDE 7

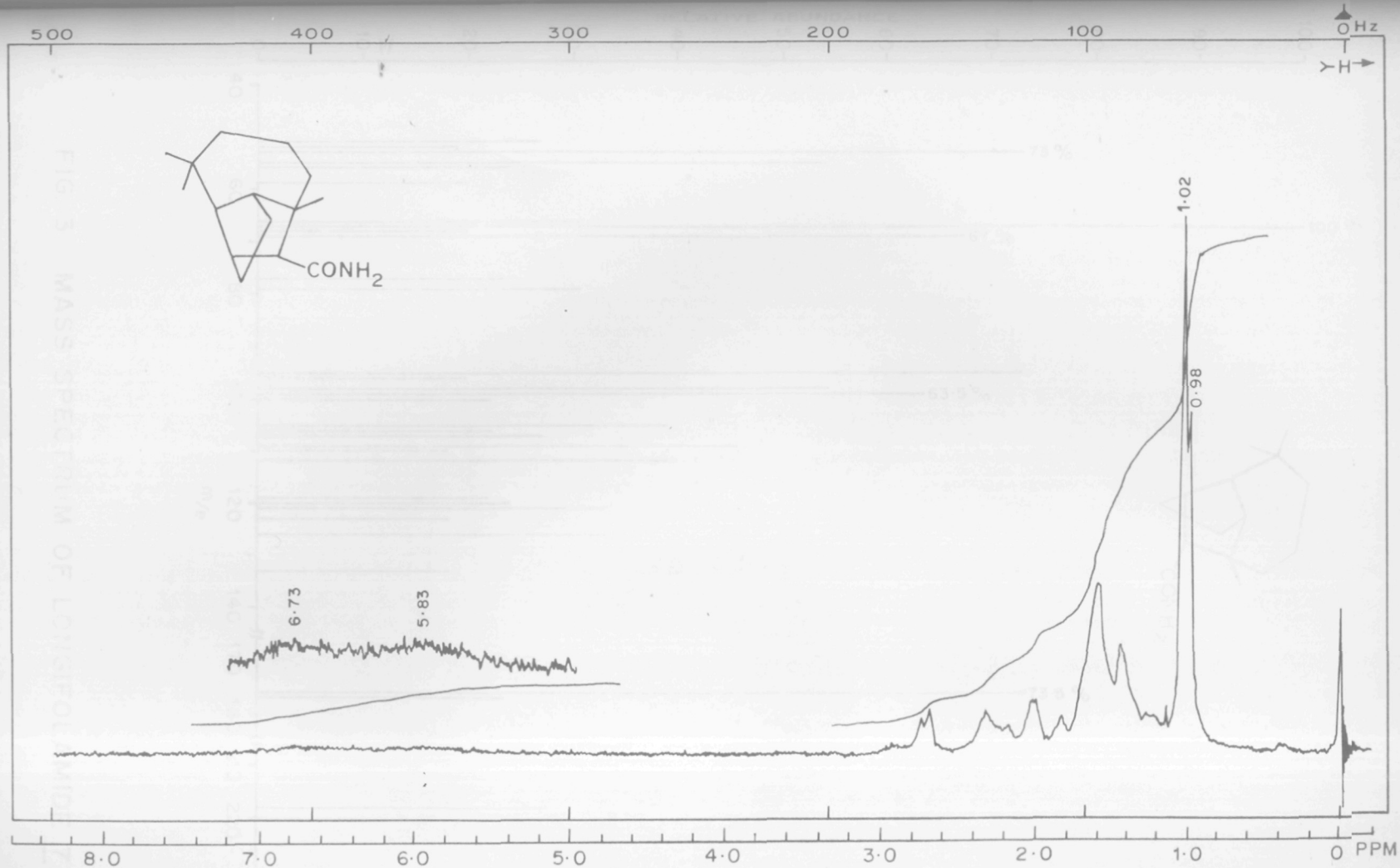


FIG. 2. PMR SPECTRUM OF LONGIFOLAMIDE 7

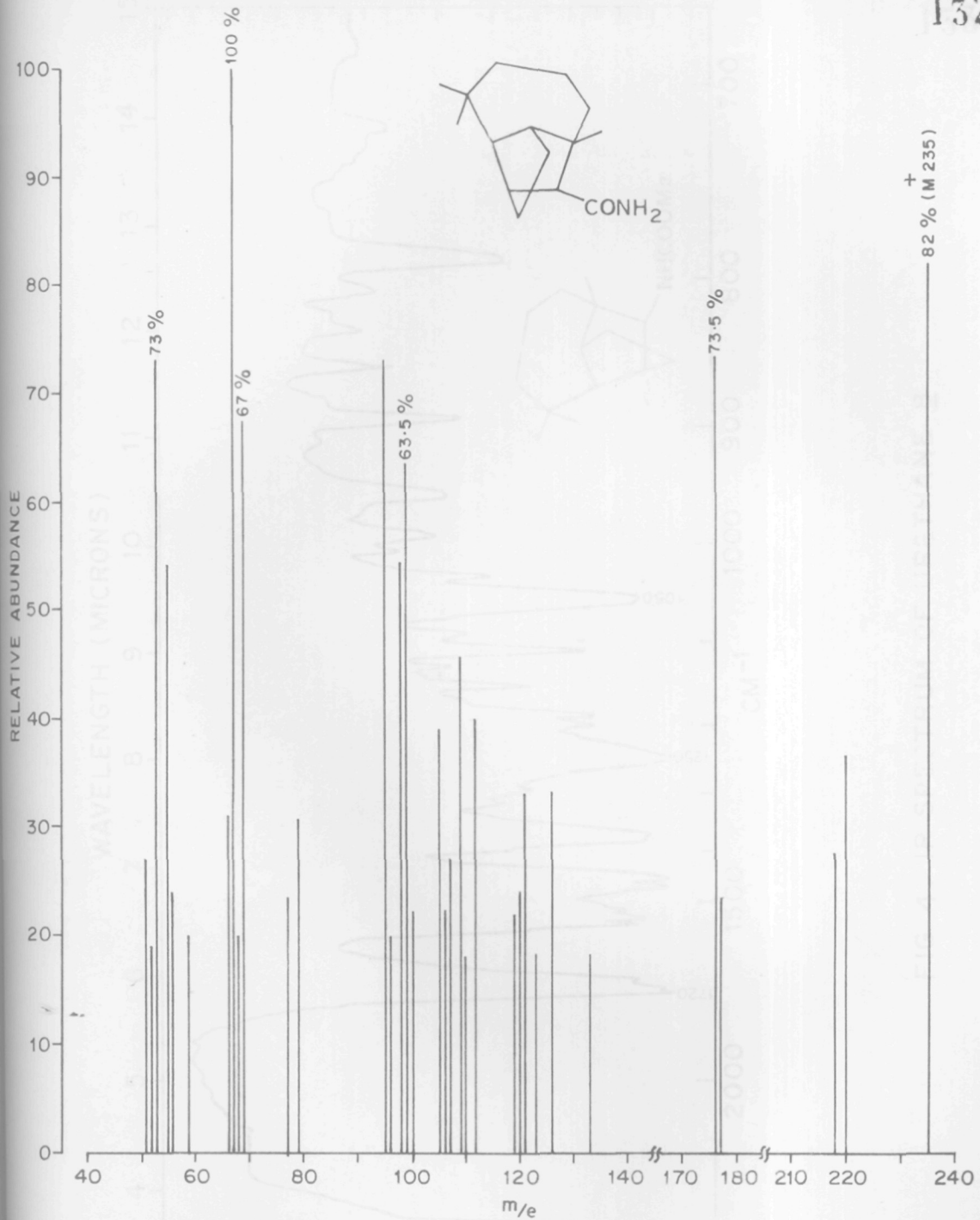


FIG. 3. MASS SPECTRUM OF LONGIFOLAMIDE 7

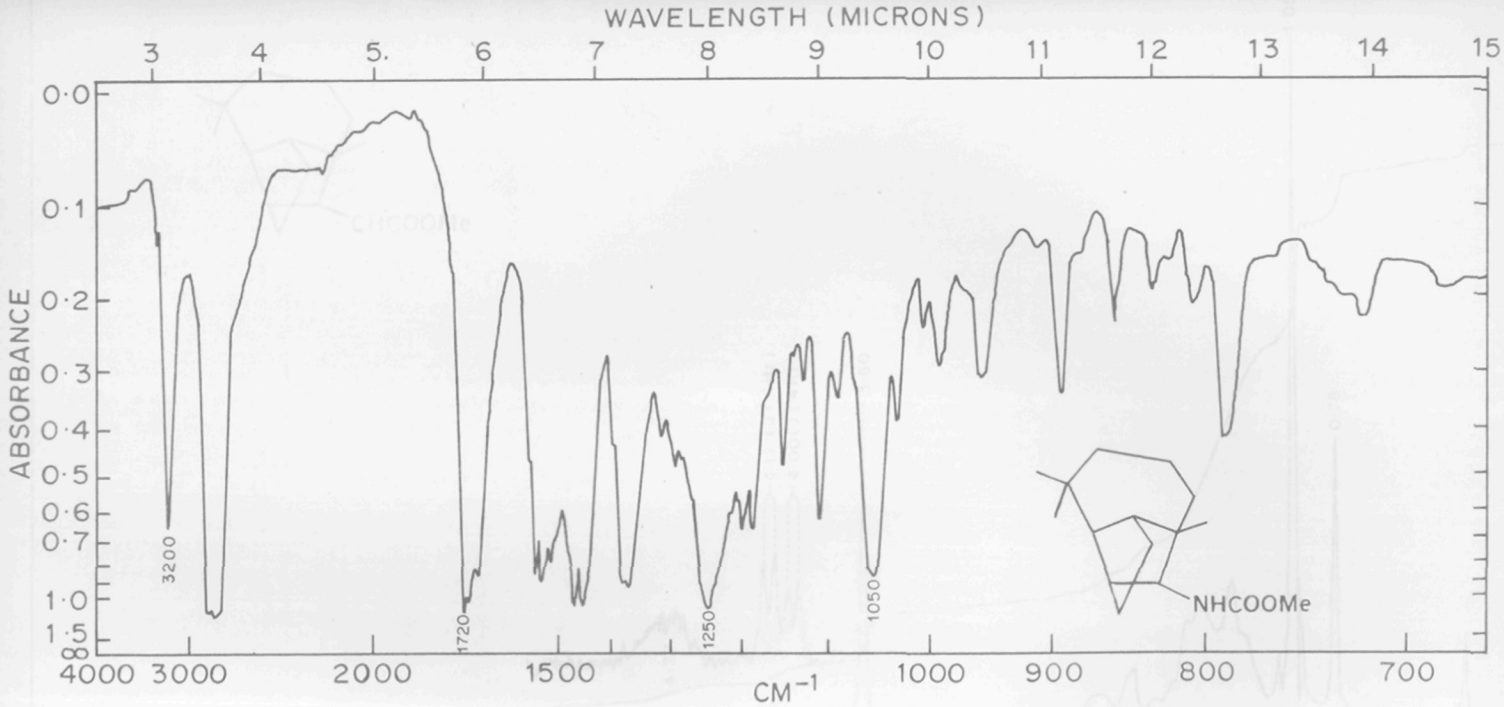


FIG. 4. IR SPECTRUM OF URETHANE 8

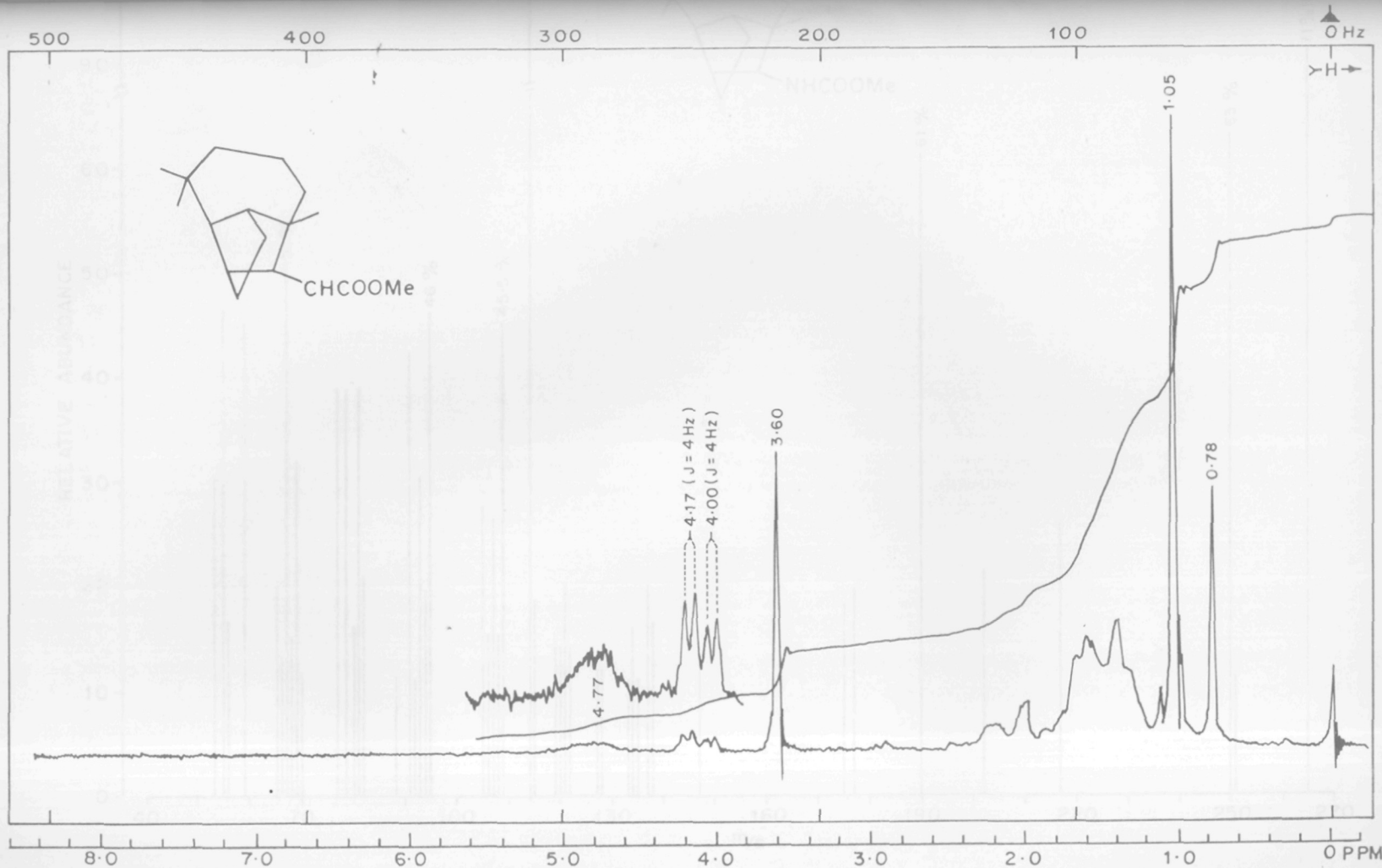


FIG. 5. PMR SPECTRUM OF URETHANE 8

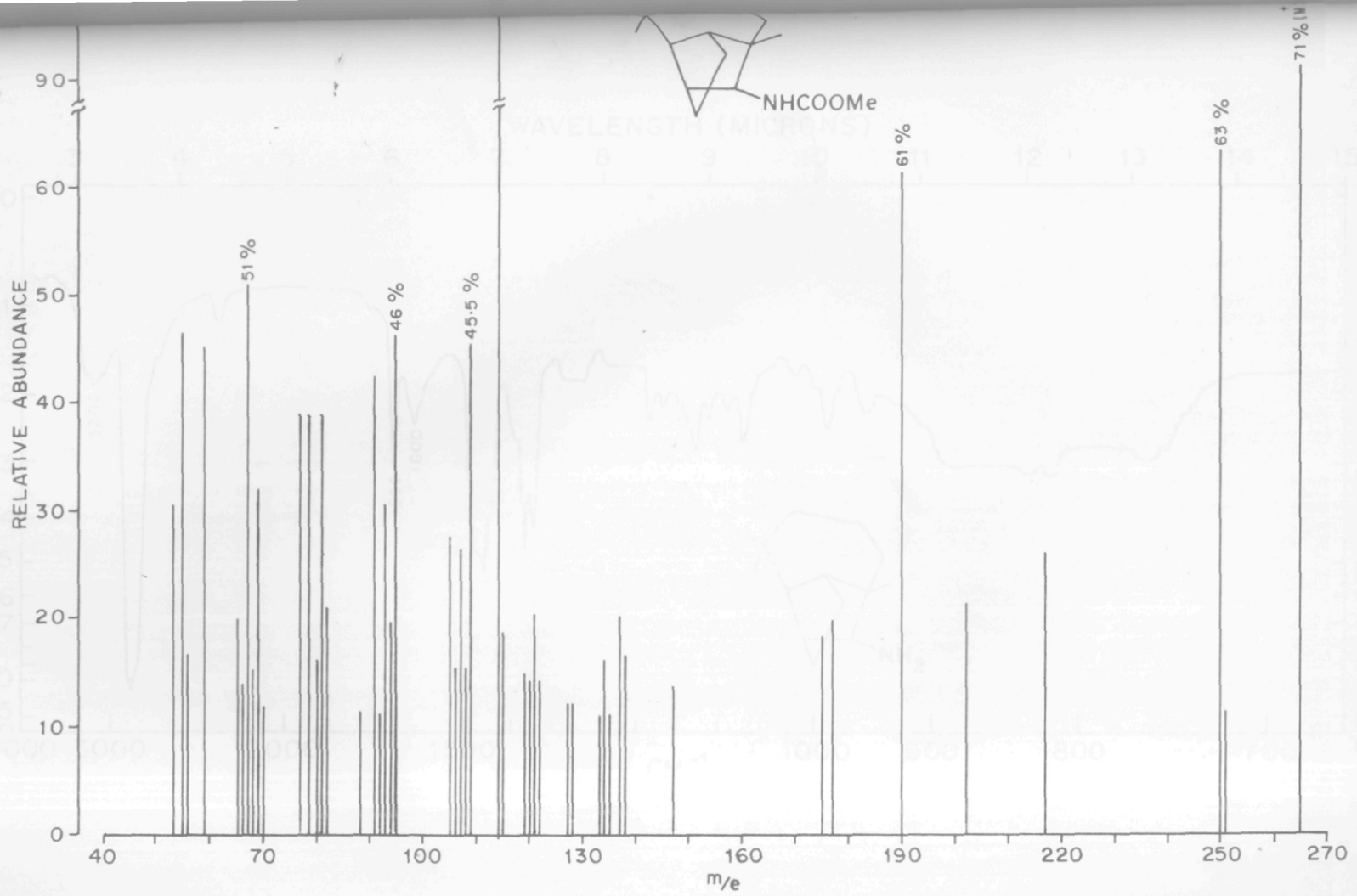


FIG. 6. MASS SPECTRUM OF URETHANE 8

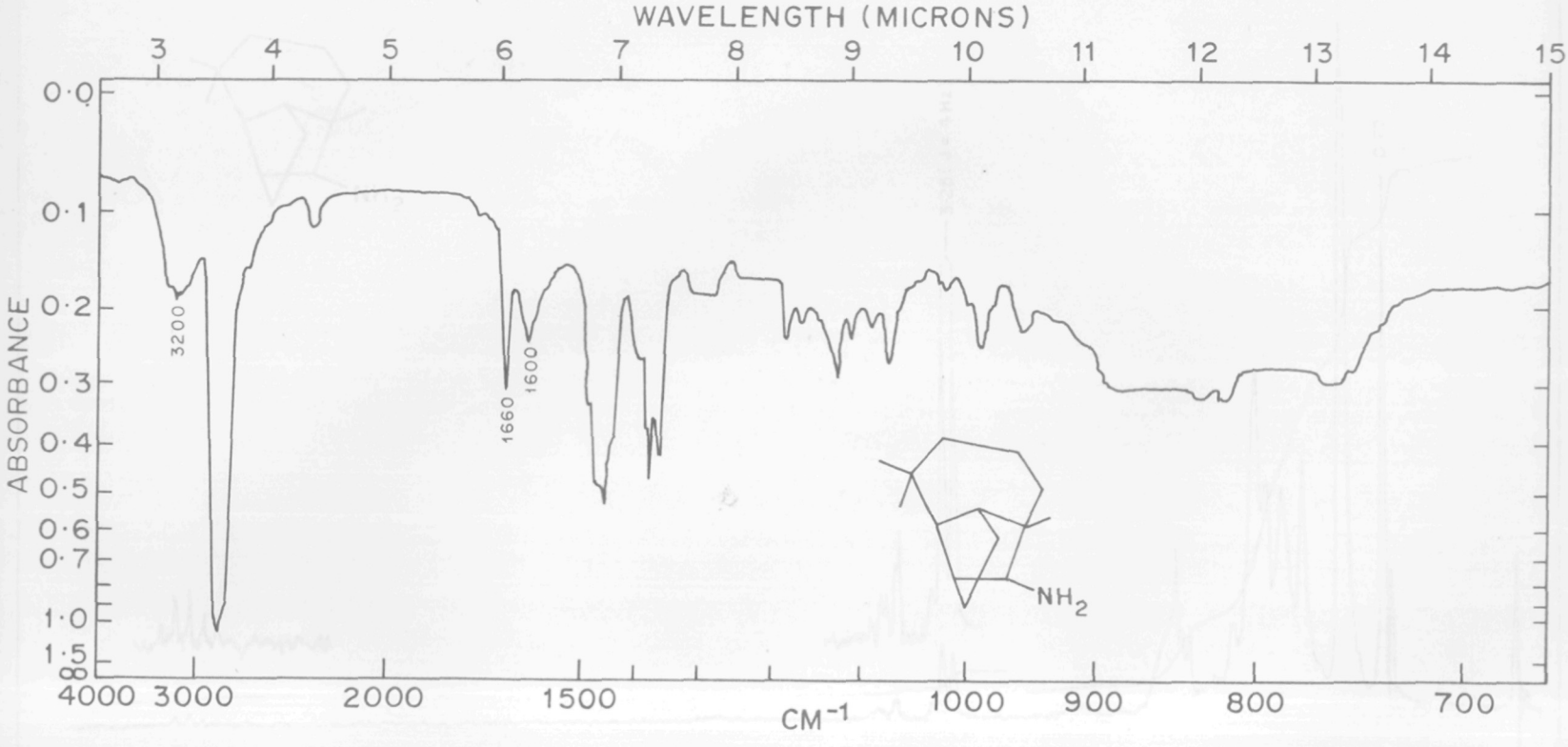


FIG. 7. IR SPECTRUM OF NORLONGIFOLAMINE 9

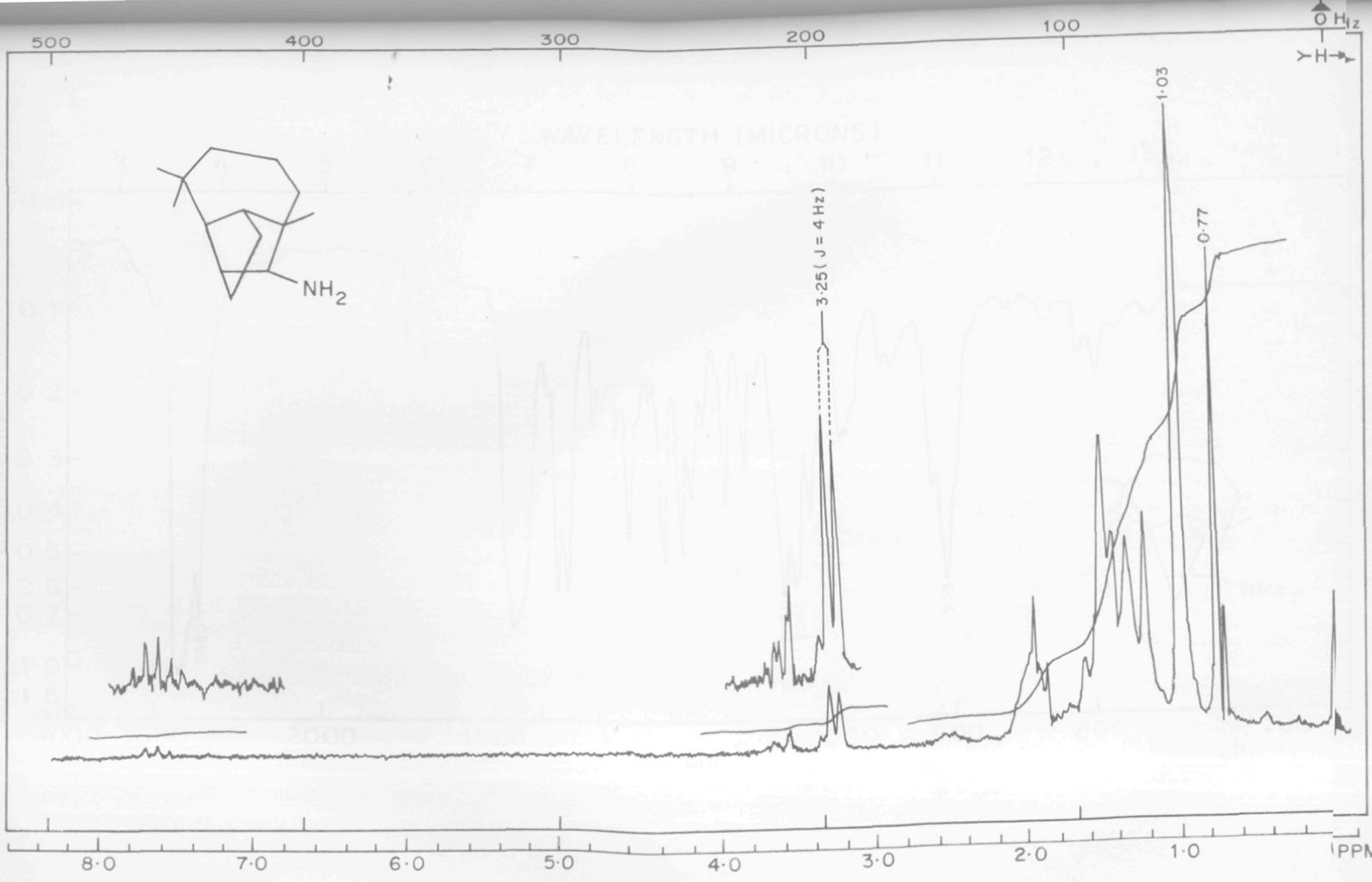


