A Study of Claisen Rearrangement on Anthraquinone Systems

B Synthetic Studies of Precursors to Daunosamine and 4-Deoxydaunosamine

by

Ranjit Singh

A thesis submitted to the
Faculty of Graduate Studies and Research
of the University of Manitoba
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for the degree
Master of Science

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ABSTRACT

Part A

The Claisen rearrangement on anthraquinone systems was studied by the pyrolysis of the allyl ethers of 1-hydroxy anthraquinone (IX), 2-hydroxy anthraquinone (XVIII), 1,2-dihydroxy anthraquinone (XIX), 1,4-dihydroxy anthraquinone (XIV), and 2,6-dihydroxy anthraquinone (XXI) in o-xylene. The main products of the rearrangement were isolated and identified. The presence of a catalytic amount of benzylamine showed a positive and a superior catalytic effect in the course of the rearrangement. Some interesting observations were made with respect to the position of the O-allyl group on the ring(s) as a rearranging group or as a substituent. In 1-allyl and 1,4-diallyl anthraquinone ethers the O-allyl group rearranged taking a normal course for the rearrangement while it remained stable in 2-allyl and 2,6-diallyl anthraquinone ethers under our usual condition of pyrolysis and gave a mixture of unidentified products when subjected to prolonged heating at higher temperatures. In 1,2-diallyl anthraquinone ether the O-allyl group on C-2 was lost while the O-allyl group on C-1 showed ortho rearrangement. In case of 1,4-diallyl anthraquinone ether, 2-propenyl quinizarin (XVII) and 2,3-diallyl quinizarin (XVIa) were isolated as the final products while the partially rearranged ether (XV) was isolated as an intermediate product.

In general, the hydrolysis of the O-allyl group was observed as a side reaction in rearranging systems during pyrolysis.

The observations can be explained postulating varying electronic interactions between the O-allyl group and the rings.

PART B

Methylvinyl-carbinol was condensed with chloroacetyl chloride to give sec-butenyl chloroacetate (XXXII) which was further condensed with the sodium salt of diethyl malonate to give α-methylene sec-butenyloxycarbonyldiethyl malonate (XXXIII). Ozonolysis of XXXIII afforded α-methylene 1-formyl-ethoxydiethyl malonate (XXXIV) which did not cyclize to 4,4-diethoxy-5-hydroxy-6-methyl-2-pyranone (XXXV). The catalytic hydrogenation of the aldehyde XXXIV gave α-methylenehydroxy-isopropyloxycarbonyldiethyl malonate (XXXVI). The alcohol XXXVI was reacted with thionyl chloride to give α-methylene-chloroisopropyloxycarbonyldiethyl malonate (XXXVII) which again did not cyclize to 4,4-diethoxy-6-methyl-2-pyranone (XXXVIII).

2,3-Dichloro-1-propene was condensed with the sodium salt of diethyl malonate (XXXIX) to give α-(2-chloro-1-propenyl)diethyl malonate (XL). The sodium salt of XL was condensed with bromo ethylacetate to give α-ethoxycarbonyl-α-(2-chloro-1-propenyl)diethyl succinate (XLI) which on hydrolysis did not yield the lactones XLII and XLIII but a mixture of keto acids.

2,3-Dichloro-1-propene was condensed with the sodium

salt of diethyl malonate to give α,α-di(2-chloro-1-propenyl)-diethyl malonate (XLIV) which on acid hydrolysis afforded 3-methylcyclohex-2-ene-1-one-5-carboxylic acid (XLV). The methyl ester XLVIII of the acid XLV on oxidative cleavage of the double bond with potassium permanganate/sodium meta-periodate gave 2-carbomethoxy-4-keto pentanoic acid (LI). The keto acid LI has the potential for exploitation to give 4-deoxydaunosamine (LVII).

TABLE OF CONTENTS

TABLE OF CONTENTS (continued)

LIST OF FIGURES

LIST OF FIGURES (continued)

LIST OF FIGURES (continued)

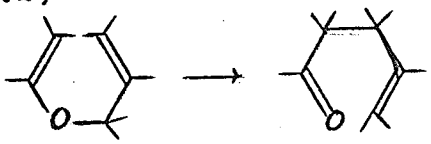
LIST OF FIGURES (continued)

PART A

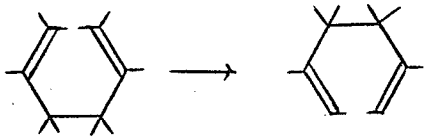
INTRODUCTION

A thermally induced rearrangement of a vinyl-allyl ether I to the corresponding homoallylic carbonyl compound II (Eq.1) was first observed by Claisen in 1912[1]. Since then, the rearrangements of vinyl and aryl allylic ethers have been extensively studied and exploited for their synthetic value.

The Claisen rearrangement is classified as an example of a (3,3) sigmatropic migration[2,3]. In aromatic systems (Scheme 1) (3,3) sigmatropic migrations encompass ortho as well as para Claisen rearrangements of which the latter is a combination of Claisen and Cope rearrangements operating in succession. (The Cope rearrangement[4] is a carbon analog of the Claisen rearrangement Eq.2)



I II (Eq. 1)

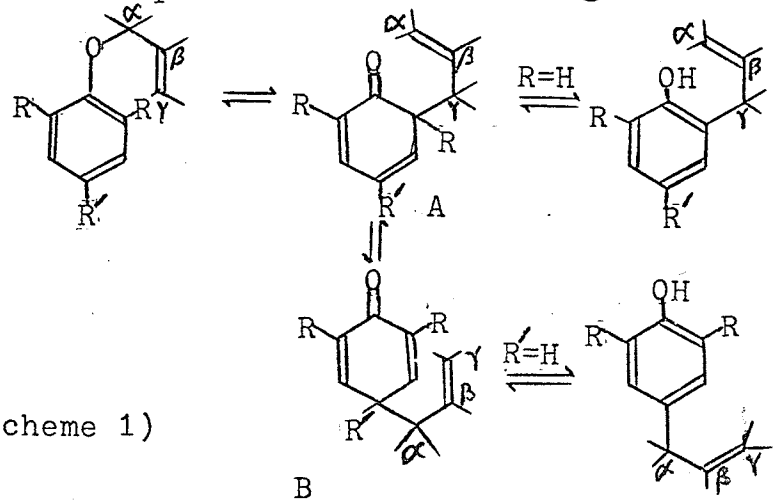


(Eq. 2)

Although the overall mechanistic picture of the Claisen rearrangement as a cyclic process involving simultaneous bond-making and -breaking processes accompanied by relocation of the unsaturated bonds was specifically described by Claisen as early as 1925[5], a detailed understanding of these reactions has developed only since about 1950. Experimentally, the problems posed by the"no-mechanism" nature of the Claisen rearrangements has been attacked using

labeling techniques, stereochemical probes, kinetic analysis, inter- and intra-molecular "crossing" experiments, and in the aromatic Claisen rearrangements, by the detection and direct study of the dienone intermediates[6-19]. Theoretical interpretations of the rearrangements based on a variety of molecular orbital approaches have been advanced[20-24], and calculations of activation parameters and transition-state geometries for some examples of the Cope rearrangement have been carried out[25-27].

The normal course of Claisen and Cope rearrangements can be illustrated with the examples from the aromatic categories (Scheme 1). In an allyl aryl ether, the first cyclic rearrangement occurs with bonding of the γ-carbon atom of the allylic portion at the ortho carbon atom of the ring to generate an orthodienone, A, in which the migrating allyl group has undergone a structural inversion. If the ortho substituent, R, is hydrogen, rapid enolization may occur at that stage, leading to an ortho allyl phenol (ortho rearrangement). Alternatively, realignment of the ortho allyl group may take place, positioning the terminal unsaturated bond opposite the para carbon of the ring.

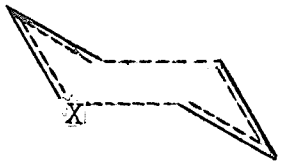


(Scheme 1)

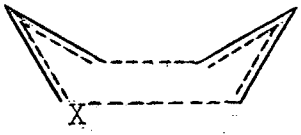
A second cyclic reorganization (now a Cope rearrangement) leads to the paradienone, B. Once more, inversion of structure in the migrating group occurs so that the original structure of the allyl side chain is restored. When the para substituent, R′, is hydrogen, rapid enolization follows with the formation of a para-substituted phenol (para rearrangement). The ortho rearrangement, then, is accomplished by a Claisen rearrangement of an allyl aryl ether, whereas the para rearrangement is, as said before, a sequence of two rearrangements, a Claisen and a Cope. The invariable structural inversion in the ortho rearrangement and structural retention in the para rearrangement have been amply verified as have the strict intramolecularity of the rearrangements, the intervention of the dienone intermediates, and the complete reversibility of the processes when the final enolization step is prohibited[10,18].

Kinetic studies show the rearrangements of both aromatic[18,28-33] and aliphatic[18,34-50] systems to be unimolecular processes with activation enthalpies, entropies, and volumes in harmony with a concerted cyclic process having a highly ordered transition-state geometry.

For suprafacial-suprafacial (3,3) sigmatropic processes exemplified by the vast majority of Claisen and Cope rearrangements, two possible geometries have been considered for the cyclic transition state, the four-centered or chairlike, C, and the six-centered or boatlike arrangement, D. For molecules which can readily adopt either arrangement, the chairlike geometry, C, is strongly favoured. Moreover,



C



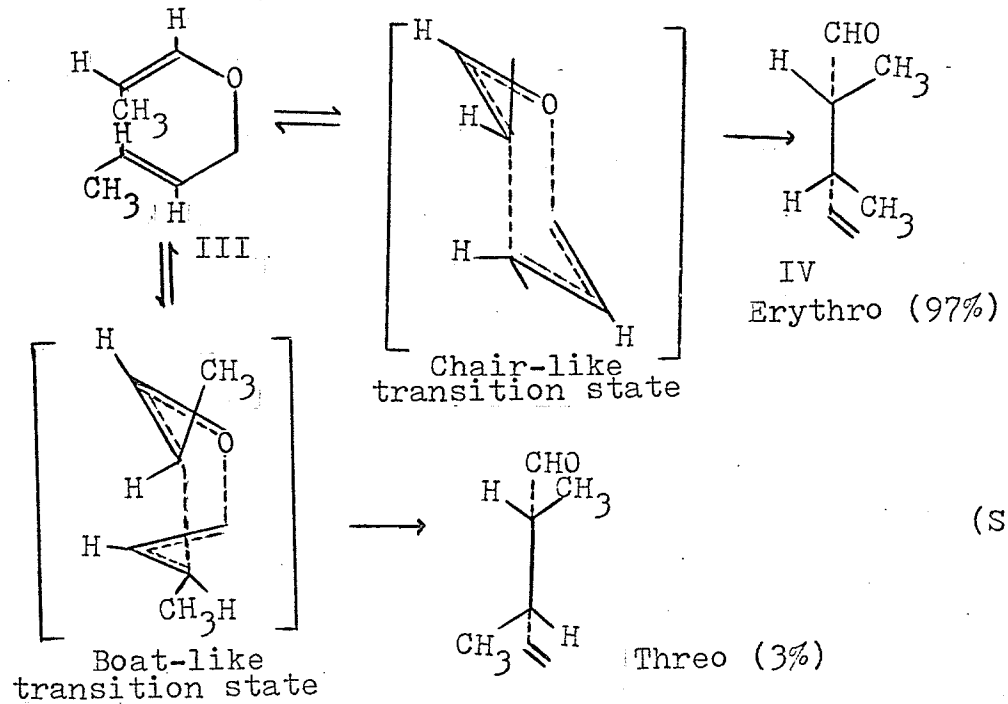
D

X = O or -C-

of two alternative chairlike arrangements, that one which minimizes 1,3-pseudo-diaxial interactions is preferred*.

* Ref. 8-10,17,18,51.

It has been illustrated by the stereoselectivity shown in the aliphatic Claisen rearrangement of the isomeric crotyl propenyl ethers[51]. The rearrangement of the trans, cis ether III, for example, proceeds through a chairlike transition state to produce the erythro isomer IV with a free energy of activation advantage of about 3 kcal/mole over that of the boat-like transition state (Scheme 2).



(Scheme 2)

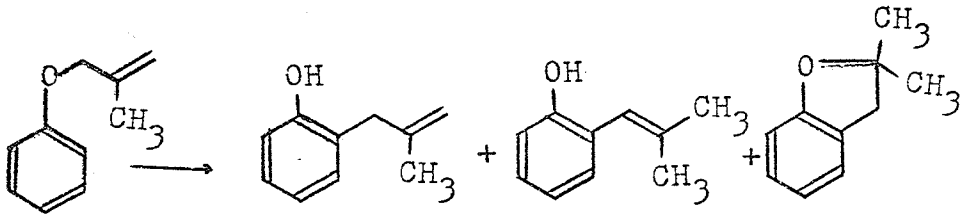
Some of the general observations made in the aromatic Claisen rearrangements will be summerized in the following paragraphs that can be compared and contrasted with our own observations made on anthraquinone systems.

It has been observed that the rearrangements of allyl aryl ethers are often accompanied by competitive ortho and para migrations[52-55], the occurrence of abnormal rearrangements leading to structural[1,6,10] and geometric[56,57,58] isomerization in the migrating group, double-bond shifts and coumaran formation[1], out-of-ring migrations[1], and occasionally, the formation of stable dienones[59] and the incursion of retro-Claisen rearrangements[60]. To some extent, these processes can be controlled by a proper choice of solvent and rearrangement conditions.

Detailed examinations of systems in which both ortho and para positions are open have shown that rearrangements to these positions can be competitive[52-55] and that mixed products are formed much more commonly than had been appreciated in earlier investigations[1]. It has been demonstrated that the ortho/para ratio is conditioned by the bulk of the substituents in the migrating allyl group[52-55], the number, size and location of the other ring substituents[52], and the solvent[52-55].

The abnormal rearrangement leading to structural[1,6,10] and geometric[56-58] isomerization in the migrating allyl group is commonly observed to accompany the ortho rearrangement of ethers bearing γ-alkyl substituents on the allyl group.

Accompanying both normal and abnormal products in the ortho rearrangement, isomeric propenyl phenols and coumarans resulting from ring closure have been observed as by-products arising from the initially formed ortho-allylic phenols[1]. The extent of these secondary reactions have been found to depend on the experimental conditions employed and the nature of the solvent. In the analysis of the products of β-methylallyl phenyl ether (VI) it has been demonstrated that the formation of coumaran VII is promoted by phenols and primary aromatic amines[61], whereas isomerization of the double bond into conjugation with the aromatic ring is specially facilitated by primary aromatic amines. Tertiary aromatic amines, on the other hand minimize these secondary reactions.

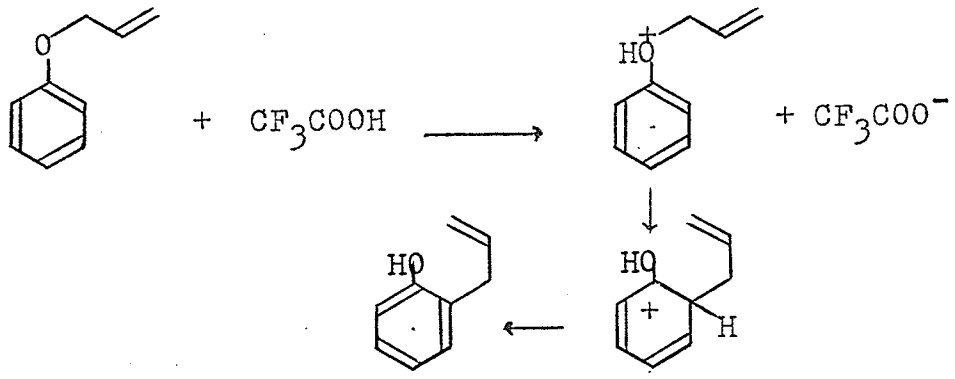


VI VII

The electronic nature of ring substituents has been found to have only minor effects on the ease of rearrangement of allyl aryl ethers[18], and no discernible pattern has been derived that suggests a consistent directive influence on the part of a given substituent.

It has also been demonstrated that rearrangements to the ortho and para positions are reversible processes and a prolonged heating ultimately leads to a thermodynamically controlled reaction mixture[52].

The effect of polarity of the solvent on the rates of some ortho-Claisen rearrangements has been examined in several studies[62-64]. With the exception of hydroxylic and phenolic media, the rate enhancement with increasing polarity has been found to be modest. Such results accord with the low polarity of the transition state in these concerted intramolecular processes. However, the rate accelaration observed for the rearrangement of allyl p-tollyl ether on changing the solvent from a non polar hydrocarbon to an aqueous alcoholic or -phenolic system is quite appreciable, ranging from 35- to 100-fold[62]. This effect is the manifestation of a super imposed acid catalysed process induced by the hydrogen bonding capacity of the hydroxylic solvent and the basic nature of the ether-oxygen. It has been further substantiated by acid catalysed rearrangement of allyl-aryl ethers in trifluoroacetic acid[65] where the kinetic data led to the conclusion that the mechanism of the rearrangement involves a highly polar transition state (Scheme 3).



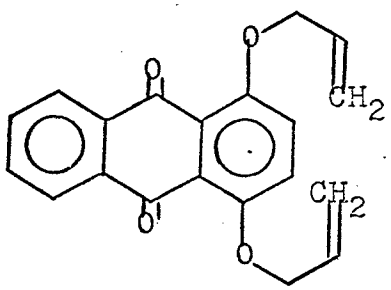
(Scheme 3)

The base catalysed rearrangement of monoallyl ether of catechol involves successive sigmatropic rearrangements to give products that differ from those obtained by

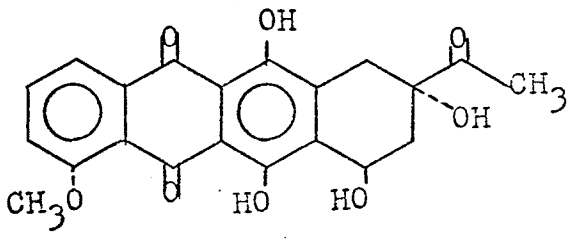
sigmatropic rearrangements under normal Claisen condition[66]. The involvement of phenolate anion has been observed in the mechanism of these rearrangements.

The use of transition metal catalysts has been reported on Cope and Claisen rearrangements[67,68]. In one of the recent investigations the catalytic effect of $TiCl_4$ on the Claisen rearrangement of allyl-aryl ethers has been demonstrated[69].

The Claisen rearrangement on 1,4-dihydroxy anthraquinone system drew interest in this laboratory due, mainly, to its synthetic value that could lead to the tetracyclic skeleton of an antibiotic Daunomycinone (XXVI). Since, the desired tetracyclic system requires several steps of synthesis, the Claisen rearrangement of diallyl quinizarin (XIV) was thought to be an easy route to ring expansion for the synthesis of Daunomycinone (XXVI). Although certain limitations were placed on this synthetic approach, nevertheless, the study of the Claisen rearrangement on quinizarin prompted further investigations on similar systems which led to this series of studies.



XIV

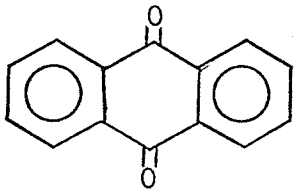


XXVI

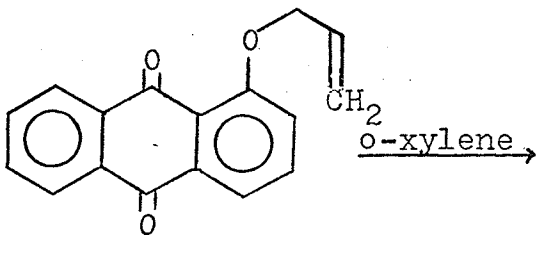
RESULTS AND DISCUSSION

The following ethers were pyrolysed in o-xylene with and without a catalytic amount of benzylamine. Wherever necessary, the progress of a reaction was monitored by t.l.c.

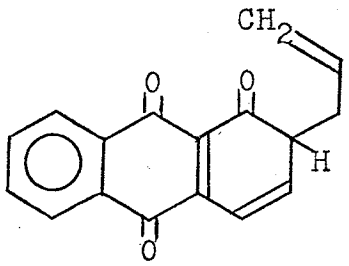
The pyrolysis of 1-allyl anthraquinone ether (IX): The reaction mixture containing benzylamine showed a rapid disappearance of the starting material and appearance of two new compounds on the t.l.c. microplates. After the complete disappearance of the starting material from the catalysed reaction mixture (between 2 and 3 hours) the components of the reaction product were separated by t.l.c. The major band (higher R_f value) was eluted to give an orange-yellow powder which was spectroscopically identified as 2-allyl,1-hydroxy anthraquinone (Xa) (Scheme 4). The infra red (i.r.) spectrum (Fig. II) showed a free and a hydrogen-bonded (chelated) carbonyl absorption of the quinone at 1670 and 1635 $cm.^{-1}$ respectively. The mass spectrum showed the molecular ion of 264. The n.m.r. spectrum (Fig. XXVIIIa) confirmed the migration of the allyl group from the oxygen to the ring. The doublet of triplets centered at $\delta = 4.10$ due to the methylene protons of the allyl group directly bonded to the oxygen in IX (n.m.r. Fig. XXVI) showed a large up-field chemical shift after the rearrangement and was relocated centered at $\delta = 3.50$ (with due consideration to the structural inversion in the migrating allyl group which leaves the methylene groups nearest to the ring indistinguishable). The up-field chemical shift of the rest of the protons in the relocated allyl group was also appreciable. A chelated phenolic proton was located

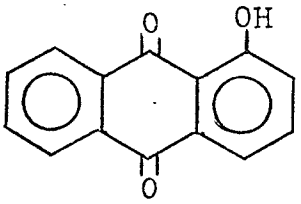


VIII

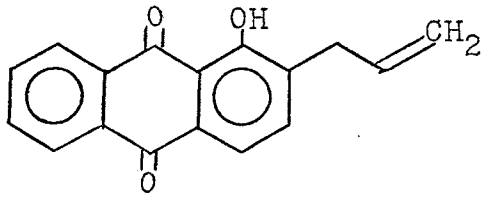


IX

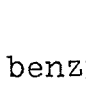


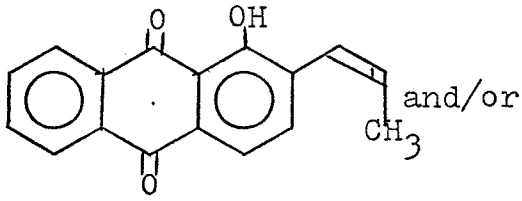


XIIIa

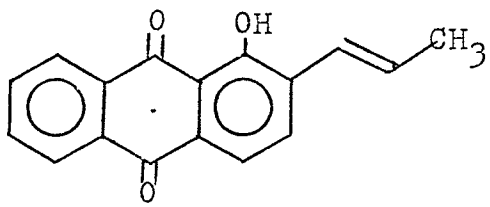


Xa





XIIa



XIa

(Scheme 4)

continued...

down-field at = 12.90.

Concerning the position of the migrated allyl group on the ring, a close scrutiny of the aromatic region in the n. m. r. spectra of several anthraquinone systems (Figs. XXVII, XXXa&b, XXXII, XXXIII, XXXV, XXXVI, XXXVII, XXXVIII and XXXIX) indicated consistently that a proton ortho to O-H, O-allyl or O-methyl groups could be singled out, specially if bonded to C-2 or its equivalent positions in anthraquinone, because of a relatively large up-field chemical shift of 0.06 to 0.08 ppm. depending on the number of oxy-functional group(s) on the ring. Normally, the protons of an unsubstituted abthraquinone (VIII) appear as two symmetrical multiplets centered at $\delta = 7.90$ and $\delta = 8.60$ each assigned to a group of four equivalent protons. The protons at C-1,4,5&8 are assigned down-field to the protons at C-2,3,6&7. The n.m.r. spectrum of the rearranged product (Fig. XXVIII) showed absence of any doublet between $\delta = 7.10$ and 7.40 with an ortho coupling of approximately 9Hz. (usually observed) and hence led to the conclusion that the migration of the allyl group was exclusively to the ortho position.

Usually, the double-bond migration in the side chain was not observed when the reaction mixture was refluxed over a minimum period for the complete disappearance of the starting material, but on one occasion when a catalysed

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Note: In the analysis of the n.m.r. spectra in this series of studies, the methylene doublet (or doublet of triplets) will refer to the protons of the methylene group either bonded to the oxygen or to the ring directly.

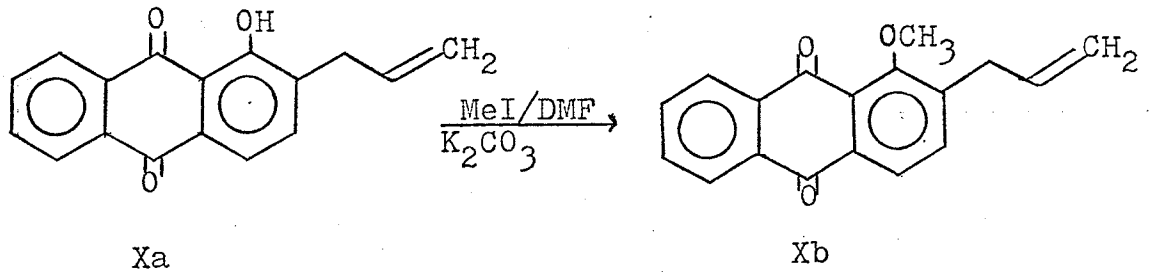
reaction mixture was left refluxing over night the rearranged product showed an extensive double-bond migration. The bond-isomers could not be separated by t.l.c. or recrystallization. However, the n.m.r. spectrum (Fig. XXIX) indicated the presence of a mixture of bond-isomers. The doublet at $\delta = 2$ could be assigned to the methyl protons in the side chain XI&XII coupled with the nearest proton and deshielded by the conjugated double bond, the splitting in the O-methyl peak at $\delta = 4$ could be attributed to the presence of two types of O-methyl groups in the mixture and the down-field peak may be assigned to the components with the double bond of the side chain conjugated with the ring system XI&XII. (The rearranged product was methylated to increase its solubility in $CDCl_3$ for n. m. r. spectrum determination.)

The minor band (lower R_f value) on elution gave a greenish-yellow power. The spectral data of the compound were identical to those of an authentic sample of 1-hydroxy anthraquinone Xa (Figs. III and XXXa)

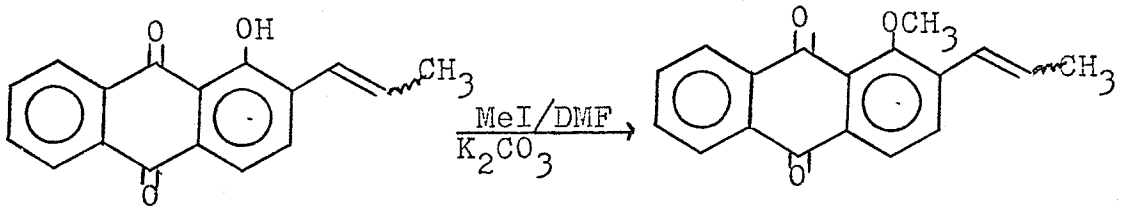
The uncatalysed reaction mixture even after 4 days of continuous refluxing showed some starting material. The components of the reaction product were separated by t.l.c. This time the major band (lower R_f value) was identified as XIIIa and the minor band (higher R_f value) as the rearranged product Xa.

Regarding the catalytic effect of benzylamine on the rearrangement, a rapid abstraction of the proton from the site of the rearrangement on the ring by the base may help expedite the enolization of the orthodienone intermediate (Scheme 4).

The pyrolysis of 1,4-diallyl anthraquinone ether (XIV): The reaction mixture containing benzylamine showed a rapid disappearance of the starting material and appearance of several spots on the t.l.c. microplates. The starting material disappeared completely between 2 and 3 hours. A regular monitoring of the rearrangement at short intervals showed an appearance and a gradual disappearance of a bright orange spot somewhere mid-way between the starting material (lowest R_f value) and the highest spot. With a complete disappearance of the starting material the mid-way spot disappeared almost completely. The components of the end product were separated by t.l.c. The major band (highest R_f value) on elution and subsequent recrystallization gave a bright red crystalline compound which was identified as 2,3-diallyl quinizarin XVIa (Scheme 5). The mass spectrum of the compound showed the molecular ion of 320. The i.r. spectrum (Fig. VI) showed one carbonyl absorption at 1635 cm^{-1} corresponding to the chelated carbonyl groups of the quinone and the aromatic (C=C) absorption at 1590 cm^{-1}. The compound XVIa was methylated to increase its solubility in $CDCl_3$. The n.m.r. spectrum of the methylated product (Fig. XXXIV) showed the methylene doublet of triplets centered at δ= 3.60 indicating the migration of the allyl group from the oxygen to the ring (comparing with the n.m.r. spectrum of the starting material Fig. XXXII). The peak at δ = 3.90 was assigned to O-methyl groups. The aromatic region showed a very symmetrical feature. The protons at C-5 and C-8 appeared as a multiplet centered at δ= 8.20 and the multiplet centered at δ= 7.70 could be assigned to

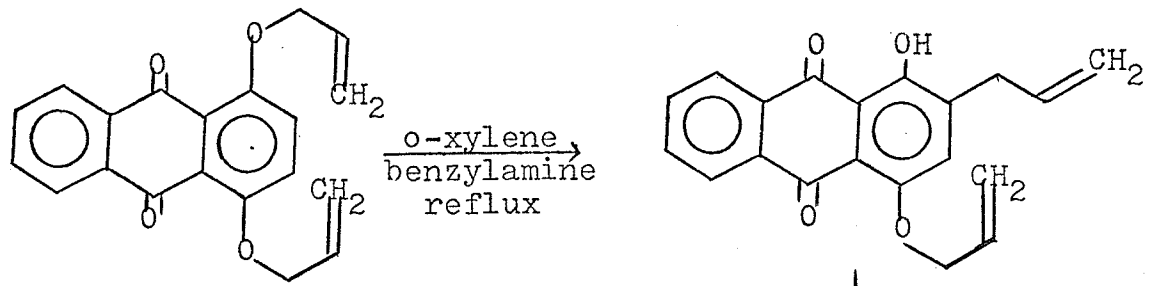


Xa Xb

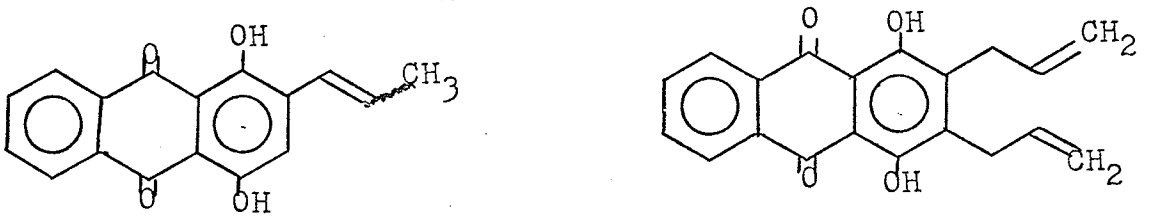


XIa/XIIa XIb/XIIb

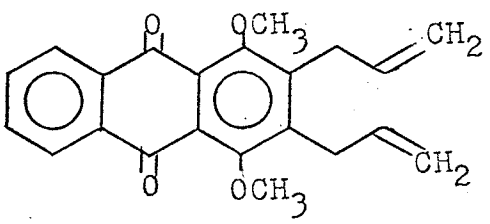
(Scheme 4)



XIV XV



XVII XVIa



XVIb

(Scheme 5)

The protons at C-6 and C-7.

Elemental analysis:

Calculated for $C_{20}H_{16}O_4$: C, 75; H, 5.

Found: C, 74.83; H, 5.19.

The second band from the top was eluted to give a red powder. The spectroscopic analysis of the compound established its identity as 2-propenyl quinizarin (XVII). The mass spectrum showed the molecular ion of 280. The i.r. spectrum (Fig. VII) showed a single absorption corresponding to the chelated carbonyl groups of the quinone. The n.m.r. spectrum (Fig. XXXV) confirmed the migration of the allyl group along with the migration of the double bond in the side chain. The absorption due to the methyl protons in the side chain appeared centered at δ=1.8. The vinyl protons were located between δ= 6.4 and 6.9. The single peak in the aromatic region at δ= 7.3 could well be attributed to the lone proton bonded to the ring. Two chelated phenolic protons appeared separately at δ= 12.7 and 13.4.

Interesting enough, this was the only instance of double-bond migration in the migrated allyl group under our normal condition of pyrolysis.

The third band (purple colour) from the top on elution gave a small amount of an amorphous powder which could not be characterized.

In another experiment when nearly 80% of the starting material had disappeared (in approximately 30 minutes) the pyrolysis was stopped and the products were separated by t.l.c. The bright orange band appearing mid-way between the

starting material (lowest R_f value) and the top band on elution gave a dark orange crystalline compound which was identified as partially rearranged ether XV. The mass spectrum showed the molecular ion of 320. The i.r. spectrum (Fig. V) showed a free and a chelated carbonyl absorption at 1660 and 1630 cm^{-1} (quinone) respectively. The absorptions at 1595 and 1220 cm^{-1} could be assigned to the aromatic (C=C) and C-O stretching frequency of the ether respectively. The n.m.r. spectrum (Fig. XXXIII) showed two methylene doublets (not further resolved due to compactness of the spectrum) centered at δ= 3.40and 4.60corresponding to the migrated and unmigrated allyl groups respectively. The lone peak in the aromatic region at δ= 7.10could be attributed to the lone proton bonded to the ring. The rest of the allylic features corresponding to both, the migrated and unmigrated allyl groups were located between δ= 4.90and 6.40. A chelated phenolic proton could be traced at δ= 13.30.

At this stage it is reasonable to presume that both the end products XVIand XVII are formed mainly through the intermediate product XV as a result of further migration of the unrearranged allyl group to the ring or its hydrolysis at an elevated temperature respectively (Scheme 5).

In one of the pyrolyses a catalysed reaction mixture was left refluxing over night but the isolated end product corresponding to the molecular ion 320 was detected solely as XVIa by its n.m.r. spectrum.

Basing the observations made in the pyrolysis of 1-allyl (IX) and 1,4-diallyl (XIV) anthraquinone ethers, although the observations may not be substantial enough to be

conclusive, it is worth mentioning that the presence of one allyl group on the ring seems to be more susceptible to undergo double-bond migration.

The uncatalysed reaction was stopped after four days of continuous refluxing. A substantial amount of the starting material was traced in the reaction mixture by t.l.c. The main reaction product was identified as XVIa.

No quinizarin could be isolated from either the catalysed or the uncatalysed reaction mixtures and hence a simultaneous hydrolysis of both the allyl groups must be a very slow process, if it occurs at all.

The pyrolysis of 2-allyl anthraquinone ether (XVIII). This ether was also pyrolysed under similar conditions as before. Both the reaction mixtures ie. with and without benzylamine failed to show any sign of the rearrangement over a period of 24 to 30 hours. At the end of the pyrolysis the starting material was recovered almost completely.

A sequence of pyrolyses was carried out under more rigorous conditions in a higher boiling solvent 1,2,4-trimethylbenzene by sealing the reaction mixture in a bomb that raised the temperature of pyrolysis up to 214°C. At higher temperatures the concentration of benzylamine was also increased gradually but a regular monitoring of the pyrolyses failed to indicate any sign of the rearrangement and a prolonged heating seemed to cause an excessive decomposition of the ether as no identifiable product could be isolated from the reaction mixture.

Since, the starting material was recovered almost completely after refluxing the ether in o-xylene for 30 hours, it appears that the O-allyl group at C-2 is stable to hydrolysis too, which was observed in the catalysed and uncatalysed pyrolysis of 1-allyl (IX) and 1,4-diallyl (XIV) anthraquinone ethers to a considerable extent.

These observations were further substantiated by pyrolysing the following ethers:

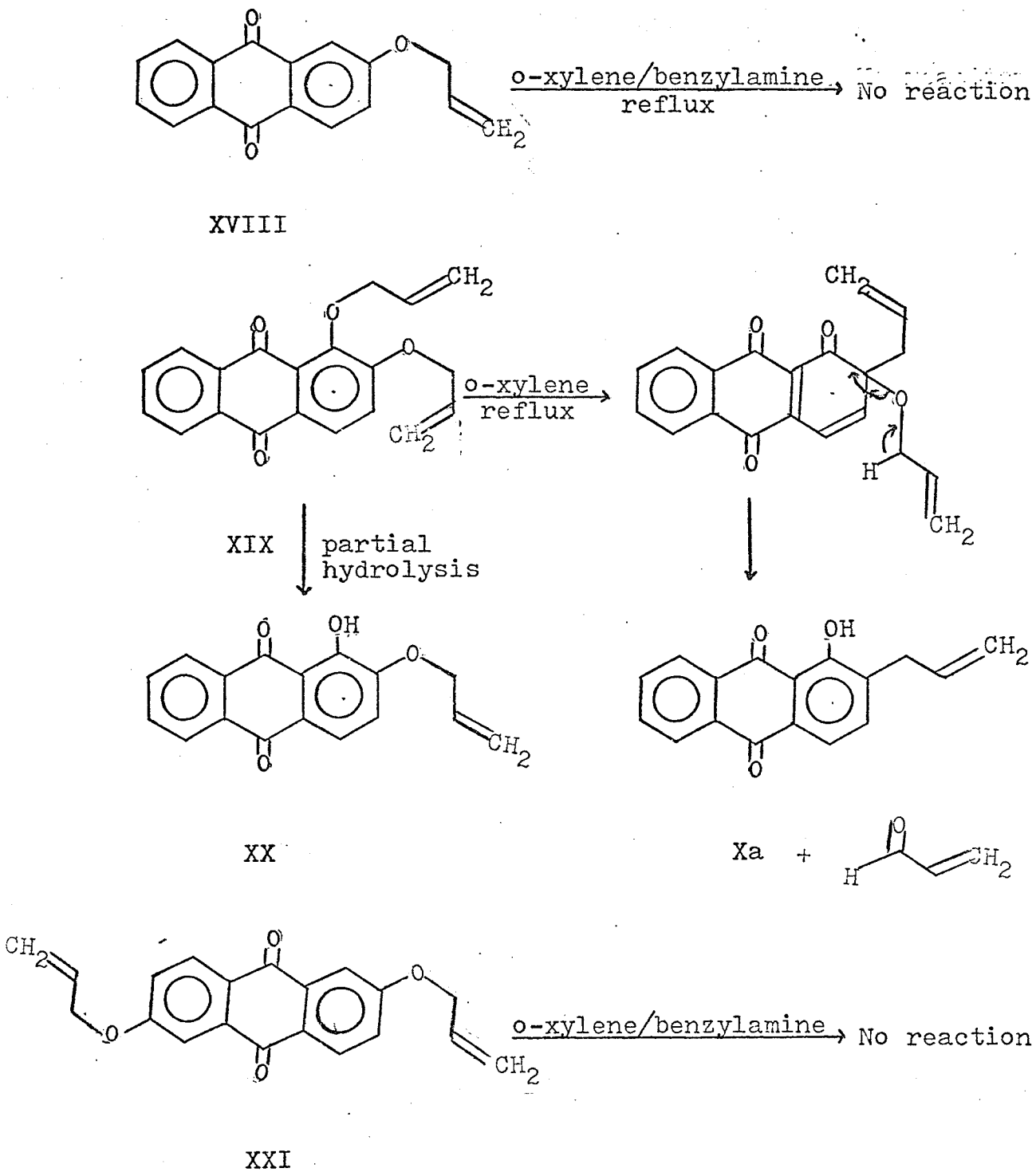
The pyrolysis of 1,2-diallyl anthraquinone ether (XIX): A rapid disappearance of the starting material was observed from the catalysed reaction mixture and two major products were spotted on the t.l.c. microplates. The products were separated by t.l.c. The major band (higher R_f value) on elution gave an orange yellow powder. The mass spectrum of the compound showed the molecular ion of 264. The i.r. spectrum showed all the significant absorptions identical to the ones observed in the i.r. spectrum of 2-allyl,1-hydroxy anthraquinone (Xa). The n.m.r. spectrum (Fig. XXVIIIb) confirmed the allyl group on the ring. The doublet due to the methylene protons (not further resolved) was located centered at δ=3.50 which was the same as observed in the n.m.r. spectrum of Xa (Fig. XXVIII). The chelated phenolic proton was located at δ= 12.90. Again, a close scrutiny of several n.m.r. spectra led to the conclusion that the methylene-doublet of the migrated allyl group shows a considerable change in chemical shift depending on the number and the type of the substituents on the ring (Figs. XXVIII, XXXI, XXXIII and XXXIV). On the basis of the spectral observations it does not seem

unreasonable to characterize the product as 2-allyl, 1-hydroxy-anthraquinone (Xa). However, a small doublet at $\delta = 2$ gives some indication of a partial double-bond migration and that could cause some discrepancies in the features of the aromatic region.

