A Synthetic Studies of Precurors to Daunomycin

B Solvolysis Studies of Hydroxythioacetals and an Attempted Synthesis of Yashabushiketol

by

Raymond James Hill

A thesis submitted to the

Faculty of Graduate Studies and Research

of the University of Manitoba

In Partial Fulfillment of the Requirements

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Masters of Science

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To my loving wife,

Dorothy

"A SYNTHETIC STUDIES OF PRECURORS TO DAUNOMYCIN

B SOLVOLYSIS STUDIES OF HYDROXYTHIOACETALS AND AN ATTEMPTED SYNTHESIS OF YASHABUSHIKETOL"

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I would like to express my gratitude to my supervisor Dr. C.M. Wong for his guidance and time given so freely, but especially for his patience in allowing me to persue my own methods even if he felt they would not work.

My thanks is due Dr. Robert J. Schwenk for moral support in times of trouble and Dr. T.-L. Ho for taking me under his wing while Dr. Wong was away for a time.

Abstract

Part A

Butadiene was added to p-benzoquinone to give 4a,5,8,8a-tetrahydro-1,4-naphthoquinone V. This Diels-Alder adduct was made aromatic, then methylated with K_2CO_3/dimethyl sulfate to give 5,8-dimethoxy-1,4-dihydronaphthalene VI. Hydrolysis of the double bond with B_2H_6/H_2O_2 followed by oxidation of the alcohol yielded 5,8-dimethoxy-2-tetralone IX. Conversion of IX to 2-hydroxy-2-acetyl-5,8-dimethoxytetralin XIII was accomplished either by addition of an acetylene Grignard followed by hydrolysis with mercuric salts or by addition of HCN to the ketone, blockage of the alcohol and then addition of methyl lithium to the nitrile.

β-Propiolactone was stirred with $NaNO_2$ to give 3-nitropropionic acid XXVII. With the acid halide XXVIII of this compound was condensed methylvinylcarbinol to yield sec-butenyl 3-nitropropionate XXIX. Ozonolysis of the product afforded 1'-formylethyl 3-nitropropionate XXX which would not cyclize to 4-nitro-5-hydroxy-6-methyl-2-pyranone.

Part B

Several α-hydroxy thioacetals were synthesized, then hydrolized with $Tl(CF_3CO_2)_3$ to test the specificity of its solvolysis reaction.

Benzyl magnesium chloride was reacted with allyl bromide to give 4-phenyl-1-butene (XXXVIII) which was epoxidized to yield 1,2-epoxy-4-phenyl butane XXXIV. To this was added the anion of cinnamaldehyde thioacetal XLI giving yashabushiketol thioketal XLIII. Solvolysis yielded not racemic yashabushiketol XLIV as hoped, but cis and trans 2-phenyl-6-(2'-phenylethyl) tetrahydro-4-pyrone.

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PART A

INTRODUCTION

Daunomycin (fig. i), a new antibiotic isolated from Streptomyces peucetius[1], has been shown to inhibit DNA and RNA synthesis in vivo in bacterial cells[2] and animal cells[3-5] and to inhibit DNA-dependent RNA polymerase and DNA polymerase in vitro.[6] This inhibition results from the fact that daunomycin binds to the DNA Template; in the case of cells, to the DNA of the chromosome.[7] Thus, daunomycin is toxic and specific for animal tumor cells which have an accelerated rate of growth.

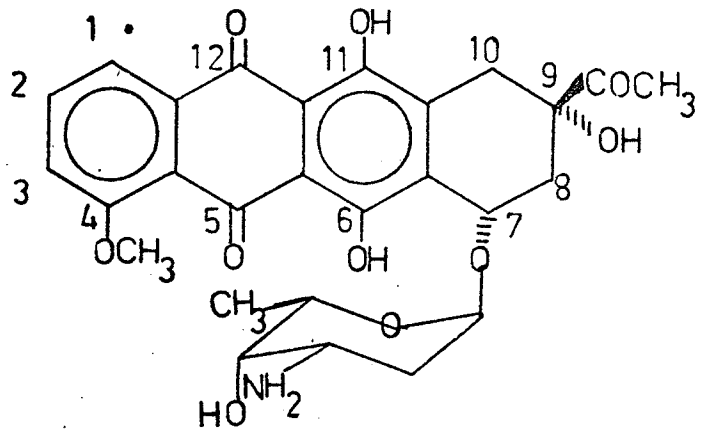
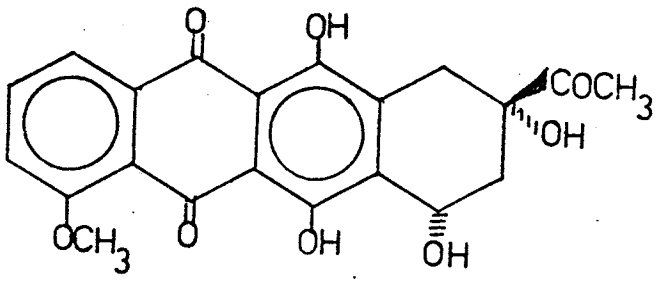


Figure i

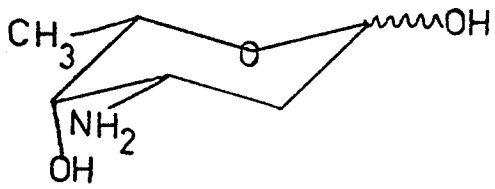
In clinical applications, a dose of 1 mg/kg per day for 6 to 8 days produces complete or good partial remission in childhood leukemia with seemingly no accumulative bone marrow damage.[8]

Daunomycin consists of two moieties: daunomycinone (fig. ii a), an aglycone, the structure of which was finally elucidated by Mondeli et al.[9,10], and an amino sugar, daunosamine (fig. iib)[11],

which is attached to the aglycone via an α-linkage at C-7.



a



b

Figure ii

THE NATURE OF THE PROBLEM

Goodman et al.[12] have synthesized the amino sugar, daunosamine, while the synthesis of racemic daunomycinone has recently been accomplished in this laboratory.[13]

The first section of the work was devoted to finding a shorter, simpler synthesis of one of the intermediates of the daunomycinone synthesis, namely, 2-hydroxy-2-acetyl-5,8-dimethoxytetralin (fig. iii). The first section also involved an approach to the synthesis of the amino sugar, daunosamine, from a "non-sugar" starting material.

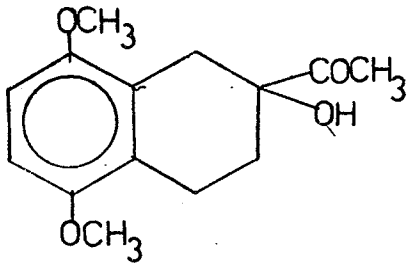


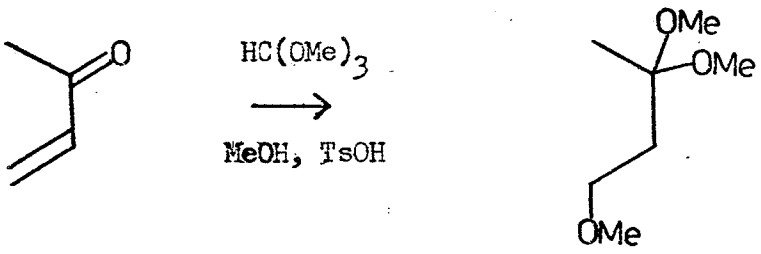
Figure iii

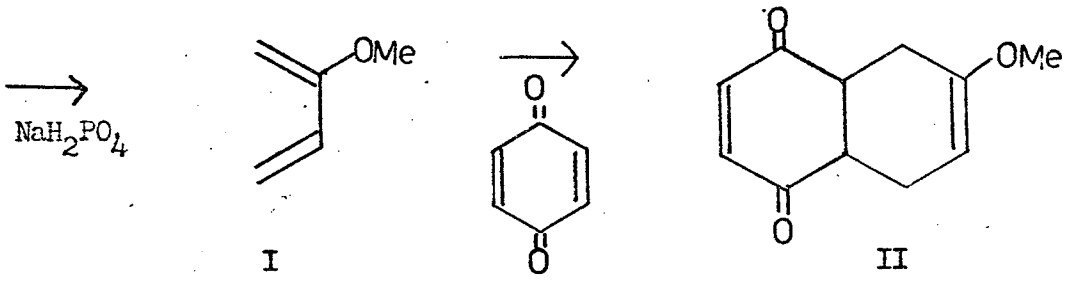
RESULTS AND DISCUSSION

5,8-dimethoxy-2-tetraline IX was prepared according to the procedure outlined by Grob and Jundt[14], scheme I, save for one small change. In lieu of sodium in methanol for enolization of the Diels-Alder adduct, II, to IIa, potassium carbonate in acetone was used. As a result, the yield from II to III was increased from 65% to 87%; otherwise, yields in scheme I were comparable to those of Grob and Jundt.

Due to the fact that the synthesis of the starting material, 2-methoxy-1,4-butadiene I, took two weeks to complete, the synthesis as outlined in scheme I was thought too lengthy and, therefore, an alternate synthesis of 5,8-dimethoxy-2-tetraline IV was devised (see scheme II).

p-Benzoquinone was reacted with butadiene in benzene at room temperature for one week to give 4a,5,8,8a-tetrahydro-1,4-naphthoquinone V in 80% yield. The melting point, 51 - 53°C (all temperatures will be given in Celcius) corresponded to that given by Van Tamelen.[15] The infrared spectrum (i.r.), figure IR-I, gave the conjugated δ-diketone absorption at 1695 cm^{-1}; the nuclear magnetic resonance spectrum (n.m.r.), figure NMR-I, was as expected and the mass spectrum showed the required P = 162.





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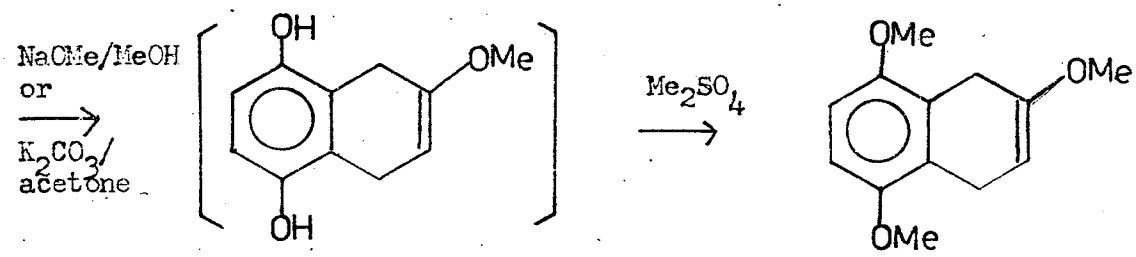
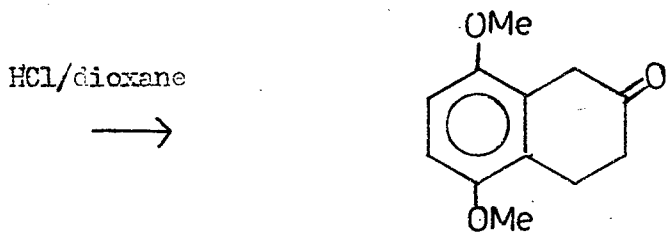


IIa III



IX

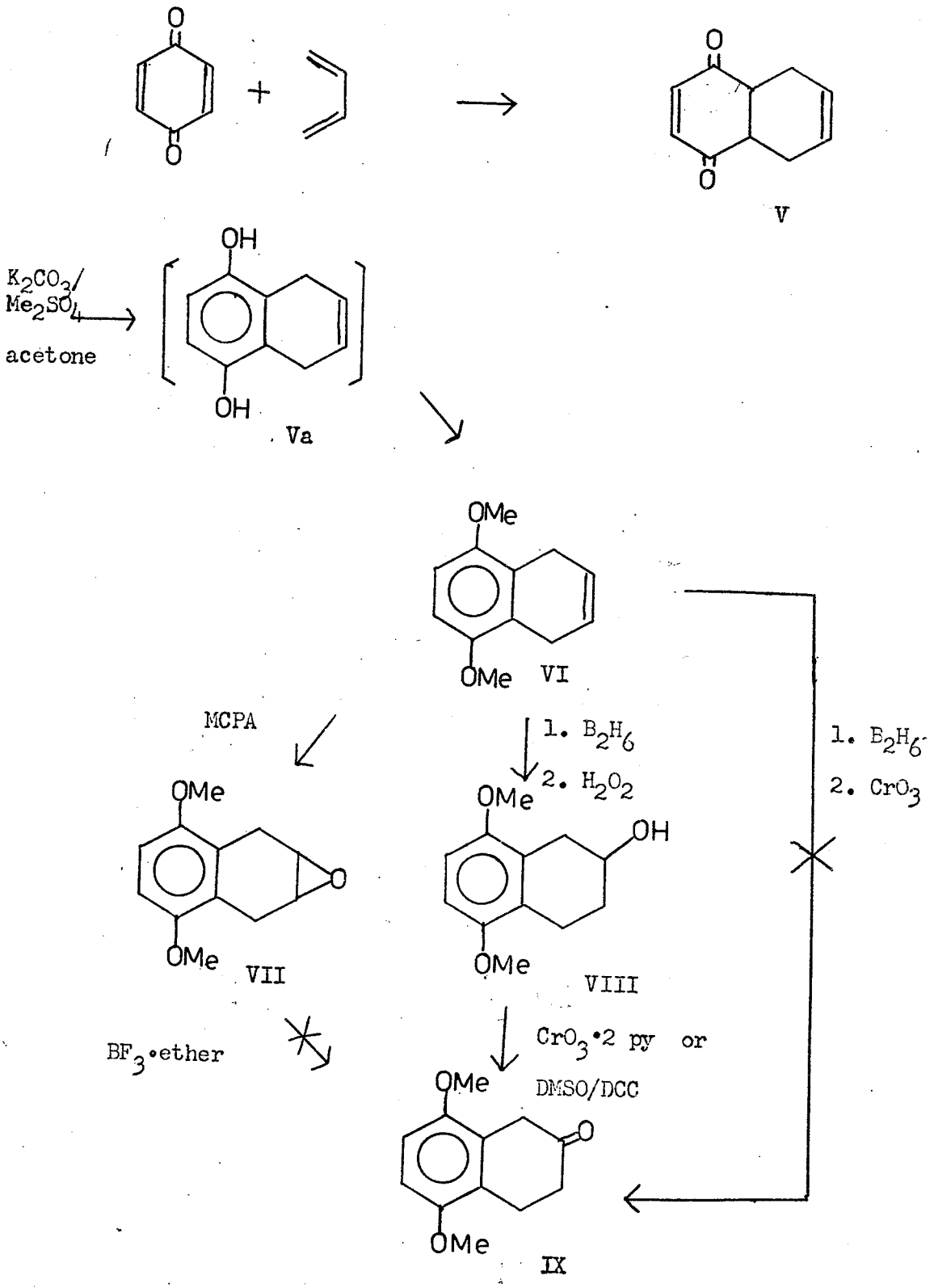
SCHEME I

The tetrahydronaphthoquinone V was then treated with K_2CO_3/Me_2SO_4 in acetone to give 5,8-dimethoxy-1,4-dihydronaphthalene VI, as a light brown oil which on distillation yielded a faintly yellow oil that crystallized on standing to a white solid m.p. 43 - 44° (Terent'ev[16] reports 50°). The i.r. (fig. IR-II) revealed no carbonyl absorption, but did show peaks corresponding to an aromatic double bond (1600 cm^{-1}), and ether linkages (1075, 1090 cm^{-1}). The n.m.r. (fig. NMR-II) was consistent with the structure VI and the mass spectrum again manifested the desired molecular ion at 190 amu.

At this point, several successful and unsuccessful attempts were made to convert the olefin VI to the tetralone IX.

One such attempt was to first convert the olefin VI to the epoxide VII, then to isomerize the epoxide to the ketone IX with BF_3 etherate. The epoxide formed smoothly at room temperature with MCPA (metachloroperbenzoic acid), giving a white crystalline solid in 75% yield, m.p. 131-132°. The i.r. (fig. IR-III) was similar to that of the olefin save for the appearance of a peak at 860 cm^{-1}, indicating the presence of the desired epoxide. The n.m.r. (fig. NMR-III) was now minus the olefinic proton absorptions and showed peaks at δ=6.61 (2H, s[singlet]) 3.75 (6H, s), ca 3.4 (4H, multiplet), and 2.5 - 3.0 (2H). The mass spectrum gave the desired P = 206. Attempts at isomerization, however, with BF_3 etherate in benzene or with acetic anhydride proved fruitless, with none of the desired ketone IX being isolated.

A one step conversion of the olefin VI to the ketone IX


V
K_2CO_3/
Me_2SO_4
acetone
Va
VI
MCPA
1. B_2H_6
2. H_2O_2
1. B_2H_6
2. CrO_3
VII
VIII
BF_3•ether
CrO_3•2 py or
DMSO/DCC
IX

SCHEME II

involving hydroboration followed by chromic acid oxidation also failed. The crude product of this procedure showed a single carbonyl peak at 1670 cm^{-1} in the i.r. so purification of the oil was not attempted. It is believed that the chromic acid attacked the susceptible benzylic position rather than cleave the alkyl-boron bond.

The successful approach to compound IX proved to be hydroboration of the olefin VI with subsequent oxidation to the alcohol VIII by H_2O_2/NaOH followed by oxidation employing the CrO_3-pyridine complex in methylene chloride.

The hydroboration of the olefin was carried out at room temperature and subsequent addition of H_2O_2 gave a snow-white crystalline crude product (m.p. 131 - 132°, Lewis reports 130.5 - 132°[17]) in essentially quantitative yield. The i.r. (fig. IR-IV) exhibited an absorption at 3640 cm^{-1} (OH stretch), along with the now familiar peaks in this series: aromatic double bonds, 1600 cm^{-1}, and ether linkages, 1095 cm^{-1}. The n.m.r. (fig. NMR-IV) showed resonances corresponding to aromatic protons at δ = 6.62 (2H, s), O<u>H</u> and C<u>H</u>OH ca 4.1 (broad, 2H), aromatic OCH_3 at 3.75 (6H, s), benzylic protons ca 2.8 (4H, multiplet), and aliphatic protons ca 1.9 (2H, multiplet). The mass spectrum was also consistent with the structure, giving fragment masses at 208 (P), 190 (P - H_2O) and 175 (P - H_2O, $\cdot CH_3$).

It was found that oxidation by CrO_3 in acetic acid was too vigorous and that the benzylic position was attacked. The mild CrO_3.2 pyridine complex oxidation was successful, however, giving

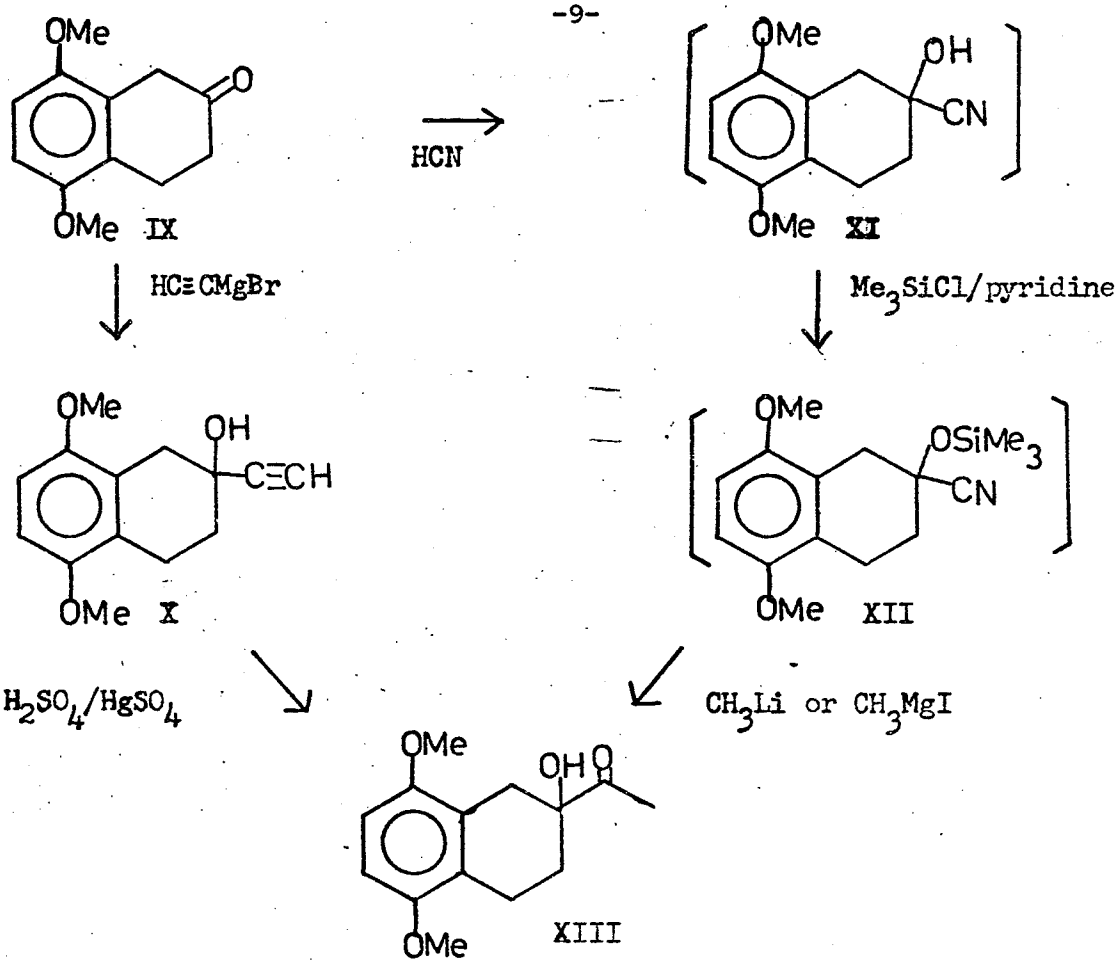
5,8-dimethoxy-2-tetraline IX in 84% yield as heavy white crystals (m.p. 98 - 99.5°).

The i.r. (fig. IR-V), n.m.r. (fig. NMR-V) and mass spectrum are identical to those given by the tetralone synthesized by Grob's method.[14] Oxidation of the alcohol VIII to the ketone IX employing dry dimethylsulphoxide (DMSO), Dicyclohexylcarbodiimide (DCC) was also successful. The yield was somewhat lower, but the method is amenable to conversion of larger quantities in a single reaction.

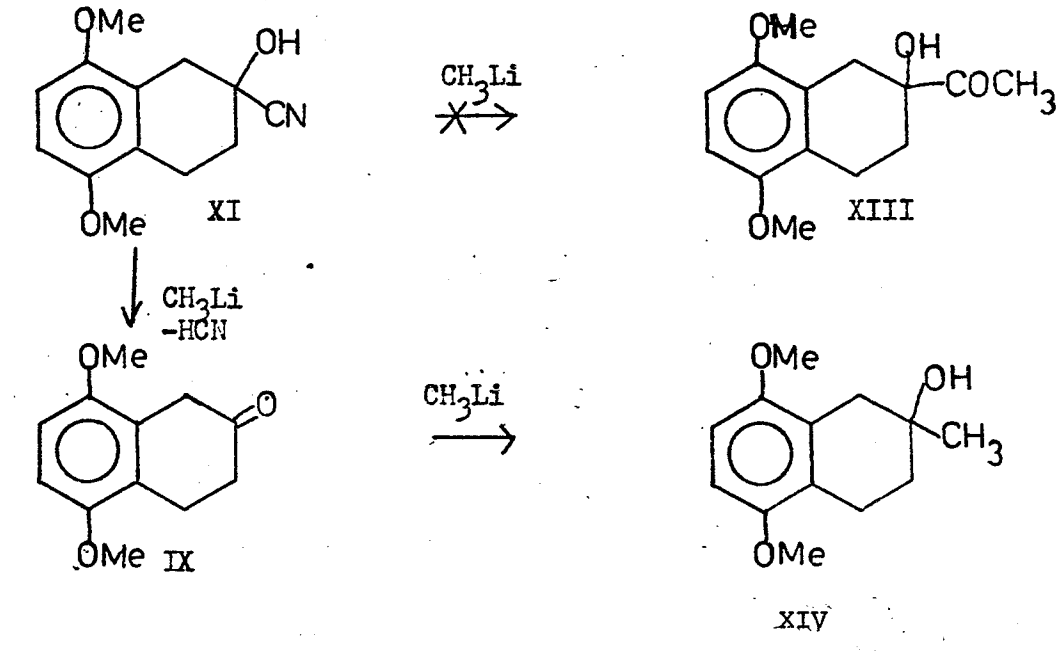
From the tetralone IX, two successful synthetic routes were found to the desired 2-hydroxy-2-acetyl-5,8-dimethoxytetralin XIII (see scheme III).

The first route involved the conversion of the tetralone via an acetylene Grignard to 2-hydroxy-2-ethynyl-5,8-dimethoxytetralin X which could be isolated as a colorless oil in 83% yield. The i.r. (fig. IR-VI), now minus a carbonyl absorption, showed an absorption for an alcohol at 3630 cm^{-1} and the sharp acetylenic hydrogen stretch peak at 3340 cm^{-1}. The n.m.r. (fig. NMR-VI) was as expected; the mass spectrum also gave the desired molecular ion at 232 amu and P - H_2O at 214.

The hydroxyacetylene, compound X, which need not be isolated, was then hydrolysed with $HgSO_4/H_2SO_4$ in wet tetrahydrofuran (thf) to give 2-hydroxy-2-acetyl-5,8-dimethoxytetralin XIII in 87% yield. The m.p., 102 - 102.5°, compared favourably to that reported by R.J. Schwenk[18] of 100 - 102°. The mixed m.p. with an authentic sample was unchanged and the i.r. (fig. IR-VII; compare IR-VIIA,



SHCEME III



SCHEME IIIA

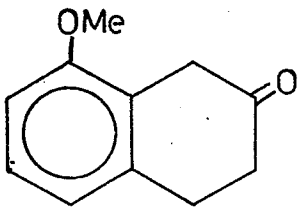
an authentic sample), n.m.r. (fig. NMR-VII) and mass spectrum were superimposable on those of the authentic sample.

The second successful approach involved: first, conversion of the ketone IX to its cyanohydrin XI (not isolated), blockage of the hydroxyl group with a trimethysilyl ether XII (also not isolated), and then the use of either methyl lithium or methyl magnesium iodide to convert the nitrile to a methyl ketone (see scheme III). Hydrolysis of the trimethylsilyl ether by dilute NH_4Cl/HCl afforded a product identical to the desired hydroxy ketone XIII.

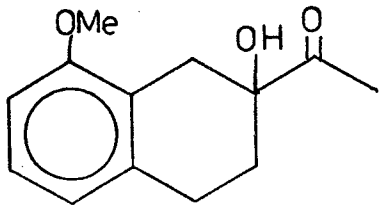
Addition of methyl lithium directly to cyanohydrins have been reported,[19] but in this case, the reaction of methyl lithium with the cyanohydrin XI gave a product which appears to have been compound XIV. The mass spectrum of the isolated product gave a molecular ion at 222 amu and the i.r. showed a hydroxyl group absorption but no carbonyl absorption. It seems that in basic medium, this cyanohydrin eliminates HCN to give the original ketone IX which then may add CH_3Li.

It might be mentioned at this point that 8-methoxy-2-tetralone XV[20] reacted analogously to the dimethoxytetraline IX, giving the hydroxyketone XVI through both the hydroxyacetylene and cyanohydrin intermediates. Since this was used as a model system, no data are reported excepting the i.r. (fig. IR-VIII) and n.m.r. (fig. NMR-VIII) of the hydroxyketone XVI.

An attempt to synthesize 2-hydroxy-2-(1'-oxo-2'-hydroxyethyl)-5,8-dimethoxytetralin XIX (which might be a useful intermediate in the



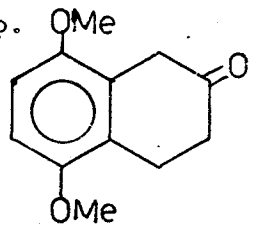
XV



XVI

proposed synthesis of adriamycinone XX,[21] the aglycone of another potent antitumor antibiotic, adriamycin) via scheme IV was a failure. The vinyl Grignard reacted in good yield with the dimethoxyketone IX to give the hydroxy olefin XVII, but subsequent attempts to epoxidize the double bond, varying reagents, conditions and blocking groups for the hydroxyl group gave at best 5% yields of compound XVIII.

Since radical conversions of α-hydroxyketones to α,α'-dihydroxyketones are already known [21, 22a, 22b] and are fairly efficient, this scheme was abandoned without attempting the final step.



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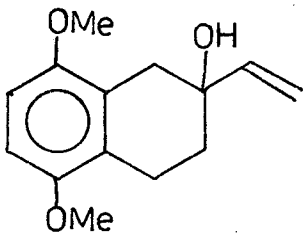
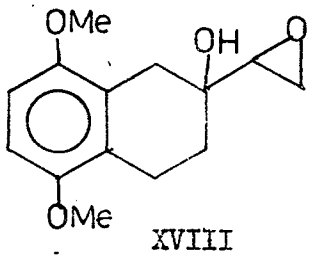
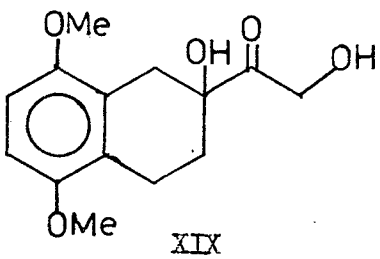


XVII

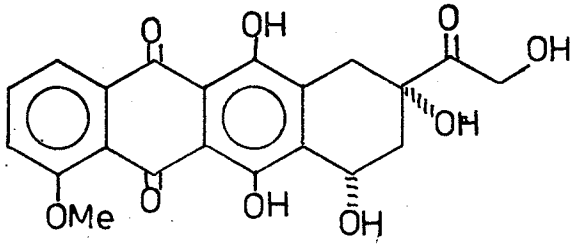


XVIII



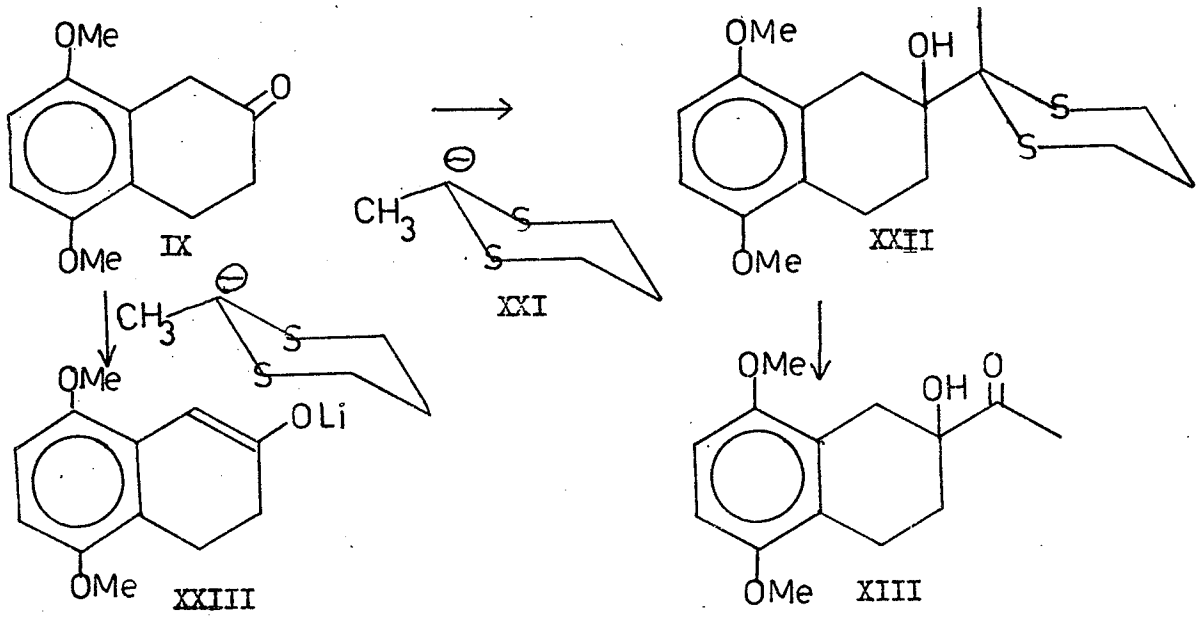
XIX

SCHEME IV



XX

Following this, the attempt to react the 2-methyldithiane anion XXI with the dimethoxytetralone IX (scheme V) also failed, giving compound XXII in yields of the order of 10% at best.



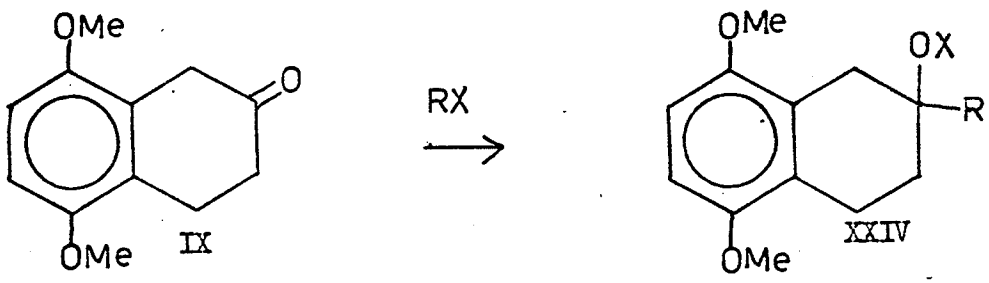
SCHEME V

Although unsuccessful in attaining the desired goals, these last two results would seem to be in agreement with an hypothesis promulgated by Pearson[23] denoting the reactivities of species in terms of hard/soft acids and bases (HSAB). He says that "hard" acids tend to react with "hard" bases and "soft" acids tend to

react with "soft" bases. The more localized the charge is, the harder the acid or base.

In this case, the C_2-carbon atom of the tetralone IX, being doubly bonded to the oxygen, would be quite electron deficient making it a much harder Lewis acid than the benzylic hydrogen.

The hard acetylene and vinyl Grignards (scheme VI), being sp and sp^2 hybridized anions respectively, preferentially attack the C_2-carbon atom while the soft lithium dithiane and ethyl Grignard (private communication from Dr. T.-L. Ho), being sp^3 anions, react with the benzylic hydrogen giving the anion XXIII (see table I)



SCHEME VI

TABLE I

Yields (%) of products of carbonyl addition of sp, sp^2, and sp^3 anions to compound XI

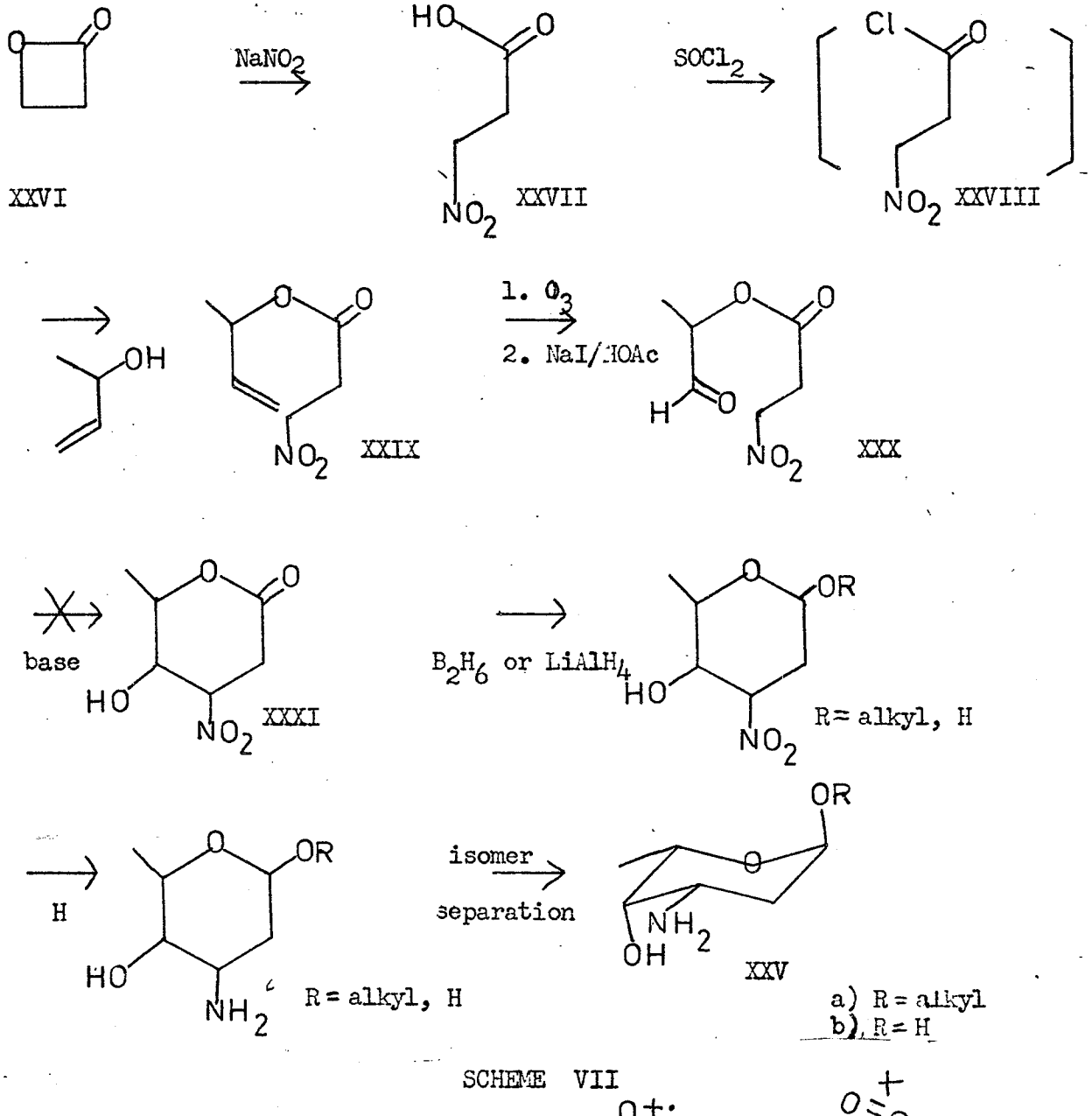
R	X	% XXIV
HC≡C	MgBr	83
H_2C=CH	MgCl	75
H_3C-CH_2	MgBr	10
$CH_3C(S)(S-(CH_2)_3)$	Li	10

In concluding this series, the synthesis of 2-hydroxy-2-acetyl-5,8-dimethoxytetralin XIII, an intermediate in the laboratory prepration of daunomycinone iia, has been shortened with some improvements in yields.

An attempt at the racemic synthesis of a second intermediate of daunomycin, its sugar moiety, daunosamine XXVb, was not nearly as successful. The limitation was placed on the project (scheme VII) that the starting materials would not be sugars, which Goodman et al.[12] had used with success in his synthesis.

β-Propiolactone XXVI was reacted with aqueous sodium nitrite[24] to give the white crystalline 3-nitropropionic acid XXVII in 22% yield (m.p. 63 - 65°). The n.m.r. (NMR-X) and i.r. (IR-X) verified the results.

3-Nitropropionic acid was converted to its acid halide XXVIII with thionyl chloride, then, without isolation, was reacted with methylvinyl-carbinol to give sec-butenyl 3-nitropropionate XXIX, as a colorless oil, in 61% yield. The n.m.r. (NMR-XI) was in agreement with the structure, the vinyl and allyl protons (deshielded by the oxygen) showing as a four proton multiplet (δ = 5.0 to 6.1), the four methylene protons as broadened triplets at δ = 4.56 (2H) and δ = 2.90 (2H), and the methyl protons as a doublet at δ = 1.31 (3H). The i.r. (IR-XI) showed an ester carbonyl absorption at 1735 cm^{-1} and peaks corresponding to a nitro group at 1560 cm^{-1} and 1380 cm^{-1}. Although the mass spectrum showed no molecular ion at 173 amu, it did show expected fragments at 55, 71, and 102 amu (fig. iv). The elemental analysis made it quite certain that the



SCHEME VII

Figure iv

isolated ester was the expected compound XXIX.

The next step was an ozonolysis to convert the olefin XXIX to the aldehyde XXX. This step provided the aldehyde ester in 77% yield. The compound was found to be unstable on silica gel and several other solid supports so could not be purified by thin layer chromatography (t.l.c.) nor by column chromatography. Further, it was found to decompose when heated, even under high vacuum distillation. Because of this, its analysis was virtually impossible so the structure of compound XXX had to be confirmed primarily by its infrared spectrum and its n.m.r.

The i.r. (IR-XII) still had the nitro and ester peaks except that the ester peak was shifted to higher wave number by 5 cm^{-1} and also, that it had become quite broad, indicating the probability of the presence of another overlapping carbonyl frequency. There was great variance in the fingerprint regions between the olefin ester XXIX i.r. (IR-XI) and the aldehyde ester XXX i.r. (IR-XII), with several notable peaks (olefin, 1647 cm^{-1}; terminal methylidene, 935 cm^{-1}) absent in the latter.

The best evidence that the assignment is correct, however, comes from the n.m.r. (NMR-XII). The complex vinyl-allyl multiplet has been replaced by a clean quartet arising from the methine proton resonance. The two sets of broad triplets from the methylene protons are still in evidence as is the methyl doublet (although now flanked by impurities). The aldehyde peak at $\delta = 9.50$ would also seem to verify the structural assignment.

The fact that the aldehyde proton is not a doublet is

not anomalous. Karabatsos and Hsi[25] showed that because of a stable conformation, the coupling constants of α-substituted aldehydes commonly fall below 2 Hz (Hertz = cycles per second). At 50 Hz sweep width, The coupling shows only as a slight broadening, indicating a coupling constant (J) of 0.5 Hz or less.

There was no molecular ion at 175 amu in the mass spectrum. Beyond this, mass spectroscopy was not used as a tool for identification since small amounts of impurities may give prominent peaks at positions incongruous with the structure.

This series ended abruptly when the aldehyde XXX refused to cyclize to compound XXXI under the influence of basic catalysts including NaH, KOtBu and NaOtBu with solvents including thf, ether, benzene and tertiary butanol.

PART B

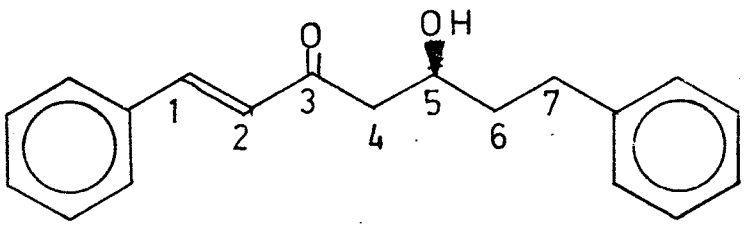
INTRODUCTION

Since the introduction of the addition of thioacetal anions to various electrophilic compounds by Corey and Seebach, there has been a flurry of activity to discover simple methods for hydrolysis of the resulting thioketals and thioacetals to their respective ketones and aldehydes. Some of these reagent-methods are: chloramine T,[26] ceric ammonium nitrate (CAN),[27] S-alkylation,[28, 29, 30] "soft" acid oxidation (Hg^{2+}, Cu^{2+}),[31, 32, 33, 34] concentrated sulphuric acid,[40] methylfluorosulphonate,[41] silver salts,[42, 43] N-halosuccinimide[44] and Tl $(CF_3CO_2)_3$[35].

THE NATURE OF THE PROBLEM

The attempted synthesis of the hydroxyketone XIII (section A) by scheme V as well as previous studies in this laboratory by T.-L. Ho and C.M.S. Wong[27, 35] prompted the study of the solvolysis of dithianes leading to α-hydroxyketones and α-hydroxyaldehydes.

The extension of this study was to carry out the racemic synthesis of the newly isolated yashabushiketol XXXIII,[36] a C_6-C_7-C_6 natural product from the male flowers of Alnus firma Sieb.



XXXIII

RESULTS AND DISCUSSION

The study began with a test of the effectiveness of thallic trifluoroacetate (Tl $(TFA)_3$) on α-hydroxythioacetals.[35] The thioacetals in Table II were prepared by Robert's method.[37] The anions were formed at -30 to -20° in thf under a dry N_2 atmosphere and took approximately 1 hour to form completely. The carbonyl was then added at -5 to -10° and allowed to react a further 3 hours. Those compounds in Table II with references are known while the other two were prepared in this laboratory for the first time. For these reactions, the yields are typically high. These high yields and the simple apparatus more than offset the little extra care needed in preparation and justify wide spread use of this reaction.

Large amounts of trifluoroacetate esters of the resulting alcohols were detected by t.l.c. when bicarbonate was used to neutralize after the reaction. To alleviate this problem and increase yields, ammonium hydroxide was used successfully in lieu of sodium bicarbonate to hydrolyse the esters while neutralizing the reaction medium.

For some reason, as yet not known, compound XXXIVe reacted with one equivalent of Tl$(TFA)_3$ to give 21% starting material and it was not until two equivalents of the thallic salt were used that the reaction went to completion, giving XXXVe in 75% yield.

