THE EFFECT OF SOME 3-OXYGEN FUNCTIONS ON THE SIMMONS-SMITH METHYLENATION OF 5,6-UNSATURATED STEROIDS

by

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ABSTRACT

The effect of 3α- (28) and 3β- (27) hydroxy, 3α- (47) and 3β- (44) acetoxy, 3-ethylene acetal (41), and 3α-methoxy (40) derivatives of 5-cholestene on the addition of the Simmons-Smith reagent to the steroidal 5,6-double bond has been investigated. Reaction was accelerated with epi-cholesterol (28) to yield chiefly 5,6β-dihydro-3'H-cyclopropa [5,6]-5α-cholestan-3α-ol (29), which was oxidized to 5,6β-dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3-one (33) by Jones reagent. Acid catalyzed ring-opening of the ketone (33) lead to the known 6α-methyl-4-cholesten-3-one (34). 3α-Ethoxy-5,6β-dihydro-3'H-cyclopropa[5,6]-5α-cholestane (42), 5,6β-dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3α-yl acetate (43), and bis(5,6β-dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3α-oxy) methane (37) were also identified as byproducts. The acetate (43) was also prepared by acetylation of the corresponding alcohol (29).

Reduction of the ketone (33) with lithium tri-tertiary-butoxyaluminium hydride gave an epimeric alcohol, 5,6β-dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3β-ol (35), which was further characterized as its acetate, 5,6β-dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3β-yl acetate (36). 5,6β-dihydro-3'H-cyclopropa [5,6]-5α-cholestan-3-one ethylene acetal (46) was also prepared by ketalization of the ketone (33). Cholesta-3,5-diene (45)

was isolated from more vigorous reaction on cholesteryl acetate (44).

Proton magnetic resonance and mass spectral data of these 5,6β-dihydro-3'H-cyclopropa[5,6]-5α-cholestane derivatives are recorded and discussed.

TABLE OF CONTENTS

TABLE OF CONTENES (cont'd)

LIST OF TABLES

LIST OF SPECTRA

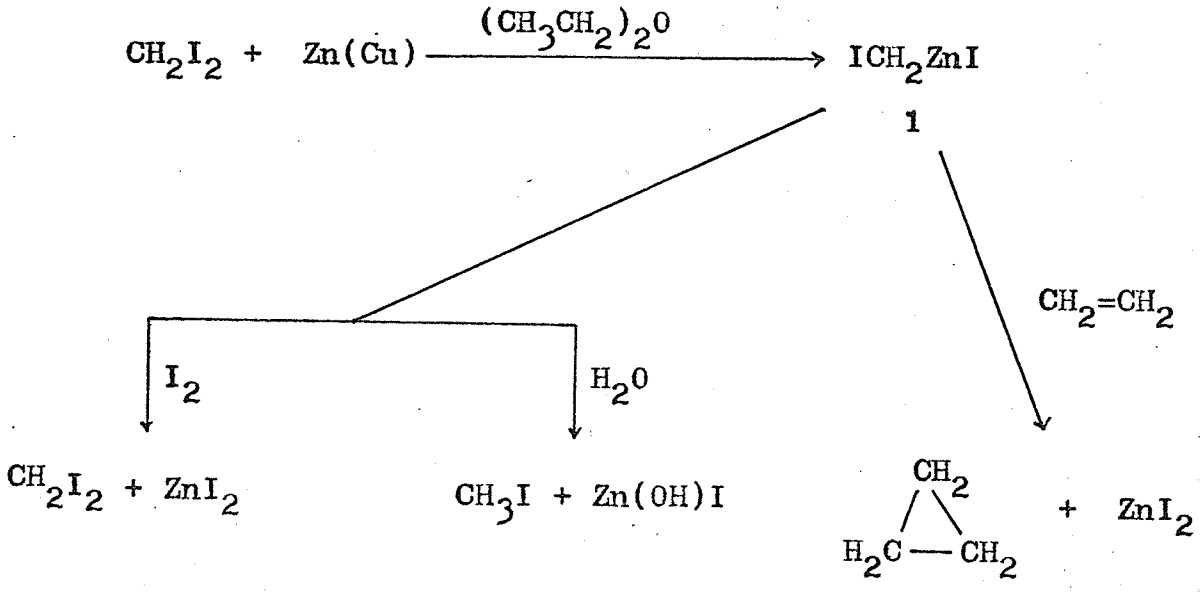
LIST OF SPECTRA (cont'd)

I. INTRODUCTION

The study of cyclopropane derivatives has been developed in recent years because of the discovery of physical methods of detection [1]. The occurrence of cyclopropane derivatives in nature as well as their importance in theoretical [2] and synthetic [3] studies had lead to further interest in these substances. Many methods have been developed for the preparation of cyclopropane derivatives, but most of the methods either demanded complex starting materials or were not general in scope.

In 1958, a novel cyclopropane-forming reaction (Scheme I) which involved the treatment of olefins with an iodomethylzinc iodide reagent, prepared from diiodomethane and a zinc-copper couple, was developed by Simmons and Smith [4]. It has found wide application in organic synthesis.

Scheme I



Simmons and Smith[4] found that diiodomethane reacted with zinc-copper couple in diethyl ether to give a solution that contained a stable organozinc intermediate (1) which reacted with iodine to regenerate diiodomethane, was hydrolyzed by water to methyl iodide, and reacted with olefins to give cyclopropane (Scheme I). The reaction could be carried out in other oxygen-containing solvents, such as ethyl acetate, tetrahydrofuran, ethylene glycol dimethyl ether, and dioxane. However, diethyl ether has so far proved to be the most effective. Mixed solvents, such as ether and tetrahydrofuran offered no advantages. Copper in the zinc-couple was shown[4] to play no role in cyclopropane formation, but serves to activate the zinc metal surface for reaction with diiodomethane. However, Šorm et al.[5] recently found that a 0.5 percent copper content of the couple, prepared by method of LeGoff[6], is optimal in the formation of 3β-acetoxy-5,7β-cyclo-5β-cholestane.

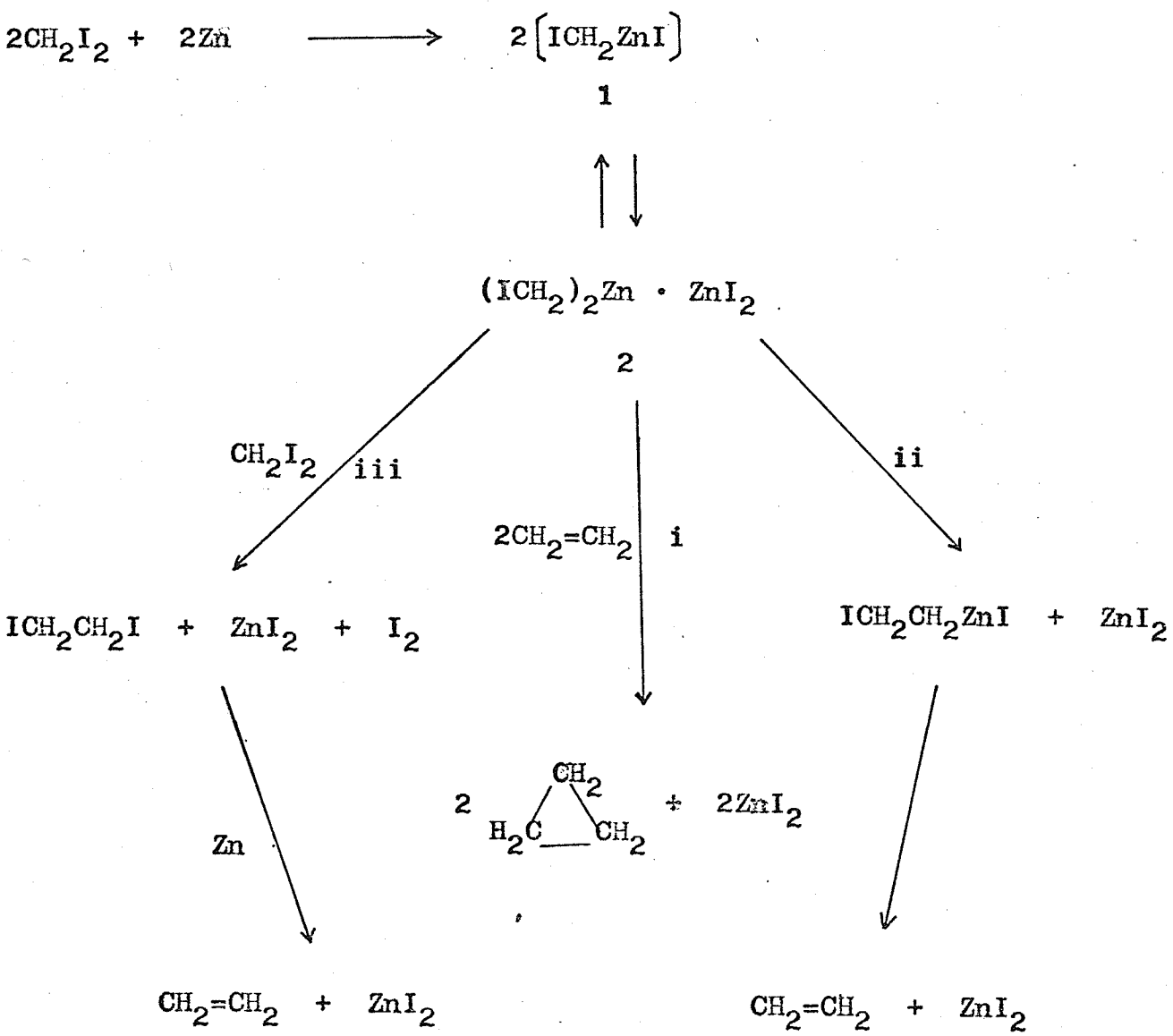
Blanchard and Simmons[7] have shown experimentally that the iodomethylzinc iodide reagent is best represented as an equilibrium between the two organozinc species, namely, 1 and 2.

$$2\ ICH_2ZnI \rightleftharpoons (ICH_2)_2Zn \cdot ZnI_2$$

1 2

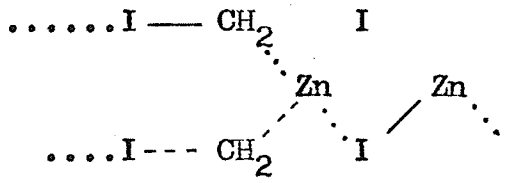
They further established that a stable intermediate containing the partial structure (.....ICH_2Zn-) and with the expected chemistry of 1 and 2, can be incorporated in the following scheme.

Scheme II



The primary reactions at the metal surface are the formation of 1 and 2. The success of the methylene-addition reaction (i) depends on it proceeding at a faster rate than ii and iii.

The structure of the organozinc intermediate as represented by 1 and 2 is complicated by the presence of an α-iodine atom in the alkyl group. In the simplest terms, the polymeric structure (3) or the monomeric structure (4) might be regarded as reasonable representations of the cyclopropane-forming reagent. The extent and type of coordination is a function of solvent and probably of concentration [7]. Little is known of the electronic structure and geometry of this coordination.



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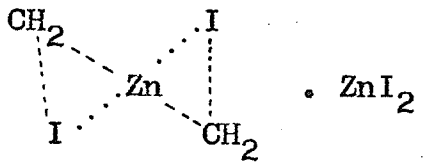

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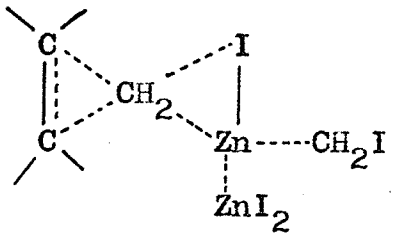
Simmons and Smith [4] have found experimentally that higher electron density at the carbon-carbon unsaturation enhances the rate of the cyclopropane formation. Later work by Rickborn and Chan [8] on the relative rates determinantion for a number of cyclic olefins showed that vinyl alkyl substituents diminished the rate of reaction with iodomethylzinc iodide in some cases, e.g., 1,2-dimethylcyclohexene. They have suggested a balance between small inductive and steric effects with the

latter predominated in these cases. Furthermore, it has been shown that reaction occurs between the organozinc reagent and a double bond with high stereospecificity [4]. A mechanism which would account for the experimental observations has been suggested [4]. It involves a " one-step methylene-transfer " (5) in which an electrophilic methylene in bis(iodomethyl)zinc · zinc iodide (2), may primarily attack an olefinic double bond, followed by simultaneous cyclopropane formation with elimination of ICH_2ZnI.



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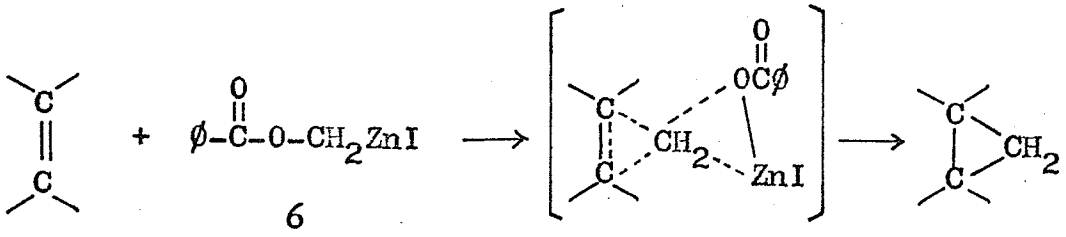
Addition of methylene to olefin involving free methylene[9] or carbene [10] was ruled out, since a filtered solution of the product from the reaction of diiodomethane and zinc-copper couple remained active in cyclopropane formation after storage for several hours at 0^{o} [4].

Wittig and Schwarzenbach [11] reported the cyclopropane formation from olefins by means of bis-benzoxymethylzinc iodide (6) which is capable of transferring methylene by an analogous one-step mechanism (Scheme III).

Scheme III



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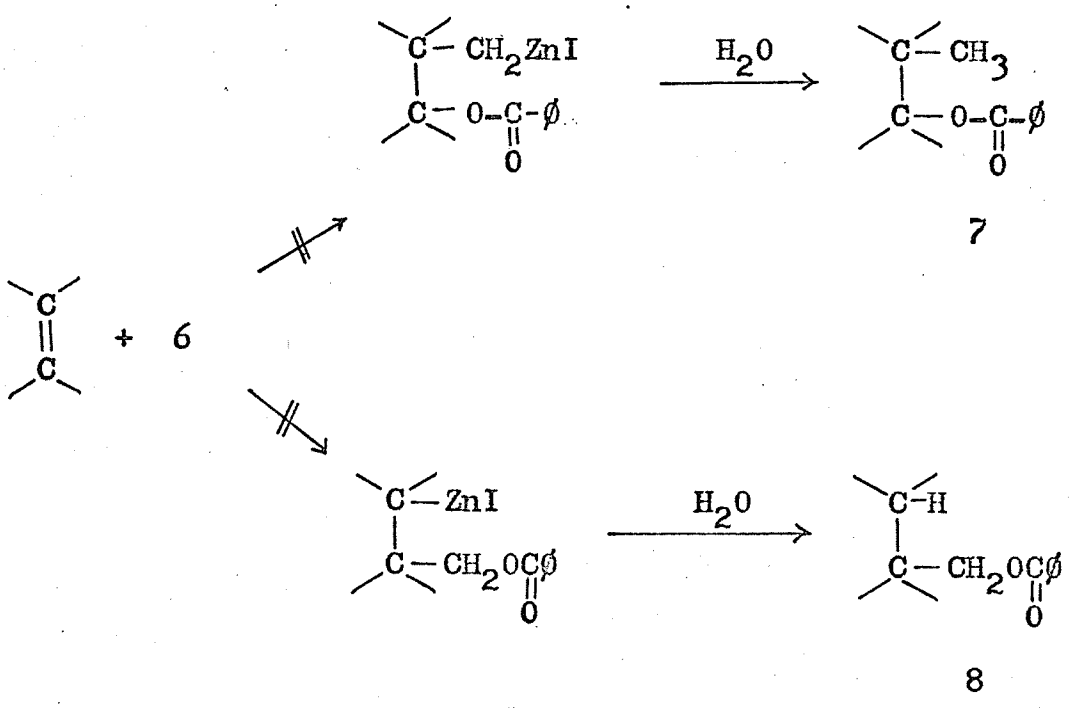
They have supported the methylene-transfer mechanism by their evidence that neither 7 nor 8 (Scheme IV), which may be expected from a four-center two-step mechanism[12], has been detected by g.l.p.c. analysis.

Scheme IV



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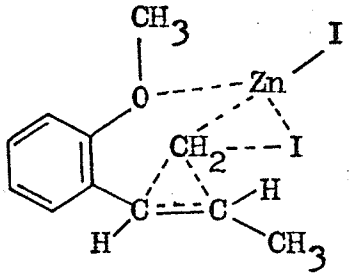
An important aspect of this methylenation reaction is the stereochemical control exerted on the developing cyclopropane ring and the rate enhancement contributed by a properly oriented neighbouring substituent carrying a lone pair of electrons, such as oxygen or nitrogen. Simmons and Smith[4] have pointed out that 1-(o-methoxyphenyl)propene with the reagent gave a higher yield of the corresponding cyclopropane than did the meta- and para- substituted isomers. They have inferred the coordination of the zinc atom in the reagent with the ether oxygen thereby stabilizing the transition state (9) in the case of the ortho-isomer.



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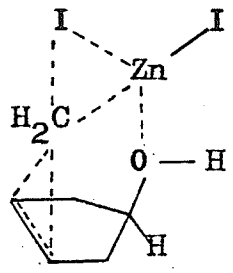
In olefinic alcohols, the hydroxy function influences not only the rate of cyclopropane formation but also the steric course of the reaction. This was first observed by Winstein *et al.*[13] in the conversion of homoallylic 3-cyclopentenol to the *cis*-bicyclo-[3·1·0]-hexan-3-ol. They have proposed a cyclic transition state (10) as follows:



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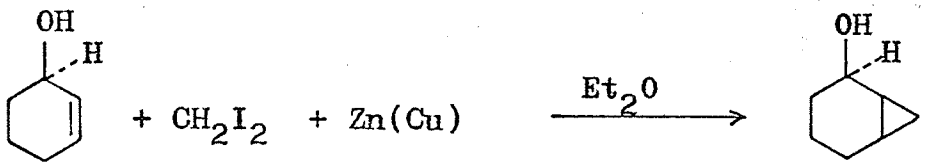
Other homoallylic alcohols, such as 3-cycloheptenol[14] and 3-cyclohexenol[15], have been found to undergo methylenation with very high cis specificity.

This effect is operative also in allylic alcohols, as shown by Dauben and Berezin[16] in the conversion of 2-cyclohexenol to the corresponding cyclopropane derivative (Scheme V).

