PHOTOCHEMICAL TRANSFORMATIONS OF 3- AND 3,6-SUBSTITUTED CHOLESTA-3,5-DIENES

by

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To Judith

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TABLE OF CONTENTS

TABLE OF CONTENTS (cont'd.)

LIST OF FIGURES

LIST OF FIGURES (cont'd.) page

LIST OF FIGURES (cont'd.) page

ABSTRACT

The photolysis of 3-alkoxycholesta-3,5-dienes in an alcohol has been found to result in a stereospecific addition of the alcohol to the Δ^3-double bond with formation of β,γ-unsaturated ketals. On silica gel, the non-cyclic β,γ-unsaturated ketals gave cholest-5-en-3-one.

The photolysis of 3-methoxycholesta-3,5-diene in ethanol-d resulted in a 1:1 mixture of 4α- and 4β-deuterio-3β-ethoxy-3α-methoxy-cholest-5-ene. A stereospecific synthesis of 4β-deuterio-3α,5-cyclo-cholestan-6β-ol is described.

Irradiation of 3-methoxy-6-substituted cholesta-3,5-dienes in an alcohol gave β,γ-unsaturated ketals. The photolysis of other 3-substituted cholesta-3,5-dienes generally gave intractable mixtures.

Mechanistic interpretations of these photo-induced reactions are discussed.

The chemical shifts of C-4 and C-6 protons in the n.m.r. spectra of fourteen cholesta-3,5-dienes are described. 3-Deuterio-cholesta-3,5-diene has been synthesized.

INTRODUCTION

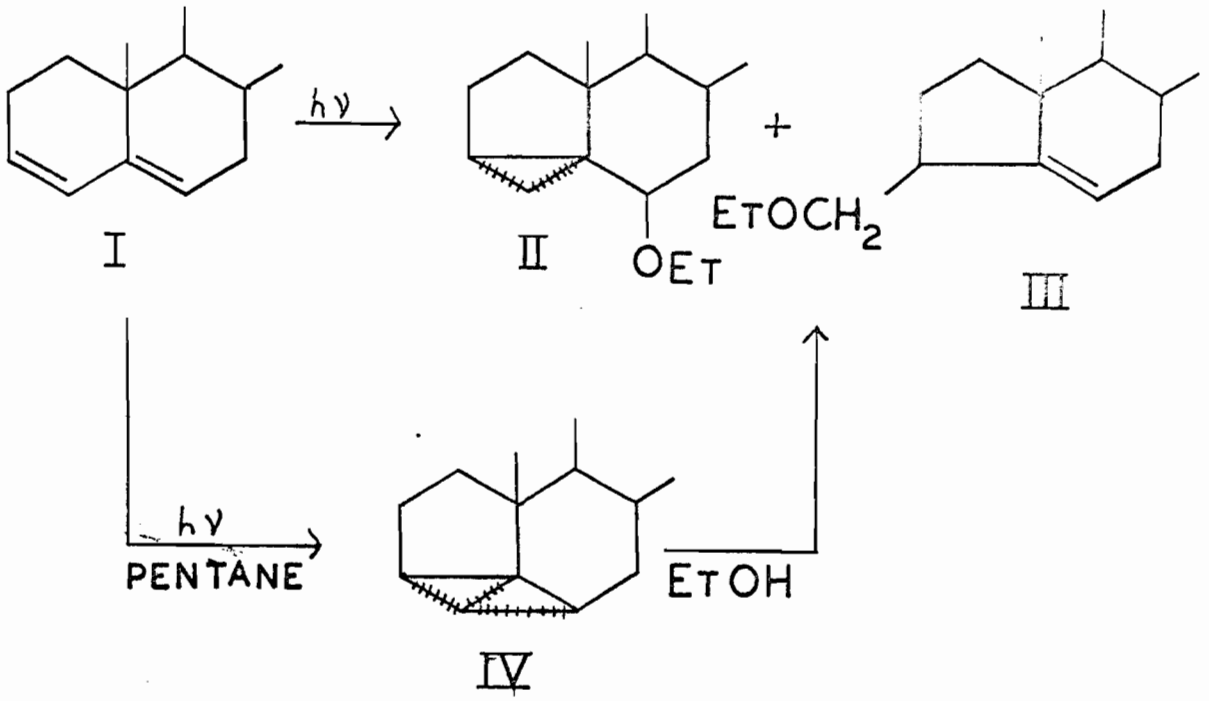
Organic chemical reactions induced by ultraviolet light have been known for a long time (1), but it was not until recently that the availability of high-pressure mercury arc lamps, the chromatographic methods for separation of complex reaction mixtures, and the spectroscopic tools for routine determination of unusual structures have permitted thorough and rapid investigation of these interesting reactions (see, i.e. 2,3,4,5,6). In many cases (7,8,9), the products of photolysis reactions are high energy systems or are compounds which would be difficult to prepare by other processes. Barton, for instance, has used photochemical reactions to functionalize the C-18 and C-19 groups of steroids by photolysis of a suitably oriented nitrite (10) or hypohalite (11) group.

The mechanistic paths by which photolyses occur are largely unknown, although many attempts are being made to interpret photochemical transformations (3,5,12,13).

At the present time, a great majority of the known photolytic reactions involve ketones (4) and homoannular dienes, such as ergosterol (4,14,15) as substrates.

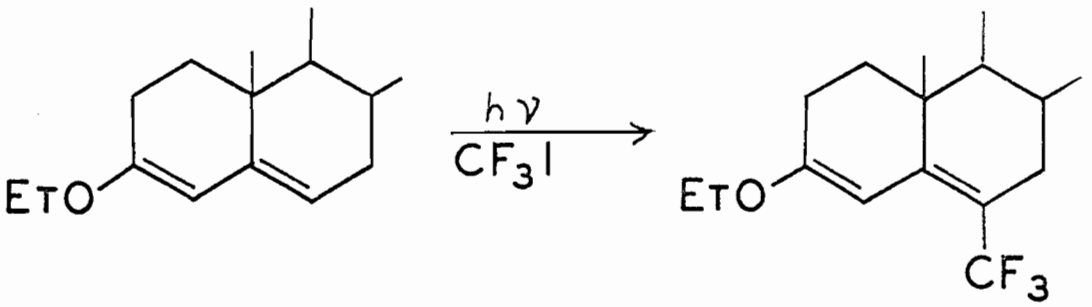
In 1958, the first example of a photolysis of a heteroannular diene was published. Dauben, Ross and Willey (16,17) reported that irradiation of cholesta-3,5-diene (I) in pentane gave 3β,5;4α,6α-bicyclo-5β-cholestane (VI), which was converted to ethers II and III by the action

of ethanol in the dark.



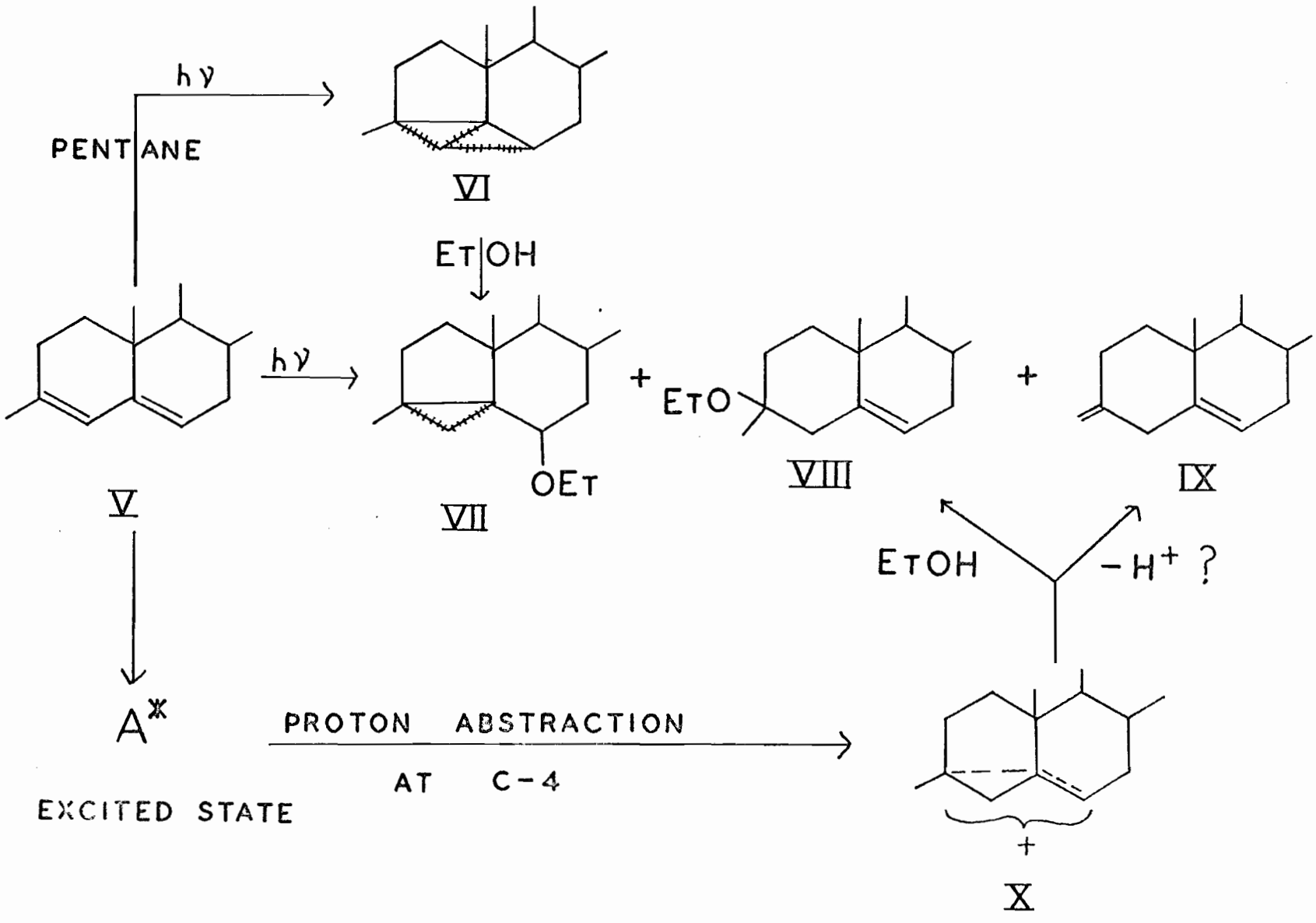
The two ethers were obtained in identical yields by irradiation of diene I in ethanol (16,17).

At about the same time, Godtfredsen and Vangedal (18) reported on the photo-induced reaction summarized on the following flowsheet.



Just and DiTullio (19) irradiated 3-methylcholesta-3,5-diene (V), in order to determine the effect of substitution on the photolysis of heteroannular dienes. Irradiation of 3-methylcholesta-3,5-diene (V) in ethanol gave ethers VII and VIII and diene IX. Photolysis of V in pentane gave 3-methyl-3β,5;4α,6α-bicyclo-5β-cholestane (VI), which on treatment with ethanol in the dark gave only ether VII. Obviously, there are at least two competing reaction pathways in the photolysis of 3-methylcholesta-3,5-diene (V) in ethanol. The bicyclobutane intermediate VI, which is formed through one reaction pathway, gave, on the addition of ethanol, only the cyclopropane ether (VII). Ether VIII must hence be formed through other reaction modes. V. DiTullio (20) postulated the formation of a homoallylic carbonium ion (X) (21,22), derived from proton abstraction by the C-4 position of an excited state (A*) of V, which adds ethanol to give ether VIII (see following flow-sheet).

The substitution of an electron-donating methyl group for hydrogen at C-3 seemed to favour the formation of a homoallylic carbonium ion. Since alkoxy groups exhibit a much higher electron-donating effect than the methyl group (23), it was believed that irradiation of 3-alkoxy-cholesta-3,5-dienes would give products wholly derived from homoallylic carbonium ions.

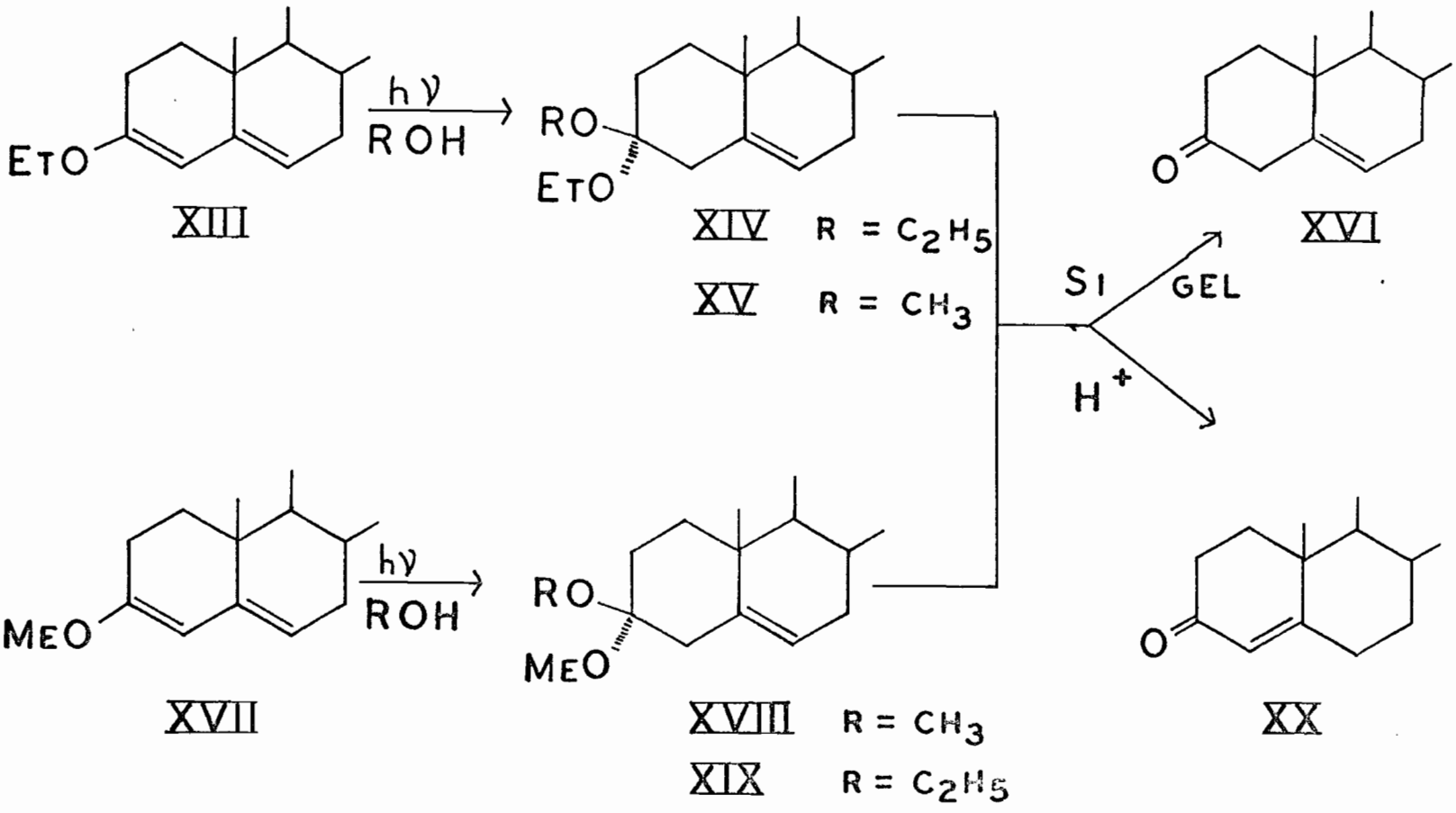

hν
PENTANE
VI
EtOH
hν
OEt
VII
+
EtO
VIII
+
IX
V
A*
EXCITED STATE
PROTON ABSTRACTION
AT C-4
EtOH
-H+ ?
+
X

RESULTS

CHAPTER I

The Photolysis of 3-Alkoxycholesta-3,5-dienes

A study of the photo-induced reactions of heteroannular dienes was initiated by irradiating some 3-alkoxycholesta-3,5-dienes in various solvents (24). An ethanolic solution of 3-ethoxycholesta-3,5-diene (XIII) (25) was irradiated with a high-pressure mercury lamp. The reaction was rapid as evidenced by the disappearance of the chromophore at 239 mμ. Purification by chromatography on alumina gave in 60% yield a crystalline compound (XIV), $C_{31}H_{54}O_2$, m.p. 49-50°. Treatment with acid resulted in the formation of cholest-4-en-3-one (XX). Chromatography of XIV on silica gel gave cholest-5-en-3-one (XVI). The infrared (Fig. 5A) and nuclear magnetic resonance (n.m.r.) data (Table I) provided substantial proof that the photo-product was 3,3-diethoxycholest-5-ene (XIV). Specifically, the n.m.r. spectrum (Fig. 1) of XIV showed two overlapping quartets centered at 3.33 p.p.m. and 3.40_5 p.p.m. characteristic of ethoxy groups and a peak at 5.25 p.p.m. due to a vinyl proton. The proposed structure (XIV) was further confirmed by synthesis in which cholest-5-en-3-one (XVI) (26a) was reacted with absolute ethanol in the presence of malonic acid (27).


EtO
hν
ROH
RO
EtO
O
XIII
XIV R = C2H5
XV R = CH3
XVI
Si GEL
H+
MeO
hν
ROH
RO
MeO
O
XVII
XVIII R = CH3
XIX R = C2H5
XX

Similarly, photolysis of 3-methoxycholesta-3,5-diene (XVII) in methanol gave 3,3-dimethoxycholest-5-ene (XVIII) in 50-60% yield, identical in all respects with a sample prepared synthetically (27).

When 3,3-diethoxycholest-5-ene (XIV) was recrystallized from methanol, a new compound (XV), $C_{30}H_{52}O_2$, m.p. 105-106°, was obtained. The infrared spectrum (Fig. 5C) showed strong absorption in the ether region and the n.m.r. spectrum (Fig. 3) showed the presence of one methoxy group, a singlet, and of one ethoxy group, a quartet (Table I), as well as an olefinic proton. The methylene protons at the C-4 position of these ketals gave a broad peak at 2.25 p.p.m.

In comparison, 3,3-dimethoxycholest-5-ene (XVIII) gives two distinct, unsplit signals for the two methoxy groups (Fig. 2) and hence it seems reasonable that compound XV is a 3-ethoxy-3-methoxycholest-5-ene, in which one ethoxy group has been stereospecifically exchanged for one methoxy group.

It is a well-known fact (28,29,30) that in solvolytic reactions of cholesteryl derivatives, the Δ^5-double bond participates to give a homoallylic carbonium ion and that the incoming group attaches itself at the 3β-position in a stereospecific manner. It hence seems reasonable to assume that in this exchange reaction, the Δ^5-double bond assists preferentially the departure of the 3β-substituent and that the resulting dialkoxy compound is 3α-ethoxy-3β-methoxycholest-5-ene (XV).

Pyrolysis of 3α-ethoxy-3β-methoxycholest-5-ene (XV) in vacuo at

TABLE I

Nuclear Magnetic Resonance Data of Photolysis Products XIV, XV, XVIII, and XIX

(T.M.S. = 0, chemical shifts in p.p.m.)

Compound	Methylene group at C-4 Single peak	3α-MeO Singlet	3β-MeO Singlet	3α-EtO Quartet center	3β-EtO Quartet center	Vinyl proton at C-6 Single peak
3,3-Diethoxycholest-5-ene	2.25	-	-	3.40_5	3.33	5.25
3,3-Dimethoxycholest-5-ene	2.23	3.125	3.04_5	-	-	5.25
3α-Ethoxy-3β-methoxycholest-5-ene	2.25	-	3.05_5	3.44	-	5.25
3β-Ethoxy-3α-methoxycholest-5-ene	2.25	3.15	-	-	3.33	5.25

190° yielded a mixture of 3-ethoxy and 3-methoxycholesta-3,5-dienes. Further attempts to eliminate one alkoxy group stereospecifically by acid-catalyzed reactions (see experimental) resulted only in hydrolysis to cholest-4-en-3-one and cholest-5-en-3-one.

It was fortuitous that ketal (XV) was obtained in a pure state since a more detailed investigation of the exchange reactions of 3,3-diethoxy and 3,3-dimethoxycholest-5-enes in methanol and ethanol respectively revealed that the 3α-alkoxy group is also exchanged. The rate of exchange of the 3β-alkoxy group was only twice that of the 3α-alkoxy group. The exchange reactions were followed by n.m.r. spectroscopy by measuring the rate of increase or decrease of the unsplit methoxy peaks in samples obtained from the reaction mixture at regular time intervals.

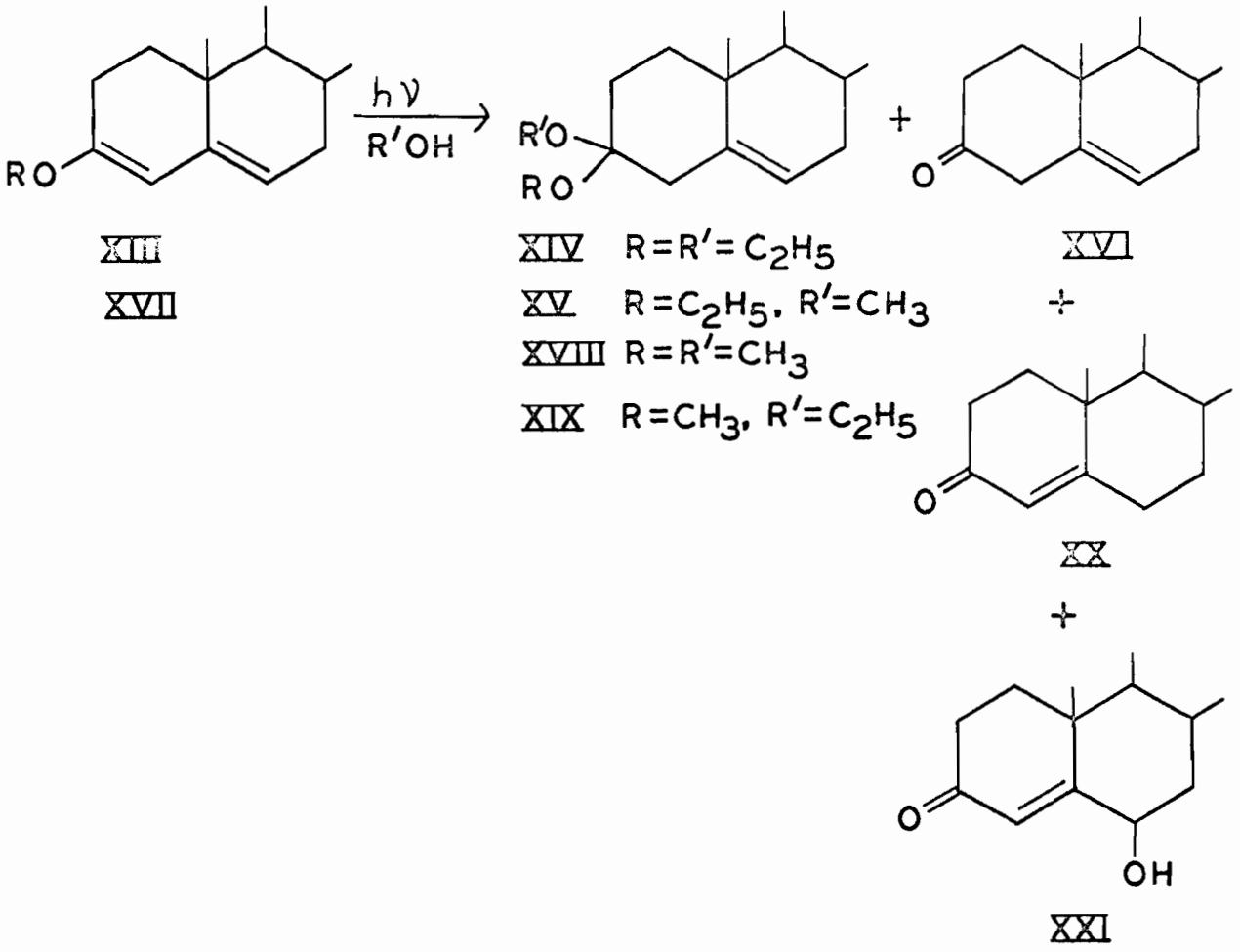
In order to complete this sequence of reactions, 3-methoxycholesta-3,5-diene (XVII) was irradiated in absolute ethanol. The main product (XIX) of the reaction, obtained in 60% yield, was isomeric with ketal XV, obtained by the methanolysis of XIV. The n.m.r. spectrum (Fig. 4) showed the presence of one ethoxy and one methoxy group. The chemical shifts of the ethoxy and methoxy groups coincide with one of the ethoxy and methoxy groups in ketals XIV and XVIII, as shown in Table I. On silica gel, XIX gave cholest-5-en-3-one (XVI) and cholest-4-en-3-one (XX). Its infrared spectrum (Fig. 5D) shows strong ether absorption and further supports the formulation of XIX as 3β-ethoxy-3α-methoxycholest-5-ene.

When 3-ethoxycholesta-3,5-diene (XIII) was photolyzed in methanol, 3,3-dimethoxycholest-5-ene (XVIII) was obtained. Obviously, the ethoxy group at C-3 was exchanged by methanol. When the reaction was repeated in the presence of a few drops of pyridine, 3α-ethoxy-3β-methoxycholest-5-ene (XV) was obtained. The product was identical with the methanolysis product of 3,3-diethoxycholest-5-ene (XIV). The n.m.r. spectrum of the crude photolysis product revealed that the reaction was not completely stereospecific, but that 5-10% of the isomeric mixed ketal (XIX) was present.

It should be noted that n.m.r. and infrared spectra were taken on all crude photolysis products, in order to ensure that no isomerizations occurred during chromatography and crystallization. The n.m.r. and infrared spectra were very characteristic for photolysis products XIV, XV, XVIII, and XIX and resulted in unambiguous identification (see Table I and Figs. 1-5).

If the assignments of stereochemistry of the epimeric mixed ketals, XV and XIX, are correct, then the chemical shifts of the 3α- and 3β-methoxy groups of 3,3-dimethoxycholest-5-ene (XVIII) are 3.12_5 and 3.04 p.p.m. respectively and the chemical shifts of the 3α- and 3β-ethoxy groups of 3,3-diethoxycholest-5-ene (XIV) are 3.40_5 and 3.33 p.p.m. respectively.

The photolyses of 3-alkoxycholesta-3,5-dienes in alcohols are accompanied by substantial hydrolysis, which does not occur in the absence of light. An infrared spectrum of the photolysis mixture showed



XIII

XIV R=R'=C_2H_5

XV R=C_2H_5, R'=CH_3

XVIII R=R'=CH_3

XIX R=CH_3, R'=C_2H_5

XVI

+

XX

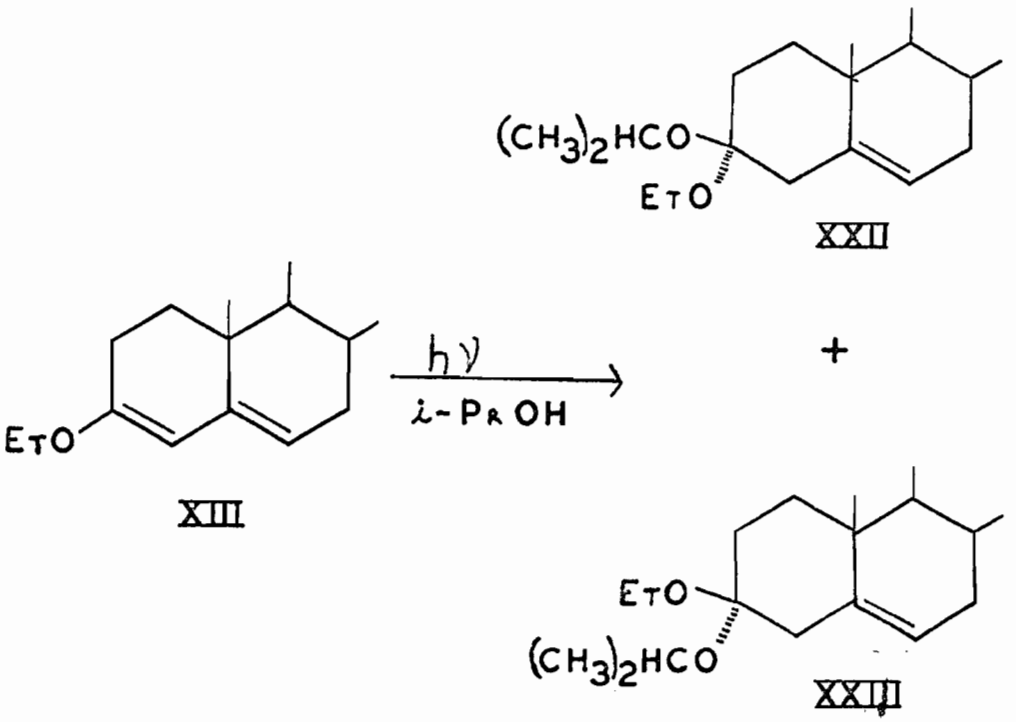
+

XXI

the presence of cholest-5-en-3-one (XVI), cholest-4-en-3-one (XX), and cholest-4-en-6β-ol-3-one (XXI). Chromatography on alumina, however, yielded 20-30% of cholest-4-en-3-one (XX) and 5-10% of cholest-4-en-6β-ol-3-one (XXI). Clearly, the cholest-5-en-3-one (XVI) has been isomerized to cholest-4-en-3-one (XX) on alumina.

When 3-ethoxycholesta-3,5-diene (XIV) was irradiated in spectrograde isopropyl alcohol, an oily mixture was obtained. Chromatography over alumina gave in 50% yield in the hexane fractions an oily product which appeared to be a 1:1 mixture of 3α-ethoxy-3β-isopropoxycholest-5-

ene (XXII) and 3β-ethoxy-3α-isopropoxycholest-5-ene (XXIII). Its n.m.r. spectrum (Fig. 6) showed a signal for an olefinic proton at 5.39 p.p.m. and a signal for a C_4 methylene group at 2.35 p.p.m. The signals in the ether region were complex but could be interpreted as consisting of two overlapping quartets centered around 3.53 p.p.m. and two overlapping septets centered at 4.13 p.p.m. This interpretation would be fully consistent with a 1:1 mixture of XXII and XXIII.



Since pure crystalline compounds could not be obtained, further irradiations in isopropyl alcohol were not attempted.

Irradiation of 3-ethoxycholesta-3,5-diene (XIV) in diethyl ether gave an inseparable mixture. The n.m.r. spectrum of the crude photolyzate

showed only broad absorption bands.

When the 3-alkoxycholesta-3,5-dienes were photolyzed in spectrograde pentane, a mixture was obtained which showed only very broad absorption in the n.m.r. spectrum. Specifically no alkoxy absorption could be detected in the n.m.r. spectrum of the photolysis product.

