THE SYNTHESIS OF 4-DEMETHOXY-9-DEOXYDAUNOMYCINONE

by

Donald August Popien

A Thesis Submitted to the

Faculty of Graduate Studies and Research

of the University of Manitoba

In Partial Fulfillment of the Requirements

For the Degree Master of Science

October 1972

AUG 15 A.M.

The University of Manitoba
Faculty of Medicine

Department of Biochemistry

770 Bannatyne Ave.
Winnipeg ~~3~~ Manitoba
R3E 0W3

8 August 1972

Dr. C. M. Wong
Dept. of Chemistry
The University of Manitoba
519 - Parker Bldg.
Fort Garry Campus

Dear Dr. Wong:

I have found the Master's thesis entitled "The Synthesis of 4-Demethoxy-9-deoxydaunomycinone" submitted by Mr. Donald A. Popien, satisfactory. The work is thorough and well presented.

Yours sincerely,

J. H. Wang, Ph.D.
Associate Professor

JHW:hm

P.S. The thesis is enclosed.

ACKNOWLEDGEMENTS

I would like to acknowledge at this time the supervision and help accorded to me by my research director Dr. C. M. Wong. His many useful ideas contributed greatly to the success of my project. I would also like to acknowledge the assistance and interest shown in my work by my coworkers Robert Schwenk, Jan te Raa, Joe Keenan, Cornelius Anema, and Raymond Hill. Special thanks are due to Marv Arnesen, Danny Fung, and Dennis Lin for running the mass spectra, and to Ted Kaiser for photographically reproducing the nuclear magnetic resonance spectra.

Lastly, I would like to acknowledge the financial assistance received from the University of Manitoba (1969-1971). This work and my education could not have been completed without this assistance.

ABSTRACT

The Synthesis of 4-Demethoxy-9-Deoxydaunomycinone

Condensing 2,5-dimethoxybenzaldehyde with 2,4-pentanedione in the presence of piperidine and acetic acid gave 3-acetyl-4-(2',5'-dimethoxyphenyl)-3-buten-2-one (14). Reduction of (14) gave 3-acetyl-4-(2',5'-dimethoxyphenyl)-2-butanone which was reacted with ethylbromoacetate to give the keto-ester (16). Hydrolysis of (16) gave 3-acetyl-4-(2',5'-dimethoxyphenyl)-butanoic acid (18). The keto-acid (18) was cyclized with hydrofluoric acid to give 3-acetyl-5,8-dimethoxy-1-tetralone (19). Reduction of the benzylic keto group of (19) gave the tetralin (21). Phthalic anhydride was condensed with (21) to give 4-demethoxy-7,9-dideoxydaunomycinone (22). Treating this compound with dimethylsulphate gave 4-demethoxy-7,9-dideoxy-6,11-di-O-methyldaunomycinone (23). The ketal of (23) was formed and bromination of the C-$_7$ benzylic position was accomplished using N-bromosuccinamide in the presence of benzoyl peroxide. Refluxing the unstable bromo compound with anhydrous methanol and removing the ketal function with dilute acid gave 4-demethoxy-7-epi-9-deoxy-6,7,11-tri-O-methyldaunomycinone (27) as the final product. Hydrolysis of the aromatic O-methyl groups of (27) with aluminum chloride gave 4-demethoxy-7-epi-9-deoxy-7-O-methyldaunomycinone (40). This compound was treated with trifluoroacetic acid to exchange the C-7 methoxyl group for a trifluoroacetate group. Hydrolysing this group with aqueous sodium carbonate/sodium bicarbonate solution gave 4-demethoxy-9-deoxydaunomycinone (42), the required product, and its C-$_7$ epimer (41).

TABLE OF CONTENTS

PAGE

THE SYNTHESIS OF 4-DEMETHOXY-9-DEOXYDAUNOMYCINONE

TABLE OF CONTENTS (continued)

LIST OF FIGURES

Figure Infrared spectrum no. PAGE

Nuclear magnetic resonance spectrum no.

LIST OF FIGURES (continued)

Figure Nuclear magnetic resonance spectrum no. PAGE

Mass spectrum no.

LIST OF FIGURES (continued)

THE SYNTHESIS OF

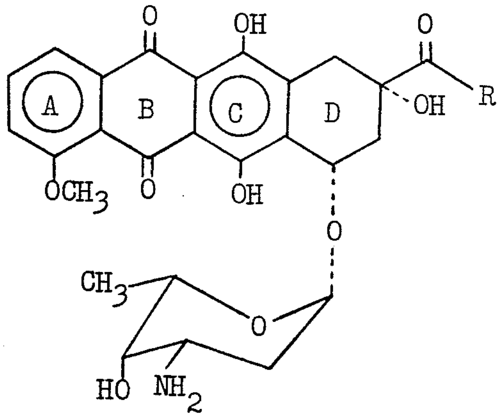
4-DEMETHOXY-9-DEOXYDAUNOMYCINONE

INTRODUCTION

Daunomycinone (1) is one of the hydrolysis products of daunomycin (2). Daunomycin (2), a member of the rhodomycin group, is a new and interesting tetracyclic metabolite isolated from the cultures of Streptomyces peucetius. Also known as rubidomycin and cerubidin, daunomycin lacks potent antibacterial properties,[1] which makes it unlike many of the other tetracyclic antibiotics isolated in recent years. However it does show a remarkably strong inhibition of the growth of tumours, and thus has proven to be a valuable addition to the chemotherapeutic drug list. Presently it finds extensive use in the treatment of certain leukaemic conditions in children as well as adults[2,3].

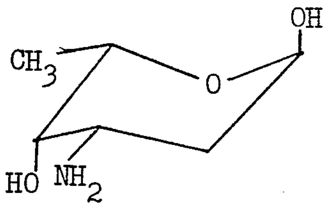
Adriamycin (3) is another tetracyclic metabolite whose structure is very similar to daunomycin. It also shows strong inhibition of the growth of tumours.

THE STRUCTURE OF DAUNOMYCINONE



(2) $R = CH_3$

(3) $R = CH_2OH$



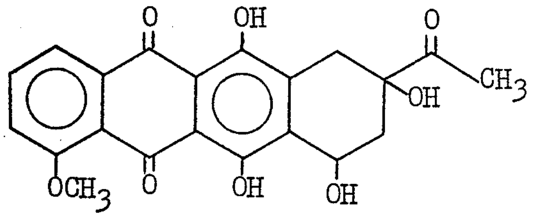
(4)

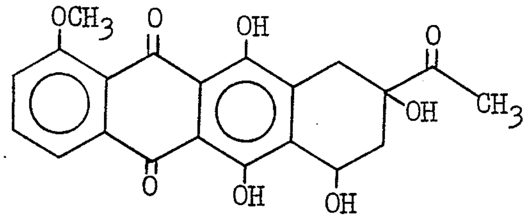
Daunomycin (2) has been hydrolysed to a red coloured hydronapthacenequinone aglycone, daunomycinone (1), and an amino sugar, daunosamine (4)[4]. The preliminary structure elucidation was done by Arcamone et al in 1964 (Scheme I)[4]. The structure of daunomycinone was elucidated on the basis of the following chemical and spectral data:

Zinc dust distillation of daunomycinone (1) gave tetracene (5) thus confirming the tetracyclic ring system. Evidence of the quinoid chromophore came from the similarity of the ultraviolet spectrum of daunomycin hydrochloride with 1,4,5-trihydroxyanthraquinones. Reduction of (1) with sodium borohydride followed by periodate oxidation gave acetaldehyde. This proved the existence of an acetyl side chain attached to an hydroxylated carbon atom. The infrared (i.r.) spectrum and the nuclear magnetic resonance (n.m.r.) spectrum substantiated this chemical evidence. The i.r. spectrum of (1) showed an aliphatic ketone carbonyl absorption at 1718 cm^{-1}, and the n.m.r. spectrum (CF_3COOH) showed a singlet at 7.13 τ. The formation of the tetraacetate (6) by treating (1) with acetic anhydride and pyridine at 60°C. proved the existence of four hydroxyls. The acetate carbonyl absorptions in the i.r. spectrum of (6) suggested alcohol acetates (1740 cm^{-1}) and phenolic acetates (1776 cm^{-1}). Treatment of (1) with either acids or bases gave bisanhydrodaunomycinone (7) which showed a conjugated ketone absorption at 1685 cm^{-1} in its i.r. spectrum. (This compound has recently been synthesized by Horii et al [5]). Bisanhydrodaunomycinone formed a diacetate which showed a carbonyl absorption at 1765 cm^{-1}, thus substantiating the evidence of there being two phenolic groups and two alcoholic groups in (1). The two alcoholic groups were involved in the dehydration reaction forming (7). The presence of two phenolic groups was also indicated in the n.m.r. spectrum ($CDCl_3$) of the monofluoroacetate of (1). Two sharp singlets at -3.00 and -3.60 τ indicated two strongly chelated phenolic hydrogens.

The n.m.r. spectrum of daunomycinone tri-O-methyl ether (8), prepared by refluxing (1) in acetone with dimethylsulphate and potassium carbonate, showed the following absorptions: four singlets, at 6.00 τ (6 H's, two aromatic OCH_3); 6.11 τ (3 H's, aromatic OCH_3); 6.44 τ (3 H's, aliphatic OCH_3); 7.60 τ (3 H's, $COCH_3$). A free hydroxyl was indicated by a singlet (1 H) at 4.98 τ which moved upfield with dilution and downfield with acid. A four line signal (1 H) at 5.08 τ was attributed to an Ar-CH-O proton, and was the X part of an ABX spectrum. The AB part was two pairs of symetric doublets at 8.13 τ (1 H) and 7.58 τ (1 H). The magnitude of the coupling constant, J_{AB} (15 cps), suggested geminal hydrogens, and the chemical shifts of H_A and H_B suggested a methylene group β to an aromatic ring. A set of doublets (2 H's) centered at 6.78 and 6.98 τ (J = 18.5 cps) indicated a benzylic methylene group which lacked vicinal hydrogens. Three protons on an aromatic ring were indicated by a complex multiplet at 2-3 τ. The recovery of salicylic acid from the alkali fusion of (1) or (7) substantiated this last conclusion drawn from the n.m.r.

The investigations of Arcamone et al did not give the stereochemistry of the D ring nor the position of the OCH_3 group on the A ring. From these initial investigations either of the following structures could be written for daunomycinone (1).



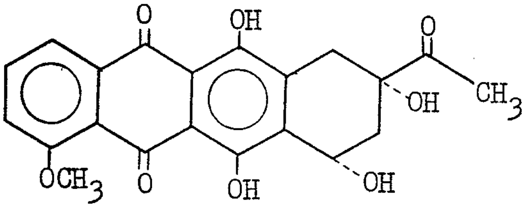


The position of the OCH_3 group on the A ring and the relative stereochemistry of the D ring was ascertained on the basis of the following data:

Treatment of the tri-O-methyl compound (8) with 2,2-dimethoxypropane in the presence of p-toluenesulphonic acid gave the 7,9-acetonide (9) (Scheme I) [6]. The formation of the acetonide (9) showed the relative <u>cis</u>-stereochemistry of the two hydroxyl groups on the D ring.

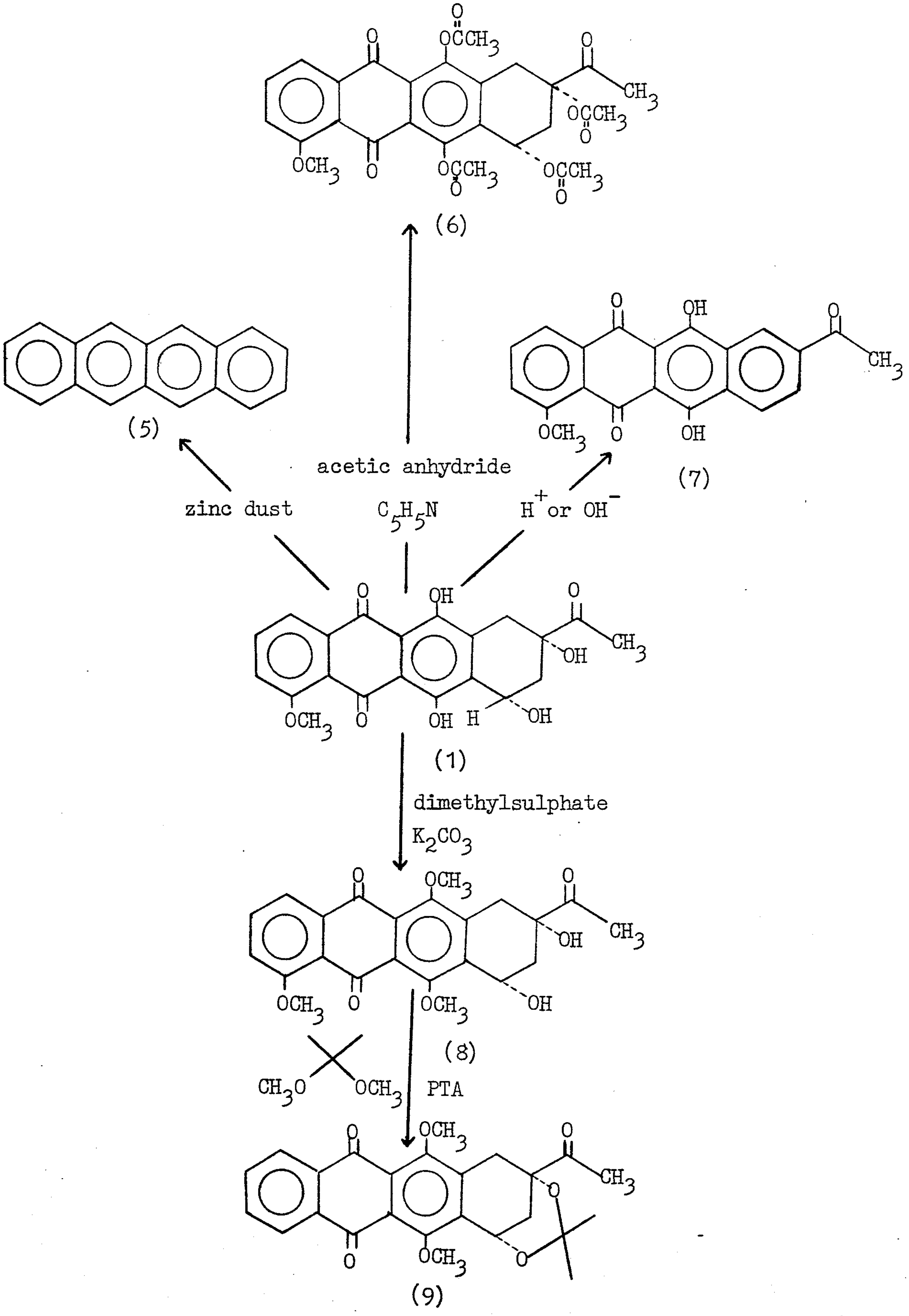
The position of the OCH_3 group on the A ring was determined by a series of chemical reactions shown in Scheme II [7]. Daunomycinone treated with chromic anhydride in acetic acid gave (10). Treatment of (10) with base gave (11) which was hydrolysed with aluminum chloride in 1,2-dichloroethane to give (12). When (12) was treated with phosgene and pyridine in chloroform followed by hydrolysis, the pericarbonate (13) was formed. The i.r. spectrum of (13) showed only chelated quinone absorptions between 1590 and 1620 cm^{-1}. This proved the hydroxylation pattern of (13) and hence of (1). (Had the OCH_3 group been in the C_{-1} position, the i.r. of its corresponding pericarbonate would have shown a free quinone absorption.)

Therefore on the basis of all the data, the following structure (1) can be written for daunomycinone.

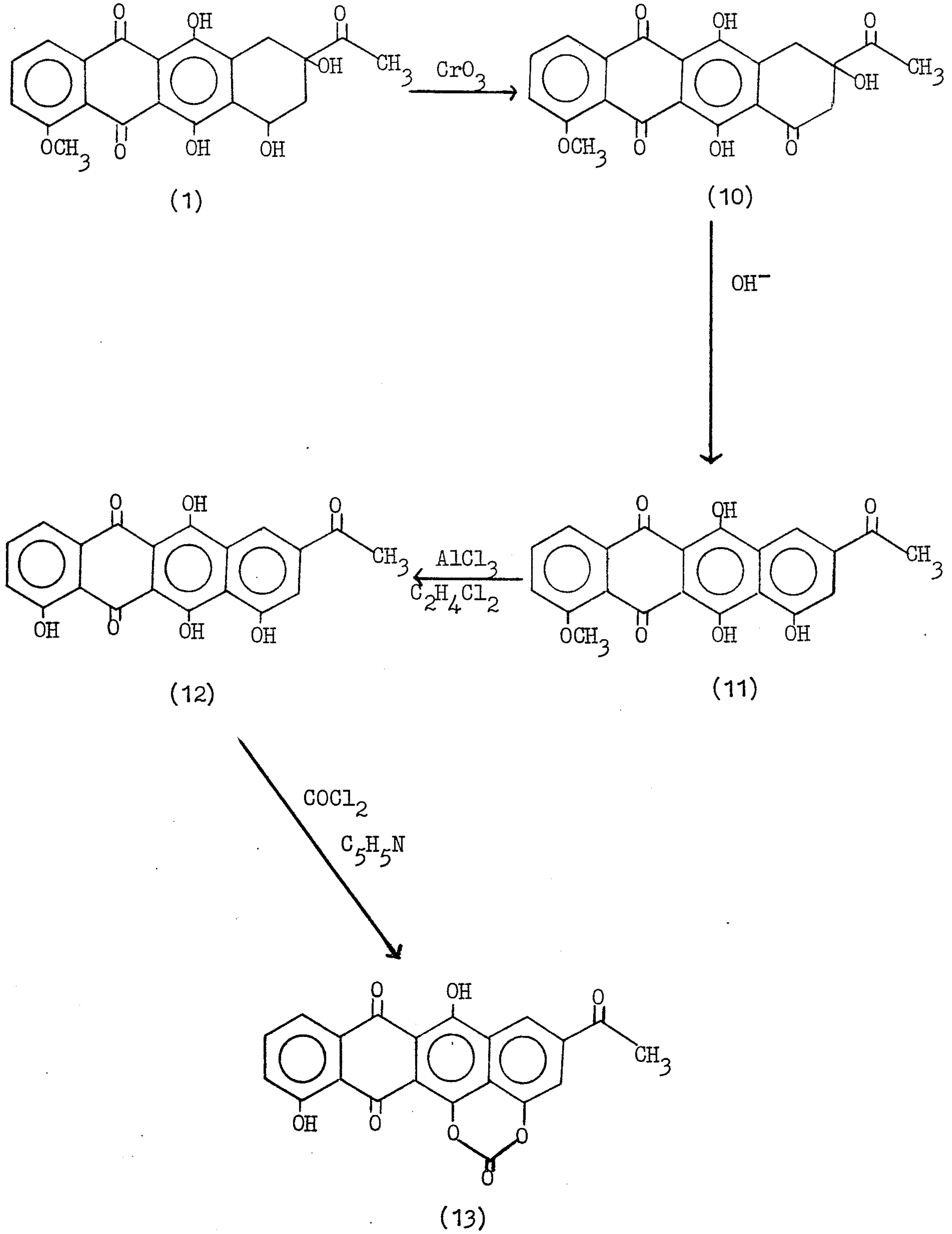


(1)

SCHEME I


(6)
(5)
(7)
acetic anhydride
C_5H_5N
zinc dust
H^+ or OH^-
(1)
dimethylsulphate
K_2CO_3
(8)
CH_3O
OCH_3
PTA
(9)

SCHEME II



RESULTS AND DISCUSSION

4-Demethoxy-9-deoxydaunomycinone has been synthesized starting from phthalic anhydride and a bicyclic compound, 2-acetyl-5,8-dimethoxytetralin.

The bicyclic compound mentioned above was prepared from a bicyclic compound first synthesized by J. te Raa and presented in his doctoral thesis [8]. His procedure for preparing the bicyclic system was slightly modified. The purification of the final product of his reaction scheme was altered and the structure of the by-product isolated with the final product was elucidated for the first time. The entire procedure for the preparation of 2-acetyl-5,8-dimethoxytetralin is reported in a paper by Wong et al and is illustrated in Scheme III and IV.

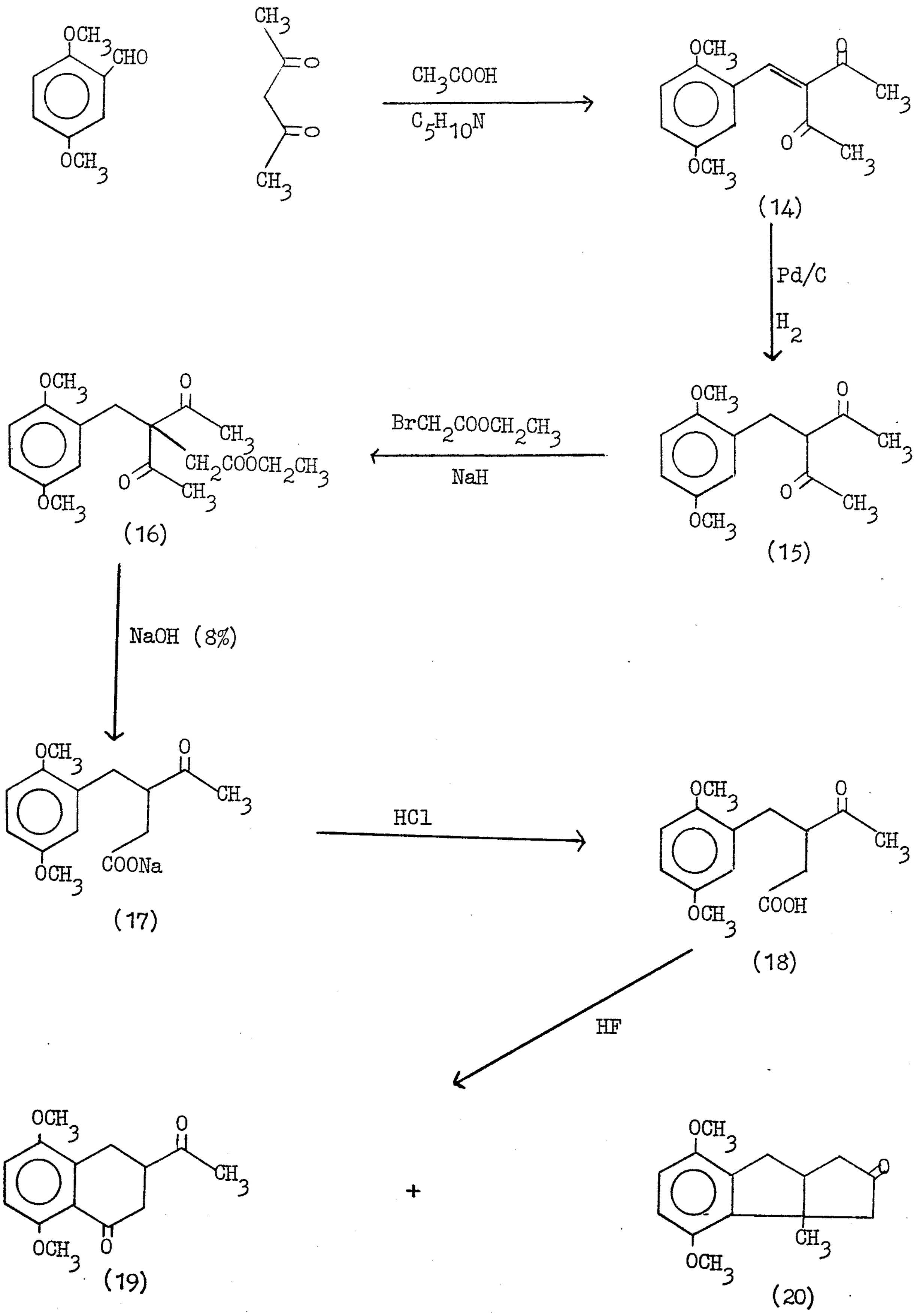
Condensing 2,5-dimethoxybenzaldehyde with 2,4-pentanedione in the presence of piperidine and acetic acid gave the unsaturated diketone (14). The diketone (14) was reduced to the diketone (15) which was purified by vacuum distillation (80 % yield). This compound existed in an equilibrium between the keto and the enol form. The n.m.r. spectrum (Fig. XIV) showed this tautomerization clearly. A small peak at $-6.50\ \tau$ corresponded to the enol proton. A singlet at $6.58\ \tau$ and a doublet centered at $7.06\ \tau$ was attributed to the benzylic hydrogens of the enol form and the keto form respectively. The i.r. spectrum (Fig. I) showed a broad carbonyl absorption at 1700 cm^{-1} and a broad aromatic C=C absorption at 1580 cm^{-1}.

The next reaction involved the alkylation of the diketone (15) with ethylbromoacetate. The product , the keto-ester (16), was treated with sodium hydroxide (8%) and underwent a reversed Claisen. The ester was hydrolysed to give the keto-acid (18) as the final product (75% yield). The i.r. spectrum of (18) (Fig. II) showed two carbonyl absorptions at 1740 and 1700 cm^{-1} for the COOH and the $COCH_3$ groups respectively. A peak at 3500 cm^{-1} was attributed to the carboxyl OH. The n.m.r. spectrum (Fig. XV) showed a singlet at -2.10 τ for the carboxyl hydrogen and a singlet at 7.68 τ due to the methyl ketone group.

The keto-acid (18) was cyclized to the tetralone (19) in the presence of hydrofluoric acid. Some lactone (20) was also isolated. The amount of lactone formed depended on the temperature of the reaction as well as the concentration of the reactants. At 0°C. the lactone was the major product. At 20°C. with a high concentration of the keto-acid in the HF, about 25% of the product was isolated as the lactone. Optimum conditions were the following: 10 ml. of HF to 1 gr. of keto-acid, reaction temperature of 20°C. Under these conditions the yield of tetralone (19) was 60%, and of the lactone (20) 6.9%. Both compounds were characterized from their respective spectral data. The i.r. spectrum (Fig. III) of the tetralone (19) showed two carbonyl absorptions at 1710 and 1685 cm^{-1} for the methyl ketone group and the conjugated benzylic keto group respectively. The n.m.r. spectrum (Fig. XVI) of (19) showed an AB pattern quartet centered at 3.16 τ for the two aromatic protons, a six proton singlet at 6.23 τ for the two methoxy groups, and a three proton singlet absorption at 7.78 τ for the methyl ketone group.

