PARTIAL SYNTHESIS OF CHAKSINE

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ABSTRACT

This thesis is concerned with the preliminary studies in the synthesis of a monoterpenoid alkaloid, chaksine.

Ethyl 2-methylcyclohexanone-6-carboxylate (XI) was hydroxymethylated with formaldehyde to give Ethyl 2-methyl-6-hydroxymethylcyclohexanone-6-carboxylate (XII). Tosylation and cleavage of this product gave 2-methyl-6-carbethoxy-6-heptenoic (XIV) acid along with the diethyl ester (XIVa). Ozonolysis of the diethyl ester yielded diethyl 2-keto-6-methyl pimelate (XV). A Wittig reaction with diethyl cyanomethyl phosphonate (XVI) gave 1-cyano-6-methyl-1-cyano-2, 6-dicarbethoxy-1-heptene (XVII).

Other related studies involved: 1) Preparation of ethyl 2-methyl-6-vinylcyclohexanone-6-carboxylate (XXII). 2) A new method for preparation of 2-imidazolidones (XXIV). 3) Preparation of 1-phenyl-2-aldehydo-6-methyl-1, 6-heptadiene (XXXIII) and 1-n-butylthio-2-aldehydo-6-methyl-1, 6-heptadiene (XXXIX).

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INTRODUCTION

Cassia absus is a plant native to India and Ceylon which grows to a height of one to two feet. Its flat, oblong seeds have been found to contain material effective in the treatment of skin affections and opthalmia, and as a cathartic.

The isolation of alkaloid principle was done by Siddiqui and Ahmed,[1] in the form of iodide and sulphate salts. The name chaksine was given to this base.

The kernel of the plant was powdered and treated with cold methanol-hydrochloric acid solution. After neutralization and acidification, methanol was removed in vacuo and the residual material was extracted with ether. After removal of ether, a brownish yellow syrupy residue was obtained. The material was dissolved in water and acidified with dilute hydrochloric acid followed by addition of potassium iodide. Elemental analysis of bicarbonate of chaksine gave the empirical formula as $C_{12}H_{20}ON_3HCO_3$.

Analysis of the iodide using Zeisel's method showed the absence of methoxy groups and by Herzig and Meyer's method, it was found that it contained an N-methyl group.

Kapur et al.[2] proved that the empirical formula assigned to chaksine was wrong and should be $C_{11}H_{20}O_2N_3OH$. This was later confirmed by Siddiqui et al.[3]

Using infrared spectra and chemical evidence, Guha and Ray[4] proposed a structure* (I) for chaksine. They

*See Plate I.

proposed a partial structure (II) for the part of the molecule bearing the nitrogen atoms. Positive Kuhn - Roth oxidation test confirmed the presence of a C - Me group. Negative Hoffman and Emde degradation tests coupled with a positive pyrrol test was interpreted to mean that the molecule contained a bicyclic structure having a quarternary nitrogen common to both rings. It was also assumed that this bicyclic system had eight carbon atoms because a C_8 fragment was usually found in several degradation reactions. Based on these observations, Guha and Ray expanded the partial structure to (III) which accounts for all but C_2H_5O in the chaksine molecule. Tribenzoyl derivative formation indicated the presence of hydroxy group and thus structure (I) was proposed.

In 1958, Wiesner and Valenta[5] published a paper proposing an entirely different structure for chaksine. Hydrolysis of chaksine with 2N sodium hydroxide gave a low yield of the ureido-hydroxy acid and the infrared spectrum of the oily ester formed from the acid showed bands at 1740 cm^{-1} (ester) and 1710 cm^{-1} (five membered cyclic urea). Also, mild oxidation with permanganate in water gave in good yield an acid which, when decarboxylated by heating to 170° under nitrogen for twenty minutes, followed by oxidation with chromium trioxide, gave ∝-methylpimelic acid (IV). The product was identified by comparing the infrared spectrum of the acid and the corresponding ethyl ester with

authentic specimens. These investigators thus assigned structure (V) to chaksine which was the first recorded example of a monoterpenoid alkaloid.

In another paper, Singh et al.[6] reported that the tricarboxylic acid $C_{10}H_{16}O_6$, obtained as the second product of the alkali fusion of the alkaloid, could be assigned structure (VI). Thus, the basic carbon skeleton, as proposed by Wiesner and Valenta, was supported. However, it was claimed that the guanidine function could also be incorporated in a six-membered ring and an alternative structure* (VII) was proposed.

Since the issue of the structure of chaksine was further confused by Guha and Ray[7] proposing the structure (VIII), Wiesner et al.[8] published a second paper citing nuclear magnetic resonance and chemical evidence to support the structure they had originally proposed. The methyl ester of the ureido acid (IX) was prepared and the nuclear magnetic resonance spectrum confirmed the proposed structure. The chemical shifts of the protons in the ureido ring corresponded with those in an authentic sample of 2-imidazolidone.

The ultimate proof of any structure elucidation lies in the unambiguous synthesis of that compound. In the partial synthesis of chaksine presented in this thesis, 2-methylcyclohexanone was treated with diethyl oxalate to

*See Plate II.

give ethyl (2'-keto-3'-methylcyclohexyl)-2-ketoacetate (X). Decarbonylation of this compound yielded ethyl 2-methylcyclohexanone-6-carboxylate[9] (XI). The ketoester was treated with formaldehyde to give ethyl 2-methyl-6-hydroxymethylcyclohexanone-6-carboxylate[10] (XII). Tosylation of the alcohol yielded 2-methyl-6-carbethoxy-6-p-toluenesulfonyloxymethyl cyclohexanone (XIII).* Cleavage of the cyclohexane ring with aqueous potassium hydroxide yielded 2-methyl-6-carbethoxy-6-heptenoic acid[11] (XIV) along with its corresponding diethyl ester (XIVa). Ozonolysis of ethyl 2-methyl-6-carbethoxy-heptenoate gave α-ketoester[12] (XV). The Wittig reaction of (XV) with diethyl cyanomethyl phosphonate (XVI) yielded a mixture of cis and trans-1-cyano-2, 6-dicarbethoxy-1-heptene[13] (XVII a) and (XVII b).

The nitrile was felt to represent a key intermediate in the chaksine synthesis. All the necessary atoms in the basic skeleton of chaksine are present. It contains the required molecular skeleton with appropriate functionality for conversion into chaksine.

Several alternative approaches were also attempted. The condensation of ethyl 2-methylcyclohexanone carboxylate (XI) with 2-bromopropionic acid benzyl** ester[14] (XVIII) yielded 2-methyl-6-carbethoxy-6-(2'-propioylbenzyloxy)

* See Plate III.

** See Plate IV.

cyclohexanone[15] (XIX). Hydrogenolysis of the benzyl ester gave 2-(1'-carbethoxy-2'-keto-3' methylcyclohexyl) propionic acid[16] (XX) along with lactol (XXI) which was hydrolyzed to the acid (XX) when treated with aqueous potassium hydroxide under mild conditions. Decarboxylation of the acid with lead tetraacetate yielded ethyl 2-methyl-6-vinylcyclohexanone-6-carboxylate[17, 18] (XXII). Treatment of the vinyl compound (XXII) with refluxing aqueous sodium carbonate in alcohol gave 2-methyl-6-carbethoxy-6-octenoic acid (XXIII). This compound contains the basic carbon skeleton of chaksine with an oxidation level one below that required for a chaksine intermediate.

During the course of this investigation we developed a new method for the preparation of 2-imidazolidones* (XXIV) from olefins. These compounds have the cyclic urea structure found in one of the key degradation products of chaksine. Olefins were treated with iodine isocyanate[19, 20, 21] in ether to give the corresponding α-iodoisocyanates (XXV) which when treated with ammonia gave (XXVI). When the solvent was replaced with ethanol and saturated with ammonia (XXVII) resulted. Finally, reaction of (XXVII) with dilute hydrochloric acid under refluxing condition gave 2-Imidazolidones (XXIV) in good yields. Although the method was quite successful when applied to

*See Plate V.

a variety of terminal and non-terminal olefins, it did not work with ethyl 2-methyl-6-vinylcyclohexanone-6-carboxylate (XXII) to produce the desired cyclic urea (XXVIII).

A further attempt to prepare a suitable intermediate for conversion to chaksine began by a condensation between 2-methylcyclohexanone and benzaldehyde to form 2-benzylidene-6-methylcyclohexanone*[22] (XXIX). This arylidine compound (XXIX) was then treated with formaldehyde to produce 2-benzylidene-6-methyl-6-hydroxymethyl-cyclohexanone (XXX). Tosylation of (XXX) with P-toluene sulfonyl chloride gave 2-benzylidene-6-methyl-6-p-toluenesulfonyloxy methyl cyclohexanone (XXXI). Reduction of the carbonyl function with sodium borohydride gave 2-benzylidene-6-methyl-6-p-toluenesulfonyloxymethyl cyclohexanol (XXXII). Cleavage of the cyclohexane ring was achieved by treating (XXXII) with potassium t-butoxide under mild conditions to give the olefinic aldehyde (XXXIII). Attempts to remove the arylidine blocking group were not successful. A second type of blocking was also attempted involving the initial reaction of 2-methylcyclohexanone with ethyl formate to form the hydroxymethylene derivative** (XXXIV). This was followed by treatment with n-butyl mercaptan to form the thioether[23] (XXXV). The thioether was then treated with

*See Plate VI.
**See Plate VII.

formaldehyde to form the corresponding hydroxymethyl compound (XXXVI). Treatment of this primary alcohol with methane sulfonyl chloride yielded the mesylate (XXXVII). Reduction of the cyclohexanone ring to the corresponding alcohol (XXXVIII) was achieved by treatment of (XXXVII) with sodium borohydride. This compound was then treated with potassium t-butoxide to give the olefinic aldehyde (XXXIX). Attempts to oxidize this aldehyde to the desired carboxylic acid, under a variety of experimental conditions, were not successful.

DISCUSSION

In our synthetic studies we approached the problem by first preparing a compound which contained the basic carbon skeleton of chaksine and with the functionality which would allow it to be converted into chaksine itself.

In the initial step it was necessary to form ethyl 2-methyl-6-hydroxymethylcyclohexanone-6-carboxylate (Plate II, XII). This compound was readily obtained from the hydroxymethylation of ethyl 2-methylcyclohexanone-6-carboxylate (XI) with formaldehyde. The nuclear magnetic resonance spectrum (n.m.r. 1) of the pure reaction product indicated that the desired compound had been produced. A doublet at τ=9.02 (J=6 Hz) was assigned to the methyl group alpha to the ketone function. A methyl triplet at τ=8.75 (J=7 Hz) and a methylene quartet at τ=5.82 (J=7 Hz) confirmed the presence of the ethyl ester. A methylene singlet at τ=6.34 and a broad peak at τ=6.97 confirmed the presence of hydroxymethyl group beta to ketone and ester functions. The infrared spectrum (i.r. 1) exhibited absorption bands at 1725 cm^{-1} (ß-ketoester), 1375 cm^{-1} (terminal methyl group), and a broad peak at 3540 cm^{-1} (hydroxyl group). In the mass spectrum, the molecular ion peak was observed at m/e 214.

Treatment of (XII) with P-toluene sulfonyl chloride in pyridine resulted in the smooth conversion of the primary alcohol to the corresponding tosylate (XIII). Formation of the tosylate was supported by spectroscopic evidence.

In the n.m.r. spectrum (n.m.r. 2), a multiplet centered at τ=2.41 characteristic of A_2B_2 system of the P-tolyl group and a singlet at τ=7.55 (methyl group of tosylate) indicated the formation of the desired compound. The i.r. spectrum (i.r. 2) showed absorptions at 1605 cm^{-1} (skeletal vibration of phenyl group) and at 1180 cm^{-1} (sulfur oxygen absorption) which confirmed formation of the tosylate.

The next step in the synthesis required conversion of the ß-ketoester moiety into the unsaturated acid (XIV). Because the tosyl group is an excellent leaving group, it was hoped that the cleavage of the cyclohexanone ring should be possible and, indeed, this goal was readily achieved by treatment of (XIII) with aqueous potassium hydroxide under mild conditions to give the olefinic acid (XIV). The n.m.r. spectrum (n.m.r. 3) had two doublets at τ=3.76 (J=7 Hz) and τ=4.39 (J=7 Hz) assigned to the olefinic protons which are cis and trans to the ester group. The compound also exhibited a singlet at τ=-3.40 corresponding to the proton of the carboxylic acid function. A downfield shift of the methyl group (τ=8.84) was consistent with it being adjacent to the carboxylic acid moiety. The infrared spectrum (i.r. 3) had an absorption at 1635 cm^{-1} (double bond) and a very broad absorption band in the CH region characteristic of carboxylic acids. It should be pointed out that during the course of this reaction an appreciable amount of corresponding ethyl ester (Plate III, XIV a)

was also formed which was useful for further reactions. The formation of this compound was confirmed by its nuclear magnetic resonance spectrum (n.m.r. 4) having two doublets at τ=3.95 and τ=4.46 (olefinic protons), and a new quartet at τ=5.94 (J=7 Hz).

At this point, it was decided to convert the olefinic diester (XIV a) to the keto diester (XV). For this purpose, ozonolysis of (XIV a) at low temperature was chosen, followed by decomposition of the ozonide with dimethyl sulfide. The mechanistic details of this reaction may be found on Plate VIII. The reason for using dimethyl sulfide[12] was that in addition to the rapidity which it reduces hydroperoxides at low temperatures it has a number of other virtues. It is highly selective, that is, carbonyl functions are not reduced; the reduction is carried out under neutral conditions; any excess of dimethyl sulfide is rapidly removed by evaporation (b.p. 37°) and the by products, methanol and dimethyl sulfoxide, cause no problems for purification. The ketoester (XV) thus formed by ozonolysis had a triplet at τ=7.30 (n.m.r. 5) corresponding to the protons adjacent to the newly formed ketone function.

At this stage, a Wittig reaction between the ketodiester (XV) and diethyl cyanomethylphosphonate (XVI) gave a mixture of cis and trans-isomers of 1-cyano-2, 6-dicarbethoxy-1-heptene (XVII a) and (XVII b). The presence of two isomers was confirmed by nuclear magnetic resonance

spectrum (n.m.r. 6) having a sharp singlet at τ=3.70 and a multiplet at τ=4.22. The stereochemical details of this reaction may be found on Plate IX. Furthermore, column chromatography of the mixture separated two geometric isomers and nuclear magnetic resonance spectra of the two compounds (n.m.r. 7) and (n.m.r. 8) supported the above conclusions. The infrared spectrum (i.r. 4) exhibited absorption bands at 2225 cm^{-1} (nitrile group) and at 1630 cm^{-1} (double bond). In the mass spectrum, the molecular ion peak was observed.

This product is considered to be a key intermediate in a chaksine synthesis. It has the required molecular skeleton with the appropriate functionality for conversion to chaksine. A 1, 4-addition of benzylamine followed by catalytic hydrogenation of the product should afford the 1, 2-diamine which can be treated with phosgene to produce the cyclic urea which is a key degradation product of chaksine. Alternatively reaction of this product with guanidine nitrate or guanidine chloride followed by reduction of the nitrile group and cyclization of the product should afford the desired five-membered heterocyclic ring.

Another approach which was also investigated involved first a condensation reaction between ethyl 2-methylcyclohexanone-6-carboxylate (XI) and benzyl 2-bromopropionate (XVIII) to give 2-methyl-6-carbethoxy-6-(2'-propioyl benzyloxy) cyclohexanone (XIX). The n.m.r.

spectrum (n.m.r. 9) indicated that the benzyl ester function was present since a singlet at τ=2.76 (aromatic protons) and a multiplet at τ=4.90 (benzylic protons) were observed.

Hydrogenolysis of the ester (XIX) gave 2-(1' carbethoxy-2'-keto-3'-methylcyclohexyl) - propionic acid (XX). The formation of the acid was supported by spectroscopic evidence. A broad absorption band in the CH region of the i.r. spectrum (i.r. 5) confirmed the presence of the carboxylic acid function. In the n.m.r. spectrum (n.m.r. 10) a broad peak at τ=-1.2 also indicated the presence of a carboxylic acid moiety. It should be pointed out that during the hydrogenolysis process some lactol (XXI) was formed which was converted to the acid (XX) when treated with alkali. The nuclear magnetic resonance and infrared spectra of the acid thus formed were the same as the spectra of the original acid (XX).

Oxidative degradation of the acid (XX) was achieved utilizing lead tetraacetate and catalytic amounts of pyridine and cupric acetate as trapping agents for the carbonium ion intermediate. The reaction mechanism may be found on Plate X.[24, 25] The formation of the olefin (XXII) was supported by spectroscopic evidence. The n.m.r. spectrum (n.m.r. 11) had two complex multiplets ranging from τ=3.45 to τ=4.25 and τ=4.62 to τ=5.12 characteristic of A_2B system of the vinyl group. The infrared spectrum (i.r. 6) showed an absorption at 1640 cm^{-1} (double bond). A peak due to the

molecular ion m/e 210 was observed in the mass spectrum.

Finally, cleavage of the cyclohexanone ring of the compound (XXII) was achieved by treatment of the vinyl ketoester with a weak alkali solution to give 2-methyl-6-carbethoxy-6-octenoic acid (XXIII). A quartet at τ=3.14 (J=7 Hz) coupled with a new methyl doublet at τ=8.08 in the n.m.r. spectrum (n.m.r. 12) showed that the double bond had migrated to the undesired non-terminal position during the reaction. The infrared spectrum (i.r. 7) exhibited a peak of medium intensity at 1650 cm^{-1} (conjugated double bond) and a broad absorption peak in the CH region characteristic of carboxylic acid moiety.

Another part of this investigation involved the development of a method for converting alkenes into 2-imidazolidones. It was hoped that such a method could be applied to (XXII) to produce the cyclic urea (XXVIII). Thus α-iodoisocyanates (XXV) of a variety of terminal and non-terminal olefins were prepared by treating the olefins with iodine isocyanate. Organic isocyanates are often very unstable being susceptible to thermolysis, photolysis, or solvolysis. Therefore, the iodoisocyanates (XXV) were treated with gaseous ammonia to produce first (XXVI) and then (XXVII). Finally treatment of (XXVII) with hydrochloric acid gave cyclic ureas (XXIV). The reaction mechanism may be found on Plate XI. The formation of terminal and non-terminal cyclic ureas was supported by analytical and

spectroscopic evidence. For example, in the n.m.r. spectrum (n.m.r. 13) of the cyclic urea obtained from 1-heptene, a singlet at τ=5.32 was assigned to two protons attached to nitrogen atoms, a multiplet at τ=6.31 corresponding to the protons of the ring carbons, another multiplet at τ=8.58 due to eight methylene protons and, finally, a triplet at τ=9.05 (J=5.5 Hz) was assigned to the terminal methyl group. The i.r. spectrum (i.r. 8) showed absorption at 3365 cm^{-1} (N-H stretching), 1685 cm^{-1} (carbonyl group), and 1612 cm^{-1} which is consistent with cyclic ureas infrared absorption. In the mass spectrum of this compound (m.s. 1), the molecular ion peak was observed along with a strong peak at m/e 127 which might be due to the formation of ion (XL) (Plate XII). An interpretation of the fragmentation pattern for this molecule may be found on Plate XII. Finally the elemental analysis of the cyclic ureas obtained by the above method were in agreement with the desired structure (Table I).

Two other approaches utilizing blocking techniques for preparation of a suitable intermediate for conversion to chaksine were attempted. The first one involved selective alkylation of the unsymmetrically substituted 2-methylcyclohexanone by introduction of a benzylidene blocking group at the methylene group alpha to the carbonyl function. This was achieved by an aldol condensation between 2-methylcyclohexanone and benzaldehyde. The

resulting product 2-benzylidene-6-methylcyclohexanone (XXIX), was converted to 2-benzylidene-6-hydroxymethyl-6-methylcyclohexanone (XXX) by treating with formaldehyde in alkali. The nuclear magnetic resonance spectrum (n.m.r. 14) indicated that the desired compound had been produced since a singlet at τ=2.75 (aromatic protons), a singlet at τ=6.48 (hydroxymethyl protons) and a methyl singlet at τ=8.95 were observed.

Treatment of (XXX) with P-toluene sulfonyl chloride resulted in the smooth conversion of the primary alcohol to the corresponding tosylate. Formation of the tosylate (XXXI) was confirmed by its nuclear magnetic resonance spectrum (n.m.r. 15). A multiplet centered at τ=2.50 characteristic of P-tolyl group and a singlet at τ=7.63 (methyl group of tosylate) indicated the formation of the desired compound.

Reduction of the carbonyl function was achieved by treating (XXXI) with sodium borohydride in methanol to yield the alcohol (XXXII). An upfield shift of the double bond hydrogen (τ=3.58) in the n.m.r. spectrum (n.m.r. 16) coupled with an upfield shift of the methyl protons (τ=9.20) was consistent with the α, β-unsaturated ketone being reduced to the alcohol (XXXII).

The next step required the rearrangement of the alcohol (XXXII) into the olefinic aldehyde (XXXIII). This was achieved by treating the alcohol (XXXII) with potassium

t-butoxide in t-butanol under mild conditions. The formation of the aldehyde was supported by spectroscopic evidence. In the n.m.r. spectrum (n.m.r. 17), a sharp singlet at τ =-1.27 assigned to the aldehyde proton and a singlet at τ=5.29 assigned to the new olefinic protons indicated the formation of the desired compound. The infrared spectrum (i.r. 9) exhibited absorptions at 1687 cm^{-1} (carbonyl group) and 1630 cm^{-1} due to double bonds.

The above blocking group suffered from the difficulty that the benzylidene group could not be easily removed from (XXXIII), hence, second type of blocking was attempted. This involved the initial reaction of ethyl formate with 2-methylcyclohexanone to produce the hydroxymethylene derivative (XXXIV). The reaction of (XXXIV) with n-butyl mercaptan yielded thioether (XXXV). The resulting compound was converted to the hydroxymethyl derivative (XXXVI) when treated with formaldehyde. The n.m.r. spectrum (n.m.r. 18) showed absorptions at τ=2.57 (olefinic proton), τ=6.56 (hydroxymethyl protons), and a triplet at τ=7.15 assigned to the methylene group adjacent to the sulfur atom indicating that the desired compound had been formed.

At this point, the primary alcohol (XXXVI) was mesylated utilizing methane sulfonyl chloride to yield the mesylate (XXXVII). A sharp singlet at τ=7.06 in the n.m.r. spectrum (n.m.r. 19) was assigned to the methyl protons

of the mesylate.

Reduction of the mesylate (XXXVII) with sodium borohydride gave the corresponding alcohol (XXXVIII). In the n.m.r. spectrum (n.m.r. 20) an upfield shift of the olefinic proton (τ=4.13) coupled with the upfield shift of the methyl protons adjacent to the hydroxyl function (τ=9.20) indicated the formation of the desired compound.

The rearrangement of (XXXVIII) into the olefinic aldehyde (XXXIX) was achieved by treating the alcohol (XXXVIII) with potassium t-butoxide in t-butanol. The formation of this compound was supported by spectroscopic evidence. In the n.m.r. spectrum (n.m.r. 21) a singlet at τ=-0.84 was assigned to the proton of the aldehyde moiety. A singlet at τ=2.80 due to the olefinic proton beta to the carbonyl function, and a new broad singlet at τ=5.35 was assigned to the newly formed olefinic protons. The infrared spectrum (i.r. 10) exhibited absorptions at 1680 cm^{-1} (carbonyl group) and 1587 cm^{-1} due to the double bond. It should be pointed out that the olefinic aldehyde (XXXIX) obtained from the above reaction sequence suffered from the difficulty that oxidation of the aldehyde moiety into the desired carboxylic acid function could not be achieved using a variety of experimental conditions.

It is interesting to note that although γ-tosyl and γ-mesyl-cyclohexanol systems generally yield bicyclic oxetanes[26] under basic conditions, this was not the case

for 2-benzylidine-6-methyl-6-p-toluenesulfonyloxy-cyclohexanol (XXXII) and 2-methyl-2-methanesulfonyloxy-6-n-butylithiomethylene-cyclohexanol (XXXVIII). The above compounds underwent rearrangement to produce carbonyl compounds (XXXIII) and (XXXIX) respectively.

ATTEMPTED WORKS

Several reactions to prepare a suitable intermediate from ethyl 2-methyl-6-vinylcyclohexanone-6-carboxylate (XXII) for conversion to the desired five-membered heterocyclic ring were attempted. The vinyl compound (XXII) was converted into the corresponding alcohol.* The alcohol (XLI) was then brominated hoping to produce the corresponding dibromo derivative, but, from spectroscopic and chemical evidence it was probable that a five-membered cyclic ether (XLII) had been formed. In another attempt ethyl 2-methyl-6-vinylcyclohexanol-6-carboxylate (XLI) was treated with iodine azide[27] to yield the corresponding iodo azide (XLIII), but, although the azide peak was observed in the infrared spectrum of the product (2100 cm^{-1}) no chemical or spectroscopic evidence was observed indicating the presence of iodine, supporting again the possibility of formation of a five-membered cyclic ether of type (XLII). In another attempt the vinyl compound (XXII) was treated with N-bromoacetamide to give the bromohydrin[28] (XLIV), but, attempts to mesylate the hydroxyl group forming a good leaving group for successive cleavage of the cyclohexane ring were not successful, possibly due to the unreactivity of neopentyl type alcohol.