FIG. 1

The nuclear magnetic resonance spectrum of

3,3-diethoxycholest-5-ene (XIV)

FIG. 1

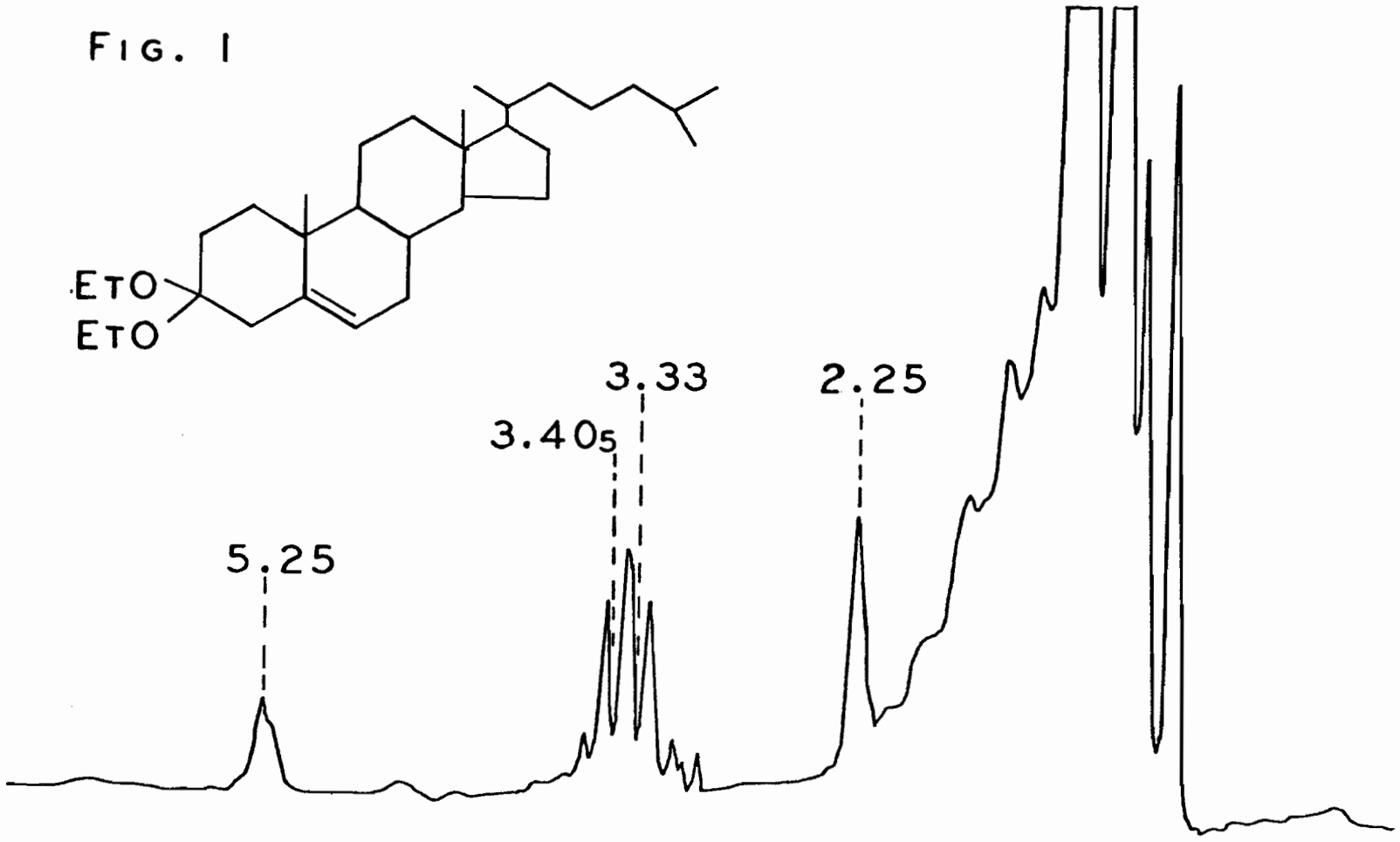


FIG. 2

The nuclear magnetic resonance spectrum of

3,3-dimethoxycholest-5-ene (XVIII)

FIG. 2

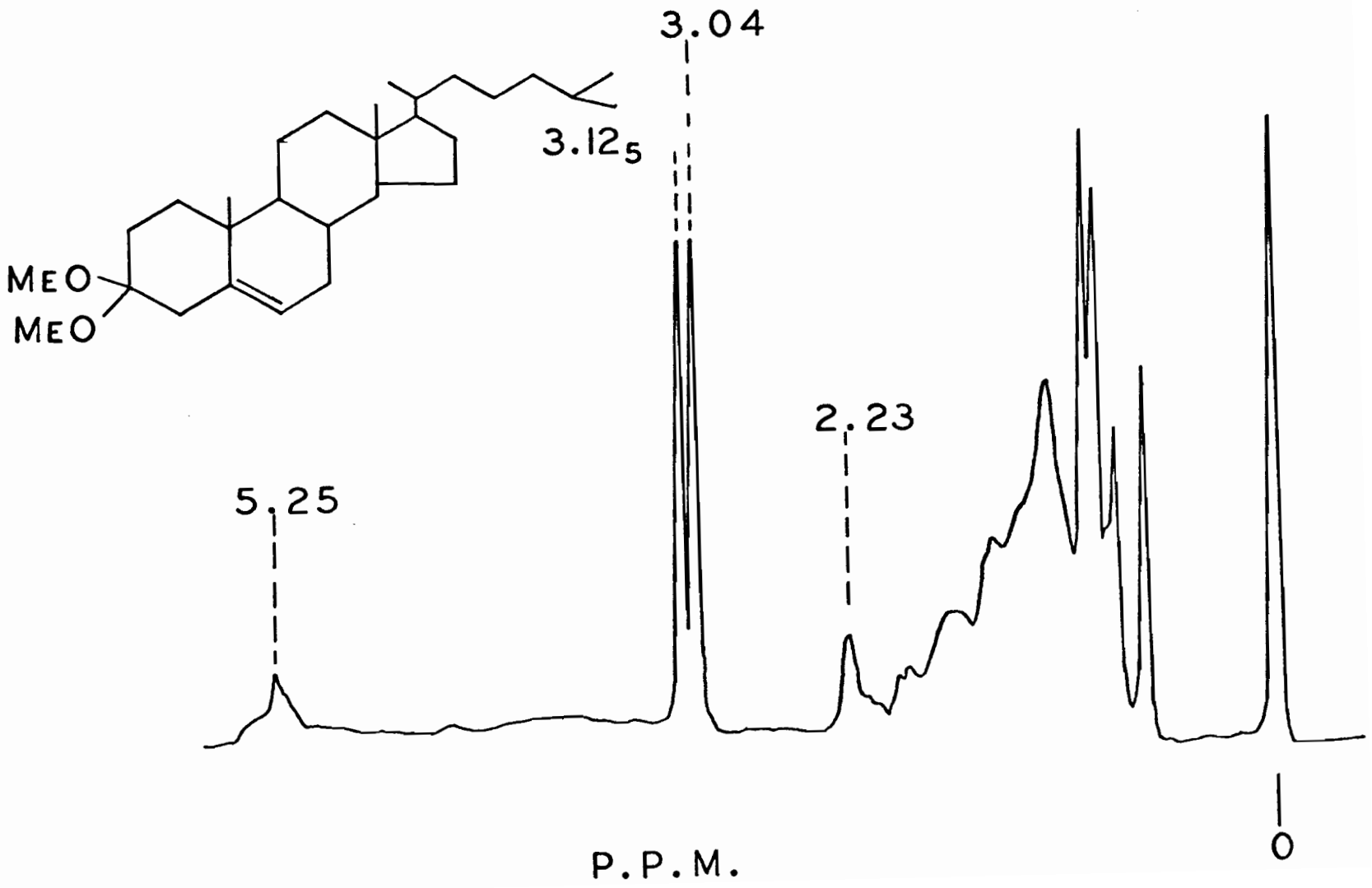


FIG. 3

The nuclear magnetic resonance spectrum of

3α-ethoxy-3β-methoxycholest-5-ene (XV)

FIG. 3

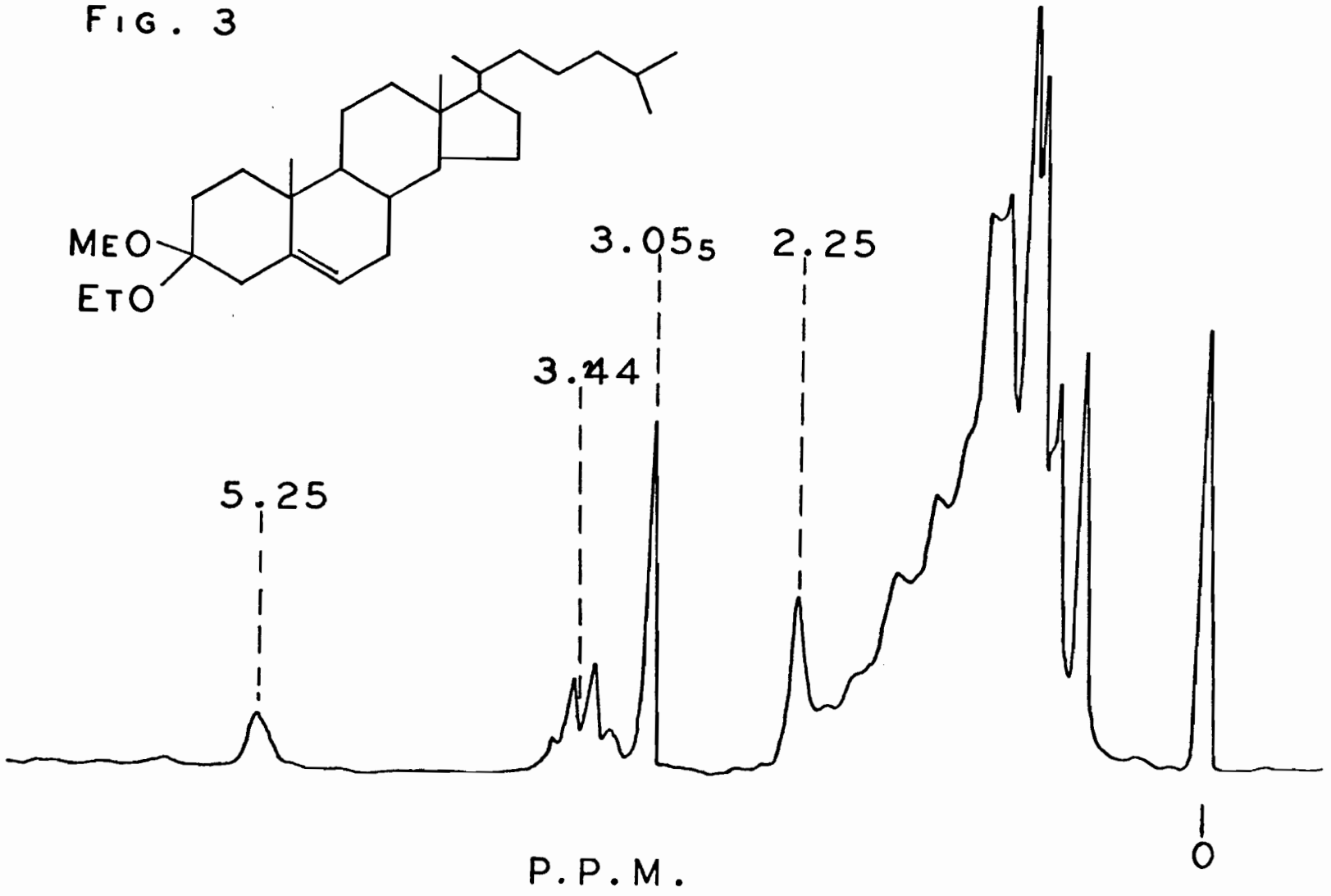


FIG. 4

The nuclear magnetic resonance spectrum of

3β-ethoxy-3α-methoxycholest-5-ene (XIX)

FIG. 4

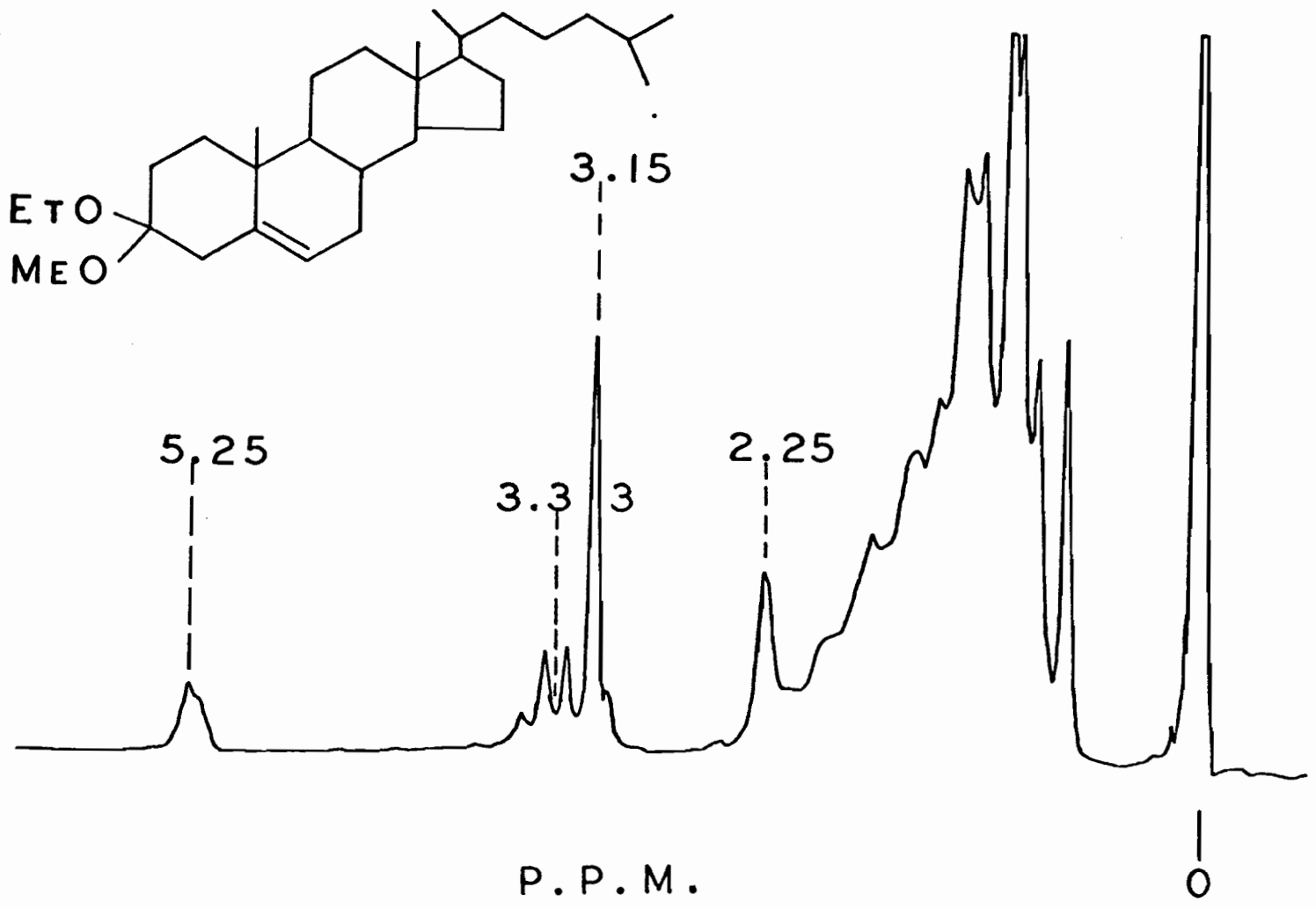


FIG. 5

The infrared spectra of

A. 3,3-diethoxycholest-5-ene (XIV)

B. 3,3-dimethoxycholest-5-ene (XVIII)

C. 3α-ethoxy-3β-methoxycholest-5-ene (XV)

D. 3β-ethoxy-3α-methoxycholest-5-ene (XIX)

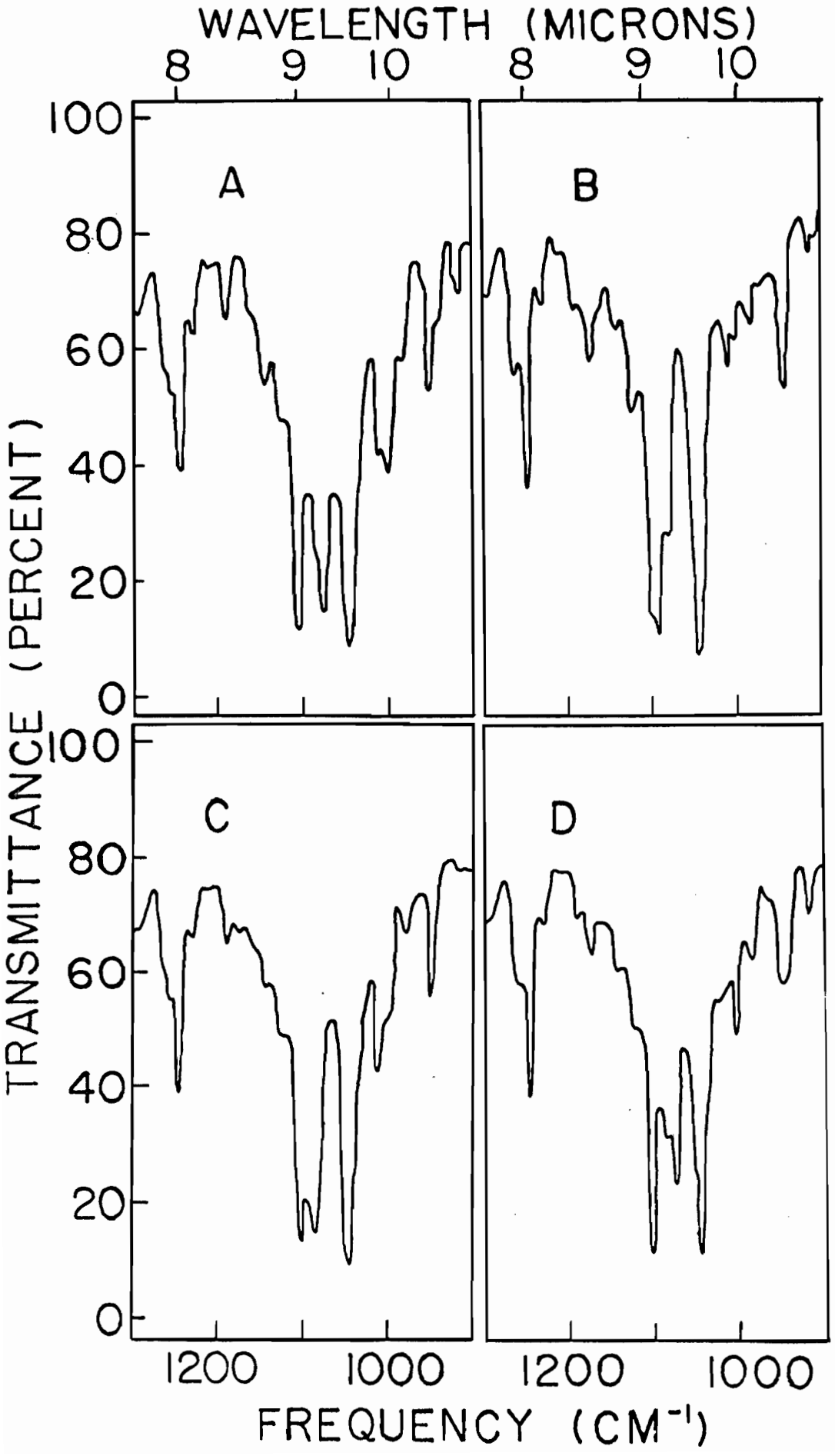
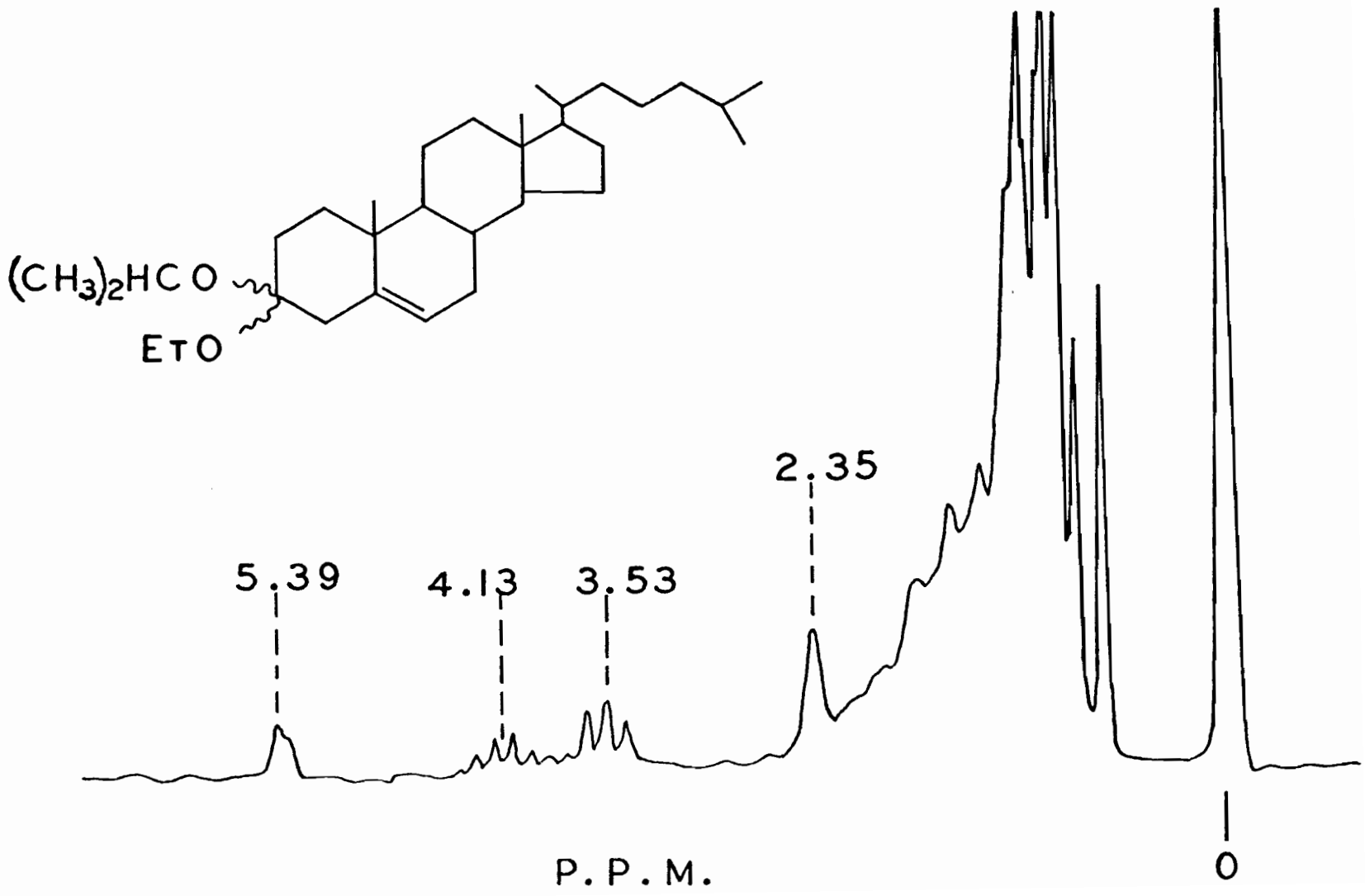

WAVELENGTH (MICRONS)
8
9
10
8
9
10
100
80
60
40
20
0
A
B
C
D
TRANSMITTANCE (PERCENT)
1200
1000
1200
1000
FREQUENCY (CM⁻¹)

FIG. 6

The nuclear magnetic resonance spectrum of a 1:1 mixture of 3α-ethoxy-3β-isopropoxycholest-5-ene (XXII) and 3β-ethoxy-3α-isopropoxycholest-5-ene (XXIII)

FIG. 6



CHAPTER II

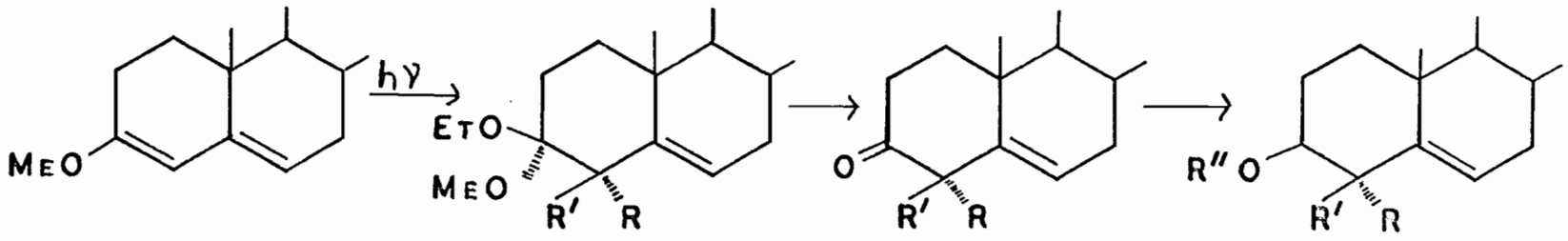
The Stereochemistry of the Photo-induced Ethanol Addition to 3-Methoxycholesta-3,5-diene

In Chapter I it has been shown that the photo-induced addition of alcohols to 3-alkoxycholesta-3,5-dienes gave in reasonably good yield 3,3-dialkoxycholest-5-enes (24) (e.g. XIII ---> XIV). The addition of the alkoxy moiety seemed to be quite stereospecific (3β). In this chapter the stereochemistry of protonation of the diene system will be described (31).

The geminal protons at C-4 are clearly shifted away from most other signals in the n.m.r. spectrum of 3,3-dialkoxycholest-5-enes (24), but appear to be equivalent and hence give rise to a single two-proton peak. In order to determine the stereochemistry of the proton addition at C-4, it was necessary to devise a means of making the two protons at C-4 non-equivalent. In principle, this can be achieved by incorporating them into a cyclopropane ring. The C-4 deuterated product could then be compared by n.m.r. spectroscopy to 4β-deuterio-3α,5-cyclocholestan-6β-ol (XXIX), stereospecifically synthesized by an independent route.

Cholest-4-en-3β-yl acetate (XXV) (32) was treated with monoperphthalic acid (33) in ether and the resulting 4α,5α-epoxycholestan-3β-yl acetate (XXVI) (34) reduced with lithium aluminum deuteride to give 4β-deuteriocholestan-3β,5α-diol (XXVII). These reductions are known to result in a trans-diaxial opening of oxide rings (34,35,36). Monoacetyl-

ation and dehydration with thionyl chloride gave 4β-deuteriocholesteryl acetate (XXVIII). Hydrolysis of the acetate (XXVIII) gave 4β-deuteriocholesterol (XXVIIIa) (37) which was shown to have 94% isotopic purity by mass spectroscopy. Tosylation of XXVIIIa gave 4β-deuteriocholesteryl tosylate (XXIVb). The n.m.r. spectrum (Fig. 8) in benzene showed a one-proton signal at 2.45 p.p.m. (doublet, J = 4.5 c.p.s.) corresponding to the C-4α proton (38). Pure cholesteryl tosylate shows a two-proton signal in the n.m.r. spectrum (Fig. 7) at 2.45 p.p.m. (doublet, J = 8.8 c.p.s.) due to the C-4 protons. Solvolysis of XXIVb yielded 4β-deuterio-3α,5-cyclocholestan-6β-ol (XXIX) (39). Whereas 3α,5-cyclocholestan-6β-ol (XXIXb) shows complex signals between 0.2 and 0.7 p.p.m. in its n.m.r. spectrum (Fig. 9) due to the cyclopropane protons, its 4β-deuterio analog showed in the n.m.r. spectrum (Fig. 10) a signal for one proton at 0.23 p.p.m. (doublet, J = 8.5 c.p.s.) only. The C-4α hydrogen is coupled with the hydrogen at C-3 and the coupling constant is that expected for cis hydrogens on a cyclopropane ring (38,40,41). The photolysis of 3-alkoxycholesta-3,5-dienes in methanol or ethanol proceeded without any difficulty (24), but this was not the case for the corresponding reaction in deuterioethanol, prepared by the decomposition of diethyl sulphite in heavy water (42). It seems that in spite of all precautions taken in its preparation, a small amount of acidic material was present in the deuterated solvent and this material hydrolyzed the 3,3-dialkoxycholest-5-ene as soon as it formed. The photolysis of 3-methoxycholesta-3,5-diene (XVII) was hence carried out in deuterioethanol containing a small amount of pyridine. Mono-4-deuterio-3β-ethoxy-3α-methoxycholest-5-ene (XIXa, XIXb) (31) was isolated in approximately 50% yield by chromatography.

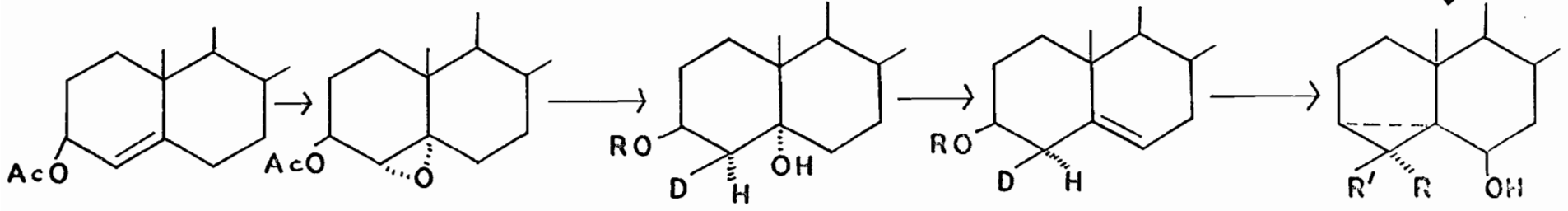


XVII

XIX R′ = R = H
XIXa R′ = D, R = H
XIXb R′ = H, R = D

XVIa R′ = D, R = H
XVIb R′ = H, R = D

XXIV R″ = R = H, R′ = D
XXIVa R″ = R′ = H, R = D
XXIVb R″ = OTs, R′ = D, R = H
XXIVc R″ = OTs, R′ = H, R = D



XXV

XXVI

XXVII R = H
XXVIIa R = OAc

XXVIII R = OAc
XXVIIIa R = H
XXIVb R = OTs

XXIX R′ = D, R = H
XXIXa R′ = H, R = D
XXIXb R′ = R = H

Its n.m.r. spectrum (Fig. 11) showed a one-proton peak at 2.56 p.p.m. (benzene), indicating that one deuterium atom had been taken up per molecule of diene. The ketal (XIXa, XIXb) was hydrolyzed with malonic acid in acetone to 4-deuteriocholest-5-en-3-one (XVIa, XVIb), which showed in the n.m.r. spectrum (Fig. 12) a signal at 2.80 p.p.m. (benzene) due to one proton at C-4. No exchange with solvent could have taken place at this stage, since any resulting non-deuterated cholest-5-en-3-one would have given (vide infra) non-deuterated 3α,5-cyclocholestan-6β-ol (39), which has a very characteristic n.m.r. spectrum in the 0.2 - 0.7 p.p.m. region (Fig. 9). Lithium aluminum hydride reduction of (XVIa, XVIb) and treatment of the resulting alcohol with p-toluenesulphonyl chloride in pyridine overnight yielded 4-deuteriocholesteryl tosylate (XXIVb, XXIVc). Its n.m.r. spectrum (Fig. 13) showed signals for the C-4 protons, equivalent to one proton, centered at 2.45 p.p.m. Since the n.m.r. spectrum was taken on a small amount of material which contained two epimers, the splitting constants could not be accurately evaluated (see Fig. 13). Solvolysis of (XXIVb, XXIVc) in buffered aqueous acetone gave 4-deuterio-3α,5-cyclocholestan-6β-ol (XXIX, XXIXa). Its n.m.r. spectrum (Fig. 14) showed two signals (approximately 0.5 protons each) in the region characteristic of cyclopropane protons. The signal at 0.23 p.p.m. (doublet, $J = 8.5$ c.p.s.) was identical to that of 4β-deuterio-3α,5-cyclocholestan-6β-ol (XXIX) (see Figs. 9 and 10). The low field signal centered at 0.48 p.p.m., showed up as a triplet. There is little doubt that this signal can be assigned to the 4β-hydrogen, and that this proton is spin-spin coupled with the hydrogen at C-3. In addition, some

long-range coupling similar to that observed in 3-methyl-3β,5-cyclocholestane (19), must also be present.

The results can only be interpreted by assuming that the deuteration at C-4 was non-specific and that an approximately 1:1 mixture of 4α- and 4β-deuterio-3β-ethoxy-3α-methoxycholest-5-ene (XIXa, XIXb) was obtained in the photo-induced reaction.

