THE SYNTHESES OF RACEMIC DAUNOMYCINONE TRIMETHYL ETHER, RACEMIC 4-O-DEMETHYLDAUNOMYCINONE AND RACEMIC DAUNOMYCINONE

by

ROBERT JOSEPH SCHWENK

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ABSTRACT

2,5-dimethoxybenzaldehyde was condensed with ethyl malonate to give ethyl 2-carboethoxy-3-(2 ,5 -dimethoxyphenyl) propenoate (XII), which was then hydrogenated catalytically to ethyl 2-carboethoxy-3-(2,5-dimethoxyphenyl) propanoate (XIII). Alkylation of compound XIII with ethyl bromoacetate followed by basic hydrolysis with sodium hydroxide afforded 3,3-dicarbohydroxy-4-(2 ,5 -dimethoxyphenyl) butanoic acid (XIV) which was subsequently dehydrated with acetic anhydride to give 2 ,5 -dimethoxybenzylsuccinic anhydride (XVII). Cyclization of this anhydride with hydrogen fluoride yielded 3-carbohydroxy-5,8-dimethoxy-1-tetralone (XVIII). Catalytic reduction with hydrogen converted this tetralone carboxylic acid to the corresponding tetralin carboxylic acid (XXV) which, on treatment with methyl lithium, gave 2-acetyl-5, 8-dimethoxytetralin (XXIV). Oxidation in basic solution of compound XXIV gave the peroxide XXX which was then reduced with zinc and acetic acid to give 2-acetyl-2-hydroxy-5,8-dimethoxytetralin (XXXI). Condensing compound XXXI with a mixture of 2-carbomethoxy-3-acetoxybenzoic acid and 2-carbomethoxy-6-acetoxybenzoic acid produced a mixture of 1,9-dihydroxy-6,11-dimethoxy-9-acetyl-7,8,9,10-tetrahydro-5, 12-naphthacenedione and 4,9-dihydroxy-6,11-dimethoxy-9-acetyl-7,8,9,10-tetrahydro-5,12-naphthacenedione (XXXV) as the final condensation products. The free phenolic hydroxyl groups of these two isomers (XXXV) was then methylated with dimethyl sulfate and the ketone side chain was converted to the corresponding ketal using ethylene glycol. Bromination of the benzylic (C_7) position of this isomeric ketal mixture XXXVII followed by methanolysis and then ketal hydrolysis gave, after careful separation by thin layer chromatography, daunomycinone trimethyl ether (XLVI) and isodaunomycinone trimethyl ether (XLV).

The similar isomeric mixture (XLII) where the methoxyl and hydroxyl substituents of the saturated D ring are trans to one another was also isolated, but not separated. Daunomycinone trimethyl ether was then hydrolysed with aluminum chloride to give 4-O-demethyl-7-O-methyldaunomycinone(XLVII). The benzylic methoxyl group of this compound was then converted to an O-trifluoroacetate substituent using trifluoroacetic acid, and the resulting trifluoroacetic ester was hydrolysed with ammonium hydroxide to produce 4-O-demethyldaunomycinone (LI). Compound XLVII was also oxidized with lead tetraacetate to 4,9-dihydroxy-7-methoxy-9-acetyl-7,8,9,10-tetrahydro-5,6,11,12-naphthacenediquinone (LIV). Methylation of this compound (LIV) with dimethyl sulfate yielded 7-O-methyldaunomycinone (LVI). Converting the benzylic methoxyl group of compound LVI to an O-trifluoroacetate substituent followed by ammonium hydroxide hydrolysis of the ester bond gave daunomycinone (LXI). An identical series of reactions was also carried out starting with isodaunomycinone trimethyl ether (XLV) to produce isodaunomycinone (LIX). All the compounds prepared were, of course, racemic mixtures.

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INTRODUCTION

Daunomycin is a new antibiotic isolated from the cultures of Streptomyces peucetius.[1] It has a weak inhibiting activity on Gram-positive and acid-resistant micro-organisms such as Staphylococcus aureus.[2] More important, however, biological testing has shown that daunomycin has a remarkable cytotoxic activity; at concentrations ranging from 0.01 to 0.1 μg/ml it completely inhibits the mitotic activity of normal and neoplastic cells in vitro.[3] Similarily, it was found to exhibit a marked inhibiting action on solid and ascites tumours.[4] This property of daunomycin was shown to result from the fact that it inhibits RNA and DNA synthesis, as demonstrated in vivo in bacterial[5] and animal cells[6-8] and in vitro on DNA-dependent RNA polymerase and on DNA polymerase.[9] It has also caused severe chromosomal damage in some cases.[3] Calendi et al[10] reported that daunomycin's inhibition to DNA and RNA synthesis results from the fact that it binds directly to the DNA acting as primeror template in the synthesis (the DNA of the chromosome in the case of cells).

Daunomycin has since come into its own as an important clinical drug. At a daily dose of 1 mg/Kgm for six to eight days it produces complete or good partial remission in the case of childhood leukemia, while its toxicity to the bone marrow does not appear to be as accumulative as with other antileukemic agents.[11]

THE STRUCTURE OF DAUNOMYCIN

Daunomycin is usually isolated as a hydrochloride salt in thin, red needles melting at 184°-186°C. Analytical results are consistent with the formula $C_{27}H_{29}O_{10}N.HCl$. On mild acid hydrolysis (0.2N hydrochloric acid for one hour at 90°C) daunomycin affords a red aglycone, daunomycinone, and an amino sugar, daunosamine.

The structure of the aglycone, daunomycinone, was first elucidated in 1964 by Mondelli et al[12] on the basis of the following chemical and spectral evidence.

Daunomycinone, $C_{21}H_{18}O_8$, m.p. 213-214°C, displayed an ultraviolet spectrum similar to that of 1,4,5-trihydroxyanthraquinone. The quinoid chromophore was also suggested by the ready reversible reduction by reducing agents and by polarographic behavior. In addition, zinc dust distillation yielded tetracene, suggesting for daunomycinone the tetracyclic structure found in the anthracyclines,[13] as shown in Fig. I.

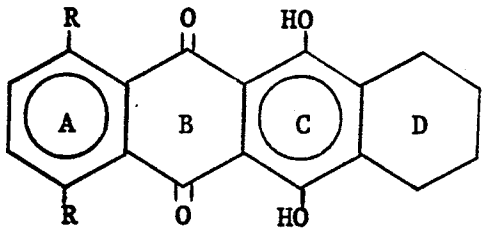


Figure I

It remained necessary, therefore, to establish the number and nature of substituents on the A and D rings.

The infrared (i.r.) spectrum showed an absorption at 1718cm.$^{-1}$ indicating the presence of an aliphatic ketone. This was further confirmed by the ready formation of a 2,4-dinitrophenylhydrazone derivative. The nuclear magnetic resonance (n.m.r.) spectrum (CF_3COOH) further corroborated this fact by displaying a singlet (3H, δ2.69)

which could be assigned to a $COCH_3$ methyl group. The n.m.r. spectrum also showed a singlet (3H,δ4.04) which could be assigned to an aromatic OCH_3, broad absorptions at δ 3.27(2H), 2.67(2H), 7.1-7.9(3 aromatic H) and a signal at δ 5.50(1H, broad) which could be attributed to proton on a benzylic carbon bearing a hydroxyl group, because on acetylation the signal shifted down field to δ 6.40. Thus it could be concluded that the A ring had a methoxyl substituent probably in one of the positions α to the quinone carbonyls and that the saturated D ring had a methyl ketone substituent at some position as well as a hydroxyl substituent in one of the benzylic positions.

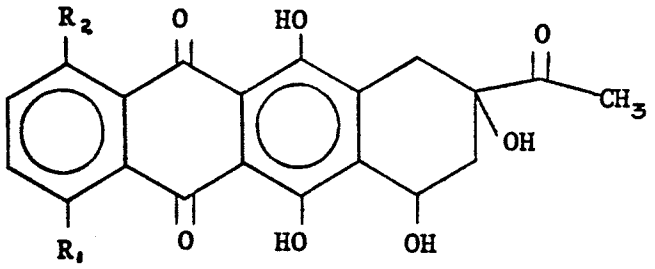
Methylation with dimethylsulfate in acetone in the presence of potassium carbonate converted daunomycinone to a trimethyl ether $C_{24}H_{24}O_8$, m.p. 193°C. The i.r. spectrum had an absorption at 3350 cm^{-1}, indicating the presence of an unmethylated hydroxylgroup. This was further suggested by the n.m.r. spectrum which had a one proton singlet at δ 5.02 which shifted upfield with dilution and downfield with acid. The methyl ether groups showed up in the n.m.r. spectrum as three sharp singlets at δ 4.00 (6H, two aromatic OCH_3), 3.89 (3H, aromatic OCH_3) and 3.56 (3H, aliphatic OCH_3). In addition the singlet at δ 2.40 (3H, $COCH_3$) was still evident. A signal was also found at δ 4.92 (1H, four lines) and this was presumed to arise from the ArCHO-proton. This signal constituted the X part of an ABX spectrum, the AB part of which could be found upfield as two symmetrical doublets centred at δ 1.87(1H) and δ 2.43(1H). A first order analysis gave JAB=15 $\pm$ 0.2Hz. suggesting geminal coupling and therefore, a methylene group. The chemical shifts of H_A and H_B suggested that the methylene group was located β to an aromatic ring. An additional two doublets (2H, J=18.5 $\pm$ 0.2Hz) could also be found centred at δ 3.02 and δ 3.22

(AB pattern) indicating two geminal protons α to the aromatic system, without vicinal hydrogens. A complex multiplet δ 7-8 (3H, ABC pattern) again showed the three aromatic protons on the one ring.

The formation of the above mentioned trimethyl ether with one remaining hydroxyl group suggested the presence of four, free hydroxyl groups in daunomycinone. This was proven by converting daunomycinone on treatment with acetic anhydride in pyridine at 60°C to a tetraacetate, $C_{29}H_{26}O_{12}$, m.p. 225°C. The i.r. spectrum showed phenolic (1776 cm^{-1}) and alcoholic (1740 cm^{-1}) acetate bands, but no hydroxyl absorption was evident. In addition, daunomycinone, in the presence of either acid or alkali, gave a bisanhydro derivative, $C_{21}H_{14}O_6$, m.p. 325°-330°C, whose i.r. spectrum showed a conjugated ketone absorption (1685 cm^{-1}). This derivative gave a diacetate, $C_{25}H_{18}O_8$, m.p. 240°-243°C, one OCH_3, phenolic acetate absorption (1765 cm^{-1}), thus showing the presence of two phenolic and two alcoholic hydroxyls in daunomycinone, the latter two being involved in the dehydration reaction. Hydrogenolysis of daunomycinone with Pd on $BaSO_4$ in dioxane afforded deoxydaunomycinone $C_{21}H_{18}O_7$, m.p. 229°-231°C, whose n.m.r. spectrum now showed signals corresponding to two benzylic CH_2 groups, indicating the loss of the benzylic hydroxyl group.

Sodium borohydride reduction of daunomycinone, followed by periodate oxidation, afforded acetaldehyde, isoalated as the 2,4-dinitrophenylhydrazone in good yield, thus proving the acetyl side chain and its attachment to a hydroxylated carbon atom.

On the basis of the preceeding data Mondelli et al were able to assign either structure Ia or Ib to daunomycinone.



I

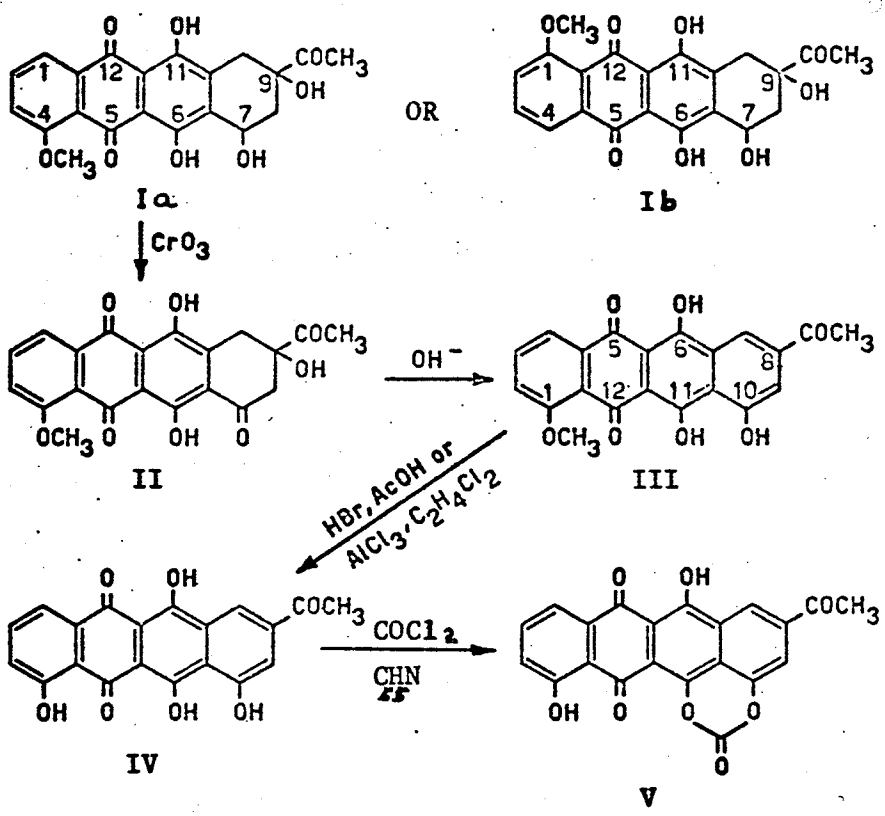
a, $R_1 = OCH_3$, $R_2 = H$

b, $R_1 = H$, $R_2 = OCH_3$

Figure II

It was not until 1968 that Mondelli et al[14] published the following data that enabled them to distinguish between structures Ia and Ib, and later[15] to establish the absolute stereochemistry of daunomycinone. Oxidation (see Scheme I) of daunomycinone with chromic anhydride in acetic acid gave the corresponding ketone II which was converted to III with 2N sodium hydroxide. Refluxing III with aluminum chloride in 1,2-dichloroethane produced IV which was then converted to the pericarbonate V by treatment with phosgene and pyridine in chloroform followed by hydrolysis of the chloroformyl groups with .5N sodium bicarbonate. The i.r. spectrum of V did not show a 1670 cm^{-1} free quinone absorption and therefore the pattern of hydroxylation must be as shown. Consequently, the structure of daunomycinone was established as being Ia rather than Ib.

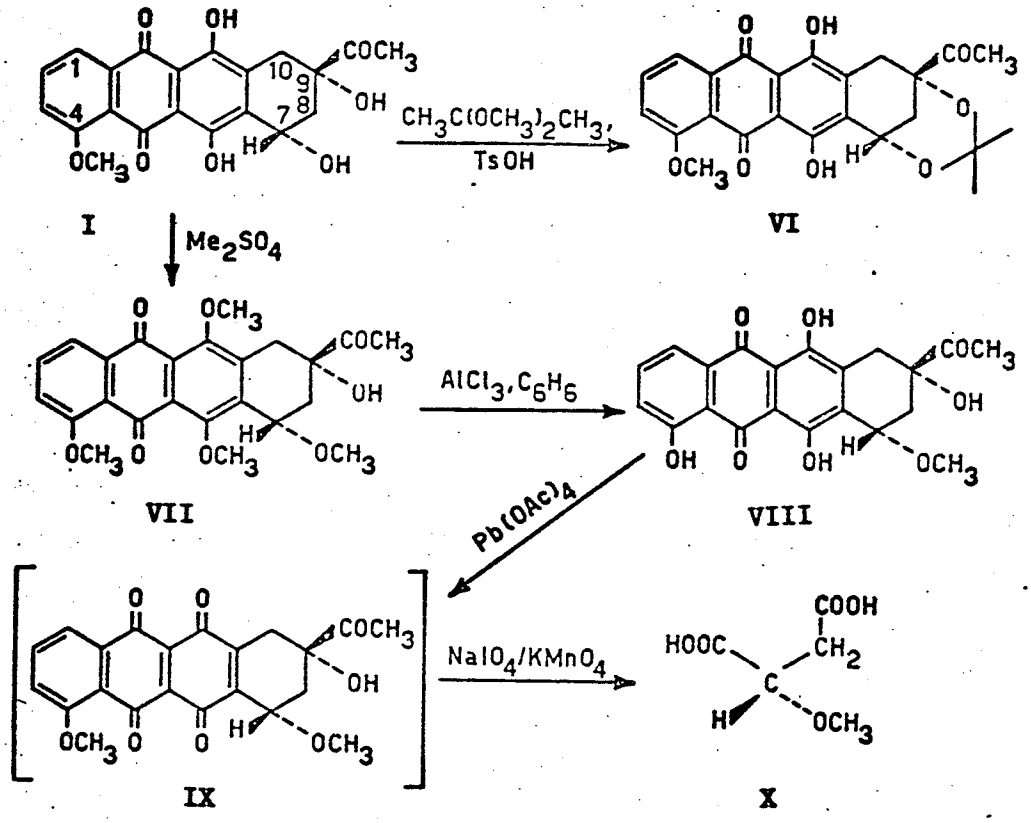
Scheme I



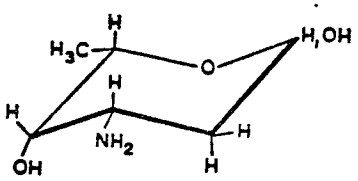
The total absolute configuration of daunomycinone was then determined by means of the chemical degradation shown in Scheme II. Daunomycinone trimethylether VII was reacted with aluminum chloride in benzene to give 7-O-methyldesmethoxydaunomycinone VIII which was then oxidized with lead tetraacetate in acetic acid to give the yellow diquinone derivative IX. This product, without isolation, was then further ozidized with a periodate - permanganate mixture to give, after purification with paper chromatography, S (-)-methoxysuccinic acid X, identified by direct comparison with a synthetic sample. Therefore, C-7 could be established as having configuration (S). C-9 was then configurationally related to C-7 by preparing the isopropylidene derivative VI by treating daunomycinone with 2,2-

dimethoxypropane and p-toluenesulfonic acid in dioxane. The cis configuration of the C-7 and C-9 hydroxyls allowed the definition of the absolute steriochemistry at C-9 as (S). Therefore, the aglycone, daunomycinone was finally established as being 7S, 9S - 9-acetyl-7,8, 9,10 - tetrahydro - 6,7,9,11 - tetrahydroxy - 4 - methoxy - 5,12 - naphthacenedione.

Scheme II



Using spectral and chemical techniques similar to those that they used in elucidating the structure of daunomycinone, Mondelli and coworkers[16] were also able to establish that the sugar residue of daunomycin, daunosamine, is an amino sugar with structure and stereochemistry 3(S), 4(S), 5(S) as shown in Fig. III.



XI

Figure III

There remained, therefore, only to establish the position and stereochemistry of the glycoside linkage.

The position of the glycoside link was deduced from n.m.r. and chemical data[14]. The 100 MHz. n.m.r. spectrum of daunomycin pentaacetate, m.p. 268-270°C, showed that the signal for H7 again was a double doublet constituting the X part of an ABX spectrum, with $\delta = 5.07$. Comparing this chemical shift with that found for H7 in daunomycinone trimethyl ether, δ 4.92, and in daunomycinone triacetate; δ 6.42, showed that the substitution at C_7 produced a glycoside oxygen instead of an O-acetate, and, therefore, the glycoside linkage was established as being at C7. This was further confirmed by the fact that catalytic hydrogenation of daunomycin with $Pd/BaSO_4$ in methanol gave 7-deoxydaunomycinone and daunosamine, thus showing that the attachment of the amino sugar is at C7.

The stereochemistry of the glycoside linkage was also established from n.m.r. data[15]. On the basis of a series of decoupling experiments involving the 100 MHz n.m.r. spectrum of N-acetyldaunomycin it was shown that H_1^1 is equatorial and that the sugar is in a ^1C conformation. Therefore an α-glycoside structure was concluded.

Therefore, the complete structure of daunomycin could be written as shown in Fig. IV.

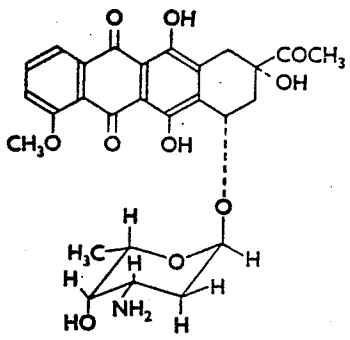


Figure IV

NATURE OF THE PROBLEM

In 1968 Goodman et al[17] reported the synthesis and characterisation of a glucose analogue of daunomycin using 7,8,9,10-tetrahydro-6,7,11-trihydroxy-5,12-naphthacenedione as the aglycone. Recently, they also published[18] the synthesis of the sugar moiety of daunomycin, daunosamine. At present, however, the total synthesis of daunomycin, which now really only involves the synthesis of its aglycone, daunomycinone, has not been reported. Only the synthesis of bisanhydrodaunomycinone has been published[19]. Therefore, we decided to try and synthesize daunomycinone as the major step towards the total synthesis of daunomycin.

The synthetic approach initially devised was to first synthesize the C and D rings of daunomycinone with all of the functional groups and then to add on the A and B rings. The synthesis was begun, therefore, with these objectives in mind.

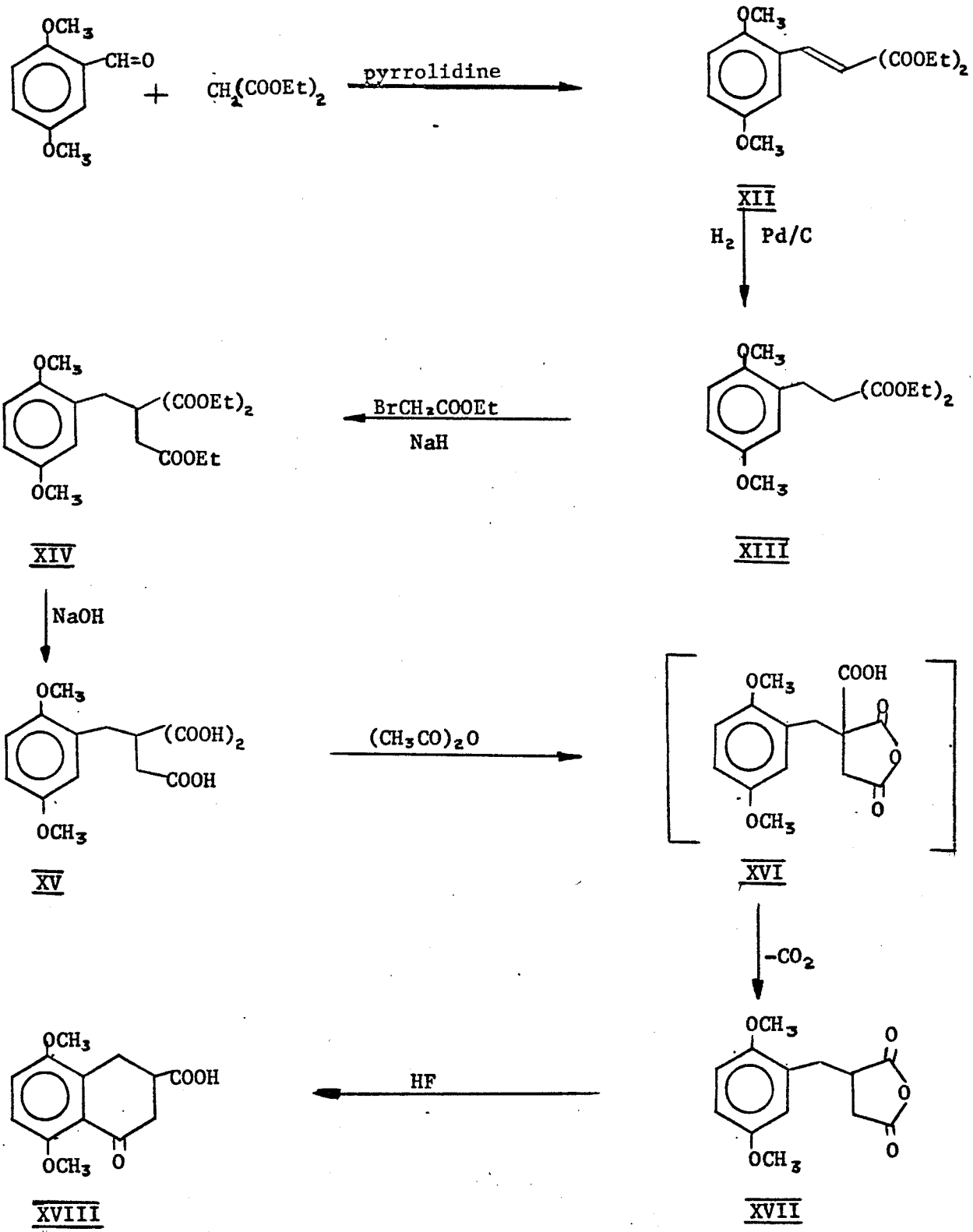
RESULTS AND DISCUSSION

2,5-dimethoxybenzaldehyde was condensed with diethyl malonate (see Scheme III) to give the unsaturated ester XII as a bright yellow liquid in essentially quantitative yield. The i.r. spectrum (Fig. X) showed a strong ester absorption at 1720 $cm.^{-1}$ and a carbon-carbon double bond absorption at 1620 $cm.^{-1}$. The n.m.r. spectrum (Fig. LVIII) was also in agreement with structure XII, showing two overlapping triplets and two overlapping quartets for theethyl esters, two singlets (3H) for the aromatic methoxyls, a multiplet (3H) for the aromatic ring protons and a low field singlet (1H) for the olefin proton.

The unsaturated ester XII was then reduced with hydrogen over palladium on charcoal to the corresponding saturated ester XIII. The product was isolated by vacuum distillation as a very pale, yellow liquid in 73% yield. The i.r. spectrum (Fig. XI) still showed an ester absorption at 1720 $cm.^{-1}$, but no longer displayed the double bond absorption at 1620 $cm.^{-1}$. In the n.m.r. spectrum (Fig. LIX) the benzylic CH_2 appeared as a two proton doublet and the adjacent CH appeared as a one proton triplet (partially hidden beneath the methoxyl singlets).

Alkylation of the diester XIII with sodium hydride and ethyl bromoacetate in refluxing tetrahydrofuran (thf) gave the triester XIV as a pale yellow liquid in 98% yield (based on undistilled product). The i.r. spectrum (Fig. XII) still showed an ester absorption (1730 $cm.^{-1}$) and the n.m.r. spectrum (Fig. LX) now revealed absorptions corresponding to three ethyl esters as well as a two proton singlet for each of the two methylene groups.

Scheme III


OCH3
CH=O
OCH3
+
CH2(COOEt)2
pyrrolidine
OCH3
(COOEt)2
OCH3
XII
H2
Pd/C
OCH3
(COOEt)2
OCH3
XIII
BrCH2COOEt
NaH
OCH3
(COOEt)2
COOEt
OCH3
XIV
NaOH
OCH3
(COOH)2
COOH
OCH3
XV
(CH3CO)2O
OCH3
COOH
O
O
O
OCH3
XVI
-CO2
OCH3
O
O
O
OCH3
XVII
HF
OCH3
COOH
OCH3
O
XVIII

Hydrolysis of the triester XIV with 10% sodium hydroxide in ethanol afforded the triacid XV as a white, crystalline solid (78% yield). This compound was characterized by its i.r. spectrum (Fig. XIII) which exhibited a broad acid OH absorption as well as an acid carbonyl absorption (2800 and 1700 $cm.^{-1}$. resp.), and by its mass spectrum (Fig. LXXXI) which had the required molecular ion peak of 280. Several attempts were then made to thermally decarboxylate the "malonic acid" part of this molecule; all,however, were unsuccessful. Although the reason for this was not immediately obvious it was felt that the presence of the third carboxyl group may have been responsible in some way. Therefore, an attempt was made to prepare the acid anhydride XVI with the hope that this compound could be decarboxylated. Dissolving and warming the triacid XV in acetic anhydride for this purpose did not, however, lead to the expected anhydride XVI, for although this compound probably formed it immediately decarboxylated, as was evidenced by the vigorous bubbling of the acetic anhydride solution well below its boiling point. Therefore, evaporation of the acetic anhydride gave the anhydride XVII; obtained as a white, crystalline solid in quantitative yield. The i.r. spectrum (Fig. XIV) showed absorptions at 1785 and 1865 $cm.^{-1}$ for the anhydride carbonyls, but no carboxylic acid absorptions were evident. The n.m.r. spectrum (Fig. LXI) was also consistent with structure XVII, showing a complex five proton multiplet for the aliphatic protons. In addition, the mass spectrum (Fig. LXXXII) had the required molecular ion peak of 250.

The anhydride XVII was then dissolved in anhydrous hydrogen fluoride to give a dark red solution. Stirring this solution for three hours at room temperature and then evaporating the hydrogen fluoride gave the ketoacid XVIII. The product was obtained as a

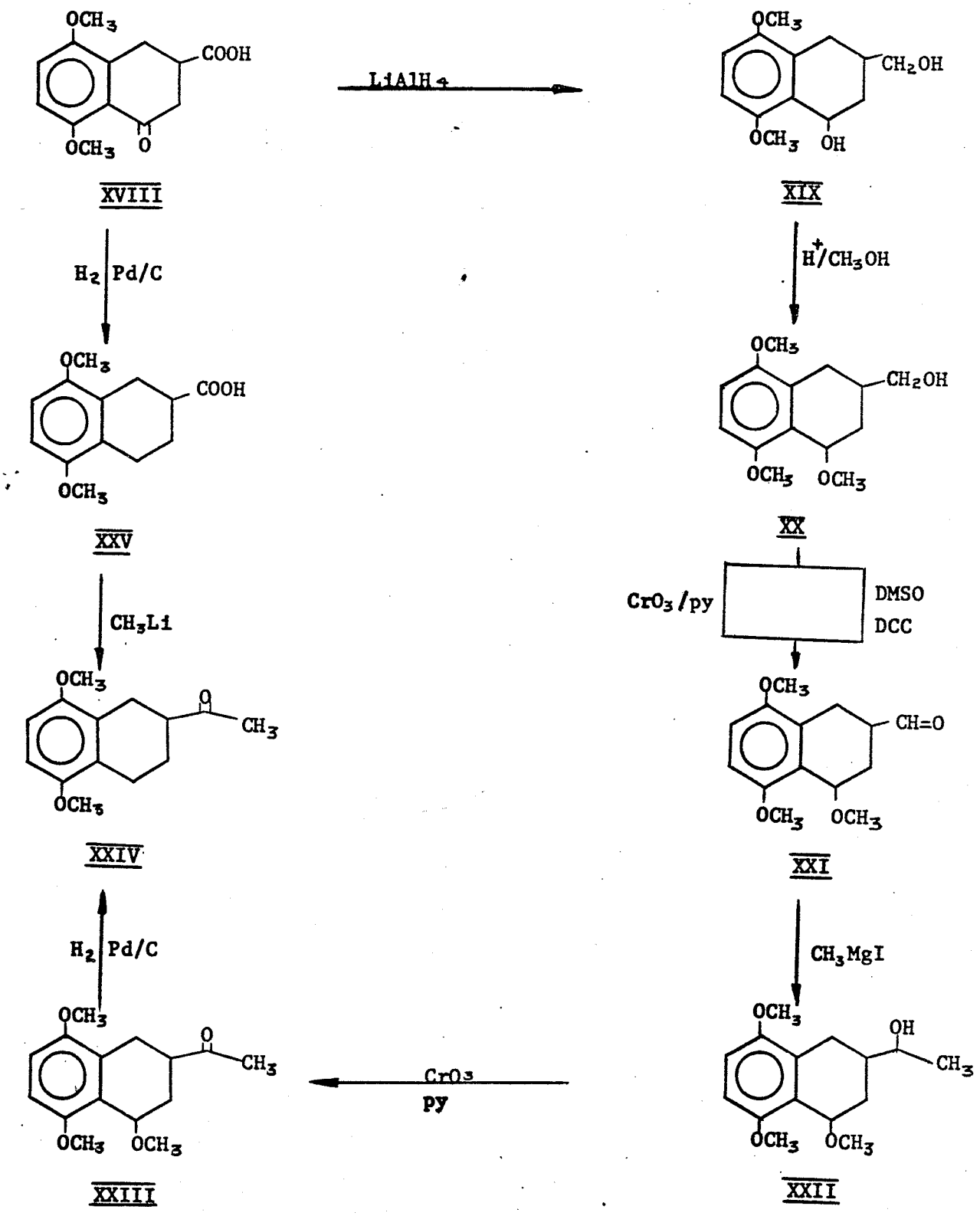
white, crystalline solid (77% yield) which gave a satisfactory elemental analysis and the expected molecular ion of 250 in the mass spectrum (Fig. LXXXIII). The i.r. spectrum (Fig. XV) showed absorptions for acid OH, acid carbonyl and α,β-unsaturated carbonyl (3150 (broad), 1720 and 1665 cm^{-1}, resp.). The aromatic ring protons now appeared as a two proton AB quartet in the n.m.r. spectrum (Fig. LXII).

The synthesis of the ketoacid XVIII thus provided the basic skeleton of the C and D rings. There only remained, therefore, the problem of converting the ketone and carboxyl functional groups of compound XVIII to the required hydroxyl and acetyl groups.

Consequently, the ketoacid XVIII was reduced (see Scheme IV) with lithium aluminum hydride to the dialcohol XIX which was isolated as a clear, glass-like material in 92% yeild. Crystallization of this substance produced a white, crystalline solid which gave the required molecular ion of 238 in the mass spectrum (Fig. LXXXV). The i.r. spectrum (Fig. XVII) displayed an alcohol OH absorption at 3460 $cm.^{-1}$ and no carboxylic acid absorptions were evident. The n.m.r. spectrum (Fig. LXIV) was also consistent with structure XIX. The benzylic proton adjacent to the benzylic hydroxyl appeared as a broad, lowfield (δ5.05) triplet and the side chain methylene protons appeared as a broad doublet. The aromatic ring protons were again observed as a sharp singlet (2H).

In order to prevent its reoxidation in subsequent reactions, the benzylic hydroxyl group was converted to a methoxyl group by stirring compound XIX with acidic methonol. The required product XX was obtained as a white, crystalline solid (86% yield) which had the required molecular ion of 252 in the mass spectrum (Fig. LXXXVI). The i.r. spectrum (Fig. XVIII) still exhibited a hydroxyl group

Scheme IV


OCH3
COOH
OCH3
O
XVIII
LiAlH4
OCH3
CH2OH
OCH3
OH
XIX
H2 Pd/C
H+/CH3OH
OCH3
COOH
OCH3
XXV
OCH3
CH2OH
OCH3
OCH3
XX
CH3Li
CrO3/py
DMSO
DCC
OCH3
O
CH3
OCH3
XXIV
OCH3
CH=O
OCH3
OCH3
XXI
H2 Pd/C
CH3MgI
OCH3
O
CH3
OCH3
OCH3
XXIII
CrO3
py
OCH3
OH
CH3
OCH3
OCH3
XXII

absorption at 3350 $cm.^{-1}$, showing that the sidechain hydroxyl was still present. In the n.m.r. spectrum (Fig. LXV) a sharp singlet (3H) about .4 p.p.m. to high field of the aromatic methoxyl absorptions verified the presence of the benzylic methoxyl group.

It is worth mentioning at this point that the cis isomer of compound XX (where cis and trans refers to the relative stereochemistry of the benzylic OCH_3 and CH_2OH groups) was produced almost exclusively. The evidence for this will be presented later. This stereoselectivity is probably the result of the preferential formation of the thermodynamically more stable diequatorial (and therefore, cis) isomer, as shown in Fig. V.

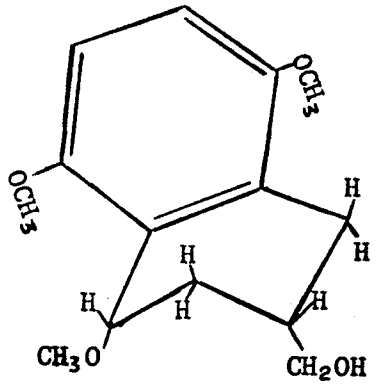


Figure V

Continuous reionization and remethylation of the benzylic position could have shifted the equilibrium between the axial-equatorial isomer and the equatorial-equatorial isomer almost entirely towards the latter.

After suitably protecting the benzylic hydroxyl group, as mentioned, the $-CH_2OH$ sidechain was subsequently oxidized to an aldehyde with chromium trioxide in pyridine. The product, after purification by thin layer chromatography (t.l.c.), could be isolated as a white, crystalline solid in 15% yield. The aldehyde sidechain displayed the expected carbon-hydrogen and carbonyl absorptions

(2725 and 1720 $cm.^{-1}$, resp.) in the i.r. spectrum (Fig. XIX). The aldehyde proton was also observed in the n.m.r. spectrum (Fig. LXVI) as a one proton singlet (δ9.74).

Since the yield of the chromium trioxide oxidation was so low, an alternative oxidation method was tried. Treating compound XX with dicyclohexylcarbodiimide in dimethyl sulfoxide according to the method developed by Moffatt et al[20,21] also gave the aldehyde XXI, but this time in a 66% yield. Therefore, this proceedure was used in all subsequent preparations of compound XXI.

The aldehyde was then reacted with methyl magnesium iodide in dry ether. The Grignard reaction proceeded smoothly and the required product XXII was isolated (72% yield) as a white, crystalline solid which gave the required molecular ion of 266 in the mass spectrum (Fig. LXXXVIII). The i.r. spectrum (Fig. XX) exhibited the required hydroxyl absorption at 3620 $cm.^{-1}$ and the n.m.r. spectrum (Fig. LXVII) showed the presence of the sidechain methyl group.

The alcohol XXII was then oxidized with chromium trioxide in pyridine to give the ketone XXIII. The product was isolated as a white, crystalline solid (65% yield) which gave a satisfactory elemental analysis and the expected molecular ion of 264 in the mass spectrum (Fig. LXXXIX). The i.r. spectrum (Fig. XXI) showed the expected ketone carbonyl absorption at 1710 $cm.^{-1}$ and the n.m.r. spectrum (Fig. LXVIII) also revealed a three proton singlet for the ketone methyl group.

Compound XXIII was found to be identical in every way with a ketone prepared by my colleague Jan teRaa[22], who used a completely different synthetic route (starting from 2,5-dimethoxybenzaldehyde and acetylacetone). However, in Mr. teRaa's approach, both the cis

and trans methoxy ketones were produced in a ratio of about twenty to one, respectively. (The minor isomer could be removed by recrystallization.) This was evident from the n.m.r. spectrum which gave two singlets for the benzylic methoxyl group (δ3.45 cis, δ3.3 trans) in the ratio of about twenty to one, and two singlets for the methyl ketone (δ2.26 cis, δ2.18 trans) also in the ratio of about twenty to one. The resonance for the cis benzylic methoxyl comes at lower field than that for the trans because the cis methoxyl lies more in the plane and therefore deshielding region of the adjacent aromatic ring. Now, ketone XXIII corresponded exactly to the cis ketone prepared by Mr. teRaa. No trans isomer was found. It is therefore reasonable to assume that compound XX, and therefore compounds XXI and XXII, were produced almost exclusively as the cis isomer, as mentioned previously, since the reactions used to convert compound XX to the ketone XXIII did not involve a change in the relative steriochemistry of the substituents. Although it is probable that a small amount of the trans isomer of compound XX did form, it was probably lost since compound XX was purified by crystallization. This fact explains why compounds XX to XXIII all gave a sharp melting point after one recrystallization.

Compound XXIII now had the benzylic oxygen functional group and acetyl sidechain that the D ring of daunomycinone required. Only the tertiary hydroxyl was missing. At this time my colleague Don Popien[23] made several attempts to condense phthalic anhydride with compound XXIII. Unfortunately, although the phthalic anhydride condensed, the only tetracyclic products Mr. Popien could isolate were ones where the D ring was aromatized. It was felt that the aromatization probably resulted from an initial loss of the benzylic methoxyl group

and, therefore, that it might be prevented if the benzylic methoxyl group were absent. Therefore, this substituent was removed (with the hope that it could be reintroduced later) by catalytic reduction with hydrogen. The resulting product, ketone XXIV, was isolated as a white, crystalline solid (85% yield) which gave a satisfactory elemental analysis and the required molecular ion of 234 in the mass spectrum (Fig. XC). An absorption at 1705 $cm.^{-1}$ in the i.r. spectrum (Fig. XXII) indicated that the acetyl sidechain was still present while in the n.m.r. spectrum (Fig. LXIX) the absence of the three proton singlet at δ 3.45 p.p.m. verified that the benzylic methoxyl group had been successfully removed. Mr. Popien then condensed phthalic anhydride with this reduced compound and was able to isolate the required tetracyclic product with the D ring remaining saturated.

Since the benzylic methoxyl group could not be retained during the phthalic acid condensation the synthetic pathway to compound XXIII was no longer of much use. Therefore, a much shorter route to compound XXIV was devised. The benzylic ketone of the keto acid XVIII was completely reduced with hydrogen over Pd on charcoal and the product was isolated as a white, crystalline solid in 80% yield. The i.r. spectrum (Fig. XVI) no longer showed the absorption at 1665 $cm.^{-1}$ and the mass spectrum (Fig. LXXXV) had the required molecular ion of 236.

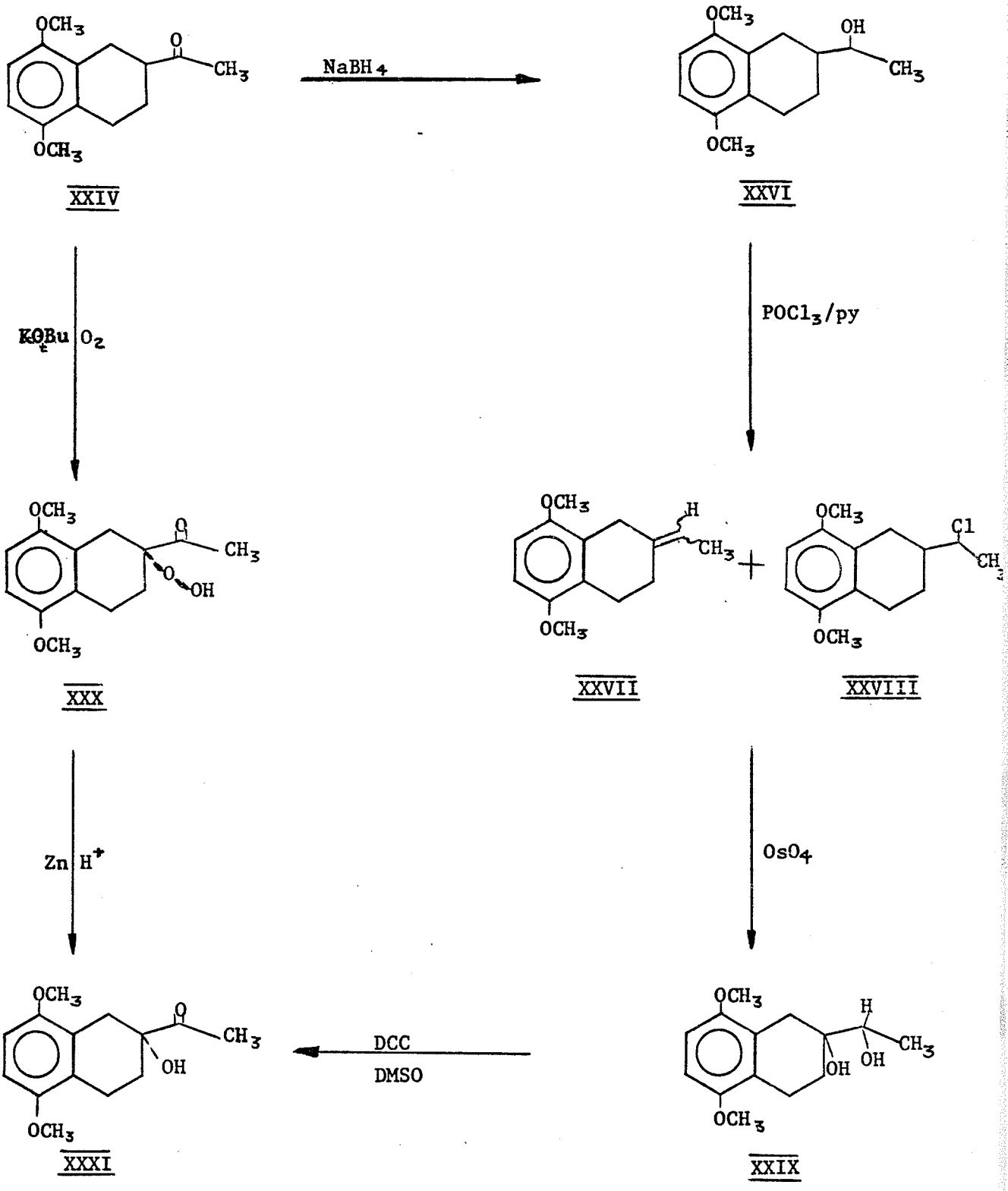
The acid XXV was then reacted with two moles of methyl lithium in anhydrous t h f to give a white solid (72% yield) identical in every way with the ketone produced by reduction of compound XXIII. It should be pointed out that unless all the precautions suggested by Jorgenson[24] were followed, a tertiary alcohol instead of a ketone sidechain was produced.

Since the D ring of daunomycinone has a tertiary hydroxyl in

the 9 position, there still remained the problem of introducing this group into our system. This was accomplished (see Scheme V) by oxidizing the ketone XXIV with potassium t-butoxide and molecular oxygen to the peroxide XXX (not isolated) which was immediately reduced with zinc in acetic acid to the required hydroxy ketone XXXI. The product, after purification by column chromatography, was isolated as a white, crystalline solid (47% yield) and gave a satisfactory elemental analysis and the required molecular ion of 250 in the mass spectrum (Fig. XCII). (If sodium t-butoxide was used instead of potassium t-butoxide then less than a 5% yield was obtained, possibly due to the low solubility of the sodium salt at the reaction temperature.) An absorption at 3490 $cm.^{-1}$ in the i.r. spectrum (Fig. XXVII) verified the introduction of the hydroxy group.

In order to ascertain that the hydroxy group was in the tertiary position, compound XXXI was also synthesized by an unambiguous route. Ketone XXIV was reduced with sodium borohydride in methanol to the corresponding alcohol XXVI in quantitative yield. In the i.r. spectrum (Fig. XXIII) the ketone absorption was replaced by a hydroxyl absorption at 3630 $cm.^{-1}$. This compound was then dehydrated with phosphorous oxychloride in dry pyridine. However, when the isolated product was subjected to t.l.c. it separated into two bands. Elution of the upper band gave the expected olefin mixture XXVII in 33% yield. The absence of the hydroxyl absorption in the i.r. spectrum (Fig. XXIV) and the presence of a one proton multiplet in the olefinic region of the n.m.r. spectrum (Fig. LXX) helped verify the presence of the double bond. Elution of the lower band on the t.l.c. plate gave a compound (37% yield) whose i.r. spectrum (Fig. XXV) was very similar to that of the olefin XXVII, but whose n.m.r. spectrum (Fig. LXXI) had no

Scheme V


OCH3
O
CH3
OCH3
NaBH4
OCH3
OH
CH3
OCH3
XXIV
XXVI
KOBut O2
POCl3/py
OCH3
O
CH3
O
OH
OCH3
OCH3
H
CH3
OCH3
OCH3
OCH3
Cl
CH
OCH3
XXX
XXVII
XXVIII
Zn H+
OsO4
OCH3
O
CH3
OH
OCH3
DCC
DMSO
OCH3
H
OH
CH3
OH
OCH3
XXXI
XXIX

absorptions in the olefin region. There was, however, a one proton multiplet centred around δ4.02. This fact, along with molecular ion peaks of 254 and 256 in the mass spectrum and a positive sodium fusion test for chlorine helped identify the compound as the chloro substitution product XXVIII. Chloro substitution rather than dehydration using these reaction conditions is not unheard of and probably proceeds according to the mechanisms described by Gerrard.[25]

The olefin mixture XXVIII was then reoxidized with osmium tetroxide to give the diol XXIX (87% yield), whose i.r. spectrum (Fig. XXVI) showed the expected hydroxyl absorption at 3600 $cm.^{-1}$. This diol, without purification, was further oridized with dicyclohexylcarbodiimide in dimethyl sulfoxide to give a hydroxy ketone identical to compound XXXI, thus verifying the position of the tertiary hydroxyl group.

The synthesis of the hydroxy ketone XXXI provided a suitable intermediate for the C and D rings of daunomycinone and, therefore, it was decided that this was a convenient point in the synthesis to add on the A and B rings. A preliminary investigation into this involving a Friedel-Crafts type of condensation (using trifluoroacetic anhydride to generate the acylium ion, as described later) of 2-carbomethoxybenzoic acid and compound XXXI showed that it was possible to obtain the tetracyclic hydronaphthacene quinone condensation product in a reasonable yield without loss of the tertiary hydroxyl group. Since the A ring of daunomycinone has a methoxyl substituent, the above condensation was again attempted using both 3-methoxy-2-carbomethoxybenzoic acid and 3-hydroxy-2-carbomethoxybenzoic acid (both prepared by my coworker, J. teRaa). In both cases, the tetracyclic condensation product could only be isolated in yields of less

than 1%. This decrease in yield probably resulted from the +M(electron donating) properties of the methoxy and hydroxy groups, which likely helped stabilize the reactive intermediate, the acylium ion (See Fig. VI), and therefore decreased its electrophylicity to the point where the reaction no longer occurred. It was felt, therefore, that an

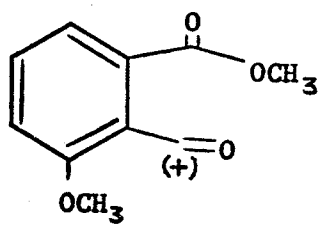
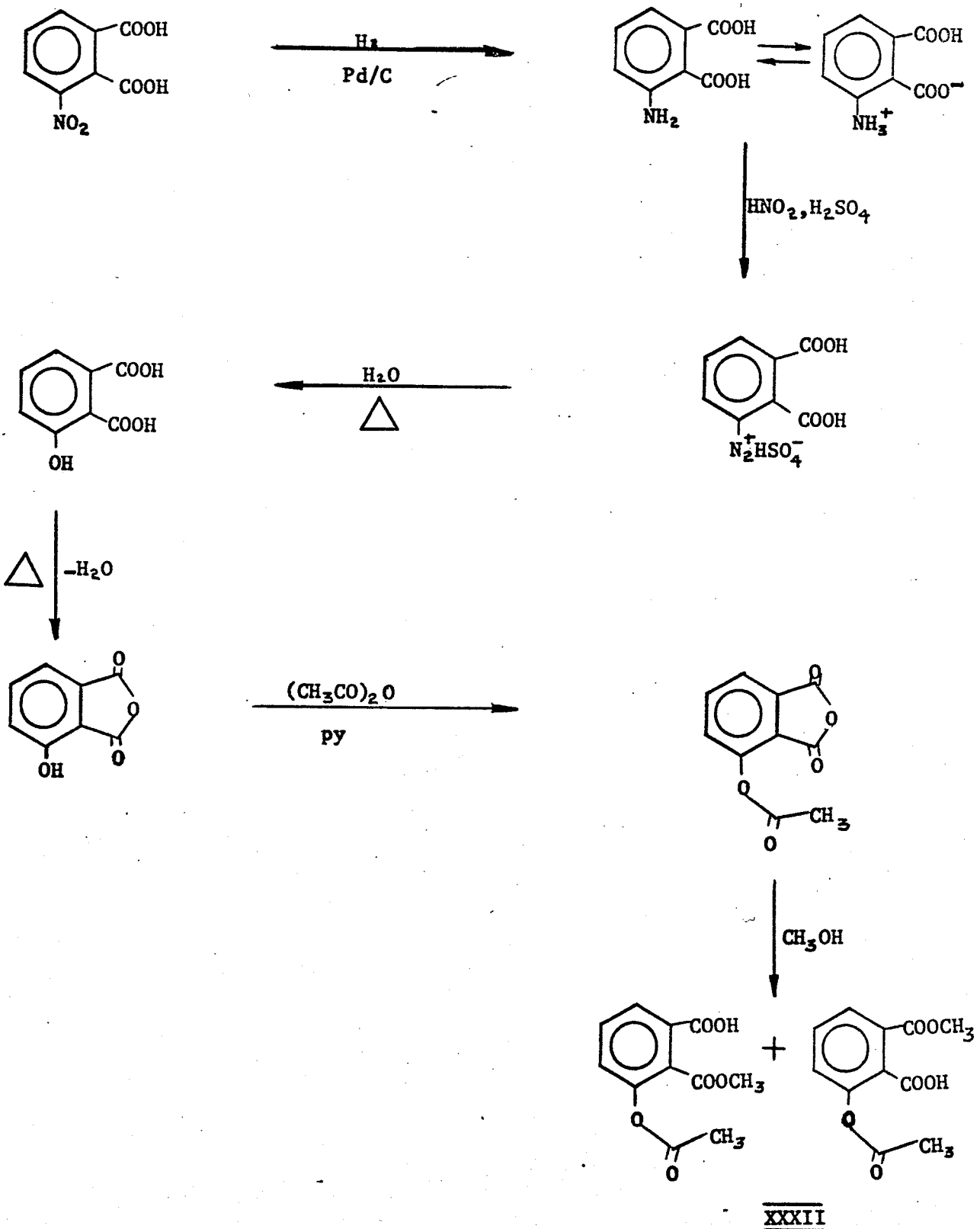


Figure VI

electron withdrawing substituent such as O-acetate would probably eliminate this problem (found to be the case) and, therefore, 3-acetoxy-2-carbomethoxybenzoic acid was prepared, as shown in Scheme VI.

3-Nitrophthalic acid was reduced according to the method of Okazaki et al[26] to give 3-aminophthalic acid in 95% yield. This amino-acid was diazotized and the resulting diazonium salt was then thermally decomposed to the corresponding phenol. The product, 3-hydroxyphthalic acid, was isolated as a thick brown syrup according to the method described by Haefele et al[27]. The hydroxy acid was then dehydrated by several sublimations under high vacuum to 3-hydroxyphthalic anhydride which was isolated as a fine, white powder (56% yield). The actual yield was somewhat higher but a considerable amount of material was lost in manipulation and repeated cleaning of the sublimation apparatus. Warming with acetic anhydride converted the 3-hydroxyphthalic anhydride to 3-acetoxyphthalic anhydride which without purification, was refluxed with methanol to give the half ester mixture XXXII, isolated as a yellow paste. The i.r. spectrum (Fig. XXVIII) of this mixture showed a broad acid hydroxyl absorption

Scheme VI



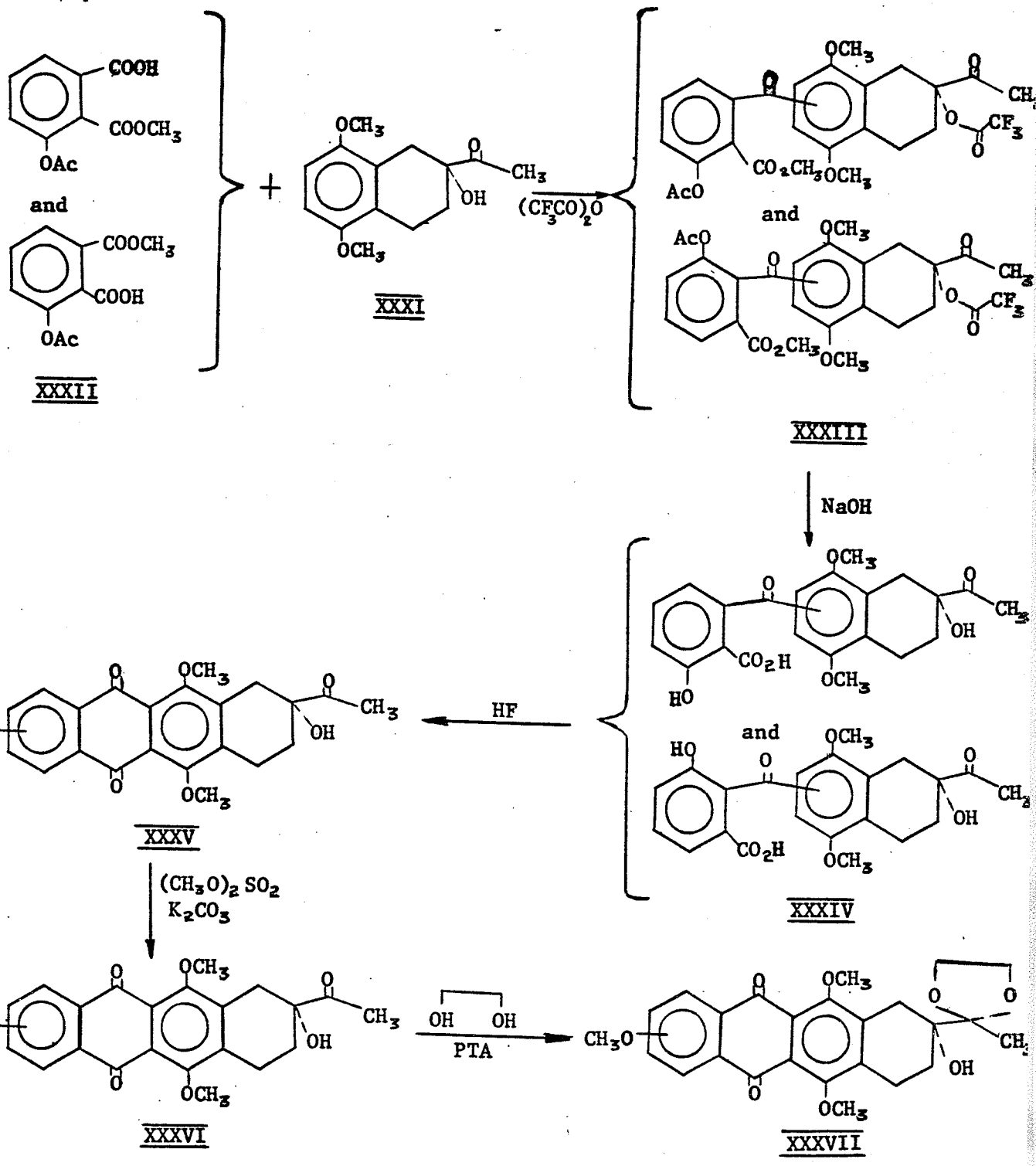
XXXII

centred at 3000 $cm.^{-1}$ and several carbonyl absorptions centred at 1710, 1740 and 1775 $cm.^{-1}$. The n.m.r. spectrum (Fig. LXXIV), which showed the product to be relatively free of impurities, displayed a singlet (3H, δ 2.28) for the acetyl methyl, a singlet (3H, δ 3.86) for the methyl ester, a singlet (1H, δ 10.18) for the acid proton and a multiplet (3H) for the aromatic ring protons.

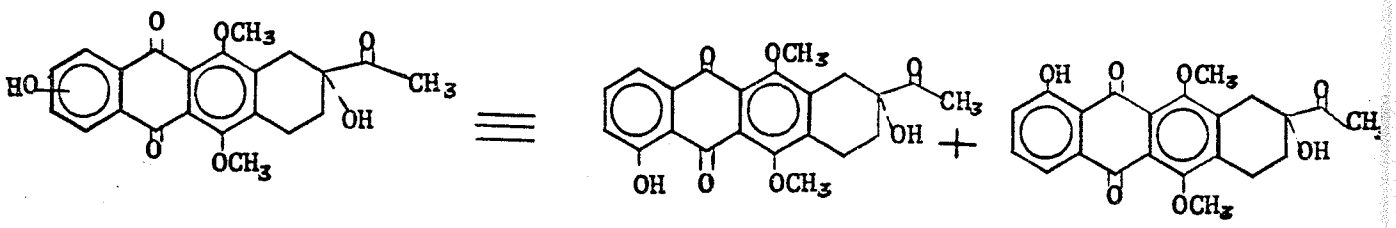
This ester mixture XXXII was then condensed (see Scheme VII) with the hydroxyketone XXXI in a Friedel-Crafts type of condensation using trifluoroacetic anhydride as the condensing agent. No attempt was made to purify or fully characterize the condensation products. However, the spectral data for the crude mixture was not inconsistent with the proposed structures XXXIII. This mixed product was then hydrolysed with sodium hydroxide solution to the proposed mixture XXXIV, which was then cyclized with anhydrous hydrogen fluoride to give the isomeric mixture XXXV. This product was isolated as a pale yellow solid (20% overall yield) which gave a satisfactory elemental analysis and the required molecular ion of 396 in the mass spectrum (Fig. XCIII). The i.r. spectrum (Fig. XXIX) was also consistent with structure XXXV showing absorptions for free and chelated quinone (1670 and 1640 $cm.^{-1}$, resp.), sidechain ketone (1710 $cm.^{-1}$) and tertiary hydroxyl group (3400 $cm.^{-1}$). A one proton singlet (δ 12.6) and a three proton multiplet in the aromatic region of the n.m.r. spectrum (Fig. LXXV) further verified the presence of the phenolic aromatic ring (A ring).

The phenol -OH of the A ring was then methylated with dimethylsulfate and potassium carbonate. The product, still a mixture of two isomers, was isolated as a pale yellow solid which gave the required molecular ion of 410 in the mass spectrum (Fig. XCIV). The i.r.

Scheme VII



where



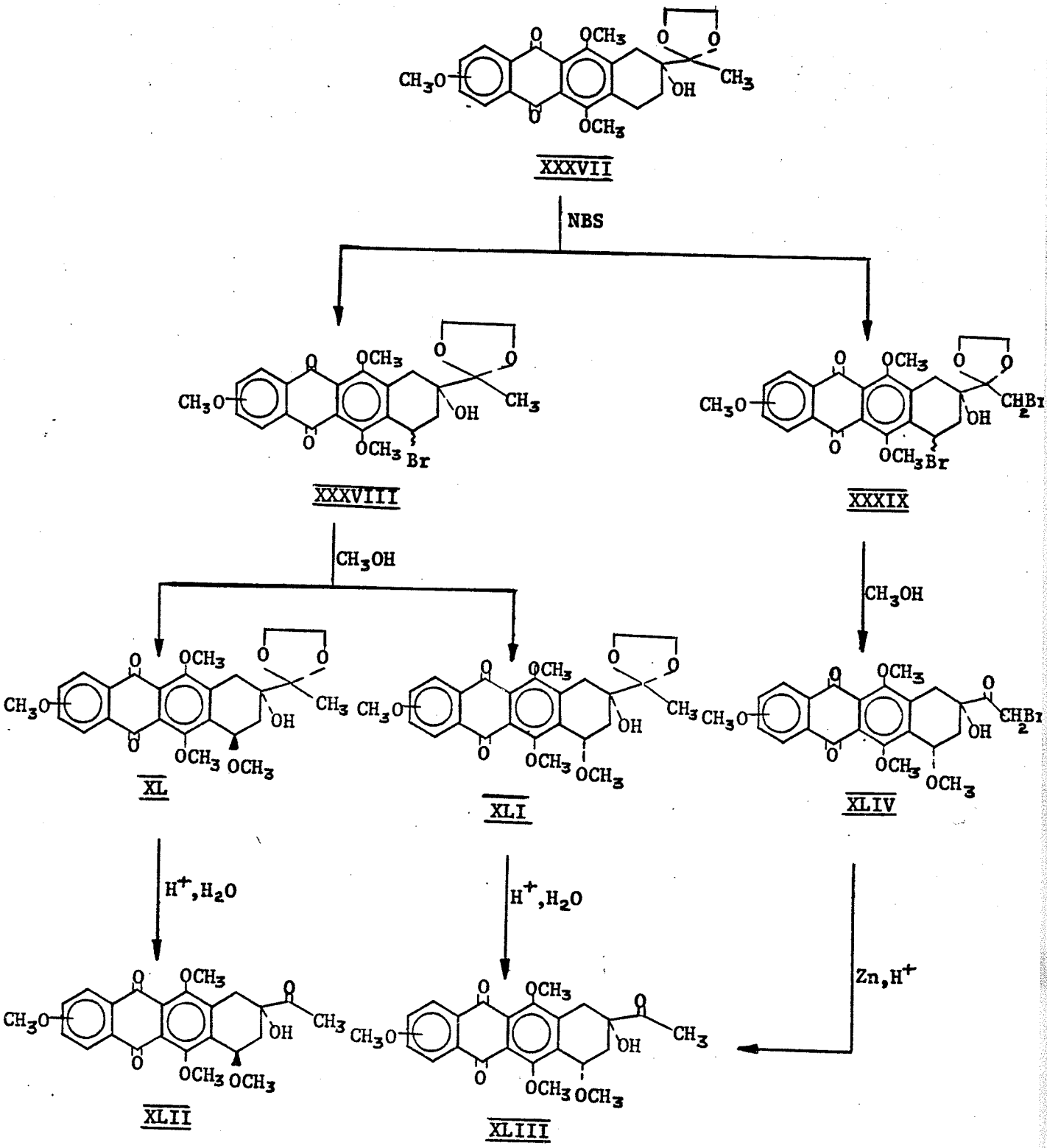
spectrum (Fig. XXX), as expected, no longer showed any absorption for chelated quinone.

The reintroduction of the benzylic (C_7) methoxyl group into the D ring of mixture XXXVI would, at this point, give daunomycinone (and isodaunomycinone) trimethyl ether. Therefore this was the next course of action undertaken in the synthesis. It was decided to first make the D ring ketone side chain as bulky as possible in order to prevent sterically any reaction from taking place at the adjacent benzylic (C_{10}) position. For this purpose, the ketone mixture XXXVI was converted to the ketal mixture XXXVII, isolated as a pale yellow solid (87.5% yield from mixture XXXV). A molecular ion of 454 in the mass spectrum (Fig. XCV) and the disappearance of the ketone absorption at 1710 $cm.^{-1}$ in the i.r. spectrum (Fig. XXXI) confirmed that the ketal formation was successful.

This isomeric ketal mixture was then brominated (see Scheme VIII) with N-bromosuccinimide and the bromination product (not isolated) was subsequently refluxed with anhydrous methanol. When the product from the methanolysis was subjected to purification by t.l.c. it separated into four, distinct, yellow bands on the t.l.c. plate (Rf values = .37, .51, .64 and .72). It turned out that this was still not a result of separation of the A ring isomers; these isomers still behaved as a single compound on the t.l.c. plate.

Elution of the lowest band on the t.l.c. plate (Rf = .37) gave a product whose i.r. spectrum showed a very weak ketone absorption at 1710 $cm.^{-1}$, suggesting that it was possibly a mixture of ketal plus some hydrolysed ketal, or ketone.