The minor band (lower R_f value) on elution gave a yellow powder. The compound was characterized from its spectral data as 2-allyl,1-hydroxy anthraquinone ether (XX). The mass spectrum showed the molecular ion of 280. The i.r. spectrum (Fig. X) showed a free and a chelated carbonyl absorption at 1670 and 1640 cm^{-1} (quinone) respectively. However, the chelated carbonyl absorption had shifted slightly towards higher frequency compared to i.r. spectral data of the similar systems (Figs. II, V, VI etc.). This shift may be attributed to the presence of an oxy-functional group at C-2 which could minimize the extent of hydrogen bonding with the nearest carbonyl group.

The main confirmation of the structure came from the n.m.r. spectrum of the compound (Fig. XXXVIII). The allyl group appeared to be bonded to the oxygen and not to the ring. The methylene doublet which undergoes a large up-field chemical shift after the rearrangement was found centered at $\delta = 4.80$as in 1,2-diallyl anthraquinone ether (Fig. XXXVII). The doublet centered at $\delta = 7.20$with a coupling constant of approximately 9Hz. could be assigned to the hydrogen ortho to the O-allyl group. The chelated phenolic proton was located at $\delta = 13$.

In the uncatalysed pyrolysis the rate of disappearance


o-xylene/benzylamine
reflux
No reaction
XVIII
o-xylene
reflux
XIX
partial
hydrolysis
XX
Xa
o-xylene/benzylamine
No reaction
XXI

(Scheme 6)

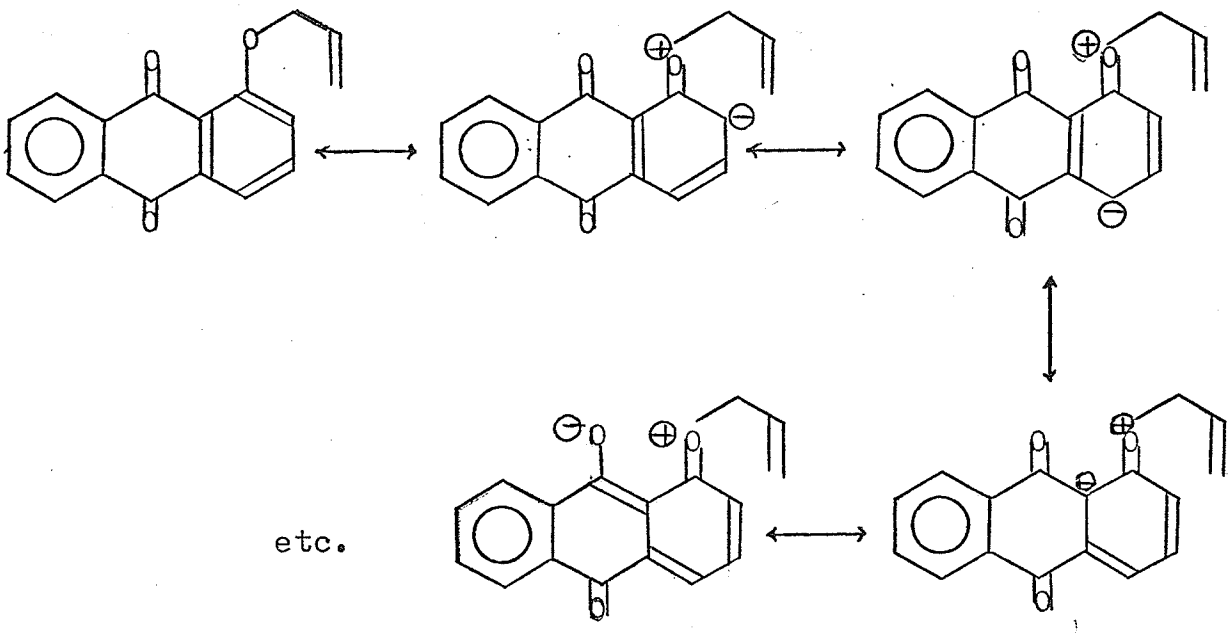
of the starting material was very slow. After 3 days of continuous refluxing the reaction mixture was separated by t.l.c. which gave a substantial amount of the starting material and the compounds Xa and XX as the minor and the major products respectively.

From the observations it was concluded that the O-allyl group at C-1 either rearranges with the migration of the allyl group to C-2 in which case the O-allyl group at C-2 is lost, or is hydrolysed at a higher temperature while the O-allyl group at C-2 remains unaffected.

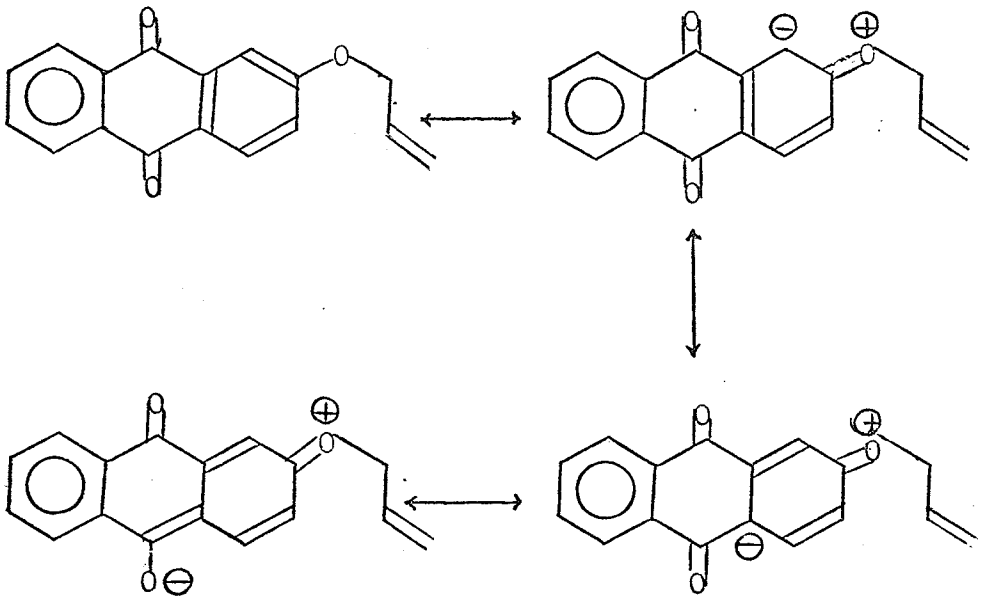
Since both the catalysed as well as uncatalysed pyrolyses gave Xa, a mechanism has been proposed to account for the observation (Scheme 6). The proposed mechanism could not be substantiated experimentally and is therefore speculative. The elusive character of acrolein under the condition of pyrolysis can very well be appreciated. The attempts to trap acrolein were unsuccessful.

The pyrolysis of 2,6-diallyl anthraquinone ether (XXI): This ether was pyrolysed using o-xylene and 1,3,4-trimethylbenzene as solvents. Benzylamine was added in increasing concentrations. The temperature of pyrolysis was realised up to 215°C when the pyrolysis was done in trimethylbenzene as a solvent in a sealed bomb. The observations were duplicated as in the pyrolysis of 2-allyl anthraquinone ether (XVIII).

On the basis of the observations made it was concluded that the O-allyl group is unusually stable at C-2 not only with respect to the rearrangement but also to the hydrolysis at higher temperatures which was observed as a side reaction



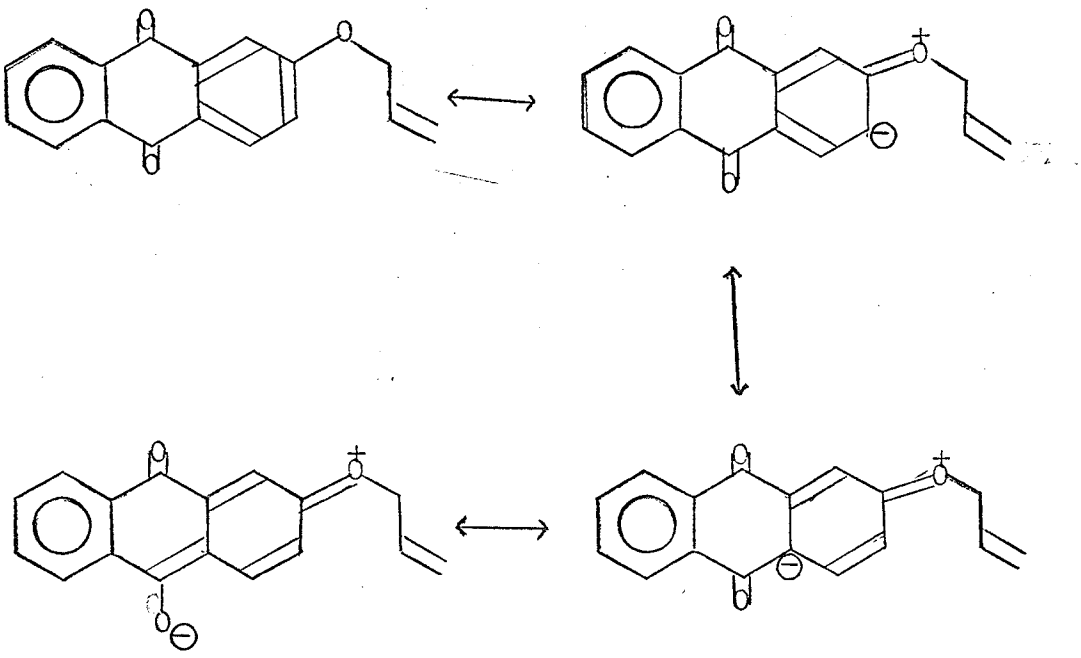
etc.



etc.

(Scheme 7)

cont'd...



(Scheme 7)

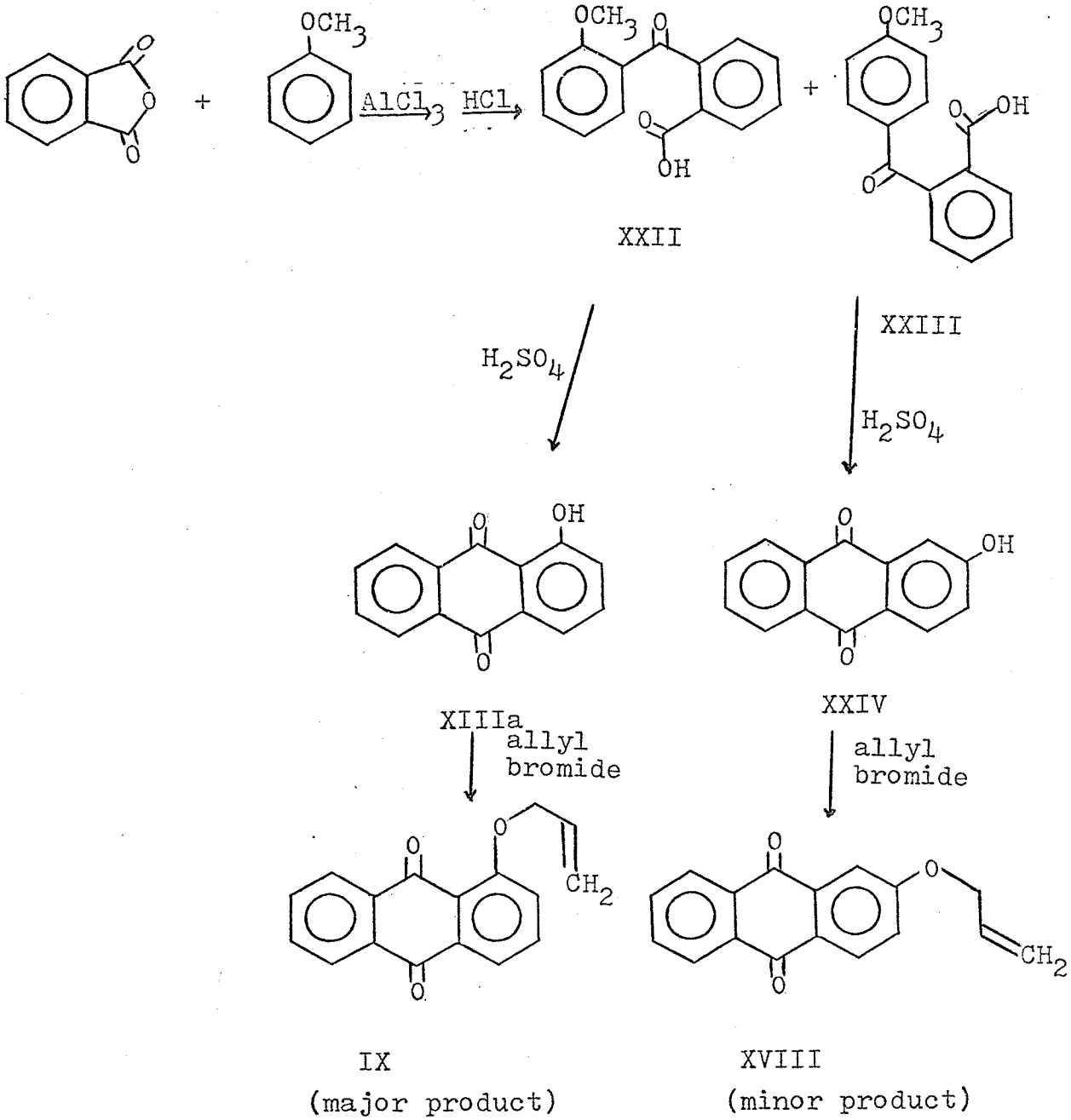
when the O-allyl group was at C-1 or its equivalent position.

The mechanism proposed (Scheme 7) to account for the facility of migration of the allyl group from the oxygen at C-1 (or its equivalent position ie. C-4) to the ring is based on the presumption that an electronic charge concentration on the carbon ortho to the O-allyl group is affected by a lone pair of electrons on the oxygen which in turn initiates the migration of the allyl group by attacking the end carbon of the double bond. The electronic charge concentration is dissipated essentially through its conjugation with the quinone system but to a lesser extent than if the O-allyl group is at C-2 (or its equivalent position i.e. C-6).

Lastly, the use of N,N-dimethylaniline as a solvent gave inferior results in rearranging systems, whereas $TiCl_4$ as a catalyst in o-xylene caused an excessive decomposition of the ethers. Under all circumstances tried, the O-allyl group on C-2 (or C-6) failed to rearrange.

Before concluding this series it is worth mentioning that information on the synthesis of 2-hydroxy anthraquinone (XXIV) is scanty. A two-step synthesis of the compound was devised in this laboratory, although the yield was low (Scheme 8).

Phthalic anhydride was condensed with anisole in the presence of aluminium trichloride using dichloroethane as a solvent to give a mixture of keto-acids XXII and XXIII in 80% yield. The mass spectrum showed the molecular ion of 256 and the n.m.r. spectrum (Fig. XL) indicated the presence of XXII and XXIII. The mixture of keto-acids without separation was


OCH3
AlCl3
HCl
OCH3
O
OH
OCH3
O
OH
XXII
XXIII
H2SO4
H2SO4
O
OH
O
O
OH
O
XIIIa
allyl
bromide
XXIV
allyl
bromide
O
O
CH2
O
O
O
CH2
IX
(major product)
XVIII
(minor product)

(Scheme 8)

stirred in concentrated sulphuric acid at 160°C for 24 hours to give a mixture of 1-hydroxy (XIII) and 2-hydroxy (XXIV) anthraquinones in 10% yield. The mass spectrum of the mixture of the hydroxy anthraquinones showed the molecular ion of 224. The i.r. spectrum showed carbonyl absorptions at 1680 and 1660 cm^{-1} indicating cyclization of the keto acids. However, hydrofluoric acid and polyphosphoric acid could not affect cyclization. The addition of aluminium trichloride to a fused stirring mixture of phthalic anhydride and anisole with the expectation to affect acylation and subsequent cyclization of the keto acids in one step resulted in a massive formation of a by-product drastically reducing the yield of the keto acids, but no cyclized product could be isolated. For our purpose the mixture of hydroxy anthraquinones XIII and XXIV was reacted with allyl bromide and the corresponding allyl ethers were separated by t.l.c. The upper band was characterized as 2-allyl anthraquinone ether (XVIII) and lower band as 1-allyl anthraquinone ether (IX).

In conclusion, the Claisen rearrangement studied on anthraquinone systems in this laboratory is not exhaustive and elaborated. The effect of various types of substituents towards the migration of the allyl group, specially, with respect to the facility and failure encountered from certain positions of the ring(s) is essential to corroborate the explanation given in terms of electronic charge concentration and its dissipation over the two rings.

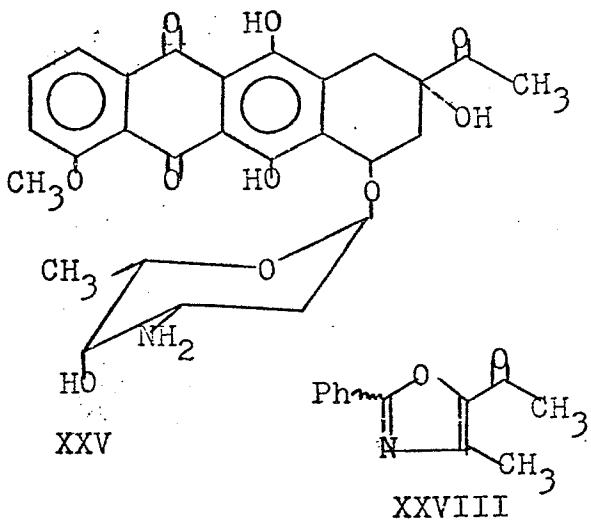
A further investigation into catalysts and abnormalities of rearrangements concerning anthraquinone systems will make an interesting subject for future studies.

PART B

INTRODUCTION

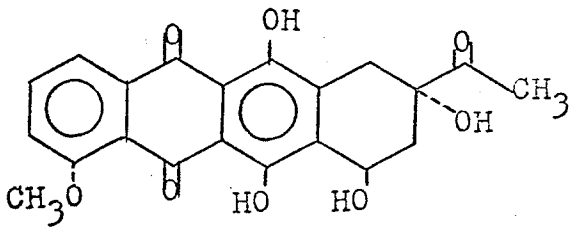
Daunomycin (XXV) is a cytotoxic antibiotic whose anti-tumor activity has been studied[70]. The compound consists of an aglycone, daunomycinone[71] (XXVI) and a sugar daunosamine[72] (XXVII). The sugar has been shown to be 3-amino-2,3,6-trideoxy-L-lyxo-hexose.

L-Daunosamine has been synthesized by Goodman and co-workers[73] and the N-acyl derivatives have been prepared by Baer et al.[74] and by Richardson[75], all starting from natural sugars. A stereospecific synthesis of dl-triacetyldaunosamine has recently been accomplished in this laboratory in several steps using a substituted oxazole XXVIII as a starting material[76].

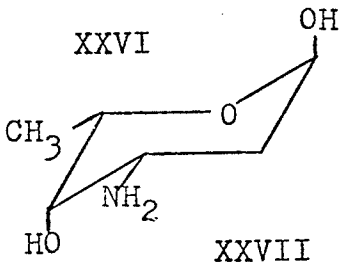


XXV

XXVIII



XXVI



XXVII

This part of the work was mainly devoted to exploring shorter and easier routes to the aminosugar daunosamine (XXVII) and its deoxygenated derivative 4-deoxydaunosamine (LVII). It is being speculated that replacing daunosamine (XXVII) by 4-deoxydaunosamine (LVII) could minimize some toxic side effects of daunomycin (XXV).

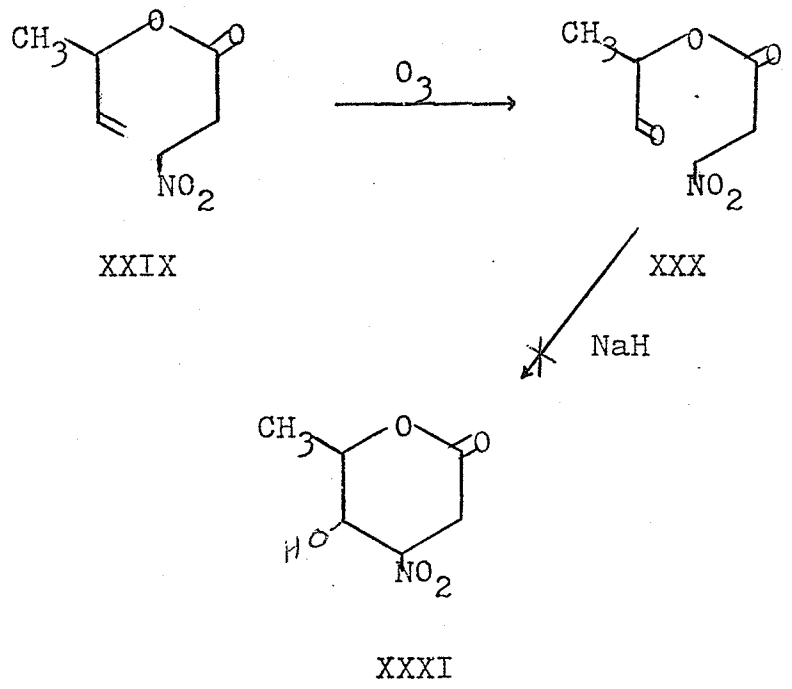
RESULTS AND DISCUSSION

Although several earlier attempts to cyclize XXX to give XXXI had failed[77] (Scheme 9), an effort was made once again to affect cyclization using methoxide base in methanol but no positive indication of the expected product was found and the results of previous attempts were duplicated. However, a better yield of the aldehyde XXX was obtained when the ozonolysis of XXIX was done in methanol followed by the reduction of the corresponding hydroperoxide by dimethyl sulphide[78].

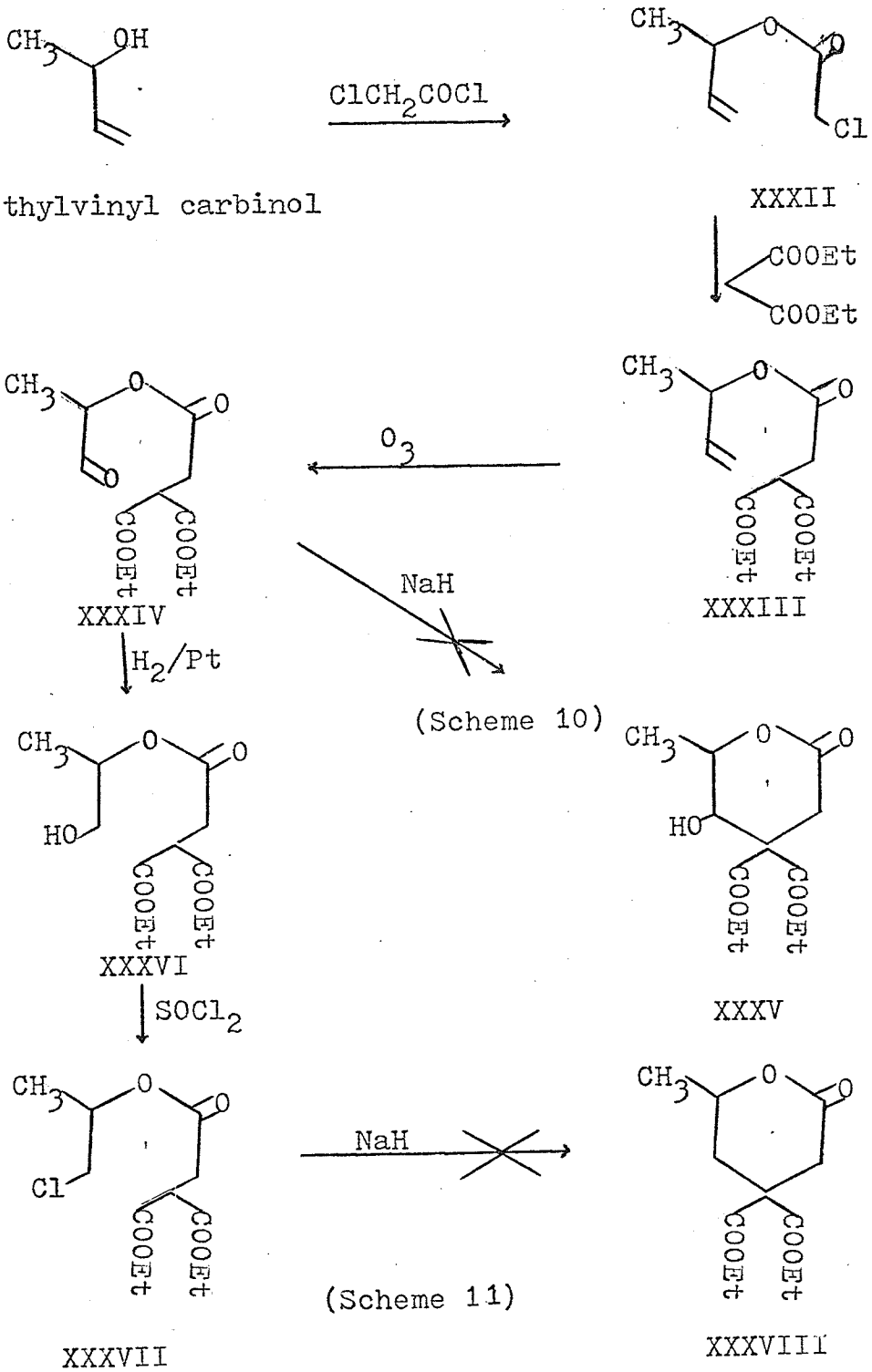
This project came to an end when one of the key starting materials β-propiolactone could not be obtained commercially.

Working on a similar approach (Scheme 10), the compound XXXIV was synthesized in four steps. It was expected that the aldehyde XXXIV would cyclize to give the substituted six-membered lactone XXXV which would be further exploited to get daunosamine(XXVII).

The scheme 10 was followed as:
Methylvinyl-carbinol was condensed with chloroacetyl chloride to give sec-butenyl chloroacetate (XXXII) in a quantitative yield. The mass spectrum showed the molecular ion of 148. In the n.m.r. spectrum a doublet centered at $\delta = 1.55$ due to methyl protons, a single absorption at $\delta = 4.10$ due to methylene protons (deshielded by the halogen and the ester group) and the vinyl and allyl protons appearing as multiplets between $\delta = 5.10$ and 6.30 (deshielded by the double bond and the oxygen) were all consistent with the expected structure.



(Scheme 9)


CH3
OH
ClCH2COCl
CH3
O
O
Cl
Methylvinyl carbinol
XXXII
COOEt
COOEt
CH3
O
O
O3
COOEt
COOEt
XXXIV
NaH
XXXIII
H2/Pt
(Scheme 10)
CH3
O
O
HO
COOEt
COOEt
XXXVI
XXXV
SOCl2
CH3
O
O
Cl
NaH
CH3
O
O
COOEt
COOEt
(Scheme 11)
XXXVII
XXXVIII

The i.r. spectrum (Fig. XII) showed an ester carbonyl absorption at 1745 cm^{-1} (shifted towards higher frequency due to α-halogen).

The chloro ester XXXII was condensed with diethyl malonate in dry t.h.f. in the presence of sodium hydride to give α-methylene sec-butenyloxycarbonyldiethyl malonate (XXXIII) in a quantitative yield as a golden yellow liquid. Diethyl malonate being used in slight excess was removed under vacuum. The product XXXIII was mainly characterized by its n.m.r. spectrum (Fig. XLII). The O-ethyl groups could be seen as a quartet and a triplet centered at δ= 4.20 and 1.25 respectively. The doublet of allylic methyl protons appeared overlapping the triplet of the O-ethyl groups. A doublet due to the saturated methylene protons centered at δ= 2.75, a triplet attributed to the lone proton on α-C and the multiplet between δ= 5 and 6.20 assigned to the allyl and vinyl protons indicated the expected structure. The i.r. spectrum (Fig. XIII) showed an ester-carbonyl absorption at 1730 cm^{-1}.

In the next step the alkene XXXIII was converted to the aldehyde XXXIV by ozonolysis in 85% yield which was characterized mainly by its n.m.r. spectrum (Fig. XLIII). The allylic methyl protons separated as a doublet centered at δ= 1.30 (a slight deshielding by aldehyde C=O). The other features of the ester XXXIII remaining unaffected, the complex vinyl-allyl multiplet disappeared instead a quartet centered at δ= 5 appeared which could be attributed to the methine proton. A low-field proton at δ= 9.30 indicated the formation of the aldehyde. However, the absence of a visible

coupling between the aldehyde proton and the methine proton is not anomalous. It has been observed[79] that because of a stable conformation, the coupling constants of -substituted aldehydes commonly fall below 2Hz. and the coupling may not be apparent.

(The traces of impurities are visible in the n.m.r. spectrum but no attempts were made to purify the aldehyde by distillation or chromatography as such attempts had led to the decomposition of a similar aldehyde[77].)

The i.r. spectrum of the aldehyde (Fig. XIV) did not show any appreciable change and the features remained dominated by the ester groups.

An attempt was made to cyclize the aldehyde XXXIV in dry t.h.f. (tetrahydrofuran) in the presence of sodium hydride but the expected lactone XXXV could not be isolated, although an intermolecular condensation of carbanion and aldehyde had been executed in this laboratory[80]. No further attempt was made at this stage towards cyclization but it was decided to convert the aldehyde XXXIV to the chloride XXXVII expecting that a halogen being a better leaving species the cyclization would be effective and the resulting lactone XXXVIII (Scheme 11) would be exploited to get 4-deoxy-daunosamine (LVII).

The aldehyde XXXIV was hydrogenated in ethyl acetate in the presence of Adams catalyst and the corresponding alcohol XXXVI was isolated in essentially quantitative yield. Again, the formation of the compound XXXVI was confirmed by its n.m.r. spectrum (Fig. XLIV). The aldehyde proton at = 9.30

disappeared and a broad hump centered at δ= 7 showed up.

(The position of the hump seemed to depend on the purity and the concentration of the sample. The shape and the nature of the absorption was strongly indicative of a fast exchanging proton characteristic of alcohols.)

The doublet due to the methylene protons nearest to the hydroxyl group seemed to be overlapping the triplet centered at δ= 3.80. The doublet due to the allylic methyl protons disappeared in the triplet of the O-ethyl groups between δ= 1.10 and 1.40. The rest of the features of the aldehyde XXXIV remained unaltered except for a small absorption at δ= 2 which could not be accounted for, and a broadening in signals observed in general. The i.r. spectrum (Fig. XV) showed a small broad absorption at 3500 cm^{-1} due to the hydroxyl group.

The crude alcohol was reacted with thionyl chloride and the final product XXXVII was purified by t.l.c. (yield 80%). The product XXXVII was characterized primarily by its n.m.r. spectrum (Fig. XLV). The low-field broad absorption due to the fast exchanging hydroxyl proton disappeared and a doublet centered at δ= 3.60 attributed to the methylene protons nearest to the halogen separated from the triplet of the lone hydrogen due to an up-field shift caused by the halogen. The i.r. spectrum (Fig. XVI) recorded the only noticiable change which was the disappearance of the broad absorption at 3500 cm^{-1} corresponding to the hydroxyl group.

Some unexpected splittings were observed in certain

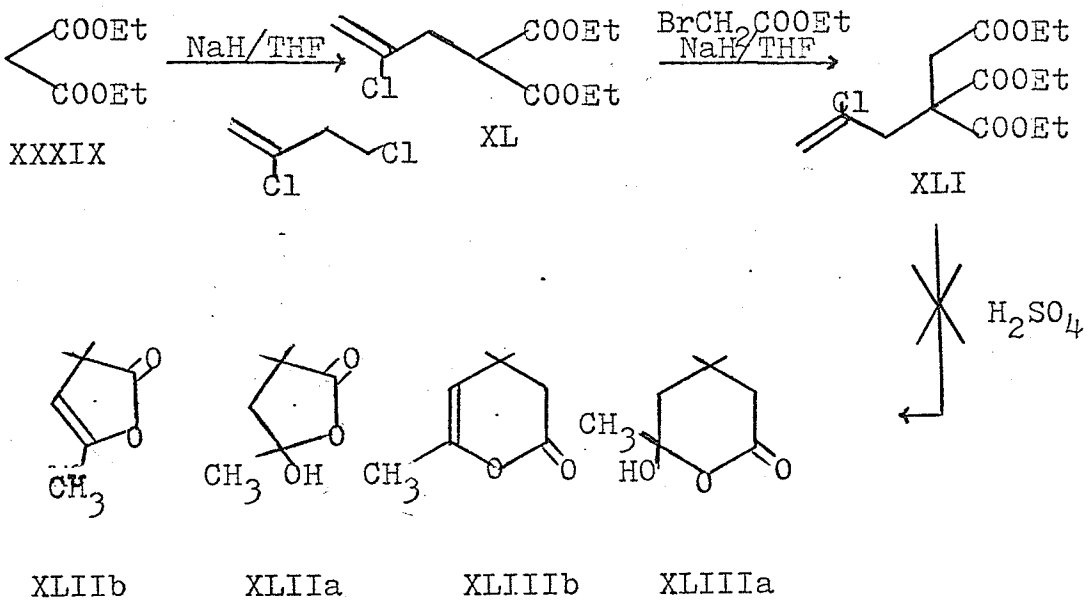
regions of the n.m.r. spectrum and it was speculated that the crowding at the carbon bearing the halogen might cause hindrance in the free rotation in the areas bearing larger substituents.

The mass spectrum failed to show the molecular ion or any large identifiable fragments.

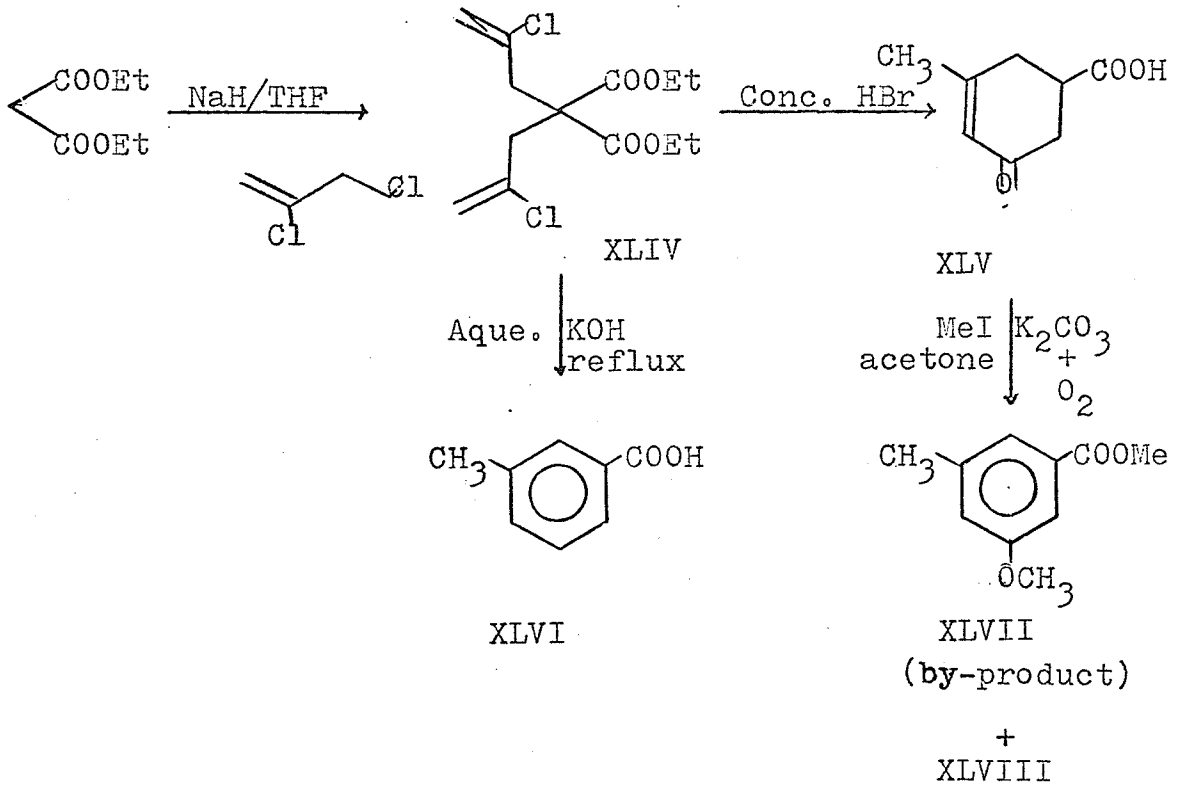
Relying on the identification of the compound XXXVII by its n.m.r. spectrum only, the attempts were made to affect the cyclization in refluxing dry t.h.f., dioxane and d.m.f. as solvents in the presence of sodium hydride but without success.

Failing in two successive attempts to affect reverse cyclization to get a lactone, the attention was switched over to more conventional systems that are known to form lactones as a result of an intramolecular cyclization when the functional groups are favourably disposed.

The scheme 12 was followed as:
2,3-dichloro-1-propene was condensed with diethyl malonate (XXXIX) to give α-(2-chloro-1-propenyl)diethyl malonate (XL) in 60% yield. In the n.m.r. spectrum (Fig. XLVI) the O-ethyl groups showed up as a triplet and a quartet centered at δ= 1.30 and 4.2 respectively. The saturated methylene protons appeared as a doublet centered at δ= 2.95 and the unsubstituted lone proton of diethyl malonate formed a triplet centered at δ= 3.75. The vinyl protons could be distinguished at δ= 5.30 with splittings due to allylic coupling. The features in the i.r. spectrum (Fig. XVII) appeared to be mainly due to the diethyl malonate-moity except for an absorption at 1640 cm^{-1}



(Scheme 12)



(Scheme 13)

continued...

which could be attributed to the double bond (C=C). The ester-carbonyl absorbed at 1730 cm^{-1}.

The mono substituted diethyl malonate XL was condensed with ethyl bromoacetate to give α-ethoxycarbonyl-α-(2-chloro-1-propenyl)diethylsuccinate (XLI) in a quantitative yield. Again, the i.r. spectrum (Fig. XVIII) did not record any appreciable changes in the features except that the relative intensity of C=C absorption decreased and the intensity of absorption at 1200 cm^{-1} due to ester (C-O) increased. The n.m.r. spectrum (Fig. XLVII) characterized the compound. The triplet centered at δ= 3.15 disappeared and two separate absorptions at δ= 3.15 and 3.30could be assigned to the allylic protons and the methylene protons nearest to the ester groups respectively. The splittings in the triplet and the quartet showed slight inequivalence in the two types of O-ethyl groups. The vinyl protons shifted slightly down-field and appeared as two separated absorptions at δ= 5.30and 5.40 showing some splittings of the order of allylic and geminal couplings. A pronounced difference in the chemical shifts of the two vinyl protons signifies an appreciable change in the chemical environment of the distant protons after the second substitution on diethyl malonate.

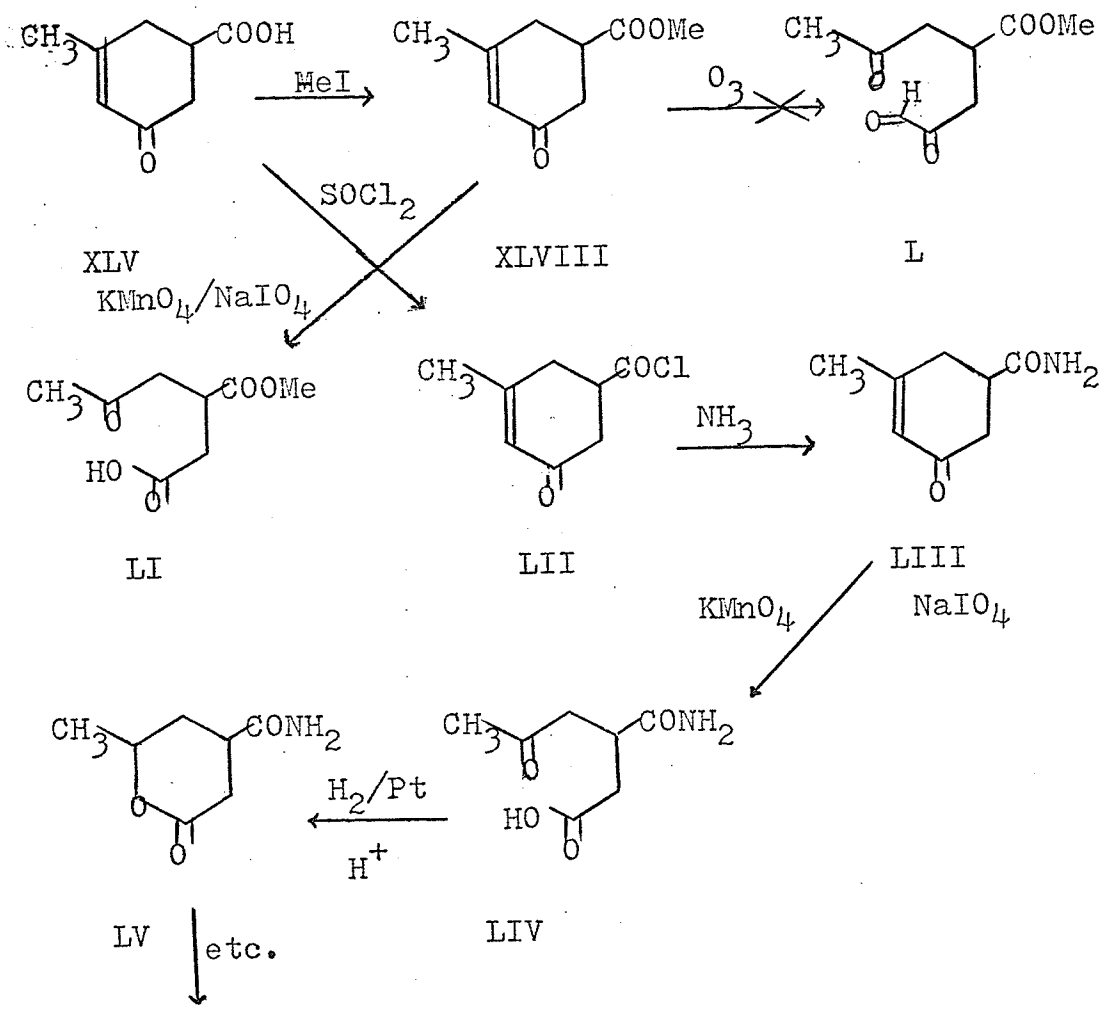
The next step was the hydrolysis of the vinyl chloride to methyl ketone and the esters to carboxyl groups. It was expected that the vinyl chloride and the esters after respective hydrolyses would give five-and six-membered substituted lactones XLII and XLIII respectively under the conditions of hydrolysis. A mild approach to hydrolyse the

vinyl chloride by stirring in a mixture of glacial acetic acid and concentrated hydrochloric acid saturated with hydrochloric acid gas at room temperature was futile. However, under vigorous conditions like refluxing in 40% sulphuric acid the vinyl chloride was hydrolysed but the cyclization remained unaffected. In the n.m.r. spectrum the crude product appeared to be a mixture of polycarboxylic keto acids.