FIG. 7

The nuclear magnetic resonance spectrum of

cholesteryl tosylate

in benzene

FIG. 7

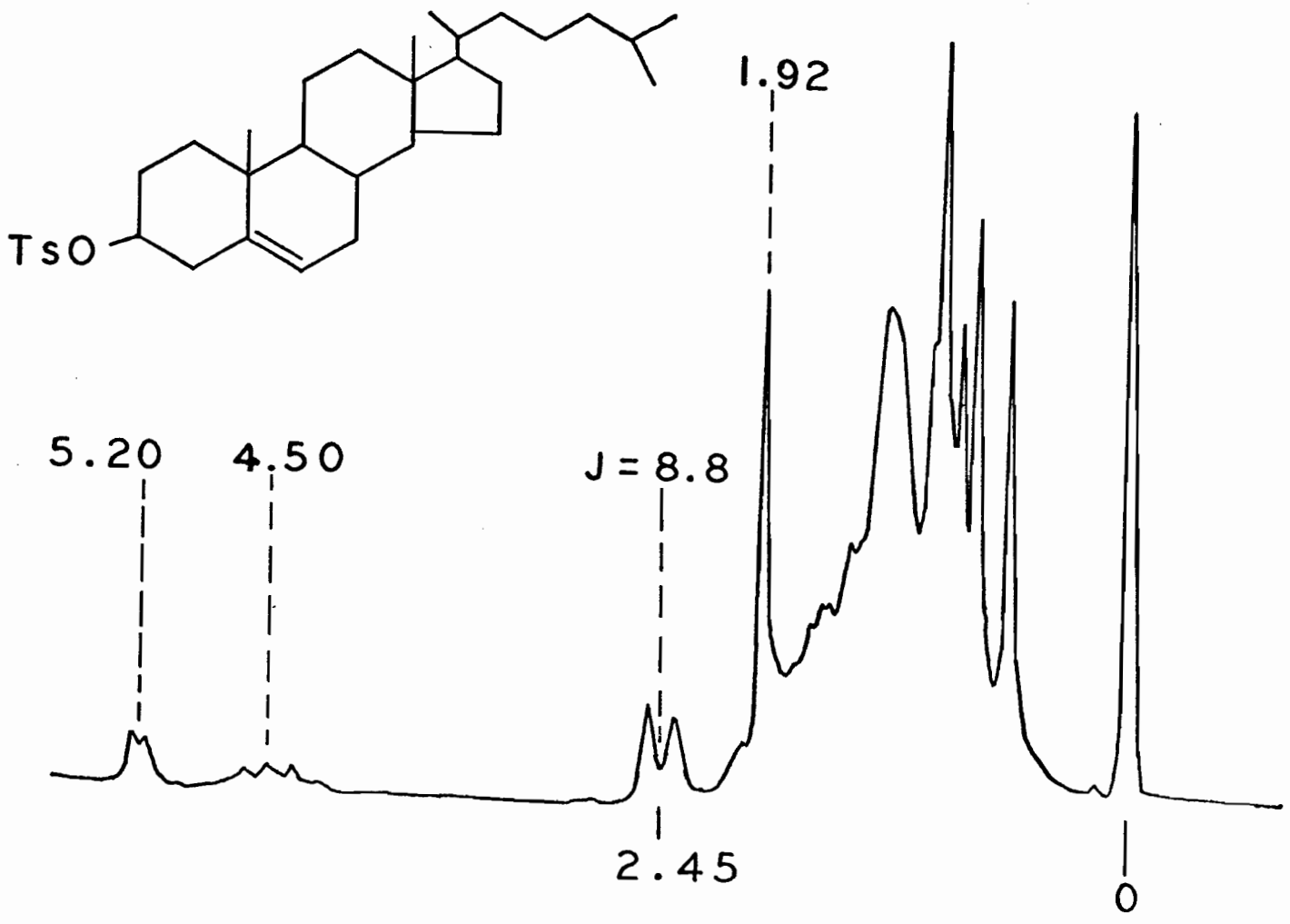


FIG. 8

The nuclear magnetic resonance spectrum of

4β-deuteriocholesteryl tosylate (XXIVb)

in benzene

FIG. 8

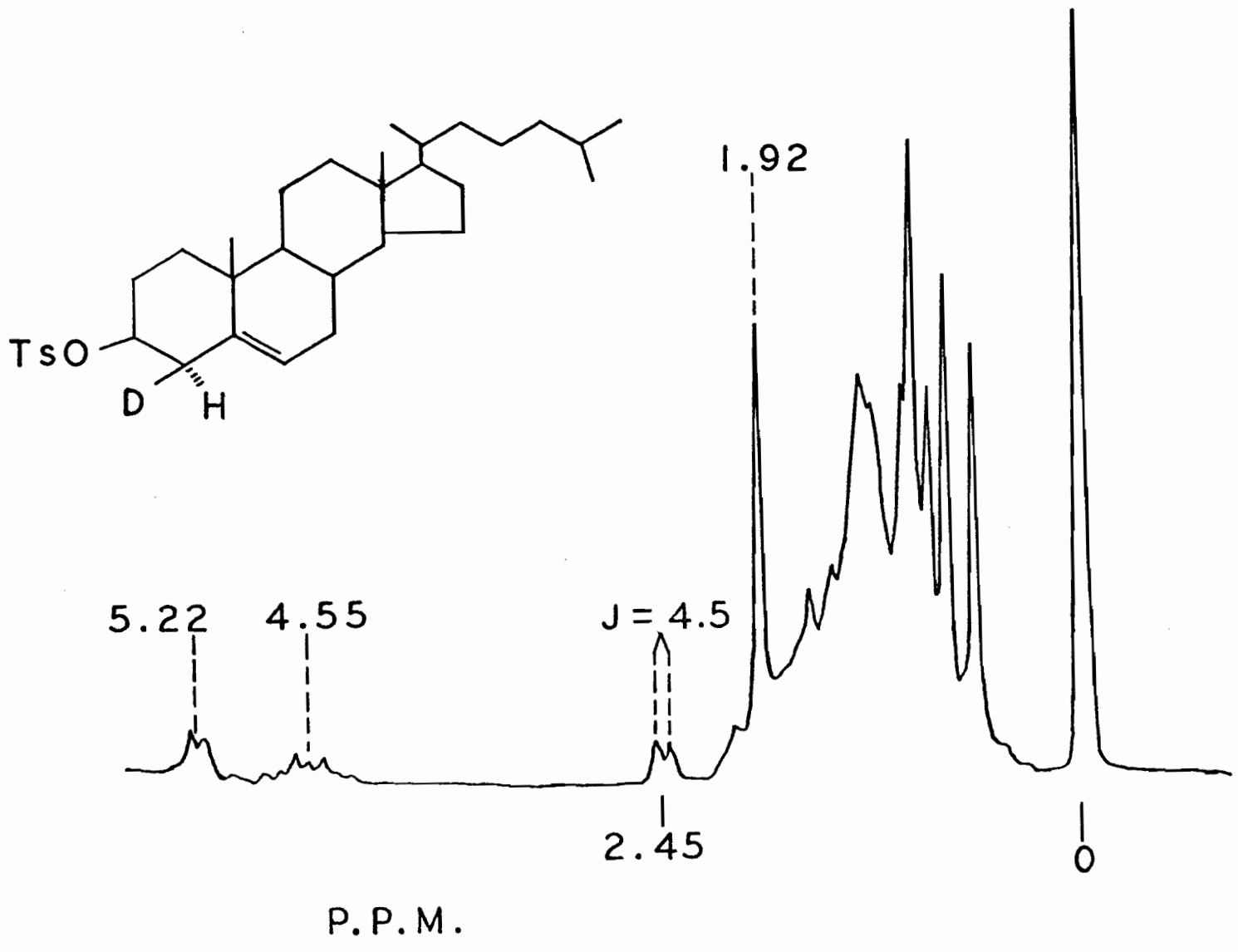


FIG. 9

The nuclear magnetic resonance spectrum of

3α,5-cyclo-5α-cholestan-6β-ol (XXIXb)

FIG. 9

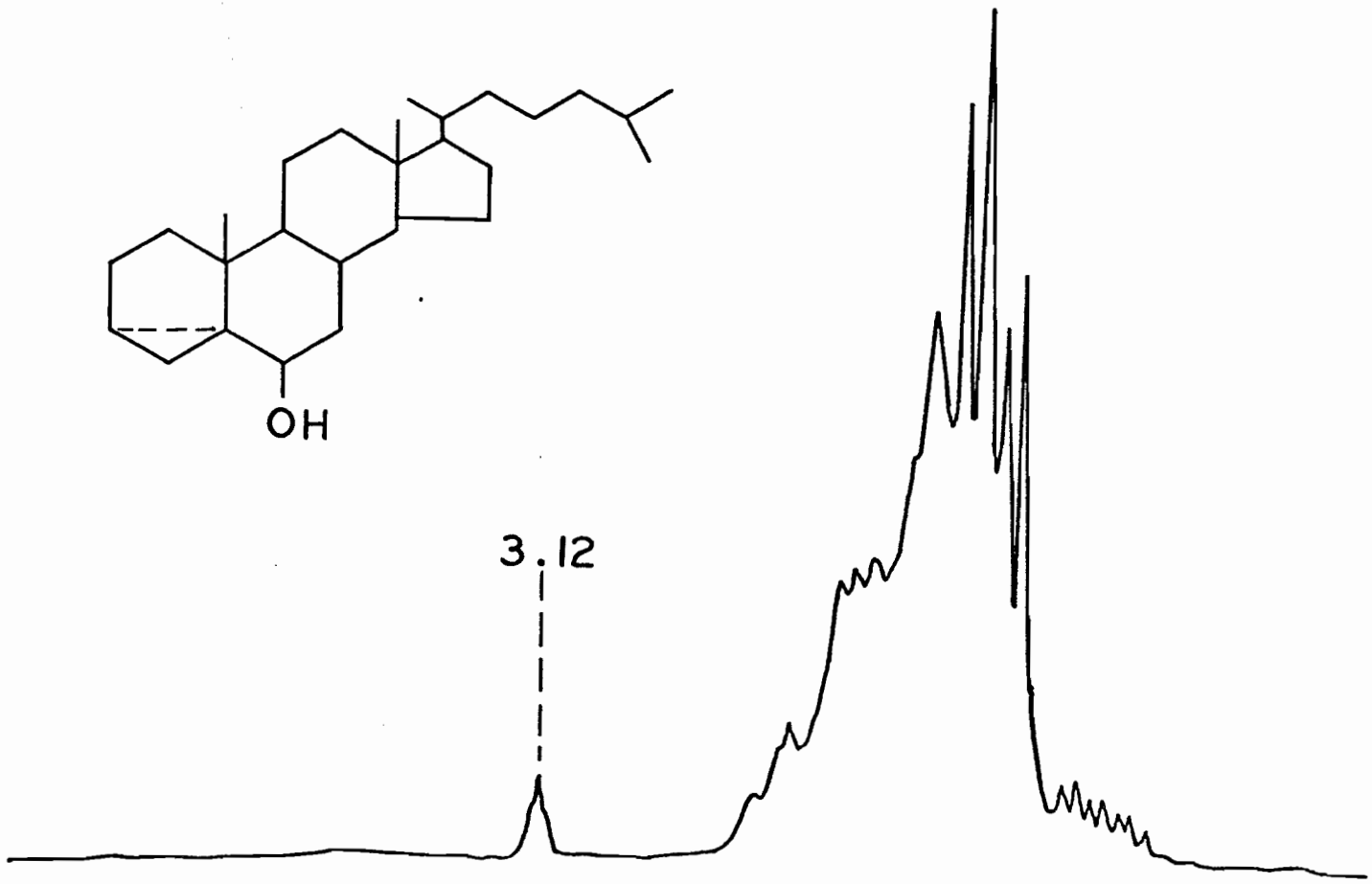


FIG. 10

The nuclear magnetic resonance spectrum of 4β-deuterio-3α,5-cyclo-5α-cholestan-6β-ol (XXIX)

FIG. 10

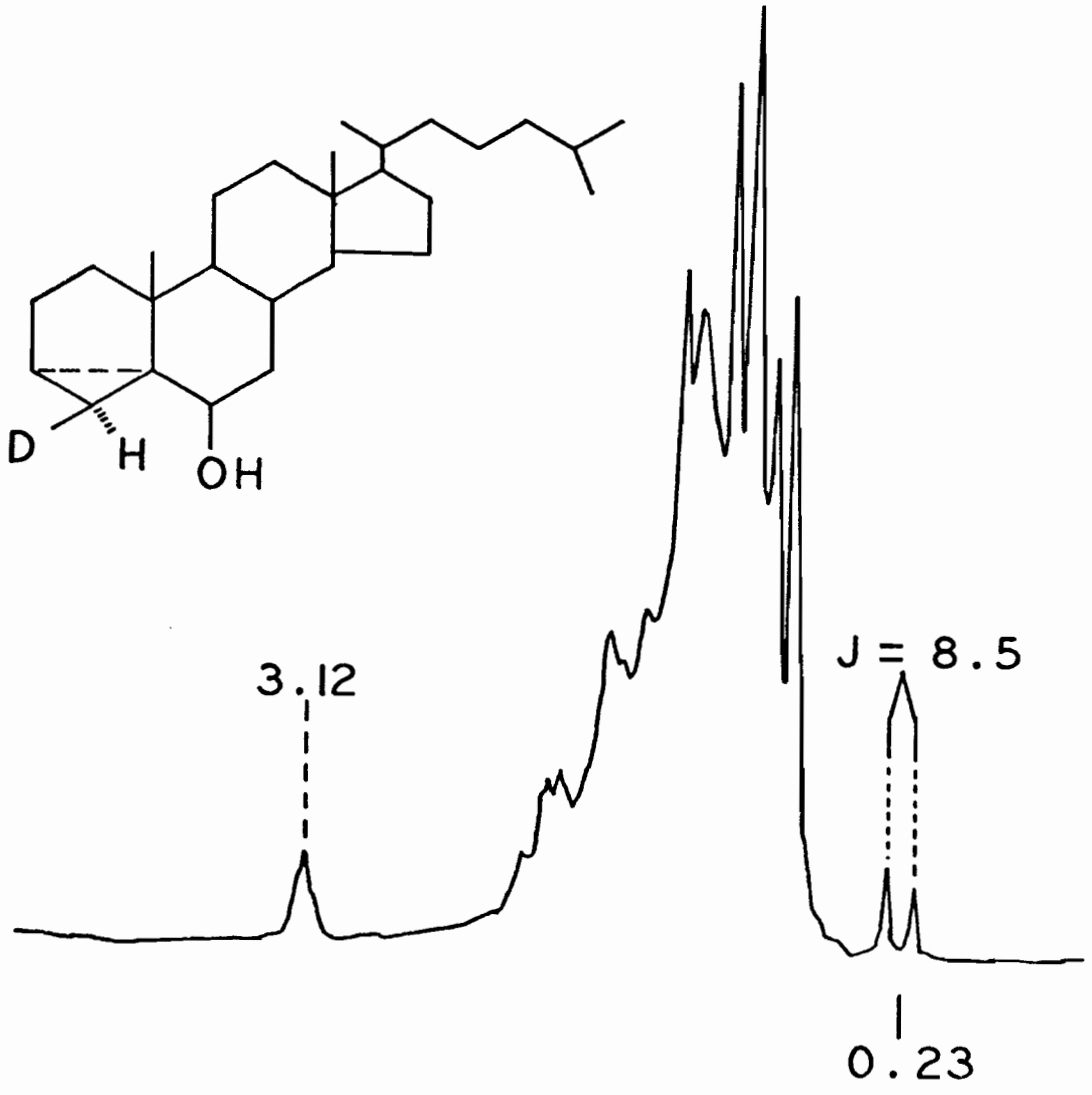


FIG. 11

The nuclear magnetic resonance spectrum of 4-deuterio-3β-ethoxy-3α-methoxycholest-5-ene (XIXa, XIXb) in benzene

FIG. 11

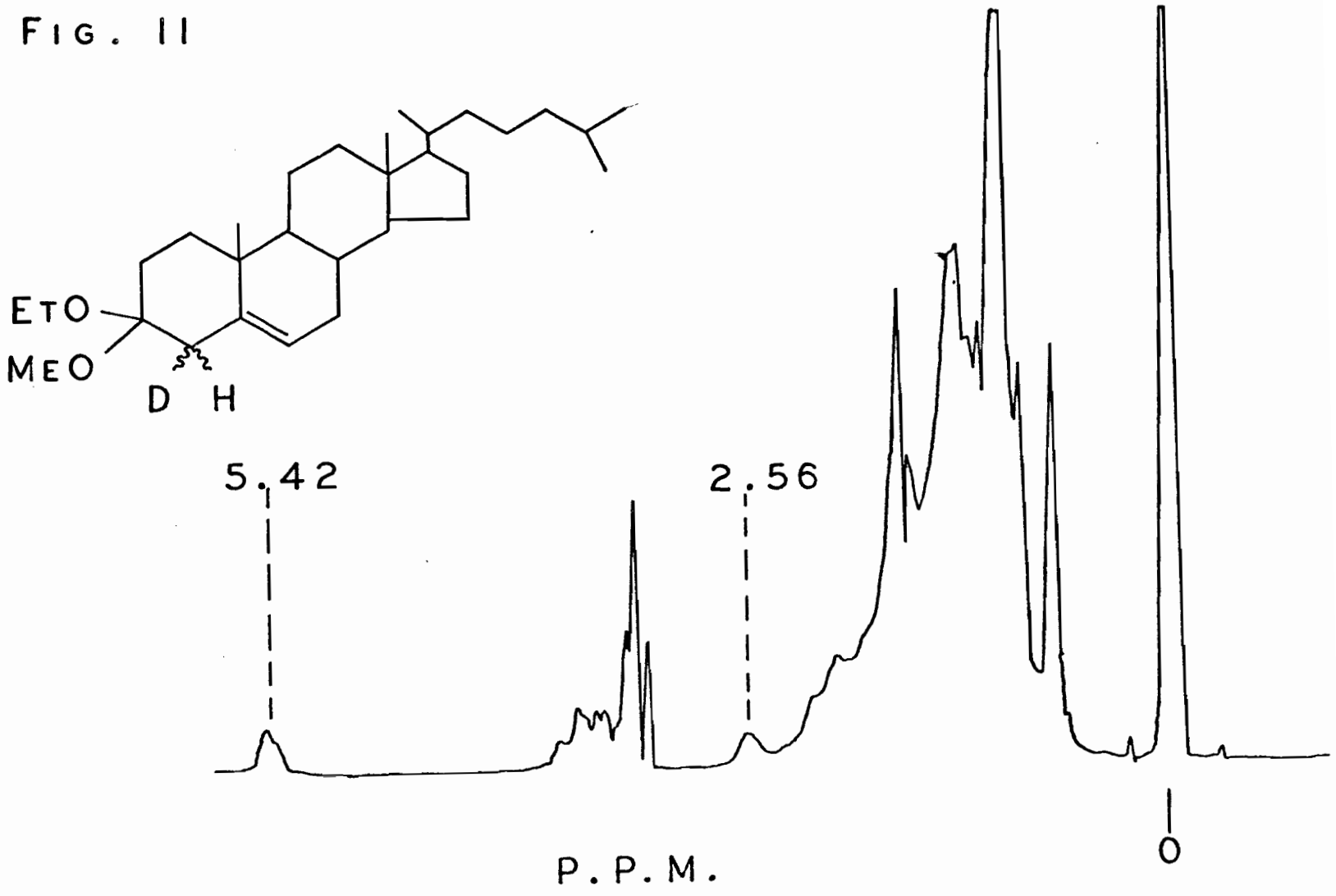


FIG. 12

The nuclear magnetic resonance spectrum of
4-deuteriocholest-5-en-3-one (XVIa, XVIb)
in benzene

FIG. 12

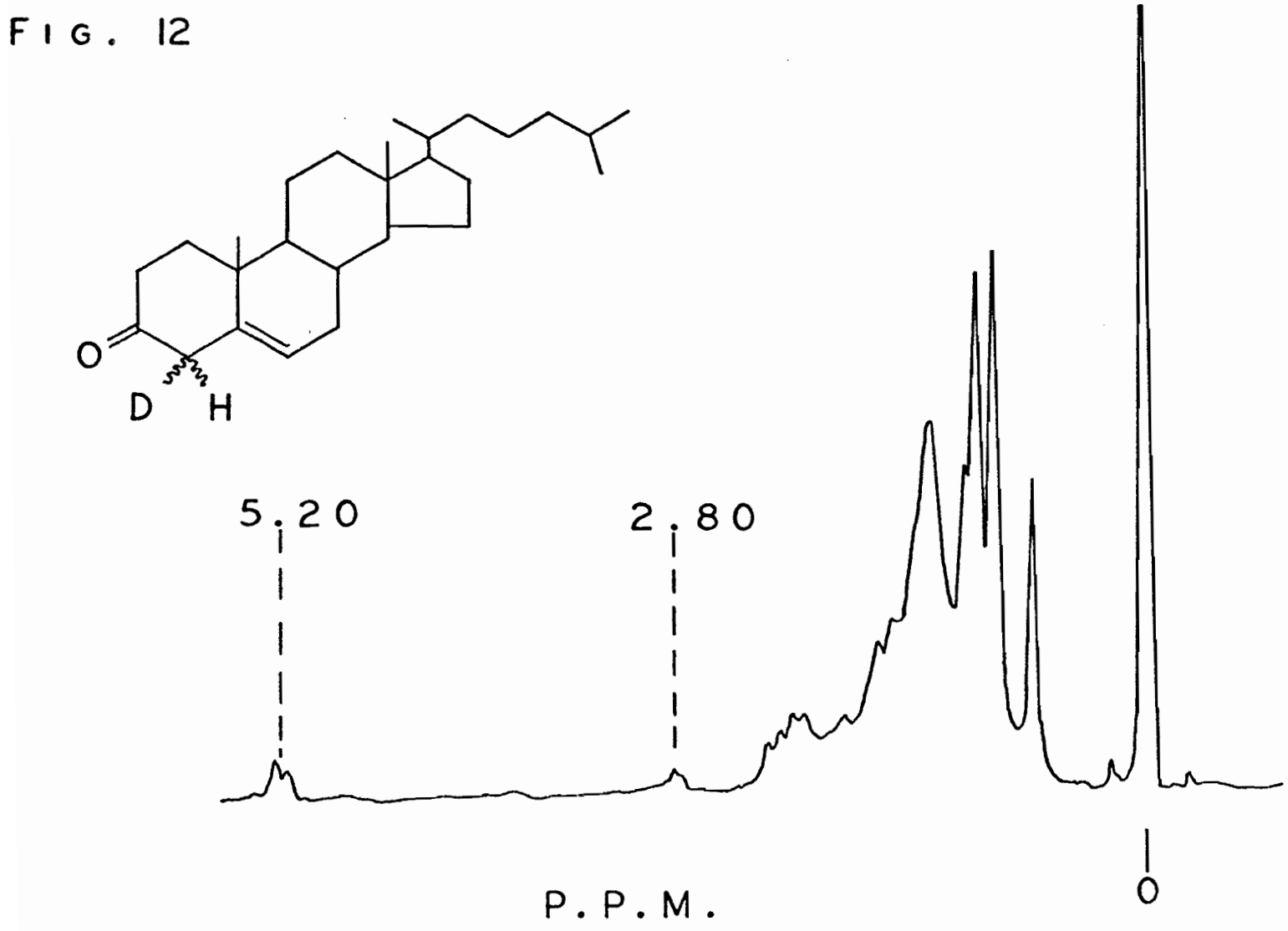


FIG. 13

The nuclear magnetic resonance spectrum of a 1:1 mixture of 4α- and 4β-deuteriocholesteryl tosylate (XXIVc, XXIVb) in benzene

FIG. 13

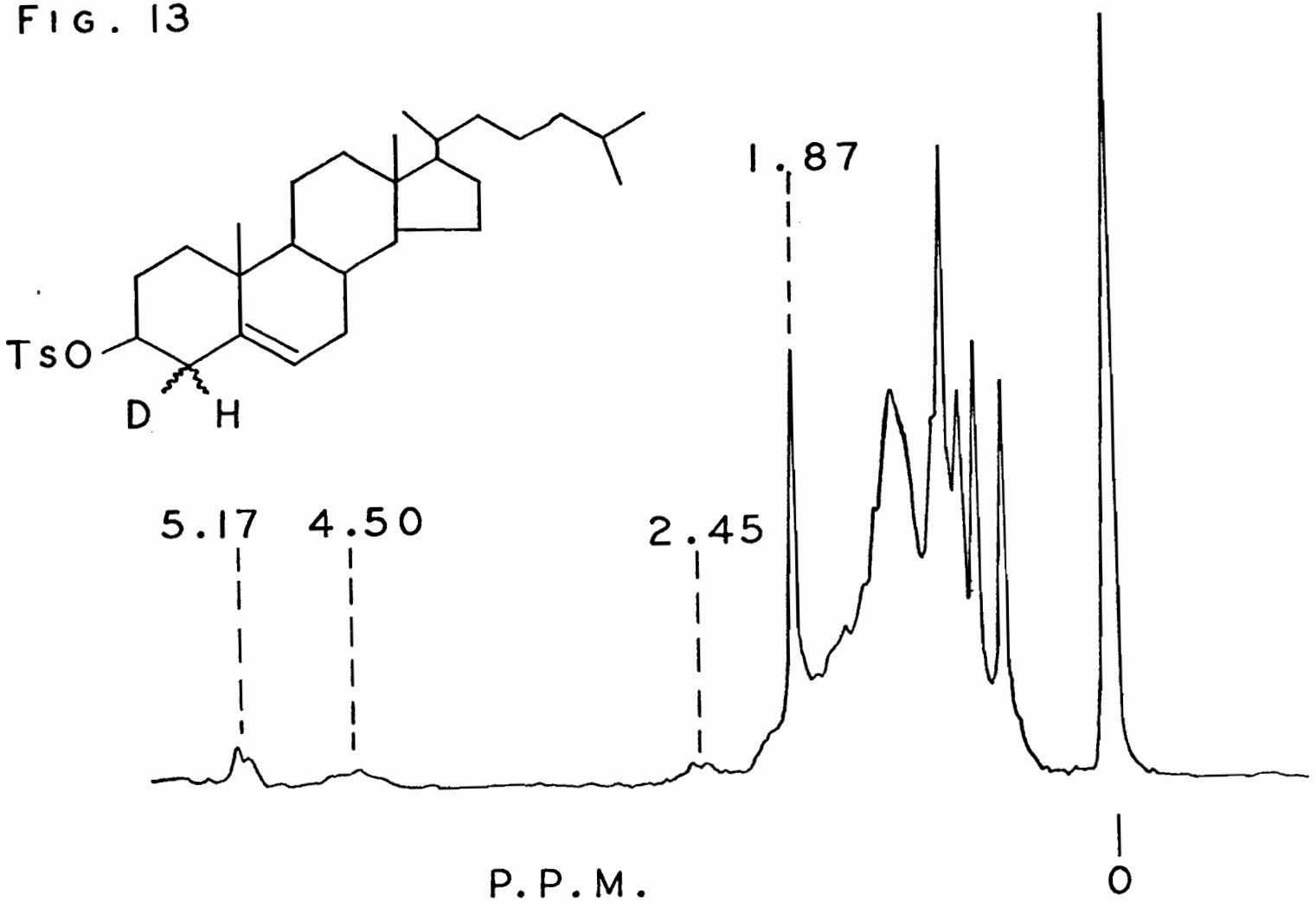
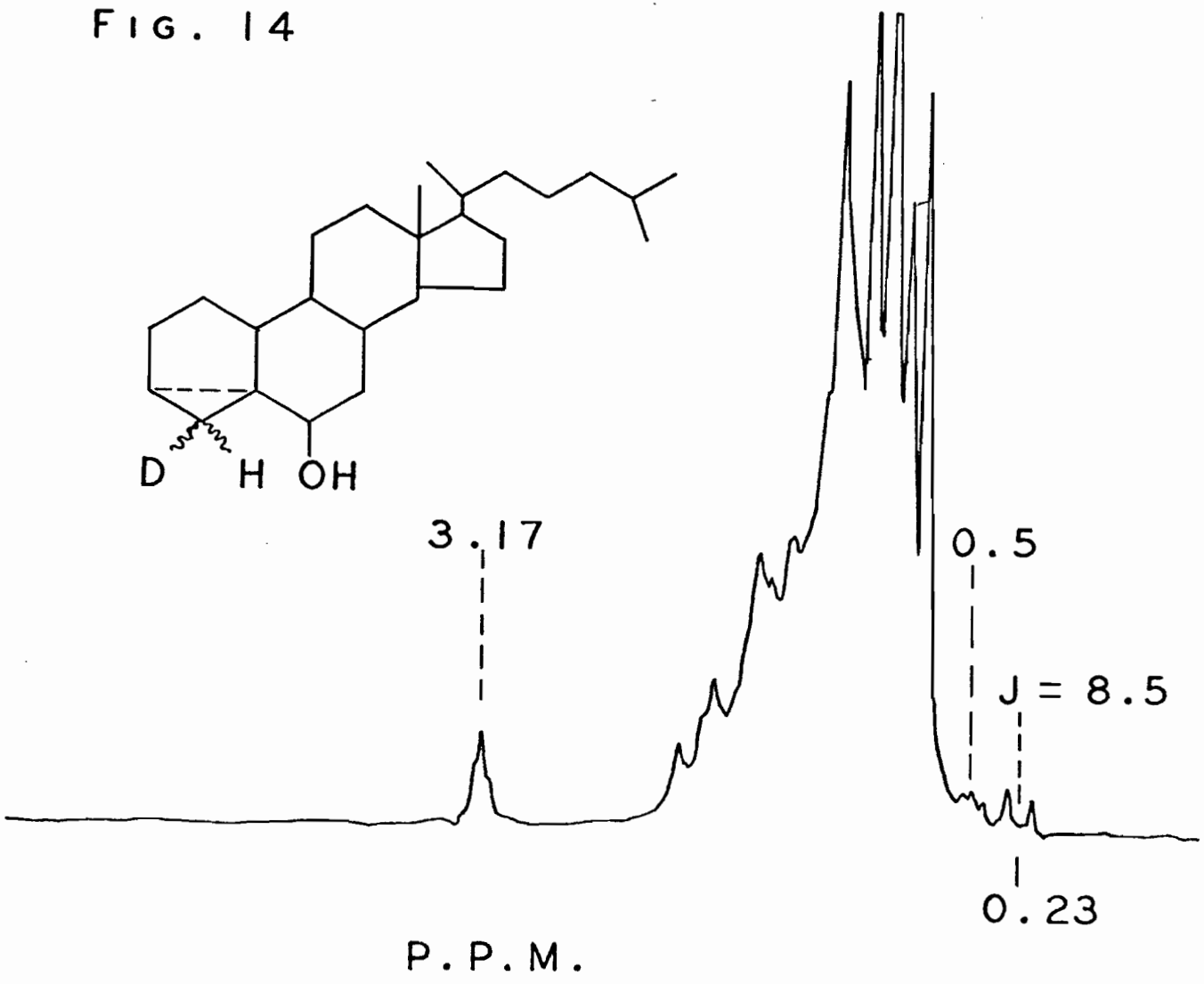


FIG. 14

The nuclear magnetic resonance spectrum of a 1:1 mixture of 4β- and 4α-deuterio-3α,5-cyclo-5α-cholestan-6β-ol (XXIX, XXIXa)

FIG. 14



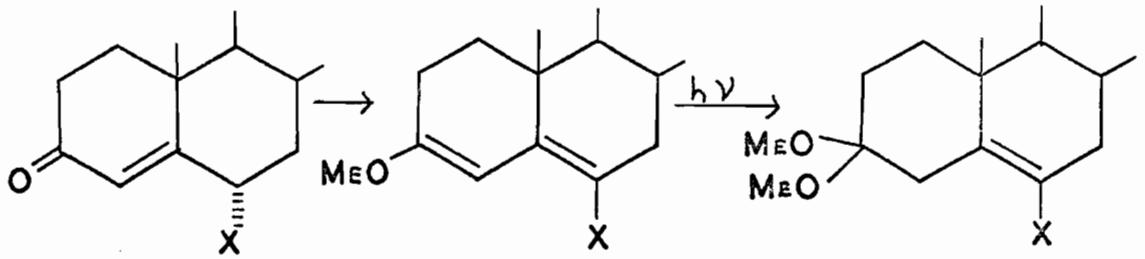
CHAPTER III

The Photolysis of 3-Methoxy-6-substituted Cholesta-3,5-dienes in Methanol

By a selection of suitable electron-donating and withdrawing substituents at the C-6 position of 3-methoxycholesta-3,5-diene (XVII), it was hoped to gain some further insight into the photochemical reaction of 3-methoxycholesta-3,5-diene in methanol.