The i.r. spectrum (Fig. IV) of the lactone (20) showed a single carbonyl absorption at 1765 cm^{-1}. The n.m.r. spectrum (Fig. XVII) showed singlet absorptions at 3.28, 6.22 and 6.25 τ for the aromatic and the two methoxy group protons. A three proton singlet at 8.18 τ was assigned to the tertiary methyl

SCHEME III

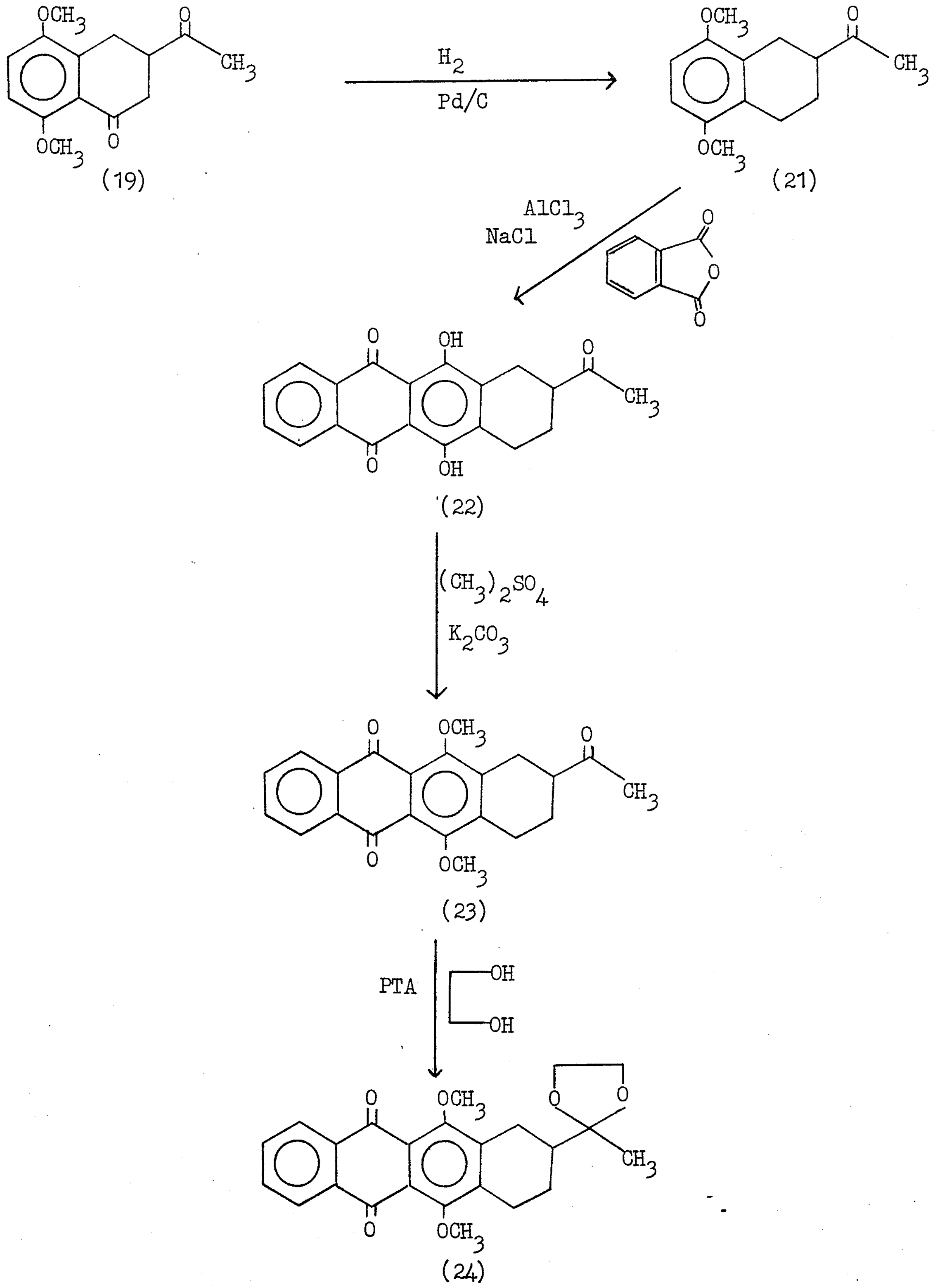

OCH3
CHO
OCH3
CH3
CH3
CH3COOH
C5H10N
OCH3
OCH3
CH3
CH3
(14)
Pd/C
H2
OCH3
OCH3
CH3
CH3
(15)
BrCH2COOCH2CH3
NaH
OCH3
OCH3
CH3
CH2COOCH2CH3
CH3
(16)
NaOH (8%)
OCH3
OCH3
CH3
COONa
(17)
HCl
OCH3
OCH3
CH3
COOH
(18)
HF
OCH3
OCH3
CH3
(19)
+
OCH3
OCH3
CH3
(20)

group. The mass spectrum (Fig. XXVII) showed the correct molecular ion of 248 mass units. The peak at 233 mass units was due to the loss of a methyl group. A peak at 190, due to loss of the lactone side chain, was assigned to the 2-methyl-4,7-dimethoxyindene cation.

Once the bicyclic system had been synthesized, an attempt was made to condense it with phthalic anhydride to form the tetracyclic ring system. The tetralone (19) and phthalic anhydride were heated in the presence of aluminum chloride and sodium chloride. No tetracyclic compound was identified in the reaction products. Therefore, it was concluded that the tetralone (19) was unstable under the above reaction conditions because of the benzylic keto group. It was decided to reduce the keto group in order to make the aliphatic ring more stable, and then make another attempt at the condensation.

The tetralone (19) was selectively hydrogenated to give the tetralin (21) (Scheme IV). The hydrogenation was done in acidic ethanol with 5% Pd/C as catalyst and hydrogen at atmospheric pressure. The compound was isolated as a white crystalline solid. The i.r. spectrum (Fig. V) of the reduced compound showed in the carbonyl region of the spectrum only the aliphatic carbonyl absorption at 1705 cm^{-1}. The n.m.r. spectrum (Fig. XVIII) showed multiplets between 7.00 and 7.50 τ due to the seven aliphatic ring hydrogens. There were also singlet absorptions for the aromatic hydrogens, the methoxyl group hydrogens and the methyl ketone group hydrogens at 3.36, 6.29 and 7.75 τ respectively. The mass spectrum (Fig. XXVIII) showed the expected molecular ion of 234. The peak at 219 mass units was due to loss of a methyl group. Loss of a methoxyl group gave the peak at 203, and loss of the methyl ketone side chain gave the peak at 191 mass units.

SCHEME IV



The tetracyclic ring system was synthesized by condensing the tetralin (21) with phthalic anhydride in the presence of sodium chloride and freshly sublimed aluminum chloride at a temperature of 170°C. (Scheme IV). After work-up and purification by thin layer chromatography (t.l.c.), the tetracyclic compound (22) was isolated as a fluffy red powder (64.5% yield). This compound gave a satisfactory elemental analysis, and the mass spectrum (Fig. XXIX) showed the molecular ion of 336 which was consistent with the structure (22). The strong peak at 293 mass units was due to loss of the methyl ketone side chain. Loss of the side chain and water gave the peak at 275 mass units. The i.r. spectrum (Fig. VI) showed a broad absorption at approximately 3400 cm^{-1} due to the strongly chelated phenolic groups. The spectrum also showed carbonyl absorptions at 1710, 1590 and 1635 cm^{-1} which were assigned to the methyl ketone carbonyl and the two quinone carbonyls respectively. The absorptions for the quinone carbonyls being lower than is usual, again showed that there was strong intramolecular hydrogen bonding (chelation) between the quinone carbonyls and the phenolic group hydrogens. The n.m.r. spectrum (Fig. XIX) showed two singlet absorptions for the phenolic group hydrogens at -3.18 and $-3.12\,\tau$. The low field absorptions were attributed to the intramolecular hydrogen bonding. The multiplet absorptions at $1.80-2.26\,\tau$ and $7.35\,\tau$ were assigned to the aromatic and the aliphatic ring hydrogens respectively. A three proton singlet absorption at $7.70\,\tau$ was assigned to the methyl ketone group hydrogens.

The tetracyclic phenol (22) was methylated with dimethylsulphate in the presence of potassium carbonate to give the di-O-methyl ether (23) after t.l.c. purification (66.5% yield).

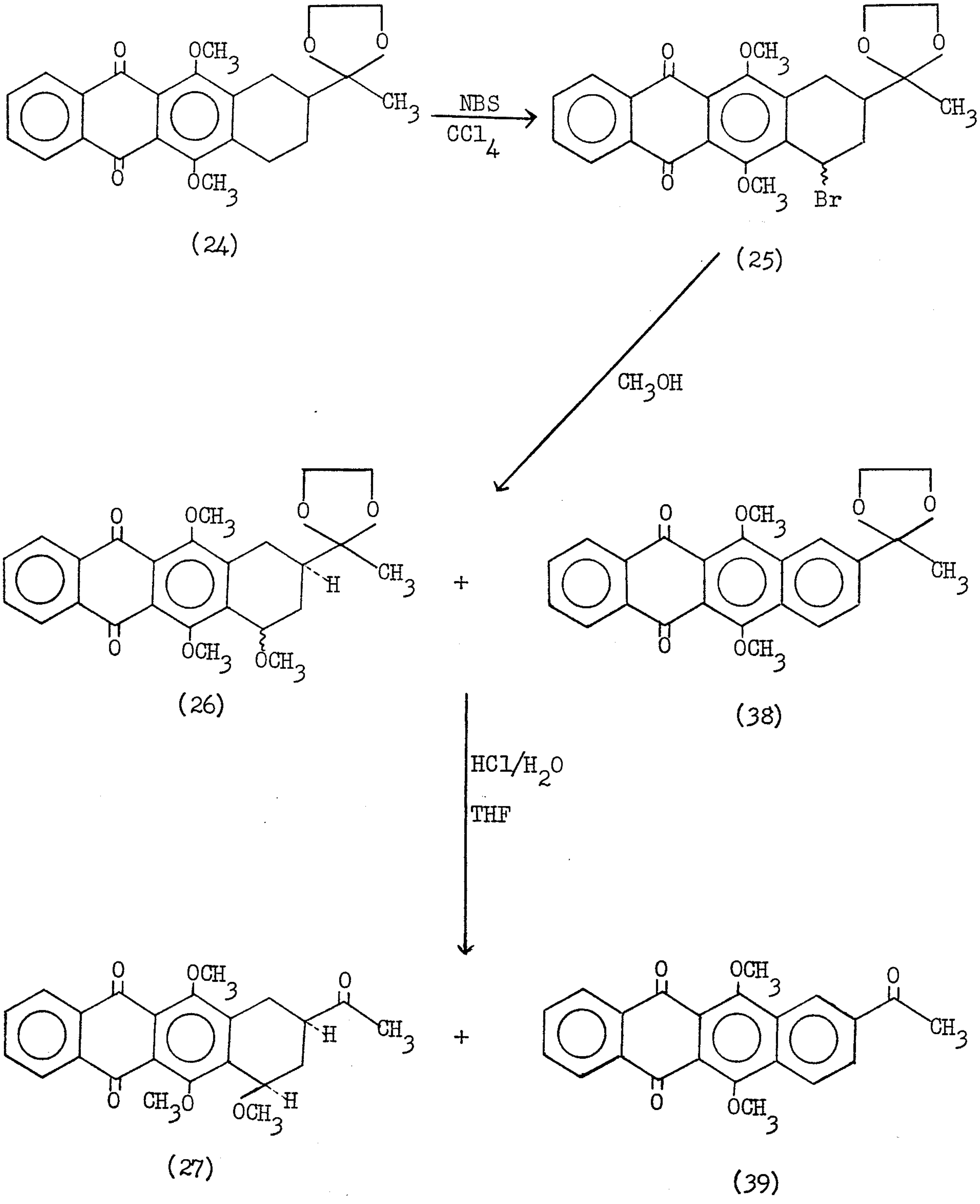
The yellow crystalline compound gave a satisfactory elemental analysis and the mass spectrum (Fig. XXX) showed the expected molecular ion of 364. The spectrum showed a peak at 349 mass units due to loss of a methyl group. Loss of the methyl ketone side chain gave the prominent peak at 321. The i.r. spectrum (Fig. VII) showed carbonyl absorptions at 1705 and 1665 cm^{-1} for the methyl ketone carbonyl and the now unchelated quinone carbonyls respectively. The n.m.r. spectrum (Fig. XX) lacked the two low field singlet absorptions due to the phenol group hydrogens and now showed two singlet absorptions due to the two methoxy groups at 6.20 and 6.18 τ. Other absorptions in the n.m.r. spectrum were as expected.

In order to make the positions α to the ketone carbonyl less reactive, and also to make the C-$_{10}$ benzylic position more hindered to attack, the ketal (24) was prepared from (23). Recrystallization of the product of the reaction of (23) with ethylene glycol in the presence of p-toluenesulphonic acid from methanol gave a bright yellow crystalline solid (95% yield). The mass spectrum showed the expected molecular ion at 408 mass units. The i.r. spectrum (Fig. VIII) lacked the absorption due to the methyl ketone carbonyl and showed in the carbonyl region of the spectrum only the quinone carbonyls at 1670 cm^{-1}. The n.m.r. spectrum (Fig. XXI) showed a four proton singlet absorption at 6.15 τ which was attributed to the two methylene groups of the ketal group. There were also the usual absorptions for the aromatic, aliphatic and methoxyl protons. The singlet absorption for the methyl group of the methyl ketone side chain was shifted upfield to 8.62 τ because of less deshielding by the ketal group.

The tri-O-methyl ether (27) was made in a series of reactions beginning with the C_7 benzylic bromination of the ketal (24) (Scheme V). N-bromosuccinamide in the presence of benzoyl peroxide was used as the brominating agent. The crude bromo compound (25) was not purified due to its instability, and was immediately refluxed in anhydrous methanol to give the tri-O-methyl ketal (26). The ketal group was removed by stirring the crude compound (26) in acidic tetrahydrofuran (THF). After t.l.c. purification, the tri-O-methyl ether (27) was isolated as a yellow crystalline compound (52.5% yield). The i.r. spectrum (Fig. IX) showed the methyl ketone carbonyl absorption at 1710 cm^{-1} and the absorption due to the quinone carbonyls at 1670 cm^{-1}. The n.m.r. spectrum (Fig. XXII) showed the presence of an additional methoxyl group absorption at 6.49 τ as well as the other two methoxyl absorptions at 6.06 and 6.13 τ. A one proton triplet absorption at 5.35 τ was assigned to the C_7 benzylic hydrogen. In addition the spectrum showed the methyl ketone absorption at 7.72 τ and the usual absorptions for the aromatic and aliphatic ring protons. The mass spectrum of (27) (Fig. XXXI) showed the expected molecular ion of 394. Loss of a methyl group gave the peak at 379 mass units. Loss of methanol gave the peak at 362, and loss of the methyl ketone side chain gave the 351 peak. Simultaneous loss of the side chain and methanol gave the prominent peak at 319 mass units.

Initially the stereochemistry of (27) was assigned on the basis of the n.m.r. spectrum (Fig. XXII) of the compound. The single absorption peak for the benzylic methoxyl group as well as the sharp melting point (m.p.) (143.5-144.5°C.) were indicative of one isomer[i]. The chemical shift for the methoxyl peak (6.49 τ) was indicative of the cis-diequatorial compound.

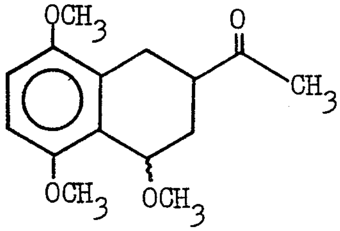
SCHEME V



A look at the mechanisms involved in the formation of the product (27) substantiated the conclusion incurred from the n.m.r. spectrum. The formation of the tri-O-methyl ketal (26) proceeds through a carbonium ion intermediate. One possible conformation for the carbonium ion is with the ketal side chain quasi-equatorial (Scheme VI). Two structures, (28) and its mirror image (29), can be drawn. Attack by methanol on the β-side of (28) gives the cis-diequatorial compound (30), which is the enantiomorph of (31), obtained by α-attack on the mirror image (29). The trans-axial-equatorial compounds (32) and (33), which also are enantiomorphs, are obtained by attack of the methanol on the α-side of (28) or the β-side of (29) respectively.

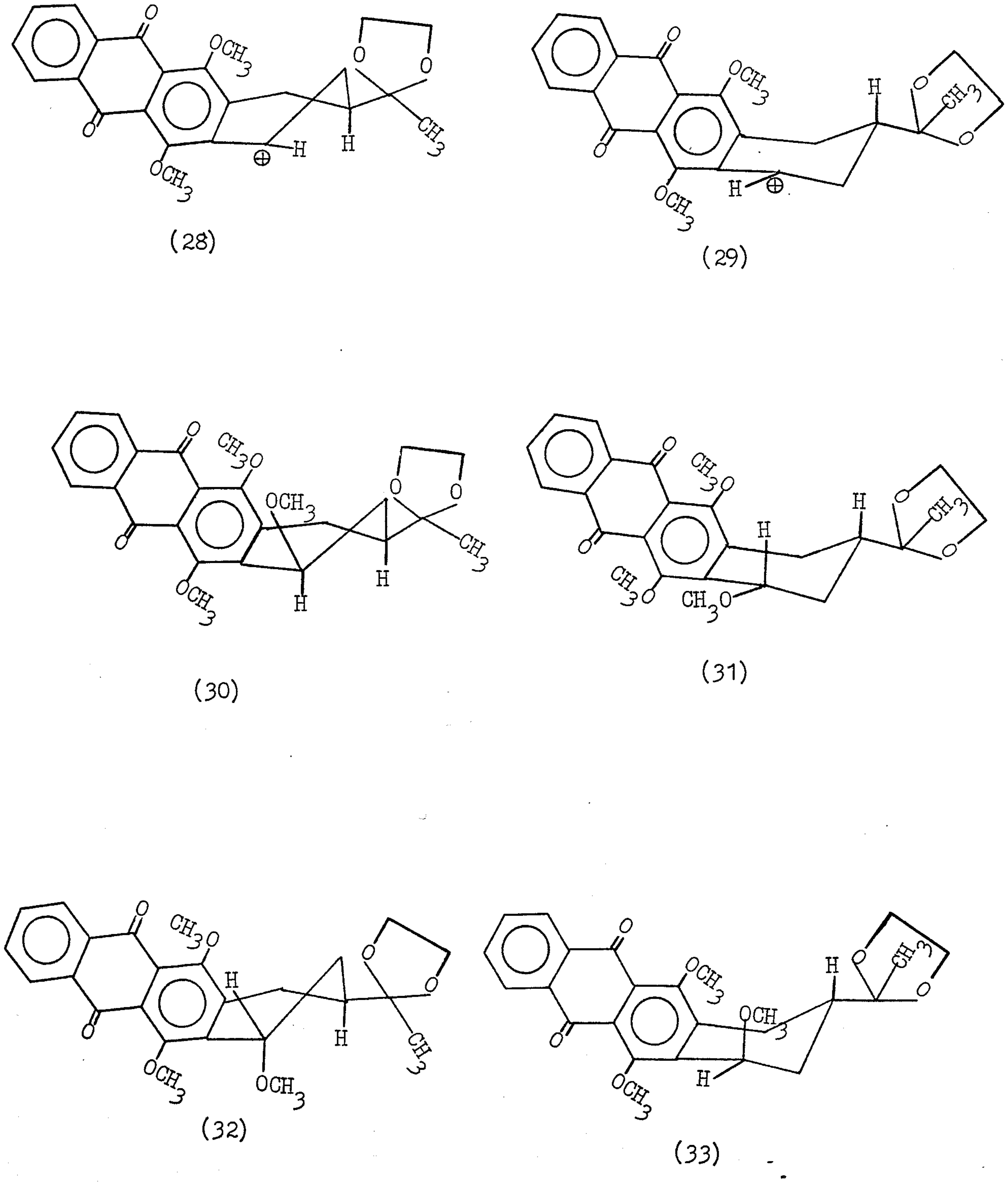
The other conformational possibility for the carbonium ion is with the ketal side chain axial as illustrated in structure (34) (Scheme VII). In this conformation the oxygens of the ketal side chain may stabilize the positively charged carbonium ion making the attack by methanol possible only on the α-side of (34) and giving the trans-axial-equatorial compound (35). Note that without the stabilizing interaction between the ketal oxygens and the positive charge of the carbonium, the ring will flip to the more

---

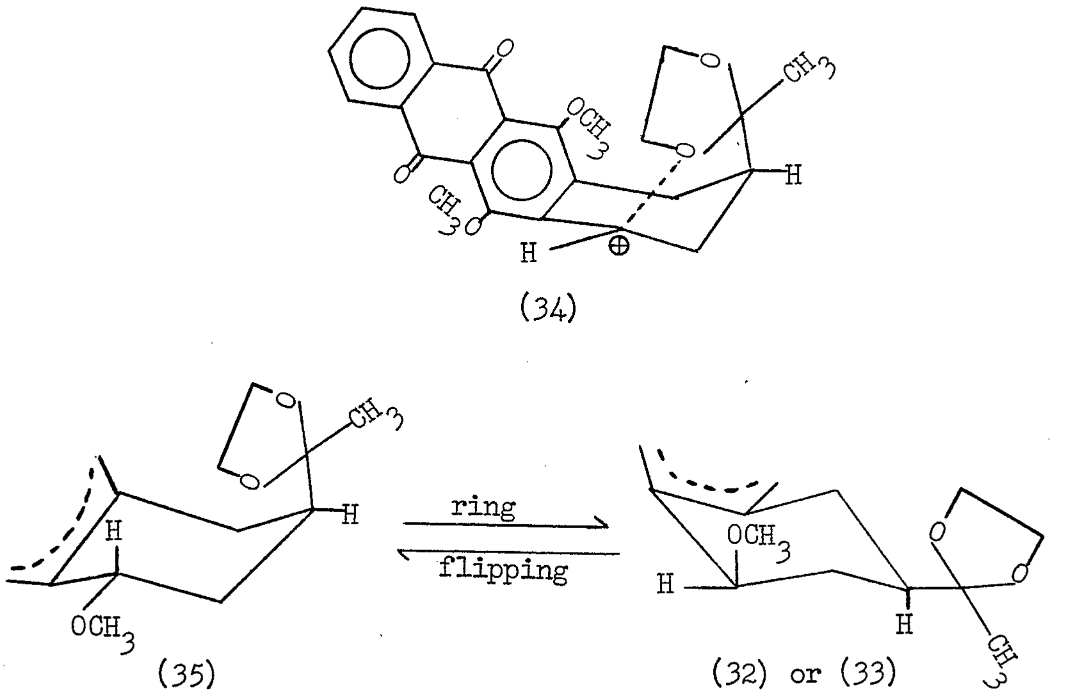


i Unpublished results from our laboratory by J. te Raa indicate that the above compound exists in two isomeric forms. The n.m.r. spectrum of the compound shows that the cis-diequatorial isomer has a chemical shift for the benzylic methoxyl of 6.50 τ while the trans-axial-equatorial isomer has a chemical shift of 6.70 τ for the methoxyl group.

SCHEME VI



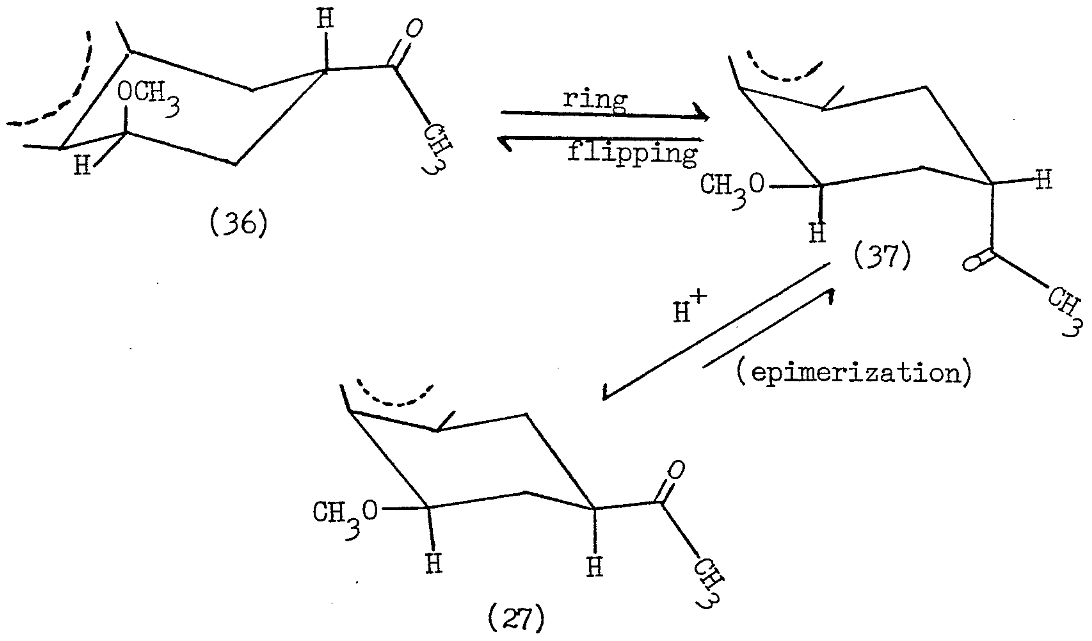
SCHEME VII



stable conformation i.e. the larger ketal side chain equatorial, the smaller methoxyl group axial. This conformation is identical to that of (32) or (33).

Thus from studying the mechinism of the methoxylation, one would expect both <u>cis</u>-diequatorial and <u>trans</u>-axial-equatorial tri-O-methyl ketal to form. Since hydrolysis of the ketal to the ketone does not change the configuration, both <u>cis</u> and <u>trans</u> tri-O-methyl ketone should be isolated. However, only one isomer was isolated. This experimental fact can be explained by looking at another reaction which can occur in the acidic reaction medium of the hydrolysis step. Once the ketone has been regenerated, keto-enol tautomerization of the carbonyl group can occur (Scheme VIII). Epimerization of the C-$_9$ carbon atom takes place because of this tautomerization, and thus any axial-equatorial ketone (36, 37)

SCHEME VIII

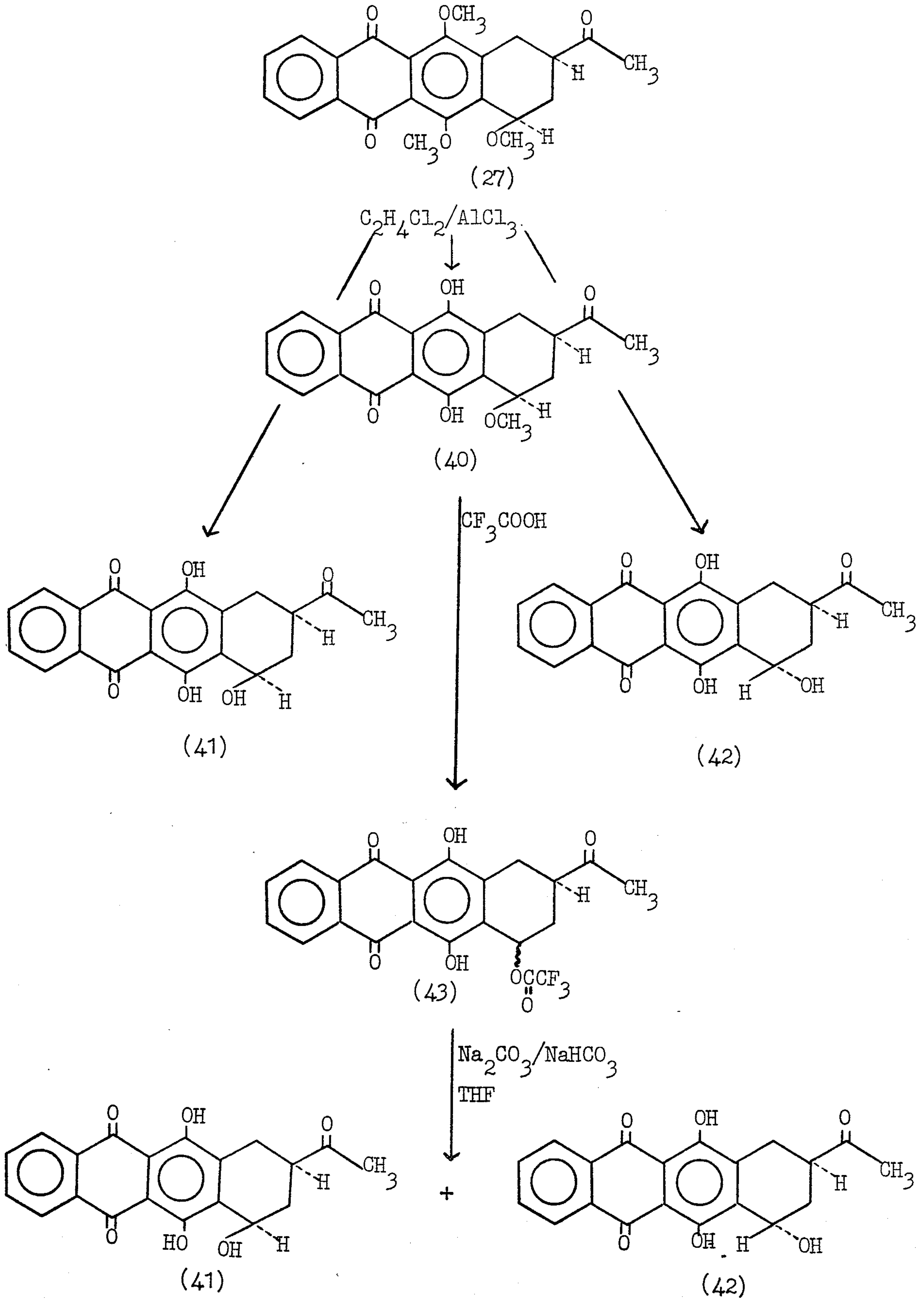


which could be formed from the hydrolysis of (32) or (33), can be converted to the thermodynamically more stable cis-diequatorial ketone (27). Note that the epimerization is a reversible process and some axial-equatorial ketone should also be isolated in the products. Experimentally, only one isomer was present in high enough yield to be isolated. One would expect this isomer to be the more stable cis-isomer; therefore (27) was assigned the structure of 4-demethoxy-7-epi-9-deoxy-6,7,11-tri-O-methyldaunomycinone.

