# COMPOUNDS LEADING TO THE TOTAL SYNTHESIS OF TETRACYCLINES

by

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## ABSTRACT

Several compounds which are intermediates in the total synthesis of tetracycline,I,and its analogs have been prepared.5-carboxy-6,8-dihydroxy-7-cyano tetralone,XXII,was prepared from glycine ethylesterhydrochloride,XI,dimethyl acetone dicarboxylate,XIII,and 2-cyclohexenone,XVI.2-methoxycarbonyl-3-methoxy-6-bromophenylacetonitrile,XLIV,was prepared from m-methoxy benzyl alcohol,XXV,via 4-bromo-7-methoxy indanone,XXXV,and 2-oxime-4-bromo-7-methoxy indandione,XLI.The 5-membered ring was opened by a second order Beckmann rearrangement.3-oxo-4-cyclohexenylcarboxamide,LV, was prepared from m-hydroxy benzoic acid via a Birch reduction.Model BCD ring systems of tetracyclines have been prepared by condensing XLIV with LV and XVI to give hydroanthracene systems.

Some suggestions to complete the synthesis of tetracyclines have also been made.

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TABLE OF REACTION SCHEMES

## INTRODUCTION

Antibiotics were introduced to the chemical and medical world with Flemings discovery of pennicilin in 1929 (1), although it was not until World War II that the discovery was utilized. The first clinical use of pennicillin was in 1941 (2) and large scale production was not feasible until 1943.

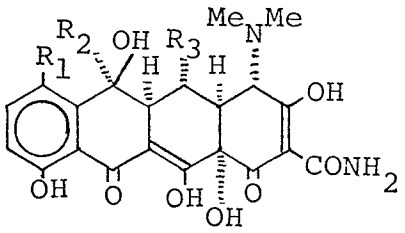
Pennicillin and Streptomycin, discovered by Waksman in 1944, were the only generally used antibiotics until 1948 (3) when Duggar (4) discovered aureomycin. At that time this antibiotic had the tremendous advantage that it could be administered either orally or intravenously whereas the other two had to be given by injection. Furthermore aureomycin had a wide range of chemotherapeutic activity including most organisms susceptible to pennicillin and streptomycin (5).

Since Duggar's discovery of aureomycin from cultures of streptomyces aureofaciens a number of tetracycline derivatives have been discovered from various strains of streptomyces and their mutants. A few of the common tetracyclines, their source and date of discovery are listed in table I.

Table I lists only a few of the earlier tetracyclines known. Barret (6) in his excellent review lists over

TABLE I

| TETRACYCLINE DERIVATIVE | STRUCTURE | SOURCE | DATE DISCOVERED | REF. |
|---|---|---|---|---|
| Tetracycline | I | Streptomyces aureofaciens | 1953 | 7,8,9 |
| Aureomycin (7-chlorotetracycline) | II | " | 1948 | 4 |
| Terramycin (5-hydroxy-tetracycline) | III | Streptomyces rimosus | 1950 | 10 |
| 6-demethyl tetracycline | IV | Streptomyces aureofaciens | 1957 | 11 |
| 6-demethyl-7-chlorotetra-cycline | V | " | 1957 | 11 |
| 7-bromotetracycline | VI | " | 1955 | 12 |




| | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| I | H | $CH_3$ | H |
| II | Cl | $CH_3$ | H |
| III | H | $CH_3$ | OH |
| IV | H | H | H |
| V | Cl | H | H |
| VI | Br | $CH_3$ | H |

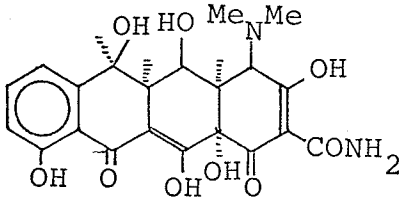
two hundred tetracyclines and tetracycline derivatives some of which are synthetically produced and others biologically from normal and mutant strains of streptomyces aureofaciens and streptomyces rimosus.

Work on the chemistry and structure of tetracyclines was started shortly after the discovery of aureomycin, not only because they were such effective chemotherapeutic agents but because they represent a new class of structurally interesting natural products. The many labile functional groups in these products makes their chemistry very complex and this represents an immediate challenge to the organic chemist. The many reactions which occur at several centres of the tetracyclines have been discussed in a number of reviews (13,14,15).

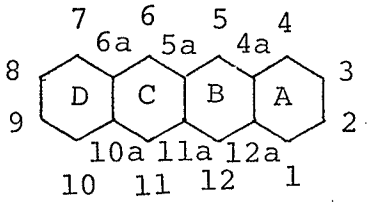
The relatively short time required for the structure of terramycin to be elucidated reflects the intense effort which went into the chemical studies of the tetracyclines. Terramycin was discovered in 1950 (10) and in 1953 Woodward published a complete structure (16) including a stereochemical structure defining the six asymmetric centres as in VII. A number of summaries of Woodward's work have been published (13,14,15). This structure differed from that (of terramycinhydrochloride) obtained by Takeuchi 1960 (17) by X-ray analysis only in the configuration about $C_4$ and $C_5$. (The numbering and labelling

of the tetracyclines is shown in VIII). III is the accepted structure of terramycin today.

Shortly after Woodward published a complete structure for terramycin it was shown that both aureomycin (18,19) and terramycin are substitution products of tetracycline I (19). Again, using X-ray techniques, it was shown that aureomycin and terramycin are not only structurally related but have the same configuration about their asymmetric centres (20). At this point it is logical




VII

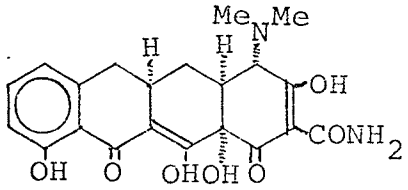



VIII

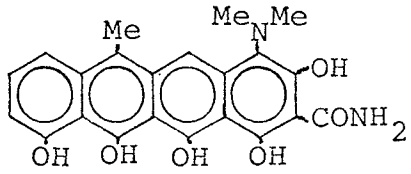
to extend the configuration of terramycin to all other tetracyclines isolated from streptomyces.

As mentioned above the structure of the tetracyclines presents a tremendous challenge to the organic chemist and synthetic work was attempted very shortly after the structure was known. Although a large number of tetracycline analogs and their derivatives were prepared (6,21) no total synthesis was reported until Woodward and coworkers reported the total synthesis of 6-demethyl-6-deoxy-tetracycline, IX, in a communication

(22). A full report was published in 1968 (23).




IX




X

In 1968 Muxfeld and coworkers in a communication reported the total synthesis of dl-terramycin, III, (24).

Although it appears very unlikely that tetracyclines will be prepared synthetically on a commercial scale due to their complex chemistry and ease of preparation of the natural product in large fermentation tanks, the analogs prepared are useful as a confirmation of structure and in the study of activity, mode of action, and biosynthetic routes. These topics have been reviewed by Barret (6)*

Some of the work done in this laboratory is aimed at the total synthesis of tetracycline analogs and precursors using an approach completely different from that taken by other workers, for example Woodward and Muxfeld (see above).

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* An excellent summary of laboratory scale preparation of tetracyclines has been published by Evans, Richard, and Castleman (25).

The problem is approached by synthesizing the AB ring system, or a close relative of it, and the D ring system and then fusing them with the formation of the C ring.

The preparation of the immediate precursor of the AB ring system of terrarubein, X, with all the correct substituents has been described by J.Buccini (26) (schemes II and III). Part of the work has been repeated and is described in this thesis (scheme II). A detailed analysis of infrared (i.r.) and nuclear magnetic resonance (n.m.r.) spectra is presented.

XXIV was prepared as follows. An isoxazole ring was condensed onto a cyclohexanone ring via a Michael addition followed by an intramolecular displacement of methoxide from a carbonyl to form a linear tricyclic tetrahydronaphthaleneisoxazole system, XVIII.

Opening of the isoxazole ring forms a nitrile and hydroxyl functions on a bicyclic hydronaphthalene system with functional groups via which all terrarubein A ring substituents can be introduced directly (schemes II and III).

The preparation of the D ring and subsequent preparation of a model BCD ring system of tetracycline is described in full detail in this thesis (schemes IV and VI).

The D ring can be prepared as a homophthalic acid derivative XLIV. 2-methoxycarbonyl-3-methoxy-6-bromophenyl-acetonitrile, XLIV, was prepared via a second order Beckmann rearrangement (27) from the corresponding oxime acetate. The bromine atom was introduced to prevent cyclization of the propionic acid to 5-methoxy indanone, which product is preferred over the required 7-methoxy indanone. If so desired the bromine atom may be readily removed (28) at a later stage.

Attempts to prepare a homophthalic acid derivative via XXXVIII failed due to an inability to form an enol acetate.

3-oxo-4-cyclohexenylcarboxamide, LV, was prepared (scheme VI) to be condensed with the homophthalic acid derivative XLIV. This product was prepared from m-methoxybenzoic acid via a Birch reduction.

The tricyclichydroanthracene system formed from the condensation of XLIV and LV forms a model BCD ring system of tetracyclines LVI (scheme VII).

The carbamoyl group was introduced to enable introduction of a double bond αβ to be carbonyl in the (tetracycline) B ring of LVIII so that a fourth ring, the A ring of tetracycline or its precurser could be condensed on.

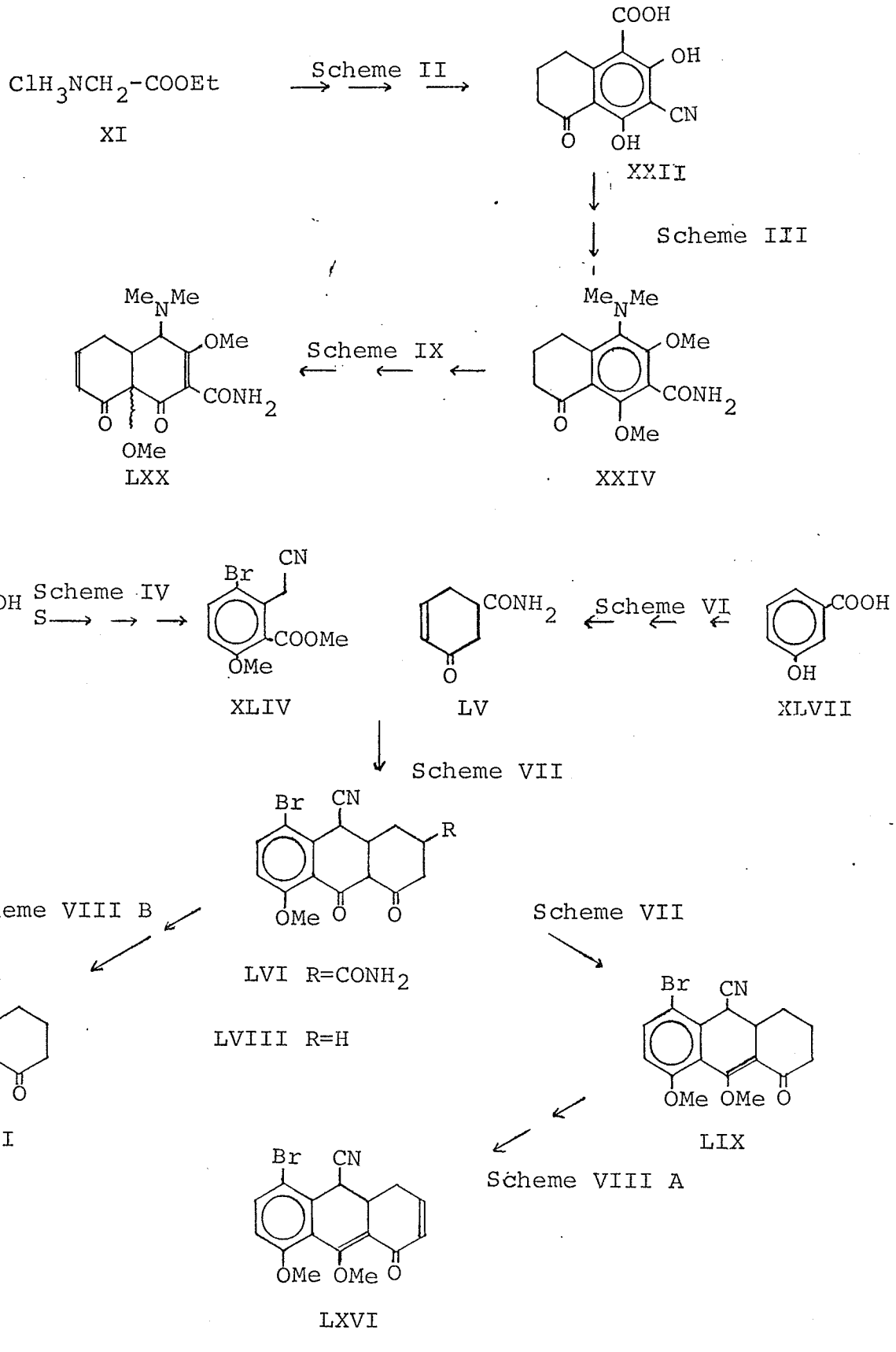
However, the carbamoyl group caused severe solubility difficulties and the approach was modified by condensing XLIV with cyclohexenone. Alternate suggestions for the

introduction of the double bond are presented in another section (scheme VIII).

It was feared that with the introduction of the double bond in the tricyclic β-diketone the whole system would aromatize. This can be prevented by introducing a substituent α to the nitrile function. To this end it was attempted to do the condensation reaction using α-(2-methoxycarbonyl-3-methoxy-6-bromophenyl)propionitrile XLV, with the hope that LVII would be obtained, scheme VII. However, the conditions required to generate the anion of XLV were too severe (sodamide in hot dioxane) and no condensation products were obtained. In another experiment, using NaH in benzene to attempt to generate the anion of XLV, a product which was probably a dimer (Michael addition) of cyclohexenone was recovered (i.r. data).

An alternate procedure for introducing a second substituent is described in another section scheme VIII.

Groups other than a nitrile could be used as an entry to introduce substituents on the carbon corresponding to $C_6$ of tetracycline, e.g. methoxycarbonyl. However, the nitrile is a versatile group. It may be left to form a 6-cyano derivative of tetracycline, it could be


ClH3NCH2-COOEt
XI
Scheme II
XXII
Scheme III
XXIV
Scheme IX
LXX
Scheme IV
XXV
XLIV
LV
Scheme VI
XLVII
Scheme VII
LVI R=CONH2
LVIII R=H
Scheme VIII B
LXVIII
Scheme VII
LIX
Scheme VIII A
LXVI

Scheme I

converted to other substituents or it may be readily removed by conversion to a carboxyl followed by decarboxylation to prepare a $C_6$ unsubstituted tetracycline (scheme VIII).

Scheme I shows the work described in this thesis in relation to the work done by John Buccine and a proposal to complete the synthesis of the AB ring system of tetracycline.

## RESULTS AND DISCUSSION

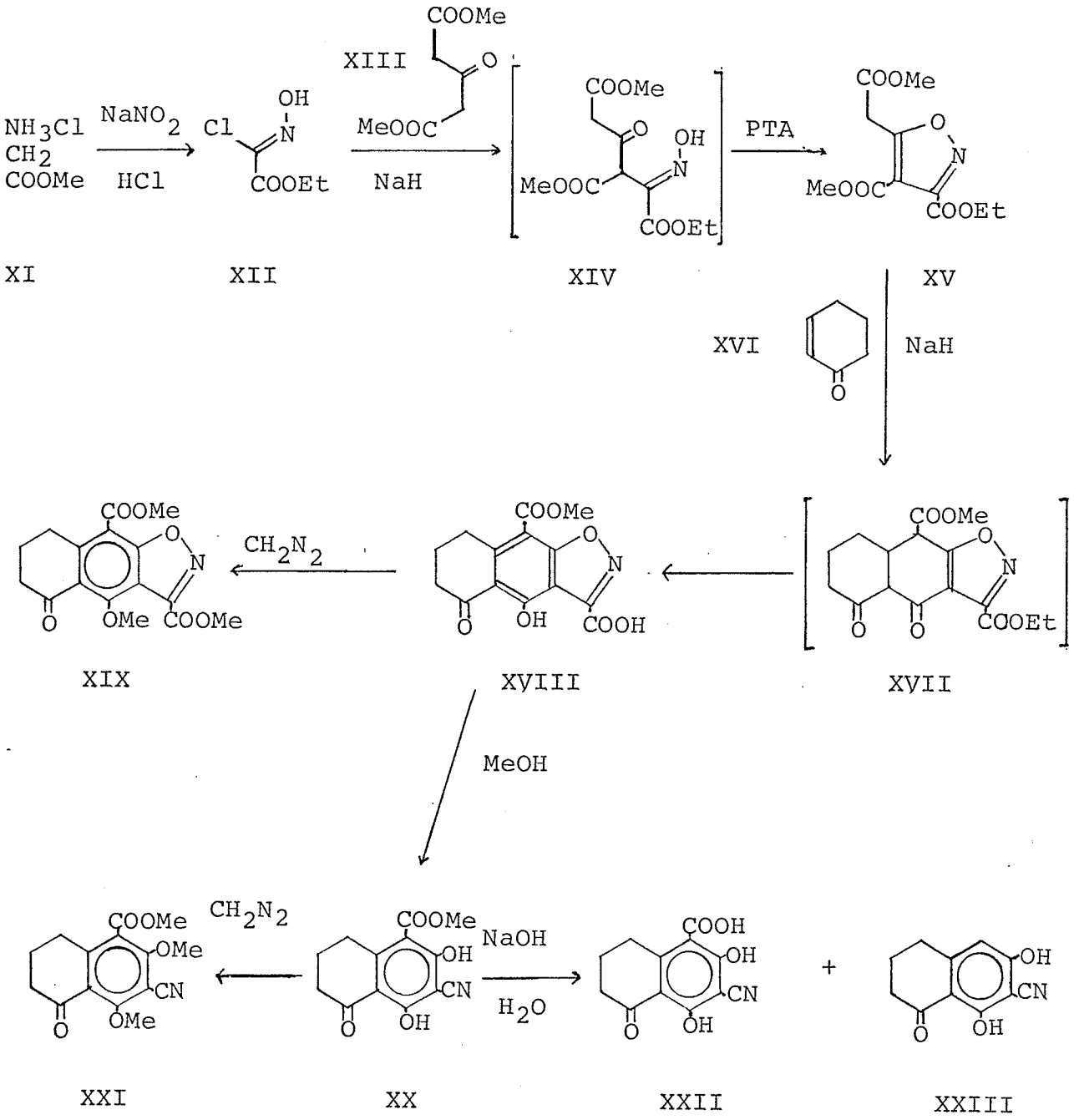
### Part A. Scheme II

Starting material for the sequence shown in scheme II was glycine ethylester hydrochloride, XI, which was converted to ethylchloroximino acetate, XII, through the action of nitrous acid according to the procedure of G.S. Skinner (29). The product was obtained as a white crystalline solid in 50% yield.

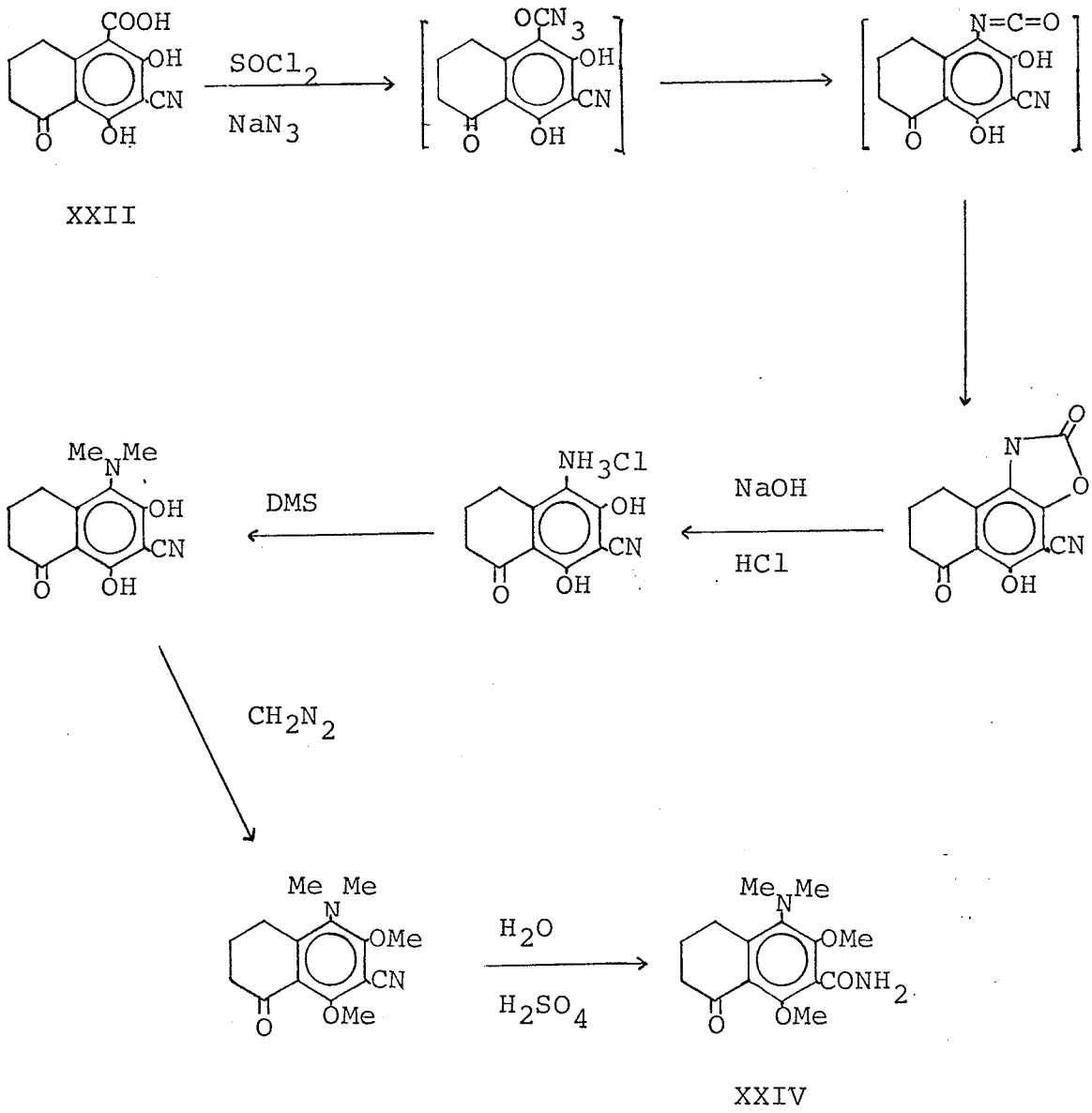
Spectral data are in accord with structure XII and are presented in figures I (i.r.) and IA (n.m.r.). The i.r. shows absorptions due to OH, CO and C=N stretching frequencies at 3500, 1740 and 1600 $cm^{-1}$ respectively. The n.m.r. spectrum shows the lowfield oxime proton at 10.1 ppm and the ethyl protons at 1.4 and 4.4 p.p.m. in a ratio of 1:2:3.

The anion of dimethyl acetone dicarboxylate,XIII, formed in refluxing benzene by treatment with sodium hydride, was condensed with XII to form the intermediate XIV with the elimination of sodium chloride. Addition of a catalytic amount of p-toluenesulfonic acid monohydrate (PTA) caused cyclization to occur with the elimination of water. The product, methyl-3-ethoxycarbonyl-4-methoxycarbonyl isoxazolyl acetate XV was obtained in poor yield, 20% as a pale yellow oil.

I.r. and n.m.r. data are presented in figures II and


NH3Cl
CH2
COOMe
NaNO2
HCl
Cl
OH
N
COOEt
XIII
COOMe
O
MeOOC
NaH
COOMe
O
OH
N
MeOOC
COOEt
PTA
COOMe
O
N
MeOOC
COOEt
XI
XII
XIV
XV
XVI
O
NaH
COOMe
O
N
O
OMe
COOMe
CH2N2
COOMe
O
N
O
OH
COOH
COOMe
O
N
O
O
COOEt
XIX
XVIII
XVII
MeOH
COOMe
OMe
CN
O
OMe
CH2N2
COOMe
OH
CN
O
OH
NaOH
H2O
COOH
OH
CN
O
OH
+
OH
CN
O
OH
XXI
XX
XXII
XXIII

Scheme II




XXII

XXIV

Scheme III

IIA respectively. The C=0 stretching absorptions are grouped together at 1740 $cm^{-1}$ and the C=C-C=N system absorbs around 1610 $cm^{-1}$. In the n.m.r. the ethyl protons absorb at 1.45 and 4.45 ppm, the active methylene at 4.2 ppm and the methoxyls at 3.75 and 3.85 ppm.

The sodioderivative of the active methylene of the isoxazole triester was formed by the action of sodium hydride in anhydrous tetrahydrofuran (THF). The anion was added to the olifinic bond of cyclohexenone XVI in a Michael type of addition. The anionic addition product, reacted intramolecularly with the 4-methoxycarbonyl group of the isoxazole ring to eliminate methoxide ion to form XVII (compare with the condensation reaction in scheme VIB). However, during the course of the reaction or during the workup the initial product was oxidized to the aromatic product XVIII. The ethoxycarbonyl group was hydrolyzed during the workup. Even when the whole procedure was carried out under a nitrogen atmosphere the aromatized product was obtained.

The crude product was purified and an i.r. spectrum, figure III, was made.The carboxylic OH absorbs at about 3000 $cm^{-1}$ while the phenolic OH has shifted to much lower wavenumber (longer wavelength) since it is strongly hydrogen bonded or chelated to the aromatic ketone. Chelation has caused the ketone carbonyl to broaden and become very intense at 1610 $cm^{-1}$. G.A. Mina and coworkers have shown that isoxazolyl acids absorb at very high

frequency (30). Therefore the absorption at 1755 $cm^{-1}$ is assigned to the carboxylic carbonyl and the absorption at 1725 $cm^{-1}$ to the ester carbonyl.

To facilitate analysis of XVIII a small amount of XIX was prepared by treating the former with diazomethane. Methylation of the phenolic OH causes the ketone carbonyl to decrease in intensity, sharpen up and shift to higher wavenumber, 1680 $cm^{-1}$. Methylation of the carboxyl group caused its carbonyl absorption to shift slightly to lower wavenumber, 1750 $cm^{-1}$ comparable to that observed by G.A. Mina (30) figure IV. The n.m.r. spectrum of XIX fig. IVA shows a total of six aliphatic protons, 2.15, 2.75 and 3.35 ppm compared to nine methoxyl protons at 4.0 4.05 and 4.1 ppm. If the product obtained from the condensation reaction were XVII there should be three more aliphatic protons.

XVIII decarboxylated very readily when pyrolysed or heated with methanol with accompanying ring opening to form a phenolic OH and aromatic nitrile (XX). The product was obtained as white needles from acetone in 41% yield calculated from XV.

The i.r. spectrum, figure V, of this bicyclic compound shows OH absorptions at 2600 and 3000 $cm^{-1}$

The very strong chelation of the phenolic OH to the ketone carbonyl has shifted the OH absorption to very low frequency. The hydroxyl ortho to the methoxycarbonyl group is less strongly hydrogen bonded and absorbs at a higher frequency. The aromatic nitrile absorbs strongly at 2250 $cm^{-1}$. The absorptions at 1600, 1640 and 1680 $cm^{-1}$ are due to the aromatic system, ketone and ester respectively. The carbonyl absorptions are shifted considerably to lower wavenumber due to hydrogen bonding. The phenolic protons could also be observed in the n.m.r. spectrum, figure VA, obtained in deuterated chloroform at 12.9 and 14.5 ppm. The aliphatic and methoxyl protons absorb at 2.1, 2.7, 3.35 and 4.05 ppm.

To facilitate spectral analysis a small amount of XX was treated with diazomethane to form XXI. The i.r. spectrum, figure VI shows aromatic absorptions at 1570 and 1580 $cm^{-1}$. The ketone and ester carbonyls absorb at 1690 and 1740 $cm^{-1}$ both having shifted to higher frequency since there is no more hydrogen bonding. As before the nitrile function absorbs at 2250 $cm^{-1}$. The n.m.r. spectrum shows three methoxyl absorptions to six aliphatic protons, figure VI A.

The diphenol ester was then hydrolyzed to the acid XXII using 10% NaOH solution. This procedure had to be

carefully controlled since the hydrolyzed acid decarboxylated very readily to form XXIII. The desired hydrolysis product is obtained as a white crystalline solid, after recrystalization from acetone/water, in 46% yield.

Spectral data are presented in figures VII (i.r.) and VIIA (n.m.r.).

When treated with diazomethane XXII is converted to XXI.

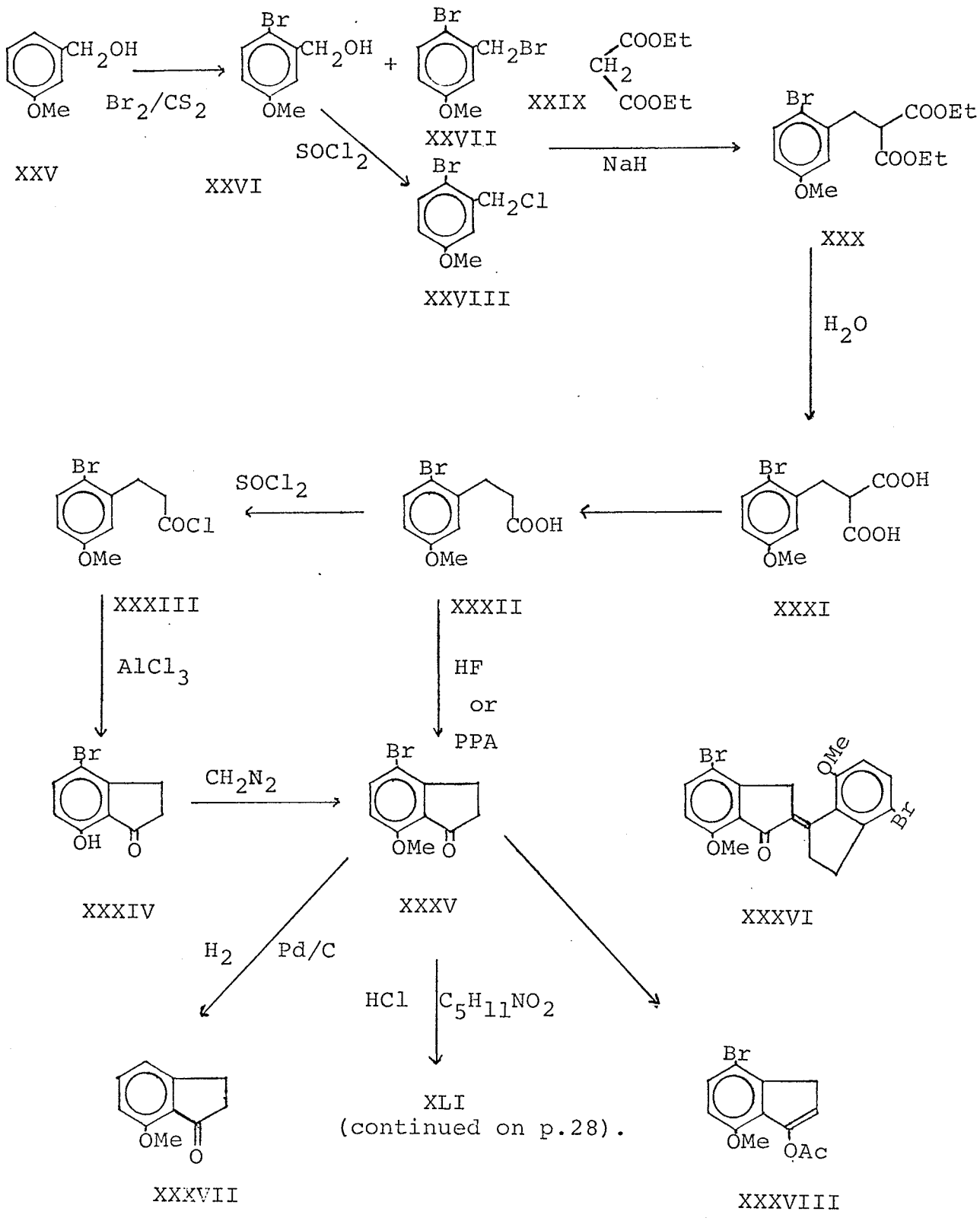
Part B Scheme IV

m-methoxybenzyl alcohol XXV was treated with m olecular bromine in carbon disulfide at low temperature ($<10^{o}$). Under these conditions only the position para to the methoxyl is brominated. HBr is produced as a side product.

The two organic products isolated from this reaction could very readily be separated by crystalization from methanol. The product remaining in the mother liquor XXVI showed a strong infrared OH absorption characteristic of alcohols fig. VIII. It was obtained as white needles in 49% yield. The precipitated dibromide XXVII was obtained as white needles in 45% yield. The yield was not appreciably changed by bubbling HBr through the reaction mixture.

The n.m.r. spectrum of XXVI, figure VIIIA, shows a OH absorption which is missing in that of XXVII (fig. IXA). Both spectra show an aromatic ABC pattern. Proton A (meta to $CH_2X$) absorbs as a doublet to lowest field showing an ortho coupling of 8.5 cps to proton B. Proton C (ortho to $CH_2X$) absorbs as a doublet at 7 and 6.95 ppm in XXVI and XXVII respectively. Meta coupling to proton B (para to $CH_2X$) is about 3.5 cps . The result is that B absorbs as a quartet to highest field. There is a slight broadening of protons A and C due to para coupling (31). Also all protons are weakly coupled to

A




(continued on p.28).

Scheme IV

the methylene protons and methoxyl protons (32).

A literature search shows that XXVI has not been prepared previously.

Reaction of XXVI with thionyl chloride in benzene solution formed XXVIII in 42% yield calculated from XXV. Recrystallization from methanol formed the product as white needles.

As expected the i.r. spectra of XXVII and XXVIII show only subtle differences in the fingerprint region. XXVIII (fig.X) lacks the absorption of XXVII at 1220 $cm^{-1}$. Similarly the only difference in the n.m.r. spectra of the two compounds is that the methylene absorption of the benzyl chloride is slightly to lower field than that of the benzyl bromide (~0.1 ppm). This is as expected on the basis of the electronegativities of the Br and Cl atoms (3.0 and 3.2 respectively (33)). The n.m.r. spectrum of XXVIII is presented in figure X A.

Both XXVII and XXVIII have relatively high vapor pressures and losses can result from excessive aspiration to remove solvents. Both are lachrymators.

In a large scale preparation the two bromination products were not separated but the mixture was treated with thionyl chloride in benzene. The mixed products were purified and reacted in the next step.

The benzyl halides obtained above were condensed with excess diethyl malonate, XXIX, using sodium hydride as condensing agent in dry THF. The condensation product XXX was obtained in 96% yield.

The crude product XXX was purified for spectral analysis using silica gel. I.r. and n.m.r. spectra are presented in figures XI and XIA respectively. The i.r. shows the aromatic doublet at 1575 and 1600 $cm^{-1}$ and the strong broad carbonyl absorption around 1740 $cm^{-1}$. The n.m.r. shows the two equivalent ethyl groups with methyl and methylene protons absorbing at 1.15 and 4.05 ppm. The benzilic protons absorb as a doublet at 3.0 ppm due to coupling with the methine proton which absorbs as a triplet at 3.7 ppm.

The condensation product, XXX, was hydrolyzed to the diacid, XXXI, using concentrated sodium hydroxide solution followed by concentrated hydrochloric acid. The excess malonic ester used is readily removed at this stage since the malonic acid formed after hydrolysis is water soluble while the condensation product, XXXI, is not. The yield, after purifying the diacid, is 73% calculated over the condensation and hydrolysis steps. A sample sublimed at $140^{\circ}$/0.3 mm decomposed at $148^{\circ}$ upon heating.

Spectral data are presented in figures XII (i.r.) and XIIA (n.m.r.)

Decarboxylation of XXXI to XXXII proceeds smoothly at 170° with evolution of carbon dioxide and discoloration of the product XXXII is obtained in 90% yield as white crystals after purification.

The i.r. spectrum, figure XIII, shows two forms of the acid present, monomer and dimer, with respective carbonyl and hydroxyl absorptions at 1740, 3500 $cm^{-1}$ and 1705, 3000 $cm^{-1}$ (34,35a). The n.m.r. (figure XIIIA) shows a low field proton at 12.8 ppm, three aromatic protons around 7.4, 6.7 and 6.5 ppm and four aliphatic protons around 2.8 ppm as an $A_2B_2$ pattern. The ultraviolet spectrum shows only an aromatic absorption (figure XIIIb).

XXXII was cyclized to XXXV using HF, polyphosphoric acid (PPA) and a sequence of $SOCl_2$, $AlCl_3$ and $CH_2N_2$. PPA was found to be the reagent of choice with yields of 71% compared to an average of 44% with HF which was about the same as for the series $SOCl_2$, $AlCl_3$, $CH_2N_2$. The PPA cyclization formed XXXVI in 11% yield (representing 22% yield of indanone) as a secondary product by condensing two indanone molecules together. This product was insignificant on a small scale preparation and should be minimized by reducing the concentration and reaction time. The byproduct was readily separated from the desired product since it was poorly soluble in methanol while the desired product was quite soluble.

The bromine atom was introduced to prevent cyclization in the position para to the methoxyl group. This would be the major product if that position were not blocked (36,37). Besides, a single product is obtained and purification is much simplified. The bromine is readily removed by hydrogenolysis.

Compound XXXV gave a satisfactory elemental analysis. I.r., n.m.r. and u.v. data are presented in figures XVI XVIA and XVIB respectively. The i.r. spectrum shows a single aromatic absorption at 1685 $cm^{-1}$ and a ketone absorption at 1705 $cm^{-1}$. The n.m.r. shows an aromatic AB pattern at 7.6 and 6.7 ppm. The latter is slightly coupled to the methoxyl protons (32) and is therefore not as sharp as the former. The aliphatic region shows a complicated $A_2B_2$ pattern at 2.85 ppm. The methoxyl absorbs at 4.0 ppm. The u.v. spectrum shows an absorption due to the ketone conjugated with the aromatic ring at 3.23 mμ (log $\varepsilon$ =3.64).

I.r., n.m.r., u.v. and mass spectral data of the secondary product are presented in figures XVII, XVIIA, XVIIB and XVIIC. The infrared spectrum shows carbonyl, aromatic and C=C absorptions at 1680, 1600, and 1580 $c,^{-1}$. The n.m.r. shows two aromatic AB patterns. The allylic benzillic methylene ($Ph-CH_2-C=C$) absorbs at 3.85 ppm. The absorption is probably broadened due to coupling with the other allylic protons which absorb at around 3.5 ppm. The absorptions at 2.95 and 3.5 ppm are due

to an $A_2B_2$ system which is unequally perturbed by an external influence.

The possibility of the other isomer rather than the structure shown, XXXVI, cannot be discounted. Although a separation was attempted on silica gel, a mixture of the two isomers is not excluded. In the other isomer there would be steric interference between the carbonyl and methoxyl groups. Therefore the isomer shown is probably the one obtained.

Compound XXXII was converted to XXXIII by thionyl chloride followed by cyclization to XXXIV with $AlCl_3$ in $CS_2$ or $CH_2Cl_2$. The infrared spectrum of XXXIII is presented in figure XIV. The carbonyl absorption of the acid chloride has shifted to 1790 $cm^{-1}$.

The cyclization product XXXIV was recovered in 47% yield. Recrystallization from methanol gave a pure product as white needles.

I.r., n.m.r., and u.v. spectra are presented in figures XV, XVA and XVB. The infrared shows a sharp phenolic OH at 3380 $cm^{-1}$. The carbonyl absorption is not low enough, 1680 $cm^{-1}$, to be strongly hydrogen bonded as is the case with sixmembered phenolic hydroxyls (compare with XVII and XX), although it is more intense than the corresponding absorption in XXXV (38). There is an aromatic absorption at 1620 $cm^{-1}$. Methylation shifts the carbonyl absorption to higher frequency and the aromatic absorption to lower frequency. The n.m.r. shows

the low field proton, an aromatic AB pattern and an aliphatic $A_2B_2$ pattern at 8.75, 7.6, 6.7 and 2.85 ppm. The ultraviolet spectrum is not appreciably different from that of XXXV.

Hydrogenolysis of XXXV using Pd/C in basic methanol solution (28) formed XXXVII in 78% yield. Spectral data is presented in figures XVIII and XVIIIA. The i.r. (figure XVIII) shows differences in the range 1000-1100 $cm^{-1}$. The n.m.r. (figures XVIIIA) shows an ABC pattern in the aromatic region. The aliphatic $A_2B_2$ system is coupled to the aromatic proton as shown by the asymetric pattern at 2.85 ppm.

The ring opening reaction via a second order Beckmann rearrangement (27) was first tried on a model system using indanone (scheme IVB). The 2-oxime-1,2-indandione was prepared from indanone using sodium hydride and isoamyl nitrite in anhydrous THF followed by acidification with a minimum amount of HCl. The solvent was removed using an aspirator and the water was removed by pumping off a benzene water azeotrope. The residue was acetylated and then converted to 2-methoxycarbonyl phenylacetonitrile.

When the reaction was tried on a larger scale on compound XXXV the final product obtained from the reaction with isoamyl nitrite was 2-methoxy-5-bromophenyl homophthalimide, XXXIX. This product was obtained by Beckmann

rearrangement of XLI during the workup, i.e. when the solvent was pumped off the residue became very acidic and caused the rearrangement.

The i.r. spectrum of the imide XXXIX, figure XIXI, shows the N-H stretching absorption at 3700 $cm^{-1}$ and a carbonyl absorption at 1640 $cm^{-1}$. Six membered imides show a carbonyl absorption around 1700-1717 $cm^{-1}$, however conjugation with an aromatic ring lowers the frequency to that observed. The n.m.r. spectrum of XXXIX figure XIXA shows the NH proton as a very broad absorption around 8.8 ppm, as shown by the integration curve, and AB quartets due to the aromatic and methylene protons at 6.7-6.9 ppm. The methoxyl protons absorb at 4.0 ppm.

The imide could be methylated with diazomethane to form the N-methyl derivative XL.

The N-methyl derivative, XL, shows a much more intense imide carbonyl absorption which is shifted to 1660 $cm^{-1}$ in the i.r. spectrum, figure XX. The n.m.r. figure XXA again shows the two AB patterns and two methyl groups attached to hetero atoms at 3.95 and 4.07.ppm.

The AB pattern due to the heterocyclic methylene protons of compounds XXXIX and XL can only arise if the heterocyclic ring is nonplanar due to the pyramidal arrangement around the nitrogen atom.

To avoid the side reaction described above XXXV was converted to XLIV by a procedure essentially that of Grob and Wiesbach (39). This procedure has the added advantage of simplicity in the preparation of XLI.

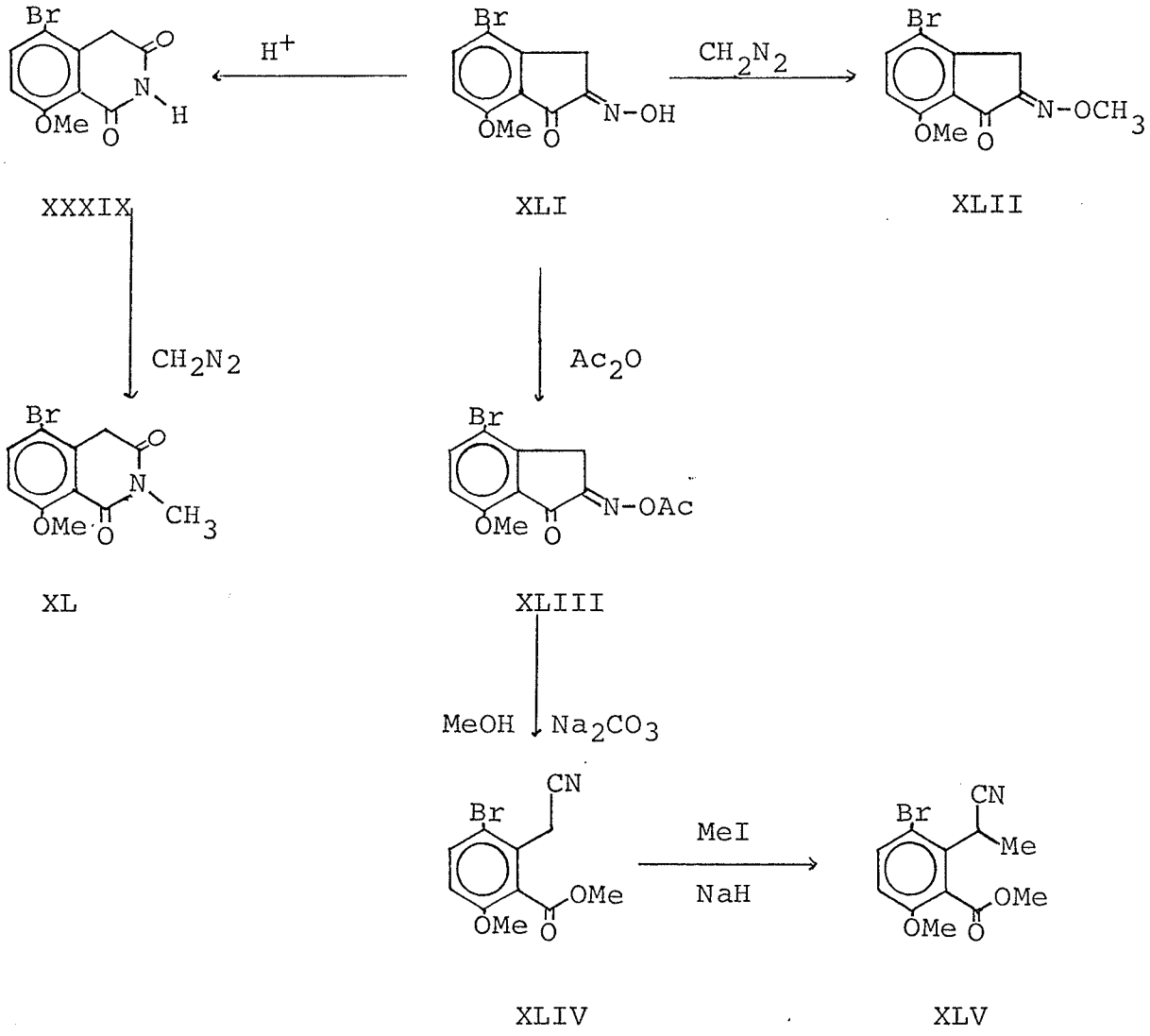
Conversion of XXXV to XLI was accomplished by reaction with isoamyl nitrite, using conc. HCl as catalyst in 56% yield. The product was obtained as yellow crystals.

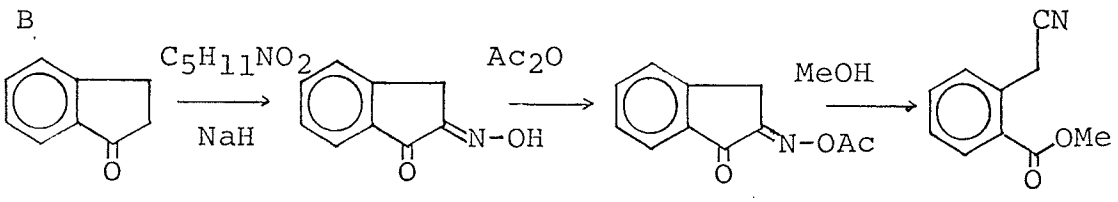
The i.r. fig. XXI, shows OH, C=0, C=N and aromatic C=C bands at 3275, 1700, 1630 and 1580 $cm^{-1}$. The n.m.r. figure XXIA, shows two aromatic AB protons a methoxyl and a sharp methylene group at 7.6, 6.85, 3.7, 3.35 ppm. The u.v. spectrum is presented in figure XXIB.

Since the oxime, XLI, was rather insoluble and therefore difficult to analyse a small sample was methylated with diazomethane to form XLII. This product was more soluble in common solvents and spectral data was easier to obtain.

The infrared carbonyl absorption of XLII is quite low, 1680 $cm^{-1}$, due to the αβ-unsaturated C=N bond. Conjugation is not very strong in this type of system and therefore the intensity of the ketone is not much different from that of XXXV. S-cis αβ-unsaturated ketones absorb to higher frequency than S-trans αβ-unsaturated ketones (35b). The aromatic band again appears at 1585 $cm^{-1}$ and a strong C=N stretching band appears at 1555 $cm^{-1}$, (Figure XXII). The n.m.r. spectrum, figure XXIIA, shows the aromatic AB pattern at 7.70 and 6.83 ppm and the methoxyl at 3.97 ppm. The most interesting feature of this spectrum is the coupling between the N-methoxyl protons and the methylene protons, 4.27 and 3.79 ppm. These peaks were expanded

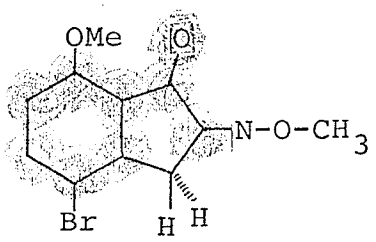
A continued from p.19




Scheme IV

on a 50 cycle sweep width (figure XXII A2) and a coupling constant 1.25 cycles was determined. When the methylene absorption was saturated in a double resonance experiment, the N-methoxyl triplet collapsed (figure XXII A1). To observe such a long range coupling is very unusual, particularly such a strong coupling. It was suggested that the methylene protons are interacting with the $\pi$ electrons which almost cover the entire molecule as shown in XLVI.




XLVI

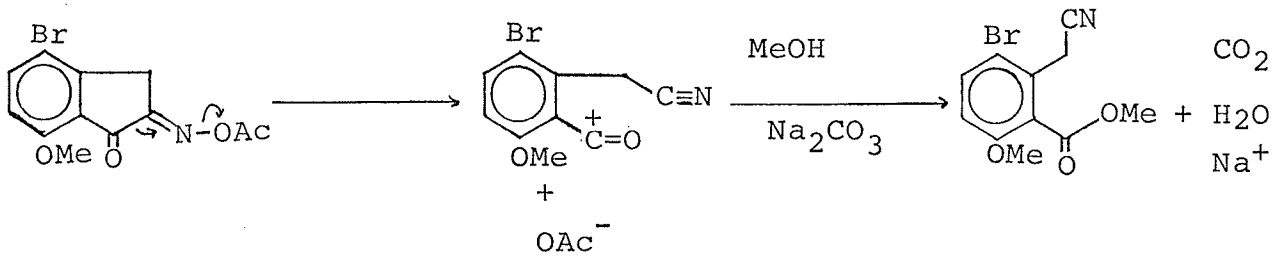
The coupling effect of the nitrogen atom, an equal number of bonds from both the methoxyl and methylene protons, is not clear. Nitrogen has a nuclear spin of 1.

An ultraviolet spectrum is presented in figure XXIIB.

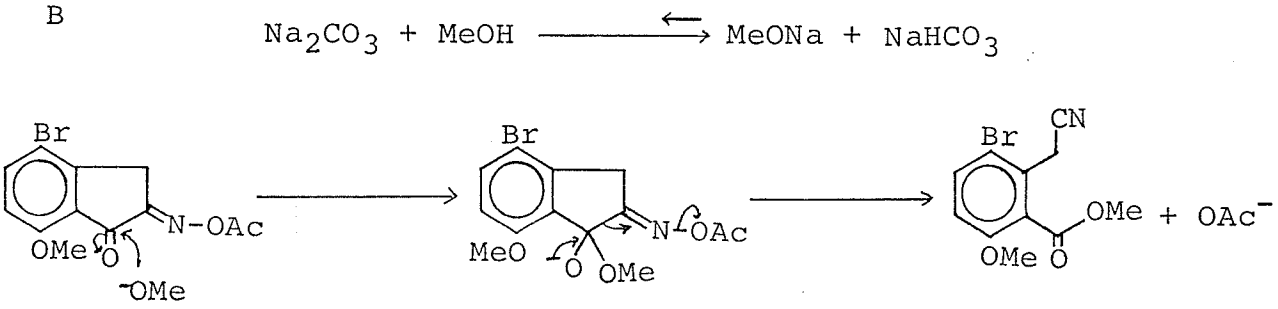
Reaction of XLI with acetic anhydride yielded XL as bright yellow crystals in 89% yield. This product was unstable to heat and/or light becoming a dark yellow upon standing at room temperature.

The i.r. spectrum, figure XXIII, shows a high frequency ester carbonyl due to the unsaturation $\alpha$ to the acetoxyl

A


Br
OMe
O
N-OAc
Br
C≡N
+
C=O
OMe
OAc⁻
MeOH
Na2CO3
Br
CN
OMe
OMe
O
CO2
H2O
Na+

B


Na2CO3 + MeOH ⟷ MeONa + NaHCO3
Br
OMe
O
N-OAc
⁻OMe
Br
MeO
O
OMe
N-OAc
Br
CN
OMe
OMe
O
OMe + OAc⁻

Scheme V

at 1785 $cm^{-1}$. The five member ketone absorption appears at 1725 $cm^{-1}$ while the C=N stretching and aromatic C=C bands appear at 1650 and 1585 $cm^{-1}$ respectively. There is a dramatic change in intensity and position of the C=N band from compound XLII to XLIII. The n.m.r. (figure XXIIIA) shows the usual aromatic pattern, a methoxyl and a methylene group. The methylene absorption (as in XLII ,figure XXIIIA) is sharp indicating that there is no coupling or at best a small coupling with the nitrogen atom. An aliphatic methyl absorption appears at 2.4 ppm.

A second order Beckmann rearrangement (27) of XLIII formed the nitrile ester XLIV in 78% yield of unrecovered starting material. 56% of the starting material is recovered as the oxime XLI.

Blatt and Barnes (40) suggest that this reaction is primarily a cleavage reaction forming the nitrile acetate ion and acylium ion which reacts with the methanol solvent. Water and $CO_2$ are formed as sideproducts (scheme VA). It was hoped that by introducing a better leaving group, trifluoroacetoxyl instead of acetoxyl the yield would be increased. However no reaction occured with the trifluoro compound.

The suggestion that the reaction proceeds via methoxyl attack on the carbonyl, (scheme V B) , is not valid since the reaction does not require anhydrous conditions.

Compound XLIV was recovered as a white crystaline product after recrystalization from methanol/ether solvent A sublimed sample gave a satisfactory elemental analysis.

The i.r. spectrum shows a weak nitrile absorption at 2280 $cm^{-1}$.Non-conjugated nitriles are much weaker than conjugated ones (compare with XXI for example).There is a strong ester carbonyl at 1730 $cm^{-1}$,figure XXIV.The n.m.r. spectrum shows the typical aromatic AB pattern and two methoxyls at 7.6, 6.85, 3.95,and 3.8 ppm.The weakly acidic methylene protons absorb at 3.8 ppm,figure XXIV A.The u.v. shows an aromatic ester absorption at 293 mμ (log ε = 3.42), figure XXIV B.

XLIV was readily converted to XLV in 90% yield by treatment with sodium hydride in dry boiling THF followed by methyl iodide.

Infrared and n.m.r. spectra are presented in figures XXV and XXV A.Predictably the i.r. is very similar to that of XLIV.The most obvious difference is the close doublet at 965 and 970 $cm^{-1}$ of XLIV compared to the wide doublet at 965 and 1005 $cm^{-1}$ of XLV.The nitrile absorption of XLV is more intense than that of XLIV.The n.m.r. shows a quartet at 4.35 ppm and methoxyl absorptions at 3.95 and 3.8 ppm.The secondary metyl absorbs as a doublet at 1.7 ppm as part of an $AX_3$ system.

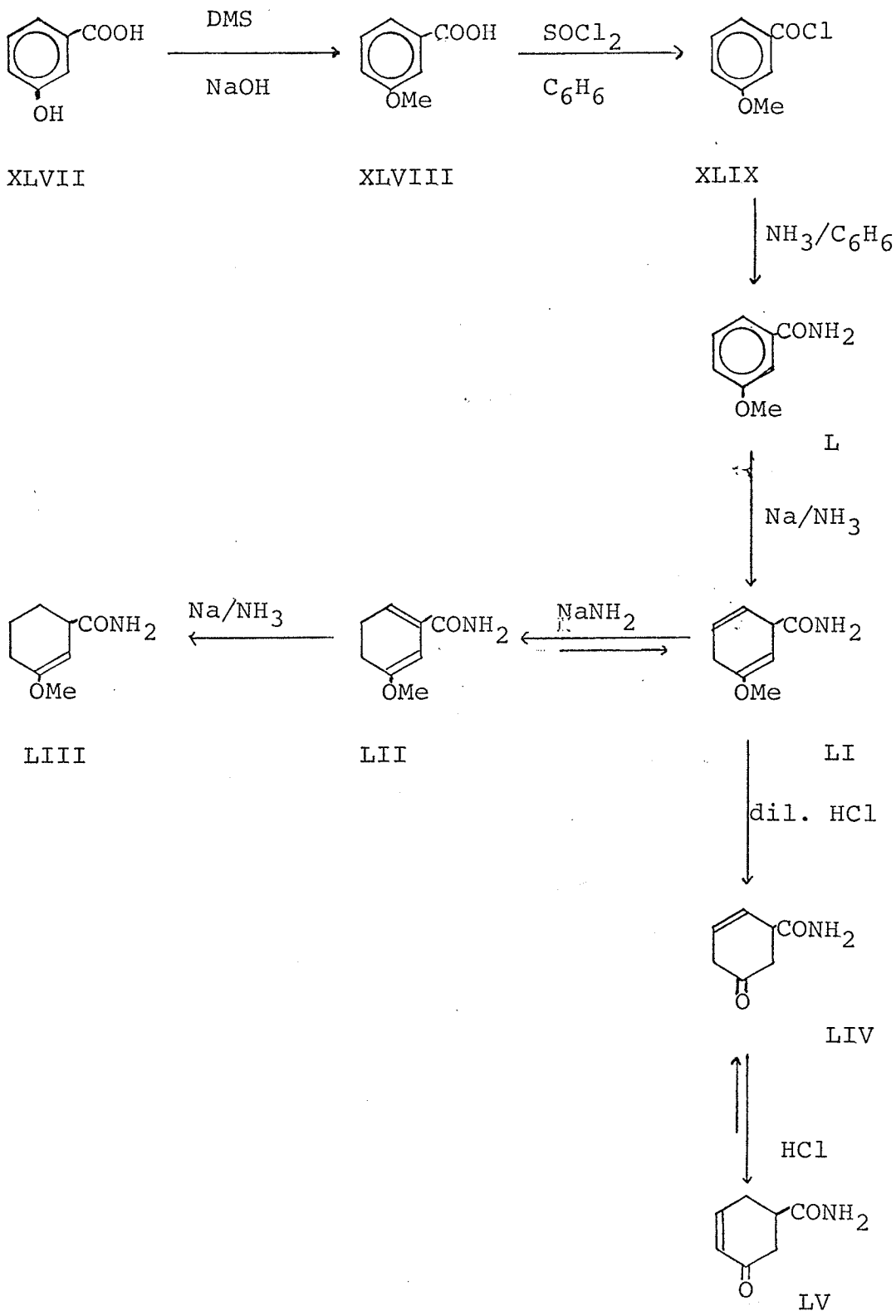
Part C Scheme VI

The ether, m-methoxy benzoic acid, XLVIII, was formed from XLVII in NaOH solution using dimethyl sulfate (41). An excess NaOH was used to hydrolyse any ester formed. The product was obtained as white crystals in 97% yield, after recrystallization from water.