The methyl, fluoro, nitro and methoxy groups were chosen as substituents. The 3-methoxy-6-methyl (XXXI), 6-fluoro-3-methoxy (XXXIa), and 3-methoxy-6-nitrocholesta-3,5-dienes (XXXIb) were prepared from 6α-methyl (XXX) (43,44), 6α-fluoro (XXXa) (45), and 6α-nitrocholest-4-en-3-ones (XXXb) (46) respectively by reaction with trimethylorthoformate. Reaction of 6β-methoxycholest-4-en-3-one (47) with trimethylorthoformate did not give pure 3,6-dimethoxycholesta-3,5-diene and similar treatment of cholestan-3,6-dione gave oily material (see experimental).

When 3-methoxy-6-methylcholesta-3,5-diene (XXXI) (characterized by its u.v., infrared (Fig. 15A), and n.m.r. (Fig. 16) spectra) was irradiated in methanol, a new compound (XXXII), $C_{30}H_{52}O_2$, m.p. 118-119° was obtained in 75% yield by direct crystallization from the reaction mixture. Its n.m.r. spectrum (Fig. 17) showed the presence of two methoxy groups at 3.12_5 and 3.23 p.p.m. and a methyl group attached to a double bond (1.66 p.p.m.). The infrared spectrum (Fig. 15B) showed



XX	X=H	XVII	X = H	XVIII	X = H
XXX	$X=CH_3$	XXXI	$X=CH_3$	XXXII	$X=CH_3$
XXXa	X=F	XXXIa	X=F	XXXIIa	X=F
XXXb	$X=NO_2$	XXXIb	$X=NO_2$		

absorption in the ether region practically identical with that of 3,3-dimethoxycholest-5-ene (XVIII) and further supported the presence of methoxy groups. Hydrolysis of XXXII with malonic acid in aqueous acetone for three days gave a mixture of 6-methylcholest-5-en-3-one (ν 1720 cm^{-1}) and 6-methylcholest-4-en-3-one (ν 1685 cm^{-1}) as indicated by an infrared spectrum of the reaction product. Evaporation of the filtrate from the photolysis reaction product (XXXII) gave an oil whose infrared spectrum showed the presence of 3,3-dimethoxy-6-methylcholest-5-ene (XXXII), 6-methylcholest-5-en-3-one, and 6-methylcholest-4-en-3-one. It seems that in this photolysis, hydrolysis products account for only 5 - 15% of the total products, compared to 40% for the 6-unsubstituted methoxy diene XVIII (see Chapter I).

Similarly, 6-fluoro-3-methoxycholesta-3,5-diene (XXXIa) (characterized by its u.v., infrared (Fig. 18A), and n.m.r. (Fig. 19) spectra) was photolyzed in methanol and a new compound (XXXIIa), $C_{29}H_{49}O_2F$, m.p. 104-104.5°, was obtained in 85% yield by direct crystallization. Its n.m.r. spectrum (Fig. 20) shows signals at 3.07 p.p.m. and at 3.16 p.p.m. corresponding to the two methoxy groups. The infrared spectrum (Fig. 18B) showed strong absorption between 1000 and 1200 cm^{-1} due to the C-O and C-F stretching frequencies (48). Evaporation of a solution of XXXIIa in carbon tetrachloride on the steam bath (24) resulted in hydrolysis of XXXIIa. The infrared spectrum of the oil showed the presence of an α,β-unsaturated ketone (ν 1695 cm^{-1}) and a saturated ketone (ν 1725 cm^{-1}). These peaks no doubt arise from the hydrolysis products of 3,3-dimethoxy-6-fluorocholest-5-ene (XXXIIa), i.e. 6-fluorocholest-5-en-3-one and 6-fluorocholest-4-en-3-one.

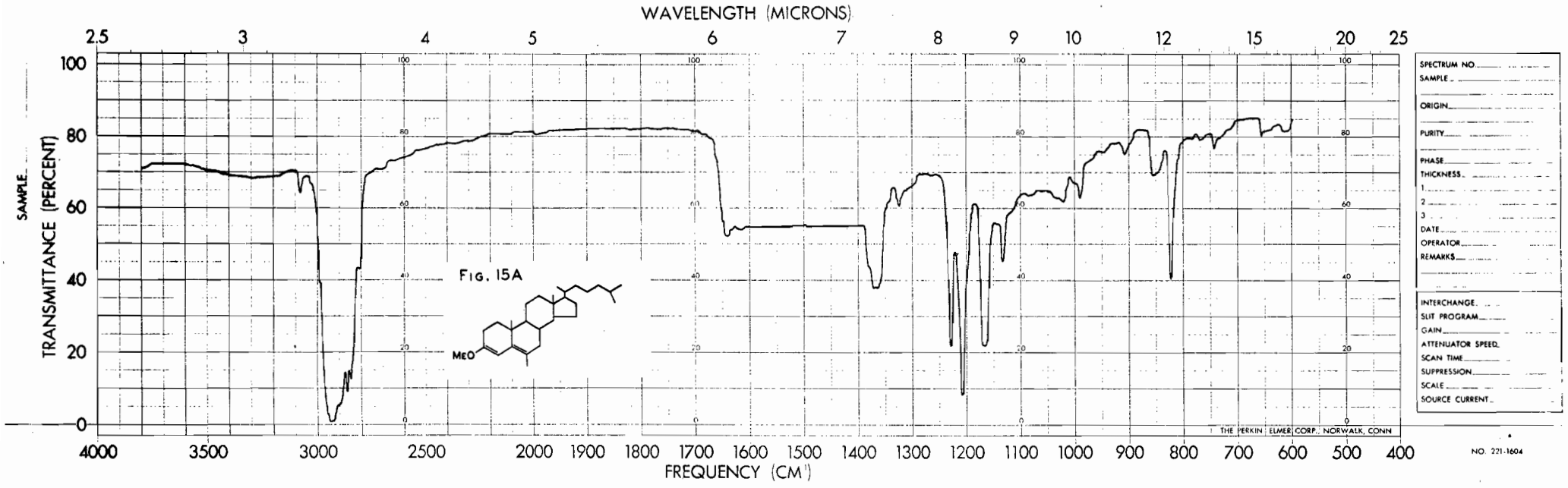
Evaporation of the mother liquors from XXXIIa gave an oil whose infrared spectrum showed the presence of 3,3-dimethoxy-6-fluorocholest-5-ene (XXXIIa), a saturated ketone (ν 1725 cm^{-1}) and an α,β-unsaturated ketone (ν 1695 cm^{-1}). Thus in this photolysis reaction, hydrolysis has accounted for only 5 - 10% of the total reaction products.

FIG. 15

The infrared spectra of

A. 3-methoxy-6-methylcholesta-3,5-diene (XXXI)

B. 3,3-dimethoxy-6-methylcholest-5-ene (XXXII)


WAVELENGTH (MICRONS)
2.5 3 4 5 6 7 8 9 10 12 15 20 25
TRANSMITTANCE (PERCENT)
100 80 60 40 20 0
SAMPLE
4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400
FREQUENCY (CM⁻¹)
FIG. 15A
MeO
SPECTRUM NO.
SAMPLE
ORIGIN
PURITY
PHASE
THICKNESS
1
2
3
DATE
OPERATOR
REMARKS
INTERCHANGE
SLIT PROGRAM
GAIN
ATTENUATOR SPEED
SCAN TIME
SUPPRESSION
SCALE
SOURCE CURRENT
THE PERKIN-ELMER CORP., NORWALK, CONN
NO. 221-1604

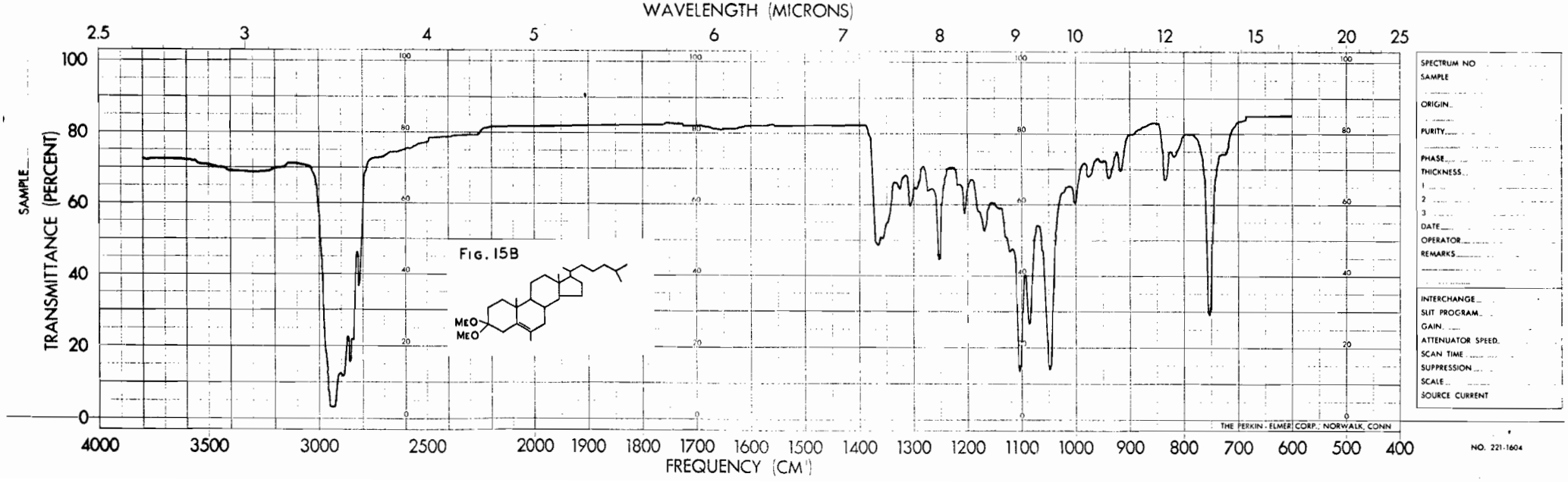

WAVELENGTH (MICRONS)
2.5 3 4 5 6 7 8 9 10 12 15 20 25
TRANSMITTANCE (PERCENT)
100 80 60 40 20 0
SAMPLE
4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400
FREQUENCY (CM⁻¹)
FIG. 15B
MeO
MeO
SPECTRUM NO
SAMPLE
ORIGIN
PURITY
PHASE
THICKNESS
1
2
3
DATE
OPERATOR
REMARKS
INTERCHANGE
SLIT PROGRAM
GAIN
ATTENUATOR SPEED
SCAN TIME
SUPPRESSION
SCALE
SOURCE CURRENT
THE PERKIN-ELMER CORP., NORWALK, CONN
NO. 221-1604

FIG. 16

The nuclear magnetic resonance spectrum of

3-methoxy-6-methylcholesta-3,5-diene (XXXI)

FIG. 16

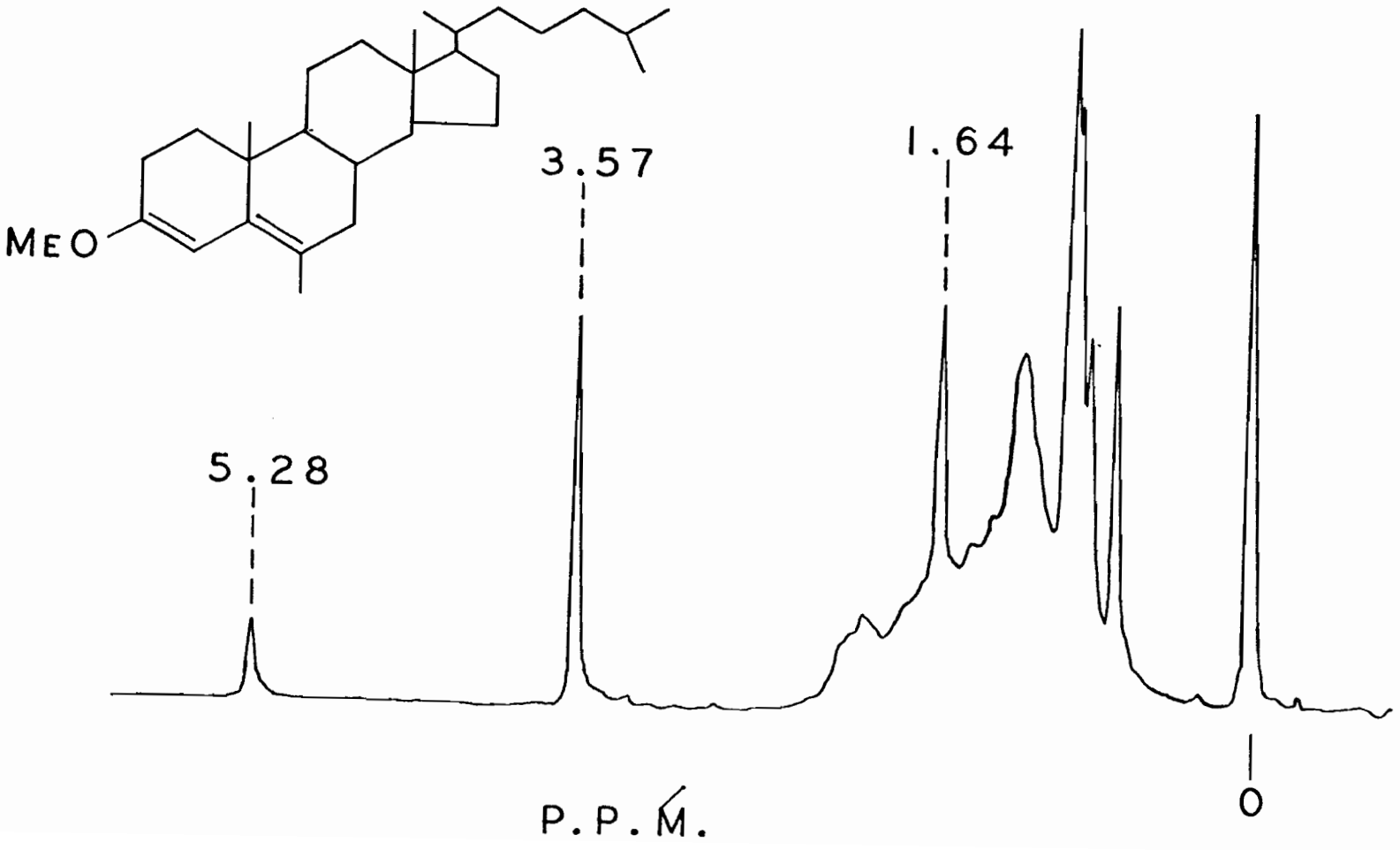


FIG. 17

The nuclear magnetic resonance spectrum of 3,3-dimethoxy-6-methylcholest-5-ene (XXXII)

FIG. 17

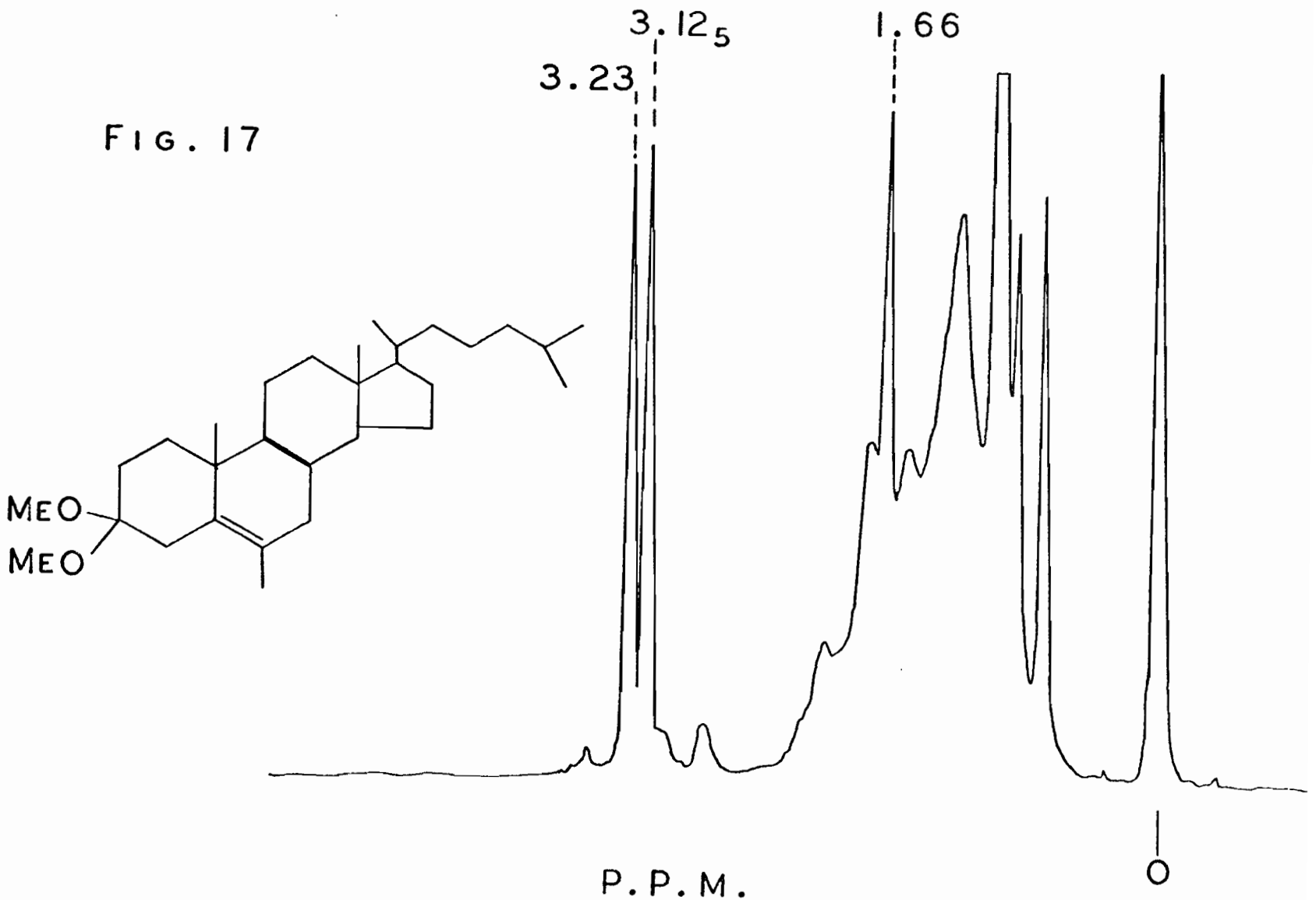


FIG. 18

The infrared spectra of

A. 6-fluoro-3-methoxycholesta-3,5-diene (XXXIa)

B. 3,3-dimethoxy-6-fluorocholest-5-ene (XXXIIa)

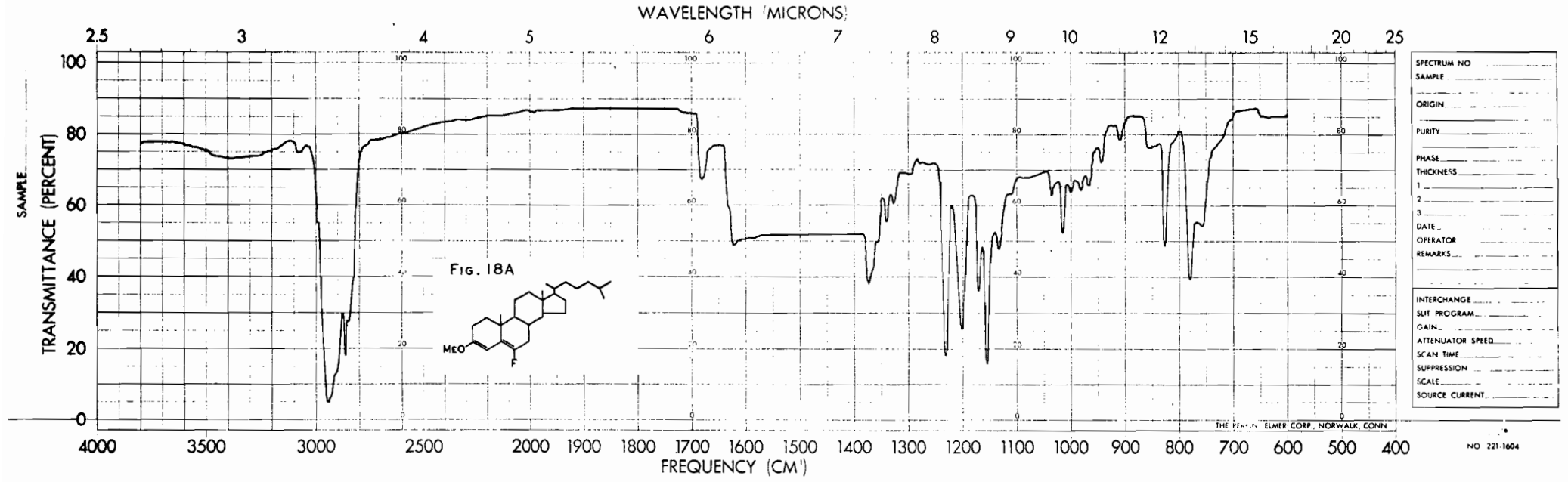


FIG. 18A

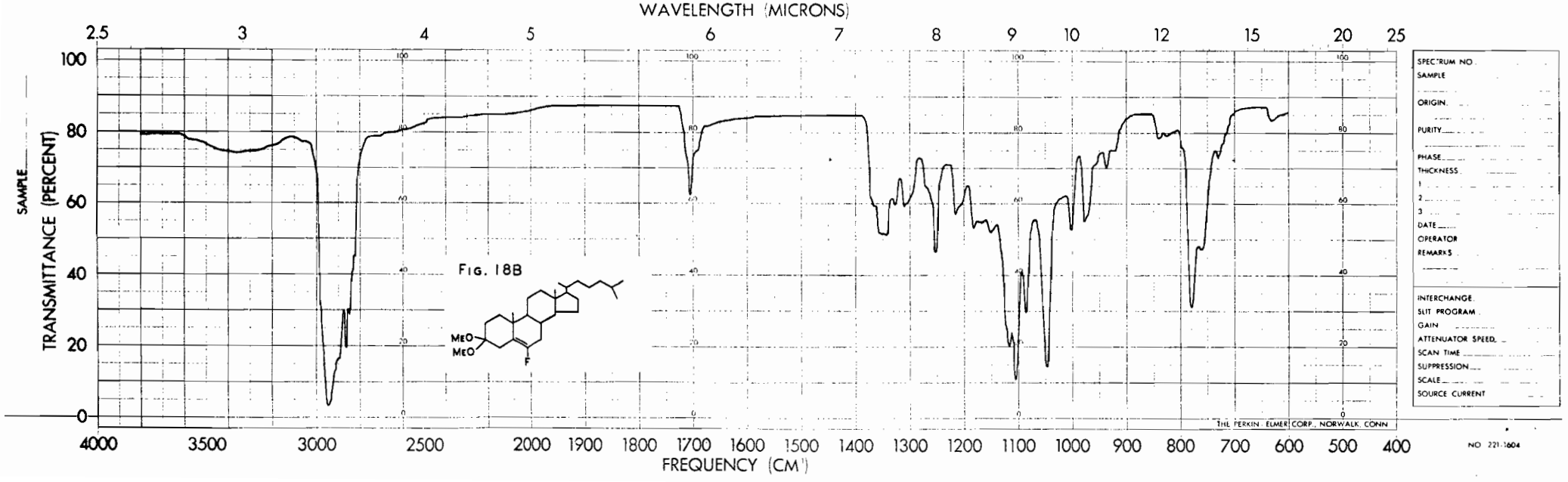


FIG. 18B

FIG. 19

The nuclear magnetic resonance spectrum of

6-fluoro-3-methoxycholesta-3,5-diene

(XXXIa)

FIG. 19

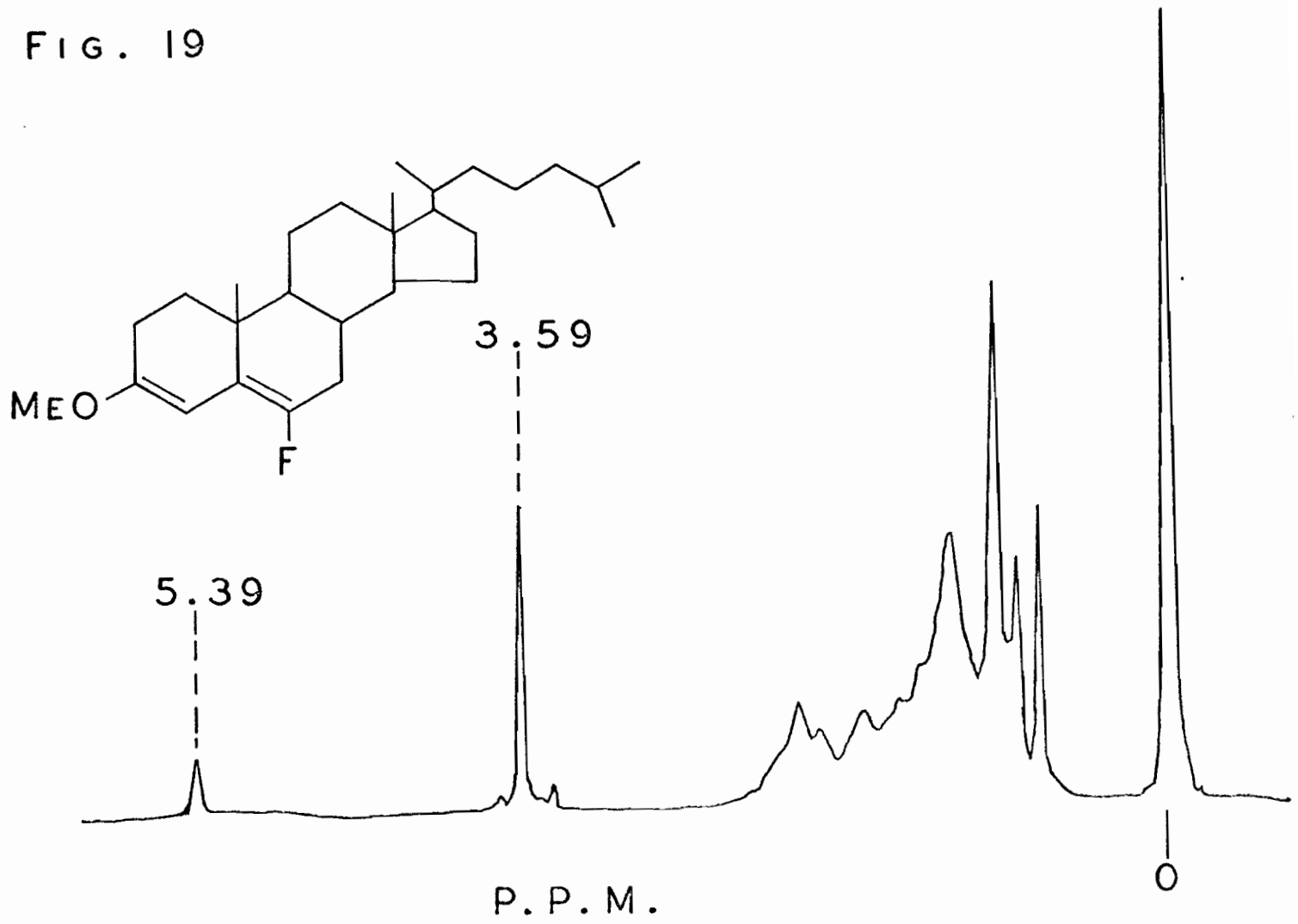
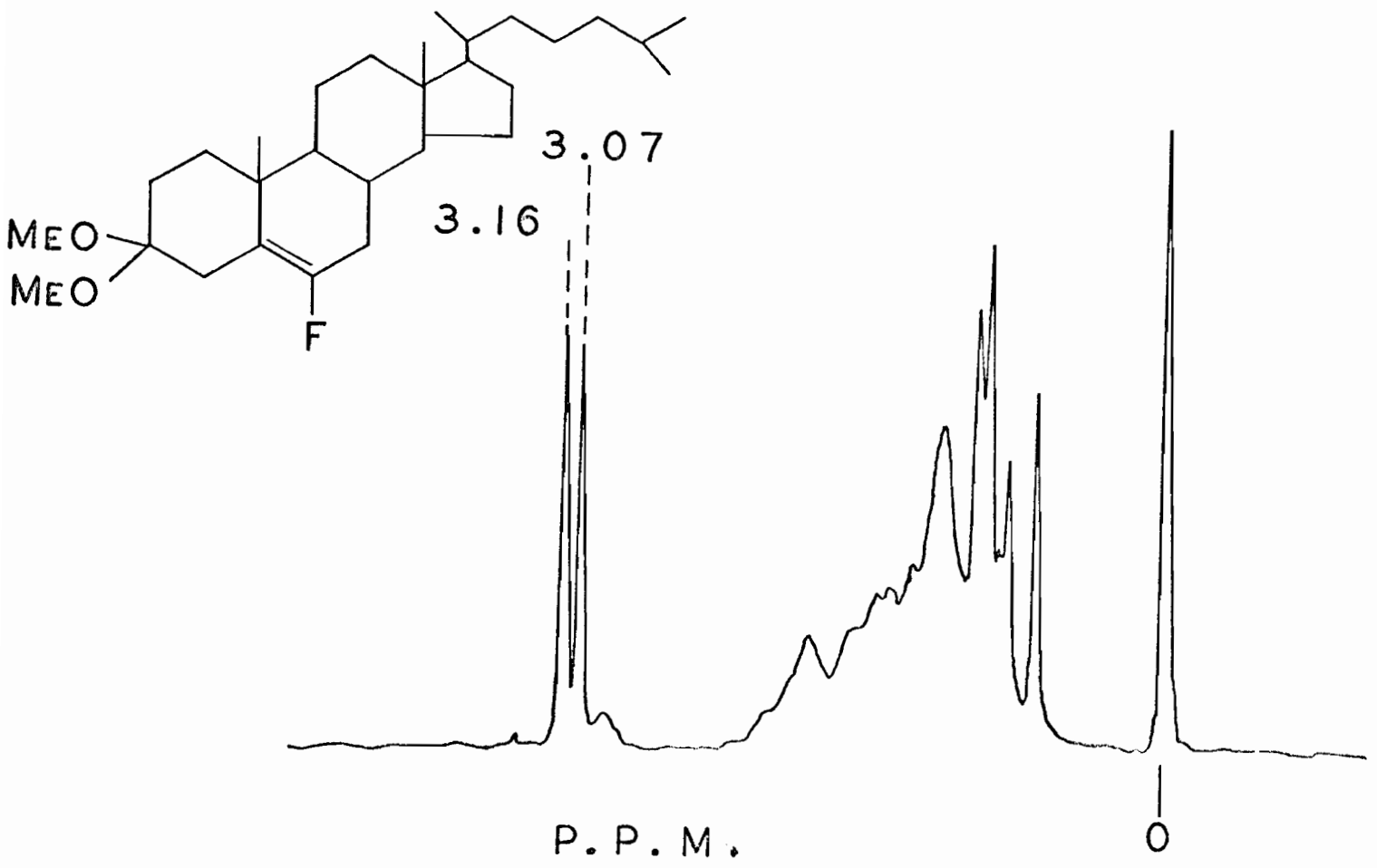


FIG. 20

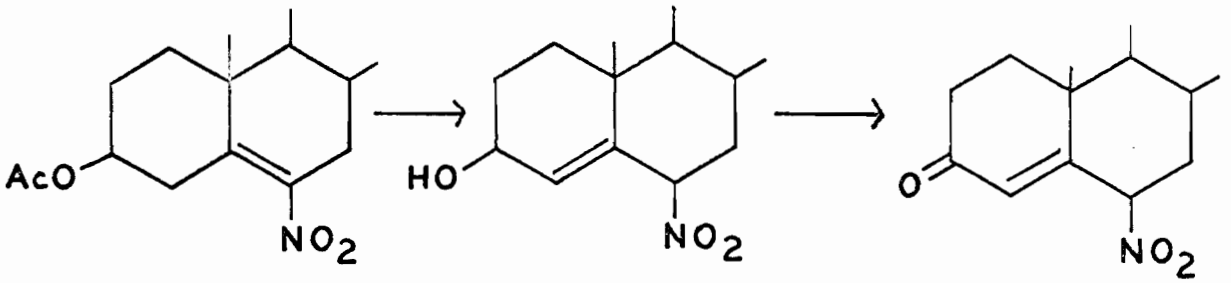
The nuclear magnetic resonance spectrum of

3,3-dimethoxy-6-fluorocholest-5-ene (XXXIIa)

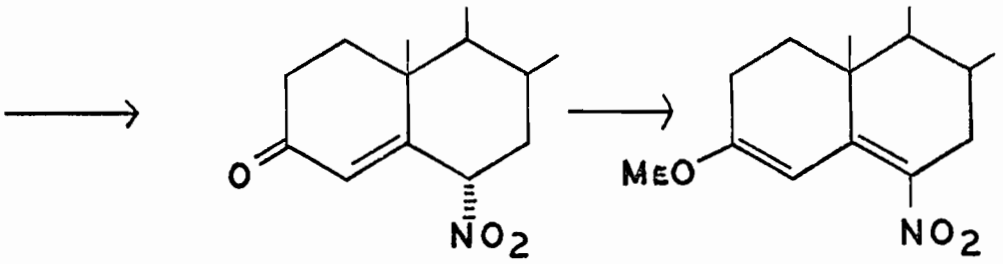
FIG. 20



In order to synthesize 3-methoxy-6-nitrocholesta-3,5-diene (XXXIb), the reaction sequence of Bowers et al. (46) was followed. The product of nitration of cholesteryl acetate, 3β-acetoxy-6-nitrocholest-5-ene (XXXIII) (49), was saponified and the solution acidified with acetic acid to give 6β-nitrocholest-4-en-3β-ol (XXXIV).