A variety of reactions were also attempted to prepare a suitable intermediate from 2-methyl-6-carbethoxy-

*See Plate XIII.

6-heptenoic acid (XIV). Treatment of (XIV) with diazomethane yielded the pyrazoline[29] (XLV), but attempts to convert this pyrazoline system into the corresponding 1, 3-diamine moiety (XLVI) utilizing high pressure hydrogenation on Rany nickel,[30] cobalt boride[31] reduction, and sulfurated sodium borohydride[32] were not successful. Alternatively, the diethyl ester of the above acid (XIV a) was brominated in glacial acetic acid to form the dibromo compound (XLVII), but, attempts to substitute a nitrile[33] group for the primary bromine atom were not successful.

EXPERIMENTAL

ANALYTICAL AND PHYSICAL DATA

The infrared spectra were recorded on a Beckman IR 12 spectrophotometer. Thin film spectra were taken on sodium chloride plate except for cyclic ureas which KBr discs were used.

The nuclear magnetic resonance spectra were recorded on a Varian A60-A spectrometer. All spectra were recorded with tetramethylsilane as internal reference, and are expressed in values as defined by the equation

$$\tau = 10 - \frac{(Me_4Si)\cdot 10^6}{\text{Oscillator Frequency (HZ)}}$$

The mass spectra were recorded on a Hitachi RMU-7 spectrometer.

The elemental analyses were done with a Perkin Elmer Elemental Analyzer, Model 240.

Whenever possible, the sample for mass spectroscopy was obtained by preparative chromatography (10% SE-30 on Gas Chrom Q) using a Perkin Elmer Gas Chromatograph, Model 881.

Ethyl 2-methycyclohexanone-6-carboxylate (XI)

A 500 ml, three necked, round-bottom flask was equipped with a mechanical stirrer, a condenser, and a dropping funnel. The flask was charged with absolute ethanol (150 ml), and sodium (11.5 g, 0.5 g-atom) without stirring to prepare a solution of sodium ethoxide. The flask was cooled to 10° with stirring whereupon a previously ice bath cooled mixture of 2-methylcyclohexanone (56 g, 0.5 mole) and diethyl oxalate (73 g, 0.5 mole) was added over about 15 minutes. After the addition, stirring in the cold was continued for one hour followed by stirring at room temperature overnight. The flask was again cooled to 5 - 10° and a mixture of 14 ml of concentrated sulfuric acid and 110 g of ice was added to decompose the reaction mixture. The solution was diluted with water (1000 ml), and the oily ethyl (2'-keto-3'-methylcyclohexyl)-2-ketoacetate (X) was separated. The aqueous phase was extracted four times with 100 ml portions of benzene and the benzene extracts were combined with the original organic phase. The benzene solution was washed twice with water and was transferred in portions to a 250 ml flask set up for distillation on steam bath. Distillation was continued until benzene no longer came over. The distillation set up was then heated with an oil bath under vacuum, and the forerun was collected below 105°/10 - 12 mm. The product ethyl (2'-keto-3'-methylcyclohexyl)-

2-ketoacetate (X) (74.5 g, yield = 70%) was collected at 155-165/10-15 mm.

The above distillate (X) was transferred to a 125 ml flask set up for distillation and approximately 1 mg of iron powder and 0.5 g of finely ground soft glass was added. The mixture was distilled at 40 mm, the decarbonylated product was collected over the range 130-145 (bath temperature 165-175°). The product ethyl 2-methylcyclohexanone-6-carboxylate (XI) (56 g, yield = 59%) was purified by distillation, bp 96-98/1 mm.

Ethyl 2-methyl-6-hydroxymethylcyclohexanone-6-carboxylate (XII)

A 100 ml, round bottom flask was charged with ethyl 2-methylcyclohexanone-6-carboxylate (11.04 g, 0.06 mole), methanol (35 ml), sodium hydroxide (40 drops of 20% aqueous solution), and formaldehyde (8 ml of 37% solution). The mixture was stirred at room temperature for four hours. The reaction mixture was concentrated by evaporating most of the solvent. The residual material was diluted with ether (400 ml). The ether solution was washed twice with water, dried over sodium sulphate, and evaporated to give ethyl 2-methyl-6-hydroxymethylcyclohexanone-6-carboxylate (XII) (11.535 g, yield = 89.8%).

The following absorptions were observed in n.m.r.

and i.r. spectra. Nuclear magnetic resonance spectrum no. 1: τ=8.75 (methyl triplet of ethyl ester); τ=5.82 (methylene quartet of ethyl ester); τ=9.02 (methyl doublet alpha to ketone moiety); τ=6.34 (singlet due to hydroxymethyl). Infrared spectrum no. 1: 1725 cm^{-1}, 1375 cm^{-1} and 3540 cm^{-1}.

Ethyl 2-methyl-6-carbethoxy-6-p-toluenes-sulfonyloxymethyl cyclohexanone (XIII)

Ethyl 2-methyl-6-hydroxymethylcyclohexanone-6-carboxylate (XII) (10.27 g, 0.048 mole) was dissolved in pyridine (50 ml). The solution was cooled in an ice bath. P-toluene sulfonyl chloride (9.34 g, 0.048 mole) was added in portions and the solution was stirred at room temperature overnight. The reaction mixture was diluted with ether (400 ml). The ether solution was washed with 20% hydrochloric acid until aqueous phase became acidic, 5% sodium bicarbonate until aqueous phase was basic, twice with water, and dried over sodium sulphate. Evaporation of the ether gave ethyl 2-methyl-6-carbethoxy-6-p-toluene-sulfonyloxymethyl cyclohexanone (XIII) (16.52 g, yield = 93.5%.

Nuclear magnetic resonance spectrum no. 2: absorptions at τ=2.41 (aromatic protons) and τ=7.55 (methyl singlet of tosylate). Infrared spectrum no. 2:

absorptions at 1605 cm^{-1} and 1180 cm^{-1}.

2-methyl-6-carbethoxy-6-heptenoic acid (XIV)

Ethyl 2-methyl-6-hydroxymethyl P-toluene sulfonate cyclohexanone-6-carboxylate (XIII) (28.05 g, 0.076 mole) was dissolved in ethanol (500 ml), followed by the addition of potassium hydroxide (100 ml of a 1.0 N solution). The reaction mixture was stirred at room temperature overnight. Most of the solvent was removed on the rotary evaporator and the residual material was extracted with ether (100 ml). The ether phase was separated from the aqueous phase, washed with water several times and dried over sodium sulphate. Removal of the ether gave ethyl 2-methyl-6-carbethoxy-6-heptenoate (XIV a) (5.72 g, yield = 31%)

The aqueous phase was acidified with hydrochloric acid and extracted three times with 150 ml portions of ether. The combined ether extracts were washed with water, dried over sodium sulphate, and evaporated to give 2-methyl-6-carbethoxy-6-heptenoic acid (XIV) (11.5 g, yield = 62%).

Nuclear magnetic resonance no. 3: absorptions at τ=3.76, τ=4.39 (olefinic protons); τ=-3.4 (proton of carboxylic acid moiety). Infrared spectrum no. 3: absorption at 1635 cm^{-1} and a broad peak in the CH region (character-

istic of carboxylic acid). Nuclear magnetic resonance spectrum of diethyl ester (n.m.r. 4): absorptions at τ=3.95; τ=4.46; τ=5.94 (new ethyl ester protons).

Diethyl 2-keto-6-methyl pimelate (XV)

A solution of ethyl 2-methyl-6-ethylcarboxy-6-heptenoate (XIV) (4.84 g, 0.02 mole) in methanol (20 ml) was cooled to -30°. Ozone was bubbled into the solution during which the temperature was gradually lowered to -60°. The ozonolysis was continued until the solution became blue. While still at -60°, the system was flushed with nitrogen and dimethyl sulfide (3 ml) was added. The solution was then stirred at -10° for one hour, then at ice bath temperature for one hour and, finally, at room temperature for one hour. The solvent was removed in vacuo and the residue was dissolved in ether. The ether solution was washed with water, dried over sodium sulphate and evaporated to give diethyl 2-keto-6-methyl pimelate (XV) (4.84 g, yield = 99%).

Nuclear magnetic resonance no. 5: absorption at τ=7.30 (triplet alpha to ketone function).

1-cyano-2, 6-dicarbethoxy-1-heptene (XVII)

Diethyl cyanomethylphosphonate (XVI) (4.64 g, 0.026 mole) was dissolved in 1, 2-dimethoxy ethane (30 ml). To this solution was added sodium hydride (1.26 g, 0.026 mole 50% dispersion in oil). The reaction mixture was stirred for ten minutes and filtered. Diethyl 2-keto-6-methyl pimelate (XV) (4.27 g, 0.017 mole) was added to the carbanion solution at 20°. The exothermic reaction increased the temperature of the mixture to about 50°. The reaction mixture was stirred at 50° for three hours. The mixture was diluted with water (30 ml) and extracted two times with 100 ml portions of ether. The combined ether extracts were washed with water until the washings became neutral, dried over sodium sulphate, and evaporated to dryness to give a mixture of cis and trans-1-cyano-2, 6-dicarbethoxy-1-heptene (XVII a) and (XVII b) (4.45 g, yield = 95%). Column chromatography (Woelm silica gel activity grade 1 - 5% ether in benzene eluent) separated 1 g of the crude product into the trans isomer (0.5 g) and the cis isomer (0.25 g).

The following absorptions were observed in i.r. and n.m.r. spectra. Infrared spectrum no. 4: 2225 cm^{-1} (nitrile group), 1630 cm^{-1} (double bond). Nuclear magnetic resonance no. 7 (trans isomer): τ=3.70 (sharp singlet, olefinic proton). Nuclear magnetic resonance no. 8 (cis isomer): τ=4.22 (multiplet, olefinic proton).

2-methyl-6-carbethoxy-6-(2'-propioyl-benzyloxy) cyclohexanone (XIX)

Sodium (1.15 g, 0.05 g-atom) was suspended in dry toluene (35 ml), to this was added ethyl 2-methylcyclohexanone-6-carboxylate (XI) (9.20 g, 0.05 mole). After the first reaction had subsided this mixture was heated at 110° for two hours. Benzyl 2-bromopropionate (XVIII) was added and the mixture was stirred at 140° overnight. The neutral reaction mixture was cooled, and diluted with toluene (150 ml). The resulting solution was washed with water, dried over sodium sulphate, and evaporated on a rotary evaporator to give 2-methyl-6-carbethoxy-6-(2'-propioylbenzyloxy) cyclohexanone (XIX) (14.8 g, yield = 85.5%).

Nuclear magnetic resonance no. 9: τ=2.76 (aromatic protons); τ=4.90 (benzylic protons).

2(1'-carbethoxy-2'-keto-3'-methyl cyclohexyl) - propionic acid (XX)

A 500 ml round bottom flask was equipped with an apparatus for hydrogenation at atmospheric pressure. The flask was charged with absolute ethanol (150 ml). 10% palladium on charcoal catalyst (1 g) was added and the mixture was saturated with hydrogen. Ethyl 2-methyl-6-(2'-benzyl propionate) cyclohexanone-6-carboxylate (XIX)

(15 g, 0.043 mole) dissolved in absolute ethanol (100 ml) was added to the flask. Hydrogenation was continued until no more hydrogen uptake was observed. The solution was filtered through Celite and the solvent was evaporated *in vacuo* to give the crude product (9.21 g, yield = 83%).

The crude product was dissolved in ether (100 ml) and extracted three times with 25 ml portions of 1.0 N sodium hydroxide. The combined aqueous solution was cooled in an ice bath, acidified with hydrochloric acid, and re-extracted three times with 100 ml portions of ether. The combined ether extracts were washed twice with water and dried over sodium sulphate. Evaporation of the ether yielded pure 2(1'-carbethoxy-2'-keto-3'-methylcyclohexyl) - propionic acid (XX) (2.8 g).

The original ether solution was washed with water until the washings became neutral, dried over sodium sulphate and evaporated to give lactol (XXI) (5.75 g).

The lactol (XXI) was dissolved in methanol (150 ml) and 20 ml of a 1.122 M potassium hydroxide solution added. The reaction mixture was stirred at room temperature overnight. The methanol was evaporated on a rotary evaporator and the residue extracted with ether (50 ml) to remove any neutral material. The aqueous solution was acidified with hydrochloric acid followed by extraction with three 100 ml portions of ether. The combined ether extracts were washed twice with water, dried over sodium sulphate, and evaporated

to give ethyl 2-methyl-6-(2'-propionic acid) cyclohexanone-6-carboxylate (XX) (2.28 g).

Nuclear magnetic resonance spectrum no. 10: τ=-0.8 (proton of carboxylic acid moiety). Infrared spectrum no. 5: broad absorption band in the CH region (carboxylic acid).

Ethyl 2-methyl-6-vinylcyclohexanone-6-carboxylate (XXII)

The oxidative decarboxylation of 2(1'-carbethoxy-2-keto-3'-methyl cyclohexyl)-propionic acid (XX) (5.17 g, 0.02 mole) was carried out by heating on an oil bath at 97° for 2 1/2 hours in a nitrogen atmosphere with a mixture of dry benzene (135 ml), lead tetraacetate (20.66 g, 0.046 mole), cupric acetate (1.13 g, 0.005 mole), and pyridine (0.73 g, 0.009 mole). During this time a white precipitate was formed. The reaction mixture was cooled and filtered, and the solid was washed with 50 ml of benzene. The combined filtrate and washing were extracted successively with 30 ml portions of water, 1.0 N sodium hydroxide, water, 1.0 N hydrochloric acid, and water. After drying over magnesium sulphate the benzene solution gave upon evaporation the desired product ethyl 2-methyl-6-vinylcyclohexanone-6-carboxylate (XXII) (3.32 g, yield = 78%).

Nuclear magnetic resonance no. 11: τ=3.4 - 4.25

and τ=4.58 - 5.10 (complex multiplets due to A_2B system of vinyl group). Infrared spectrum no. 6: absorption at 1640 cm^{-1}.

2-methyl-6-carbethoxy-6-octenoic acid (XXIII)

Ethyl 2-methyl-6-vinylcyclohexanone-6-carboxylate (0.42g, 0.002 mole) was dissolved in ethanol (40 ml). The solution was heated in an oil bath to the reflux point. An aqueous solution of sodium carbonate (0.19 g, 0.0018 mole dissolved in 10 ml water) was added in portions over a period of 1/2 hour. The reaction mixture was refluxed with stirring overnight. The ethanol was removed on a rotary evaporator and the residue was extracted with ether to remove the neutral material. The aqueous phase was cooled in an ice bath, acidified with concentrated hydrochloric acid, and extracted three times with 50 ml portions of ether. The combined ethereal extracts were washed twice with water, dried over sodium sulphate, and evaporated to dryness to give 2-methyl-6-carbethoxy-6-octenoic acid (0.4 g, yield = 89%).

Nuclear magnetic resonance no. 12: τ=3.14 (quartet due to olefinic proton); τ=8.08 (methyl doublet alpha to the double bond). Infrared spectrum no. 7: 1650 cm^{-1} (conjugated double bond), broad absorption peak in the CH region (carboxylic acid).

2-imidazolidones

General procedure:

A 100 ml round bottomed flask was equipped with magnetic stirrer and drying tube. The flask was charged with absolute ether (15 ml) and cooled to -5° in an ice-salt bath. Resublimed iodine (2.7 g, 0.011 mole) and freshly prepared silver isocyanate (2.25 g, 0.015 mole) were added to the flask. The slurry was stirred for fifteen minutes to produce iodine isocyanate. Olefin (0.01 mole) was added and the reaction mixture was stirred at -5° for three hours. After removal of the inorganic salts by filtration (silver iodide and silver isocyanate) and washing the solid materials two times with 15 ml portions of ether, ammonia was bubbled into the ethereal filtrate to give (XXVI). The ether was then evaporated in vacuo, and the residue was dissolved in absolute ethanol (100 ml). The ethanolic solution was again saturated with ammonia, and was left to stand at room temperature for three days. The solvent was then evaporated on a rotary evaporator and the residue was diluted with chloroform (75 ml), and filtered to remove ammonium iodide produced during the course of reaction. The chloroform solution was evaporated to dryness to give (XXVII). This oily material was dissolved in 3% hydrochloric acid (60 ml) and the solution was heated over-night under reflux. The reaction mixture was cooled in an

ice bath, and extracted with ether (25 ml) to remove any neutral materials. The aqueous solution was again cooled in an ice bath, neutralized with 20% sodium hydroxide solution, and extracted three times with 100 ml portions of chloroform. The combined chloroform extracts were washed two times with 20 ml portions of water, dried over sodium sulphate, and evaporated to dryness to give 2-imidazolidones. All crystalline products were recrystallized from n-hexane. Table I represents the cyclic ureas obtained following the above procedure.

	m.p.	Yield* %	Anal. (caltd.) C	H	N	Anal. (found) C	H	N
1-Hexene	81	49	59.15	9.86	19.72	58.63	10.04	19.65
1-Heptene	77	53	61.54	10.26	17.95	61.02	10.31	17.84
1-Octene	87	50	63.53	10.59	16.47	63.89	10.99	16.65
1-Nonene	86	56	65.22	10.87	15.22	65.22	10.95	15.68
1-Decene	95	46	66.67	11.11	14.14	67.17	11.37	14.00
cis-5-Decene	--**	51	66.67	11.11	14.14	66.18	11.29	14.37
trans-5-Decene	--**	74						
trans-4-Octene	--**	67						
2-Octene	--**	47						

*Based on starting olefin.
**Product is liquid.

TABLE I

2-benzylidene-6-methyl-6-hydroxymethylcyclohexanone (XXX)

2-benzylidene-6-methylcyclohexanone (XXIX) (5.83 g, 0.031 mole) was dissolved in methanol (15 ml). Sodium hydroxide (18 drops of 20% aqueous solution) and formaldehyde (3 ml of 37% solution) were added. The mixture was stirred at room temperature for four hours. Most of the solvent was removed on a rotary evaporator and the residual material was diluted with ether (250 ml). The ether solution was washed twice with water, dried over sodium sulphate, and evaporated to dryness to give 2-benzylidene-6-methyl-6-hydroxymethylcyclohexanone (XXX) (5.50 g, yield = 82%).

Nuclear magnetic resonance no. 14: τ=2.75; τ=6.48 (hydroxymethyl protons); τ=8.95 (methyl singlet).

2-benzylidene-6-methyl-6-p-toluene-sulfonyloxy methyl cyclohexanone (XXXI)

A 100 ml, round bottom flask was charged with 2-benzylidene-6-methyl-6-hydroxymethylcyclohexanone (XXX) (5.5 g, 0.024 mole) and pyridine. The solution was cooled in an ice bath. P-toluene sulfonyl chloride (4.8 g, 0.025 mole) was added in portions and the solution was stirred at room temperature overnight. The reaction mixture was diluted with ether (250 ml). The ethereal solution was

washed with 20% hydrochloric acid until the aqueous phase became acidic, 5% sodium bicarbonate until the aqueous phase was basic, twice with water, and dried over sodium sulphate. Evaporation of ether gave 2-benzylidene-6-methyl-6-p-toluenesulfonyloxy methyl cyclohexanone (XXXI) (8.17 g, yield = 88%).

Nuclear magnetic resonance spectrum no. 15: τ=2.5 (tolyl group); τ=7.63 (methyl group of tosylate).

2-benzylidene-6-methyl-6-p-toluenesulfonyloxy methyl cyclohexanol (XXXII)

A solution of tosylate (XXXI) (5.58 g, 0.014 mole) in methanol (150 ml) was cooled to 0°. Sodium borohydride (1.5 g, 0.039 mole) was added in small portions over a period of 1/2 hour. The reaction mixture was stirred at room temperature overnight. The methanol was then removed on a rotary evaporator and the residue was diluted with ether. The ether solution was washed three times with water, dried over sodium sulphate, and evaporated to give 2-benzylidene-6-methyl-6-p-toluenesulfonyloxy methyl cyclohexanol (XXXIII) (4.59 g, yield = 82%).

Nuclear magnetic resonance spectrum no. 16: τ=3.58 (double bond proton); τ=9.20 (methyl singlet).

1-phenyl-2-aldehydo-6-methyl-1, 6-heptadiene (XXXIII)

A 100 ml, round bottom flask was charged with dry t-butanol (25 ml) and potassium (0.235 g, 0.006 g-atom) to prepare a solution of potassium t-butoxide. To this solution was added 2-benzylidene-6-methyl-6-hydroxymethyl P-toluene sulfonate cyclohexanol (1.93 g, 0.005 mole). The reaction mixture was stirred at room temperature in nitrogen atmosphere for twenty hours. The mixture was diluted with ether (300 ml). The ether solution was washed three times with water, dried over sodium sulphate, and evaporated to dryness to give 1-phenyl-2-aldehydo-6-methyl-1, 6-heptadiene (XXXIII) (0.81 g, yield = 75%). Column chromatography (Camag aluminum oxide activity 1 neutral-benzene eluent) gave the pure product (0.40 g).

Nuclear magnetic resonance spectrum no. 17: τ=-1.27 (aldehyde proton); τ=5.29 (new olefinic protons). Infrared spectrum no. 9: absorptions at 1687 cm^{-1} (carbonyl group); 1630 cm^{-1}.

2-methyl-2-hydroxymethyl-6-n-butylthiomethylene cyclohexanone (XXXVI)

2-methyl-6-n-butylthiomethylene cyclohexanone (XXXV) (12.2 g, 0.057 mole) was dissolved in methanol (30 ml). To this solution were added sodium hydroxide (36 drops of 20% aqueous solution) and formaldehyde (6 ml of 37% solution). The reaction mixture was stirred for four hours. Most of the solvent was removed on a rotary evaporator and the residue was diluted with ether. The ethereal solution was washed twice with water, dried over sodium sulphate, and evaporated to give 2-methyl-2-hydroxymethyl-6-n-butylthiomethylene cyclohexanone (XXXVI) (12.7 g, yield = 91%).

Nuclear magnetic resonance no. 18: τ =2.57 (olefinic proton); τ=6.56 (hydroxymethyl protons); τ=7.15 (methylene triplet due to protons alpha to sulfur atom).

2-methyl-2-hydroxymethyl methane sulfonate-6-n-butylthiomethylene cyclohexanone (XXXVII)

2-methyl-2-hydroxymethyl-6-n-butylthiomethylene cyclohexanone (XXXVI) (12.7 g, 0.052 mole) was dissolved in pyridine (70 ml). The solution was cooled in an ice bath and methane sulfonyl chloride (6.52 g, 0.057 mole) was added in portions. The reaction mixture was stirred at room temperature overnight. The mixture was diluted with

ether (400 ml). The ether solution was washed with 20% hydrochloric acid until the aqueous phase became acidic, 5% sodium bicarbonate until the aqueous phase was basic, twice with water, and dried over sodium sulphate. Evaporation of the solvent gave the mesylate (XXXVII) (14.81 g, yield = 88%).

Nuclear magnetic resonance spectrum no. 19: τ =7.06 (singlet due to methyl protons of mesylate).

2-methyl-2-hydroxymethyl methane sulfonate-6-n-butylthiomethylene cyclohexanol (XXXVIII)

(XXXVIII) was prepared according to the procedure used to reduce (XXXI) using (XXXVII) (14.81 g, 0.04 mole), sodium borohydride (4 g, 0.105 mole) and methanol (140 ml) to yield (XXXVIII) (12.66 g, yield = 85%).

Nuclear magnetic resonance spectrum no. 20: τ =4.13 (olefinic proton); τ =9.20 (methyl singlet).

1-n-butylthio-2-aldehydo-6-methyl-1, 6-heptadiene (XXXIX)

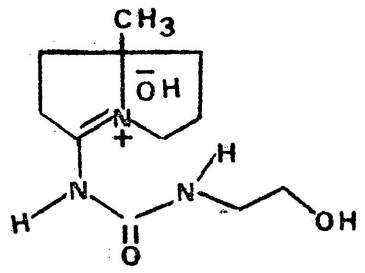
A 100 ml, round bottom flask was charged with dry t-butanol (60 ml) and potassium (0.6 g, 0.015 mole) to prepare a solution of potassium t-butoxide. 2-methyl-2-hydroxymethyl methane sulfonate-6-n-butylthiomethylene

cyclohexanol (XXXVIII) (4.2 g, 0.013 mole) was added and the mixture was heated at 80° in nitrogen atmosphere for one hour. The reaction mixture was cooled and diluted with ether (500 ml). The ether solution was washed three times with water, dried over sodium sulphate, and evaporated to dryness to give 1-n-butylthio-2-aldehydo-6-methyl-1, 6-heptadiene (XXXIX) (2.5 g, yield = 85%).