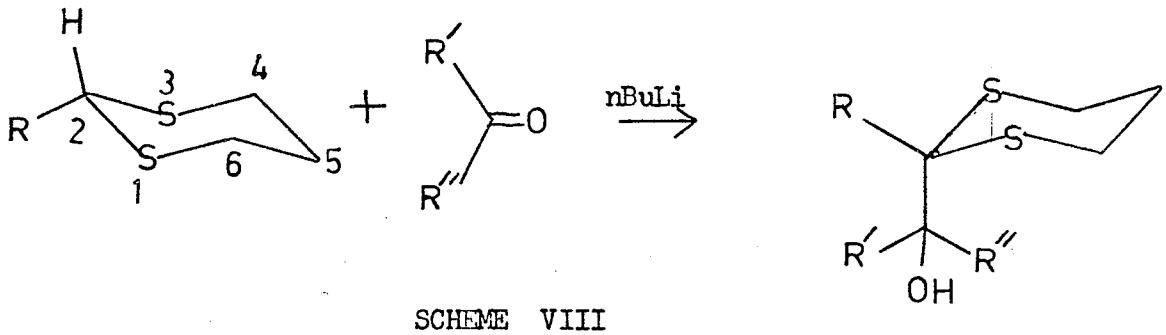
The solvolysis of 2-hydroxydiphenylmethyl-2-methyldithiane XXXIVd did not proceed as expected. The crude i.r. showed no trace of a carbonyl absorption in the region ca 1720 cm^{-1}, so that is was apparent that simple hydrolysis had not occurred.

The infrared of the purified hydrolysis product (IR-XXIV)

TABLE II

Synthesis of α-hydroxythioacetals

compound	R	R',R"	% yield	reference
XXXIVa	H	ø, ø	77	33
b	CH_3	$-(CH_2)5-$	83	33
c	ø	ø, H	81.5	--
d	CH_3	ø, ø	69	33
e	ø	$-(CH_2)_4-$	91.5	--



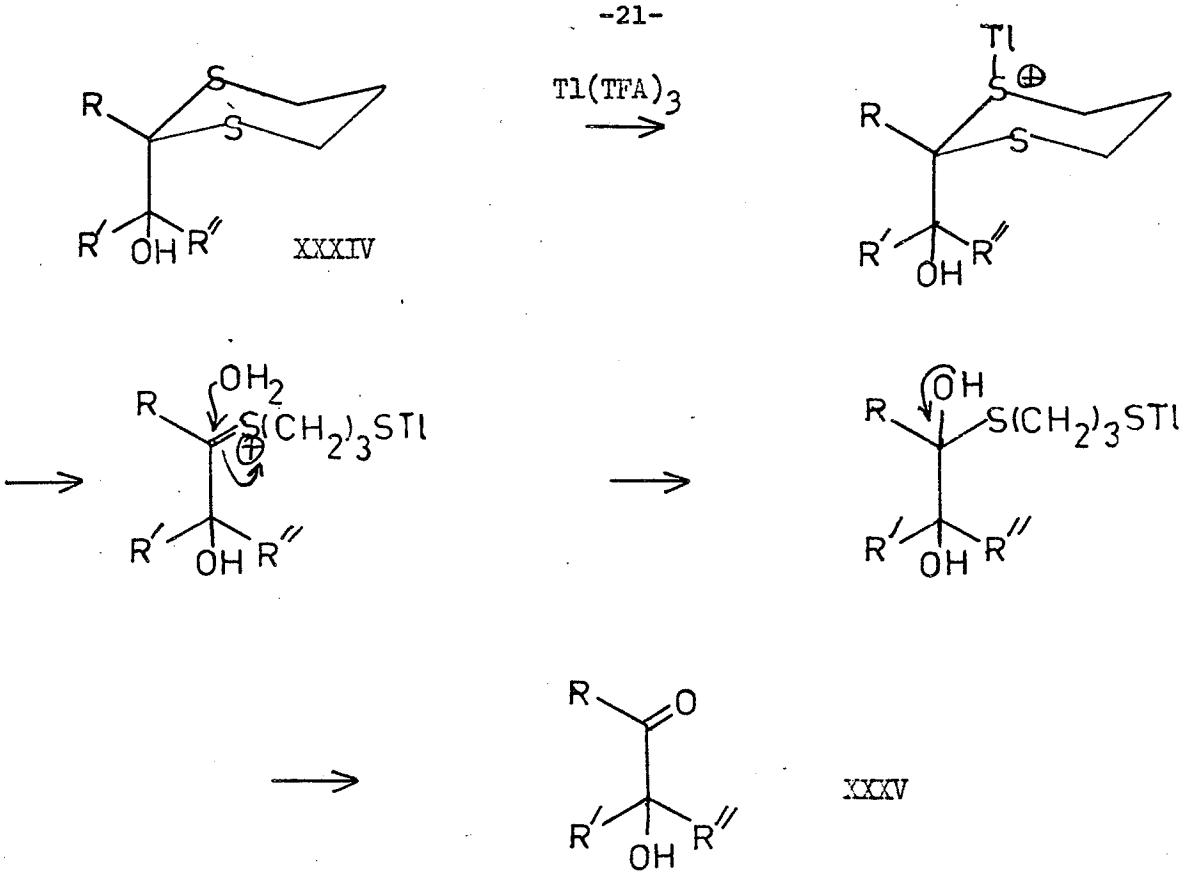
SCHEME VIII

TABLE III

Solvolysis of α-hydroxythioacetals according to scheme IX

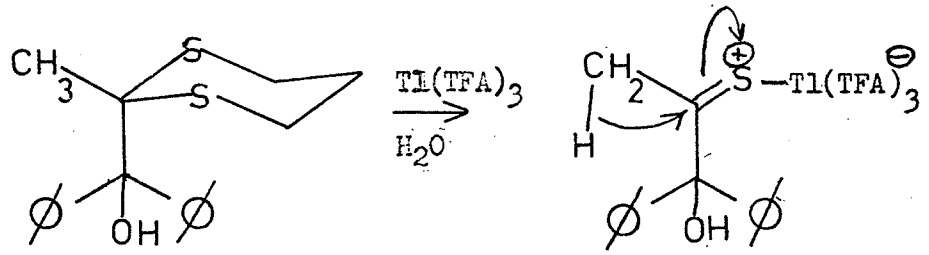
compound	% yield	reaction time (hours)	$Tl(TFA)_3$ (equivalents)
XXXVa	79	2	1
b	70	0.5	1
c	77	0.5	1
d	_a	1	1
e	75	1	2

a Reacts according to scheme X.

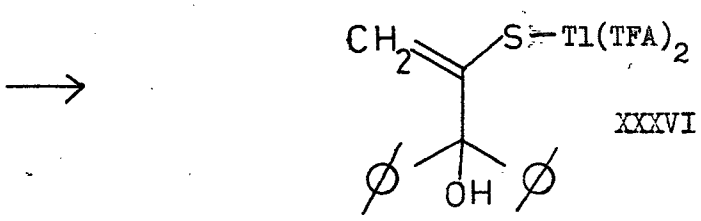


XXXV

SCHEME IX



XXXIVd



XXXVI

SCHEME X

was similar to that of the starting material (IR-XVIII) showing only minor differences in the positions and intensities of the major bands. The n.m.r. (NMR-XXIV, compare NMR-XVIII) showed the aromatic protons having some change in environment and showed resonances for what could still be the methylene protons of the thioketal moiety. The most dramatic change was the replacement of the methyl group resonance of the starting material by an absorption for what appears to be 2 non-equivalent vinyl protons (δ= 5.05 to 5.35).

The reaction then, it would seem, proceeded via scheme X, the bulky phenyl groups blocking attack by water at the carbonium ion. This steric hindrance hypothesis is supported by the fact that the other similar diphenyl compound XXXIVa takes 2 hours, a relatively long time, to solvolyse to the aldehyde.

This one exception, however, does not limit greatly the effectiveness of this reagent as a fairly specific hydrolyzer of thioketals and thioacetals. The yields were generally high (Table III, 75 - 79%), thus $Tl(TFA)_3$ was mild enough so as not to harm the fairly sensitive α-hydroxyketones produced. The most encouraging result is the production of the δ-hydroxyaldehyde XXXVa in 79% yield. Even the mild cupric and mercuric salts would most likely oxidize this product.

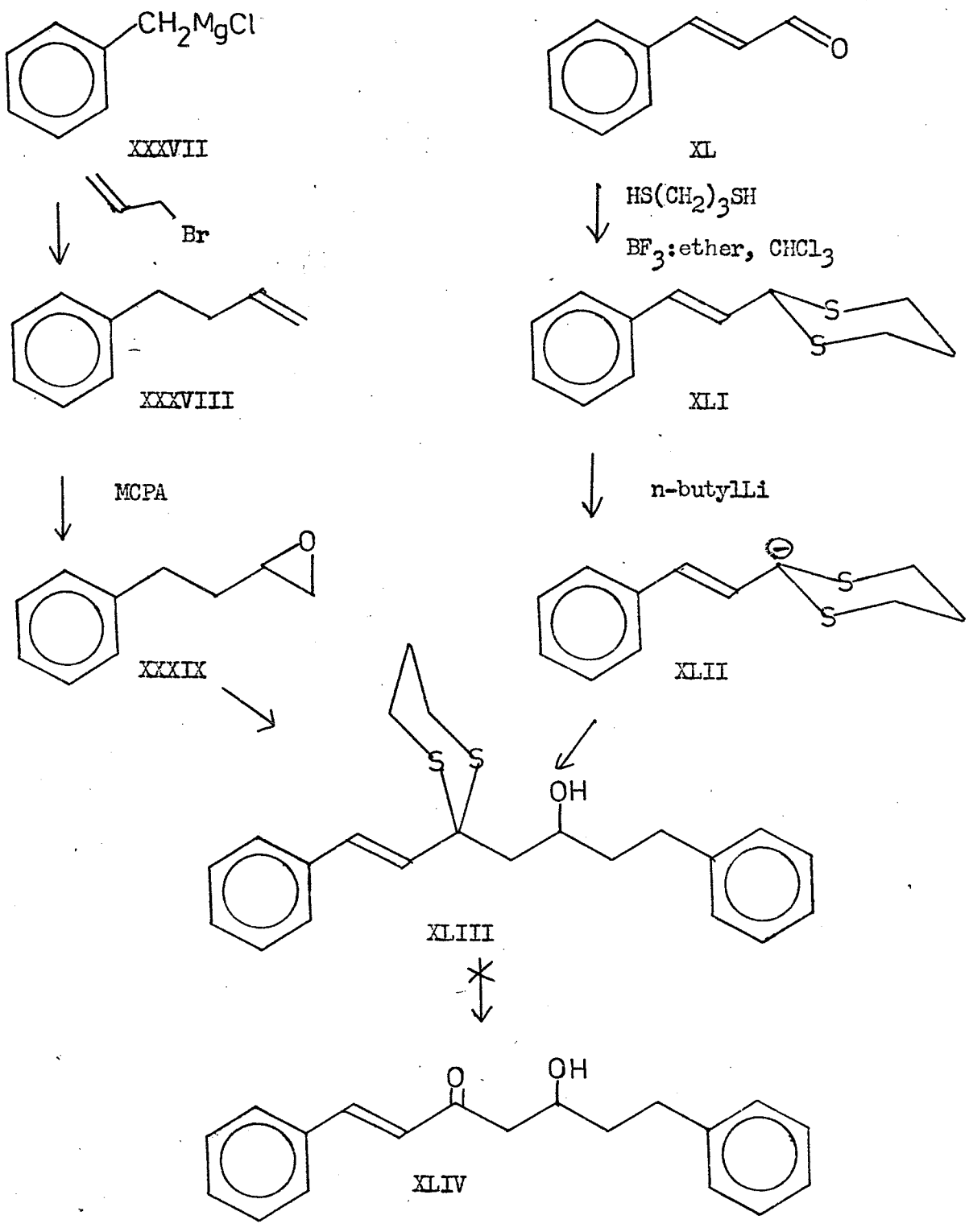
Since condensations of thioacetal anions and their subsequent hydrolysis to aldehydes and ketones are quite predictably high yield reactions, it was at this point decided to attempt the synthesis of a natural β-hydroxyketone, yashabushiketol XXXIII. This

mild solvolysis reaction was thought to be a good choice for this synthesis since under too acidic or too basic conditions a β-hydroxycarbonyl is so susceptible to elimination.

According to scheme XI, benzyl magnesium chloride XXXVII, was reacted with allyl bromide in ether to give 4-phenyl-1-butene[38] XXXVII (bp = 183 - 185°) as a colorless oil in 65% yield. The i.r. (IR-XXV) showed the presence of a terminal double bond (1640 cm^{-1}, 905 cm^{-1}) and the n.m.r. (NMR-XXV) was consistent with the given structure showing resonances for 5 aromatic protons (δ=6.9 - 7.3),4 methylene protons (δ=2.0 - 2.85) and 3 vinyl protons (δ=4.75 - 6.15).

The epoxidation of compound XXXVIII with MCPA in $CHCl_3$ proceded in 82% yield to give 1,2-epoxy-4-phenylbutane[39] XXXIV as a colorless oil (bp = 105° @ 12 mm Hg). The double bond absorption of 4-phenylbutane gave way in the i.r. (IR-XXVI) to epoxide bands at 825 cm^{-1} and 905 cm^{-1} indicating that the desired reaction had occurred. The n.m.r. (NMR-XXVI) was also in accord, the resonance for the vinyl protons having moved "up-field" so that there were absorptions for 5 aromatic protons (δ = 7.13) and 7 alkyl protons spread from δ = 1.60 to 3.00.

In the meantime, cinnamaldehyde XL was stirred with propane-1,3-dithiol (BF_3:ether catalyst) to give the corresponding thioketal XLI (85% yield) as a light yellow oil which upon distillation solidified to white crystals (mp = 57 - 58°). The n.m.r. (NMR-XXVII) showed an absorption for the 5 aromatic protons (δ = 7.0 - 7.7), an ABX pattern by virtue of the two vinyl protons and the methine proton respectively (δ = 4.6 - 7.0) and broad


CH2MgCl
XXXVII
Br
XXXVIII
MCPA
XXXIX
O
XL
HS(CH2)3SH
BF3:ether, CHCl3
S
S
XLI
n-butylLi
XLII
OH
XLIII
OH
O
XLIV

SCHEME XI

absorptions for the 6 methylene protons of the thioketal moiety (δ = 1.60 - 3.25). The i.r. (IR-XXVII) was in accord with this structure and the elemental analysis was satisfactory.

The deep red anion XLII of the thioacetal formed immediately on addition of n-butyllithium. Addition of the epoxide XXXIV to the anion XLII caused the deep red color to fade to a light green in about 10 minutes, indicating that the reaction is quite fast.

Since the oil formed by this reaction would not crystallize and decomposed upon distillation, purification was carried out by t.l.c. (thin layer chromatography). Thus purified, the β-hydroxythioketal XLIII (89.5% yield) is a viscose, light yellow oil.

The i.r. showed an OH absorption (3625 cm^{-1}) indicating that the condensation had taken place. This was confirmed by the mass spectrum (MS-I) which gave the desired molecular ion at 370 amu. The n.m.r. (NMR-XXVIII) showed the ABX multiplet had given way to an AB quartet (2H) centered at δ = 6.45 revealing that the anion had attacked via the 2 position of the dithiane ring, rather than the position immediately adjacent to the phenyl ring (fig. v).

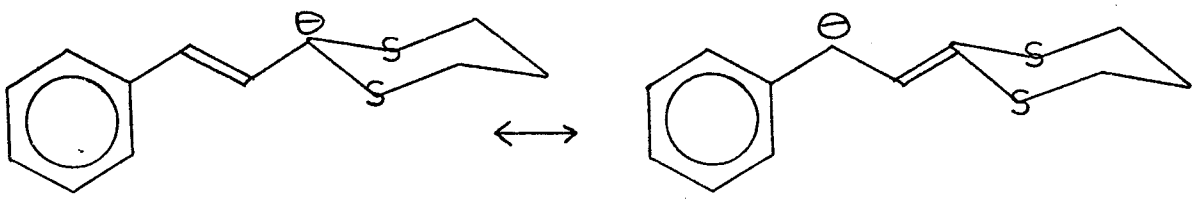


Figure v

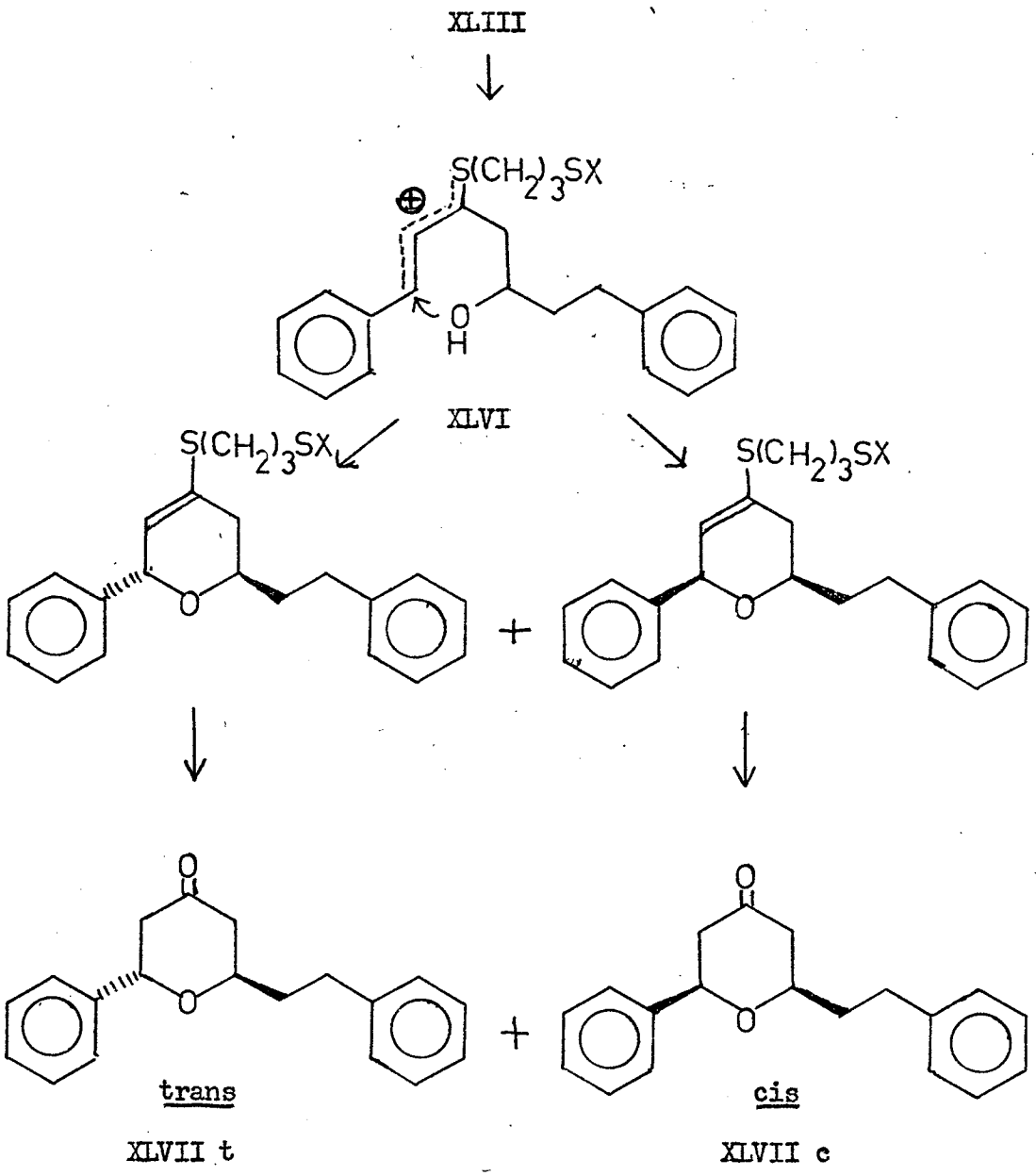
Integration showed 10 aromatic protons (δ = 7.05 - 7.55), 2 vinyl protons (AB quartet, δ = 6.54), one proton bonded to the carbon of the alcohol (multiplet δ = 3.85 - 4.25) and 13 aliphatic protons (δ = 1.45 - 3.20).

Since compound XLIII was purified only by thin layer chromatography, no elemental analysis was done; however, it was felt that sufficient data had been gathered to identify the compound. The next step also contributed to evidence in favour of its assigned structure.

The hydrolysis of this β-hydroxythioketal did not proceed as expected. Although a variety of reagents were employed (table IV along with other reagents), there was no yashabushiketol XXXIII isolated or even detected by spectroscopic means. Upon hydrolysis, the molecule rather cyclized (scheme XII) to form the cis and trans isomers of 2-phenyl-6-(2'-phenylethyl)tetrahydro-4-pyrone.

In an attempt to prevent cyclization, the hydroxyl group was blocked by acetyl, trifluoroacetyl and trimethylsilyl groups. This effort proved in vain, however, since the only reaction products isolated from these derivatives were either the starting blocked alcohol or small amounts of the tetrahydropyrone mixture XLVII, which seemingly resulted from hydrolysis of the blocking group (by traces of water in the reagents or solvents) followed by cyclization. A probable explanation is that the blocking group sterically hinders attack on the sulfurs, preventing their oxidation and formation of the cation necessary for hydrolysis.

Fortunately, these isomeric tetrahydropyrones could be separated from each other by thin layer chromatography on silica gel.



XLVII t

XLVII c

SCHEME XII

Both were viscous oils with identical boiling points (bp = 120° @ 0.2 mm), their elemental analyses were the same and acceptable while their i.r. and n.m.r. spectra were different enough to allow fairly definite assignment of the isomeric structures.

The stereoisomeric assignment was made initially on the basis of the infrared spectra.

The i.r. (IR-XXIX) of the cis compound XLVII c, while showing no hydroxyl absorption, did show an absorption at 1720 cm^{-1} corresponding to an unconjugated ketone carbonyl. The i.r. (IR-XXX) of the trans compound XLVII t was quite similar to that of the cis, except that the carbonyl band was slightly broader and more significantly, was at a higher frequency, suggesting greater ring strain as might be expected from the trans compound. More precisely, in either chair configuration, compound XLVII t will have an axial substituent which by way of a reflex effect[45] reduces the internal angle of the carbonyl, raising its stretching frequency. The broader bandwidth of the absorption probably denotes rapid conformational changes expected from the less stable trans compound (see fig. vi), further reinforcing the allegation that IR-XXX is the i.r. of the trans compound. The i.r. of the cis compound, having a fairly sharp absorption for $\nu_{C=O}$, was deemed to have the stable chair conformation illustrated in figure vii.

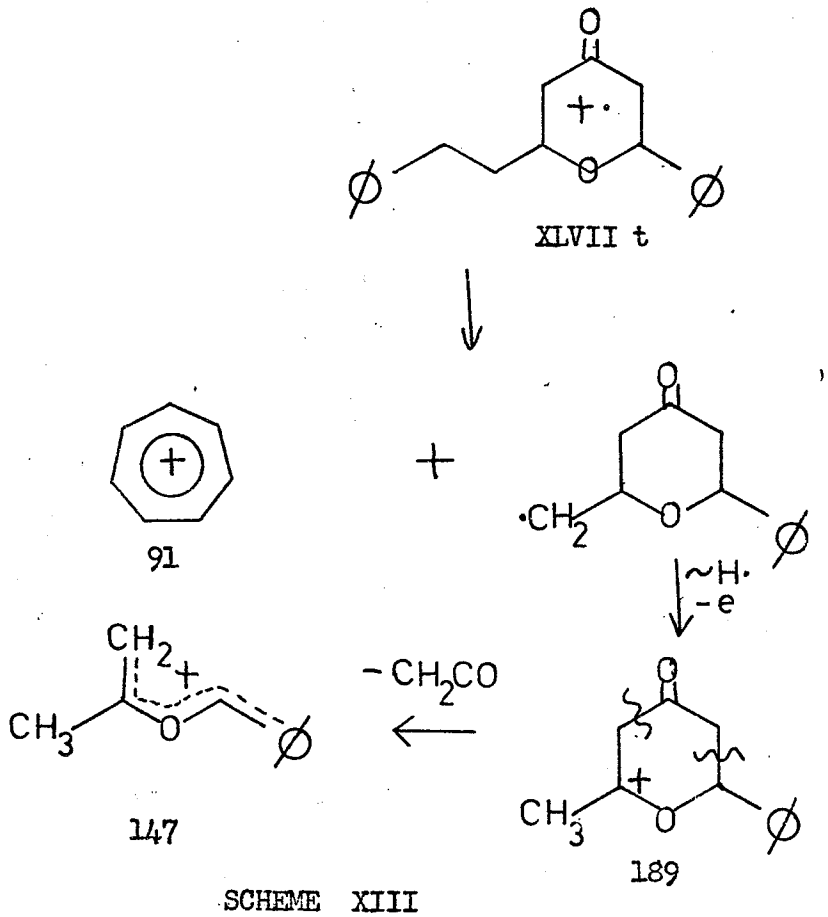
Both stereoisomers exhibited molecular ion peaks at 280 amu in their mass spectra (cis MS-II, trans MS-III). The majority of peaks for the trans compound can be accounted for by way of scheme XIII. The cis compound, however, exhibits a more complex

pattern. Scheme XIV seems to account for the extra fragments although the reason for the appearance of the peaks at 218 and 220 is not entirely clear. It should be noted that all these "extra" peaks appear in the mass spectrum of the trans compound but in lower intensities. Thus both isomers fragment to some degree by both schemes.

The mass spectra, then, do not differentiate between the two stereoisomers but are quite consistent with the conjecture that the products are stereoisomers.

The n.m.r. of the cis compound (NMR-XXIX) was assigned according to figure vii. The spectrum showed resonances for two sets of aromatic protons (5H, pseudosinglet, δ = 7.23; 5H, pseudosinglet, δ = 7.08). The methylene protons appeared as a broad multiplet from δ = 1.55 to 2.90. The chemical shift of the C-6 proton was about one ppm higher than that of the C-2 proton, the latter being benzylic (signals were centered at δ = 3.45 and δ= 4.45 respectively). The splitting of the H_{2a} signal ("a" denoting axial and "e" denoting equatorial) from coupling with the axial and equatorial C-3 protons (J_{2a3a} = 9.5 Hz, J_{2a3e} = 5.0 Hz) was clearly observed, the conformation of the molecule thus being stable enough for the observation of the coupling.

This type of coupling is not observed in the n.m.r. spectrum (NMR-XXX) of the trans tetrahydropyrone, which again suggests that the rapid equilibrium indicated in figure vi is taking place. This rapid equilibrium is further suggested by the fact that the aromatic protons of compound XLVII t appear as single peak in the n.m.r.



SCHEME XIII

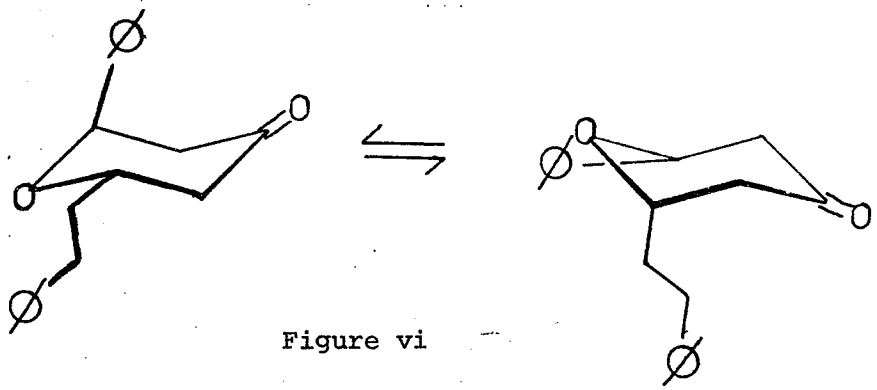


Figure vi

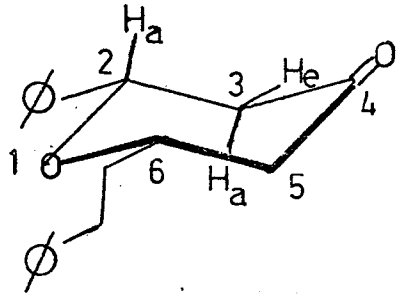
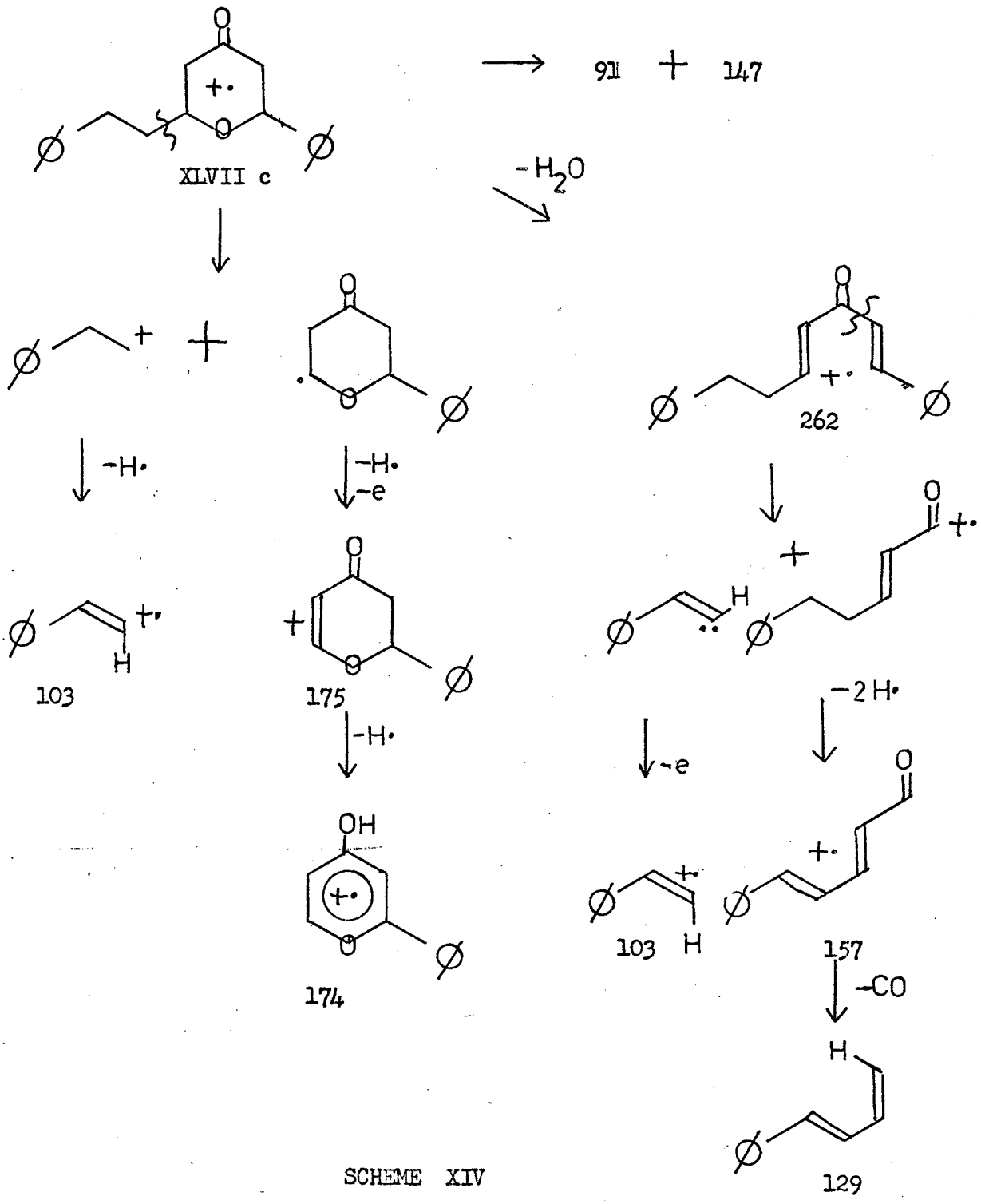


Figure vii



SCHEME XIV

spectrum, therefore indicating an averaging of the environments of these phenyl protons. The aromatic protons of compound XLVII c on the other hand, appear as two single peaks of about five protons each, which indicates a relatively stable environment for each phenyl ring.

The analysis, is not completely without question. Generally it is found in an n.m.r. spectrum, that an axial proton appears at higher field than an equatorial proton, yet, H_2 and H_6 of the cis compound, which are deduced to be axial, appear approximately 0.2 ppm to lower field than H_2 and H_6 of the trans compound, even though these latter protons should spend a greater portion of their time in the equatorial position.

TABLE IV

Yields of cis and trans tetrahydropyrones from compound XLII

reagent	% trans	% cis	net trans + cis
$Tl(TFA)_3$	43	57	53%
MeI	45	55	53%
$CuCl_2/CF_3CO_2H$	43	57	65%
HgO/BF_3	78	22	45.5%
$HgCl_2/NaHCO_3$	43	58	49%

In the course of the studies of the attempted hydrolysis of the thioketal precursor XLIII of racemic yashabushiketol XLIV, several diverse reagents were tried to cause the conversion to

yashabushiketol (table IV). From the mechanism proposed in scheme XII, it would be expected that the nature of the reagent should have little bearing on the ratio of cis to trans and, remarkably enough, this holds true almost to within 1%. The anomalous behaviour of HgO/BF_3 may be due to the strong Lewis acid's (BF_3) equilibrating the mixture. The fact that all other mixtures are approximately 1:1 in ratio supports XLVI as an intermediate with no preferred side of attack by the hydroxyl group on the carbonium ion.

It was found by infrared spectroscopy that trifluoracetic acid established an equilibrium between the thioketal XLIII and the pyrone mixture XLVII. Equilibrium was reached in about 2 hours and there was no change in the i.r. of the mixture after several days. The exact ratio of tetrahydropyrone to thioketal was not determined but was estimated from its spectrum to be about 1:10.

It was surmised that the major reason for the equilibrium was not the potency of the reagent acid, but the facile formation of the carbonium ion at C-3 of the thioketal (see compound XXXIII for numbering). To test this conjecture, the same procedure as above as tried on the thioacetal of benzaldehyde with no aldehyde being detected by i.r.

To shift the equilibrium towards the pyrone, $CuCl_2$ was added to oxidize the thiol. While $CuCl_2$ or $CuCl_2/CuO$ were alone ineffective in promoting hydrolysis, table IV shows that $CuCl_2/CF_3CO_2H$ gave the best yield of all the reagents. This mild method was also tried on the thioacetal of benzaldehyde and after 2 days at room temperature afforded only a trace of benzaldehyde (ca 5%) which was

detected by the infrared spectrum of the crude mixture.

This method then, would not seem to be of general application, but was instrumental in pointing to XLVI as an intermediate in the solvolysis of compound XLIII and supports scheme XII as the most likely route to the tetrahydrone mixture XLVII.

Although the synthesis of racemic yashabushiketol XLIV was not successfully completed, the reaction of its precursor to form a mixture of cis and trans 2-phenyl-6-(2'-phenylethyl)tetrahydro-4-pyrone proved to be of interest.

EXPERIMENTAL

The infrared (i.r.) spectra were recorded on a Perkin Elmer model 710 i.r. spectraphotometer neat, in methylene chloride solution or as a "Nujol" mull. All nuclear magnetic resonance (n.m.r.) spectra were recorded on a Varian HA-56/60A spectrometer neat, in $CDCl_3$ solution or CCl_4 solution using tetramethylsilane (TMS) as internal standard. Chemical shifts are given in δ units and the coupling constant, J, in hertz (Hz).

The mass spectra were recorded on a Finnigan model 1015 mass spectrometer. Microanalyses were conducted by Kolbe Laboratories in West Germany and melting points were obtained from a Fisher-Johns melting point apparatus and are uncorrected. Alumina and silica gel for column and thin layer chromatography (t.l.c.) was Camag brand from Mondray Ltd., Montreal. T.l.c. was done employing 1 mm thick adsorbent on 20 x 20 cm glass support plates.

PART A

1,4,6-Trimethoxy-5,8-dihydroxynaphthalene III

To 8.0 g (0.058 formula units) of potassium carbonate and 75 ml acetone mechanically stirred in a 200 ml three necked round bottomed (r.b.) flask equipped with a condenser, was added 3.84 g (0.02 moles) of 6-methoxy-4a,5,8,8a-tetrahydro-1,4-naphthoquinone II with external cooling. After 0.5 hour of stirring at gentle reflux, 2.1 ml (2.8 g, 0.022 moles) of dimethyl sulfate was added over 5

minutes with external cooling. The solution was then allowed to come to a reflux. Heat was subsequently applied and refluxing was continued over a total of 4 hours. After cooling, water was added until dissolution of the salts had occurred. The solution was extracted with chloroform (2 x 50 ml). The organic extract was dried over magnesium sulfate, filtered the chloroform evaporated and the residue distilled (140 - 142°C @ 2 mm) to give 3.83 g (87%) of compound III as a light yellow oil. The oil crystallized on sitting to an almost white solid which was identical in mixed mp, i.r., n.m.r. and mass spectrum to material prepared by Grob's method[14].

4a,5,8,8a-tetrahydro-1,4-naphthoquinone V

Into a 500 ml r.b. flask, were placed 50 g of practical grade p-benzoquinone and 350 ml of benzene. The mixture was cooled to < 10°C in an ice bath and 30 g butadiene dissolved into the solution. The resulting dark solution was sealed and stirred 6 days at room temperature. It was then charged with ca (circa) 5g charcoal, stoppered and stirred overnight. The mixture was then filtered, evaporated and the solid residue recrystallized from 1 liter of hexanes to give 60 g (80%) of white fluffy crystals with a melting point (mp) of 45 - 48°C. Another recrystallization from hexane gave material with mp = 51 - 53°C.

i.r. (IR-I): absorption at 1695 cm^{-1} (conjugated δ-diketone)

n.m.r. (NMR-I): resonances at 6.66 [2H, singlet(s), quinone protons], 5.69 [2H, triplet(t), J - 1.5 Hz, olefinic], 3.0 - 3.4 [2H, multiplet(m), methine] and 1.9 - 2.8 (4H, m, methylene).

mass spectrum: $\overset{+}{P}$ = 162 amu

5,8-Dimethoxy-1,4-dihydronaphthalene VI

The same procedure was used as for the isomerization and methylation of compound II, except that compound V was used as starting material. The oil from this procedure was distilled at 145 - 150°C @ 15 mm (air condenser) giving compound VI as massive crystals (mp = 43 - 44°C) in near quantitative yields.

i.r. (IR-II): absorptions at 1600 cm^{-1} (aromatic double bonds), and 1075 and 1090 cm^{-1} (ether linkages).

n.m.r. (NMR-II): resonances at 6.58 (2H,s,aromatic), 5.85 (2H, t, J = 2 Hz, olefinic), 3.73 (6H,s, methoxyl) and 3.25 [4H, doublet(d), J = 2 Hz, allylic-benzylic].

mass spectrum: $\overset{+}{P}$ = 190, 175 (P - CH_3) and 159 (P - OCH_3).

2,3-Epoxy-5,8-dimethoxytetralin VII

380 mg of the olefin VI, 425 mg of 85% metachloroperbenzoic acid (MCPA) and 20 ml of benzene were stirred overnight at room temperature. The solution was then extracted with 10% aqueous NaOH (2 x 25 ml), evaporated and the residue recrystallized from $CHCl_3$ to give 307 mg (74.5%) of compound VII as white crystals (mp = 131 - 2°C).

i.r.(IR-III): absorptions at 1600 cm^{-1} (aromatic double bonds), 1090 cm^{-1} (ether linkages) and 860 cm^{-1} (epoxide).

n.m.r. (NMR-III): resonances at 6.61 (2H, s, aromatic), 3.75 (6H, s, methoxyl), 3.25 - 3.50 (4H, m, benzylic) and 2.50 - 3.0 (2H, m, epoxide protons).

mass spectrum: P = 206

2-Hydroxy-5,8-dimethoxyteralin VIII

To 1.70 g distilled olefin VI in 15 ml tetrahydrofuran (thf) with 0.140 g $NaBH_4$ powder suspended was added over 20 minutes 0.63 ml BF_3:etherate and the resulting mixture was stirred for another 70 minutes under N_2. Excess B_2H_6 was destroyed with 0.5 ml water and then 2 ml of 3 N NaOH were added followed by 1.5 ml 30% peroxide (exothermic). The aquous layer was saturated with sodium chloride. The thf layer was then removed, diluted to 60 ml with benzene, washed with saturated sodium chloride solution, dried and evaporated to a small volume. Petroleum ether was then added to precipitate 1.79 g (96%) compound VIII as fluffy white crystals. Thus prepared, the alcohol VIII melted at 131 - 2°C and could not be further purified by recrystallization ($CHCl_3$/pet ether). Lewis[17] reports a mp of 130.5 - 132°C.

i.r. (IR-IV): absorptions at 3640 cm^{-1} (OH), 1600 cm^{-1} (aromatic double bonds) and 1095 cm^{-1} (ether).

n.m.r. (NMR-IV): resonances at 6.62 (2H, s, aromatic), 3.85 - 4.25 (2H, m, C<u>H</u>O<u>H</u>), 3.75 (6H, s, methoxyl), 2.5 - 3.3 (4H, m, benzylic) and 1.8 - 2.1 (2H, m, methylene).

mass spectrum: $\overset{+}{P}$ = 208, 190 (P - H_2O) and 175 (P - H_2O, CH_3) amu

5,8-Dimethoxy-2-tetraline IX

A. Into a mechanically stirred solution of 7.5 g of CrO_3 pyridyl complex dissolved in 100 ml CH_2Cl_2 (dried by passing through column grade neutral alumina; 10 g for 100 ml methylene chloride) in a 250 ml r.b. three-necked flask equipped with a drying tube, was added in one portion, 2.0 g of alcohol VIII in 25 ml of warm dry CH_2Cl_2. After 5 minutes of stirring, the mixture was filtered, evaporated to dryness, the residue taken up into benzene and the solution filtered and evaporated to remove the remaining pyridine.

6 ml of saturated aqueous $NaHSO_3$ was added and the mixture agitated overnight. The mixture was triturated with ether, the solid collected and the tetralone was separated with saturated aqueous $NaHCO_3$ solution. This mixture was extracted with chloroform and the chloroform layer dried and evaporated to give 1.665 g (84%) of the tetralone IX which after recrystallization from ether had a mp of 98 - 99.5°C.

i.r. (IR-V): absorptions at 1707 cm^{-1} (carbonyl), 1600 cm^{-1} (aromatic double bonds) and 1090 cm^{-1} (ether).

n.m.r. (NMR-V): resonances at 6.67 (2H, s, aromatic), 5.27 (impurity) 3.77, 3.73 (6H, 2 singlets, methoxyl), 3.46 (2H, broad singlet, benzylic α-keto protons), 2.9 - 3.25 (2H, m, benzylic) and 2.3 - 2.65 (2H, m, α'-keto protons).

mass spectrum: $\overset{+}{P}$ = 206 and 191 (P - CH_3) amu

B. To 400 mg alcohol VIII in 2 ml of benzene, 2 ml dimethylsulfate (DMSO) and 80 l H_3PO_4, was added 1.0 g dicyclohexylcarbodiimide (DCC). The solution was stirred 1.5 hours at room temperature, diluted with 10 ml of benzene, filtered, washed with water (3 x 30 ml) and dried over $MgSO_4$. It was then applied to a column of silica gel (10 g) and eluted with $CHCl_3$ to give 0.225 g (57%) of white crystalline material identical in every way to that prepared by method A.