XXXIII XXXIV XXXV



XXXIb XXXI

Its n.m.r. spectrum (Fig. 21) gave signals at 5.72_5 p.p.m., 4.50 p.p.m., 4.04 p.p.m., and 3.31 p.p.m. due to the olefinic, the C-6α, the C-3α, and the hydroxy protons respectively. The position of the hydroxy proton was proved unequivocally by exchanging the proton with heavy water and examining the effect of this procedure on the n.m.r. spectrum. Its I.R. spectrum (Fig. 25A) showed the presence of the nitro and hydroxy groups.

Oxidation of XXXIV with Jones reagent (50,51,52) gave 6β-nitrocholest-4-en-3-one (XXXV). Its n.m.r. spectrum (Fig. 22) showed absorption bands at 6.02 p.p.m. and 4.83 p.p.m. corresponding to the C-4 olefinic and the C-6α protons respectively. Its I.R. spectrum (Fig. 26A) showed the presence of a nitro group at 1540 cm^{-1} and an α,β-unsaturated ketone at 1670 cm^{-1}. Isomerization of XXXV with base gave 6α-nitrocholest-4-en-3-one (XXXb). Its n.m.r. spectrum (Fig. 23) gave signals at 5.38 p.p.m. (doublet, J = 1.8 c.p.s.) and at 5.14 p.p.m. (multiplet) corresponding to the C-4 olefinic and C-6β protons respectively. The C-4 proton which appears as a doublet is apparently coupled with the C-6β hydrogen (53). The infrared spectrum (Fig. 26B) of XXXb showed the typical nitro absorption at 1543 cm^{-1} and an α,β-unsaturated ketone peak at 1672 cm^{-1}. Treatment of XXXb with trimethylorthoformate gave 3-methoxy-6-nitrocholesta-3,5-diene (XXXIb). Its u.v., infrared (Fig. 25B), and n.m.r. (Fig. 24) spectra were fully consistent with the assigned structure.

A methanolic solution of 3-methoxy-6-nitrocholesta-3,5-diene (XXXIb) was irradiated until the absorption maximum at 233 mμ decreased to 5% of its original absorption (10 minutes). Evaporation of the solvent gave an oil. The n.m.r. spectrum of the photolyzate showed only broad absorption bands and indicated the formation of a mixture.

FIG. 21

The nuclear magnetic resonance spectrum of

6β-nitrocholest-4-en-3β-ol (XXXIV)

FIG. 21

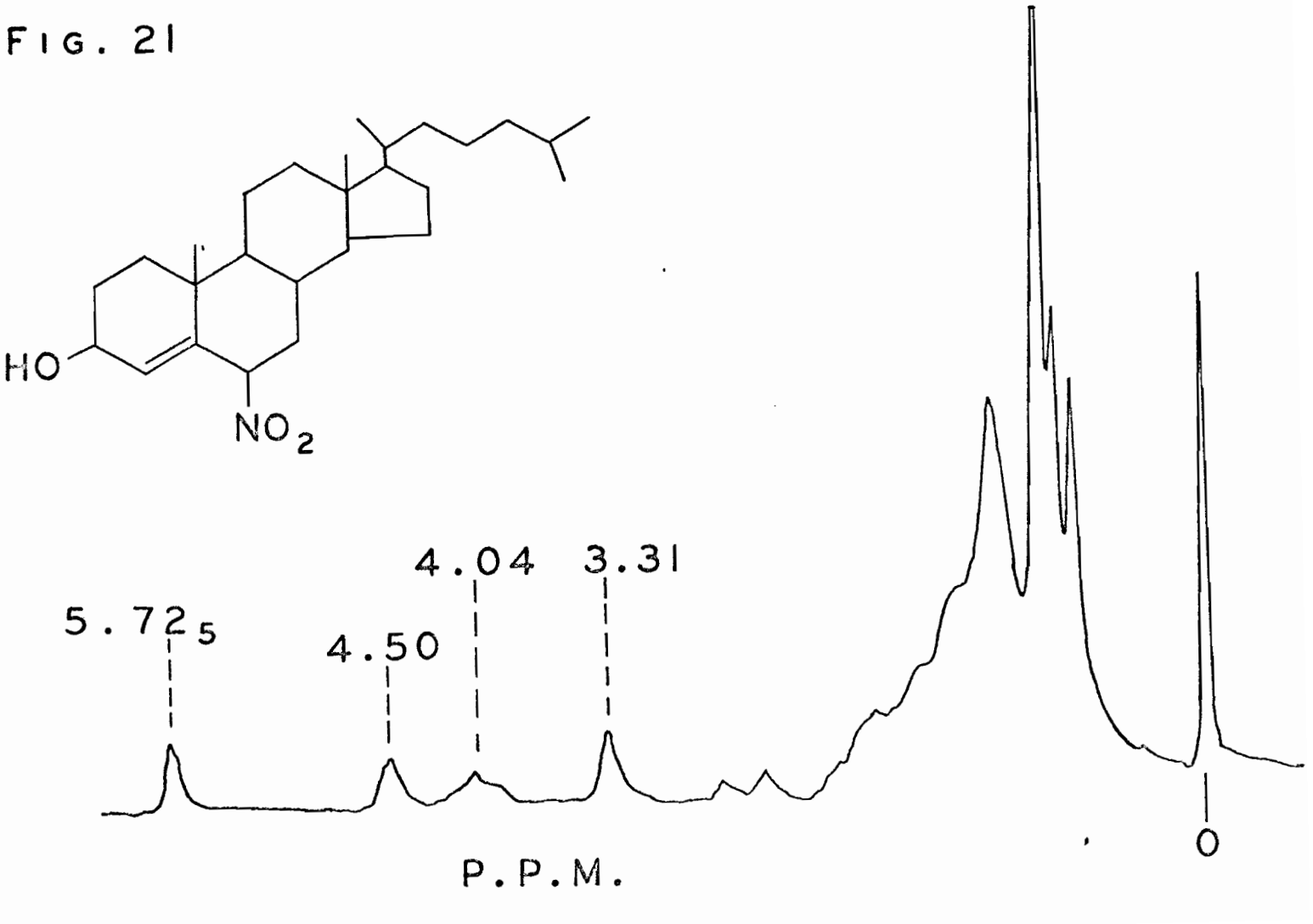


FIG. 22

The nuclear magnetic resonance spectrum of

6β-nitrocholest-4-en-3-one (XXXV)

FIG. 22

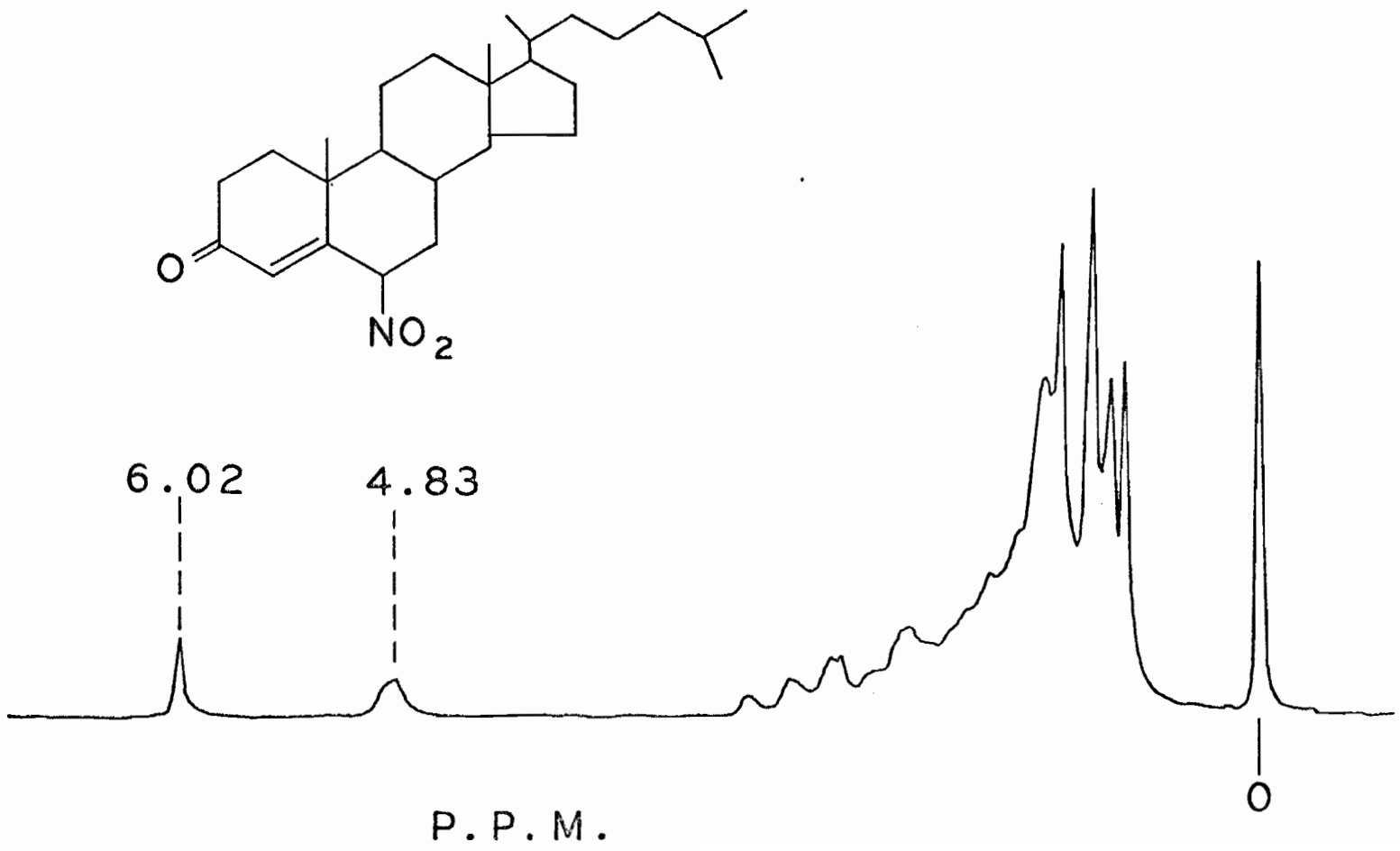


FIG. 23

The nuclear magnetic resonance spectrum of

6α-nitrocholest-4-en-3-one (XXXb)

FIG. 23

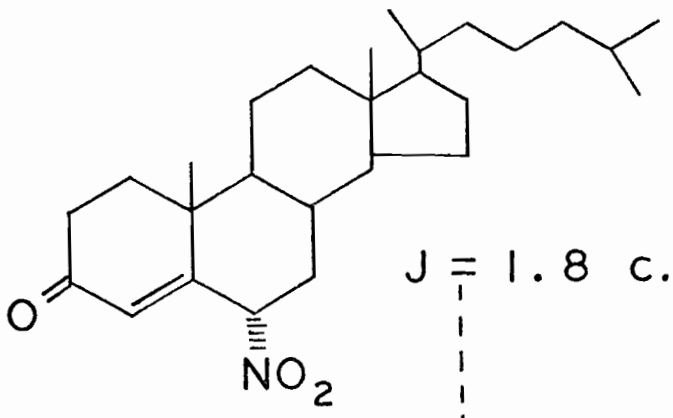


FIG. 24

The nuclear magnetic resonance spectrum of 3-methoxy-6-nitrocholesta-3,5-diene (XXXIb)

FIG. 24

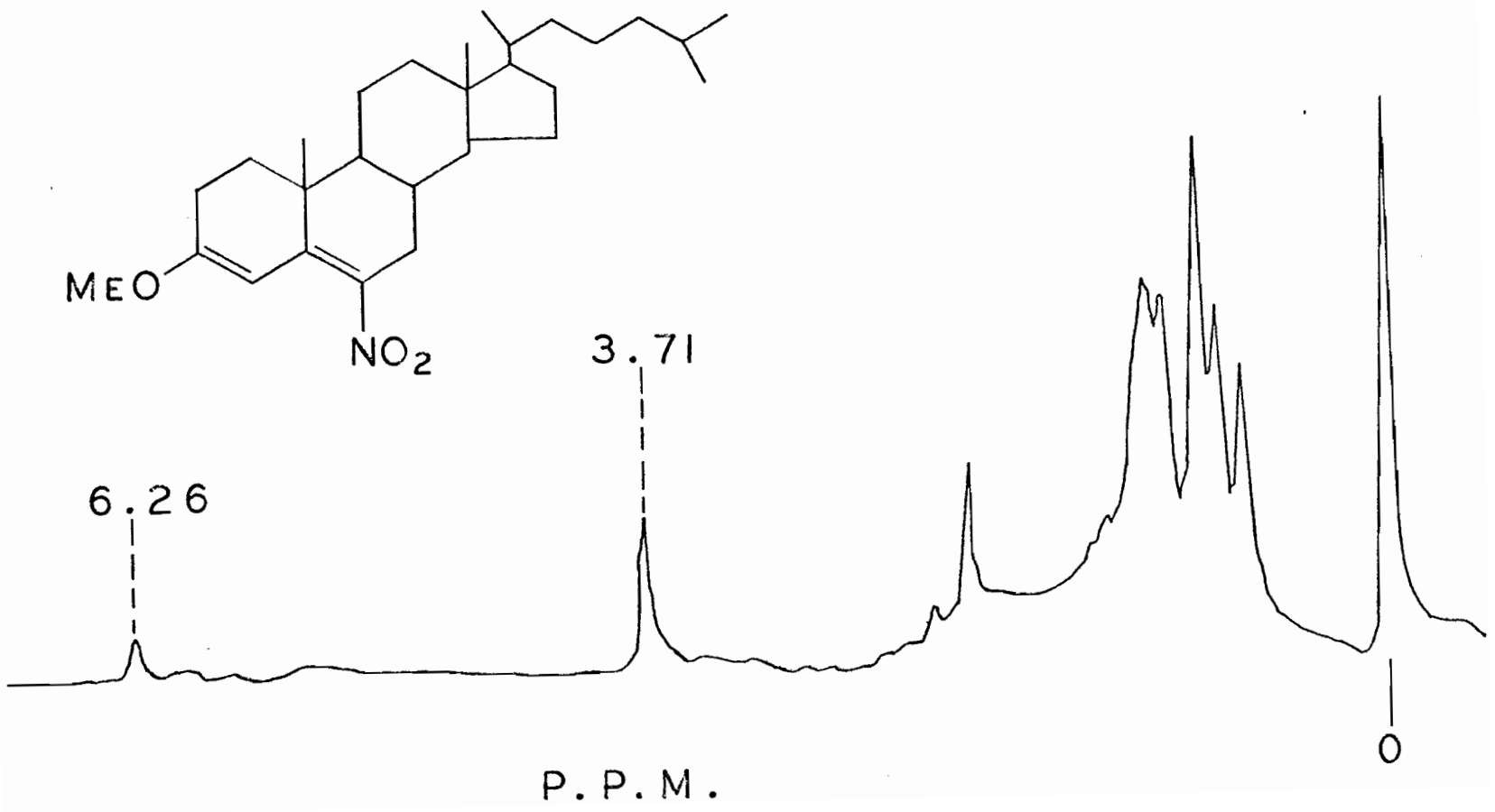
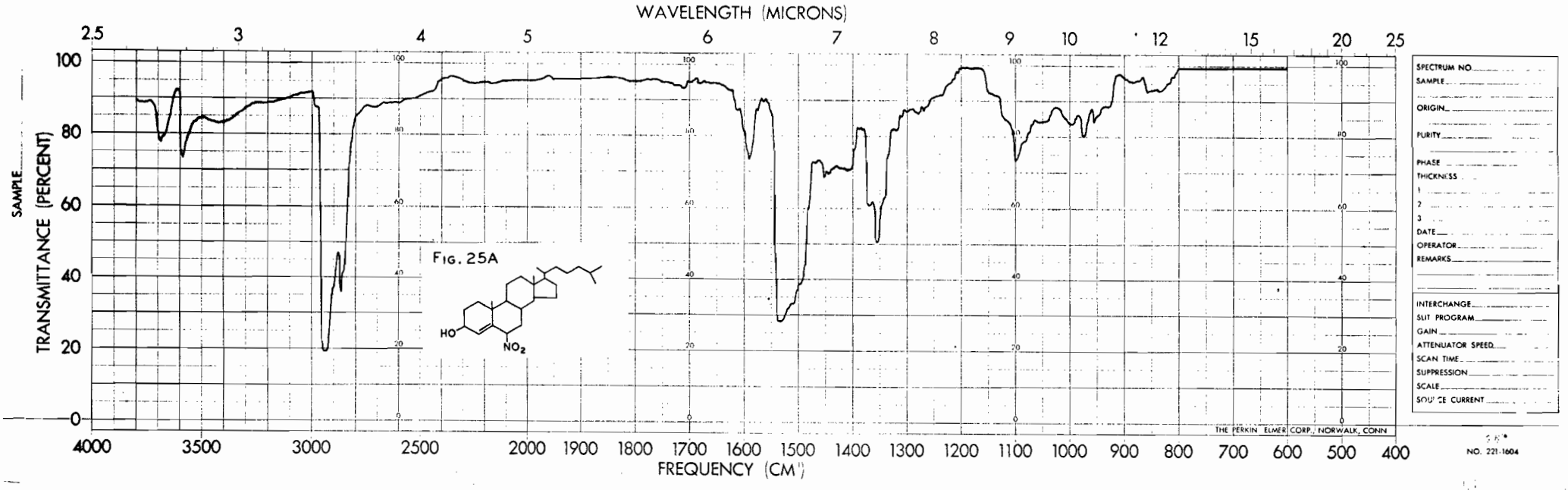


FIG. 25

The infrared spectra of

A. 6β-nitrocholest-4-en-3β-ol (XXXIV) in chloroform

B. 3-methoxy-6-nitrocholesta-3,5-diene (XXXIb) in chloroform;
(dotted line) in carbon disulphide


WAVELENGTH (MICRONS)
2.5 3 4 5 6 7 8 9 10 12 15 20 25
TRANSMITTANCE (PERCENT)
100 80 60 40 20 0
SAMPLE
4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400
FREQUENCY (CM⁻¹)
FIG. 25A
HO
NO2
SPECTRUM NO.
SAMPLE
ORIGIN
PURITY
PHASE
THICKNESS
1
2
3
DATE
OPERATOR
REMARKS
INTERCHANGE
SLIT PROGRAM
GAIN
ATTENUATOR SPEED
SCAN TIME
SUPPRESSION
SCALE
SOURCE CURRENT
THE PERKIN ELMER CORP., NORWALK, CONN
NO. 221-1604

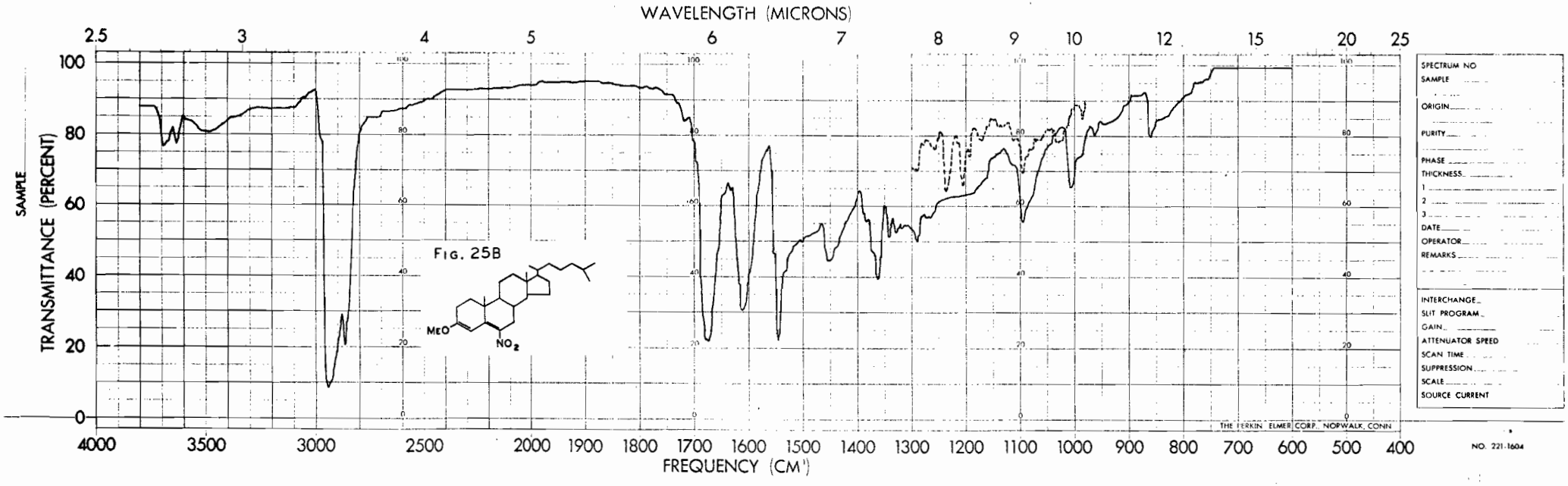
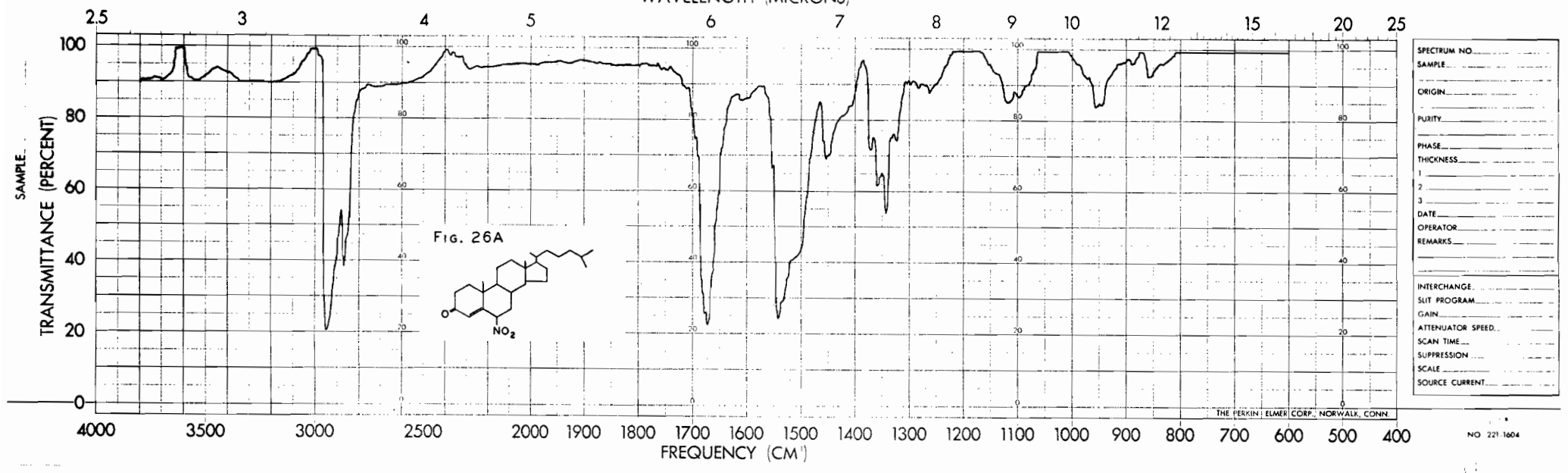

WAVELENGTH (MICRONS)
2.5 3 4 5 6 7 8 9 10 12 15 20 25
TRANSMITTANCE (PERCENT)
100 80 60 40 20 0
SAMPLE
4000 3500 3000 2500 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400
FREQUENCY (CM⁻¹)
FIG. 25B
MeO
NO2
SPECTRUM NO.
SAMPLE
ORIGIN
PURITY
PHASE
THICKNESS
1
2
3
DATE
OPERATOR
REMARKS
INTERCHANGE
SLIT PROGRAM
GAIN
ATTENUATOR SPEED
SCAN TIME
SUPPRESSION
SCALE
SOURCE CURRENT
THE PERKIN ELMER CORP., NORWALK, CONN
NO. 221-1604

FIG. 26

The infrared spectra of

A. 6β-nitrocholest-4-en-3-one (XXXV) in chloroform

B. 6α-nitrocholest-4-en-3-one (XXXb) in chloroform


WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
20
25
TRANSMITTANCE (PERCENT)
100
80
60
40
20
0
SAMPLE
4000
3500
3000
2500
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
FREQUENCY (CM⁻¹)
FIG. 26A
O
NO2
SPECTRUM NO.
SAMPLE
ORIGIN
PURITY
PHASE
THICKNESS
1
2
3
DATE
OPERATOR
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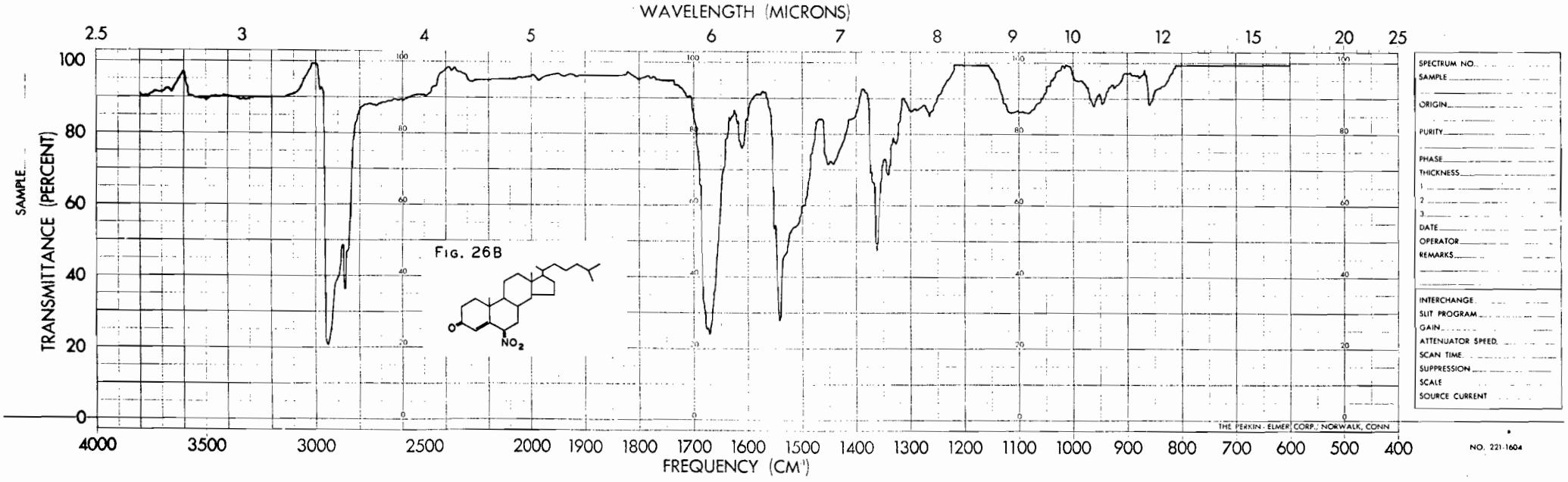
THE PERKIN-ELMER CORP., NORWALK, CONN.
NO. 221-1604


WAVELENGTH (MICRONS)
2.5
3
4
5
6
7
8
9
10
12
15
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25
TRANSMITTANCE (PERCENT)
100
80
60
40
20
0
SAMPLE
4000
3500
3000
2500
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
FREQUENCY (CM⁻¹)
FIG. 26B
O
NO2
SPECTRUM NO.
SAMPLE
ORIGIN
PURITY
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1
2
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CHAPTER IV

The Photolysis of Some 3-Substituted-cholesta-3,5-dienes

As shown in previous chapters, the photolyses of 3-alkoxy-cholesta-3,5-dienes proceeded to give primarily one product, but irradiation of 3-methylcholesta-3,5-diene in ethanol gave three products (19). It was thus hoped that irradiation of other 3-substituted cholesta-3,5-dienes would give useful information about the effect of different substituents on the photolysis of cholesta-3,5-dienes (54).

A 0.2% ethanolic solution of 3-chlorocholesta-3,5-diene (XXXVI) (55,56) was irradiated for four hours until the absorption maximum of the solution had dropped to less than 5% of the original absorption. When the solvent was evaporated and a n.m.r. spectrum of the crude photolysis mixture taken, the presence of cyclopropyl protons was detected at 0.25 p.p.m. and at 0.5 p.p.m. Chromatography on silica gel or aluminum oxide gave in the hexane fraction about 50% of oily crystals from which was obtained by successive crystallizations 3 - 4% of impure XXXVII, m.p. 111-113°. Since no pure product could be obtained by a combination of column chromatography and crystallizations, the crude photolyzate was purified by thin-layer chromatography (TLC). TLC revealed the presence of eighteen products, seven of them in trace amounts.

Fractions 1-6 (designated according to decreasing R_f values) yielded non-chlorinated hydrocarbons, except for fraction 3, m.p. 67-71°,

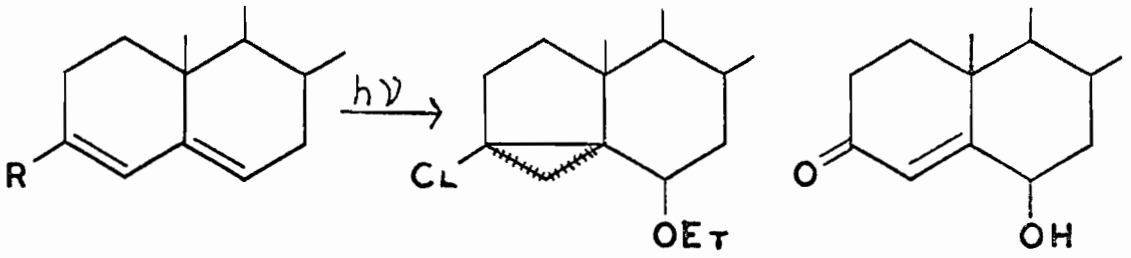
whose analysis and n.m.r. spectrum (Fig. 27) were identical to 3β-chlorocholest-5-ene (26c).

