SYNTHETIC STUDIES TOWARDS TERRARUBEIN

by

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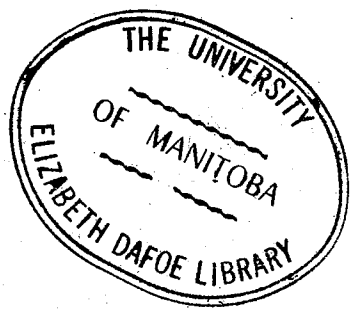

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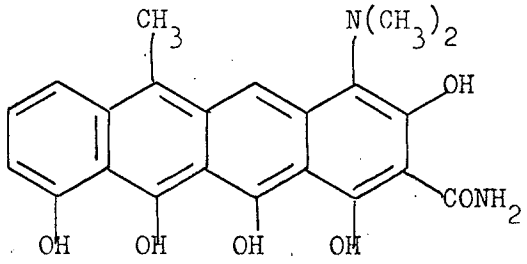
The author also would like to express her appreciation for the financial support in 1968-69 from the University of Manitoba.

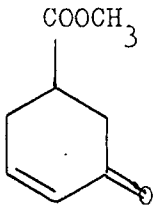
ABSTRACT

An intermediate to an important compound terrarubein (XIV) was prepared. Methyl cyclohex-2-ene-1-one-5-carboxylate (XLI) was synthesized from 3,5-dihydroxybenzoic acid through high pressure hydrogenation, methylation with diazomethane and sodium borohydride reduction. The ethylene acetal of 2-methoxy-6-(3-hydroxypropyl)-benzaldehyde (LXVI) was synthesized from 1,7-dihydroxynaphthalene (LVII) through the following sequence: methylation with dimethyl sulfate, followed by dissolving metal reduction, acid hydrolysis, acetylation, ozonolysis, methylation with diazomethane, acetal formation and lithium aluminum hydride reduction. Attempts to convert the corresponding alcohol (LXVI) to the olefin (LXVIII) by pyrolyzing the corresponding acetate, benzoate and tosylate were unsuccessful. However, the indene (LXXV) was prepared from the ester (LXIV) by Dieckmann condensation. The bicyclic compound (XLV), the aromatic ring of which is similar to that of terrarubein (XIV), a distant relative of tetracycline, was synthesized from the condensation of the isoxazole (XLII) and the cyclohexenone (XLI) with sodium hydride in anhydrous tetrahydrofuran followed by methylation with diazomethane. The conversion of the

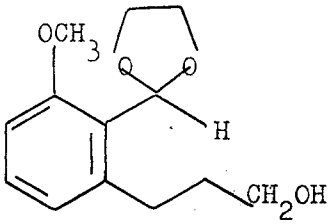
tetralone (XLV) to terrarubein (XIV) will be studied other students.



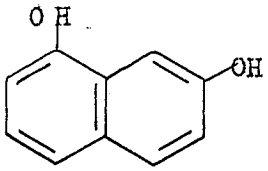
XIV



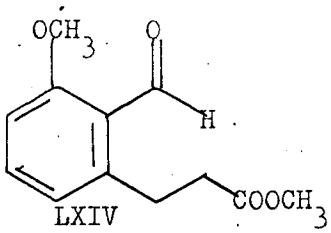
XLI



LXVI



LVII



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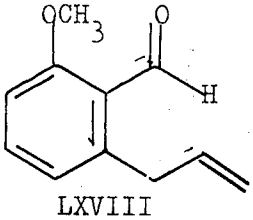

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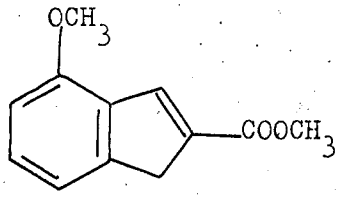
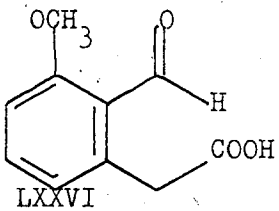
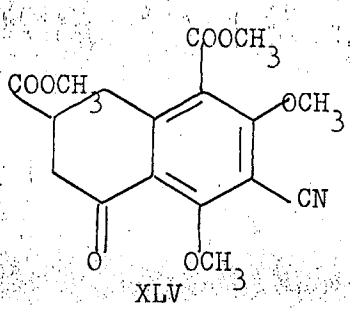


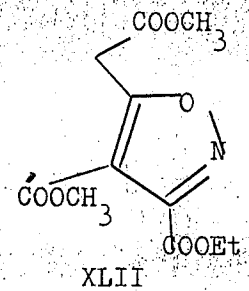
LXXV



LXXVI



XLV



XLII

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INTRODUCTION

Tetracyclines are pale yellow crystalline solid with antibiotic activity. They are produced from various strains of Streptomyces and have a tetracyclic skeleton of the general structure as shown in Scheme 1. Examples are:

Aureomycin	I	R=H	R_1=Cl
Terramycin	II	R=OH	R_1=H
Tetracycline	III'	R=R_1=H	
7-bromotetracycline	IV	R=H	R_1=Br

The first tetracycline, aureomycin (I) (chlorotetracycline), was isolated in 1948 by Duggar[1]. It was obtained from Streptomyces aureofaciens. Streptomyces is a common inhabitant of soil from which antibiotics, notably streptomycin, aureomycin, terramycin and neomycin, are obtined. In 1950, Finlay[2] prepared terramycin (II) from fermentation of Streptomyces rimosus. Tetracycline (III) was obtained from hydrogenolysis of chlorotetracycline in 1953[3]. In 1957, McCormick[4] found a family of tetracyclines which have no methyl group attached to the C-6 position, e.g. demethylchlorotetracycline (V).

Tetracyclines are widely used in clinical practice. Similar to Penicillin, tetracycline is effective against

both gram-positive and gram-negative bacteria[5]. It is also active against rickettsiae and viruses such as members of lymphogranuloma[5]. Tetracyclines act principally by interfering with the normal protein synthesis of the microorganism.

Due to the wide application of tetracycline in medicine, extensive research has been performed in the past twenty years. The main research in tetracycline chemistry is divided into three branches.

(a) Isolation and determination of structures of new tetracyclines.

(b) Degradative studies of naturally occurring tetracyclines and studies of their antibiotic activity.

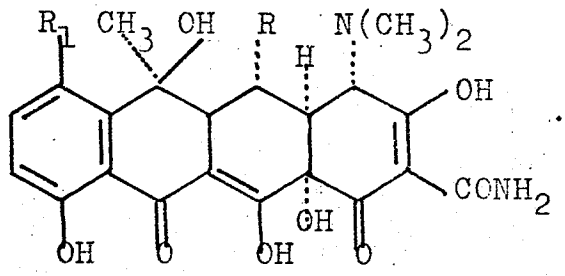
(c) Total synthesis of tetracycline or its biologically active derivatives.

The first tetracycline whose structure was completely elucidated was terramycin (II), reported by Woodward et al[7,8] in 1952 and 1953. This structural assignment was furthur substantiated by x-ray study[9]. The biological conversion of 1,3,10,11,12-pentahydroxynaphthacene-2-carboxamide (VII) to the antibiotic[10] illustrates the close relation of tetracycline to naphthacene[10].

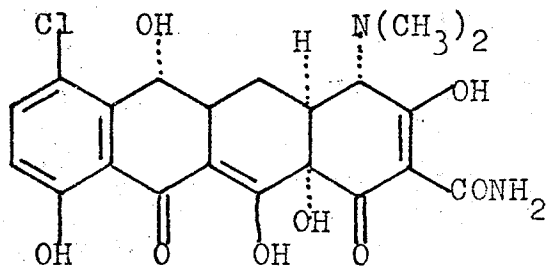
The antibiotic activity of tetracycline depends on the structure and stereochemical features of (VI). Variations other than in the stereochemistry of R_1, R_2, R_3, R_4, cause a decrease or complete elimination of the biological activity[11].

Epimerisation at positions 4 and 5a results in complete loss of activity while inversion at C-6 affects the biological activity slightly. It was also shown that the carboxamide substituent at the C-2 position is also essential. Replacement of the carboxamide by cyanide or acetoxy group reduces the activity greatly. Removal of 12a hydroxy group also removes the biological activity [12].

Fermentation of a non-chlorinating mutant of Streptomyces aureofaciens produces 7-chloro-6-demethyltetracycline (IX) from a substituted pretetramid (VIII). Pretetramid (X) was also converted to 6-demethyltetracycline (XI) by using non-chlorinating mutants of Streptomyces aureofaciens[10]. Similarly, both 6-methyl-pretetramid (XII) and terrarubein (XIV) gave the corresponding tetracyclines. However, it seems pretetramid is a better precusor than terrarubein because the latter gave a lower yield of tetracycline than the former[10].



SCHEME 1. I, II, III, IV.



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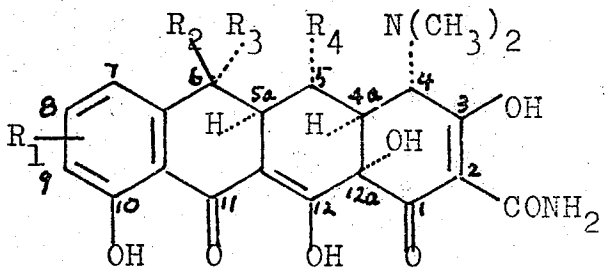
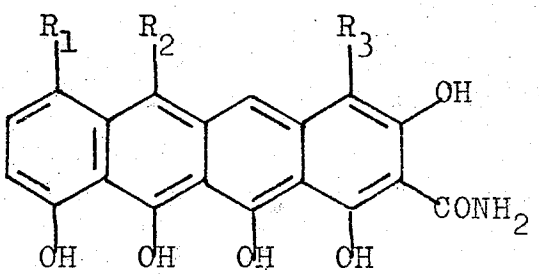
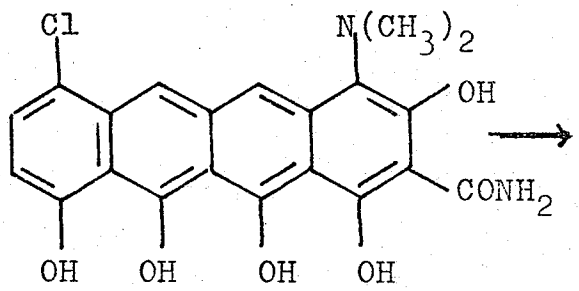


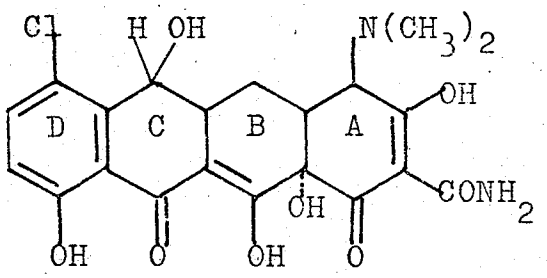
VI



VII $R_1=R_2=R_3=H$



VIII



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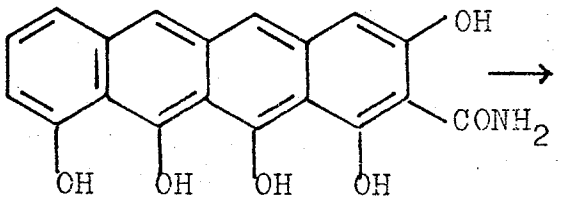
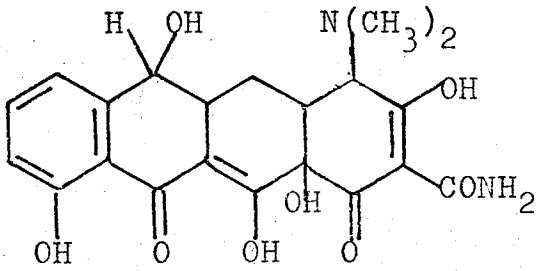
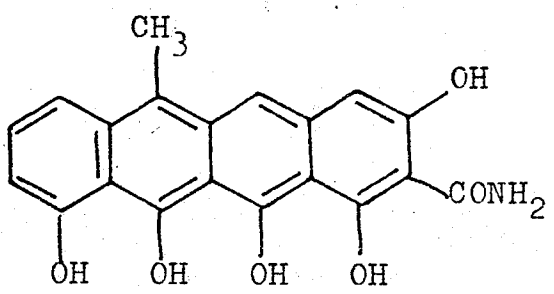


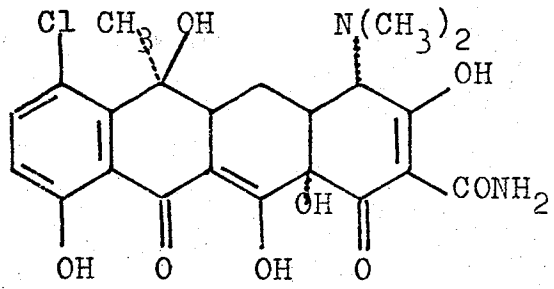
X



XI



XII



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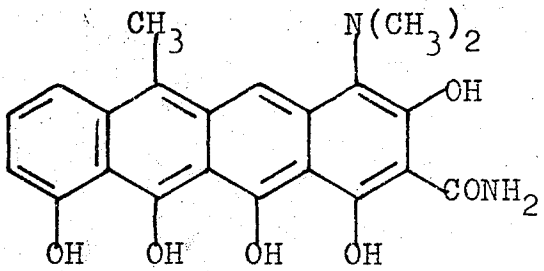
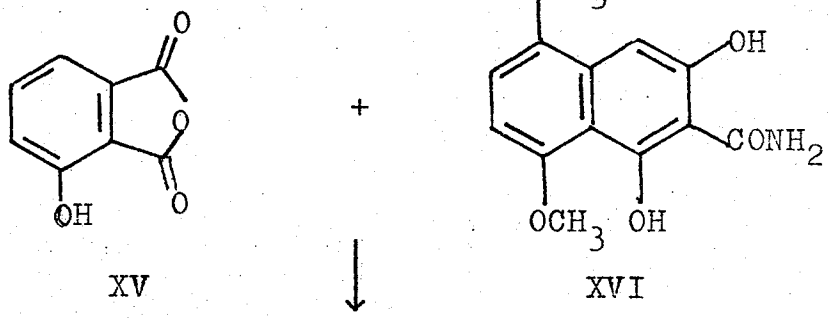
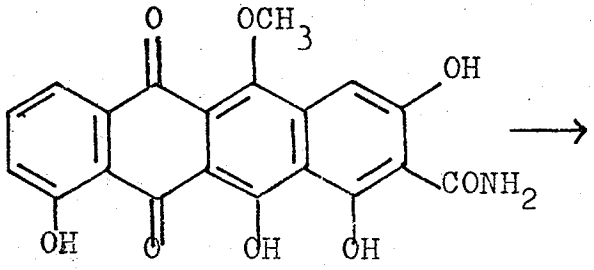


XIV



XV + XVI



Pretetramid (X)

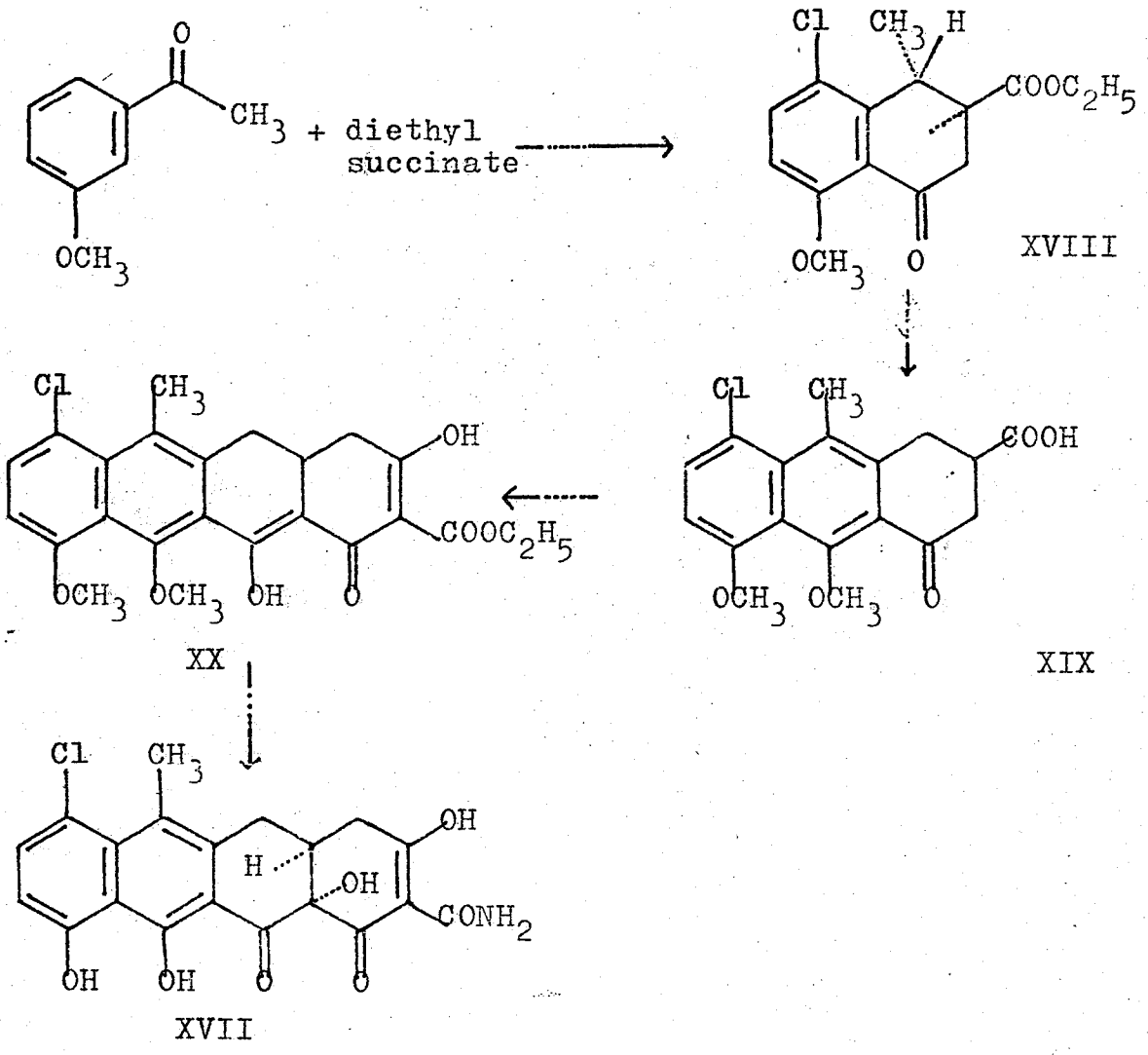
SCHEME 2. Synthesis of pretetramid (X).

It was reported[10] that pretetramid is obtained by fusing 3-hydroxyphthalic anhydride (XV) and 1,3-dihydroxy-5,8-dimethoxynaphthalene-2-carboxamide (XVI) in the presence of aluminum chloride and sodium chloride. The product was converted to pretetramid by refluxing with phenol in the presence of hydriodic acid and potassium hypophosphite. (Scheme 2).

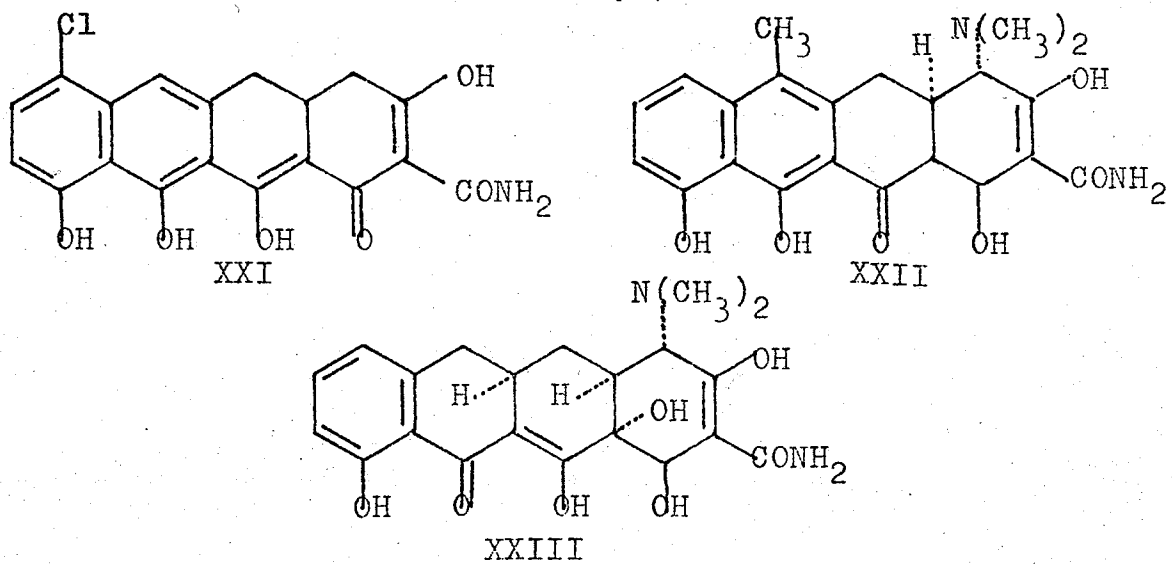
Muxfeldt et al[13] synthesized dedimethylamino-anhydro-aureomycin (XVII) by stepwise fusion of rings D, C, B and A.

The initial step involved a Stobbé condensation of 3-methoxy-acetophenone and diethylsuccinate. Catalytic hydrogenation followed by chlorination, dealkylation and cyclization gave trans-3-carboethoxy-4-methyl-5-chloro-8-methoxy-1-tetralone (XVIII) which was subsequently converted to (XIX). Fusion with malonic ester and cyclization in the presence of sodium hydride gave the tetracyclic skeleton (XX) which was later converted to the desired product (XVII). (Scheme 3) .

Other similar methods are shown in Boothe's[14] synthesis of (±)-dedimethylamino-12a-deoxy-6-demethylanhydrochlorotetracycline (XXI), Shemyakin's[15] synthesis of 12a-deoxy-5a,6-anhydrotetracycline (XXII) and Woodward's[16]



SCHEME 3. Synthesis of dedimethylamino-anhydroaureomycin (XVII)
(——→ - many steps)

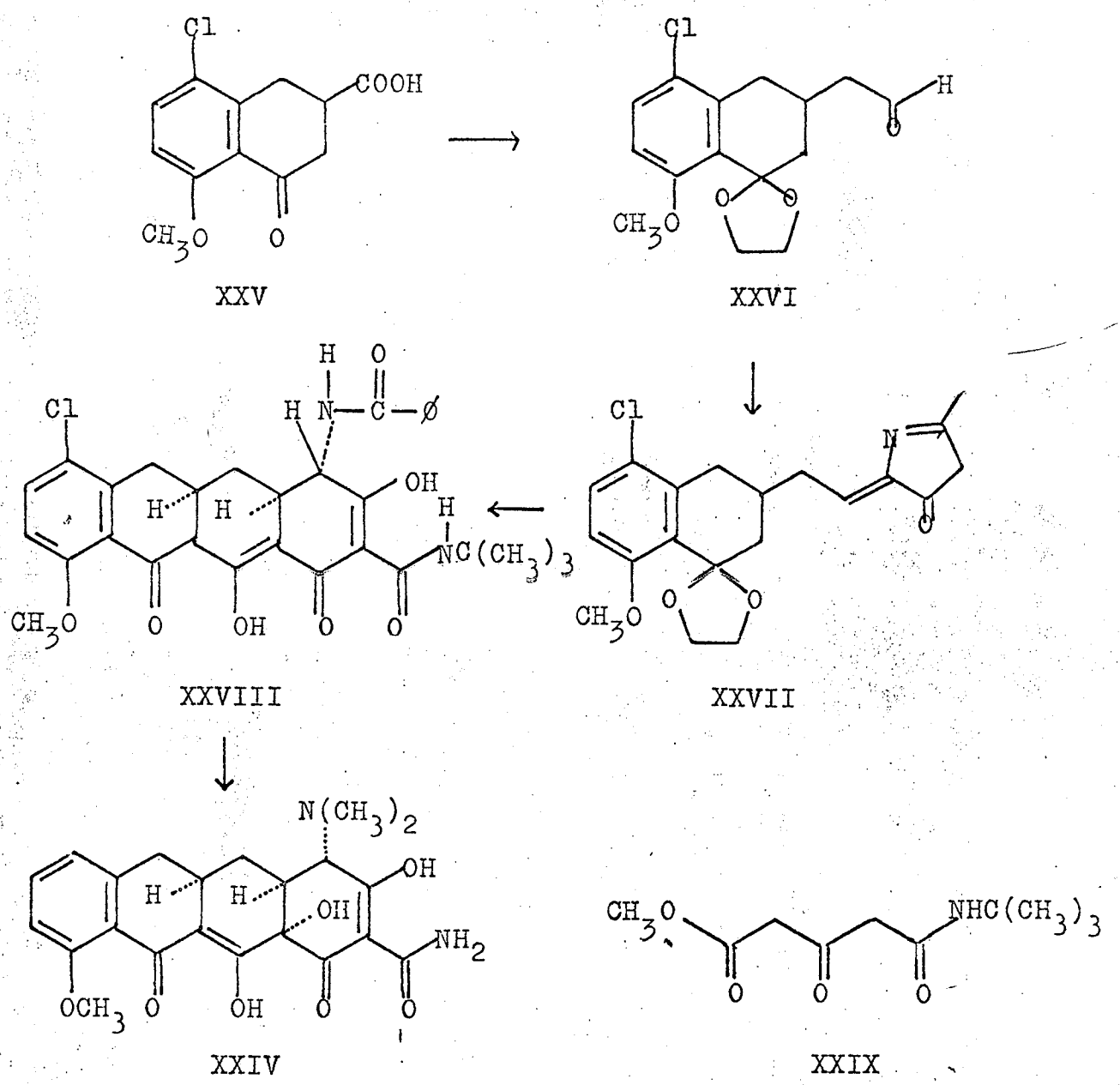


synthesis of dl-6-demethyl-6-deoxytetracycline (XXIII), all of which consisted of a stepwise fusion of rings C to D and then B and A .

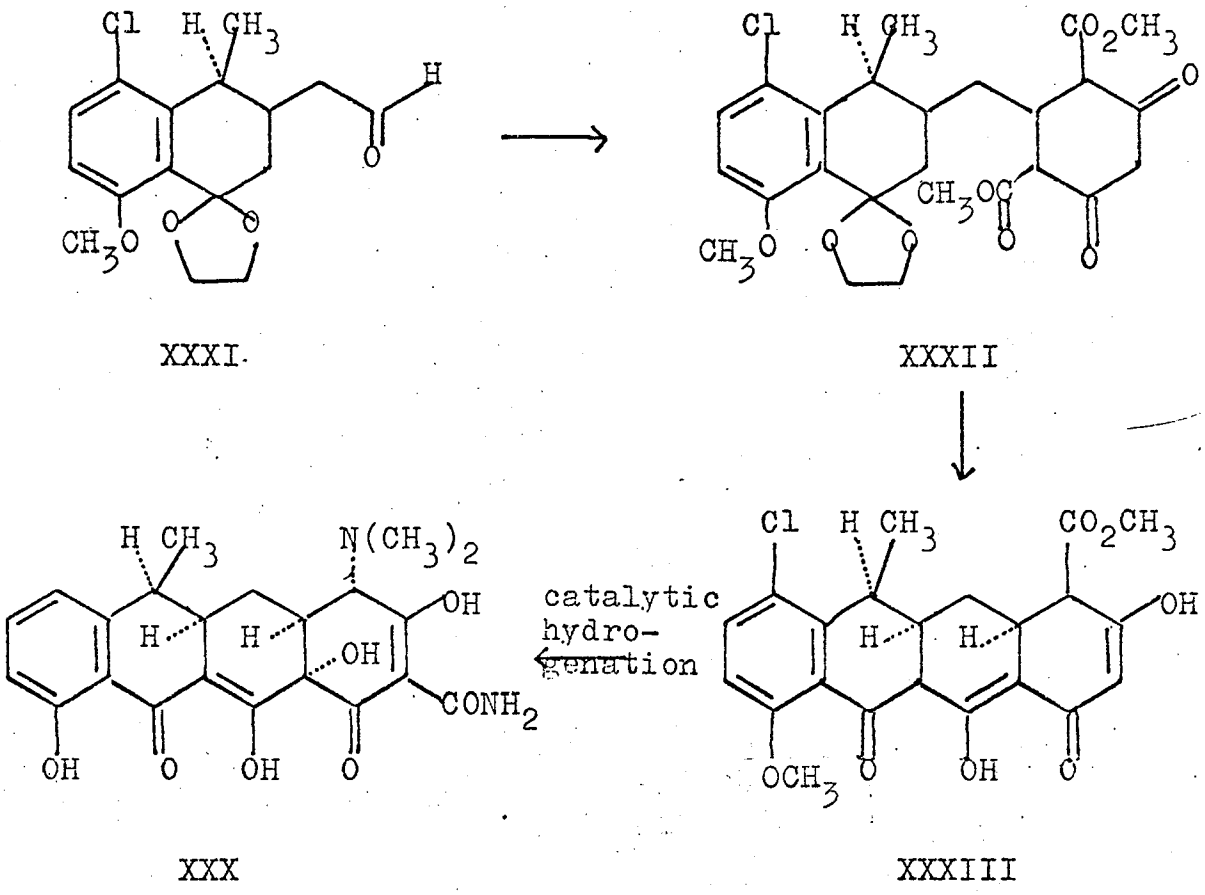
In Muxfeldt's[17] synthesis of dl-6-deoxy-6-demethyl-tetracycline (XXIV), the tetralone (XXV) was also used. Instead of a stepwise fusion of the tetralone (XXV) to the B ring, (XXV) was converted to the aldehyde-ketal (XXVI), which was condensed with hippuric acid in acetic anhydride and lead tetraacetate to give (XXVII). A tetracyclic compound (XXVIII) was obtained in one step by condensing (XXVII) with methyl-N-t-butyl-3-oxoglutaramate (XXIX) in the presence of sodium hydride. (Scheme 4).