Scheme VIII


XXXVII
NBS
XXXVIII
XXXIX
CH3OH
CH3OH
XL
XLI
XLIV
H+,H2O
H+,H2O
Zn,H+
XLII
XLIII

Hydrolysis of this product with aqueous acid afforded a yellow solid whose i.r. spectrum (Fig. XXXVI) now showed a strong ketone absorption (1710 $cm.^{-1}$) as well as the quinone absorption (1675 $cm.^{-1}$) and hydroxyl group absorption (3500 $cm.^{-1}$). Therefore, the hypothesis that the product from the t.l.c. plate was a mixture of ketal plus ketone was probably correct. In the n.m.r. spectrum (Fig. LXXX) a sharp singlet (3H, δ 3.3) which could be assigned to an aliphatic methoxyl and a quartet (1H, centred δ 4.98) which could be assigned to an ArCHO-proton suggested that the benzylic methoxyl group had been successfully introduced. This was further confirmed by the mass spectrum (Fig. XCVI) which had a molecular ion peak of 440. Further inspection of the n.m.r. spectrum, however, revealed that the chemical shift for the tertiary hydroxyl proton (δ 3.9) had not changed significantly from its value in the n.m.r. spectra of compounds XXXV and XXXVI, where as the chemical shift for the tertiary hydroxyl proton of daunomycinone trimethyl ether is somewhat larger (δ 5.02). Consequently, this product was tentatively assigned structure XLII, that is, the A ring isomeric mixture of the trans-trimethyl ether (where cis and trans refer to the relative steriochemistry of the benzylic methoxyl and tertiary hydroxyl groups of the D ring).

Elution of the next spot on the t.l.c. plate (Rf=.51) gave a product whose i.r. spectrum (Fig. XXXII) lacked the ketone absorption at 1710 $cm.^{-1}$ suggesting that the product was still a ketal. Hydrolysis of this product with aqueous acid gave a new product isolable as a yellow solid which gave a molecular ion of 440 in the mass spectrum (Fig. XCVI). The i.r. spectrum now displayed a ketone absorption (1710 $cm.^{-1}$) as well as the quinone absorption (1675 $cm.^{-1}$) and hydroxyl group absorption (3460 $cm.^{-1}$). The n.m.r. spectrum was

found to be identical to that for daunomycinone trimethyl ether except for the fact that the three proton singlet (δ 3.89, aromatic OCH_3) reported for daunomycinone trimethyl ether was replaced by two singlets (δ 3.89, δ 3.93) whose total area corresponded to three protons. Therefore this product was assigned structure XLIII and the two singlets (δ 3.89, δ 3.93) could be attributed to the fact that the product was still the A ring isomeric mixture. This assignment was later verified rigorously, as will be explained further on in this thesis.

The similarity between the n.m.r. and mass spectra of mixture XLIII and mixture XLII further confirmed the correctness of structure XLII. The fact that the chemical shift of the tertiary hydroxyl proton in mixture XLIII is 1.12 ppm lower than in mixture XLII may be attributed to the intramolecular hydrogen bonding between the cis hydroxyl and methoxyl groups in mixture XLIII. This type of hydrogen bonding is not possible in mixture XLII due to the trans nature of these same substituents, in this case.

Elution of the next spot on the t.l.c. plate (Rf=.64) gave a product identical to that obtained on hydrolysis of the ketal mixture XLI, that is, the ketone mixture XLIII. The fact that both cis- and trans-ketones were obtained after the methanolysis reaction showed that some ketal hydrolysis was taking place during the methanolysis. This probably resulted from the small traces of water and acid remaining in the "anhydrous" methanol used. The small number of moles of the ketal XXXVIII (M.W.=533) used in the methanolysis would require only a few mg. of water to effect the amount of hydrolysis observed.

It is worth mentioning that a 42% yield (based on compound XXXVII) of the cis-trimethyl ethers was obtained as compared to only an 18% yield of the trans-trimethyl ethers. There are two possible

reasons for this predominant production of cis-isomer. First of all, if the ketone or ketal side chain was involved in stabilizing the benzylic carbonium ion generated during the methanolysis reaction (see Fig. VII) then the attack of the methanol on the side of the ring

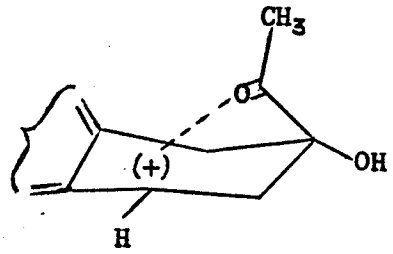
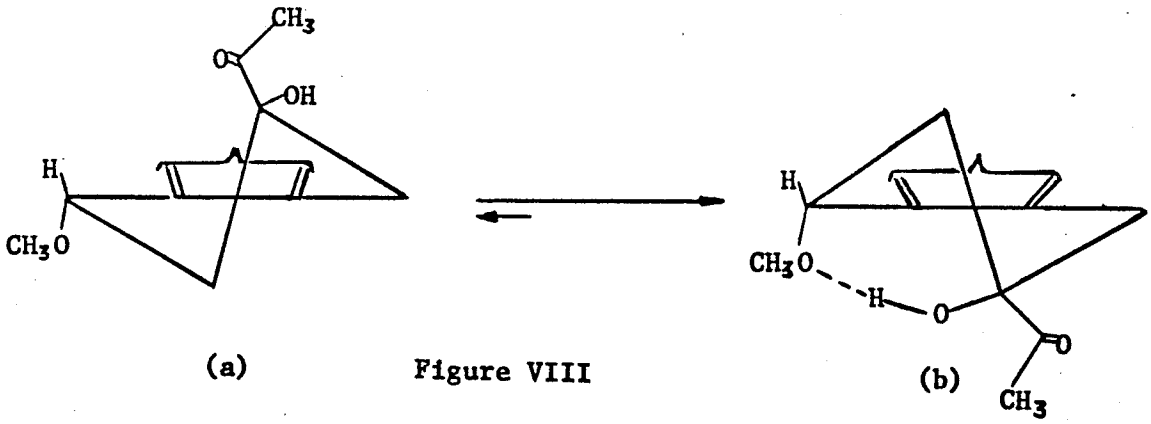


Figure VII

trans to the tertiary hydroxyl group would be sterically less favourable than attack from the side leading to the cis product. Therefore, one would expect a predominance of cis product to be formed. One would also expect more cis-isomer if this isomer were thermodynamically more stable than the trans-isomer. The n.m.r. spectrum of the cis-isomer shows that the tertiary hydroxyl group is hydrogen bonded to the benzylic methoxyl group. Therefore, the D ring must exist in predominantly in conformation b (see Fig. VIII) rather than in



(a) Figure VIII (b)

conformation a. Since there is this predominance of conformation b it is reasonable to assume that the hydrogen bonding taking place here leads to a net stabilization effect. Since this type of net stabilization is not possible for the trans-isomer it is reasonable

to assume that the cis-isomer is thermodynamically more stable than the trans-isomer. This, as mentioned, could be another reason for a higher yield of the cis-isomer.

The isolation of products XL, XLI, XLII and XLIII from the bromination and subsequent methanolysis reaction represents really only the isolation of expected products. There was, however, another band on the forementioned t.l.c. plate (Rf=.72) and elution of this band gave a small amount of product a little more difficult to identify. The mass spectrum (Fig. XCVII) gave molecular ion peaks of 518 and 520 suggesting that the compound contained a bromine atom. The i.r. spectrum (Fig. XXXVII) gave a peak at 1740 $cm.^{-1}$ suggesting an $\mathcal{L}$ - halo and therefore, $\mathcal{L}$ - bromoketone. This was confirmed by treating this bromo mixture with zinc and acetic acid, since only the ketone mixture XLII was obtained as product. Therefore the bromo mixture was assigned structure XLIV. This is not unreasonable since the bromination of the $\mathcal{L}$ - position of ketals has been reported in the literature. The fact that only the cis-isomer was obtained could again be explained as being due to the stabilization of the benzylic carbonium ion by the ketone side chain (see Fig. IX). The presence of the $\mathcal{L}$ - bromine would make

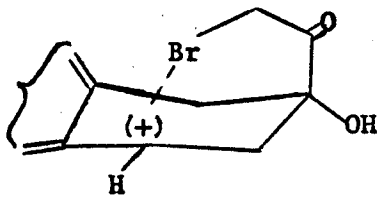


Figure IX

this type of stabilization much more predominant than in the case of just the methyl ketone. The bromine would also make the attack of the methanol from the ketone side much more sterically difficult.

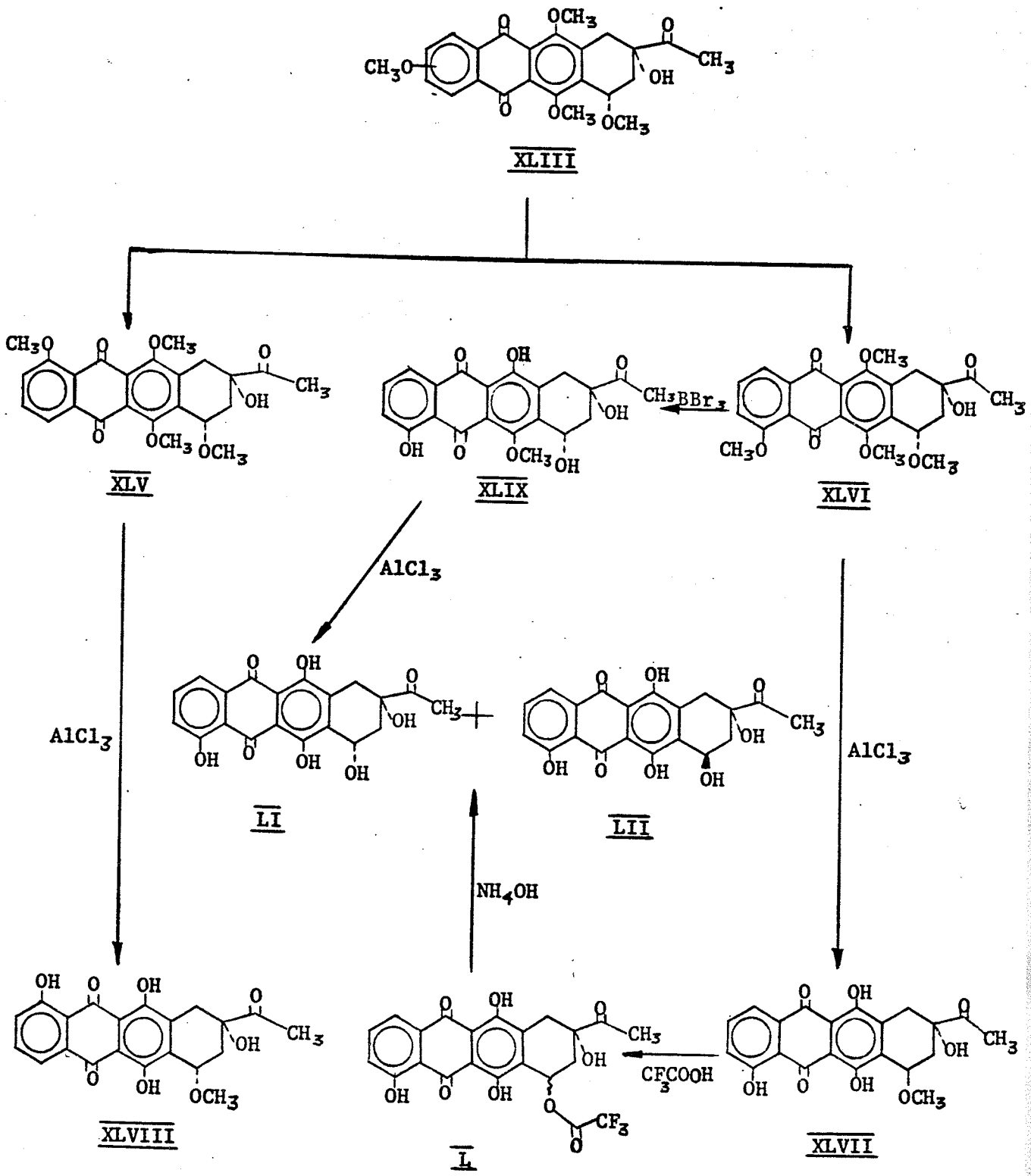
It should be mentioned that the n.m.r. spectrum (Fig. LXXXI) of

product XLIV is anomalous and difficult to explain. The methyl ketone ($-COCH_3$) resonance absorption is, as expected, absent. The other absorptions are also as expected, except that the tertiary hydroxyl proton gives two singlets (δ5.19, δ5.22) and the $-CH_2Br$ protons give what appears to be three singlets (δ4.58, 4.61, 4.82). This may be the result of a hydrogen bonding interaction between the tertiary hydroxyl group and the ketone oxygen, a phenomenon which would restrict the rotation of the $-CH_2Br$ group making its two protons non-equivalent in the n.m.r. spectrum. However, this is only supposition and further work should be done before any real conclusions can be reached.

At this point in the synthesis, the two isomers which made up mixture XLIII were separated (see Scheme IX) using t.l.c. . Isomer XLVI was isolated as a yellow, crystalline solid and was found to be spectroscopically identical (i.r. spectrum (Fig. XXXIII); n.m.r. spectrum (Fig. LXXVIII); mass spectrum (Fig. XCVI)) with natural daunomycinone trimethyl ether (i.r. spectrum (Fig. XXXIV)). Isomer XLV, 1-methoxy-4-demethoxy-daunomycinone trimethyl ether (isodaunomycinone trimethyl ether), was also isolated as a yellow, crystalline solid whose i.r. spectrum (Fig. XXXV) differed only slightly in the fingerprint region from the i.r. spectrum of compound XLVI. The first order n.m.r. spectrum (Fig. LXXIX) of compound XLV was identical to the n.m.r. spectrum of compound XLVI except for a small difference in the chemical shift of the A ring methoxy group. The mass spectra of the two compounds were identical. The empirical formula of each compound was also in agreement with that established from its high resolution mass spectrum.

The preparation of compound XLVI represented the total synthesis of (dl)-daunomycinone trimethyl ether. At this point, a selective

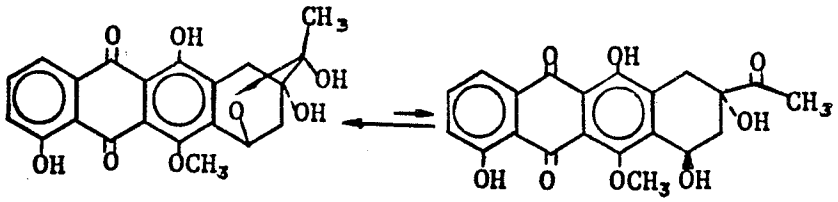
Scheme IX


XLIII
XLV
XLIX
XLVI
AlCl3
AlCl3
AlCl3
LI
LII
NH4OH
XLVIII
L
CF3COOH
XLVII

hydrolysis of the methoxyl groups in the 6,7 and 11 positions of the C and D rings would lead directly to daunomycinone. Since Horii et al[19], in their synthesis of bisanhydrodaunomycinone, had apparently effected a very similar, selective hydrolysis using boron tribromide, we decided to try this reagent on compound XLVI. Hydrolysis of compound XLVI with boron tribromide gave a red, crystalline solid (27% yield) whose mass spectrum (Fig. CI) was identical to the mass spectrum of natural daunomycinone. This fact established that three methoxyl groups were hydrolysed and that one of these was the methoxyl group of the saturated D ring. The i.r. spectrum (Fig. XL) of this compound, however, was different from the i.r. spectrum (Fig. LVI) of natural daunomycinone. Therefore, the remaining methoxyl group was not in the 4 position of the A ring. Since there was no absorption in the i.r. spectrum corresponding to non-chelated quinone, the product from the boron tribromide hydrolysis was tentatively assigned structure XLIX. This structure is probably correct because aluminum chloride hydrolysis of compound XLIX gave another red, crystalline solid (90% yield) which was identified as 4-O-demethyldaunomycinone LI from its i.r. spectrum (Fig. XLIII) and mass spectrum (Fig. XCIX) which were identical to the i.r. spectrum (Fig. XLII) and mass spectrum of 4-O-demethyldaunomycinone obtained from aluminum chloride hydrolysis of natural daunomycinone.

It is worth mentioning that a red, solid hyproduct was also isolated (24% yield) from the boron tribromide hydrolysis reaction. The i.r. spectrum of this product showed absorptions at 3550 $cm.^{-1}$ and 3450 $cm.^{-1}$ for free and hydrogen bonded hydroxyls, 1620 $cm.^{-1}$ and 1580 $cm.^{-1}$ for chelated quinone carbonyl and 1720 $cm.^{-1}$ (notably weak) for the ketone carbonyl. The n.m.r. spectrum showed a large singlet at δ 1.25 and a small singlet at δ 2.44, for the methyl ketone. The total area

of these two singlets corresponded to three protons. There was also a singlet (3H) at δ 4.06 for aromatic methoxyl. On the basis of this spectral data, the hyproduct was tentatively assigned structures XLIX(a) and XLIX (b), as shown.



XLIX (a) XLIX (b)

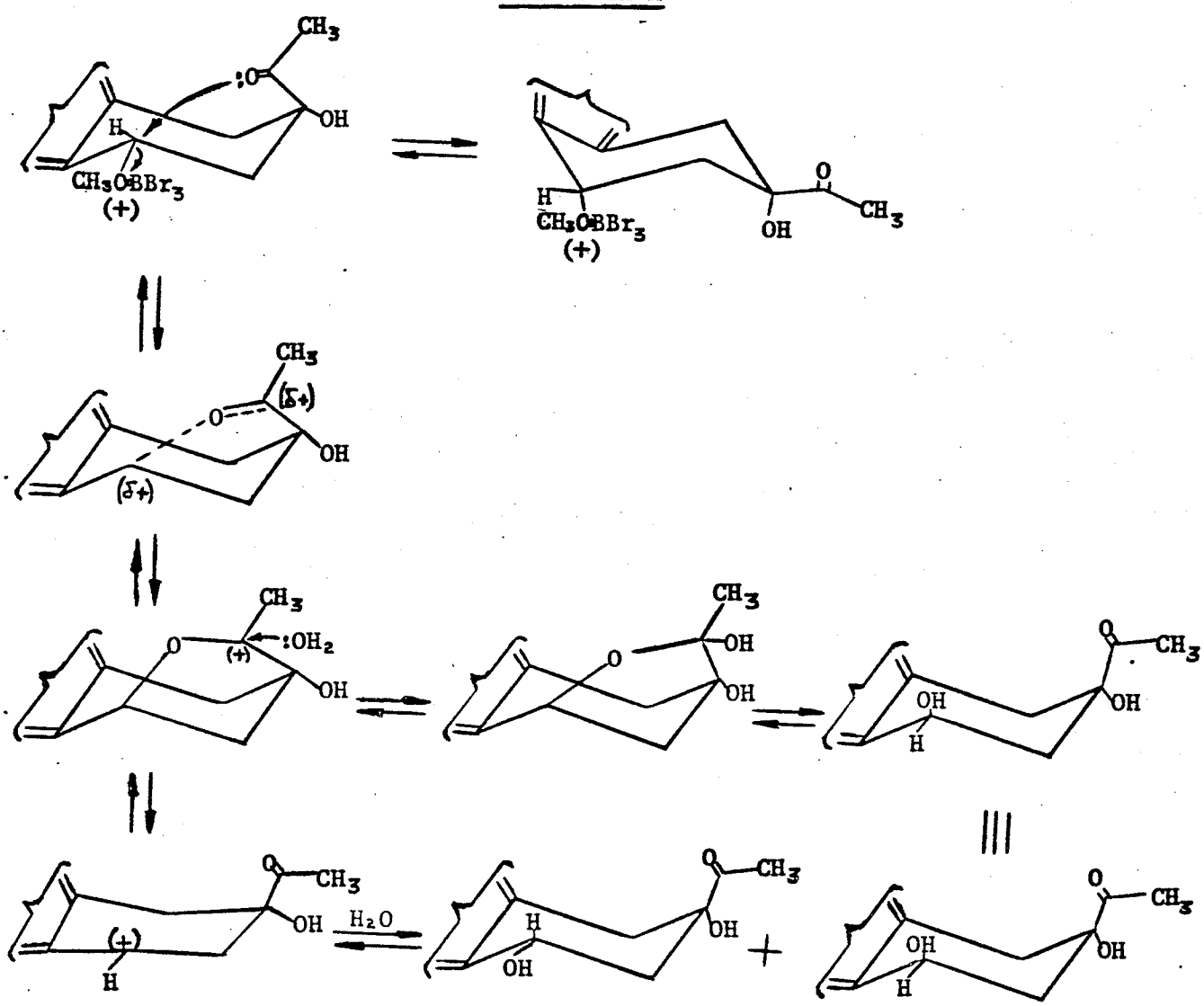
The equilibrium between these two compounds would explain the weak ketone carbonyl absorption in the i.r. spectrum. Also, the singlet at δ 1.25 in the n.m.r. spectrum could correspond to the methyl group of the side-chain of XLIX (a), while the singlet at δ 2.44 could correspond to the ketone sidechain of XLIX (b).

A plausible mechanism for the formation of this byproduct equilibrium mixture would involve displacement of the boron-ether complex by the ketone sidechain (neighbouring group participation), as shown in Scheme IX-A.

This type of hemiketal product was not obtained from any other reaction involving the substituent in the benzylic (C-7) position. The reason for this is not known.

Since the boron tribromide hydrolysis did not give daunomycinone, the trimethyl ether XLVI was then hydrolysed with aluminum chloride to give 4-0-demethyl-7-0-methyldaunomycinone XLVII. This product was isolated as a red, crystalline solid (94% yield) which gave the required molecular ion of 398 in the mass spectrum (Fig. XCVIII). The fragmentation pattern of the mass spectrum indicated that the remaining methoxyl group was the benzylic methoxyl of the D ring. The i.r. spectrum (Fig. XXXVIII) was also consistent with structure XLVII, showing a strong absorption

Scheme IX-A



for chelated quinone at 1600 cm.$^{-1}$. Aluminum chloride hydrolysis of the isoether XLV also gave a red, crystalline solid (91% yield) whose i.r. spectrum (Fig. XXXIX) and mass spectrum (Fig. XCVIII) were consistent with structure XLVIII. The empirical formula of each compound (XLVII and XLVIII) was also in agreement with that established from its high resolution mass spectrum.

It was decided at this point to convert the benzylic methoxyl group of compound XLVII to a hydroxyl group since this would provide a synthesis of 4-O-demethyldaunomycinone and also further verify the

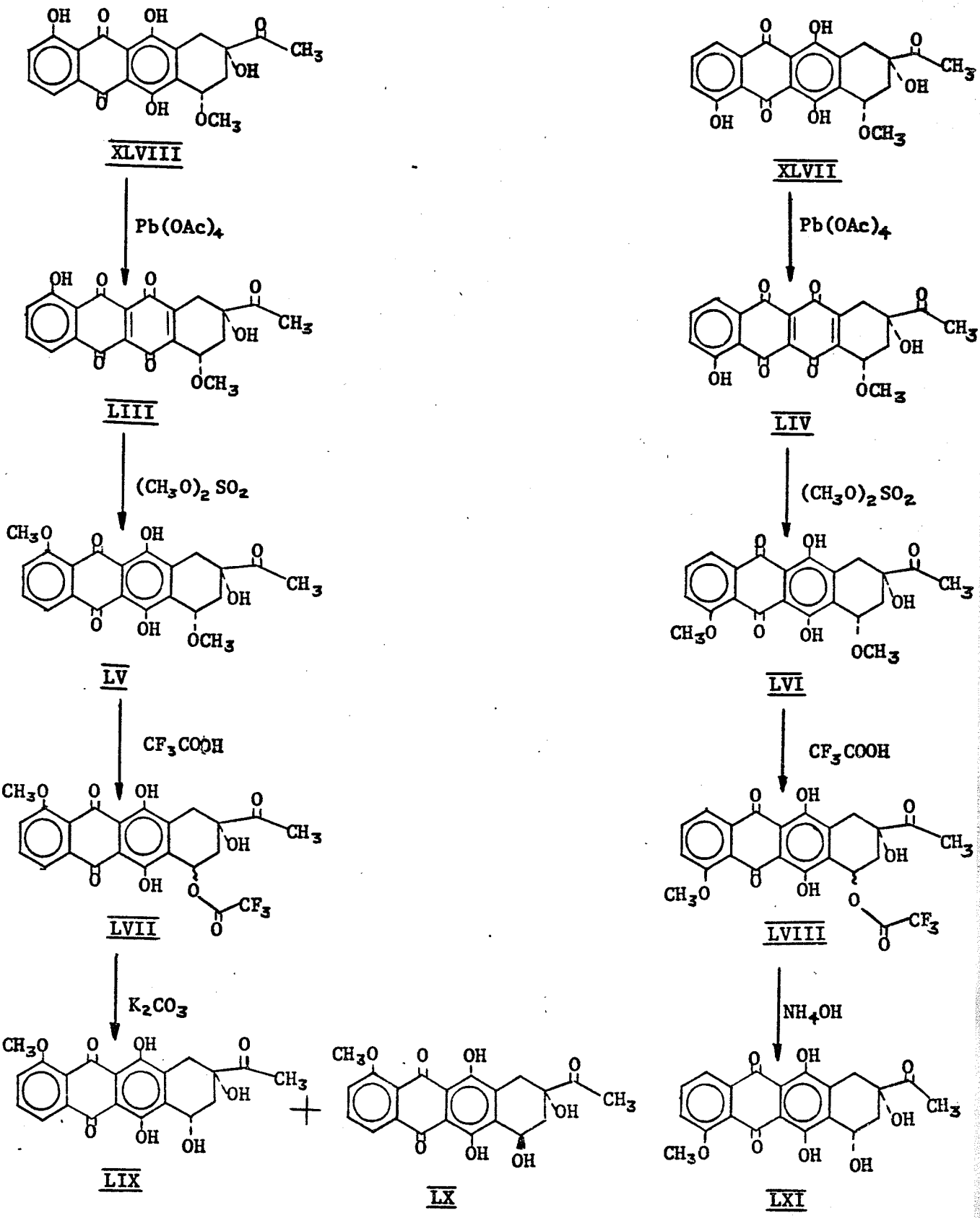
correctness of structure LI. To accomplish this, compound XLVII was treated with trifluoroacetic acid to give the epimeric trifluoroacetate mixture L, isolated as a red solid (100% yield, based on crude material). The appearance of a carbonyl absorption at 1785 $cm.^{-1}$ in the i.r. spectrum (Fig. XLI) verified the introduction of the trifluoroacetate group. This epimeric trifluoroacetic ester mixture was then hydrolysed with dilute base. The hydrolysis product, when subjected to purification by t.l.c. gave two red bands on the t.l.c. plate. Elution of the upper red band gave, as hoped, 4-O-demethyldaunomycinone LI, as a red, crystalline solid (24% yield) which was spectroscopically identical (i.r. spectrum (Fig. XLIV); mass spectrum (Fig. XCIX)) to the 4-O-demethyldaunomycinone obtained from aluminum chloride hydrolysis of natural daunomycinone. Elution of the lower red band gave another red, crystalline solid (24.2% yield) whose i.r. spectrum (Fig. XLV) was only slightly different from the i.r. spectrum of compound LI and whose mass spectrum (Fig. XCIC) was identical to the mass spectrum of compound LI. Therefore, this compound was assigned structure LII, that is, the C_7 epimer of 4-O-demethyldaunomycinone. This product is expected, since, as mentioned, the trifluoroacetate L was probably produced as an epimeric mixture.

The formation of equal amounts of products LI and LII is not consistent with the results obtained from other reactions which involved attack at the C_7 carbonium ion. In all other cases, the product obtained from the attack of the nucleophile on the side of the D ring cis to the tertiary (C_9) hydroxyl group was always the major product. Perhaps the stabilization of the carbonium ion intermediate leading to LI and LII by the ketone sidechain is not possible in this case, so that attack from above and below the D ring is equally feasible.

Since attempts at selective hydrolysis of daunomycinone trimethyl ether XLVI (and of the isoether XLV) were unsuccessful, the only other approach to daunomycinone was to attempt a selective methylation of the A ring phenolic hydroxyl group of the hydrolysis product XLVII. This was accomplished (see Scheme X) by first oxidizing compound XLVII to the corresponding diquinone LIV. This product was identified from its i.r. spectrum (Fig. XLVI) which now showed a strong carbonyl absorption at 1690 $cm.^{-1}$. The change in the i.r. spectrum in going from compound XLVII to the diquinone LIV also compared favourably to the change in the i.r. spectrum in going from quinizarin to 1,4,9,10-anthradiquinone. The diquinone LIV was then methylated at room temperature using dimethylsulfate. During the course of this reaction, the diquinone was reduced back to the monoquinone, and therefore, several methylation products were produced. The required product, 7-O-methyldaunomycinone LVI, was isolated from the other methylation products as a red solid (10.2% yield, based on consumed starting material) by careful t.l.c. . The i.r. spectrum (Fig. XLVIII) for this compound now showed two chelated quinone absorptions at 1620 $cm.^{-1}$ and 1580 $cm.^{-1}$, similar to the i.r. spectrum for natural daunomycinone. The low yield for the methylation reaction is attributable to overoxidation of compound XLVII by the lead tetraacetate, since at least 50% of the recovered material from the t.l.c. plate is very polar, "base-line" material. However, direct methylation of 4-O-demethyl-7-O-methyldaunomycinone XLVII without the lead tetraacetate oxidation gives almost no 7-O-methyldaunomycinone LVI at all.

In a similar manner, the hydrolysed isoether XLVIII was oxidized

Scheme X


XLVIII
Pb(OAc)4
LIII
(CH3O)2 SO2
LV
CF3COOH
LVII
K2CO3
LIX
LX
XLVII
Pb(OAc)4
LIV
(CH3O)2 SO2
LVI
CF3COOH
LVIII
NH4OH
LXI

to the diquinone LIII, i.r. spectrum (Fig. XLVII), and then methylated with dimethylsulfate to give compound LV. This product was isolated as a red solid (9.5% yield, based on consumed starting material) and gave the required molecular ion of 412 in the mass spectrum (Fig. C). The i.r. spectrum (Fig. XLIX) also showed two peaks for chelated quinone at 1620 $cm.^{-1}$ and 1580 $cm.^{-1}$.

Once 7-0-methyldaunomycinone LVI was prepared, all that was required to get daunomycinone was to convert the benzylic methoxyl group to a hydroxyl group. It was decided to first attempt this conversion on the isomeric compound LV, using this as a sort of model system. Therefore, compound LV was treated with trifluoroacetic acid to give the epimeric trifluoroacetate mixture LVII, isolated as a red solid (100% yield, based on crude material). The appearance of a carbonyl absorption at 1785 $cm.^{-1}$ in the i.r. spectrum (Fig. LII) verified the introduction of the trifluoroacetate group. This trifluoroacetic ester mixture was then hydrolysed using a saturated potassium carbonate solution as the base. The hydrolysis product, when subjected to purification by t.l.c., separated into two red bands on the t.l.c. plate. Elution of the upper, red band gave a red, crystalline solid (27.2% yield) which gave a mass spectrum (Fig. CI), which was identical to the mass spectrum (Fig. CI) of natural daunomycinone. The i.r. spectrum (Fig. LIII) showed absorptions at 3480 $cm.^{-1}$ (hydrogen bonded OH), 1715 $cm.^{-1}$ (ketone C=O) and 1620 $cm.^{-1}$ and 1580 $cm.^{-1}$ (chelated quinone C=O), and a fingerprint region quite similar to the fingerprint region of the i.r. spectrum of natural daunomycinone. Elution of the lower, red band gave another red solid (12.8% yield) which was obtained in too small an amount to crystallize properly for a mass spectrum. (At least 4 or 5 mg. quantities were

necessary for crystallization since several mg. of these compounds seemed to bind tightly to the glass walls of their flasks). This compound had an i.r. spectrum (Fig. LIV) which showed absorptions at 3530 cm.$^{-1}$ (OH), 1715 cm.$^{-1}$ (ketone C=O) and 1620 cm.$^{-1}$ and 1580 cm^{-1} (chelated quinone C=O), and a fingerprint region very similar to the fingerprint region of the i.r. spectrum of the compound isolated from the upper red band on the t.l.c. plate.

In the separation of 4-O-demethyldaunomycinone LI (identified rigorously by comparison to the natural product) from its epimer LII, compound LI had the higher Rf value. It was assumed that compound LIX, isodaunomycinone, would behave in a similar way and have a higher Rf value than its epimeric compound LX. Therefore, the red solid isolated from the upper band on the t.l.c. plate was assigned structure LIX, on the basis of its i.r. and mass spectra and relative Rf value. The red solid isolated from the lower band was thus, assigned structure LX. A further verification for the correctness of this structural assignment came from the position of the hydroxyl absorption in the i.r. spectra of the two compounds. Compound LIX should show a hydroxyl absorption at lower wave number than the hydroxyl absorption for compound LX, due to the intramolecular hydrogen bonding that exists in compound LIX. This was observed in the i.r. spectra of the two isolated compounds.

Since 1-methoxy-4-demethoxydaunomycinone (isodaunomycinone) LIX was prepared via the trifluoroacetate LVII, it was now felt that this would be a safe method to convert 7-O-methyldaunomycinone LVI to daunomycinone. Therefore compound LVI was treated with trifluoroacetic acid to give the epimeric trifluoroacetate mixture LVIII, isolated as a red solid (100% yield, based on crude material). The i.r. spectrum

(Fig. L) of this compound was identical to the i.r. spectrum (Fig. LI) of the trifluoroacetic ester obtained on treating natural daunomycinone with the trifluoroacetic acid. This trifluoroacetic ester mixture was then hydrolysed using a saturated potassium carbonate solution as the base. The hydrolysis product, when subject to purification by t.l.c., separated into two red bands on the t.l.c. plate. The upper red band had an Rf value identical to that of natural daunomycinone. Elution of these two t.l.c bands, however, gave only small amounts of material which were too insoluble to get a good i.r. spectrum for comparison to natural daunomycinone. Apparently, the saturated potassium carbonate solution was too strongly basic for the hydrolysis and gave mostly fully aromatic product.

The basic hydrolysis was then repeated on a small amount of the trifluoroacetic ester mixture LVIII using dilute ammonium hydroxide as the base. Evaporation of the reaction solution gave a product LXI whose i.r. spectrum (Fig. LV) was identical to the i.r. spectrum (Fig. LVI) of natural daunomycinone. There was too small an amount of product to allow proper crystallization for a mass spectrum. However, since this product, LXI and its precursor, the trifluoroacetic ester LVIII, were correlated directly to the natural compounds by their i.r. spectra, it can be assumed with certainty that the final product was indeed daunomycinone.

It is concluded, therefore, that (dl)-daunomycinone trimethyl ether (XLVI), (dl)-isodaunomycinone trimethyl ether (XLV), (dl)-4-O-demethyldaunomycinone (LI) (and its epimer (LII)), (dl)-isodaunomycinone (LIX) (and its epimer (LX)) and (dl)-daunomycinone (LXI) have all been synthesized.

EXPERIMENTAL

All infrared (i.r.) spectra were recorded on either a Perkin-Elmer model 700 or a Perkin-Elmer model 710 i.r. spectrophotometer using methylene chloride solutions, chloroform solutions or nujol mulls of the samples. The nuclear magnetic resonance (n.m.r.) spectra were recorded on a Varian A-56/60 A spectrometer using CCl_4, $CDCl_3$ or dimethylsulfoxide-d_6 (DMSO-d_6) as solvent and tetramethylsilane (TMS) as internal standard. Chemical shifts are given in δ 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 either a Hitachi Perkin-Elmer RMU-6D mass spectrometer or a Finnigan Model 1015 mass spectrometer. High resolution mass spectra were recorded in the MS9 mass spectrometer of the Chemistry Department, University of Alberta, Edmonton, Alberta. Microanalyses were performed by Dr. Daessle of Montreal and Dr. Yates of Arizona. Melting points were measured on a Fisher-Johns melting point apparatus and are uncorrected. The alumina and silica gel used in column chromatography and thin layer chromatography (t.l.c.) were "Camag" brand, obtained from Mondray Ltd., Montreal. The t.l.c. separations were carried out using glass plates coated with a 1 mm. layer of adsorbent. All physical data reported is for unresolved (dl)-mixtures.

(1) Preparation of Ethyl 2-carboethoxy-3-(2,5-dimethoxyphenyl) propenoate (XII):

A solution of 2,5-dimethoxybenzaldehyde (49.9 gms., 0.3 moles), ethyl malonate (48.0 gms., 0.3 moles), pyrrolidine (5 ml.) and benzene (600 ml.) was prepared in a 1 l. round bottom flask equipped with a Dean-Stark water separator and a condenser. The solution was refluxed overnight and then cooled. Removing the benzene and pyrrolidine by

distillation under reduced pressure gave the required diester (XII) as a bright yellow liquid (92.4 gms., 99% yield). This diester was used in the next step without further purification.

Infrared spectrum (Fig. X): absorptions ($cm.^{-1}$) at 1720 (ester C=O); 1620 (olefin C=O).

N.m.r. spectrum (Fig. LVII): absorptions at 1.21, 1.30 (triplets, J = 7Hz., 3H each, $-OCH_2\underline{CH_3}$); 3.64, 3.74 (singlets, 3H each, $-OCH_3$); 4.15, 4.18 (quartets, J = 7Hz., 2H each, $-O\underline{CH_2}CH_3$); 6.65 - 6.87 (m, 3H, aromatic H); 7.77 (S, 1H, -CH = C-).

(2) Preparation of Ethyl 2-carboethoxy-3-(2,5-dimethoxyphenyl) propanoate (XIII):

The diester (XII) (92.4 gms., 0.3 mole) was dissolved in 200 ml. of distilled ethanol and poured into a 2 l. flask containing Pd/C (5%, 9.3 gms.) and distilled ethanol (500 ml.). The solution was then hydrogenated at atmospheric pressure until the uptake of hydrogen ceased. The catalyst was removed by suction filtration and the ethanol evaporated under reduced pressure. The residue was distilled (b.p. = 153-156°C at 0.2 mm. Hg) to give the diester XIII (67.8 gms., 73% yield) as a very, pale yellow liquid.

Infrared spectrum (Fig. XI): absorptions ($cm.^{-1}$) at 1725 (ester C=O); 1590 (aromatic C=C).

N.m.r. spectrum (Fig. LIX): absorptions at 1.17 (t, J = 7Hz., 6H, $-OCH_2\underline{CH_3}$); 3.1 (d, J = 7.5Hz., 2H, $-\underline{CH_2}$-CH-); 3.58 (t, J = 7.5Hz., 1H, $-CH_2-\underline{CH}$-) 3.62, 3.71 (singlets, 3H each, $-OCH_3$); 4.02 (q, J = 7Hz., 4H, $-O\underline{CH_2}CH_3$); 6.54 (s, 3H, aromatic H).

(3) Preparation of Ethyl 3,3-dicarboethoxy-4-(2,5-dimethoxyphenyl) butanoate (XIV):

Sodium hydride (11.6 gms., 50% mineral oil suspension) was added

in small portions to a solution of the diester XIII (67.8 gms., 0.22 moles) in freshly distilled tetrahydrofuran (1 l.) in a three neck 3 l. flask equipped with a mechanical stirrer, a condenser and a dropping funnel. The solution was brought to a gentle reflux and then ethyl bromoacetate (36.7 gms., 0.22 moles) was added through the dropping funnel over a period of ½ hour. The solution was allowed to reflux an additional 2½ hours, during which time a precipitate of NaBr formed. The NaBr was removed by suction filtration and then the tetrahydrofuran was removed by distillation under reduced pressure to give the triester XIV (84.7 gms., 98% yield) as a pale yellow liquid. This triester was used in the next step without further purification.

Infrared spectrum (Fig. XII): absorptions ($cm.^{-1}$) at 1730 (ester C=O); 1690 (aromatic C=C).

N.m.r. spectrum (Fig. LX): absorptions at 1.22 (t, J = 7Hz., 3H, $-OCH_2\underline{CH_3}$); 2.67 (s, 2H, $-\underline{CH_2}CO$); 3.3 (s, 2H, $Ar\underline{CH_2}$); 3.58, 3.62 (singlets, 3H each, $-OCH_3$); 4.02 (q, J = 7Hz., 3H, $-O\underline{CH_2}CH_3$); 4.08 (q, J = 7Hz., 6H, $-O\underline{CH_2}CH_3$); 6.38-6.53 (m, 3H, aromatic H).

(4) Preparation of 3,3-dicarbohydroxy-4-(2,5-dimethoxyphenyl)butanoic acid(XV):

The triester (XIV)(84.7 gms., 0.22 moles) was hydrolysed by refluxing in a sodium hydroxide solution (10%, 700 ml.) for four hours and then stirring overnight. The basic solution was then washed with chloroform (3X100 ml.) and acidified with cold concentrated hydrochloric acid. The triacid precipate (XV) was filtered and recrystallized from water to give a white, crystalline product (52.0 gms., 78% yield), m.p. = 167-169°C with apparent decarboxylation.

Infrared spectrum (Fig. XIII); absorptions ($cm.^{-1}$) at 2800 (broad, acid -OH); 1700 (broad, acid C=O).

Mass spectrum (Fig. LXXXII): M^+/e at 312; 296(P-CH_2O); 282; 268 (P-CO_2); 250 (P-(CO_2 + H_2O)); 222; 208; 151; 121.

(5) Preparation of 2',5'-dimethoxybenzylsuccinic anhydride (XVII):

The acid(XV) (46.8 gms., 0.15 moles) was dissolved in acetic anhydride (400 ml.) in a 1 l. flask equipped with a condenser and a drying tube. The solution was refluxed for 20 minutes. The acetic anhydride was then removed by an evaporator connected to a water aspirator to give the anhydride (XVII) as a white solid (37.4 gms., 100% yield). A small sample was recrystallized from chloroform/petroleum ether to give the product(XVII) as white, needle crystals, m.p. = 75-76°C.

Infrared spectrum (Fig. XIV): absorptions ($cm.^{-1}$) at 1785, 1865 (anhydride C=O); 1595 (aromatic C=C).

N.m.r. spectrum (Fig. LXI): absorptions at 2.64-3.62 (m, 5H, -CH_2-CH-CH_2-); 3.72, 3.76 (singlets, 3H each, OCH_3); 6.66-6.77 (m, 3H, aromatic H).

Mass spectrum (Fig. LXXXIII): M^+/e at 250; 235 (P-CH_3); 208 (P-CH_2CO); 178 (P-(CO_2 + CO)); 163; 151; 135; 121.

(6) Preparation of 3-carbohydroxy-5,8-dimethoxy-1-tetralone (XVIII):

The anhydride (XVII) (37.4 gms., 0.15 moles) was added with stirring into polyethylene reaction flask containing hydrofluoric acid (200 ml.). After stirring for 3 hours in a water bath at 20°C., the temperature was raised to 40°C. to evaporate the remaining hydrofluoric acid. Water (150 ml.) was added and the precipitated tetralone acid (XVIII) was collected by suction filtration. This crude acid was recrystallized from methanol to give the product (XVIII) as white, needle crystals (28.7 gms., 77% yield), m.p. = 207-208°C.

ANALYSIS	C	H
Calculated	62.39	5.64
Reported	62.40	5.48

Infrared spectrum (Fig. XV): absorptions ($cm.^{-1}$) at 3.75 (broad, acid OH); 1720 (acid C=O); 1660 (aryl ketone C=O); 1580 (aromatic C=C).

N.m.r. spectrum (Fig. LXII): absorptions at 2.64-2.78 (m, 3H, $-CH-CH_2-CO$); 2.98-3.10 (m, 2H, Ar-CH_2); 3.73, 3.80 (singlets, 3H each, OCH_3); 6.83-7.30 (AB, 2H, aromatic); 12.3 (s, 1H, acid OH).

Mass spectrum (Fig. LXXXIV): M^+/e at 250, 205 (P-COOH); 187; 175; 162; 121; 99.

(7) Preparation of 1-hydroxy-3-hydroxymethyl-5,8-dimethoxytetralin (XIX):

The tetralone acid (XVIII) (17.6 gms., 0.07 moles) was dissolved in freshly distilled tetrahydrofuran (300 ml.) in a 1 l. flask equipped with a condenser and a drying tube. Lithium aluminum hydride (5 gms.) was added in small portions and the solution was then refluxed over night. The solution was then cooled and sufficient methanol was added to destroy any excess lithium aluminum hydride. The lithium and aluminum salts were removed by suction filtration and the filtrate was evaporated under reduced pressure to a small volume (40 ml.). Water (100 ml.) was added and the solution was then extracted with chloroform (3 x 100 ml.). The chloroform extracts were combined, dried over magnesium sulfate and evaporated to give the alcohol (XIX) as a white solid (15.2 gms., 92% yield). A small sample was recrystallized from water to give the product as white crystals, m.p. = 118-119°C.

Infrared spectrum (Fig. XVII): absorptions ($cm.^{-1}$) at 3460 (alcohol OH); 1600 (aromatic C=C).

N.m.r. spectrum (Fig. LXIV): absorptions at 1.6-3.2 (m, 5H,

$-CH_2-CH-CH_2-$); 3.57-3.65 (d, J = 5Hz., 2H, $-C\underline{H}_2OH$); 3.74, 3.82 (singlets, 3H each, OCH_3); 3.96 (broad s, -OH); 5.05 (t, J = 6Hz., 1H, Ar-C<u>H</u>(OH)-); 6.67 (s, 2H, aromatic H).

Mass spectrum (Fig. LXXXVI): M^+/e at 238; 220 ($P-H_2O$): 189 ($P-(H_2O + CH_2OH)$); 174; 115.

(8) Preparation of 1,5,8-trimethoxy-3-hydroxymethyltetralin (XX):

The tetralin alcohol (XIX) (4.75 gms., 0.02 moles) was dissolved in a solution of methanol (80 ml.), concentrated hydrochloric acid (8 drops) and water (4 drops). The solution was shaken for one hour at room temperature, neutralized with saturated sodium bicarbonate solution and evaporated to a small volume (15 ml.). Water (50 ml.) was added and the solution was extracted exhaustively with chloroform. The chloroform was dried over magnesium sulfate and evaporated to give the tetralin (XX) as a white solid (4.35 gms., 86% yield). A small sample was recrystallized from water/methanol to give the product as white crystals, m.p. = 108-109°C.

Infrared spectrum (Fig. XVIII): absorptions ($cm.^{-1}$) at 3350 (OH); 1600 (aromatic C=C).

N.m.r. spectrum (Fig. LXV): absorptions at .92-3.08 (m, 5H, $-CH_2CH-CH_2-$); 3.42 (s, 3H, aliphatic OCH_3), 3.55-3.63 (d, J = 5Hz., 2H, $-C\underline{H}_2OH$); 3.74, 3.80 (singlets, 3H each, aromatic OCH_3); 4.63 (t, J = 2.5Hz., 1H, $ArC\underline{H}(OCH_3)-$); 6.68 (s, 2H, aromatic H).

Mass spectrum (Fig. LXXXVII): M^+/e at 252; 237 ($P-CH_3$) 221 ($P-CH_2OH$); 220 ($P-CH_3OH$); 203; 190.

(9) Preparation of 1,5,8-trimethoxy-3-formyltetralin (XXI):

(a) A solution of the alcohol (XX) (0.72 gms., 3.0 m moles) in freshly distilled pyridine (15 ml.) was added slowly to an ice cooled solution of chromium trioxide (1 gm., 9 m moles) in freshly distilled

pyridine (20 ml.). When the addition was complete the solution was warmed up to 40°C. and stirred at this temperature overnight. The solution was then poured into water (100 ml.) and the aqueous solution was extracted exhaustively with ether. The ether was dried over magnesium sulfate and evaporated under reduced pressure to give a residue which was purified by t.l.c. on silica gel ($CH_3OH/CHCl_3$ = 4/100). Elution of the main band gave the aldehyde (XXI) as a white solid (.11 gms., 15% yield) which was sublimed under high vacuum to give the product as white crystals, m.p. = 65-66°C.

(b) Dicyclohexylcarbodimide (7.42 gms., 0.036 moles) was added to a solution of the alcohol (XX) (3.01 gms., 0.012 moles), phosphoric acid (0.59 gms., 0.066moles), benzene (15 ml.) and dimethyl sulfoxide (15 ml., freshly distilled from CaH_2). The resulting solution was stirred for 2 hours at room temperature, during which time a precipitate of dicyclohexylurea formed. The solution was filtered and additional benzene (100 ml.) was added. The solution was then washed with water (3 x 100 ml.), dried over magnesium sulfate and evaporated under reduced pressure to give a residue which was purified by t.l.c. on silica gel ($CH_3OH/CHCl_3$ = 4/100). Elution of the main band gave the aldehyde as a white solid (1.97 gms., 66% yield) which was used without further purification the next step.

Infrared spectrum (Fig. XIX): absorptions ($cm.^{-1}$) at 2730 (aldehyde C-H); 1720 (aldehyde C=O); 1600 (aromatic C=C).

N.m.r. spectrum (Fig. LXVI): absorptions at 1.13-3.23 (m, 5H, $-CH_2CHCH_2-$); 3.45 (s, 3H, aliphatic OCH_3); 3.75, 3.80 (singlets, 3H each, aromatic OCH_3); 4.66 (t, J = 2.5Hz., 1H, $ArC\underline{H}(OCH_3)-$); 6.66 (s, 2H, aromatic H); 9.74 (s, 1H, aldehyde H).

(10) Preparation of 1,5,8-trimethoxy-3-(1'-hydroxyethyl) tetralin (XXII):

The aldehyde (XXI) (2.28 gms., 9.0 m moles) dissolved in anhydrous ether (50ml.) was added via a syringe to a solution of methyl magnesium iodide (1arge excess) in anhydrous ether (100 ml.) in a 250 ml. flask equipped with a syringe cap, condenser and drying tube. The resulting solution was allowed to stir for 2 hours at room temperature. The solution was then poured slowly into water (200 ml.) to destroy the excess Grignard reagent and this aqueous solution was then extracted exhaustively with ether. The ether was dried over magnesium sulfate and evaporated under reduced pressure to give a residue which was purified by t.l.c. on silica gel ($CH_3OH/CHCl_3$ = 4/100). Elution of the main band gave the tetralin alcohol (XXII) as a white solid (1.74 gms. 74% yield) which was recrystallized from carbon tetrachloride to give the product as white crystals, m.p. = 128-130°C.

Infrared spectrum (Fig. XX): absorptions ($cm.^{-1}$) at 3260 (alcohol OH); 1600 (aromatic C=C).

N.m.r. spectrum (Fig. LXVII): absorptions at 1.18, 1.28 (d, J = 6Hz., 3H, $-CH(OH)CH_3$); 1.08-3.16 (m, 5H, $-CH_2CHCH_2-$); 3.40 (s, 3H, aliphatic OCH_3); 3.72, 3.76 (singlets, 3H each, aromatic OCH_3); 4.56 (t, J = 2.5 Hz., 1H, $ArC\underline{H}(OCH_3)-$); 6.60 (s, 2H, aromatic H).

Mass spectrum (Fig. LXXXVIII): M^+/e at 266; 251 ($P-CH_3$); 235 ($P-OCH_3$); 217; 189; 174.

(11) Preparation of 1,5,8-trimethoxy-3-acetyltetralin (XXIII):

The alcohol (XXII) (0.50 gms., 2m moles) dissolved in freshly distilled pyridine (10 ml.) was added to an ice cooled solution of chromium trioxide (0.60 gms., 6m moles) dissolved in freshly distilled pyridine (15 ml.) and the resulting solution was stirred in the ice

bath for ½ hour. The solution was then stirred for 24 hours at 40°C. Methanol (5 ml.) was then added and the stirring was continued for an additional ½ hour. The solution was then evaporated to a small volume and poured into water (100 ml.). The aqueous solution was filtered and extracted with ether (3 x 80 ml.). The ether was dried over magnesium sulfate and evaporated to give a residue which was purified by t.l.c. on silica gel ($CH_3OH/CHCl_3$ = 1/100). Elution of the main band gave the ketone (XXIII) as a white solid (0.31 gms., 65% yield) which was recrystallized from light petroleum ether to give the product as white crystals, m.p. = 80-81°C.

ANALYSIS	C	H
Calculated	68.18	7.63
Reported	68.08	7.38

Infrared spectrum (Fig. XXI): absorptions ($cm.^{-1}$) at 1710 (ketone C=O); 1600 (aromatic C=C).

N.m.r. spectrum (Fig. LXVIII): absorptions at 1.22-3.3 (m, 5H, $-CH_2CHCH_2-$); 2.26 (s, 3H, $-COCH_3$); 3.47 (s, 3H, aliphatic OCH_3); 3.77, 3.82 (singlets, 3H each, aromatic OCH_3); 3.97 (t, J = 2.5Hz., 1H, $ArCH(OCH_3)-$); 6.72 (s, 2H, aromatic H).

Mass spectrum (Fig. LXXXIX): M^+/e at 264; 249 ($P-CH_3$); 232 ($P-CH_3OH$); 201; 189.

(12) Preparation of 2-carbohydroxy-5,8-dimethoxytetralin (XXV):

The tetralone acid (XVIII) (2.0 gms., 8.0m moles) was added to a 250 ml. flask containing Pd/C (5%, 0.5 gms.), distilled ethanol (70 ml.), water (12 ml.) and concentrated hydrochloric acid (1.6 ml.). The solution was then hydrogenated at atmospheric pressure until the uptake of hydrogen ceased. The catalyst was then removed by suction filtration and the filtrate was evaporated under reduced pressure to

give a white, solid residue. The residue was dissolved in 10% sodium hydroxide solution (100 ml.) and extracted with chloroform (2 x 50 ml.) to remove the small amount of ester formed. The basic solution was then cooled and acidified with concentrated hydrochloric acid to give the acid (XXV) as a white precipitate which was filtered and dried. This solid was recrystallized from methanol to give the product as white crystals (1.50 gms., 80% yield), m.p. = 180-182°C.

Infrared spectrum (Fig. XVI): absorptions ($cm.^{-1}$) at 2900 (broad, acid OH); 1710 (acid C=O); 1600 (aromatic C=C).

N.m.r. spectrum (Fig. LXIII): absorptions at 1.4-3.2 (aliphatic H); 3.72 (s, 6H, OCH_3); 6.69 (s, 2H, aromatic H); 12.05 (broad s, 1H, acid OH).

Mass spectrum (Fig. LXXXV): M^+/e at 236; 190 (P-HCOOH); 175; 159; 115.

(13) Preparation of 2-acetyl-5,8-dimethoxytetralin (XXIV):

(a) The tetralin ketone (XXIII) (0.26 gms., 1.0m moles) was added to a flask containing Pd/C (5%, 0.1 gms.) distilled ethanol (14 ml.), water (2.5 ml.) and concentrated hydrochloric acid (0.32 ml.). The resulting solution was hydrogenated at atmospheric pressure until the uptake of hydrogen ceased. The catalyst was removed by suction filtration and the filtrate was evaporated under reduced pressure to give a white, solid residue which was purified by t.l.c. on silica gel ($CHCl_3$). Elution of the major band gave the product (XXIV) as a white solid (0.30 gms., 85% yield) which was recrystallized from ethanol to give white crystals, m.p. = 82-82°C.

(b) Methyl Lithium (44 mgs., 2.0m moles) in ether was added drop wise from a syringe to a rapidly stirred solution of the tetralin acid (XXV) (0.47 gms., 2.0m moles) in distilled tetrahydrofuran (50 ml.) in a 100 ml.

flask equipped with a condenser, drying tube and syringe cap. The solution was stirred for 5 minutes at room temperature after the addition of the methyl lithium was complete, during which time the lithium salt of the acid precipitated. The solution was then brought to a reflux and additional methyl lithium (44 mgs., 2.0m moles) in ether was added drop wise by syringe. The solution was then refluxed overnight. Upon cooling the solution was added drop wise to a rapidly stirred, saturated ammonium chloride solution and the resulting water - tetrahydrofuran solution was extracted with ether (2 x 75 ml.). The ether was washed with water (1 x 100 ml.), dried over magnesium sulfate and evaporated under reduced pressure to give a white, solid residue which was purified by t.l.c. on silica gel ($CHCl_3$). Elution of the main band gave the ketone (XXIV) as a white solid (0.34 gms., 72% yield) which was recrystallized from ethanol to give white crystals, m.p. = 82-83°C.

Infrared spectrum (Fig. XXII): absorptions ($cm.^{-1}$) at 1705 (ketone C=O); 1600 (aromatic C=C).

N.m.r. spectrum (Fig. LXIX): absorptions at 1.22-3.17 (m, 7H, aliphatic H); 2.18 (s, 3H, $-COCH_3$); 3.72 (s, 6H, OCH_3); 6.56 (s, 2H, aromatic H).

Mass spectrum (Fig. XC): M^+/e at 234; 219 ($P-CH_3$); 191 ($P-COCH_3$); 175; 160.

(14) Preparation of 2-(1'-hydroxyethyl)-5,8-dimethoxytetralin (XXVI):

Sodium borohydride (0.38 gms., 10m moles) was added to a solution of the ketone (XXIV) (0.50 gms., 2.1m moles) in methanol (40 ml.) and this solution was then stirred in a water bath at room temperature for ½ hour. The solution was then evaporated under reduced pressure to a small volume and water (50 ml.) was added. The aqueous solution

was extracted with ether (3 x 30 ml.) and the ether was dried over magnesium sulfate and evaporated under reduced pressure to give the product (XXVI) as a white solid (0.51 gms., 100% yield) which was used without further purification in the next step.

Infrared spectrum (Fig. XXIII): absorptions ($cm.^{-1}$) at 3630 (alcohol OH); 1600 (aromatic C=C).

(15) Preparation of Olefin mixture (XXVII):

The alochol (XXVI) (0.51 gms., 2.12 m moles) was dissolved in freshly distilled pyridine (5 ml.) in a 10 ml. flask and then phosphorous oxychloride (0.62 ml.) was added. The reaction flask was sealed and allowed to stand overnight. Water (40 ml.) was then added and the resulting aqueous solution was extracted with ether (3 x 30 ml.). The ether was dried over magnesium sulfate and evaporated under reduced pressure to give a residue which was purified by t.l.c. on silica gel (benzene / petroleum ether = 10/100). Two major bands were obtained on the t.l.c. plate. Elution of the band with the highest Rf value gave the olefin mixture (XXVII) as a colorless oil (0.15 gms., 33% yield).

Infrared spectrum (Fig. XXIV): absorptions ($cm.^{-1}$) at 1600 (aromatic C=C).

N.m.r. spectrum (Fig. LXX): absorptions at 1.57, 1.70 (d (further split by long range coupling), 3H, $-C=CH(\underline{CH_3})$); 2.13-2.90 (m, 4H, $-CH_2-CH_2-$); 3.36 (s(broad), 2H, benzylic CH_2); 3.70, 3.74 (singlet, 3H each, OCH_3); 5.13-5.60 (m, 1H, olefin H); 6.56 (s, 2H, aromatic H).

Elution of the band with the lower Rf value gave the chloro-substitution product (XXVIII) as a white solid (0.20 gms., 37% yield),

Infrared spectrum (Fig. XXV): absorptions ($cm.^{-1}$) at 1600

(aromatic C=C).

N.m.r. spectrum (Fig. LXXI): absorptions at 1.48, 1.60 (d, J = 7Hz., 3H, $-CHClC\underline{H}_3$); 1.60-3.22 (m, 6H, aliphatic H); 3.72 (s, 6H, OCH_3); 3.85-4.34 (m, 1H, $-C\underline{H}ClCH_3$); 6.57 (s, 2H aromatic H).

Mass spectrum: M^+/e at 256, 254; 241; 239 (P-15); 218, 203; 191; 177; 164.

(16) Preparation of 2-hydroxy-2-(1'-hydroxyethyl)-5,8-dimethoxytetralin (XXIX):

The olefin mixture (XXVII) (0.10 gms., 0.46 m moles) and osmium tetroxide (0.13 gms., 0.50 m moles) were dissolved in freshly distilled pyridine (2 ml.) and the solution was then stirred for 24 hours. A solution of sodium bisulfite (0.22 gms., 2.1 m moles) in water (3 ml.) and pyridine (2 ml.) was then added and stirring was continued for another 2 hours. The solution was then extracted with methylene chloride (3 x 20 ml.). The methylene chloride extract was dried over magnesium sulfate and evaporated under reduced pressure to give the diol (XXIX) as a colorless, viscous oil (0.10 gms., 85% yield), which could be crystallized from chloroform - petroleum ether to give a white, crystalline solid, m.p. = 148-149°C.

Infrared spectrum (Fig. XXVI): absorptions ($cm.^{-1}$) at 3600 (alcohol OH); 1600 (aromatic C=C).

N.m.r. spectrum (Fig. LXXII): absorptions at 1.18, 1.28 (d, J = 6.5Hz., 3H, $-CH(OH)C\underline{H}_3$), 3.75, 3.76 (singlets, 3H each, OCH_3), 6.62-6.69 (m, 2H, aromatic H).

Mass spectrum (Fig. XCI): M^+/e at 252; 234 ($P-H_2O$); 207 ($P-CH_2(OH)CH_3$); 189.

(17) Preparation of 2-acetyl-2-hydroxy-5,8-dimethoxytetralin (XXI):

(a) The tetralin ketone (XXIV) (5.0 gms., 0.02 moles) dissolved in

dry t-butanol (50 ml.) was added to an oxygen saturated solution of potassium (6.95 gms., 0.18 moles) in dry t-butanol (350 ml.) in a 1 l. flask. Dry oxygen was bubbled through a gas dispersion tube into this solution for exactly 5 minutes, the reaction temperature being kept at 35°C. The solution was then cooled in an ice bath and glacial acetic acid was added until the solution became acidic (the solution colour changed from purple to yellow). Zinc dust (20 gms.) was added immediately and the solution was then stirred at room temperature for 6 hours. The zinc was then removed by filtration and the filtrate was evaporated to a syrupy residue at 40°C. under reduced pressure. The residue was diluted with water (300 ml.) and extracted with chloroform (4 x 100 ml.). The chloroform solution was washed with water (1 x 100 ml.), saturated sodium bicarbonate solution (3 x 100 ml.) and water (1 x 100 ml.) and then dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give the crude hydroxyketone (XXXI) (5.15 gms.) as a white solid. The entire above procedure was repeated a second time and another batch of crude hydroxyketone (5.10 gms.) was collected and combined with the first.

Attempts to recrystallize the crude hydroxyketone from chloroform - petroleum ether provided only 1.02 gms. of white, crystalline material. The remainder of the material was dissolved in a small amount of benzene and passed onto a column of grade I alumina (400 gms.) prepared with benzene as solvent. The column was eluted with benzene until all the starting material and dehydrated material (1.25 gms. in all) was removed and pure hydroxy ketone was being collected. The column was then eluted with chloroform to give a total of 3.98 gms. of pure hydroxy ketone. This material was then combined with the 1.02 gms. of hydroxyketone obtained from the initial crystallization

and the combined material was recrystallized from chloroform - petroleum ether to give the product (XXXI) (5.0 gms., 47% yield) as white crystals, m.p. = 100-102°C.

ANALYSIS	C	H
Calculated	67.12	7.20
Reported	67.18	7.20

Infrared spectrum (Fig. XXVII): absorptions ($cm.^{-1}$) at 3500 (alcohol OH); 1705 (ketone C=O); 1600 (aromatic C=C).

N.m.r. spectrum (Fig. LXXIII): absorptions at 1.72-1.45 (m, 2H, $ArCH_2\underline{CH_2}$-); 2.22 (s, 3H, $-COCH_3$); 2.66-3.95 (m, 4H, benzylic H); 3.45 (s, 1H, OH); 3.68, 3.72 (singlets, 3H each, OCH_3); 6.59 (s, 2H, aromatic H).

Mass spectrum (Fig. XCII): M^+/e at 250; 234; 232 ($P-H_2O$); 219 ($P-OCH_3$); 217; 207 ($P-COCH_3$); 189.

(b) Dicyclohexylcarbodiimide (0.25 gms., 1.2m moles) was added to a solution of the diol (XXIX) (0.10 gms., 0.4m moles), phosphoric acid (0.02 gms., 0.2m moles), benzene (1 ml.) and dry dimethylsulfoxide (1 ml.). The resulting solution was stirred for 3 hours at room temperature, during which time a precipitate of dicyclohexylurea formed. The solution was then filtered and additional benzene (15 ml.) was added. The benzene solution was then washed with water (3 x 30 ml.), dried over anhydrous magnesium sulfate and then evaporated under reduced pressure to give the hydroxyketone (XXXI) as the residue (0.085 gms., 85% yield). Purification of this residue by t.l.c. on silica gel ($CH_3OH/CHCl_3$ = 3/100) gave a compound identical to the hydroxyketone (XXXI) prepared by method 17(a).

(18) Preparation of the Acetoxycarbomethoxybenzoic acid Mixture (XXXII):

A solution of 3-hydroxyphthalic anhydride (30 gms., 0.18 moles), pyridine (1 ml.) and acetic anhydride (250 ml.) was stirred at 50°C. overnight. The acetic anhydride and pyridine were then removed by evaporation under reduced pressure to give 3-acetoxyphthalic anhydride as a solid residue. The 3-acetoxyphthalic anhydride was then dissolved in methanol (250 ml.) and this solution was refluxed for exactly 2 hours. Removal of the methanol by evaporation under reduced pressure gave the mixture (XXXII) of 2-carbomethoxy-3-acetoxybenzoic acid and 6-carbomethoxy-2-acetoxybenzoic acid as a yellow paste (43.5 gms.).

Infrared spectrum (Fig. XXVIII): absorptions ($cm.^{-1}$) at 2300-3500 (broad, acid OH); 1710 (acid C=O); 1740 (ester C=O); 1780 (acetate C=O); 1590, 1600 (aromatic C=C).

N.m.r. spectrum (Fig. LXXIV): absorptions at 2.28 (s,3H, $-OCOCH_3$); 3.86 (s, 3H, $-COOCH_3$); 6.9-8.0 (m, 3H, aromatic H); 10.18 (s, 1H, acid).

(19) Preparation of the isomeric hydronaphthacene quinone mixture (XXXV):

A solution of the hydroxyketone (XXXI) (4.0 gms., 0.016 moles) and the acid mixture (XXXII) (15.2 gms., 0.065 moles) in trifluoroacetic anhydride (20 ml.) was refluxed for 20 hours under a dry nitrogen atmosphere. Most of the trifluoroacetic anhydride was then removed by evaporation under reduced pressure and the residue was taken up in ether (200 ml.). The ether solution was washed with water (3 x 100 ml.), saturated sodium bicarbonate solution (1 x 100 ml.) and water (1 x 100 ml.), and then dried over magnesium sulfate and evaporated under reduced pressure to give 15.6 gms. of crude condensation product (XXIII) as residue. This residue was then dissolved in ethanol (100 ml.) and 2N sodium hydroxide (200 ml.) was added and the resulting solution

was stirred at 55°C for 20 hours under a nitrogen atmosphere. Water (100 ml.) was then added and the still basic solution was extracted with chloroform (1 x 150 ml.). The solution was then acidified with concentrated hydrochloric acid and extracted with chloroform (4 x 100 ml.). The chloroform solution was dried over magnesium sulfate and evaporated under reduced pressure to give 4.90 gms. of crude, hydrolysed condensation product (XXIV) as residue. This residue was added with stirring into a polyethylene reaction flask containing hydrofluoric acid (70 ml.). After stirring for 3 hours in a water bath at 20°C, the temperature was raised to 40°C to evaporate the remaining hydrofluoric acid. Water (150 ml.) was added and the aqueous solution was extracted with chloroform (4 x 100 ml.). The chloroform solution was washed with water (1 x 100 ml.), dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give a residue which was purified by t.l.c. in silicia gel (CH_3OH/ $CHCl_3$ = 3/100). Elution of the main band gave the isomeric hydro naphthacene quinone mixture (XXXV) as a yellow solid (1.08 gms., 19.2% yield, based on compound (XXXI)).