2-Hydroxy-2-ethynyl-5,8-dimethoxytetralin X

Fifteen mmoles (millimoles) of acetylene Grignard was prepared in 100 ml of dry thf, according to the method of Skattebøl et al.[46] To this solution, was added over a 30 minute period 2.06 g of the tetralone IX in 10 ml of dry thf and the resulting solution was then stirred overnight under a dry nitrogen atmosphere. The solution was then added to 100 ml cold saturated aqueous ammonium chloride solution. The resulting layers were then separated and the aqueous phase extracted with ether (2 x 50 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to give 1.93 g (83%) of almost colorless oil (used without purification in the next step). After separation by t.l.c. (2% CH_3OH:$CHCl_3$ on silica gel, R_f = 0.4), compound X was obtained as a pinkish oil which gave the following spectra:

i.r. (IR-VI): absorptions at 3630 cm^{-1} (OH), 3340 cm^{-1} (ethynyl C-H), 1600 cm^{-1} (aromatic double bonds) and 1090, 1070 and 1030 cm^{-1} (ether and alcohol C-0).

n.m.r. (NMR-VI): resonances at 6.44 (2H, s, aromatic), 3.66 and 3.63 (6H, s, methoxyl), 2.5 - 3.25 (5H, m, OH and benzylic protons), 2.19 (1H, s, methine) and 1.65 - 2.05 (2H, m, methylene).

mass spectrum: P^{+} = 232 and 214 (P - H_2O)

2-Hydroxy-2-acetyl-5,8-dimethoxytetralin XIII

A. To 1.16 g of crude acetylene alcohol X in 10 ml of thf with 0.2 g powdered $HgSO_4$ was added 2 ml of 10% aqueous H_2SO_4. After 3 hours of stirring at room temperature. The solution was decanted, washed with 10 ml saturated aqueous NaCl and 20 ml of ether was added. The solution was washed with bicarbonate, dried, filtered and evaporated. The residue was recrystallized from $CHCl_3$- pet ether to give 1.09 g (87%) of white crystals melting at 102 - 102.5°C and identical spectroscopically and in mixed mp to a sample of compound XIII prepared by R. Schwenk.[18]

i.r. (IR-VII): absorptions at 3520 cm^{-1}(OH), 1705 cm^{-1} (carbonyl), 1600 cm^{-1} (aromtic double bonds) and 1080 cm^{-1} (ether or alcohol OH).

n.m.r. (NMR-VII): resonances at 6.47 (2H, s, aromatic), 3.71, 3.67 (each 3H, singlets, aromatic methoxyl), 3.27 (1H, s, OH), 2.5 - 2.9 (4H, m, benzylic), 2.17 (3H, s, -$COCH_3$) and 1.56 - 1.90 (2H, m, methylene).

mass spectrum: P^{+} = 250, 234(P - H_2O) and 207(P - $COCH_3$)

B. To a stirred solution of 1.22 g of crude blocked

cyanohydrin XII (next two preparations) in 15 ml dry thf under N_2 was added 2.0 ml (10% excess) of 2.3 N MeLi (methyl lithium) in ether and the solution stirred 1 hour at room temperature. The solution was carefully poured over 50 ml of saturated aqueous ammonium chloride solution containing 1 ml concentrated HCl solution and stirred for an additional 3 hours. After extraction with ether (3 x 50 ml), drying ($MgSO_4$) and evaporation of the solvent the crude material was purified by t.l.c. (2% MeOH:$CHCl_3$ on silica gel, R_f 0.4). It was then recrystallized from $CHCl_3$-pet. ether to give 0.733 g (73%) of compound XIII.

2-Hydroxy-2-cyano-5,8-dimethoxytetralin XI

1.03 g (5 mmoles) of 5,8-dimethoxy-2-tetralone IX were dissolved into a suspension of 3.5 g NaCN in 20 ml of methanol. 7.5 ml of acetic acid were added and the mixture stirred for 3 hours at room temperature. 50 ml of water were then added and the mixture was extracted with $CHCl_3$ (3 x 50 ml). The combined $CHCl_3$ extracts were then dried over Na_2SO_4 and the solvent evaporated. The yield of compound XI as an impure oil was 1.04 g (89.5%). The product was not isolated for the next step.

2-Trimethylsiloxy-2-cyano-5,8-dimethoxytetralin XII

To a solution of 1.04 g of the crude cyanohydrin XI in 10 ml of benzene and 1 ml of pyridine (dried over KOH) was added 2 ml of chlorotrimethylsilane and this resulting solution was then stirred for 2 hours at room temperature under the protection of a drying tube.

The mixture was then evaporated in vacuo to remove the excess chlorotrimethylsilane. The solid residue was taken up into 20 ml of benzene and washed with ice-cold water (25 ml) and 5% sodium bicarbonate solution (2 x 25 ml) and then dried over $MgSO_4$.

The benzene was removed in vacuo; more benzene was added to be again removed in vacuo. This procedure was repeated until the last traces of pyridine had been removed. The crude compound XII (1.28 g, 94%) was again not purified, but was used directly in the reaction with methyl lithium to make the hydroxyketone XIII two steps preceding.

2-Hydroxy-2-acetyl-8-methoxytetralin XVI

This compound was prepared from 8-methoxy-2-tetralone XV using the above two procedures with similar results. Via the acetylene grignard, the overall yield was 76% and via the blocked cyanohydrin, 51%. The product was a colorless oil that was not analysed.

i.r. (IR-VIII): absorptions at 3520 cm^{-1}(OH), 1720 cm^{-1} (carbonyl), 1600 cm^{-1} (aromatic double bonds) and 1120,1105 and 1090 cm^{-1} (ether and alcohol C-O).

n.m.r. (NMR-VIII): resonances at 6.40 - 7.15 (3H, m, aromatic), 3.70 (3H, s, $ArOCH_3$), 3.34 (1H, s, OH), 2.60 - 3.08 (4H, m. benzylic), 2.14 (3H, s, $-COCH_3$) and 1.57 - 1.94 (2H, m, methylene).

2-Hydroxy-2-vinyl-5,8-dimethoxytetralin XVII

412 mg of 5,8-dimethoxy-2-tetralone IX in 5 ml of t.h.f. was added over 5 minutes to 1.5 ml (2.8 M) vinylmagnesium chloride in 5 ml thf. The reaction mixture was refluxed 15 minutes and then cautiously poured into 10 ml of saturated aqueous NH_4Cl solution. The layers were separated and the organic layer washed with saturated NaCl solution (2 x 10 ml), dried over $MgSO_4$, evaporated and the residue purified by t.l.c. (silica gel, 2% methanol/$CHCl_3$, R_f = 0.25) to give 352 mg (75%) of compound XVII as a pinkish oil.

i.r. (IR-IX) absorption at 3620 cm^{-1} (OH), 1640 cm^{-1} (C = C, olefinic), 1600 cm^{-1} (aromatic C = C), 1100 and 1080 cm^{-1} (ether and alcohol C - 0) and 920 cm^{-1} (terminal vinyl CH_2).

n.m.r. (NMR-IX): resonances at 6.58 (2H, s, aromatic), 4.93 - 6.28 (3H, m, vinyl protons), 3.74, 3.71 (each 3H, s, $ArOCH_3$), 1.55 - 2.94 (6H, m, methylenes), 6.88, 6.26, 4.13 and 3.27 (spinning side bands).

3-Nitropropionic acid XXVII

18 g of β-propiolactone was added dropwise to a cooled, stirred solution of 25 g of $NaNO_2$ in 50 ml of water (15 - 20°C). Stirring was continued 4 hours and then the red solution was cooled to -5°. Ether was added (25 ml) and then H_3PO_4 was added dropwise until the solution was acidic (ca 10 ml). During acidification, the ether was decanted frequently and fresh portions added. The

combined ether solutions were dried, evaporated and the oil frozen (dry ice). The frozen oil was placed on a suction filter and allowed to thaw, leaving a white solid. This freeze-thaw procedure was repeated twice more on the remaining oil to give a total of 6.0 g (22%) of the nitro acid XXVII. Recrystallization (CH_2Cl_2) gave stable white needles with a mp = 63 - 65°C.

i.r. (IR-X): absorptions at 2900 cm^{-1} broad ($-CO_2H$), 1755 and 1720 cm^{-1} (β-substituted acid), 1560 and 1380 cm^{-1} (nitro and 1140 cm^{-1} (C-O bond).

n.m.r. (NMR-X): resonances at 9.30 (1H, s, carboxylic acid), 4.47 - 4.83 2H, m, α-nitro methylene) and 2.90 - 3.20 (2H, m, α-acid methylene).

Sec-butenyl 3-nitropropionate XXIX

3.6 g of nitro acid XXVII was placed in a 250 ml r.b. flask in an ice bath (fume hood). 10 ml thionyl chloride was then added dropwise with swirling over 10 minutes. The reaction was stoppered loosely and let stand 0.5 hour with intermittent warming on a steam bath (35 - 45°C) and swirling. The $SOCl_2$ was then pumped off in vacuo (ca 40°) with benzene being added to remove the last traces of thionyl chloride. 10 ml of benzene was added. The flask was then immersed in an ice bath and a solution of 2.6 ml (2.2 g) of methylvinyl alcohol, 20 ml of benzene and 3 ml of pyridine was added dropwise, with the temperature not being allowed to exceed 15°C. The flask was equipped with a drying tube and the contents

stirred for 1 hour, still below 15°C. 30 ml of water was added and the flask shaken till dissolution of the solid. The benzene layer was separated and the aqueous layer extracted with more benzene (2 x 50 ml). The combined benzene extracts were dried ($MgSO_4$) and evaporated and the oil residue distilled to (75 - 85° @ 0.4 mm) to give 3.19 g (61%) of compound XXIX as a colorless oil with η_D^{25} (index of refraction) = 1.448.

analysis	%C	%H
calculated	48.55	6.40
found	48.50	6.36

i.r. (IR-XI): absorptions at 1735 cm^{-1} (ester carbonyl), 1560 and 1380 cm^{-1} (NO_2), 1195 cm^{-1} (ester C-O) and 935 cm^{-1} (vinyl CH_2).

n.m.r. (NMR-XI): resonances at 5.0 - 6.2 (4H, m, vinyl and methine), 4.56 (2H, t, J = 6.5 Hz, α-nitro methylene), 2.90 (2H, t, J = 6.5 Hz, α-ester methylene) and 1.31 (3H, d, J = 6.5 Hz, methyl).

mass spectrum: ions at 102, 71 and 55 amu (see figure XXXII).

1'-Formylethyl 3-nitropropionate XXX

Through a solution of 0.5 g of nitro ester XXIX and 50 ml $CHCl_3$ cooled to -10°C in an ice-salt bath, was bubbled ozone for 1.5 hours (ca 10 l/hour). The ozone was generated from bottled oxygen. The solvent was evaporated in vacuo in a warm (50°) water bath then the residue cooled to room temperature. 3.5 ml of acetic acid were added, and then with stirring, 2 g of powdered NaI was slowly added

while the temperature was kept below 30° by a water bath. Stirring was continued 15 minutes at which time a saturated solution of sodium thiosulfate was added to decolorize the iodine. The product was extracted with $CHCl_3$ (3 x 50 ml), and then the $CHCl_3$ solution was dried and evaporated to give aldehyde XXX as a colorless oil in 77% yield (0.338 g).

There was no analysis because of the instability of the compound. This instability also prevented sufficient purification (The aldehyde decomposed on silica gel plates and decomposed at its bp 90 - 100°C @ 0.4 mm) to obtain a mass spectrum without a large number of impurity peaks.

i.r. (IR-XII): absorptions at 1740 cm^{-1} (ester and aldehyde carbonyl), 1560 and 1380 cm^{-1} (NO_2) and 1185 cm^{-1} (ester C-O).

n.m.r. (NMR-XII): resonances at 9.50 (1H, s, aldehyde proton), 5.11 (1H, q = quartet, J = 7.0 Hz, methine), 4.54 - 4.83 (2H, m, α-nitro methylene), 2.85 - 3.22 (2H, m, α-ester methylene) and 1.40 (3H, d, J = 7.0 Hz, methyl).

Attempted cyclizations of the nitro aldehyde XXX

A. 215 mg of 57% NaH/oil was washed twice with 20 ml portions of petroleum ether. To this NaH, stirred and suspended in 5 ml of thf was added 875 mg of crude aldehyde XXX in 5 ml of thf and stirring was continued under N_2 overnight (16 hours) at room temperature. 500 mg of oxalic acid was added and stirring was continued for an additional 2 hours. The mixture was then diluted with 20 ml

of benzene and filtered. The filtrate was pumped down several times, with benzene being added each time to remove water and thf. The material was then leached from the oxalate salts with 10% MeOH/$CHCl_3$ to give 727 mg (85%) of golden oil.

The crude i.r. showed absorptions for hydroxyl and carbonyl groups with the nitro groups showing greatly decreased intensity, but no cyclized product was isolated, purification having been tried by t.l.c. of the oil on silica gel, neutral alumina and cellulose.

B. 500 mg of crude aldehyde XXX in 3 ml of dry t-butanol was added to 125 mg (before washing with pet ether) of 57% NaH/oil dissolved in 10 ml of dry t-butanol. The mixture was stirred 6 hours, then worked up in the same manner as in A.

Again, the i.r. was promising, showing this time besides the hydroxyl peaks, full strength nitro absorptions, however, attempted isolation proved fruitless.

PART B

Formation of thioacetals[37] (table II)

To a solution of 0.01 moles of aldehyde and 0.011 moles (1.19 g, 1.1 ml) 1,3-propane dithiol in 10 ml of $CHCl_3$ was added 0.25 ml of BF_3 etherate. The resulting solution was stirred 3 hours, then washed: 1 x 10 ml H_2O, 2 x 10 ml 2N NaOH and 1 x 10 ml H_2O. It was then dried ($MgSO_4$), the solvent evaporated *in vacuo* then the residue recrystallized or distilled, with the following results (see table II):

Acetaldehydethioacetal[18] (R = CH_3)

yield 87%; bp 125 - 128°C @ 40 mm

i.r. (IR-XIII); n.m.r. (NMR-XIII)

Benzaldehydethioacetal (R = Ø)

yield 89%; mp 69.5 - 71°C (methanol)

i.r. (IR-XIV); n.m.r. (NMR-XIV)

1,3-Dithiane[47] (R = H) was prepared by the slow addition of 1.0 ml (0.89 g, 0.012 mole) of methylal and 1.0 ml (1.08 g, 0.01 mole) of 1,3-propanedithiol in 10 ml $CHCl_3$ to 0.25 ml BF_3 etherate in 5.0 ml $CHCl_3$ at reflux. Work-up was performed in the same manner as in the previous preparation. The yield was 86.5% (1.04 g) of 1,3-dithiane as white crystals mp 50 - 50.5°C (methanol).

i.r. (IR-XV); n.m.r. (NMR-XV)

Addition of the thioketal anions to carbonyl compounds

1) Formation of the anion

5 mmoles of commercial 2N n-butyl lithium in ether was added to 5 mmoles of thioacetal in 15 ml dry thf which was stirred under dry nitrogen rid of O_2 by a Fieser solution and dried with NaOH pellets and Drierite. During addition, the solution was maintained at -30°C in a dry ice - methanol/water (1/2) bath and the stirring was continued at -20 to -30°C for 1 hour.

2) Reaction with the carbonyl

To the above solution of the anion, was added 5 mmoles of carbonyl compound in 5 ml of dry thf. The resulting solution was stirred at -5 to -10°C for 3 hours. To the mixture was slowly added 20 ml of saturated aqueous NH_4Cl; the lower layer was then run off and the organic phase washed once more with 20 ml of saturated NaCl. The thf was evaporated and the residue distilled or recrystallized to give the following compounds:

2-Hydroxy-2,2-diphenylacetaldehydethioacetal XXXIV a (R = H, R' = R" = Ø)
mp (hexane) = 136 - 137°C (reported 136 - 136.5°C[33])
i.r. (IR-XVI); n.m.r. (NMR-XVI)

Methyl-1'-hydroxycyclohexylketonethioketal XXXIV b
bp = 125 - 130°C @ 0.2 mm (reported 165°C @ 1.2 mm[33])
i.r. (IR-XVII); n.m.r. (NMR-XVII)

1-Hydroxy-1,1-diphenylacetonethioketal XXXIV d

mp = 134 - 135°C (methanol; reported 136 - 137.5°C[33])

i.r. (IR-XVIII); n.m.r. (NMR-XVIII)

Benzointhioketal XXXIV c

Analysis	%C	%H
calc.	67.51	6.00
found	67.53	6.03

mp = 130.5 - 131.5°C (methanol).

i.r. (IR-XIX); absorptions at 3635 cm^{-1} (OH), 1600 cm^{-1} (aromatic C = C) and 1190 cm^{-1} (thioketal).

n.m.r. (NMR-XIX): resonances at 6.70 - 7.80 (10 H, m, aromatic), 4.95 (1 H, s, α-hydroxyl), 2.25 - 2.85 (5 H, m, OH and methylene) and 1.70 - 2.10 (2 H, m, methylene).

Phenyl-1'-hydroxycyclopentylketonethioketal XXXIV e

Analysis	%C	%H
calc.	64.24	7.19
found	64.30	7.15

bp = 140°C @ 0.2 mm; mp = 84 - 85.5°C (ether-petroleum ether)

i.r. (IR-XX): absorptions at 3605 cm^{-1} (OH), 1600 cm^{-1} (aromatic C = C) and 1190 cm^{-1} (thioketal).

n.m.r. (NMR-XX): resonances at 7.17 - 8.20 (5 H, m, aromatic) 2.45 - 3.05 (5 H, m, OH and thioketal methylenes) and 1.10 - 2.45 (10 H, m, methylenes).

Thallium III trifluoroacetate hydrolysis of the thioketals

To 1 mmole of thioketal in 2 ml of wet thf (1 drop H_2O) was added 600 mg (1200 mg in the case of XXXV e, table III) $Tl(CF_3CO_2)_3$. The solutions did not warm noticibly (unlike the cases studied by Ho and Wong[35]) and the reaction took from 0.5 to 2 hours (table III) to go to completion. 10 ml of water was added and the solution was extracted with $CHCl_3$ (2 x 20 ml). The combined extracts were dried and evaporated and the residue distilled or recrystallized.

After the extraction of compound XXXV e, the residue after evaporation of the solvent was hydrolysed in 5 ml of acetone and 2 ml conc NH_4OH to convert the trifluoroacetate to alcohol. This solution was extracted with $CHCl_3$; the organic layer was then dried, evaporated and the residue recrystallized.

2-Hydroxy-2,2-diphenylacetaldehyde XXXV a

mp = 232 - 234°C (semicarbazone; reported 238.5°C[36])

i.r. (IR-XXI); n.m.r. (NMR-XXI)

Methyl-1'-hydroxycyclohexylketone XXXV b

bp = 95°C @ 15 mm

i.r. (IR-XXII); n.m.r. (NMR-XXII)

Benzoin XXXV c

mp, mixed mp, i.r., n.m.r. and mass spectrum identical to authentic sample

Phenyl-1'-hydroxycyclopentylketone XXXV e

mp = 193 - 195°C (reported 198°C[37])

i.r. (IR-XXIII)

4-phenyl-1-butene XXXVIII

In a 250 ml r.b. flask equipped with an efficient stirrer, was placed 4.86 g (0.2 mole) Mg turnings, 20 ml of ether and an I_2 crystal. 10 ml of a solution of 23 ml (0.2 mole) of benzyl chloride in 100 ml of ether was added to initiate the reaction and the remainder added over the next 0.5 hour.

20 ml (0.23 mole) of allyl bromide in 20 ml of ether was then added over 0.5 hour, slowly at first, then more rapidly as the reaction came to completion. The mixture was stirred and refluxed a further 0.5 hours. 50 ml of 10% aqueous NH_4Cl solution was added slowly (frothing!) then enough water was added to make 2 clear layers. 200 ml of benzene was added and the layers separated. The organic layer was dried over $MgSO_4$, the solvent evaporated and the residue distilled to give 17.2 g (65%) of 4-phenyl-1-butene as a colorless oil which was collected between 175 and 185°C. Aronheim[38] reports a boiling point of 175 - 177°C.

i.r. (IR-XXVI) absorptions at 1640 cm^{-1} (olefinic C = C), 1600 cm^{-1} (aromatic C = C) and 905 cm^{-1} (olefinic CH_2).

n.m.r. (NMR-XXV): resonances at 7.05 (5 H, s, aromatic), 4.76 - 6.15 (3 H, m, vinyl) and 2.02 - 2.82 (4 H, m, benzylic and allylic methylenes).

1,2-Epoxy-4-phenylbutane XXXIX

2.64 g (20 mmoles) of 4-phenyl-1-butene XXXVIII and 5.0 g (24.6 mmoles) of 85% MCPA in 50 ml $CHCl_3$ were stirred together at room temperature for 3.5 hours. The reaction product was then washed with 50 ml of 20% aqueous K_2CO_3, 10% aqueous NaOH (2 x 30 ml), and 25 ml of water. The solvent from the organic layer was evaporated and the residue distilled (bp 105°C @ 12 mm) to give 2.425 g (82%) of 1,2-epoxy-4-phenylbutane XXXIX as a sweet smelling colorless oil. The reported[39] boiling point is 106 - 109° C @ 31 mm.

i.r. (IR-XXVI): absorptions at 1600 cm^{-1} (aromatic C = C) and 825 and 850 cm^{-1} (epoxide).

n.m.r. (NMR-XXVI): resonances at 7.15 (5 H, s, aromatic), 2.25 - 3.0 (5H, m, benzylic and epoxide protons) and 1.55 - 1.98 (2 H, m, C-3 protons).

Cinnamaldehydethioacetal XLI

To a solution of 0.63 ml (5.0 mmoles) of cinnamaldehyde and 0.61 ml (5.5 mmoles) of 1,3-propanedithiol in 20 ml of $CHCl_3$ was added 0.25 ml of BF_3 etherate and the resulting cloudy mixture was stirred 6 hours. This mixture was then washed with 30 ml water, 2 N NaOH (2 x 20 ml), and then another 30 ml of water. The solution was then dried, the solvent evaporated and the residue distilled (145 - 150°C @ 0.2 mm) to give 945 mg (85%) of cinnamaldehydethioacetal XLI as a light yellow oil which crystallized on standing to give white crystals melting at 57.5 - 58°C (when recrystallized from methanol).

Analysis	%C	%H
calc.	64.84	6.35
found	64.89	6.30

i.r. (IR-XXVII): absorptions at 1640 cm^{-1} (olefinic C = C), 1600 cm^{-1} (aromatic C = C) and 1160 cm^{-1} (thioacetal).

n.m.r. (NMR-XXVII): resonances at 7.24 (5 H, s, aromatic), 6.77 (1 H, d, J = 16 Hz, olefinic), 6.23 (1 H, q, J = 16 Hz, 7 Hz, olefinic), 4.75 (1 H, d, J = 7 Hz, C-2 of dithiane), 2.67 - 3.20 (4 H, m, dithiane methylenes) and 1.60 - 2.20 (2 H, m, methylene).

5-Hydroxy-1,7-diphenyl-1-hepten-2-onethioketal or racemic yashabushiketonethioketal XLIII

To a solution of 700 mg (3.17 mmoles) of cinnamaldehydethioacetal XLI in 10 ml of dry thf under N_2 at -30°C was added 1.4 ml of 2.3 M (3.23 mmoles) n-butyllithium in ether, the deep red anion forming almost immediately. The solution was allowed to stand for 0.5 hour and then 0.5 ml (3.5 mmole) of 4-phenyl-1,2-epoxybutane XXXIX was then added. The red color completely disappeared after only 10 minutes at -5 to -10°C, but stirring was continued for a further 30 minutes.

10 ml of saturated aqueous NH_4Cl was then slowly added, and the layers separated. The organic layer was then dried and the solvent evaporated. The residue was purified by t.l.c. on silica gel plates (2% methanol/$CHCl_3$, R_f = 0.4) to give 1.048 g (89.5%) of compound XLIII as a light yellow oil that would not crystallize. The compound boiled at 210°C @ 0.2 mm with some decomposition.

i.r. (IR-XXVIII): absorptions at 3630 cm^{-1} (OH), 1600 cm^{-1} (aromatic C = C) and 1060 cm^{-1} (C-O).

n.m.r. (NMR-XXVIII): resonances at 7.05 - 7.55 (10 H, m, aromatic), 6.88 (1 H, d, J = 16 Hz, olefinic), 6.23 (1 H, d, J = 16 Hz, olefinic), 3.83 - 4.23 (1 H, m, = CHOH) and 1.50 - 3.27 (13 H, m, OH and methylenes)

mass spectrum (MS-I): P = 370

Preparation of mixture XLVII, cis and trans isomers of 2-phenyl-6-(2'-phenylethyl) tetrahydro-4-pyranone and separation of the isomers

A. $Tl(CF_3CO_2)_3$

To 185 mg (0.5 mmole) of thioketal XLIII in 2 ml of thf, was added 300 mg of thallium trifluoroacetate with stirring continued over 1 hour. The work-up, outlined for hydrolysis by $Tl(CF_3CO_2)_3$ previously, provided 118 mg of crude oil. This was purified by t.l.c. on silica gel plates ($CHCl_3$:benzene, 1:1) to give two fractions; cis and trans isomers with respect to C-2 and C-6 substituents of 2-phenyl-6-(2'-phenylethyl)tetrahydro-4-pyranone.

The cis isomer XLVII c (42 mg, 30%) had an R_f value of 0.55 and bp = 120° C @ 0.2 mm and was a colorless oil.

Analysis	%C	%H
calc.	81.40	7.19
found	81.32	7.25

i.r. (IR-XXIX): absorptions at 1720 cm^{-1} (C = O), 1600 cm^{-1} (aromatic C = C) and 1040 cm^{-1} (ether C-O).

n.m.r. (NMR-XXIX): resonances at 7.23 (5 H, 2, aromatic), 7.08 (5 H, s, aromatic), 4.45 (1 H, q, $J_{2a,3a}$ = 9.5 Hz, $J_{2a,3e}$ = 5.0 Hz, ArCH-O), 3.37 - 3.78 (1 H, m, C-6 proton) and 1.55 to 2.90 (8 H, m, methylene).

mass spectrum (MS-II): P^{+} = 280 amu, 262 (P - H_2O), 175, 174, 157, 129, 103.

The trans isomer XLVII t (32 mg, 23%) had an R_f value of 0.30, a bp = 120°C @ 0.2 mm and was a light yellow oil.

Analysis	%C	%H
calc.	81.40	7.19
found	81.19	7.28

i.r. (IR-XXX): absorptions at 1725 cm^{-1} (C = O), 1600 cm^{-1} (aromatic C = C) and 1040 cm^{-1} (ether C-O).

n.m.r. (NMR-XXX): resonances at 7.08 (10 H, m, aromatic), 4.03 - 4.40 (1 H, m, ArCH-O), 2.95 - 3.28 (1 H, m, = CH-O) and 1.57 - 2.95 (8 H, m, methylene).

mass spectrum (MS-III): P^{+} = 280, 262 (P - H_2O), 220, 218, 189, 184, 147, 130, 127, 103 and 91.

B. Methyl iodide

A solution of 185 mg of thioketal XLIII, 1.0 ml MeI and 5.0 ml of wet acetone was refluxed overnight. The resulting solution was then taken up into benzene, washed with water, the solvent evaporated and the residue purified by t.l.c. with a net yield of cis -

trans isomers of 53% (see table IV for individual yields of cis and trans isomers).

C. $CuCl_2/CF_3CO_2H$

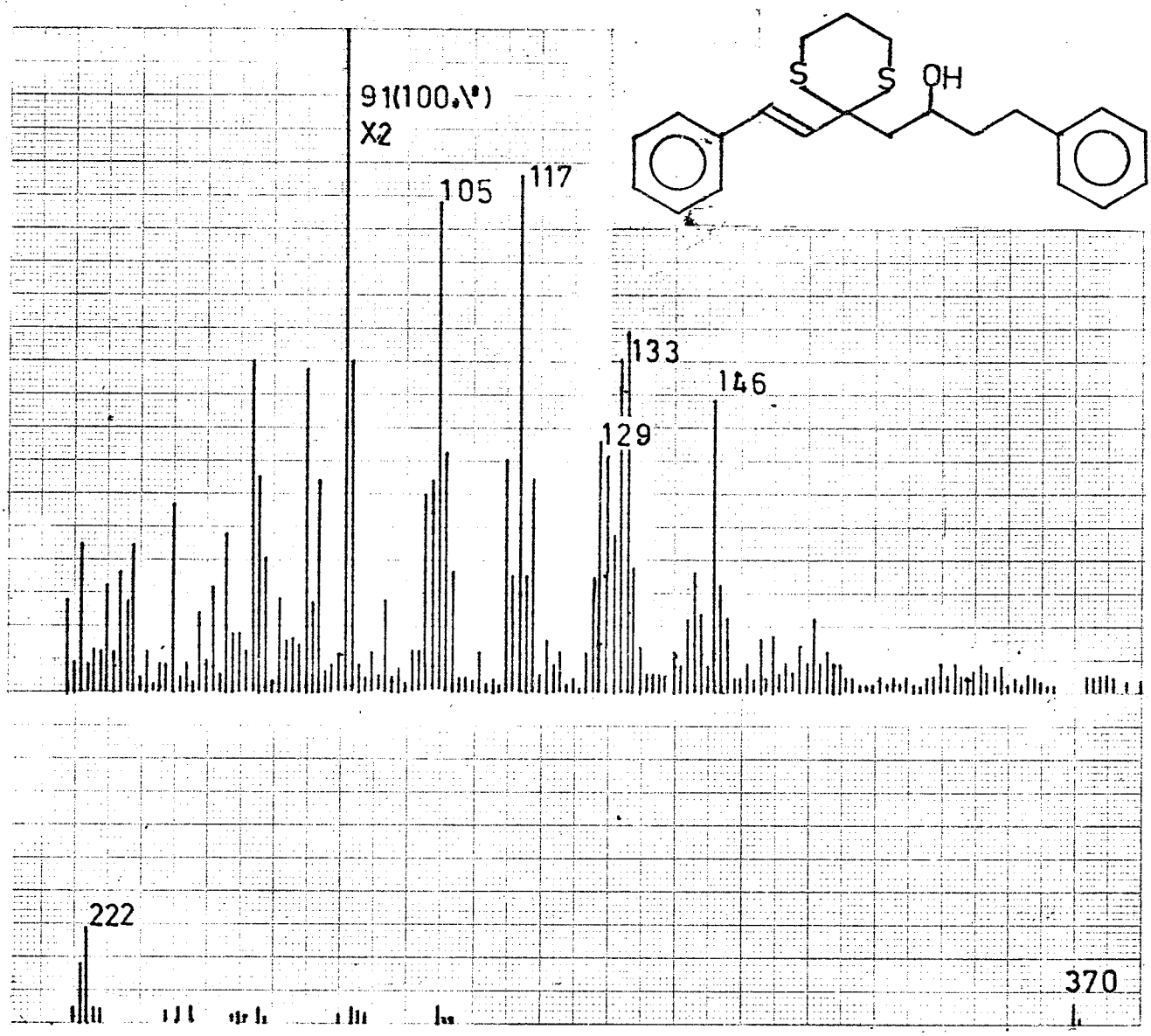
To a solution of 185 mg of thioketal XLIII in 5 ml of $CHCl_3$, 0.1 ml of trifluoroacetic acid and one drop of water, was added 150 mg of $CuCl_2.H_2O$ and the resulting mixture was stirred overnight. The mixture was then washed with silute aqueous bicarbonate, the solvent evaporated and the residue distilled.

D. H_gO/BF_3 etherate

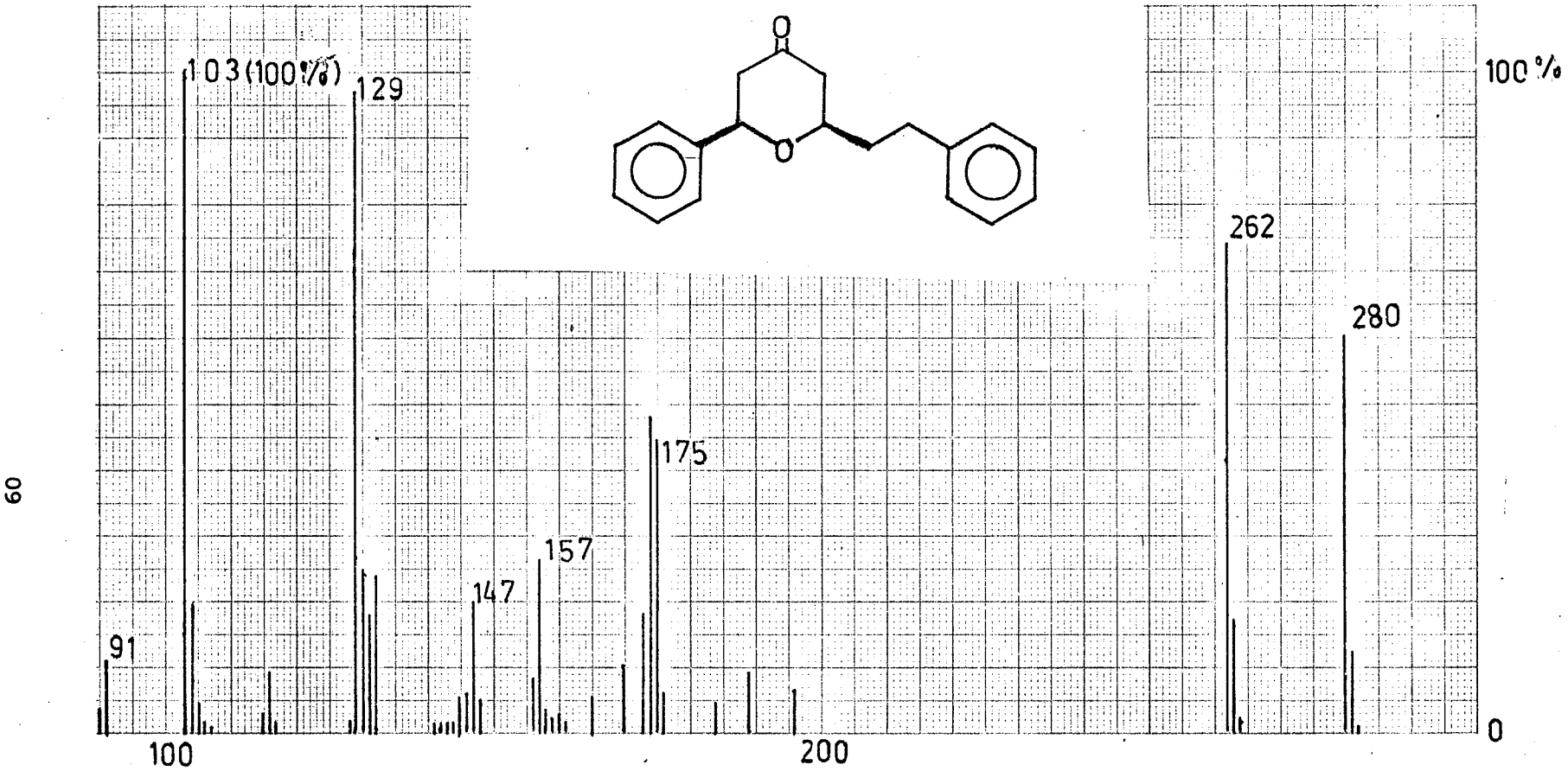
185 mg of thioketal XLIII, 275 mg HgO(1 mmole), 0.15 ml of BF_3 etherate (1 mmole) and 5 ml thf were stirred overnight, then taken up in $CHCl_3$ and washed with bicarbonate. The solvent was evaporated and the residue purified by t.l.c.

E. $HgCl_2$/bicarbonate

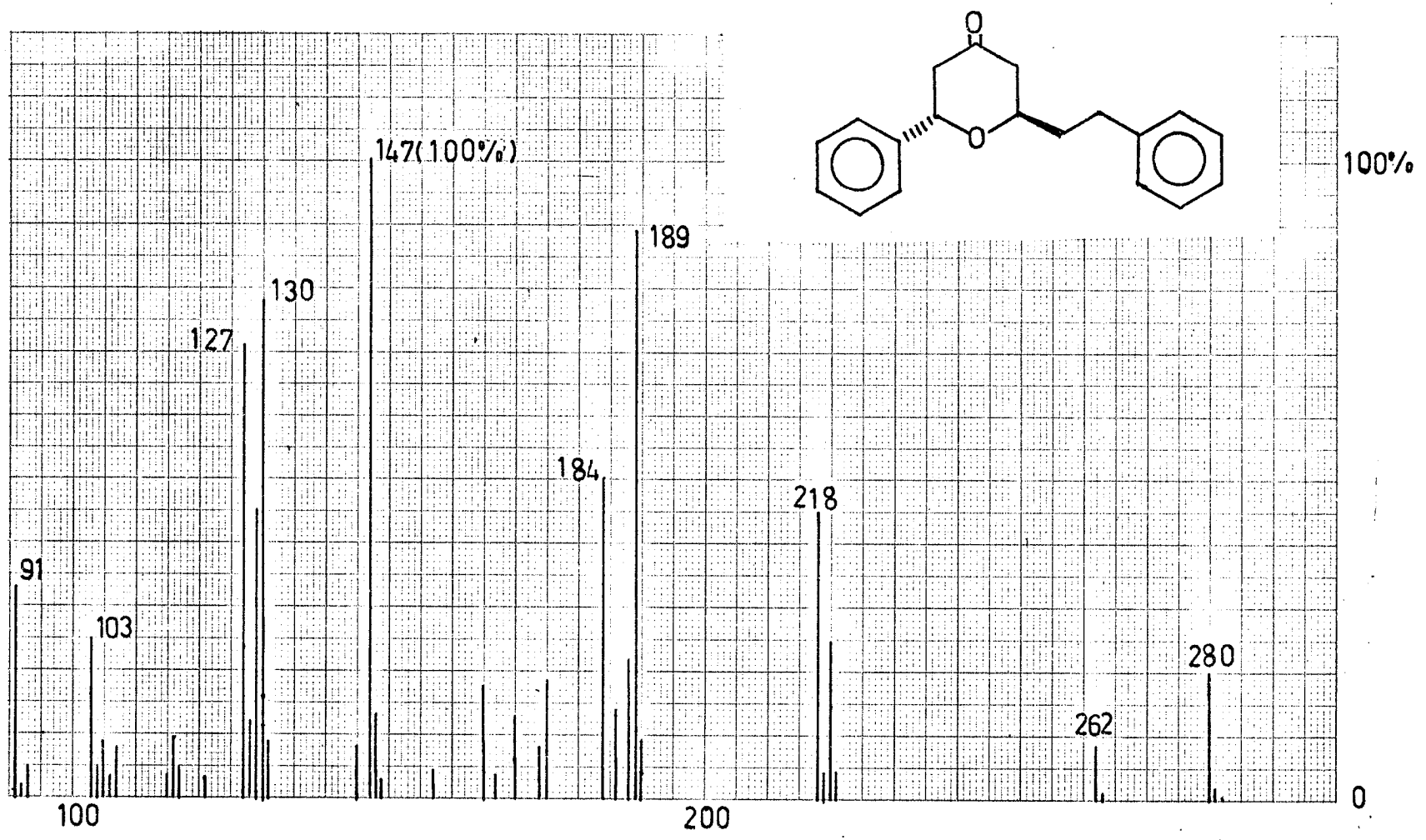
185 mg of thioketal XLIII was stirred overnight with 310 mg $HgCl_2$(1 mmole) and 200 mg of sodium bicarbonate in 5 ml of thf. The mixture was taken up into benzene and washed with aqueous sodium bicarbonate. The solvent was then evaporated and the residue purified by t.l.c.