In the synthesis of 6-deoxy-6-epitetracycline (XXX)[18], a tetralone derivative (XXXI) was also used. Reaction with malonic acid-dimethylester lengthened the side chain at the centre corresponding to C-4a in tetracycline, which was cyclised to form the A ring in (XXXII). The latter compound was cyclised in anisole in the presence of sodium hydride to give the C ring and therefore the tetracyclic product (XXXIII). (Scheme 5).

A Diels-Alder condensation was used by Muxfeldt[19] as the initial reaction in the synthesis of terramycin (II).



SCHEME 4. Synthesis of dl-6-deoxy-6-demethyltetracycline (XXIV).



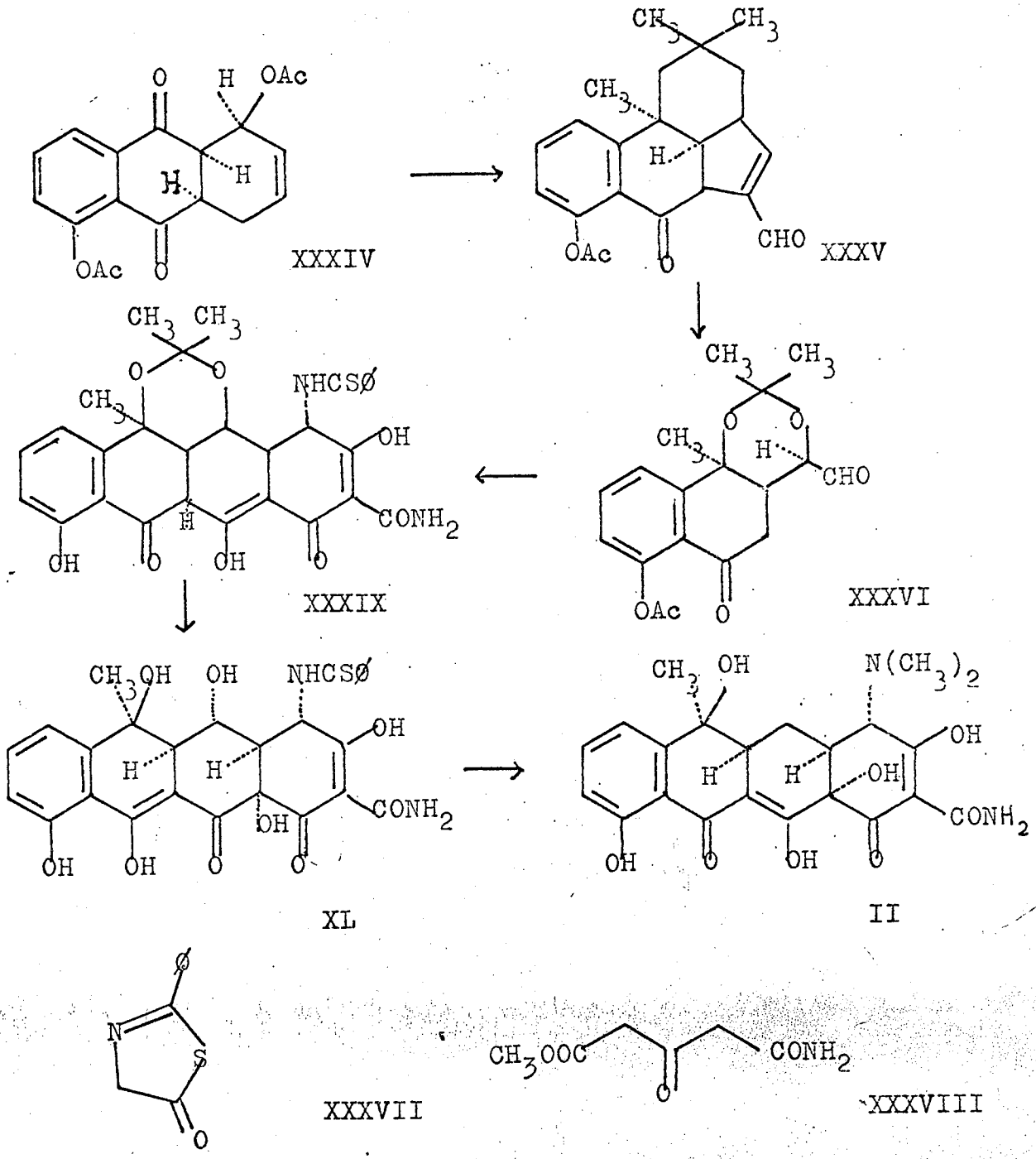
XXXI XXXII

XXX XXXIII

SCHEME 5. Synthesis of 6-deoxy-6-<u>epi</u>tetracycline (XXX).

Juglone acetate and 1-acetoxybutadiene were condensed to form (XXXIV) which was converted to the aldehyde (XXXV) and subsequently to (XXXVI) by ozonolysis, hydrolysis and cleavage with aqueous sodium carbonate. (XXXVI) was reacted with thiazolone (XXXVII) and then methyl-3-oxoglutaramate (XXXVIII) to give (XXXIX). Acid hydrolysis of (XXXIX) followed by hydroxylation in basic medium with molecular oxygen gave the tetracyclic skeleton (XL). (Scheme 6).

Although some natural tetracyclines and a few compounds with naphthacenic skeleton have been synthesized, terrarubein (XIV) has not been synthesized. It is our aim to synthesize this compound. From a synthetic viewpoint, the high concentration of functional groups on ring A of terrarubein has made it the most difficult part of the whole molecule to prepare. Since ring A in terrarubein is aromatic, the difficulty in synthesizing the ring A of tetracycline is less. Therefore, instead of constructing the B, C and D ring first, as in the syntheses of terramycin or 6-deoxy-6-demethyltetracycline, it may be preferable in this case to build up the ring A first and then link it to B, C, D rings of terrarubein. Thus our first stage is the construction of the A ring of terrarubein, with suitable functional groups that with furthur development might lead to the synthesis of terrarubein.

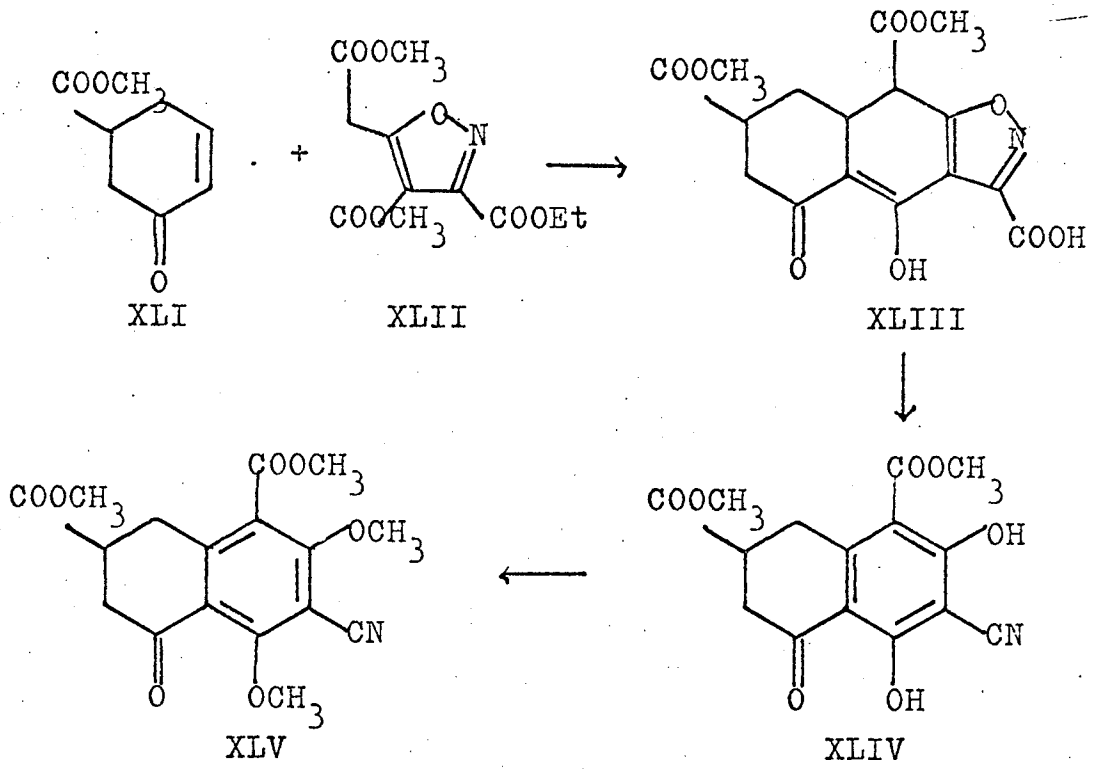


SCHEME 6. Synthesis of terramycin(II).

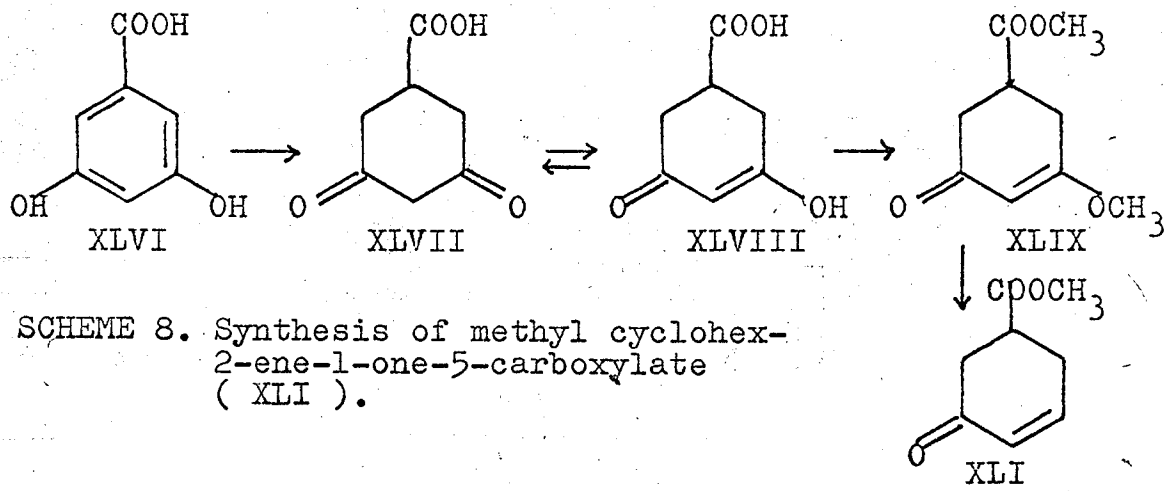
DISCUSSION AND RESULTS

The construction of the A ring and B ring of terrarubein was accomplished by condensing methyl cyclohex-2-ene-1-one-5-carboxylate (XLI) and 3-carboethoxy-4-carbomethoxy-5-(carbomethoxymethylene)-isoxazole (XLII) together, under nitrogen and anhydrous conditions. Sodium hydride was used as the base to convert the isoxazole (XLII) into the corresponding anion which condensed with the cyclohexenone (XLI) to give (XLIII) as shown in (Scheme 7). This unstable intermediate (XLIII) was oxidized by refluxing in methanol and decomposed to 3,5-dicarbomethoxy-6,8-dihydroxy-7-cyano-1-tetralone (XLIV) which was then methylated with diazomethane to the tetralone (XLV). (infrared spectrum no. 1; nuclear magnetic resonance spectrum no. 1; mass spectrum no. 1).

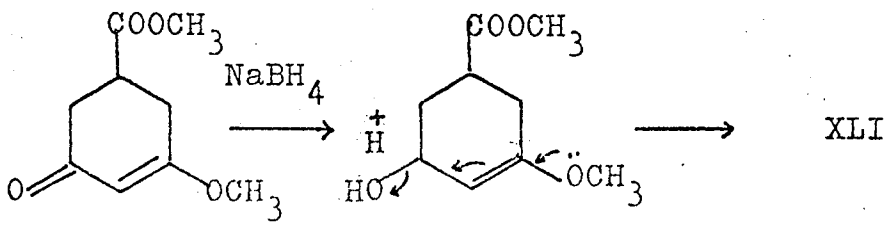
The cyclohexenone (XLI) was prepared according to the scheme outlined in (Scheme 8). The reduction of 3,5-dihydroxybenzoic acid (XLVI) was carried out in aqueous basic solution to give the corresponding diketoacid (XLVII) using palladium/charcoal as the catalyst instead of W-1 Raney nickel as described by Van Tamelen[20]. (i. r. no. 2). The melting point reported was 178.5-180°. The tautomer (XLVIII) of the diketoacid (XLVII) was methylated and then reduced with sodium



SCHEME 7. Condensation of isoxazole (XLII) and cyclohexenone (XLI)



SCHEME 8. Synthesis of methyl cyclohex-2-ene-1-one-5-carboxylate (XLI).

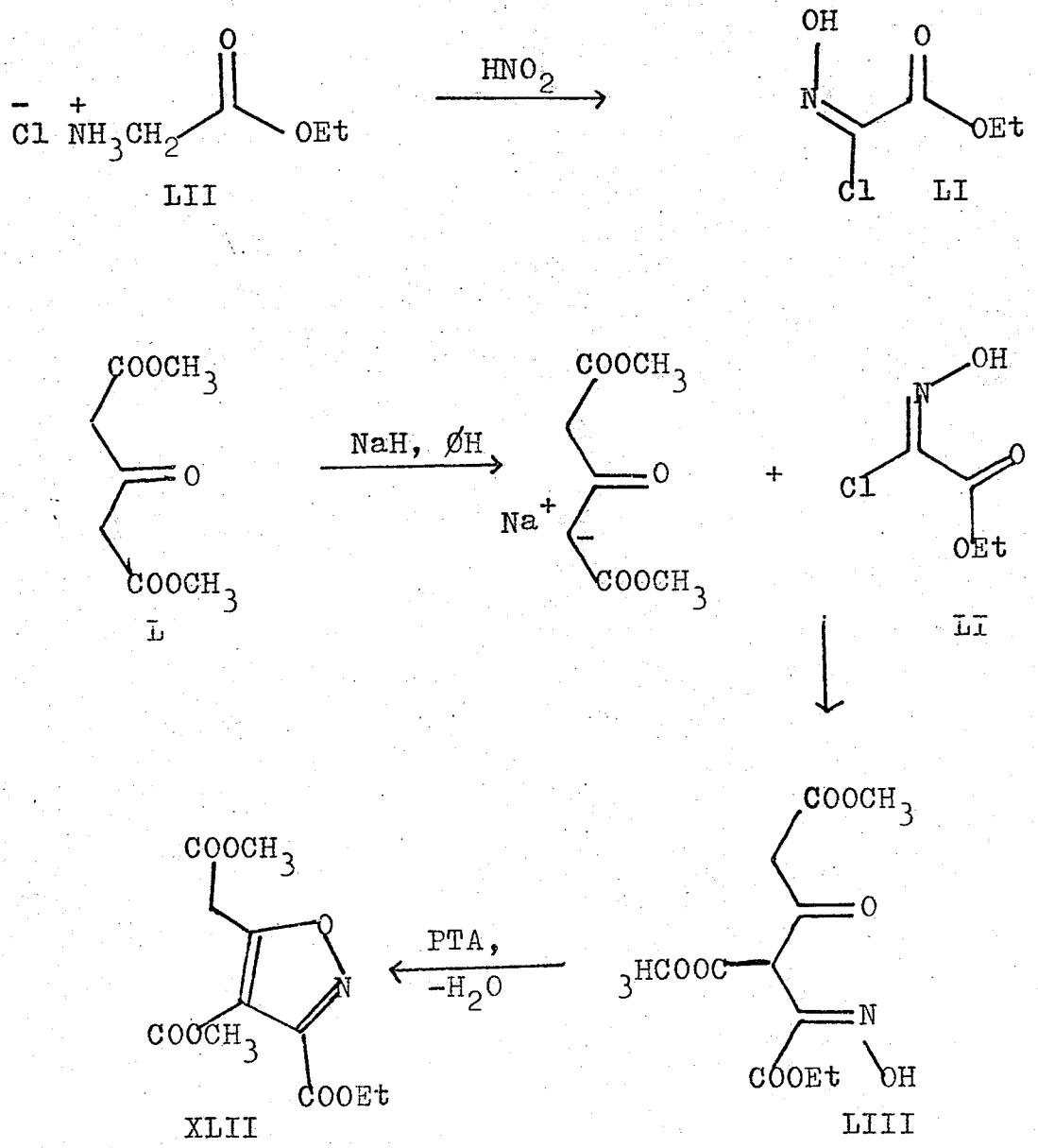


SCHEME 9. Reduction of (XLIX).

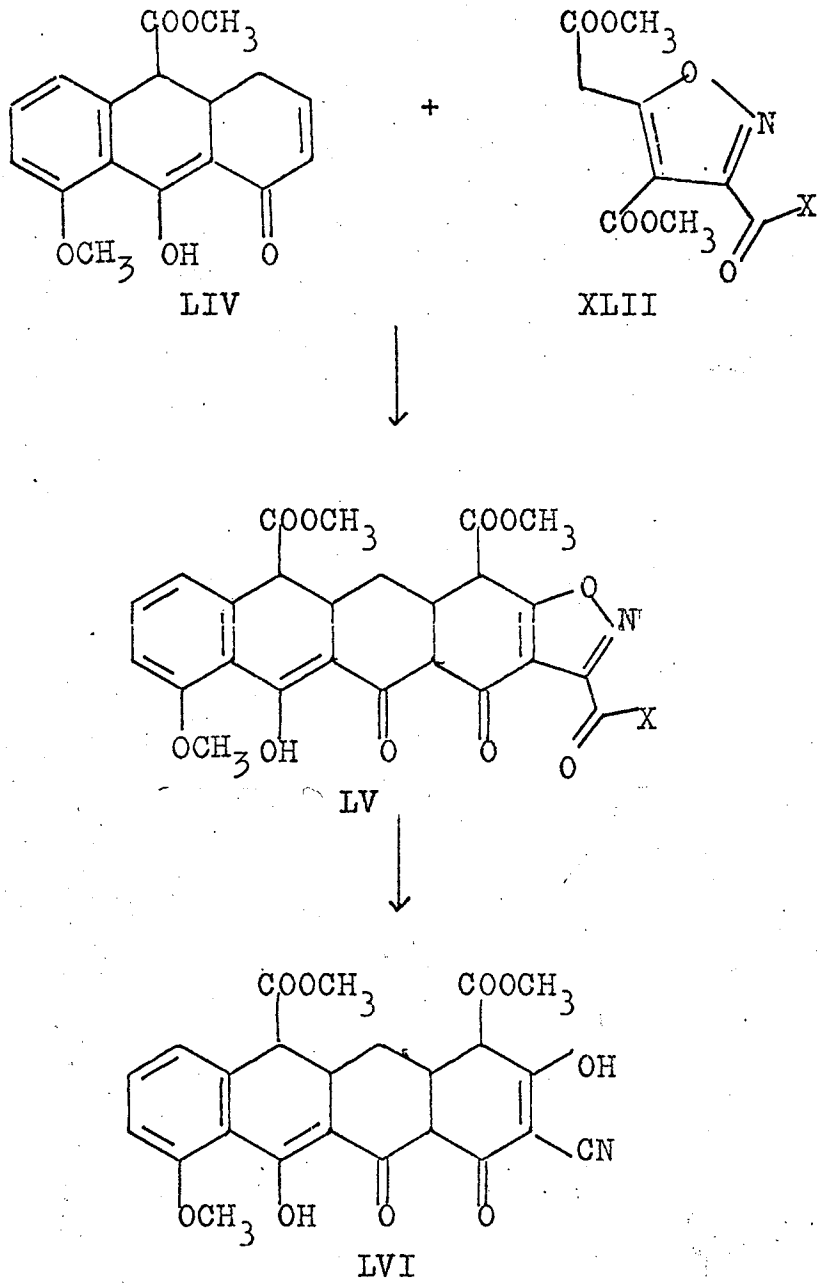
borohydride and on acidification gave the cyclohexenone (XLI) as shown in (Scheme 9). (i.r.no. 4; n.m.r. no. 3).

The synthesis of the isoxazole (XLII) is outlined in (Scheme 10). The isoxazole (XLII) was prepared from the condensation of dimethylacetone dicarboxylate (L) and ethylchlorooximinoacetate (LI), the latter being obtained from the reaction of glycine ethyl ester hydrochloride (LII) with nitrous acid[21]. The dimethyl-acetone dicarboxylate (L) was converted to its anion with sodium hydride as the base and anhydrous benzene as the solvent. The anion was condensed with the oxime (LI) to form the intermediate (LIII). Dehydration of the intermediate with p-toluenesulfonic acid monohydrate gave the isoxazole (XLII). (i.r. no. 6; n.m.r. no. 5).

Since the condensation of the isoxazole (XLII) and the cyclohexenone (XLI) goes fairly smoothly , it may be possible to condense the isoxazole (XLII) with a tricyclic system like (LIV). This would lead directly to the tetracyclic system similar to terrarubein (XIV) or, if one could stop the oxidation process that leads from (LV) to (LVI), the formation of the pentacyclic system (LV). Such a system could eventually lead to



SCHEME 10. Preparation of the isoxazole (XLII).



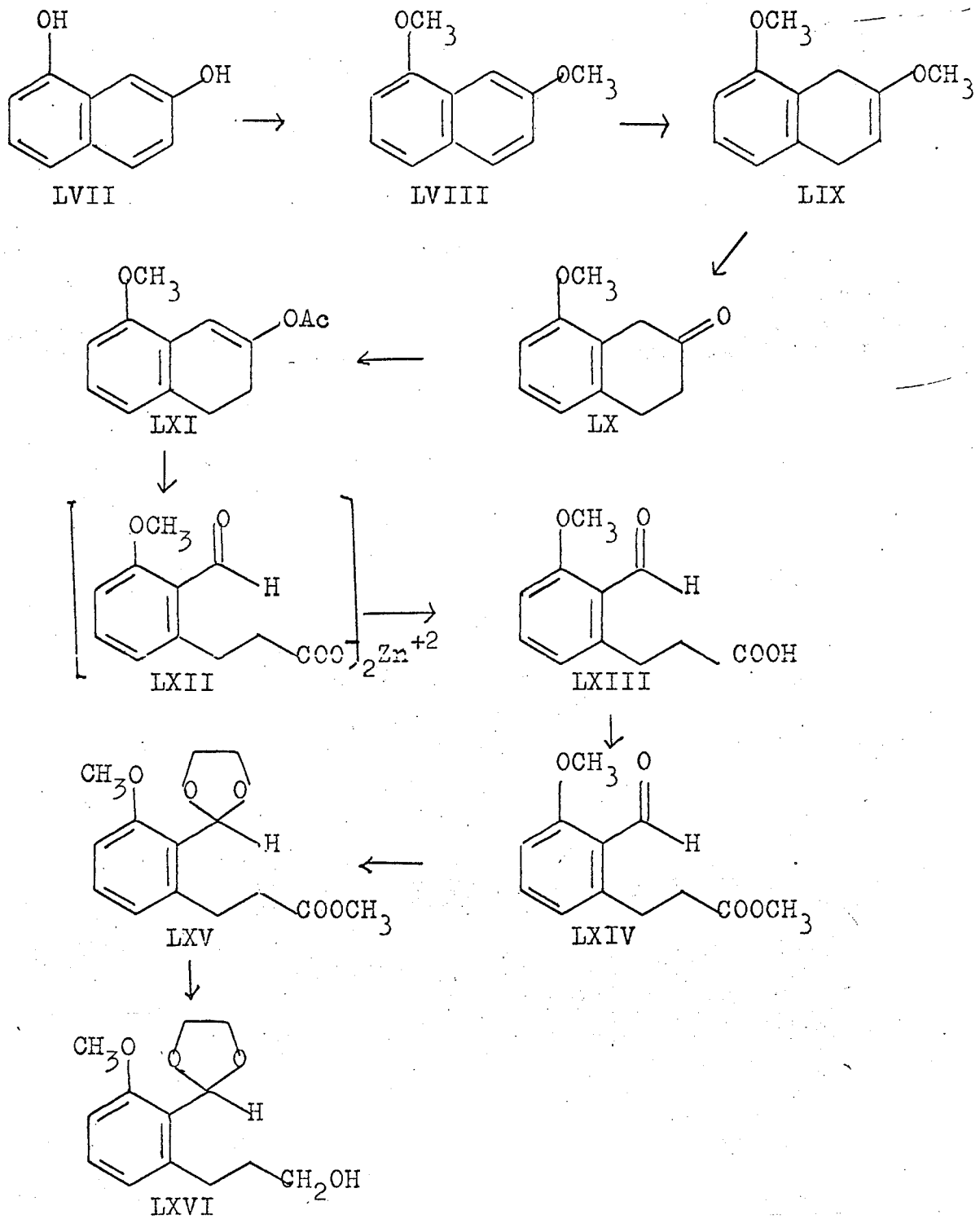
SCHEME 11. Synthesis of the hydroanthracene system (LIV).

the synthesis of terrarubein or tetracyclines respectively. (Scheme 11). With this idea in mind, we worked on the synthesis of the hydroanthracene (LIV).

The starting material, 1,7-dihydroxynaphthalene (LVII) was methylated in the presence of dimethyl sulfate and potassium hydroxide to give 1,7-dimethoxynaphthalene (LVIII). (i.r. no. 7; n.m.r. no. 6). (Scheme 12). (LVIII) was then converted to the enol ether, 1,4-dihydro-3,5-dimethoxynaphthalene (LIX) by dissolving metal reduction under nitrogen[21]. The enol ether (LIX) was extremely unstable in base and was readily oxidized back to (LVIII) on standing for one hour at room temperature. Therefore it was immediately converted to the ketone, 8-methoxy-2-tetralone (LX) by acidification with concentrated hydrochloric acid with methanol as the solvent. (i.r. no. 8; n.m.r. no. 7). 8-methoxy-2-tetralone (LX) was converted to the enol acetate, 1,2-dihydro-3-acetoxy-5-methoxy-naphthalene (LXI) by refluxing under nitrogen in acetic anhydride and pyridine. The enolization occurs preferentially at 1,2 rather than 2,3 position as a result of increased stablization through conjugation. This fact is shown by (i.r. no. 9 and n.m.r. no. 8).

Ozonolysis of the enol acetate (LXI) gave the ozonide, which upon reduction by zinc dust in methanol produced a zinc salt of the acid (LXII). This salt was then decomposed to zinc sulfide and 3-(2-formyl-3-methoxyphenyl)-propanoic acid (LXIII) by hydrogen sulfide. (i.r. no. 10; n.m.r. no. 9). No carboxylic acid proton was observed in the low field region of the nuclear magnetic resonance spectrum probably due to impurities exchanging with the acidic proton. However, methylation of (LXIII) with diazomethane produced the ester, methyl-3-(2-formyl-3-methoxyphenyl)-propanoate (LXIV), (i.r. no. 11; n.m.r. no. 10). thus showing the presence of a carboxylic acid functional group in (LXIII).

