THE UNIVERSITY OF MANITOBA

NAPHTHALENE PRECURSOR OF TERRARUBEIN

by

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ABSTRACT

Allyl diethyl malonate (XXV) was prepared by refluxing the sodium salt of diethyl malonate and allyl bromide. The sodium salt of (XXV) was then condensed with ethyl bromoacetate to produce α-ethylcarboxylate-α-allyldiethylsuccinate (XXVI). Allyl succinic anhydride (XXVIII) was produced by hydrolysing the triester (XXVI) to the triacid (XXVII) followed by refluxing in acetic anhydride. An alternate and simpler method of producing allyl succinic anhydride involved a high pressure condensation of propene and maleic anhydride. Methylcyclohex-2-ene-1-one-5-carboxylate (XXXI) was produced by cyclizing allyl succinic anhydride with aluminum chloride followed by methylation of the acid with diazomethane.

Methyl-3-carbethoxy-4-carbomethoxy-5-isoxolylacetate (XXXV) was prepared by reacting the sodium salt of dimethyl acetonedicarboxylate (XXXII) with ethyl chloroximinoacetate (XXXIII), followed by acid catylized dehydration. The sodium salt of (XXXV) was condensed with 2-cyclohexene-1-one to give 5-carbomethoxy-6,8-dihydroxy-7-cyano-1-tetralone (XXXVII). Methylation of (XXXVII) with diazomethane produced 5-carbomethoxy-6,8-dimethoxy-7-cyano-1-tetralone (XXXVIII), while methylation of (XXXVII) with basic dimethyl sulfate produced 5-carbomethoxy-6-methoxy-7-cyano-8-hydroxy-1-tetralone (XXXIX). The alpha-bromoketone (XLI) was produced by treating (XXXVIII) with acetic anhydride followed by bromination of the enol acetate (XL). The alpha-bromoketone (2-bromo-5-carbo-

methoxy-6,8-dimethoxy-7-cyano-1-tetralone) (XLI) was also produced by reacting (XXXVIII) with pyrrolidone hydrotribromide (PHT). 1-carbomethoxy-2,4,5-trimethoxy-3-cyanonaphthalene (XLIII) was produced by the dehydrohalogenation of (XLI) with triethylamine followed by methylation with diazomethane. 1-carbomethoxy-2,4,5-trimethoxy-3-cyano-6-bromonaphthalene (XLVI) was produced as a by-product of (XLIII) and also by the direct bromination of (XLIII). 1-carbamyl-2,4,5-trimethoxy-3-cyanonaphthalene (XLVIII) was produced by reacting (XLIII) with ammonia in a sealed vessel. 1-carbamyl-2,4,5-trimethoxy-3-cyano-8-bromonaphthalene (IL) was produced by the bromination of (XLVIII) and by reacting (XLVII) with ammonia in a sealed vessel. 1-amino-2,4,5-trimethoxy-3-cyanonaphthalene (L) was produced by treating (XLVIII) with lead tetraacetate followed by hydrolysis with sodium hydroxide.

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INTRODUCTION

The tetracycline antibiotics [Scheme I] are a group of natural products having notable antibacterial activity toward a broad range of pathogenic microorganisms and are characterized by very low toxicity to humans having these pathogens. These properties, together with the fact that the compounds are well absorbed and fully active when administered orally, have made the tetracyclines one of the most useful families of chemotherapeutic agents.

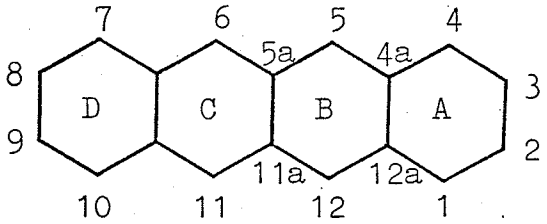
The first of this family was reported in 1948 by Duggar[1]. A pale yellow antibiotic was isolated from a previously undescribed species of Streptomyces. Because of the pigment, the antibiotic was called aureomycin (7-chlortetracycline) (II) and the microbe Streptomyces aureofaciens. Two years later another antibiotic was isolated from yet another new species, Streptomyces rimosus, and given the name terramycin (5-oxytetracycline) (III)[2,3].

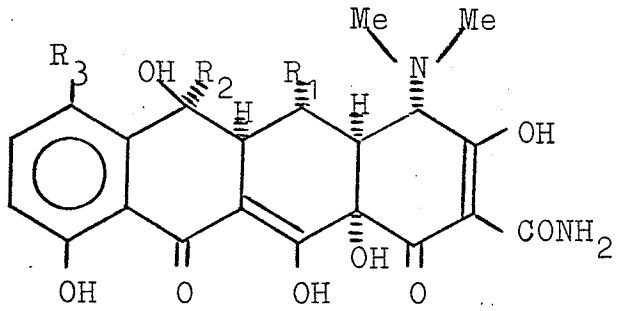
It was apparent that these two antibiotics had a similar antibacterial spectrum and were shown to be chemically related[4,5].

The parent compound, tetracycline (I), was prepared independently in the laboratories of Lederle and Pfizer by catalytic dehalogenation of aureomycin[6,7]. Tetracycline was later isolated directly as a fermentation product of Streptomyces aureofaciens[8].

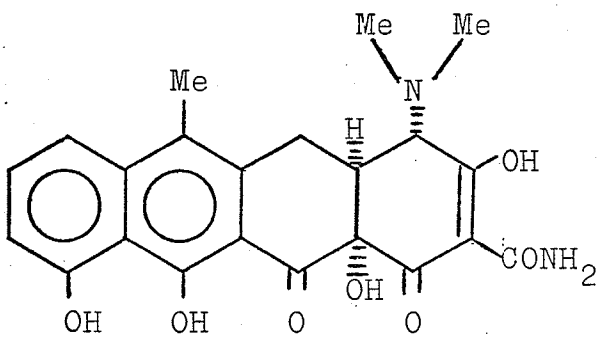
In 1957, a new family of demethyl tetracycline .

SCHEME I



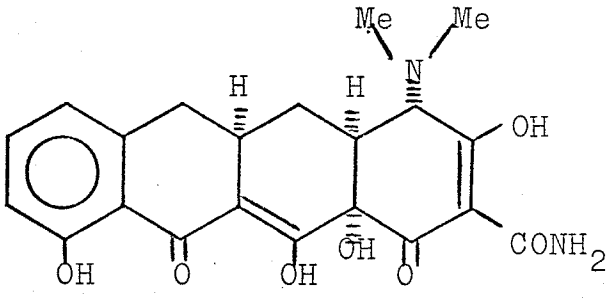


		R_1	R_2	R_3
(I)	Tetracycline	H	Me	H
(II)	Aureomycin	H	Me	Cl
(III)	Terramycin	OH	Me	H
(IV)	6-demethyl tetracycline	H	H	H
(V)	6-demethyl-7-chlorotetracycline	H	H	Cl



(VI)

Anhydrotetracycline



(VII)

6-demethyl-6-deoxytetracycline

compounds was reported which differ from the parent antibiotics in that they lack a methyl group in the 6-position. Two of these, 6-demethyl tetracycline (IV) and 6-demethyl-7-chlorotetracycline (V) are produced by a mutant of the original aureomycin-producing strain of Streptomyces aureofaciens[9,10].

The practical importance of the 6-demethyl tetracyclines lies in their greater acid stability as compared with the normal tetracyclines which contain a tertiary benzylic hydroxyl at C_6 which is readily lost to form the anhydrotetracyclines (VI). These latter substances are strongly bound to serum proteins and are not clinically useful as antibiotics. The tendency to form anhydrotetracyclines is diminished by removal of the C_6 methyl group.

The simplest structure which embodies all of the elements necessary for activity is 6-demethyl-6-deoxytetracycline (VII). The total synthesis of dl-6-demethyl-6-deoxytetracycline was first accomplished[11] by R.B. Woodward and his group. This work was the subject of two preliminary reports[12,13]. A totally different approach was successfully completed later[14] by H. Muxfeldt and W. Rogalski.

The structures of terramycin[15] and aureomycin[5,16] were established by chemical experiments. The structure of tetracycline was apparent from its simple relationship to aureomycin[6,7].

An X-ray analysis of aureomycin hydrochloride confirmed[17] structure (II) and established the relative configuration at each of the asymmetric centers.

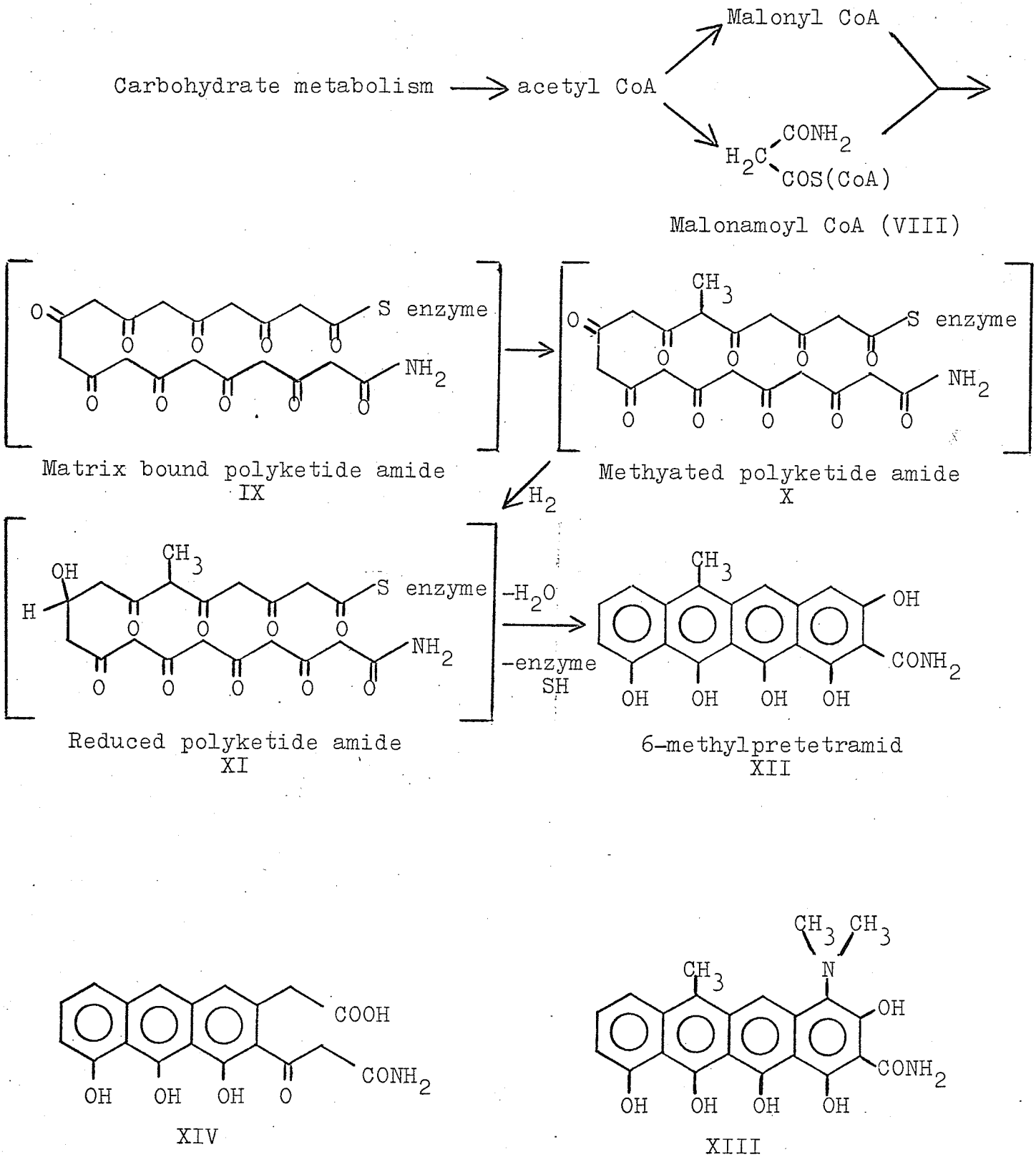
Tetracycline is comparably defined[18] by structure (I) because the only molecular change involved in preparing the compound from aureomycin is replacement of chlorine by hydrogen.

In the case of terramycin, the gross structure was again confirmed by X-ray studies but these did not define the relative stereochemistry at C_5. The structure (III), in which the hydroxyl group at C_5 is trans to that at C_6, is supported by n.m.r. evidence[19,20] and by a re-examination of the early X-ray data[21].

In addition to the structure elucidation of tetracyclines there has been a continued interest in the biological origin. The main assumption made is that all of the tetracyclines arise by essentially the same biosynthetic pathway, and in view of the similarities within the family and the lack of other close relatives this assumption seems valid.

J.R.D. McCormick has reviewed[22] the many studies that have a bearing on defining the gross pathway by which these compounds are biologically synthesized [Scheme II]. From the pretetramids, the pathway to the tetracycline antibiotics is on sound experimental ground. The presence of a 6-methyl group on the antibiotic depends only on the presence or absence of the 6-methyl group in the pretetramid derivative used as a precursor. This constitutes the principal evidence that 6-methylation precedes cyclization. The observation that the presence of a 7-chloro substituent in the antibiotic can be achieved either by use of the corresponding chlorinated pretetramid derivative or by the use of a blocked

SCHEME II


Carbohydrate metabolism
acetyl CoA
Malonyl CoA
CONH2
H2C
COS(CoA)
Malonamoyl CoA (VIII)
S enzyme
NH2
CH3
Matrix bound polyketide amide
IX
Methyated polyketide amide
X
H2
OH
H
-H2O
-enzyme
SH
Reduced polyketide amide
XI
6-methylpretetramid
XII
COOH
CONH2
XIV
N
XIII

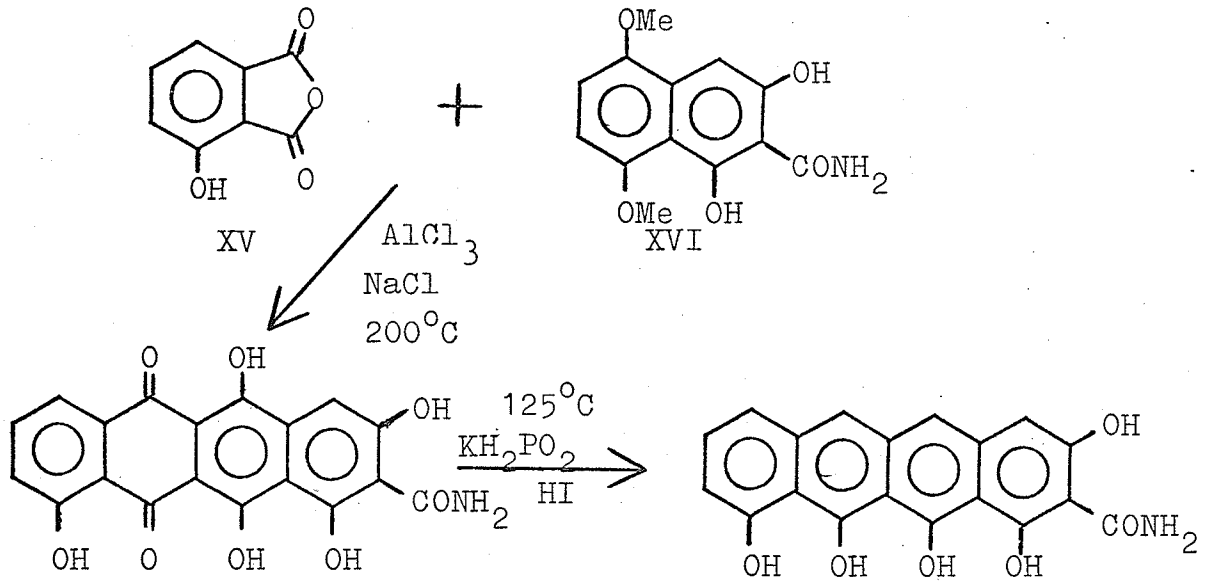
mutant which has genetically-determined chlorinating ability shows that chlorination is normally accomplished after the pretetramid stage[22].

Terrarubein (XIII), a degradation product of terramycin[15], has also been converted to tetracycline[23] but at a slower rate than 6-methylpretetramid (XII). Protetrone (XIV), isolated from a blocked mutant culture, appears to be a shunt product resulting from an imperfection in the cyclization process[24].

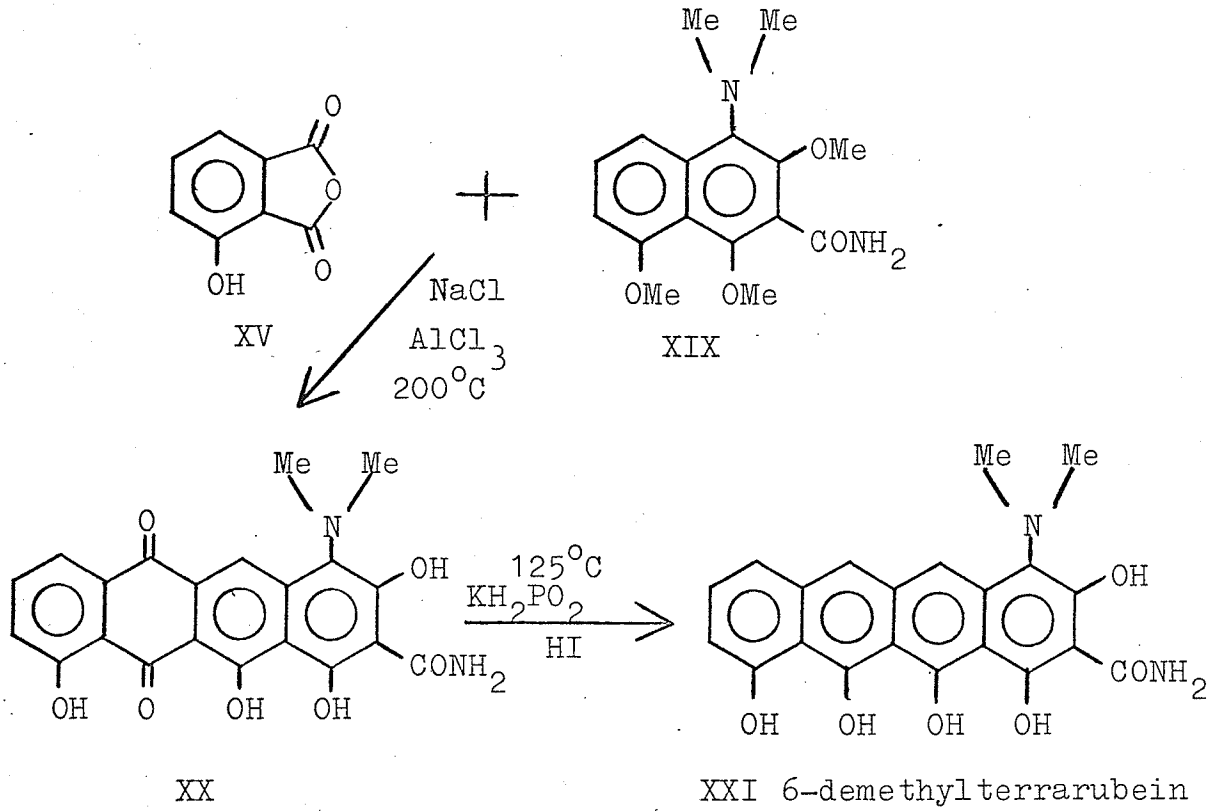
It was reported[23] that pretetramid is obtained by fusing 3-hydroxy phthalic anhydride (XV) and 1,3-dihydroxy-5,8-dimethoxy naphthalene-2-carboxamide (XVI) in the presence of aluminum chloride and sodium chloride. The product was converted to pretetramid by refluxing with phenol in the presence of hydiodic acid and potassium hypophosphite [Scheme III]. This synthetic substance was then biologically converted to 6-demethyl-7-chlorotetracycline (V) by Streptomyces aureofaciens.

It was hoped that the above approach[23] could be used to synthesize terrarubein. In order for this approach to work it would be necessary to synthesize a naphthalene compound (XIX) with all the correct functional groups of the terrarubein 'A' ring. Also by using this approach various substituents could be introduced in the 7-position of phthalic anhydride and the 8-position of the naphthalene compound to achieve the corresponding substituted terrarubein compound [Scheme IV].

SCHEME III



SCHEME IV



RESULTS AND DISCUSSION

Methyl cyclohex-2-ene-1-one-5-carboxylate (XXXI) was synthesized from 3,5-dihydroxy benzoic acid through high pressure hydrogenation, methylation with diazomethane and sodium borohydride reduction by a coworker in an overall yield of 13%.[25] Attempts to improve this yield led to the following new series of reactions.

In the preparation of benzo[c]phenanthrenes, Phillips and Johnson[26] used as their initial reaction the Friedel-Crafts' condensation between beta-methallylsuccinic anhydride (XXII) and benzene. In this initial reaction they obtained a lower-boiling fraction which they could not immediately identify but which later[27] proved to be 3-methylcyclohex-2-ene-1-one-5-carboxylic acid [(XXIII) (Scheme V)].

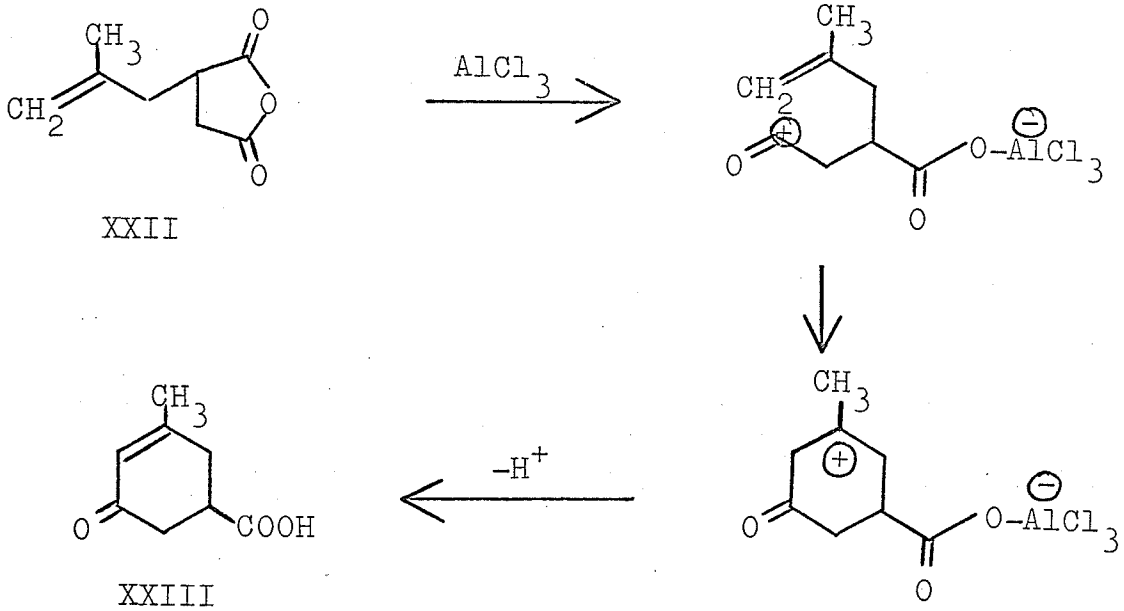
By substituting allyl succinic anhydride for beta-methallylsuccinic anhydride the end product would be cyclohex-2-ene-1-one-5-carboxylic acid. The acid upon methylation would be the desired product.

Attempts to form allyl succinic anhydride by the condensation of allyl bromide with the sodium salt of succinic anhydride proved unsuccessful due to the inability of forming the sodium salt of the anhydride.

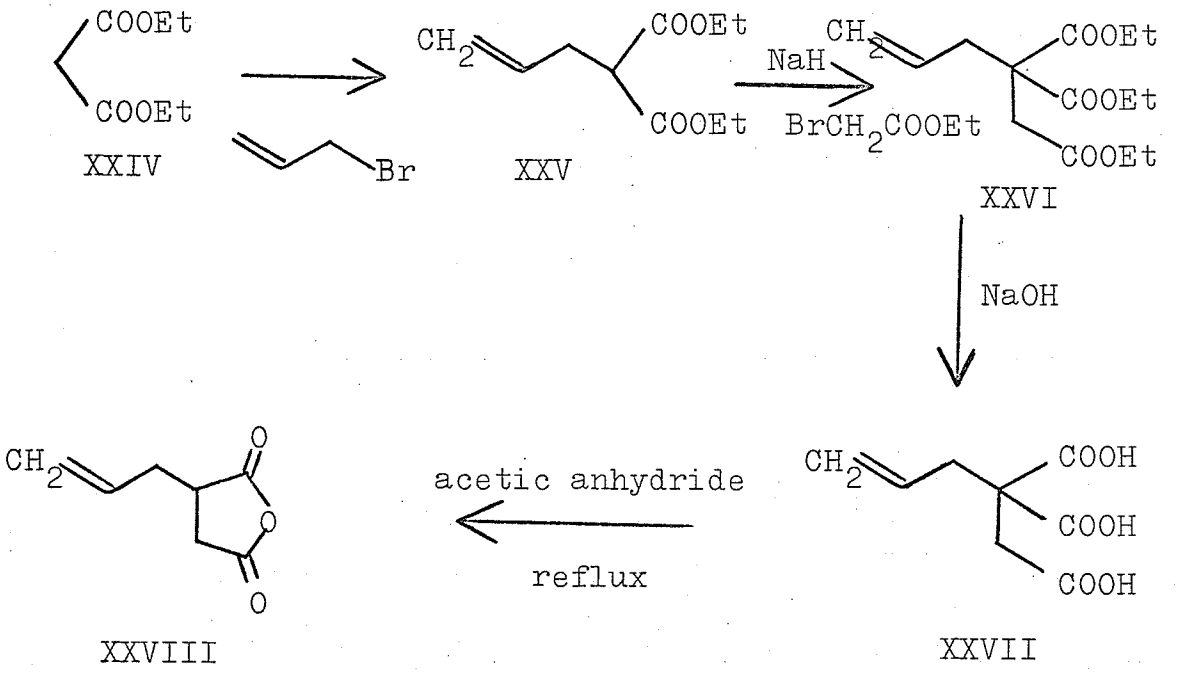
Diethyl malonate [(XXIV) (Scheme VI)] was the starting material of a successful approach to the compound.

Allyl diethyl malonate (XXV) was produced in dry tetrahydrofuran by the condensation of allyl bromide with

SCHEME V



SCHEME VI



the sodium salt of diethyl malonate. The n.m.r. spectrum of this compound [Fig.XIX] showed absorptions at 5.85 and 8.77 τ for the two ethyl groups, 3.8-5.2 τ for three olefinic protons and 6.4-7.6 τ for three aliphatic protons. The compound was purified by distillation, b.p.= 47-50°C at 0.05 mm. of Hg.

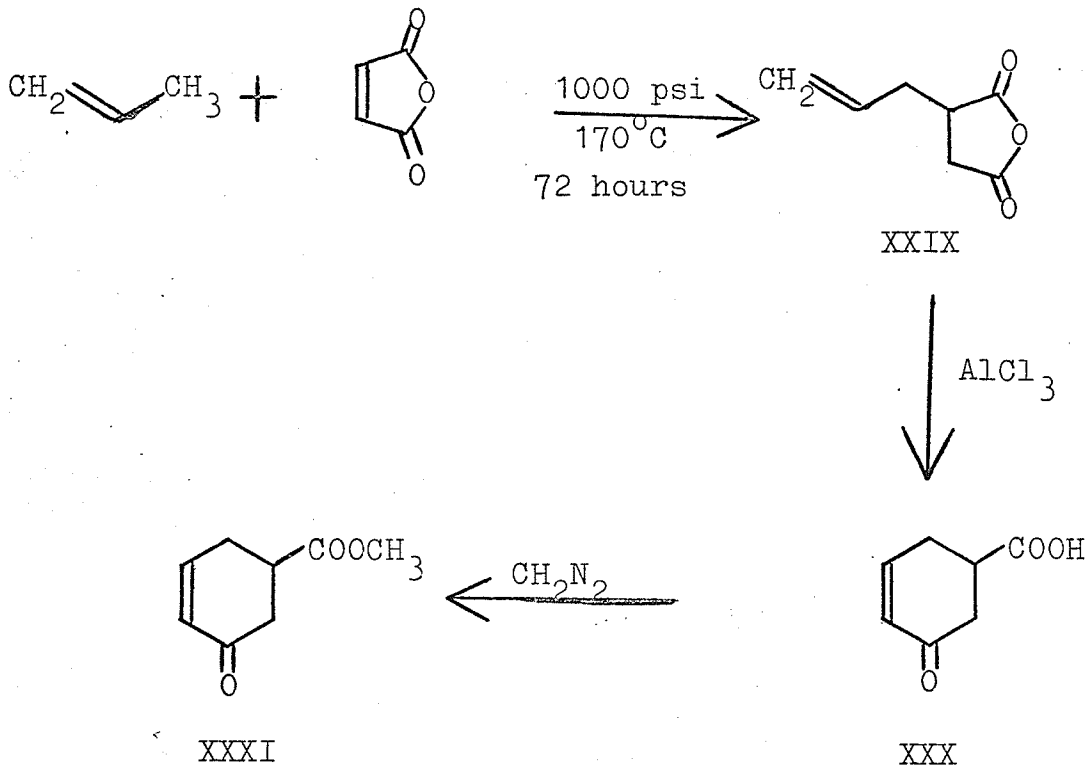
α-ethylcarboxylate-α-allyldiethylsuccinate (XXVI) was prepared by the addition of ethyl bromoacetate to the sodium salt of allyl diethyl malonate. After vacuum distillation, b.p.= 90-93°C at 0.05 mm. of Hg. the triester (XXVI) was a clear liquid. Hydrolysis of the ester in 10% sodium hydroxide gave the triacid (XXVII) in a 57% yield.