At this stage the approach was modified to get a system XLV (Scheme 13) that would serve as a key intermediate to 4-deoxydaunosamine (LVII).

The scheme 13 was followed as:
2,3-dichloro-1-propene was condensed with diethyl malonate to give α,α-di(2-chloro-1-propenyl)diethyl malonate (XLIV) in quantitative yield. The slightly coloured compound forms needle shaped crystals at lower temperatures and was easily characterized by its n.m.r. spectrum (Fig. XLVIII). Apart from the features due to O-ethyl groups, a single absorption at δ= 3.20 due to saturated methylene protons and an absorption at δ= 5.40 assigned to the vinyl protons were consistent with the expected structure. The i.r. spectrum (Fig. XIX) showed a strong relative absorption at 1635 cm^{-1} due to C=C.

In the first attempt it was decided to hydrolyse the ester groups in an aqueous base expecting that the base would not affect the hydrolysis of the vinyl chloride. However, refluxing XLIV in 40% aqueous potassium hydroxide gave meta-toluic acid (XLVI) which could be sublimed out of the reaction mixture. The combined spectral data readily identified the acid XLVI. The mass spectrum showed the

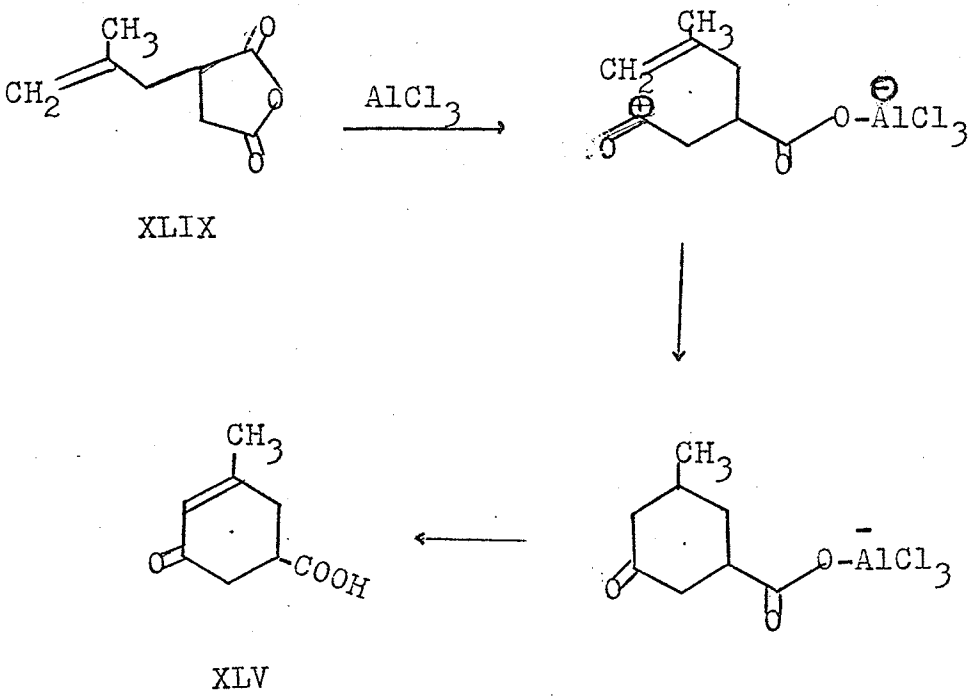

CH3
COOH
MeI
COOMe
O3
H
SOCl2
XLV
XLVIII
L
KMnO4/NaIO4
HO
LI
COCl
NH3
CONH2
LII
LIII
KMnO4
NaIO4
H2/Pt
H+
LIV
LV
etc.

(Scheme 13)

molecular ion of 136. The i.r. and n.m.r. spectra were identical to the standard spectra of the compound XLVI available in the literature (i.r. spectrum Fig. XXI, n.m.r. spectrum Fig. L).

A positive identification of meta-toluic acid led to the conclusion that the condition of hydrolysis was too drastic and it could be modified to give the desired keto acid XLV in one step. In subsequent attempts the compound XLIV was hydrolysed at higher temperatures in 30% sulphuric acid, concentrated hydrobromic acid and in a mixture of glacial acetic acid and concentrated hydrochloric acid saturated with hydrochloric acid gas to give XLV in good yields. It was observed that the hydrolysis was slow in sulphuric and hydrochloric acids but the hydrolysis in hydrobromic acid increased the formation of a by-product which could not be identified. The aromatization was another side reaction which occured when the reaction mixture was not kept under nitrogen. The compound XLVII was isolated with the keto ester XLVIII after the methylation of the crude acid XLV.

The acid was first isolated as a by-product during the preparation of benzo(c)phenanthrenes through an initial condensation of beta-methallylsuccinic anhydride XLIX and benzene in the presence of aluminium trichloride[81]. The by-product could not be identified immediately but was later characterized as 3-methylcyclohex-2-ene-1-one-5-carboxylic acid XLV. The formation of the acid XLV was explained as a result of intramolecular acylation (Scheme 14). The authors laid an emphasis on the importance of XLV as a desirable



XLIX

XLV

(Scheme 14)

intermediate in the total synthesis of steroids.

In this laboratory the acid XLV was characterized spectroscopically. The mass spectrum showed the molecular ion of 156. The i.r. spectrum (Fig. XX) showed absorptions at 1710 1670 cm^{-1} for the carboxyl and the conjugated C=O respectively. The conjugated double bond appeared as a shoulder at 1640 cm^{-1} and a broad absorption extending over the range 3000-2500 cm^{-1} was taken due to the carboxylic OH (bonded). The n.m.r. spectrum (Fig. XLIX) was in agreement with the structure. The methyl protons appeared at $\delta = 2$ (deshielded by the conjugated double bond). The doublet centered at $\delta = 2.60$ could be assigned to the protons at C-3 and C-6 and a pentet centered at $\delta = 3$ to the lone proton at C-5. The lone proton at C-2 appeared at $\delta = 6$ and the carboxyl proton at $\delta = 11.60$.

After the structural verification of the acid XLV, attention was focused on an oxidative cleavage of the conjugated double bond (C=C) which would give a model system LI leading to the desired lactone LVI. Working on the methyl ester XLVIII (i.r. spectrum Fig. XXIII, n.m.r. spectrum Fig. LII), two succesive attempts of ozonolysis (Scheme 13) failed to give the expected glyoxal L which on further oxidative cleavage by sodium metaperiodate would give LI. However, the cleavage of the double bond was executed successfully by potassium permanganate/sodium metaperiodate in one step to give LI. The compound LI was readily identified spectroscopically. The i. r. spectrum (Fig. XXIV) showed a complete disappearance of the conjugated ketone at 1670 cm^{-1}

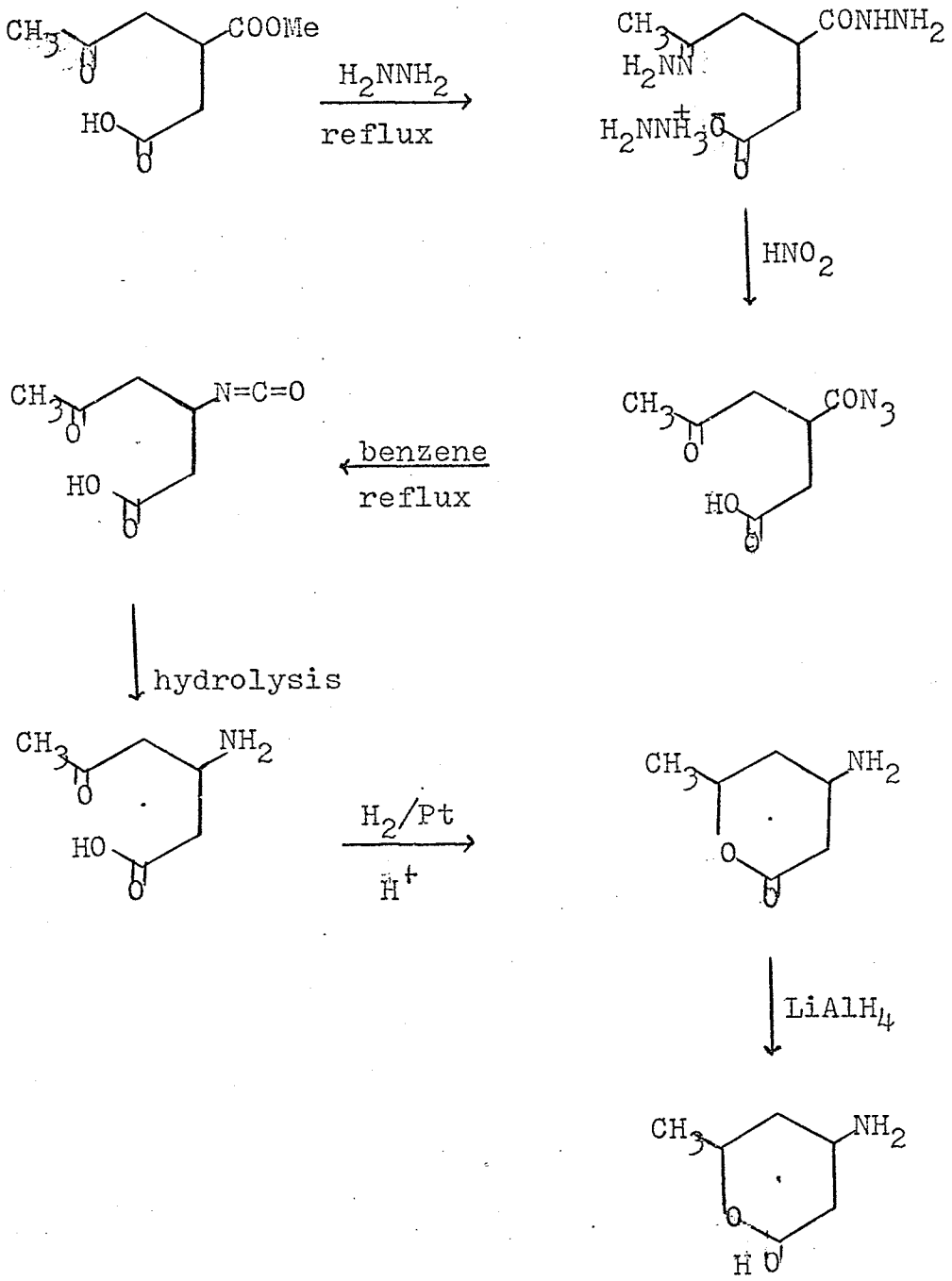
instead a broad carbonyl absorption with a point at 1710 cm^{-1} (ketone and carboxyl, C=O) and a shoulder at 1735 cm^{-1} (ester, C=O) along with a broad absorption with sub-maxima at 2500 cm^{-1} gave a good indication of LI. The n.m.r. spectrum (Fig. LIII) showed all the expected features. The methyl proton appeared at δ= 2.20 (deshielded by ketone), the doublets centered at δ= 2.70 and 2.90 could be attributed to the methylene protons nearest to the ketone and the carboxyl groups respectively. A broad and splitting triplet centered at δ=3.2 could be assigned to the lone proton nearest to the ester group. The protons of O-methyl appeared at δ= 3.70 and the carboxyl proton at δ= 10.30

At this stage it was decided to convert XLV to the corresponding amide LIII which by Hoffman rearrangement would introduce an amino group at the desired position at a suitable stage (Scheme 13).

The acid XLV was reacted with thionyl chloride and the corresponding acid chloride LII (i.r. spectrum Fig. XXV) was reacted with aqueous ammonia which caused an excessive polymerization even at low temperatures. As an alternative the keto ester LI was stirred with aqueous ammonia with intermittent warming of the reaction mixture for three days with the intention to drive the reaction to completion. Although the n.m.r. spectrum of the crude product showed a complete disappearance of the O-methyl peak, it could not be positively characterized as the desired amide LIV.

Theoretically, the Curtius approach to introduce the amino group in the keto ester LI seems sound and promising

for further steps (Scheme 15). Investigations are under way.



(Scheme 15)

EXPERIMENTAL

All infrared (i.r.) spectra were recorded on a Perkin-Elmer model 710 i.r. spectrometer using liquid cells and methylene chloride solutions of samples. The nuclear magnetic resonance (n.m.r.) spectra were recorded on a Varian A-56/60 A MHz spectrometer using $CDCl_3$ as solvent and tetramethylsilane as internal standard. Chemical shifts are given in delta (δ) units and the coupling constant, J, in Hertz (Hz). The mass spectra were recorded on a Finnigan model 1015 mass spectrometer. The melting points (m.p.) were obtained on a Fisher-John melting point apparatus and are uncorrected. Thin layer chromatography (t.l.c.) was done on Camag brand silica gel. Glass plates with a 1 mm. coating of absorbent were used for t.l.c. separations. Dr. Daessele of Montreal performed the microanalysis.

PART A

(1) Preparation of 2-allyl anthraquinone ether (XVIII).

Phthalic anhydride (9g., 0.06 mole) and anisole (8.2 ml., 0.07 mole) were dissolved in dichloroethane (200 ml.) in a 500 ml. flask equipped with a magnetic stirrer and a reflux condenser with a drying tube on top. To the stirring solution at 50°C was added freshly sublimed aluminum trichloride (10 g.) slowly and carefully with the minimum exposure to the moisture over a period of 10 minutes and the temperature was raised to 80°C. After 32 hours of stirring the reaction mixture was cooled and acidified with 5% hydrochloric acid to destroy aluminium trichloride.

The organic layer was separated and extracted with a saturated aqueous solution of sodium carbonate. The aqueous extract was acidified and finally extracted with ethyl acetate. After removing the solvent under reduced pressure a solid mixture of keto acids XXII and XXIII was isolated (12g., 0.05 mole).

The mixture of keto acids XXII and XXIII was digested in twice its weight of concentrated sulphuric acid in a closed bomb. After stirring the solution at 160°C for 24 hours the reaction mixture was cooled down and extracted with chloroform several times. The chloroform extracts were combined and washed with sodium bicarbonate solution to remove traces of acid. Evaporation of chloroform after drying over magnesium sulphate left a greenish yellow solid (a mixture of 1-hydroxy and 2-hydroxy anthraquinones) which was reacted with allyl bromide as outlined in the subsequent step and the allyl ethers were separated by t.l.c. using benzene as a solvent. The upper band on elution gave a light yellow solid (yield 4%) (minor product).

Mass spectrum: $M^+/e = 264$ (molecular ion).

Infrared spectrum (Fig. VIII): absorptions cm^{-1} at 1680 (quinone C=O); 1600 (aromatic C=C).

N.m.r. spectrum (Fig. XXXVI): absorptions between 4.60 and 6.40 (allyl group); at 7.20 (two doublets, 1H, aromatic); multiplets beyond 7.20 (all aromatic).

A general preparations of allyl ethers:

The following allyl ethers were prepared by stirring 6-8 moles excess of allyl bromide with the corresponding

hydroxy anthraquinones dissolved in dry d.m.f. In each case the reaction was carried out in a flask equipped with a magnetic stirrer and a reflux condenser with a drying tube on top. Approximately 10 moles excess of finely ground potassium carbonate was added to each reaction mixture to catalyse the reaction. The addition of potassium carbonate developed a dark purple colour in each case which gradually faded with the progress of the reaction and eventually the reaction mixtures turned yellow to orange in colour. A complete disappearance of purple colour (between 2 and 3 hours at 70°C) was taken as an indication of complete reaction. The reaction mixtures were diluted with water and the products were extracted in chloroform followed by a thorough washing of the chloroform extract with water to remove d.m.f. The subsequent drying over magnesium sulphate and evaporation of chloroform left solid allyl ethers which were recrystallized from a mixture of chloroform and ether.

(2) 1-Allyl anthraquinone ether (IX):

The ether on recrystallization gave a flaky yellow solid.

Mass spectrum: M^+/e = 264 (molecular ion).

Infrared spectrum (Fig. I): absorptions (cm^{-1}) at 1670 (quinone C=O); 1590 (aromatic C=C).

N.m.r. spectrum (Fig. XXVII): absorptions between 4.20and 6.60(allyl group); 7.30(a doublet of doublets, 1H, aromatic); multiplets beyond 7.30(aromatic).

(3) 1,4-Diallyl anthraquinone ether (XIV):

The ether on recrystallization gave an orange

crystalline solid.

Mass spectrum: M^+/e = 320 (molecular ion).

Infrared spectrum (Fig. IV): absorptions (cm^{-1}) at 1670 (quinone C=C); 1580 (aromatic).

N.m.r. spectrum (Fig. XXXII): absorptions between 4.60and 6.50(allyl group); 7.350(aromatic, 2H); multiplets beyond 7.30(aromatic).

(4) 1,2-Diallyl anthraquinone ether (XIX):

The ether on recrystallization gave a yellow crystalline solid of fine structure.

Mass spectrum: M^+/e = 320 (molecular ion).

Infrared spectrum (Fig. IX): absorptions (cm^{-1}) at 1670 (quinone C=O); 1590 (aromatic C=C).

N.m.r. spectrum (Fig. XXXVII): absorptions between 4.4 and 6.60(allyl group); 7.30(doublet, 1H, aromatic); multiplets beyond 7.30(aromatic).

(5) 2,6-Diallyl anthraquinone ether (XXI):

The ether on recrystallization gave a flaky yellow solid.

Mass spectrum: M^+/e = 320 (molecular ion).

Infrared spectrum (Fig. XI): absorptions (cm^{-1}) at 1670 (quinone C=O); 1590 (aromatic C=C).

N.m.r. spectrum (Fig. XXXIX): absorptions between 4.60and 6.40(allyl group); 7.20(a doublet of doublets, 2H, aromatic at C-3 and C-7); 7.70(doublet, 2H, aromatic at C-4 and C-8).

All the ethers that showed rearrangement were pyrolysed in a 25 ml. flask fitted with a condenser having a nitrogen balloon on top. 400 mg. of an ether was dissolved in

2-4 ml. of o-xylene and 0.5 ml. of benzylamine was added to the solution. The heating was done either by an oil bath or an electric mantle. A pyrolysis was stopped at a desired stage and the products were separated by t.l.c. after removing most of the solvent under vacuum. Normally, the use of benzene as a solvent gave a fairly good separation of the components in t.l.c. The bands were eluted with chloroform/methanol.

(6) The pyrolysis of 1-allyl anthraquinone ether (IX):

Products:

(i) 2-Allyl, 1-hydroxy anthraquinone (Xa): yield 40%; m.p. 114-116°C.

(ii) 1-Hydroxy anthraquinone (XIIIa): yield 10%.

(7) The pyrolysis of 1,4-diallyl anthraquinone ether (XIV):

Products:

(i) 2-Allyl, 4-allyloxy, 1-hydroxy anthraquinone (XV): maximum yield 20%; m.p. 67-68°C.

(ii) 2,3-Diallyl quinizarin (XVIa): maximum yield 25%; m.p. 115-117°C.

(iii) 2-Propenyl quinizarin (XVII): maximum yield 20%.

(8) The pyrolysis of 1,2-diallyl anthraquinone ether (XIX):

Products:

(i) 2-Allyl, 1-hydroxy anthraquinone (Xa): yield 30%.

(ii) 2-Allyl, 1-hydroxy anthraquinone ether: yield 5%.

A general procedure of methylating hydroxy anthraquinones:

The following hydroxy anthraquinones were methylated by the same procedure as outlined in the general preparation of allyl ethers. Methyl iodide was used as a methylating

reagent. Normally, 1.5 moles excess of methyl iodide 10 moles excess of finely ground potassium carbonate brought about the complete methylation between 1-2 hours at 35°C. The yields were essentially quantitative.

(9) 2-Allyl, 1-hydroxy anthraquinone (Xa) was methylated to 2-allyl, 1-methoxy anthraquinone (Xb).

N.m.r. spectrum (Fig. XXXI).

(10) A mixture of 2-allyl, 1-hydroxy anthraquinone (Xa) and 2-propenyl, 1-hydroxy anthraquinone (XIa and XIIa) was methylated to the corresponding mixture of methyl ethers Xb, XIb and XIIb respectively.

N.m.r. spectrum (Fig. XXIX).

(11) 2,3-Diallyl quinizarin (XVI was methylated to the corresponding dimethoxy compound XVIb.

N.m.r. spectrum (Fig. XXXIV).

PART B

(12) 1-Formylethyl 3-nitropropionate (XXX)

The compound was prepared from nitro ester XXIX following the same procedure as outlined in the preparation of the aldehyde XXXIV from the alkene XXXIII.

(13) Sec-butenyl chloroacetate (XXXII)

Chloroacetyl chloride (5 ml., 0.061 mole) was taken in 20 ml. of dry benzene in a 50 ml. flask and the flask was immersed in an ice bath. To the stirring solution was added methylvinyl alcohol (5.5 ml., 0.065 mole) slowly. The ice bath was removed and the reaction mixture was allowed to warm up to the room temperature over a period of one hour. Benzene was flash evaporated carefully. The brown liquid residue

The benzene was flash evaporated carefully. The brown liquid residue (8.50 g.,0.059 mole, 98%) was found to be satisfactorily pure compound XXXII.

Infrared spectrum (Fig. XII). N.m.r. spectrum (Fig. XLI).

(14) α-Methylene sec-butenyloxycarbonyldiethyl malonate (XXXIII):

To a solution of diethyl malonate (10 ml.,0.07 mole) and dry t.h.f. (25 ml.) in 50 ml. flask was added sodium hydride (3.40 g. of 50% suspension in oil, 0.07 mole) washed with dry benzene, over a period of 10 minutes. To the stirring solution was added chloro ester XXXII (8.50 g.,0.059 mole) dropwise over a period of 20 minutes and the reaction mixture was immersed in a water bath at 60°C. The stirring was continued for 2 hours. The reaction mixture was dumped into ice water, acidified with dil. hydrochloric acid and extracted with chloroform (3 X 10 ml.). The chloroform extract was dried over magnesium sulphate and the low boiling liquids were removed by flash evaporation leaving an oil residue which was subjected to vacuum evaporation until the n.m.r. spectrum stopped showing any significant amount of unreacted diethyl malonate. The final residue weighed 14.60 g.(94%).

Infrared spectrum (Fig. XIII). N.m.r. spectrum (Fig. XLII).

(15) α-Methylene 1-formylethoxycarbonyldiethyl malonate (XXXIV):

Through a solution of 14.60 g. of alkene XXXIII and 70 ml. of methanol cooled to -70°C in an acetone-dry ice bath was bubbled ozone until a bluish tinge appeared. While still at -70°C the system was flushed with nitrogen and 10 ml. (0.136 mole) of dimethyl sulphide was added. The solution was stirred at -10°C for an hour, then at ice bath

temperature for one hour and, finally, at room temperature for one houre. The solvent was removed under vacuum and the residue extracted with chloroform and water. The chloroform solution was washed with water several times, dried over magnesium sulphate and flash evaporated. The oil residue weighed 12.27 g. (85%).

Infrared spectrum (Fig. XIV). N.m.r. spectrum (Fig. XLIII).

Attempted cyclization of the aldehyde (XXXIV):

To the stirring solution of 270 mg. of the aldehyde XXXIV and 10 ml. of dry t.h.f. was added 50 mg. (50% suspension in oil) of sodium hydride washed with dry benzene. The stirring was continued overnight. The reaction mixture was dumped into cold water and extracted with chloroform after acidification. The chloroform was dried over magnesium sulphate and evaporated. The n.m.r. spectrum of the residue failed to indicate cyclization.

(16) α-Methylenehydroxyisopropyloxycarbonyldiethyl malonate (XXXVI):

12.0 g. of the aldehyde XXXIV was dissolved in 200 ml. of ethyl acetate in a 500 ml. flask. Approximately 1 g. of Adams catalyst was dispersed in the solution and the stirring solution was kept in contact with hydrogen gas for 1 week. The catalyst was filtered out and the solvent evaporated under vacuum. The residue (crude alcohol XXXVI) weighed approximately 12 g. (100%).

Infrared spectrum (Fig. XV). N.m.r. spectrum (Fig. XLIV).

(17) α-Methylenechloroisopropyloxycarbonyldiethyl malonate (XXXVII).

12.0 g. of the crude alcohol XXXVI was stirred with

50 ml. of distilled thionyl chloride overnight at room temperature. The excess of thionyl chloride was removed under vacuum and the traces of thionyl chloride were co-evaporated with benzene. The residue was purified by t.l.c. and column chromatography using silica gel as a base and chloroform as a solvent (9.8 g. , 80%).

Infrared spectrum (Fig. XVI). N.m.r. spectrum (Fig. XLV).

Attempted cyclization of the chloro compound XXXVII:

450 mg. (0.01 mole) of 50% suspension of NaH/oil was washed with dry benzene and transferred to a predried 3-necked 100 ml. flask fitted with a reflux condenser having a nitrogen baloon on top. 1.2 g. (0.004 mole) of the chloro compound XXXVII dissolved in 25 ml. of dry t.h.f. was transferred to the flask containing sodium hydride under anhydrous condition. The system was sealed off to the atmosphere and the stirring reaction mixture was refluxed overnight. The reaction mixture was worked up as usual. The compound recovered was identified as the starting material. The attempt was repeated using dioxane and d.m.f. as solvents. Again, the starting material was recovered from dioxane but d.m.f. caused the formation of a tarry material which could not be identified.

(18) α-(2-chloro-1-propene)diethyl malonate (XL):

To 16 ml. (0.1 mole) of diethyl malonate was added slowly 5 g. (50% suspension in oil) of sodium hydride washed with dry benzene, over a period of 15 minutes and the contents of the flask were stirred for 10 minutes. To the reaction flask was introduced 7.5 ml. (0.08 mole) of 2,3-dichloro —

1-propene dropwise and the stirring was continued for 2 hours at room temperature. The reaction mixture was dumped into ice water, acified with dil. hydrochloric acid and extracted with chloroform (2 X 10 ml.). The chloroform was dried and flash evaporated. The compound was purified by vacuum distillation, b.p. 80-95° at 0.4 mm. of Hg. (11.50 g., 60%). Infrared spectrum (Fig. XVII). N.m.r. spectrum (Fig. XLVI).

(19) α-Ethoxycarbonyl-α-(2-chloro-1-propene)diethyl-succinate (XLI):

4.60 g. (0.02 mole) of the mono substituted diethyl malonate XL and 5 g. (0.03 mole) of bromo ethylacetate were taken in 10 ml. of dry t.h.f. To the stirring solution was added 1 g. (0.02 mole) of 50% suspension of NaH/oil after washing with dry benzene and the stirring was continued for 1 hour. The reaction mixture was dumped into ice water and extracted with chloroform (2 X 10 ml.). The chloroform was dried and flash evaporated. The unreacted bromo ethylacetate was removed under vacuum. The product was found to be satisfactorily pure (6.0 g., 95%).

Infrared spectrum (Fig. XVIII). N.m.r. spectrum (Fig. XLVII).

(20) α,α-Di(2-chloro-1-propene)diethyl malonate (XLIV):

16 ml. (0.1 mole) of diethyl malonate and 24 ml. (0.25 mole) of 2,3-dichloro-1-propene were mixed in 25 ml. of dry t.h.f. in a 200 ml. flask. To the stirring solution was added 5 g. of 50% suspension of NaH/oil after washing with dry benzene, over a period of 15 minutes. The reaction mixture was refluxed for 4 hours and the product was worked up as in the preparation of XLI. Vacuum distillation gave a

slightly coloured liquid, b.p. 95-107°C at 0.02 mm. of Hg. (28.0 g., 90%).

Infrared spectrum (Fig. XIX). N.m.r. spectrum (Fig. XLVIII).

(21) 3-Methylcyclohex-2-ene-1-one-5-carboxylic acid (XLV):

The disubstituted diethyl malonate (XLIV) was taken with 8 times its weight of concentrated hydrobromic acid in a closed bomb and the temperature was raised slowly with stirring to 100°C. The organic layer dissolved slowly in hydrobromic acid after 4-5 hours of stirring at 100°C and the reaction mixture turned dark brown. The reaction mixture was cooled down and a suspended black solid material was filtered out. The filtrate was extracted several times with ethyl acetate. The combined extract was washed with water, dried over magnesium sulphate and flash evaporated to leave a brown viscous liquid with white crystalline solid. The liquid was dissolved in methylene chloride leaving out the solid (by-product). The methylene chloride was evaporated and white crystalline acid was sublimed out from the residue followed by recrystallization from a mixture of chloroform/benzene, m.p. 85-86°C, (maximum yield realized, 55%).

Infrared spectrum (Fig. XX). N.m.r. spectrum (Fig. XLIX).

(22) Methyl ester XLVIII of the keto acid (XLV):

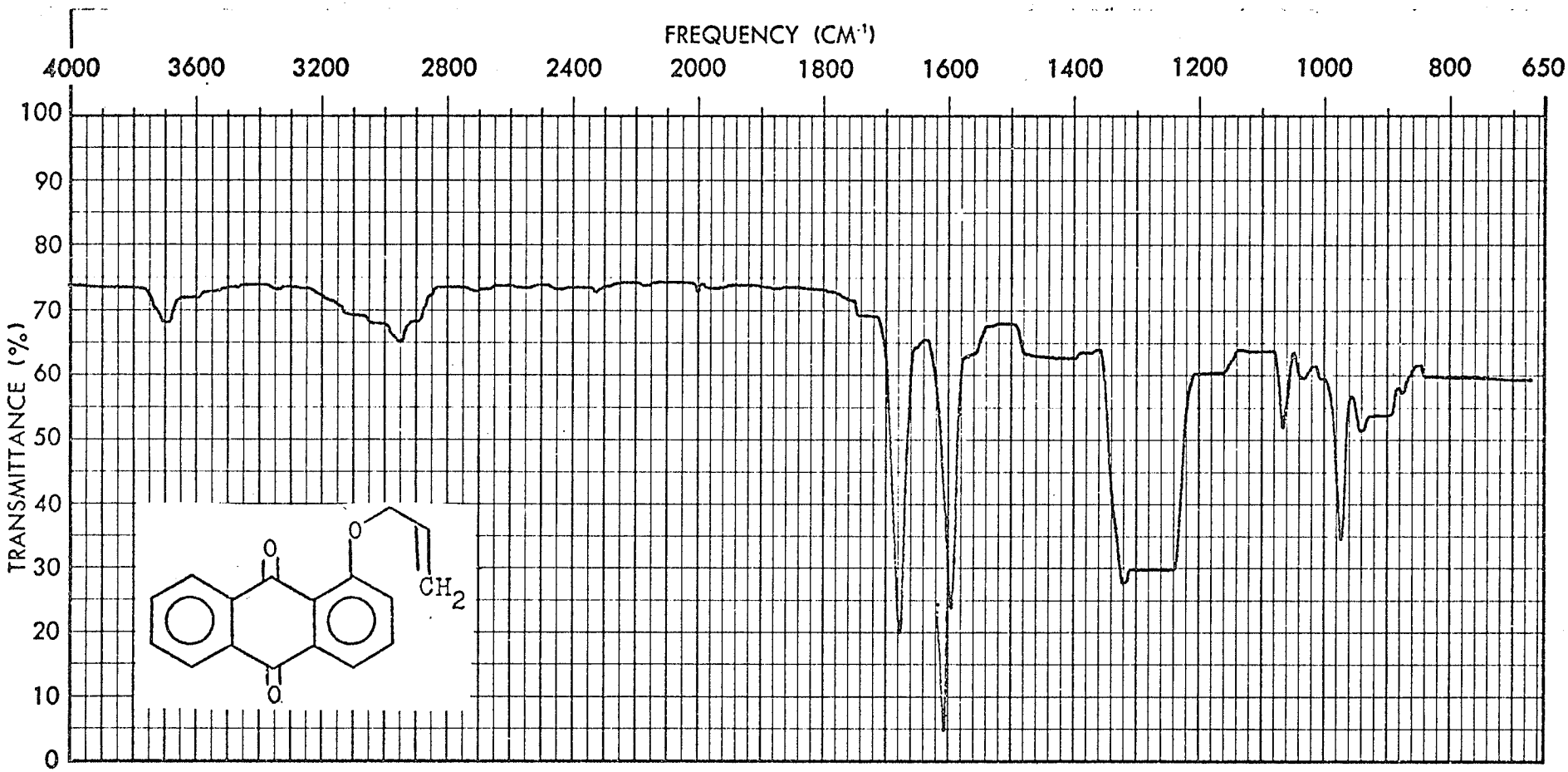
3 g. (0.02 mole) of the keto acid XLV was dissolved in 20 ml. of dry acetone in a 50 ml. flask. To the stirring solution was added 5 g. (approx. 0.03 mole) of finely ground potassium carbonate followed by 6 ml. of methyl iodide (used in excess). The reaction mixture was stirred overnight under nitrogen at room temperature. The excess of

methyl iodide and the solvent were evaporated and the residue was extracted with water and chloroform. The chloroform was dried and evaporated. The residue was found to be satisfactorily pure methyl ester XLVIII, (3.20 g., 95%).

(23) 2-Carbomethoxy-4-keto-pentanoic acid (LI):

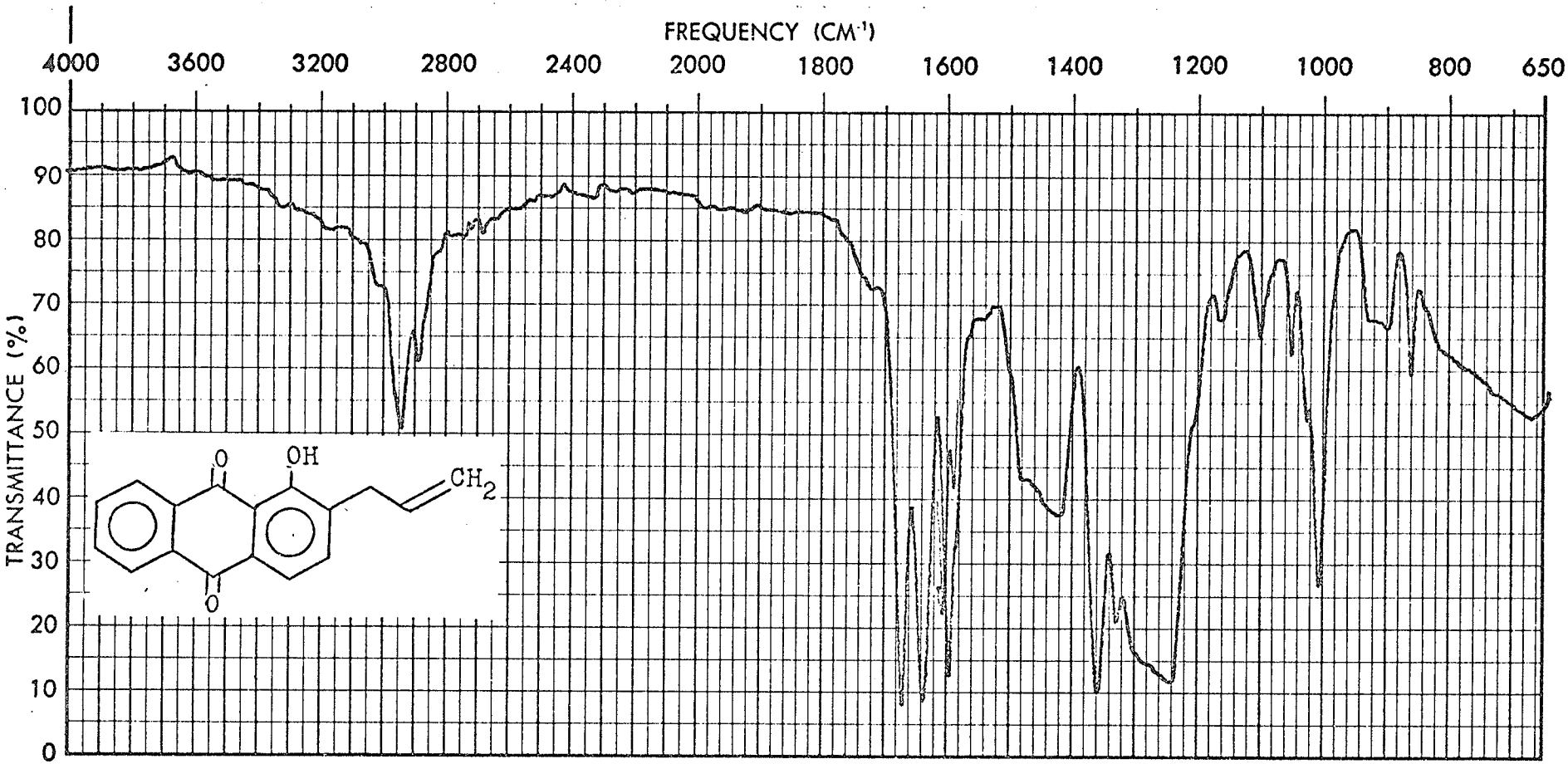
400 mg. (0.0023 mole) of the keto ester XLVIII was dissolved in 15 ml. of t-butanol/water azeotrope. To the stirring solution was added 280 mg. of potassium carbonate dissolved in 8 ml. of water followed by 2 g. of sodium meta-periodate dissolved in 25 ml. of water. 1.5 Ml. of 0.8% aqueous solution of potassium permangnate was added to the reaction mixture dropwise to maintain a reddish tinge in the bulk. The reaction mixture was stirred at room temperature for 1 hour. The excess of potassium permanganate was added destroyed by adding a saturated aqueous solution of sodium bisulphite until an iodine colour developed. The resulting reaction mixture was concentrated under vacuum, acidified with ice cold 50% sulphuric acid and extracted with ether (4 X 10 ml.). The ether extract was washed with sodium bisulphite solution until the iodine colour disappeared. Finally, the ether extract was washed with water, dried over magnesium sulphate and flash evaporated to leave a viscous liquid (300 mg., 75%).

Infrared spectrum (Fig. XXIV). N.m.r. spectrum (Fig. LIII).