FIG. 8. PMR SPECTRUM OF NORLONGIFOLAMINE 9

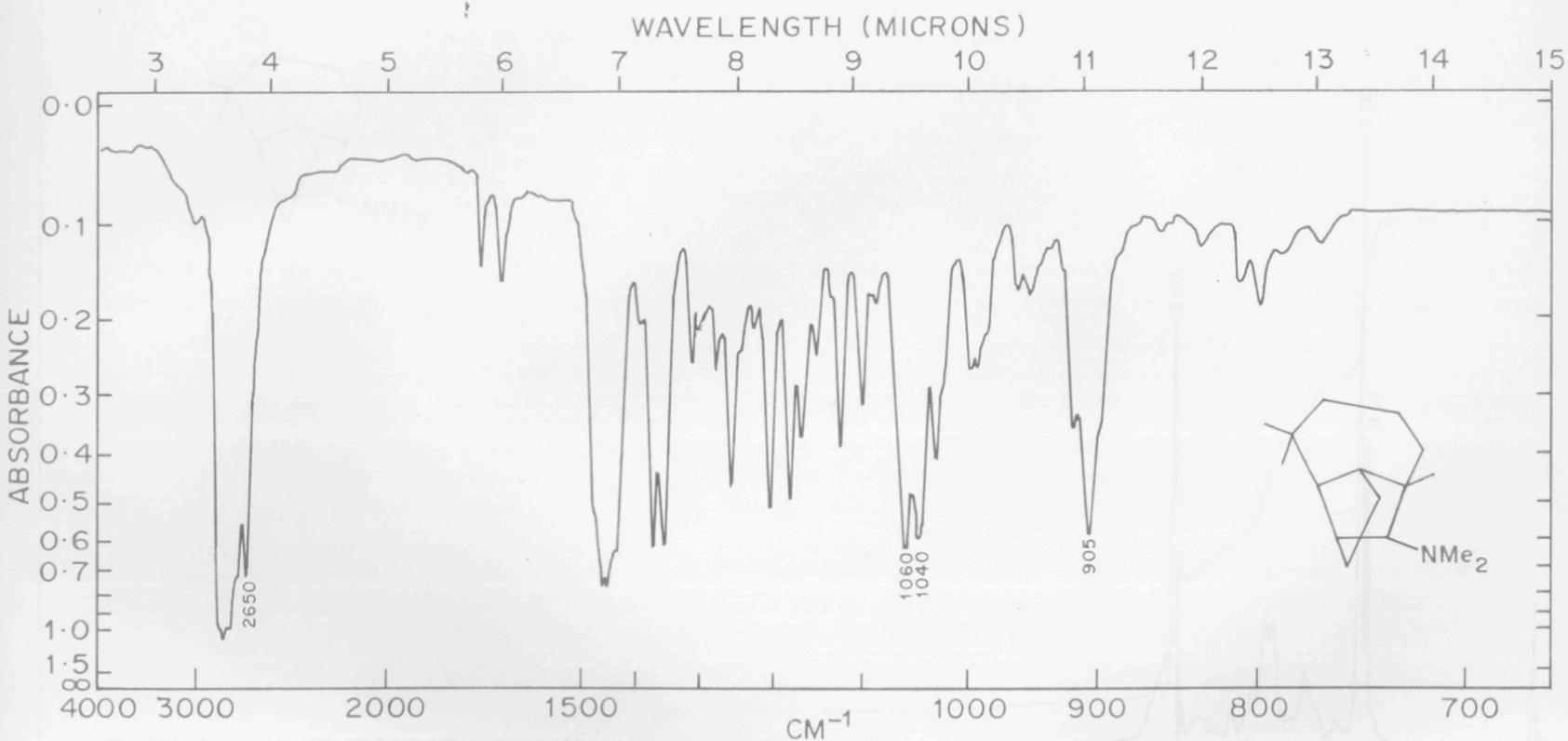


FIG. 9. IR SPECTRUM OF N,N-DIMETHYL NORLONGIFOLAMINE 10

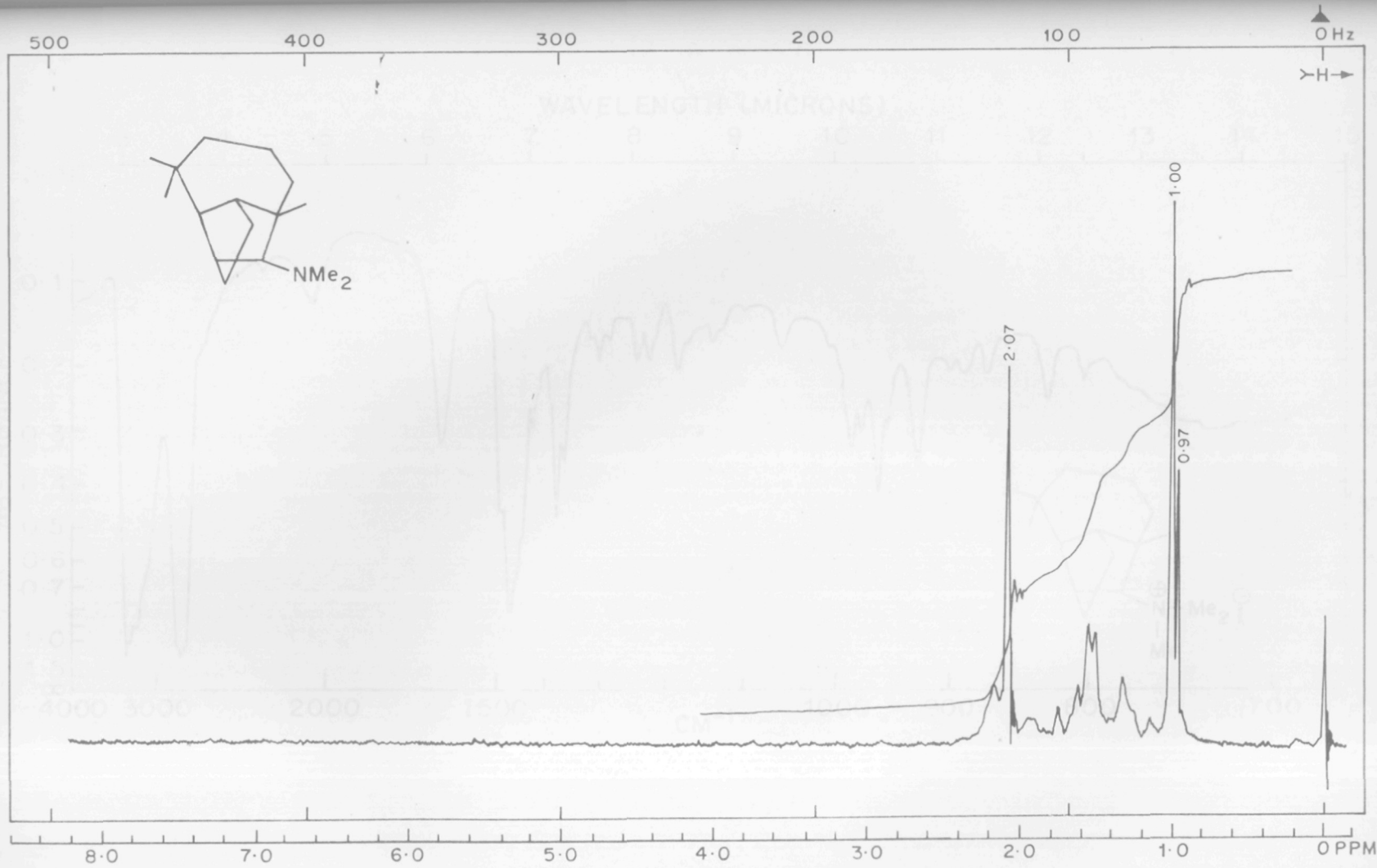


FIG. 10. PMR SPECTRUM OF N,N-DIMETHYL NORLONGIFOLAMINE 10

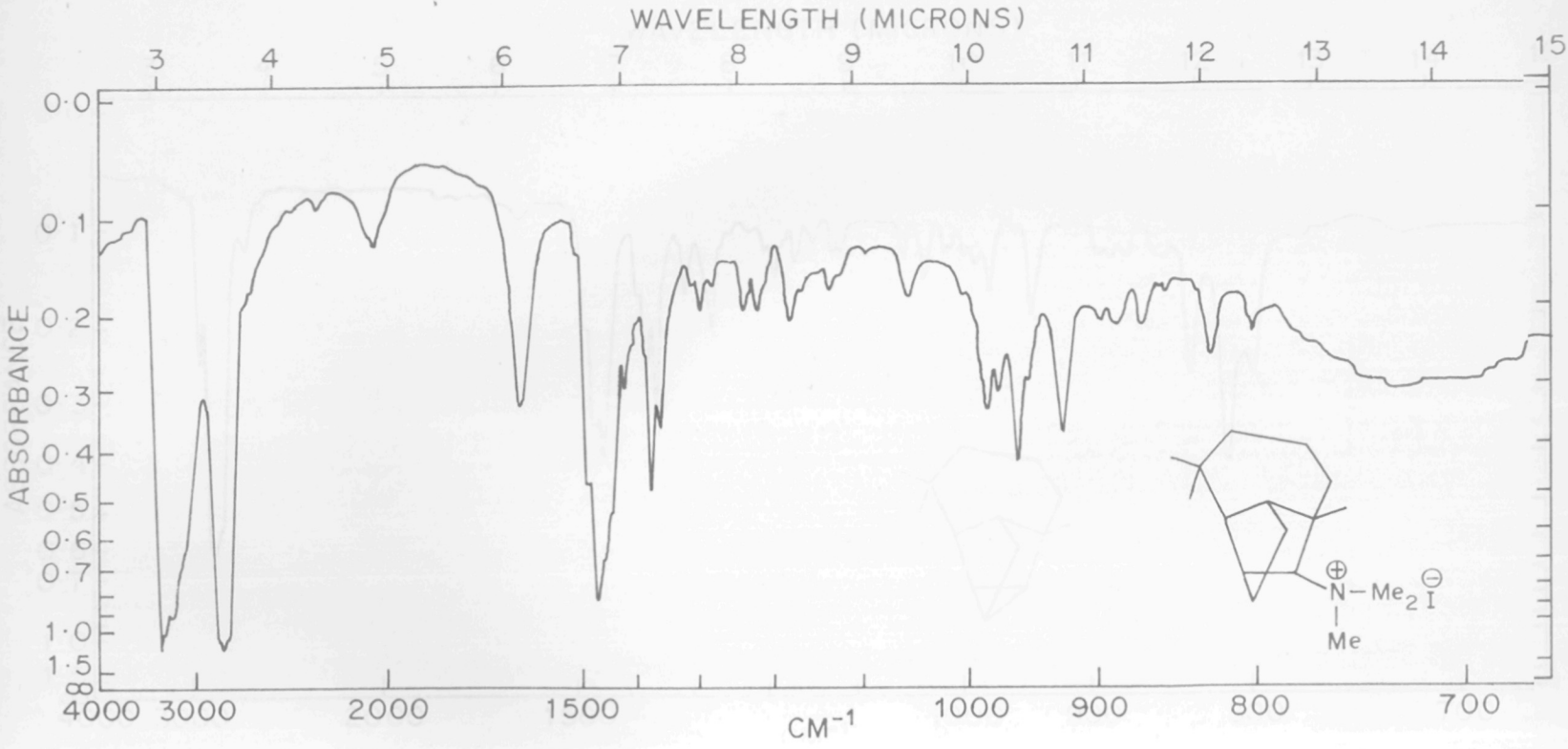


FIG. 11. IR SPECTRUM OF METHIODIDE 11

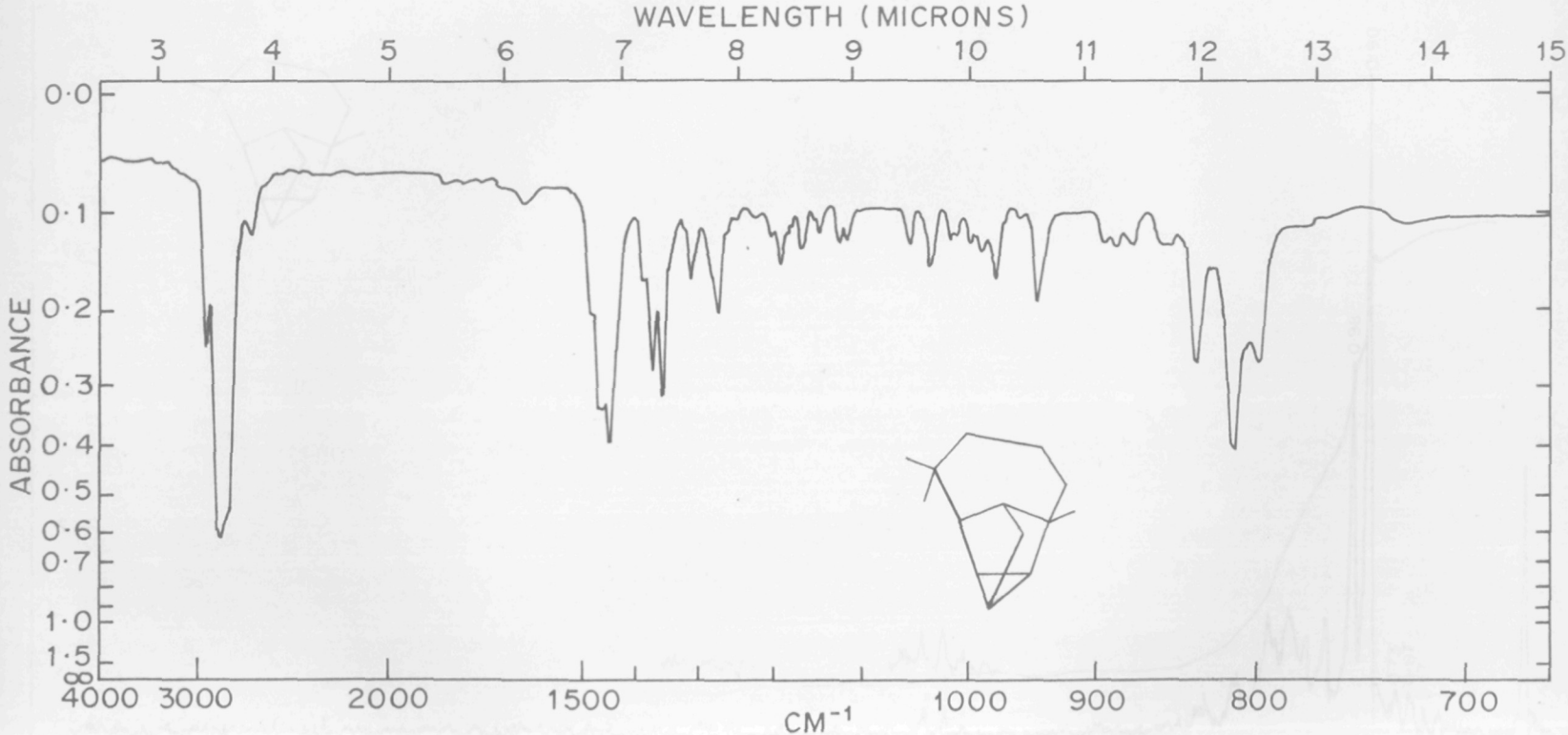


FIG. 12. IR SPECTRUM OF NORLONGICYCLENE 12

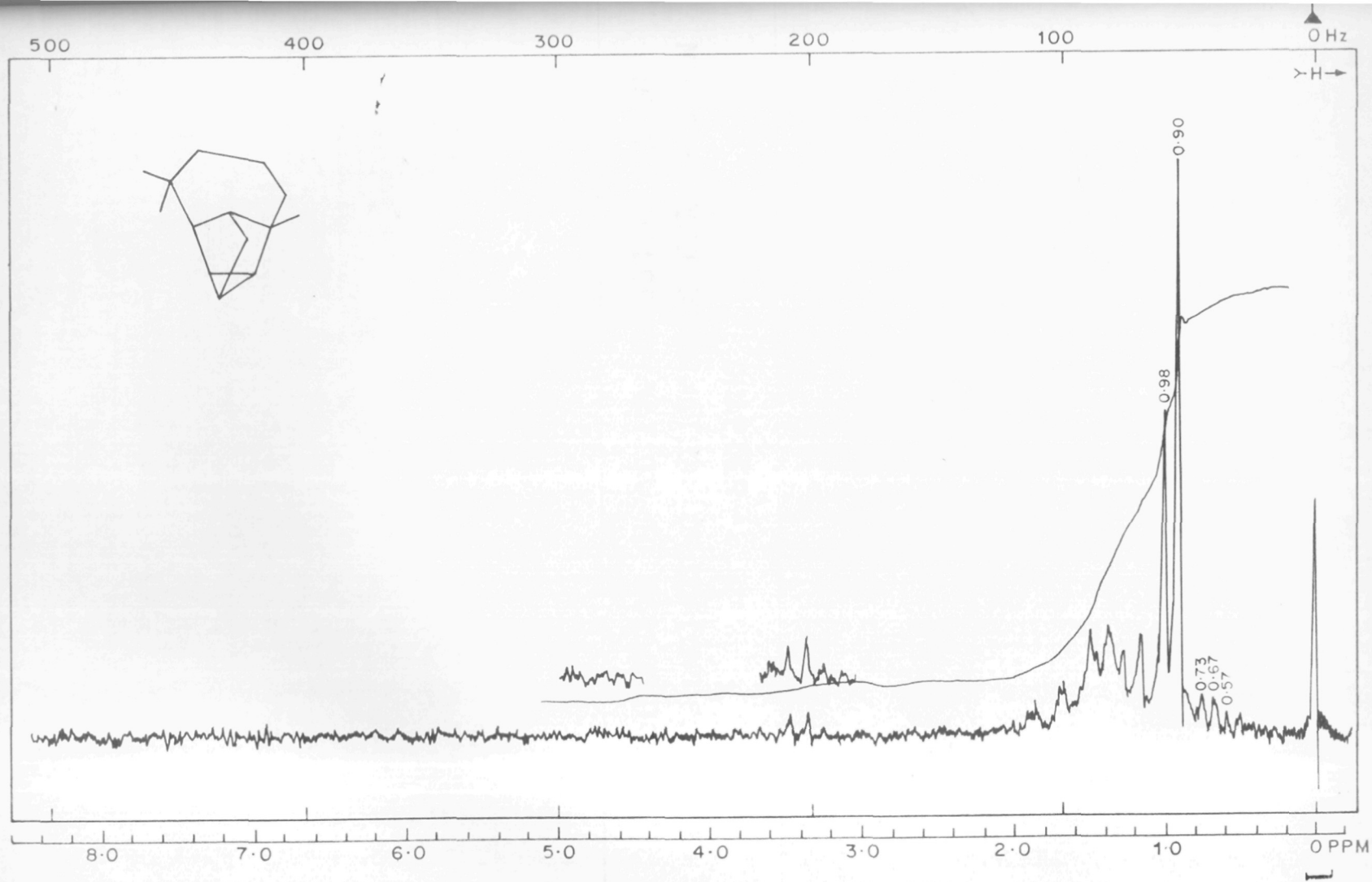


FIG. 13. PMR SPECTRUM OF NORLONGICYCLENE 12

CHAPTER – 2