Reaction with thionyl chloride produced the acid chloride, XLIX, which was converted to the amide, L, with ammonia in 75% yield.

Birch reduction of L with sodium in distilled, dried, liquid ammonia produced the 1,4-dihydrobenzene derivative, LI, (42a) in 70% yield. The remainder is probably recovered as the tetrahydro derivative, LIII, (42b, 43,44) as shown by the n.m.r. spectrum. The yield is much better than that reported by Kuehne and Lambert (44).

The tetrahydro product is formed as shown in scheme V. The sodamide formed in the initial reduction reaction isomerizes the nonconjugated diene to the conjugated diene, LII, (42c) which can then be further reduced to the tetrahydro derivative. The sodamide formed can be destroyed, before it has a chance to isomerize the primary product, if the reaction is carried out in the presence of a proton donor such as ethanol or water. However, when there was either methanol or water present mainly starting material was recovered when moderate ( 1.5-2 equivalents) quantities of sodium were used, as reported previously (44).


COOH
OH
DMS
NaOH
COOH
OMe
SOCl2
C6H6
COCl
OMe
XLVII
XLVIII
XLIX
NH3/C6H6
CONH2
OMe
L
Na/NH3
CONH2
OMe
NaNH2
CONH2
OMe
Na/NH3
CONH2
OMe
LIII
LII
LI
dil. HCl
CONH2
O
LIV
HCl
CONH2
O
LV

Scheme VI

The infrared spectrum of LI, figure XXVIII shows the N-H stretching doublet at 3430 and 3550 $cm^{-1}$. The amide carbonyl and the typical N-H bending band absorb at 1690 and 1580 $cm^{-1}$. The C=C stretching band of the enol ether appears at 1650 $cm^{-1}$ and the vinyl ether C-O-C stretching at 1220 $cm^{-1}$. The n.m.r. spectrum of LI , figure XXVIII.A,shows the methylene doublet 2.7 ppm and the methoxyl protons at 3.55 ppm. The methine proton shows as a broad band around 3.7 ppm. The two adjacent olifinic protons absorb at 5.8 ppm, while the single olifinic proton absorbs as a doublet at 4.7 ppm due to coupling with the methine proton. The amide protons appear as a broad band centred at 5.7 ppm.

The action of cold dilute HCl converts LI to LV through the intermediate LIV,of which a small amount was isolated. The intermediate LIV was found to be unstable at room temperature, keeping only a few days, but more stable at $-20^{o}$, although even then it decomposed slowly to form LV and some very insoluble side product. Treatment of LIV with acid forms LV. LIV is more soluble in chloroform than in water. The reverse is true of LV.

The i.r. spectrum of LIV shows the typical primary amide absorptions, the vinyl ether absorptions have disappeared and a cyclic non-conjugated ketone appears at 1720 $cm^{-1}$, figure XXIX , The n.m.r., figure XXIX A,shows the broad amide proton absorption around 6 ppm. The complex doublet at 6 ppm is due to the two vinyl protons, the

allylic methylene protons show a doublet at 2.9 ppm and the methylene protons coupled to the methine protons absorb as a broad band around 3.5 ppm. Dreiding models show that the angles between the methine and methylene protons are approximately $180^{\circ}$ and $60^{\circ}$ when the carbamoyl is in the quasi equatorial position (45) which is expected to be the most stable conformation. This would produce coupling of approximately 9.2 and 1.7 cps according to Karplus' prediction (46). The observed coupling are 9.0 and 2.5 cps.

The product LV was obtained in 65% yield from LI.

The pure material is colorless but upon standing at room temperature it becomes yellow, the color deepening with time. Spectra presented below compare well with those of 3-oxo-4-cyclohexenylcarboxylate prepared by former colleaque, Ida Chang (47).

The i.r. figure XXX , shows features typical of primary amides and αβ-unsaturated ketones. The two carbonyl functions are superimposed at 1690 $cm^{-1}$. The intensity is much greater than the comparable absorption in XLVIII figure XXVIII, when compared to the N-H bending band. The n.m.r., figure XXX A, shows two olifinic protons at 7.2 and 6.0 ppm. The olifinic proton α to the carbonyl absorbs to higher field, it is the less complicated pattern. The u.v. spectrum, figure XXX B is identical with that obtained by Kuehne and Lambert (44).

Part D Scheme VII

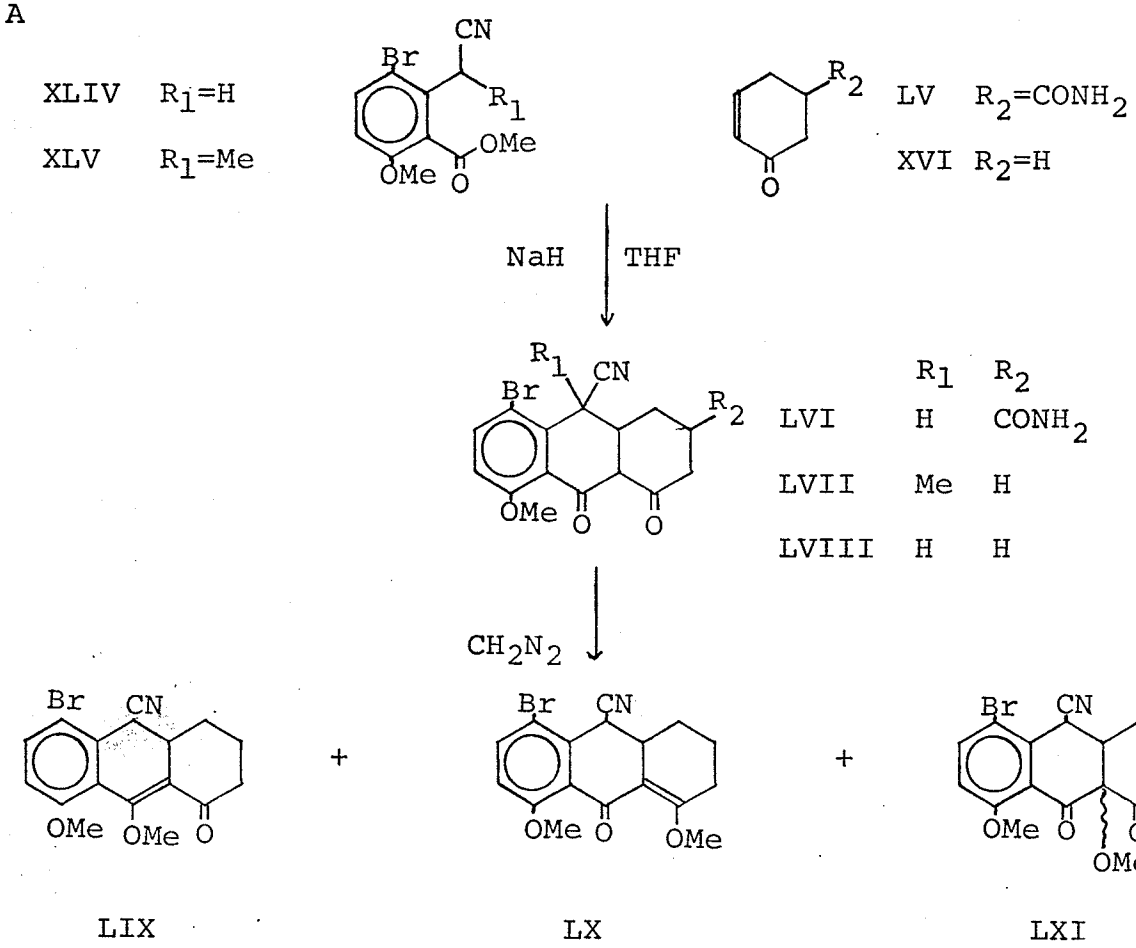
Michael condensation of LV and XLIV using sodium hydride as condensing agent formed a rather insoluble product LVI which was obtained in 20% yield. Upon heating the product decomposed at 250-260°.

The infrared nujol spectrum, figure XXXI, shows the amide doublet at 3360 and 3470 $cm^{-1}$, a nitrile at 2260 $cm^{-1}$ and the amide carbonyl at 1675 $cm^{-1}$. The β-diketone absorbs as a broad band at 1600 $cm^{-1}$ while the shoulder at 1570 $cm^{-1}$ is due to the aromatic C=C stretching frequency. A u.v. ethanol spectrum is presented in figure XXXI B. These compare very well with those obtained of LVIII (see below).

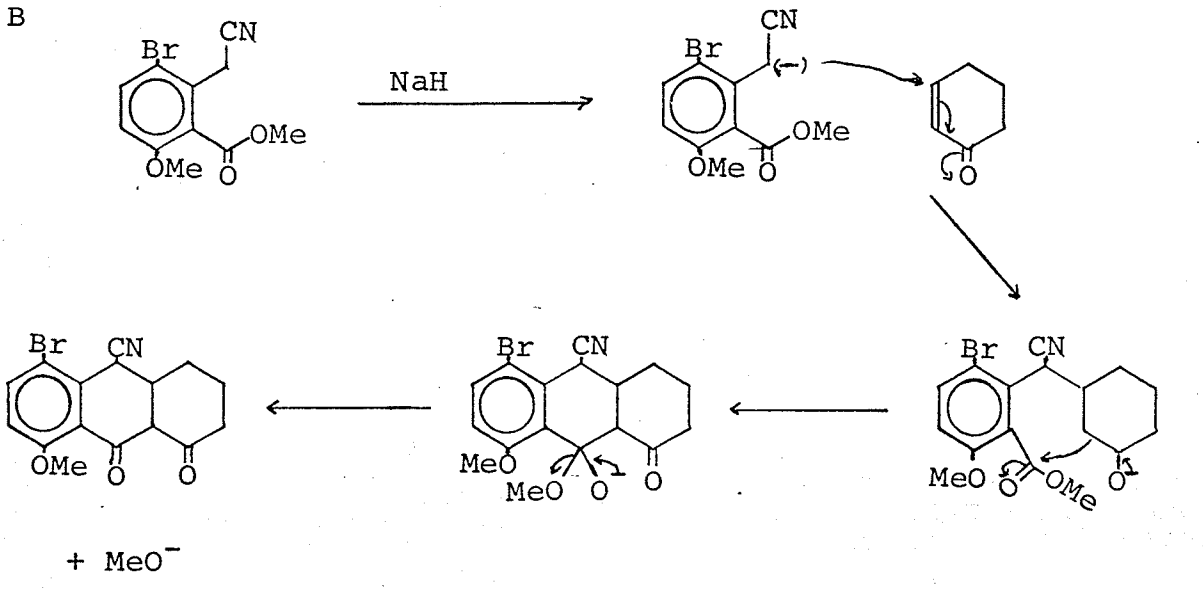
The condensation product, LVIII of XLIV with XVI (a mechanism is shown in scheme VIB) was obtained in 32% yield using dry THF as solvent and sodium hydride as base. The product was obtained as pale yellow crystals after recrystallization from methylene chloride/petroleum ether.

The i.r. spectrum of LVIII, figure XXXII , shows the presence of the β-diketone by the broad intense absorption at 1600 $cm^{-1}$. The nitrile shows very weakly at 2260 $cm^{-1}$. In the n.m.r. spectrum, figure XXXII A, the benzilic proton absorbs as a doublet (J = 4 cps) at 4.3 ppm due to coupling with the α methine proton. The very low field absorption, at 16.35 ppm, is typical of

A




B




Scheme VII

enolic β-diketones (34b). The aromatic AB pattern, the methoxyl and the seven aliphatic protons absorb in the expected regions of the spectrum. The u.v. spectrum is presented in figure XXXII B. The mass spectrum, figure XXXII C, shows a parent ion $m^+/e$ = 347 (Br = 79) as is required by the structure LVIII. A sample sublimed at 120°/0.3 mm Hg gave a satisfactory elemental analysis.

Treatment of LVIII with excess etheral diazomethane formed two O-methylated products LIX and LX (plus a very minor product which appeared to be C-methylated LXI in 39 and 57% yield respectively. Both recrystallized from methylene chloride/petroleum ether as pale yellow crystals, LIX as grannular and LX as floculent crystals.

LIX showed a strong u.v. absorption band at 344 mμ ($\lambda_{max}$) figure XXXIII B, while LX absorbed at 328 mμ ($\lambda_{max}$) figure XXXIV B. On this basis structures LIX and LX were assigned since the u.v. absorption shifts to longer wavelength as the conjugation is extended.

This argument is supported by the i.r. absorption data. The infrared spectra of LIX and LX are presented in figures XXXIII and XXXIV respectively. In LX the C = C bond is conjugated with the carbonyl and absorbs at around 1560 $cm^{-1}$. In LIX the olifinic bond is further conjugated with the aromatic ring and the absorption is lowered to 1540 $cm^{-1}$ (35c). Similarly, the ketone in LIX has an α β-unsaturated bond only and the carbonyl absorption occurs at 1655 $cm^{-1}$, i.e. it has been shifted

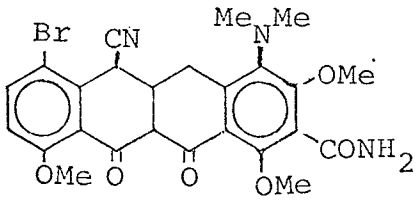
to lower frequency as is to be expected (35 b).

The n.m.r. spectrum of LIX, figure XXXIII A, shows the aromatic AB pattern, a doublet for the benzillic proton at 4.25 ppm ( $J = 4.5$ cps), two methoxyl absorptions at 3.8 and 3.95 ppm. The absorption at 3.4 ppm is an impurity which is partially removed by recrystallization from methylene chloride. (it is probably some C-methylated product LXI). The n.m.r. spectrum of LX, figure XXXIV is similar to that of LIX except that the methoxyls are magnetically equivalent. This supports the assignment made of structures LIX and LX since the methoxyls of LX are more likely to be in a similar environment than those of LIX.

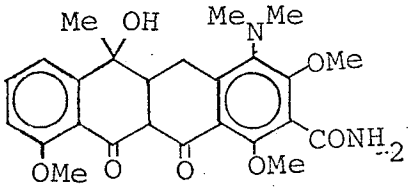
The mass spectra of LIX and LX both show a parent ion $m^{\div}/e$ = 361 (Br =79) as expected, figures XXXIII C and XXXIV C.

## Suggestions for further Research

Compound LIX was prepared to permit introduction of a double bond in the C ring to form LXVI, as shown in the scheme VIII A, so that it could be condensed with the isoxazole triester XV. The products could then be converted to the tetracycline derivative or to terrarubein X through procedures analogous to schemes II and III via LXII.



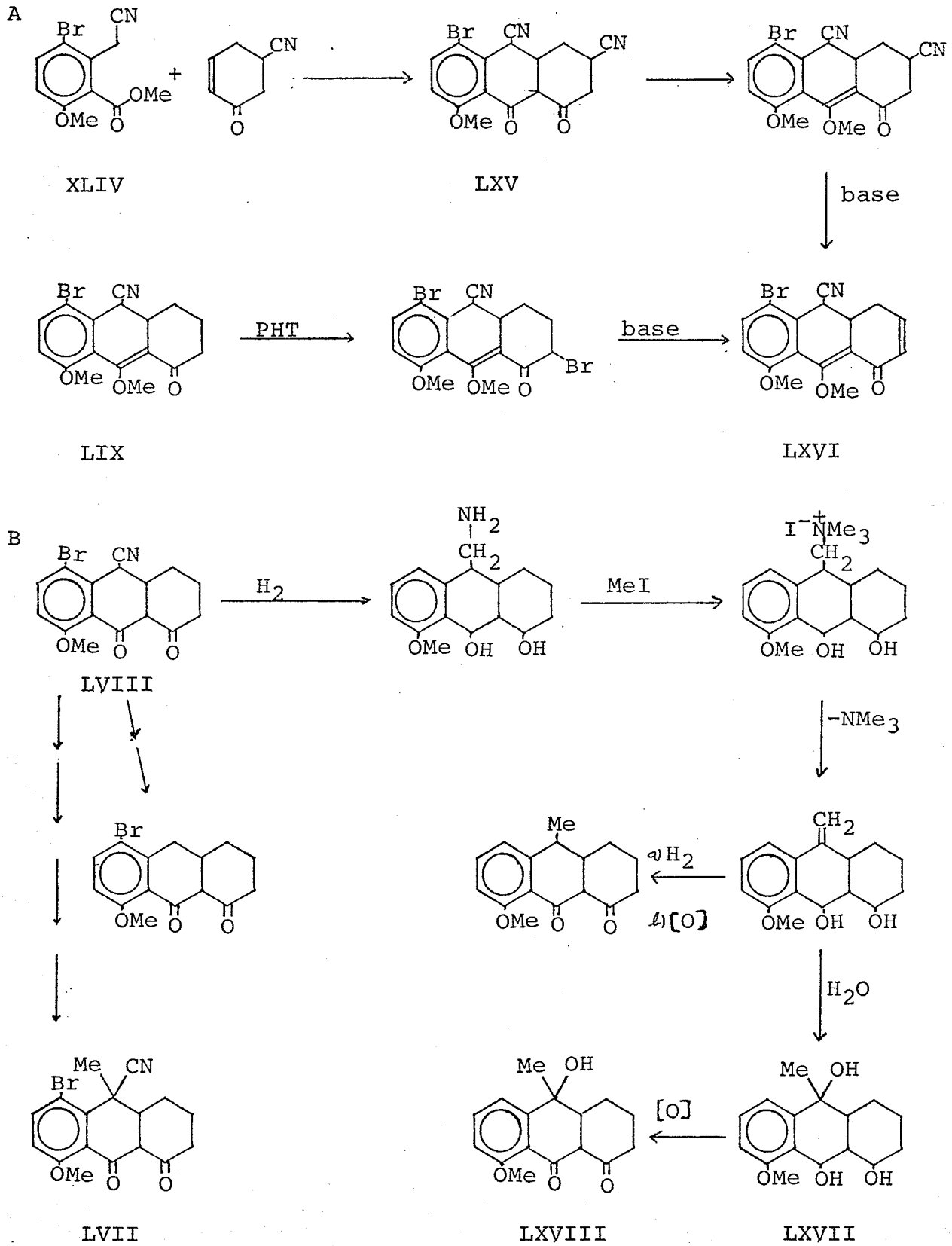

LXII




LXIII

Two suggestions for preparing LXVI are shown in scheme VIII A. LXIV could be prepared in a procedure analogous to that used to prepare LV. The condensation product obtained by reaction with XLIV would be more workable than LVI. Elimination of HCN using strong base would form LXVI after suitably protecting the β-diketone.

Alternately a bromine atom can be introduced as shown using pyrrolidone hydrotribromide (PHT),(48), followed by dehydrohalogenation.


A
Br
CN
OMe
OMe
O
+
CN
O
Br
CN
CN
OMe
O
O
Br
CN
CN
OMe
OMe
O
XLIV
LXV
base
Br
CN
OMe
OMe
O
PHT
Br
CN
OMe
OMe
O
Br
base
Br
CN
OMe
OMe
O
LIX
LXVI
B
Br
CN
OMe
O
O
H2
NH2
CH2
OMe
OH
OH
MeI
I-
+
NMe3
CH2
OMe
OH
OH
LVIII
-NMe3
Br
OMe
O
O
Me
a) H2
b) [O]
OMe
O
O
CH2
OMe
OH
OH
H2O
Me
CN
Br
OMe
O
O
Me
OH
[O]
OMe
O
O
Me
OH
OMe
OH
OH
LVII
LXVIII
LXVII

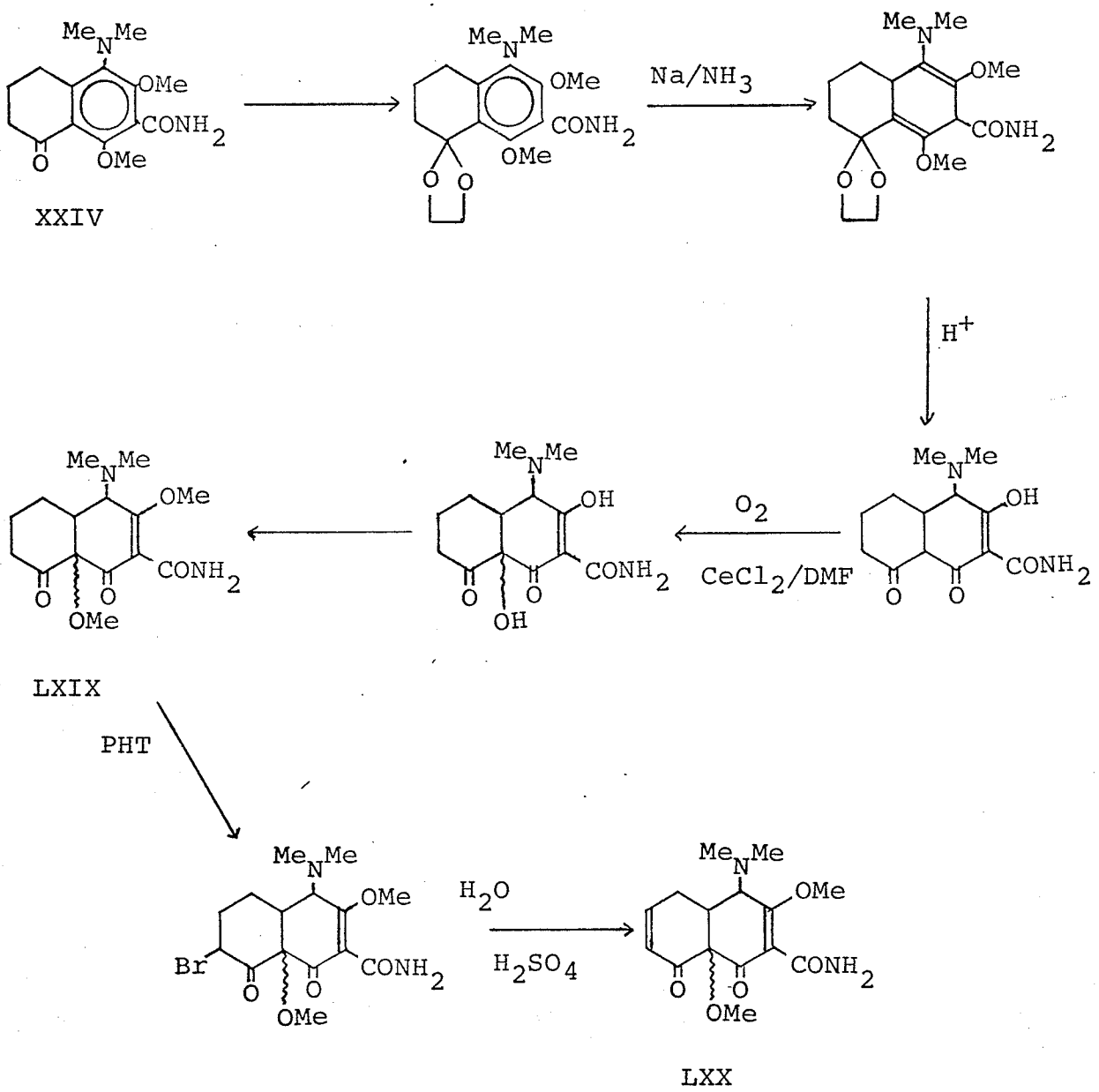
Scheme VIII

To prepare the BCD ring system of tetracycline the nitrile and β-diketone can be reduced as shown in scheme VIIIB. The exocyclic methylene can be prepared by exhaustive methylation of the amine followed by elimination of trimethylamine via a Hoffmann degradation (49,50,51). Acid catalysed addition of water to the double bond would give LXVII which can be oxidized to form LXVIII. A procedure analogous to that described in scheme VIII A would introduce a double bond which would permit condensation with the isoxazole XV and after suitable reactions LXIII would be obtained.

It would be difficult to selectively reduce the A ring of LXIII. The D ring, having fewer electron releasing substituents, would probably be reduced first.

An alternate procedure to synthesize tetracycline derivatives is suggested in scheme IX beginning with XXIV prepared by J. Buccini. The ketal is prepared to prevent Birch reduction of the ketone which reduces faster than the aromatic ring. The Birch reduction should go as shown (42 a).

A tertiary hydroxyl has been introduced into a similar system using cerium chloride and molecular oxygen in dimethylformamide solution (22).


Me N Me
OMe
CONH2
O
OMe
XXIV
Na/NH3
H+
OH
O2
CeCl2/DMF
LXIX
PHT
Br
H2O
H2SO4
LXX

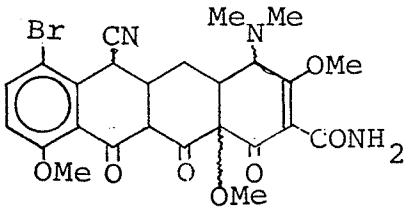
Scheme IX

To condense the CD rings onto this system a double bond must be introduced into the B ring. This can be done using PHT as described above.

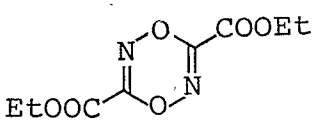
It is necessary to introduce the tertiary hydroxyl before bromination since this reaction would preferentially go in the tertiary position.

Methylation is required to prevent dehydration to an aromatic system.

Condensation of LXX with XLIV would give 7-bromo-6-demethyl-6-deoxy-3,10,12a-methoxytetracycline, LXXI.



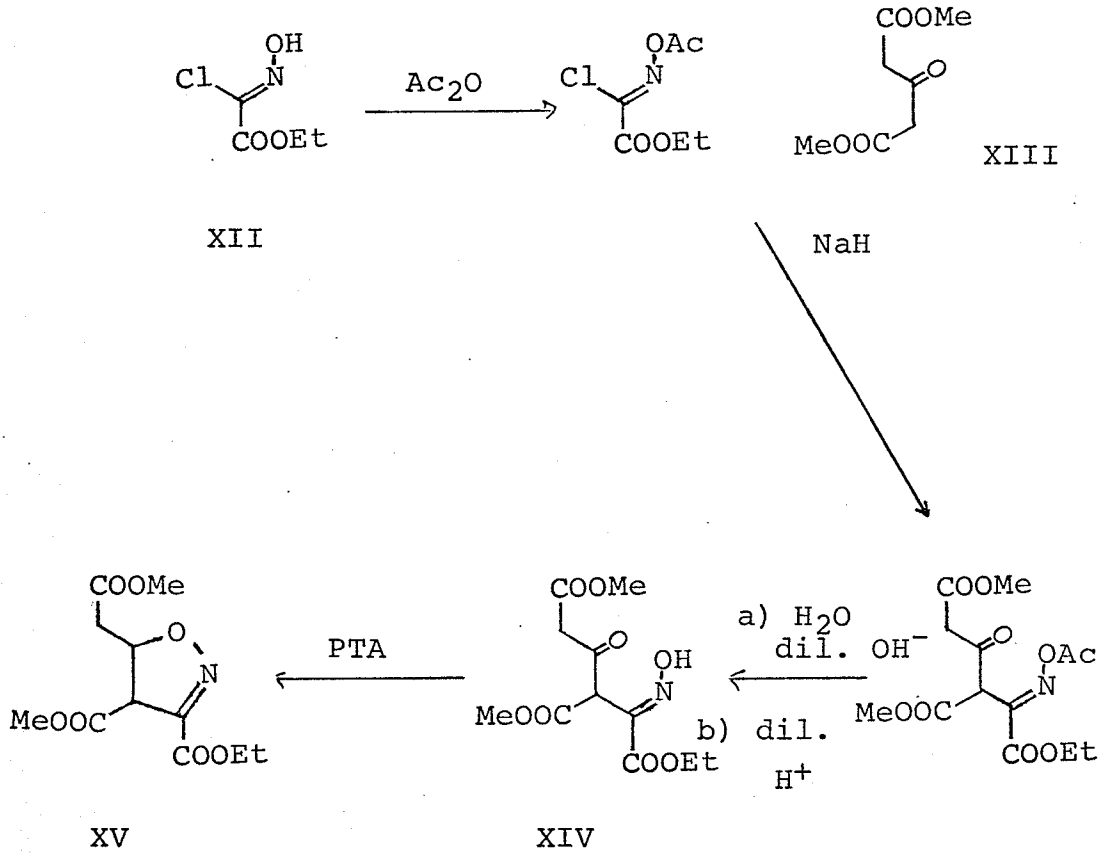

LXXI




LXXII

The preparation of the isoxazole XV as described in scheme II causes significant amounts of oximino anion to be present, since oximes are more acidic than dimethylacetonedicarboxylate XIII. This causes condensation of two molecules of ethylchloro oximinoacetate to form a six member oxygen, nitrogen and carbon heterocycle,LXXII. Some of this product has been isolated and identified by n.m.r. spectroscopy (B.pt.<140°/0.5 mm Hg) but has not been fully characterized.

A slight modification in the procedure would avoid the oximino anion and would therefore substantially


OH
Cl
N
COOEt
Ac2O
OAc
Cl
N
COOEt
COOMe
MeOOC
XIII
XII
NaH
COOMe
COOMe
COOMe
a) H2O
dil. OH−
PTA
OAc
N
OH
N
O
N
MeOOC
MeOOC
MeOOC
b) dil.
H+
COOEt
COOEt
COOEt
XV
XIV

Scheme X

increase the yield.

Oximes are readily acetylated with acetic anhydride or acetyl chloride. When the oxime hydroxyl is thus protected it will not interfere with the anion of dimethylacetonedicarboxylate. After the condensation the acetoxime is readily hydrolysed by dilute base, scheme X (compare with the acetylation and hydrolysis of compounds XLI and XLIII).

Complication could arise if the ethyl ester also hydrolyzed as readily.

It would be interesting to prepare some variations of 2-methoximino-4-bromo-7-methoxy indanone XLII to investigate the coupling mechanism of the methoxyl and methylene protons and also to determine the effect, if any, of the nitrogen atom.

It was suggested that the coupling mechanism occurs via the $\pi$ electrons. The coupling with protons above the $\pi$ cloud could be investigated if a methyl were introduced in position 3. These protons presumably would not interact with the $\pi$ electrons.

## EXPERIMENTAL

### Part A Scheme II

### Preparation of ethylchloroximinoacetate XII

600 gms (4.1 mole) glycine ethylester hydrochloride, XI, in 800 ml water was placed in a 5 l three-necked flask equipped with a thermometer, dropping funnel, overhead stirrer, and acetone-dry ice cooling bath.

Solution A was prepared by dissolving 600 gm $NaNO_2$ in 870 ml water.

The solution was cooled to $-5^{\circ}$ and after addition of 360 ml conc HCl again cooled to $-5^{\circ}$. Half of solution A was added through a dropping funnel at such a rate that the temperature did not exceed $0^{\circ}$. A further 360 ml conc. HCl was then added and the solution again cooled to $-5^{\circ}$ followed by addition of the remaining part of solution A at a reaction temperature of less than $0^{\circ}$.

After the sodium nitrite solution was added the reaction mixture was stirred for a further 20 minutes at $-5^{\circ}$.

Upon standing the product floated to the top as a scum. The aqueous layer was decanted into a large beaker leaving a small amount of aqueous solution along with the product in the reaction flask. The

product was taken up in 500 ml chloroform and the aqueous layer separated and combined with the main aqueous solution. The combined aqueous solution was then washed three times with 500 ml chloroform.

The combined chloroform solutions were then dried over magnesium sulfate. After filtering off the drying agent the solvent was removed using a rotavapor leaving an oily residue with a fairly high vapor pressure. Upon cooling it crystalized readily to a white solid.

The product recrystallized readily from 200 ml benzene upon addition of 750 ml petroleum ether or hexane. Yield 330 gm (2.18 mole) 53%.

M.pt. 75-78$^{o}$, lit.80$^{o}$ (29).

I.r. fig.I $cm^{-1}$: OH 3500 (sharp) C=O 1740
C=N 1600

N.m.r. fig.IA ppm: OH 10.1, $CH_2$ 4.4 $CH_3$ 1.4

Caution: The product is a severe skin irritant.

Preparation of methyl-3-ethoxycarbonyl-4-methoxy carbonylisoxazolylacetate XV

174 gm (1 mole) dimethyl acetone dicarboxylate were dissolved in three liters distilled benzene in a 5 l three-necked flask equipped with an overhead stirrer, Dean-Stark water separator, condenser, drying tube and heating mantle.

Over a period of twenty minutes 48 gm (1 mole) 50% NaH/nujol were added, waiting for the frothing to subside between additions. During the addition the solution became yellow and hydrogen gas was evolved. The yellow solution was stirred for 20 minutes whereupon 140 gms (0.93 mole) ethyl chlorooximinoacetate was added over a period of 15 to 20 minutes. The reaction mixture was stirred at room temperature for 4 hrs.

A catalytic amount of p-toluenesulfonic acid monohydrate (2.5 gm) was added and the solution refluxed for 5½ hrs. and permitted to cool overnight.

The benzene solution was then washed three times with 500 ml water. The combined aqueous extracts were washed with 500 ml benzene which was combined with the main body of benzene which was then dried over magnesium sulfate. The magnesium sulfate was filtered off and washed with benzene. The benzene washings were combined with the filtrate.

An oily residue remained after the benzene had been removed with a rotavapor. The residue was allowed to stand in a separatory funnel and the nujol (24 gm) was separated off.

The product was then distilled under high vacuum and the fraction boiling at 140-145$^{o}$/0.5 mm Hg was collected. Yield 40 gms (0.15 mole) 20% of unrecovered starting material. Approximately 40 gm (0.23 mole)

dimethyl acetone dicarboxylate was recovered.

I.r. fig. II $cm^{-1}$: three C=0 s around 1740, C=C and C=N 1600.

N.m.r. Fig. II A ppm: $CH_3$ 1.45, $CH_2$ 4.2, $OCH_2$ 4.45 $OCH_3$ 3.75, 3.85.

Preparation of 3-carboxy-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-9-methoxycarbonylnaphth-(2,3-d)isoxazole XVIII

To a solution of 36 gm (0.14 mole) of the triester isoxazole,XV,in 2.7 l dry tetrahydrofuran (THF) (prepared by distilling from lithium aluminum hydride (LAH)) in a 3 l three-necked flask equipped with an overhead stirrer, condenser, drying tube, and heating mantle was added 7.4 gm 50% NaH/nujol (0.16 mole) in portions, waiting for the frothing to subside before the next addition.

The reaction mixture was stirred at room temperature for an hour under a nitrogen atmosphere and then refluxed for an hour. 18 ml cyclohexenone was then added and the mixture refluxed for about 45 hrs.

The THF was then distilled off until about one liter of solution remained. The residue was poured into a separatory funnel and diluted with approx. 2.5 l ether. The ethereal solution was then extracted four times with 500 ml 2% NaOH solution. After acidifying,the aqueous layer was extracted four times with 500 ml chloroform. The chloroform extracts were concentrated to a volume of approx. 200 ml after drying over sodium sulfate.

I.r. FigureIII. $cm^{-1}$: OH acid - 3000,
phenolic - 2800 (very broad),

C=0 acid 1755, ester 1720, ketone 1600 (broad).

Preparation of 3,9-dimethoxy carbonyl-4-methoxy-5-oxo-5,6,7,8-tetrahydronaphth-(2,3-d)-isoxazole XIX

A small amount ~75 mg of the tricyclic acid was treated overnight with excess ethereal diazomethane. The solvent was removed using an aspirator and the product purified using silica gel chromatography (1.5% MeOH in $CHCl_3$).

I.r. fig. IV $cm^{-1}$: C=0 keto 1680 arylester 1705, isoxazolylester 1750.

N.m.r. fig IVA ppm; aliphatic protons: 2.15, 2.75, 3.35, $OCH_3$ 4.0 4.05, 4.1.

Preparation of 5-methoxycarbonyl-6,8-dihydroxy-7-cyano-1-tetralone XX

In a 1 lit. flask 200 ml methanol was added to the chloroform solution obtained above and refluxed for 4 hrs with stirring using an overhead stirrer . Vigorous stirring is required to prevent bumping since the product precipitates out of solution. A large flask is required since frothing occurs due to evolution of carbon dioxide.

After cooling, the product was filtered off. The mother liquor was concentrated and refiltered. Yield 11.8 gm (4.5 m mole). The mother liquor after again concentrating yielded a further 2.6 gm crude product which was recrystallized to yield 2.5 gm product (9.6 m mole). The crude product was dissolved in acetone and water was added until the solution became just cloudy. The product recrystalized overnight. Total yield 14.3 gm (54.5 m mole),39% calculated from the isoxazole triester.

M.pt. 201-205°.

I.r. fig. V $cm^{-1}$: OH chelated to ketone 2600 hydrogen bonded to ester 3000, C≡N 2250, C=0 ester 1680, ketone 1640, aromatic C=C 1600

N.m.r. fig. V A ppm: OH 14.5 12.9 , $OCH_3$ 4.05, aliphatic 2.1, 2.7, 3.35

Preparation of 5-methoxy carbonyl-6,8-dimethoxy-7-cyano-1-tetralone XXI

A small amount of bicyclic ester diphenol, XX, was treated with excess diazomethane and purified by silica gel chromatography. The product isolated was an oil which solidified on standing.

I.r. fig. VI $cm^{-1}$; aromatic C=C 1570, 1580, C=0 ester 1740, ketone 1690, CN 2250.

N.m.r. fig. VI A ppm: $OCH_3$ 3.95, 4.05, 4.15,aliphatic protons 2.1, 2.75.

Preparation of 5-carboxy-6,8-dihydroxy-7-cyanotetralone XXII

11.8 gm (4.8 m moles) bicyclic ester was hydrolysed for 7 hrs in 60 ml water containing 6 gm NaOH at $75^{o}$. The temperature was regulated by immersing the reaction vessel in an oil bath controlled at $75^{o} \pm 3^{o}$. The conditions are critical since the product decarboxylates readily to form XXIII. The reaction mixture was then poured into a beaker, cooled and acidified with 25 ml conc. HCl.

The acidic products were filtered off, dried overnight and dissolved in 80 ml acetone followed by an equal amount of water. Crystallization occured overnight. The mother liquor yielded a further 0.35 gm when the recrystallization procedure was repeated.

5.2 gm (22 m.moles), 46%, grey crystals were recovered. Recrystallization from acetone water gave a white solid which decomposed upon heating.

I.r. fig. VII $cm^{-1}$: C=0 ketone 1610, acid 1640

N.m.r. fig. VII A ppm: OH 7.55, aliphatic obscured by DMSO.

Part B scheme IV

Preparation of 2-bromo-5-methoxybenzyl alcohol XXVI and 2-bromo-5-methoxybenzyl bromide XXVII

A solution of 10 gm (73 m mole) 3-methoxybenzyl alcohol XXV in 100 ml $CS_2$ was placed in a 500 ml three-necked flask equipped with thermometer, magnetic stirrer, dropping funnel and an ice-salt bath.

After cooling to $-10^{\circ}$ a solution of 11.8 gm (74 m mole) $Br_2$ in 100 ml $CS_2$ was added at such a rate that the temperature of the reaction mixture did not exceed $0^{\circ}$ ( approx. ½ hr). The solution was then permitted to warm to room temperature with stirring over a period of several hours.

Approximately 175 ml $CS_2$ was then distilled off and the remaining solvent removed using an aspirator. The residue, a mixture of XXVI and XXVII, solidified when the solvent was removed.

9.2 gm (33 m mole) 45% XXVII was recovered as colorless needles by recrystallization from 100 ml MeOH.

m.pt. $90-1^{\circ}$. Lit. $91-91.7^{\circ}$ (52).

I.r. fig. IX, $cm^{-1}$: aromatic C=C 1570, 1590

N.m.r. fig. IX A ppm: aromatic 7.35, 6.95, 6.65

$CH_2$ 4.45, $OCH_3$ 3.75 . Lit. 7.5-7.6, 4.52, 3.74 (52).

The alcohol XXVI was obtained in 45% yield as an oil which solidified on standing. Recrystallization from methylene chloride/petroleum ether gave a pure sample which melted at 45-45.5°.

I.r. fig. VIII $cm^{-1}$; aromatic C=C 1570, 1590.

N.m.r. fig. VIII A ppm: aromatic 7.35, 7.0, 6.65 $CH_2$ 4.6, $OCH_3$ 3.75, OH 2.2.

Preparation of 2-bromo-5-methoxy -benzylchloride XXVIII

2-bromo-5-methoxybenzyl alcohol obtained above was dissolved in 50 ml benzene in a 250 ml flask equipped with a magnetic stirrer, reflux condenser and heating mantle.

25 ml thionyl chloride was added and the solution refluxed until $SO_2$/HCl evolution ceased ~2 hrs.

The benzene and excess thionyl chloride was removed using an aspirator and the crude product recrystallized from 50 ml methanol. 7.1 gm (30 m.mole) of benzyl chloride XXVIII was recovered; 42% calculated from m-methoxy benzyl alcohol.

A sample recrystallized from methanol melted at 76-77°, lit. 75.4-76 (53).

I.r. fig. X $cm^{-1}$: aromatic C=C 1570 1590.

N.m.r. fig. X A ppm: aromatic 7.25, 6.85, 6.55, $CH_2$ 4.5 $OCH_3$ 3.7.

Preparation of diethyl-2-bromo-5-methoxybenzyl malonate XXX

11 gms (69 m.moles) diethyl malonate was weighed into a 500 ml three-necked flask followed by distilling 150 ml dry THF into the flask. The flask is then equipped with heating mantle, magnetic stirrer, condenser, drying tube and stoppers.

3.3 gm (70 m mole) 50% NaH/nujol was then added in portions, letting the frothing subside between additions. The benzyl halides obtained above (63 m mole) were then added and the solution refluxed overnight during which time sodium halide precipitated out of solution.

Approximately 125 ml THF was distilled off and the remainder was removed using an aspirator. The product was taken up in 200 ml ether and washed three times with 100 ml water acidified with 10 ml conc. HCl.

The ether was removed using an aspirator leaving an oily residue. The condensation product was obtained in 96% yield.

I.r. fig. XI $cm^{-1}$; aromatic C=C 1595, 1585 C=O 1750.

N.m.r. fig. XI A ppm; aromatic 7.3, 6.75, 6.6, $OCH_3$ 3.7, $OCH_2$ 4.1, CH 3.7, Ph $-CH_2$ 3.15, $C-CH_3$ 1.2 .

Preparation of 2-bromo-5-methoxybenzyl malonic acid XXXI

To the crude product obtained above was added, with stirring, a solution of 14 gms NaOH in 26 ml water. The mixture was warmed on a steam bath and stirred until it solidified whereupon another 50 ml water was added and the reaction mixture refluxed for two hours.

After cooling the solution was extracted twice with 50 ml chloroform to remove neutral material and filtered, if necessary, to remove solid impurities.

Carefully, with cooling and stirring sufficient conc. HCl was added to make the solution acidic to congo red ( approx. 35 ml). The yellow precipitate formed was filtered off, dried and leached with 70 ml carbon tetrachloride to remove the yellow impurities and any decarboxylated material (very little).

14 gm. (46 m mole) of white crystalline solid was obtained which decomposed at 155°. This is 73% calculated from XXVII and XXVIII. A sample sublimed at 140°/0.3 mm decomposed at 148° when heated.

I.r. fig XII $cm^{-1}$: OH 2650, C=O 1700 (broad), aromatic C=C 1580, 1595 .

N.m.r. fig. XII A ppm: aromatic 7.35, 6.75, 6.7, $OCH_3$ 3.6, CH 3.5 , $CH_2$ 3.0 .

Preparation of β-2-Bromo-5-methoxyphenylpropionic acid XXXII

21 gm (69 m mole) of the disubstituted malonic acid were placed in a 125 ml flask and heated to 170° in an oil bath maintained at 170±3°. Heating was continued until $CO_2$ evolution ceased, approx. 15 min. The brown melt, 18 gms (69 m moles), was allowed to cool and was then taken up in 125 ml chloroform. The chloroform solution was washed twice with 20 ml slightly acidic water, filtered and dried over magnesium sulfate.

The solution was then concentrated to a volume of approximately 30 ml and an equal volume of petroleum ether added. Crystallization occurred in an hour and a half at -20°. A second crop of crystals was obtained by concentrating the mother liquor and repeating the recrystallization procedure.

16 gm (62 m moles) XXXII were recovered 90%.

M.pt. 81.5-82. Lit. 83.7-84.4 (54)

N.m.r. fig. XIII A ppm: aromatic 7.3, 6.4, 6.75. $OCH_3$ 3.7, Aliphatic $A_2B_2$ 7.8, OH 12.9

I.r. Fig. XIII $cm^{-1}$: OH 3510(sharp), 3000(broad), C=0 1720, 1710, aromatic C=C 1575, 1600

U.v. fig. XIII B $\lambda_{max}$ (log ε): 229(3.95), 276 (3.27), 288 (3.23).

Preparation of 4-bromo-7-methoxy-indanone XXXV

(a) Using $SOCl_2$, $AlCl_3$, $CH_2N_2$

Preparation of β-2-bromo-5-methoxyphenylpropanoyl-chloride XXXIII

0.85 gm (3.3 m mole) XXXII was refluxed in thionyl chloride for 1½ hr. to form the acid chloride. The excess $SOCl_2$ was removed under reduced pressure. The residue was dissolved in 20 ml benzene which was also pumped off. This was repeated until the odor of thionyl chloride was no longer detectable ( 3 times).

This intermediate was not purified further but reacted directly in the next step.

I.r. fig. XIV $cm^{-1}$: C=0 1790, aromatic C=C 1600, 1570

Cyclization with $AlCl_3$ 4-bromo-7-hydroxyindanone XXXIV

The acid chloride, XXXIII, was taken up in 40 ml distilled methylene chloride and 3.0 gm (2.3 m mole) freshly sublimed $AlCl_3$ was added. The mixture was refluxed and permitted to stand overnight. The reaction mixture was protected with a drying tube.

The methylene chloride was pumped off with an

aspirator and the residue decomposed with water. The aqueous solution was acidified and extracted with chloroform.

After the solvent was removed 0.32 gm (1.6 m mole), 48%, XXXIV was recovered as a white crystalline solid after recrystallization from methanol.

M.pt.146-146.5 , lit 146.2-46.9$^{o}$ (54).

I.r. fig. XV $cm^{-1}$: OH 3375, C=0 1680, aromatic C=C 1620.

N.m.r.fig. XV A ppm: OH 8.95, aromatic AB 7.55, 6.65 , aliphatic $A_2B_2$ 2.85 .

U.v. fig. XV B $\lambda_{max}$ (log $\varepsilon$): 227(4.22), 250(3.77),257(3.79),325(3.47).

Methylation with $CH_2N_2$

75 mg (0.33 m mole) XXXIV was treated with excess ethereal diazomethane and purified on silica gel (TLC) using 2% MeOH in $CHCl_3$.

74 mg (0.31 m mole) XXXV was recovered, 94%.

(b) Cyclization with HF

2.02 gm (7.8 m mole) XXXII was added to 30 ml HF at room temperature in a polyethylene bottle with screw cap and narrow vent and was stirred for 2 hrs. 15 min. The hydrogen fluoride was evaporated off by warming gently with a lukewarm water bath. After the HF was removed the residue was suspended in water and washed 3 times with 20 ml chloroform.

The red chloroform solution after drying over sodium sulfate was evaporated and the residue taken up in a minimum volume of ethanol which was diluted with twice the volume ether.

Crystallization occured overnight in the freezer. 0.63 gm (2.6 m moles) was obtained; a further 0.19 gm (0.79 m mole) was recovered from the mother liquor. Total yield 3.39 m moles, 43%.

Cyclization with polyphosphoric acid (PPA)

Polyphosphoric acid was prepared in a stoppered large necked 500 ml flask by dissolving 109 gm $P_2O_5$ in 91 gm 85% phosphoric acid. The mixture was stirred very vigorously with a heavy magnetic stirring bar until only a few undissolved pieces of $P_2O_5$ remained. Much heat is generated in this procedure and the reagent was allowed to cool to room temperature before using.

13 gm (50 m moles) of β-2-bromo-5-methoxyphenyl-propanoic acid, XXXII, was then stirred into the reagent with a spatula. The mixture was heated on a steam bath and vigorously stirred for 35 min. during which time the mixture turned a deep red.

The reaction mixture was decomposed with 120 gm of ice while cooling in an ice bath and then further diluted with 150 ml water. The suspension was extracted with 100 ml chloroform followed by three extractions of

50 ml. each.

The combined chloroform extracts were washed with 50 ml 10% sodium bicarbonate solution and dried over anhydrous sodium sulfate.

After the chloroform was pumped off the residue was taken up in methanol and filtered. The precipitate after washing with a small amount of methanol weighed 2.5 gms (5.4 m moles) 11%, XXXVI.

The chloroform filtrate was pumped off and the residue dissolved in 40 ml benzene and diluted with an equal volume of petroleum ether. The crystals were filtered off and the mother liquor reworked to obtain a second crop of crystals.

Total yield 8.5 gm (35 m moles) pale yellow crystals 70%. The color is due to a small amount of XXXVI.

An analytical sample of XXXV was prepared by purifying 120 mg with silica gel chromatography followed by recrystallization from a minimum volume of methanol by dilution with twice the volume of ether followed by sublimation at $80^{\circ}/0.3$ mm Hg.

This sample melted at $135\text{-}135.5^{\circ}$ Lit. 133.6-134.2 (54)

I.r. fig. XVI $cm^{-1}$: C=0 1705, aromatic C=C 1585.

N.m.r. fig. XVI A ppm: Aromatic AB 7.6, 6.7, $OCH_3$ 3.95, aliphatic $A_2B_2$ 2.85.

U.v. fig. XVI B $\lambda_{max}$(log$\varepsilon$): 225(4.36) 252(3.91),285(3.91),323(3.64).

Elemental analysis: $C_{10}H_9O_2Br$ M=241.11

| | C | H | Br |
|---|---|---|---|
| Calculated | 49.87 | 3.76 | 33.15 |
| Found | 49.47 | 3.70 | 33.23 |

A small amount of XXXVI was recrystallized from methylene chloride as pale greenish yellow crystals which melted at 233-37°.

I.r. fig. XVII $cm^{-1}$: C=O 1680, aromatic C=C 1600, C=C 1580.

N.m.r. fig. XVII A ppm: two aromatic AB patterns at 6.5-7.6, two $OCH_3$ 3.95, $Ph-CH_2-C=C$ 3.85, $A_2B_2$ pattern 2.8-3.7.

U.v. fig. XVII B $\lambda_{max}$(log ε): 221(4.21), 256(3.85), 327(3.96), 361(4.07).

Mass spectrum fig. XVII C; parent ion $m^+/e$ =462 (Br=79)

Preparation of 7-methoxyindanone XXXVII

46 mg (0.18 m mole) XXXIV, 25 mg triethylamine (0.25 m mole) and 35 mg 5% palladium on charcoal was stirred vigorously in 10 ml methanol under a hydrogen atmosphere for 40 mins.

The solvent was pumped off, after the charcoal was removed by filtration, and the residue taken up in chloroform and washed with some dilute acid to remove the base.

After drying the chloroform was removed and the

residue purified on silica gel (TLC) using 0.75% MeOH/ $CHCl_3$. Melting point after recrystallizing from methanol/ether was 99-102. Lit 102-3° (55), 106 (38).

25 mg (0.14 m mole), 78%, 7-methoxyindanone was recovered.

I.r. fig. XVIII $cm^{-1}$: C=o 1700, aromatic C=C 1595.

N.m.r. fig. XVIIIA ppm: aromatic ABC pattern around 7.2, $OCH_3$ 3.9, aliphatic $A_2B_2$ 2.85.

Preparation of 3-bromo-6-methoxyhomophthalimide XXXIX

1.35 gm (5.6 m moles) XXXV was dissolved in 25 ml dry THF in a 50 ml flask equipped with magnetic stirrer, heating mantle, reflux condenser, and drying tube.

0.29 gms 50% NaH/nujol (6.05 m moles) were added and the solution warmed for a short time ( approx.one minute) until it was dark red. After cooling somewhat 0.7 ml isoamyl nitrite was added and the solution refluxed for a few minutes and permitted to cool to room temperature. A minimum amount of HCl was added so that the solution was just acidic.

The solvent was removed under reduced pressure and the water was removed by pumping off a benzene water azeotrope.

0.39 gm (1.45 m moles), 26%, XXXIX was recovered. When recrystallized several times from benzene the product was recovered as white crystaline plates which melted at 203-205° after drying at 50°.

I.r. fig. XIX $cm^{-1}$: NH str. 3700, C=O six member imide 1640, aromatic C=C 1600.

N.m.r. fig. XIX A ppm: AB quartets. aromatic 7.75 6.82(J=7.5 cps) methylene 7.82, 6.95 (J=9 cps), $OCH_3$ 4.0

U.v. fig. XIX B $\lambda_{max}$(log ε): 220(4.31), 247(3.91), 271(370),305(3.81),330(3.69),343(3.82)358(3.76)

Preparation of N-methyl-3-bromo-6-methoxyhomophthalimide XL

A small amount of XXXIX was treated overnight with excess diazomethane. The product was purified by silica gel chromatography. After recrystallizing several times from benzene the product was obtained as colorless plates which melted at 144.5-145° after drying at 50° overnight.

I.r. fig. XX $cm^{-1}$: Six member imide carbonyls 1660, aromatic C=C 1610

N.m.r. fig. XX A ppm: AB quartets aromatic 7.92 6.70 (J=8 cps) methylene 7.73,675 (J=9 cps), $OCH_3$ 3.96, $NCH_3$ 4.07

U.v. fig. XX B $\lambda_{max}$(log ε):217(4.34), 248(4.01) 264(3.87),271(3.91),292(3.88), 302(3.91), 329(3.74), 342(3.88),357(3.82).

Preparation of 2-oxime -4-bromo-7-methoxy-1,2-indandione XLI

In a 50 ml flask, equiped with a magnetic stirrer and reflux condenser, 8.5 gm XXXV (35 m moles) was dissolved in 120 ml distilled methanol. The solution was warmed on a hot water bath and 10 ml freshly distilled isoamylnitrite was added with stirring through the reflux condenser, causing the solution to boil vigorously, followed by 4 ml conc. HCl.

The reaction mixture was stirred on a hot water bath for an hour and then cooled in the freezer ($-20^{o}$). The crystals formed were filtered off and washed with a small amount of chloroform followed by some ether.

When dry 5.3 gms (19 m moles) 56% XXI was recovered as yellow crystals, which decomposed at 230-$240^{o}$. Lit 233-6 (56).

I.r. fig. XXI $cm^{-1}$: OH 3250, C=O 1700, C=N 1630, aromatic C=C 1590.

N.m.r. fig. XXI A ppm: aromatic AB 7.7, 6.8, $OCH_3$ 3.9, $CH_2$ 3.8 .

U.v. fig. XXI B $\lambda$max (log $\varepsilon$): 220(4.10), 246(4.03), 227(4.02), 349(3.71).

Preparation of 2-methoximino-4-bromo-7-methoxyindanone XLII

100 mg (0.37 m mole) XLI was treated overnight with excess ethereal diazomethane in methanol/ether solution. The residue, after the solvent was removed, was taken up in chloroform and purified on silica gel (TLC).

80 mg (0.27 m mole) methylated product was recovered, 76%.

Recrystallization from chloroform/petroleum ether (1:2 vol) yielded pale greenish yellow crystals which decomposed at 180-90°.

I.r. fig. XXII $cm^{-1}$: C=O 1685, aromatic C=C 1590, C=N 1560.

N.m.r. fig. XXII A ppm: aromatic AB 7.7, 6.83, $NOCH_3$ 4.27, $OCH_3$ 3.97, $CH_2$ 3.79.

U.v. fig. XXII B $\lambda_{max}$(log ε): 3.15(3.94), 361(3.70).

Preparation of 2-acetoximino-4-bromo-7-methoxyindanone XLIII

4.5 gm (16.6 m mole) oxime XLI was suspended in 30 ml acetic anhydride, in a 100 ml flask, and heated on a steam bath with stirring for an hour and a half.

The acetylated product precipitated out of solution and was filtered off after cooling in the freezer (-20°) for an hour. A second crop of crystals was obtained after the mother liquor was concentrated and cooled.

Total yield, 4.6 gm (14.7 m moles), 89%. This product is unstable at room temperature and slowly discolors overnight. Melting point 180-95°.

I.r. fig. XXIII $cm^{-1}$: C=O ester 1785, ketone 1725, C=N 1685, aromatic C=C 1590.

N.m.r. fig. XXIII A ppm: aromatic AB 7.25, 6.85, $OCH_3$ 4.0, $CH_2$ 3.8, $C-CH_3$ 2.4.

Preparation of 2-bromo-5-methoxy-6-methoxycarbonyl-phenyl acetonitrile XLIV

In a 100 ml flask 4.6 gm (15 m mole) XLIII was suspended in 50 ml distilled methanol and warmed on a steam bath. 1.5 gm anhydrous sodium carbonate was added and the suspension stirred on a steam bath for ½ hr. The remaining 2-acetoximino-4-bromo-7-methoxy-indanone goes into solution with the evolution of $CO_2$ gas. Not all the sodium carbonate is was consumed.

Most of the methanol was then pumped off with an aspirator and the residue taken up in 75 ml chloroform. Part of the residue dissolved and the remainder was suspended in the chloroform. The chloroform solution was then washed with 5% NaOH solution until the washings were colorless.

2.3 gm (8.5 m mole) oxime, XLI, was recovered from the NaOH solution after acidifying with HCl and filtering.

After drying over sodium sulfate the chloroform was removed under reduced pressure. The residue was taken up in a minimum volume of hot chloroform and recrystallized by addition of twice the volume of methanol and cooling in the freezer. A second crop of crystals was obtained from the mother liquor.

Total yield: 1.44 gm (5.1 m mole), 79%, calculated from unrecovered starting material.

An analytical sample was prepared by recrystallizing a sample from methanol and then subliming it at $95^{\circ}/0.3$ mm. Melting point: $152.5\text{-}53^{\circ}$.

I.r. fig. XXIV $cm^{-1}$: C≡N 2280, C=0 1730, aromatic C=C 1585.

N.m.r. fig. XXIV A ppm: aromatic AB 7.6,6.85, $CH_2$ 3.80, $OCH_3$ 3.80, 3.95.