The other major product of this series of reactions leading to the formation of the tri-O-methyl ether (27) was the fully aromatized compound (39). The mass spectrum (Fig. XXXII) of the bright yellow crystalline compound showed the molecular ion of 360 which was consistent with the structure (39). Loss of the methyl ketone side chain gave the peak at 317 mass units. The peak at 345 mass units was due to loss of a methyl group. The i.r. spectrum (Fig. X) showed an aryl ketone absorption at 1690 cm^{-1}. The n.m.r. spectrum (Fig. XXIII) showed extra multiplet absorptions in the aromatic region of the spectrum, and the aromatic protons integrated to seven. The singlet absorption for the methyl ketone group was shifted downfield to 7.29 τ due to the extra deshielding by the adjacent aromatic ring. The two singlet absorptions for the methoxyl groups were also shifted downfield to 5.90 and 5.95 τ for the same reason.

The mono-O-methyl ether (40) was formed by removing the phenolic O-methyl groups (Scheme IX). Removal of the two groups was accomplished by stirring the tri-O-methyl compound (27) dissolved in 1,2-dichloroethane with freshly sublimed aluminum chloride. Following work-up and t.l.c. purification, three bands were identified on the t.l.c. plate. The major band (largest R_f value) was isolated as a fluffy red powder (78% yield), and was found to be the mono-O-methyl ether (40). This compound gave a molecular ion of 366 in its mass spectrum (Fig. XXXIII) which was consistent with the structure (40). Aromatization of the aliphatic ring by loss of methanol and two hydrogens gave the peak at 332 mass units. Simultaneous loss of methanol and the methyl ketone side chain gave the large peak at 291. The i.r. spectrum (Fig. XI) showed an absorption at 1710 cm^{-1} due to the methyl ketone. The quinone carbonyl absorptions at 1620 and 1590 cm^{-1} indicated that they were again chelated to the newly formed phenol group hydrogens. The n.m.r. spectrum (Fig. XXIV) showed two low field singlets at -3.19 and -3.00 τ due to the chelated phenol hydrogens. The n.m.r. also showed two singlet absorptions at 6.49 and 7.72 τ which were assigned to the

SCHEME IX



benzylic methoxyl group and the methyl ketone respectively. A triplet at 5.36 τ was assigned to the single benzylic hydrogen on the C_7 carbon atom.

A small amount of the fully hydrolysed compound (42) (4.4% yield), and its epimer (41) (3% yield) were also isolated in the other two bands identified from the t.l.c. plate. Since they were the major products isolated in the next reaction, they will be discussed below.

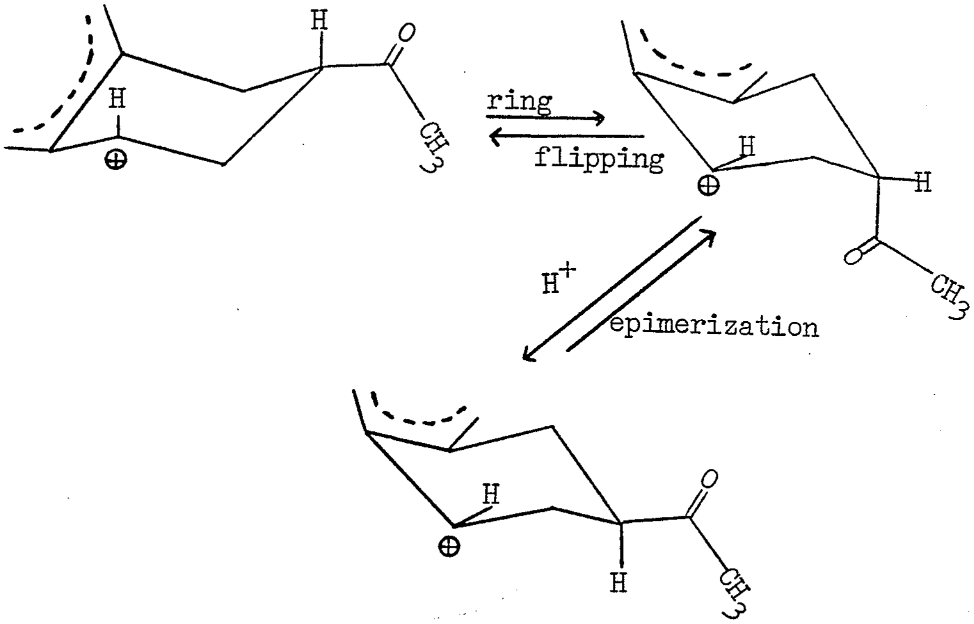
The next step in the synthesis was to hydrolyse the benzylic methoxy group (Scheme IX). For ease of hydrolysis the methoxy group was exchanged for a trifluoroacetate group by refluxing (40) in trifluoroacetic acid. Hydrolysis of the crude trifluoroacetate was accomplished with an aqueous THF solution of sodium carbonate and sodium bicarbonate. The products of the hydrolysis were purified by t.l.c. The major band (lower R_f value), 4-demethoxy-7-epi-9-deoxydaunomycinone (41) was isolated as a red powder after recrystallization from chloroform/methanol. The mass spectrum (Fig. XXXV) of this product showed a molecular ion of 352 which was consistent with the structure (41) The peak at 334 mass units was due to loss of water. Simultaneous loss of water and methyl ketone side chain gave the large peak at 291 mass units. The i.r. spectrum (Fig.XIII) showed an absorption at 3575 cm^{-1} which was assigned to the benzylic alcoholic group. The absorption at 1710 cm^{-1} was due to the methyl ketone carbonyl, and the absorptions at 1620 and 1590 cm^{-1} were due to the chelated quinone carbonyls. The n.m.r. spectrum (Fig.XXVI) lacked the singlet absorption due to the benzylic methoxyl group. A three proton singlet absorption at 7.72 τ was assigned to the methyl ketone group.

A one proton multiplet at 4.93 τ was assigned to the single C_7 benzylic hydrogen. Singlet absorptions at -3.00 and -2.75 τ were assigned to the chelated phenol group hydrogens.

The minor band (higher R_f value), 4-demethoxy-9-deoxydaunomycinone, (42) was isolated as a red powder (13.3% yield). The mass spectrum (Fig. XXXIV) showed the expected molecular ion of 352. Loss of the benzylic hydroxyl group and an adjacent hydrogen as water gave the peak at 334 mass units. The peak at 291 was due to the simultaneous loss of the methyl ketone side chain and water. The i.r. spectrum (Fig XII) showed major absorptions identical to those in the i.r. spectrum of its epimer (41). The only difference in the i.r. spectra of the two isomers was an extra absorption at 1010 cm^{-1} in the spectrum of (42). The n.m.r. spectrum (Fig. XXV) showed an absorption at 7.72 τ due to the methyl ketone group. The single C_7 benzylic hydrogen absorption appeared to come at 4.93 τ. The low field absorptions at -3.50 and -3.00 τ were due to the chelated phenol group hydrogens. Note that the only major difference between the spectrum of the two isomers (41) and (42) is the chemical shifts of the phenol group hydrogens.

The stereochemistry of the two isomers (41) and (42) was proposed on the basis of the experimental yields. The _cis_-diequatorial conformation was assigned to the isomer isolated in major yield i.e. (41). This conformation is thermodynamically more stable than the axial-equatorial conformation, and one would expect a higher yield of the more stable isomer.

On the basis of the mechinisms of the reactions leading to the formation of (41) and (42), this proposal can be justified. The substitution of the benzylic methoxy group of (40) by a trifluoroacetate group proceeds through attack of the trifluoroacetic acid on any of the carbonium ions shown below. Note that while attack on the carbonium ion is taking place, conformational ring flipping and epimerization of the C-$_9$ carbon atom due to keto-enol tautomerization is also occuring. The stereochemistry of the trifluoroacetate (43) cannot be predicted, or established due to the instability of the trifluoroacetate group which hydrolyses slowly on purification.



Hydrolysis of the trifluoroacetate group does not change the stereochemistry at the C-$_7$ (the benzylic carbon atom) position, but in the basic solution used for the hydrolysis, epimerization of the C-$_9$ carbon atom can again occur. (Epimerization can take place in both acidic or basic mediums because keto-enol tautomerization, through which epimerization occurs, is catalysed by either acid or base.) The epimerization of the C-$_9$ carbon atom will result in the isomer of greater stability, the <u>cis</u>-diequatorial isomer, predominating in the reaction products. Once the base is removed in the work-up, the stereochemistry cannot change, and the <u>cis</u>-isomer should be the isomer isolated in major yield.

Experimentally, one isomer was isolated in major yield. On the basis of the above argument, this isomer was assigned the <u>cis</u>-diequatorial conformation. Therefore, the isomer isolated in major yield (41) was assigned the structure of 4-demethoxy-7-epi-9-deoxydaunomycinone. The isomer isolated in minor yield (42) was assigned the structure of 4-demethoxy-9-deoxydaunomycinone.

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. The following abbreviations have been used when referring to the n.m.r. spectra: s = singlet, d = doublet, t = triplet, m = multiplet. Chemical shifts are given in tau (τ) units. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6D mass spectrometer or a Finnigan 1015 mass spectrometer. Melting points (m.p.) were obtained on a Fisher-Johns 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 adsorbent were used for t.l.c. separations. Dr. Daessele of Montreal performed any microanalyses.

(1) Preparation of 3-Acetyl-4-(2',5'-dimethoxyphenyl)-2-Butanone (15):

2,5-Dimethoxybenzaldehyde (100 g., .60 mole), 2,4-pentanedione (80 g., .80 mole), piperidine (5 ml.), and acetic acid (8 ml.) were dissolved in benzene (500 ml.) in a 1 l. flask equipped with a condenser and a water separator. After refluxing for 1.5 hours, the benzene was removed under reduced pressure. The crude residue was dissolved in freshly distilled ethanol (.5 l.), and filtered into a 2 l. flask containing 5% Pd/C (14 g.) and distilled ethanol (.5 l.). The solution was hydrogenated at one atmospheric pressure until the uptake of hydrogen ceased (about 3.5 hours). The catalyst was filtered off and the ethanol was removed under reduced pressure leaving a viscous brown residue. The residue was purified by vacuum distillation (b.p. = 150-155°C. at 0.5 mm. Hg) to give (15) as a light yellow oil (120 g., .48 mole, 80%).

Infrared spectrum no. 1 (Fig. I): absorptions (cm^{-1}) at 1700 (broad, 1,3-diketone); 1580 (aromatic C=C).

N.m.r. spectrum no. 1 (Fig. XIV): absorptions at -6.50 (s, enol H); 3.46-3.62 (m, aromatic H's); 6.30, 6.33 (singlets, OCH_3 groups of keto form); 6.42 (s, OCH_3 groups of enol form); 6.58 (s, benzylic H's of enol form); 7.06 (d, benzylic H's of keto form); 8.00, 8.05 (singlets, CH_3 groups of enol and keto forms respectively).

(2) Preparation of 3-Acetyl-4-(2',5'-dimethoxyphenyl)-Butanoic Acid (18):

The diketone (15) (40 g., .16 mole) was dissolved in dry tetrahydrofuran (THF) (800 ml.) contained in a 1 l. 3-neck flask equipped with an overhead stirrer, a dropping funnel, and a reflux condenser. Sodium hydride (50% mineral oil suspension, 8 g., .17 mole) was added in small portions to the flask. Ethyl bromoacetate (27 g., .16 mole) in dry THF (50 ml.) was added from the dropping funnel over a period of 30 minutes. The mixture was refluxed for 1 hour and then the THF was distilled off. Sodium hydroxide (8%, 500 ml.) was added to the residue, and the temperature of the contents was held at 65°C. for 3 hours. The contents of the flask were extracted exhaustively with benzene, ice was added to the basic layer, and it was acidified with cold concentrated hydrochloric acid. The keto-acid (18) precipitated as yellowish-white crystals which were filtered off and dried. The keto-acid was further purified by recrystallization from methanol giving a white crystalline solid, m.p. = 106-107°C. (31.9 g., .12 mole,75%).

Infrared spectrum no. 2 (Fig. II): absorptions (cm^{-1}) at 1700 (aliphatic ketone C=O); 1740 (carboxyl C=O).

N.m.r. spectrum no. 2 (Fig. XV): absorptions at -2.10 (s, 1 H, COOH); 2.75 (m, 3 H's, aromatic); 5.93, 6.00 (singlets, 3 H's each, OCH_3); 6.58-7.36 (m, 5 H's, alkyl side chain); 7.68 (s, 3 H's,-$COCH_3$).

(3) Preparation of 3-Acetyl-5,8-Dimethoxy-1-Tetralone (19):

The keto-acid (18) (20 g., .07 mole) was stirred into hydrofluoric acid (200 ml.) contained in a polyethylene reaction flask kept at 20°C. in a water bath. After 3 hours the hydrofluoric acid was evaporated by raising the temperature of the water bath to 40°C. Water (20 ml.) was added to the reaction flask, and the residue was exhaustively extracted into chloroform. The chloroform extracts were washed with saturated sodium bicarbonate solution (2 x 150 ml.), water (150 ml.), and dried over magnesium sulphate. The chloroform was removed under reduced pressure giving a brown oily residue. Addition of methanol to the residue caused the tetralone (19) to crystallize. After filtration to remove the tetralone, the mother liquor was evaporated to dryness and the residue was dissolved in a solution of THF (50 ml.) and sodium hydroxide (8%, 25 ml.). The solution was stirred at room temperature for 2 hours and the THF was removed under reduced pressure. The basic solution was extracted with chloroform (2 x 10 ml.), and the basic layer was set aside for the isolation of the lactone (20). The chloroform extracts were washed with water (15 ml.) and dried over magnesium sulphate. Evaporation of the chloroform under reduced pressure gave a white crystalline solid which upon recrystallization from methanol gave a further .6 g. of tetralone. The total yield of tetralone was 11.2 g. (.045 mole, 60%), m.p. = 123-125°C.

Infrared spectrum no. 3 (Fig. III): absorptions (cm^{-1}) at 1710 (aliphatic ketone C=O); 1685 (conjugated ketone C=O); 1590 (aromatic C=C).

N.m.r. spectrum no. 3 (Fig. XVI): absorptions at 3.16 (q, 2 H's, aromatic); 6.23 (s, 6 H's, two OCH_3 groups); 6.58-7.32 (m, 5 H's, aliphatic ring); 7.78 (s, 3 H's, $-COCH_3$).

The basic layer from the chloroform extracts was acidified with hydrochloric acid and extracted into chloroform (2 x 10 ml.). The chloroform extracts were washed with sodium bicarbonate solution (10 ml.) and dried over magnesium sulphate. The chloroform was removed under reduced pressure to give the lactone (20) which was purified by recrystallization from methanol (1.2 g., .005 mole, 6.9%) m.p. = 137-138°C.

Infrared spectrum no. 4 (Fig. IV): absorptions (cm^{-1}) at 1765 (lactone C=O); 1605 (aromatic C=C).

N.m.r. spectrum no. 4 (Fig XVII): absorptions at 3.28 (s, 2 H's, aromatic); 6.22, 6.25 (singlets, 3 H's each, OCH_3); 6.75-7.75 (m, 4 H's, aliphatic hydrogens); 8.18 (s, 3 H's, tertiary CH_3).

Mass spectrum no 1 (Fig XXVII): M^+/e = 248, 233, 205, 190, 173, 159.

(4) Preparation of 2-Acetyl-5,8-Dimethoxytetralin (21):

The tetralone (19) (10 g., .04 mole) was dissolved in a solution of distilled ethanol (400 ml.), concentrated hydrochloric acid (10 ml.), and water (40 ml.). Pd/C (5%, 2 g.) was added and the solution was hydrogenated at atmospheric pressure for 6 hours. Filtering off the catalyst and evaporating the ethanol under reduced pressure gave a clear greenish-white oil which, upon the addition of petroleum ether and ethanol, gave the white crystalline tetralin (21), m.p. = 81-82°C. (8.4 g., .036 mole, 90%).

Infrared spectrum no. 5 (Fig. V): absorptions (cm^{-1}) at 1705 (aliphatic ketone C=O); 1605 (aromatic C=C).

N.m.r. spectrum no. 5 (Fig. XVIII): absorptions at 3.36 (s, 2 H's, aromatic); 6.29 (s, 6 H's, two OCH_3 groups); 7.00-7.50 (m, 7 H's aliphatic ring); 7.75 (s, 3 H's, $-COCH_3$).

Mass spectrum no. 2 (Fig. XXVIII): M^+/e = 234, 219, 191, 175, 115, 91, 77, 43.

(5) Preparation of 4-Demethoxy-7,9-Dideoxydaunomycinone (22):

Sodium chloride (.8 g., 13.6 mmole), freshly sublimed aluminum chloride (4 g., 30 mmole), phthalic anhydride (.35 g., 2.4 mmole), and the tetralin (21) (.498 g., 2.1 mmole) were mixed together in a stoppered 50 ml. flask. The flask was flushed with dry nitrogen, sealed with a rubber stopper, and heated at 170°C. in a sublimation oven. The flask was rotated frequently to mix the reddish-black melt. After 2 hours the contents of the flask were poured into a cold saturated solution of oxalic acid (50 ml.). The flask was rinsed with cold saturated oxalic acid solution (4 x 10 ml.), and the combined dark red solutions were extracted exhaustively with chloroform. The chloroform extracts were washed with water (2 x 50 ml.)

and dried over magnesium sulphate. Evaporating the chloroform under reduced pressure gave a dark red residue which was purified by t.l.c. on silica gel ($CH_3OH/CHCl_3$ = 3/100). Elution of the major band and recrystallization from methanol gave a bright red powder, m.p. = 188-190°C. (.462 g., 1.37 mmole, 64.5%).

ANALYSIS	C	H	O
Calculated	71.42	4.80	23.78
Reported	71.48	4.83	23.69

Infrared spectrum no. 6 (Fig. VI): absorptions (cm^{-1}) at 1710 (aliphatic ketone C=O); 1590, 1635 (chelated quinone carbonyl C=O).

N.m.r. spectrum no. 6 (Fig. XIX): absorptions at -3.18, -3.12 (singlets, 1 H each, chelated phenolic OH); 1.80-2.26 (m, 4 H's, aromatic); 7.35 (m, 7 H's, aliphatic ring); 7.70 (s, 3 H's, $-COCH_3$).

Mass spectrum no. 3 (Fig. XXIX): M^+/e = 336, 293, 205, 189, 149.

(6) Preparation of 4-Demethoxy-7,9-Dideoxy-6,11-Di-O-Methyl-daunomycinone (23):

The diphenol quinone (22) (881 mg., 2.6 mmole) was dissolved in dry acetone (25 ml.). Dimethylsulphate (3.3 g., 26.2 mmole) and potassium carbonate (4.35 g., 31.6 mmole) were added, and the mixture was refluxed under dry nitrogen for 6 hours. The colour of the contents of the flask changed from red to yellow during the course of the reaction. The acetone was evaporated under reduced pressure, water (15 ml.) was added, and the yellowish-brown residue was extracted into chloroform (3 x 10 ml.). The chloroform extracts were dried over magnesium sulphate and then evaporated under reduced pressure. Any remaining dimethylsulphate was removed using a high vacuum pump.

The yellowish-brown residue was purified by t.l.c. on silica gel ($CH_3OH/CHCl_3 = 3.5/100$). The major band was eluted and recrystallized from methanol giving a bright yellow product, m.p. = 144-146°C. (636 mg., 1.74 mmole, 66.5%).

ANALYSIS	C	H	O
Calculated	72.51	5.53	21.96
Reported	72.42	5.45	22.13

Infrared spectrum no. 7 (Fig. VII): absorptions (cm^{-1}) at 1705 (aliphatic ketone C=O); 1665 (quinone C=O); 1600, 1605 (aromatic C=C).

N.m.r. spectrum no. 7 (Fig. XX): absorptions at 2.00, 2.41 (multiplets, 2 H's each, aromatic); 6.20, 6.18 (singlets, 3 H's each, two OCH_3 groups); 7.08-7.33 (m, 7 H's, aliphatic ring); 7.72 (s, 3 H's, $-COCH_3$).

Mass spectrum no. 4 (Fig. XXX): M^+/e = 364, 321, 289, 275, 205.

(7) Preparation of 4-Demethoxy-7,9-Dideoxy-6,11-Di-O-Methylethylenedioxydaunomycinone (24):

A benzene solution (70 ml.) of p-toluenesulphonic acid (50 mg.), ethylene glycol (3.6 g., 58 mmole), and the di-O-methyl ether (23) (636 mg., 1.74 mmole) was distilled at a slow rate until about 15 ml. of the benzene remained in the reaction flask. The distillation was protected from atmospheric moisture with a drying tube. The remaining benzene was removed under reduced pressure, saturated sodium bicarbonate solution (10 ml.) was added , and the residue was extracted into chloroform (3 x 10 ml.). The chloroform extracts were dried over magnesium sulphate and evaporated under reduced pressure leaving a yellowish-brown residue. Recrystallization of the residue from methanol gave the ketal (24) as bright yellow crystals, m.p. = 151-152°C. (673 mg., 1.65 mmoles, 95%).

Infrared spectrum no. 8 (Fig. VIII): absorptions (cm^{-1}) at 1670 (quinone C=O); 1590, 1550 (aromatic C=C).

N.m.r. spectrum no. 8 (Fig. XXI): absorptions at 1.92, 2.40 (multiplets, 2 H's each, aromatic); 6.05 6.18 (singlets, 3 H's each, two OCH_3 groups); 6.15 (s, 4 H's, $-O-CH_2CH_2-O-$); 8.62 (s, 3 H's, $-COCH_3$).

(8) Preparation of 4-Demethoxy-7-Epi-9-Deoxy-6,7,11-Tri-O-Methyldaunomycinone (27):

The ketal (24) (1.2 g., 2.94 mmole) was dissolved in carbon tetrachloride (60 ml.). N-bromosuccinamide (565 mg., 3.18 mmole), and a trace of benzoyl peroxide were added and the solution was refluxed under dry nitrogen for 1 hour. The carbon tetrachloride was removed under reduced pressure until 5 ml. remained. No external heating was used during the evaporation. The remaining solution was suction filtered to remove the precipitated succinamide, and the filtrate was evaporated to dryness using no external heating. Anhydrous methanol (60 ml.) was added to the residue and the solution was refluxed overnight under dry nitrogen. Evaporating the methanol under reduced pressure gave a yellowish-brown residue. Without purification, the residue was dissolved in a solution of distilled THF (30 ml.), concentrated hydrochloric acid (2 ml.), and water (10 ml.), and was stirred overnight under nitrogen.

The THF was removed under reduced pressure and the residue was extracted into chloroform (2 x 10 ml.). The chloroform was removed under reduced pressure to give a yellowish-brown residue which was subjected to t.l.c. on silica gel ($CH_3OH/CHCl_3$ = 4/100). Two large bands were observed near the top of the plate, the band of lower R_f being the major one.

(a) Characterization of 4-demethoxy-7-epi-9-deoxy-6,7,11-tri-O-methyldaunomycinone (27):

Elution of the major t.l.c. band gave a solid (610 mg., 1.54 mmole, 52.5%) which was recrystallized from methanol to give yellow crystals, m.p. = 143.5-144.5°C.

Infrared spectrum no. 9 (Fig. IX): absorptions (cm^{-1}) at 1710 (aliphatic ketone C=O); 1670 (quinone C=O); 1600, 1560 (aromatic C=C).

N.m.r. spectrum no. 9 (Fig. XXII): absorptions at 1.88, 2.32 (multiplets, 2 H's each, aromatic); 5.35 (t, 1 H, C_7 benzylic hydrogen); 6.06, 6.13 (singlets, 3 H's each, aromatic OCH_3); 6.49 (s, 3 H's, benzylic OCH_3); 6.59-7.42 (multiplets, 6 H's, aliphatic); 7.72 (s, 3 H's, $-COCH_3$).

Mass spectrum no. 5 (Fig. XXXI): M^+/e = 394, 371, 351, 319, 305, 289, 275, 189, 149.

(b) Characterization of 2-acetyl-11,12-dimethoxy-9,10-naphthacenequinone (39):

Elution of the minor t.l.c. band gave a solid (300 mg., 1.2 mmole, 40%) which was recrystallized from methanol to give bright yellow crystals, m.p. = 191.5-193°C.

Infrared spectrum no. 10 (Fig. X): absorptions (cm^{-1}) at 1690 (conjugated ketone C=O); 1670 (quinone C=O); 1610, 1590, 1570 (aromatic C=C).

N.m.r. spectrum no. 10 (Fig. XXIII): absorptions at 1.25, 1.60, 1.90, 2.40 (multiplets, 7 H's, aromatic); 5.90, 5.95 (s, 3 H's each, OCH_3); 7.29 (s, 3 H's, $-COCH_3$).

Mass spectrum no. 6 (Fig. XXXII): M^+/e = 360, 331, 317, 259, 231, 203, 187, 175.

(9) Hydrolysis of 4-Demethoxy-7-Epi-9-Deoxy-6,7,11-Tri-O-Methyldaunomycinone (27):

The tri-O-methyl ether (27) (114 mg., .289 mmole) was dissolved in dry 1,2-dichloroethane (20 ml.). Sublimed aluminum chloride (270 mg., 20 mmole), and sea sand (400 mg.) were added to the yellow solution. The solution, which turned red upon the addition of the aluminum chloride, was stirred under dry nitrogen for 20 minutes and then poured into a cold saturated oxalic acid solution. The resulting solution was exhaustively extracted with chloroform. The chloroform extracts were washed with water (2 x 20 ml.) and dried over magnesium sulphate. The chloroform was removed under reduced pressure, and the red residue was purified by t.l.c. on silica gel ($CH_3OH/CHCl_3$ = 4/100). One major band and two minor bands were observed on the plate, the major band having the higher R_f value.

(a) Characterization of 4-demethoxy-7-epi-9-deoxy-7-O-methyldaunomycinone (40):

The major band was eluted to give a solid (85.2 mg., .231 mmole, 78%) which was recrystallized from methanol to give a bright red powder, m.p. = 218.5-220.5°C.

Infrared spectrum no. 11 (Fig. XI): absorptions (cm^{-1}) at 1710 (aliphatic ketone C=O); 1620, 1590 (chelated quinone C=O).

N.m.r. spectrum no. 11 (Fig. XXIV): absorptions at -3.19, -3.00 (singlets, phenolic OH); 1.89-2.41 (multiplets, aromatic); 5.36 (t, C_7 benzylic hydrogen); 6.50 (s, benzylic OCH_3); 7.72 (s, $-COCH_3$).

Mass spectrum no. 7 (Fig. XXXIII): M^+/e = 366, 332, 291, 274, 233, 189, 176.

(b) Characterization of 4-demethoxy-9-deoxy-daunomycinone (42):

The first minor band below the major band was eluted to give a solid (4 mg., .012 mmole, 4.4%) which was recrystallized from chloroform/methanol (5/5) to give a red fluffy powder, m.p. = 216-220°C.

Infrared spectrum no. 12 (Fig. XII): absorptions (cm^{-1}) at 3575 (benzylic alcohol OH); 1710 (aliphatic ketone C=0); 1620, 1590 (chelated quinone C=0).

N.m.r. spectrum no. 12 (Fig XXV): absorptions at -3.50, -3.00 (singlets, chelated phenol H's); 1.84, 2.32 (multiplets, aromatic); 4.93 (m, C_7 benzylic hydrogen); 7.72 (s, $-COCH_3$).

Mass spectrum no. 8 (Fig. XXXIV): M^+/e = 352, 334, 291, 274, 254, 189, 178.

(c) Characterization of 4-demethoxy-7-epi-9-deoxy-daunomycinone (41):

The second minor band below the major band was eluted to give a solid (3 mg., .009 mmole, 3%) which was recrystallized from chloroform/methanol (5/5) to give a red fluffy powder, m.p. = 182.5-184.5°C.

Infrared spectrum no. 13 (Fig. XIII): absorptions (cm^{-1}) at 3575 (benzylic alcohol OH); 1710 (aliphatic ketone -C=0);

1620, 1590 (chelated quinone C=O).

N.m.r. spectrum no. 13 (Fig. XXVI): absorptions at -3.00, -2.75 (singlets, 1 H each, chelated phenol H's); 1.93, 2.16 (multiplets, 2 H's each, aromatic); 4.93 (multiplet, 1 H, C_7 benzylic hydrogen); 7.02, 7.28, 7.50 (multiplets, total of 5 H's, aliphatic ring hydrogens); 7.72 (s, 3 H's, $-COCH_3$).