To produce allyl succinic anhydride, the triacid was refluxed in acetic anhydride. Vacuum distillation b.p.= 72-74°C at 0.2 mm. of Hg. gave the pure compound. The i.r. spectrum [Fig. I] showed absorptions at 1780 and 1860 cm^{-1} (anhydride) and 1640 cm^{-1} (C=C).

A second and improved method of forming allyl succinic anhydride used propene and maleic anhydride[27] (Scheme VII). Propene was pumped into a Parr high pressure reactor at 100 psi. which contained maleic anhydride. This was heated to 170°C and rocked for 72 hours. The compound produced was similar in i.r., n.m.r. and b.p. to the one produced via the triester.

Methylcyclohex-2-ene-1-one-5-carboxylate (XXXI) was produced by stirring the anhydride and aluminum chloride in dry 1,1,2,2-tetrachloroethane, followed by methylation with diazomethane. After the crude material was purified

SCHEME VII

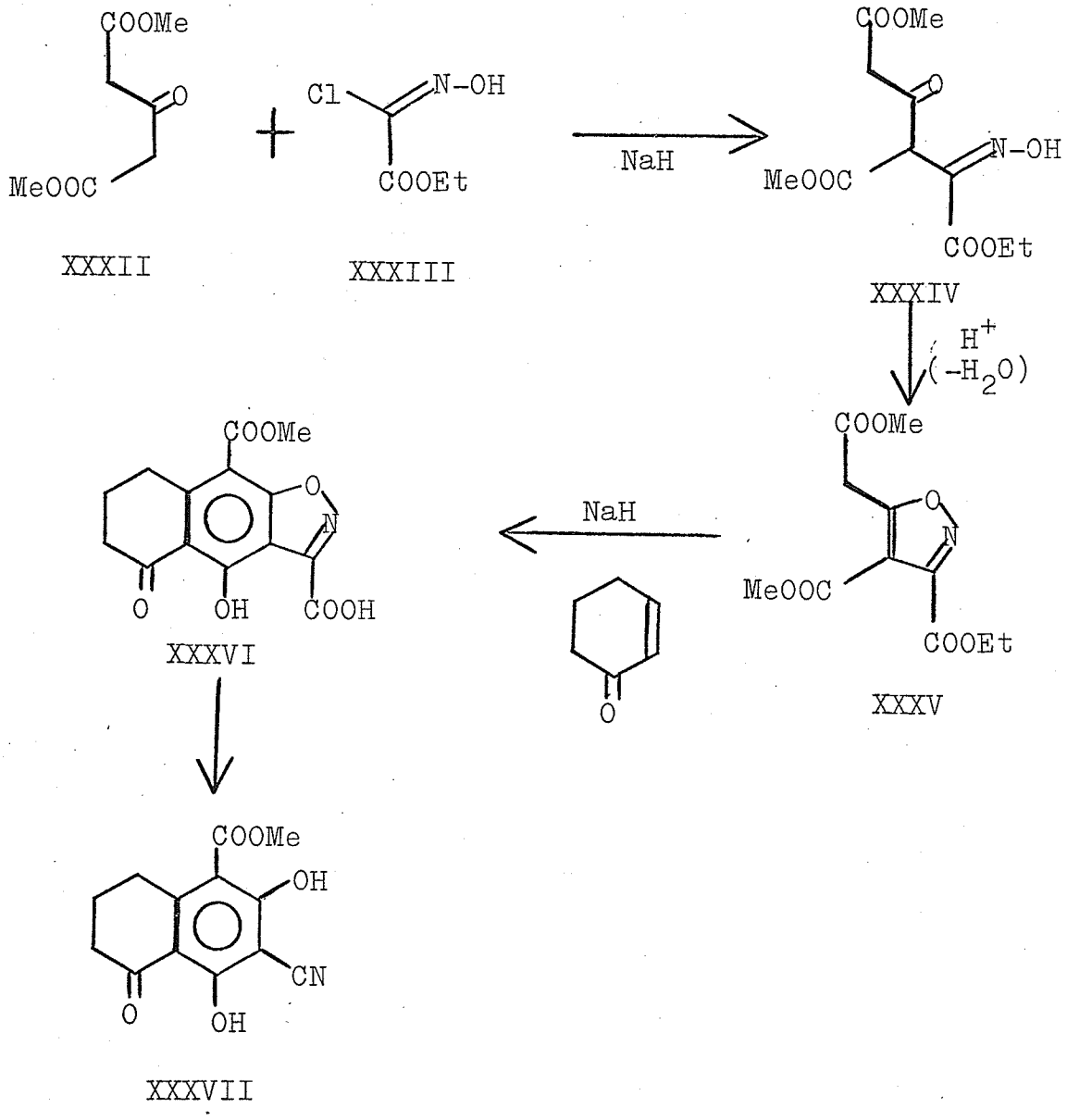

CH2
CH3
1000 psi
170°C
72 hours
CH2
XXIX
AlCl3
COOH
XXX
CH2N2
COOCH3
XXXI

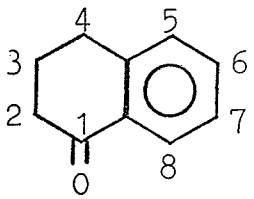
once by t.l.c. the fingerprint region of the i.r. was identical with the compound produced and characterized by a coworker[25] but there was an additional absorption at 1780 cm^{-1}. The i.r. spectrum [Fig. V] showed absorptions at 1730 (ester) and 1680 cm^{-1} (alpha,beta unsaturated ketone). Several other attempts were made to produce the pure alpha, beta unsaturated ketone. The compounds produced gave a good n.m.r. spectrum however the i.r. spectrum had an additional absorption at 1700 cm^{-1}. Attempts to purify the compound by t.l.c. on both silica gel and alumina reduced the absorption but never completely eliminated it.

The synthetic route to the naphthalene precursor of terrarubein began with the condensation of the oxime (XXXIII) with the sodium salt of dimethyl acetone dicarboxylate [(XXXII) (Scheme VIII)]. The condensation product (XXXIV) was cyclized without isolation by acid-catylized dehydration in refluxing benzene. The isoxazole triester (XXXV) was purified by vacuum distillation, b.p. 118-120°C at 0.05 mm. of Hg. The i.r. spectrum [Fig. VI] shows a strong carbonyl absorption at 1740 and an absorption at 1610 cm^{-1} typical of the isoxazole ring.

The addition of the sodium salt of (XXXV) to 2-cyclohexene-1-one was carried out in refluxing tetrahydrofuran. The product (XXXVI) was never isolated but was decomposed with refluxing methanol to give the diphenol ester (XXXVII). The diphenol ester gave an i.r. spectrum [Fig. VII] in agreement with structure (XXXVII). There was an absorption at 2250 cm^{-1} for the cyano group and absorptions at 1675 cm^{-1}

SCHEME VIII





1-tetralone

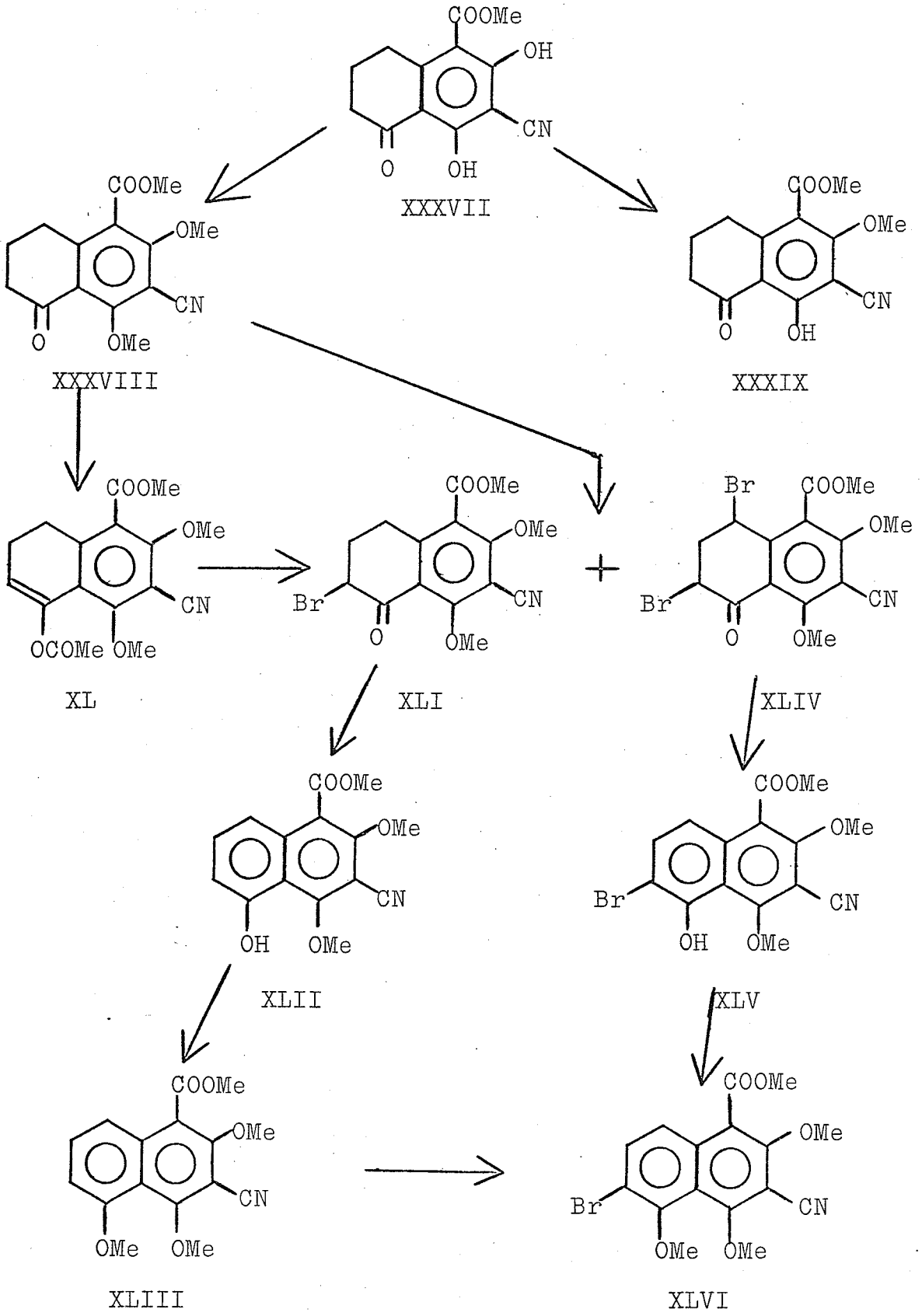
and 1635 cm^{-1} indicating that the carbonyl groups of both the ester and the ketone were chelated to the adjacent hydroxy groups. A yield of 40% was achieved for the conversion of the isoxazole triester to the diphenol ester.

Methylation of the diphenol ester with basic dimethyl sulfate failed to methylate the hydroxyl group chelated to the ketone and produced compound (XXXIX). The i.r. spectrum [Fig. IX] showed the shift of the absorption from 1675 to 1730 cm^{-1} indicating the ester is no longer chelated. The n.m.r. spectrum [Fig. XXIV] showed absorptions for two methoxy groups, one proton at low field and six ring protons.

Methylation of the diphenol ester with diazomethane gave a crystalline product [(XXXVIII) (Scheme IX)]. The i.r. spectrum of this compound [Fig. VIII] showed absorptions for the nitrile, ester and ketone groups (2260,1735 and 1690 cm^{-1} respectively) and the n.m.r. spectrum [Fig.XXIII] showed the presence of three methoxy groups as well as six ring protons.

In order to obtain a fully aromatic compound which would hopefully undergo a Friedel-Crafts reaction to form a tetracyclic compound the alpha-bromoketone (XLI) was synthesized. There were two methods of preparation for this compound [Scheme IX]. The first method involved two steps and had as its intermediate the enol acetate (XL). The dimethoxy ester (XXXVIII) was refluxed overnight under nitrogen with acetic anhydride and sodium acetate. The enol acetate was purified on silica gel to give i.r. spectrum no. 10 [Fig. X]. The n.m.r. spectrum [Fig.XXV]

SCHEME IX


COOMe
OH
CN
O
OH
XXXVII
COOMe
OMe
CN
O
OMe
XXXVIII
COOMe
OMe
CN
O
OH
XXXIX
COOMe
OMe
CN
OCOMe
OMe
XL
COOMe
OMe
CN
Br
O
OMe
XLI
Br
COOMe
OMe
CN
Br
O
OMe
XLIV
COOMe
OMe
CN
OH
OMe
XLII
COOMe
OMe
CN
Br
OH
OMe
XLV
COOMe
OMe
CN
OMe
OMe
XLIII
COOMe
OMe
CN
Br
OMe
OMe
XLVI

showedabsorptions for four methyl groups, four ring protons and a triplet for the lone olefinic proton. The enol acetate was converted to the alpha-bromoketone by bromination in carbon tetrachloride solution.

The second method of forming the alpha-bromoketone involved the direct bromination of the dimethoxy ester using pyrrolidone hydrotribromide. D.V.C. Awang and S. Wolfe found[28] that the relative reactivities of a ketone, an olefin and an enol acetate towards bromination in tetrahydrofuran by "pyrrolidone-bromine complex", $(pyrrolidone)_3 \cdot HBr$, (PHT) are ketone$\gg$ olefin$>>$ enol acetate. The dimethoxy ester and PHT were stirred for two hours in dry tetrahydrofuran. The alpha-bromoketone was produced in 88% yield. The i.r. spectrum [Fig.XI] showed absorptions at 2250,1735 and 1690 cm^{-1} for the cyano group, ester and ketone respectively. The n.m.r. spectrum [Fig. XXVI] showedthe presence of three methyl groups, four ring protons and a triplet for the proton on the same carbon as the bromine.

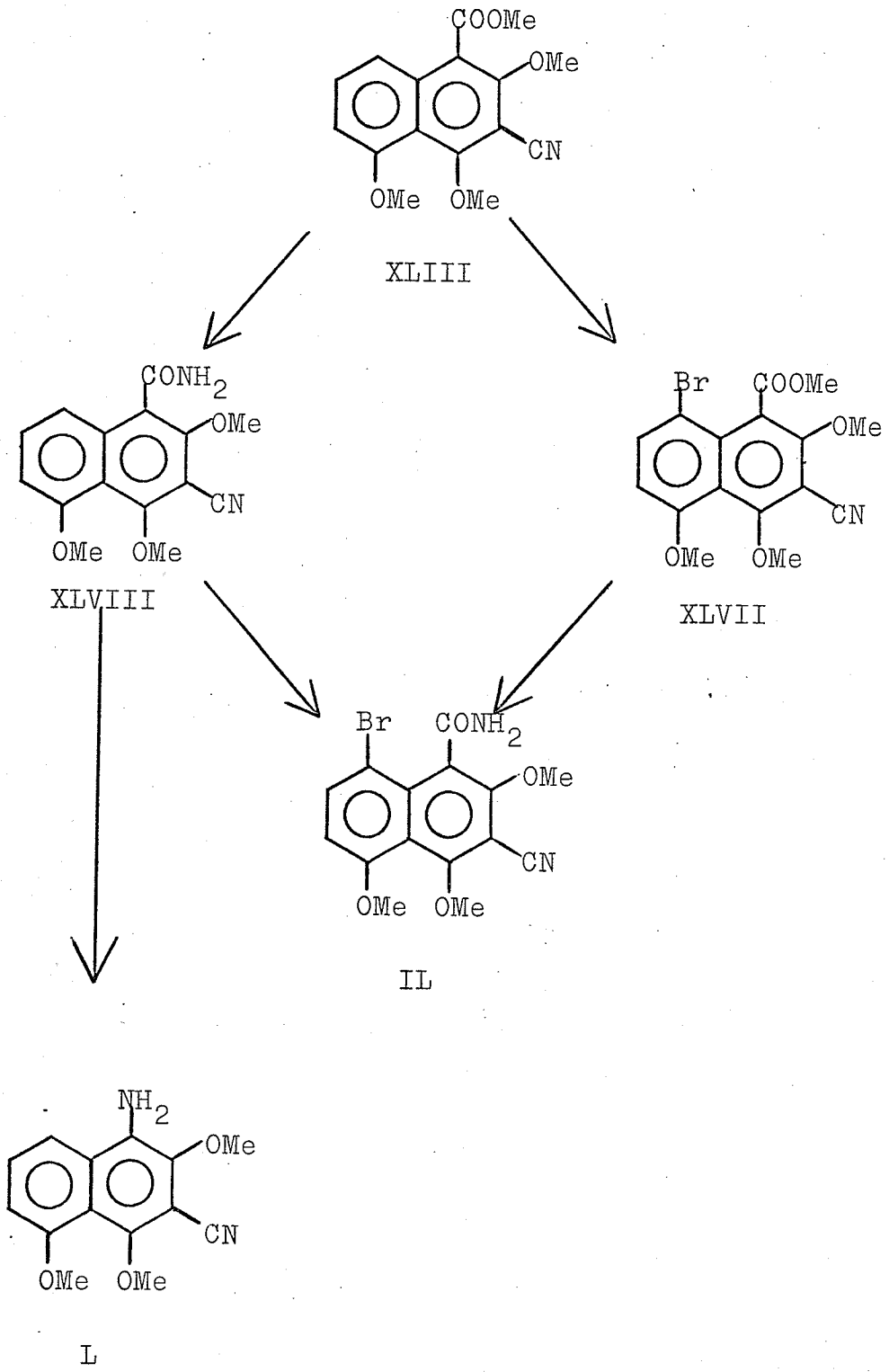
Refluxing the alpha-bromoketone in triethyl amine yielded the fully aromatic compound (XLII). Treatment of this compound with diazomethane gave the trimethoxy ester (XLIII). In most of the preparations of the trimethoxy ester the phenolic intermediate (XLII) was not isolated but was methylated as the crude product. The trimethoxy ester was purified on silica gel and then recrystallized from methanol to give white needles. The i.r. spectrum

of XLIII [Fig. XIII] showed absorptions at 2260 and 1730 cm^{-1} for the cyano group and the ester respectively. The n.m.r. spectrum [Fig. XXVII] showed absorptions for four methyl groups and three aromatic protons.

In the t.l.c. separation on silica gel of compound XLIII there was a small band immediately above the trimethoxy ester. From the i.r. and n.m.r. spectra, it was assigned the structure (XLVI). Although the intermediates XLIV and XLV were not isolated, this seems like the only possible pathway to the formation of XLVI. The n.m.r. spectrum [Fig.XXVIII] showed the presence of four methyl groups and also an AB spectrum for the two aromatic protons. Compound XLVI was also formed by the treatment of the trimethoxy ester with bromine in carbon disulfide or acetic acid.

The next step in the series was to convert the ester to an amide so that this group would not hydrolize and decarboxylate during a fusion with aluminum chloride in a Friedel-Craft's condensation. The trimethoxy ester (XLIII) was taken up in methanol and liquid ammonia was added. This reaction mixture was placed inside a Parr high pressure reactor and allowed to warm up to 60°C. The conversion from the ester to the amide [(XLVIII) (Scheme X)] was completed in quantitative yield. The i.r. spectrum [Fig. XV] showed absorptions at 3540 and 3320 cm^{-1} for the amide, 2230 cm^{-1} for the nitrile and 1720 cm^{-1} for the amide carbonyl group. The n.m.r. spectrum [Fig. XXX] showed absorptions for the three methyl groups, the three aromatic protons and two protons for the amide.

SCHEME X


COOMe
OMe
CN
OMe OMe
XLIII
CONH2
OMe
CN
OMe OMe
XLVIII
Br COOMe
OMe
CN
OMe OMe
XLVII
Br CONH2
OMe
CN
OMe OMe
IL
NH2
OMe
CN
OMe OMe
L

In the tetracyclic compounds the functional group in the four position of the 'A' ring is an amine and not an amide. Many attempts were made to convert the amide to the amine via the Hofmann degradation before a successful reaction was found. This aromatic amide was found to be very unreactive to the normal Hofmann degradation conditions.

Certain aromatic amides have been converted to the corresponding amines by going through the intermediate carbamate. In 1965 it was reported[29] that by using lead tetraacetate in acetic acid, amides could be converted to acyl amines. The reaction however failed with benzamide. Later it was reported[30,31] that by using an alcohol instead of acetic acid the product would be the carbamate. Since this reaction worked for aromatic amides, the resulting carbamate could then be hydrolized to the amine. The amine (L) was prepared in this manner by treating the amide (XLVIII) with lead tetraacetate in the presence of methanol. The intermediate aryl carbamate (not isolated) was then hydrolized to the amine. The i.r. spectrum [Fig. XVI] showed absorptions at 3530 and 3420 cm^{-1} for the amine and 2230 cm^{-1} for the nitrile. The n.m.r. spectrum [Fig. XXXII] showed three methyl groups, three aromatic protons and the two protons of the amine.

Since the conversion of the amide to the amine was a low yield reaction it was decided to attempt the fusion of the amide rather than the amine.

Before the fusion was attempted it was necessary to put a blocking group at the eight position of the naphthalene

molecule to insure that the condensation would produce a straight chain tetracyclic compound.

The bromoamide (IL) was produced in two ways; by the bromination of the amide (XLVIII) and by the bromination of the ester (XLIII) followed by conversion of the ester to the amide [(IL) (Scheme X)]. The amide (XLVIII) was dissolved in glacial acetic acid and a catalytic amount of ferric chloride was added. A quantitative amount of bromine was added and allowed to stir for two hours. The acetic acid was pumped off under vacuum and the remaining material taken up in chloroform and washed with sodium thiosulfite. The chloroform was dried and flash evaporated to give the bromoamide (IL). This structure was confirmed by both i.r. and n.m.r. spectra. The i.r. spectrum [Fig. XVII] showed absorptions at 3540 and 3320 cm^{-1} for the amide NH_2, at 2230 cm^{-1} for the nitrile and at 1725 cm^{-1} for the carbonyl amide. The n.m.r. spectrum [Fig. XXXI] showed absorptions for three methoxy groups, an AB spectrum for the two aromatic protons and two protons for the amide.

There was a slight difficulty in interpreting the n.m.r. spectra for compounds (XLVI) and (XLVII) [Figs. XXVIII and XXIX]. Both spectra showed absorptions for four methoxy groups and an AB spectrum for the two aromatic protons. The problem was in determining which AB spectrum belonged to which structure. In chapter 3-6 of a book[32] authored by L.M. Jackman and S. Sternhell the chemical shifts are tabulated for various substituents on aromatic compounds. The basic chemical shifts for the protons on

the naphthalene molecule are 7.81 for the proton in the '1' position and 7.46 for the proton in the '2' position [Table 3-6-2]. Table 3-6-1 gives the effect of substituents on the chemical shift of benzene. The negative sign denotes a downfield shift. While the substituent effects on naphthalene are not quite equal to those on benzene, they operate in the same direction and are of the same order of magnitude. For compound (XLVI) the following shifts are estimated: 7.81 -1.00 +0.13 +0.37 (ester, m-Br, p-OMe)= 7.31; 7.46 -0.22 +0.09 (o-Br, m-OMe)= 7.33. For compound (XLVII) the following shifts are estimated: 7.46 -0.22 +0.09 (o-Br, m-OMe)= 7.33; 7.46 +0.13 +0.43 (m-Br, o-OMe)= 8.02. As can be seen by these values the chemical shifts for compound (XLVI) are fairly close together (7.31,7.33) and therefore should have the more compact and symmetrical AB spectrum [Fig. XXVIII]. Since the chemical shifts for compound (XLVII) are farther apart (7.33,8.02) it was assigned the more spread out AB spectrum [Fig. XXIX].

The alternate pathway of producing the bromoamide (IL) is through the intermediate bromoester (XLVII). The trimethoxy ester (XLIII) was dissolved in glacial acetic acid. Ferric chloride and bromine were added and the reaction mixture was allowed to stir. The acetic acid was pumped off and the residue taken up in chloroform and washed with sodium bisulfite. The chloroform was dried and flash evaporated to give the bromoester (XLVII). The i.r. spectrum [Fig. XV] showed absorptions at 2250 for the nitrile and 1740 cm^{-1} for the ester. The n.m.r. spectrum

[Fig. XXIX] showed absorptions for four methyl groups and the AB pattern for the two aromatic protons. The bromo-ester was then converted to the bromoamide in the same way as the ester (XLIII) was converted to the amide (XLVII). The bromoamide has the same i.r. and n.m.r. spectra in both approaches.

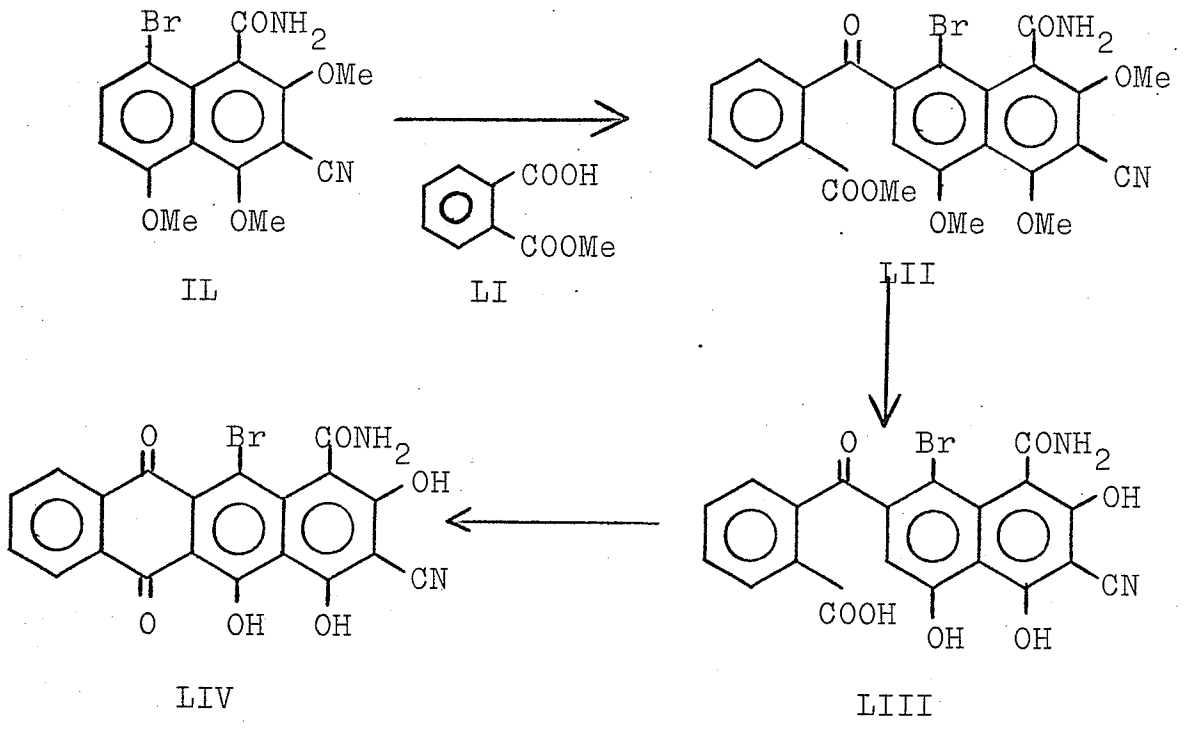
Two methods were attempted to produce a tetracyclic compound using the bromoamide (XLVII).

The bromoamide was added to the half ester of phthalic acid (LI), which was produced by refluxing phthalic anhydride in methanol, in trifluoroacetic anhydride. However after work up and separation on silica gel t.l.c. plates no compound could be found which resembled the expected product (LII) (Scheme XI).

In another attempt (Scheme XII) the bromoamide and phthalic anhydride were heated to 150^{o}C with a mixture of aluminum chloride and sodium chloride. The resulting brown mass was dumped into ice water containing oxalic acid. This was then extracted with chloroform. The chloroform was dried and flash evaporated. The orange residue was then methylated with basic dimethyl sulfate and separated on silica gel t.l.c. plates. There was one band on the t.l.c. plate whose i.r. spectrum showed absorptions for the amide, nitrile and the quinone system however the mass spectrum for this compound showed that the parent ion was 612 a.m.u.

Due to a lack of research time, no further fusions could be attempted to characterize the products.