ANALYSIS	C	H
Calculated	66.66	5.09
Reported	66.86	4.90

Infrared spectrum (Fig. XXIX): absorptions ($cm.^{-1}$) at 3500 (alcohol OH); 1710 (ketone C=O); 1670 (quinone C=O); 1640 (chelated quinone C=O); 1580, 1600 (aromatic C=C).

N.m.r. spectrum (Fig. LXXV): absorptions at 1.95 (t, J = 7Hz., 2H, $ArCH_2\underline{CH_2}$-); 2.37 (s, 3H, $COCH_3$); 2.90-3.24 (m, 4H, benzylic CH_2); 3.82, 3.89 (singlets, 3H each, OCH_3); 7.10-7.73 (m, 3H, aromatic $\underline{H}$); 12.60 (s, 1H, phenol OH).

Mass spectrum (Fig. XCIII): M^+/e at 396; 378 (P-H_2O); 353 (P-$COCH_3$); 338.

(20) Methylation of the hydronaphthacene quinone mixture (XXXV):

A solution of the isomeric hydronaphthacene quinone mixture (XXXV) (3.47 gms., 8.8m moles), potassium carbonate (5.77 gms., 0.04 moles), and dimethylsulfate (2.22 gms., 17m moles) in spectro-grade acetone (100 ml.) was refluxed for 3½ hours under a nitrogen atmosphere. The solution was then evaporated under reduced pressure to a small volume and water (100 ml.) was added. The aqueous solution was extracted with chloroform (3 x 75 ml.). The chloroform solution was washed with water (3 x 100 ml.), dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give the isomeric hydro-naphthacene quinone mixture (XXXVI) (3.60 gms., 100% yield based on crude material) as a yellow solid which was used without further purification in the next step (21).

Infrared spectrum (Fig. XXX): absorptions ($cm.^{-1}$) at 3500 (alcohol OH); 1710 (ketone C=O); 1680 (quinone C=O); 1590, 1560 (aromatic C=C).

N.m.r. spectrum (Fig. LXXVI): absorptions at 1.93 (t, J = 7Hz., 2H, $ArCH_2\underline{CH_2}$-); 2.35 (s, 3H, $COCH_3$); 2.90-3.17 (m, 4H, benzylic CH_2); 3.85, 3.87, 3.88,3.92, 3.97 (singlets, total of 9H, OCH_3); 7.13-7.79 (m, 3H, aromatic H).

Mass spectrum (Fig. XCIV): M^+/e at 410; 392 (P-H_2O); 367 (P-$COCH_3$).

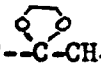
(21) Preparation of the isomeric ketal mixture (XXXVII):

A benzene solution (250 ml.) of the hydronaphthacene quinone mixture (XXXVI) (4.48 gms., 12m moles), ethylene glycol (4 ml.) and anhydrous p-toluenesulfonic acid (5 mg.) was distilled at a very

slow rate. After about 100 ml. of benzene was collected, the residual benzene was washed with saturated sodium bicarbonate solution (3 x 100 ml.) and water (1 x 100 ml.), then dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give the ketal mixture (XXXVII) as a solid, yellow residue. The residue was recrystallized from benzene - ether to give 3.40 gms. of yellow solid plus 1.77 gms. of mother liquor residue. This residue was purified by t.l.c. in silica gel ($CH_3OH/CHCl_3$ = 4/100). Elution of the main band gave an additional 0.93 gms. of purified ketal mixture, which when combined with the 1.77 gms. obtained from crystallization gave 4.33 gms. (88% yield) of the ketal mixture (XXXVII).

Infrared spectrum (Fig. XXXI): absorptions ($cm.^{-1}$) at 3580 (alcohol OH); 1675 (quinone C=O); 1590, 1560 (aromatic C=C).

N.m.r. spectrum (Fig. LXXVII): absorptions at 1.40 (s, 3H, side chain CH_3); 1.62-2.14 (m, 2H, $ArCH_2\underline{CH_2}$); 2.33 (s, 1H, alcohol OH); 2.95 (broad s, 4H, benzylic CH_2); 3.88, 3.92, 3.96, 4.02 (singlets, total of 13H, OCH_3 + ketal CH_2); 7.12-7.80 (m, 3H, aromatic H).

Mass spectrum (Fig. XCV): M^+/e at 454; 439 ($P-CH_3$); 368 (P- ).

(22) Introduction of the benzylic methoxyl group:

A solution of the ketal mixture (XXXVII) (1.5 gms., 3.3 m moles), N-bromosuccinimide (0.68 gms., 3.8m moles) and dibenzoylperoxide (2 mg.) in carbontetrachloride (100 ml.) was refluxed for ¾ hour in a 250 ml. flask equipped with a drying tube. The solution was then evaporated under reduced pressure to a small volume (10 ml.) and the precipitated succinimide was removed by suction filtration. The filtrate was transfered to another flask equipped with a drying tube and anhydrous methanol (100 ml.) was added. The methanol solution was refluxed

overnight and then evaporated under reduced pressure to give a foam-like residue. The reaction was repeated a second time (same quantities) and the combined residues were purified by t.l.c. on silica gel ($CH_3OH/CHCl_3$ = 4/100). After developing the t.l.c. plates, four distinct yellow bands were observed on each plate (Rf values = .37, .51, .64 and .72).

Elution of the lowest band in the t.l.c. plate (Rf = .31) gave a mixture (0.65 gms.) of the isomeric trans-ketal mixture (XL) and the isomeric trans-ketone mixture (XLII). This ketal-ketone mixture was dissolved in a solution of tetrahydrofuran (50 ml.) water (10 ml.) and concentrated hydrochloric acid (4 ml.) and the resulting solution was stirred for four days at room temperature. This solution was evaporated under reduced pressure to a small volume (10 ml.) and water (50 ml.) was then added. The aqueous solution was extracted with chloroform (3 x 30 ml.). The chloroform solution was then dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give a residue (0.63 gms.) of crude hydrolysis product which was repurified by t.l.c. on silica gel ($CH_3OH/CHCL_3$ = 4/100). Elution of the main band gave the isomeric trans-ketone mixture (XLII) (0.52 gms., 18% yield based on mixture (XXXVII)) as a yellow solid.

Infrared spectrum (Fig. XXXVI): absorptions ($cm.^{-1}$) at 3500 (alcohol OH); 1710 (ketone C=O); 1675 (quinone C=O); 1670, 1690 (aromatic C=C).

N.m.r. spectrum (Fig. LXXX): absorptions at 1.95 (2 doublets, B part of ABX spectrum, νB=1.95, J_{AB}=15Hz., J_{BX}=4.7Hz.); 2.36 (s, 3H, $COCH_3$); 2.64 (2 doublets, A part of ABX spectrum, νA=2.64, J_{AB}= 15Hz., J_{AX}=3.3Hz.); 3.12, 3.27 (AB quartet, 2H, benzylic CH_2, J_{AB}= 16Hz.); 3.30 (s, 3H, aliphatic OCH_3); 3.90-3.96 (m, 10H, aromatic OCH_3

+ alcohol OH); 4.99 (q, X part of ABX spectrum, ν_X=4.99, J_{AX}=3.3Hz., J_{BX}=4.7Hz.); 7.12-7.83 (m, 3H, aromatic).

Elution of the next band on the t.l.c. plate (Rf = .51) from the initial t.l.c. separation gave the isomeric cis-ketal mixture (XLI) as a yellow foam (0.87 gms.). This cis-ketal mixture was hydrolysed, under the same conditions that the trans-ketal was hydrolysed, to give (0.86 gms.) of crude hydrolysis product. This crude product was then purified by t.l.c. on silica gel ($CH_3OH/CHCl_3$ = 3/100). Elution of the main band gave the isomeric cis-ketone mixture (XLIII) (0.59 gms.) as a yellow solid.

Infrared spectrum: absorptions ($cm.^{-1}$) at 3460 (alcohol OH); 1710 (ketone C=O); 1675 (quinone C=O); 1590, 1565 (aromatic C=C).

N.m.r. spectrum: see Section 24.

Elution of the next spot on the t.l.c. plate (Rf = .64) from the initial t.l.c. separation gave the isomeric cis-ketone mixture (XLIII) (0.61 gms.) identical to the cis-ketone mixture (XLIII) obtained from the hydrolysis of the cis-ketal mixture (XLI). Therefore, a total amount of 1.2 gms. (42% yield) of the isomeric cis-ketone mixture (XLIII) was collected.

Elution of the next spot on the t.l.c. plate (Rf = .72) gave the isomeric cis-α-bromoketone mixture (XLIV) (0.20 gms., 5.8% yield) as a yellow solid.

Infrared spectrum (Fig. XXXVII): absorptions ($cm.^{-1}$) at 3450 (alcohol OH); 1740 (α-bromoketone C=O); 1680 (quinone C=O): 1590, 1565 (aromatic C=C).

N.m.r. spectrum (Fig. LXXXI): absorptions at 3.59 (s, 3H, aliphatic OCH_3); 3.92-3.00 (m, 9H, aromatic OCH_3); 7.17-7.83 (m, 3H, aromatic).

Mass spectrum (Fig. XCVII): M^+/e at 520, 518; 474; 469; 439 (P-Br); 407; 397 (P-$COCH_2Br$); 365 (P-($COCH_2Br$ + CH_3OH)).

(23) Zinc reduction of the α-bromoketone mixture (XLIV):

A solution of the isomeric α-bromoketone mixture (XLIV) (0.04 gms., 0.08m moles) in glacial acetic acid (6 ml.) was stirred with zinc powder (1 gm.) for 20 minutes at 15°C. The zinc was then removed by suction filtration and the filtrate evaporated under reduced pressure to dryness to give a residue which was purified by t.l.c. on silica gel ($CH_3OH/CHCl_3$ = 4/100). Elution of the main band gave the isomeric cis-ketone mixture (XLIII) (0.02 gms., 60% yield) as a yellow solid. There were several other trace bands on the t.l.c. plate, all of which contained less than 2 mg. each of unidentifiable material.

(24) Separation of the isomeric hydronaphthacene quinone mixture (XLIII):

The isomeric hydronaphthacene quinone mixture (XLIII) was separated by t.l.c. on silica gel ($CH_3OH/CH_3COOC_2H_5$ = 1/100) into two yellow bands.

Elution of the lower band gave daunomycinone trimethyl ether (XLVI) as a yellow solid which was recrystallized from methanol to give yellow crystals, m.p. = 185-186°C.

ANALYSIS

Molecular ion calculated for $C_{24}H_{24}O_8$: 440.1471

Found (from high resolution mass spectrum): 440.1464

Infrared spectrum (Fig. XXXIII): absorptions ($cm.^{-1}$) at 3460 (alcohol OH); 1715 (ketone C=O); 1680 (quinone C=O); 1590, 1560 (aromatic C=C).

N.m.r. spectrum (Fig. LXXVIII): absorptions at 1.91 (2 doublets, B part of ABX spectrum, ν B=1.91, J_{AB}=15Hz., J_{BX}=3.82Hz.); 2.40 (s, 3H, $COCH_3$); 2.46 (2 doublets, A part of ABX spectrum, ν A=2.46, J_{AB}= 15Hz., J_{AX}=2.42Hz.); 3.02, 3.26 (AB quartet, 2H, benzylic CH_2, J_{AB}= 19Hz.); 3.56 (s,3H, aliphatic OCH_3); 3.89 (s, 3H, aromatic OCH_3); 4.00 (s, 6H, aromatic OCH_3); 4.92 (q, X part of ABX spectrum, ν X=4.92, J_{AX}=2.42Hz., J_{BX}=3.82Hz.), 5.02 (s, 1H, OH); 7.16-7.82 (m, 3H, aromatic).

Mass spectrum (Fig. XCVI): M^+/e at 440; 422 ($P-H_2O$); 408 ($P-CH_3OH$); 397 ($P-COCH_3$); 365 ($P-(COCH_3 + CH_3OH)$); 337.

Elution of the upper band gave isodaunomycinone trimethyl ether (XLV) as a yellow solid which was recrystallized from methanol to give yellow crystals, m.p. = 226-227°C.

ANALYSIS

Molecular ion calculated for $C_{24}H_{24}O_8$: 440.1471

Found (from high resolution mass spectrum): 440.1464

Infrared spectrum (Fig. XXXV): absorptions ($cm.^{-1}$) at 3460 (alcohol OH); 1715 (ketone C=O); 1680 (quinone C=O); 1590, 1560 (aromatic C=C).

N.m.r. spectrum (Fig. LXXIX): absorptions at 1.91 (2 doublets, B part of ABX spectrum, ν B=1.91, J_{AB}=15Hz., J_{BX}=3.30Hz.); 2.40 (s, 3H, $COCH_3$); 2.46 (2 doublets, A part of ABX spectrum, ν A=2.46, J_{AB}=15Hz., J_{AX}=2.30 Hz.); 3.02, 3.26 (AB quartet, 2H, benzylic CH_2, J_{AB}=19Hz.), 3.56 (s, 3H, aliphatic OCH_3); 3.93 (s, 3H, aromatic OCH_3); 4.00 (s, 6H, aromatic OCH_3); 4.91 (q, X part of ABX spectrum, ν X=4.91, J_{AX}=2.30 Hz., J_{BX}=3.30 Hz.); 5.02 (s, 1H, OH); 7.16-7.88 (m, 3H, aromatic).

Mass spectrum (Fig. XCVI): M^+/e at 440; 422 ($P-H_2O$); 408 ($p-CH_3OH$); 397 ($P-COCH_3$); 365 ($P-(COCH_3 + CH_3OH)$); 337.

(25) Aluminum chloride hydrolysis of daunomycinone trimethyl ether (XLVI) and isodaunomycinone trimethyl ether (XLV):

(a) A solution of daunomycinone trimethyl ether (XLVI) (0.22 gms., 0.51m moles) in 1,2-dichloroethane (30 ml.) was stirred with freshly sublimed aluminum chloride (0.77 gm., 5.6m moles) overnight at room temperature. This mixture was then poured into a saturated oxalic acid solution (100 ml.) and the resulting solution was then extracted with chloroform (3 x 100 ml.). The chloroform extracts were combined, washed with water (100 ml.), dried over magnesium sulfate and then evaporated to a small volume (20 ml.) during which time a red precipitate of 4-0-demethyl-7-0-methyldaunomycinone (XLVII) (178mg.) formed. The precipitate was collected by filtration and the resulting mother liquir was then evaporated to dryness. Purification of the residue by t.l.c. on silica gel ($CH_3OH/CHCl_3$ = 3/100) gave an additional 13.2 mg of product, so that the total amount of 4-0-demethyl-7-0-methyldaunomycinone (XLVII) recovered was 191.2 mg. (93.5% yield). Recrystallization from chloroform gave the product as red crystals, m.p. = 246-250°C.

ANALYSIS

Molecular ion calculated for $C_{21}H_{18}O_8$: 398.1002

Found (from high resolution mass spectrum): 398.1002

Infrared spectrum (Fig. XXXVIII): absorptions ($cm.^{-1}$) at 3440 (alcohol OH); 1715 (ketone C=O); 1600 (chelated quinone C=O).

Mass spectrum (Fig. XCVIII): M^+/e at 398; 380 ($P-H_2O$); 348; 323 ($P-(COCH_3 + CH_3OH)$); 306; 295.

(b) Isodaunomycinone trimethyl ether (XLV) (0.17 gms., 0.39m moles) was hydrolysed and worked up in an identical manner to that described in 25 (a) to give 1-hydroxy-4-demethoxy-7-0-methyldaunomycinone

(XLVIII) (0.14 gms., 91% yield). Recrystallization from chloroform gave the product as red crystals, m.p. = 236-240°C.

ANALYSIS

Molecular ion calculated for $C_{21}H_{18}O_8$: 398.1002

Found (from high resolution mass spectrum): 398.1002

Infrared spectrum (Fig. XXXIX): absorptions ($cm.^{-1}$) at 3460 (alcohol OH); 1715 (ketone C=O); 1600 (chelated quinone C=O).

Mass spectrum (Fig. XCVIII): M^+/e at 398, 380 (P-H_2O); 348; 323 (P-($COCH_3$ + CH_3OH)); 306; 295.

(26) Boron tribromide hydrolysis of daunomycinone trimethyl ether (XLVI):

A solution of boron tribromide (0.25 gms., 1m mole) in methylene chloride (5 ml.) was cooled to -70°C in a dry-ice-acetone bath and then added via a syringe to a solution of daunomycinone trimethyl ether (XLVI) (0.04 gms., 0.1m moles) in methylene chloride (5 ml.) which was also cooled to -70°C in a dry-ice-acetone bath. When the addition was complete the dry-ice-acetone bath was removed and the solution was allowed to come to room temperature. As soon as the solution reached room temperature it was poured into ice water (50 ml.) and stirred for 15 minutes. The methylene chloride layer was then removed, dried over magnesium sulfate and evaporated to give a red solid residue. Chromatography of this residue using t.l.c. on silica gel ($CH_3OH/CHCl_3$ = 3/100) gave two, red bands on the t.l.c. plate. Elution of the smaller, lower red band gave a red solid, tentatively assigned structure (XLIX) (10.5 mg., 27% yield).

Infrared spectrum (Fig. XL): absorptions ($cm.^{-1}$) at 3500 (alcohol OH); 1700 (ketone C=O); 1620, 1575 (chelated quinone C=O).

Mass spectrum (Fig. CI): M^+/e at 398, 380 (P-H_2O); 362 (P-$2H_2O$); 355 (P-$COCH_3$); 337 (P-($COCH_3$ + H_2O)); 309; 217.

(27) Aluminum chloride hydrolysis of compound (XLIX):

Compound (XLIX) (10 mg., 0.25m moles) was hydrolysed with aluminum chloride and worked up in an identical manner to that described in section 25 to give 4-0-demethyldaunomycinone (LI) (8.7 mg., 90% yield). Crystallization from chloroform gave the product as red crystals which appeared to decompose $\sim 240^{\circ}C$.

Infrared spectrum (Fig. XLIII): absorptions ($cm.^{-1}$) at 3480 (alcohol OH); 1715 (ketone C=O); 1605 (chelated quinone C=O).

Mass spectrum (Fig. XCIC): M^{+}/e at 384; 366 ($P-H_2O$); 348 ($P-2H_2O$); 323 ($P-(COCH_3 + H_2O)$); 295.

(28) Preparation of the trifluoroacetic ester (L):

4-0-demethyl-7-0-methyldaunomycinone (XLVII) (16 mg., 0.04m moles) was dissolved in trifluoroacetic acid (10 ml.) and the solution was stirred overnight at room temperature. The trifluoroacetic acid was then evaporated under reduced pressure to give the trifluoroacetic ester mixture (L) as a red, solid residue which was used without further purification in the next step (29).

Infrared spectrum (Fig. XLI): absorptions ($cm.^{-1}$) at 3460 (alcohol OH); 1785 (trifluoroacetic ester C=O); 1720 (ketone C=O); 1600 (chelated quinone C=O).

(29) Basic hydrolysis of trifluoroacetic ester (L):

Dilute ammonium hydroxide (6 drops) was added to a solution of the trifluoroacetic ester mixture (L) (19 mg., 0.04m moles) in acetone (15 ml.) and the resulting basic solution was then heated in a steam bath for six hours. The solution was then evaporated to dryness under reduced pressure to give a solid residue which was purified by t.l.c. on silica gel ($CH_3OH/CHCl_3$ = 1/100). The t.l.c. plate was developed three times to separate two red bands as the

major products.

Elution of the upper band gave 4-0-demethyldaunomycinone (L1) (3.7 mg., 24% yield) as a red solid. Recrystallization from chloroform gave the product as red crystals which appeared to decompose ~ 240°C.

Infrared spectrum (Fig. XLIV): absorptions ($cm.^{-1}$) at 3480 (alcohol OH); 1715 (ketone C=O); 1605 (chelated ketone C=O).

Mass spectrum (Fig. XCIC): M^+/e at 384; 366 ($P-H_2O$); 348 ($P-2H_2O$); 323 ($P-(COCH_3 + H_2O)$); 295.

Elution of the lower band gave the epimeric compound (LII) (3.7 mg., 24% yield) as a red solid which was recrystallized from chloroform to give red crystals.

Infrared spectrum (Fig. XLV): absorptions ($cm.^{-1}$) at 3540 (alcohol OH); 1715 (ketone C=O); 1605 (chelated ketone C=O).

Mass spectrum (Fig. XCIX): M^+/e at 384; 366 ($P-H_2O$); 348 ($P-2H_2O$); 323 ($P-(COCH_3 + H_2O)$); 295.

(30) Lead tetraacetate oxidation of 4-0-demethyl-7-0-methyldaunomycinone (XLVII) and of 1-hydroxy-4-demethoxy-7-0-methyldaunomycinone (XLVIII):

(a) Freshly recrystallized lead tetraacetate (75 mg., 0.17m moles) was added to a slurry of 4-0-demethyl-7-0-methyldaunomycinome (XLVII) (55 mg., 0.14m moles) in acetic acid (2 ml.) and the resulting mixture was stirred for 15 minutes. Chloroform (30 ml.) was then added and the resulting chloroform solution was washed with water (30 ml.). The chloroform solution was then dried over magnesium sulfate and evaporated under reduced pressure to give a quantitative recovery of the diquinone (LIV) which was used without purification in the next step (31).

Infrared spectrum (Fig. XLVII): absorptions ($cm.^{-1}$) at 3460 (alcohol OH); 1715 (ketone C=O); 1685 (quinone C=O); 1630 (C=C).

(b) Freshly recrystallized lead tetraacetate (0.25 gm., 0.56m moles) was added to a slurry of 1-hydroxy-4-demethoxy-7-0-methyl-daunomycinome (XLVIII) (0.18 gm., 0.47m moles) in acetic acid (2 ml.). The mixture was stirred for 15 minutes and then worked up as described in 30 (a) to give a quantitative recovery of the diquinone (LIII) which was used without purification in the next step (32).

Infrared spectrum (Fig. XLVII): absorptions ($cm.^{-1}$) at 3460 (alcohol OH); 1715 (ketone C=O); 1685 (quinone C=O); 1630 (C=C).

(31) Methylation of diquinone (LIV):

Anhydrous potassium carbonate (0.10 gm., 0.74m moles) and then dimethyl sulfate (55 mg., 0.44m moles) were added to a solution of the diquinone (LIV) (58 mg., 0.15m moles) in spectrograde acetone (25 ml.) and the resulting mixture was stirred overnight at room temperature. The acetone solution was then evaporated under reduced pressure to a small volume (10 ml.) and poured into water (50 ml.). The aqueous solution was neutralized with dilute hydrochloric acid and then extracted with chloroform (3 x 50 ml.). The chloroform extracts were combined, dried over magnesium sulfate and evaporated under reduced pressure to give a residue which was purified by t.l.c. on silica gel. The t.l.c. plate was developed six times ($CHCl_3$) to give two red bands near the top of the plate and two yellow bands with lower Rf values. Elution of the upper red band gave reduced starting material, 4-0-demethyl-7-0-methyldaunomycinone (2.6 mg.). Elution of the yellow bands gave methylation products other than the required product (LVIII). These methylation products were rehydrolysed with aluminum chloride according to method (25) to give an additional 14.5 mg. of reduced starting material. Elution of the lower red band gave 7-0-methyldaunomycinone (LVI) (4.0 mg., 10.2% yield, based on

consumed starting material) as a red solid.

Infrared spectrum (Fig. XLVIII): absorptions ($cm.^{-1}$) at 3460 (alcohol OH); 1720 (ketone C=O); 1620, 1585 (quinone C=O).

(32) Methylation of diquinone (LIII):

Anhydrous potassium carbonate (0.32 gms., 2.3m moles) and then dimethylsulfate (0.12 gms., 0.93m moles) were added to a solution of the diquinone (LIII) (0.18 gms., 0.47m moles) in spectrograde acetone (30 ml.) and the resulting mixture was stirred for 48 hours at room temperature. Work up and purification in a manner identical to that described in method (31) gave a total of 79 mg. of recovered reduced starting material, 1-hydroxy-4-demethoxy-7-0-methyldaunomycinone (XLVIII), and 10.3 mg. (9.5% yield, based on consumed starting material) of 1-methoxy-4-demethoxy-7-0-methyldaunomycinone (LV) as a red solid.

Infrared spectrum (Fig. XLIX): absorptions ($cm.^{-1}$) at 3460 (alcohol OH); 1720 (ketone C=O); 1620, 1585 (quinone C=O).

Mass spectrum (Fig. C): M^+/e at 412; 380 ($P-CH_3OH$); 337 ($P-(COCH_3 + CH_3OH)$); 309.

(33) Preparation of the trifluoroacetic ester mixture (LVII):

A solution of 1-methoxy-4-demethoxy-7-0-methyldaunomycinone (LV) (13 mg., 0.03m moles) in trifluoroacetic acid (20 ml.) was stirred at room temperature for 2 hours. The trifluroracetic acid was then evaporated under reduced pressure to give the trifluoroacetic ester mixture (LVII) as a red, solid residue which was used without further purification in the next step (34).

Infrared spectrum (Fig. LII): absorptions ($cm.^{-1}$) at 3480 (alcohol OH); 1785 (trifluoroacetic ester C=O); 1720 (ketone C=O); 1620, 1585 (quinone C=O).

(34) Basic hydrolysis of the trifluoroacetic ester mixture (LVII):

A saturated potassium carbonate solution (2 ml.) was added to a solution of the trifluoroacetic ester mixture (LVII) (15.5 mg., 0.03m moles) in acetone (4 ml.) and the resulting solution was stirred for 1 hour at room temperature. The solution was then poured into water (30 ml.) and the aqueous solution was neutralized with dilute hydrochloric acid and extracted with chloroform (50 ml.). The chloroform extract was dried over magnesium sulfate and evaporated under reduced pressure to give a red residue. Purification of this residue by t.l.c. on silica gel ($CH_3OH/CHCl_3$ = 3/100) gave two red bands on the t.l.c. plate.

Elution of the upper red band gave isodaunomycinone (LIX) (3.4 mg., 27.2% yield) as a red solid which was recrystallized from chloroform to give red crystals, m.p. = 216-218°C.

Infrared spectrum (Fig. LIII): absorptions ($cm.^{-1}$) at 3480 (alcohol OH); 1715 (ketone C=O); 1620, 1580 (quinone C=O).

Mass spectrum (Fig. CI): M^+/e at 398, 362 ($P-2H_2O$); 337 ($P-(COCH_3 + H_2O)$); 217.

Elution of the lower red band gave the epimeric compound (LX) (1.6 mg., 12.8% yield) as a red solid.

Infrared spectrum (Fig. LIV): absorptions ($cm.^{-1}$) at 3530 (alcohol OH); 1715 (ketone C=O); 1620, 1580 (quinone C=O).

(35) Preparation of the trifluoroacetic ester mixture (LVIII):

A solution of 7-O-methyldaunomycinone (LVI) (10.4 mg., 0.03 m moles) in trifluoroacetic acid (20 ml.) was stirred at room temperature for 2 hours. The trifluoroacetic acid was then evaporated under reduced pressure to give the trifluoroacetic ester mixture (LVIII) as a red, solid residue which was used without further

purification in the next step (36).

Infrared spectrum (Fig. L): absorptions ($cm.^{-1}$) at 3480 (alcohol OH); 1785 (trifluoroacetic ester C=O); 1715 (ketone C=O); 1620, 1580 (quinone C=O).

(36) Basic hydrolysis of the trifluoroacetic ester mixture (LVIII):

Dilute ammonium hydroxide (2 drops) was added to a solution of the trifluoroacetic ester (LVIII) (2 mg.) in acetone (3 ml.) and the resulting solution was heated for 1 hour in the steam bath. The solvent was then evaporated under reduced pressure to give a red, solid residue which, after washing with a little ether, gave an infrared spectrum identical to the infrared spectrum of natural daunomycinone.

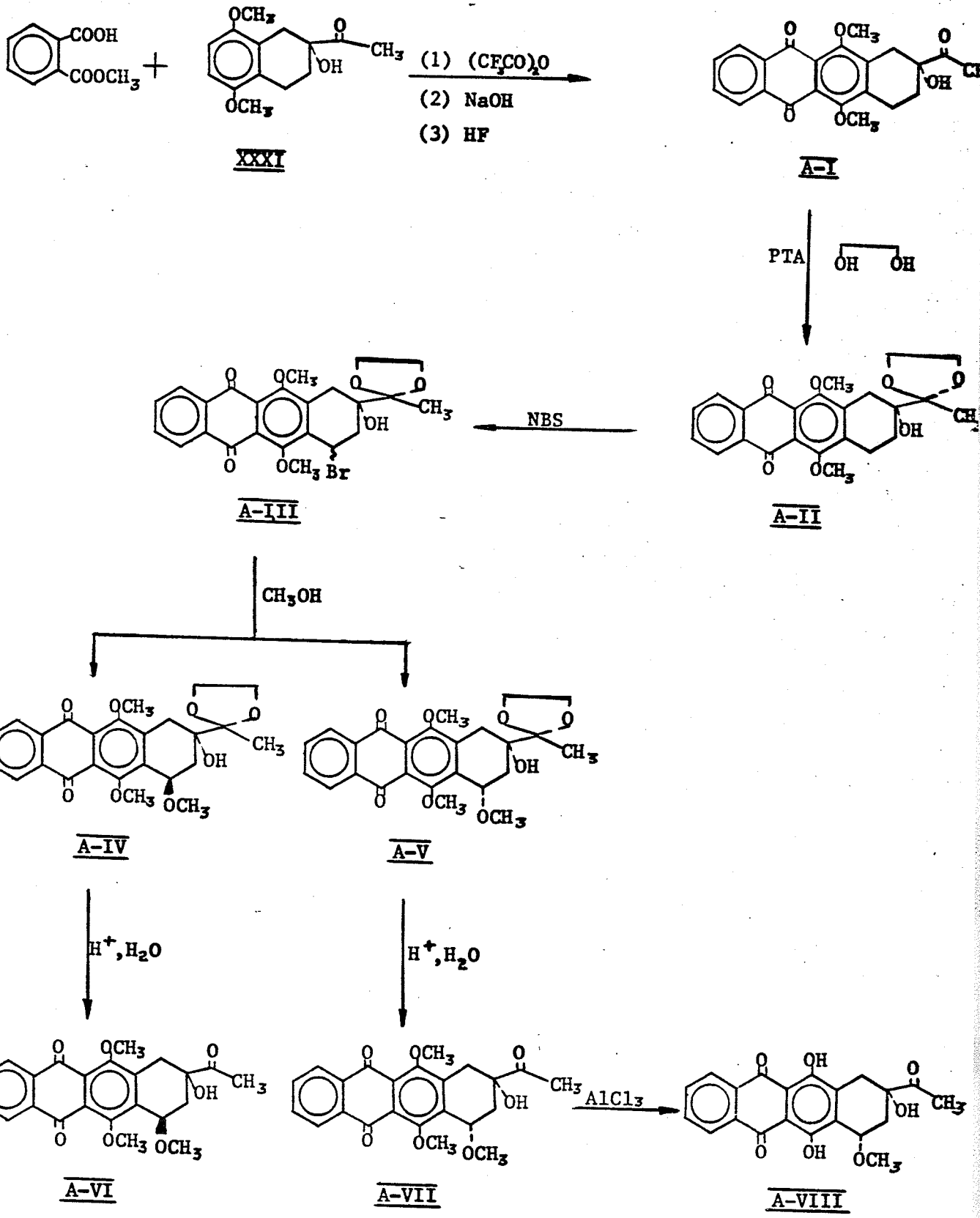
Infrared spectrum (Fig. LV): absorptions ($cm.^{-1}$) at 3480 (alcohol OH); 1715 (ketone C=O); 1620, 1585 (quinone C=O).

APPENDIX

Prior to condensing (see Scheme VII) the acetoxycarbomethoxybenzoic acid mixture XXXII with the tetralin hydroxyketone XXXI to give (see Scheme VIII); eventually, daunomycinone trimethyl ether XLVI and isodaunomycinone trimethyl ether XLV, a model system study[28] was made in which 2-carbomethoxylbenzoic acid was condensed (see Scheme A-1) with the tetralin hydroxyketone XXXI to give, eventually, 4-demethoxy-7-O-methyldaunomycinone, A-VIII. This model study series of reactions will be briefly discussed in this appendix. All reaction conditions, work ups, chromatographic separations and structural assignments based upon spectroscopic data which were used in this model study are exactly the same as those used in the synthesis of the analogous compounds which are shown in Scheme VII and Scheme VIII. Since these conditions have been discussed previously, they will not be rediscussed here. Analytical and spectral data will be given in a section after the discussion.

2-carbomethoxybenzoic acid was condensed with the tetralin hydroxyketone XXXI (see Scheme A-1) in a three step process identical to that described for the synthesis of the isomeric hydronaphthacene quinone mixture XXXV. The product, 9-acetyl-9-hydroxy-6,11-dimethoxy-7,8,9,10-tetrahydro-5,12-naphthacenedione, A-I, was isolated as a pale yellow, crystalline solid (23.5% yield, m.p. = 184-186°C) which gave a satisfactory elemental analysis and the required molecular ion of 380 in the mass spectrum. This compound A-I was then reacted with ethylene glycol in the presence of p-toluenesulfonic acid to give the corresponding ethylene ketal A-II, isolated as a pale yellow, crystalline solid (100% yield, m.p. = 185-187°C) which gave the required molecular ion of 424 in the mass spectrum. The C_7 benzylic position of the D ring

Scheme A-I


COOH
COOCH3
OCH3
O
CH3
OH
OCH3
(1) (CF3CO)2O
(2) NaOH
(3) HF
XXXI
A-I
PTA
OH
OH
NBS
A-III
A-II
CH3OH
A-IV
A-V
H+, H2O
H+, H2O
A-VI
A-VII
AlCl3
A-VIII

of compound A-II was then selectively brominated by reacting compound A-II with N-bromosuccinimide in the presence of dibenzoylperoxide. The resulting bromination product A-III (not isolated) was then immediately refluxed with anhydrous methanol to give, after separation by t.l.c. and ketal hydrolysis, 4-demethoxy-7-epidaunomycinone trimethyl ether A-VI and 4-demethoxydaunomycinone trimethyl ether A-VII . Product A-VII was isolated as a yellow, crystalline solid (42% yield, m.p. = 193.5-194.5°C.) which gave a satisfactory elemental analysis and the required molecular ion of 410 in the mass spectrum. Product A-VI was also isolated as a yellow, crystalline solid (14% yield, m.p. = 192-193°C.) and gave an identical mass spectrum to that obtained from compound A-VII. (A small amount of an α-bromoketone product analogous to mixture XLIV was also isolated, even though this is not shown in Scheme A-1). The 4-demethoxydaunomycinone trimethyl ether A-VII was then hydrolysed with aluminum chloride to give 4-demethoxy -7-O-methyldaunomycinone A-VIII, isolated as a red crystalline solid (80% yield, m.p. = 250-254°C.) whose empirical formula was in agreement with that determined from its high resolution mass spectrum.

ANALYTICAL AND SPECTRAL DATA

(1) 9-acetyl-9-hydroxy-6,11-dimethoxy-7,8,9,10-tetrahydro-5,12-naphthacenedione A-I:

ANALYSIS	C	H
Calculated	69.49	5.29
Reported	69.55	5.13

Infrared spectrum: absorptions ($cm.^{-1}$) at 3520 (alcohol OH); 1705 (ketone C=O); 1665 (quinone C=O); 1600 (aromatic C=C).

N.m.r. spectrum: absorptions at 1.97 (broad t, J = 7Hz., 2H,

$ArCH_2\underline{CH}_2$-); 2.39 (s, 3H, $COCH_3$); 3.09 (broad s, 4H, benzylic H); 3.80 (s, 1H, OH); 3.85 (s, 3H, OCH_3); 3.90 (s, 3H, OCH_3); 7.66-8.27 (m, 4H, aromatic H).

Mass spectrum: M^+/e at 380; 362 (P-H_2O), 337 (P-$COCH_3$).

(2) 4-demethoxydaunomycinone trimethyl ether A-VII:

ANALYSIS	C	H
Calculated	67.31	5.40
Reported	67.30	5.33

Molecular ion calculated for $C_{23}H_{22}O_7$: 410.1365

Found (from high resolution mass spectrum): 410.1360

Infrared spectrum: absorptions ($cm.^{-1}$) at 3490 (alcohol OH); 1715 (ketone C=O); 1670 (quinone C=O); 1600 (aromatic C=O).

N.m.r. spectrum: absorptions at 1.76-3.07 (d of d, B part of ABX spectrum, 1H, J_{AB} = 15 HZ., J_{BX} = 4 Hz.); 2.33-2.65 (m, 1H, C_8-H); 2.42 (s, 3H, $COCH_3$); 3.15-3.30 (m, 2H, C_{10}-H_2); 3.58 (s, 3H, aliphatic OCH_3); 3.90 (s, 3H, aromatic OCH_3); 3.99 (s, 3H, aromatic OCH_3); 4.96 (d of d, X part of ABX spectrum, 1H, J_{AX} = 2Hz., J_{BX} = 4Hz.); 5.04 (s, 1H, OH); 7.77-8.30 (m, 4H, aromatic H).

Mass spectrum: M^+/e at 410; 392 (P-H_2O); 360 (P-(H_2O + CH_3OH)); 335 (P-(CH_3OH + $COCH_3$)); 307 (P-(CH_3OH + $COCH_3$ + CO)).

(3) 4-demethoxy-7-epidaunomycinone trimethyl ether A-VI:

Infrared spectrum: absorptions ($cm.^{-1}$) at 3525 (alcohol OH); 1715 (ketone C=O); 1670 (quinone C=O); 1600 (aromatic C=C).

N.m.r. spectrum: absorptions at 1.96 (d of d, B part of ABX spectrum, 1H, J_{AB} = 15 Hz., J_{BX} = 4.5 Hz.); 2.38 (s, 3H, $COCH_3$); 2.71 (d of d, A part of ABX spectrum, 1H, J_{AB} = 15 Hz., J_{AX} = 2Hz.); 2.88-3.50 (AB quartet, 2H, J_{AB} = 15 Hz., C_{10}-H_2); 3.35 (s, 3H, aliphatic OCH_3); 3.86 (s, 1H, OH); 3.92 (s, 3H, aromatic OCH_3); 3.97 (s, 3H

aromatic OCH_3); 5.05 (q, X part of ABX spectrum 1H, J_{AX} = 2Hz., J_{BX} = 4.5 Hz.); 7.77-8.30 (m, 4H, aromatic H).

Mass spectrum: M^+/e at 410; 392 (P-H_2O); 360 (P-(H_2O + CH_3OH)); 335 (P-(CH_3OH + $COCH_3$)); 307 (P-(CH_3OH + $COCH_3$ + CO)).

(4) 4-demethoxy-7-O-methyldaunomycinone A-VIII:

ANALYSIS

Molecular ion calculated for $C_{21}H_{18}O_7$: 382.1053

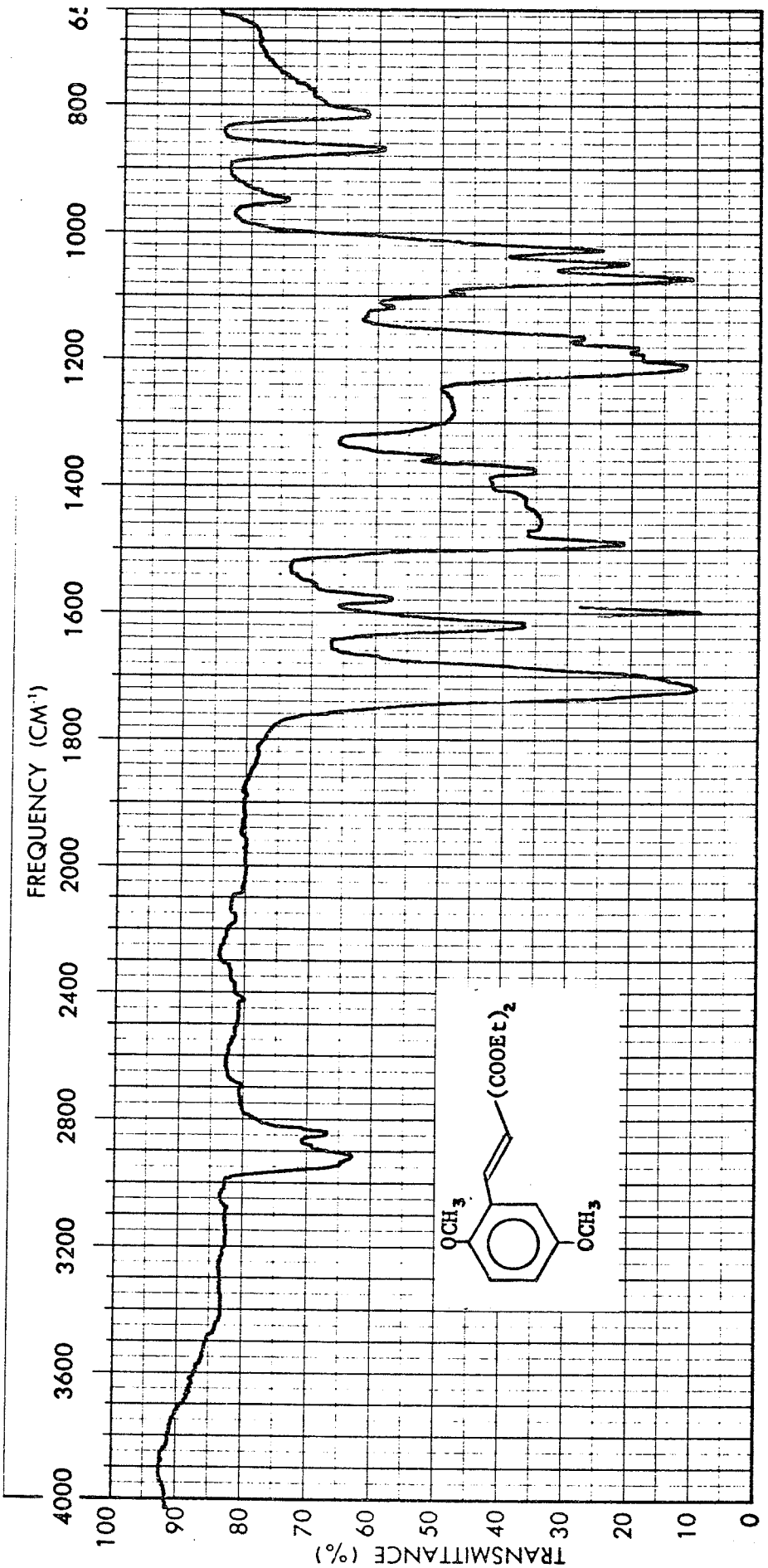
Found (from high resolution mass spectrum): 382.1050

Infrared spectrum: absorptions ($cm.^{-1}$) at 3400 (alcohol OH); 3400-2700 (phenolic OH); 1715 (ketone C=O); 1625 (chelated quinone C=O); 1595 (aromatic C=C).

N.m.r. spectrum (recorded with the help of a Varian Model C-1024 time averaging computer): absorptions at 2.63 (s, 3H, $COCH_3$); 3.36 (q, 2H, C_{10}-H_2); 3.80 (s, 3H, OCH_3); 5.08 (d of d, 1H, C_7-H); 5.20 (s, 1H, alcohol OH); 7.97-8.50 (m, 4H, aromatic H); 13.20 (s, 1H, phenolic OH); 13.50 (s, 1H, phenolic OH).

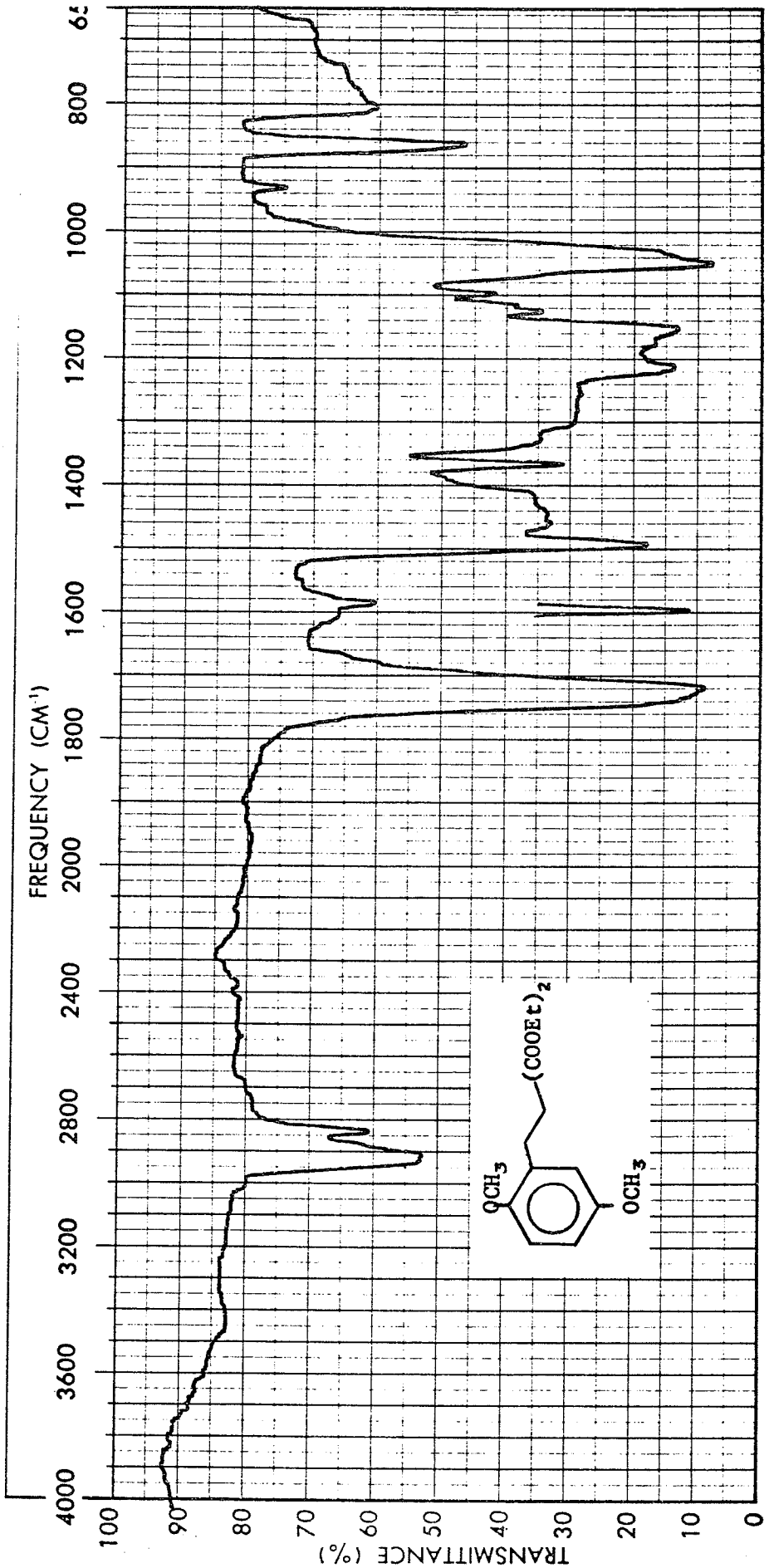
Mass spectrum: M^+/e at 382; 332 (P-(H_2O + CH_3OH)); 307 (P-(CH_3OH + $COCH_3$)); 289.

Figure X



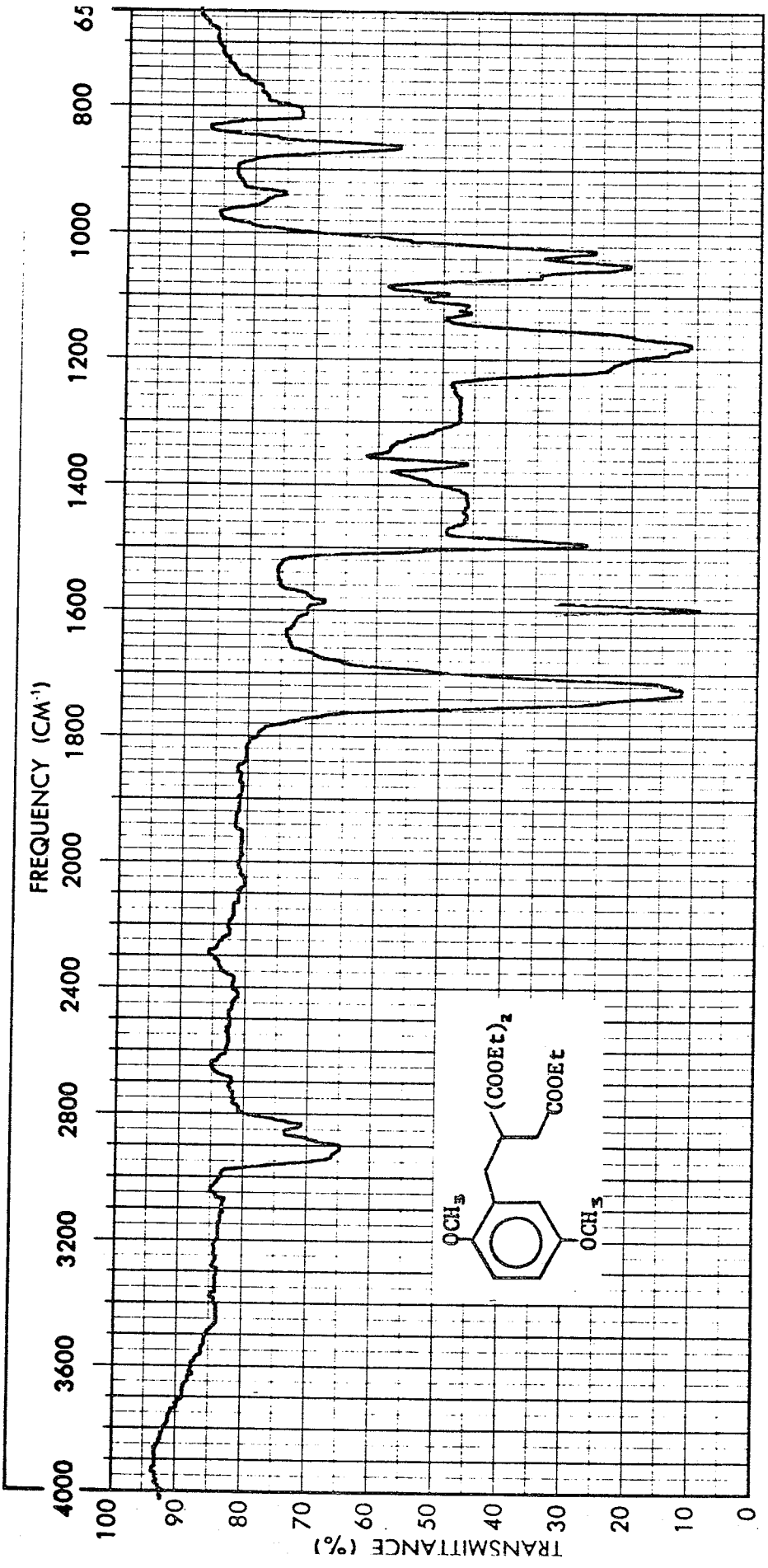
Infrared spectrum no. 1: Ethyl 2-carboethoxy-3-(2,5-dimethoxyphenyl) propenoate (XII), in CH_2Cl_2 solution.

Figure XI



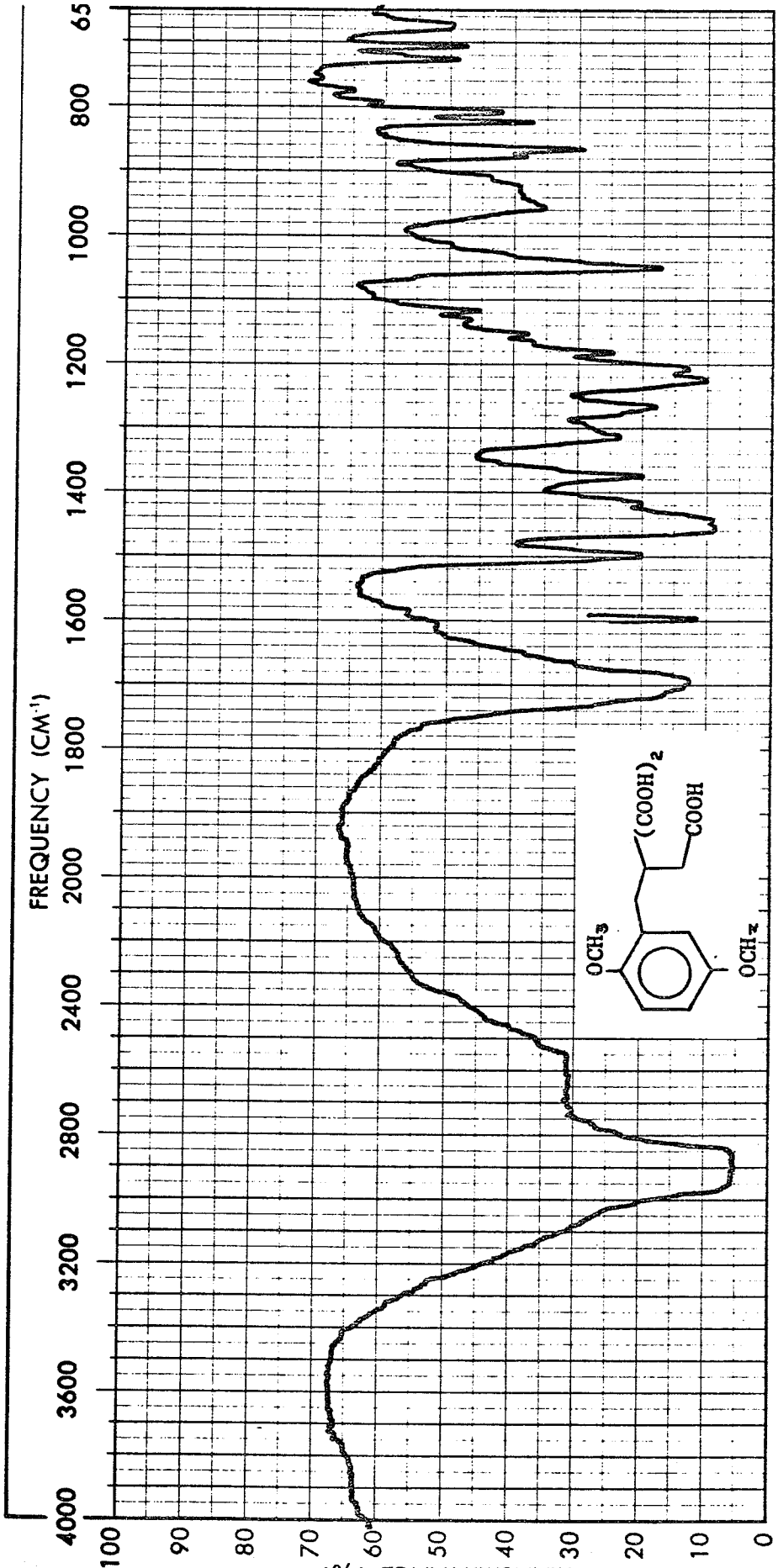
Infrared spectrum no 2: Ethyl 2-carboethoxy-3-(2,5-dimethoxyphenyl) propanoate (XIII), in CH_2Cl_2 solution.

Figure XII



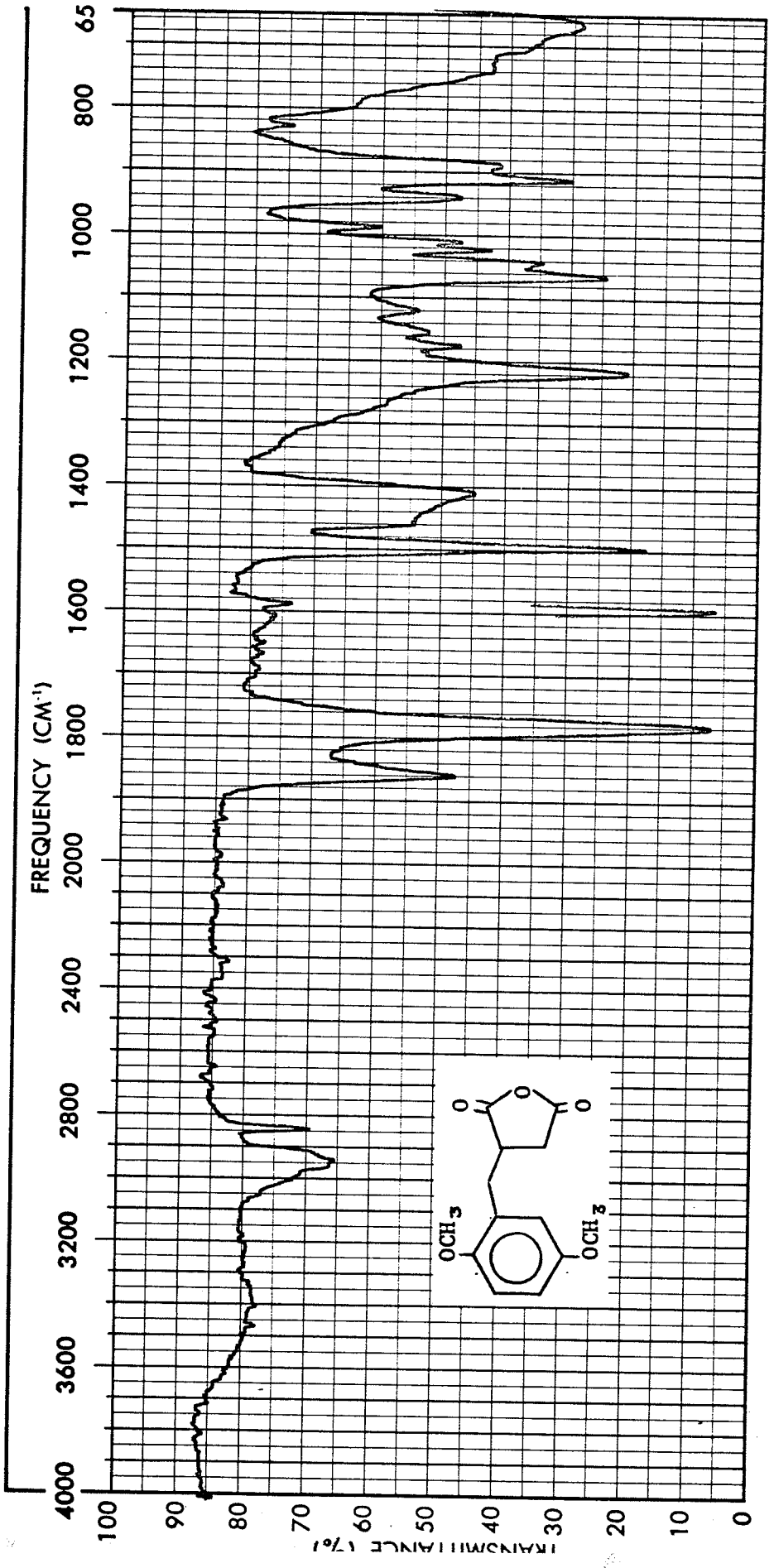
Infrared spectrum no. 3: Ethyl 3,3-dicarboethoxy-4-(2,5-dimethoxyphenyl) butanoate (XIV), in CH_2Cl_2 solution.

Figure XIII



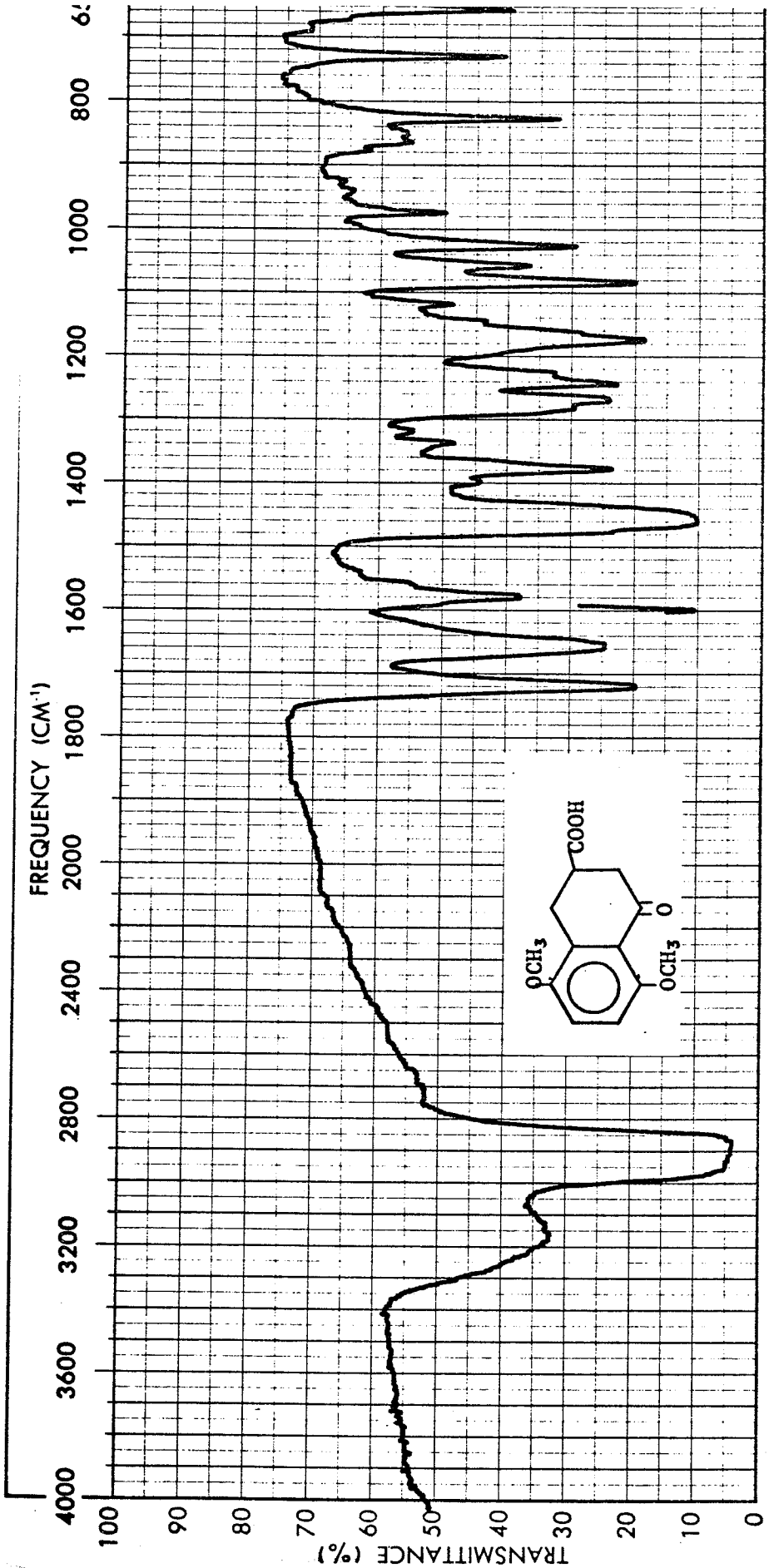
Infrared spectrum no. 4: 3,3-dicarbohydroxy-4-(2,5-dimethoxyphenyl) butanoic acid (XV), nujol mull.

Figure XIV



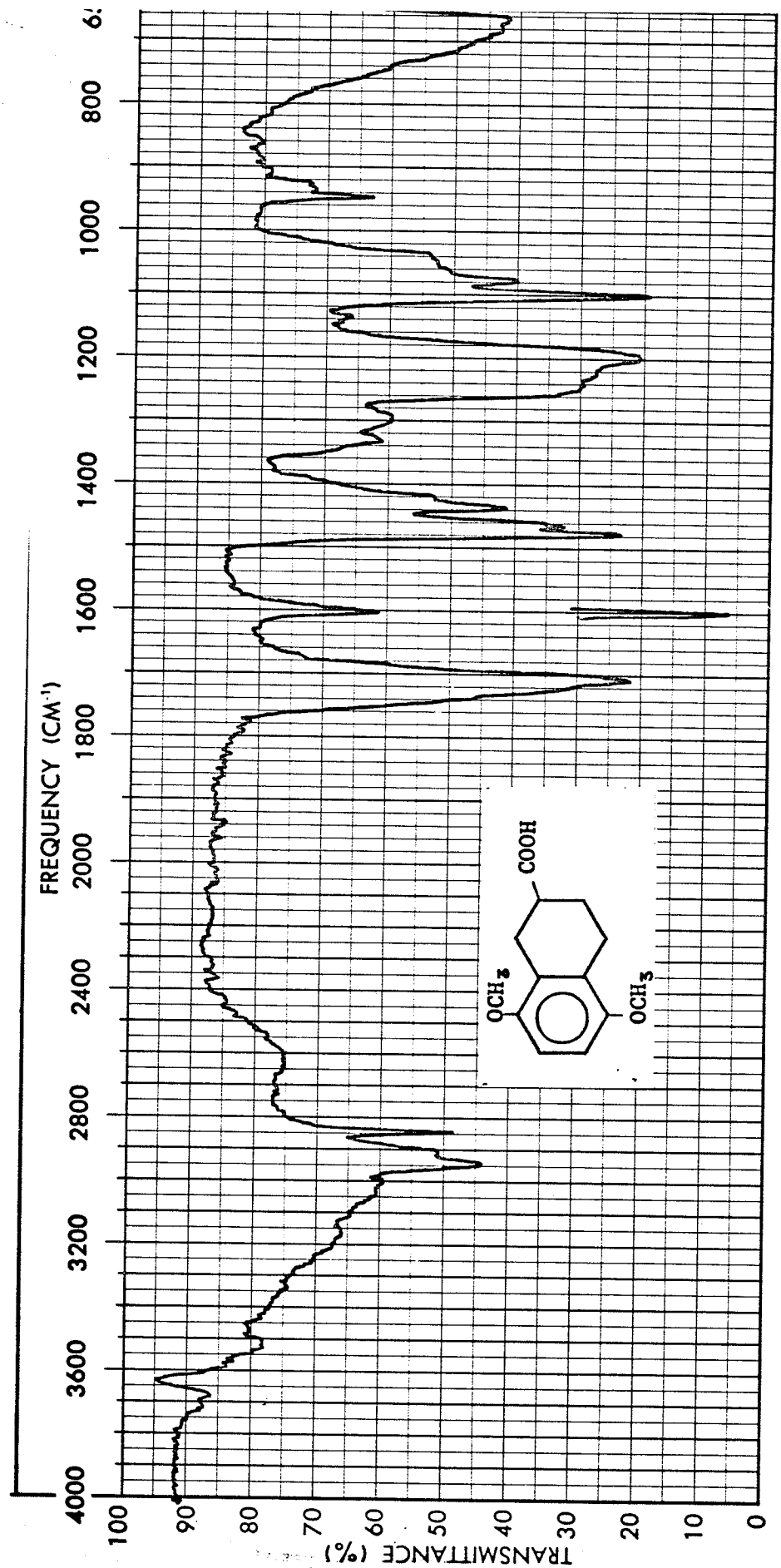
Infrared spectrum no. 5: 2',5'-dimethoxybenzylsuccinic anhydride (XVII), in CH_2Cl_2 solution.