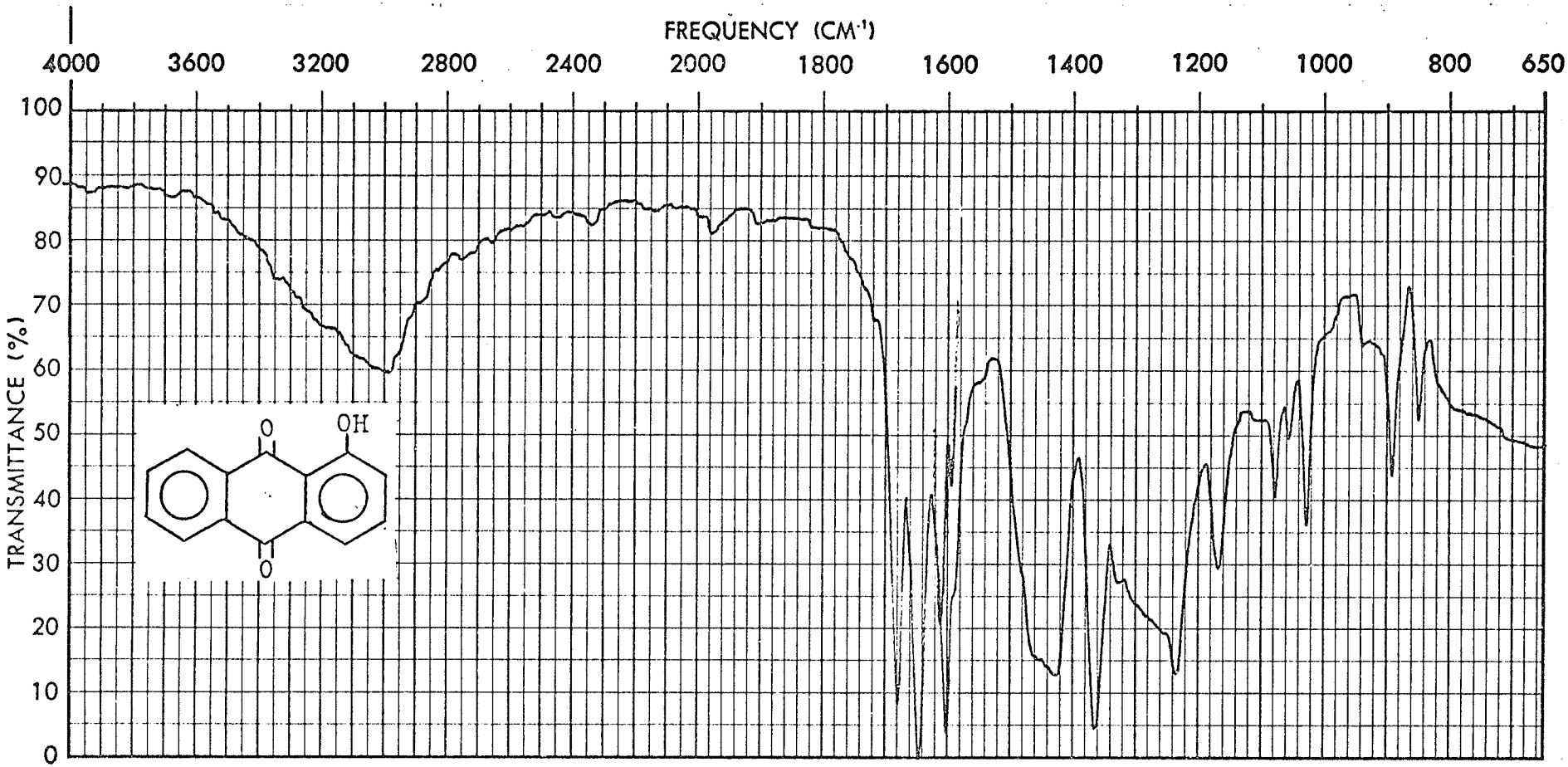
Infrared spectrum no. 1: 1-allyl anthraquinone ether (IX).

(Fig. I)



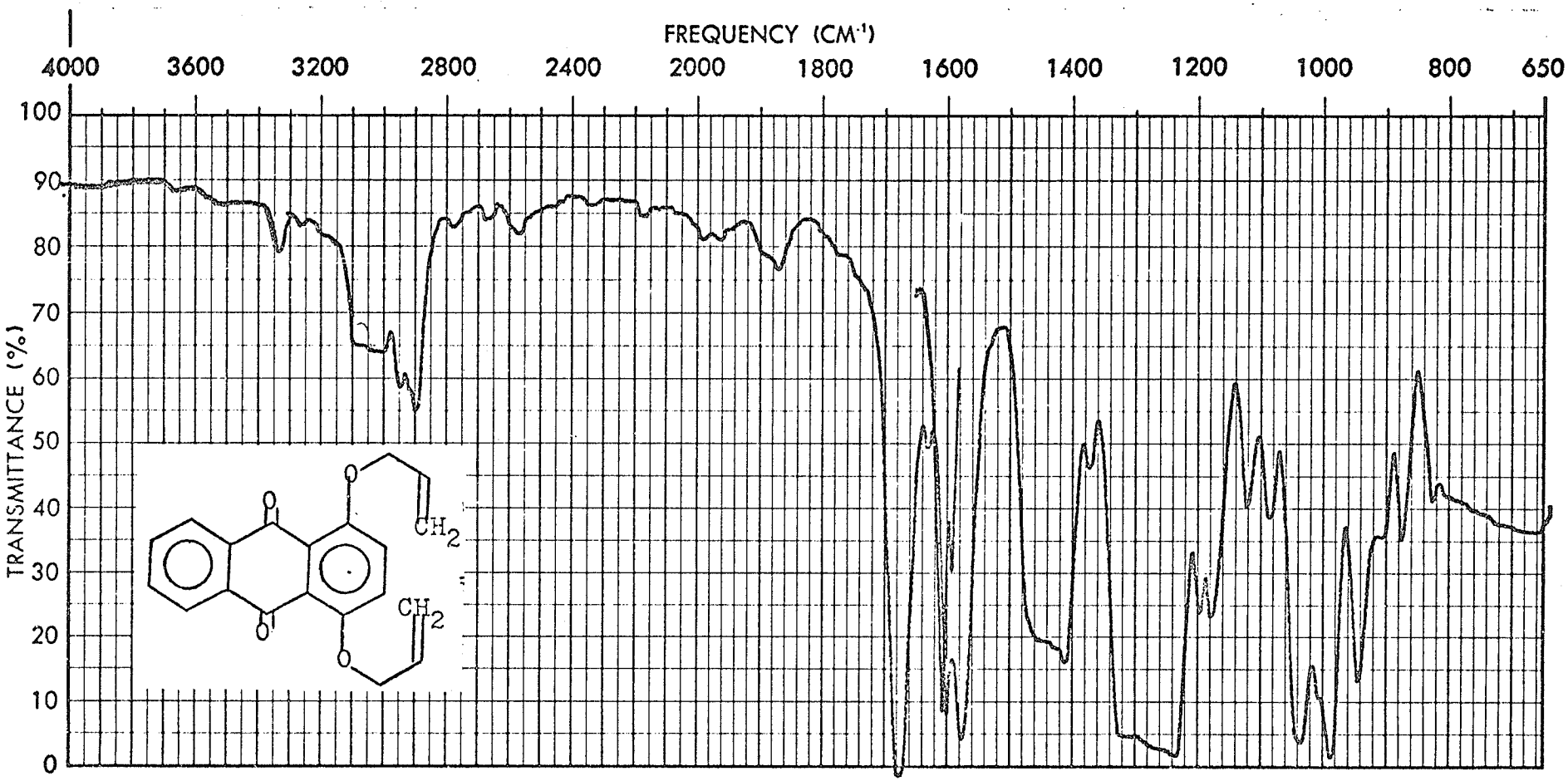
Infrared spectrum no. 2: 2-allyl, 1-hydroxy anthraquinone. (Xa).

(Fig. II)



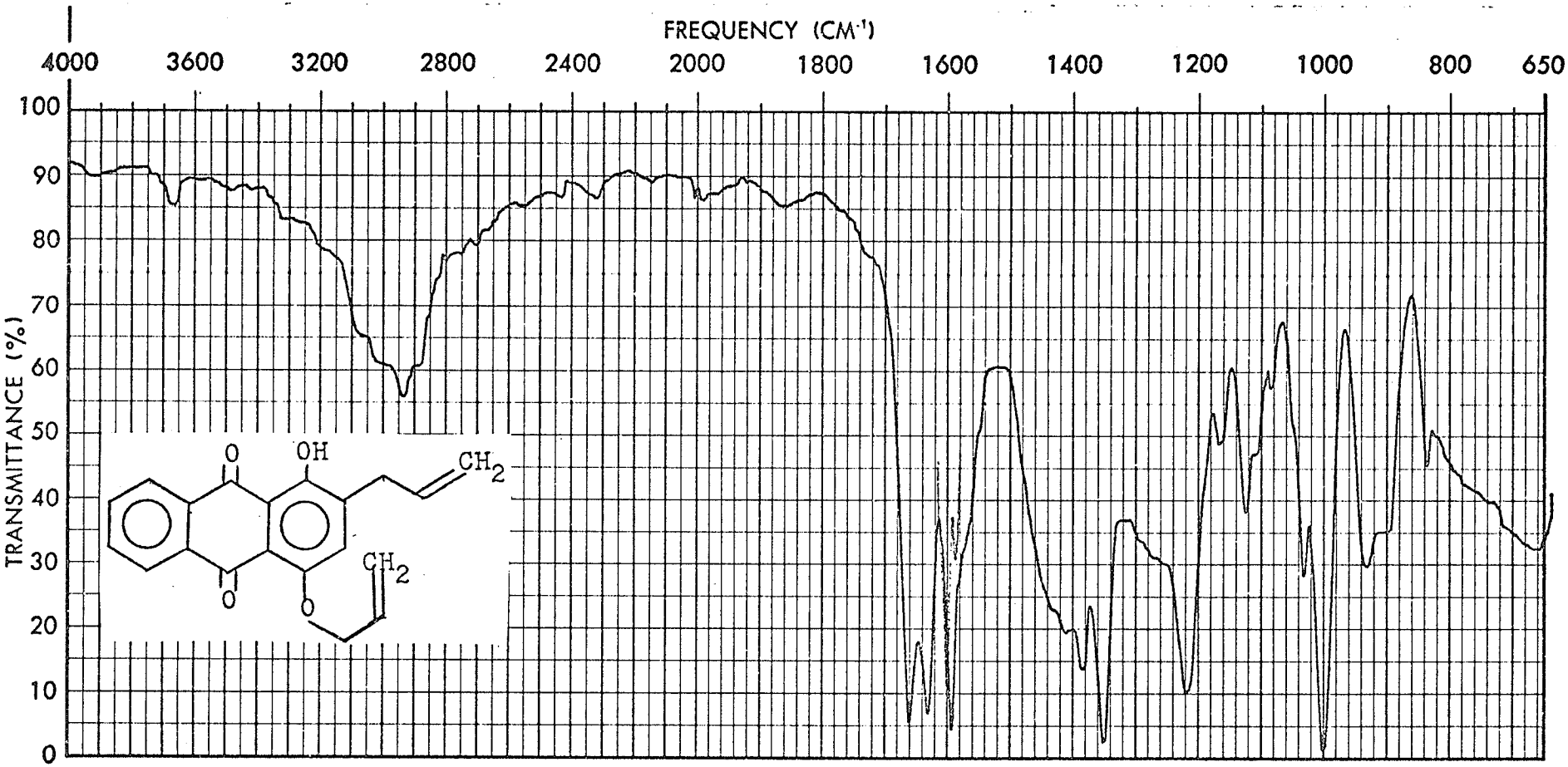
Infrared spectrum no. 3: 1-hydroxy anthraquinone (XIII).

(Fig. III)



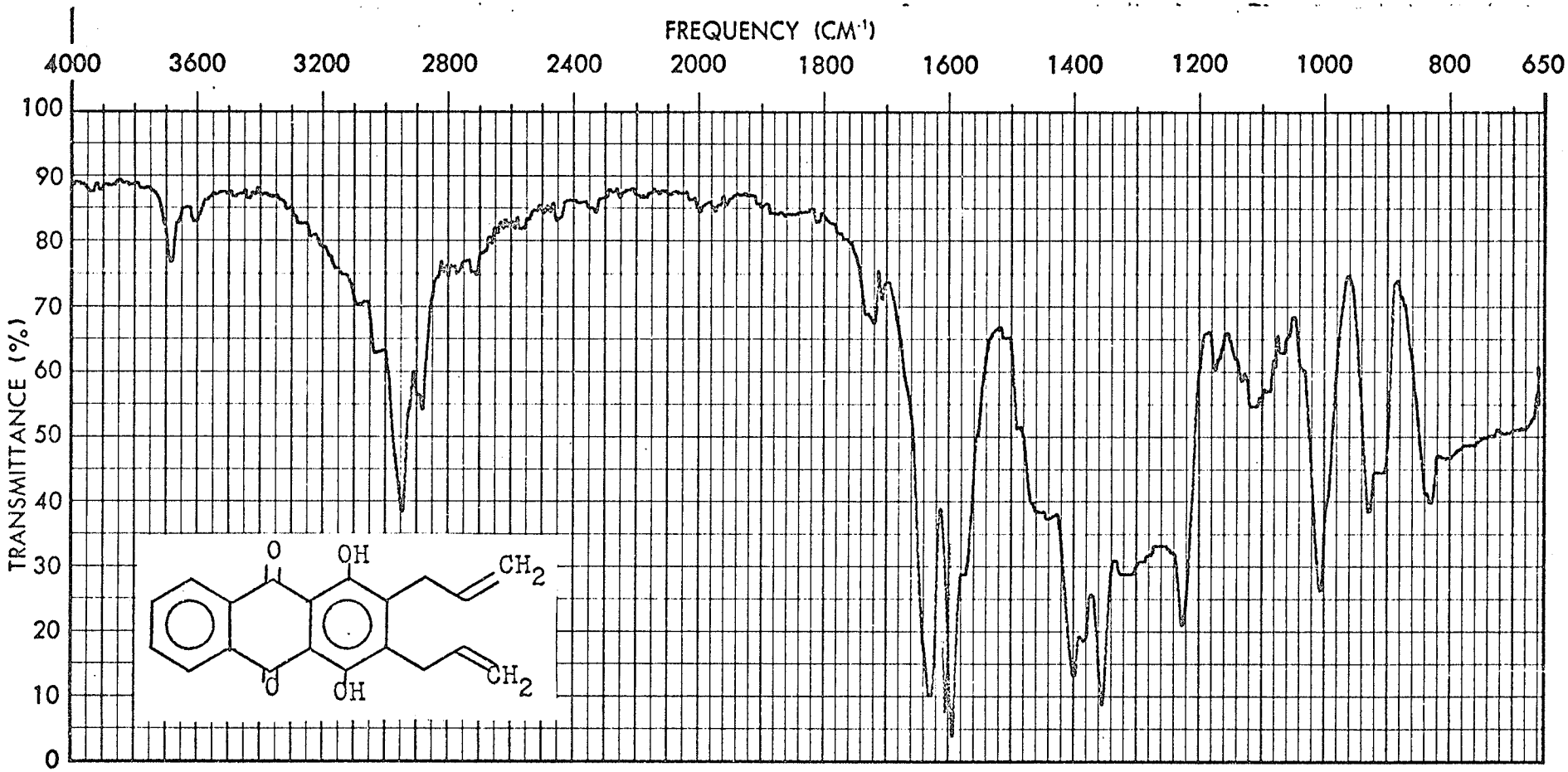
Infrared spectrum no. 4: 1,4-diallyl anthraquinone ether (XIV).

(Fig. IV)



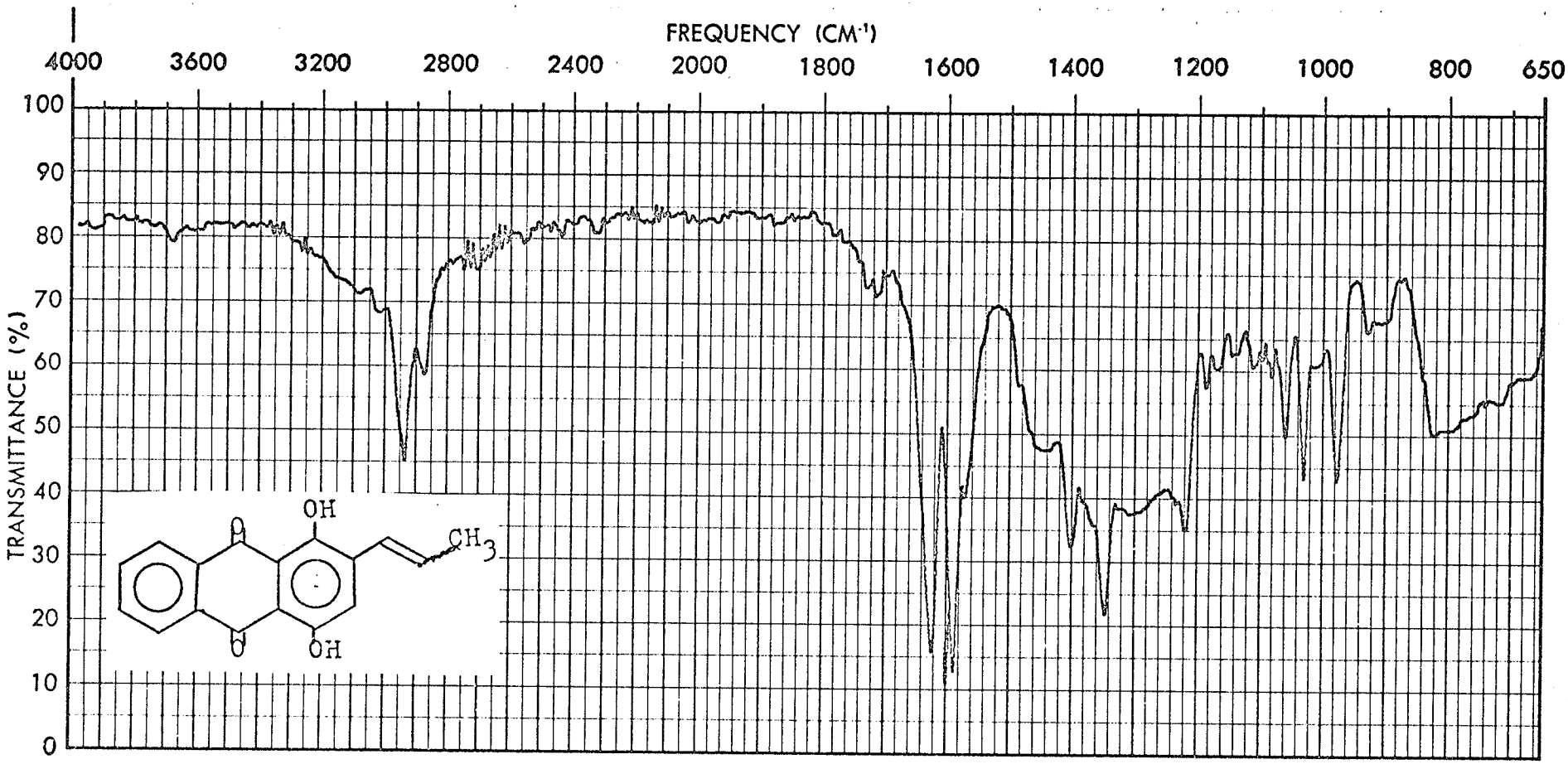
Infrared spectrum no. 5: 2-allyl, 4-allyloxy, 1-hydroxy anthraquinone (XV).

(Fig. V)



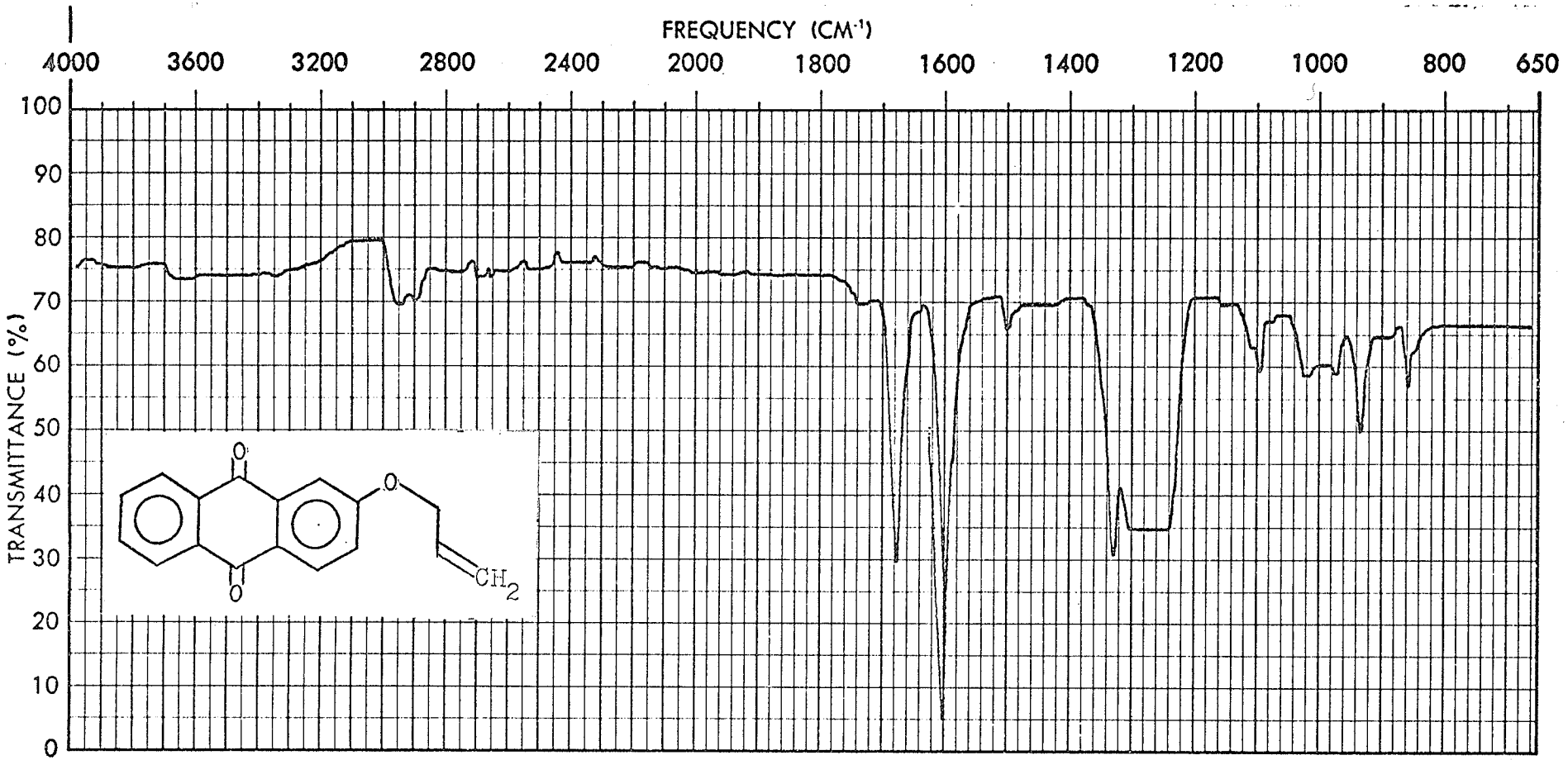
Infrared spectrum no. 6: 2,3-diallyl quinizarin (XVIa).

(Fig VI)



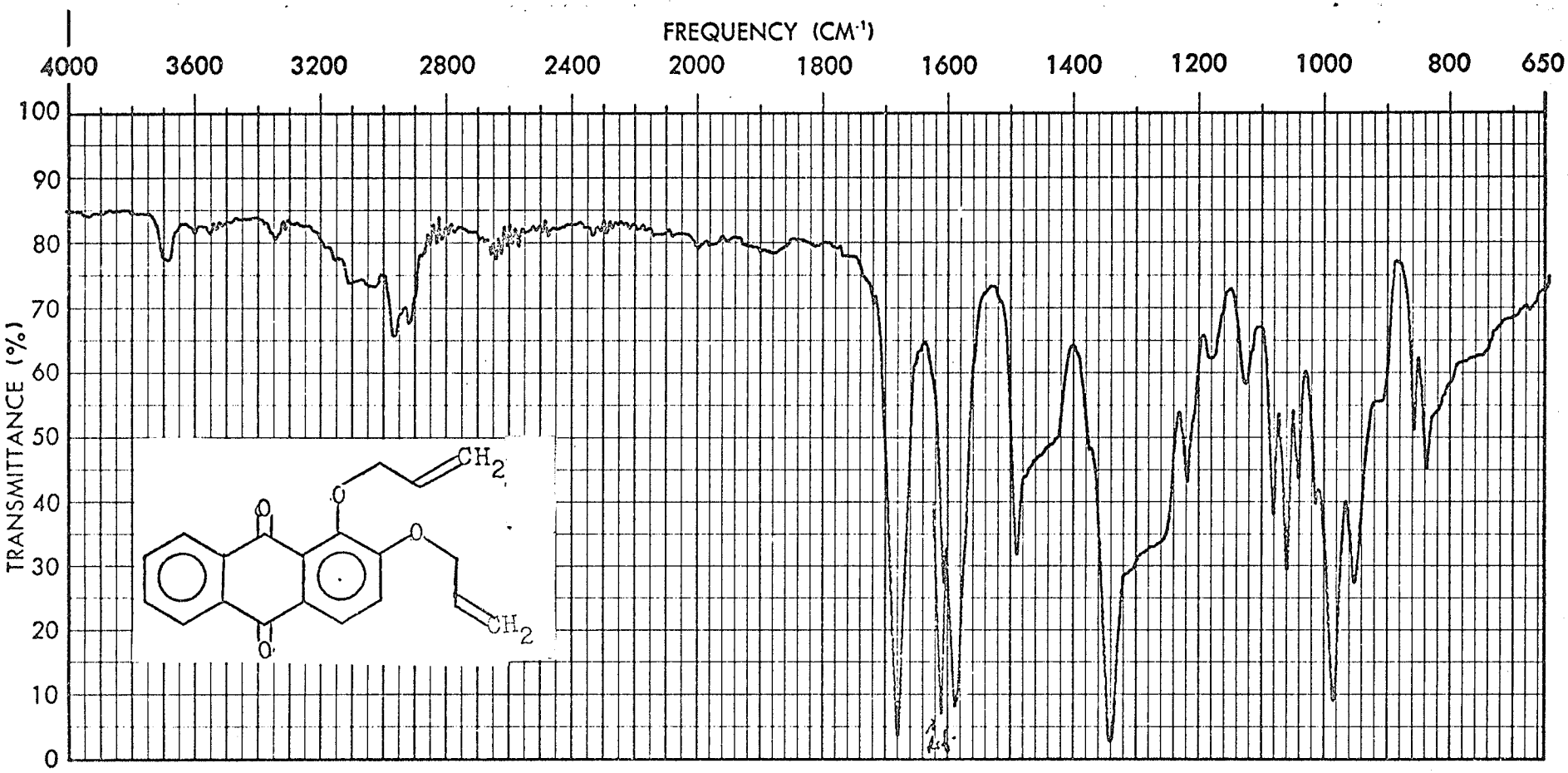
Infrared spectrum no 7: 2-propenyl quinizarin (XVII).

(Fig. VII)



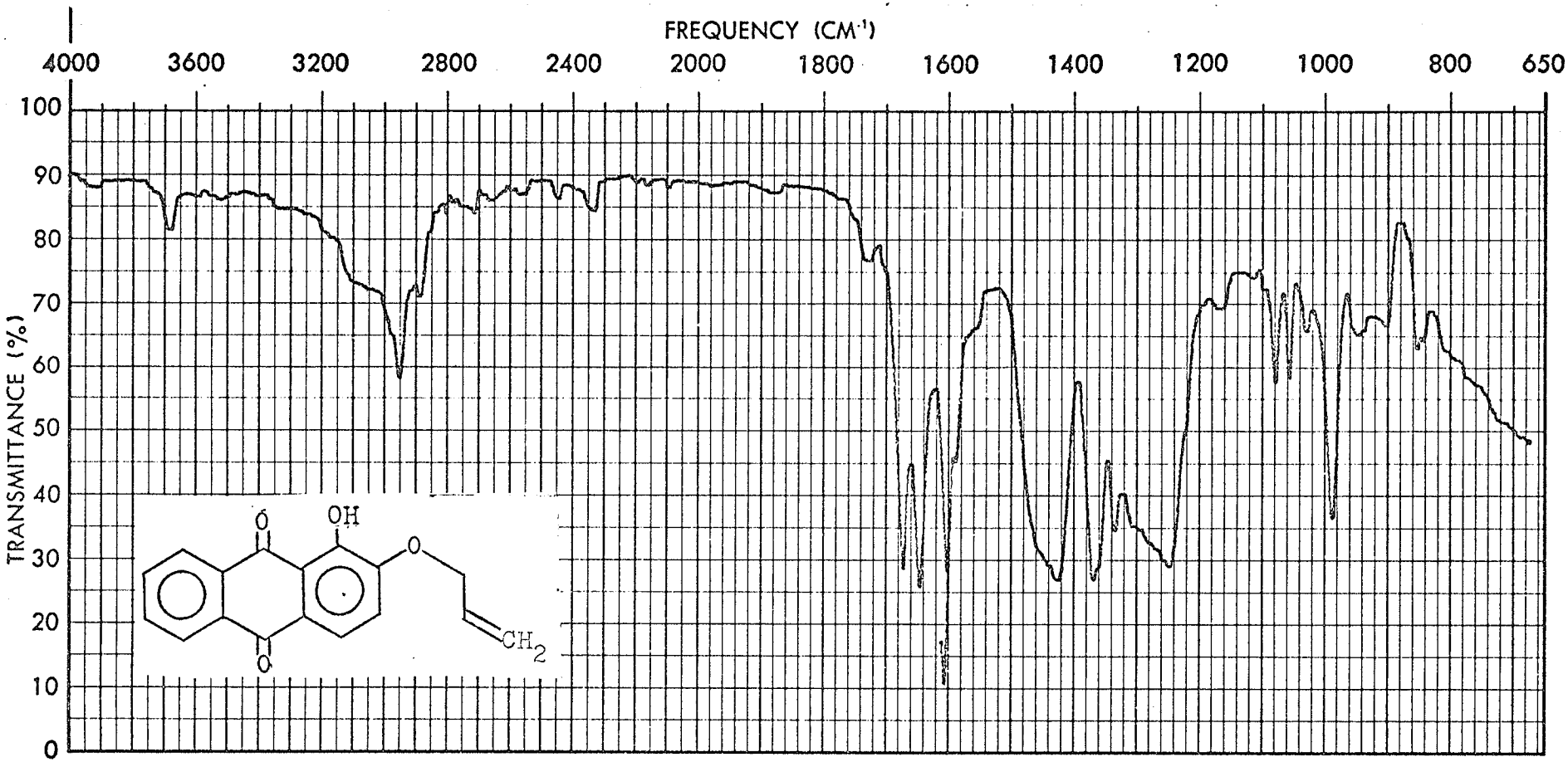
Infrared spectrum no. 8: 2-allyl anthraquinone ether (XVIII).

(Fig. VIII)



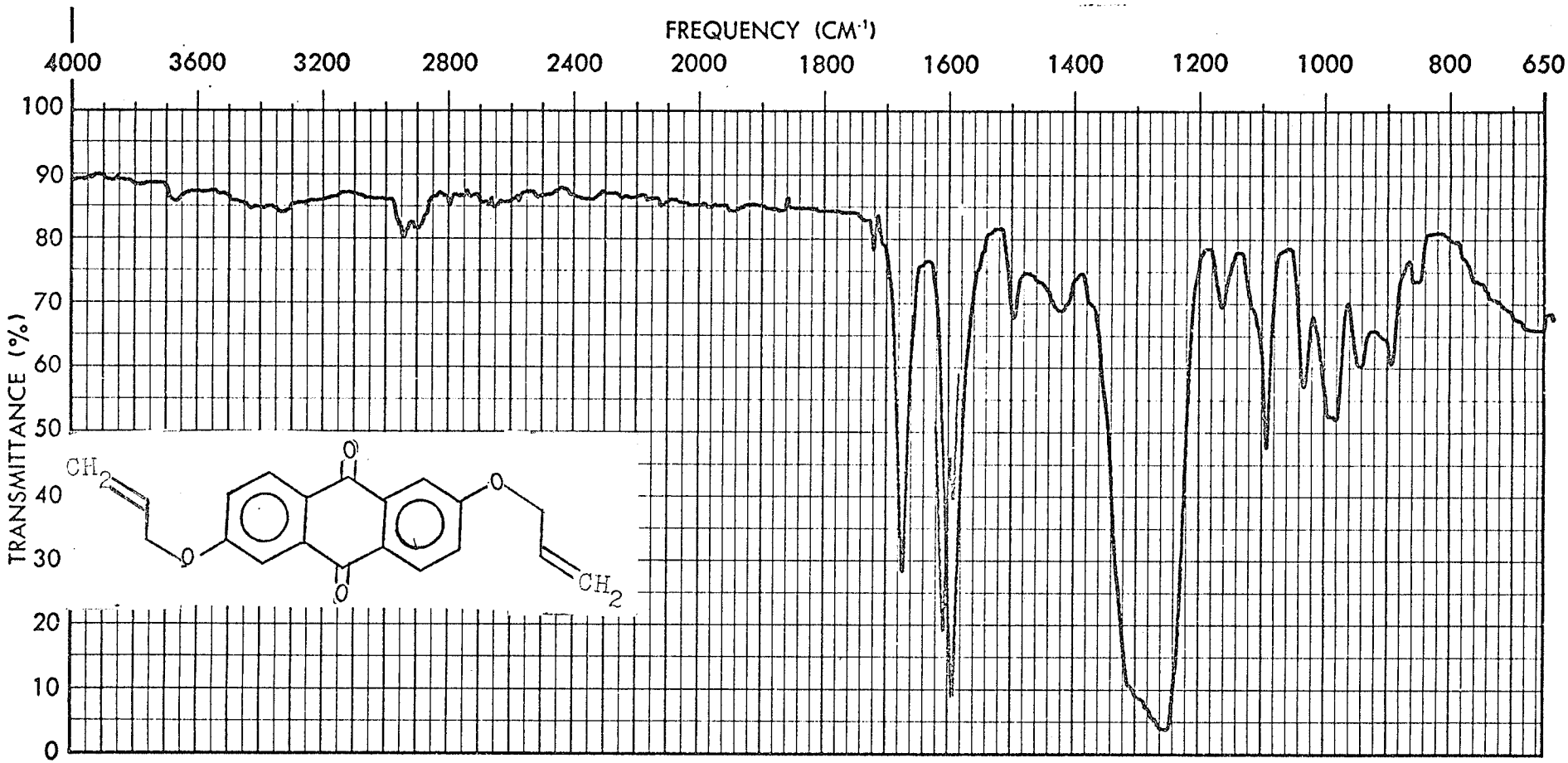
Infrared spectrum no. 9: 1,2-diallyl anthraquinone ether (XIX).

(Fig. IX)



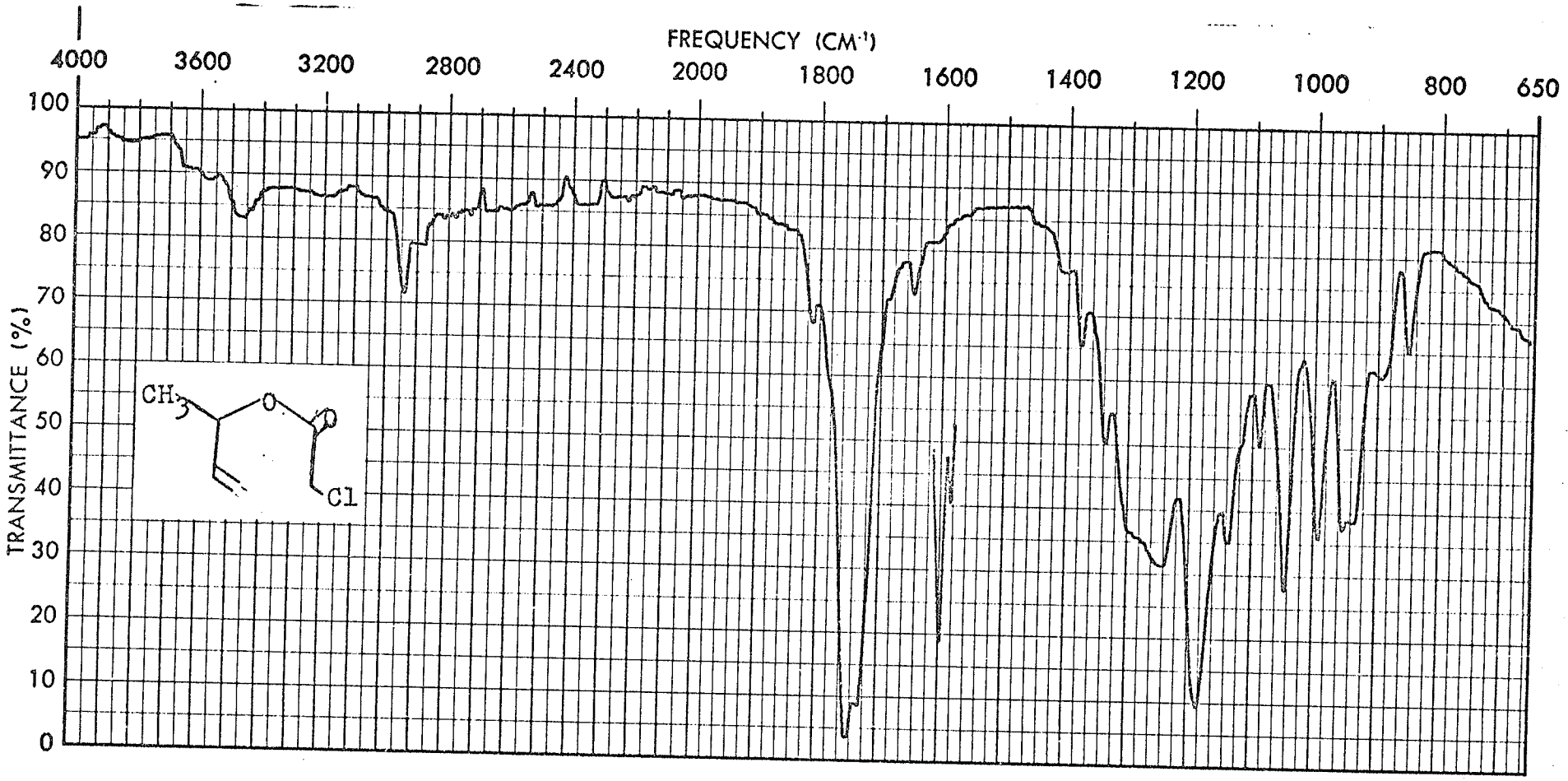
Infrared spectrum no. 10: 2-allyl, 1-hydroxy anthraquinone ether (XX).

(Fig. X)



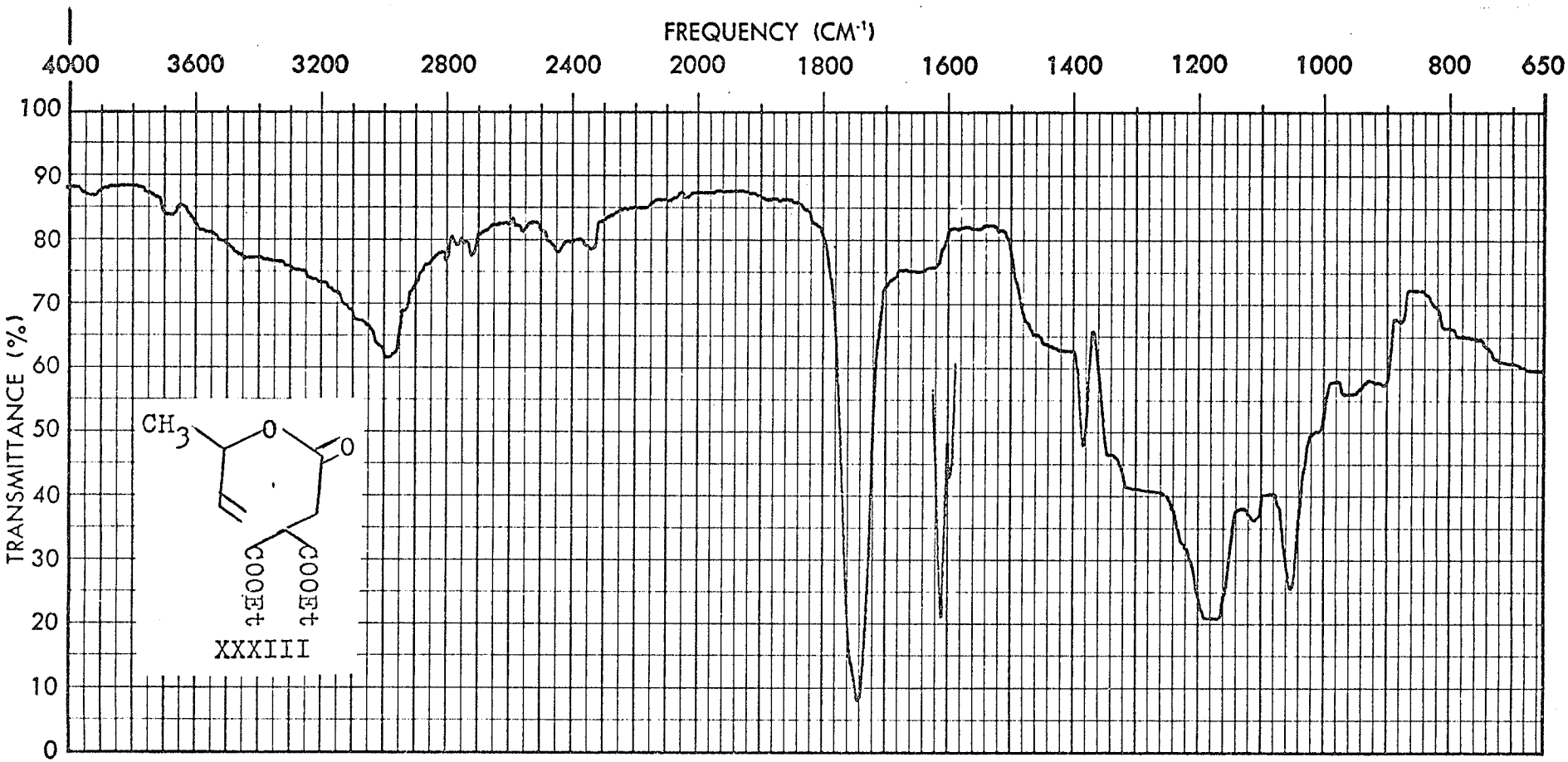
Infrared spectrum no. 11: 2,6-diallyl anthraquinone ether (XXI).