Nuclear magnetic resonance spectrum no. 21: τ =2.8 (olefinic proton beta to carbonyl group); τ =-0.84 (aldehyde proton); τ =5.35 (new olefinic protons). Infrared spectrum no. 10: absorptions at 1680 cm^{-1} (carbonyl group) and 1587 cm^{-1}.

SPECTRA

PLATE I



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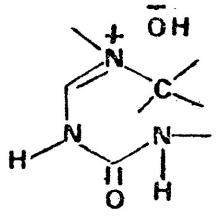

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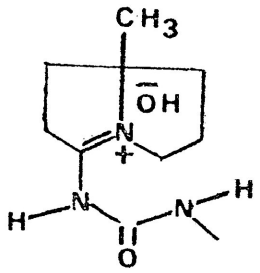

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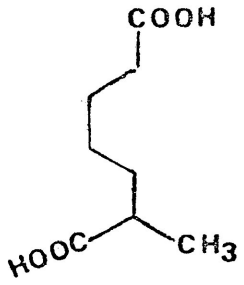

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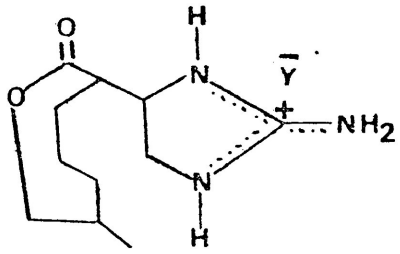

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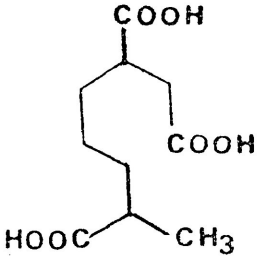
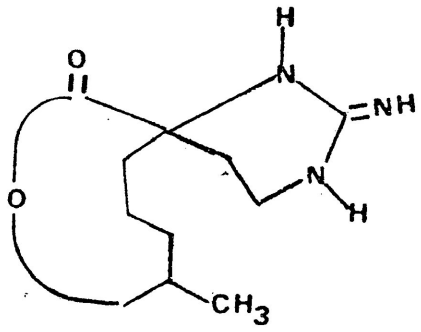


VI

PLATE II



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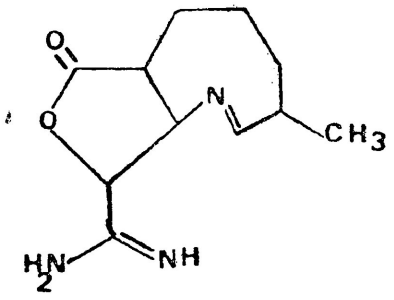

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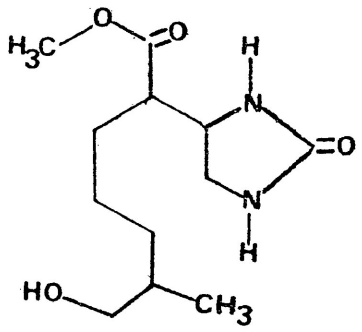

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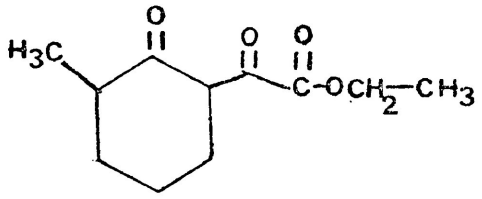

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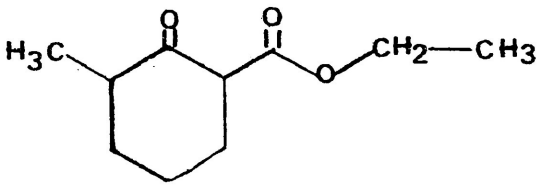

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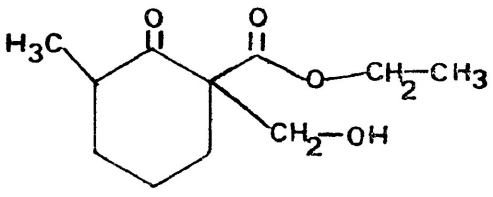
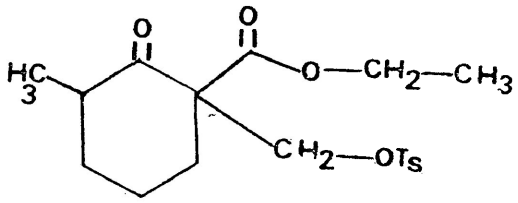


XII

PLATE III



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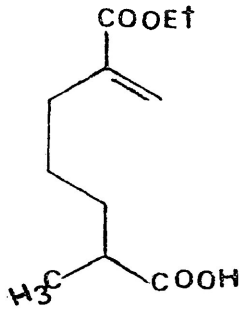

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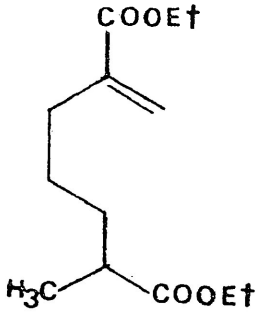

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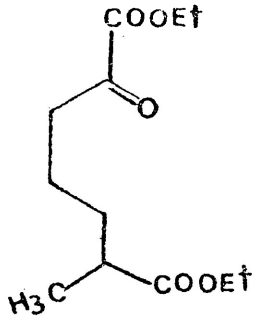

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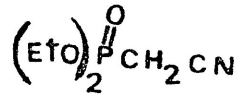

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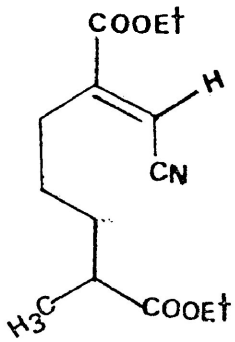
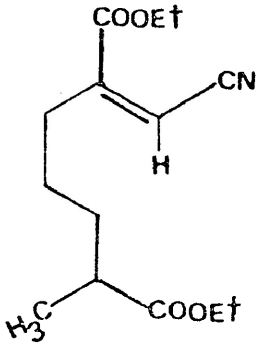
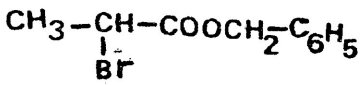


XVIIa

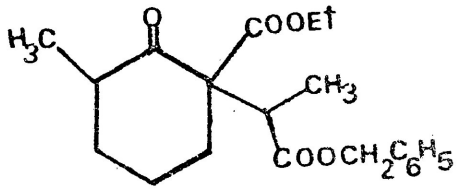


XVIIb

PLATE IV



XVIII



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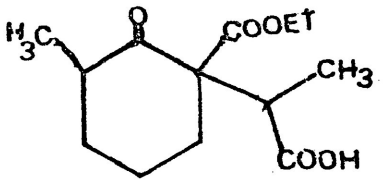

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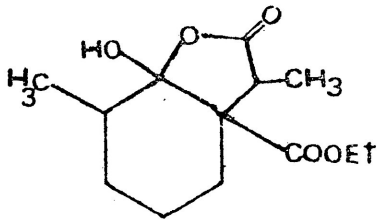

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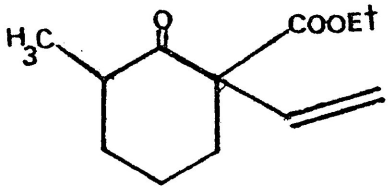

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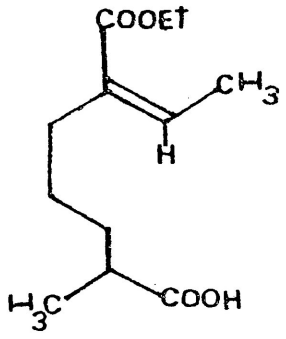

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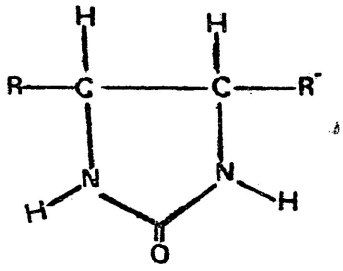
PLATE V



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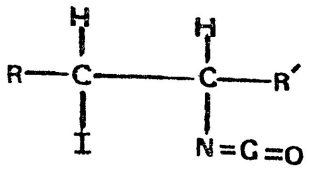

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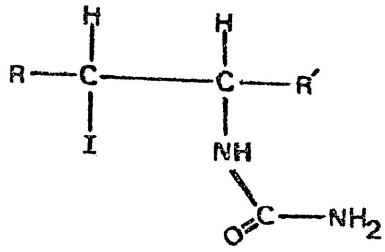

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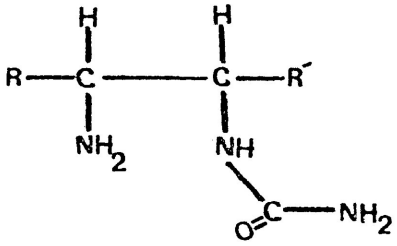

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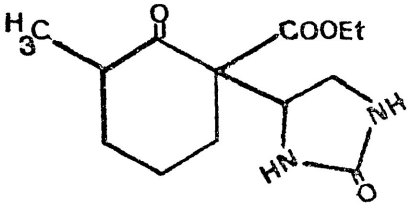

XXVIII

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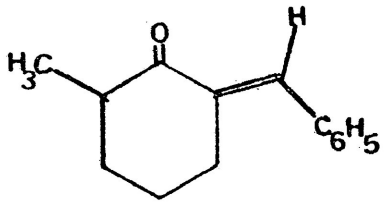

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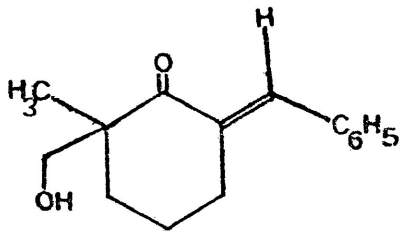

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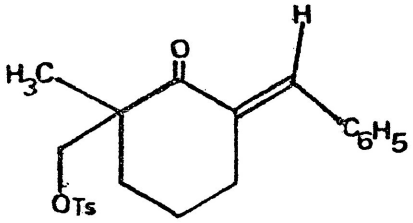

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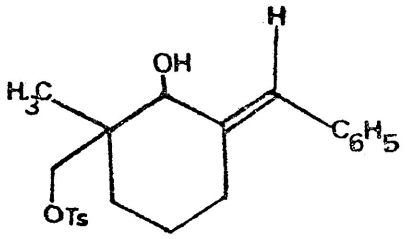

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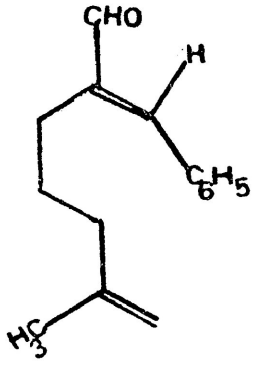

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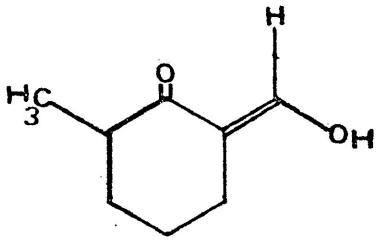

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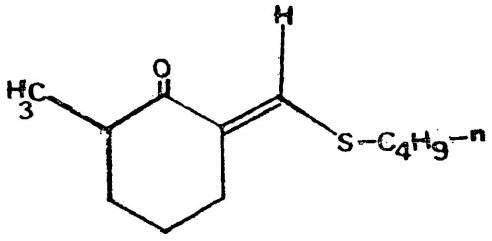

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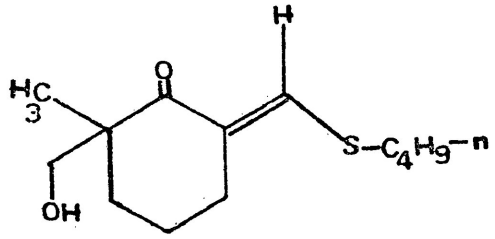

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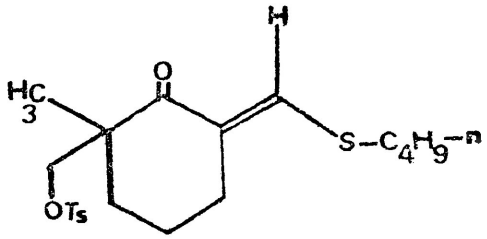

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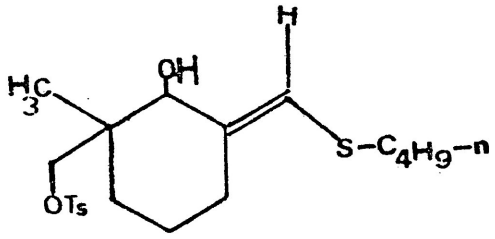

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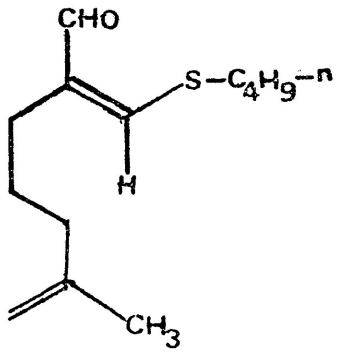

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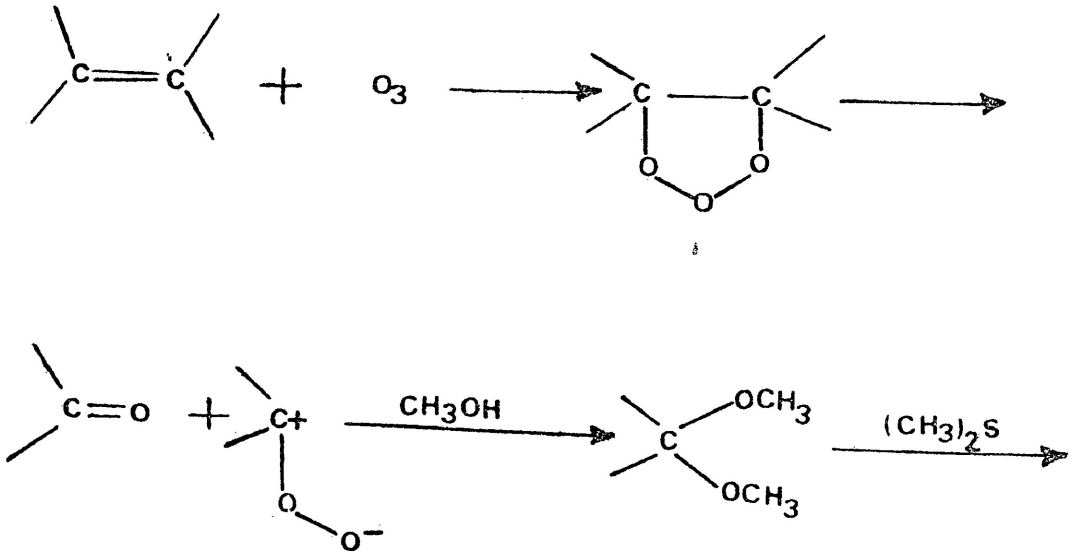
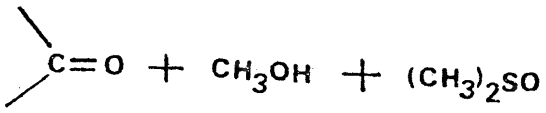
PLATE VIII





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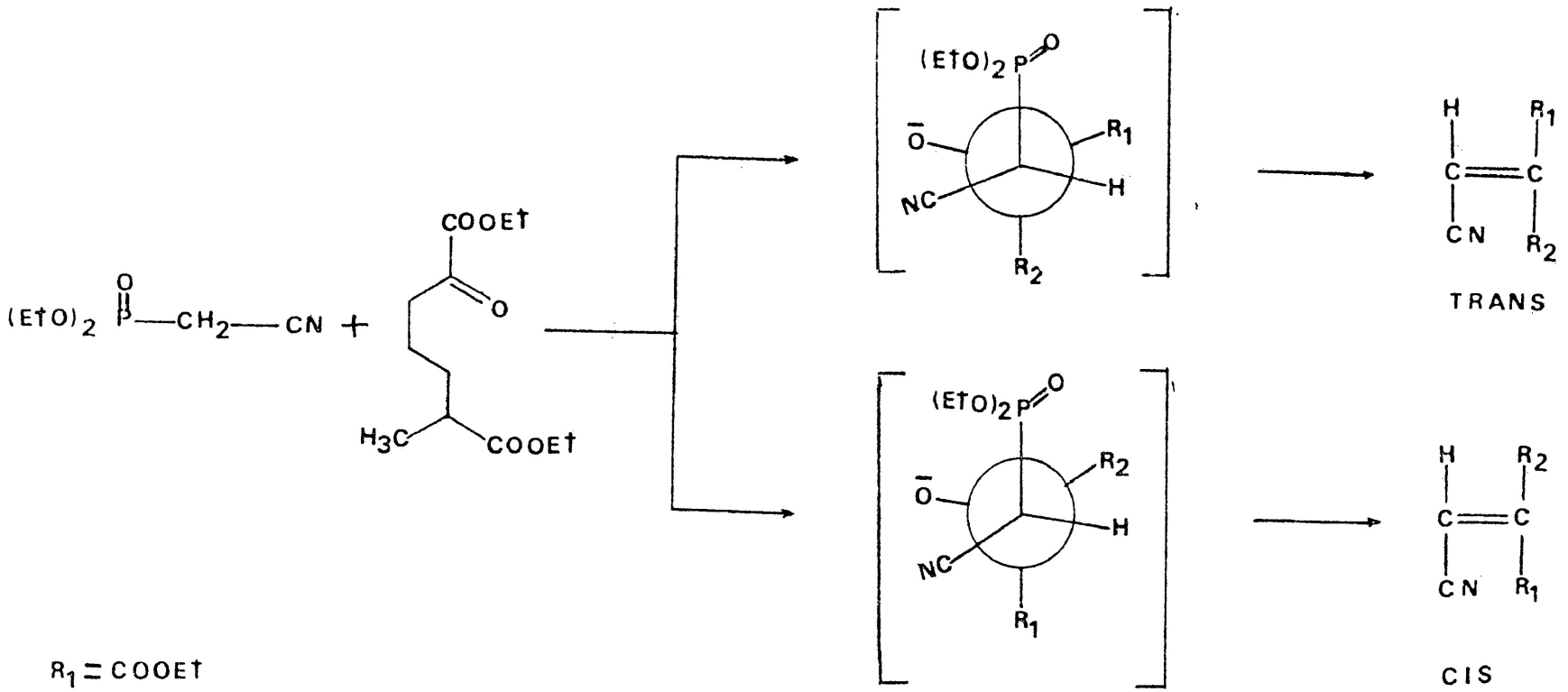
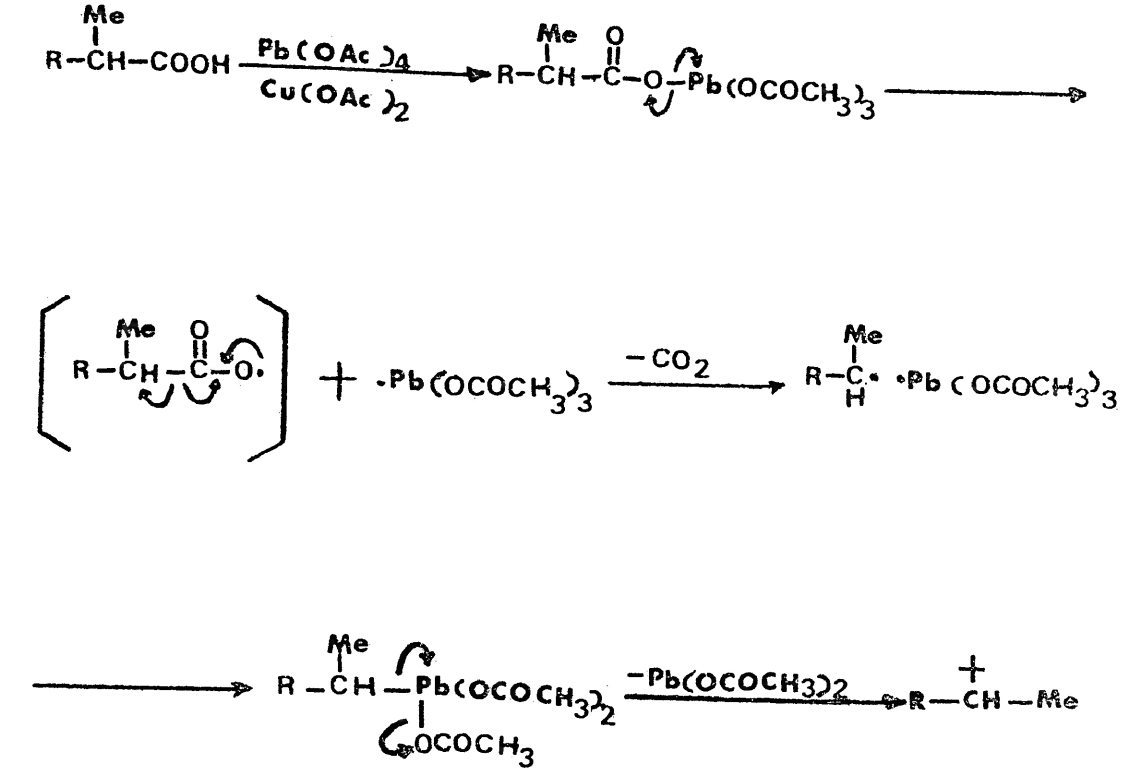


$R_1 = COOEt$

$R_2 = CH_2—CH_2—CH(CH_3)—COOEt$

PLATE X


Me
R–CH–COOH
Pb(OAc)4
Cu(OAc)2
R–CH–C–O–Pb(OCOCH3)3
–CO2
·Pb(OCOCH3)3
R–C·
H
·Pb(OCOCH3)3
OCOCH3
–Pb(OCOCH3)2
R–CH–Me
R–CH=CH2