Figure XV



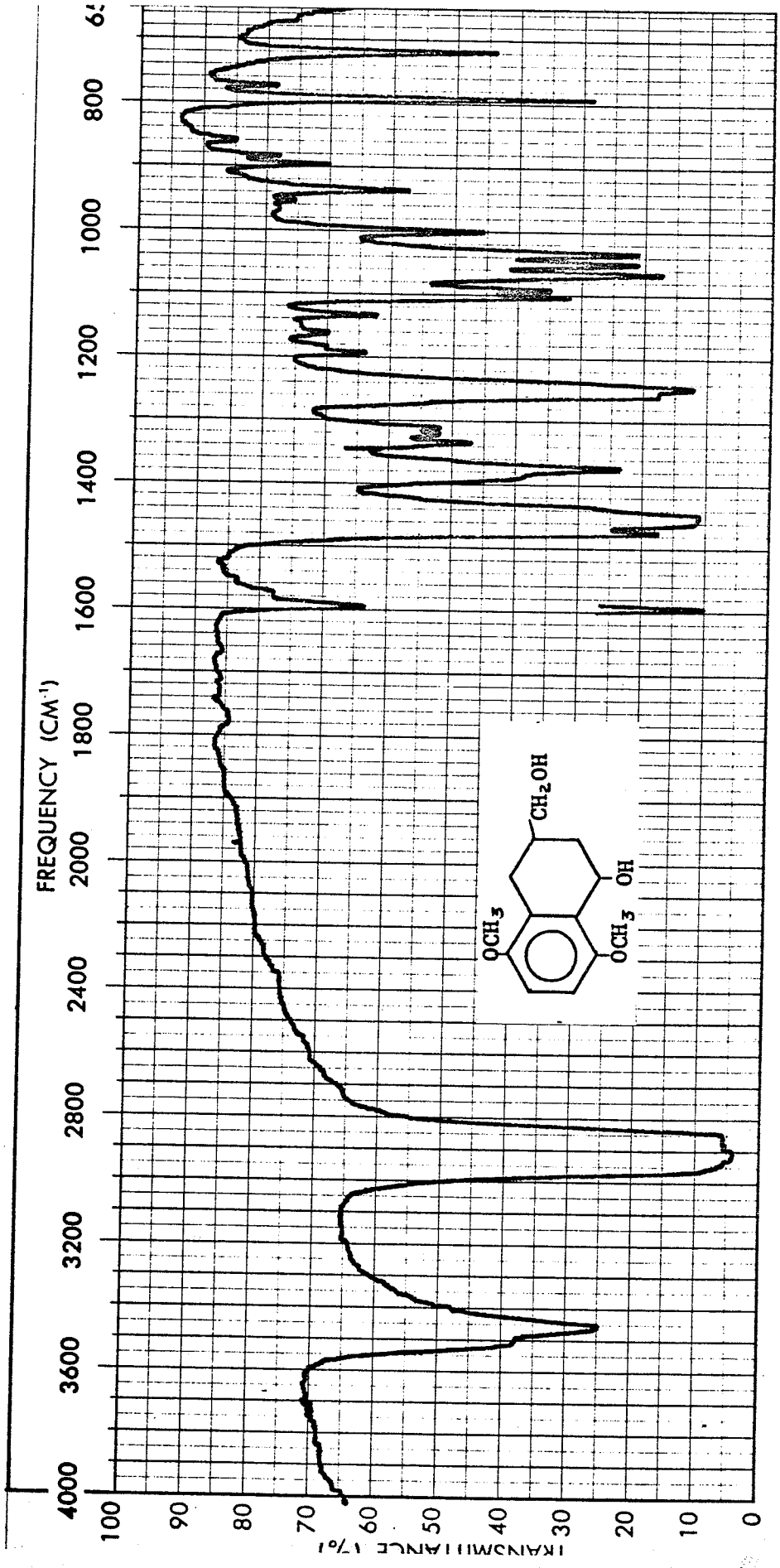
Infrared spectrum no. 6: 3-carbohydroxy-5,8-dimethoxy-1-tetralone (XVIII), nujol mull.

Figure XVI



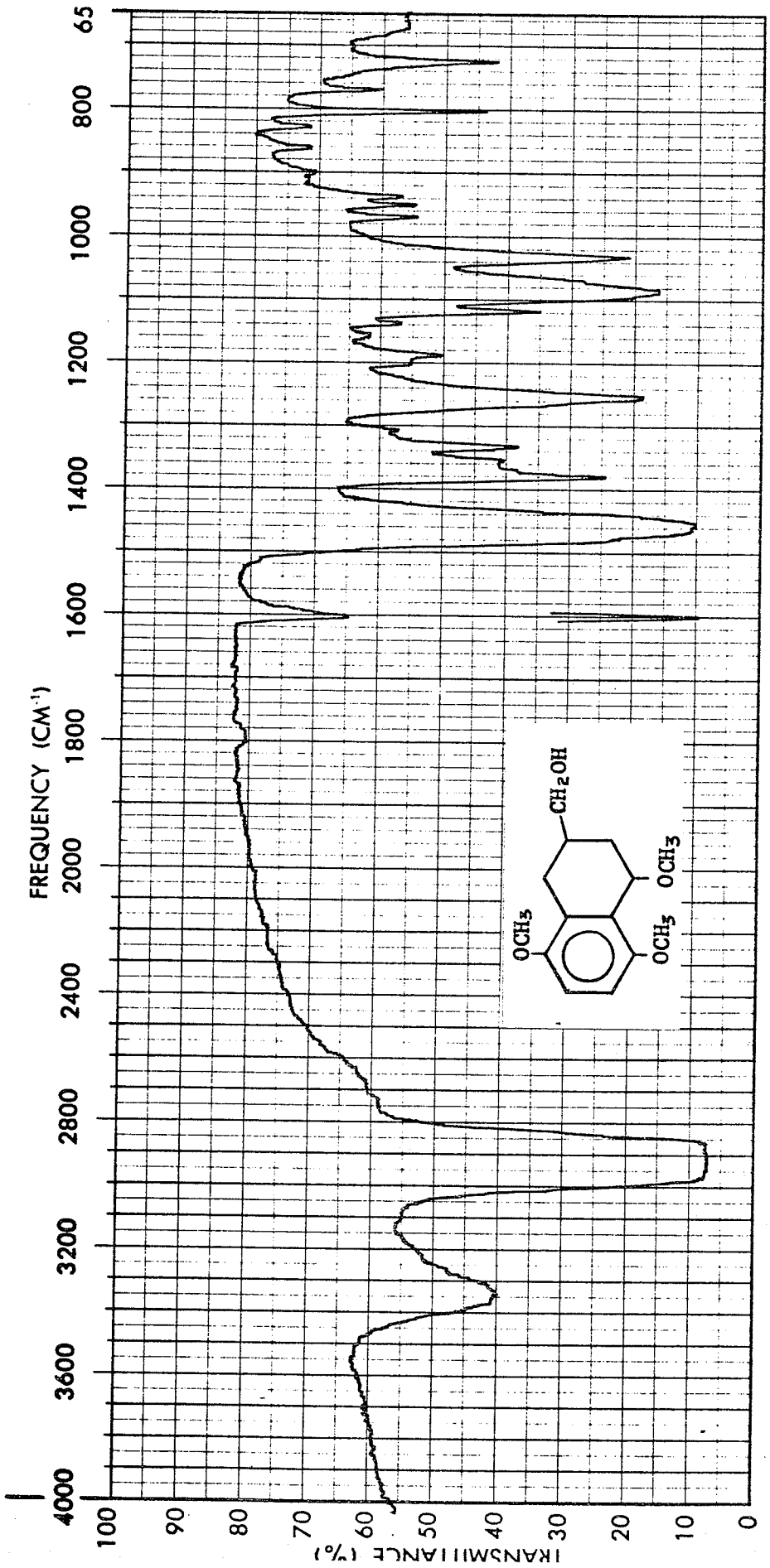
Infrared spectrum no. 7: 2-carbohydroxy-5,8-dimethoxytetralin (XXV), in $CHCl_3$ solution.

Figure XVII



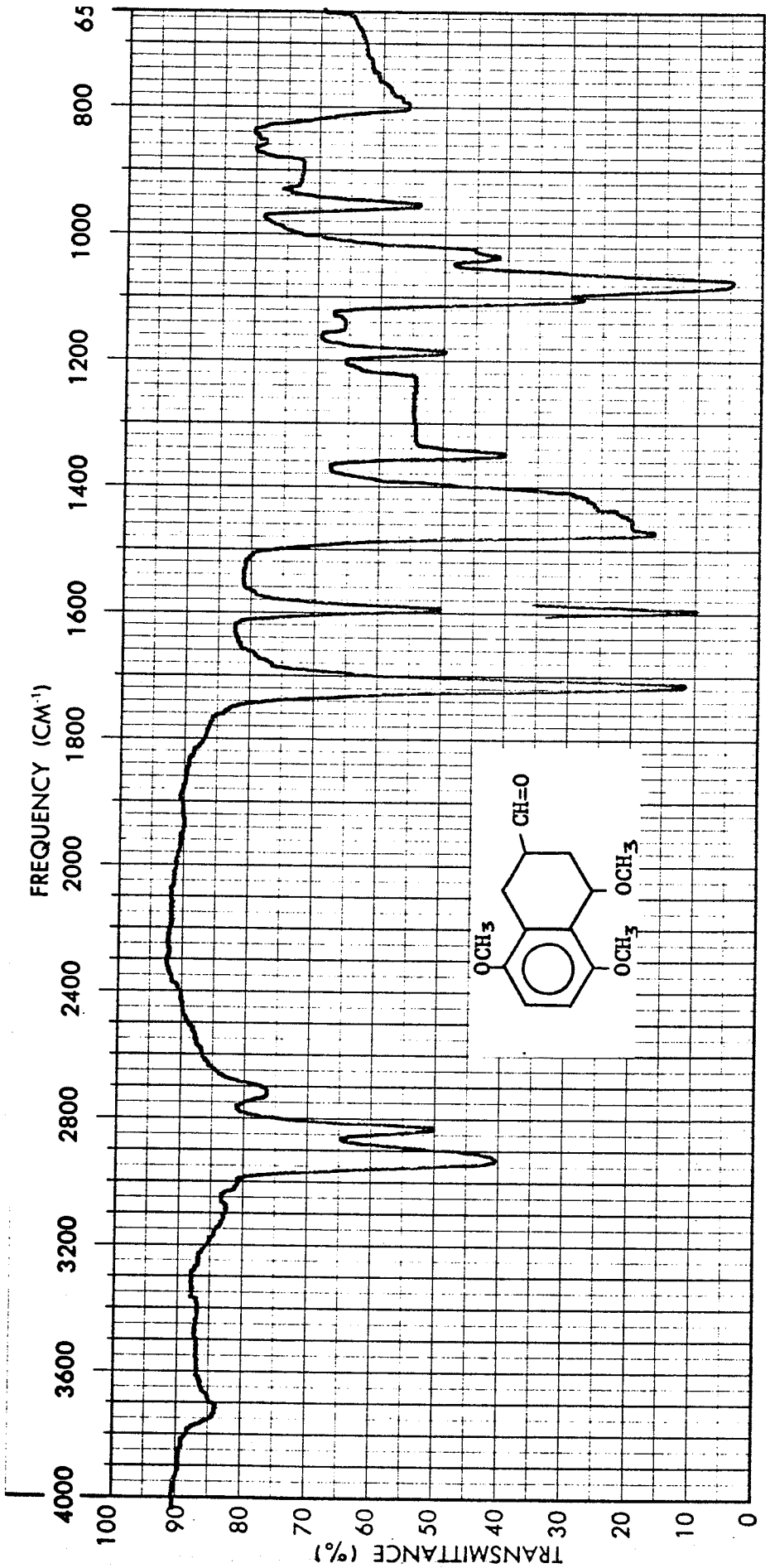
Infrared spectrum no. 8: 1-hydroxy-3-hydroxymethyl-5,8-dimethoxytetralin (XIX), nujol mull.

Figure XVIII



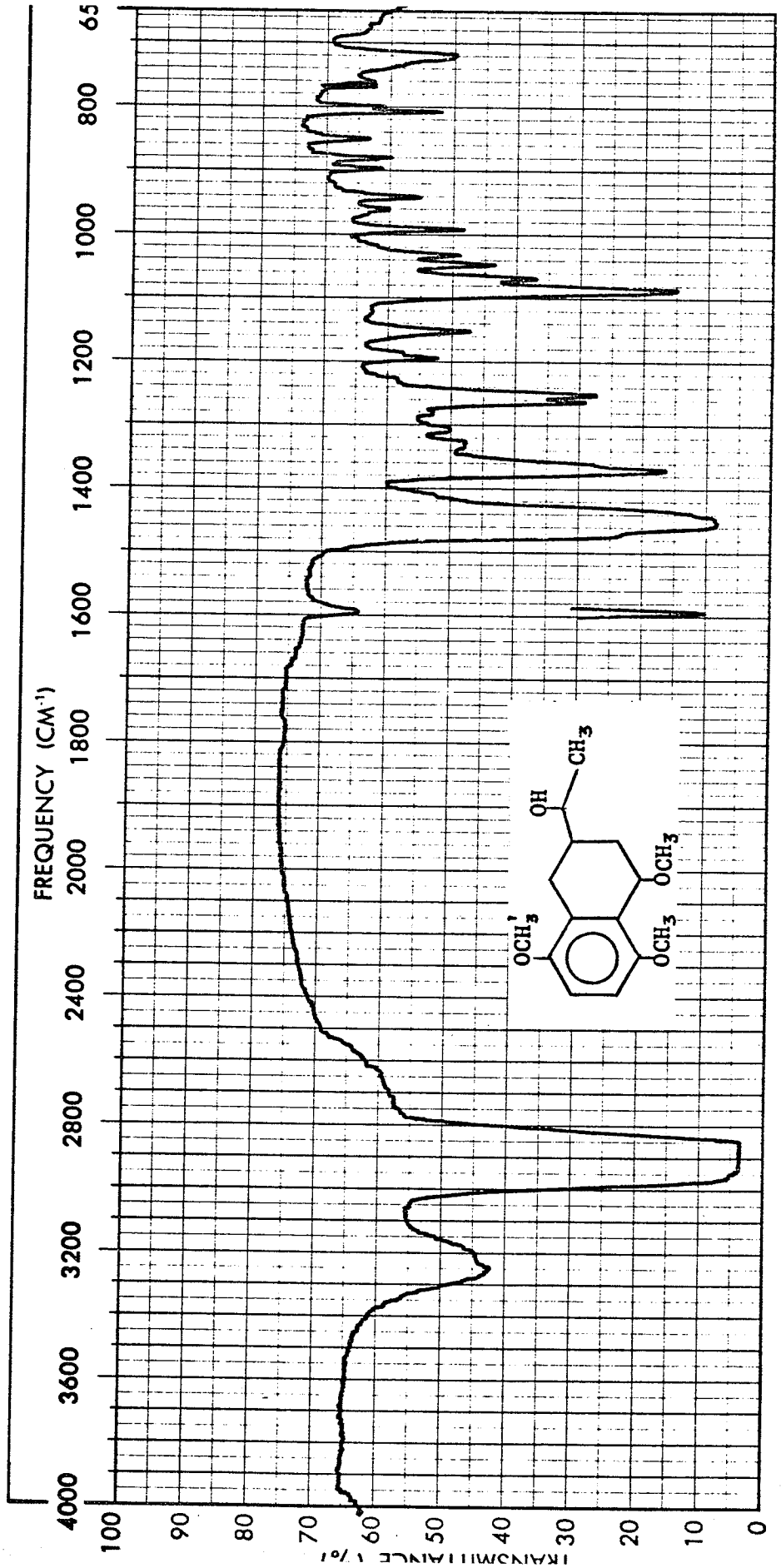
Infrared spectrum no. 9: 1,5,8-trimethoxy-3-hydroxymethyltetralin (XX), nujol mull.

Figure XIX



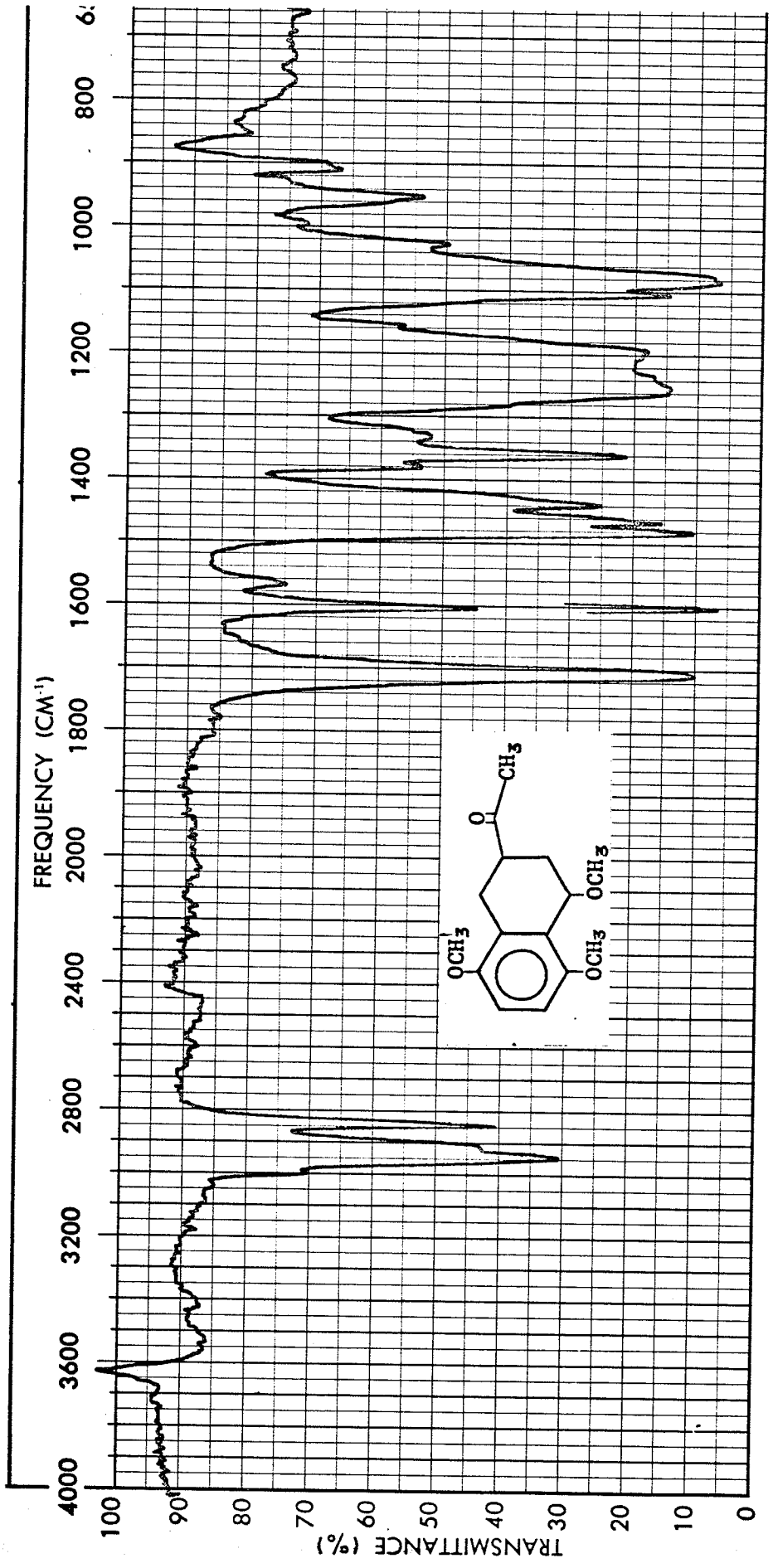
Infrared spectrum no. 10: 1,5,8-trimethoxy-3-formyltetralin (XXI), in CH_2Cl_2 solution.

Figure XX



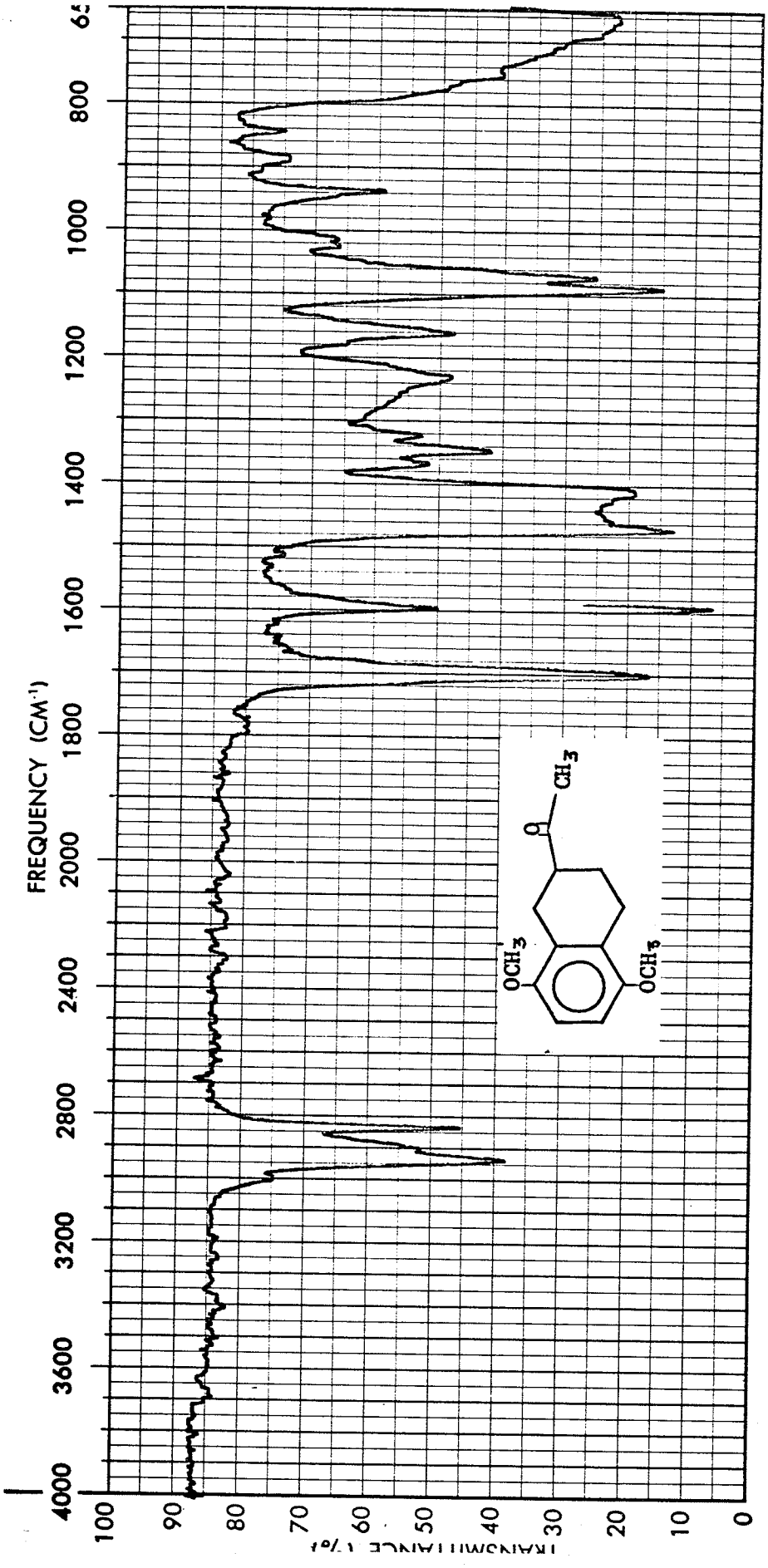
Infrared spectrum no. 11: 1,5,8-trimethoxy-3-(1'-hydroxyethyl) tetralin (XXII), nujol mull.

Figure XXI



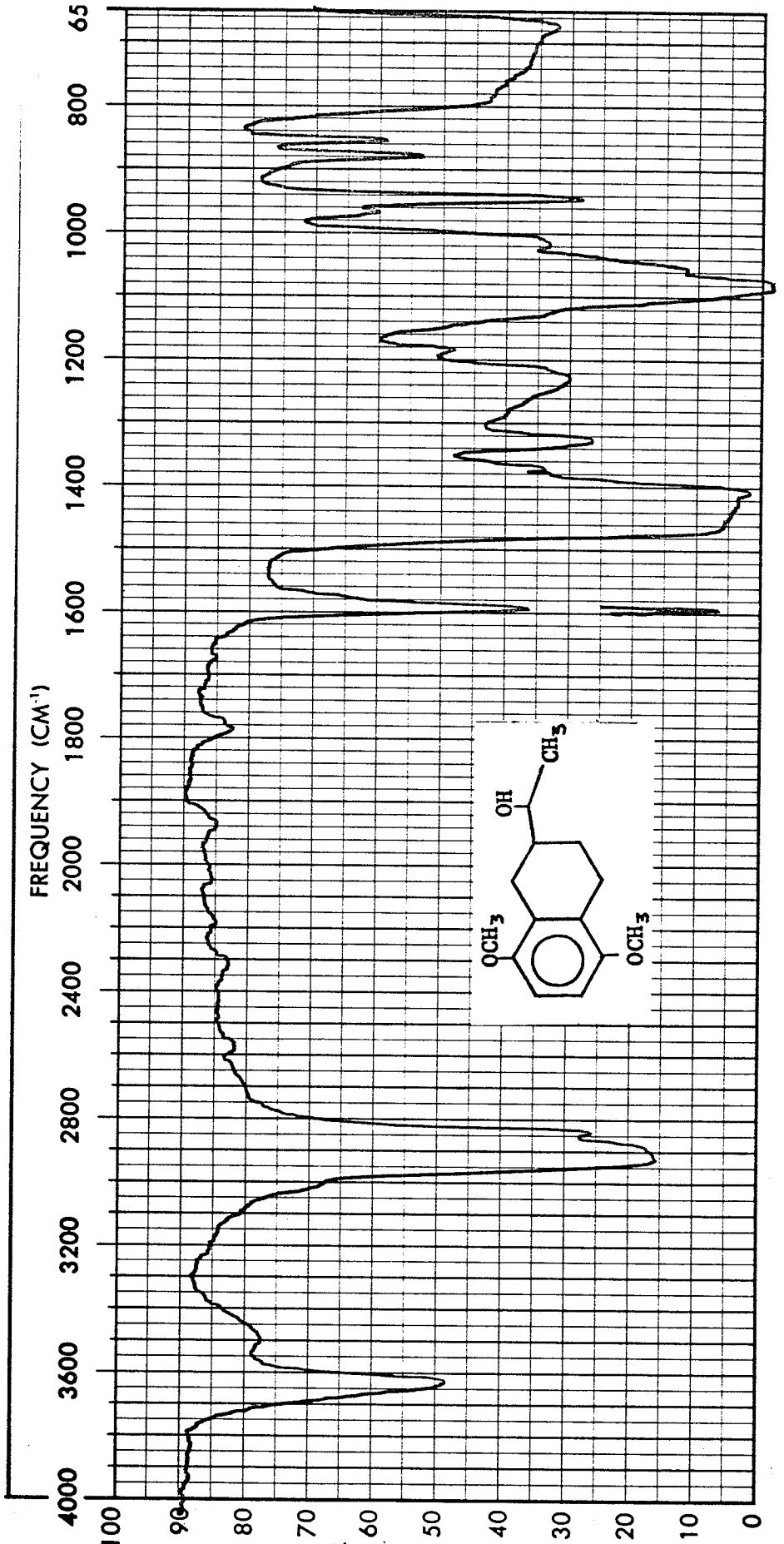
Infrared spectrum no. 12: 1,5,8-trimethoxy-3-acetyltetralin (XXIII), in $CHCl_3$ solution.

Figure XXII



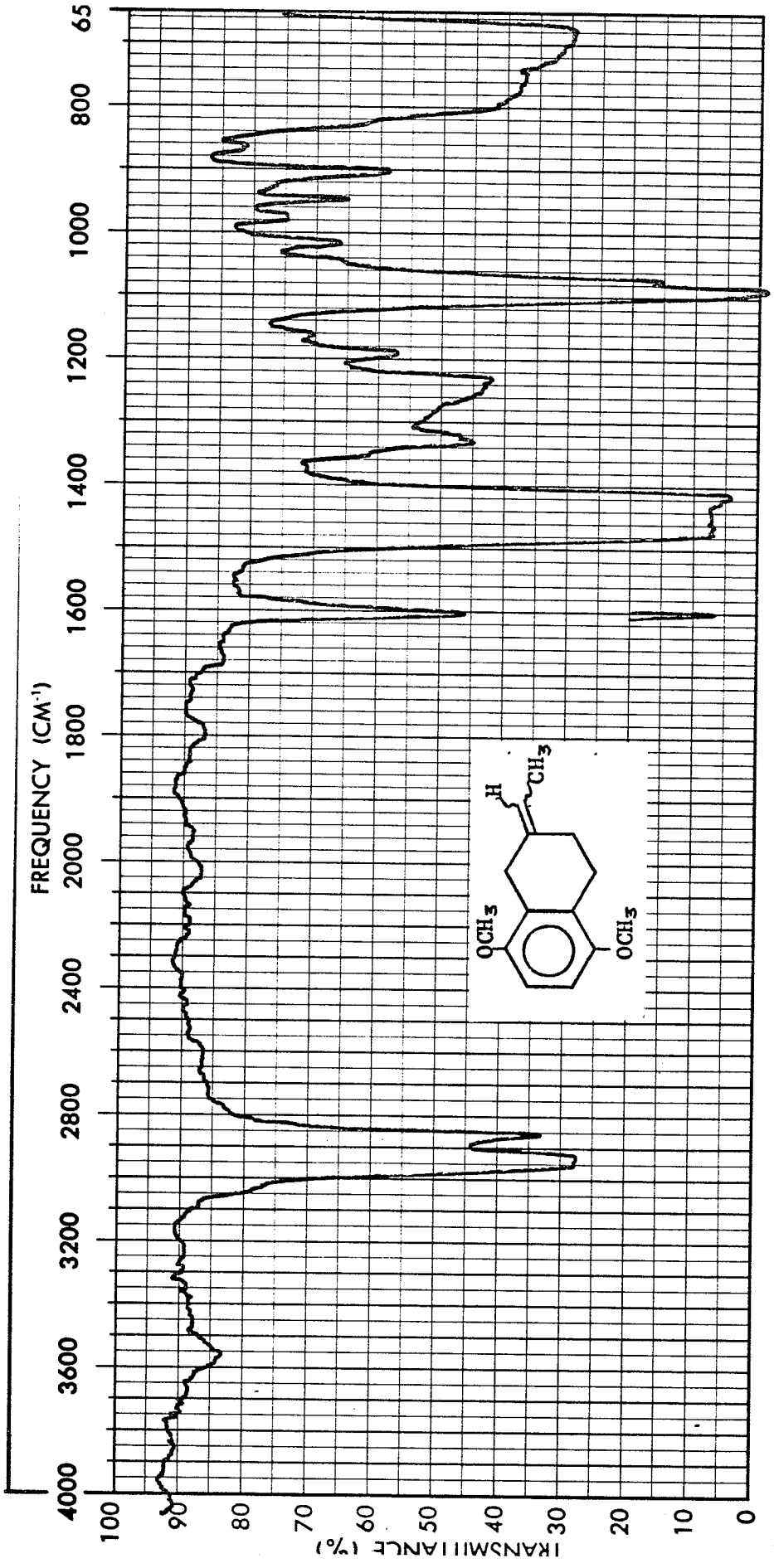
Infrared spectrum no. 13: 2-acetyl-5,8-dimethoxytetralin (XXIV), in CH_2Cl_2 solution.

Figure XXIII



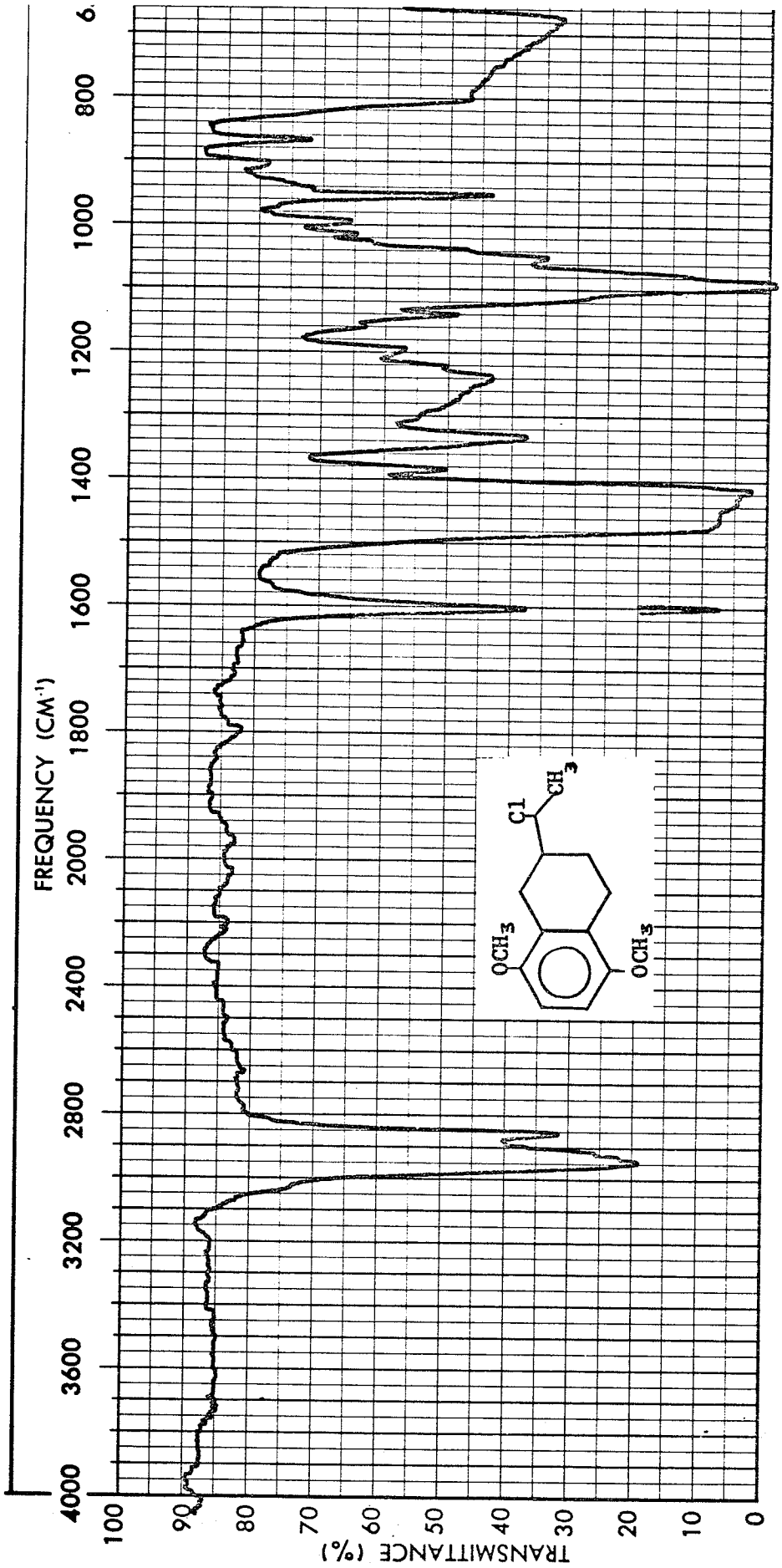
Infrared spectrum no. 14: 2-(1'-hydroxyethyl)-5,8-dimethoxytetralin (XXVI), in CH_2Cl_2 solution.

Figure XIV



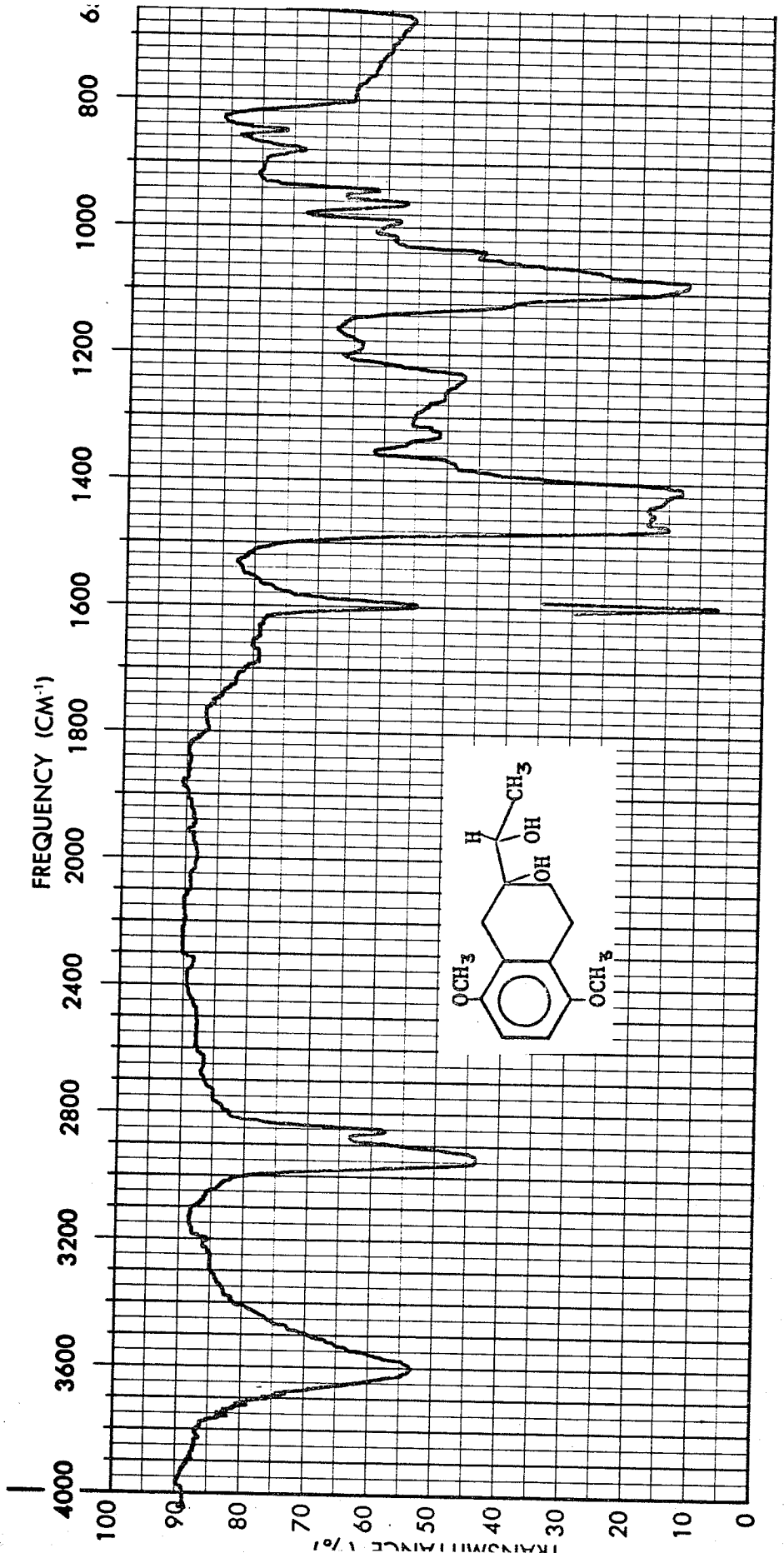
Infrared spectrum no. 15: Olefin mixture (XXVII), in CH_2Cl_2 solution.

Figure XXV



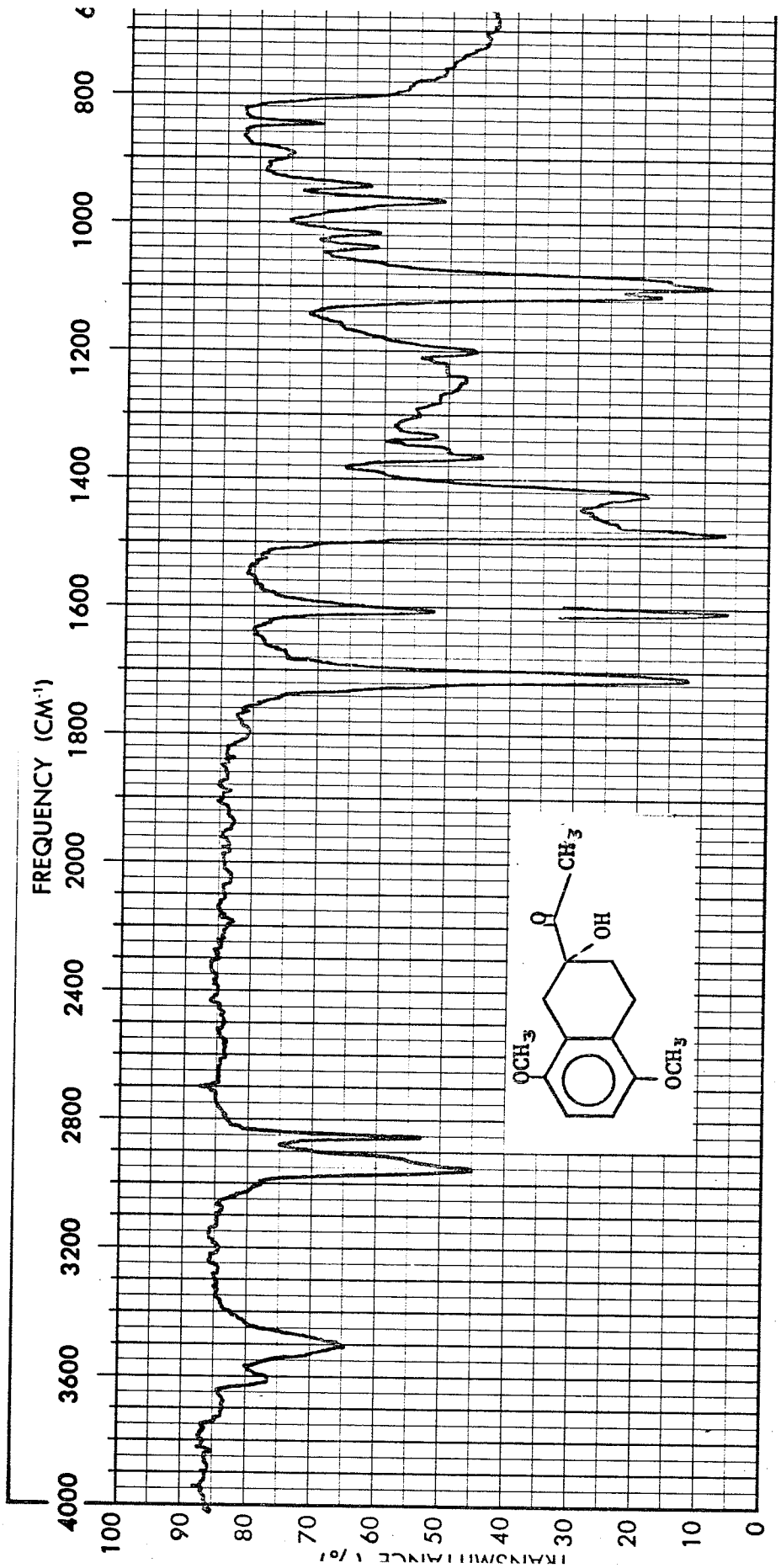
Infrared spectrum no. 16: 2-(1'-chloroethyl)-5,8-dimethoxytetralin (XXVIII), in CH_2Cl_2 solution.

Figure XXVI



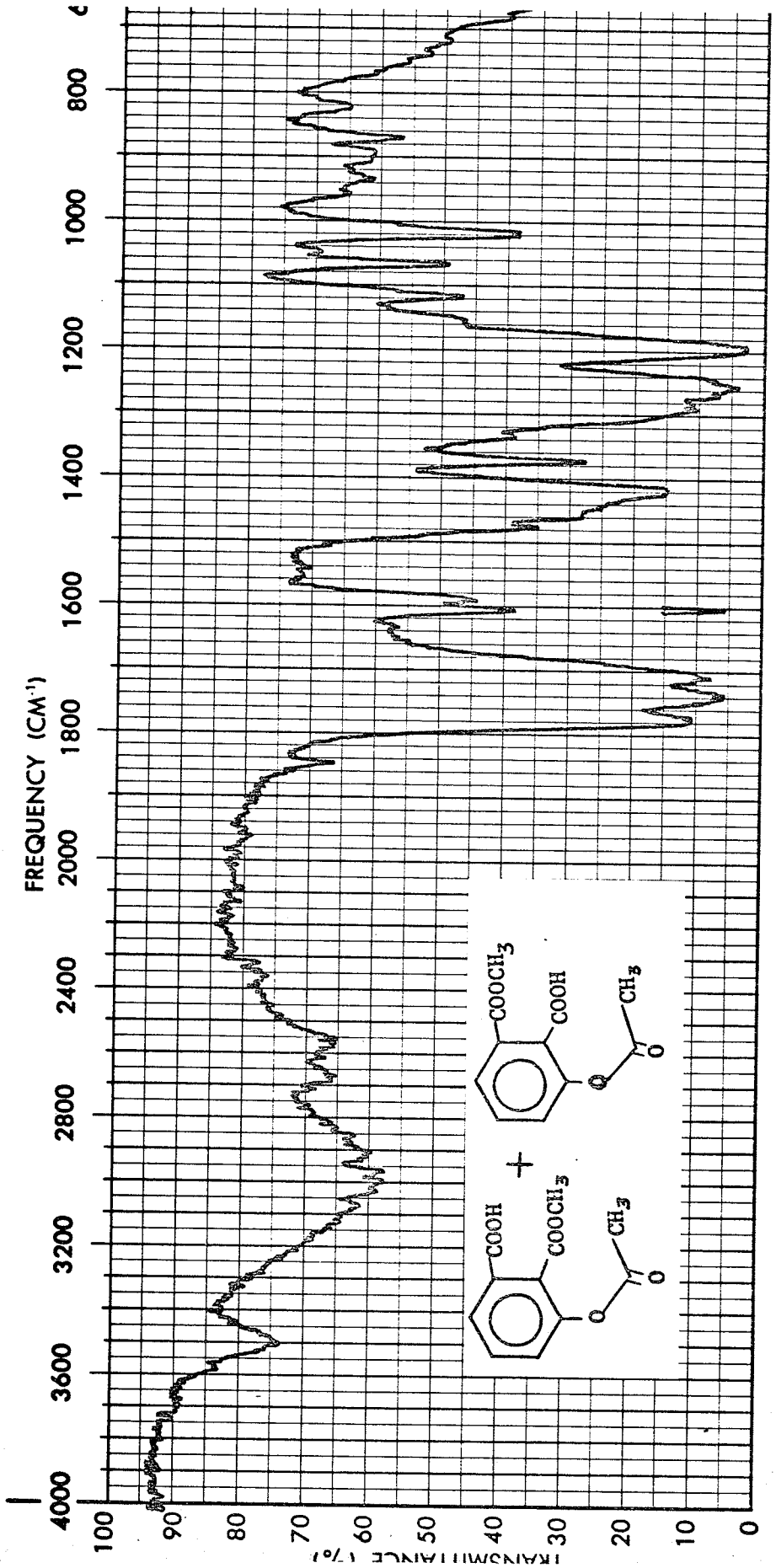
Infrared spectrum no. 17: 2-hydroxy-2-(1'-hydroxyethyl)-5,8-dimethoxytetralin (XXIX), in CH_2Cl_2 solution.

Figure XXVII



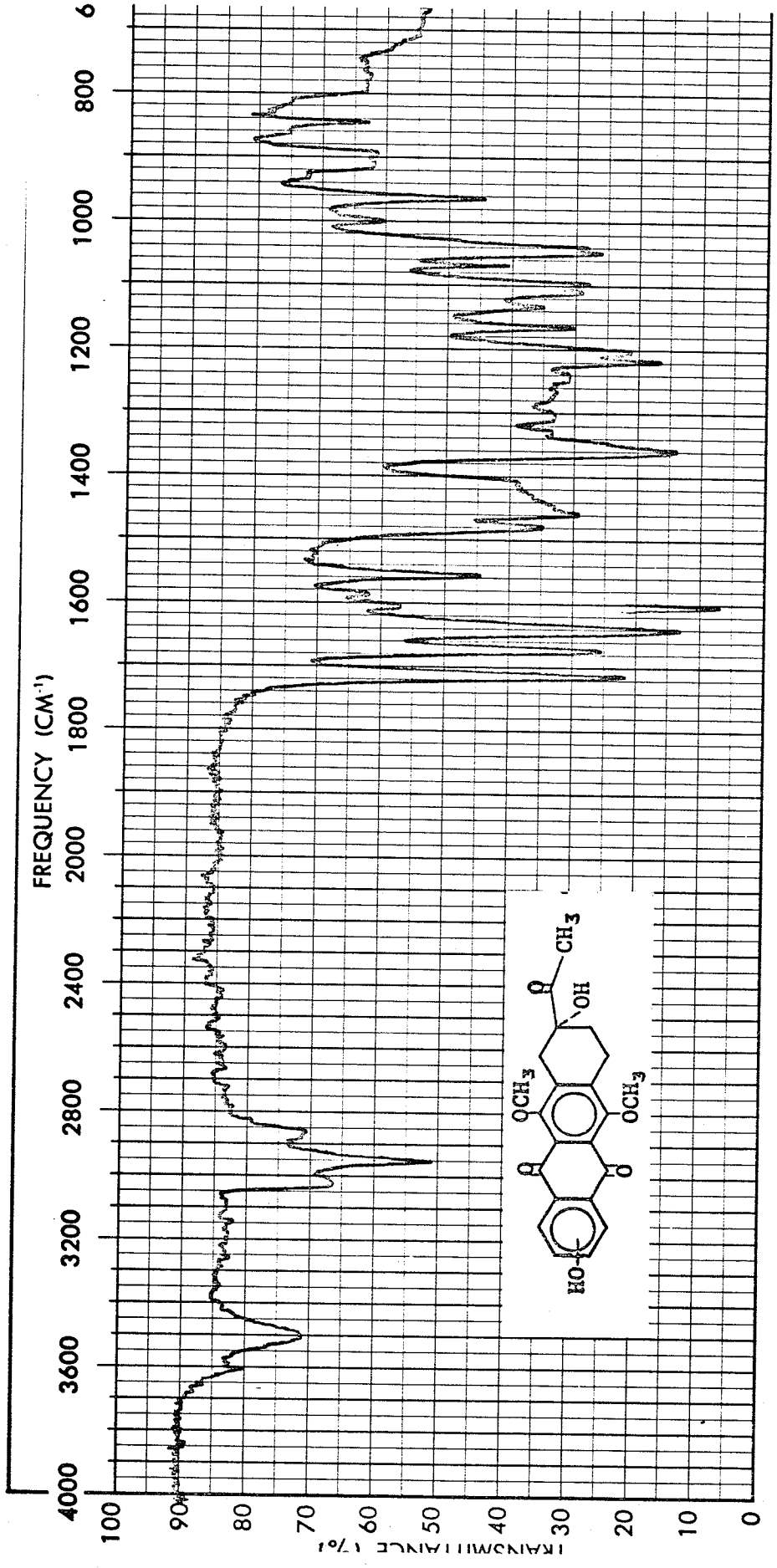
Infrared spectrum no. 18: 2-acetyl-2-hydroxy-5,8-dimethoxytetralin (XXXI), in CH_2Cl_2 solution.

Figure XXVIII



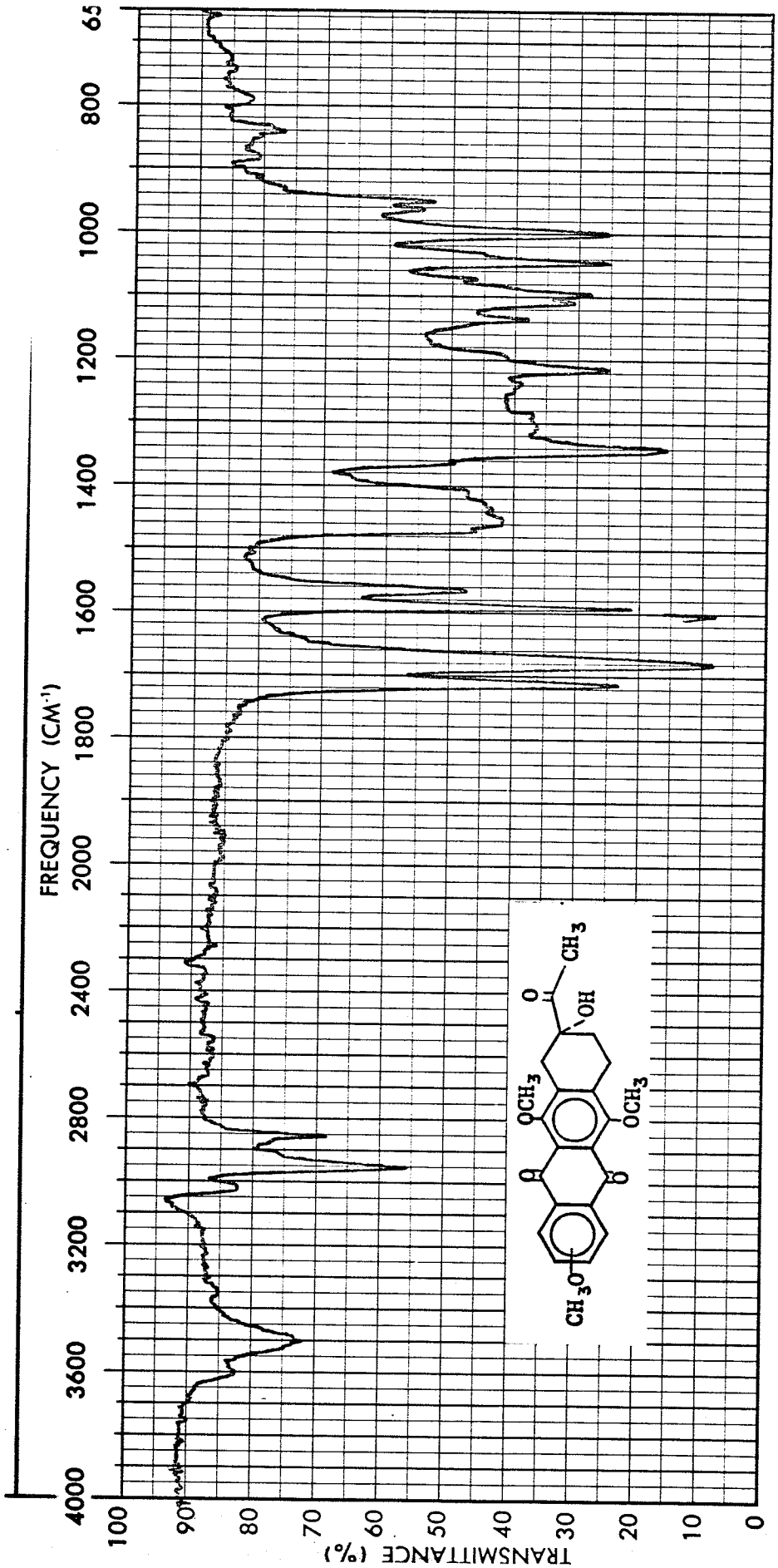
Infrared spectrum no. 19: Acetoxycarbomethoxybenzoic acid mixture (XXXII), in $CHCl_3$ solution.

Figure XXIX



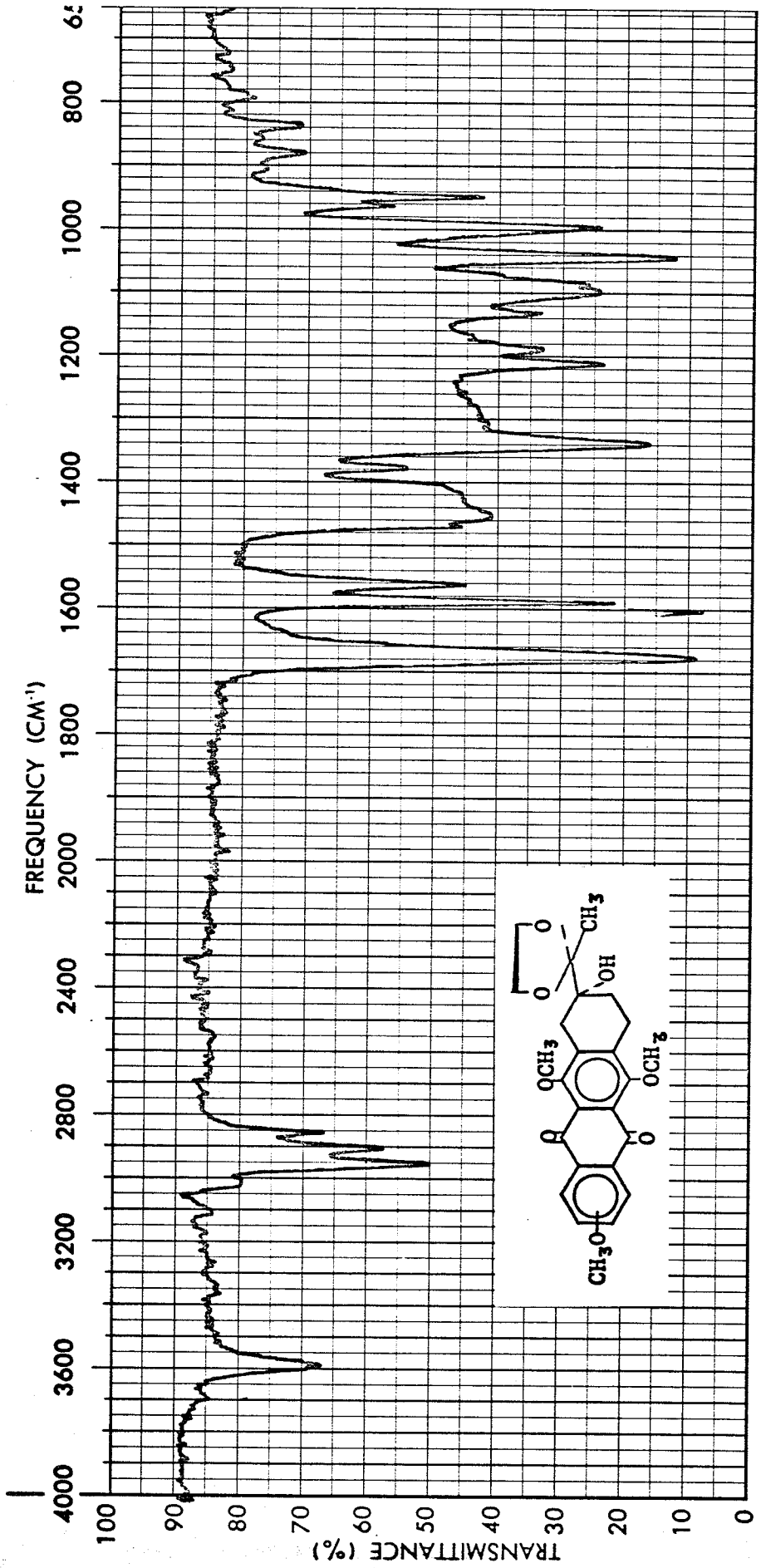
Infrared spectrum no. 20: Isomeric hydronaphthacene quinone mixture (XXXV), in CH_2Cl_2 solution.

Figure XXX



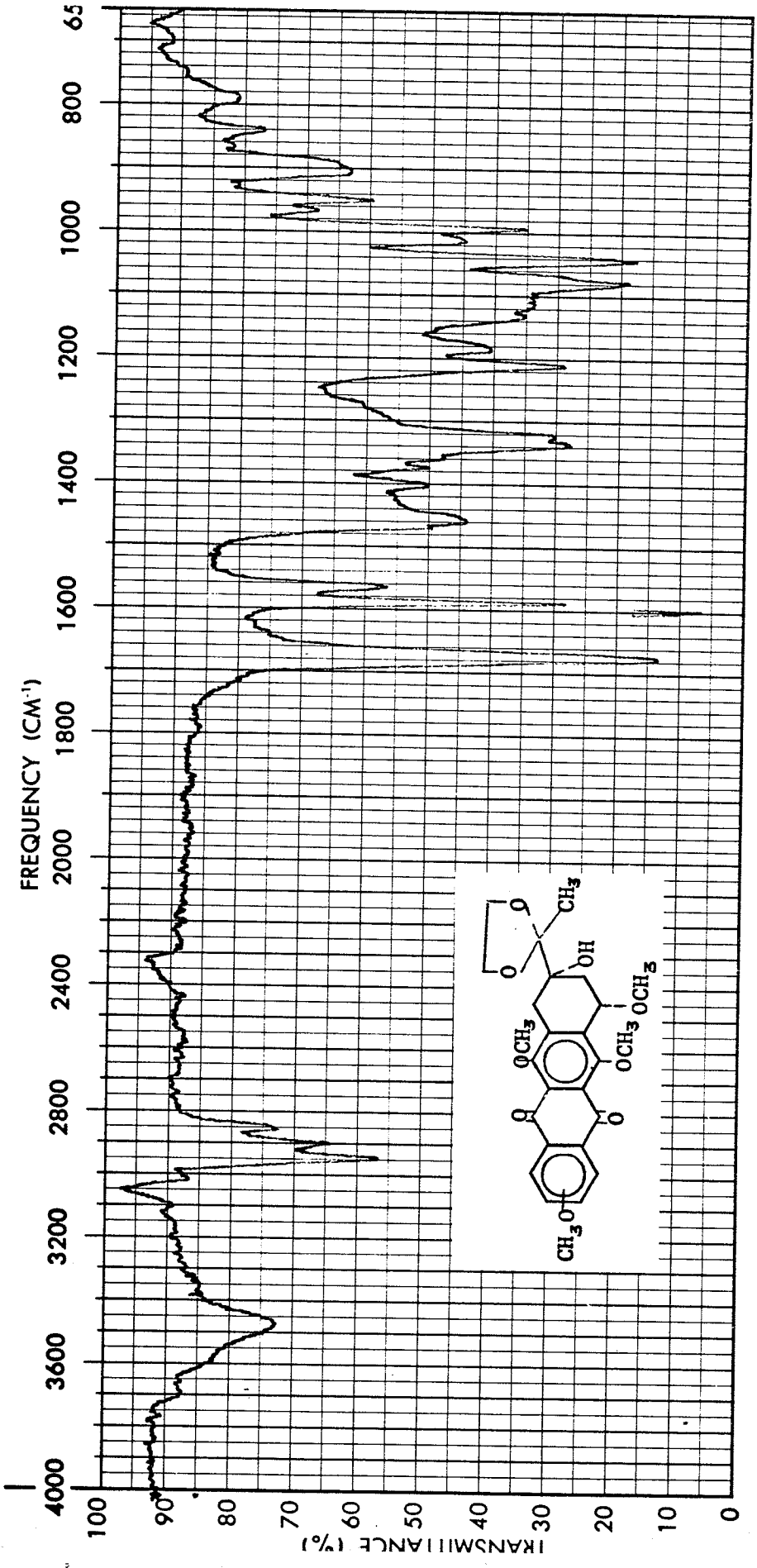
Infrared spectrum no. 21: Isomeric hydronaphthacene quinone mixture (XXXVI), in CH_2Cl_2 solution.

Figure XXXI



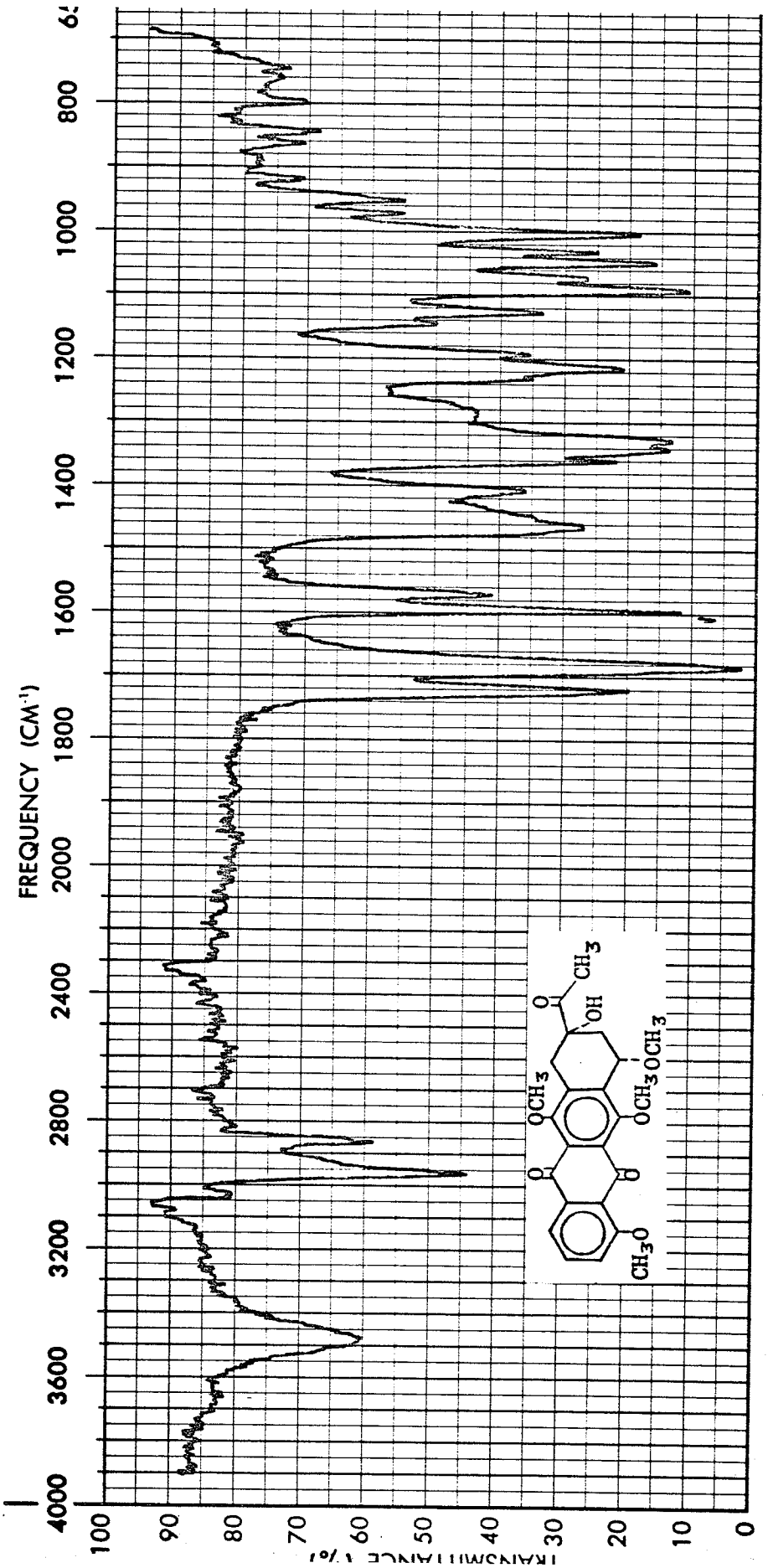
Infrared spectrum no. 22: Isomeric hydronaphthacene quinone ketal mixture (XXXVII), in CH_2Cl_2 solution.