(Fig. XI)



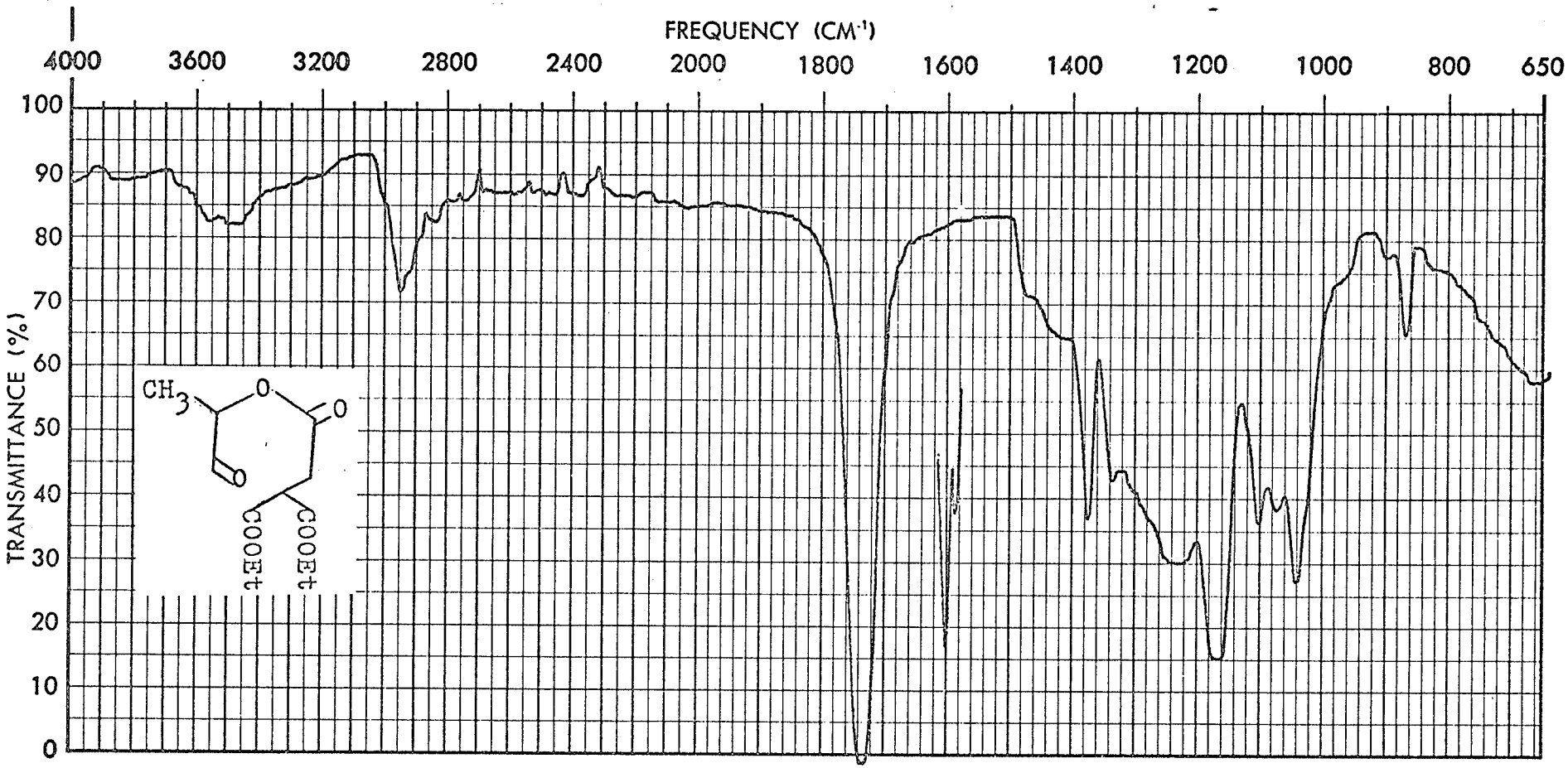
Infrared spectrum no. 12: Sec-butenyl chloroacetate (XXXII).

(Fig. XII)



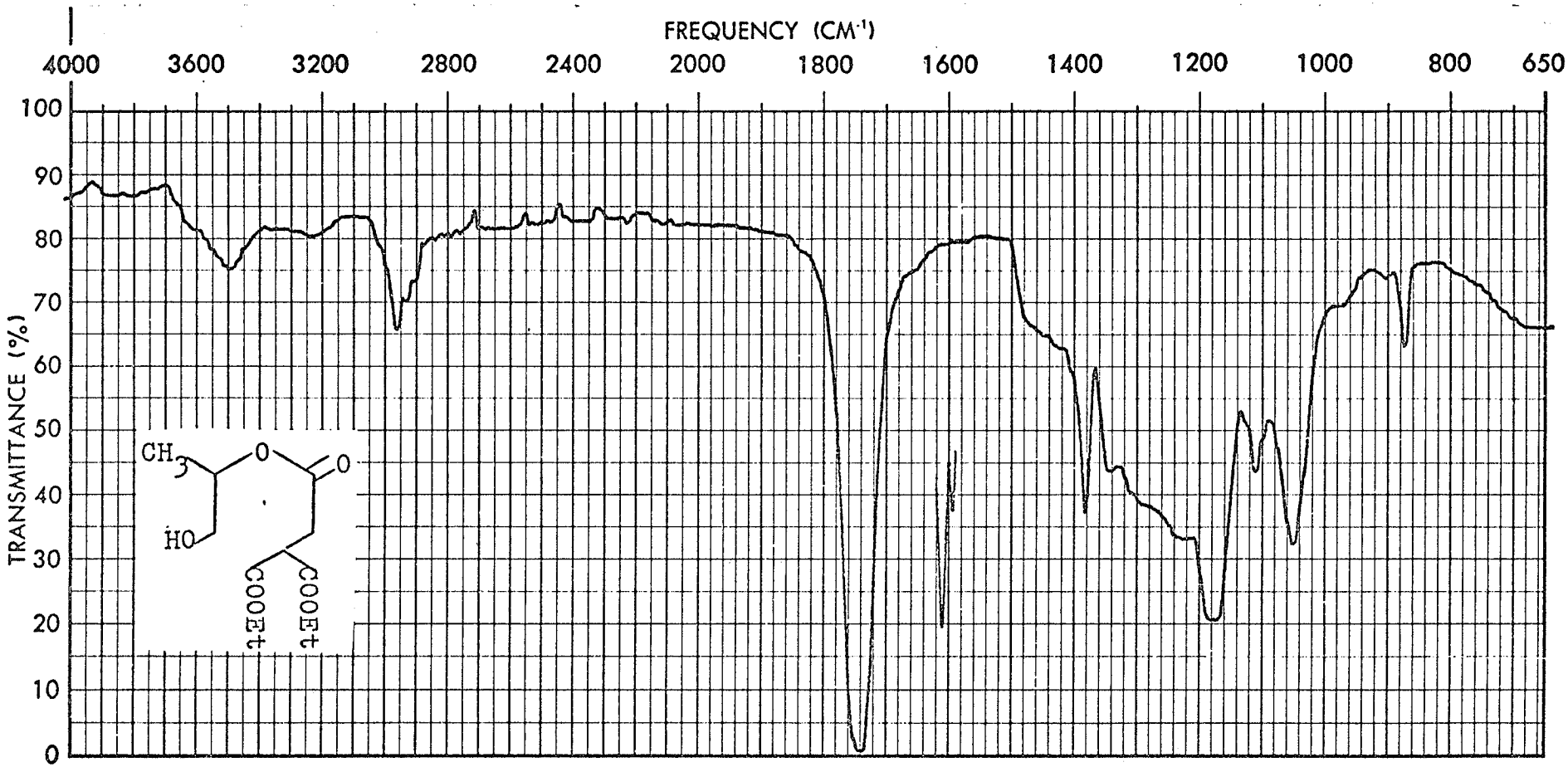
Infrared spectrum no. 13: α-methylene sec-butenyloxycarbonyldiethyl malonate (XXXIII).

(Fig. XIII)



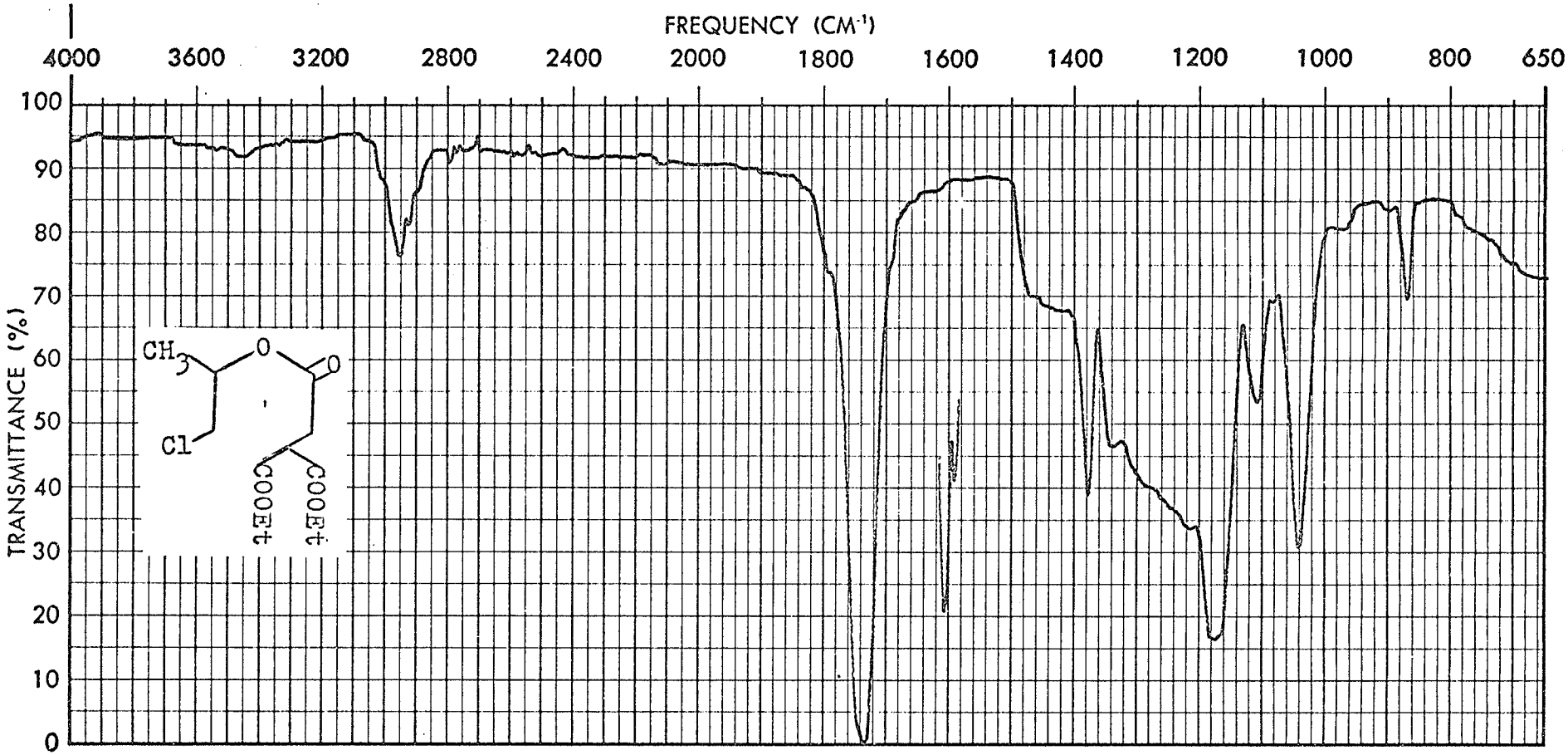
Infrared spectrum no. 14: α-methylene 1-formylethoxycarbonyldiethyl malonate (XXXIV).

(Fig. XIV)



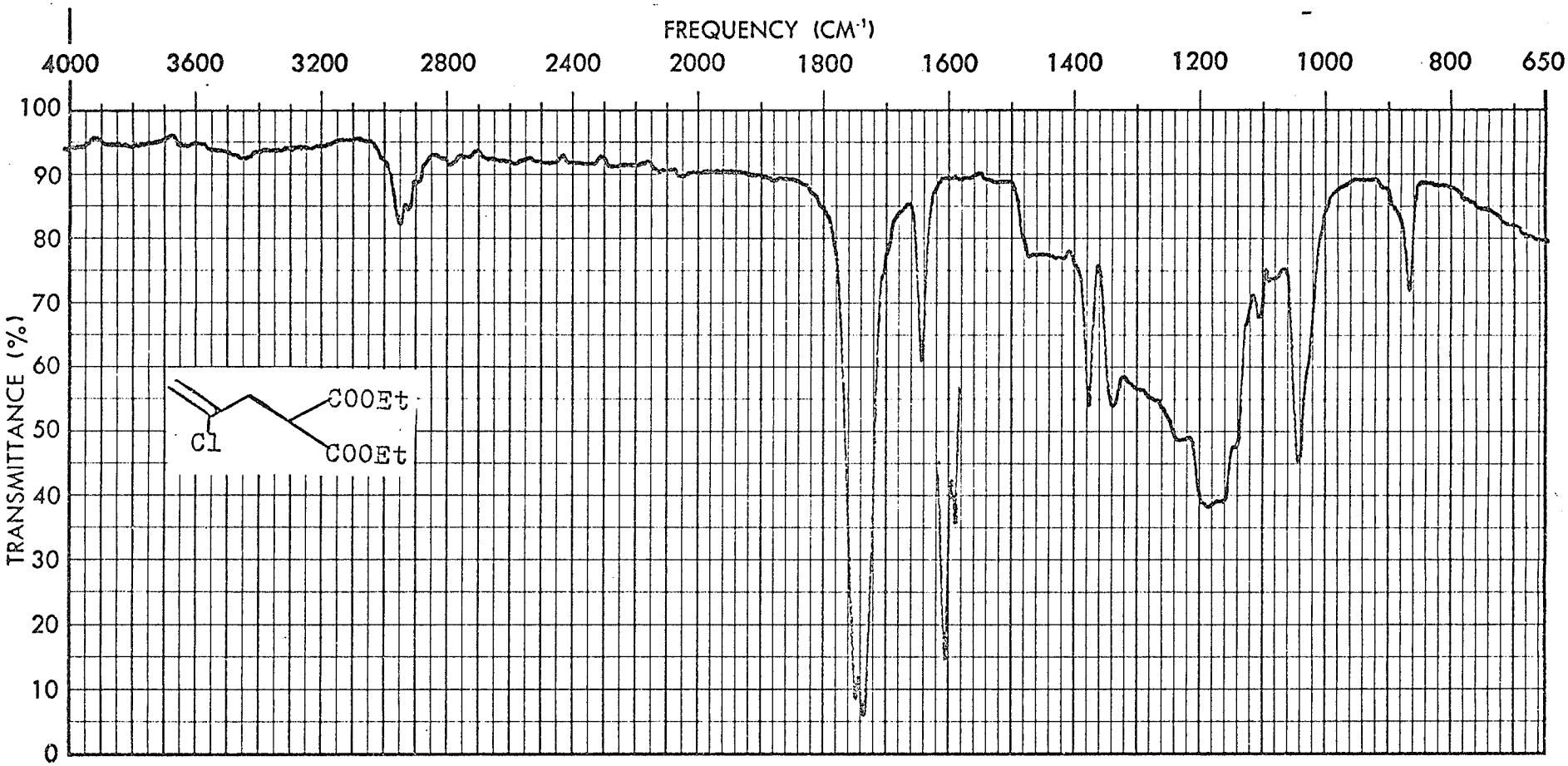
Infrared spectrum no. 15: α-methylenehydroxyisopropyloxycarbonyldiethyl malonate (XXXVI).

(Fig. XV)



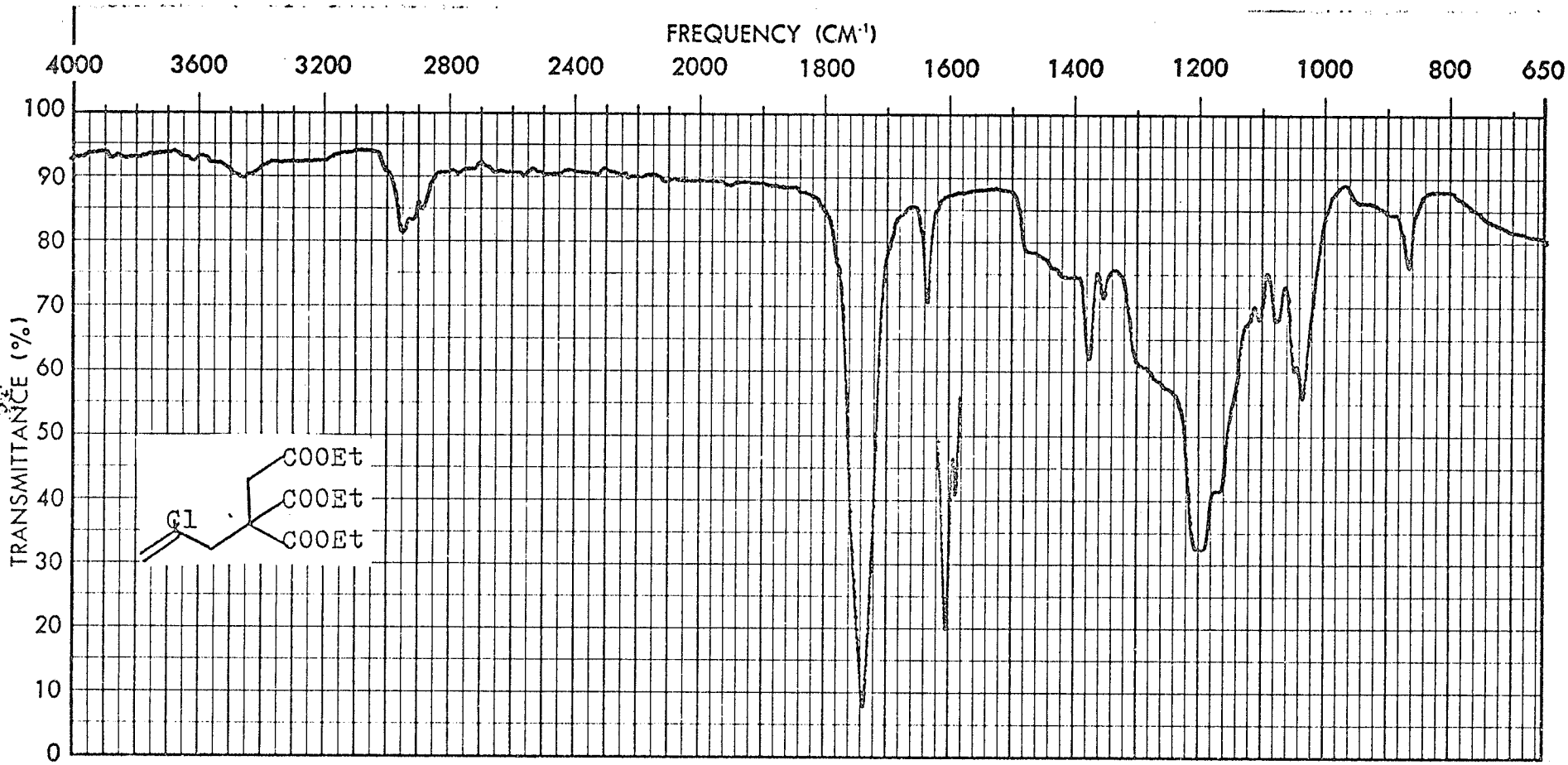
Infrared spectrum no. 16: α-methylenechloroisopropyloxycarbonyldiethyl malonate (XXXVII).

(Fig. XVI)



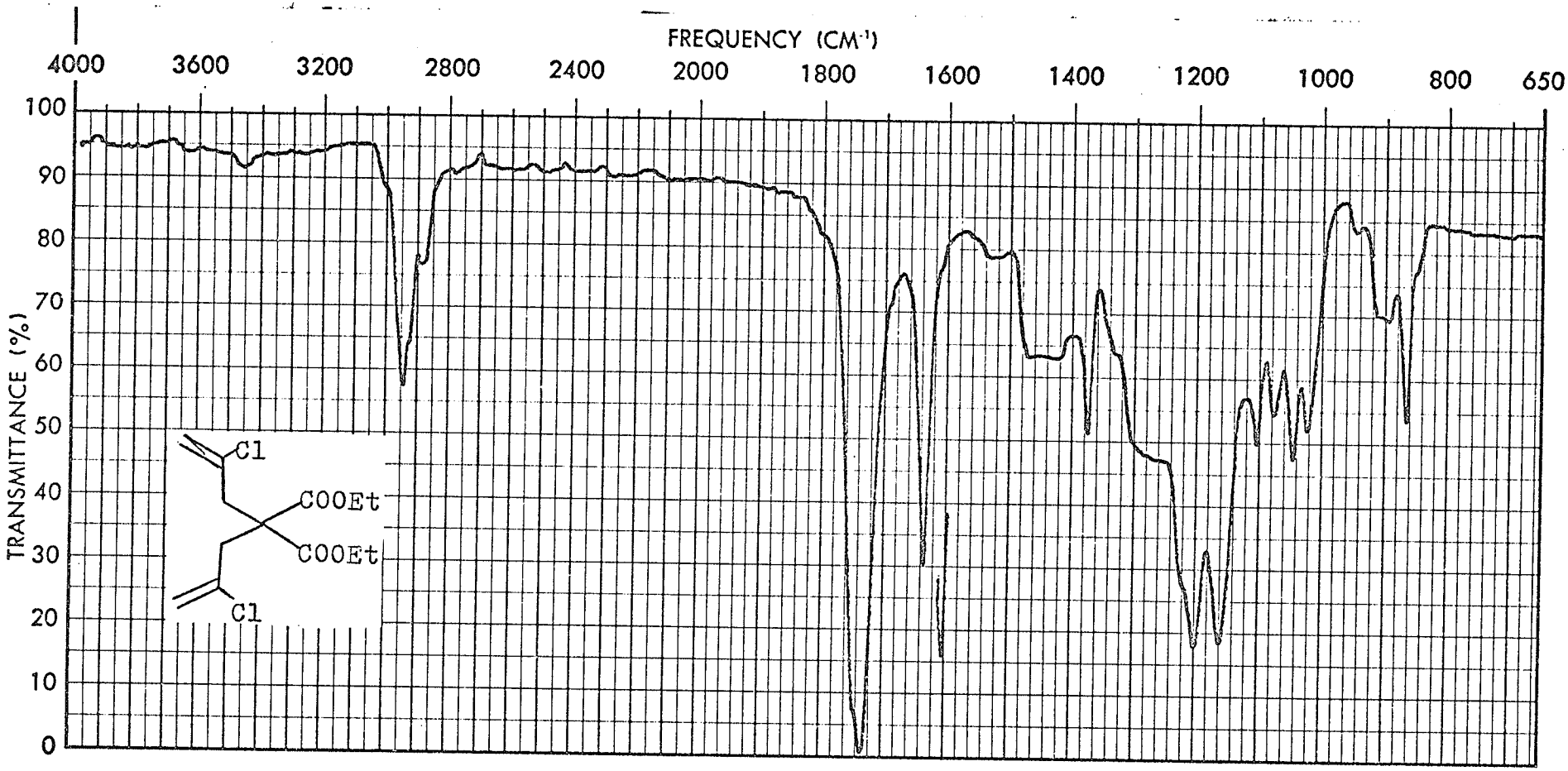
Infrared spectrum no. 17: α-(2-chloro-1-propene)diethyl malonate (XL).

(Fig. XVII)



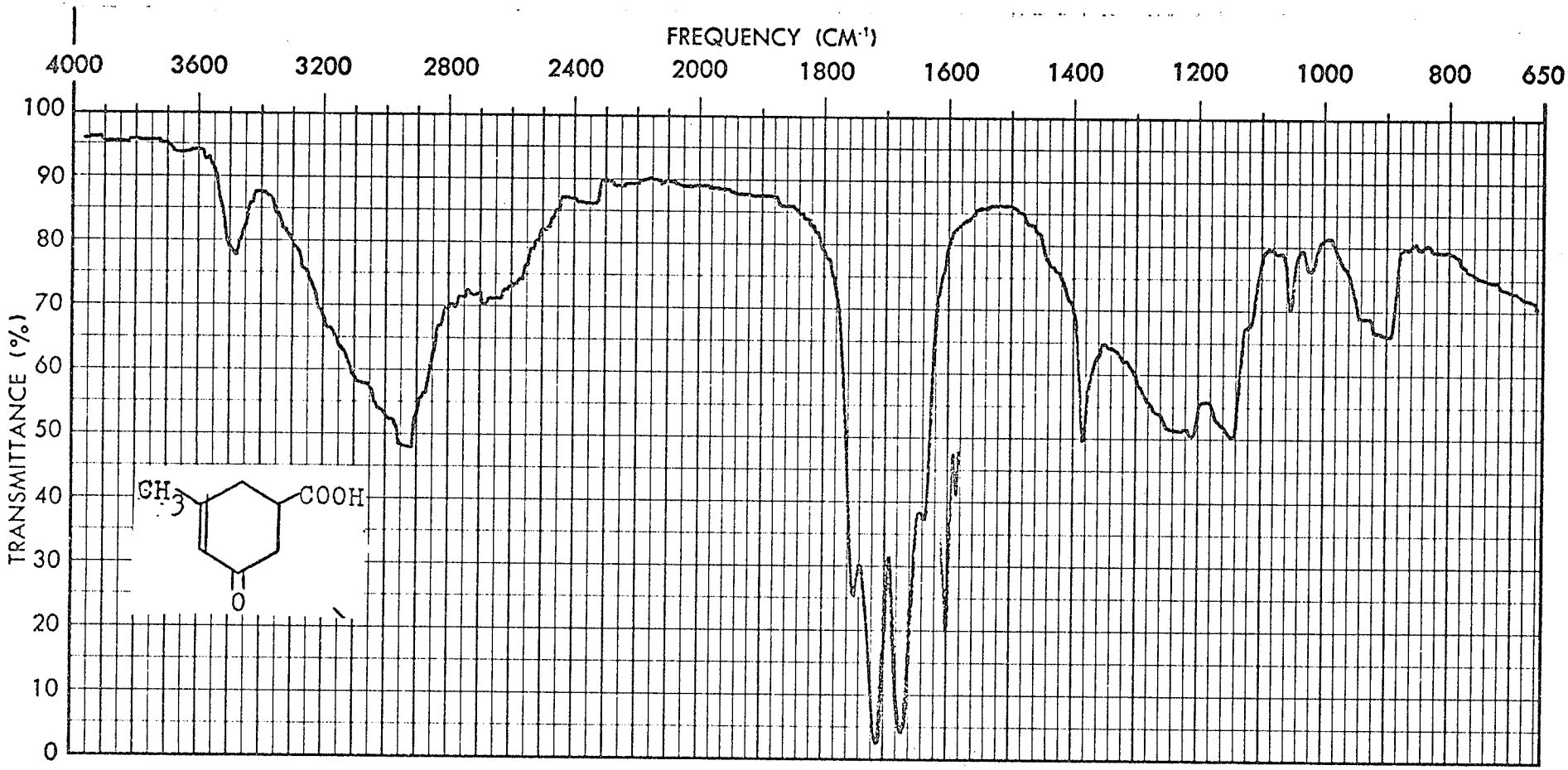
Infrared spectrum no. 18: α-ethoxycarbonyl-α-(2-chloro-1-propene)diethyl succinate (XLI).

(Fig. XVIII)



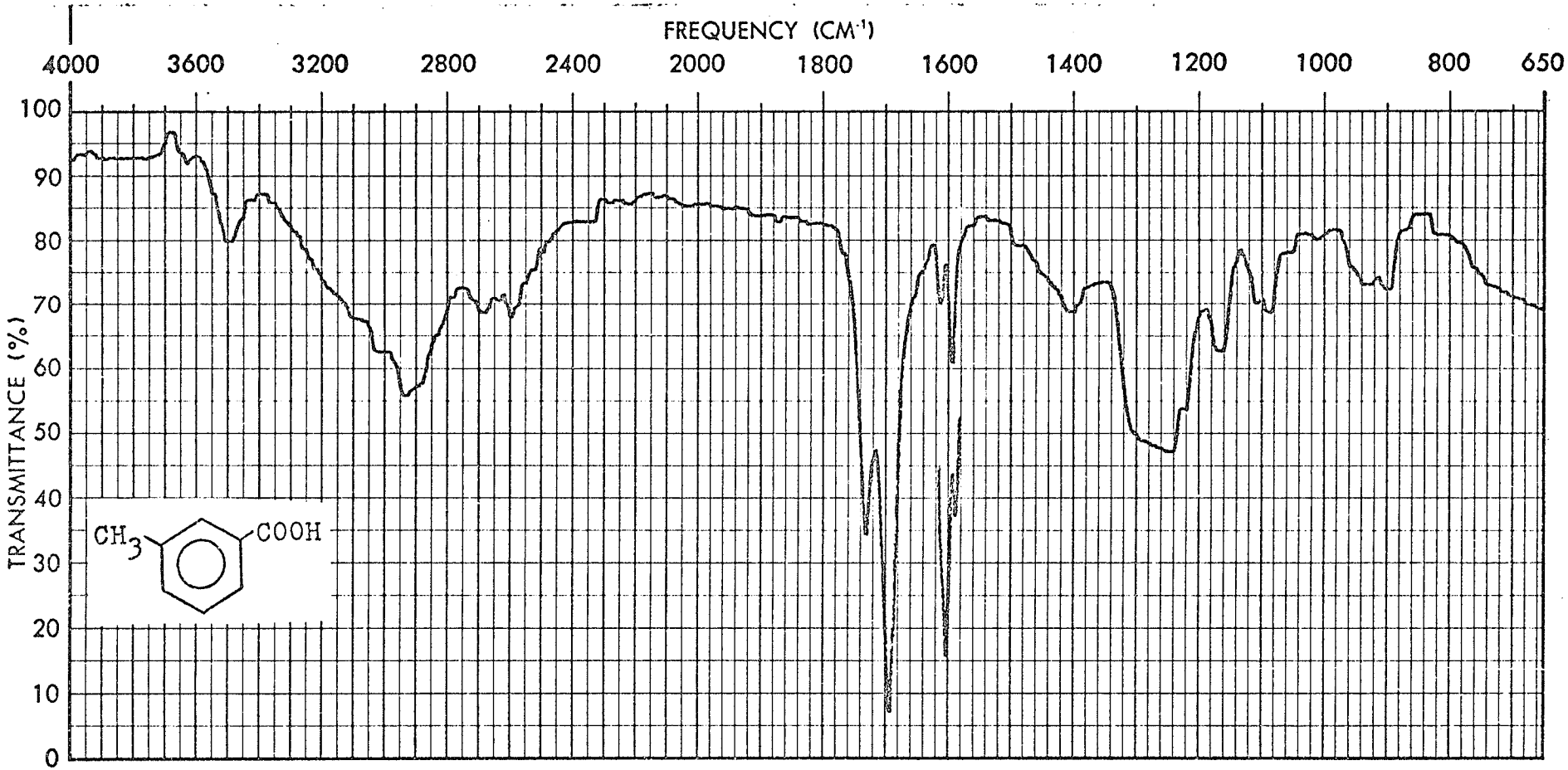
Infrared spectrum no. 19: ∝-∝-di(2-chloro-1-propene)diethyl malonate (XLIV).

(Fig. XIX)



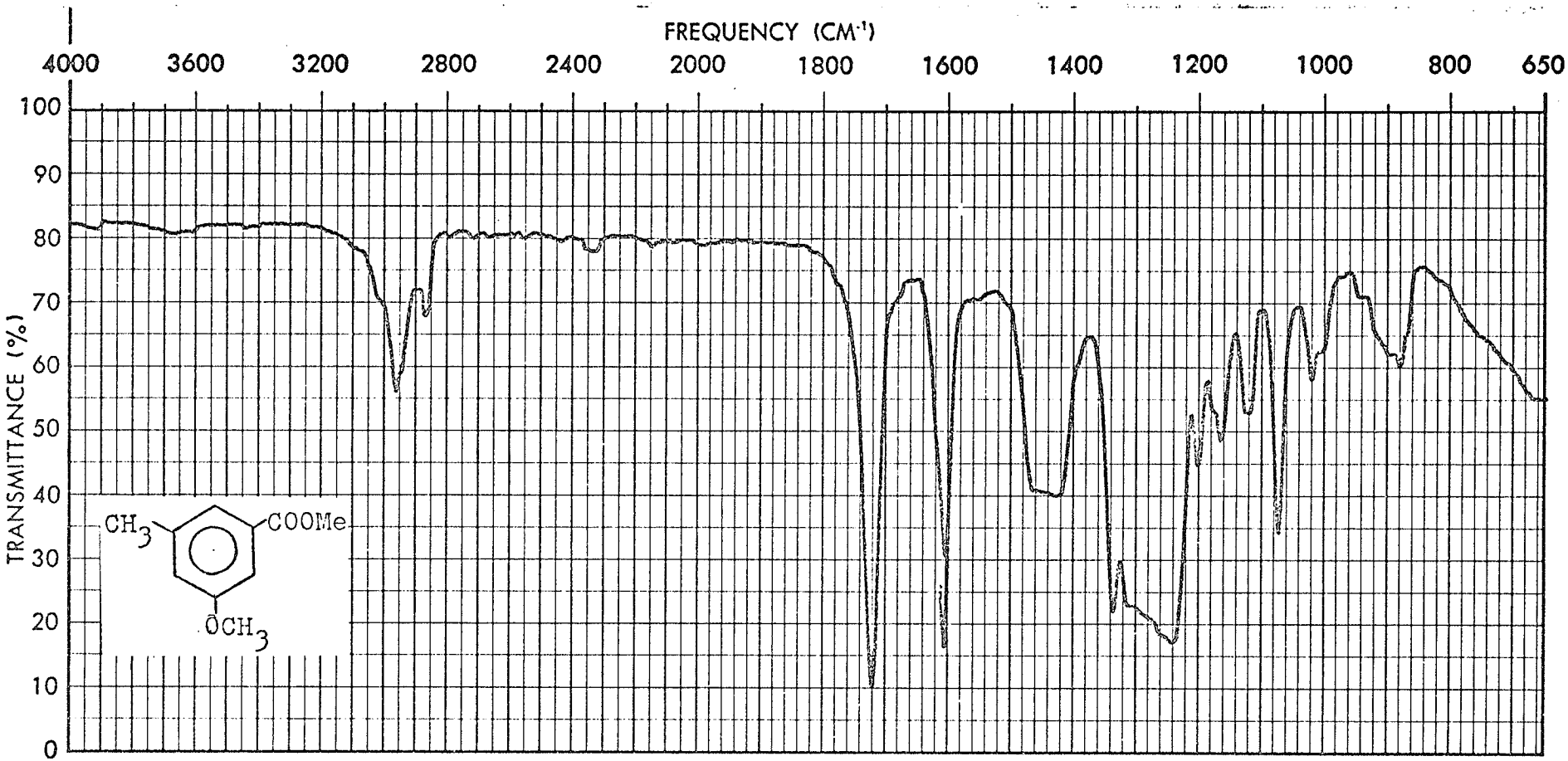
Infrared spectrum no. 20: 3-methylcyclohex-2-ene-1-one-5-carboxylic acid (XLV).

(Fig. XX)



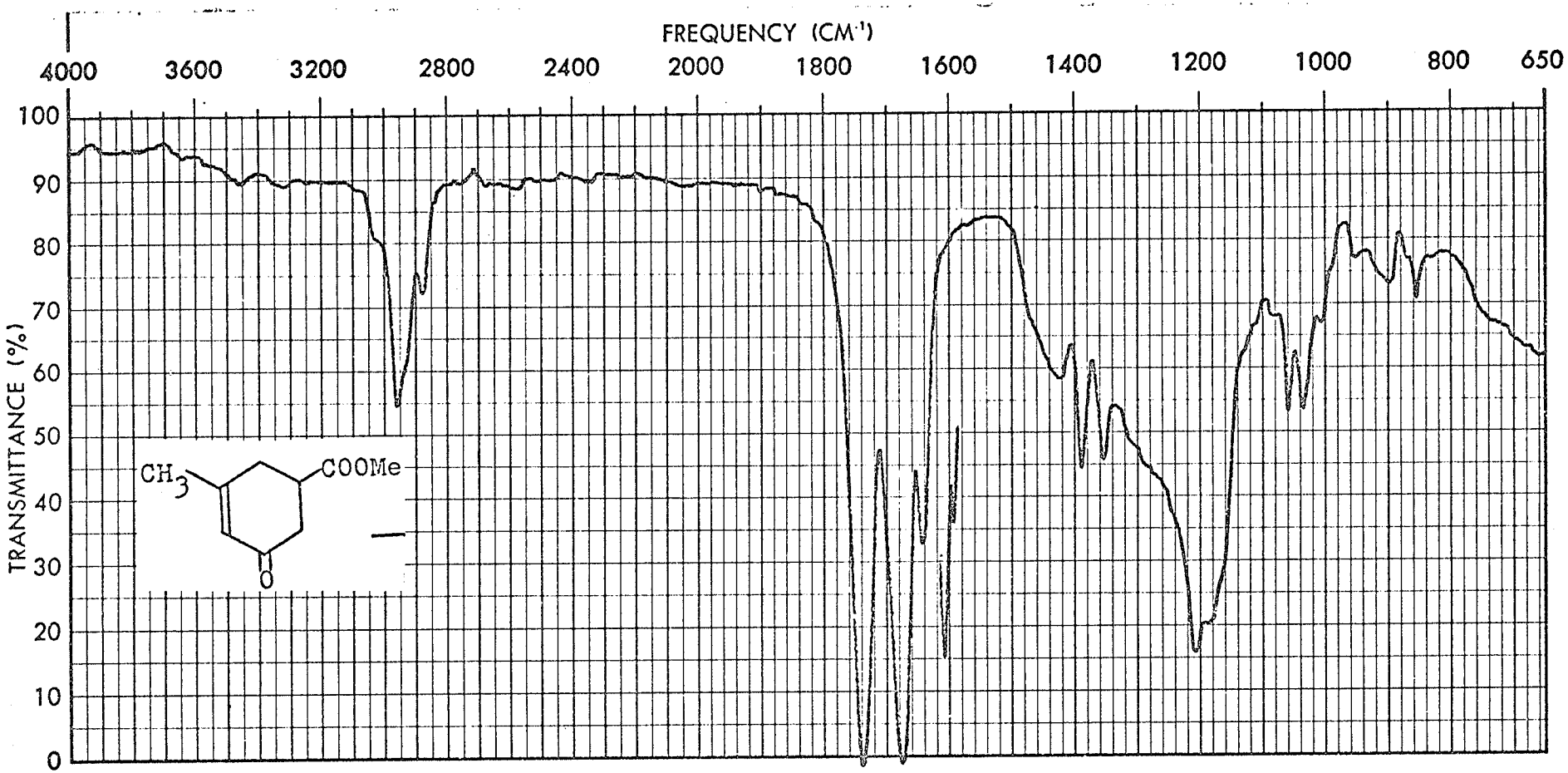
Infrared spectrum no. 21: Meta-toluic acid (XLVI).