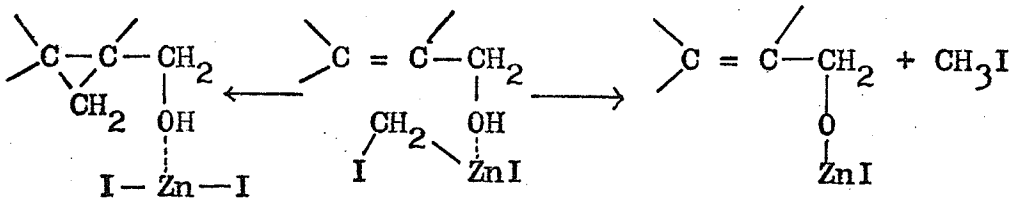
Scheme V



Dauben and Berezin[16] have suggested that the first stage in the reaction of the Simmons-Smith reagent with an olefinic alcohol, is the formation of a zinc-oxygen complex(11). This complex can then undergo decomposition to form the alkoxyzinc iodide (12)

and methyl iodide or when the geometry is favorable by insertion of the methylene group onto a double bond.

Scheme VI

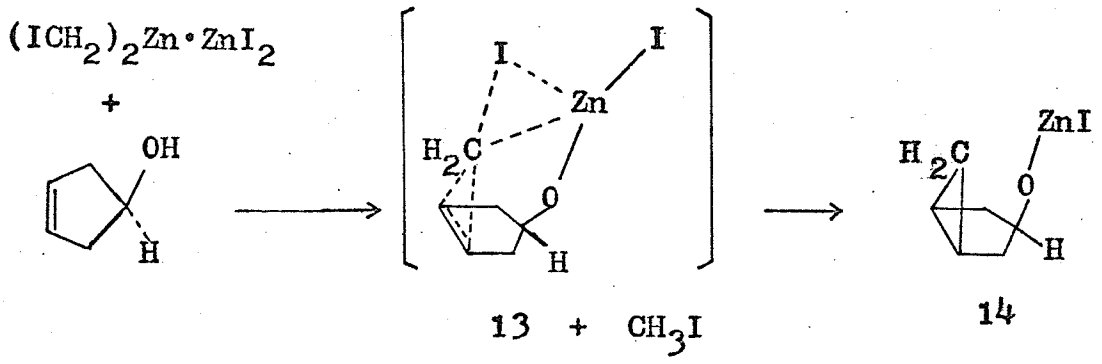


11 12

The suggestion of the formation of a complex such as 11 involving an unshared electron pair on the oxygen of the hydroxy function was further indicated by the isolation of only cis-2-bicyclo-[4.1.0]-heptylmethyl ether from the Simmons-Smith reaction with 2-cyclohexenylmethyl ether.

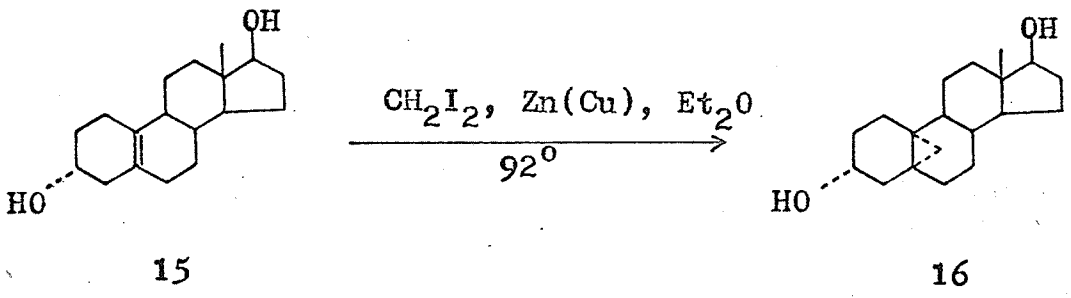
Concurrently, Blanchard and Simmons [7], noted that nearly equal amounts of methyl iodide and cyclopropyl derivative was formed in the reaction with 3-cyclopentenol (Scheme VII). Here, the Simmons-Smith reagent reacts with the oxygen function with the formation of intermediate 13 and methyl iodide. Intramolecular methylene-transfer would then yield cis-3-bicyclo-[3.1.0]-hexanol after hydrolysis of 14. The high stereoselectivity observed in the addition to this hydroxy-containing olefin can only be accounted for by prior complex formation or reaction of the reagent with the hydroxy group.

Scheme VII



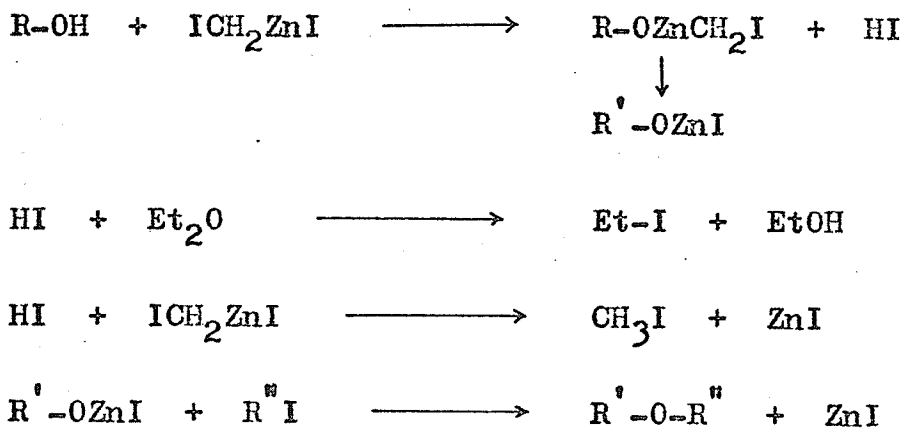
Data supporting alcoholysis have been obtained by Ginsig and Cross[17] from a homoallylic system. They carried out the Simmons-Smith reaction on estr-5(10)-ene-3α,17β-diol (15) (Scheme VIII) at 92° in a sealed tube, the product (16) obtained was extensively contaminated with methoxy- and ethoxy- derivatives of the alcohol.

Scheme VIII



A dramatic improvement resulted when the alcohol (15), an excess of diiodomethane, and zinc-copper couple, and ether were removed to half-volume prior to sealing in the tube. Reaction at 92° then afforded a good yield of 16 and formation of ethereal byproducts was minimized. These results indicate that the reagent initially reacts with alcohols. This reaction forms hydrogen iodide which reacts further with the reagent or solvent to release alkyl iodides. Formation of ethers can then proceed by the following steps (Scheme IX) in the reaction without prior distillation. In the reaction with distillation the resulting alkyl iodides were simply removed by distillation, thereby avoiding steroid ether formation.

Scheme IX



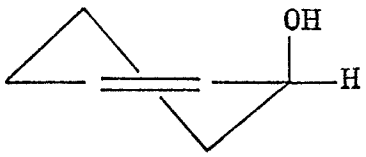
$R'' = CH_3-$; CH_3CH_2-

R' = alkyl group

R = alkenyl group

In the allylic system, Dauben and Berezin [16] found that mixing equivalent amounts of the organozinc reagent and 2-cyclopentenol gave cyclopropyl derivative in eighty percent yield. Rapid prior alcoholysis is clearly precluded by this result. Furthermore, both 2-cyclohexenol and 2-cyclohexenyl methyl ether were found to react readily with the reagent to give exclusively the cis-cyclopropane derivatives in good yield. This stereochemical result could be obtained if the alcohol and the methyl ether reacted by different mechanisms. In competition studies [15], however, the alcohol is methylenated only twice as fast as the methyl ether, whereas a larger difference would be expected if a particularly facile reaction route were available to the alcohol via alcoholysis. No further evidence has so far been found to support prior alcoholysis in the allylic system.

Stereochemical studies on the Simmons-Smith reaction showed that the conformation of the hydroxy function and/or the orientation of the coordinated reagent is the important factor in accounting for the rate enhancement as well as stereoselectivity of the reaction. It has been previously suggested [16] that stereospecific methylenation of allylic alcohols in the cyclohexenyl series involves reaction through the axial hydroxy conformation (17). More recently, Chan and Rickborn [15], from rate data, have concluded that the reaction of allylic cyclohexenols occurs through the quasi-equatorial hydroxy conformation (18).



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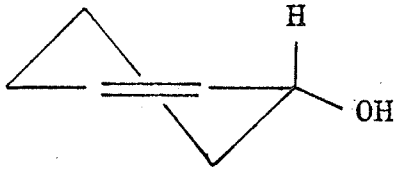
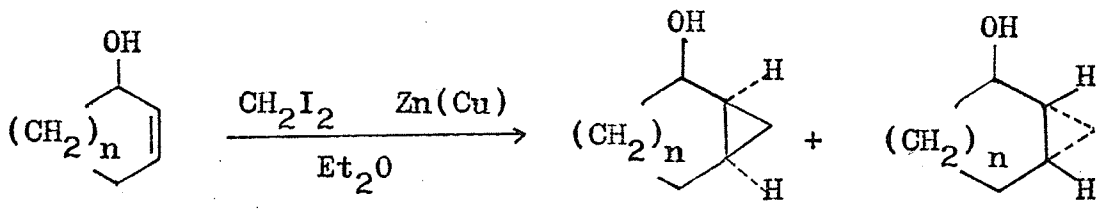


18

Moreover, they have suggested, from the observed epimer rate difference in the reaction of the 3α- and 3β- epimers of estr-5(10)-ene-17β-ol, that there is a fundamental difference in the mechanism of methylenation of allylic and homoallylic alcohols, namely, reaction through the equatorial and axial conformations, respectively. In these compounds the 3α-hydroxy will be predominantly equatorial and the 3β-hydroxy should exist preferentially in the axial conformation [18].

A more general rationalization has been given by Poulter, Friedrich, and Winstein [19] who studied the steric course of methylene addition to the cyclic allylic alcohols (Scheme X) and found that five, six, and seven member alcohols (19a-c) predominated <u>syn</u> addition, as reported previously [14,16.20], whereas eight and nine member alcohols (19d-e) gave <u>anti</u> addition products (20d-e). The reactions were highly stereoselective. This result was explained by assuming complexation between the hydroxy group and the reagent, followed by methylene-transfer to the nearest face of the double bond.

Scheme X



19

a n = 1
b n = 2
c n = 3
d n = 4
e n = 5

syn

a n = 1
b n = 2
c n = 3

anti

20

d n = 4
e n = 5

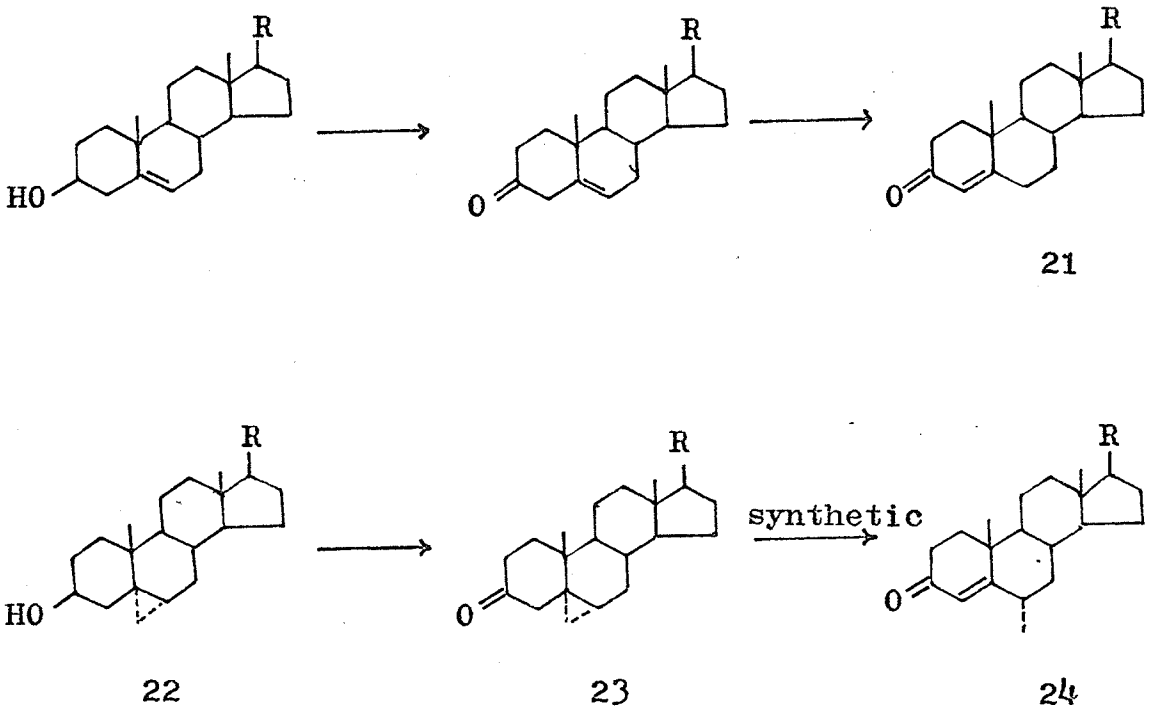
Besides hydroxy function, in allylic systems, ether [16,21], ketone [21], and ester [22] groups are effective in controlling the steric course of the reaction. The enolic ether oxygen has been shown [15] to add the reagent more readily than the analogous double bond, whereas enolic esters are less reactive than the corresponding olefin [23]. Enamines[24,25] also add methylene with the reagent. In homoallylic systems, only the effect of the hydroxy group on the reaction has been reported [13,14,15]. This effect is initiated by an interaction between the electron-donating group with the metal, prior to transfer of methylene, through formation of a zinc oxygen bond [7] or by coordination [16].

The application of this reaction to steroidal olefins has been studied, and it is found useful in the preparation of

cyclo-[5] and cyclopropano-[26] steroids as well as the stereospecific introduction of methyl groups [17,27] through ring opening. Structural modification of steroids have been carried out in order to (a) increase a useful biological activity, i.e., increase potency; (b) increase oral activity; (c) alter duration of action; (d) effect a separation of biological activities; and (e) obtain better solubility properties. The structural modification which has been shown to be most effective in enhancing the useful biological activity of steroids are those which protect the molecule from metabolic oxidation with a minimal structural change. The cyclopropane ring, therefore, by replaceing a double bond, can produce a modified structure which retains an area of high electron density with minimal change in geometry of the molecule. In relation to the metabolically reactive double bond one may expect greater resistance to metabolism.

The object of the present study is to determine the effect of various oxygen functions in the steroid 3-position on the addition of the iodomethylzinc iodide reagent to the 5,6-double bond. The conversion (Scheme XI) is widely known [28] to occur in steroid-forming tissues as a general metabolic pathway. Preparation of steroids of the type (22) produces molecules analogous to the natural structure with respect to their oxygen function at C_3 and high electron density at C_5, but without the possibility of C_5 to C_4 isomerization.

Scheme XI

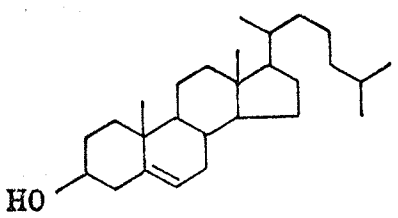


Furthermore, molecules of the type (23) are capable of ring-opening synthetically to yield 6-methyl derivatives (24) which have been shown [29] to protect the 4,5-double bond from metabolic reduction in compounds of the type (24), thereby enhancing progestational activity.

Although many methods [30] are available to prepare 6-methyl steroids, no simple and efficient route has been found for making 6,6-dimethylsteroids [31]. From the present study, we may obtain an effective pathway towards 6,6-dimethylsteroids. The 6,6-di-

methylsteroids have similar 1,3-steric interactions to the 4,4-dimethylsteroids [32]. The 1,3-diaxial interactions between C_6-β- and C_{10} methyl groups of 6,6-dimethylsteroid may distort ring B to a certain extent, thereby affecting the conformation of ring A.

II. RESULTS AND DISCUSSION



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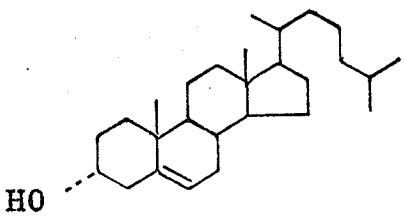

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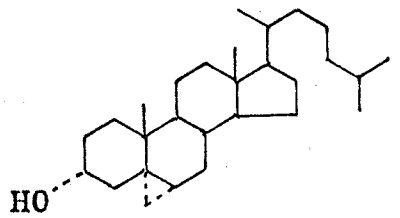

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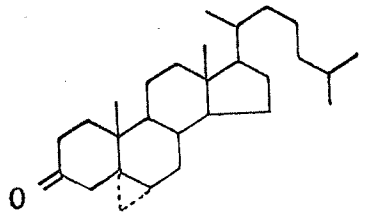

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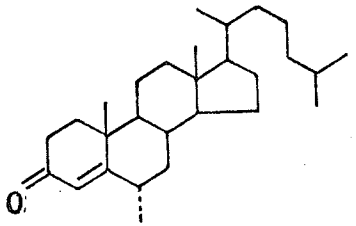

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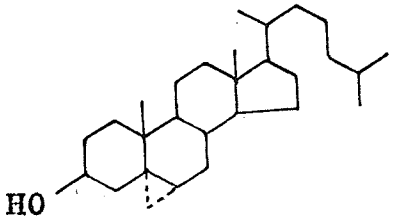

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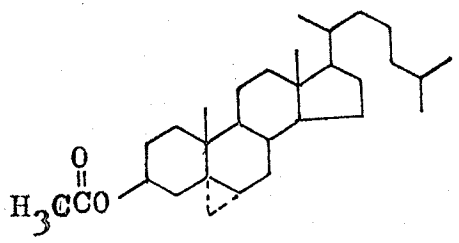

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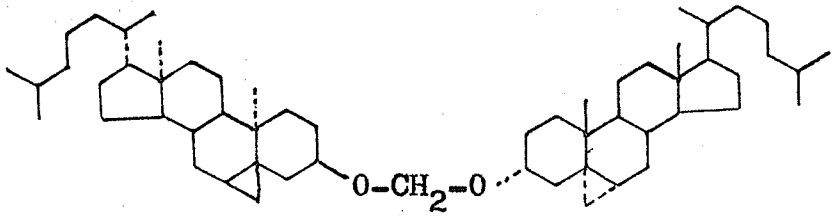

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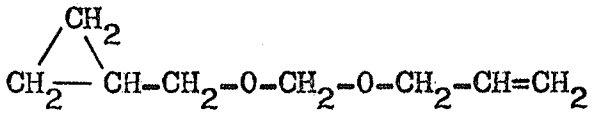

