SYNTHETIC STUDIES ON CHAKSINE

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© M. A. J. MIAH

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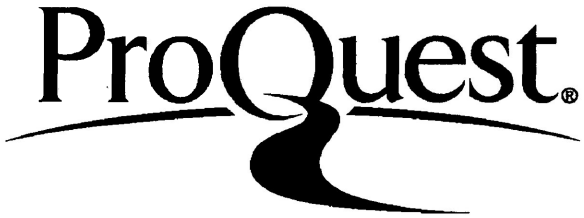

ABSTRACT

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

Ethyl 2-n-butyl-4-bromoacetoacetate (11) was treated with sodium azide to give ethyl 2-n-butyl-4-azidoacetoacetate (12). Catalytic hydrogenation of (12) in presence of hydrochloric acid followed by the reaction of the hydrogenation product (13) with potassium cyanate afforded 4-(1'-carbethoxypentyl)-2-imidazolone (14) or 4-(1'-carboxypentyl)-2-imidazolone (15) depending on reaction condition.

4-(1'-carbethoxymethyl)-2-imidazolone (25) was also prepared starting from ethyl 4-bromoacetoacetate (23a) following the same series of reaction as described for the compound (14). Ethyl 2-[4'-methyl-5'-(2"-tetrahydropyranyloxyl)pentyl] acetoacetate (20) was prepared from the reaction of ethyl

acetoacetate and 5-bromo-2-methyl-1-(2'-tetrahydropyranyloxyl)pentane (19). Removal of the 3,4-dihydropyran protecting group from (20) yielded ethyl 2-(4'-methyl-5'-hydroxypentyl)acetoacetate (21). The compound (21) was also prepared directly by the reaction of ethylacetoacetate with 5-bromo-2-methylpentanol (18). The compound (21) was then subjected to bromination to give (22a) followed by the treatment of (22a) with sodium azide to yield ethyl 2-(4'-methyl-5'-hydroxypentyl)-4-azidoacetoacetate (22b).

The compound (21) was also acylated to give ethyl 2-(4'-methyl-5'-acetoxypentyl) acetoacetate (26). Ethyl 2-(4'-methyl-5'-acetoxypentyl)-4-bromoacetoacetate (27) was prepared by the bromination of (26). Treatment of (27) with sodium azide yielded ethyl 2-(4'-methyl-5'-acetoxypentyl)-4-azidoacetoacetate (28).

Other related studies involved: 1) Preparation of 2-(N'-carbethoxy)-2-(2',3'-dihydroxy-3'-

methylcyclohexyl)acetonitrile (34). 2) Preparation of 1-methyl-3-(2'-aminoethylidene)-cyclohexene (36). 3) Preparation of 1-cyanomethylene-2,3-dihydroxy-3-methylcyclohexane (40), and 4) 2-Butyl-2-tosyl-4-butyrolactam (47).

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M.A.J. Miah

The Author

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INTRODUCTION

INTRODUCTION

Cassia absus is a plant native to India and Ceylon (now Sri Lanka) which grows to a height of one to two feet. Its flat, oblong seeds have been found[1] to contain material effective in the treatment of skin affections and opthalmia, and as a cathartic.

Siddiqui and Ahmed[1] succeeded in isolating, in the form of iodide and sulfate salts, the alkaloidal principle present. The name chaksine was given to this base.

The powdered kernel of the plant was treated with cold methanol-hydrochloric acid solution. After neutralization and subsequent acidification, methanol was removed under reduced pressure and the residual material was extracted with ether. After removal of the ether, a brownish yellow syrupy residue was obtained. The material was dissolved in water and acidified with dilute hydrochloric acid. Addition of potassium iodide to the acidic solution yielded a white crystalline material identified as chaksine

iodide. The bicarbonate of chaksine was subjected to elemental analysis and the empirical formula was reported as $C_{12}H_{20}ON_3HCO_3$.

By Zeisel's method, the residue was found to contain no methoxyl groups and by Herzig and Mayer's method, it was found to contain no N-methyl groups.

In a subsequent paper, Kapur et al[2] suggested that the empirical formula assigned to chaksine was incorrect 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* (1) for chaksine. A partial structure (2) was proposed for the part of the molecule containing the nitrogen atoms. Positive Kuhn-Roth oxidation confirmed the presence of a C-Me group. A positive pyrrole test coupled with the resistance of the molecule to Hoffman and Emde degradation was interpreted to indicate a bicyclic structure in which the quaternary nitrogen atom is common to both rings.

*Plate I

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 (3) which accounts for all but C_2H_5O in the chaksine molecule. Tribenzoyl derivative formation indicated the presence of hydroxy group and thus structure (1) was proposed.

In 1958, Wiesner and Valenta[5] published a paper proposing an entirely different structure for chaksine. A ureido-hydroxy acid was obtained from hydrolysis of chaksine with 2N sodium hydroxide and the infrared spectrum of the oily ester formed from the acid showed bands at 1740 cm^{-1} and 1710 cm^{-1}, indicating a five-membered cyclic urea. Also, mild oxidation of chaksine with permanganate in water gave an acidic product which, when decarboxylated by heating to 170° under nitrogen for twenty minutes, followed by chromium trioxide oxidation, gave α-methylpimelic acid (4). This product was identified by comparing the infrared spectrum of the acid and the corresponding ethyl ester with authentic specimens. These investi-

gators thus assigned structure (5) to chaksine which was the first recorded example of a monoterpenoid alkaloid.

In another communication Singh et al[6] reported that the tricarboxylic acid $C_{10}H_{16}O_6$, obtained as the second product by alkaline hydrolysis of the alkaloid, could be assigned structure (6), a fact which was verified by synthesis. 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 (7)* was proposed.

The problem was further complicated when Guha and Ray[7] proposed an entirely new structure (8).

Wiesner et al[8] then published a second paper citing chemical and nuclear magnetic resonance evidence supporting the structure they had originally proposed. The methyl ester (9) of the ureido-acid was prepared and the nmr spectrum confirmed the proposed

* Plate II

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. But the total synthesis of chaksine has not yet been accomplished. This thesis describes the attempts we have made toward the total synthesis of chaksine.

An attempt was made to prepare a model compound of the ureido-hydroxy acid derived from chaksine. Ethyl 2-n-butyl-acetoacetate[9] (10) and ethyl 2-n-butyl-4-bromoacetoacetate (11) were prepared by standard methods. Ethyl 2-n-butyl-4-azidoacetoacetate (12) was prepared from (11) by the treatment with sodium azide. Hydrogenation of the azido compound in presence of hydrochloric acid gave ethyl 2-n-butyl-4-aminoacetoacetate as the hydrochloride salt* (13). Compound (13) was treated with potassium cyanate to give the cyclic ureido compound (14) or (15) depending on the reaction

*Plate III

conditions. The imidazolidone ring of compound (16), obtained by hydrogenation of (14), represents the heterocyclic part of the compound (9), an alkaline degradation product of chaksine, and could, in principle, be transformed to the cyclic guanidine part of chaksine itself. Therefore, it was thought that it would be of great value if we could replace the n-butyl group by a 2-methylpentanol moiety. Hence ethyl 5-bromo-2-methylpentanoate (17) was prepared following standard procedure[10,11] and was reduced with lithium borohydride to 5-bromo-2-methylpentanol[10] (18). The bromo derivative (18) was then converted to 5-bromo-2-methyl-1'-(2'-tetrahydropyranyloxyl)-pentane* (19)[10] to protect the hydroxyl group before using as an alkylating agent. Ethyl 2-[4'-methyl-5'-(2''-tetrahydropyranyloxyl)pentyl]acetoacetate (20) was prepared by the reaction of (19) with ethylaceto-acetate in dimethyl formamide using sodium hydride as a base. Bromination of (20) was found to be unsatisfactory as the 3,4-dihydropyran protecting group was lost during the bromination reaction. So the hydroxyl group of (20) was left unprotected and the resulting

*Plate IV

compound (21) was subjected to bromination followed by the preparation of ethyl 2-(4'-methyl-5'-hydroxypentyl)-4-azidoacetoacetate (22b). The compound (22b) was hydrogenated to the amine as before and allowed to react with potassium cyanate. But despite expectation, no cyclic ureido compound was obtained. It was thought that this might be due to the presence of the free hydroxyl group which might have somehow interfered in the cyclization reaction. So an attempt was made to prepare the cyclic ureido compound* (25) following the same series of reactions as before. This compound was then subjected to alkylation at the appropriate position by using n-butyl bromide and 5-bromo-2-methylpentanol. But in no case was the alkylation attempt successful.

Again we have attempted to attach first the compound (18) to ethyl acetoacetate and converted the resulting compound (21) to ethyl 2-(4'-methyl-5'-acetoxypentyl) acetoacetate (26). The bromination of the compound (26) to (27) followed by the prepara-

*Plate V

tion of azide (28) were satisfactory. However, the hydrogenation and the subsequent cyclization again were not successful. It was also found that the acetoxy group was solvolysed during hydrogenation.

Some other approaches have also been attempted.

1-methyl-3-chloro-1-cyclohexene was reacted with ethyl cyanoacetate to give ethyl 2-(3'-methyl-2'-cyclohexenyl) cyanoacetate (29) which upon treatment with hydrazine hydrate yielded 2-(3'-methyl-2'-cyclohexenyl)-2-cyanoacethydrazide (30). The hydrazide (30) was converted by its reaction with sodium nitrite and hydrochloric acid into azide (31) and the azide was transformed into a urethan, 2-(N'-carbethoxy)-2-(3'-methyl-2'-cyclohexenyl) acetonitrile (32). The epoxy compound (33) was obtained by reaction of (32) with m-chloroperoxybenzoic acid. This was hydrolysed under acidic conditions to give a dihydroxy compound, 2-(N'-carbethoxy)-2-(2',3'-dihydroxy-3'-methylcyclohexyl)acetonitrile (34). But the treatment of the diol (34) with sodium metaperiodate to give a dicarbonyl product proved unproductive.

In another effort, 3-methylcyclchexen-2-en-1-one was subjected to a Horner-Emmons reaction using diethylcyanomethylphosphonate. This yielded 1-cyanomethylene-3-methyl-2-cyclohexene (35) which was reduced by lithium aluminumhydride to 1-methyl-3-(2'-aminoethylidene)-cyclohexene (36). The epoxidation of the double bond using m-chloroperoxybenzoic acid yielded epoxy compound (37) along with many other products. Hence, the epoxy compound, 2,3-oxirino-3-methyl-cyclohexan-1-one (38) was first prepared from 3-methylcyclohex-2-en-1-one by its reaction with sodium hydroxide and hydrogen peroxide. This epoxy ketone was then allowed to undergo Horner-Emmons reaction to give 1-cyanomethylene-2,3-oxirino-3-methylcyclohexane (39). The compound (39) was hydrolysed in acidic conditions to give 1-cyanomethylene-2,3-dihydroxy-3-methyl-cyclohexane (40). However the preparation of a dicarbonyl compound from (40) by its reaction with sodium metaperiodate again was unsuccessful.

Consideration was also given to theuse of a sulfone intermediate which could be converted to chak-

sine. Ethyl 2-butyl-2-tosyl-4-pentenoate (41)[12] was prepared following the usual procedure and was subjected to hydroboration reaction to give ethyl 2-butyl-5-hydroxy-2-tosylpentanoate (42). The compound (42) was oxidized by chromium trioxide to monoethylester of 2-butyl-2-tosyl glutaric acid (43) and (43) was converted into an acyl chloride, 4-carbethoxy-4-tosyl-octanoyl chloride (44) by its reaction with thionyl chloride. The azide (45) was then prepared from (44) by its reaction with hydrazoic acid which in turn afforded, on heating, an isocyanate derivative (46). Attempts were then made to prepare a heterocyclic compound from (46) by reaction with ethanolic ammonia and urea respectively. But no attempts were found to be satisfactory. The compound (46) could be hydrolysed to yield an amine. However, the hydrolysis resulted in the formation of a compound which was probably the five-membered lactam derivative (47).

DISCUSSION

DISCUSSION

In our synthetic studies we explored various approaches to the problem of a chaksine synthesis. Various compounds were prepared which contained the basic carbon skeleton and with the functionality which would allow them to be converted into chaksine itself.

Our general plan followed two different strategies.* First, to add a six-membered carbon skeleton to a four-membered anionic species with requisite functionality to bring the total number of carbon to ten, the basic carbon skeleton of the desired compound. Second, to attach a seven-membered carbon skeleton to a two-membered anionic species with requisite functionality and then adding a single carbon atom bringing the total number to ten.

We first attempted to prepare a model compound of the cyclic ureido hydroxy acid derived from

*Plate X

chaksine.

In the initial step, ethyl 2-n-butyl-4-bromoacetoacetate* (11) was prepared by the bromination of ethyl 2-n-butylacetoacetate* (10). The nuclear magnetic resonance spectrum (n.m.r. -1) of the reaction product indicated that the desired compound had been formed. A methyl triplet at δ = 1.27 (J = 7 Hz) and a methylene quartet at δ = 4.16 (J = 7 Hz) confirmed the presence of ethyl ester. A triplet at δ = 3.78 (J = 7 Hz) showed the presence of a methine proton. A singlet at δ = 4.05 confirmed the presence of methylene protons attached to carbon atom bearing the bromine atom.

Treatment of (11) with sodium azide in 2-(2-methoxyethoxy)ethanol resulted in its smooth conversion to the corresponding azide (12). The formation of the azide was supported by spectroscopic evidence. In the ^{1}H n.m.r. spectrum (n.m.r.

*Plate II

- 2), a methyl triplet at δ = 1.27 (J = 7 Hz) and a methylene quartet at δ = 4.18 (J = 7 Hz) confirmed the presence of ethyl ester. A methine triplet was evident at δ = 3.49 (J = 7 Hz). A singlet at δ = 4.06 confirmed the presence of methylene protons attached to carbon atom bearing the azide function. The i.r. spectrum (i.r. - 1) showed strong absorptions at 1735 cm^{-1} (ketone and ester carbonyl) and at 2120 cm^{-1} (azide).

The next step involved the conversion of the azide (12) by catalytic hydrogenation to the amino compound (as hydrochloride salt)* (13). The ^1H n.m.r. spectrum (n.m.r. - 3) had a triplet at δ = 1.25 and a quartet at δ = 4.17 indicating ethyl ester. A multiplet centred at δ = 3.71 showed the presence of the methylene protons attached to carbon atom bearing the amino group and the methine proton. Two broad bands at δ = 6.9 and 8.15 indicated the presence of protons of the amino group. The infrared spectrum

*Plate III

(i.r. - 2) showed absorptions at 1730 cm^{-1} (ketone and ester carbonyl), 2980 cm^{-1} (N — H stretch, a very broad band).

The final step in this scheme was to prepare the cyclic ureido derivative (14) from the reaction of (13) with potassium cyanate under acidic conditions at 60°C. Evidence from elemental analysis and various spectra confirmed that the desired compound had been produced. In the nuclear magnetic resonance spectrum (n.m.r. - 4), a methyl triplet at δ = 1.24 (J = 7 Hz) and a methylene quartet at δ = 4.12 (J = 7 Hz) confirmed the presence of the ethyl ester. A broad singlet at δ = 6.11 showed the presence of double bond proton. Two broad bands around δ = 9.99 and δ = 10.24 indicated the presence of protons in N — H functions. The i.r. spectrum (i.r. - 3) showed absorptions at 1630 cm^{-1} (double bond), 1700 cm^{-1} and 1730 cm^{-1} (cyclic urea and ester carbonyls) and at 3200 cm^{-1} (N — H stretch). The mass spectrum showed the presence of molecular ion

peak at m/e 226. Other intense peaks* were observed at 197, 183, 169, 153, 111, 97 and 83.

However, the reaction of amino compound (13) with potassium cyanate at refluxing temperature in the absence of acid resulted in the formation of the cyclic ureido compound (15). The formation of (15) has been confirmed by the mass spectrum and elemental analysis. The mass spectrum indicated the presence of molecular ion peak at m/e 198.

It was then attempted to prepare the ureido-hydroxy compound (9, as ethyl ester). In the initial step ethyl 2-[4'-methyl-5'-(2"-tetrahydropyranyloxyl)-pentyl] acetoacetate** (20) was prepared from the reaction of ethyl acetoacetate and 5-bromo-2-methyl-1-(2'-tetrahydropyranyloxyl)pentane** (19). The nuclear magnetic resonance spectrum (n.m.r. - 5) indicated the formation of compound (20). A doublet at $\delta = 0.91$ ($J = 6$ Hz) showed the presence of

*Plate IX **Plate IV

a secondary methyl group. A triplet at δ = 1.28 (J = 7 Hz) and a quartet at δ = 4.18 (J = 7 Hz) confirmed the presence of the ethyl ester. The methyl ketone protons appeared as a singlet at δ = 2.22. A broad peak at δ = 4.53 indicated the presence of the acetal proton. However, the bromination of (20) was found difficult caused by the loss of tetrahydropyran protecting group. The protecting group, therefore, was removed by treatment of compound (20) with acetic acid and water in tetrahydrofuran which resulted in the formation of compound (21). Compound (21) was also prepared directly by the reaction of (18) with ethyl acetoacetate. The n.m.r. spectrum (n.m.r. - 6) showed that the required compound had been formed. A doublet at δ = 0.89 (J = 6 Hz) indicated the presence of the secondary methyl protons. A methyl triplet at δ = 1.27 (J = 7 Hz) and a methylene quartet at δ = 4.18 (J = 7 Hz) confirmed the presence of the ethyl ester. A singlet at δ = 2.23 was due to the methylketone protons. A multiplet centred at δ = 3.4 was due to the methine proton and the two methylene protons attached

to the carbon atom bearing the hydroxy group.

Next, the bromo compound (22a) and azido compound (22b) were prepared. The nuclear magnetic resonance spectrum (n.m.r. - 7) of the compound (22a) was consistent with its proposed structure. The secondary methyl group appeared as a doublet at δ = 0.92 (J = 6 Hz). A triplet at δ = 1.25 (J = 7 Hz) and a quartet at δ = 4.18 (J - 7 Hz) showed the presence of the ethyl ester. A singlet at δ = 4.03 was due to the protons attached to carbon atom bearing bromine. The i.r. spectrum (i.r. - 4) of compound (22b) showed the absorptions at 1745 cm^{-1} (ketone and ester carbonyls), 2120 cm^{-1} (azide) and 2960 cm^{-1} (C — H stretch). The proton n.m.r. spectrum of (22b) showed a singlet at δ = 4.05 due to the methylene protons attached to carbon bearing azide function.

As the hydrogenation of (22b) and subsequent cyclization of the hydrogenation product were found unsatisfactory, we attempted to prepare first

a cyclic ureido compound* (25) and then to attach the requisite carbon skeleton to it. Ethyl 4-bromo-acetoacetate (23a) and ethyl 4-azidoacetoacetate* (23b) were prepared and spectroscopic evidence confirmed their formation (see experimental section, P. 46 & 47). The subsequent formation of amino compound (24) and cyclic ureido compound (25) were performed as previously described for the n-butyl substituted compounds. The proton n.m.r. spectrum of compound (25) showed a broad singlet at δ = 6.01 (double bond proton). The i.r. spectrum (i.r. - 6) showed absorptions at 1670-1710 cm^{-1} (double bond and urea carbonyls), 1745 cm^{-1} (ester carbonyl) and 3200 cm^{-1} (N — H stretch). The mass spectrum showed the molecular ion peak at m/e 170. But the attachment of the remaining carbon skeleton by means of alkylation at the appropriate position of (25) was not found satisfactory.

The next attempt involved the preparation of ethyl 2-(4'-methyl-5'-acetoxypentyl) acetoacetate

*Plate V

(26) from (21) by its reaction with acetic anhydride and pyridine. The nuclear magnetic resonance spectrum (n.m.r. - 10) showed that the desired compound had been formed. A doublet at δ = 0.91 (J - 6 Hz) showed the presence of secondary methyl group. A triplet at δ = 1.26 (J = 7 Hz) and a quartet at δ = 4.17 (J = 7 Hz) confirmed the presence of the ethyl ester. The methyl group α to the ketone group appeared as a singlet at δ = 2.20. The methyl protons of the acetyl group showed as a singlet at δ = 2.03. The subsequent preparation of bromo compound (27) and azido compound (28) were found satisfactory. The n.m.r. spectrum (n.m.r. - 11) of compound (27) showed a doublet at δ = 0.91 (J = 6 Hz) for the secondary methyl protons. A triplet at δ = 1.25 (J = 7 Hz) and quartet at δ = 4.16 (J = 7 Hz) confirmed the presence of the ethyl ester. A singlet at δ = 2.03 indicated the presence of the methyl protons of the acetyl group. A methylene singlet at δ = 4.01 was evident for the protons attached to carbon bearing the bromine atom. The i.r. spectrum (i.r. - 7) of (28) showed absorp-

tions at 1750 cm^{-1} (ketone and ester carbonyls), 2120 cm^{-1} (azide) and 2960 cm^{-1} (C — H stretch).

In another approach, we attempted to prepare ethyl 2-(3'-methyl-2'-cyclohexenyl)-2-cyanoacetate* (29) from the reaction of ethyl cyanoacetate with 1-methyl-3-chloro-1-cyclohexene. Spectroscopic evidence indicated that the desired compound had been obtained as mixture of diastereoisomers. The n.m.r. spectrum (n.m.r. - 12) had a triplet at δ = 1.32 (J = 7 Hz) and a quartet at δ = 4.27 (J = 7 Hz) showing the presence of the ethyl ester. A singlet at δ = 1.7 appeared due to the methyl protons adjacent to double bond. Two doublets at δ = 3.38 and δ = 3.47 indicated the presence of a proton attached to carbon atom bearing nitrile group. Also there appeared two doublets (poorly resolved) at δ = 5.18 and δ = 5.34 showing the presence of a double bond proton. All these double absorptions due to a single proton pro-

*Plate VI

vided evidence that the compound (29) was a mixture of its diastereoisomers. In i.r. spectrum (i.r. - 8), absorptions were observed at 1630 cm^{-1} (double bond), 1755 cm^{-1} (ester carbonyl), 2218 cm^{-1} (nitrile) and 2950 cm^{-1} (C — H stretch). The compound (29) was then converted by reaction with hydrazine hydrate to 2-(3'-methyl-2'-cyclohexenyl)-2-cyanoacethydrazide (30). Spectral data (see experimental, p. 53) was consistent with structure (30).

The next steps in this scheme were to prepare the azide, 2-(3'-methyl-2'-cyclohexenyl)-2-cyanoacylazide (31) and the urethan, 2-(N'-carbethoxy)-2-(3'-methyl-2'-cyclohexenyl)acetonitrile (32). The azide (31) was prepared from the reaction of hydrazide (30) with sodium nitrite and hydrochloric acid. The azide (31) was then converted to urethan (32) by heating under reflux in ethanol. The preparation of urethan (32) had been confirmed by n.m.r. and i.r. spectra. The n.m.r. spectrum (n.m.r. - 14) had a triplet at δ = 1.27 (J = 7 Hz) and a quartet at δ = 4.17 (J = 7 Hz) confirming the presence of the ethyl ester. A

singlet at δ = 1.72 indicated the presence of the methyl group on the double bond. The double bond proton afforded a multiplet (poorly resolved) centered at δ = 5.35. A broad band centred around δ = 2.50 showed the presence of proton attached to nitrogen. The i.r. spectrum (i.r. - 10) had absorptions at 1675 cm^{-1} (double bond), 1740 cm^{-1} (carbonyl), 2260 cm^{-1} (nitrile) and 3460 cm^{-1} (N — H stretching).

The compound, 2-(N'-carbethoxy)-2-(2',3'-oxirino-3'-methylcyclohexyl)acetonitrile (33) was then prepared from (32) by its reaction with m-chloroperoxyzoic acid. In the n.m.r. spectrum (n.m.r. - 15) of the epoxy compound (33), a triplet at δ = 1.27 (J = 7 Hz) and a quartet at δ = 4.17 (J = 7 Hz) indicated the presence of the ethyl ester. A singlet at δ = 1.36 showed the presence of the methyl group. Two doublets at δ = 3.10 and δ = 3.20 appeared due to the single proton attached to carbon bearing the epoxy oxygen atom. The single proton attached to carbon bearing nitrile group was observed

as multiplet centred at δ = 4.67.

The oxirino compound (33) was then hydrolysed under acidic condition to yield 2-(N'-carbethoxy)-2-(2',3'-dihydroxy-3'-methylcyclohexyl) acetonitrile (34) and the proton n.m.r. spectrum (n.m.r. - 16) again provided evidence for its formation. A triplet at δ = 1.27 (J = 7 Hz) and a quartet at δ = 4.17 (J = 7 Hz) showed the presence of the ethyl ester. The methyl group appeared as a singlet at δ = 1.57. The methine proton attached to carbon bearing nitrile group appeared as a multiplet further downfield centred around δ = 5.05

But all attempts to prepare a dicarbonyl compound from (34) by the reaction with sodium metaperiodate were unsuccessful and hence the scheme was not pursued.

In another approach we carried out a Horner-Emmons reaction between 3-methylcyclohexan-2-en-1-one and diethylcyanomethyl phosphonate to give

1-cyanomethylene-3-methyl-2-cyclohexene* (35). Spectroscopic evidences indicated that the desired compound had formed. In n.m.r. spectrum (n.m.r. - 17), a singlet at δ = 1.26 showed the presence of a methyl group attached to the ring double bond. A doublet (poorly resolved) at δ = 4.87 was due to the proton on the exocyclic double bond. Two other doublets (poorly resolved) at δ = 6.01 and δ = 6.45 represented the proton on the endocyclic double bond. The appearance of two doublets could be explained as due to the presence of two iosmeric components of (35). The i.r. spectrum (i.r. - 12) showed absorptions at 1640 cm^{-1} and 1675 cm^{-1} (double bonds), 2218 cm^{-1} (conjugated nitrile) and 2940 cm^{-1} (C — H stretch). The nitrile group of compound (35) was then selectively reduced by lithium aluminum hydride to 1-methyl-3-(2'aminoethylidene)cyclohexene (36). In n.m.r. spectrum (n.m.r. - 18), the methyl group on the ring double bond appeared as a singlet at δ = 1.27. A multiplet at δ = 3.37 indicated the methyl-

*Plate VII

ene protons attached to carbon atom bearing amino group. A multiplet centered at δ = 5.20 indicated the presence of the exocyclic double bond proton and two other multiplets at δ = 5.82 and δ = 6.15 were observed for the proton of the endocyclic double bond. The two distinct absorptions for a single proton could be interpreted as being due to the presence of two isomers. Epoxidation of the endocyclic double bond of (36) produced several other products along with the desired product (37). So this scheme was not investigated further due to the complex nature of the reaction product.

Instead, 2,3-oxirino-3-methylcyclohexan-1-one (38) was first prepared from the reaction of 3-methylcyclohex-2-en-1-one with alkaline hydrogen peroxide. The n.m.r. spectrum (n.m.r. - 19) showed a singlet at δ = 1.46 for the methyl protons. A singlet at δ = 3.65 appeared due to the methine proton adjacent to the carbonyl group. The i.r. spectrum (i.r. - 14) had absorption at 1720 cm^{-1}

(carbonyl). The compound (38) was then subjected to Horner-Emmons reaction to produce 1-cyanomethylene-2,3-oxirino-3-methylcyclohexane(39). The i.r. (i.r. - 15) and n.m.r. (n.m.r. - 20) spectra indicated that the required compound had been produced. The singlets at δ = 1.43 showed the presence of methyl protons. Two singlets at δ = 3.25 and δ = 3.75 confirmed the presence of the oxirino methine proton. Two triplets at δ = 5.42 and δ = 5.5 appeared due to the double bond proton. The n.m.r. spectrum was consistent with the fact that the product would be a mixture of geometric isomers. The i.r. spectrum showed absorptions at 1635 cm^{-1} (double bond), 2215 cm^{-1} (conjugated nitrile). Acidic hydrolysis of the compound (39) yielded 1-cyanomethylene-2,3-dihydroxy-3-methylcyclohexane (40) as crystalline compound. In n.m.r. spectrum (n.m.r. - 21), a singlet at δ = 1.06 appeared due to the methyl protons. A doublet at δ = 4.08 appeared for the allylic methine proton. The double bond proton was observed as a multiplet centered at δ = 5.53. The off resonance spectra (n.m.r. - 21a, 21b, 21c) of

compound (40) suggested that coupling occurred among the double bond proton, the allylic methine proton and one or both of the allylie methylene protons. It was observed that by irradiating the allylic methine proton at 340.8 Hz the peak due to double bond proton collapsed to a singlet and the splitting pattern due to the allylic methylene protons was simplified. The change in splitting patterns of the peaks due to double bond proton and the allylic methine proton were also observed by irradiating the allylic methylene proton at 166.7 Hz. Irradiation of the double bond proton at 442.2 Hz also reduced the complexity of the splitting patterns of peaks due to allylic methine and allylic methylene protons. In i.r. spectrum (i.r. - 16) absorptions were found at 1635 cm^{-1} (double bond), 2218 cm^{-1} (conjugated nitrile) and 3400 cm^{-1} (hydroxyl). The mass spectrum showed a molecule ion peak at m/e 167. But, unfortunately, the attempt to prepare a dicarbonyl compound from (40) by the reaction with sodium metaperiodate was unsuccessful.

In another approach, consideration was given to the use of a sulfone intermediate. Ethyl 2-n-butyl-2-tosyl-4-pentenoate (41) was prepared from ethyl 2-tosylacetate by the usual procedure[12]. The compound (41) was subjected to a hydroboration reaction to yield ethyl 2-n-butyl-5-hydroxy-2-tosyl pentanoate (42). The proton magnetic resonance spectrum (n.m.r.-22) provided evidence for its formation. A triplet at δ = 1.27 (J = 7 Hz) and a quartet at δ = 4,08 (J = 7 Hz) indicated the presence of an ethyl ester. A singlet at δ = 2.44 showed the presence of the methyl group attached to aromatic ring. The aromatic protons appeared as two doublets at δ = 7.28 and δ = 7.67 (J = 8 Hz). Residual traces of the solvent diglyme was found to interfere with the peak due to the methylene protons α to the hydroxyl group. Hence the compound (42) was acetylated by the reaction with acetic anhydride in pyridine and the formation of the acetyl derivative was indicated by n.m.r. spectrum thereby confirming the presence of a hydroxyl group in (42). Monoethyl ester of 2-butyl-2-tosylglutaric acid (43) was then

obtained by the oxidation of (42) with chromium trioxide. The n.m.r. spectrum (n.m.r. -23) indicated that the desired product had been formed. A methyl triplet δ = 1.18 (J = 7 Hz) and a methylene quartet at δ = 4.12 (J = 7 Hz) confirmed the presence of the ethyl ester. A singlet appeared at δ = 2.45 for the methyl group attached to aromatic ring. Two doublets at δ = 7.31 and δ = 7.67 (J = 8 Hz) appeared due to the aromatic protons. A broad band centered at δ = 10.08 indicated the proton of carboxylic group. The next step was the preparation of 4-carbethoxy-4-tosyloctanoylchloride (44) from (43) by its reaction with thionyl chloride. The i.r. spectrum (i.r. - 17) showed absorptions at 1740 cm^{-1} (ester carbonyl) and 1780 cm^{-1} (acid chloride carbonyl). The n.m.r. spectrum showed no acidic proton. The compound (44) was then converted first to 4-carbethoxy-4-tosyloctanoylazide (45) by the reaction with hydrazoic acid. The azide on heating underwent rearrangement to 4-carboethoxy-4-tosyloctylisocyanate (46). The i.r. spectrum of (45) showed absorptions at 1725 cm^{-1} and 2130 cm^{-1} ($-\overset{O}{\overset{\|}{C}}-N_3$). The i.r.

spectrum (i.r. - 18) of (46) had absorptions at 1745 cm^{-1} (ester carbonyl), 2280 cm^{-1} (isocyanate) and 2960 cm^{-1} (C — H stretch). However, the reaction of (46) with ammonia or urea to give an intermediate which could be transformed into cyclic ureido-compound was found unsatisfactory. Therefore, it was decided to hydrolyse (46) to yield an amine as a straight-forward product. But it has been observed from the spectral data and elemental analysis that the hydrolysis of (46) has actually resulted in the formation of 2-butyl-2-tosyl-4-butyro-lactam (47). The i.r. spectrum (i.r. - 19) showed absorptions at 1710 cm^{-1} (carbonyl in γ-lactam), 2960 cm^{-1} (C — H stretch) and 3100-3300 cm^{-1} (broad bands, N — H stretching). In the n.m.r. spectrum (n.m.r. - 24), a singlet at δ = 2.45 was due to the presence of methyl group attached to aromatic ring. A broad singlet at δ = 5.92 indicated the proton attached to nitrogen. Two doublets at δ = 7.31 and δ = 7.76 (J = 8 Hz) showed the presence of four aromatic protons. The mass spectrum showed the highest peak at 296 which should be the peak

corresponding to the molecular weight (M + 1) of the lactam formed.

EXPERIMENTAL

ANALYTICAL AND PHYSICAL DATA

Melting points were determined with a Gallenkamp melting points apparatus and reported in degrees Celsius. Thin layer chromatography was performed on glass plates coated with silica gel (silica gel Woelm TLC, M. Woelm, Eschwege, Germany) to a thickness of 0.3 mm. The infrared spectra were taken by the author using a Beckman spectrophotometer, Model IR-12.

The nuclear magnetic resonance spectra were determined by Dr. T. Griffith and Associates on a Bruker Model WP-80 n.m.r. spectrometer. All spectra, unless otherwise specified, were recorded in deuterated chloroform with tetramethylsilane as internal reference and are expressed in values as defined by the equation:

$$\delta = \frac{\text{observed shift(Hz)} \times 10^6}{\text{observed frequency(Hz)}}$$

The chemical shifts and coupling constants were only approximately obtained by first order analysis of splitting patterns for stated coupling constants and by measurements of approximate centres of

multiplets for chemical shifts. The mass spectra were recorded by Dr. T. Griffith and Mr. K. Pringnitz on a Hitachi RMU-7 spectrometer. The elemental analyses were done by Mr. C. Mallard and Mr. K. Pringnitz with a Perkin-Elmer Elemental Analyser, Model 240.

Ethyl 2-n-butyl-4-bromoacetoacetate[13] (11):

To a solution of ethyl 2-n-butylacetoacetate (7.28 g, 0.056 mole) in $CHCl_3$ (35 mL) bromine (8.94 g, 0.056 mole) in $CHCl_3$ (5 mL) was added dropwise at 0° and the resulting solution was left for 16 hours at room temperature. A stream of nitrogen was passed through the solution for one hour. After drying (Na_2SO_4) the solvent was removed in vacuum to give 10.091 g (yield = 97.3%) of the product as a yellow oil.

The proton magnetic resonance spectrum (n.m.r. No - 1):

δ = 1.27 (t, J = 7 Hz, 3H) $- OCH_2\underline{CH_3}$

δ = 3.78 (t, J = 7 Hz, 1H) $- \overset{O}{\overset{\|}{C}} - \underline{CH} - \overset{O}{\overset{\|}{C}} -$

δ = 4.05 (s, 2H) $- \overset{O}{\overset{\|}{C}} - \underline{CH_2} - Br$

δ = 4.16 (q, J = 7 Hz, 2H) $- O\underline{CH_2} - CH_3$

Ethyl 2-n-butyl-4-azidoacetoacetate (12):

Ethyl 2-n-butyl-4-bromoacetoacetate (1.02 g, 3.84 mmol) was dissolved in 2-(2-methoxyethoxy)ethanol (3 mL) and water (0.5 mL). To this was added sodium azide (0.375 g, 5.76 mmol) with stirring. Almost immediately the solution turned purple and the resulting solution was allowed to stand at room temperature overnight. Ether was added and the resulting solution was washed thrice with water, dried ($MgSO_4$) and the ether was removed under vacuum on a rotary evaporator. Yield, 0.811 g (93%). The proton magnetic resonance spectrum (n.m.r. No. - 2):

δ = 1.275 (t, J = 7 Hz, 3H) $- OCH_2\underline{CH_3}$

δ = 3.49 (t, J = 7 Hz, 1H) $- \overset{O}{\overset{\|}{C}} - \underline{CH} - \overset{O}{\overset{\|}{C}} -$

δ = 4.06 (s, 2H) $- \overset{O}{\overset{\|}{C}} - \underline{CH_2} - N_3$

δ = 4.18 (q, J = 7 Hz, 2H) $- O\underline{CH_2} - CH_3$

IR (i.r. No. - 1):

1735 cm^{-1} (carbonyl, ketone and ester)

2120 cm^{-1} (azide,), 2945 cm^{-1}(C - H stretch).