U.v. fig. XXIV B $\lambda_{max}$(log ε): 228(3.89),292(3.42)

Mass spectrum fig. XXIV C: parent ion $m^+/e$ 282 (Br=79)

Elemental analysis: $C_{11}H_9O_3BrN$ M= 284.11

| | C | H | N | Br |
|---|---|---|---|---|
| Calculated | 46.50 | 3.55 | 4.93 | 28.13 |
| Found | 46.57 | 3.71 | 5.06 | 28.28 |

Preparation of α-2-methoxycarbonyl-3-methoxyphenyl propionitrile XLV

140 mg (0.5 m mole) XLIV was dissolved in 5 ml dry THF. Upon addition of 30 mg NaH/nujol the solution became yellow due to formation of the anion. The color became deep red after a few minutes standing or refluxing. Addition of 0.75 ml methyl iodide caused sodium iodide to precipitate out of solution.

After refluxing for an hour the solvent was removed with an aspirator and the residue taken up in chloroform and water, 10 ml each. The aqueous layer was extracted twice more with 10 ml chloroform and the combined chloroform solutions dried over sodium sulfate.

The slightly yellowish residue obtained after the chloroform was pumped off was purified on silica gel (TLC).

130 mg (0.44 m mole) 89% of XLV was recovered as an oil which crystallized on standing. Melting point after recrystallization from methanol/ether (1:2 vol) 88-88.5°.

I.r. fig. XXV $cm^{-1}$: C≡N 2275, C=O 1725, aromatic C=Cl580

N.m.r. fig. XXVI A ppm: aromatic AB 7.55, 6.8, methine proton 4.37, $OCH_3$ 3.95, 3.80, $C-CH_3$ 1.67.

Part C Scheme VI

Preparation of m-methoxybenzoic acid XLVIII

A 250 ml three-necked flask equipped with an ice-salt bath, overhead stirrer, thermometer, and dropping funnel was used.

20 gm (0.15 mole) m-hydroxy benzoic acid was dissolved in a solution of 17 gm sodium hydroxide in 160 ml water and cooled to approx $10^{o}$ in the reaction flask. 42 ml (58 gm, 0.4 mole) dimethylsulfate (DMS) was added over a period of half an hour from the dropping funnel. The temperature was maintained at approx $10^{o}$ and the reaction mixture vigorously stirred at that temperature for 2 hrs.

Another 6 gms NaOH was then added and the solution refluxed for an hour. After cooling, the solution was filtered to remove solid impurities and acidified to congo red with conc. HCl.

After cooling, the product, m-methoxybenzoic acid XLVIII, was filtered off and recrystallized from 600 ml hot water. 21.2 gm (0.14 mole) 97%, was recovered.

Melting point 103-4. Lit. 107-8° (57).

I.r. fig. XXVI $cm^{-1}$: OH 2900, 3550, C=O 1700, 1760, aromatic C=C 1595, 1610, C-O-C 1060.

N.m.r. fig. XXVI A ppm: OH 11.2, aromatic 8.0, $OCH_3$ 4.1.

Preparation of m-methoxybenzamide L

21.2 gm (0.14 mole) m-methoxybenzoic acid was suspended in 150 ml distilled benzene in a 1 l. three-necked flask equipped with an efficient overhead stirrer, heating mantle, condenser and drying tube.

50 ml thionyl chloride was then added and the solution refluxed until $SO_2$/HCl evolution ceased. The benzene was then removed under reduced pressure and fresh benzene added and again removed.

This procedure was repeated until the $SOCl_2$ odor was no longer detectable ( approx 2x100 ml).

The residue, m-methoxybenzoyl chloride, XLIX, was then dissolved in 200 ml benzene and filtered to remove insoluble material.

While stirring vigorously, and with occasional cooling, ammonia was bubbled into the solution for about 15 min. After cooling, the precipitate which had formed was filtered off, dried, and recrystallized from 200 ml water.

15.9 gm (0.11 mole) of m-methoxybenzamide was recovered after drying, 75%.

Melting point after a second recrystallization from water was 132-3. Lit. 134° (58).

I.r. fig. XXVII $cm^{-1}$: N-H str. 3575, 3450, C=O 1680, aromatic C=C 1595, C-O-C 1050.

N.m.r. fig. XXVII A ppm: aromatic 7.4, $NH_2$ 6.1, $OCH_3$ 3.8.

U.v. fig. XXVII B $\lambda_{max}$(log $\varepsilon$):212(4.23), 225(3.89), 292(3.40).

Preparation of 1-carbamoyl-3-methoxy-1,4-dihydrobenzene LI

200 ml ammonia was distilled into a 500 ml 3-necked flask equipped with a magnetic stirrer, dry ice/acetone reflux condenser, sodalime drying tube and 25 gm (13.2 m mole) L. The ammonia vapor was dried by passing it through a column of soda lime.

0.8 gm Na (3.3 m mole) in small pieces was then quickly added to the solution which was then stirred for about 5 min. 10 ml ethanol was then added as rapidly as was permitted by the vigorously boiling solution, followed immediately by sufficient ammonium chloride to remove the yellow color of the solution approx 2.5 gms. This reaction was very vigorous.

The solvent was removed by warming the reaction flask gently with a warm water bath.

The residue was suspended in about 30 ml water and extracted with chloroform (100 ml and 2x50 ml). The chloroform extracts were dried over sodium sulfate.

1.65 gms product was recovered after the solvent was pumped off. This was dissolved in about 20 ml chloroform and recrystallized in the freezer for 48 hrs. The product floated on the mother liquor.

1.4 gm (0.92 m mole) dihydromaterial was recovered, 70%. The very fine needles obtained after recrystallizing twice from chloroform and twice from benzene melted at 158-9°. Lit 158-60° (44).

I.r.fig. XXVIII $cm^{-1}$ N-H str. 3430, 3550 bend 1580, C=O 1690, vinyl ether C=C 1650

N.m.r.fig. XXVIIIA ppm: $CH_2$ 2.7, $OCH_3$ 3.55, methine proton 3.7, CH=CH- 5.8, O-C=CH- 4.7, $NH_2$ 5.7

Preparation of 3-oxo-4-cyclohexenyl carboxamide LV

0.5 gm (3.27 m moles) LI was stirred into 3 ml 3% HCl solution until solution is complete at ice bath temperature. Stirring was continued for approx, 20 mins. to obtain equilibrium (59).

The acidic solution was washed three times with 5 ml chloroform to remove nonisomerized βγ-unsaturated ketone LIV.

The aqueous solution was then neutralized with sodium carbonate and evaporated to dryness. The residue was leached 3 times with hot chloroform, 20 ml. The $CHCl_3$ leachings were combined, dried over $Na_2SO_4$, filtered and pumped off with an aspirator. The residue was taken up in a minimum volume of chloroform and diluted with an equal volume of benzene to induce crystallization.

0.25 gm (1.8 m mole) 55% LV was recovered, m. pt. 116-8. This product was further purified by thin layer chromatography (silica gel) and again recrystallized from chloroform/benzene. The melting point had then improved to 118-9. Lit. 122-3° (44).

I.r. fig. XXX $cm^{-1}$: NH str. 3430, 3550, bend.1595, C=O amide and αβ-unsaturated ketone 1690.

N.m.r. fig. XXX A ppm: C=CH-C=O 6, CH=C-C=O 7.2, 7 protons 2-3.5.

U.v. fig. XXX B $\lambda_{max}$(log ε): 222(3.53) lit.221(3.83) (44).

A small amount of LIV was obtained when the chloroform washings obtained above were pumped off. m.pt.80-4°.

I.r. fig. XXIX $cm^{-1}$: NH str. 3240, 3560 bend 1595, C=O amide 1690, ketone 1720.

N.m.r.fig. XXIX A ppm: $NH_2$ 6.0 -CH=CH- 6.0, allylic methylene 2.9, methine proton 3.5, $-CH_2-$(CH ) 2.7.

Condensation products of 2-methoxycarbonyl-3-methoxy-6-bromophenyl acetonitrile Part D Scheme VII

Preparation of 1,2,3,4,4a,9,9a,10-octahydro-2-carbamoyl-4,10-dioxo-5-methoxy-8-bromo-9-cyanoanthracene LVI

200 mg XLIV (0.71 m mole) was dissolved in 10 ml anhydrous THF and its anion formed by addition of 70 mg (1.45 m mole) NaH/nujol, 50%. When the solution was a deep red color 100 mg (0.72 m mole) LV was added and the solution refluxed overnight ( approx 16 hrs).

The THF solution was acidified with a few drops of con.HCl after it was allowed to cool. The precipitate formed (NaCl), was filtered off and the filtrate pumped off with an aspirator. The residue was taken up in a small amount of methanol and the product LVI filtered off. Yield - 20% M.pt. 250°.

I.r. fig. XXXI $cm^{-1}$: NH str. 3470, 3360, C≡N 2260, C=O amide 1675, β-diketone 1600, aromatic C=C 1570.

U.v. fig. XXXI C $\lambda_{max}$ (log ε): 227(4.02), 258(3.54) 265(3.49), 349(3.90).

Preparation of 1,2,3,4,4a,9,9a,10-octahydro-4,10-dioxo-5-methoxy-8-bromo-9-cyanoanthracene LVIII

1.8 gm XLIV (6.35 m mole) was dissolved in 50 ml anhydrous THF in a 100 ml flask equipped with stirrer, drying tube, reflux condenser, and heating mantle.

When 0.7 gm (14.5 m moles) sodium hydride/nujol (50%) was added hydrogen gas was evolved and the solution became yellow due to the anion formed. After refluxing for a few minutes during which time the solution became deep red 0.7 gm (7.3 m mole) cyclohexenone XVI was added and the solution refluxed for 8 hrs.

The solvent was then pumped off under reduced pressure and the residue taken up in 25 ml 3.7% HCl and extracted overnight with chloroform. The chloroform extract was dried over $Na_2SO_4$ and then pumped off to leave the residue extracted from the aqueous solution.

The residue was purified on silica gel (TLC) using 2% methanol in chloroform. Recrystallization from 5 ml chloroform with 12 ml petroleum ether formed red crystals, 0.62 gm. A further 0.1 gm was recovered from the mother liquor (2.05 m mole ) 32.5%.

A sample recrystallized from methylene chloride/ petroleum ether (0.31 gm, 2 ml/5ml) formed translucent crystals containing one half mole methylene chloride per mole product ( nmr data) ($CH_2Cl_2$ was removed at 100° when a melting point was obtained). Pale cream colored crystals were obtained when the product was dried overnight, m.pt. 152-3°.

I.r. fig. XXXII $cm^{-1}$; β-diketone 1600, aromatic C=C 1580, C≡N 2260 (v.weak).

N.m.r. fig. XXXII A ppm:O=C-CH-C=O 16.35, aromatic

AB 7.65, 6.95, CH-CN 4.3, $OCH_3$ 3.9, aliphatic 1.5-3.6.

U.v. fig XXXII B $\lambda_{max}$(log ε): 231(4.17) 258(3.62), 265(3.60), 349 (4.04).

Mass spectrum fig. XXXII C : parent ion $m^+/e$=347 (Br=79).

Elemental analysis: $C_{16}H_{14}O_3NBr$ M=348.04

| | C | H | N | Br |
|---|---|---|---|---|
| Calculated | 55.17 | 4.05 | 4.02 | 22.96 |
| Found | 54.80 | 4.17 | 4.19 | 23.09 |

Preparation of 1,2,3,4,9,9a-hexahydro-4-oxo-5,10-dimethoxy--8-bromo-9-cyanoanthracene LIX, and 1,2,3,9,9a,10-hexahydro-4,5-dimethoxy-8-bromo-9-cyano-10-oxo-anthracene LX

0.23 gm crude LVIII (0.6 m mole) was treated overnight with ethereal diazomethane. The residue, after the solvent was recovered, was purified on silica gel (TLC 2% MeOH/$CHCl_3$).

Two major bands were obtained. The band with lowest $R_f$ was found to contain 135 mg LX (0.37 m mole). When recrystallized several times from $CH_2Cl_2$/petroleum ether, a pale yellow product was obtained as flocculent crystals of melting point 122-3°.

I.r. fig. XXXIV $cm^{-1}$; C≡N 2250, C=O 1650, aromatic and olifinic C=C 1560.

N.m.r. fig. XXXIV A ppm: aromatic AB 7.6, 6.9, CH-CN 4.25, $OCH_3$ 3.85, aliphatic 1.4-3.15.

U.v. fig. XXXIV B $\lambda_{max}$(log ε): 226(4.07),

328(3.86)

Mass spectrum fig. XXXIV C parent ion $m^+/e$ 361 (Br=79).

The band with greater $R_f$ 92 mg, separated into 2 components using alumina gel chromatography (TLC) 1% MeOH/$CHCl_3$. The slower component present in only a small amount is believed to be the carbon methylated product LXI. Only a small amount of this product was obtained and no further analysis was made.

The faster band on alumina gel was found to be LIX. When recrystallized from methylene chloride/petroleum ether pale yellow granular crystals were obtained, m.pt. 196-8°.

I.r. fig. XXXIII $cm^{-1}$ C≡N 2260 (v.weak), C=0 1665, C=C aromatic 1580, olifinic 1540.

N.m.r. fig. XXXIII A ppm: aromatic AB 7.6,6.95, CH-CN 4.25, $OCH_3$ 3.8,3.95, aliphatic 3.2-1.3.

U.v. fig. XXXIII $\lambda_{max}$(log ε): 230(390), 307(3.77) 344(392)

Mass spectrum fig. XXXIII C : parent ion $m^+/e$ =361 (Br=79).

## SPECTRA

I.r. spectra were recorded on a Perkin Elmer 700 spectrophotometer.A Varian A-56/60A spectometer was used to make all n.m.r. spectra except those presented in figures XVII A, XVII A2 and XVII A2,which were made on a Varian DA-60-I spectrometer with an internal TMS reference signal.U.v. spectra were made on a Unicam SP 800 B spectrophotometer. Mass spectra were obtained on a Hitachi RMU 6 D mass spectrometer.

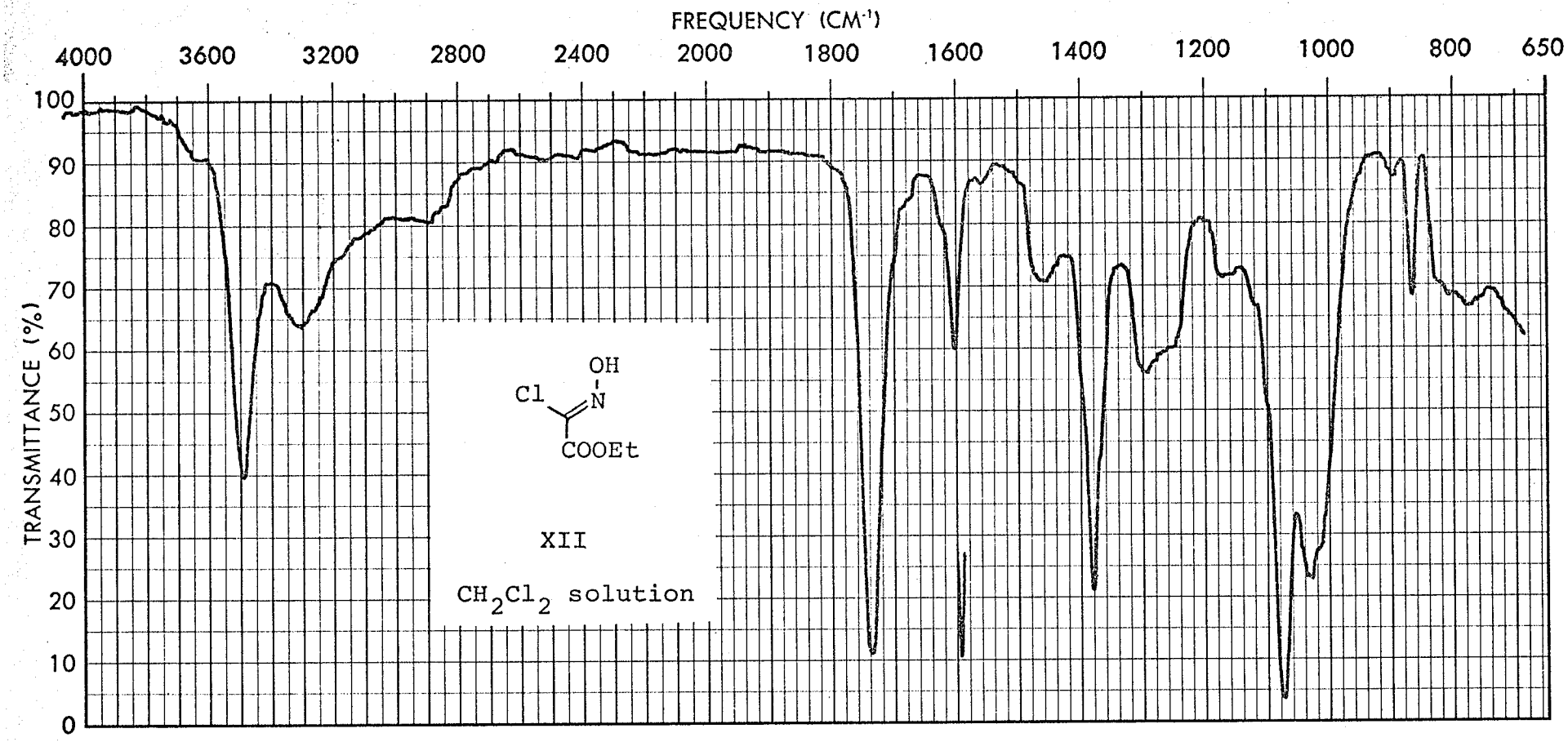



Figure 1

Infrared spectrum of ethylchloroximinoacetate

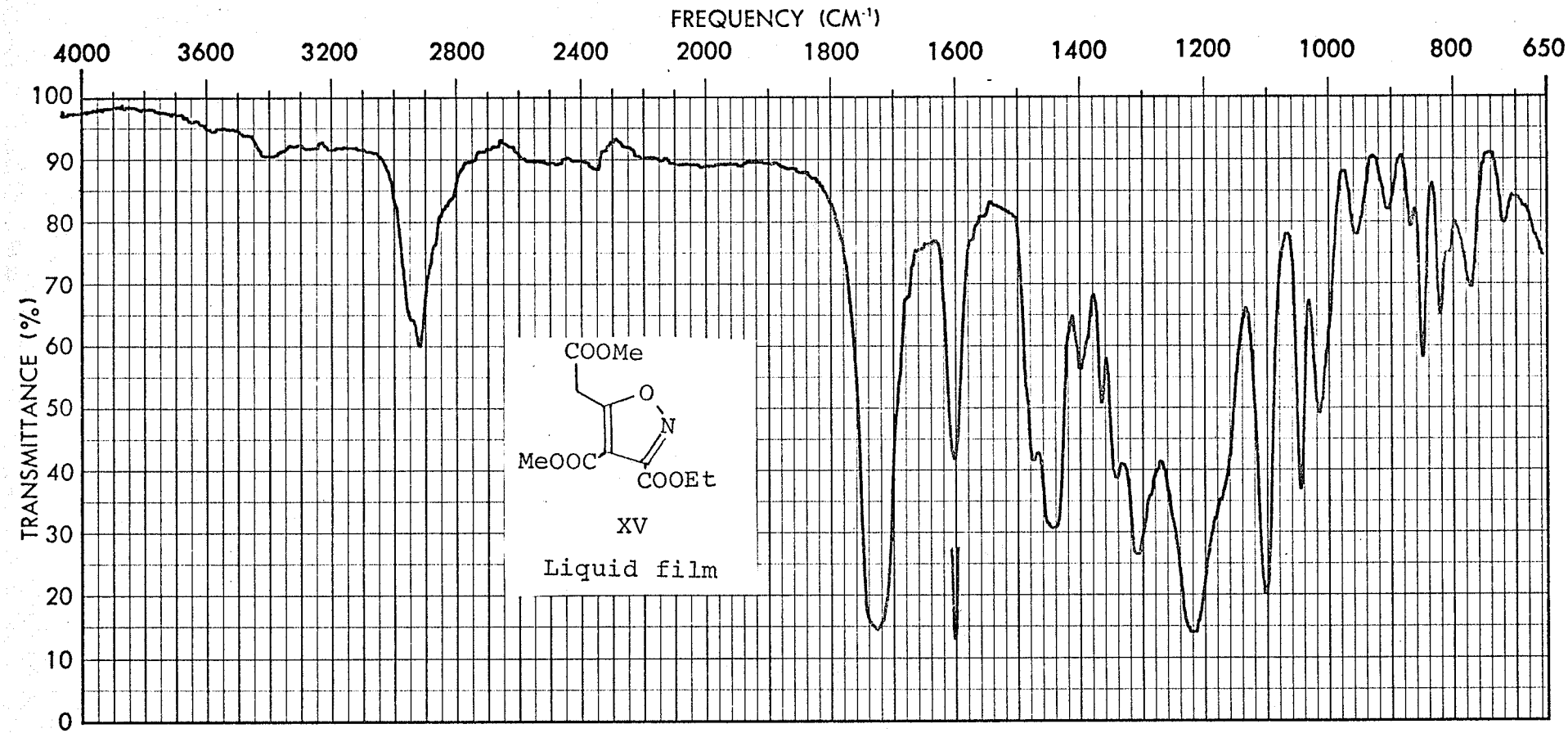



Figure II

I.r. spectrum of methyl-3-ethoxycarbonyl-4-methoxy-carbonylisoxazolylacetate

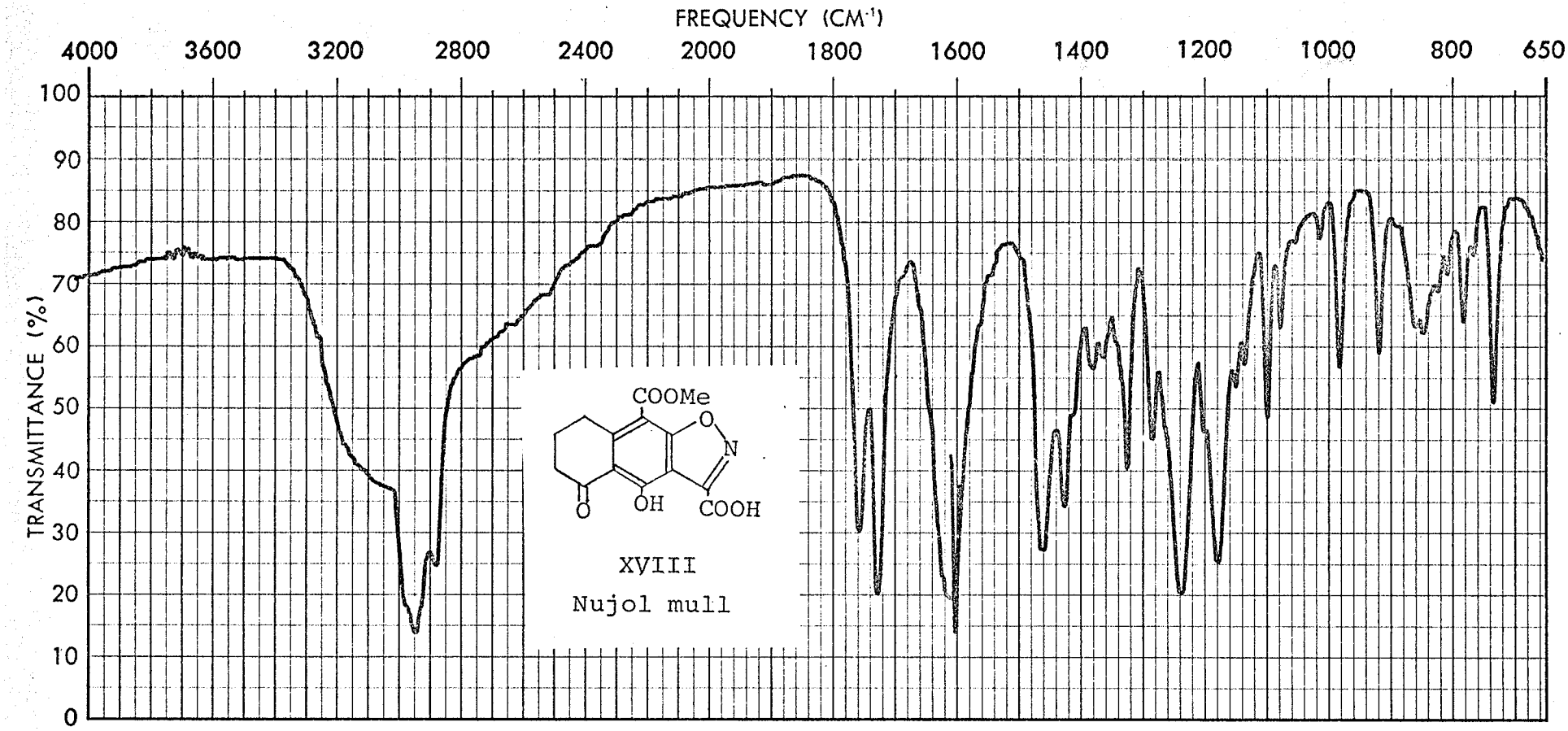



Figure III

I.r. spectrum of 3-carboxy-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-9-methoxycarbonylnaphth-(2,3-d)isoxazole

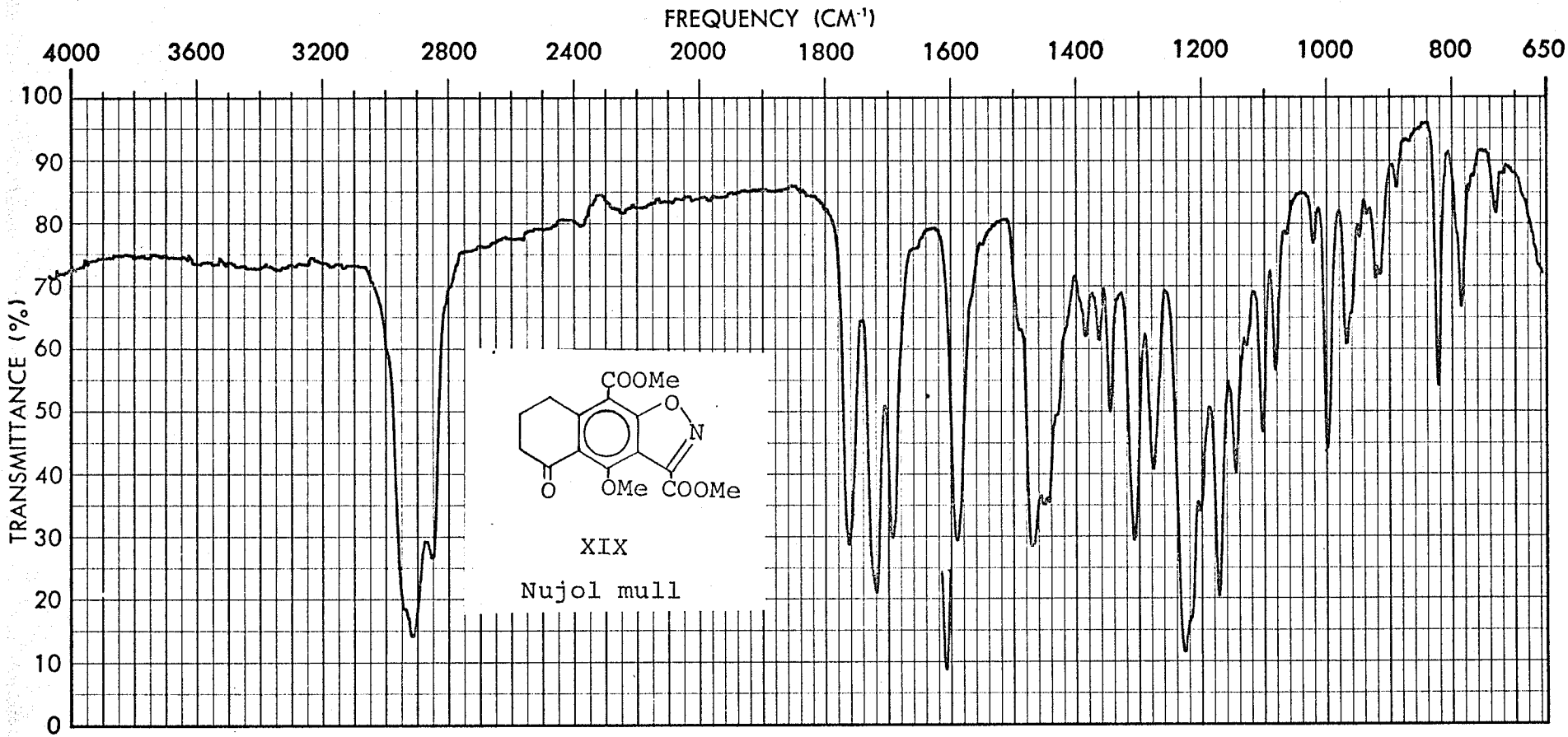



Figure IV

I.r. spectrum of 3,9-dimethoxycarbonyl -4-methoxy-5-oxo-5,6,7,8-tetrahydronaphth-(2,3-d)isoxazole

