SYNTHETIC STUDIES ON

CHAKSINE

by

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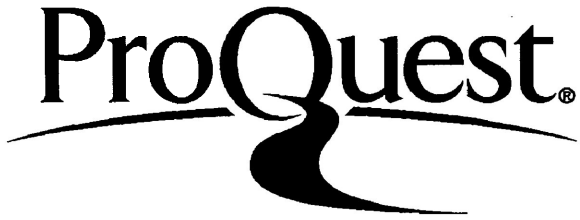

ABSTRACT

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

Diethyl methylmalonate was alkylated with 1,3-dibromo propane to give 2-(3-bromopropyl)-2-methylmalonate. Hydrolysis and decarboxylation of this product gave the mono acid which was then converted to the corresponding ethyl ester. Reduction with lithium borohydride yielded the primary alcohol to which a tetrahydropyran protective group was added. Alkylation with diethyl malonate followed by acylation with the mixed anhydride of isovaleric acid and carbobenzyloxyglycine gave diethyl 2-(4-methyl-5-2′-tetrahydropyranyloxylpentyl)-2-carbobenzyloxyglycine - malonate.

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INTRODUCTION

The plant, Cassia absus, which is native to India and Ceylon, 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 opthalmia and skin affections, and as a cathartic.

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

The powdered kernel of the plant was treated with cold methanolic hydrochloric acid. After neutralization and subsequent acidification, the alcohol was removed under reduced pressure and the residue was extracted with ether. After removal of the ether, the material was dissolved in water and acidified with dilute hydrochloric acid. Addition of potassium iodide to the acid 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 iodide was found to contain no methoxyl groups and by Herzig and Meyer's method, it was found to contain no N-methyl groups.

In a subsequent paper, Ray 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] After further studies, Guha and Ray[4] published a proposed structure for

chaksine* (I) based on infrared spectra and chemical evidence. A partial structure (II) was proposed for the part of the molecule containing the nitrogen atoms. Kuhn - Roth oxidation indicated the presence of one C - Me group. A positive pyrrole test coupled with the resistence of the molecule to Hoffman and Emde degradation was interpreted to indicate a bicyclic structure in which the quarternary nitrogen is common to both rings. Since a C_8 fragment was usually obtained in various degradation reactions, it was assumed that eight carbon atoms made up the bicyclic structure. Based on these observations, Guha and Ray expanded the partial structure to (III) which accounted for all but C_2H_5O in the chaksine molecule. The presence of an hydroxyl group was indicated by the formation of the tribenzoyl derivative and thus structure (I) was proposed.

Wiesner et al.[5] were also engaged in studies on chaksine and, in a later paper, proposed an entirely different structure. A ureido - hydroxy acid was obtained from hydrolysis of chaksine with 2N sodium hydroxide and the infrared spectrum of the ester formed from the acid showed bands at 1740 $cm.^{-1}$ and 1710 $cm.^{-1}$, indicating a five-membered cyclic urea. Also, under mild oxidizing conditions, chaksine yielded an acidic product which, when decarboxylated by heating under nitrogen followed by chromium trioxide oxidation, gave α methylpimelic acid (IV). This product was identified by a comparison of the infrared spectrum with that of an authentic sample. These investigators thus assigned structure (V) to chaksine. This was the

* see Plate I

first recorded example of a monterpernoid alkaloid.

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

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

Wiesner et al.[8] then submitted a second communication citing chemical and nuclear magnetic resonance evidence supporting the structure they had originally proposed. The methyl ester of the ureido acid (IX) was prepared and the N.M.R. spectrum confirmed the proposed structure. The chemical shifts of the protons in the ureido ring correspond with those in an authentic sample of 2-imidizolidone.

The ultimate proof of any structure elucidation lies in the unambiguous synthesis of that compound. The author, under the direction of Dr. D. Orr, attempted the synthesis of chaksine.

In the partial synthesis of chaksine presented in this thesis, diethyl methylmalonate (X) was alkylated with 1, 3-dibromo propane (XI) to give diethyl 2-(3-bromopropyl)-2-methylmalonate (XII). Hydrolysis of the ester and subsequent decarboxylation in hydrobromic acid yielded 5-bromo-2-methylpentanoic acid* (XIII). The corresponding ethyl ester, ethyl 5-bromo-2-methylpentanoate (XIV), was formed by

* see Plate II

treatment with ethanol under acidic conditions.

Reduction of the ester with lithium borohydride yielded 5-bromo-2-methylpentanol (XV). The primary hydroxyl group thus produced was protected by forming the tetrahydropyran derivative in the usual way. This halogenated derivative was then alkylated with diethyl malonate to yield the mono adduct (XVII).

A suitable derivative to react with (XVII) was then prepared by condensing the acid chloride of isovaleric acid (XVIII) with carbobenzyloxyglycine* (XIX) to give the mixed anhydride of isovaleric acid and carbobenzyloxyglycine (XX).

The mixed anhydride was then treated with the malonic ester derivative (XVII) to yield (XXI). The compound (XXI) was felt to represent a key intermediate in the chaksine synthesis. All the necessary atoms in the basic skeleton of chaksine appear to be present with the exception of one carbon and two nitrogen atoms. It contains the required molecular skeleton with appropriate functionality for conversion into chaksine.

An alternative approach was also attempted.† The bromine derivative (XVI) under went a Grignard reaction with allyl chloride to yield 7-methyl-8-(2′-tetrahydropyranyloxyl)-1-heptene (XXII). Incorporation of the olefin in the five - membered heterocyclic ring and addition of an ester function to this ring should yield the required compound.

* See Plate IV

† See page 12

DISCUSSION

In our synthetic studies of chaksine, we approached the problem by first forming the basic carbon skeleton with required functionality and then attempted to add the five-membered heterocyclic ring.

In the initial step, it was necessary to form diethyl-2-(3-bromo Propyl)-2-methylmalonate (Plate II, XII). This compound was readily obtained from the alkylation of diethyl methylmalonate with 1,3-dibromo-propane. The nuclear magnetic resonance spectrum (n.m.r. 1) of the pure reaction product afforded evidence that the desired compound had been formed. A methyl triplet at τ=8.75 (J=7 Hz) and a methylene quartet at τ=5.85 (J=7 Hz) confirmed the presence of ethyl esters. A singlet at τ=8.62 was assigned to the methyl group and the protons alpha to the bromine appeared as a multiplet centered at τ=6.64. The infrared spectrum (i.r. 1) exhibited absorption bands at 1740 $cm.^{-1}$ (saturated ester) and 1375 $cm.^{-1}$ (terminal methyl).

Treatment of XII with an aqueous solution of hydrobromic acid resulted in the smooth conversion of the diethyl ester into the corresponding acid. This product was decarboxylated in solution, by increasing the reaction temperature. Visible evidence for this was supplied by the copious evolution of gas bubbles from the reaction mixture. The formation of 5-bromo-2-methylpentanoic acid (XIII) was supported by i.r. and n.m.r. spectra. The broad absorption band found in the i.r. (i.r. 2) extending from 3500 $cm.^{-1}$ to 2400 $cm.^{-1}$ is characteristic of carboxylic acids.

The compound also exhibited peaks at 1695 $cm.^{-1}$ (carbonyl stretching) and 1375 $cm.^{-1}$ (terminal methyl). The n.m.r. spectrum (n.m.r. 2) had a doublet at τ=8.68 (J = 6 Hz.) which was assigned to the methyl group and a singlet τ = -1.7 was assigned to the proton of the carboxylic acid function. The protons alpha to the bromine appeared as a multiplet centered at τ=6.62.

The next step in the synthesis required the conversion of the carbonyl moiety into the corresponding primary alcohol. The reduction of the carboxylic acids requires vigorous reaction conditions, and since the problem was complicated by the strong possibility of reducing the alkyl halide portion, it was decided to first convert the 5-bromo-2-methylpentanoic acid (XIII) into the corresponding ethyl ester. This was readily achieved by heating (XIII) under reflux in an acidic ethanol - benzene solution and removing the water by azeotropic distillation. The presence of a methyl triplet at τ=8.78 (J = 7 Hz.) and a methyl quartet at τ=5.92 (J = 7 Hz.) (n.m.r. 3) confirmed that the conversion to the ester had occurred. The absorption peaks for the remaining portion of the molecule were found at the expected values. The i.r. spectrum (i.r. 3) gave absorptions at 1720 $c.m.^{-1}$ (saturated ester) and 1370 $cm.^{-1}$ (terminal methyl). In the mass spectrum (m.s. 1), molecular ion peaks were recorded in equal abundance at m/e values of 222 and 224. The presence of two molecular ions may be explained by the fact that there are two naturally occurring isotopes of bromine found in equal proportions and differing by two atomic mass units. An interpretation of some of the other fragmentation peaks may be found on Plate V.

The desired primary alcohol was now readily obtained by reduction of the ethyl ester (XIV) with lithium borohydride. The reaction was followed by examining the i.r. spectra of the products derived from the aliquots, and when the carbonyl absorption peak had disappeared, the mixture was worked up. The i.r. spectrum (i.r. 4) of the product showed a sharp absorption band at 3520 $cm.^{-1}$ (free OH) and a broader peak at 3400 $cm.^{-1}$ (intermolecular hydrogen bond) confirming the presence of the hydroxyl moiety. The n.m.r. spectrum (n.m.r. 4) showed that the methyl doublet had shifted further upfield and was centered at τ=9.1 (J=6 Hz) ($\Delta\tau$ =0.4 Hz). The methylene protons attached to the same carbon atom as the hydroxyl and bromine functions appeared as a broad multiplet centered at τ =6.62. In the mass spectrum of this compound, (m.s. 2), the molecular ion peak was not observed. An interpretation of the fragmentation pattern may be found on Plate VI.

The acetate was prepared from the primary alcohol in the usual fashion. This simplified the splitting pattern of the methylene protons. Since the ester function has a stronger withdrawing influence than the hydroxyl group, it would be expected that these methylene protons would undergo a diamagnetic shift. The expected shift was observed in the n.m.r. spectrum (n.m.r. 5) with the methylene protons of the acetate carbon appearing as a doublet centered at τ=6.16 (J=6 Hz) The protons alpha to the bromine function appeared as a triplet

centered at τ=6.68 (J=6 Hz). A sharp singlet at τ =8.02 was assigned to the methyl group of the acetate and the methyl doublet was observed at τ =9.23.

At this point, a protective group was added to the primary alcohol by treating (XV) with 3,4-dihydropyran. The tetrahydropyran group is stable under basic conditions, but can be readily removed under acidic conditions. A sharp singlet at τ =5.5 in the n.m.r spectrum (n.m.r. 6) of this product was assigned to the lone proton on the acetal carbon. The methyl group appeared as a doublet at τ =9.08 (J= 6 Hz). The i.r. spectrum (i.r. 5) did not exhibit peaks in either the carbonyl or hydroxyl regions. The molecular ion peak was not observed in the mass spectrum of this product (m.s. 3) however, this, along with a peak at m/e 85, seems to be characteristic of tetrahydropyranyl esters.[9] An interpretation of the fragmentation pattern for this molecule may be found on Plate VII.

At this stage, diethyl malonate was incorporated into the molecule via an alkylation reaction to give (XVII). The n.m.r. spectrum (n.m.r. 7) indicated that the ester functions were present since a triplet centered at τ =8.72 (J= 7 Hz) and a quartet centered at τ =5.88 (J= 7 Hz) were observed. The acetal hydrogen appeared as a singlet at τ =5.5 and the methyl group as a doublet centered at

τ=9.1 (J = 6 Hz.). The ester groups exhibited strong absorptions bands at 1720 cm.$^{-1}$ (i.r. 6). Elemental analyses were in agreement with the calculated results. (see experimental)

A suitable derivative with which to acylate the diester (XVII) was the mixed anhydride of isovaleric acid and carbobenzloxyl-glycine, prepared by reacting isovaleryl chloride with carbobenzyloxy-glycine. This, on reaction with the anion of the diester (XVII), gave a product (XXI) which was characterized by its n.m.r. spectrum (n.m.r. 8). The protons of the aromatic ring appeared as a sharp singlet at τ=2.72 and the methylene protons of the benzylic carbon appeared as a sharp singlet at τ=4.87. The proton on the nitrogen was observed as a broad absorption centered at τ=4.68. When a carbon tetrachloride solution of this product was shaken with deuterium oxide the N - H peak disappeared and the protons that it was splitting collapsed to form a sharp singlet at τ=5.46[10]. The i.r. spectrum (i.r. 7) exhibited absorption bands at 3420 cm.$^{-1}$ (N - H stretching), 1740 cm.$^{-1}$ (saturated ester), and 1500 cm.$^{-1}$, and 1450 cm.$^{-1}$ (aromatic system). Elemental analyses also indicated the incorporation of the nitrogen into the molecule.

This product is considered to be a key intermediate in a chaksine synthesis. It combines the required molecular skeleton with the appropriate functionality for conversion to chaksine. The carbobenzyloxy protective group should be readily removed by hydrogenation and the resulting amino ketone could then be incorporated into the five - membered heterocyclic ring by reacting with potassium cyanate.[11]

An alternative approach involving a Grignard reaction with the alkyl halide (XVI) and allyl chloride was considered. The infrared spectrum (i.r. 8) was not particularly characteristic, but was different from the infrared spectrum (i.r. 5) of the alkyl halide. In the n.m.r. spectrum (n.m.r. 10), the acetal hydrogen appeared as a singlet at τ =5.5 and the methyl group appeared as a doublet at τ =9.1 (J=6 Hz.). A broad multiplet centered at τ=5.0 was assigned to the olefinic protons.

This olefin might then be brominated allylically and converted to the nitrile by reaction with sodium cyanide. Bromination of the cyano olefin followed by treatment with sodium azide, should give the diazide. Reduction of the diazide would give the diamine which could readily be converted to the heterocyclic urea by reacting with phosgene.[12] Hydrolysis of the nitrile would give the ureido-hydroxy acid.

FUTURE WORK

We have considered alternative routes to the synthesis of chaksine, several of which are currently being investigated. One involves the initial formation of the five-membered heterocycle-2-imidazolone*[13] (XXIII). This compound is obtained by reacting 1-amino-2-diethoxy ethane with potassium cyanate, followed by hydrolysis and cyclization in dilute sulphuric acid.

The remaining portion of the molecule is formed by reacting 2-carboethoxy cyclopentanone with methyl iodide to yield 2-carboethoxy-2-methyl cyclopentanone. Treatment with a sodium ethoxide solution gives α-methyl diethyl adipate. Hydrolysis of the primary ester function is achieved using a molar equivalent of base. The mono acid is converted to 5-carboethoxy hexanoyl chloride (XXIV) with thionyl chloride.

Condensation of (XXIII) and (XXIV) is achieved via a Friedel Crafts reaction to yield 4-(ethyl hexanyl-1-one-5-carboxylate) 2-imidazolone (XXV). This compound has the basic skeleton of the chaksine molecule. The remainder of the synthesis will involve conversion to the proper functionality. This should be achieved via hydrogenation to give the saturated heterocycle followed by reduction of the ketone to the corresponding secondary alcohol. Tosylation of the alcohol followed by reaction with sodium cyanide would form the nitrile derivative. Reduction of the ethyl ester and hydrolysis of the nitrile should give the desired ureido-hydroxy acid.

Another route under consideration involves a Michael addition between acrolein (XXVI) and diethyl methymalonate (X) to give diethyl pentan-1-al-4,4-dicarboxylate(XXVII). Reduction of the aldehyde to the primary alcohol and treatment with P-toluene sulphonic acid chloride would introduce a good leaving group.

* see Plate VIII

Displacement of this tosyl group with diethyl malonate followed by hydrolysis with a molar equivalent of base should yield the mono acid. Reacting with thionyl chloride would form 2-carboethoxy-6,6-dicarboethoxy heptanoyl chloride (XXVIII).

Conversion of the acid chloride to the amino ketone might be achieved by a reaction with diazo methane followed by reduction. Alternatively the nitrile could be formed from the acid chloride and this product reduced to the amino ketone. A reaction with potassium cyanate would convert the amino ketone to the five-membered cyclic urea.

It would now be necessary to hydrolize and decarboxylate the triester and convert one of the remaining carboxyl group to a primary alcohol.

EXPERIMENTAL

Diethyl-2-(3-bromopropyl)-2-methylmalonate (XII)

A dry 500 ml. three - necked flask was equipped with a reflux condenser, magnetic stirrer, dropping funnel, and calcium chloride drying tubes. Anhydrous benzene (250 ml. distilled over calcium hydride) and sodium (4.7 g.; 0.2 moles) were then added to the flask in a nitrogen atmosphere. The stirred mixture was heated to 70°C. and diethyl methylmalonate (35.8 g.; 0.2 moles) was added over a period of three hours. The resulting viscous mixture was transferred to a 500 ml. dropping funnel and added, with stirring, over a period of two hours to 1,3-dibromopropane (80.4 g.; 0.4 moles) in dry benzene (250 ml.) The resulting solution was heated to 70°C. in a 1 l. three - necked flask fitted with a reflux condenser and drying tubes. The reaction mixture was held at 70°C. for sixteen hours, then cooled to room temperature and transferred to a separating funnel. The organic layer was washed with three 100 ml. portions of distilled water and dried over anhydrous sodium sulphate. After filtration, the solvent was removed *in vacuo* yielding a clear yellow oil (35.2 g.). Purification by fractional distillation gave a clear, colourless product (21.3 g.) b.p. 115°C. at 1.1 mm., which was homogeneous by thin layer chromatography (silica gel: ether and petroleum ether b.p. 30° - 60°C. eluent). The distilled product represented a 35% yield.