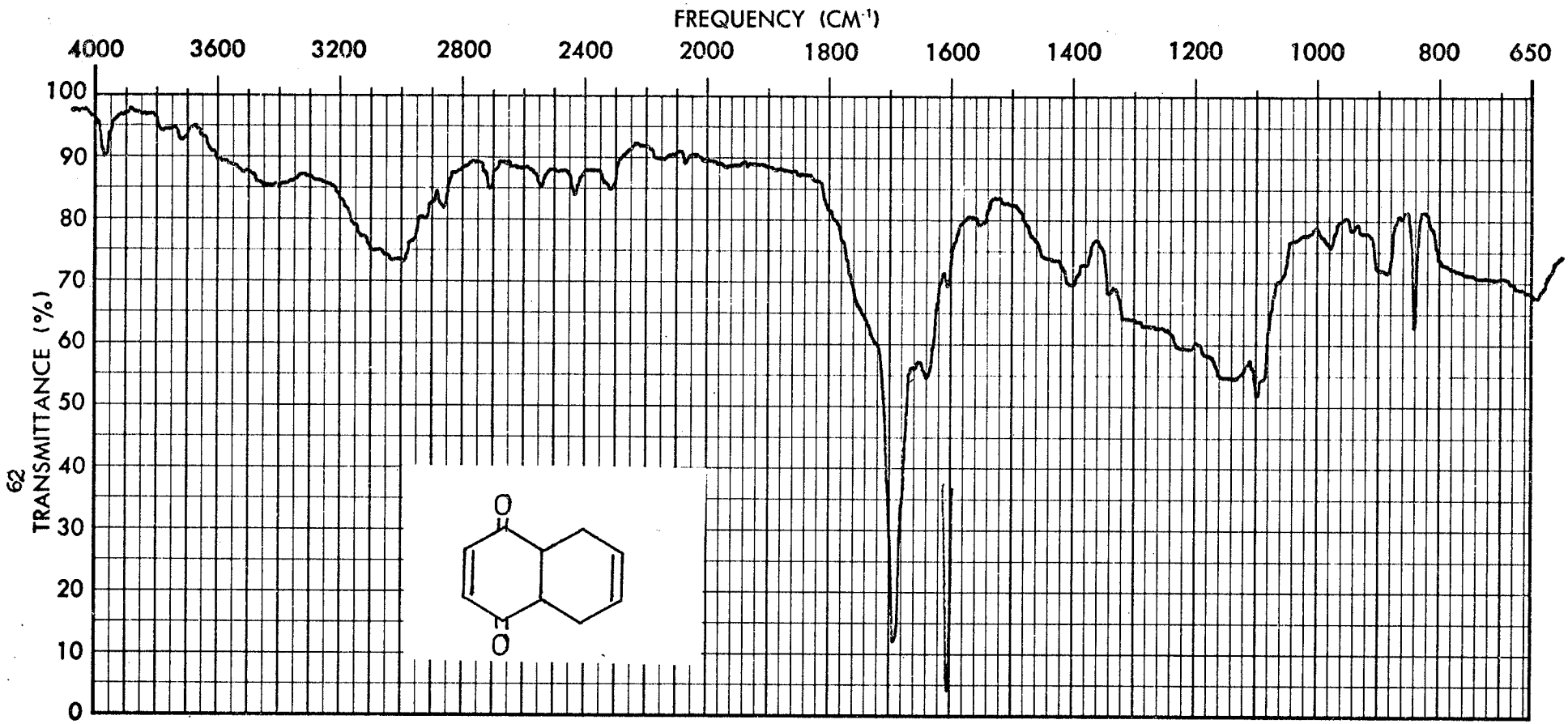
MS-I Racemic yashabushiketonethioketal XLIII: 100°C



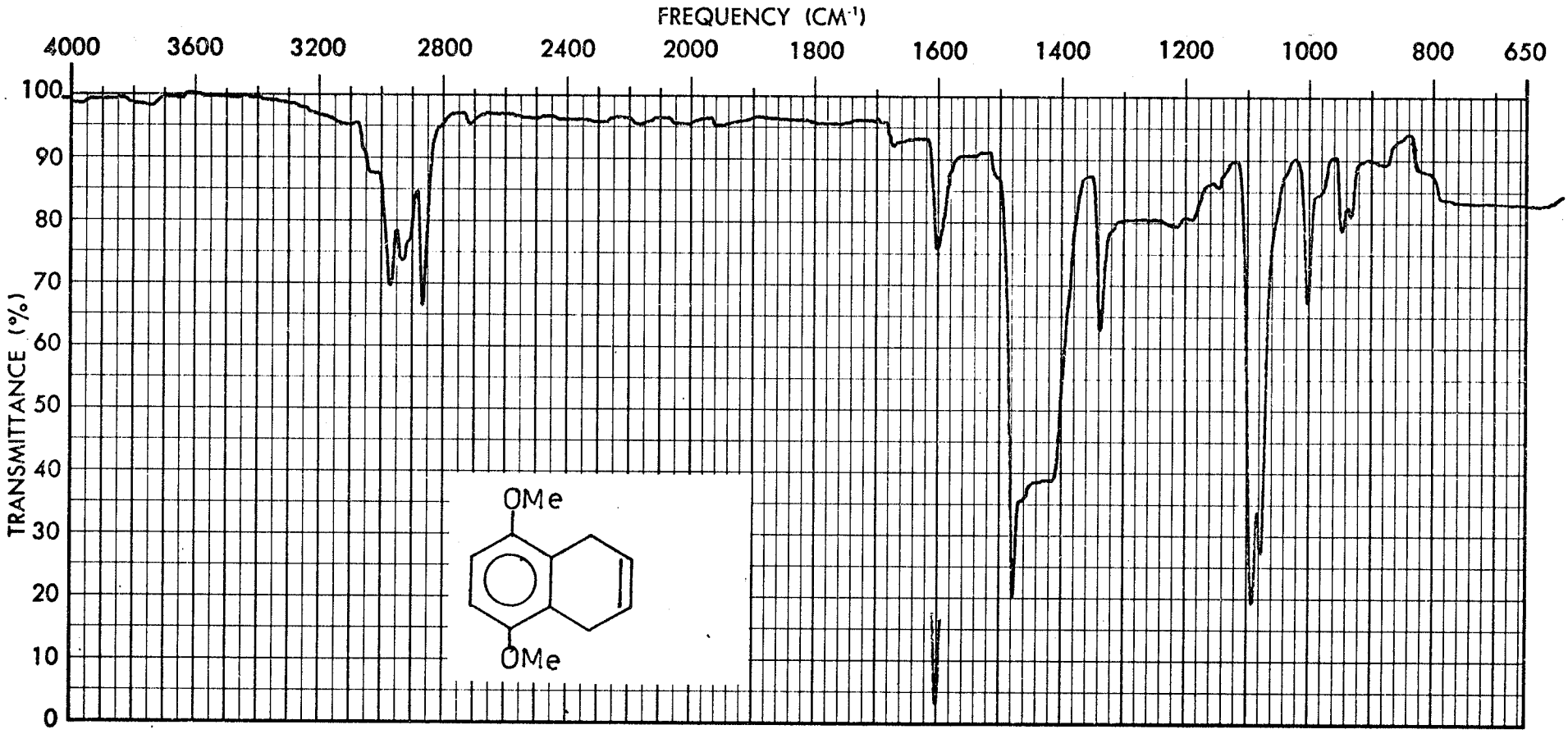
MS-II cis-2-phenyl-6-phenylethyltetrahydro-4-pyranone XLVIIc: 80°C



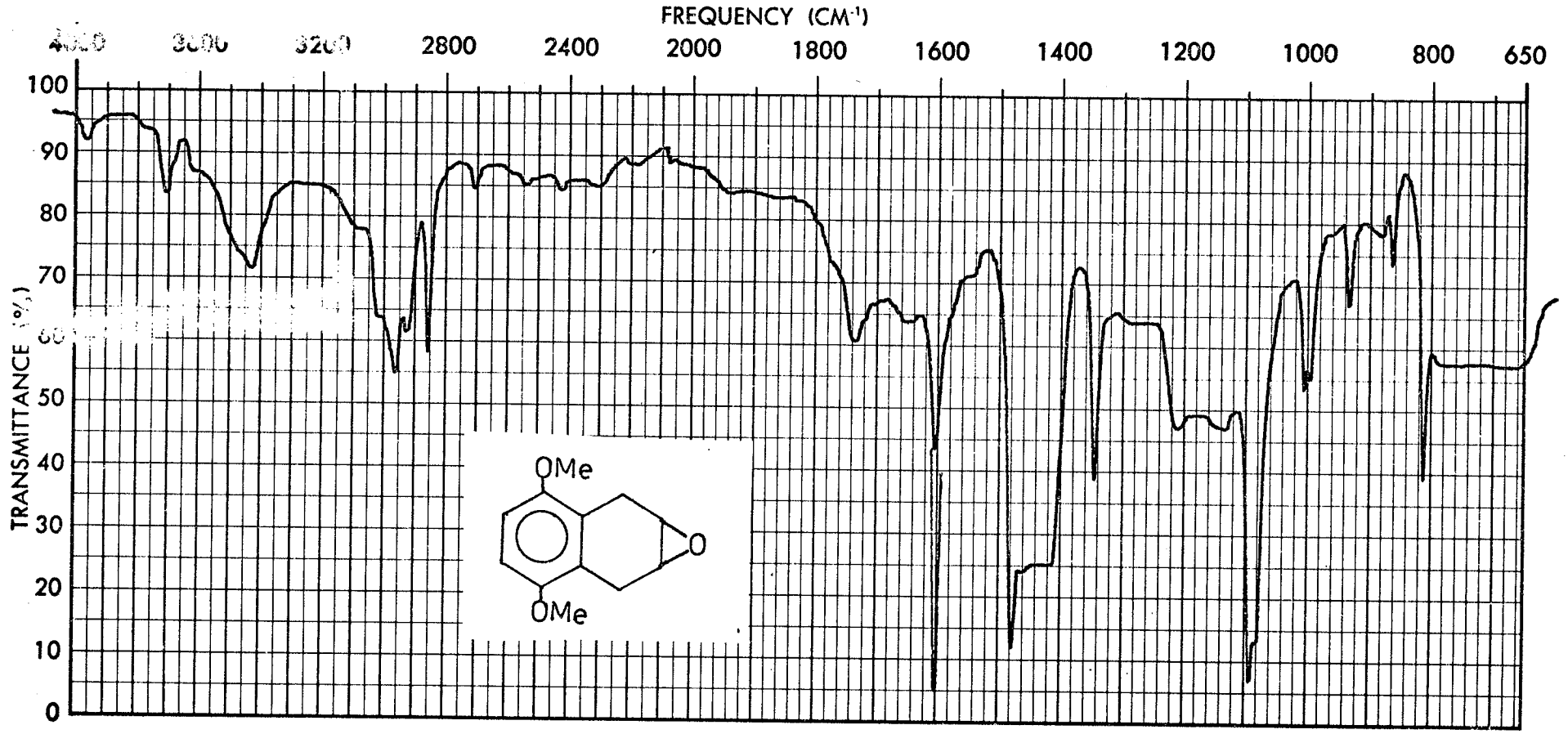
MS-III Trans-2-phenyl-6-phenylethyltetrahydro-4-pyranone XLVIIt: 80°C



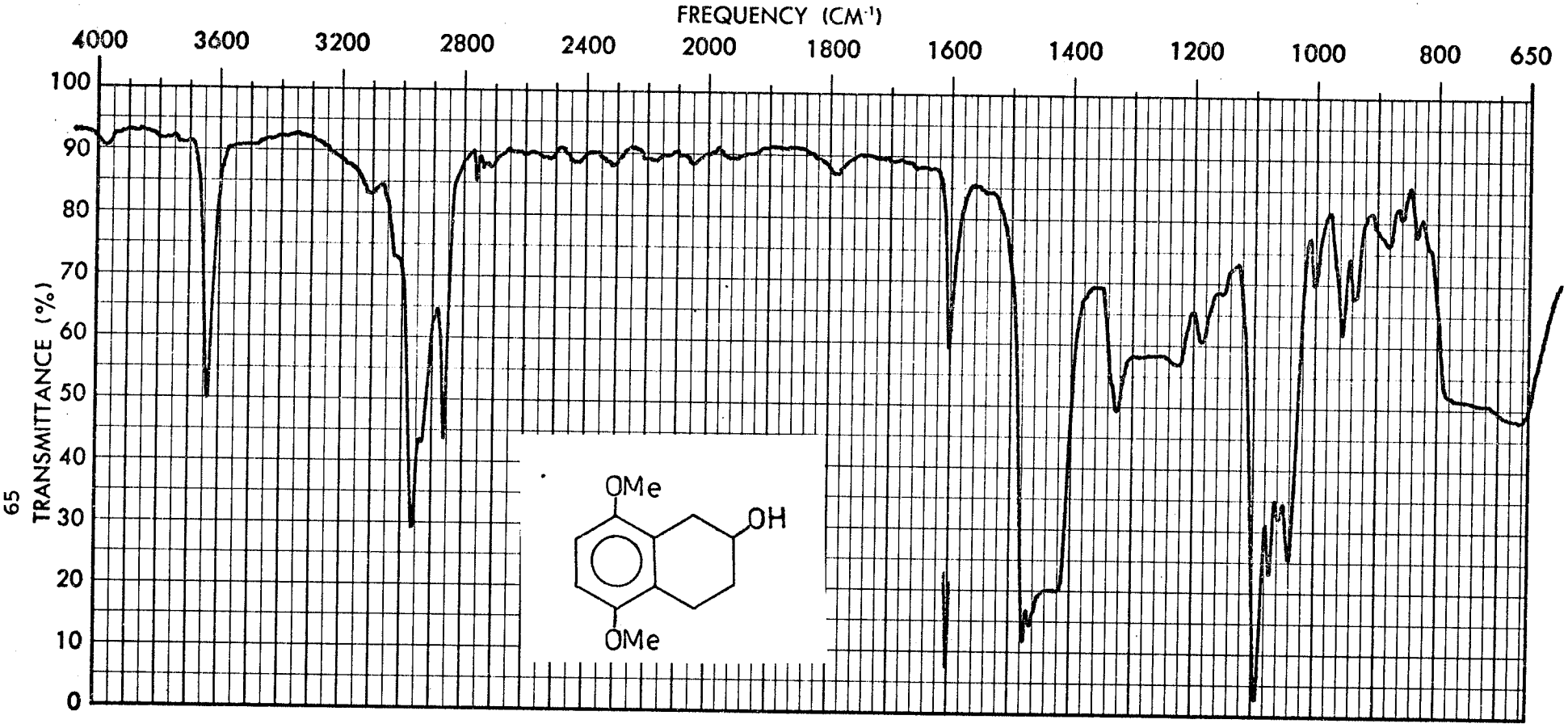
IR-I 4a,5,8,8a-tetrahydro-1,4-naphthoquinone V: CH_2Cl_2



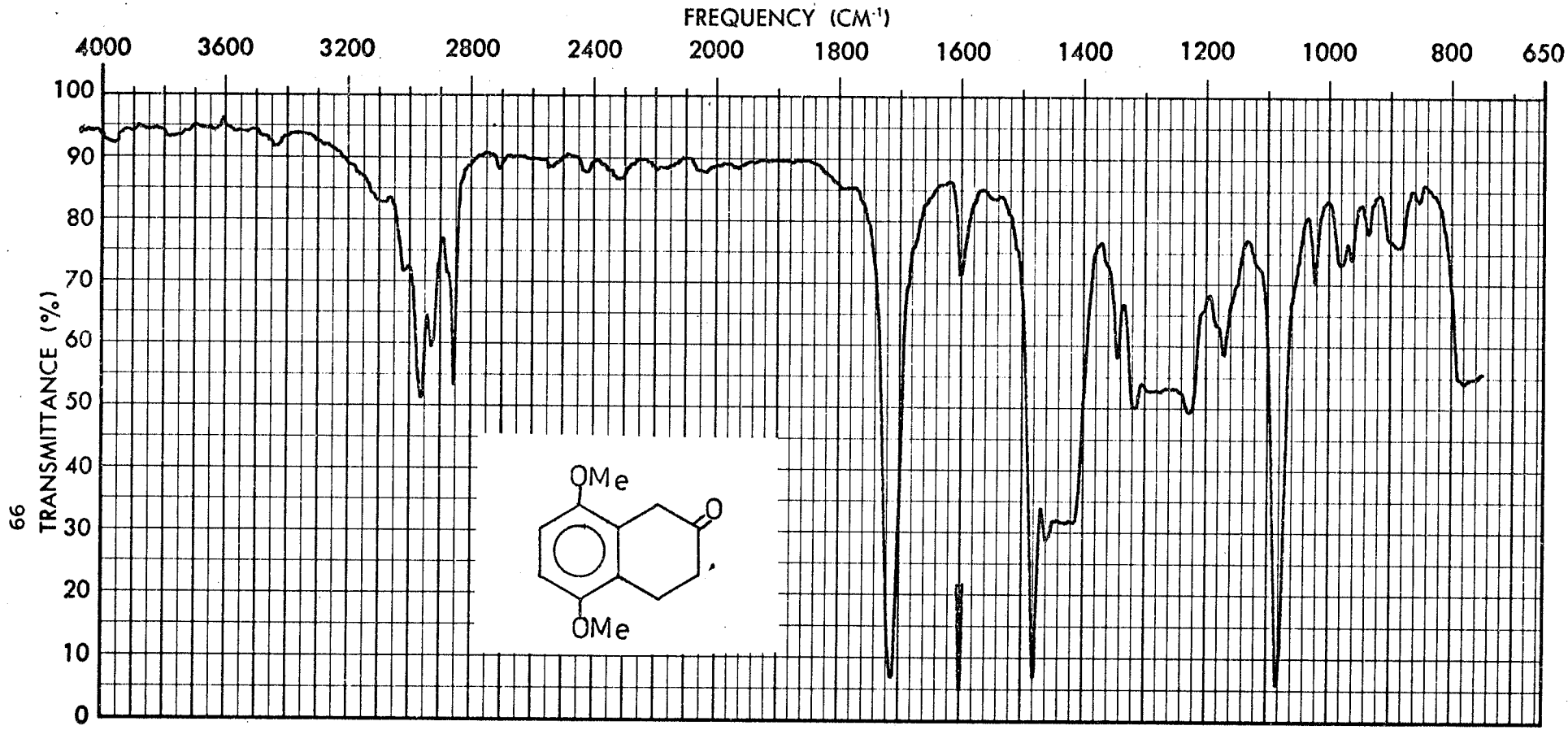
IR-II 5,8-dimethoxy-1,4-dihydronaphthalene VI: CH_2Cl_2



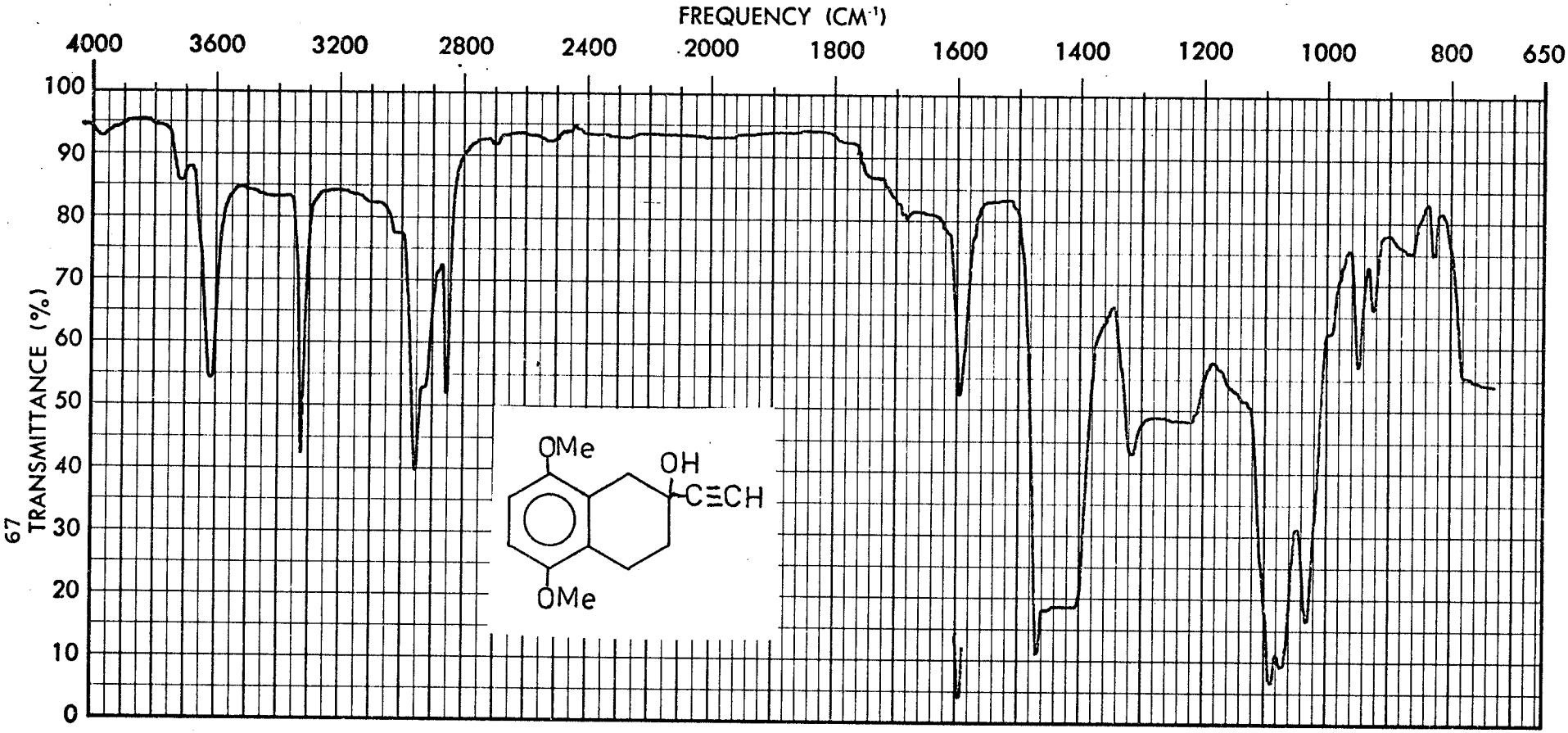
IR-III 2,3-epoxy-5,8-dimethoxytetralin VII: CH_2Cl_2



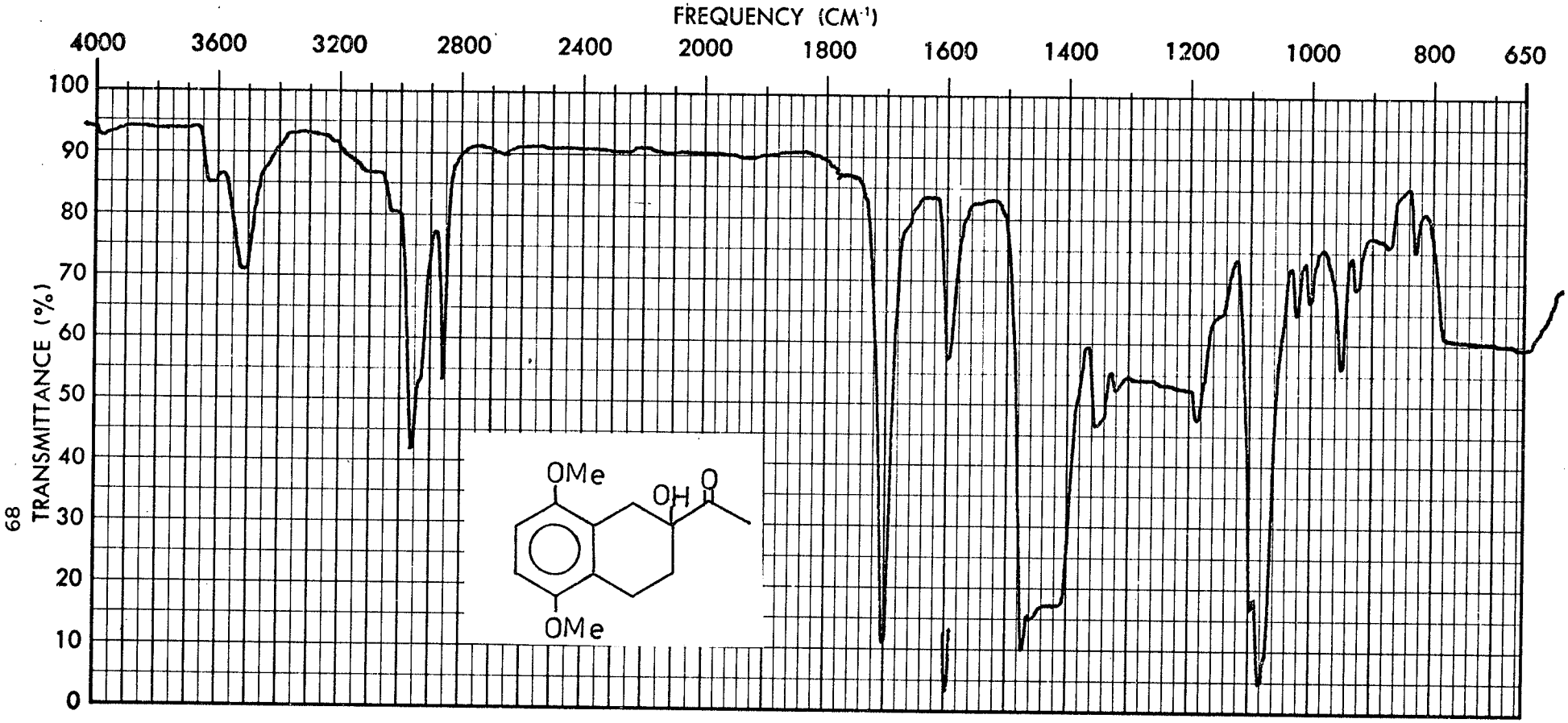
IR-IV 2-hydroxy-5,8-dimethoxytetralin VIII: CH_2Cl_2



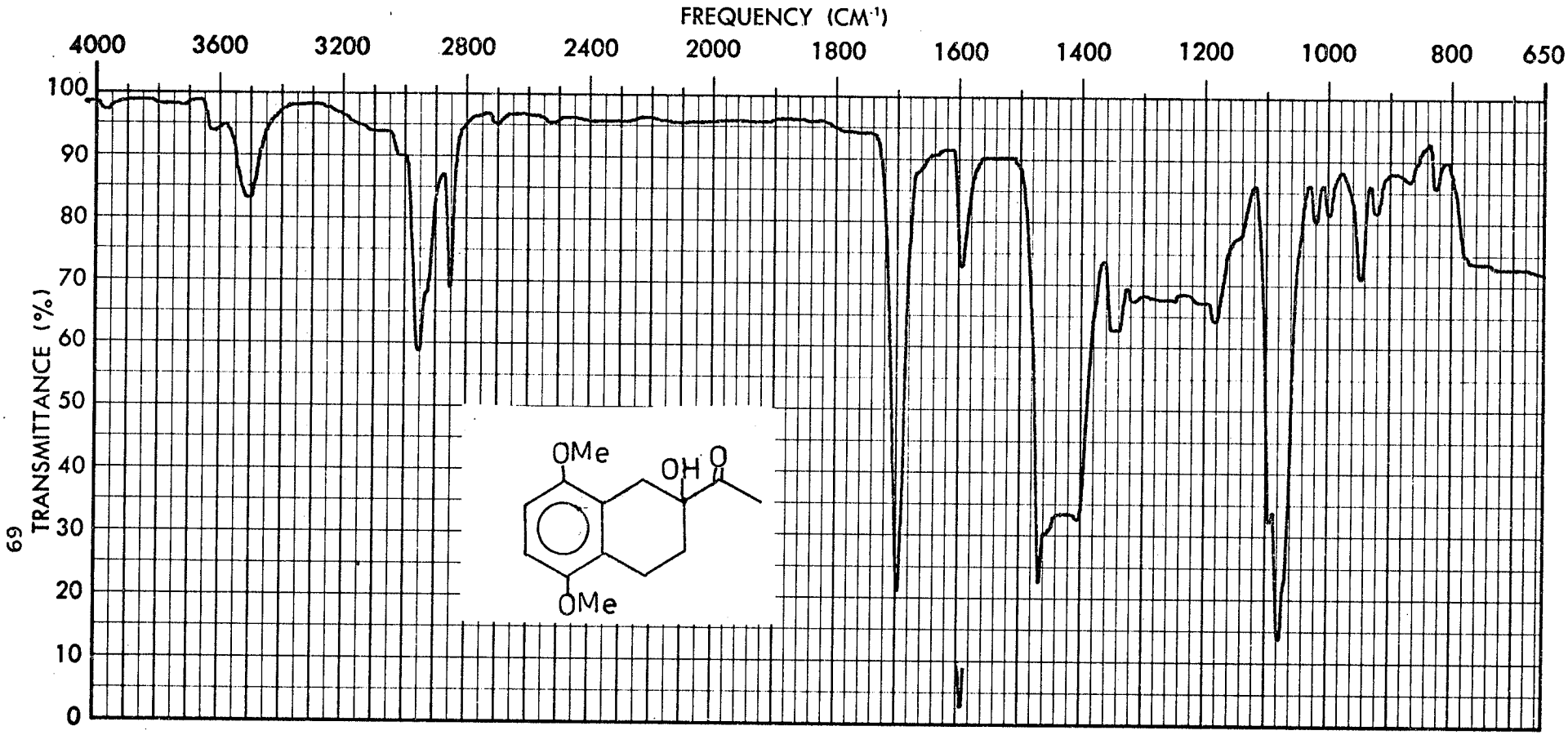
IR-V 5,8-dimethoxy-2-tetralone IX: CH_2Cl_2



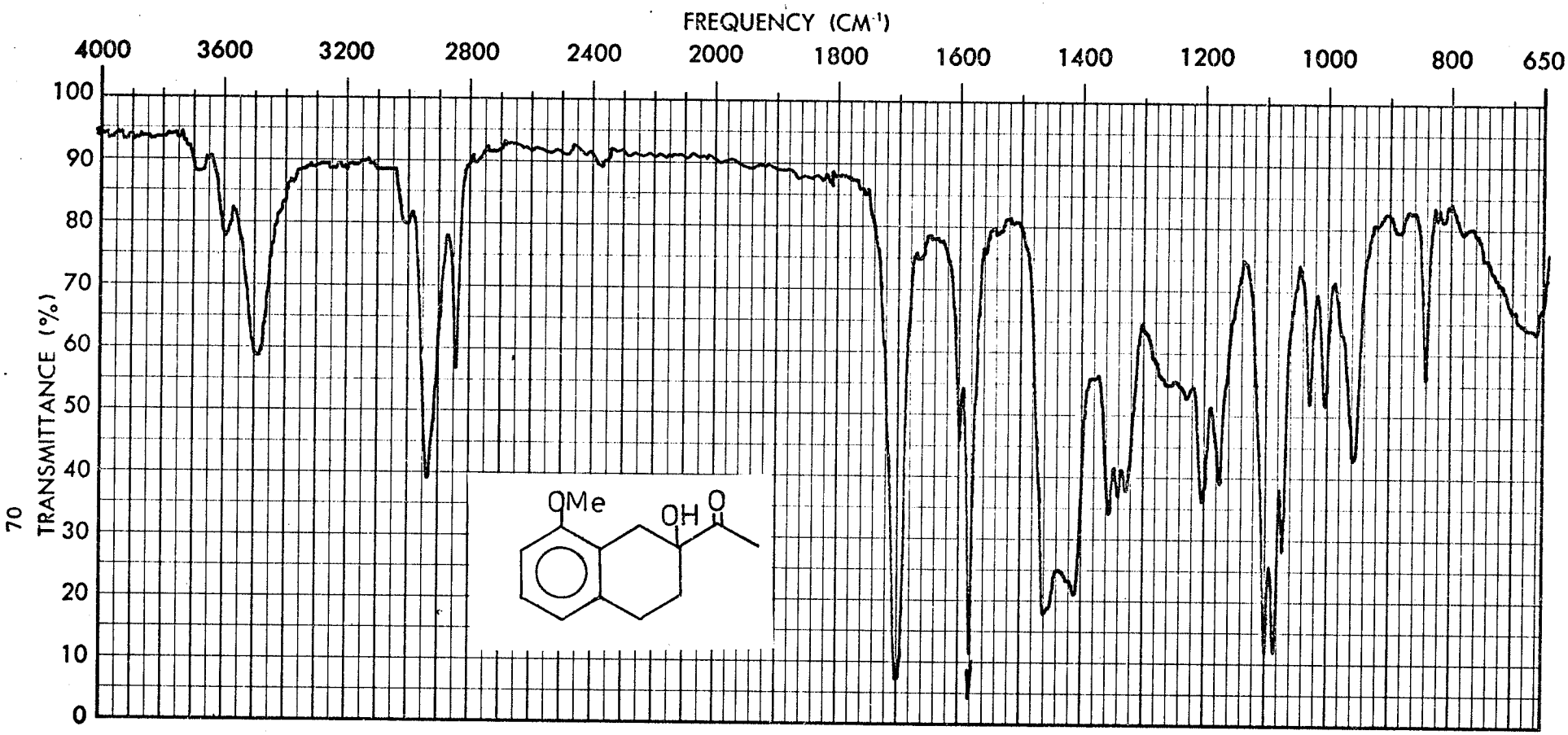
IR-VI 2-hydroxy-2-ethynyl-5,8-dimethoxytetralin X: CH_2Cl_2



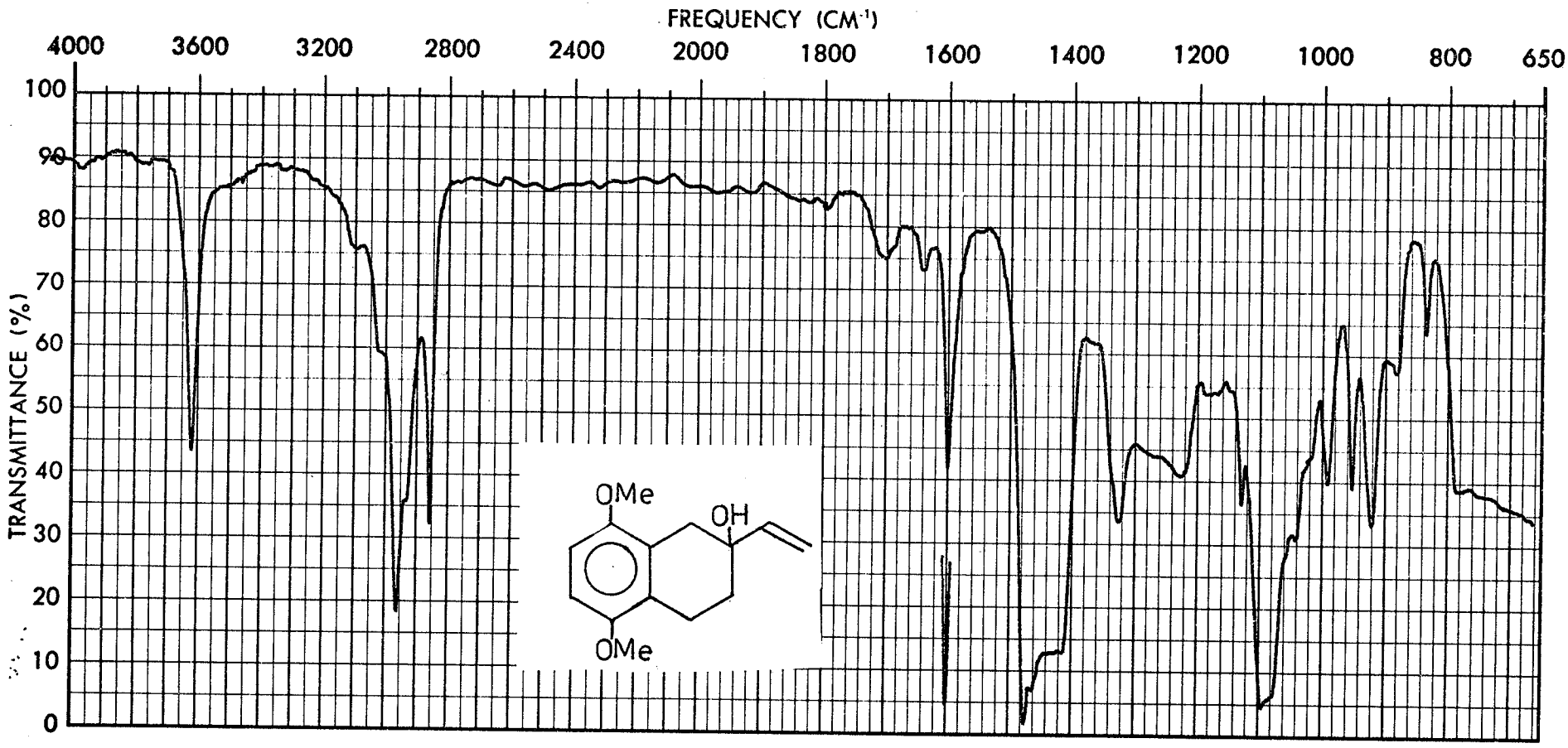
IR-VII 2-hydroxy-2-acetyl-5,8-dimethoxytetralin XIII: CH_2Cl_2



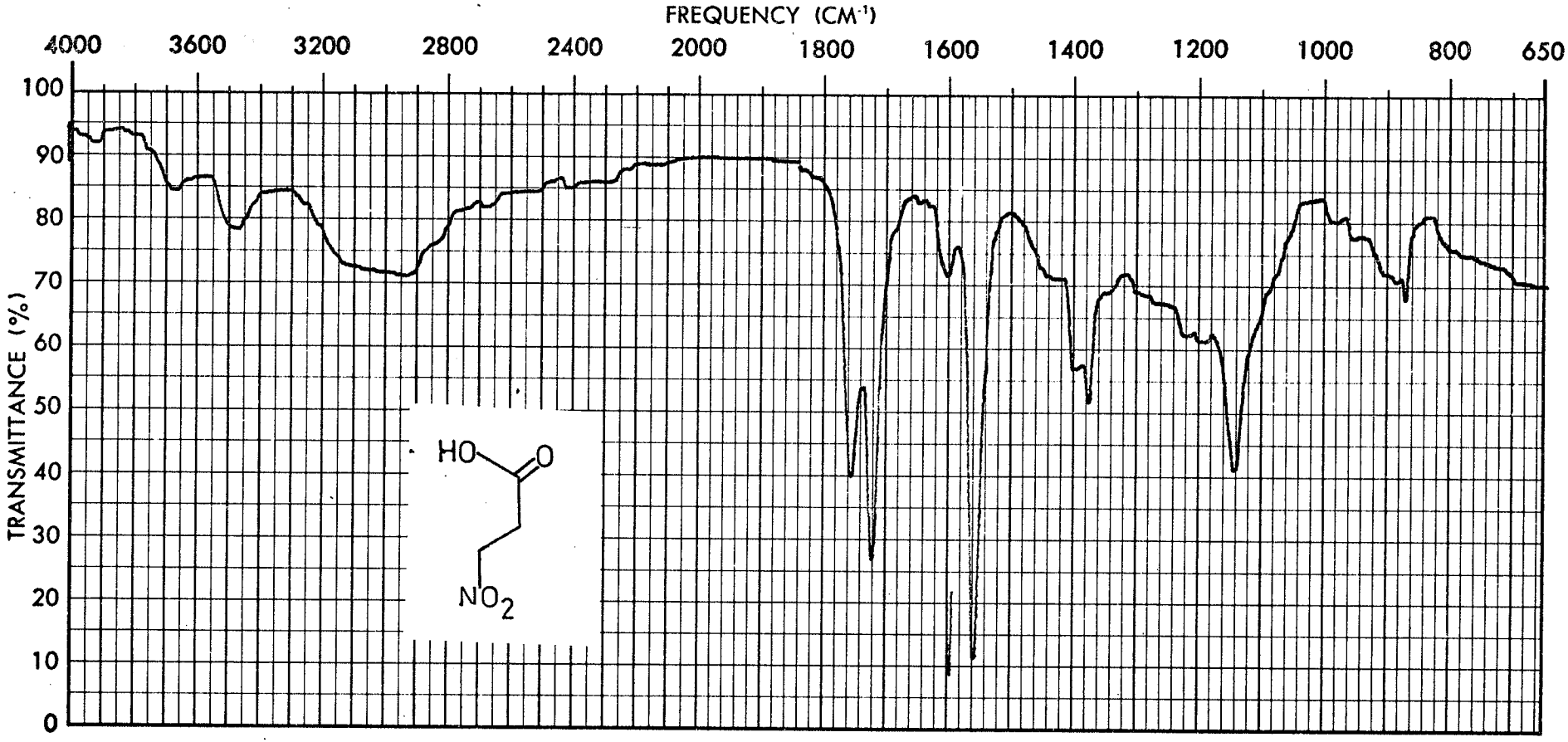
IR-VIIA 2-hydroxy-2-acetyl-5,8-dimethoxytetralin XIII authentic sample: CH_2Cl_2



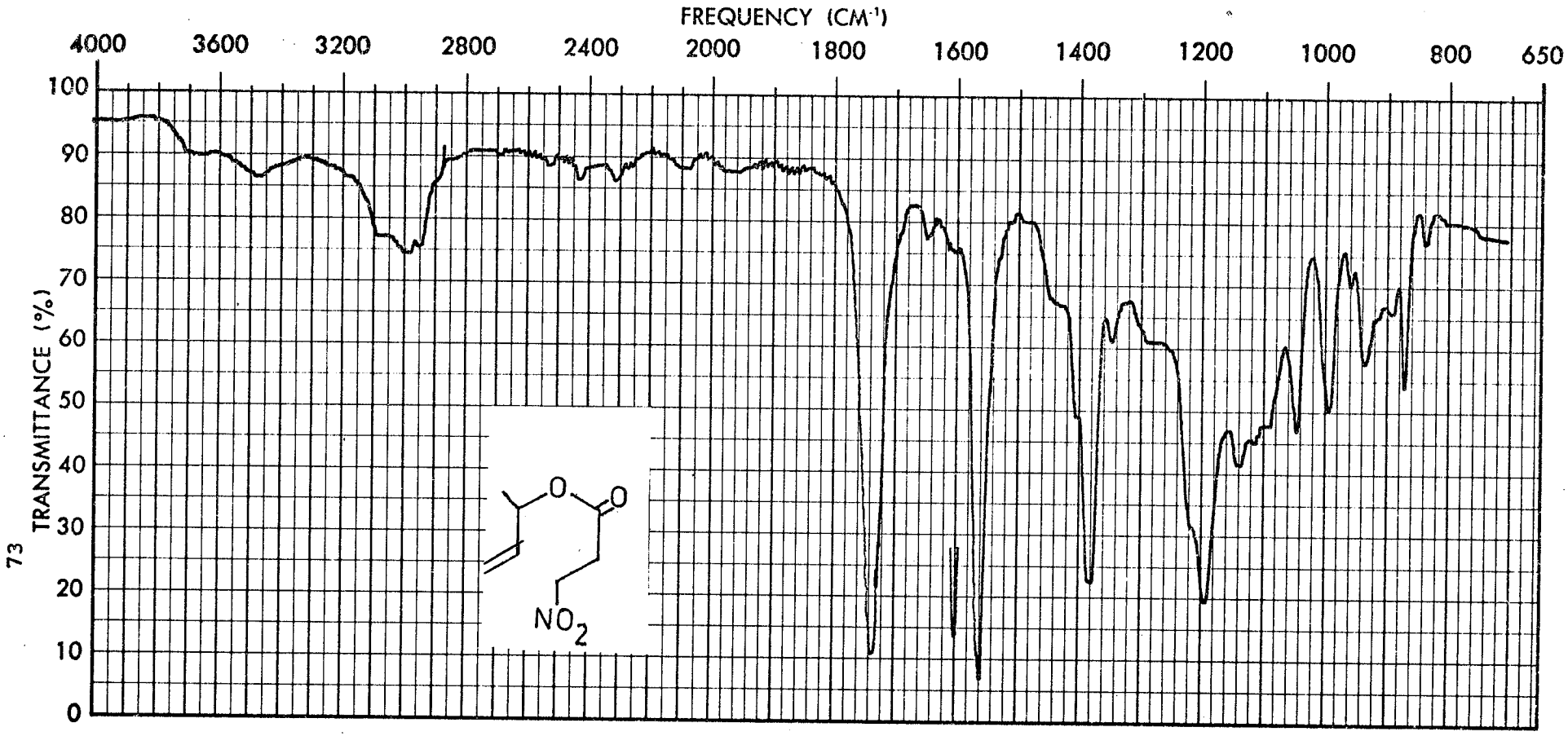
IR-VIII 2-hydroxy-2-acetyl-8-methoxytetralin XVI: CH_2Cl_2



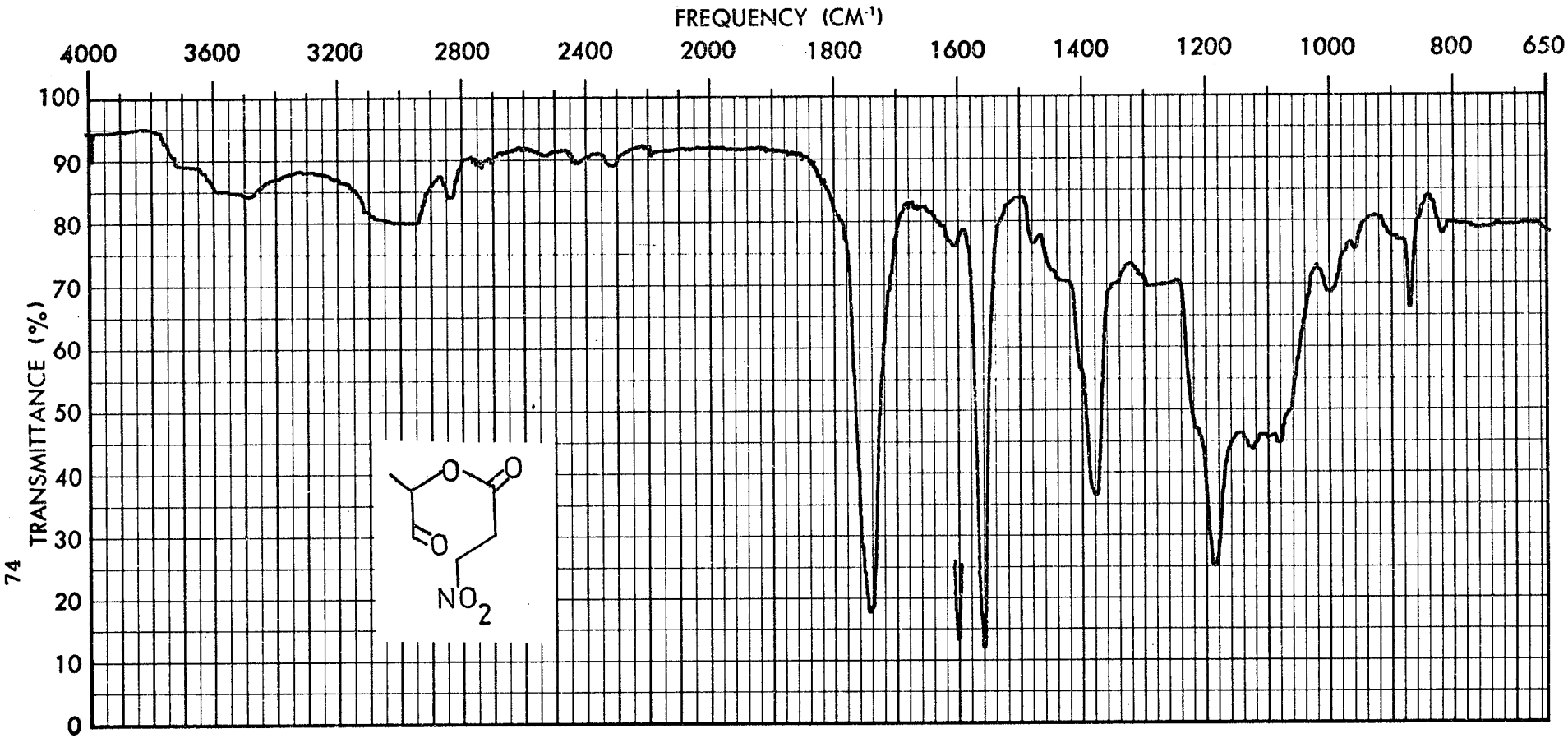
IR-IX 2-hydroxy-2-vinyl-5,8-dimethoxytetralin XVII: Neat



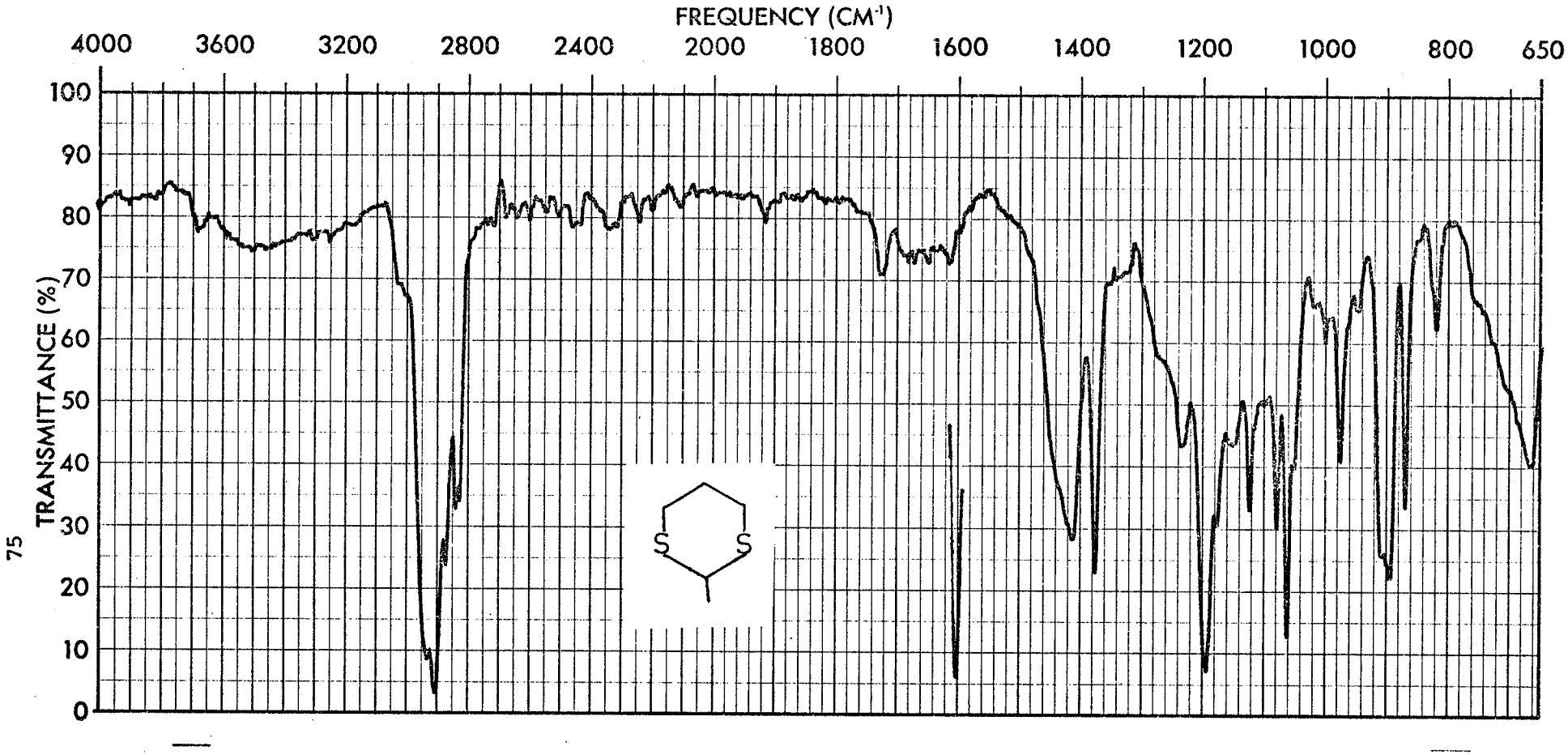
IR-X 3-nitropropionic acid XXVII: CH_2Cl_2