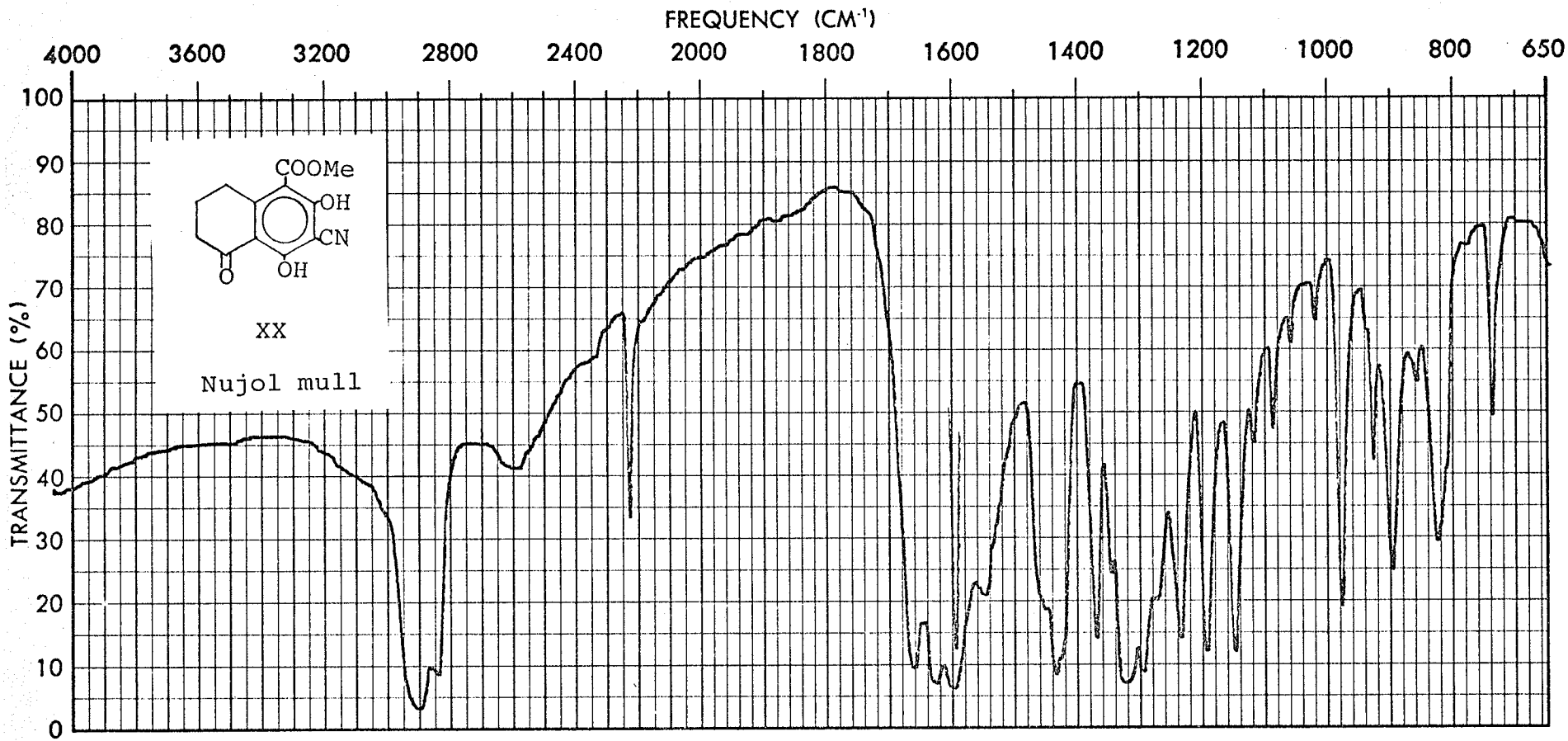



Figure V

I.r. spectrum of 5-methoxycarbonyl-6,8-dihydroxy-7-cyano-1-tetralone

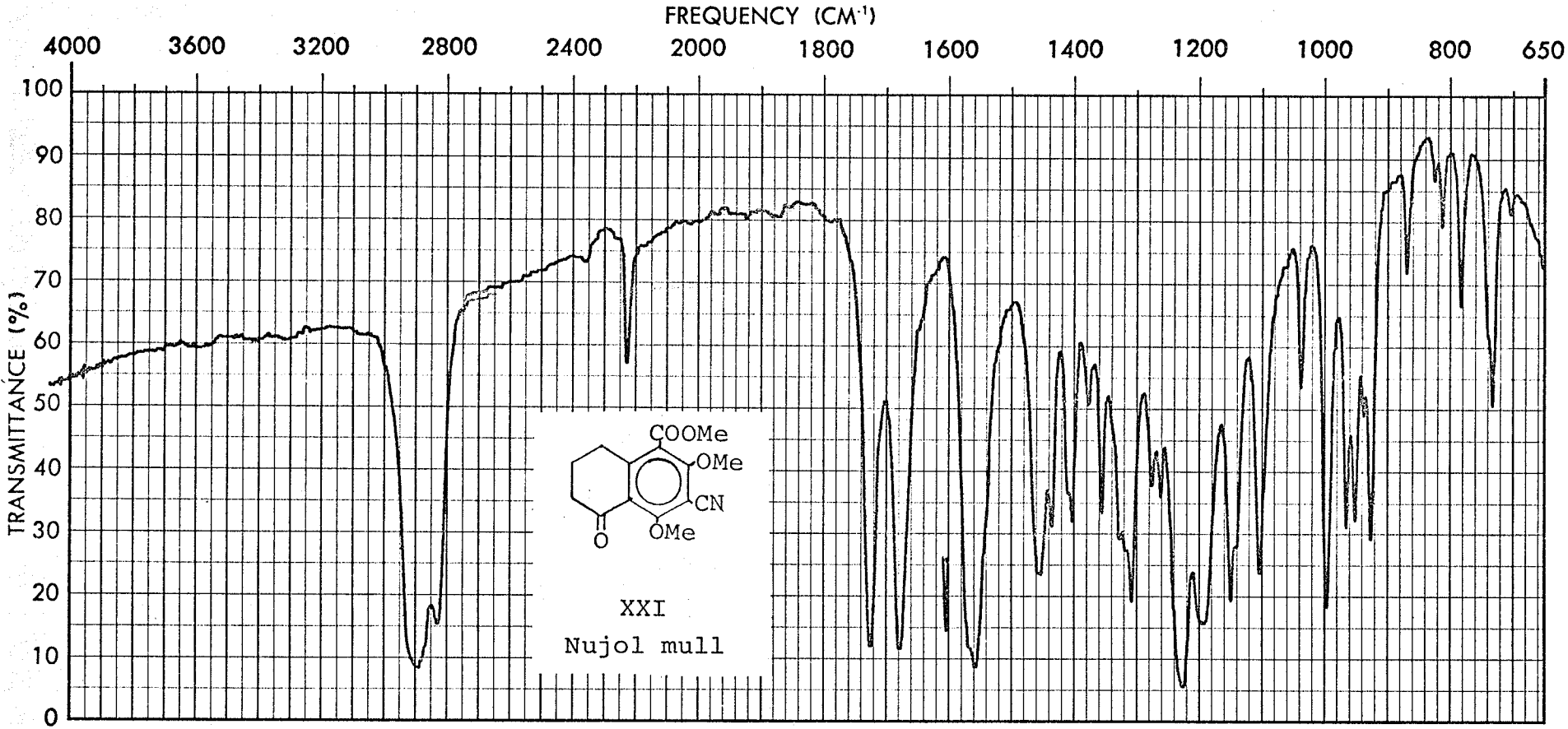



Figure VI

I.r. spectrum of 5-methoxycarbonyl -6,8-dimethoxy-7-cyano-1-tetralone

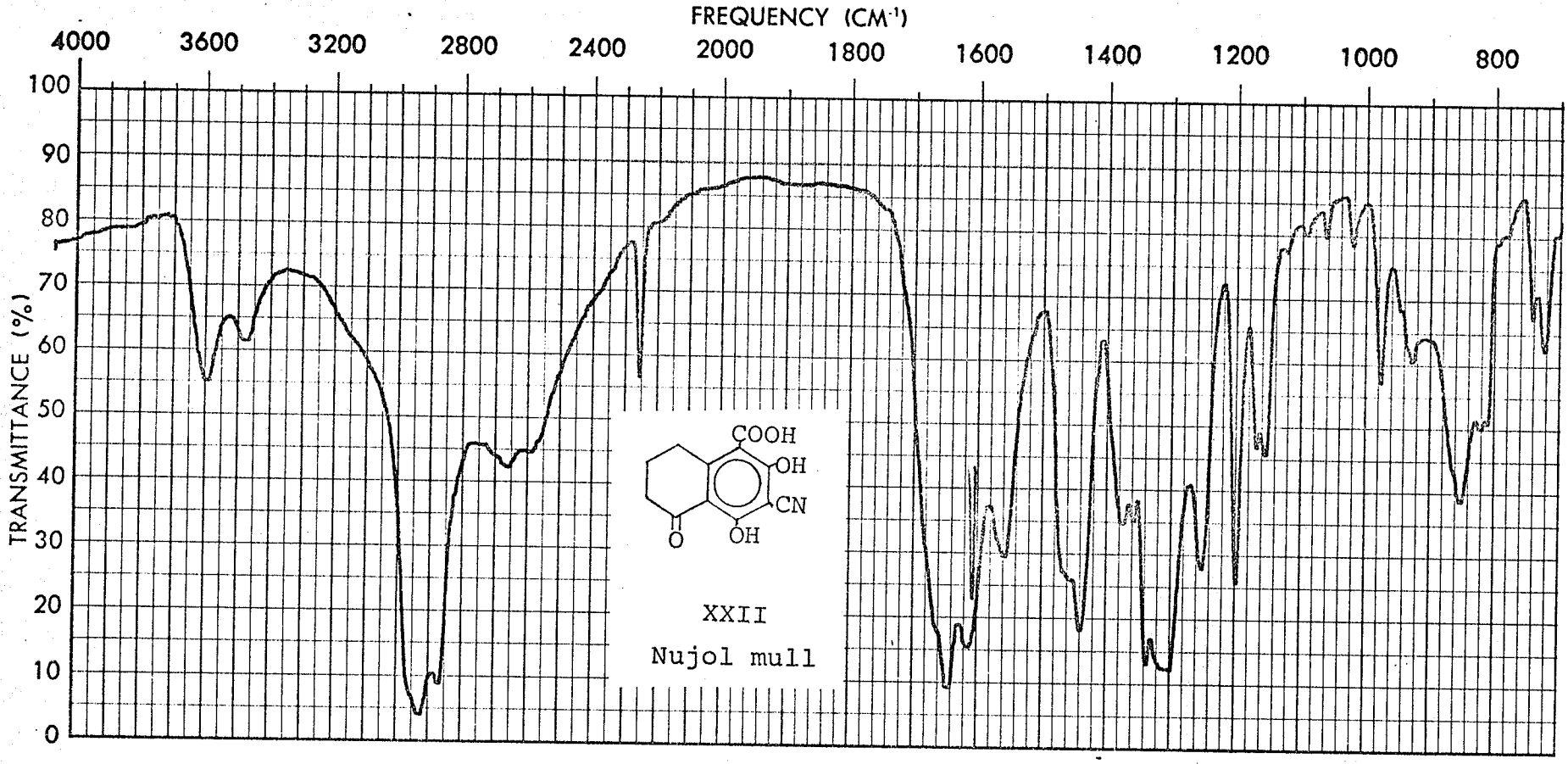



Figure VII

I.r. spectrum of 5-carboxy-6,8-dihydroxy-7-cyanotetralone

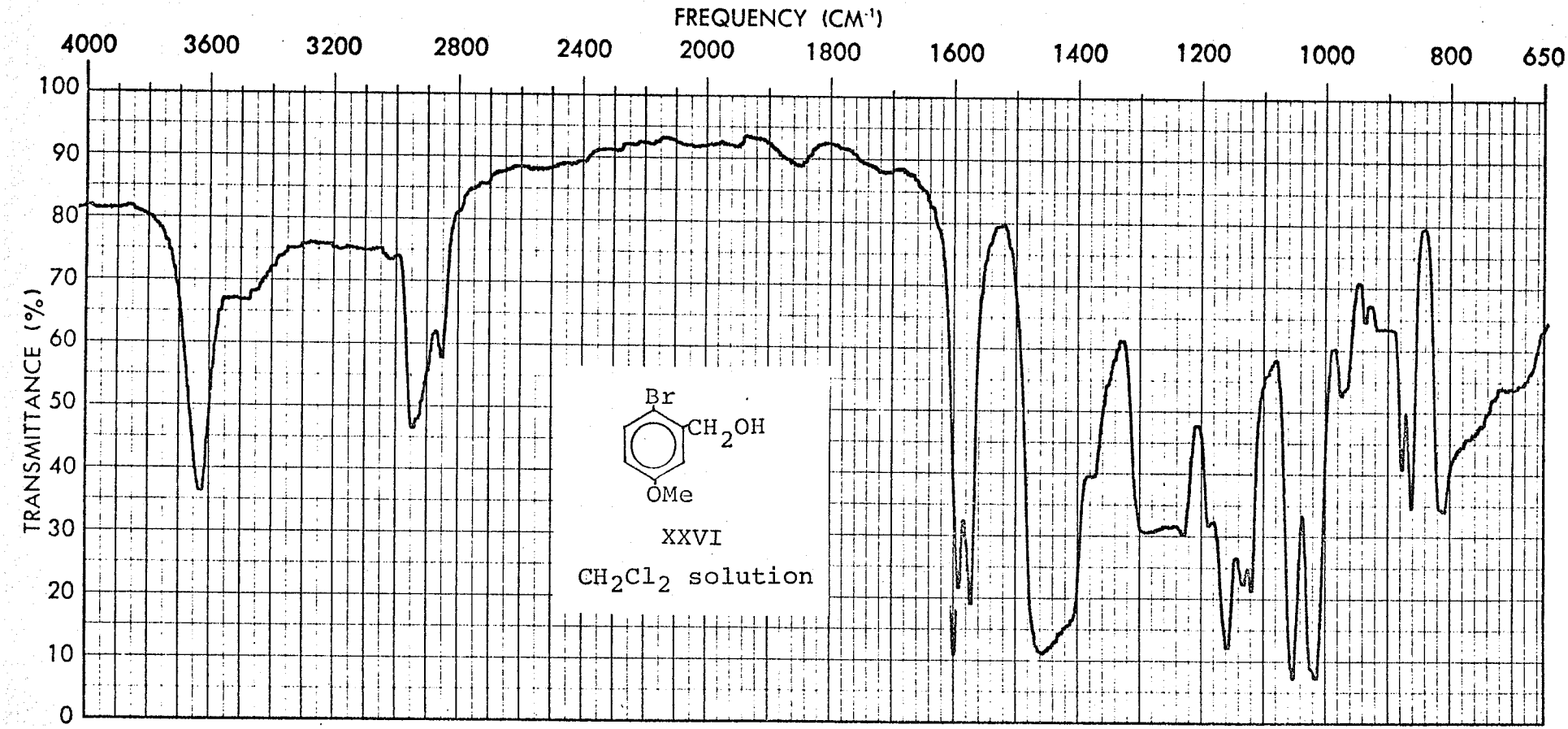



Figure VIII

I.r. spectrum of 2-bromo-5-methoxybenzyl alcohol

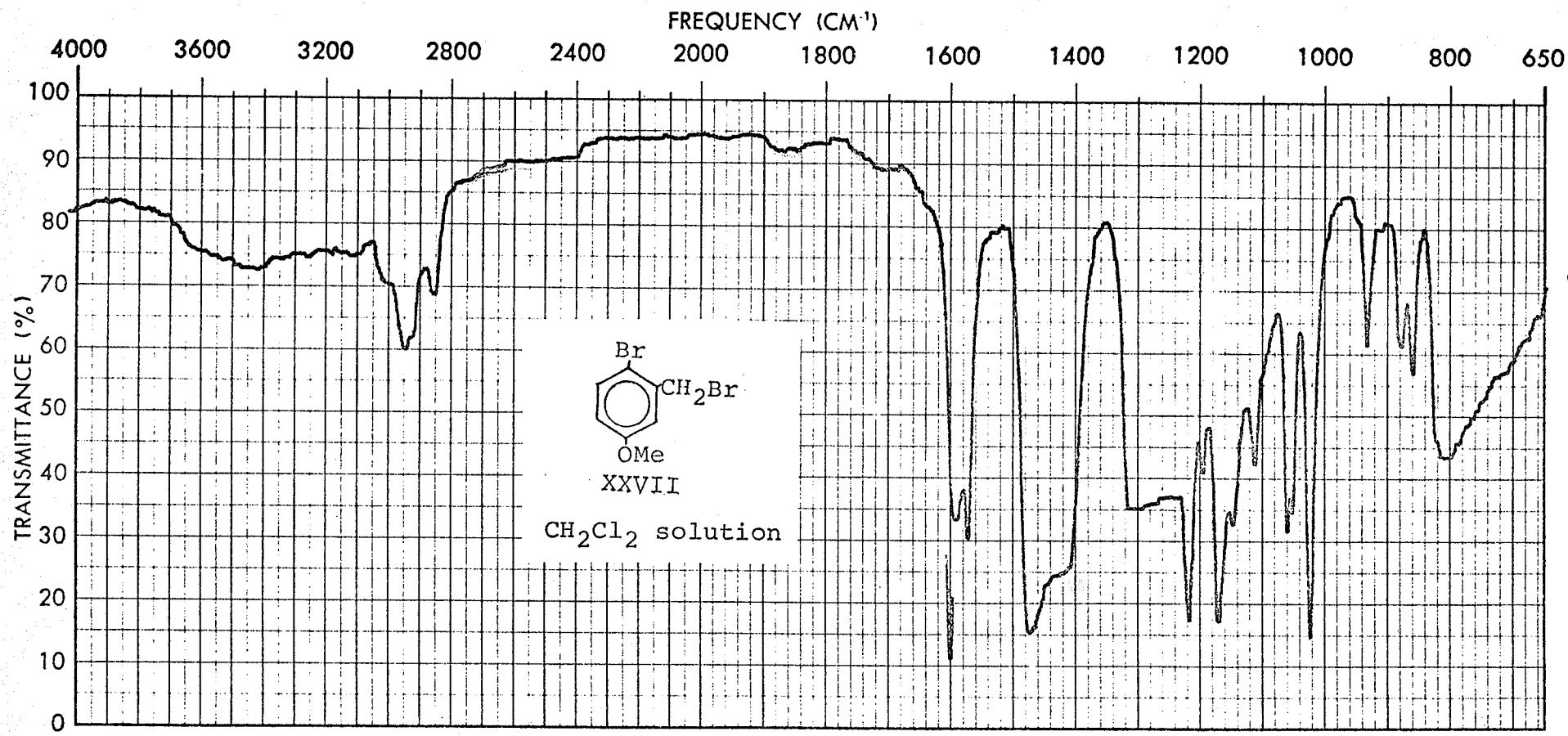



Figure IX

I.r. spectrum of 2-bromo-5-methoxybenzyl bromide

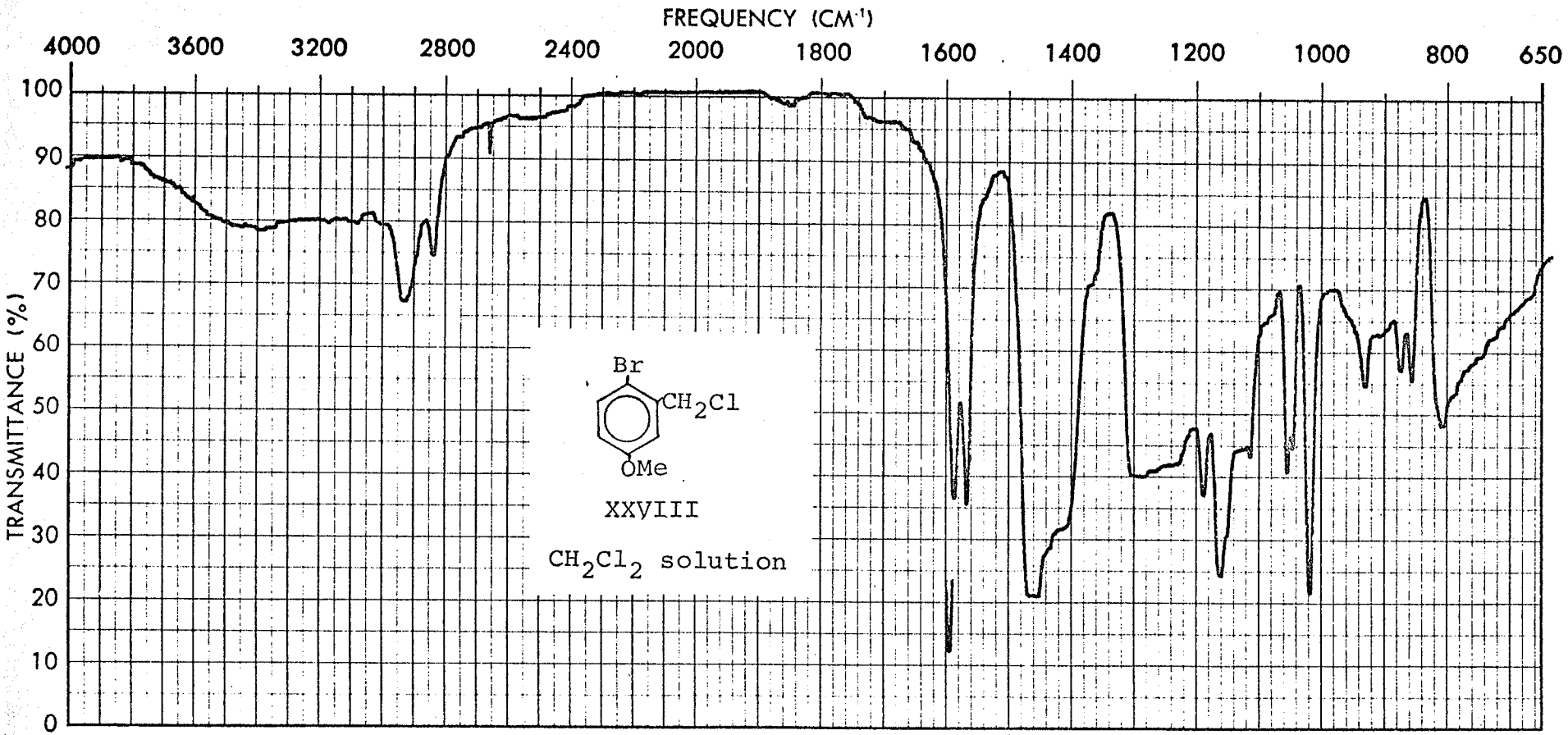



Figure X

I.r. spectrum of 2-bromo-5-methoxybenzyl chloride

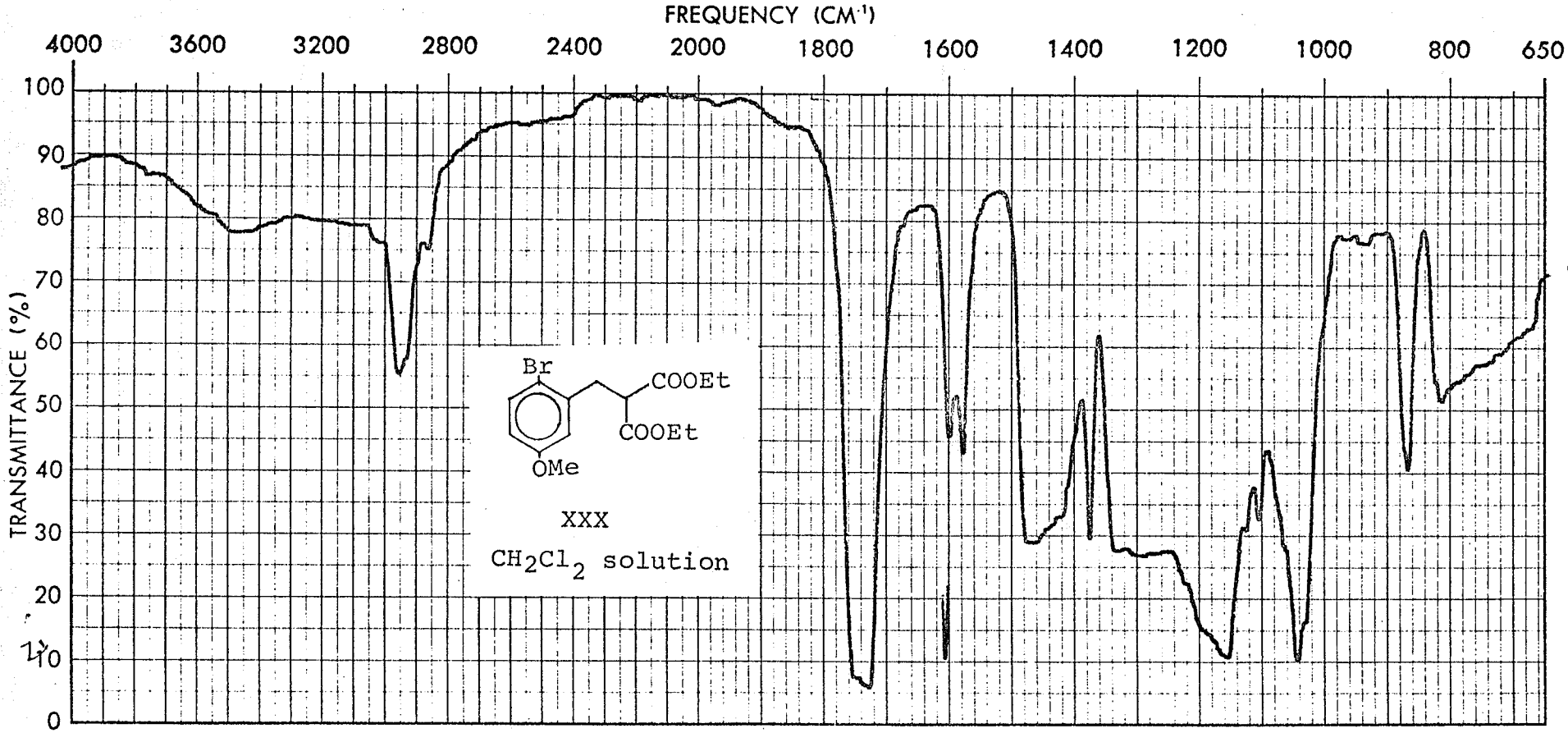



Figure XI

I.r. spectrum of diethyl-2-bromo-5-methoxybenzyl malonate

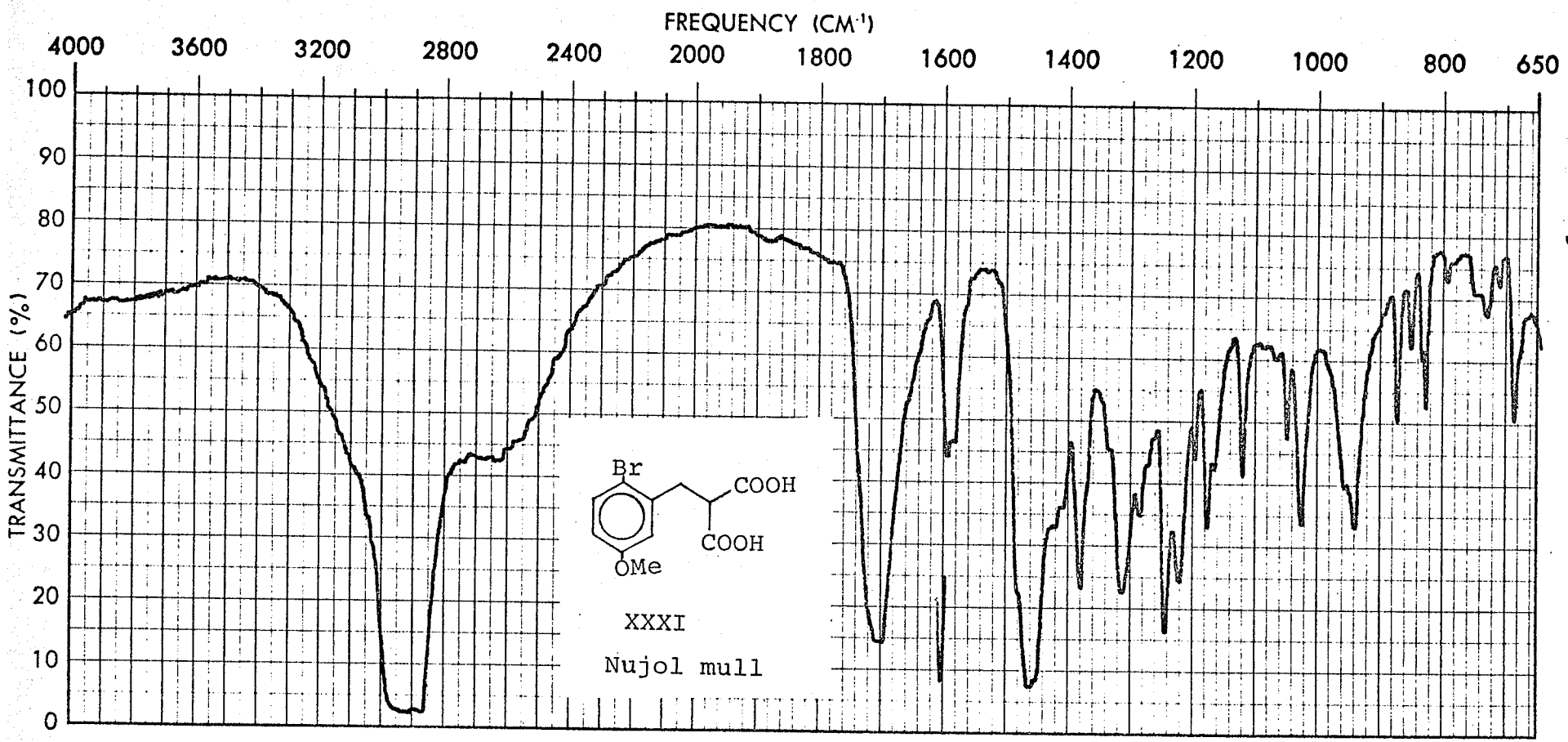



Figure XII

I.r. spectrum of 2-bromo-5-methoxybenzyl malonic acid

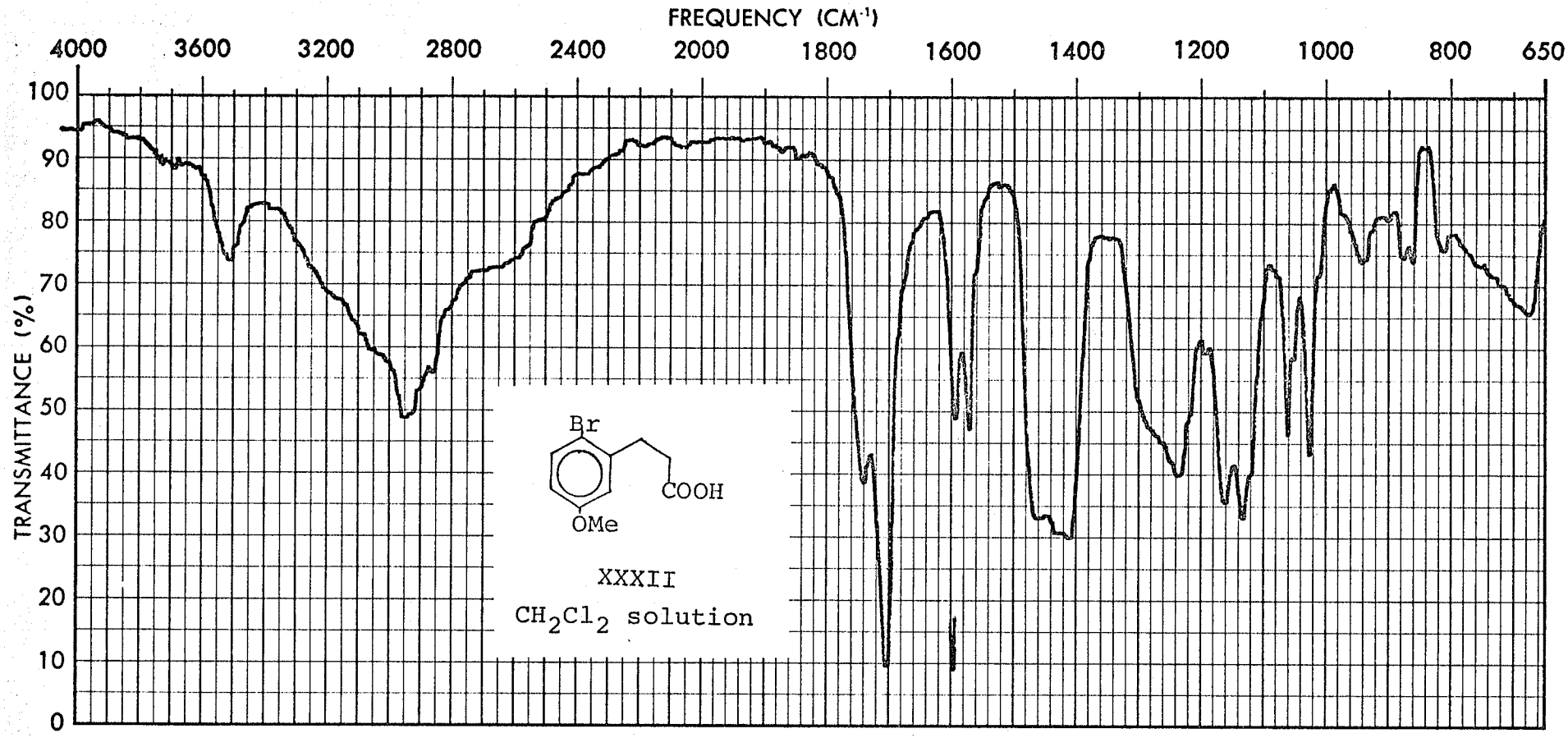



Figure XIII

I.r. spectrum of β-2-bromo-5-methoxyphenylpropionic acid

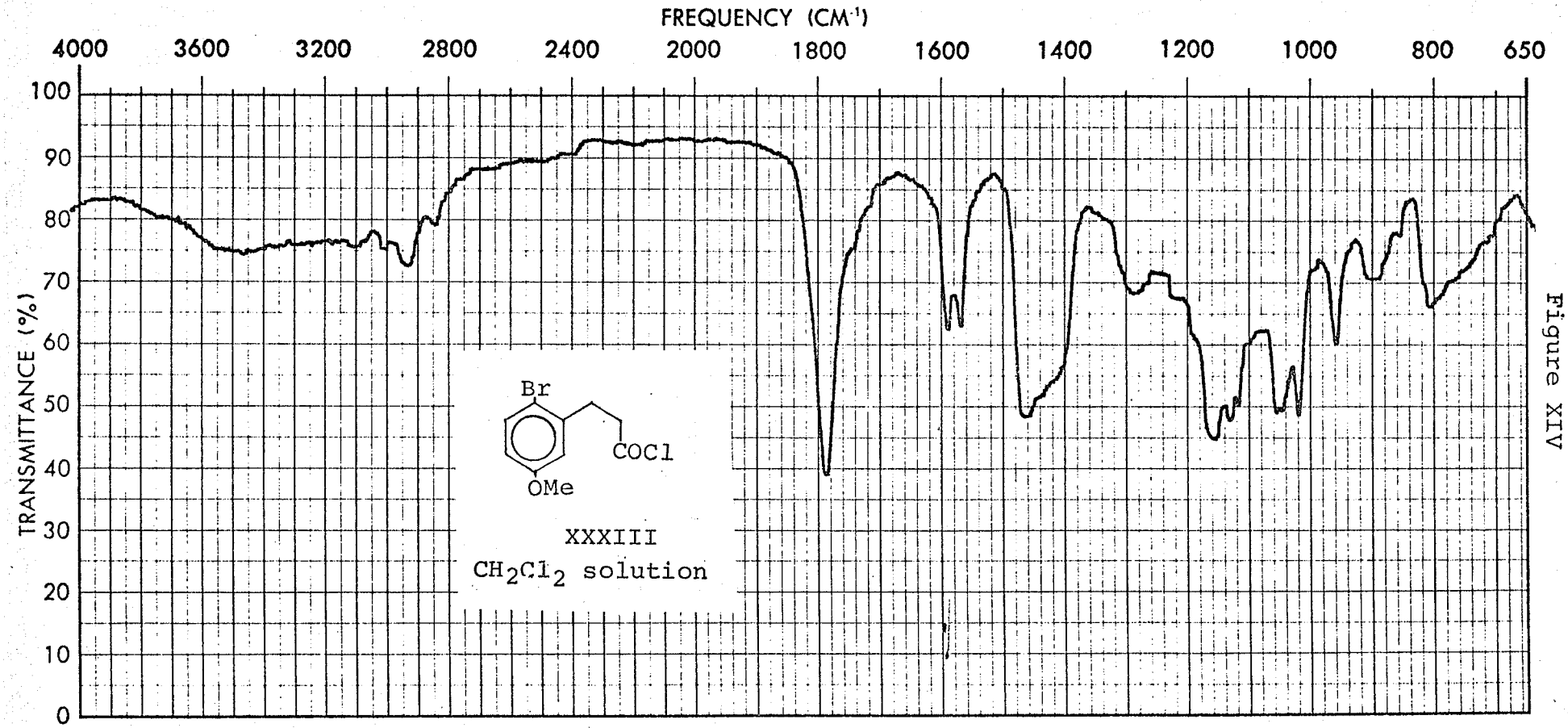



Figure XIV

I.r. spectrum of β-2-bromo-5-methoxyphenylpropionyl chloride

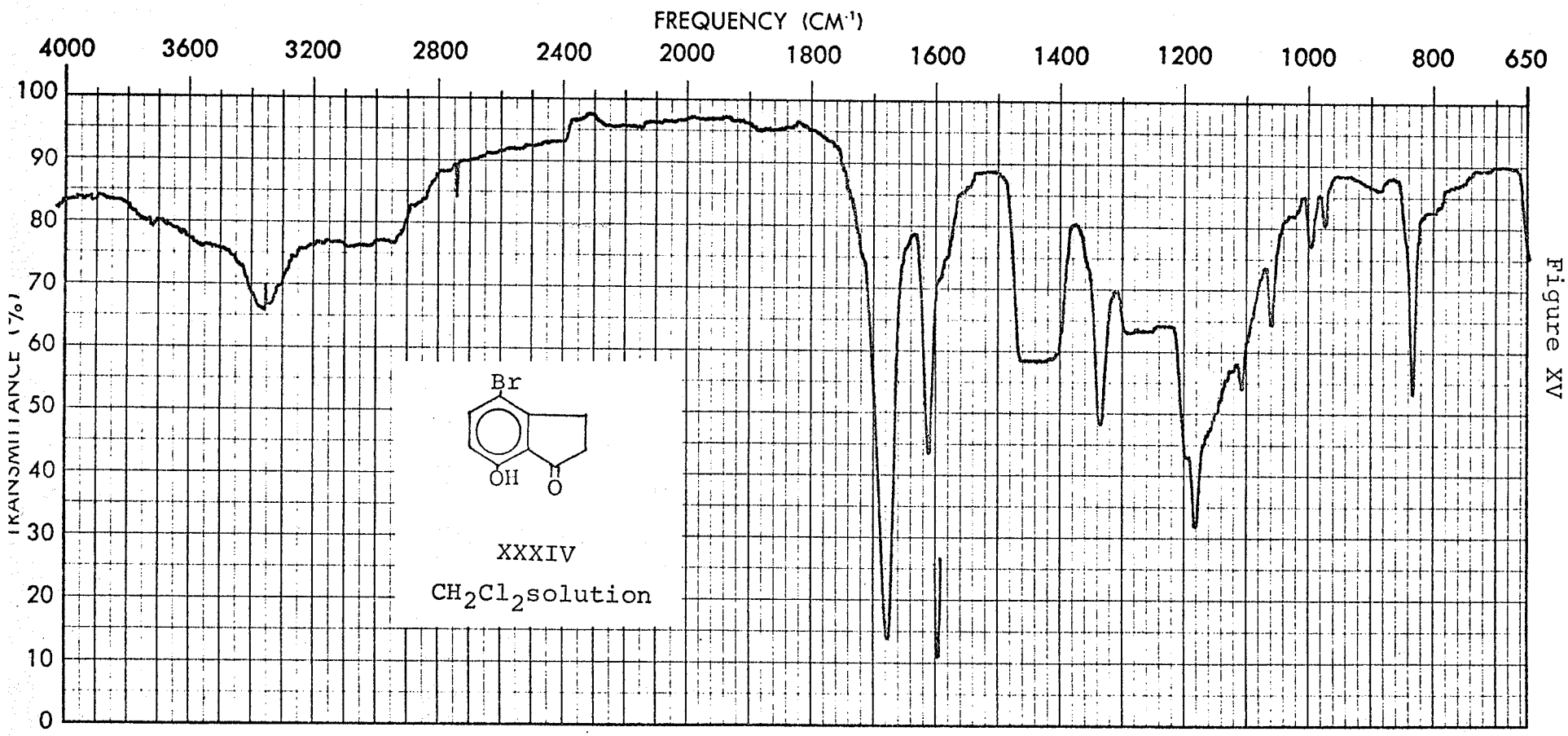



Figure XV

I.r. spectrum of 4-bromo-7-hydroxyindanone

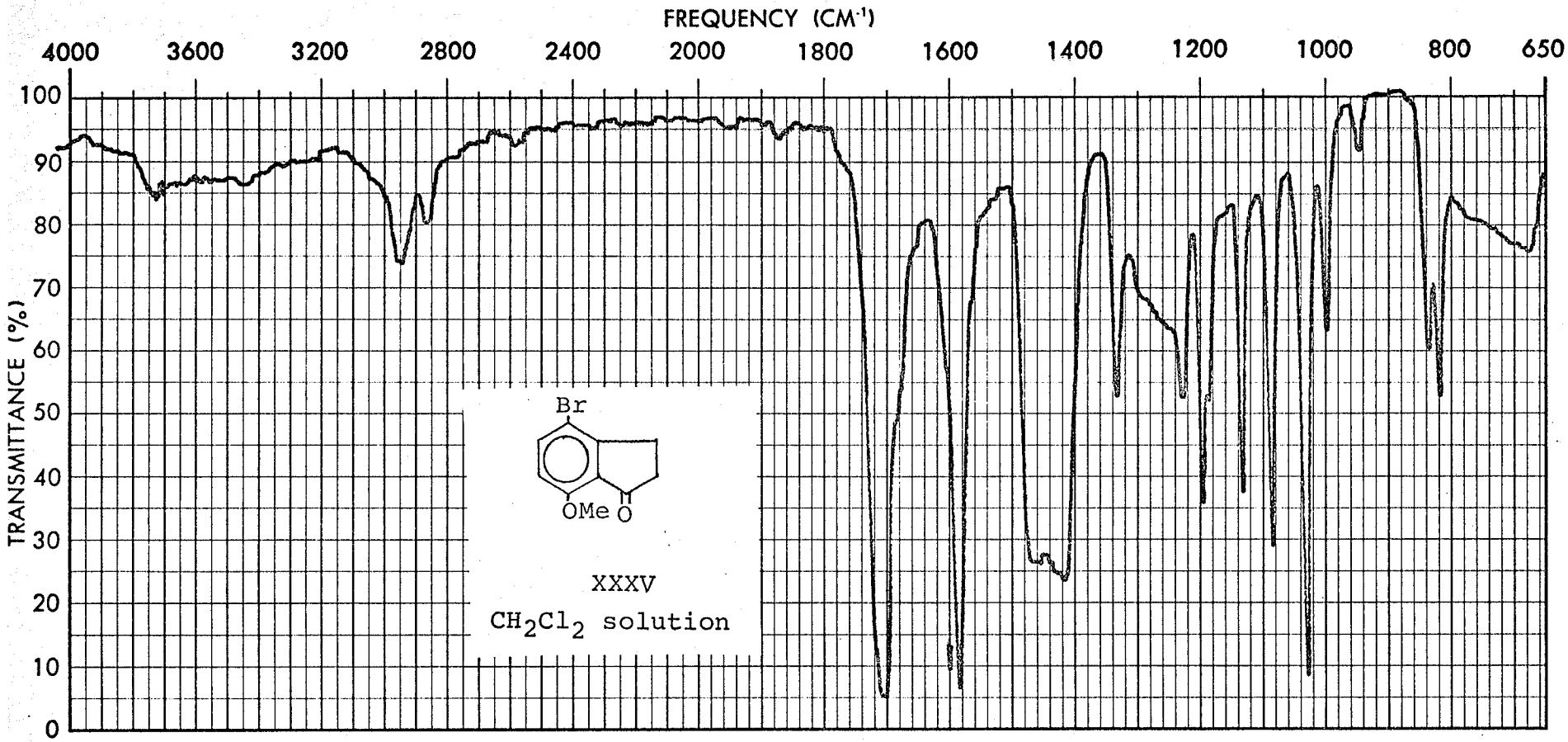



Figure XVI

I.r. spectrum of 4-bromo-7-methoxy-indanone

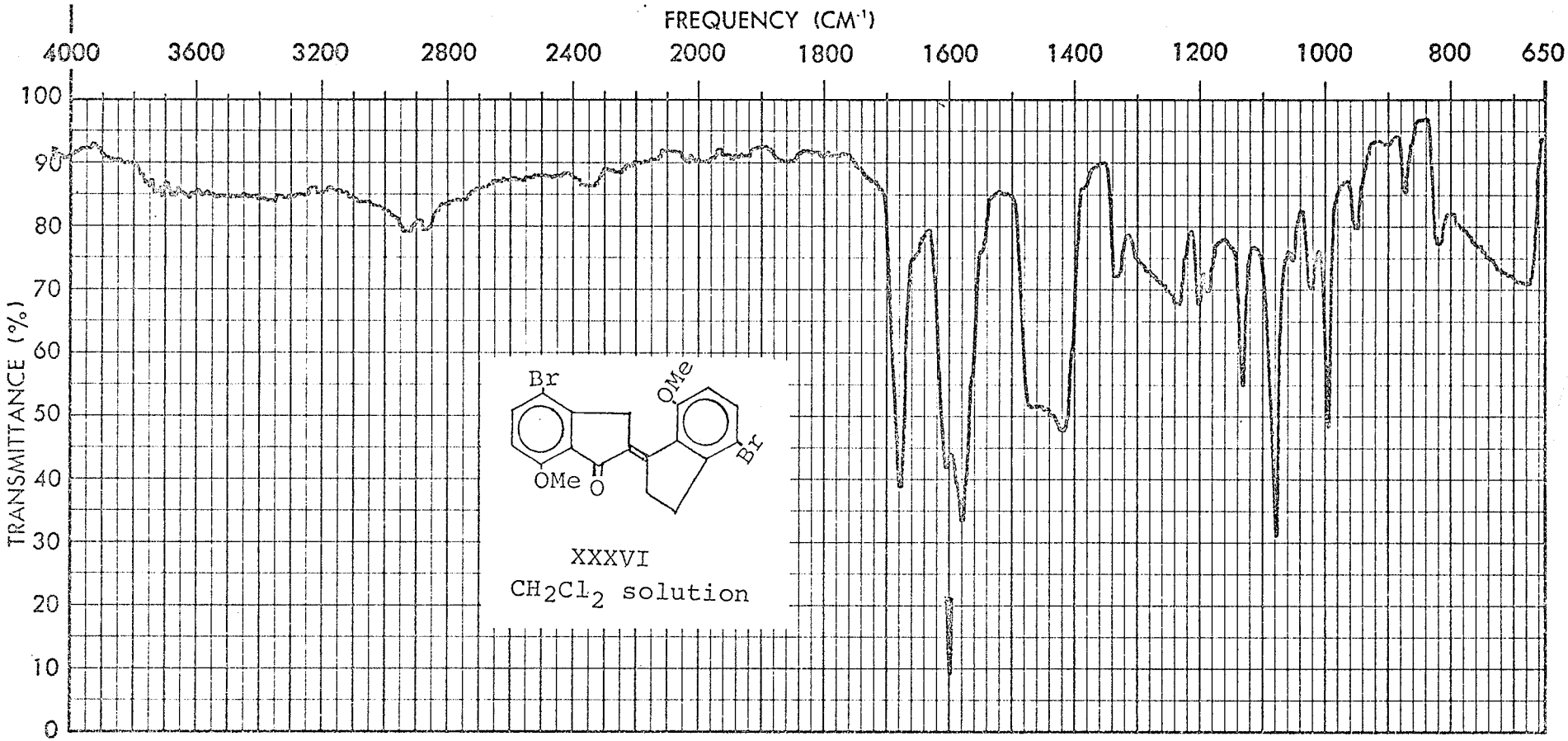



Figure XVII

I.r. spectrum of 1'-oxo-2,3,3'-trihydro-4,4'-dibromo-7,7'-dimethoxy-1,2'-indenylidene