The acetal of the ester (LXIV) was obtained smoothly by refluxing the ester in a mixture of ethyleneglycol and benzene with a trace of p-toluenesulfonic acid as a catalyst. (i.r. no. 12; n.m.r. no. 11). The acetal (LXV) thus formed was reduced with lithium aluminum hydride in anhydrous ether to give the ethylene acetal of 2-methoxy-6-(3-hydroxypropyl)-benzaldehyde (LXVI). (i.r. no. 13; n.m.r. no. 12). (LXVI) was purified by thin layer chromatography on alumina plate (t.l.c.). The acidity of the silica gel ordinarily used was sufficient to hydrolyse

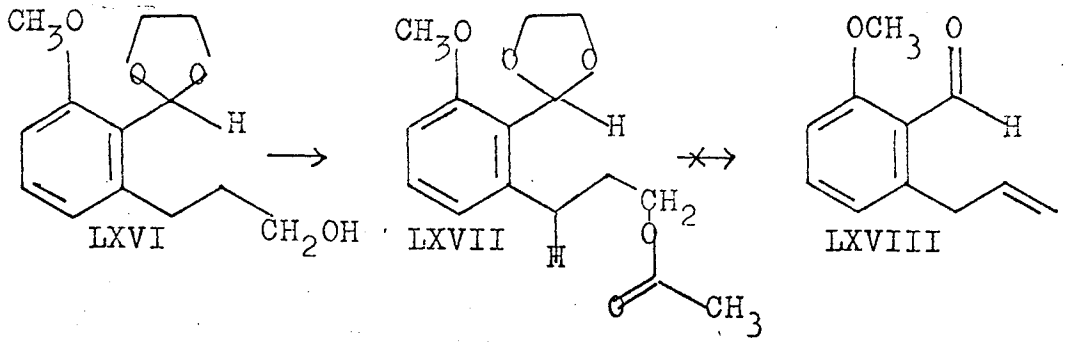


SCHEME 12. Synthesis of 2-methoxy-6-(3-hydroxypropyl)-benzaldehyde (LXVI).

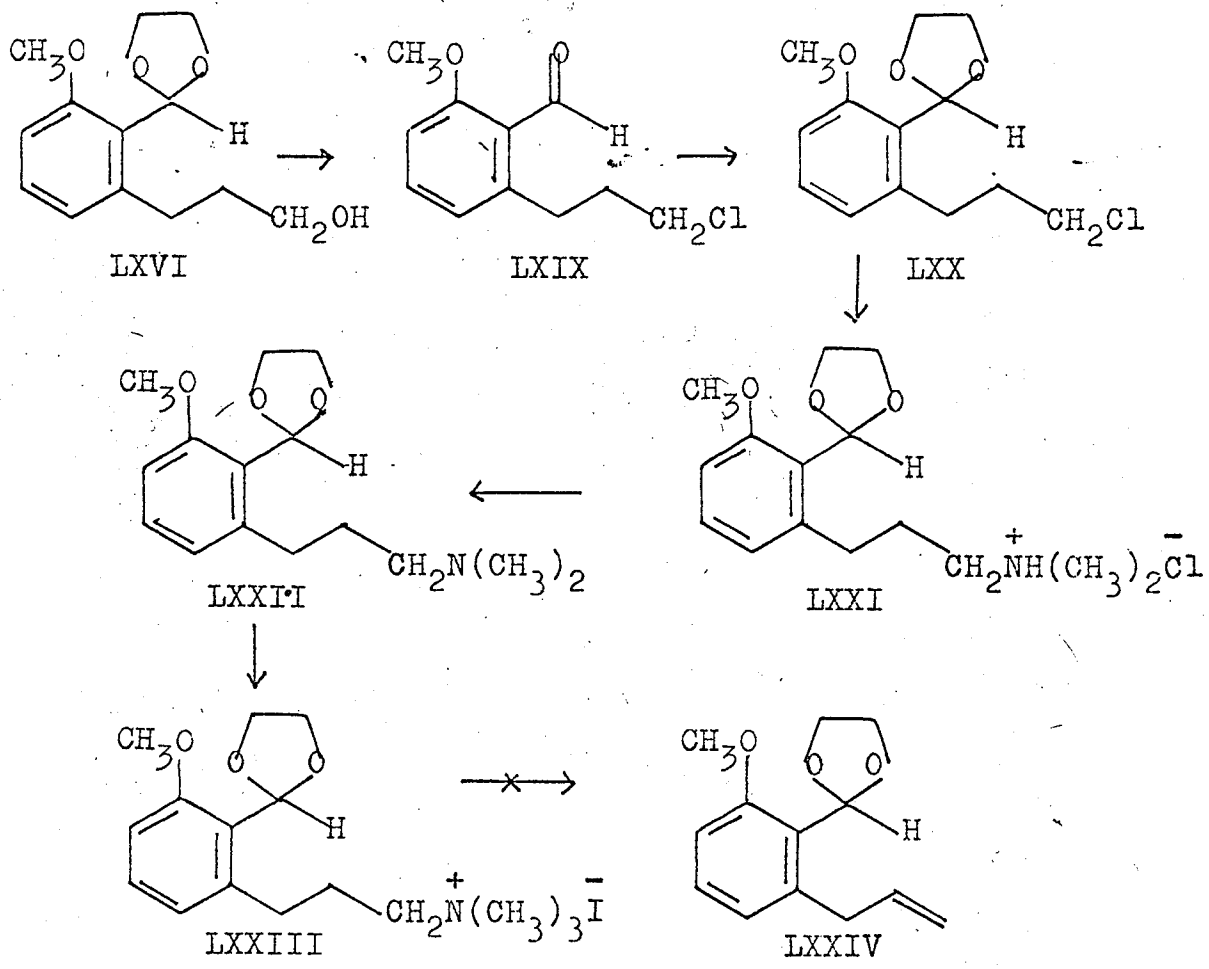
the acetal back to the aldehyde. The acetal is also unstable towards moisture in air and was stored under anhydrous condition.

The alcohol (LXVI) was converted to the acetate (LXVII) by refluxing in acetic anhydride and pyridine. Pyrolysis of the acetate (LXVII) did not give the olefin, 2-methoxy-6-(2 -propenyl)-benzaldehyde (LXVIII), as shown in (Scheme 13). Pyrolysis of the corresponding tosylate and benzoate were also unsuccessful.

An alternative approach to the olefin (LXVIII) is a Hoffman elimination of the quaternary salt (LXXIII), prepared as follows. The alcohol (LXVI) was treated with thionyl chloride to give 2-methoxy-6-(3 -chloropropyl)-benzaldehyde (LXIX). (Scheme 14). The acetal functional group is hydrolysed to the aldehyde due to acidity of the hydrochloric acid liberated. Since the aldehyde is unstable in strong base, (LXIX) was converted back to the acetal (LXX) by the usual method of acetal formation. It was then heated with dimethyl amine in a sealed tube at 70°C to form the amine salt (LXXI). Upon passing through a basic alumina column, the amine salt (LXXI) gave the tertiary amine (LXXII) which was reacted



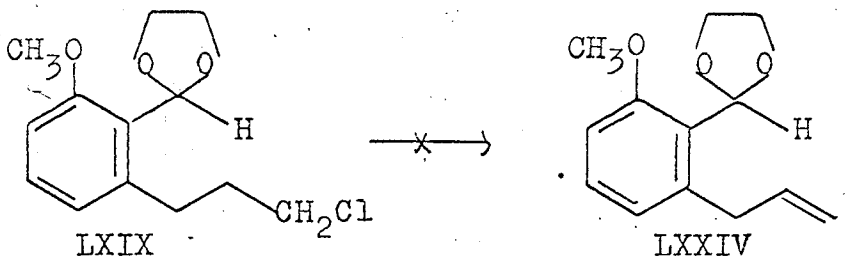
SCHEME 13. Pyrolysis of the acetate (LXVII).



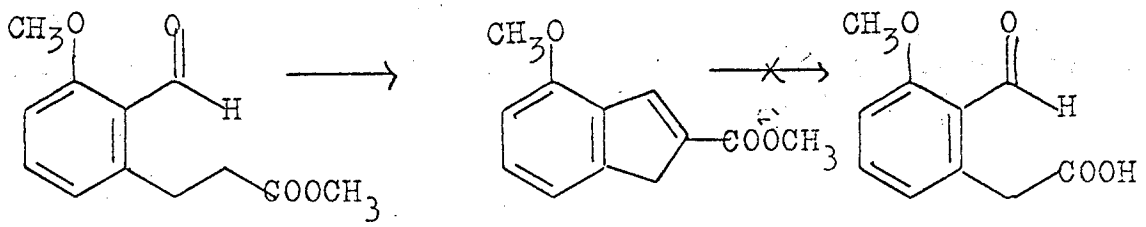
SCHEME 14. Elimination of tertiary amine in the quaternary salt (LXXIII).

with methyl iodide to give the quaternary salt (LXXIII). No reaction occurred when elimination in base was attempted. (Scheme 14). Heating the chloride (LXIX) with triethylamine in a sealed - tube or refluxing the former with potassium tertiary butoxide in tertiary butanol did not give the desired product (LXXIV). (Scheme 15).

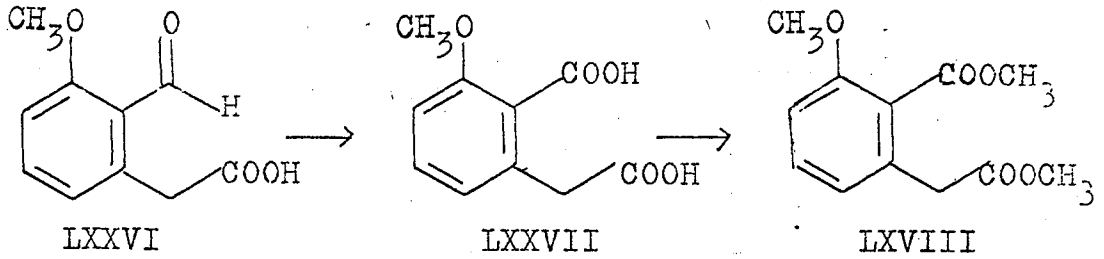
Finally, a Dieckmann cyclization of the ester (LXIV) to the indene (LXXV) was accomplished by sodium hydride in anhydrous tetrahydrofuran. It was expected that oxidative cleavage of the double bond in the indene (LXXV) would lead to the formation of (LXXVI). (Scheme 16). With the formation of (LXXVI), a diester (LXXVIII) can be obtained easily by oxidation of the aldehyde functional group in (LXXVI), followed by methylation. (Scheme 17). Condensation of the diester (LXXVIII) and the cyclohexenone (XLI) with sodium hydride in anhydrous tetrahydrofuran will give the tricyclic compound (LXXIX), convertable to the hydroanthracene system (LXXX). More material will be required to carry on the experiment on the formation of (LXXVI).

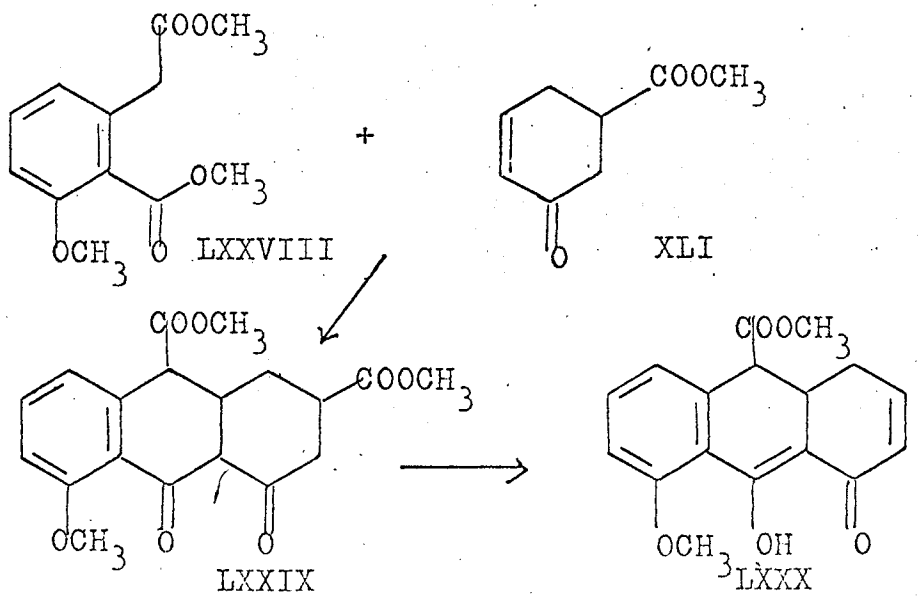


SCHEME 15. Elimination in the acetal (LXIX).



SCHEME 16. Dieckman cyclization of the ester (LXIV).

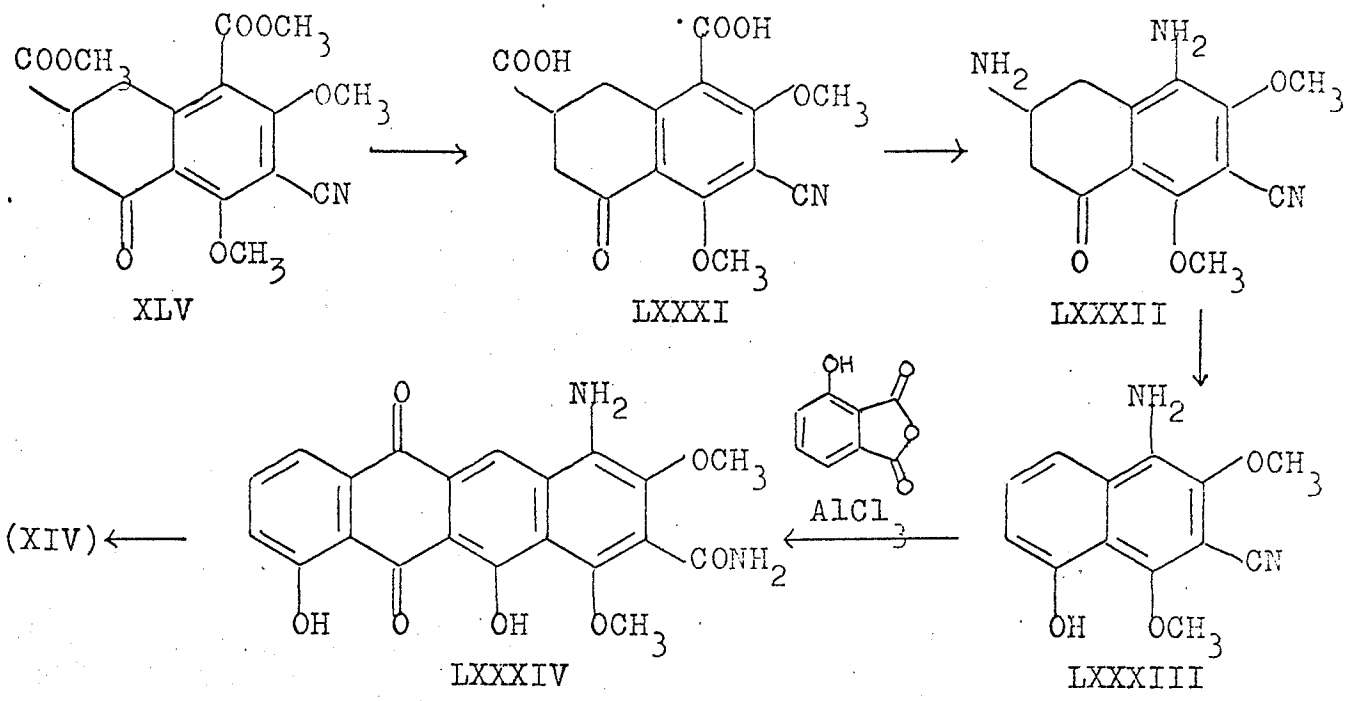




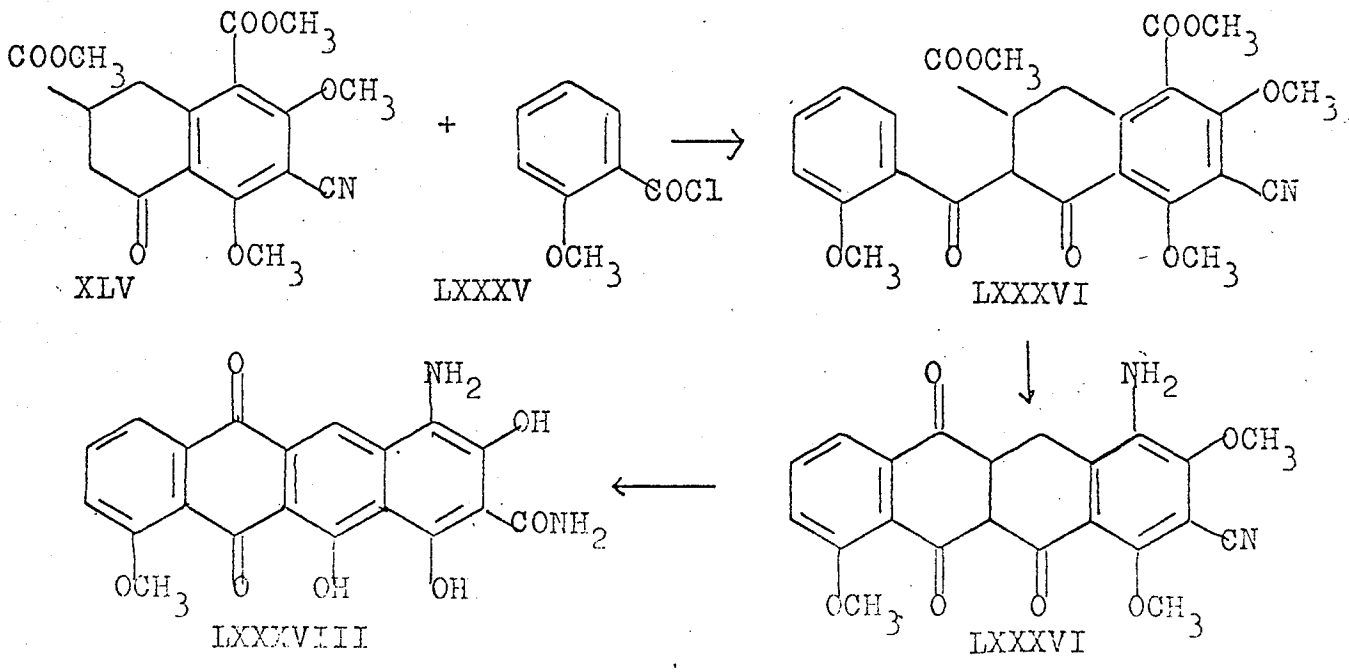
SCHEME 17. Synthesis of the hydroanthracene system (LXXX).

At this stage, it is evident that two different approaches may lead to the construction of terrarubein (XIV). The first starts with the conversion of the tetralone (XLV) to the corresponding diacid (LXXXI), (Scheme 18), which on treatment with thionyl chloride followed by sodium azide would undergo a Schmidt rearrangement to the diamine (LXXXII). Elimination of ammonia from the diamine (LXXXII) followed by isomeriation should lead to the naphthalene (LXXXIII). Amide formation followed by condensation with 3-hydroxyphthalic anhydride should give the tetracyclic quinone (LXXXIV) which can be converted to terrarubein.

The alternative approach is the condensation of (XLV) with 2-methoxybenzoyl chloride (LXXXV) leading to the formation of (LXXXVI) which on an intramolecular Friedel-Craft should give (LXXXVII). Schmidt reaction on the corresponding azide followed by acid hydrolysis would give the tetracyclic quinone (LXXXVIII). (Scheme 19).



SCHEME 18. Synthesis of terrarubein (XIV).



Scheme 19. Synthesis of tetracyclic quinone (LXXXVIII).

EXPERIMENTAL

All infrared spectra were taken with a Perkin Elmer 700 infrared spectrophotometer using methylene chloride as solvent or as otherwise specified. Nuclear magnetic resonance spectra were taken with a Varian model A 56/60 60 Mc machine using deuterated chloroform as the solvent and tetramethylsilane as the internal standard. Chemical shifts are in τ units.

(1) Condensation of cyclohexenone (XLI) and isoxazole (XLII).

Anhydrous tetrahydrofuran was distilled directly into a 50 ml. round bottom flask in which the isoxazole (XLII) (630 mg.) was placed. A 50:50 mixture of sodium hydride in mineral oil (170 mg.) was added and the reaction mixture was refluxed for one hour. The cyclohexenone (XLI) (364 mg.) dissolved in anhydrous tetrahydrofuran was added to the reaction mixture and refluxing was continued for two days. The tetrahydrofuran was then removed by distillation. Ether and 2% sodium hydroxide was added and the mixture was stirred for one hour. The aqueous layer was then washed with ether, acidified with concentrated hydrochloric acid, and extracted four times with chloroform. The brown liquid obtained after

evaporation of the chloroform was dissolved in methanol and refluxed for one hour. The solvent was then evaporated to give a solid which was then added to a diazomethane ether solution and allowed to stand overnight. The residue obtained upon evaporation of the ether was purified by t.l.c. on silica gel developed with 5% methanol in chloroform. 170 mg. (25%) of the tetralone (XLV) was obtained as a pale yellow solid after recrystallization from ether/hexane. m.p. 100-102°C.

Infrared spectrum no. 1. ν_{max} 2850 cm^{-1}($-OCH_3$), 2250 cm^{-1}(-CN). 1730 cm^{-1}($-COOCH_3$), 1690 cm^{-1}($-\overset{O}{\overset{\|}{C}}-C=C$).

Nuclear magnetic resonance spectrum no. 1. 6.25(s, 3H,$-COOCH_3$), 6.05(s, 3H, $-COOCH_3$), 6(s, 3H, $-OCH_3$), 5.85 (s, 3H, $-OCH_3$), 7(m, 5H).

Mass spectrum no. 1.

(2) Reduction of 3,5-dihydroxybenzoic acid (XLVI).

Palladium on charcoal (5%) (2.5 g.) was added to 3,5-dihydroxybenzoic acid (10 g.), (m.p. 236-238°C), and dissolved in a solution of sodium hydroxide (5.8 g.) in distilled water (20 ml.). The hydrogenation was carried out in a Parr high pressure reactor at 115°C and 1200 p.s.i. for nine to ten hours. The catalyst was then filtered through a scintered glass funnel and washed with

20 ml. of water. The pale green solution was cooled in an ice bath and acidified with about 12 ml. of concentrated hydrochloric acid. The acidified solution was allowed to stand overnight for crystallization. The resultant yellow crystals of 5-carboxy-3-hydroxy-2-cyclohexen-1-one (XLVIII) were filtered off and recrystallized from methanol and water. The total yield was 4.8 g. (48%). m.p. 174-178°C.

Infrared spectrum no. 2. ν_{max} 1720 cm^{-1}(-COOH), 1595 cm^{-1}(-C(=O)-C=C-OH).

(3) Methylation of 5-carboxy-3-hydroxy-2-cyclohexen-1-one (XLVIII).

5-carboxy-3-hydroxy-2-cyclohexen-1-one (XLVIII) (2 g.) was suspended in 10 ml. of chloroform. Freshly distilled diazomethane was added dropwise until nitrogen evolution ceased. The solvent was evaporated under reduced pressure to dryness. A quantitative yield of 5-carbomethoxy-3-methoxy-2-cyclohexen-1-one (XLIX) was obtained as a yellow solid. m.p. 72-75°C.

Infrared spectrum no. 3. ν_{max} 1730 cm^{-1}($-COOCH_3$), 1660 cm^{-1} ($_3HCO-C=C-C=O$).

Nuclear magnetic resonance spectrum no. 2. 4.62(S, 1H, C_2H), 6.25(S, 6H, $COOCH_3$, OCH_3), 7.4(m, 5H).

(4) Sodium borohydride reduction of methyl cycohex-2-ene-1-one-5-carboxylate-enol ether (XLIX).

A mixture of the ester (XLIX) (1.0 g.) and sodium borohydride (1.06 g.) were dissolved in 65 ml. of isopropyl alcohol and 26 ml. of methanol. This mixture was stirred at ice temperature for 50 minutes. 20 ml. of water was added to the mixture to destroy the excess sodium borohydride. Concentrated hydrochloric acid was added until the solution was acid to litmus. The organic solvent was evaporated as much as possible and the solution was extracted with chloroform. The chloroform extract was dried with anhydrous sodium sulphate and evaporated under reduced pressure. The crude product (0.85 g.) was purified by t.l.c. on silica gel using 2% methanol in chloroform as the developing solvent. The desired cyclohexenone (XLI) was obtained as a yellow oil and weighed (0.25 g.) (29%).

Infrared spectrum no. 4. ν_{max} 1730 cm^{-1}($-COOCH_3$), 1680 cm^{-1}($-C=C-C=O$).

Nuclear magnetic resonance spectrum no. 3. 7.4(m, 5H), 6.24(S, 3H, $-COOCH_3$), 4(m, 1H, C_2H), 3.05(m, 1H, C_3H).

Mass spectrum no. 2.

(5) Preparation of ethylchlorooximinoacetate (LI).

Glycine ethyl ester hydrochloride (LII) (600 g.) dissolved in 800 ml. of water, was placed in a five litre three-necked round bottom flask equipped with a thermometer, an overhead stirrer and a one litre separatory funnel. The solution was cooled to $5^{\circ}C$ in a dry ice bath. Concentrated hydrochloric acid (360 ml.) was added in one portion to the reaction mixture during which the temperature was kept below $-5^{\circ}C$. Sodium nitrite (300 g.) dissolved in 435 ml. of water was then added slowly so that the temperature of the mixture remained below $0^{\circ}C$. Addition of 360 ml. of concentrated hydrochloric acid and 300 g. of sodium nitrite was repeated once again as above. The mixture was stirred for twenty minutes at a temperature below $0^{\circ}C$. A white solid and a green solution resulted. The cake was then filtered off, and dissolved in warm chloroform. The chloroform layer was separated from the aqueous layer, dried with anhydrous sodium sulphate and evaporated to dryness. An oil which solidified quickly was obtained. The aqueous layer was extracted with chloroform. The chloroform extract, dried with anhydrous sodium sulfate was evaporated to dryness. A total yield of 321 g. of ethylchlorooximino-

acetate (LI) was obtained by reprecipitating the combined fractions from benzene and hexane. m.p. 75-78°C.

Infrared spectrum no. 5. γ_{max} 3500 cm^{-1}(-OH), 1730 cm^{-1}(-COOEt,α,β unsaturated).

Nuclear magnetic resonance spectrum no. 4. 5.6(m, 2H, $-CH_2-$), 8.6(t, 3H, CH_3), 0 (s, 1H, -OH).

(6) Preparation of isoxazole (XLII).

Dimethylacetone dicarboxylate (L) (174 g.) dissolved in three litre of benzene was placed in a five litre three-necked round bottom flask equipped with an overhead stirrer, a heating mantle, a Dean-Starke water separator and a condenser. Sodium hydride/oil (48 g.) was added over twenty minutes to the benzene solution and the mixture was stirred for an additional twenty minutes. Ethylchlorooximinoacetate (LI) (140 g.) was added over fifteen minutes. The reaction mixture was stirred for three hours at room temperature. p-Toluenesulfonic monohydrate was then added and the reaction mixture was refluxed for five and a half hours and then allowed to cool overnight. The reaction mixture was extracted three times with water (500 ml.) and the water extracts were back washed with benzene. The benzene solutions were

combined and evaporated to dryness. The oily residue obtained consisted of two layers: the lower layer was vacuum distilled to give 60 g. of the desired product (LXII) as a yellow liquid.

Infrared spectrum no. 6. ν_{max} 2950 cm^{-1}(C-H, alkane), 1740 cm^{-1}(ester, saturated).

Nuclear magnetic resonance spectrum no. 5. 8.6(t, 3H, CH_3), 6.25(s, 3H, $COOCH_3$), 6.15(s, 3H, $COOCH_3$), 5.8(s, 2H, CH_2), 5.54(m, 2H, CH_2).

(7) Methylation of 1,7-dihydroxynaphthalene (LVII).

1,7-dihydroxynaphthalene (LVII) (100 g.) was dissolved in a solution of potassium hydroxide (140 g.) in water (2500 ml.). The solution was placed in a 5000 ml. three-necked round bottom flask equipped with an overhead stirrer and a separatory funnel. After 230 ml. of dimethyl sulphate was added dropwise from the separatory funnel, the reaction mixture was cooled to below 20°C. The mixture was then stirred overnight at room temperature. The temperature of the resulting solution was raised to 50-60° and potassium hydroxide was added until the solution was basic. It was then extracted with chloroform. The extract was washed once

with water, twice with dilute hydrochloric acid and then with water again until the washings were neutral. The organic solvent was evaporated under reduced pressure. The crude product was purified by vacuum distillation, giving 92 g. of 1,7-dimethoxynaphthalene (LVIII) as a yellow liquid, b.p. 123°C (15 mm), n_D^{25} 1.6187.

Infrared spectrum no. 7. ν_{max} 2850 cm^{-1}($-OCH_3$), 1580 cm^{-1}, 1600 cm^{-1}, 1620 cm^{-1}(C-C multiple bond).

Nuclear magnetic resonance spectrum no. 6. 6.1(s, 6H, $-OCH_3$), 2.8(m, 6H, ar).

(8) Reduction of 1,7-dimethoxynaphthalene (LVIII).