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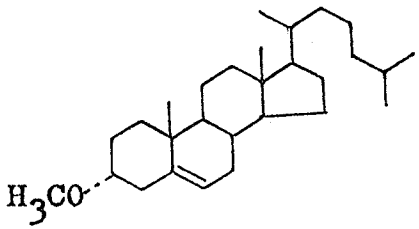

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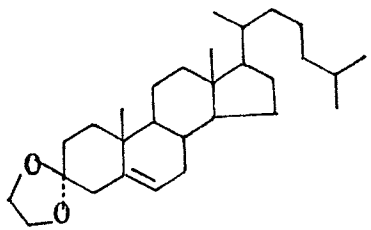

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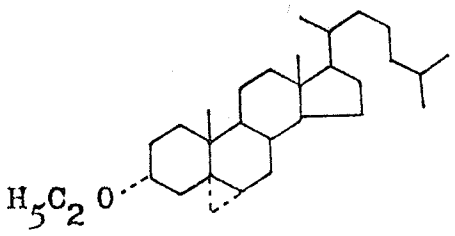

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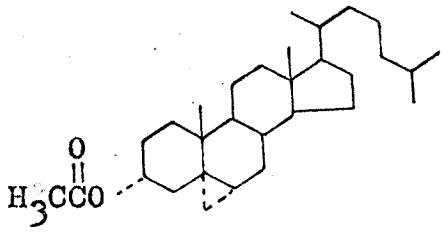
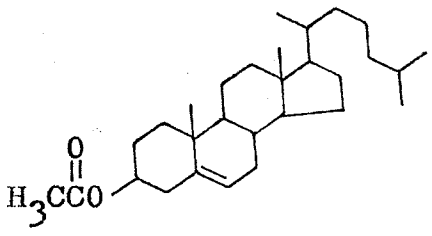
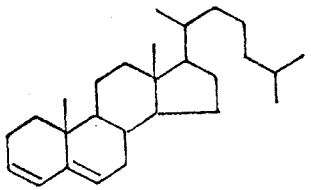


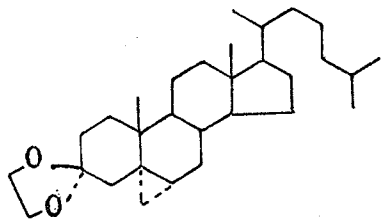
43



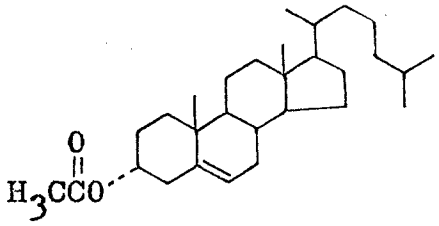
44



45



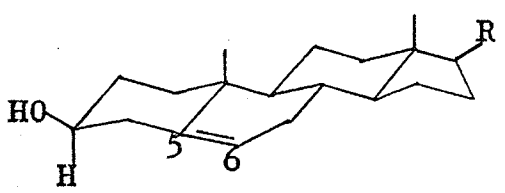
46



47

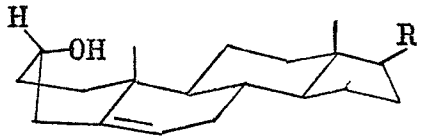
It would be expected that addition of the iodomethylzinc iodide reagent (2) from the α-face of the steroidal 5,6-double bond, would be accelerated and stereochemically controlled by the presence of a 3-axial oxygen function capable of coordination or reaction with the reagent.

β-face



25

α-face

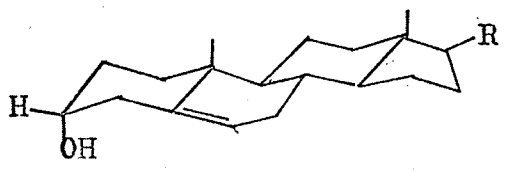


26

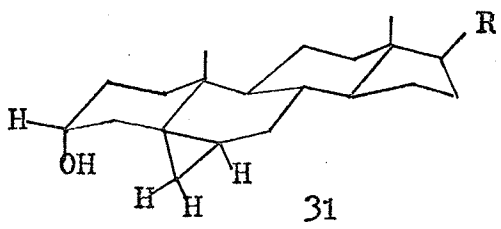
Alternatively, the rigid steroid molecule would hold a 3-equatorial oxygen (25) in such a position that any zinc oxygen interaction would leave the reagent spacially removed from the double bond, and sterically hindered by the 19-methyl group from approaching the double bond from the β-face. Although ring A in 25 is free to assume the boat conformation (26) in which the 3β-oxygen function becomes quasi-axial , the instability associated with the boat form of cyclohexane itself would be augmented by a strong interaction between methyl and hydroxyl groups at C_3 and C_{10}. In the absence of very special structural features, ring A is assumed to be in the chair form, as in 25. An axial conformation which has been postulated [15] as the reacting conformation for homoallylic alcohols is thus

not possible in the rigid steroid molecule containing a 3-equatorial oxygen substituent.

This expectation was confirmed when cholesterol (27) was treated with the Simmons-Smith reagent in refluxing ether, since only starting material was recovered. However, when epi-cholesterol (28) carrying an axial 3α-hydroxy group was similarly treated, the product contained no starting material by thin layer chromatography (t.l.c.) and after chromatographic separation several products were obtained. The major product was a cyclopropane containing alcohol in sixty percent yield, whose spectral properties are consistent with those of the expected 5,6β-dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3α-ol (29). The proton magnetic resonance spectrum (p.m.r. No.1) no longer showed the vinylic proton of epi-cholesterol but had typical high-field cyclopropane ring hydrogen resonance (δ , 0.22 ppm) [33]. The infrared spectrum (i.r. No.1) showed a weak absorption band characteristic of cyclopropyl C-H stretching ($\sim$3050 cm^{-1}) [34]. By analogy [17,27] with other homoallylic steroidal alcohols methylenation is concluded to have occurred cis to the hydroxy group (30 → 31).

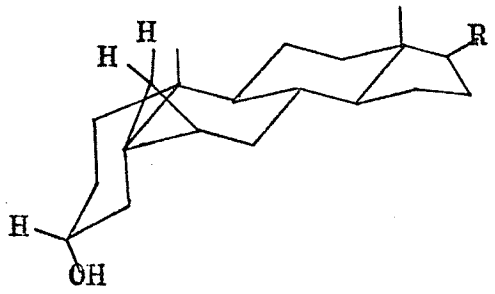


30



31

The 5α,6α-structure for 31 was supported by the p.m.r. spectrum showing that the 3β-hydrogen in 31 has a band width at half height (7 Hz) characteristic of a 3-equatorial hydrogen [35]. Dreiding models show that for such a 3β-hydrogen to adopt an equatorial conformation, ring A in 31 should exist in a normal chair form and trans-fused with ring B, i.e., C_5 in α-configuration. Conversely, in the 5β,6β-structure (32), ring A interconvertsto a chair form in which the 3β-hydrogen adopts an axial conformation characterized by a larger band width at half height (15-30 Hz) in the p.m.r. [35]. Evidence from the p.m.r. spectrum and dreiding models therefore suggests that 31 has the 5α,6α configuration.



32

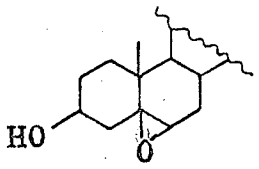
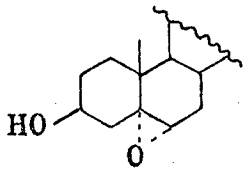
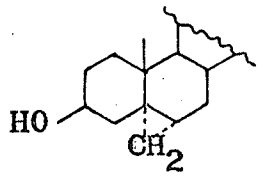
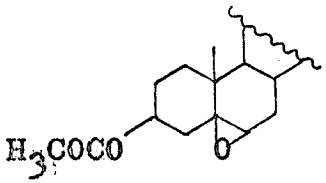
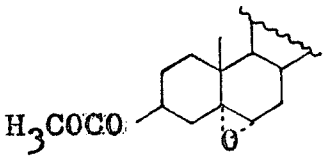
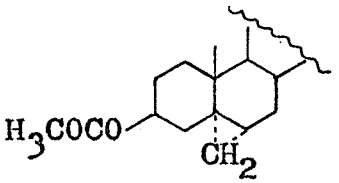
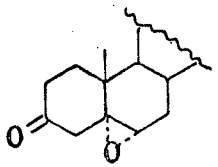
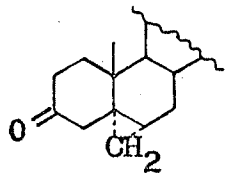
Further proof of the stereochemistry of the 5α,6α-cyclopropane ring system was obtained by oxidation of the alcohol (29) with chromic acid [36] to the saturated ketone (33) which still contained the cyclopropane ring (p.m.r. No.2; i.r. No.2). Treatment of this ketone with perchloric acid in glacial acetic

acid gave the known 6α-methyl-4-cholesten-3-one (34) [37] (i.r. No.9; u.v. No.1). Reduction of the ketone (33) with lithium tri-tertiary-butoxyaluminium hydride [38] gave an epimeric alcohol (35) (p.m.r. No.3; i.r. No.3) further characterized as its acetate (36) (p.m.r. No.4; i.r. No.4).

The specific rotations of the above compounds were determined. It has been shown that the specific rotation differences for corresponding steroidal epoxides and cyclopropane derivatives were similar [39]. The 5α,6α-configuration for these compounds is consistent with the rotations of the corresponding epoxides [40] (Table 1). The 5α,6α-cyclopropane derivatives are levorotatory as are the corresponding 5α,6α-epoxides [40]; whereas the 5β,6β-epoxides [40] are more dextrorotatory relative to the 5α,6α-derivatives (Table 1).

From the same reaction a dialkoxymethane (37) analogous to those reported [41] as a byproduct of the Simmons-Smith reaction with several low molecular weight allylic alcohols has also been isolated. This substance, a relatively high melting solid, had spectral properties in agreement with the structure, bis(5,6β-dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3α-oxy)methane (37) (p.m.r. No.5; i.r. No.5). The mass spectrum of 37 (m.s. No.5) has a very weak signal corresponding to the molecular ion as does bis(cyclohexoxy)methane [42]. This is in contrast to simple alicyclic dialkoxymethane derivatives which do not show a molecular ion peak [41,42]. Signal corresponding

Table 1 Optical rotation of some cholestane derivatives

5β,6β-Epoxides	$[\alpha]_D$	5α,6α-Epoxides	$[\alpha]_D$	5α,6α-Cyclopropanes	$[\alpha]_D$
	+10°		-46°		-52°
	-0.5°		-46°		-53°
			-39°		-10°

All values of $[\alpha]_D$ were taken in $CHCl_3$.

to R^+, RO^+, and $ROCH_2^+$ ions are indicative of a structure of this type where cleavage of the ether bonds would be more favored than partial fragmentation of the hydrocarbon structure (see page 34). The formation of this substance from a homoallylic alcohol might suggest a similar intermediate to that leading to the formation of bis(alkoxy)methane derivative found with allylic alcohols. The equivalent unsymmetfical formal intermediate (38) suggested by Majerski and Schleyer [41] for the allylic dialkoxymethane is unlikely because of the unreactivity of the 3α-methyl ether (40) and 3-ethylene acetal (41) derivatives of 5-cholestene under the same reaction conditions.

The presence of ethoxy derivative has previously been noted [17] with the suggestion that they arise through formation of hydrogen iodide followed by cleavage of the diethyl ether solvent to form ethyl iodide, this reaction being supressed if the diethyl ether were first removed by distillation (see page 11). From the reaction of <u>epi</u>-cholesterol (28) small quantities of 3α-ethoxy-5,6β-dihydro-3'H-cyclorpopa[5,6]- 5α-cholestane (42) (p.m.r. No.6; i.r. No.6) have been isolated although the reaction mixture was distilled during addition of the ethereal solution of the steroidal alcohol. There was no evidence of methyl ether formation probably because of the more efficient removal of methyl iodide (b.p. 42°) with respect to ethyl iodide (b.p. 72°).

Although the zinc-copper couple was carefully washed with dry ether to remove acetic acid, it was possible to isolate 5,6β-dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3α-yl acetate (43) (p.m.r. No.7; i.r. No.7). This substance was also prepared by acetylation of the alcohol (29) and was identical in all respects with that product.

Šorm et al.[5] state that reaction occurs between the Simmons-Smith reagent and C_3 oxygen substituted C_5-unsaturated B-norsteroids at 100°. The 3α- and 3β- acetates give much higher yields of methylene addition products than could be obtained from the corresponding alcohols. Complete stereochemical control of addition was lost and principally addition from the α-face occured irrespective of the stereochemistry at C_3. Stereochemical control in the 3β-derivatives is undoubtedly due to normal addition to the α-face, approach of the reagent from the β face was sterically hindered by the C_{10} methyl group and not through interaction between the reagent and oxygen substituent, whereas for the 3α-derivatives both factors may operate.

Cholesteryl acetate (44), was recovered in high yields from reactions under normal Simmons-Smith conditions as well as reaction at 75° for 18 hours. In contrast, under the conditions described by Šorm et al.[5] (100° for 5 hours), the major product isolated from the reaction was cholesta-3,5-diene[43] (45), whose u.v. spectrum was identical with the reported

data (u.v. No.2), a weak vinyl C-H stretching band at 3020 cm^{-1} which does not show in the i.r. spectra of other 5-cholestene derivatives was visible in the spectrum of 45 (i.r. No.10). This product gave the expected molecular ion determined by mass spectrum for cholesta-3,5-diene. Another product recovered from this reaction were cholesterol (27) and a small amounts of starting material (44). In this reaction, the addition of methylene to the 5,6-double bond was again not successful, since the elimination of the hydroxy group apparently proceeds faster than the addition reaction.

The greater reactivity of the B-norsteroids is consistent with the enhanced rate of methylene addition to trisubstituted cyclopentene compared to the corresponding cyclohexene as shown by the rate measurements of Chan and Rickborn[15].

Because of the relative difficulty of preparing 3α-hydroxy-5,6-unsaturated steroids [44], it was hoped to take advantage of the established ketalization of the steroidal 4-en-3-one system to place an oxygen atom in the 3-axial position of a steroidal 5-ene. Treatment of 3-ethylene acetal of 5-cholesten-3-one (41) with the Simmons-Smith reagent in refluxing ether gave no cyclopropane containing products as determined by p.m.r. spectrometry and only starting material was recovered. Prolongation of the reaction peroid (6 days) did not improve the addition of methylene, but destroyed the 3-ethylene acetal function as shown by the p.m.r. spectrum of

the crude reaction product with comparison to that of 5,6β-dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3-one ethylene acetal (46) (p.m.r. No.8; i.r. No.8) prepared from the ketone (33) by ketalization [45].

Of the C_3 oxygen substituted 5-cholestene derivatives (27, 28, 40,41, 44,47) studied only the 3α-hydroxy function (28) has been capable of effecting the addition of the iodomethylzinc iodide reagent to the 5,6-double bond. It has been suggested [7] that homoallylic alcohols, unlike allylic alcohols react with the iodomethylzinc iodide reagent prior to methylenation. If it were the correct mechanism by which methylenation took place with epi-cholesterol (28), then acceleration by other C_3 oxygen substituents (27, 40, 41, 44, 47) would be ruled out. This proposal is consistent with the unreactivity of 27, 40, 41, 44, and 47 to the iodomethylzinc iodide reagent.

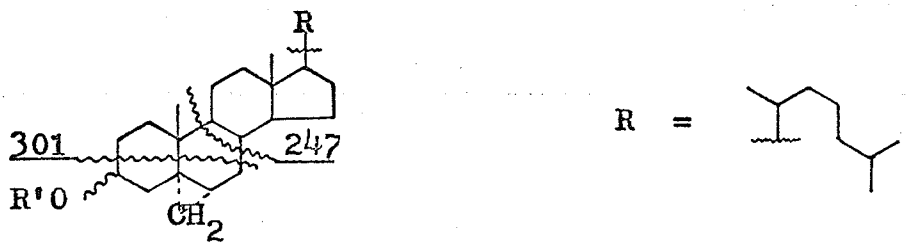
Table 2 Mass spectrum data of 5,6β-dihydro-3'H-cyclopropa(5,6)-5α-cholestane derivatives

(Relative intensity m/e)

Compounds	M^+	M^+-CH_3	M^+-HOR'	M^+-CH_3 -HOR'	M^+-R	M^+-R -HOR'	M^+-R-42	M^+-HOR' -R-42	Other		Metastable ions
29	100 400	20 385	57 382	27 367	21 287	13 269	20 245	45 227	10 327	40 301	44 365.5
									36 302	17 247	
35	28 400	-	-	28 367	25 287	14 269	24 245	20 227	83 329	42 301	
									18 327	24 247	
									32 302		
43	17 442	-	100 382	16 367	-	13 269	5 287	29 227	13 302	7 247	19 330.3
									7 301		
36	2 442	-	100 382	27 367	-	18 269	7 287	25 227	11 302	9 247	
									14 301		
42	21 428	6 413	100 382	40 367	14 287	27 269	7 273	33 227	88 384	34 302	1 344.5
									34 383	35 301	
									73 329	23 247	
37	0.6 812	-	67 382	14 367	21 287	14 269	21 287	16 227	7 429	93 383	
									48 413	16 329	
									25 400	19 302	
									29 399	29 301	
									30 384	20 247	
33	70 398	10 383	-	-	11 285	-	29 243	-	8 327	13 301	
									12 302	7 247	
46	33 442	-	-	-	-	-	-	-	100 99	4 343	

Mass spectrometric fragmentation of 5,6β-dihydro-3'H-cyclopropa [5,6]-5α-cholestane derivatives