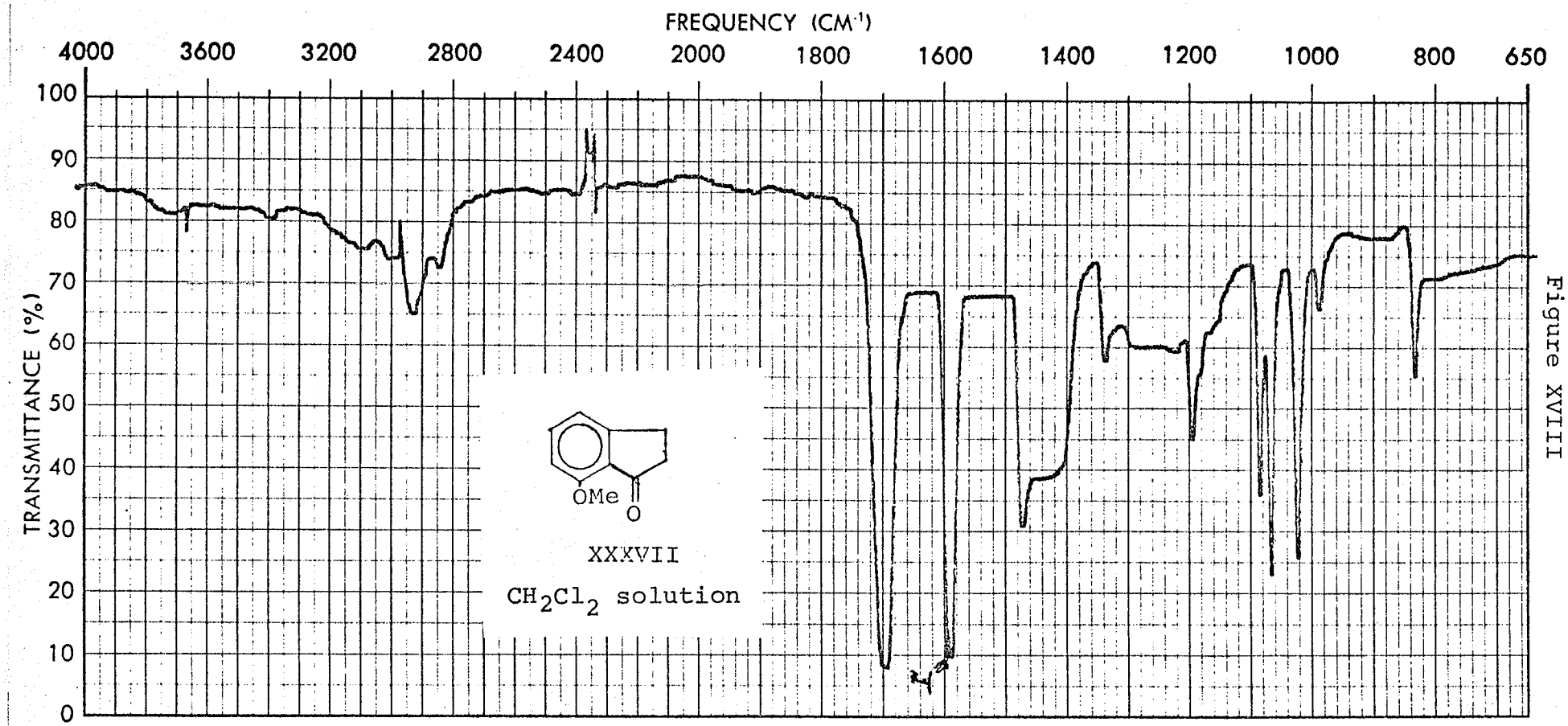



Figure XVIII

I.r. spectrum of 7-methoxyindanone

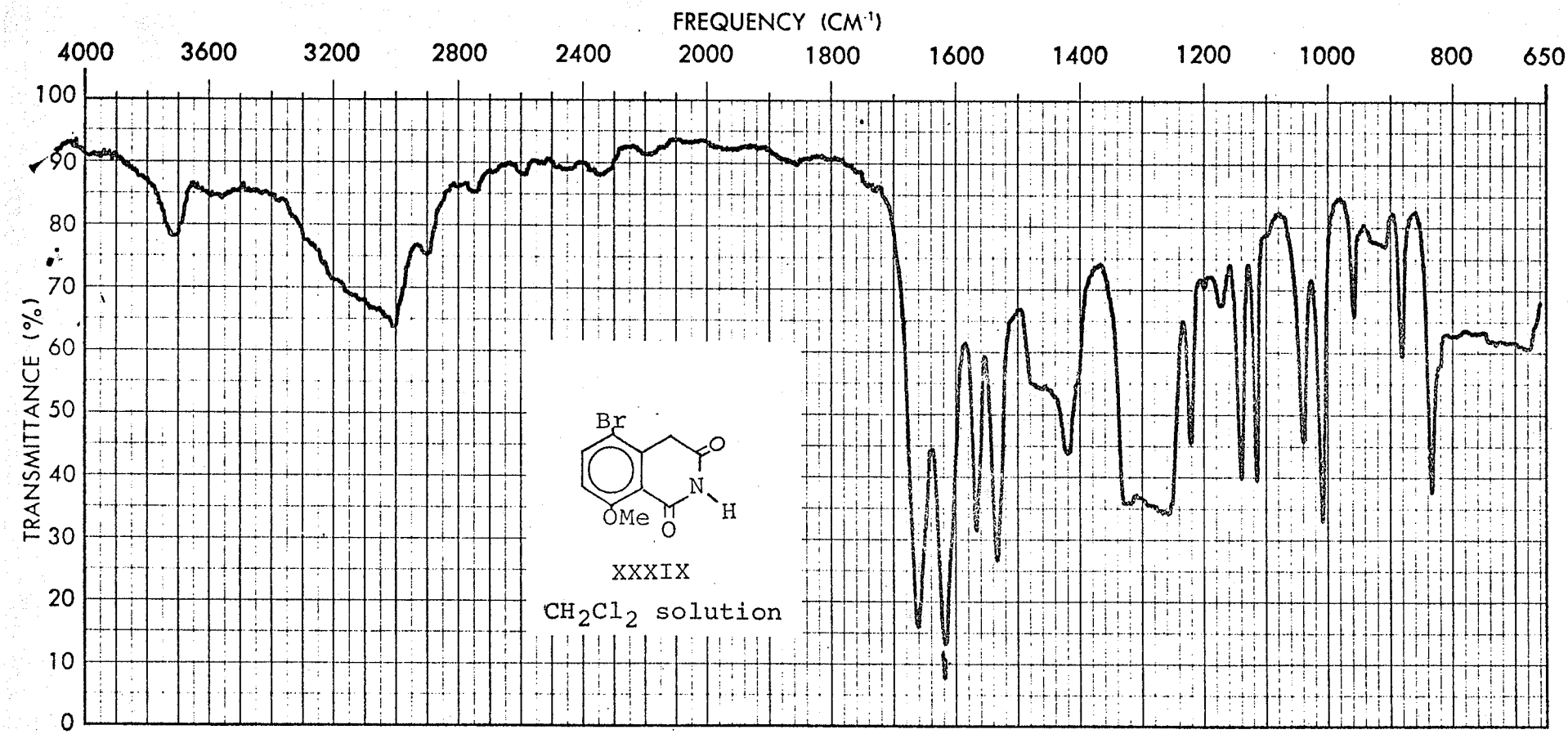



Figure XIX

I.r. spectrum of 3-bromo-6-methoxyhomophthalimide

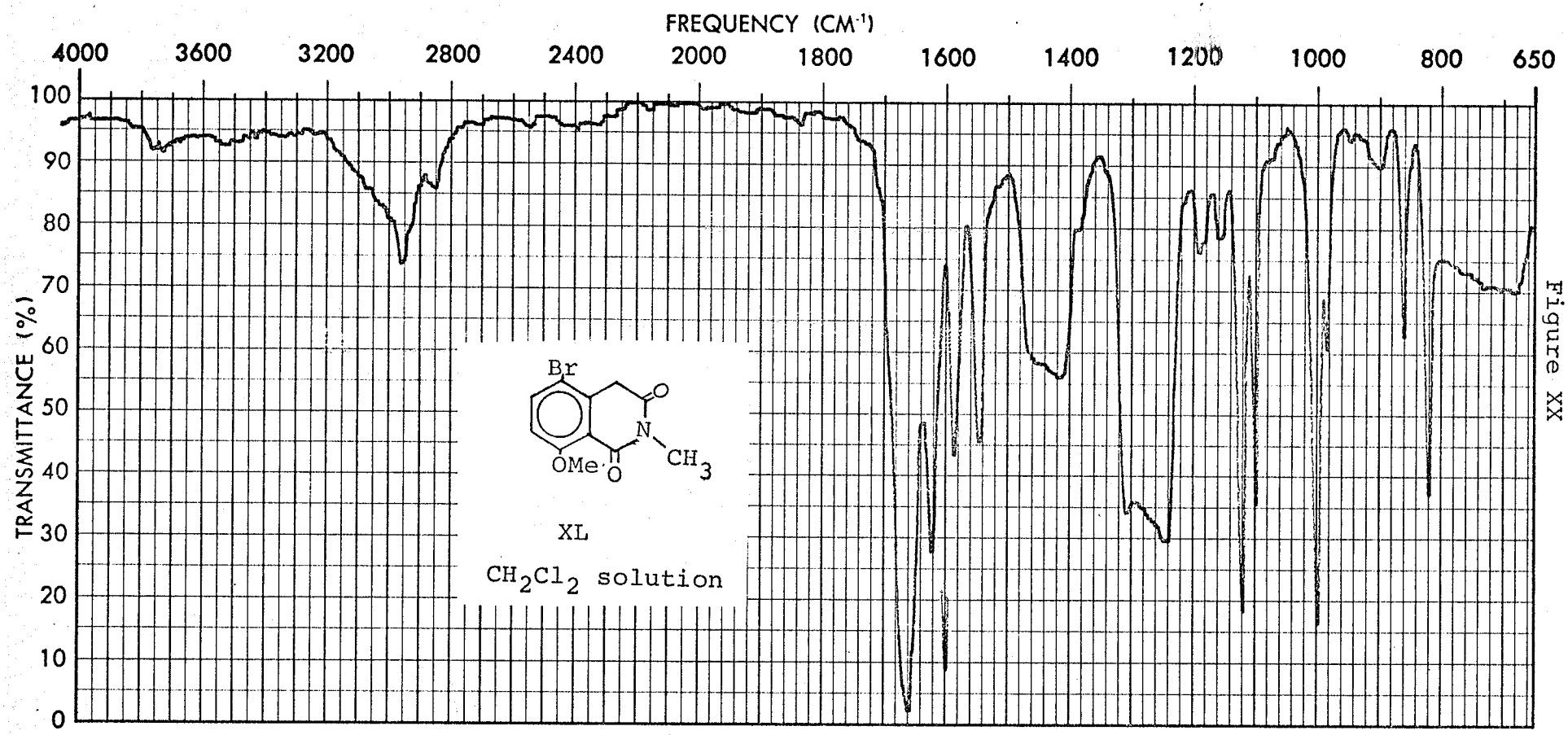



Figure XX

I.r. spectrum of N-methyl-3-bromo-6-methoxyhomophthalimide

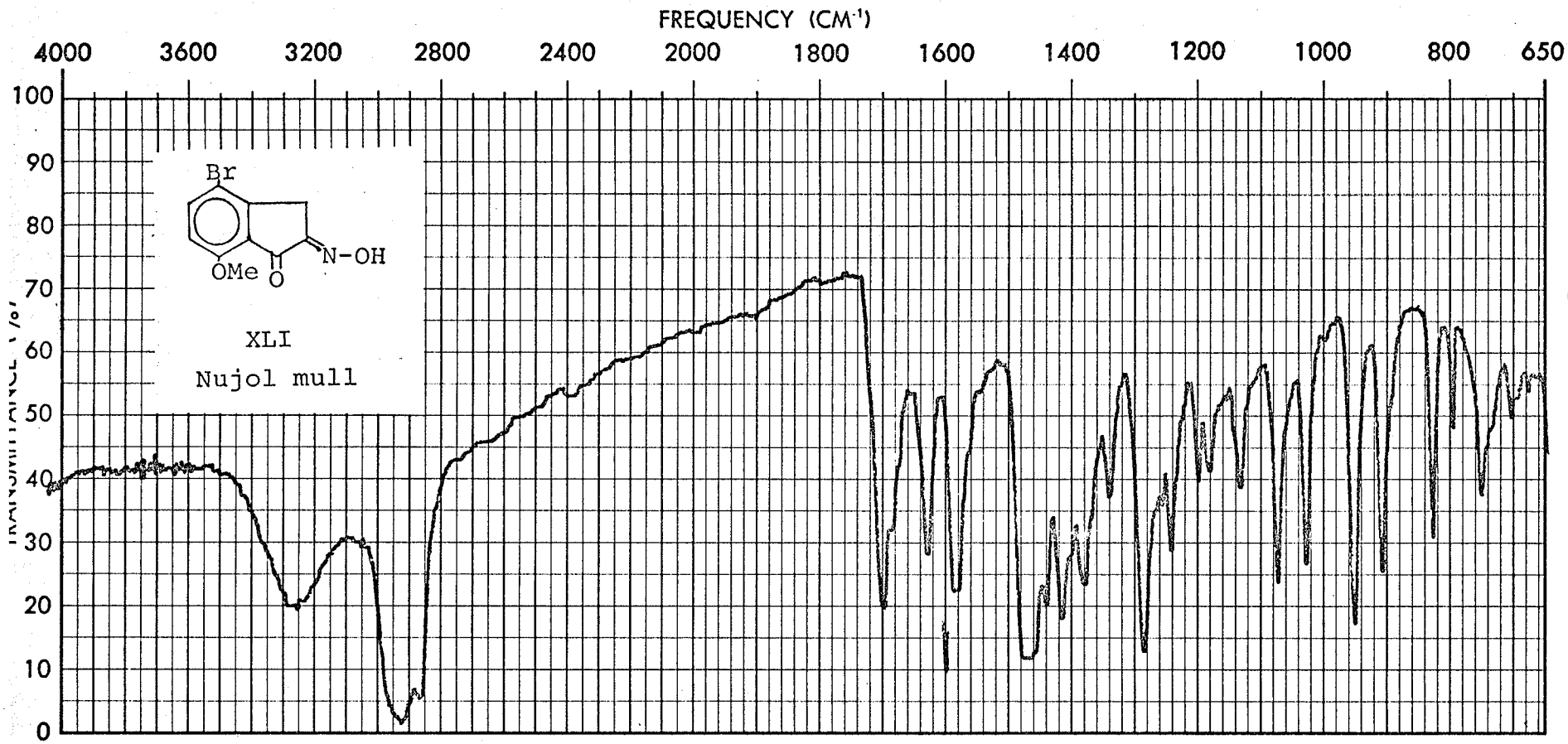



Figure XXI

I.r. spectrum of 2-oxime-4-bromo-7-methoxy-1,2-indandione

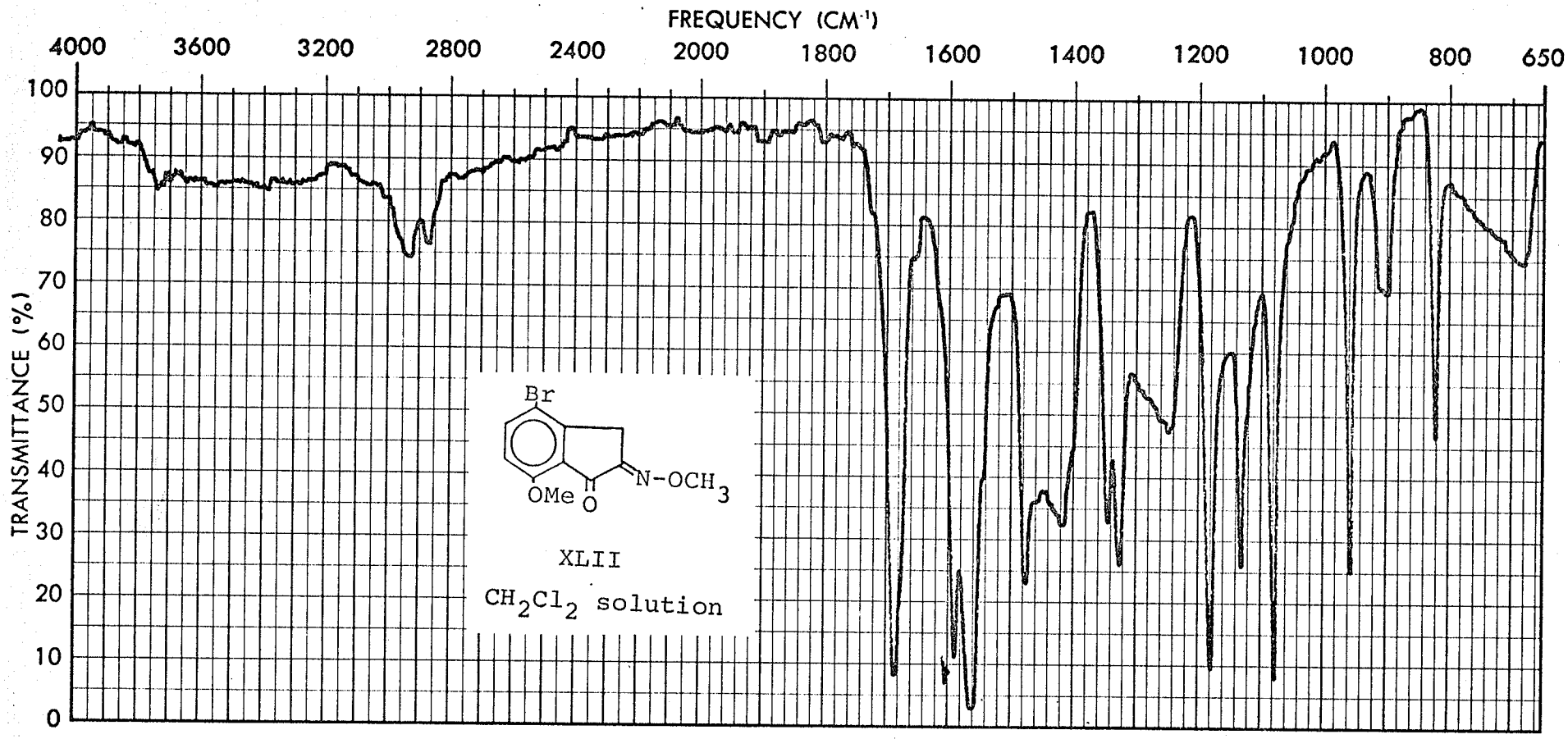



Figure XXII

I.r. spectrum of 2-methoximino-4-bromo-7-methoxyindanone

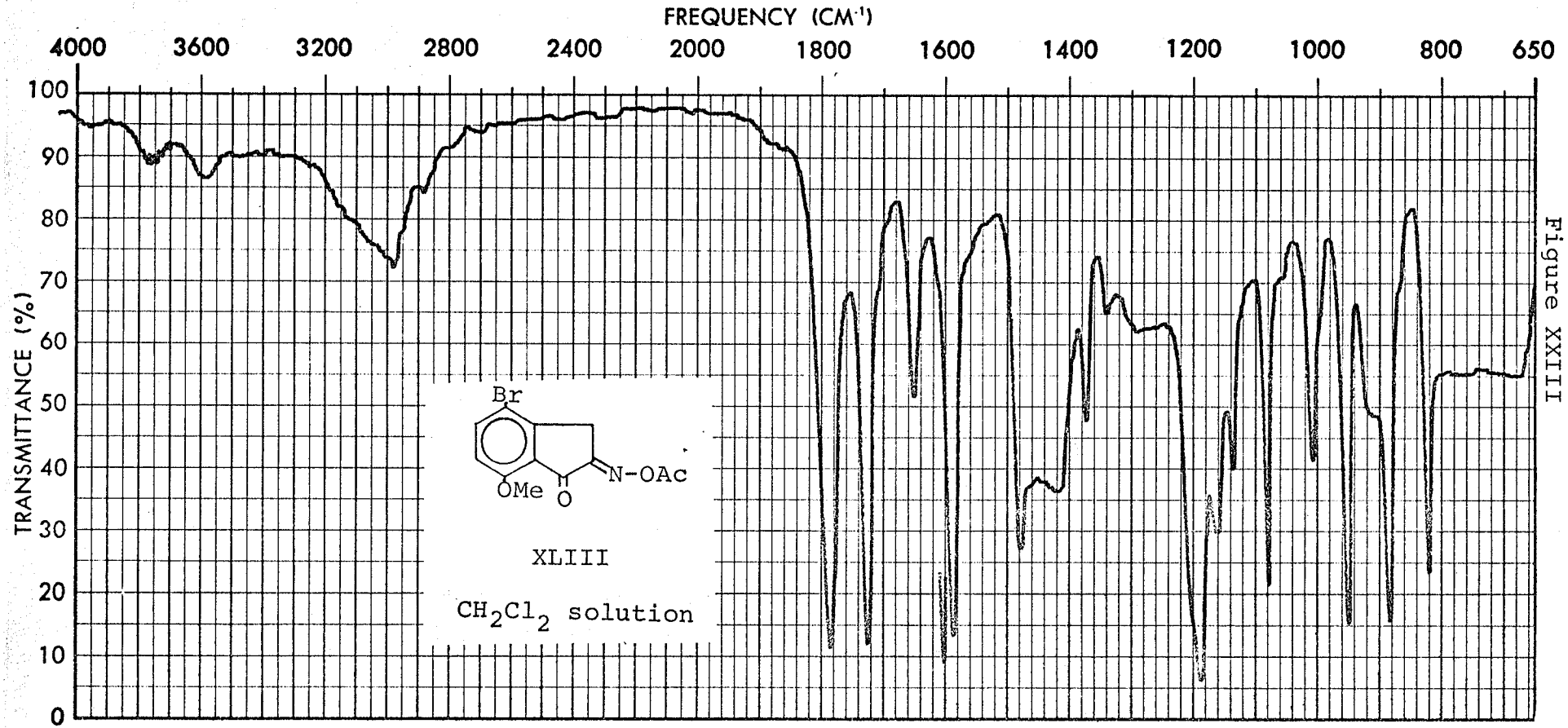



Figure XXIII

I.r. spectrum of 2-acetoximino-4-bromo-7-methoxyindanone

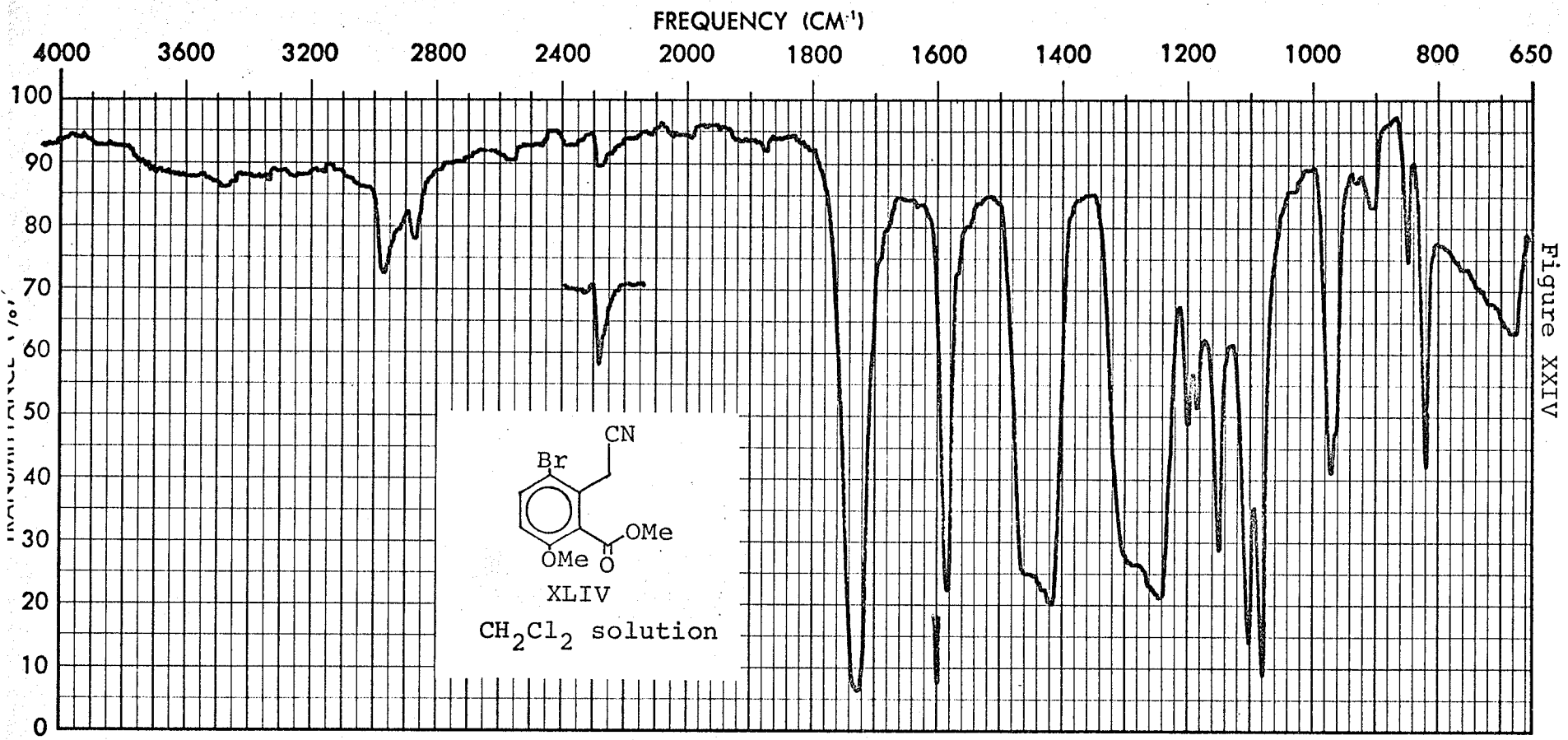



Figure XXIV

I.r. spectrum of 2-bromo-5-methoxy-6-methoxycarbonylphenyl acetonitrile

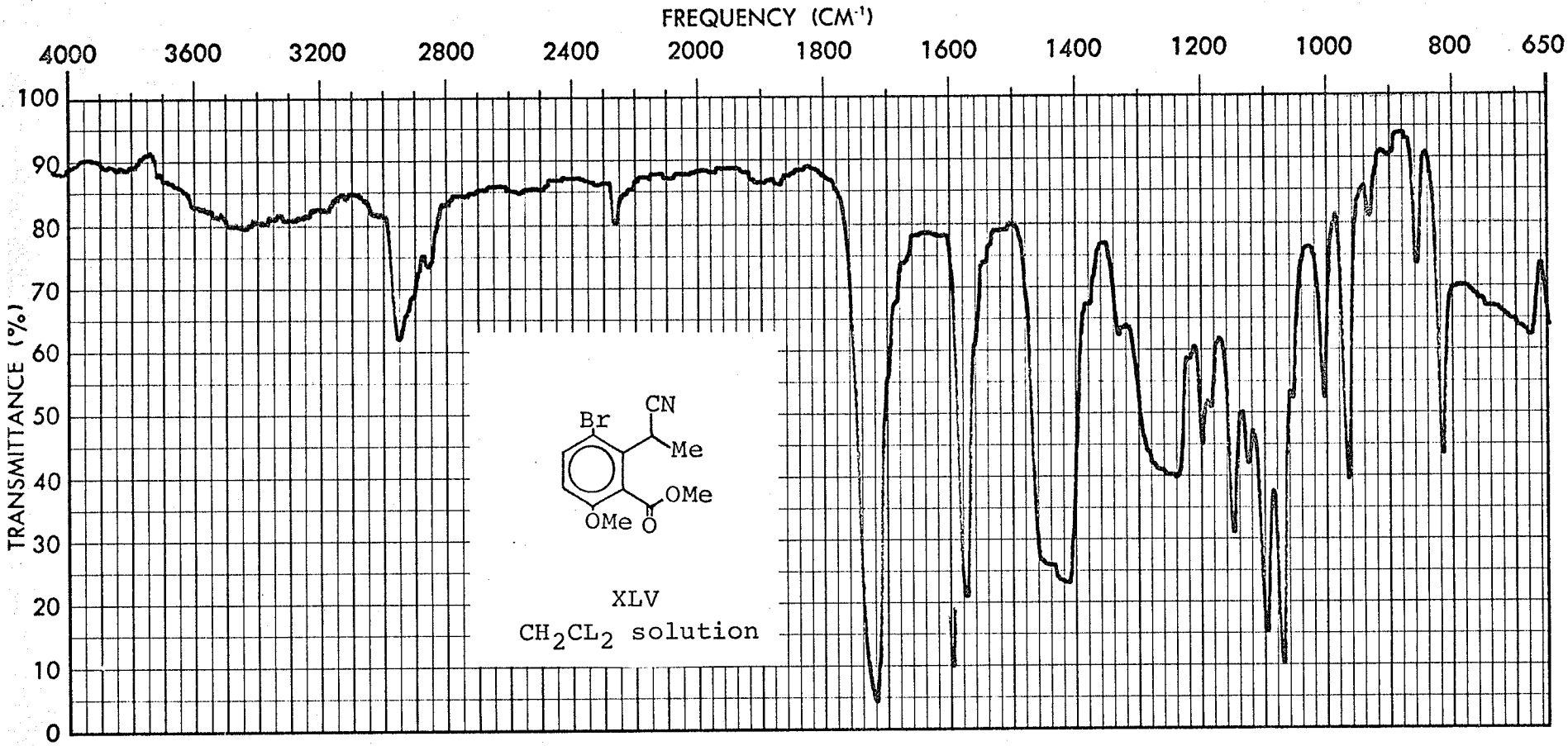



Figure XXV

I.r. of α-2-methoxycarbonyl-3-methoxyphenyl propionitrile

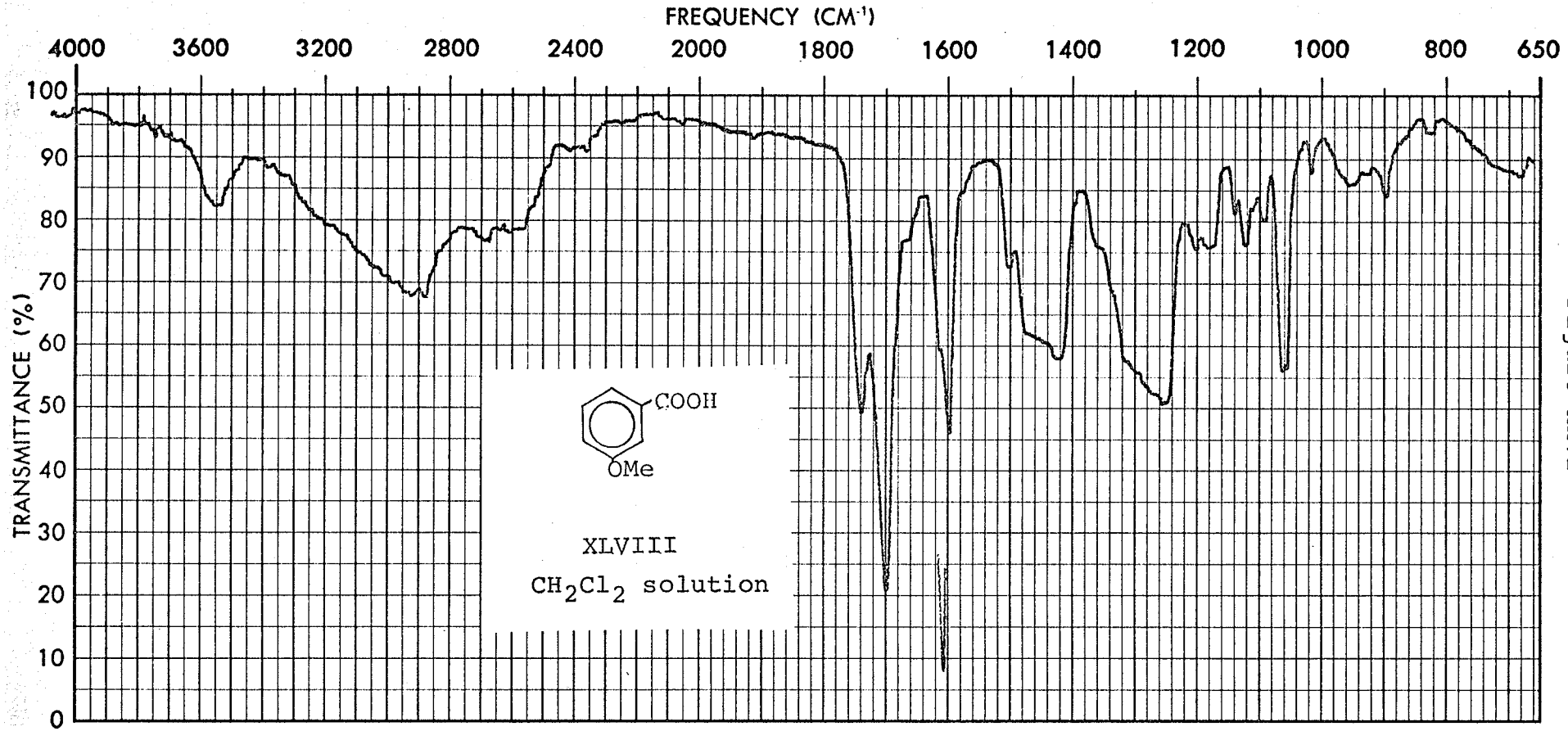



Figure XXVI

I.r. spectrum of m-methoxybenzoic acid

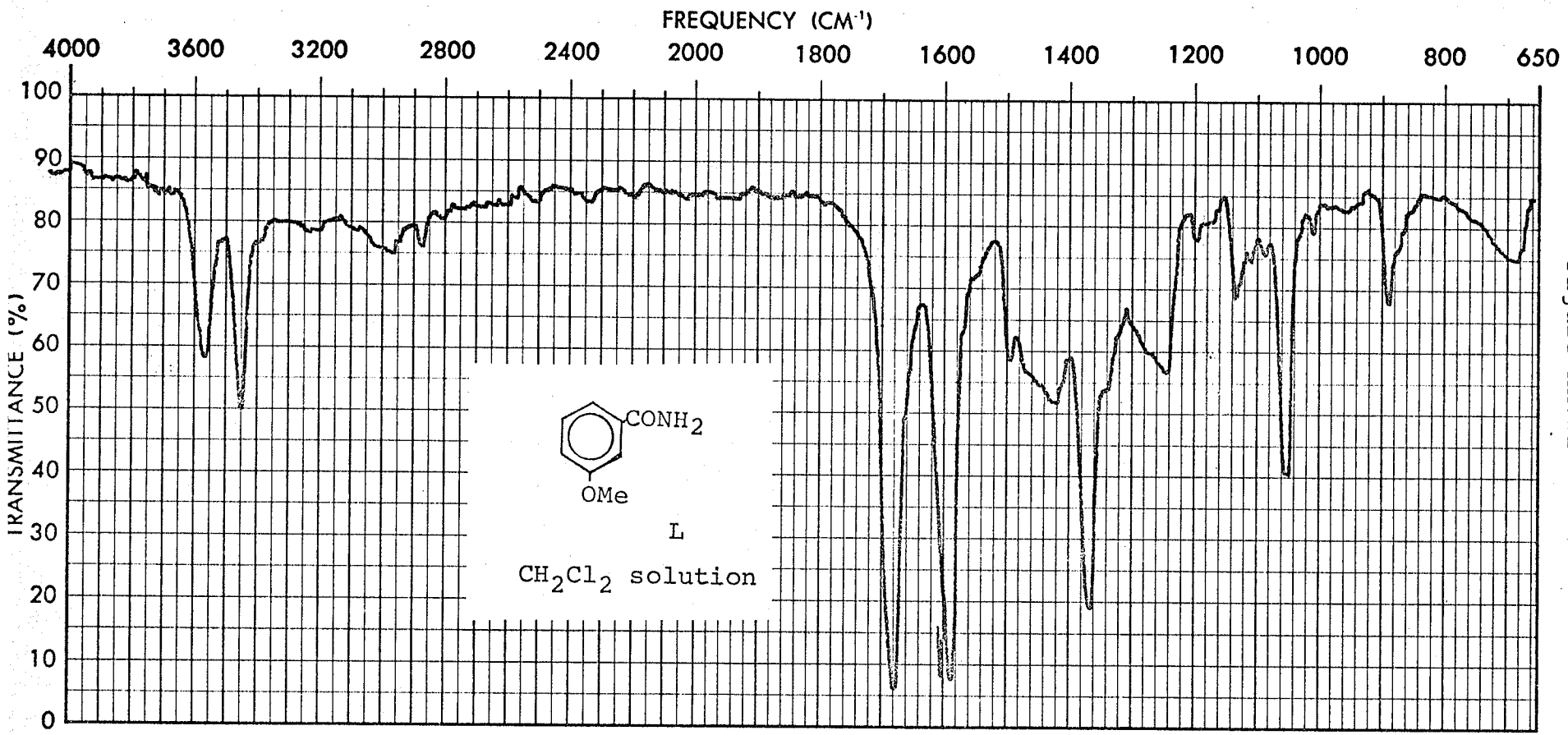



Figure XXVII

I.r. spectrum of m-methoxybenzamide

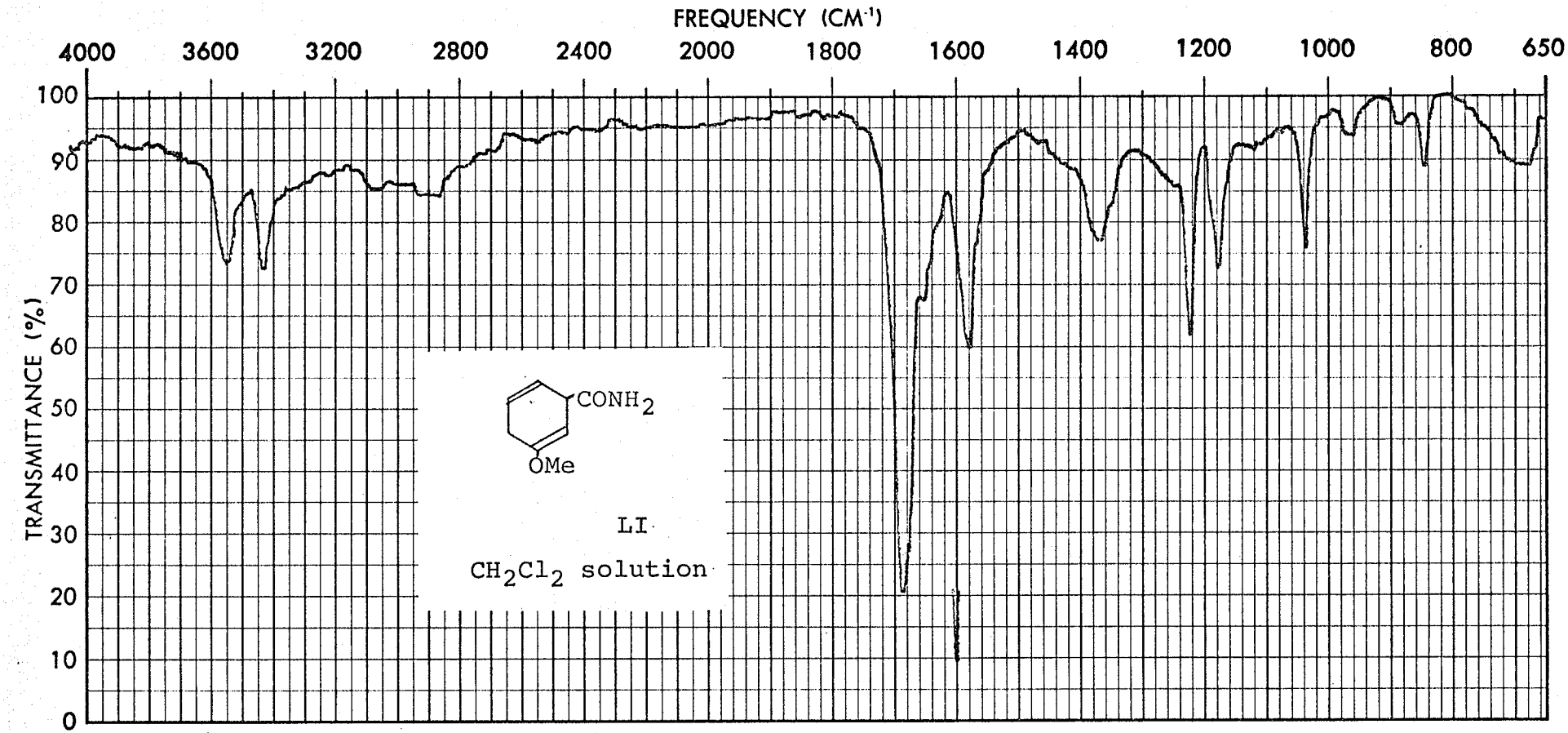



Figure XXVIII

I.r. spectrum of 1-carbamoyl-3-methoxy-1,4-dihydrobenzene

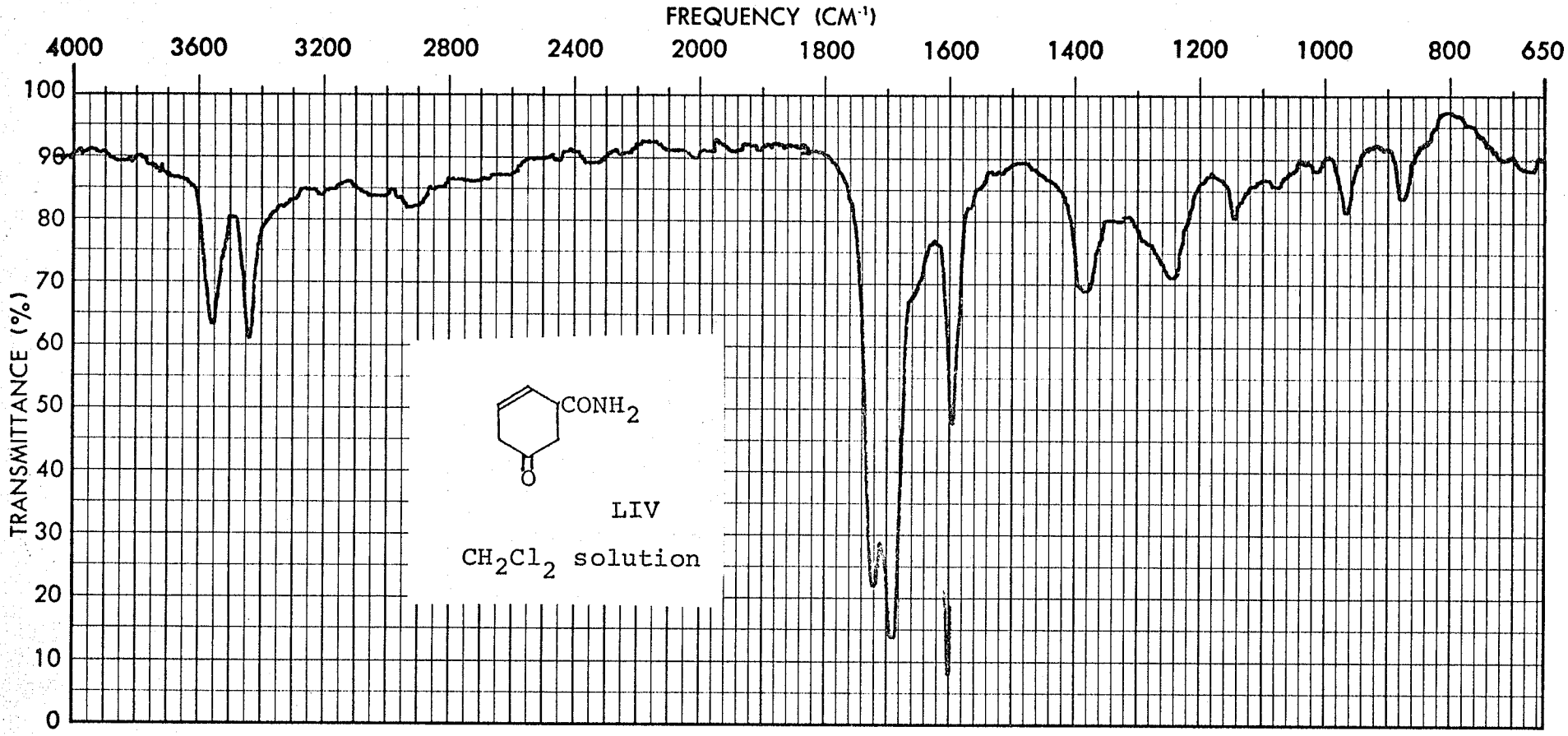



Figure XXIX

I.r. spectrum of 3-oxo-5-cyclohexenyl carboxamide

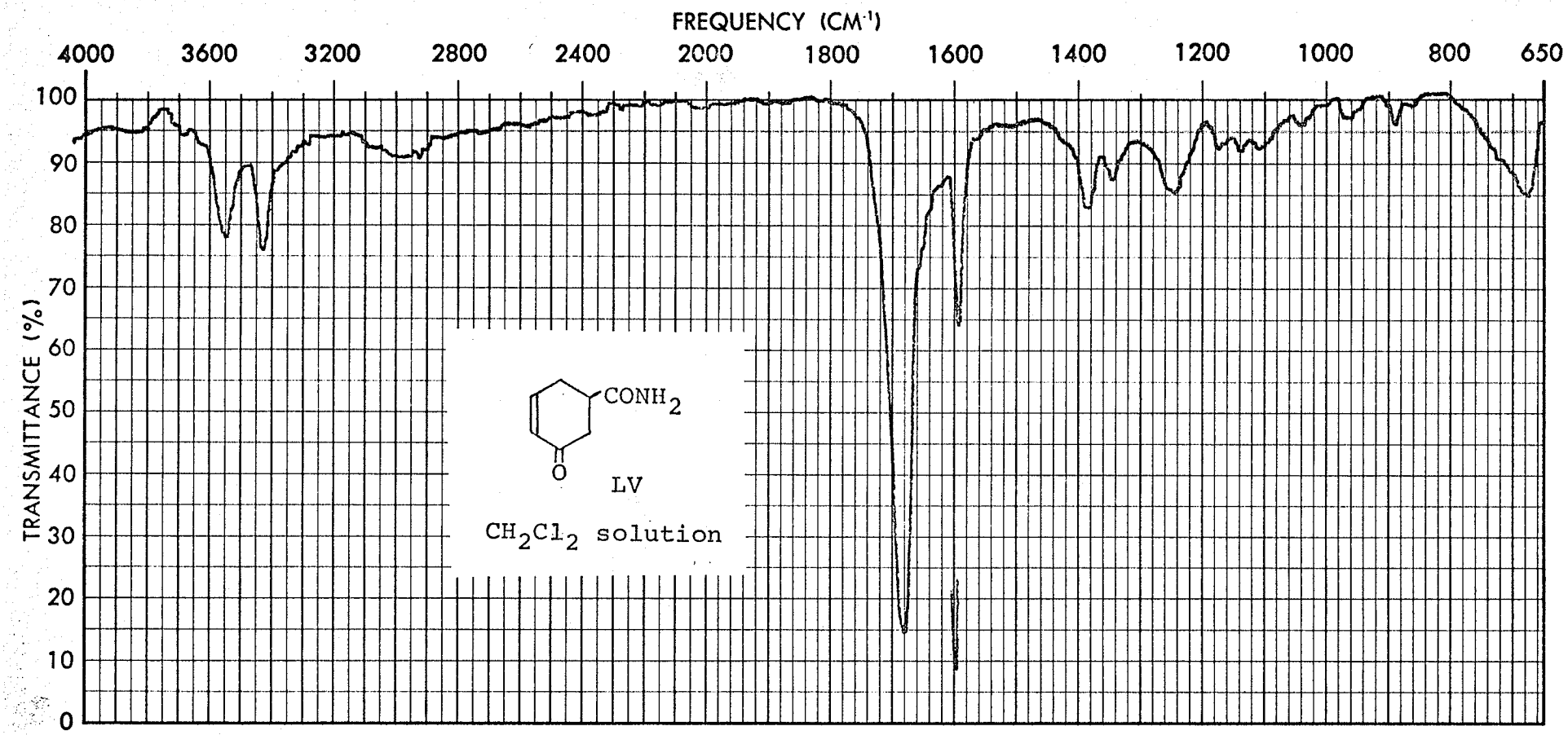



Figure XXX

I.r. spectrum of 3-oxo-4-cyclohexenyl carboxamide

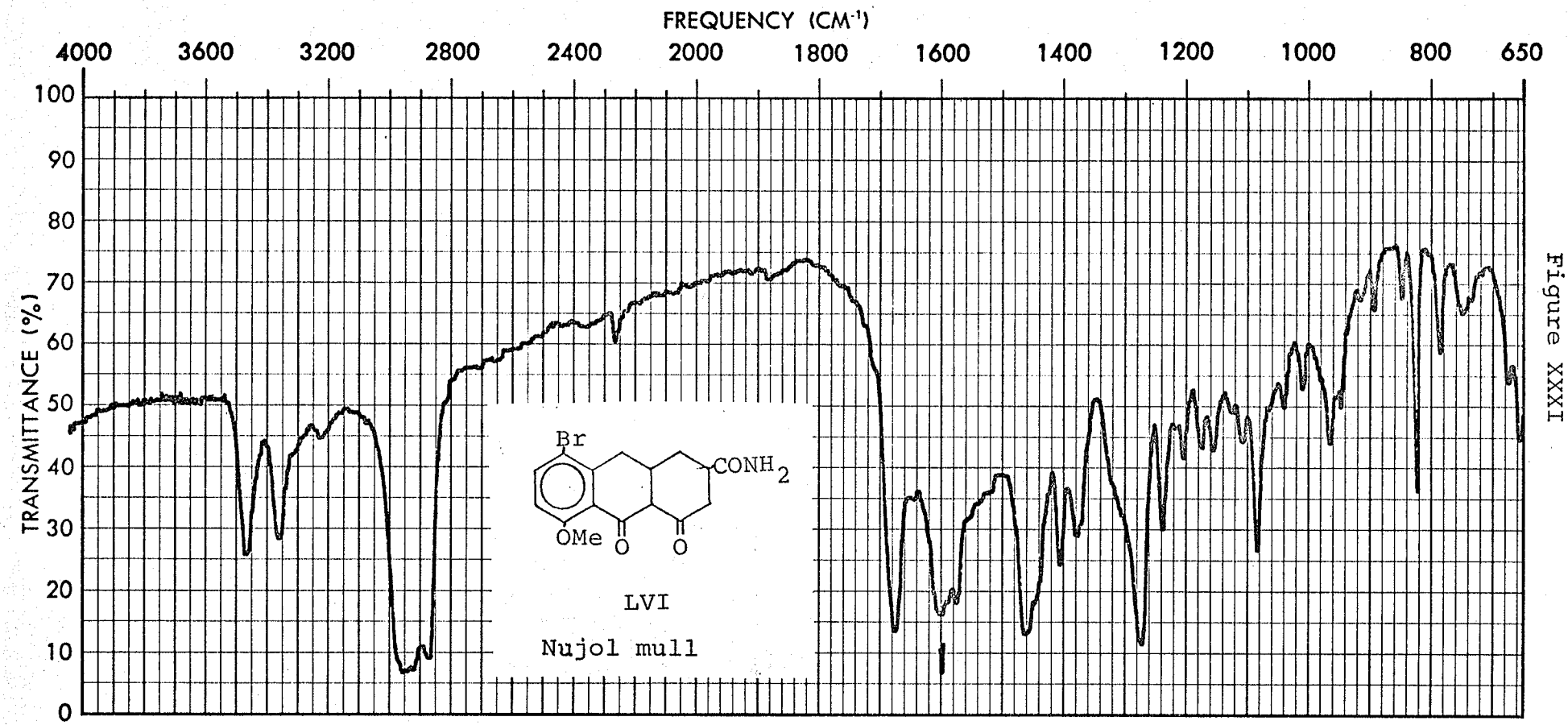



Figure XXXI

I.r. spectrum of 1,2,3,4,4a,9,9a,10-octahydro-2-carbamoyl-4,10-dioxo-5-methoxy-8-bromo-9-cyanoanthracene

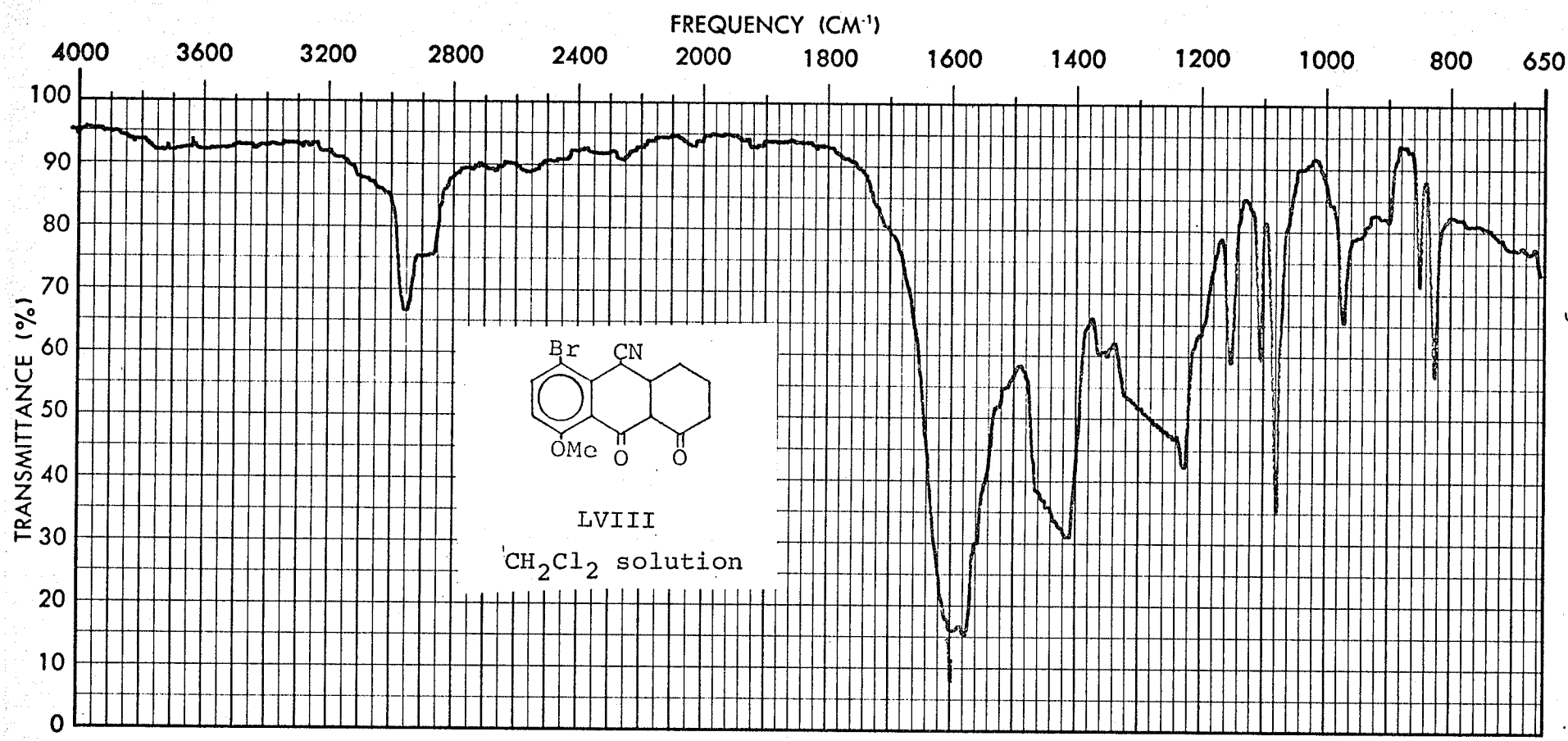



Figure XXXII

I.r. spectrum of 1,2,3,4,4a,9,9a,10-octahydro-4,10-dioxo-5-methoxy-8-bromo-9-cyanoanthracene

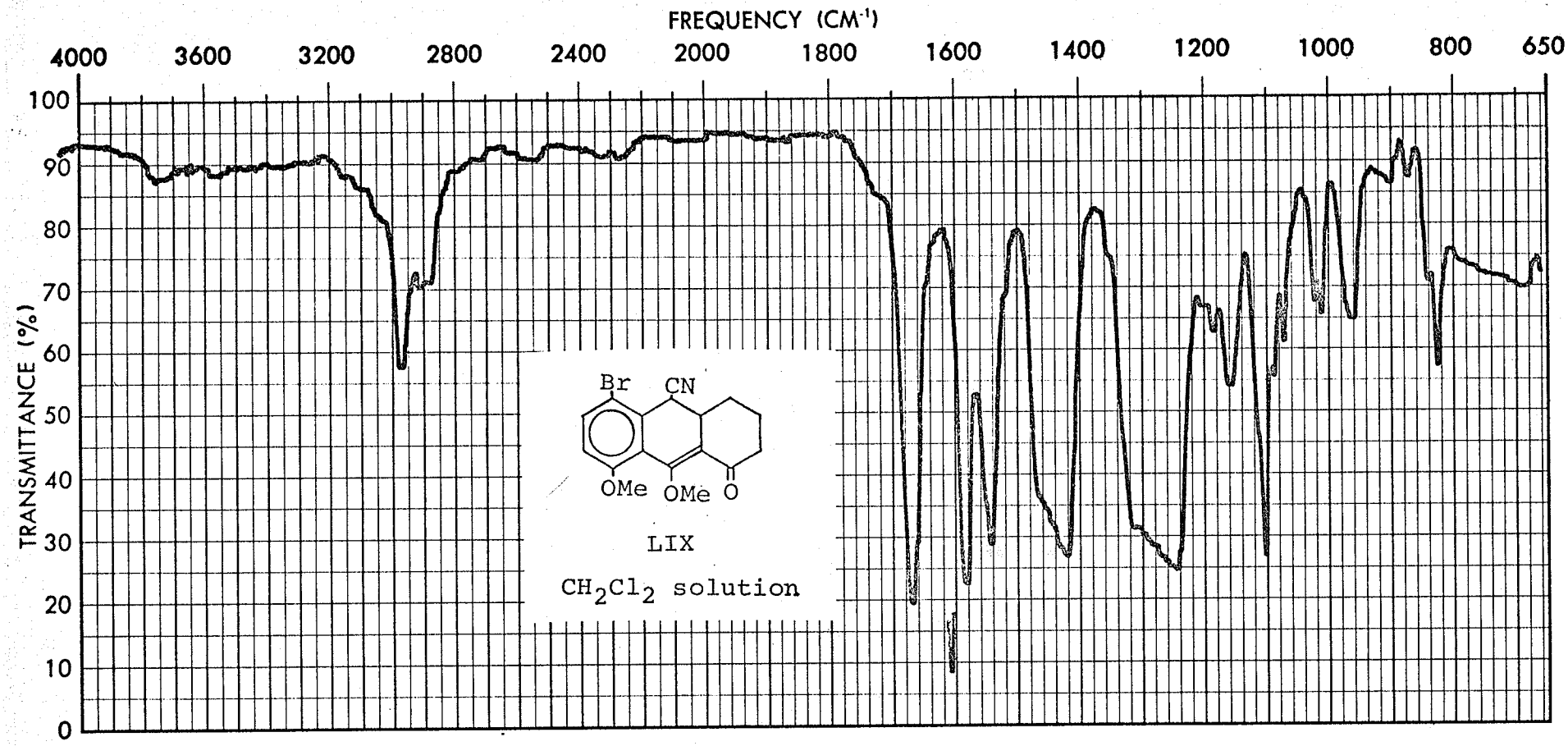



Figure XXXIII

I.r. spectrum of 1,2,3,4,9,9a-hexahydro-4-oxo-5,10-dimethoxy-8-bromo-9-cyanoanthracene

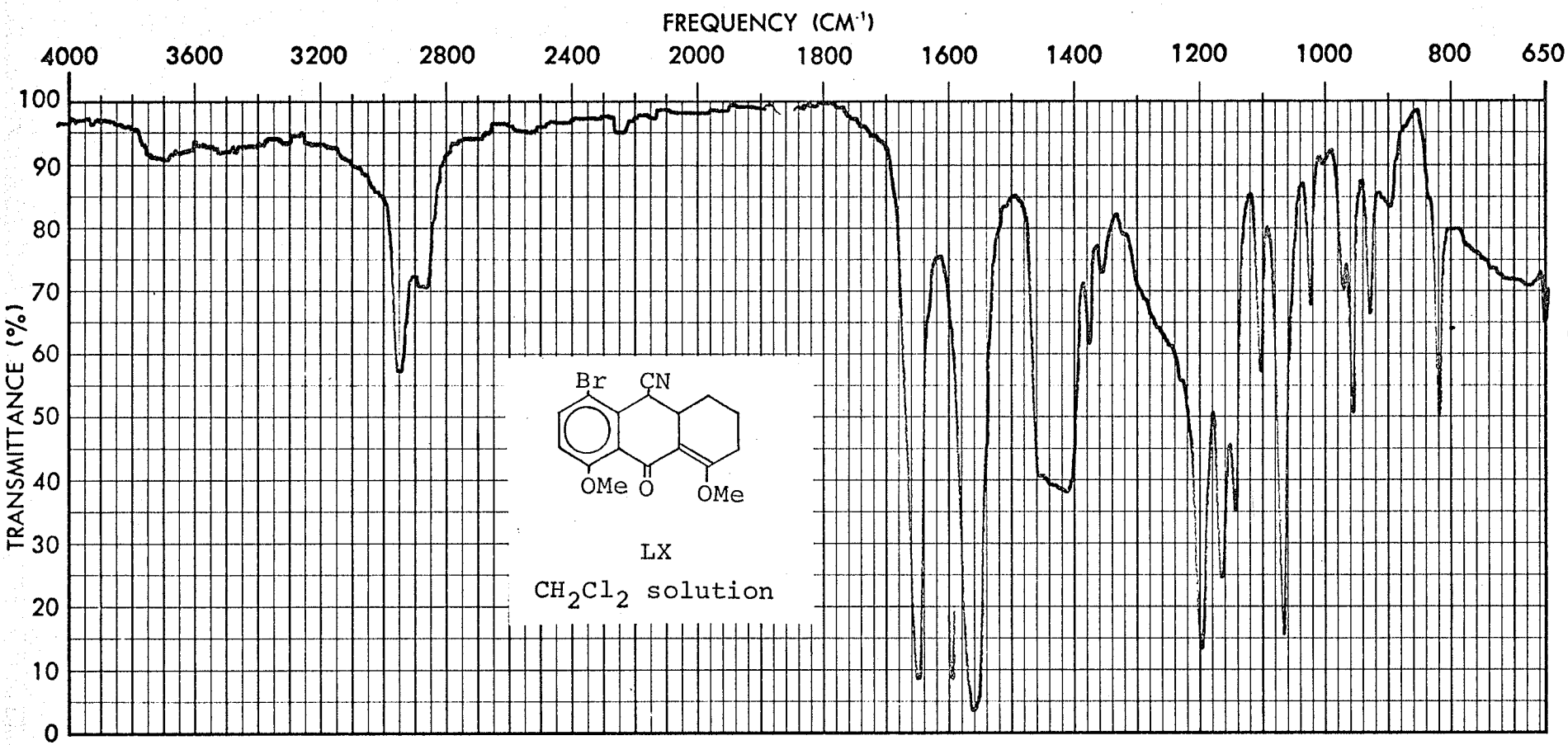
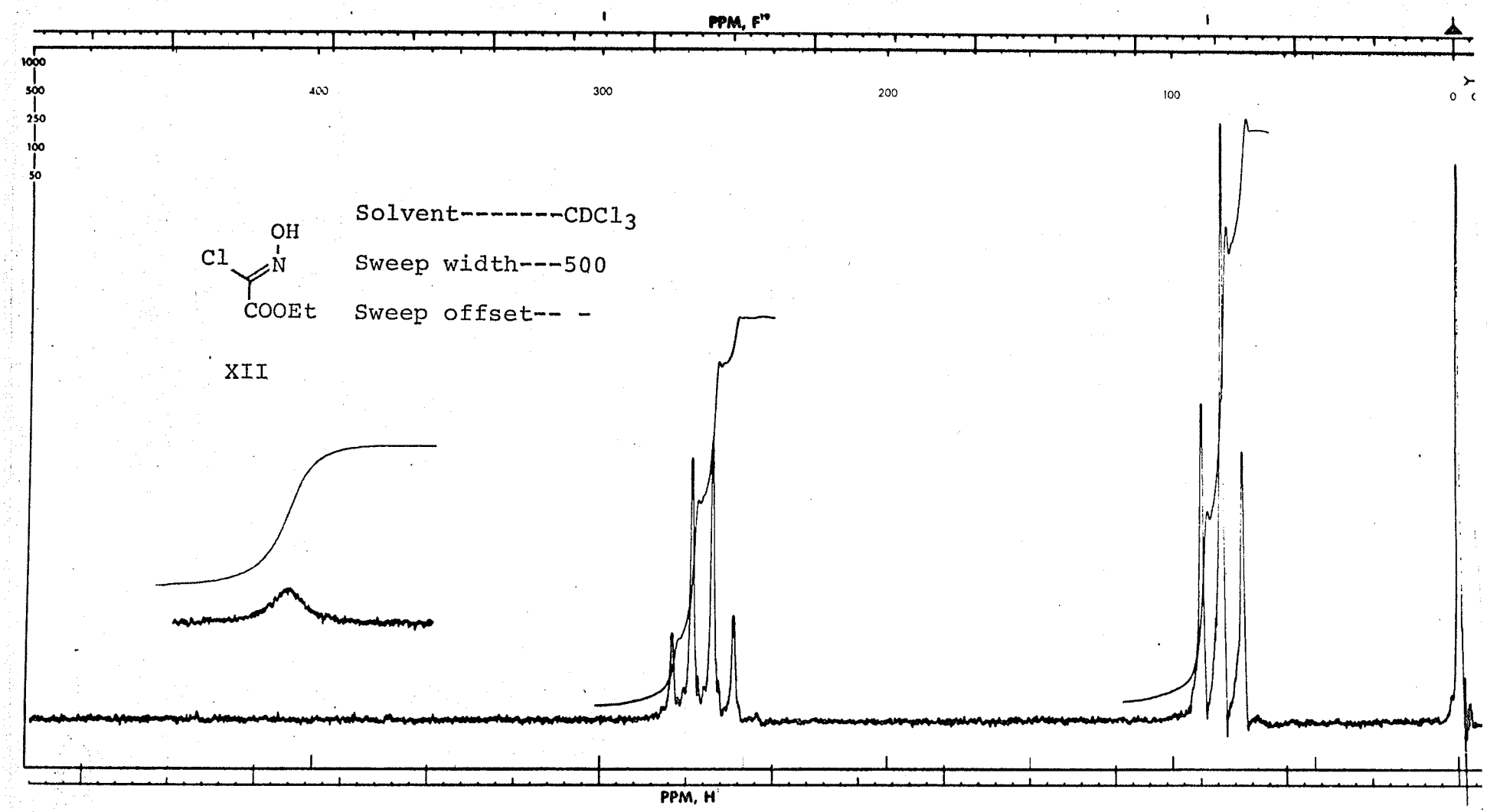



Figure XXXIV

I.r. spectrum of 1,2,3,9,9a,10-hexahydro-4,5-dimethoxy-8-bromo-9-cyano-10-oxoanthrancene




-116-
Figure IA

N.m.r. spectrum of ethylchloroximinoacetate

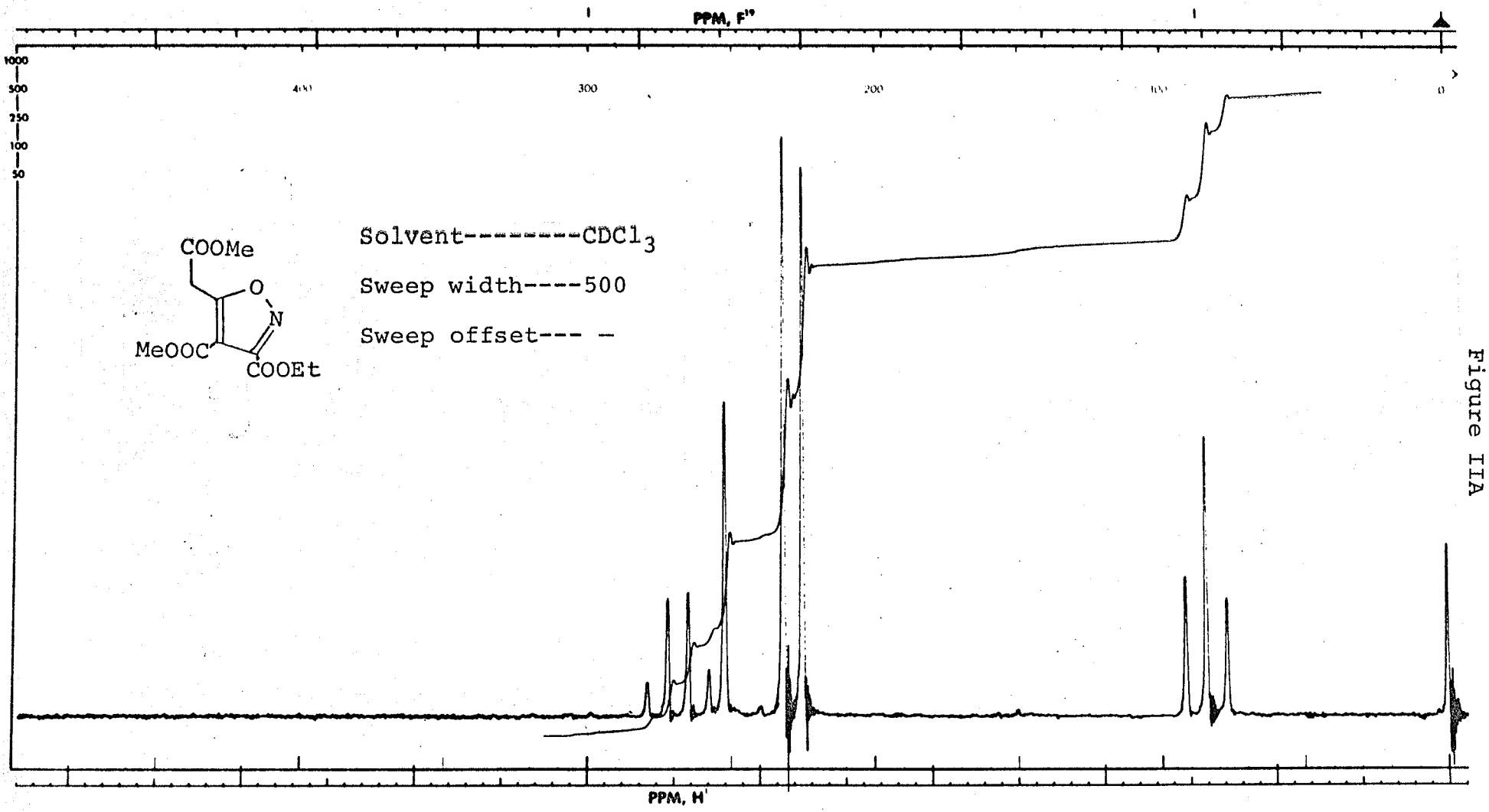



Figure IIA

N.m.r. spectrum of methyl-3-ethoxycarbonyl-4-methoxy-carbonylisoxazolylacetate

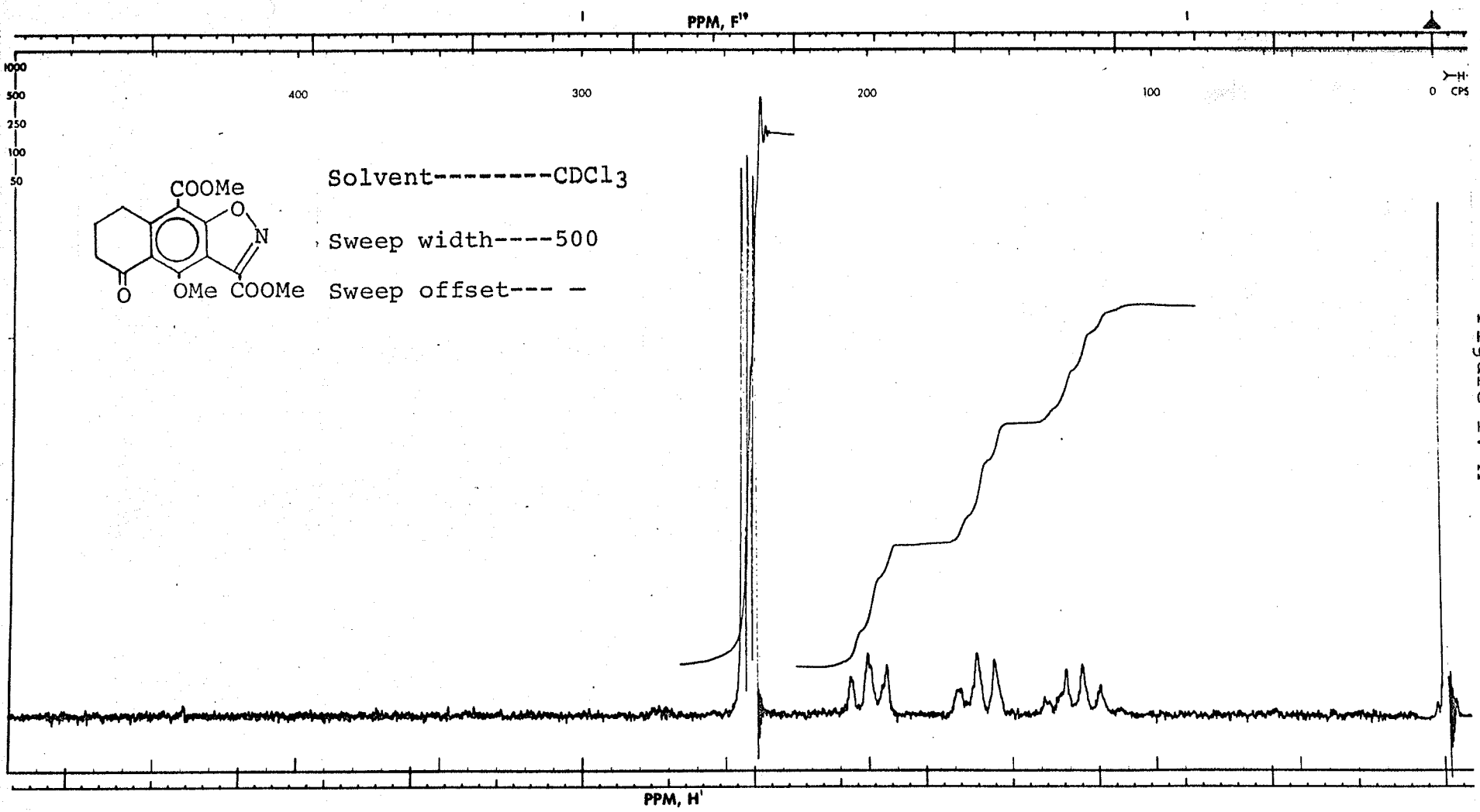
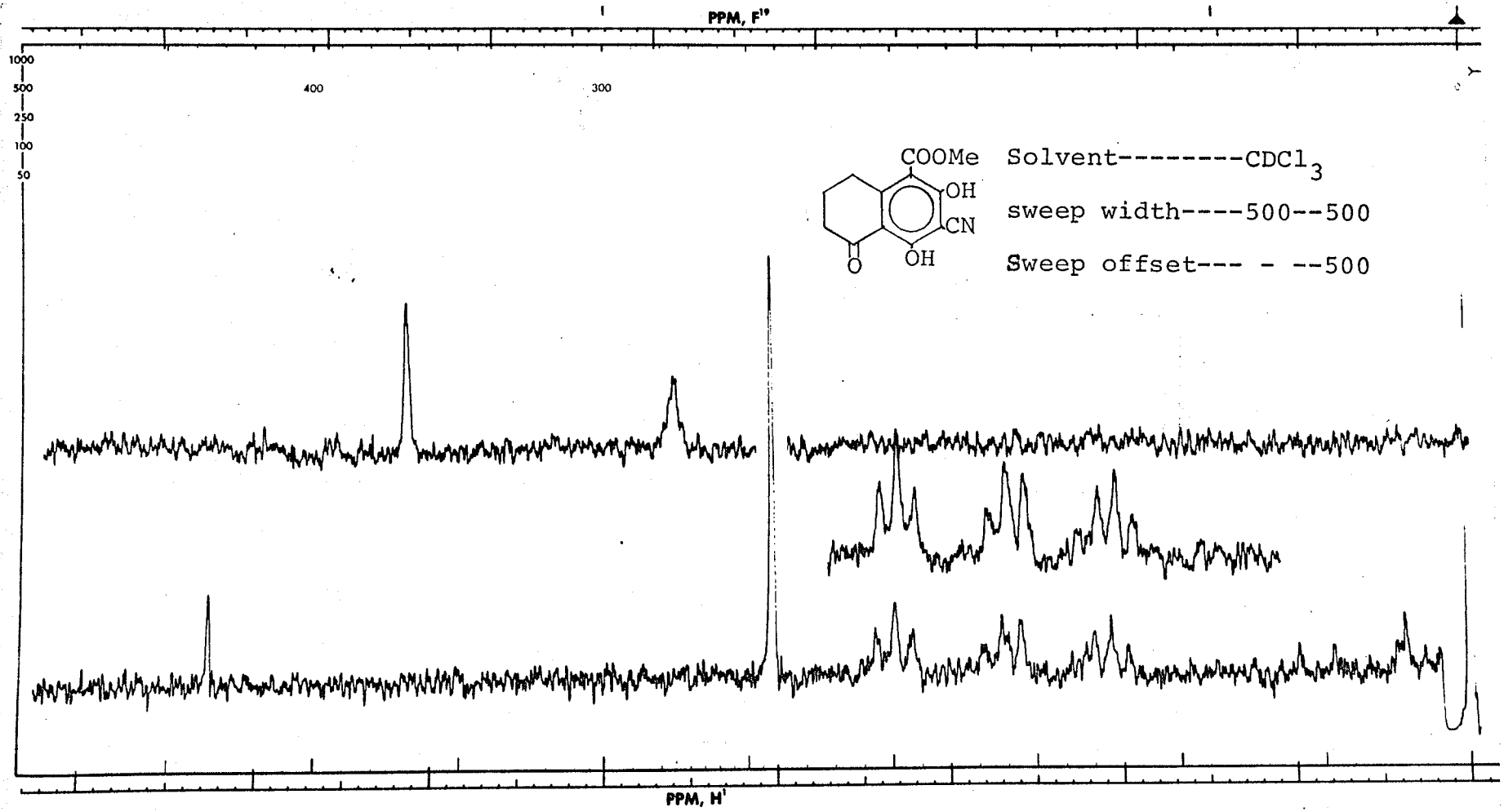



Figure IV A

N.m.r. spectrum of 3,9- dimethoxycarbonyl-4-methoxy-5-oxo-5,6,7,8-tetrahydronaphth-(2,3-d)isoxazole