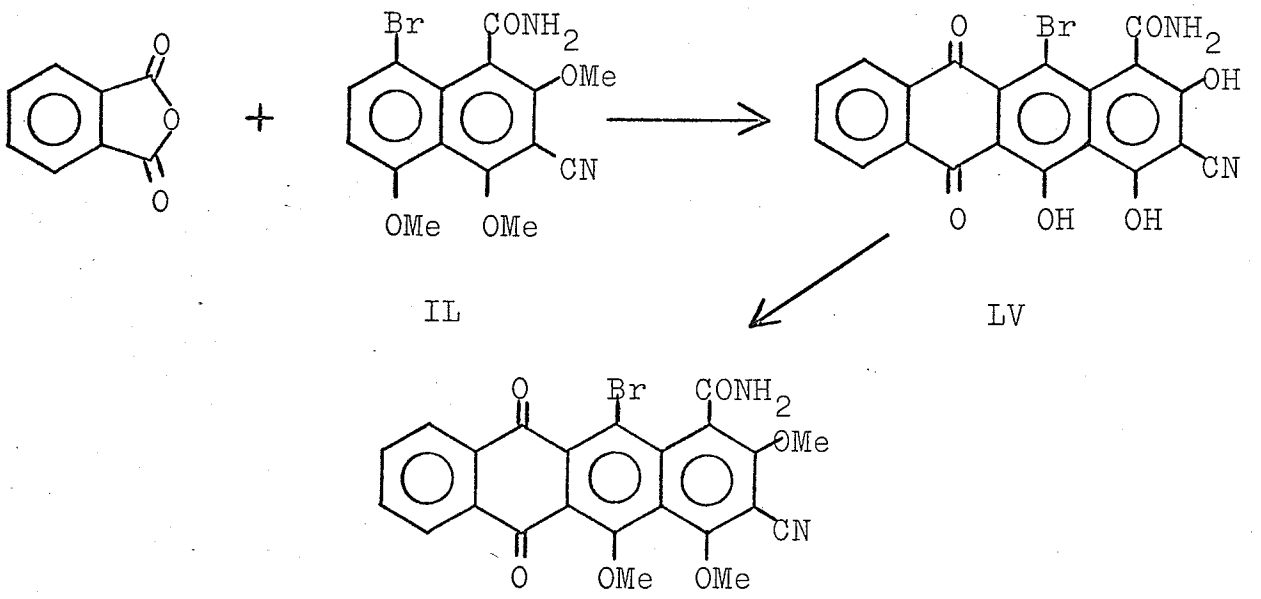
SCHEME XI



IL LI LII

LIII LIV

SCHEME XII



IL LV

LVI

EXPERIMENTAL

All infrared (i.r.) spectra were recorded on a Perkin-Elmer 700 spectrophotometer using methylene chloride solutions, nujol mulls or liquid films of the samples. The nuclear magnetic resonance (n.m.r.) spectra were recorded on a Varian A-56/60 A spectrometer using deuterated chloroform as solvent and tetramethylsilane (TMS) as internal standard. Chemical shifts are given in τ units and the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, J = coupling constant. The mass spectra were obtained on a Finnigan 1015 mass spectrometer. Melting points were measured on a Fisher-Johns melting point apparatus and are uncorrected. The silica gel used in thin layer chromatography (t.l.c.) was "Camag" brand, obtained from Mondray Ltd., Montreal. The t.l.c. separations were carried out using glass plates coated with a one mm. layer of silica gel.

(1) Preparation of allyl diethyl malonate (XXV):

A solution of diethyl malonate (80 gm., 0.5 moles) and dry tetrahydrofuran (600 ml.) was placed in a one liter 3-neck round bottom flask equipped with a condenser and a separatory funnel. A 50% suspension of NaH/oil (24 gm., 0.5 moles) was added to the tetrahydrofuran solution over a period of 15 minutes. After completing the addition, the mixture was stirred for one hour and then allyl bromide (43.3 ml., den. 1.398 g/ml., 0.5 moles) was added dropwise

from the separatory funnel. After this addition was complete the reaction mixture was refluxed for two hours. The condenser was then fitted for distillation and most of the tetrahydrofuran was distilled off. The remaining reaction mixture was dumped into cold water and extracted with chloroform (3 X 200 ml.). The chloroform was dried and removed by flash evaporation to give an oil residue. Vacuum distillation of the oil gave the pure product, b.p. 47-50°C at 0.05 mm. of Hg. (66 gm., 0.33 moles, 66%).

Infrared spectrum no. 1 [Fig. I]: Absorptions (cm^{-1}) at 1740 (ester), 1650 (C=C).

N.m.r. spectrum no. 1 [Fig. XIX]: Absorptions at 3.84-5.16 (m, 3 H's, olefinic protons); 5.87 (q, J = 7 Hz., 4 H's, $CH_3\underline{C}H_2$-); 6.43-7.6 (m, 3 H's, aliphatic protons); 8.77 (t, J = 7 Hz., 6 H's, $C\underline{H}_3CH_2$-).

(2) Preparation of α-ethylcarboxylate-α-allyl diethyl-succinate (XXVI):

To a solution of allyl diethyl malonate (XXV) (66 gm., 0.33 moles) and dry tetrahydrofuran (600 ml.) in a one liter flask was added over a fifteen minute period a 50% suspension of NaH/oil (15.85 gm., 0.33 moles). To the reaction mixture was added dropwise ethyl bromoacetate (36.4 ml., den. 1.514 gm/ml., 0.33 moles). The reaction mixture was then allowed to reflux for three hours, after which 400 ml. of tetrahydrofuran was distilled off. Methanol was added to destroy the excess NaH and the remaining methanol and tetrahydrofuran were distilled off. The remaining reaction

mixture was dumped onto ice water and extracted with chloroform (3 X 200 ml.). The chloroform was dried and flash evaporated to give a crude product which was purified by vacuum distillation, b.p. 87-90°C at 0.03 mm. of Hg. (47.6 gm., 0.167 moles, 50.5%).

Infrared spectrum no. 2 [Fig. II]: Absorptions (cm^{-1}) at 1740 (ester), 1650 (C=C).

N.m.r. spectrum no.2 [Fig. XX]: Absorptions at 4.08-5.16 (m, 3 H's, olefinic protons), 5.87 (q, J = 7 Hz., 4 H's, $CH_3\underline{CH}_2$-), 5.95 (q, J = 7 Hz., 2 H's, $CH_3\underline{CH}_2$-), 6.33-6.55 (m, 4 H's, aliphatic protons), 8.78 (t, J = 7 Hz., 9 H's, $\underline{CH}_3CH_2$-).

(3) Hydrolysis of ∝-ethylcarboxylate-∝-allyl diethylsuccinate (XXVI):

The triester (XXVI) (10 gm., 0.035 moles) was added to a solution of 10% sodium hydroxide (100 ml.) and ethanol (10 ml.). This solution was refluxed under nitrogen for 3.5 hours. Most of the ethanol was then distilled off and the solution was cooled and acidified with concentrated sulfuric acid. The acid solution was flash evaporated and extracted with chloroform (3 X 25 ml.) to remove any starting material. The remaining triacid (XXVII) and inorganic salts were then extracted with 15% MeOH/$CHCl_3$ (3 X 30 ml.). The 15% MeOH/$CHCl_3$ solution was flash evaporated to give the triacid (XXVII) (4.04 gm., 0.02 moles, 57.2%).

The triacid was recrystallized from chloroform to give white crystals, m.p. = 156-158°C.

Infrared spectrum no. 3 [Fig. III]: Absorptions (cm^{-1}) at 3100 (acid -OH), 1710 (acid C=O).

(4) Preparation of allyl succinic anhydride (XXVIII):

(a) via the triacid (XXVII):

The triacid (XXVII) (4.04 gm., 0.02 moles) was refluxed with acetic anhydride (60 ml.) for one hour. The acetic anhydride was removed by flash evaporation and the allyl succinic anhydride (XXVIII) was purified by vacuum distillation, b.p. 65-68°C at 0.05 mm. of Hg. (1.76 gm., 0.0124 moles, 61%).

Infrared spectrum no. 4 [Fig. IV]: Absorptions (cm^{-1}) at 1860 and 1780 (anhydride), 1640 (C=C).

N.m.r. spectrum no. 3 [Fig. XXI]: Absorptions at 3.91-5.16 (m, 3 H's, olefinic protons); 6.27-8.07 (m, 5 H's, aliphatic protons).

Mass spectrum no. 1 [Fig. XXXIII]: M^+/e 140, 112, 95, 68, 67.

(b) via maleic anhydride: according to a method by Phillips and Johnson[27] with slight modifications listed below.

Maleic anhydride (15.3 gm., 0.156 moles) was added to benzene (35 ml.) in a 100 ml. round bottom flask. The flask was placed into a Parr high pressure reactor and more benzene (20 ml.) was placed inside the reactor. The reactor was sealed and propene (1000 psi) was allowed to flow into the reactor. This was heated to 170°C. and rocked for 72 hours. The reactor was cooled and the excess propene was released. The allyl succinic anhydride (XXVIII) was then purified by vacuum distillation. The maleic anhydride distilled at 30-60°C at 0.05 mm. of Hg. crystallizing in the condenser.

After the reaction flask reached 60°C the condenser was cleaned and the allyl succinic anhydride (XXVIII) was distilled (5.47 gm., 0.0391 moles, 25%).

The anhydride produced was similar in i.r., n.m.r., m. spec., and b.p. to the one produced via the triacid.

(5) Preparation of methylcyclohex-2-ene-1-one-5-carboxylate (XXXI): according to a method by Phillips and Johnson[27] with slight modifications listed below.

Over a ½ hour period sublimed aluminum chloride (0.73 gm., 5.46 mmoles) was added to a cooled (0°C) solution of anhydride (XXIX) (1.047 gm., 7.46 mmoles) and dry 1,1,2,2-tetrachloroethane (15 ml.). This reaction mixture was allowed to stir at room temperature for 24 hours. The solution was then poured onto ice water and the organic material was taken up in chloroform (3 X 25 ml.). The chloroform solution was then extracted with a saturated sodium carbonate solution (3 X 25 ml.) and upon acidification the solution became cloudy. This acid solution was put in a continuous chloroform extractor and extracted for 14 hours. The chloroform was removed by flash evaporation and the resulting oil was methylated with an ethereal solution of diazomethane. The methylated product was purified on a t.l.c. plate developed with a 1% $MeOH/CHCl_3$ solution. Three separations were needed to obtain a pure product (65 mg., 0.422 mmoles, 5.7%).

Infrared spectrum no. 5 [Fig. V]: Absorptions (cm^{-1}) at 1730 (ester C=O), 1680 (alpha,beta unsaturated ketone), 1620 (C=C). Literature value[27]: 1739, 1681, 1626 cm^{-1}.

N.m.r. spectrum no. 4 [Fig. XXII]: Absorptions at 3.24 (m, 1 H, olefinic proton), 3.94-4.16 (m, 1 H, olefinic proton), 4.72 (methylene chloride), 6.32 (s, 3 H's, $COOCH_3$), 7.40 (m, 5 H's, aliphatic ring protons), 9.63 (TMS spinner).

(6) Preparation of methyl-3-carbethoxy-4-carbomethoxy-5-isoxolylacetate (XXXV): according to a method by J.A. Buccini[33] with slight modifications listed below.

A solution of dimethyl acetone dicarboxylate (106 gm., 0.609 moles) and dry benzene (2.5 liters) was placed in a three necked five liter round bottom flask equipped with an overhead stirrer, a heating mantle and a Dean-Stark water separator and condenser. A 50% suspension of NaH/oil (29.2 gm., 0.609 moles) was added to the benzene solution over a fifteen minute period. After completing the addition, the mixture was stirred for one hour and then ethyl chloroximinoacetate (XXXIII) (88.6 gm., 0.585 moles) was added and the reaction mixture stirred for 2.5 hours at room temperature. A catalytic amount (515 mg.) of p-toluenesulfonic acid monohydrate was added to the mixture which was then refluxed for five hours with removal of water formed in the reaction. The reaction mixture was cooled, extracted with water (3 X 400 ml.) and the benzene removed by flash evaporation. An oily residue was obtained which separated into two layers, the top layer being the mineral oil. The layers were separated and after vacuum distillation of the lower layer the isoxazole triester (XXXV) was obtained as a clear oil, b.p. 118-120°C at 0.05 mm. of Hg. (26.1 gm., 0.096 moles, 16.5%).

Infrared spectrum no. 6 [Fig. VI]: Absorptions (cm^{-1}) at 1740 (ester C=O), 1610 (isoxazole ring).

(7) Preparation of 5-carbomethoxy-6,8-dihydroxyl-7-cyano-1-tetralone (XXXVII): according to a method by J.A. Buccini[33] with slight modifications listed below.

To one liter of anhydrous tetrahydrofuran was added the isoxazole triester (XXXV) (17.3 gm., 0.064 moles). A 50% suspension of NaH/oil (3.07 gm., 0.064 moles) was added slowly to the tetrahydrofuran solution and allowed to stir for one hour. Following the addition of 2-cyclohexene-1-one (9.216 gm., 0.096 moles) the reaction mixture was allowed to reflux for 43 hours. Most of the tetrahydrofuran was then distilled off and the reaction mixture was allowed to cool. The residue in the reaction flask was transferred to a separatory funnel, diluted with ether (2 liters) and extracted with cold 3% NaOH (4 X 300 ml.). The aqueous extracts were combined, acidified with concentrated HCl and extracted with chloroform (4 X 300 ml.). The chloroform was flash evaporated and the solid residue was refluxed in methanol (150 ml.) for 1.5 hours. Suction filtration gave the diphenol ester (XXXVII) as a pale cream solid (6.65 gm., 0.025 moles, 39.8%). Recrystallization from methanol gave white needles, m.p. 203-205°C.

Infrared spectrum no. 7 [Fig. VII]: Absorptions (cm^{-1}) at 2650 (OH, chelated to ester and ketone); 2250 (-CN); 1675 (ester C=O chelated to -OH); 1635 (ketone chelated to -OH); 1610 (aromatic).

(8) Preparation of 5-carbomethoxy-6,8-dimethoxy-7-cyano-1-tetralone (XXXVIII): according to a method by J.A. Buccini[33] with slight modifications listed below.

An excess of ethereal diazomethane was added to a suspension of the diphenol ester (XXXVII) (2.76 gm., 10.6 mmoles) in chloroform and the mixture was stirred for one hour to give a clear solution. The solvents were removed by flash evaporation and the residue crystallized from methanol. (9.45 mmoles, 2.73 gm., 89%). Recrystallization from methanol gave white needles, m.p. 73-74°C.

Infrared spectrum no. 8 [Fig. VIII]: Absorptions (cm^{-1}) at 2270 (-CN), 1740 (ester C=O), 1695 (aryl ketone).

N.m.r. spectrum no 5 [Fig. XXIII]: Absorptions at 5.85, 5.96, 6.05 (s, 3 H's each, $-OCH_3$), 7.00-8.70 (m, 6 H's, ring protons).

(9) Preparation of 5-carbomethoxy-6-methoxy-7-cyano-8-hydroxy-1-tetralone (XXXIX):

The diphenol ester (XXXVII) (190 mg., 0.73 mmoles) was dissolved in acetone (25 ml.). To this solution was added sodium bicarbonate (200 mg., 2.38 mmoles) and dimethyl sulfate (250 mg., 1.98 mmoles). The reaction mixture was allowed to reflux for five hours, then cooled and the acetone removed by flash evaporation. Water (25ml.) and ether (25 ml.) were added to the residue in a separatory funnel and the ether extract was pumped down to yield the crude product (180 mg., 0.655 mmoles, 90%). Recrystallization from methanol gave white crystals, m.p. 84-85°C.

Infrared spectrum no. 9 [Fig. IX]: Absorptions (cm^{-1})

at 2250 (-CN), 1730 (ester C=O), 1640 (ester chelated to -OH).

N.m.r. spectrum no. 6 [Fig. XXIV]: Absorptions at 3.9 (s, 1 H, -OH chelated to ketone), 5.78, 6.06 (s, 3 H's each, $-OCH_3$), 7.0-8.5 (m, 6 H's, ring protons).

Mass spectrum no. 2 [Fig. XXXIV]: M^+/e 275, 244, 243, 214.

(10) Preparation of 1-acetoxy-3,4-dihydro-5-carbomethoxy-6,8-dimethoxy-7-cyanonaphthalene (XL):

To acetic anhydride (30 ml.) and sodium acetate (1.85 gm., 22.6 mmoles) was added some dimethoxy ester (XXXVIII) (770 mg., 2.66 mmoles). This was allowed to reflux under nitrogen for 24 hours. The reaction vessel was cooled and the acetic anhydride removed by flash evaporation. Benzene (3 X 25 ml.) was then added and flash evaporated to remove all acetic anhydride. Benzene (50 ml.) was added again and the unreacted sodium acetate was filtered off and the benzene flash evaporated. The crude product (530 mg., 1.60 mmoles, 60%) was used in the preparation of the alpha bromoketone (XLI).

Infrared spectrum no. 10 [Fig. X]: Absorptions (cm^{-1}) at 2240 (-CN), 1750 (acetoxy), 1720 (carbomethoxy), 1645 (C=C).

N.m.r. spectrum no. 7 [Fig. XXV]: Absorptions at 4.26 (t, 1 H, $CH_2-C\underline{H}=C$), 4.70 (CH_2Cl_2), 6.02 (s, 3 H's, $-OCH_3$), 7.87 (s, 3 H's, $-OCOC\underline{H}_3$), 7.08-8.83 (m, 4 H's, ring protons).

(11) Preparation of 2-bromo-5-carbomethoxy-6,8-dimethoxy-7-cyano-1-tetralone (XLI):

(a) via the enol acetate (XL):

The enol acetate (XL) (500 mg., 1.51 mmoles) was dissolved in carbon tetrachloride (50 ml.). To this was added a quantitative amount of bromine and the solution was allowed to stir for two hours. The solution was washed with sodium bisulfite solution, dried and flash evaporated. The crude product was purified on t.l.c. silica gel plates developed with 2% $MeOH/CHCl_3$. (m.p. = 145-147°C.) (365 mg., 0.99 mmoles, 65.5%).

Infrared spectrum no. 11 [Fig. XI]: Absorptions (cm^{-1}) at 2250 (-CN), 1735 (ester), 1690 (ketone).

N.m.r. spectrum no. 8 [Fig. XXVI]: Absorptions at 5.35 (t, 1 H, $-CH_2-C\underline{H}Br-C$), 5.83, 5.98, 6.03 (s, 3 H's each, $-OCH_3$), 6.67-7.67 (m, 4 H's, ring protons).

Mass spectrum no. 3 [Fig. XXXV]: M^+/e 369, 367, 288, 256, 218, 201.

(b) using pyrrolidone hydrotribromide (PHT):

To dry tetrahydrofuran (200 ml.) was added some dimethoxy ester (XXXVIII) (1.908 gm., 6.6 mmoles) and pyrrolidone hydrotribromide (PHT) (3.275 gm., 6.6 mmoles). This reaction mixture was allowed to stir for two hours during which time the hemihydrobromide [$(pyrrolidone)_2 \cdot HBr$] was precipitated from solution as colorless needles. The formation of this precipitate provides a convenient visual assay of the extent of the reaction and also facilitates isolation of the product. The hemihydrobromide was filtered from the tetrahydrofuran solution and then the tetrahydrofuran was flash evaporated. The residue was taken up in

methanol from which the product (XLI) precipitates immediately (2.228 gm., 6.06 mmoles, 92%) (m.p. = 145-147°C). The i.r. and n.m.r. spectra were identical to the ones listed in (a).

It should be noted here that the 2.228 gm. and 92% yield is actually the yield of (XLI) and (XLIV) combined. Based on the fact that the bromotrimethoxy ester (XLVI) was found in a 4% yield of the final product (XLIII), it can be assumed that (XLIV) is 4% of 2.228 gm. and therefore the actual yield of (XLI) is (2.14 gm., 5.81 mmoles, 88%).

(12) Preparation of 1-carbomethoxy-2,4,5-trimethoxy-3-cyano-naphthalene (XLIII):

To triethylamine (40 ml.) was added alpha bromoketone (XLI) (1.427 gm., 3.87 mmoles) and the reaction mixture was refluxed for three hours. The triethylamine was removed by flash evaporation and the oily brown residue was taken up in chloroform (50 ml.) and washed with dilute hydrochloric acid (3 X 25 ml.). The chloroform was then dried over sodium sulfate. To the cooled chloroform solution was added an excess of diazomethane. After the methylation was complete the chloroform was removed by flash evaporation and the crude product was purified by t.l.c. on silica gel plates developed with 2% MeOH/$CHCl_3$ (602 mg., 2.00 mmoles, 51.7%). The product was recrystallized from methanol, m.p. = 127.5-129°C.

Infrared spectrum no. 13 [Fig.XIII]: Absorptions (cm^{-1}) at 2250 (-CN), 1625 (ester).

N.m.r. spectrum no. 9 [Fig. XXVII]: Absorptions at 2.27-3.19 (m, 3 H's, aromatic protons), 5.93, 5.96, 5.98, 6.00 (s, 3 H's each, $-OCH_3$).

Mass spectrum no. 4 [Fig. XXXVI]: M^+/e 301, 270, 254, 243, 227,200, 184, 170, 154.

(13) Preparation of 1-carbomethoxy-2,4,5-trimethoxy-3-cyano-6-bromonaphthalene (XLVI):

(a) as a by-product of (XLIII):

The bromotrimethoxy ester (XLVI) was first isolated as a by-product in the formation of the trimethoxy ester (XLIII). It was isolated in 4% yield during the t.l.c. of (XLIII).

(b) by bromination of the trimethoxy ester (XLIII):

To glacial acetic acid (5 ml.), some trimethoxy ester (50 mg., 0.166 mmoles) and ferric chloride (50 mg.) were added. Bromine (26.6 mg., 0.166 mmoles) was added dropwise to the stirring reaction mixture. This was allowed to stir for one hour. The acetic acid was removed by flash evaporation and the residue taken up in chloroform (30 ml.). The chloroform solution was washed with 3% sodium bisulfite (3 X 15 ml.), dried and flash evaporated. The product was purified by t.l.c. on silica gel. (45 mg., 0.118 mmoles, 71%).

Infrared spectrum no. 14 [Fig. XIV]: Absorptions (cm^{-1}) at 2250 (-CN), 1725 (ester).

N.m.r. spectrum no. 10 [Fig. XXVIII]: Absorptions at 2.30 (d, 1 H, aromatic), 2.65 (d, 1 H, aromatic), 5.92, 5.97, 6.03, 6.12 (s, 3 H's each, $-OCH_3$).

(14) Preparation of 1-carbomethoxy-2,4,5-trimethoxy-3-cyano-8-bromonaphthalene (XLVII):

To glacial acetic acid (12 ml.), some trimethoxy ester (48 mg., 0.159 mmoles) and ferric chloride (100 mg.) were added. Bromine (25.5 mg., 0.159 mmoles) was added dropwise to the solution. This was allowed to stir for two hours. The acetic acid was removed by flash evaporation and the product was taken up in chloroform (30 ml.) and washed with 3% sodium bisulfite (3 X 10 ml.). The chloroform was dried and removed by flash evaporation and the bromoester (XLVII) was purified by t.l.c. on silica gel. (42 mg., 0.111 mmoles, 70%).

Infrared spectrum no. 15 [Fig. XV]: Absorptions (cm^{-1}) at 2250 (-CN), 1740 (ester).

N.m.r. spectrum no. 11 [Fig. XXIX]: Absorptions at 2.70 ($CHCl_3$), 2.13 (d, 1 H, aromatic), 3.20 (d, 1 H, aromatic), 5.90, 5.95, 5.96, 5.98 (s, 3 H's each, $-OCH_3$). The insert is the amplification of the AB spectrum.

(15) Preparation of 1-carbamyl-2,4,5-trimethoxy-3-cyano-naphthalene (XLVIII):

In a 100 ml. flask, the trimethoxy ester (XLIII) (1.42 gm., 4.72 mmoles) was dissolved in 30 ml. of methanol.

20 ml. of liquid ammonia was added to the solution. The flask was quickly transferred to a Parr high pressure reactor and sealed. The reactor was then heated at 60°C for three hours with constant rocking. The reactor was allowed to cool and the ammonia was vented. The crude amide (XLVIII) was crystallized from methanol, m.p. = 154-155°C (1.27 gm., 4.44 mmoles, 94%).

Infrared spectrum no. 16 [Fig. XVI]: Absorptions (cm^{-1}) at 3540 and 3420 ($CONH_2$), 2230 (-CN), 1720 ($\underline{CO}NH_2$).

N.m.r. spectrum no. 12 [Fig. XXX]: Absorptions at 2.50-2.80 (m, 2 H's, aromatic), 3.08-3.50 (m, 3 H's, 1 H aromatic, 2 H's amide), 5.98, 6.02, 6.05 (s, 3 H's each, $-OCH_3$).

(16) Preparation of 1-carbamyl-2,4,5-trimethoxy-3-cyano-8-bromonaphthalene (IL):

(a) via the amide (XLVIII):

To glacial acetic acid (15 ml.), trimethoxy amide (49 mg., 0.171 mmoles) and ferric chloride (100 mg.) were added. Bromine (38 mg., 0.171 mmoles) was added dropwise to the solution. The acetic acid was removed by flash evaporation and the bromoamide (IL) was purified by t.l.c. on silica gel (45 mg., 0.123 mmoles, 72%). The product was recrystallized from methanol, m.p. = 156-157°C.

Infrared spectrum no. 17 [Fig. XVII]: Absorptions (cm^{-1}) at 3540 and 3420 ($CONH_2$), 2230 (-CN), 1720 ($\underline{CO}NH_2$).

N.m.r. spectrum no. 13 [Fig. XXXI]: Absorptions at 2.42 (d, 1 H, aromatic), 3.36 (s, 2 H's, $-CONH_2$), 3.50 (d,

1 H, aromatic), 6.03, 6.11, 6.11 (s, 3 H's each, $-OCH_3$).

Mass spectrum no. 5 [Fig. XXXVII]: M^+/e 366, 364, 335, 333, 320, 318, 285, 270, 255.

(b) via the bromoester (XLVII):

The ester of (XLVII) was converted to the amide of (IL) using the Parr high pressure reactor and the same conditions as in preparation (15). The i.r. and n.m.r. spectra were identical to the ones in (a) above.

(17) Preparation of 1-amino-2,4,5-trimethoxy-3-cyanonaphthalene (L):

To methanol (25 ml.) was added some trimethoxy amide (XLVIII) (104 mg., 0.364 mmoles) and lead tetraacetate (495 mg., 1.12 mmoles). This was allowed to reflux for three hours. The methanol was removed by flash evaporation and the residue taken up in ether. The ether solution was then washed (2 X water, 2 X sodium bicarbonate). The ether was then flash evaporated and the residue was dissolved in a 1:1 mixture of MeOH/H_2O (25 ml.). Sodium hydroxide (3gm.) was added and the mixture was refluxed for two hours. The amine was then extracted from the cooled basic solution (30 mg., 0.116 mmoles, 32%). The product was recrystallized from methanol, m.p. = 102-103°C.

Infrared spectrum no. 18 [Fig. XVIII]: Absorptions (cm^{-1}) at 3530 and 3420 ($-NH_2$), 2230 (-CN).

N.m.r. spectrum no. 14 [Fig. XXXII]: Absorptions at 2.50-3.42 (m, 3 H's, aromatic), 3.80 (2 H's, $-NH_2$), 6.00, 6.06, 6.23 (s, 3 H's each, $-OCH_3$).