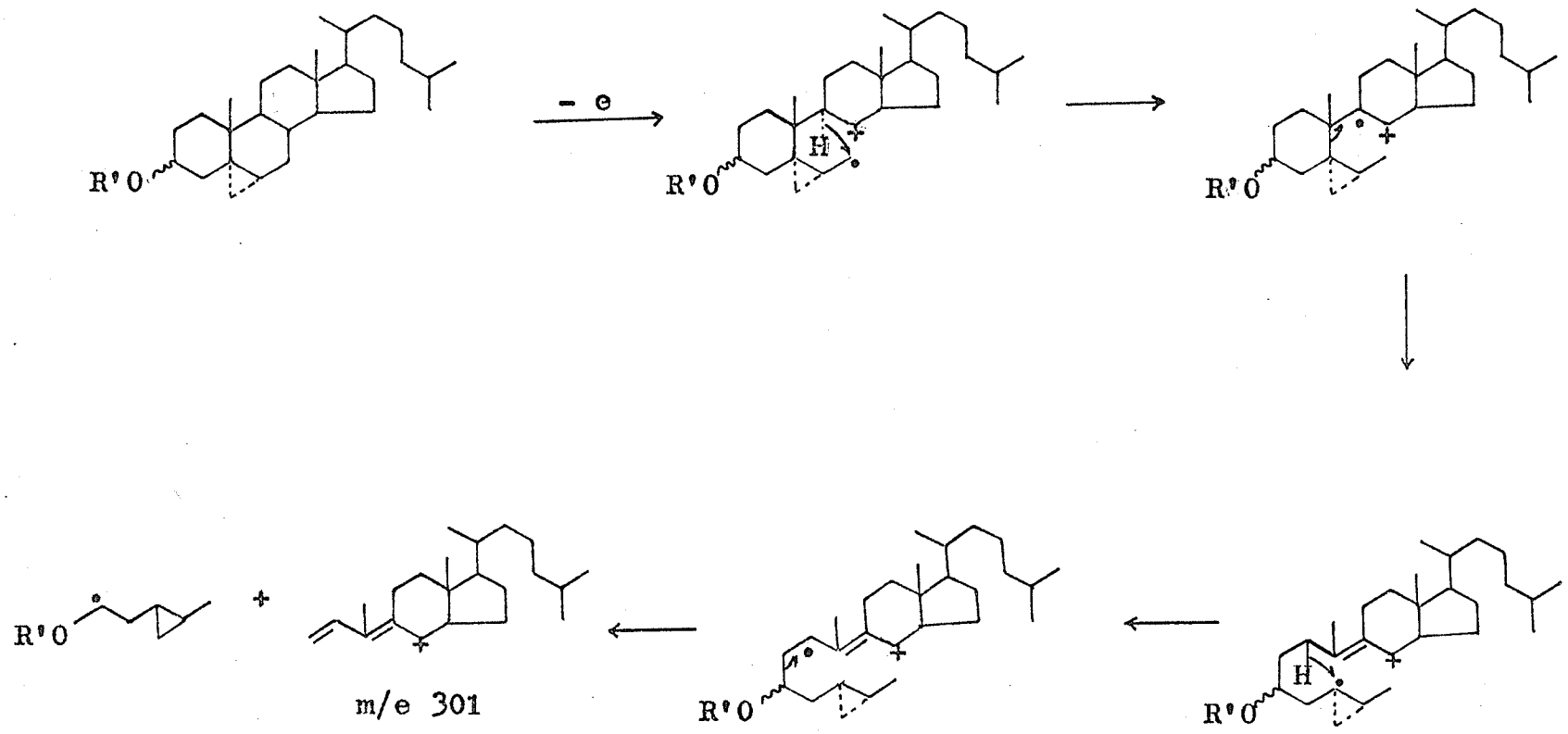
The mass spectrometric fragmentation of steroids has become of primary importance in the structure determination of known and unknown compounds. The mass spectra of eight 5,6β-dihydro-3'H-cyclopropa[5,6]-5α-cholestane derivatives (29, 33, 35, 36, 42, 43, and 46) were recorded, their major fragments are listed in Table 2. In most cases, the basic fragmentations were similar, including the $[M^+ - CH_3]$, $[M^+ - HOR']$, $[M^+ - R]$, $[M^+ - R - HOR']$, $[M^+ - (R + 42)]$, $[M^+ - HOR' - (R + 42)]$, $[M^+ - (\text{ring A} + \text{ring B})]$ (m/e 247), and $[M^+ - C_6H_{10}OR']$ (m/e 301) ions as shown in the following structure (48).



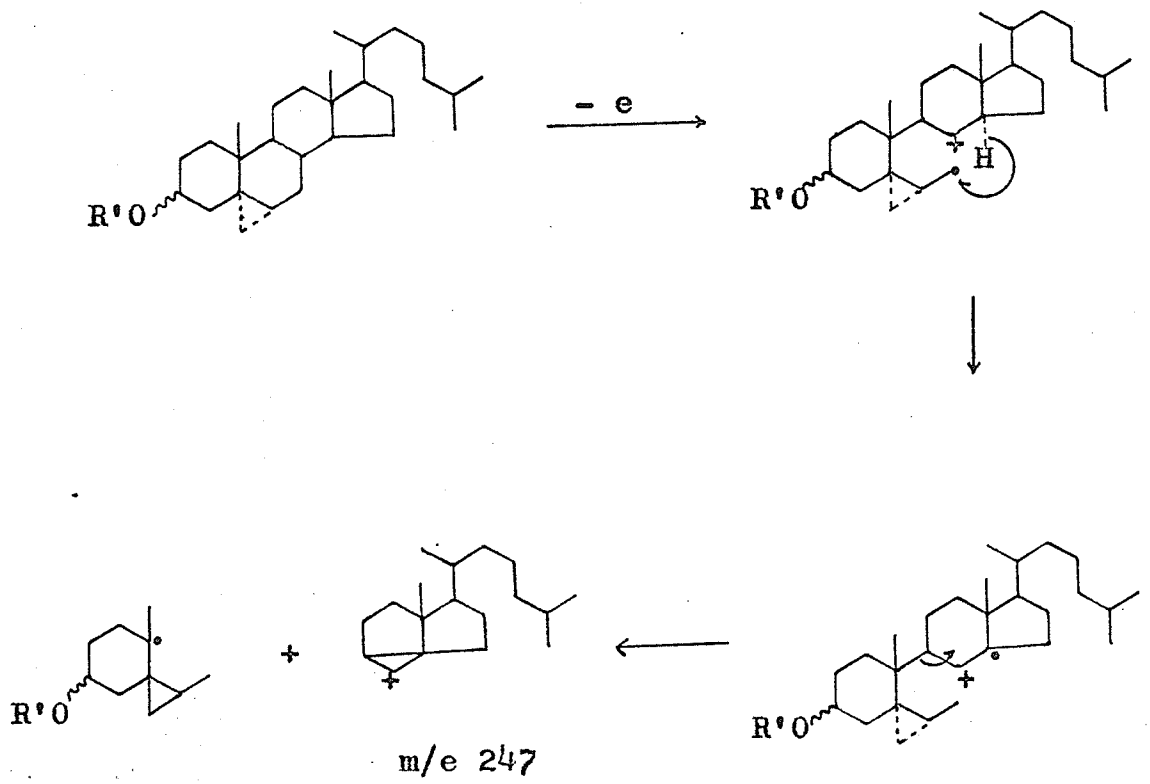
48

The formation of $[M^+ - CH_3]$, $[M^+ - HOR']$, $[M^+ - R]$, and $[M^+ - (R + 42)]$ ions are well known in steroidal derivatives[46]. The presence of m/e 301 (Scheme XII) and m/e 247 (Scheme XIII) ions may arise mechanistically as follows:

Scheme XII

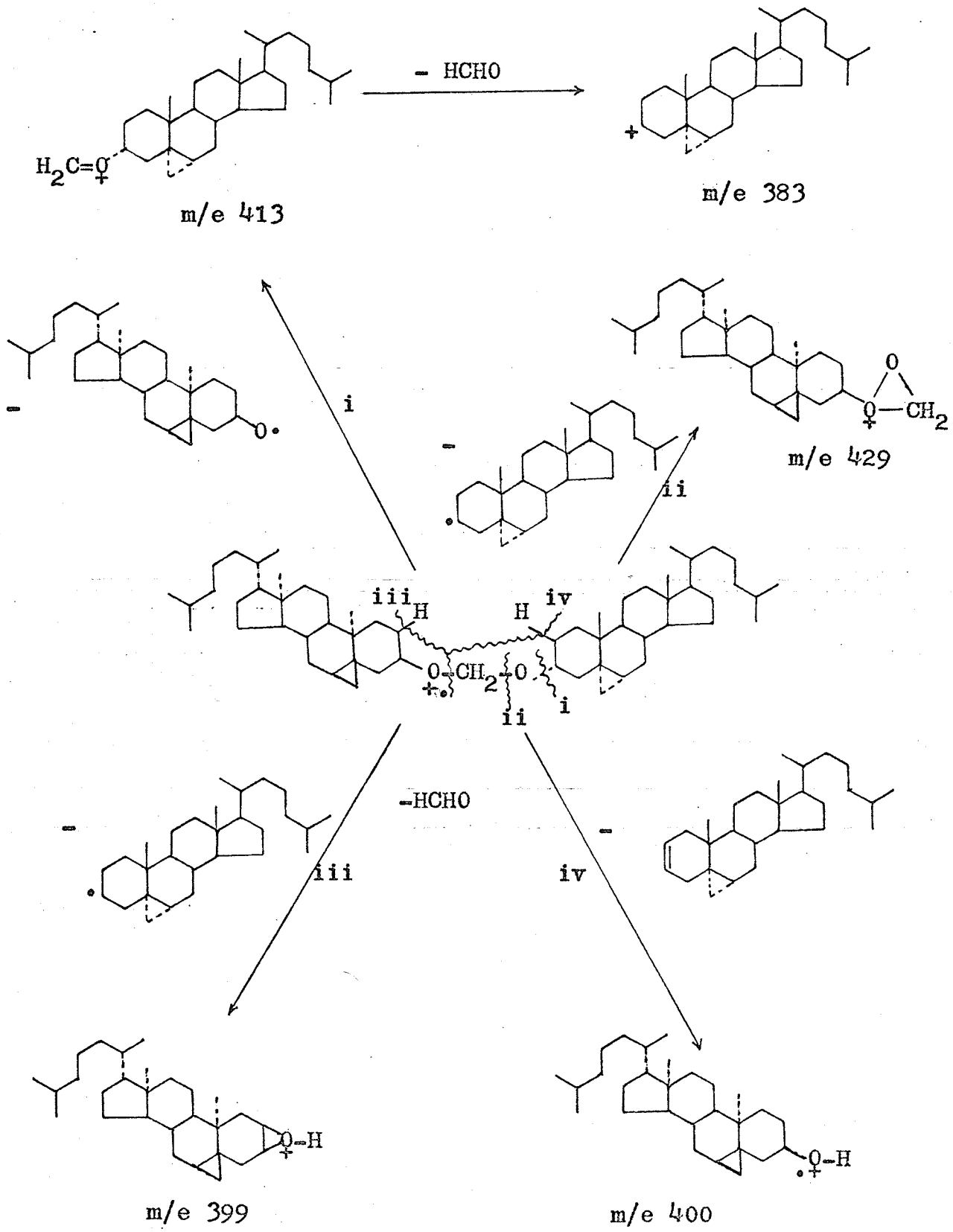


Scheme XIII



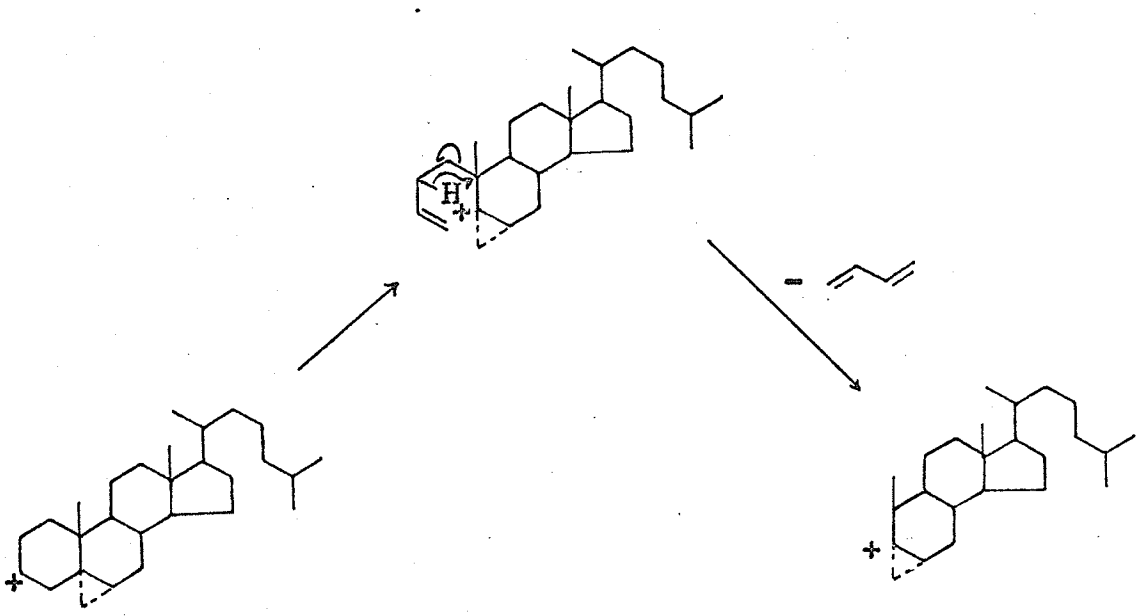
Besides the general fragmentation processes mentioned above, a few compounds show characteristic fragmentations. The spectrum of 37 (m.s. No.5) showed a weak molecular ion peak which is characteristic of compounds of this type [42]. Strong and moderately strong signals at m/e 383, 399, 400, 413, and 429 were observed, these ions are formed from the following routes similar to those for bis(cyclohexoxy)methane [42] (Scheme XIV).

Scheme XIV



The m/e 329 signal may arise from the m/e 383 ion by the following fragmentation of the hydrocarbon structure (Scheme XV).

Scheme XV

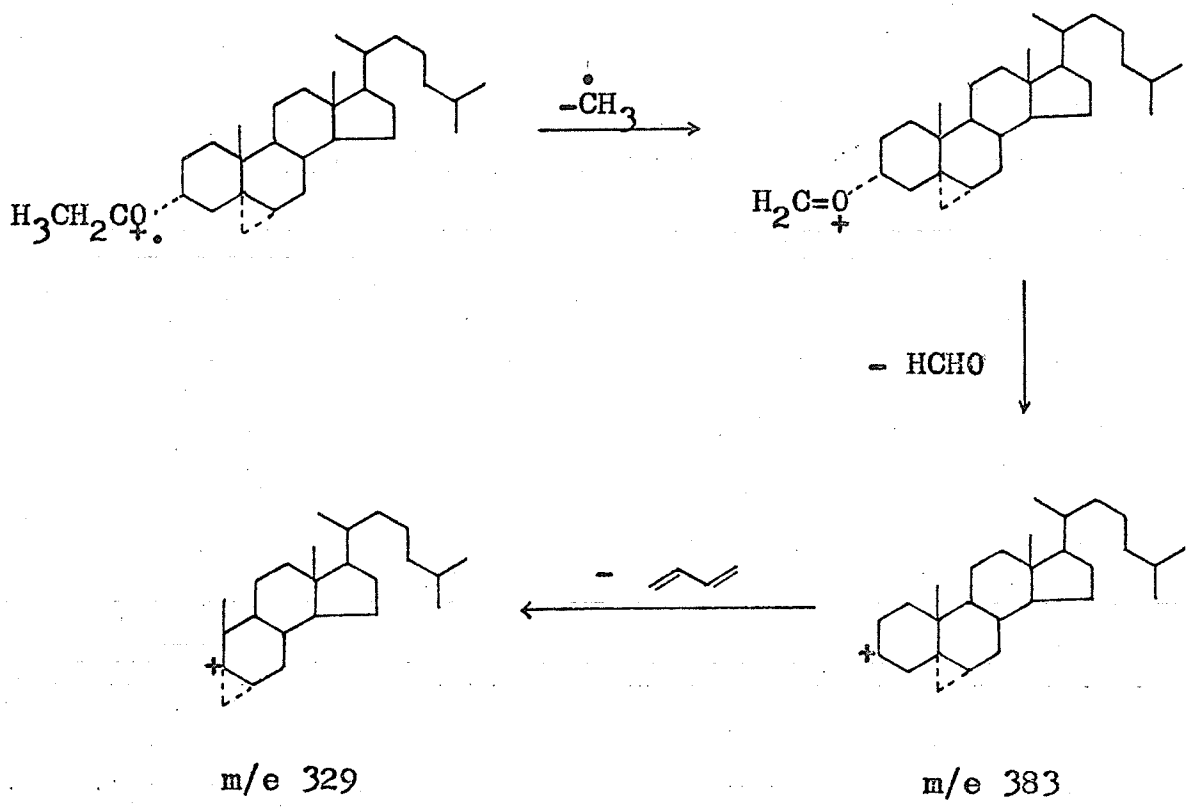


m/e 383 m/e 329

The ethyl ether (42) (m.s. No.6) has m/e 329 ion which also arise through formation of the same m/e 383 ion (Scheme XVI).

The presence of m/e 329 ion in the spectrum of 35 (m.s. No.3) can not be rationalized by this processes, since there is no possibility of forming a m/e 383 ion in structure 35 as is possible with structures 37 and 42.

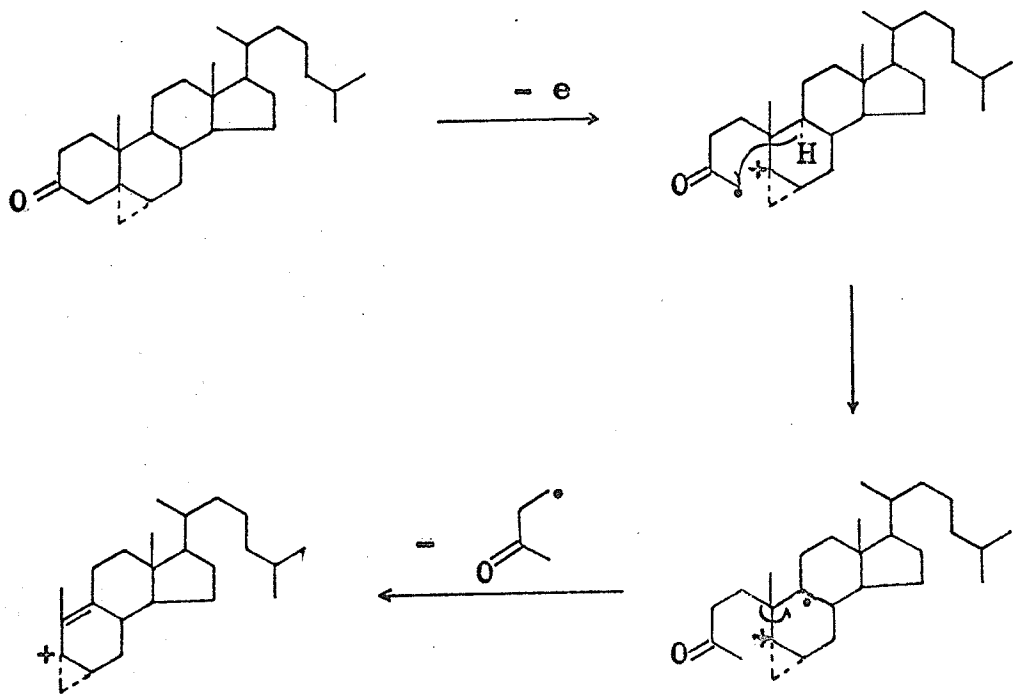
Scheme XVI



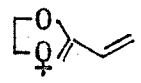
m/e 329 m/e 383

For the ketone (33) (m.s. No.2), formation of m/e 327 ion may be derived from a modification of the fragmentation of some saturated 5α-3-keto steroids [47] (Scheme XVII). In both the spectra of the 3α- (29) (m.s. No.1) and 3β- (35) (m.s. No.3) alcohols, the m/e 327 ion may arise by a similar route to the ketone (33).