N.m.r. spectrum of 5-methoxycarbonyl-6,8-dihydroxy-7-cyano-1-tetralone

Figure V A

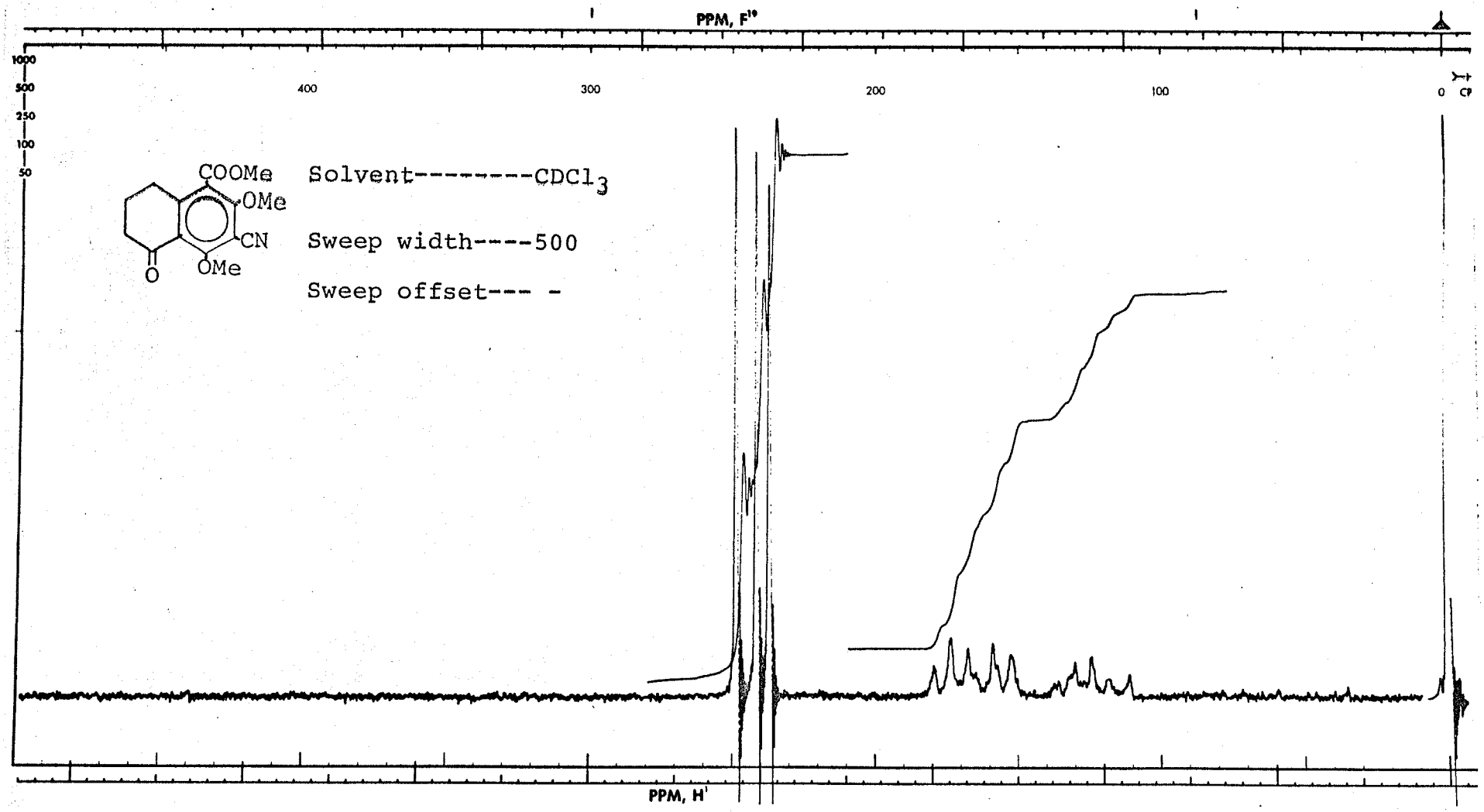



Figure VIA

N.m.r. spectrum of 5- methoxycarbonyl-6,8-dimethoxy-7-cyano-1-tetralone

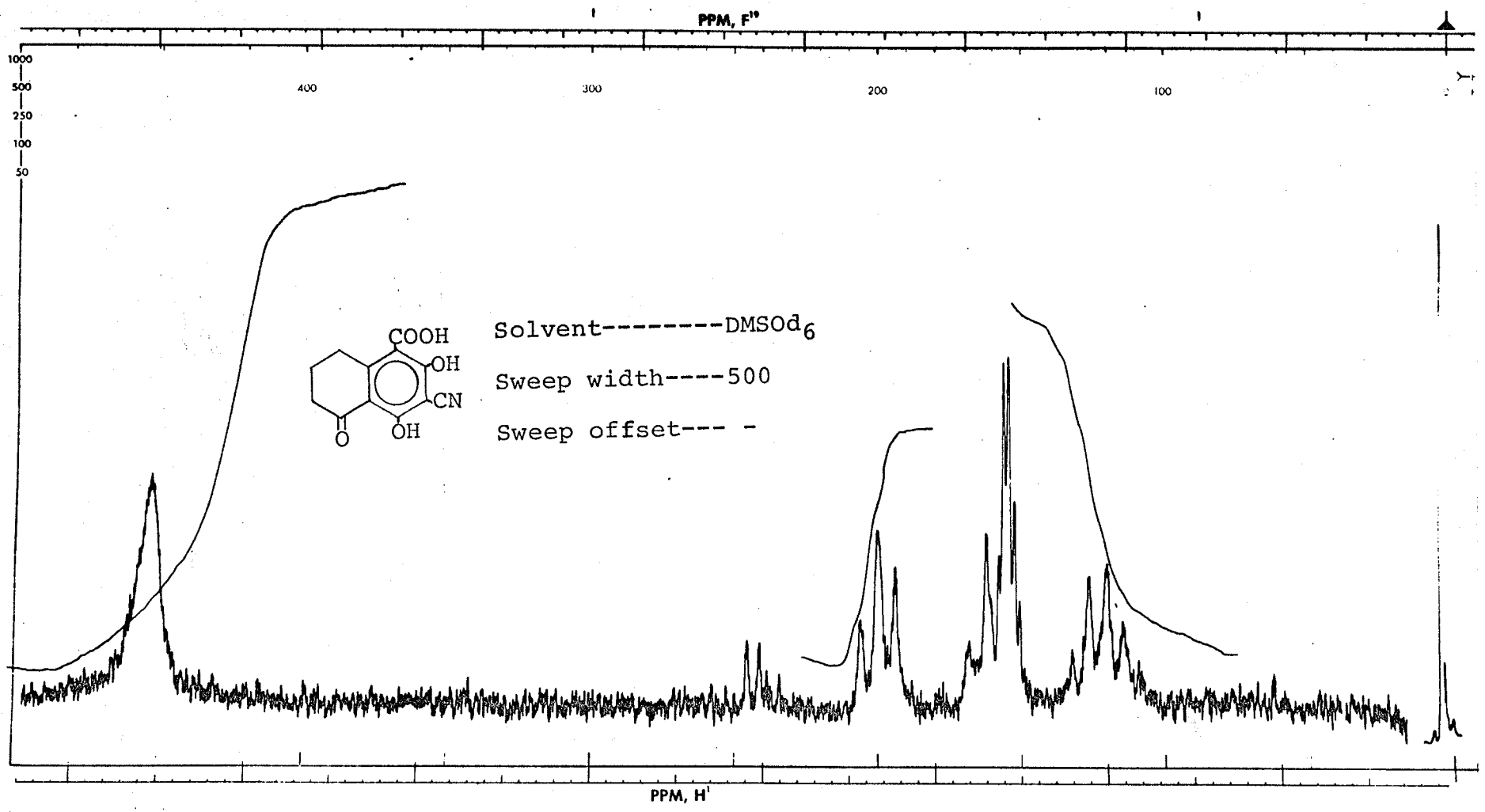



Figure VII A

N.m.r. spectrum of 5-carboxy-6,8-dihydroxy-7-cyanotetralone

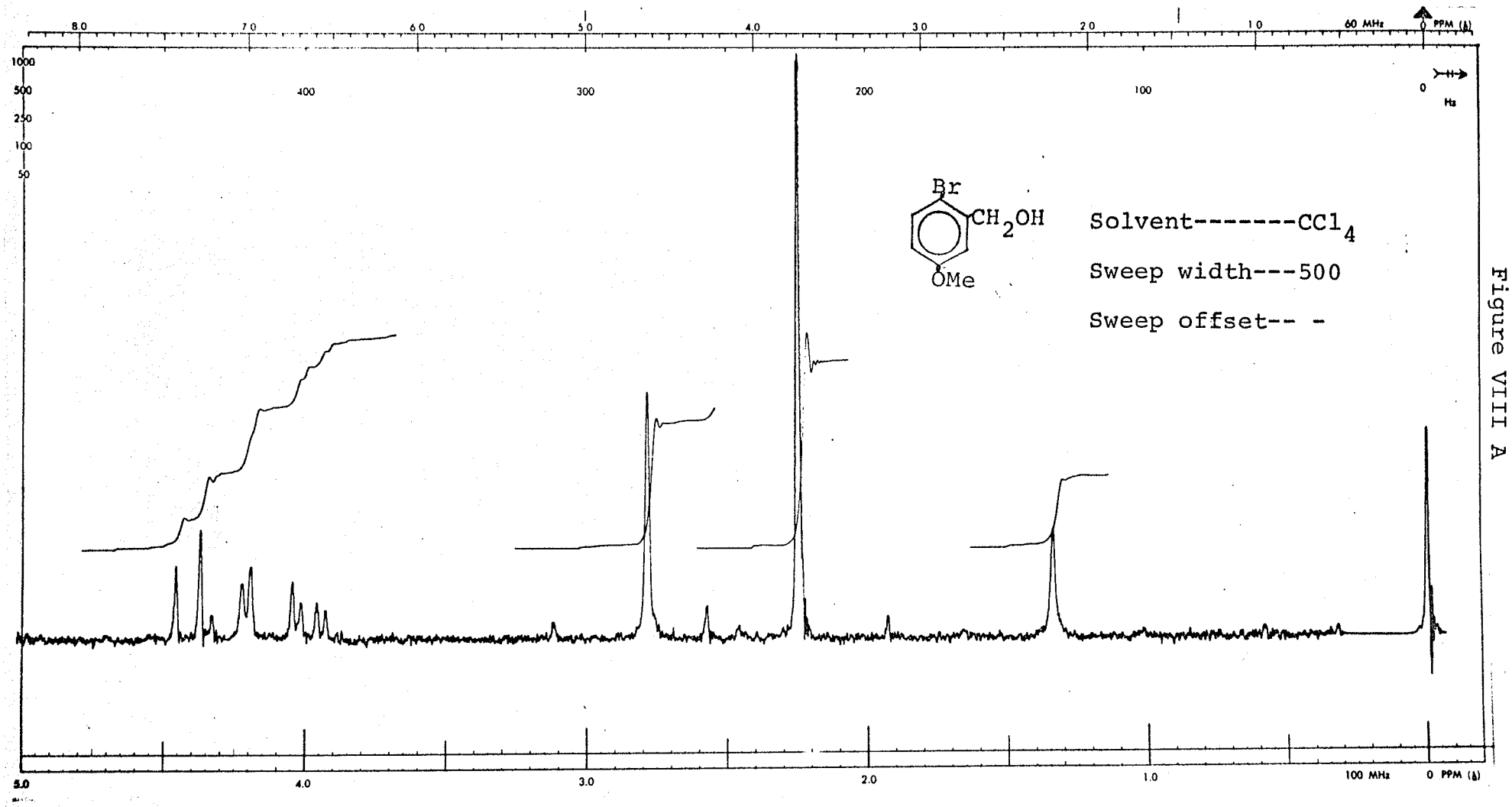



Figure VIII A

N.m.r. spectrum of 2-bromo-5-methoxybenzyl alcohol

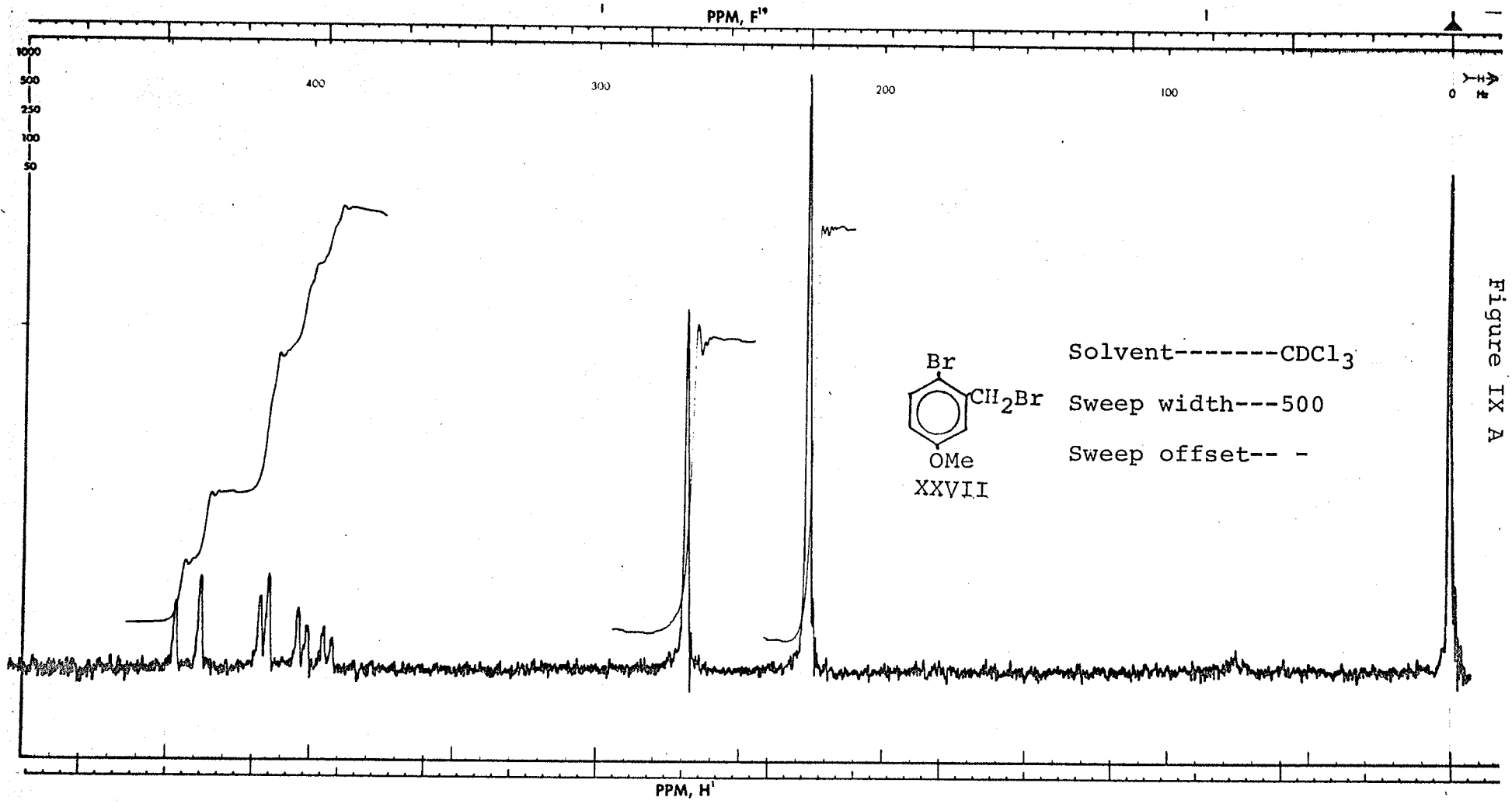



Figure IX A

N.m.r. spectrum of 2-bromo-5-methoxybenzyl bromide

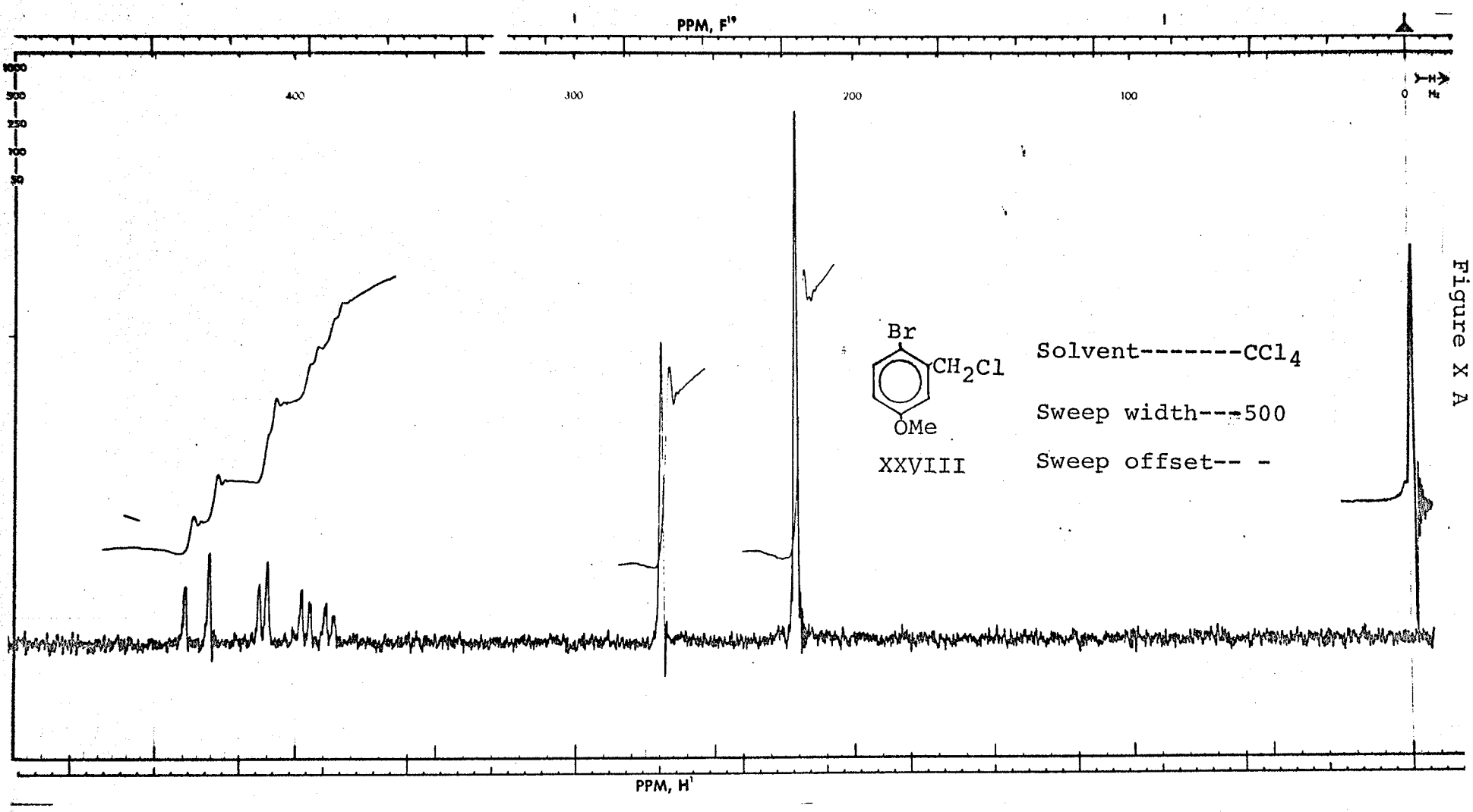



Figure X A

N.m.r. spectrum of 2-bromo-5-methoxybenzyl chloride

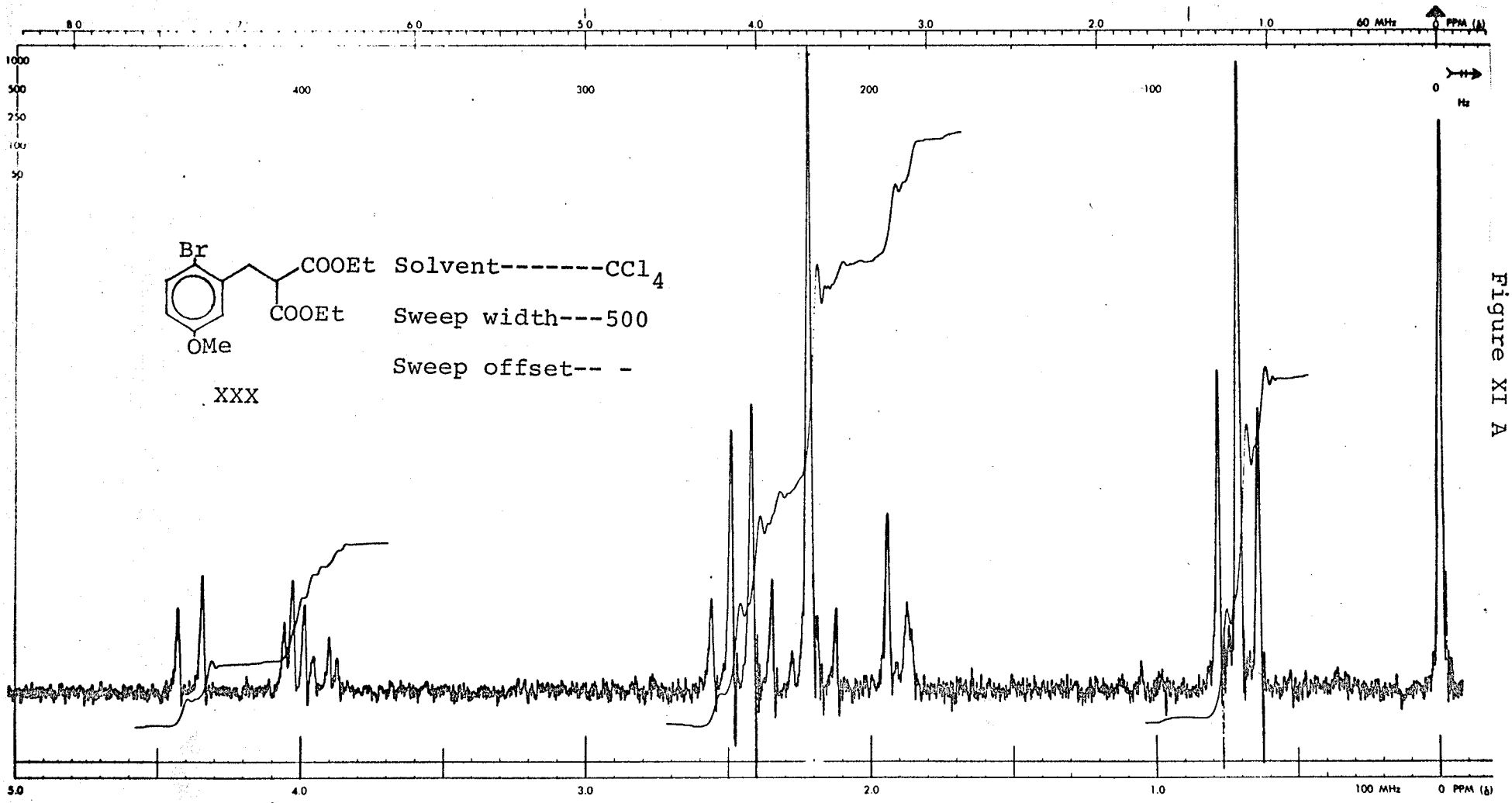



Figure XI A

N.m.r. spectrum of diethyl-2-bromo-5-methoxybenzyl malonate

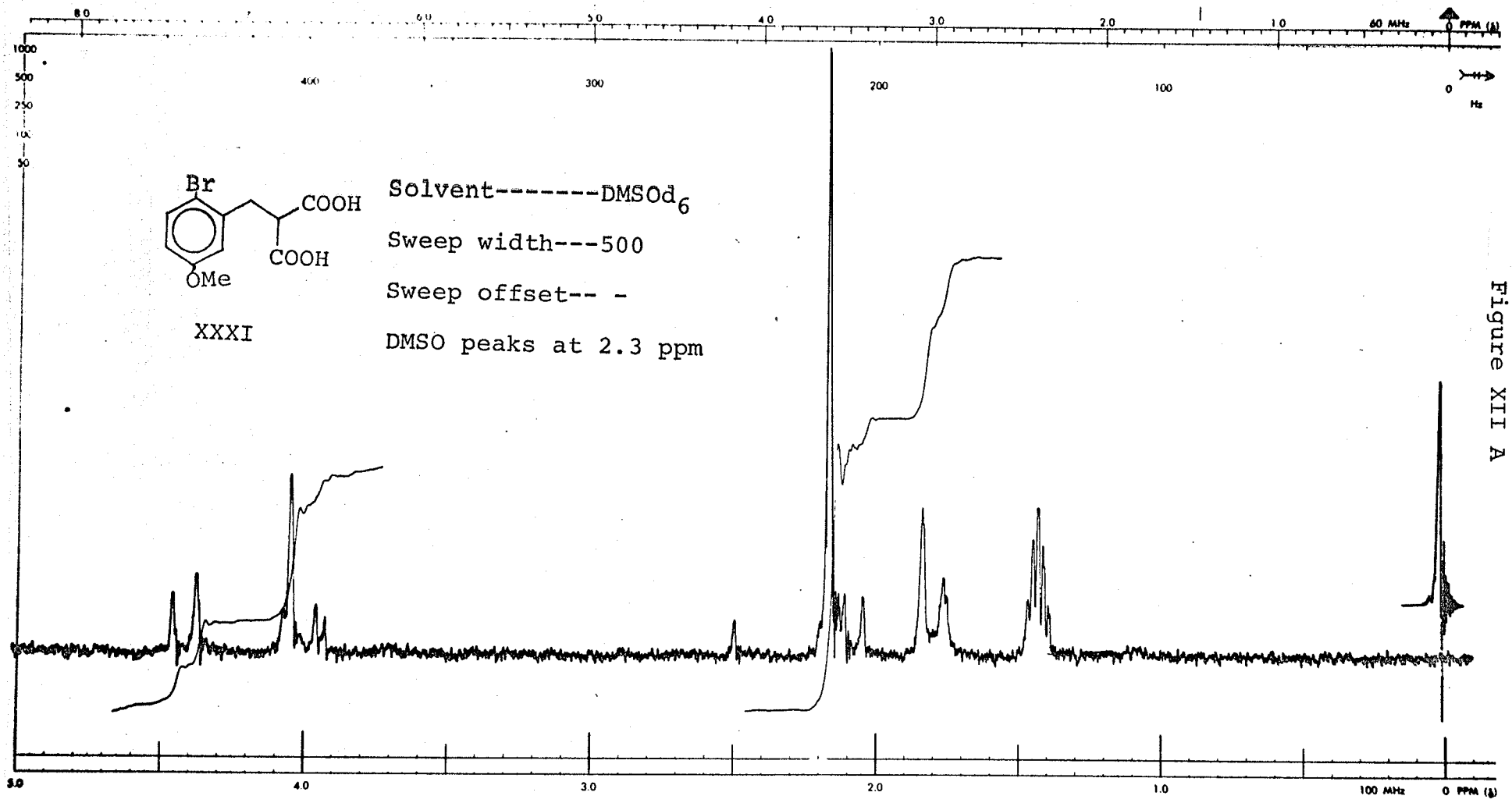



Figure XII A

N.m.r. spectrum of 2-bromo-5-methoxybenzyl malonic acid

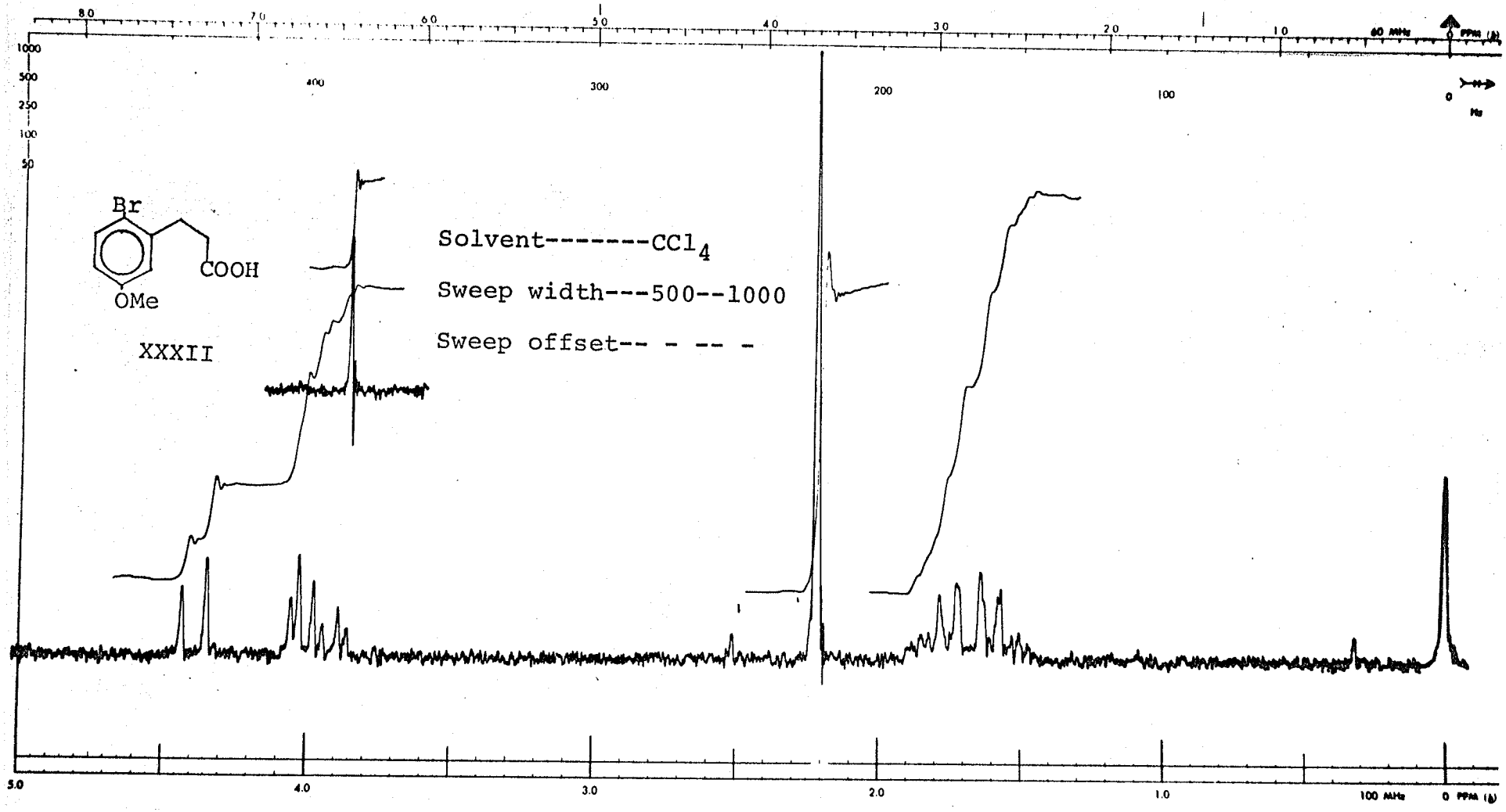



Figure XIII A

N.m.r. spectrum β-2-bromo-5-methoxyphenylpropionic acid

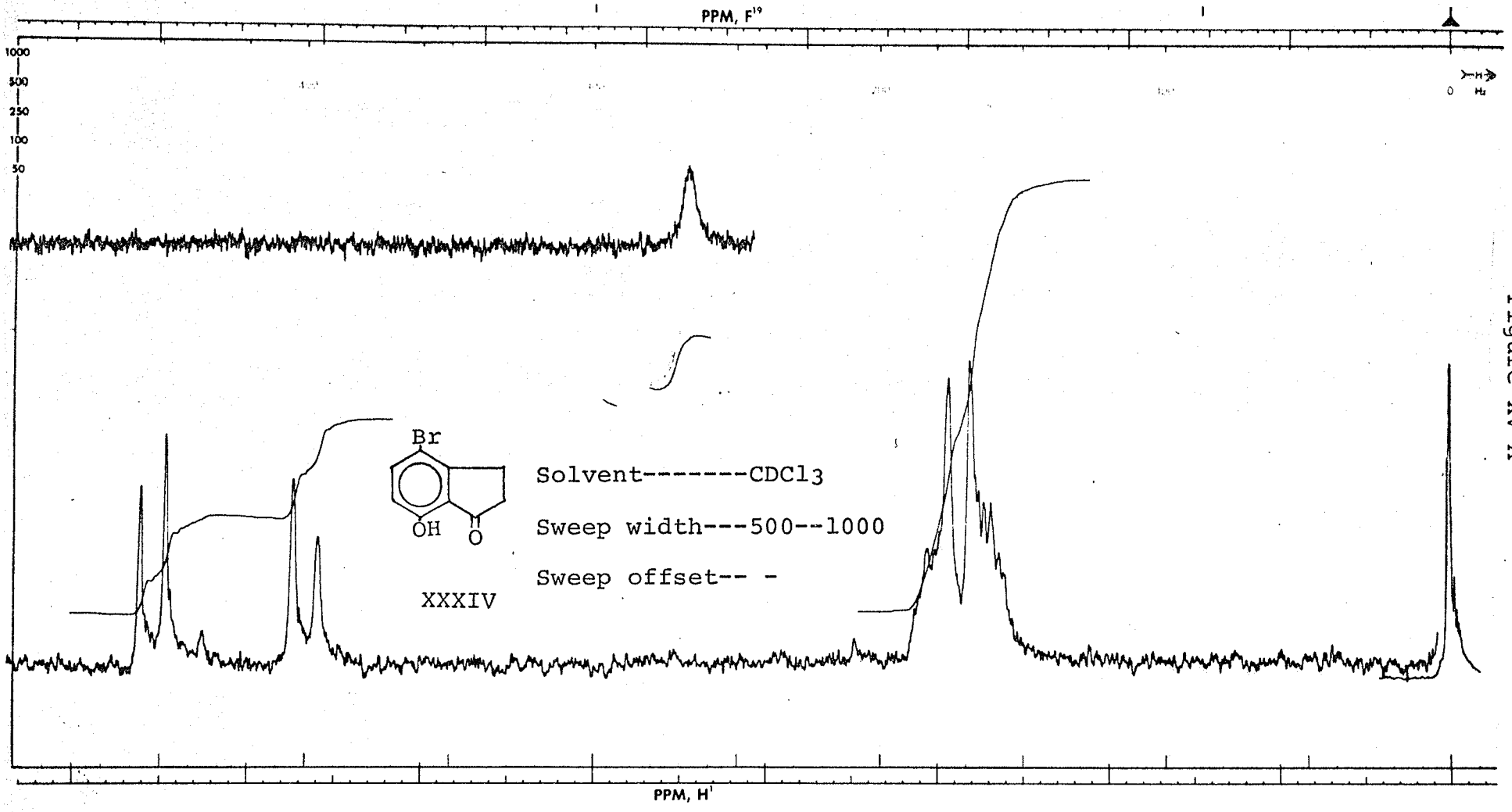



Figure XV A

N.m.r. spectrum of 4-bromo-7-hydroxyindanone

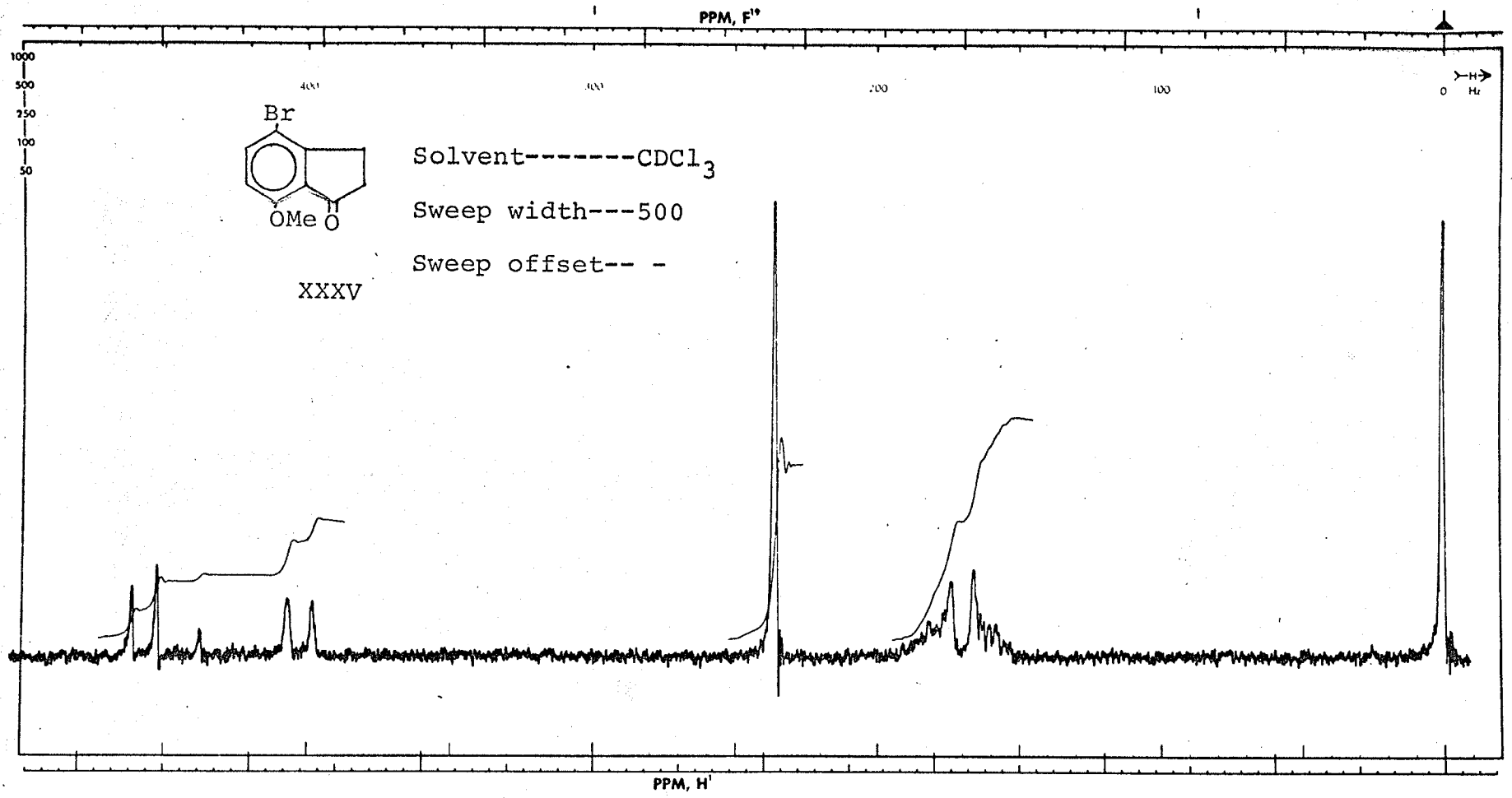



Figure XVI A

N.m.r. spectrum of 4-bromo-7-methoxy-indanone

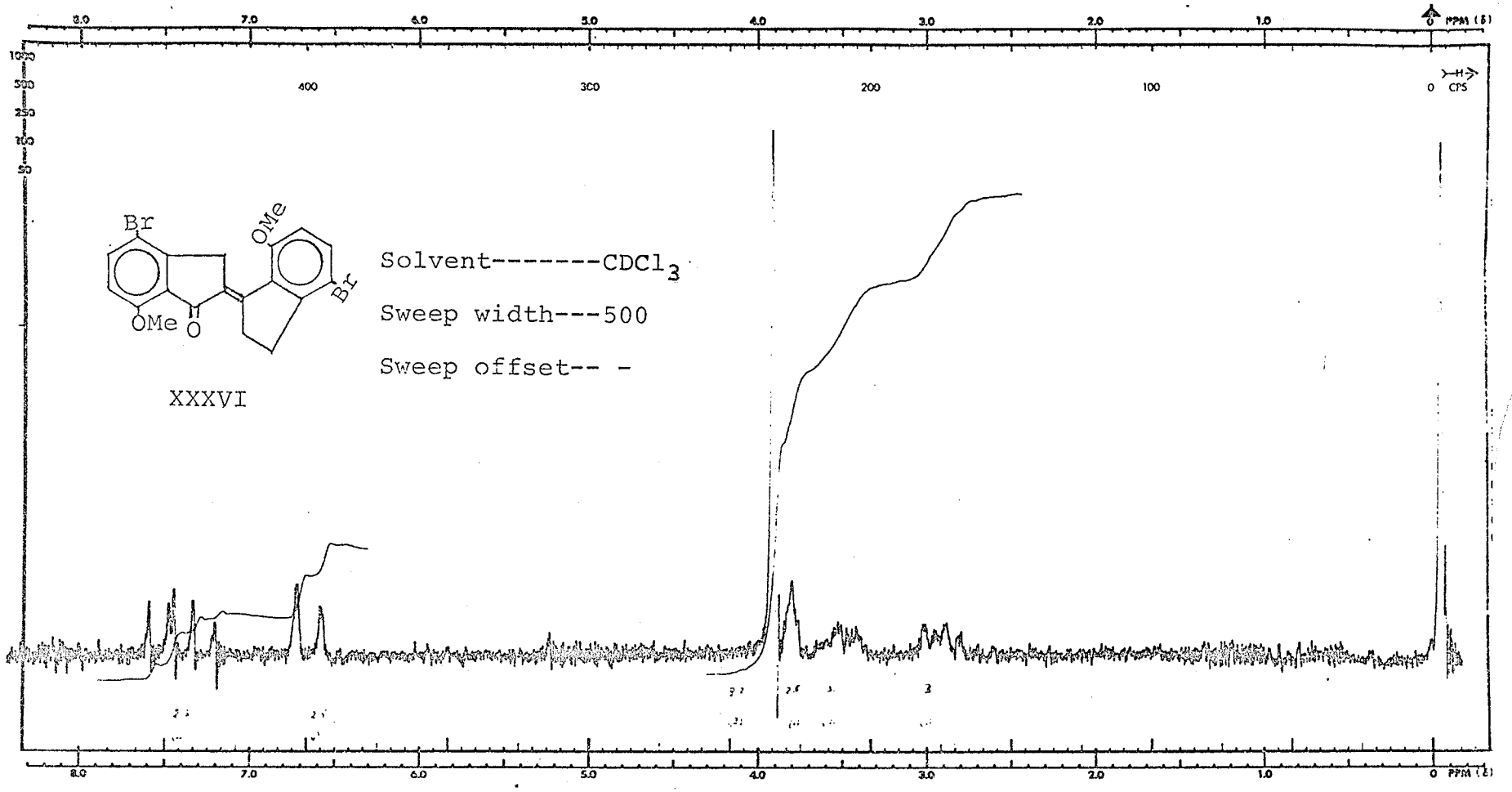



Figure XVII A

N.m.r. spectrum of 1'-oxo-2,3,3'-trihydro-4,4'-dibromo-7,7'-dimethoxy-1,2'-indenylidene

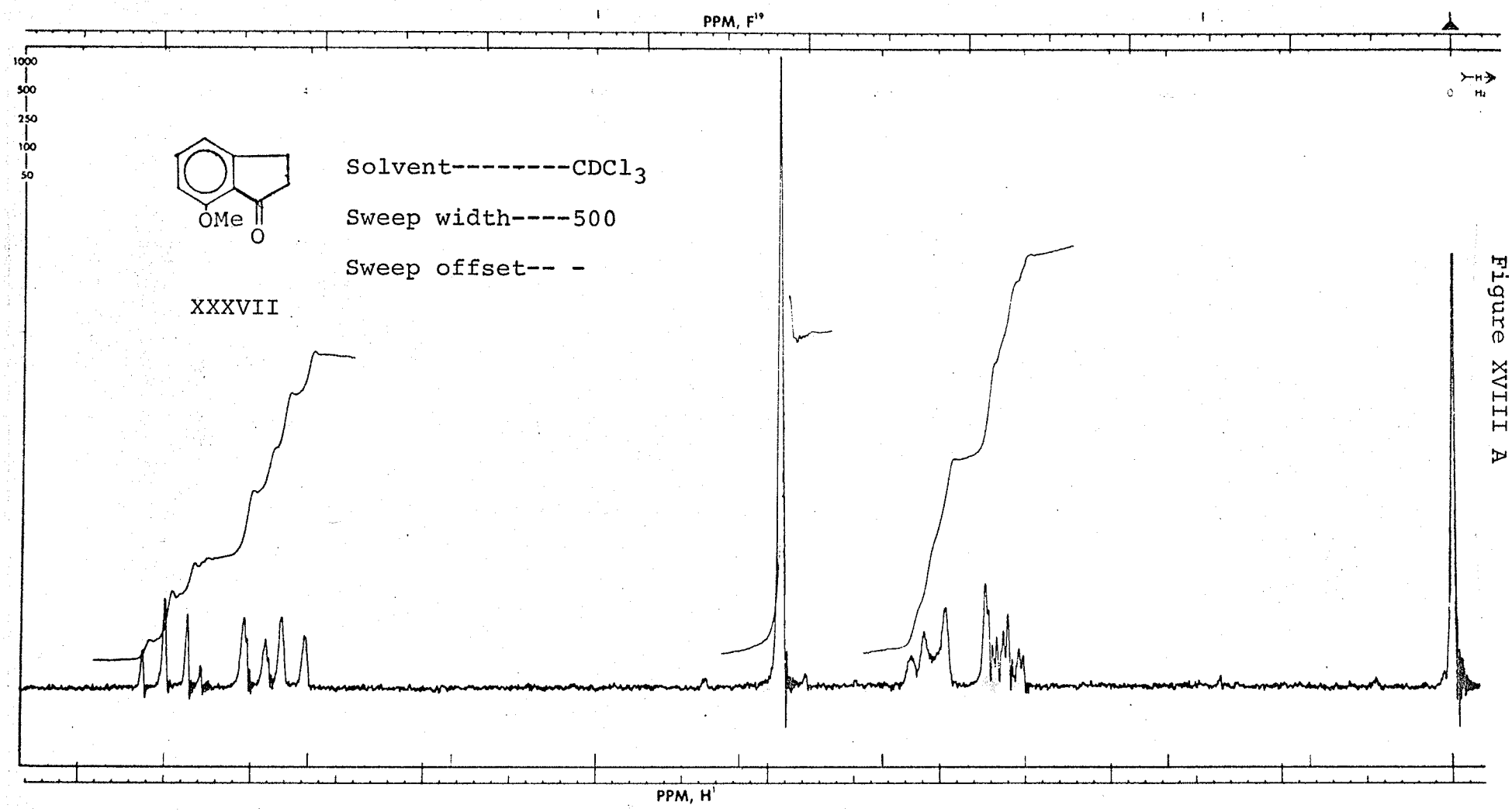
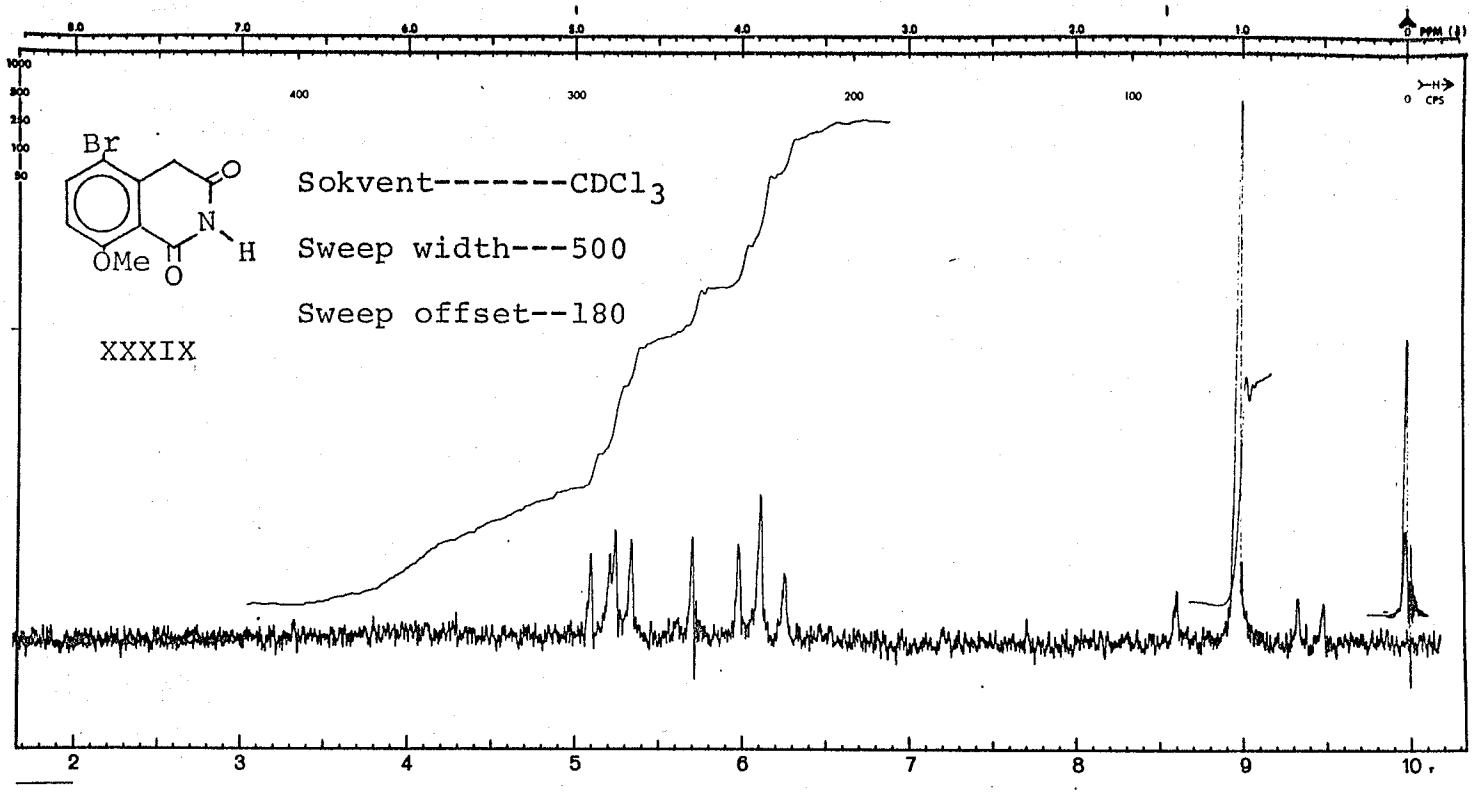



Figure XVIII A

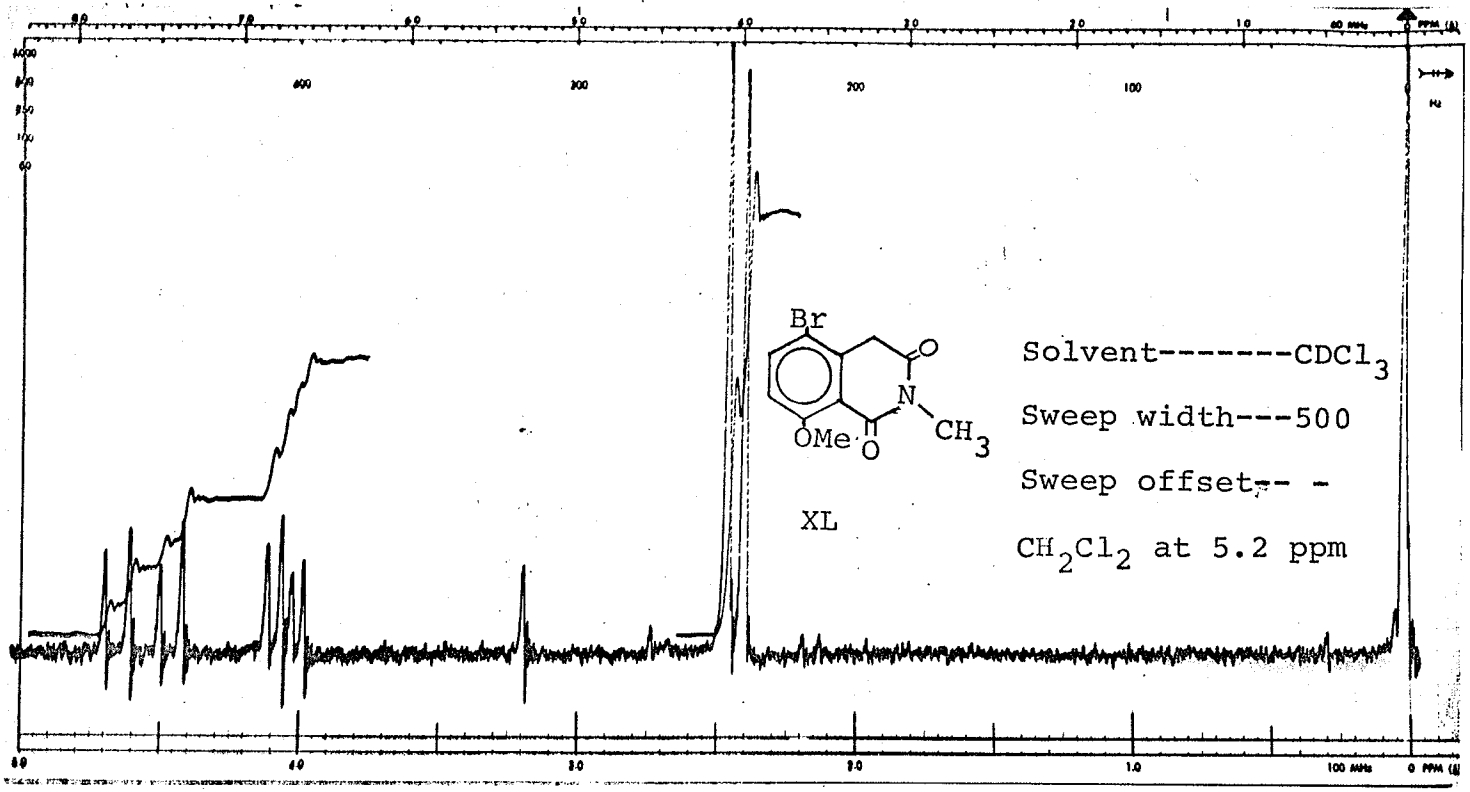
N.m.r. spectrum of 7-methoxyindanone

Figure XIX A




N.m.r. spectrum of 3-bromo-6-methoxyhomophthalimide

Figure XX A




N.m.r. spectrum of N-methyl-3-bromo-6-methoxyhomophthalimide

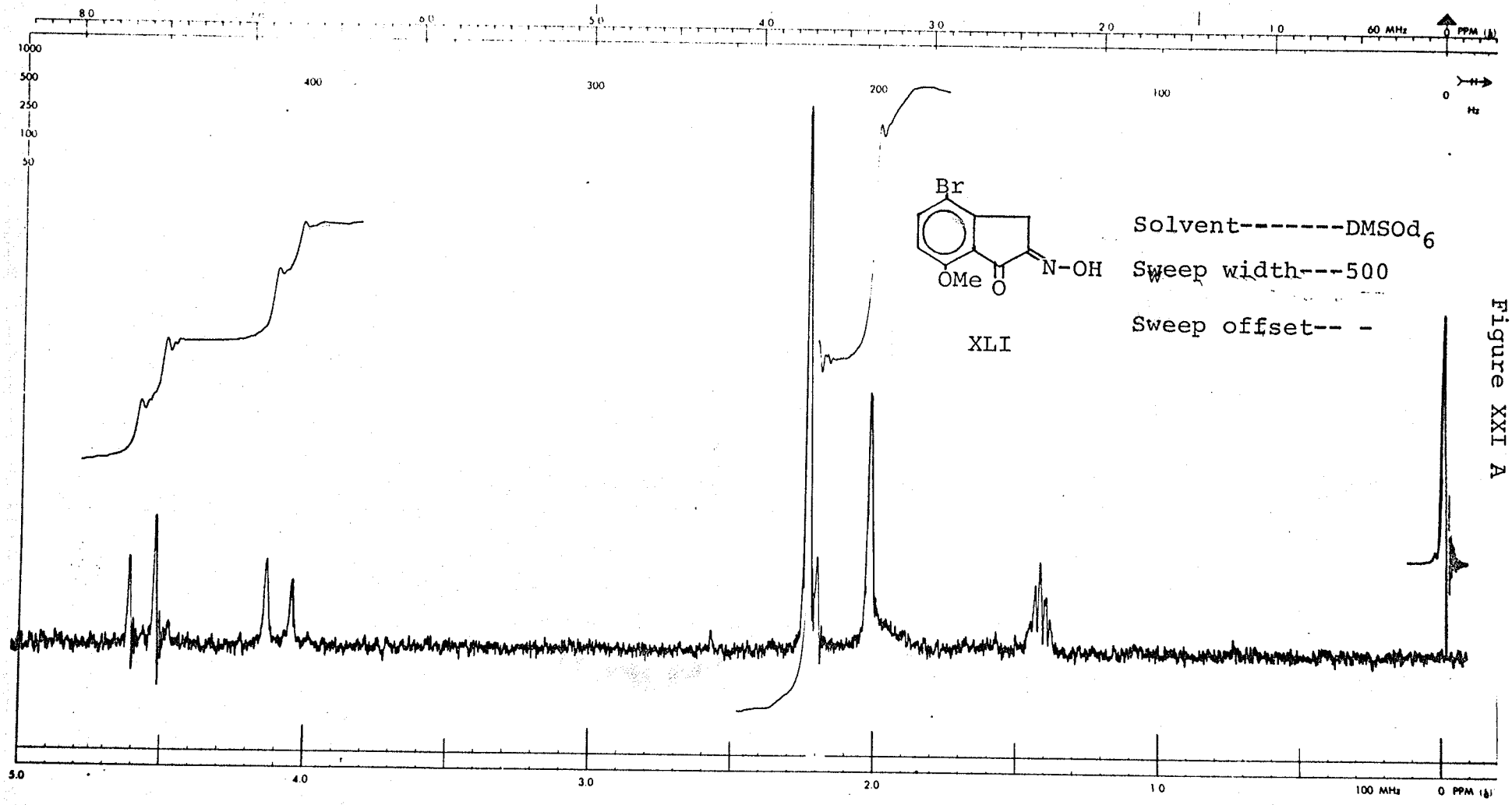
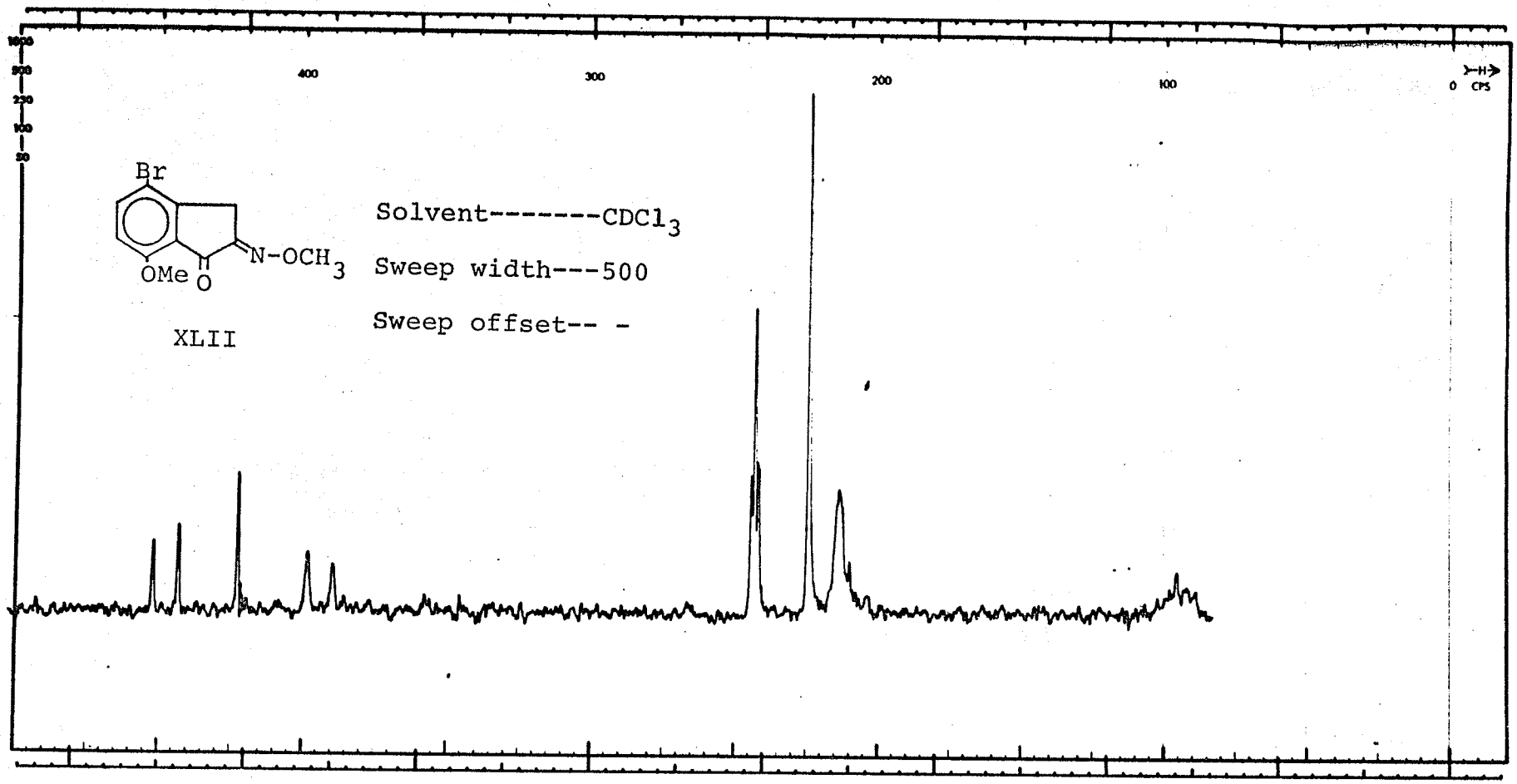



Figure XXI A

N.m.r. spectrum of 2-oxime-4-bromo-7-methoxy-1,2-indandione

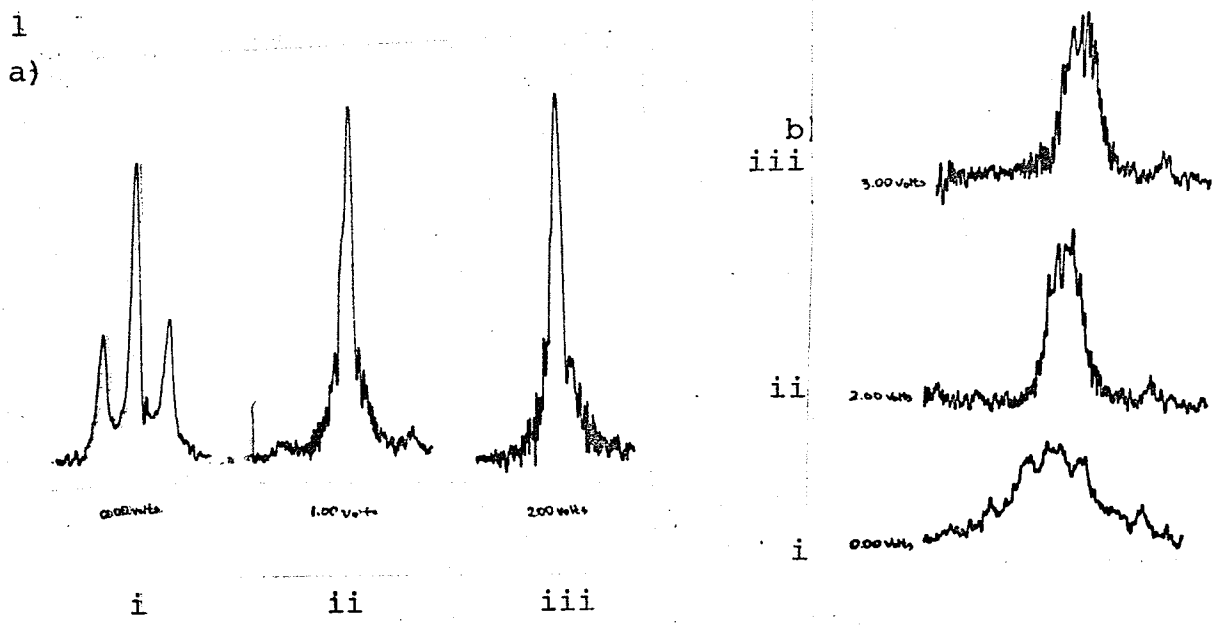



XLII

Figure XXII A

N.m.r. spectrum of 2-methoximino-4-bromo-7-methoxyindanone

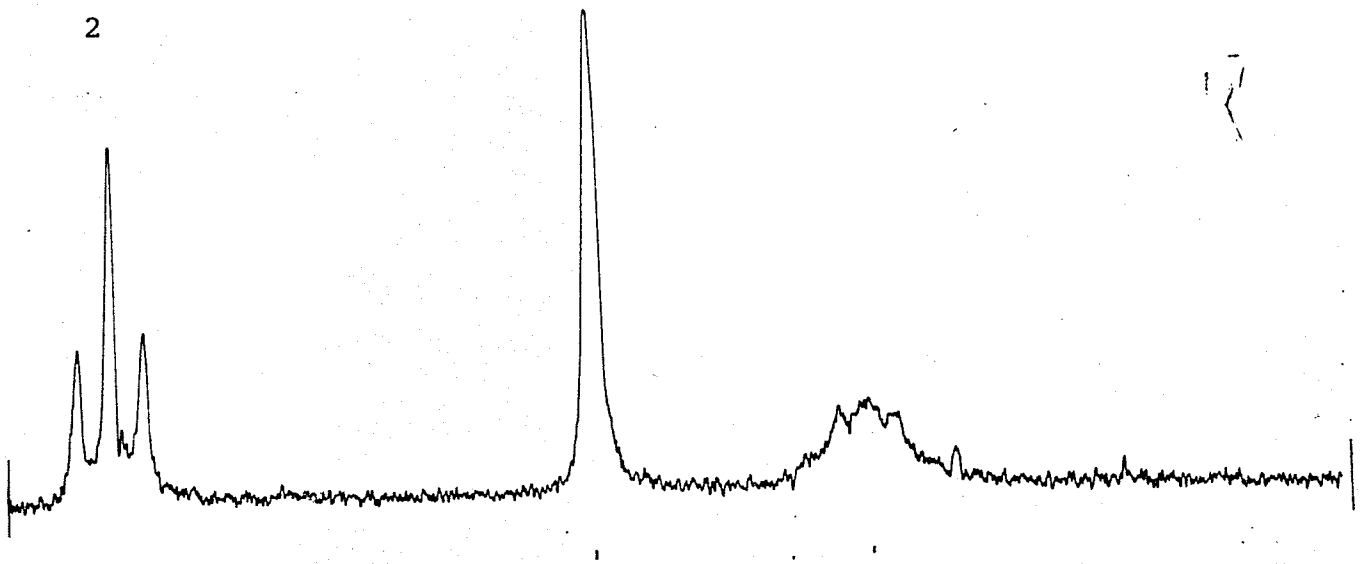
Figure XXII A (cont.)




Double spectrum of XLII in $CDCl_3$

a) hitting $CH_2$ group at 227.64 Hz. with i,0 ii,1.00 iii,2.00 volts

b) hitting $CH_3$ group at 256.9 Hz. with i,o ii,2.00 iii,3.00 volts




Partial n.m.r. spectrum of XLII in $CDCl_3$ Sweep width 50 $H_3$.

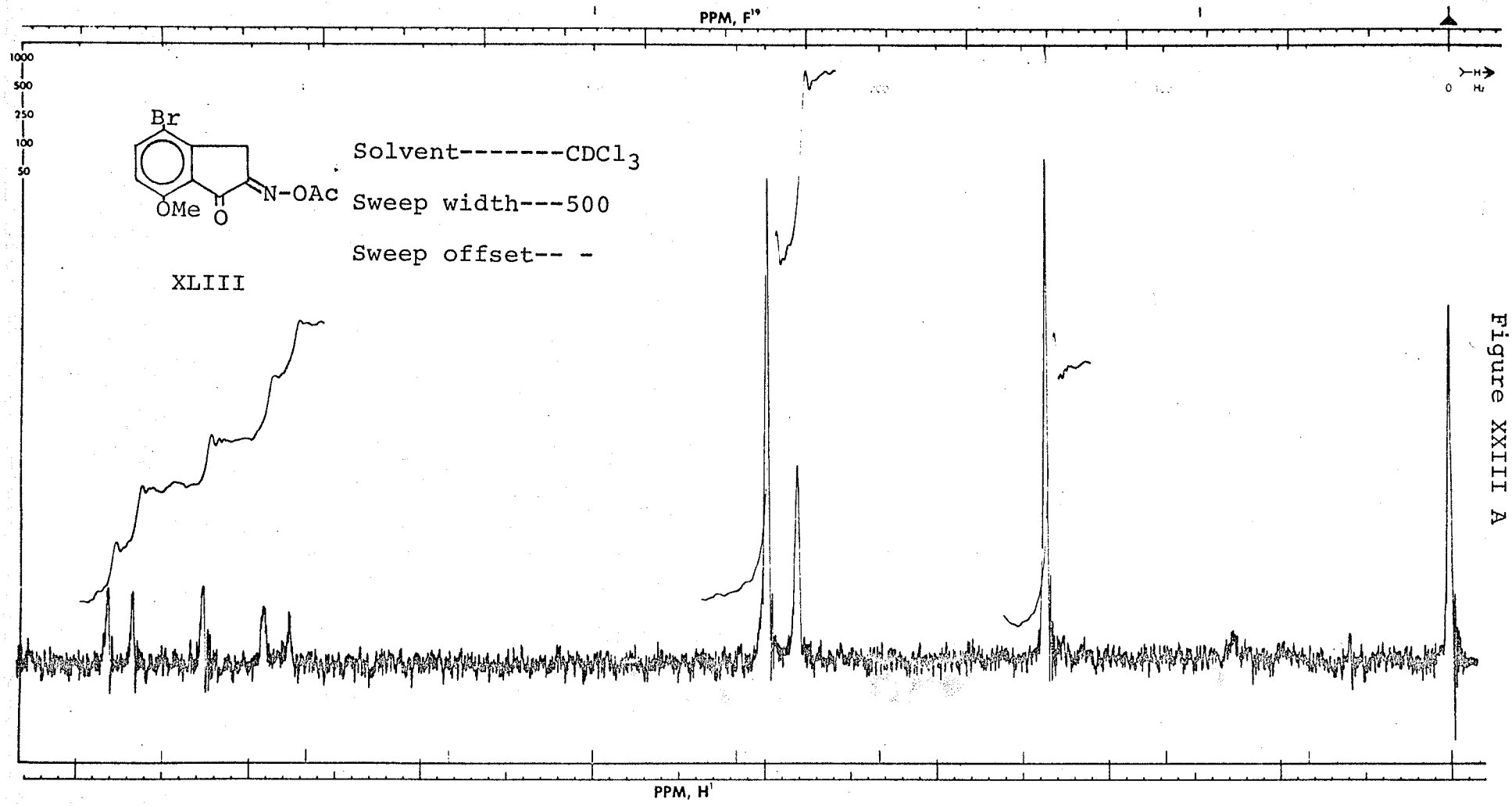



Figure XXIII A

N.m.r. spectrum of 2-acetoximino-4-bromo-7-methoxyindanone

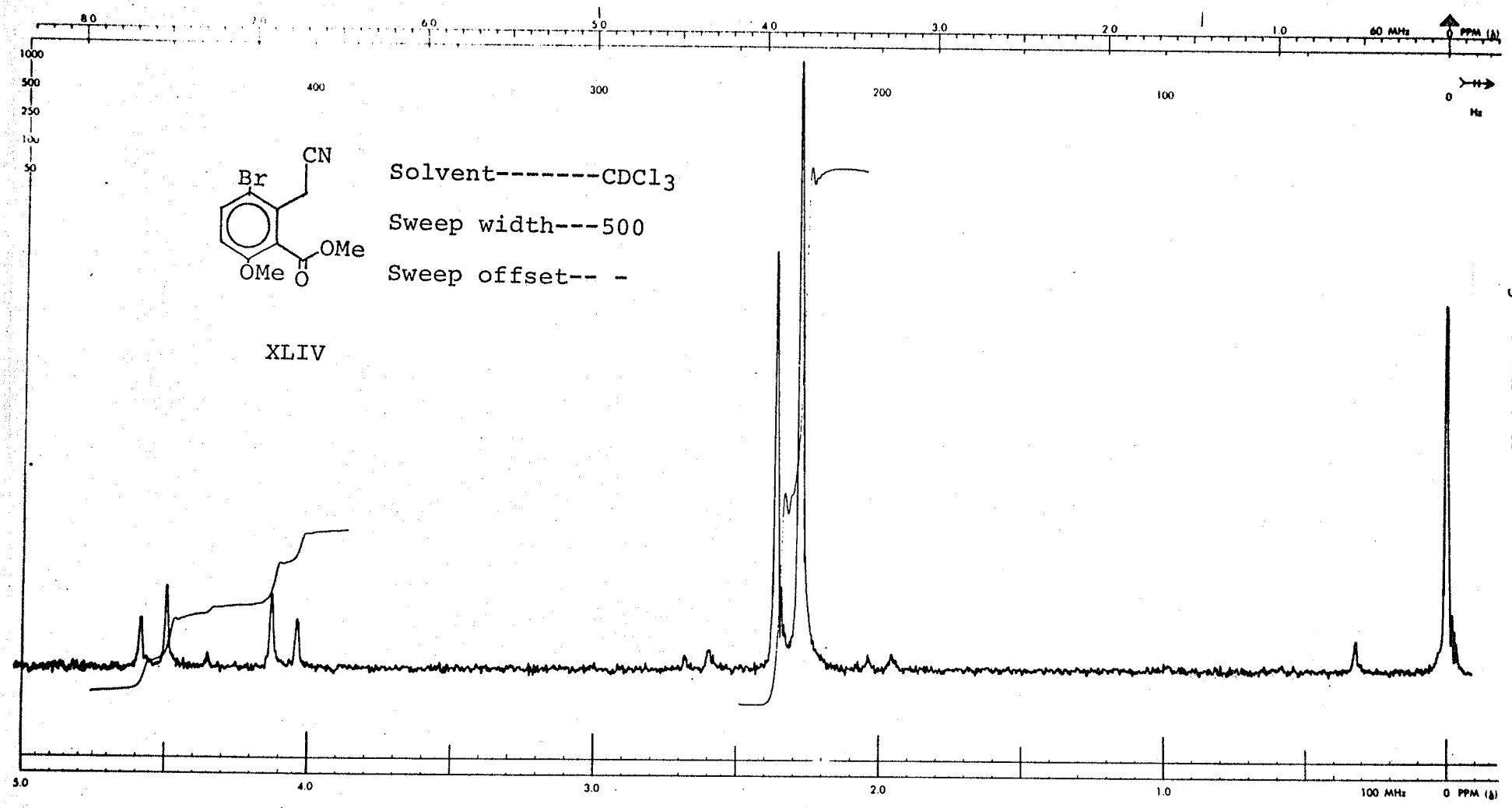
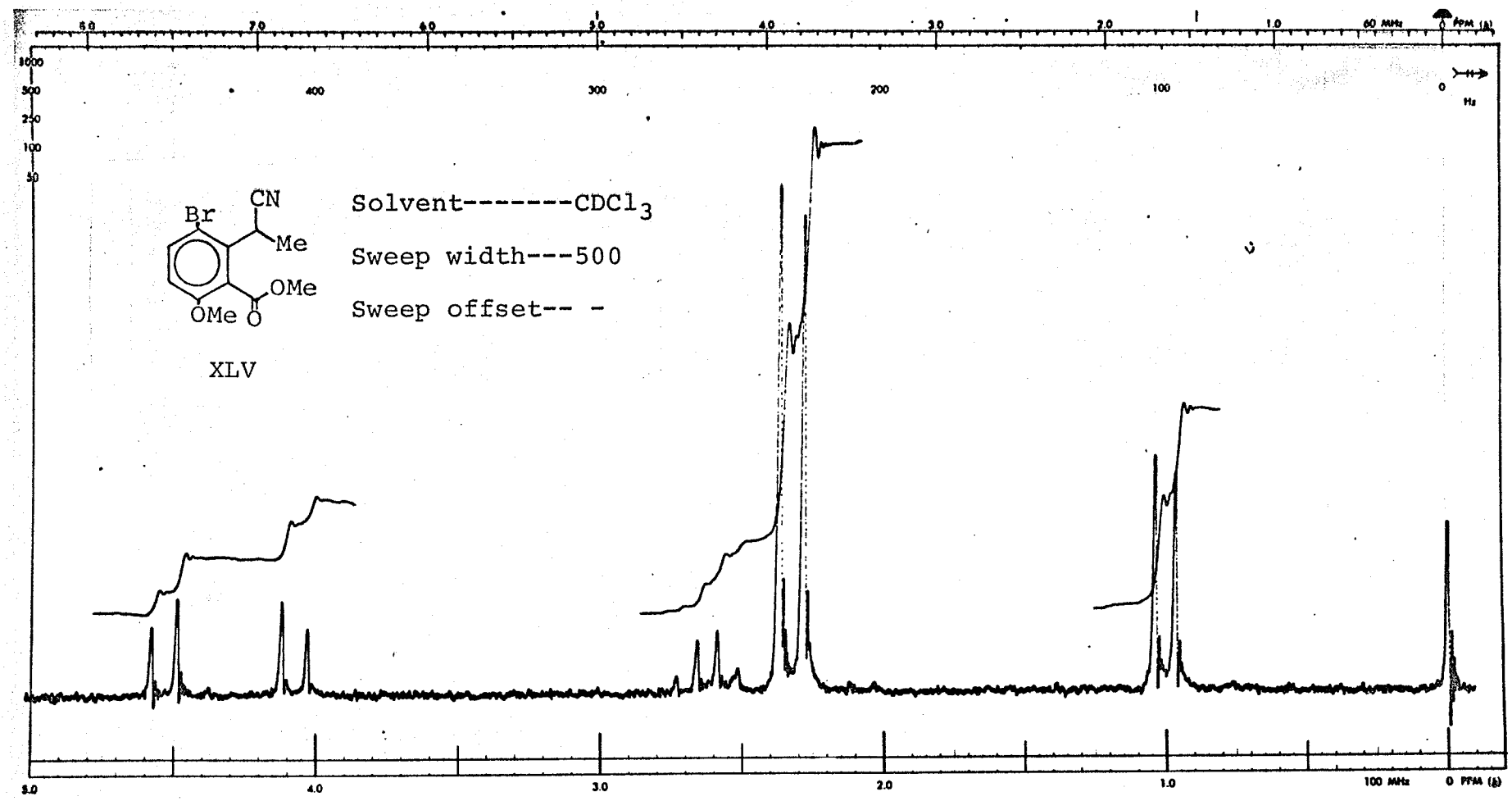