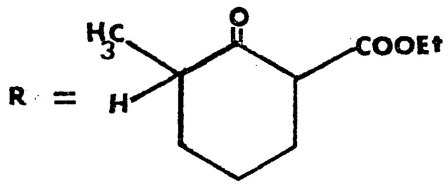

R =
H3C
H
O
COOEt

PLATE XI

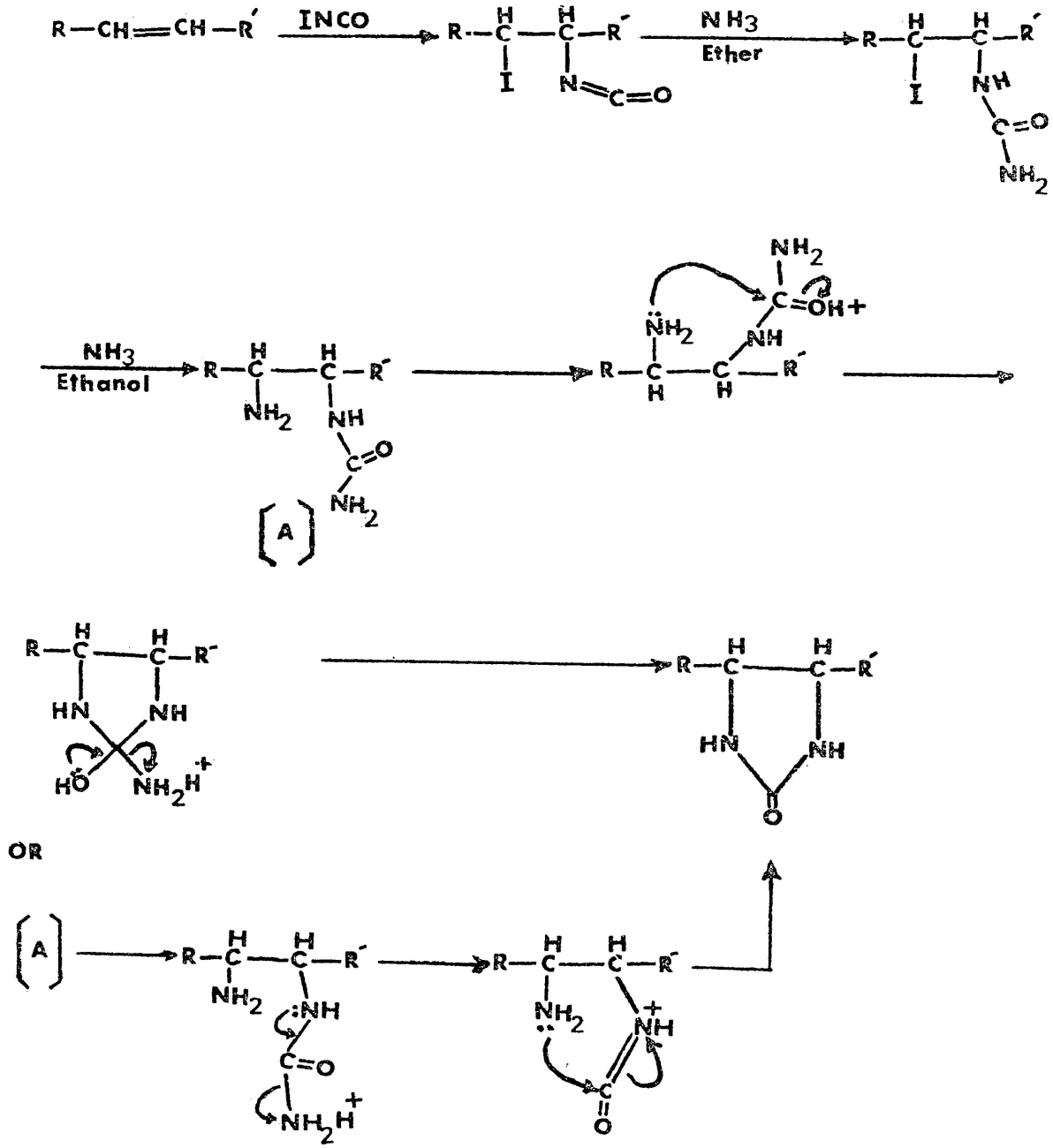
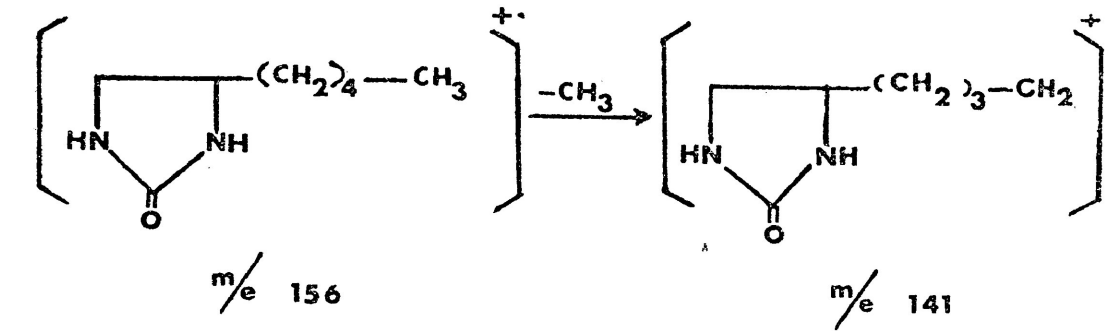
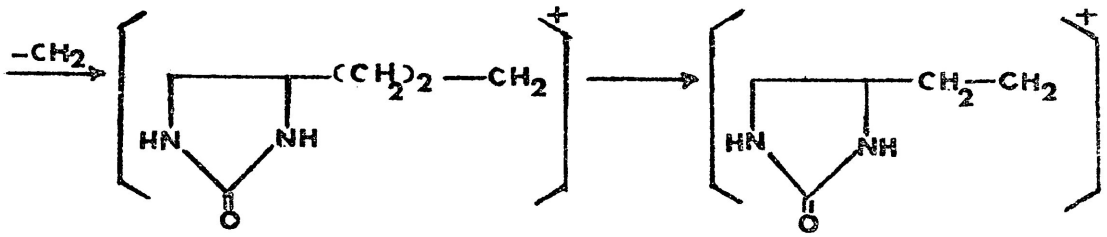


PLATE XII

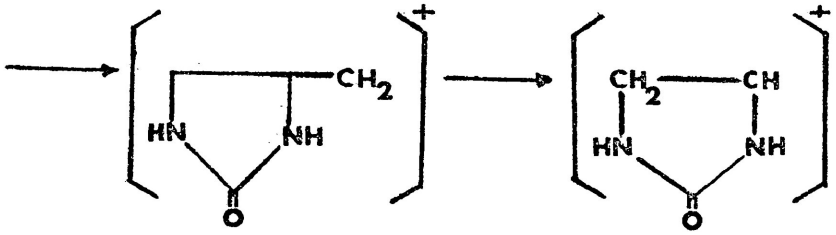


m/e 156 m/e 141

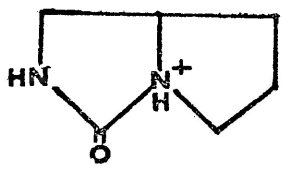


m/e 127 m/e 113

XL

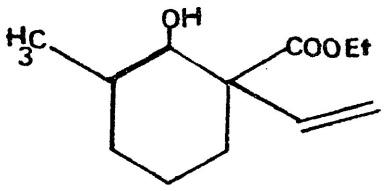


m/e 99 m/e 85

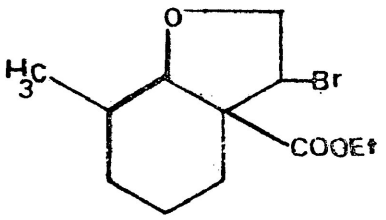


XL

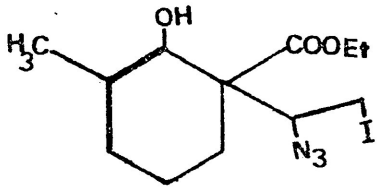
PLATE XIII



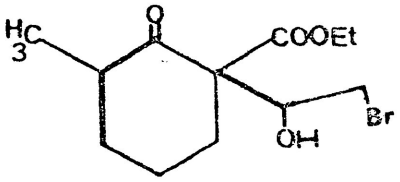
XLI



XLII



XLIII



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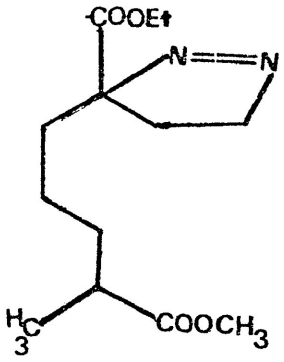

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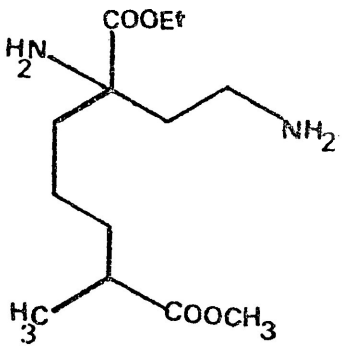
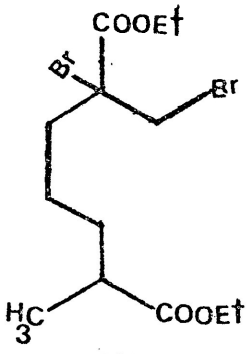
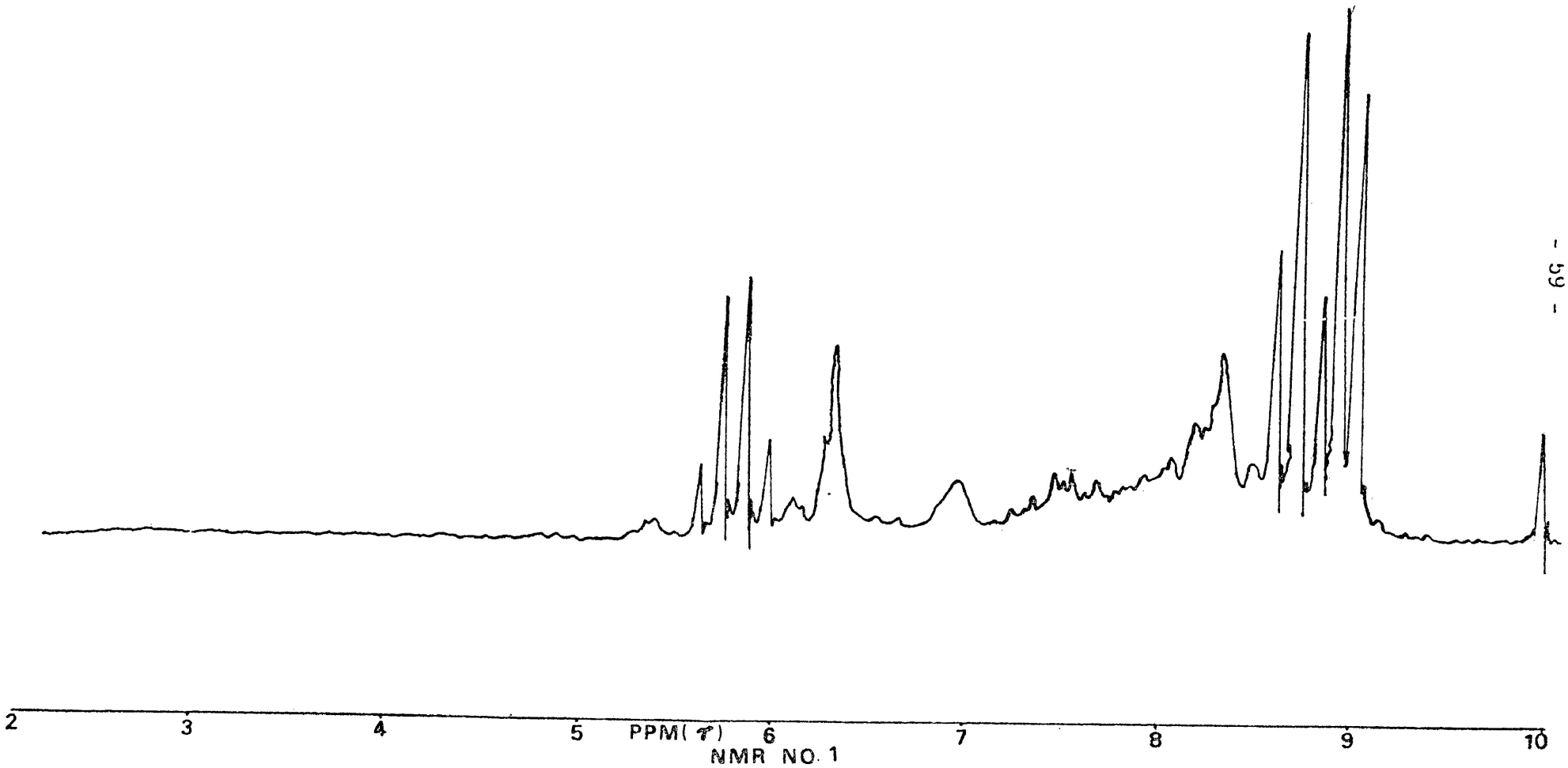