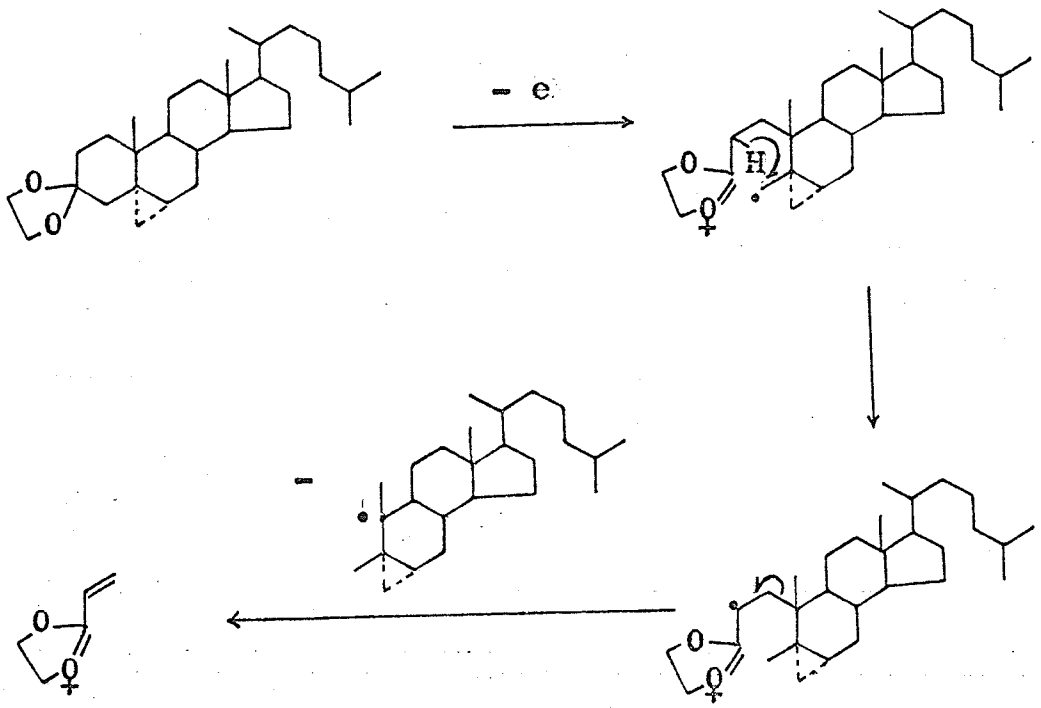
Scheme XVII



m/e 327

Fragmentation of 46 (m.s. No.8) was similar to that of the saturated steroidal 3-ethylene acetals [47]. They showed a moderately strong molecular ion peaks and an extremely strong signal at m/e 99 corresponded to  which has been shown [47] in saturated steroidal acetals to arise from the following processes (Scheme XVIII). This ion is also common in the spectra of some C_5-unsaturated steroidal 3-ethylene acetals[48]. The m/e 125 and m/e 112 ions reported [47] for saturated steroidal 3-ethylene acetals were not observed in the spectrum of 46.

Scheme XVIII



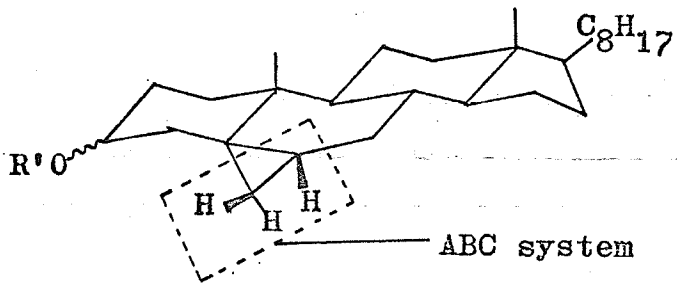
Metastable ions (Table 2) with moderately strong intensities were observed in the spectra of 29 and of 43. These corresponded to the elimination of water from the alcohol (29) (m_1 = 400, m_2 = 382, m^* = 365.5), and of acetic acid from the acetate (43) (m_1 = 442, m_2 = 382, m^* = 330.3). A very weak metastable ion was also seen in the spectrum of the ethyl ether (42) , corresponding to the loss of ethanol from 42 (m_1 = 428, m_2 = 382, m^* = 344.5).

Proton magnetic resonance spectrometry of 5.6β-dihydro-3'H-cyclopropa[5,6]-5α-cholestane derivatives

Proton magnetic resonance has been employed in differentiation of isomers in steroids[49]. Chemical shift differences between epimers are generally not great and in many cases both isomers are required for conclusive assignments to be made. The fact that diaxial vicinal coupling constants are much greater than diequatorial or axial-equatorial coupling[50], also can be used to assign configurations to steroidal epimers. In general, when an electronegative substituent is attached to the steroid framework, the geminal proton is found downfield free from the saturated C-H region of the spectrum. However, such a proton will usually be adjacent to several others and will give rise to a broad band in which the number of closely spaced lines due to spin-spin coupling are not readily discernible. The width of such a band, measured at one-half its height (half-width or $W^{1/2}$) [35] will reflect the magnitude of the vicinal coupling constants. Thus, an axial proton, split by adjacent axial (J~9 Hz) and equatorial protons (J~2 Hz), should give rise to a much wider band than an equatorial proton split by adjacent axial (J~2 Hz) and equatorial protons (J~2 Hz). The utility of half-width in assignment of stereochemistry in steroids has been demonstrated [35]. The half-width of the bands due to equatorial proton coupling is 5 - 10 Hz, while that for axial proton coupling is 15 - 30 Hz. These correlations were applied to the spectra of 5,6β-dihydro-3'H-cyclo-

propa[5,6]-5α-cholestane derivatives (see page 23). The results further reflected that the configuration of the cyclopropane ring at C_5-C_6 was α in all compounds.

The presence of a cyclopropane ring was also established by p.m.r. spectrometry based on its characteristic high field protons resonance [33]. The spectra of the 5,6β-dihydro-3'H-cyclopropa[5,6]-5α-cholestane derivatives (p.m.r. No.1 -8) showed that two protons appeared in the region of δ = 0.00 - 0.50 ppm. Since the cyclopropane ring should give rise an ABC system (49) in these derivatives, there was an additional cyclopropane ring proton which was obscured by the methylene-envelop and further identification was prevented.



49

Examination of the patterns of peaks caused by the cyclopropane ring protons in the epimeric pair of alcohols (29 and 35) and acetates (36 and 43) showed that the chemical shifts of these protons were strongly dependent on the conformation as well as type of substituents [51] at C_3 (Table 3).

Table 3 Chemical shifts of cyclopropane ring protons

Compounds	Chemical shifts (ppm)
5,6β-Dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3α-ol (29)	0.50
5,6β-Dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3β-ol (35)	0.00 - 0.40
5,6β-Dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3α-yl acetate (43)	0.40 - 0.46
5,6β-Dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3β-yl acetate (36)	0.20 - 0.36
Bis(5,6β-dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3α-oxy) methane (37)	0.45
3α-Ethoxy-5,6β-dihydro-3'H-cyclopropa[5,6]-5α-cholestane (42)	0.45
5,6β-Dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3-one (33)	0.18 - 0.33
5,6β-Dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3-one ethylene acetal (46)	0.36 - 0.45

The 3α(axial)- substituents exerted a stronger deshielding effects on the cyclopropane ring protons than did the 3β(equatorial)- substituents. This effect applied to each cyclopropane ring proton to a different extent and gave rise to a singlet in most cases of the 3α-substituted compounds and a complex multiplet in the 3β-substituted series. The 3-keto and 3-ethylene acetal groups showed an intermediate effect between the 3α- and 3β- series on the cyclopropane ring protons (Table 3).

This deshielding effect is very unlikely to be due to inductive effects which usually give a difference of several ppm in magnitude [49]. In all compounds the cyclopropane ring protons are separated by five σ bonds from the C_3-substituent. Inductive effects are negligible through five σ bonds. The most obvious factors that would cause paramagnetic shifts of cyclopropane ring protons in the 3α-substituted derivatives were steric distortion and the long range magnetic anisotropy effect. The magnitude of these effects is dependent on the angles and distances involved. This may account for the difference in chemical shifts and patterns of the cyclopropane ring protons in both series.

III. EXPERIMENTAL

Unless otherwise stated the following instruments and procedures have been used.

Melting points were carried out on a Thomas-Hoover capillary apparatus and are uncorrected. Optical rotations were measured in choloform solution on a Bellingham and Stanley (Model A) Polarimeter (concentration range 0.4 - 1.5 %) in a 1 dm tube. Infrared spectra were determined on a Beckmann Model 8 Spectrophotometer using 2.5 % solution in carbon tetrachloride. All infrared spectra were calibrated at 1603 cm^{-1}. Proton magnetic resonance spectra were taken on a Varian A56/60A instrument using deuterochloroform as solvent, with and without tetramethylsilane as an internal standard. Ultraviolet spectra were determined on a Beckmann DU Model 2400 Spectrophotometer using 1 cm silica cells. Mass spectra were recorded on a A.E.I. MS 12 instrument by the Chemistry Department, University of Alberta, Edmonton. Elemental analyses were performed by Pascher and Pascher, Microanalytical Laboratory, Bonn, West Germany. Petroleum ether refers to the fraction boiling within the range of 60^{o} to 80^{o}. Thin layer chromatography was carried out on silica gel coated glass plates, developed with 10 - 25 % v/v ethyl acetate in petroleum ether, visulized by spraying with 4 % v/v concentrated sulfuric acid in ethanol followed by heating at approximately 100^{o}. Silver nitrate treated plates were prepared by spraying the above plates with 0.1 N silver nitrate and drying at 100^{o} for 30 minutes before use.

Simmons-Smith reaction

Zinc-copper couple:

A 1.85% w/w zinc-copper couple was freshly prepared essentially by method of LeGoff[6] as follows: zinc dust (15 mmoles) was added to a hot (bath temperature 130°) stirred solution of copper acetate monohydrate (0.28 mmoles) in glacial acetic acid (2 ml). The reaction container was quickly removed from the heat and excess acetic acid removed by pipette. The residue was washed with acetic acid (2 ml) followed by dry ether (3 x 20 ml) to remove excess acetic acid.

Iodomethylzinc iodide reagent:

To the freshly prepared couple in dry ether (20 ml) was added dry diiodomethane (10 mmoles), m.p. 5-6°, dried over molecular sieves 4A, in dry ether (10 ml). Refluxing usually occurred spontaneously and the reaction was refluxed for 30-60 minutes.

Reaction with the unsaturated steroid:

The dry steroid (1 mmole) dissolved in dry ether (10-25 ml) was added to the reaction mixture and refluxed. In reaction carried out with a steroid containing a hydroxyl group, the steroid was added dropwise over 20-30 minutes while ether was distilled at a rate slightly greater than the addition. Dry ether was added if required to maintain the volume.

Reaction work-up:

The reaction mixture was poured into excess saturated aqueous sodium bicarbonate and the resulting slurry extracted with ether. The ether solution was washed with water, brine, dried over anhydrous sodium sulfate, filtered and evaporated at reduced pressure to give the crude reaction product.

epi-Cholesterol (28)

epi-Cholesterol (10 mmoles) was treated as described above and small aliquots removed and worked up at intervals. T.l.c. on $SiO_2/AgNO_3$ plates indicated no starting material after 6 hours. Reactions run up to 18 hours gave analogous results. Chromatography of the crude reaction product on alumina gave on elution with petroleum ether a fraction (806 mg) which on crystallization from ether yielded bis(5,6β-dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3α-oxy)methane (37). Recrystallization gave 287 mg: m.p. 221-2°; $[\alpha]_D^{23}$ -40° ; i.r.No.5 ν_{max}: 3060 (cyclopropyl C-H stretching), 1027 cm^{-1} (c-O stretching) ; p.m.r. No. 5 δ : 4.61 (2H, singlet, formal protons), 3.90 (2H, unresolved multiplet, $W^{1/2}$ = 7.0 Hz, C_3 equatorial proton), 1.04 (singlet, C_{19} methyl protons), 0.60 (singlet, C_{18} methyl protons), 0.45 ppm (2H, singlet, cyclopropyl protons) ; m.s. No. 5 m/e : 812 (M^+).

Anal. Calcd. for $C_{57}H_{96}O_2$: C, 84.16 ; H, 11.89.

Found : C, 84.12 ; H, 12.10.

Residue from the mother liquor was recrystallized from methanol to yield 3α-ethoxy-5,6β-dihydro-3'H-cyclopropa[5,6]-5α-cholestane (42)(66mg): m.p. 117.5° ; $[\alpha]_D^{23}$ -43° ; i.r.No.6 V_{max} : 3060 cm^{-1} (cyclopropyl C-H stretching); p.m.r. No. 6 δ : 3.76 (1H, unresolved triplet,overlying quartet due to the methylene protons, $W^{1/2}$ = 7.5 Hz, C_3 equatorial proton), 3.60 (2H, quartet, J = 7.0 Hz, ethoxy methylene protons), 1.13 (singlet, C_{19} methyl protons), 0.66 (singlet, C_{18} methyl protons), 0.45 ppm (2H, broad singlet, cyclopropyl protons); m.s. No. 6 m/e : 428 (M^+).

Anal. Calcd. for $C_{30}H_{51}O$: C, 84.24 ; H, 12.01.
Found : C, 84.05 ; H, 12.21.

Elution of the column with 5% v/v benzene-petroleum ether gave 5,6β-dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3α-yl acetate (43) (420 mg) recrystallized from methanol : m.p. 131-2° ; mixed melting point was not depressed and the i.r. spectrum (KBr) was identical with the acetate of 29 (see page 50).

Elution of the column with benzene gave 5,6β-dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3α-ol (29) (2.4 g), recrystallized from acetone: m.p. 120-1° ; $[\alpha]_D^{23}$ -65° ; i.r. No.1 V_{max} : 3600 (free O-H stretching), 3060 cm^{-1} (cyclopropyl C-H stretching); p.m.r. No. 1 δ : 4.00 (1H, unresolved myltiplet, $W^{1/2}$= 7.5 Hz, C_3 equatorial proton), 1.05 (singlet, C_{19} methyl protons), 0.61 (singlet, C_{18}methyl protons), 0.50 ppm (2H, broad singlet, cyclopropyl protons); m.s. No. 1 m/e : 400 (M^+).

Anal. Calcd. for $C_{28}H_{48}O$: C,83.93 ; H, 12.07.

Found : C,83.74 ; H, 12.07.

In some experiments the alcohol (29) could be crystallized from acetone directly from the crude reaction product in 50% yield.

Cholesterol (27)

Cholesterol (1.2 g) was subjected to the Simmons-Smith reaction under the same conditions described for 28. Chromatography on alumina gave on elution with 3 : 1 v/v benzene-ether, a fraction (772 mg) which was recrystallized from methanol : m.p. 148° ; mixed melting point with starting material was not depressed ; i.r. spectrum was identical with cholesterol.

Cholesteryl acetate (44)

Cholesteryl acetate (1.28 g), under Simmons-Smith conditions as for 28, gave a crude reaction product which showed a major spot corresponding to the starting material on t.l.c. Recrystallization from methanol yielded 44 (926 mg) : m.p. 112-3°; mixed melting point with starting material was not depressed and both showed identical i.r. spectra.

The reaction was also carried out at 75° for 18 hours on 44 (1.7 g). The crude product again showed a major spot on t.l.c. Chromatography over alumina on elution with 5-30% v/v benzene-petroleum ether gave material (1 g) which after crystallization from methanol showed no depression on mixed melting

point with 44, The i.r. spectrum of the compound recovered was identical with 44.

Cholesteryl acetate (1.5 g) was subjected to Simmons-Smith reaction at 100° as described by Šorm et al.[5]. The crude reaction product showed three major spots on t.l.c. Chromatography on alumina gave an elution with petroleum ether a fraction (586 mg) which on recrystallization from acetone yielded cholesta-3,5-diene (45) : m.p. 78-9° ; $[\alpha]_D^{23}$ -56° ; i.r. No. 10 ν_{max} : 3020 cm^{-1} (vinyl C-H stretching); u.v. No.2 λ_{max}^{hexane} : 244 (ϵ 11,040), 237 (ϵ 18,700), 229nm(ϵ 15,880); m.s. m/e : 368 (M^+).

Elution with benzene gave a fraction (98 mg) which was identical with cholesteryl acetate (44) by t.l.c. and i.r. spectrum.

Elution with 15 : 4 : 1 v/v benzene -ether-methanol gave cholesterol (27) (315 mg) which was recrystallized from methanol : m.p. 148° ; no depression on mixed melting point with cholesterol was observed; i.r. spectrum was identical with cholesterol.

epi-Cholesteryl acetate (47)

epi-Cholesteryl acetate (992 mg) was subjected to Simmons-Smith reaction under the conditions described for 28 but without distillation. The starting material was recovered (672 mg) : m.p. 84-5° ; mixed melting point was not depressed ; i.r. spectrum of the mother liquor indicated the absence of methylene-addition product.

3α-Methoxy-5-cholestene (40)

3α-Methoxy-5-cholestene (389 mg) subjected to Simmons-Smith reaction as for 28 was recovered (333 mg) : m.p. 124-6°; mixed melting point was not depressed; i.r. spectra were identical.

5-Cholesten-3-one ethylene acetal (41)

5-Cholesten-3-one ethylene acetal (1.28 g) was subjected to Simmons-Smith reaction as for 28, the crude starting material recovered (955 mg) on recrystallization gave 652 mg : m.p. 131-2°.

The same reaction was carried out for 6 days. The starting material was recovered (314 mg) : m.p. 131-2°; p.m.r. spectrum of the mother liquor showed no signal at 3.76 ppm corresponding to the 3-ethylene acetal protons.