Mass spectrum no. 9 (Fig. XXXV): M^+/e = 352, 334, 291, 274, 254, 189, 178.

(10) Preparation of 4-Demethoxy-9-Deoxydaunomycinone (42):

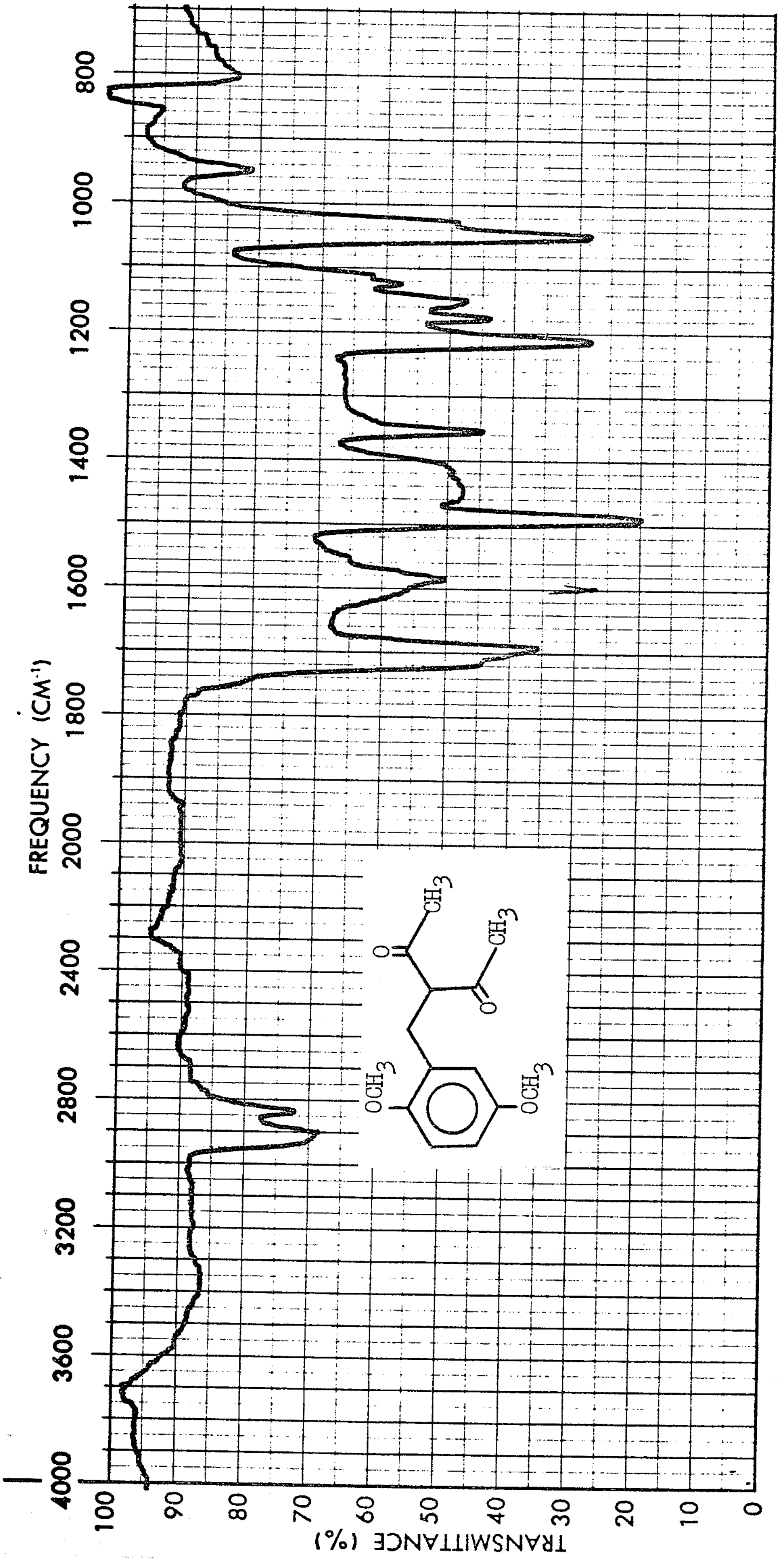
The mono-O-methyl ether (40) (100 mg., .273 mmole) was dissolved in trifluoroacetic acid (15 ml.) and was refluxed under dry nitrogen for 10 minutes. Without external heating, the trifluoroacetic acid was evaporated under reduced pressure. The dark red residue was dissolved in a solution of THF (15 ml.) and saturated sodium bicarbonate solution (5 ml.). Sodium carbonate solution (10%) was added until the solution turned a purple colour. The solution was stirred at room temperature for two hours and then acidified with dilute hydrochloric acid. Chloroform (3 x 10 ml.) was used to extract the products. Evaporating the chloroform under reduced pressure gave a dark red solid which was purified by t.l.c. ($CH_3OH/CHCl_3$ = 4.5/100). A major and a minor band were observed near the middle of the plate. The major band had the lower R_f value and was eluted to give a red solid which was recrystallized from chloroform/methanol (5/5) to give (41) as a fluffy red powder, m.p. = 182.5-184.5°C., (36.2 mg., .103 mmole, 37.8%).

Infrared spectrum no. 13 (Fig. XIII). N.m.r. spectrum no. 13 (Fig. XXVI). Mass spectrum no. 9 (Fig. XXXV).

The minor band was eluted to give a dark red solid which was recrystallized from chloroform/methanol (5/5) to give (42) as a fluffy red powder, m.p. = 216-220°C., (12.8 mg., .036 mmole, 13.3%).

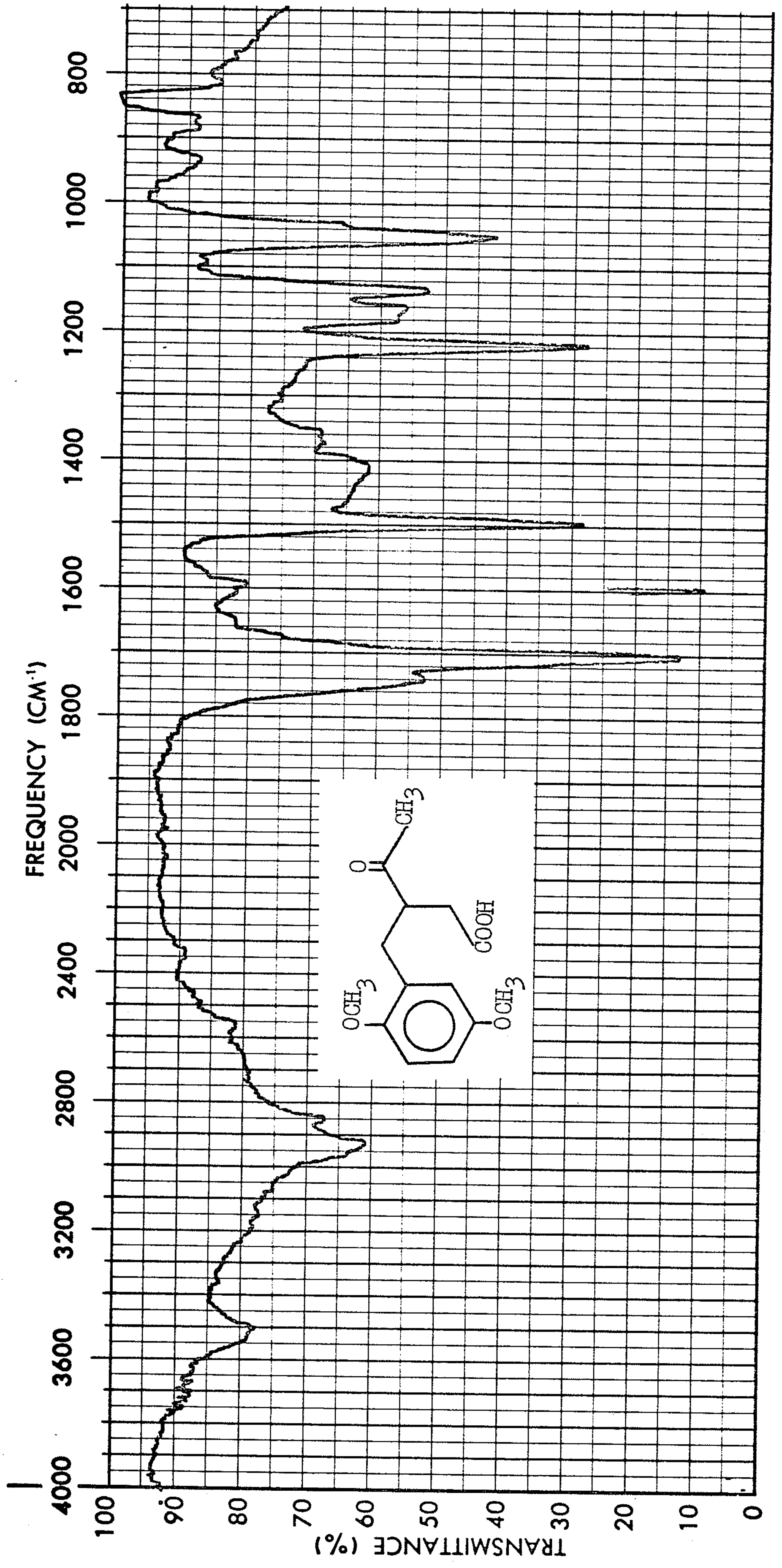
Infrared spectrum no. 12 (Fig. XII). N.m.r. spectrum no. 12 (Fig. XXV). Mass spectrum no. 8 (Fig. XXXIV).

Figure I



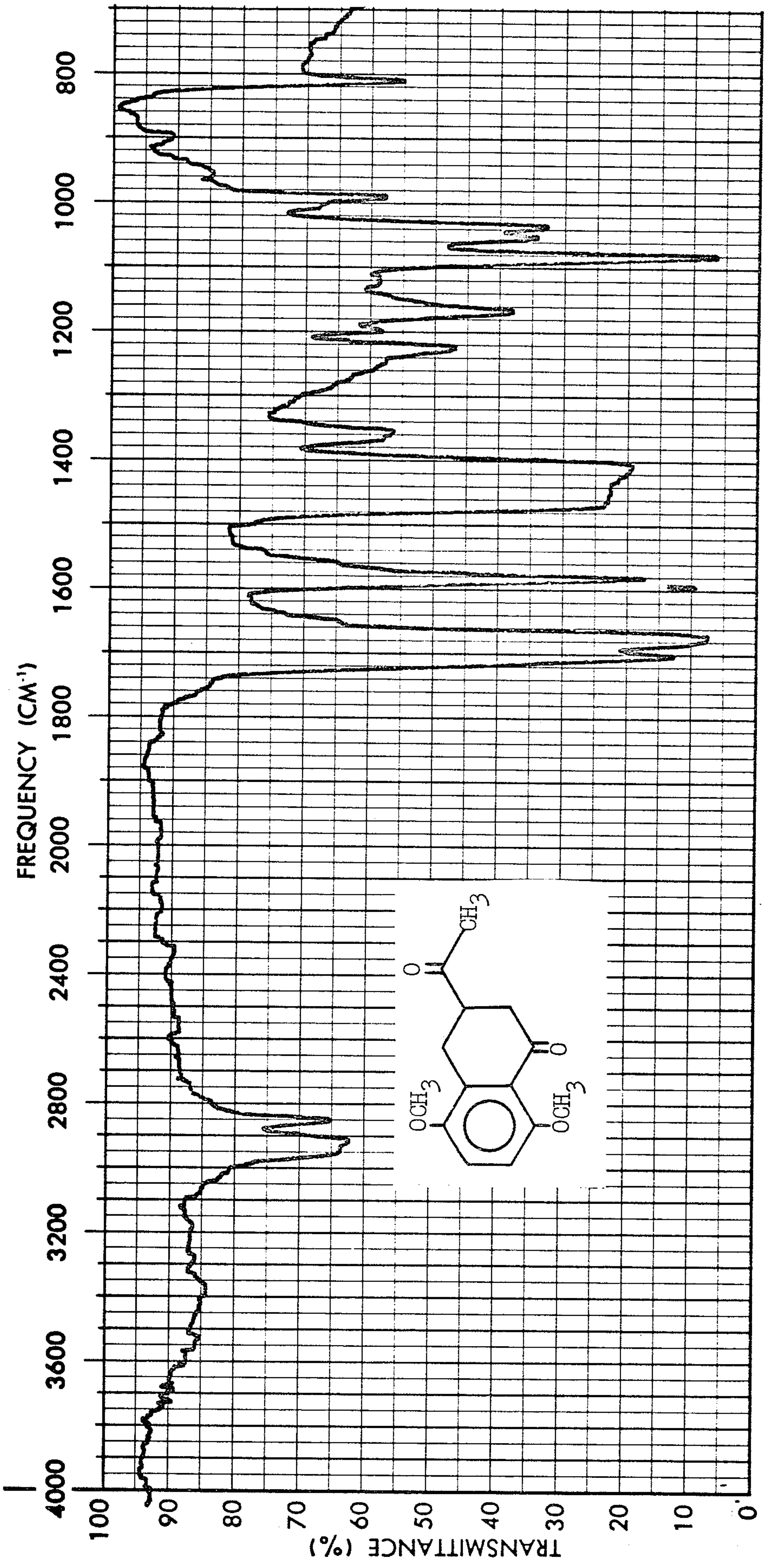
Infrared spectrum no. 1: 3-acetyl-4-(2',5'-dimethoxyphenyl)-2-butanone (15)

Figure II



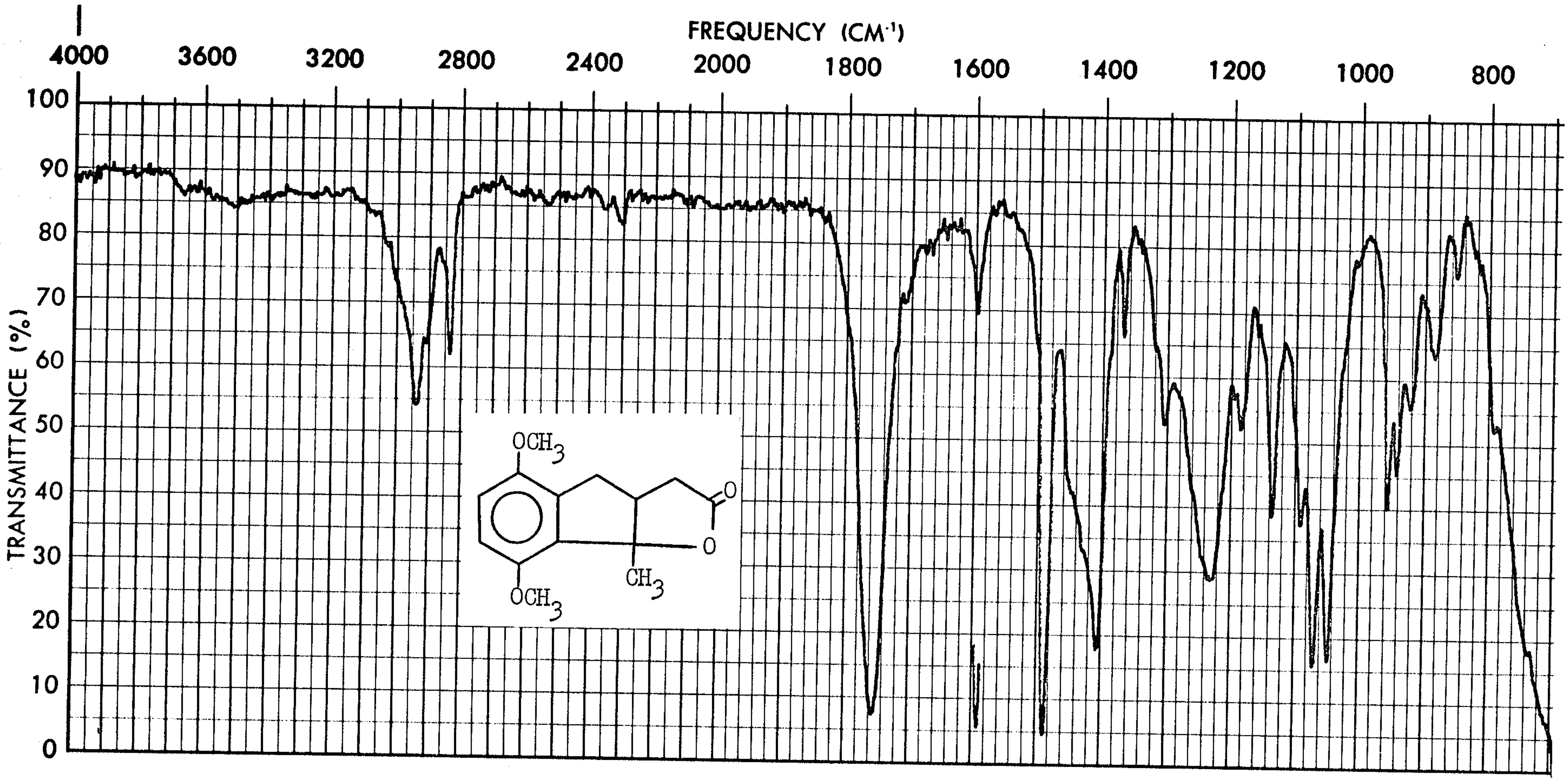
Infrared spectrum no. 2: 3-acetyl-4-(2',5'-dimethoxyphenyl)-butanoic acid (18)

Figure III



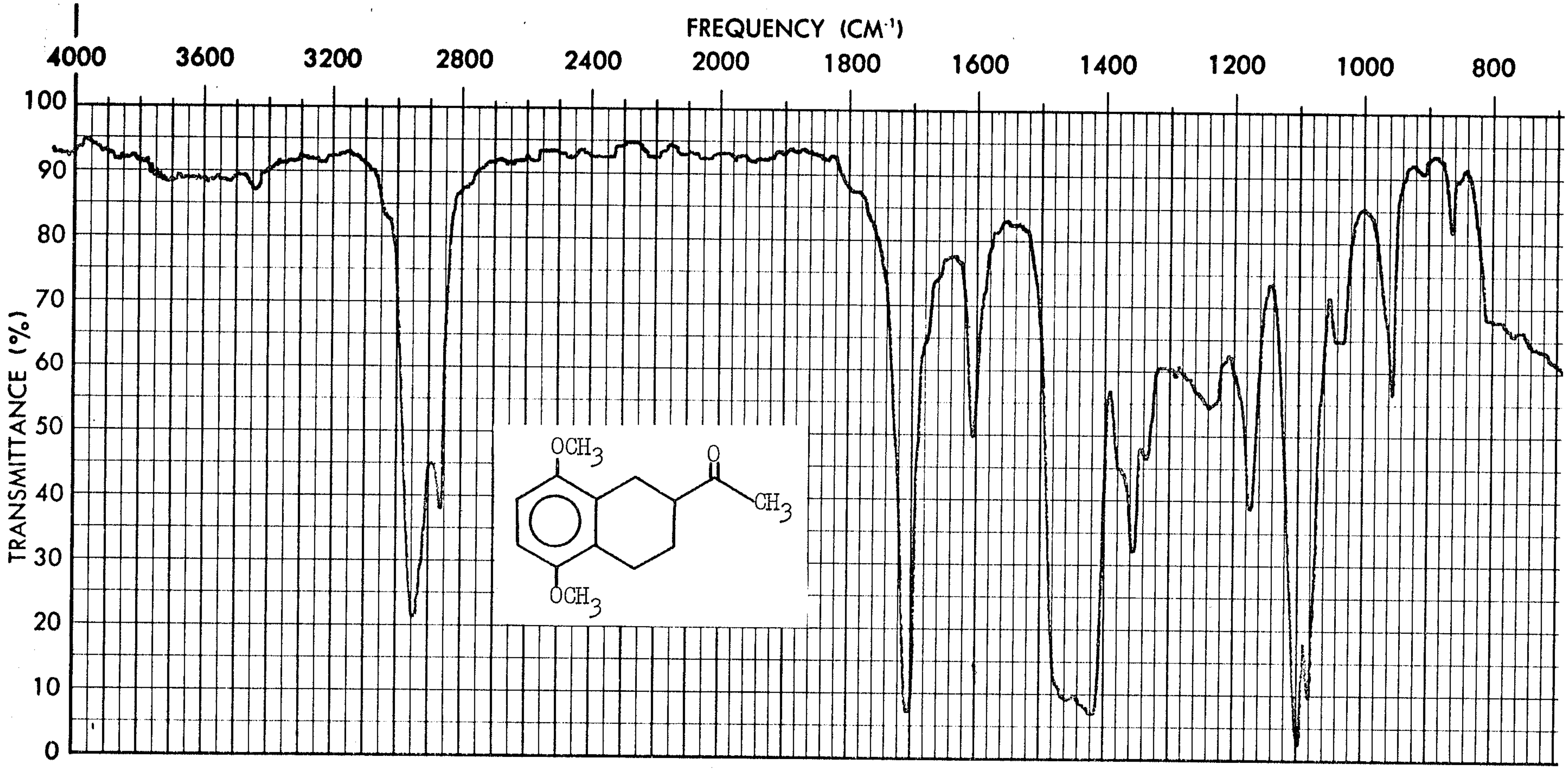
Infrared spectrum no. 3: 3-acetyl-5,8-dimethoxy-1-tetralone (19)

Figure IV



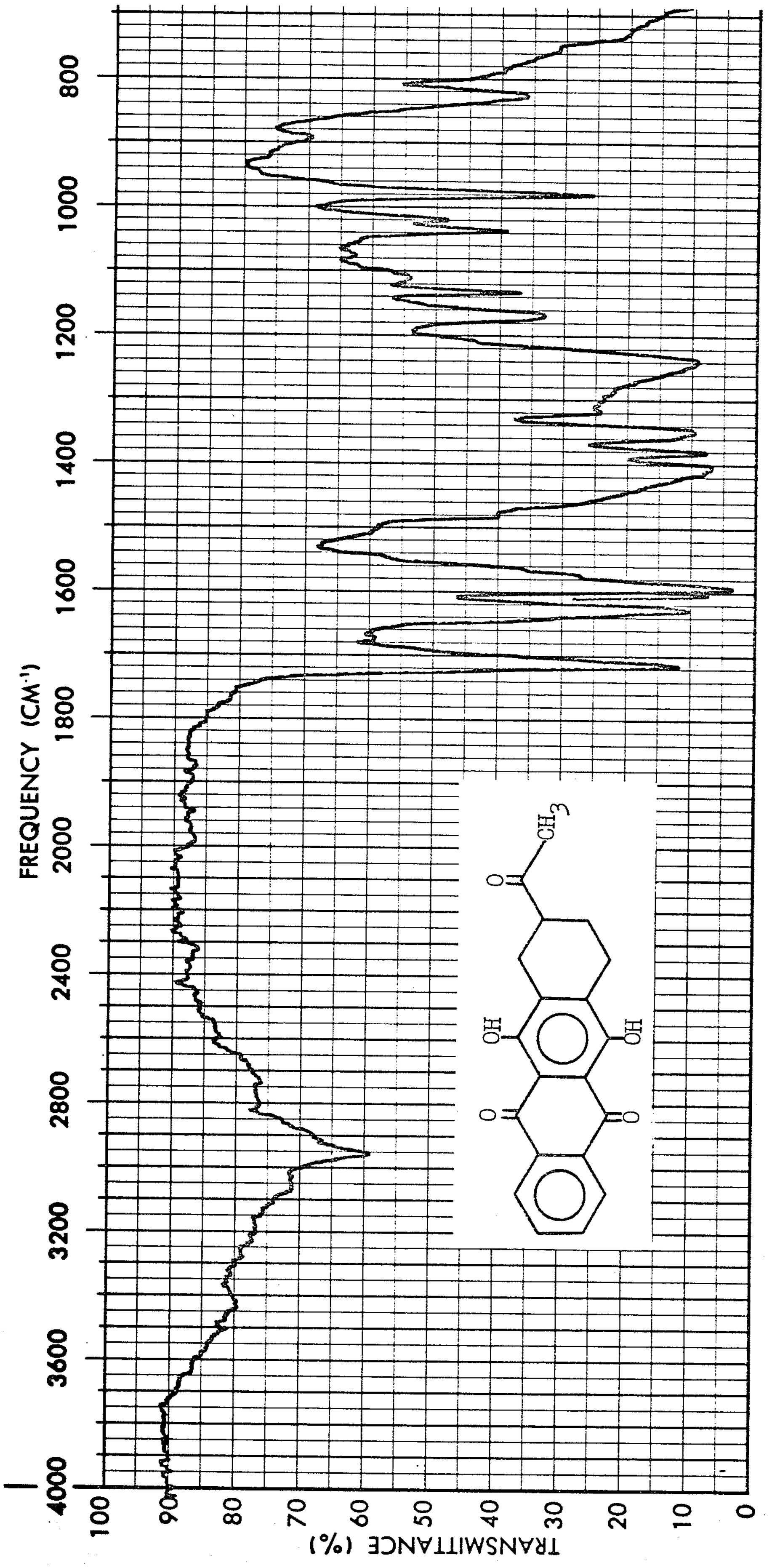
Infrared spectrum no. 4: 1-methyl-1-hydroxy-4,7-dimethoxy-2-indanylethanoic acid lactone (20)

Figure V



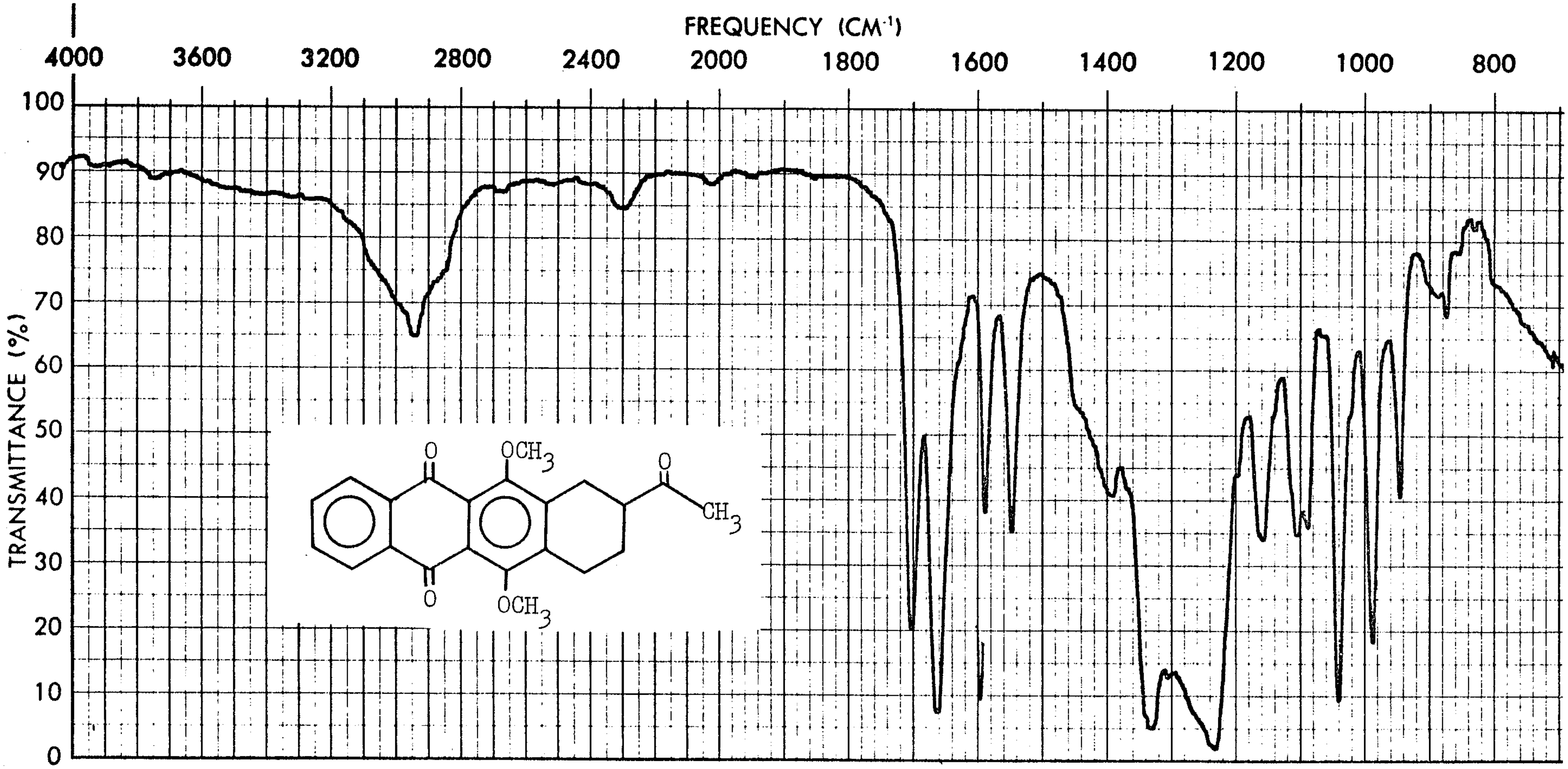
Infrared spectrum no. 5: 2-acetyl-5,8-dimethoxytetralin (21)