NITROUS ACID DEAMINATION OF NORLONGIFOLAMINE: NOVEL CYCLOPROPANATION TO NORLONGICYCLENE

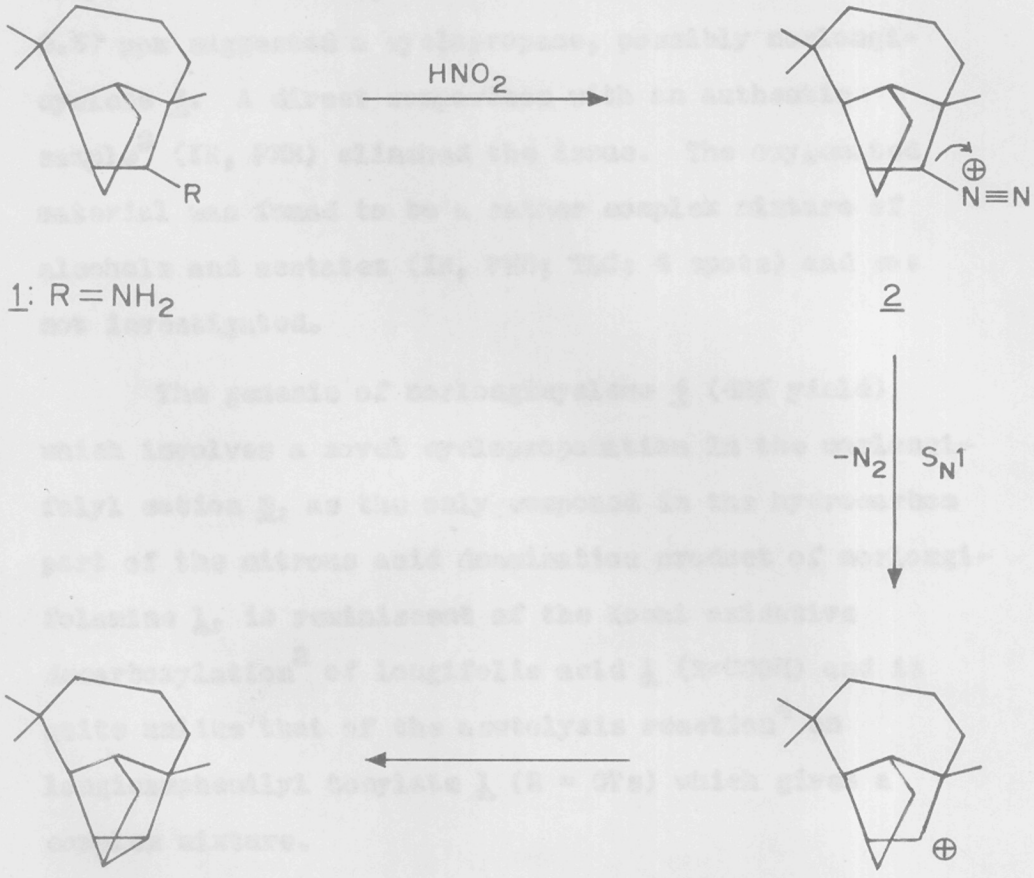
ABSTRACT

The fate of the norlongifolyl cation 3 (generated by the nitrous acid deamination of norlongifolamine 1), sterically-constrained for alkene formation in the normal course, has been studied: a novel cyclopropanation, resulting from a 1,3-proton loss, stabilizes 3 to procreate norlongicyclene in a fair yield (42%).

NITROUS ACID DEAMINATION OF NORLONGIFOLAMINE: NOVEL CYCLOPROPANATION TO NORLONGICYCLENE