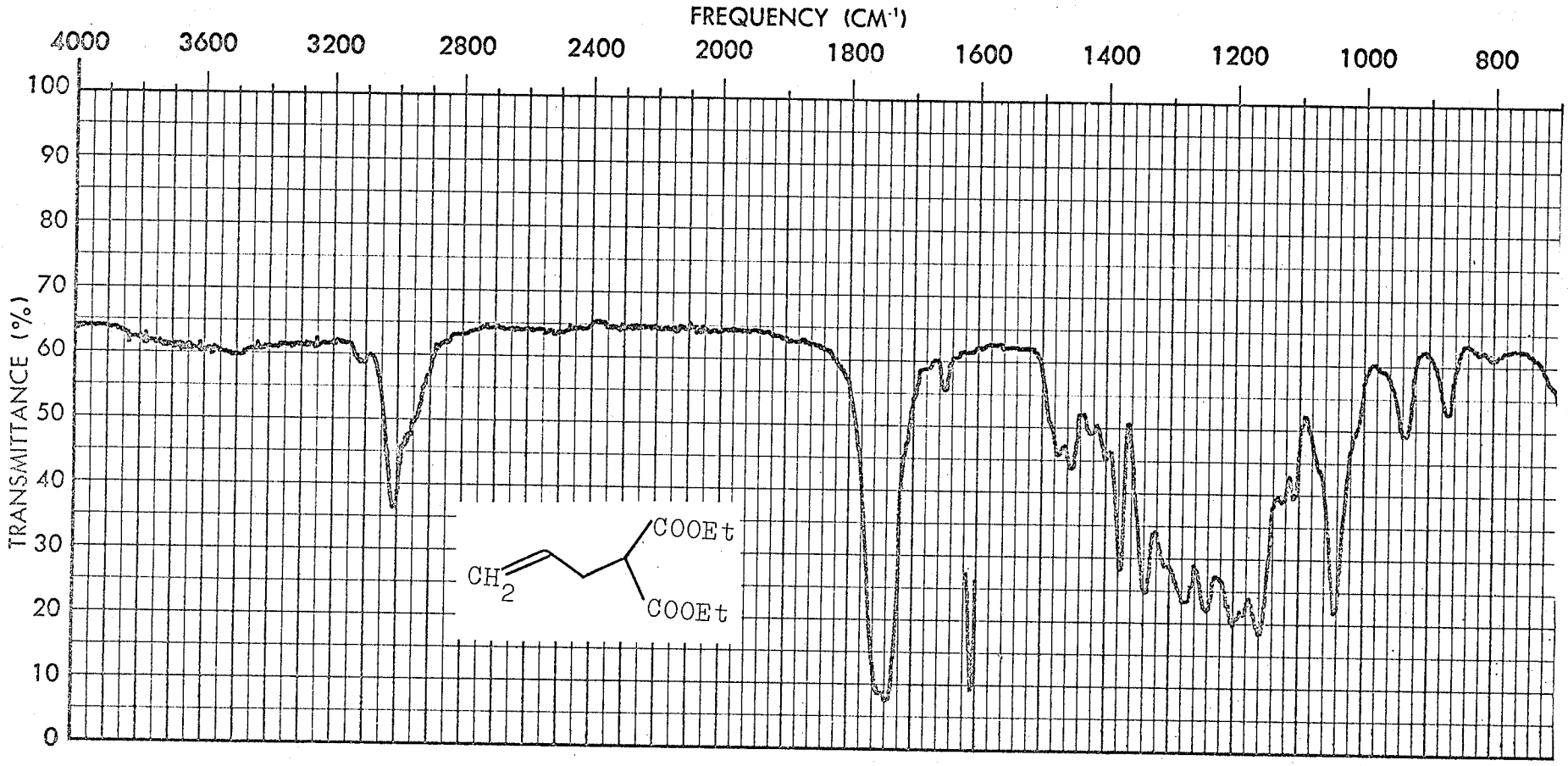


Figure I

Infrared spectrum no. 1: Allyl diethyl malonate (XXV), liquid film.

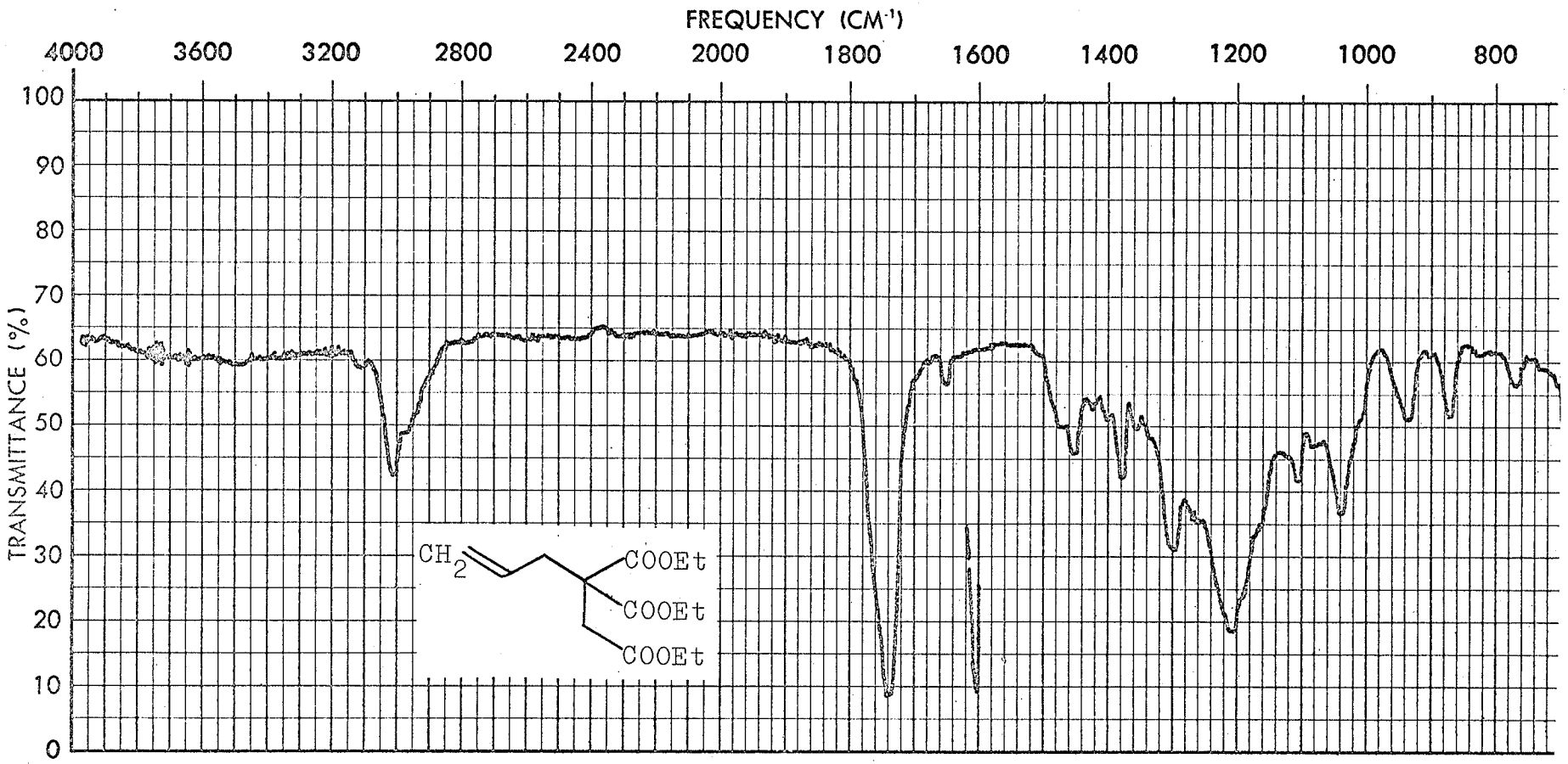


Figure II

Infrared spectrum no. 2: 2-ethylcarboxylate-2-allyldiethylsuccinate (XXVI), liquid film.

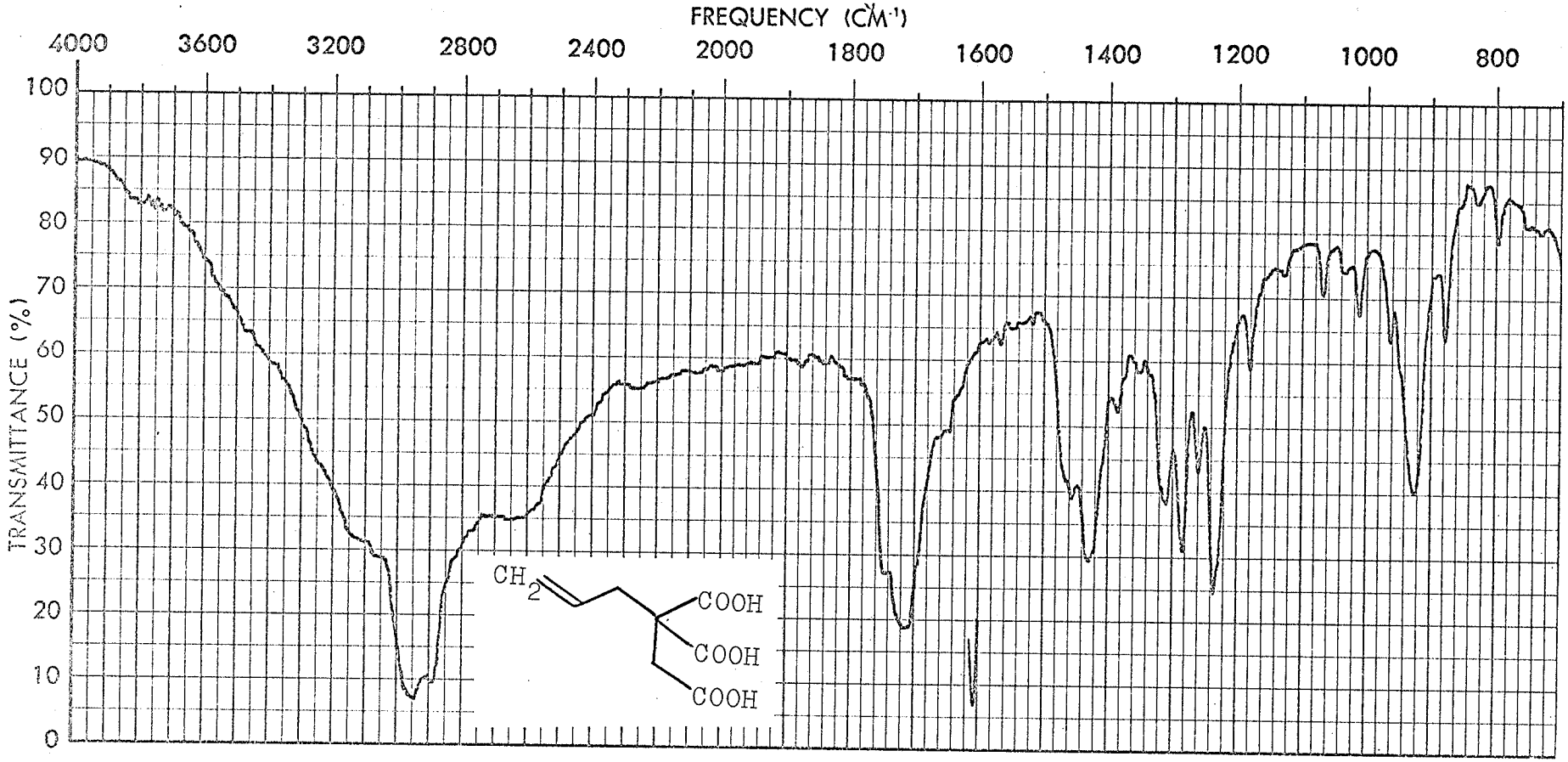


Figure III

Infrared spectrum no. 3: 2-carboxy-2-allylsuccinic acid (XXVII), nujol mull.

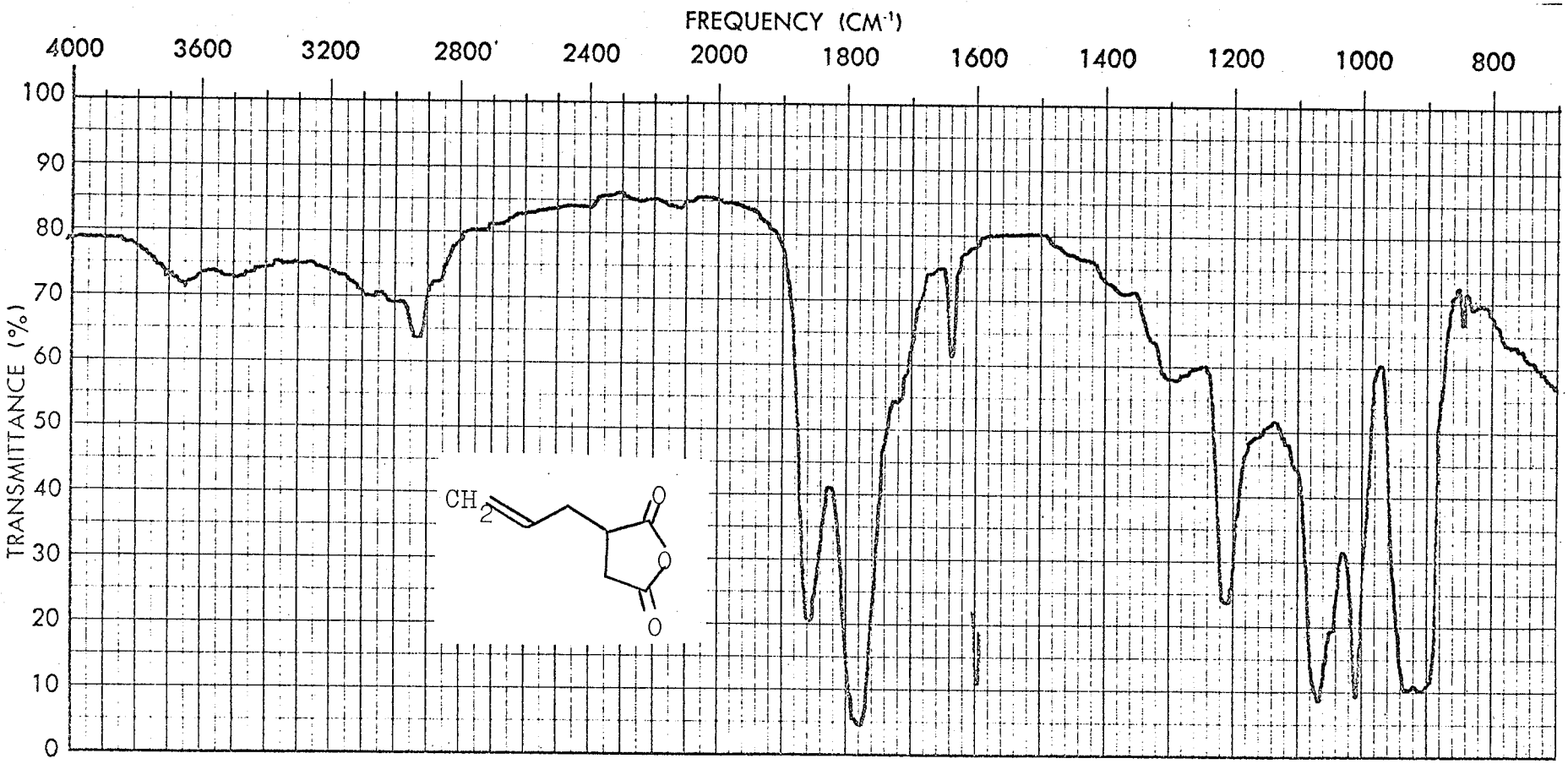


Figure IV

Infrared spectrum no. 4: Allyl succinic anhydride (XXVIII), in CH_2Cl_2 solution.

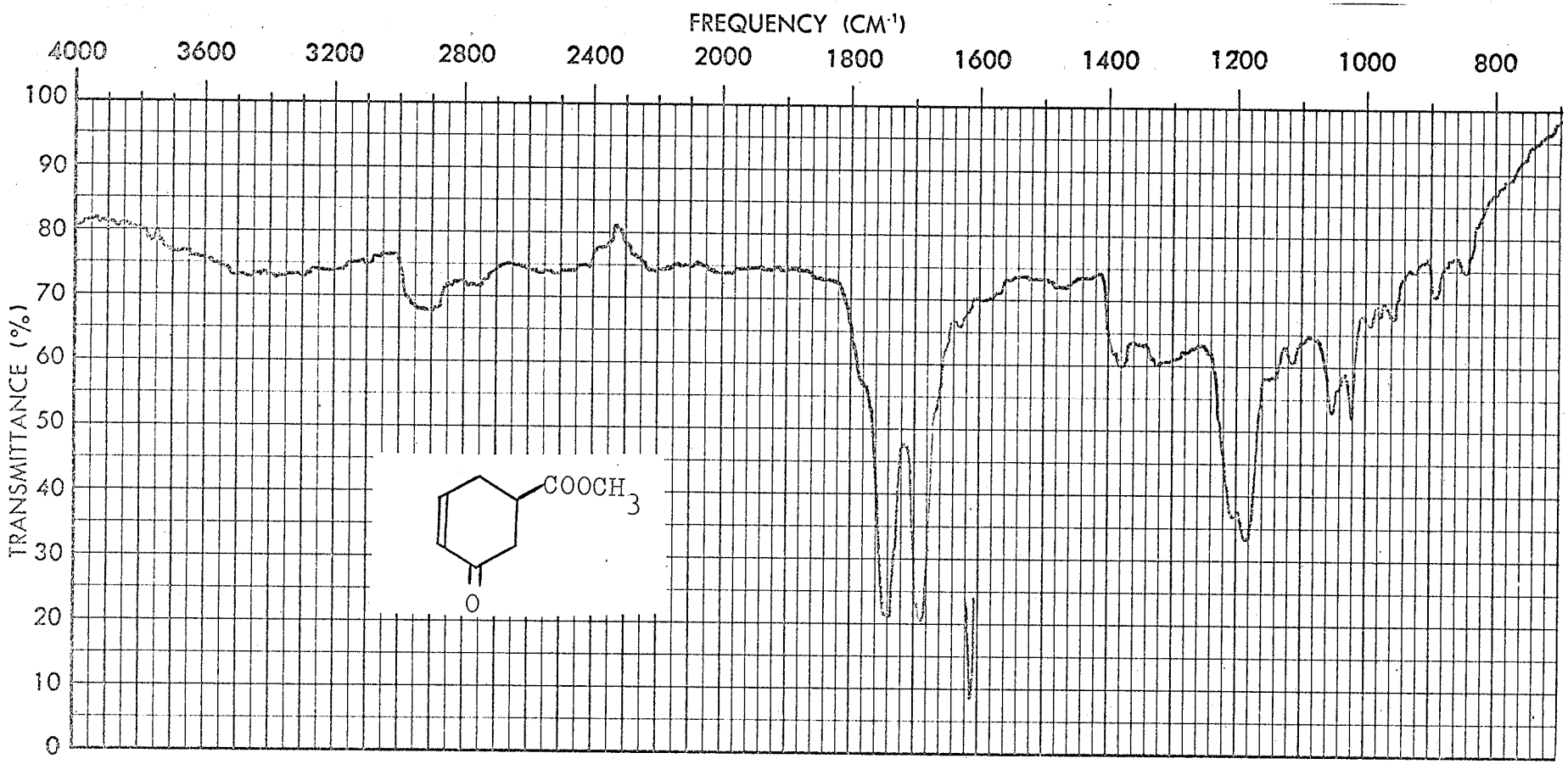


Figure V

Infrared spectrum no. 5: Methylcyclohex-2-ene-1-one-5-carboxylate (XXXI), in CH_2Cl_2 solution.

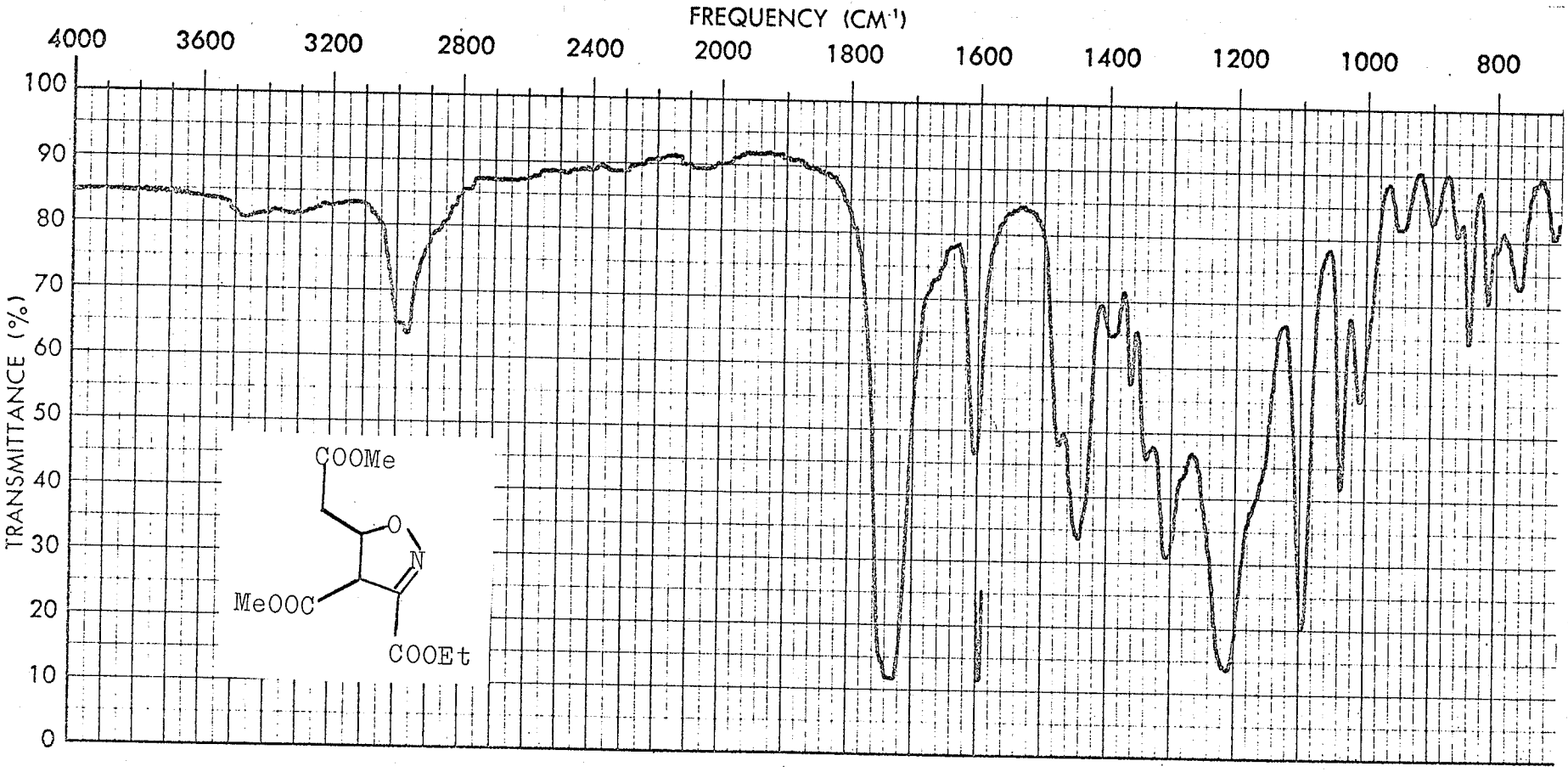


Figure VI

Infrared spectrum no. 6: Methyl-3-carbethoxy-4-carbomethoxy-5-isoxolyl-acetate (XXXV), liquid film.

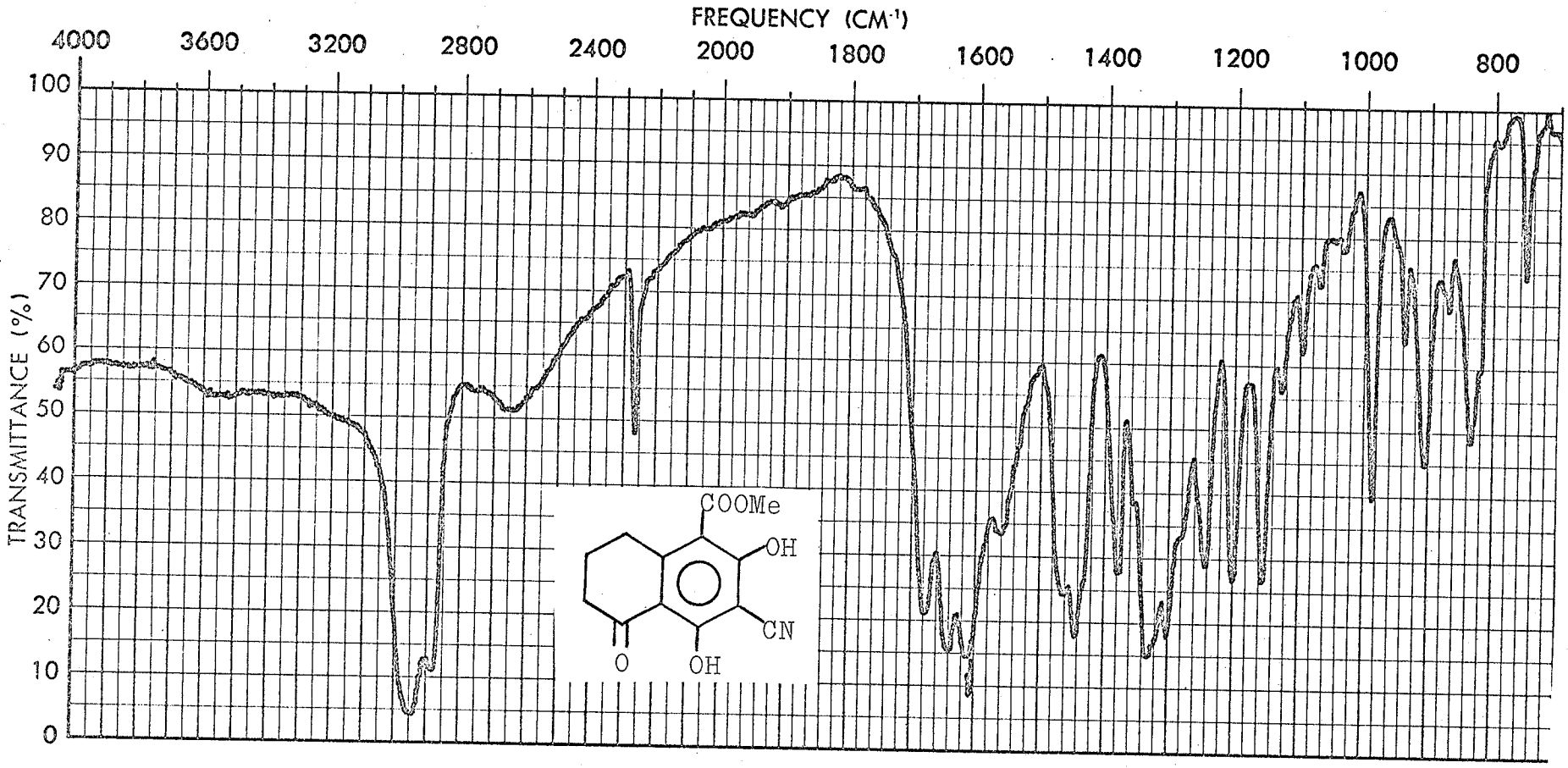


Figure VII

Infrared spectrum no. 7: 5-carbomethoxy-6,8-dihydroxy-7-cyano-1-tetralone (XXXVII), nujol mull.

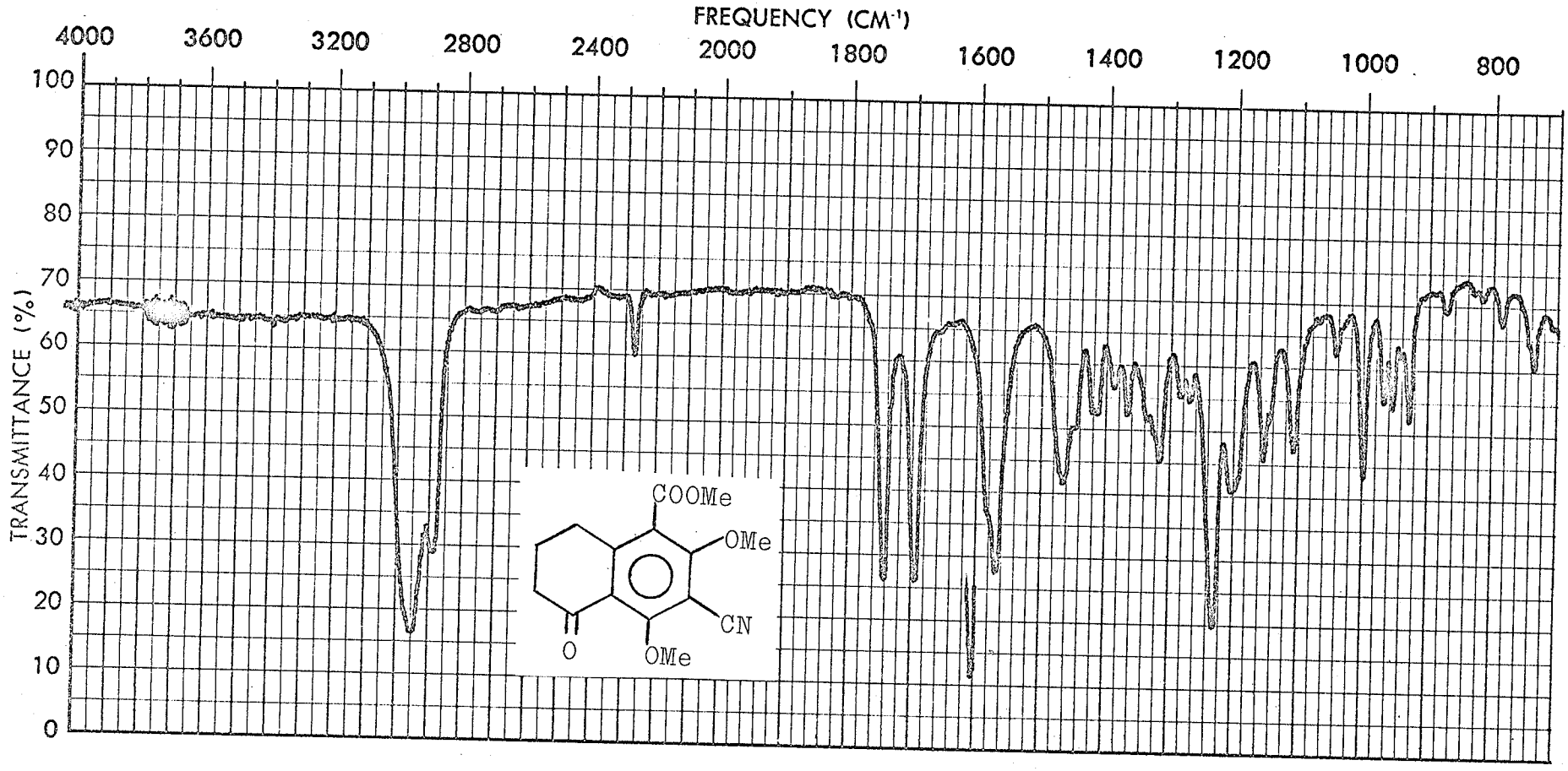


Figure VIII

Infrared spectrum no. 8: 5-carbomethoxy-6,8-dimethoxy-7-cyano-1-tetralone (XXXVIII), nujol mull.