Figure XXIV A

S N.m.r. spectrum of 2-bromo-5-methoxy-6-methoxycarbonylphenyl acetonitrile




N.m.r. of α-2-methoxycarbonyl-3-methoxyphenyl propionitrile

Figure XXV A

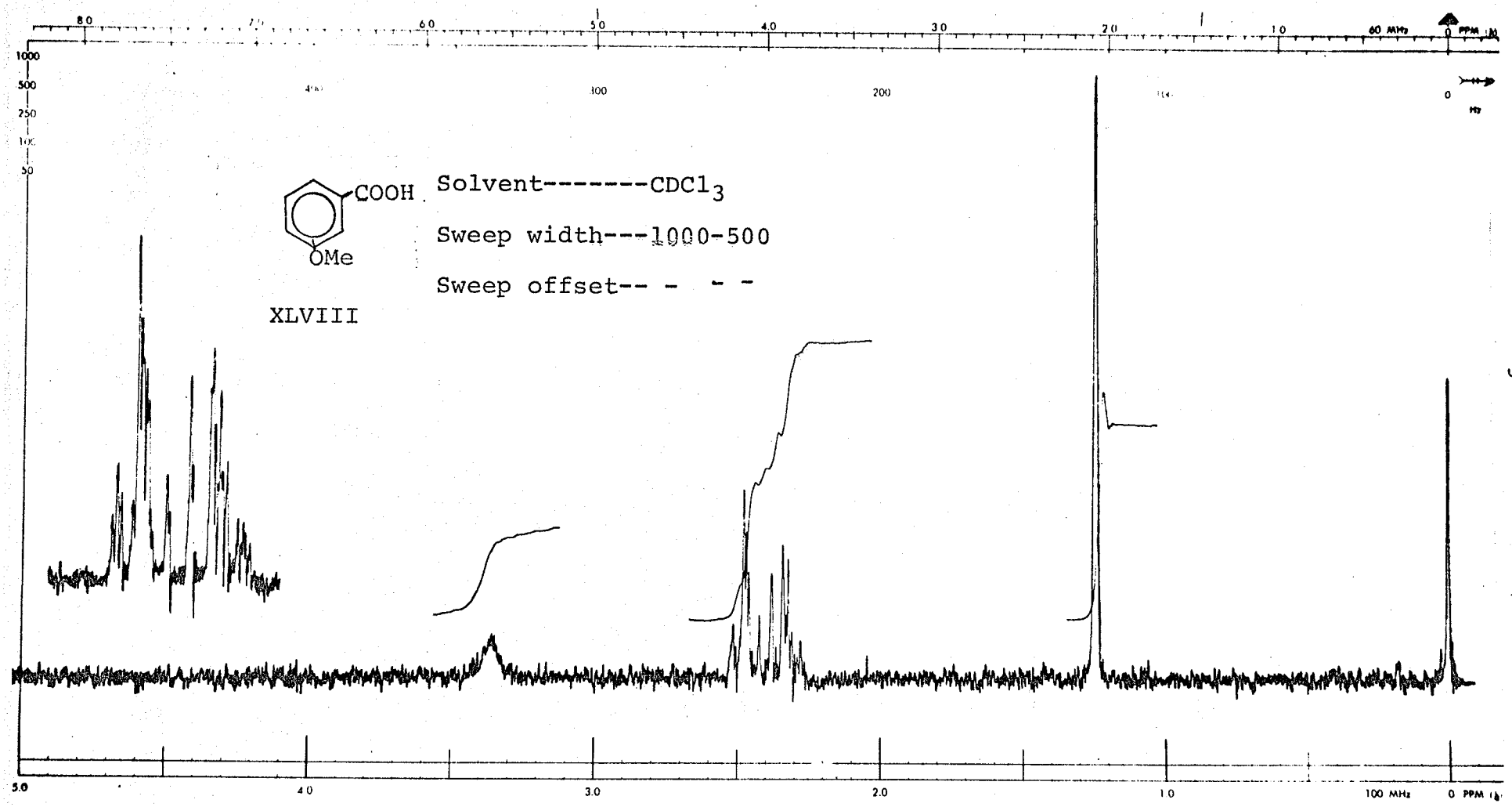



Figure XXVI A

N.m.r. spectrum of m-methoxybenzoic acid

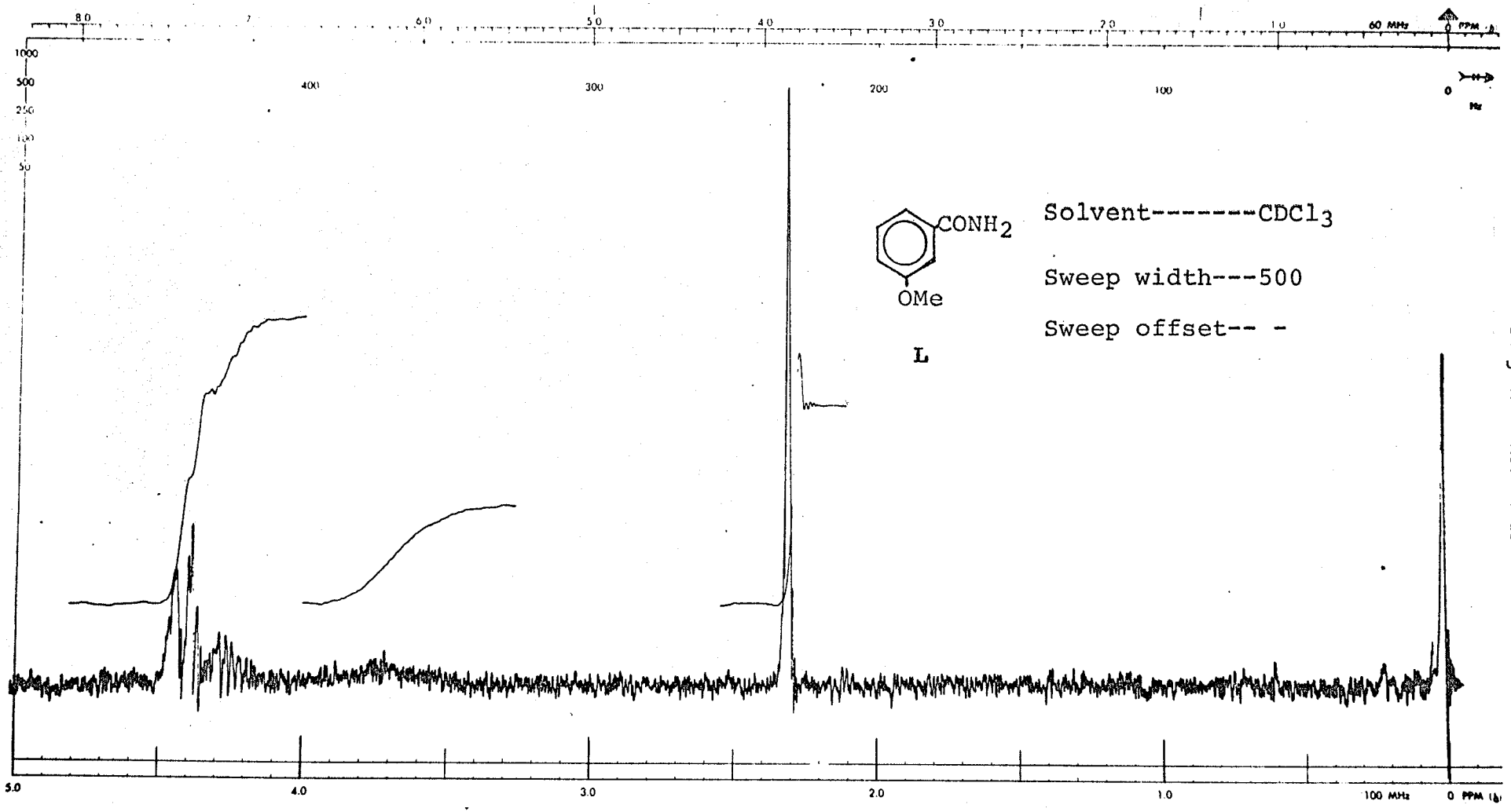



Figure XXVII A

N.m.r. spectrum of m-methoxybenzamide

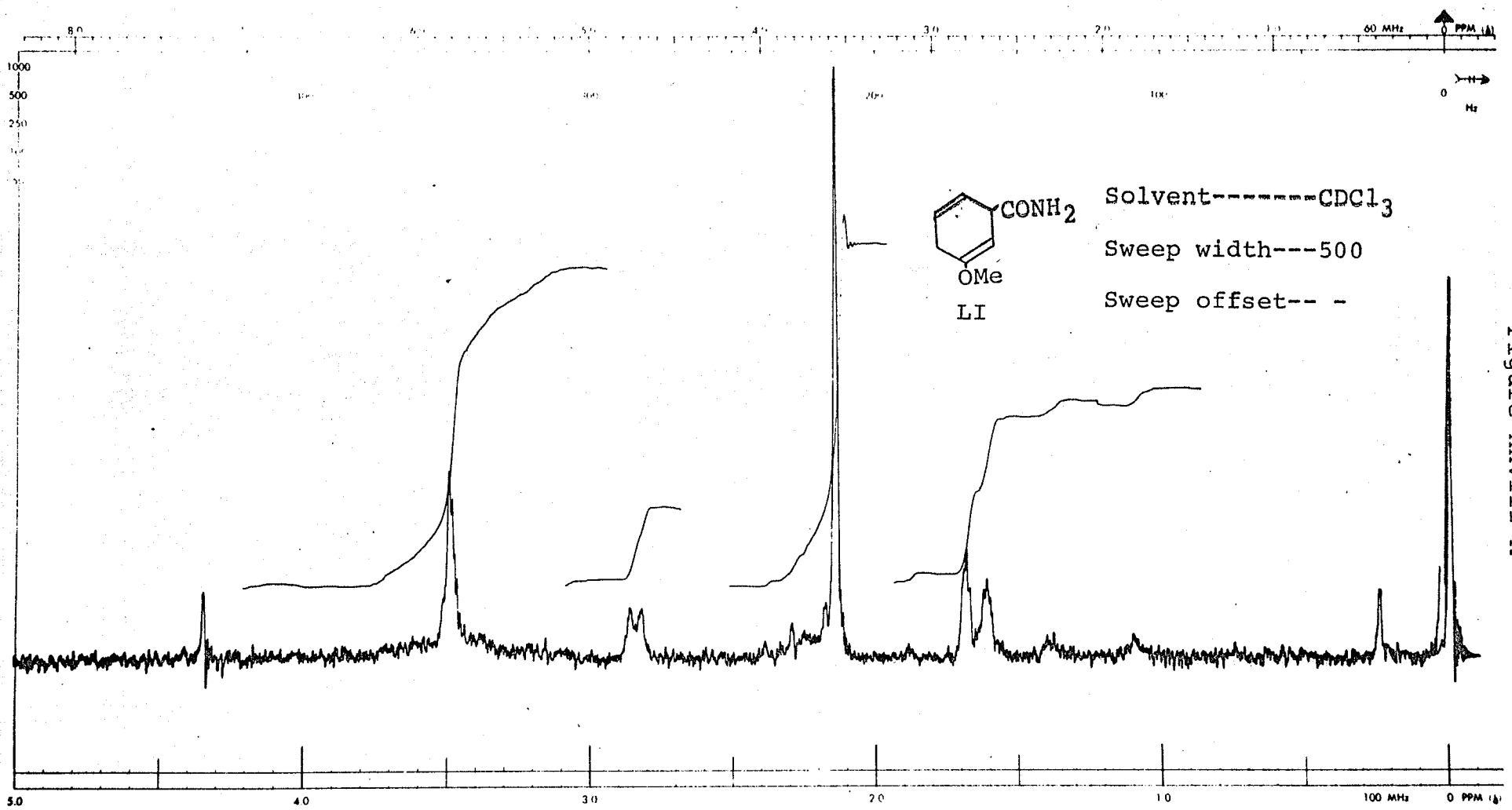



Figure XXVIII A

N.m.r. spectrum of 1-carbamoyl-3-methoxy-1,4-dihydrobenzene

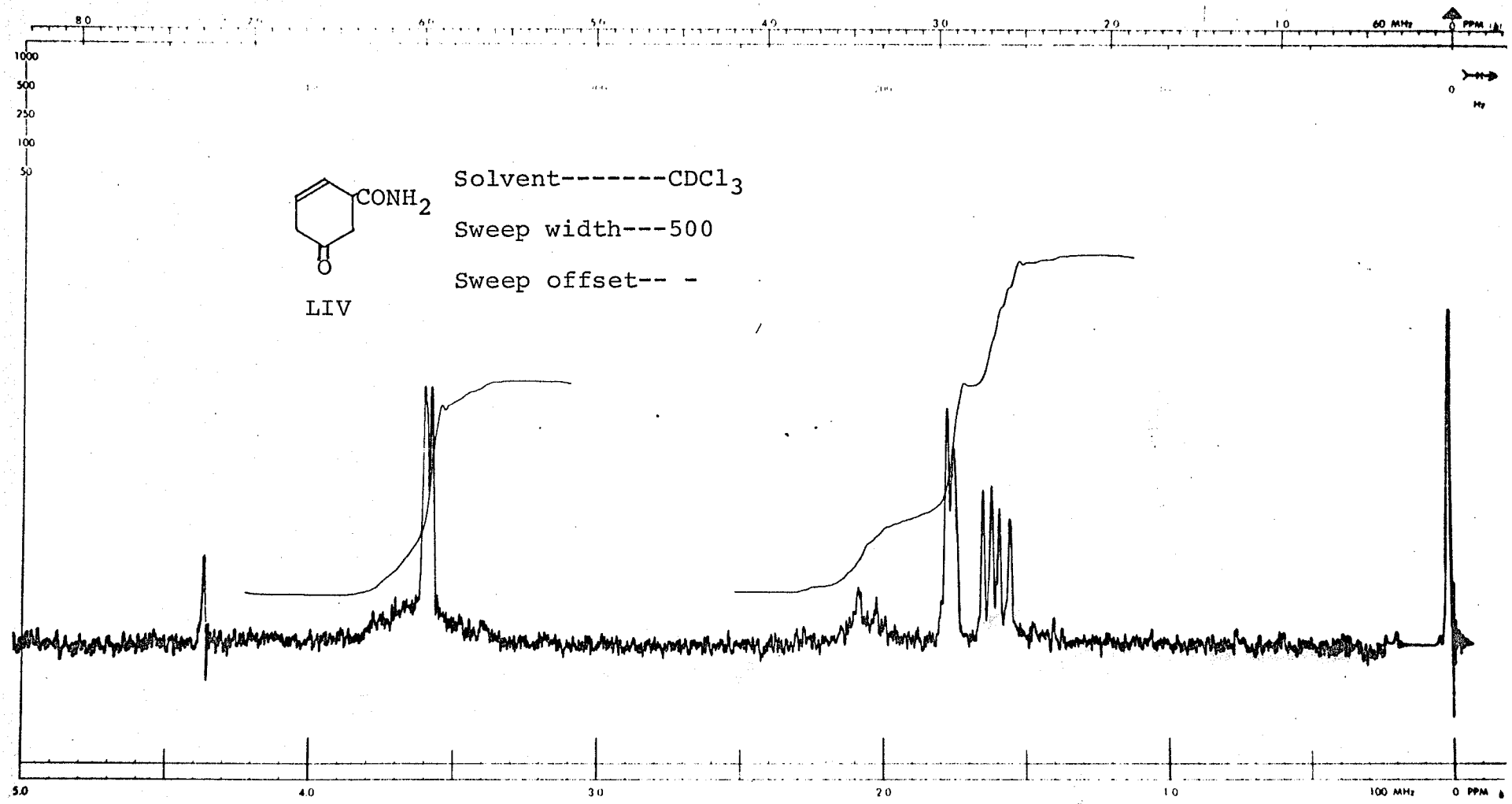



Figure XXIX A

N.m.r. spectrum of 3-oxo-5-cyclohexenyl carboxamide

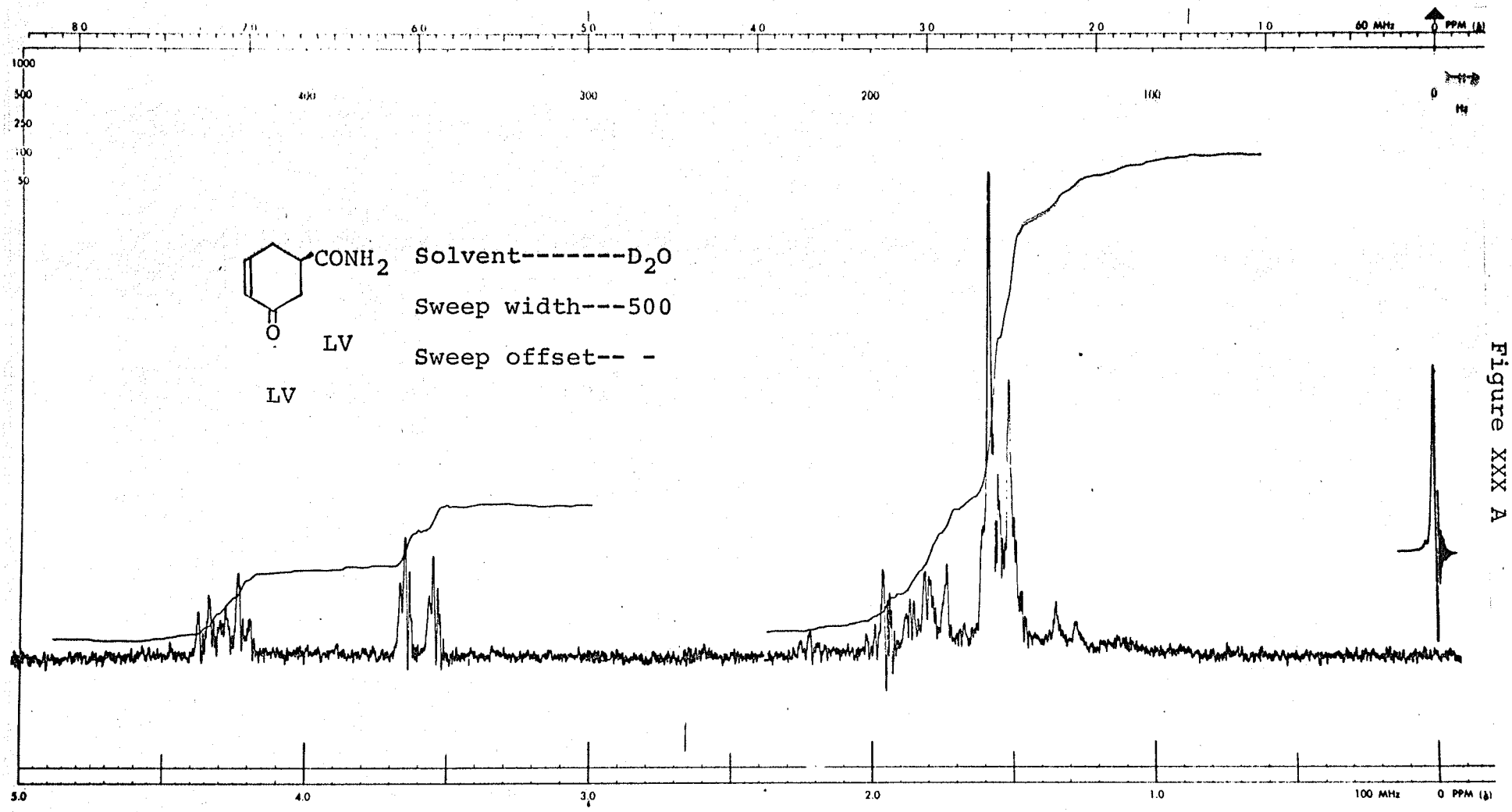



Figure XXX A

N.m.r. spectrum of 3-oxo-4-cyclohexenyl carboxamide

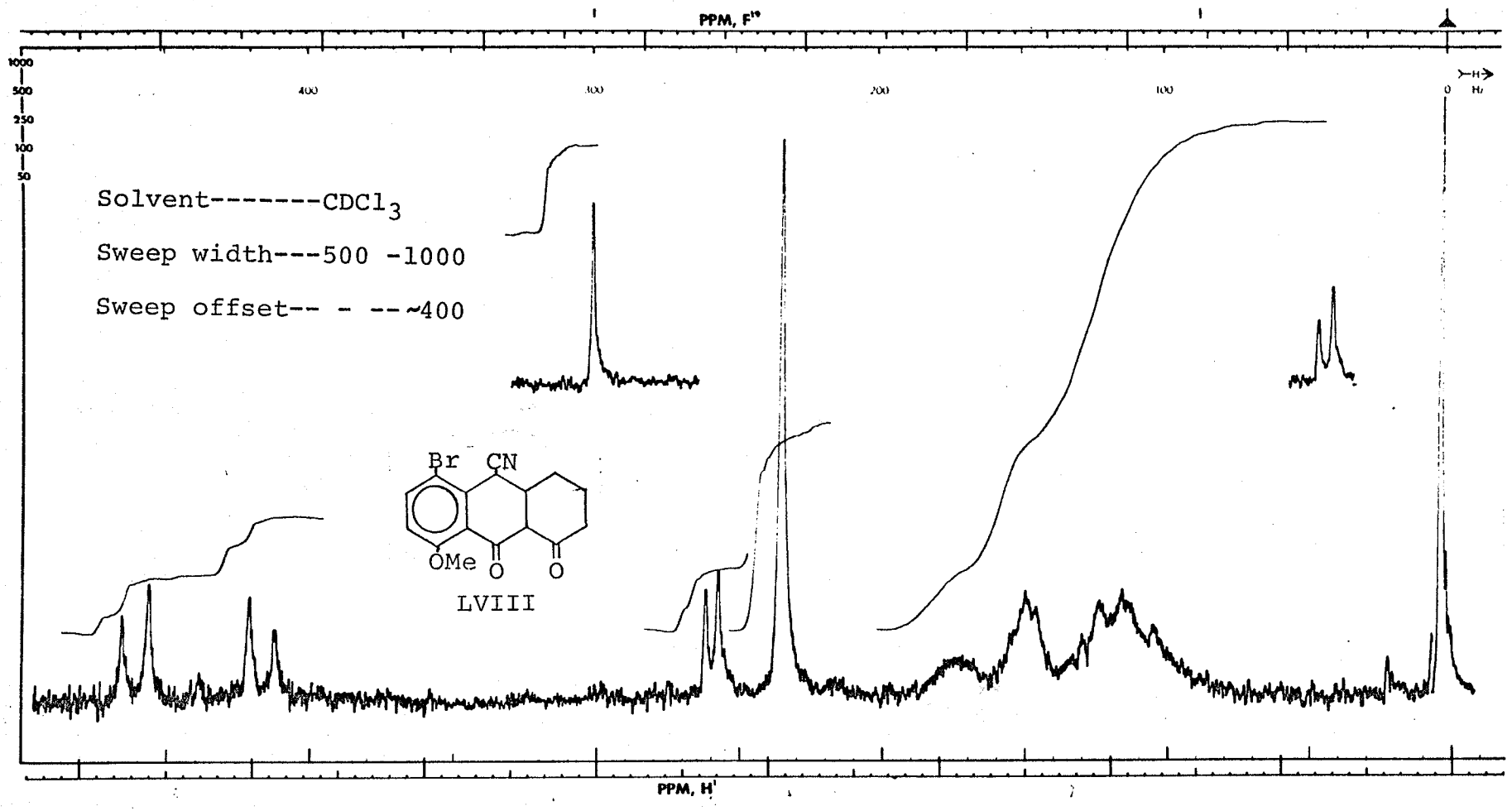



Figure XXXII A

N.m.r. spectrum of 1,2,3,4,4a,9,9a,10-octahydro-4,10-dioxo-5-methoxy-8-bromo-9-cyanoanthracene

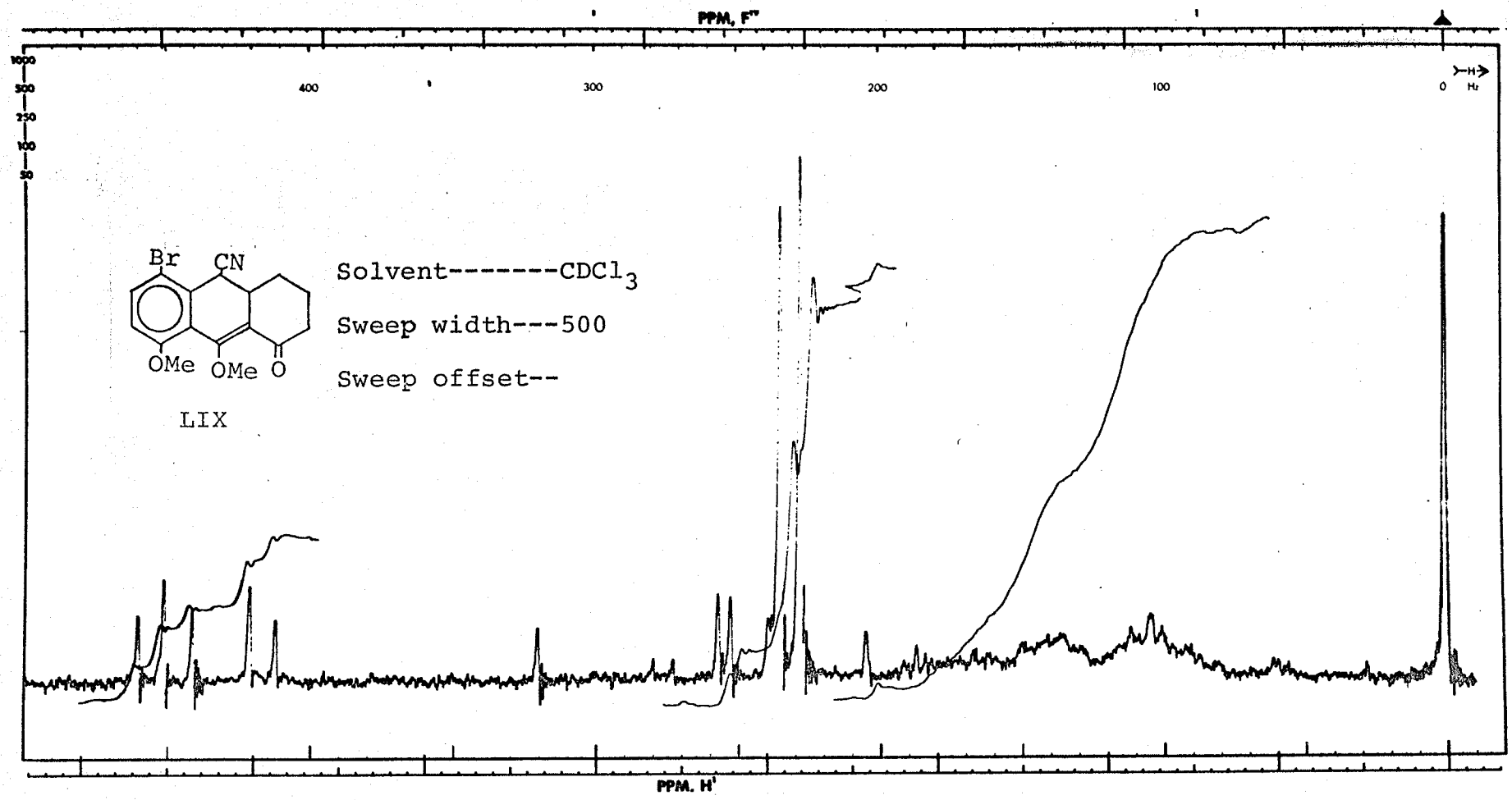



Figure XXXIII A

N.m.r. spectrum of 1,2,3,4,9,9a-hexahydro-4-oxo-5,10-dimethoxy-8-bromo-9-cyanoanthracene

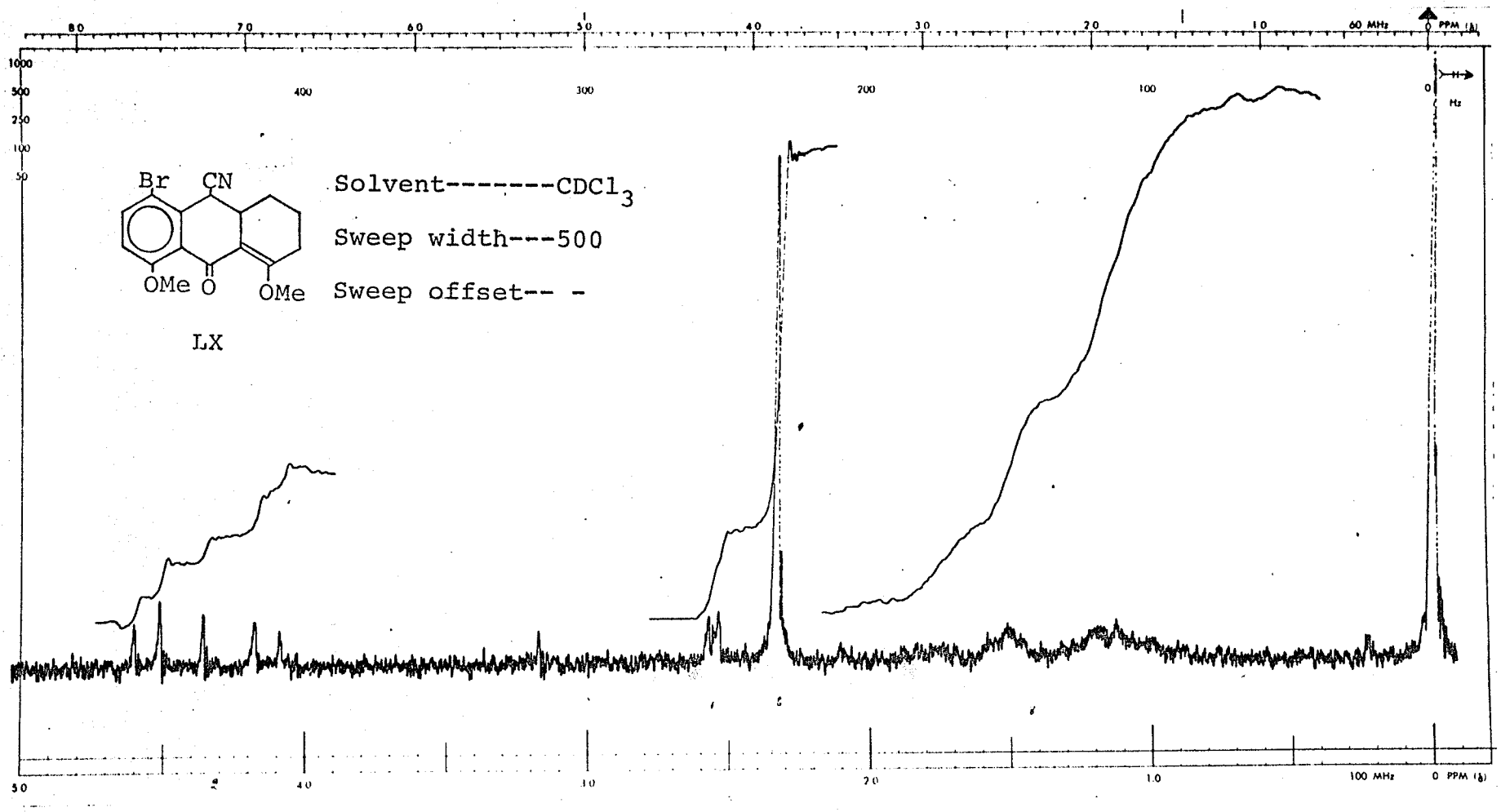



Figure XXXIV A

N.m.r. spectrum of 1,2,3,9,9a,10-hexahydro-4,5-dimethoxy-8-bromo 9-cyano-10-oxoanthracene

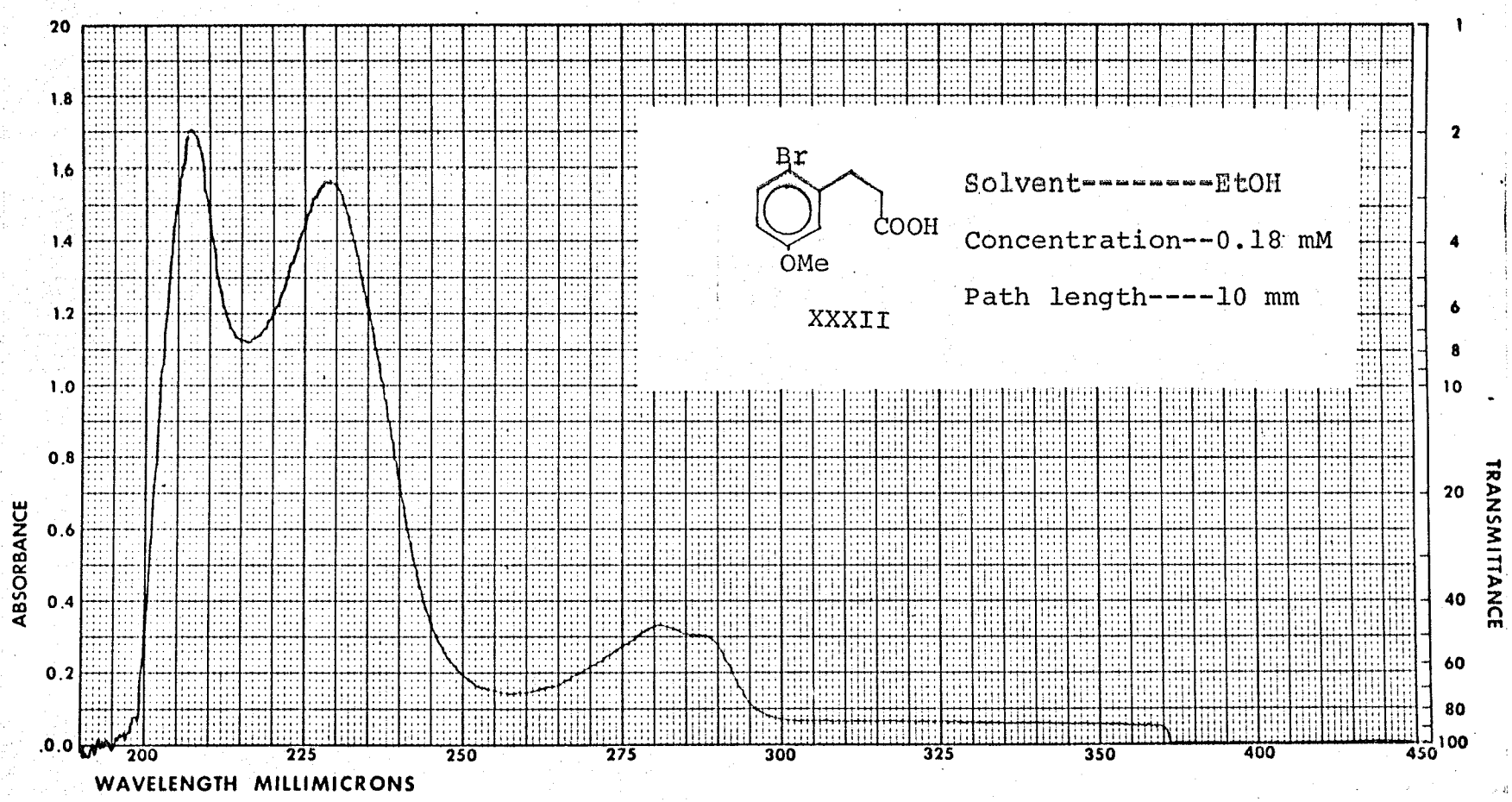



Figure XIII B

U.v. spectrum of β-2-bromo-5-methoxyphenylpropionic acid

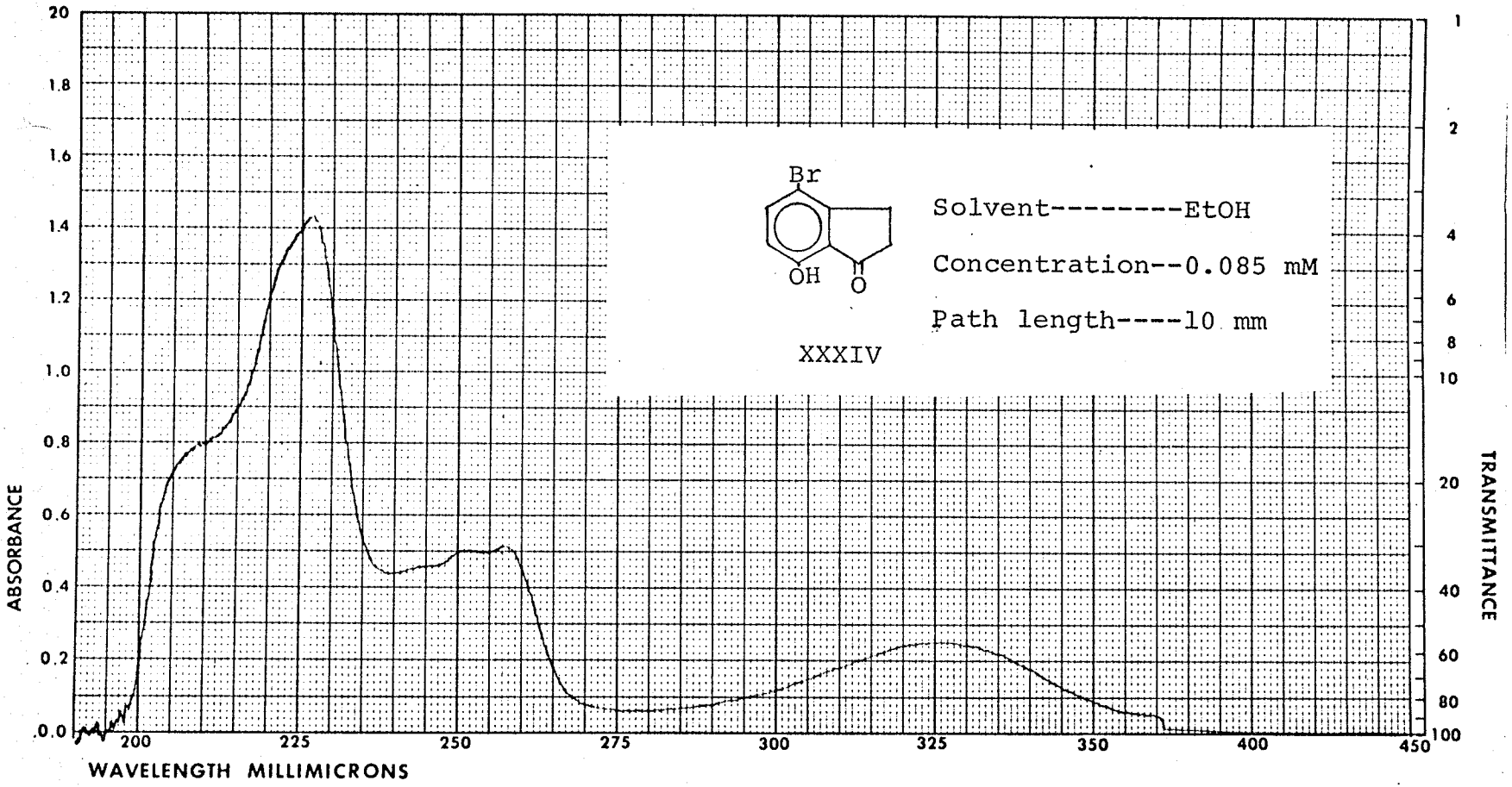



Figure XV B

U.v. spectrum of 4-bromo-7-hydroxyindanone

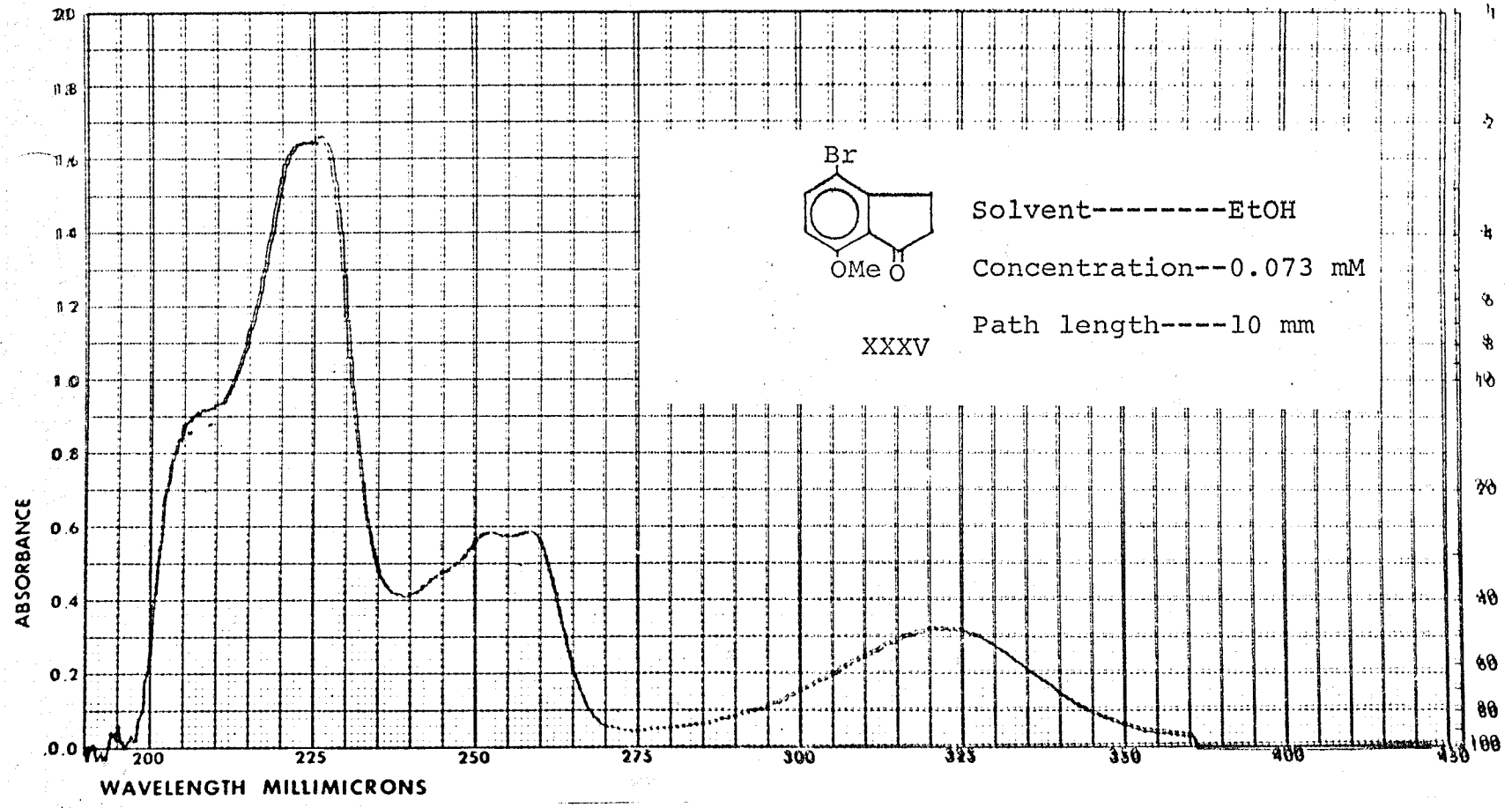



Figure XVI B

U.v. spectrum of 4-bromo-7-methoxy-indanone

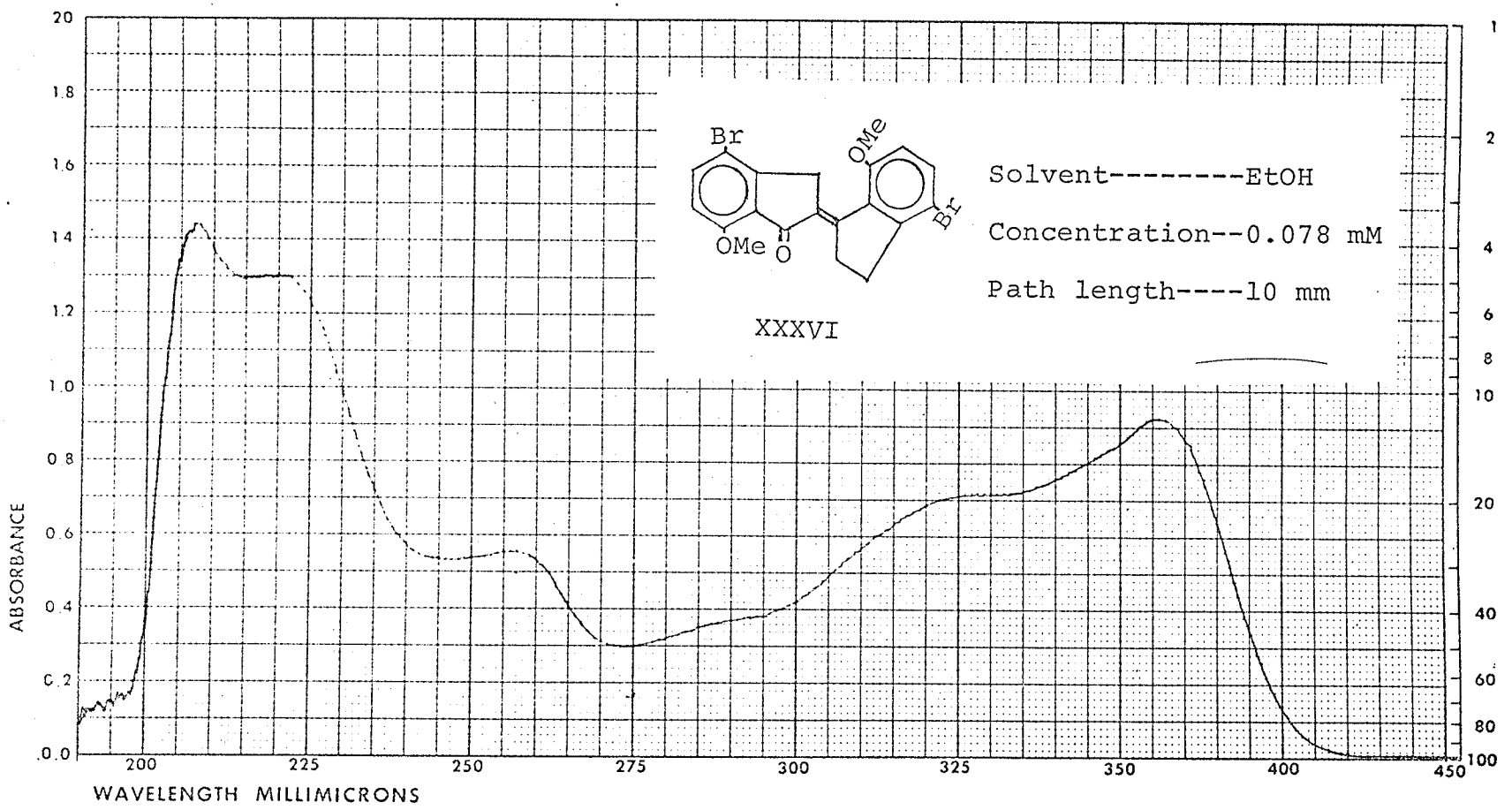



Figure XVII B

U.v. spectrum of 1'-oxo-2,3,3'-trihydro-4,4'-dibromo-7,7'-dimethoxy-1,2'-indenylidene

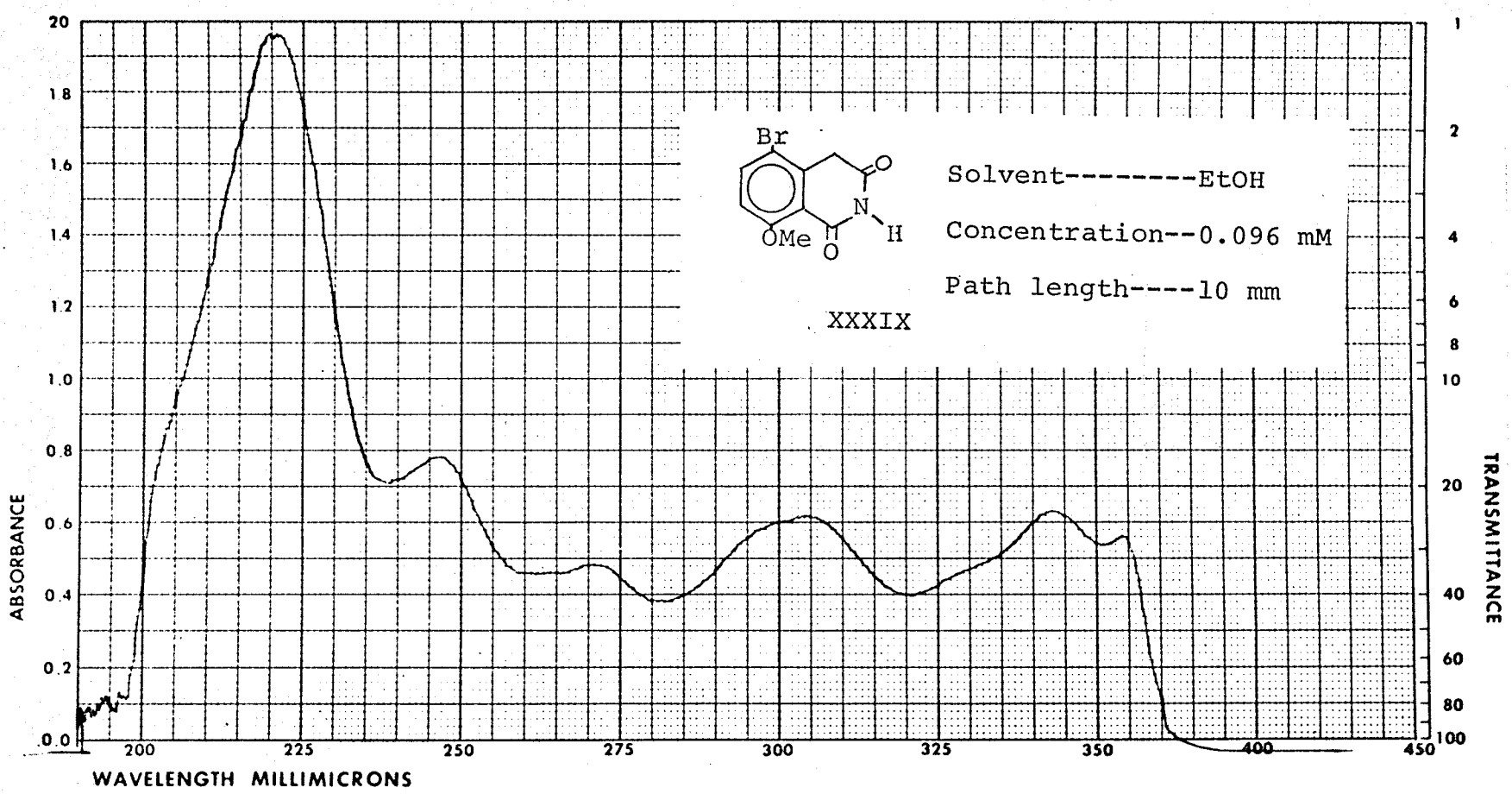
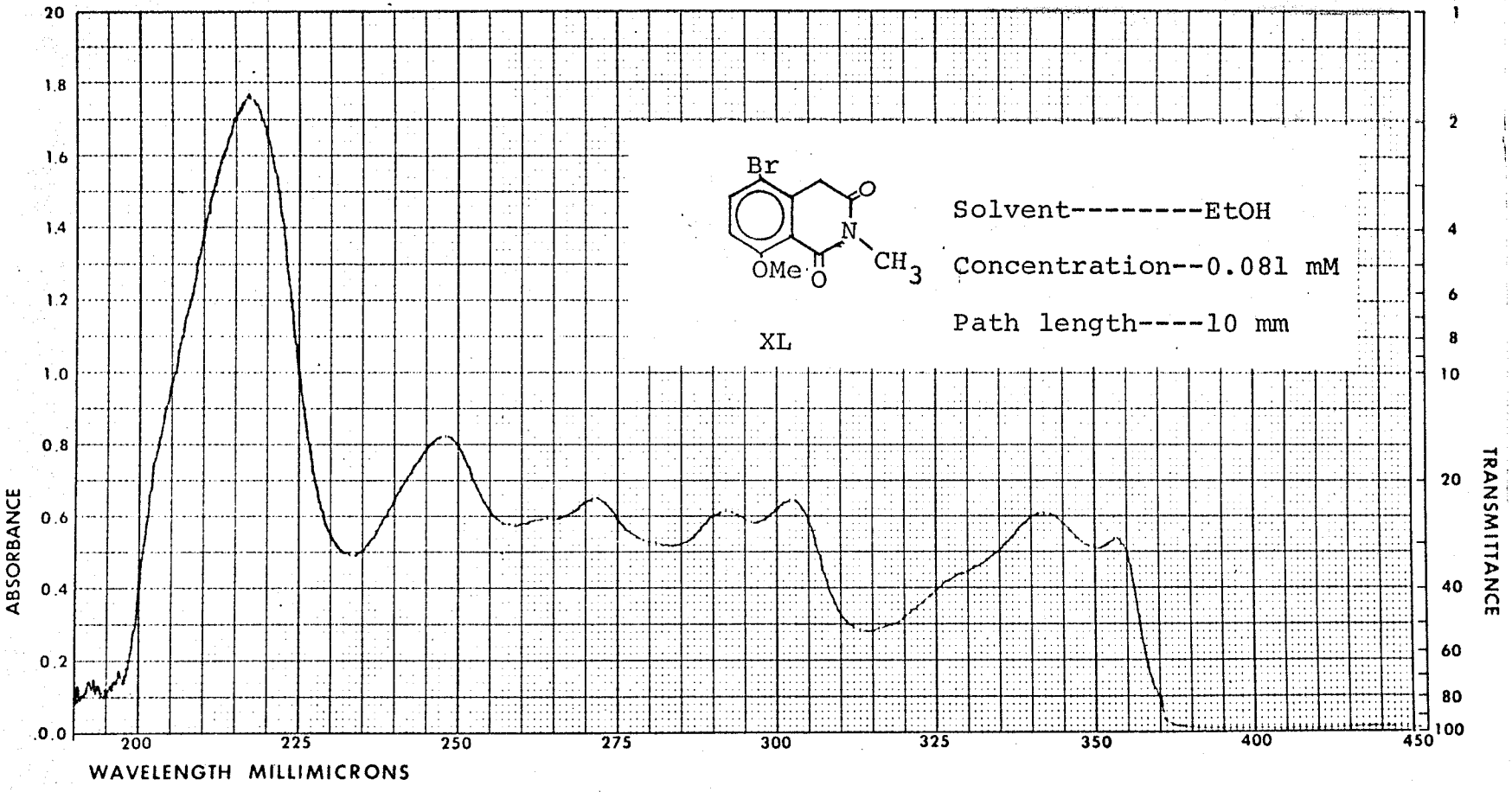