Figure XXXII



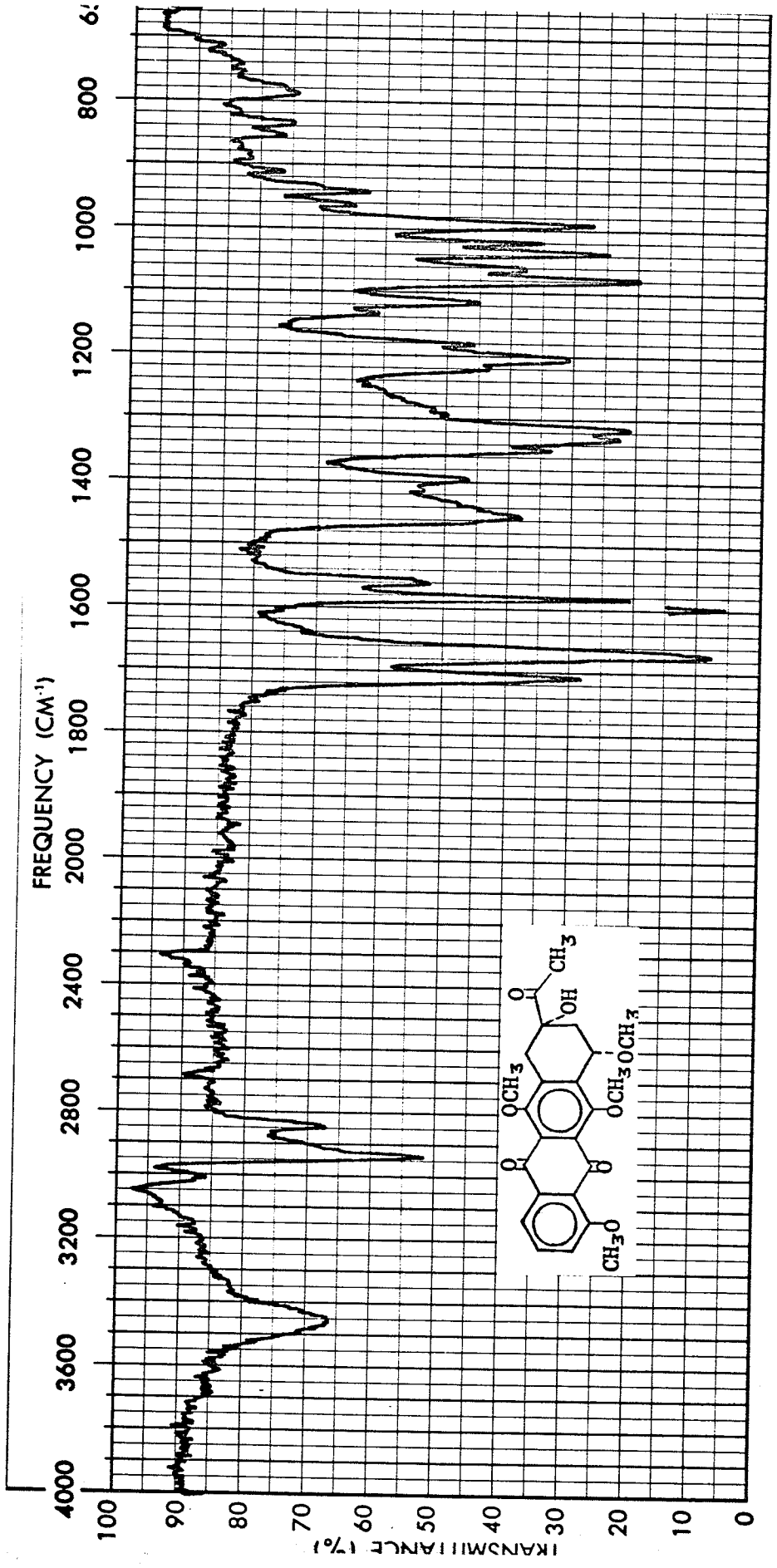
Infrared spectrum no. 23: Isomeric hydronaphthacene quinone ketal mixture (XLI), in CH_2Cl_2 solution.

Figure XXXIII



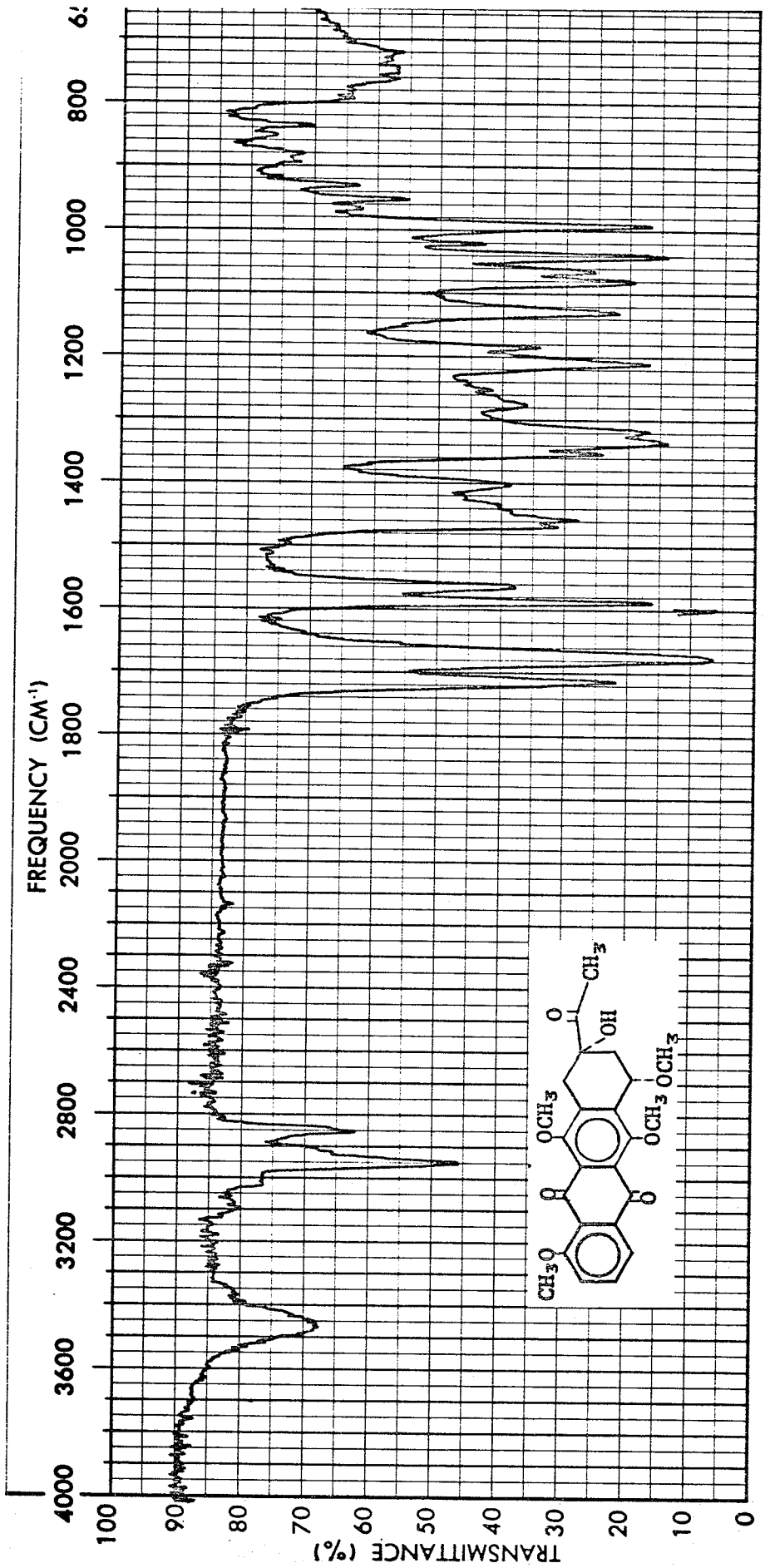
Infrared spectrum no. 24: Synthetic daunomycinone trimethyl ether (XLVI), in CH_2Cl_2 solution.

Figure XXXIV



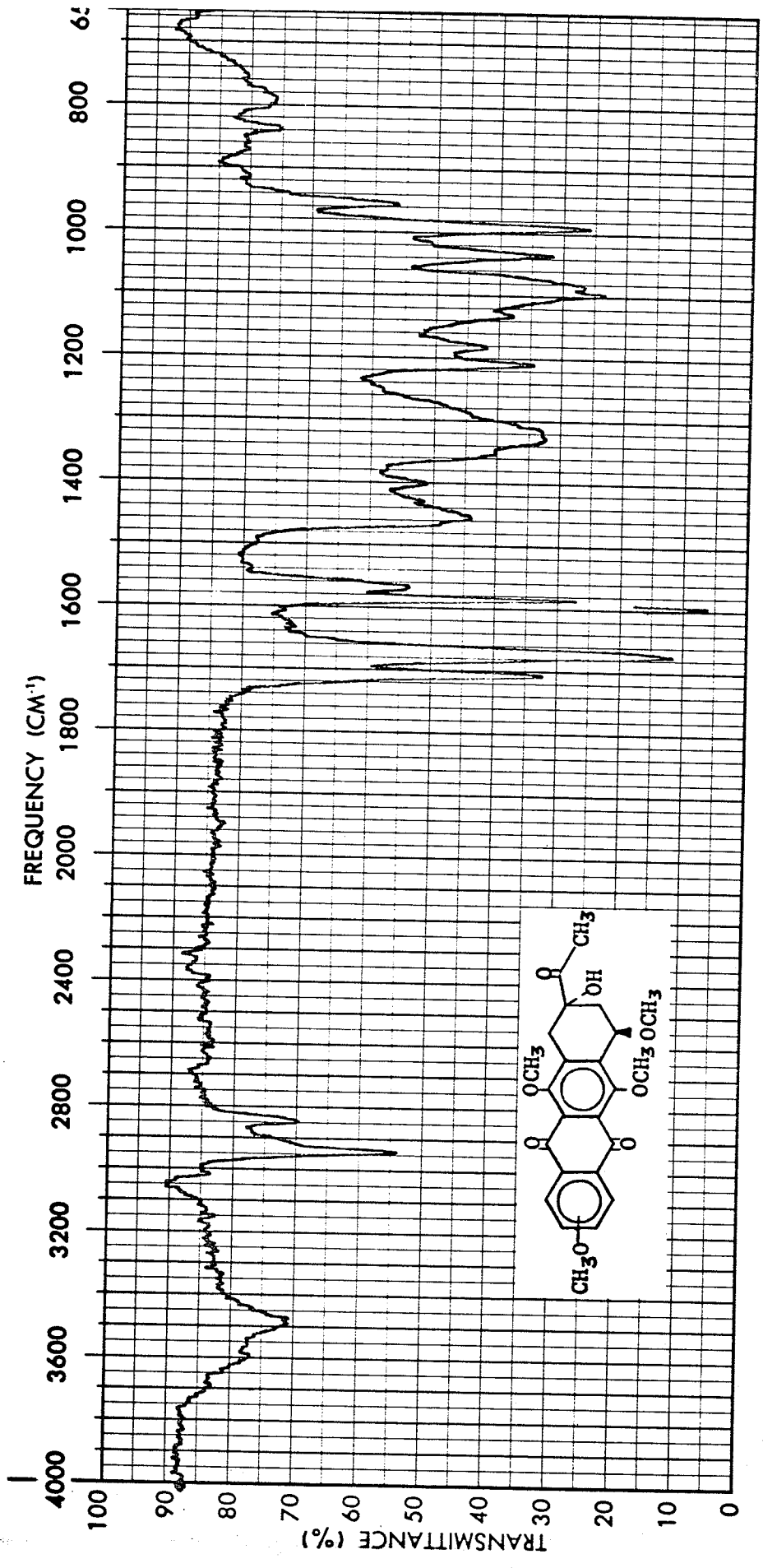
Infrared spectrum no. 25: Daunomycinone trimethylether (from natural daunomycinone), in CH_2Cl_2 solution.

Figure XXXV



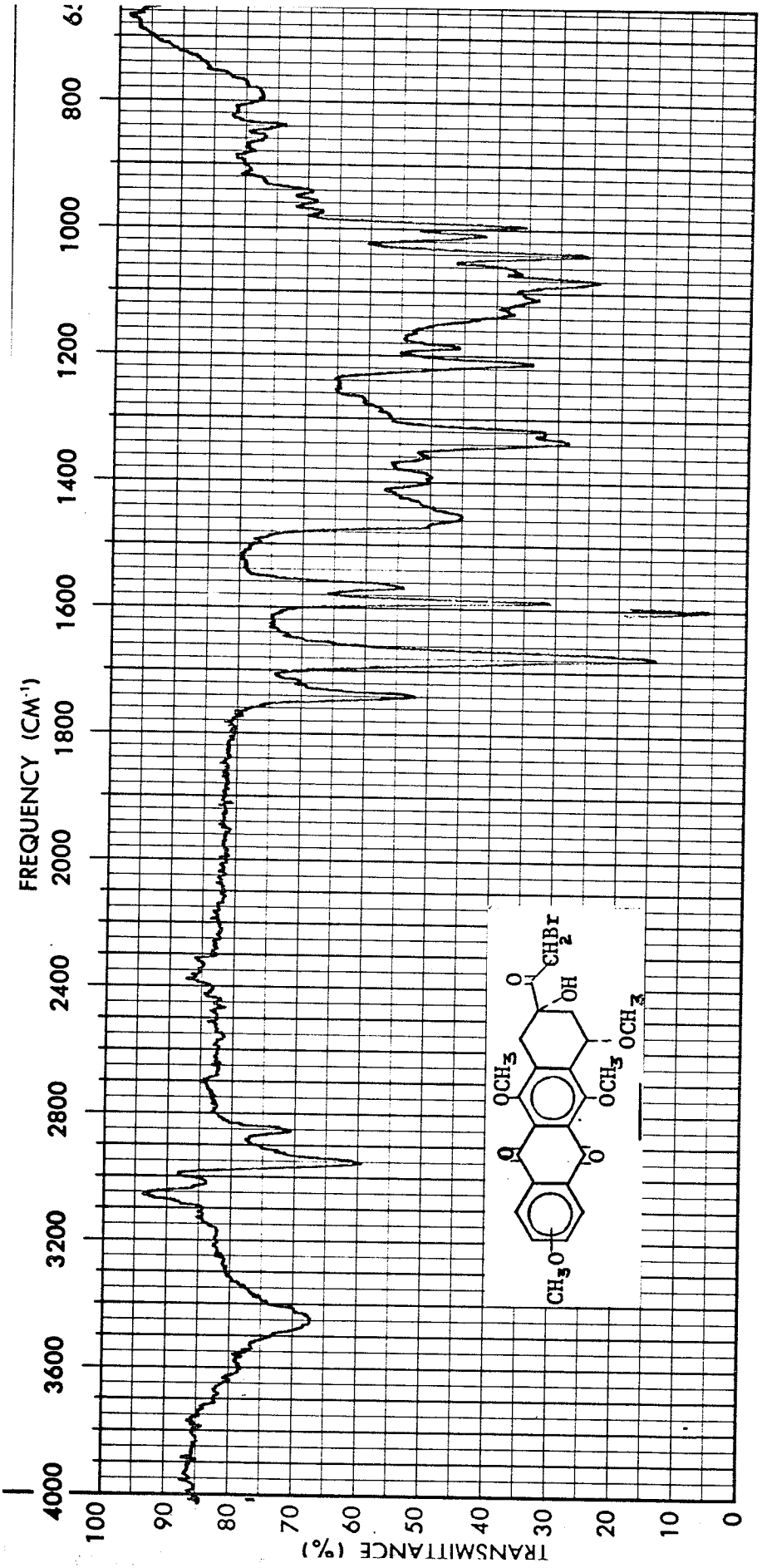
Infrared spectrum no. 26: Synthetic isodaunomycinone trimethylether (XLV), in CH_2Cl_2 solution.

Figure XXXVI



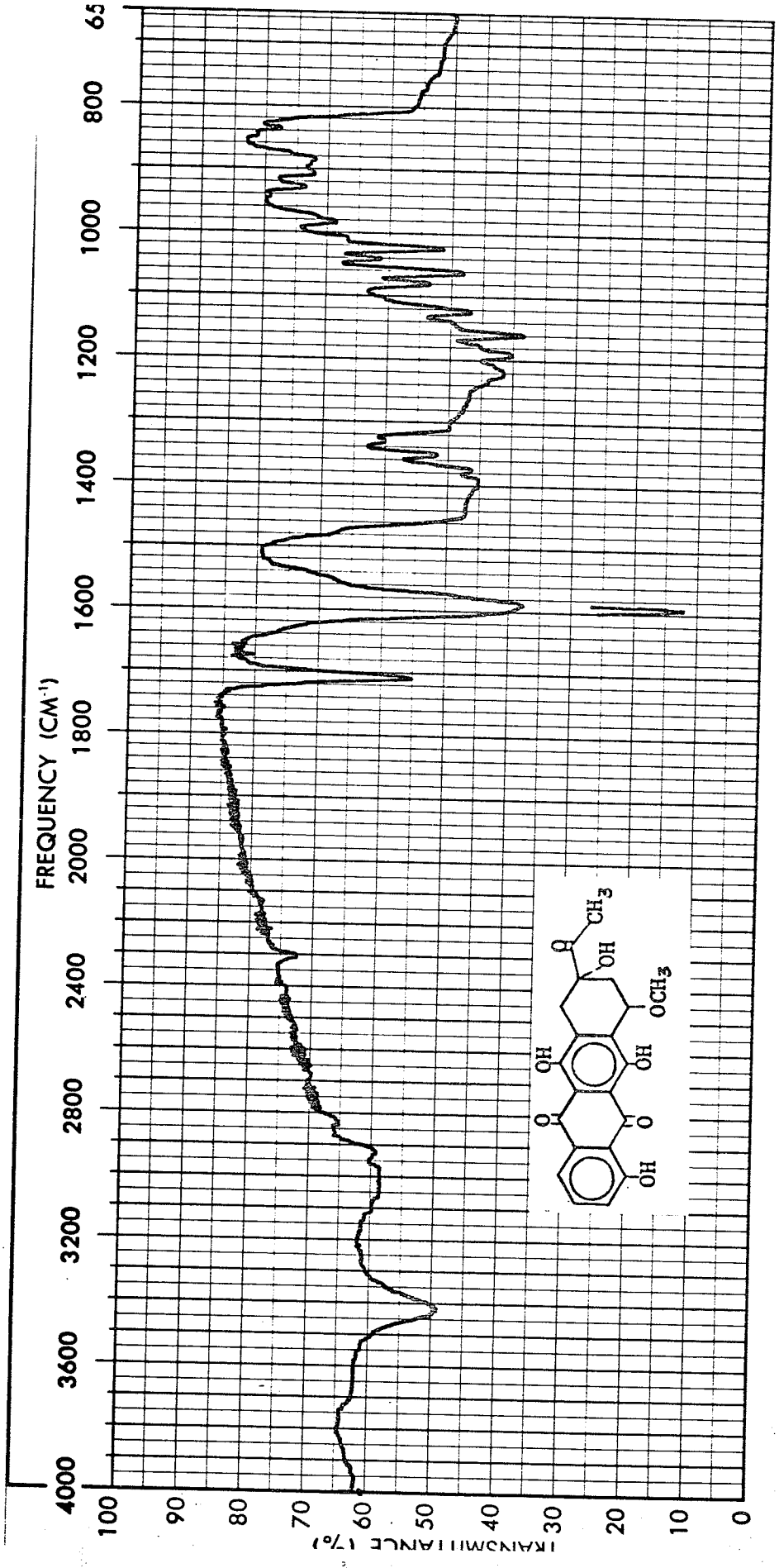
Infrared spectrum no. 27: Isomeric hydronaphthacene quinone mixture (XLII), in CH_2Cl_2 solution.

Figure XXXVII



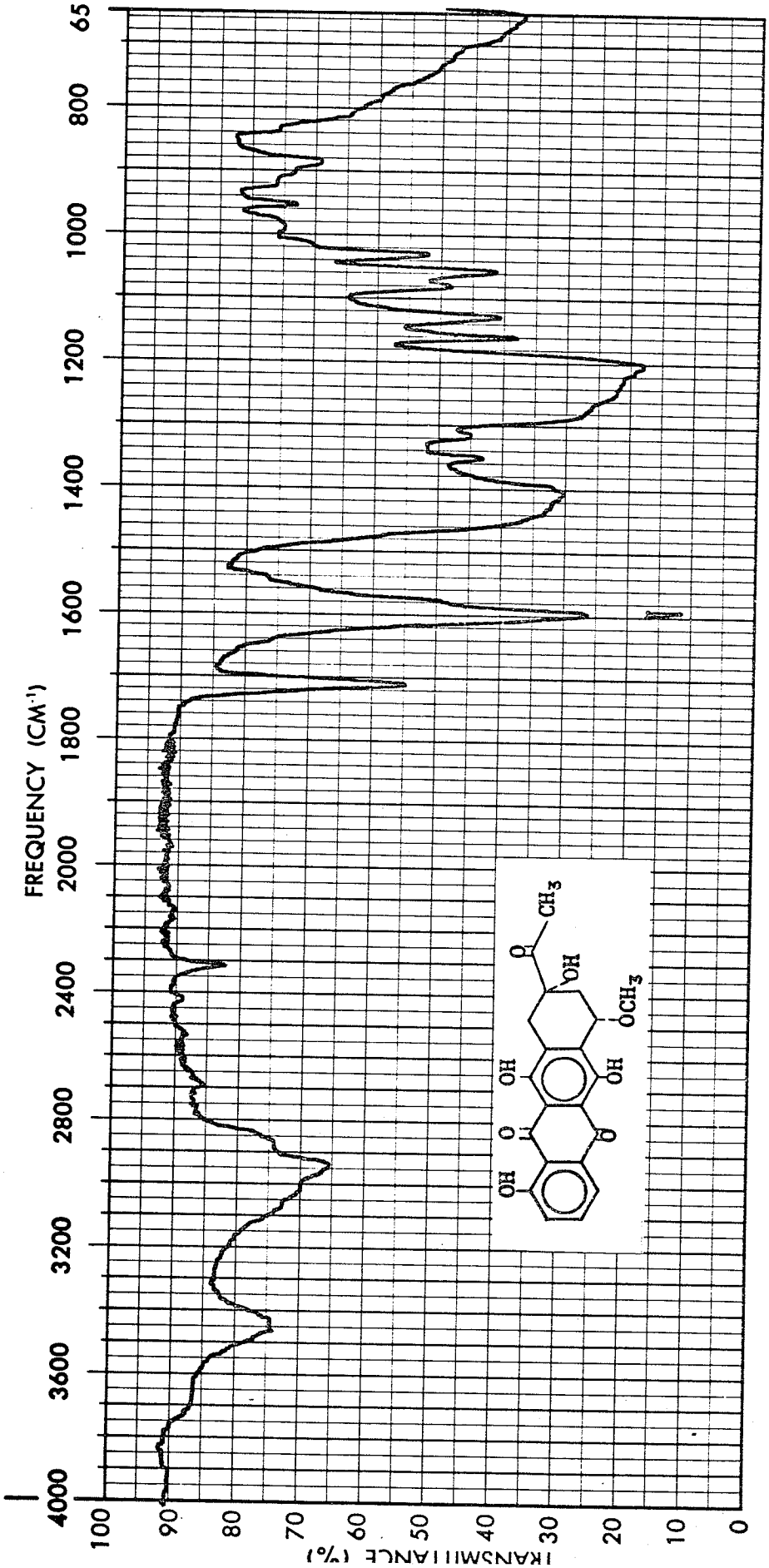
Infrared spectrum no. 28: Isomeric hydronaphthacene quinone-$\mathcal{L}$-bromoketone mixture (XLIV), in CH_2Cl_2 solution.

Figure XXXVIII



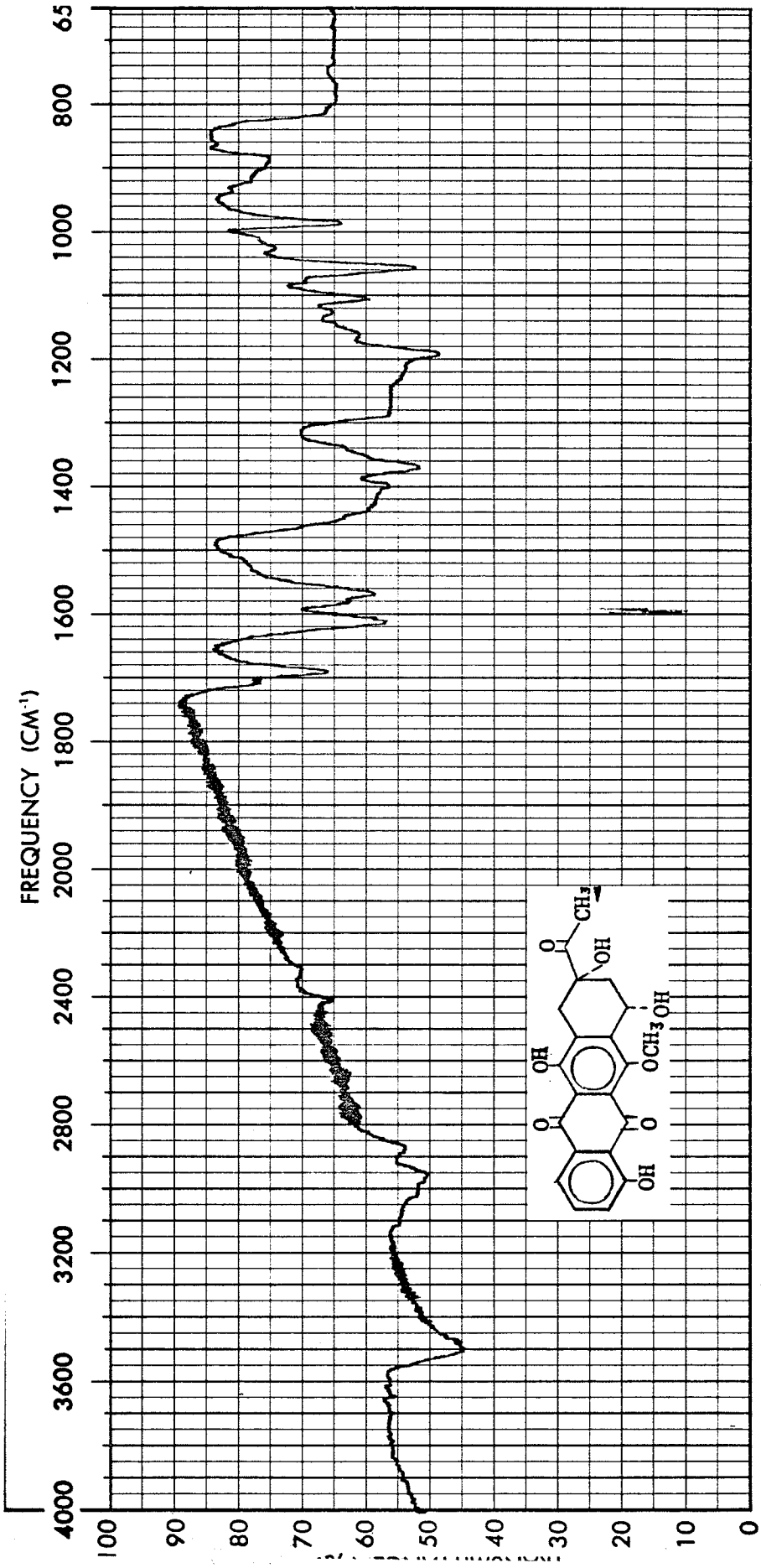
Infrared spectrum no. 29: Racemic 4-O-demethyl-7-O-methyldaunomycinone (XLVII), in CH_2Cl_2 solution.

Figure XXXIX



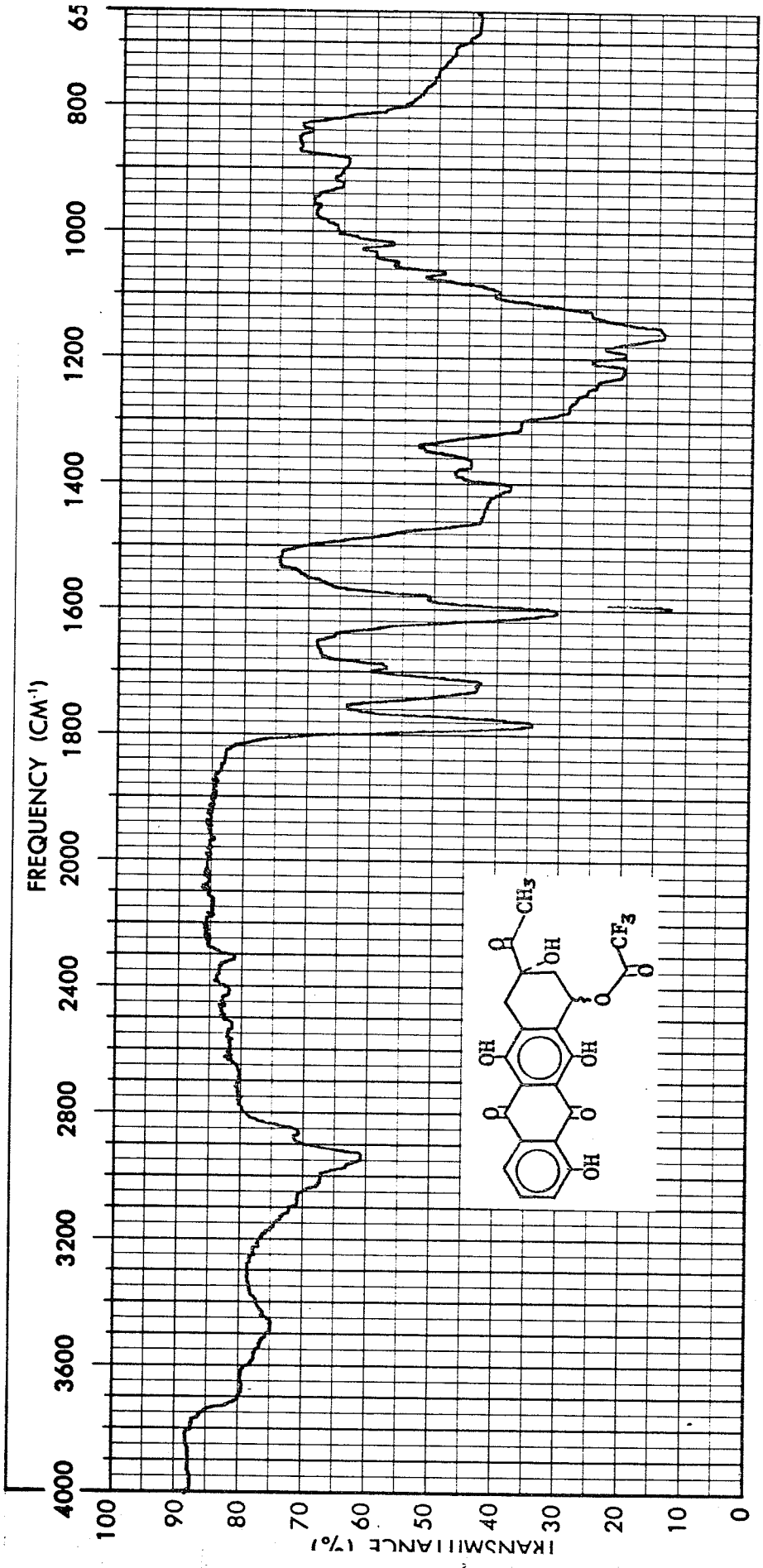
Infrared spectrum no. 30: Racemic 1-hydroxy-4-demethoxy-7-O-methyldaunomycinone (XLVIII), in CH_2Cl_2 solution.

Figure XL



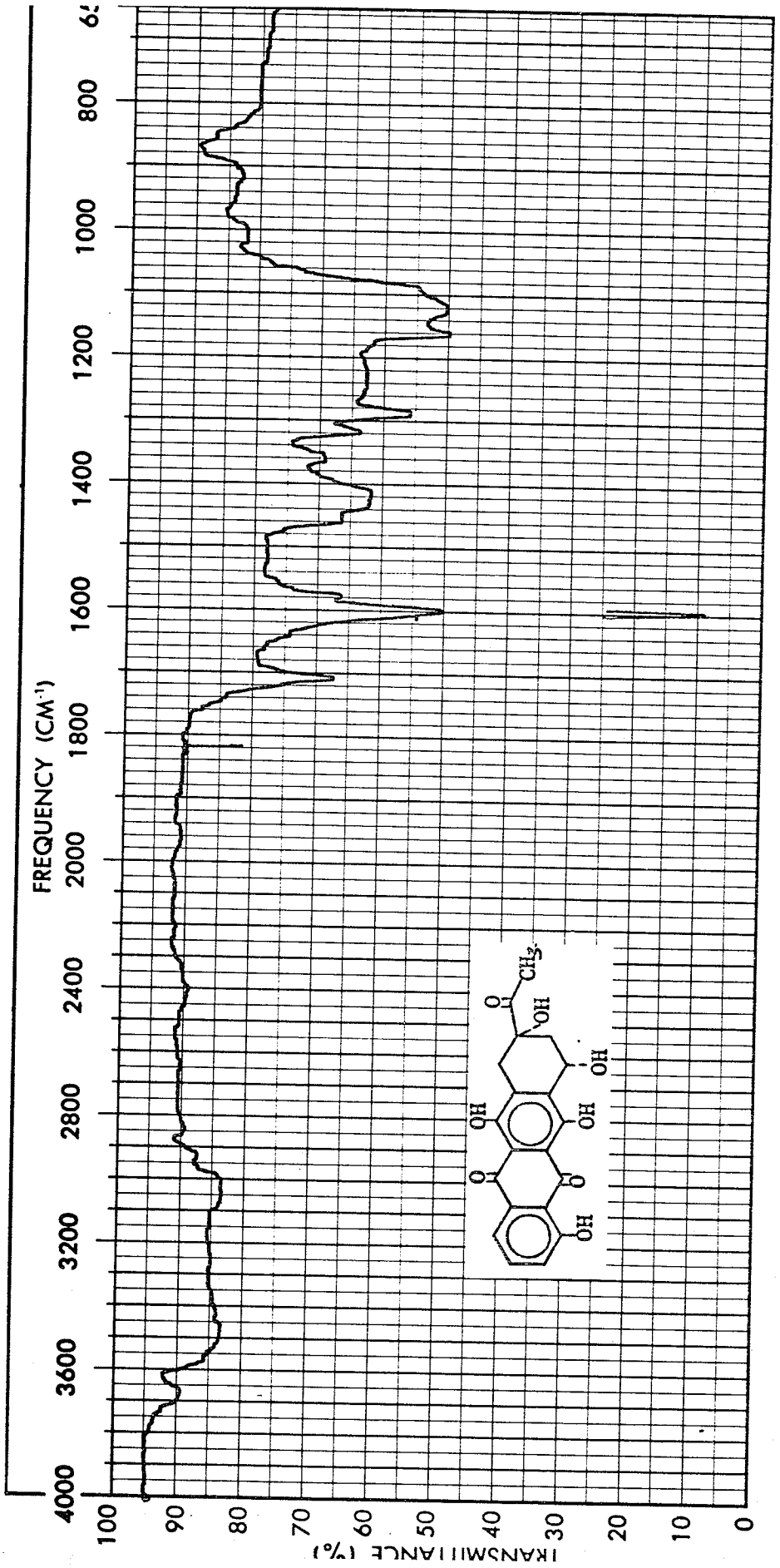
Infrared spectrum no. 31: Boron tribromide hydrolysis product of synthetic daunomycinone trimethylether (XLIX), in CH_2Cl_2 solution.

Figure XLI



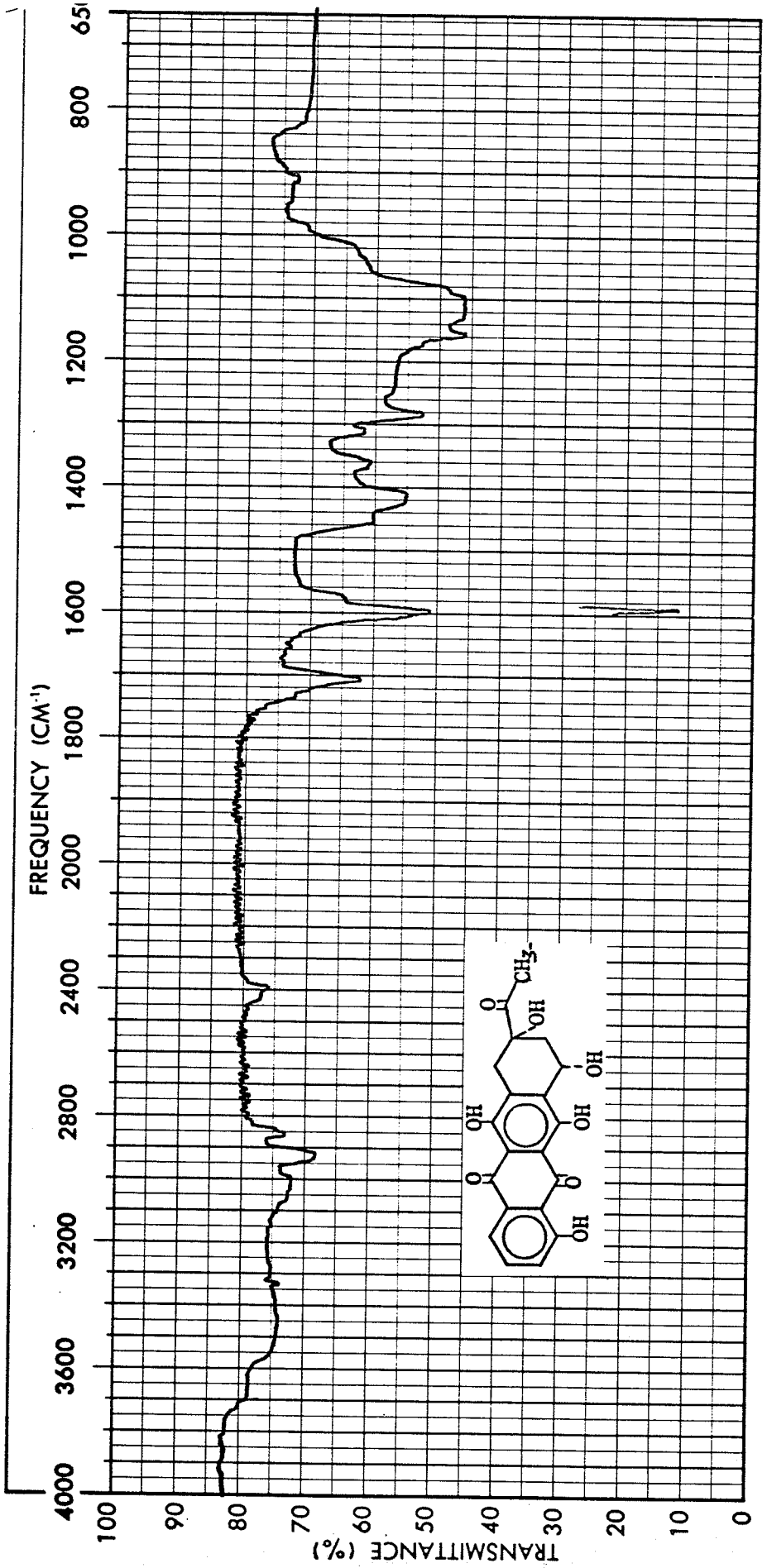
Infrared spectrum no. 32: Trifluoroacetic ester mixture (L), in CH_2Cl_2 solution.

Figure XLII



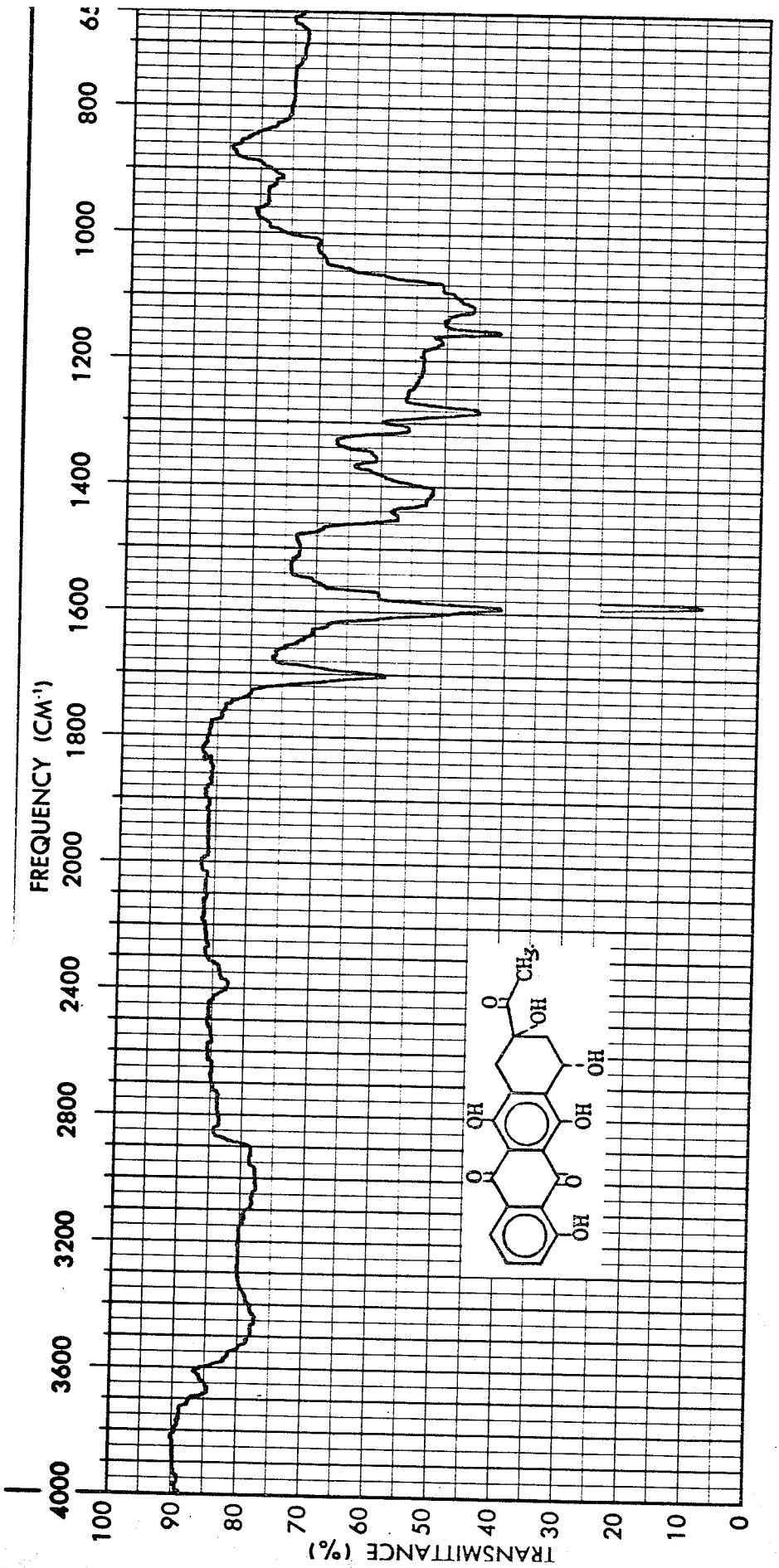
Infrared spectrum no. 33: 4-O-demethyldaunomycinone (from natural daunomycinone), in $CHCl_3$ solution.

Figure XLIII



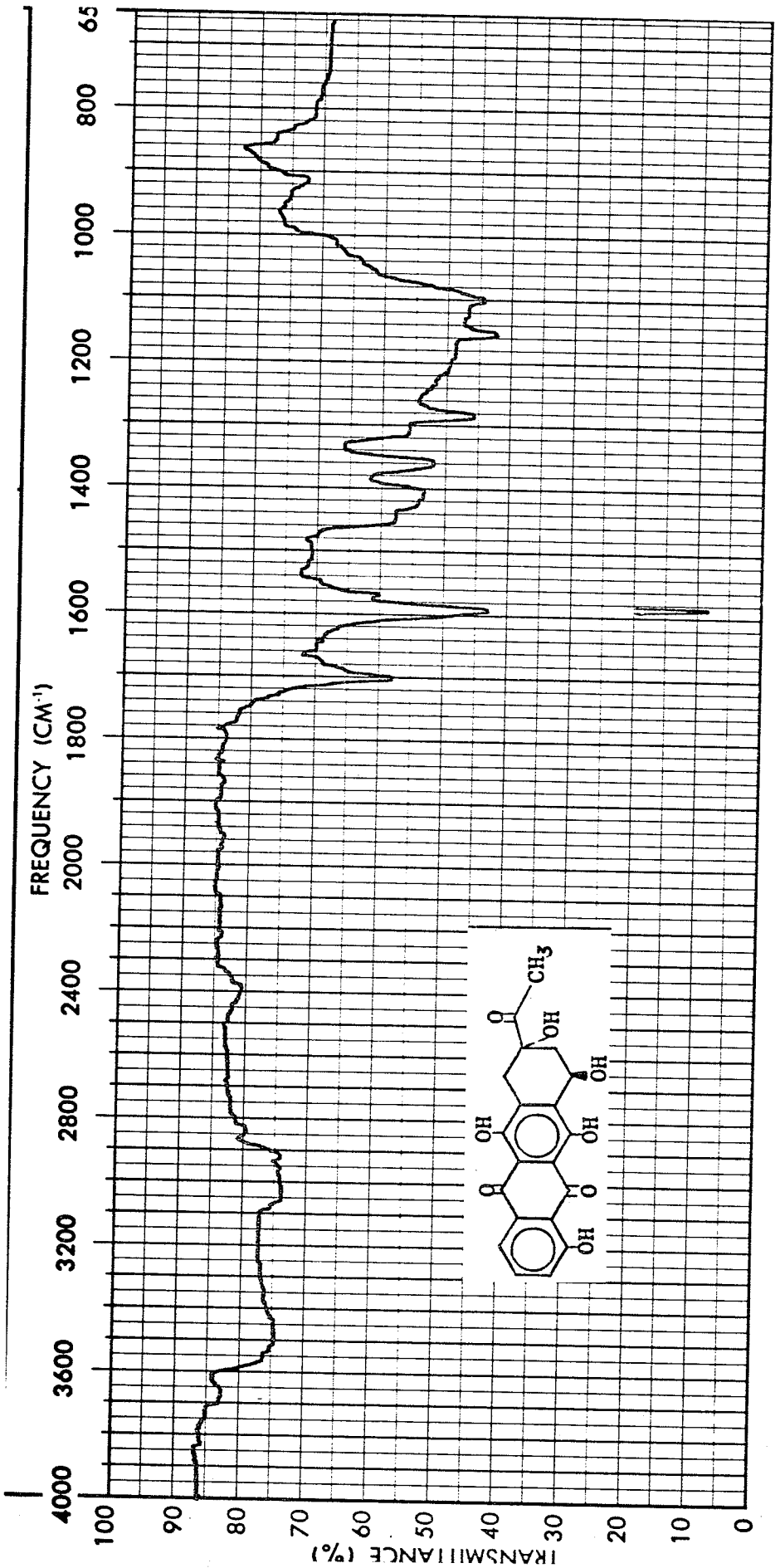
Infrared spectrum no. 34: Racemic 4-O-demethyldaunomycinone (LI), (from compound (XLIX)), in $CHCl_3$ solution.

Figure XLIV



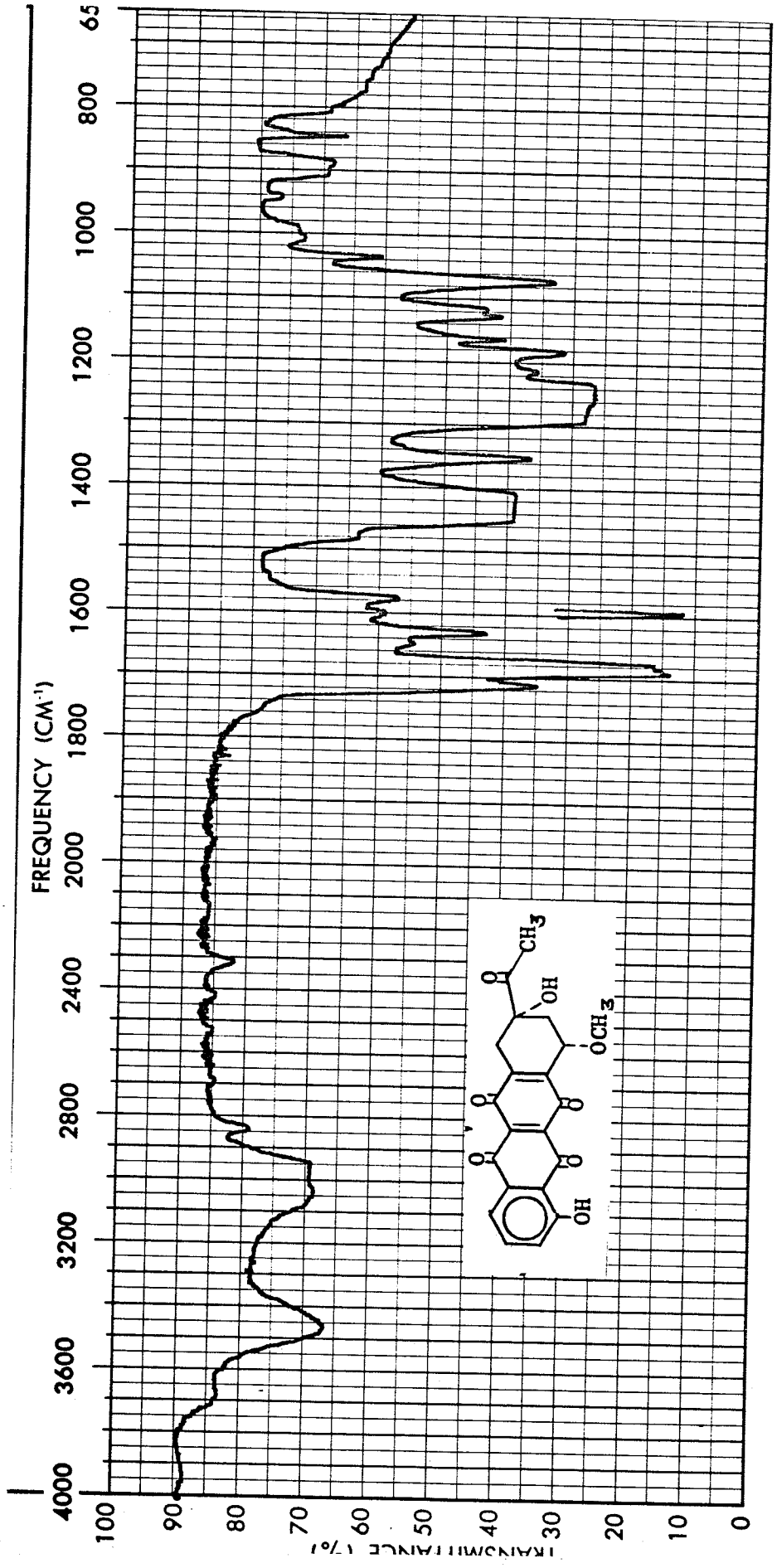
Infrared spectrum no. 35: Racemic 4-O-demethyldaunomycinone (LI) (from compound (L)), in $CHCl_3$ solution.

Figure XLV



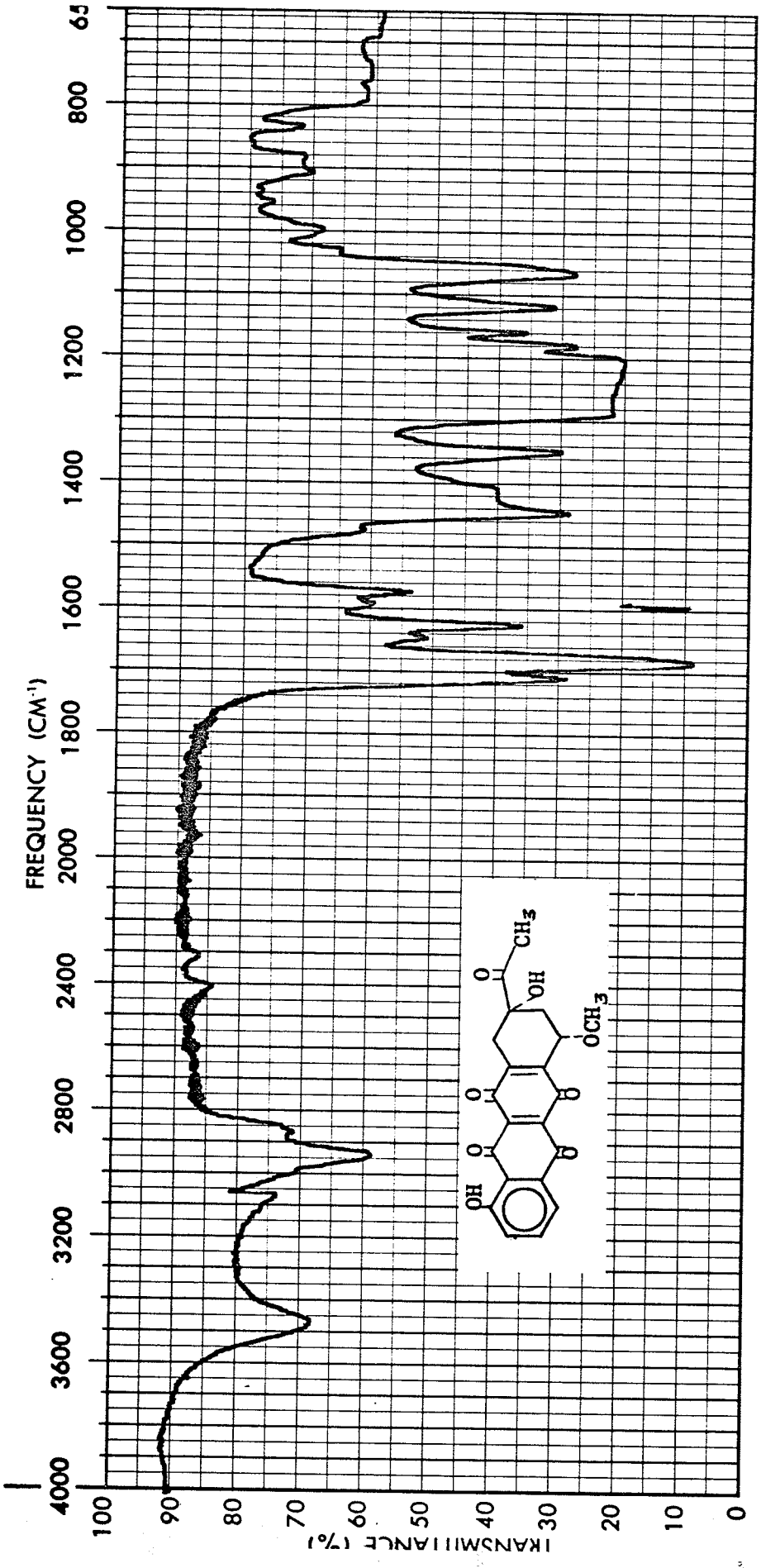
Infrared spectrum no. 36: Racemic 7-epi-4-O-demethyldaunomycinone (LII), in $CHCl_3$ solution.

Figure XLVI



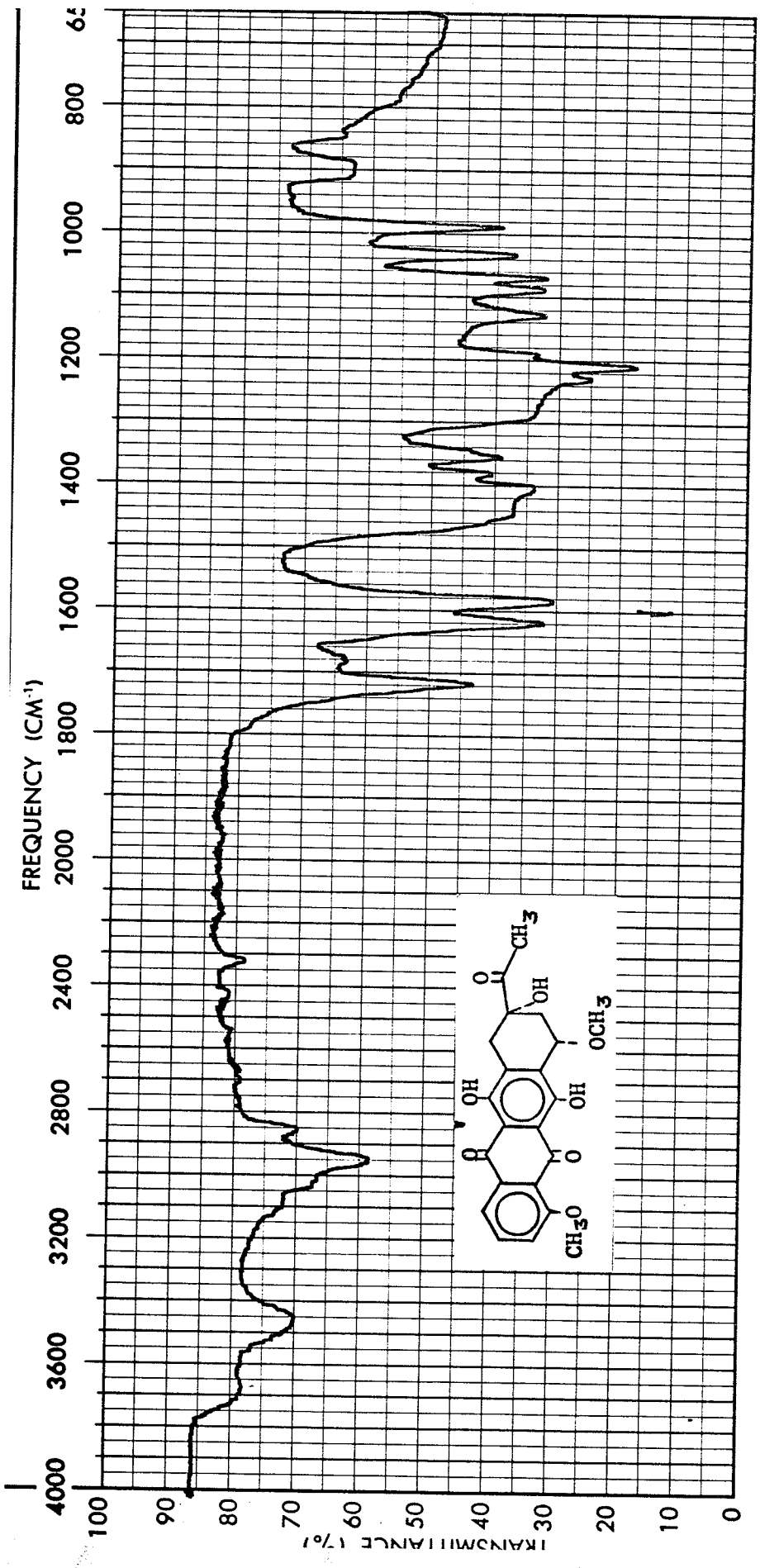
Infrared spectrum no. 37: Racemic 9-acetyl-7,8,9,10-tetrahydro-4,9-dihydroxy-7-methoxy-5,6,11,12-naphthacenediquinone (LIV), in CH_2Cl_2 solution.

Figure XLVII



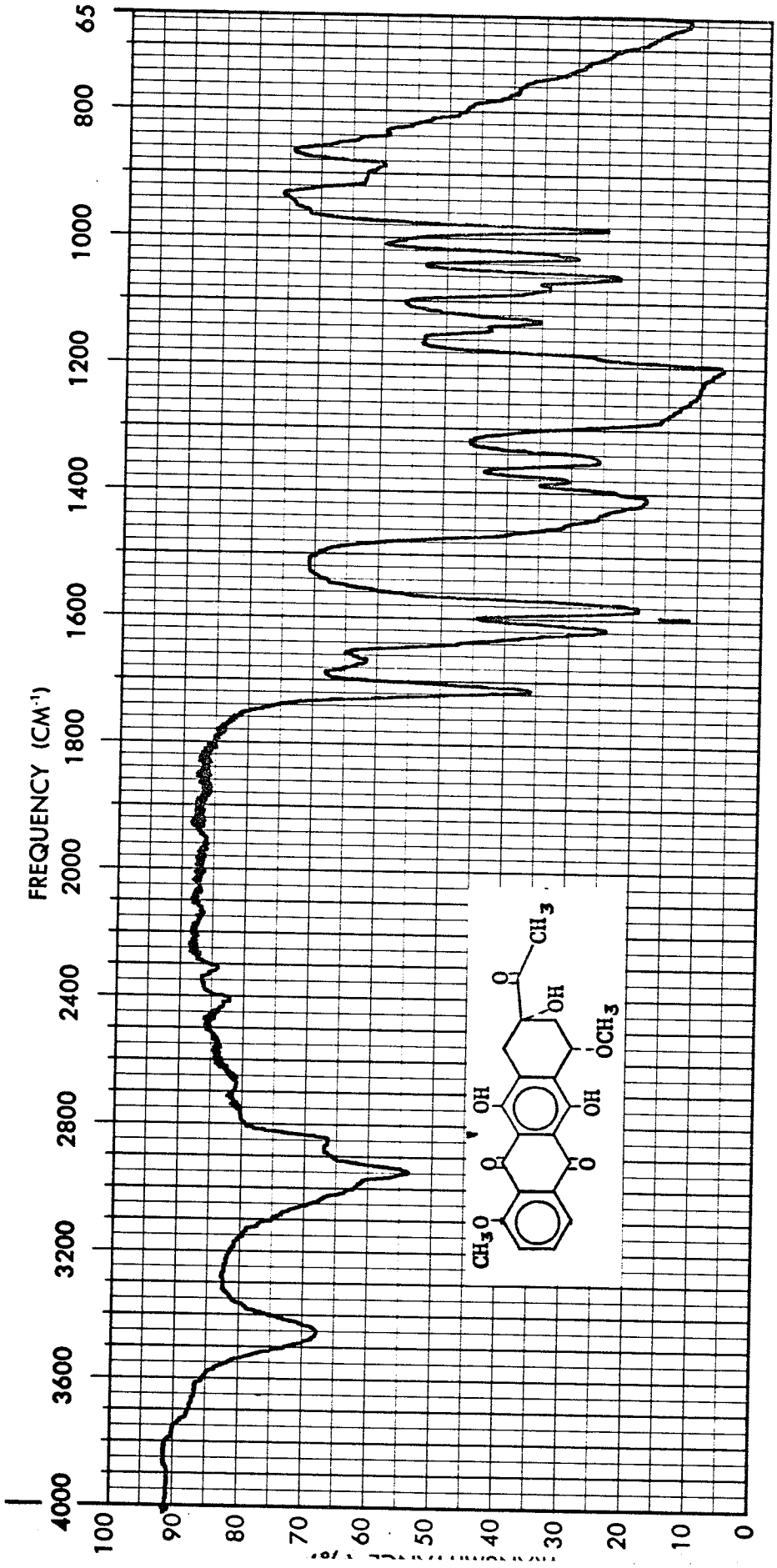
Infrared spectrum no. 38: Racemic 9-acetyl-7,8,9,10-tetrahydro-1,9-dihydroxy-7-methoxy-5,6,11,12-naphthacenediquinone (LIII), in CH_2Cl_2 solution.

Figure XLVIII



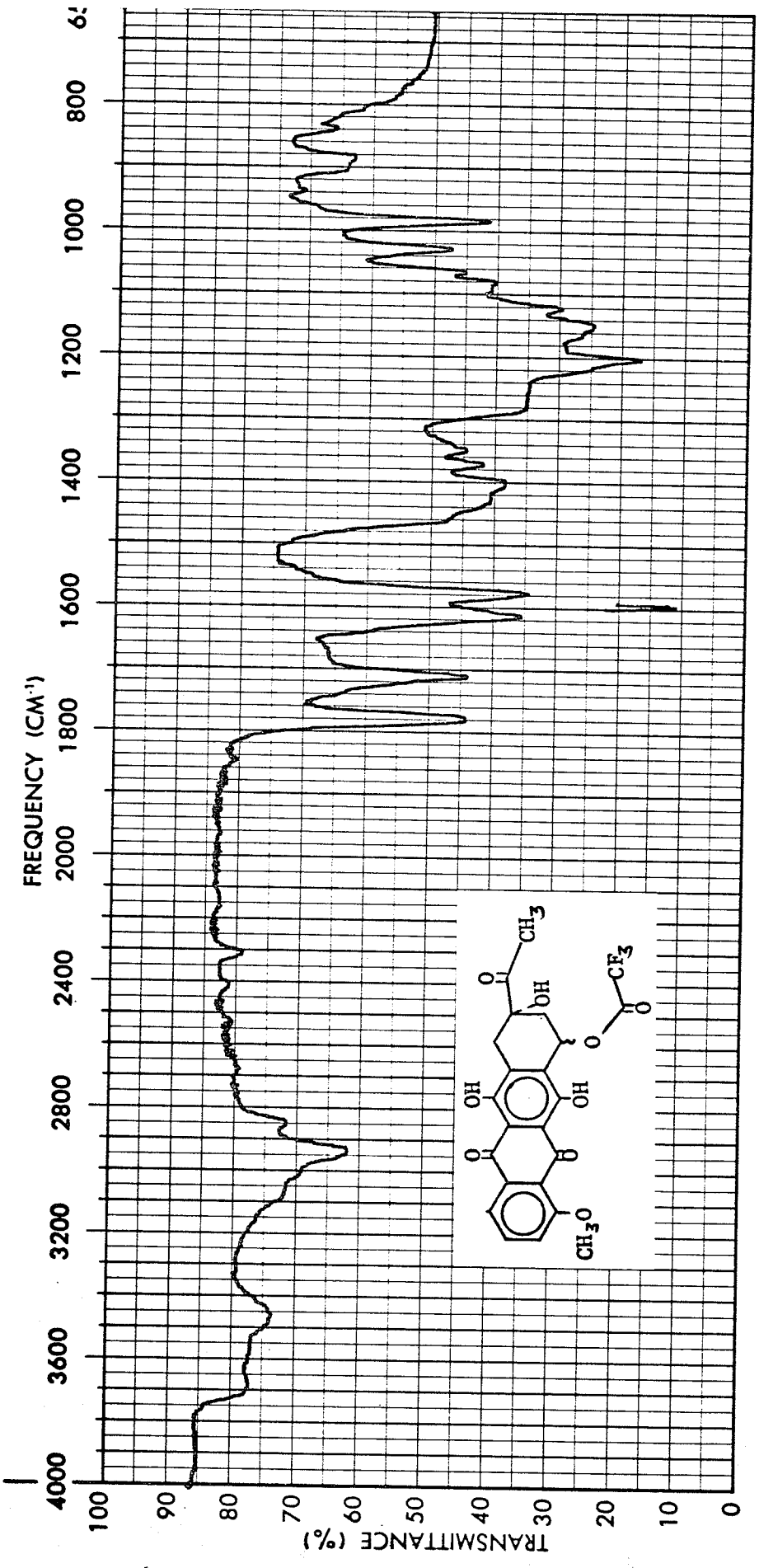
Infrared spectrum no. 39: Racemic 7-O-methyldaunomycinone (LVI), in CH_2Cl_2 solution.