XLVI

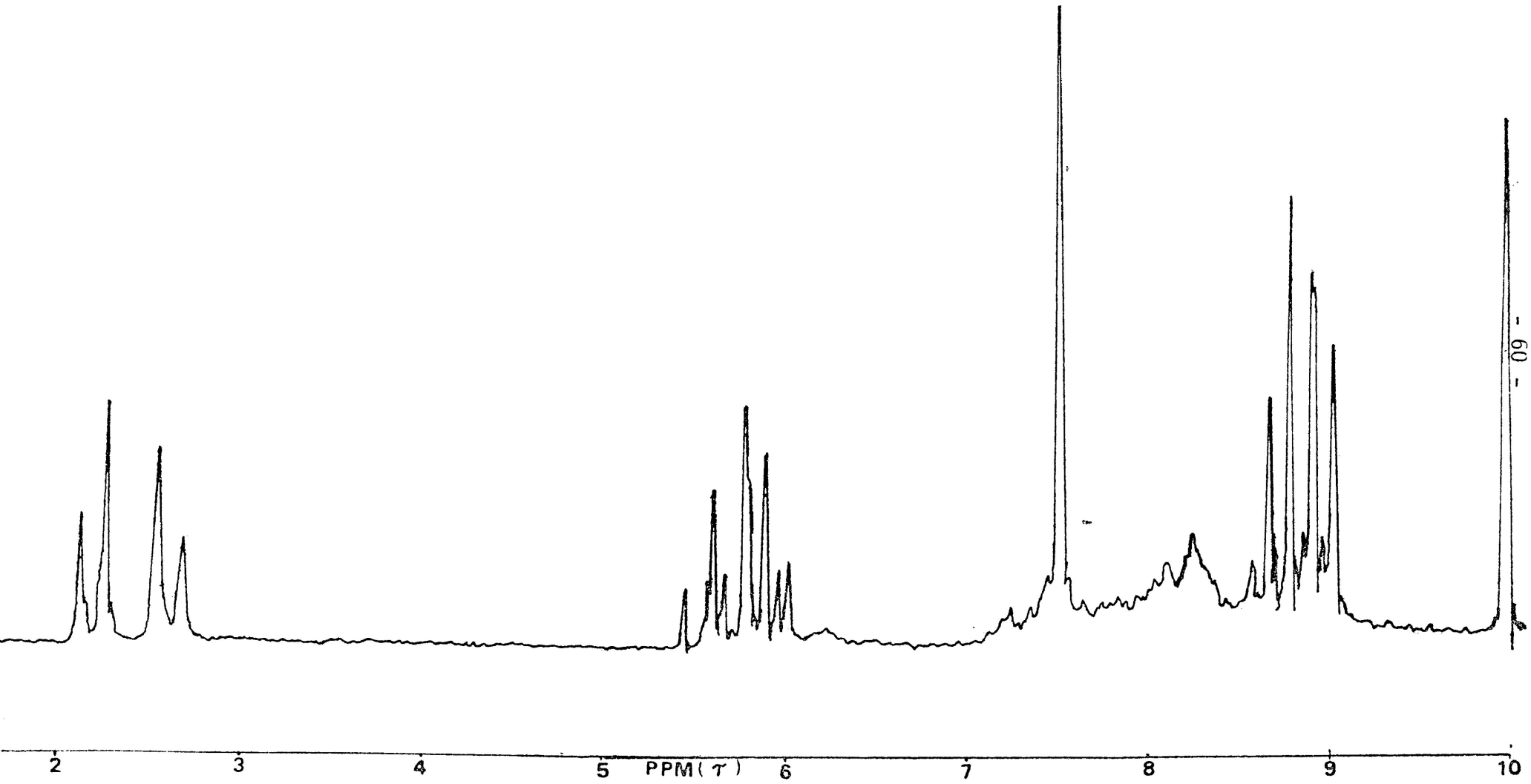


XLVII



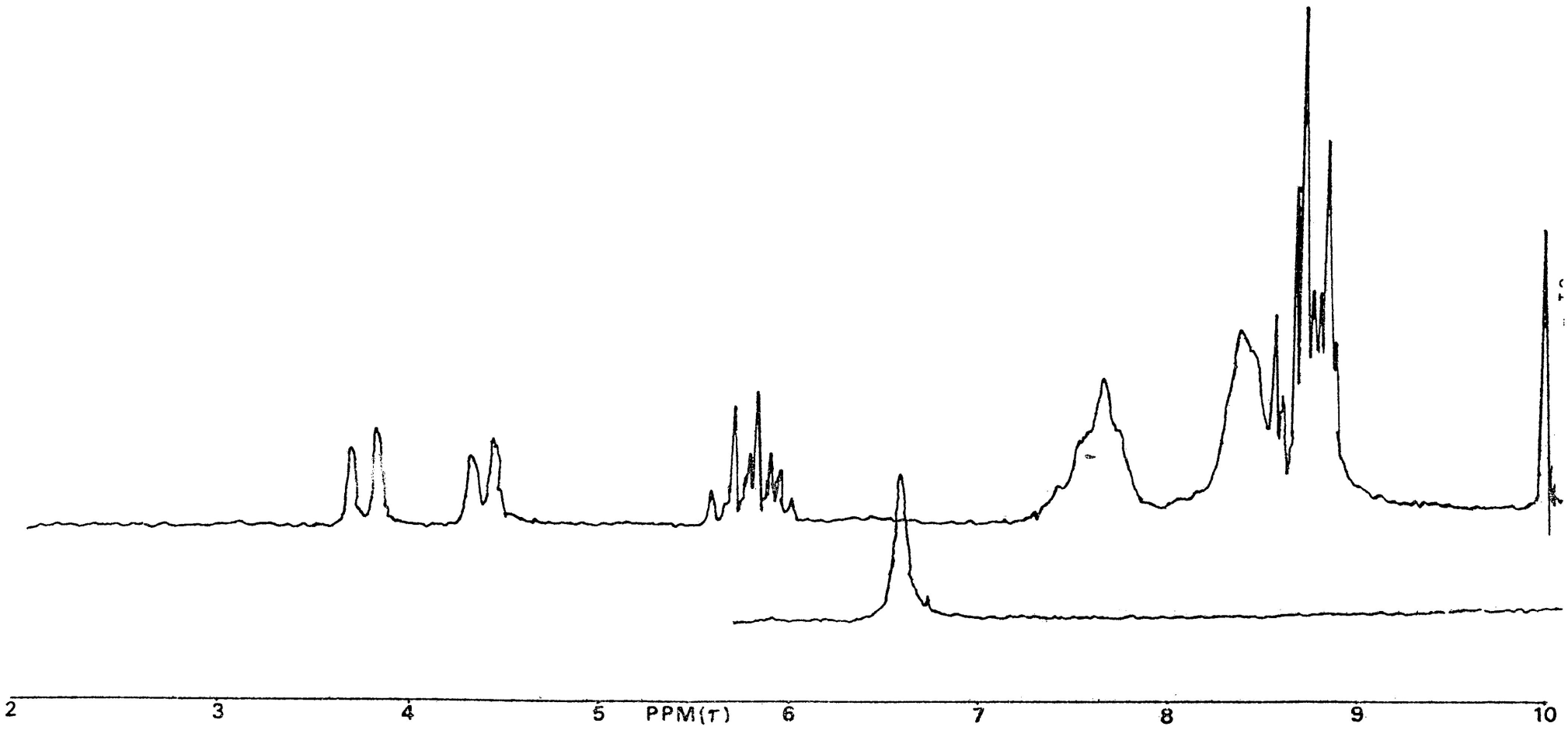
NMR NO. 1

ETHYL 2-METHYL-6-HYDROXYMETHYLCYCLOHEXANONE-6-CARBOXYLATE



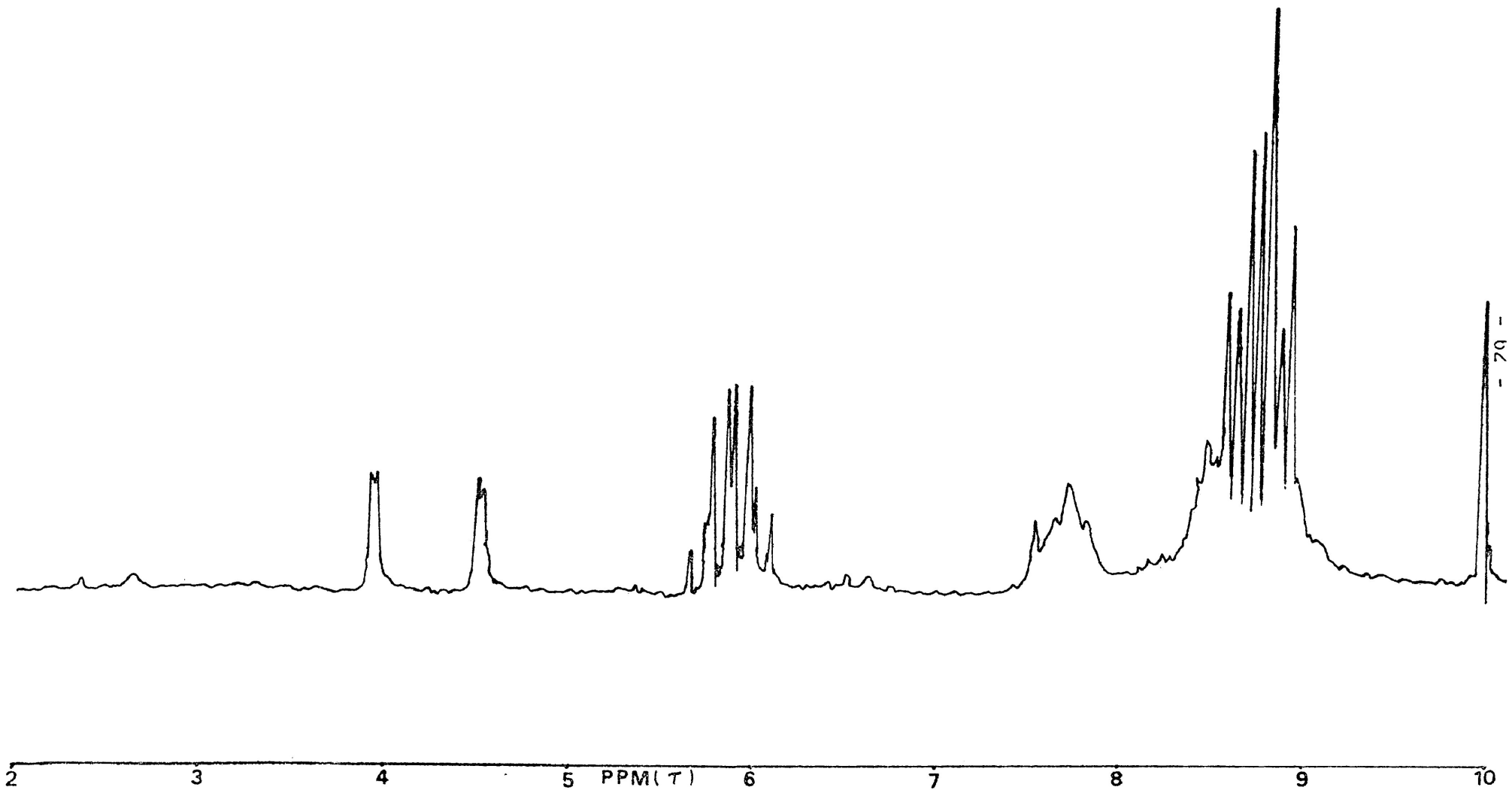
NMR NO. 2

ETHYL-2-METHYL-6-HYDROXYMETHYL P-TOLUENE SULFONATE CYCLOHEXANONE-6-CARBOXYLATE



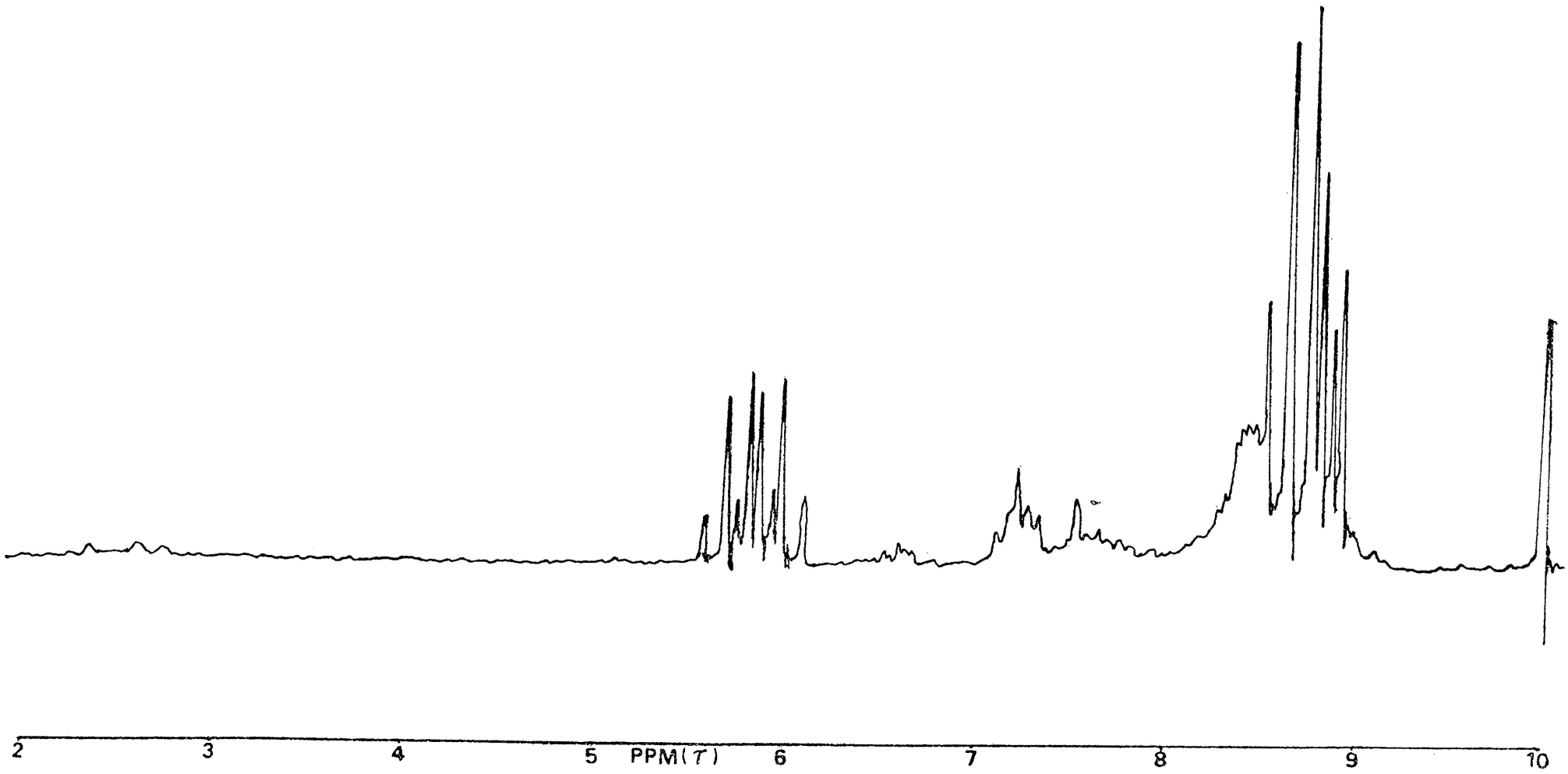
NMR NO. 3

2-METHYL-6-ETHYLCARBOXY-6-HEPTENOIC ACID



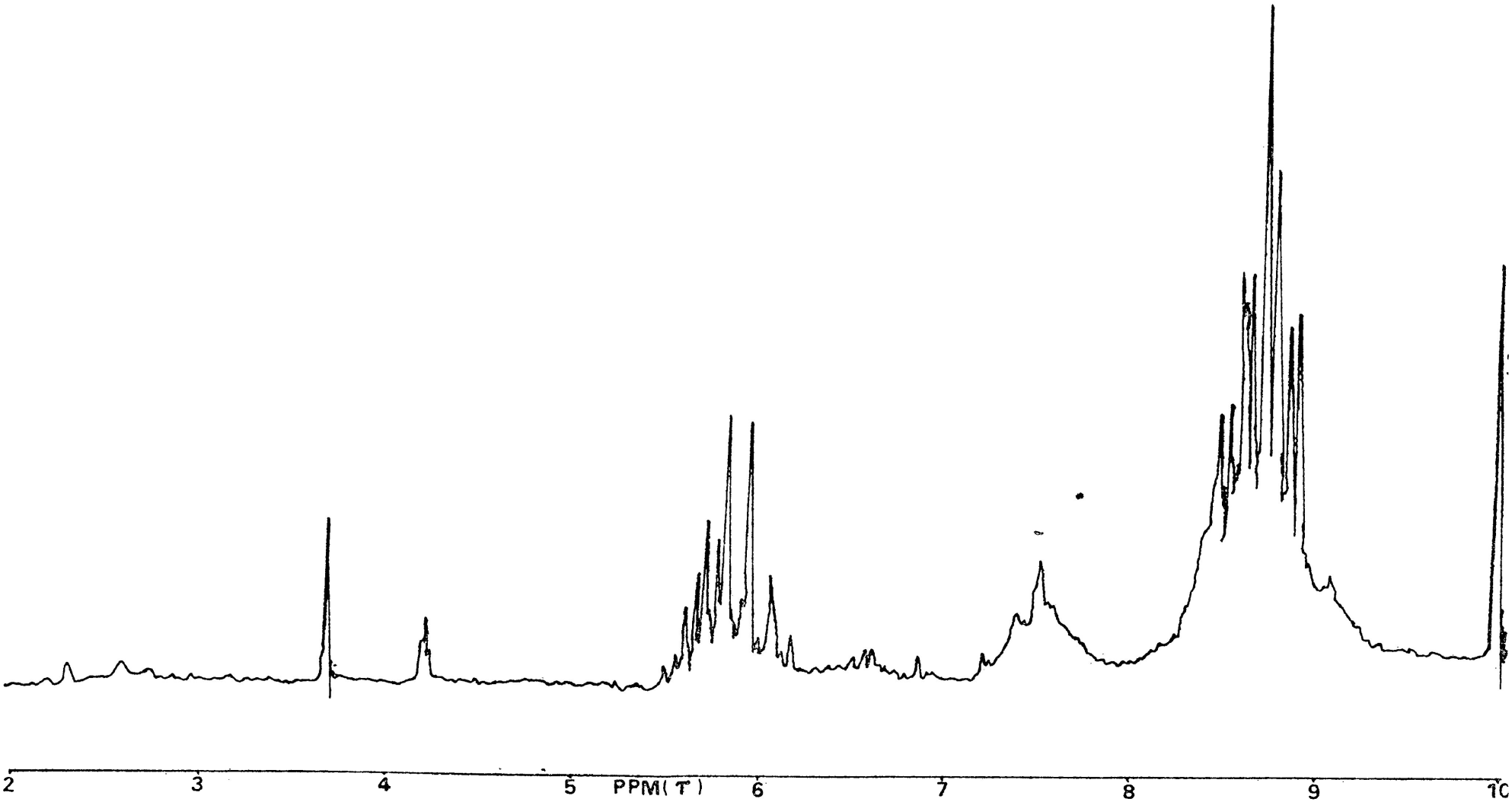
NMR NO. 4

ETHYL-2-METHYL-6-ETHYLCARBOXY-6-HEPTENOATE



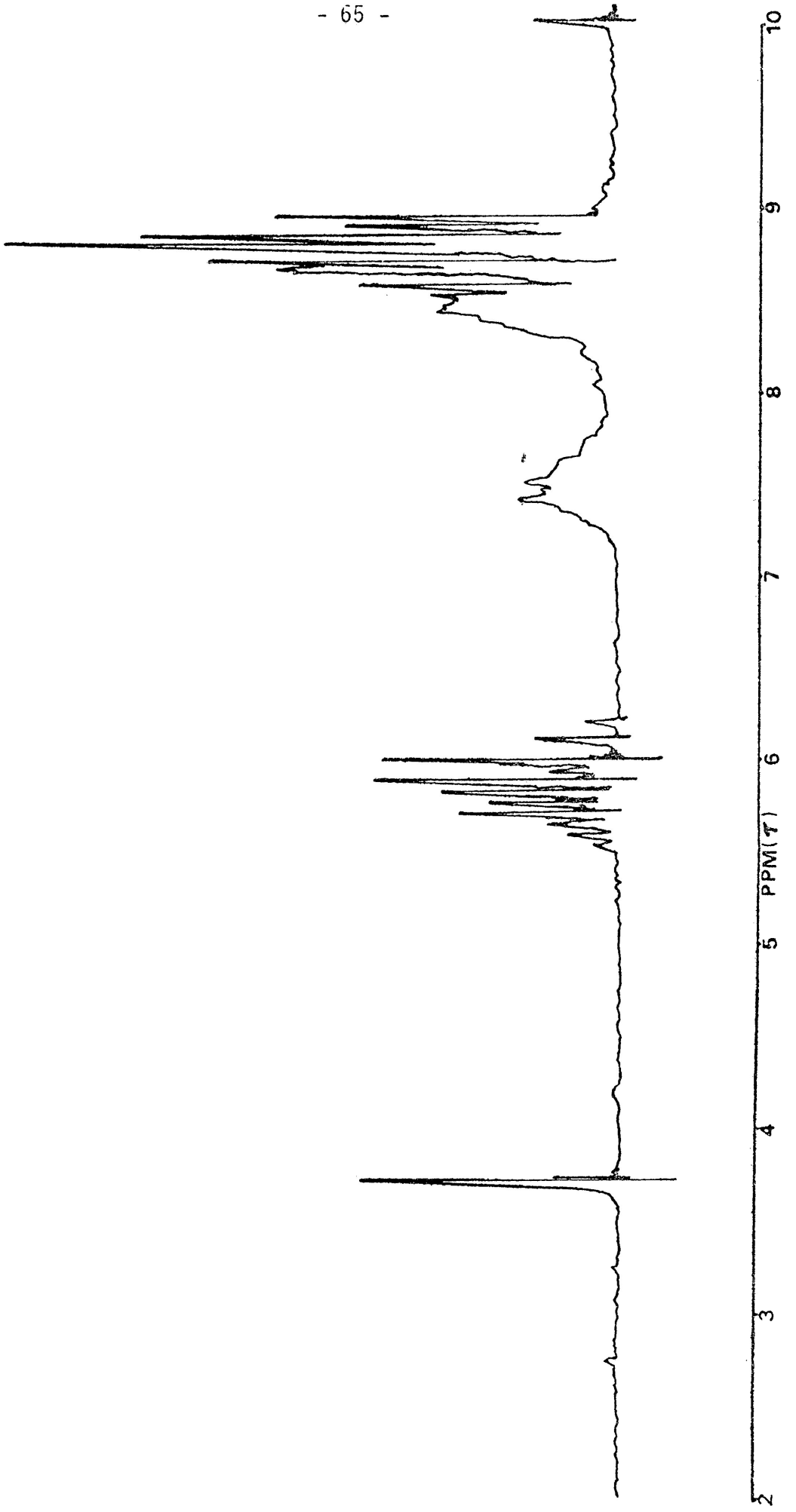
NMR NO. 5

DIETHYL 2-KETO-6-METHYL PIMELATE



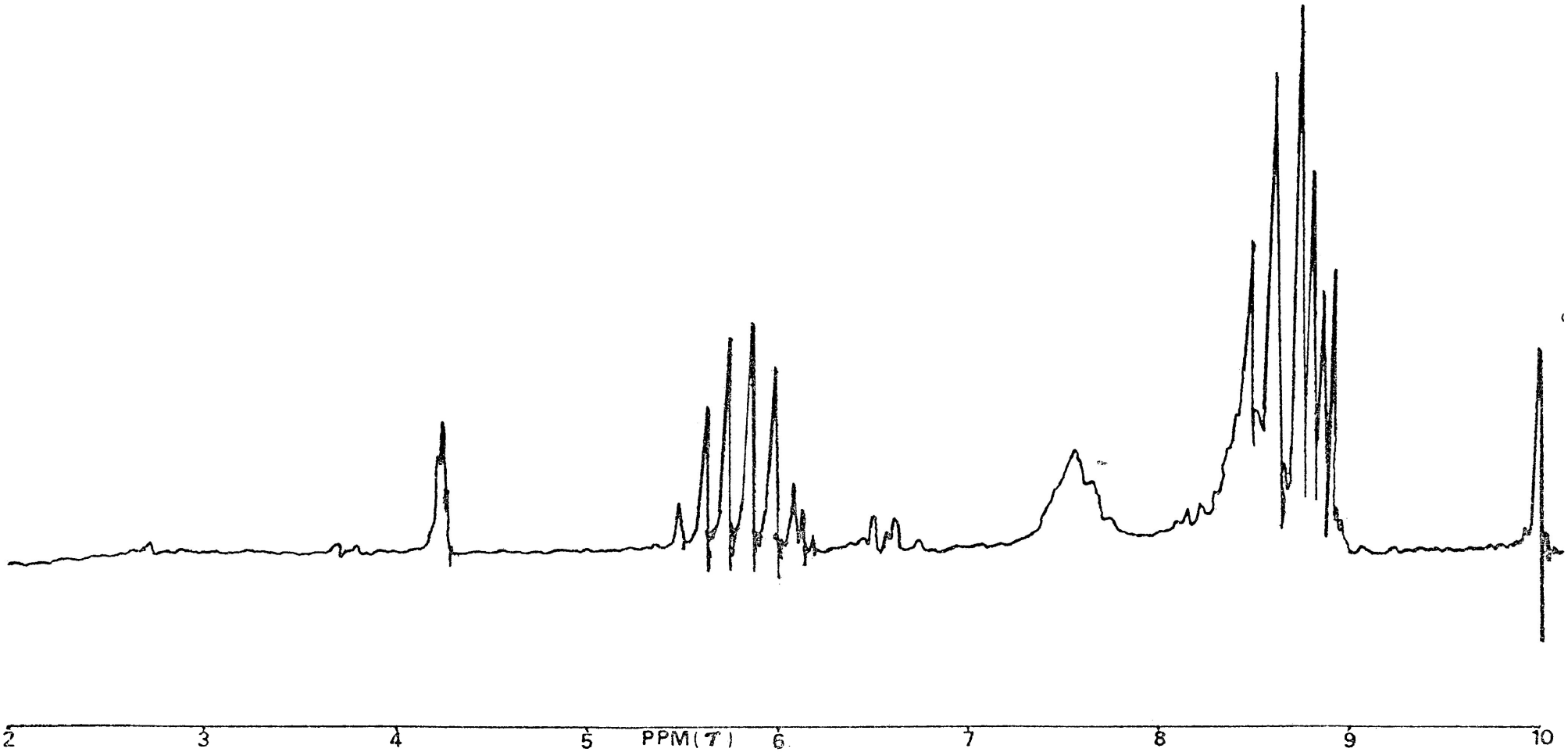
NMR NO. 6

1-CYANO-2,6-DICARBETHOXY-1-OCTENE



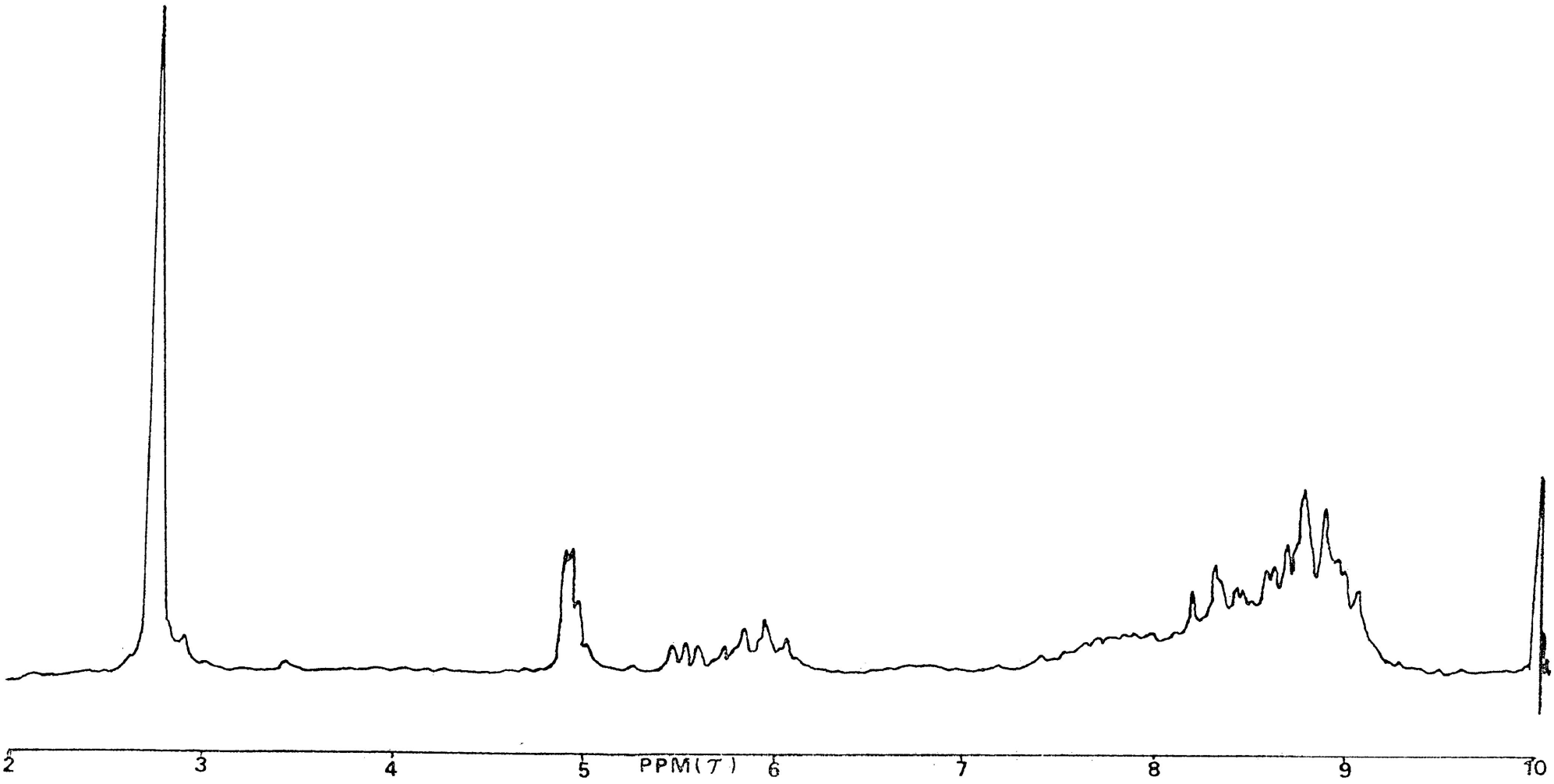
NMR NO. 7

TRANS ISOMER



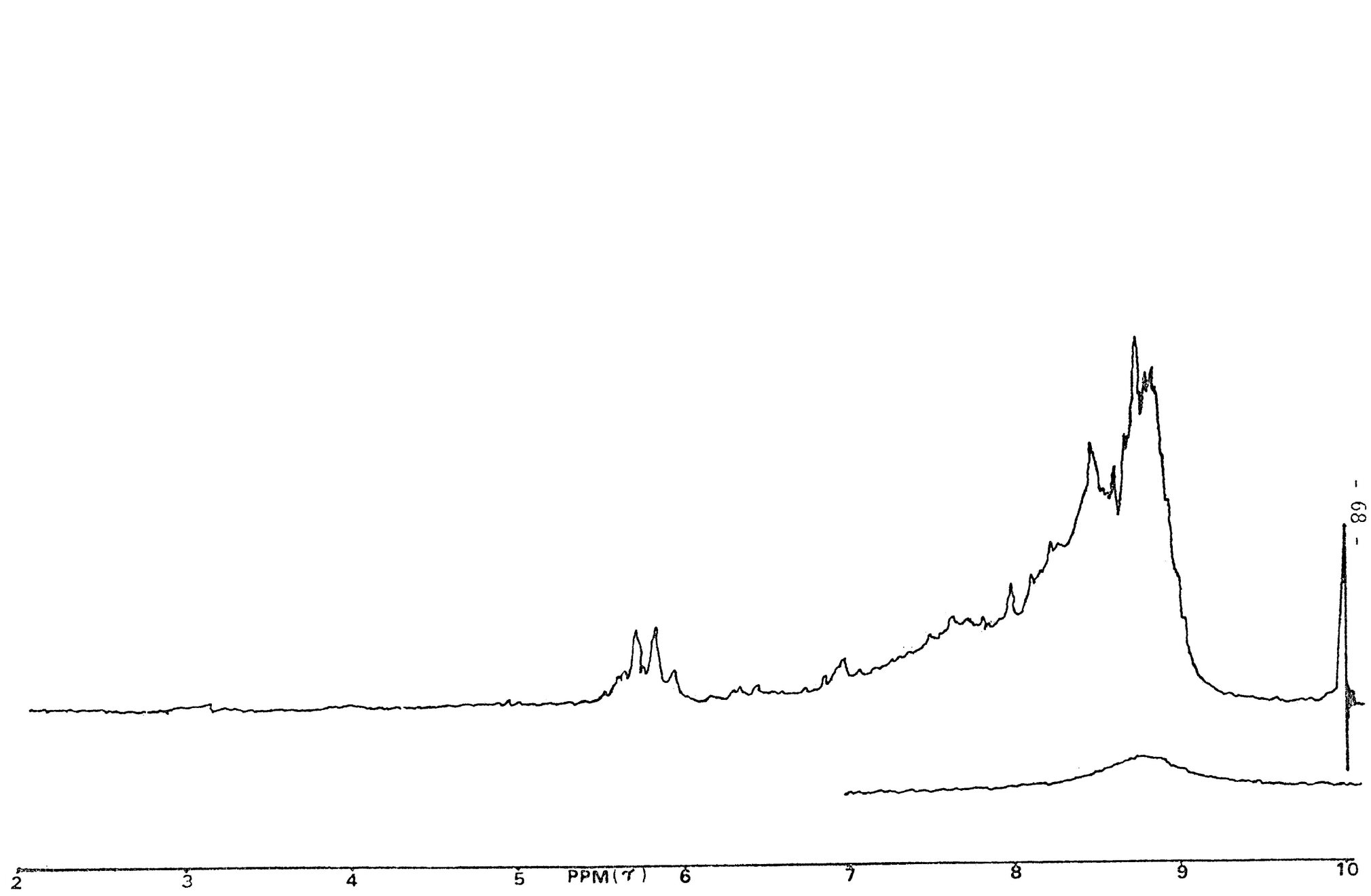
NMR NO. 8

CIS ISOMER



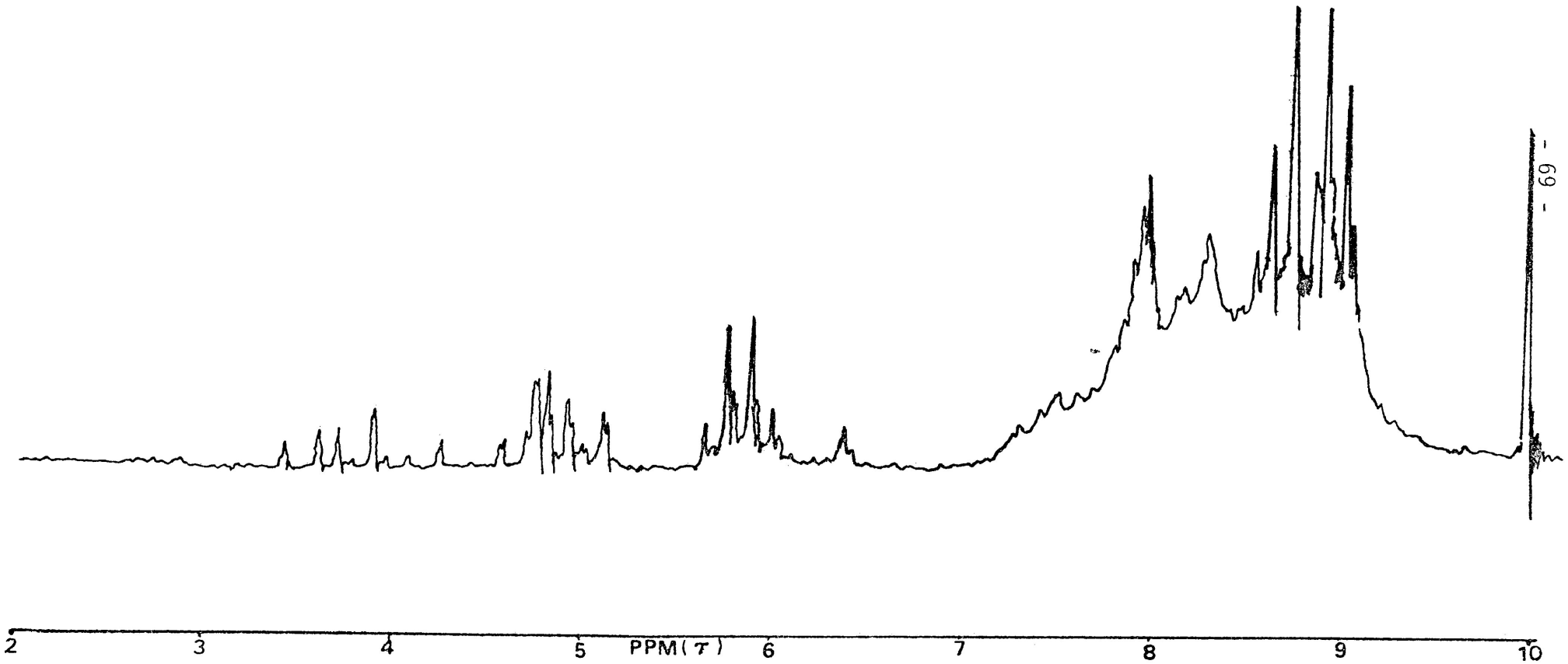