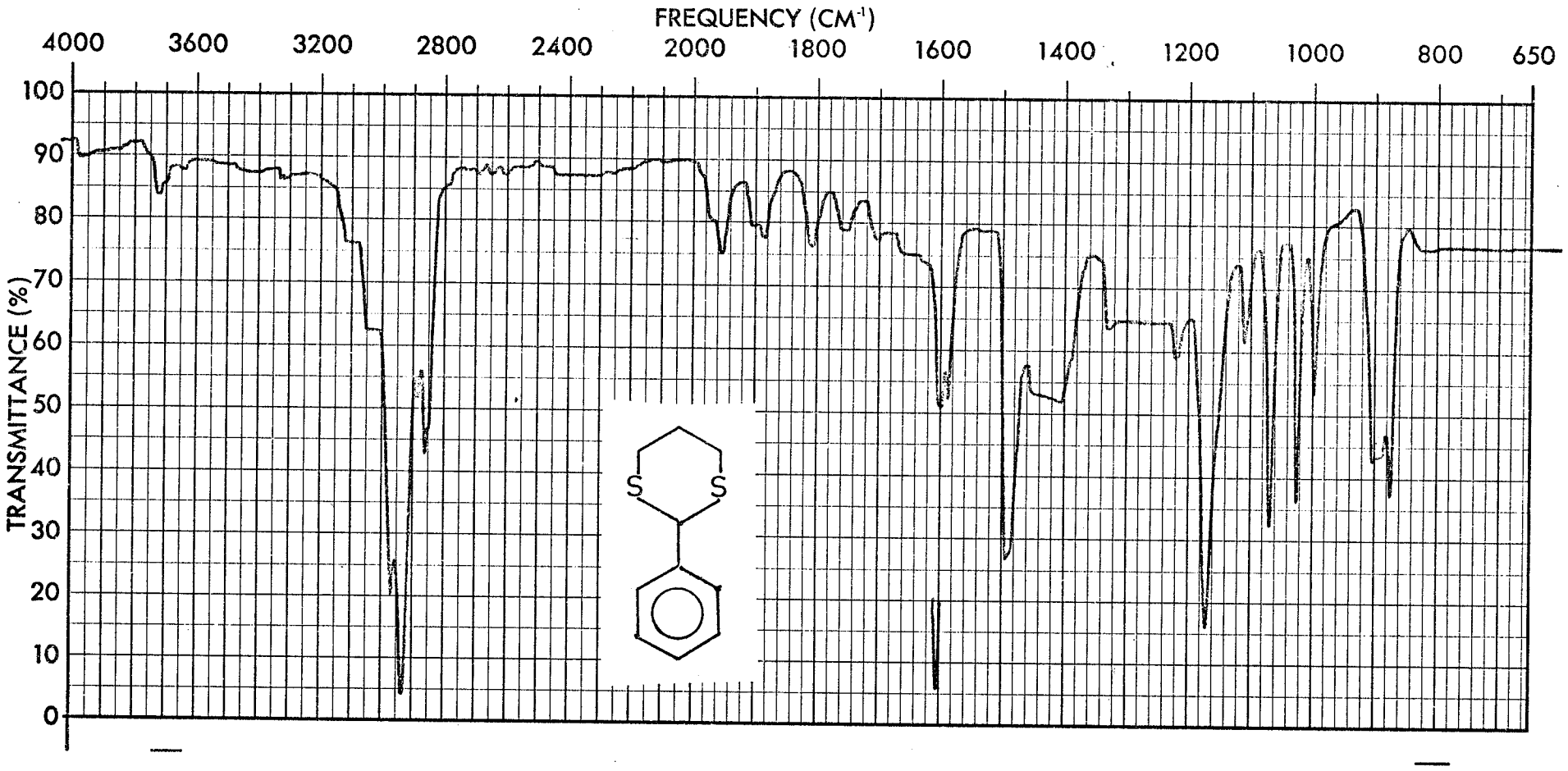
IR-XI sec-butenyl 3-nitropropionate XXIX: CH_2Cl_2



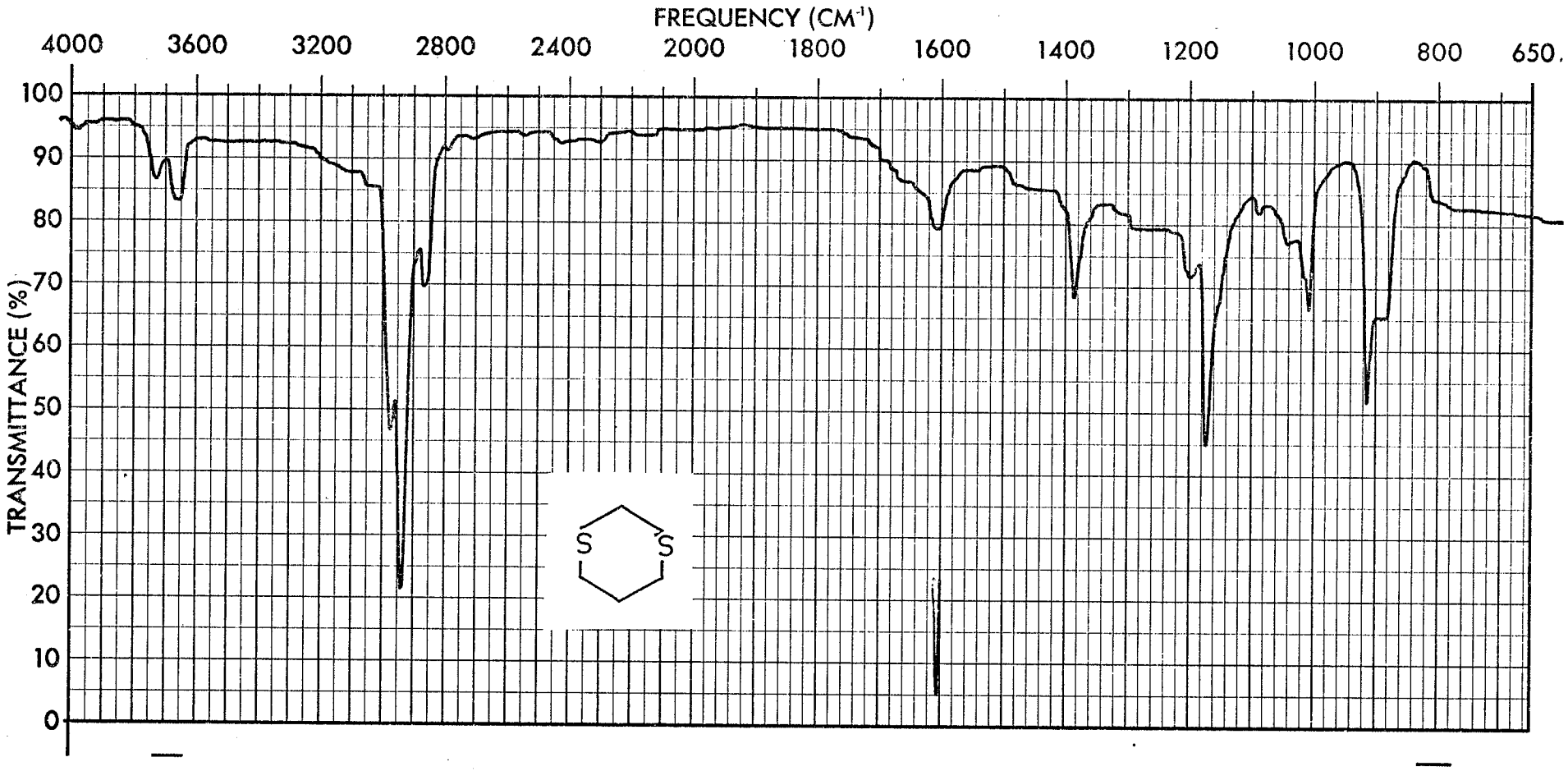
IR-XII 1'-formylethyl 3-nitropropionate XXX: CH_2Cl_2



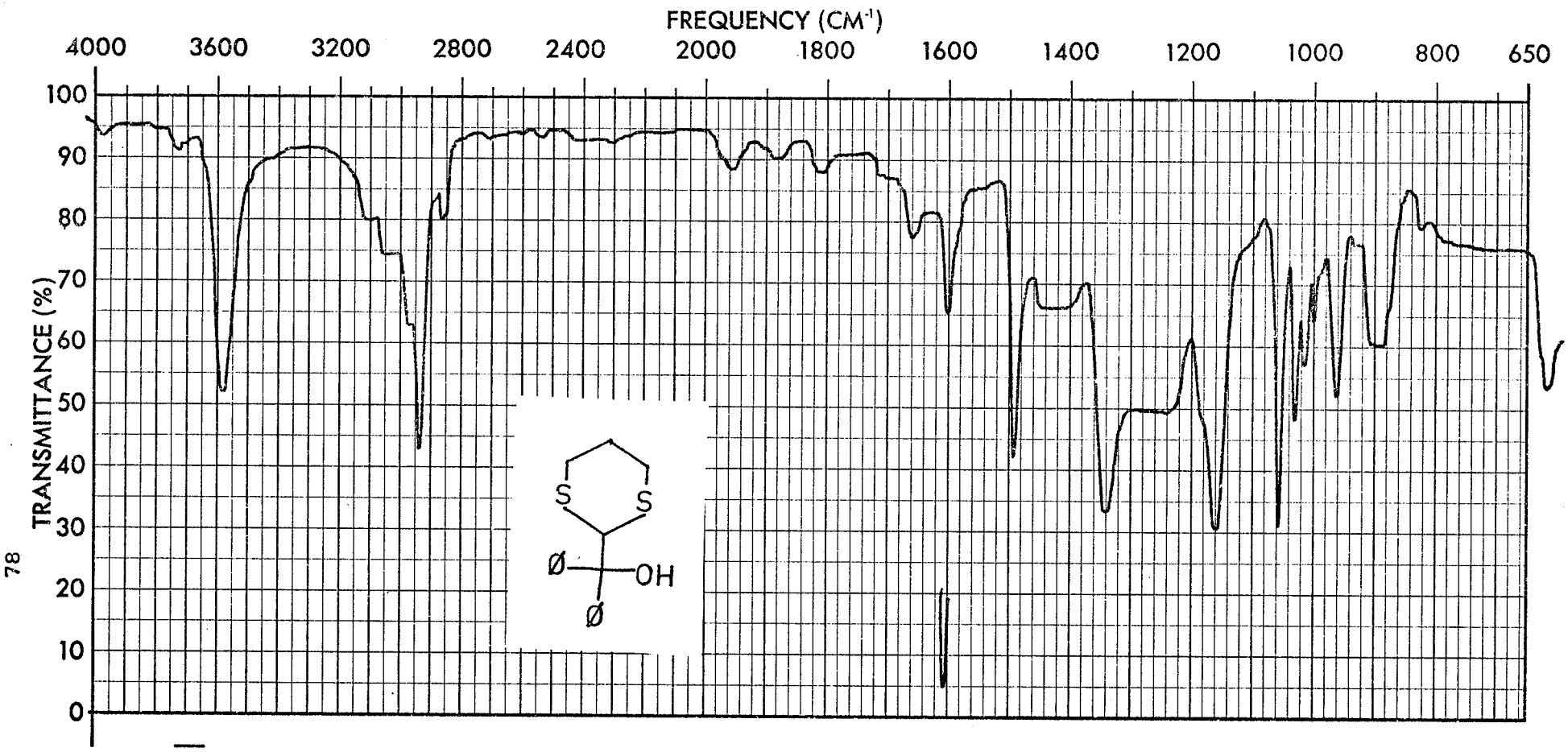
IR-XIII acetaldehydethioacetal: CH_2Cl_2



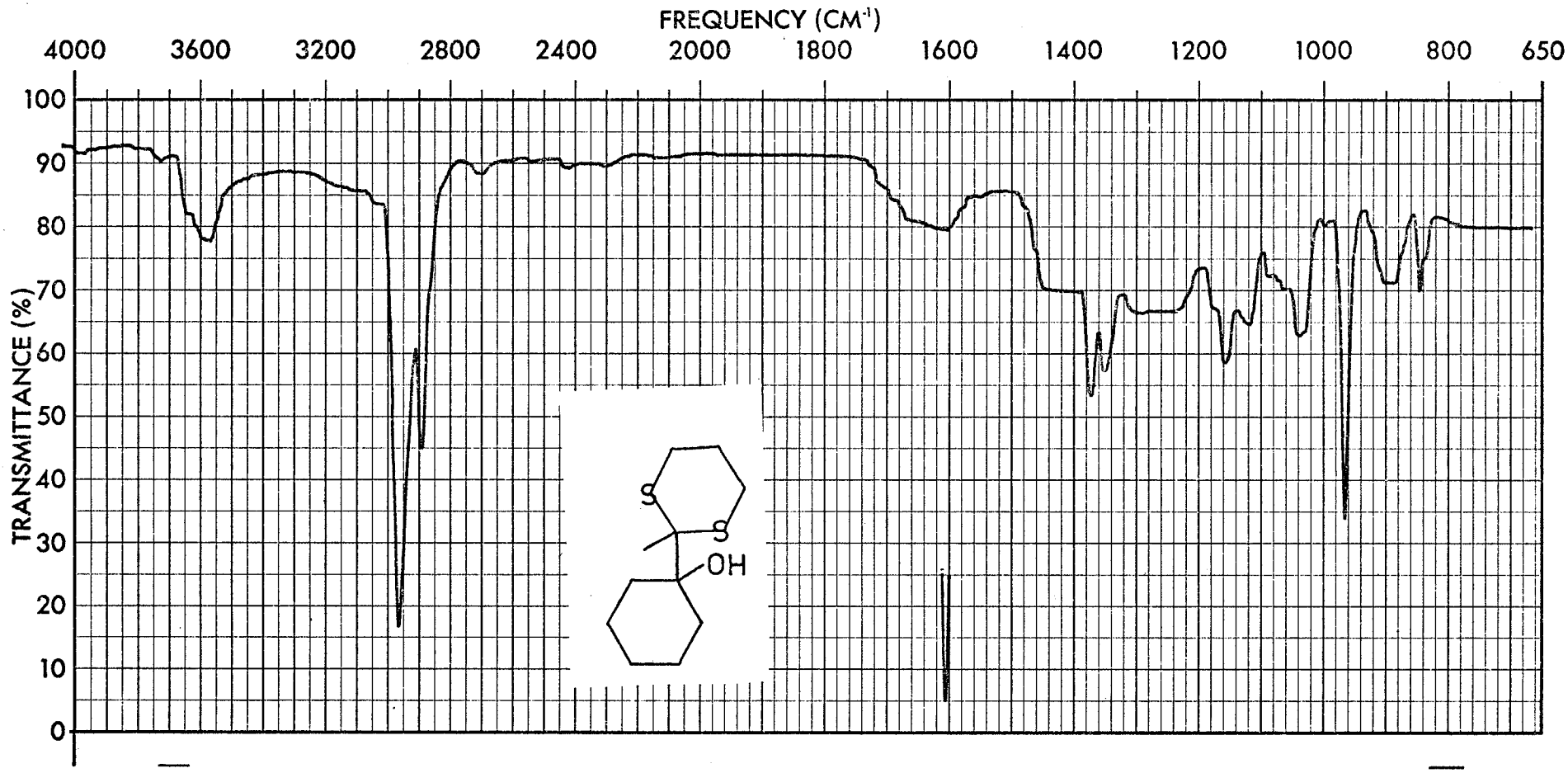
IR-XIV benzaldehydethioacetal: CH_2Cl_2



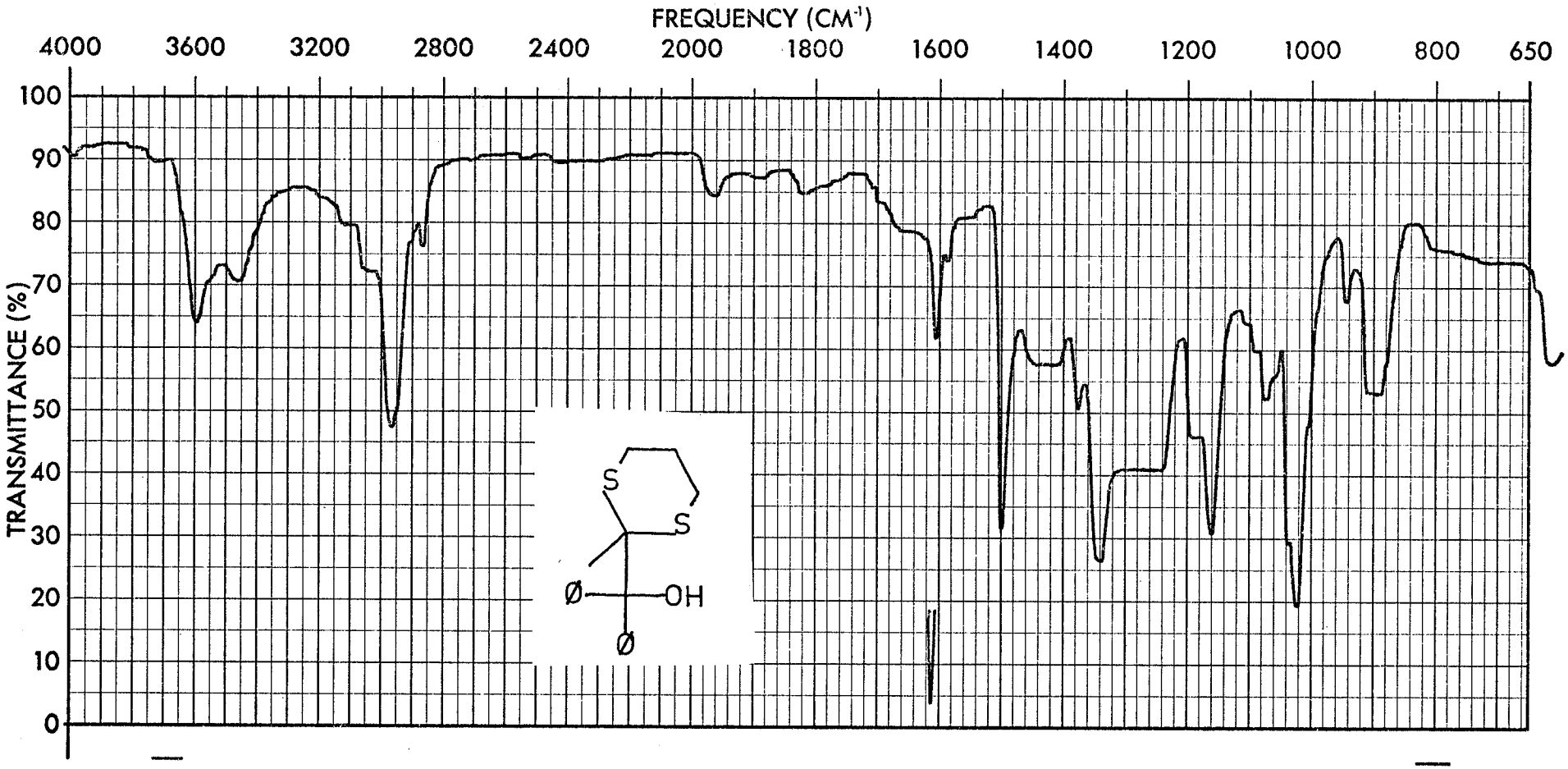
IR-XV 1,3-dithiane: CH_2Cl_2



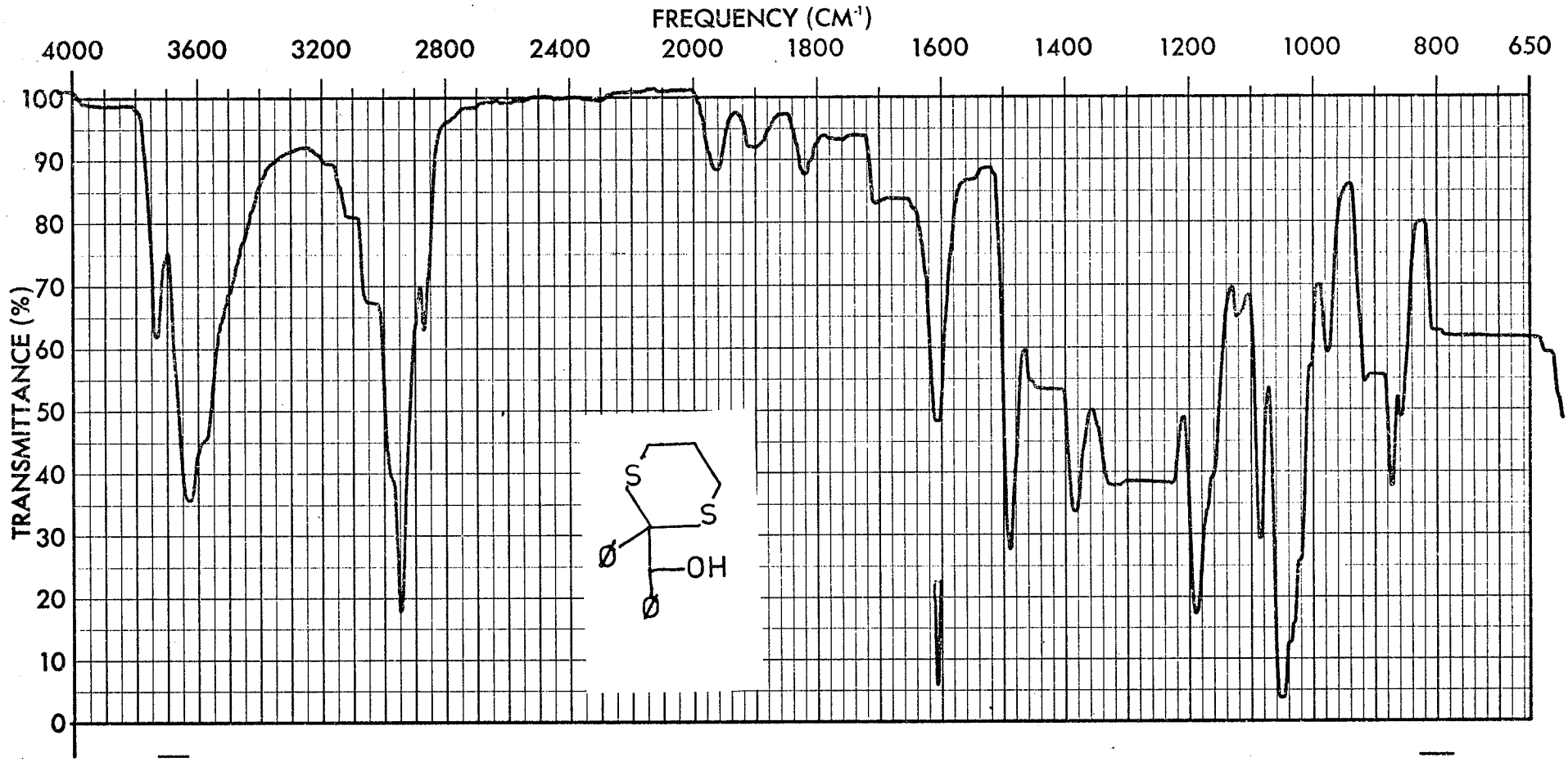
IR-XVI 2-hydroxy-2,2-diphenylacetaldehydethioacetal XXXIVa: CH_2Cl_2



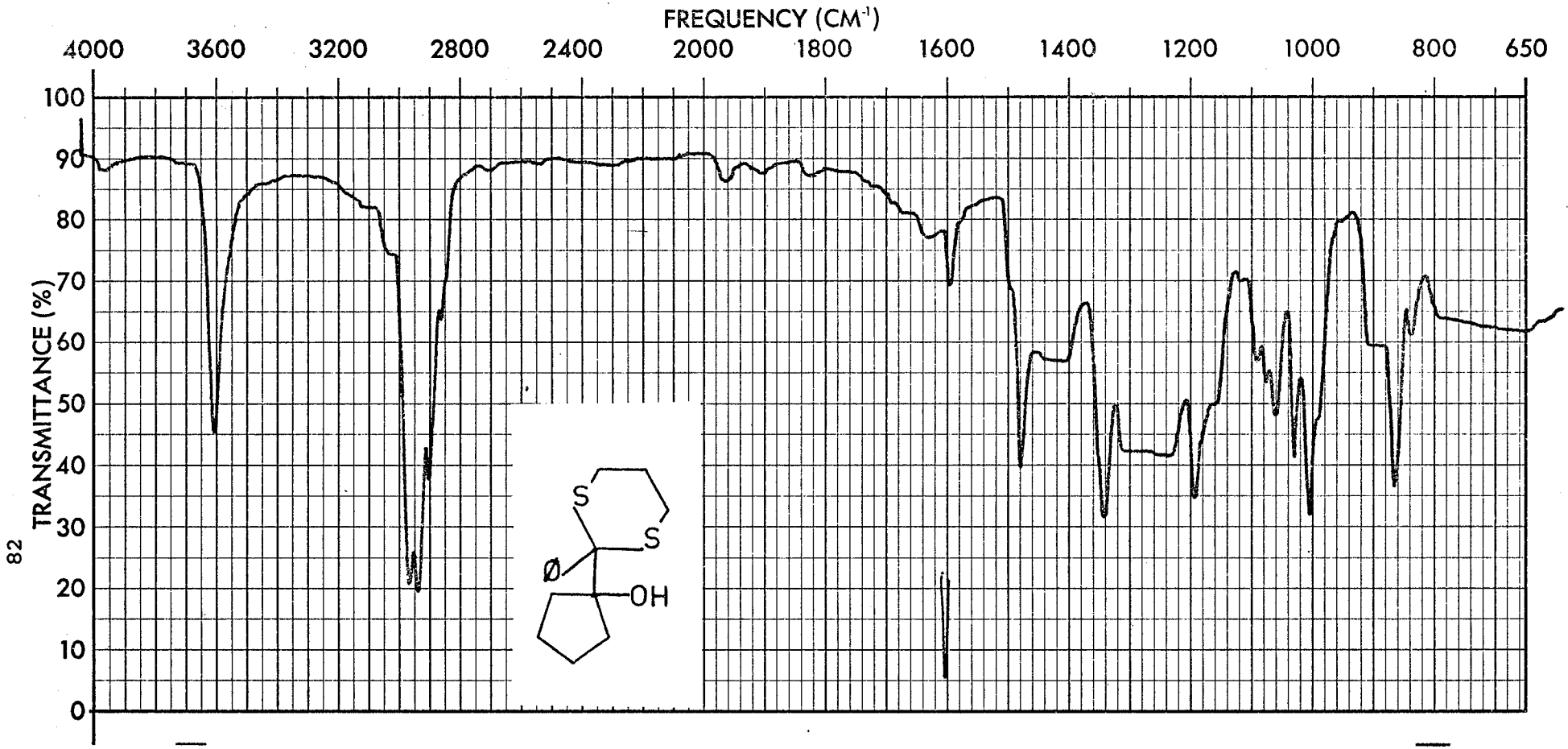
IR-XVII methyl-1'-hydroxycyclohexylketonethioketal XXXIVb: CH_2Cl_2



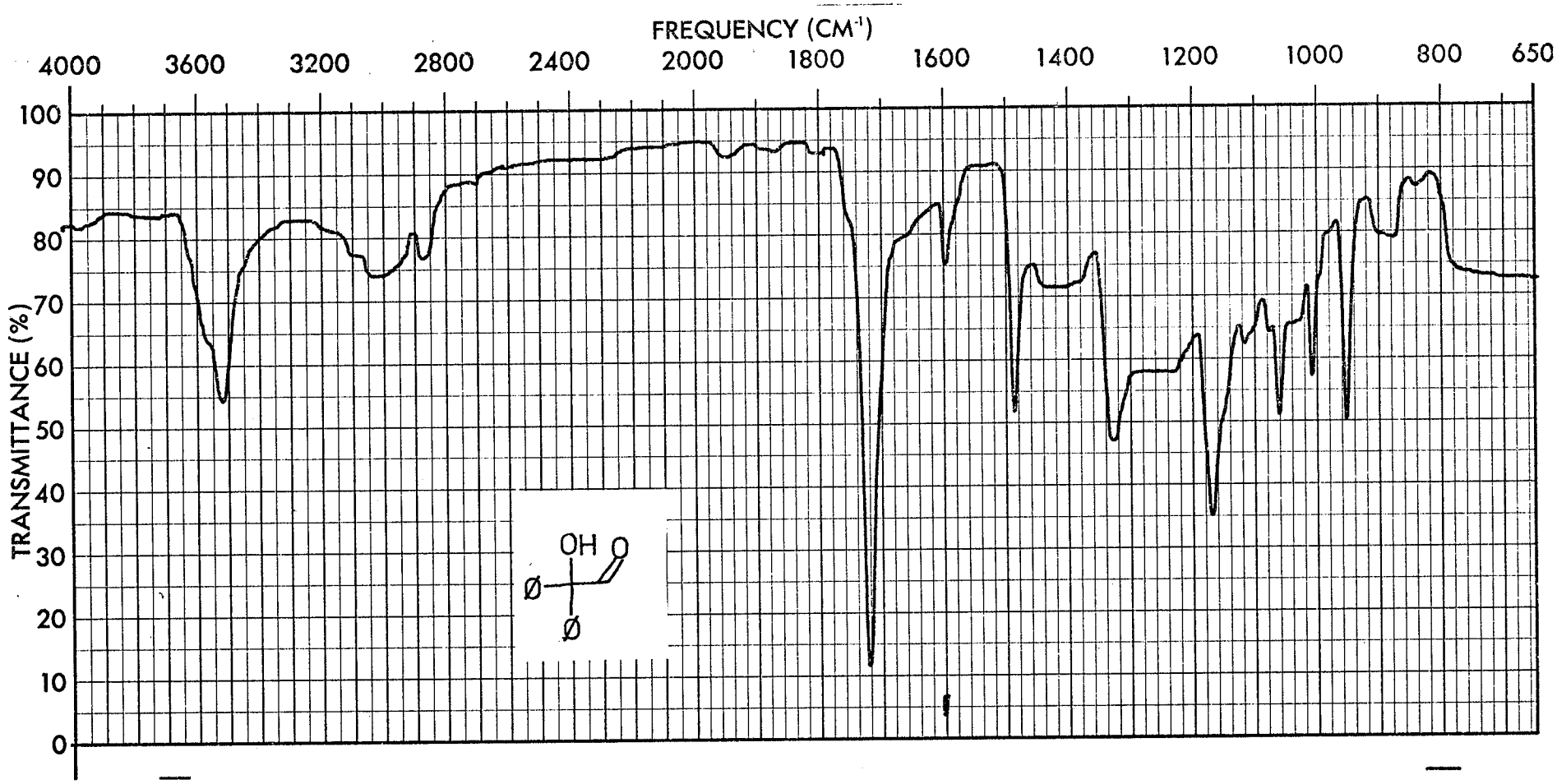
IR-XVIII 1-hydroxy-1,1-diphenylacetonethioketal XXXIVd: CH_2Cl_2



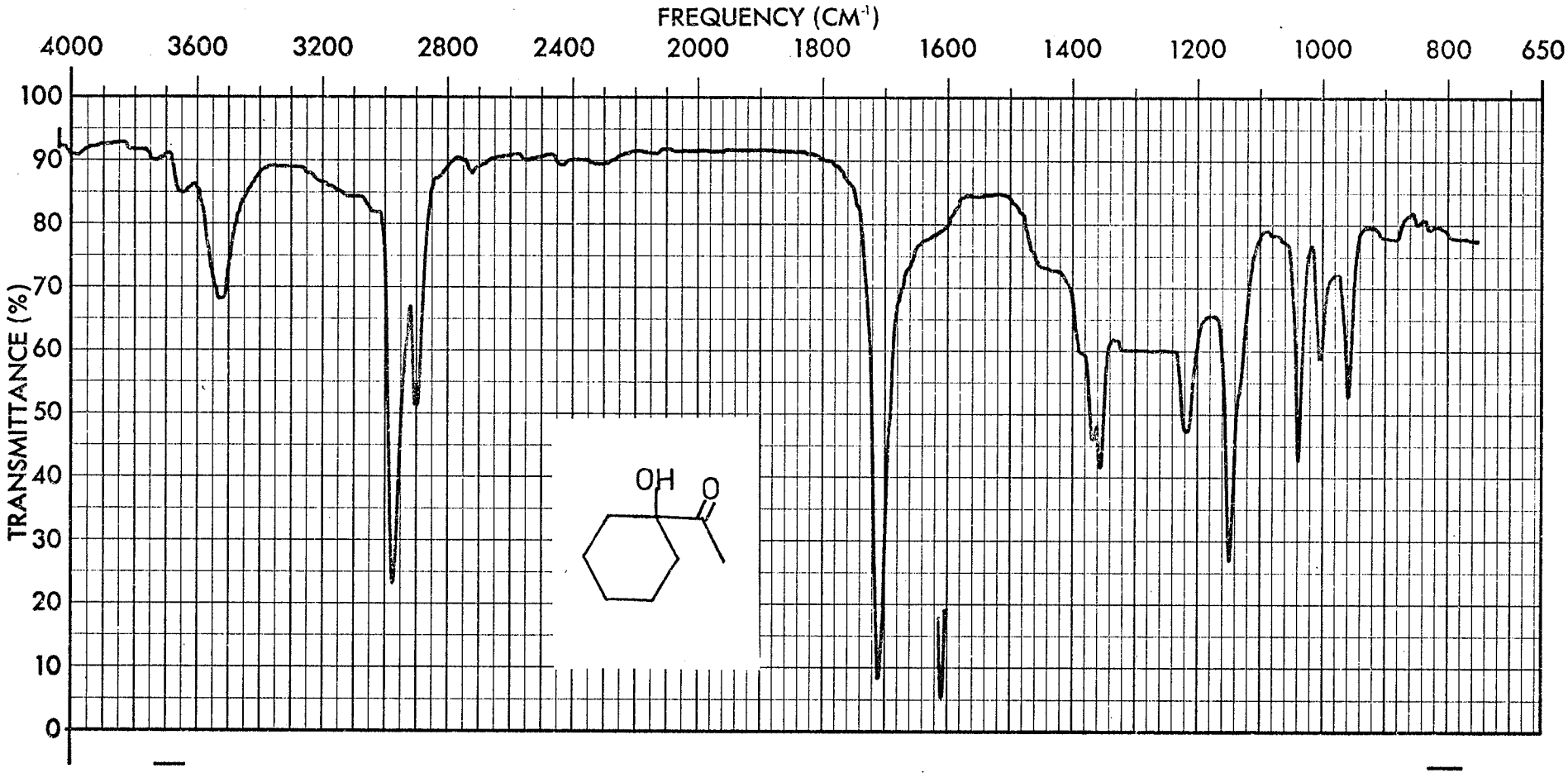
IR-XIX benzointhioketal XXXIVc: CH_2Cl_2



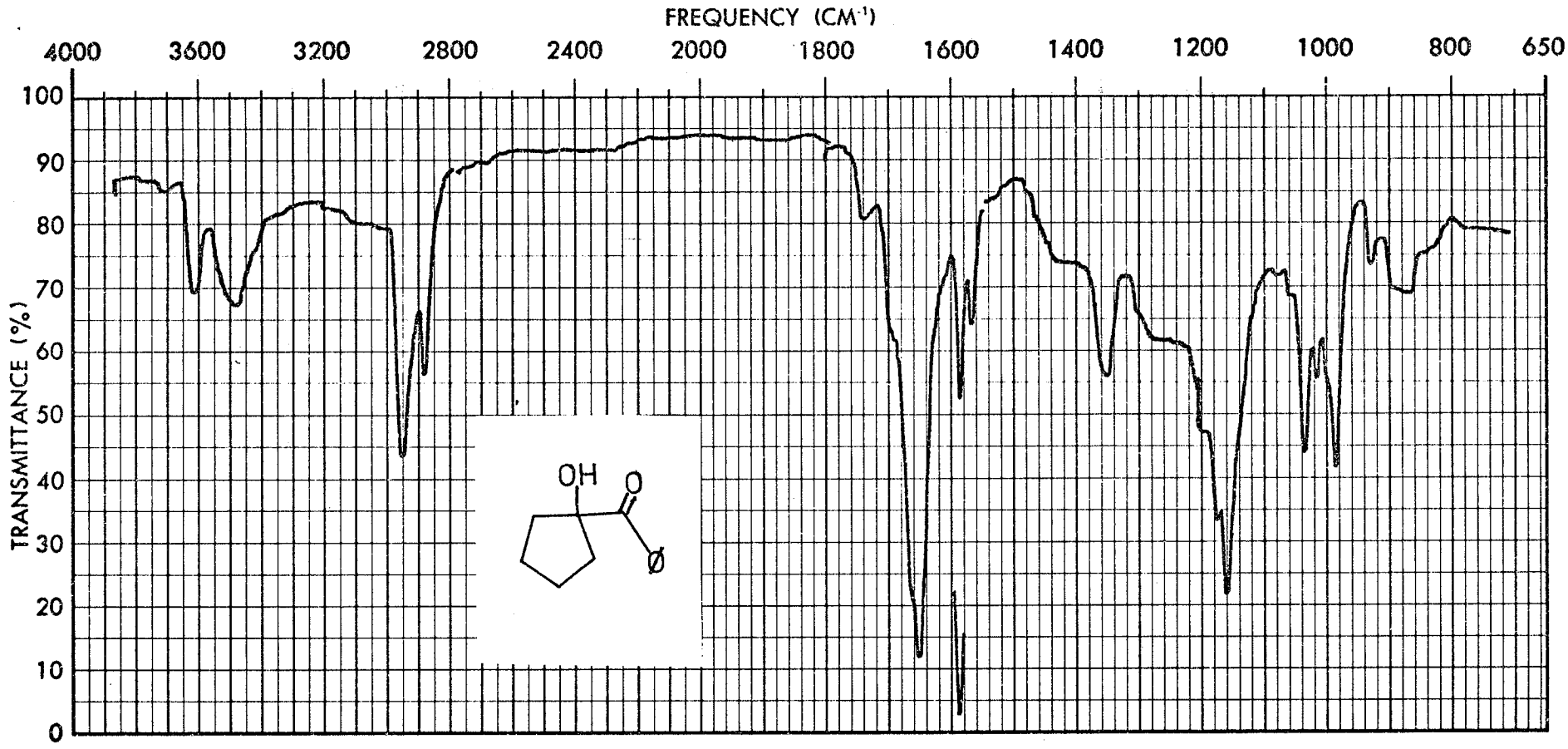
IR-XX phenyl-1'-hydroxycyclopentylketonethioketal XXXIVe: CH_2Cl_2



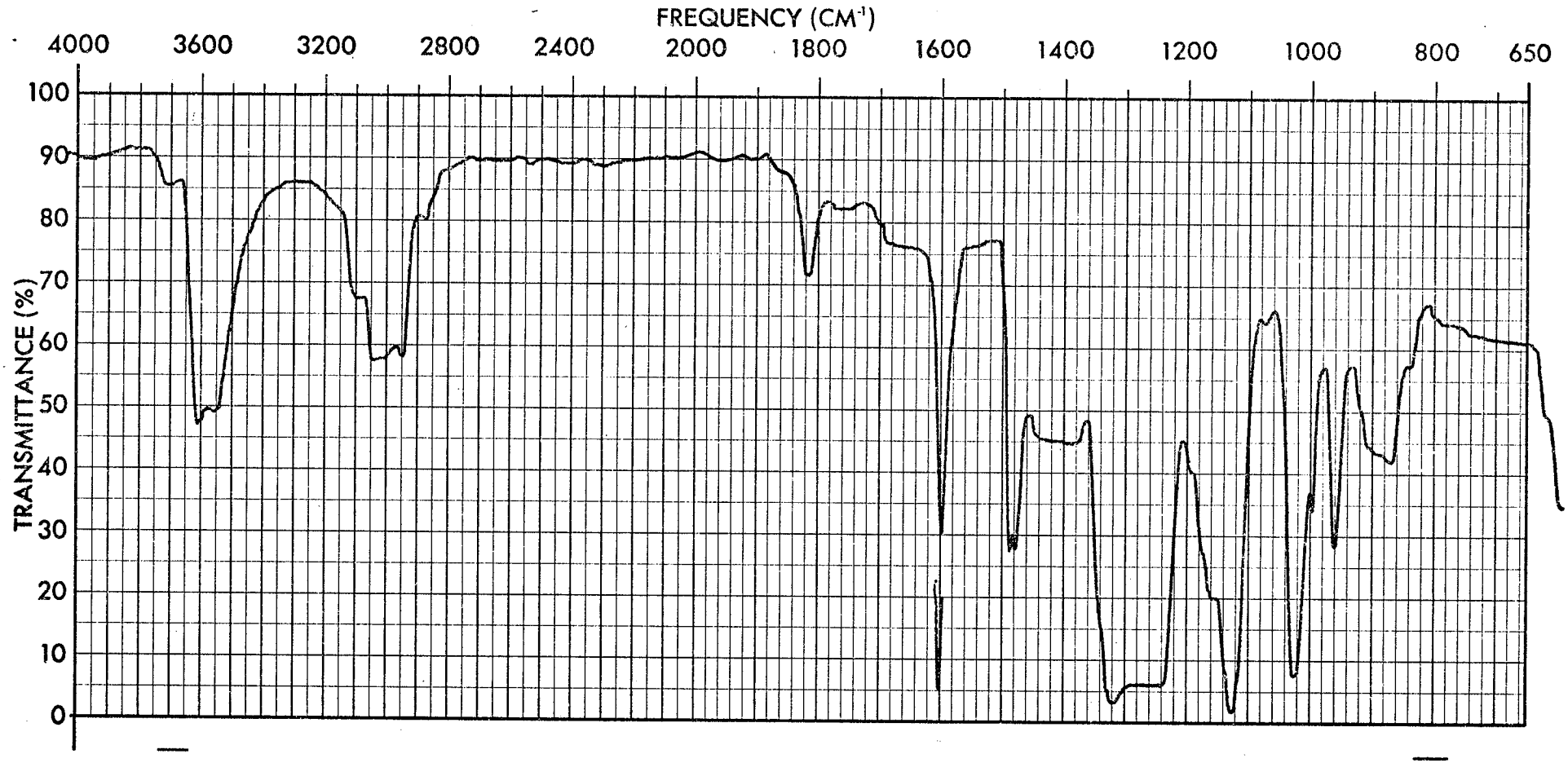
IR-XXI 2-hydroxy-2,2-diphenylacetaldehyde XXXVa: CH_2Cl_2