Aliphatic/alicyclic diazonium salts, generated by the action of nitrous acid on primary amines, have never been isolated because they decompose almost instantly to the parent carbonium ions and molecular nitrogen. Alcohols and alkenes of both rearranged and intact structures are formed and this multiplicity[1] of products usually prevents its use as a practical reaction. The generation and study of the fate of the norlongifolyl cation 3 via the diazonium ion 2 from norlongifolamine 1, by the action of nitrous acid, offered interesting theoretical possibilities in view of the steric-constraints imposed in 3 for alkene formation in the normal course.

The preparation of norlongifolamine 1 from longifolic acid 1 (R=CO$_2$H) via the Hofmann bromamide route[2] has been described by us recently. When the amine 1 in acetic acid was treated with aqueous sodium nitrite, evolution of nitrogen readily took place and gave a mixture of oxygenated and non-oxygenated products (85% yield). On chromatography over silica gel and elution with light petroleum, the hydrocarbon was easily separated. Homogeneous by GLC and $AgNO_3$-TLC it analysed for $C_{14}H_{22}$ (M^+ 190); a



1: R = NH_2

2

3

4

faint yellow colour with tetranitromethane but a transparent olefinic region in the PMR spectrum coupled with weak high-field singlets at 0.73, 0.67, 0.57 ppm suggested a cyclopropane, possibly norlongicyclene 4. A direct comparison with an authentic sample[3] (IR, PMR) clinched the issue. The oxygenated material was found to be a rather complex mixture of alcohols and acetates (IR, PMR; TLC: 4 spots) and was not investigated.