Figure VI



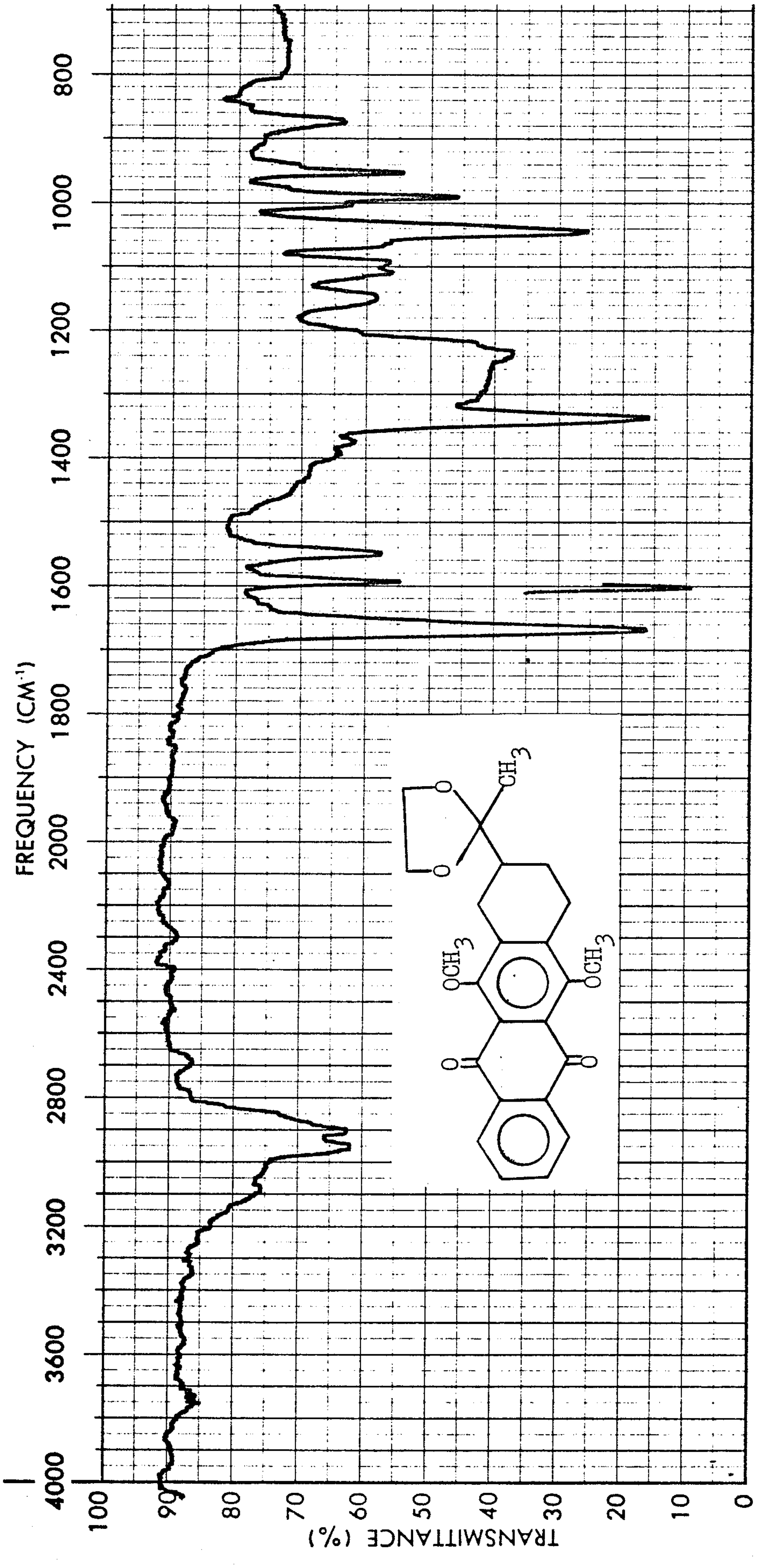
Infrared spectrum no. 6: 4-demethoxy-7,9-dideoxydaunomycinone (22)

Figure VII



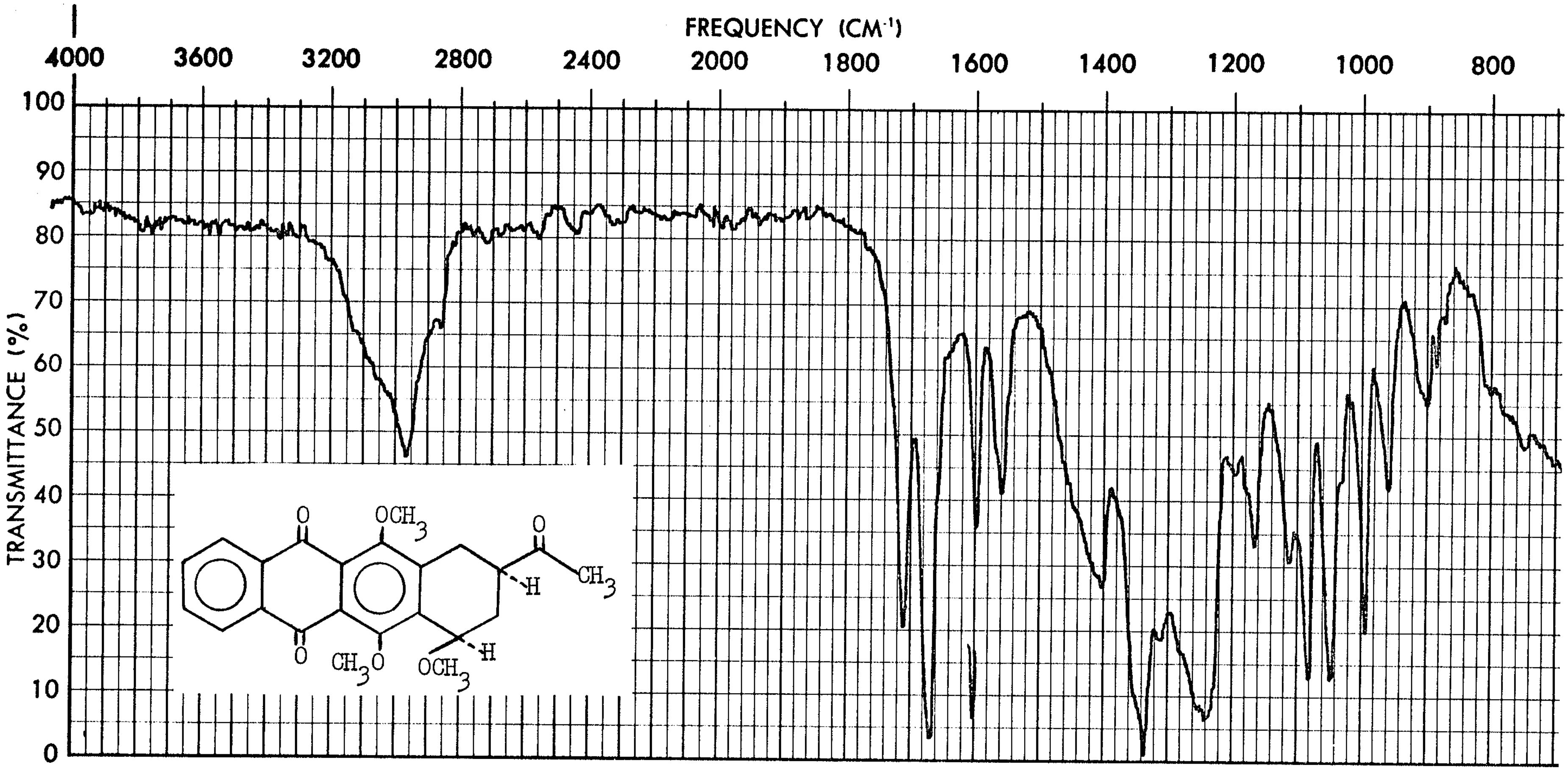
Infrared spectrum no. 7: 4-demethoxy-7,9-dideoxy-6,11-di-O-methyldaunomycinone (23)

Figure VIII



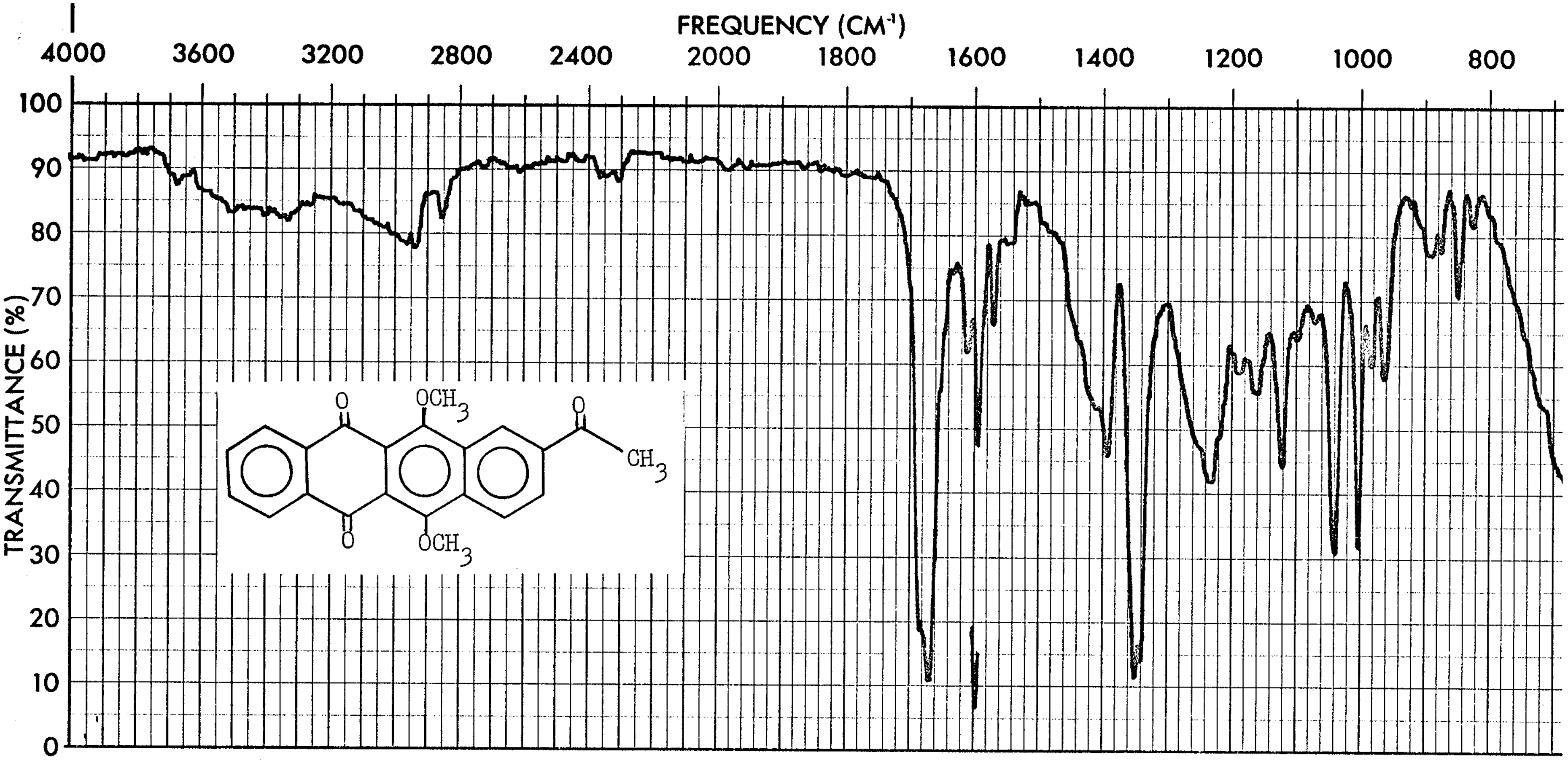
Infrared spectrum no. 8: 4-demethoxy-7,9-dideoxy-6,11-di-O-methylethylene-dioxydaunomycinone (24)

Figure IX



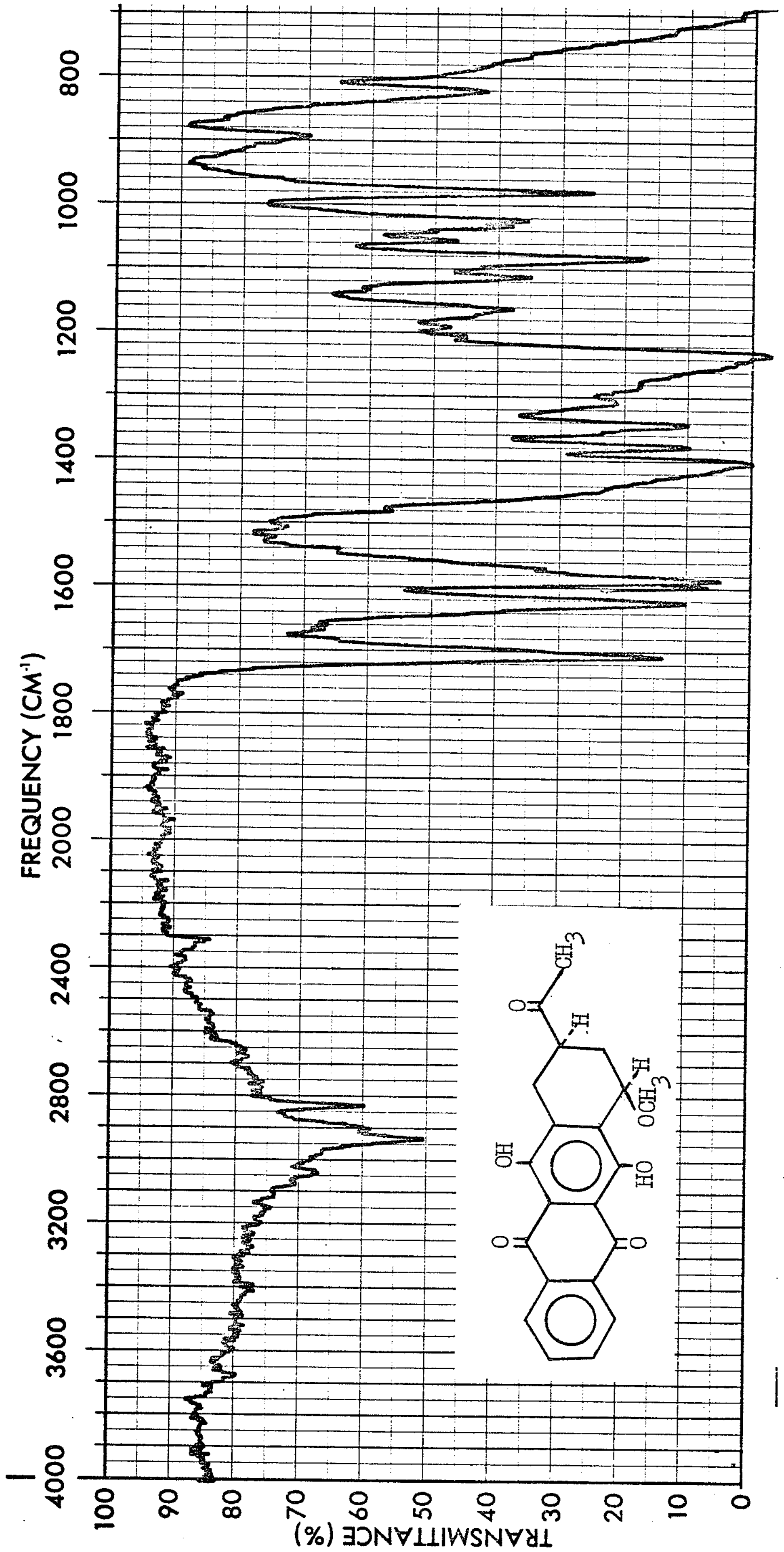
Infrared spectrum no. 9: 4-demethoxy-7-epi-9-deoxy-6,7,11-tri-O-methyl-daunomycinone (27)

Figure X



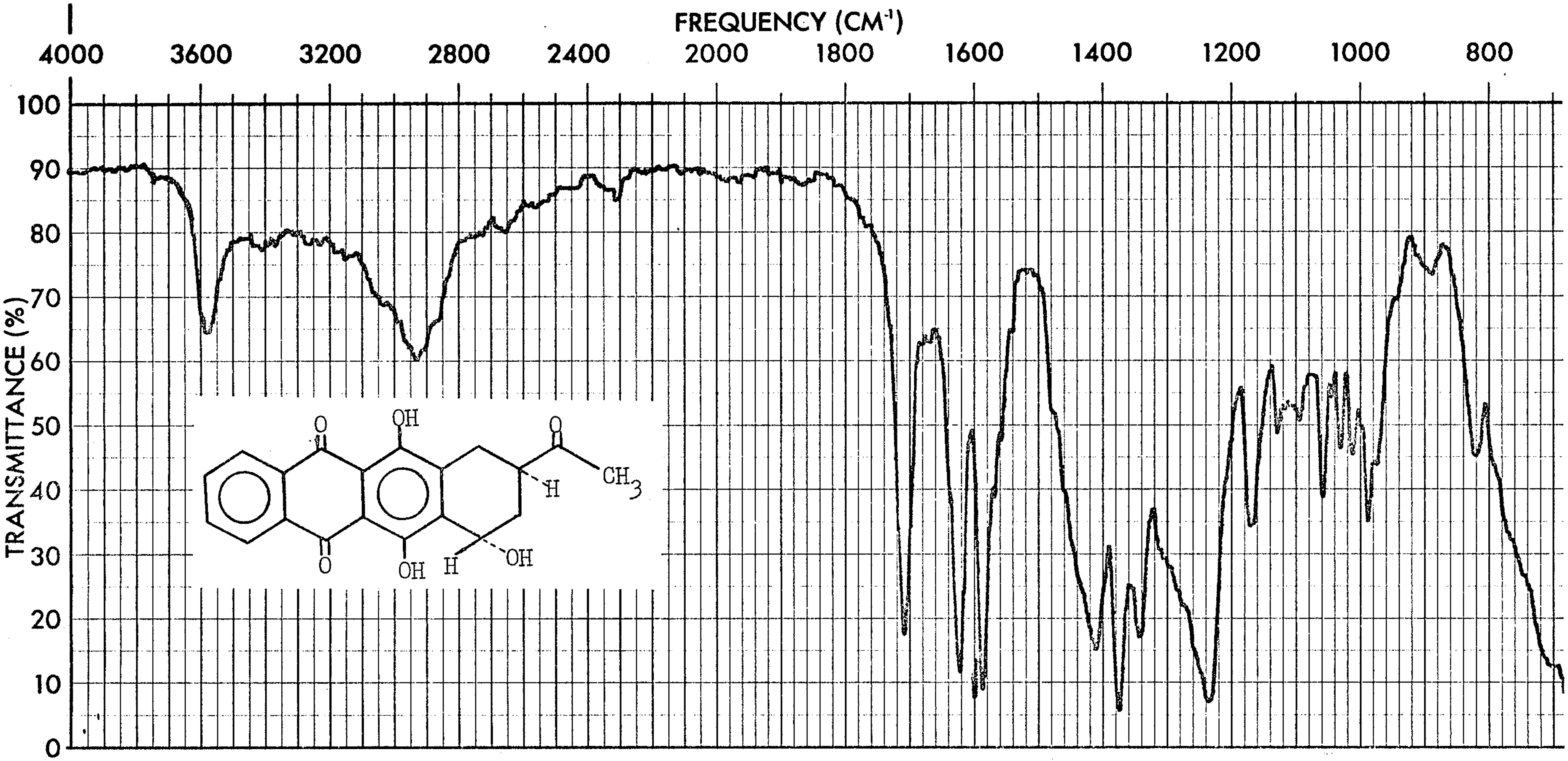
Infrared spectrum no. 10: 2-acetyl-11,12-dimethoxy-9,10-naphthacenequinone (39)

Figure XI



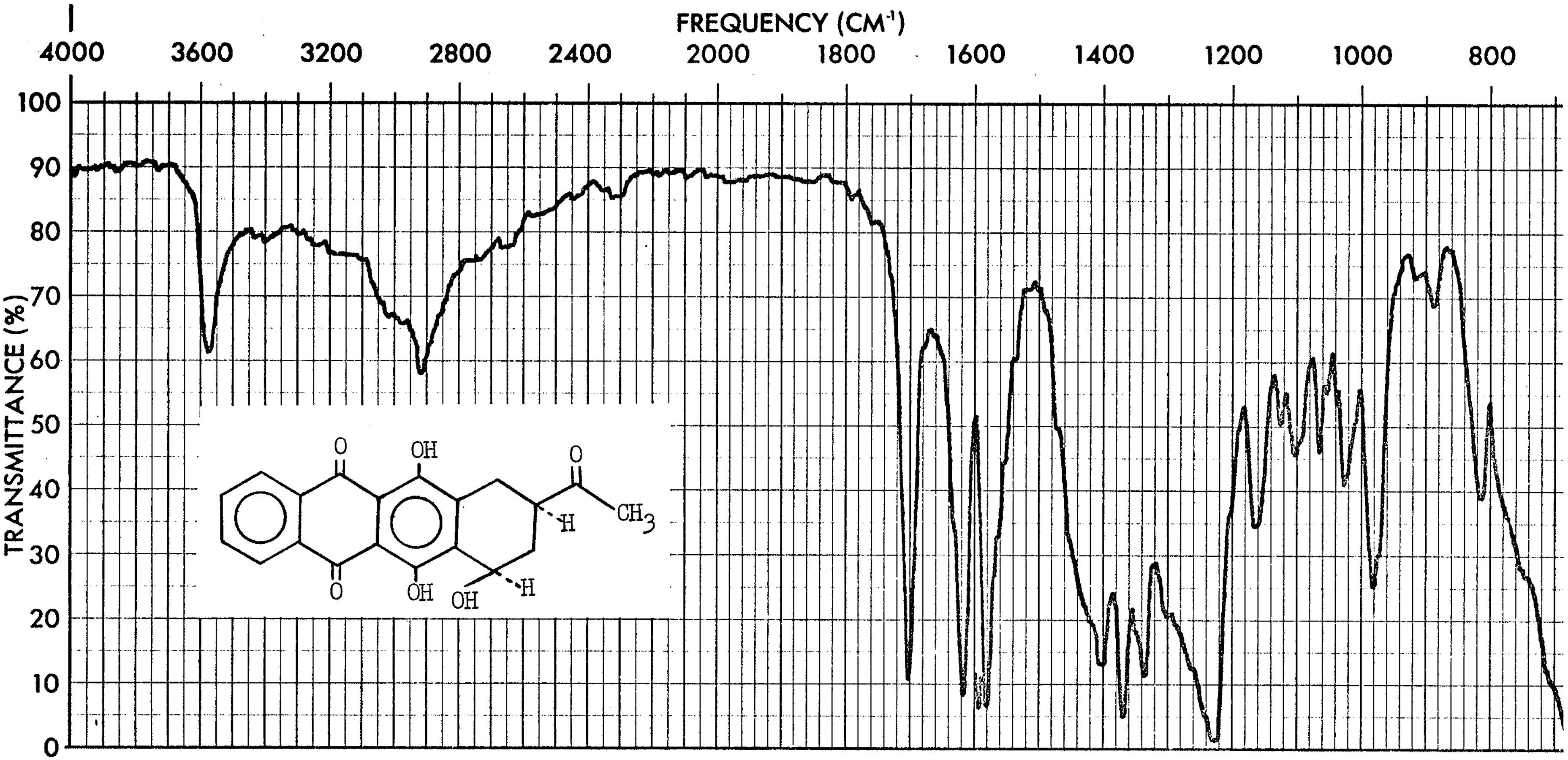
Infrared spectrum no. 11: 4-demethoxy-7-epi-9-deoxy-7-O-methyldaunomycinone (40)

Figure XII



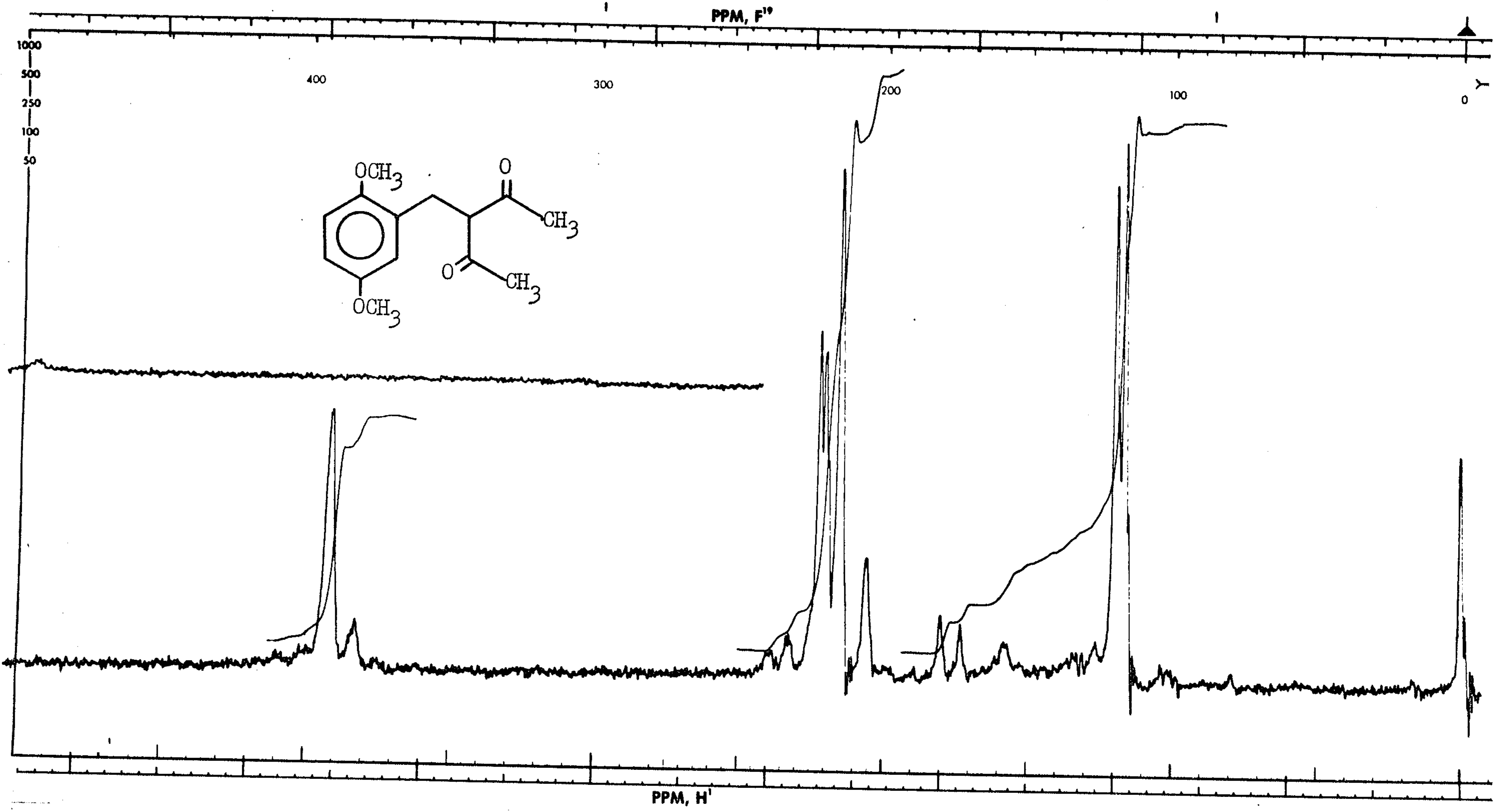
Infrared spectrum no. 12: 4-demethoxy-9-deoxydaunomycinone (42)