Ethyl 2-n-butyl-4-amino (as hydrochloride salt) - acetoacetate (13):

Ethyl 2-n-butyl-4-azidoacetoacetate (5.654 g, 24.9 mmol) was dissolved in ethanol (100 mL). To this was added 10% palladium on charcoal (0.600 g) and concentrated hydrochloric acid (6.5 mL). Then hydrogen was passed into the solution with stirring for 3 hours. After filtration the ethanol was removed in vacuum on a rotavapor to give 4.105 g (yield = 69.45%) of the product.

The proton magnetic resonance spectrum (n.m.r. No. - 3):

δ = 1.25 (t, 3H) - $OCH_2\underline{CH_3}$

δ = 3.71 (m, 3H) $-\overset{O}{\overset{\|}{C}}-\underline{CH_2}-NH_2$ and $-\overset{O}{\overset{\|}{C}}-\underline{CH}-\overset{O}{\overset{\|}{C}}-$

δ = 4.17 (q, 2H) $-O\underline{CH_2}CH_3$

δ = 6.9 and 8.15 (broad band) $-CH_2\underline{NH_2}\cdot HCl$

The i.r. spectrum (i.r. No. - 2):

1730 cm^{-1} (ketone and ester carbonyl)

2980 cm^{-1} (very broad band, N - H stretch).

4-(1'-Carbethoxy pentyl)-2-imidazolone[14] (14):

The amino compound (as hydrochloride salt) (13) (1.70 g, 7.1 mmol) was dissolved in water (10 mL). Hydrochloric acid was added in order to maintain the pH of the reaction below 7. Potassium cyanate (1.90 g, 21.3 mmol) was added with stirring. The reaction mixture was heated to 60° and stirring was continued for 30 minutes. A white crystalline compound was formed which was separated by filtration and recrystallized from ethanol-water mixture. Yield 0.402 g (25%). Melting point: 110-112°C.

The n.m.r. spectrum (n.m.r. No. - 4):

δ = 1.24 (t, J = 7 Hz, 3H) - $OCH_2\underline{CH_3}$

δ = 4.12 (q, J = 7 Hz, 2H) - $O\underline{CH_2}CH_3$

δ = 6.11 (s, 1H) $\rangle C = \underline{CH}$ -

δ = 9.90 (broad band) two - $\underline{NH}$ -

The i.r. spectrum (i.r. No. - 3):

1630 cm^{-1} (double bond), 1700 cm^{-1} and 1730 cm^{-1} (cyclic urea and ester carbonyls), 2980 cm^{-1}, (C - H stretch) and 3200 cm^{-1} (broad band, N - H stretch).

The mass spectrum showed molecular ion peak at m/e 226. Some other peaks were observed at 197, 183, 169, 153, 111, 97 and 83. (See Plate IX).

Elemental analysis:

Mol. formula: $C_{11}H_{18}N_2O_3$

	%C	%H	%N
Expected:	58.4	7.9	12.38
Found:	57.07	7.94	11.83

4-(1'-Carboxypentyl)-2-imidazolone (15):

When the above reaction was carried out at refluxing temperature and without added acid a crystalline compound was obtained, identified as the carboxylic acid formed by hydrolysis of the ester.

M.P. 215 - 218°C

Elemental analysis:

Mol. formula: $C_9H_{14}N_2O_3$

	%C	%H	%N
Expected:	54.5	7.07	14.14
Found:	52.19	6.79	14.45

Mass spectrum showed the presence of the molecular ion peak at m/e 198.

Ethyl 2-[4'-methyl-5'-(2"-tetrahydropyranyloxyl)-pentyl] acetoacetate (20):

This compound (20) was prepared by the method used for the preparation of ethyl 2-n-butyl-acetoacetate[9] using the following amount of materials.

1. Ethyl acetoacetate, 2.96 g (0.028 mole)
2. 5-Bromo-2-methyl-1-(2'-tetrahydropy-ranyloxyl)pentane, 6.032 g (0.028 mole)
3. Sodium , 0.522 g (0.028 mole)
4. Ethanol , 30 mL

Yield, 4.27 g (60%)

The proton magnetic resonance spectrum (n.m.r. No. - 5):

δ = 0.91 (d, J = 6.00 Hz, 3H) - $\underset{|}{CH}$ - $\underline{CH_3}$

δ = 1.28 (t, J = 7.0 Hz, 3H) - $OCH_2\underline{CH_3}$

δ = 2.22 (s, 3H)	$-\overset{O}{\overset{\|\|}{C}}-\underline{CH_3}$
δ = 4.18 (q, J = 7.0 Hz, 2H)	$-O\underline{CH_2}-CH_3$
δ = 4.53 (broad peak 1H)	$-O-\underline{\overset{\|}{C}H}-O-$

Ethyl 2-(4'-methyl-5'-hydroxy pentyl)acetoacetate (21):

The compound (20)(1.55 g, 0.005 mole) was dissolved in acetic acid (12 mL), tetrahydrofuran (10 mL) and water (5 mL). The resulting solution was heated at 60° for 3 hours. The solution was then neutralized with $NaHCO_3$ solution (5%), extracted with ether (60 mL) and the ether extract was washed with water (3 x 20 mL), dried ($MgSO_4$). The ether was removed in a rotavapor to give the desired product. Yield, 0.834 g (73.5%).

This compound was also prepared by the reaction of ethyl acetoacetate with 5-bromo-2-methyl-pentanol (hydroxyl group unprotected) using dimethyl-formamide as solvent and sodium hydride as base. (Yield, 50%).

The proton magnetic resonance spectrum (n.m.r. No. - 6):

δ = 0.89 (d, J = 6 Hz, 3H) $-\underset{|}{CH}-\underline{CH_3}$

δ = 1.27 (t, J = 7 Hz, 3H) $-OCH_2-\underline{CH_3}$

δ = 2.23 (s, 3H) $-\overset{O}{\overset{\|}{C}}-\underline{CH_3}$

δ = 3.40 (m, 3H) $-\overset{O}{\overset{\|}{C}}-\underline{\underset{|}{CH}}-\overset{O}{\overset{\|}{C}}-$ and $-\underline{CH_2}-OH$

δ = 4.78 (q, J = 7 Hz, 2H) $-O\underline{CH_2}-CH_3$

<u>Ethyl 2-(4'-methyl-5'-hydroxypentyl)-4-bromoacetoacetate[13] (22a), Ethyl 2-(4'-methyl-5'-hydroxypentyl)-4-azidoacetoacetate (22b), Ethyl-4-bromoacetoacetate[13] (23a) and Ethyl 4-azidoacetoacetate (23b)</u>:

The compounds (22) and (23) (a and b) were prepared following the methods as were used for the preparation of the compounds (11) and (12) respectively (see pages 37 & 38).

IR and ^{1}Hnmr of the compounds (22) and (23) (a and b) were recorded.

(22a): The proton magnetic resonance spectrum (n.m.r. No. -7):

δ = 0.92 (d, J = 6.00 Hz, 3H) $-\underset{|}{CH}-\underline{CH_3}$

δ = 1.25 (t, J = 7 Hz, 3H) $-OCH_2-\underline{CH_3}$

δ = 3.43 (m, 3H) $-\overset{O}{\overset{\|}{C}}-\underset{|}{\underline{CH}}-\overset{O}{\overset{\|}{C}}-$

and $-\underline{CH_2}-OH$

δ = 4.03 (s, 2H) $-\overset{O}{\overset{\|}{C}}-\underline{CH_2}-Br$

δ = 4.18 (q, J = 7 Hz, 2H) $-O\underline{CH_2}-CH_3$

(22b): IR (i.r. No. - 4): 1745 cm^{-1} (ketone and ester carbonyls), 2120 cm^{-1} (azide), 2960 cm^{-1} (C - H stretch).

(23a): ^{1}Hnmr (n.m.r. No. - 8):

δ = 1.28 (t, J = 7 Hz, 3H) $-OCH_2\underline{CH_3}$

δ = 3.67 (s, 2H) $-\overset{O}{\overset{\|}{C}}-\underline{CH_2}-\overset{O}{\overset{\|}{C}}-$

δ = 4.05 (s, 2H) $-\overset{O}{\overset{\|}{C}}-\underline{CH_2}-Br$

δ = 4.18 (q, J = 7 Hz, 2H) $-O\underline{CH_2}-CH_3$

(23b): (n.m.r. No. - 9):

δ = 1.28 (t, J = 7.0 Hz, 3H) $-OCH_2-\overline{CH_3}$

δ = 3.50 (s, 2H) $-\overset{O}{\overset{\|}{C}}-\underline{CH_2}-\overset{O}{\overset{\|}{C}}-$

δ = 4.08 (s, 2H) $-\overset{O}{\overset{\|}{C}}-\underline{CH_2}-N_3$

δ = 4.18 (q, J = 7.0 Hz, 2H) $-O\underline{CH_2}-CH_3$

(23b): (i.r. No. - 5):

1745 cm^{-1} (ketone and ester carbonyls), 2120 cm^{-1} (azide), 3000 cm^{-1} (C - H stretch).

Ethyl 4-amino (as hydrochloride salt) acetoacetate (24) and 4-(1'-carbethoxymethyl)-2-imidazolone[14] (25):

The compounds (24) and (25) were prepared by the procedures used for the preparation of the compounds (13) and (14) respectively (see pages 39 & 40)

The various evidences in favour of the formation of the compound (25) were recorded.

Melting, point, 165-68°.

IR (i.r. No. - 6):

1670 - 1710 cm^{-1} (double bond and urea carbonyls),

1745 cm^{-1} (ester carbonyl),

3200 cm^{-1} (N - H stretch, broad band).

The substance was insoluble in $CHCl_3$, acetone and F_3CCOOH and soluble in dimethylsulfoxide. So ^{1}Hnmr in DMSO-d_6 was recorded.

δ = 6.01 (broad Singlet) $\rangle C = CH -$

Elemental analysis:

Mol. formula: $C_7H_{10}N_2O_3$

	%C	%H	%N
Expected	49.4	5.88	16.47
Found	49.2	5.68	16.42

Mass spectrum showed the molecular ion peak at m/e 170.

Ethyl 2-(4'-methyl-5'-acetoxypentyl) acetoacetate (26):

The compound (21) (1.80 g, 0.008 mole) was dissolved in acetic anhydride (5 mL) and pyridine (5 mL) and was allowed to stand at room temperature overnight. The resulting soln. was then diluted with ether (200 mL), washed successively with HCl (10%, 4 x 25 mL), $NaHCO_3$ (5%, 3 x 30 mL) and water (3 x 30 mL), dried ($MgSO_4$). The ether was removed under reduced pressure to give 2.005 g (yield, 94.5%) of the desired product. TLC (silica gel, ether and ethyl acetate (3:1) as eluent) showed a pure product.

The proton magnetic resonance spectrum (n.m.r. No. - 10):

δ = 0.91 (d, J = 6.00 Hz, 3H) $-\underset{|}{CH}-\underline{CH_3}$

δ = 1.26 (t, J = 7 Hz, 3H) $-OCH_2-\underline{CH_3}$

δ = 2,03 (s, 3H) $-O-\overset{\overset{O}{\|}}{C}-\underline{CH_3}$

δ = 2.2 (s, 3H) $-\overset{\overset{O}{\|}}{C}-\underline{CH_3}$

δ = 3.84 (d, J = 6 Hz, 2H) $-\underline{CH_2}-OAC$

δ = 4.17 (q, J = 7 Hz, 2H) $-O\underline{CH_2}-CH_3$.

Ethyl 2-(4'-methyl-5'-acetoxypentyl)-4-bromoacetoacetate[13] (27) and ethyl 2-(4'-methyl-5'-acetoxypentyl)-4-azidoacetoacetate (28):

Compounds (27) and (28) were prepared according to the methods described for the preparation of compounds (11) and (12) respectively (see pages 37-38) 'Hnmr and IR of these compounds were recorded below:

(27): ^{1}Hnmr (n.m.r. No. - 11):

δ = 0.91 (d, J = 6.00 Hz, 3H) $-\underset{|}{CH}-CH_3$

δ = 1.25 (t, J = 7 Hz, 3H) $-OCH_2-CH_3$

δ = 2.03 (s, 3H) $-O-\overset{\overset{O}{\|}}{C}-CH_3$

δ = 3.85 (d, J = 6 Hz, 2H) $-CH_2-OAc$

δ = 4.01 (s, 2H) $-\overset{\overset{O}{\|}}{C}-CH_2-Br$

δ = 4.16 (q, J = 7 Hz, 2H) $-OCH_2-CH_3$

(28):

IR (i.r. No. - 7):

1750 cm^{-1} (ketone and ester carbonyl), 2120 cm^{-1} (azide), 2960 cm^{-1} (C - H stretch).

Ethyl 2-(3'-methyl-2'-cyclohexenyl)-2-cyanoacetate (29):

Sodium (1.23 g, 0.054 mole) was added to ethanol (50 mL) and after the reaction was complete

ethyl cyanoacetate (6.072 g, 0.054 mole) was added dropwise. Finally, 1-methyl-3-chloro-1-cyclohexene (prepared freshly[15], 7.003 g, 0.054 mole) in ethanol (10 mL) was added dropwise with stirring. The colour of the mixture turned brown very quickly. The resulting solution was heated under reflux overnight. Excess base was neutralized with 5% HCl (5 mL) and the ethanol solution was concentrated and extracted with ether (3 x 150 mL). The combined ether extract was washed with water (3 x 30 mL), dried ($MgSO_4$) and removed under vacuum in a rotavapor. Thin layer chromatography on silica gel using ethyl acetate as eluent showed two spots. Fractional distillation under reduced pressure yielded the desired product (6.95 g, yield = 58%).

The proton magnetic resonance spectrum (n.m.r. No. - 12):

δ = 1.325 (t, J = 7 Hz, 3H) $-OCH_2\underline{CH_3}$

δ = 1.71 (s, 3H) $\underline{H_3C} - C = CH -$

δ = 3.38 and 3.47 (two doublets, 1H) $-\underset{|}{\underline{CH}}-CN$

δ = 4.27 (q, = 7 Hz, 2H) $-O\underline{CH_2}-CH_3$

δ = 5.18 and 5.34 (d, poorly resolved, 1H) $CH_3-\underset{|}{C}=\underline{CH}-$

IR (i.r. No. - 8)

1630 cm^{-1} (double bond), 1755 cm^{-1} (carbonyl, ester), 2218 cm^{-1} (nitrile) and 2950 cm^{-1} (C — H stretch).

2-(3'-methyl-2'-cyclohexenyl)-2-cyanoacethydrazide[16] (30):

Ethyl 2-(3'-methyl-2'-cyclohexenyl)-2-cyanoacetate (4.700 g, 0.023 mole) was dissolved in ethanol (50 mL) and hydrazine hydrate (2.302 g, 0.046 mole) was added with stirring. The resulting solution was stirred overnight at room temperature. The ethanol was evaporated in a rotary evaporator and the residue was extracted successively with ether (2 x 100 mL) and chloroform (100 mL). The ether and chloroform extracts were washed with water (each, 3 x 20 mL), the combined solution was dried (Na_2SO_4) and then evaporated under pressure in a rotavapor to give 2.65 g of the product. TLC on

silica gel using ethyl acetate as eluent showed two spots one of which corresponded to the starting cyanoester. The other spot assumed to be due to the desired product. Column chromatography with silica gel using benzene : ether (1:1) as eluent gave the desired product (1.71 g, yield = 39%).

The proton magnetic resonance spectrum (n.m.r. No. -13):

δ = 1.72 (s, 3H) $\underline{H_3}C - \overset{|}{C} = \overset{|}{C}H$

δ = 3.37 (d, two superimposed, 1H) $- C\underline{H} - CN$

δ = 2.88 and 4.00 (broad band) $- \overset{O}{\overset{||}{C}} - N\underline{H} - \underline{NH_2}$

δ = 5.25 (d, broad band) $CH_3 - \overset{|}{C} = C\underline{H} -$

IR (i.r. No. - 9):

1655 cm^{-1} (double bond and $- \overset{O}{\overset{||}{C}} - NHNH_2$), 2260 cm^{-1} (nitrile), 2940 cm^{-1} (C - H stretch), 3330 cm^{-1} (N - H stretch).

Mass spectrum showed molecular ion peak at m/e 193.

2-(3'-methyl-2'-cyclohexenyl)-2-cyanoacylazide[16](31) and 2-(N'-carbethoxy)-2-(3'-methyl-2'-cyclohexenyl) acetonitrile[16](32):

2-(3'-methyl-2'-cyclohexenyl)-2-cyano-acethydrazide (0.789 g, 0.005 mole) was dissolved in hydrochloric acid (15%, 15 mL), cooled to $-4^{o}C$ and covered with a layer of ether (15 mL). Sodium nitrite (0.989 g, 0.014 mole) in water (3 mL) was added dropwise to the stirred mixture. The azide, on formation, passed into the ether layer. Stirring was continued for half an hour and the ether layer was separated. The aqueous layer was rapidly extracted with two fresh portions (30 mL) of ether. The extracts were combined, dried (Na_2SO_4) and filtered into absolute ethanol (30 mL). The ether was evaporated under reduced pressure and the azide (in ethanol) was heated under reflux on a waterbath for one hour to complete the transformation to the urethan (32).

The ethanol was removed by distillation at reduced pressure to give the product (0.600 g, yield = 56.5%). TLC on silica gel using ethyl acetate as eluent showed only one spot. The n.m.r. and i.r. spectra of compound (32) recorded below.

The proton magnetic resonance spectrum (n.m.r. No. - 14):

δ = 1.27 (t, J = 7 Hz, 3H) $- OCH_2 - \underline{CH_3}$

δ = 1.72 (s, 3H) $\underline{CH_3} - \overset{|}{C} = CH-$

δ = 2.50 (broad band) $- \underline{NH} -$

δ = 4.17 (q, J = 7 Hz, 2H) $- O\underline{CH_2} - CH_3$

δ = 5.35 (d, poorly resolved, 1H) $CH_3 - \overset{|}{C} = \underline{CH} -$

IR (i.r. No. - 10):

1675 cm^{-1} (double bond), 1740 cm^{-1} (carbonyl), 2260 cm^{-1} (nitrile), 3460 cm^{-1} (N - H stretch).

2-(N'-carbethoxy)-2-(2',3'-oxirino -3'-methylcyclohexyl) acetonitrile (33):

2-(N'-carbethoxy)-2-(3'-methyl-2'-cyclohexenyl) acetonitrile (1.98 g, 0'009 mole) was dissolved in methylene chloride (100 mL) and m-chloroperoxybenzoic acid (1.553 g, 0.009 mole) was added to the solution at 0°. After stirring for 4 hours at 0°, the solution was kept overnight in the cold, diluted with methylene chloride (100 mL), neutralized with sodium bicarbonate solution, washed with water (3 x 50 mL) and dried over $MgSO_4$. The solvent was removed on a rotavapor giving the product (1.19 g, yield = 55.4%). TLC on silica gel using ethyl acetate as eluent indicated the formation of a new compound.

The proton magnetic spectrum (n.m.r. No. - 15):

δ = 1.27 (t, J = 7 Hz, 3H) $-OCH_2-CH_3$

δ = 1.36 (s, 3H) 3H) $CH_3-C(O)-CH-$

δ = 3.10 and 3.20 (two doublets, 1H) $CH_3 - C(O) - \underline{CH} -$

δ = 4.17 (q, J = 7 Hz, 2H) $- O\underline{CH_2}CH_3$

δ = 4.67 (m, 1H) $- \underline{CH} - CN$

2-(N'-carbethoxy)-2-(2',3'-dihydroxy-3'-methylcyclohexyl)acetonitrile (34):

2-(N'-carbethoxy)-2-(2',3'-oxirino-3'-methylcyclohexyl)acetonitrile (33) (1.19 g, .005 mole), was dissolved in dioxane (15 mL) and water (10 mL) and concentrated sulfuric acid was added (1 mL). After stirring at room temperature for 6 hours, the dioxane was removed under reduced pressure in a rotary evaporator and the remaining aqueous phase was extracted with ether (2 x 100 mL), and ether extract washed with water (3 x 30 mL), dried ($MgSO_4$) and the ether evaporated in vacuum. Yield of the product was 0.740 g. TLC on silica gel using ethyl acetate as eluent showed only one spot.

The proton magnetic resonance spectrum (n.m.r. No. -16):

δ = 1.27 (J = 7 Hz, 3H) — $OCH_2\underline{CH_3}$

δ = 1.57 (s, 3H) — $\underline{CH_3} - \overset{|}{\underset{|}{C}} - OH$

δ = 4.17 (q, J = 7 Hz, 2H) — $OCH_2\underline{CH_3}$

δ = 5.05 (m, 1H) — $\rangle\underline{CH} - CN$

1-cyanomethylene-3-methyl-2-cyclohexene[17] (35):

To NaH (0.511 g, 0.021 mole) in dry tetrahydrofuran (20 mL) was added dropwise with stirring under nitrogen a solution of diethylcyanomethylphosphonate (3.77 g, 0.021 mole) in THF (20 mL). The resulting solution was stirred for 3 hours under an atmosphere of nitrogen. To this solution was added 3-methyl-2-cyclohexen-1-one (2.35 g, 0.021 mole) in THF (10 mL). After the addition was complete, the solution was heated under reflux with stirring for 24 hours. After cooling, water was added and the

mixture after saturation with NaCl was extracted with ether. The ethereal phase was washed first with HCl (20%, 2 x 20 mL) and then with saturated $NaHCO_3$ solution (3 x 30 mL). After drying ($MgSO_4$) the solvent was removed under reduced pressure giving the crude product (2.54 g). TLC on silica gel using benzene:ethylacetate (1:1) as eluent showed two spots. Column chromatography on silica gel using benzene as eluent afforded 1.61 g (yield = 57.7%) of the desired product. TLC showed a single spot.

The proton magnetic resonance spectrum (n.m.r. No. - 17):

δ = 1.26 (s, 3H) $\underline{CH_3} - \overset{|}{C} =$

δ = 4.87 (d, poorly resolved, 1H) $\rangle C = C\underline{H} - CN$

δ = 6.01 and 6.45 (d, poorly resolved, 1H) $CH_3 - \overset{|}{C} = C\underline{H} -$

IR (i.r. No. - 12):

1640 cm^{-1} (double bond), 2218 cm^{-1} and 1675 cm^{-1} (conjugated nitrile)

2940 cm^{-1} (C - H stretch).

1-Methyl-3-(2'-aminoethylidene)-cyclohexene (36):

1-cyanomethylene-3-methyl-2-cyclohexene (0.321 g, 0.002 mole) was dissolved in dry ether (30 mL) and $LiAlH_4$ (0.182 g, 0.005 mole) was added with stirring over a 5 minute period. The stirring was continued overnight at room temperature. Excess $LiAlH_4$ was destroyed by adding wet methanol and the resulting mixture was then extracted with ether (3 x 50 mL). The ether extract was washed with water (2 x 25 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure in a rotavapor to give the desired product (0.321 g, 97%). TLC indicated a pure product.

The proton magnetic resonance spectrum (n.m.r. No. - 18):

δ = 1.27 (s, 3H) $\underline{CH_3} - \overset{|}{C} =$

δ = 3.37 (m, poorly resolved, 2H) $- \underline{CH_2} - NH_2$

δ = 5.2 (m, 1H) $\rangle C = \underline{CH} - CH_2$

δ = 5.82 and 6.15 (m, 1H) $CH_3 - \overset{|}{C} = \underline{CH} -$

I.R. (i.r. No. - 13):

1655 cm^{-1} (double bond), 2940 cm^{-1} (C — H stretch).

2,3-oxirino-3-methylcyclohexan-1-one[18](38):

3-methyl-2-cyclohexen-1-one (3.00 g, 0.027 mole), H_2O_2 (30%, 7.9 mL, 0.082 mole) and methanol (25 mL) were placed in a flask and cooled to 0° by ice-salt bath. Aqueous NaOH (6N, 2.3 mL) was added dropwise to it while maintaining the temperature below $20^{\circ}C$. After the addition was complete, the mixture was stirred for 3 hours at room temperature. The reaction mixture was poured

into 50 mL of water and the resulting mixture was extracted with ether (2 x 30 mL). The combined extract was washed with water and dried ($MgSO_4$). Evaporation of the ether yielded the product (1.51 g, 44%). Thin layer chromatography on silica gel with ethyl acetate as eluent showed a single spot indicating a pure compound.

The proton magentic resonance spectrum (n.m.r. No. -19):

δ = 1.46 (s, 3H) $\underline{CH_3}$ — C(—O—)— CH —

δ = 3.05 (s, 1H) CH_3 — C(—O—)— $\underline{CH}$ —

IR (i.r. No. - 14):

1720 cm^{-1} (carbonyl), 2960 cm^{-1} (C — H stretch).

1-cyanomethylene-2,3-oxirino-3-methylcyclohexane[17] (39):

A Horner Emmons reaction between 2,3-oxirino-3-methylcyclohexan-1-one (1.452 g, 0.0115 mole) and diethylcyanomethylphosphonate (2.039 g, 0.0115 mole) was performed following the procedure used for the preparation of compound (35). Yield of the crude product was 1.813 g. TLC on silica gel with ethyl acetate as eluent indicated a mixture of products. Column chromatography with silica gel using benzene:ether (1:1) as eluent yielded 0.965 g (56%) of the desired product. TLC of this product indicated a mixture of two diastereomeric components.

The proton magnetic resonance spectrum (n.m.r. No. -20):

δ = 1.43 (singlets, 3H) $\underline{CH_3}$ — C(—O—)(—)—CH

δ = 3.25 and 3.75 (two s, 1H) CH_3 — C(—O—)(—)—$\underline{CH}$ —

$$\delta = \begin{matrix} 5.42 \\ \text{and} \\ 5.5 \end{matrix} \text{ (two t, 1H) } \rangle C = C\underline{H} - CN$$

The chromatographed compound was distilled between 105-115° at 0.3 mm pressure and n.m.r. was recorded which was found to be identical as above.

I.R. (i.r. No. -15):

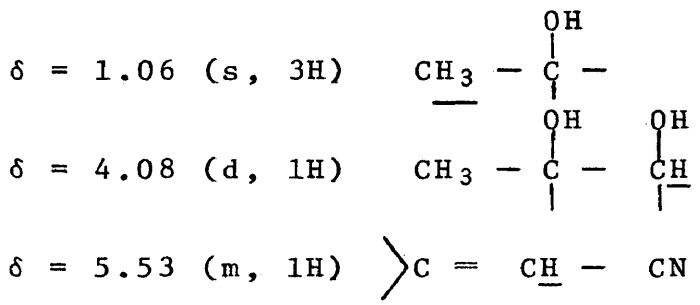
1635 cm^{-1} (double bond), 2215 cm^{-1} (conju-(gated nitrile), 2960 cm^{-1} (C — H stretch).

1-cyanomethylene-2,3-dihydroxy-3-methylcyclohexane (40):

1-cyanomethylene-2,3-oxirino-3-methyl-cyclohexane (2.09 g, 0.014 mole) was dissolved in dioxane (12 mL), water (12 mL) and concentrated sulfuric acid (3 drops) was added. The solution was heated at 60° - 65°C for 24 hours. The dioxane was removed under reduced pressure in a rotary evaporator and the remaining aqueous phase was extracted with ether (2 x 150 mL), washed with water

(3 x 30 mL), dried ($MgSO_4$) and the ether evaporated in vacuum. Yield of the product was 1.1 g. TLC on silica gel using ethyl acetate as eluent indicated a mixture of products. Column chromatography with silica gel using benzene:ether (1:1) as eluent gave a crystalline compound which was again recrystallized from a mixture of ethanol and ether. Yield 0.67 g (28.6%). TLC indicated a pure compound. M.P. 110 - 112°C.

The proton magnetic resonance spectrum (n.m.r. No. -21) in acetone - d_6:



I.R. (i.r. No. -16):

1635 cm^{-1} (double bond), 2218 cm^{-1} (conjugated nitrile), 2960 cm^{-1} (C — H stretch), 3400 cm^{-1} (hydroxyl).

Elemental analysis:

Mol. formula: $C_9H_{13}NO_2$

	%C	%H	%N
Calculated	64.67	7.78	8.38
Found	63.68	7.67	8.49

Mass spectrum showed the molecular ion peak at m/e 167.

Ethyl 2-butyl-5-hydroxy-2-tosylpentanoate[19](42):

A three-necked flask (100 mL) was equipped with a condenser, a dropping funnel and a magnetic stirrer. The top of the dropping funnel was fitted with a rubber septum to permit introduction of materials with the aid of a hypodermic syringe. In the flask were placed (0.109 g, 0.003 mole, 6% excess) of sodium borohydride, diglyme (10 mL) and ethyl 2-n-butyl-2-tosyl-4-pentenoate (1.692 g, 0.006 mole). The apparatus was flushed with nitrogen and a static nitrogen pressure was maintained during the oxidation stage. The flask was immersed in an ice-water bath keeping the contents at 10 - 15°C.

Hydroboration was initiated by dropwise addition of borontrifluoride etherate (3 mmol, 10% excess) to the well stirred reaction mixture and the stirring was continued for a further period of one hour.

The excess hydride was then destroyed by the dropwise addition of water (2 mL), followed by the addition of aq. sodium hydroxide (3M, 2 mL). The flask was then immersed in ice-water bath and the borinic acid intermediate was oxidized at 25 - 30° by the slow addition of aq. hydrogen peroxide (30%, 1 mL) to the well stirred reaction mixture. The mixture was then stirred overnight at room temperature. The reaction mixture was extracted with ether (25 mL) and the ether extract was washed with ice-water (5 x 25 mL) to remove the diglyme (still trace of diglyme was present in the product). The ether extract was dried ($MgSO_4$) and ether was removed in a rotavapor to give 1.41 g (yield, 79%) of the product. TLC on silica gel using ethyl acetate as eluent indicated the formation of a new compound. The proton magnetic resonance spectrum showed the

absence of the double bond.

The proton magnetic resonance spectrum (n.m.r. No. - 22):

δ = 1.17 (t, J = 7 Hz, 3H) $- OCH_2\underline{CH_3}$

δ = 2,44 (s, 3H) $- C_6H_4 - \underline{CH_3}$

δ = 4.08 (q, J = 7 Hz, 2H) $- O\underline{CH_2}CH_3$

δ = 7.28 (d, J = 8 Hz, 2H aromatic)

δ = 7.67 (d, J = 8 Hz, 2H aromatic)

However, the solvent diglyme interfered with the peaks due to hydrogens α to the hydroxyl group ($- CH_2OH$), the absorption of which should be in the same region as diglyme.

Monoethylester of 2-n-butyl-2-tosylglutaric acid (43):

Ethyl 2-n-butyl-5-hydroxy-2-tosylpentanoate (0.800 g) was dissolved in pyridine and chromium

trioxide (0.500 g) was added with stirring and stirring was continued for 24 hours at room temperature. The reaction mixture was diluted with water (50 mL) and the pyridine was neutralized by adding conc. HCl. The solution was extracted with ether (2 x 50 mL). Ether extract washed with water (4 x 20 mL), dried ($MgSO_4$) and ether was evaporated to give 0.603 g (yield, 73%) of the product. TLC on silica gel using ethyl acetate as eluent indicated the formation of a new compound.

The proton magnetic resonance spectrum (n.m.r. No. - 23):

δ = 1.18 (t, J = 7 Hz, 3H) — $OCH_2\underline{CH_3}$

δ = 2.45 (s, 3H) — $C_6H_5 - \underline{CH_3}$

δ = 4.12 (q, J = 7 Hz, 2H) — $O\underline{CH_2} - CH_3$

δ = 7.31 (d, J = 8 Hz, 2H aromatic)

δ = 7.68 (d, J = 8 Hz, 2H aromatic)

δ = 10.08 (broad band) — $\overset{O}{\overset{\|}{C}} - O\underline{H}$

4-carbethoxy-4-tosyloctanoylchloride (44):

The acidic compound (43) (3.00 g) was heated under reflux with thionyl chloride (excess) for 2 hours and excess thionyl chloride was removed under vacuum in a rotavapor to give the acyl chloride (44) as an oil (2.11 g, 70%).

I.R. spectrum (i.r. No. - 17):

1605 cm^{-1} (benzene ring), 1740 cm^{-1} (carbonyl, ester), 1790 cm^{-1} (carbonyl, acidchloride).

The proton magnetic spectrum showed no acidic proton.

4-carbethoxy-4-tosyloctanoylazide[20] (45) and 4-carbethoxy-4-tosyloctylisocyanate[20] (46):

The acyl chloride (44) (1.61, 4.32 mmol) was dissolved in toluene (10 mL) and cooled by an ice-salt bath. From dropping funnel a mixture of hydra-

zoic acid[21] (4.32 mmol) and pyridine (4.32 mmol) in toluene (10 mL) was slowly added with stirring at around -5^{o}. After a few seconds pyridinium chloride began to precipitate. After addition was complete, the cooling bath was taken away and stirring was continued at ambient temperature for one hour. The precipitate was separated by suction filtration and the filtrate was subjected to aspirator vacuum in a rotary evaporator for a few minutes at ambient temperature to remove the excess of hydrazoic acid. The solution thus obtained gave an I.R. spectrum in which two new bands at 1725 cm^{-1} and 2130 cm^{-1} confirmed the presence of $-CON_3$ group. The azide in toluene solution was heated under reflux for one hour. The toluene was removed under reduced pressure on a rotary evaporator. Yield of isocyanate was 1.08 g (71.5%) on the basis of acid chloride used. TLC of the product on silica gel using benzene as eluent showed a single spot.

I.R. spectrum of isocyanate (i.r. No - 18):

1605 cm^{-1} (benzene ring), 1745 cm^{-1} (ester carbonyl), 2280 cm^{-1} (isocyanate), 2960 cm^{-1} (C — H stretch).

2-butyl-2-tosyl-4-butyrolactam[22](47):

To a solution of the isocyanate (46) (3.00 g) in toluene (20 mL) was added acetic acid: water (2:1, 40 mL) and the resulting solution was heated at 60° for 3 days. Water (30 mL) was added. The resulting solution was extracted with ether to remove the neutral compounds. The solution was then made alkaline with 10% sodium hydroxide solution. The alkaline solution was extracted with ether and the ether extract washed once with water, dried ($MgSO_4$) and then evaporated in vacuum on a rotary evaporator giving a crystalline product (1.01 g, yield = 32%). TLC on silica gel using benzene:ether (9:1) as eluent showed one spot indicating a pure product. The evidences from different spectra and elemental analysis suggested the formation of a lactam derivative (47). M.P. 151 - 152°C.

The n.m.r. spectrum (n.m.r. No - 24):

δ = 2.45 (s, 3H) $-C_6H_4\underline{CH_3}$

δ = 5.92 (broad singlet 1H) $-\underline{NH}-\underset{|}{C}=O$

δ = 7.31 (d, J = 8 Hz, 2H aromatic)

δ = 7.76 (d, J = 8 Hz, 2H aromatic)

I.R. spectrum (i.r. No. - 19):

1605 cm^{-1} (benzene ring), 1710 cm^{-1} (γ -lactam carbonyl), 2960 cm^{-1} (C — H stretch), 3200 cm^{-1} (broad band, N — H stretch).

Elemental analysis:

Mol. formula: $C_{15}H_{21}NO_3S$

	%C	%H	%N
Expected:	59.824	7.917	4.10
Found:	60.24	7.11	4.86

Mass spectrum showed the presence of highest peak at m/e 296 which should be the peak corresponding to molecular weight (M+1) of the lactam formed.