The genesis of norlongicyclene 4 (42% yield) which involves a novel cyclopropanation in the norlongifolyl cation 3, as the only compound in the hydrocarbon part of the nitrous acid deamination product of norlongifolamine 1, is reminiscent of the Kochi oxidative decarboxylation[3] of longifolic acid 1 (R=COOH) and is quite unlike that of the acetolysis reaction[4] on longicamphenilyl tosylate 1 (R = OTs) which gives a complex mixture.

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

Light petroleum refers to the fraction b.p. 60-80°. Solvent extracts were dried over anhydrous Na_2SO_4.

IR spectra were recorded on a Perkin-Elmer Infracord model 137-E. PMR spectra were measured in 10-20% CCl_4 solution on a Varian T-60 spectrometer using TMS as internal standard. Mass spectra were measured on a CEC spectrometer model 21-110B using an ionizing voltage of 70 eV and a direct inlet system.

Norlongifolamine 1. This was prepared from longifolic acid via the bromamide degradation as described[2] earlier.

Nitrous acid deamination of norlongifolamine 1: Isolation of norlongicyclene 4. To a magnetically-stirred mixture of norlongifolamine 1 (2.0 g) in AcOH (2.2 ml) and water (0.4 ml), cooled in ice water, was added dropwise, a soln. of $NaNO_2$ (1.0 g) in water (3 ml). After 15 minutes the mixture was heated on the waterbath for another 15 minutes for complete evolution of N_2. The mixture was cooled, basified with 2% aq. KOH (20 ml), extracted with ether (20 ml x 3), washed with water, brine and dried. Distillation of the residue gave a liquid mixture b.p. 80-110°/0.8 mm (1.66 g) which was chromatographed on

SiO_2 gel/IIa (60 g; 57 cm x 1.5 cm) with TLC monitoring: Fr.(a), light petroleum 50 ml x 4, pure; Fr.(b), 5% MeOH in EtOAc 50 ml x 6, mixture.

Fr.(a) was distilled: colourless liquid, b.p. 75°/0.8 mm (0.74 g) identified as norlongicyclene[3] (IR, PMR, Mass).

Fr.(b) was distilled: b.p. 130°(bath)/0.8 mm (0.58 g). Mixture of alcohols and acetates (IR, PMR; TLC: 4 spots); not investigated.

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PART – IV

NEW LONGIFOLANE – BASED AMIDES

CHAPTER-1

EPIMERIZATION OF LONGIFOLENE / CAMPHENE-DERIVED SECONDARY CARBOXYLIC ACIDS WITH THIONYL CHLORIDE

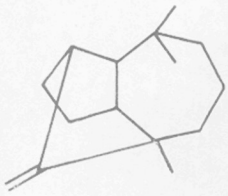
ABSTRACT

Reaction of terpene-derived secondary carboxylic acids with thionyl chloride followed by exposure to warm alkali constitutes a convenient method for generating the thermodynamically more stable, epimerized acids: α-longiforic acid 2 → β-longiforic acid 3, longifolic acid 4 → isolongifolic acid 5 and camphenilanic acid 7 → isocamphenilanic acid 8.

EPIMERIZATION OF LONGIFOLENE/CAMPHENE-DERIVED SECONDARY CARBOXYLIC ACIDS WITH THIONYL CHLORIDE

The configurational change of the carboxyl group occurring during the epimerisation of a secondary acid is important from two view points: (a) the process generates the thermodynamically more stable epimer and (b) the new spatial disposition of the carboxyl group, relative to another intramolecular functionality, can be strategically significant in some cases. For example, epimerisation of the secondary carboxyl group of α-longiforic acid 2 (a 5,7-bicyclic cis-1,4-dicarboxylic acid from longifolene 1) into the trans β-longiforic acid 3 was of vital importance to prevent lactam formation in the Schmidt[1] reaction on 2. In this connection, the reported cumbersome method of epimerisation by heating 2 with HBr[2] in AcOH in a sealed tube at 140° was simplified by us and the transformation was easily achieved by exposing the molten acid 2 to p-TsOH[3] catalyst (250°/5 minutes). The use of thionyl chloride in the epimerization of three terpene-derived carboxylic acids is now described in this communication.

The distinctly different, epimeric, longifolene-derived monobasic acids-longifolic acid[4] (exo, 4)/isolongifolic acid[4] (endo, 5) - on reaction with thionyl chloride at reflux (3 hr)



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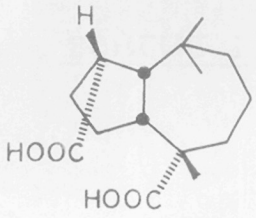

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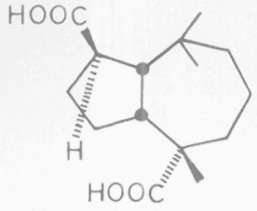

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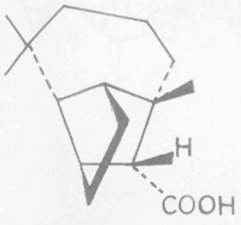

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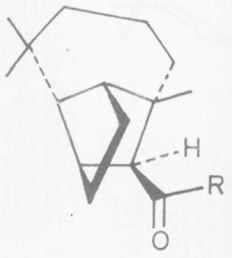
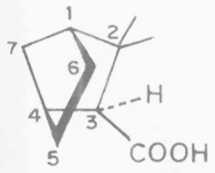


5 : R = OH

6 : R = Cl



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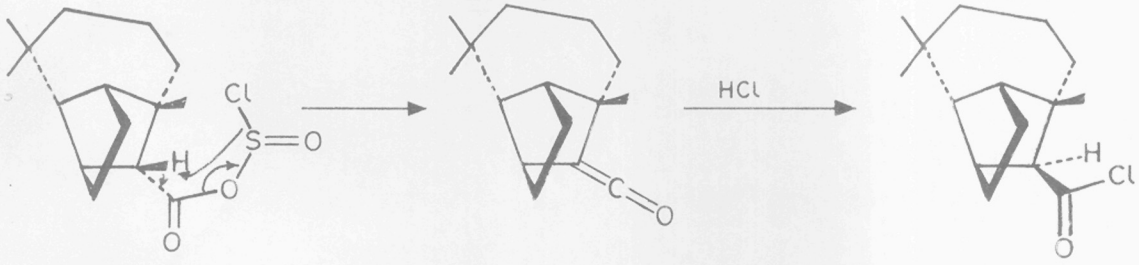
8 : C-3 epimer

SCHEME I



9 10 6

unexpectedly gave the same acid chloride (IR, PMR) which was characterized as 6 since on exposure to warm alkali it furnished pure isolongifolic acid 5; in the case of 4 this transformation constitutes an epimerization. Under the same reaction conditions, epimerization was also achieved with two other substrates: 2 → 3 and the camphene-derived camphenilanic acid 7 → isocamphenilanic acid[5] 8.

Conceivably, the initially formed mixed anhydride 9 (in the case of longifolic acid 4) generates the ketene 10 which then reacts with HCl (also formed in the reaction) to produce the more stable, inverted acid chloride 6 as shown in Scheme I.

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

Recorded temperatures are uncorrected. IR spectra were taken on a Perkin-Elmer Infracord model 137-E. PMR spectra were measured in CCl_4 on a Varian T-60 spectrometer.

General procedure for epimerization

A mixture of the appropriate acid and $SOCl_2$ (excess) was refluxed on a waterbath for 3 hr (gas absorption trap), with frequent swirling. After removing the excess of $SOCl_2$ completely, the residue was distilled under vacuum to furnish the pure acid chloride.

A mixture of the acid chloride and an excess of 10% aq. KOH solution was warmed on a water bath till the former dissolved in the alkaline phase (15 minutes). Acidification with conc. HCl (Congo red), filtration of the precipitated solid followed by recrystallisation from MeCN (or EtOAc) gave the pure epimerized acid. In each case purity of the product was established by direct comparison with the spectra (IR, PMR) of an authentic sample (acid/methyl ester). The results have been summarized in Table I.