The following absorptions were observed in i.r. and n.m.r. spectra. Infrared spectrum no. 1: 1740 $cm.^{-1}$, 1375 $cm.^{-1}$. Nuclear magnetic resonance spectrum no. 1: τ =8.75 and 5.85 (ester hydrogens), τ=8.11 (methyl doublet), τ=6.64 (multiplet due to protons α to the bromine.

5-Bromo-2-methylpentanoic acid (XIII)

Diethyl-2-(3-bromopropyl)-2-methylmalonate (XII) (10 g.; 0.034 moles), was placed in a 500 ml. round - bottomed flask fitted with a reflux condenser and a magnetic stirrer. Hydrobromic acid (150 ml. of 50% solution) was added and the mixture kept at 100°C. for twelve hours. The temperature was then increased to 160°C. for an additional eight hours. After cooling, the reaction mixture was diluted with diethyl ether (200 ml.) and washed with three 100 ml. aliquots of distilled water. The ether layer was dried over anhydrous sodium sulphate, filtered, and evaporated to dryness. The crude product (4.3 g.), a clear, yellow oil, was further purified by fractional distillation. The clear, colourless product (3.25 g.) was collected at 93°C. (2.6 mm.) and represented a 49% yield. The material was homogeneous on thin layer chromatography (silica gel - 20% ether in petroleum ether b.p. 30° - 60°C.).

Infrared spectrum no. 2: absorptions at 3500 - 2400 $cm.^{-1}$; 1695 $cm.^{-1}$; 1375 $cm.^{-1}$. Nuclear magnetic resonance spectrum no. 2: absorptions at τ=8.68 (methyl doublet); τ = -1.7 (proton of the carboxylic acid moiety).

Ethyl 5-bromo-2-methylpentanoate (XIV)

5-Bromo-2-methylpentanoic acid (XIII) (3.2 g.; 0.016 moles), ethanol (5 ml.) and a catlytic amount of sulphuric acid were added to a 250 ml. round-bottomed flask equipped with a water separator and reflux condenser. The solution was heated under reflux for twelve hours and then allowed to cool to room temperature. The reaction mixture was diluted with benzene (100 ml.) and washed with three 50 ml. portions of water. The organic layer was dried over anhydrous magnesium sul-

phate, filtered, and the benzene removed on a rotary evaporator, giving a clear, colourless product. A clear, colourless product (2.65 g.) was obtained by fractional distillation b.p. 80°C. at 1mm., yield 73%.

Infrared spectrum no. 3: absorptions at 1720 cm^{-1}; 1370 $cm.^{-1}$. Nuclear magnetic resonance spectrum no. 3: absorptions at τ=8.78; τ=5.92 (ethyl ester). Mass spectrum no. 1: m/e peaks at 224, 222. (molecular ion).

5-Bromo-2-methylpentanol (XV)

5-Bromo-2-methylpentanol (XIV) was prepared by dissolving ethyl-5-bromo-2-methylpentanoate (5 g., 0.002 moles) in diethyl ether (150 ml. distilled from lithium aluminum hydride) in a 250 ml. round-bottomed flask fitted with a calcium chloride drying tube and a reflux condenser. Lithium borohydride (0.500 g., 0.016 moles) was added in small portions to the flask over a fifteen minute period. The mixture was heated under reflux for thirty hours and then cooled in an ice bath. Wet methanol, followed by water, was added cautiously in drop-wise fashion to destroy any remaining lithium borohydride. The solution was washed with three 50 ml. portions of water. The resulting ether solution was dried over anhydrous sodium sulphate, filtered, and evaporated to dryness. The crude product, (3 g.), fractionally distilled at 70°C. and 1 mm. pressure, gave 2.65 g. of a clear, colourless oil. The distilled material represented a 66% yield.

Infrared spectrum no. 4: absorptions at 3520 $cm.^{-1}$; 3400 $cm.^{-1}$. Nuclear magnetic resonance spectrum no. 4: absorptions at τ=9.1 (methyl doublet); τ=6.62 (multiplet for methylene protons of bromine and hydroxyl groups). Mass spectrum no. 2: m/e peaks at 151, 149, 100, 83, and 69.

5-Bromo-2-methyl-1-acetoxypentane

5-Bromo-2-methylpentanol (XV) (0.175 g.) was dissolved in 3 ml. of anhydrous pyridine and 3 ml. of acetic anhydride. The reaction mixture was allowed to stand in the dark, at room temperature, for sixteen hours. Benzene (40 ml.) was added and the solvents were removed on a rotary evaporator. The residual material was diluted with benzene (30 ml) and washed with a 2% sodium bicarbonate solution (40 ml), 5% hydrochloric acid (25 ml.), and distilled water (25 ml.) The organic layer was dried over anhydrous magnesium sulphate, filtered, and evaporated to dryness. The crude product (0.163 g.) was a yellow oil.

Nuclear magnetic resonance spectrum no. 5: absorption at τ=8.02. (methyl group)

5-Bromo-2-methyl-1-(2'-tetrahydropyranloxyl)pentane (XVI)

5-Bromo-2-methylpentanol (XV) (3.0 g., 0.017 moles) was dissolved in dry ether (50 ml.), followed by the addition of 3,4-dihydropyran (1.5 g., 0.018 moles), and a catalytic amount of concentrated hydrochloric acid. The solution was stoppered and stirred at room temperature for sixteen hours. After washing with three 50 ml. portions of water, the organic layer was dried over anhydrous magnesium sulphate, filtered, and evaporated to dryness. Thin layer chromatography (silica gel: 10% ether - petroleum ether eluent) of the oily product (3.8 g.), showed one main component with trace impurities present. Column chromatography (Woelm silica gel activity grade 1-benzene eluent) gave 2 g. of material which corresponded to a 50% yield.

Infrared spectrum no. 5: no absorptions in either the carbonyl region or the hydroxyl region. Nuclear magnetic resonance spectrum no. 6: absorptions at τ=5.5 (single proton on the acetal carbon); τ=9.08 (methyl doublet). Mass spectrum no. 2: m/e peaks at 151, 149, 100, 83, and 69.

Diethyl 2-(4-methyl-5-2'-tetrahydropyranloxyl)pentyl malonate (XVII)

Sodium (0.200 g., 0.009 moles) was added to absolute ethyl alcohol (50 ml. distilled from sodium and diethyl phthalate)-contained in a three-necked, 100 ml. flask equipped with a reflux condenser and dropping funnel, both fitted with drying tubes. The stirred mixture was heated to 70°C. and freshly distilled diethyl malonate (1.1 g., 0.008 moles), dissolved in 20 ml. of dry ethanol was added, dropwise, over a period of one hour. When all the sodium had reacted, the pyran derivative (XVI) (1 g., 0.004 moles), dissolved in 10 ml. of dry ethanol, was added over a period of one hour. The mixture was then heated at 70°C. for an additional sixteen hours. The excess of ethanol was distilled off and the remaining reaction product was cooled to room temperature and diluted with 75 ml. of benzene. The benzene solution was washed with three 50 ml. portions of water, dried over anhydrous magnesium sulphate, filtered, and evaporated to dryness. The crude product (1.2 g.) was a clear, yellow oil. Column chromatography (Woelm silica gel activity grade 1 - 5% ether in benzene eluent) gave the desired material (0.750 g.) in a 58% yield.

A sample was sublimed at 110°C. and 0.7 mm. pressure for analysis. Calculated for $C_{18}H_{32}O_6$: C, 62.77% ; H, 9.36% ; O, 27.87%. Found: C, 63.4% ; H, 9.50% ; O, 27.15%.

Infrared spectrum no. 6: absorptions at 1720 $cm.^{-1}$. Nuclear magnetic resonance spectrum no. 7: absorptions at τ=8.72 and τ=5.88 (ethyl esters); τ=5.5 (acetal hydrogen); τ=9.1 (methyl doublet).

Isovaleryl chloride (XVIII)

In a three-necked, 100 ml., round bottomed flask equipped with a reflux condenser, a magnetic stirrer, a dropping funnel, and drying tubes was placed isovaleric acid (5.0 g., 0.05 moles) in dry benzene (50 ml.). Thionyl chloride (6.0 ml.) was added in dropwise style to the refluxing, stirred mixture over a period of fifteen minutes. The solution was heated under reflux for an additional two and one half hours and then allowed to cool to room temperature. The excess of thionyl chloride and benzene was removed from the reaction flask in vacuo, and in such a way as to avoid exposure of the reaction product to the atmosphere.

Diethyl 2-(4-methyl-5-2′-tetrahydropyranyloxylpentyl)-2-carbobenzyloxyglycine-malonate (XXI)

Carbobenzyloxyglycine (3.0 g., 0.014 moles) and triethylamine (1.1 g., 0.015 moles) were dissolved in toluene (50 ml. distilled over calcium hydride) contained in a dry, 250 ml., three-necked, round bottomed flask equipped with reflux condenser, dropping funnel

and calcium chloride drying tubes. The toluene solution was cooled to 0°C. and isovaleryl chloride (1.7 g., 0.015 moles) was added, dropwise, in a nitrogen atmosphere. The mixture was kept at 0°C. for one hour.

The diester (XXI) (2.6 g., 0.008 moles), dissolved in 20 ml. of benzene, was added, dropwise, to a stirred mixture of sodium hydride (0.37 g. of a 50% mineral oil dispersion) and dry benzene (50 ml.) at 70°C. contained in a 100 ml., dry, round bottomed, three-necked flask fitted with reflux condenser, dropping funnel, and drying tubes. The temperature was held at 70°C. for one hour and then the reaction flask was cooled to 0°C.

This diester anion solution was then added in dropwise fashion to the mixed anhydride of isovaleric acid and carbobenzyloxyglycine at 0°C. over a period of one and one half hours. The flask was stoppered and stored at 0°C. for sixteen hours.

The mixture was filtered, and the organic layer of the filtrate was washed with 1% sodium hydroxide solution (50 ml.) followed by 2% hydrochloric acid solution (50 ml.). The organic layer was dried over anhydrous sodium sulphate, filtered, and evaporated to dryness. The crude product was purified by chromatography (Woelm silica gel activity no. 1, 10% ether in benzene eluent) to give a yellow oil (0.46 g.) in an 11% yield.

Infrared spectrum no. 7: absorptions at 3420 $cm.^{-1}$; 1740 $cm.^{-1}$; 1500 $cm.^{-1}$; 1450 $cm.^{-1}$.

Nuclear magnetic resonance spectrum no. 8: absorptions at τ=2.72 (aromatic system); τ=4.68 (proton on nitrogen); τ=8.72 and τ=5.88 (ethyl esters).

7-Methyl-8(2'-tetrahydropyranyloxyl)-1-heptene (XXII)

Allyl chloride (1.0 g., 0.13 moles) dissolved in 10 ml. of dry ether was added, dropwise, to a stirred mixture of magnesium (0.33 g., 0.13 moles) in ether (10 ml.) contained in a dry, 50 ml., three-necked flask equipped with calcium chloride drying tubes and reflux condenser.

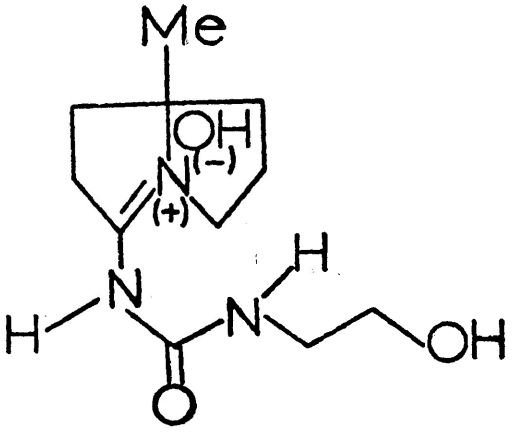
5-Bromo-2-methyl-1-(2'-tetrahydropyranloxyl) pentane (XVI) (1.0 g., 0.006 moles) dissolved in dry ether (10 ml.) was added in dropwise fashion to the Grignard reagent and the mixture was heated under reflux for twelve hours.

The reaction mixture was cooled to room temperature and washed with a saturated solution of ammonium chloride until the washings were neutral to litmus. The organic layer was dried over anhydrous sodium sulphate, filtered, and evaporated to dryness. The crude product (1.2 g.) was a clear, yellow oil.

Infrared spectrum no. 8: peak at 1640 cm^{-1} (C=C)
Nuclear magnetic resonance spectrum no. 10: absorptions at τ=9.1 (methyl doublet) and τ=5.0 (multiplet due to olefinic protons).

SPECTRA

PLATE I



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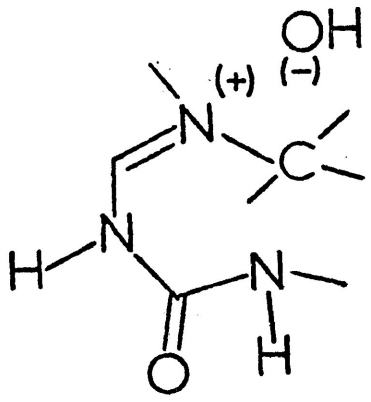

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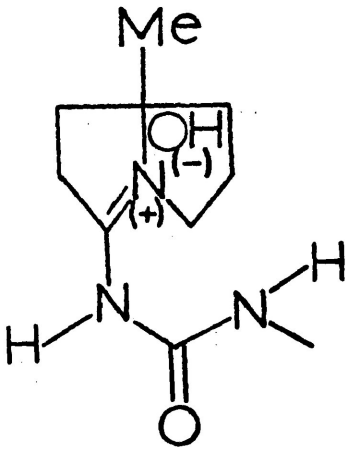

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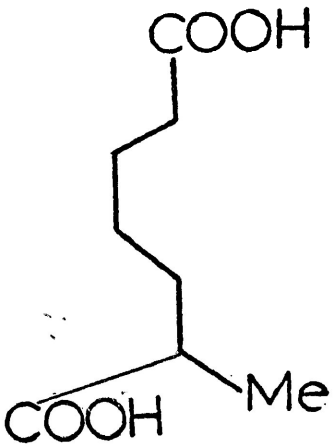

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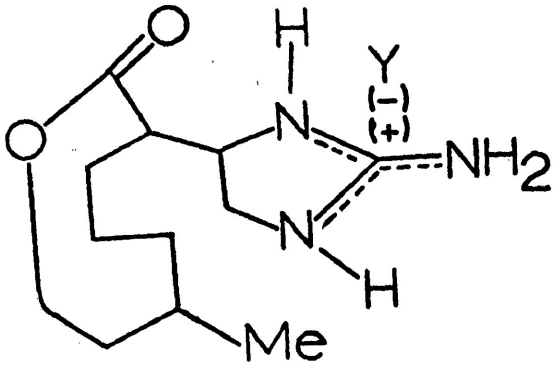

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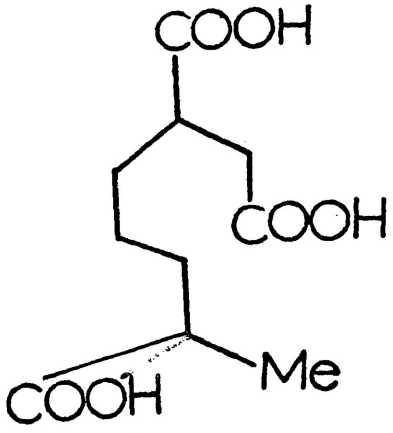

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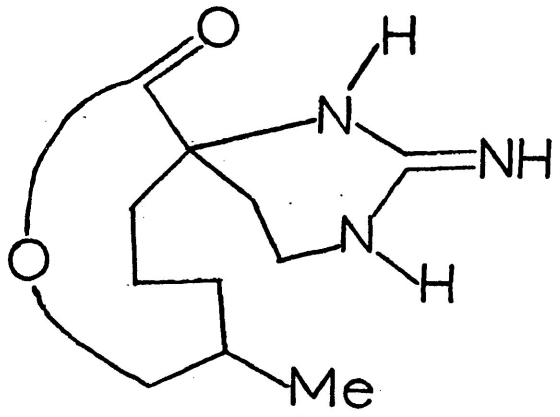
PLATE II



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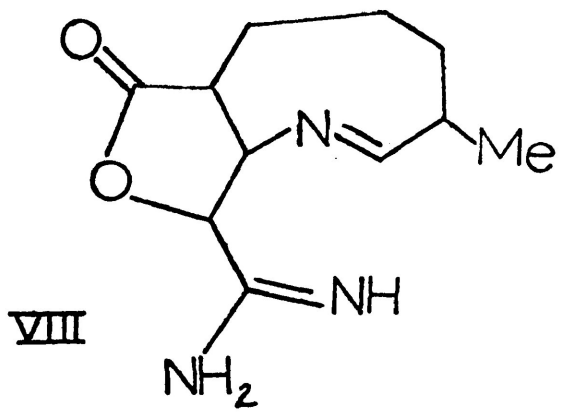

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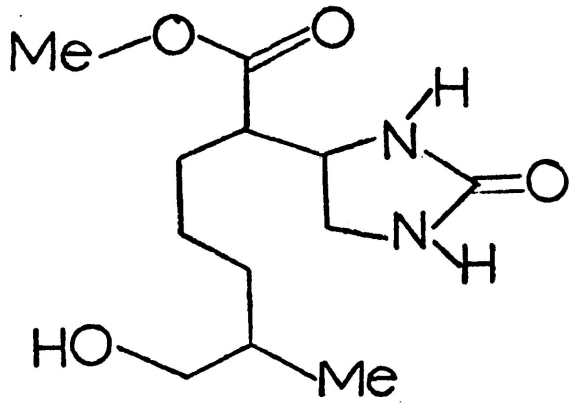