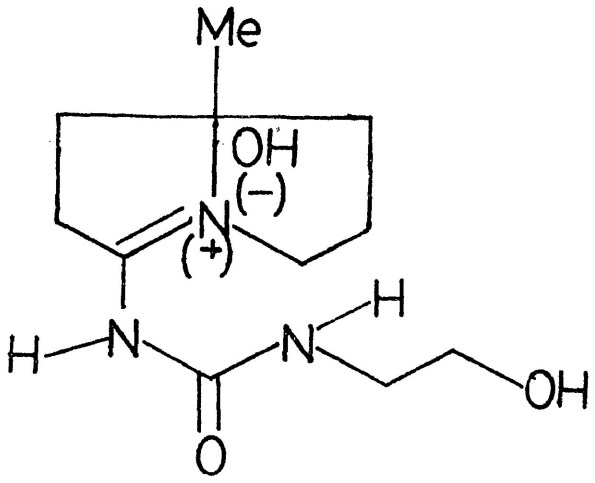
Sodium metaperiodate cleavage of Compounds 34 and 40:

2-(N-carbethoxy)-2-(2',3'-dihydroxy-3'-methylcyclohexyl)acetonitrile (34) (500 mg.) was dissolved in methanol (20 mL) and sodium metaperiodate (0.5M, 25 mL0 was added. The resulting solution was heated in the dark at 100°C for 48 hours. The methanol was evaporated in a rotary evaporator and the remaining substance was dissolved in ether (150 mL) and washed with water (3 x 30 mL), dried ($MgSO_4$) and the ether evaporated in vacuum to give the product, 450 mg. TLC on silica gel using ethyl acetate as eluent showed a mixture of products. The proton n.m.r. spectrum also indicated a complex mixture of unidentifiable compounds.

1-Cyanomethylene-2,3-dihydroxy-3-methyl-cyclohexane (40) was treated in the same way.

PLATES

PLATE I



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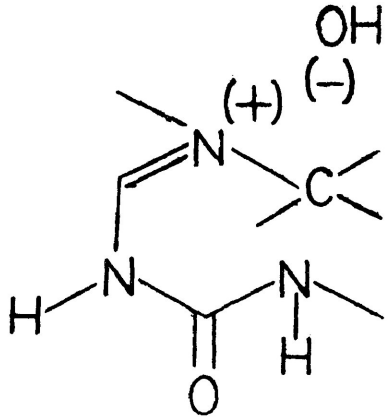

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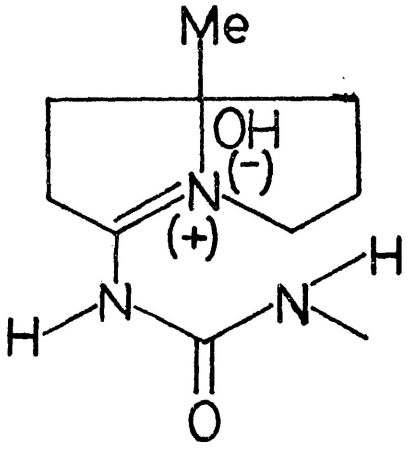

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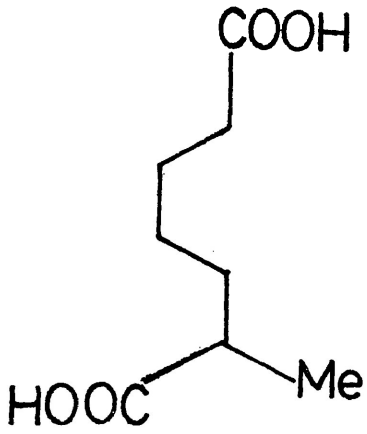

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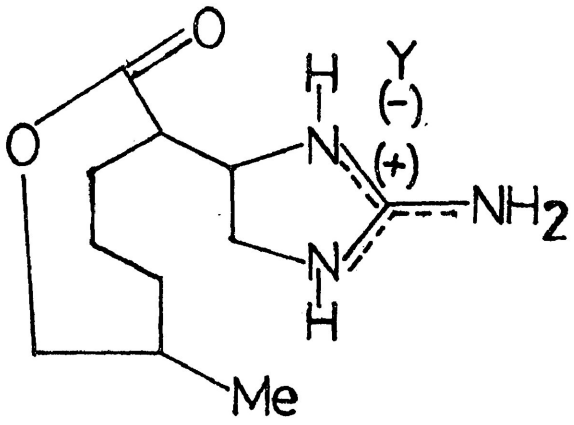

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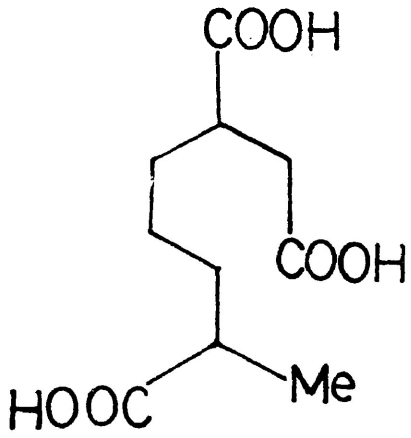

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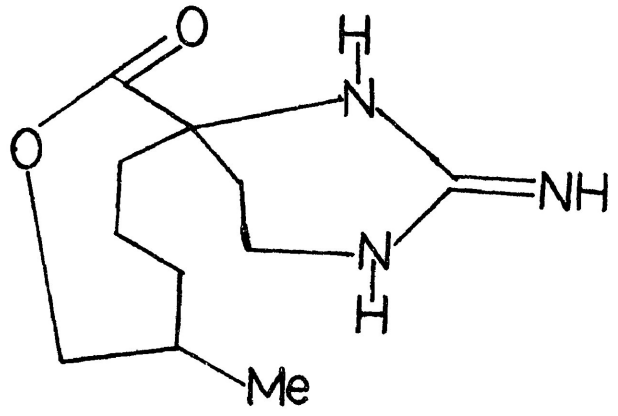
PLATE II



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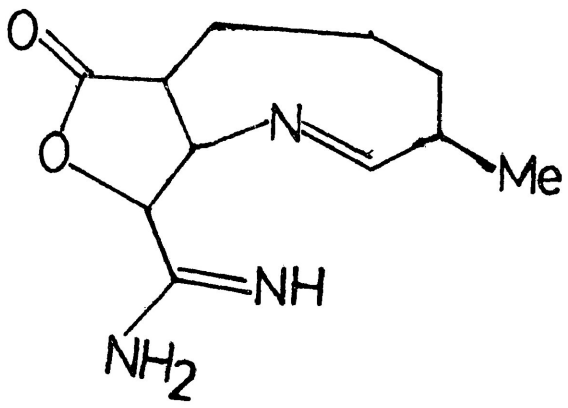

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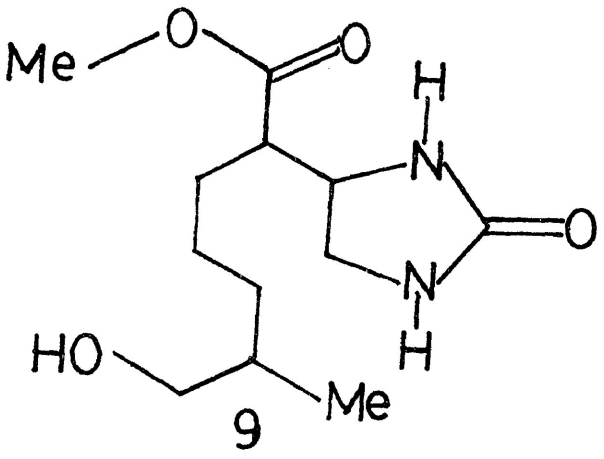

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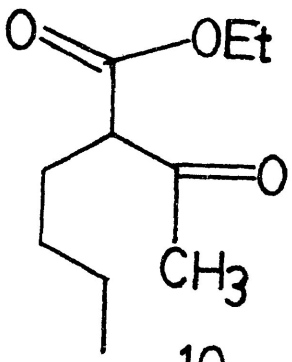

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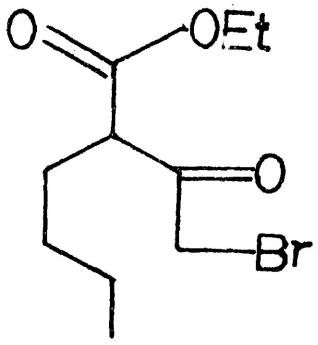

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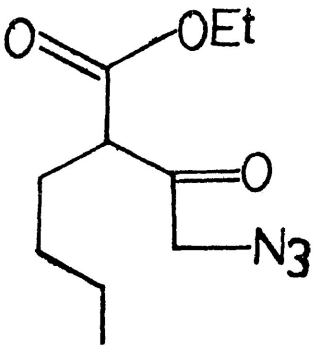

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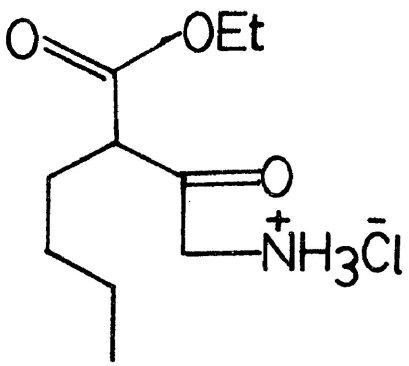
PLATE III



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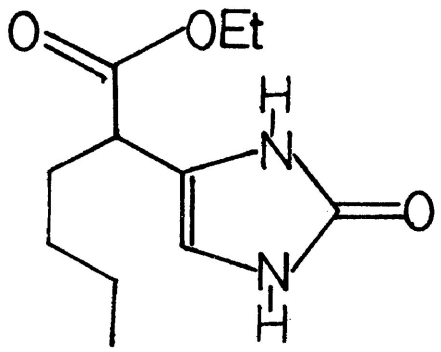

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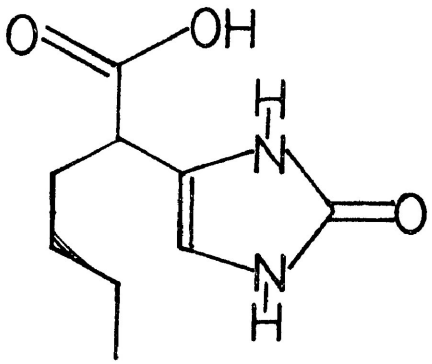

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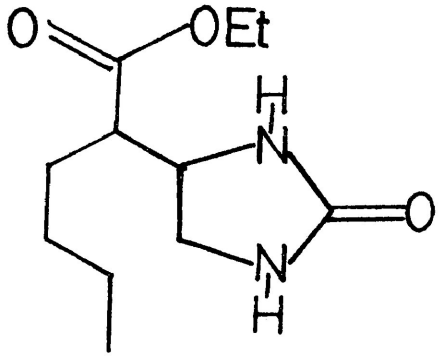

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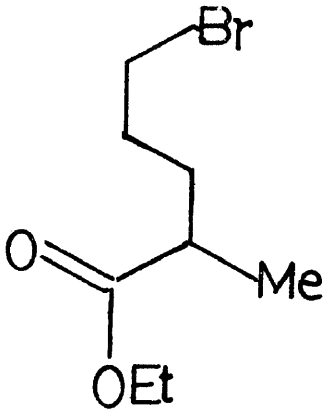

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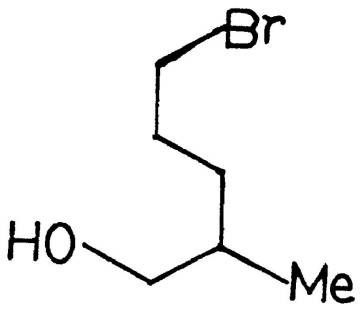

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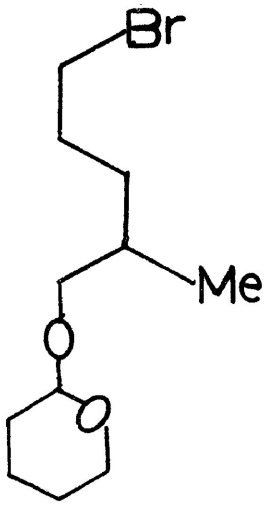
PLATE IV



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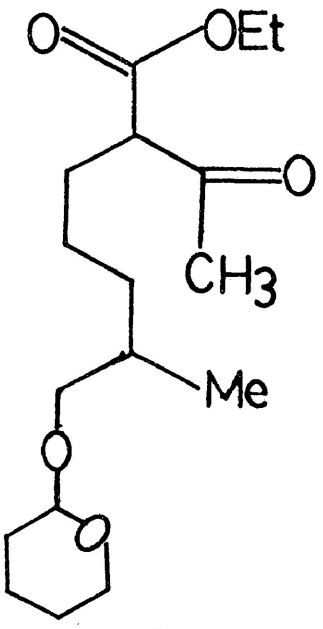

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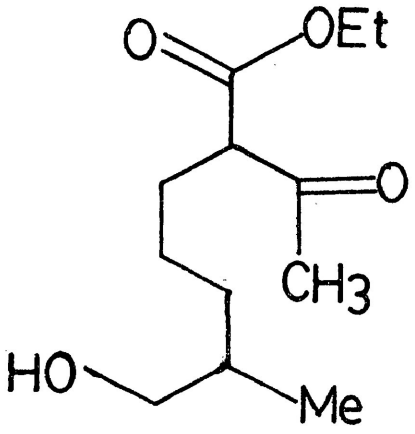

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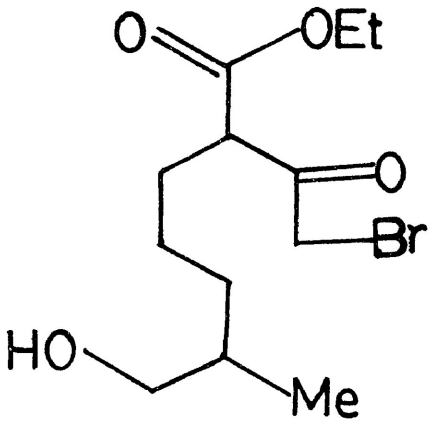

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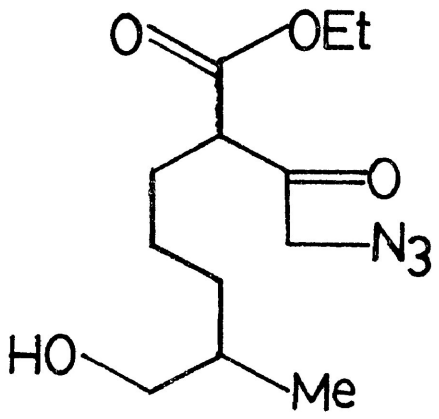

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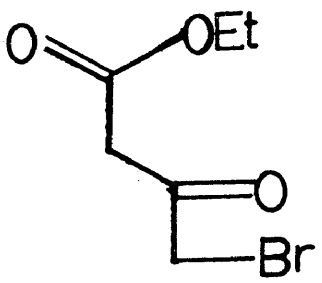

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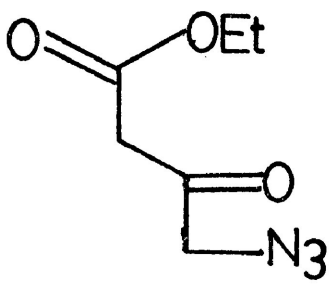
PLATE V



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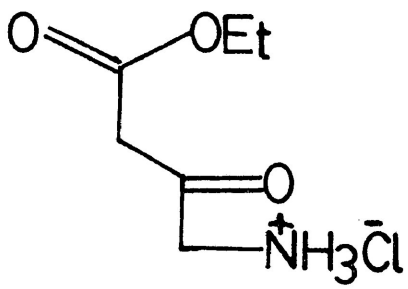

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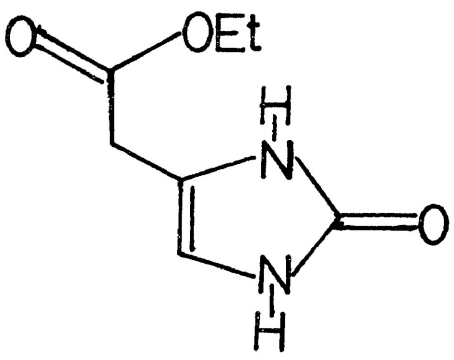

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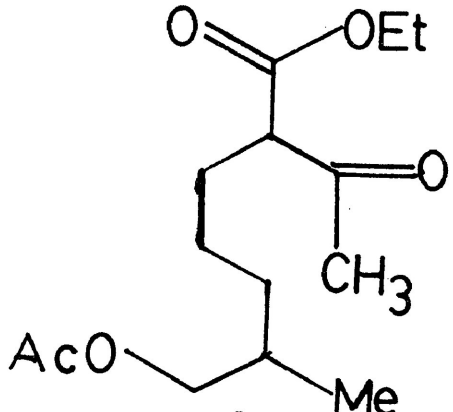

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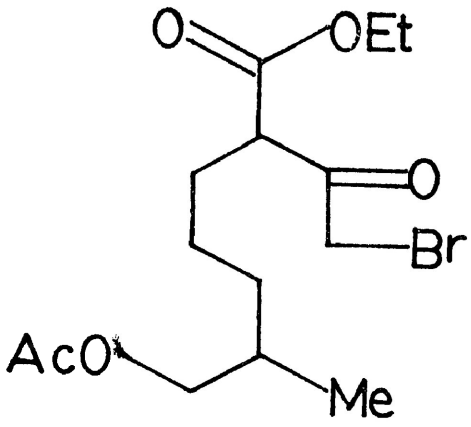

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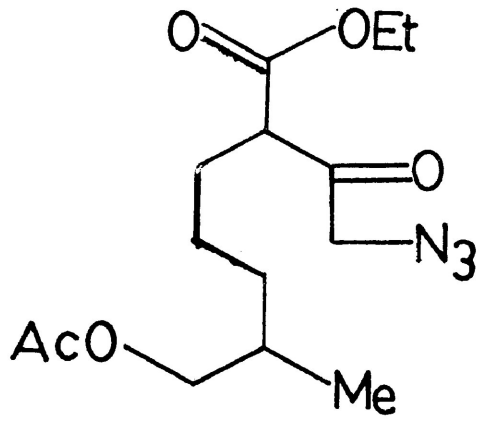

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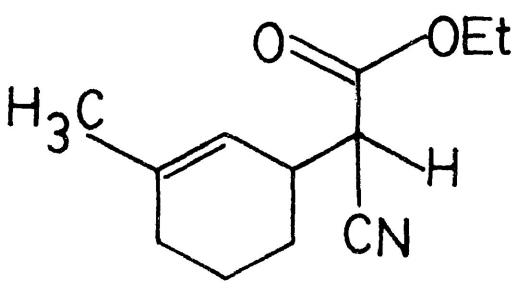
PLATE VI



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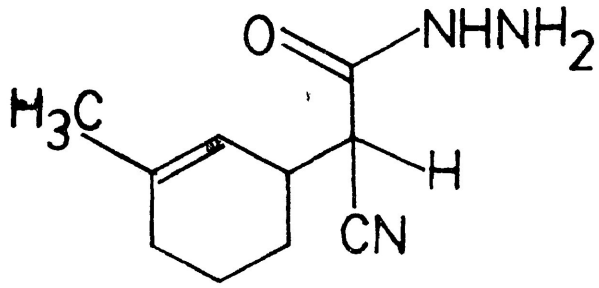

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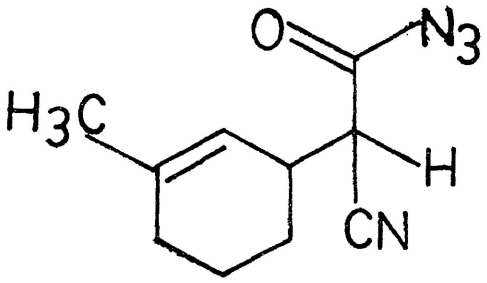

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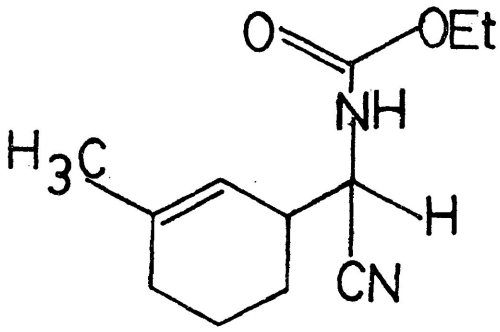

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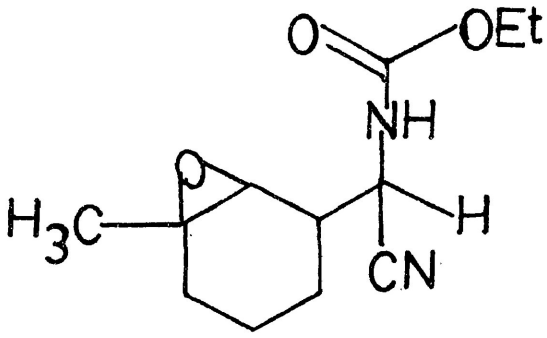

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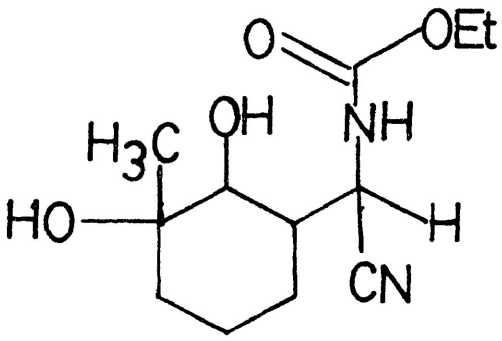

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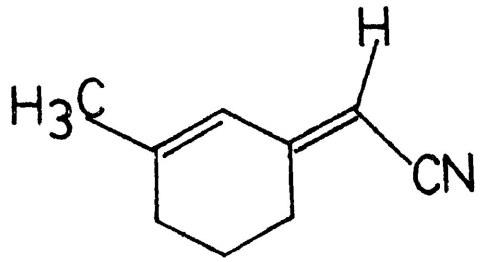
PLATE VII



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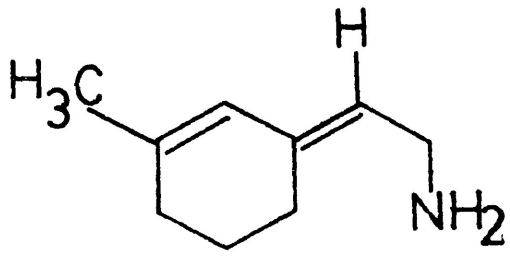

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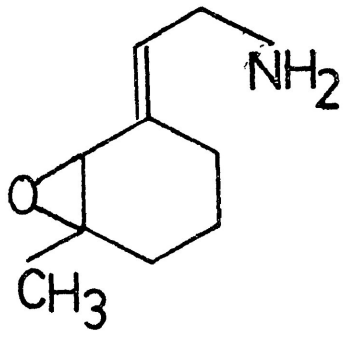

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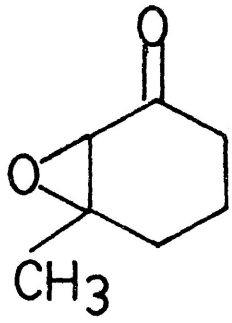

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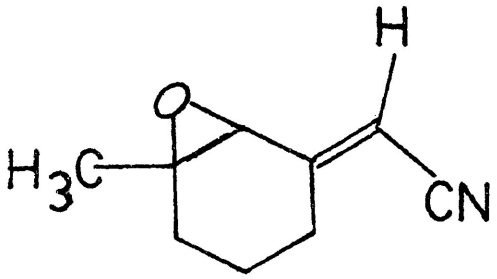

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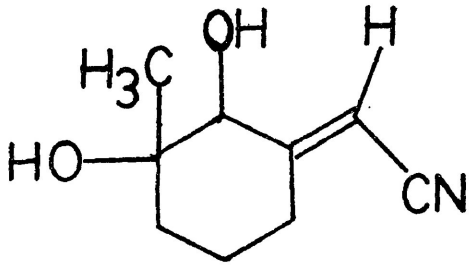

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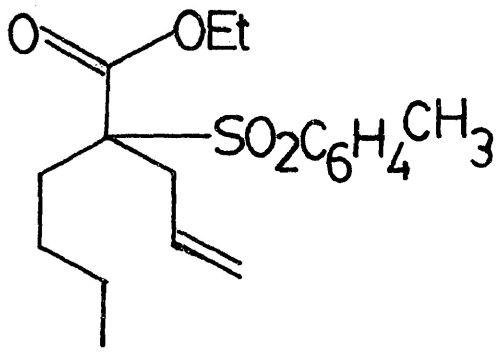
PLATE VIII



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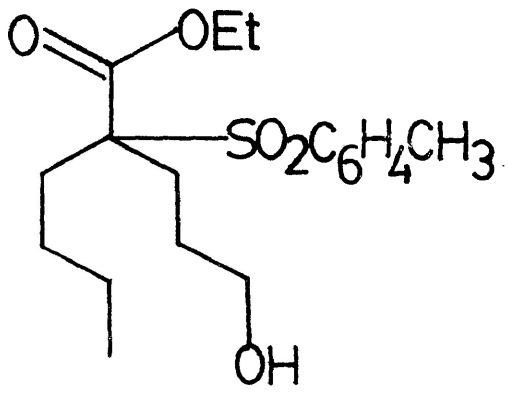

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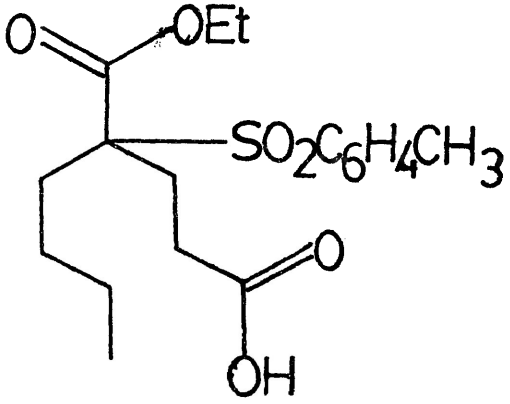

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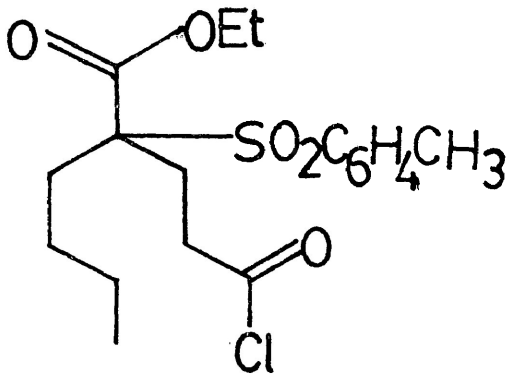

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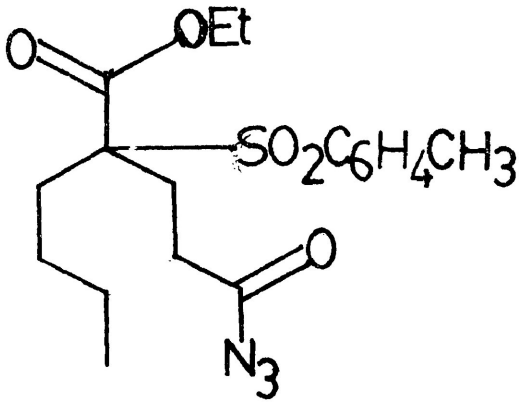

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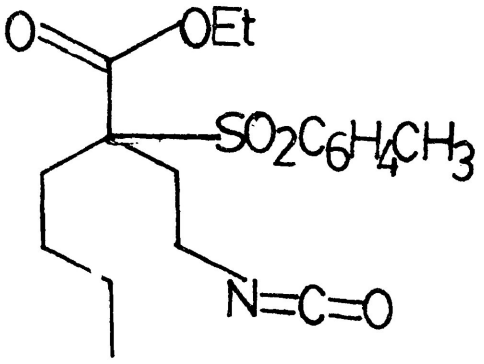

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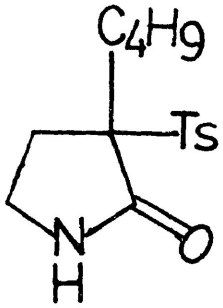

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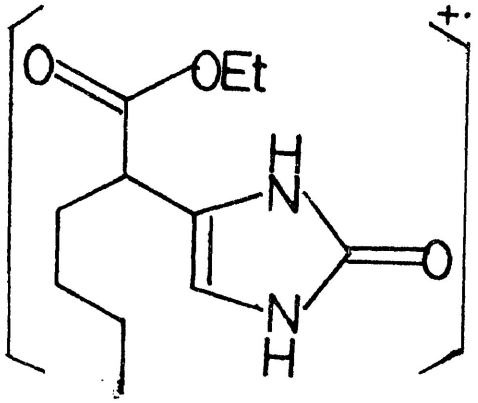
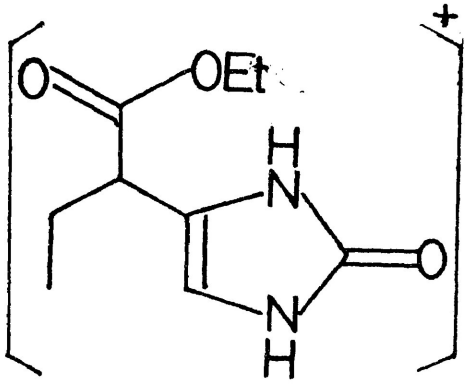
PLATE IX



m/e 226



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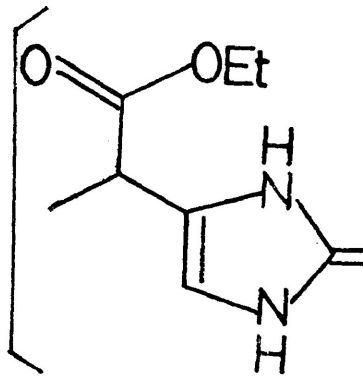

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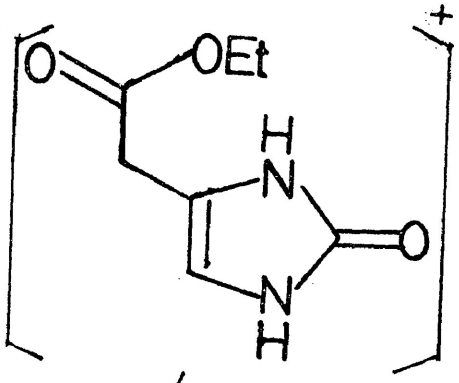

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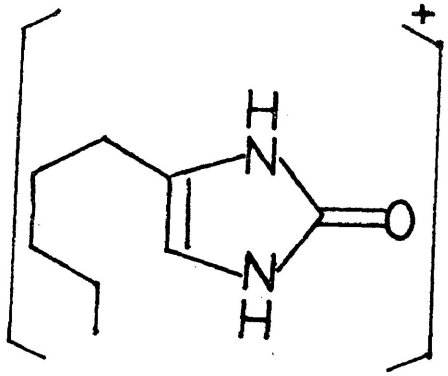
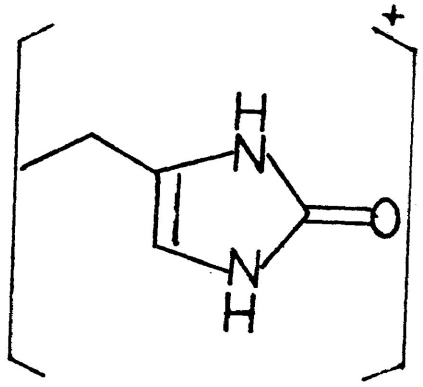
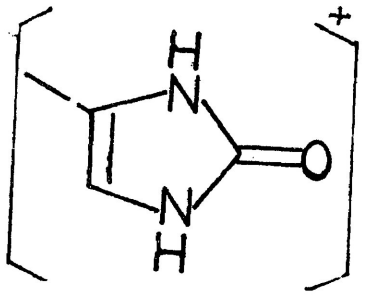


m/e 153



m/e 111



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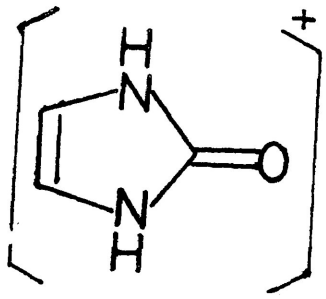
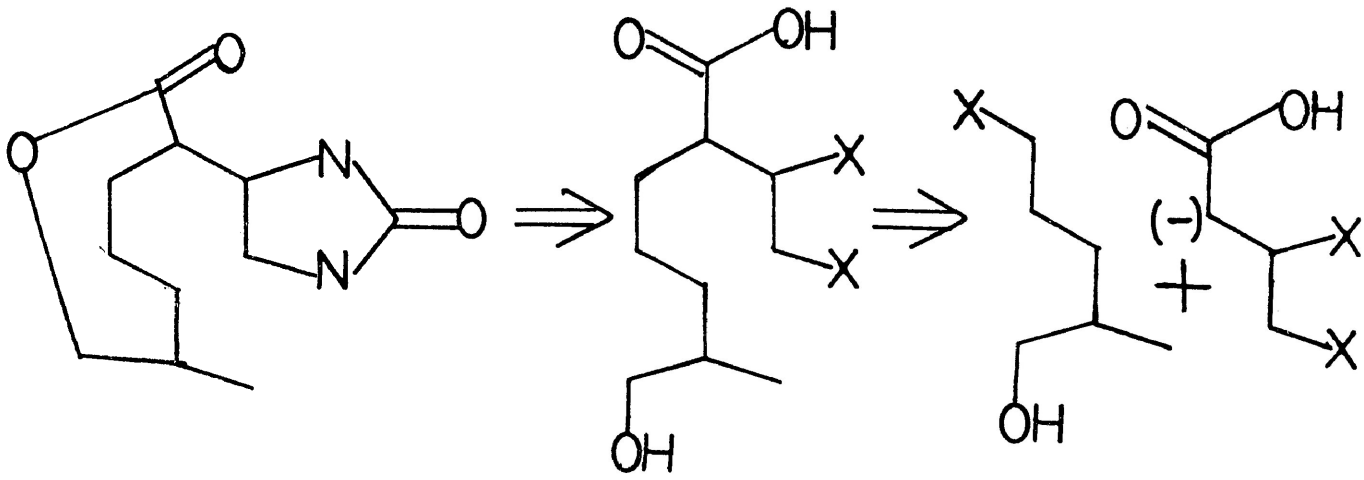
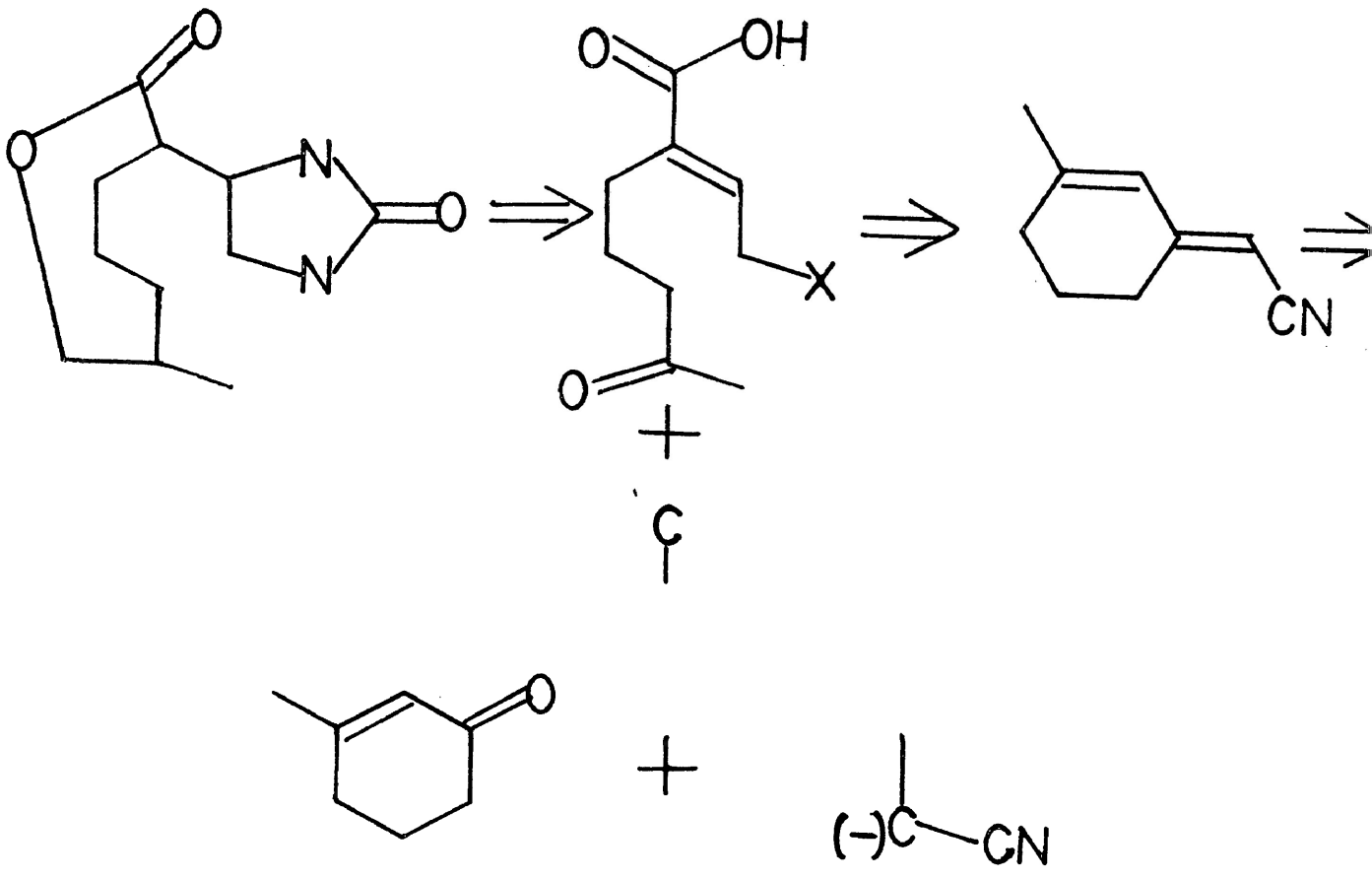