TABLE I - EPIMERIZATION OF SECONDARY CARBOXYLIC ACIDS WITH $SOCl_2$

Acid	m.p.	Wt.	$SOCl_2$	Epimerized acid	m.p.	Yield
2	226-27°	1.34 g	5 ml	0.93 g	198-99°	55%
4	143-44°	2.36 g	5 ml	2.15 g	136-37°	91%
7	75-76°	2.61 g	5 ml	2.00 g	117-18°	77%

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CHAPTER - 2

NEW LONGIFOLANE - BASED SATURATED AND $\alpha\beta$ - UNSATURATED AMIDES

ABSTRACT

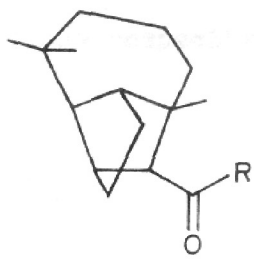
Primary/secondary/tertiary methyl amides and isobutylamides of the saturated isolongifolic acid 2 and the α,β-unsaturated Prins acid 3 derived from longifolene 1, when prepared and tested for their possible insecticidal response, were found to be quite inactive. The biological passivity of the amides notwithstanding, the allylic methine resonances of the α,β-unsaturated carbonyl derivatives 8 → 11 have provided additional PMR support to the E-configuration 3 assigned earlier for the Prins acid.

NEW LONGIFOLANE-BASED SATURATED AND α,β-UNSATURATED AMIDES

Many naturally-occurring isobutylamides[1] of long-chain fatty acids (C_{10}-C_{18}) are known to possess a pyrethrin-like insecticidal activity. Amide derivatives of mono- and sesquiterpenoid substrates apparently have not been studied for their insecticidal activity so far. Our abiding interest in the chemistry[2]/utilization of the abundant Chir pine sesquiterpene-longifolene 1, prompted us to prepare a variety of amides of the saturated/unsaturated acids (e.g. isolongifolic acid[3] 2/Prins acid[4] 3), easily derived from 1, for the possible exploitation of their biological activity.

Eight amides (4 to 11) were prepared by reaction of the acid chloride of 2 / 3 in benzene with the appropriate amine (NH_3, $MeNH_2$, Me_2NH or $Me_2CH.CH_2NH_2$). The physical/analytical data of the various amides have been recorded in Table 1 and their spectral data (IR, PMR) given in Table 2. When screened for their insecticidal activity against yellow fever mosquito larvae (Aedes aegypti), none of the eight amides 4 → 11 showed any significant response (0% at 10 ppm); in the absence of even the slightest positive lead, further work in this direction appeared futile and has been discontinued.

1



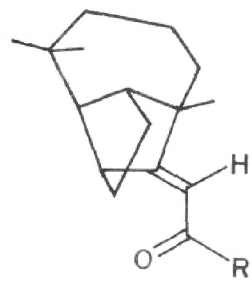
2: R = OH

4: R = NH_2

5: R = NHMe

6: R = NMe_2

7: R = $NHCH_2CHMe_2$



3: R = OH

8: R = NH_2

9: R = NHMe

10: R = NMe_2

11: R = $NHCH_2CHMe_2$

The biological passivity of the amides notwithstanding, the allylic methine resonance of the α,β-unsaturated carbonyl derivatives 8 → 11 have provided additional PMR support to the E-configuration 3 assigned earlier[4] for the Prins acid; the strong deshielding[4] (1.47 ppm) of the allylic methine (at 4.05 ppm) in the methyl ester of 3 (with respect to that of 1) is also borne out nicely in the amide derivatives 8 → 11 (4.10, 4.20, 3.77 and 4.10 ppm respectively; see Table 2).

TABLE 1 - PHYSICAL/ANALYTICAL DATA OF LONGIFOLANE-BASED AMIDES

Amide	m.p./b.p. (bath)	Mol. formula	Yield %	M^+	Found %			Calc. %		
					C	H	N	C	H	N
4	106-107°	$C_{15}H_{25}ON$	56	235	75.70	10.51	5.36	76.54	10.71	5.95
5	159-160°	$C_{16}H_{27}ON$	72	249	77.09	11.02	5.35	77.06	10.91	5.62
6	165-170°/ 0.7 mm	$C_{17}H_{29}ON$	76	263	76.10	10.99	5.12	77.51	11.08	5.33
7	140-141°	$C_{19}H_{33}ON$	34	291	78.78	11.62	4.31	78.29	11.41	4.81
8	143-144°	$C_{16}H_{25}ON$	72	247	77.27	10.34	5.36	77.68	10.19	5.66
9	163-164°	$C_{17}H_{27}ON$	71	261	78.10	10.46	5.09	78.11	10.41	5.36
10	200-205°/ 0.6 mm	$C_{18}H_{29}ON$	70	275	79.23	10.70	4.99	78.49	10.61	5.09
11	158-159°	$C_{20}H_{33}ON$	42	303	78.58	11.01	4.74	79.15	10.96	4.62

TABLE 2 - IR/PMR SPECTRAL DATA OF LONGIFOLANE-BASED AMIDES

Amide	IR* (cm^{-1})	PMR (CCl_4; ppm)			
		olefinic H	allylic methine	N-Me	methyls
4	3200,3100,1650,1600	-	-	-	1.02,1.02,0.98 (all s)
5	3100,1640,1550,1530	-	-	2.68 (d, 3H,J=6 Hz)	1.00,0.95,0.95 (all s)
6	1640	-	-	2.97 (br.s 6H,NMe_2)	1.03,1.00,1.00 (all s)
7	3200,1650,1555	-	-	-	1.02,0.97,0.97 (all s); 0.90 (d, $CHMe_2$, J=7 Hz)
8	3300,3100,3000,1650, 1600	5.37(s, 1H)	4.10(br d, 1H)	-	1.00,0.93,0.93 (all s)
9	3100,1650,1610,1540	5.40 (s,1H)	4.20(br d, 1H)	2.77(d,3H, J=5 Hz)	0.97,0.93,0.93 (all s)
10	1650,1610	5.67 (s,1H)	3.77(br d, 1H)	3.00(s,6H, NMe_2)	1.03,0.97,0.97 (all s)
11	3150,3000,1660,1625, 1550	5.23 (s,1H)	4.10(br d, 1H)	-	1.00,1.00,0.95 (all s) 0.93 (d, $CHMe_2$, J = 8 Hz)

*In Nujol (solids) and smear (liquids).

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

Recorded temperatures are uncorrected. Light petroleum refers to fraction b.p. 60-80° (essentially hexane). Solvent extracts were dried over anhydrous Na_2SO_4. IR spectra were recorded on a Perkin-Elmer Infracord model 137-B. PMR spectra were taken on a Varian T-60 spectrometer. Mass spectra were obtained on a CEC spectrometer model 21-110B using an ionizing voltage of 70 eV and a direct inlet system.

Ammonia (28% aq. solution), methylamine and dimethylamine (both 38% aq. solution) were used. Isobutylamine was freshly distilled, b.p. 65-67°.

General procedure for amides using aqueous solutions of amines

A typical procedure for the N-methyl amide 9 from the unsaturated acid 3 is described.[5]

Prins acid[4] 3 (2.5 g) and $SOCl_2$ (5 ml) was refluxed on the waterbath for 3 hr and the reaction mixture taken to dryness to furnish the crude acid chloride.

Methylamine solution (23 ml) was taken in a 3-necked flask fitted with a stirrer, dropping funnel and condenser (connected to a gas absorption trap at the

top). The flask was cooled in an ice-salt bath and the acid chloride in dry benzene (20 ml) was added dropwise to the stirred solution. Stirring was continued for 4 hr and the mixture left overnight at room temperature. The mixture was diluted with water (100 ml), the benzene layer was separated and the aqueous part extracted with benzene (50 ml x 3). The combined extracts were washed with 5% aq. KOH (2 x 50 ml) to remove any acid. The organic layer was washed with water, brine and dried. Removal of solvent gave the crude N-methyl amide 9 which was recrystallised from light petroleum: colourless needles, m.p. 163-64° (1.85 g, 71%).

General procedure for isobutylamides

The procedure for ω-carboxylongifolene isobutylamide 11 is typical. The crude acid chloride from the Prins acid 8 (1.8 g) in dry benzene (30 ml) was cooled in ice water and treated with isobutylamine (3 ml) while stirring. The mixture was left overnight at room temperature and refluxed on the waterbath for 0.5 hr. Water (7 ml) was then added and further heated for 15 minutes. The benzene layer was separated, diluted with more benzene (50 ml), washed with 5% aq. KOH (2 x 25 ml), water, brine, dried and the solvent removed to furnish the crude amide 11 which was recrystallised from light petroleum: colourless crystals m.p. 158-59° (0.92 g, 42%).

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