Figure XLIX



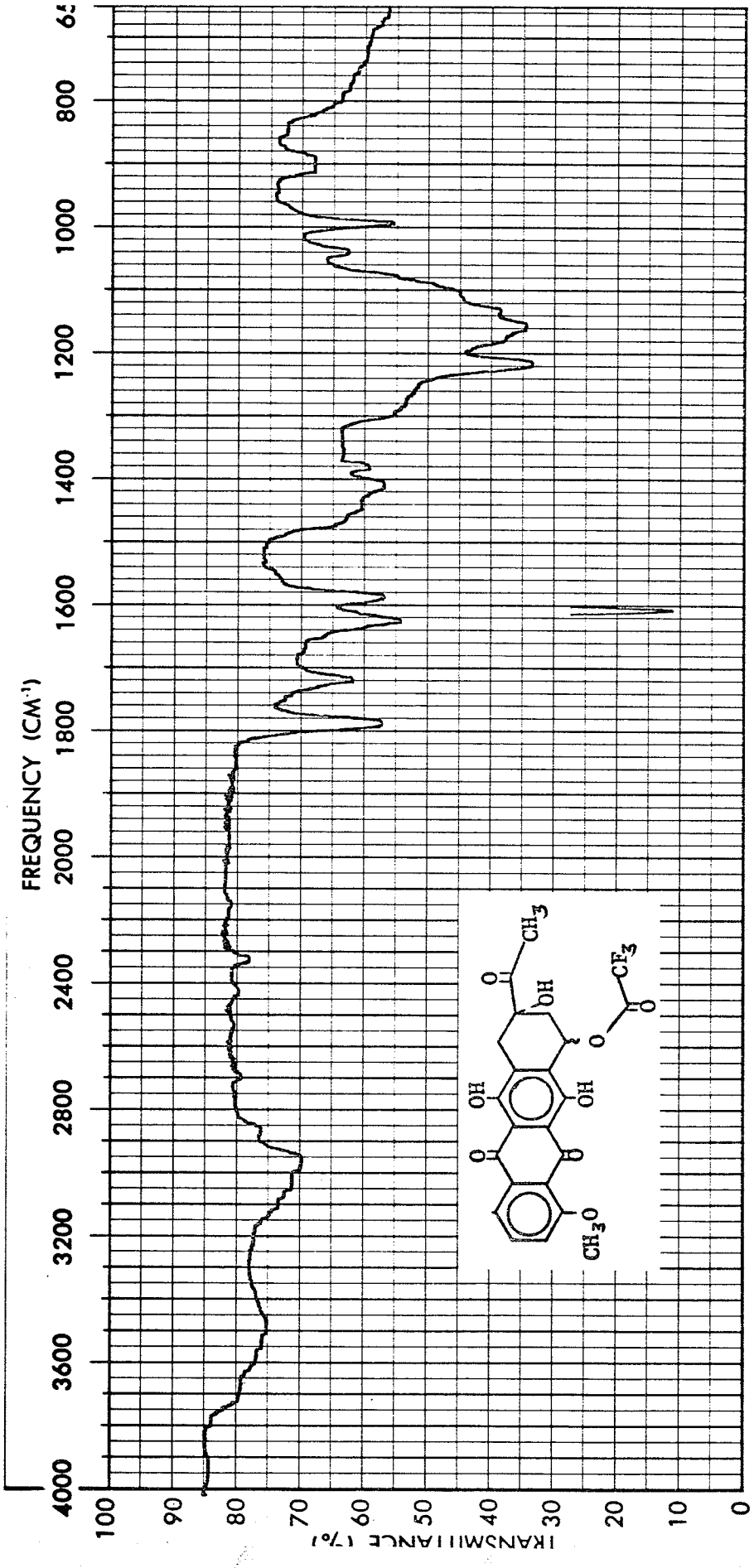
Infrared spectrum no. 40: Racemic 1-methoxy-4-demethoxy-7-O-methyldaunomycinone (LV), in CH_2Cl_2 solution.

Figure L



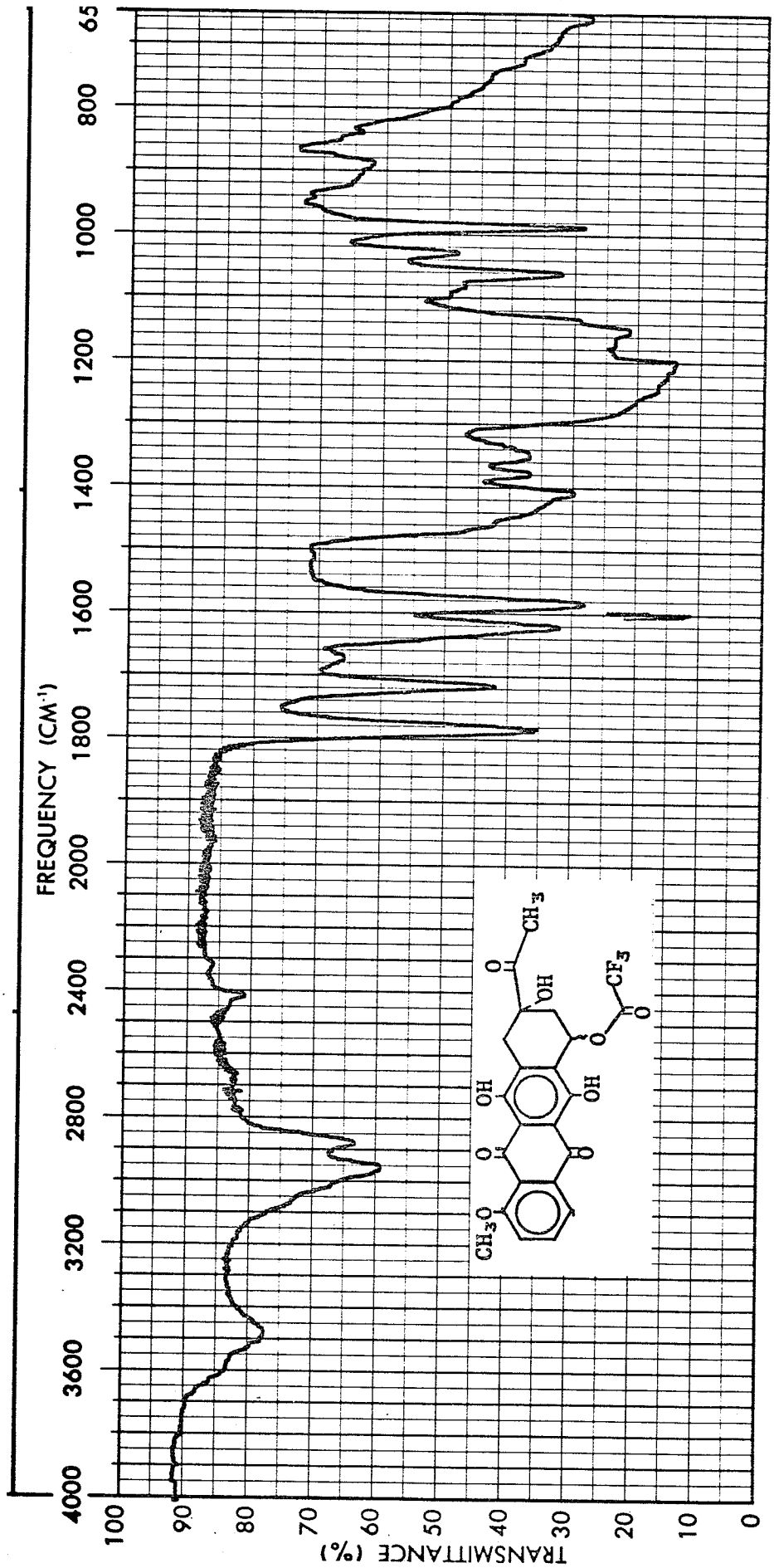
Infrared spectrum no. 41: Synthetic trifluoroacetic ester mixture (LVIII), in CH_2Cl_2 solution.

Figure LI



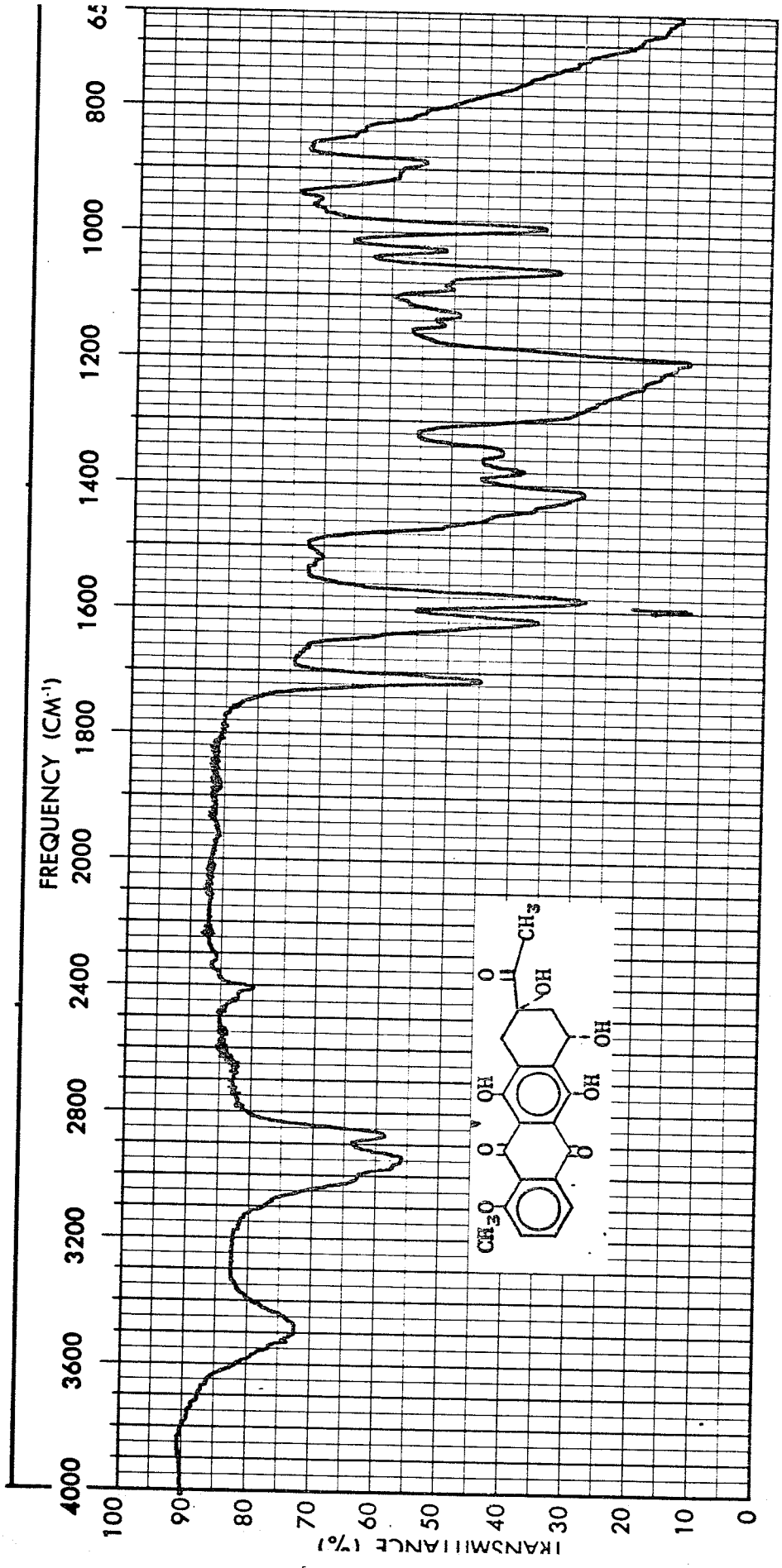
Infrared spectrum no. 42: Trifluoroacetic ester mixture (LVIII), (from natural daunomycinone), in CH_2Cl_2 solution.

Figure LII



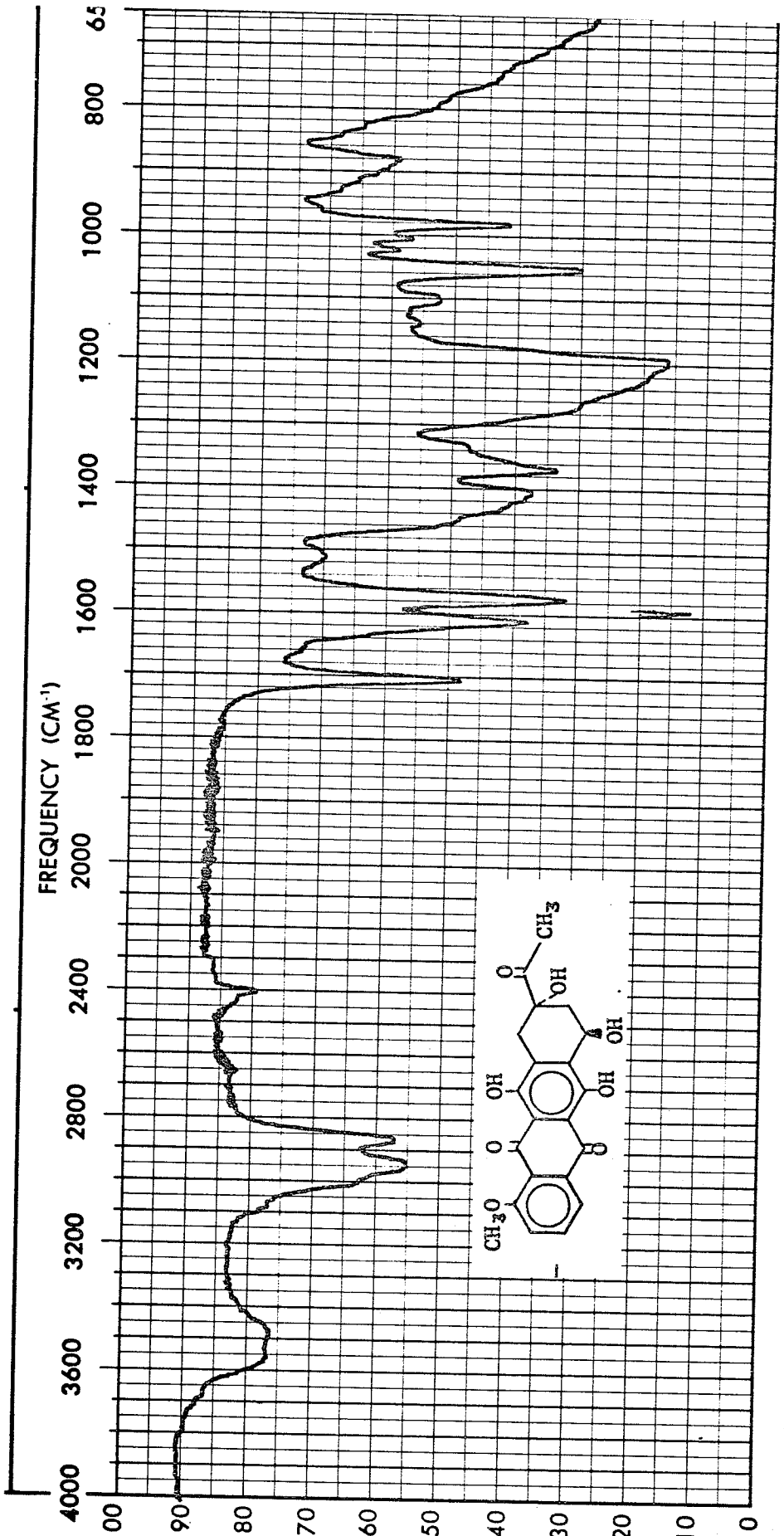
Infrared spectrum no. 43: Trifluoroacetic ester mixture (LVII), in CH_2Cl_2 solution.

Figure LIII



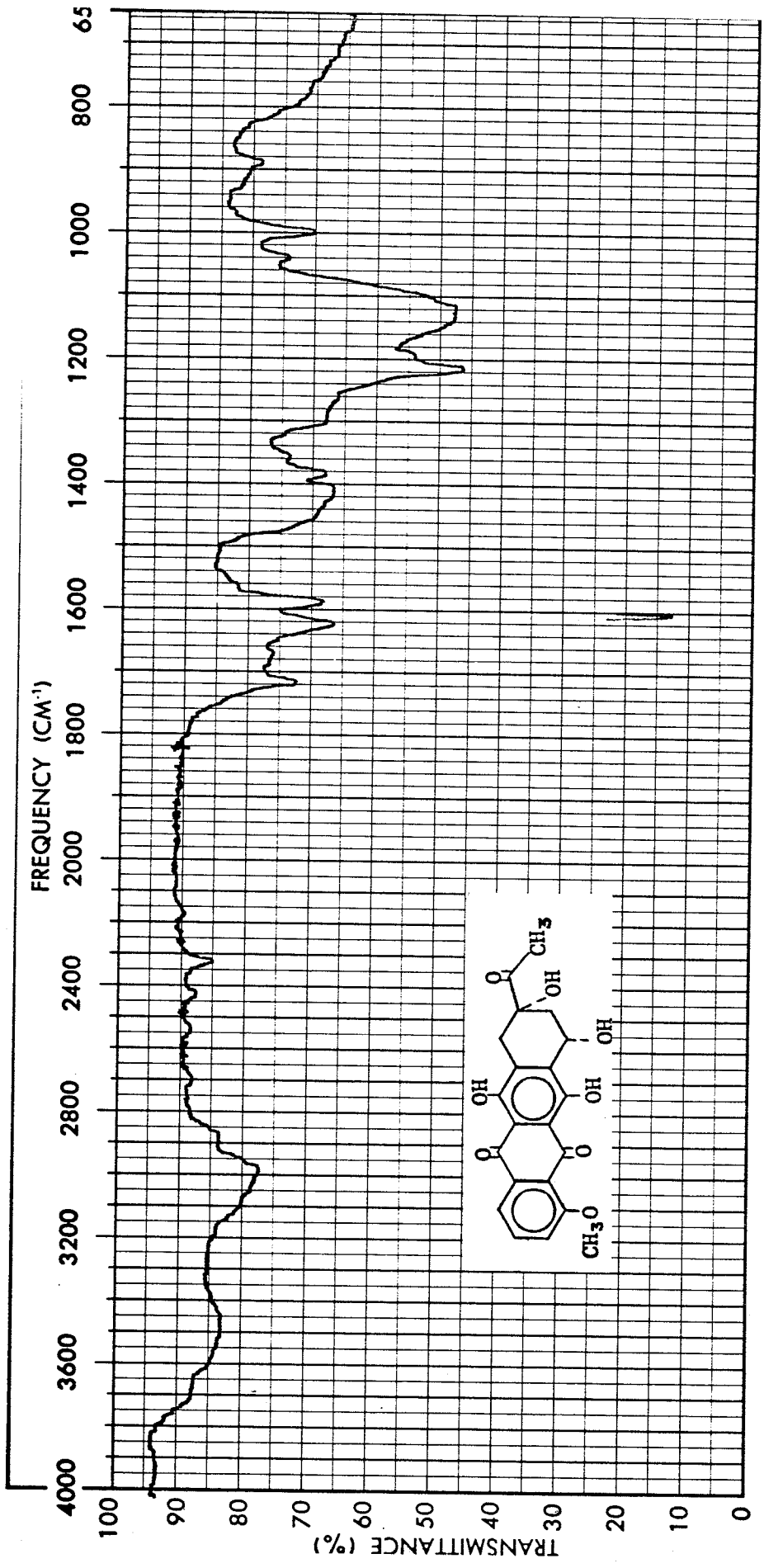
Infrared spectrum no. 44: Racemic 1-methoxy-4-demethoxy-daunomycinone (isodaunomycinone (LIX), in CH_2Cl_2 solution.

Figure LIV



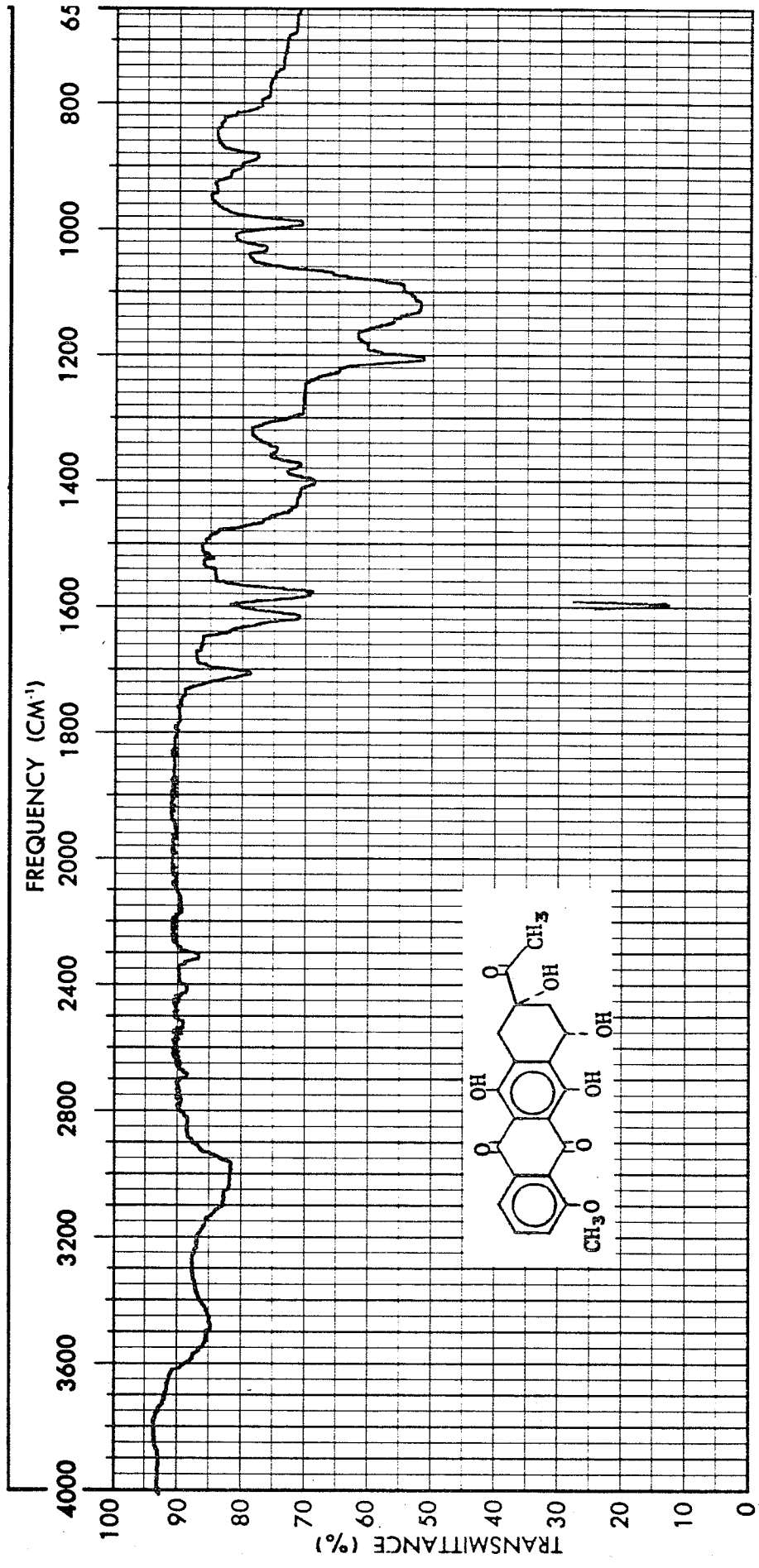
Infrared spectrum no. 45: Racemic 1-methoxy-4-demethoxy-7-epidaunomycinone (7-epiisodaunomycinone) (LX), in CH_2Cl_2 solution.

Figure LV



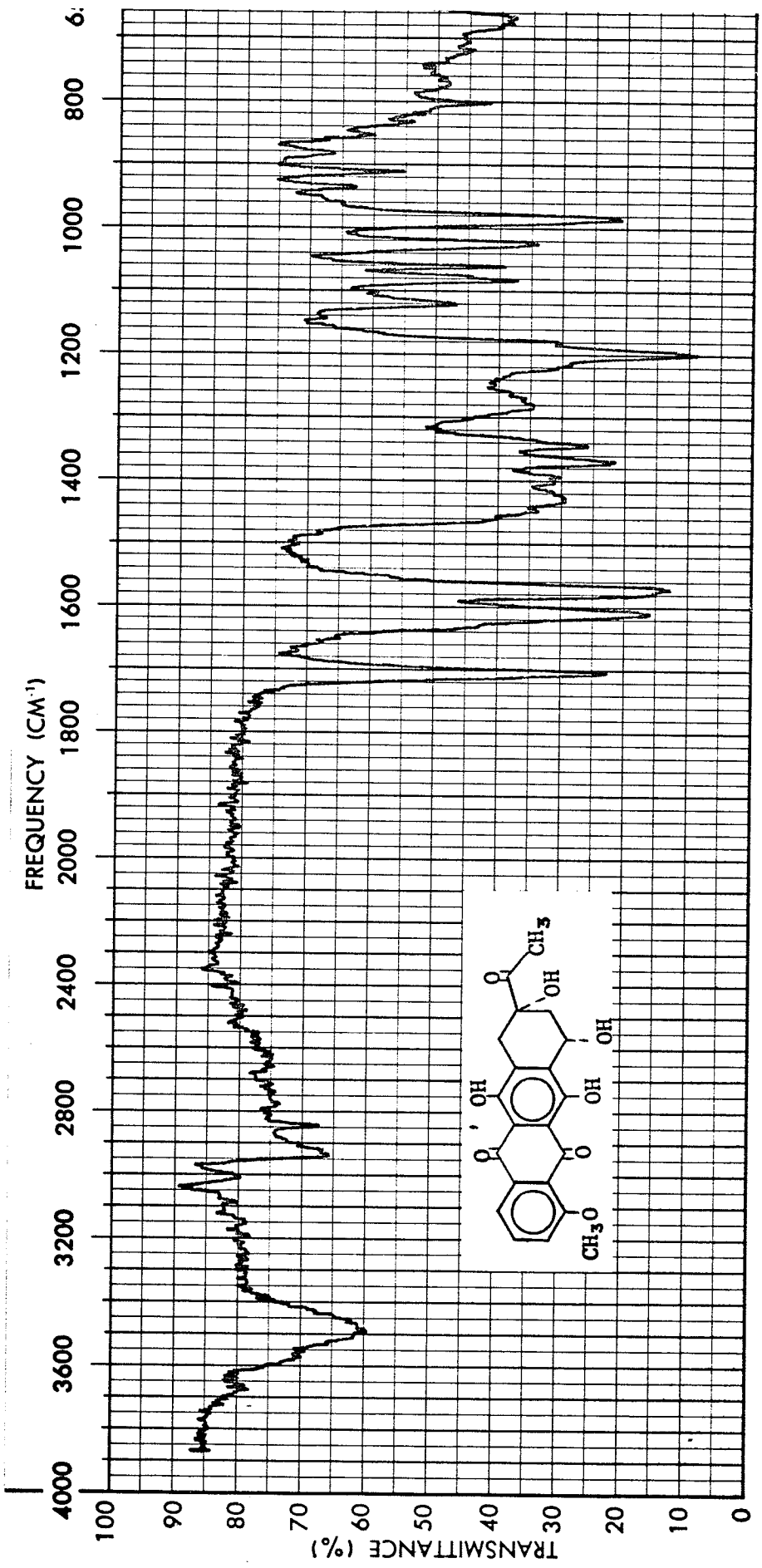
Infrared spectrum no. 46: Synthetic daunomycinone (LXI), in CH_2Cl_2 solution.

Figure LVI



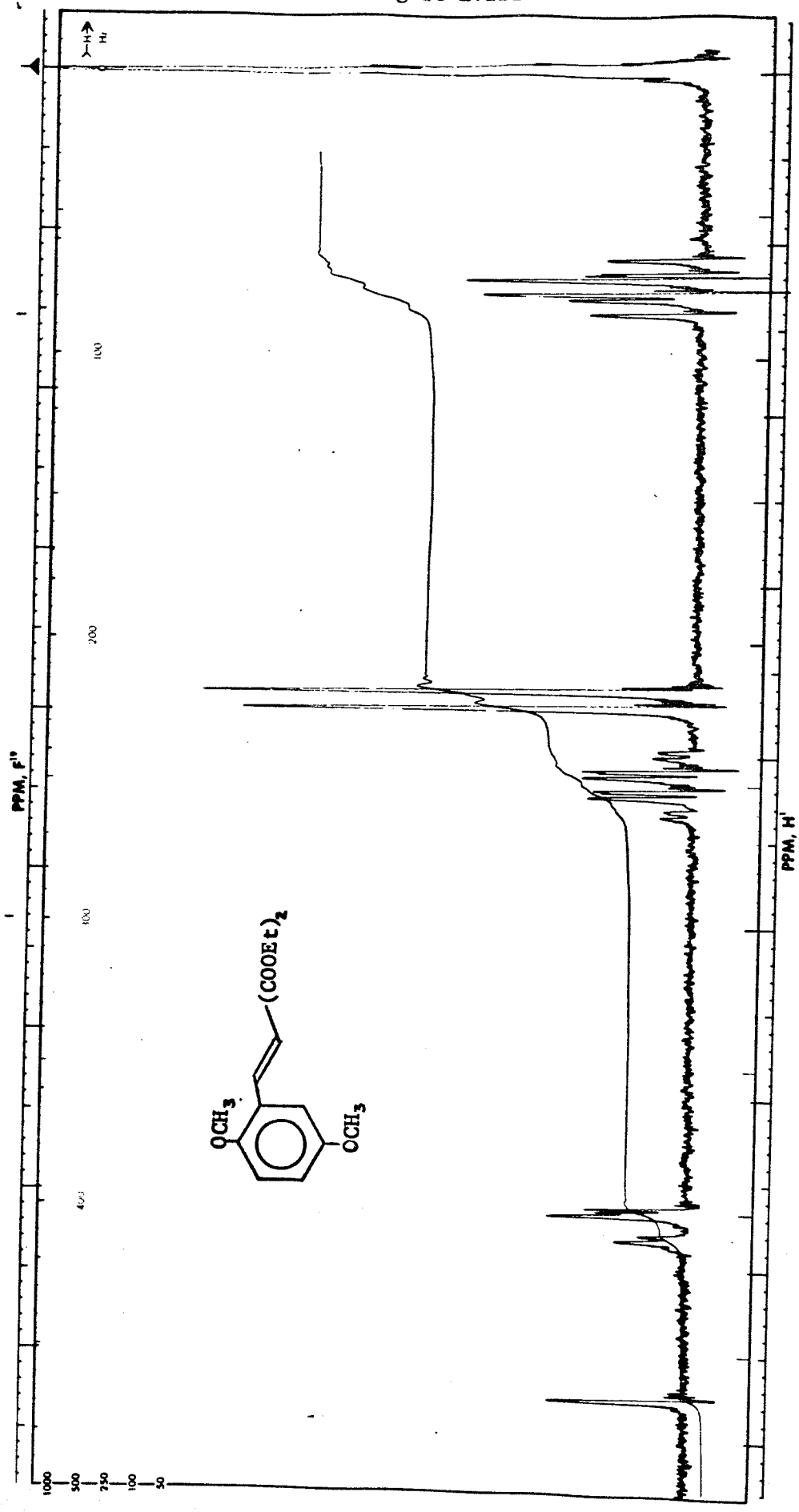
Infrared spectrum no. 47: Natural daunomycinone, in CH_2Cl_2 solution (dilute).

Figure LVII



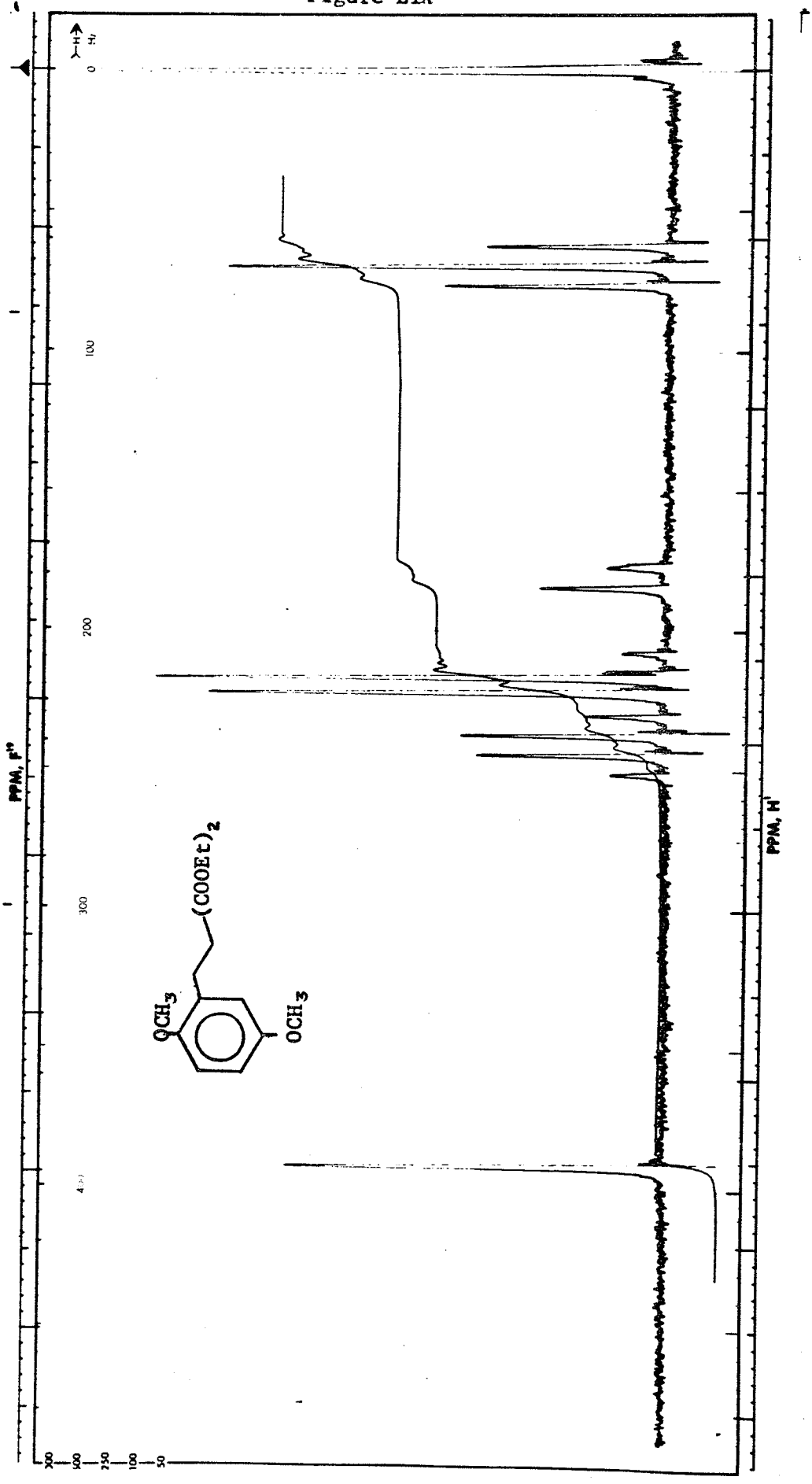
Infrared spectrum no. 48: Natural daunomycinone, in CH_2Cl_2 solution.

Figure LVIII



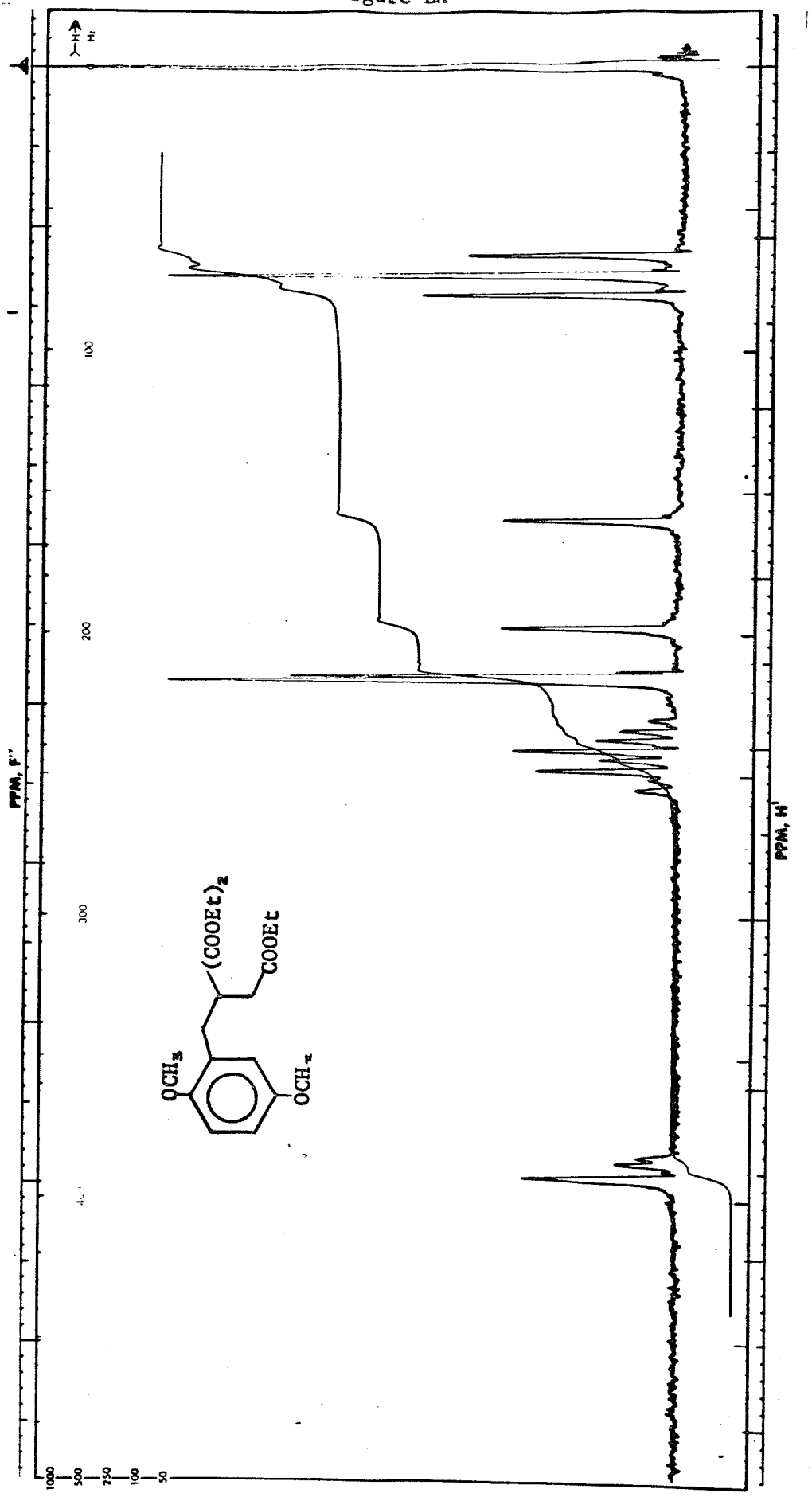
Nuclear magnetic resonance spectrum no. 1: Ethyl 2-carboethoxy-3-(2,5-dimethoxyphenyl) propenoate (XII), in CCl_4. Sweep width = 500 Hz.

Figure LIX



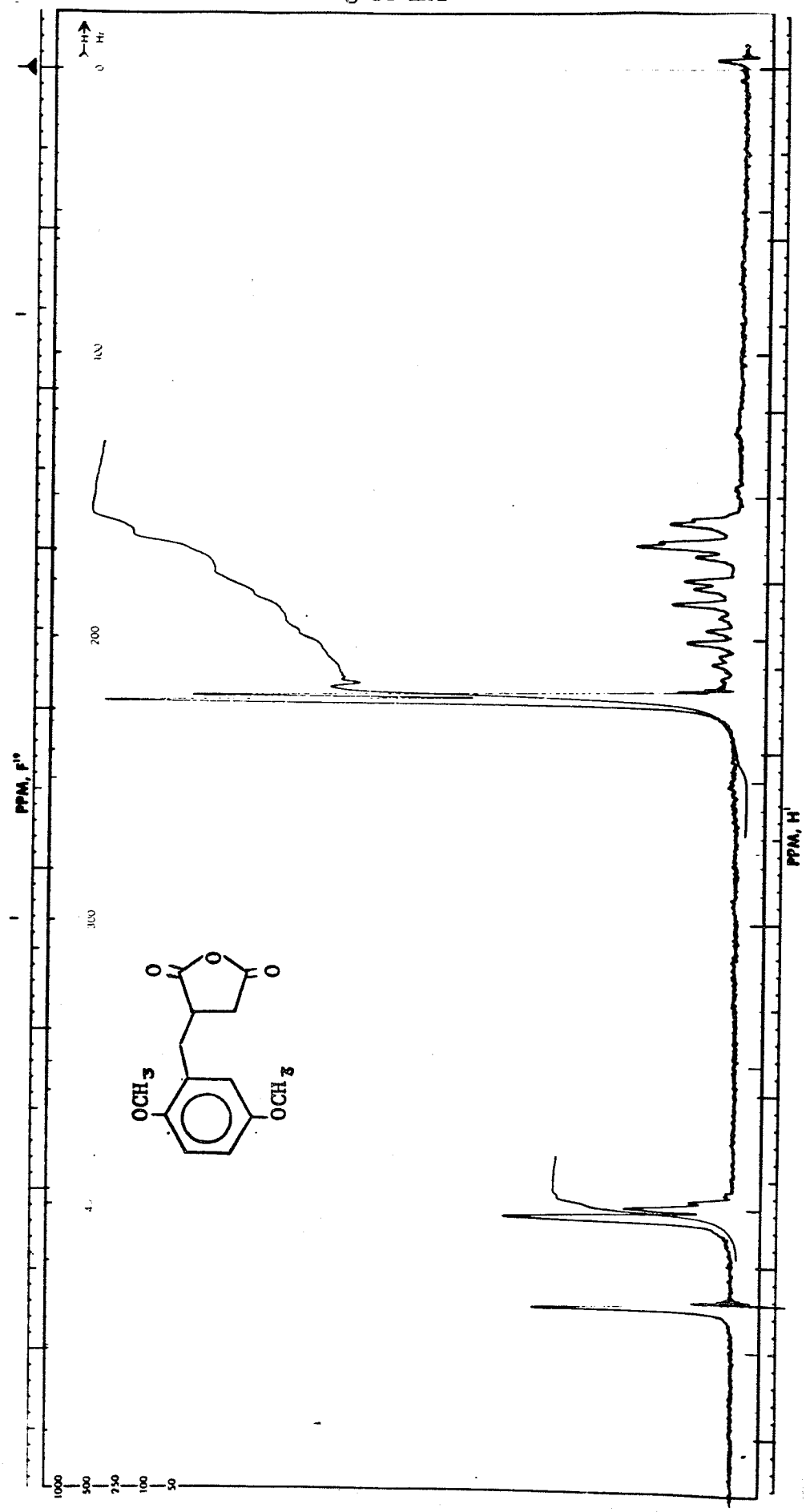
Nuclear magnetic resonance spectrum no. 2: Ethyl 2-carboethoxy-3-(2,5-dimethoxyphenyl) propanoate (XIII), in CCl_4, Sweep width = 500 Hz.

Figure LX



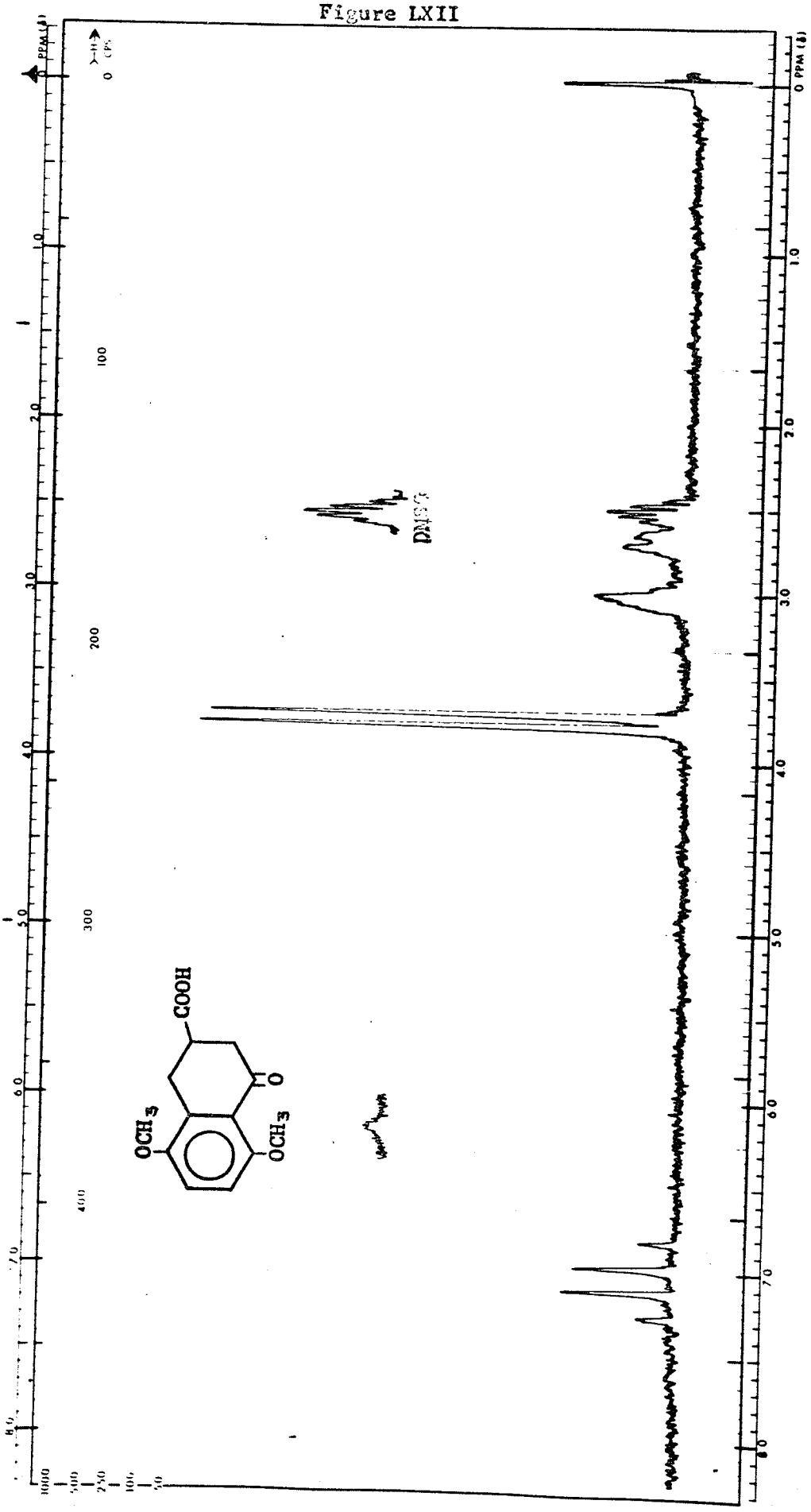
Nuclear magnetic resonance spectrum no. 3: Ethyl 3,3-dicarboethoxy-4-(2,5-dimethoxyphenyl) butanoate (XIV), in CCl_4. Sweep width = 500 Hz.

Figure LXI



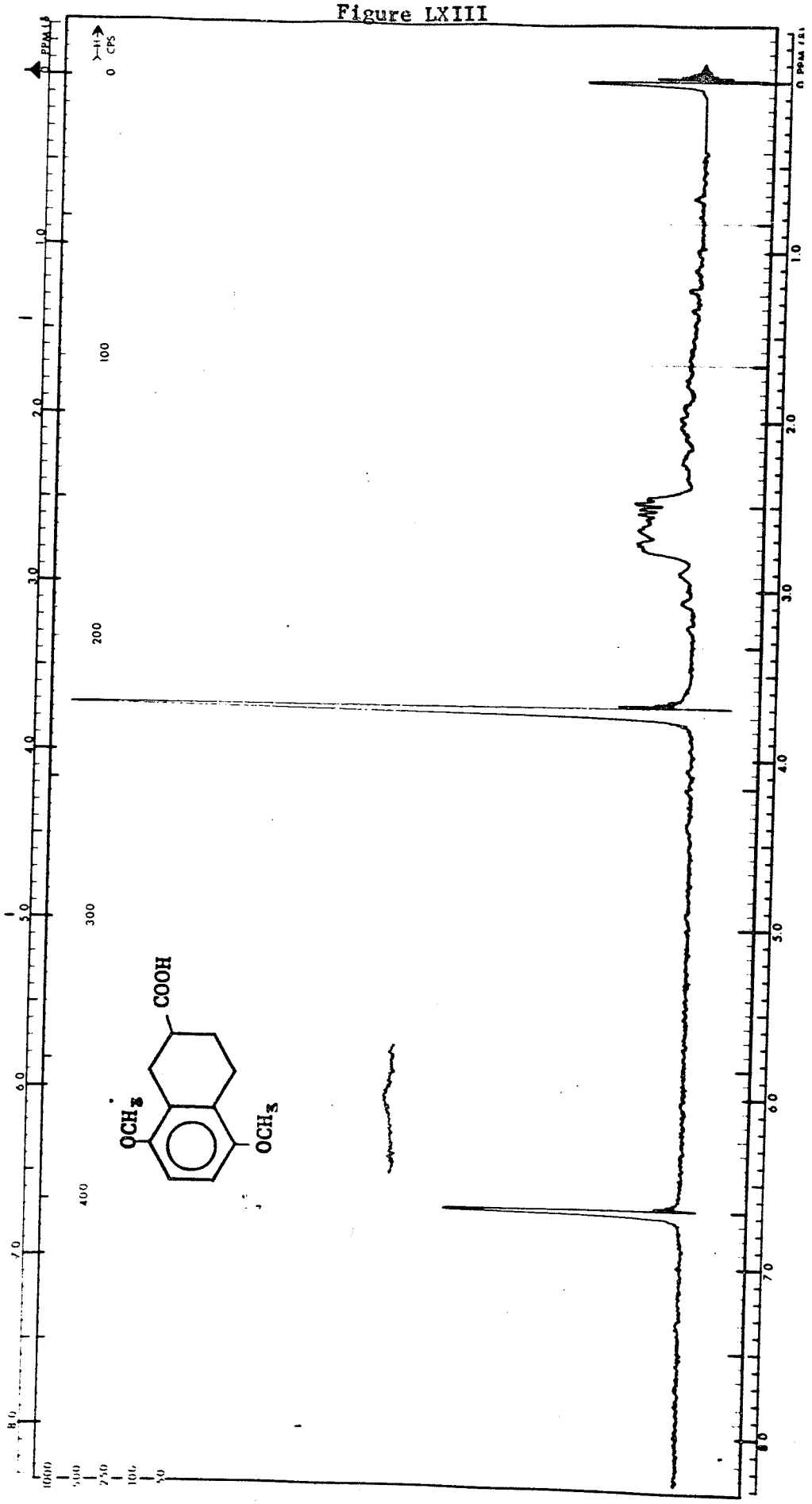
Nuclear magnetic resonance spectrum no. 4: 2'5'-dimethoxybenzylsuccinic anhydride (XVII), in $CDCl_3$. Sweep width = 500 Hz.

Figure LXII



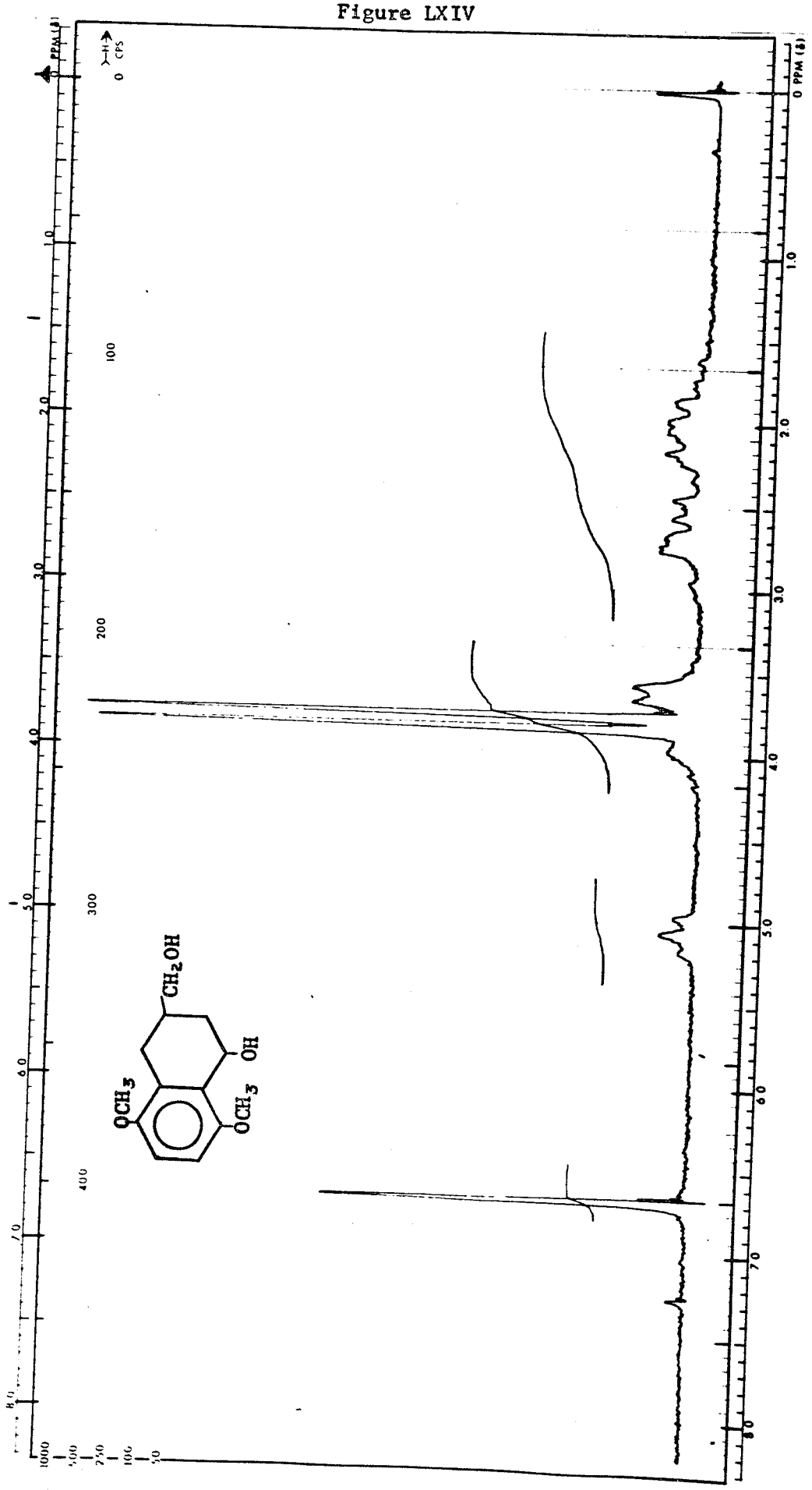
Nuclear magnetic resonance spectrum no. 5: 3-carbohydroxy-5,8-dimethoxy-1-tetralone (XVIII), in DMSO-d_6. Sweep width = 500 Hz., insert is on sweep width = 1000 Hz.

Figure LXIII



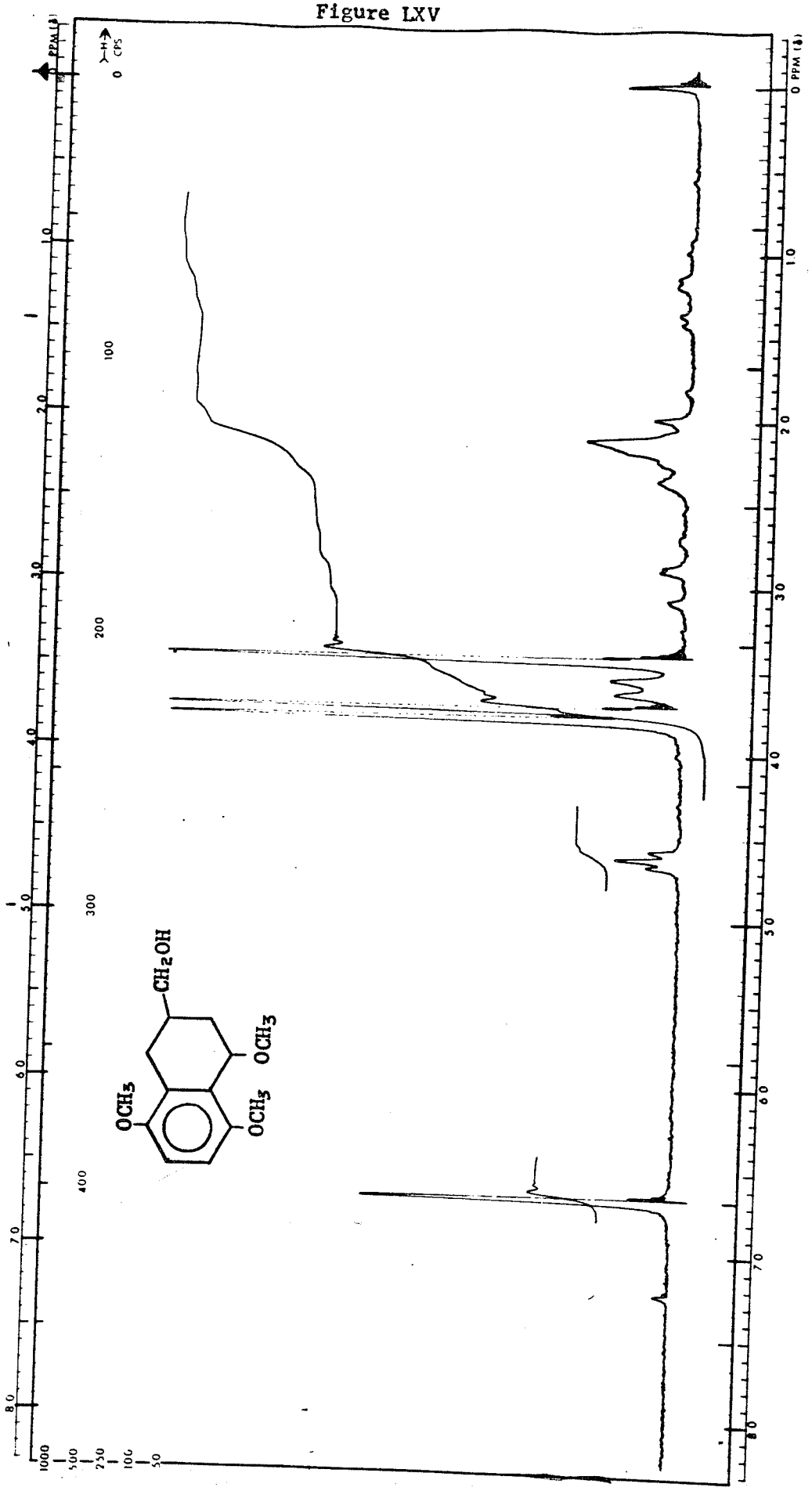
Nuclear magnetic resonance spectrum no. 6: 2-carbohydroxy-5,8-dimethoxytetralin (XXV), in DMSO-d_6. Sweep width = 500 Hz., insert is on sweep width = 1000 Hz.

Figure LXIV



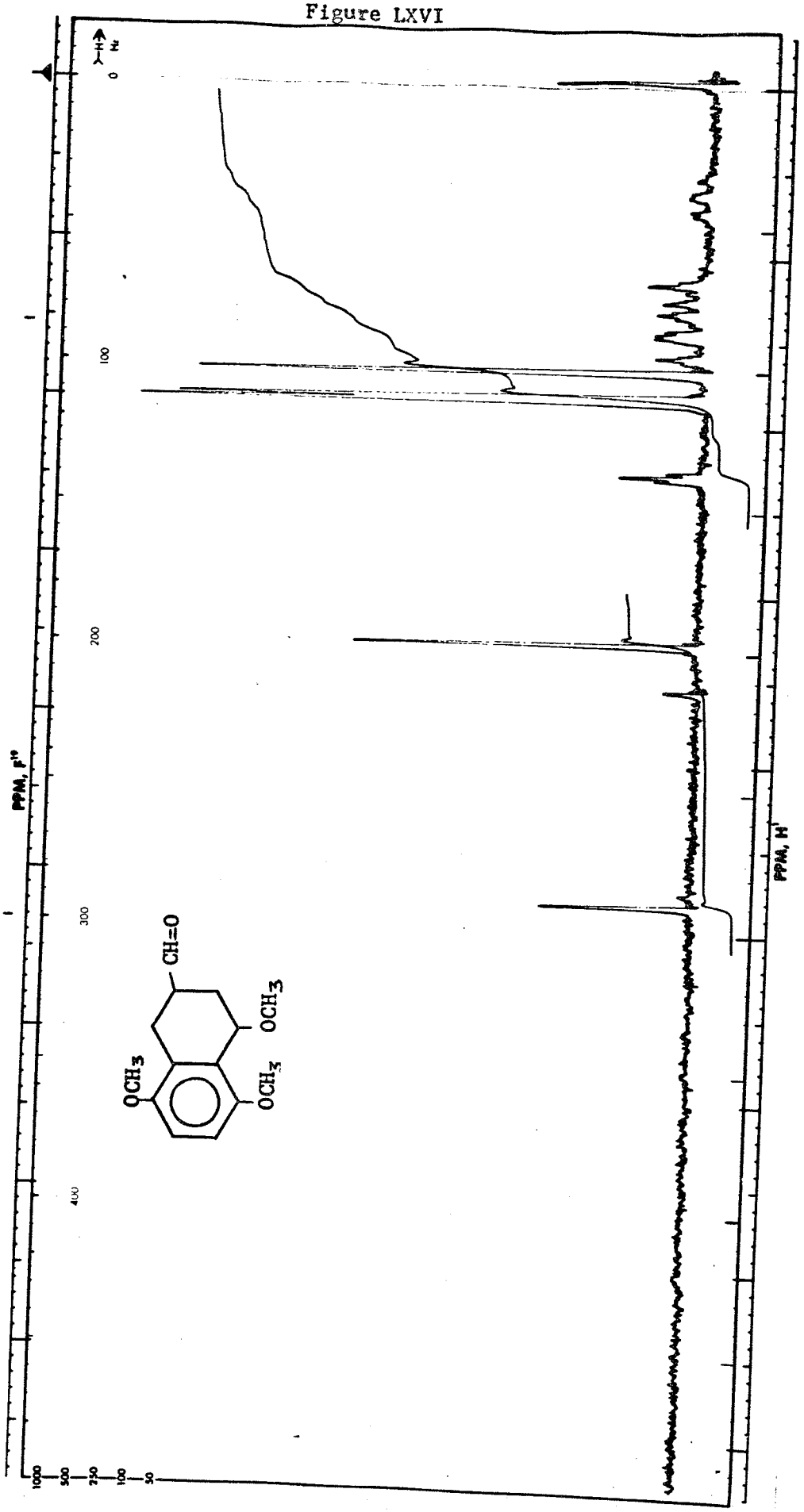
Nuclear magnetic resonance spectrum no. 7: 1-hydroxy-3-hydroxymethyl-5,8-dimethoxytetralin (XIX), in $CDCl_3$. Sweep width = 500 Hz.

Figure LXV



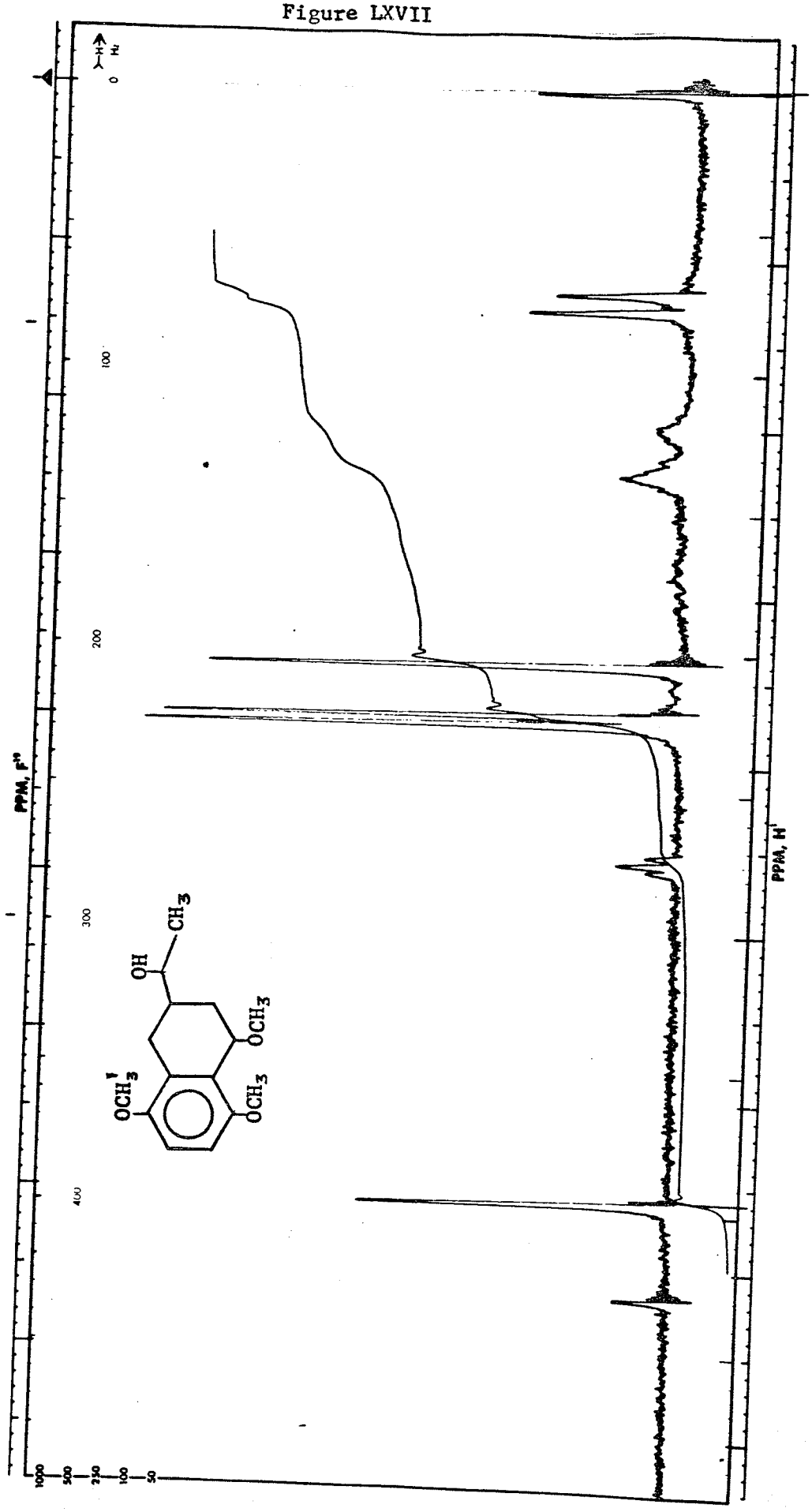
Nuclear magnetic resonance spectrum no. 8: 1,5,8-trimethoxy-3-hydroxymethyltetralin (XX), in $CDCl_3$. Sweep width = 500 Hz.