NMR NO. 9

ETHYL 2-METHYL-6-(2'-BENZYLPROPIONATE) CYCLOHEXANONE - 6 - CARBOXYLAT



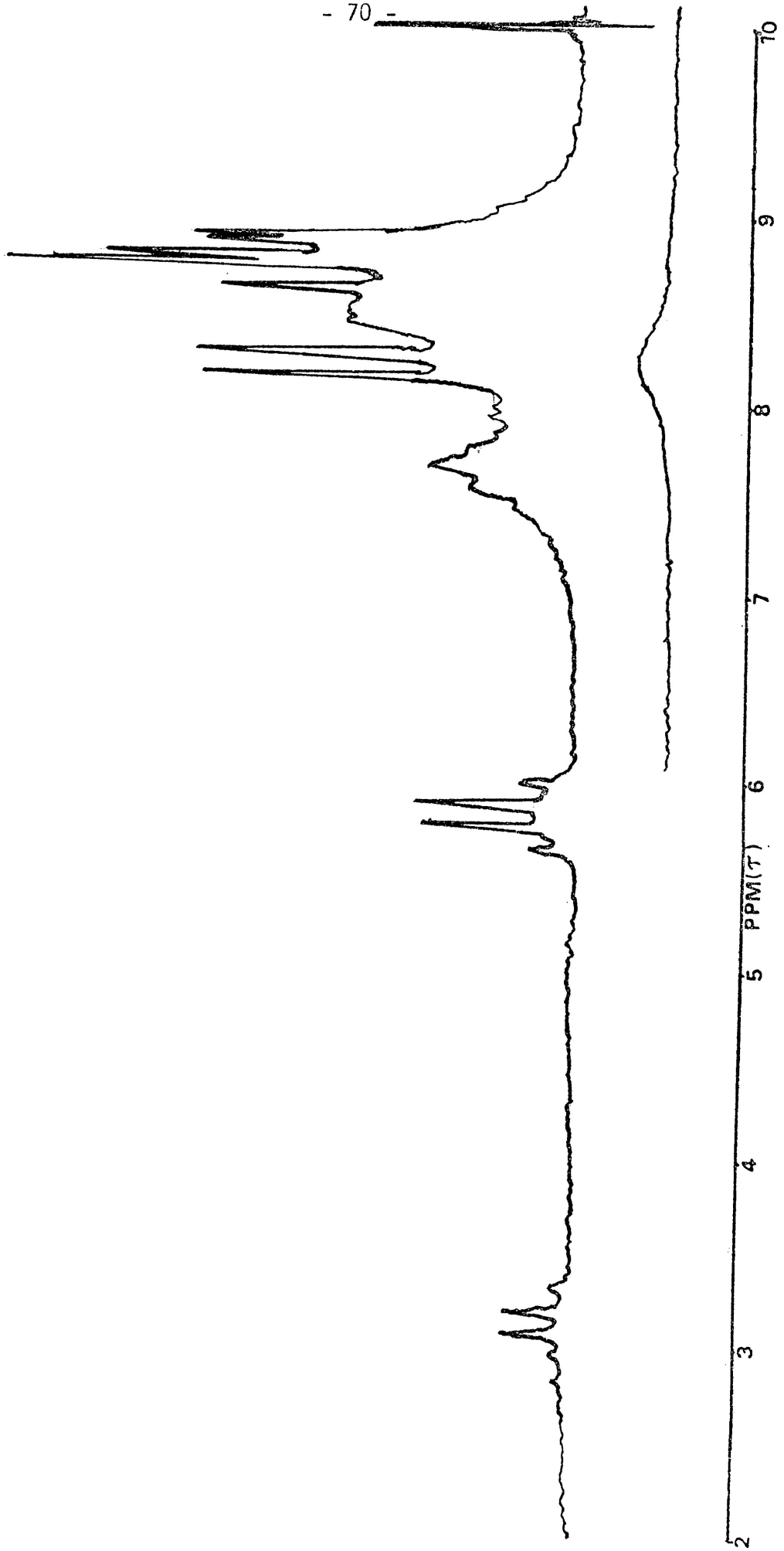
NMR NO. 10

ETHYL 2-METHYL-6-(2'-PROPIONIC ACID) CYCLOHEXANONE-6-CARBOXYLAT



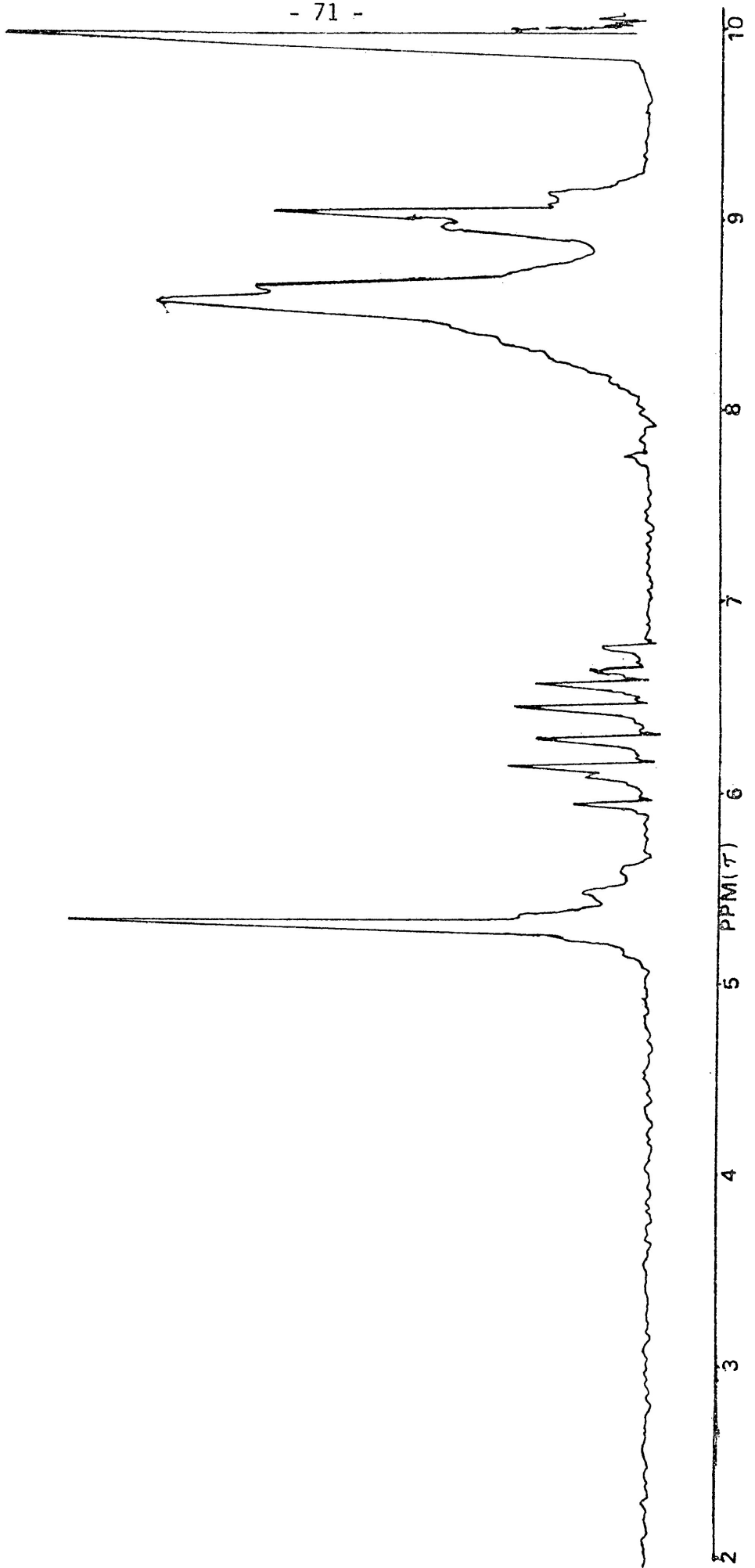
NMR NO. 11

2 – METHYL – 6 – VINYLCYCLOHEXANONE – 6 – CARBOXYLATE



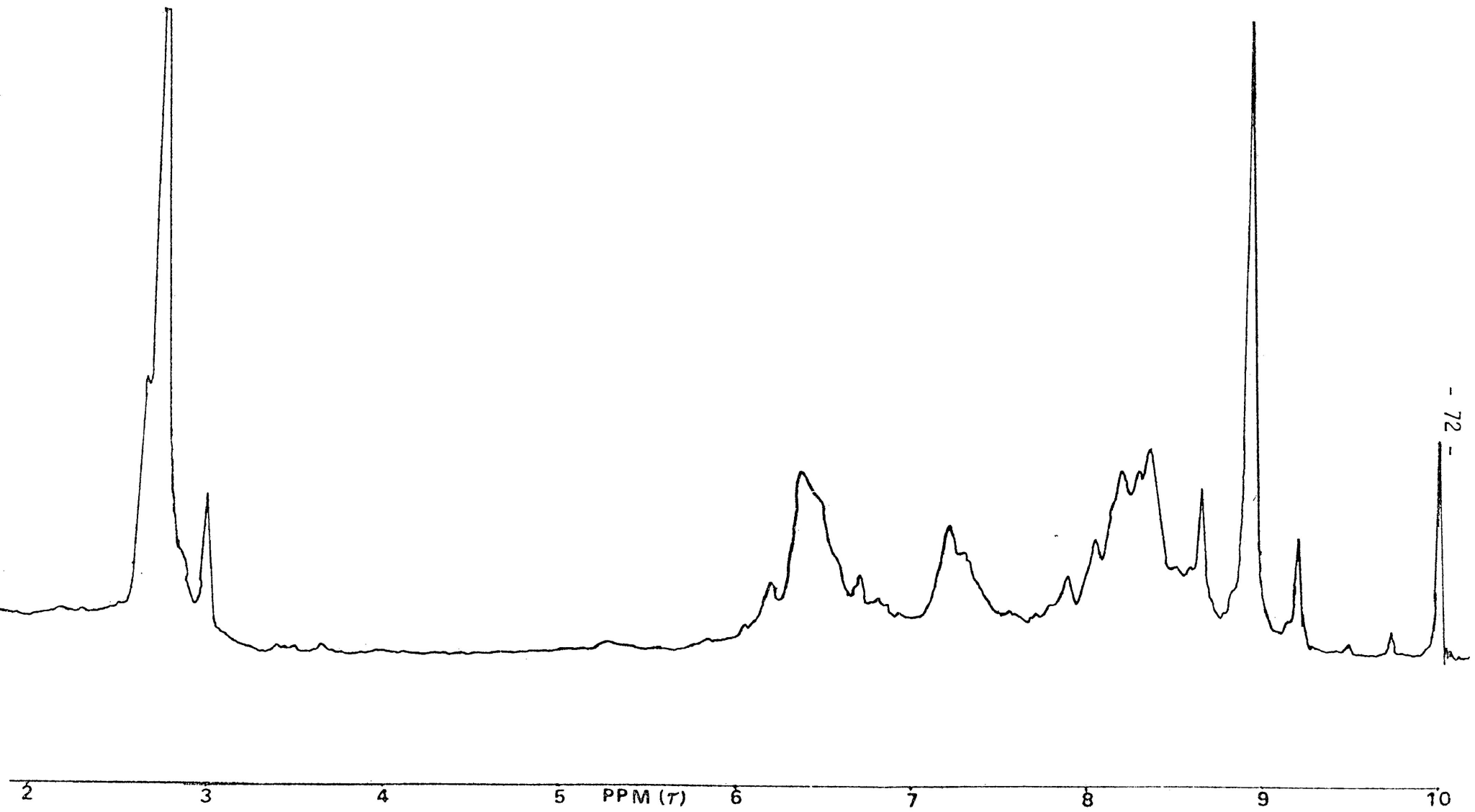
NMR NO. 12

2-METHYL-6-CARBTHOXY-6-OCTENOIC ACID



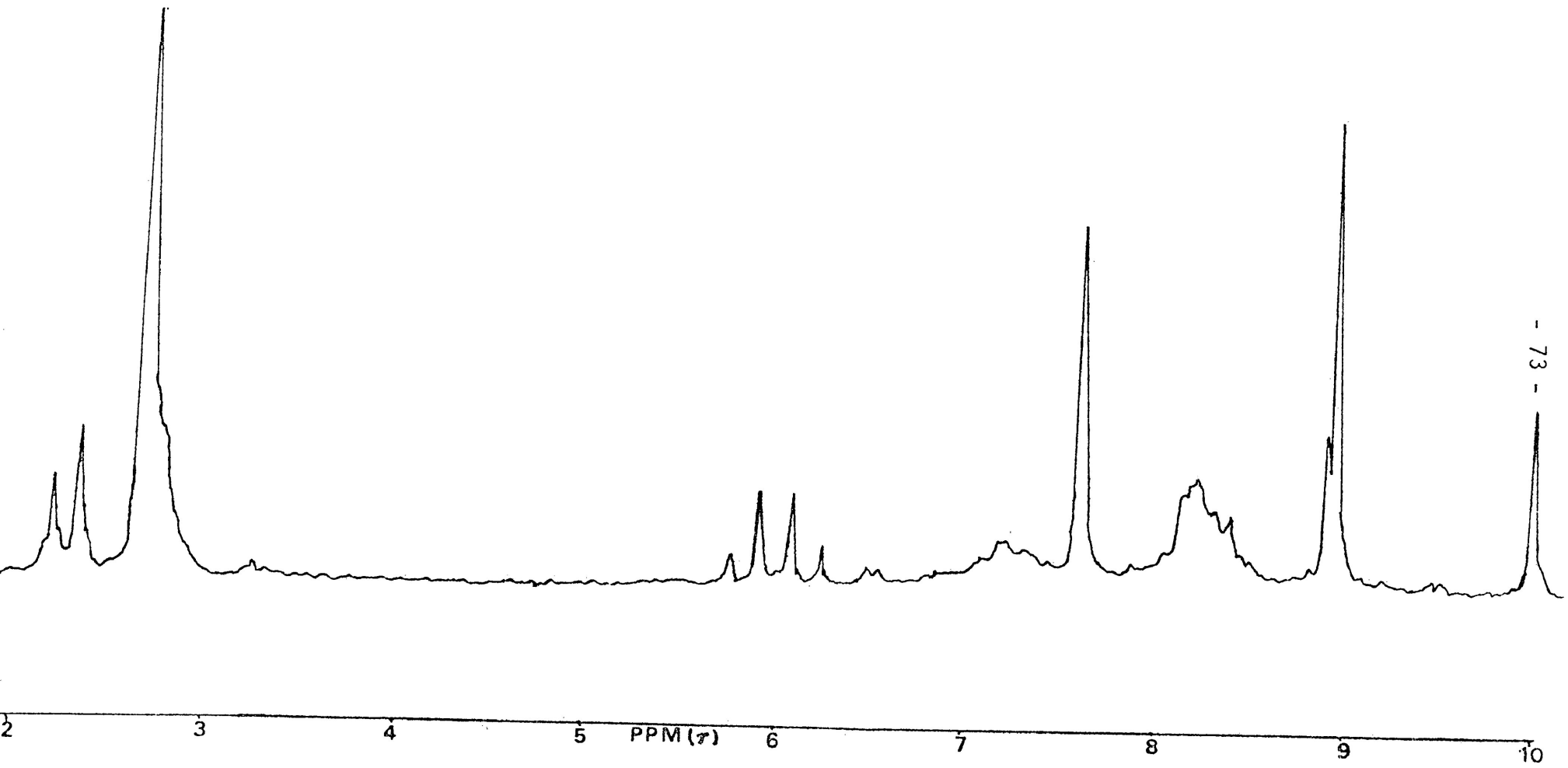
NMR NO. 13

4-PENTYL IMIDAZOLID-2-ONE



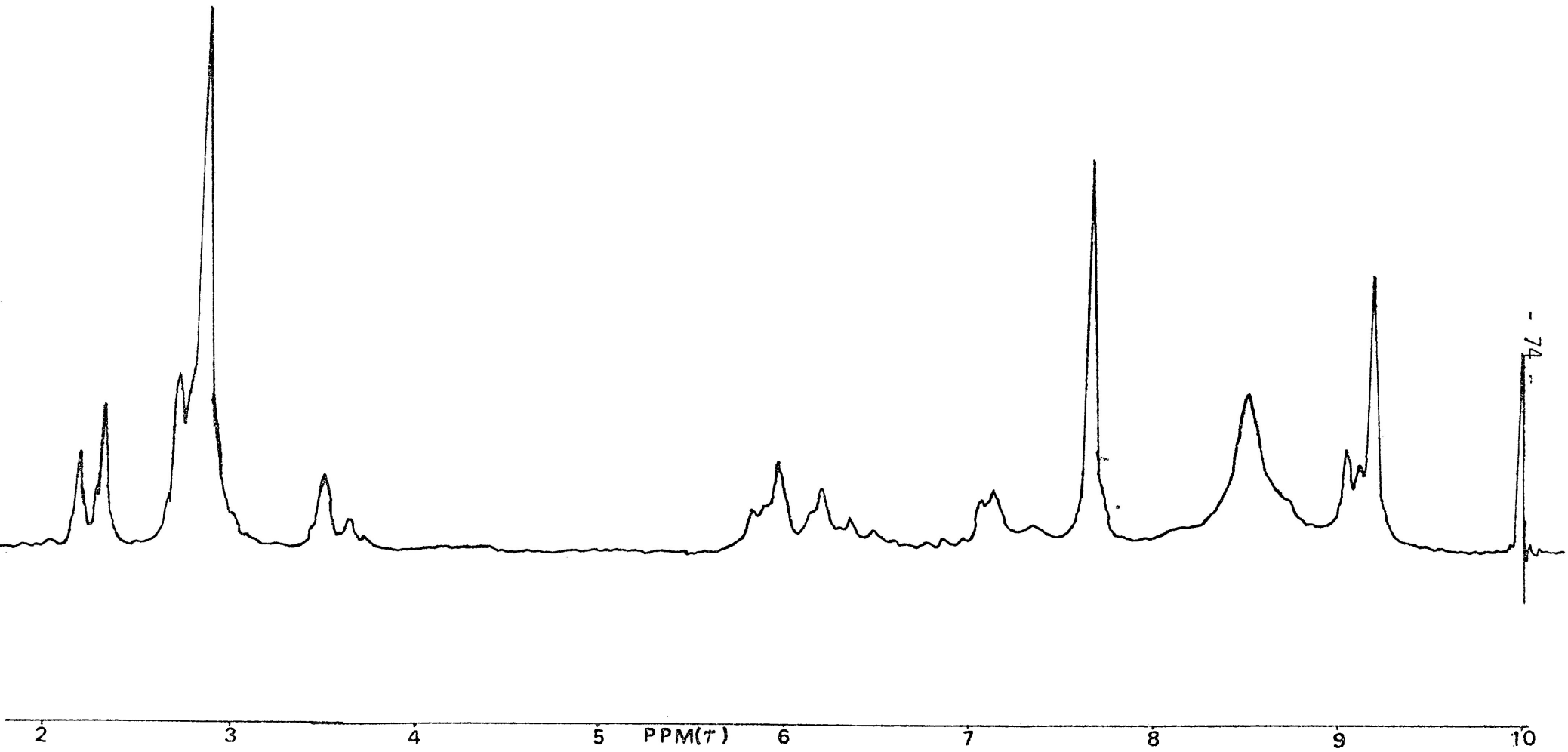
NMR NO. 14

2-BENZYLIDENE-6-METHYL-6-HYDROXYMETHYLCYCLOHEXANON



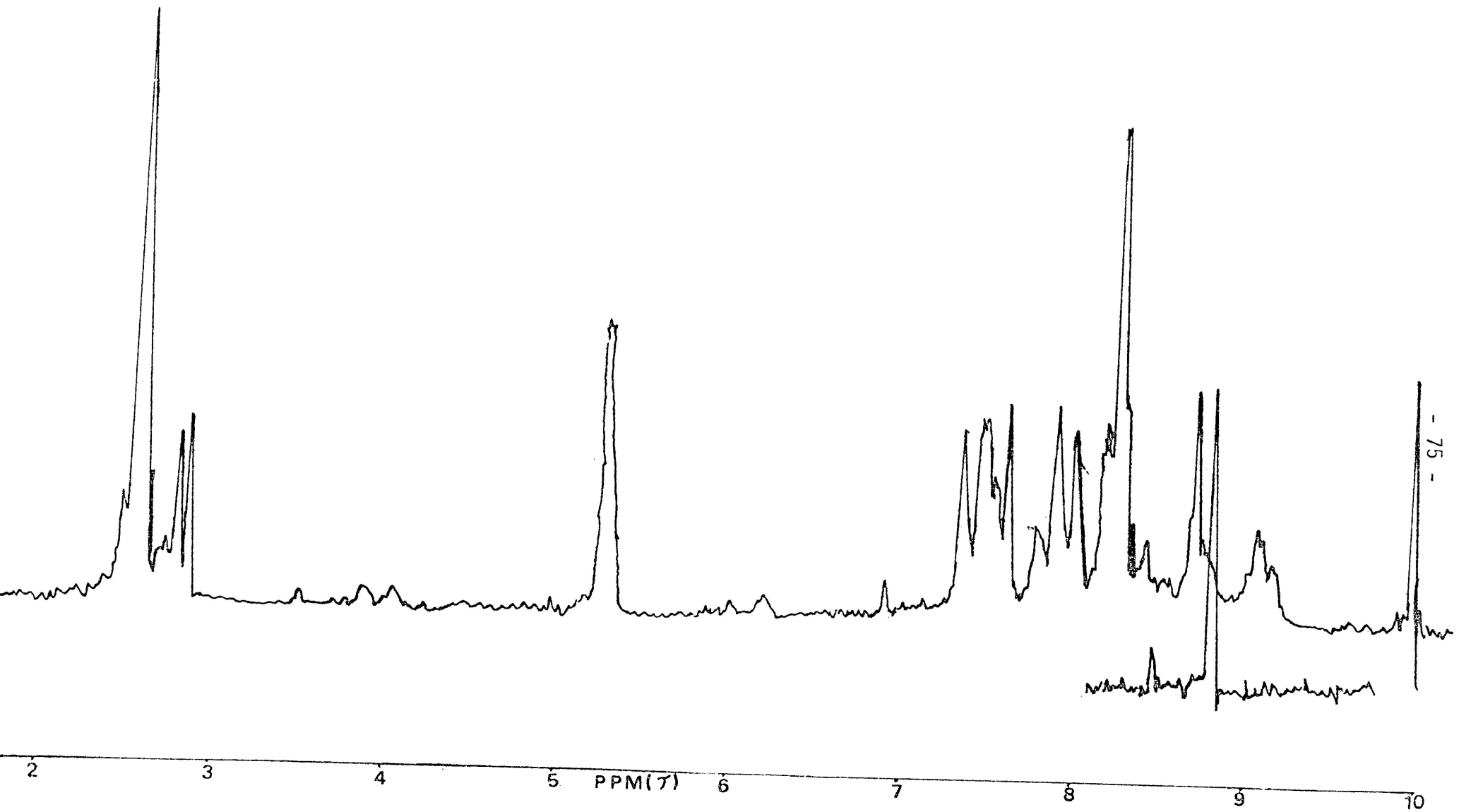
NMR NO.15

2-BENZYLIDENE-6-METHYL-6-HYDROXYMETHYL P-TOLUENE SULFONATE CYCLOHEXANONE



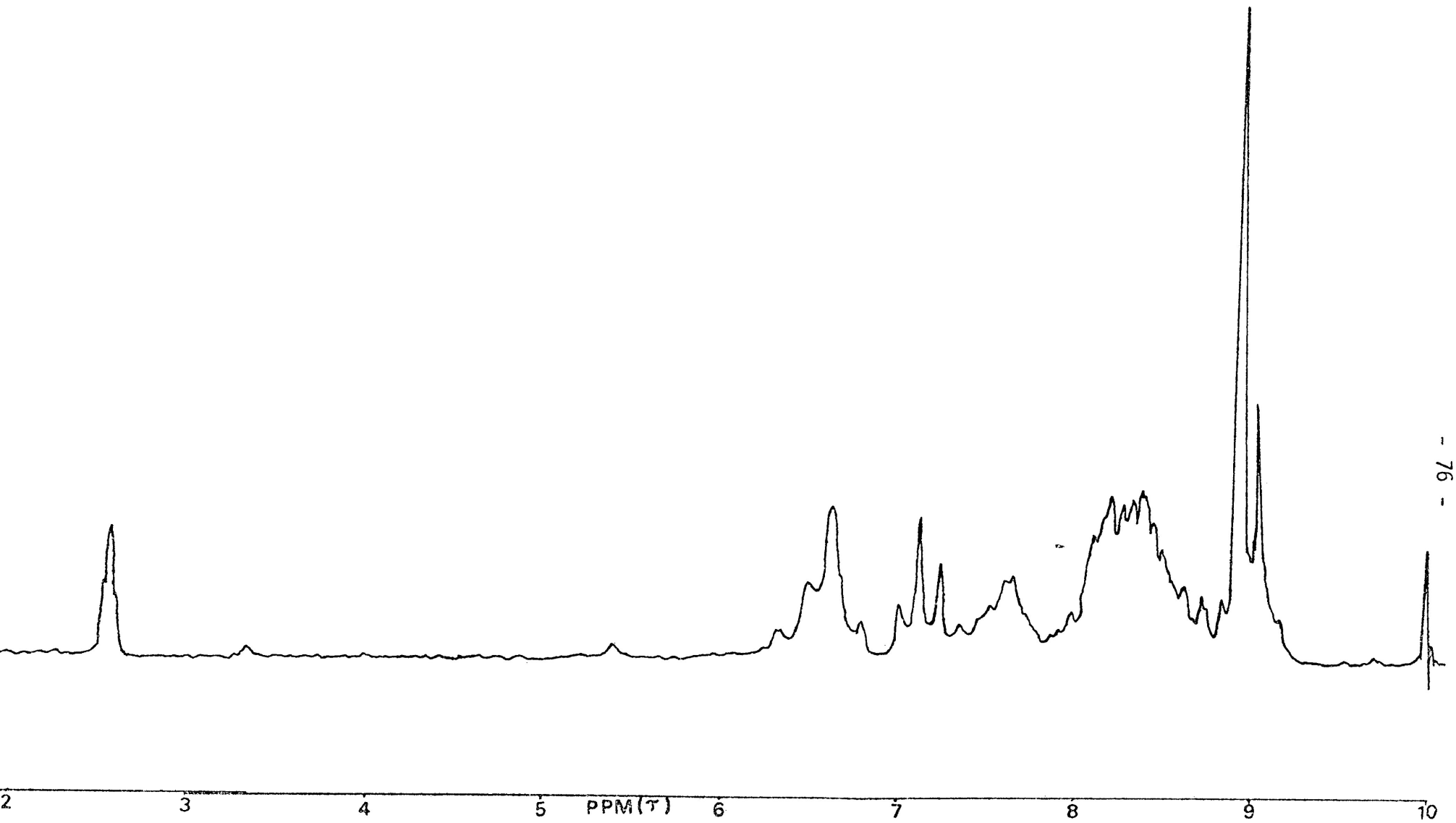
NMR NO. 16

2-BENZYLIDENE-6-METHYL-6-HYDROXYMETHYL P-TOLUENE SULFONATE CYCLOHEXANOL