Fraction 9 yielded a saturated chloro ether XXXVII, m.p. 131-133°, as indicated by its infrared spectrum (Fig. 29). The assignment was corroborated by its n.m.r. spectrum (Fig. 28) which showed signals at 0.25 p.p.m. (one proton, J = 4.0 c.p.s.) and 0.5 p.p.m. (shoulder) characteristic of geminal protons attached to a cyclopropane ring (40, 41), and a complex, poorly resolved signal between 3.20 and 3.80 p.p.m. due to the three protons alpha to the oxygen function. The latter absorption was virtually identical to that observed for 6β-ethoxy-3β,5-cyclocholestane (II) (16) and its 3-methyl analog (VII) (19) and provides substantial evidence for the formulation of XXXVII as 3-chloro-6β-ethoxy-3β,5-cyclocholestane.

The infrared spectra of fractions 15-18 indicated that they were mixtures of saturated ketones, α,β-unsaturated ketones, and hydroxy ketones.

Photolysis of XXXVI in spectrograde pentane yielded an inseparable mixture.

When a 0.2% solution of 3-acetoxycholesta-3,5-diene (XXXVIa) (57) was photolyzed in ethanol, methanol or pentane, the absorption maximum at 234 mμ decreased rapidly (1 hour). The only product which could be isolated from the complex reaction mixture in approximately 10% yield was cholest-4-en-3-on-6β-ol (XXI), identified by comparison with an authentic sample (26b).



XXXVI R = Cl XXXVII XXI

XXXVIa R = OAc

XXXVIb R = Ph

XXXVIc R = p-OEtPh

XXXVId R = SEt

XXXVIe R = $N(CH_2)_4$

The irradiation of a 0.1% ethanolic solution of 3-phenyl-cholesta-3,5-diene (XXXVIb) (58) for twenty-four hours gave a mixture, inseparable by column chromatography.

Similarly, the photolysis of 3-(p-ethoxyphenyl)cholesta-3,5-diene (XXXVIc) in ethanol or pentane-acetic acid for seven hours gave mixtures which could not be resolved by column or thin-layer chromatography. The n.m.r. spectrum (Fig. 30) of XXXVIc showed signals at 6.84 p.p.m. (a quartet, corresponding to the four aromatic protons); 6.10 p.p.m. (sharp singlet, attributed to the C-4 proton); 5.35 p.p.m. (broad peak due to the C-6 proton); and 3.84 p.p.m. (a quartet, due to the CH_3-$\underline{CH_2}$-O protons).

Irradiation of 3-ethylthiocholesta-3,5-diene (XXXVId) (59) in methanol or ethanol containing pyridine for one hour resulted in the formation of a dark brown oil which could not be separated into its components by column chromatography.

A pentane solution of 3-N-pyrollidinylcholesta-3,5-diene (XXXVIe) (60,61) was irradiated for six hours under helium and the solvent evaporated at room temperature. The n.m.r. spectrum of the photolyzate showed very broad absorption peaks indicating that a mixture had been obtained.

FIG. 27

The nuclear magnetic resonance spectrum of a benzene solution of 3β-chlorocholest-5-ene, obtained in the photolysis of 3-chlorocholesta-3,5-diene

FIG. 27

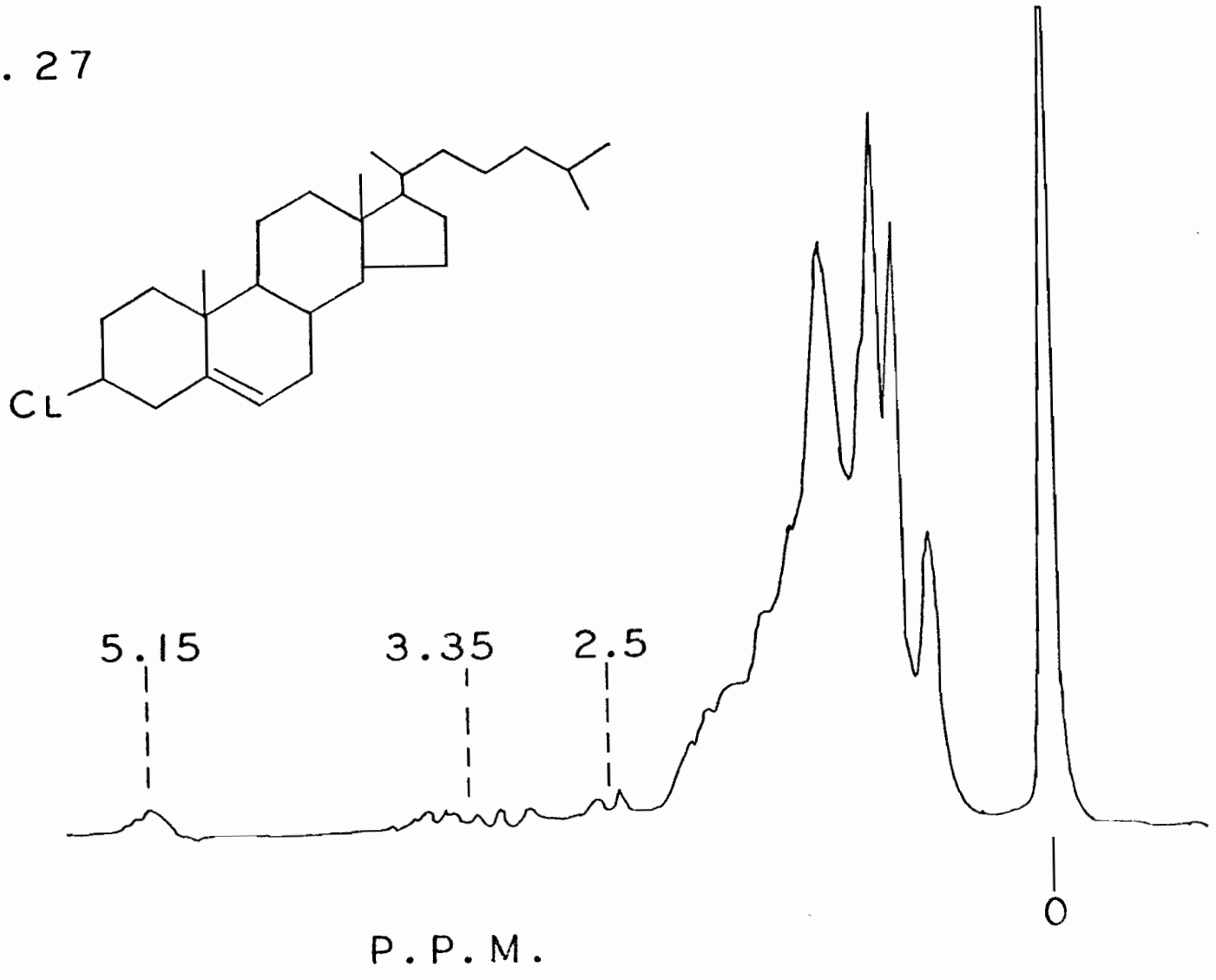


FIG. 28

The nuclear magnetic resonance spectrum of 3-chloro-6β-ethoxy-3β,5-cyclo-5β-cholestane (XXXVII) in benzene

FIG. 28

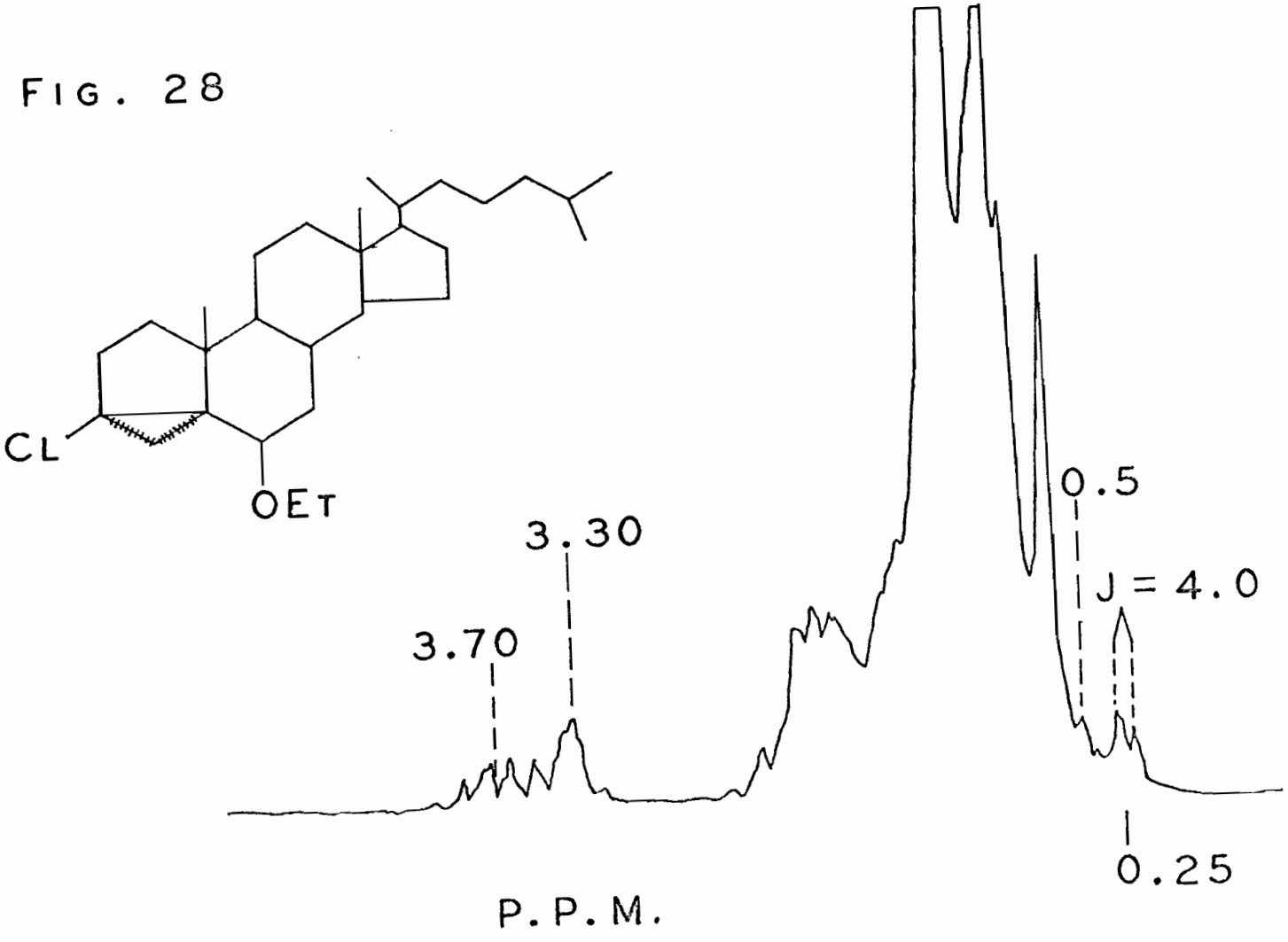
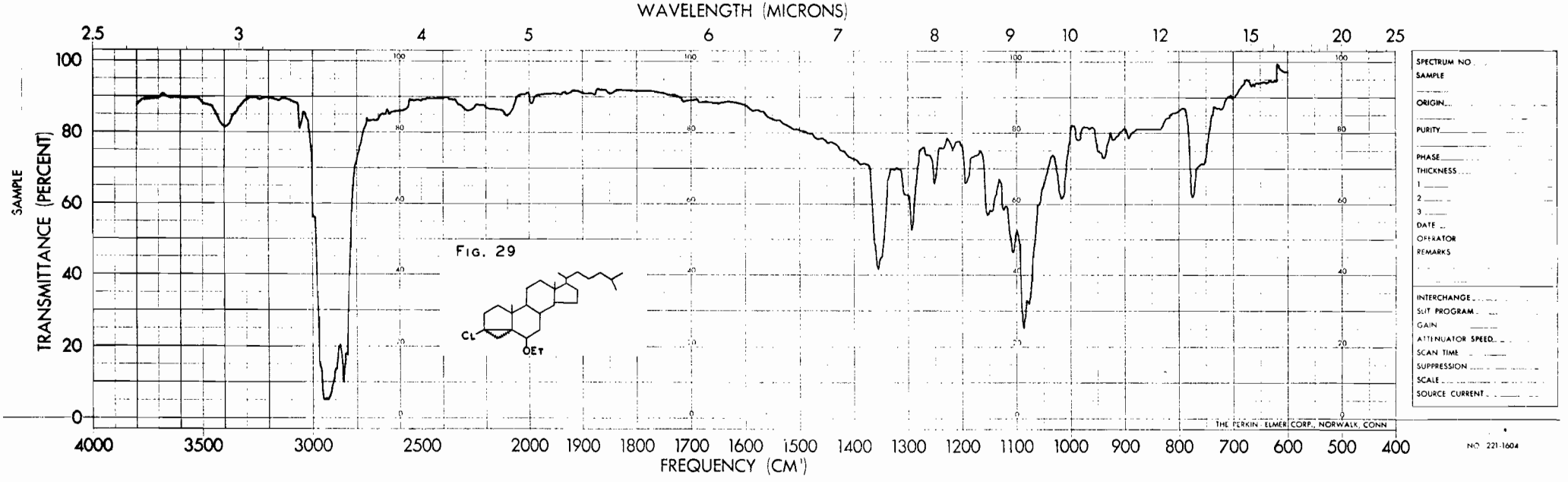


FIG. 29

The infrared spectrum of

3-chloro-6β-ethoxy-3β,5-cyclo-5β-cholestane

(XXXVII)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FREQUENCY (CM⁻¹)
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THICKNESS
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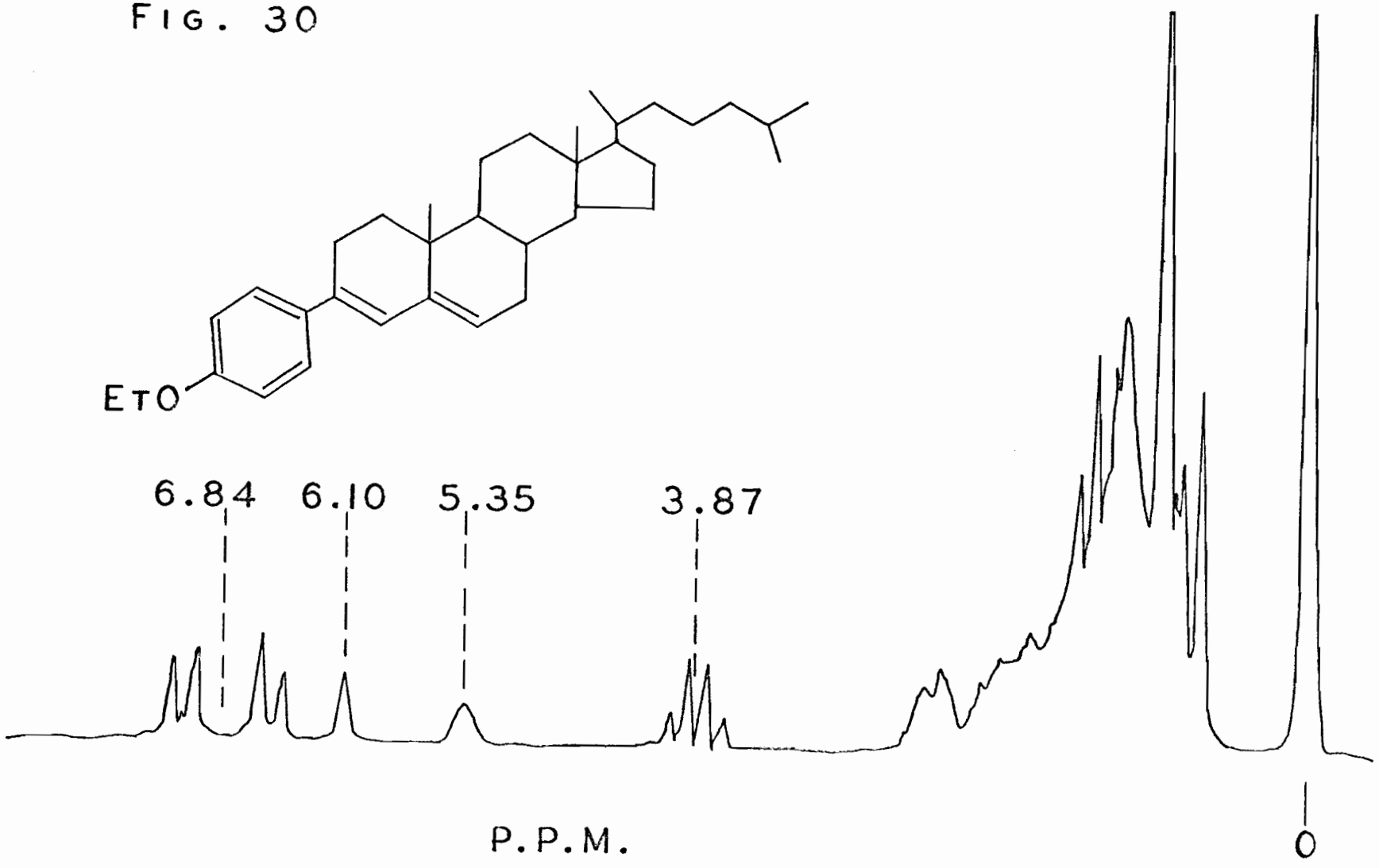
FIG. 29

CL
OEt

FIG. 30

The nuclear magnetic resonance spectrum of 3-(p-ethoxyphenyl)cholesta-3,5-diene (XXXVIc) in carbon disulphide

FIG. 30



CHAPTER V

Miscellaneous Reactions Required for Mechanistic Interpretations

In order to obtain more information about the mechanism of the photolysis of 3-alkoxycholesta-3,5-dienes, a solution of 3-ethoxycholesta-3,5-diene in absolute alcohol, saturated with oxygen, was irradiated for one hour. 3,3-Diethoxycholest-5-ene was obtained in a yield identical to that obtained in the absence of oxygen.

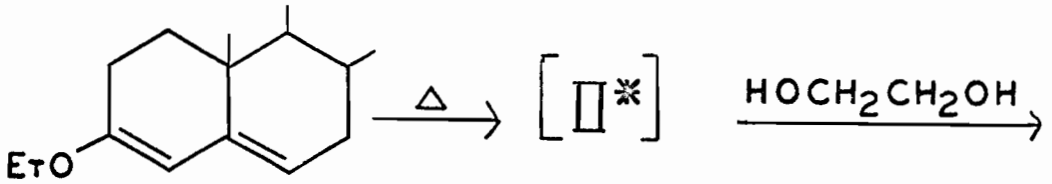
The effect of benzophenone on the photolysis was investigated. Using a "pyrex" filter to filter out light below 330 mμ, 3-ethoxycholesta-3,5-diene was irradiated in ethanol, containing benzophenone, for 2.5 hours. Chromatography of the resulting oil on alumina gave 20% of starting material, 50% of cholest-4-en-6β-ol-3-one (XXI), and some cholest-4-en-3-one. No ketal (XIV) could be detected in the reaction mixture.

When 3-ethoxycholesta-3,5-diene was irradiated (using a "pyrex" filter) for 2.5 hours in ethanol in the absence of benzophenone, no reaction occurred. Thus benzophenone sensitized the photo-reaction.

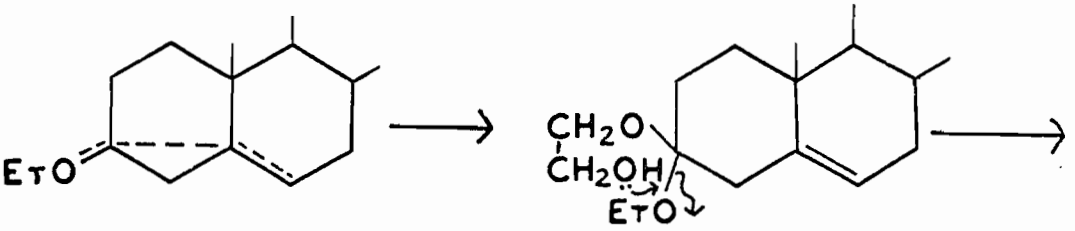
In many cases, thermal and photo-induced reactions yield identical products (62). To test this, 3-ethoxycholesta-3,5-diene was reacted with a suitable high boiling alcohol. 3-Ethoxycholesta-3,5-diene was refluxed in dry ethylene glycol, containing pyridine, for four hours and after the work-up (see experimental, Chapter V) cholest-5-en-3-one ethylene ketal (XXXVIII) was formed. Cholest-4-en-3-one (XX)

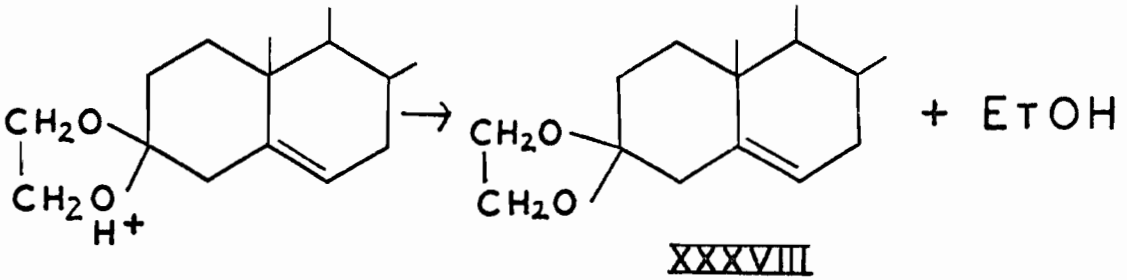
was reacted with ethylene glycol under the same conditions and no reaction occurred. Thus the ethylene glycol reacted directly with the alkoxydiene to give a ketal.

When 3-ethoxycholesta-3,5-diene (XIII) was reacted with ethanol, containing pyridine, in a sealed tube at 175° for six hours, only starting material and some hydrolysis product, cholest-4-en-3-one (XX) was obtained. The latter product was probably formed due to the presence of some water in the ethanol.



XIII





XXXVIII

CHAPTER VI

N.M.R. Data for Cholesta-3,5-dienes

In the course of investigating the photolyses of cholesta-3,5-dienes, it was observed that the chemical shifts of the C-4 proton of the cholesta-3,5-dienes varied by as much as 2 p.p.m. In order to compare them it was necessary to provide a standard. The n.m.r. spectrum of cholesta-3,5-diene exhibits unresolved peaks between 5.20 and 5.90 p.p.m. By introducing deuterium at C-3, it was hoped to simplify the n.m.r. spectrum of this compound.

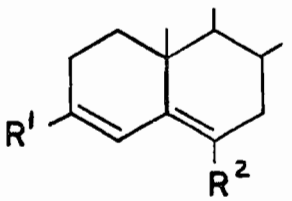
Cholest-4-en-3-one was reacted with lithium aluminum deuteride, and the resulting 3-deuteriocholest-4-en-3-ol, was dehydrated directly by refluxing with hydrochloric acid in ethanol to give 3-deuteriocholesta-3,5-diene. The 3-deuteriocholesta-3,5-diene showed signals at 5.79 and 5.22 p.p.m. due to the C-4 and C-6 protons respectively. The C-4 proton appears in all 3-substituted cholesta-3,5-dienes as a singlet, and the C-6 proton as a broad signal due to coupling with the C-7 protons.

The chemical shifts of the C-4 and C-6 protons of fourteen cholesta-3,5-dienes are recorded in Table I.

TABLE I

Nuclear magnetic resonance data of some cholesta-3,5-dienes

(T.M.S. = 0, chemical shifts in p.p.m.)



R^1	R^2	δ C_4-H	δ C_6-H
$N(CH_2)_4$	H	4.53	4.79
MeO	H	5.13	5.25
EtO	H	5.26	5.37
MeO	CH_3	5.28	-
MeO	F	5.39	-
AcO	H	5.61	5.31_5 [c]
Me	H	5.66[c]	5.25[c]
EtS	H	5.67	5.20
H	H	5.78[a,b]	5.22[b]
D	H	5.79[b]	5.22[b]
Cl	H	6.06	5.40
p-OEtPh	H	6.10	5.35
Ph	H	6.24	5.40
MeO	NO_2	6.26	-

a. Doublet, J = 10 c.p.s. (64a).

b. These values are the average values of five n.m.r. scans and are accurate to ± 0.05 p.p.m.

c. V. DiTullio (private communication).

Deshielding due to a negative inductive effect cannot be important except, perhaps, for 3-chlorocholesta-3,5-diene (63), in which the C-4 proton is deshielded compared to cholesta-3,5-diene by 0.28 p.p.m. The deshielding of the C-4 protons in 3-phenyl and 3-(p-ethoxyphenyl)cholesta-3,5-dienes can be attributed to the paramagnetic effect of the benzene rings, which are probably coplanar with the diene system (64b).

When an oxygen or nitrogen atom is attached at C-3, the C-4 proton is strongly shielded. This shielding is more likely due to the interaction of the lone-pair electronsof the oxygen or nitrogen atoms with the diene system, rather than a long-range magnetic anisotropy effect of the oxygen or nitrogen atoms (65,66,67). The interaction of the p-electrons reduces the olefinic character of the diene system, especially at C-4 and makes the hydrogen at C-4 appear more alkane-like.

The large deshielding effect of the 6-nitro group (1.13 p.p.m.) is not unusual (68) and overrides the shielding effect of the methoxy group in 3-methoxy-6-nitrocholesta-3,5-diene.

The chemical shifts of the C-6 protons of cholesta-3,5-dienes are only slightly affected by the substituent at C-3.

FIG. 31

The nuclear magnetic resonance spectrum of

cholesta-3,5-diene

FIG. 31

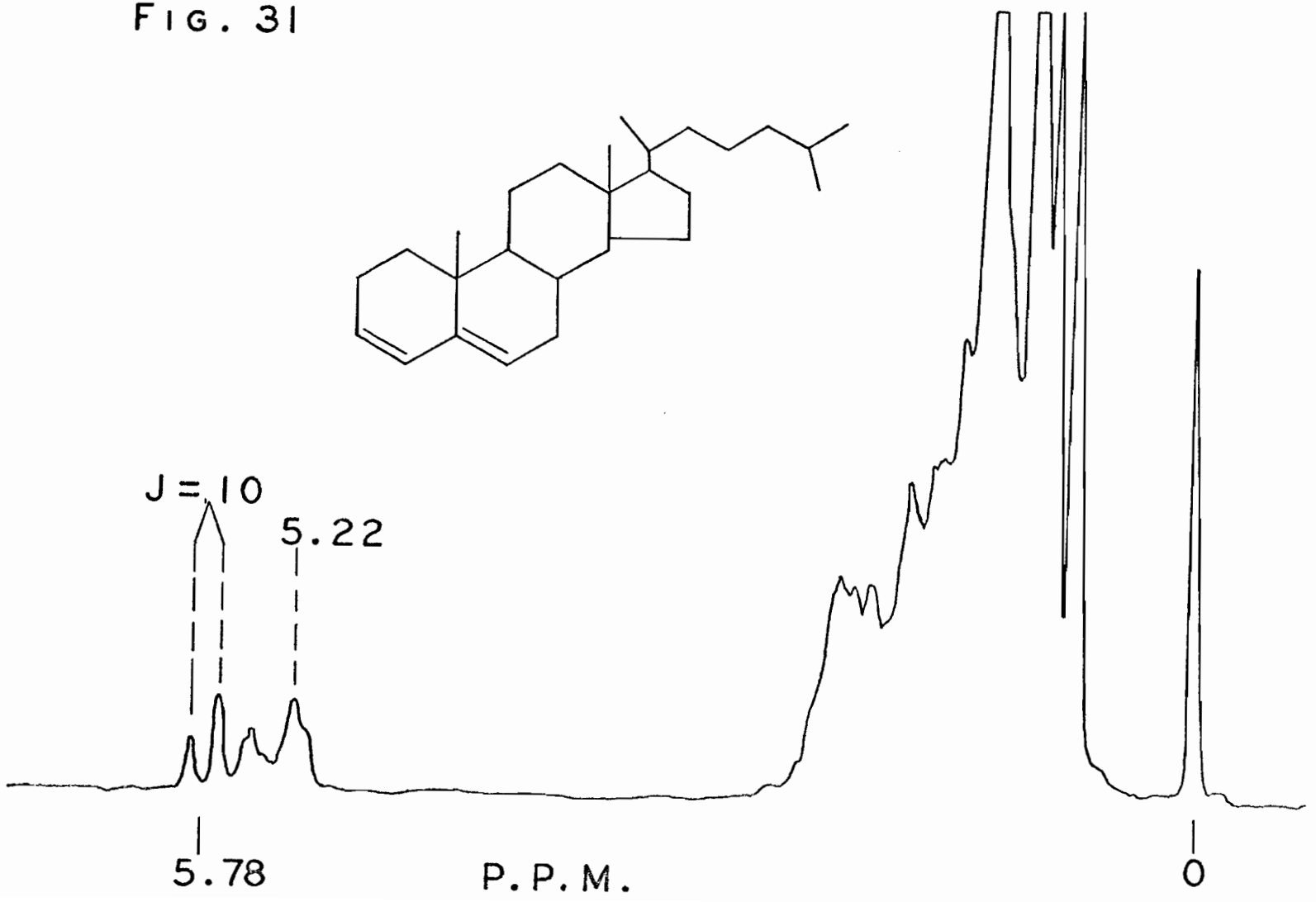
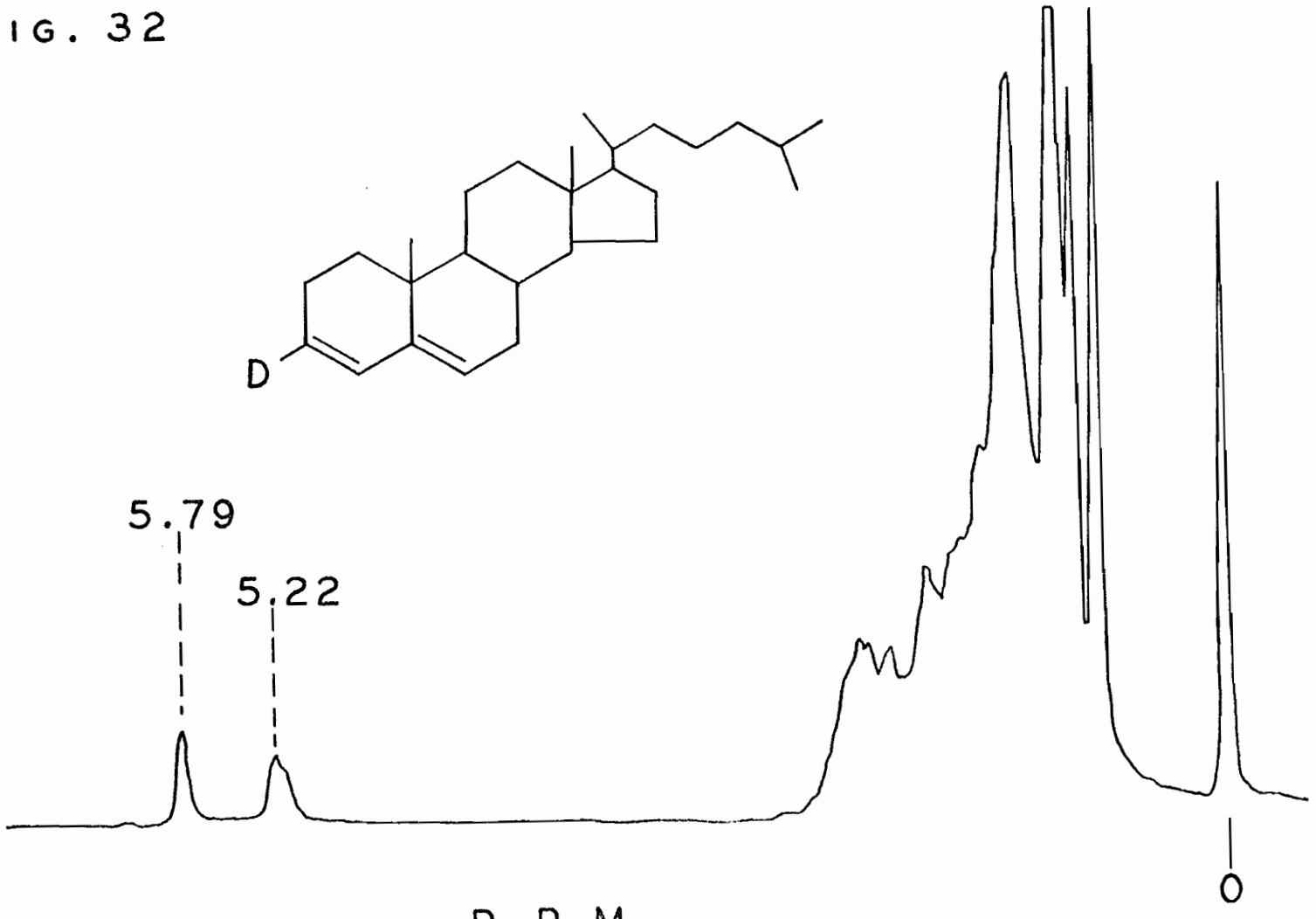


FIG. 32

The nuclear magnetic resonance spectrum of

3-deuteriocholesta-3,5-diene

FIG. 32

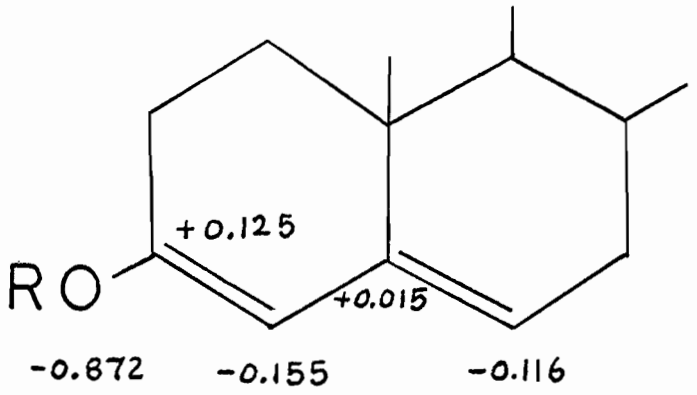


DISCUSSION

The photolysis of 3-alkoxycholesta-3,5-dienes in alcohols results in the addition of alcohol across the Δ^3-double bond to give 3,3-dialkoxycholest-5-enes (24).