Figure LXVI



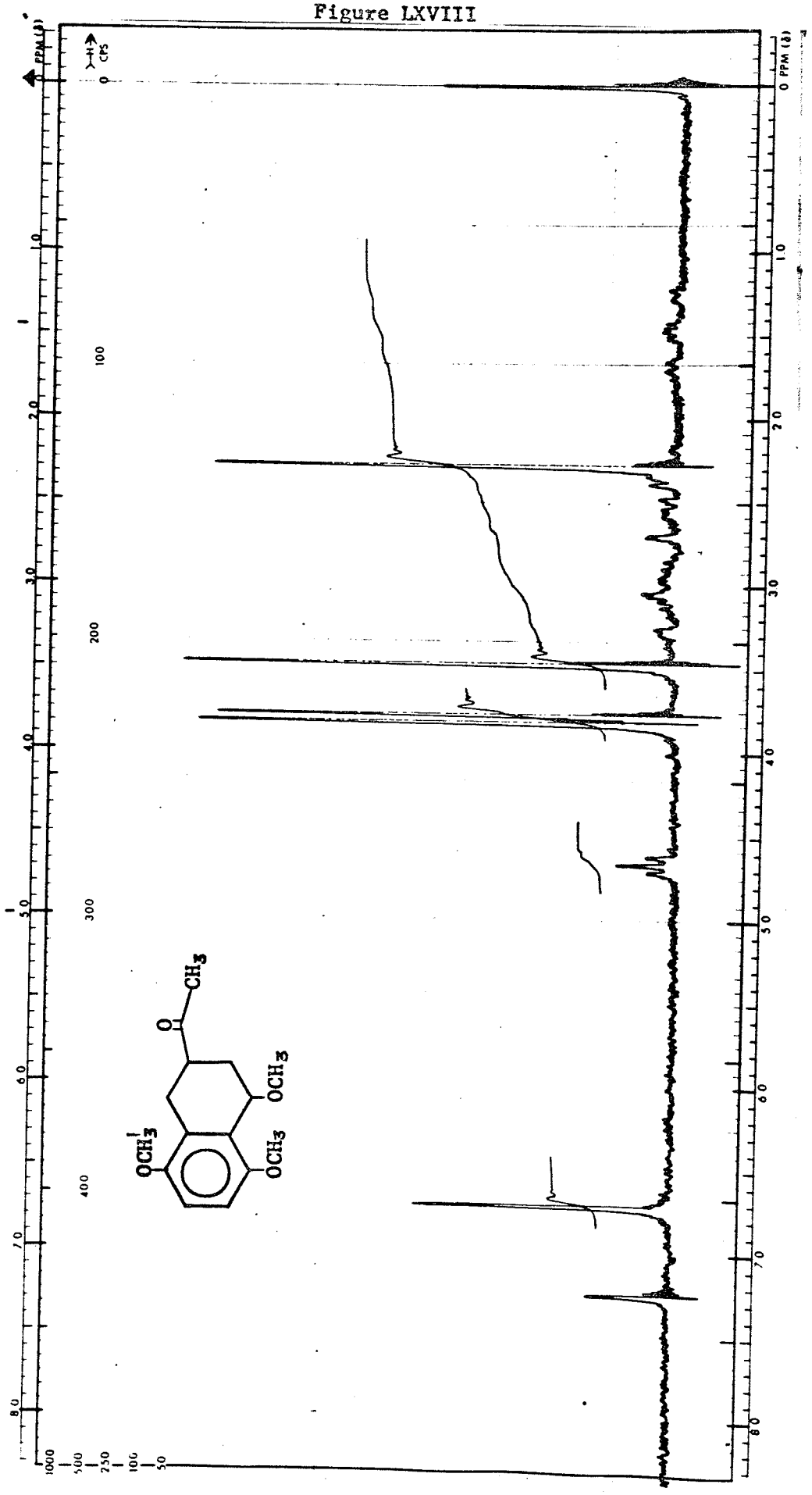
Nuclear magnetic resonance spectrum no. 9: 1,5,8-trimethoxy-3-formyltetralin (XXI), in $CDCl_3$. Sweep width = 1000 Hz.

Figure LXVII



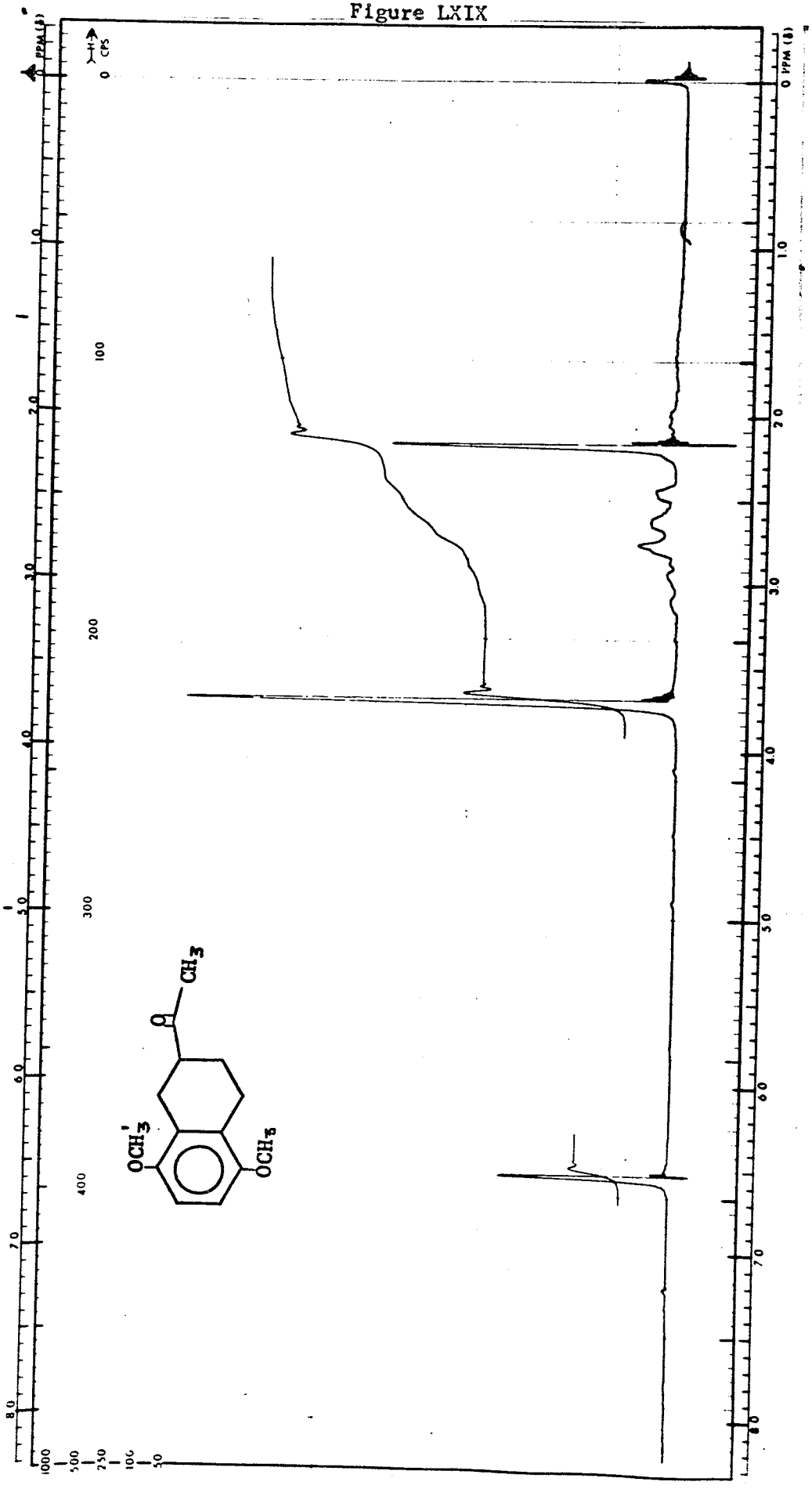
Nuclear magnetic resonance spectrum no. 10: 1,5,8-trimethoxy-3-(1'-hydroxyethyl) tetralin (XXII), in $CDCl_3$. Sweep width = 500 Hz.

Figure LXVIII



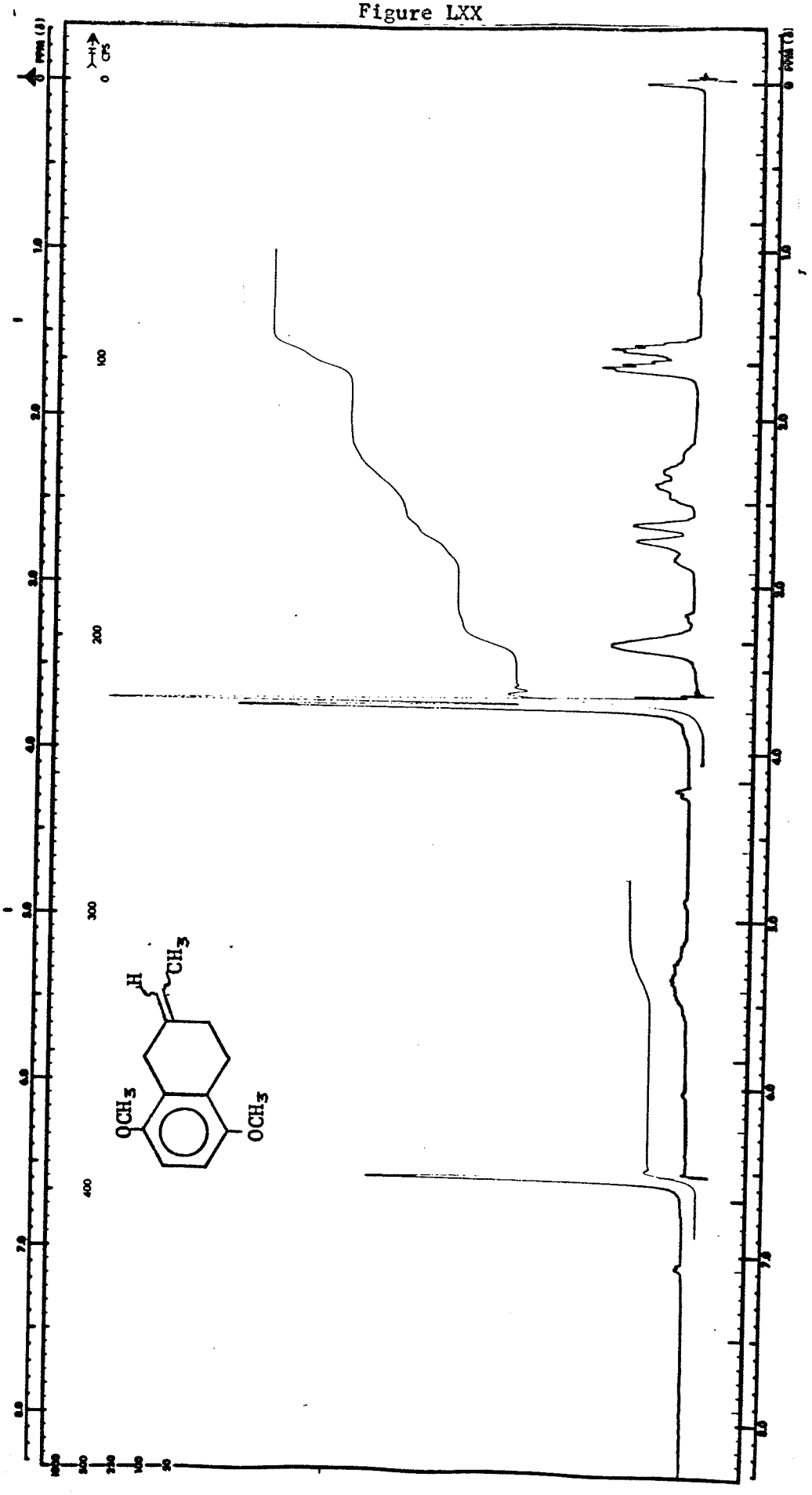
Nuclear magnetic resonance spectrum no. 11: 1,5,8-trimethoxy-3-acetyltetralin (XXIII), in $CDCl_3$. Sweep width = 500 Hz.

Figure LXIX



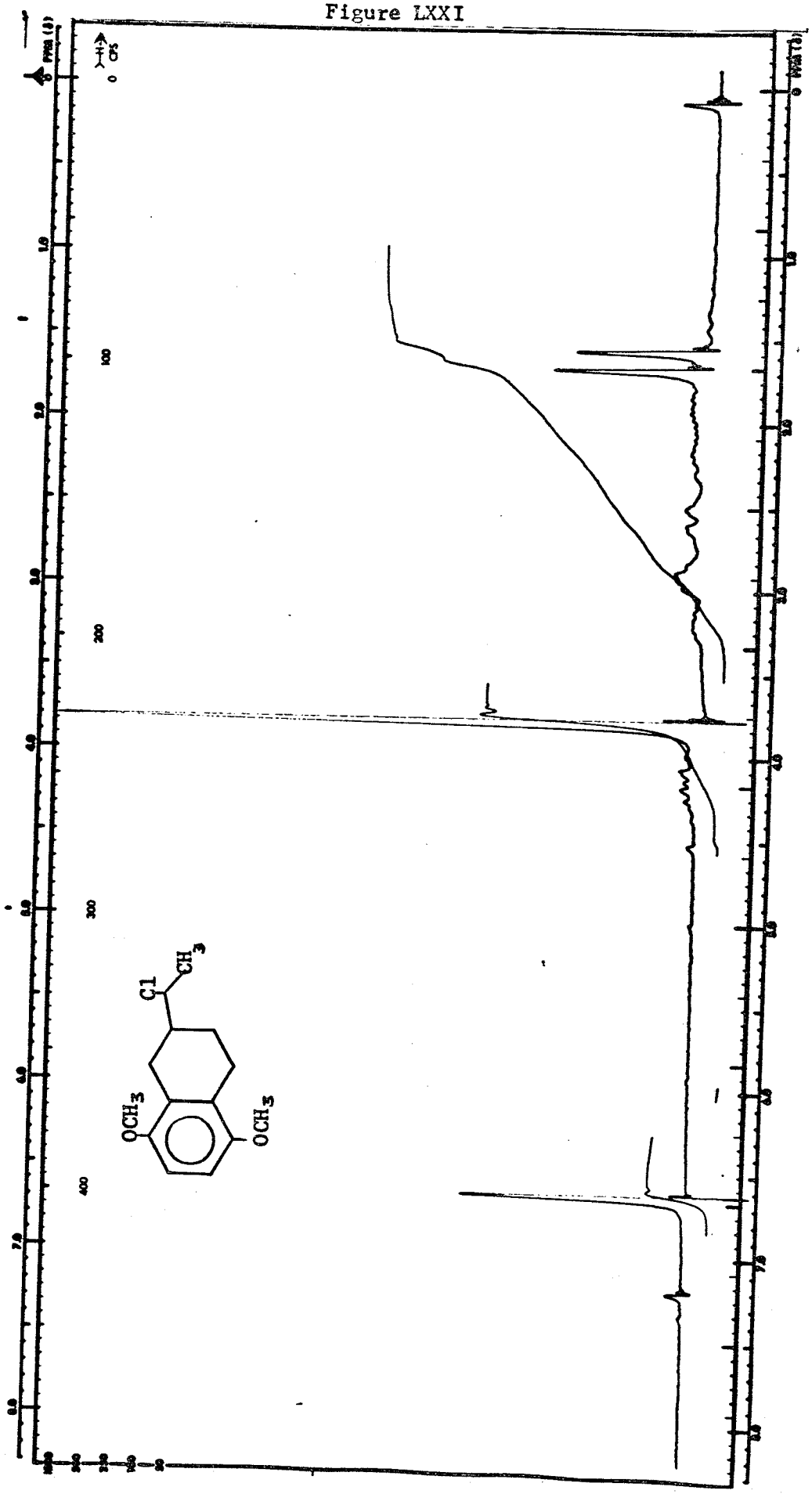
Nuclear magnetic resonance spectrum no. 12: 2-acetyl-5,8-dimethoxytetralin (XXIV), in $CDCl_3$. Sweep width = 500 Hz.

Figure LXX



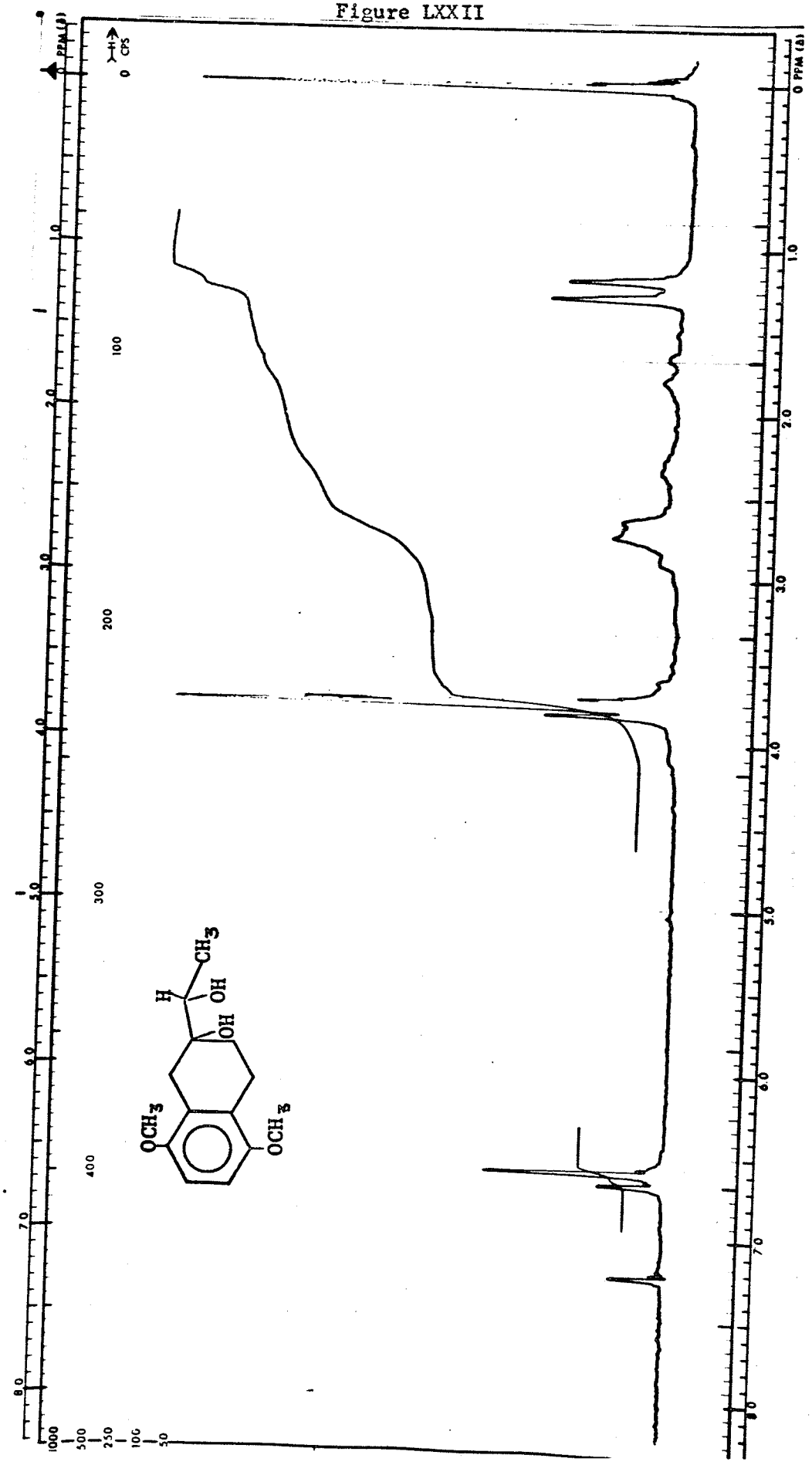
Nuclear magnetic resonance spectrum no. 13: Olefin mixture (XXVII), in $CDCl_3$. Sweep width = 500 Hz.

Figure LXXI



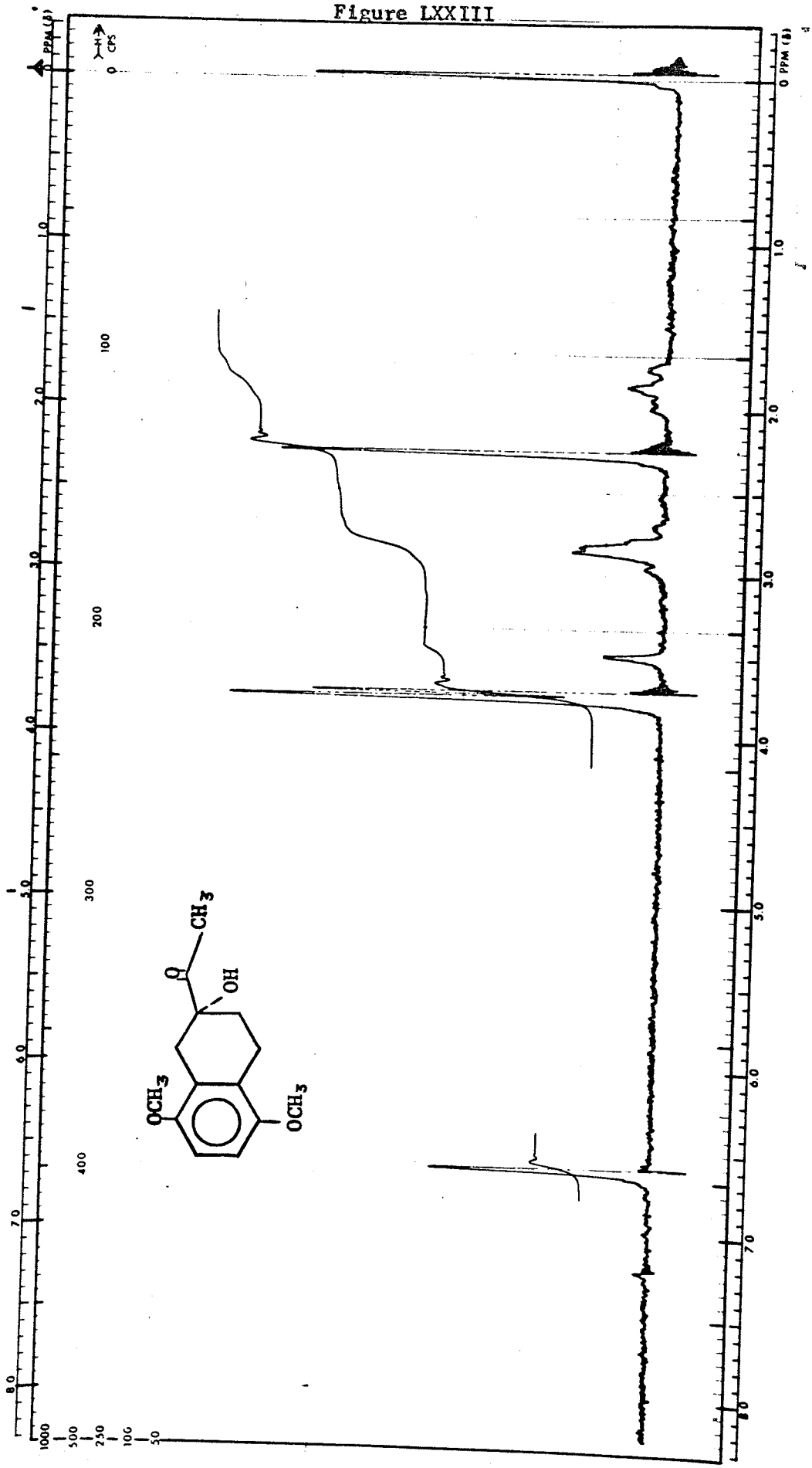
Nuclear magnetic resonance spectrum no. 14: 2-(1'-chloroethyl)-5,8-dimethoxytetralin (XXVIII), in $CDCl_3$. Sweep width = 500 Hz.

Figure LXXII



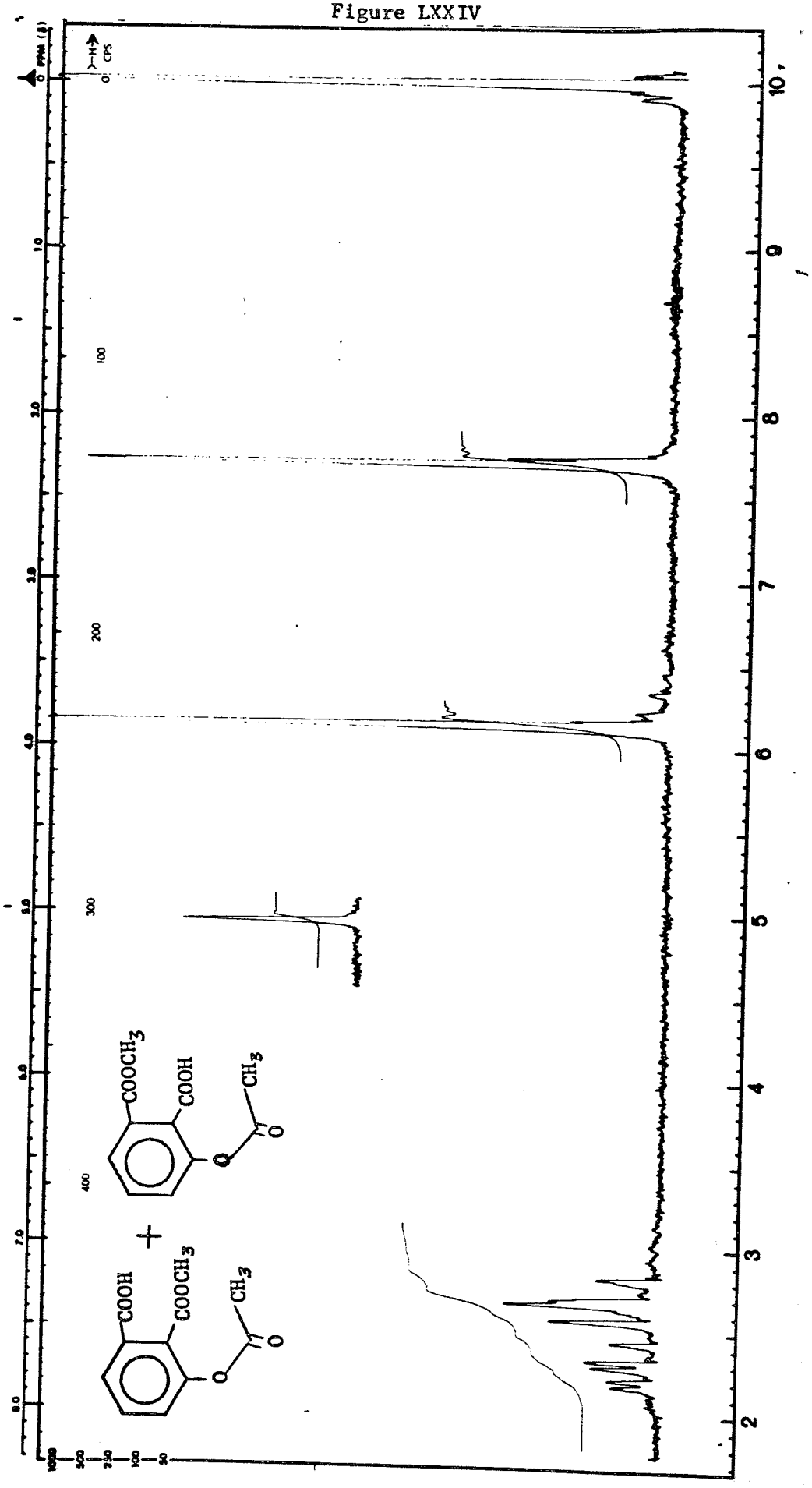
Nuclear magnetic resonance spectrum no. 15: 2-hydroxy-2-(1'-hydroxyethyl)-5,8-dimethoxytetralin (XXIX), in $CDCl_3$. Sweep width = 500 Hz.

Figure LXXIII



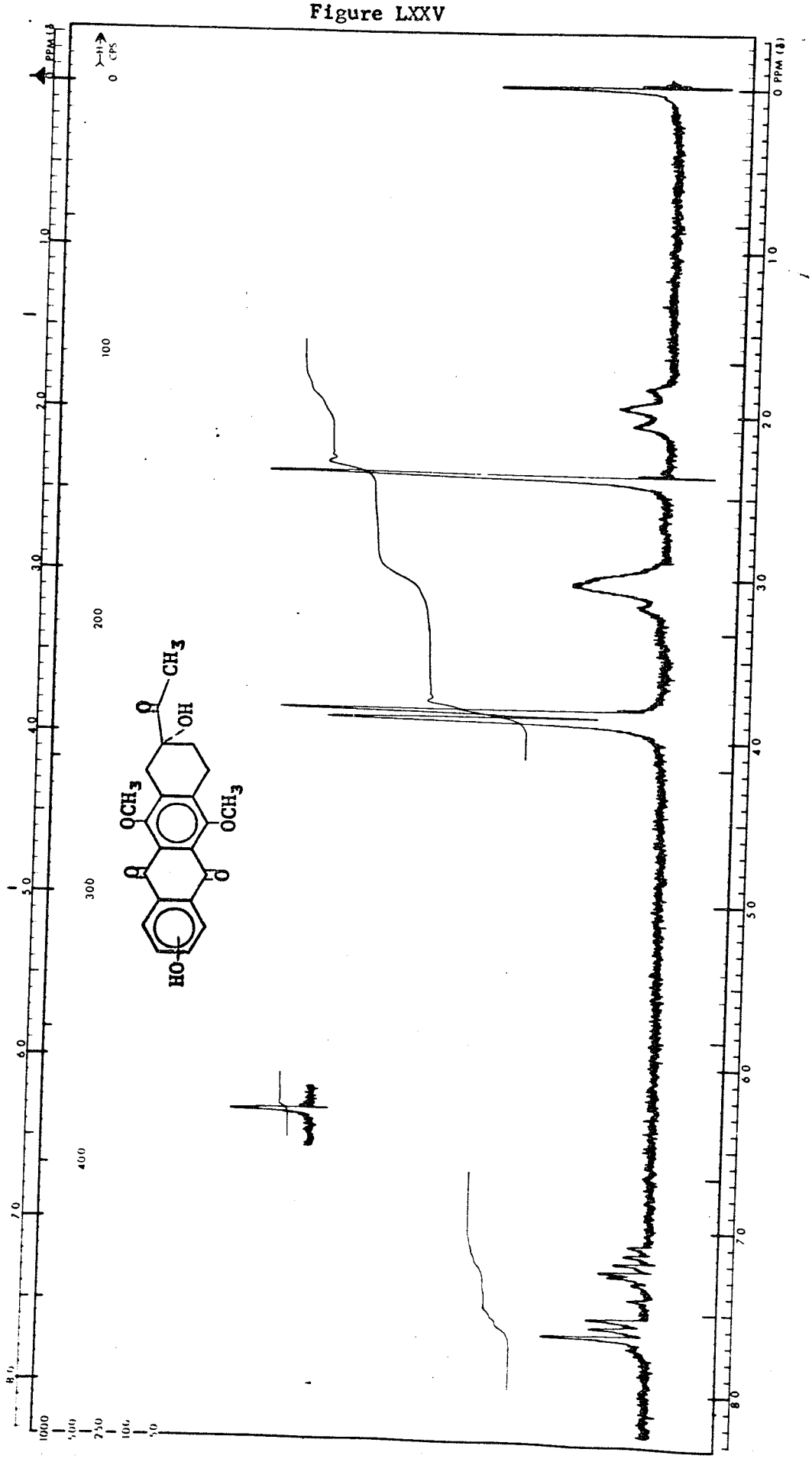
Nuclear magnetic resonance spectrum no. 16: 2-acetyl-2-hydroxy-5,8-dimethoxytetralin (XXXI), in $CDCl_3$. Sweep width = 500 Hz.

Figure LXXIV



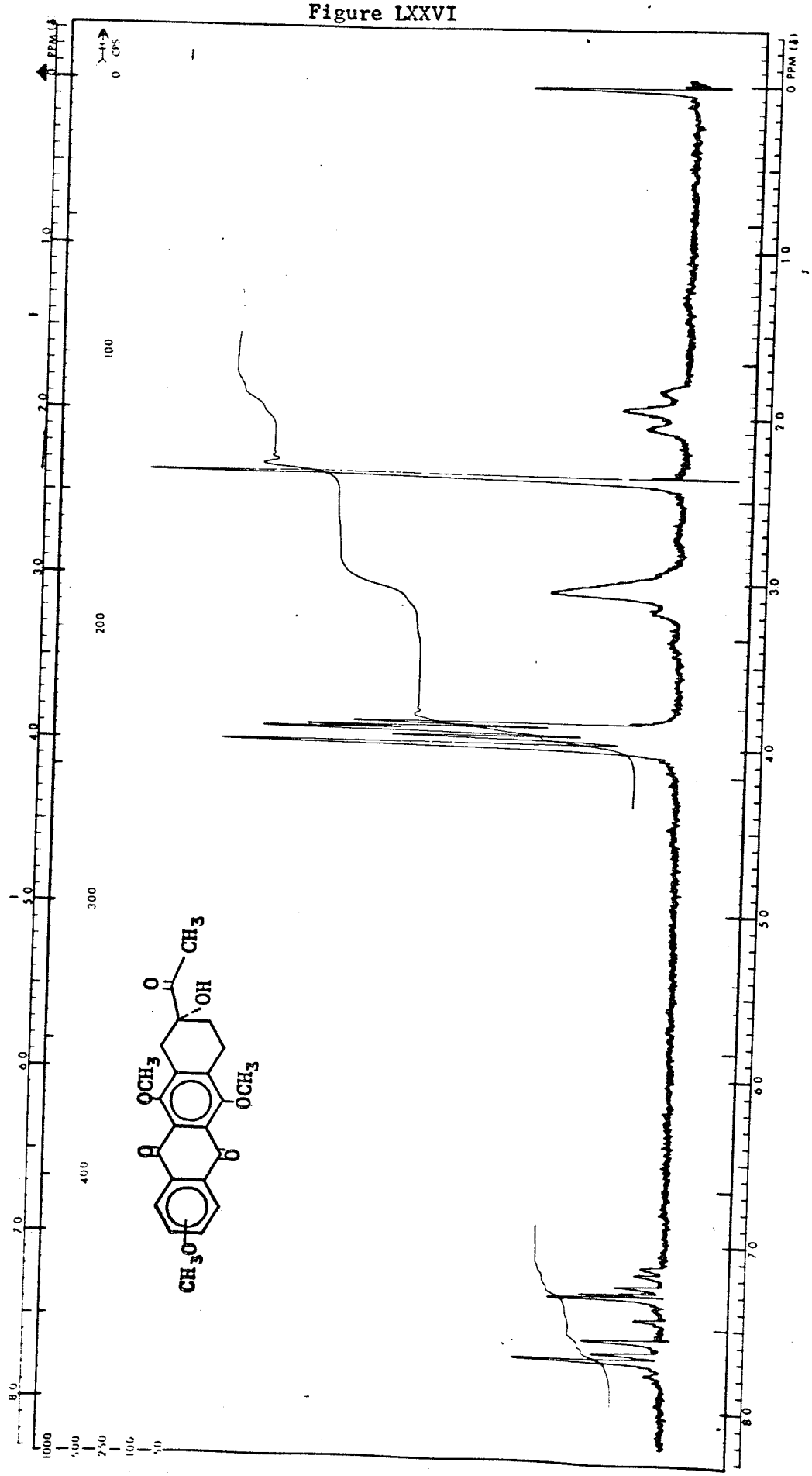
Nuclear magnetic resonance spectrum no. 17: Acetoxycarbomethoxybenzoic acid mixture (XXXII), in $CDCl_3$. Sweep width = 500 Hz., insert is on sweep width = 1000 Hz.

Figure LXXV



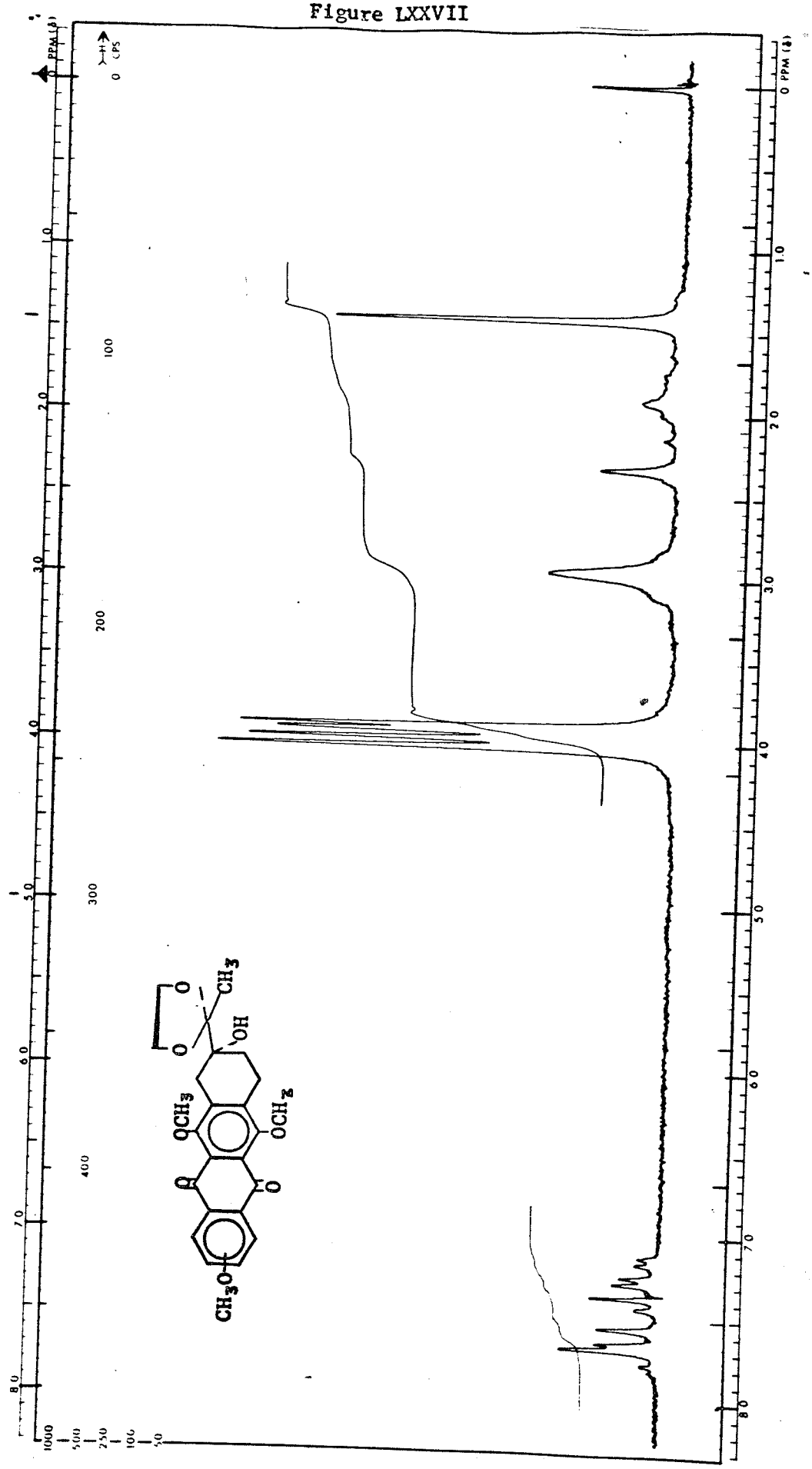
Nuclear magnetic resonance spectrum no. 18: Isomeric hydronaphthacene quinone mixture (XXXV), in $CDCl_3$. Sweep width = 500 Hz., insert is on sweep width = 1000 Hz.

Figure LXXVI



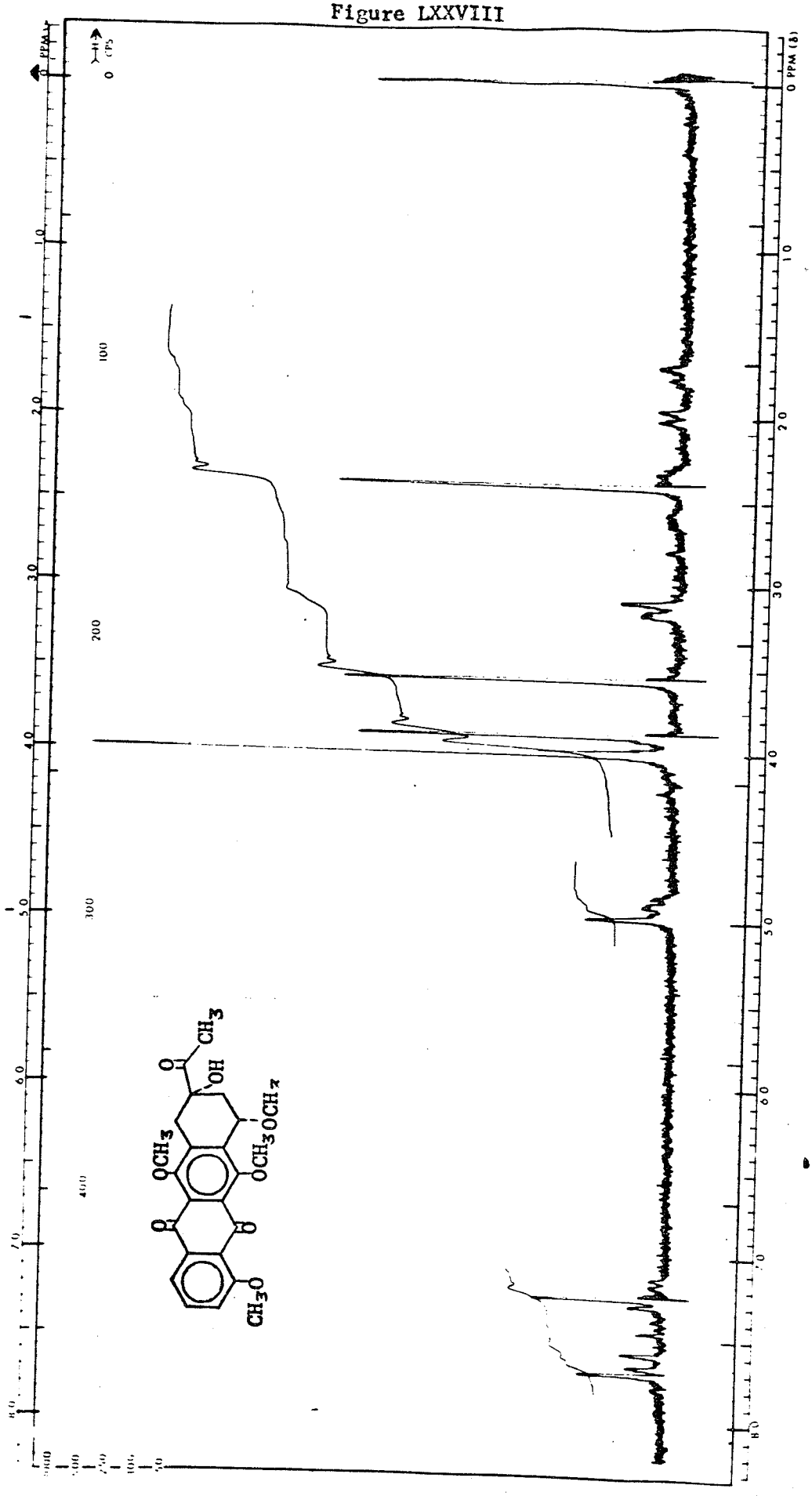
Nuclear magnetic resonance spectrum no. 19: Isomeric hydronaphthacene quinone mixture (XXXVI), in $CDCl_3$. Sweep width = 500 Hz.

Figure LXXVII



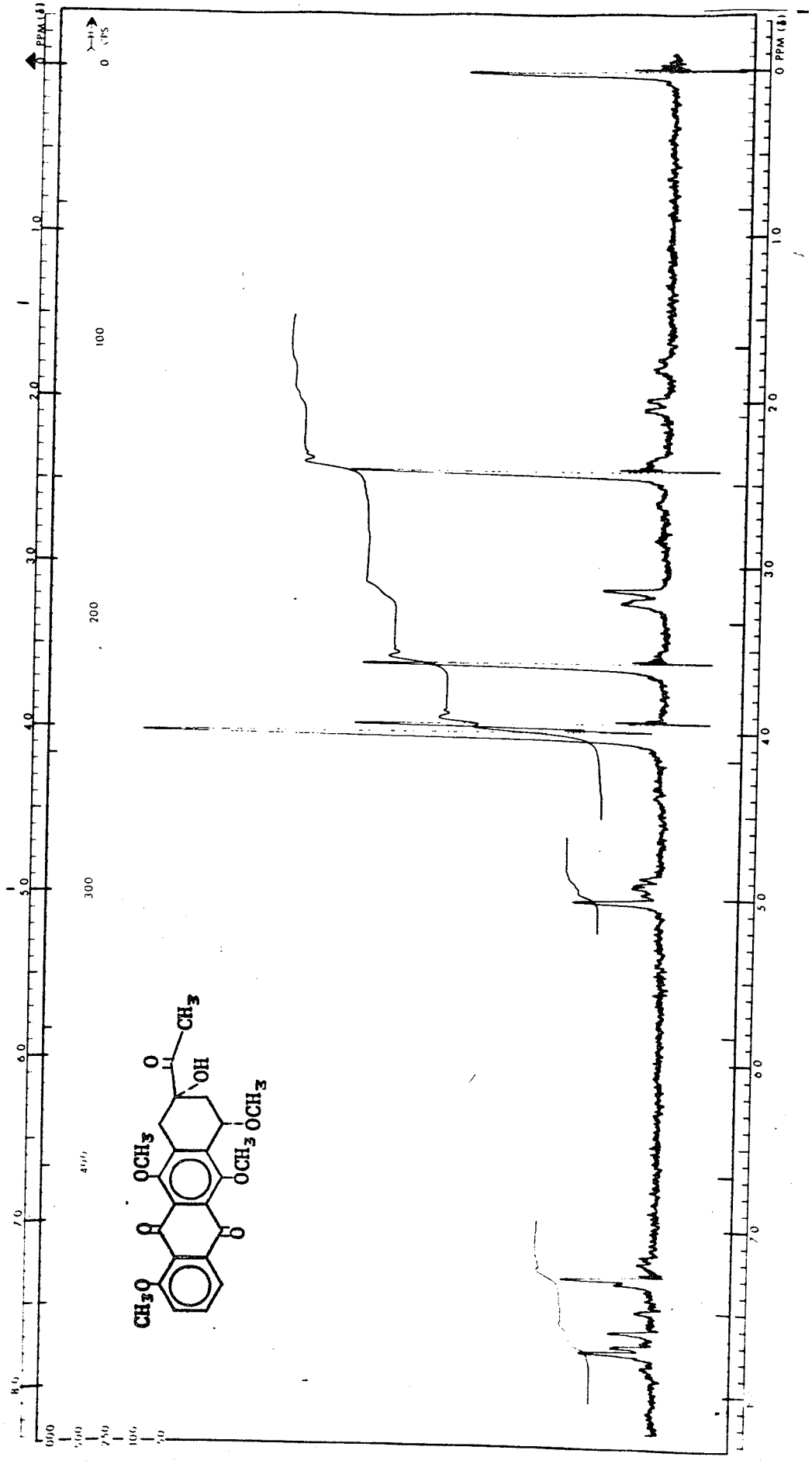
Nuclear magnetic resonance spectrum no. 20: Isomeric hydronaphthacene quinone ketal mixture (XXXVII), in $CDCl_3$. Sweep width = 500 Hz.

Figure LXXVIII



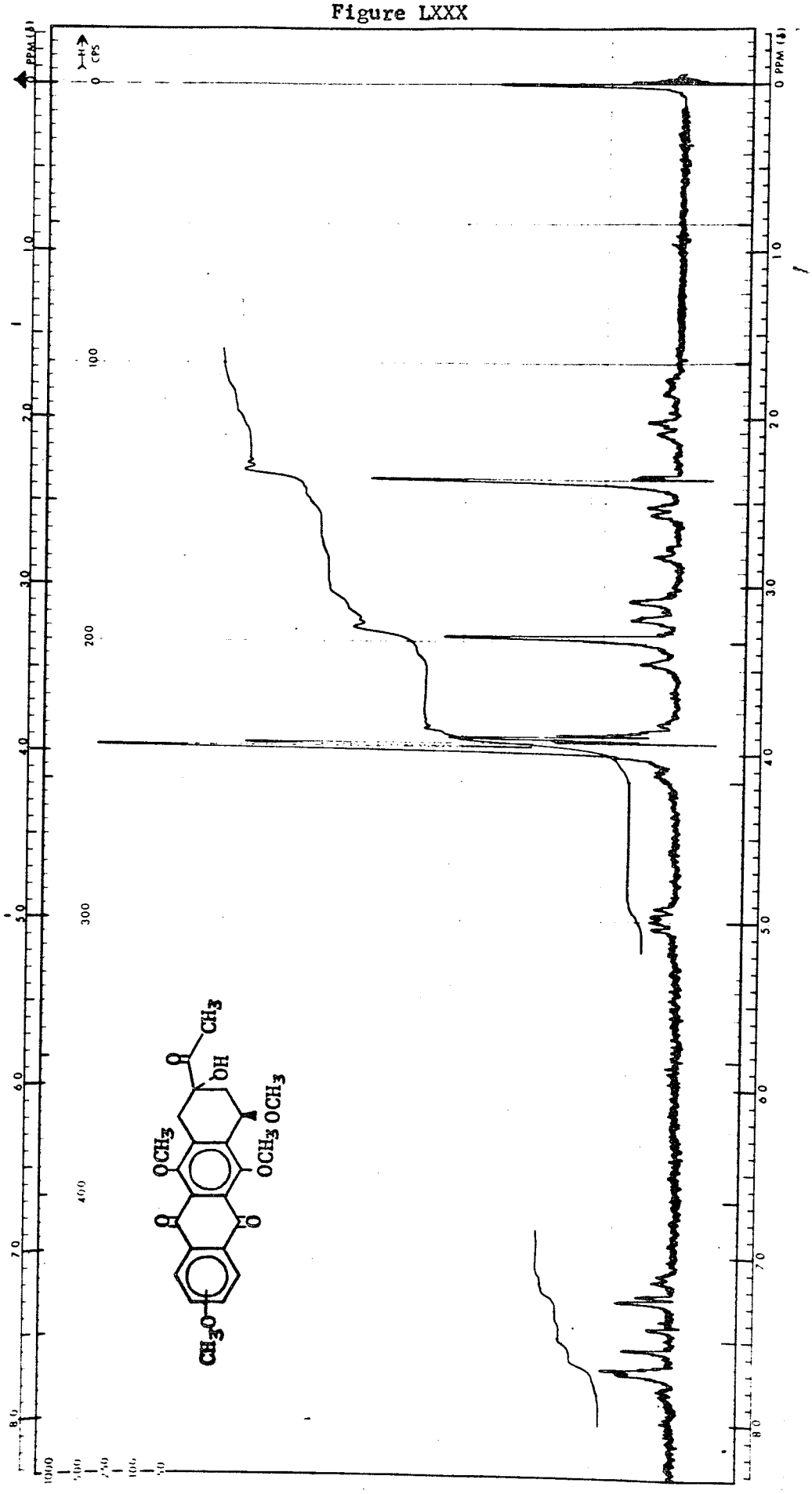
Nuclear magnetic resonance spectrum no. 21: Synthetic daunomycinone trimethyl ether (XLVI), in $CDCl_3$. Sweep width = 500 Hz.

Figure LXXIX



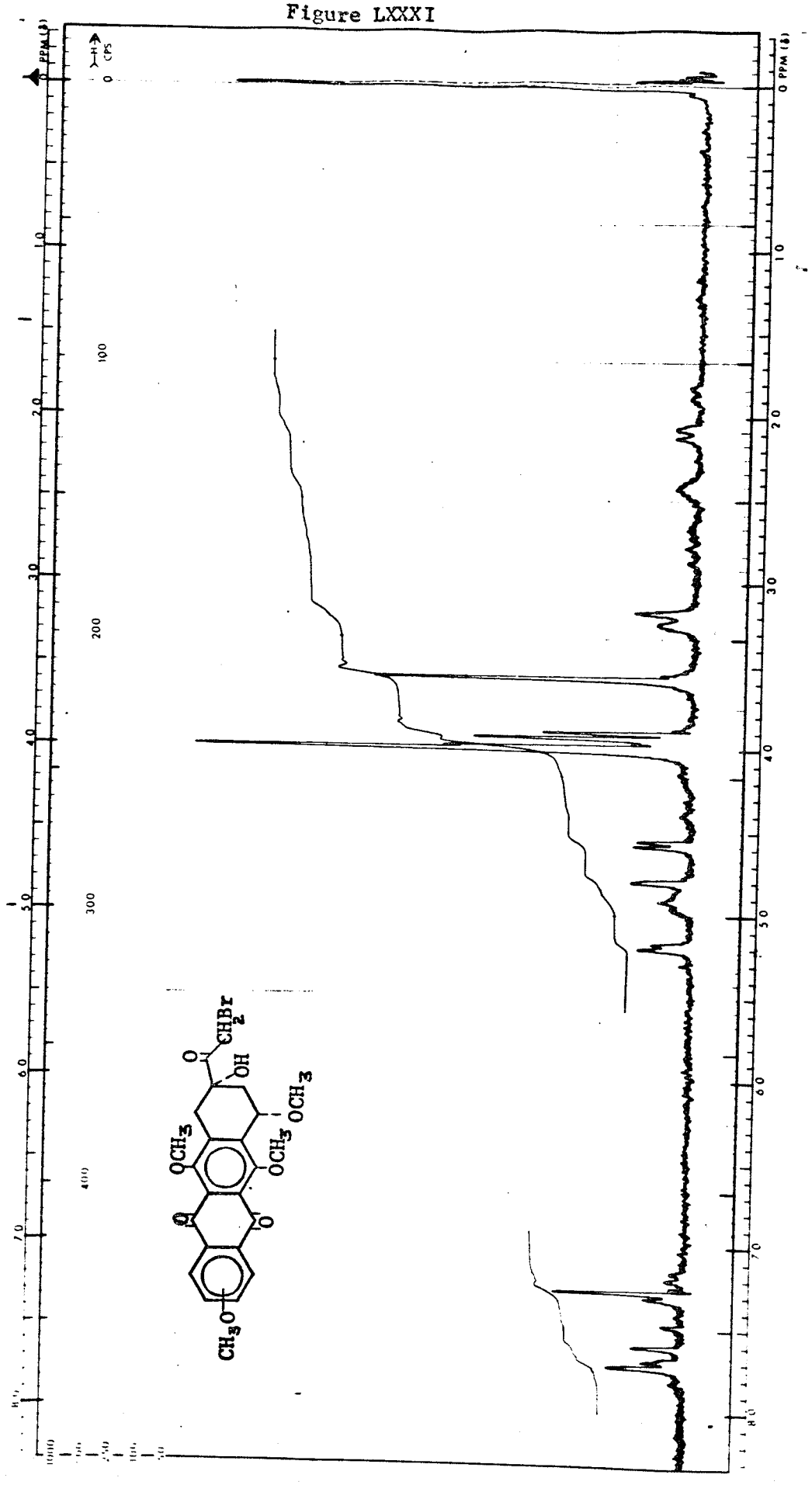
Nuclear magnetic resonance spectrum no. 22: Synthetic isodaunomycinone trimethyl ether (XLV), in $CDCl_3$. Sweep width = 500 Hz.

Figure LXXX



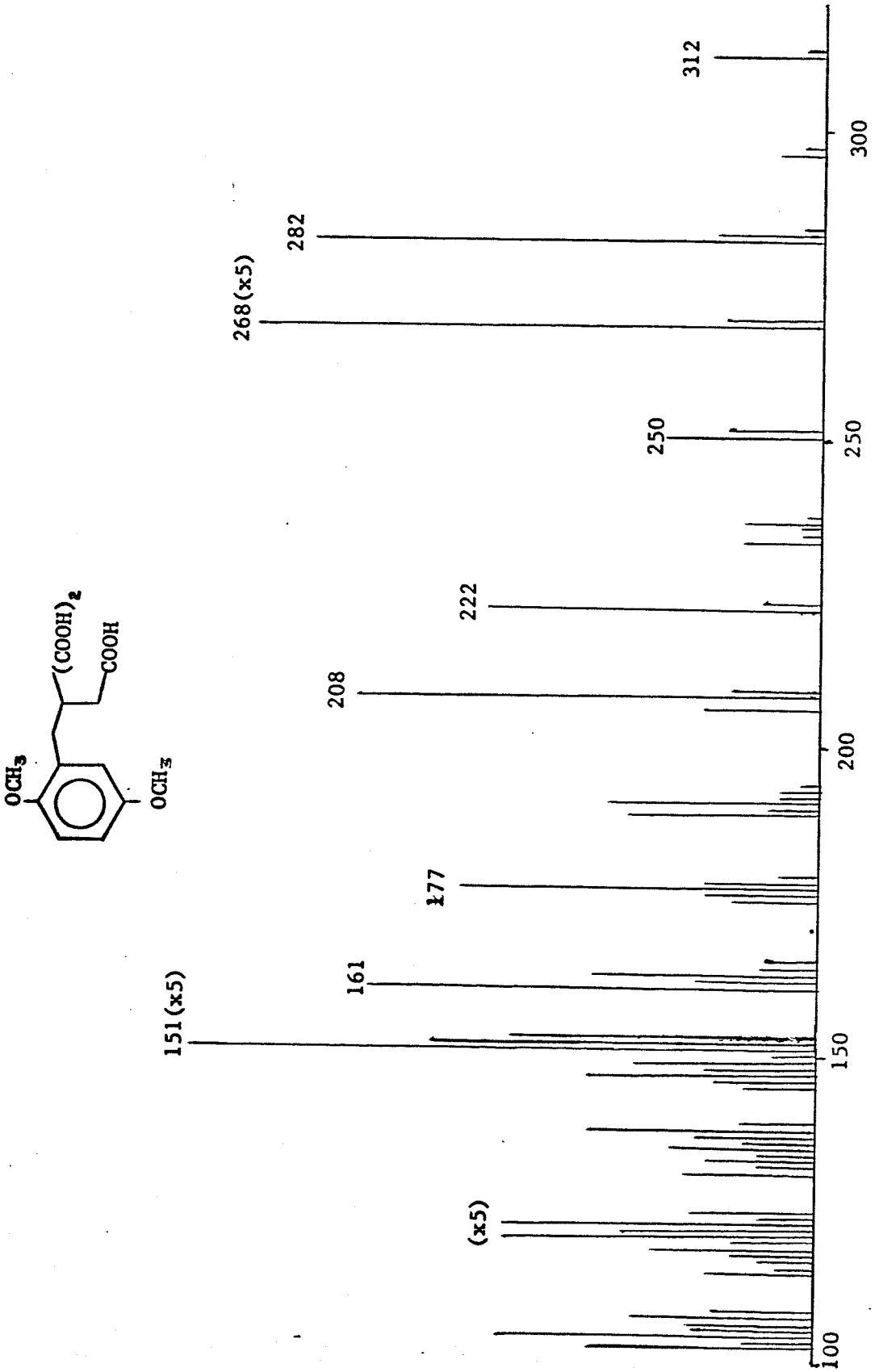
Nuclear magnetic resonance spectrum no. 23: Isomeric hydronaphthacene quinone mixture (XLII), in $CDCl_3$. Sweep width = 500 Hz.

Figure LXXXI



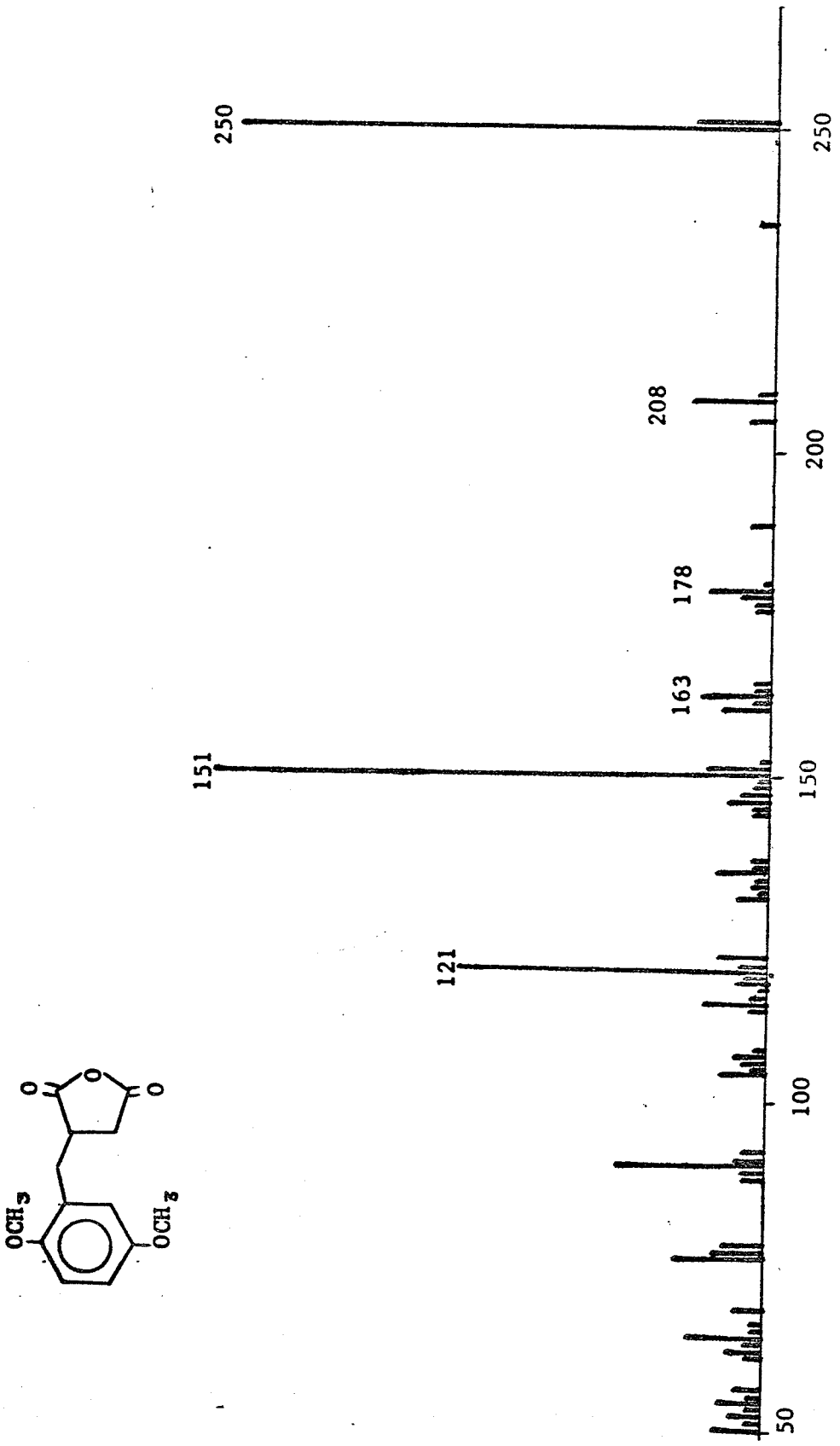
Nuclear magnetic resonance spectrum no. 24: Isomeric hydronaphthacene quinone-α-bromoketone mixture (XLIV), in $CDCl_3$. Sweep width = 500 Hz.

Figure LXXXII



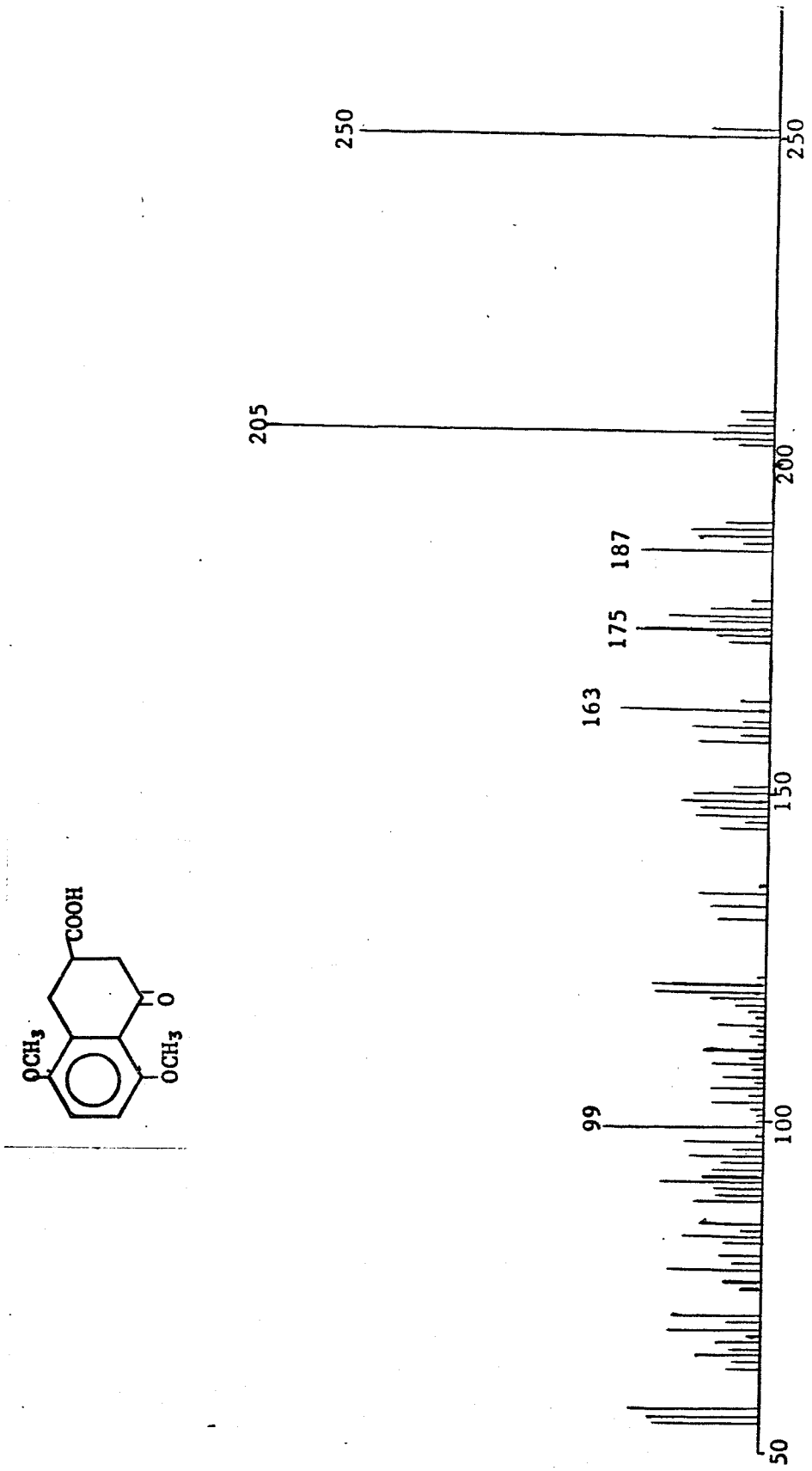
Mass spectrum no. 1: 3,3-dicarbohydroxy-4-(2,5-dimethoxyphenyl) butanoic acid (XV).