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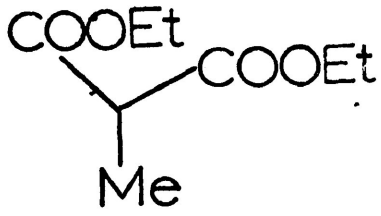

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XI

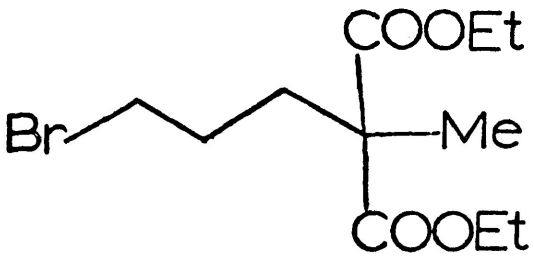

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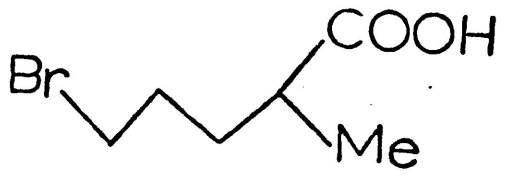
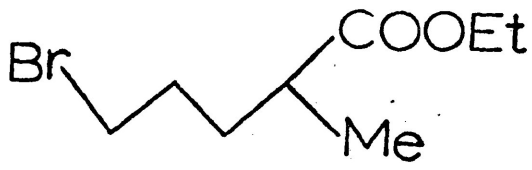
PLATE III



XIII



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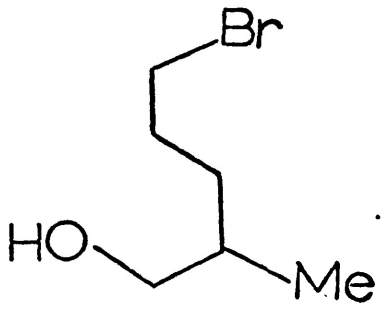

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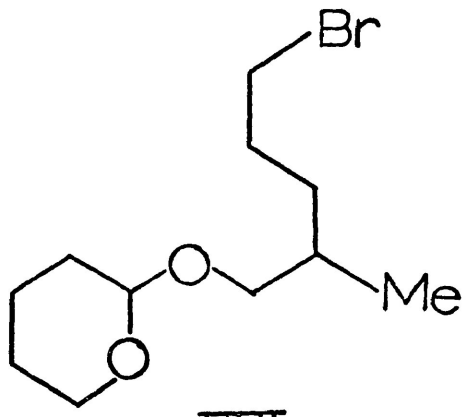

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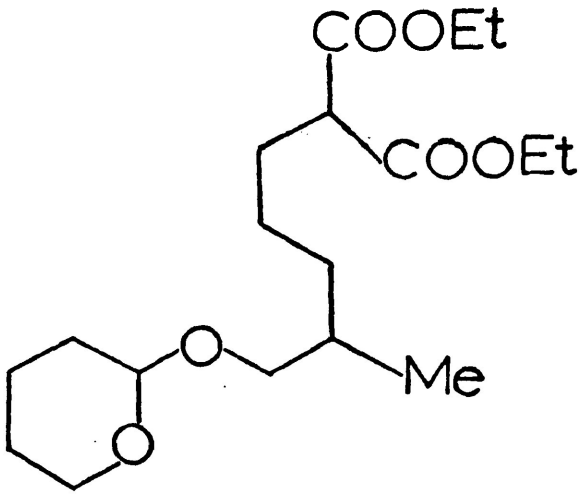

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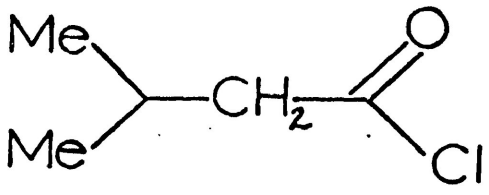
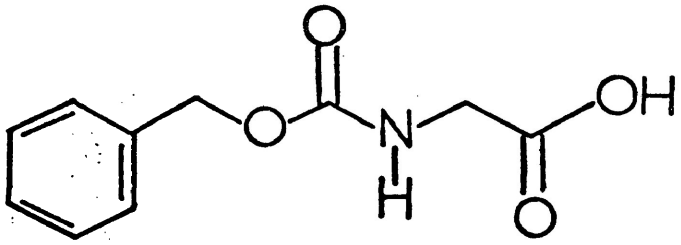


XVIII

PLATE IV



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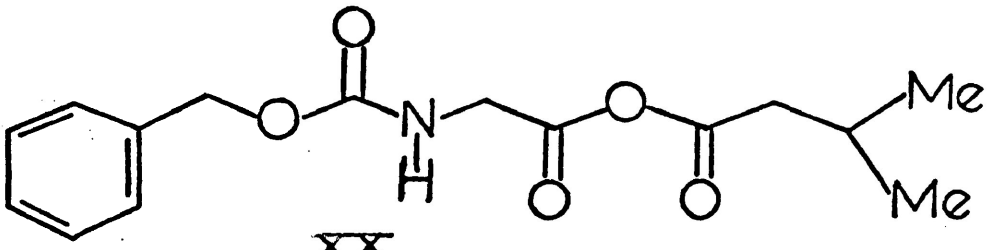

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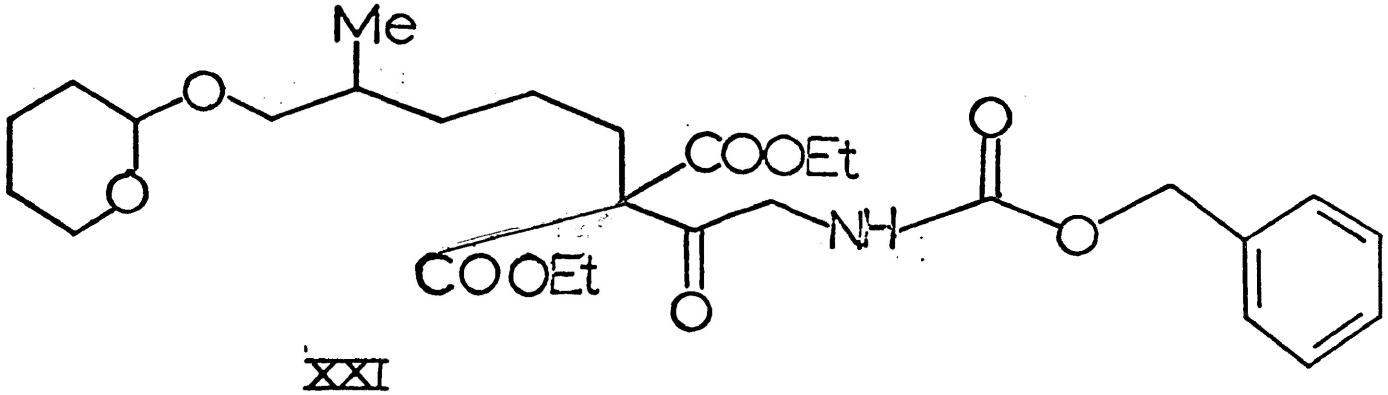

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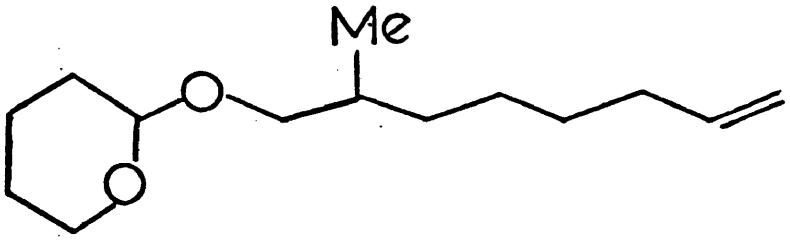


XXII

PLATE V

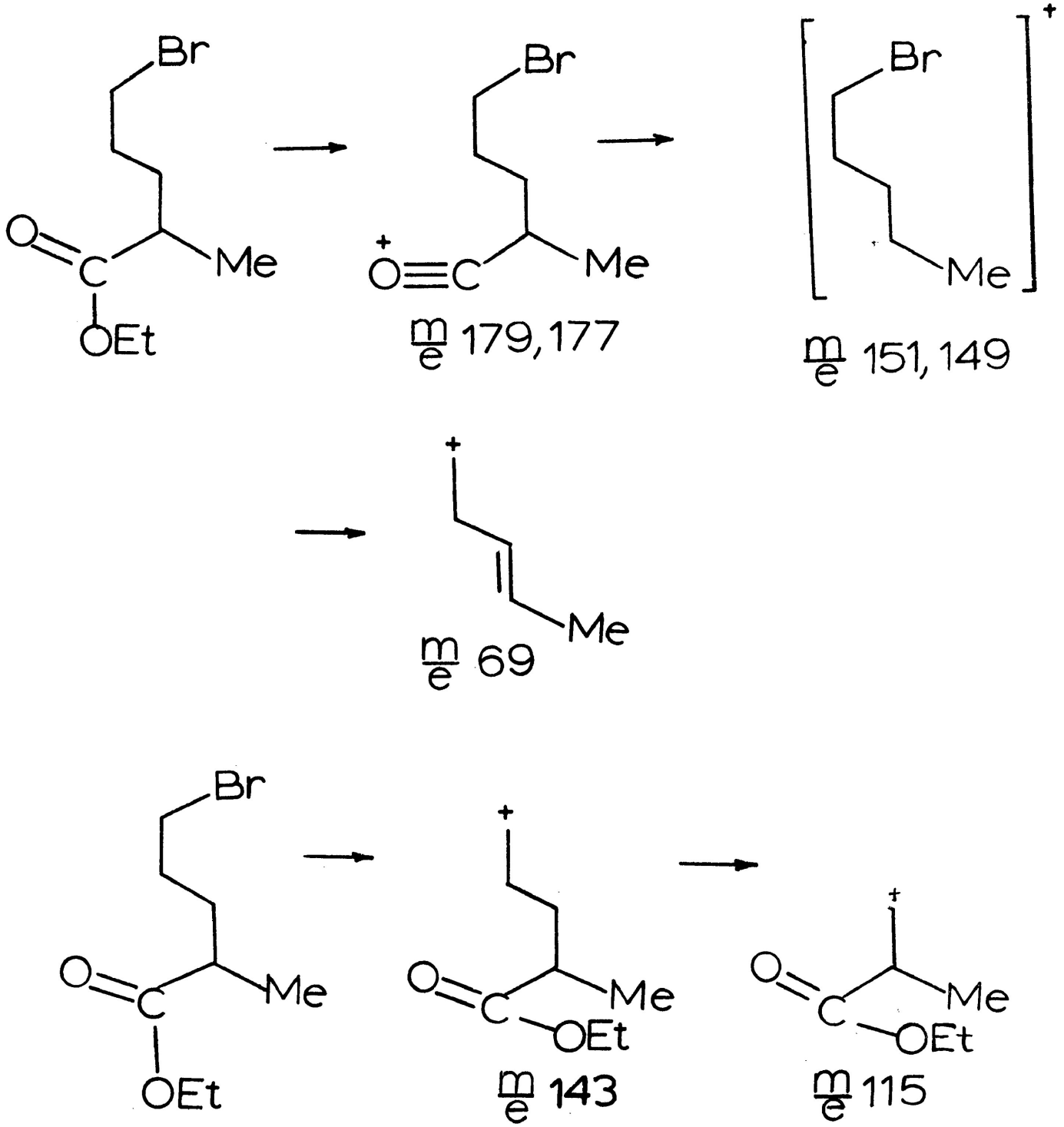

Br
O
C
Me
OEt
Br
+
O≡C
Me
m/e 179,177
Br
Me
+
m/e 151,149
+
Me
m/e 69
Br
O
C
Me
OEt
+
O
C
Me
OEt
m/e 143
+
O
C
Me
OEt
m/e 115

PLATE VI

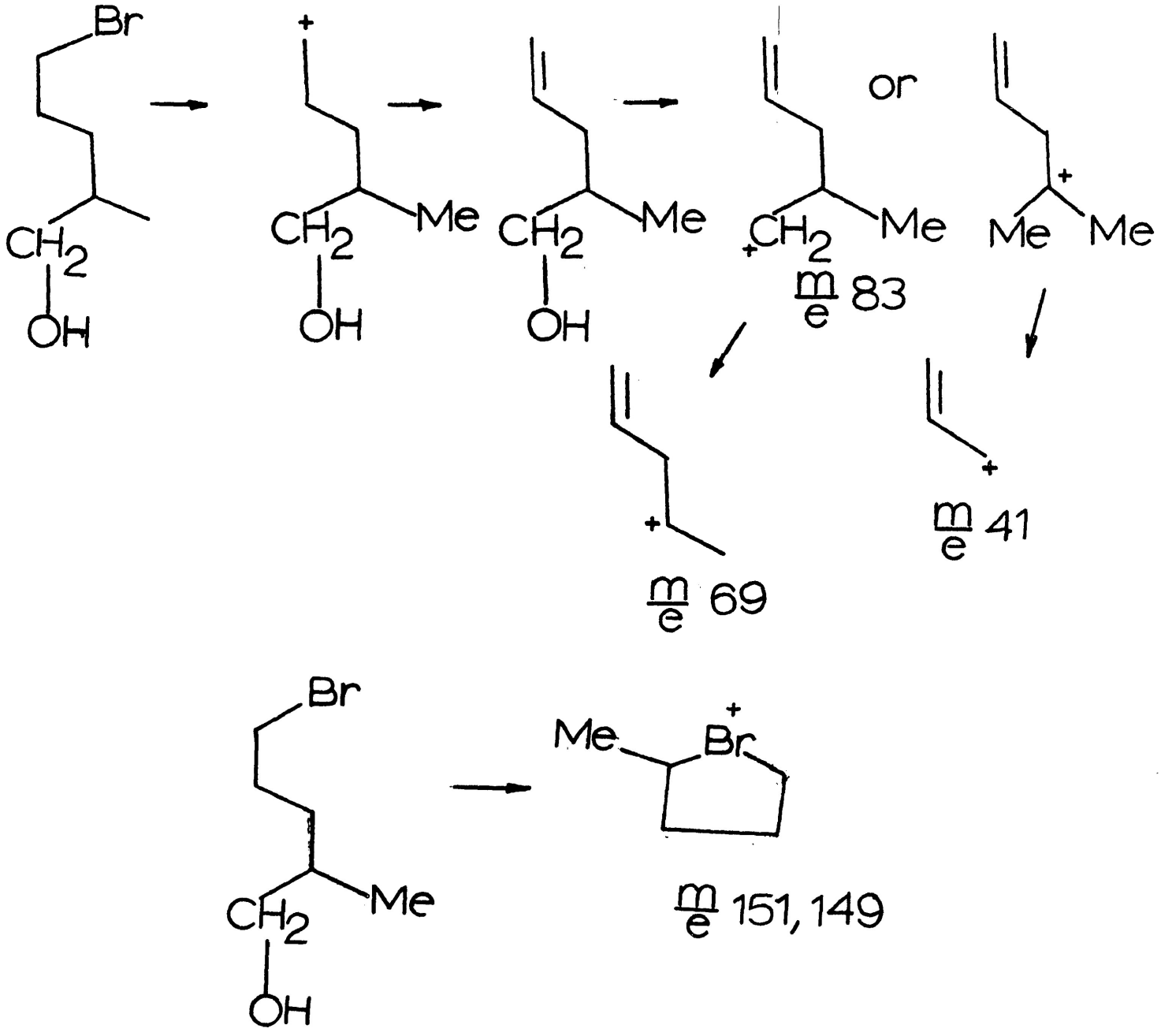

Br
CH2
OH
+
CH2
Me
OH
CH2
Me
OH
or
CH2
Me
m/e 83
Me
Me
+
+
m/e 69
+
m/e 41
Br
CH2
Me
OH
Me
Br
+
m/e 151, 149