1,7-dimethoxynaphthalene (LVIII)(10 g.) in 56 ml. of isopropyl alcohol was placed in a 100 ml. round bottom three-necked flask equipped with a large condenser and calcium chloride drying tube. Sodium metal (7.2 g.), freshly cut into small pieces, was added. The sodium started to dissolve when the temperature of the solution was raised slightly. The reactant was cooled under nitrogen and as much alcohol as possible was evaporated under reduced pressure. A small amount of water was added and the solution was extracted with ether. After evaporating the ether under reduced pressure, the

product thus obtained was dissolved in 20 ml. of methanol and 5 drops of concentrated hydrochloric acid. The mixture was stirred for half an hour and then the solvent was evaporated. The ketone (LX) thus obtained was purified by recrystallization from petroleum ether to give 8.0 g.(84%) of pale yellow crystals, m.p. 50-51°C.

Infrared spectrum no. 8 ν_{max} 2850 cm^{-1}($-OCH_3$), 1720 cm^{-1}(ketone), 1580 cm^{-1}(C-C multiple bond, aromatic).

Nuclear magnetic resonance spectrum no. 7. 7.5(m, 2H, C_2H), 7(t, 2H, C_1H), 6.5(s, 2H, C_4H), 6.2(s, 3H, OCH_3), 3.2(m, 3H, ar).

(9) Formation of enol acetate (LXI) from ketone (LX).

The ketone (LX) (26 g.) was dissolved in acetic anhydride (500 ml.) and pyridine (18 ml.) in a round bottom flask equipped with a large condenser and a dryerite drying tube. The mixture was refluxed for 72 hours under a nitrogen atmosphere. The solvent was evaporated under reduced pressure. The brown and viscous crude material was subjected to vacuum distillation giving 23.3 g. (73%) of pure enol acetate (LXI) as a pale yellow liquid, b.p. 80-110° (0.02 mm).

Infrared spectrum no. 9. $_{max}$ 2580 cm^{-1}($-OCH_3$), 1750 cm^{-1}(-OAc), 1660 cm^{-1}(-C=C-), 1580 cm^{-1}(-C=C-, aromatic).

Nuclear magnetic resonance spectrum no. 8. 3.15 (m, 3H, ar), 3.5(s, 1H, C_4H), 6.3(s, 3H, OCH_3), 7.35(m, 4H, C_1H, C_2H).

(10) Ozonolysis of the enol acetate (LXI).

Enol acetate (LXI) (13 g.) was dissolved in 100 ml. of distilled hexane in a 250 ml. round bottom flask immersed in an ice bath. Ozone was bubbled into the flask for 6 hours. The ozonide which resulted appeared as white gummy solid. After the reaction was complete, nitrogen was flushed in through the reaction mixture to remove excess ozone. The solvent was evaporated under reduced pressure. The ozonide was dissolved in methanol and zinc dust (3.0 g.) was added to reduce the ozonide. The mixture was stirred at room temperature for half an hour. The zinc dust was filtered off and the solvent was evaporated to give the acid (LXIII) in the form of a zinc salt (LXII). The zinc salt was dissolved in 30 ml. of chloroform and 20 ml. of water. Hydrogen sulfide was bubbled into the chloroform solution to give a pale yellow milky precipitate of zinc

sulfide. The mixture was filtered and the chloroform layer was separated from the aqueous layer; the latter was furthur extracted with an additional 30 ml. of chloroform. The combined chloroform extracts were dried with anhydrous sodium sulphate and evaporated under reduced pressure. The acid (LXIII) (4.2 g.) (34%) was obtained as a pale yellow solid, which was recrystallized from chloroform and methanol, m.p. 142.5-144°.

Infrared spectrum no. 10. γ_{max} 1705 cm^{-1}(-COOH), 1680 cm^{-1}(-CHO), 1590 cm^{-1} and 1580 cm^{-1}(-C=C-, aromatic).

Nuclear magnetic resonance spectrum no. 9. -0.63(s, 1H, -CHO), 2.95(m, 3H, ar), 6.2(s, 3H, $-OCH_3$), 7.05(m, 4H).

Analysis:	C	H
Calculated:	63.46	5.76
Found:	63.39	5.82

(11) Methylation of 3-(2-formyl-3-methoxyphenyl)-propanoic acid (LXIII).

The acid (LXIII) was dissolved in a small amount of chloroform. Diazomethane was added dropwise until nitrogen evolution ceased. The solvent was evaporated

under reduced pressure. A quantitative yield of the ester (LXIV) was obtained as a brownish yellow liquid.

Infrared spectrum no. 11. γ_{max} 1730 cm^{-1}($-COOCH_3$), 1680 cm^{-1}(-CHO), 1590 $cm^{-1}$and 1580 cm^{-1}(aromatic).

Nuclear magnetic resonance spectrum no. 10. -0.63 (s, 1H, -CHO), 2.9(m, 3H, ar), 6.15(s, 3H, $-OCH_3$), 6.4(s, 3H, $-COOCH_3$), 7.1(m, 4H).

(12) Acetal formation of the ester (LXIV).

A mixture of benzene (50 ml.), p-toluenesulfonic acid (100 mg.) and ethylene glycol (3 g.) were refluxed for one hour in a 100 ml. round bottom flask equipped with a Dean-Starke water separator, a condenser and a dryerite drying tube. The ester (LXIV) was added and refluxing was continued for five to six hours under nitrogen. The solution was then transferred to a separatory funnel and washed once with sodium carbonate solution and three times with water. The benzene solution was dried with anhydrous sodium sulphate and evaporated to dryness. 1 g. (91%) of the acetal (LXV) was obtained.

Infrared spectrum no. 12. γ_{max} 1730 cm^{-1}($-COOCH_3$), 960 cm^{-1}($-O-CH_2-CH_2-O-$).

Nuclear magnetic resonance spectrum no. 11. 3(m, 3H, ar), 3.7(s, 1H, O_2CH), 6(m, 4H, CH_2-CH_2), 6.3(s, 3H, $-OCH_3$), 6.4(s, 3H, $-COOCH_3$), 7.15(m, 4H).

(13) Lithium aluminum hydride reduction of the acetal (LXV).

The acetal (LXV) (1.9 g.) was placed in a 100 ml. three-necked round bottom flask equipped with a dropping funnel , a condenser and a drying tube. Lithium aluminum hydride (800 mg.) in dry ether was added slowly through the dropping funnel. The mixture was refluxed for one and a half hours under a nitrogen atmosphere. Excess lithium aluminum hydride was decomposed with water. The solution was extracted with ether. The residue was furthur extracted with hot tetrahydrofuran to recover any trapped organic material. The combined extracts, dried with anhydrous sodium sulphate and evaporated to dryness, gave 1.31 g. of crude alcohol (LXVI). The alcohol chromatographed on alumina plates and developed with 5% methanol in chloroform gave 1 gm. (58%) of the alcohol (LXVI) as a brown liquid.

Infrared spectrum no. 13. ν_{max} 3600 cm^{-1}, 3450 cm^{-1} (-OH), 1590 cm^{-1} (aromatic), 960 cm^{-1} (acetal).

Nuclear magnetic resonance spectrum no. 12. 3.15(m, 3H, ar), 3.75(s, 1H, O_2CH), 6.1(m, 4H, $-OCH_2CH_2O-$), 6.4(s, 3H, $-OCH_3$), 6.7(m, 3H), 7.25(t, 2H, $-CH_2-$), 8.3(m, 2H, $-CH_2-$).

(14) Acetylation of the alcohol (LXVI).

The alcohol (LXVI) (102 mg.) was dissolved in pyridine (0.2 ml.) in a 10 ml. round bottom flask. Acetic anhydride (1.15 ml.) was added and the mixture was refluxed overnight under nitrogen. The solvent was removed and the crude product was purified by t.l.c. on silica gel using 1% methanol in chloroform as the developing solvent. 100 mg. (98.9%) of the acetate (LXVII) was obtained.

Infrared spectrum no. 14. ν_{max} 1730 cm^{-1}(-OAC), 1590 cm^{-1}(aromatic), 960 cm^{-1}(acetal).

(15) Formation of the chloride (LXIX) from the alcohol (LXVI).

The alcohol (LXVI) (1.4 g.) was refluxed with 30 ml. of thionyl chloride for four and a half hours under a nitrogen atmosphere. The solvent was evaporated under reduced pressure. The crude product was purified

by t.l.c on silica gel using chloroform as the developping solvent. 1 g. (80.0%) of the chloride (LXIX) was obtained.

Infrared spectrum no. 15. ν_{max} 1590 cm^{-1}(aromatic), 1680 cm^{-1}(aldehyde).

(16) Formation of the acetal (LXX) from the chloride (LXIX).

Ethylene glycol (4 g.) and p-toluene sulfonic acid (50 mg.) in 50 ml. of benzene were refluxed for one hour in 100 ml. round bottom flask equipped with a Dean-Starke water separator and a condenser with a drying tube. The chloride (LXIX) (1 g.) was added and the resulting solution refluxed overnight. The excess p-toluenesulfonic acid was removed by washing with sodium carbonate solution. The benzene solution was then washed with water and dried with anhydrous sodium sulphate. Evaporation yielded 0.9 g. (74%) of the acetal (LXX) as a brown liquid.

Infrared spectrum no. 16. ν_{max} 1580 cm^{-1}(aromatic), 960 cm^{-1}(acetal).

(17) Formation of the tertiary amine (LXXII).

The acetal (LXX) (56 mg.) was put into a thick-walled glass tube immersed in liquid nitrogen. Excess dimethyl amine was added and the tube was then sealed and heated at 70°C overnight. The resulting product was dissolved in chloroform and passed through a basic alumina column. The tertiary amine was thus obtained as a brown liquid. 33.6 mg (56%) was obtained.

Infrared spectrum no. 17. ν_{max} 2800 cm^{-1}($-N\begin{matrix}CH_3\\CH_3\end{matrix}$), 1580 cm^{-1}(aromatic), 960 cm^{-1}(acetal).

(18) Formation of the quaternary salt of amine (LXXIII).

The tertiary amine (LXXII) (33.6 mg.) was placed in a 10 ml. round bottom flask along with 1 ml. of methyl iodide. The mixture was stirred for five minutes at room temperature. Excess methyl iodide was evaporated and the yellow residue was dissolved in chloroform and washed through a basic alumina column to give (LXXIII). 42 mg. (50%) was obtained as yellow crystals.

Infrared spectrum no. 18. ν_{max}^{nujol} 2700 cm^{-1}(salt).

(19) Dieckmann condensation of the ester (LXIV).

Absolute methanol was distilled directly into a 100 ml. flask containing 100 mg. of sodium metal. Absolute methanol was also distilled into a 50 ml. flask containing the ester (LXIV) (651 mg.). The solution was kept out of contact with atmospheric moisture by sealing the flask immediately with a rubber cap. The solution of the ester (LXIV) in absolute methanol was transferred by a syringe into the 100 ml. flask containing the sodium methoxide. The mixture was refluxed overnight under anhydrous conditions. The solution was then cooled in ice and acidified with concentrated hydrochloric acid. The methanol was evaporated off under reduced pressure and 15 ml. of water was added. The aqueous solution was extracted with benzene and the benzene extract was dried with anhydrous sodium sulphate. The crude product, obtained on evaporation of the benzene, was purified by preparative t.l.c. on silica gel and developed with 2% methanol in chloroform. 265 mg. (44.2%) of the condensation product (LXXV) was thus obtained as white crystals, m.p. 52-54°C.

Infrared spectrum no. 19. ν_{max} 1700 cm^{-1}($-COOCH_3$), 1650 cm^{-1}(-C=C-), 1600 $cm^{-1}$and 1580 cm^{-1}(aromatic).

Nuclear magnetic resonance spectrum no. 13.

2.8(m, 4H, aromatic and $-C_2H$), 6.25(s, 3H, $-OCH_3$), 6.3(s, 3H $-COOCH_3$), 6.5(d, 2H, $-CH_2-$).

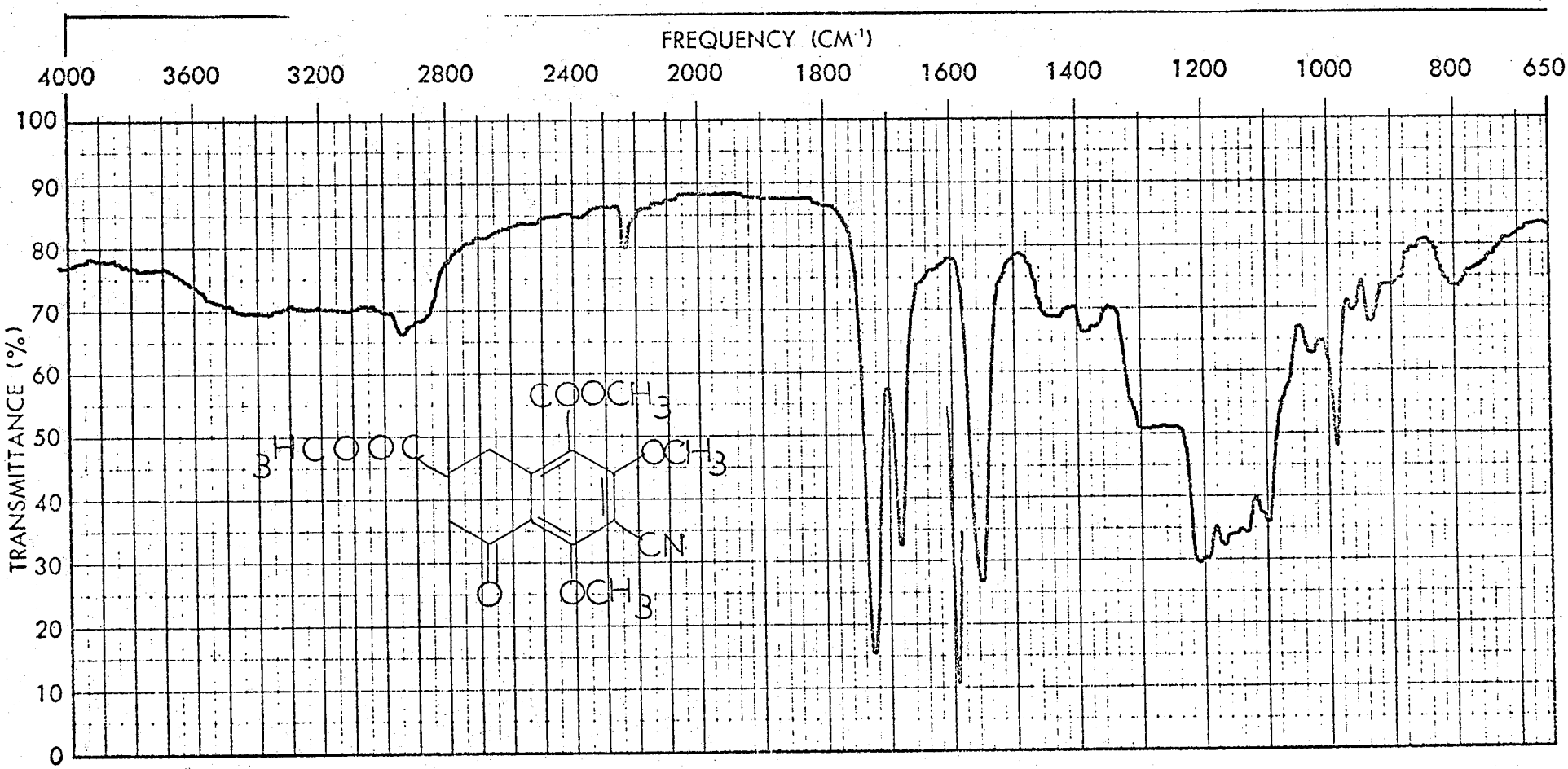


FIGURE 1. Infrared spectrum no. 1. Tetralone (XLV).

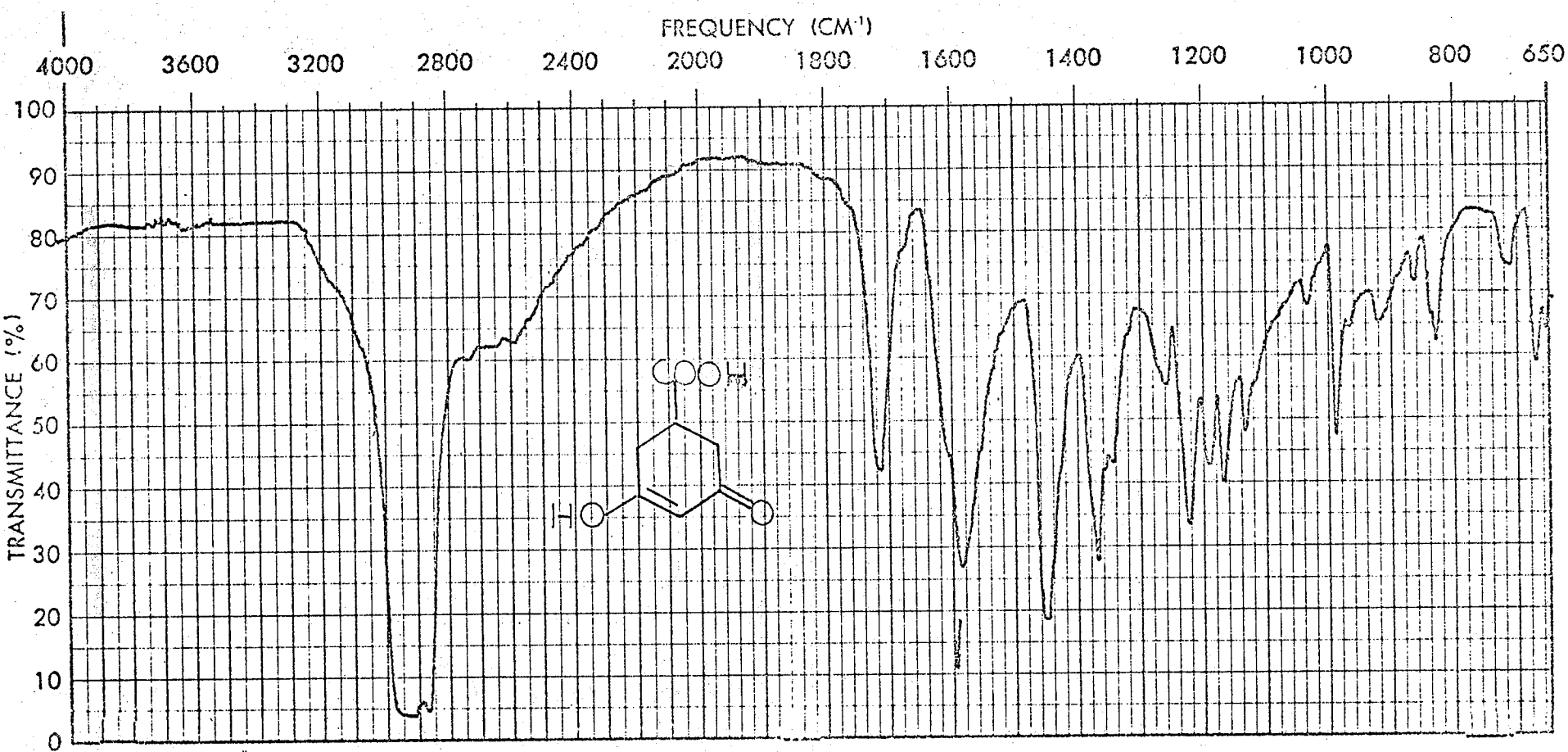


FIGURE 2. Infrared spectrum no. 2. The diketoacid (XLVIII).

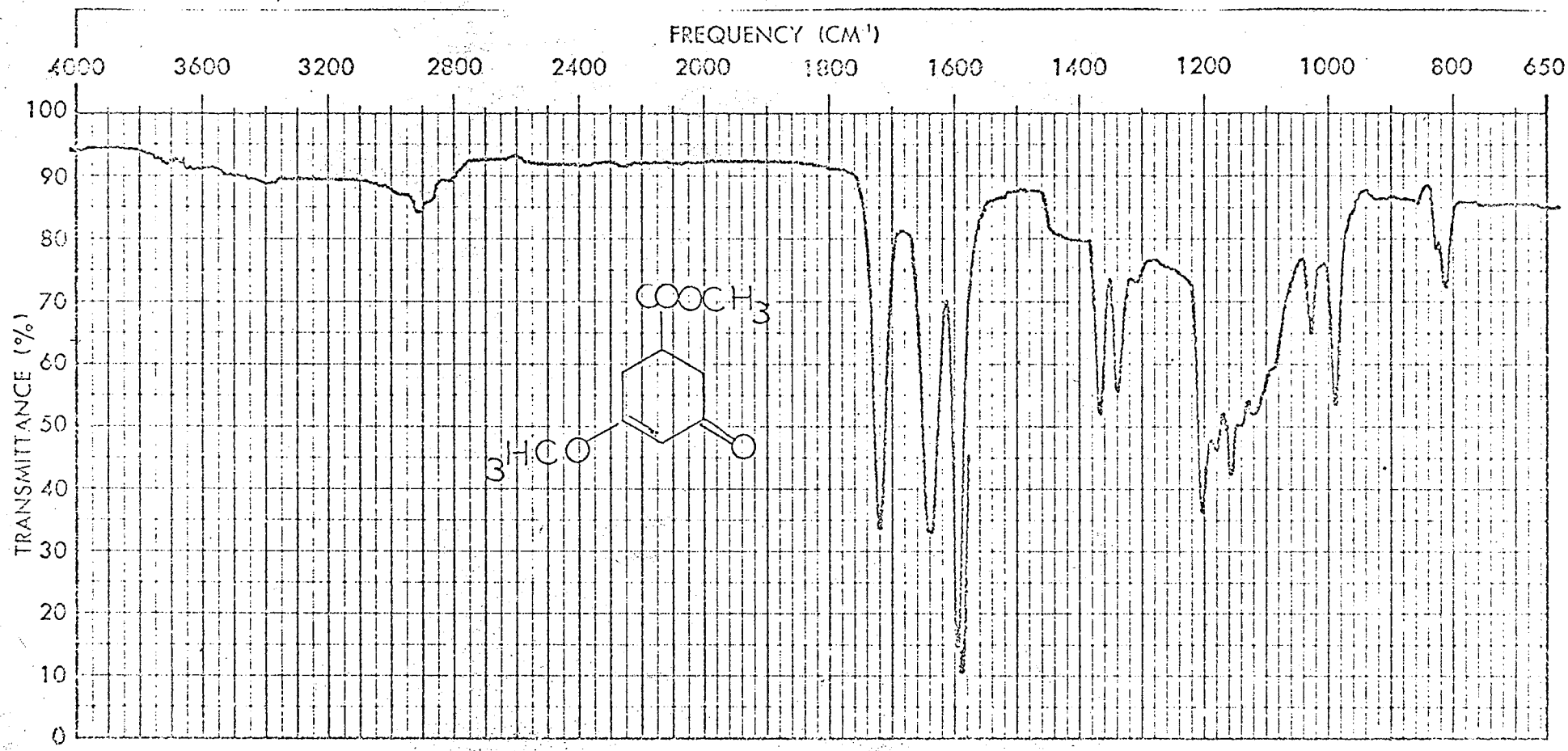


FIGURE 3. Infrared spectrum no. 3. Methyl cyclohex-2-ene-1-one-5-carboxylate-methyl ether (XLIX).

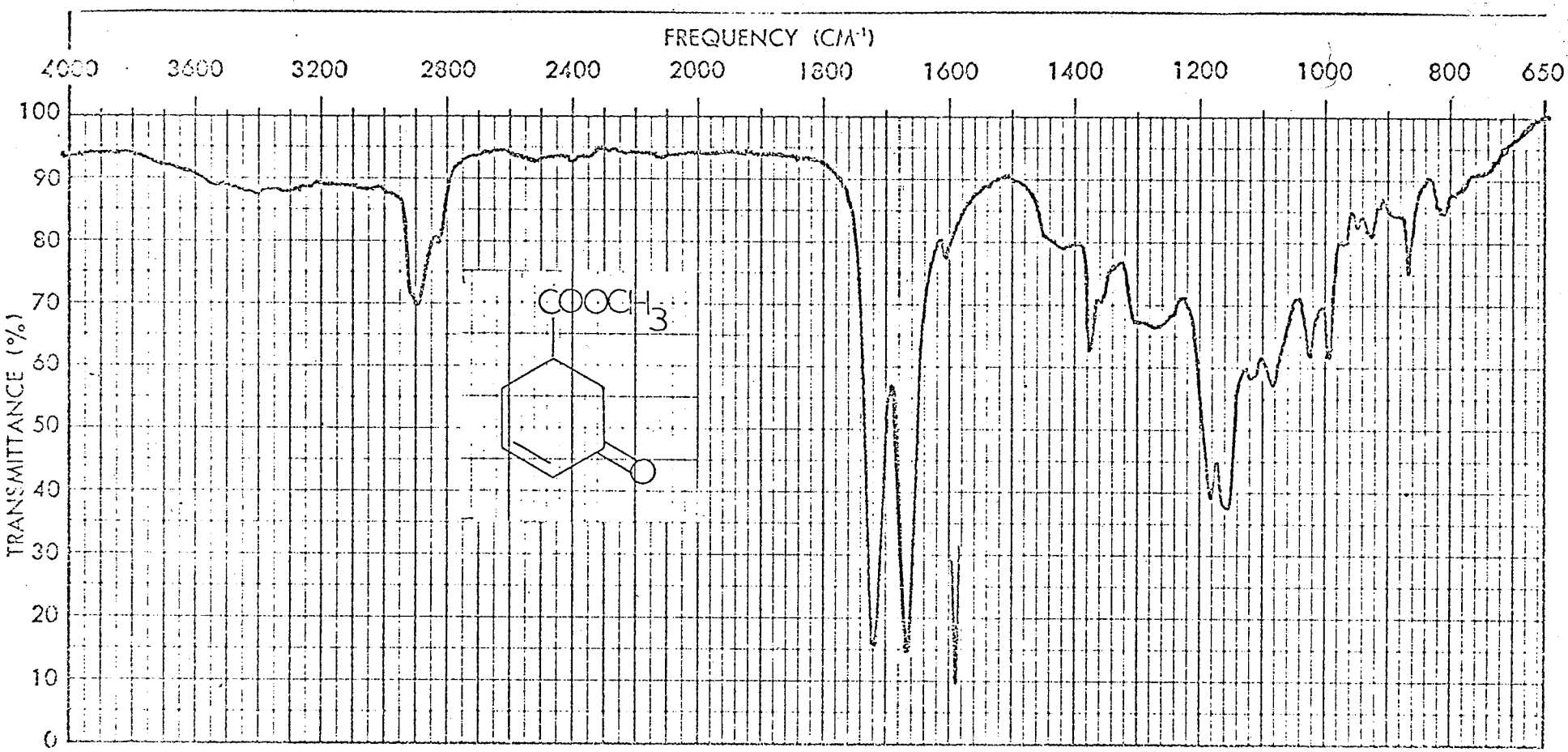


FIGURE 4. Infrared spectrum no. 4. Methyl cyclohex-2-ene-1-one-5-carboxylate (XLIX).