Figure LXXXIII



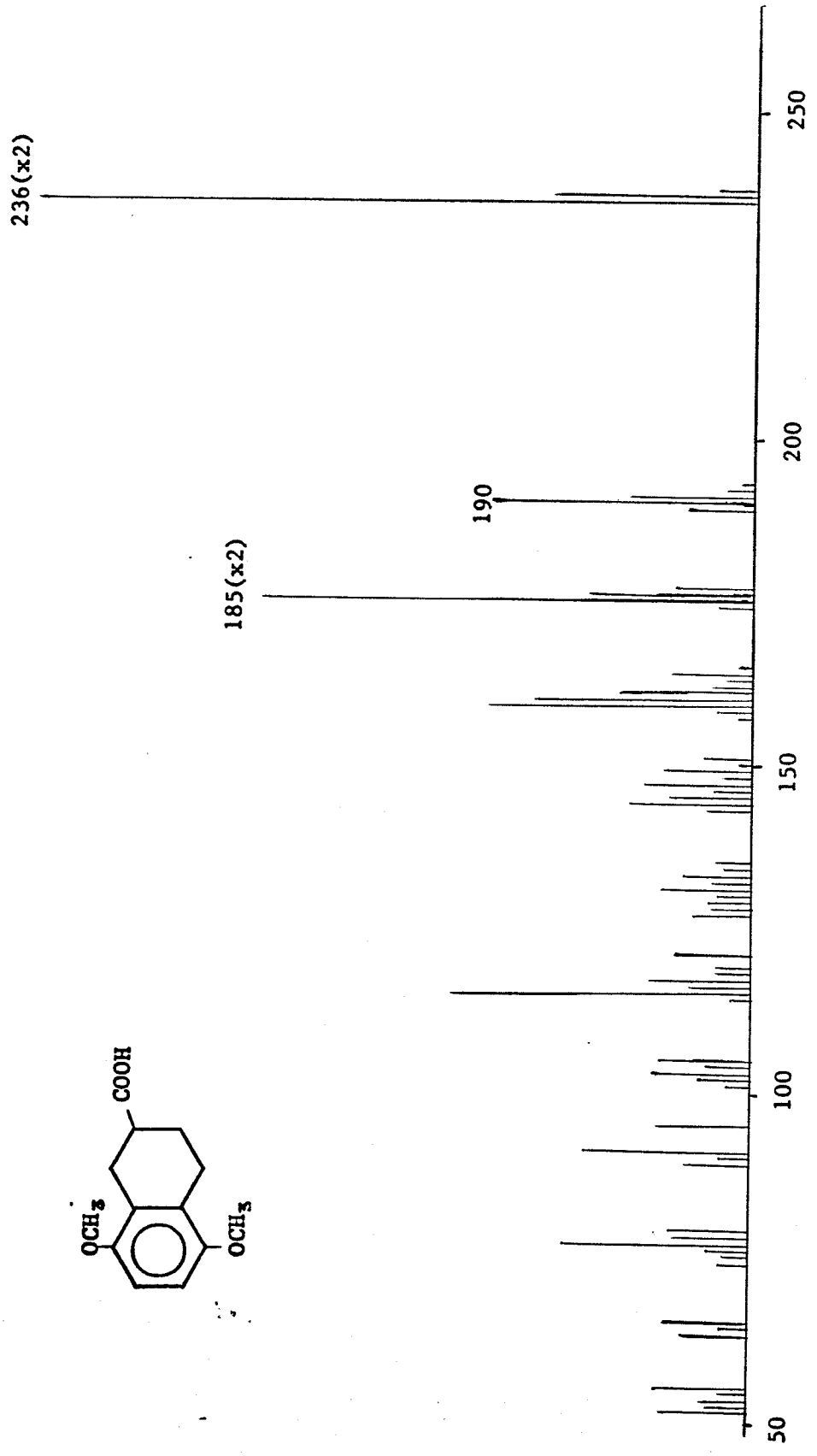
Mass spectrum no. 2: 2',5'-dimethoxybenzylsuccinic anhydride (XVII).

Figure LXXXIV



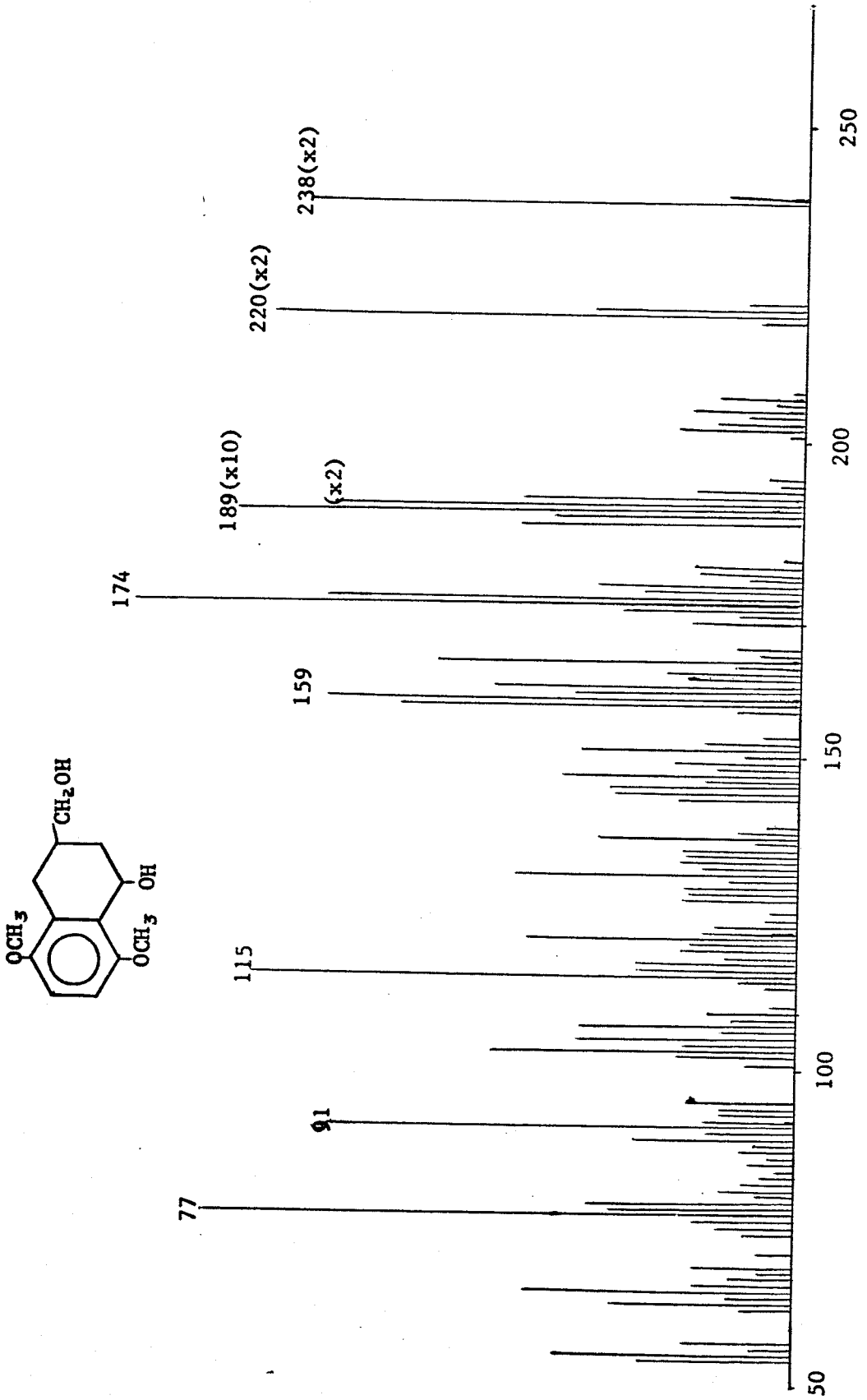
Mass spectrum no. 3: 3-carbohydroxy-5,8-dimethoxy-1-tetralone (XVIII).

Figure LXXXV



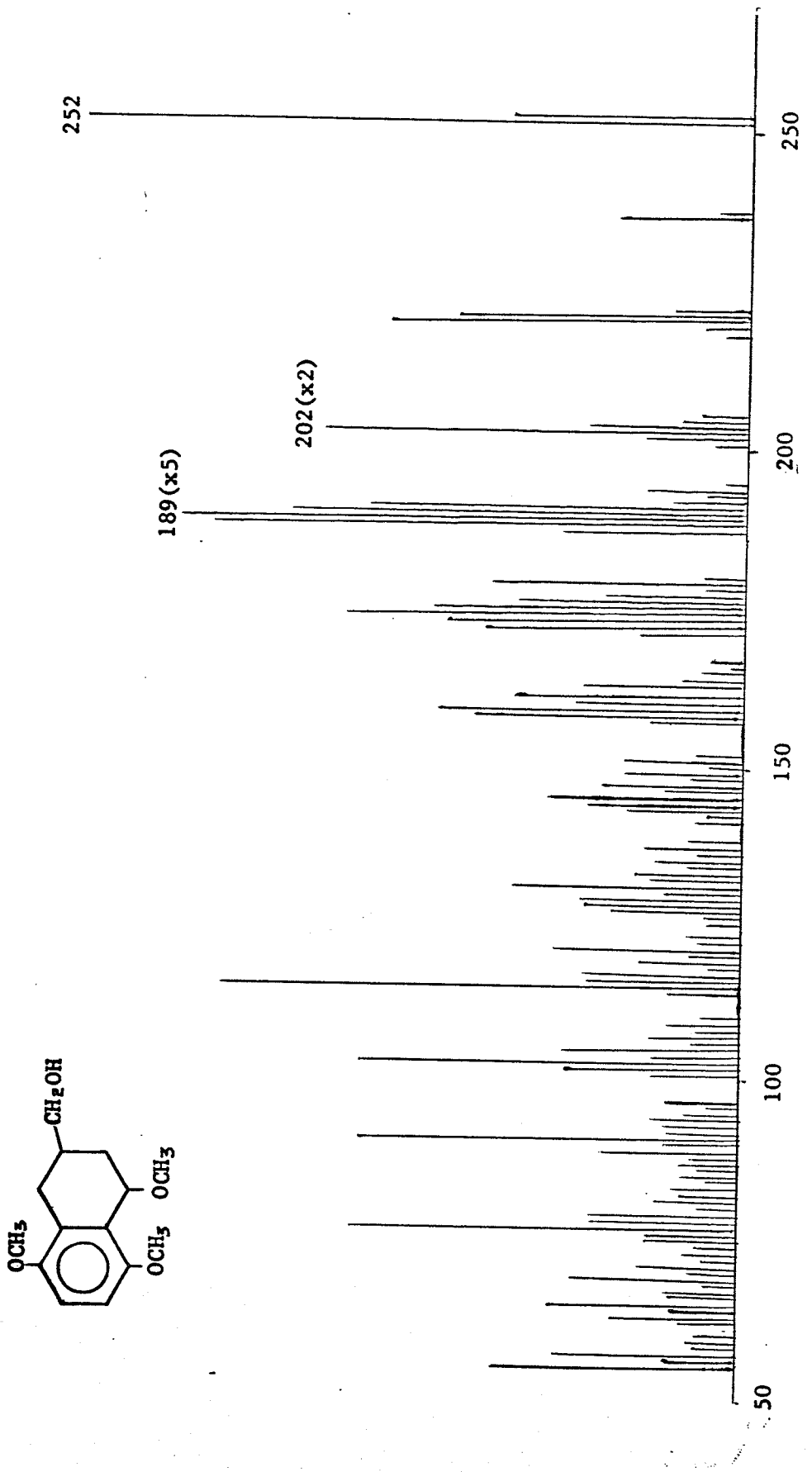
Mass spectrum no. 4: 2-carbohydroxy-5,8-dimethoxytetralin (XXV).

Figure LXXXVI



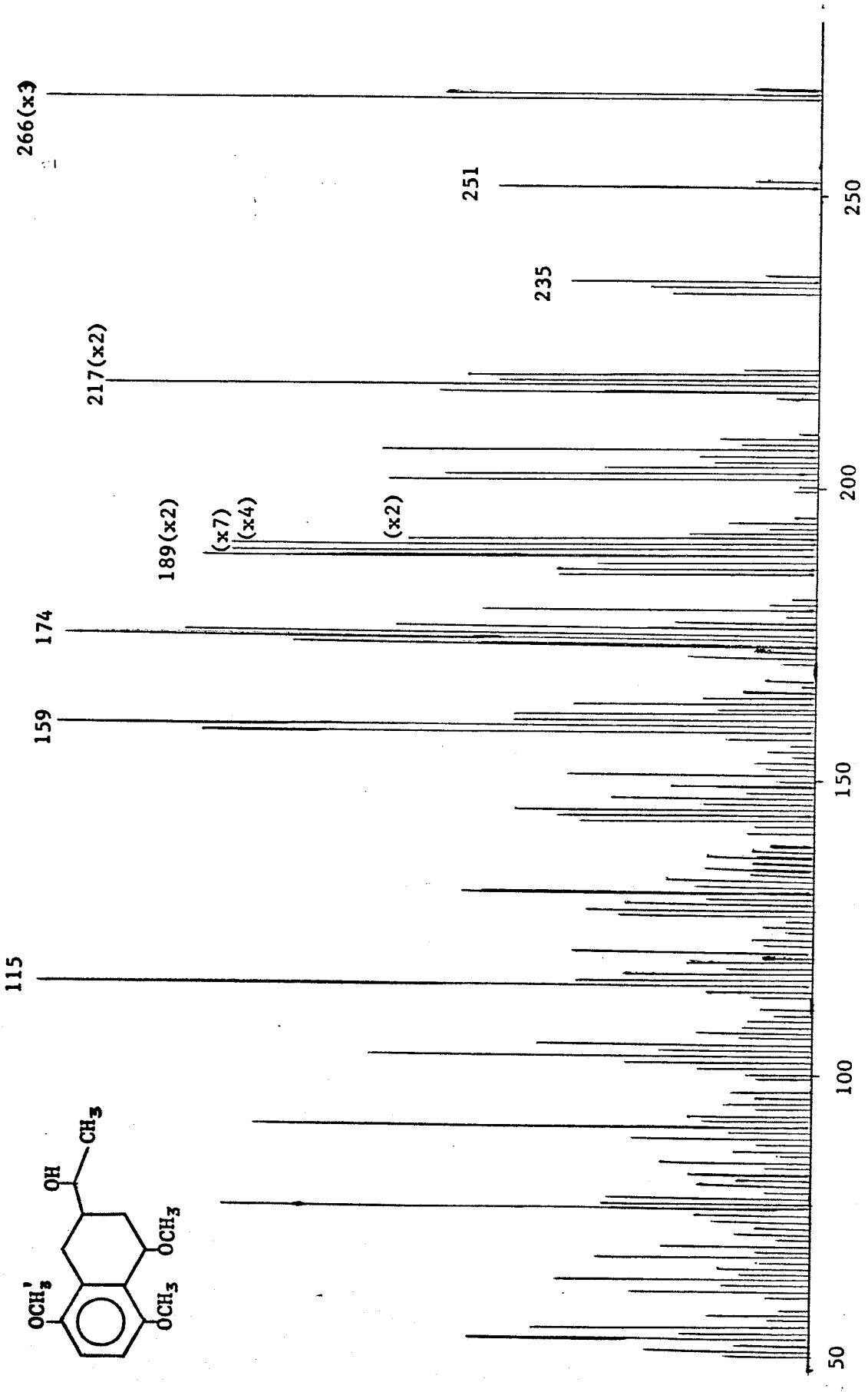
Mass spectrum no. 5: 1-hydroxy-3-hydroxymethyl-5,8-dimethoxytetralin (XIX).

Figure LXXXVII



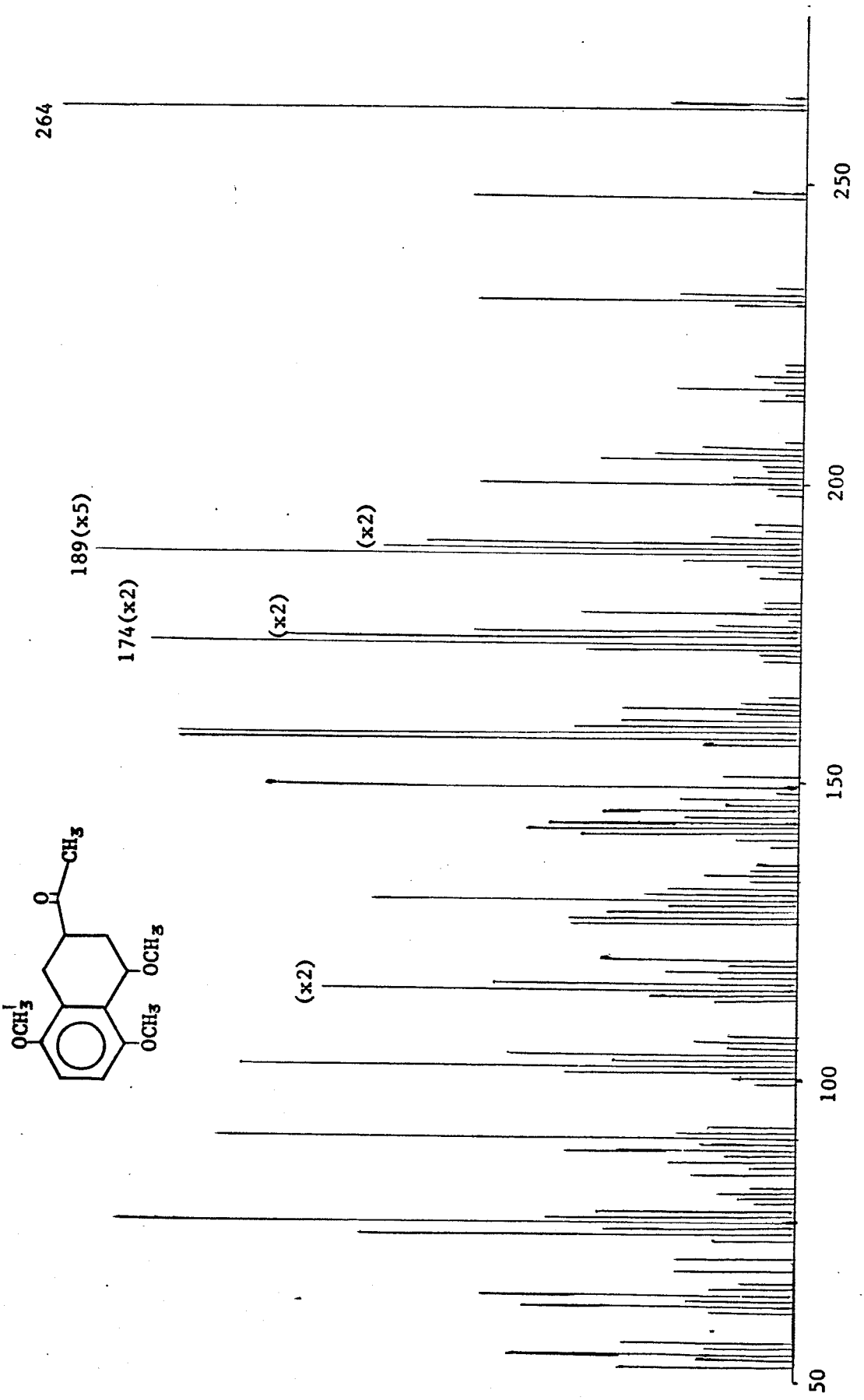
Mass spectrum no. 6: 1,5,8-trimethoxy-3-hydroxymethyltetralin (XX).

Figure LXXXVIII



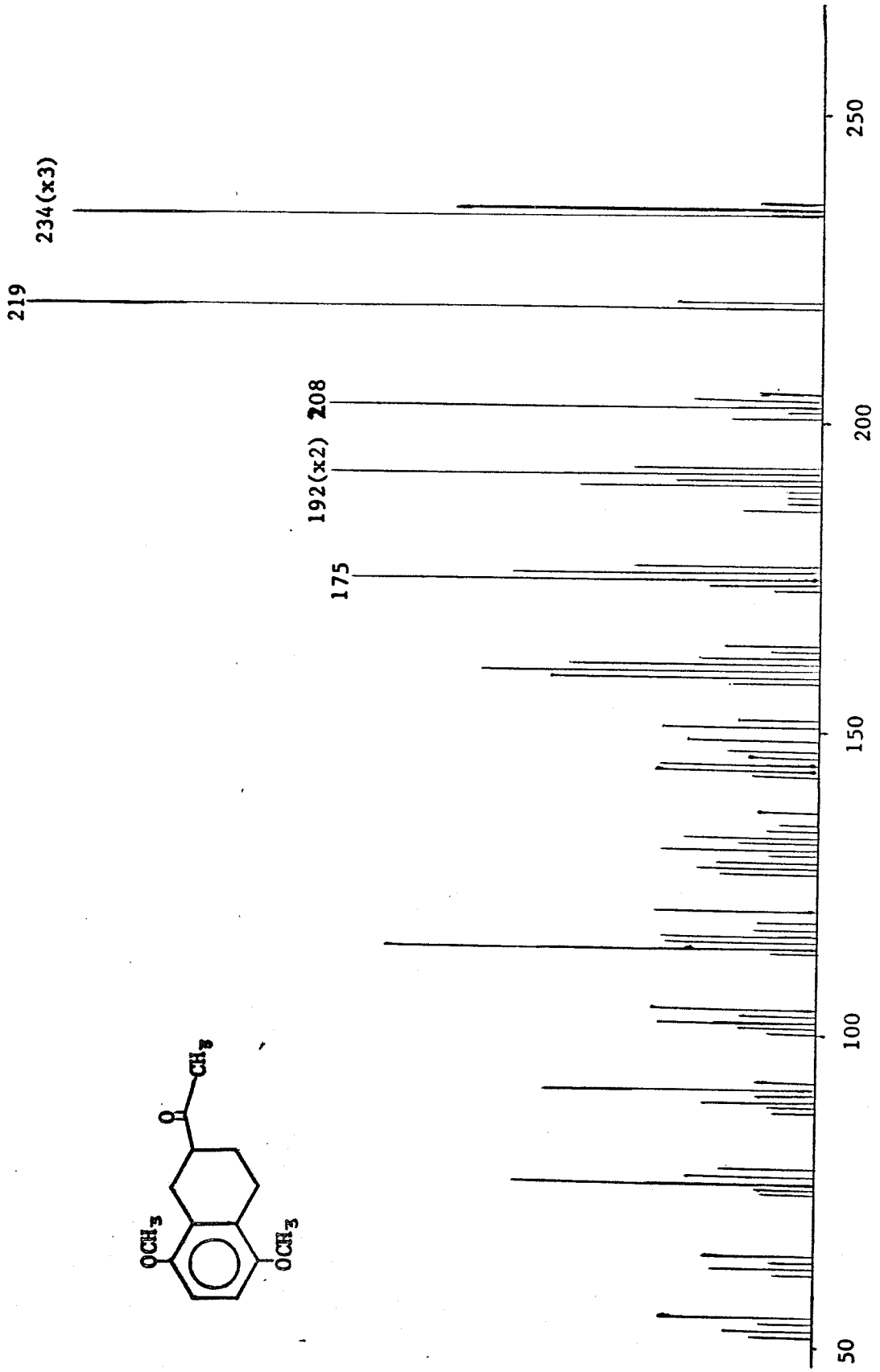
Mass spectrum no. 7: 1,5,8-trimethoxy-3-(1'-hydroxyethyl) tetralin (XXII).

Figure LXXXIX



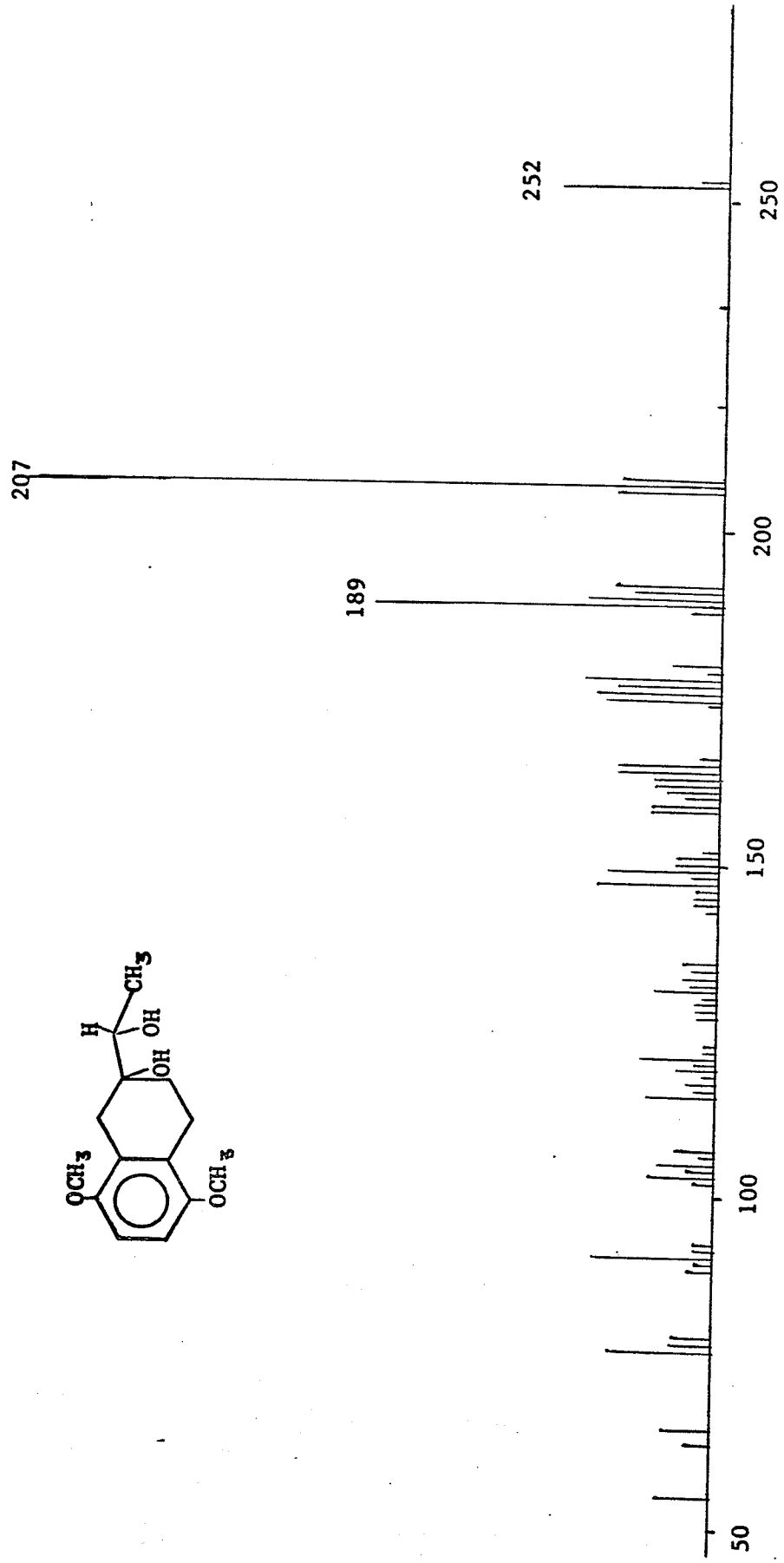
Mass spectrum no. 8: 1,5,8-trimethoxy-3-acetyltetralin (XXIII).

Figure XC



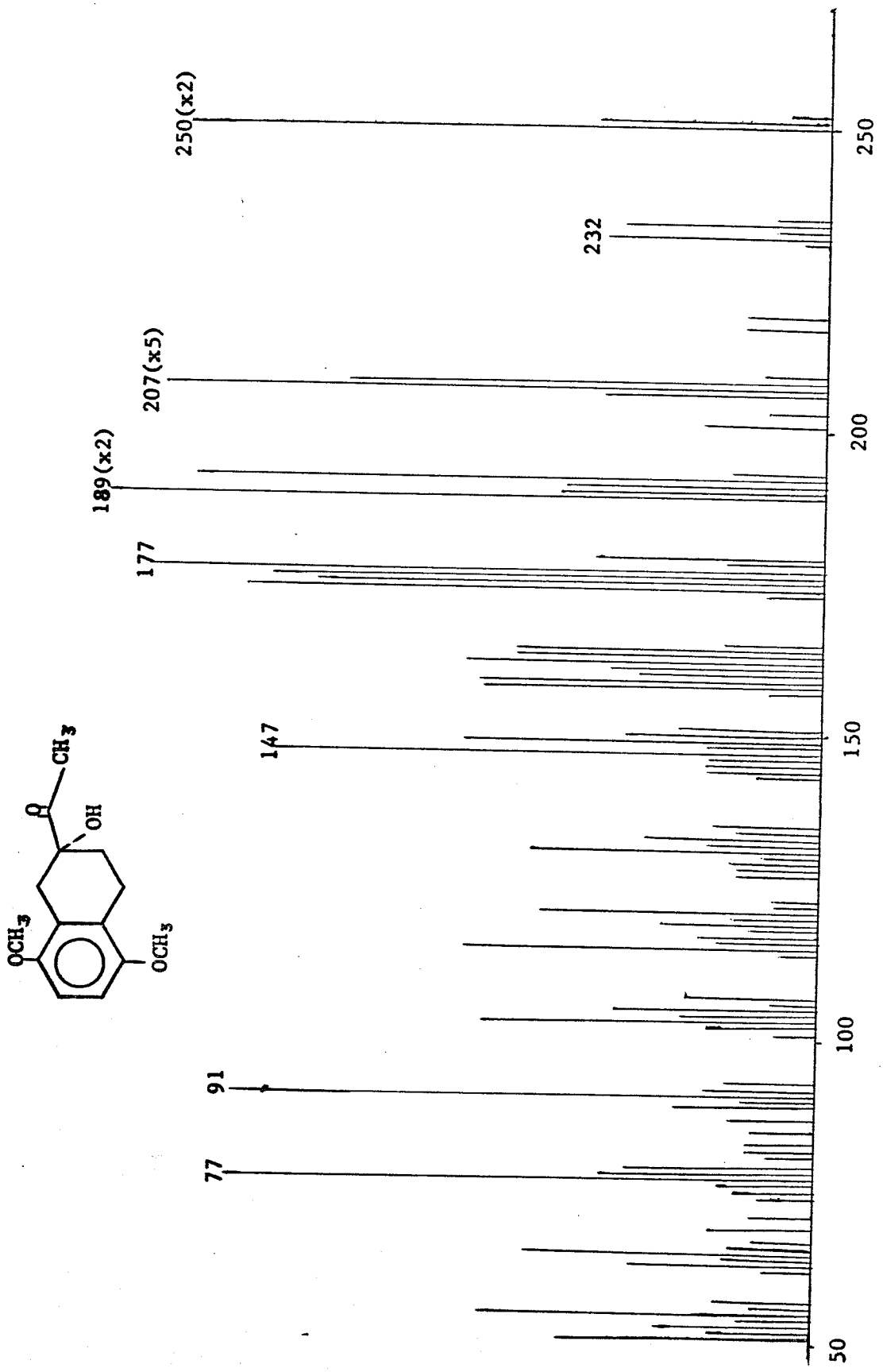
Mass spectrum no. 9: 2-acetyl-5,8-dimethoxytetralin (XXIV).

Figure XCI



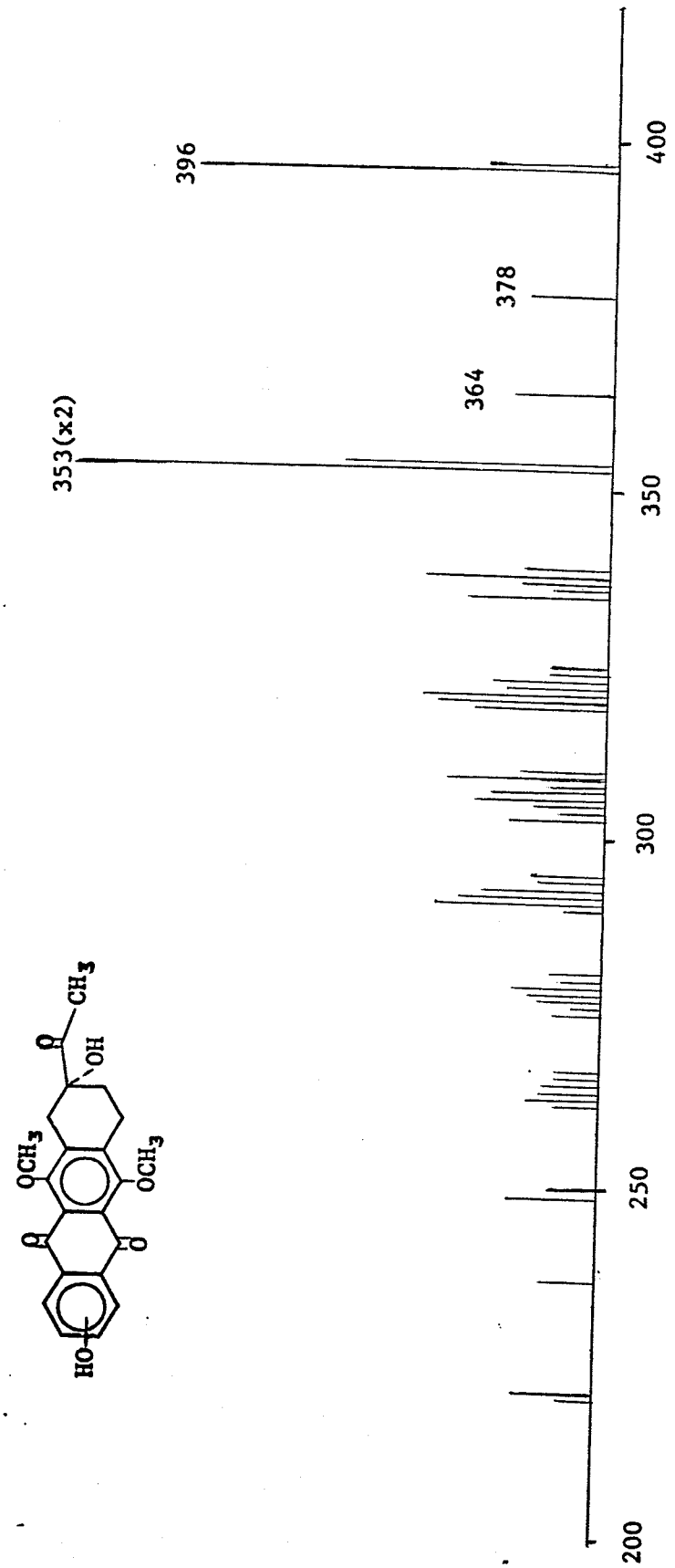
Mass spectrum no. 10: 2-hydroxy-2-(1'-hydroxyethyl)-5,8-dimethoxytetralin (XXIX).

Figure XCII



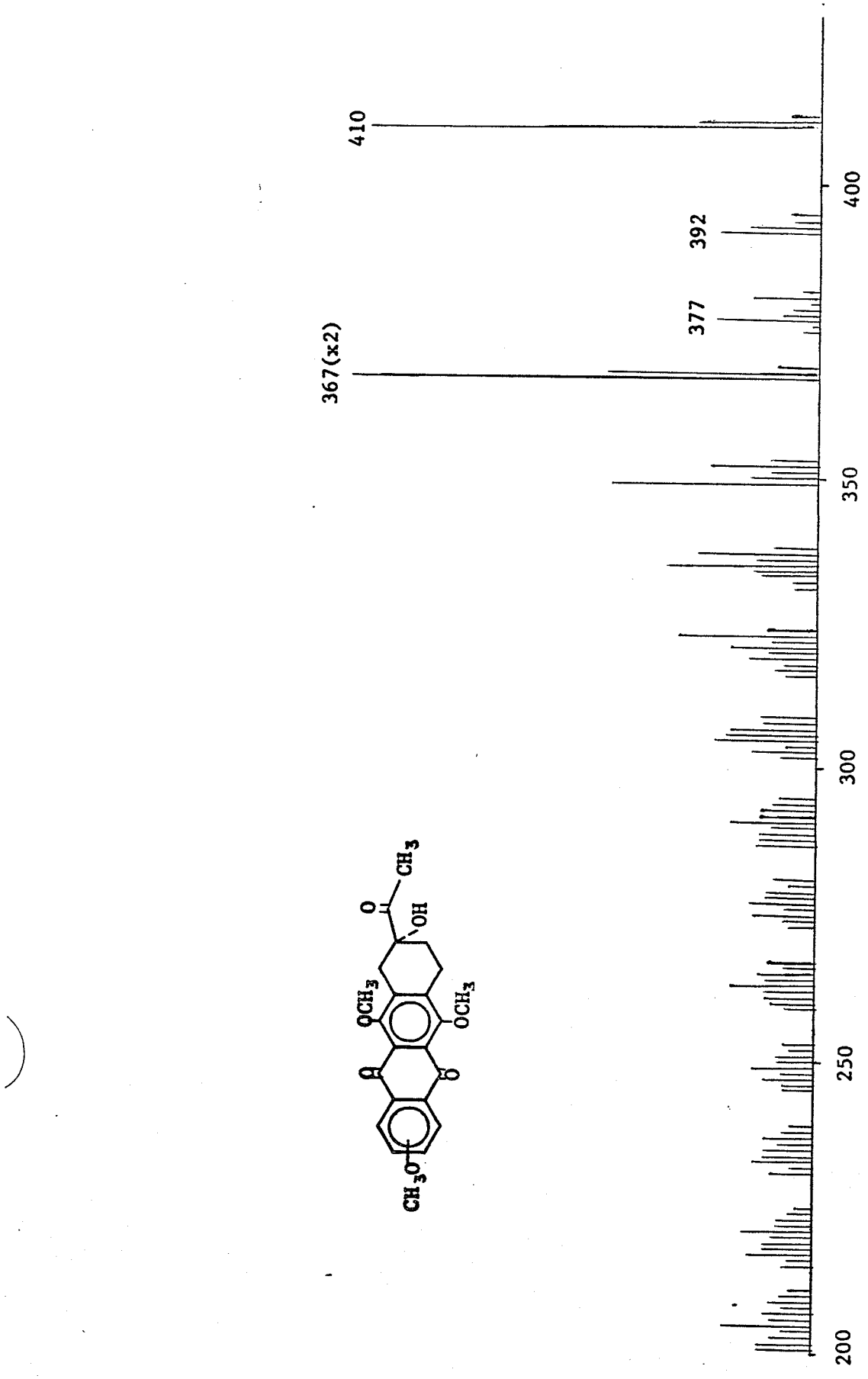
Mass spectrum no. 11: 2-acetyl-2-hydroxy-5,8-dimethoxytetralin (XXXI).

Figure XCIII



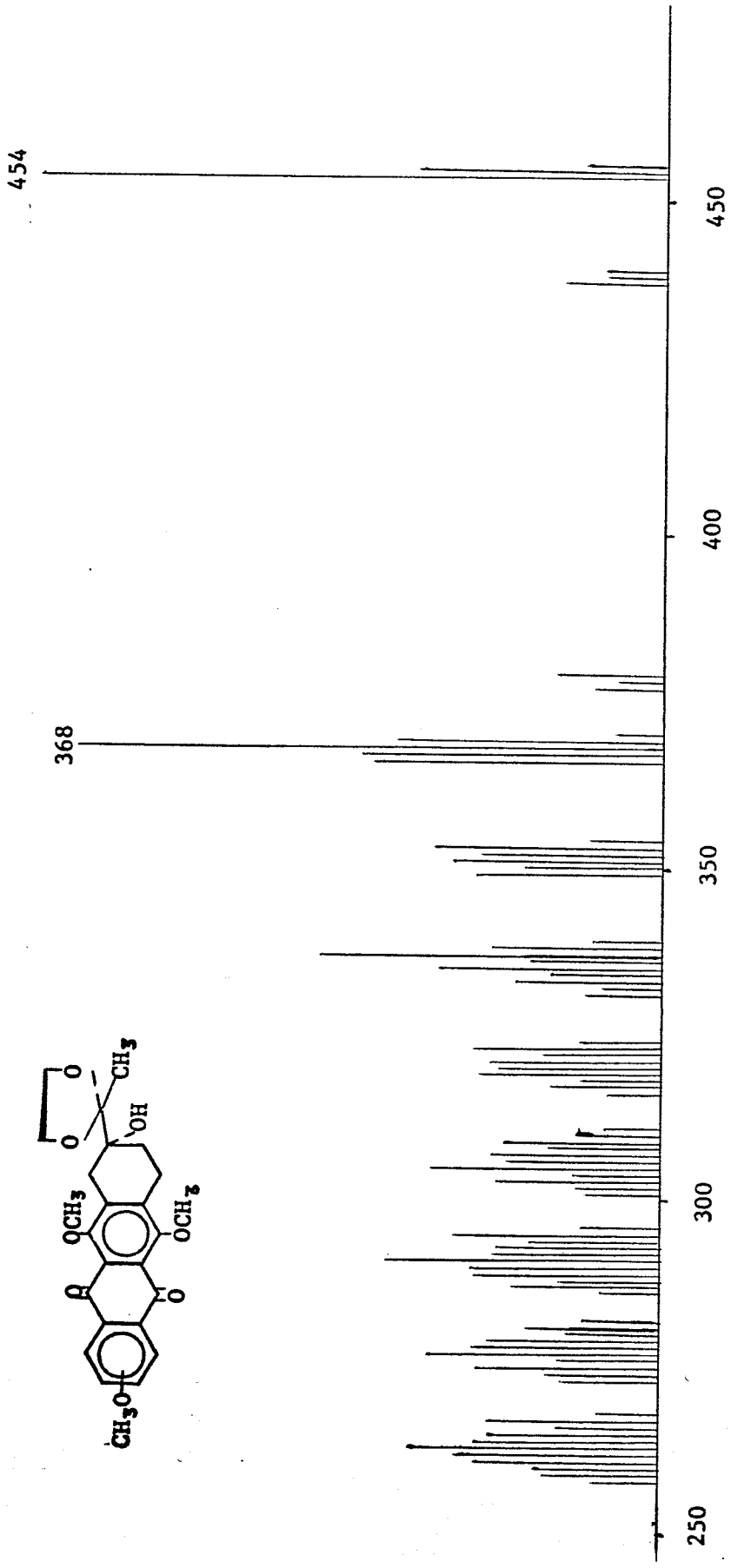
Mass spectrum no. 12: Isomeric hydronaphthacene quinone mixture (XXXV).

Figure XCIV



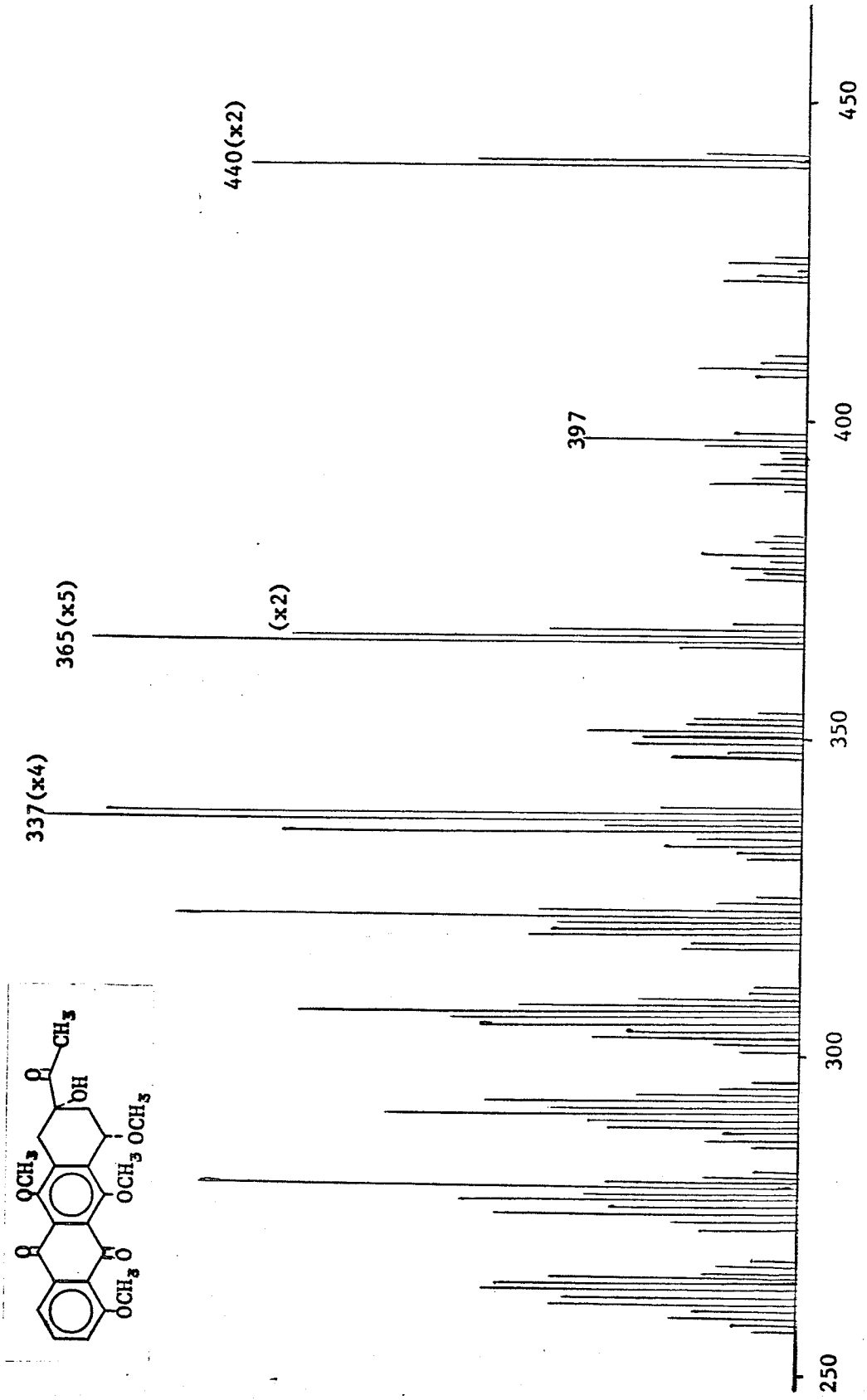
Mass spectrum no. 13: Isomeric hydronaphthacene quinone mixture (XXXVI).

Figure XCV



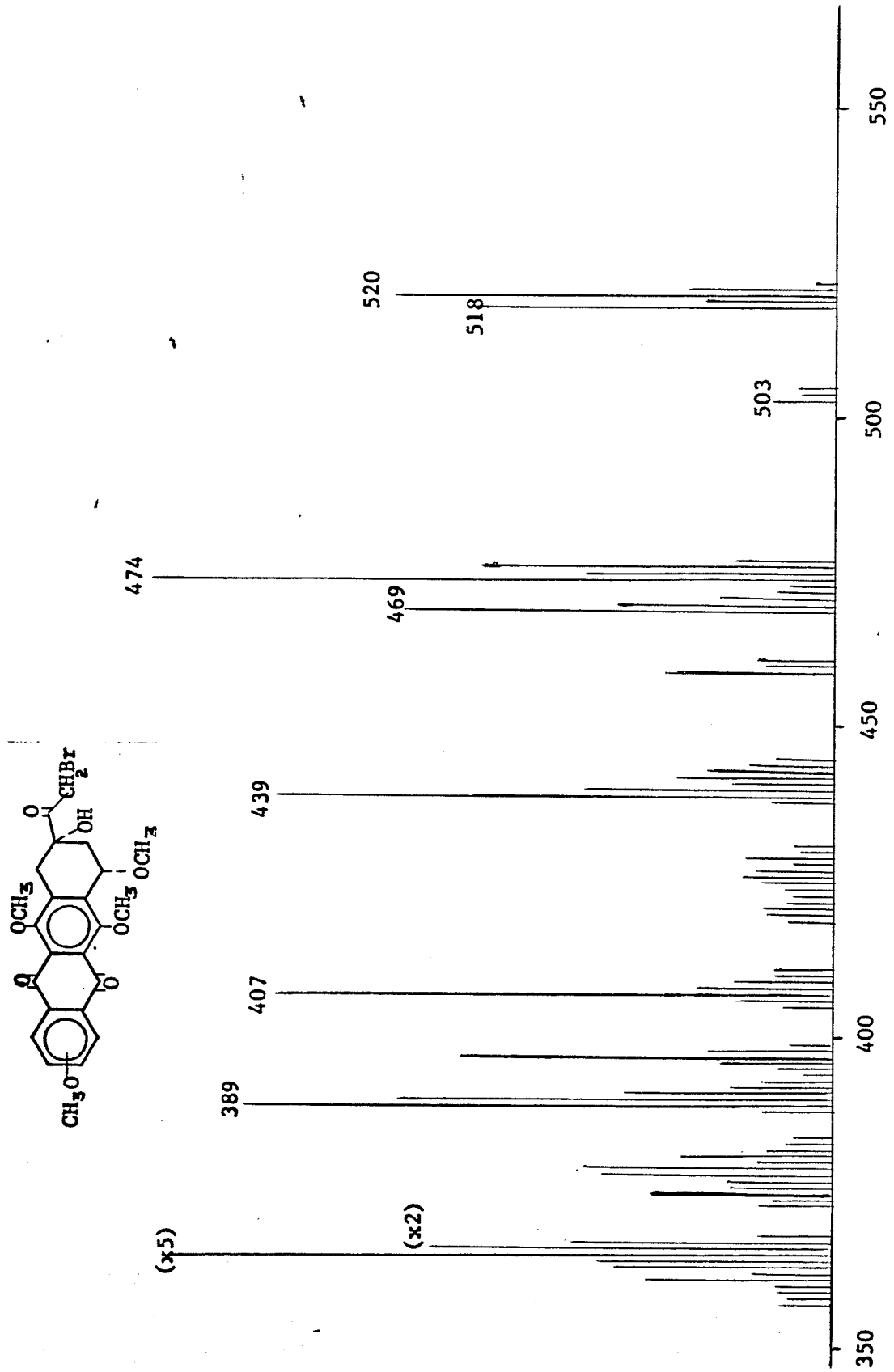
Mass spectrum no. 14: Isomeric hydronaphthacene quinone ketal mixture (XXXVII).

Figure XCVI



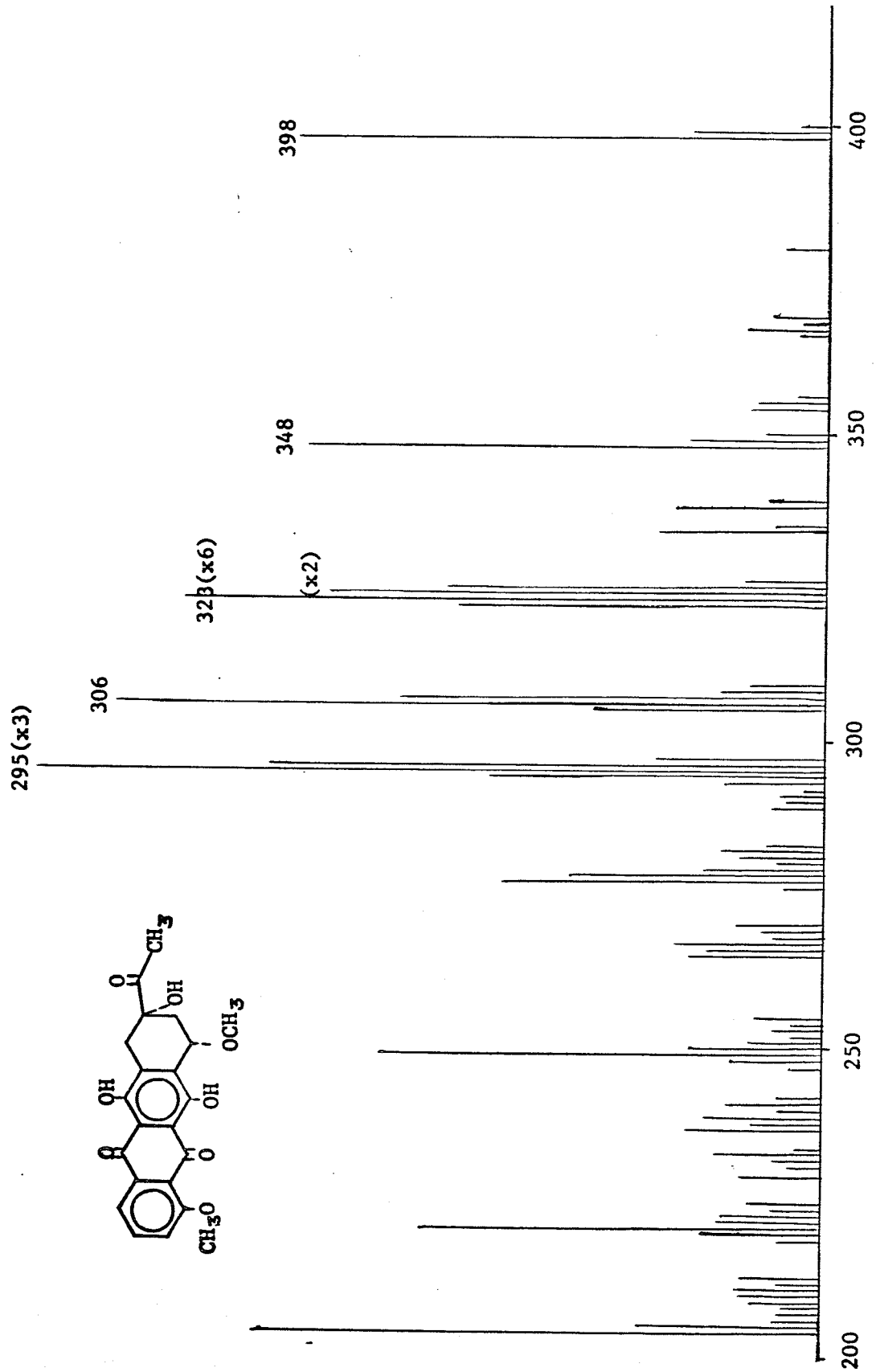
Mass spectrum no. 15: Daunomycinone trimethylether (XLVI), (also mass spectrum for compounds XLII and XLV).

Figure XCVII



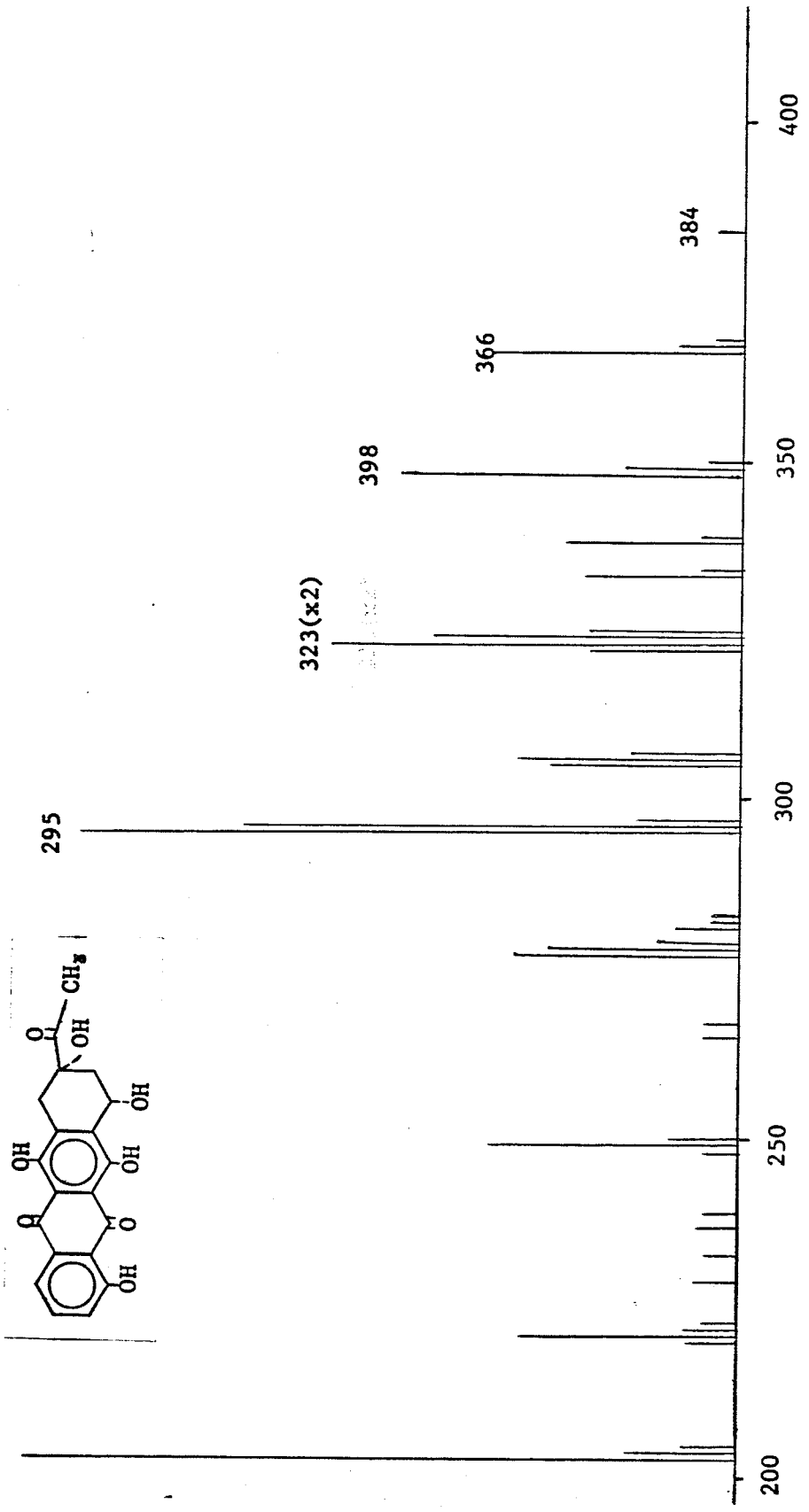
Mass spectrum no. 16: Isomeric hydronaphthacene quinone-$\mathcal{L}$- bromoketone mixture (XLIV)

Figure XCVIII



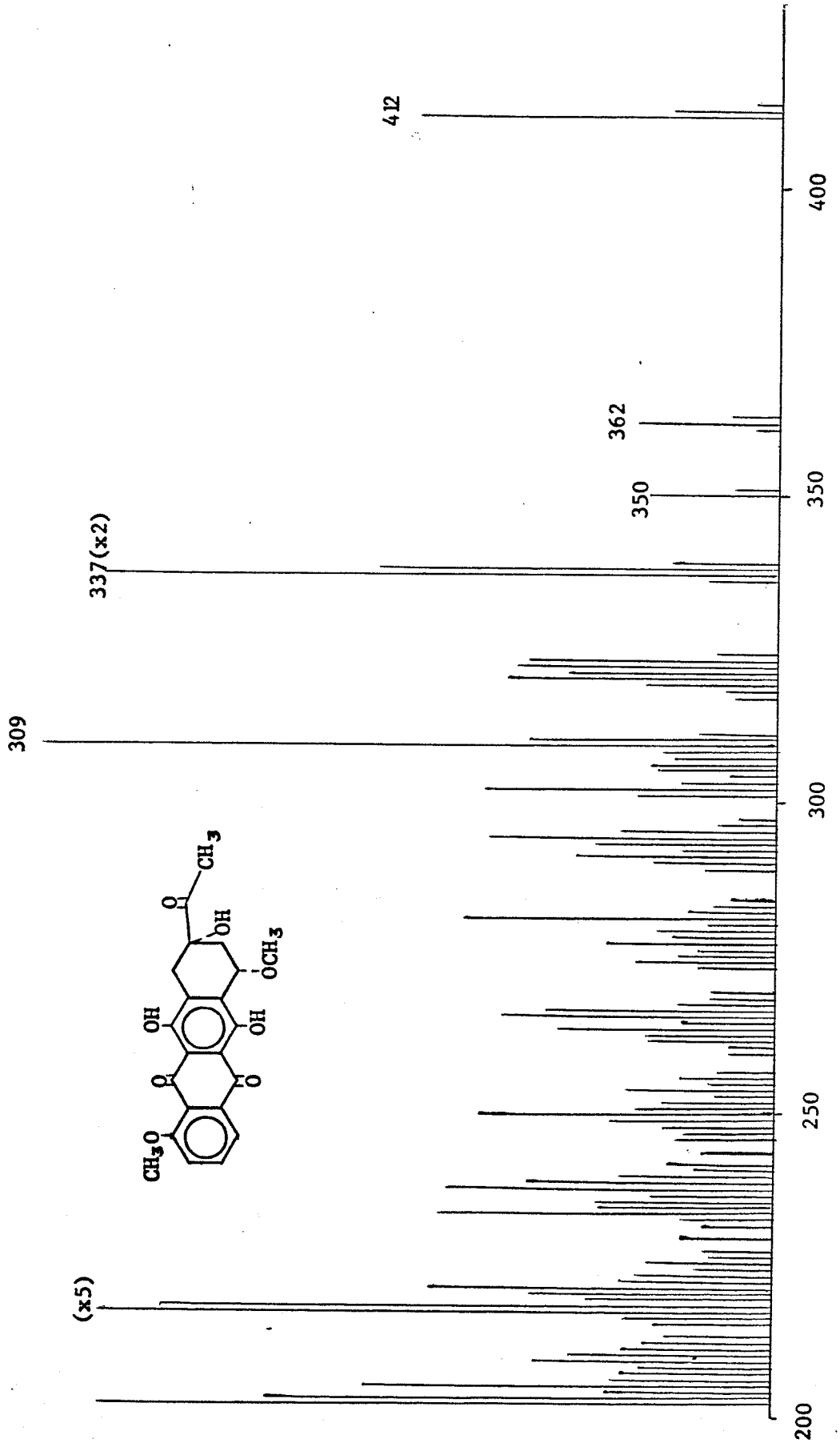
Mass spectrum no. 17: 4-O-demethyl-7-O-methyldaunomycinone (XLVII), (also mass spectrum for compound XLVIII).

Figure XCIX



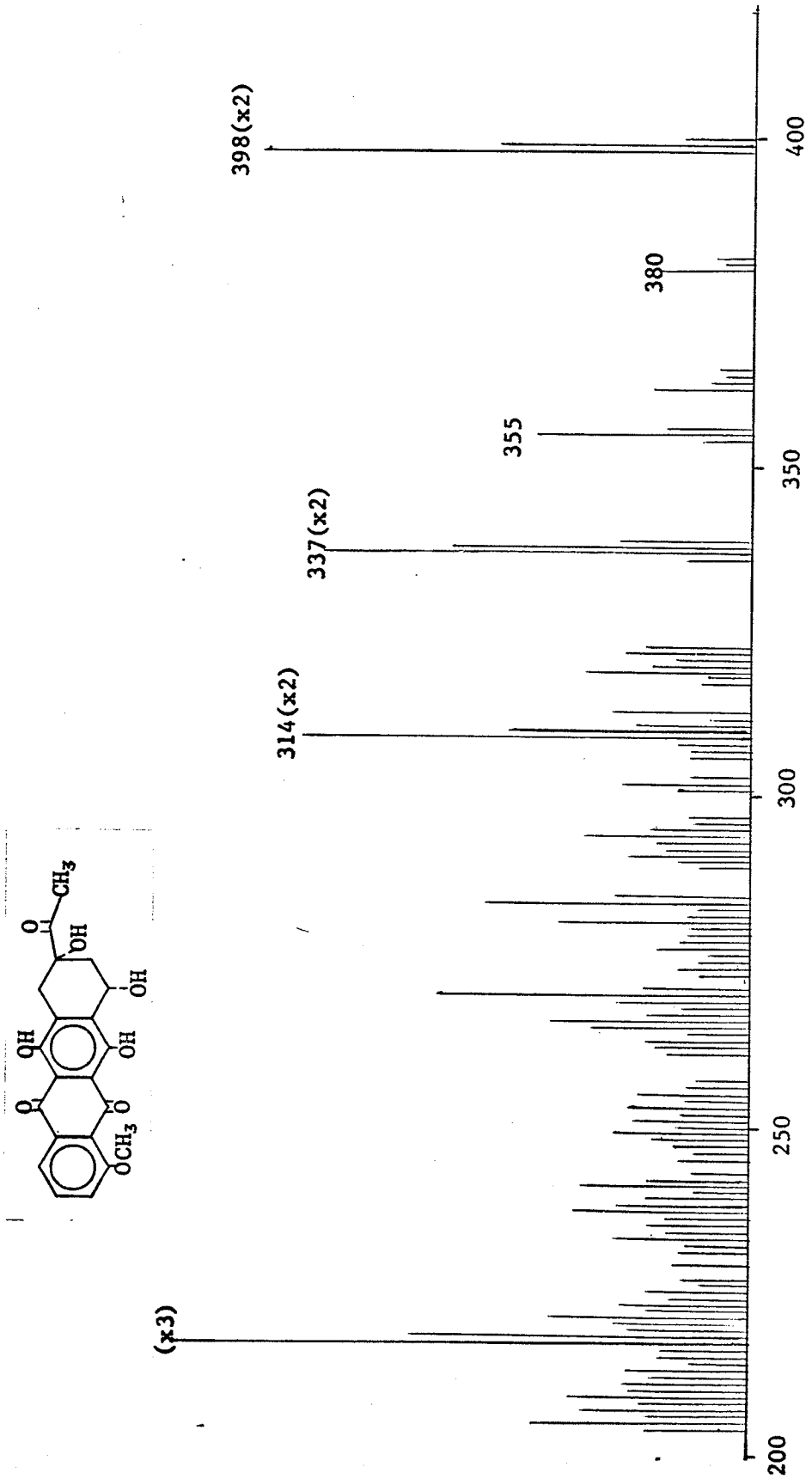
Mass spectrum no. 18: 4-O-demethyldaunomycinone (LI), (also mass spectrum for compound LII).

Figure C



Mass spectrum no. 19: 1-methoxy-4-demethoxy-7-O-methyldaunomycinone (LV).

Figure CI



Mass spectrum no. 20: Natural daunomycinone, (also mass spectrum for compounds XLIX and LIX).

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