m/e 83

PLATE X

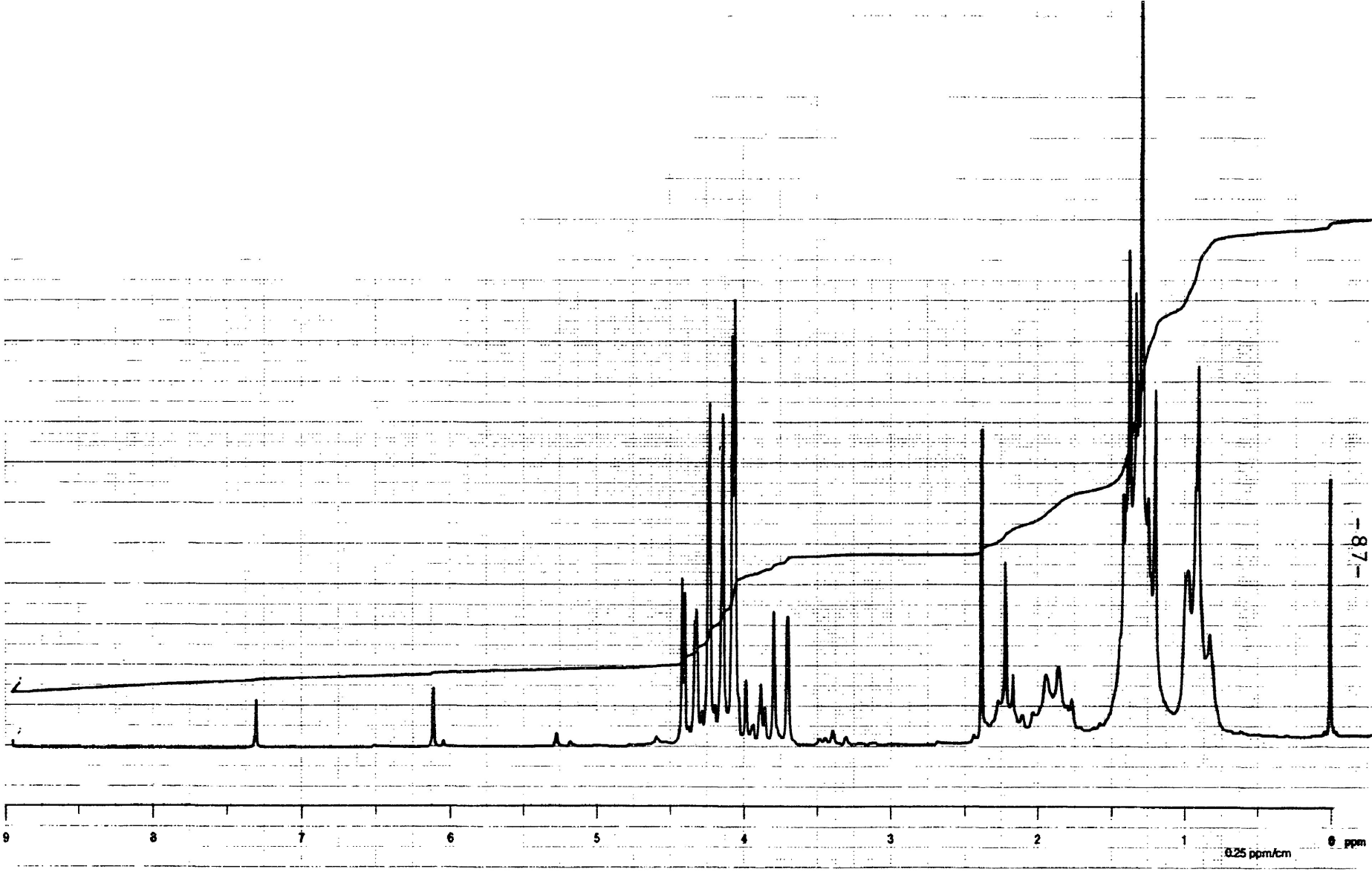


PLAN I

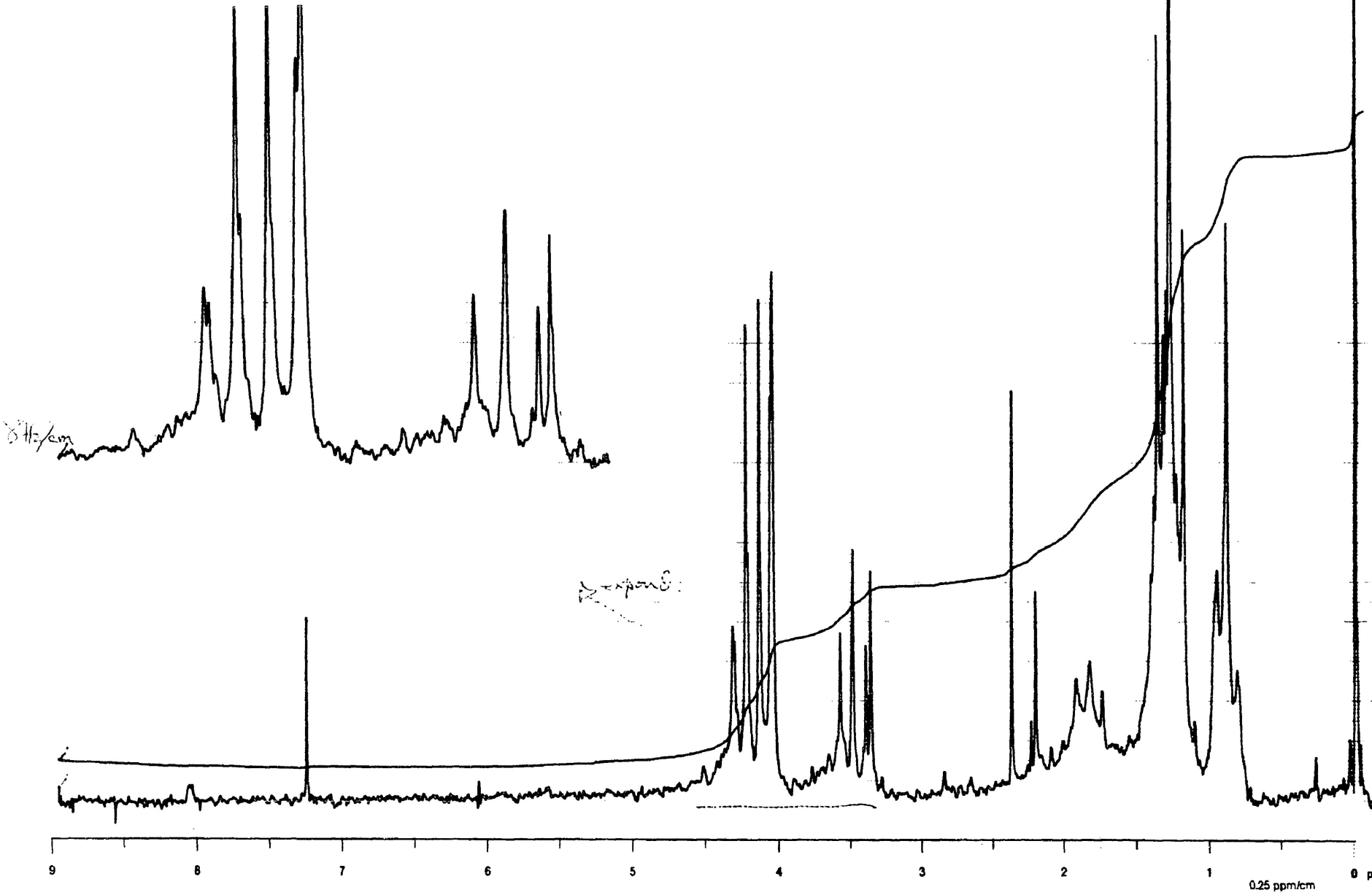


PLAN II

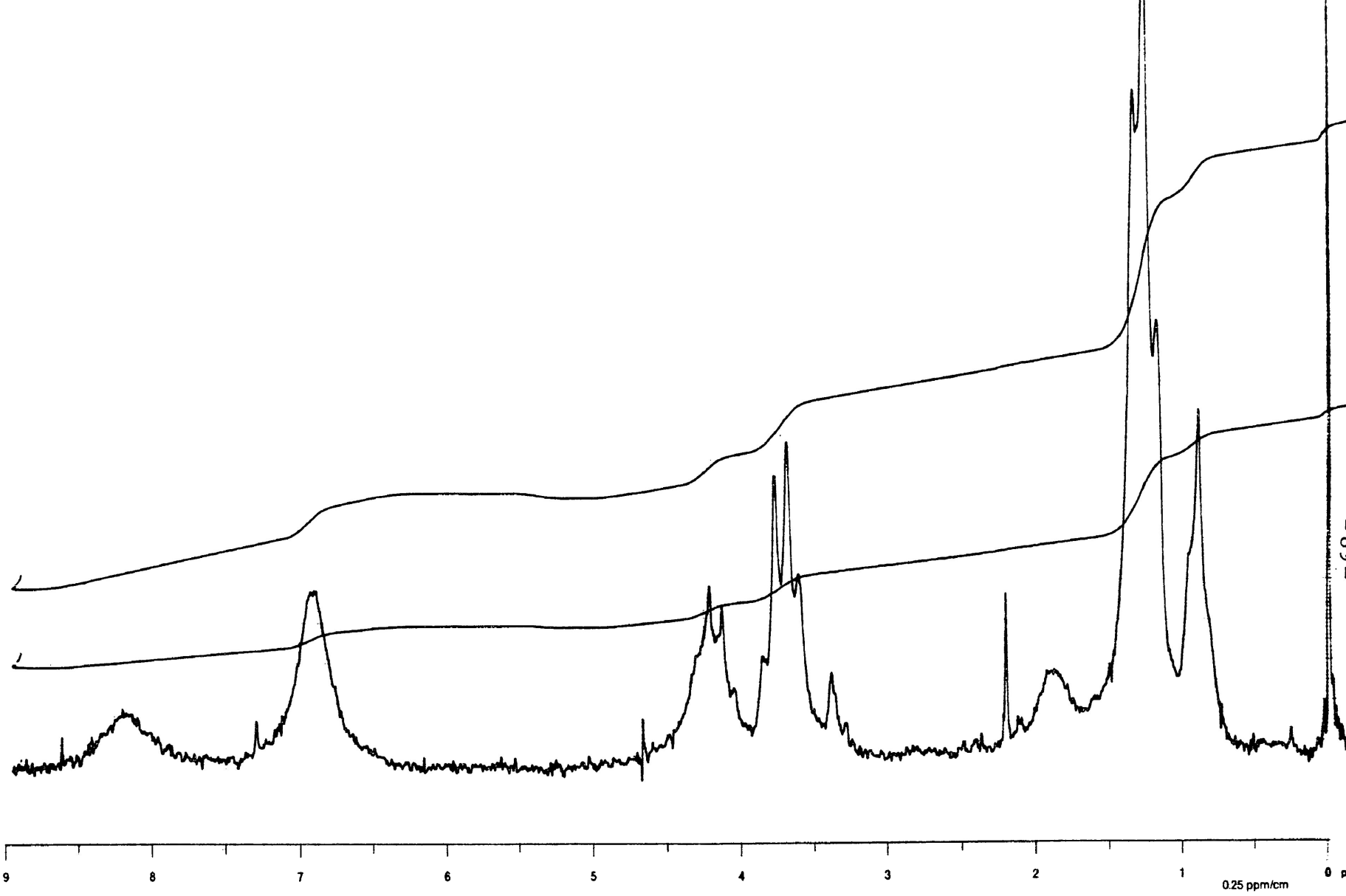
SPECTRA



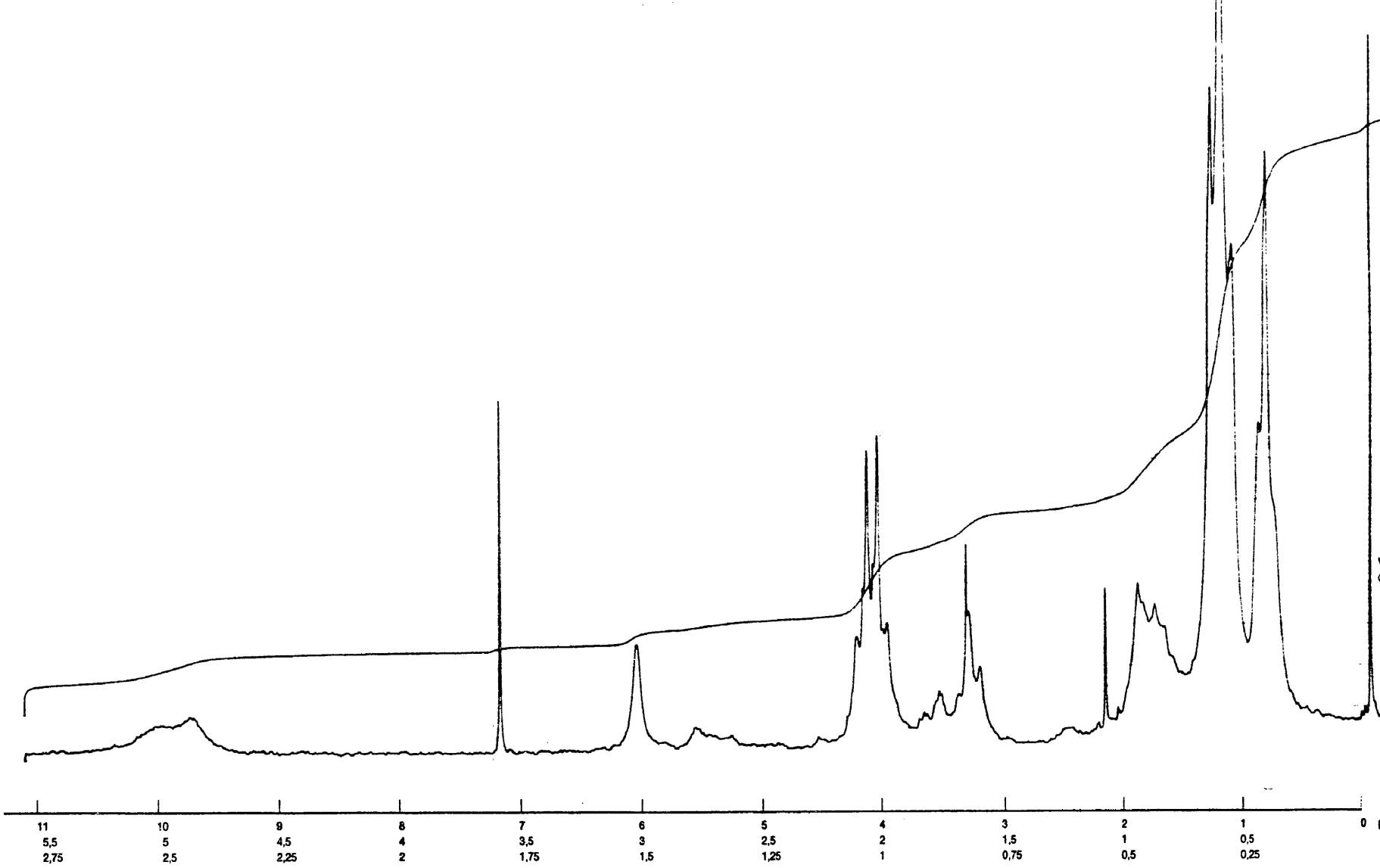
NMR NO. 1. Ethyl 2-n-butyl-4-bromoacetoacetate



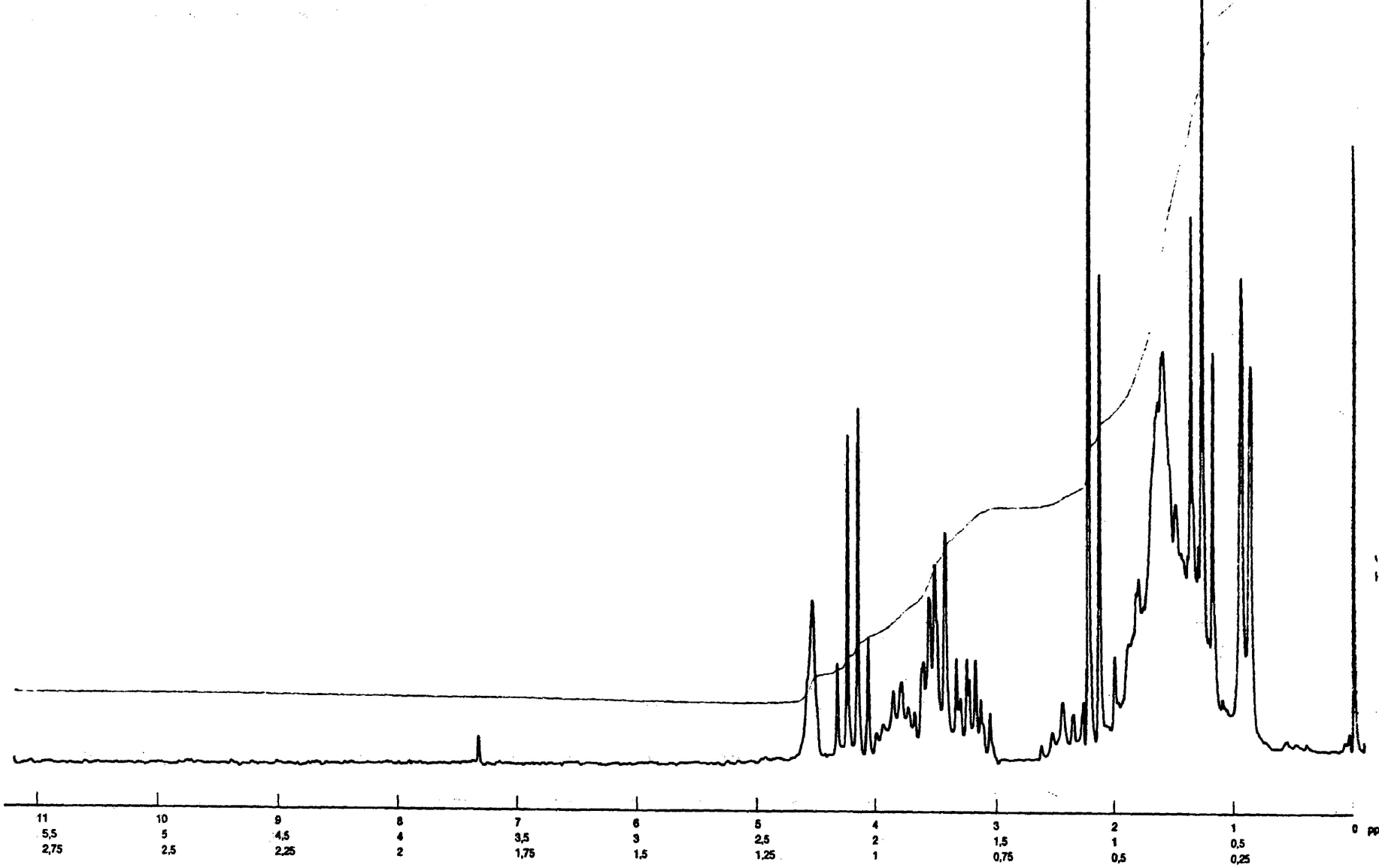
NMR NO. 2. Ethyl 2-n-butyl-4-azidoacetoacetate



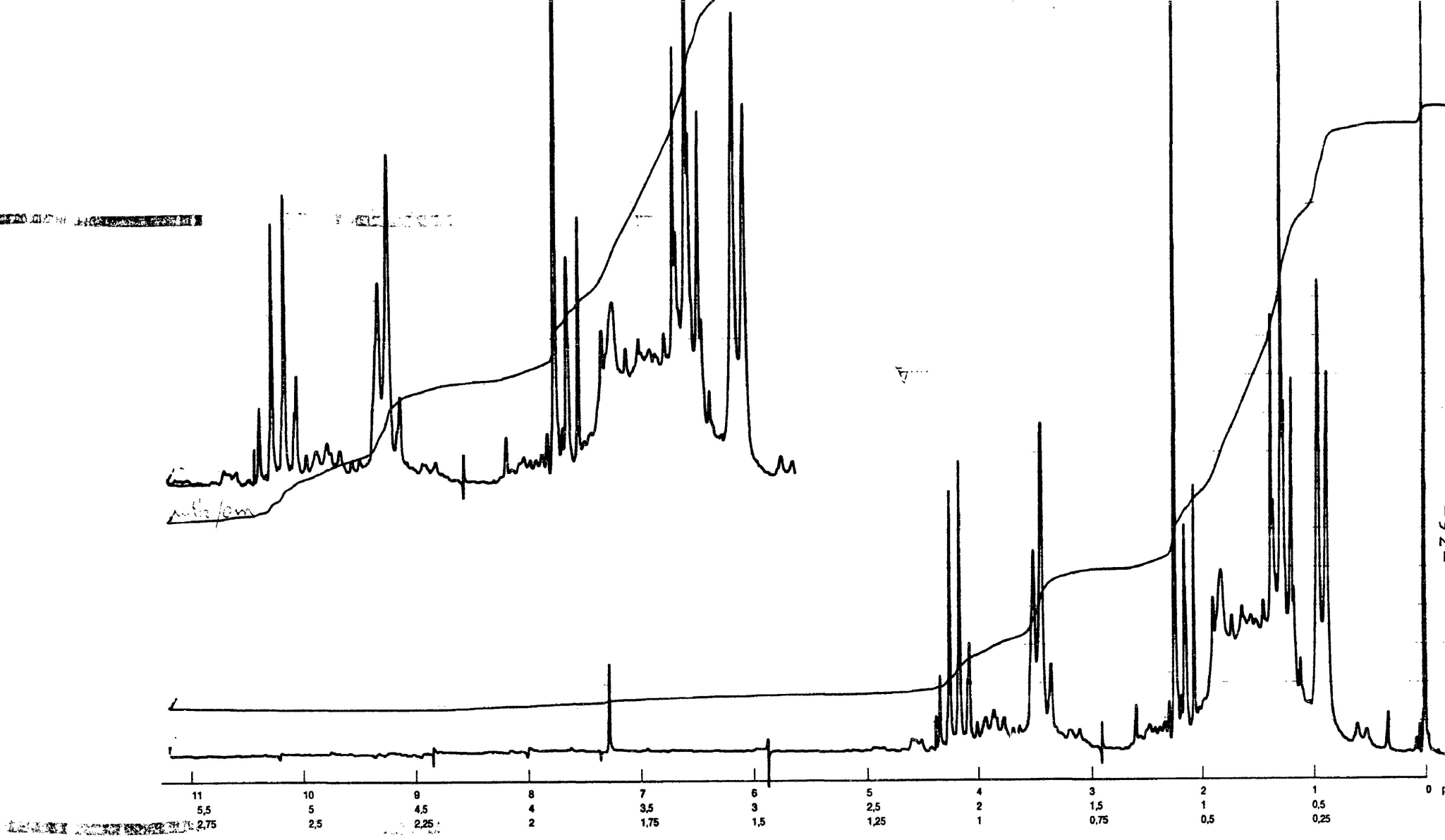
NMR NO. 3. Ethyl 2-n-butyl-4-aminoacetoacetate (as hydrochloride)



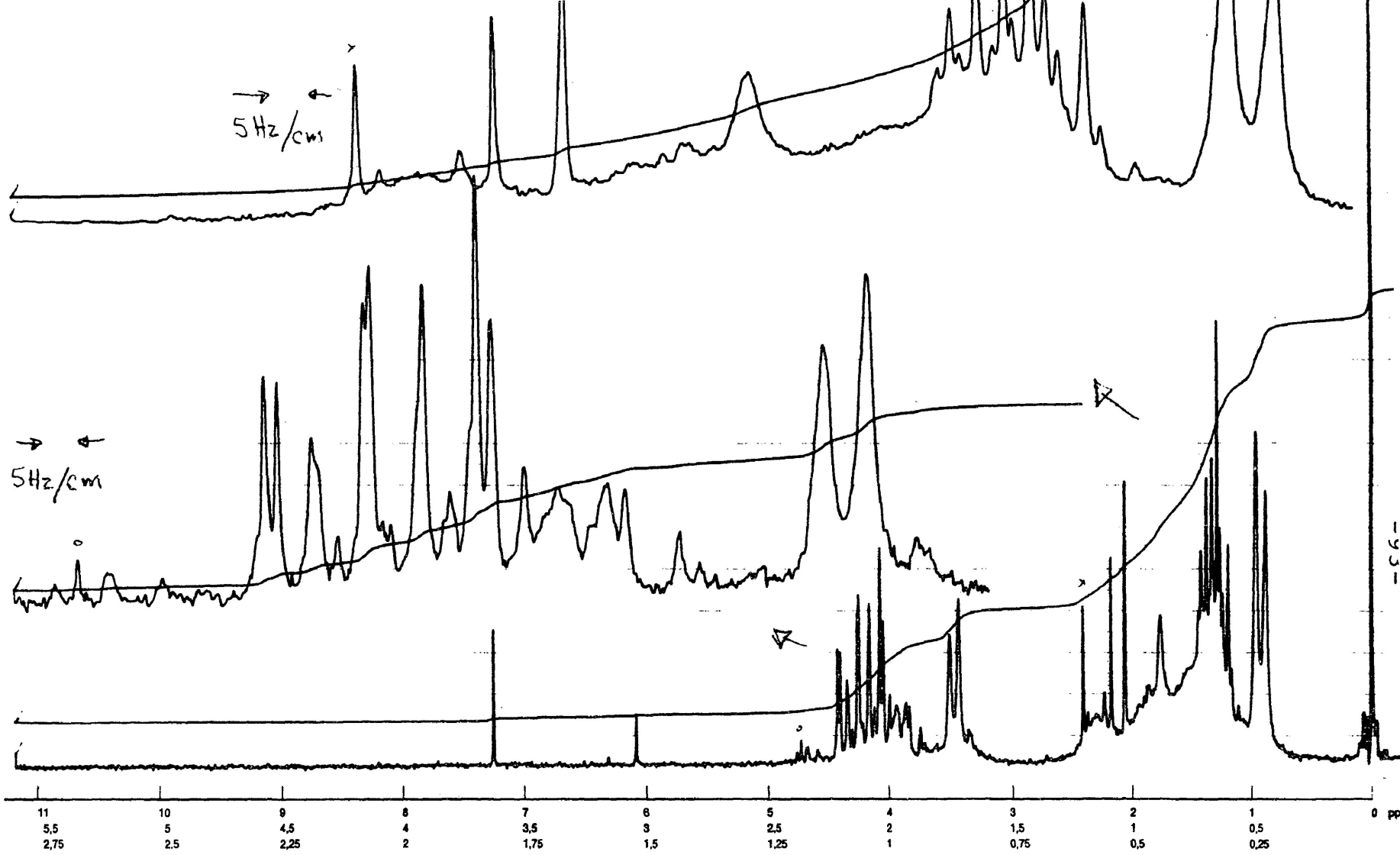
NMR NO. 4. 4-(1'-Carbethoxypentyl)-2-imidazolone



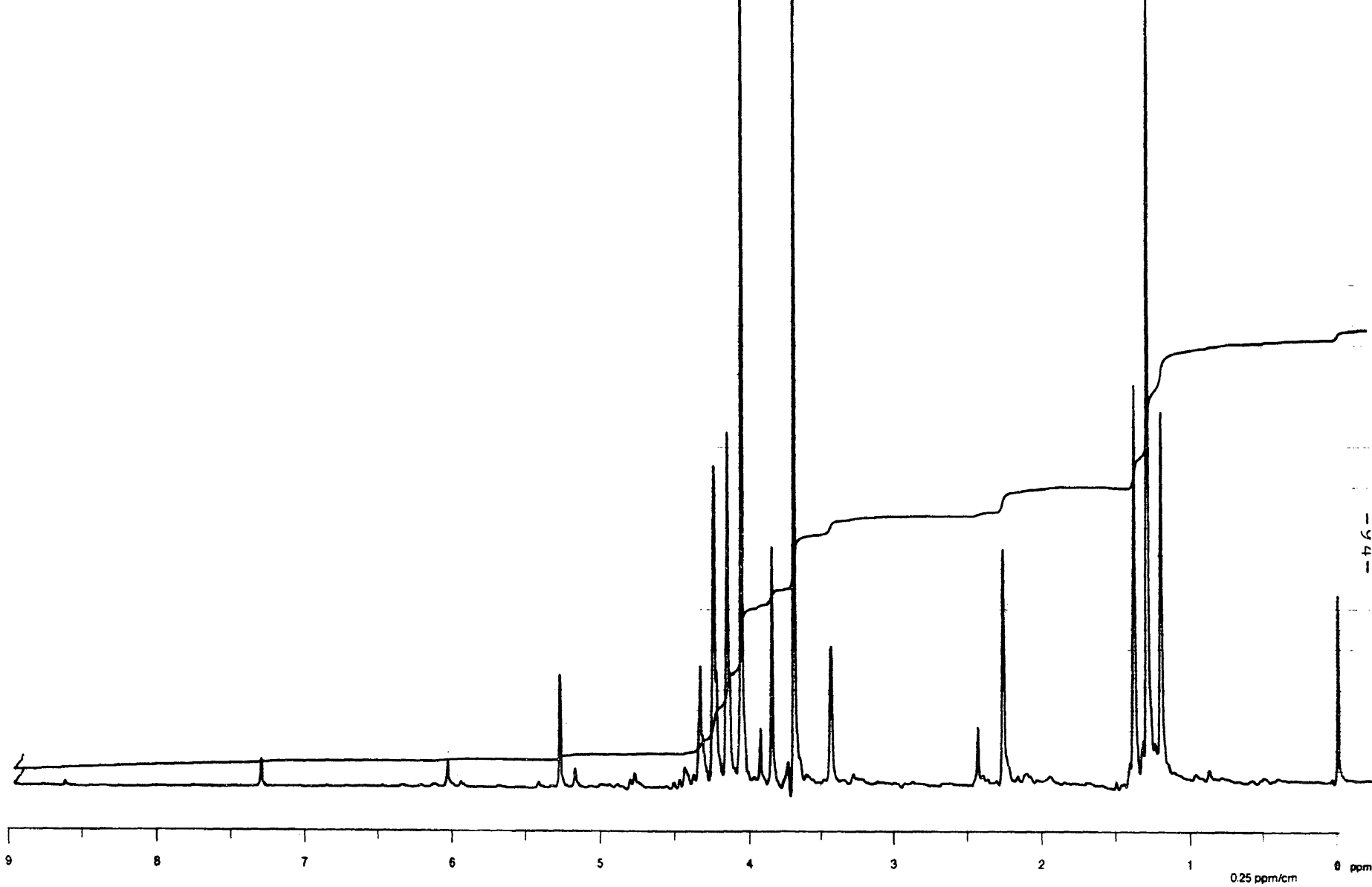
NMR NO. **5.** Ethyl 2-(4'-methyl-5'-(2''-tetrahydropyranyloxyl)pentyl)acetoacetate



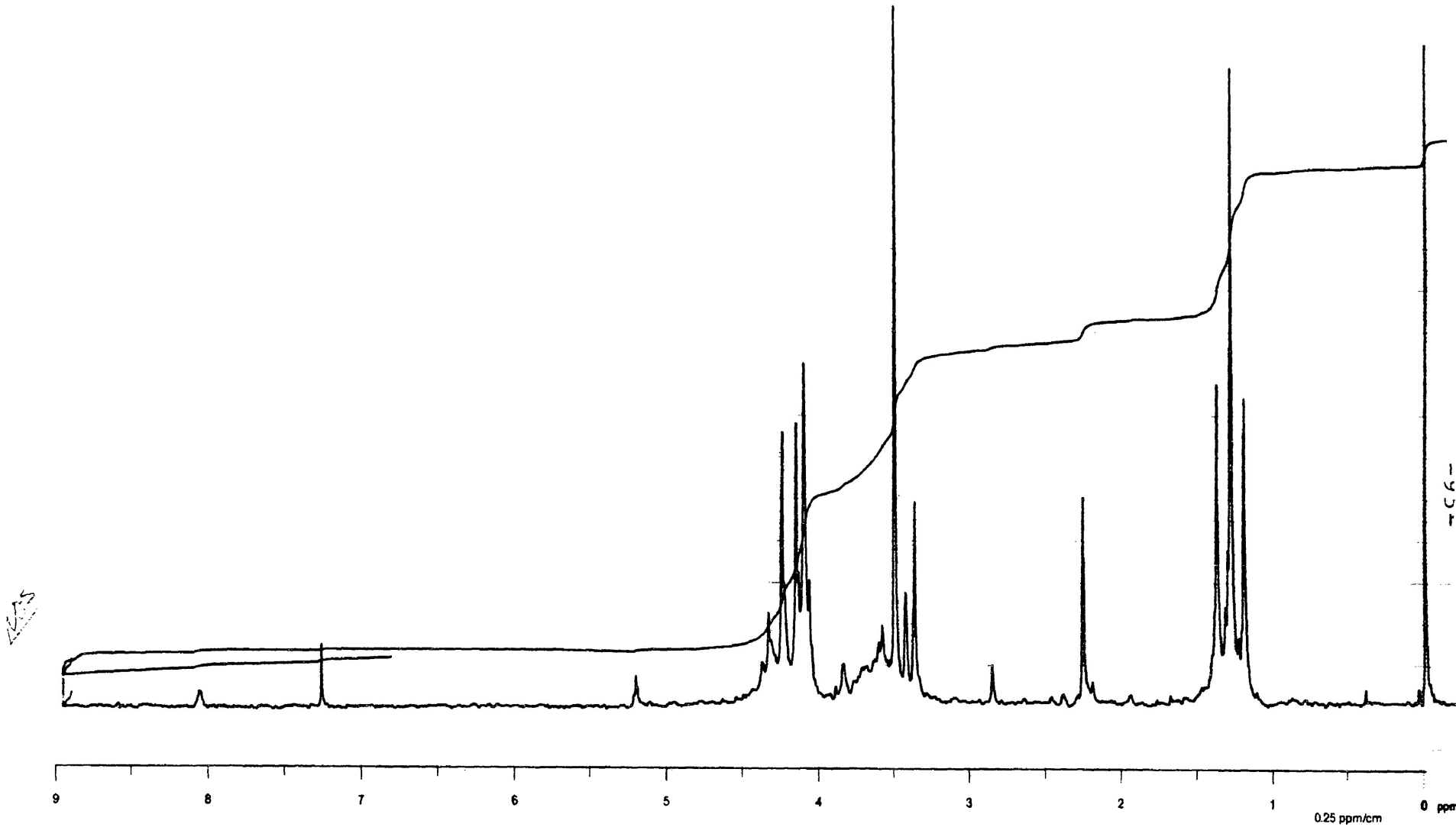
NMR NO. 6. Ethyl 2-(4'-methyl-5'-hydroxypentyl)acetoacetate