5,6β-Dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3α-yl acetate (43)

5,6β-Dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3α-ol (29) (142 mg) was acetylated in pyridine acetic anhydride (2 : 1). After standing at room temperature overnight the reaction was poured into ice and water and extracted with ether to give a crude reaction product which showed a single spot running faster than the starting material on t.l.c. analysis. Recrystallization from methanol afforded the acetate (43) (125 mg) : m.p. 133°; $[\alpha]_D^{23}$ -44° ; i.r. No. 7 V_{max} : 3060 (cyclopropyl C-H stretching), 1730 (acetate carbonyl stretching), 1280-1180 cm^{-1} (acetate C-O stretching); p.m.r. No. 7 δ : 5.04 (2H, unresolved triplet, $W^{1/2}$ = 7.0 Hz, C_3 equatorial proton), 2.00 (3H, singlet, acetate methyl protons), 1.06 (singlet, C_{19} methyl protons), 0.62 (singlet, C_{18} methyl protons), 0.40-0.46 ppm (2H, multiplet, cyclopropyl protons); m.s. No.7 m/e : 442 (M^+).

Anal. Calcd. for $C_{30}H_{50}O_2$: C, 81.02 ; H, 11.79.
Found : C, 81.13 ; H, 11.52.

5,6β-Dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3-one (33)

5,6β-Dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3α-ol (29) (2.35 g) was dissolved in acetone (250 ml) and oxidized with Jones reagent [36]. The crude product showed one faster spot on t.l.c. Recrystallization form methanol afforded 2.2 g : m.p. 144° ; $[\alpha]_D^{23}$ -10° ; i.r. No.2 V_{max} : 3060 (cyclo-

propyl C-H stretching), 1715 cm^{-1} (carbonyl stretching) ; p.m.r. No.2 δ : 3.04 (1H, pair of doublet, J = 1 and 16 Hz, C_4 methylene proton), 1.28 (singlet, C_{19} methyl protons), 0.65 (singlet, C_{18} methyl protons), 0.33, 0.18 ppm (2H, unresolved multiplet, cyclopropyl protons); m.s. No.2 m/e : 398 (M^+).

Anal. Calcd. for $C_{28}H_{46}O$: C, 84.35 ; H, 11.63.
Found : C, 84.46 ; H, 11.94.

6α-Methyl-4-cholesten-3-one (34)

The ketone (33) (260 mg) was treated with glacial acetic acid (30 ml) containing 60% w/v percholric acid (3 ml) for 15 minutes on an oil bath (temperature 100°). The reaction was cooled, poured into water and extracted with ether. The crude product was recrystallized from methanol to give 34 (140 mg) : m.p. 125-6° ; $[\alpha]_D^{23}$ (dioxane) + 61° ; i.r. No. 9 ν_{max} : 1675, 1630 cm^{-1} (conjugated carbonyl stretching); u.v. No.1 λ_{max}^{hexane} : 231 nm (ϵ 15,100).

5,6β-Dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3-one ethylene acetal (46)

The ketone (33) (300 mg) was added to a mixture of benzene (50 ml) and ethylene glycol (1 ml). After reflux of the mixture for 40 minutes with a Dean-Stark apparatus, p-toluenesulfonic acid monohydrate (2 mg) was added, and refluxing

continued for a further 3 hours. The resulting mixture was washed with excess saturated sodium bicarbonate solution and water. The benzene solution was filtered through anhydrous sodium sulfate and evaporated. The crude reaction product (328 mg) showed a single spot on t.l.c. Recrystallization from methanol gave 46 (300 mg) : m.p. 117-8° ; $[\alpha]_D^{24}$ -50° ; i.r. No. 8 ν_{max} : 3070 (cyclopropyl C-H stretching), 1090 cm^{-1} (C-O stretching); p.m.r. No. 8 δ : 3.76 (4H, singlet, ethylene acetal protons), 1.09 (singlet, C_{19} methyl protons), 0.62 (singlet, C_{18} methyl protons), 0.45-0.36 ppm (2H, multiplet, cyclopropyl protons); m.s. No. 8 m/e : 442 (M^+).

Anal. Calcd. for $C_{30}H_{50}O_2$: C, 81.45 ; H, 11.31.

Found : C, 81.69 ; H, 11.21.

5,6β-Dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3β-ol (35)

The ketone (33) (800 mg) and lithium tri-t-butoxyaluminium hydride (560 mg) in dry ether (80 ml) were stirred at room temperature for 20 hours. The reaction mixture was poured into saturated ammonium chloride and extracted with ether. The crude residue showed three spots on t.l.c. which after column chromatography on alumina were separated. Elution of the column with 20-40 % v/v benzene-petroleum ether gave starting material (33) (195 mg) : mixed melting point 144° ; identical i.r. spectrum with 33.

Elution with 50-100 % v/v benzene-petroleum ether gave 5,6β-dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3α-ol (29)

(88 mg) : mixed melting point 120-1° ; i.r. spectrum was identical to the previous compound (29).

Elution with 2-15 % v/v ethyl acetate-benzene gave 5,6β-dihydro-3'H-cyclopropa[5,6]-5α-cholestan-3β-ol (35) (500 mg). Recrystallization from petroleum ether yielded needles (458 mg) : m.p. 155-6° ; $[\alpha]_D^{23}$ -52° ; i.r. No. 3 ν_{max} : 3600 (free O-H stretching), 3060 cm^{-1} (cyclopropyl C-H stretching); p.m.r. No. 3 δ : 3.70 (1H, multiplet, $W^{1/2}$ = 21 Hz, C_3 axial proton), 1.16 (singlet, C_{19} methyl protons), 0.60 (singlet, C_{18} methyl protons), 0.44-0.00 ppm (2H, multiplet, cyclopropyl protons); m.s. No.3 m/e : 400 (M^+).

Anal. Calcd. for $C_{28}H_{48}O$: C, 83.93; H, 12.07.

Found : C, 83.85; H, 11.96.

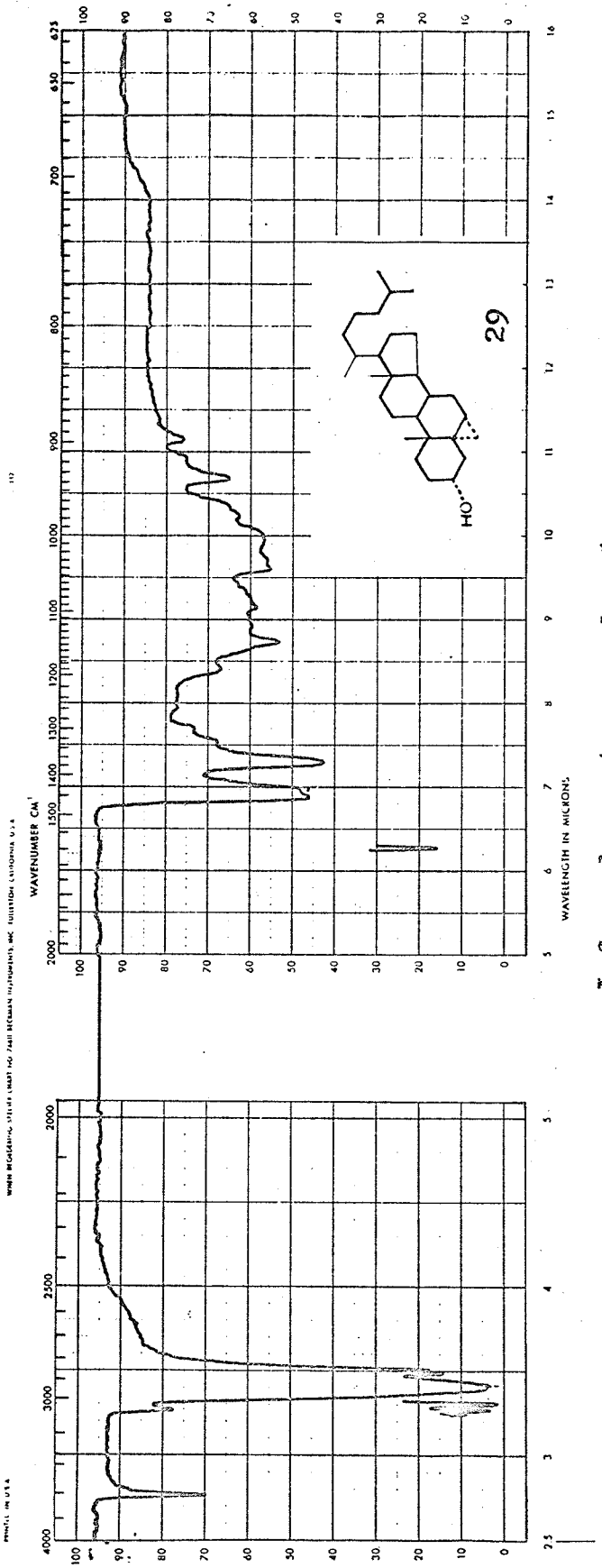
5,6β-Dihydro-3'H-cyclopropa [5,6]-5α-cholestan-3β-yl acetate (33)

The alcohol (35) (250 mg) was acetylated in dry pyridine acetic anhydride by the same method as compound 43. The crude reaction product showed a single spot on t.l.c. Recrystallization from methanol yielded the acetate (36) (250 mg) : m.p. 117-8° ; $[\alpha]_D^{23}$ -53° ; i.r. No. 4 ν_{max} : 3060 (cyclopropyl C-H stretching), 1730 (acetate carbonyl stretching), 1230 cm^{-1} (acetate C-O stretching) ; p.m.r. No.4 δ : 4.84 (1H, broad multiplet, $W^{1/2}$ = 23 Hz, C_3 axial proton), 2.00 (3H, singlet, acetate methyl protons), 1.12 (singlet, C_{19} methyl protons), 0.62 (singlet, C_{18} methyl protons), 0.36-0.20 ppm (2H, multiplet, cyclopropyl protons); m.s. No. 4 m/e : 442 (M^+).

Anal. Calcd. for $C_{30}H_{50}O_2$: C, 81.02 ; H, 11.79.

Found : C, 81.09 ; H, 11.81,

IV. SPECTRA



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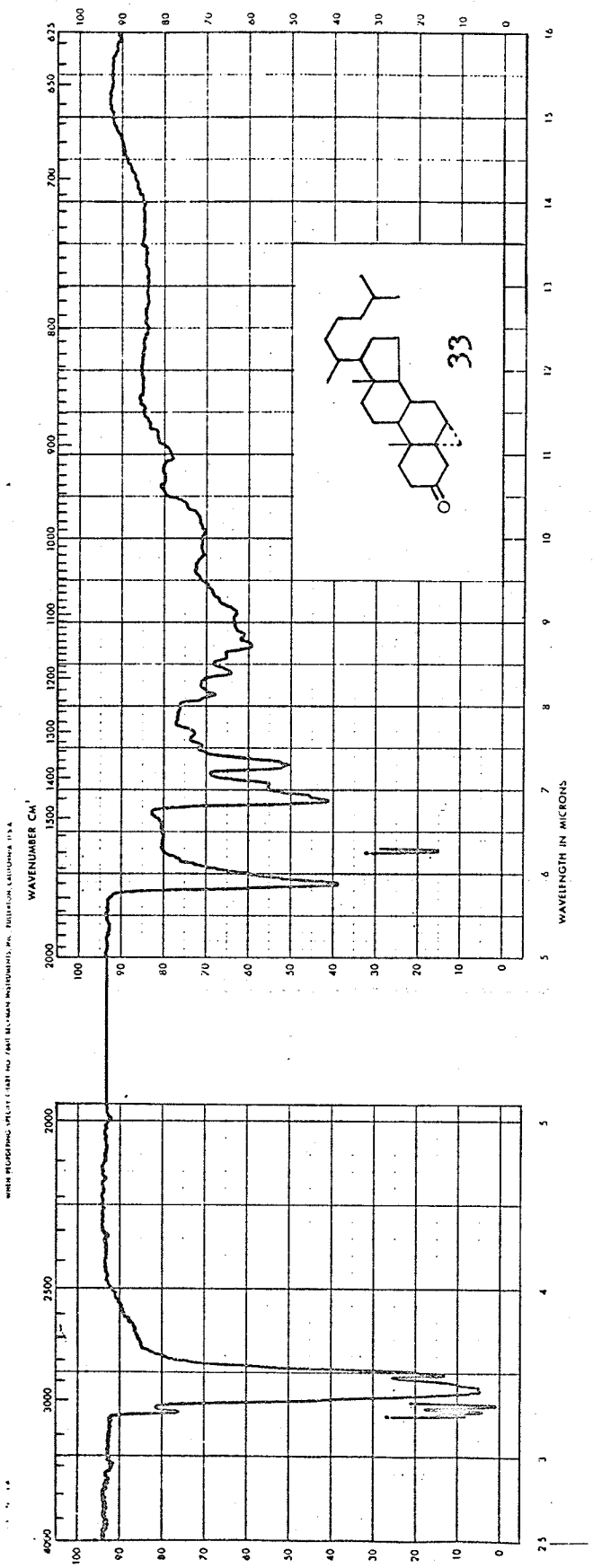

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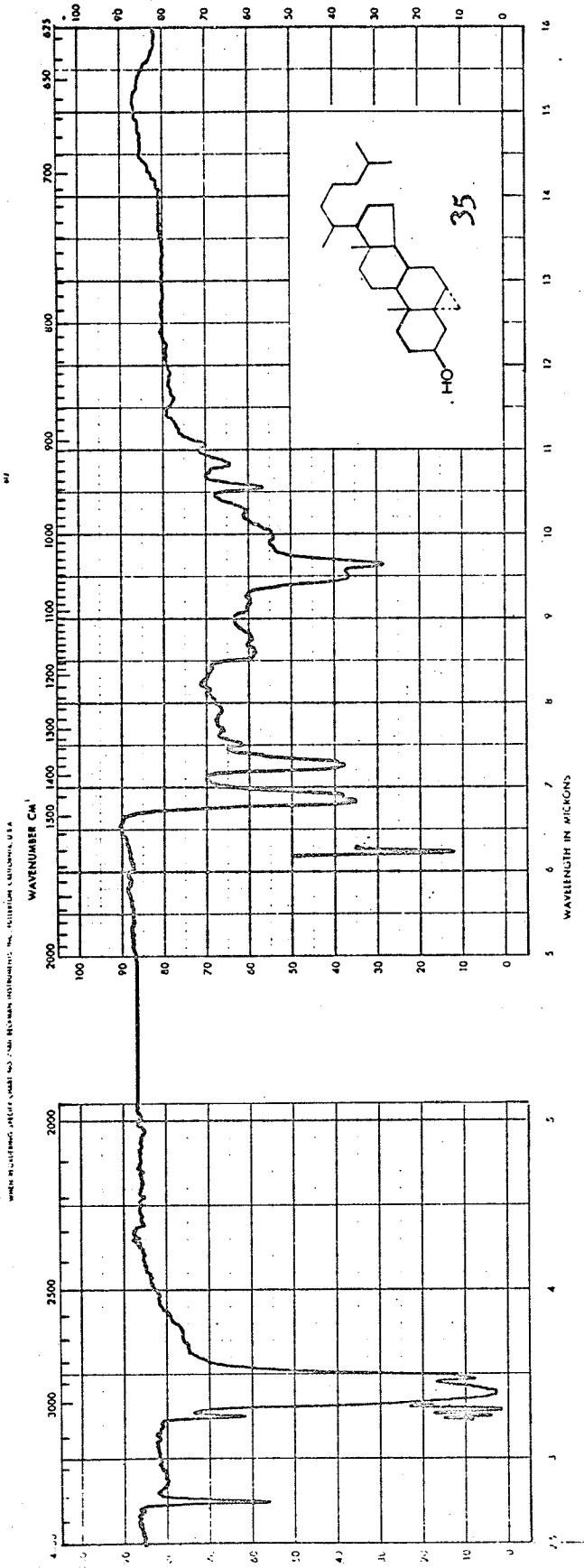

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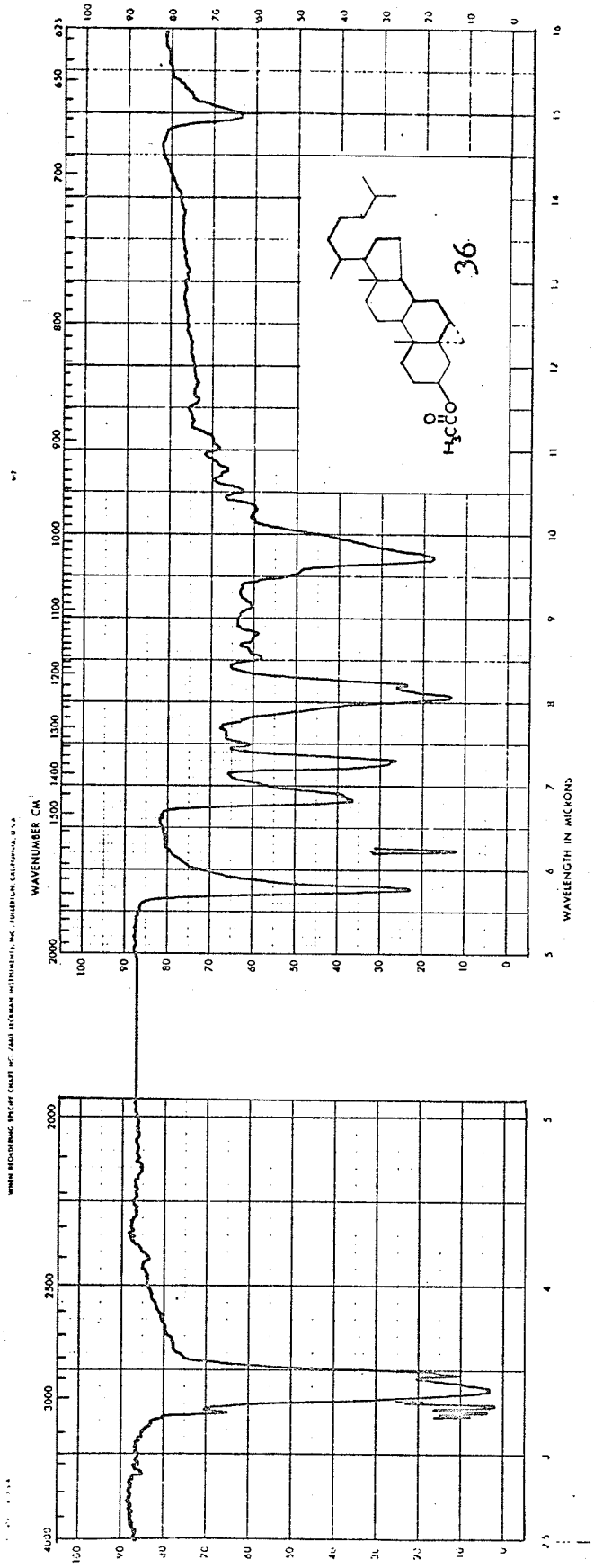