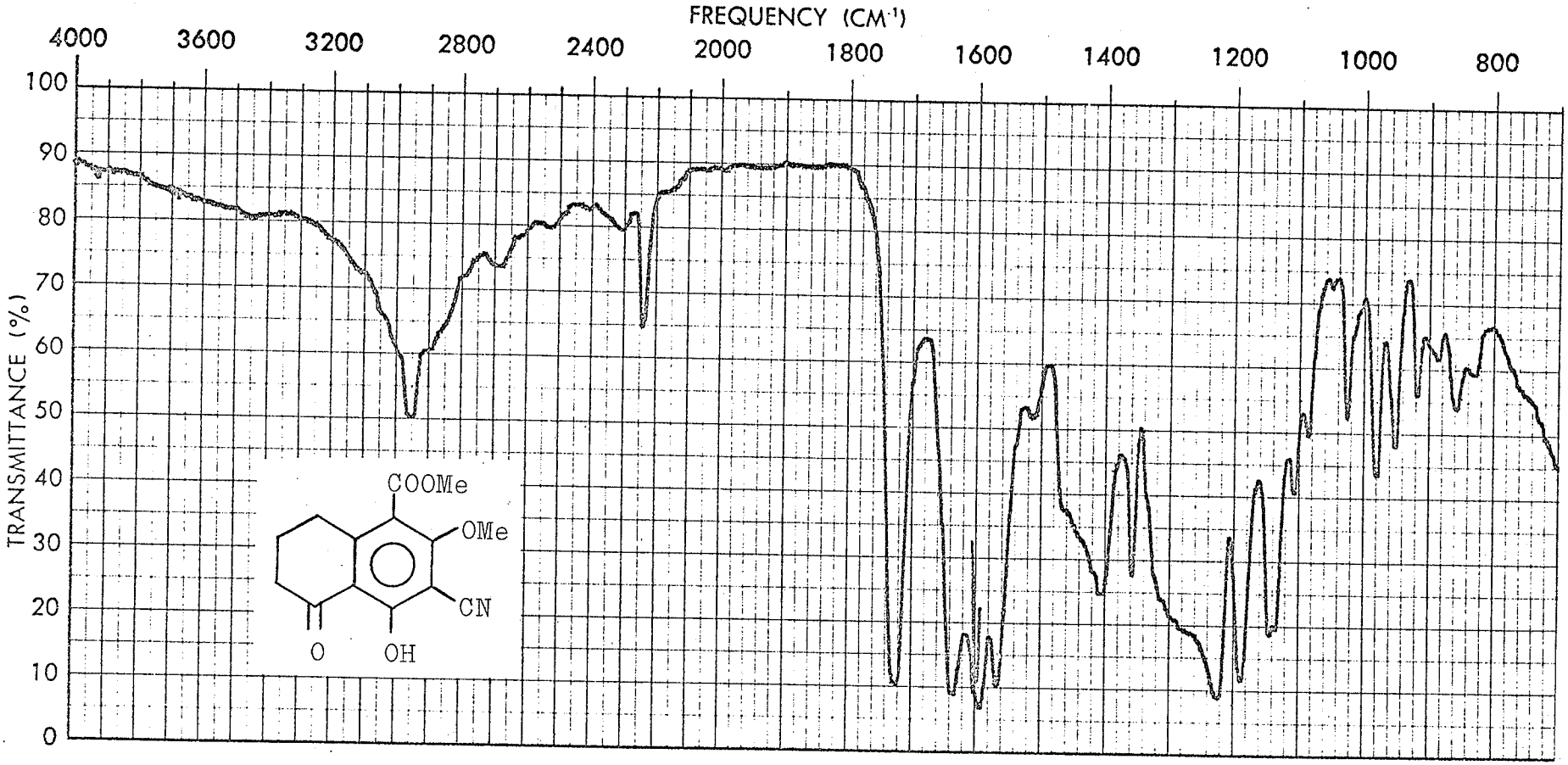


Figure IX

Infrared spectrum no. 9: 5-carbomethoxy-6-methoxy-7-cyano-8-hydroxy-1-tetralone (XXXIX), in CH_2Cl_2 solution.

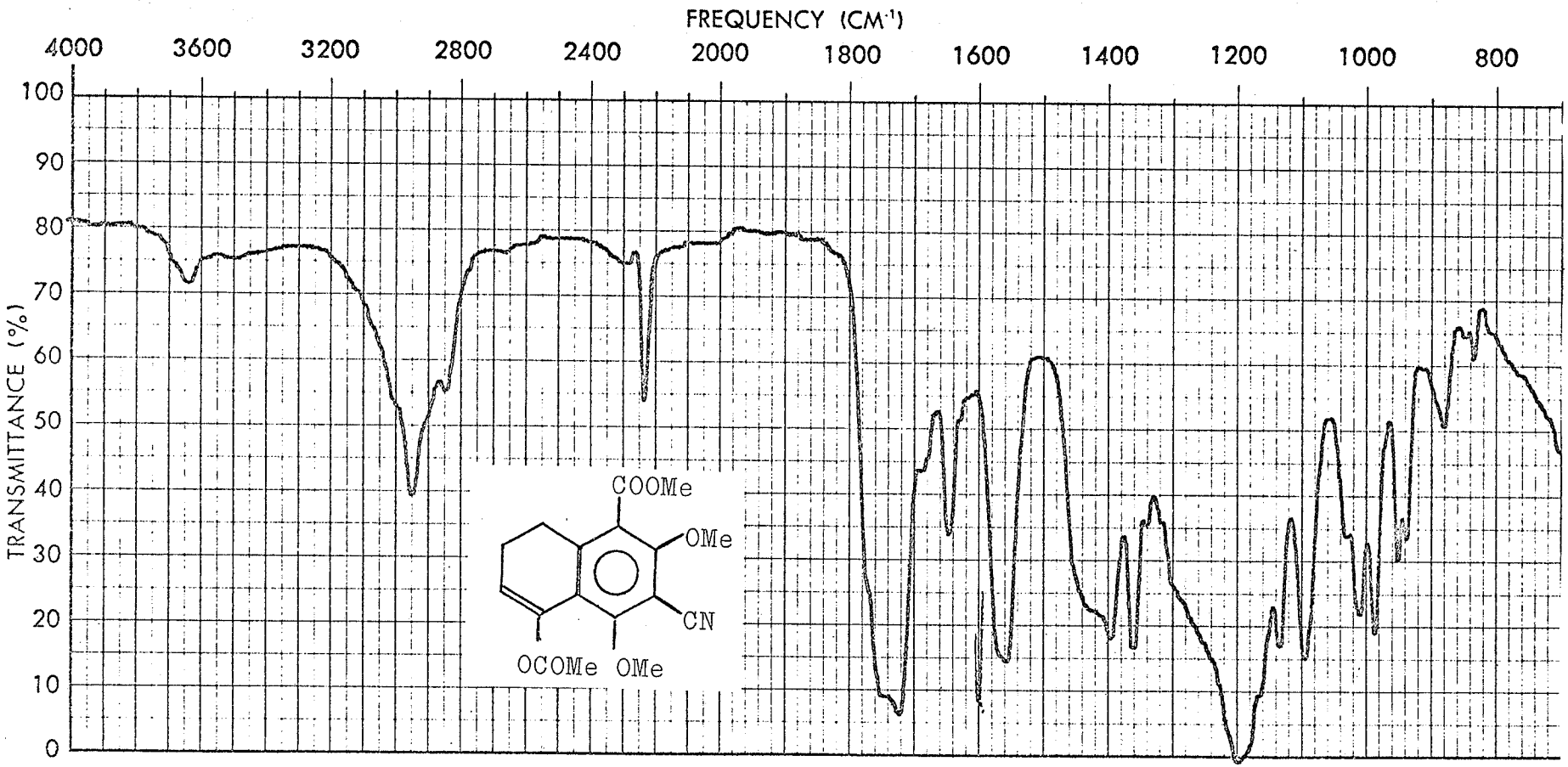


Figure X

Infrared spectrum no. 10: 1-acetoxy-3,4-dihydro-5-carbomethoxy-6,8-dimethoxy-7-cyanonaphthalene (XL), in CH_2Cl_2 solution.

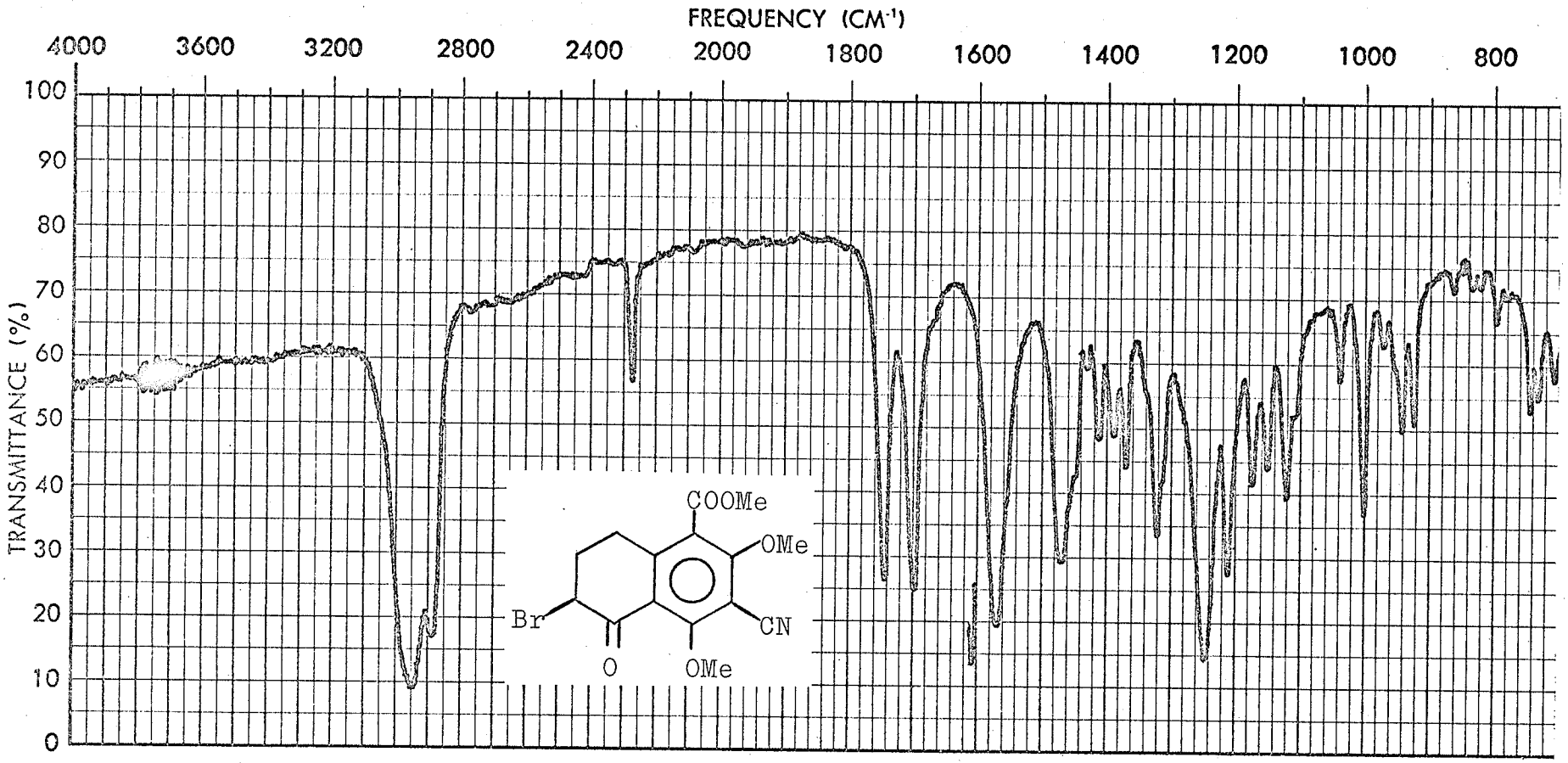


Figure XI

Infrared spectrum no. 11: 2-bromo-5-carbomethoxy-6,8-dimethoxy-7-cyano-1-tetralone (XLI), nujol mull.

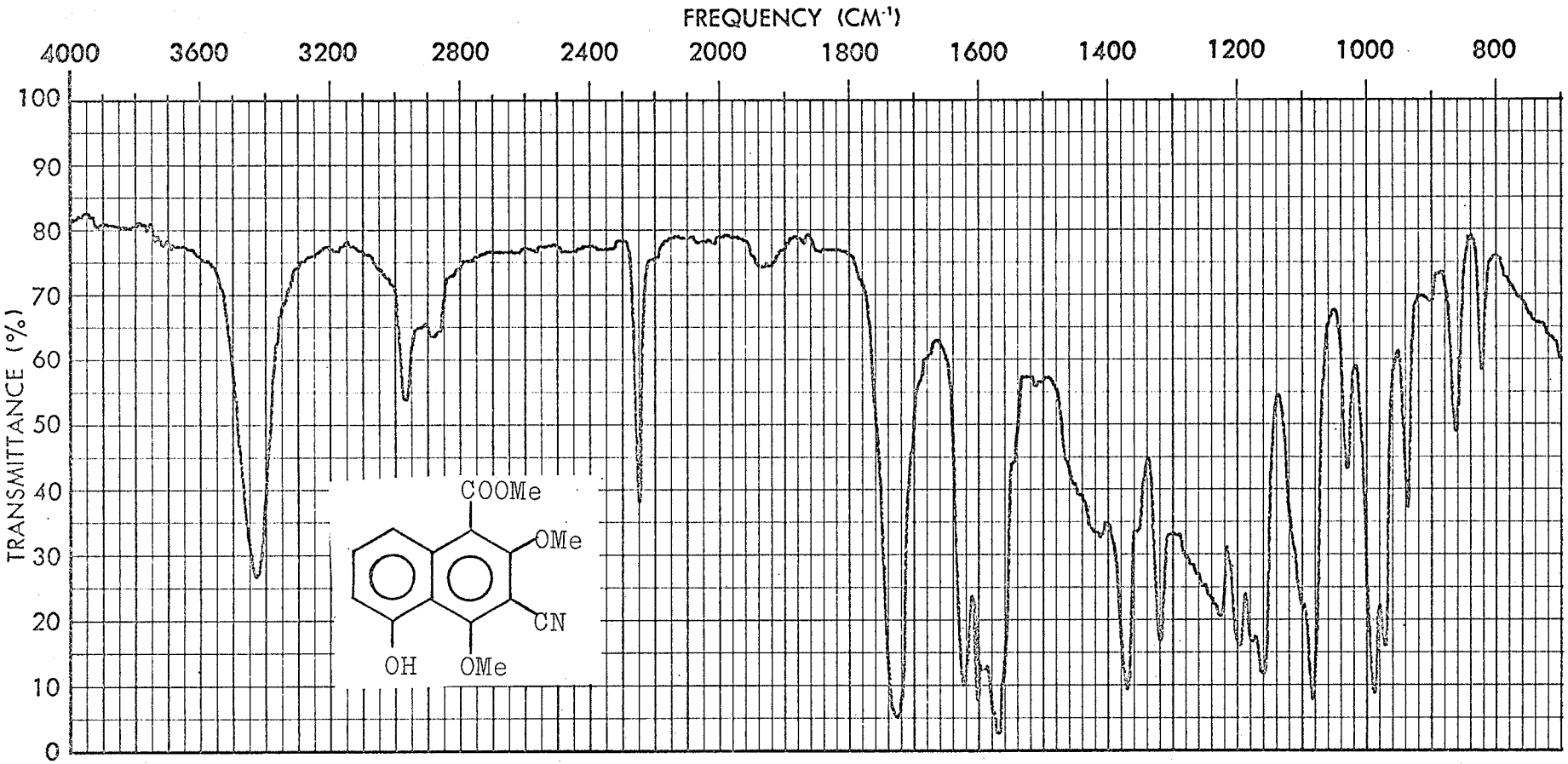
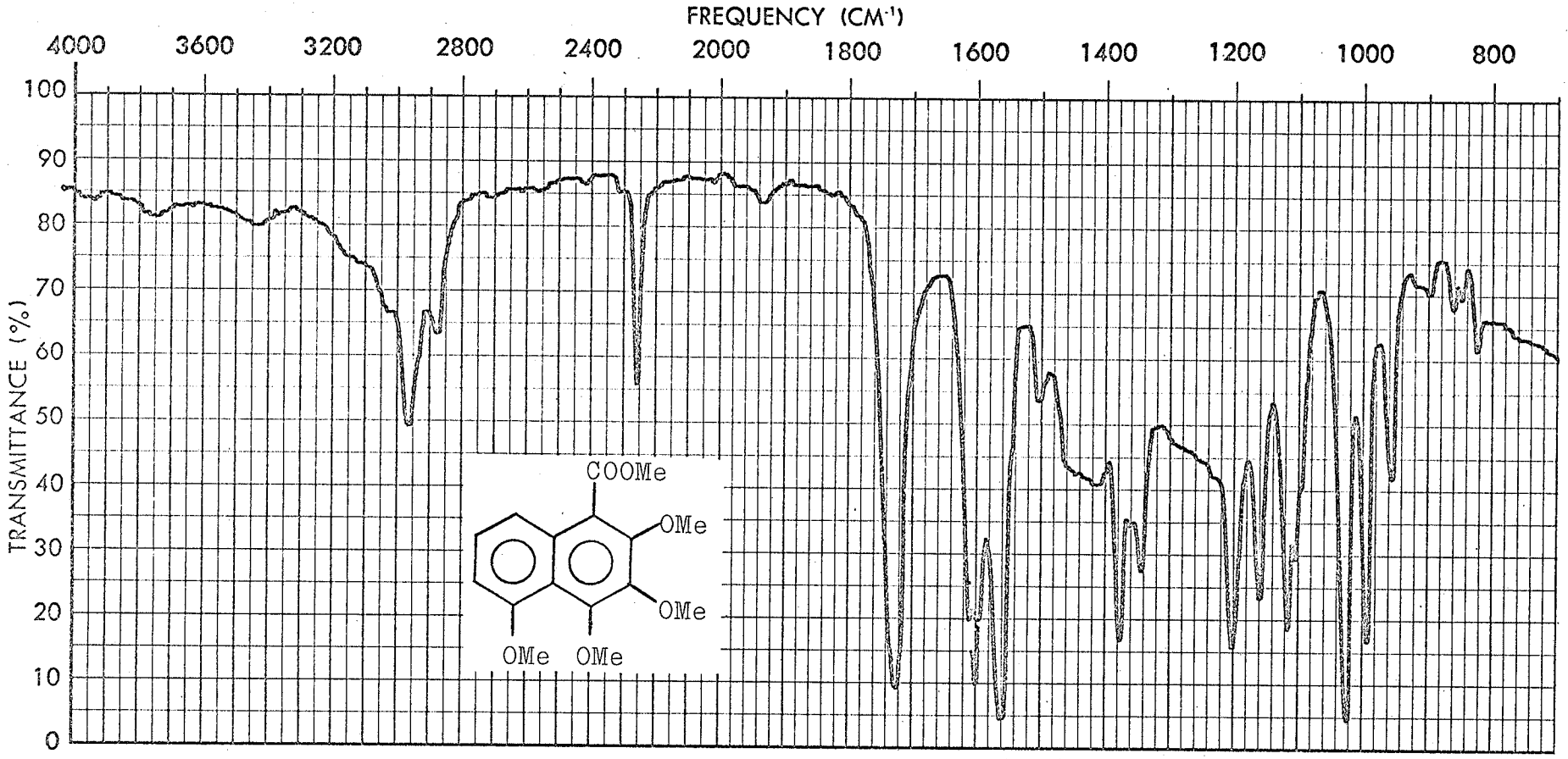


Figure XII

Infrared spectrum no. 12: 1-carbomethoxy-2,4-dimethoxy-3-cyano-5-hydroxynaphthalene (XLII), in CH_2Cl_2 solution.

Figure XIII



Infrared spectrum no. 13: 1-carbomethoxy-2,4,5-trimethoxy-3-cyano-naphthalene (XLIII), in CH_2Cl_2 solution.

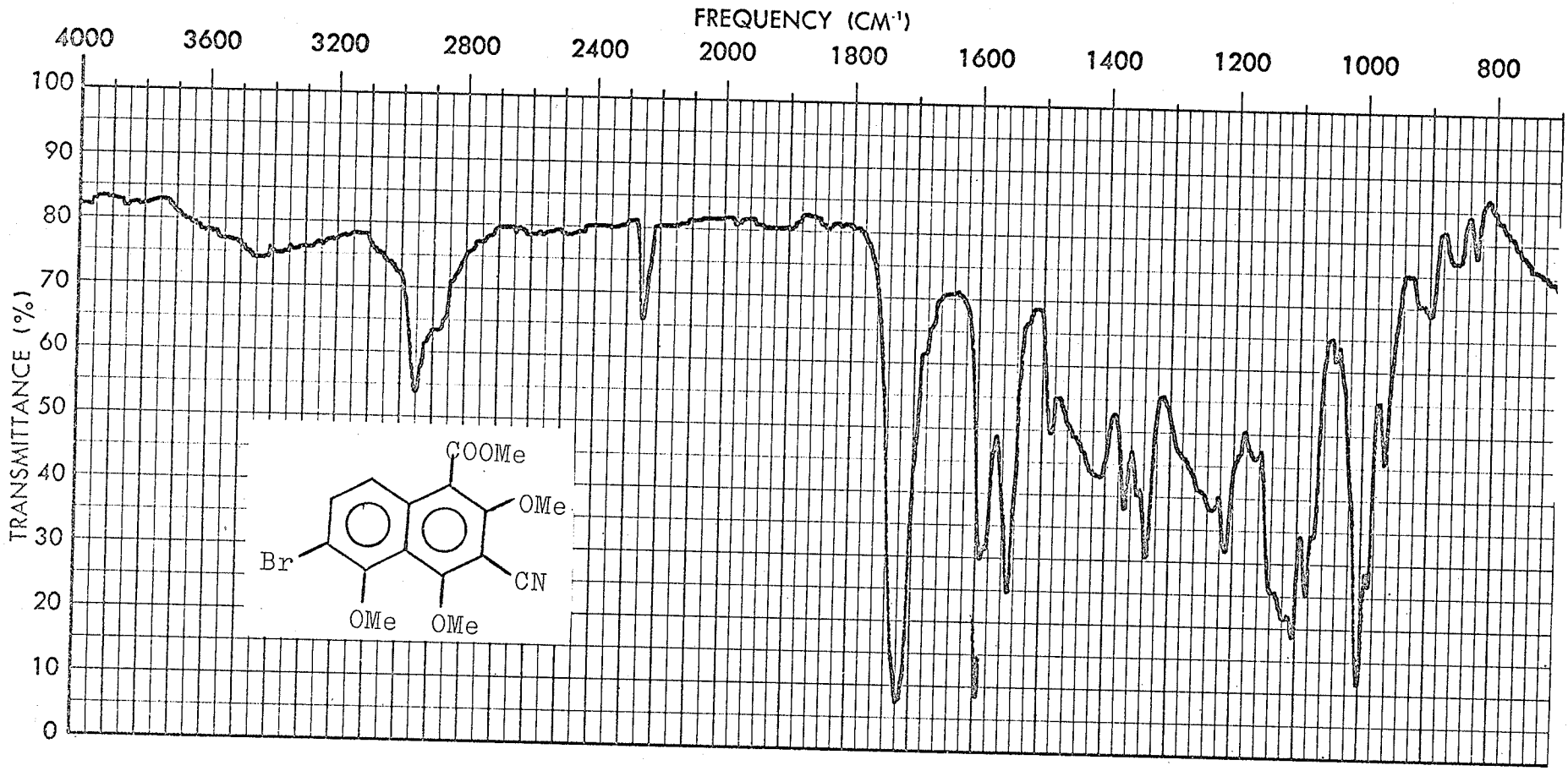


Figure XIV

Infrared spectrum no. 14: 1-carbomethoxy-2,4,5-trimethoxy-3-cyano-6-bromonaphthalene (XLVI), in CH_2Cl_2 solution.

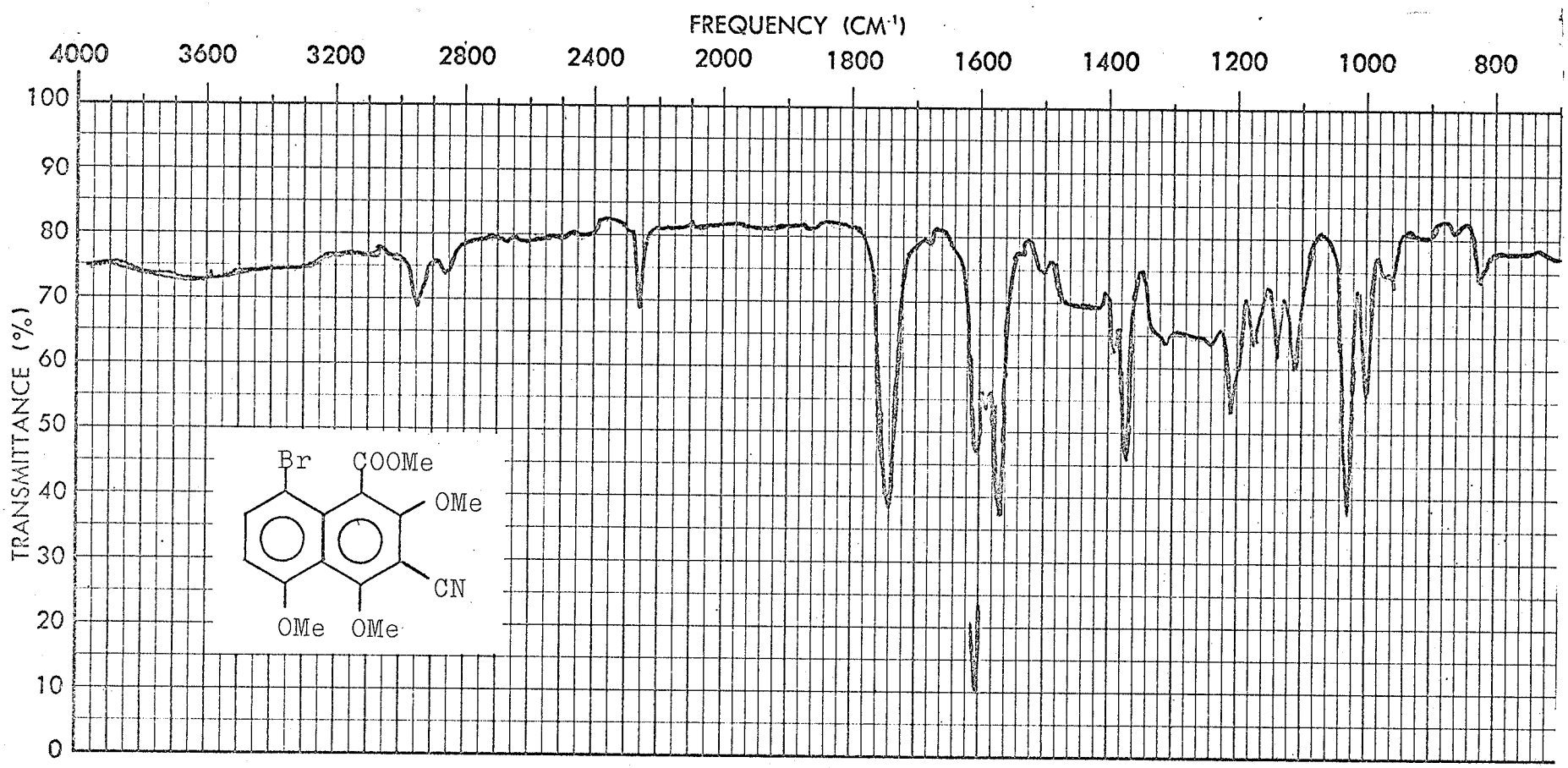


Figure XV

Infrared spectrum no. 15: 1-carbomethoxy-2,4,5-trimethoxy-3-cyano-8-bromonaphthalene (XLVII), in CH_2Cl_2 solution.