Figure XIII



Infrared spectrum no. 13: 4-demethoxy-7-epi-9-deoxydaunomycinone (41)

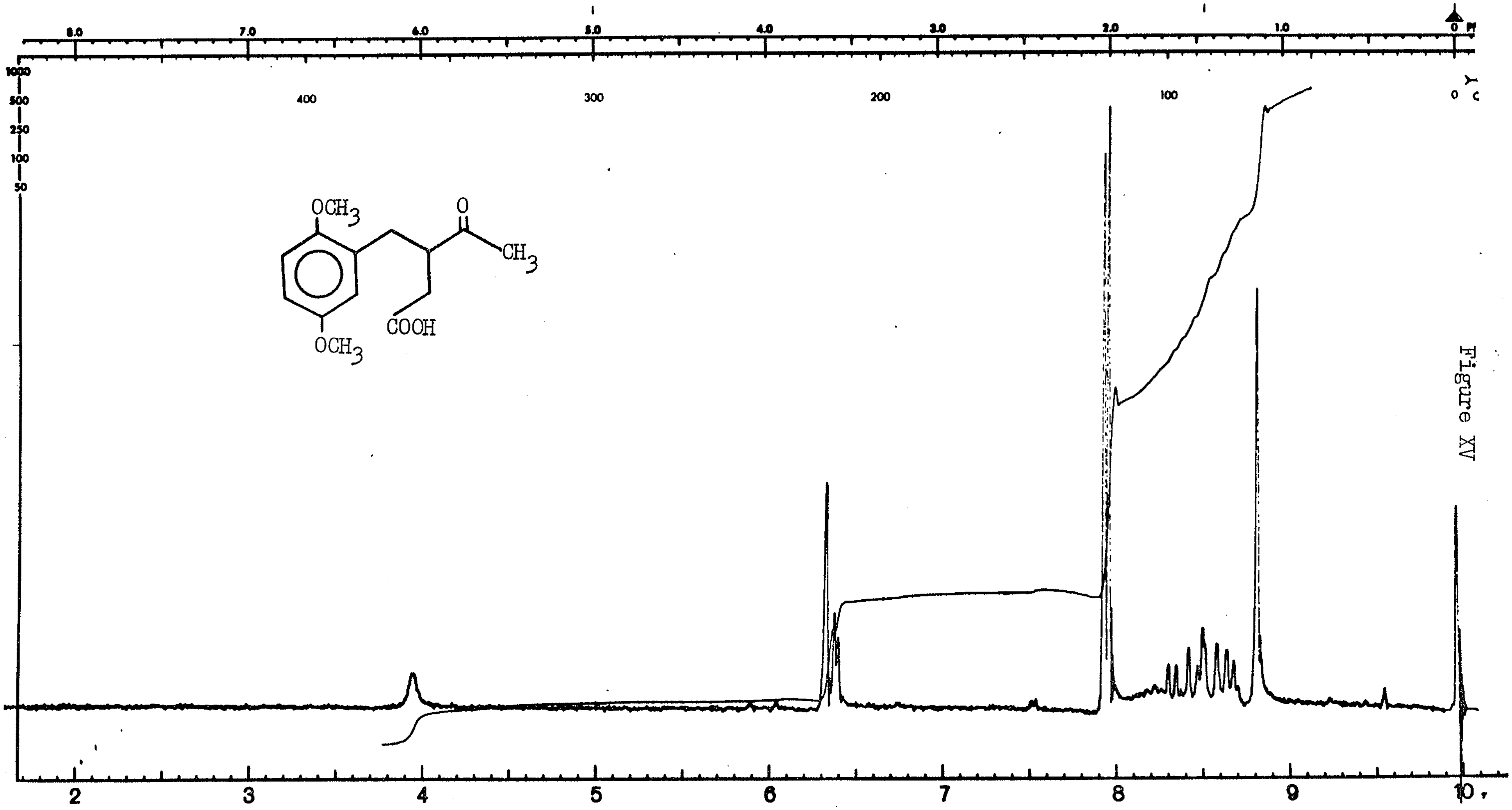
Figure XIV



Nuclear magnetic resonance spectrum no. 1: 3-acetyl-4-(2',5'-dimethoxyphenyl)-2-butanone (15), in $CDCl_3$

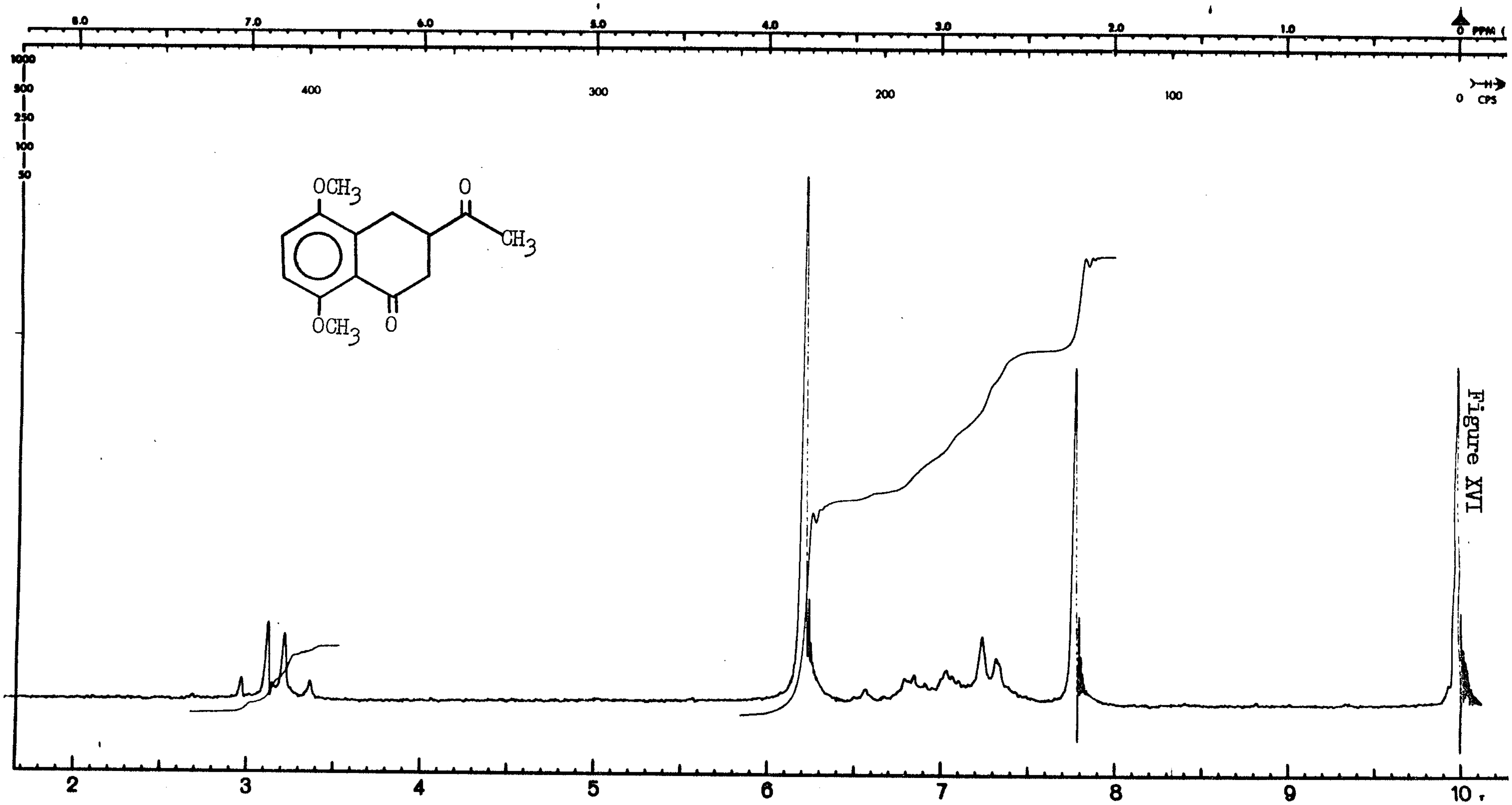
Sweep width = 500 Hz., insert is offset 500 Hz.

Figure XV



Nuclear magnetic resonance spectrum no. 2: 3-acetyl-4-(2',5'-dimethoxyphenyl)-butanoic acid (18), in $CDCl_3$. Sweep width = 1000 Hz.

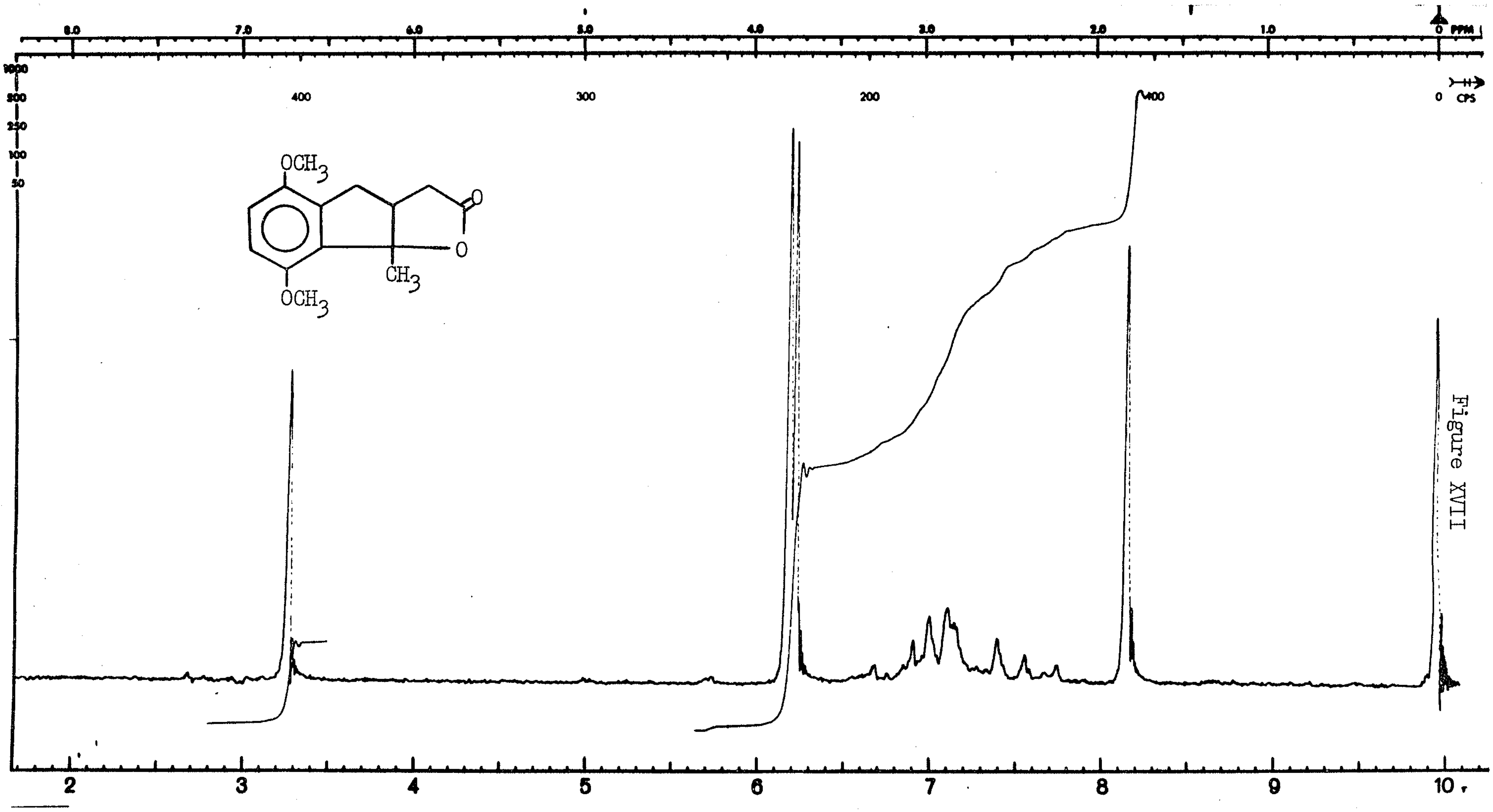
Figure XVI



Nuclear magnetic resonance spectrum no. 3: 3-acetyl-5,8-dimethoxy-1-tetralone (19), in CDCl$_3$.

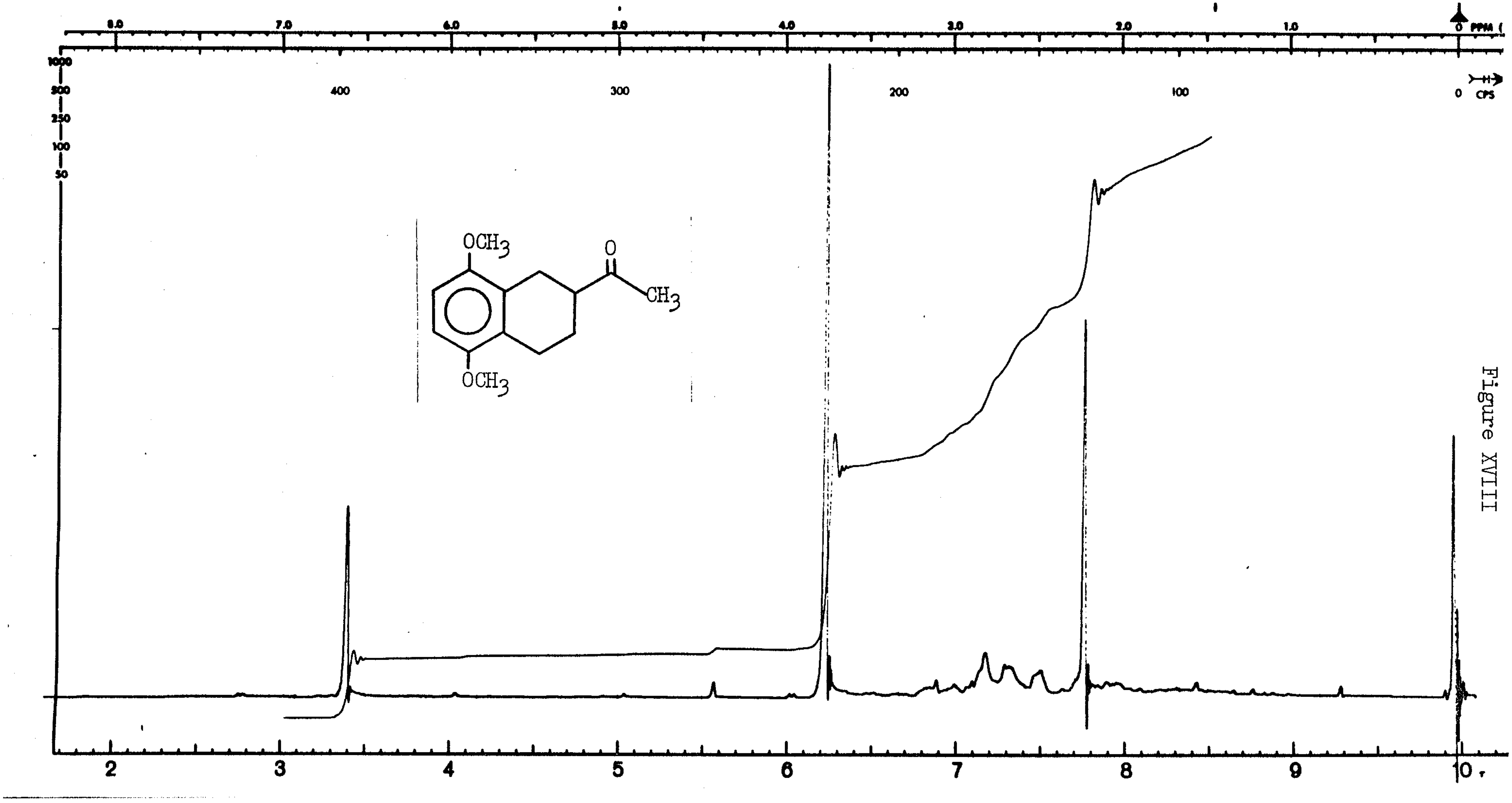
Sweep width = 500 Hz.

Figure XVII



Nuclear magnetic resonance spectrum no. 4: 1-methyl-1-hydroxy-4,7-dimethoxy-2-indanylethanoic acid lactone (20), in $CDCl_3$. Sweep width = 500 Hz.

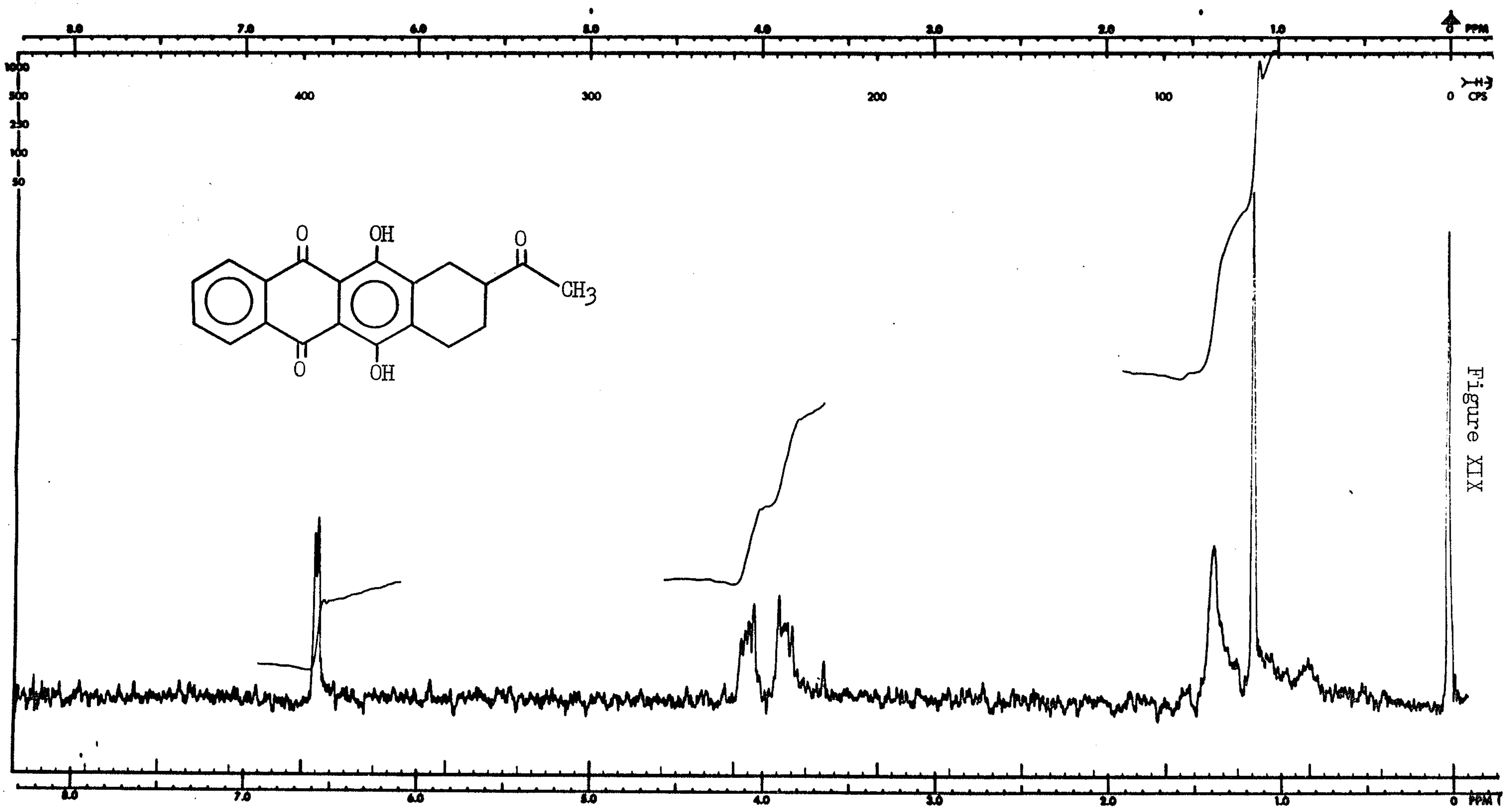
Figure XVIII



Nuclear magnetic resonance spectrum no. 5: 2-acetyl-5,8-dimethoxytetralin (21), in $CDCl_3$.

Sweep width = 500 Hz.

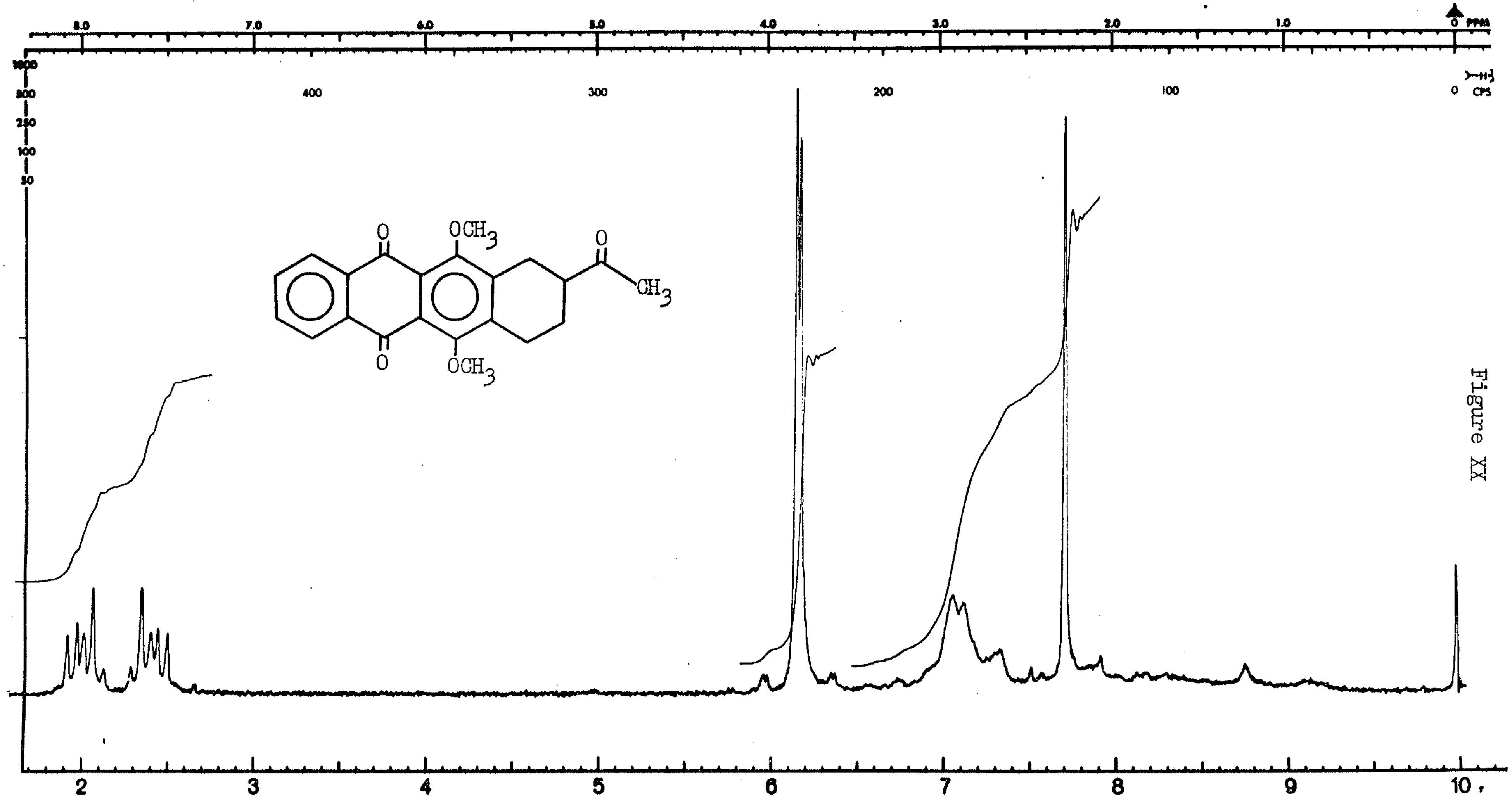
Figure XIX



Nuclear magnetic resonance spectrum no. 6: 4-demethoxy-7,9-dideoxydaunomycinone (22), in $CDCl_3$

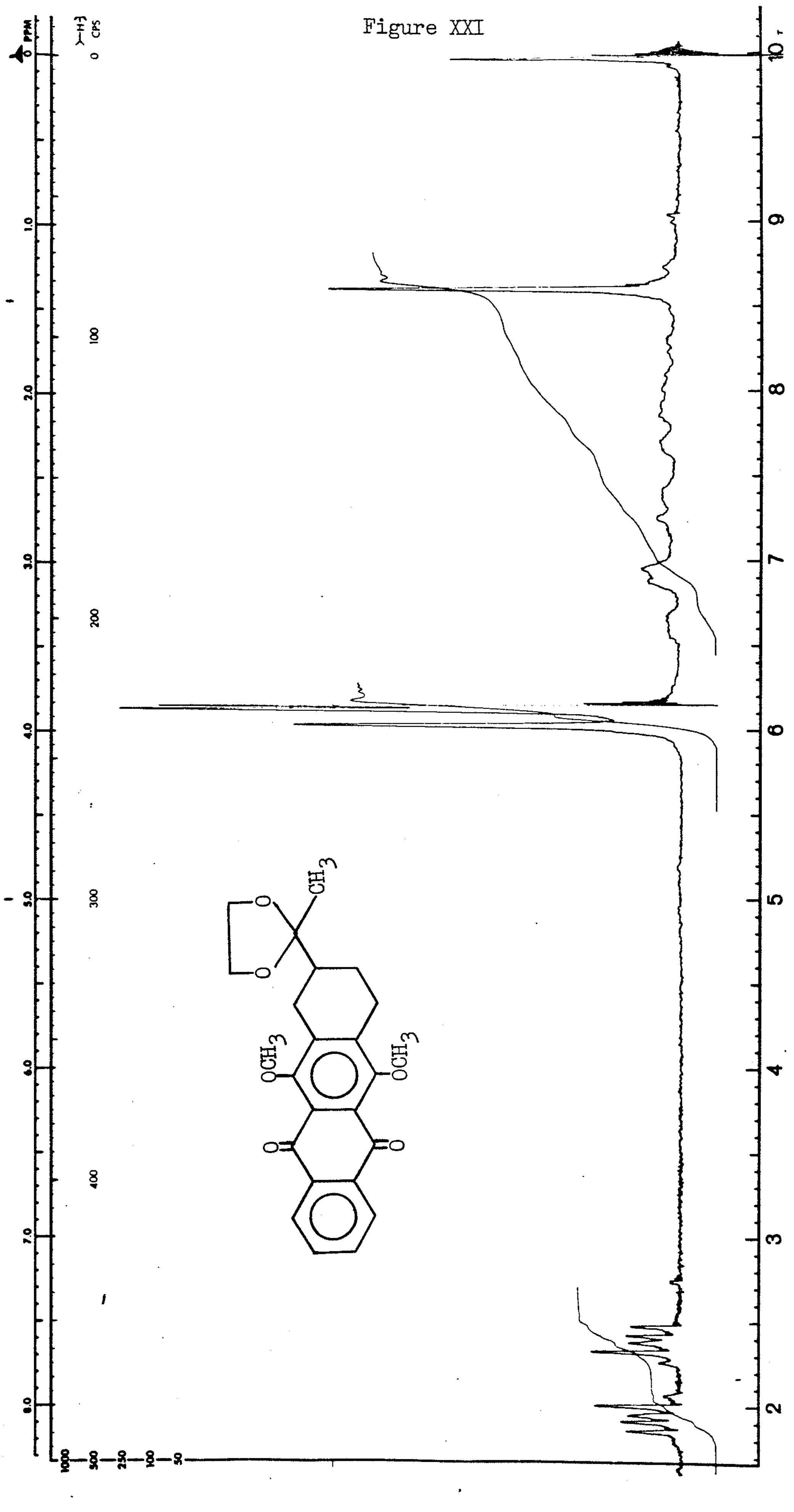
Sweep width = 1000 Hz.