Figure XIX B

U.v. spectrum of 3-bromo-6-methoxyhomophthalimide

Figure XX B




U.v. spectrum of N-methyl-3-bromo-6-methoxyhomophthalimide

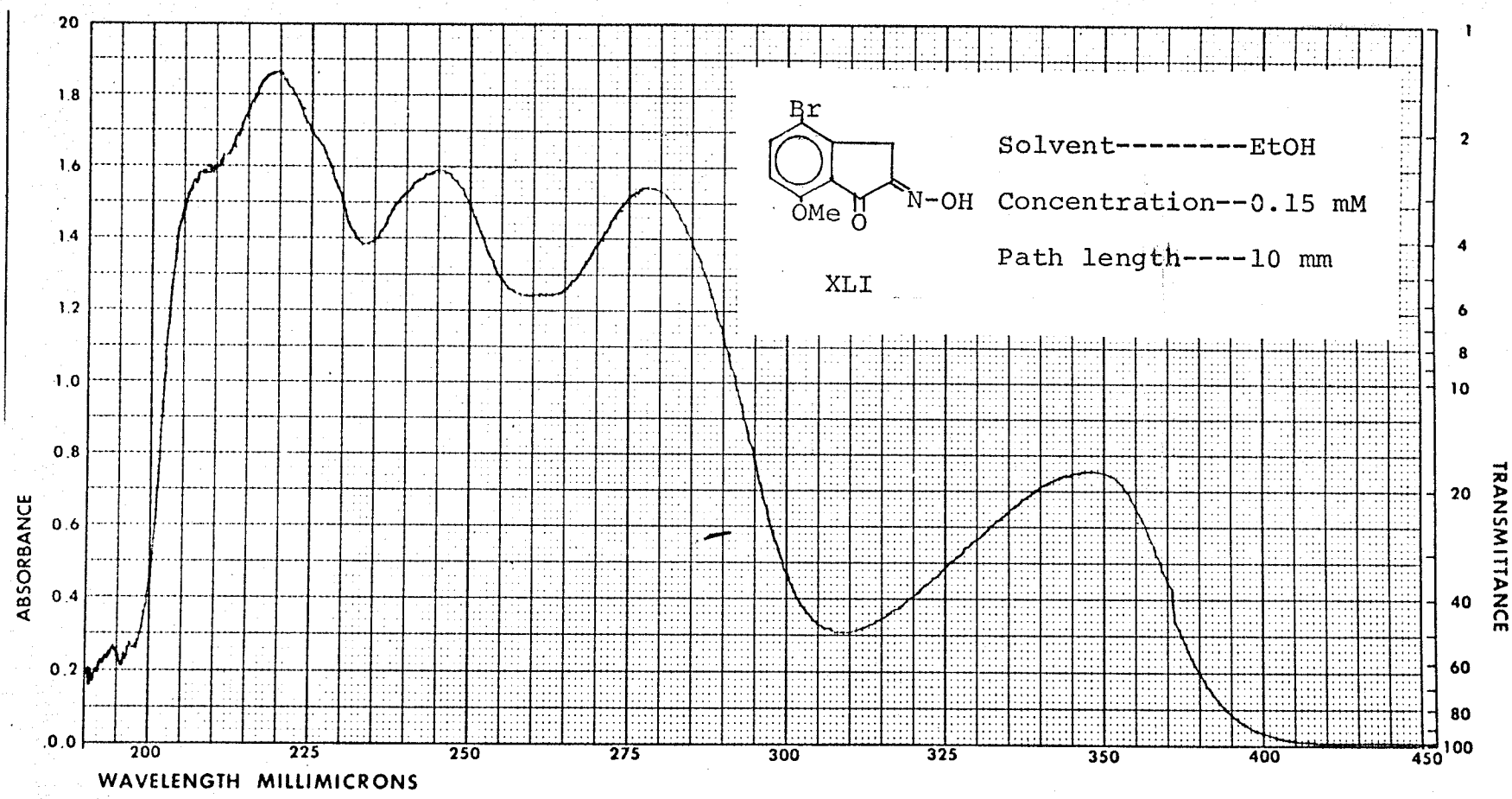



Figure XXI B

U.v. spectrum of 2-oxime-4-bromo-7-methoxy-1,2-indandione

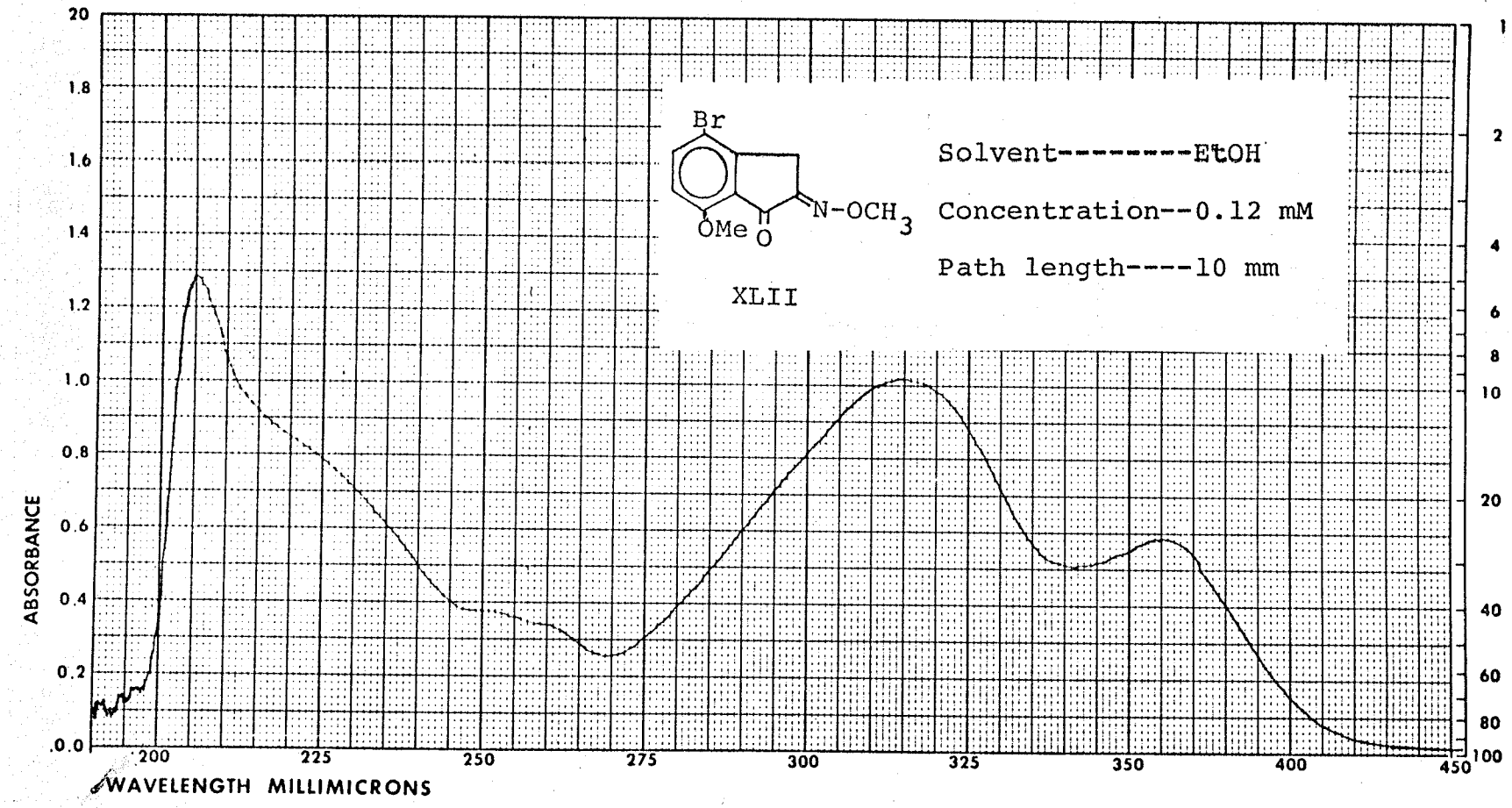
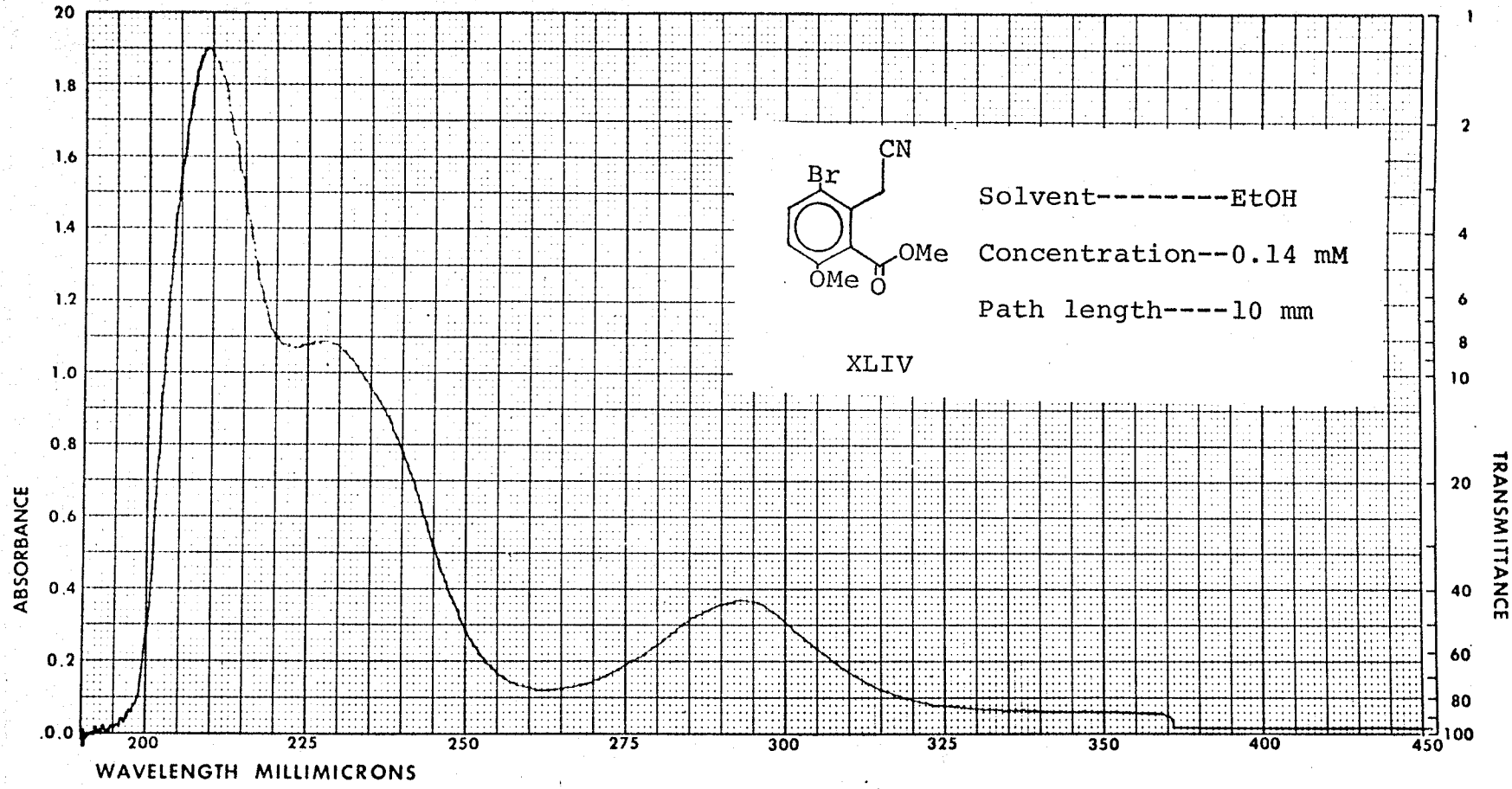



Figure XXII B

U.v. spectrum of 2-methoximino-4-bromo-7-methoxyindanone

Figure XXIV B




U.v. spectrum of 2-bromo-5-methoxy-6-methoxycarbonylphenyl acetonitrile

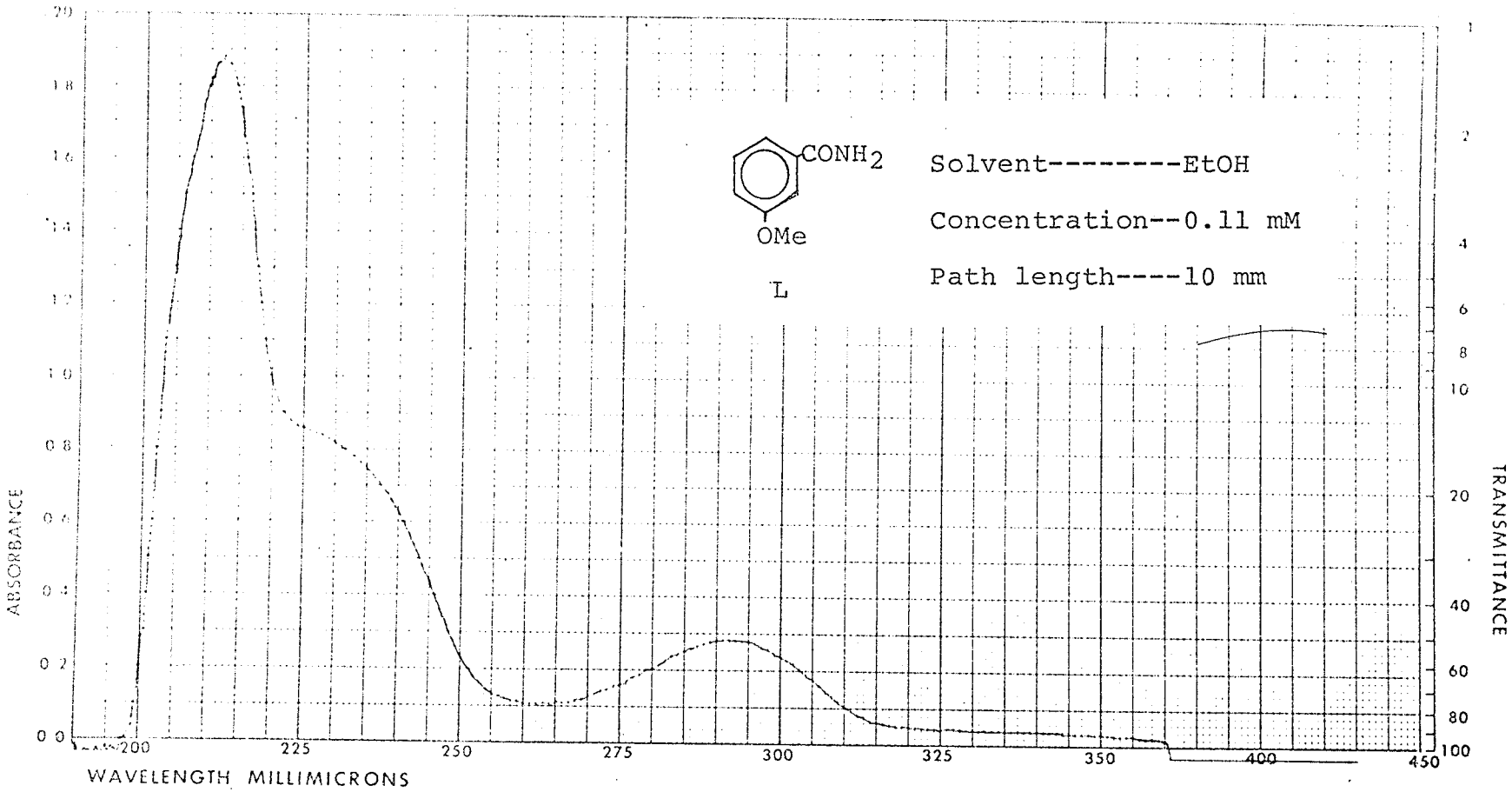
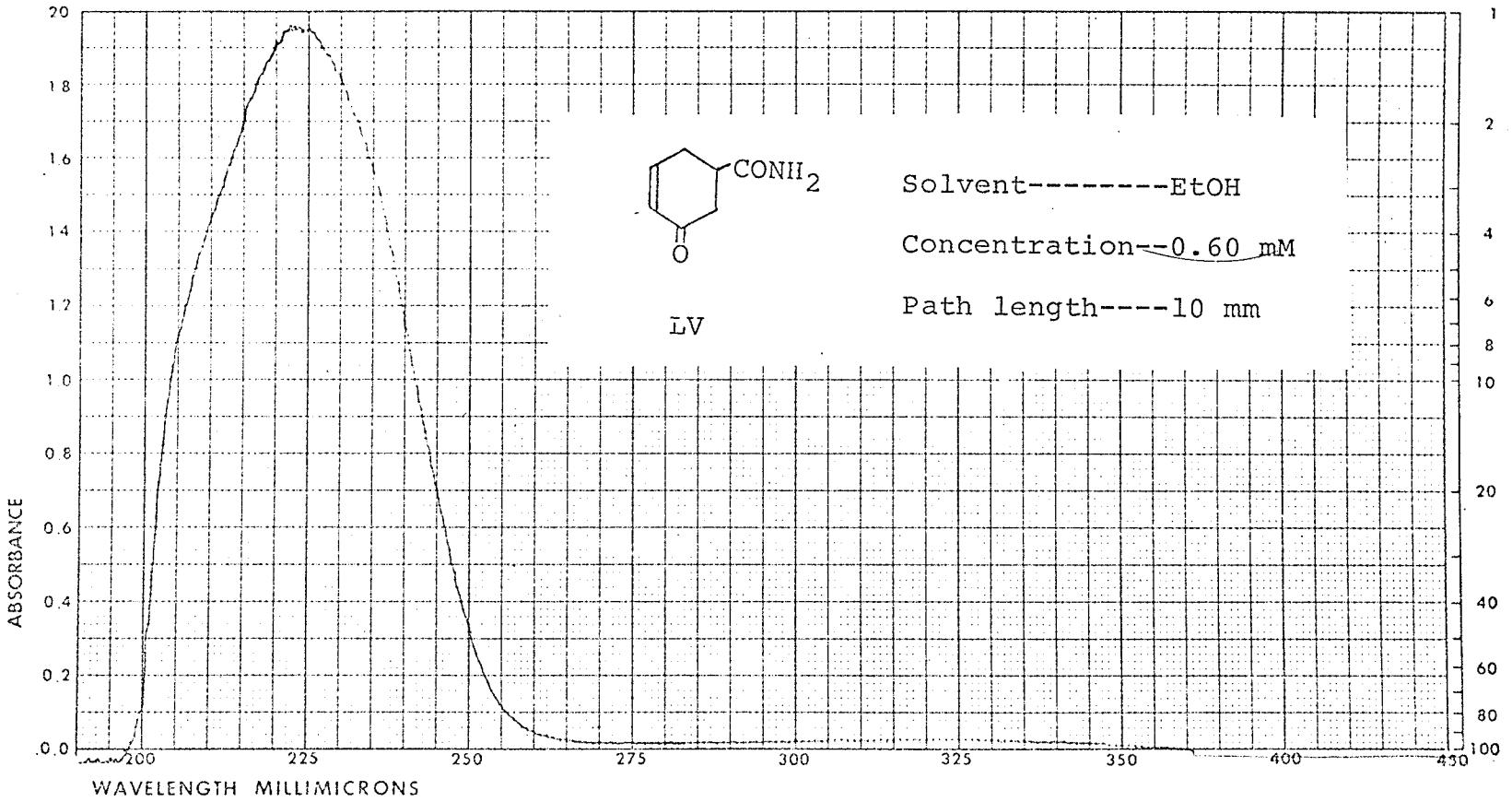



Figure XXVII B

U.v. spectrum of m-methoxybenzamide

Figure XXX B




U.v. spectrum of 3-oxo-4-cyclohexenyl carboxamide

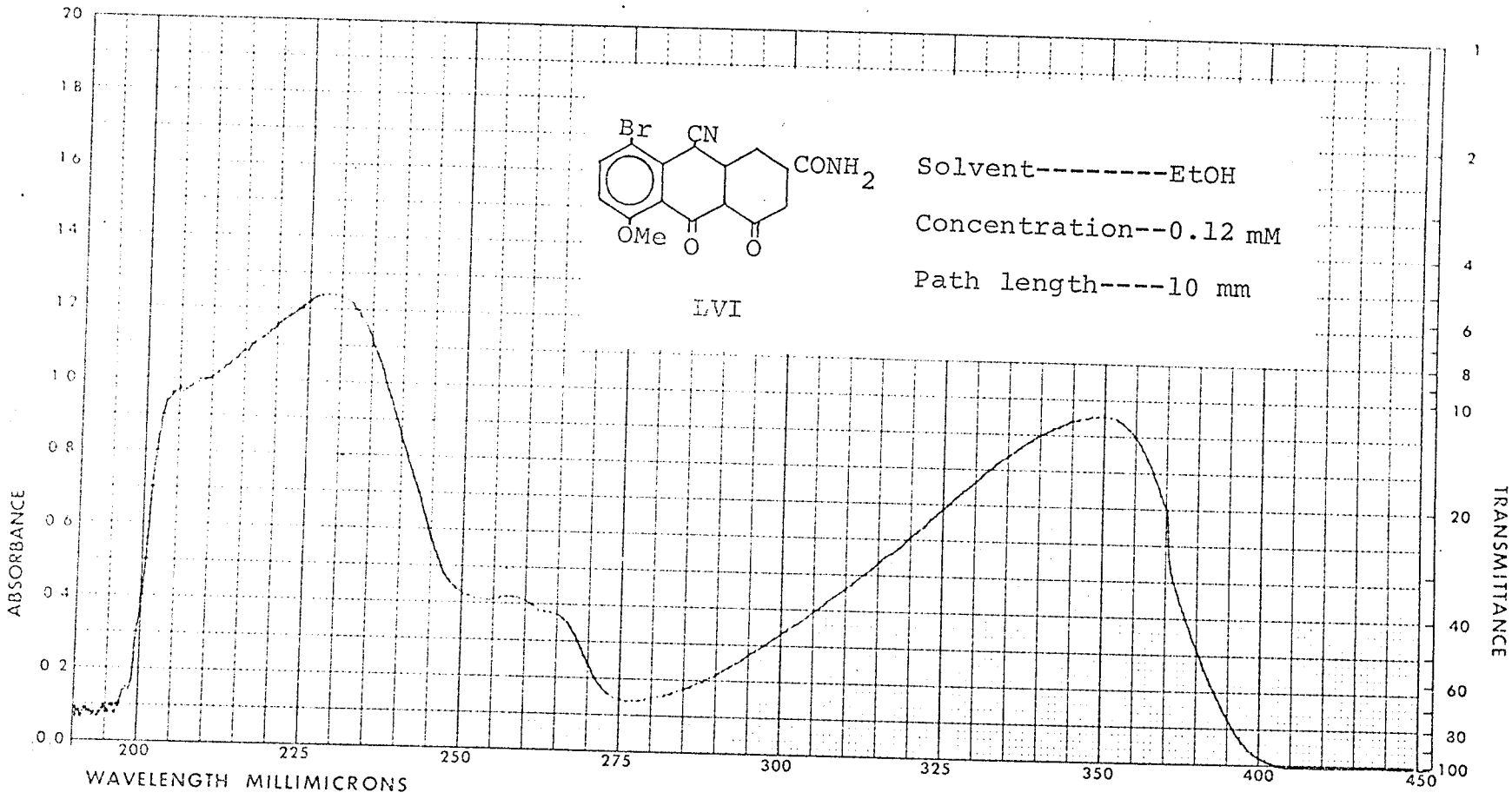
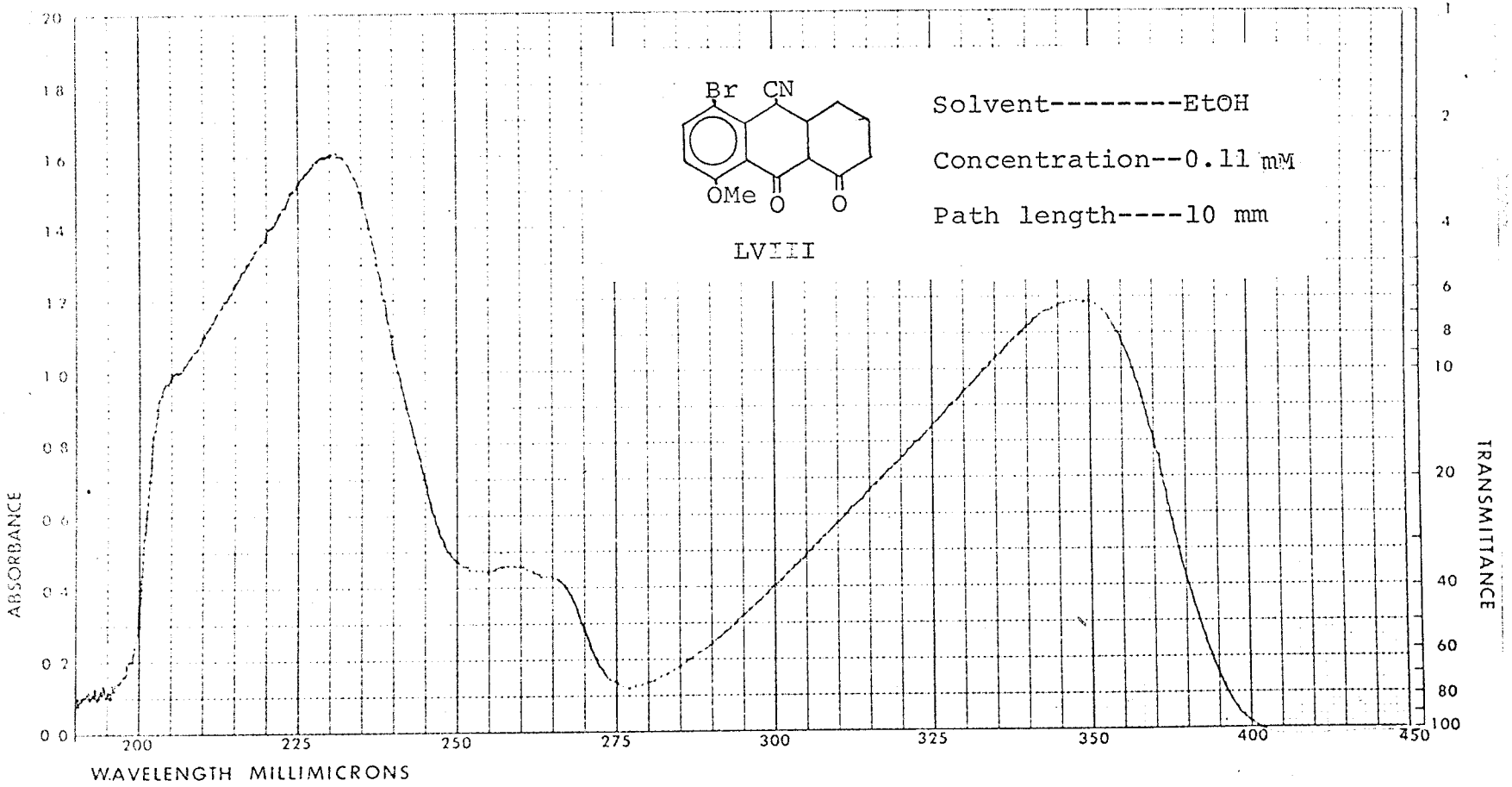



Figure XXXI C

U.v. spectrum of 1,2,3,4,4a,9,9a,10-octahydro-2-carbamoyl-4,10-dioxo-5-methoxy-8-bromo-9-cyanoanthracene

Figure XXXII B




U.v. spectrum of 1,2,3,4,4a,9,9a,10-octahydro-4,10-dioxo-5-methoxy-8-bromo-9-cyanoanthracene

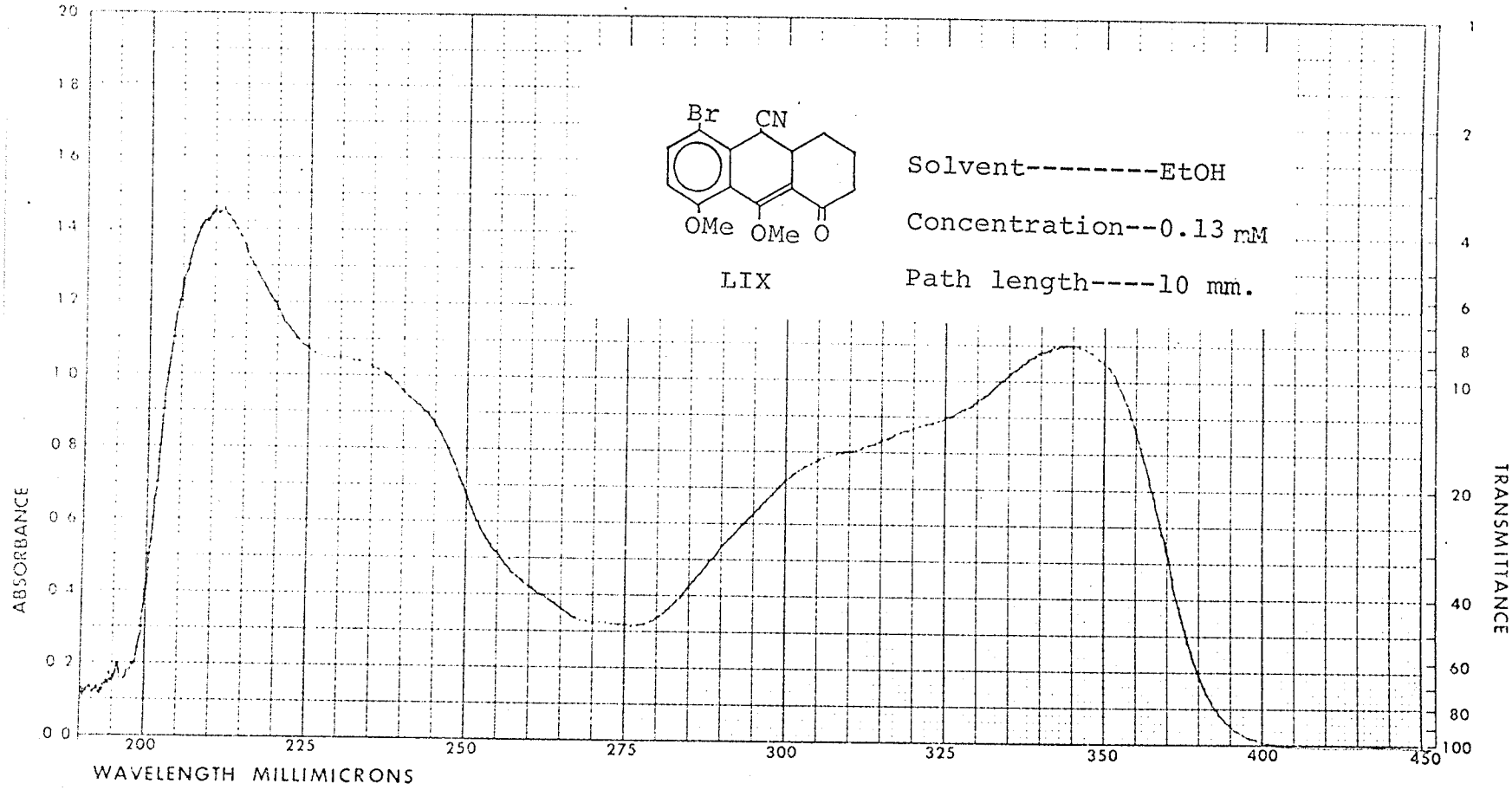



Figure XXXIII B

U.v. spectrum of 1,2,3,4,9,9a-hexahydro-4-oxo-5,10-dimethoxy-8-bromo-9-cyanoanthracene

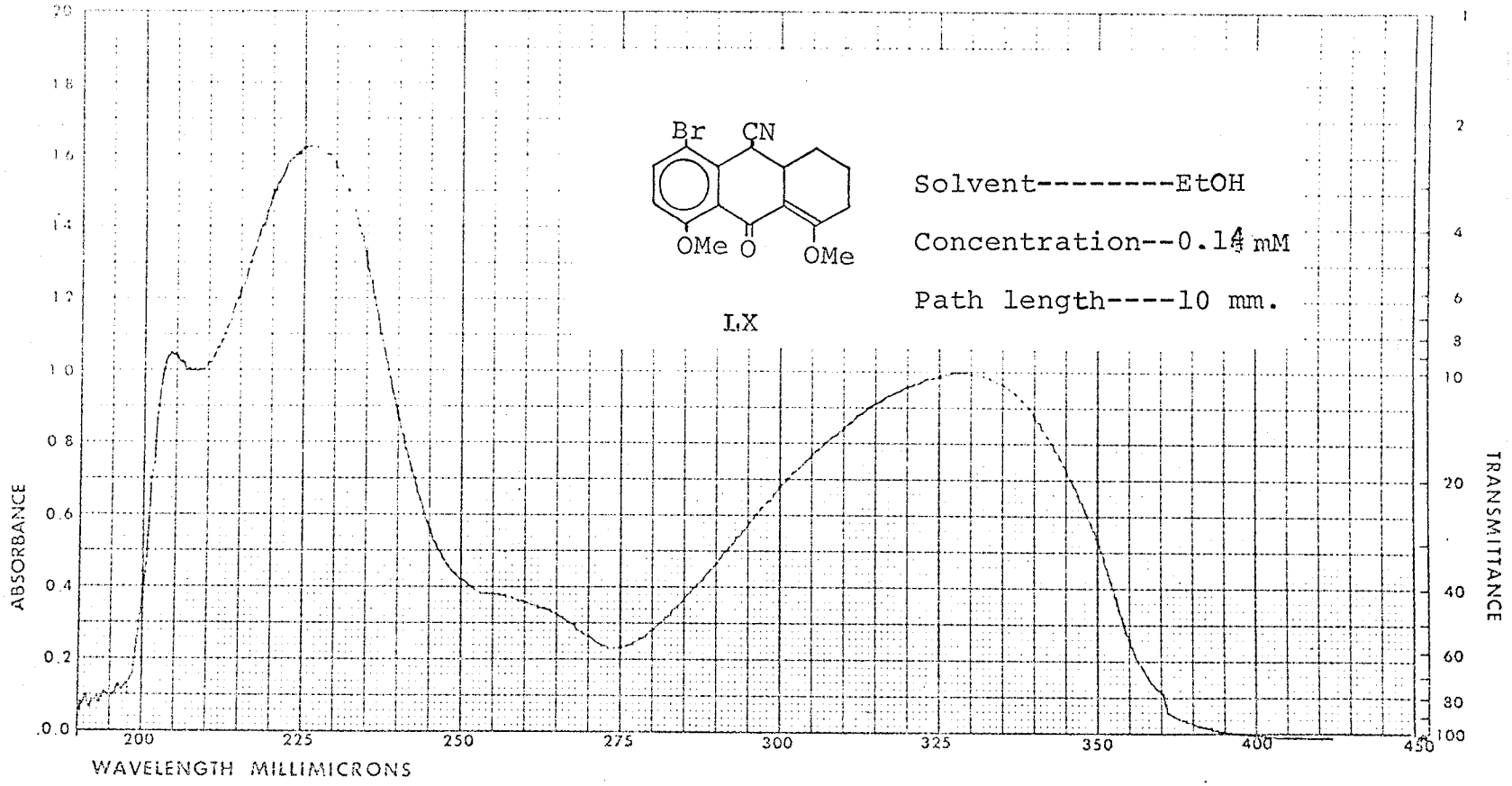
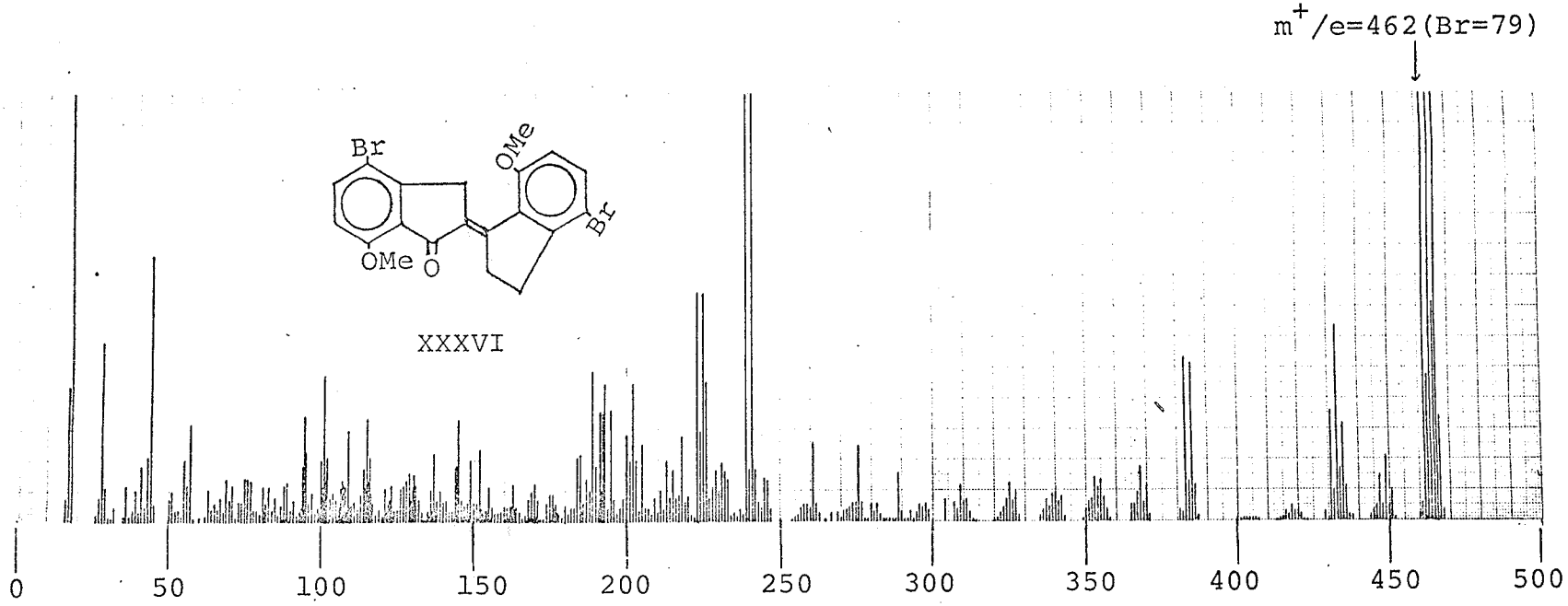



Figure XXXIV B

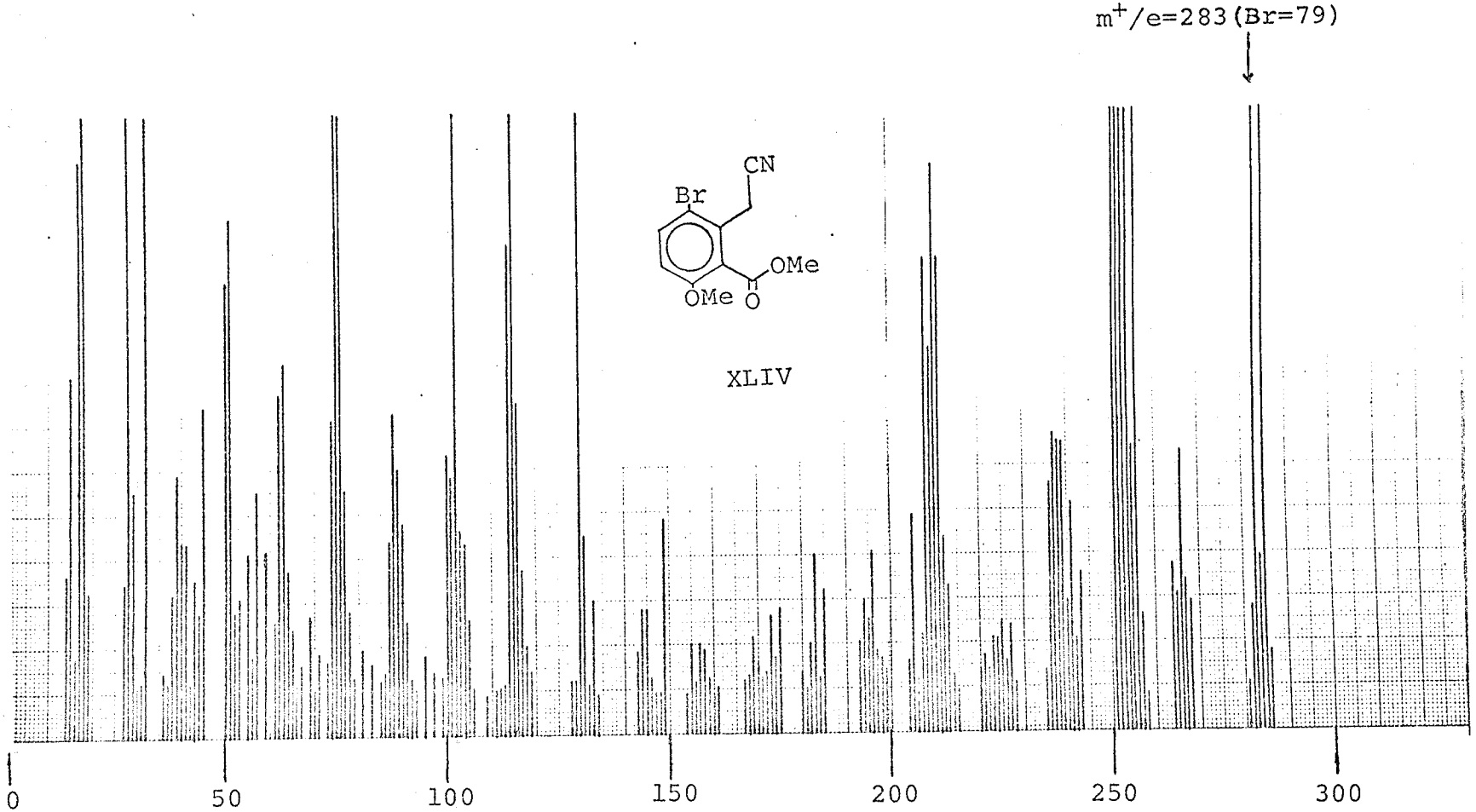
U.v. spectrum of 1,2,3,9,9a,10-hexahydro-4,5-dimethoxy-8-bromo-9-cyano-10-oxoanthracene

Figure XVII C




XXXVI

Mass spectrum of 1'-oxo-2,3,3'-trihydro-4,4'-dibromo-7,7'-dimethoxy-1,2'-indenylidene




Mass spectrum of 2-bromo-5-methoxy-6-methoxycarbonylphenyl acetonitrile

Figure XXIV C

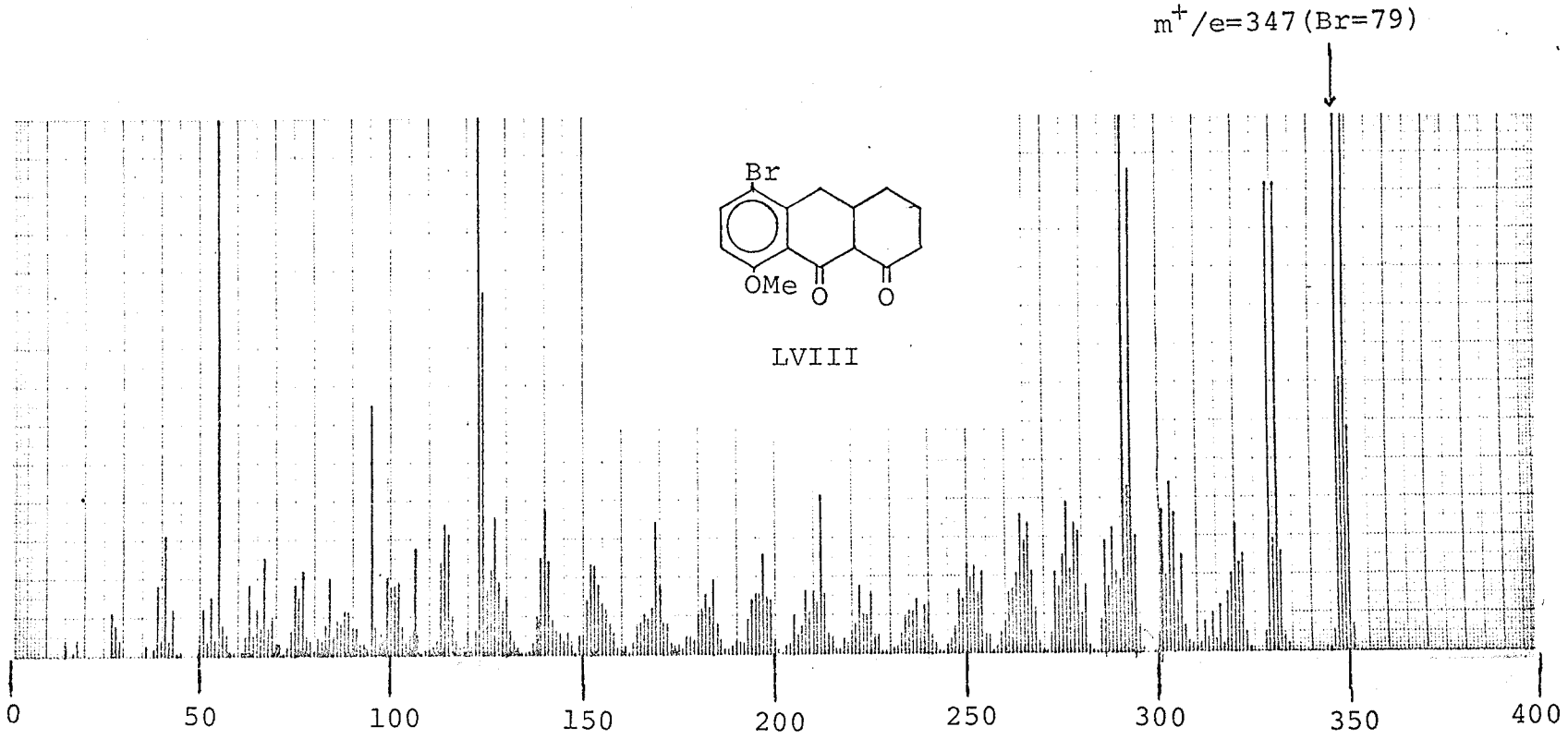



Figure XXXII C

Mass spectrum of 1,2,3,4,4a,9,9a,10-octahydro-4,10-dioxo-

5-methoxy-8-bromo-9-cyanoanthracene

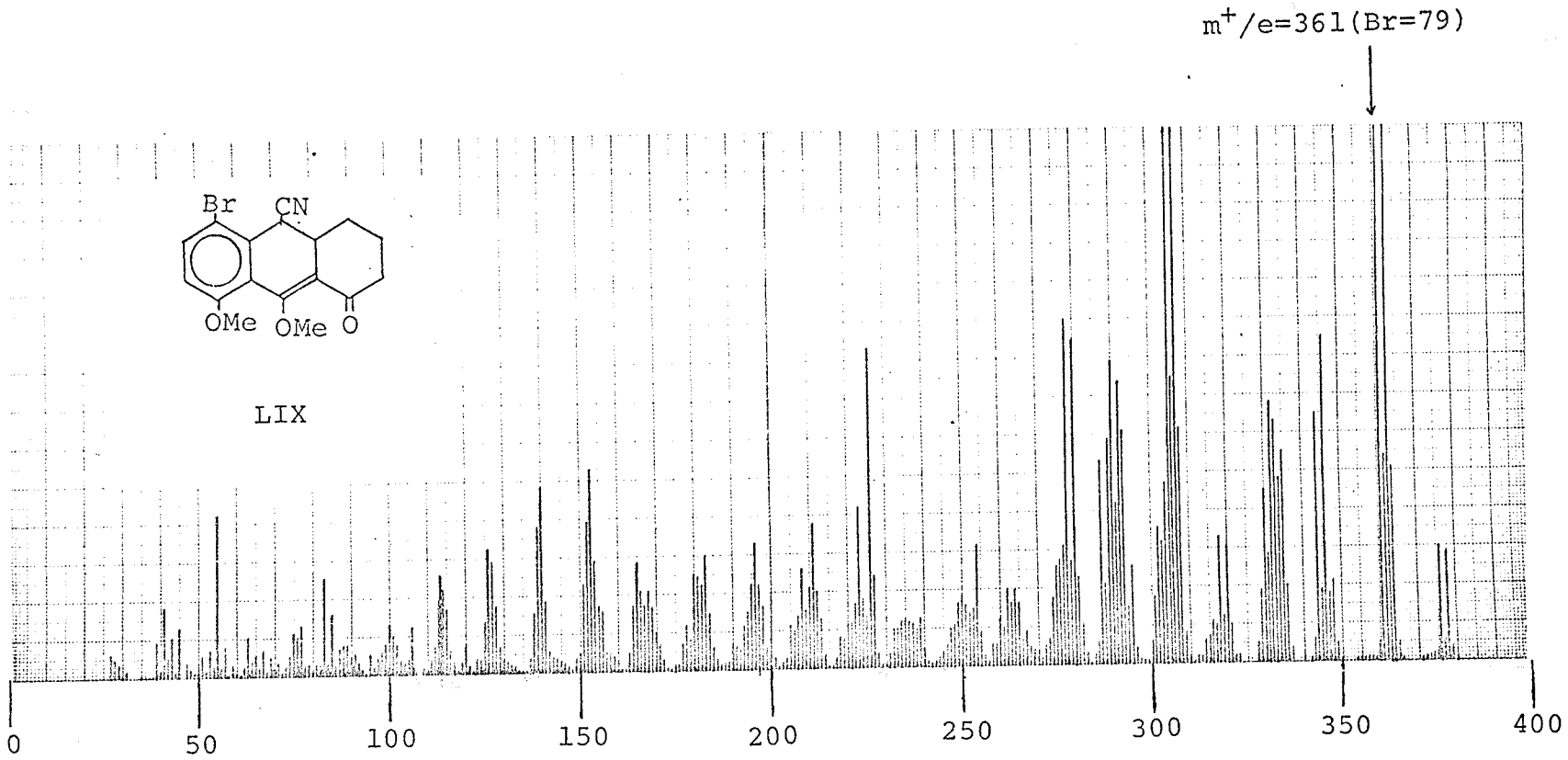



Figure XXXIII C

Mass spectrum of 1,2,3,4,9,9a-hexahydro-4-oxo-5,10-dimethoxy-8-bromo-9-cyanoanthracene

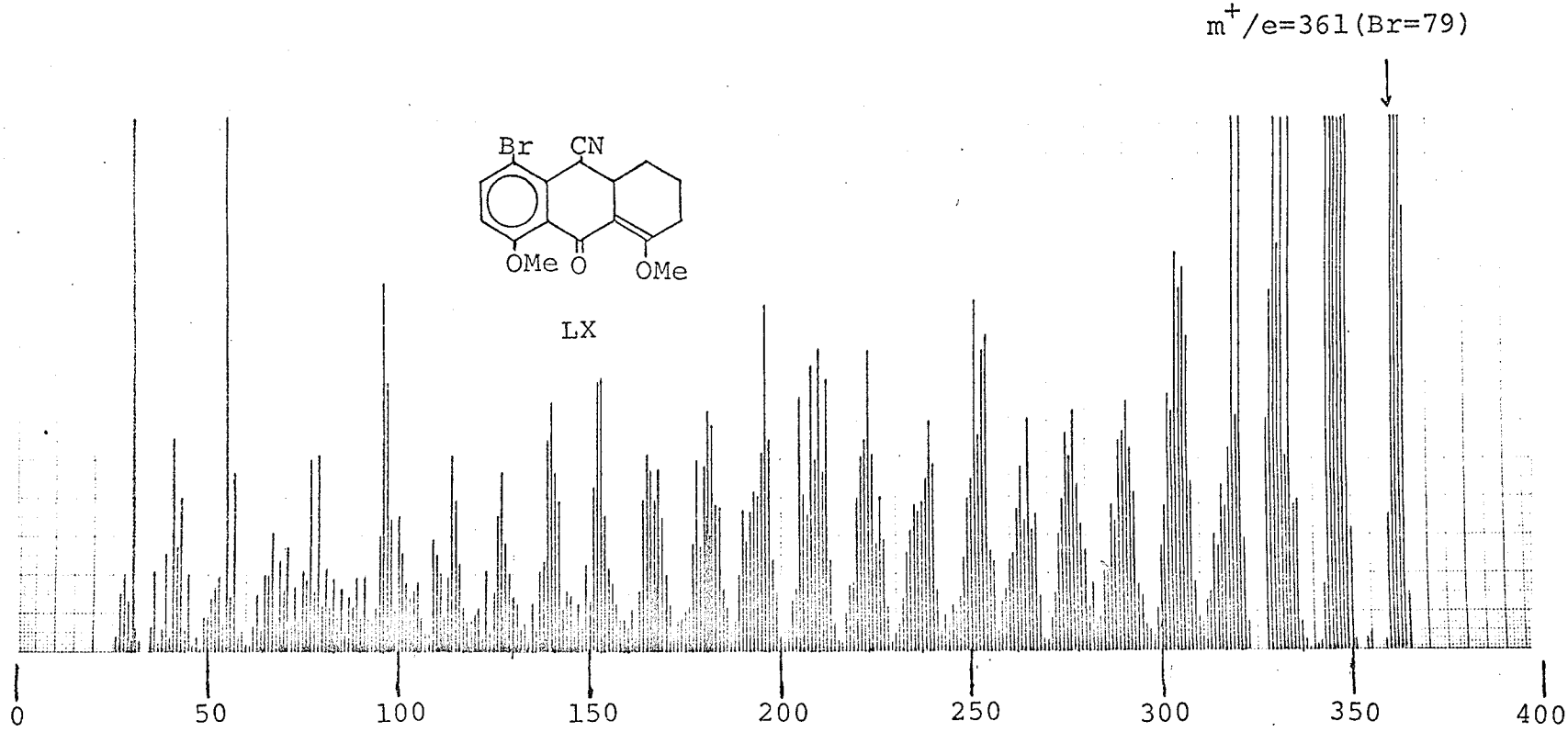



Figure XXXIV C

Mass spectrum of 1,2,3,9,9a,10-hexahydro-4,5-dimethoxy-8-bromo-9-cyano-10-oxoanthracene

## REFERENCES


1. A. Fleming, Br.J. Exp. Path 10, 226, 1929
2. E.P. Abraham, E. Chain, C.M. Fletcher, A.D.Gardner, N.G. Heatley, M.A. Jennings, H.W. Florey, Lancet II, (VII), 177, 1941.
3. R.M. Evans, The Chem. of the Antibiotics used in Medicines, Pergammon Press 1965.
4. B.M. Duggar, Ann. of N.Y. Acad. of Sci. 51, 177, 1948 Quoted from ref.6
5. M. Barber, Y.P. Garrod, Antibiotics and Chemotherapy, E & S. Livingstone Ltd. 1963
6. G.C. Barrett, J. Pharm. Sci. 52, 309, 1963
7. J.H. Booth, J. Morton, J.P. Petisi, R.G. Wilkinson, J.G. Williams, JACS 75, 4621, 1953
8. Y.G. Connover, W.J. Moreland, A.R. English, C.R. Stephens, F.J. Pilgrim, JACS 75, 4622, 1953
9. P.P. Miniri, M.C. Firman, A.G. Minstretta, A. Abbey, C.E. Bricker, N.E. Rigler, H. Sokol, Antibiotics Annual 1953-4. Ed. H. Welch, Med. Encyclopedia Inc. New York, N.Y. p.81
10. A.C. Finley, G.L. Hobby, S.Y. Pan, P.P. Regna, J.B. Routien, D.B. Sealey, G.M. Schull, B.A. Sobin, I.A. Solomons, J.W. Vincon, J.H. Kane, Science 111, 85, 1950.
11. J.R.D. McCormick, N.O. Sjolander, U.Hirsh, E.R.Jensen, A.P. Doerschuck, JACS 79, 456, 1957
12. A.P. Doerschuck, J.R.D.McCormick, J.J. Goodman, S.A. Szumski, J.A. Growich, P.A. Miller, B.A. Bitler, E.R.

Jensen,M.A.Petty,A.S.Phelps,JACS 78, 1508, 1956.

13. D.L.J. Clive, Quart. Rev. 22, 435, 1968

14. H. Muxfeld, R. Bangut, Fortschritte, d. Org. Naturstoffe, 21, 80, 1963

15. J. Money, A.I. Scott, Progr. in Org. Chem, 7,1, 1968

16. F.A. Hochstein, C.R. Stephens, L.H. Connover, P.P. Regna, R. Pasternak, P.M. Gordon, F.J. Pilgrim, K.J. Brunnings, R.B. Woodward, JACS 75, 5455, 1953

17. Y. Takeuchi, M.I. Buerger, Proc. Nat. Acad. Sci. (USA) 46, 1366, 1960.

18. C.R. Stephens, L.H. Connover, R. Pasternack, F.A. Hochstein, W.L. Moreland, P.P. Regna, F.J. Pilgrim, K.J. Brunings, R.B. Woodward, JACS 76, 3568, 1954

19. C.R. Stephens, L.H. Connover, F.A. Hochstein, P.P. Regna, F.J. Pilgrim, K.J. Brunings, R.B. Woodward, JACS 74, 4976, 1952

20. S. Hirokawa, Y. Okaya, F.M. Lovell, R. Pepinski, Abstr. Am. Cryst. Assoc. Meetings, Cornell Univ. Ithaca, N.Y. July 1959, p. 44 (Quoted from 13).

21. H. Muxfeld, Angew. Chemie (Intnl. Ed) 1, 372, 1962.

22. L.H. Connover, K. Butler, J.D. Johnson, J.J. Korst, R.B. Woodward, JACS 84, 3222, 1962.

23. J.J. Korst, J.D. Johnson, K. Butler, E.J. Bianco, L.H. Connover, R.B. Woodward, JACS 90, 439, 1968.

24. H. Muxfeld, S. tz Hardtmann, F. Kathawala, E. Vedejs, J.B. Mooberry, JACS 90, 6534, 1968.

25. Technology of Tetracyclines, Biochem. ref. Series, Vol.I

Evans Richard and Castleman,Ed. Quad. Press N.Y. 1968.

26. J. Buccini , Ph.D. thesis, U of M, 1970.

27. A. Werner, A. Piquet, Ber. 37, 4295, 1904.

28. R.L. Augustine, Catalytic Hydrogenation, Marcel Dekker Inc. N.Y. 1965.

29. G.S. Skinner, JACS 46, 731, 1924.

30. G.A. Mina, L. Rateb, G. Soliman, J. Chem. Soc. 4234, 1962.

31. I. Fleming, D.H.Williams, Spectroscopic Methods in Organic Chem. McGraw Hill, 1966, p.20

32. R.W. Crecely, K.W. McKracken, J.H. Goldstein, Tetrahedron, 25, 877, 1969.

33. V. Gutman, Ed. Halogen Chem. Vol. I, Acad. Press, 1967, p.8

34. J.R. Dyer, Application of Absorption Spectroscopy of Organic Compounds. Prentice Hall Inc. Englewood Cliffs, N.J. 1965,(a) p.44, (b) p.85.

35. R.M. Silverstein, G.C. Bassler, Spectrometric Identification of Organic Compounds, 2nd. Ed. John Wiley & Sons, Inc. N.Y. 1968 (a) p.90, (b) p.87, (c) p.81,

36. Organic Reactions, Vol. II, John Wiley & Sons, Inc. New York, 1944, p.160.

37. R.V. Heinzelmann, H.G. Kolloff, J.H. Hunter, JACS, 70, 1380, 1946.

38. V.C. Farmer, N.F. Hayes, R.H. Thomson, J. Chem. Soc. 3600 1956,

39. C.A. Grob, O. Wiesbach, Helv. Chim. Acta 44, 1736, 1961.

40. A.H. Blatt, R.P. Barnes, JACS 56, 1148, 1934.

41. A.I. Vogel, Textbook of Practical Organic Chemistry, Longman's 3rd. ed. 1967, p.669.

42. H.O. House, Modern Synthetic Reactions, W.A. Benjamin Inc. 1965. (a) p.67, (b) p.66, (c) p.68

43. A.J. Birch, J. Chem. Soc. 430, 1944.

44. M.E. Kuehne, B.F. Lambert, JACS 81, 4278, 1959.

45. O.L. Chapman, p. Fitton, JACS 85, 41, 1963.

46. M. Karplus, J. Chem. Phys. 30, 11, 1959.

47. I. Chang, M.Sc. thesis, U of M 1970.

48. D.N.C. Awang, S. Wolfe, Can. J. Chem. 47, 706, 1969.

49. C.K. Ingold, Structure & Mechanism in Org. Chem., Cornell Uni. Press, 1953, Chap. VIII.

50. H. Kranch, W. Kunz, Organic Name Reactions, J. Wiley & Sons Inc. 1964, p.231.

51. J. Hine, Physical Organic Chemistry, McGraw Hill Book Co. Inc. New York, 1962, Chapt. 8

52. R. Breslow, S. Garrett, T. Kaplan, D. Lafolette, JACS 90, 4051, 1968.

53, J, H. Gardner, T.F. McDonnell, JACS 63, 2279, 194.

54. R.A. Barnes, E.R. Kraft, L. Gordon, JACS 71, 3523, 1949.

55. J.D. London, R.K. Radzan, J. Chem. Soc. 4299, 1954.

56. M. Matsui, K. Mori, S. Arasaki, Agr. Biol.Chem. (Tokyo) 28, 896, 1964 (C.A. 62 14614 f).

57. A.J. Ewins, J. Chem. Soc. 548, 1912.

58. O.L.Brady,F.P.Dunn,J. Chem. Soc. 123, 1780, 1923 (p. 1802).

59. N.Heap, G.H. Whitman, J. Chem. Soc. (B Phys. Org.), 1966, 164.