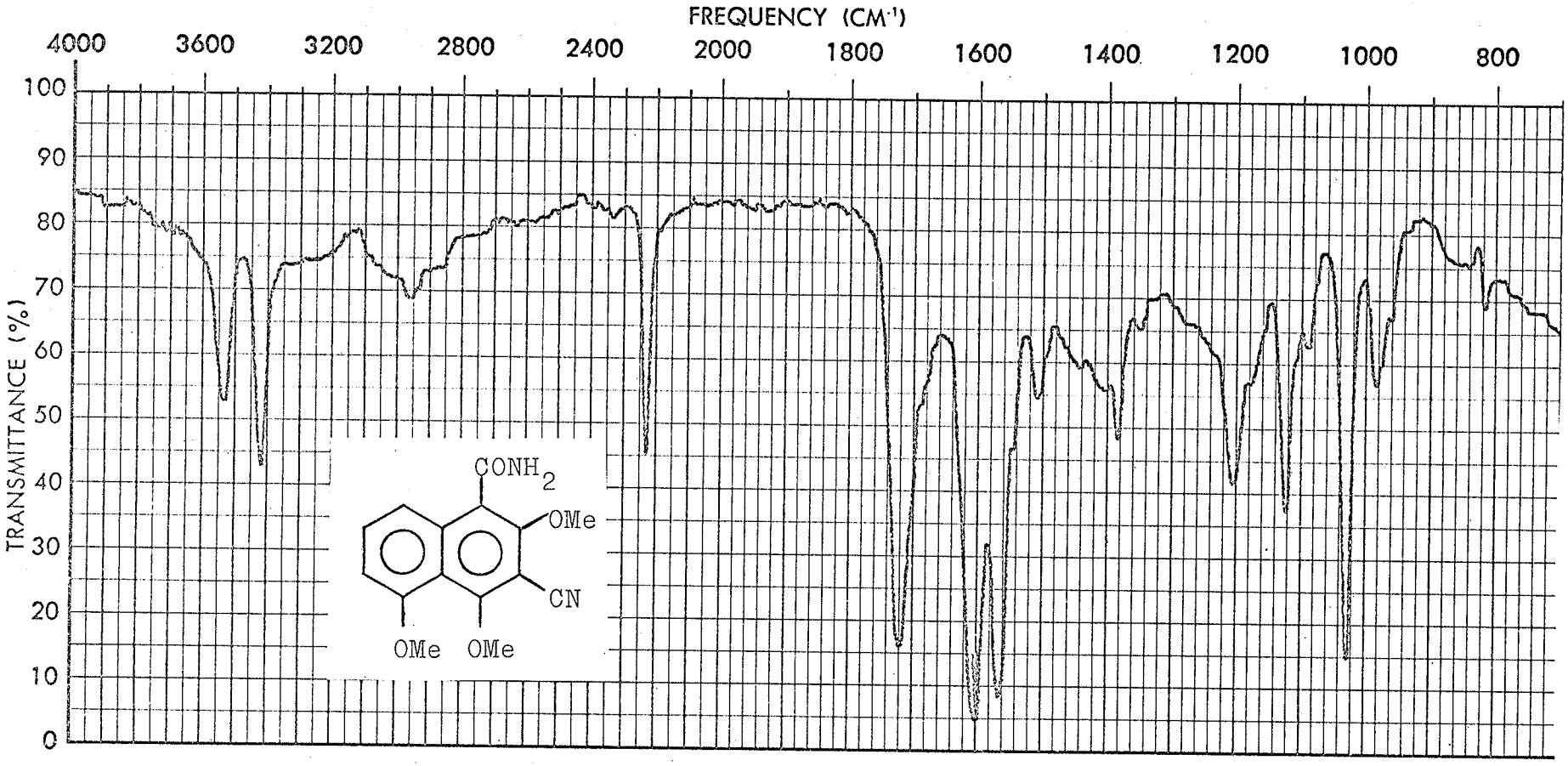


Figure XVI

Infrared spectrum no. 16: 1-carbamyl-2,4,5-trimethoxy-3-cyanonaphthalene (XLVIII), in CH_2Cl_2 solution.

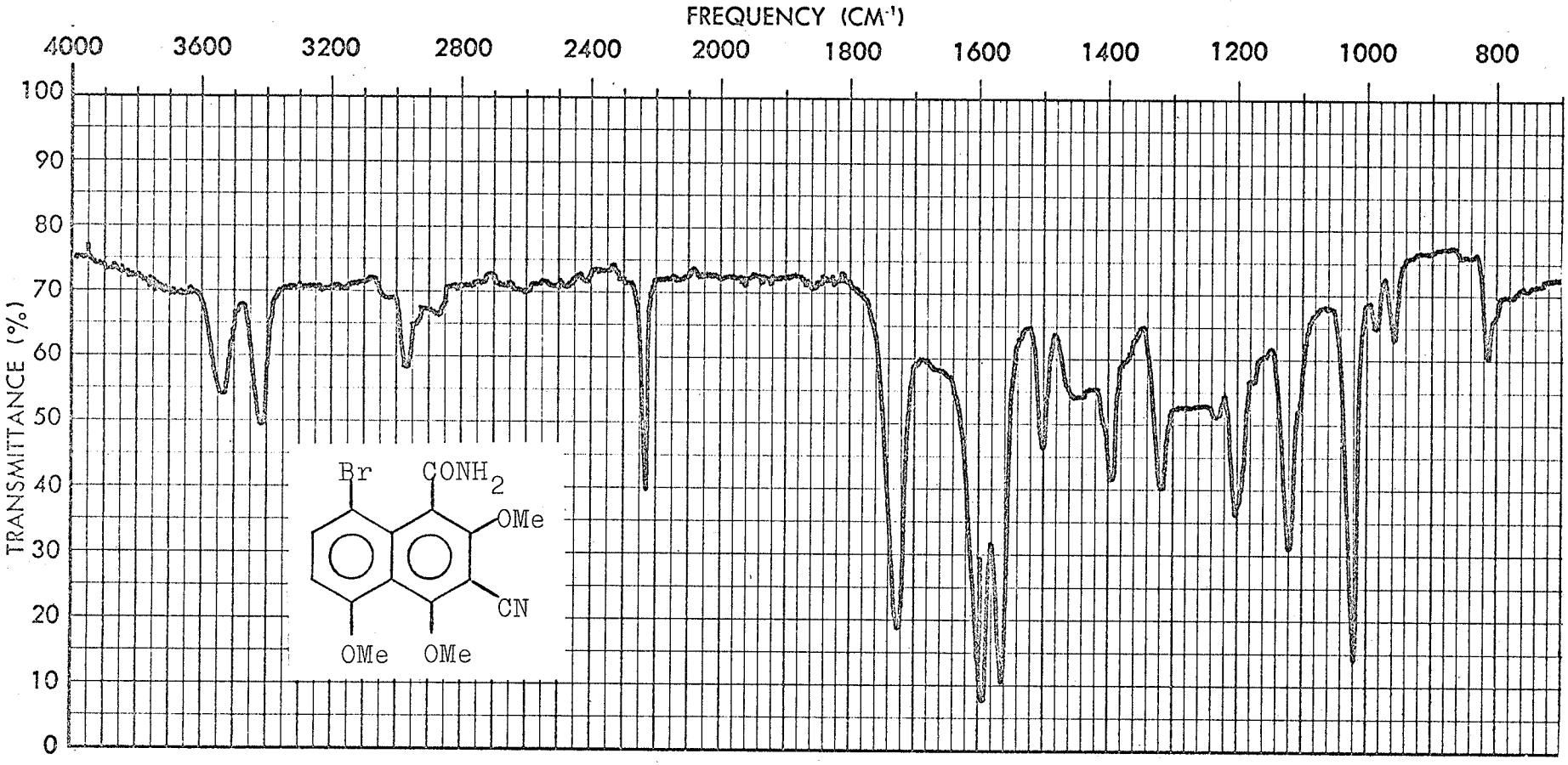


Figure XVII

Infrared spectrum no. 17: 1-carbamyl-2,4,5-trimethoxy-3-cyano-8-bromo-naphthalene (IL), in CH_2Cl_2 solution.

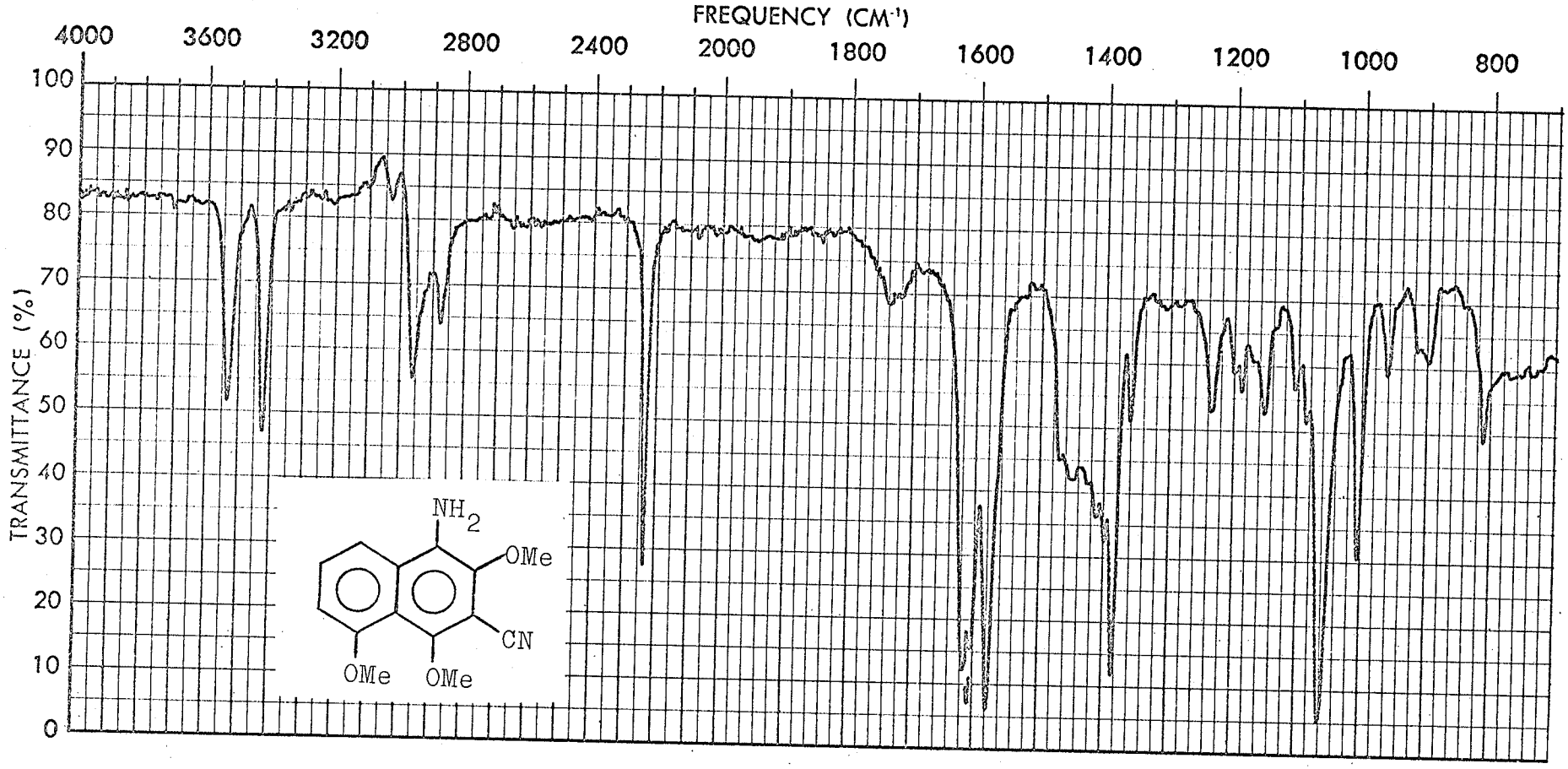
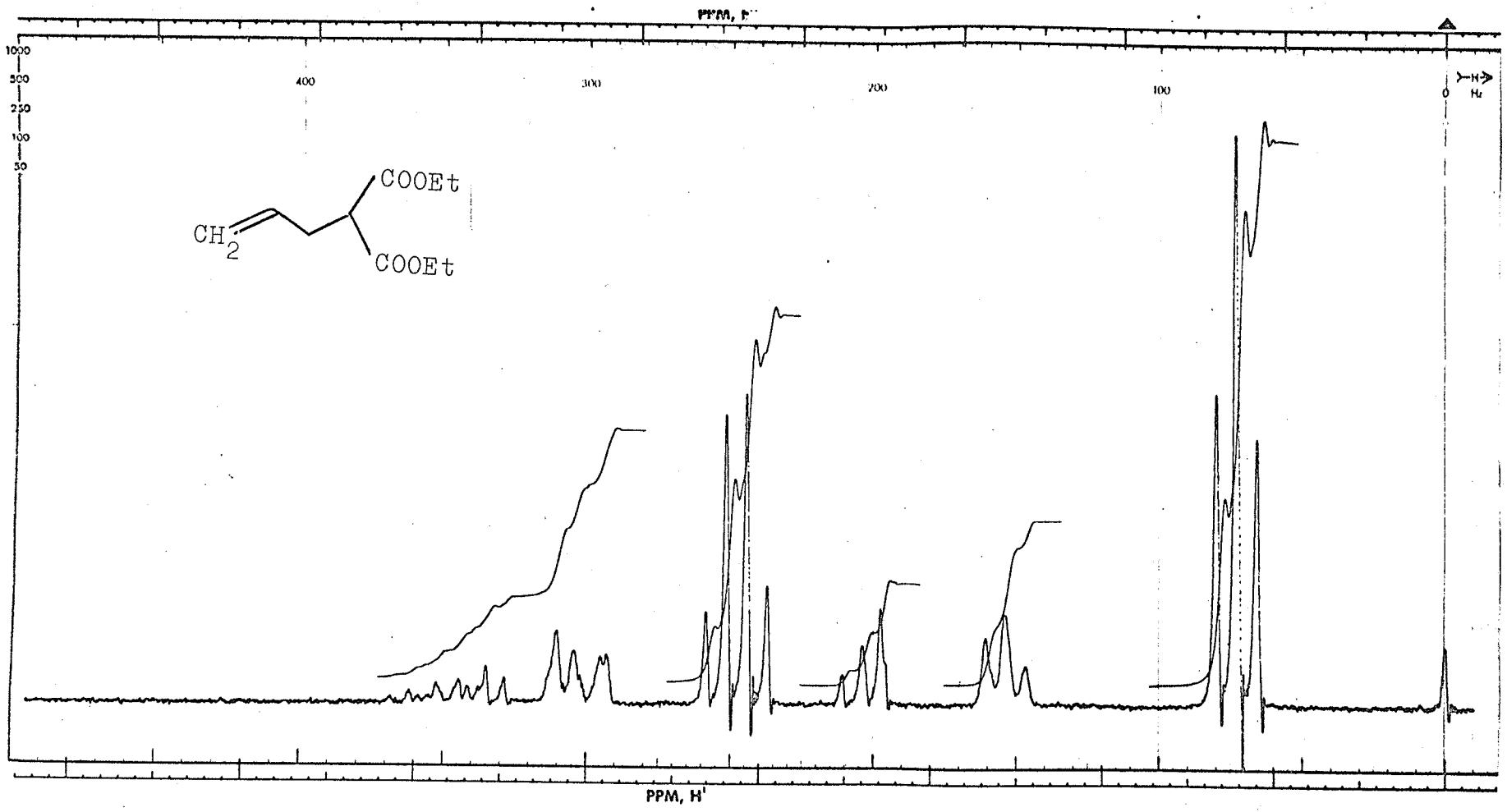


Figure XVIII

Infrared spectrum no. 18: 1-amino-2,4,5-trimethoxy-3-cyanonaphthalene (L), in CH_2Cl_2 solution.

Figure XIX



Nuclear magnetic resonance spectrum no. 1: Allyl diethyl malonate (XXV), neat liquid. Sweep width = 500 Hz.

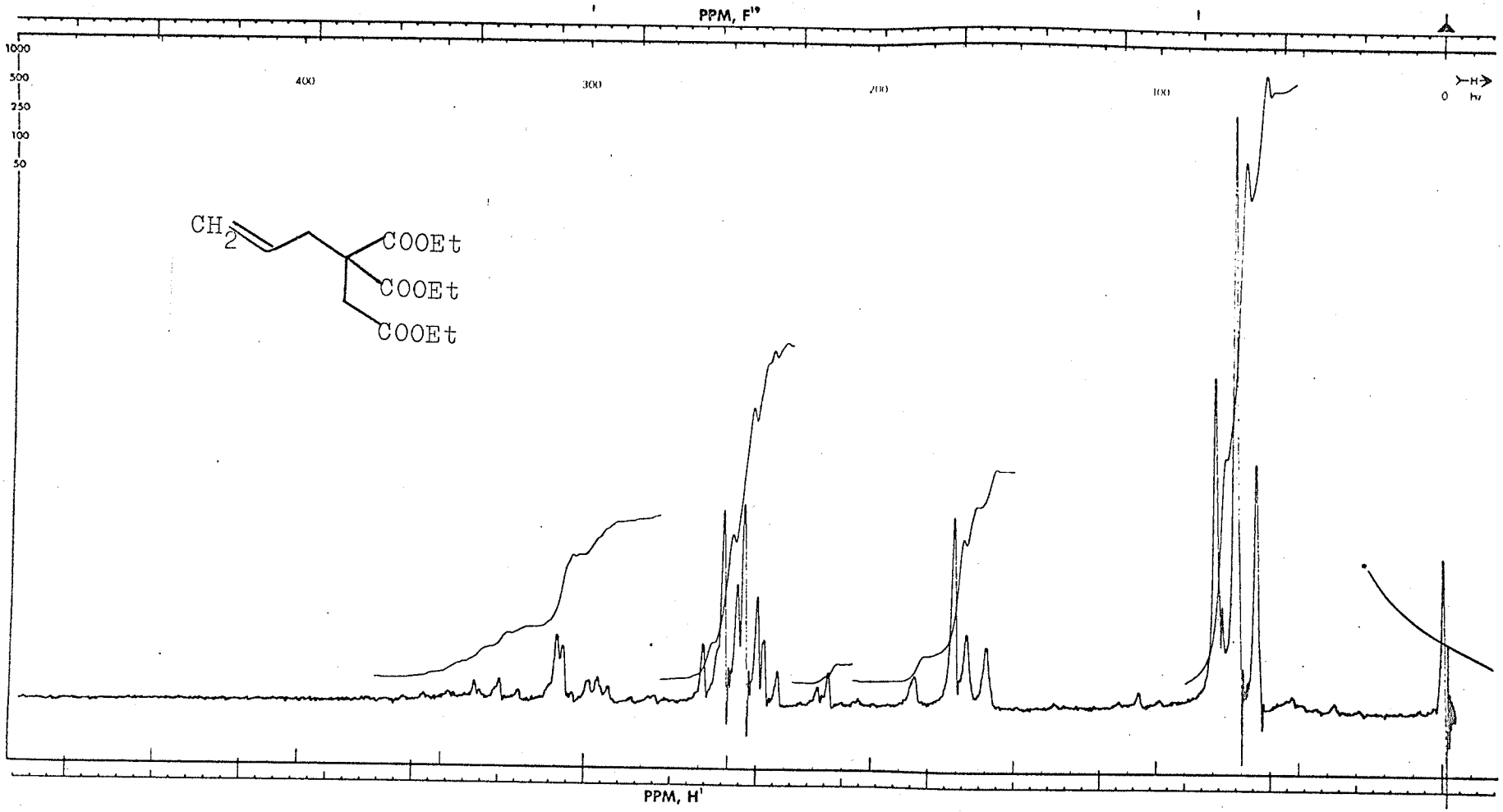


Figure XX

Nuclear magnetic resonance spectrum no. 2: 2-ethylcarboxylate-2-allyl-diethylsuccinate (XXVI), neat liquid. Sweep width = 500 Hz.

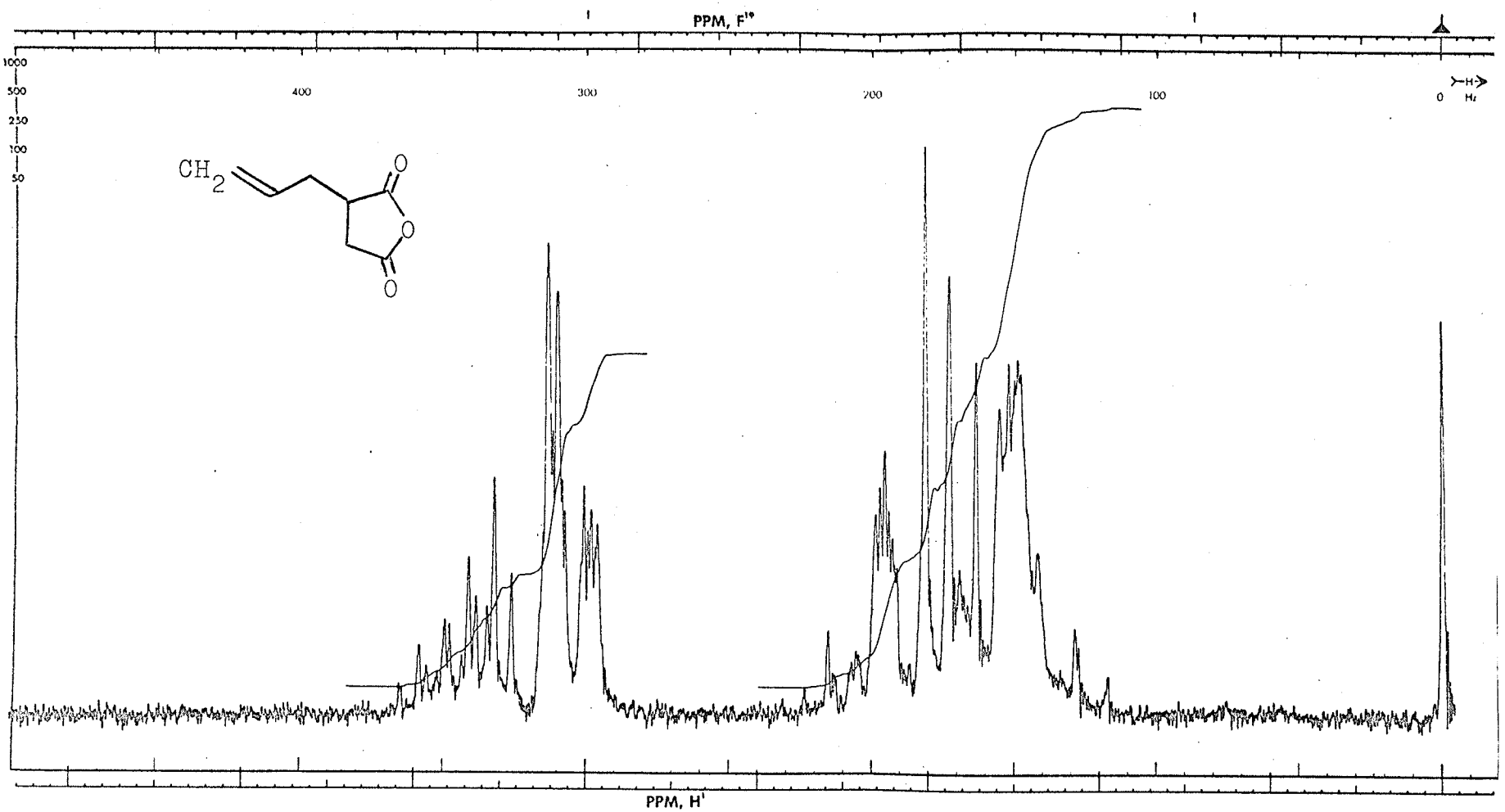


Figure XXI

Nuclear magnetic resonance spectrum no. 3: Allyl succinic anhydride (XXVIII), neat liquid. Sweep width = 500 Hz.

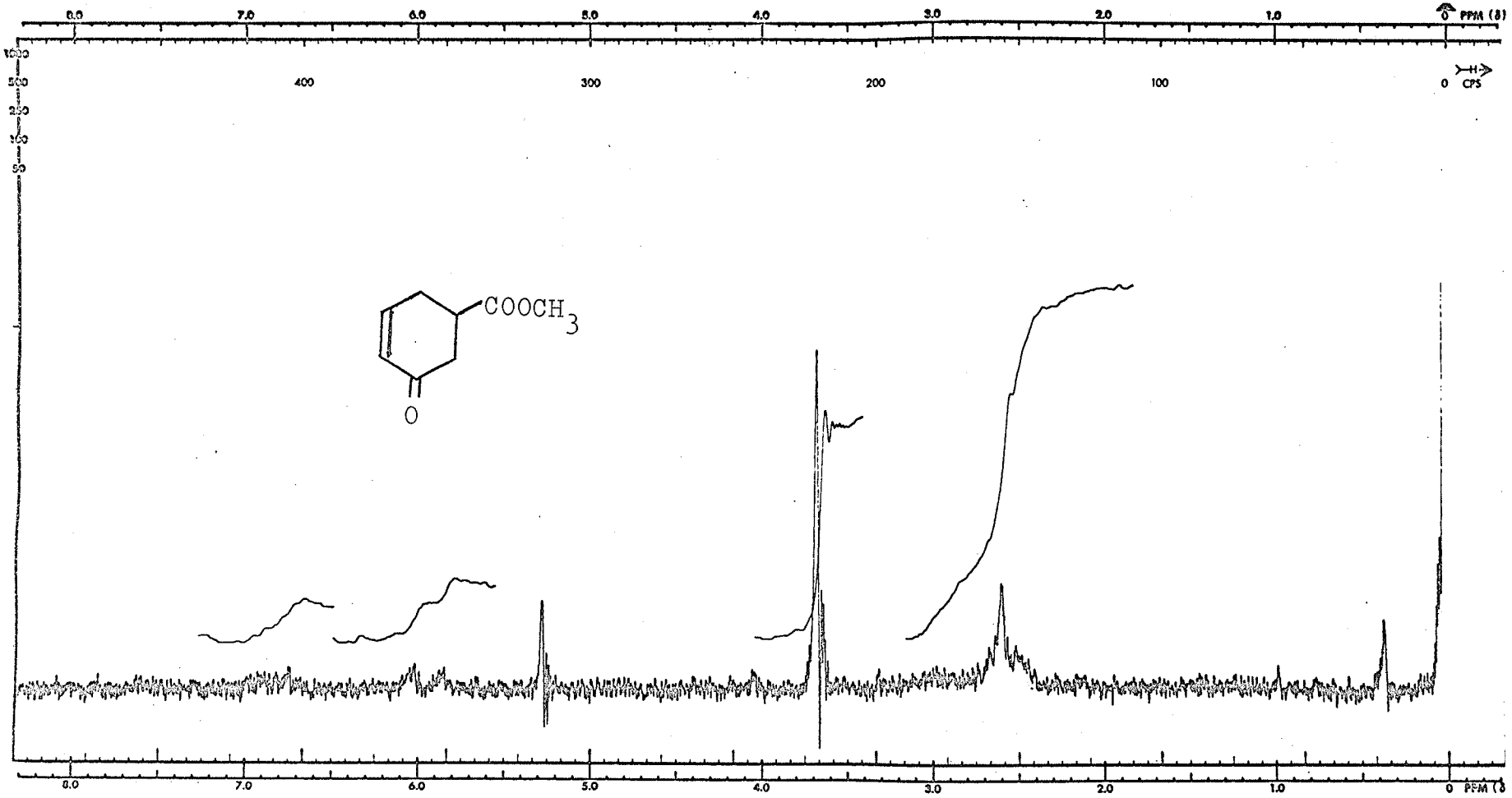


Figure XXII

Nuclear magnetic resonance spectrum no. 4: Methylcyclohex-2-ene-1-one-5-carboxylate (XXXI), in CCl_4. Sweep width = 500 Hz.