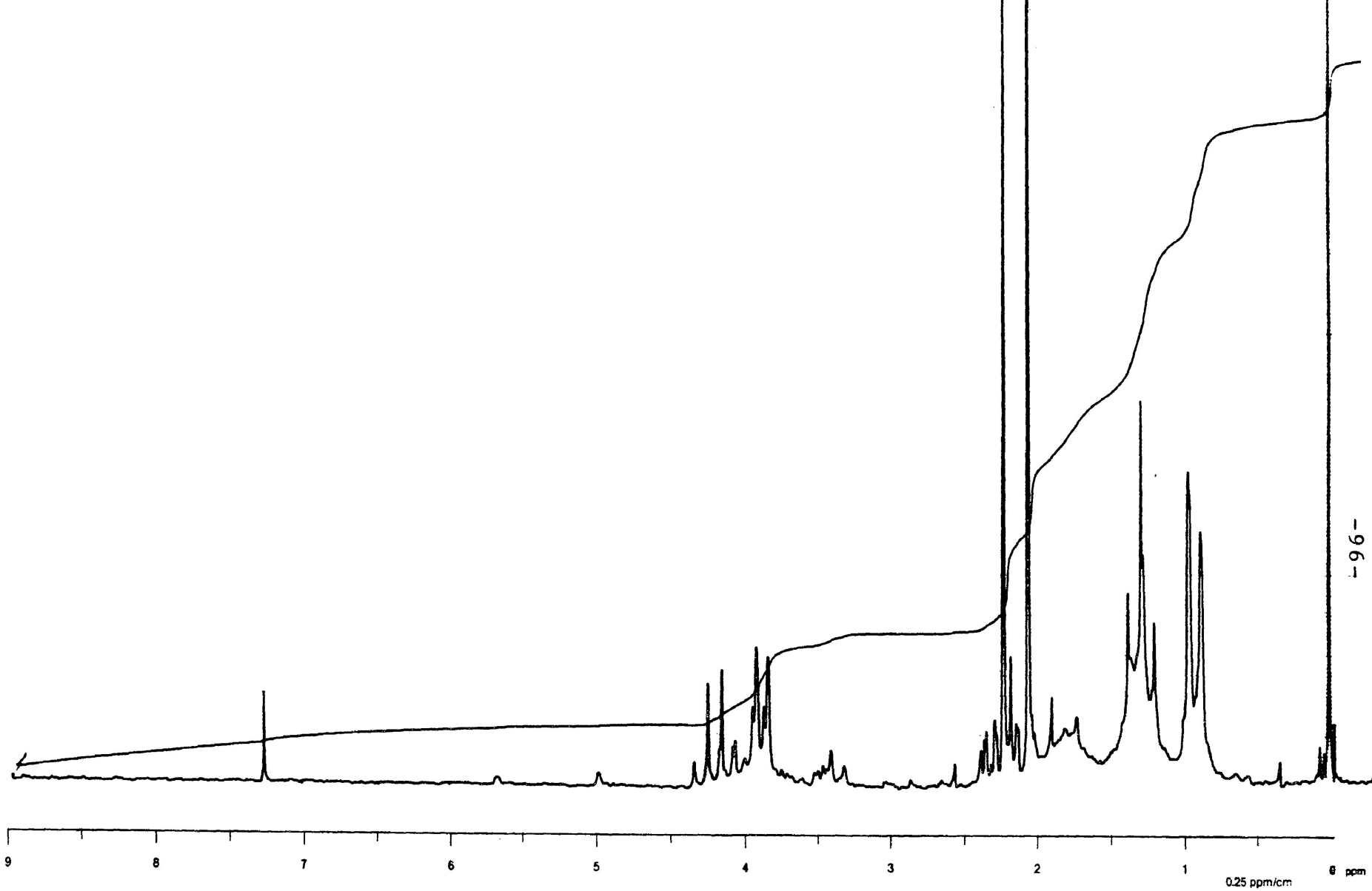
NMR NO. 7. Ethyl 2-(4'-methyl-5'- hydroxypentyl)-4-bromoacetoacetate



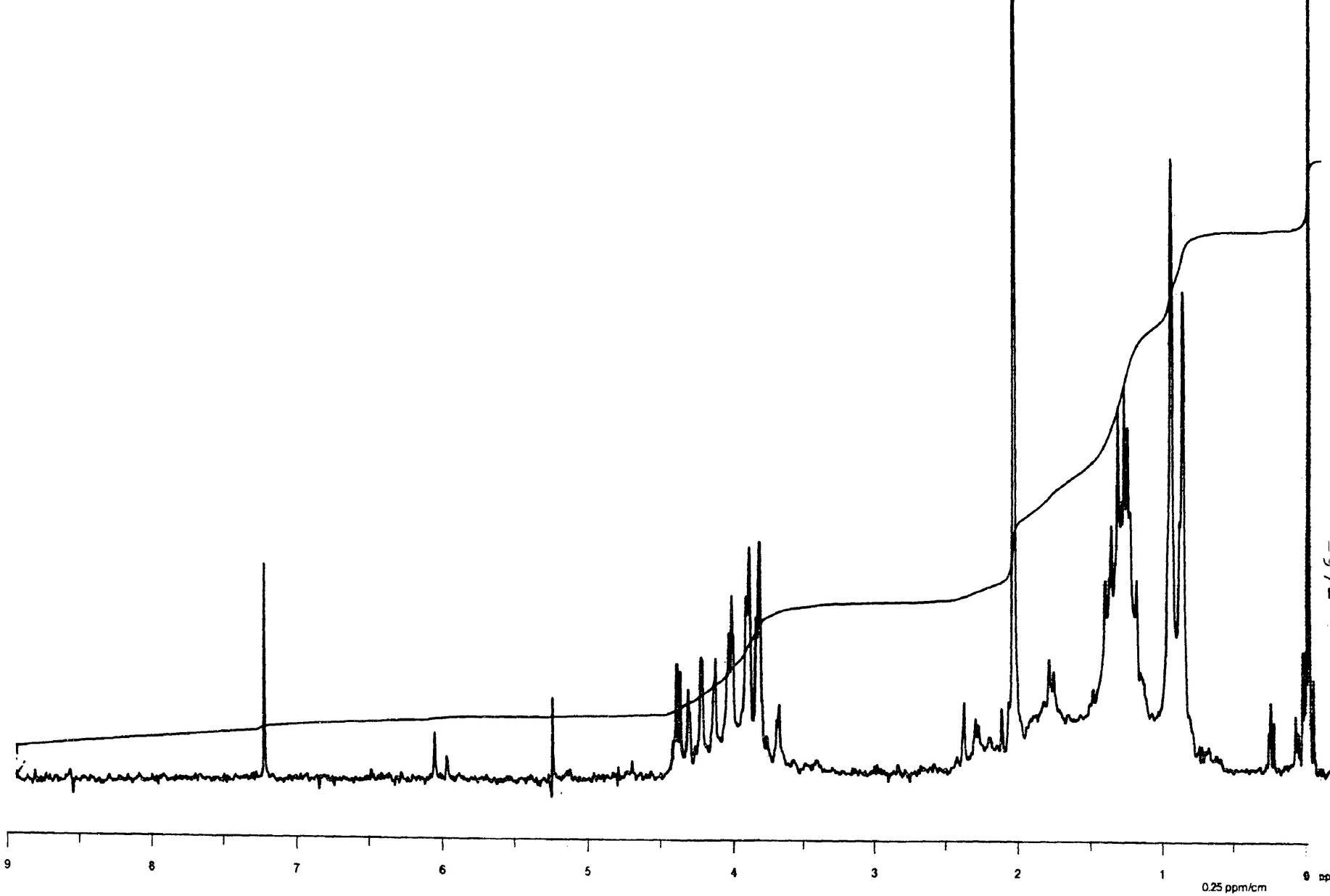
NMR NO. 8. Ethyl 4-bromoacetoacetate



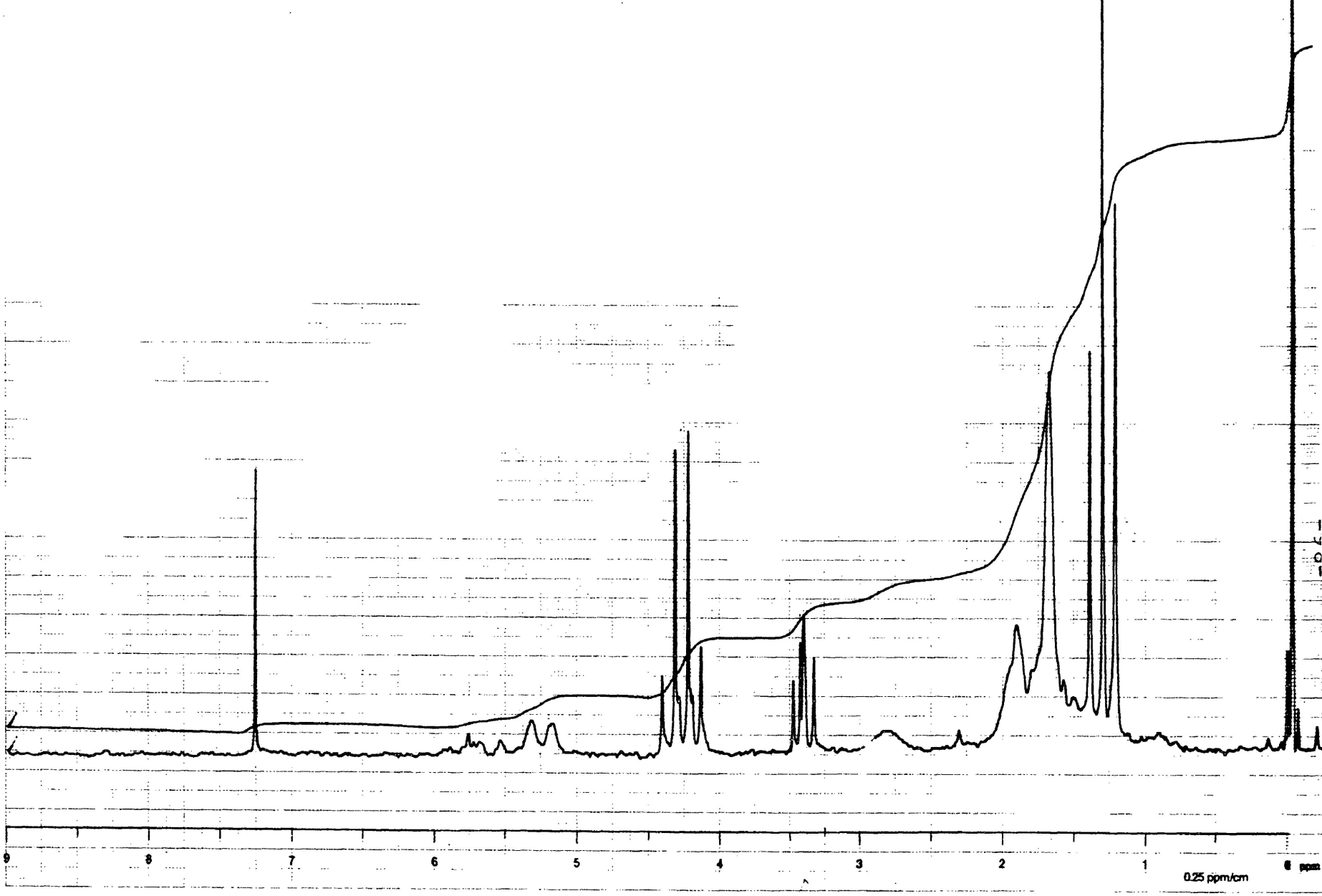
NMR NO. 9. Ethyl 4-azidoacetoacetate



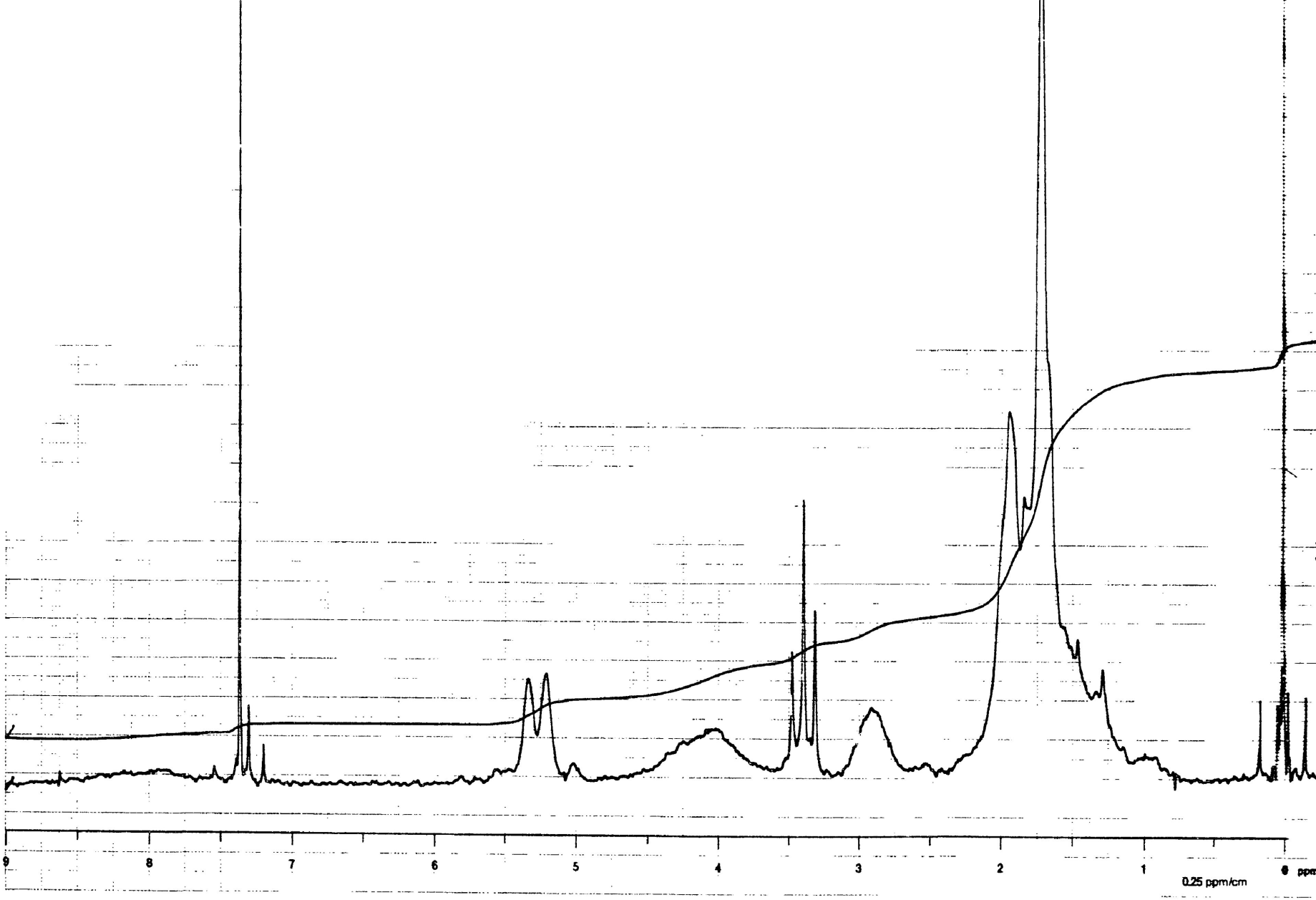
NMR NO. 10. Ethyl 2-(4'-methyl-5'-acetoxypentyl) acetoacetate



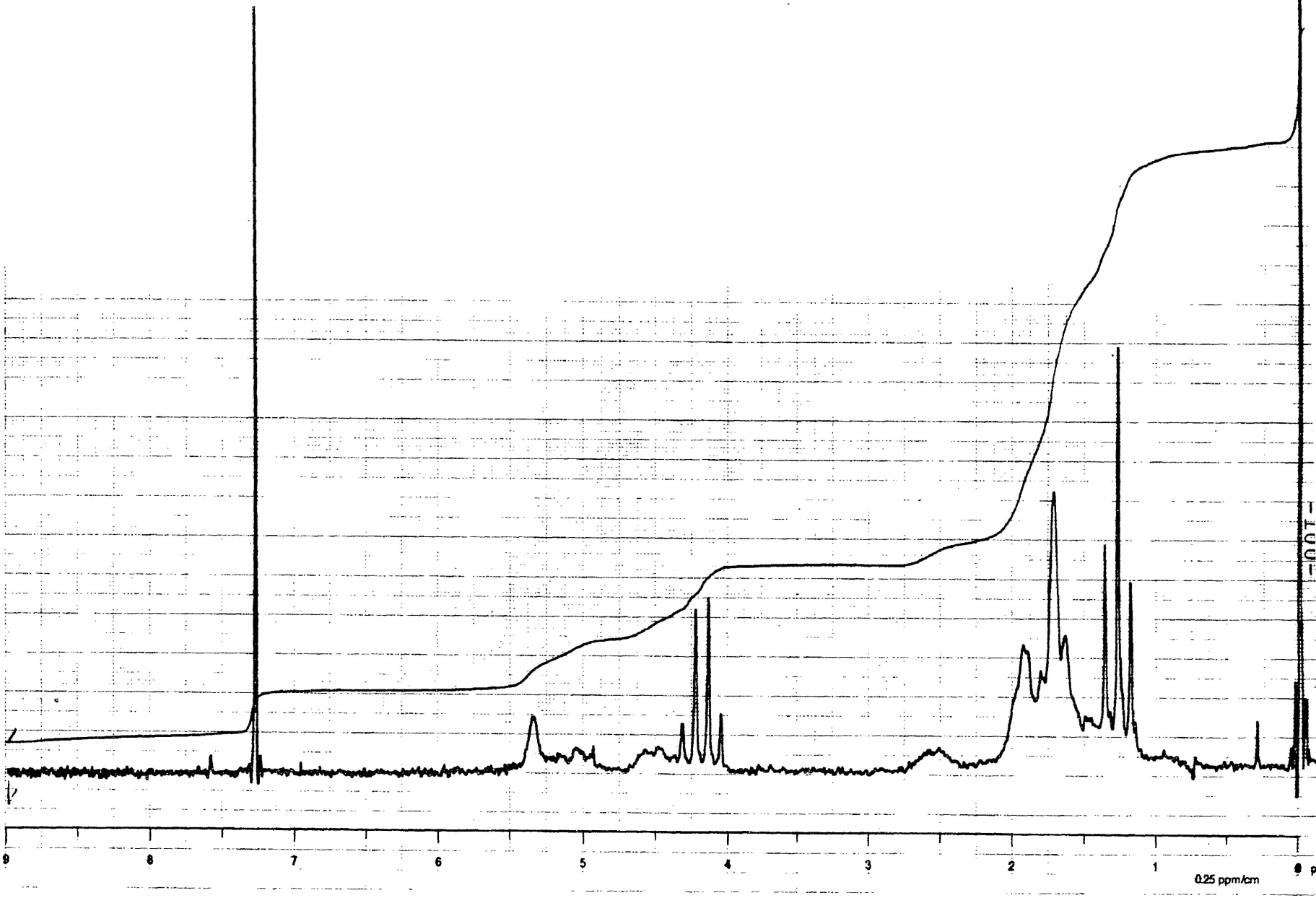
NMR NO. 11. Ethyl 2-(4'-methyl-5'-acetoxypentyl)-4-bromoacetoacetate



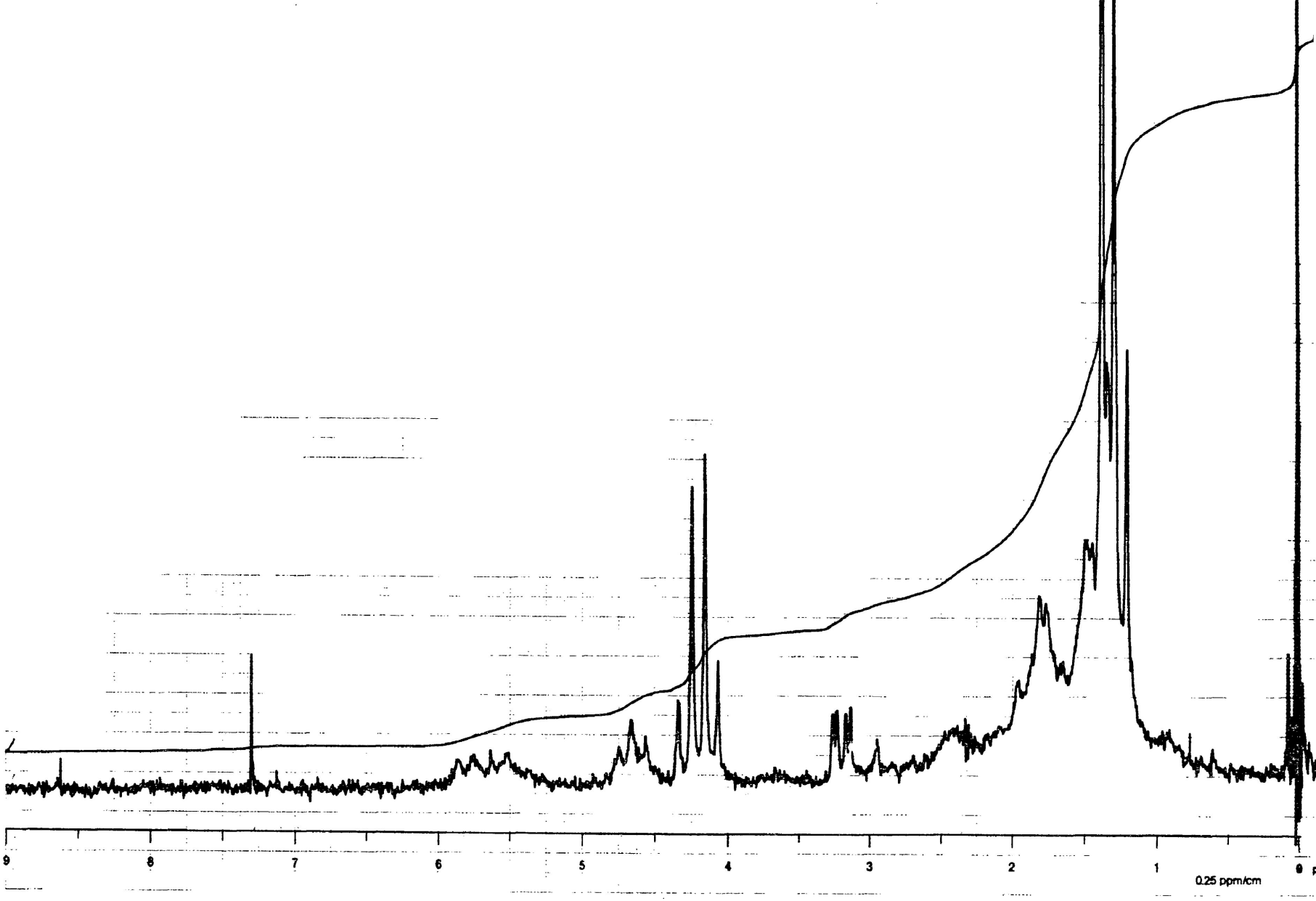
NMR NO. 12. Ethyl 2-(3'-methyl-2'-cyclohexenyl)-2-cyanoacetate



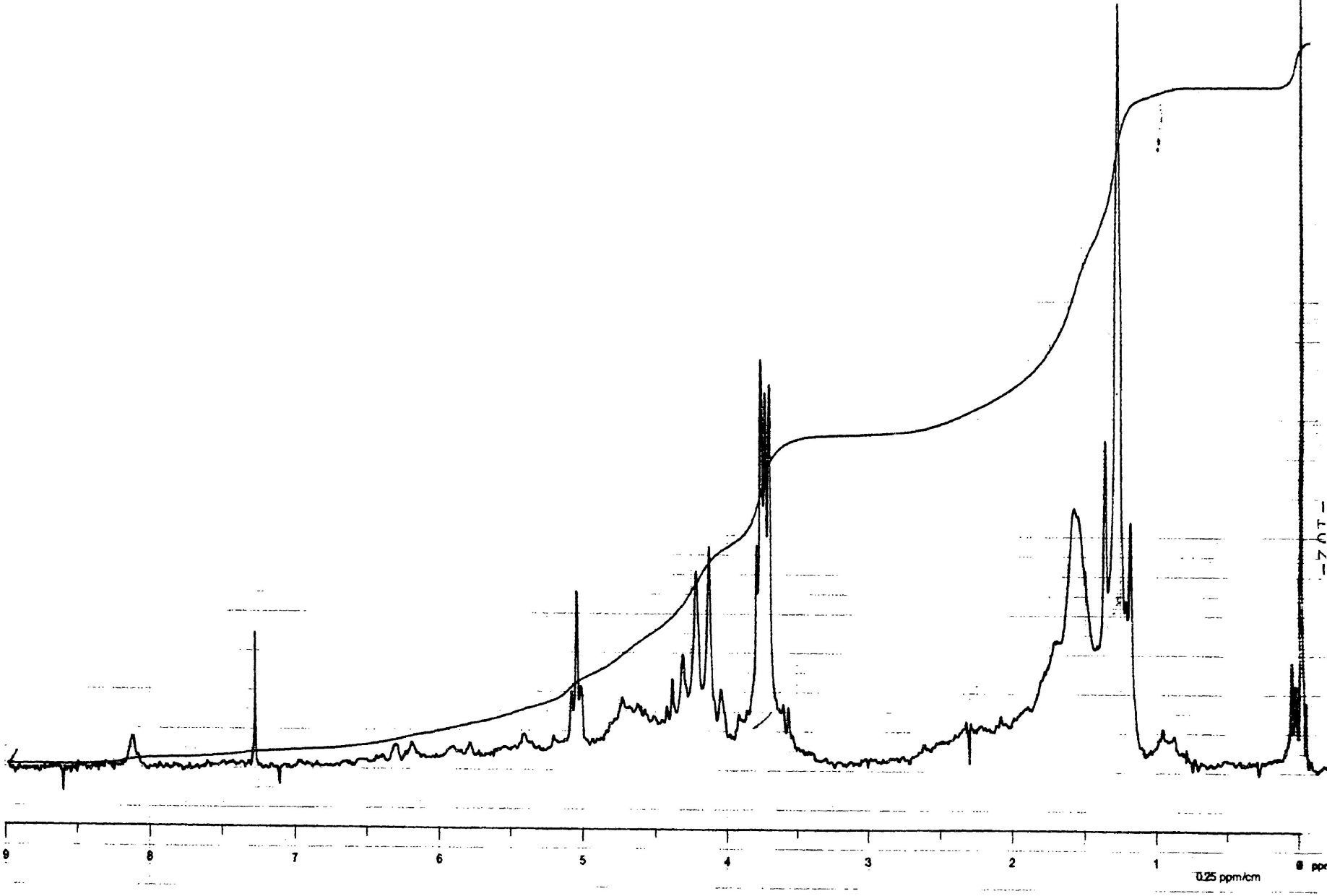
NMR NO. 13. 2-(3'-methyl-2'-cyclohexenyl)-2-cyanoacethydrazide



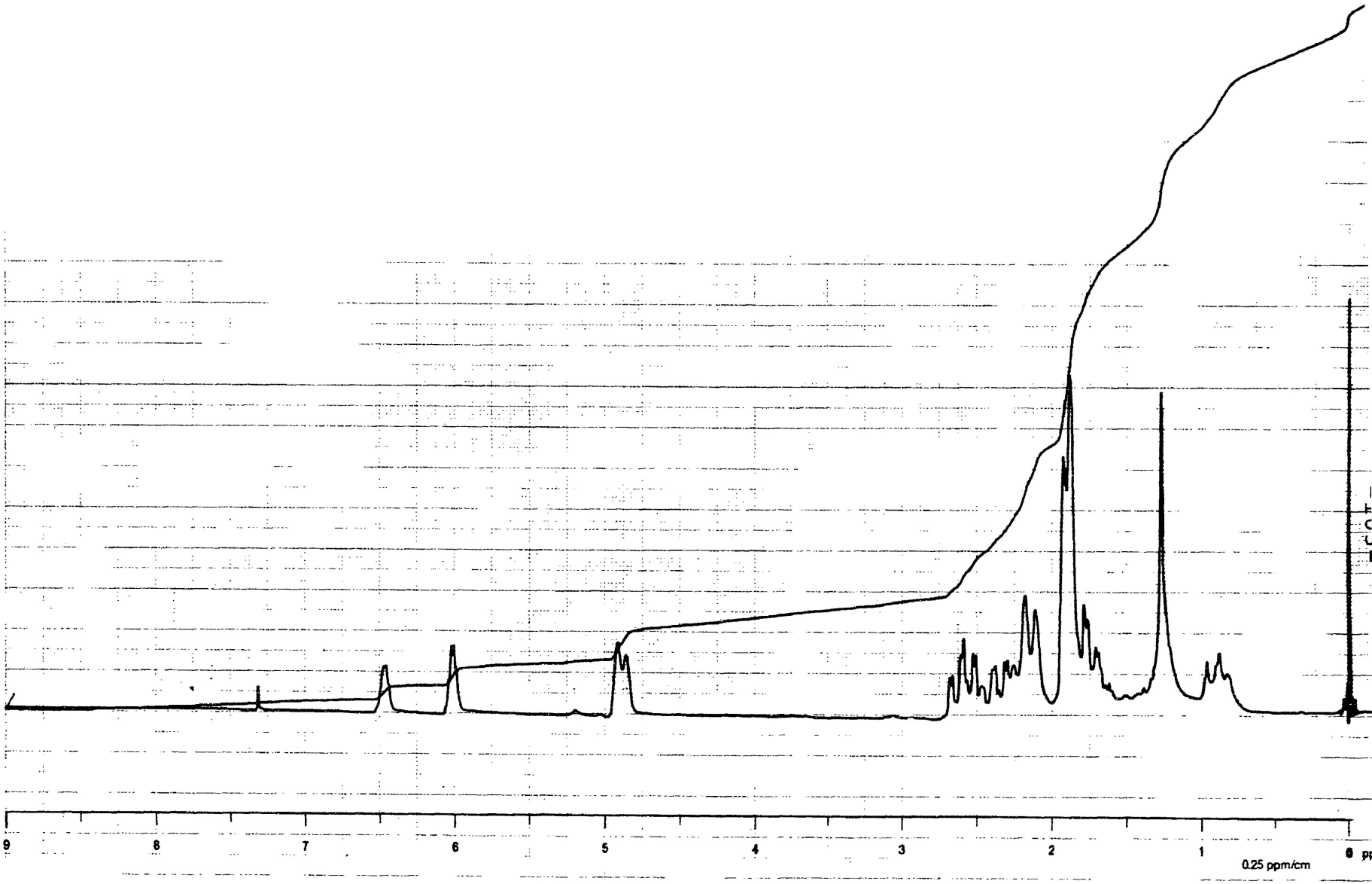
NMR NO. 14. 2-(N'-carbethoxy)-2-(3'-methyl-2'-cyclohexenyl)acetonitrile



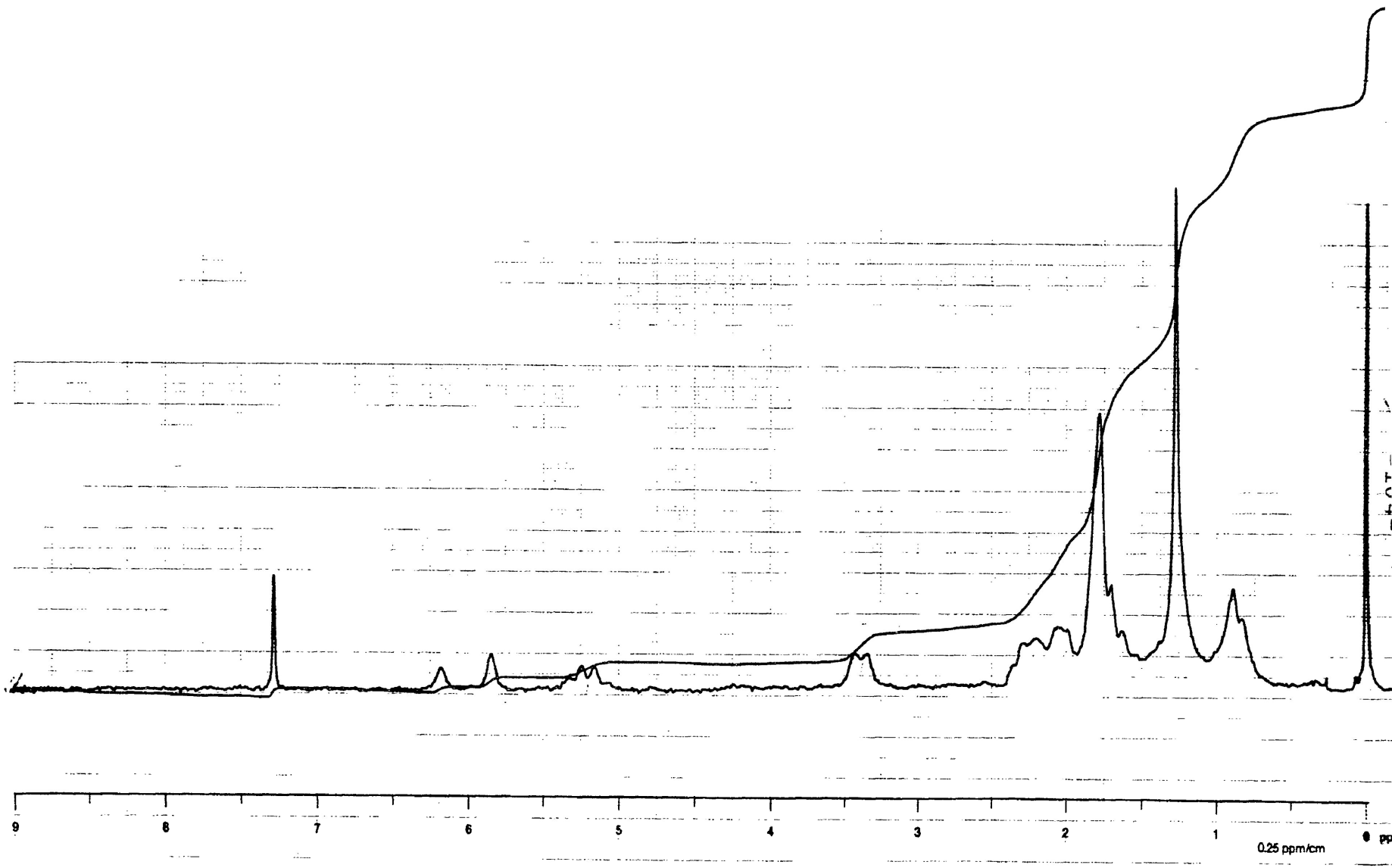
NMR NO. 15. 2-(N'-carbethoxy)-2-(2',3'-oxirino-3'-methylcyclohexyl)acetonitrile