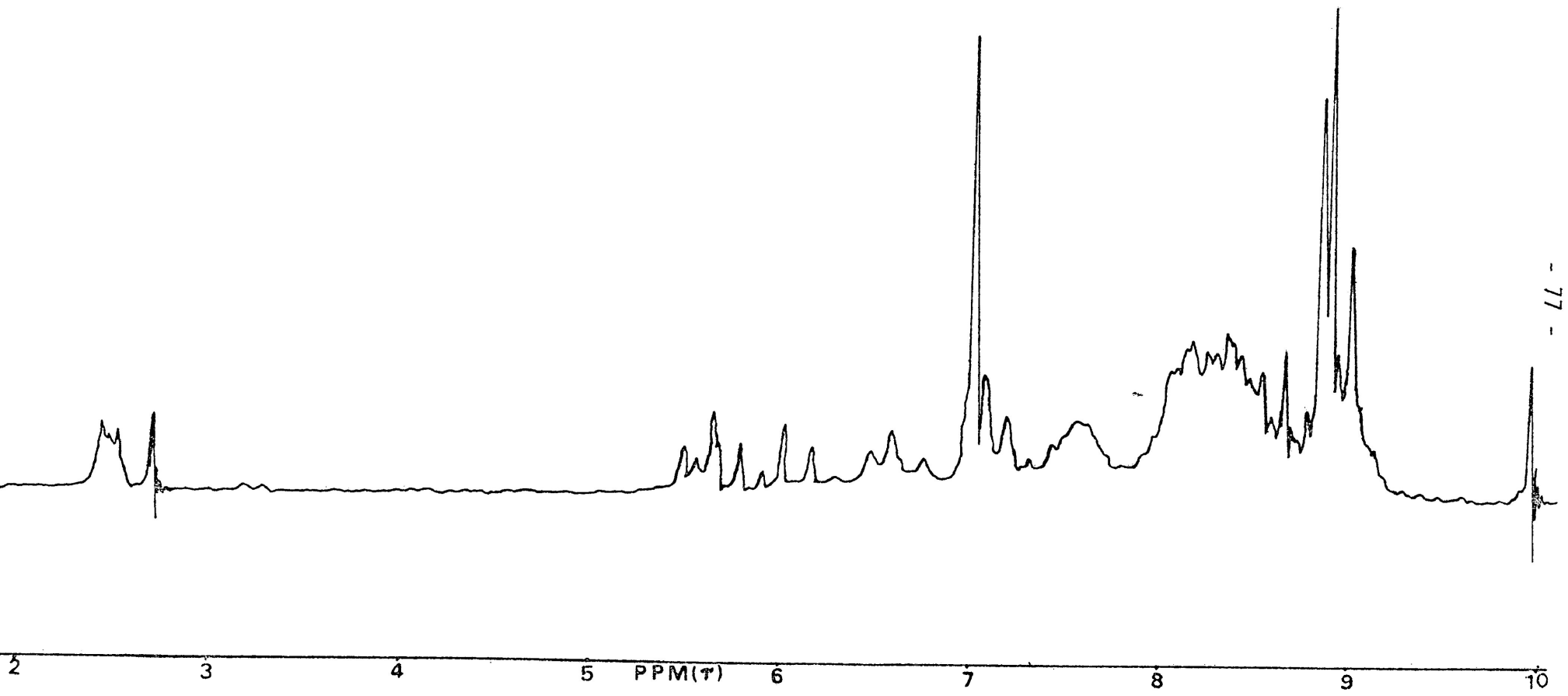
NMR NO. 17

1-PHENYL-2-ALDEHYDO-6-METHYL-1, 6-HEPTADIENE



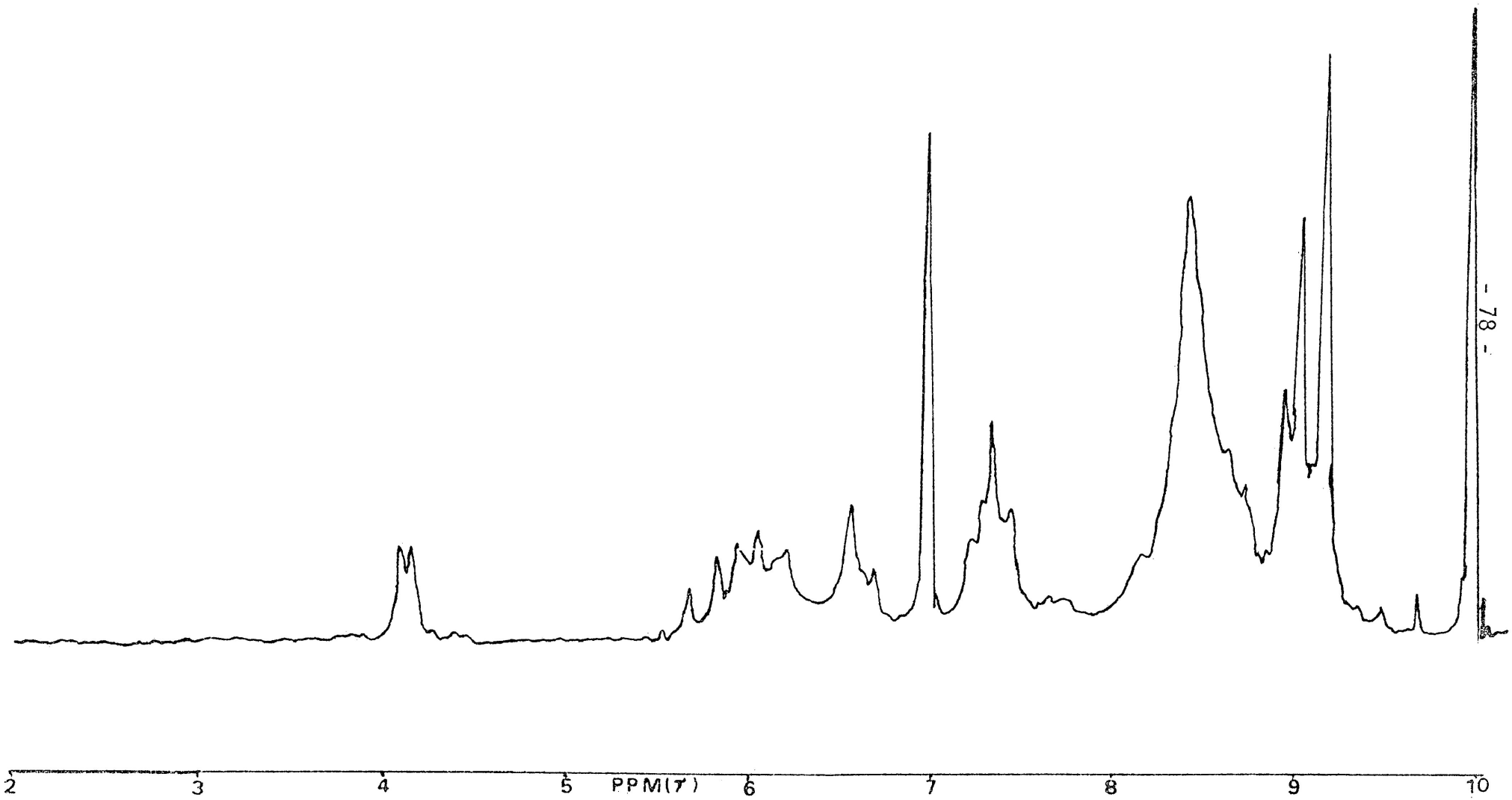
NMR NO.18

2-METHYL-2-HYDROXYMETHYL-6-n-BUTYLTHIOMETHYLENE CYCLOHEXANONE



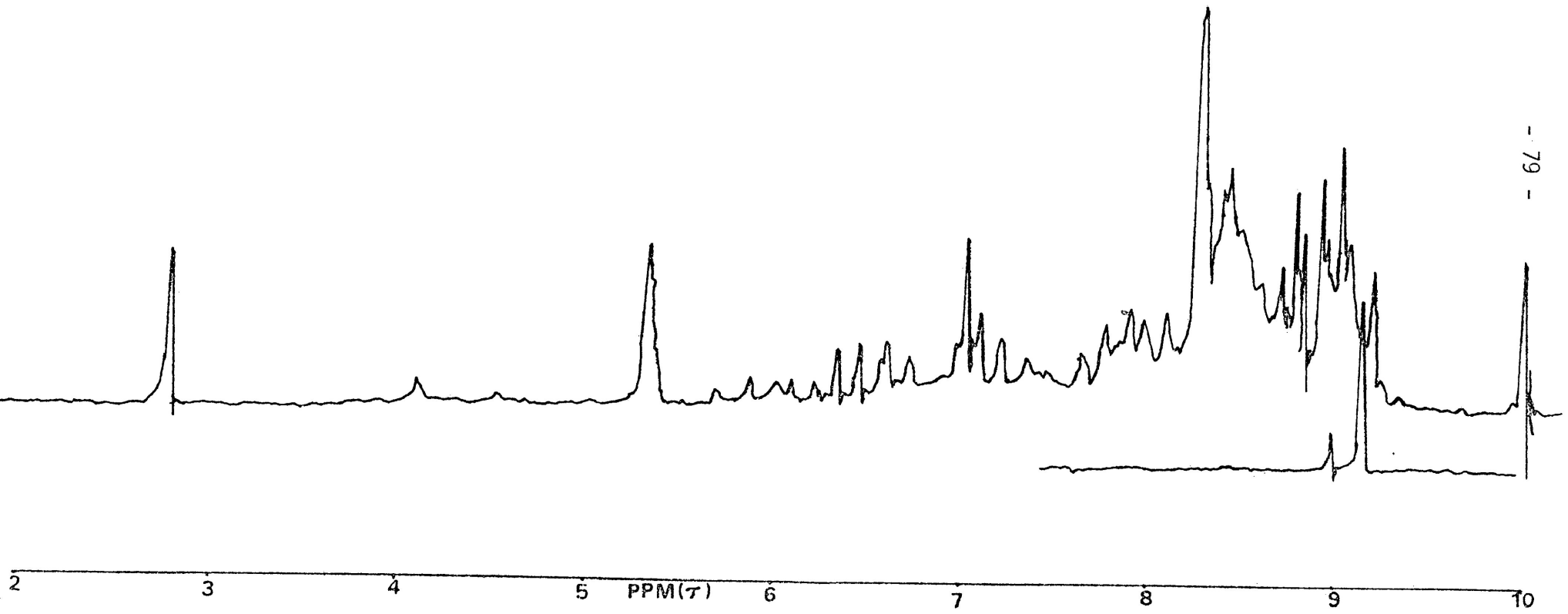
NMR NO.19

2-METHYL-2-HYDROXYMETHYL METHANE SULFONATE-6-n-BUTYLTHIOMETHYLENE CYCLOHEXANON



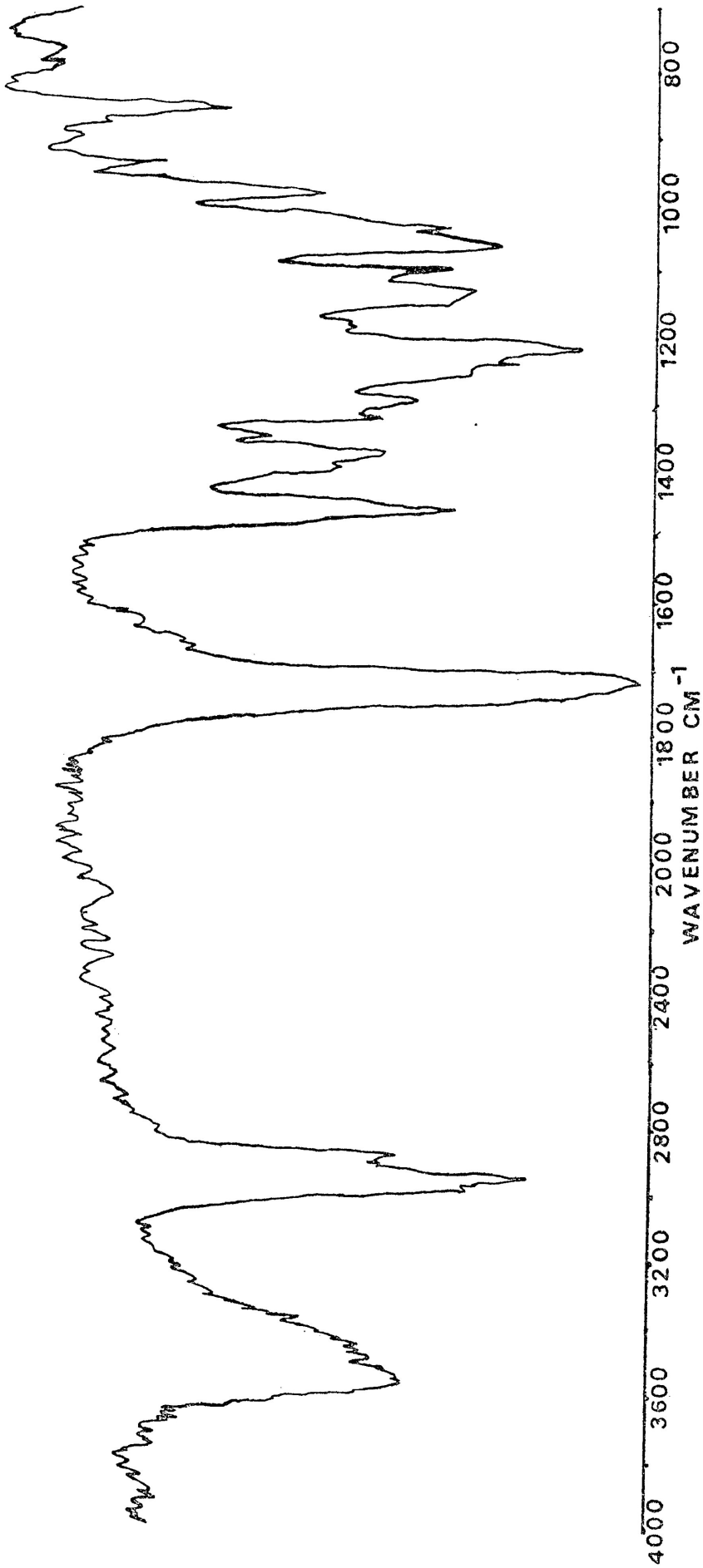
NMR NO. 20

2-METHYL-2-HYDROXYMETHYL METHANE SULFONATE-6-n-BUTYLTHIOMETHYLENE CYCLOHEXANOL



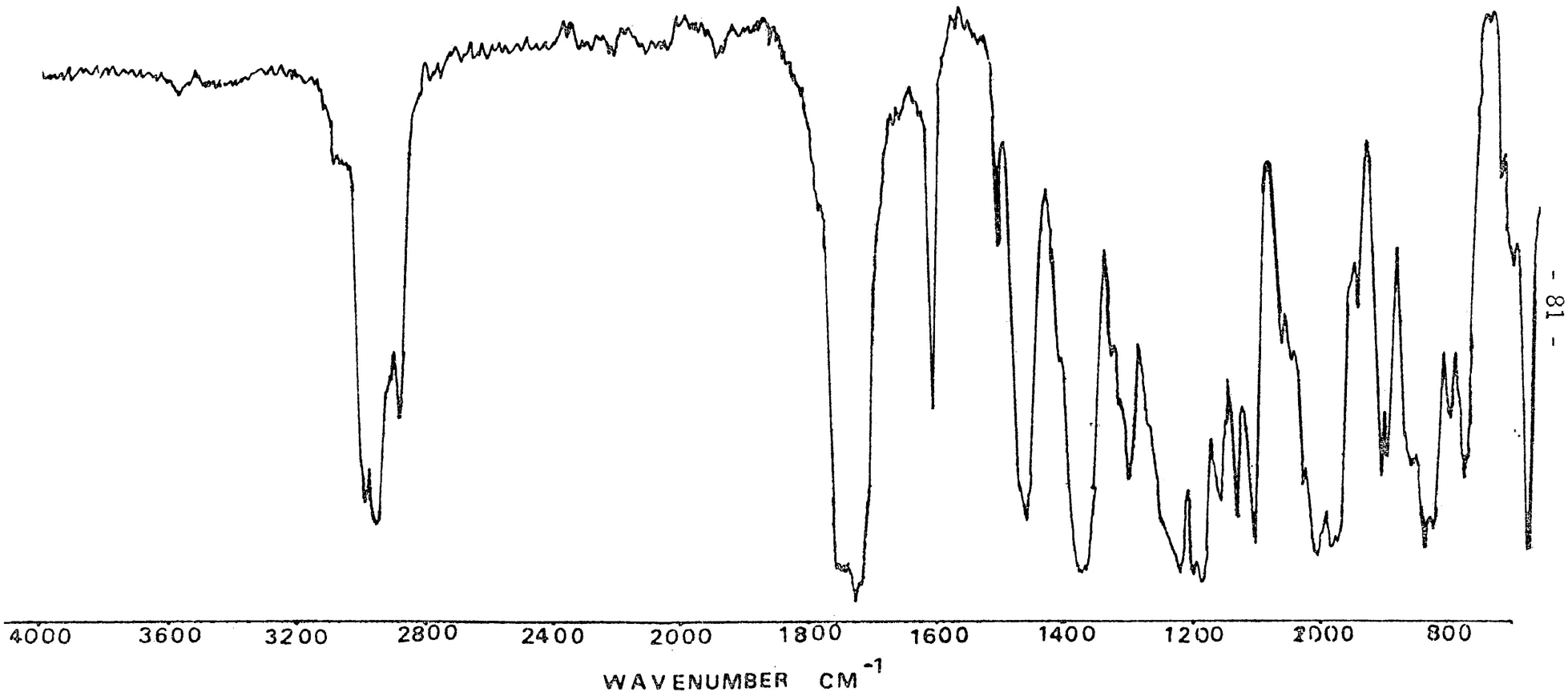
NMR NO. 21

1-n-BUTYLTHIO-2-ALDEHYDO-6-METHYL-1,6-HEPTADIENE



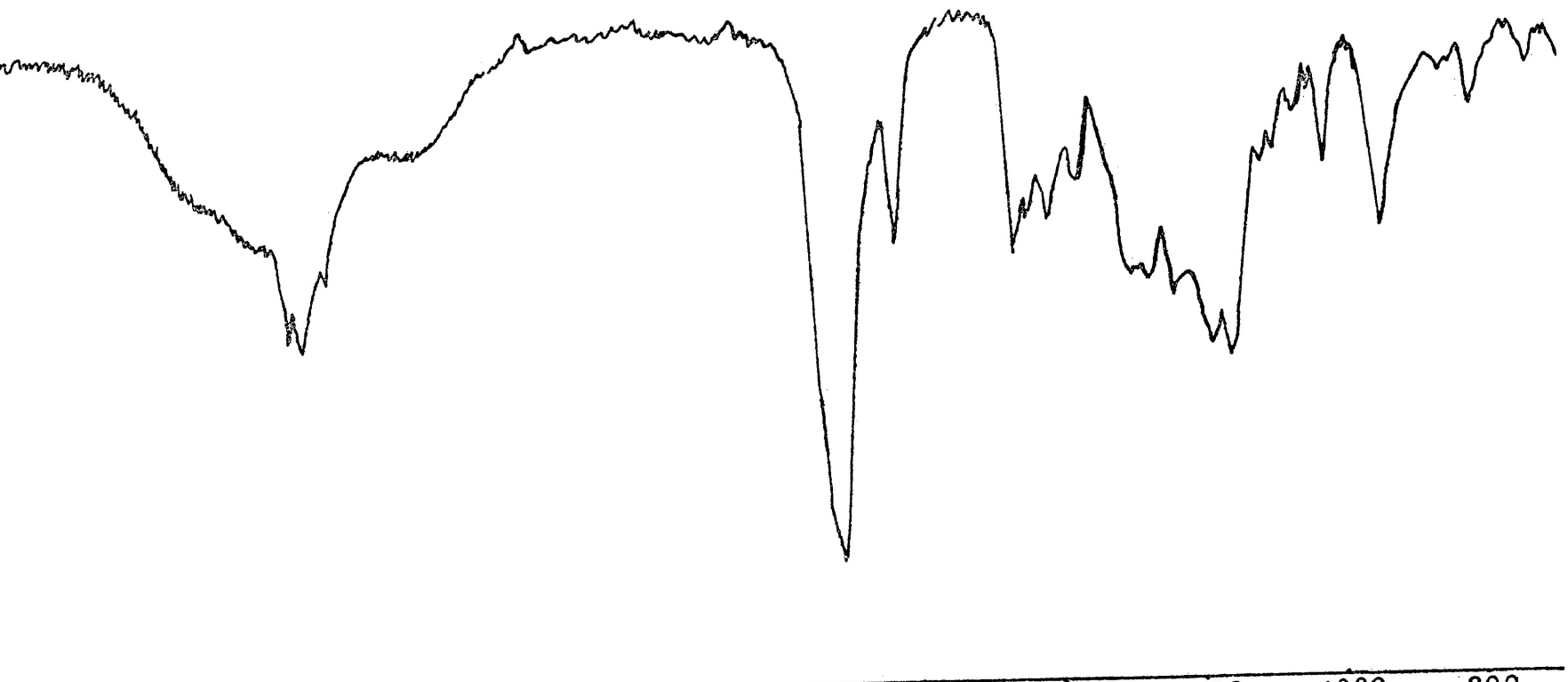
IR NO. 1

ETHYL 2-METHYL-6-HYDROXYMETHYLCYCLOHEXANONE-6-CARBOXYLATE



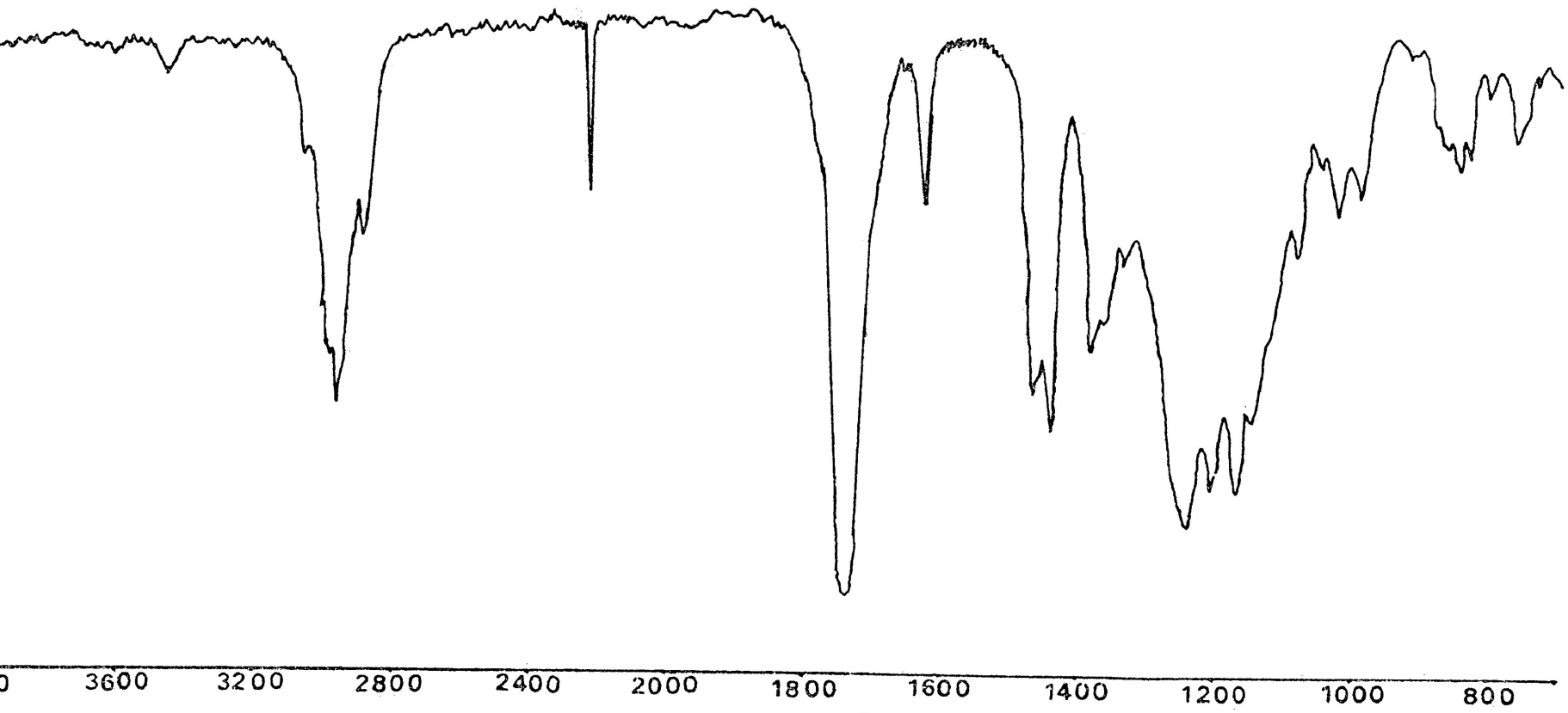
IR NO. 2

ETHYL-2-METHYL-6-HYDROXYMETHYL P-TOLUENE SULFONATE CYCLOHEXANONE-6-CARBOXYLATE