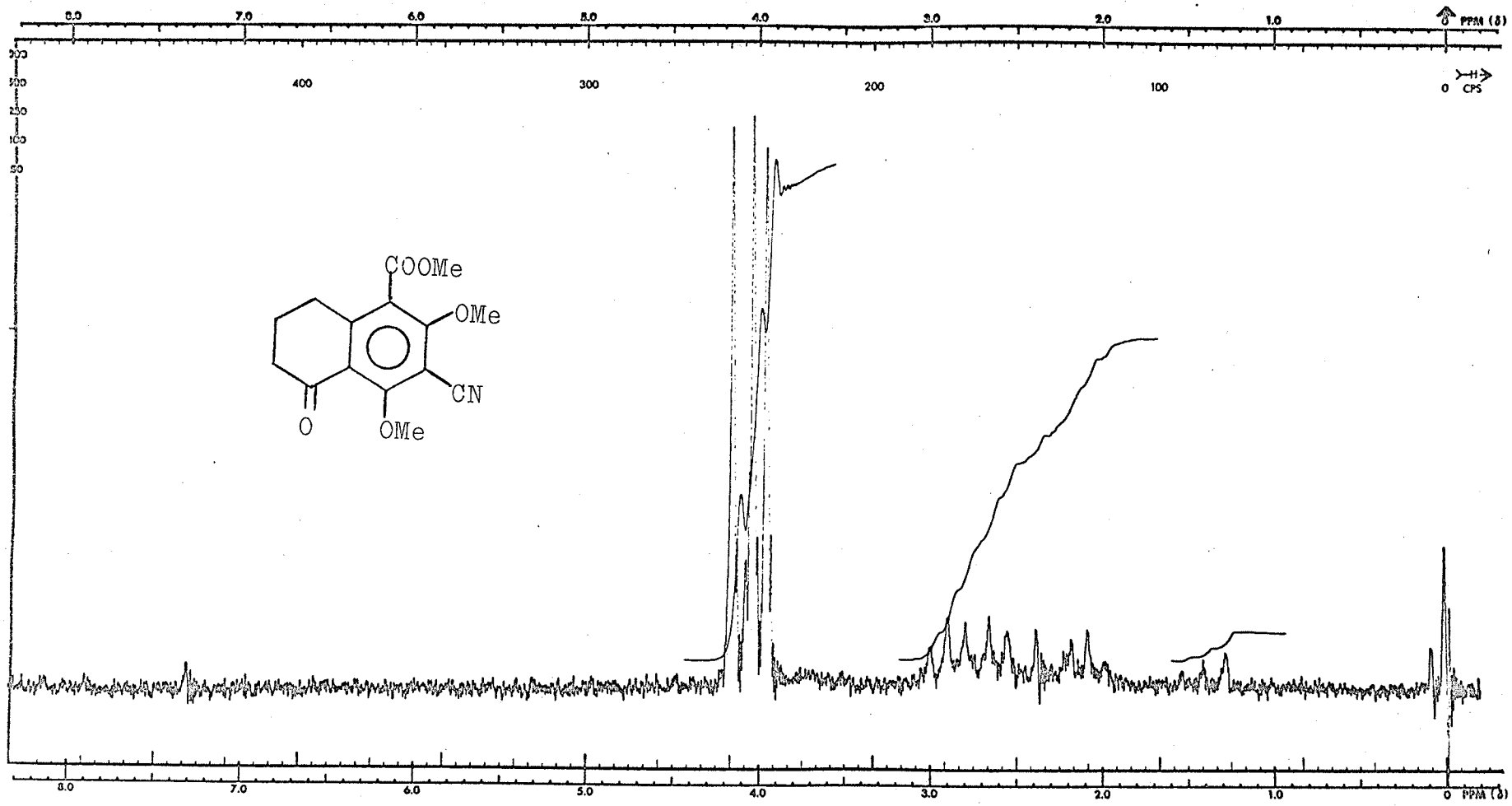
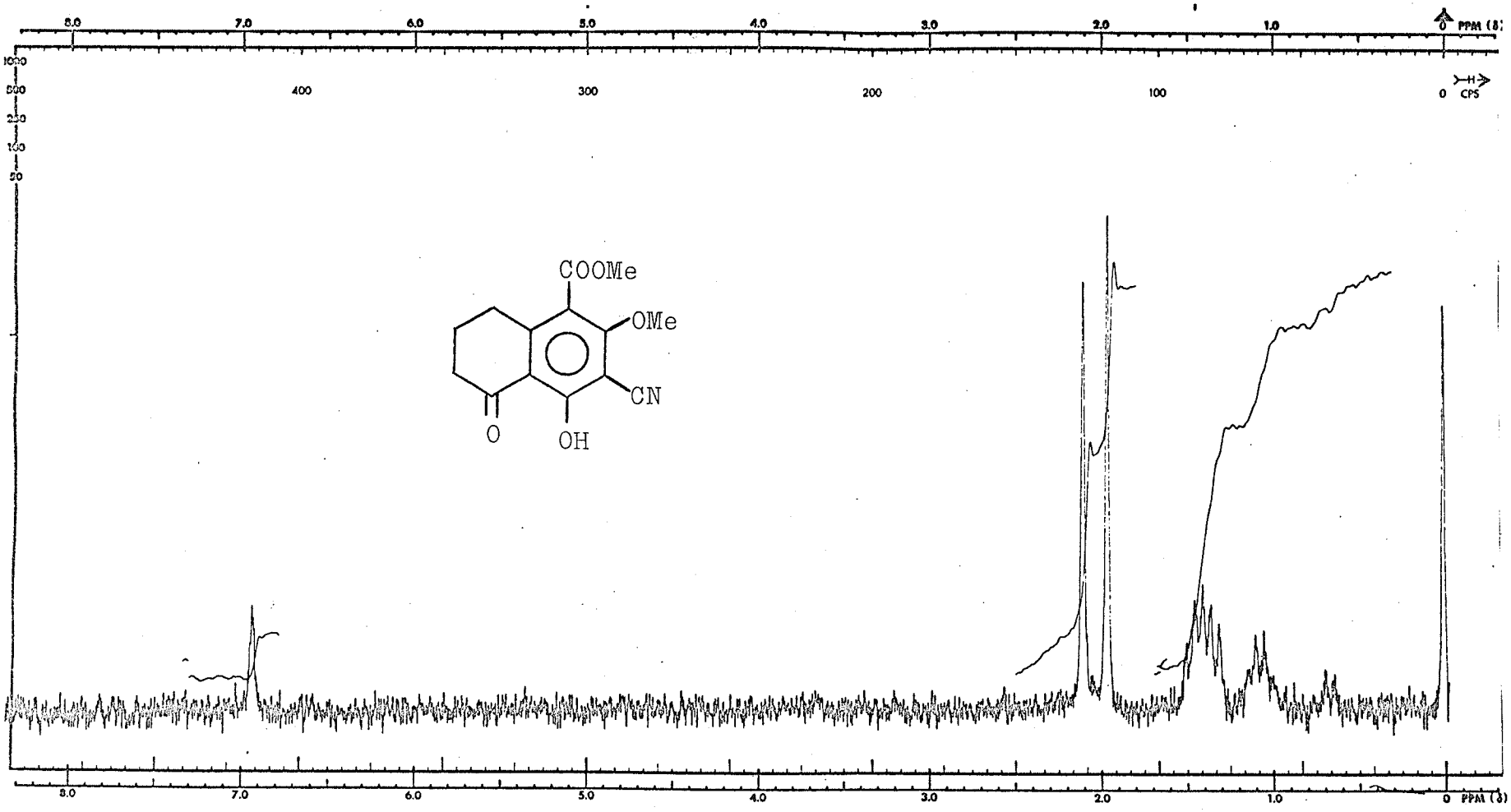


Figure XXIII

Nuclear magnetic resonance spectrum no. 5: 5-carbomethoxy-6,8-dimethoxy-7-cyano-1-tetralone (XXXVIII), in $CDCl_3$. Sweep width = 500 Hz.

Figure XXIV



Nuclear magnetic resonance spectrum no. 6: 5-carbomethoxy-6-methoxy-7-cyano-8-hydroxy-1-tetralone (XXXIX), in $CDCl_3$. Sweep width = 1000 Hz.

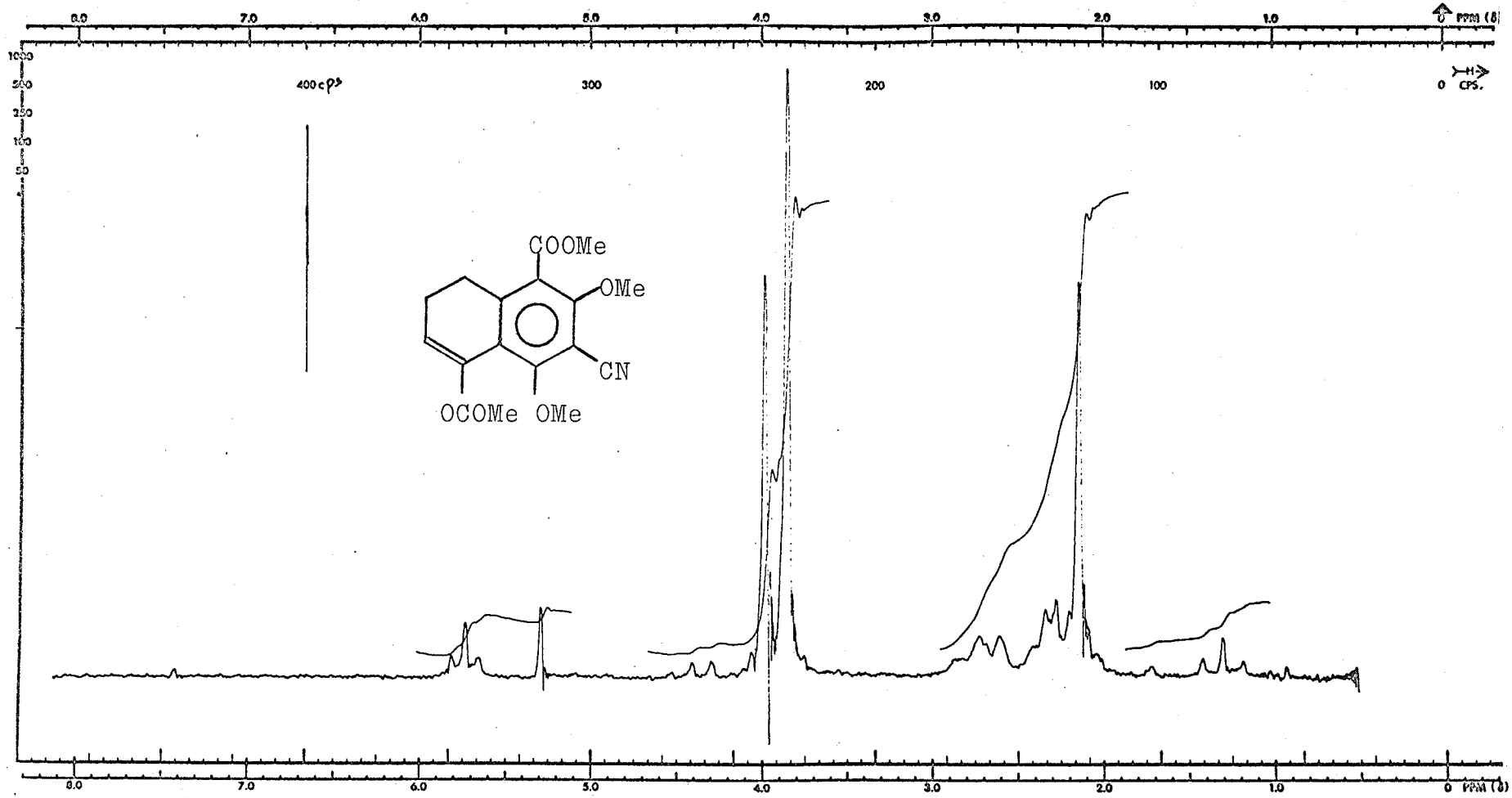


Figure XXV

Nuclear magnetic resonance spectrum no. 7: 1-acetoxy-3,4-dihydro-5-carbomethoxy-6,8-dimethoxy-7-cyanonaphthalene (XL), in $CDCl_3$. Sweep width = 500 Hz.

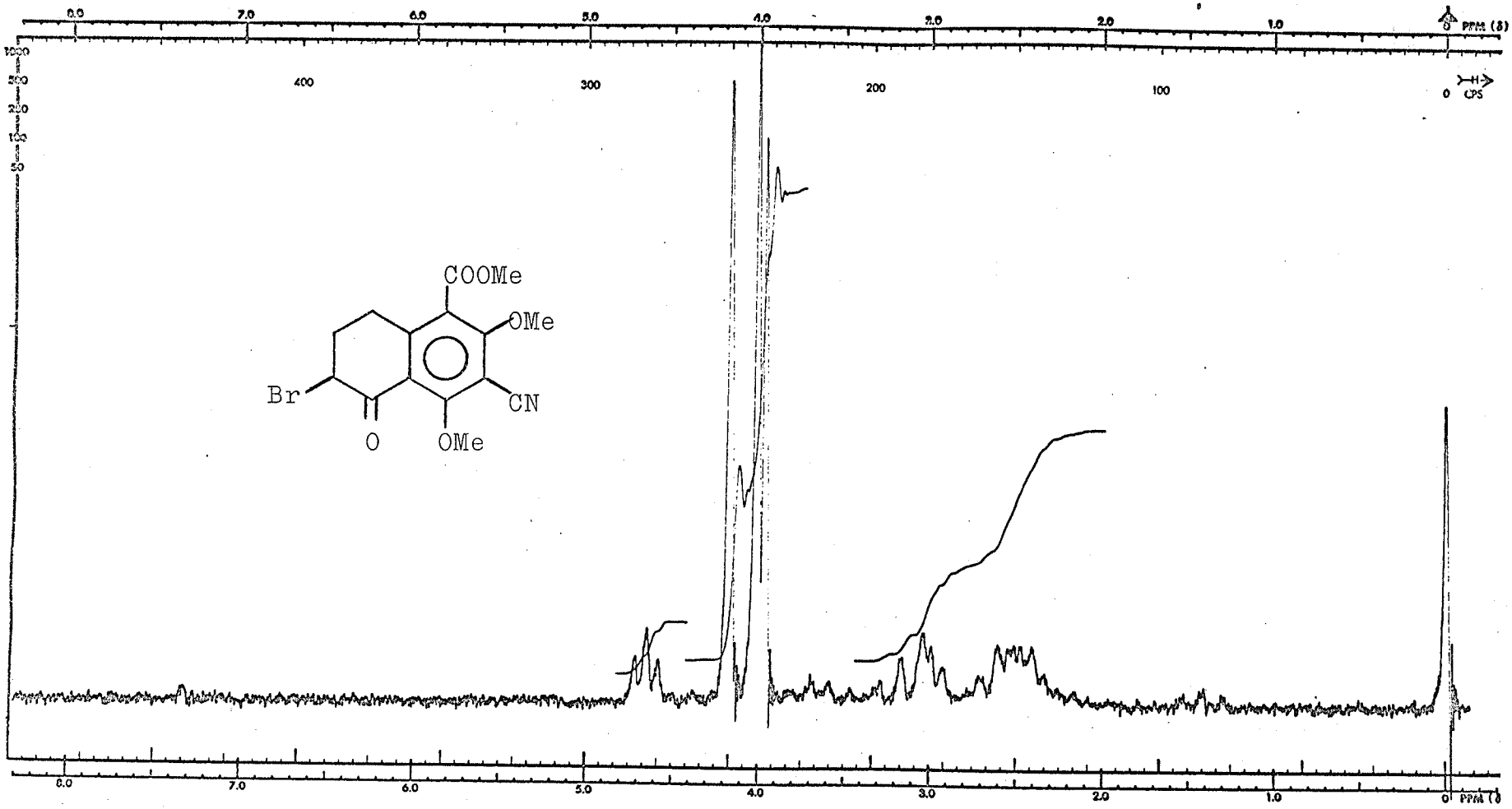


Figure XXVI

Nuclear magnetic resonance spectrum no. 8: 2-bromo-5-carbomethoxy-6,8-dimethoxy-7-cyano-1-tetralone (XLI), in $CDCl_3$. Sweep width = 500 Hz.

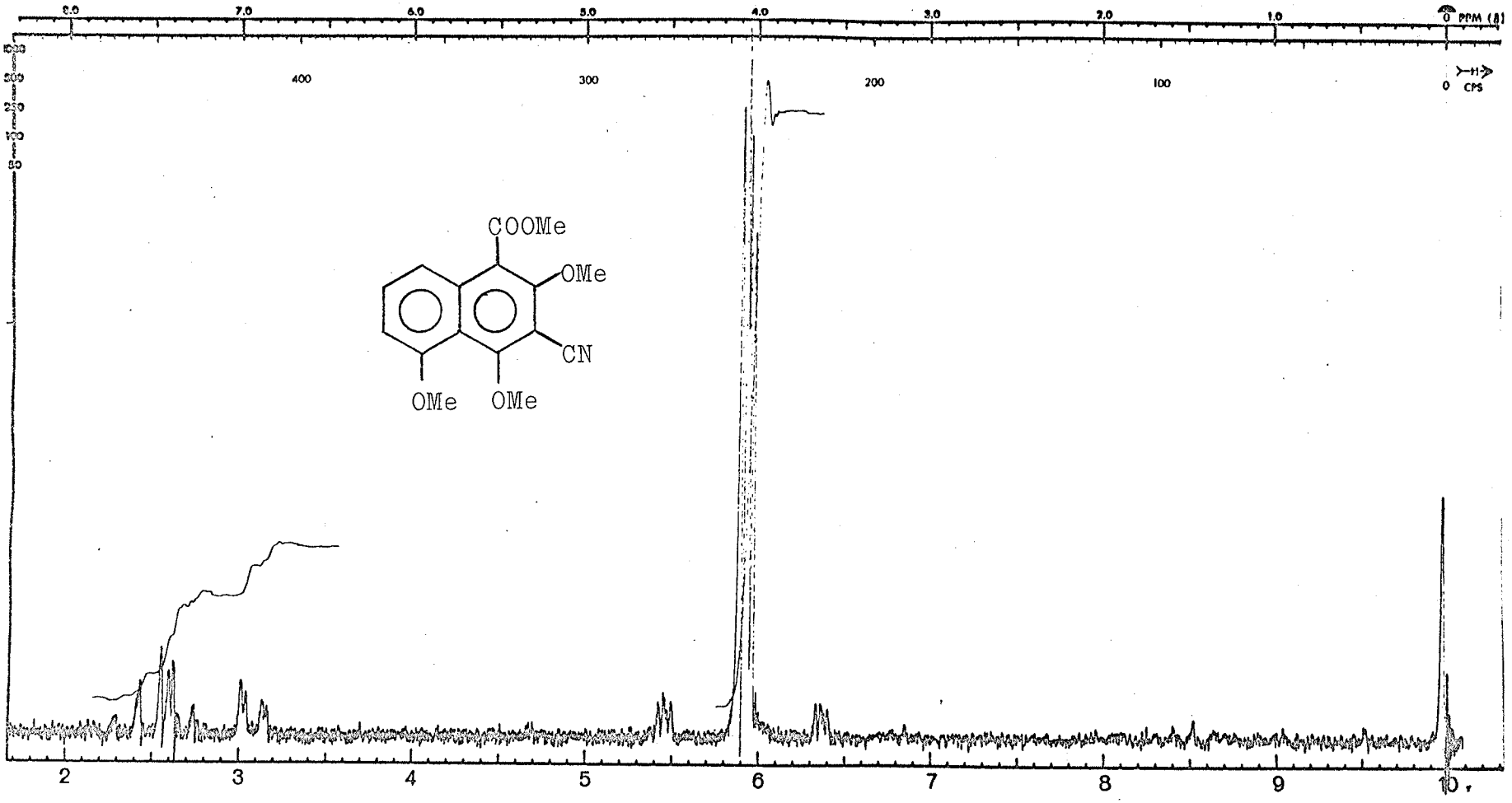


Figure XXVII

Nuclear magnetic resonance spectrum no. 9: 1-carbomethoxy-2,4,5-trimethoxy-3-cyanonaphthalene (XLIII), in $CDCl_3$. Sweep width = 500 Hz.

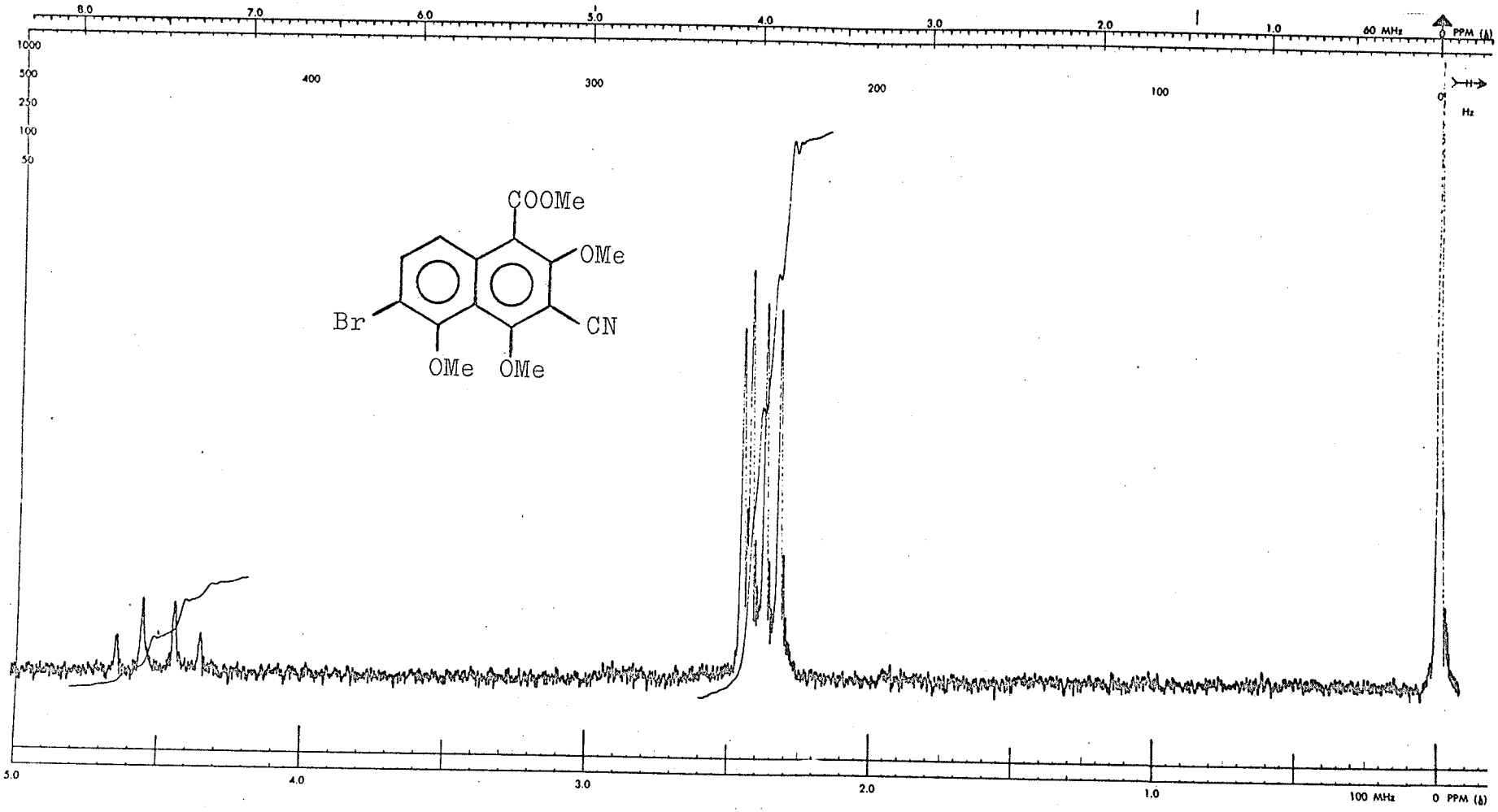


Figure XXVIII

Nuclear magnetic resonance spectrum no. 10: 1-carbomethoxy-2,4,5-trimethoxy-3-cyano-6-bromonaphthalene (XLVI), in $CDCl_3$. Sweep width = 500 Hz.

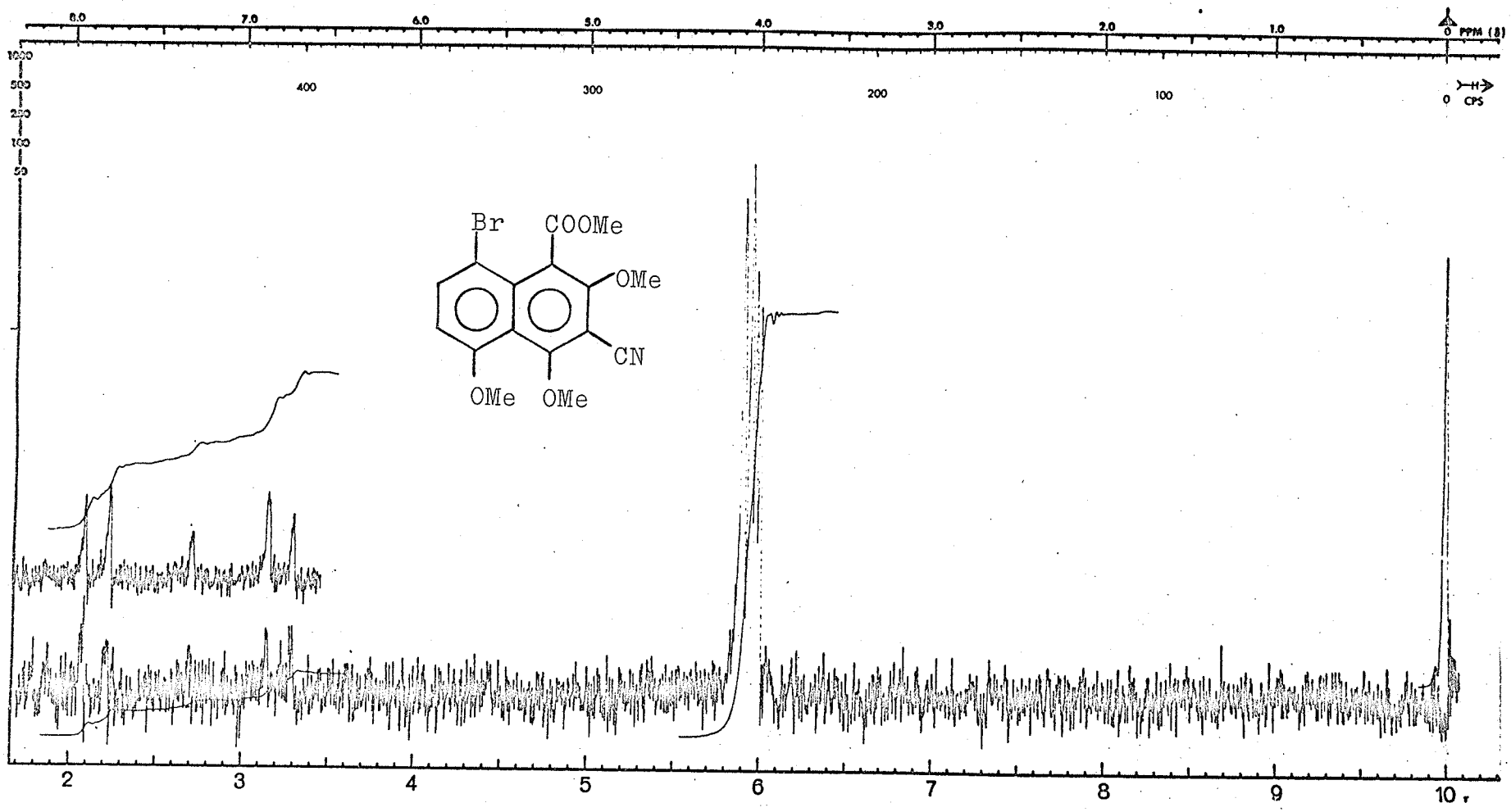


Figure XXIX

Nuclear magnetic resonance spectrum no. 11: 1-carbomethoxy-2,4,5-trimethoxy-3-cyano-8-bromonaphthalene (XLVII), in $CDCl_3$. Sweep width = 500 Hz. The insert is the amplification of the AB spectrum.

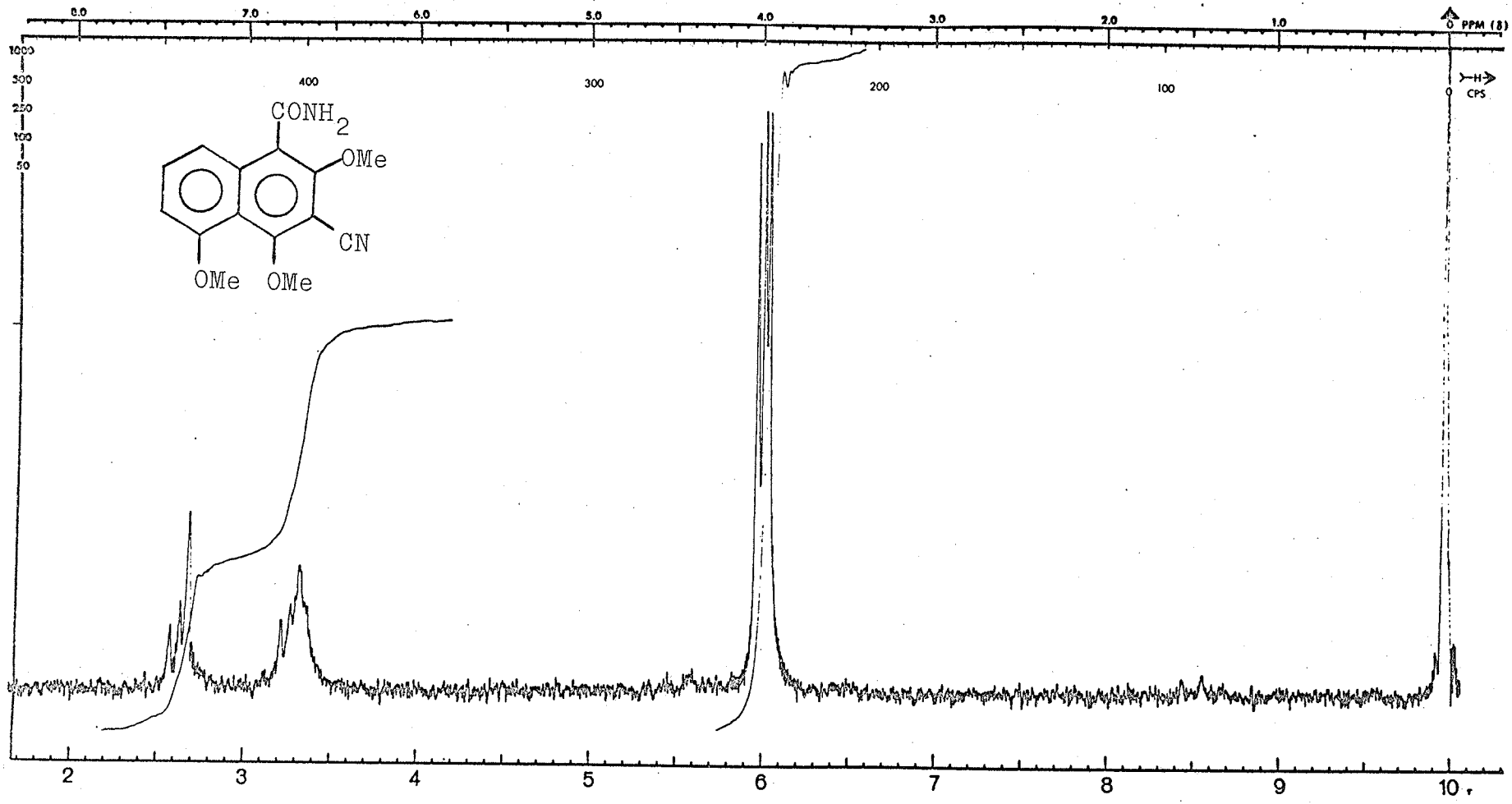


Figure XXX

Nuclear magnetic resonance spectrum no. 12: 1-carbamyl-2,4,5-trimethoxy-3-cyanonaphthalene (XLVIII), in $CDCl_3$. Sweep width = 500 Hz.