(Fig. XXI)



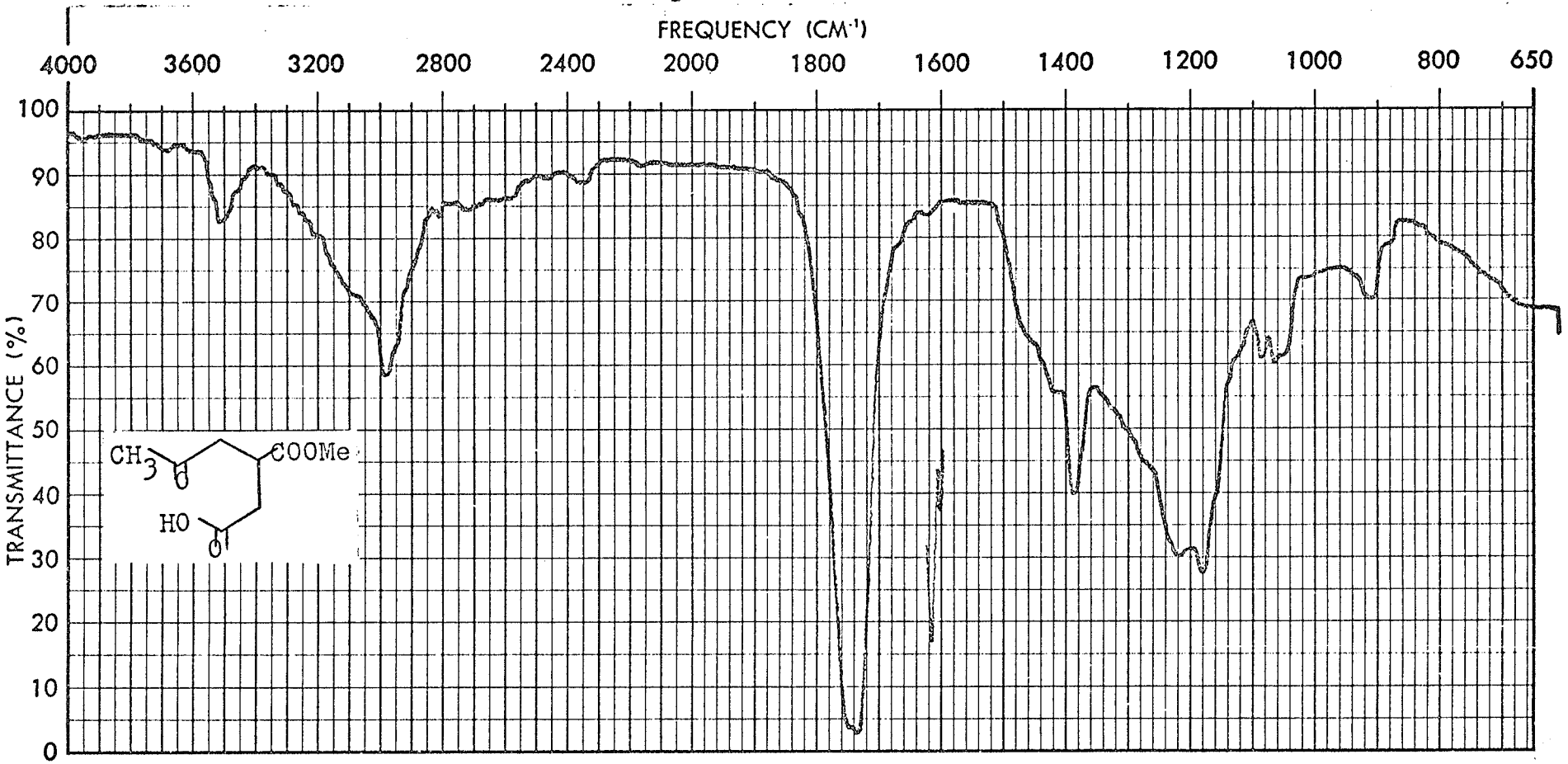
Infrared spectrum no. 22: 3-methoxy methyl m-toluate (XLVII)

(Fig. XXII)



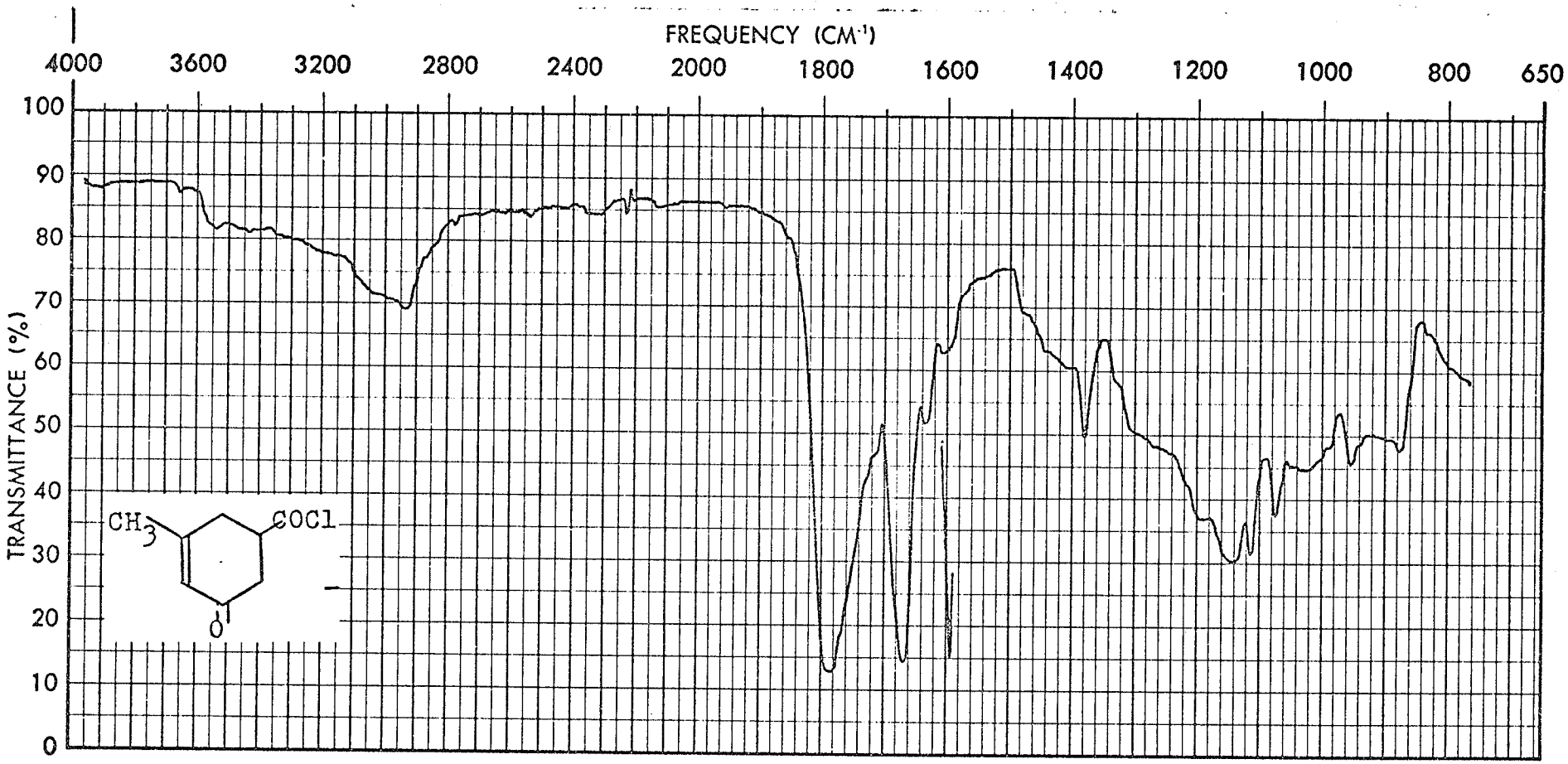
Infrared spectrum no. 23: Methyl 3-methylcyclohex-2-ene-1-one-5-carboxylate (XLVIII).

(Fig. XXIII)



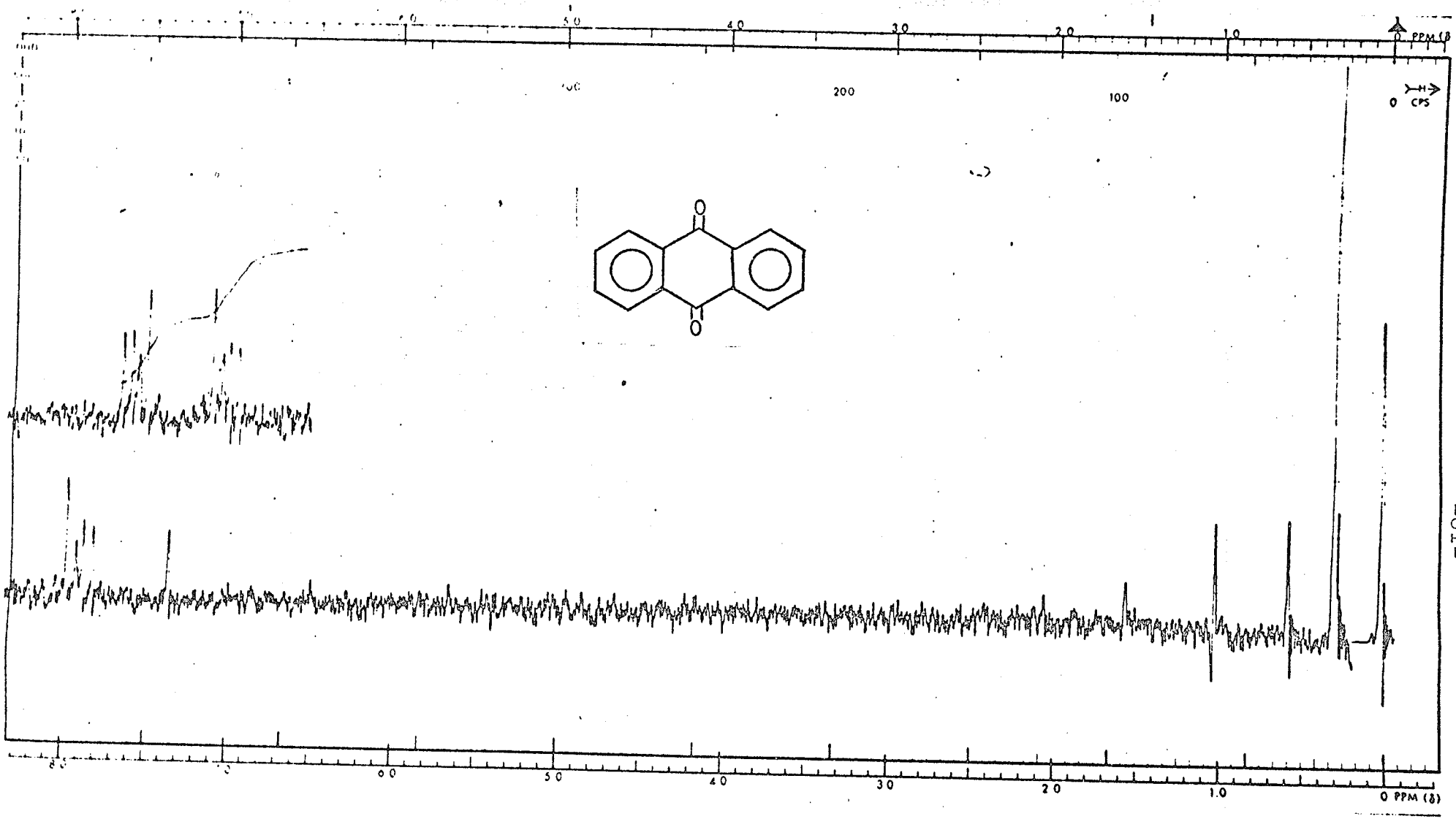
Infrared spectrum no. 24: 2-carbomethoxy-4-keto-pentanoic acid (LI).

(Fig. XXIV)



Infrared spectrum no. 25: acid chloride (LII)

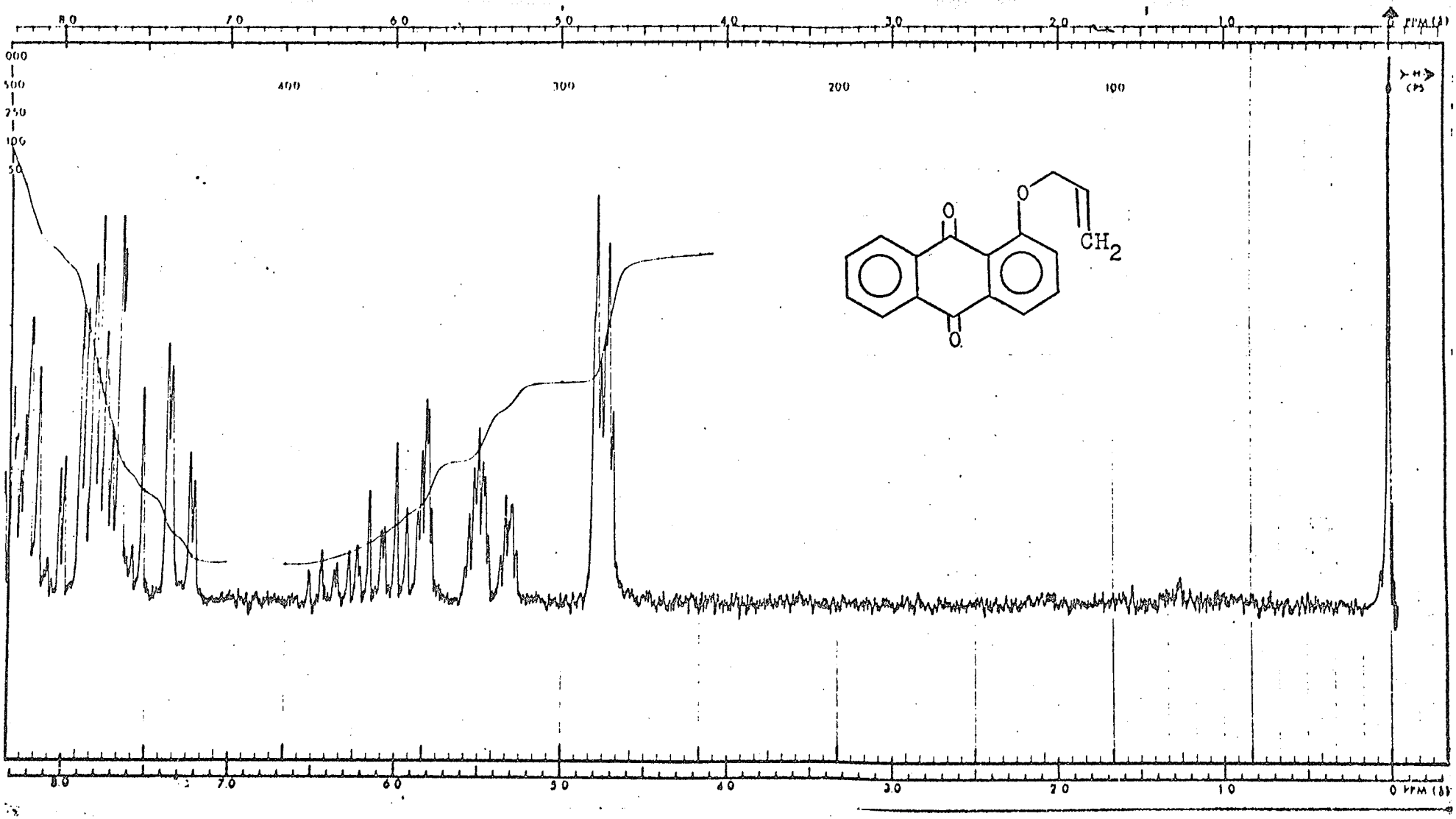
(Fig. XXV)



Nuclear magnetic resonance spectrum no. 1: anthraquinone (VIII) in $CDCl_3$.

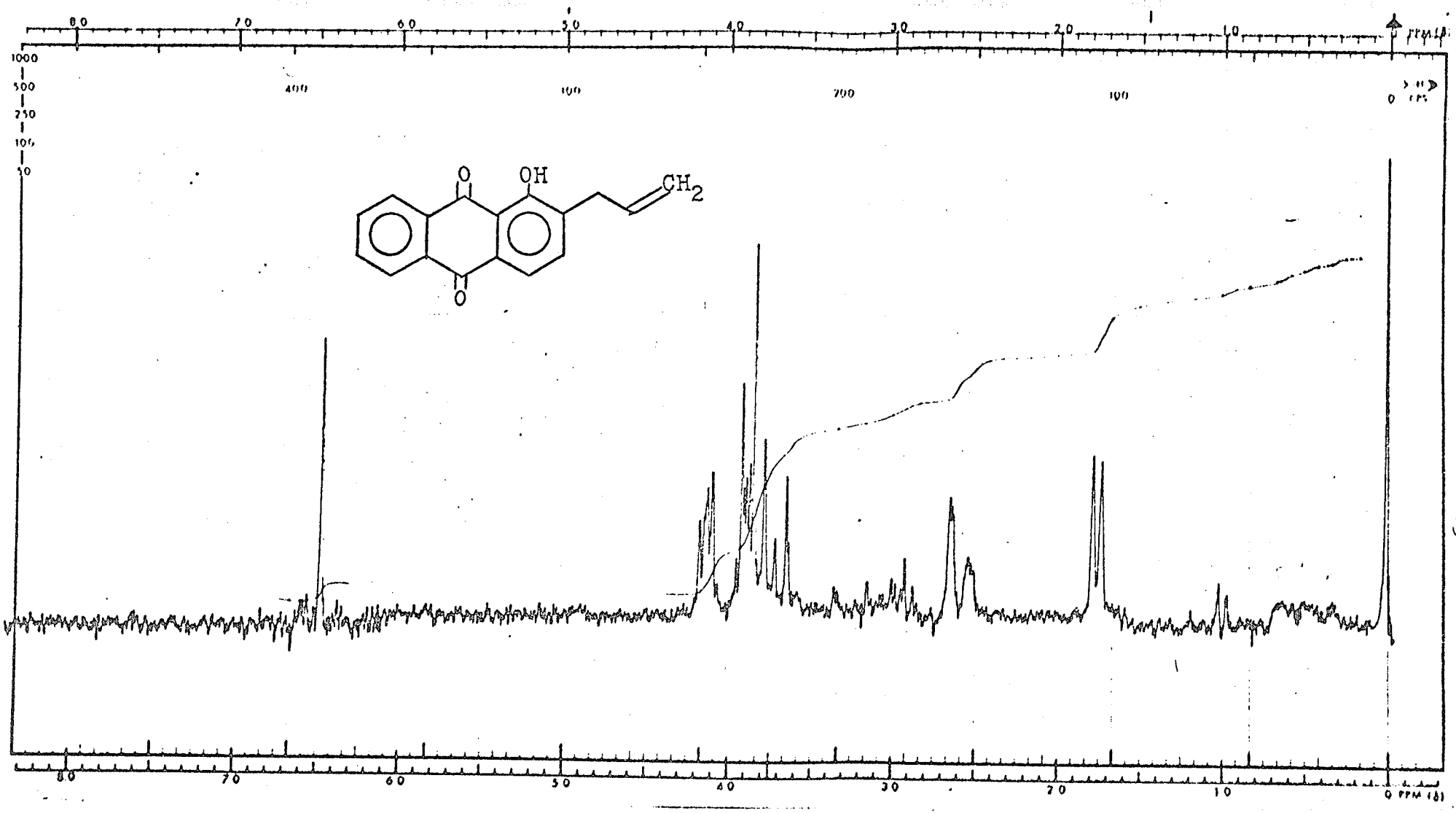
Sweep width = 500 Hz.

(Fig. XXVI)



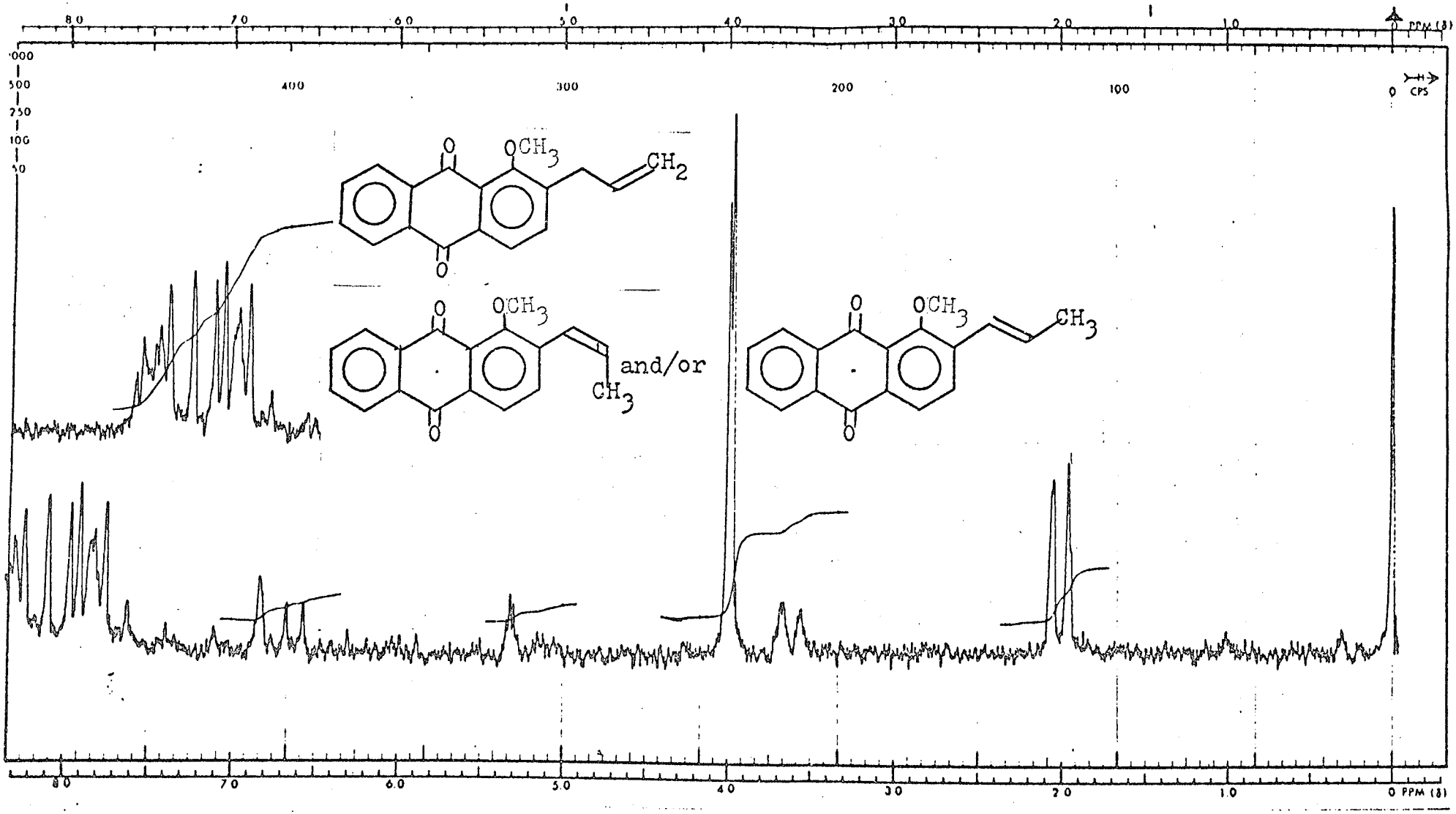
Nuclear magnetic resonance spectrum no. 2: 1-allyl anthraquinone ether (IX) in $CDCl_3$. Sweep width = 1000 Hz.

(Fig. XXVII)



Nuclear magnetic resonance spectrum no. 3: 2-allyl 1-hydroxy anthraquinone (Xa) in $CDCl_3$. Sweep width = 1000 Hz.

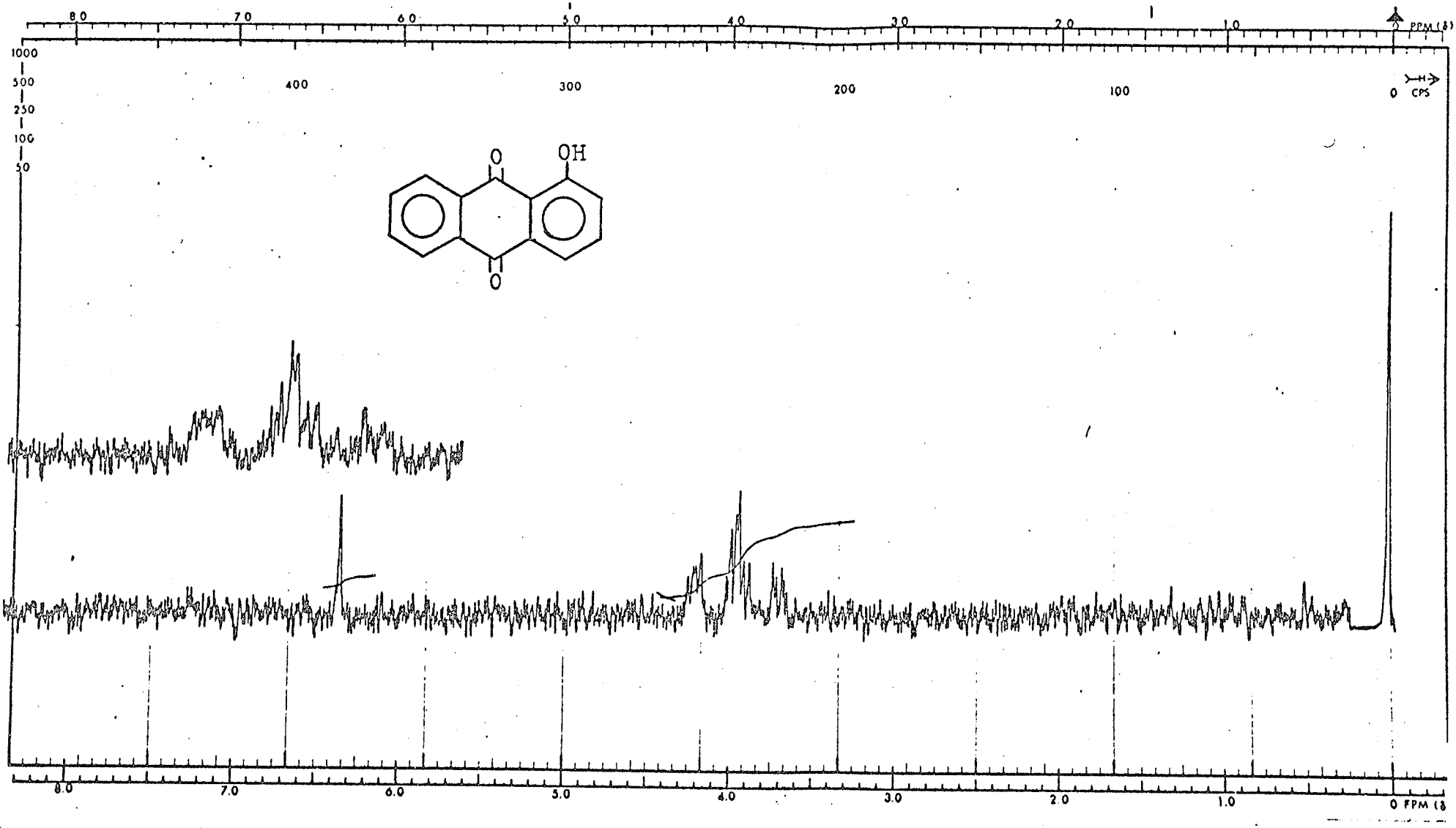
(Fig. XXVIII)



Nuclear magnetic resonance spectrum no 4: mixture of 2-allyl, 1-methoxy and 1-methoxy, 2-propenyl anthraquinones (Xb+XIb+XIIb) in $CDCl_3$.

Sweep width = 500 Hz.

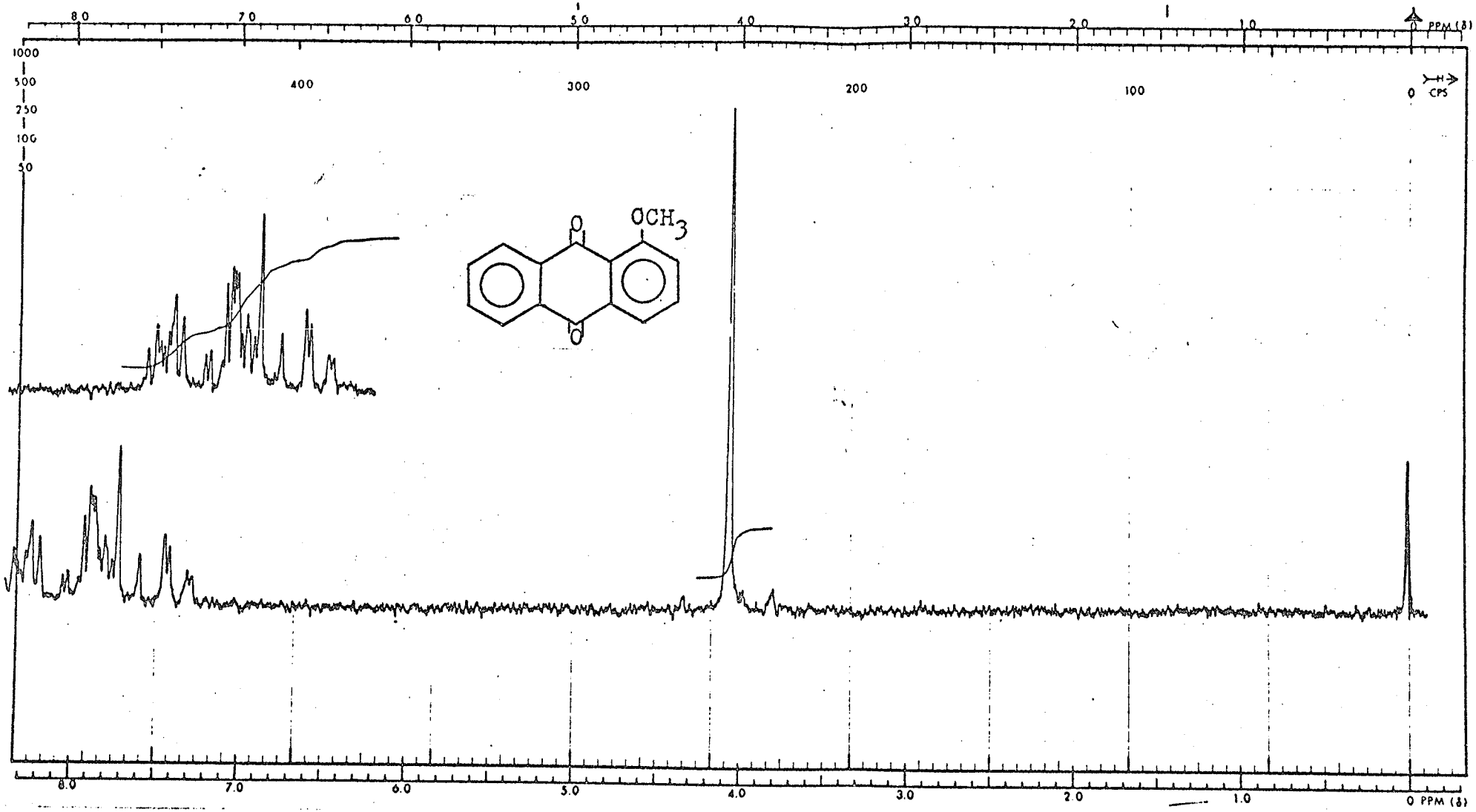
(Fig. XXIX)



Nuclear magnetic resonance spectrum no. 5: 1-hydroxy anthraquinone (Xb)

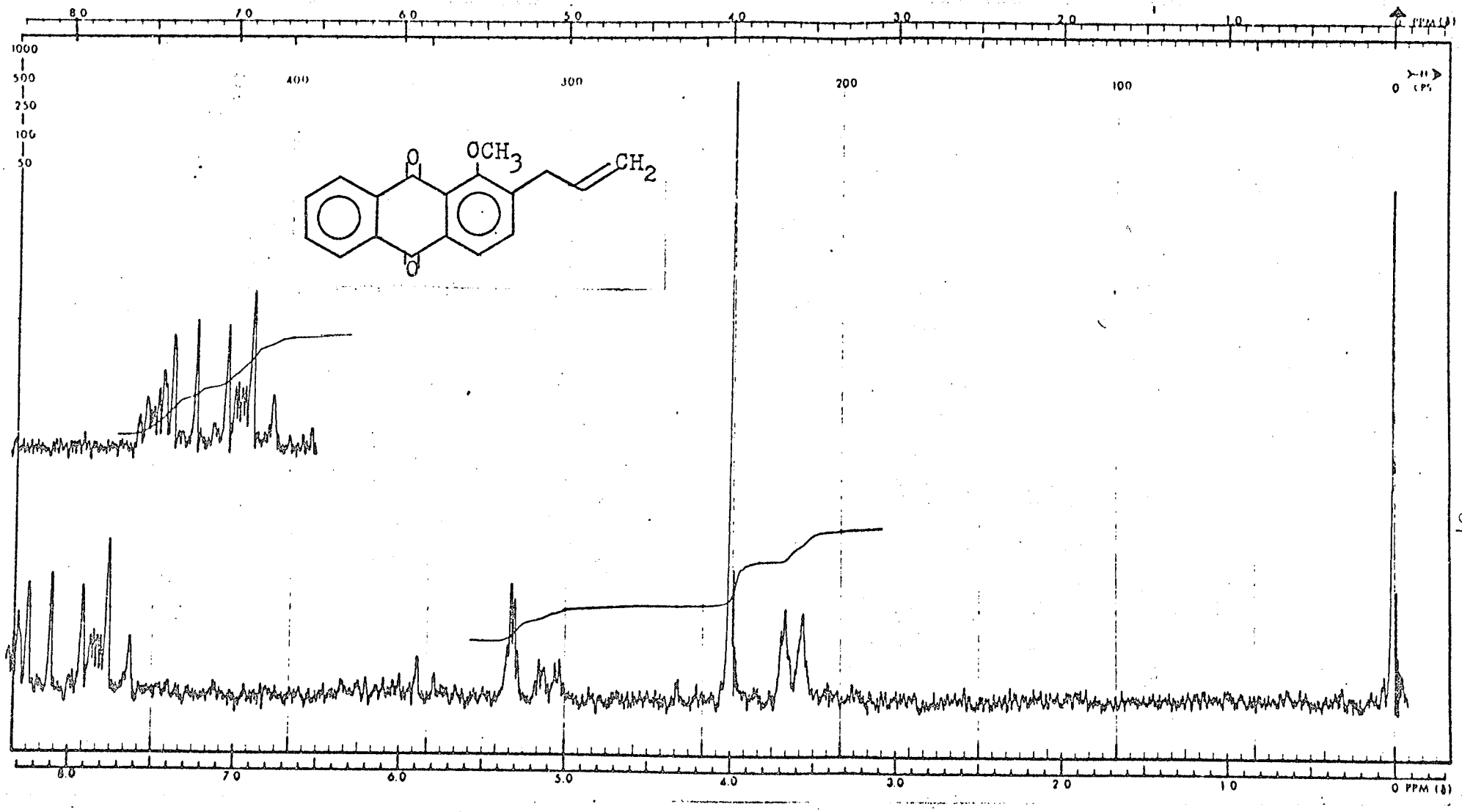
in $CDCl_3$. Sweep width = 1000 Hz.

(Fig. XXXa)



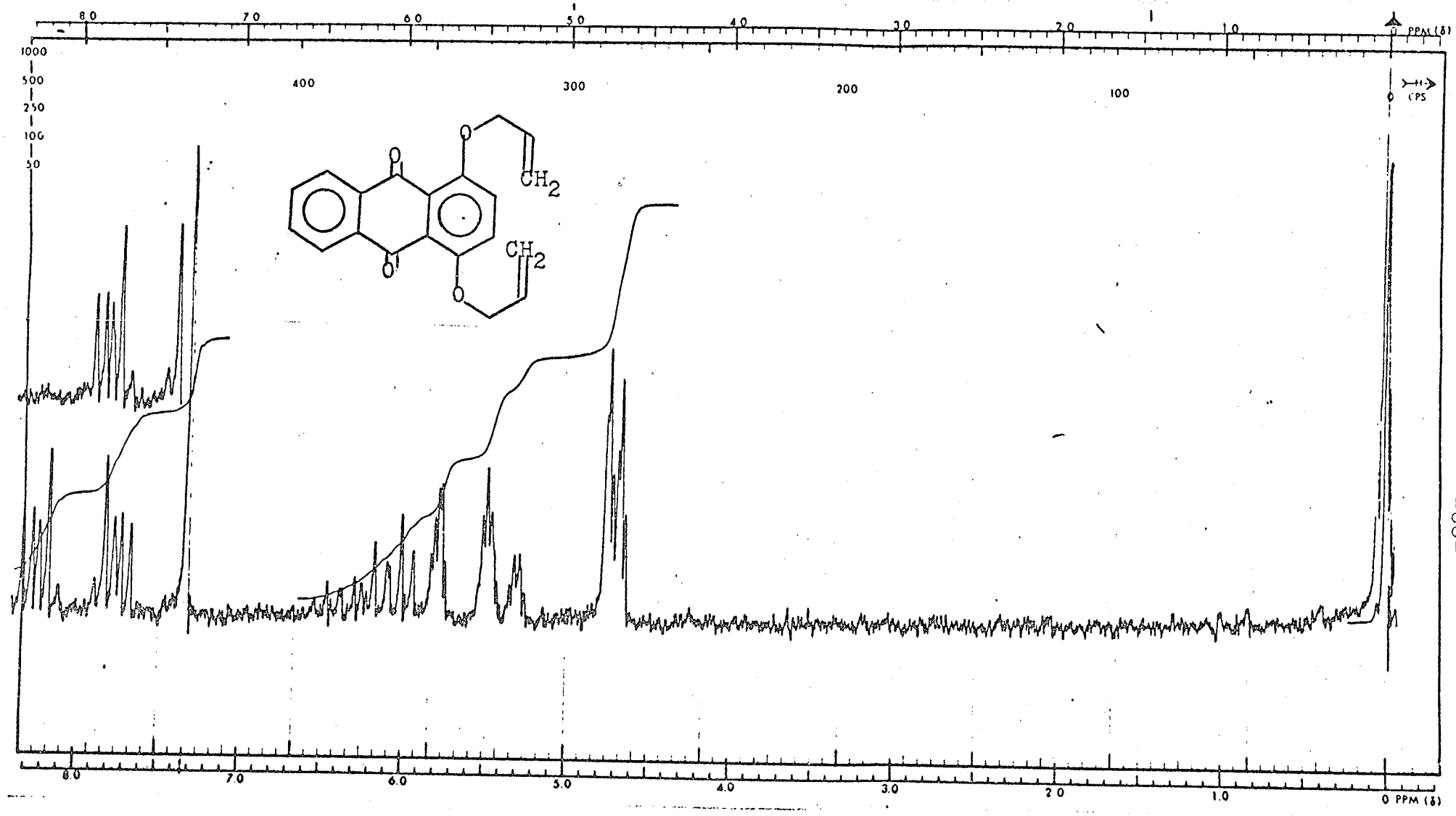
Nuclear magnetic resonance spectrum no 6: 1-methoxy anthraquinone (XIIIa) in $CDCl_3$. Sweep width = 500 Hz.