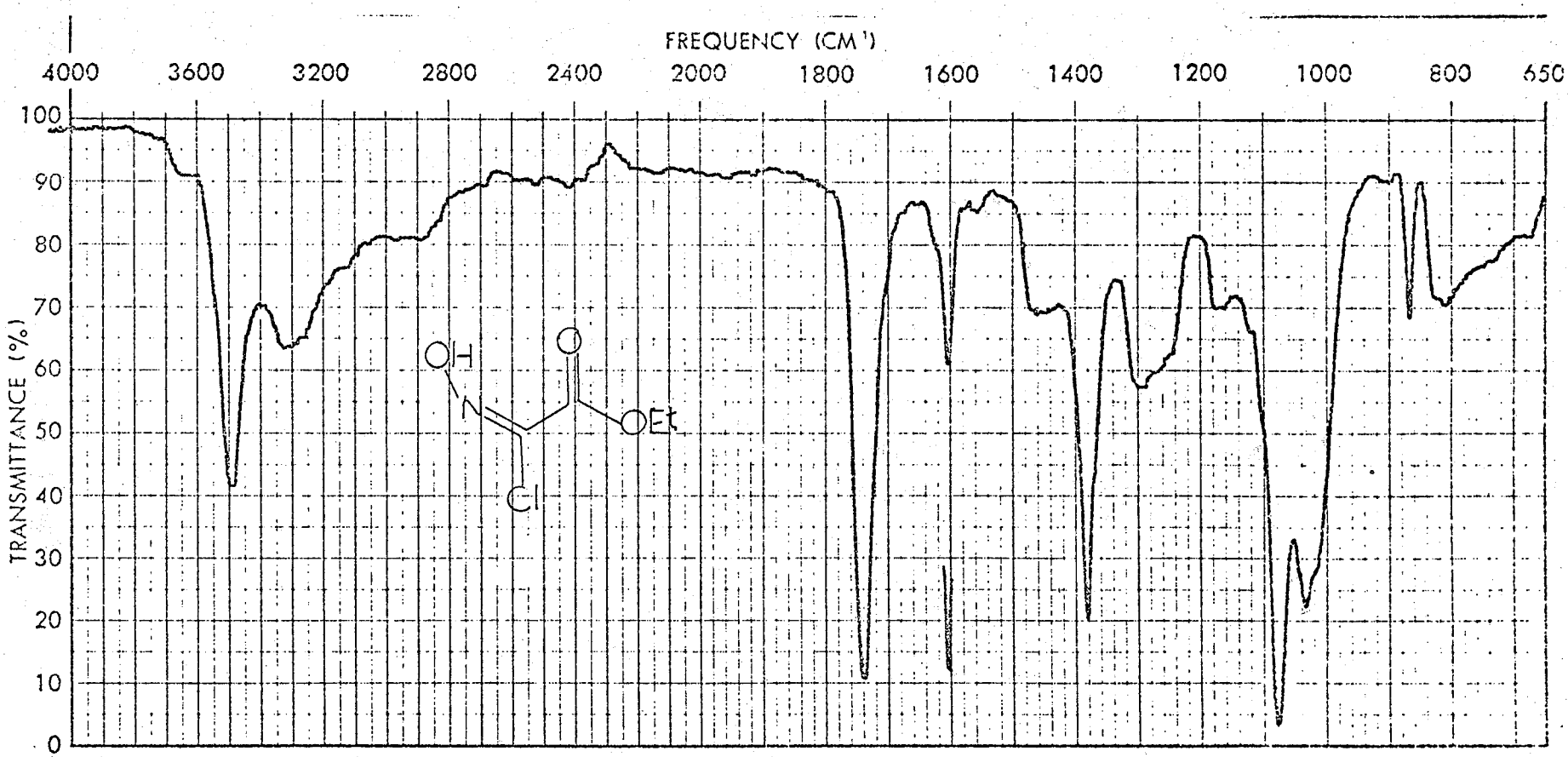


FIGURE 5. Infrared spectrum no. 5. Ethylchlorooximinoacetate (LI).

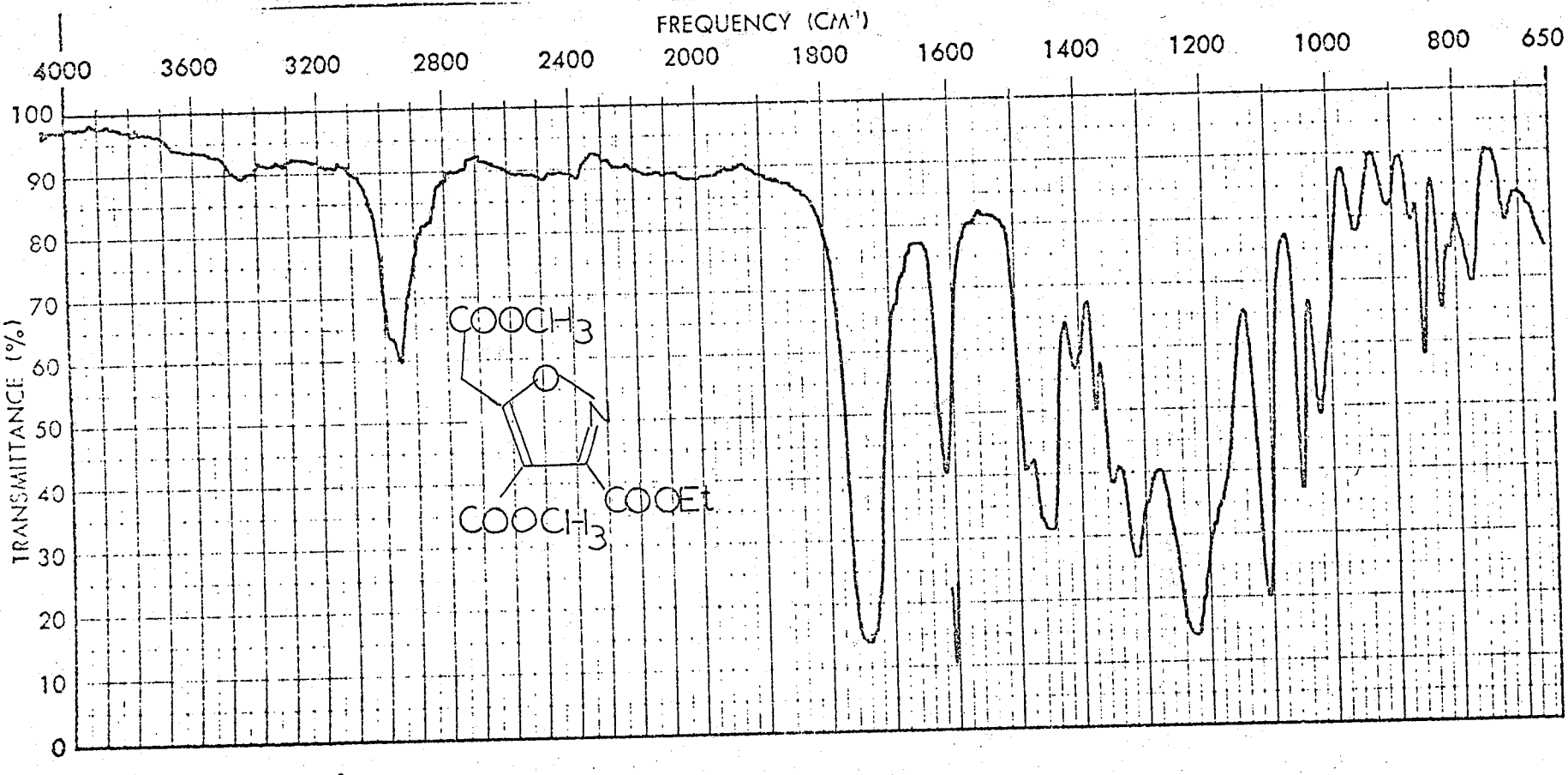


FIGURE 6. Infrared spcetrum no. 6. Isoxazole (XLII).

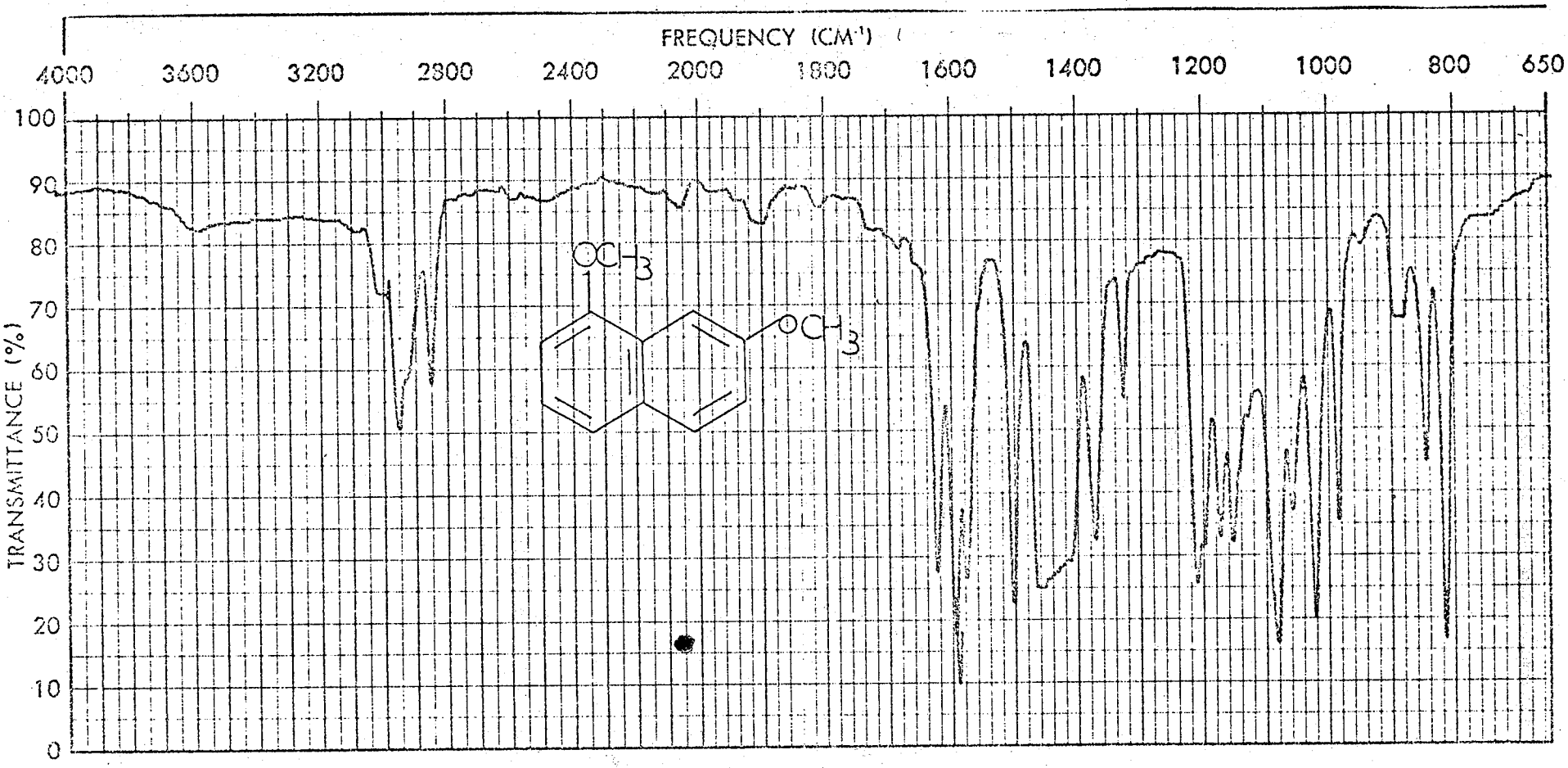


FIGURE 7. Infrared spectrum no. 7. 1,7-dimethoxynaphthalene (LVIII).

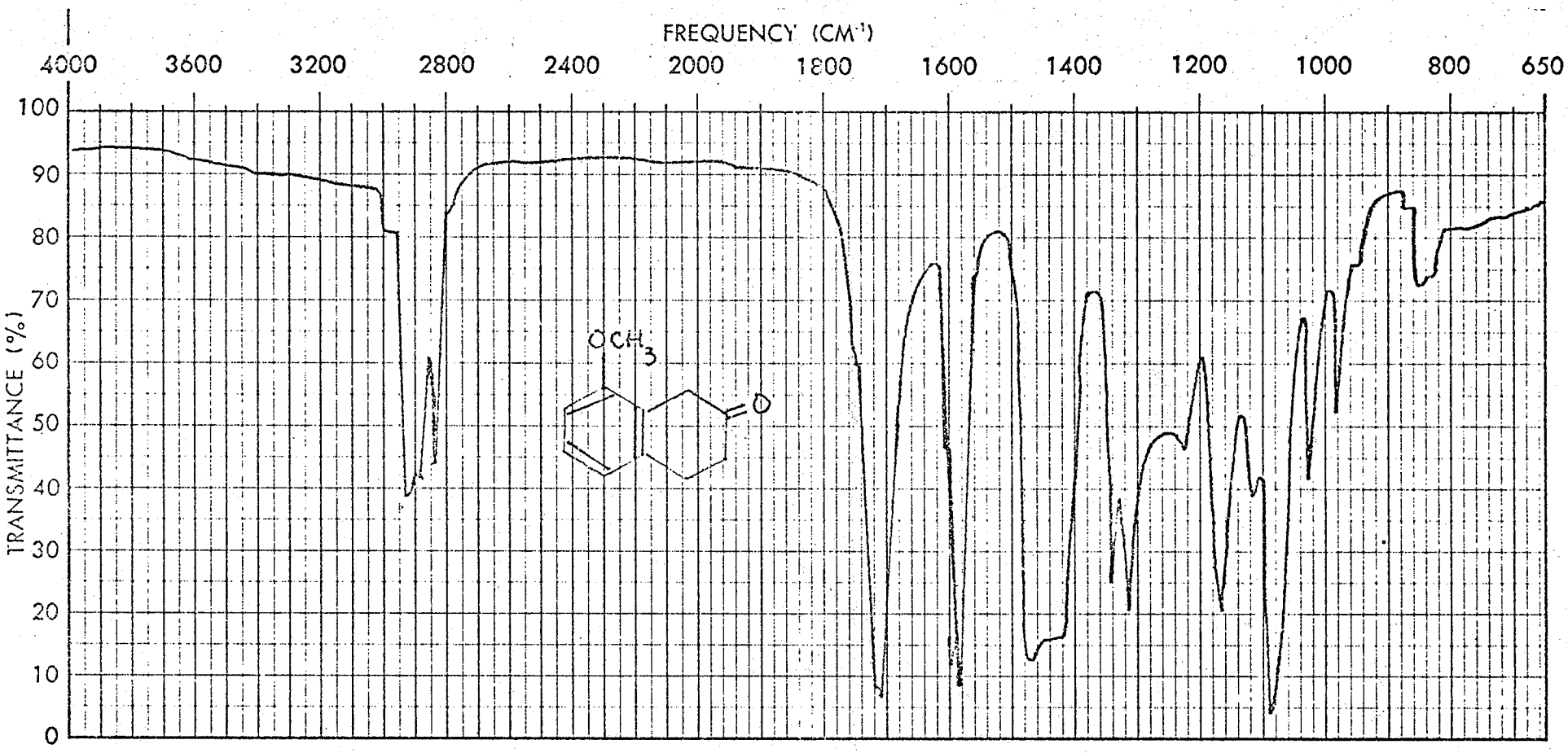


FIGURE 8. Infrared spectrum no. 8. 8-methoxy-2-tetralone (LX).

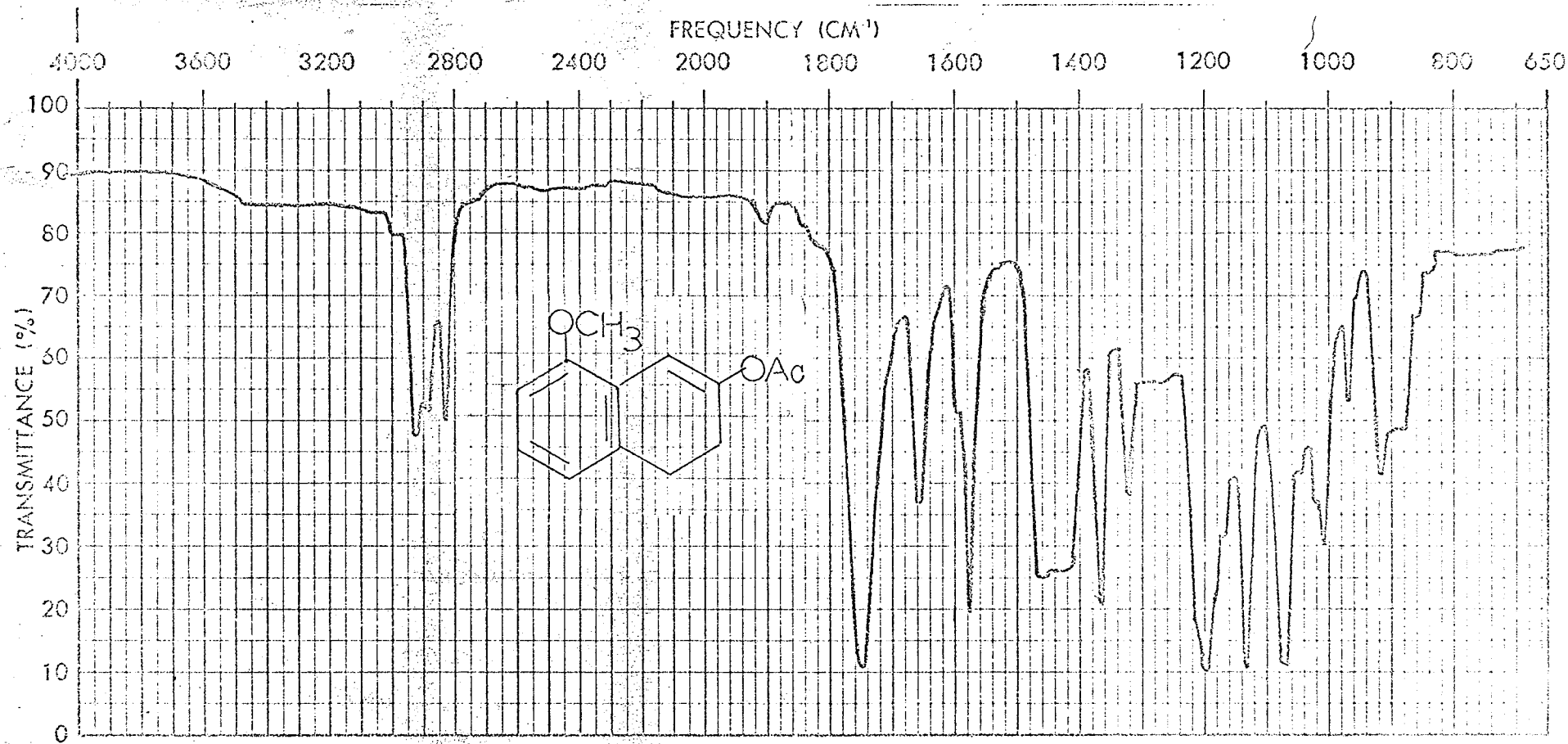


FIGURE 9. Infrared spectrum no. 9. 1,2-dihydro-3-acetoxy-5-methoxynaphthalene (LXI).

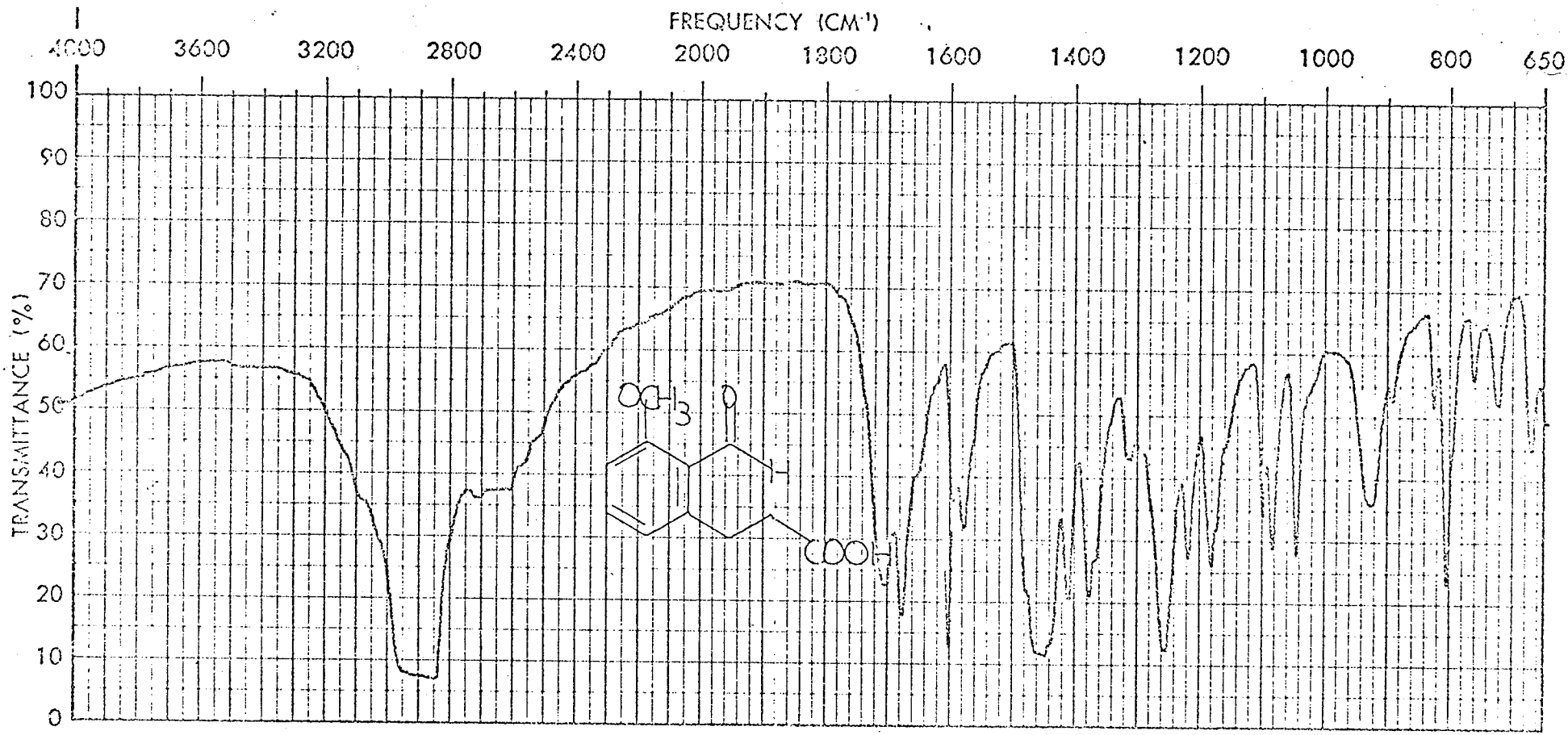


FIGURE 10. Infrared spectrum no. 3-(2-formyl-3-methoxyphenyl)-propanoic acid (LXIII).

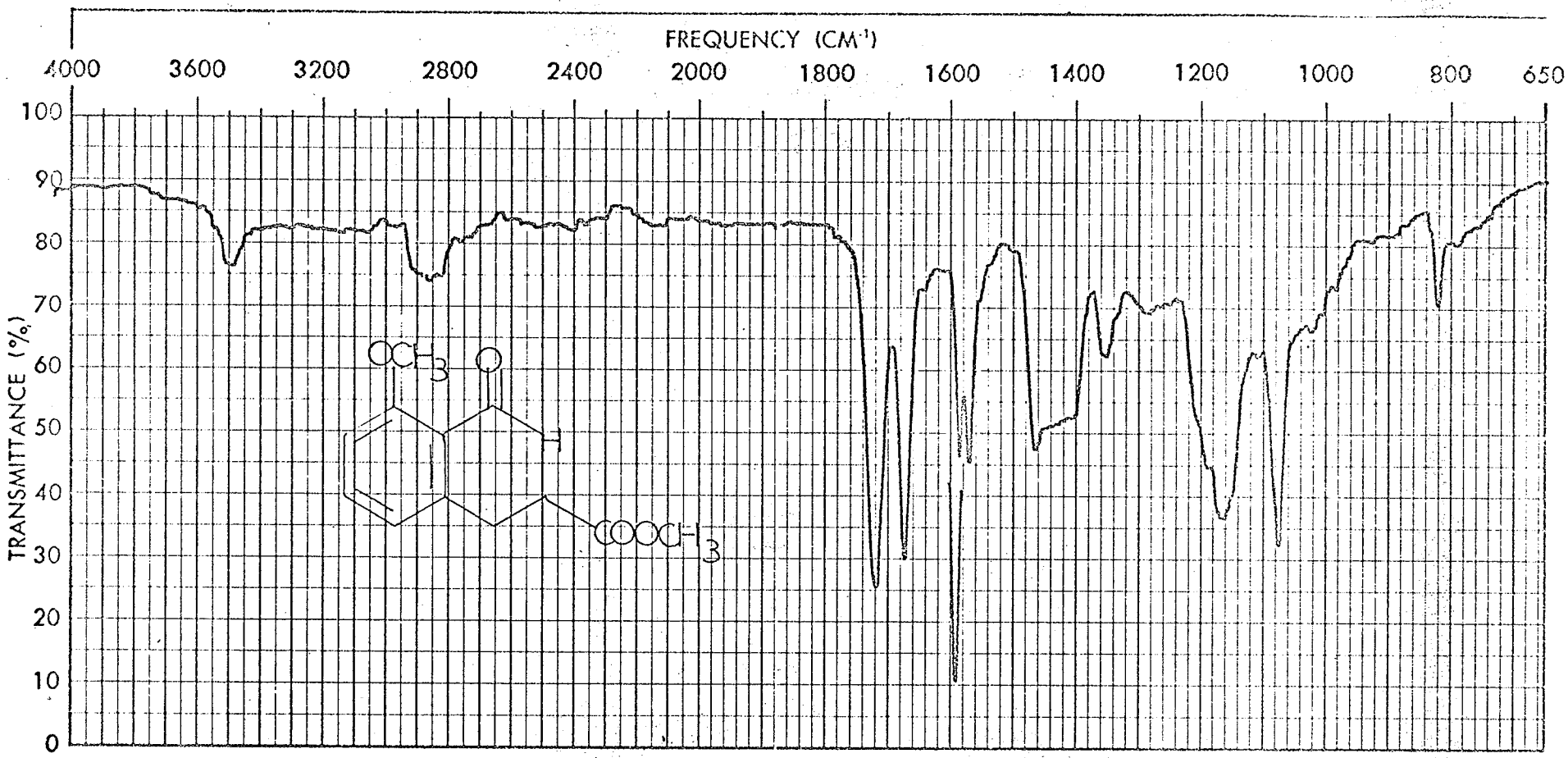


FIGURE 11. Infrared spectrum no. 11 methyl-3-(2-formyl-3-methoxy-phenyl)-propanoate (LXIV).

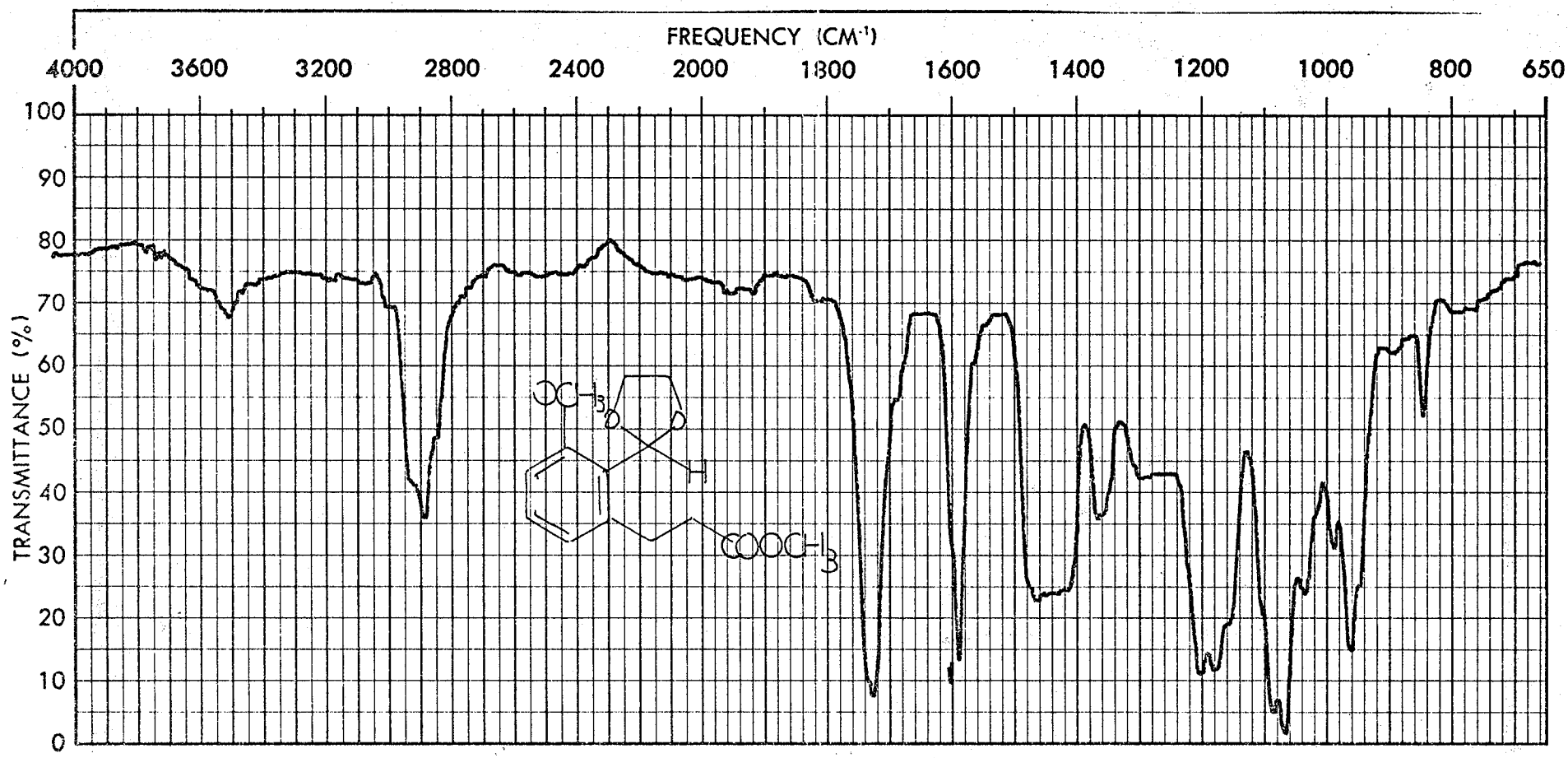


FIGURE 12. Infrared spectrum no. 12. The acetal (LXV) from (LXIV).