PLATE VII

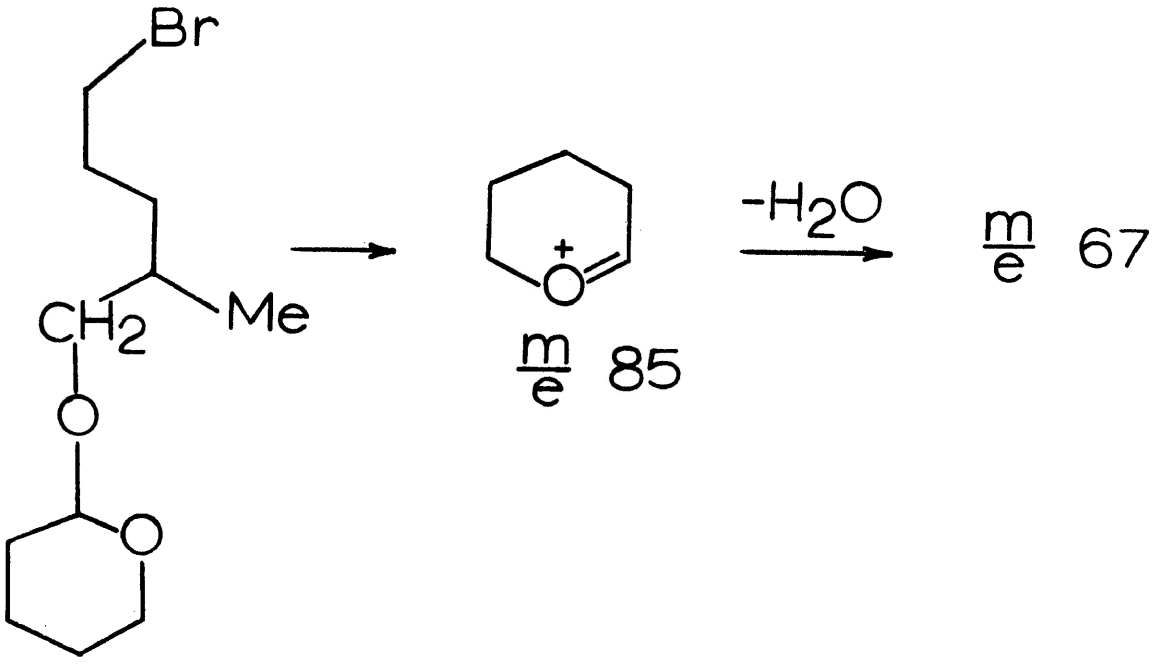
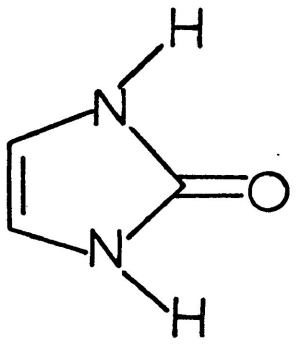
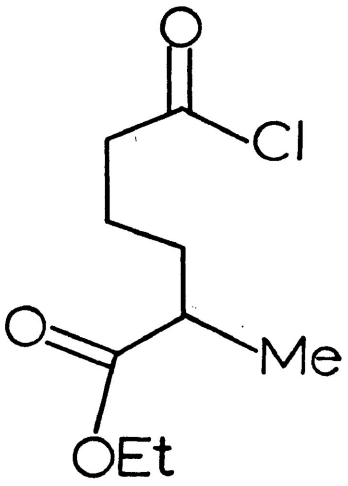


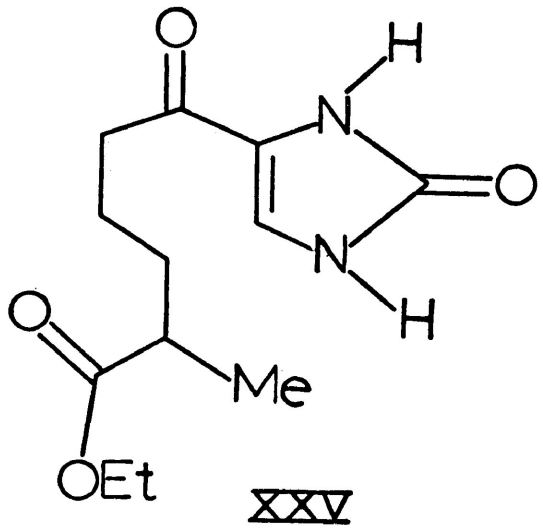
PLATE VIII



XXIII



XXIV



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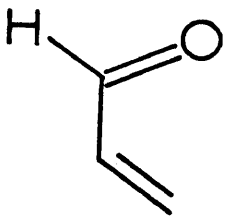

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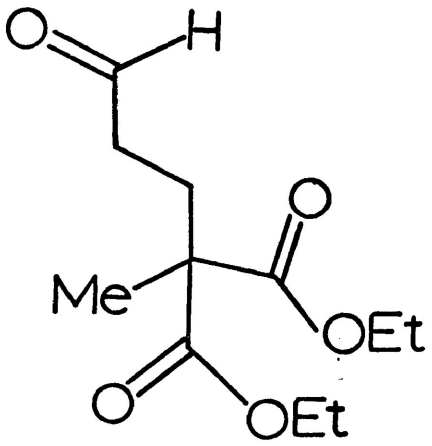

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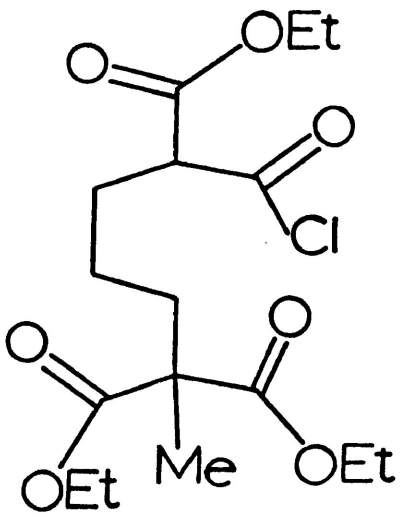
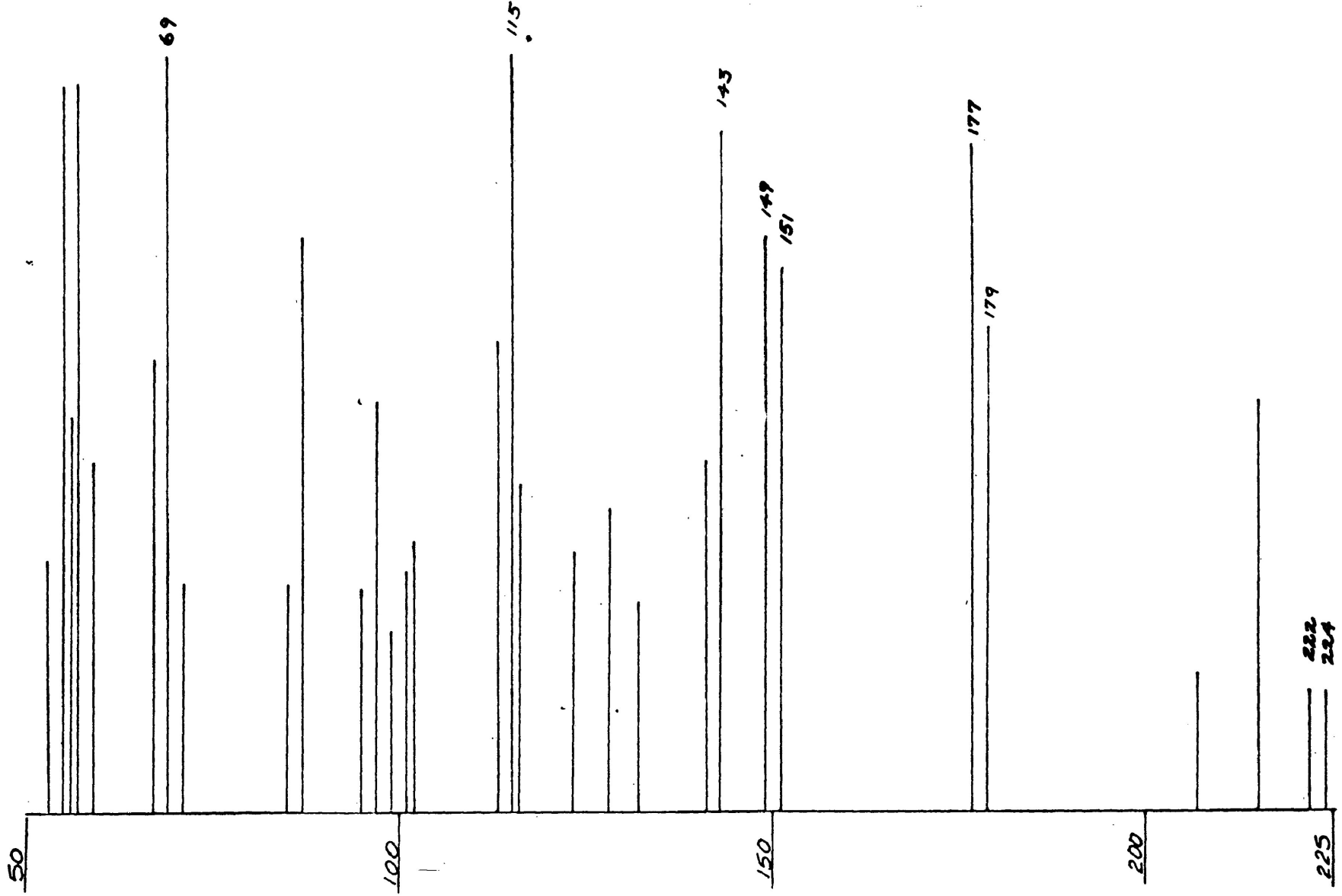
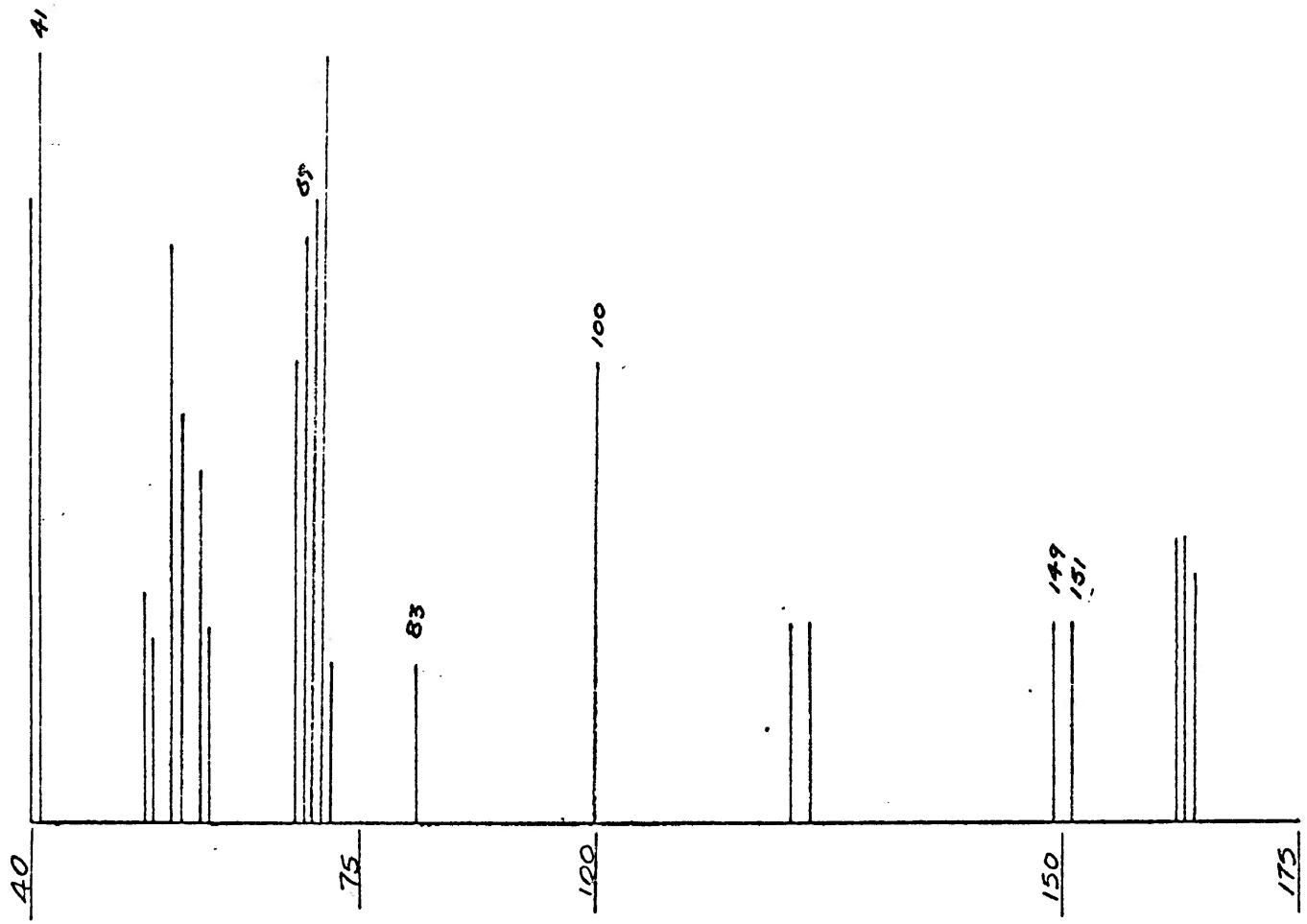