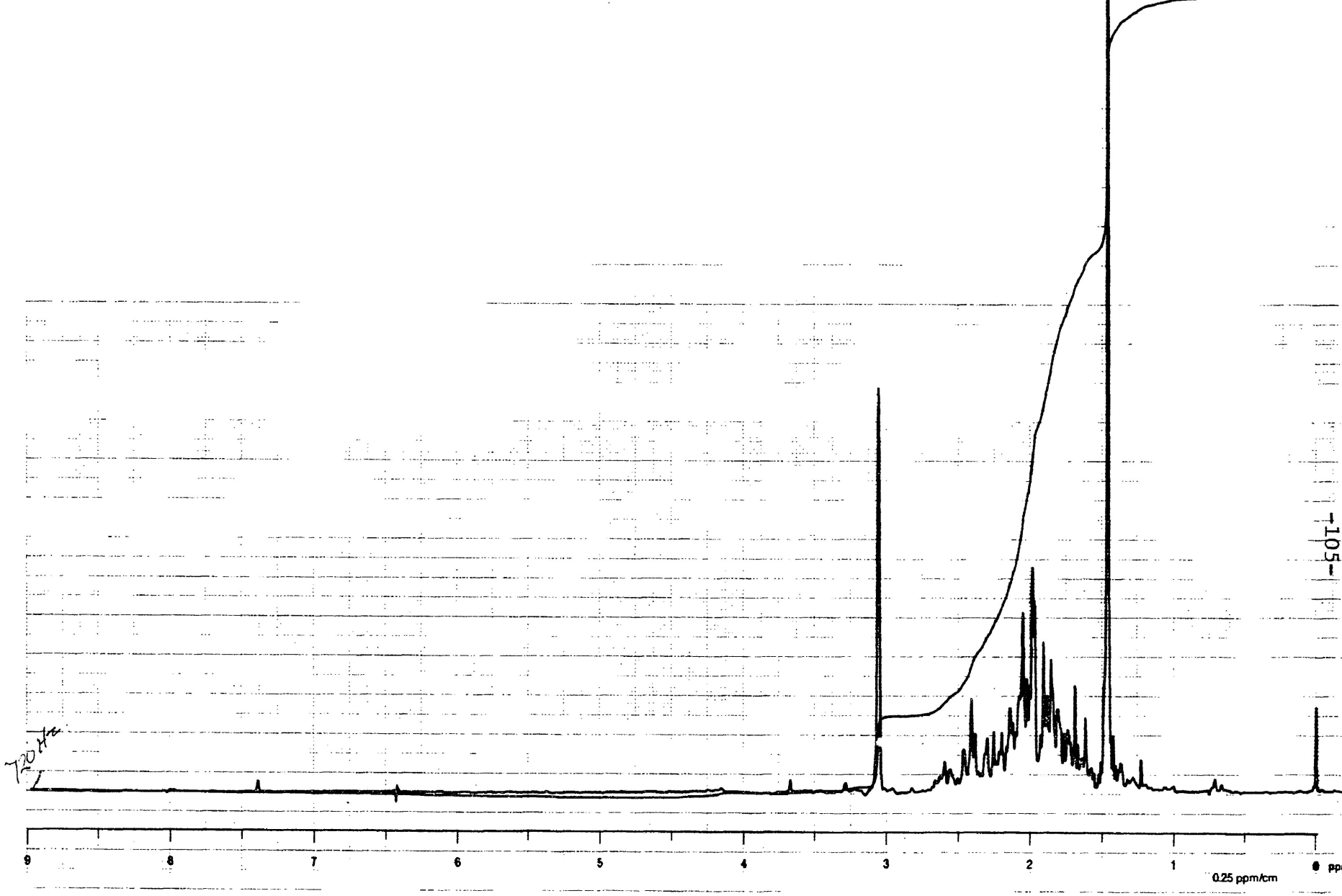
NMR NO. 16. 2-(N'- carbethoxy)-2-(2',3'-dihydroxy-3'-methylcyclohexyl)acetonitrile



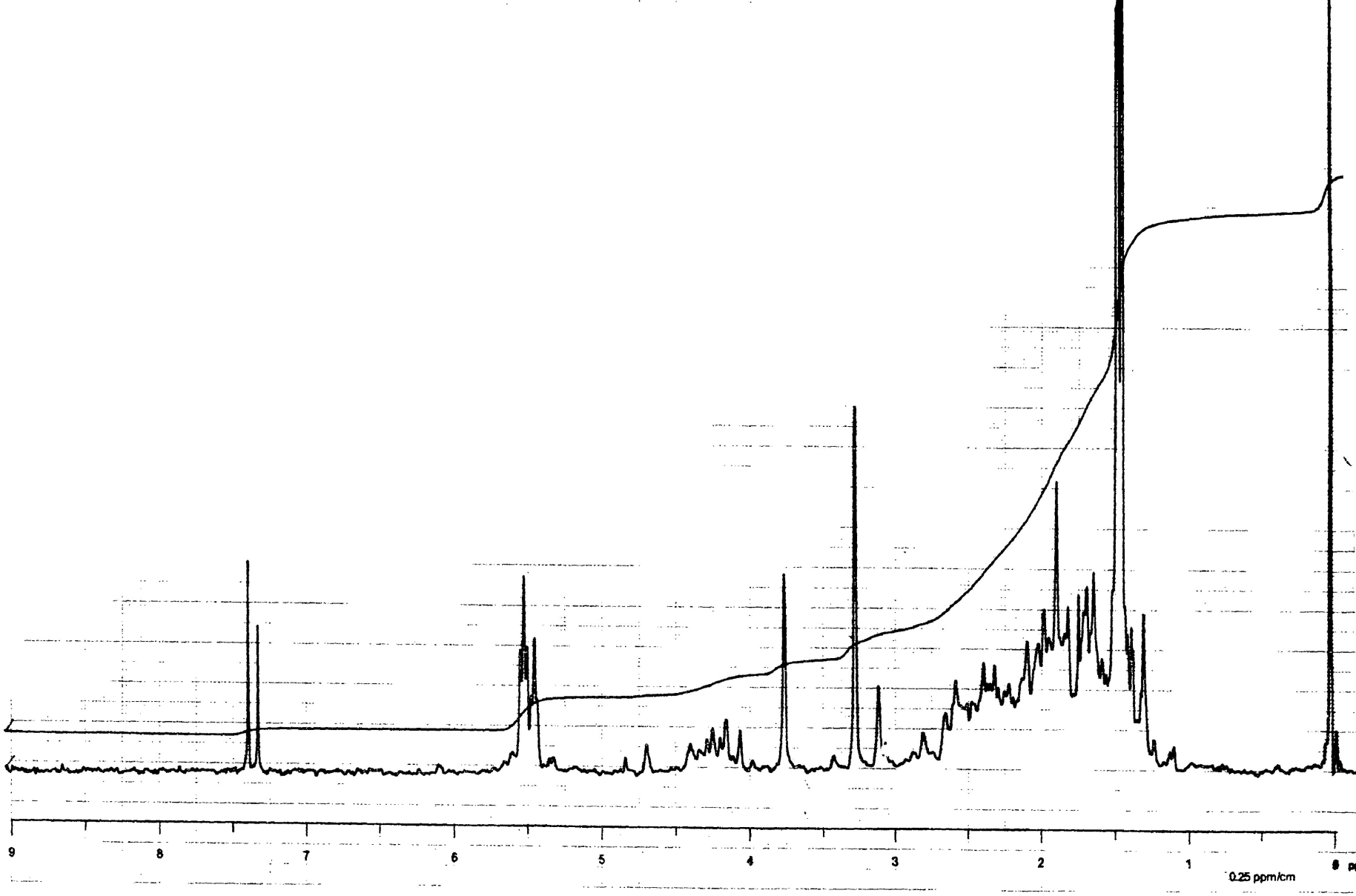
NMR NO. 17. 1-Cyanomethylene-3-methyl-2-cyclohexene



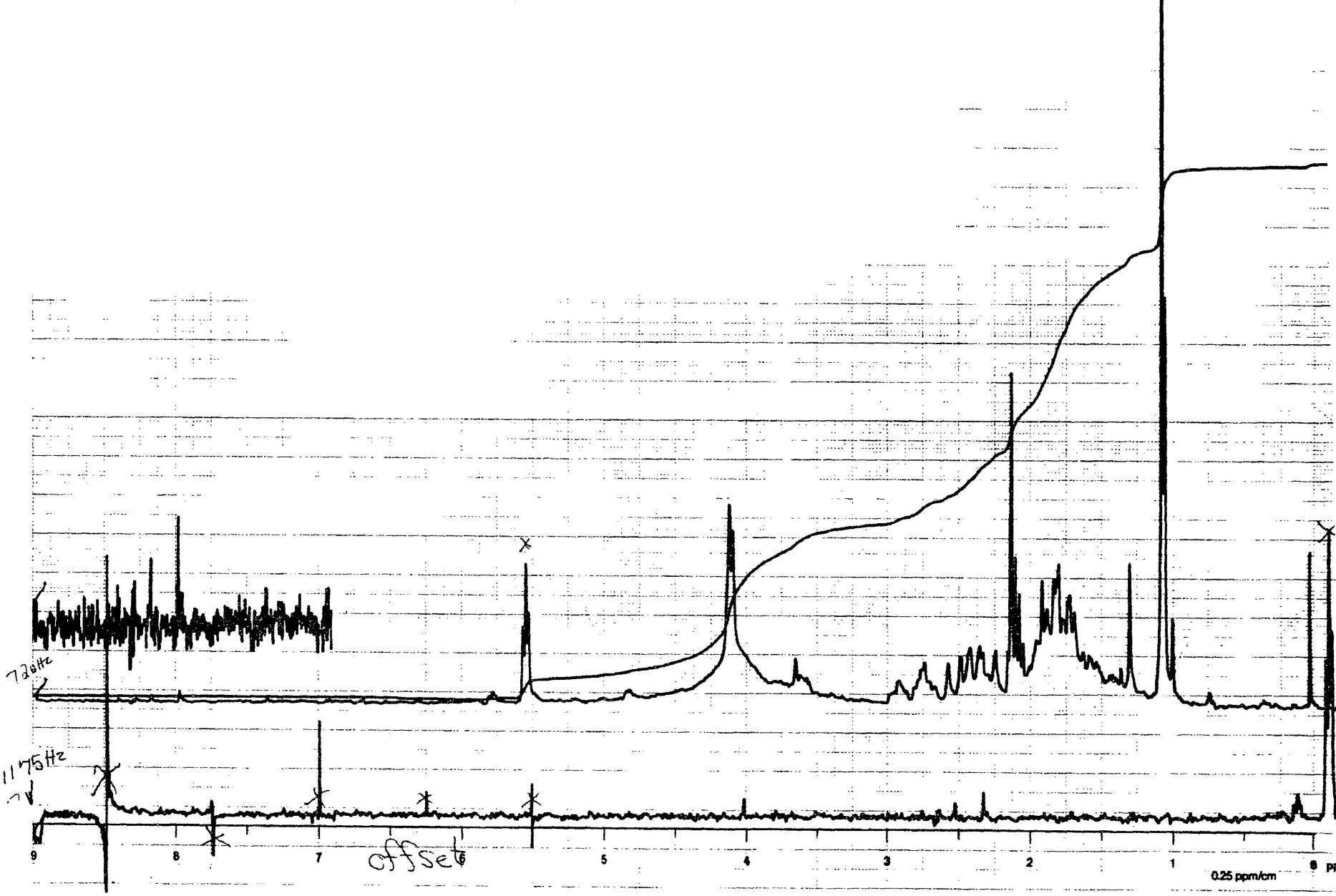
NMR NO. 18. 1-Methyl-3-(2'-aminoethylidene)cyclohexene



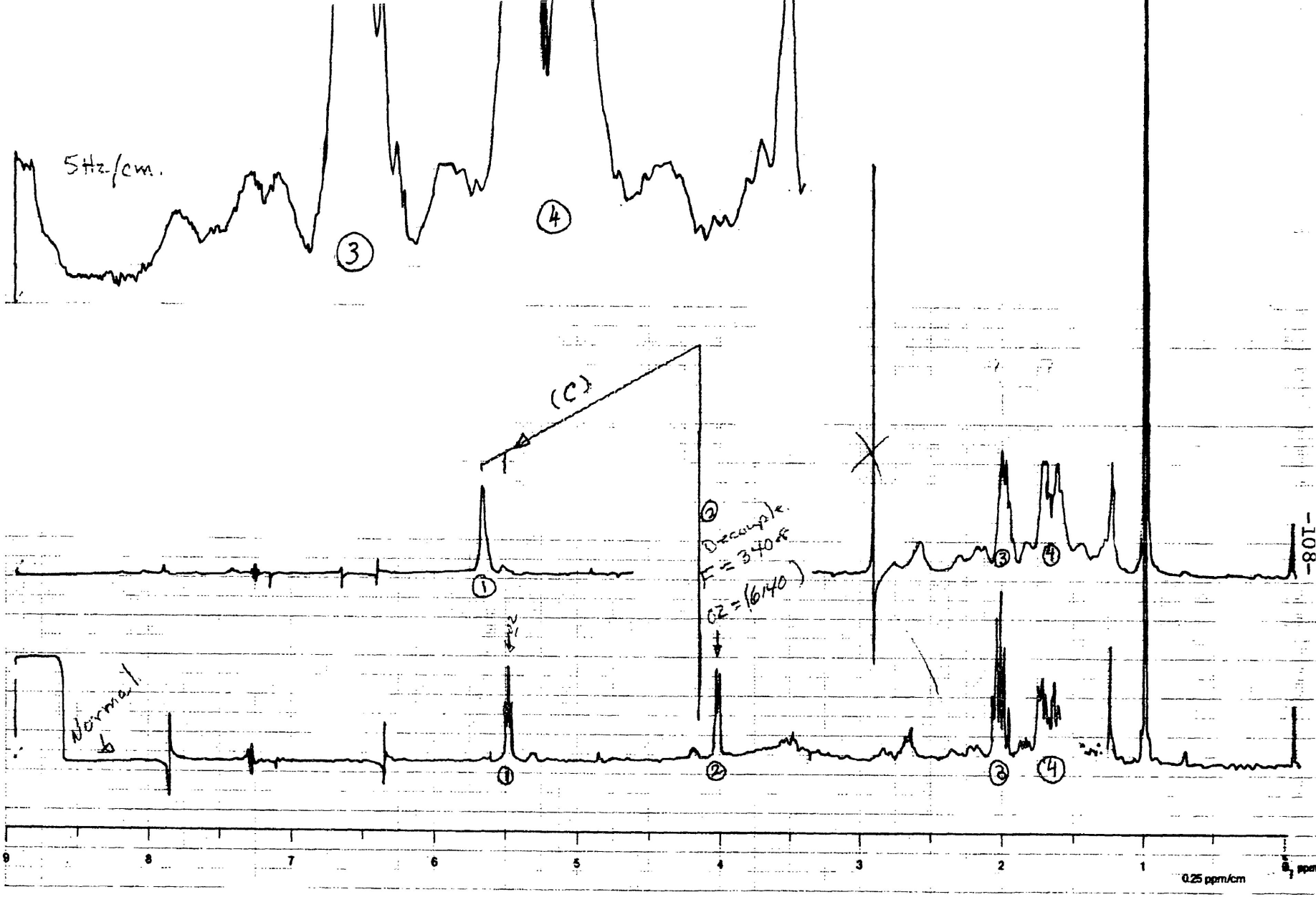
NMR NO. 19. 2,3-Oxirino-3-methylcyclohexan-1-one



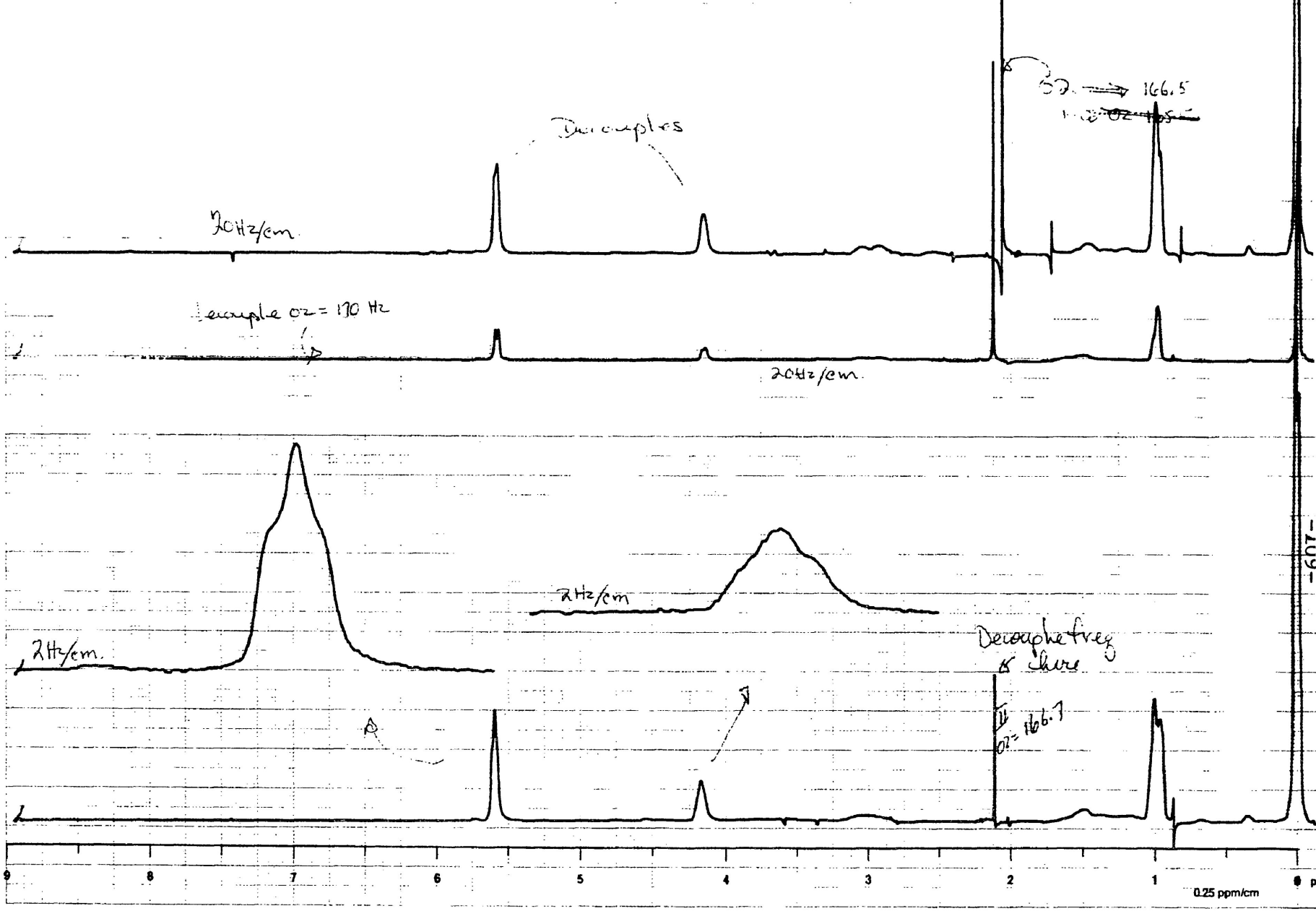
NMR NO. 20. 1-Cyanomethylene-2,3-oxirino-3-methylcyclohexane



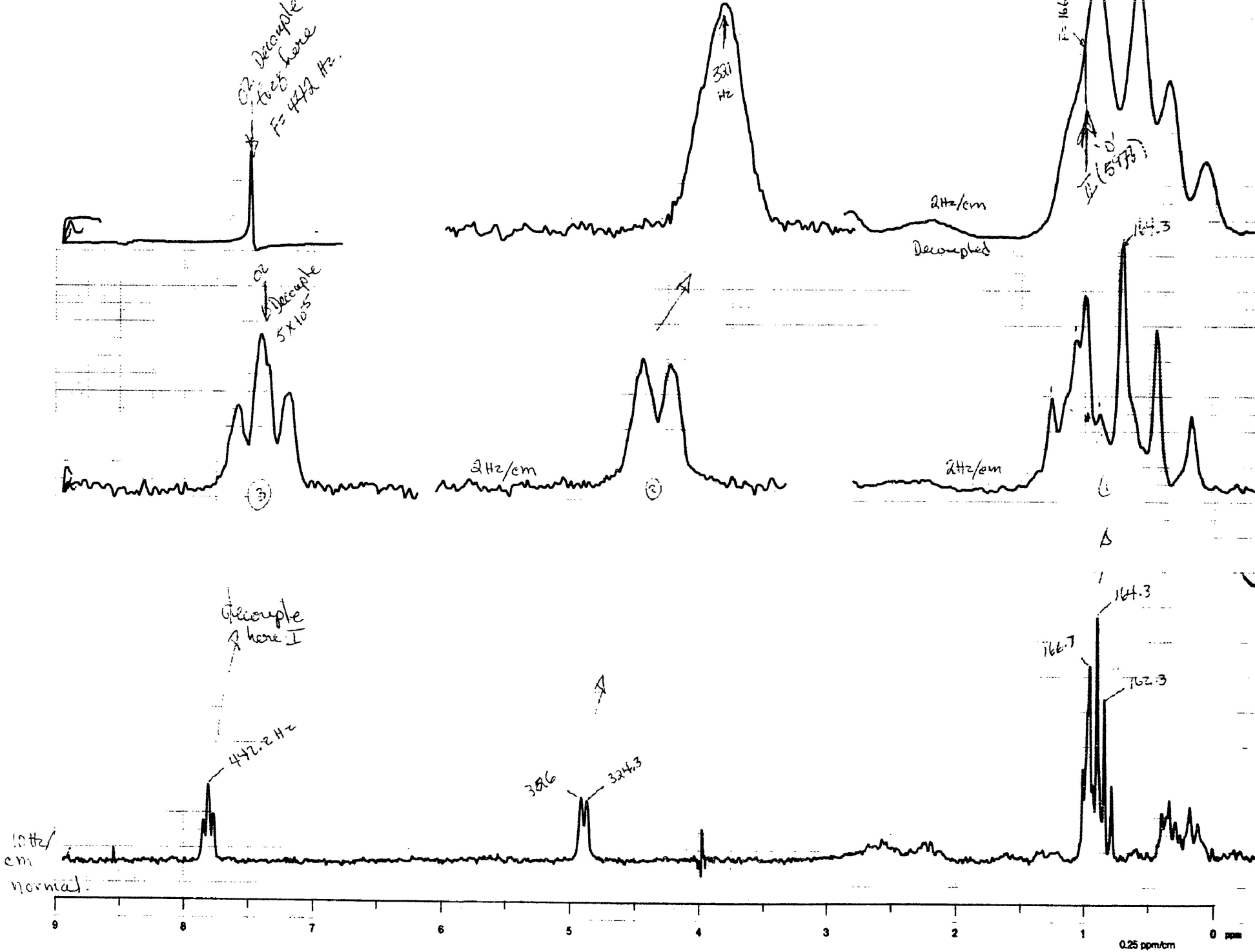
NMR NO. 21. 1-Cyanomethylene-2,3-dihydroxy-3-methylcyclohexane



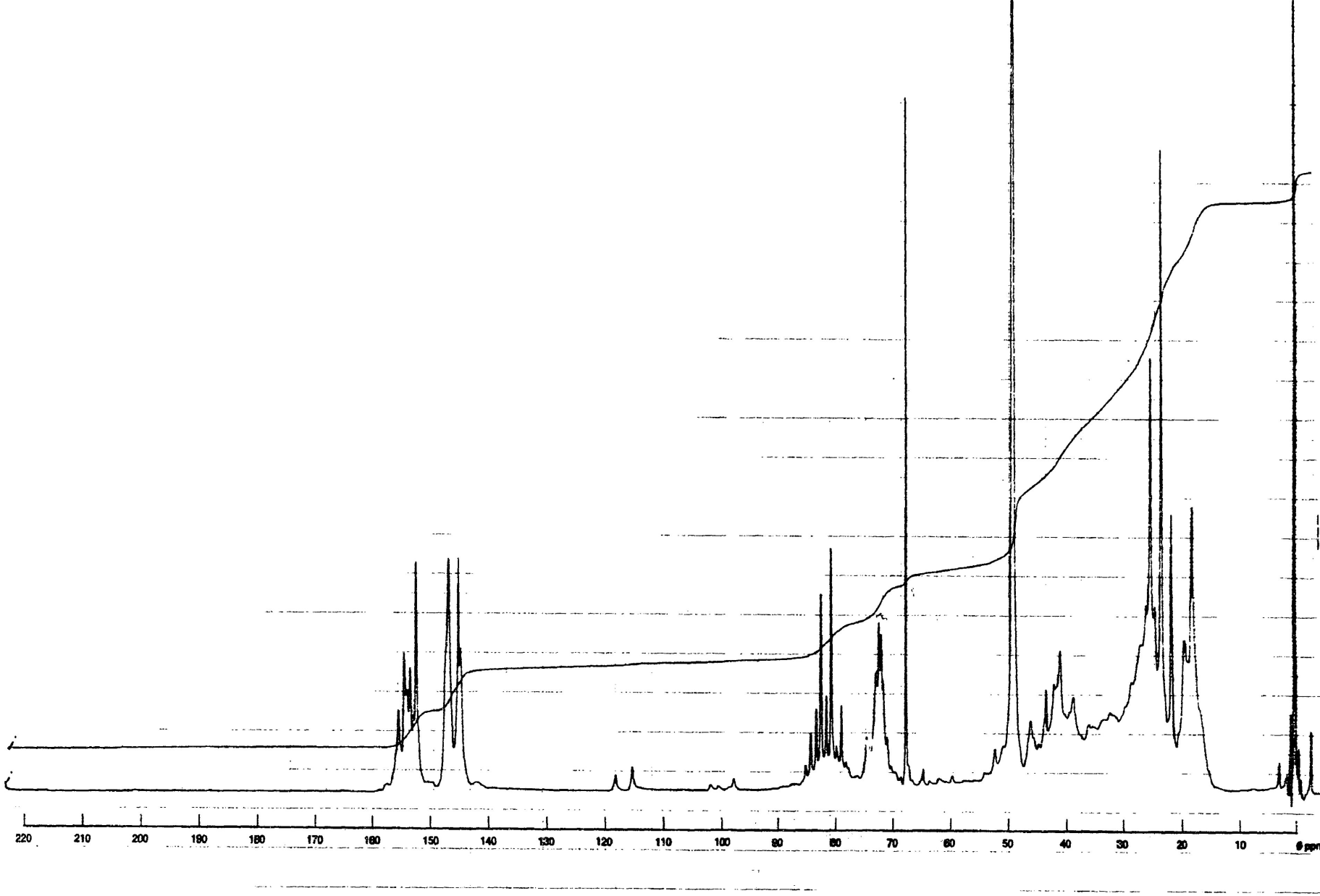
NMR NO. 21a


Decouples
20Hz/cm
Decouple σ_2 = 130 Hz
20Hz/cm
2Hz/cm
2Hz/cm
2Hz/cm
Decouple freq
& Shift
σ_2 = 166.7
166.5
9
8
7
6
5
4
3
2
1
0.25 ppm/cm

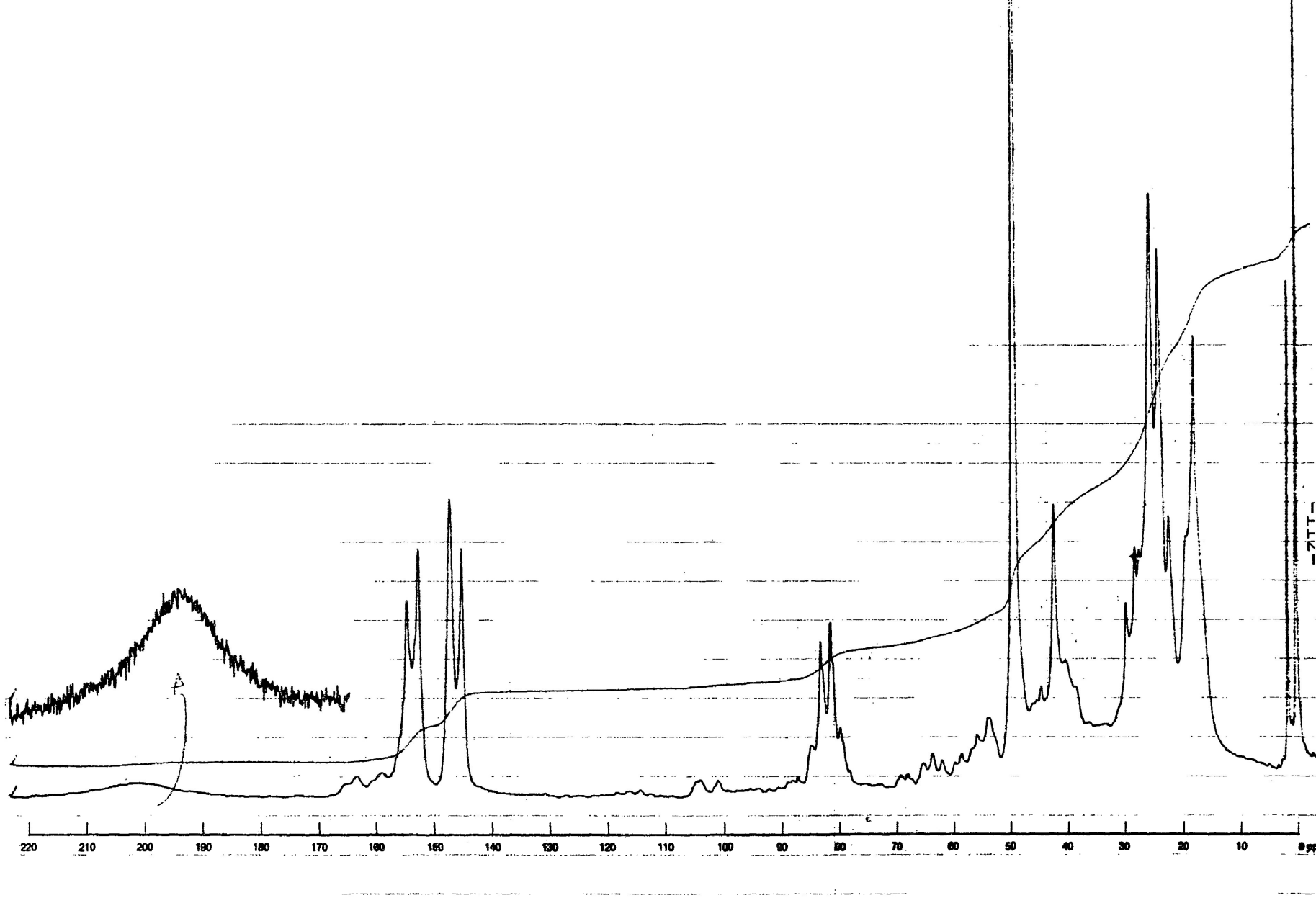
NMR NO. 21b


O2 Decouple here F= 447 Hz.
331 Hz
2Hz/cm
Decoupled
O2 Decouple 5X10^5
2Hz/cm
2Hz/cm
Decouple here I
447.2 Hz
386
324.3
164.3
166.7
162.3
10 Hz/cm normal
9
8
7
6
5
4
3
2
1
0 ppm
0.25 ppm/cm

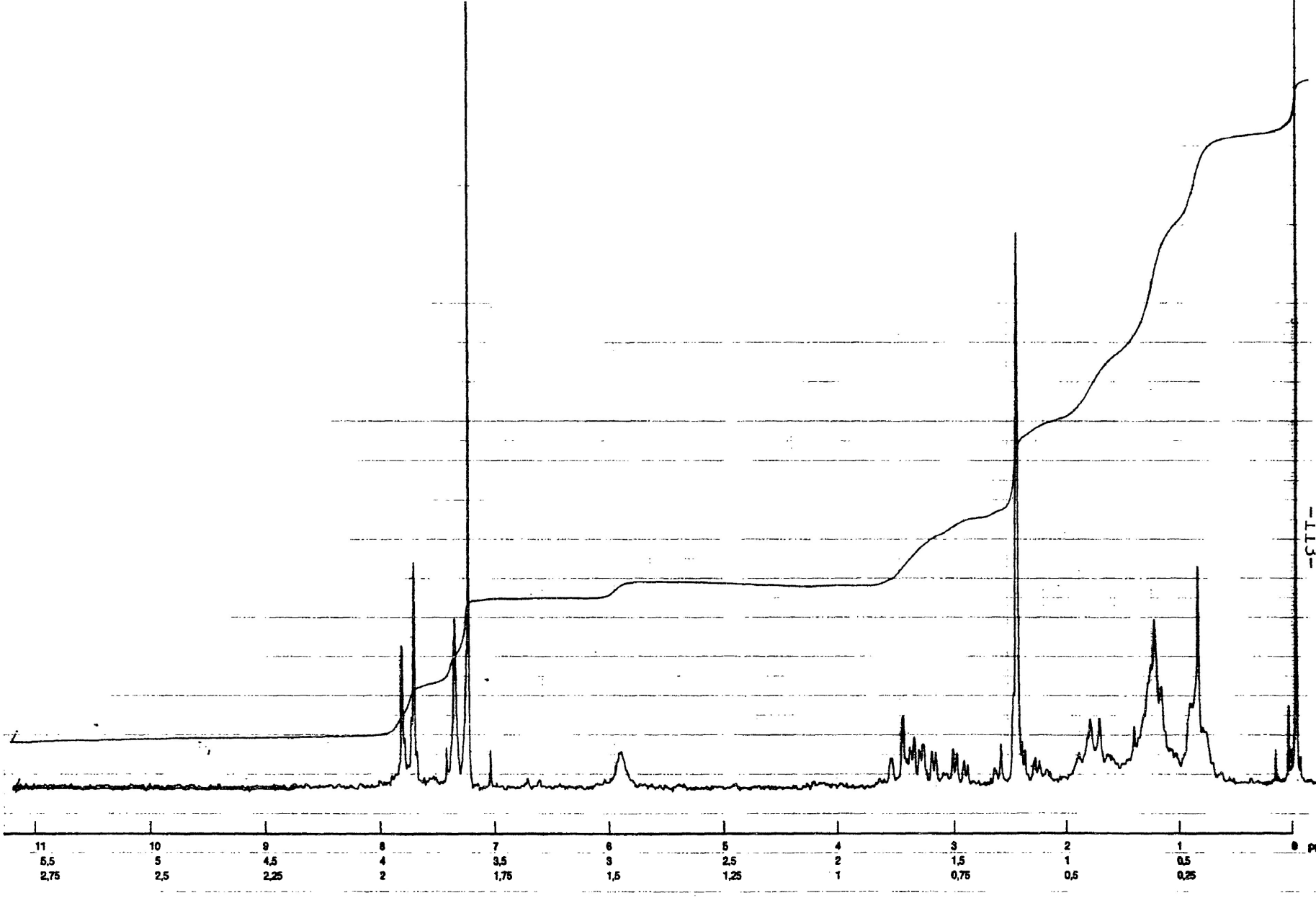
NMR NC. 21c



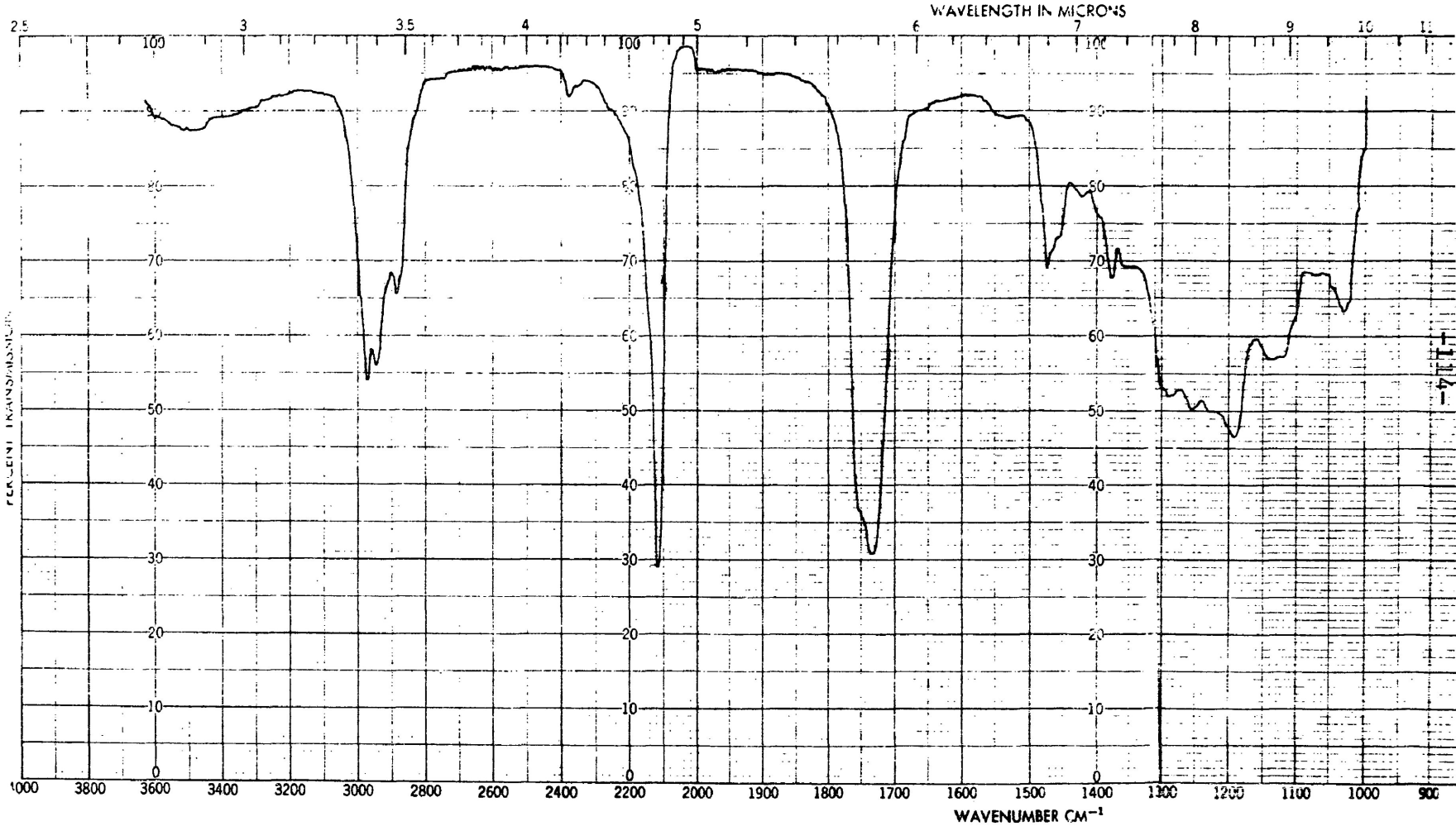
NMR NO. 22. Ethyl 2-n-butyl-5-hydroxy-2-tosylpentanoate