Figure XX



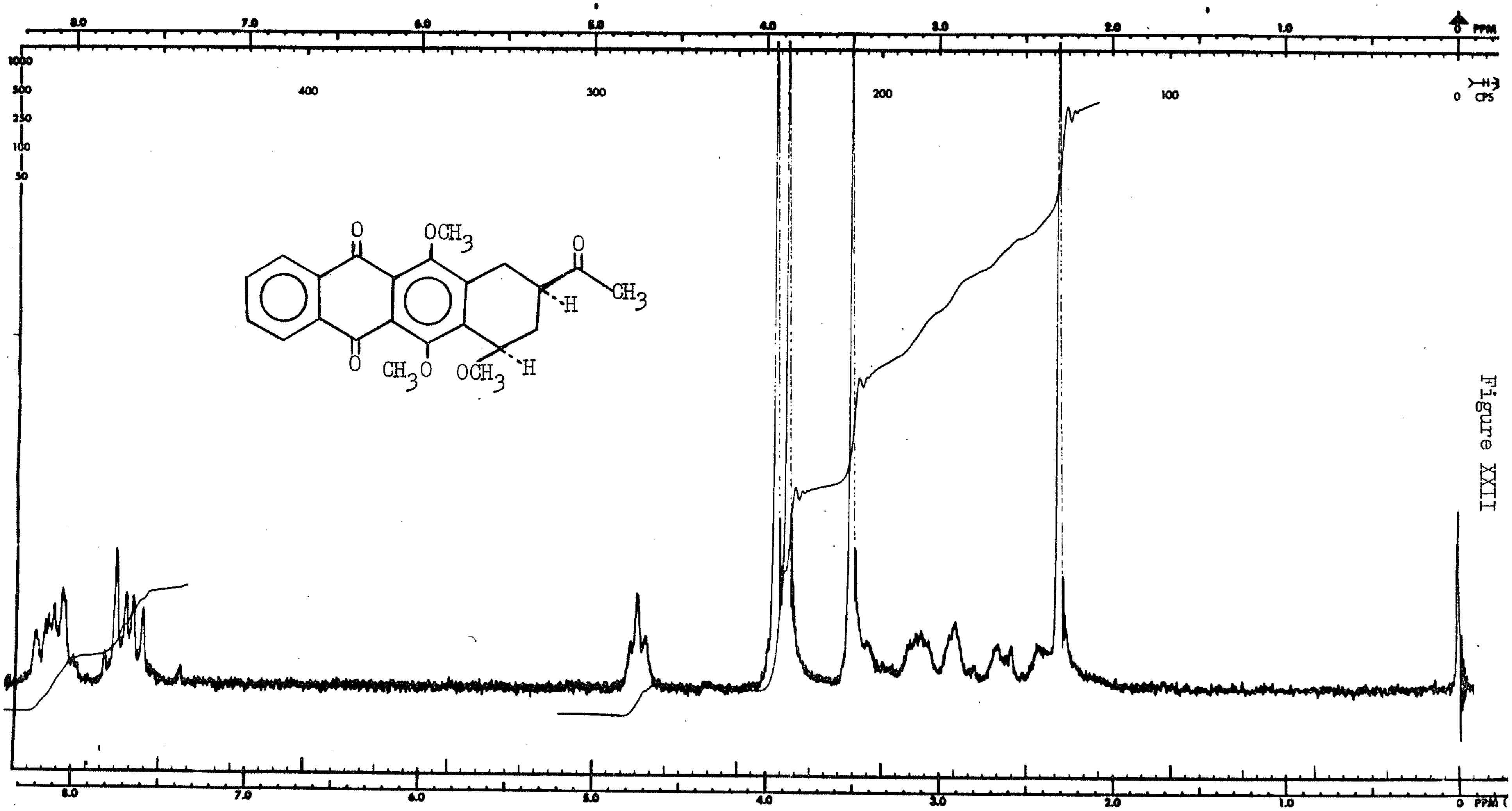
Nuclear magnetic resonance spectrum no. 7: 4-demethoxy-7,9-dideoxy-6,11-di-O-methyl-daunomycinone (23), in $CDCl_3$. Sweep width = 500 Hz.

Figure XXI



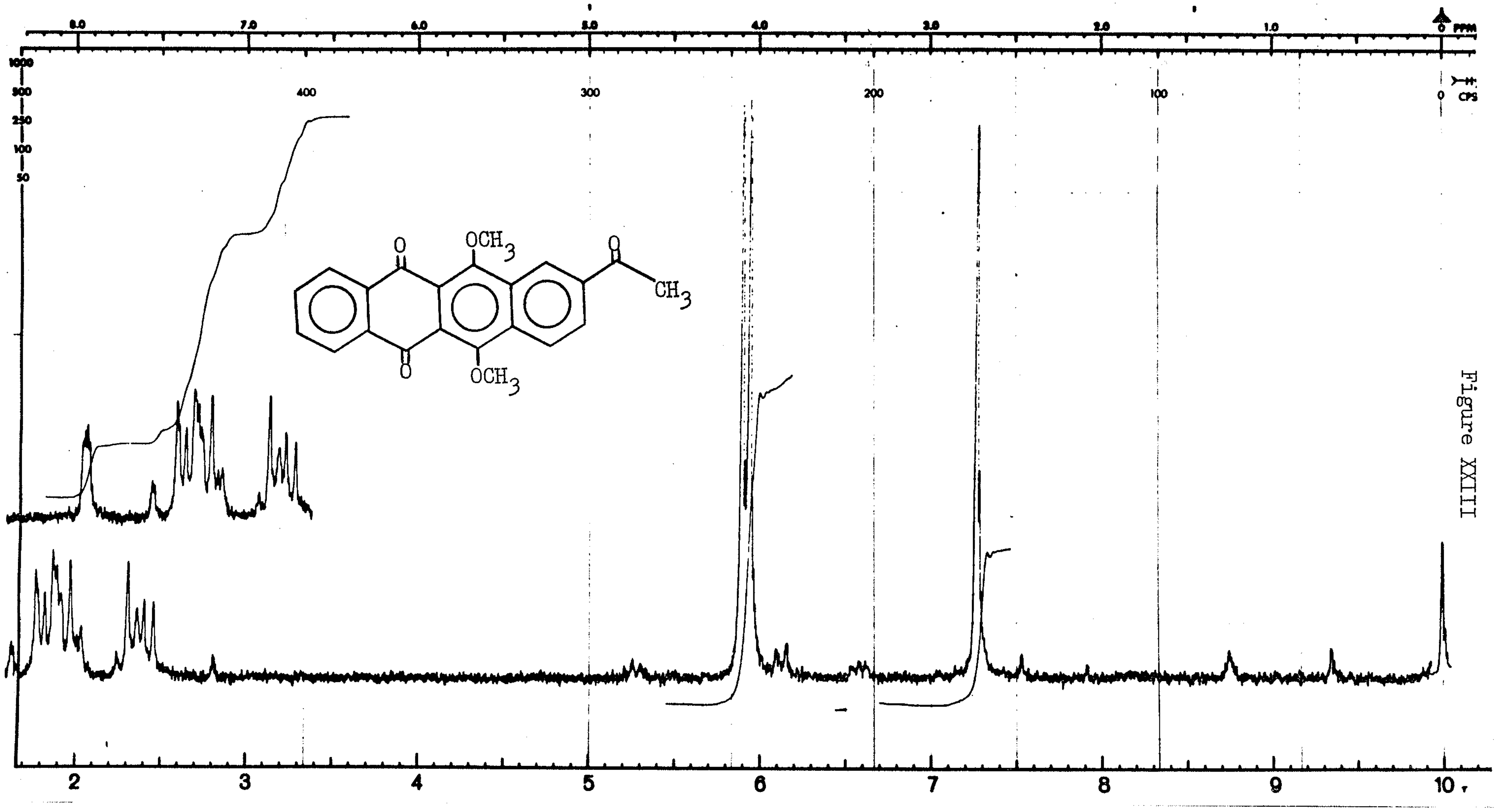
Nuclear magnetic resonance spectrum no. 8: 4-demethoxy-7,9-dideoxy-6,11-di-O-methylethylene-dioxydaunomycinone (24), in $CDCl_3$. Sweep width = 500 Hz.

Figure XXII



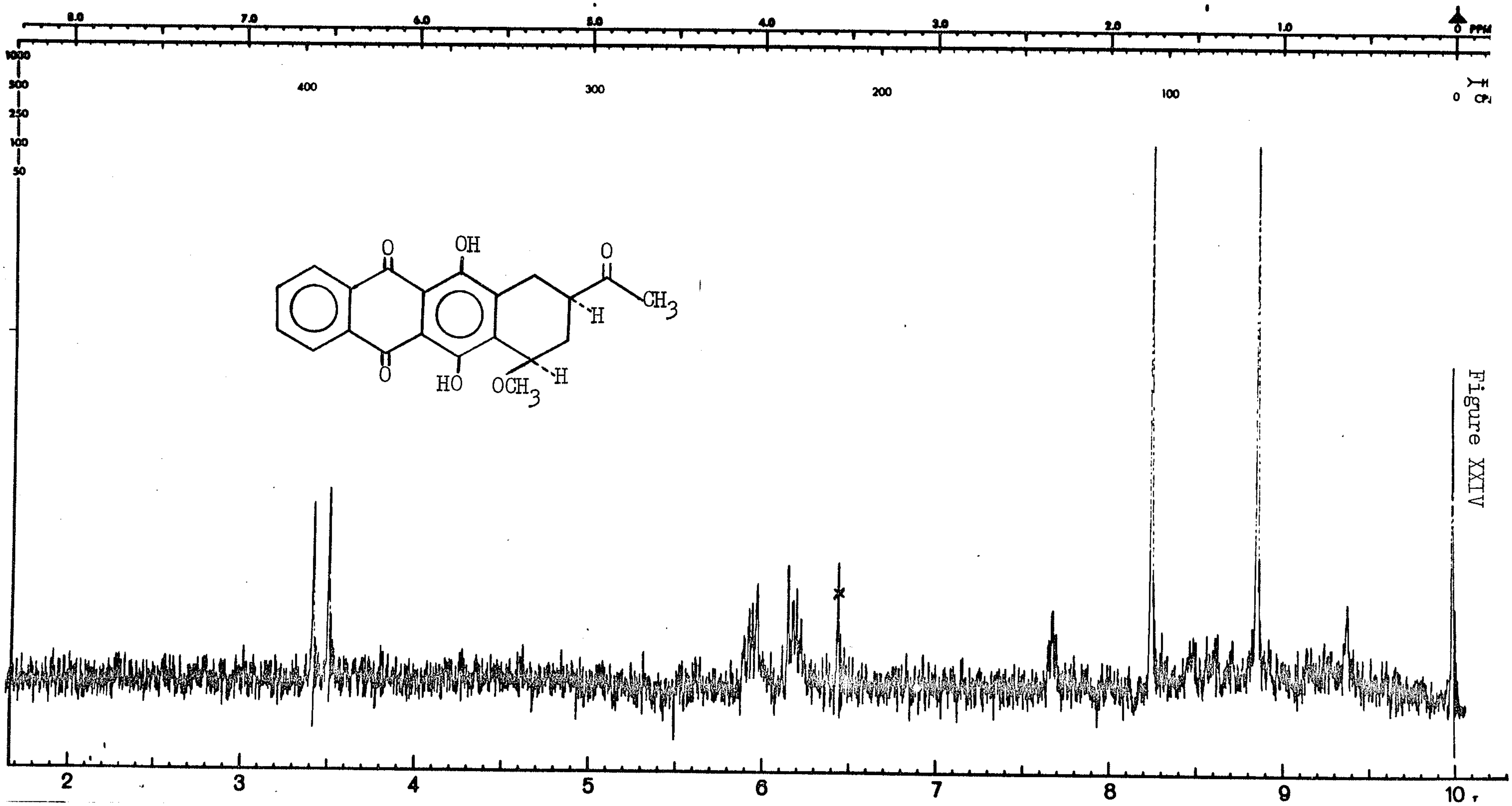
Nuclear magnetic resonance spectrum no. 9: 4-demethoxy-7-epi-9-deoxy-6,7,11-tri-O-methyldaunomycinone (27), in $CDCl_3$. Sweep width = 500 Hz.

Figure XXIII



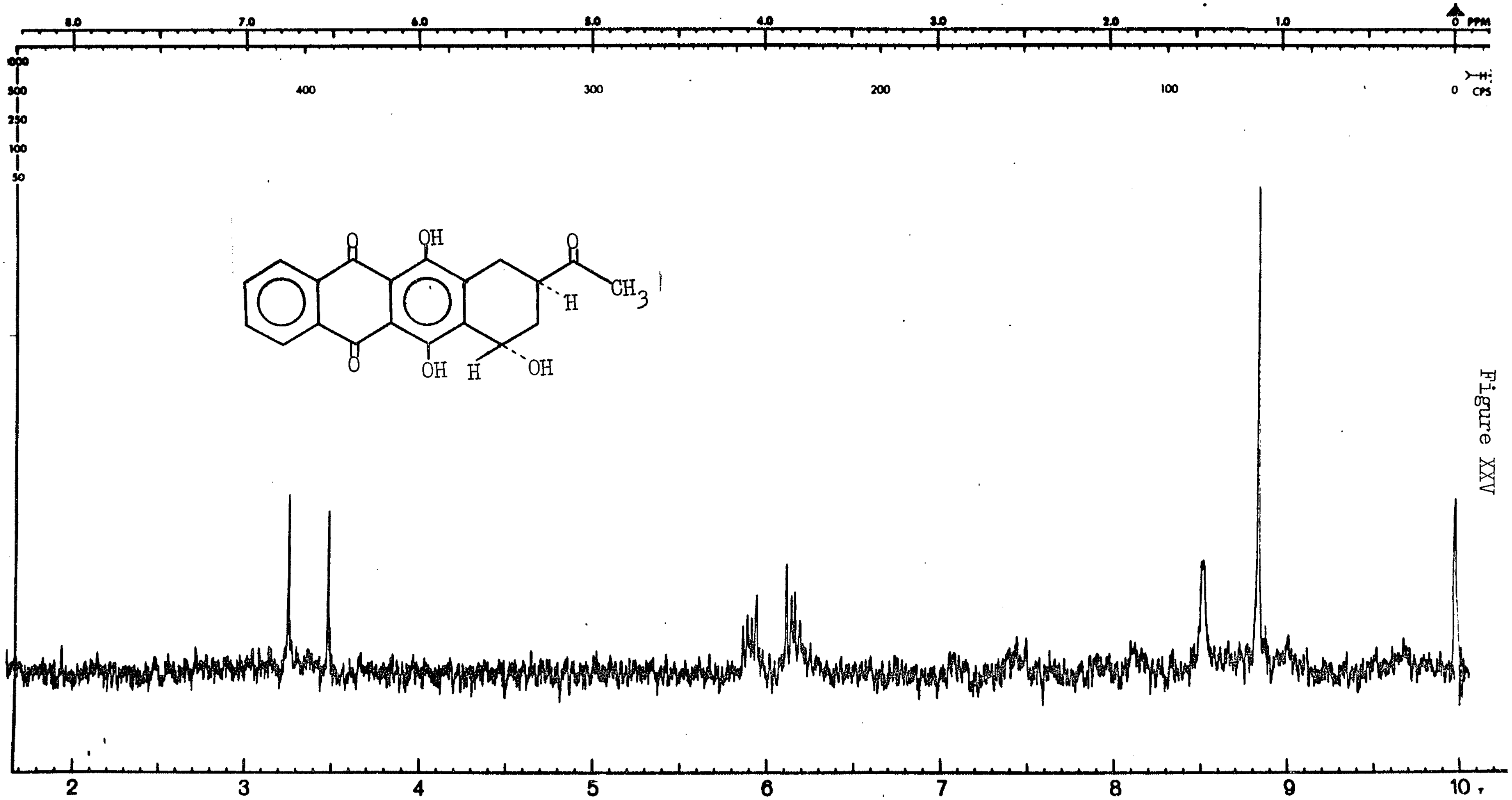
Nuclear magnetic resonance spectrum no. 10: 2-acetyl-11,12-dimethoxy-9,10-naphthacenequinone (39), in $CDCl_3$. Sweep width = 500 Hz.

Figure XXIV



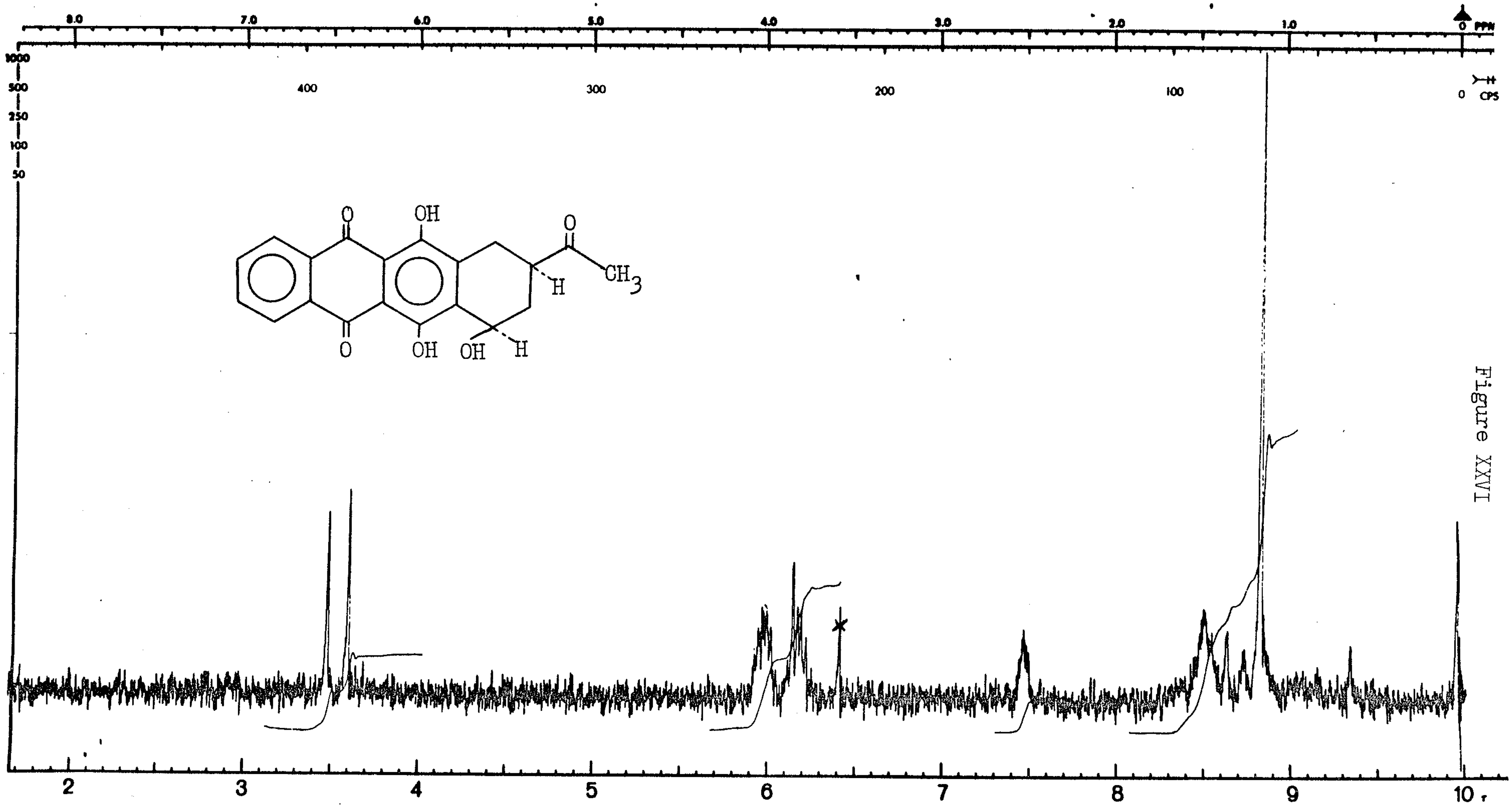
Nuclear magnetic resonance spectrum no. 11: 4-demethoxy-7-epi-9-deoxy-7-O-methyldaunomycinone (40), in $CDCl_3$. Sweep width = 1000 Hz.

Figure XXV



Nuclear magnetic resonance spectrum no. 12: 4-demethoxy-9-deoxydaunomycinone (42), in $CDCl_3$. Sweep width = 1000 Hz

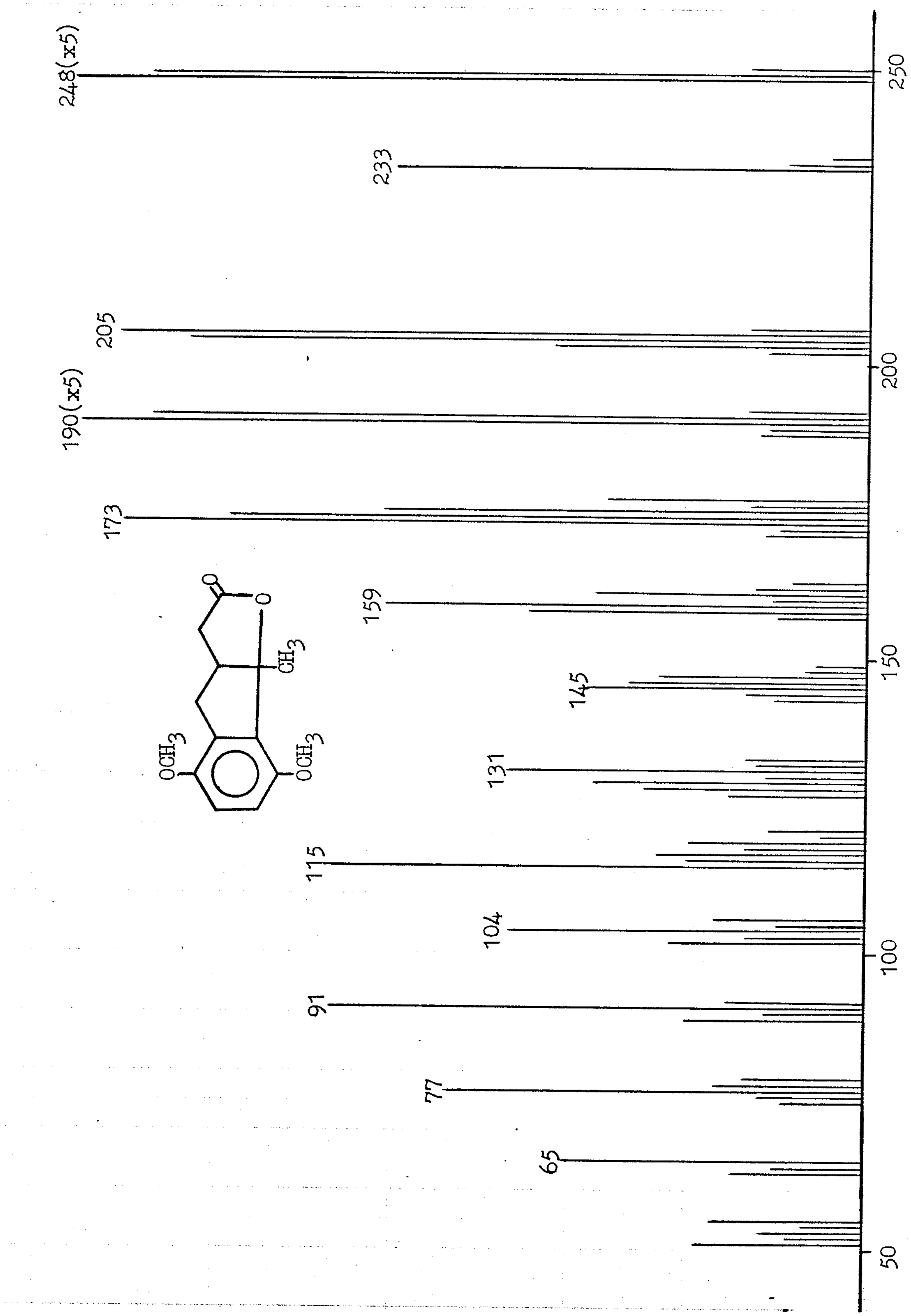
Figure XXVI



Nuclear magnetic resonance spectrum no. 13: 4-demethoxy-7-epi-9-deoxydaunomycinone (41),

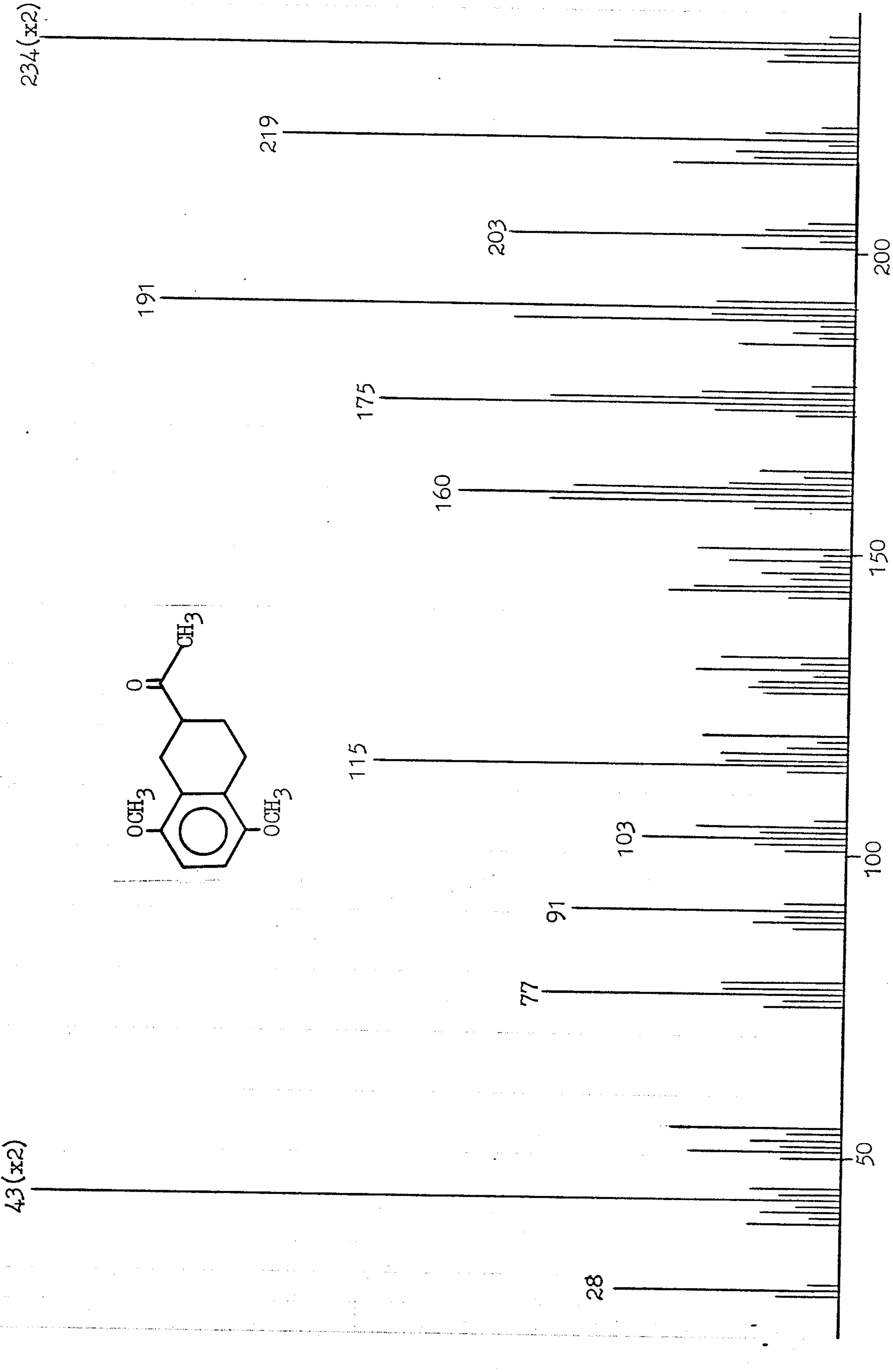
in $CDCl_3$. Sweep width = 1000 Hz.