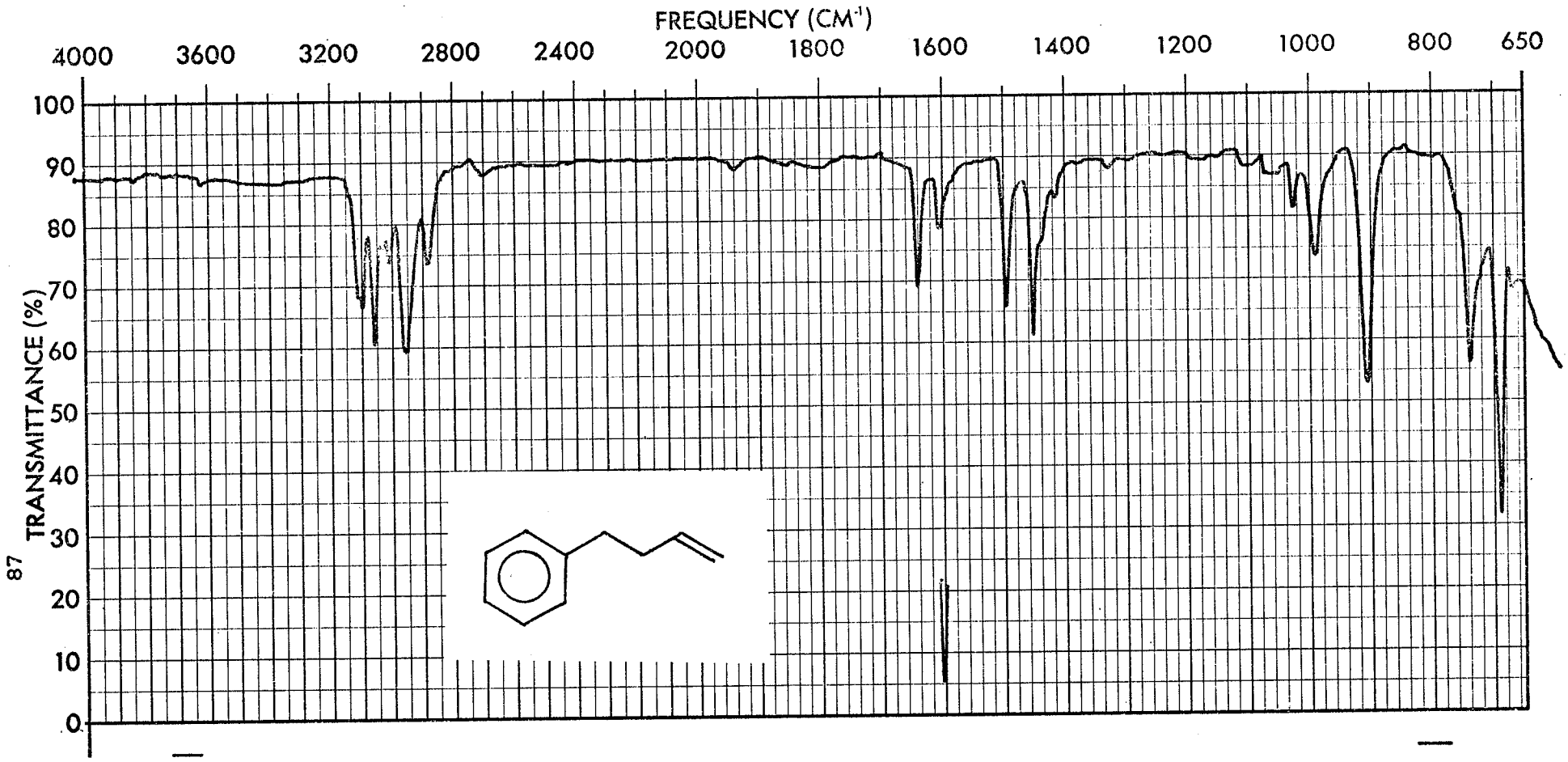
IR-XXII methyl-1'-hydroxycyclobexylketone XXXVb: CH_2Cl_2



IR-XXIII phenyl-1'-hydroxycyclopentylketone XXXVe: CH_2Cl_2



IR-XXIV hydrolysis product from 1-hydroxy-1,1-diphenylacetonethioketal XXXIVd: CH_2Cl_2



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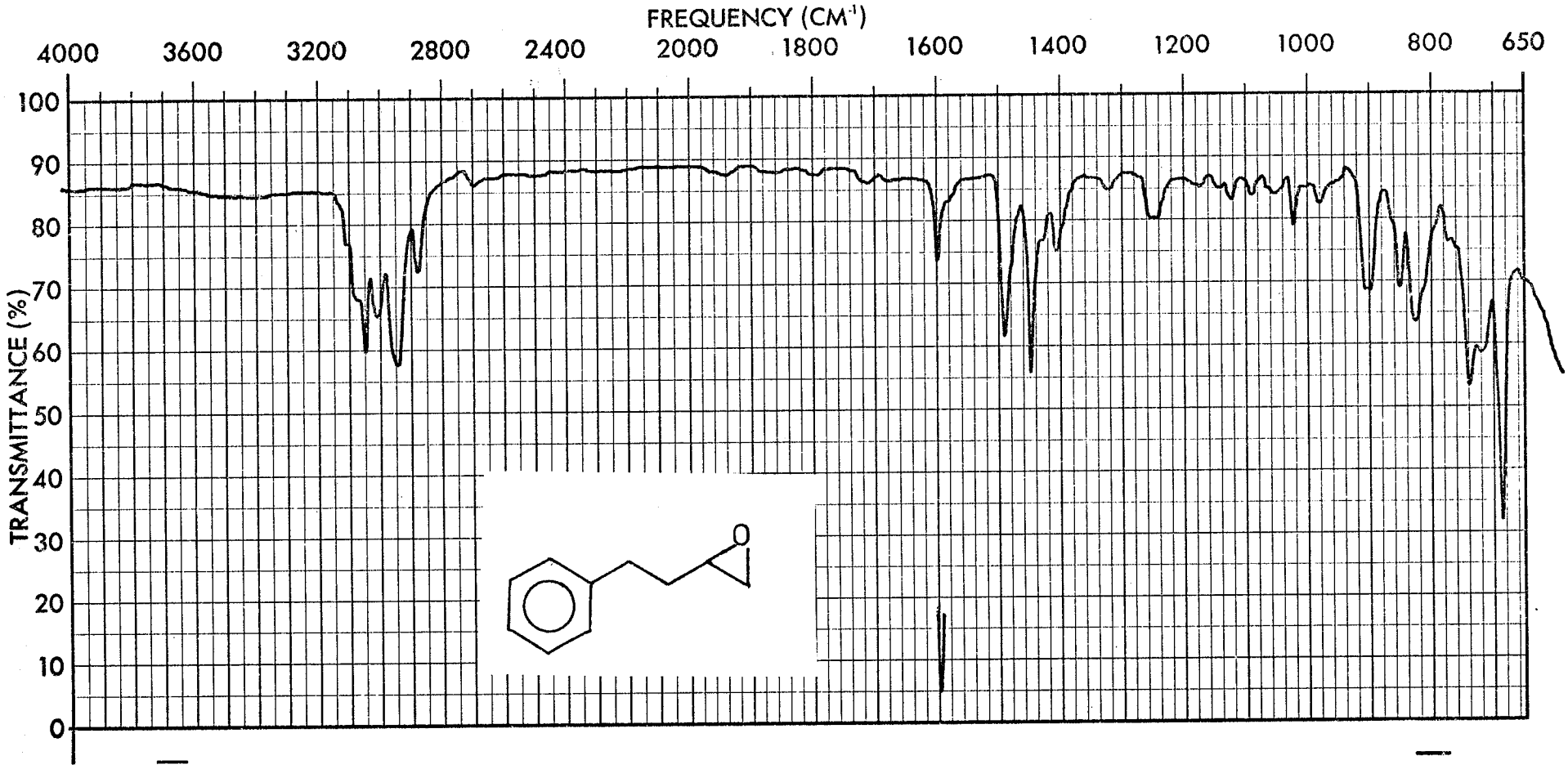
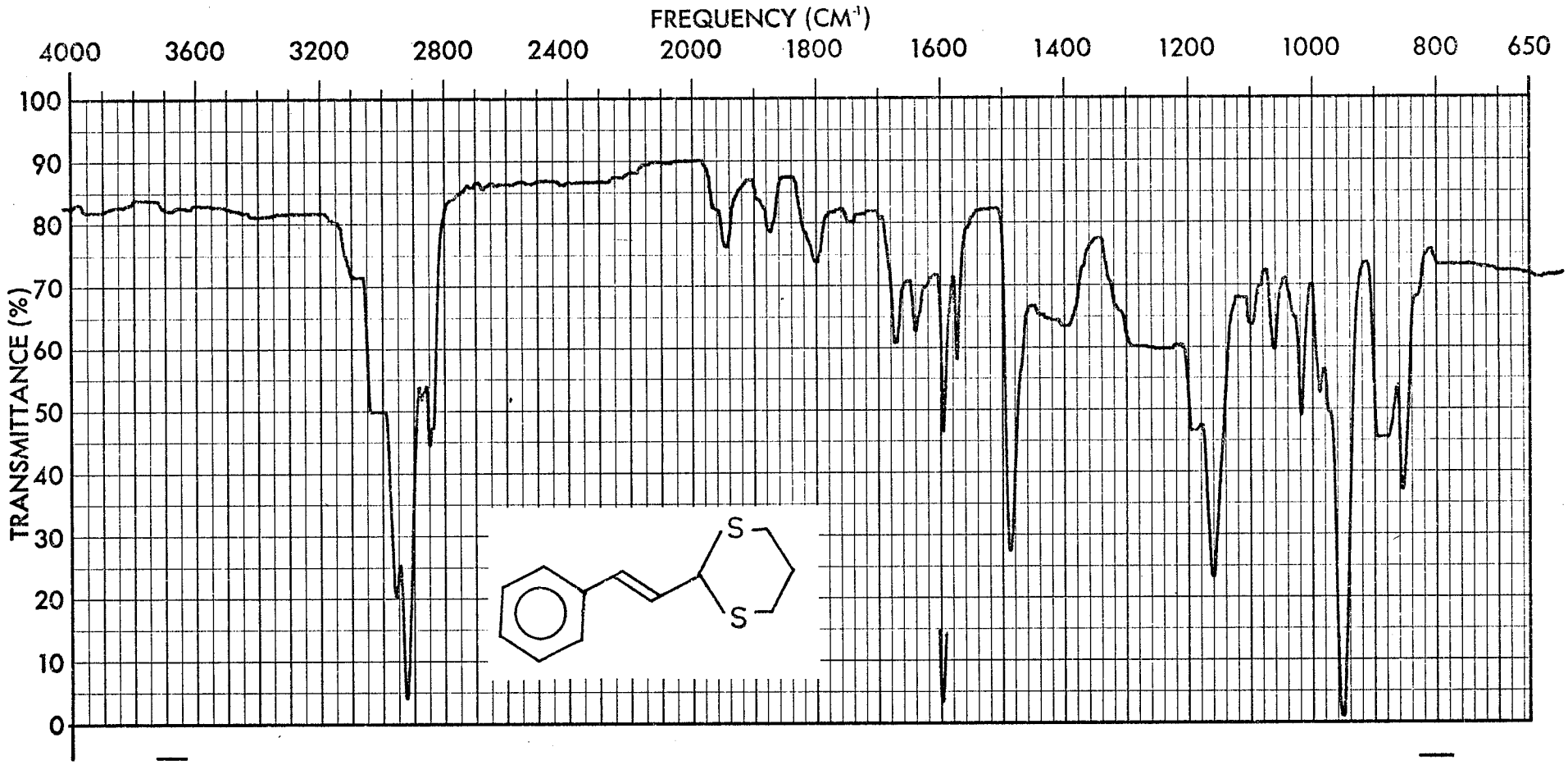
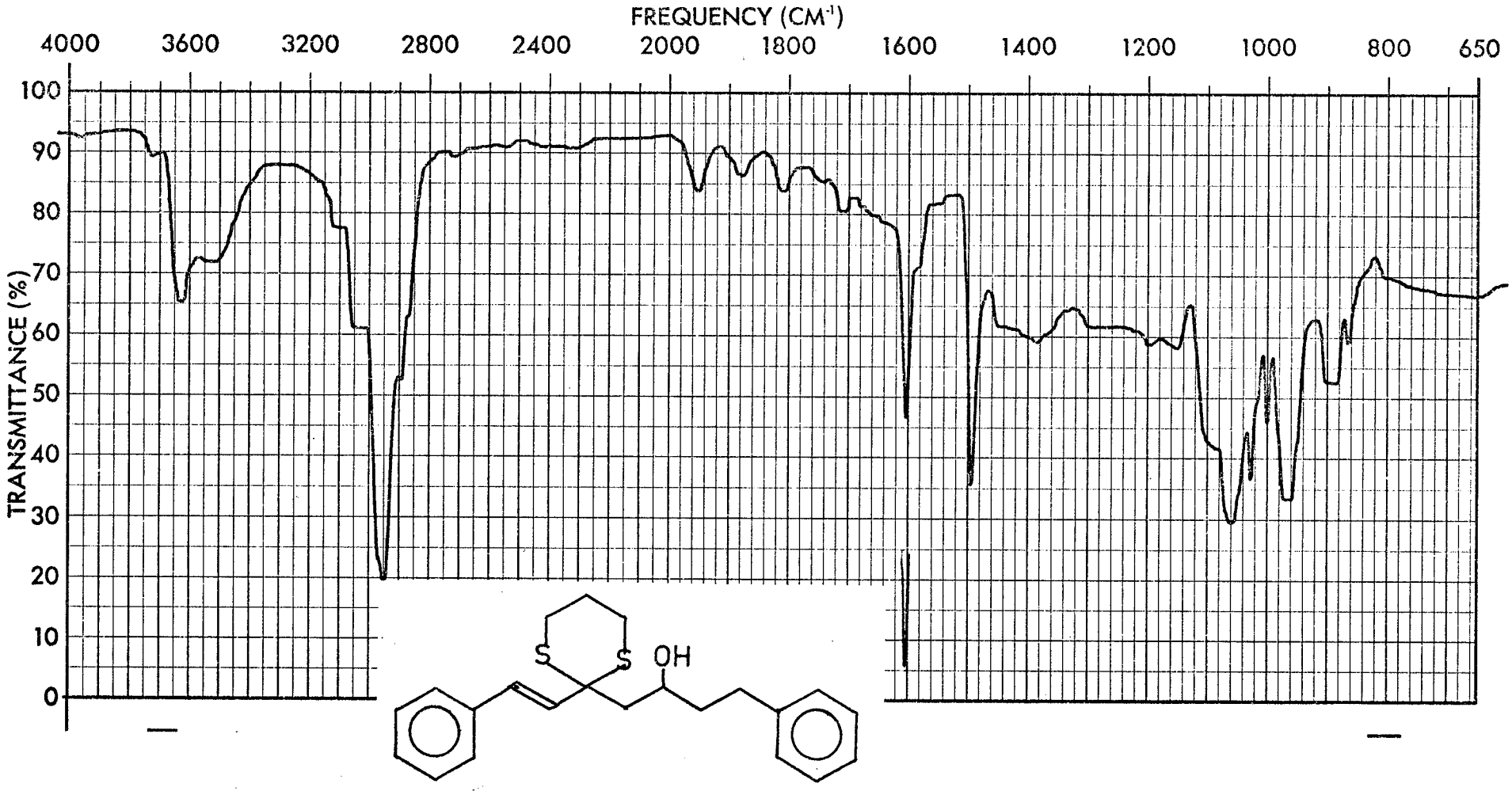
IR-XXV 4 phenyl-1-butene XXXVIII: Neat



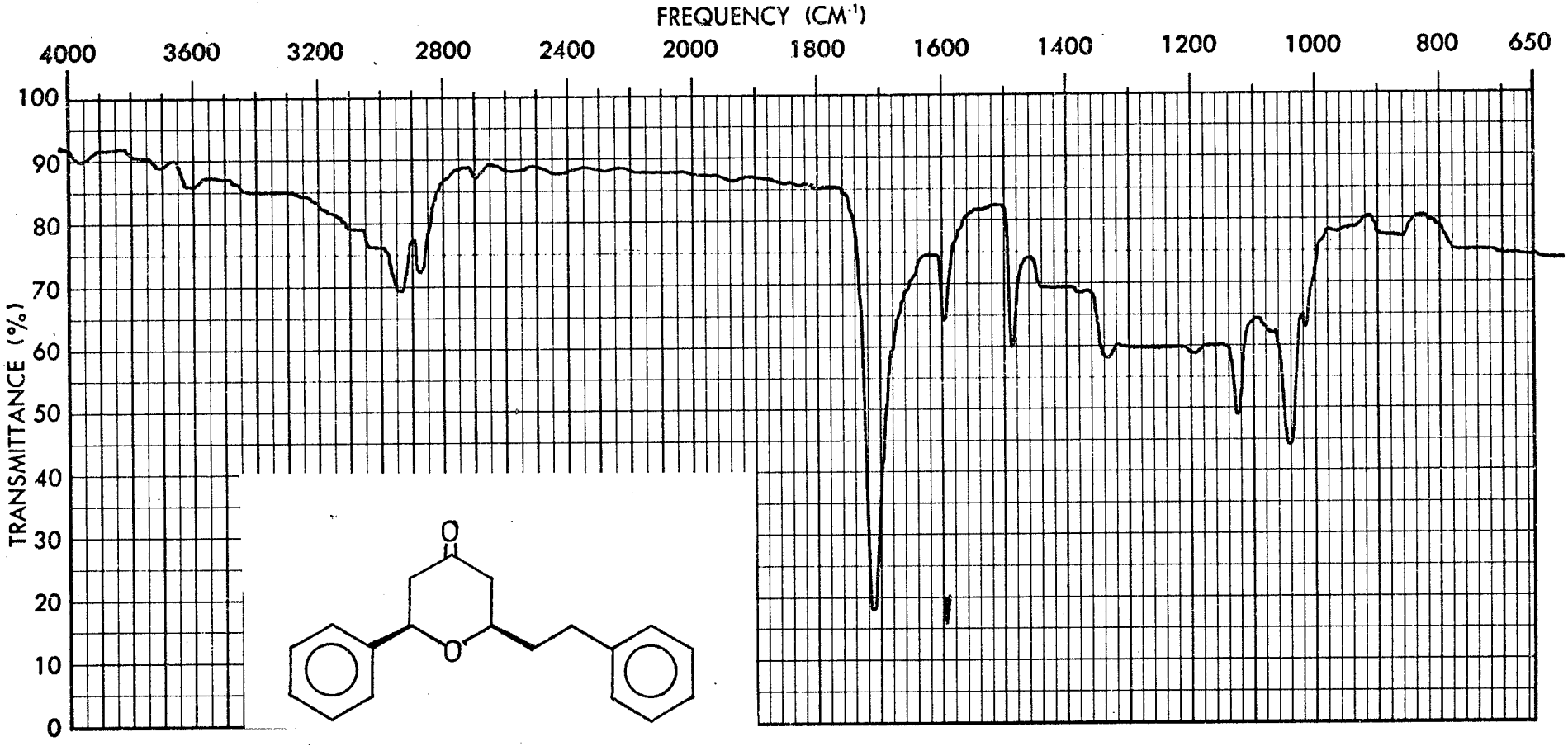
IR-XXVI 1,2-epoxy-4-phenylbutane XXXIX: Neat



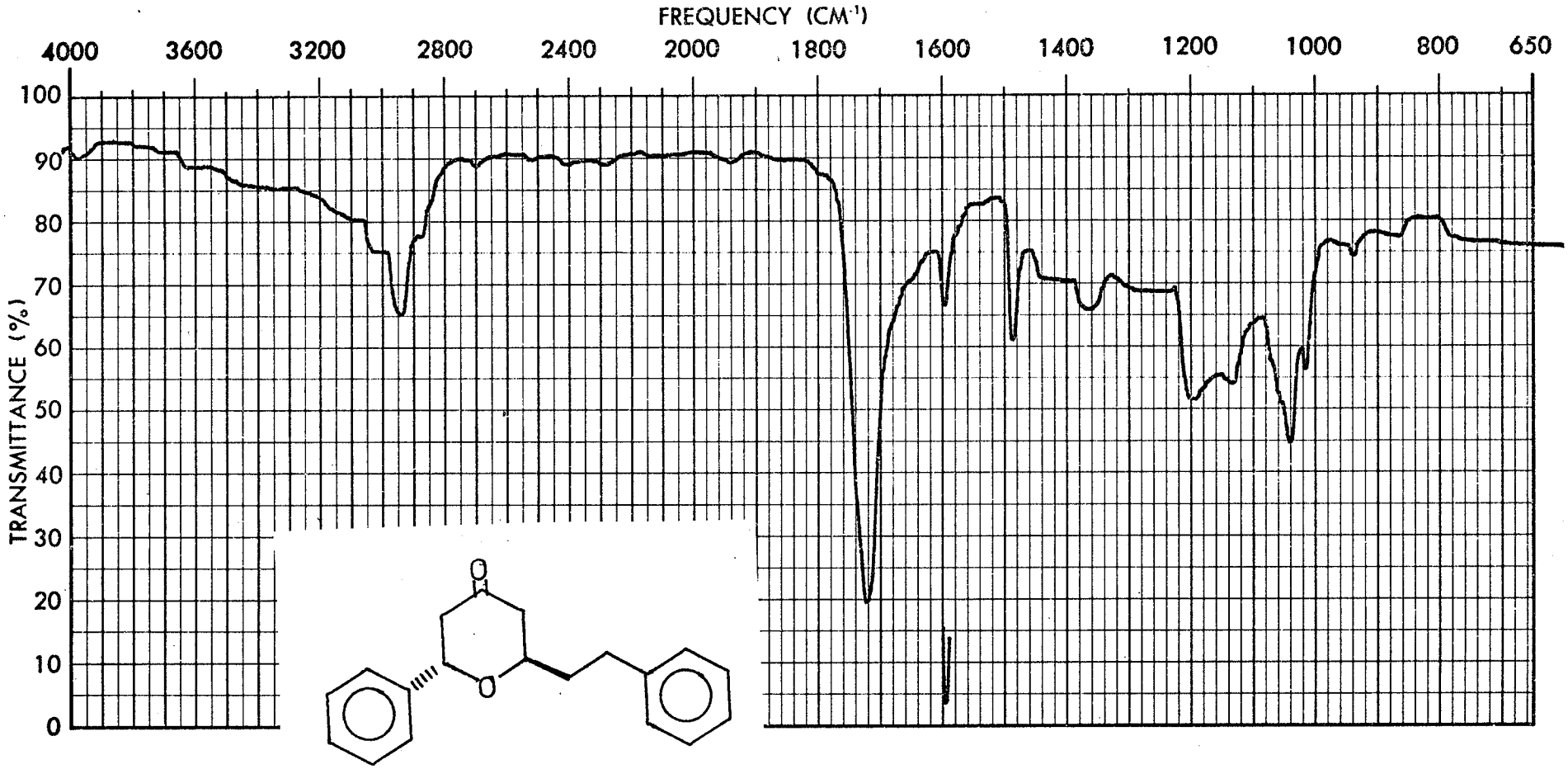
IR-XXVII cinnamaldehydethioacetal XLI: CH_2Cl_2



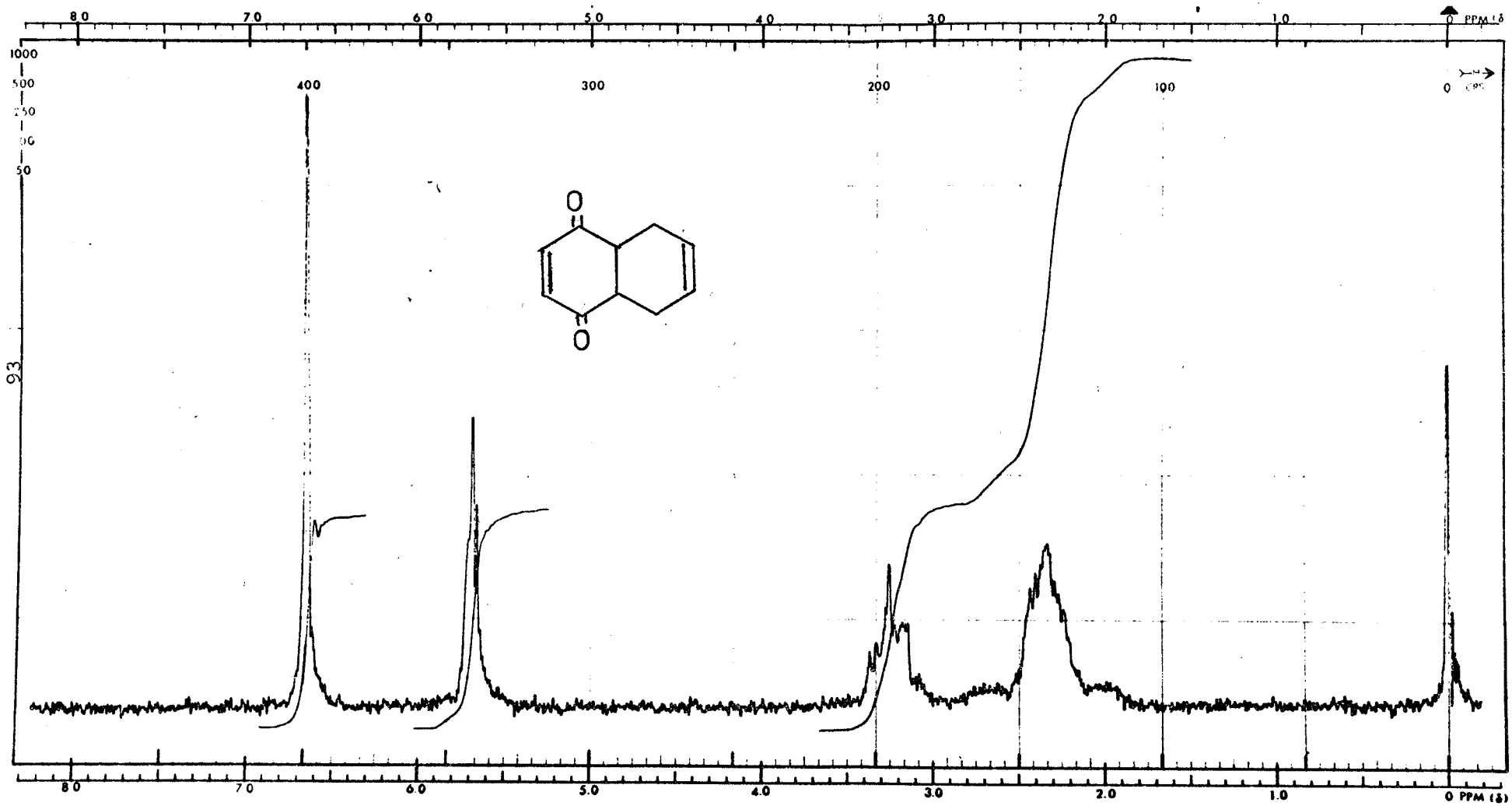
IR-XXVIII racemic yashabushiketonethioketal XLIII: CH_2Cl_2



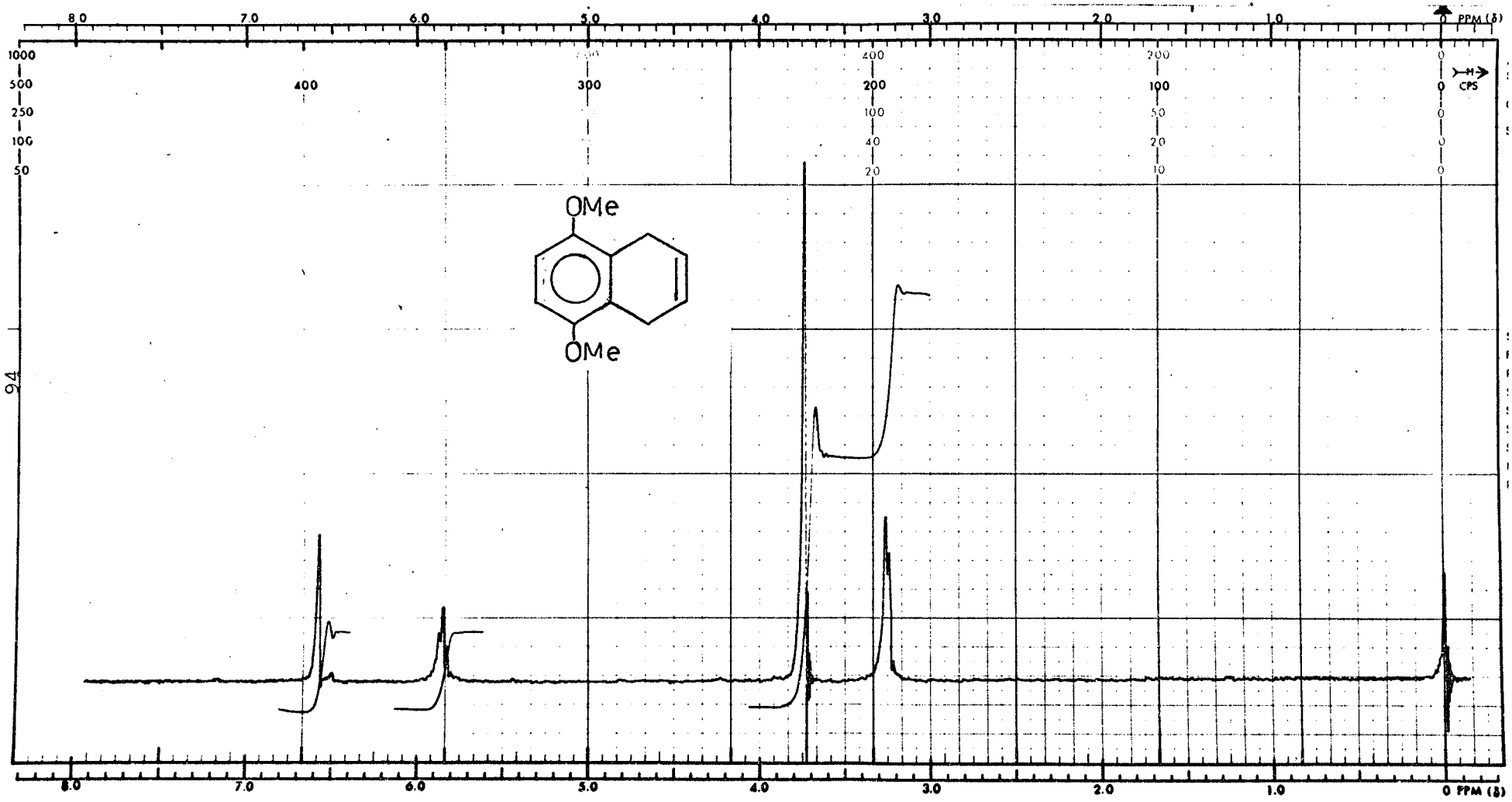
IR-XXIX cis-2-phenyl-6-(2'-phenylethyl)tetrahydro-4-pyranone XLVIIc: CH_2Cl_2



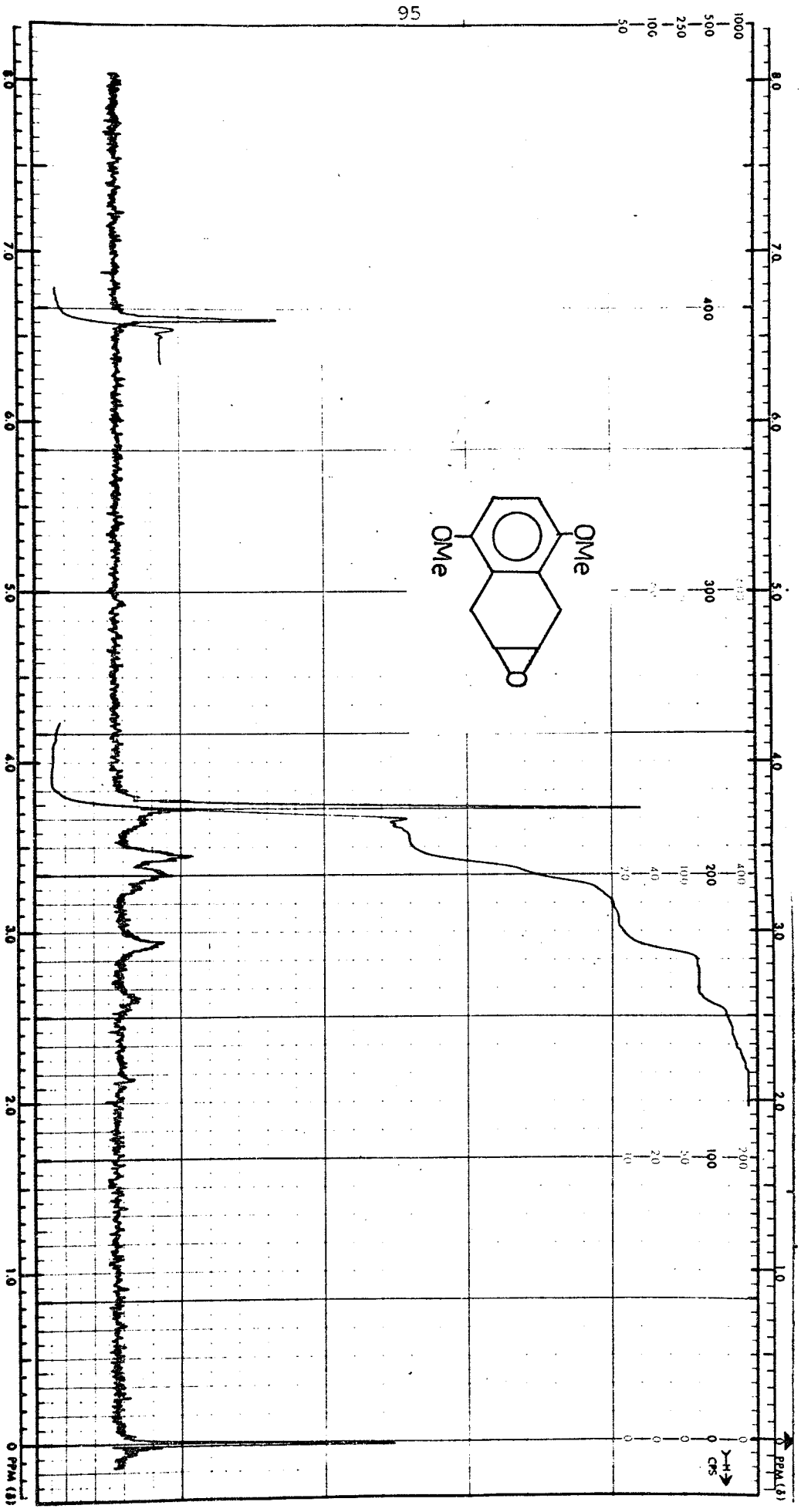
IR-XXX <u>trans</u>-2-phenyl-6-(2'-phenylethyl)tetrahydro-4-pyranone XLVIIt: CH_2Cl_2



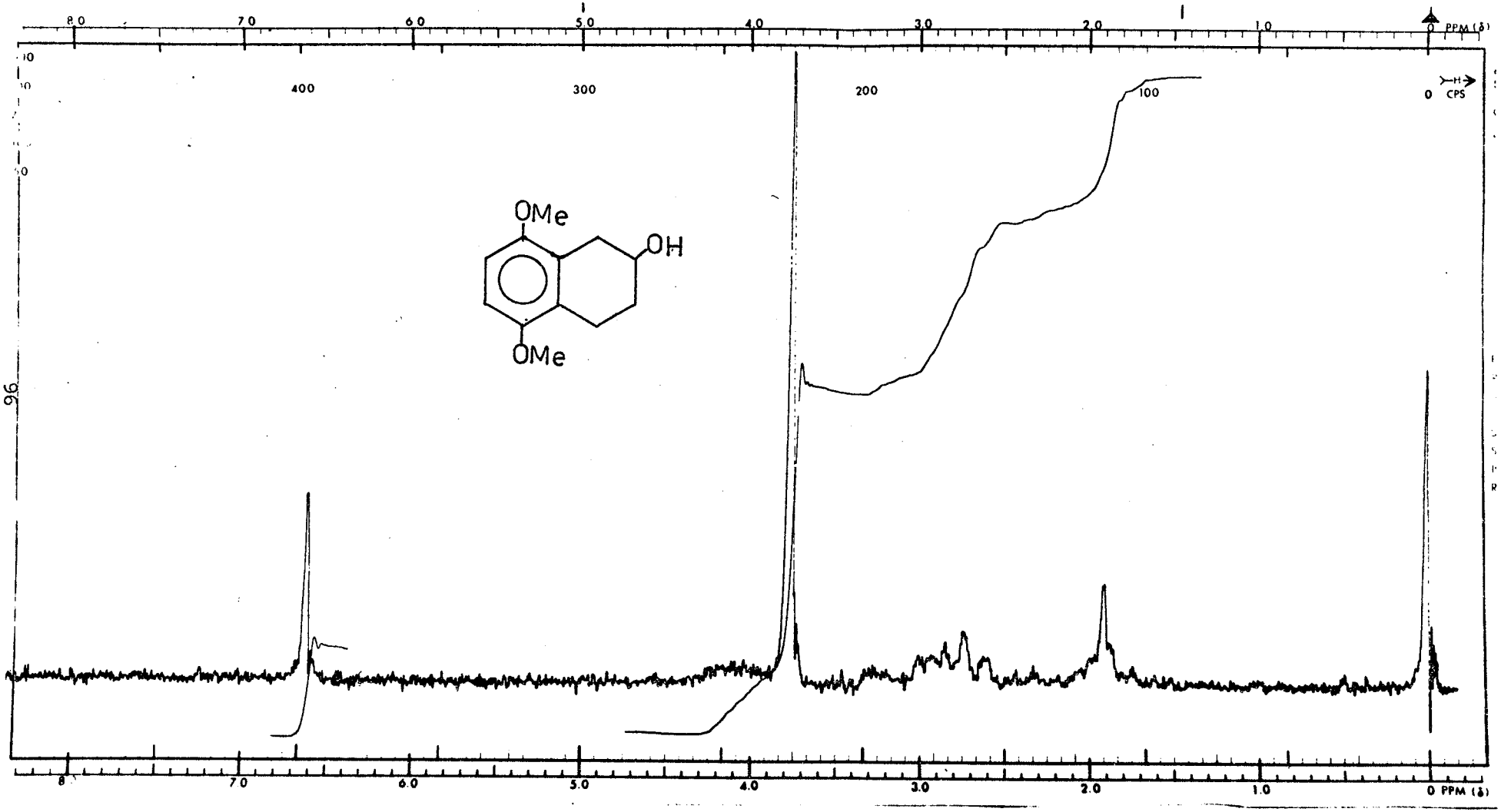
NMR-I 4a,5,8,8a-tetrahydro-1,4-naphthoquinone V: 1000Hz sweep, CCl_4



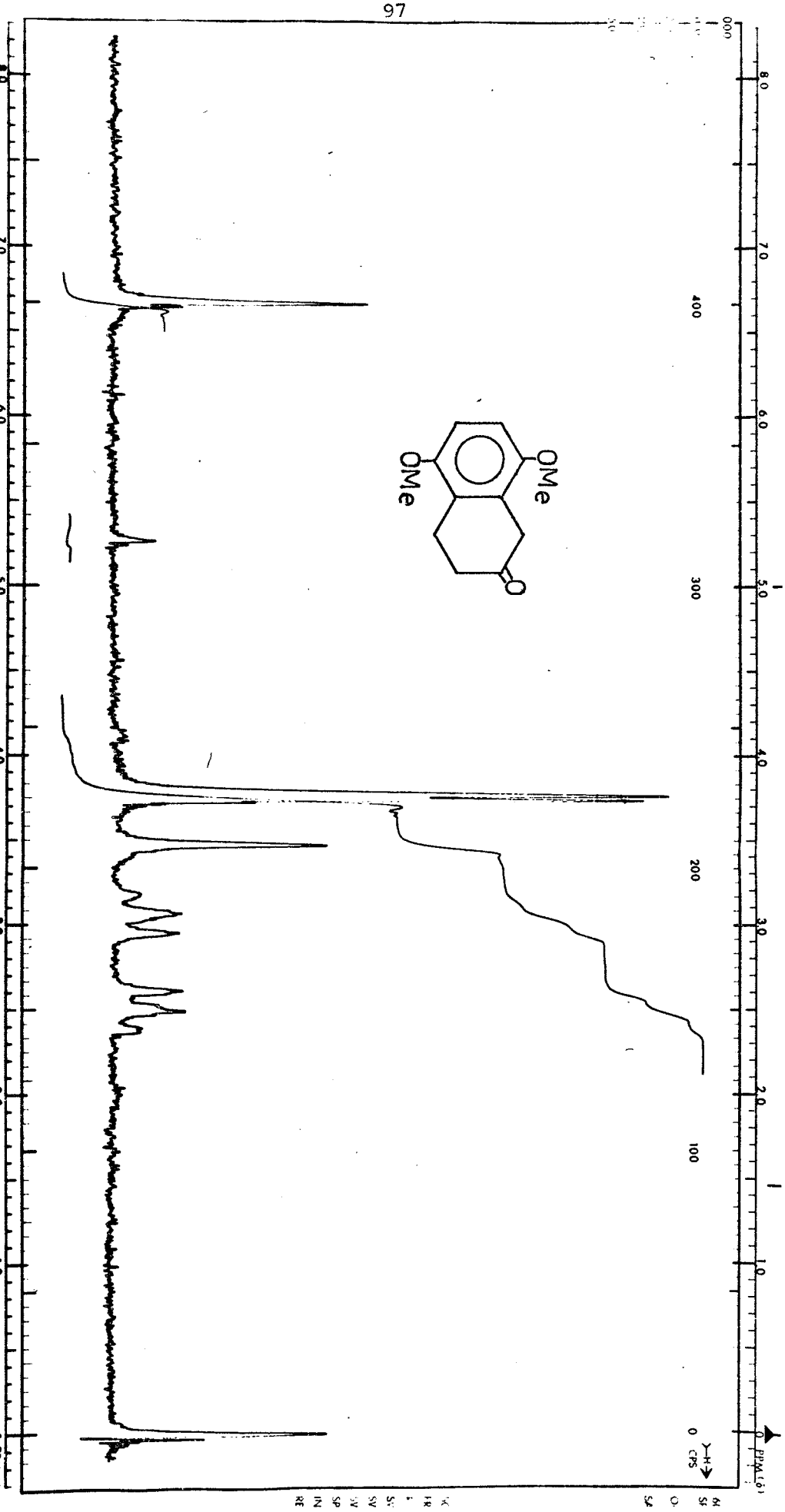
NMR-II 5,8-dimethoxy-1,4-dihydronaphthalene VI: 1000Hz sweep, CCl_4



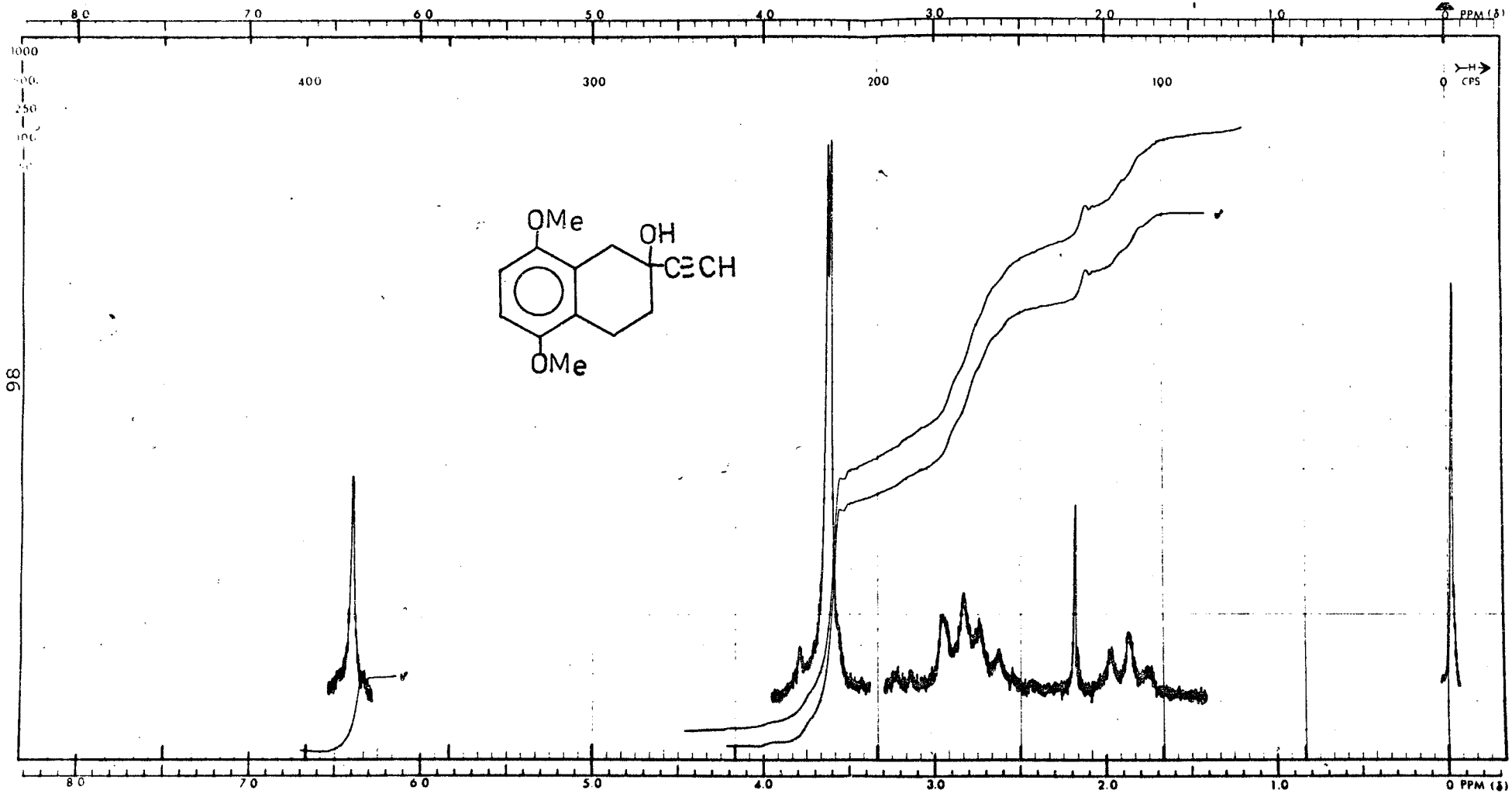
NMR-III 2,3-epoxy-5,8-dimethoxytetralin VII: 1000Hz sweep, CCl_4