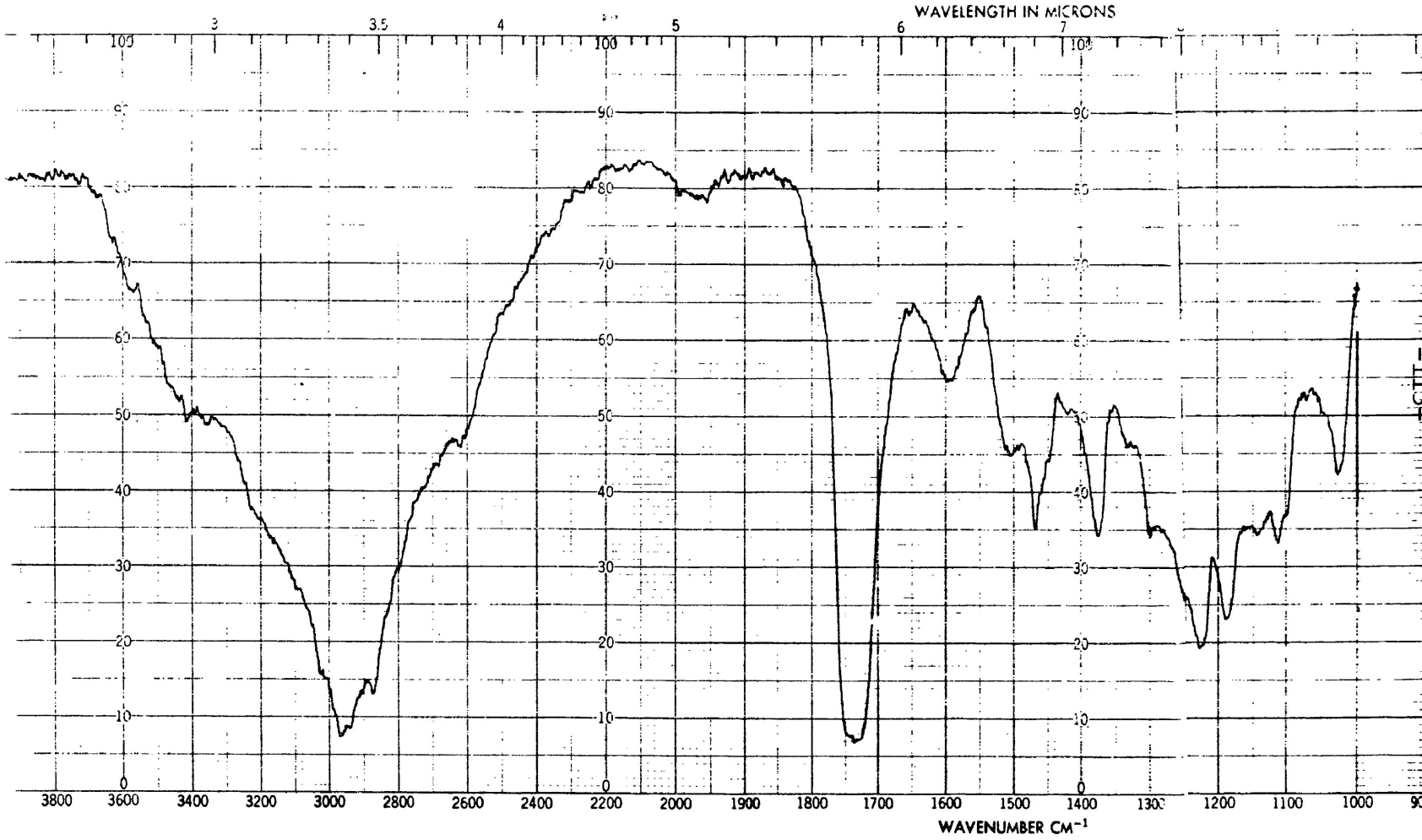
NMR NO. 23. Monoethyl ester of 2-butyl-2-tosylglutaric acid



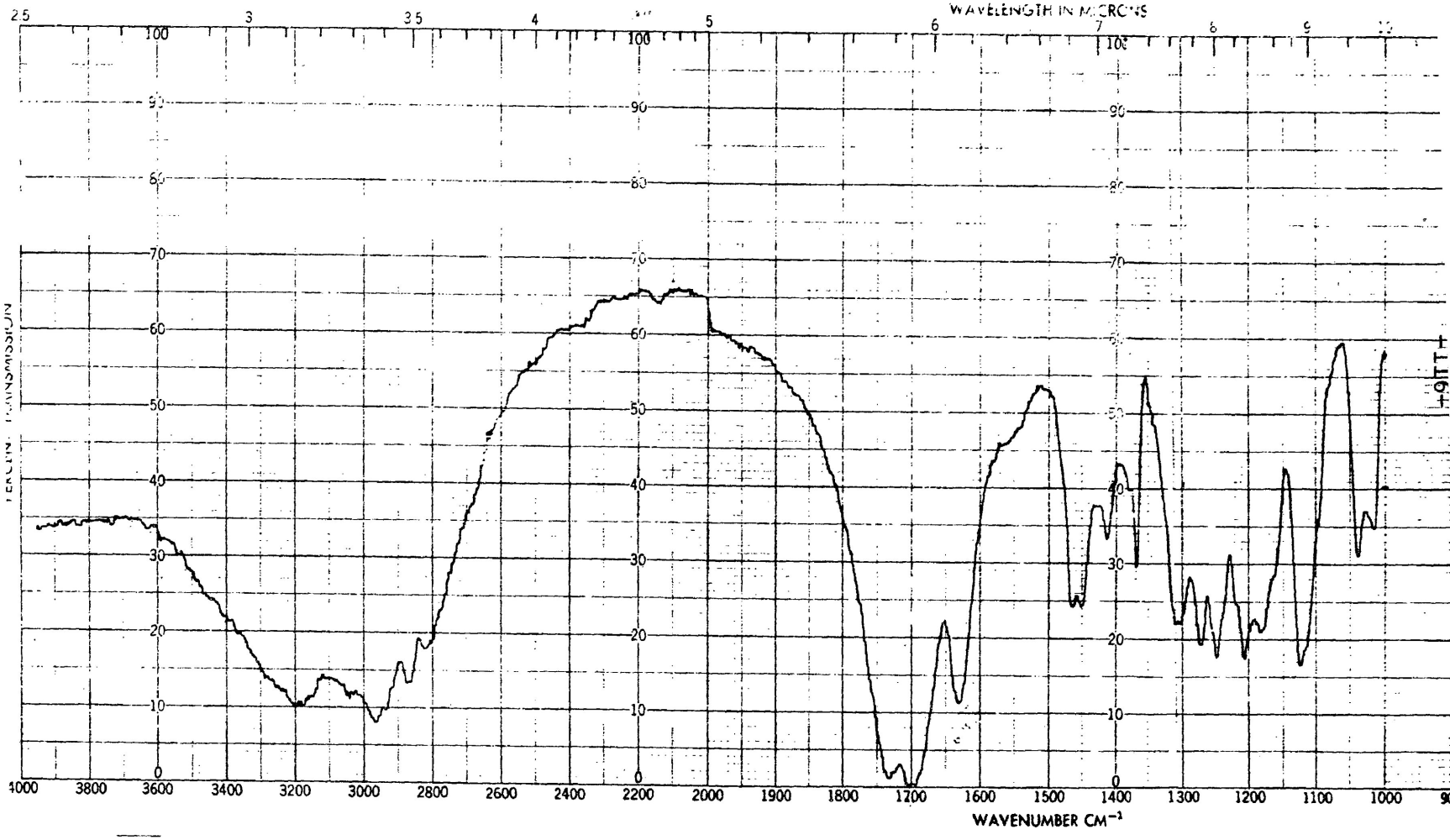
NMR NO. 24. 2-Butyl-2-tosyl-4-butyrolactam



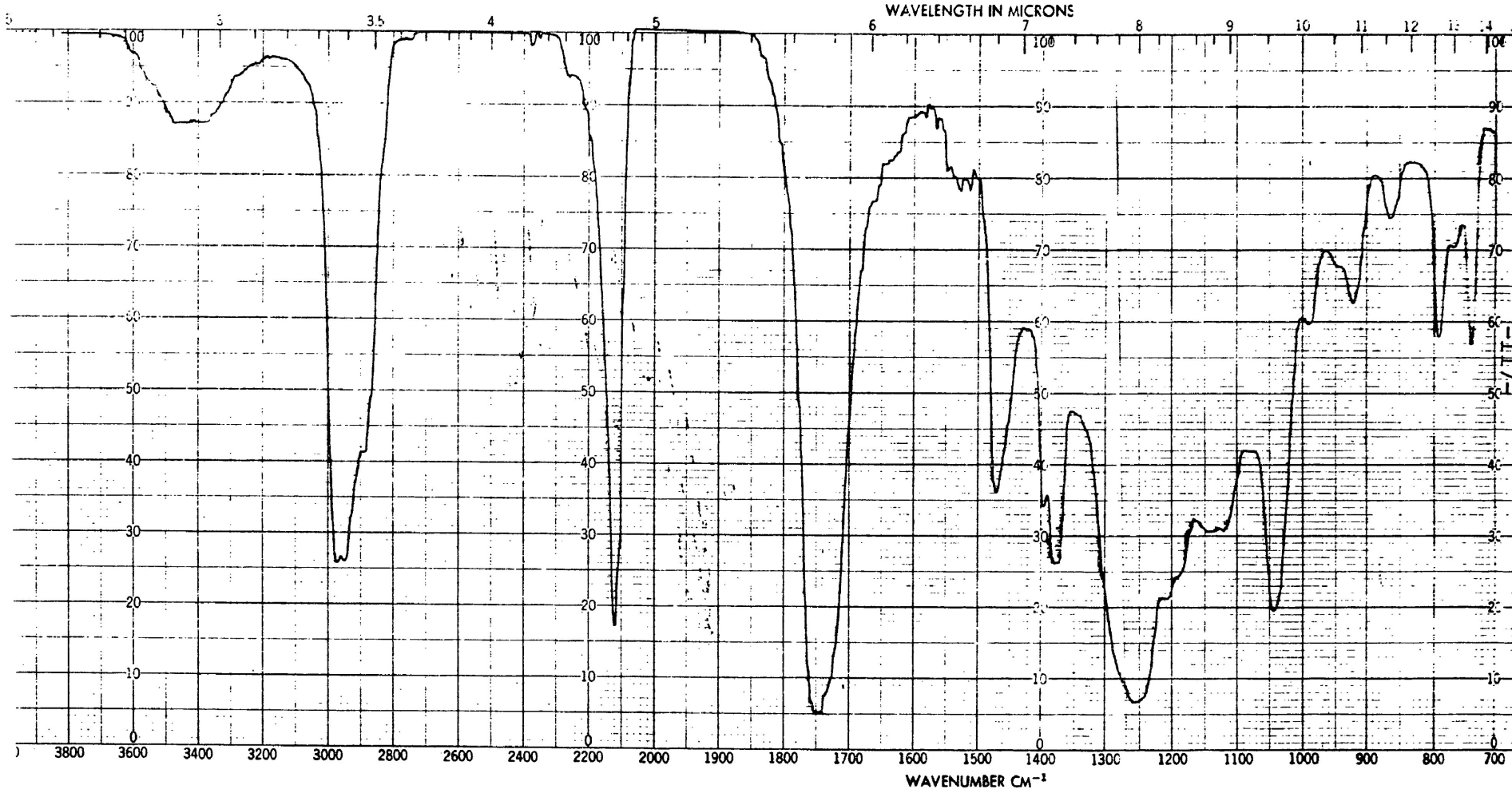
IR NO. 1. Ethyl 2-n-butyl-4-azidoacetoacetate



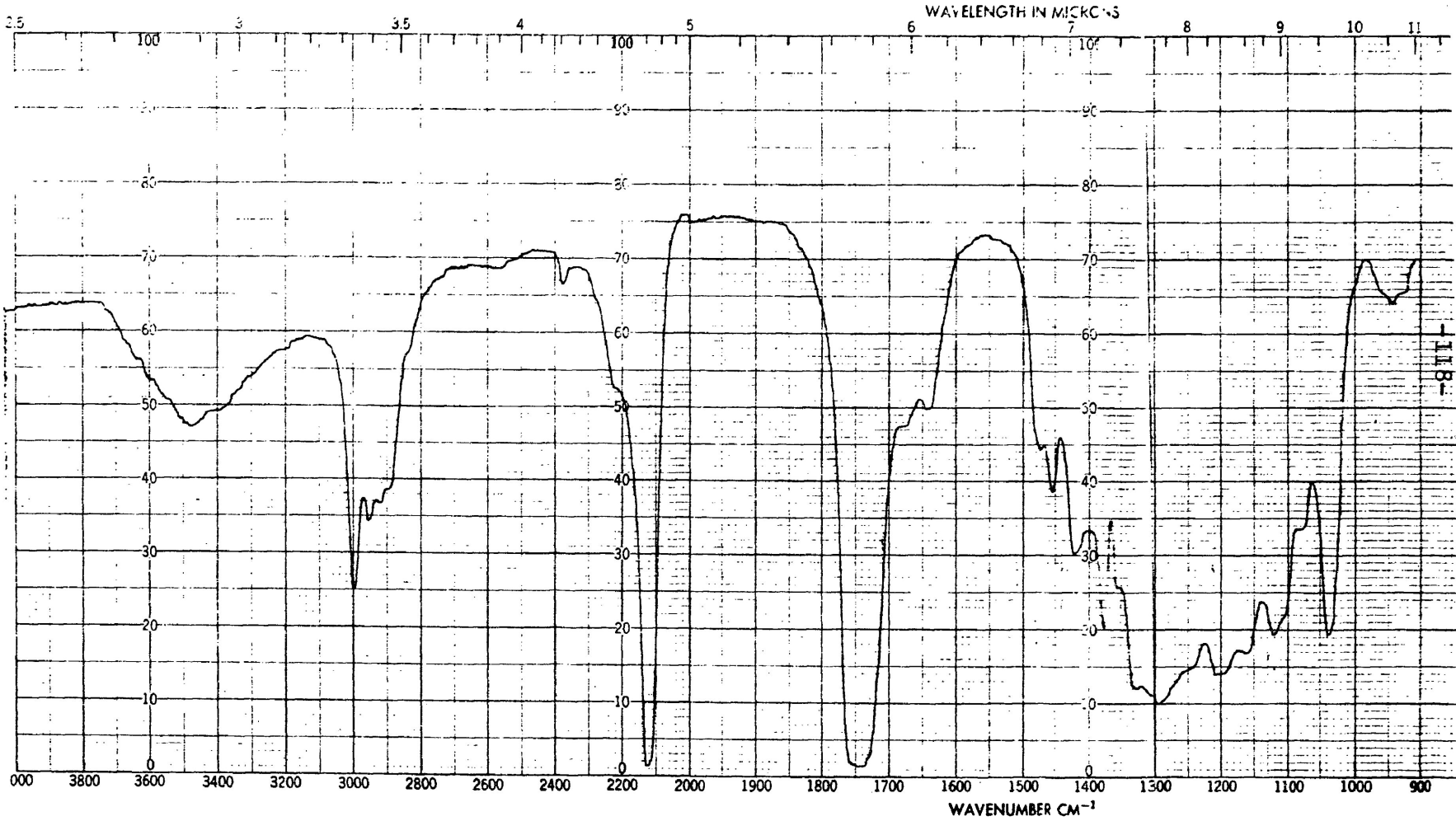
IR NO. 2. Ethyl 2-n-butyl-4-aminoacetoacetate (as hydrochloride)



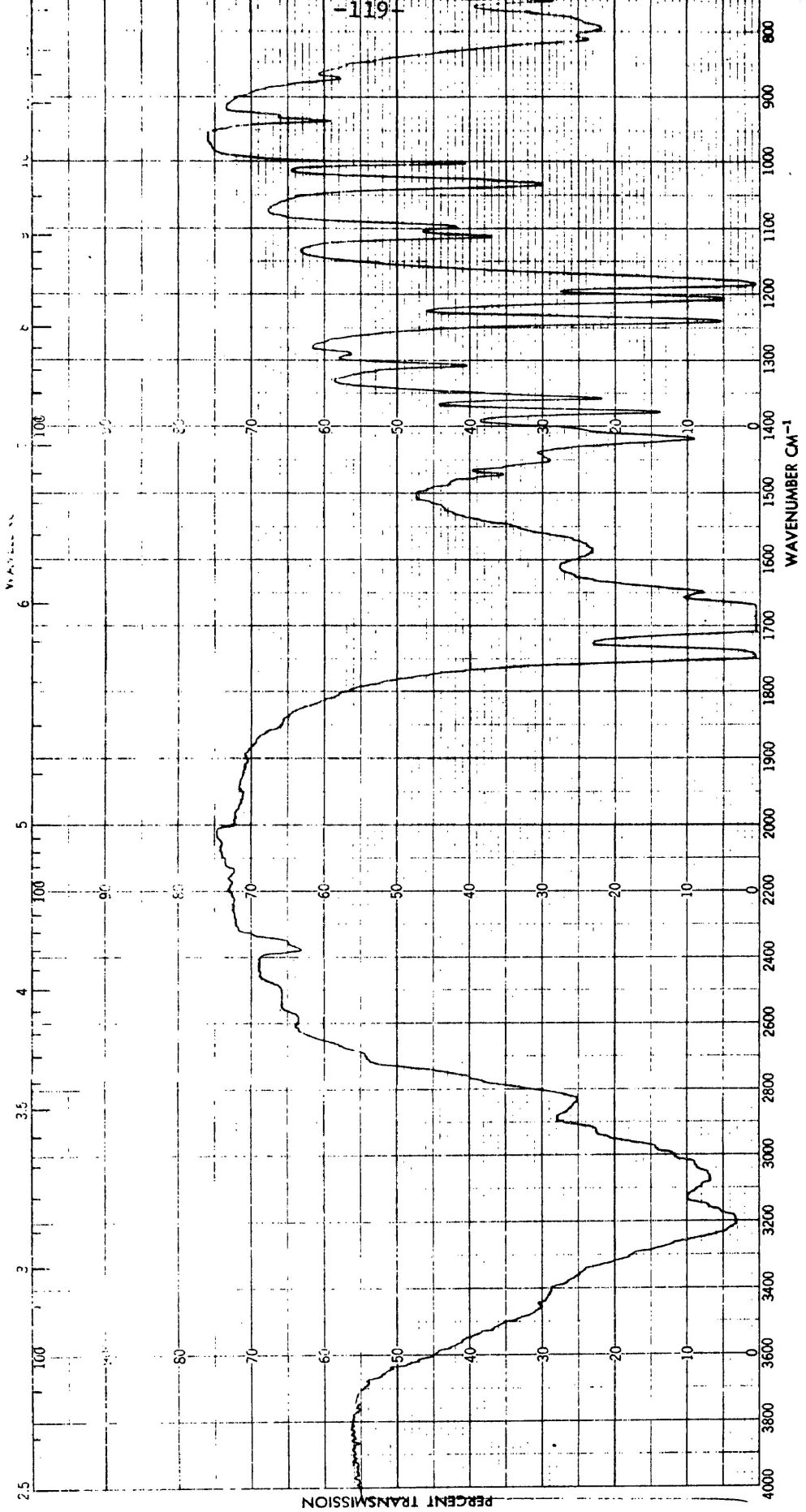
IR NO. 3. 4-(1'-carbethoxypentyl)-2-imidazolone



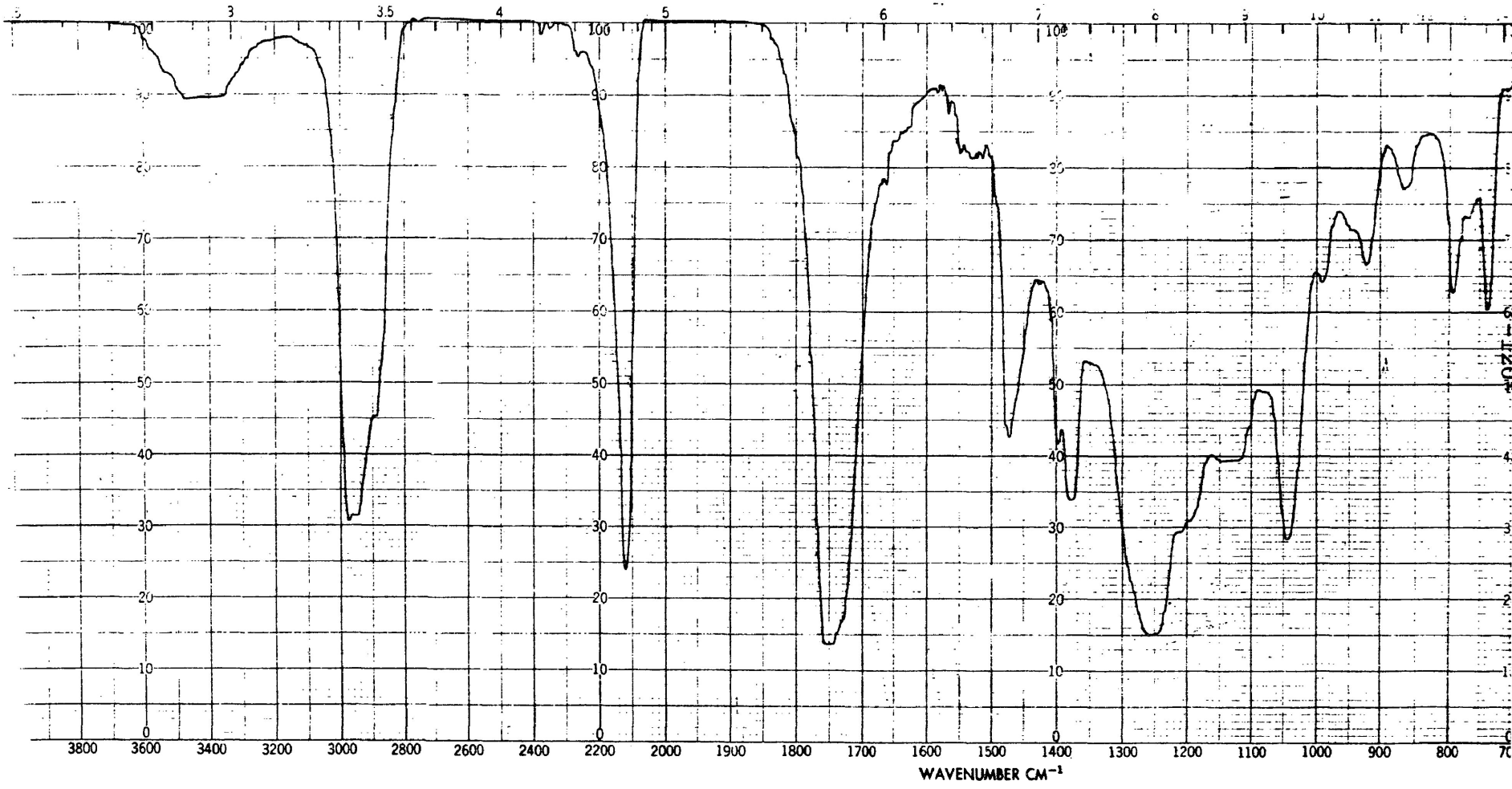
IR NO. 4. Ethyl 2-(4'-methyl-5'-hydroxypentyl)-4-azidoacetoacetate



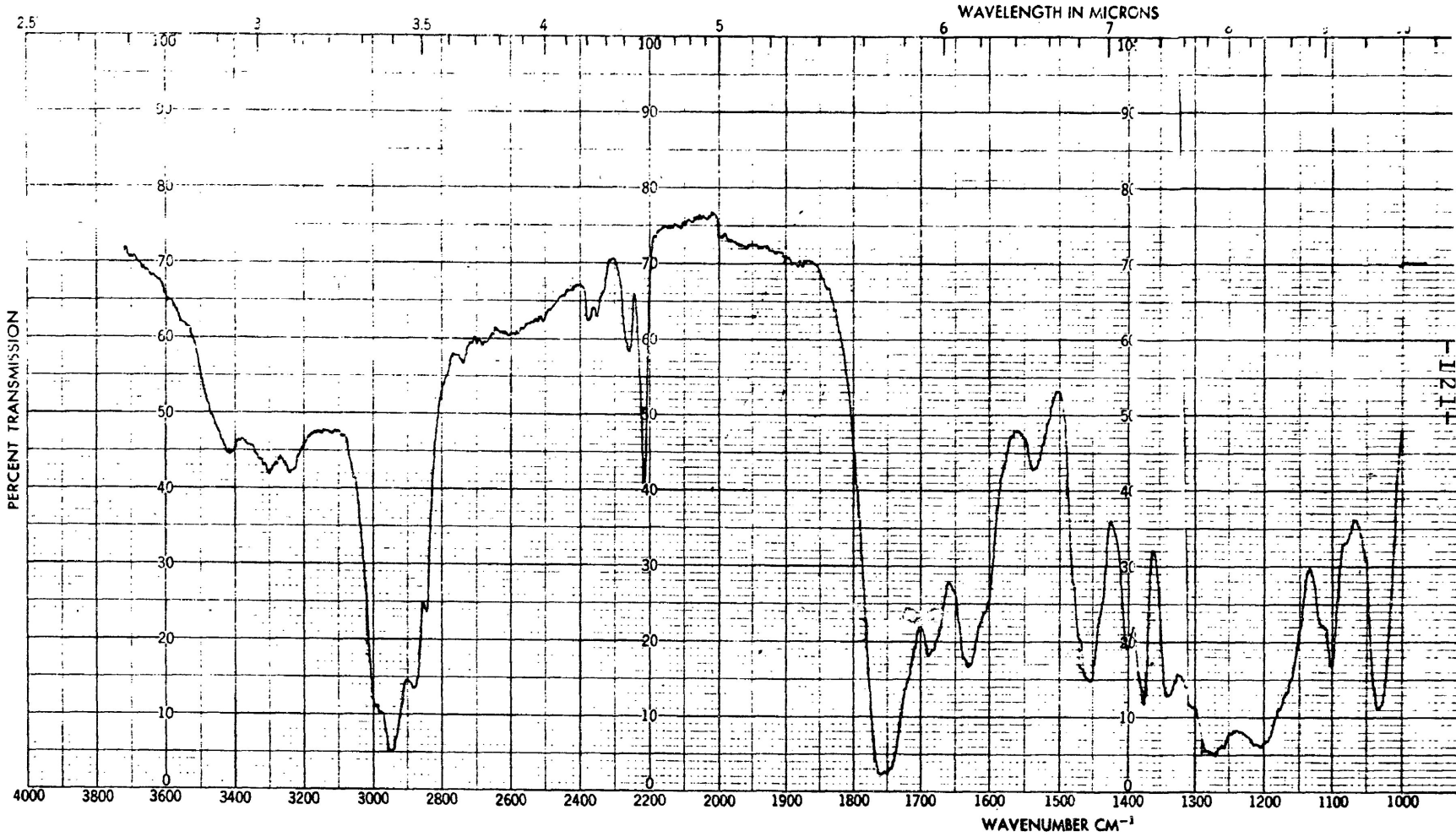
IR NO. 5. Ethyl 4-azidoacetoacetate



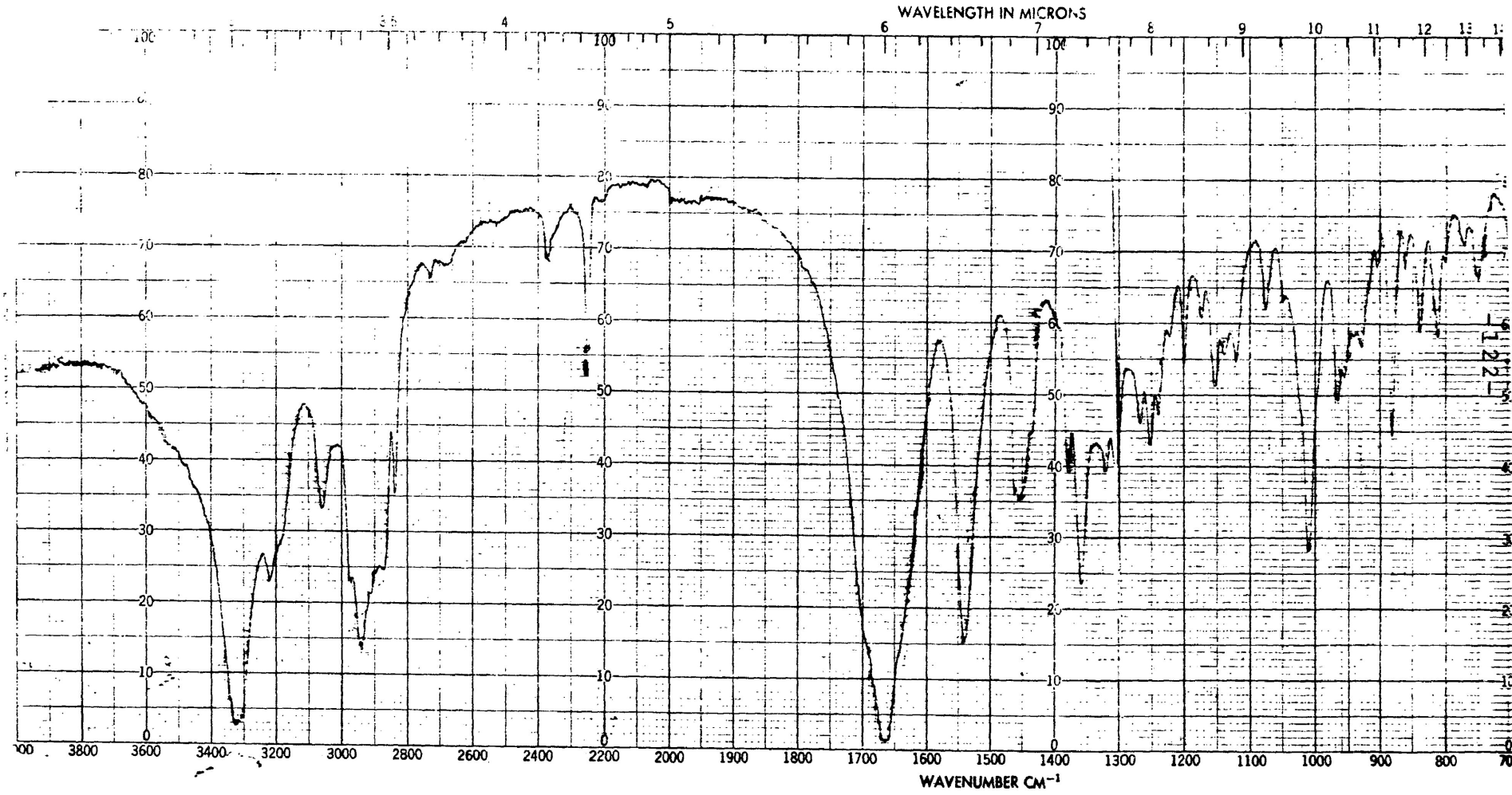
IR NO. 6. 4-(1'-Carbethoxymethyl)-2-imidazolone



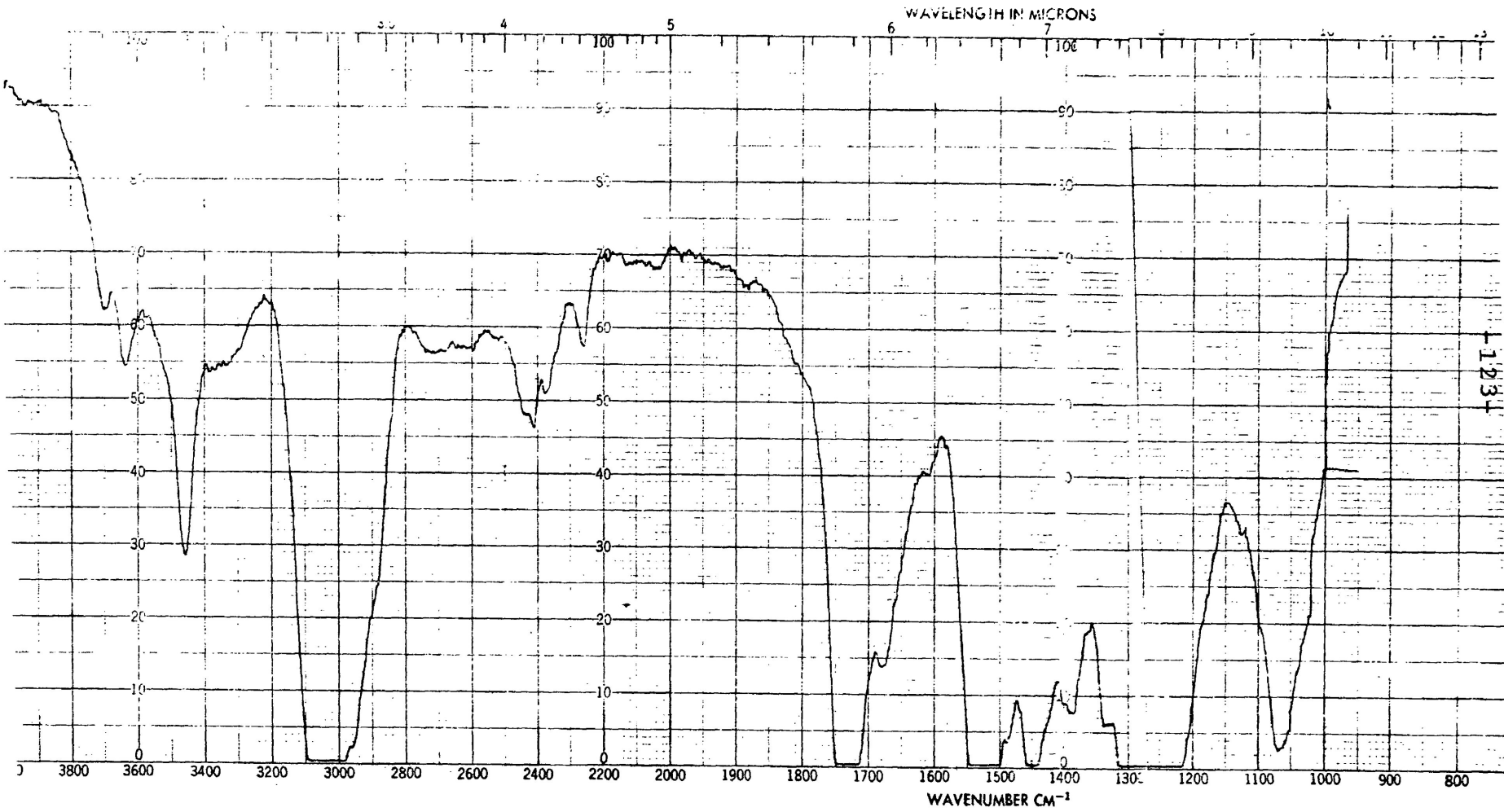
IR NO. 7. Ethyl 2-(4'-methyl-5'acetoxypentyl)-4-azidoacetoacetate