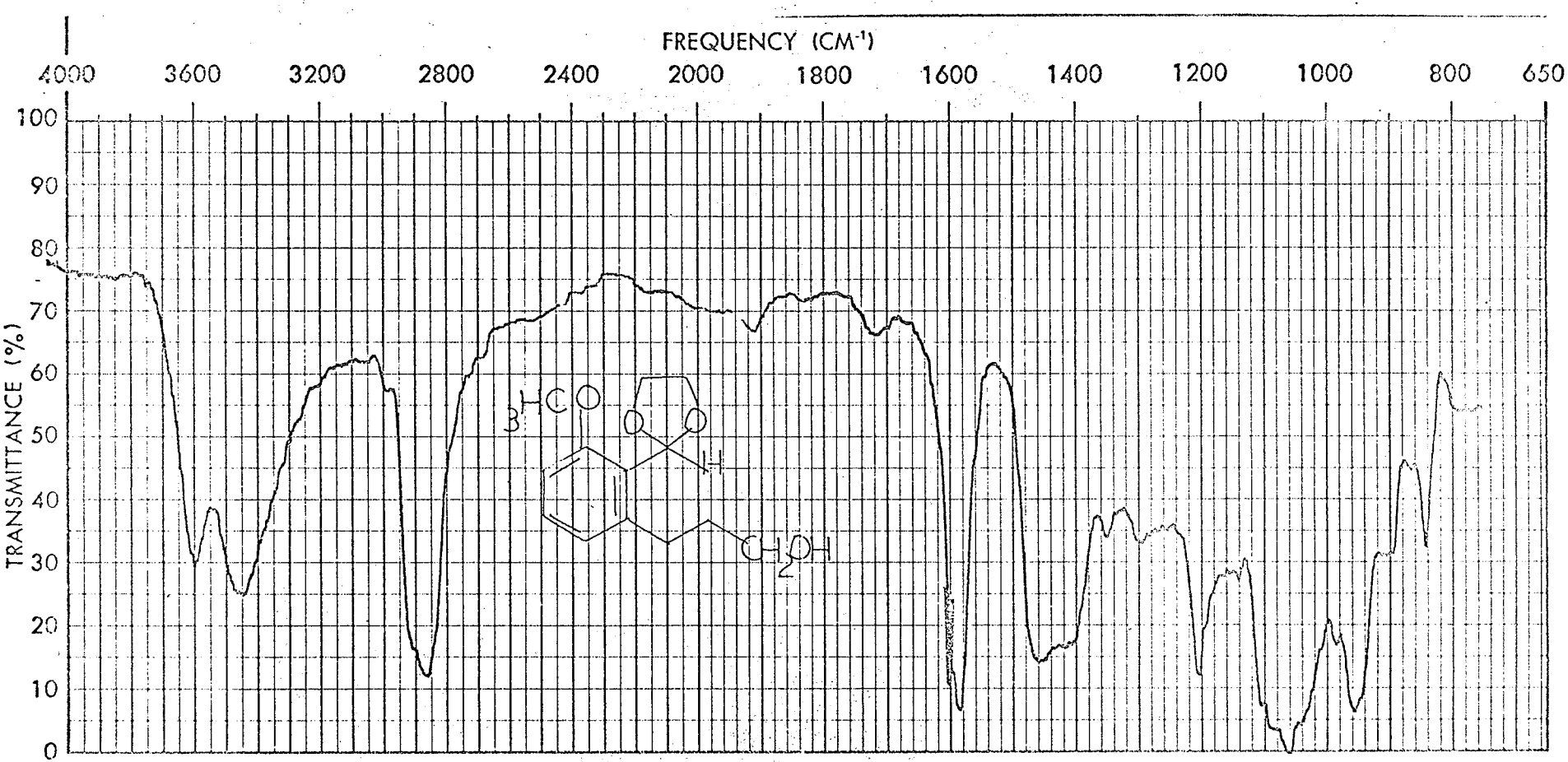


FIGURE 13. Infrared spectrum no. 13. 2-methoxy-6-(3-hydroxypropyl)-benzaldehyde (LXVI).

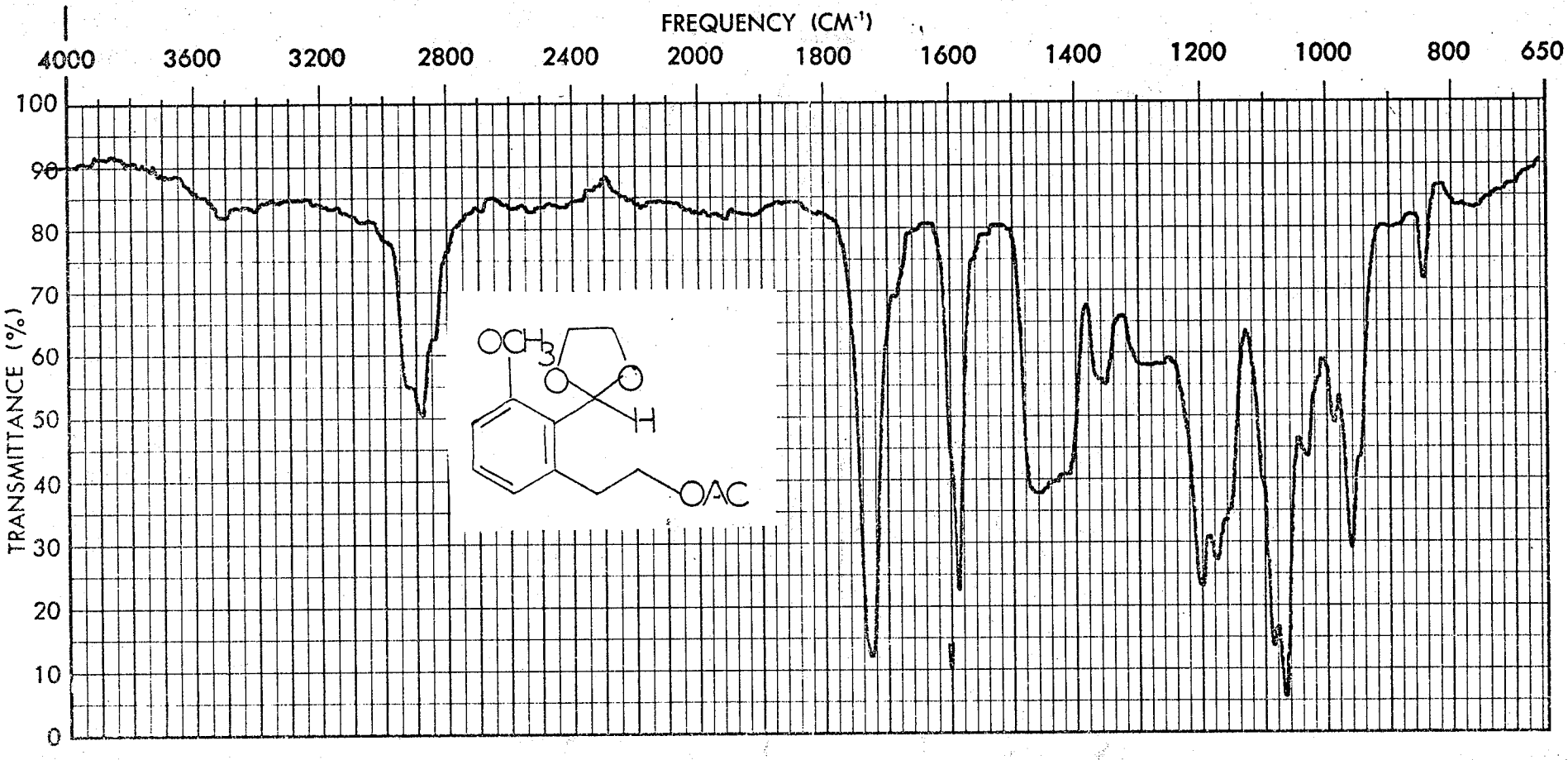


FIGURE 14. Infrared spectrum no. 14. The acetate (LXVII) from the alcohol (LXVI).

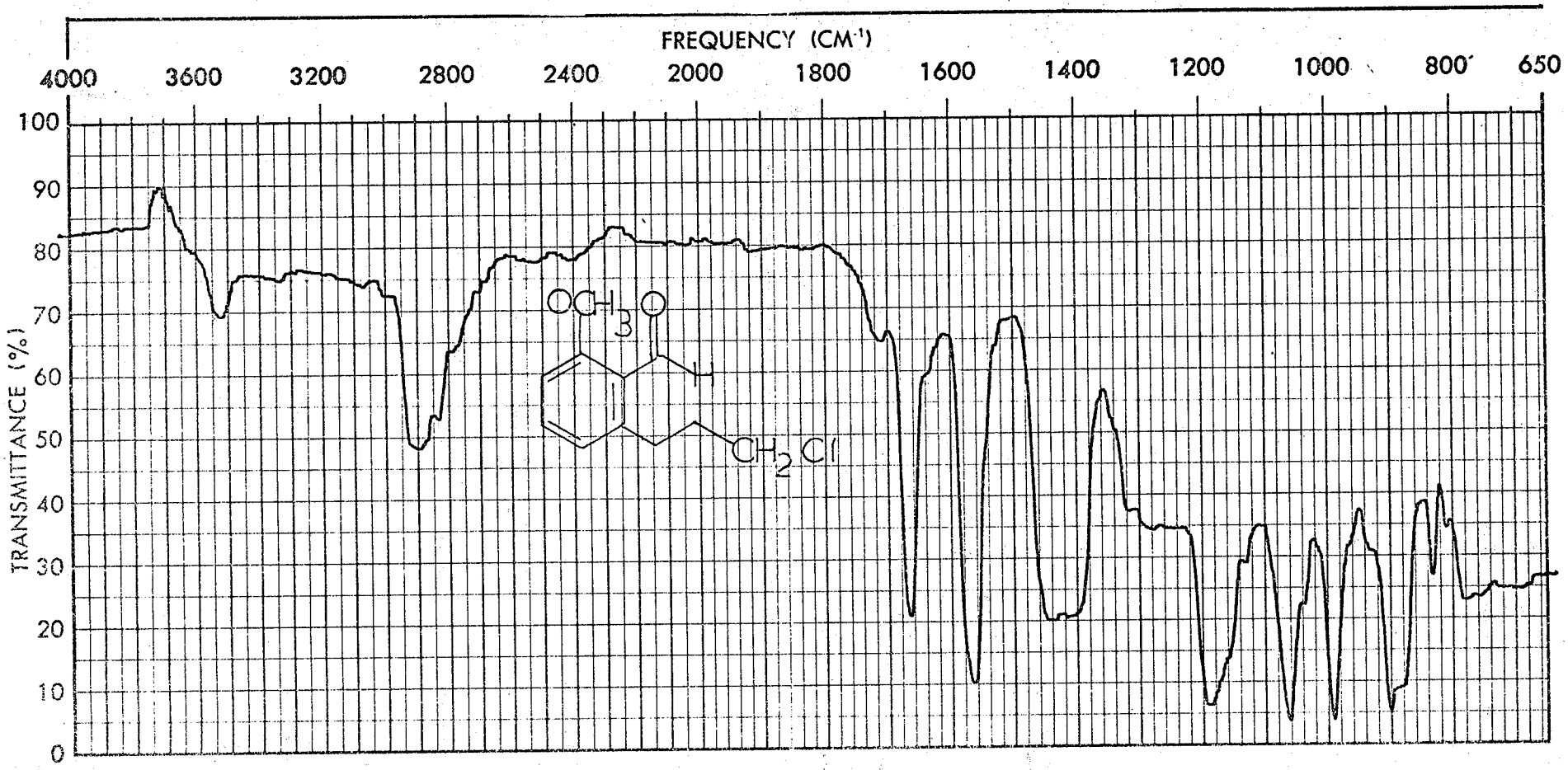


FIGURE 15. Infrared spectrum no. 15. 2-methoxy-6-(3 -chloropropyl)-benzaldehyde
(LXIX)

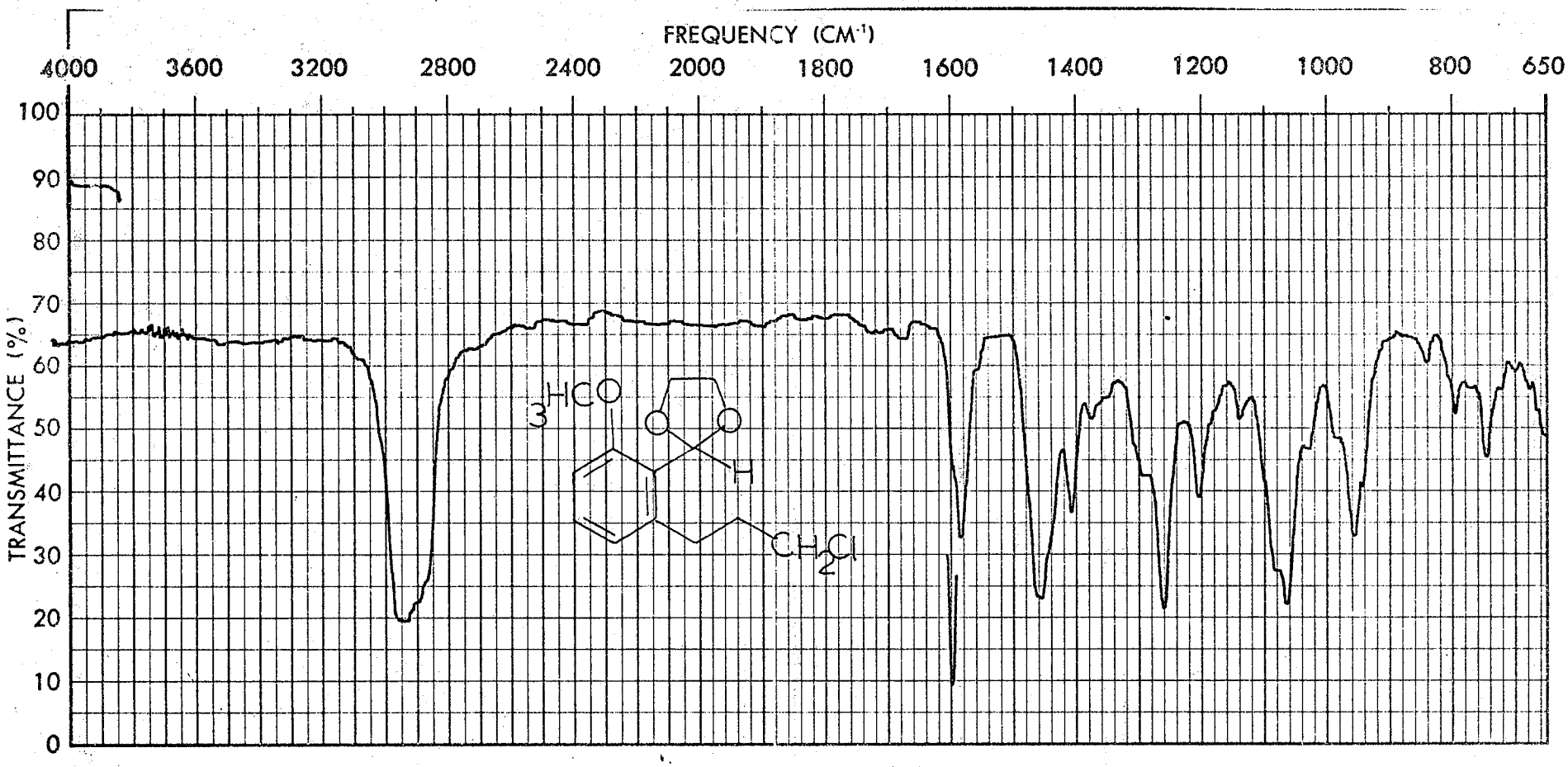


Figure 16. Infrared spectrum no. 16. The acetal (LXX) of 2-methoxy-6-(3 -chloropropyl)-benzaldehyde (LXIX).

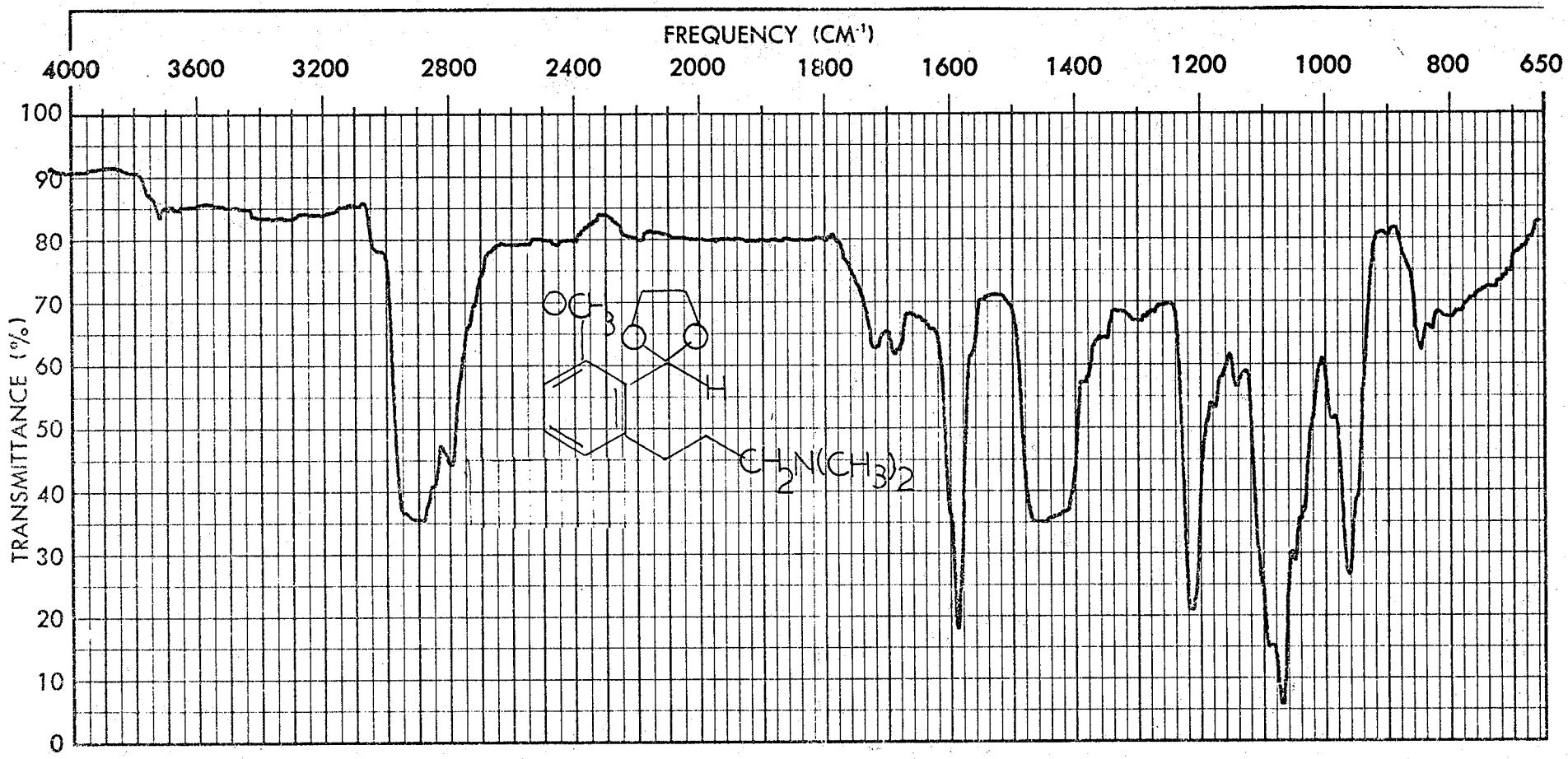


FIGURE 17. Infrared spectrum no. 17. The dimethyl amine (LXXII).

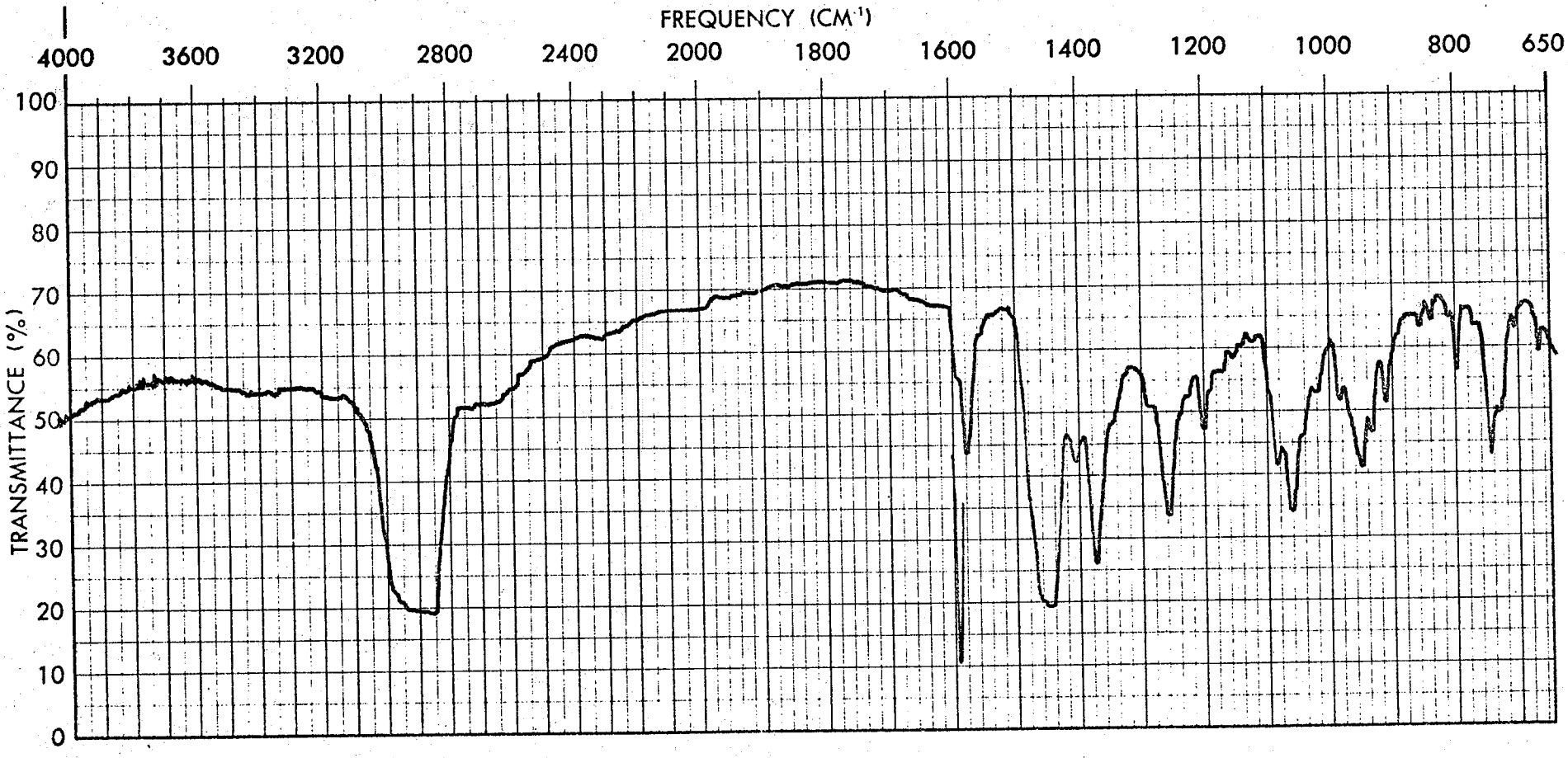


FIGURE 18. Infrared spectrum no. 18. Quaternary salt of the amine,(LXXIII).

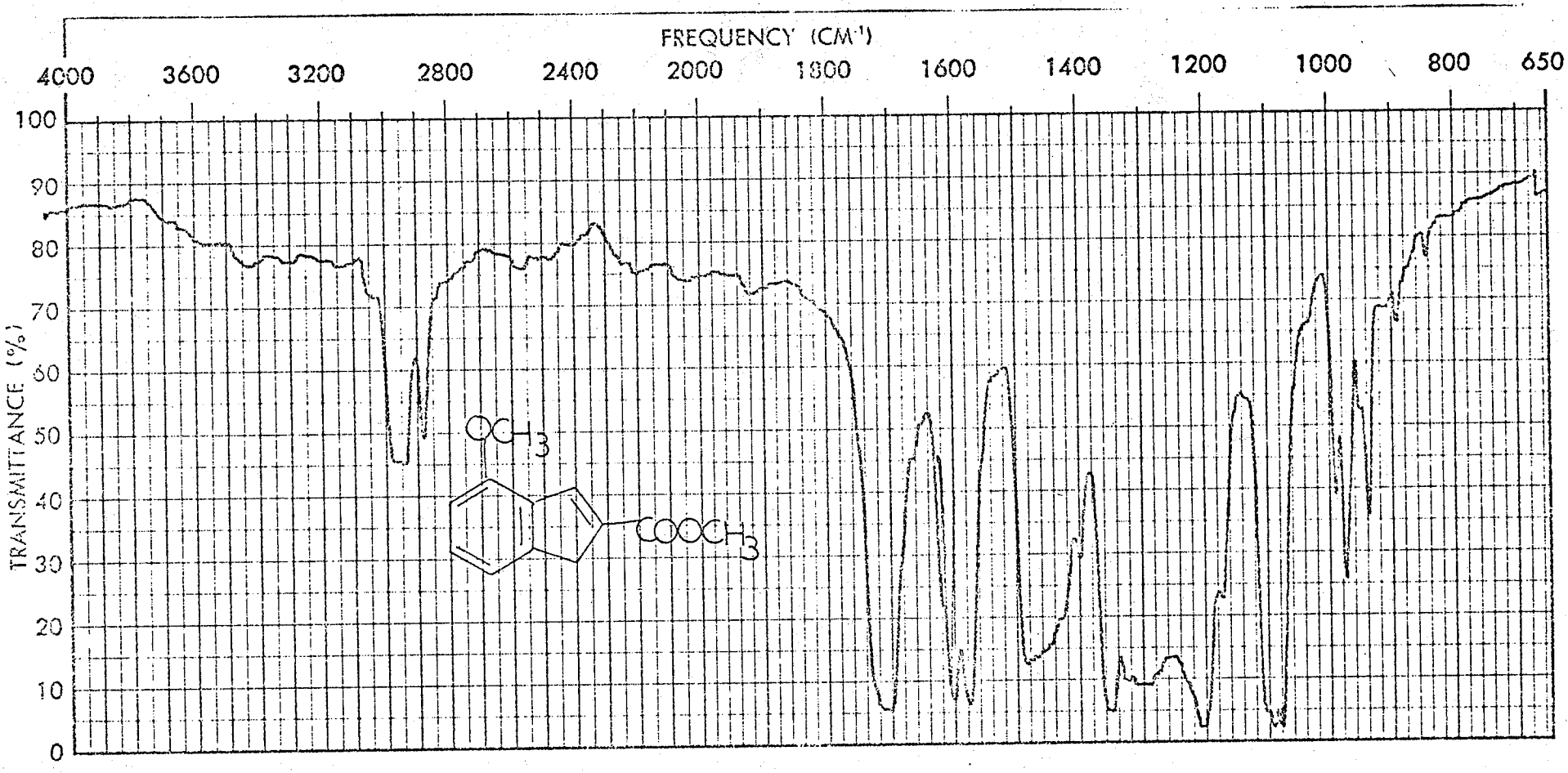


FIGURE 19. Infrared spectrum no. 19. 2-carbomethoxy-4-methoxy-indene (LXXV).