Figure XXVII



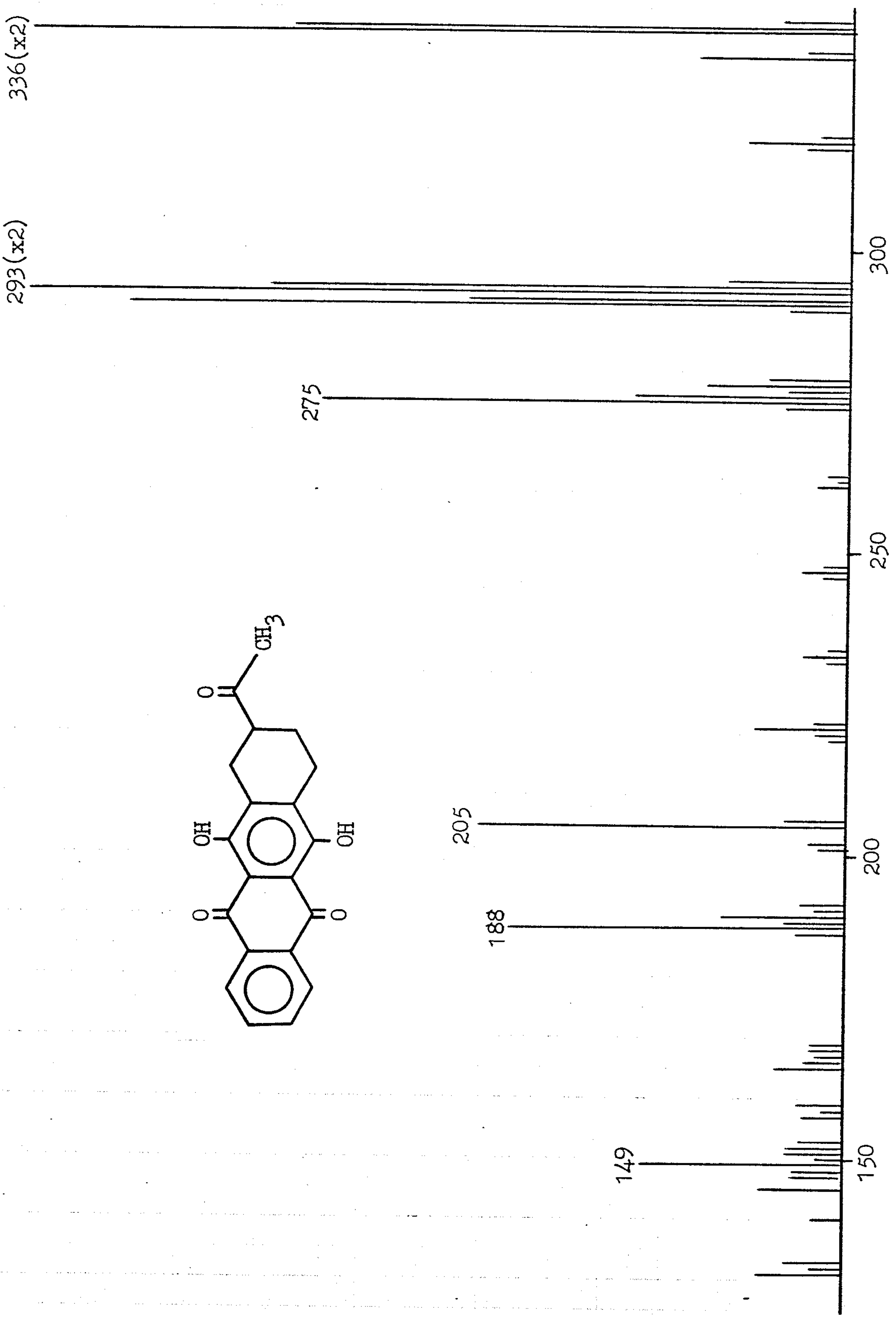
Mass spectrum no. 1: 1-methyl-1-hydroxy-4,7-dimethoxy-2-indanylethanoic acid lactone (20).

Figure XXVIII



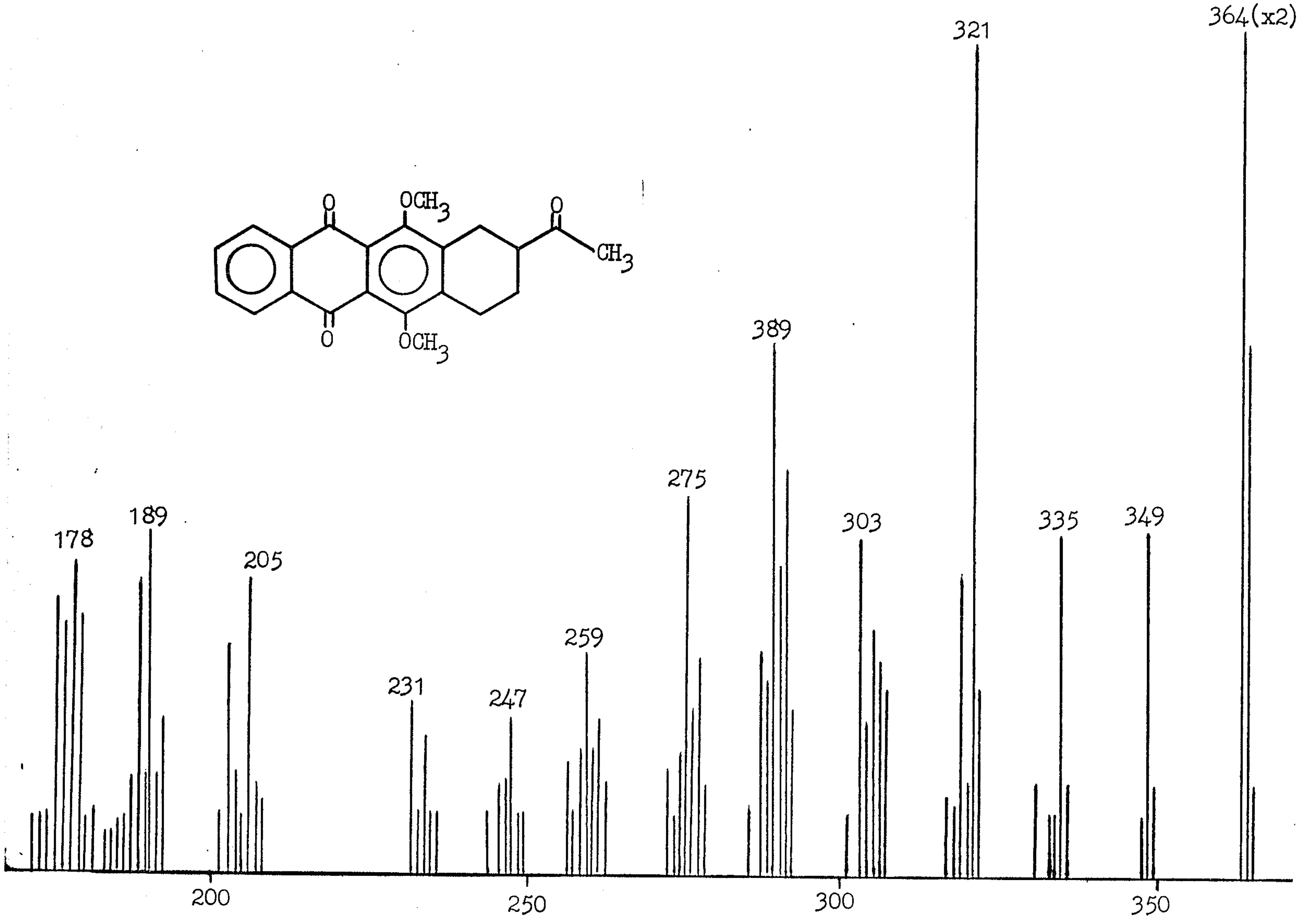
Mass spectrum no. 2: 2-acetyl-5,8-dimethoxytetralin (21).

Figure XXIX



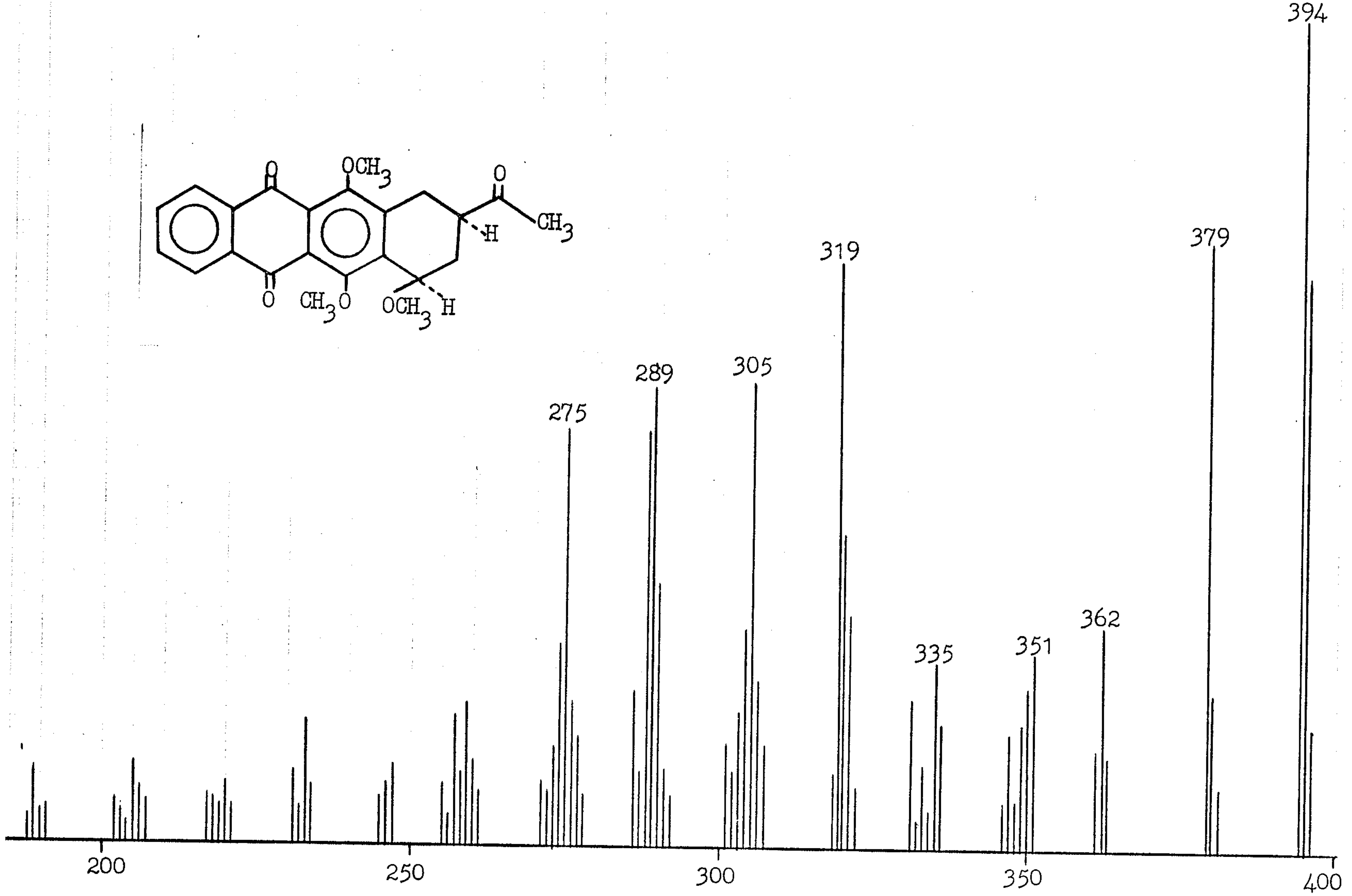
Mass spectrum no. 3: 4-demethoxy-7,9-dideoxydaunomycinone (22).

Figure XXX



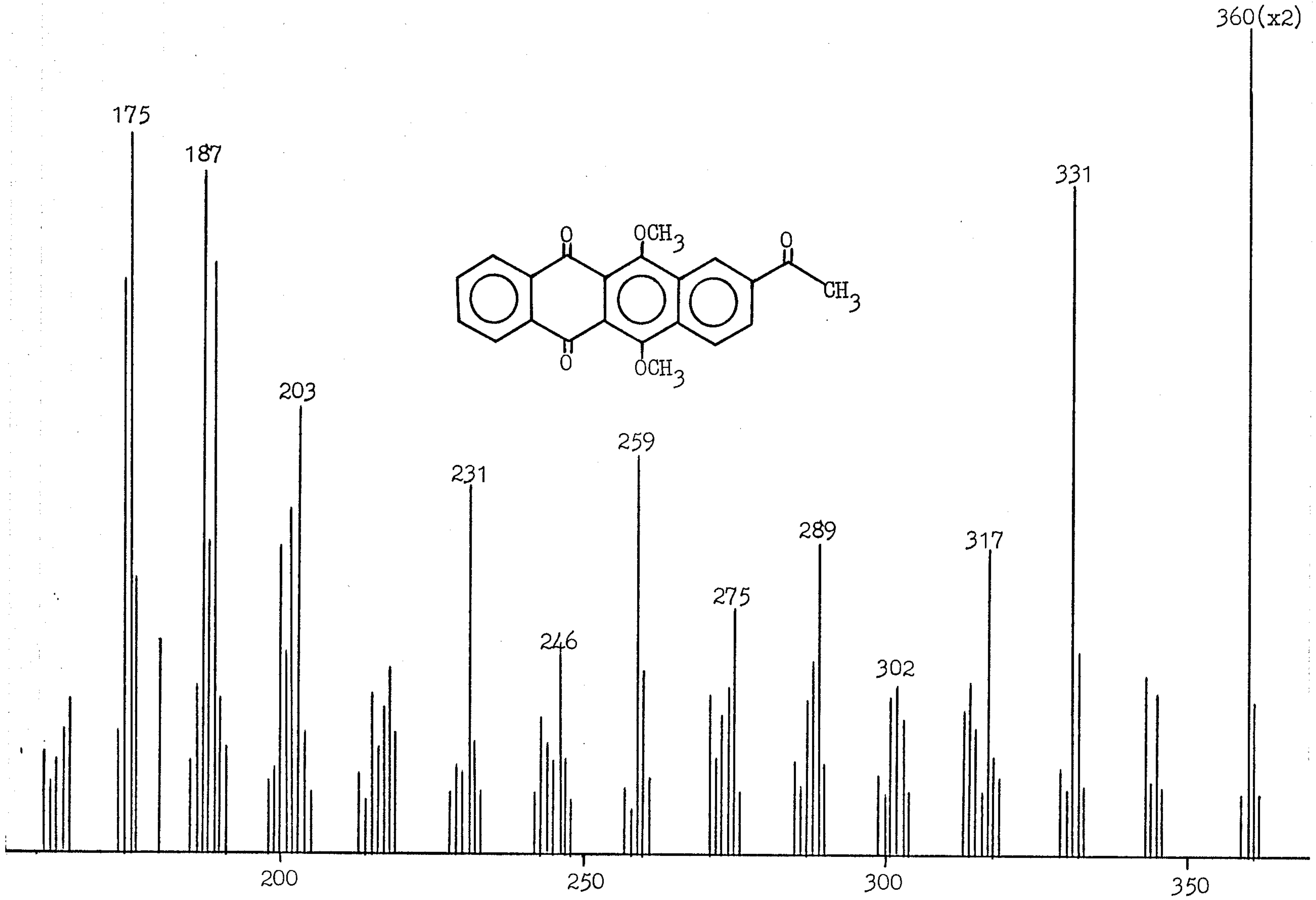
Mass spectrum no. 4: 4-demethoxy-7,9-dideoxy-6,11-di-O-methyldaunomycinone (23).

Figure XXXI



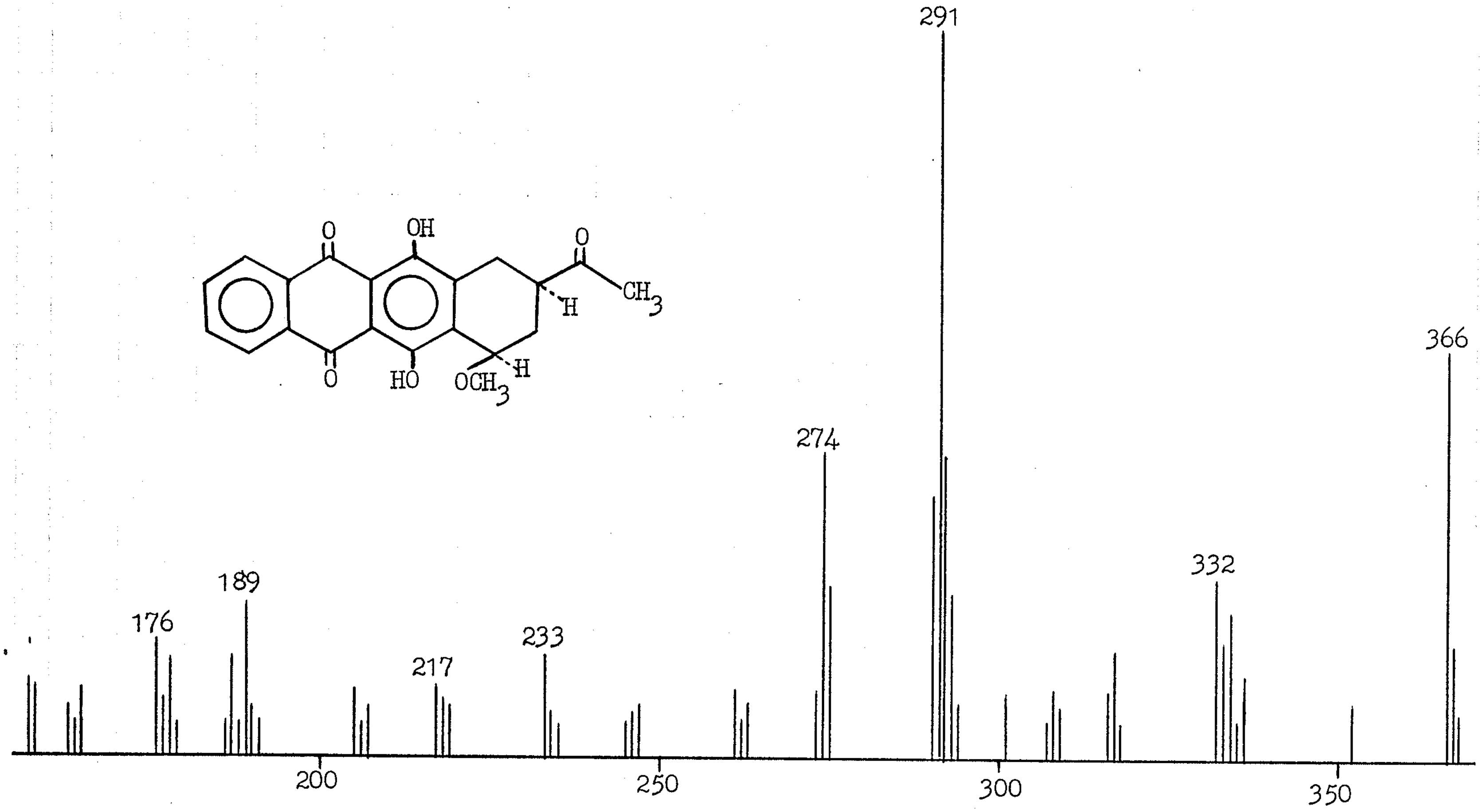
Mass spectrum no. 5: 4-demethoxy-7-epi-9-deoxy-6,7,11-tri-O-methyldaunomycinone (27).

Figure XXXII



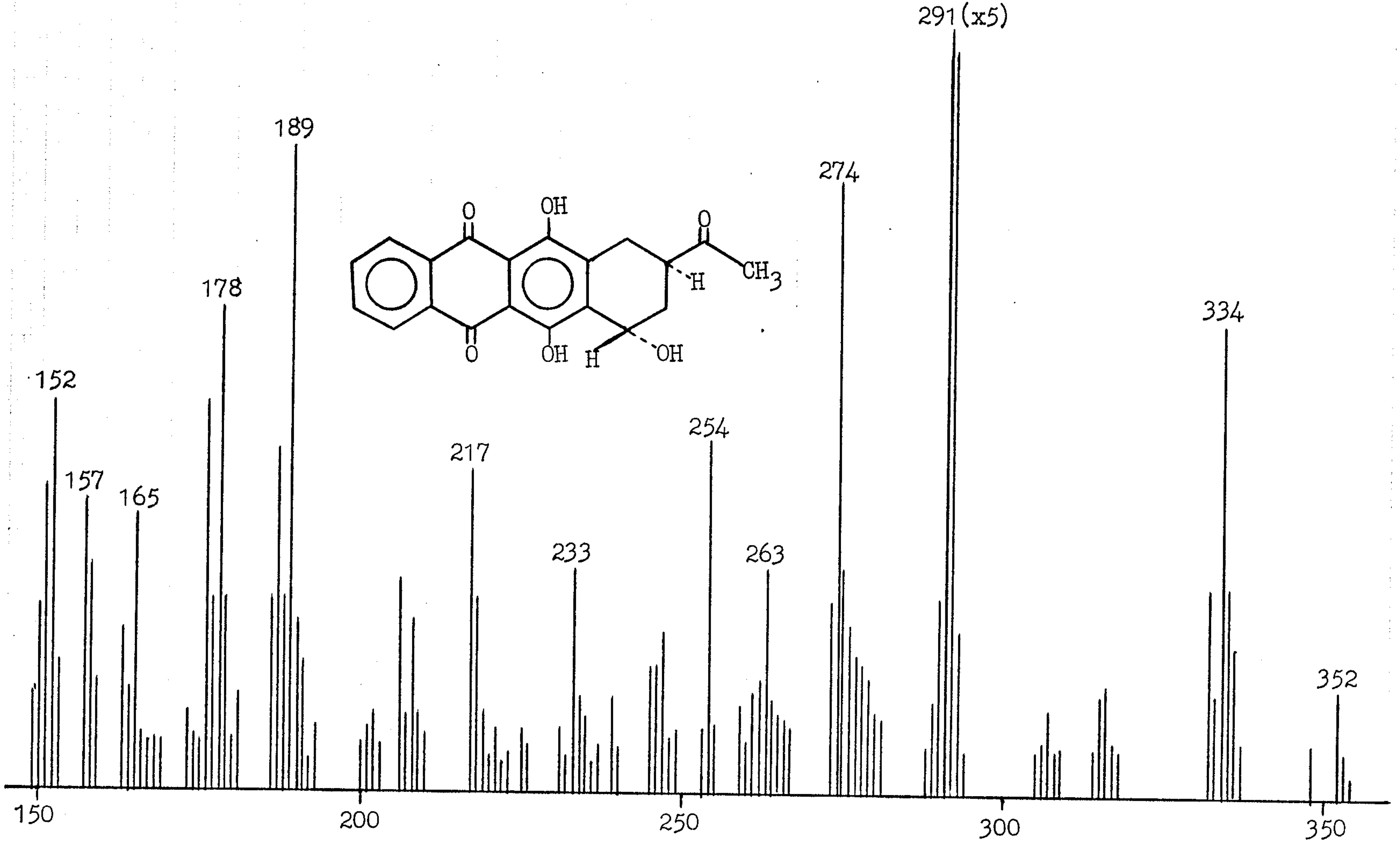
Mass spectrum no. 6: 2-acetyl-11,12-dimethoxy-9,10-naphthacenequinone (39).

Figure XXXIII



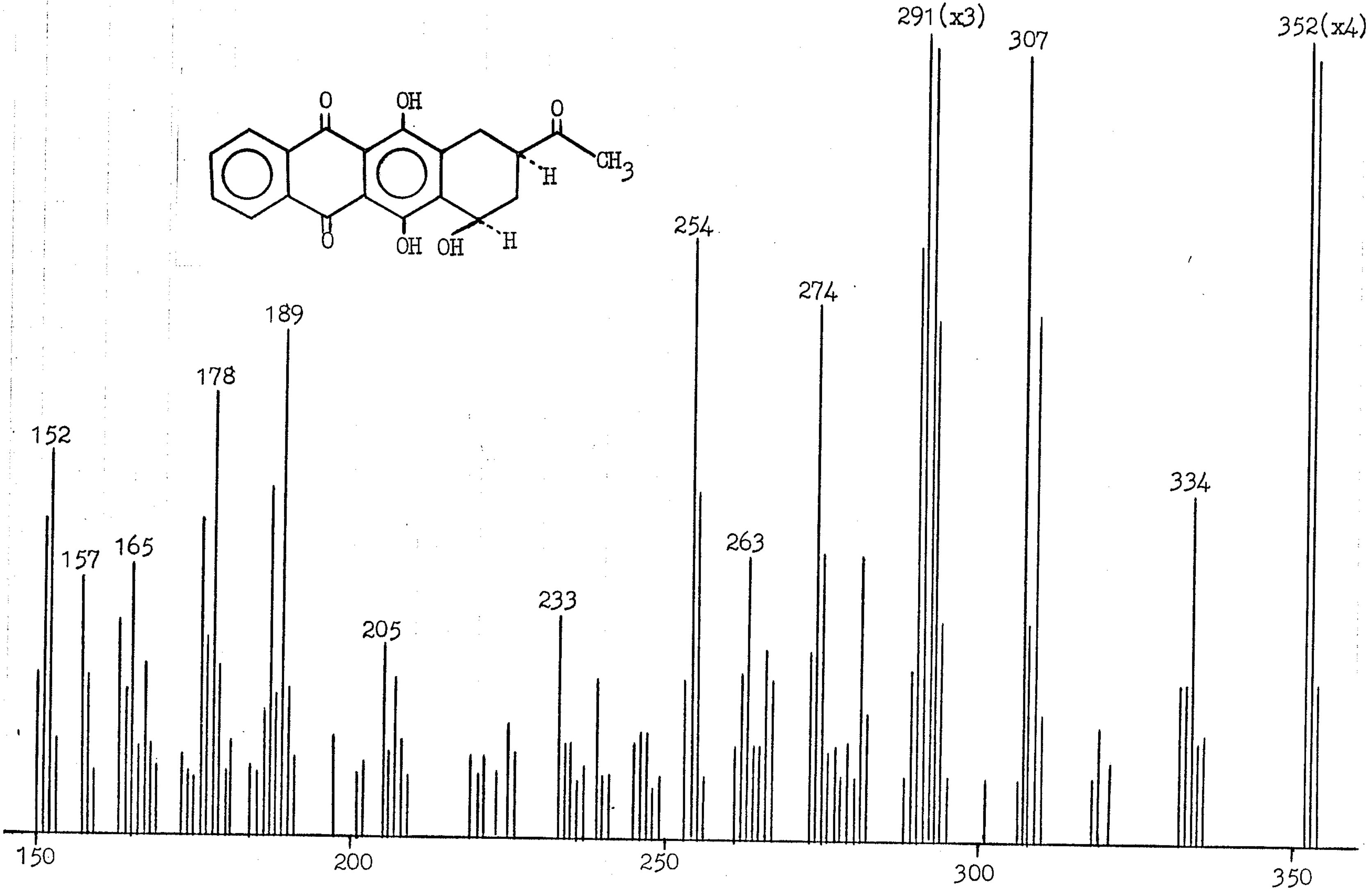
Mass spectrum no. 7: 4-demethoxy-7-epi-9-deoxy-7-O-methyldaunomycinone (40).

Figure XXXIV



Mass spectrum no. 8: 4-demethoxy-9-deoxydaunomycinone (42).

Figure XXXV



Mass spectrum no. 9: 4-demethoxy-7-epi-9-deoxydaunomycinone (41).

BIBLIOGRAPHY

(1) A. Di Marco, M. Gaetani, P. Orezzi, B. M. Scarpinato, R. Silvestrini, M. Soldati, T. Dasdia, and L. Valentini, Nature, 201, 706 (1964).

(2) J. A. Stock, Chem. in Brit., 6 No.1, 11 (1970).

(3) M. A. Burgess, O. Margaret Garson, and G. C. De Gruchy, Med. J. Aust., 13, 629 (1970).

(4) F. Arcamone, G. Franceschi, P. Orezzi, G. Cassinelli, Wanda Barbieri, and Rosana Mondelli, J. Am. Chem. Soc., 86, 5334 (1964).

(5) Z. Horii, Y. Ozaki, S. Yamamura, M. Hanaoka, and T. Mamose, Chem. Pharm. Bull., 19, 2000 (1971).

(6) R. H. Iwamoto, P. Lim, and N. S. Bhacca, Tetrahedron Lett., 36, 3891 (1968).

(7) F. Arcamone, G. Franceschi, P. Orezzi, and S. Penco, Tetrahedron Lett., 30, 3349 (1968).

(8) A. J. te Raa, Part B, Synthetic Approaches to Daunomycin, (1972).

(9) C. M. Wong, D. Popien, R. Schwenk, and J. te Raa, Can. J. Chem., 49, 2712 (1971).