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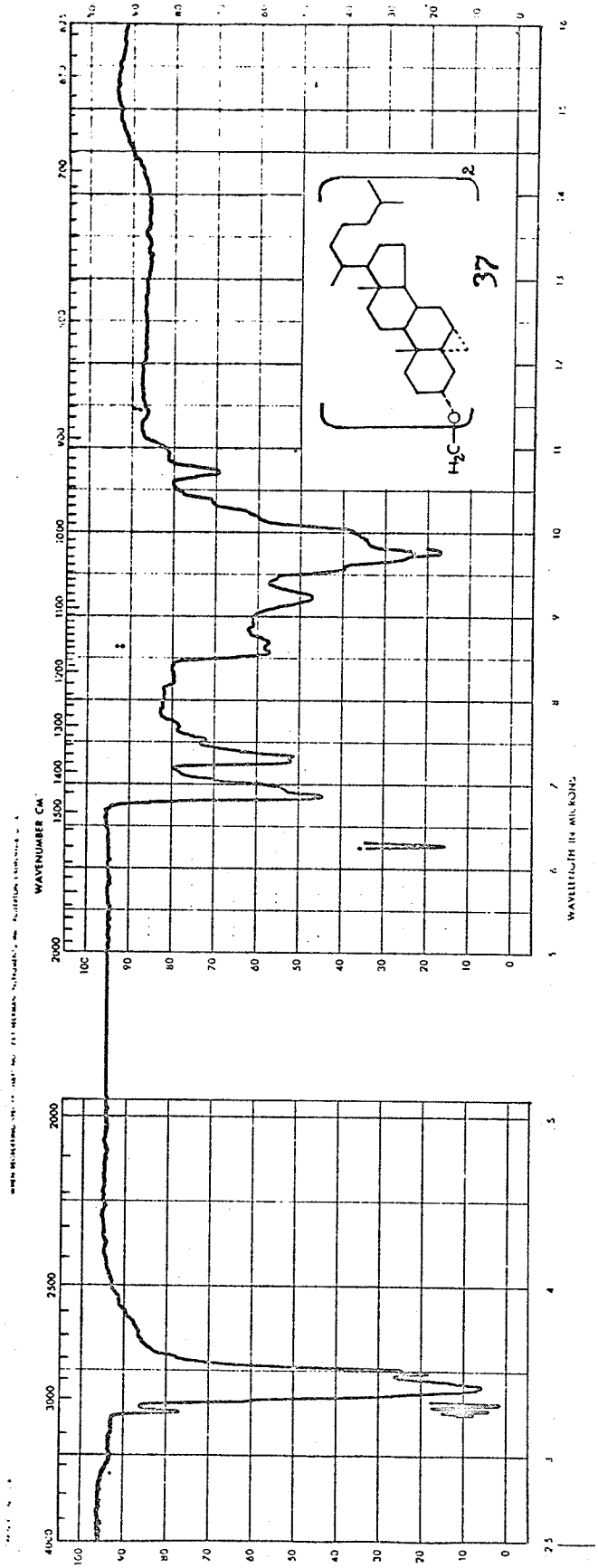

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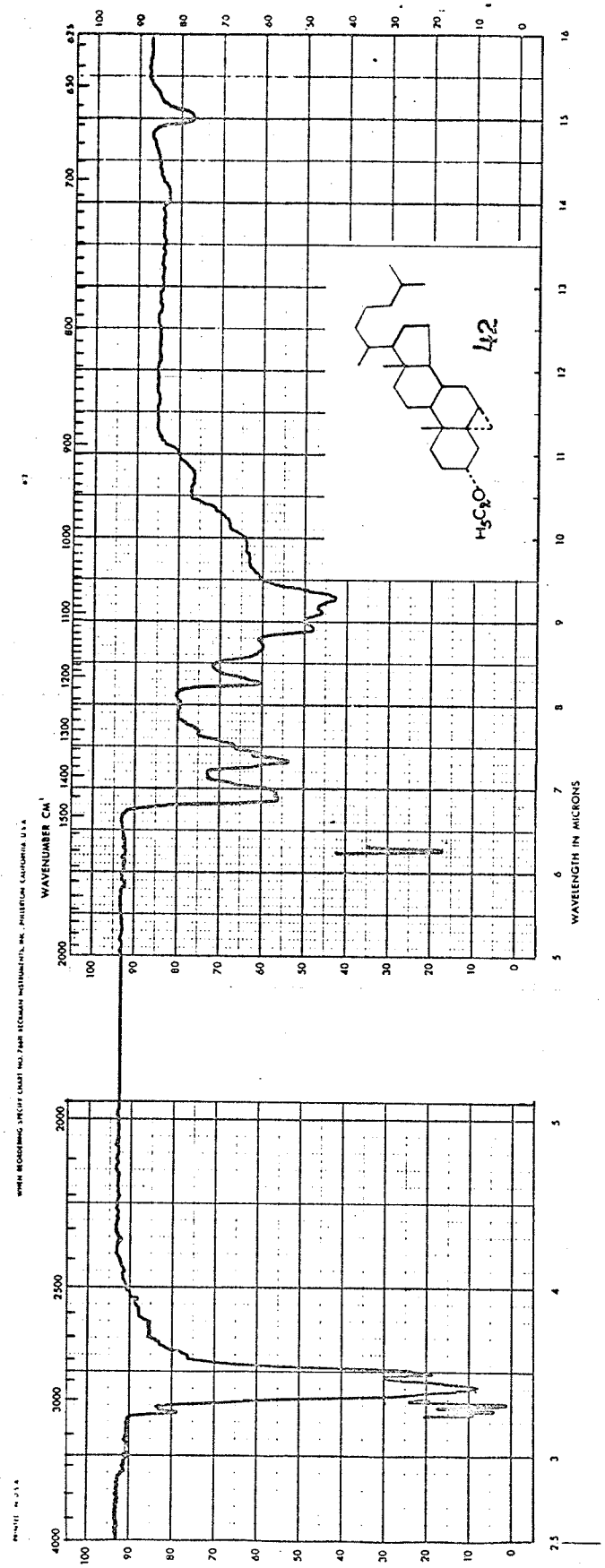

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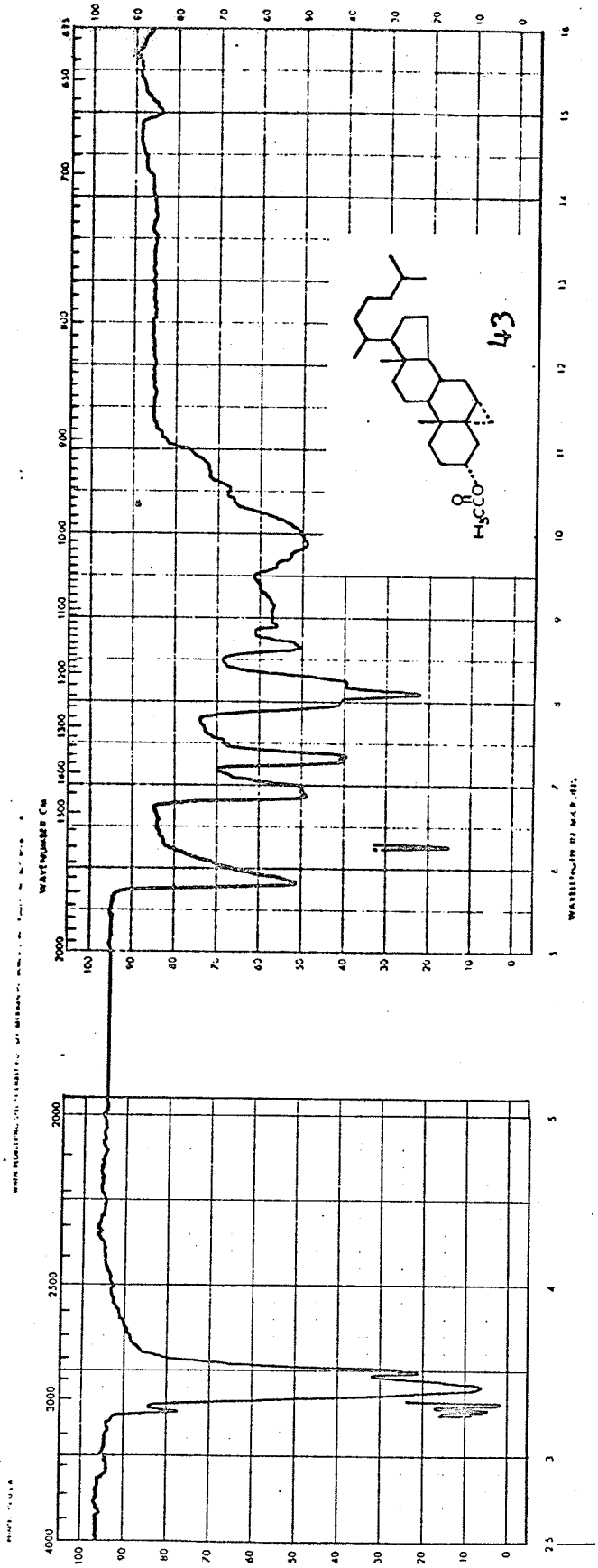

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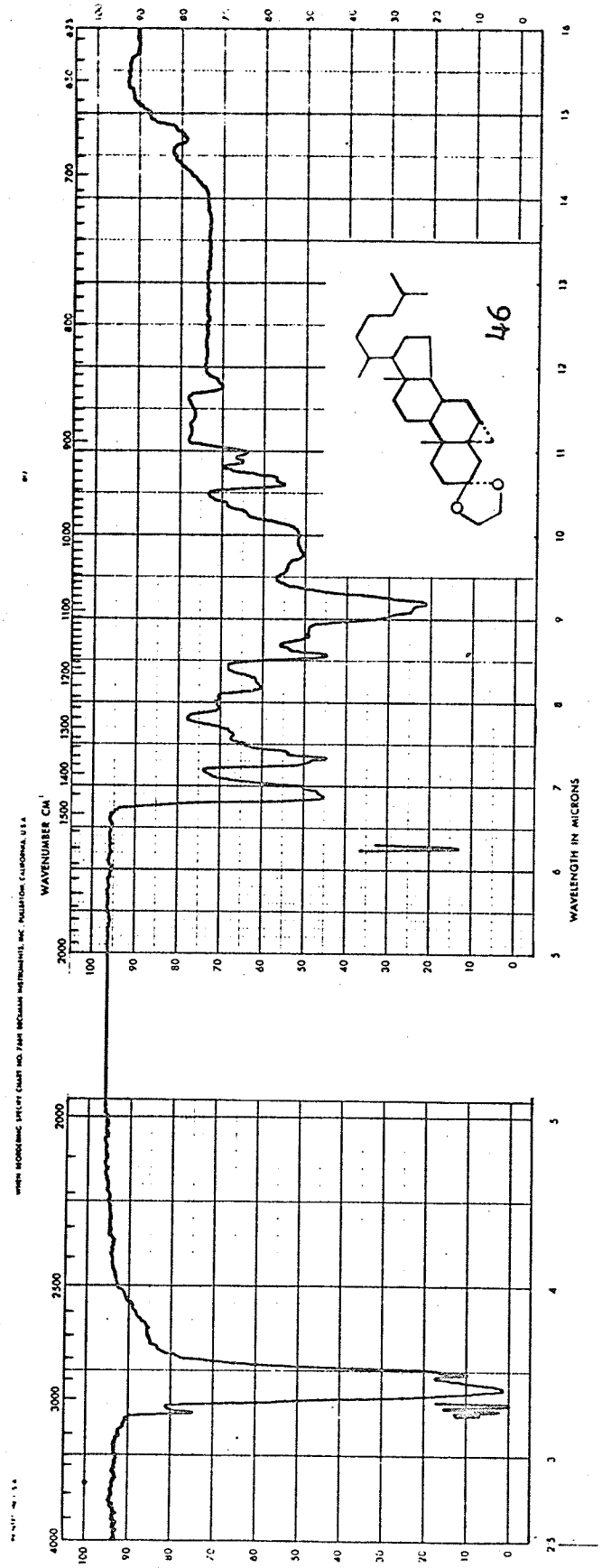

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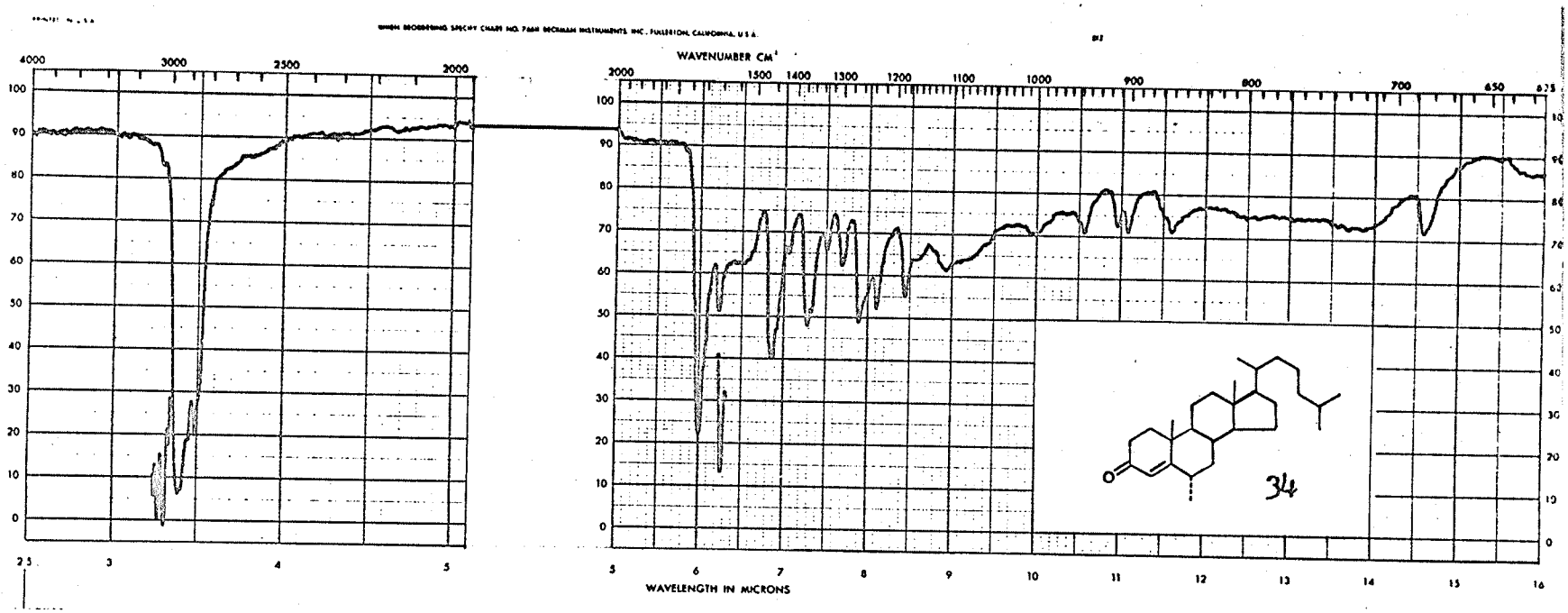

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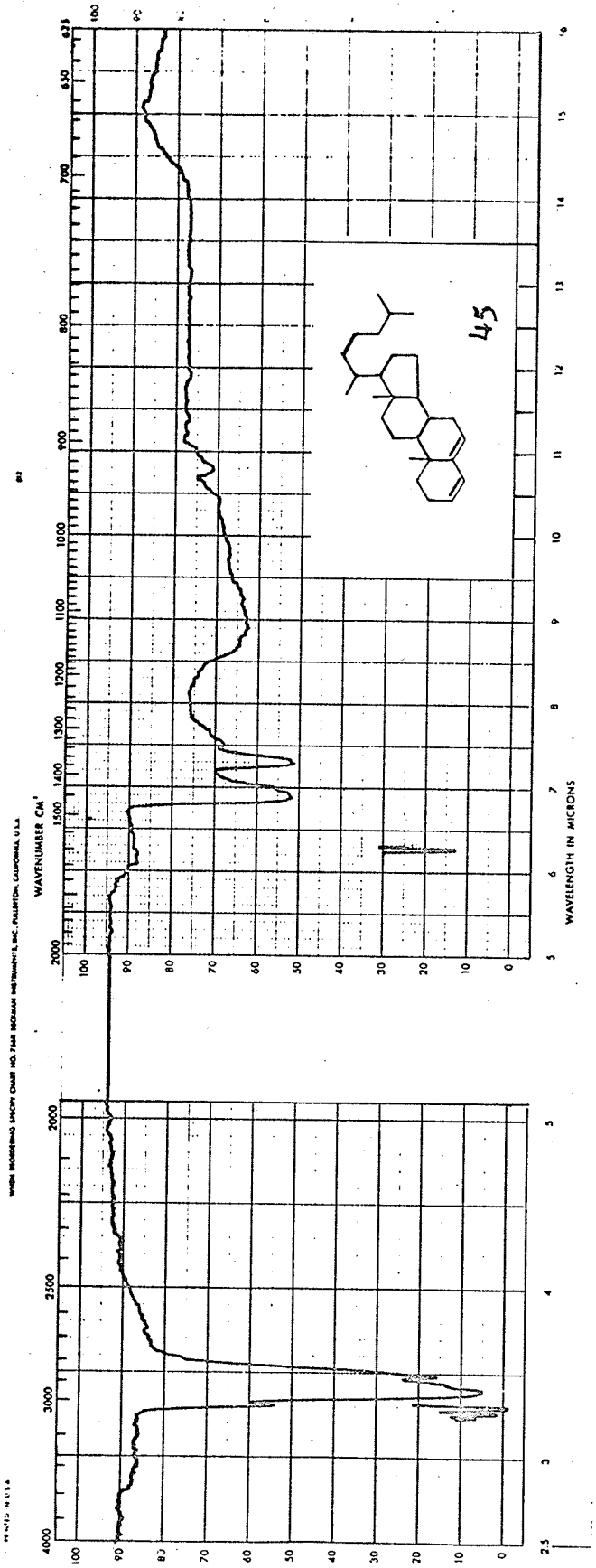