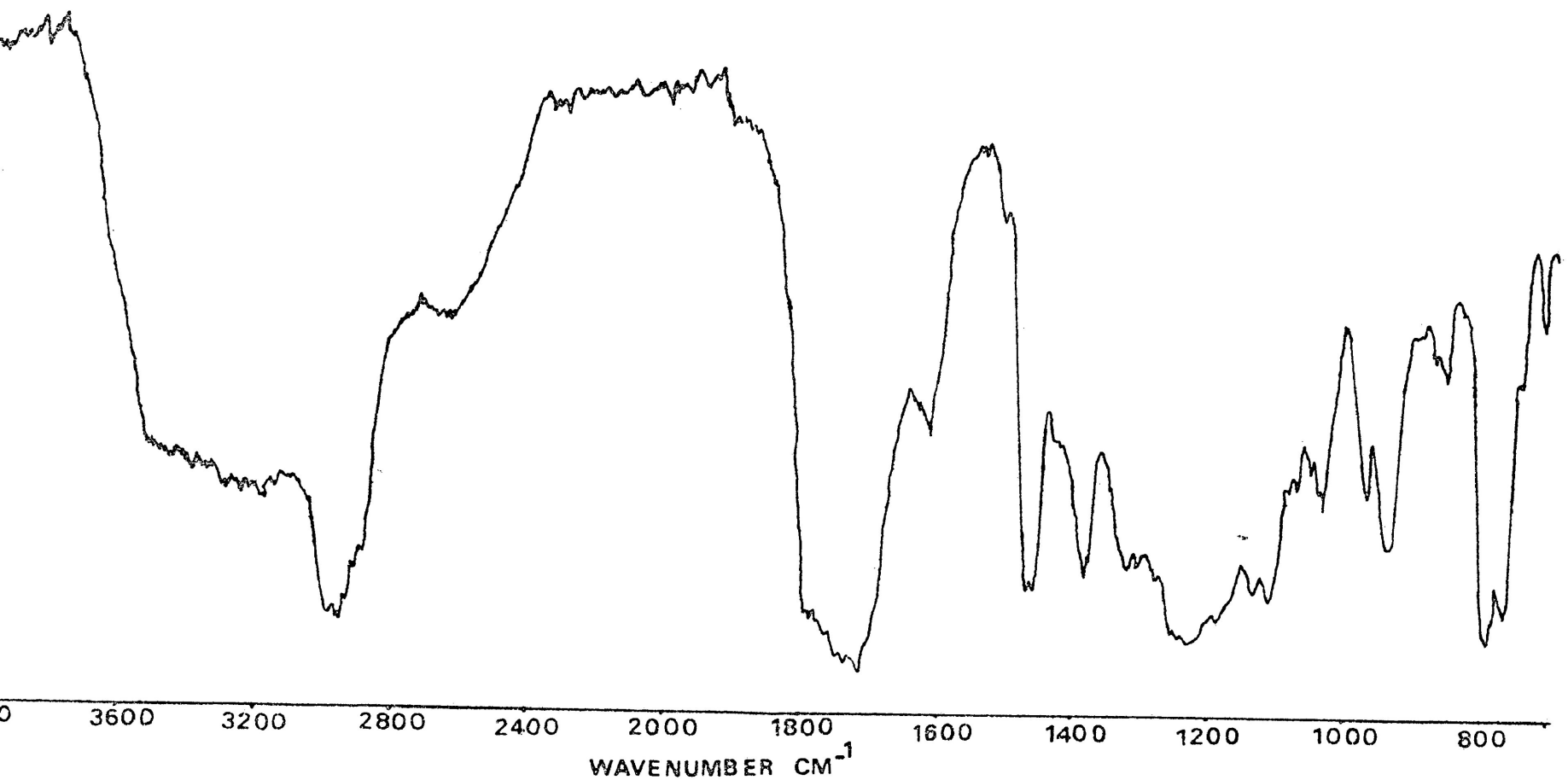
IR NO. 3

2-METHYL-ETHYLCARBOXY-6-HEPTENOIC ACID



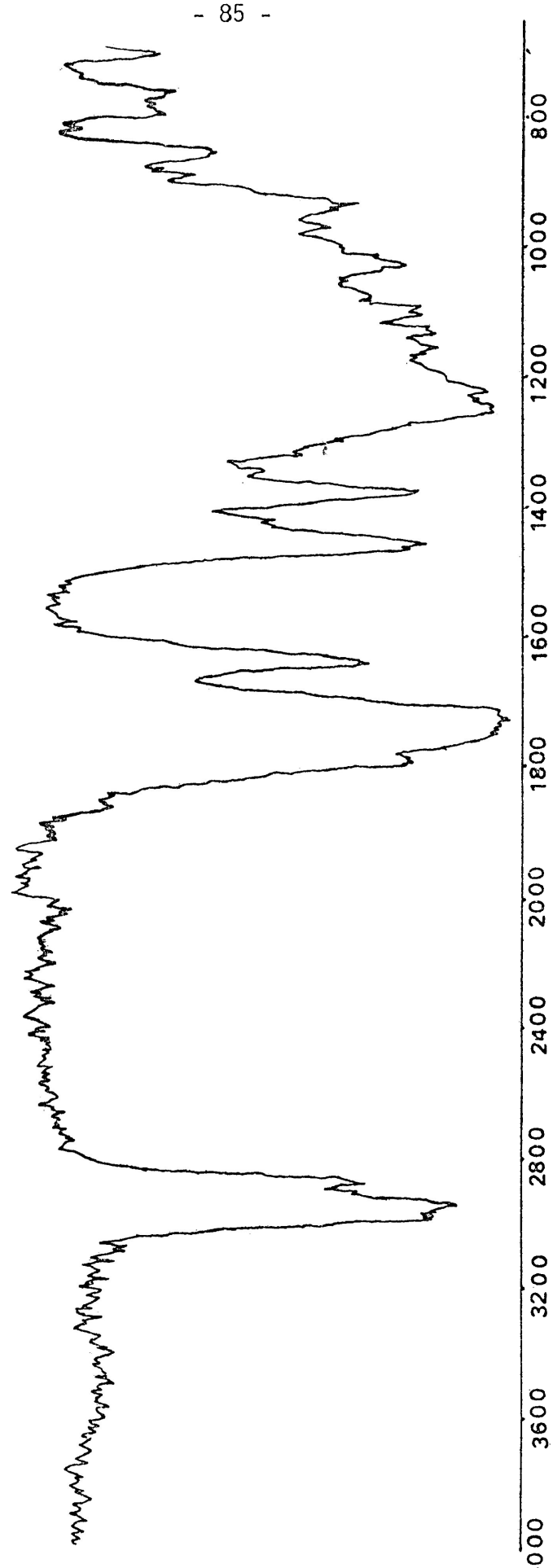
IR NO. 4

1-CYANO-2,6-DICARBETHOXY-1-OCTENE



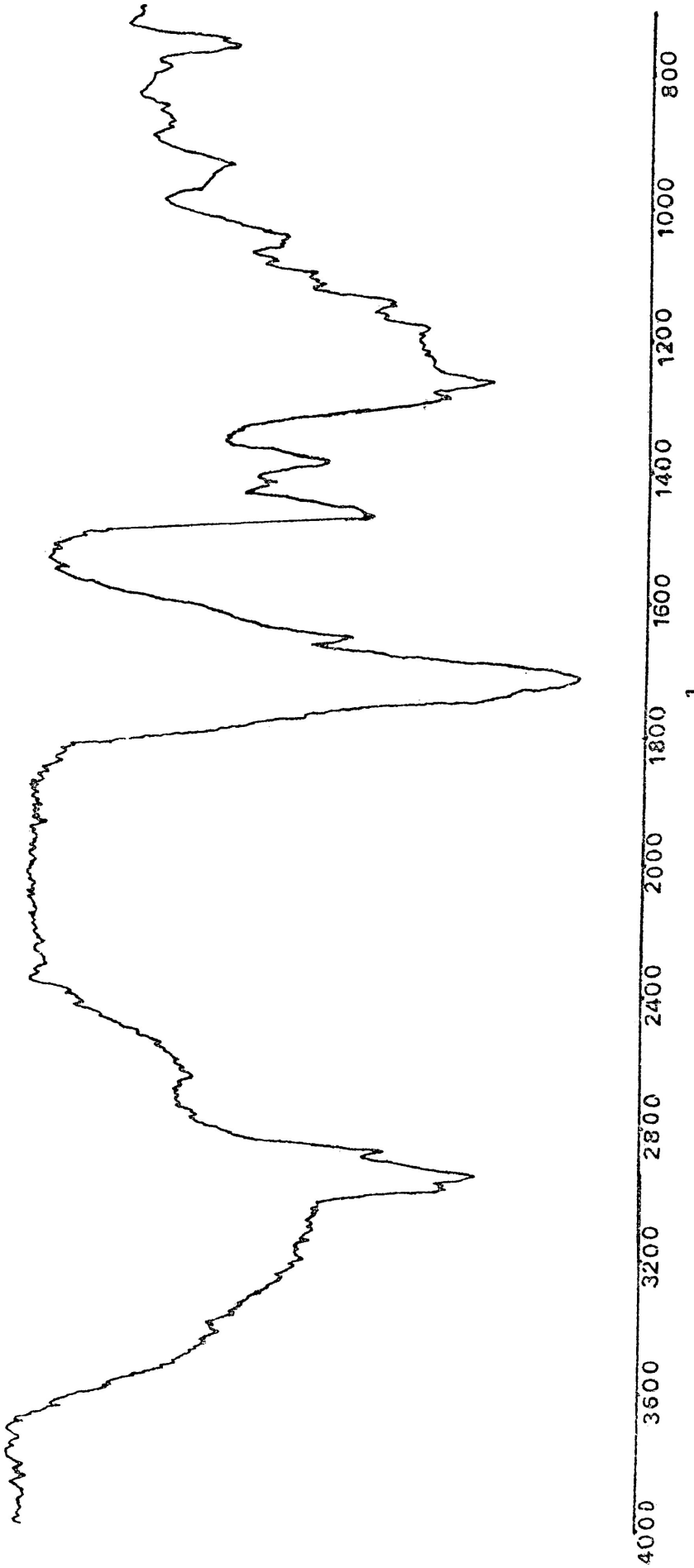
IR NO. 5

ETHYL 2-METHYL-6-(2'-PROPIONIC ACID)CYCLOHEXANONE-6-CARBOXYLATE



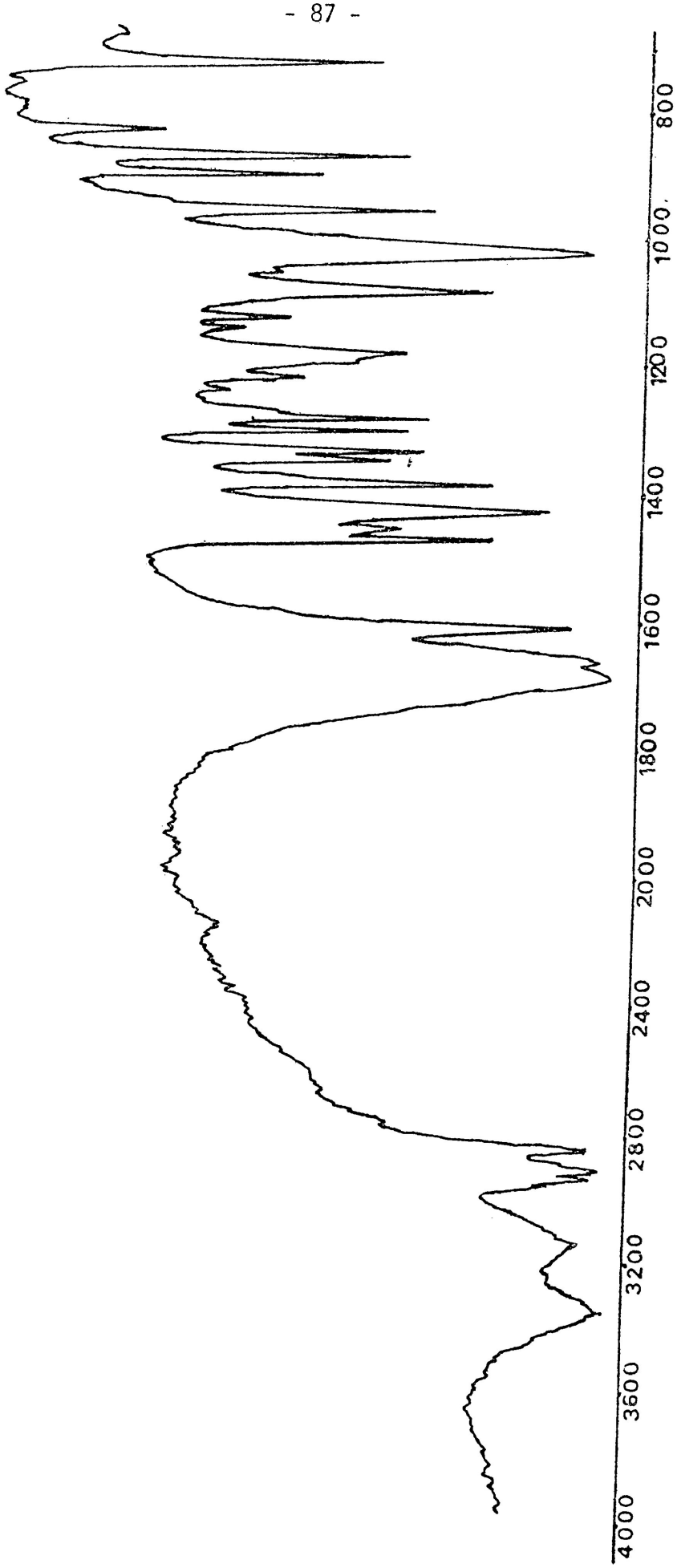
IR NO-6

ETHYL 2-METHYL-6-VINYLCYCLOHEXANONE-6-CARBOXYLATE



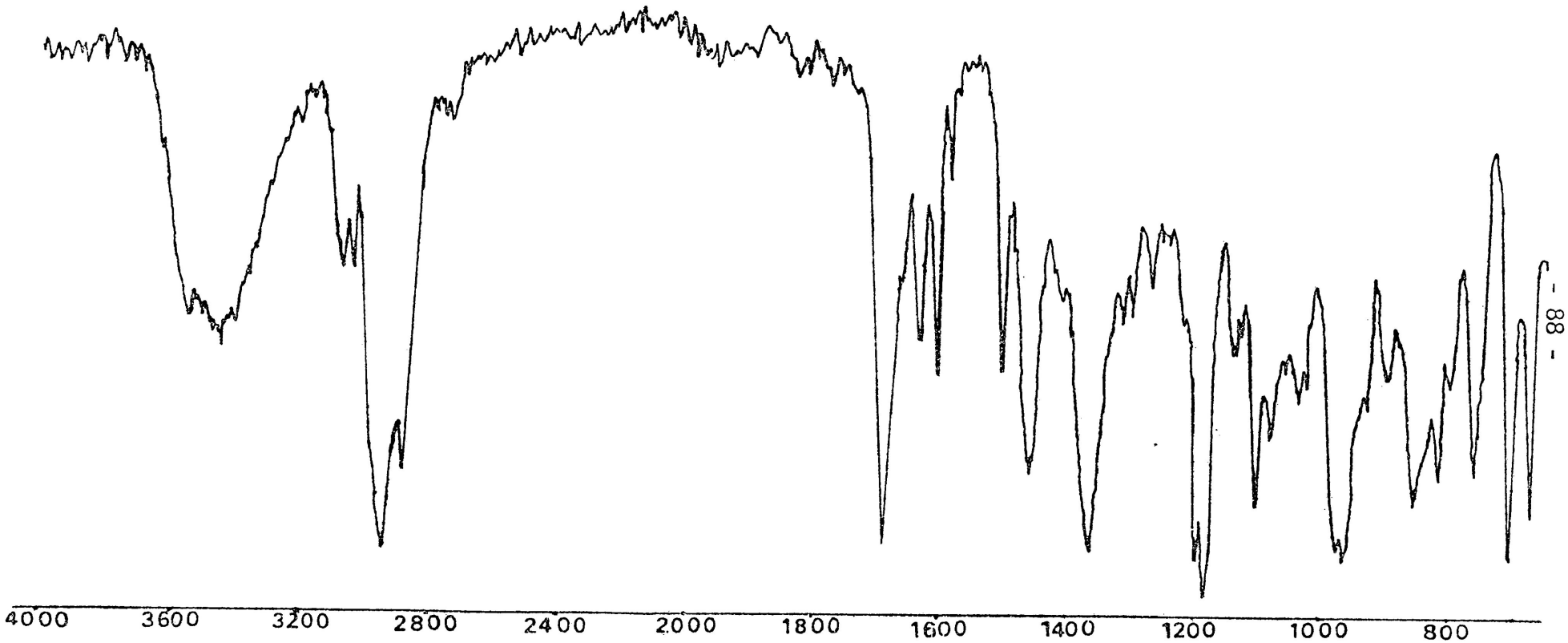
IR NO. 7

2-METHYL-6-CARBETHOXY-6-OCTENOIC ACID



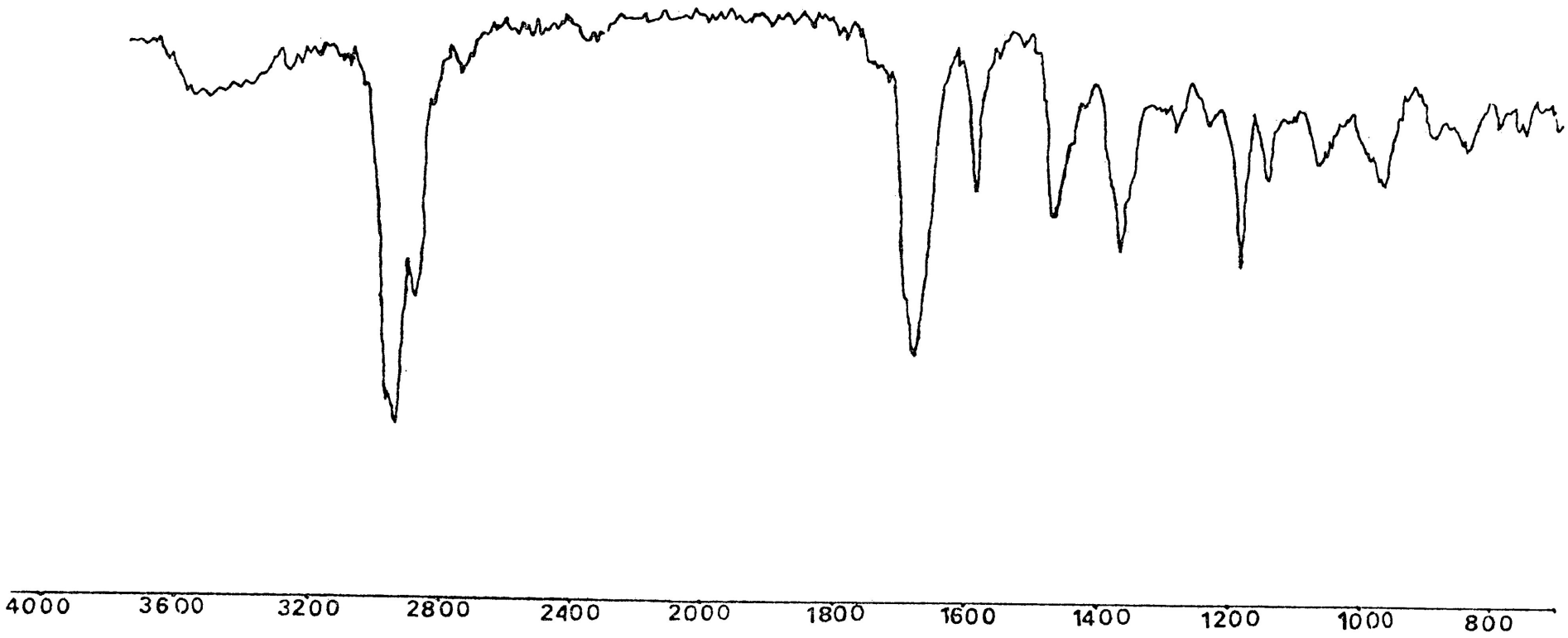
IR NO. 8

4-PENTYLIMIDAZOLID-2-ONE



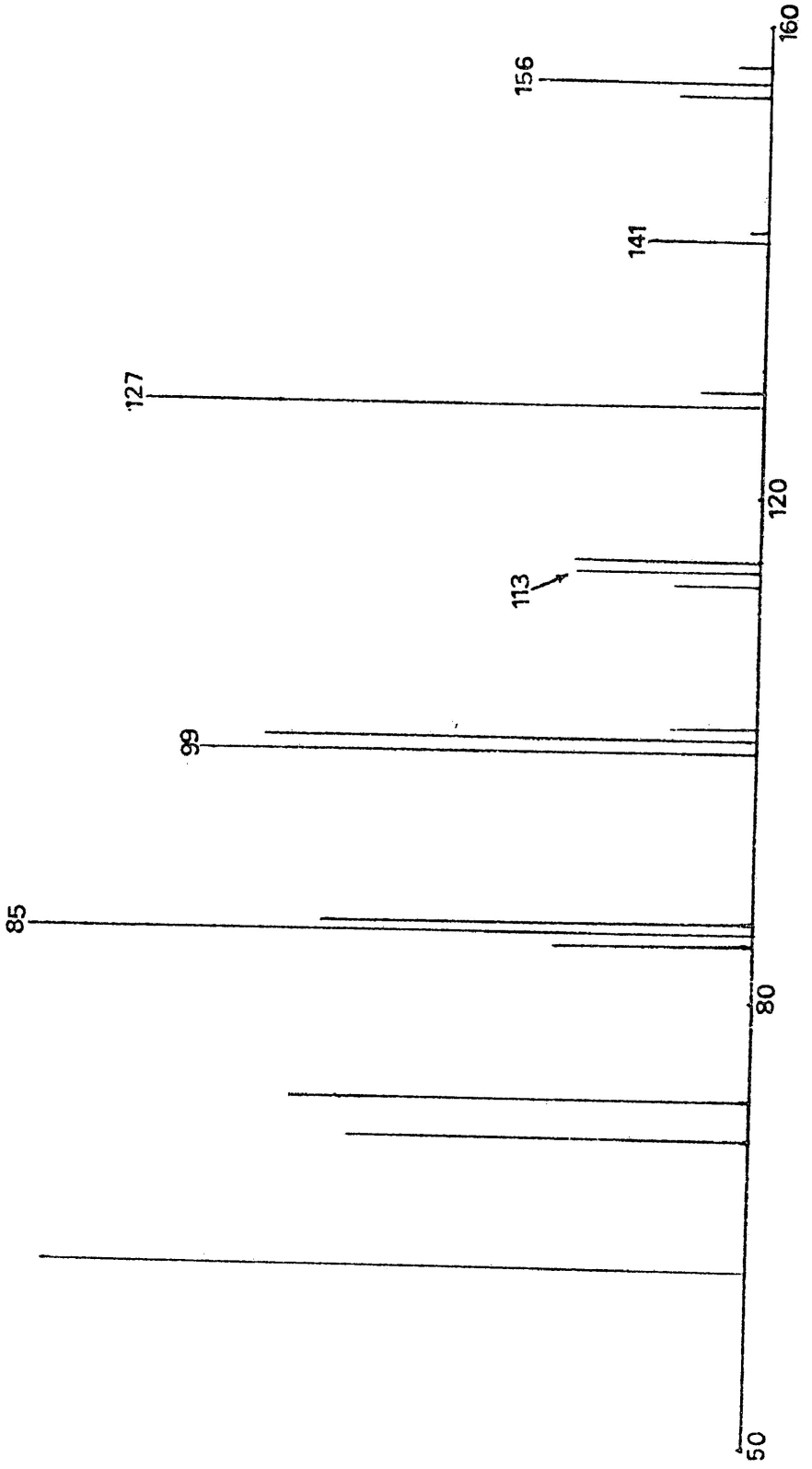
IR NO.9

1-PHENYL-2-ALDEHYDO-6-METHYL-1,6-HEPTADIENE



IR NO. 10

1-n-BUTYLTHIO-2-ALDEHYDO-6-METHYL-1,6-HEPTADIENE



MASS SPECTRUM NO.1

4-PENTYL IMIDAZOLID-2-ONE

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