(Fig. XXXb)



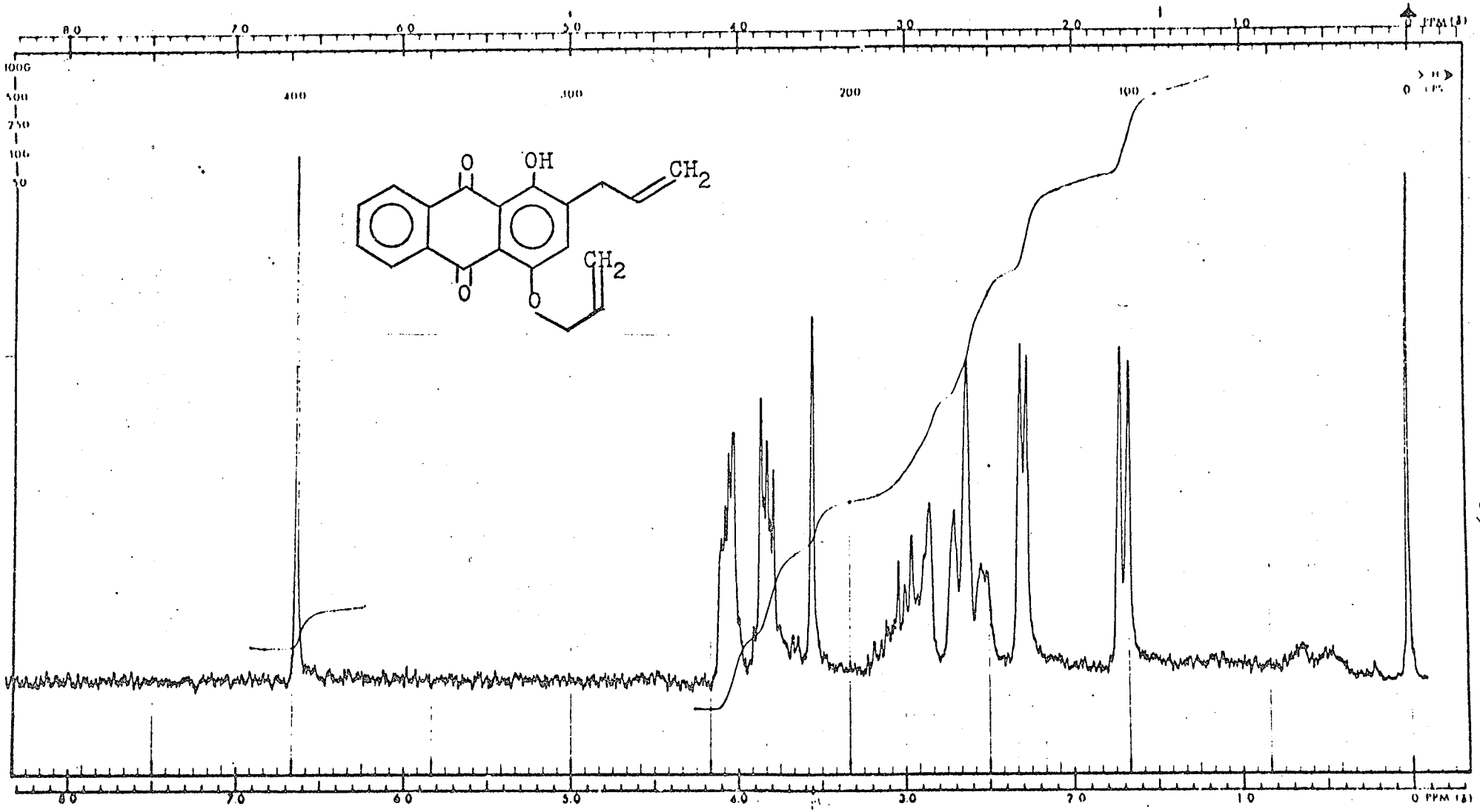
Nuclear magnetic resonance spectrum no. 7: 2-allyl, 1-methoxy anthraquinone in (XIIIb) in $CDCl_3$. Sweep width = 500 Hz.

(Fig. XXXI)



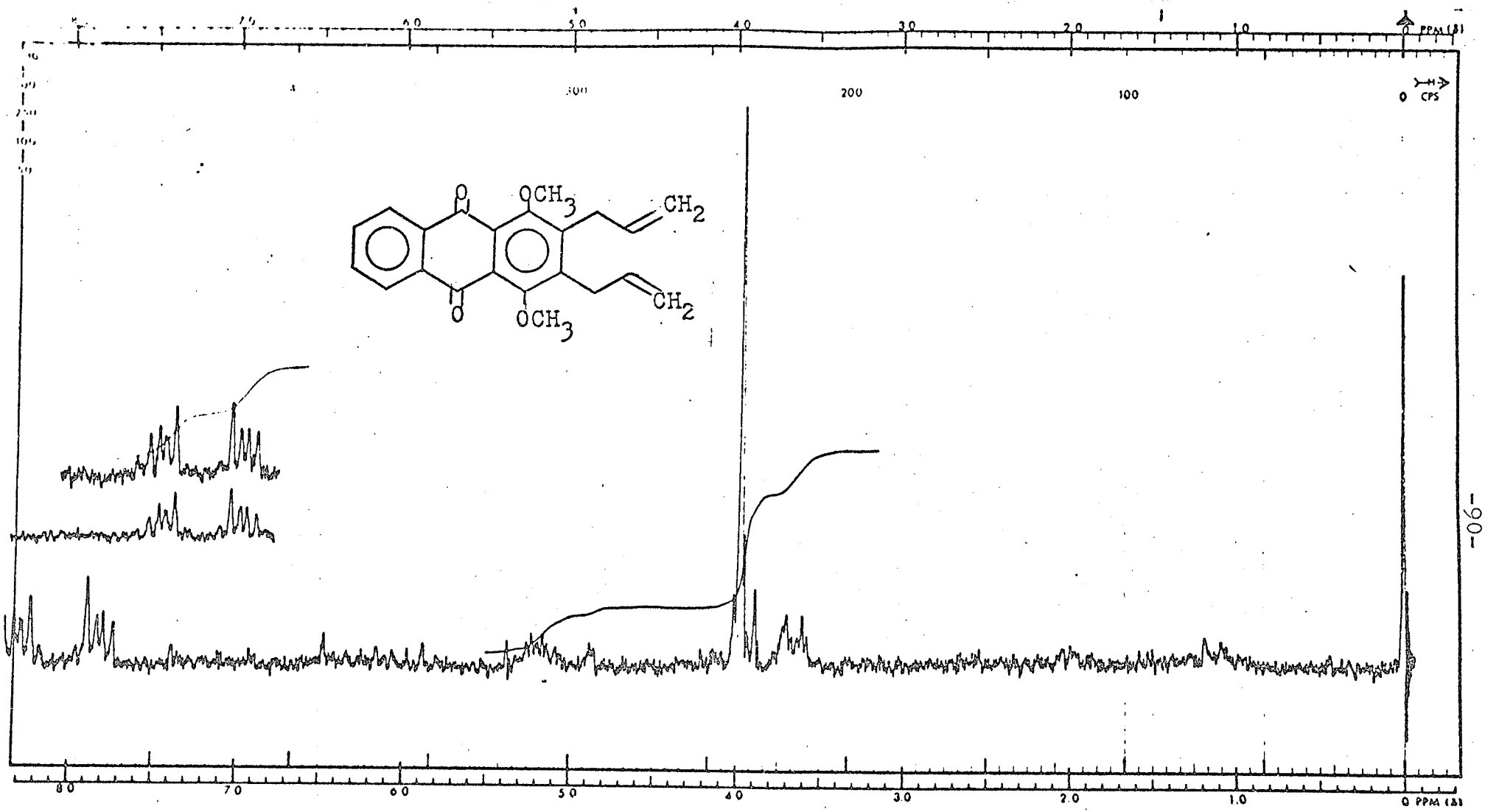
Nuclear magnetic resonance spectrum no. 8: 1,4-diallyl anthraquinone ether (XIV) in $CDCl_3$. Sweep width = 500 Hz.

(Fig. XXXII)



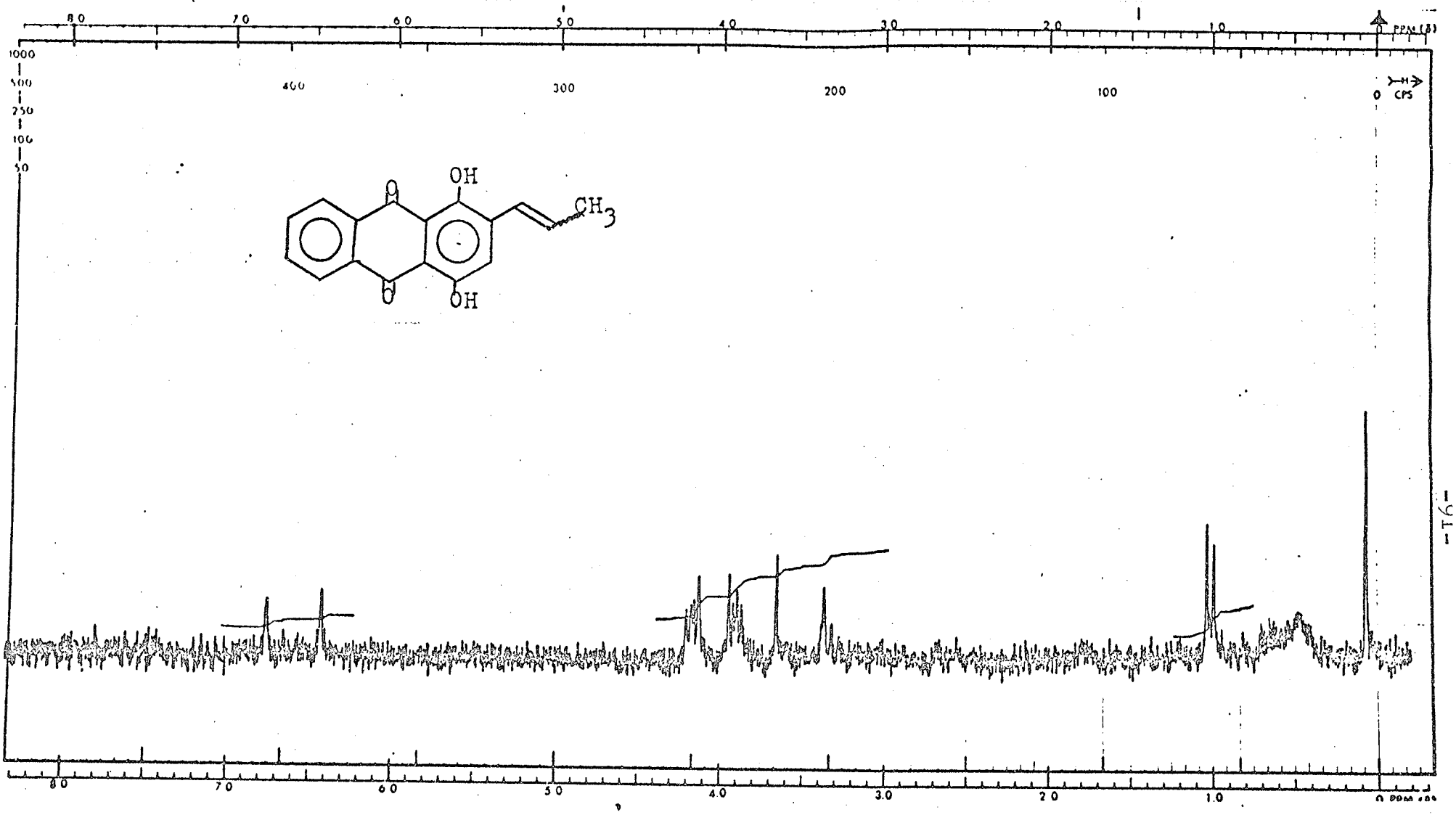
Nuclear magnetic resonance spectrum no. 9: 2-allyl, 4-allyloxy, 1-hydroxy anthraquinone (XV) in $CDCl_3$. Sweep width = 1000 Hz.

(Fig. XXXIII)



Nuclear magnetic resonance spectrum no. 10: 2,3-diallyl, 1,4-dimethoxy anthraquinone (XVIb) in $CDCl_3$. Sweep width = 500 Hz.

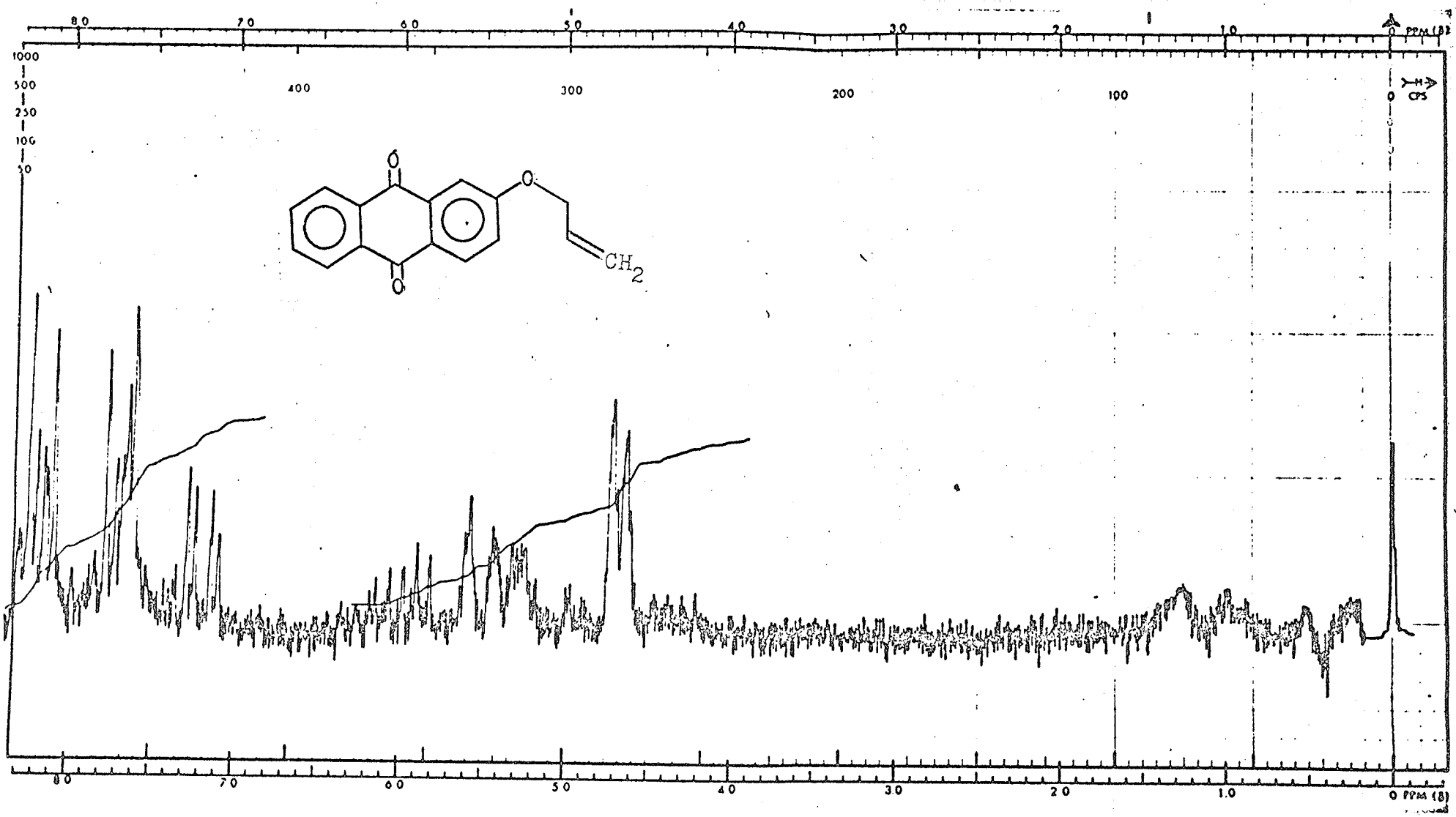
(Fig. XXXIV)



Nuclear magnetic resonance spectrum no. 11: 2-propenyl quinizarin (XVII) in $CDCl_3$.

Sweep width = 1000 Hz.

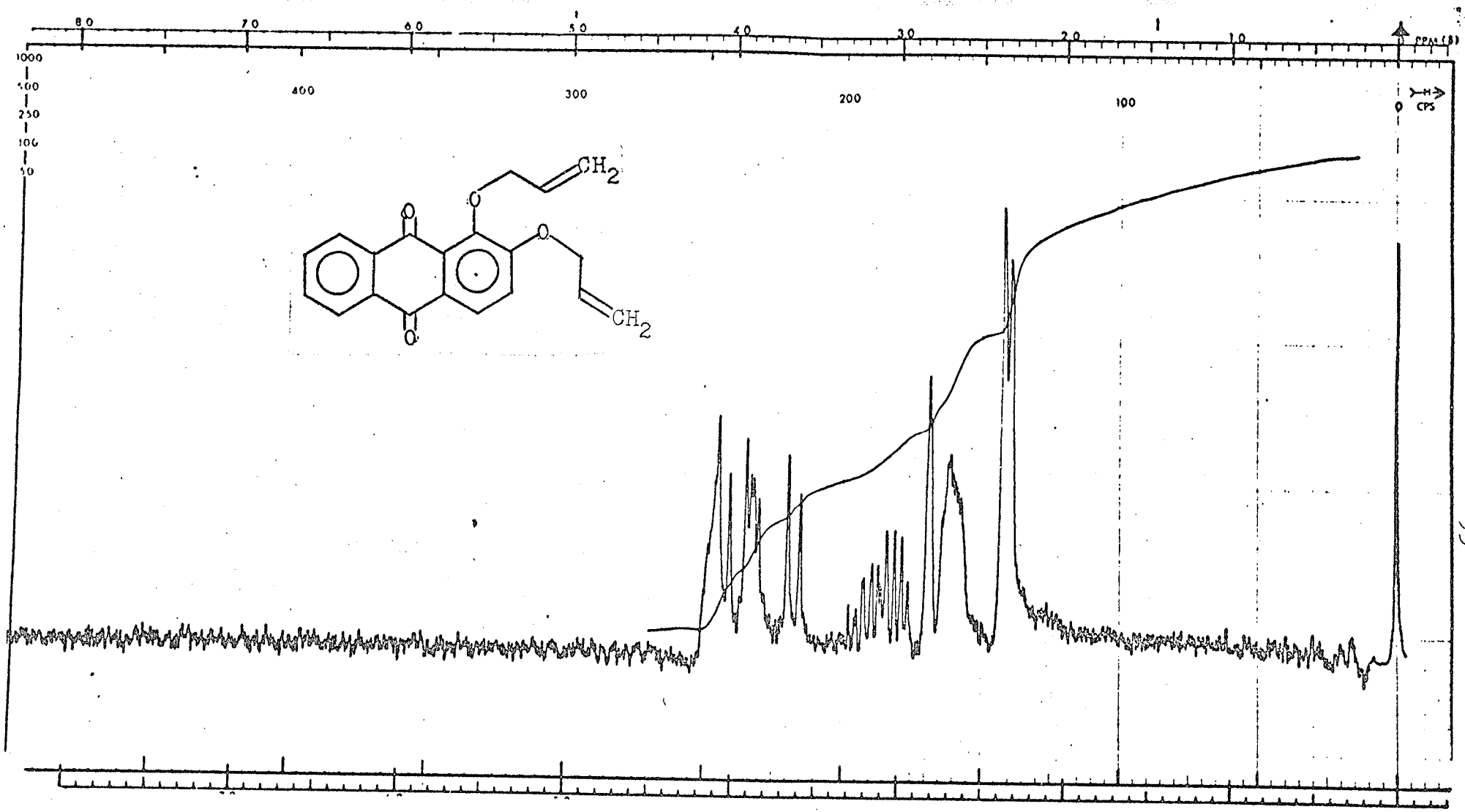
(Fig. XXXV)



Nuclear magnetic resonance spectrum no. 12: 2-allyl anthraquinone ether (XVIII) in $CDCl_3$.

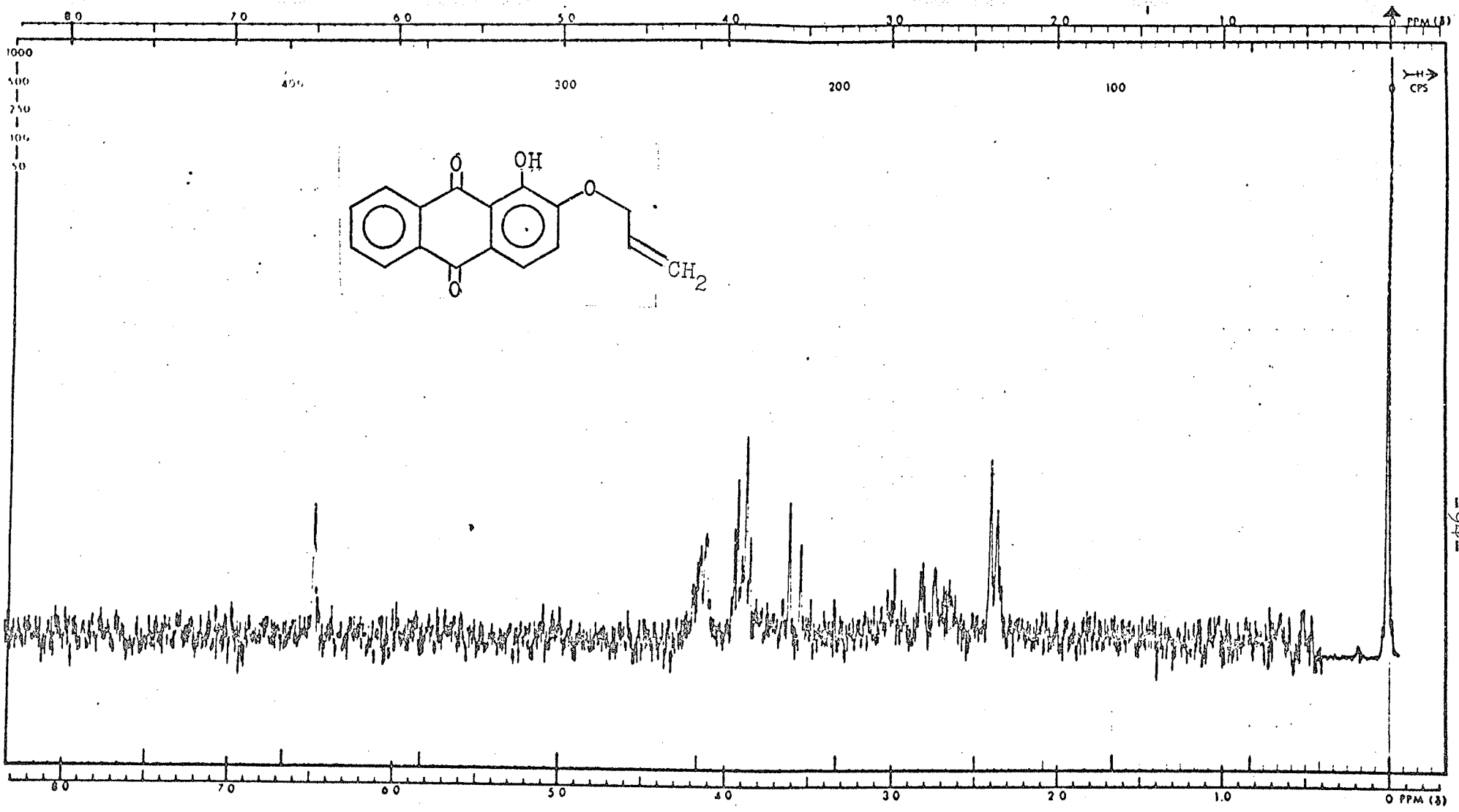
Sweep width = 500 Hz.

(Fig. XXXVI)



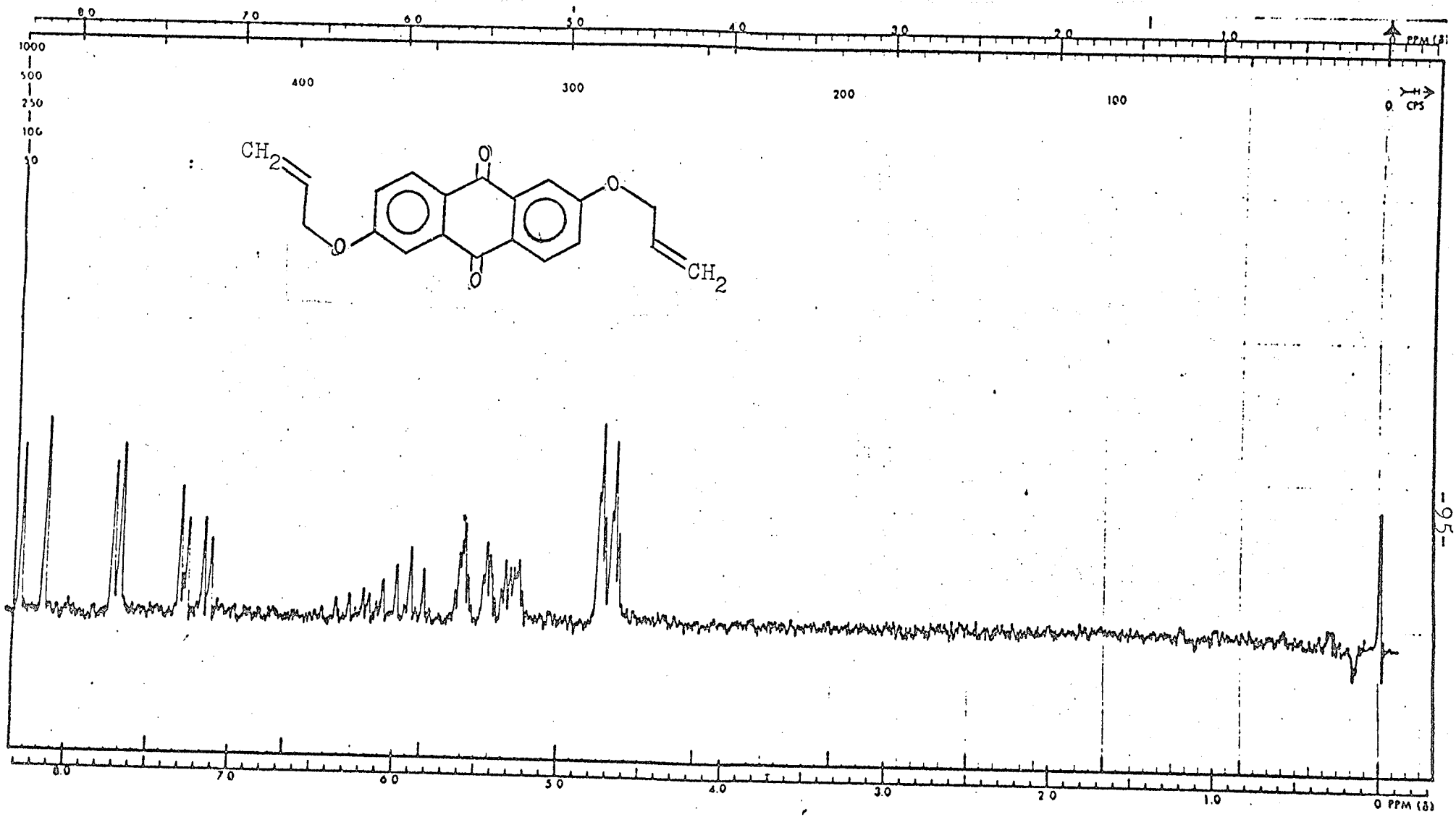
Nuclear magnetic resonance spectrum no. 13: 1, 2-diallyl anthraquinone ether (XIX) in $CDCl_3$. Sweep width = 500 Hz.

(Fig. XXXVII)



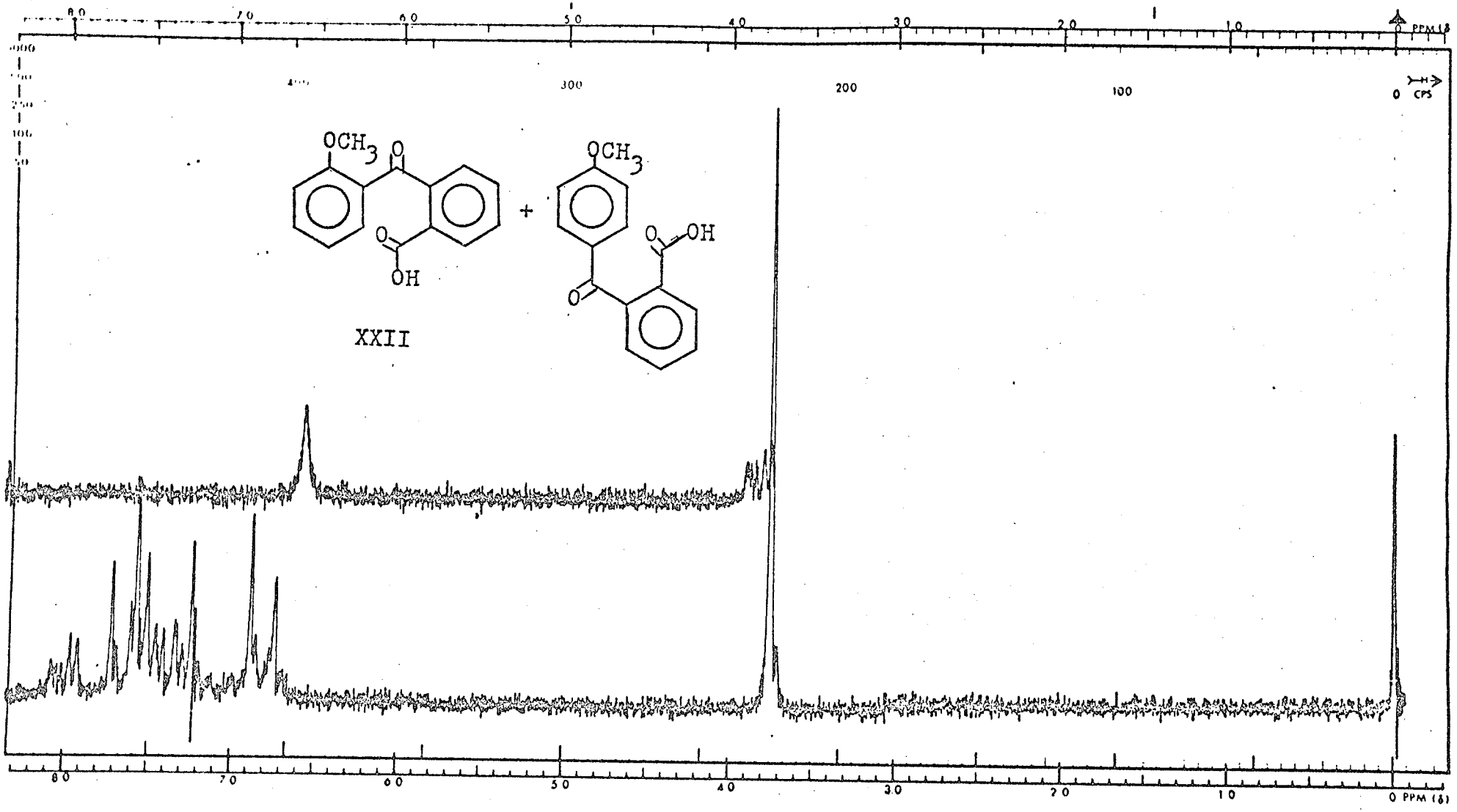
Nuclear magnetic resonance spectrum no. 14: 2-allyl, 1-hydroxy anthraquinone ether (XX) in $CDCl_3$. Sweep width = 1000 Hz.

(Fig. XXXVIII)



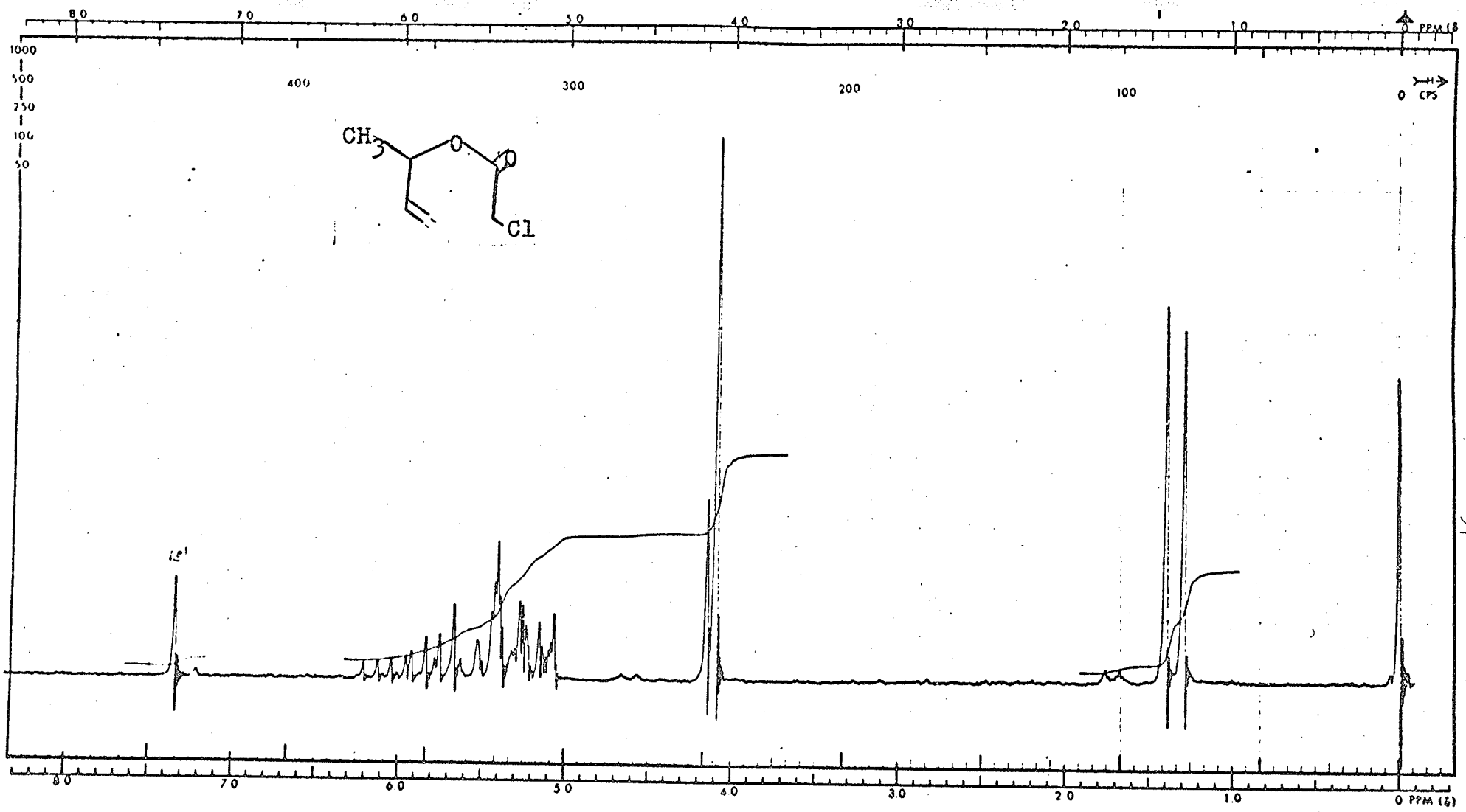
Nuclear magnetic resonance spectrum no. 15: 2,6-diallyl anthraquinone ether (XXI) in $CDCl_3$. Sweep width = 500 Hz.

(Fig. XXXIX)



Nuclear magnetic resonance spectrum no. 16: Mixture of keto acids (XXII) and (XXIII) in $CDCl_3$. Sweep width = 1000 Hz.

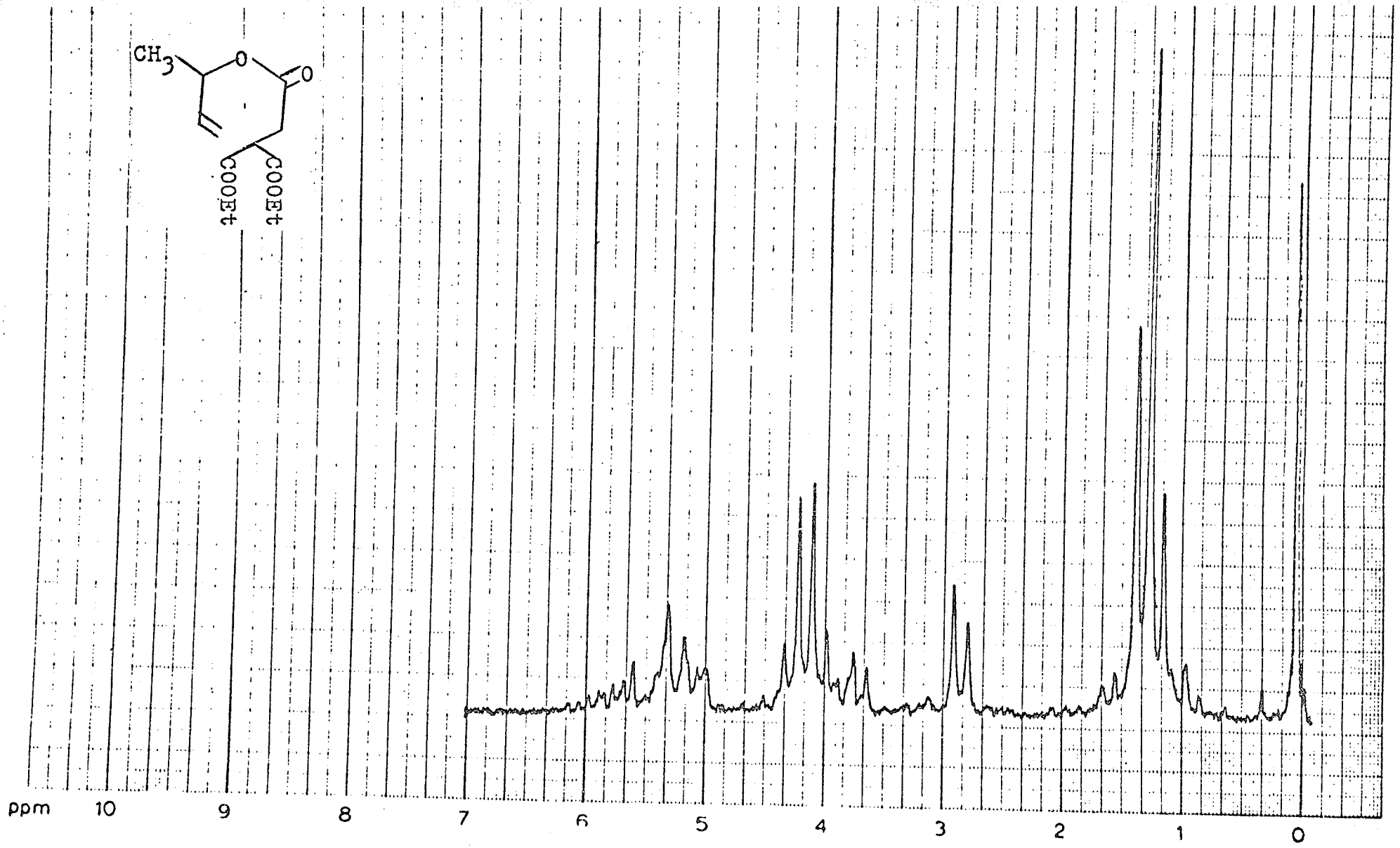
(Fig. XL)



Nuclear magnetic resonance spectrum no. 17: Sec-butenyl chloroacetate (XXXII) neat.

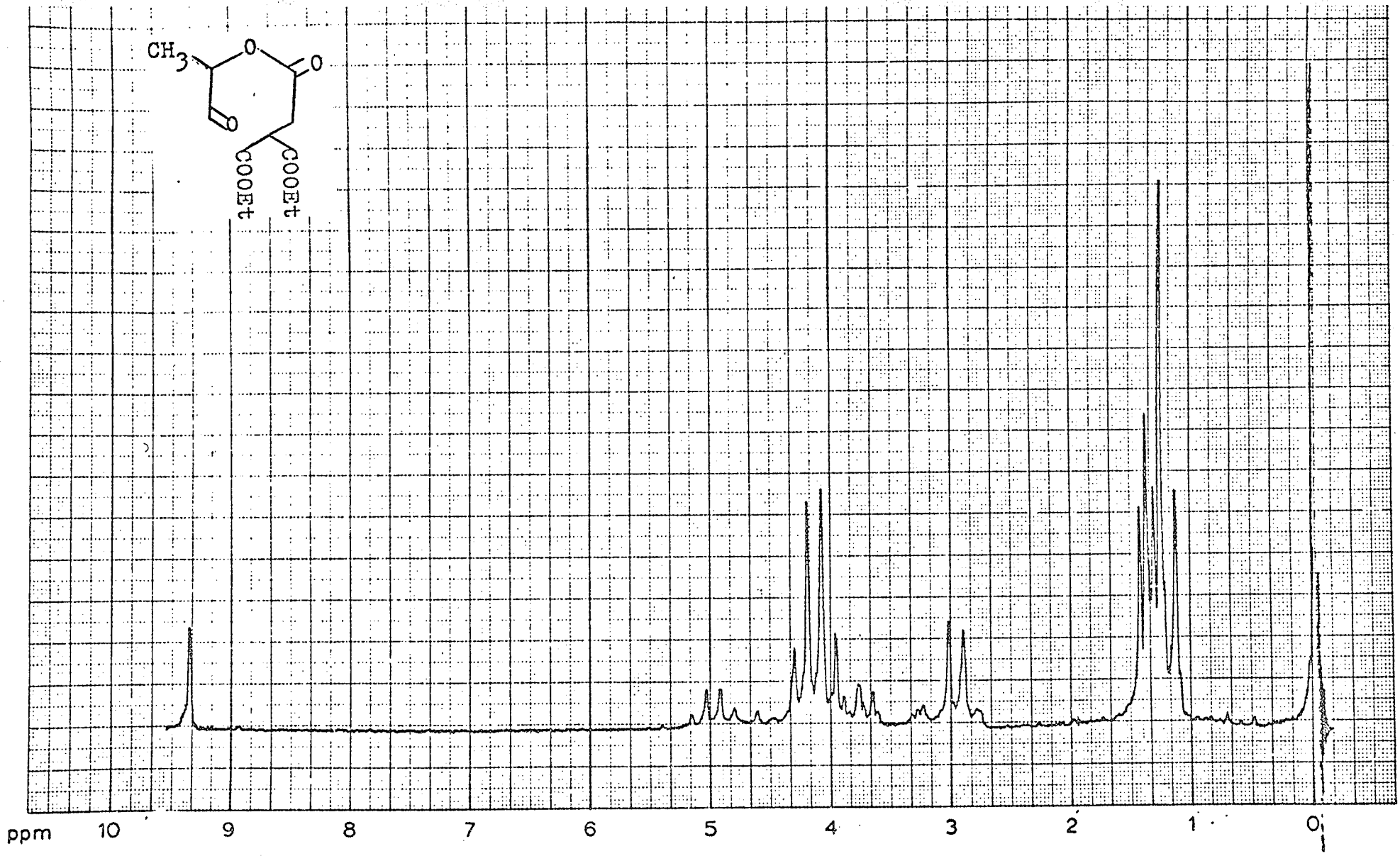
Sweep width = 500 Hz.