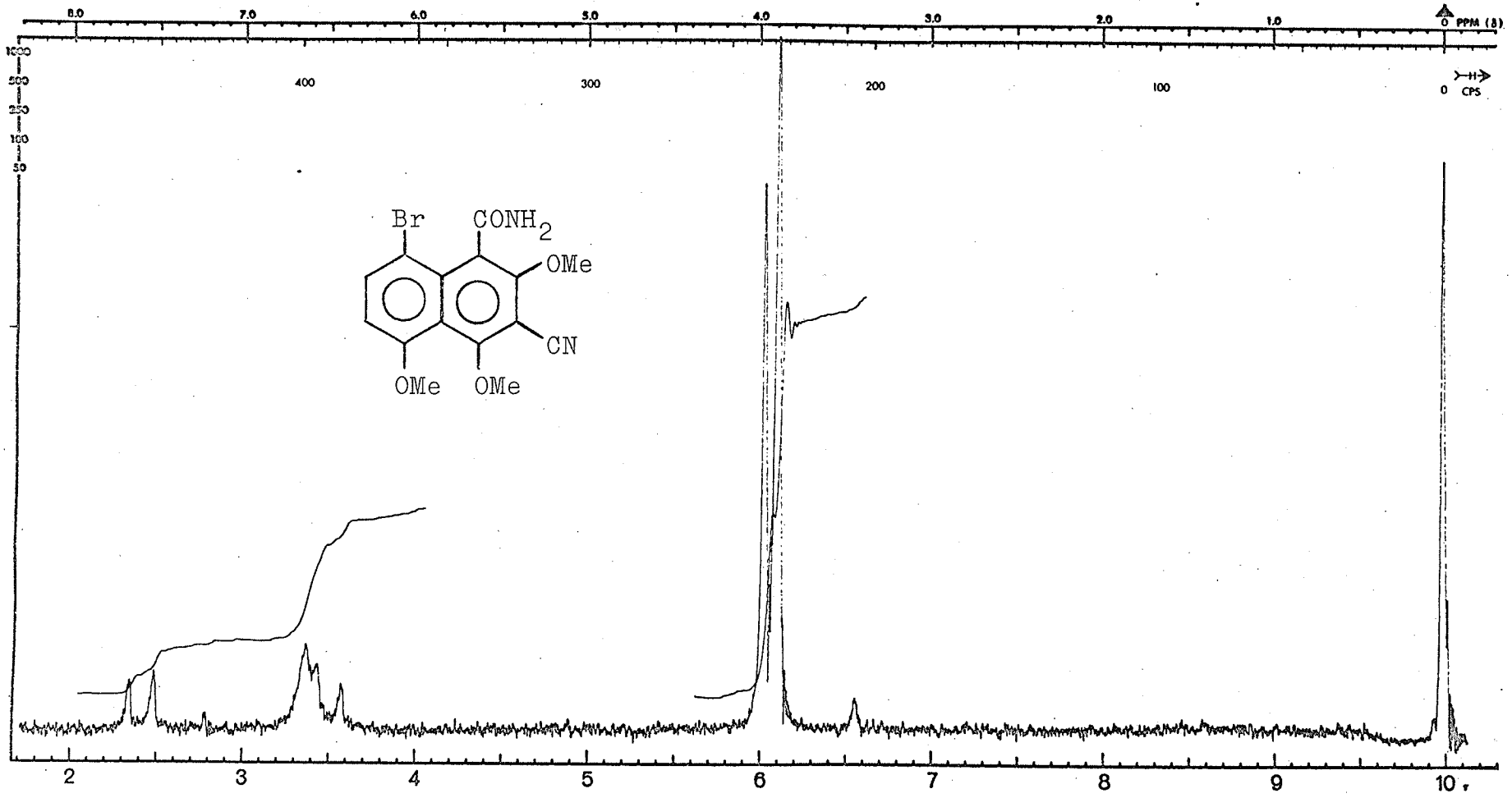


Figure XXXI

Nuclear magnetic resonance spectrum no. 13: 1-carbamyl-2,4,5-trimethoxy-3-cyano-8-bromonaphthalene (IL), in $CDCl_3$. Sweep width = 500 Hz.

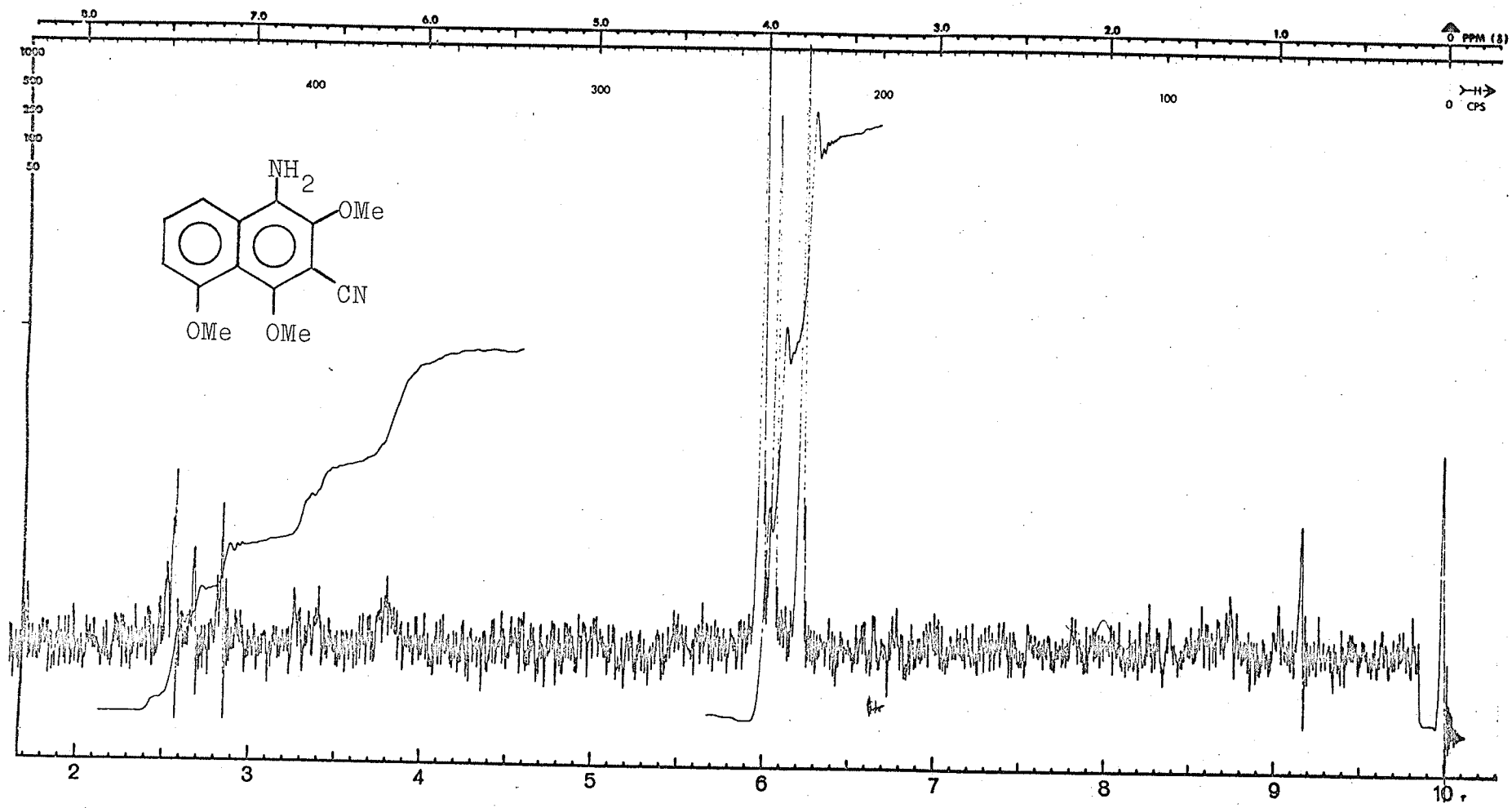
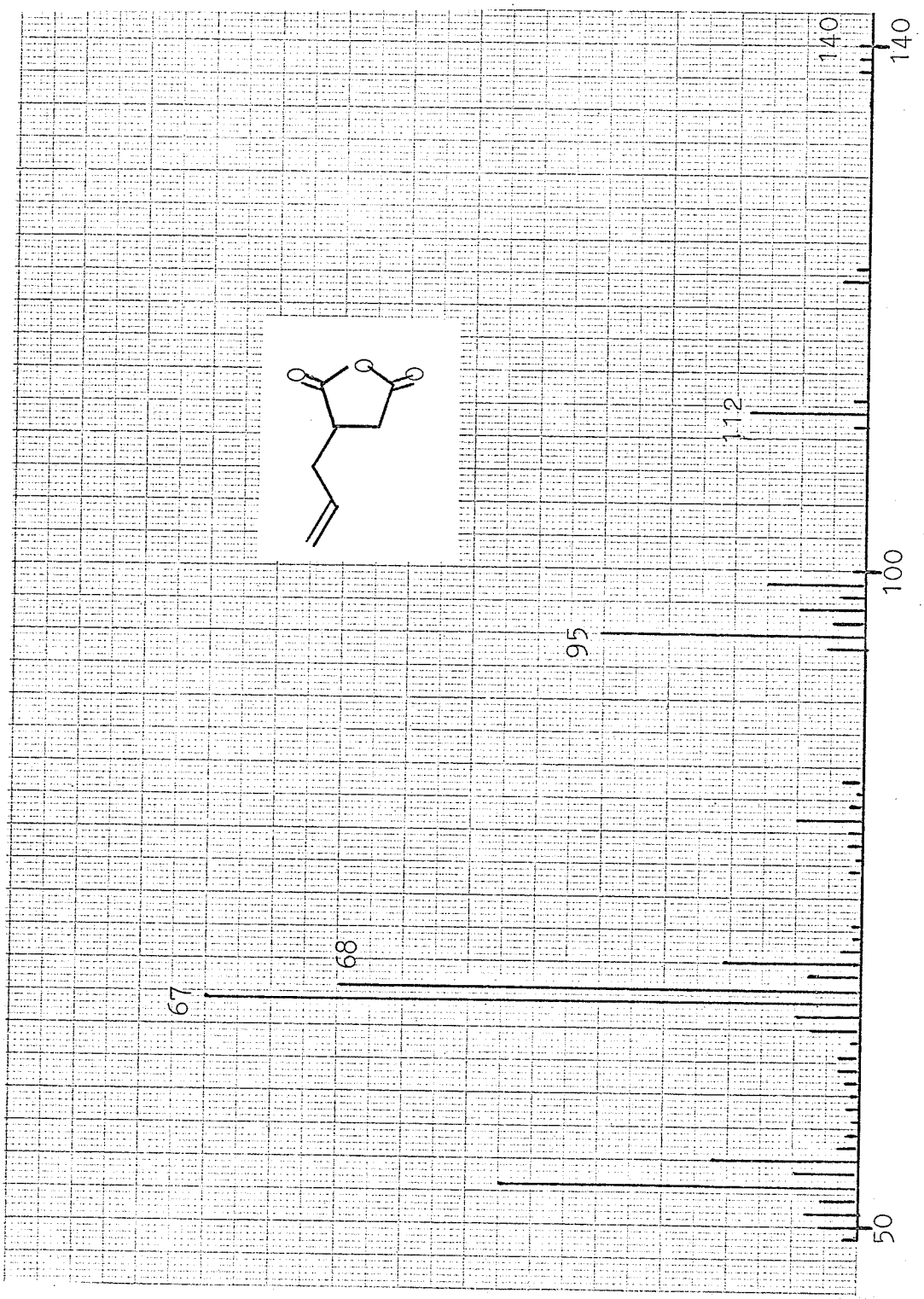


Figure XXXII

Nuclear magnetic resonance spectrum no 14: 1-amino-2,4,5-trimethoxy-3-cyanonaphthalene (L), in $CDCl_3$. Sweep width = 500 Hz.

Figure XXXIII



Mass spectrum no. 1: Allyl succinic anhydride (XXVIII).

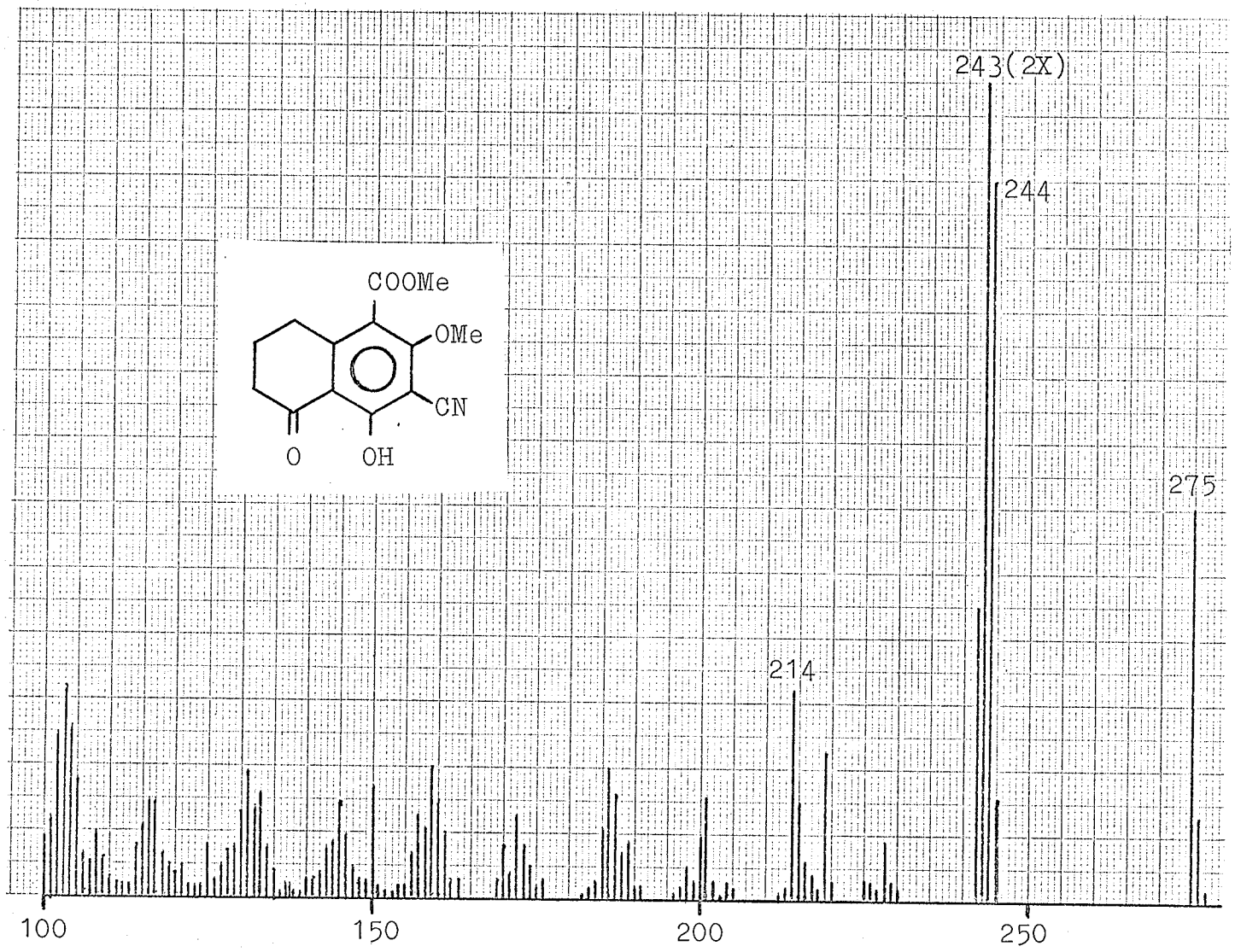
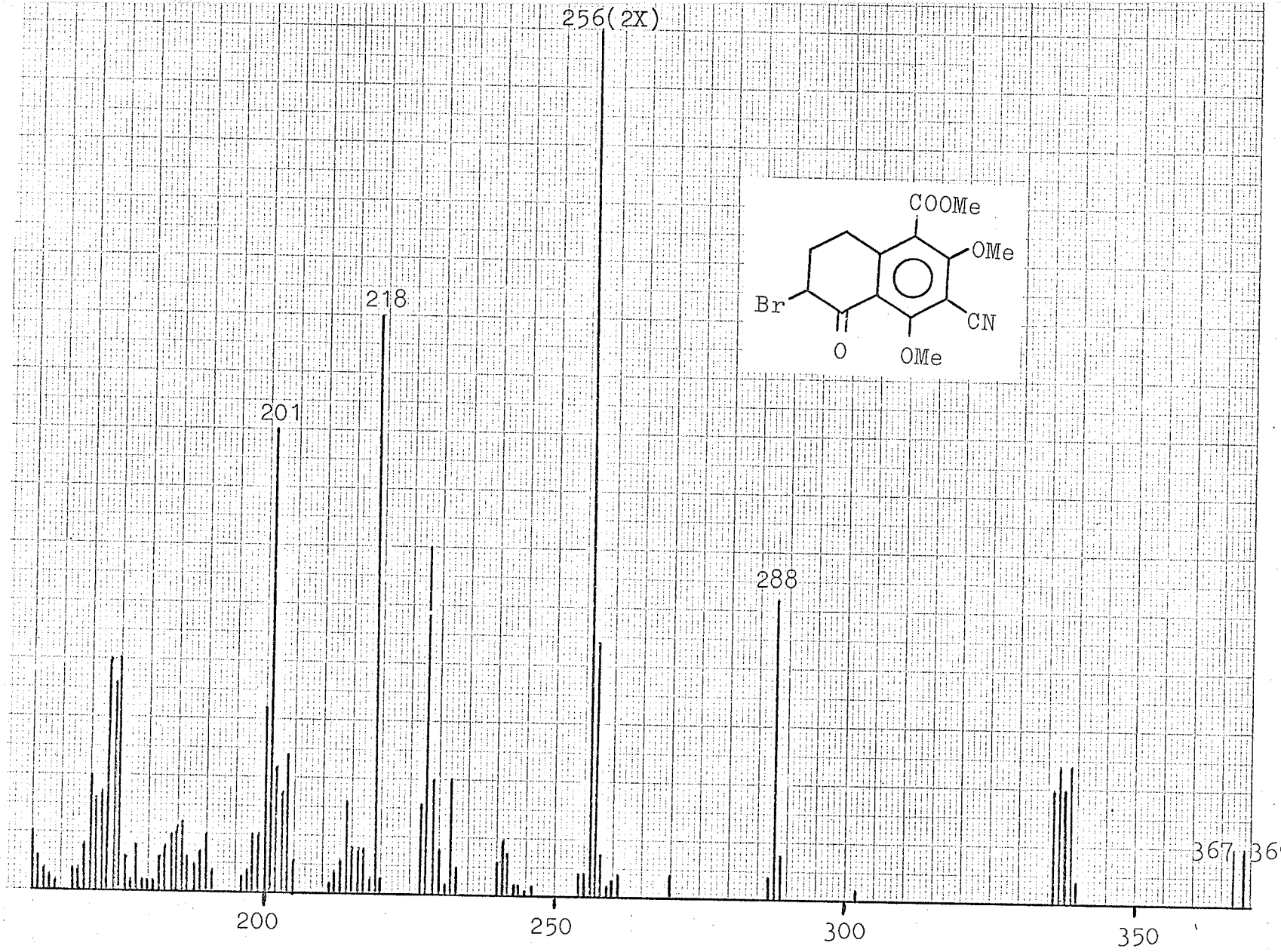


Figure XXXIV

Mass spectrum no. 2: 5-carbomethoxy-6-methoxy-7-cyano-8-hydroxy-1-tetralone (XXXIX).



Mass spectrum no. 3: 2-bromo-5-carbomethoxy-6,8-dimethoxy-7-cyano-1-tetralone (XLI).

Figure XXXV

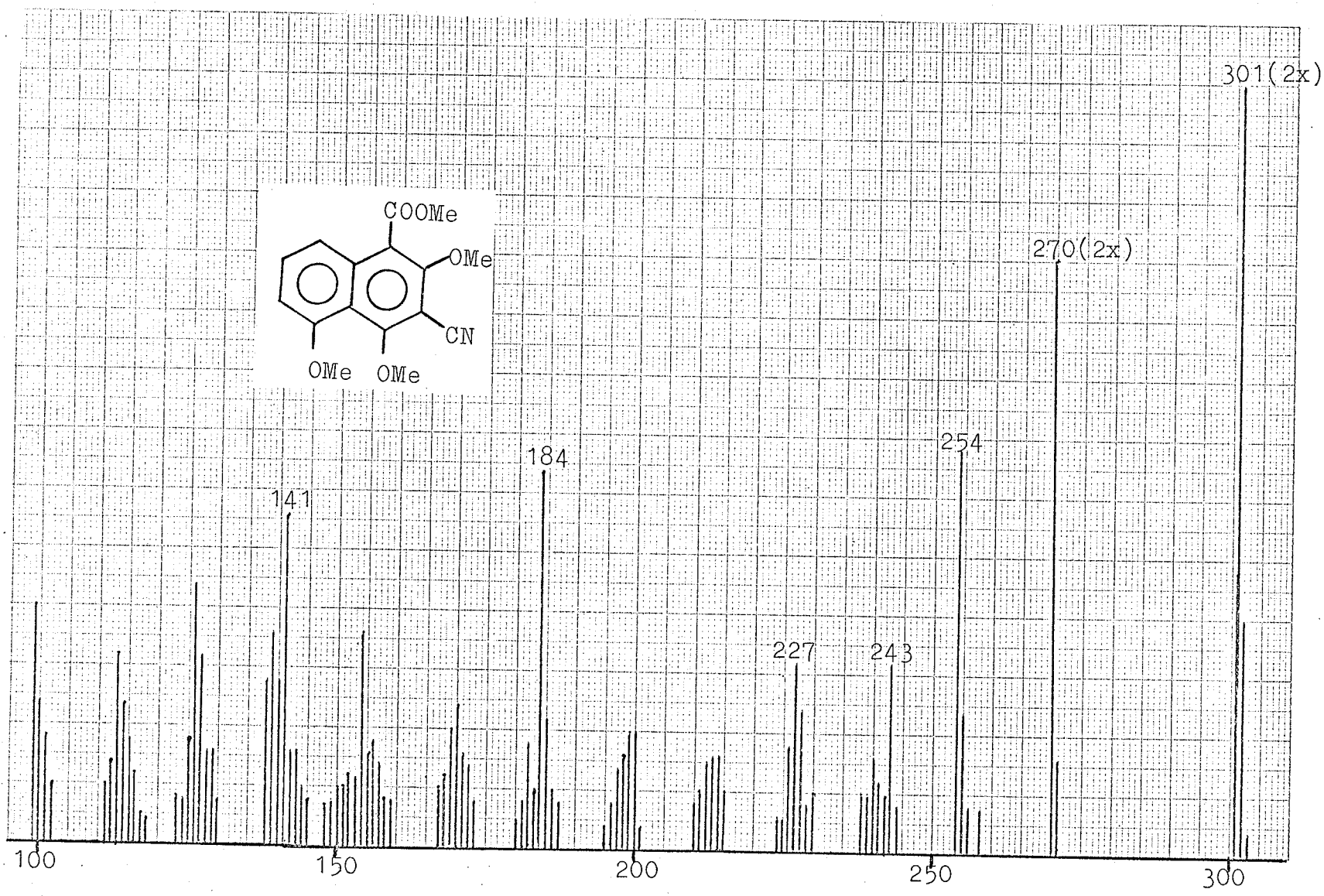


Figure XXXVI

Mass spectrum no. 4: 1-carbomethoxy-2,4,5-trimethoxy-3-cyanonaphthalene (XLIII).

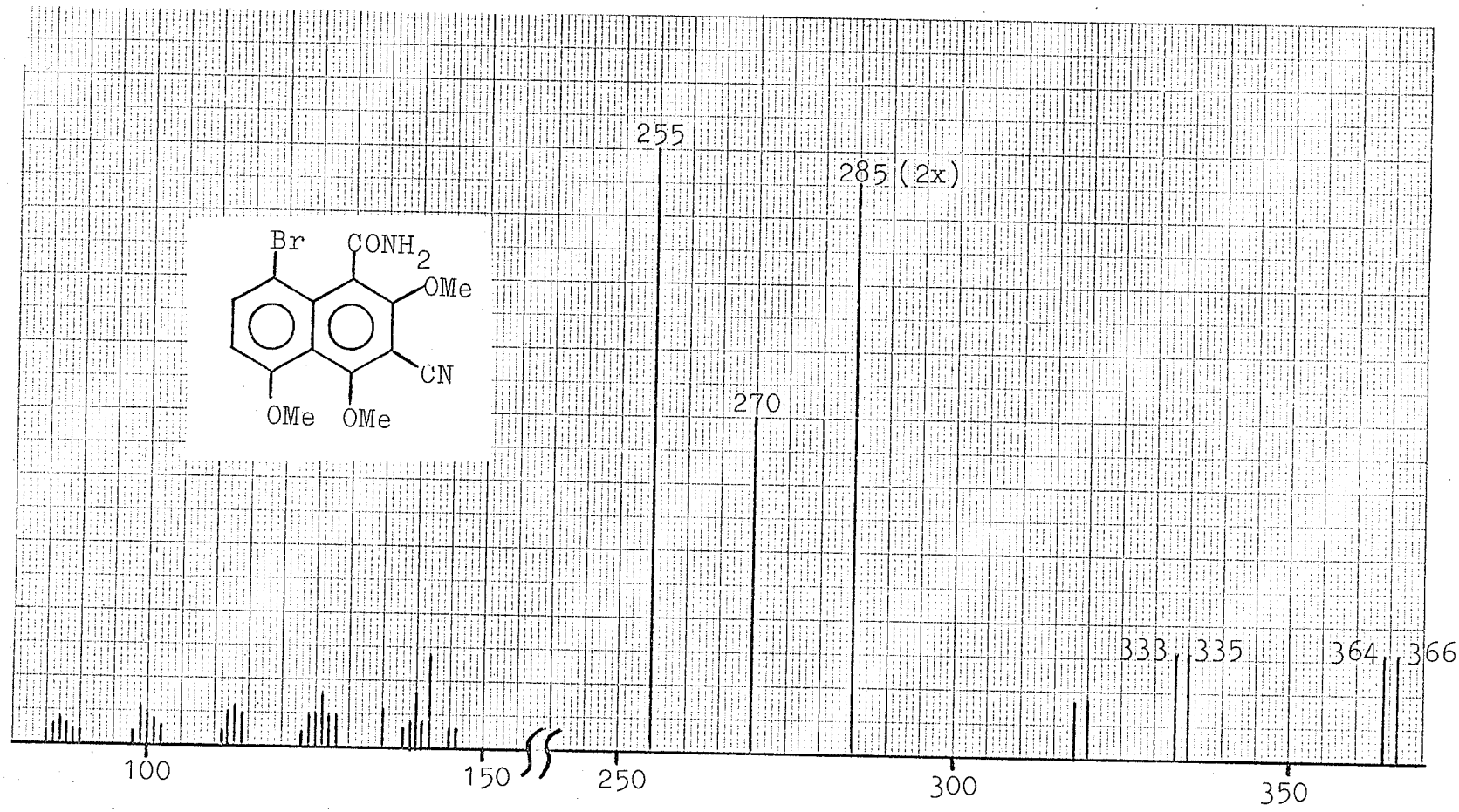


Figure XXXVII

Mass spectrum no. 5: 1-carbamyl-2,4,5-trimethoxy-3-cyano-8-bromo-naphthalene (IL).

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