XXVIII



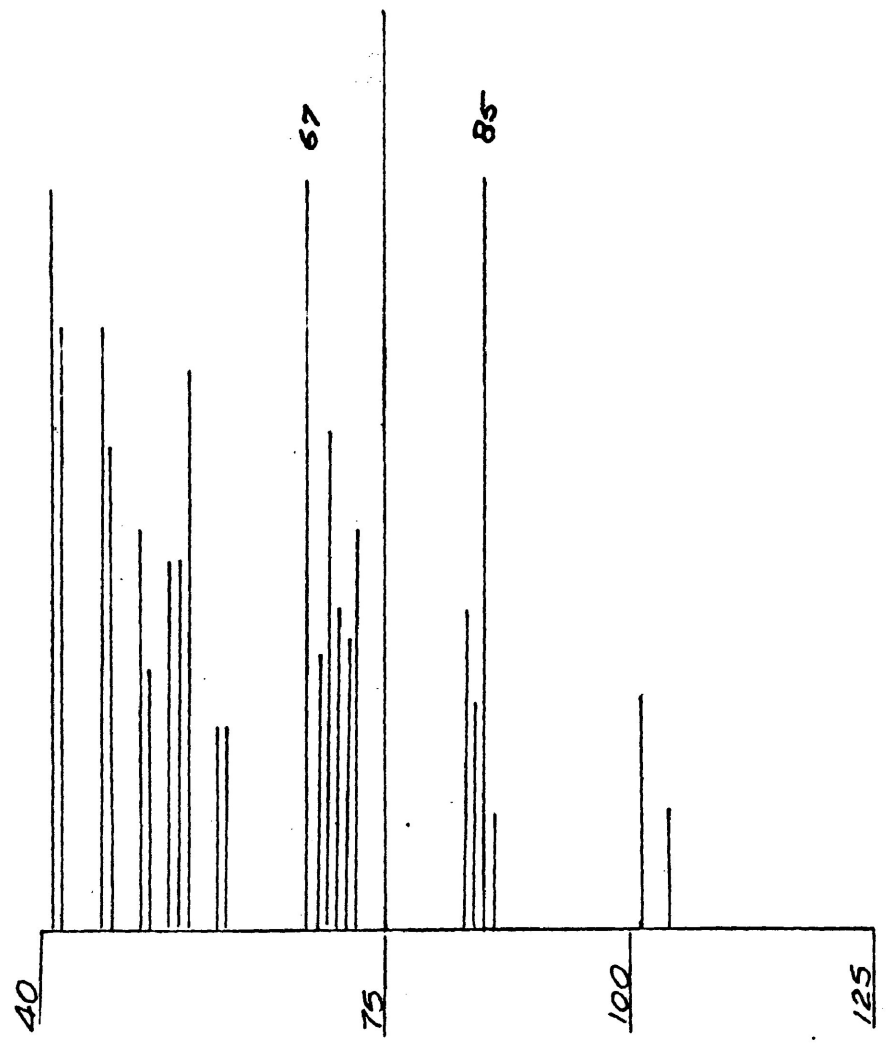
MASS SPECTRUM NUMBER : 1

NAME OF COMPOUND : Ethyl-5-bromo-2-methylpentonate XIII



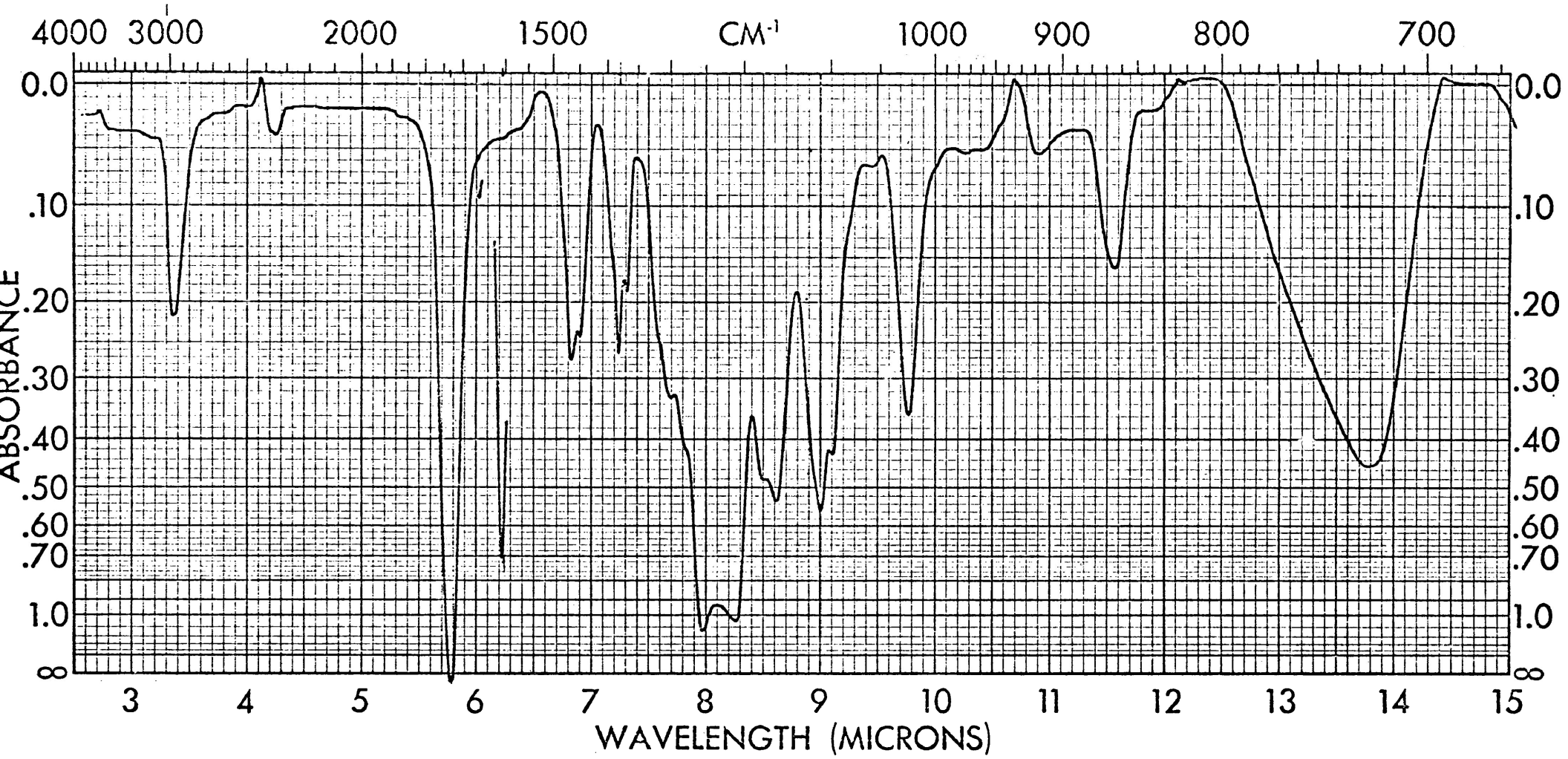
MASS SPECTRUM NUMBER: 2

NAME OF COMPOUND: 5-bromo-2-methylpentanol XV



MASS SPECTRUM NUMBER : 3

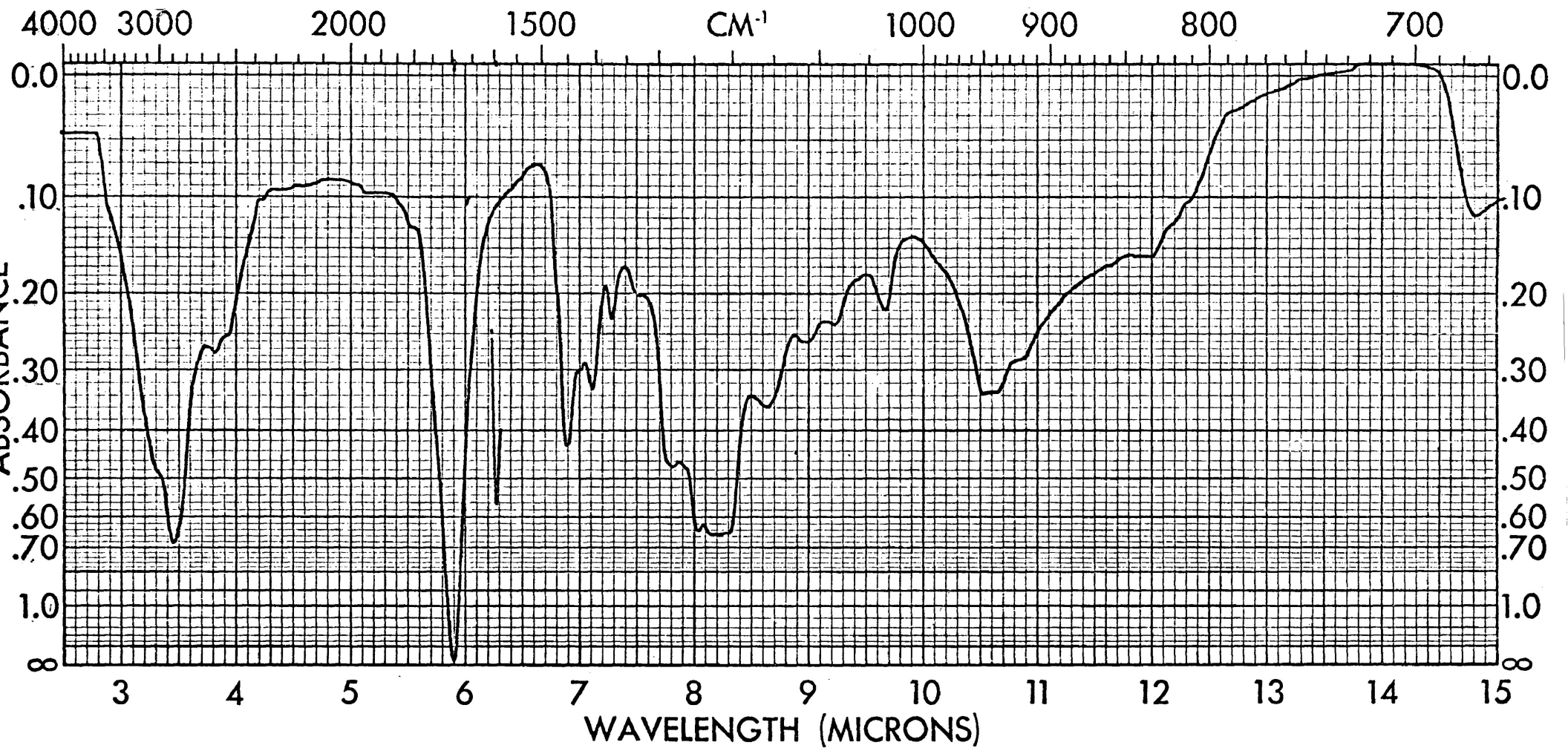
NAME OF COMPOUND: 5-bromo-2-methyl-1-(2′-tetrahydro pyranoxyl) pentane XVI