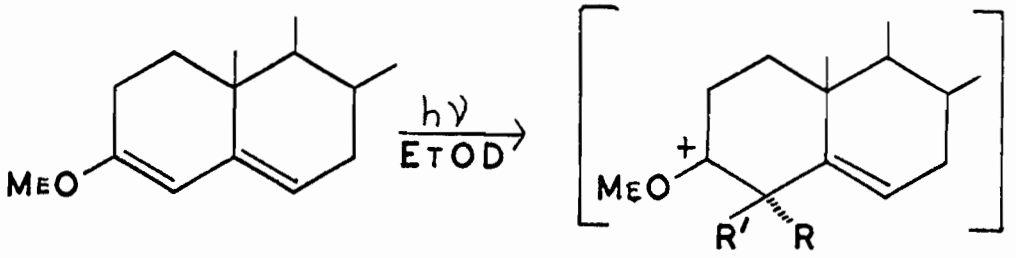
It has been shown that the acidic hydrogen of the alcohol is abstracted by the C-4 position of the diene system to give a 1:1 mixture of 4α- and 4β-protonated species (see Chapter II). On the other hand, the alkoxy moiety of the alcohol adds at C-3 of the diene system in a stereospecific manner (3β) (see Chapter I).

Molecular orbital calculations for the diene system of 3-alkoxycholesta-3,5-dienes have recently been carried out by Warkentin and Lam (69). Using simple Hückel molecular orbital calculations (70, 71), and putting $\alpha_o = \alpha_c + 2\beta$ for the Coulomb integral of oxygen and $\beta_{co} = \beta_{cc}$, the charge densities at the atoms indicated were calculated. Molecular orbital calculations indicate that for the ground state



electronic configurations, the C-4 position of the diene system is the most basic. However, the electronic distribution in any excited state induced by irradiation is most likely not to be the same as that in the ground state.

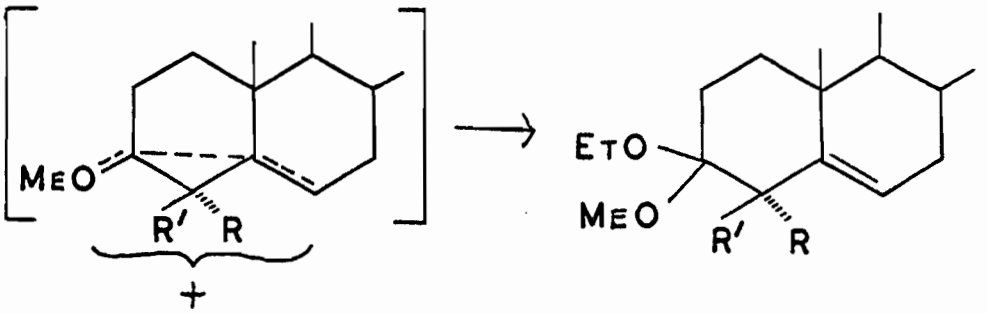
It is likely that protonation of the diene system at C-4 is a primary step in the photolysis of 3-alkoxycholesta-3,5-dienes. The alkoxy moiety then reacts with the resulting carbonium ion to give ketals.



XVII

A R′=H, R=D

A′ R′=D, R=H



B R′=H, R=D

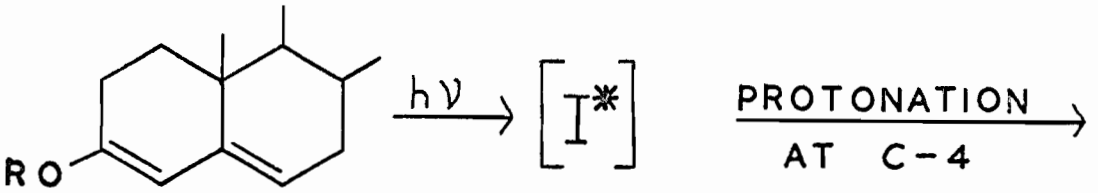
B′ R′=D, R=H

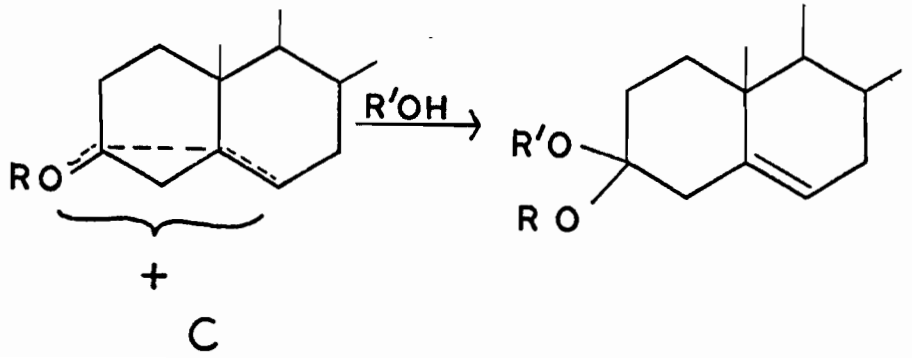
XIXa R′=D, R=H

XIXb R′=H, R=D

It is difficult to say how much the Δ^5-double bond of carbonium ions, A and A', participate to give homoallylic carbonium ions of the type B and B', but the fact that the alkoxy moiety adds preferentially at the C-3β position indicates that some participation does occur. The exchange reactions of the 3,3-dialkoxycholest-5-enes (XIII, XVII) (see Chapter I) also showed that the 3β substituent is exchanged more rapidly than the 3α substituent and that this difference is most likely due to participation of the Δ^5-double bond.

A general mechanism for the photolysis of 3-alkoxycholesta-3, 5-dienes can be written.





A detailed examination of the primary processes leading to the formation of an excited intermediate, such as $[I^*]$, and a description of the excited state itself is an extremely difficult problem (2).

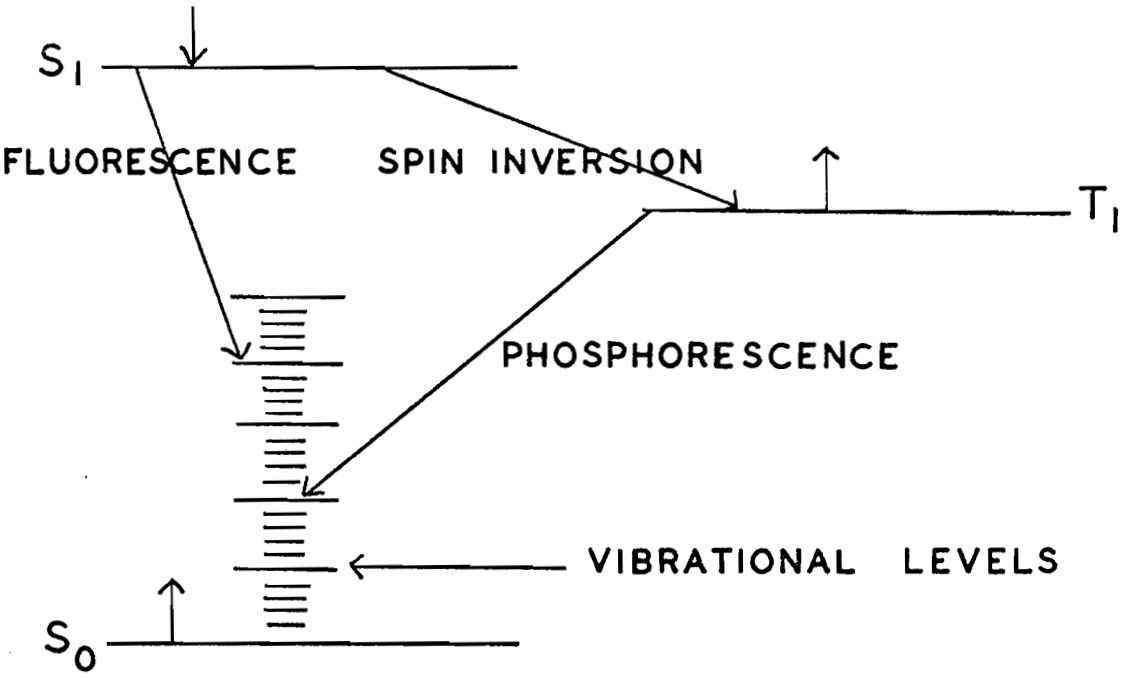
[1] Most organic molecules have even numbers of electrons which, in the ground state, are all spin-paired. Such states possess no net spin angular momentum and are called singlets; the ground singlet is labelled S_o. Absorption of light promotes an electron to a vacant orbital; two electrons become orbitally unpaired. Unless the electrons remain spin-paired, the transition is highly forbidden and can occur only with very low intensity. Nearly all absorption bands observed in ordinary absorption spectroscopy are the result of singlet-singlet transitions. Since the Pauli principle does not demand that the spins of the electrons remain paired in most excited configurations, spin inversion may take place, forming a second excited state, a triplet.

With rare exceptions, emission of light occurs from only the lowest-lying excited singlet, S_1, and the lowest-lying triplet, T_1. The former process is known as fluorescence, and the latter is called phosphorescence. Fluorescence lifetimes are of the order of 10^{-7} to 10^{-8} seconds. Since most substances do not fluoresce in solution, nonradiative degradation to the ground state must actually shorten the lifetime of excited singlet states. Phosphorescence lifetimes range upward from 10^{-4} second. The slowness of these radiative processes is associated with the fact that spin inversion is involved. The same factor contrives

---

1. Abstracted from reference 2.

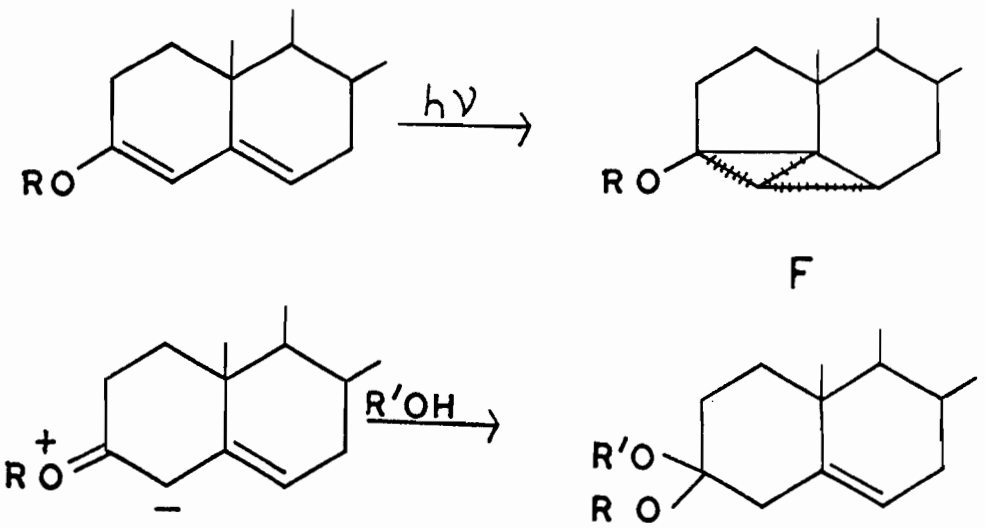
to slow down the nonradiative degradative processes which deactivate triplets. The following schematic diagram shows that although the singlet state has the higher energy, the triplet state is often the only state that retains electronic excitation long enough to undergo chemical reaction. Collision times of molecules in solution are of the order of 10^{-12} second (72), and hence reaction through singlet states do occur in many systems.



In the photolysis of cholesta-3,5-diene (I) (17) (see Introduction), Dauben and Willey suggested the formation of a bicyclobutane intermediate. Irradiation of 3-methylcholesta-3,5-diene (V) (19) in pentane also gave an intermediate bicyclobutane VI. 3-Methylbicyclobutane VI, however, on reaction with ethanol in the dark gave only one

product, 6β-ethoxy-3-methyl-3β,5-cyclo-5β-cholestane (VII), while irradiation of 3-methylcholesta-3,5-diene (V) in ethanol gave VII and 3β-ethoxy-3α-methylcholest-5-ene (VIII). It thus seems reasonable to assume that in the photolysis of 3-methylcholesta-3,5-diene (V), two mechanisms are competing. Ether VII is derived from a bicyclobutane intermediate and ether VIII is probably derived from an excited singlet state (20).

The 3,3-dialkoxycholest-5-enes, obtained in the photolysis of 3-alkoxycholesta-3,5-dienes, are structurally similar to the postulated singlet product, 3β-ethoxy-3α-methylcholesta-3,5-diene (VIII), obtained in the photolysis of 3-methylcholesta-3,5-diene (V) (19). Thus, it might be suspected that the dialkoxy dienes are also obtained by reaction of an excited singlet state of a 3-alkoxycholesta-3,5-diene. It is possible, however, that the same products could be obtained by reaction of a postulated 3-alkoxybicyclobutane (F) intermediate with ethanol.



Although the above mechanism is very plausible and closely corresponds to the reaction pathway proposed in the photolyses of cholesta-3,5-diene (I) (17), the experimental evidence does not favour this interpretation.

Firstly, irradiation of 3-alkoxycholesta-3,5-dienes in pentane under a helium atmosphere did not give a 3-alkoxybicyclobutane (F). Specifically the n.m.r. spectrum of the reaction product did not show the presence of an alkoxy substituent (24).

It is a well known fact that oxygen reacts with triplets (73, 74). The presence of oxygen in the photolysis of 3-ethoxycholesta-3,5-diene (XIII) did not eliminate or reduce the yield of 3,3-diethoxycholest-5-ene (XIV) (see Chapter V) and hence XIV could not be derived from the triplet state. It should be noted, however, that in some cases, oxygen is not an efficient quencher of triplets (75). Irradiation of 3-methylcholesta-3,5-diene (V) in ethanol saturated with oxygen resulted in a decreased yield of 6β-ethoxy-3-methyl-3β,5-cyclo-5β-cholestane (VII) (76), which is derived from the 3-methylbicyclobutane VI. Thus, it is indicated that the bicyclobutane intermediates are derived from triplet states (74,77).

When the 3-methylbicyclobutane intermediate VI was reacted with deuterioethanol, the deuterium was incorporated at the C-4 position in a stereospecific manner (4β) (20), but irradiation of 3-methoxycholesta-3,5-diene (XVII) in deuterioethanol resulted in a random incorporation of deuterium at C-4 (31). It is conceivable, but not very likely, that a proposed 3-alkoxybicyclobutane (F) is sufficiently

different from the 3-methylbicyclobutane VI to account for the difference in protonation patterns.

Transfer of electronic excitation from one molecule to another is an important photochemical process.

$$A \xrightarrow{h\nu} A^*$$

$$A^* + B \longrightarrow A + B^*$$

It is known that benzophenone, under excitation, undergoes spin inversion $S_1 - T_1$ with high efficiency (78,79) and it is now well established that absorption of light by benzophenone can ultimately effect the photochemical transformation of butadiene (80) as well as other systems (81). Reaction of 3-ethoxycholesta-3,5-diene (XIII) in the presence of benzophenone resulted in the complete inhibition of ketal formation (see Chapter V). Although the formation of 3,3-diethoxycholest-5-ene (XIV) by this sensitized reaction would have strongly indicated the intermediacy of a triplet state, its lack of formation does not, however, rule out the formation of a triplet state, as benzophenone does not always transfer its excitation energy with high efficiency (82).

It seems quite evident that the intermediacy of a bicyclobutane precursor cannot be involved in the formation of 3,3-dialkoxycholest-5-enes by irradiation of 3-alkoxycholesta-3,5-dienes in alcohols.

Since the photolysis reaction probably does not proceed through the triplet state, the reaction through a singlet state may be responsible

for the formation of the 3,3-dialkoxycholest-5-enes.

Srinivasan, however, has postulated that the photolysis of butadiene to give bicyclobutane occurs through a high-level vibrationally excited ground state (77), which is formed presumably by demotion of an electron from the first excited singlet state. Franck and Sponer (62) have also correlated photolysis and thermal reactions as occurring through excited ground state vibrational levels, the photolysis occurring through demotion of a first excited singlet electron and the thermal reaction occurring through promotion of a ground state electron to a high vibrational level.

It has been shown (see Chapter V) that a thermal reaction of 3-ethoxycholesta-3,5-diene (XIII) with ethylene glycol readily occurs to give cholest-5-en-3-one ethylene ketal (XXXVIII). An attempted thermal reaction of 3-ethoxycholesta-3,5-diene (XIII) with ethanol, however, gave only cholest-4-en-3-one (XX) and starting material (see Chapter V). Recovery of starting material could be explained simply as a lack of reactivity or may be due to the fact that pyrolysis of 3,3-diethoxycholest-5-ene (XIV) to give 3-ethoxycholesta-3,5-diene (XIII) readily occurs at 190° (see Chapter I). In the reaction with ethylene glycol, however, the pyrolysis of the ethylene ketal is unlikely due to its stability.

These experiments suggest that the photolysis of 3-alkoxycholesta-3,5-dienes can occur via a high-level vibrationally excited ground state, but in no way precludes the possibility of reaction

occurring through the first excited singlet state.

It has been shown that a 3-alkoxybicyclobutane (F) is not responsible for the formation of 3,3-dialkoxycholest-5-enes. The main photolysis product, however, accounts for only 60% of the reaction mixture. About 10% of the remaining material consisted of cholest-4-en-6β-ol-3-one (XXI) and the other 30% of cholest-4-en-3-one (XX). This latter product could arise through the photoaddition of water to the 3-alkoxycholesta-3,5-dienes. Since hydrolysis of 3-alkoxycholesta-3,5-dienes in alcohols occurs only very slowly in the absence of ultraviolet irradiation, it seems likely that a photo-induced hydrolysis has taken place. The photo-induced hydrolysis may occur through a triplet state of the 3-alkoxycholesta-3,5-dienes. One supporting piece of evidence for this is the fact that irradiation of 3-ethoxycholesta-3,5-diene (XIII) in the presence of benzophenone gave cholest-4-en-6β-ol-3-one (XXI) in about 50% yield, compared to a 10% yield of XXI upon direct irradiation of XIII in ethanol in the absence of benzophenone. Thus, it is not improbable that cholest-4-en-6β-ol-3-one (XXI) arises from a triplet state of 3-ethoxycholesta-3,5-diene (XIII). Furthermore, the remaining 50% of the reaction mixture consisted mostly of cholest-4-en-3-one (XX) and cholest-5-en-3-one (XVI).

In the photolysis of 3-methoxy-6-methylcholesta-3,5-diene (XXXI) and 6-fluoro-3-methoxycholesta-3,5-diene (XXXIa), the hydrolysis products only accounted for 5 - 15% of the total reaction mixture, compared to 40% in the irradiation of 3-methoxycholesta-3,5-diene (XVII). It would be difficult at this time to account for this difference in

in terms of intermediate excited states.

Summarizing, it may be stated that irradiation of 3-alkoxy-cholesta-3,5-dienes in alcohols to give 3,3-dialkoxycholest-5-enes does not proceed through a bicyclobutane intermediate. Since it was shown that the bicyclobutane intermediate VI probably arises from the triplet state (76), the reactive intermediate in the photolysis of 3-alkoxy-cholesta-3,5-dienes is most likely not derived from a triplet state. A differentiation of mechanisms between an excited singlet state and a high-level vibrationally excited ground state seems premature at this time.

EXPERIMENTAL

1. The melting points were determined on a Kofler microscope hot-stage and are corrected.

2. The analyses were carried out by Dr. C. Daessle, Montreal; A. Bernhardt, Mülheim, Germany; and Schwarzkopf Microanalytical Laboratories, Woodside 77, N.Y.

3. The infrared spectra were determined on a Perkin-Elmer 421 grating spectrophotometer using one millimeter sodium chloride cells and carbon disulphide as solvent, unless otherwise stated.

4. The ultraviolet absorption spectra were measured by means of a Beckman recording spectrophotometer Model DK1.

5. Nuclear magnetic resonance spectra were recorded on a Varian H.R. 60 instrument using carbon tetrachloride as solvent and tetramethylsilane (0 p.p.m.) as an internal standard.

6. Optical Rotations were performed with a Carl Zeiss automatic polarimeter using a 0.5 dm. tube.

7. All irradiations were performed with a Hanovia 450 watt lamp in a standard water-cooled immersion apparatus.

8. Woelm alumina, activity II-III, and Davidson No. 923 silica gel were used for column chromatography.

9. Merck A.G. silica gel was used for thin-layer chromatography (TLC).

CHAPTER I

Irradiation of 3-Ethoxycholesta-3,5-diene (XIII) in Ethanol

A solution of 3.0 g. of XIII, λ_{max}^{EtOH}, 239 mμ (ε 17,900), was irradiated until no absorption could be detected in the ultraviolet (1.5 hours). After evaporation, one-half of the crude material was chromatographed on silica gel. Elution with hexane, hexane-benzene, and benzene-ether gave 0.5 g. of crude cholest-5-en-3-one (XVI), m.p. 118-120°. Recrystallization from cyclohexane afforded 0.1 g. of XVI, m.p. 119-125°. The melting point was not depressed upon admixture of authentic XVI (26a). The infrared spectra were superimposible.

The other half of the crude photolysis product was chromatographed on alumina. Elution with pentane gave impure 3,3-diethoxycholest-5-ene (XIV) in 60% yield. Several crystallizations from ethanol gave XIV, m.p. 49-50°, $[\alpha]_D$ -28.4° (c, 1.06 in chloroform).

Calc. for $C_{31}H_{54}O_2$:	C, 81.16; H, 11.87%.
Found:	C, 81.26; H, 11.96%.

Further elution with benzene gave 20% of cholest-4-en-3-one (XX), m.p. 81-82°, not depressed upon admixture of authentic XX. Infrared and ultraviolet spectroscopy further proved the identity of the two products.

Further elution with ether gave 25 mg. of cholest-4-en-6β-ol-3-one (XXI) (26b), m.p. 181-182°, λ_{max}^{EtOH}, 237 mμ (ε 12,800), ν_{CHCl_3}

3570 cm^{-1} (free O-H), 3380 cm^{-1} (hydrogen bonded O H), 1685 cm^{-1} (α,β-unsaturated ketone). The melting point was not depressed on admixture with authentic XXI.

3,3-Diethoxycholest-5-ene (XIV) and 3,3-Dimethoxycholest-5-ene (XVIII)

Following the procedure described by Ueberwasser et al. (27), a solution of cholest-5-en-3-one (XVI) (1.0 g.) and 0.5 g. of malonic acid in 60 ml. absolute ethanol was stirred for 20 hours at 20-25°. The solution was worked up as described and the resulting oil chromatographed on alumina. Elution with pentane yielded 0.38 g. of pure 3,3-diethoxycholest-5-ene (XIV), m.p. 48-49°, in 32% yield, identical (infrared, m.p. and mixed m.p.) with that obtained by photolysis.

Similarly, the reaction of cholest-5-en-3-one, 1.0 g. and 0.5 g. of malonic acid in 60 ml. of absolute methanol yielded 0.685 g. of pure 3,3-dimethoxycholest-5-ene (XVIII), m.p. 96°, identical (infrared, m.p. and mixed m.p.) with that obtained by photolysis.

3-Methoxycholesta-3,5-diene (XVII)

To cholest-4-en-3-one (10 g.) and 10 ml. of trimethylorthoformate in 50 ml. of dioxane, was added two drops of concentrated sulphuric acid in 1.5 ml. of dioxane and the mixture refluxed for 0.5 hours. Pyridine (0.25 ml.) was then added and the solution evaporated to an oil which was covered with methanol and allowed to crystallize. Recrystallization from ether-methanol yielded 5.8 g. of pure XVII, m.p.

67-68°, $[\alpha]_D$ -97.1° (c, 1.12 in pyridine), λ_{max}^{EtOH} 239 mμ (ε 19,900).

Calc. for $C_{28}H_{46}O$: C, 84.35; H, 11.63%.

Found: C, 84.19; H, 11.97%.

Irradiation of 3-Methoxycholesta-3,5-diene (XVII) in Methanol

Irradiation of 0.5 g. of XVII in 1800 ml. of absolute methanol for 30 minutes yielded, after evaporation, 0.6 g. of an oil. Chromatography on alumina and elution with pentane gave 200 mg. of 3,3-dimethoxycholest-5-ene (XVIII), m.p. 93°. Recrystallization from acetonitrile-ether gave pure XVIII, m.p. 95.7-96.0°, $[\alpha]_D$ -35.5° (c, 1.07 in chloroform), identical (infrared, m.p. and mixed m.p.) with that described above.

Calc. for $C_{29}H_{50}O_2$: C, 80.87; H, 11.70%.

Found: C, 81.19; H, 11.82%.

Methanolysis of 3,3-Diethoxycholest-5-ene (XIV)

The crude irradiation product of 1.65 g. of 3-ethoxycholesta-3,5-diene (XIII) in ethanol was chromatographed on alumina. The oily hexane eluate (0.90 g.) was covered with methanol. After a few days, 0.36 g. of 3α-ethoxy-3β-methoxycholest-5-ene (XV), m.p. 88-91°, was obtained. Two recrystallizations from methanol raised the m.p. to 105-106°.

Calc. for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79%.

Found: C, 80.70; H, 12.05%.

In a second run, 100 mg. of pure 3,3-diethoxycholest-5-ene (XIV) was heated for 12 hours in methanol on a steam bath and the solvent allowed to evaporate. Crystallization of the reaction product from methanol gave 40 mg. of XV, m.p. 96-98°. The very characteristic infrared and n.m.r. spectra of the products, m.p. 96-98°, and m.p. 105-106°, were indistinguishable.

Cholest-4-en-3-one (XX) from 3α-Ethoxy-3β-methoxycholest-5-ene (XV)

When a 90 mg. sample of XV in carbon tetrachloride was taken to dryness on the steam bath, an oily mixture was recovered. Chromatography on aluminum oxide and elution with hexane-benzene mixtures gave cholest-4-en-3-one (XX), m.p. 81-82°. The melting point was not depressed on admixture of authentic XX. Comparison of the infrared spectra confirmed the identity of the two compounds.

Further elution with ether gave 25 mg. of a crystalline material, which melted at 182-183° after recrystallization from hexane. The melting point was not depressed on admixture with the material obtained in the chromatogram of the photolysis product of XIII in ethanol and XVII in methanol.

Rate of Alcoholysis of the 3,3-Dialkoxycholest-5-enes

Ketals XVIII and XIV were heated under reflux with ethanol and methanol respectively. Aliquots were withdrawn periodically and their n.m.r. spectra recorded.

In the methanolysis of XIV the 3β-ethoxy group was replaced at a rate twice as fast as the 3α-ethoxy group. The 3β-ethoxy group disappeared in the n.m.r. spectrum after 10 hours, the 3α group after 20 hours.

When 3,3-diethoxycholest-5-ene (XIV) in 55 ml. of methanol plus two drops of pyridine was refluxed overnight, 3,3-dimethoxycholest-5-ene was obtained.

Irradiation of 3-Methoxycholesta-3,5-diene (XVII) in Ethanol

Irradiation of 2.0 g. of XVII in 1800 ml. of absolute ethanol for 3 hours gave 2.3 g. of product which, on chromatography on alumina, yielded 1.1 g. of 3β-ethoxy-3α-methoxycholest-5-ene (XIX). The n.m.r. spectrum of this material indicated the presence of some epimeric 3α-ethoxy-3β-methoxycholest-5-ene (XV) in small amounts. Recrystallization from ethanol gave pure XIX, m.p. 98-99°, $[\alpha]_D$ -32.3° (c, 1.26 in chloroform).

Calc. for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79%.

Found: C, 81.43; H, 12.07%.

Effect of Silica Gel on β,γ-Unsaturated Ketals

3β-Ethoxy-3α-methoxycholest-5-ene (70 mg.) was chromatographed on 20 g. of silica gel. A mixture of cholest-4-en-3-one (XX) and cholest-5-en-3-one (XVI) was obtained as indicated by the infrared spectrum of the eluate, ν 1735 cm^{-1} (saturated ketone), 1690 cm^{-1} (α,β-

unsaturated ketone).

Chromatography of pure cyclic diethylene ketal of cholest-5-en-3-one (83) on silica gel resulted in complete recovery of starting material.

Irradiation of 3-Ethoxycholesta-3,5-diene (XIII) in Methanol with Pyridine

Irradiation of 0.8 g. of XIII in 1500 ml. of methanol and 0.25 ml. of pyridine for 30 minutes gave by direct crystallization on evaporation of most of the solvent 0.25 g. of pure 3α-ethoxy-3β-methoxycholest-5-ene (XV), m.p. 110-112°. Recrystallization from ether-methanol gave pure XV, m.p. 112-113°, $[\alpha]_D$ -30.1° (c, 1.13 in chloroform). The infrared and n.m.r. spectra further proved the identity of this material.

Pyrolysis of 3,3-Dimethoxycholest-5-ene (XVIII) and 3α-Ethoxy-3β-methoxycholest-5-ene (XV)

Ketal XVIII (100 mg.) was distilled in vacuo (1 mm Hg) at 190° for four hours. The distillate (25 mg.) was shown to be 3-methoxycholesta-3,5-diene (XVII) by its m.p. mixed m.p., and infrared spectrum.