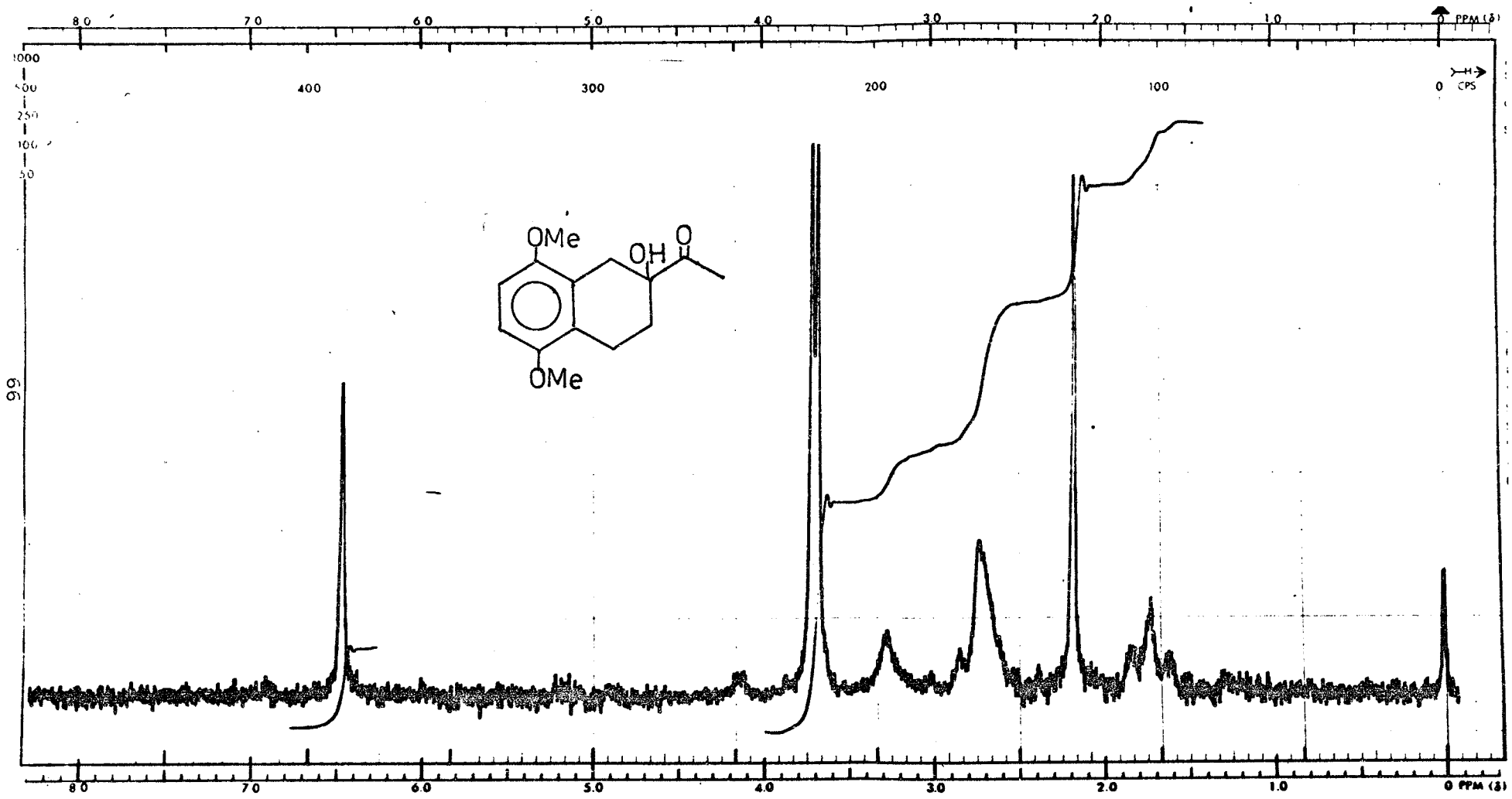
NMR-IV 2-hydroxy-5,8-dimethoxytetralin VIII: 1000Hz sweep, CCl_4



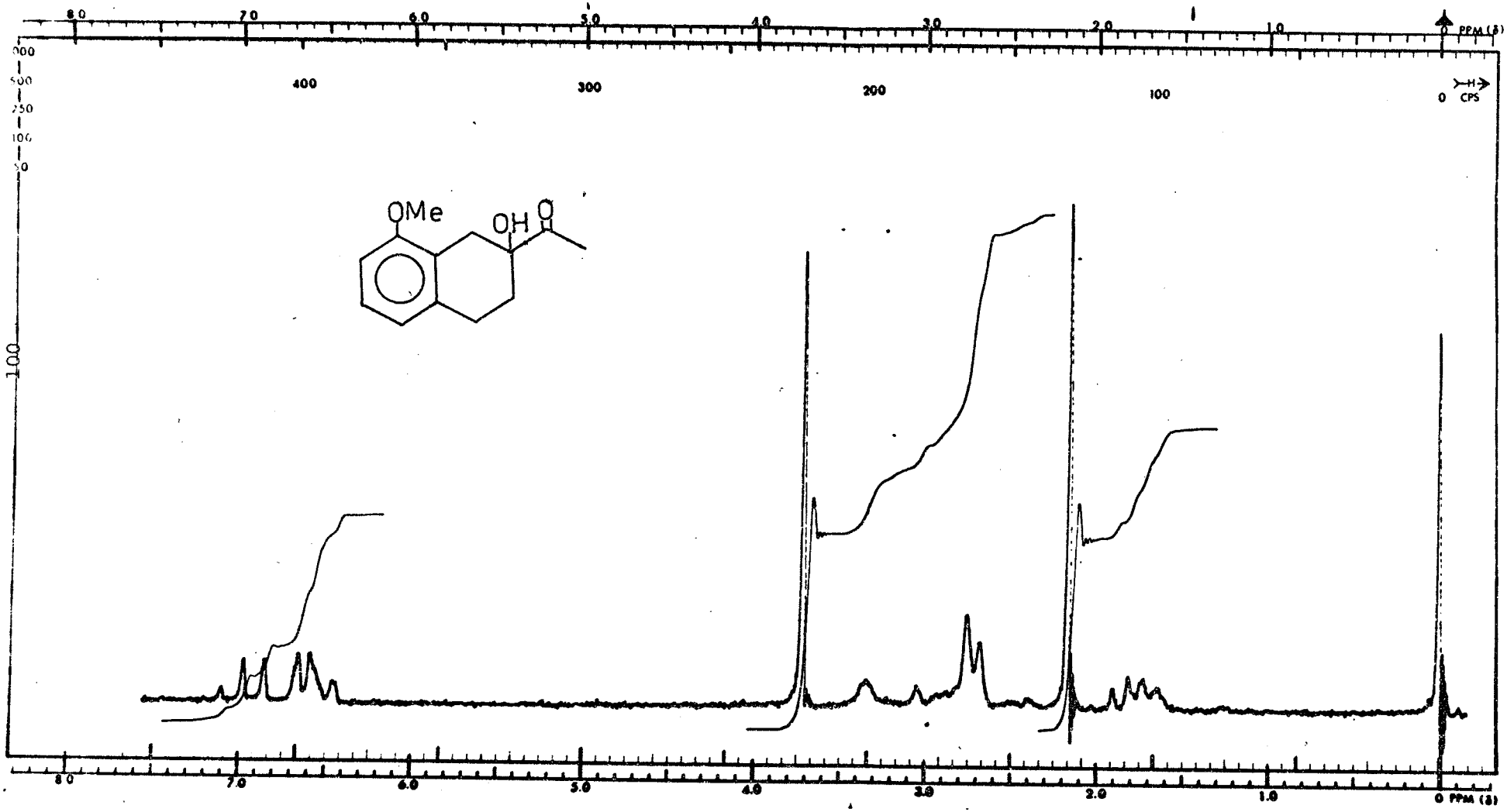
NMR-V 5,8-dimethoxy-2-tetralone IX: 1000Hz sweep, CCl_4



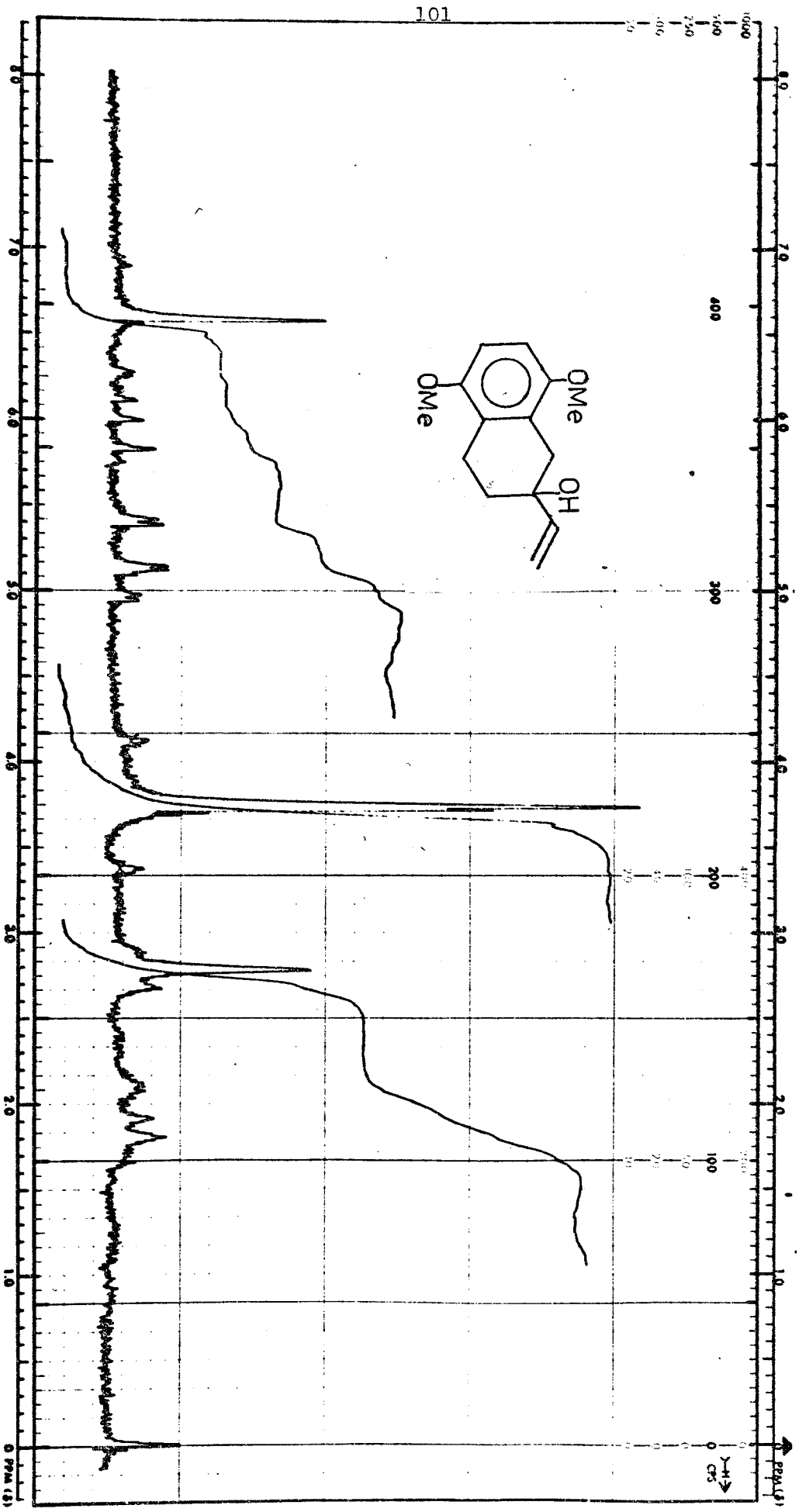
NMR-VI 2-hydroxy-2-ethynyl-5,8-dimethoxy tetralin X: 1000Hz sweep, CCl_4



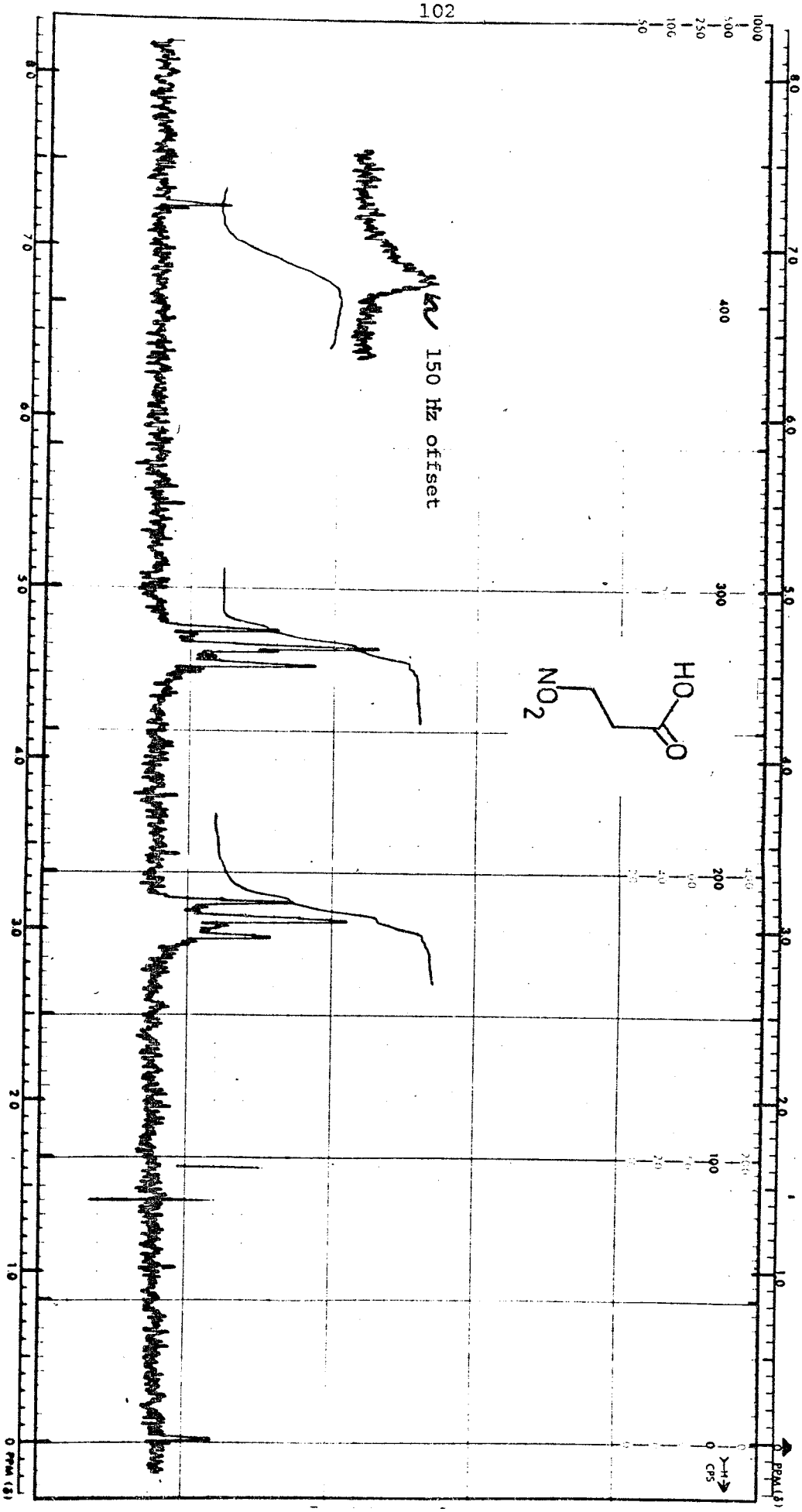
NMR-VII 2-hydroxy-2-acetyl-5,8-dimethoxytetralin XIII: 1000Hz sweep, CCl_4



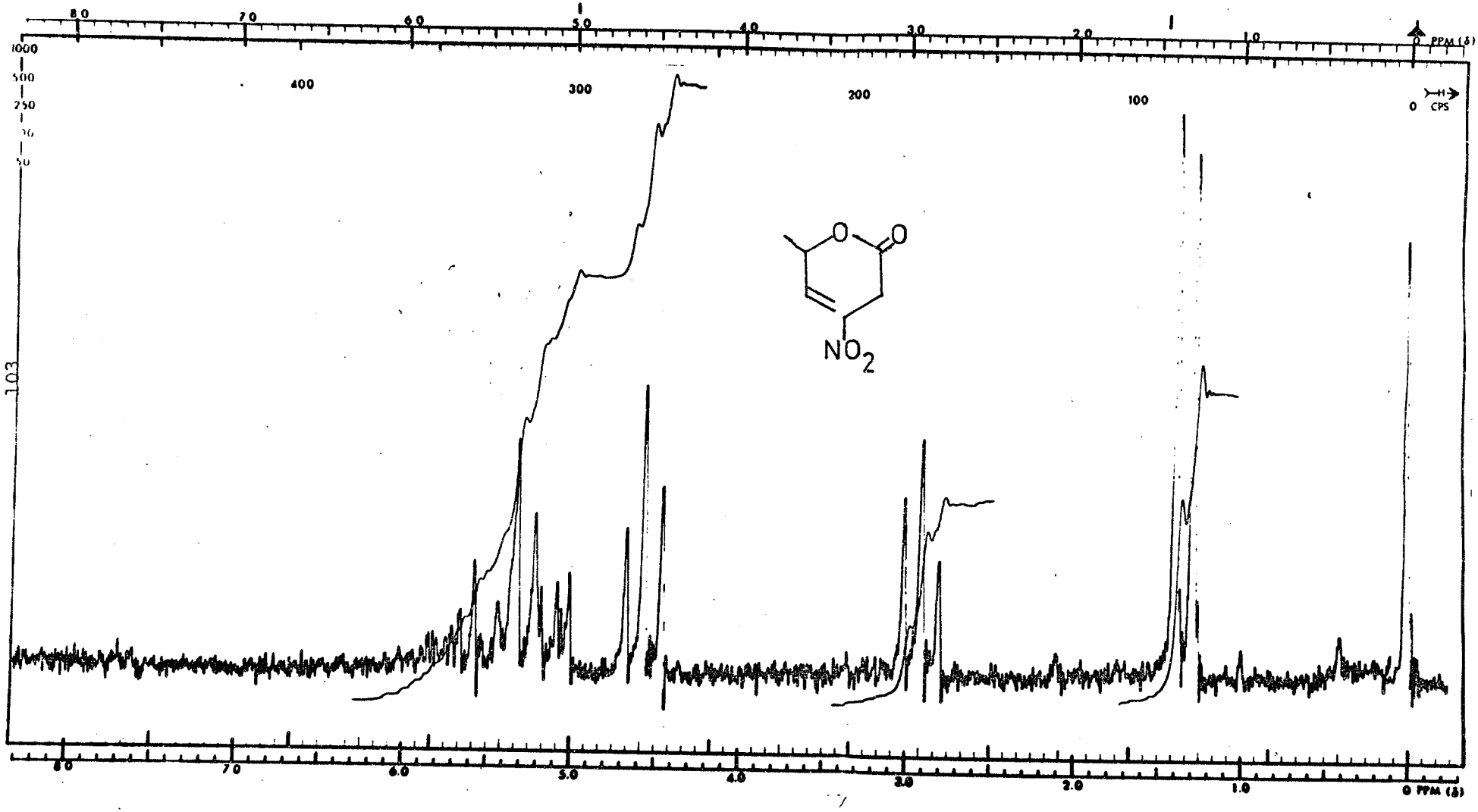
NMR-VIII 2-hydroxy-2-acetyl-8-methoxytetralin XVI: 1000Hz sweep, CCl_4



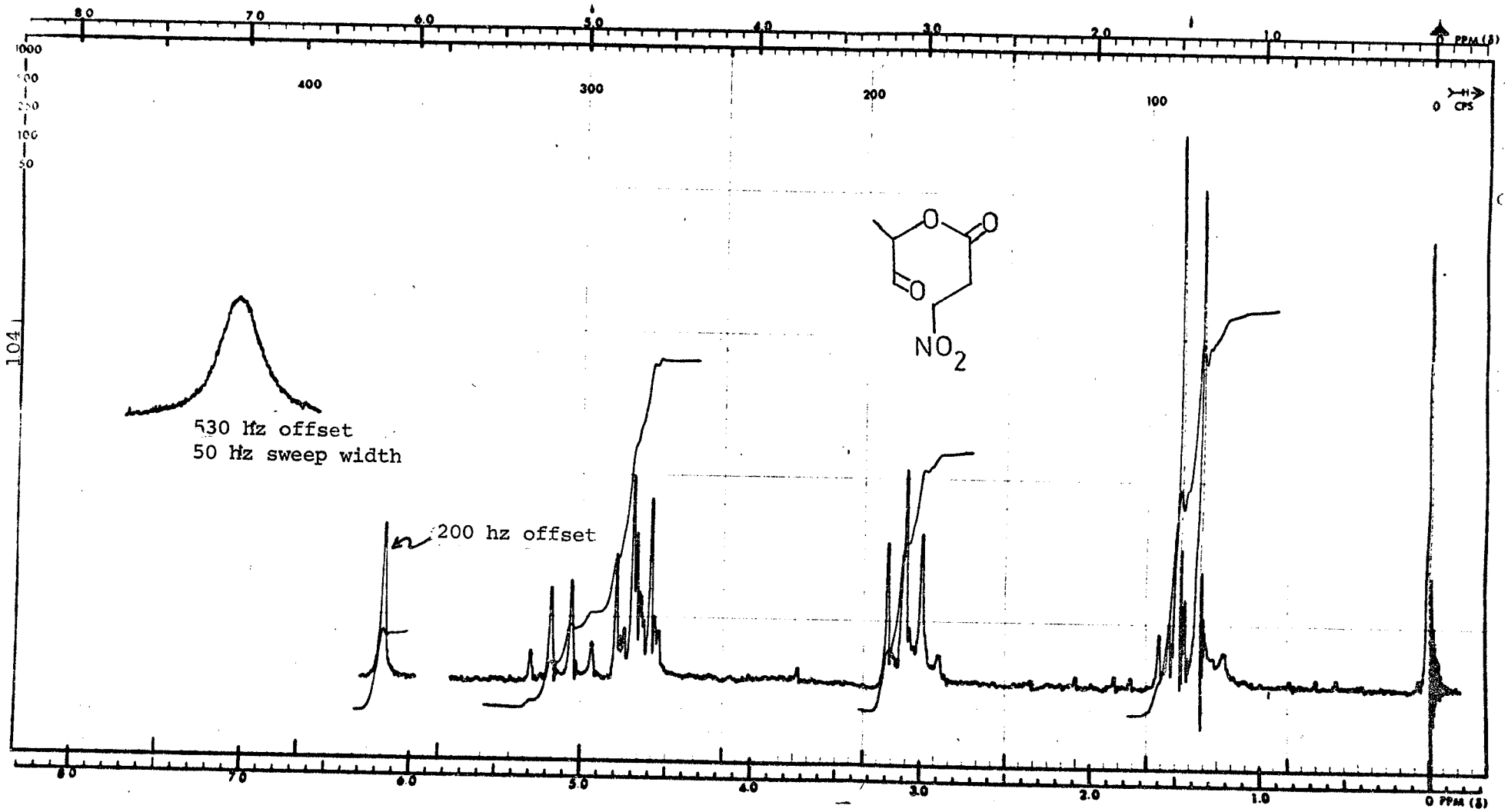
NMR-IX 2-hydroxy-2-vinyl-5,8-dimethoxytetralin XVII: 1000Hz sweep, CCl_4



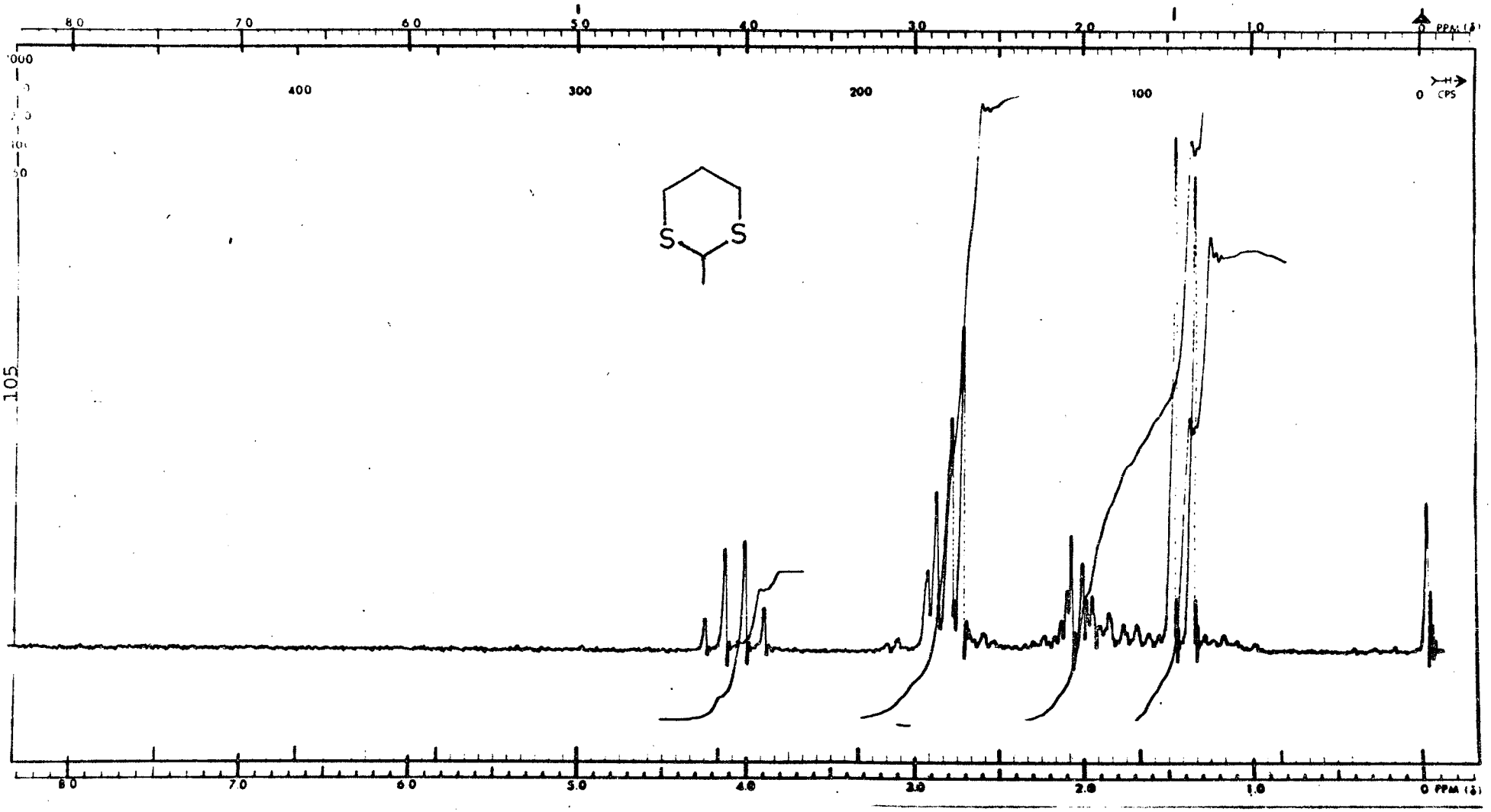
NMR-X 3-nitropropionic acid XXVII: 1000Hz sweep, $CDCl_3$



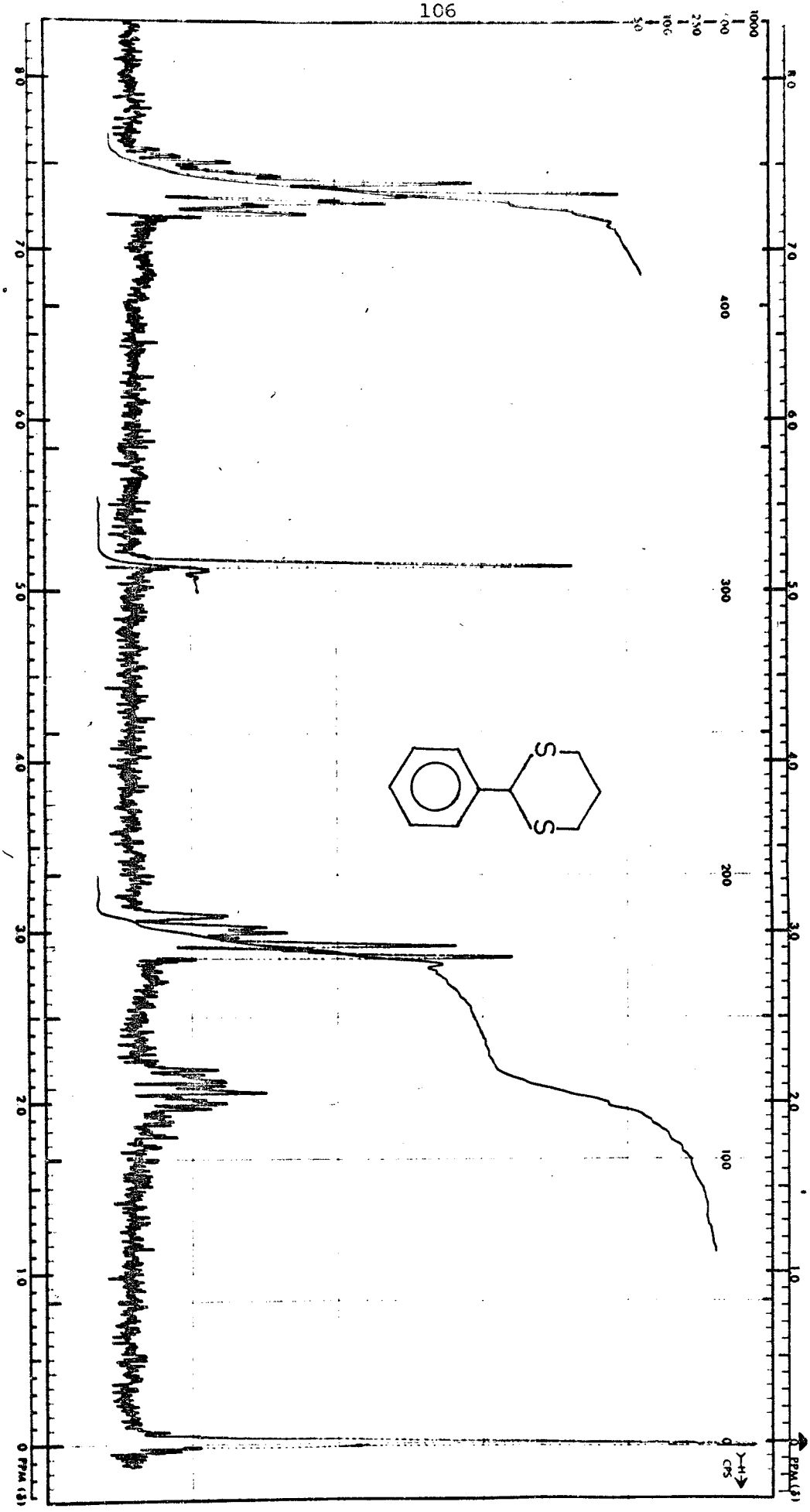
NMR-XI sec-butenyl 3-nitropropionate XXIX: 1000Hz sweep, CCl_4



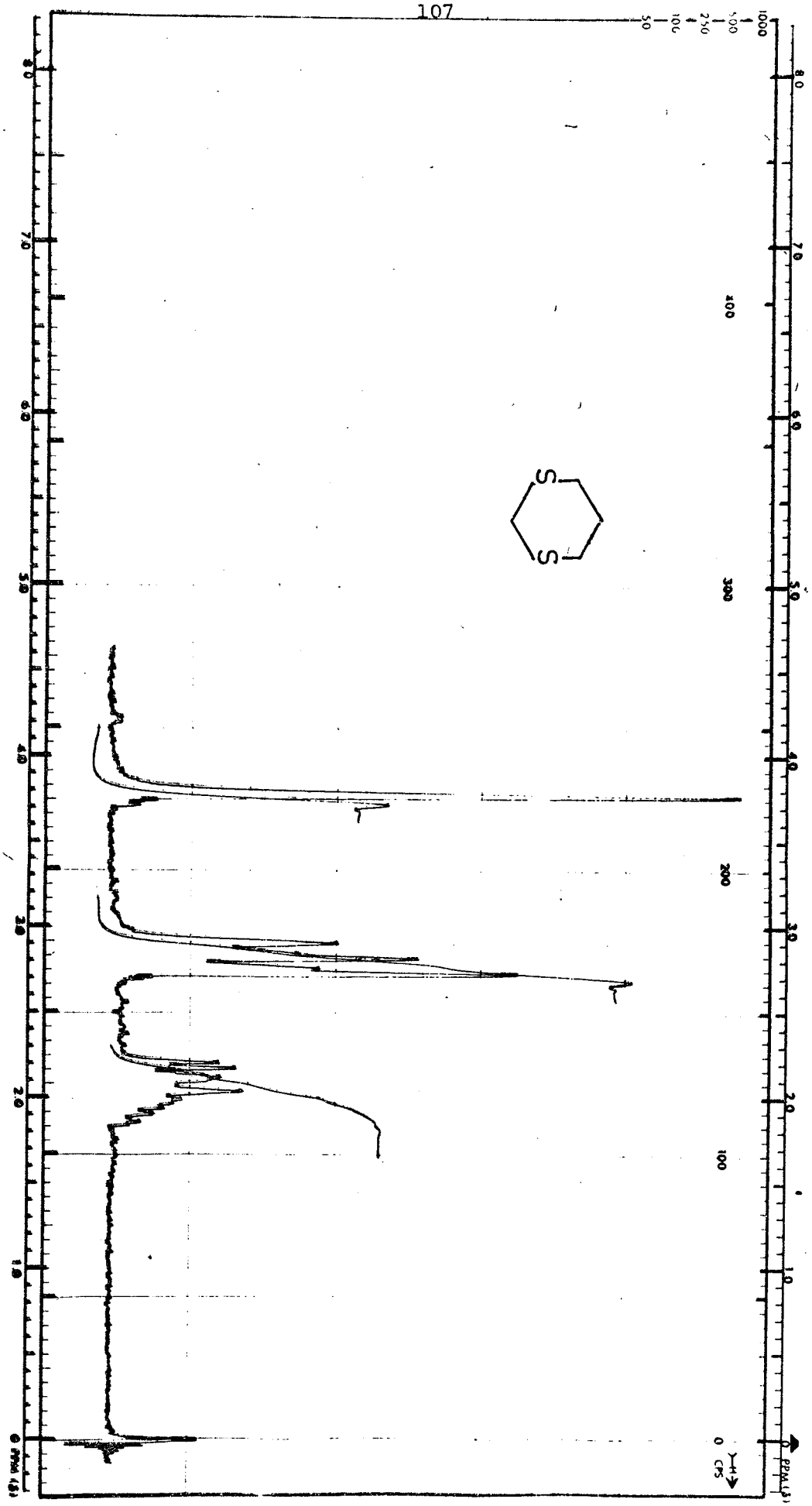
NMR-XII 1-'formylethyl 3-nitropropionate XXX: 1000Hz sweep, CCl_4



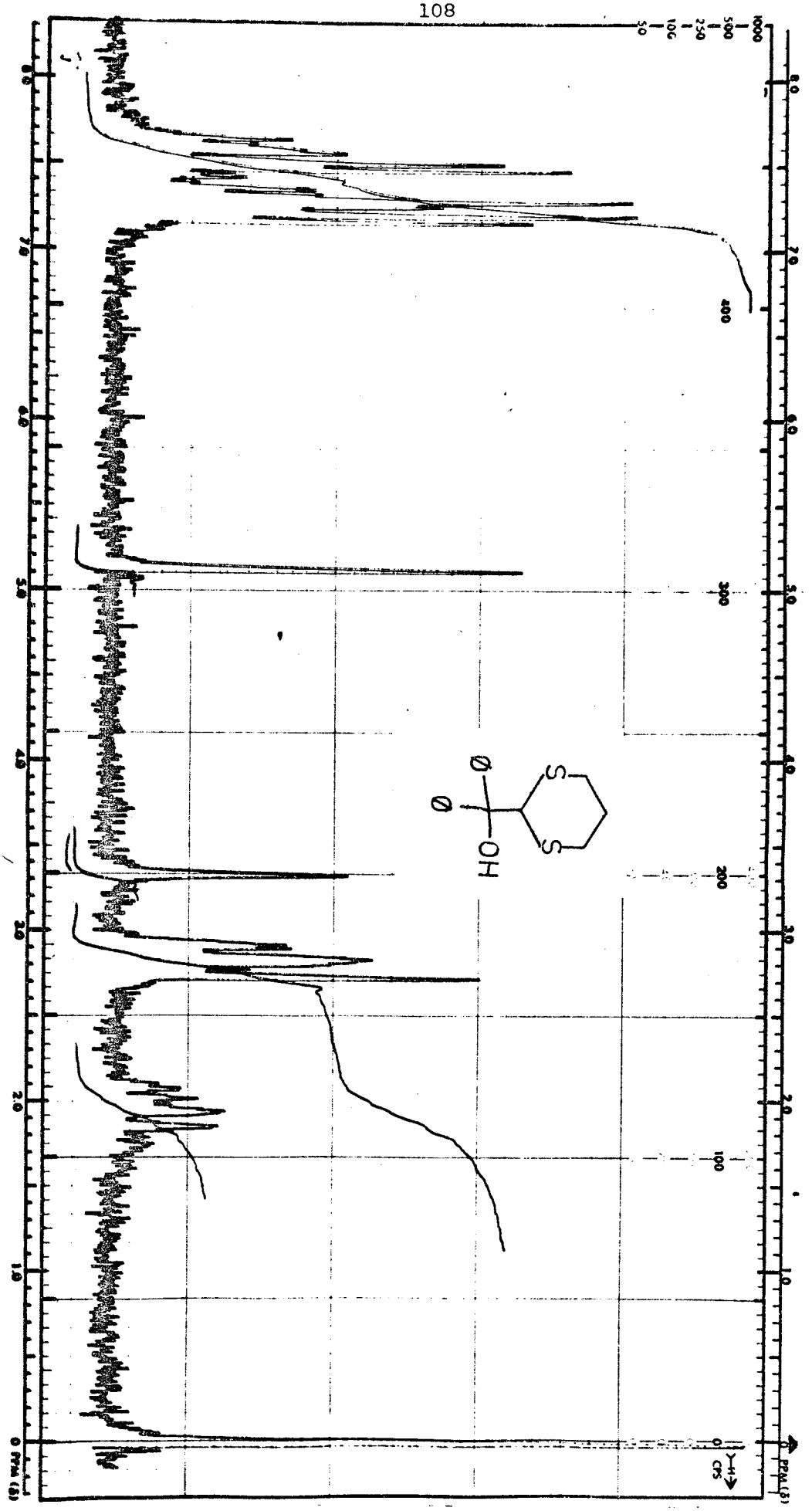
NMR-XIII acetaldehydethioacetal: 500Hz sweep, CCl_4



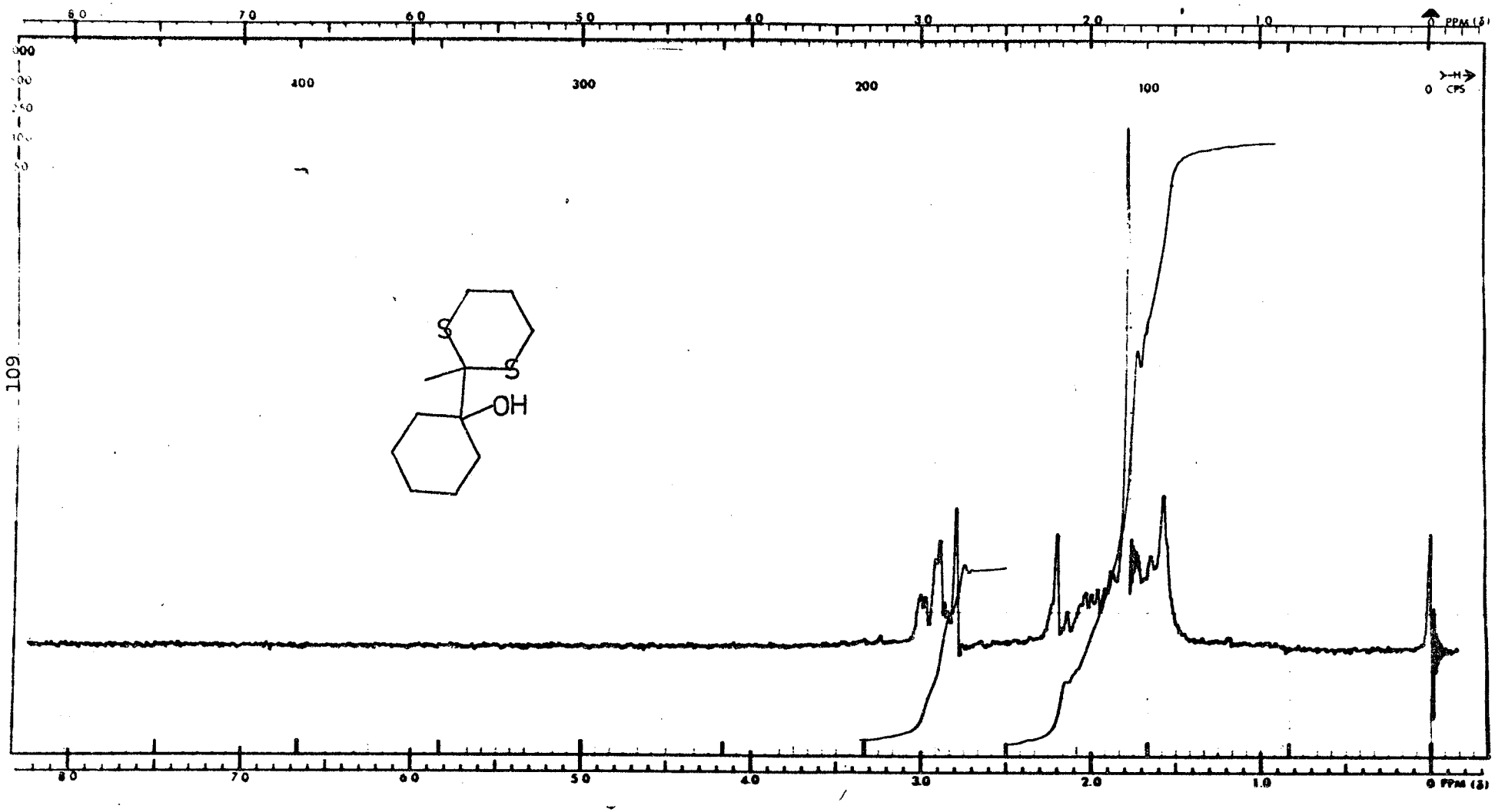
NMR-XIV benzaldehydethioacetal; 1000Hz sweep, CCl_4



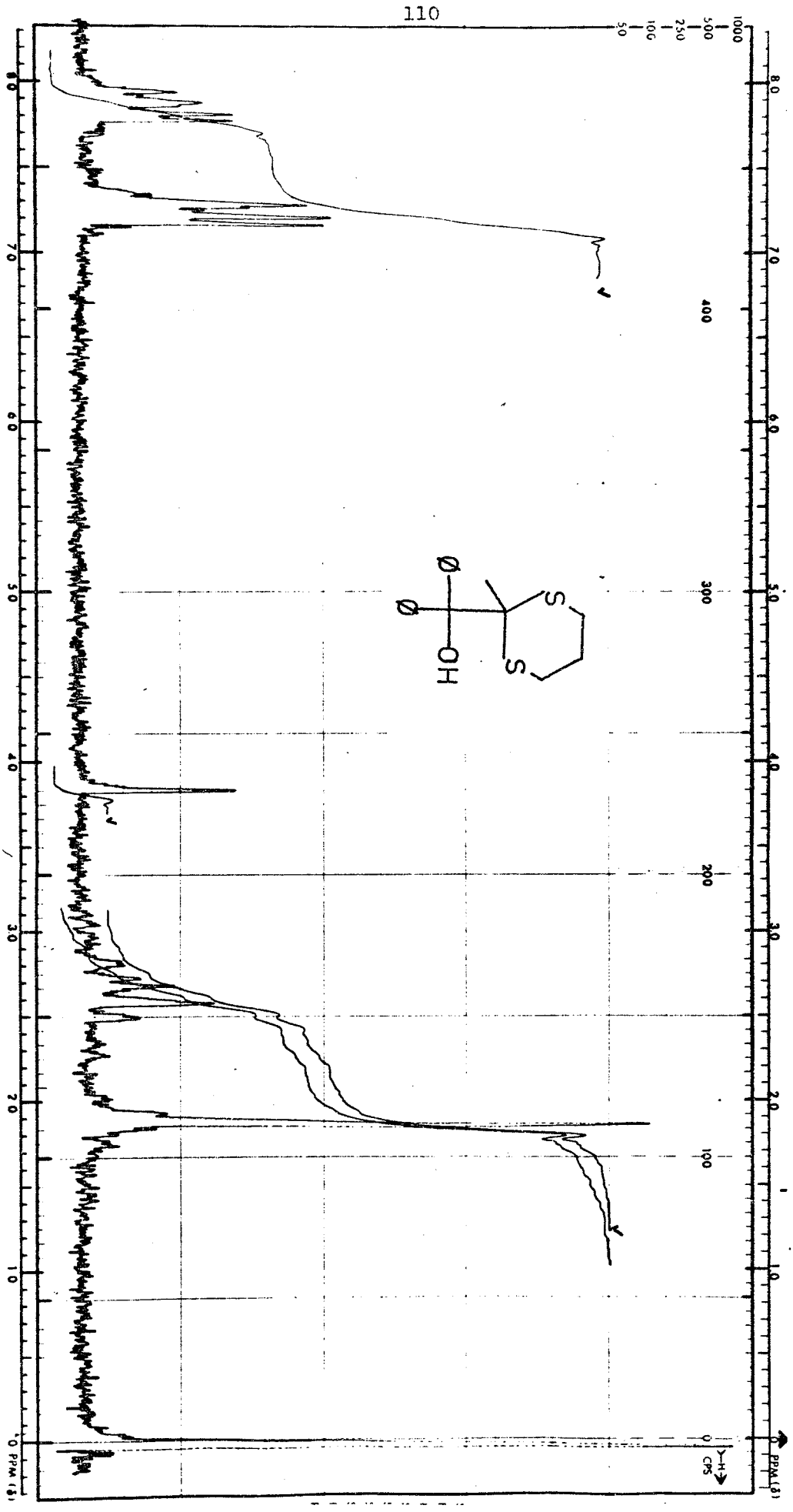
NMR-XV 1,3-dithiane: 1000Hz sweep, CCl_4