INFRARED SPECTRUM NUMBER : 1

NAME OF COMPOUND : Diethyl-2-(3-bromo propyl)-2-methyl malonate XII

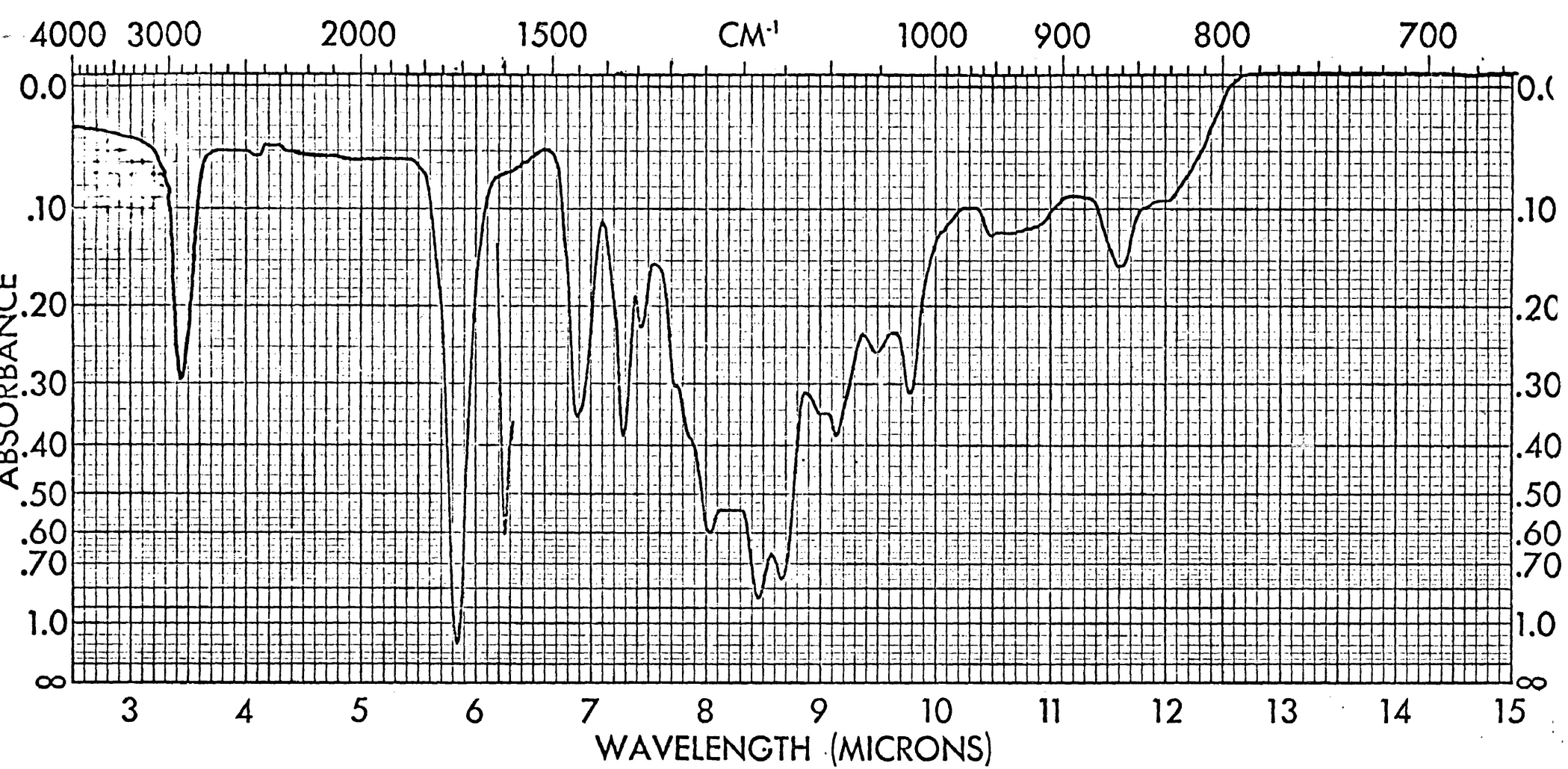
SOLVENT : $CHCl_3$



INFRARED SPECTRUM NUMBER: 2

NAME OF COMPOUND: 5-bromo-2-methyl pentanoic acid XIII

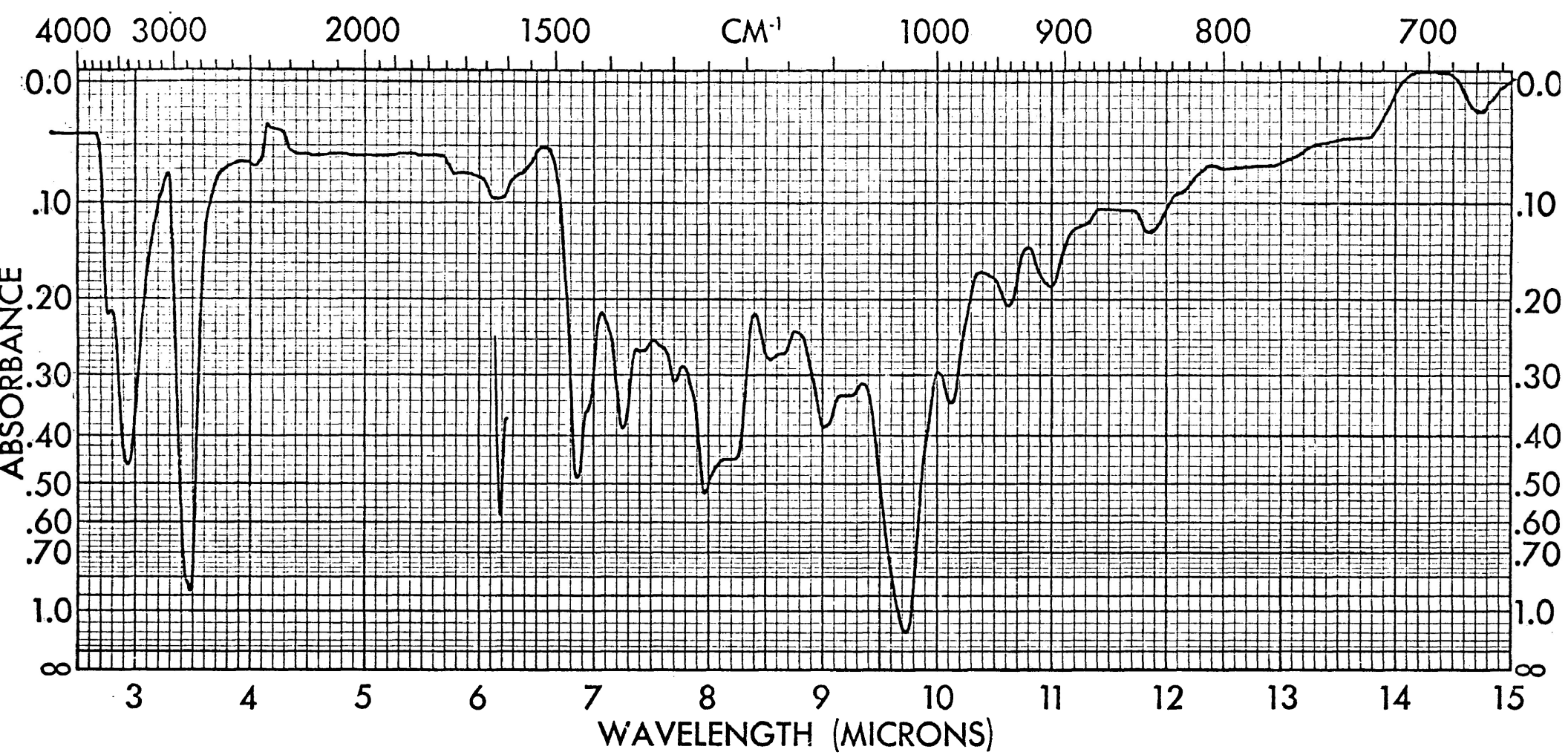
SOLVENT: $CHCl_3$



INFRARED SPECTRUM NUMBER : 3

NAME OF COMPOUND : Ethyl-5-bromo-2-methylpentonate XIV

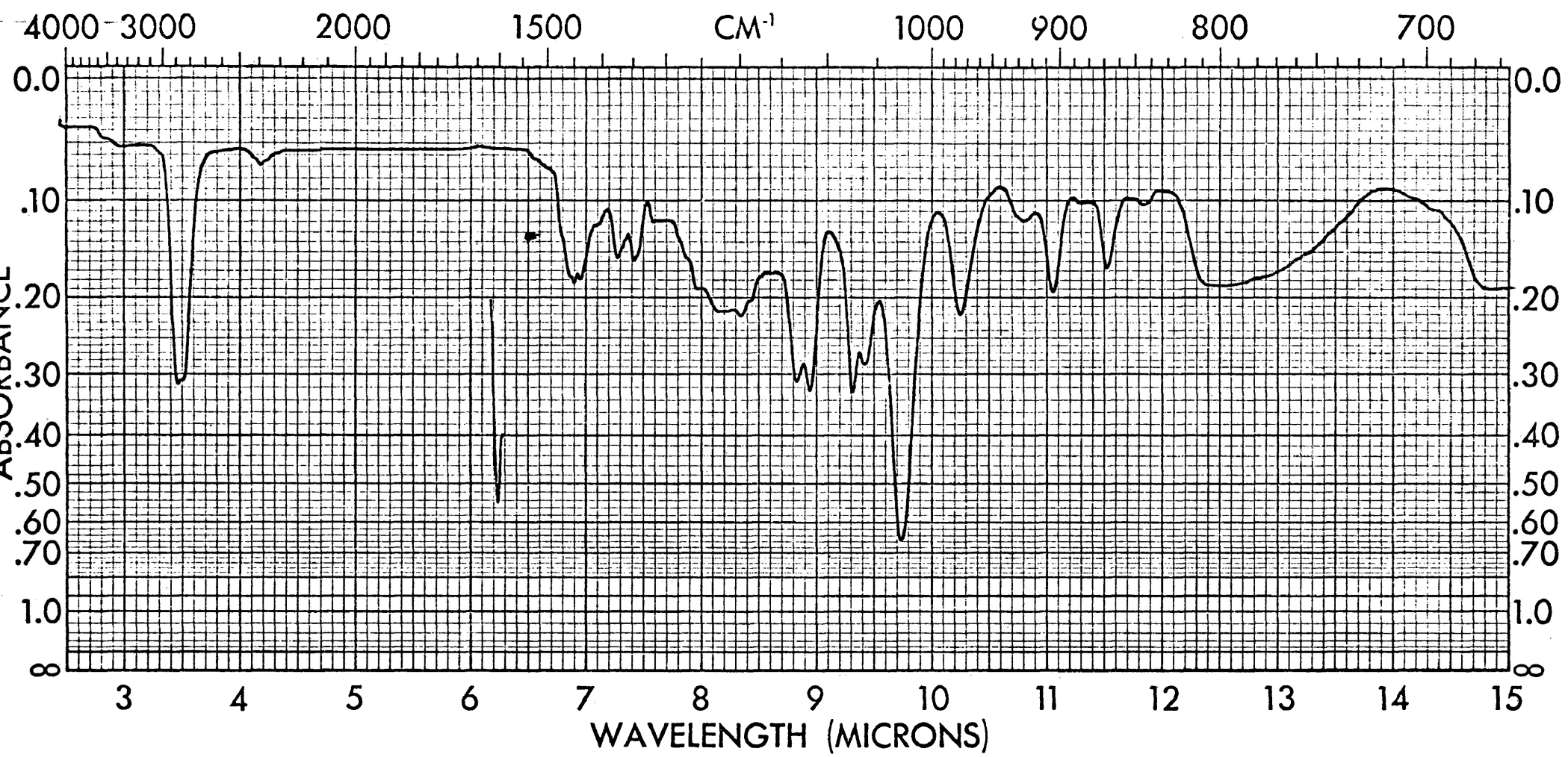
SOLVENT : $CHCl_3$



INFRARED SPECTRUM NUMBER: 4

NAME OF COMPOUND: 5-bromo-2-methyl pentanol XV

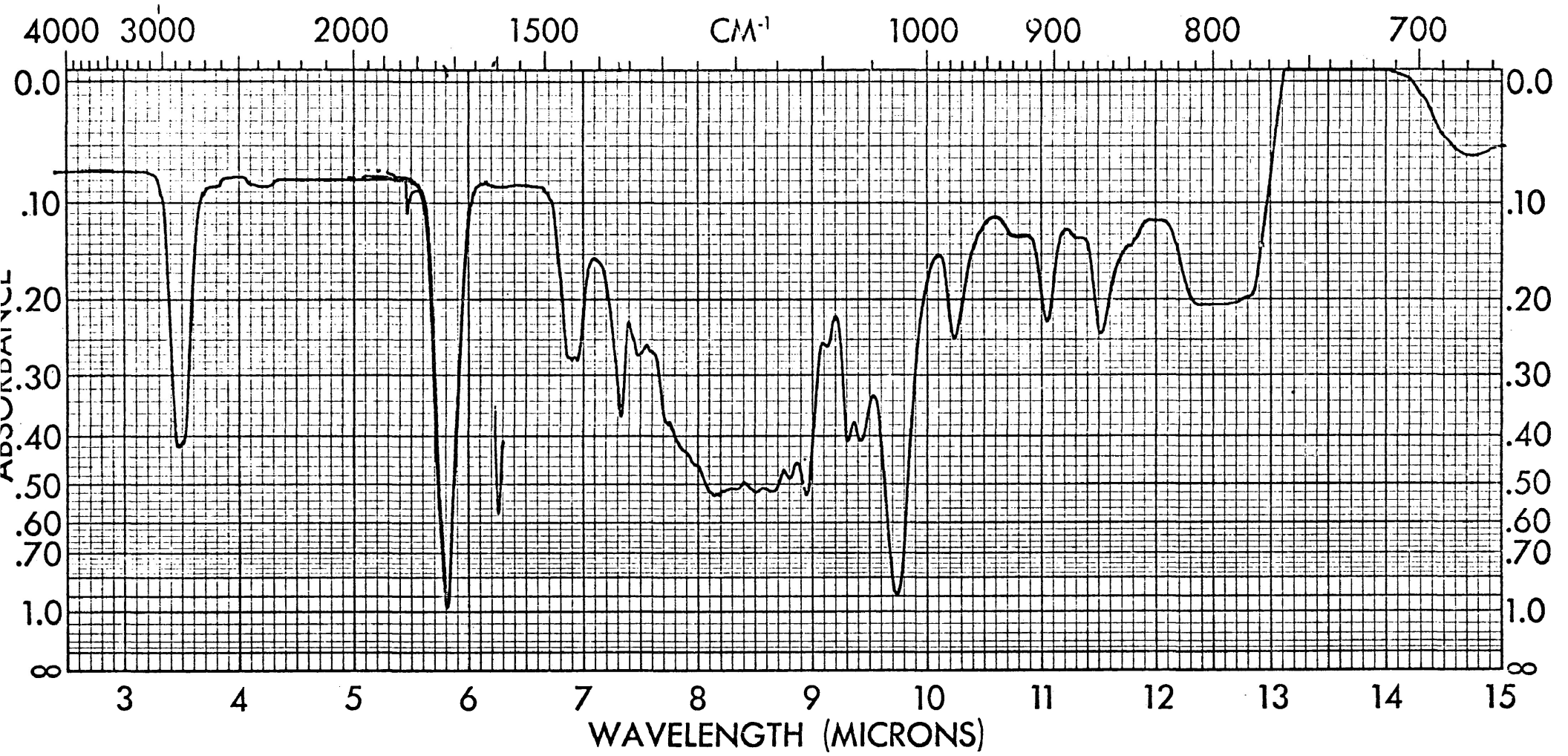
SOLVENT: $CHCl_3$



INFRARED SPECTRUM NUMBER: 5

NAME OF COMPOUND: 5-bromo-2-methyl-1-(2′-tetrahydro-pyranyloxyl) pentane XVI

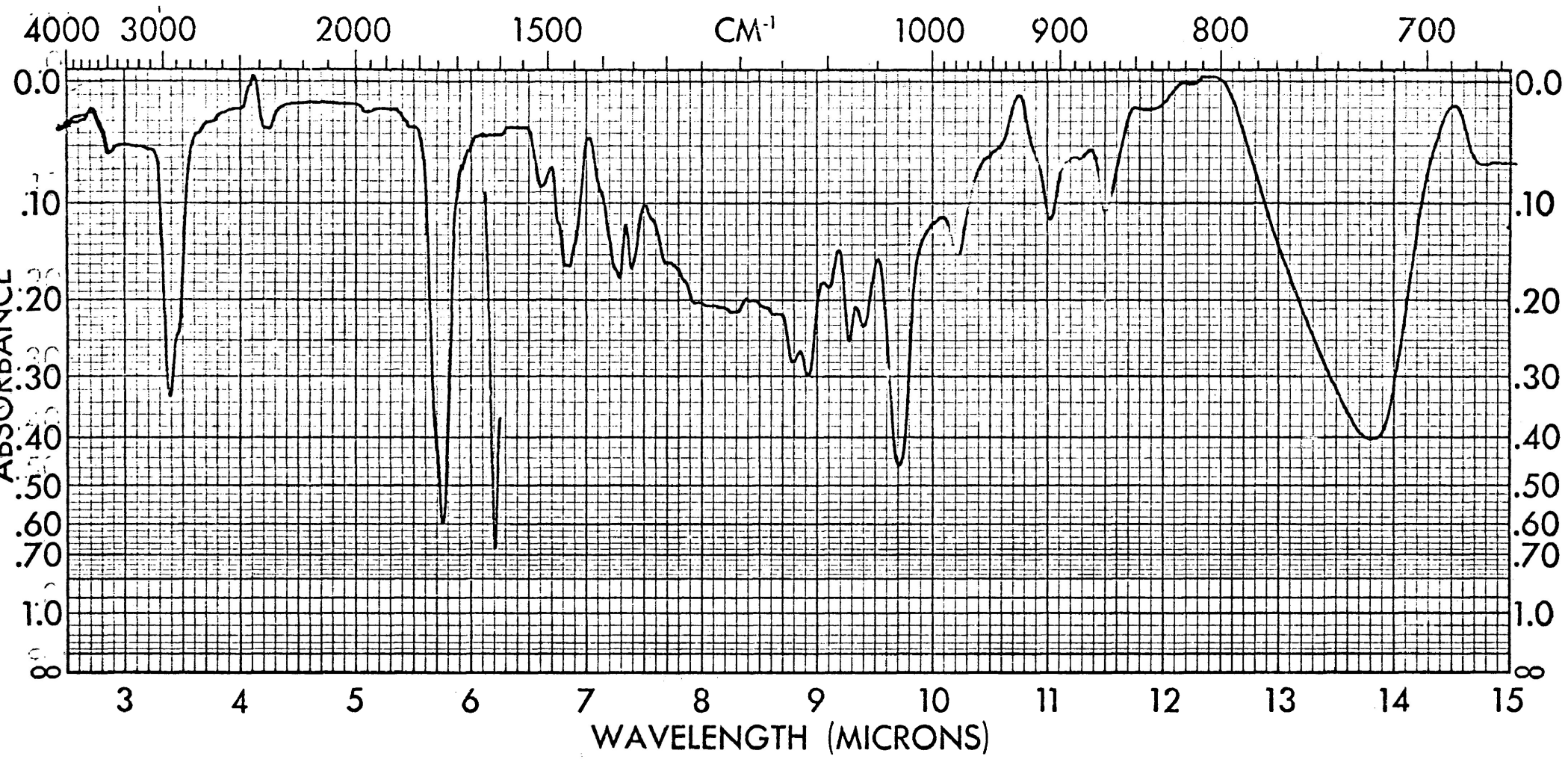
SOLVENT: $CHCl_3$



INFRARED SPECTRUM NUMBER: 6

NAME OF COMPOUND: Diethyl-2-(4-methyl-5-2′-tetrahydro-pyranyloxyl pentyl) malonate XVII

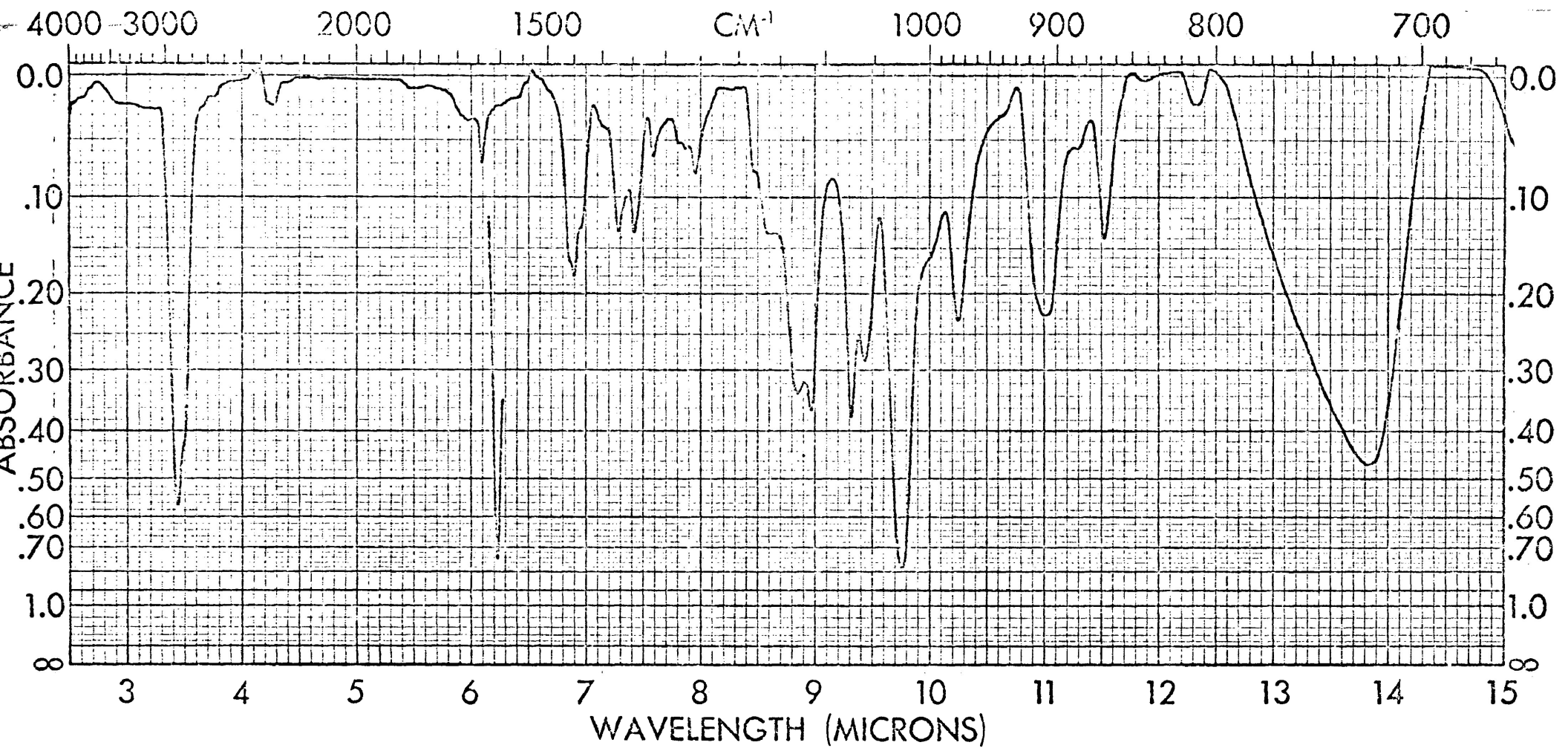
SOLVENT: $CHCl_3$



INFRARED SPECTRUM NUMBER : 7

NAME OF COMPOUND : Diethyl-2-(4-methyl-5-2´-tetrahydro-pyranyloxyl pentyl)-2-carbobenzyloxy glycine malonate XXI