(Fig. XLI)



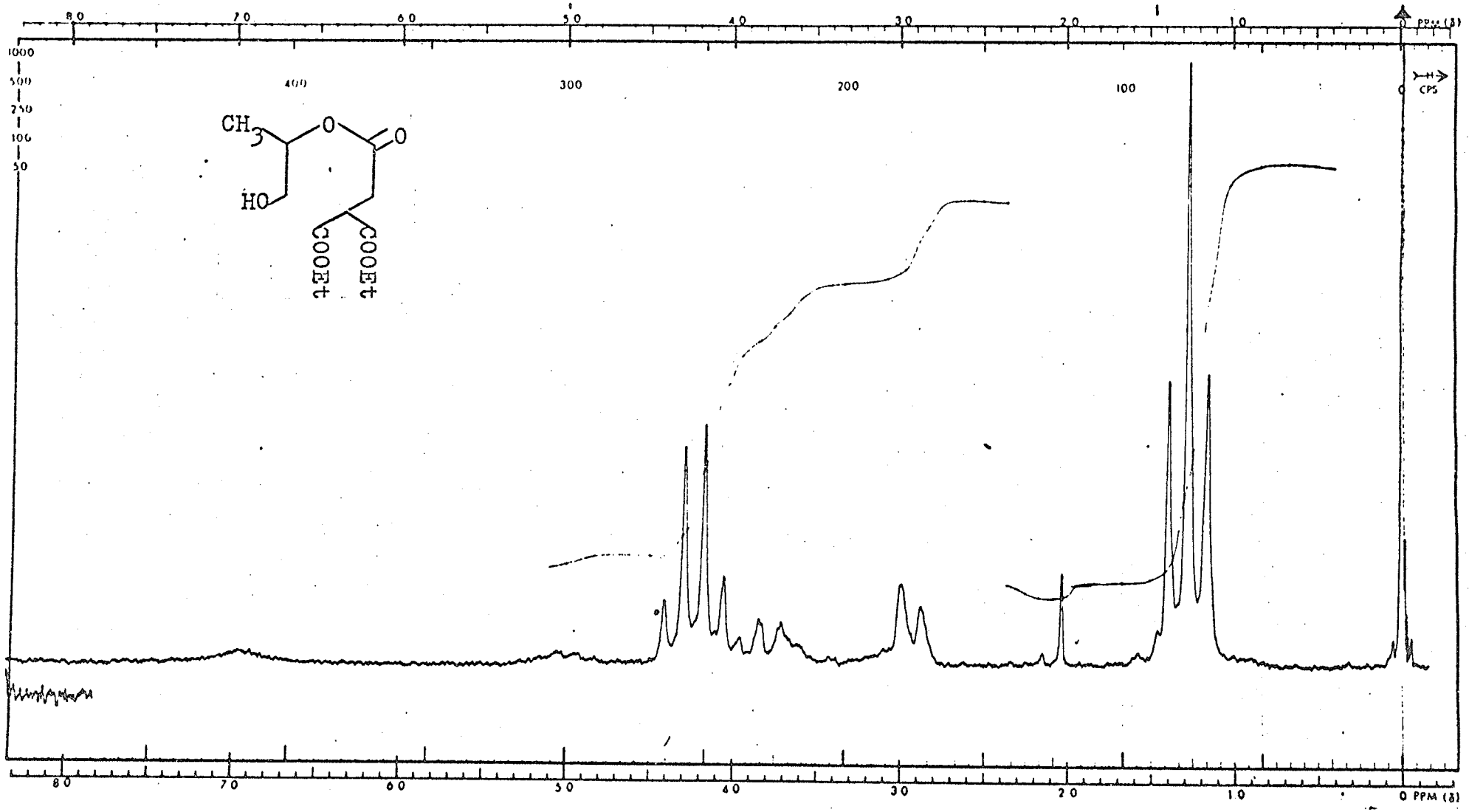
Nuclear magnetic resonance spectrum no 18: α-methylene sec-butenyloxycarbonyldiethyl malonate (XXXIII) neat. Sweep width = 500 Hz.

(Fig. XLII)



Nuclear magnetic resonance spectrum no. 19: α-methylene 1-formylethoxycarbonyldiethyl malonate (XXXIV) diluted in $CDCl_3$.

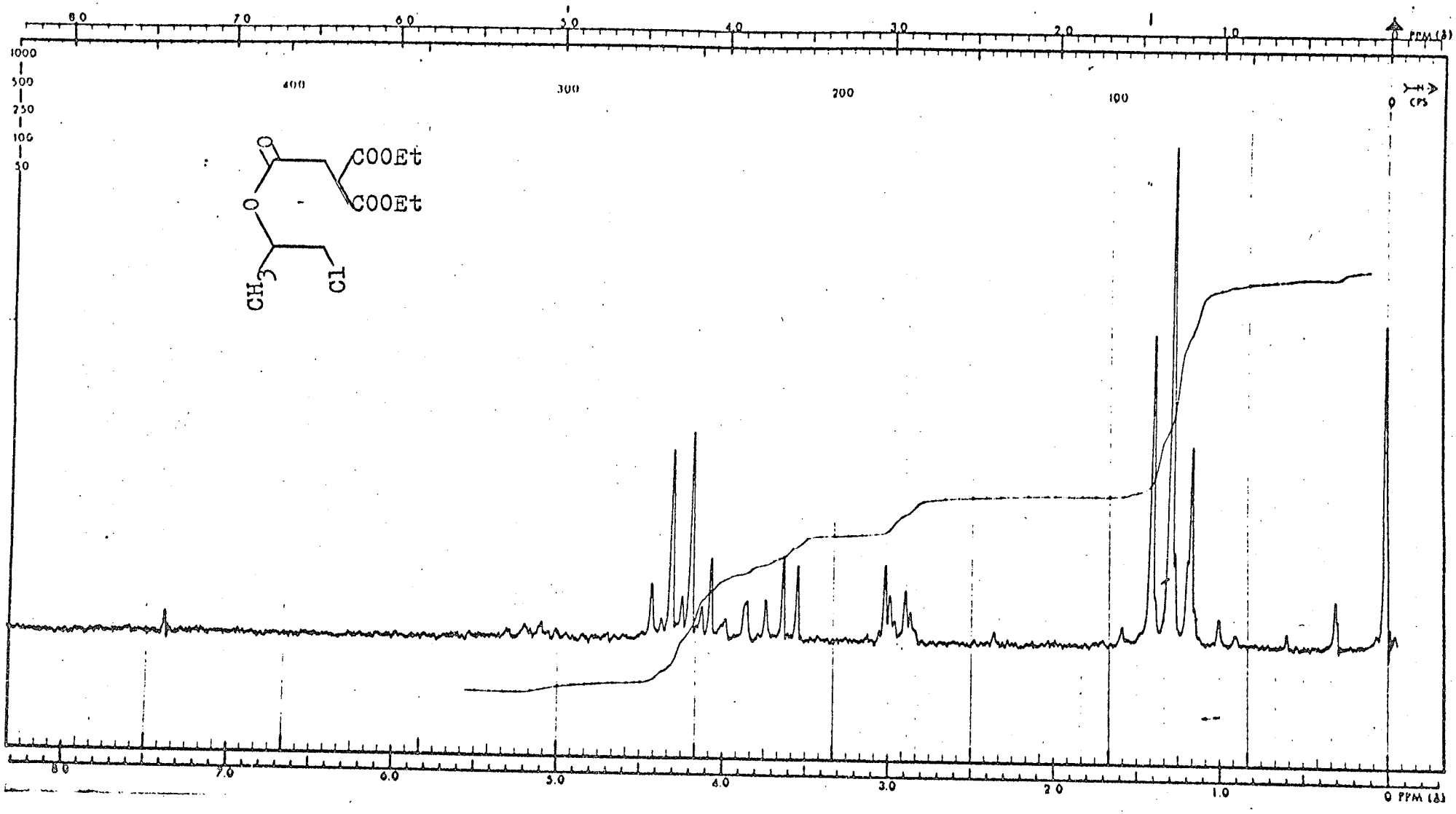
(Fig. XLIII)



Nuclear magnetic resonance spectrum no. 20: α-methylenehydroxyisopropyloxycarbonyl-diethyl malonate (XXXVI) diluted in $CDCl_3$.

Sweep width = 500 Hz.

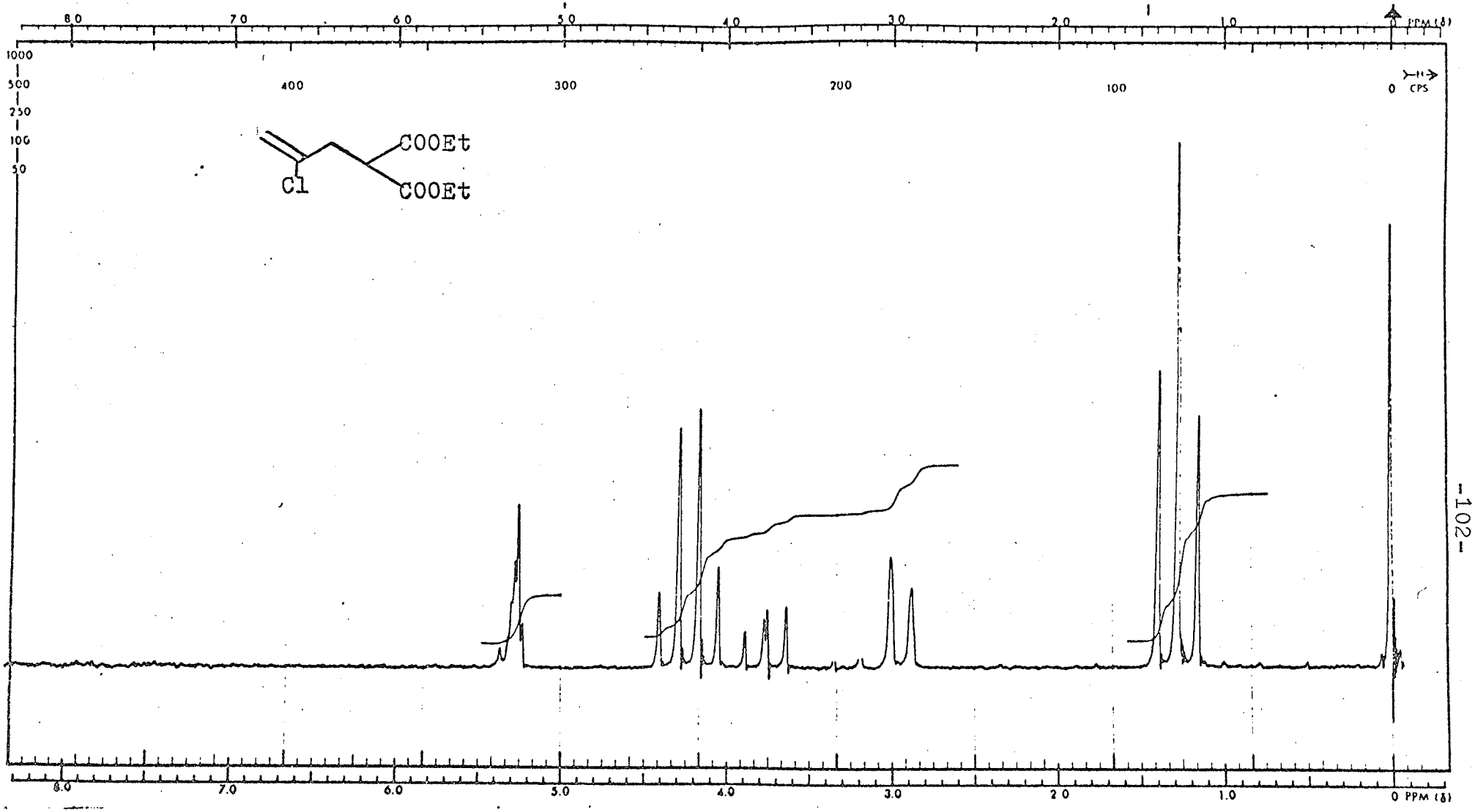
(Fig. XLIV)



Nuclear magnetic resonance spectrum no. 21: ∝-methylenechloroisopropyloxycarbonyl-diethyl malonate (XXXVII) diluted in $CDCl_3$.

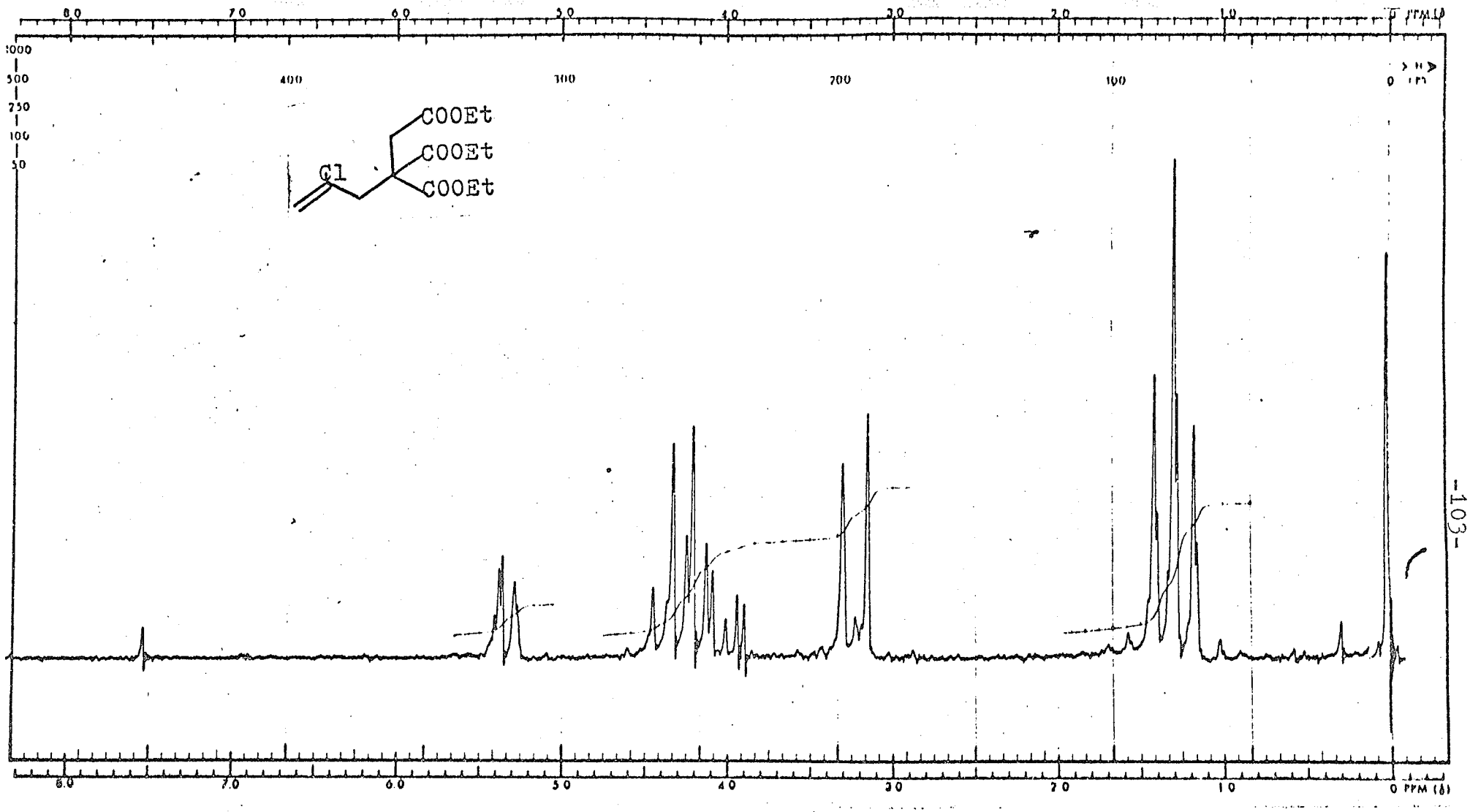
Sweep width = 500 Hz.

(Fig. XLV)



Nuclear magnetic resonance spectrum no. 22: α-(2-chloro-1-propene)diethyl malonate (XL) diluted in $CDCl_3$. Sweep width = 500 Hz.

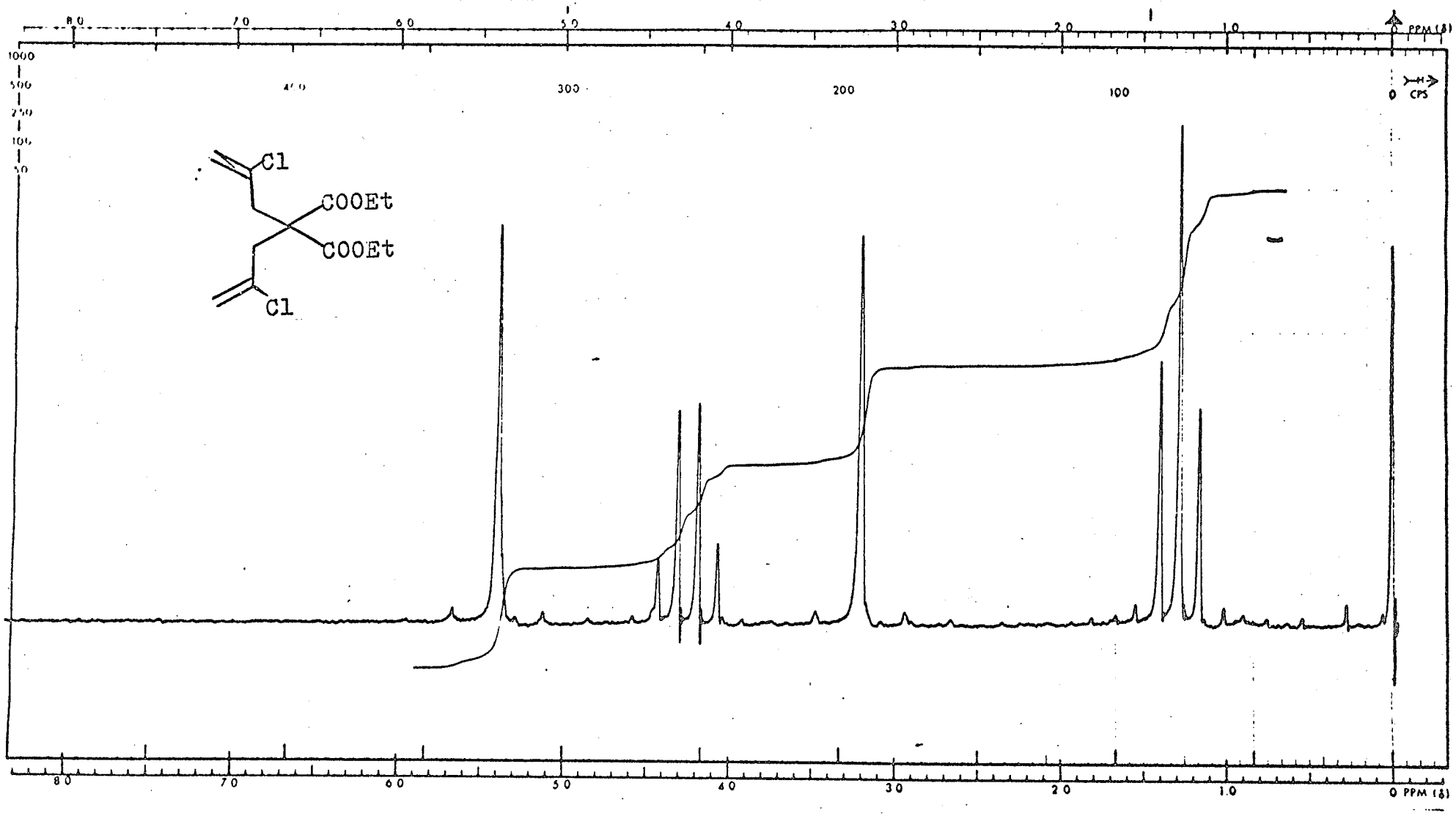
(Fig. XLVI)



Nuclear magnetic resonance spectrum no. 23: α-ethoxycarbonyl-α-(2-chloro-1-propene)-diethyl succinate (XLI) diluted in $CDCl_3$.

Sweep width = 500 Hz.

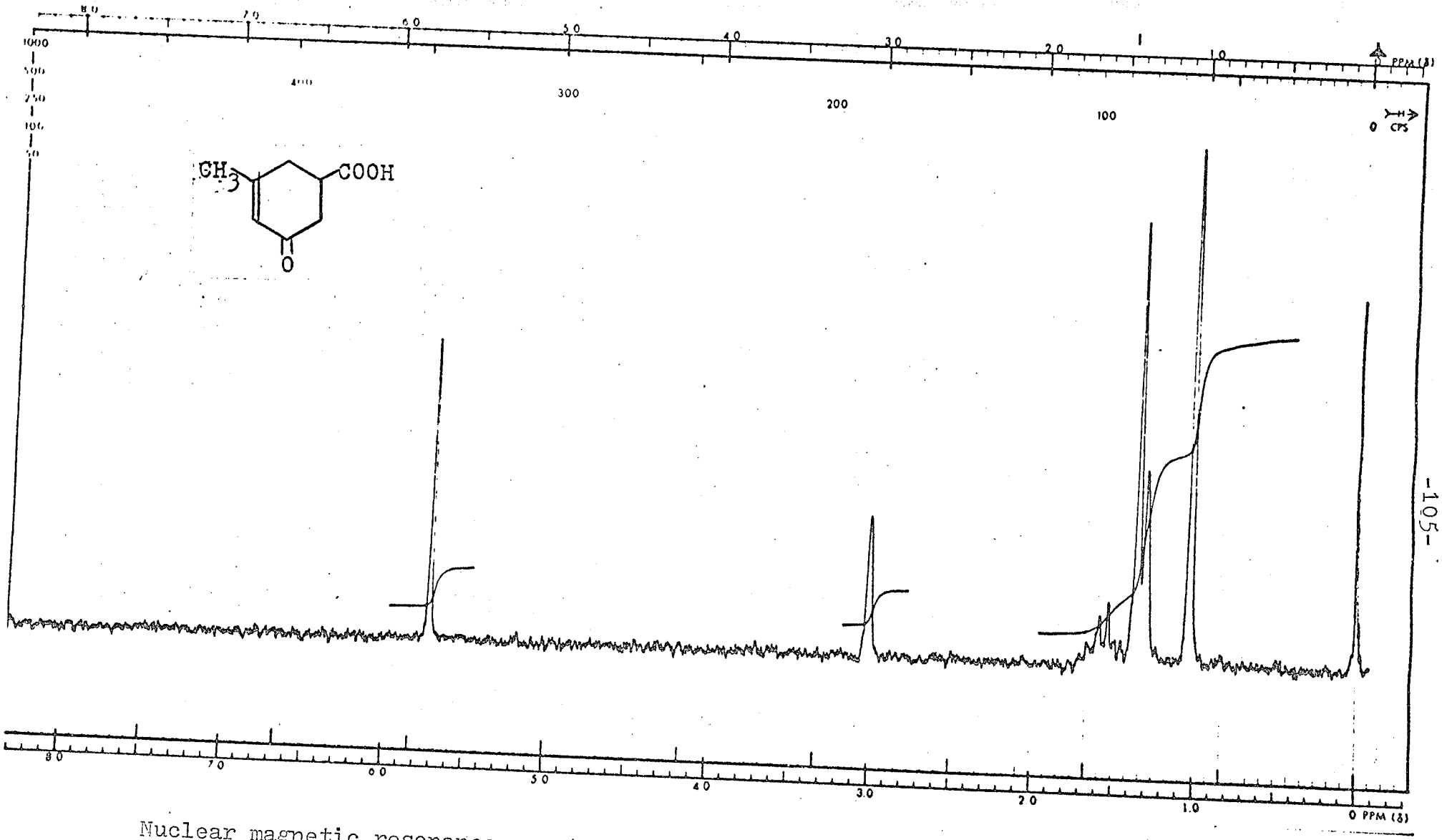
(Fig. XLVII)



Nuclear magnetic resonance spectrum no. 24: α-α-di(2-chloro-1-propene)diethyl malonate (XLIV) diluted in $CDCl_3$.

Sweep width = 500 Hz.

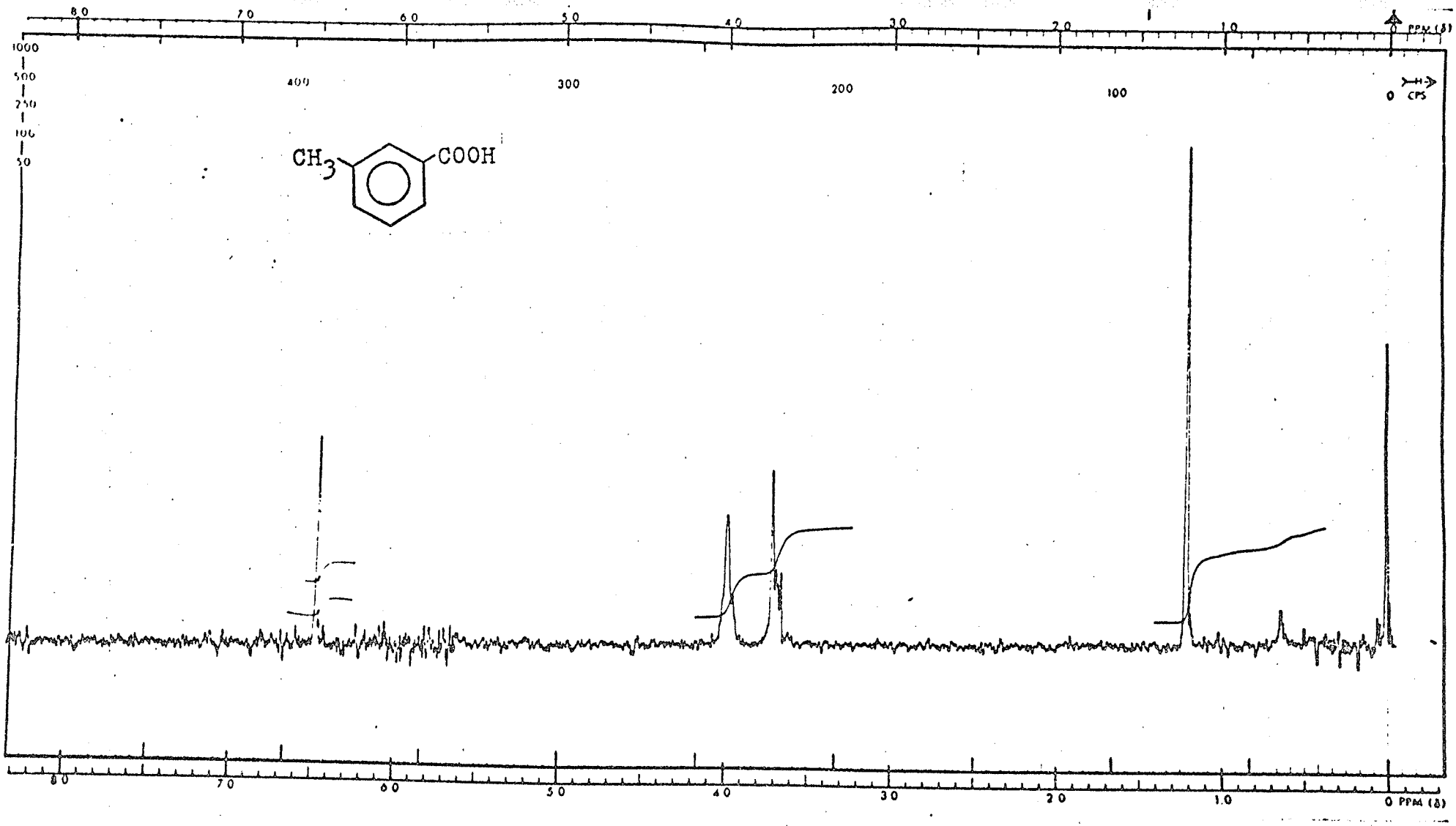
(Fig. XLVIII)



Nuclear magnetic resonance spectrum no. 25: 3-methylcyclohex-2-ene-1-one-5-carboxylic acid (XLV) in $CDCl_3$.

Sweep width = 1000 Hz.

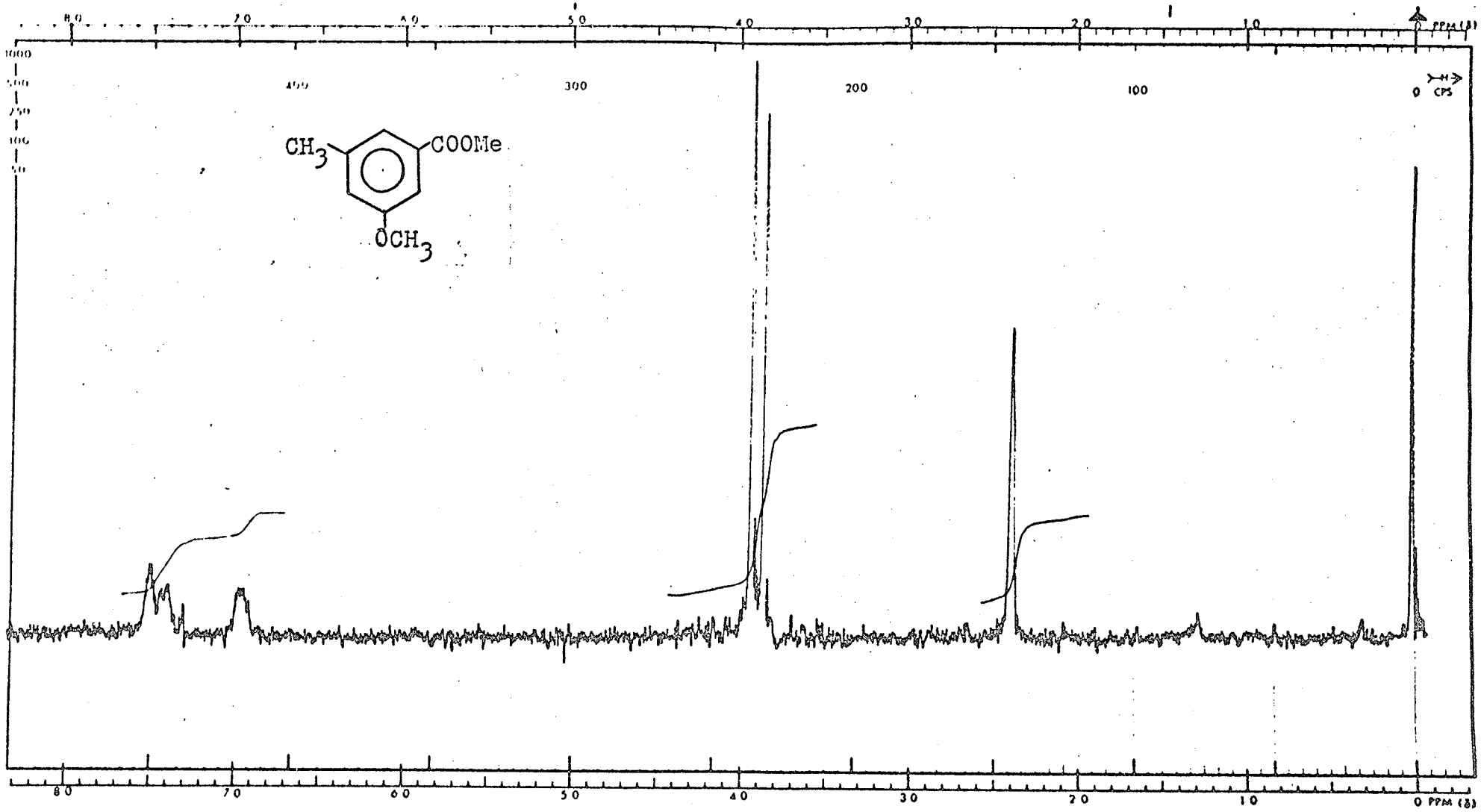
(Fig. XLIX)



Nuclear magnetic resonance spectrum no. 26: Meta-toluic acid (XLVI) in $CDCl_3$.

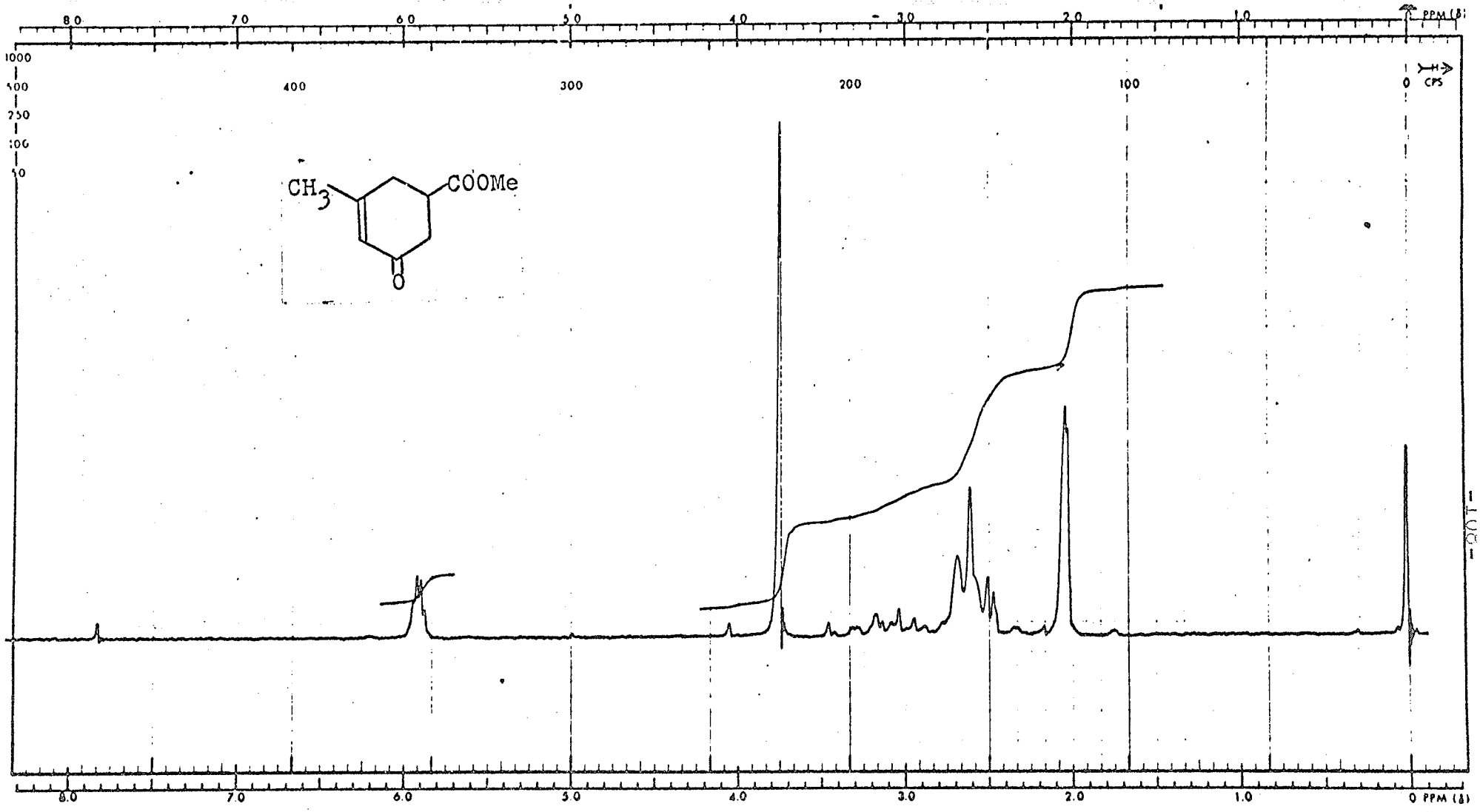
Sweep width = 1000 Hz.

(Fig. L)



Nuclear magnetic resonance spectrum no. 27: 3-methoxy methyl m-toluate (XLVII) diluted in $CDCl_3$. Sweep width = 500 Hz.

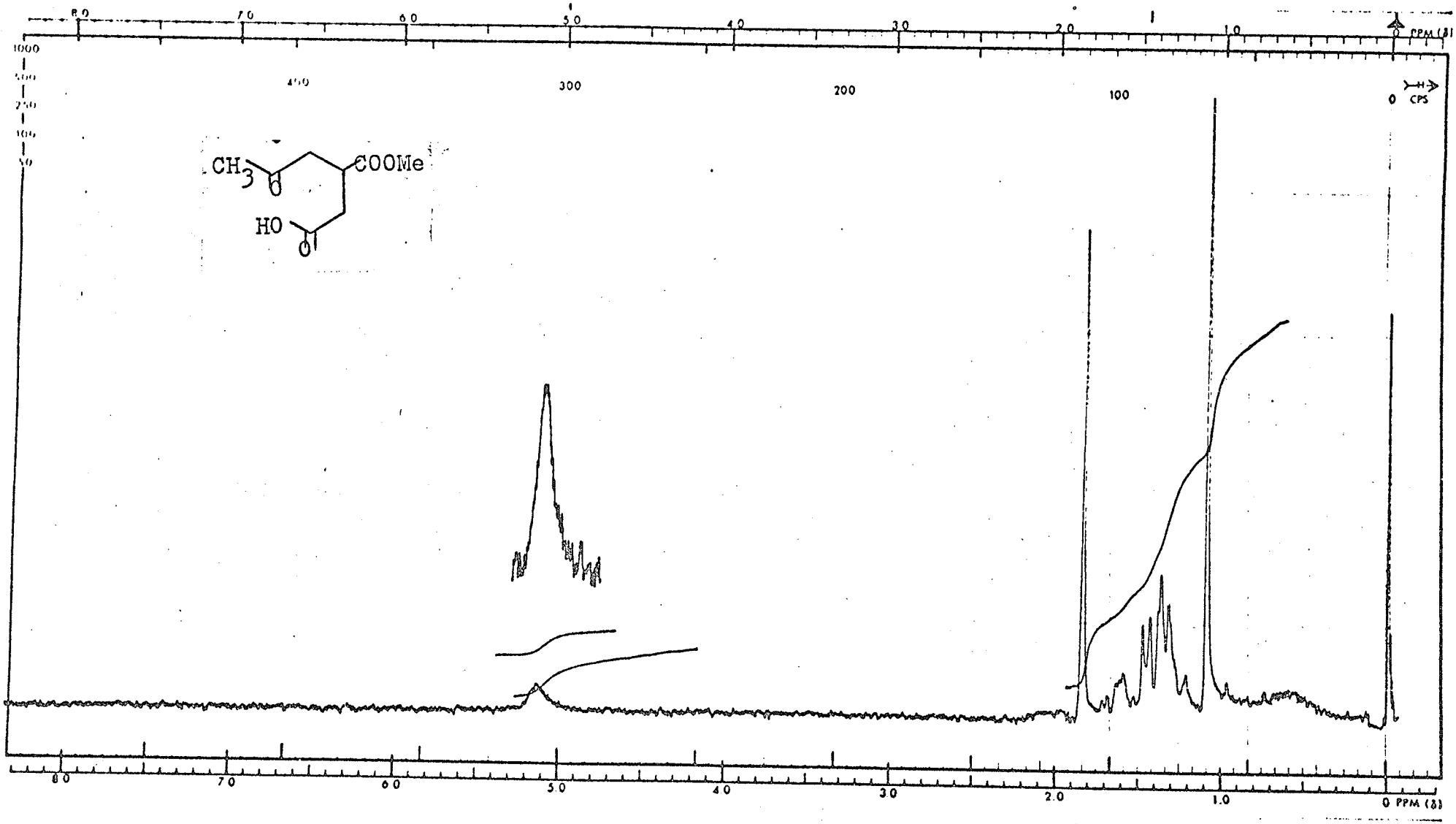
(Fig. LI)



Nuclear magnetic resonance spectrum no. 28: Methyl 3-methylcyclohex-2-ene-1-one-5-carboxylate (XLVIII) diluted in $CDCl_3$.

Sweep width = 500 Hz.

(Fig. LII)



Nuclear magnetic resonance spectrum no. 29: 2-carbomethoxy-4-keto-pentanoic acid (LI) ciluted in $CDCl_3$.

Sweep width = 1000 Hz.

(Fig. LIII)

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