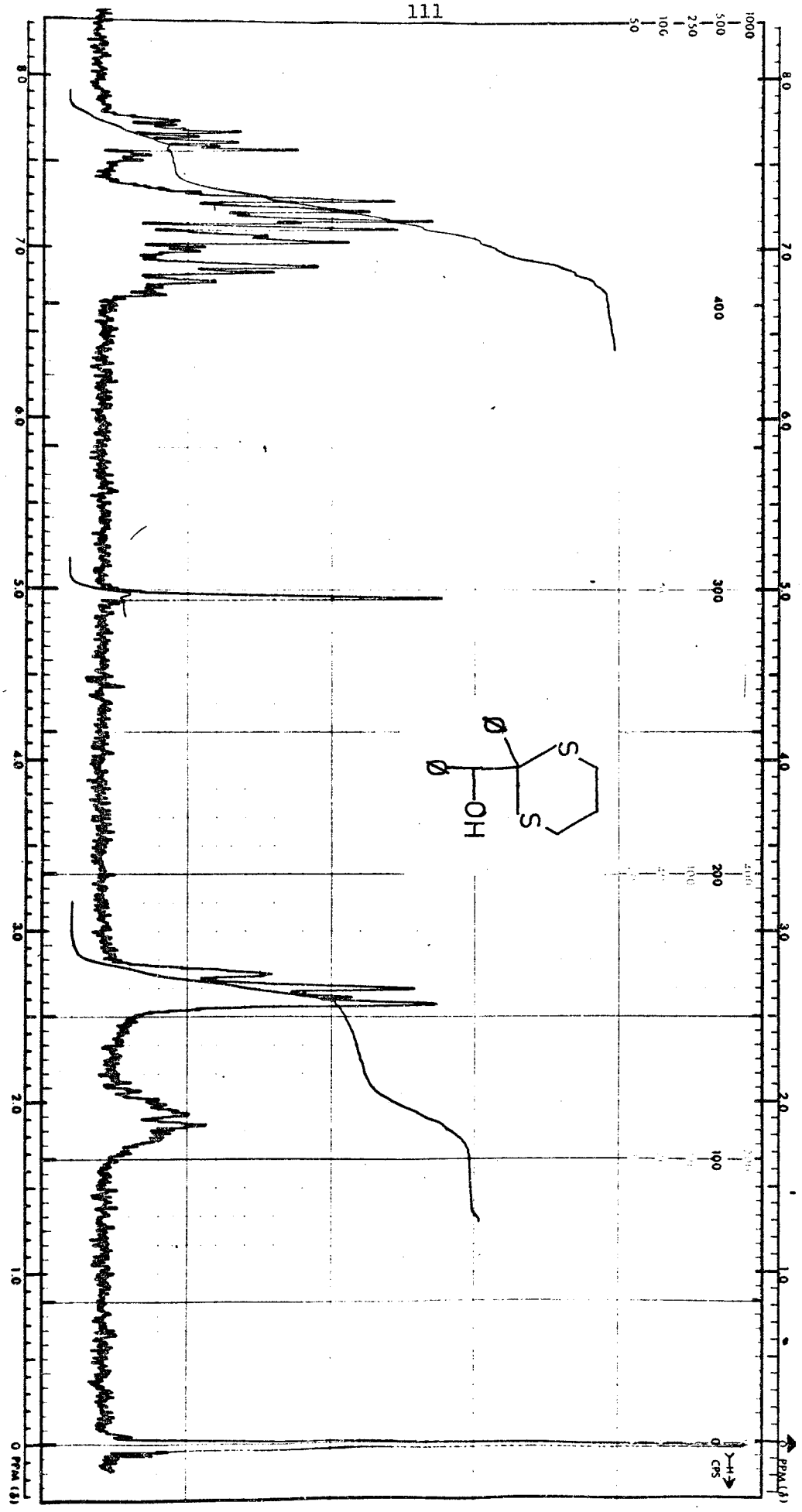
NMR-XVI 2-hydroxy-2,2-diphenylacetaldehydethioacetal XXXIVa: 1000Hz sweep, CCl_4



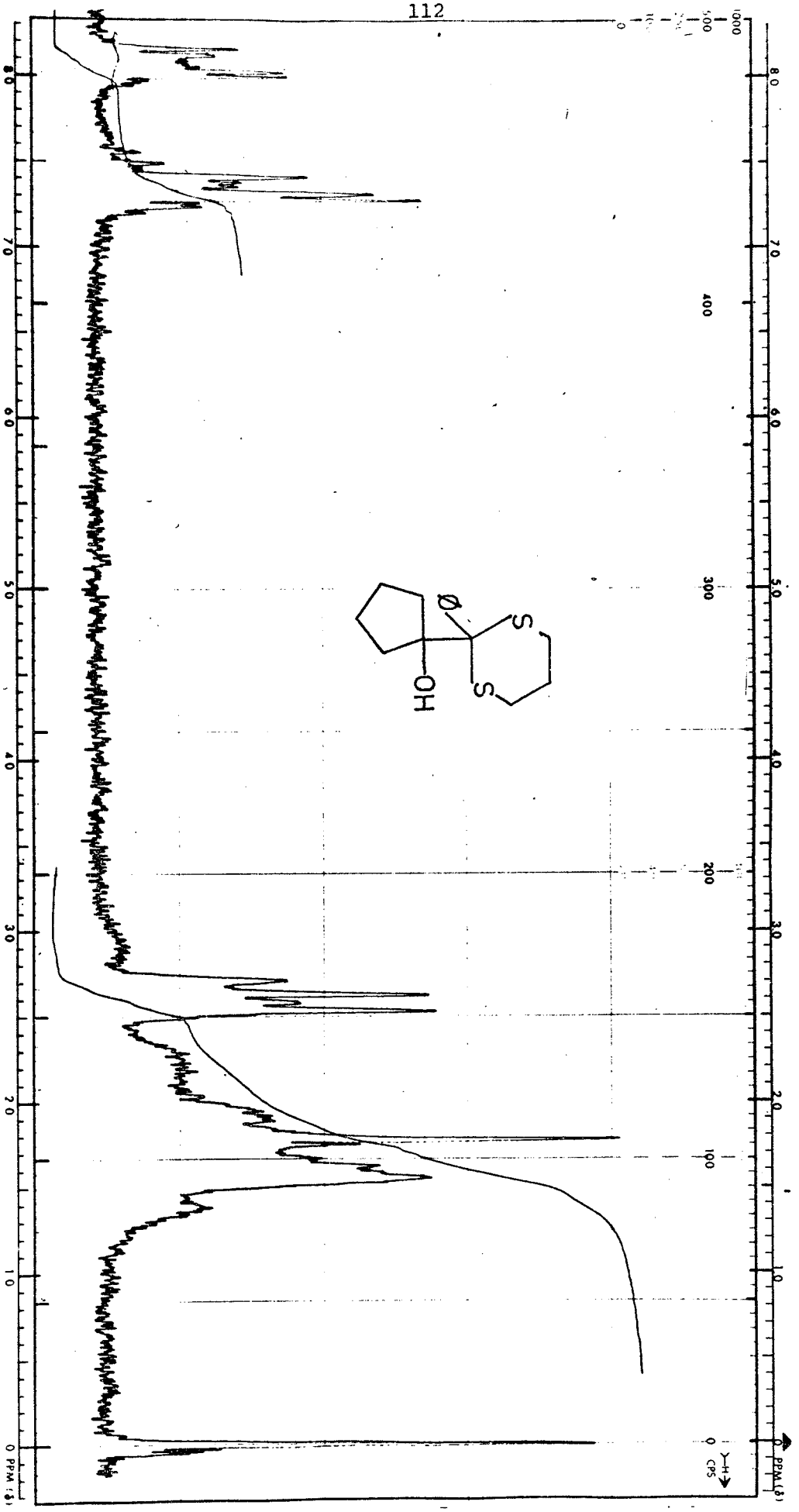
NMR-XVII methyl-1'-hydroxycyclohexyketonethioketal XXXIVb: 1000Hz sweep, CCl_4



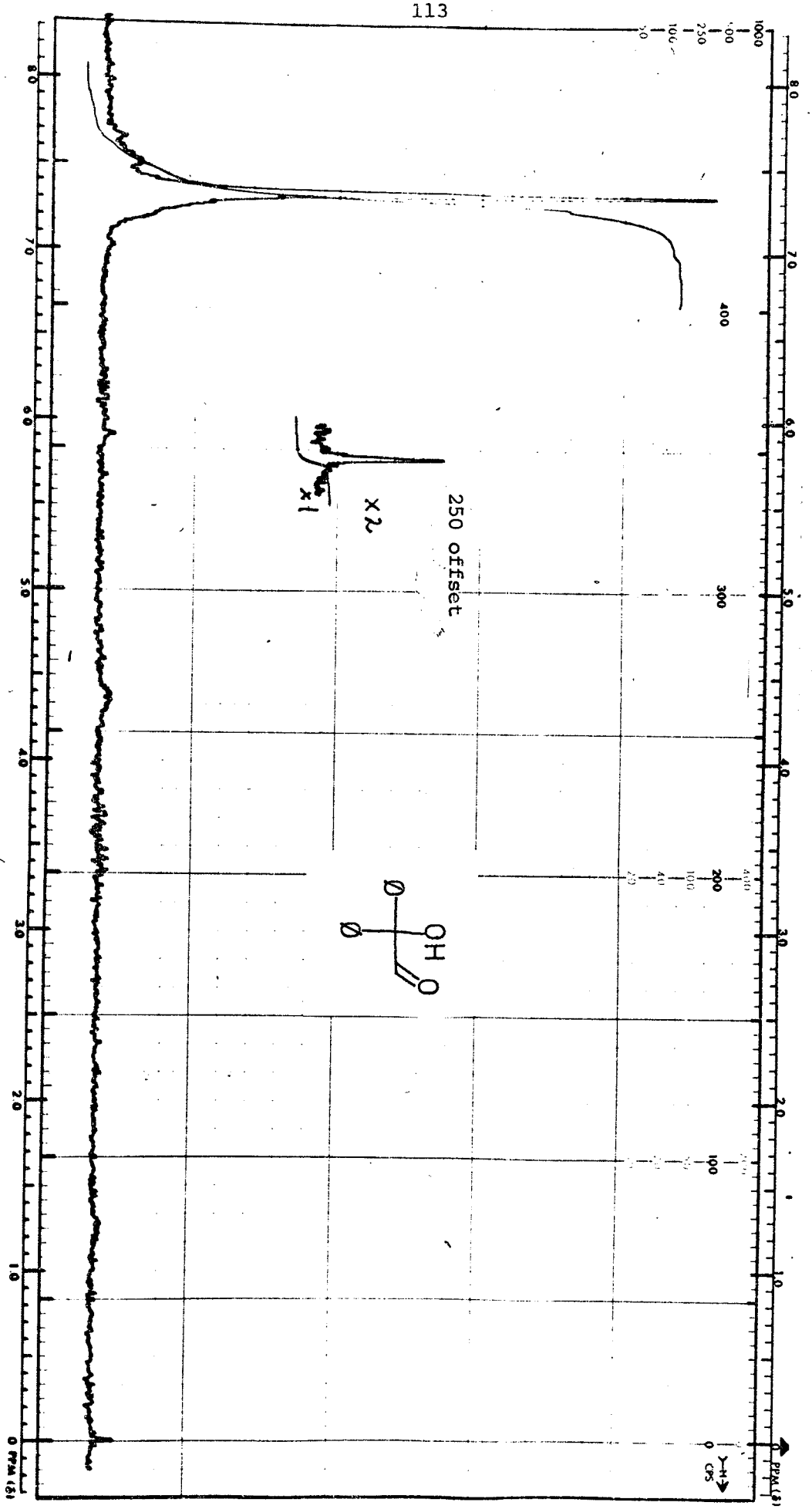
NMR-XVIII 1-hydroxy-1,1-diphenylacetonethioketal XXXIVd: 1000Hz sweep, CCl_4



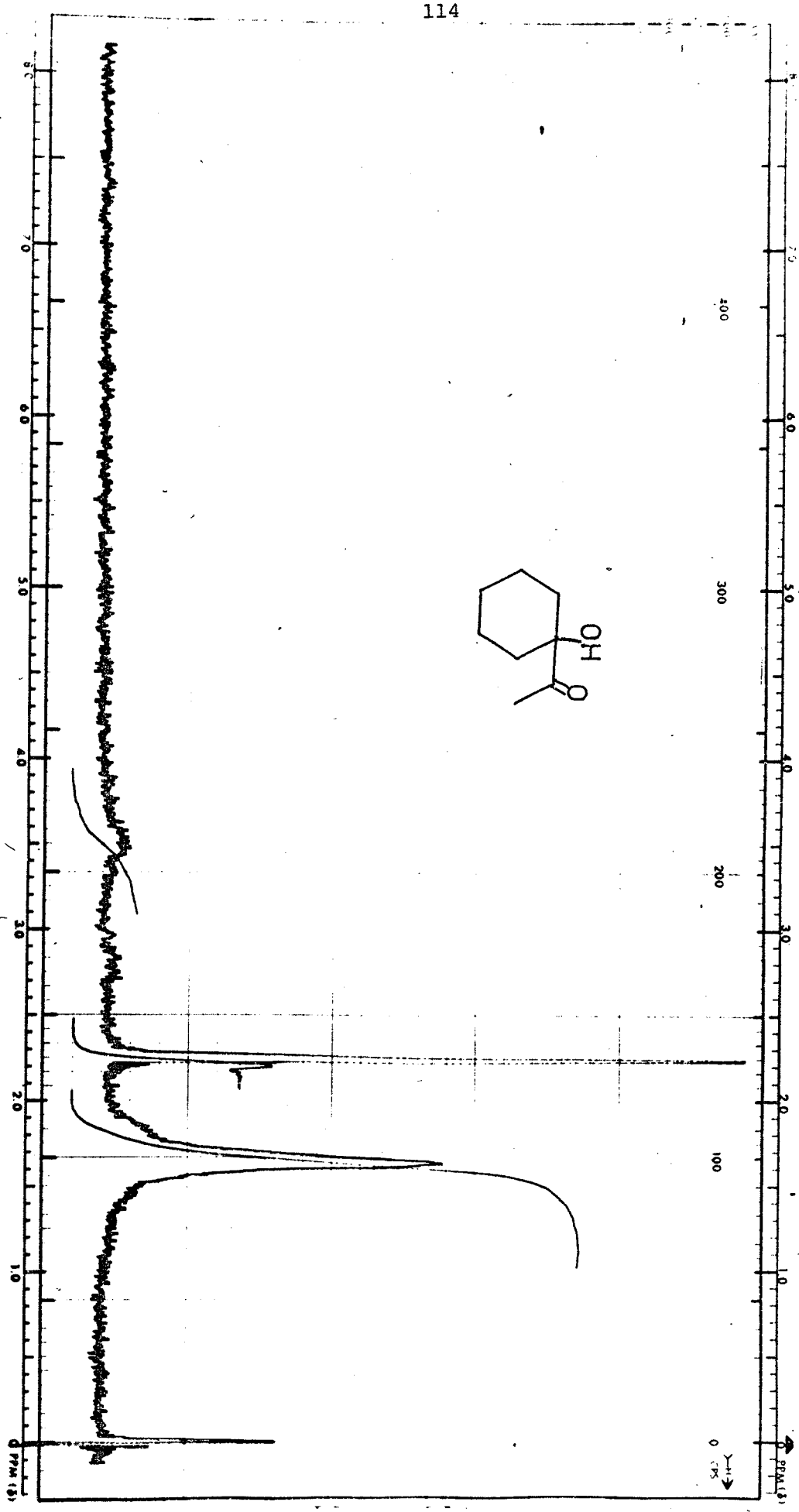
NMR-XIX benzointhioketal XXXIVc: 1000Hz sweep, CCl_4



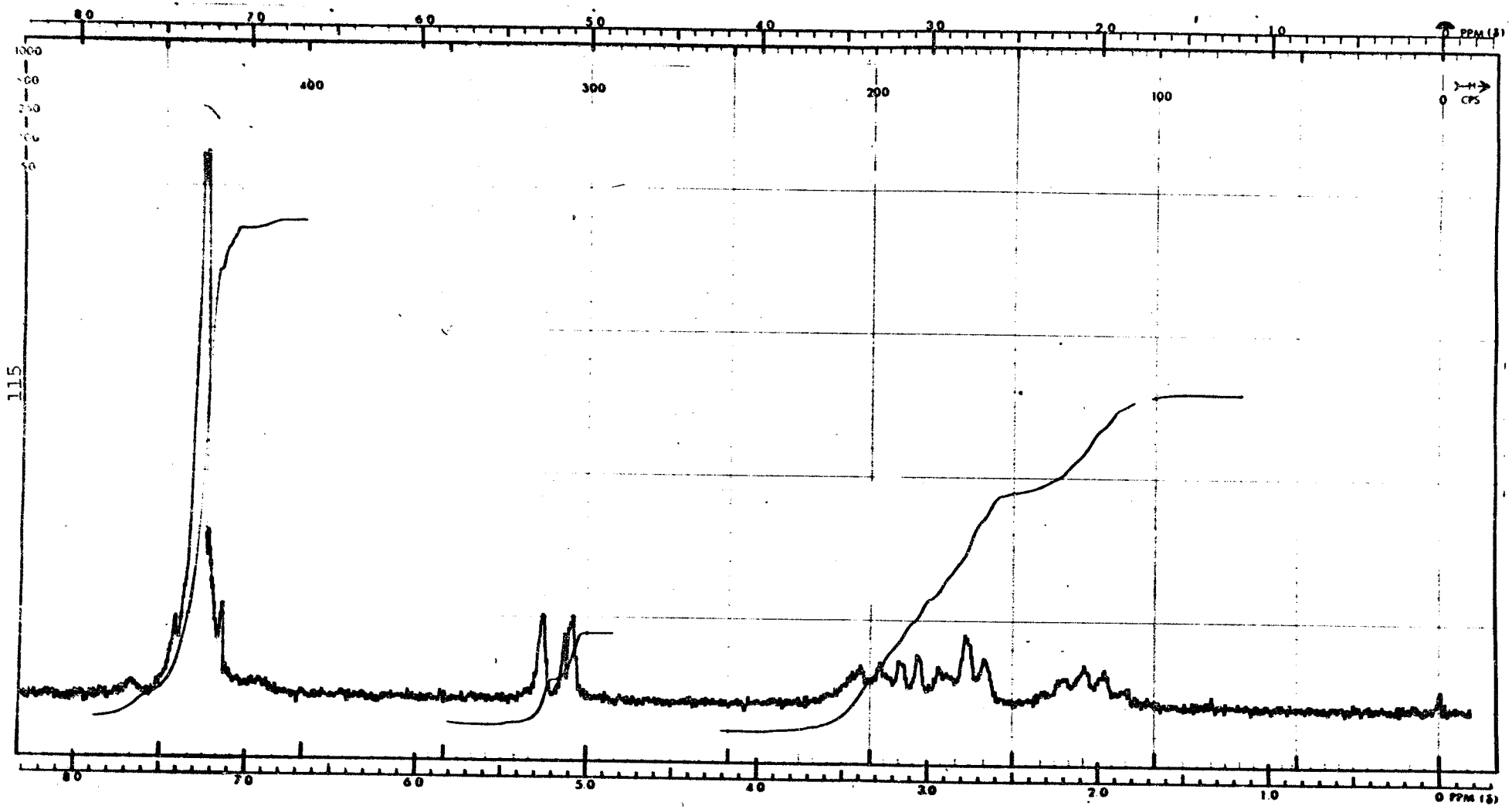
NMR-XX phenyl-1'-hydroxycyclopentylketonethioketal XXXIVe: 1000Hz sweep, CCl_4



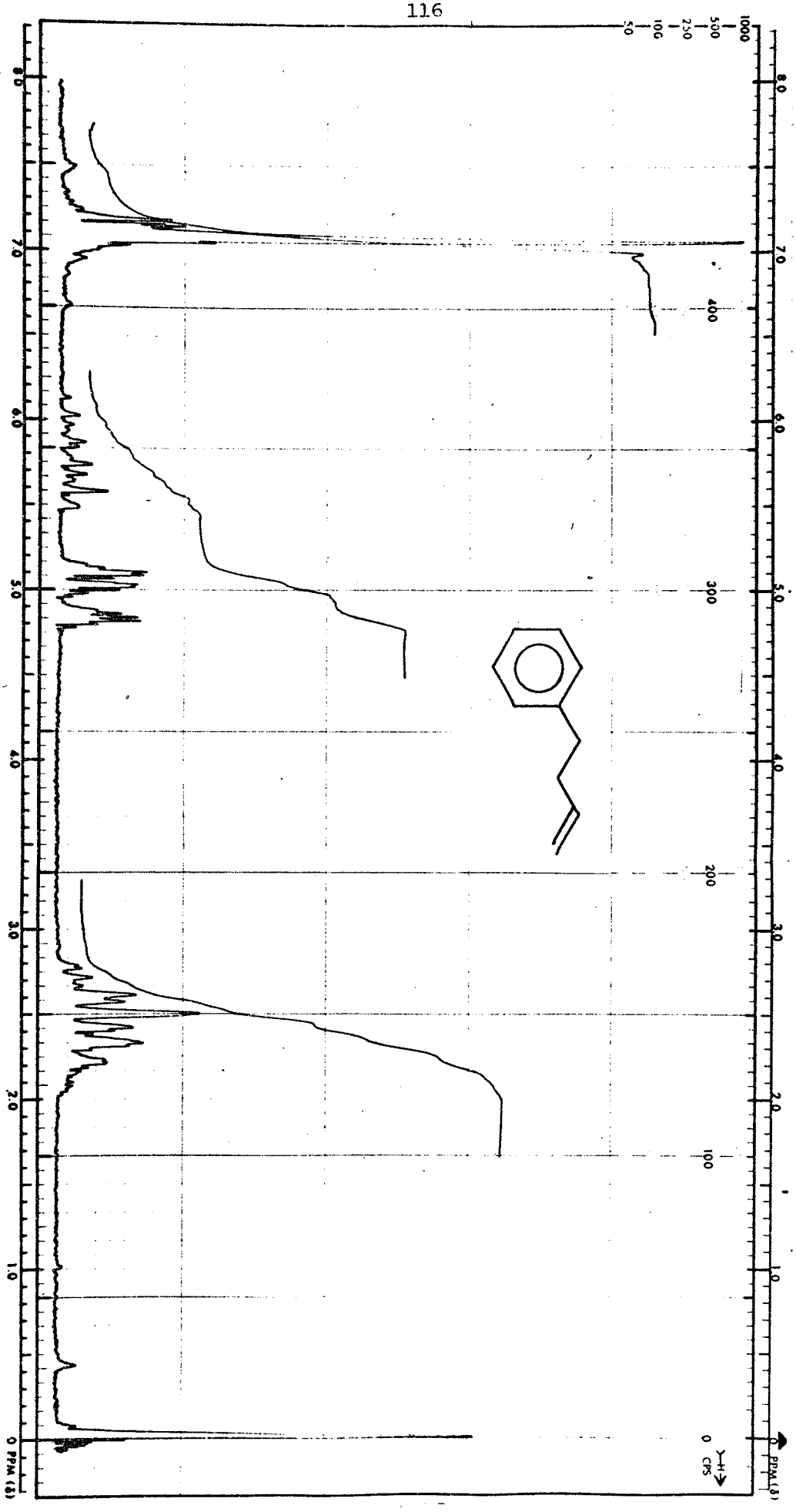
NMR-XXI 2-hydroxy-2,2-diphenylacetaldehyde XXXVa; 1000hz sweep, CCl_4



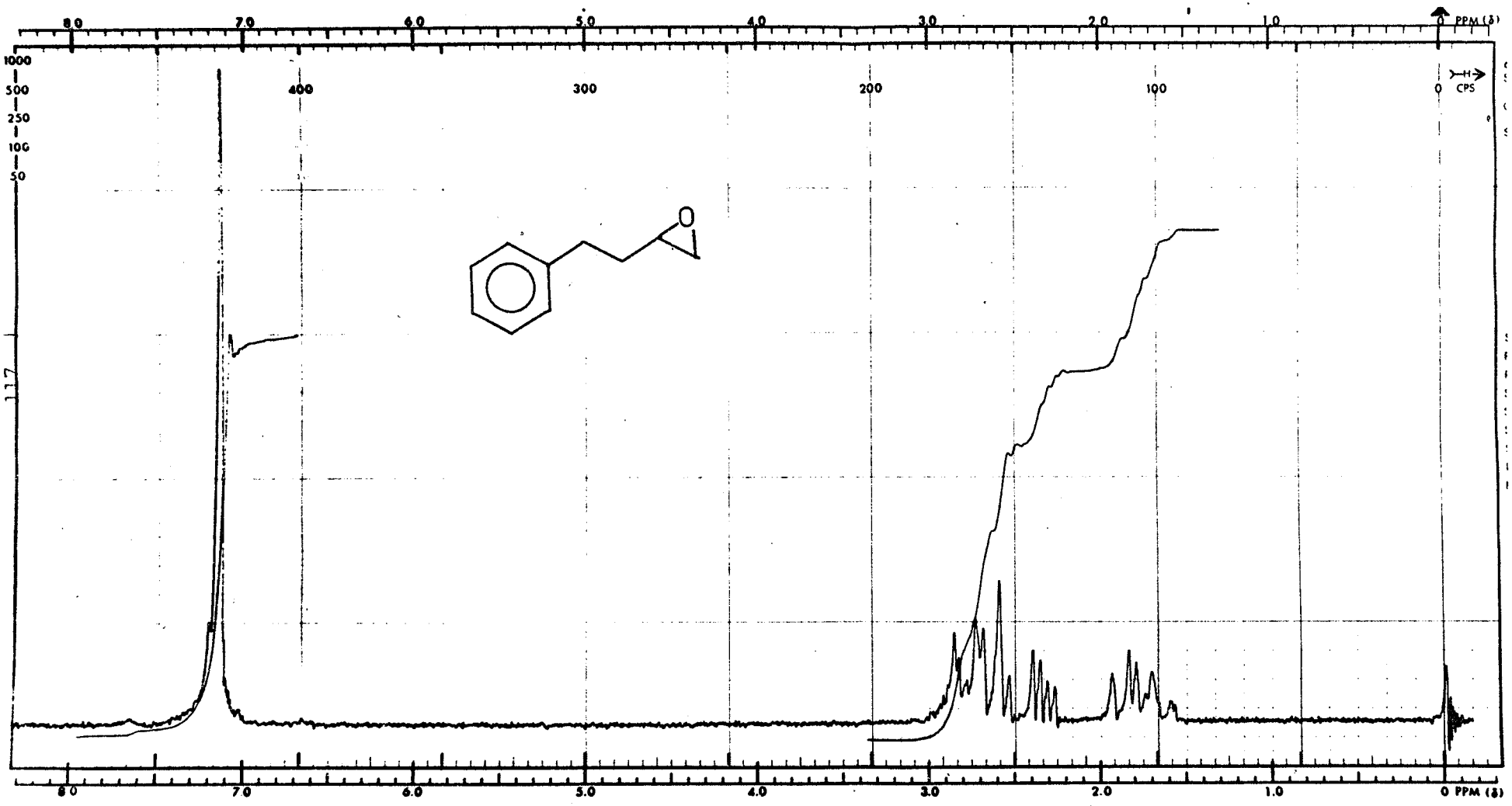
NMR-XXII methyl-1'-hydroxycyclohexylketone XXXVb: 1000Hz sweep, CCl_4



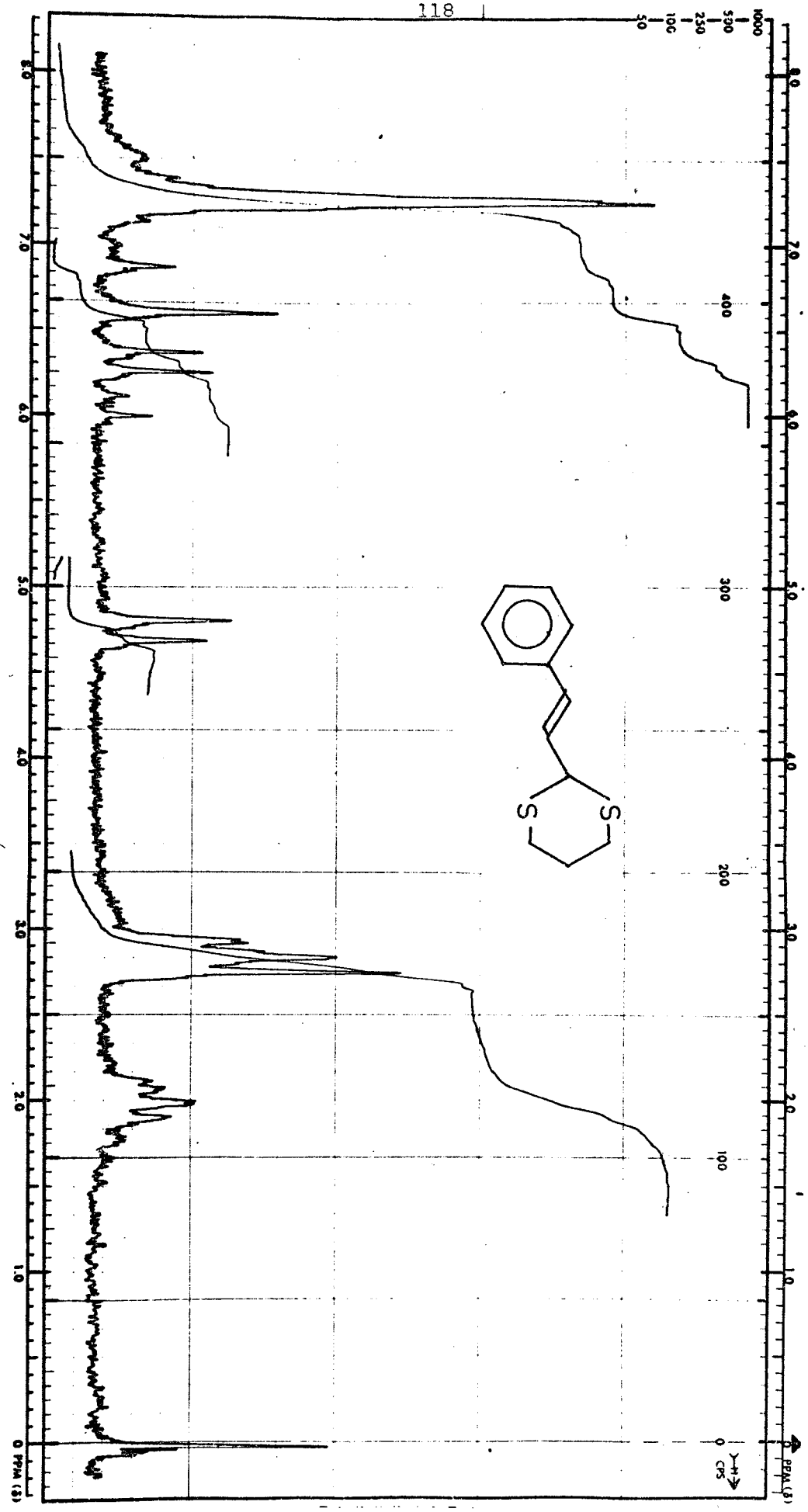
NMR-XXIV hydrolysis product from 1-hydroxy-1,1-diphenylacetonethioketal XXXIVd: 1000Hz sweep, $CDCl_3$



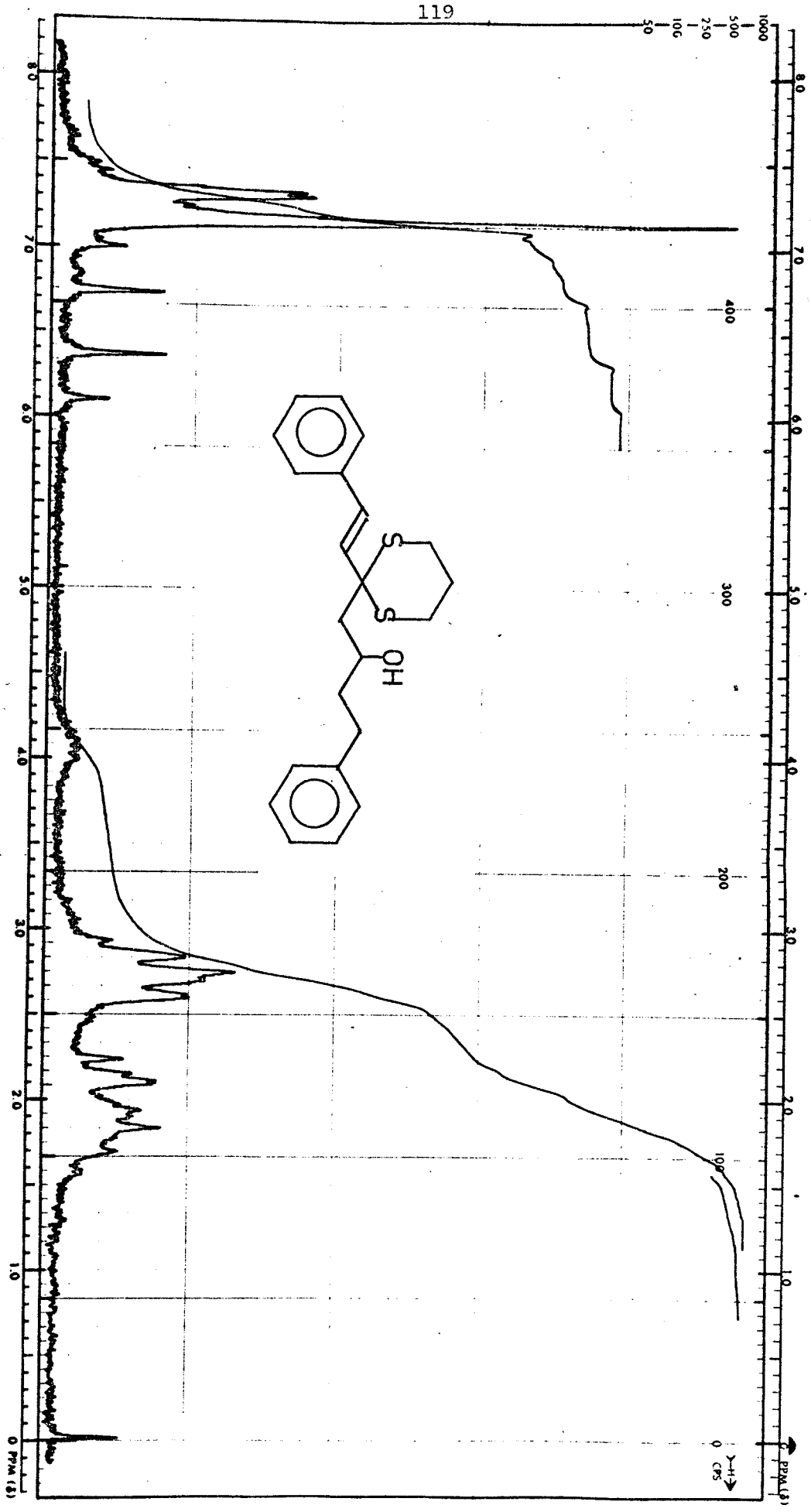
NMR-XXV 4-phenyl-1-butene XXXVIII: 1000Hz sweep, CCl_4



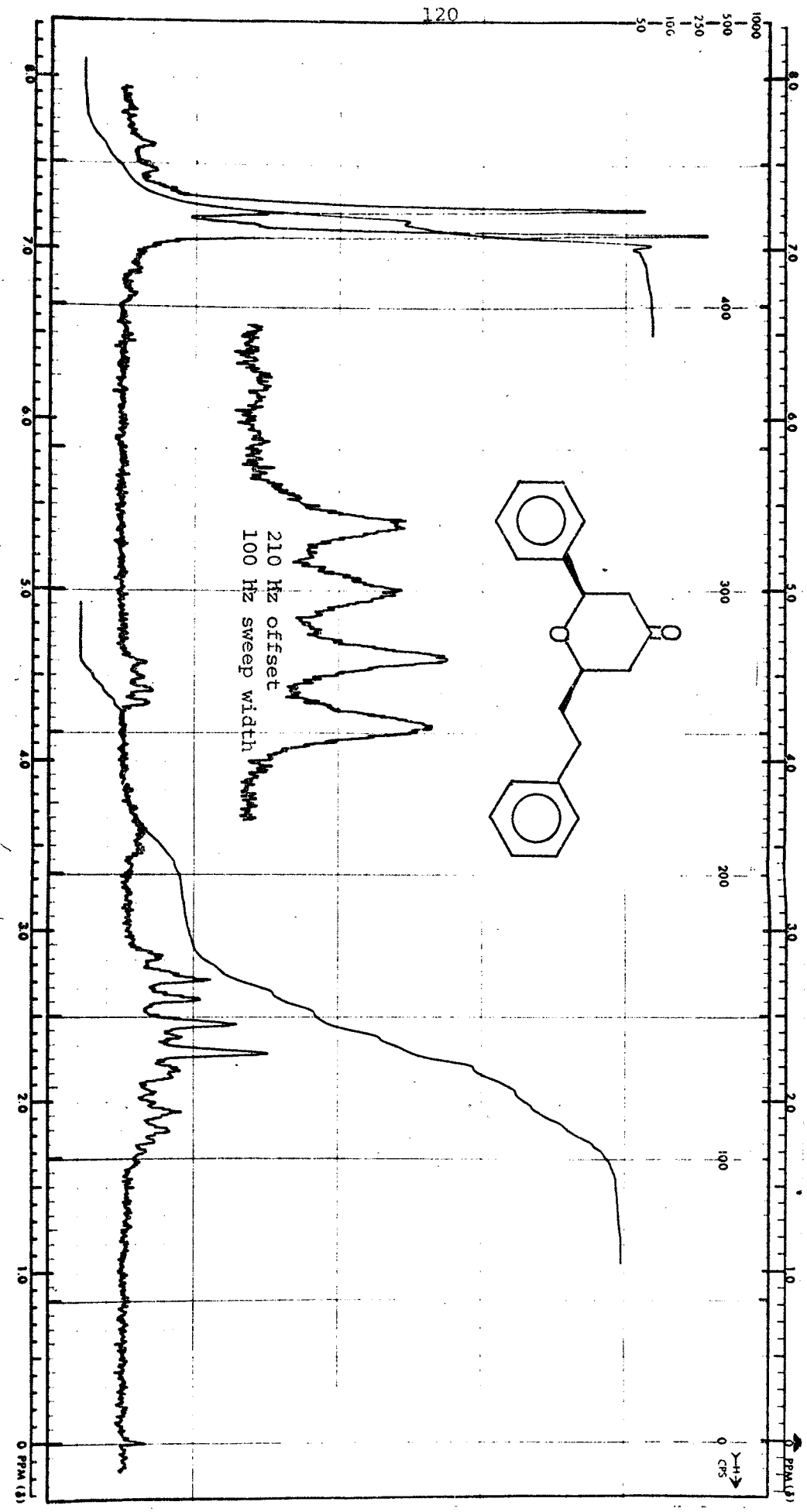
NMR-XXVI 1,2-epoxy-4-phenylbutane XXXIX: 1000Hz sweep, CCl_4



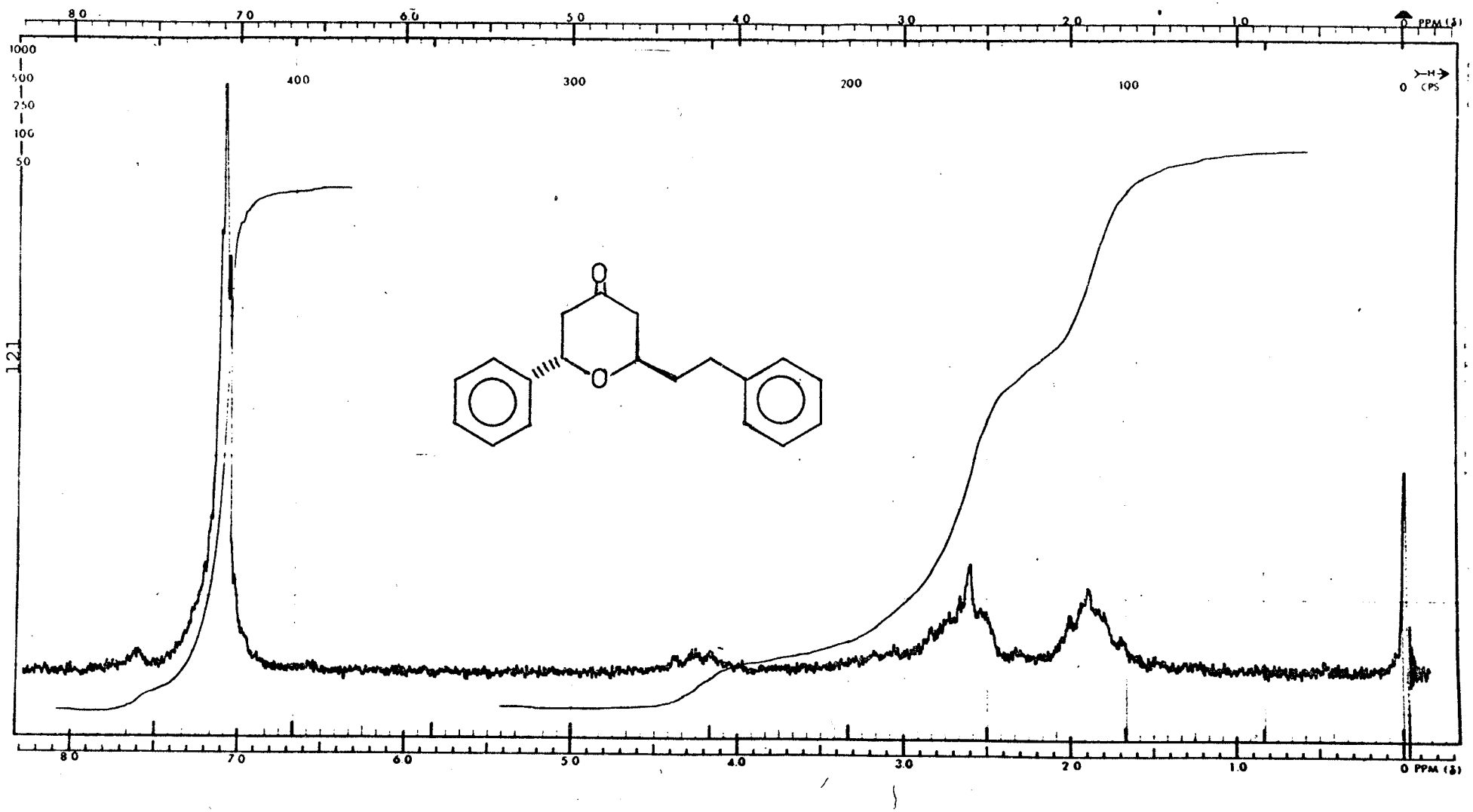
NMR-XXVII cinnamaldehydethioacetal XLI; 1000Hz sweep, CCl_4



NMR-XXVIII racemic yashabushiketonethioketal XLIII: 1000Hz sweep, $CDCl_3$



NMR-XXIX cis-2-phenyl-6-(2'phenylethyl) tetrahydro-4-pyranone XLVIIc: 1000Hz sweep, $CDCl_3$



NMR-XXX trans-2-phenyl-6-(2'-phenylethyl) tetrahydro-4-pyranone XLVIIt: 1000Hz sweep, $CDCl_3$

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