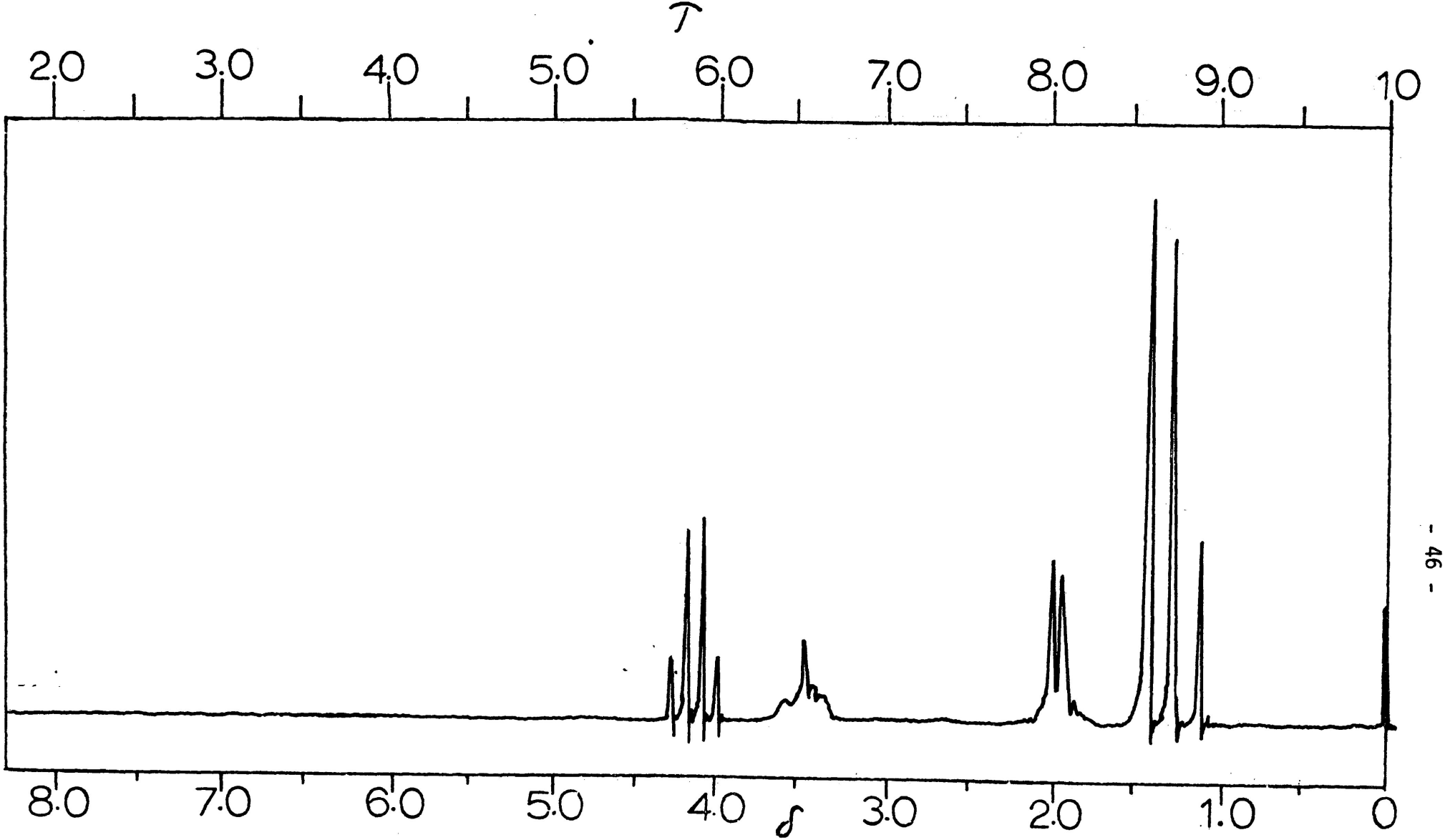
SOLVENT : $CHCl_3$



INFRARED SPECTRUM NUMBER : 8

NAME OF COMPOUND : 7-methyl-8(2′-tetrahydropyranyl)-1-heptene XXII

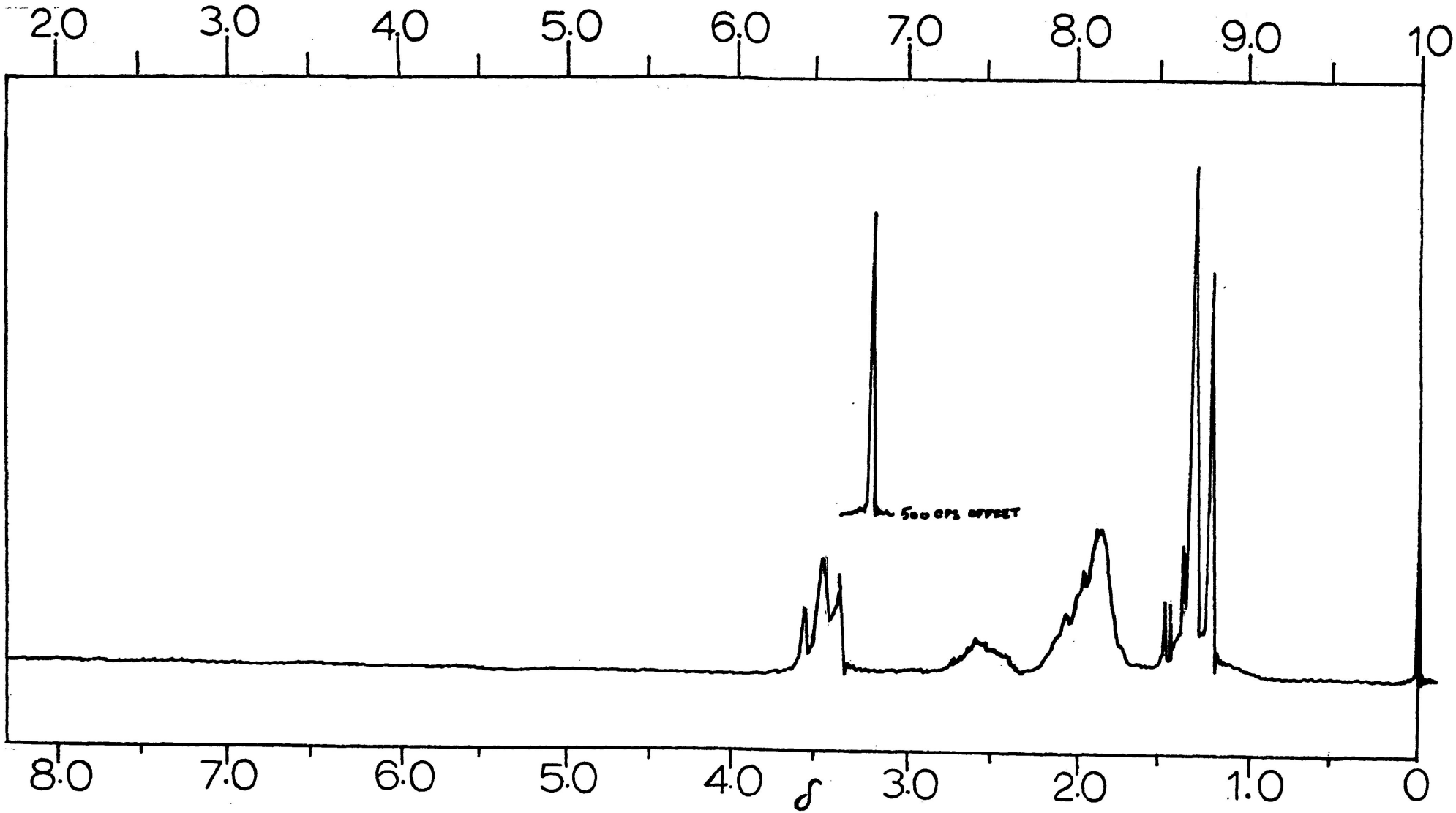
SOLVENT : $CHCl_3$



NMR SPECTRUM NUMBER : 1

NAME OF COMPOUND: Diethyl-2-(3-bromopropyl)-2-methyl malonate XII

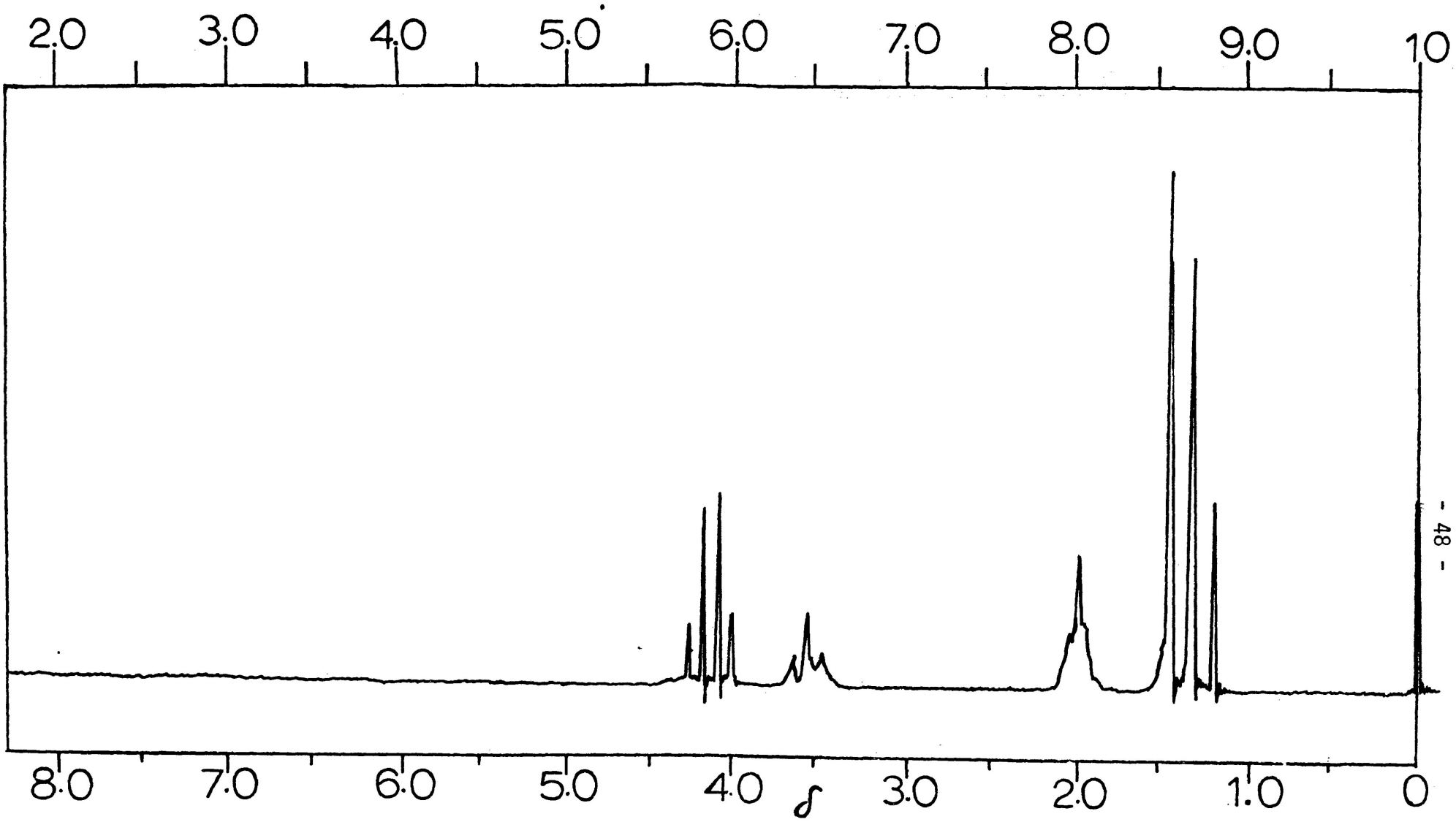
SOLVENT : CCl_4



NMR SPECTRUM NUMBER: 2

NAME OF COMPOUND: 5-bromo-2-methylpentanoic acid XIII

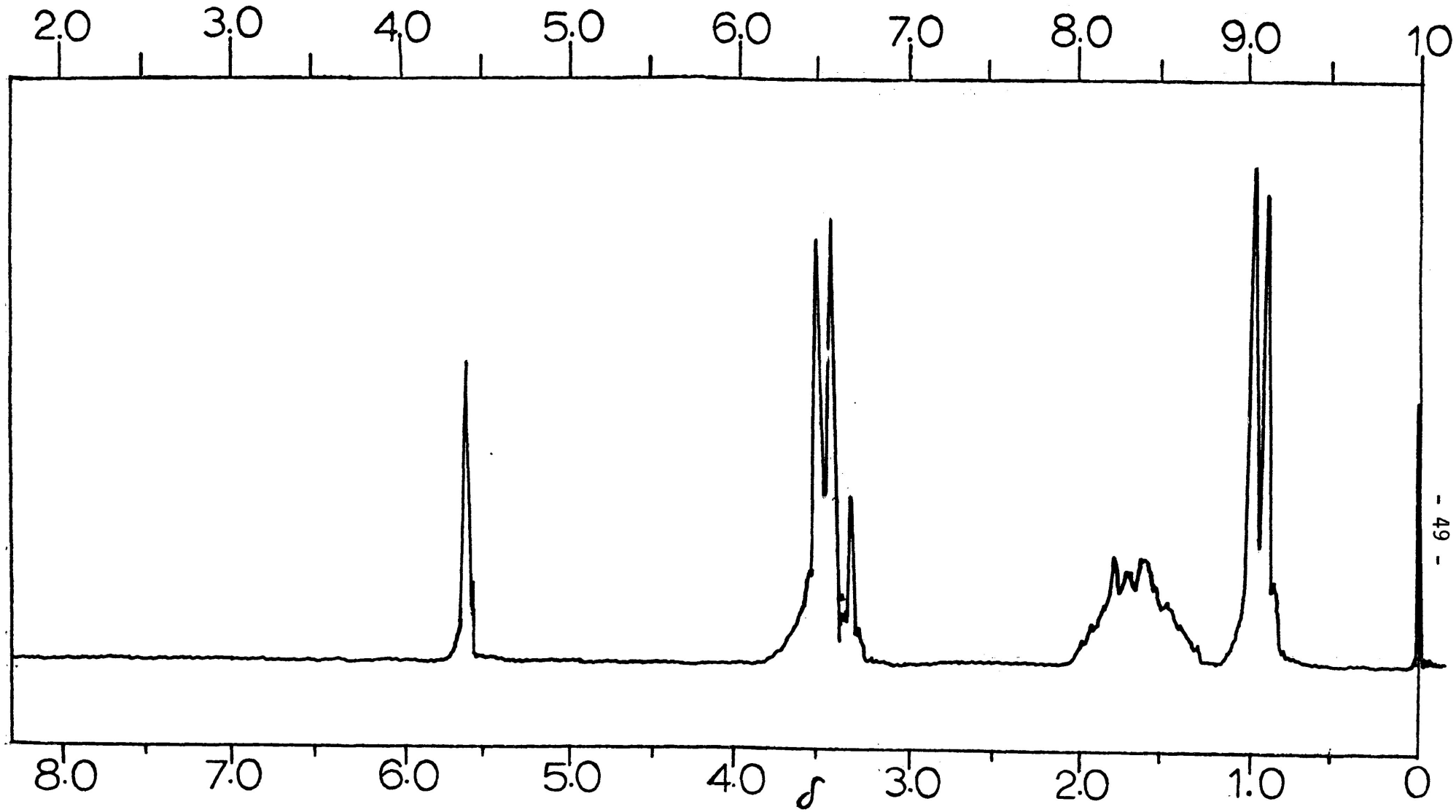
SOLVENT: CCl_4



NMR SPECTRUM NUMBER: 3

NAME OF COMPOUND: Ethyl-5-bromo-2-methylpentonate XIV

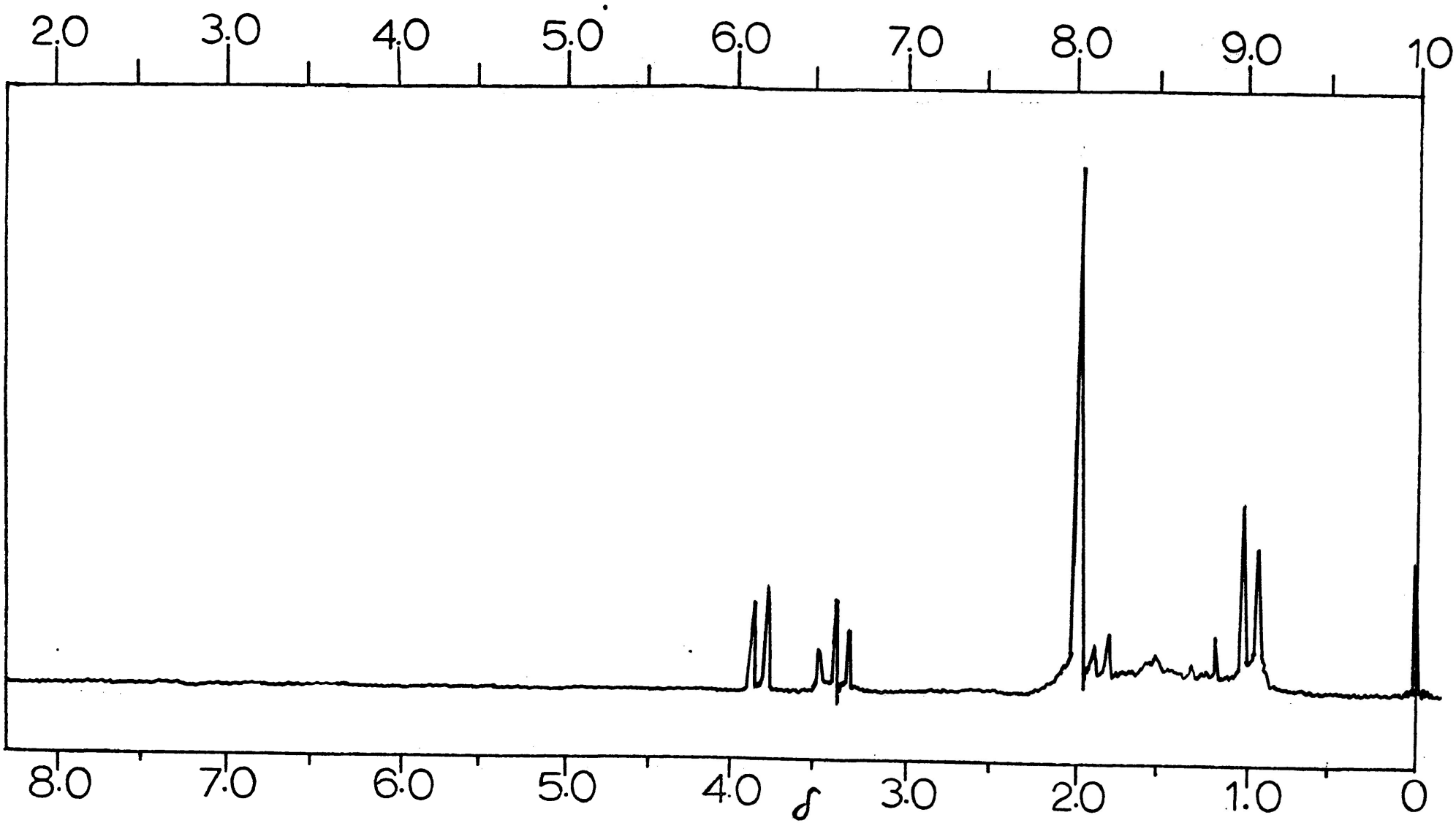
SOLVENT : CCl_4



NMR SPECTRUM NUMBER: 4

NAME OF COMPOUND: 5 - bromo - 2 - methylpentanol XV

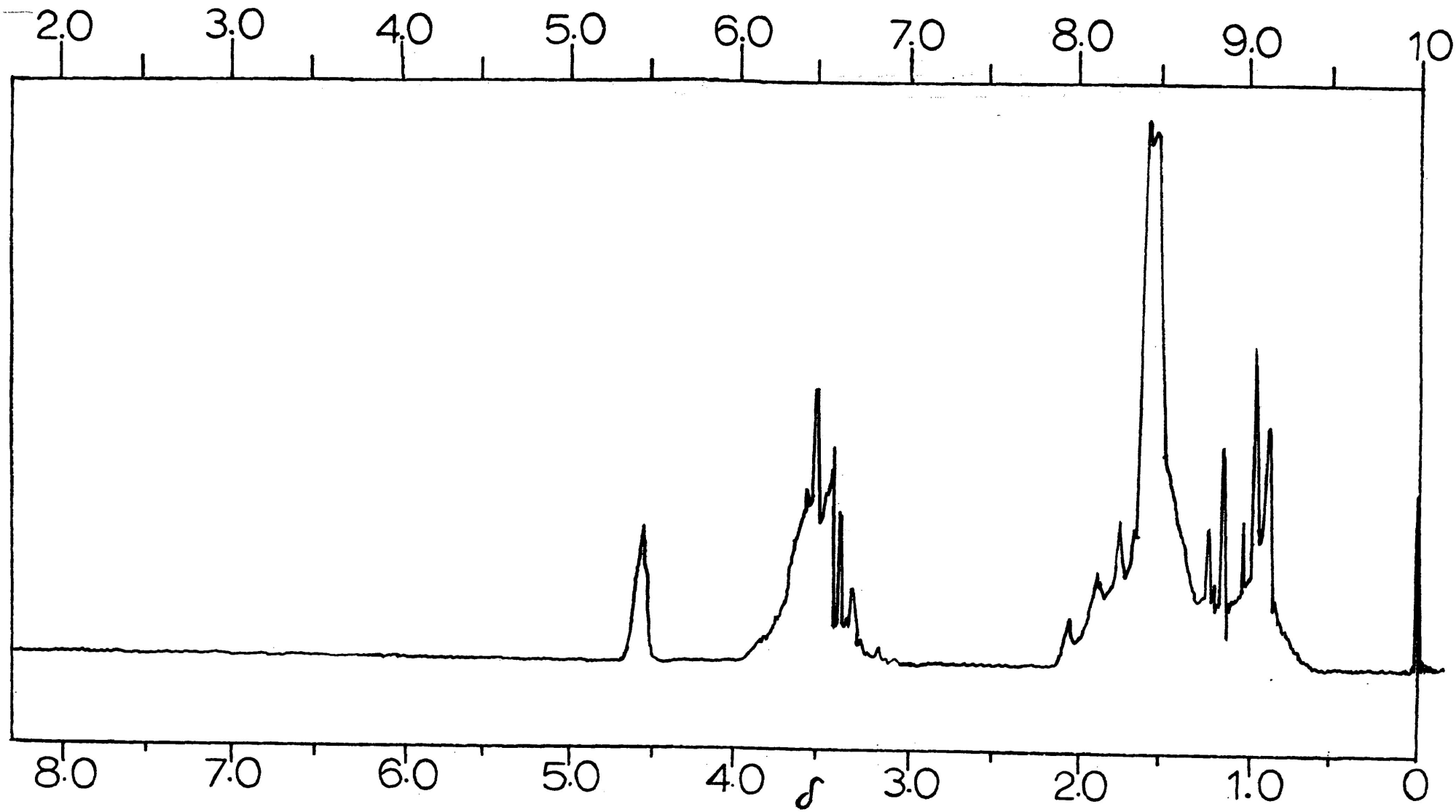
SOLVENT : CCl_4



NMR SPECTRUM NUMBER: 5

NAME OF COMPOUND: 5-bromo-2-methyl-1-acetoxy pentane

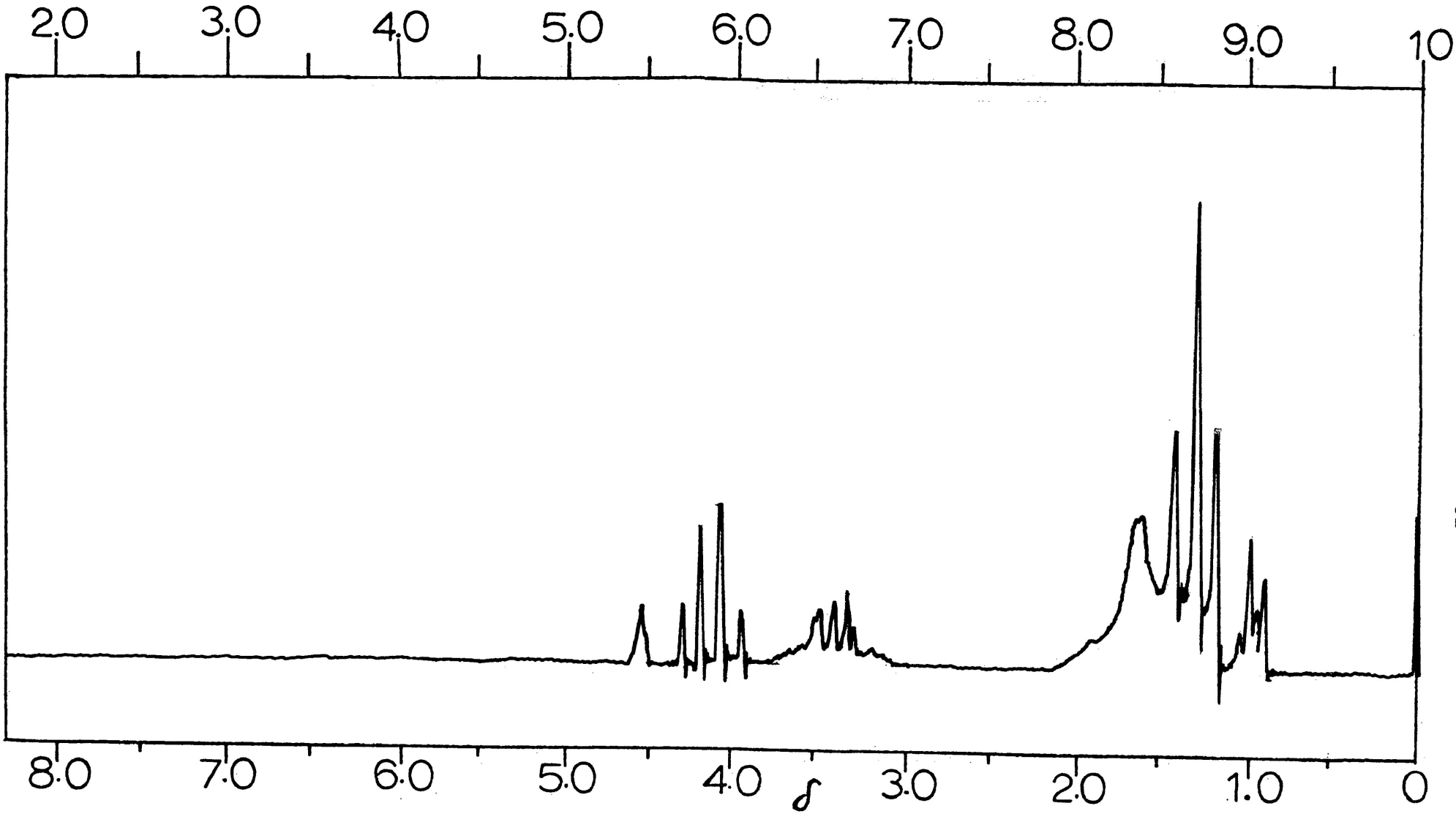
SOLVENT : CCl_4



NMR SPECTRUM NUMBER: 6

NAME OF COMPOUND: 5-bromo-2-methyl-1-(2'-tetrahydro pyranloxyl) pentane XVI

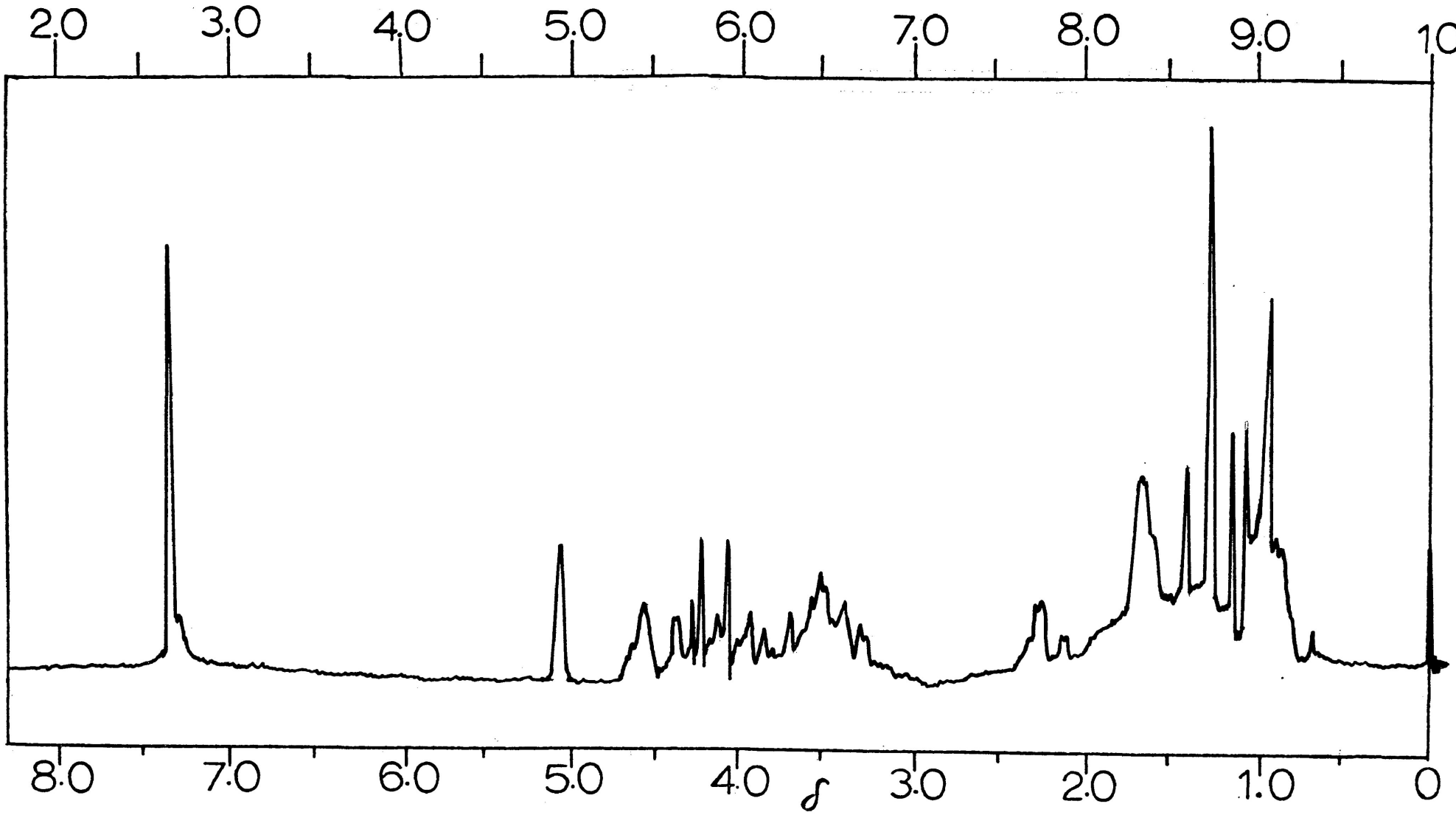
SOLVENT: CCl_4