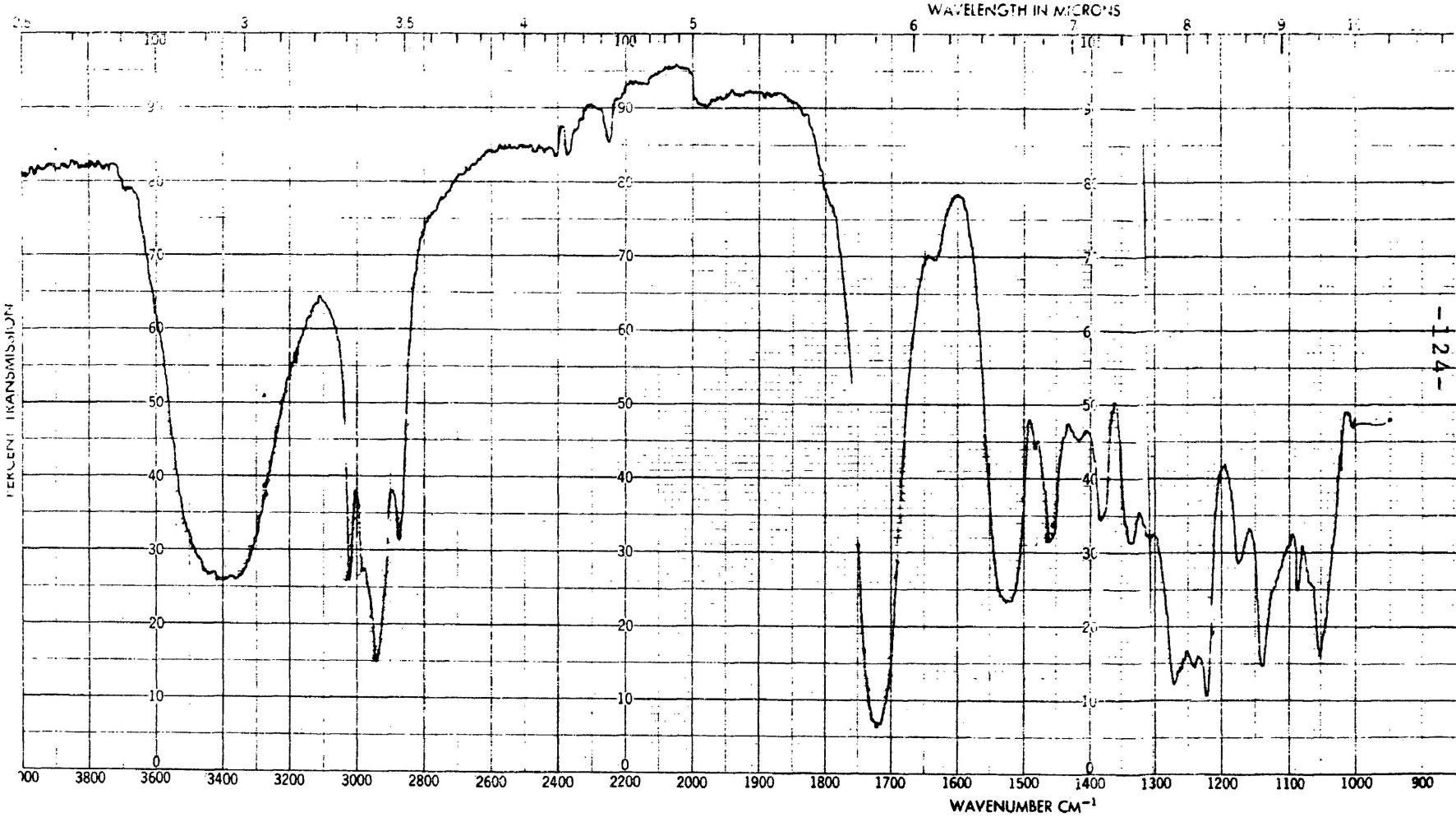
IR NO. 8. Ethyl 2-(3'-methyl-2'-cyclohexenyl) cyanoacetate



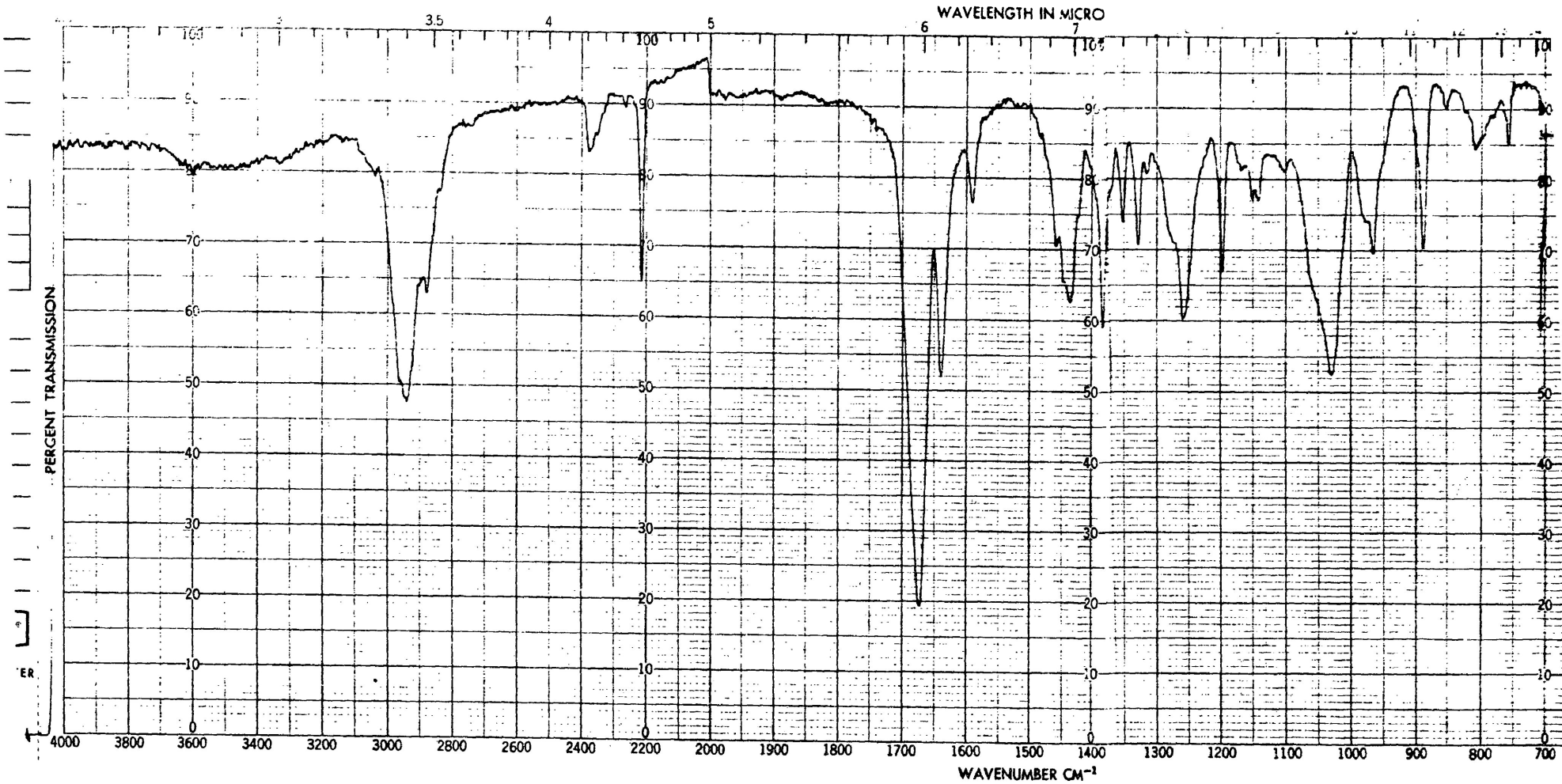
IR NO. 9. 2-(3'-methyl-2'-cyclohexenyl)-2-cyanoacethydrazide



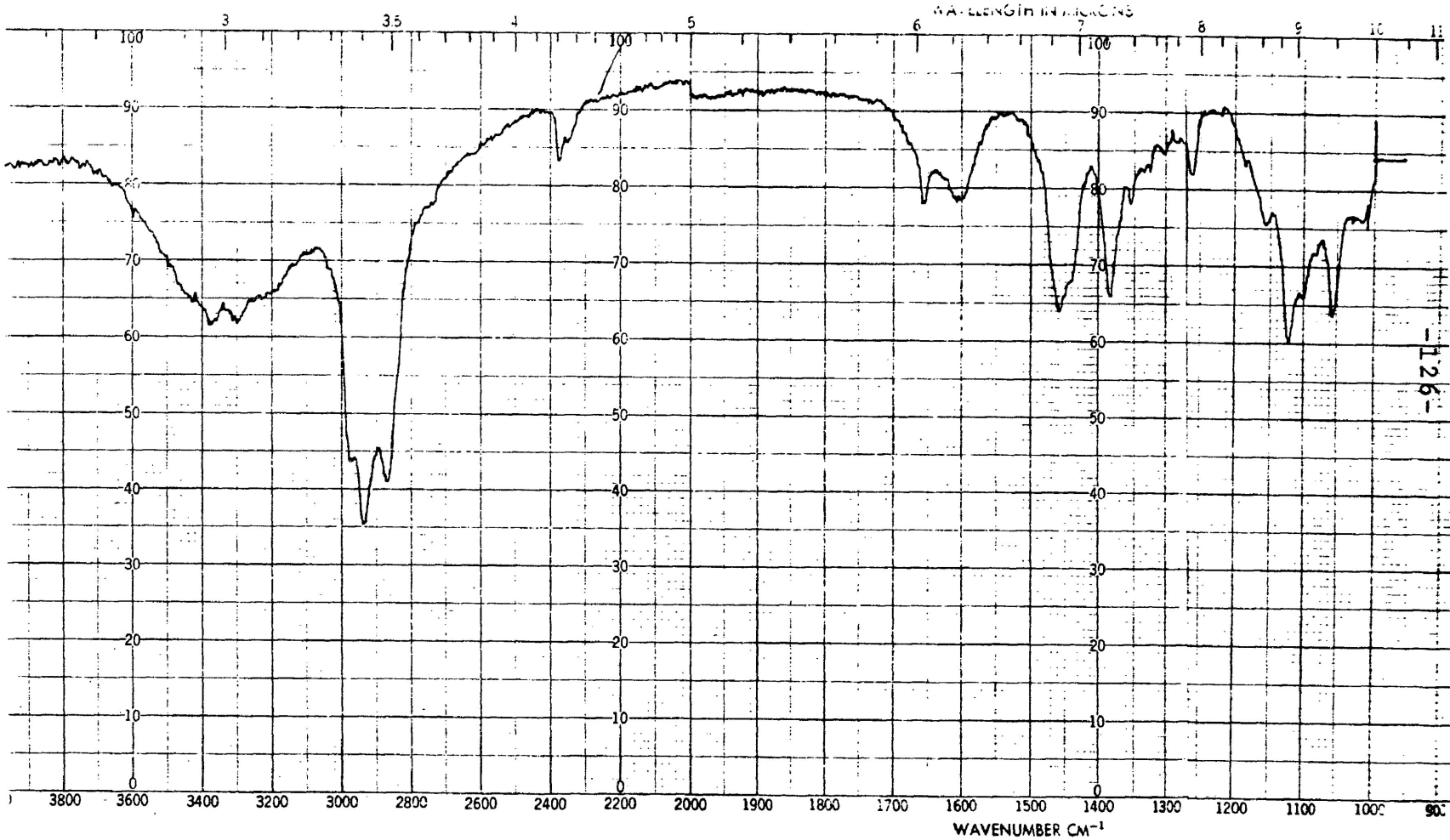
IR NO. 10. 2-(N'-carbethoxy)-2-(3'-methyl-2'-cyclohexenyl)acetonitrile



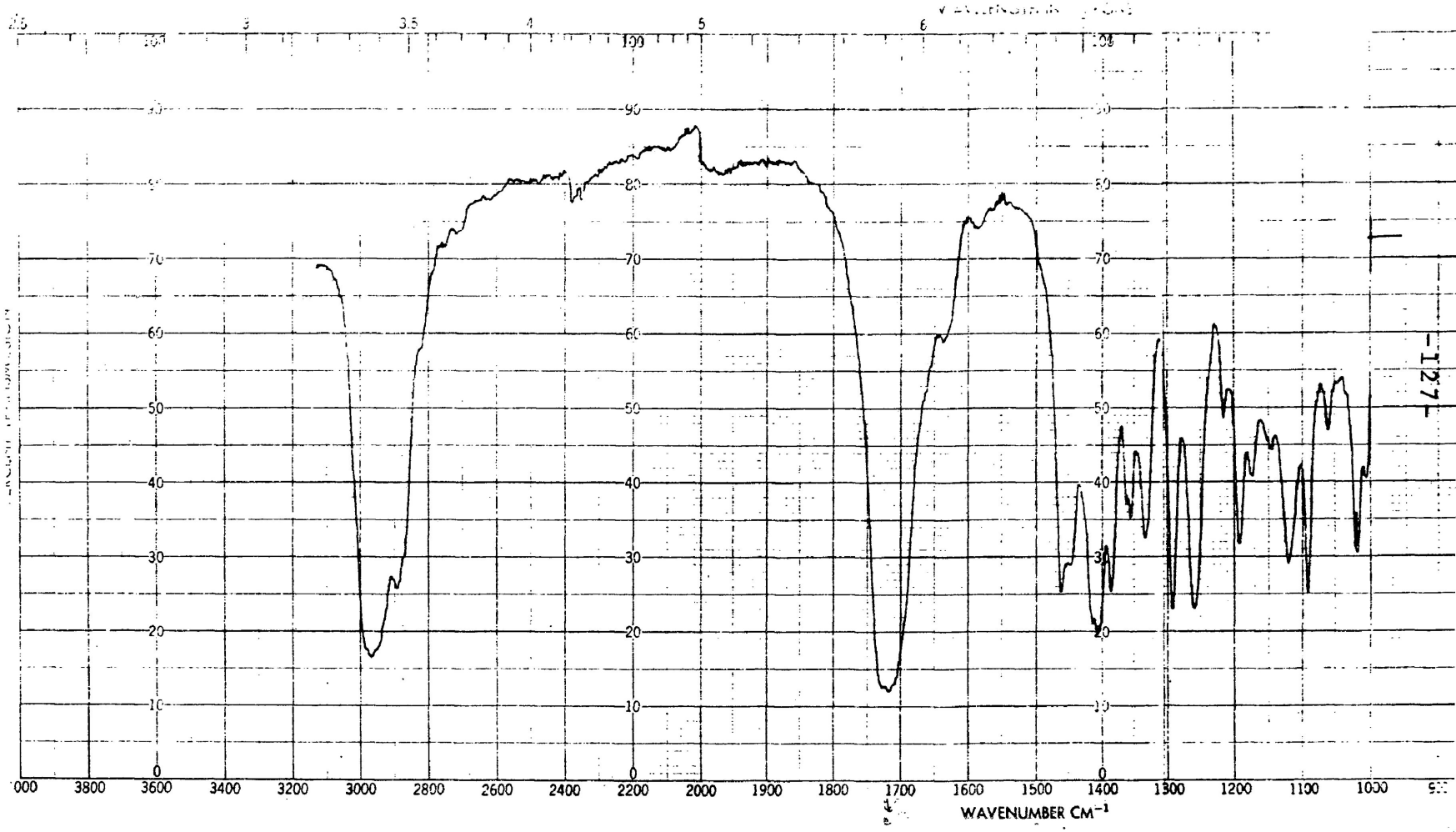
IR NO. 11. 2-(N'-carbethoxy)-2-(2'-3'-dihydroxy-3'-methylcyclchexyl)acetonitrile



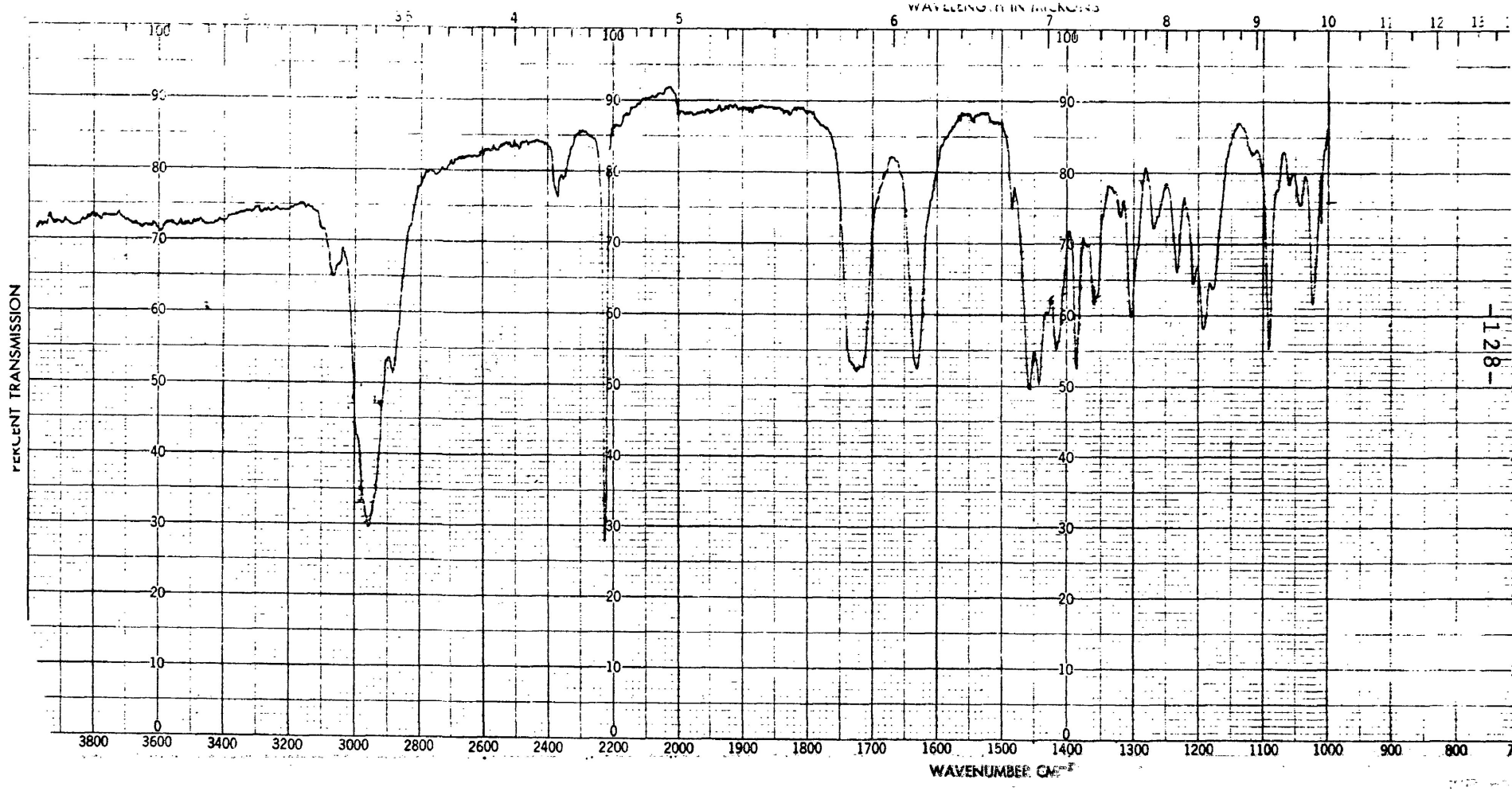
IR NO. 12. 1-Cyanomethylene-3-methyl-2-cyclohexene



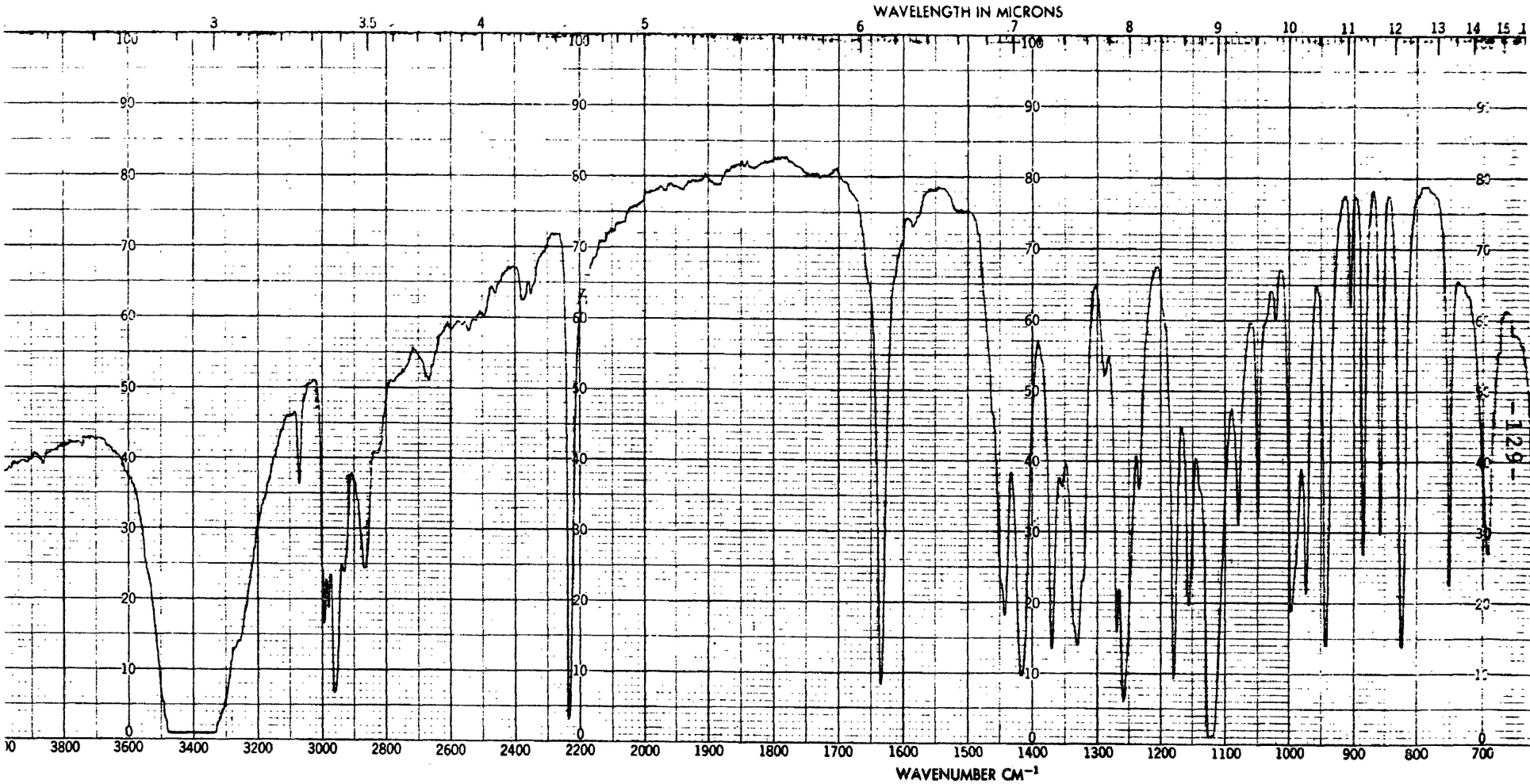
IR NO. 13. 1-methyl-3-(2'-aminoethylidene)cyclohexene



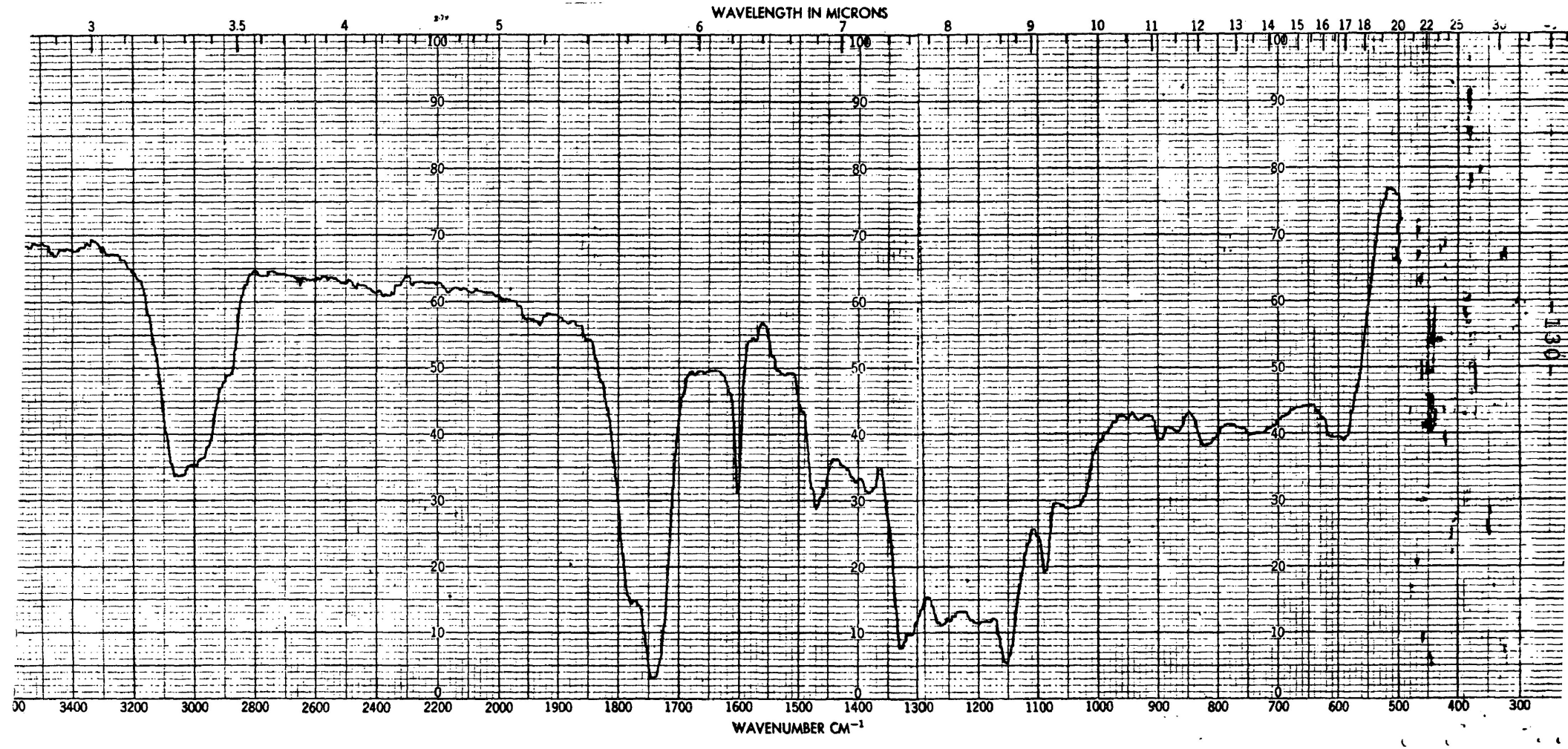
IR NO. 14. 2,3-Oxirino-3-methylcyclohexan-1-one



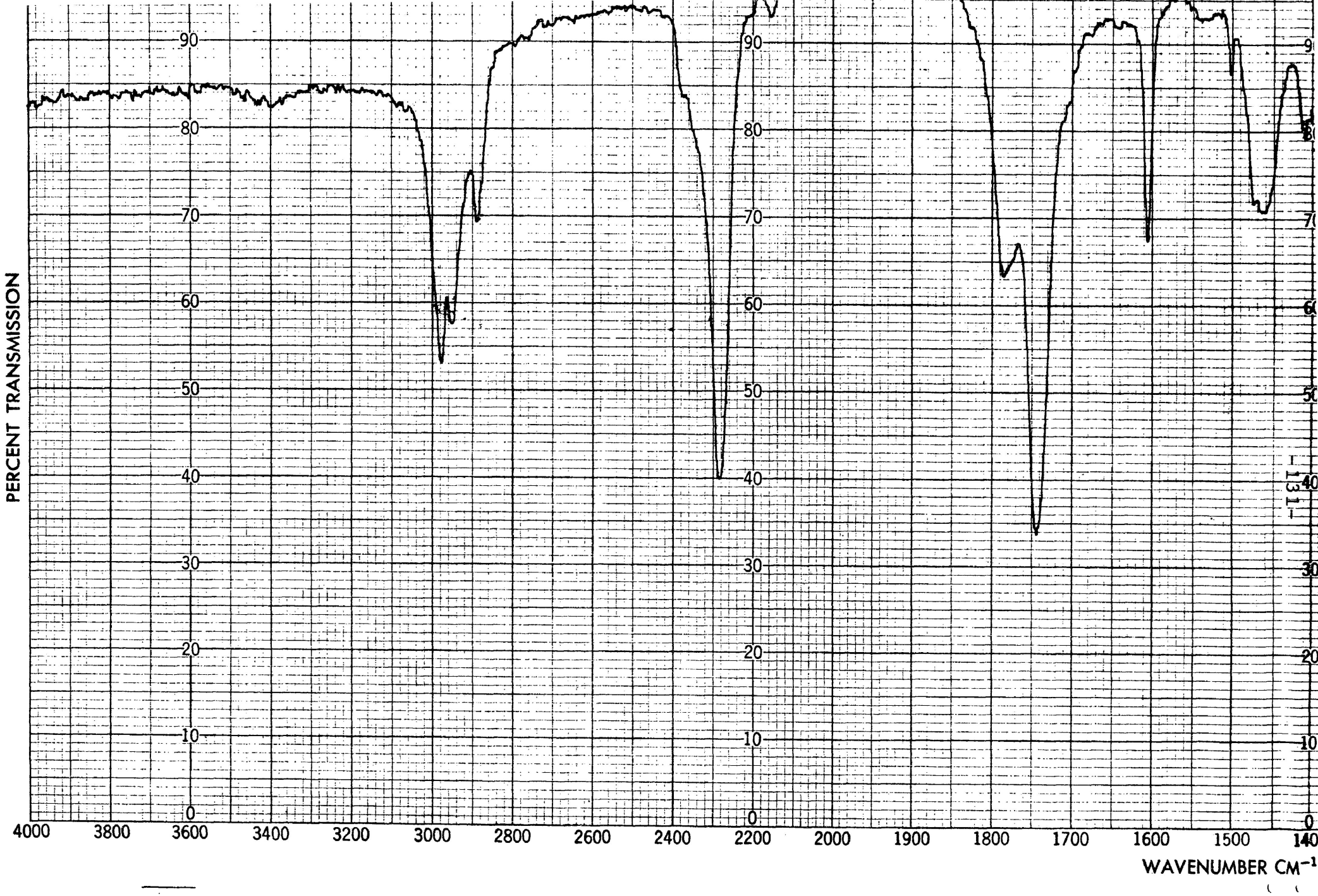
IR NO. 15. 1-Cyanomethylene-2,3-oxirino-3-methylcyclohexane



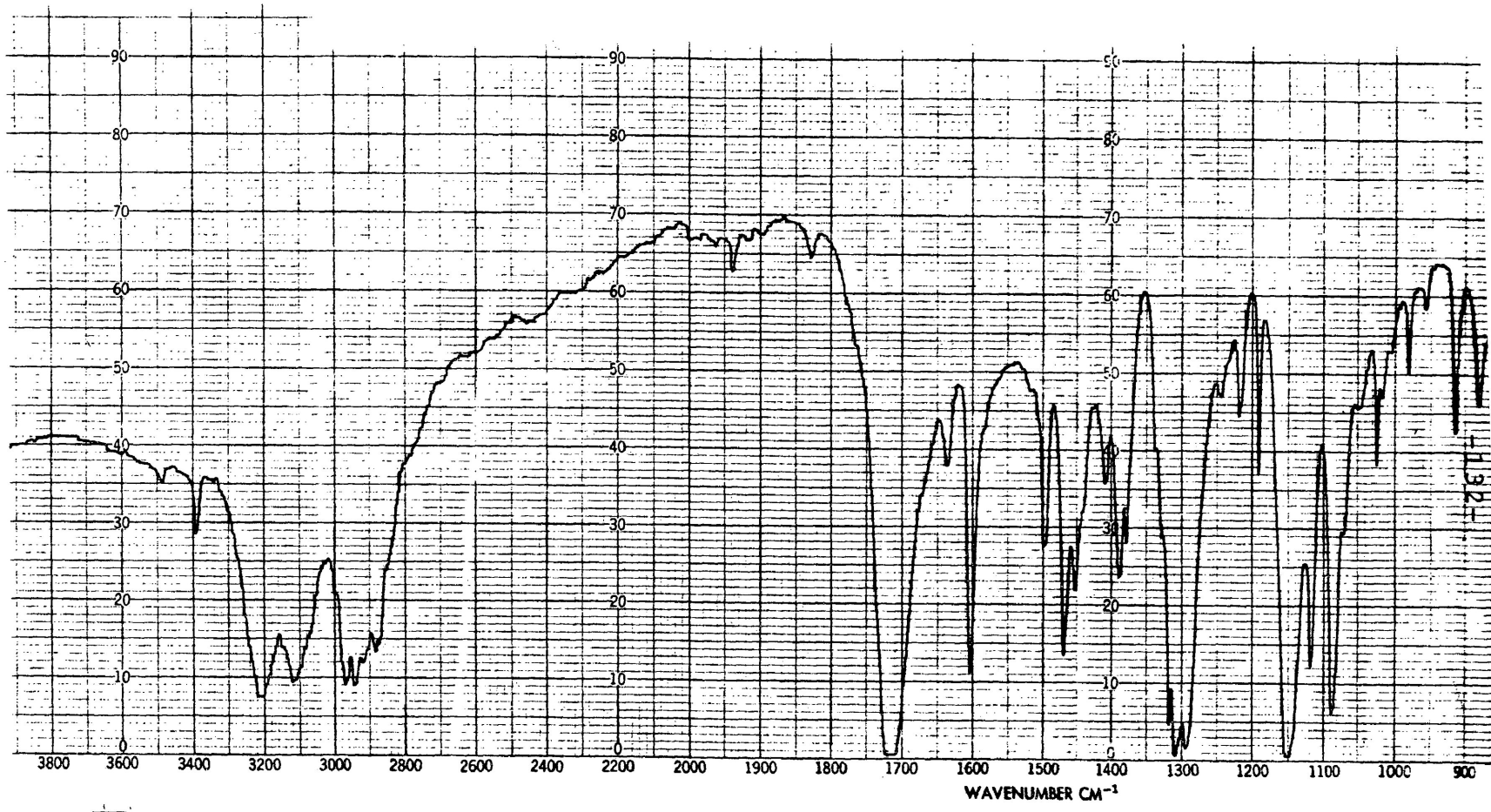
IR NO. 16. 1-Cyanomethylene-2,3-dihydroxy-3-methylcyclohexane



IR NO. 17. 4-Carbethoxy-4-tosyloctanoylchloride



IR NO. 18. 4-Carbethoxy-4-tosyloctylisocyanate



IR NO. 19. 2-Butyl-2-tosyl-4-butyrolactam

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