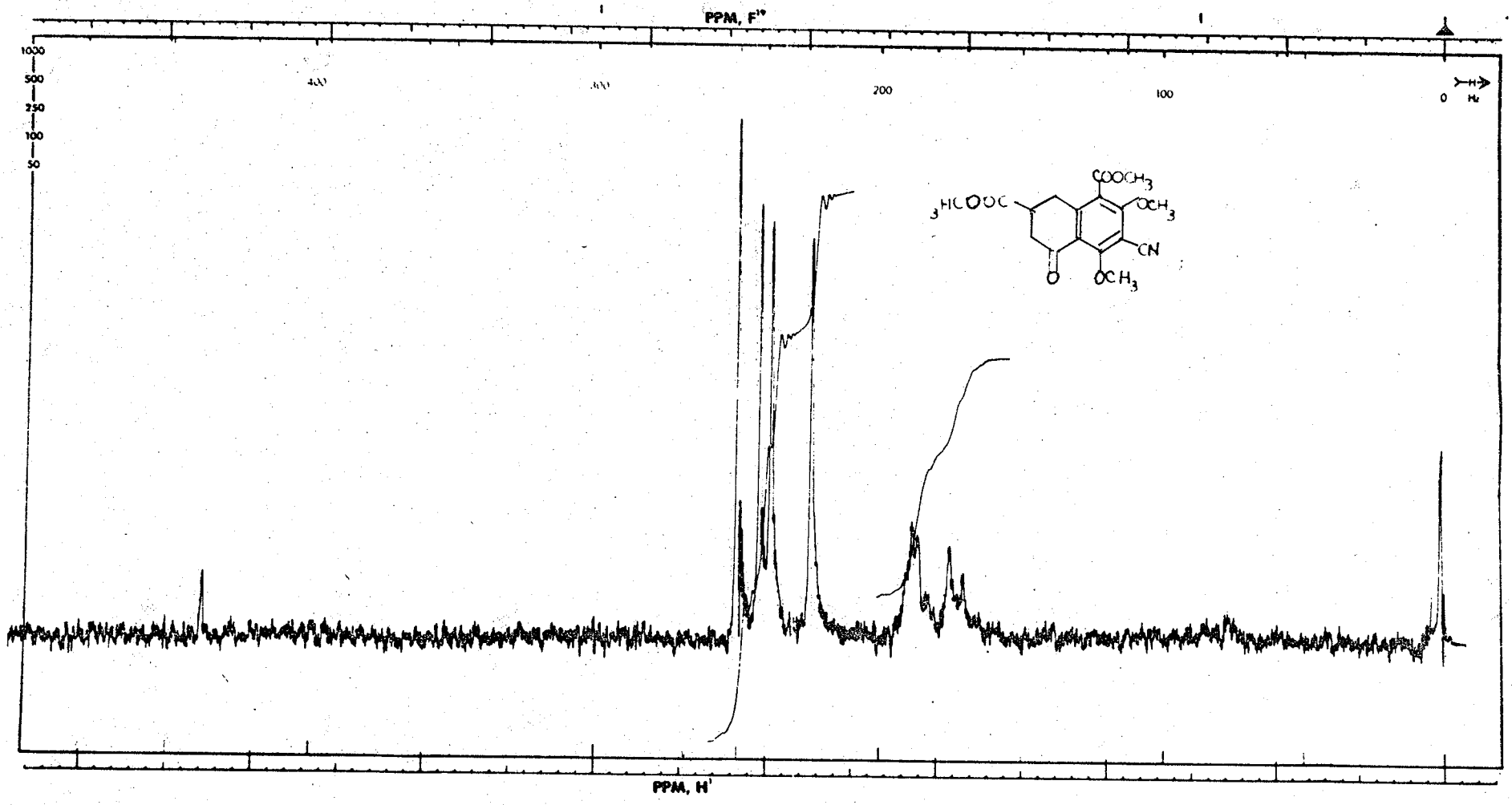


FIGURE 20. Nuclear magnetic resonance spectrum no. 1. Tetralone (XLV).

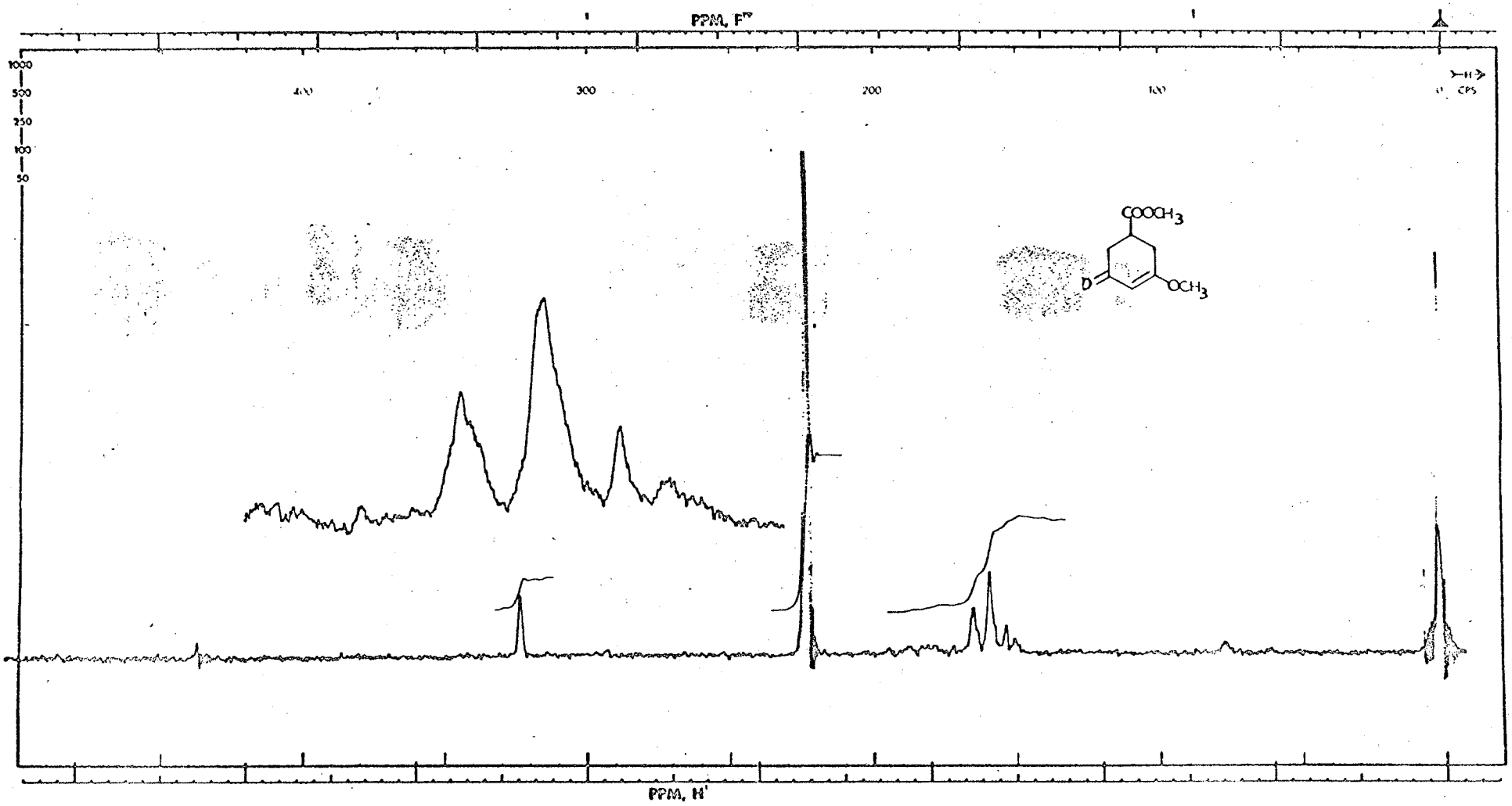


FIGURE 21. Nuclear magnetic resonance spectrum no. 2. Methyl cyclohex-2-ene-1-one-5-carboxylate-methyl ether (XLIX).

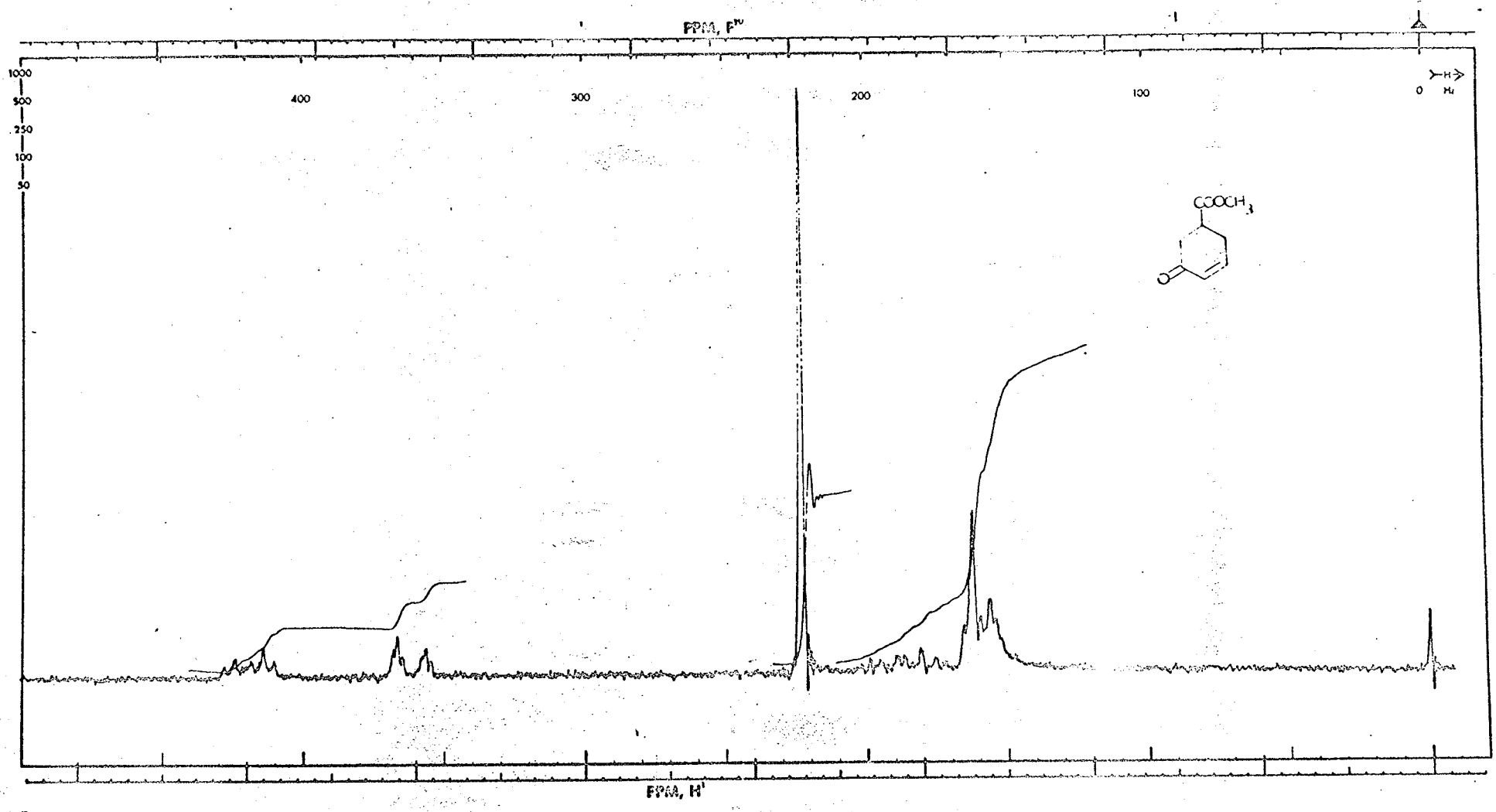


FIGURE 22. Nuclear magnetic resonance spectrum no. 3.
Methyl cyclohex-2-ene-1-one-5-carboxylate (XLI).

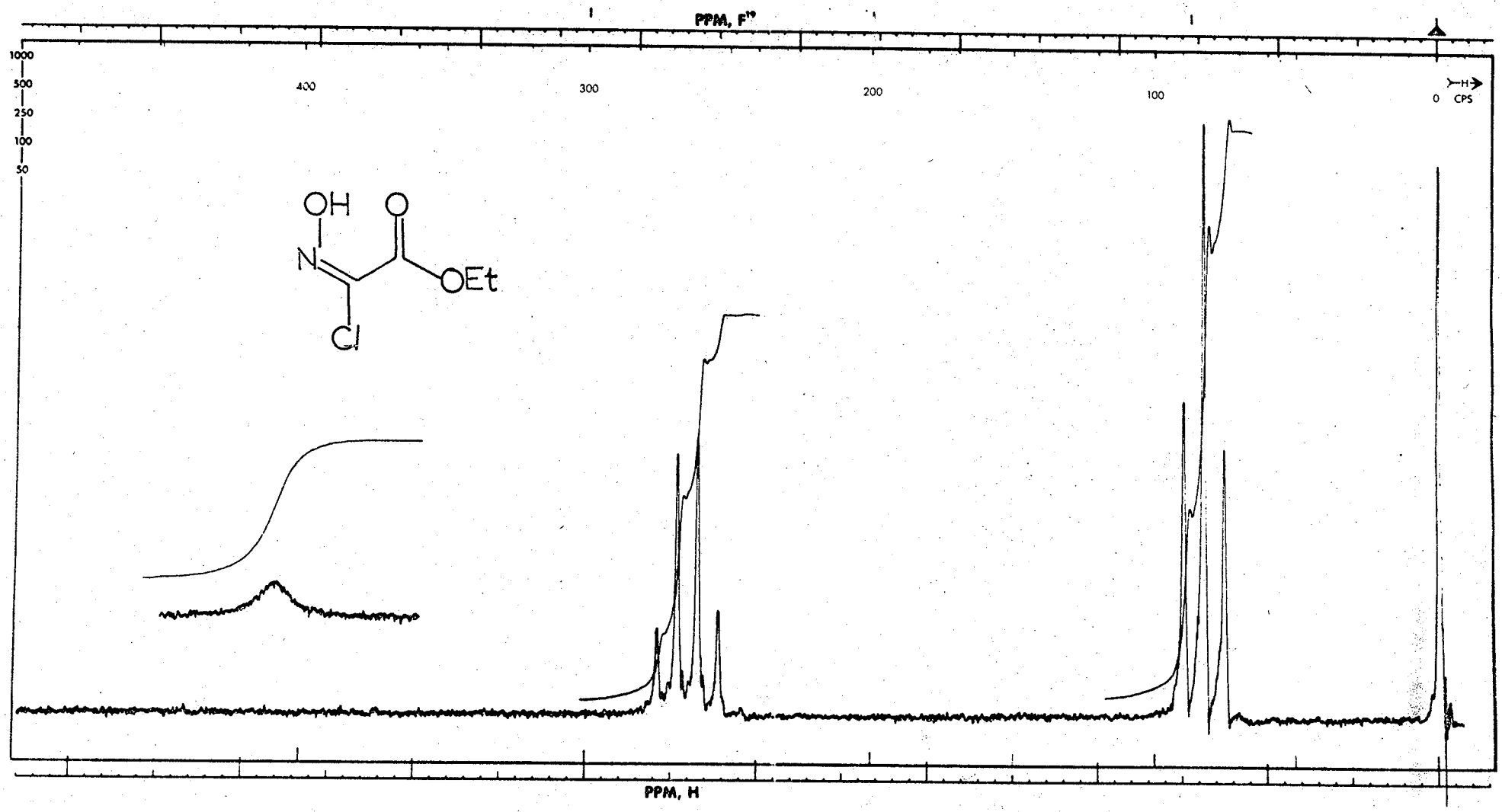


FIGURE 23. Nuclear magnetic resonance spectrum no. 4.
Ethylchlorooximinoacetate (LI).

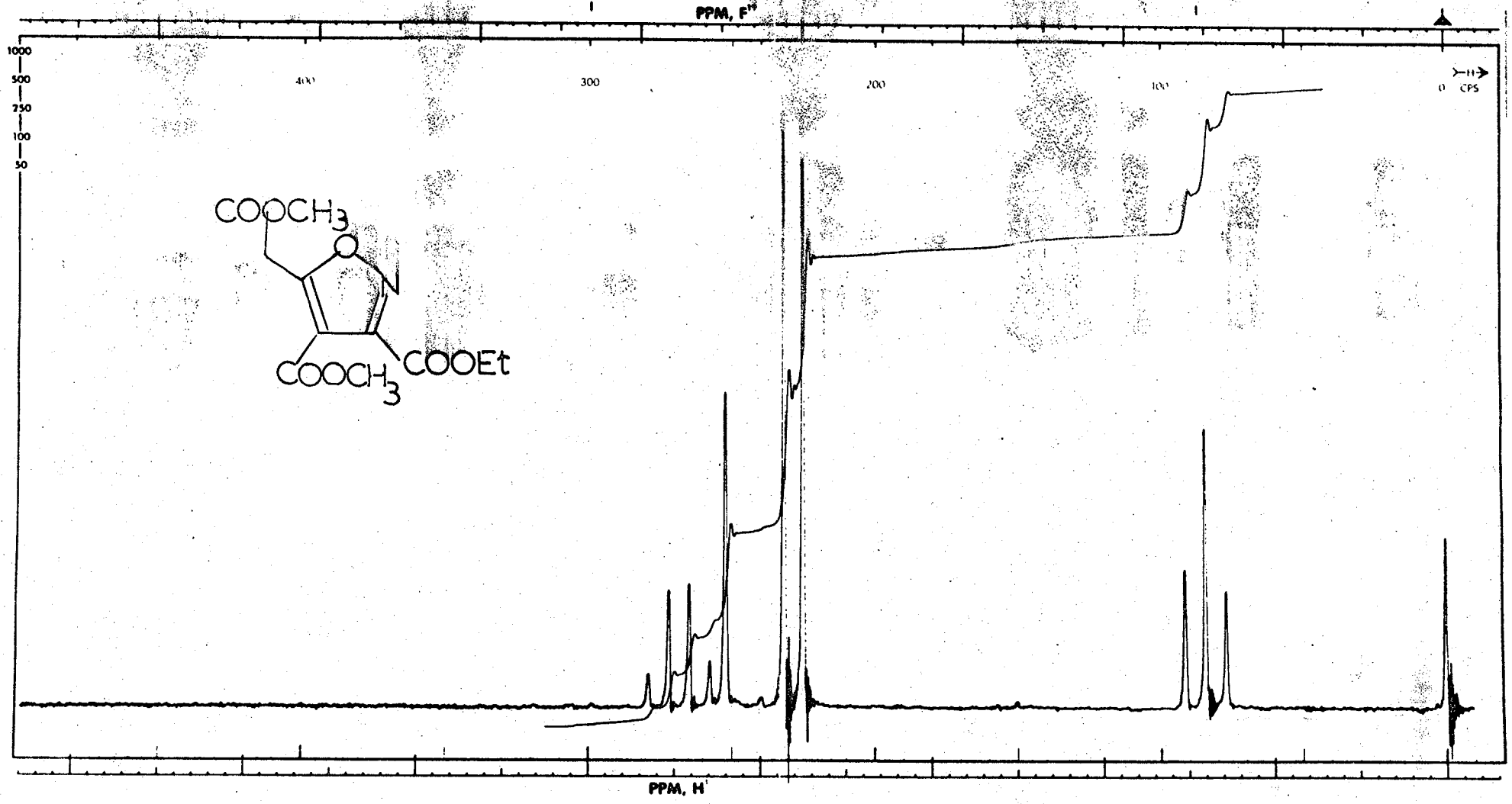


FIGURE 24. Nuclear magnetic resonance spectrum no. 5. Isoxazole (XLII).

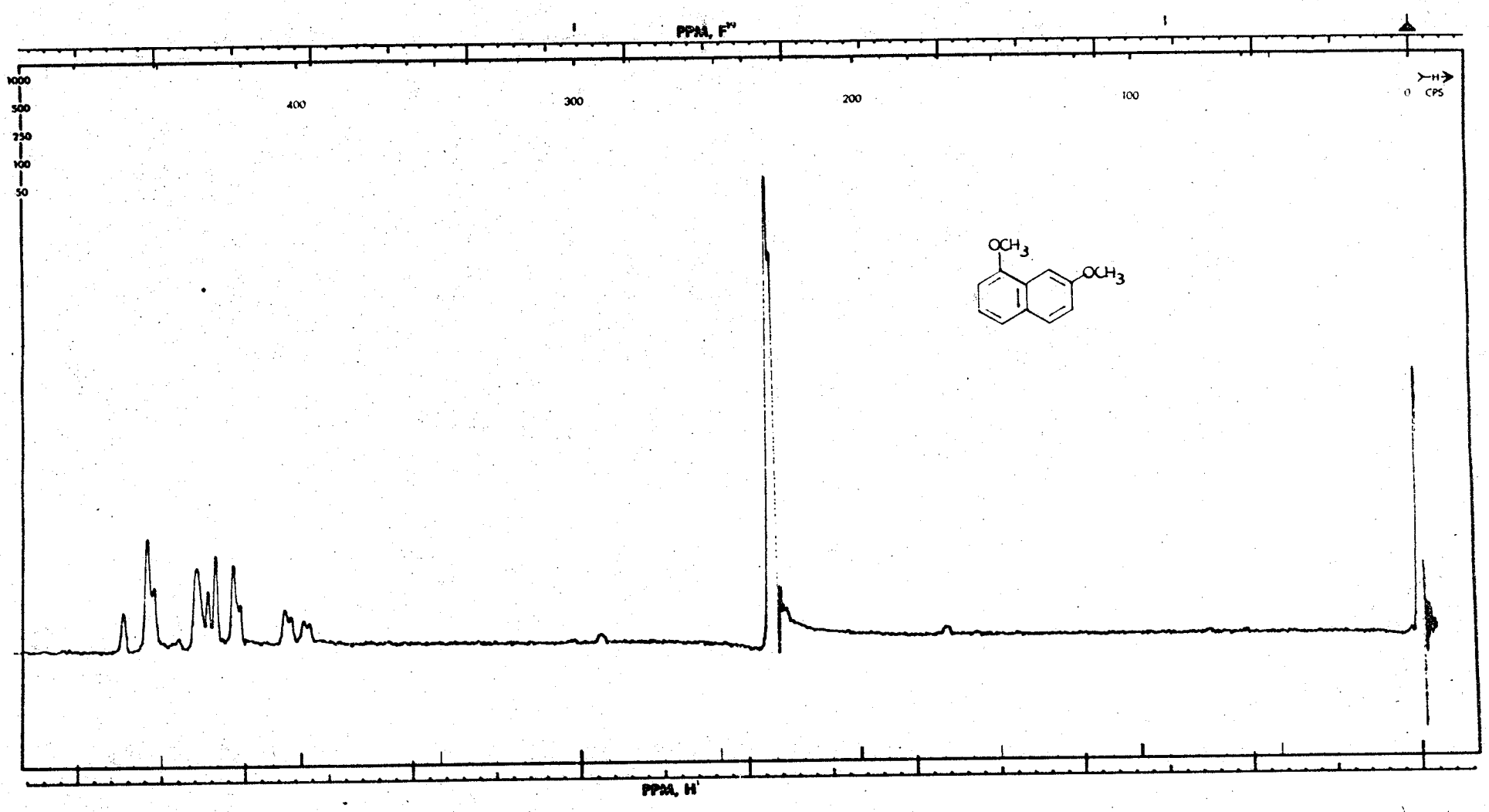


FIGURE 25. Nuclear magnetic resonance spectrum no. 6. 1,7-dimethoxynaphthalene (LVIII).

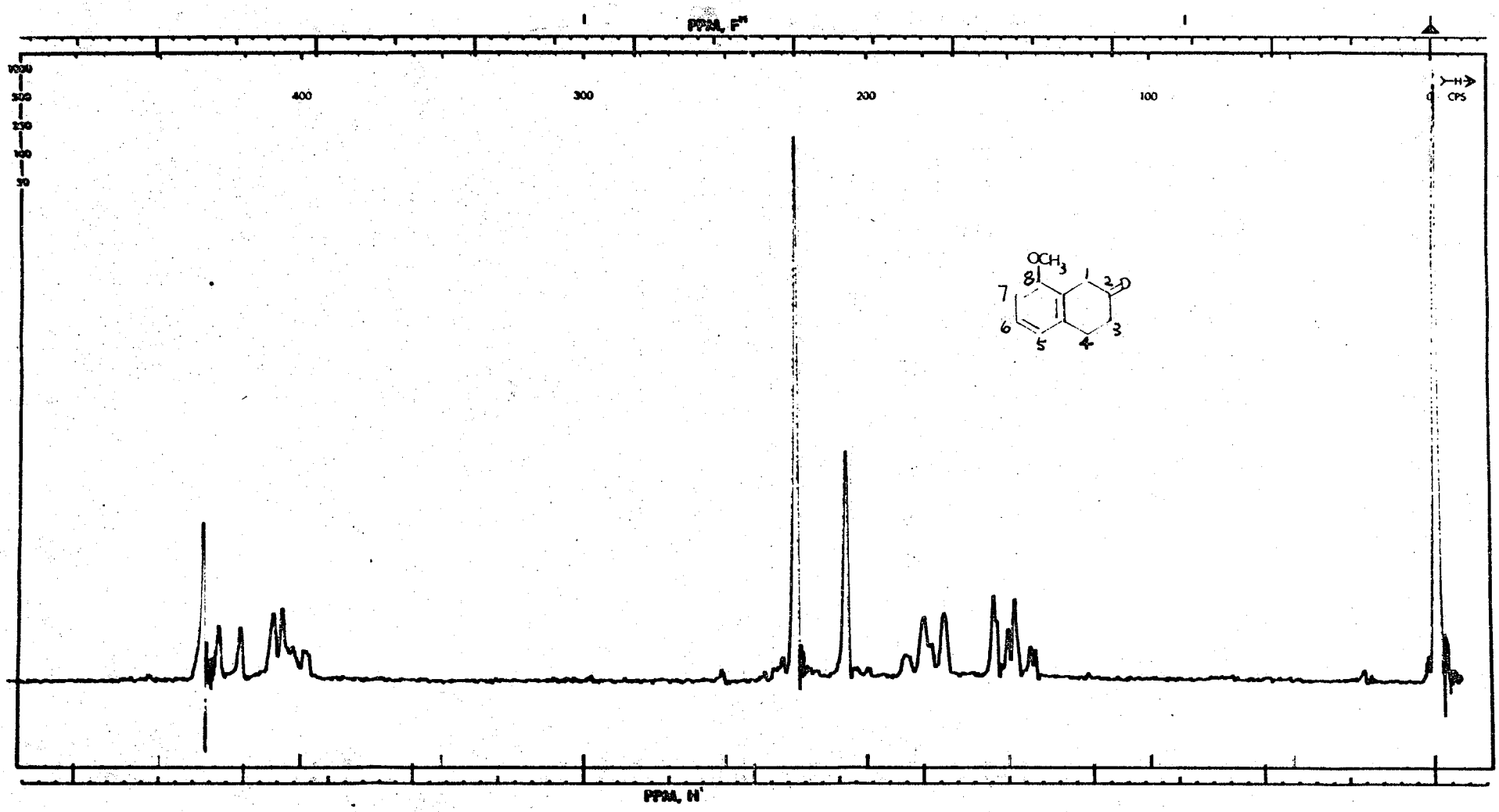


FIGURE 26, Nuclear magnetic resonance spectrum no. 7.
8-methoxy-2-tetralone (LX).

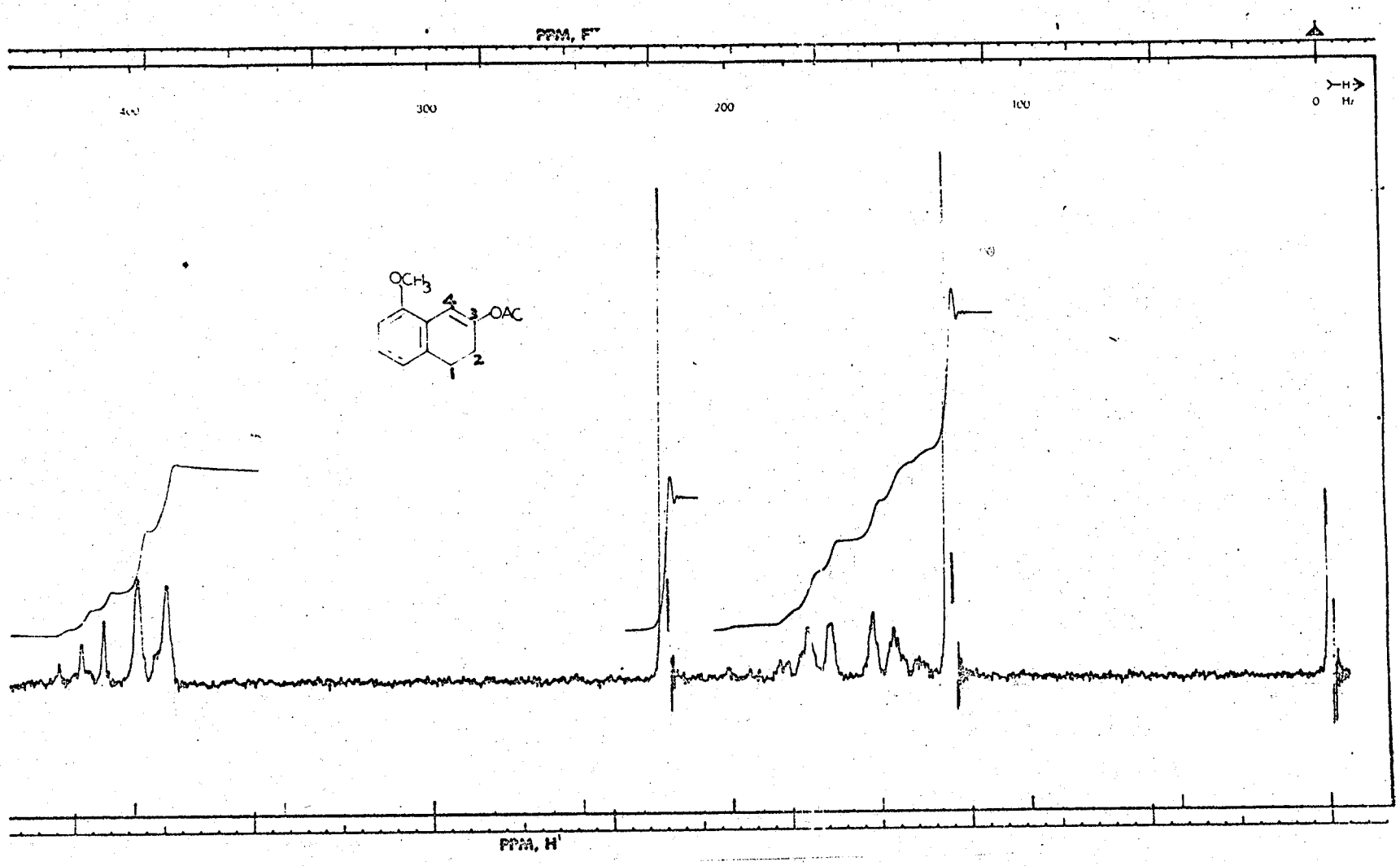


FIGURE 27. Nuclear magnetic resonance spectrum no. 8.
1,2-dihydro-3-acetoxy-5-methoxynaphthalene (LXI).