NMR SPECTRUM NUMBER: 7

NAME OF COMPOUND: Diethyl-2-(4-methyl-5-2′-tetrahydro pyranyloxyl pentyl) malonate XVII

SOLVENT: CCl_4

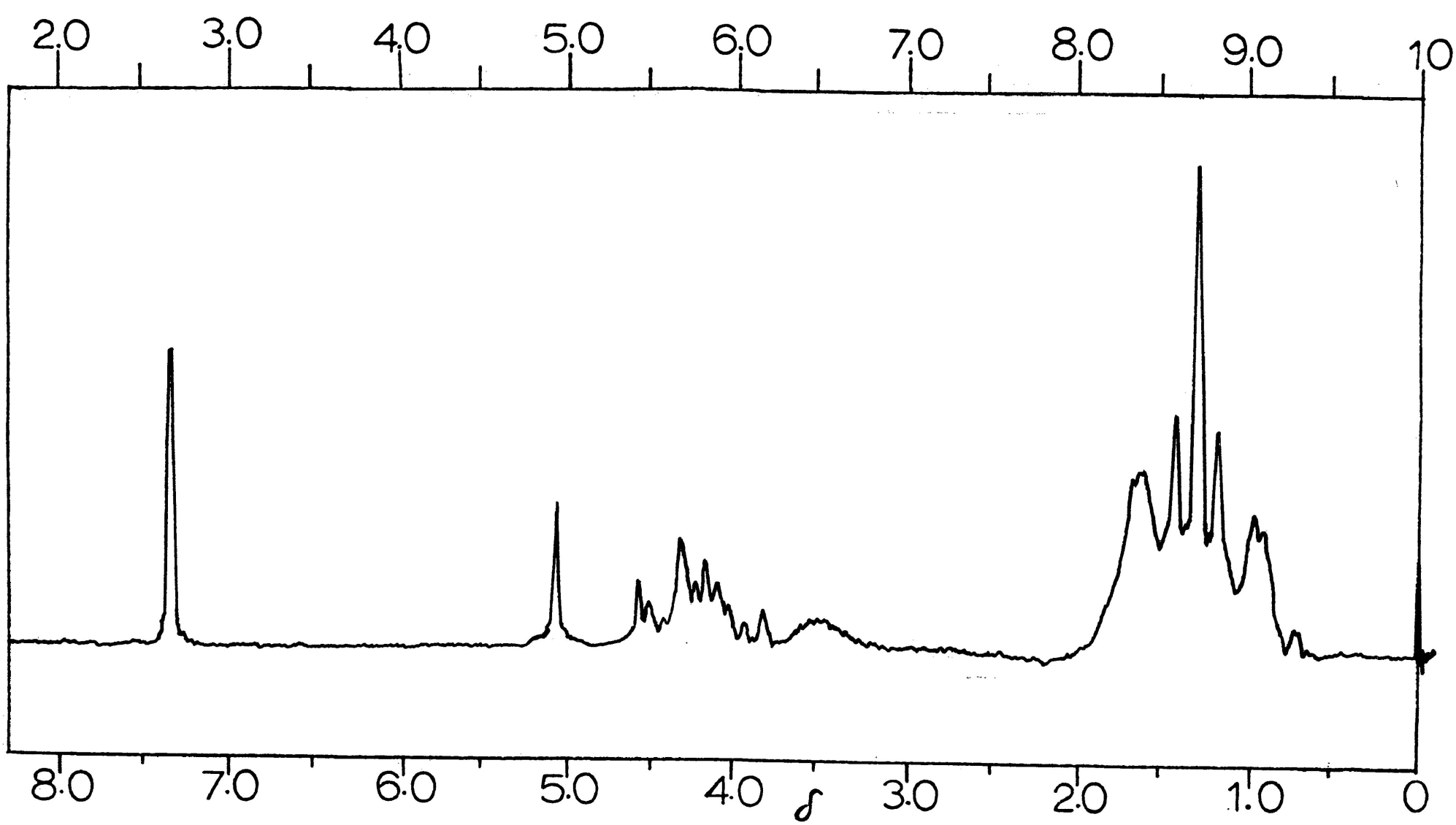


NMR SPECTRUM NUMBER: 8

NAME OF COMPOUND: Diethyl 2-(4-methyl-5-2′-tetrahydropyranyl oxylpentyl)-2-carbobenzyloxyglycine malonate

SOLVENT : CCl_4

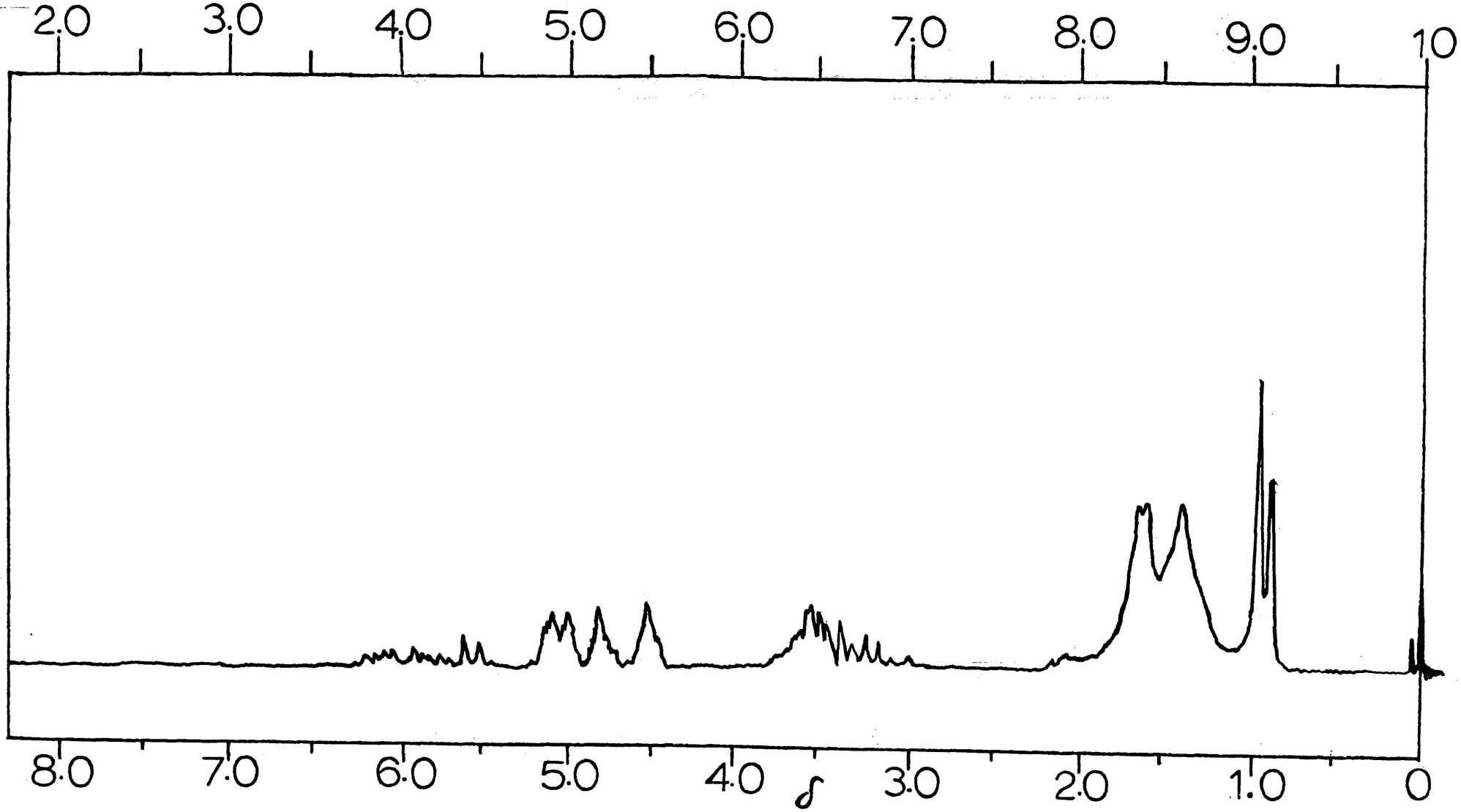
XXI



NMR SPECTRUM NUMBER: 9

NAME OF COMPOUND: Diethyl 2-(4-methyl-5-2′-tetrahydro pyranyloxyl pentyl)-2-N deutero-carbobenzyloxy glycine malonate

SOLVENT : CCl_4 & D_2O



NMR SPECTRUM NUMBER: 10

NAME OF COMPOUND: 7-methyl-8(2′-tetrahydropyranyloxyl)-1-heptene XXII

SOLVENT: CCl_4

REFERENCES

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ANALYTICAL AND PHYSICAL DATA

The infrared spectra were taken by the author, using a Perkin - Elmer Infrared Spectrophotometer, Model 137. Solution spectra were taken in sodium chloride cells (0.1 mm.).

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

$$\tau = 10 - \frac{(Me_4Si) \cdot 10^6}{\text{oscillator frequency (Hz.)}}$$

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