When ketal XV was distilled in vacuo at 190°, a mixture of 3-ethoxy and 3-methoxycholesta-3,5-dienes was obtained. The mixture melted at 70-71° and showed a green fluorescence on cooling from 80-72°. the cold melt then fluoresces a dull blue. Pure 3-ethoxycholesta-3,5-diene, m.p. 83-84°, fluoresces royal blue on cooling from 97-92°. Pure 3-methoxycholesta-3,5-diene fluoresces dull blue and dull red on cooling

from 65-50°. An artificially prepared mixture of 3-ethoxy and 3-methoxycholesta-3,5-dienes, m.p. 70-72°, fluoresces green on cooling from 80-72°, in the same manner as the mixture of dienes obtained by pyrolysis.

Some Acid-catalyzed Reactions of 3,3-Dimethoxycholest-5-ene (XVIII)

A solution of 50 mg. of XVIII in 10 ml. anhydrous ether containing two drops of sulphuric acid was stirred for two minutes. After neutralization with pyridine, the solution was washed with water, dried over magnesium sulphate and evaporated to give an oil whose infrared spsctrum showed primarily saturated and α,β-unsaturated ketones.

To a solution of 50 mg. of XVIII in 10 ml. of hexane was added a few drops of boron trifluoride etherate. After stirring for one minute, 0.25 ml. of pyridine was added and the solution extracted with ether, washed with water, and evaporated to dryness. An infrared spectrum of the resulting oil showed the presence of saturated and α,β-unsaturated ketones.

When XVIII (50 mg.) in 10 ml. hexane and 10 drops of acetic anhydride was refluxed overnight, no reaction occurred.

Irradiation of 3-Ethoxycholesta-3,5-diene (XIII) in Isopropyl Alcohol

Irradiation of 2.0 g. of XIII in 1500 ml. of spectrograde

isopropyl alcohol for 1.5 hours, gave 2.3 g. of product, which on chromatography on alumina yielded 1.0 g. of a 1:1 mixture of 3α-ethoxy-3β-isopropoxycholest-5-ene (XXII) and 3β-ethoxy-3α-isopropoxycholest-5-ene (see Fig. 4).

Irradiation of 3-Ethoxycholesta-3,5-diene (XIII) in Ether

A solution of 2.0 g. of XIII in 1800 ml. of ether was irradiated for 1.33 hours. Chromatography on alumina yielded some starting material (0.3 g.) and a complex mixture of compounds.

Irradiation of 3-Ethoxycholesta-3,5-diene (XIII) and 3-Methoxycholesta-3,5-diene (XVII) in Pentane

Photolysis of 0.5 g. of either XIII or XVII in 525 ml. pentane for 1.5 hours gave a complex mixture which could not be separated on column chromatography.

CHAPTER II

3β-Acetoxy-4α,5α-oxidocholestane (XXVI)

To a solution of XXV (32) (7.5 g.) in 40 ml. ether was added 100 ml. of an ether solution of monoperphthalic acid (0.081 g./ml.). The mixture was allowed to stand at room temperature (20°) for 18 hours. A further portion of 50 ml. of ether solution of monoperphthalic acid was added and the solution allowed to stand for a further 18 hours. After washing with a saturated solution of sodium bicarbonate and water, the ether solution was dried over sodium sulphate and evaporated to dryness. Crystallization from acetone-methanol yielded 6.0 g. of XXVI, m.p. 104-107° (Lit. m.p. 114-115° (34)).

4β-Deuteriocholestan-3β,5α-diol 3β-acetate (XXVIIa)

To 0.30 g. of lithium aluminum deuteride in 20 ml. of anhydrous ether was added 2.0 g. of solid XXVI. Anhydrous ether (20 ml.) was then added and the mixture stirred for two hours. After careful addition of water, the solution was washed neutral, dried over sodium sulphate and evaporated to dryness to give 1.9 g. of crystals, m.p. 198-218°. Recrystallization from ethyl acetate gave 1.2 g. of 4β-deuteriocholestan-3β,5α-diol (XXVII), m.p. 221° (Lit. m.p. 224.5-225.5° (84)).

About 1.2 g. of XXVII in 40 ml. of pyridine and 15 ml. of acetic anhydride was left standing overnight at room temperature. After the usual work-up, recrystallization from acetone-methanol gave 1.2 g.

of 4β-deuteriocholestan-3β,5α-diol 3β-acetate (XXVIIa), m.p. 184-185° (Lit. m.p. 184.6-185.6° (85)).

4β-Deuteriocholesteryl Acetate (XXVIII)

To a solution of 1.15 g. of XXVIIa in 20 ml. of pyridine at 0°, 3 ml. of thionyl chloride was added and the solution stirred for 20 minutes. Ice water was added and after the usual work up, the oily crystals were crystallized twice from acetone-methanol to give 500 mg. of XXVIII, m.p. 105-109°.

4β-Deuterio-3α,5-cyclocholestan-6β-ol (XXIX)

About 425 mg. of XXVIII was hydrolyzed (34) and 300 mg. of 4β-deuteriocholesterol (XXVIIIa), m.p. 146-148°, was obtained after crystallization from acetone-methanol.

Tosylation of 260 mg. of XXVIIIa gave 290 mg. of 4β-deuteriocholesteryl tosylate (XXIVb), m.p. 131-132° (39).

A solution of XXIVb (238 mg.) in 12 ml. of acetone and 3 ml. of water was refluxed with 200 mg. of sodium acetate for 15 hours. Ether extraction, and chromatography of the resulting oil on 4 g. of alumina gave 60 mg. of crystals, eluted by hexane-benzene mixtures. Recrystallization from acetone afforded 50 mg. of XXIX, m.p. 61-63° (identified by m.p. and mixed m.p. with an authentic sample (39)).

Irradiation of 3-Methoxycholesta-3,5-diene XVII in Ethanol-d

A solution of 2.1 g. of XVII in 475 ml. of dry pentane, 55 ml. of ethanol-d (C_2H_5OD), and 0.25 ml. of pyridine was irradiated for 3.5 hours until little absorption could be detected in the ultraviolet. After evaporation, the crude photolysis product was chromatographed on alumina. Elution with hexane gave 1.1 g. of oily 4-deuterio-3β-ethoxy-3α-methoxycholest-5-ene (XIXa, XIXb). Crystallization from ethanol gave 500 mg. of (XIXa, XIXb), m.p. 92-93° (24).

4-Deuteriocholest-5-en-3-one (XVIa, XVIb)

A solution of 500 mg. of 4-deuterio-3β-ethoxy-3α-methoxy-cholest-5-ene (XIXa, XIXb) in 30 ml. acetone and 3 ml. of water containing 100 mg. of malonic acid was allowed to evaporate slowly at room temperature. After 66 hours, 350 mg. of 4-deuteriocholest-5-en-3-one (XVIa, XVIb), m.p. 127-128°, was obtained by filtration. Its m.p. was not depressed upon admixture of cholest-5-en-3-one (26a).

4-Deuterio-3α,5-cyclocholestan-6β-ol (XXIX, XXIXa)

To 350 mg. of lithium aluminum hydride in 25 ml. of ether was added 350 mg. of the 3-ketone (XVIa, XVIb) obtained above. After stirring for two hours, the reaction mixture was worked up and 355 mg. of crystals were obtained. Recrystallization from acetone-methanol gave 210 mg. of 4-deuteriocholesterol (XXIV, XXIVa), m.p. 138-140°. Its m.p. was not depressed upon admixture of cholesterol.

Tosylation (39) of 4-deuteriocholesterol obtained above gave 230 mg. of 4-deuteriocholesteryl tosylate (XXIVb, XXIVc).

Solvolysis of 230 mg. (see before) (39) of the tosylate (XXIVb, XXIVc) gave 130 mg. of XXIX, XXIXa). Crystallization from acetone yielded 38 mg. of (XXIX, XXIXa), m.p. 64-66°. Its m.p. was not depressed upon admixture of an authentic sample (m.p. lit. 63-65° (39)).

CHAPTER III

5α,6α-Oxidocholestan-3β-ol

About 105 g. of cholesterol in 700 ml. of dry benzene was treated with 1200 ml. of monoperphthalic acid (33) (0.072 g./ml.) and allowed to stand for 72 hours. The ether solution was washed with a saturated solution of sodium bicarbonate and with water, dried over sodium sulphate and evaporated to dryness. Recrystallization from ethyl acetate yielded 50 g. of 5α,6α-oxidocholestan-3β-ol, m.p. 138-141° (Lit. m.p. 142-144° (86)).

6β-Methylcholestan-3β,5α-diol

To 10 g. of 5α,6α-oxidocholestan-3β-ol in 150 ml. of dry benzene was added over a 15-minute period a solution of methyl magnesium iodide (prepared from 8.0 g. of magnesium and 20 ml. of methyl iodide) in 100 ml. of dry ether. Part of the ether was driven off and a further 100 ml. of dry benzene was added. When the temperature of the distillate reached 78°, the solution was refluxed for a further four hours.

The excess Grignard was destroyed by adding 200 ml. of ice water containing 0.04 moles of ammonium chloride. The solution was extracted with ether and after the usual work up gave 6.2 g. of 6β-methylcholestan-3β,5α-diol, m.p. 178-179°, in 60% yield (Lit. m.p. 181-181.5° (44)).

6β-Methylcholestan-5α-ol-3-one

To a mixture of 3.0 g. of 6β-methylcholestan-3β,5α-diol in 60 ml. acetone at 0°, Jones reagent (50,51,52) was added drop by drop until the solution was pale-green. The solution was stirred at 0° for 20 minutes. Water was added and the product filtered, washed with methanol until colourless and recrystallized from acetone-methanol to give 2.0 g. of 6β-methylcholestan-5α-ol-3-one, m.p. 199-200° (Lit. m.p. 215.5-216° (44)).

6α-Methylcholest-4-en-3-one (XXX)

Into a solution of 2.0 g. of 6β-methylcholestan-5α-ol-3-one in 20 ml. of chloroform, anhydrous hydrochloric acid was bubbled for 10 minutes. Evaporation of the solvent left an oil which was chromatographed on alumina. Elution with hexane-benzene mixtures gave 0.7 g. of XXX, m.p. 122-123° (Lit. m.p. 127-128.5° (44)). The infrared spectrum of XXX confirmed the structure.

3-Methoxy-6-methylcholesta-3,5-diene (XXXI)

To 0.55 g. of XXX in 5 ml. of dioxane and 0.5 ml. of trimethylorthoformate was added one drop of concentrated sulphuric acid in 0.5 ml. of dioxane and the solution was refluxed for two minutes. Pyridine (0.25 ml.) was added and the solvent was evaporated in vacuo. The resulting oil was covered with methanol and allowed to crystallize overnight. Recrystallization from methanol gave 0.47 g. of XXXI, m.p.

89.5-91°, λ_{max}^{EtOH} 247 mμ (ϵ = 24,800) (c.f. 87), $[\alpha]_D$ -127° (c, 1.0 in pyridine).

Calc. for $C_{29}H_{48}O$: C, 84.40; H, 11.72%.

Found: C, 84.24; H, 11.73%.

Irradiation of 3-Methoxy-6-methylcholesta-3,5-diene (XXXI) in Methanol

Irradiation of 0.4 g. of XXXI in 70 ml. of pentane and 450 ml. of methanol for 30 minutes gave directly by concentration of the solution and filtration 0.32 g. of 3,3-dimethoxy-6-methylcholest-5-ene (XXXII), m.p. 118-119°, in 75% yield. Recrystallization from ether-methanol gave XXXII, m.p. 119-121°, $[\alpha]_D$ -43.5° (c, 1.14 in chloroform).

Calc. for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79%.

Found: C, 81.55; H, 11.82%.

Evaporation of the mother liquors left 110 mg. of an oil whose infrared spectrum indicated the presence of ketal XXXII, an α,β-unsaturated ketone, ν 1685 cm^{-1}, and a saturated ketone, ν 1720 cm^{-1}.

A solution of 125 mg. of XXXII, 50 mg. of malonic acid, 10 ml. of acetone and 1 ml. of water was allowed to stand for four days at room temperature. An infrared spectrum of the product, obtained after the usual work up, showed that complete hydrolysis had occurred to give an α,β-unsaturated ketone, ν 1685 cm^{-1}, and a saturated ketone, ν 1720 cm^{-1}.

6β-Fluorocholestan-3β,5α-diol

Boron trifluoride etherate (5 ml.) was added to a solution of 5α,6α-oxidocholestan-3β-ol (5.0 g.) in a 1:1 mixture of anhydrous ether-benzene (500 ml.) and the solution was allowed to stand for three hours at room temperature. The solution was washed with 5% sodium bicarbonate solution, water dried over sodium sulphate and evaporated to dryness. The residue was dissolved in 150 ml. of benzene-ether (4:1) and adsorbed on alumina suspended in benzene as the initial solvent. Elution with benzene-ether (4:1) (450 ml.) gave an oil and further elution with 1200 ml. of ether gave starting material. Elution with absolute ethanol gave 3.0 g. of impure 6β-fluorocholestan-3β,5α-diol (45), m.p. 185-200°. (Lit. crude m.p. 189-202°, pure m.p. 219-221° (45)). This product was not further purified.

6β-Fluorocholestan-5α-3-one

A solution of crude 6β-fluorocholestan-3β,5α-diol (3.0 g.) in 150 ml. of acetone at 0° was treated with an excess of Jones reagent (50,51,52). After standing for three minutes at 0°, water was added and the precipitate was filtered to give 2.0 g. of 6β-fluorocholestan-5α-ol-3-one, m.p. 210-225° (Lit. crude m.p. 223-227°, pure m.p. 230-231° (45)). The precipitate was washed with methanol until colourless and the material was used directly in the next step.

6α-Fluorocholest-4-en-3-one (XXXa)

Into a solution of 1.7 g. of 6β-fluorocholestan-5α-ol-3-one in 20 ml. of chloroform, anhydrous hydrogen chloride was bubbled for 15 minutes. After standing for one hour, the chloroform was evaporated and the oily residue was chromatographed on alumina. Elution with hexane-benzene (1:2) gave 650 mg. of XXXa, m.p. 115-116° (Lit. m.p. 116-118° (45)). Its infrared spectrum showed peaks for an α,β-unsaturated ketone (ν 1695 cm^{-1}) and for carbon-fluorine stretching (ν 1067 cm^{-1}).

6-Fluoro-3-methoxycholesta-3,5-diene (XXXIa)

To a solution of 0.375 g. of XXXa in 5 ml. of dioxane and 0.5 ml. of trimethylorthoformate was added one drop of concentrated sulphuric acid in 0.5 ml. of dioxane and the solution was refluxed for two minutes. Pyridine (0.25 ml.) was added and the solvent was evaporated in vacuo. The oil obtained was covered with methanol to induce crystallization. Recrystallization from ether-methanol (containing one drop of pyridine) afforded 0.30 g. of XXXIa, m.p. 90.5-91.5°, $[\alpha]_D$ -107.5° (c, 0.93 in pyridine), λ_{max}^{EtOH}, 239 mμ (ε 22,600).

Calc. for $C_{28}H_{45}OF$: C, 80.71; H, 10.89; F, 4.56%.

Found: C, 80.18; H, 10.26; F, 4.65%.

Irradiation of 6-Fluoro-3-methoxycholesta-3,5-diene (XXXIa) in Methanol

Irradiation of 0.20 g. of XXXIa in 50 ml. of pentane and 475

ml. of methanol for 20 minutes gave directly by concentration of the solution and filtration 0.175 g. of 3,3-dimethoxy-6-fluorocholest-5-ene (XXXIIa) in 85% yield. Recrystallization from ether-methanol gave XXXIIa, m.p. 104-104.5°, $[\alpha]_D$ -31.4° (c, 1.0 in chloroform).

Calc. for $C_{29}H_{49}O_2F$: C, 77.63; H, 11.01; F, 4.23%.

Found: C, 77.29; H, 10.78; F, 4.67%.

Evaporation of the mother liquors gave 35 mg. of oil whose infrared spectrum indicated the presence of ketal XXXIIa, an α,β-unsaturated ketone (ν 1695 cm^{-1}), and a saturated ketone (ν 1730 cm^{-1}).

A solution of 25 mg. of XXXIIa in 5 ml. of carbon tetrachloride was evaporated in vacuo at 80° on the steam bath. The resulting oil showed absorption in the infrared spectrum at 1730 cm^{-1} and 1695 cm^{-1} indicating the formation of saturated and α,β-unsaturated ketones respectively.

6β-Nitrocholest-4-en-3β-ol (XXXIV) (46)

A solution of 3β-acetoxy-6-nitrocholest-5-ene (XXXIII) (5.0 g.) (49) in 300 ml. of methanol, containing 3.0 g. of potassium hydroxide, was heated under reflux for 1.5 hours. Acidification with acetic acid, addition of water and filtration gave a product which was crystallized from aqueous methanol to yield 1.83 g. of XXXIV. Recrystallization from methanol gave XXXIV, m.p. 141-142°, $[\alpha]_D$ -98.9° (c, 0.89 in chloroform).

Calc. for $C_{27}H_{45}O_3N$: C, 75.13; H, 10.51; N, 3.25%.

Found: C, 75.01; H, 10.74; N, 3.70%.

6β-Nitrocholest-4-en-3-one (XXXV)

To a solution of 1.0 g. of XXXIV in 60 ml. of acetone at 0° was added an excess of Jones reagent (50,51,52) and the solution was stirred for two minutes. Addition of water and filtration of the resulting precipitate gave 1.0 g. of XXXV. Recrystallization from ether-methanol gave 0.8 g. of XXXV, m.p. 118-119°, $[\alpha]_D$ -98.8°, (c, 0.87 in chloroform), λ_{max}^{EtOH}, 233 mμ (ε 12,600).

Calc. for $C_{27}H_{43}O_3N$: C, 75.48; H, 10.09; N, 3.26%.

Found: C, 75.44; H, 10.47; N, 3.29%.

6α-Nitrocholest-4-en-3-one (XXXb)

A solution of 600 mg. of XXXV in 5 ml. of methanol, containing 25 mg. of potassium hydroxide, was kept at room temperature for two minutes. After acidification with acetic acid, addition of water gave 600 mg. of XXXb. Recrystallization from methanol gave pure XXXb, m.p. 136-137°, $[\alpha]_D$ +78.0° (c, 0.91 in chloroform), λ_{max}^{EtOH}, 232 mμ (ε 15,800).

Calc. for $C_{27}H_{43}O_3N$: C, 75.48; H, 10.09; N, 3.26%.

Found: C, 75.55; H, 9.99; N, 2.47%.

3-Methoxy-6-nitrocholesta-3,5-diene (XXXIb)

To a solution of 350 mg. of XXXb in 5 ml. of dioxane and 0.5 ml. of trimethylorthoformate was added one drop of concentrated sulphuric acid in 0.5 ml. of dioxane and the solution was refluxed for two minutes. Pyridine (0.25 ml.) was added and the solvent removed in vacuo at 80°. The oil was covered with methanol and after standing in the cold over-

night, 250 mg. of XXXIb, m.p. 135-136°, was obtained. Recrystallization from ether-methanol (containing one drop of pyridine) decreased the m.p. of XXXIb to 129-136°, $[\alpha]_D$ -8.3° (c, 1.27 in pyridine), λ_{max}^{EtOH} 233 mμ (ε 14,000).

Calc. for $C_{28}H_{45}O_3N$: C, 75.80; H, 10.22; N, 3.16%.

Found: C, 76.01; H, 10.20; N, 2.58%.

Irradiation of 3-Methoxy-6-nitrocholesta-3,5-diene (XXXIb) in Methanol

Irradiation of 0.2 g. of XXXIb in 10 ml. of pentane and 515 ml. of methanol for 10 minutes gave upon evaporation of the solvent 0.23 g. of oil. Its n.m.r. spectrum showed broad absorption peaks indicative of a complex mixture of compounds.

6β-Methoxycholest-4-en-3-one (XXXd) (47)

A solution of 2.9 g. of cholest-4-en-3-one (26b), 4.46 g. of cupric bromide, 1.6 ml. of pyridine and 40 ml. of methanol was refluxed for 35 minutes. The solution was cooled and the inorganic precipitate was filtered. The filtrate was evaporated and treated with ethyl acetate in order to precipitate all of the cupric bromide. Filtration gave an ethyl acetate solution, which was evaporated to an oil and treated with ether-methanol to effect crystallization. About 500 mg. of 6β-methoxycholest-4-en-3-one (XXXd) were obtained in this manner. Chromatography of the mother liquors on alumina gave in the hexane-benzene (1:2) fractions a further 1.0 g. of XXXd, m.p. 107-108°. Recrystallization from methanol gave XXXd, m.p. 113-114°, λ_{max}^{EtOH} 234 mμ

(ν 14,400). Its infrared spectrum showed absorption peaks at 1690 cm^{-1} and at 1095 cm^{-1} due to the α,β-unsaturated ketone and the 6β-methoxy group respectively.

It was attempted to prepare 3,6-dimethoxycholesta-3,5-diene by treatment of XXXd with trimethylorthoformate (see before) but a mixture of dienes and ketones resulted as indicated by an infrared spectrum of the oily product.

An attempt to prepare 3,6-dimethoxycholesta-3,5-diene by similar treatment of cholestan-3,6-dione (26d) with trimethylorthoformate also failed.

Cholest-4-en-6-one (44)

To a solution of 12 g. of 5α,6α-oxidocholestan-3β-ol in 200 ml. of dry benzene was added a mixture of approximately 15 g. of anhydrous magnesium bromide in 50 ml. of diethyl ether (anhydrous magnesium bromide was prepared by adding bromine dropwise with shaking over a 30-minute period to 3.0 g. of magnesium in 10 ml. of ether). The solution was distilled until the temperature of the distillate was 78° and 100 ml. of benzene was added. The solution was then refluxed for five hours. After cooling, water was added and the solution was worked up as usual. Chromatography of the resulting oil on alumina gave in the hexane-benzene (1:1) fractions 1.0 g. of cholest-4-en-6-one. Recrystallization from methanol gave cholest-4-en-6-one, m.p. 107-108° (Lit. m.p. 107-108° (44)). Its infrared spectrum showed the presence of an α,β-

unsaturated ketone at 1690 cm^{-1}.

An attempt to prepare 6-ethoxycholesta-3,5-diene by treatment of cholest-4-en-6-one with triethylorthoformate was unsuccessful (see before).

CHAPTER IV

Irradiation of 3-Chlorocholesta-3,5-diene (XXXVI) in Ethanol

A solution of 1.8 g. of XXXVI (55,56), λ_{max}^{EtOH}, 242 mμ (ε 22,400), 250 (i) and 230 (i) mμ (ε 20,400 and 15,300) in 450 ml. ethanol and 50 ml. of pentane was irradiated until no ultraviolet absorption could be detected (4 hours). After evaporation of the solvent, the photolysis mixture was separated by TLC (silica gel). Using hexane as eluant, two fast (A and B) and two slow-moving bands (C and D) were evident. Desorption of bands A and B with ether gave 200 mg. of oil, which was separated by TLC (hexane) into four major and two minor bands. Fractions 1, 2 and 6 contained less than 0.5% chlorine. Their infrared spectra showed only bands characteristic of hydrocarbons.

Fraction 3 (50 mg.), m.p. 55-65°, on recrystallization from methanol yielded 14 mg. of a compound, m.p. 67-71°, whose n.m.r. and infrared spectra were virtually identical with that of 3β-chlorocholest-5-ene, m.p. 97° (26c).

Calc. for $C_{27}H_{45}Cl$: C, 80.04; H, 11.19; Cl, 8.75%.

Found: C, 79.21; H, 11.17; Cl, 9.38%.

Desorption of band C with ether and rechromatography (TLC, hexane-benzene 4:1) yielded fractions 7-14. Fraction 9 gave 53 mg. of crystals, m.p. 125-129°. Recrystallization from hexane gave 16 mg. of pure 3-chloro-6β-ethoxy-3β,5-cyclocholestane (XXXVII), m.p. 131-133°, [α] +6.8° (c, 1.5 in chloroform).

Calc. for $C_{29}H_{49}OCl$: C, 77.56; H, 11.00; Cl, 7.90%.
Found: C, 77.54; H, 10.57; Cl, 8.01%.

Fractions 7, 8, 10, 11, 12, 13, and 14 could not be sufficiently purified for structural studies.

Band D, after extraction with ether, was rechromatographed (TLC, benzene-ether (19:1)). Fractions 15-18, accounting for 65% of the photolysis products, were obtained but could not be characterized.

Irradiation of 3-Acetoxycholesta-3,5-diene (XXXVIa)

A solution of 1.1 g. of XXXVIa (57) λ_{max}^{EtOH} 234 mμ (ε 16,000) in 1700 ml. of ethanol, methanol, or methanol containing a few drops of pyridine was irradiated until the absorption maximum had decreased to less than 5% of the original absorption (1 hour). Chromatography on alumina yielded in the ether fractions 100 mg. of cholest-4-en-6β-ol-3-one (XXI), m.p. 160-165°. Recrystallization from hexane gave XXI, m.p. 181-184° (mixed m.p. with an authentic sample is 181-184°).

Irradiation of XXXVIa in pentane yielded intractable mixtures.

3-(p-Ethoxyphenyl)cholesta-3,5-diene (XXXVIc)

p-Bromophenetole (9 ml.) in 40 ml. of anhydrous ether was added slowly to 2.75 g. of magnesium, activated by a few crystals of iodine. After completion of the reaction (3 hours), 10 g. of cholest-4-en-3-one was added to the Grignard reagent and the reaction mixture was

stirred under reflux overnight. A 20% solution of hydrochloric acid in ethanol was added slowly to the reaction mixture to destroy excess Grignard and the mixture was refluxed for four hours to ensure dehydration of the reaction product.

About 8.0 g. of XXXVIc, m.p. 120-121°, λ_{max}^{EtOH}, 288 mμ (ε 25,900), λ_{max}^{EtOH}, 227 mμ (ε 10,300), 234 mμ (shoulder), was obtained in 63% yield.

Calc. for $C_{35}H_{52}O$: C, 86.00; H, 10.72%.

Found: C, 86.00; H, 10.38%.

Irradiation of 1.2 g. of XXXVIc in either ethanol or pentane-acetic acid for seven hours yielded intractable mixtures.

Irradiation of 3-Phenylcholesta-3,5-diene (XXXVIb) in Ethanol

Irradiation of 1.2 g. of XXXVIb (58) in 1300 ml. of ethanol and 400 ml. of pentane for 24 hours gave 2.8 g. of product. Chromatography on alumina gave a total of 1.6 g. of oily fractions. The n.m.r. spectrum of the major fraction indicated a mixture.

Irradiation of 3-Ethylthiocholesta-3,5-diene (XXXVId) in Ethanol

Irradiation of 0.37 g. of XXXVId (59) in 425 ml. of ethanol, 100 ml. pentane and 0.25 ml. pyridine for 0.5 hours yielded 0.5 g. of a brown evil-smelling oil. Chromatography on alumina did not result in further purification.

Irradiation of 3-N-Pyrrolidinylcholesta-3,5-diene (XXXVIe) in Pentane

Irradiation of 0.5 g. of XXXVIe (60,61) in 525 ml. of pentane for one hour gave 0.5 g. of a clear oil upon evaporation of the pentane in vacuo at room temperature. The n.m.r. spectrum of the clear oil showed very broad absorption characteristic of an intractable mixture.

CHAPTER V

Irradiation of 3-Ethoxycholesta-3,5-diene (XIII) in Ethanol Saturated with Oxygen

A solution of 0.8 g. of XIII in 565 ml. of ethanol, through which oxygen had been bubbling for 40 minutes, was irradiated until the absorption maximum of XIII had decreased to 2% of its original intensity (1 hour). Chromatography on alumina gave, in the hexane fractions, 525 mg. of 3,3-diethoxycholest-5-ene, m.p. 48-49°. Its m.p. and infrared spectrum were identical with that of an authentic sample (24). Elution with ether yielded 75 mg. of cholest-4-en-6β-ol-3-one, m.p. 182-183°, identified by a mixed m.p. with an authentic sample (26b). Both products had been formed in similar yields when oxygen had been excluded from the photolysis reaction (24).

Irradiation of 3-Ethoxycholesta-3,5-diene (XIII) in Ethanol Using Benzophenone as a Photosensitizer

Irradiation (utilizing a "pyrex" sleeve to absorb radiation below 330 mμ) of 0.5 g. of XIII in ethanol (525 ml.), containing 0.5 g. of benzophenone, for 2.5 hours resulted in a decrease of the absorption maximum to less than 20% of the original absorbance. Evaporation of the solvent gave 0.2 g. of benzpinacol as crystals. The remaining oil (0.6 g.) was chromatographed on alumina. Elution with hexane gave 90 mg. of XIII. Further elution with hexane-benzene mixtures gave fractions which seemed to contain benzophenone, benzpinacol, and cholest-

4-en-3-one as indicated by their infrared spectra. Elution with ether gave 190 mg. of crude cholest-4-en-6β-ol-3-one (XXI), from which 60 mg. of XXI, m.p. 186-187°, was obtained by crystallization from hexane.

The same irradiation performed in the absence of benzophenone showed no reaction after 2.5 hours.

Thermal Reaction of 3-Ethoxycholesta-3,5-diene (XIII) in Dry Ethylene Glycol and Pyridine

A solution of 50 ml. of ethylene glycol and 200 ml. of benzene was distilled until all of the benzene was removed. About 0.5 g. of XIII was added to the refluxing ethylene glycol and 1 ml. of pyridine was dropped into the mixture. After refluxing for four hours the solution was allowed to cool to room temperature. The solution was extracted with ether, washed eight times with water, dried over sodium sulphate and evaporated to dryness to give 0.3 g. of an oil, which crystallized on standing. Two recrystallizations from ether-isopropanol gave cholest-5-en-3-one ethylene ketal (XXXVIII), m.p. 130-131°. The infrared spectrum of the ketal and a mixed m.p. with authentic material (83) confirmed the identity of the product.

Reaction of 0.5 g. of cholest-4-en-3-one (XX), under identical conditions as above resulted in complete recovery of starting material.

Thermal Reaction of 3-Ethoxycholesta-3,5-diene (XIII), in Ethanol and Pyridine

A solution of 0.1 g. of XIII, 8 ml. of ethanol, and 0.5 ml. of

pyridine was heated at 175° for six hours in a sealed tube. The solution was cooled to room temperature and the solvent evaporated in vacuo. An infrared spectrum of the resulting oil did not show any bands characteristic of 3,3-diethoxycholest-5-ene (XIV) (24). Only the presence of starting material and an α,β-unsaturated ketone (cholest-4-en-3-one from hydrolysis of XIII) were indicated by the infrared spectrum.

CHAPTER VI

3-Deuteriocholesta-3,5-diene

To a mixture of 0.2 g. of lithium aluminum deuteride in 20 ml. of ether was added as a solid 0.5 g. of cholest-4-en-3-one and the solution was stirred for one hour. A solution of 2 ml. of concentrated hydrochloric acid in 10 ml. of ethanol was added, and the reaction mixture allowed to reflux for one hour. After the usual work-up, 0.3 g. of pure 3-deuteriocholesta-3,5-diene, m.p. 81°, was obtained. Its melting point was not depressed on admixture of authentic cholesta-3,5-diene (26e).

CLAIMS TO ORIGINAL RESEARCH

I. The photolysis of 3-alkoxycholesta-3,5-dienes was investigated.

II. A simple procedure for preparing β,γ-unsaturated mixed ketals has been described.

III. The photolyses of other 3-substituted cholesta-3,5-dienes were described.

IV. Mechanistic interpretations of the irradiations were suggested.

V. N.m.r. data of fourteen cholesta-3,5-dienes were given.

VI. 3-Deuteriocholesta-3,5-diene, 4β-deuterio-3α,5-cyclocholestan-6β-ol, 4β-deuteriocholesterol and other deuterated cholesteryl derivatives were stereospecifically synthesized.

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