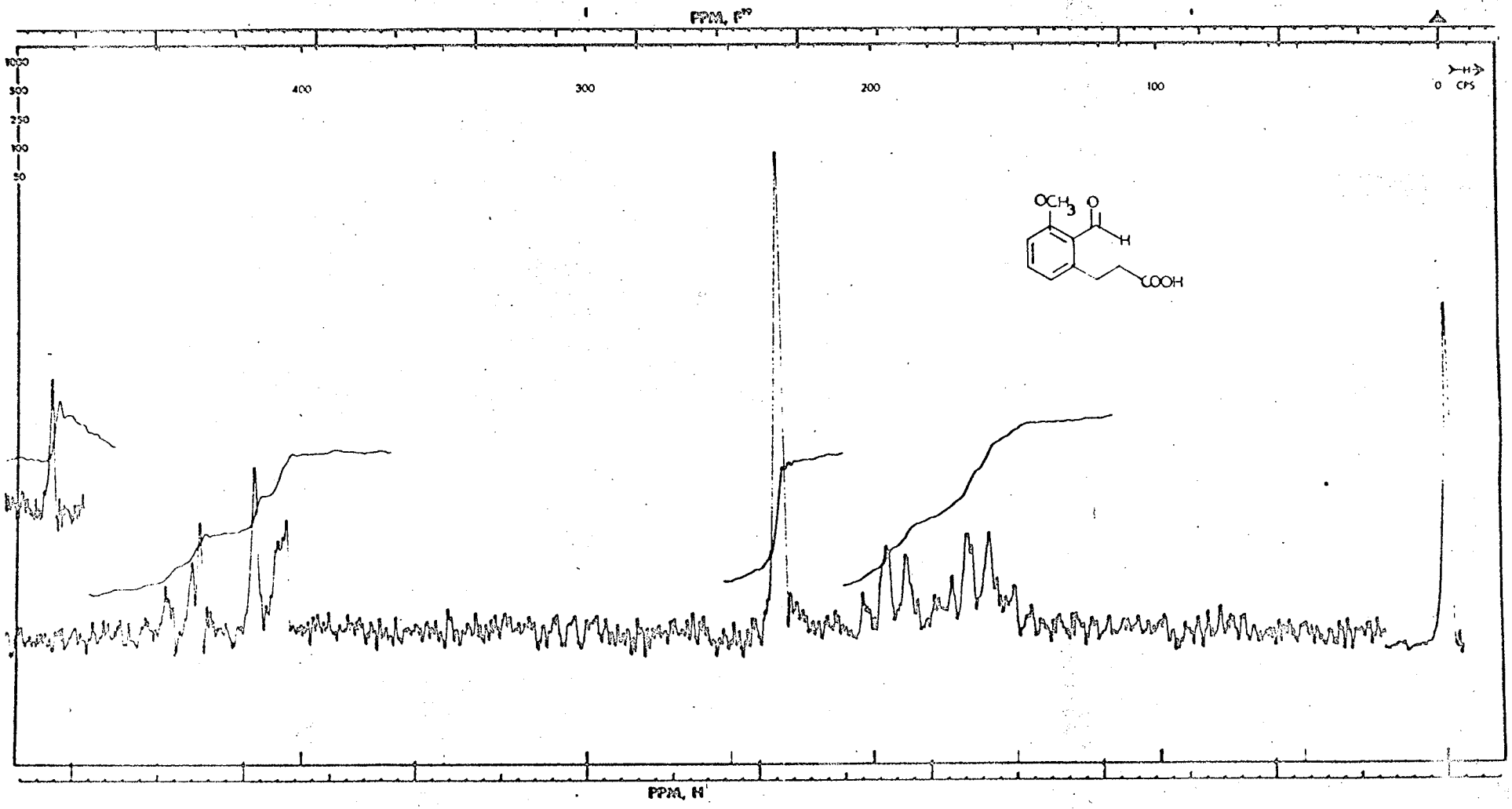


FIGURE 28 Nuclear magnetic resonance spectrum no. 9. 3-(2-formyl-3-methoxyphenyl)-propanoic acid (LXIII).

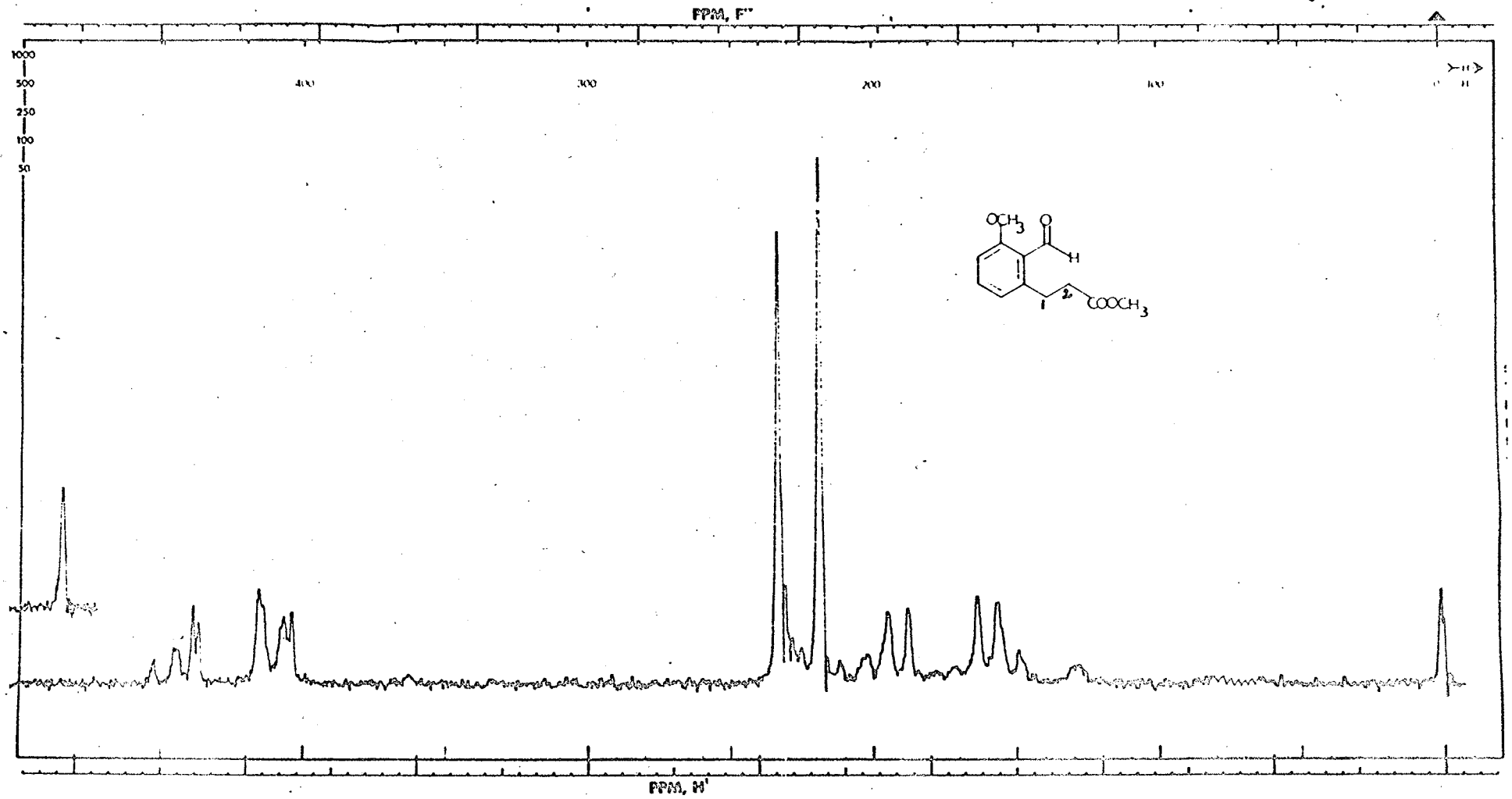


FIGURE 29. Nuclear magnetic resonance spectrum no. 10. methyl-3-(2-formyl-3-methoxyphenyl)-propanoate (LXIV).

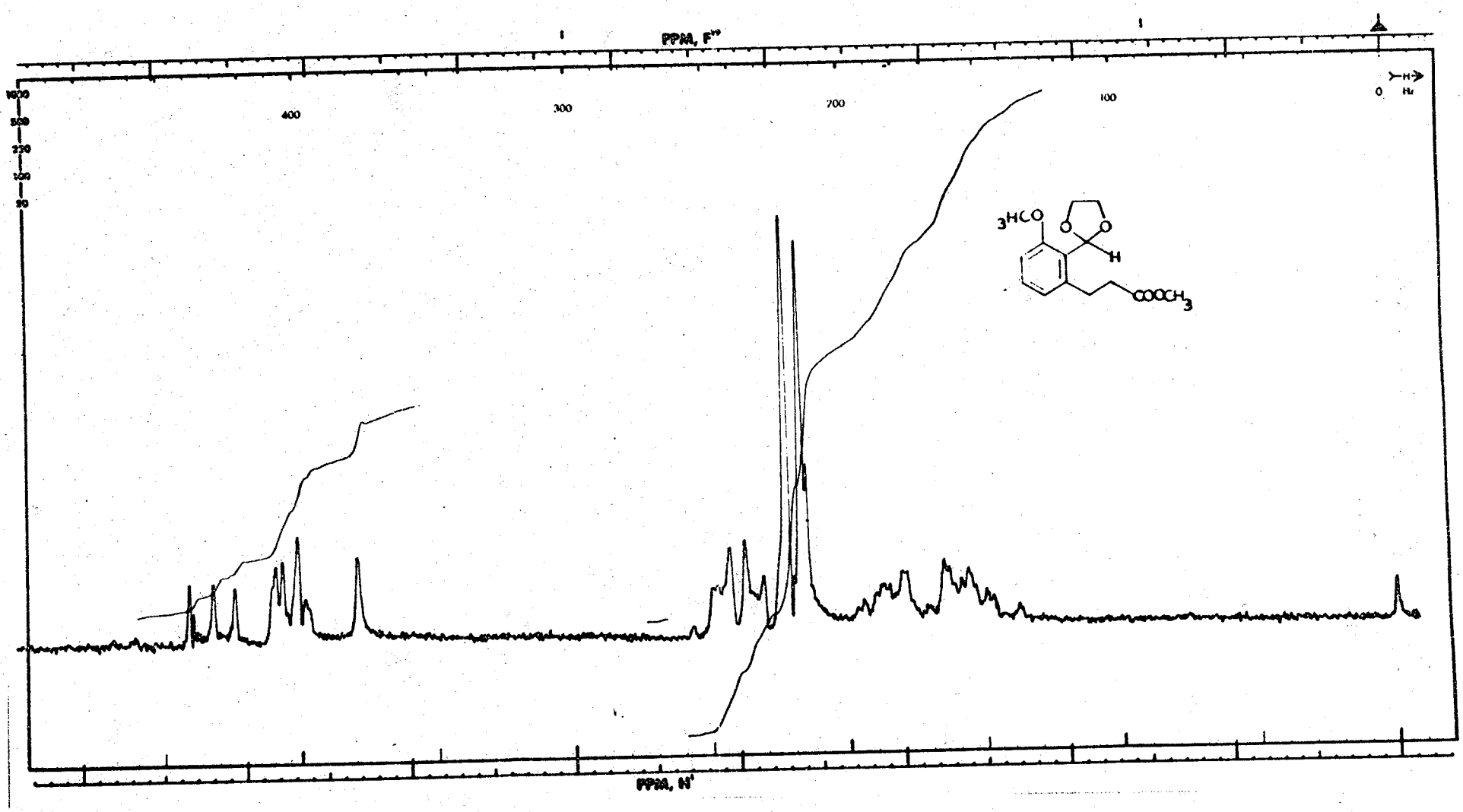


FIGURE 30. Nuclear magnetic resonance spectrum no. 11. The acetal (LXV) from the ester (LXIV).

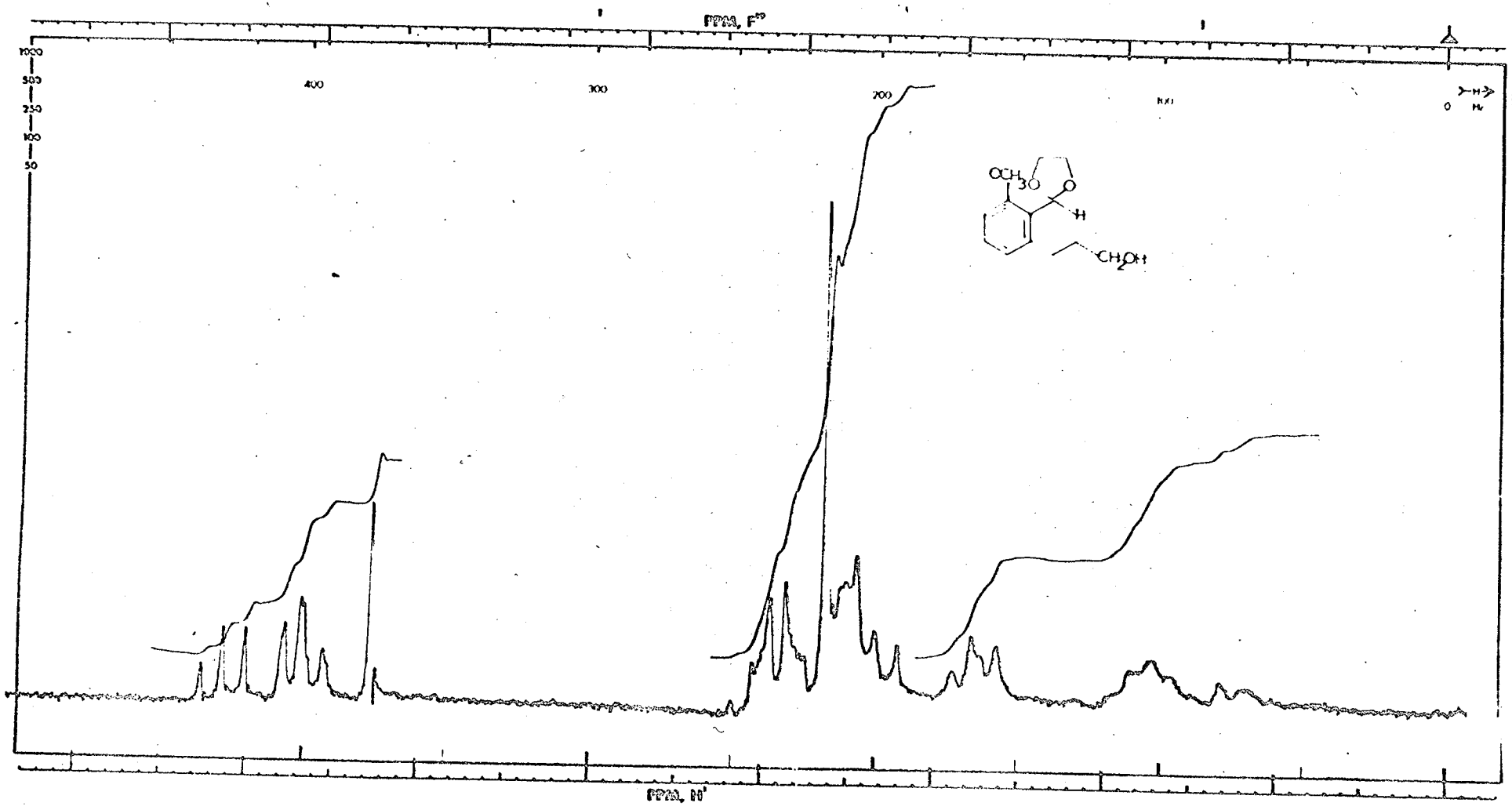


FIGURE 31. Nuclear magnetic resonance spectrum no. 12. 2-methoxy-6-(3-hydroxypropyl)-benzaldehyde (LXVI).

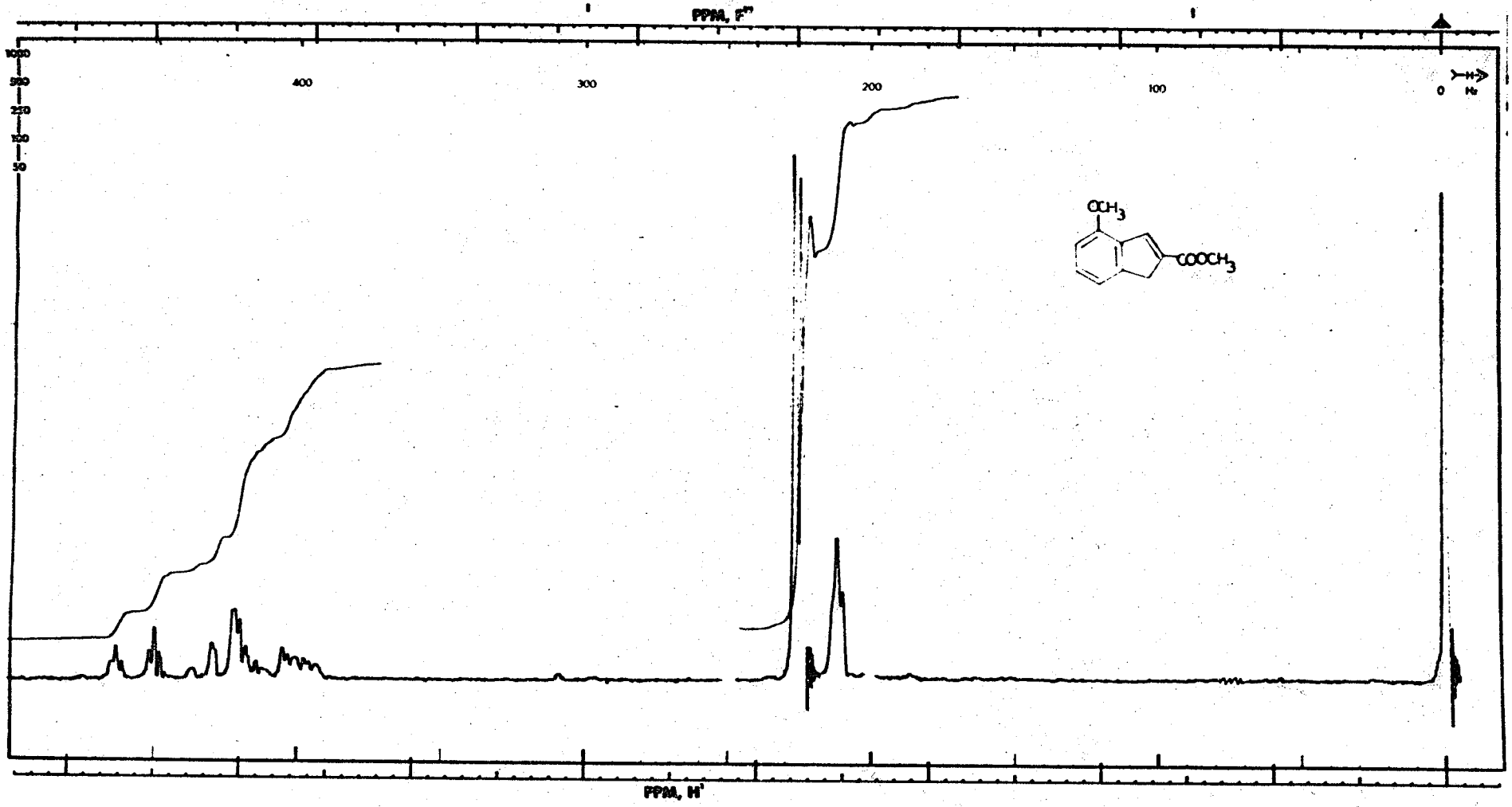


FIGURE 32. Nuclear magnetic resonance spectrum no. 13. 2-carbomethoxy-4-methoxy-indene (LXXV).

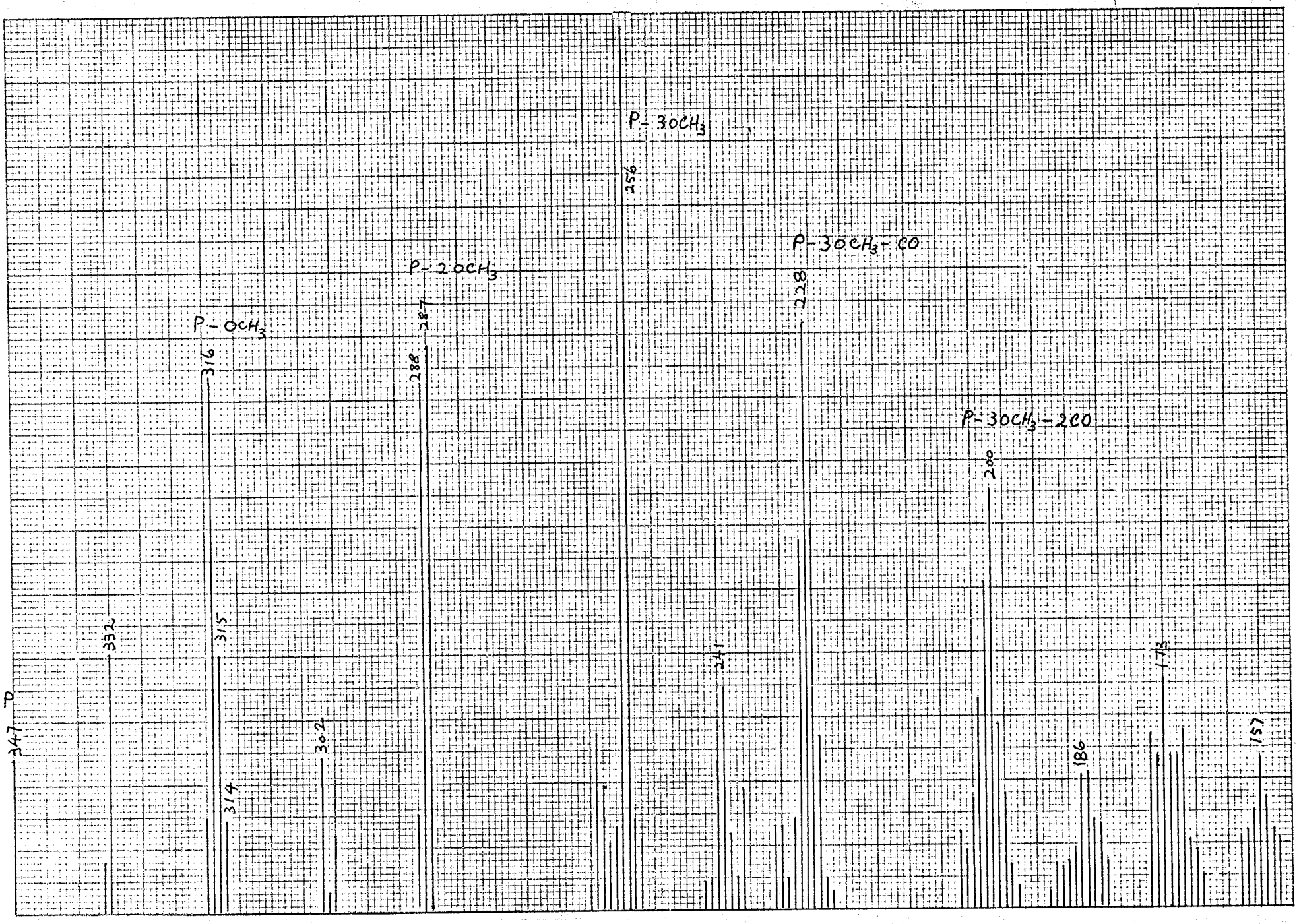


FIGURE 33. Mass spectrum no. 1. Tetralone (XLV).

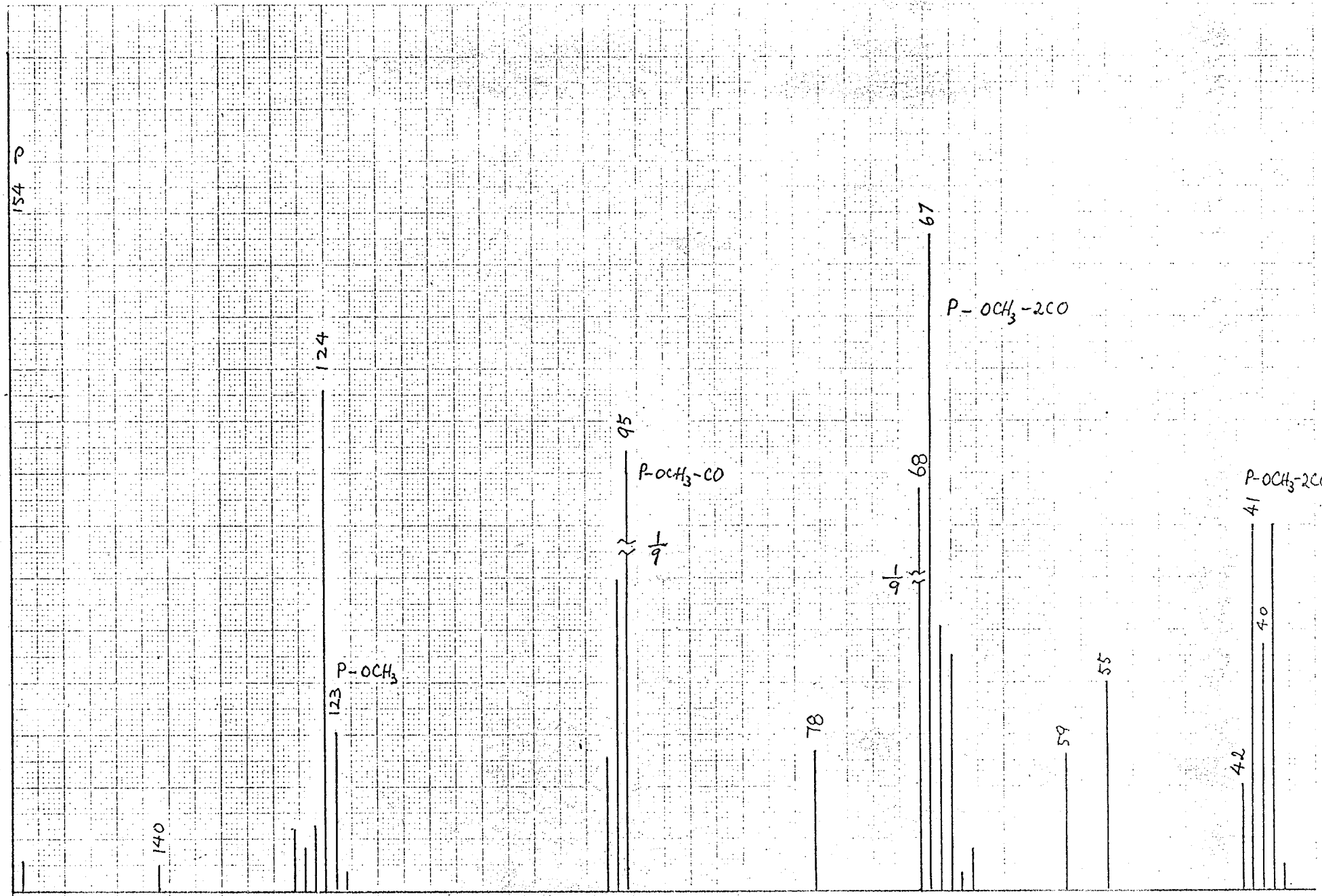


FIGURE 34. Mass spectrum no.2. Methyl cyclohex-2-ene-1-one-5-carboxylate (XLI).

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