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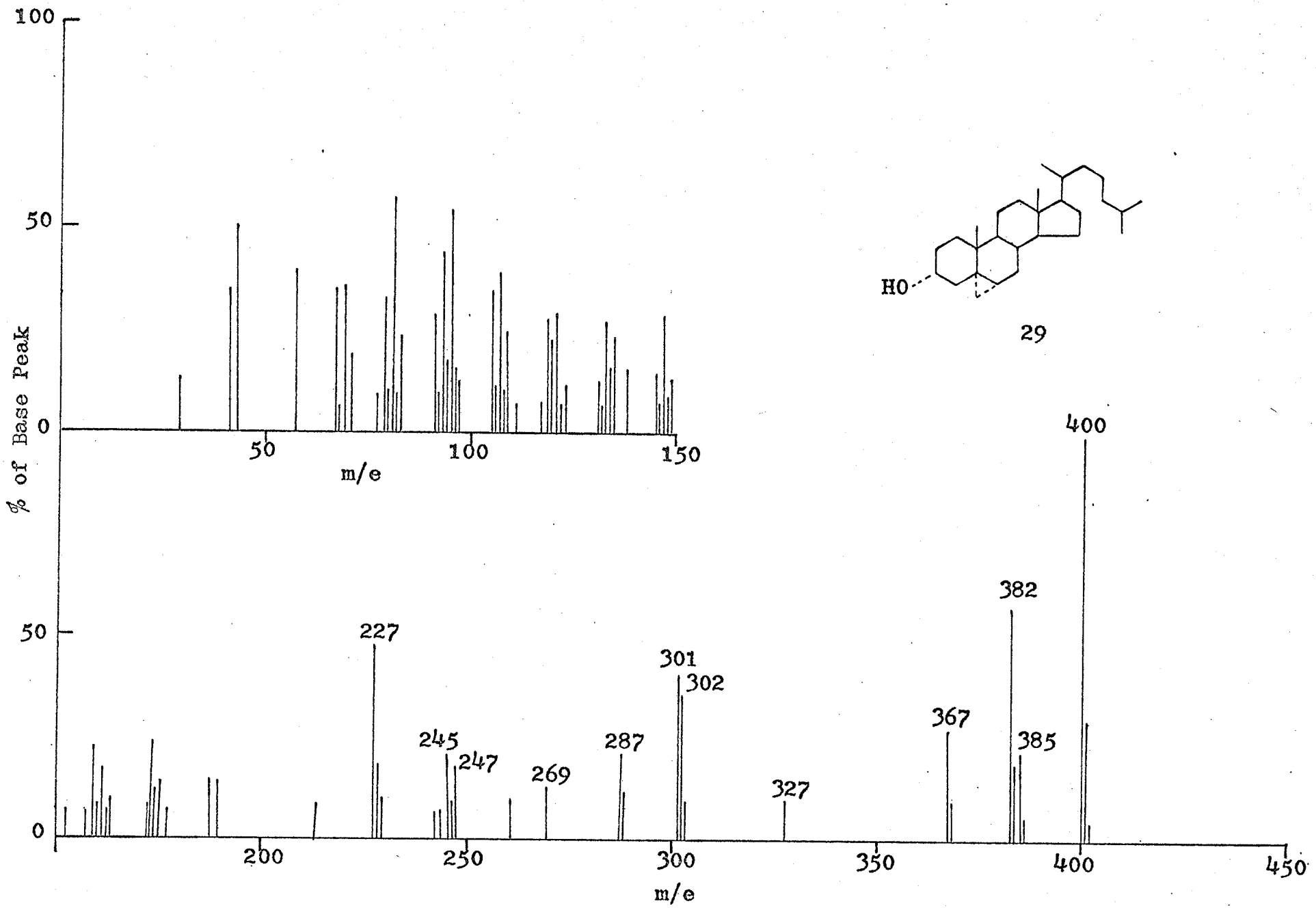

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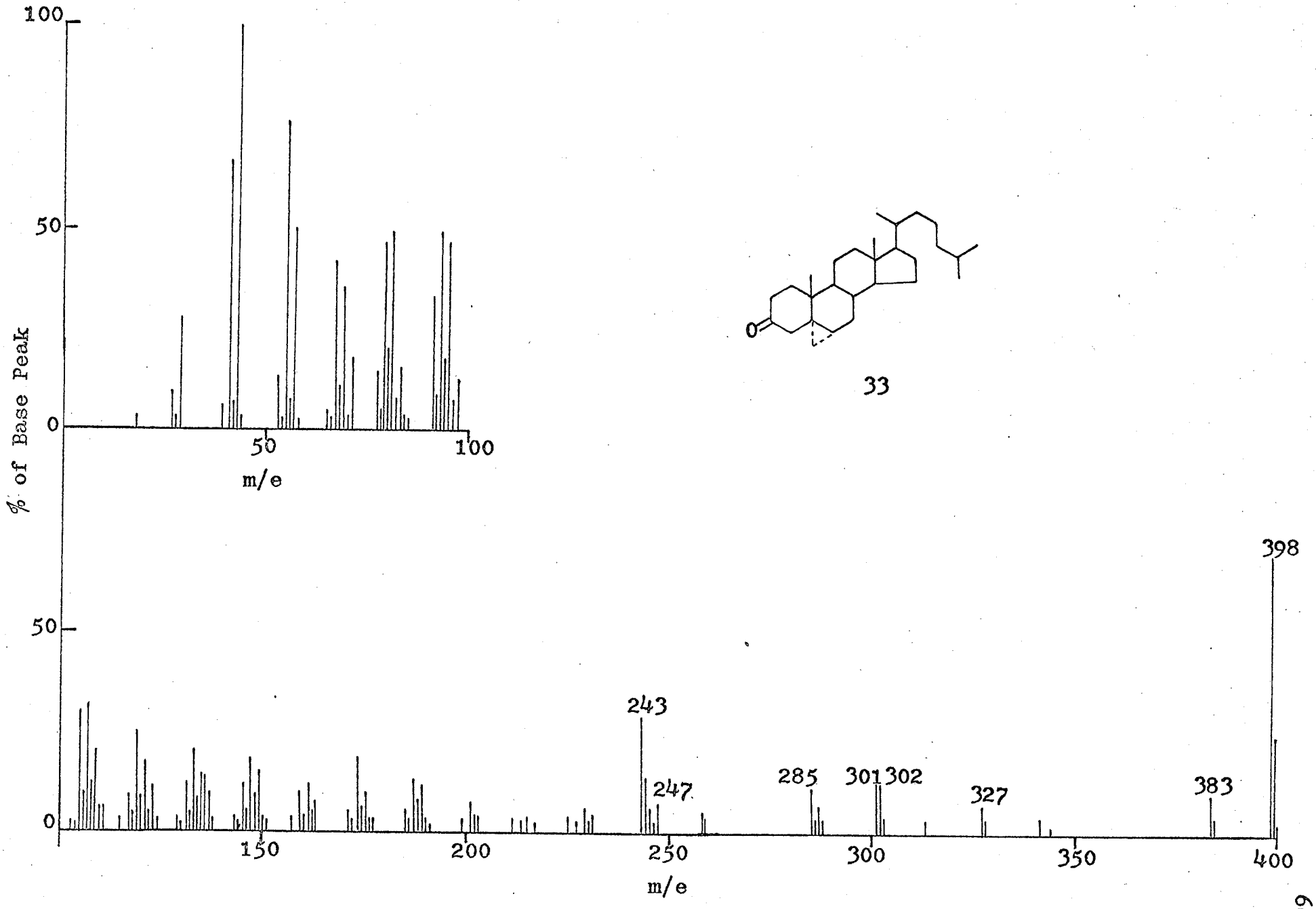

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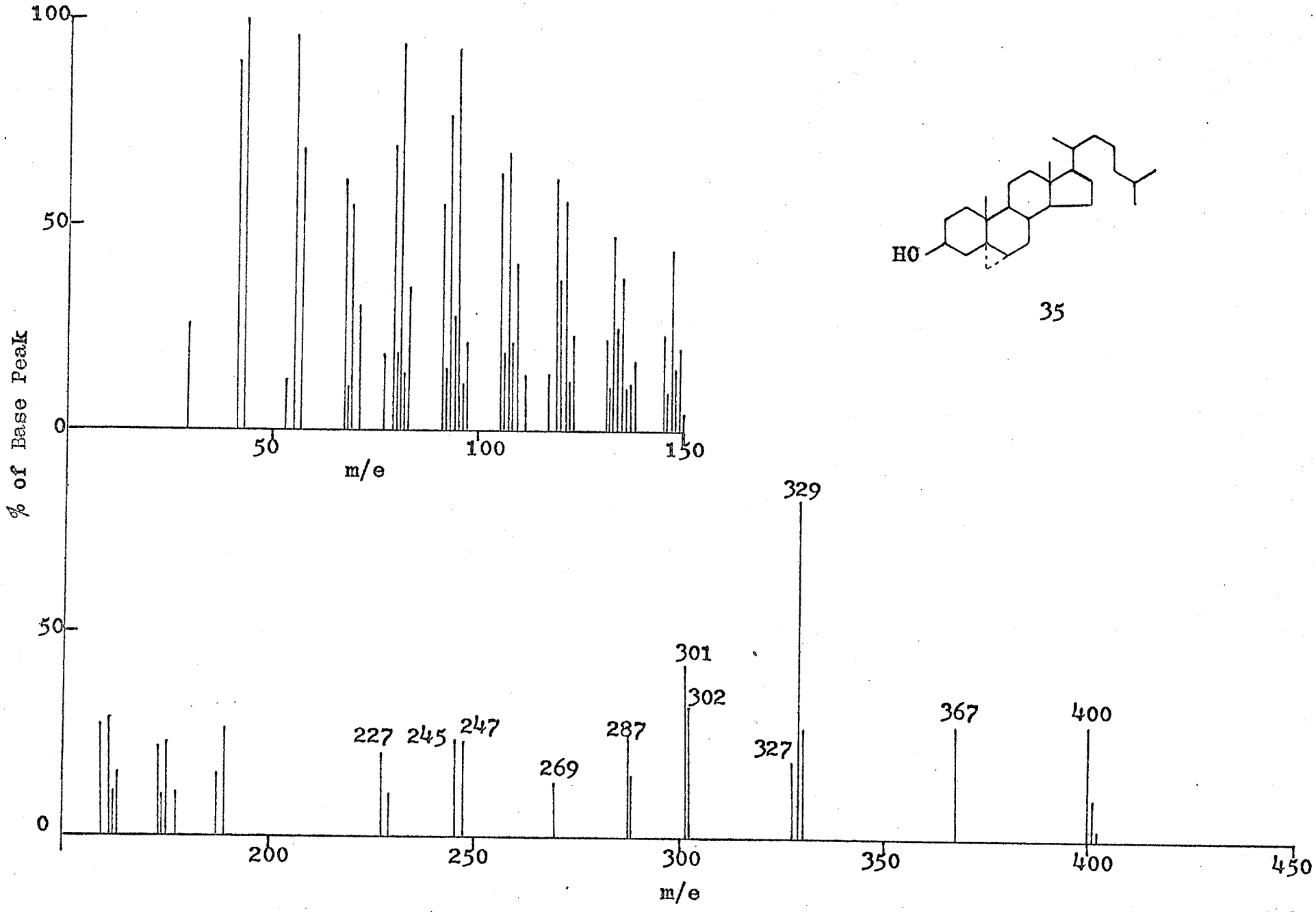

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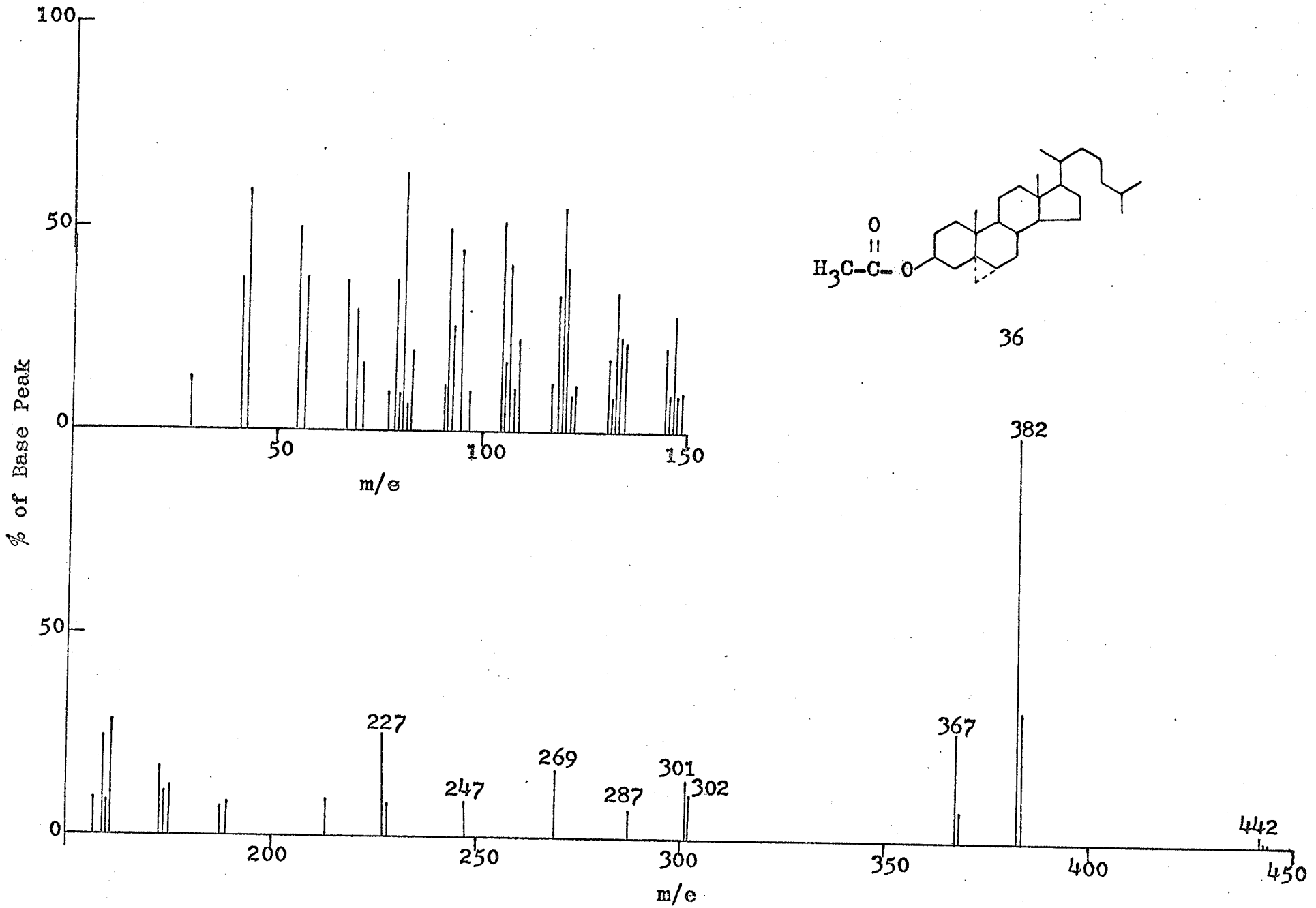

36

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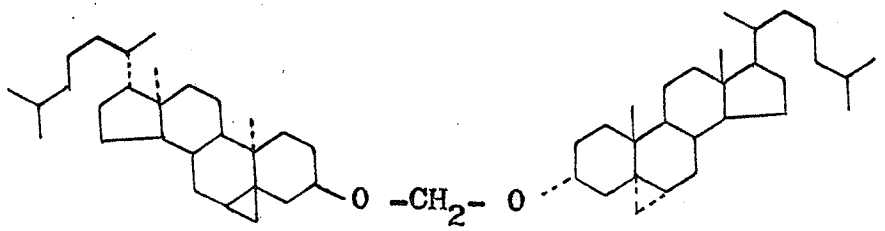

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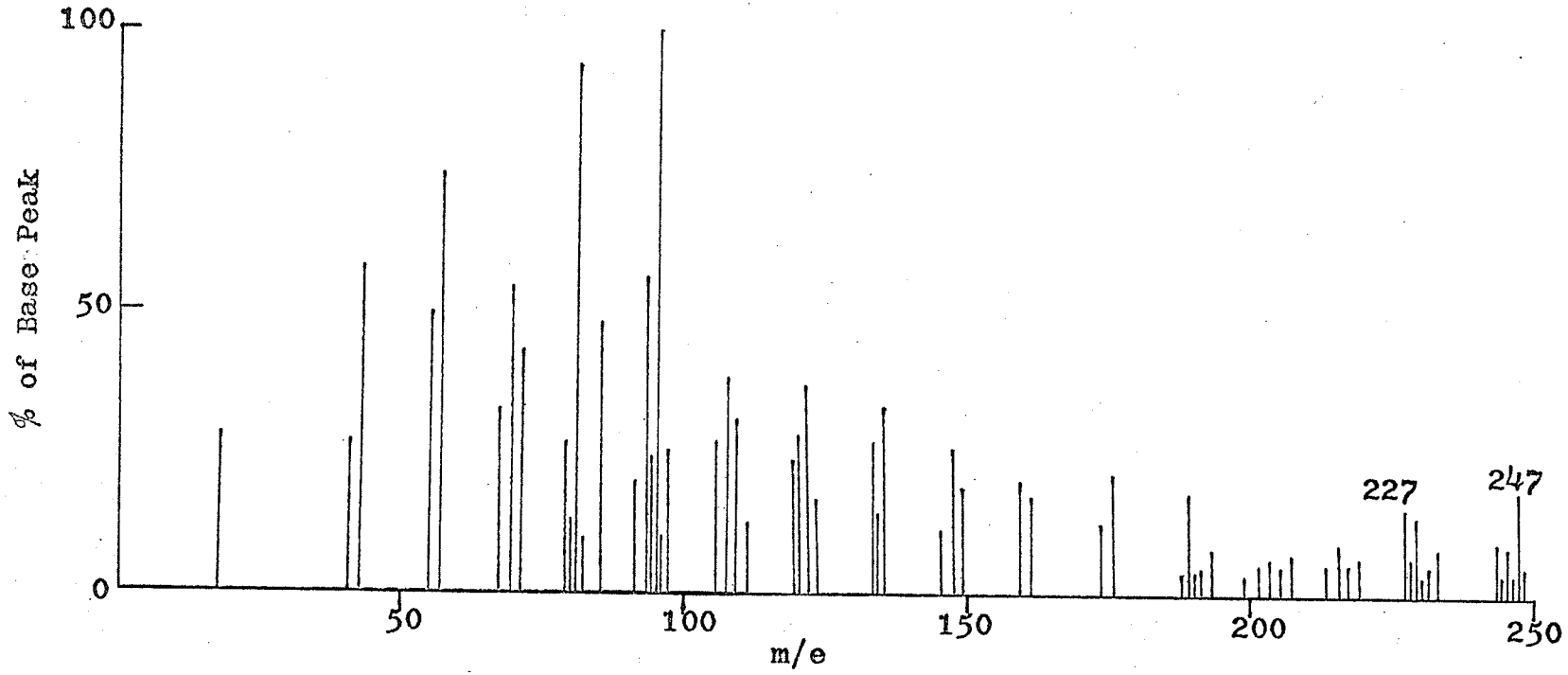
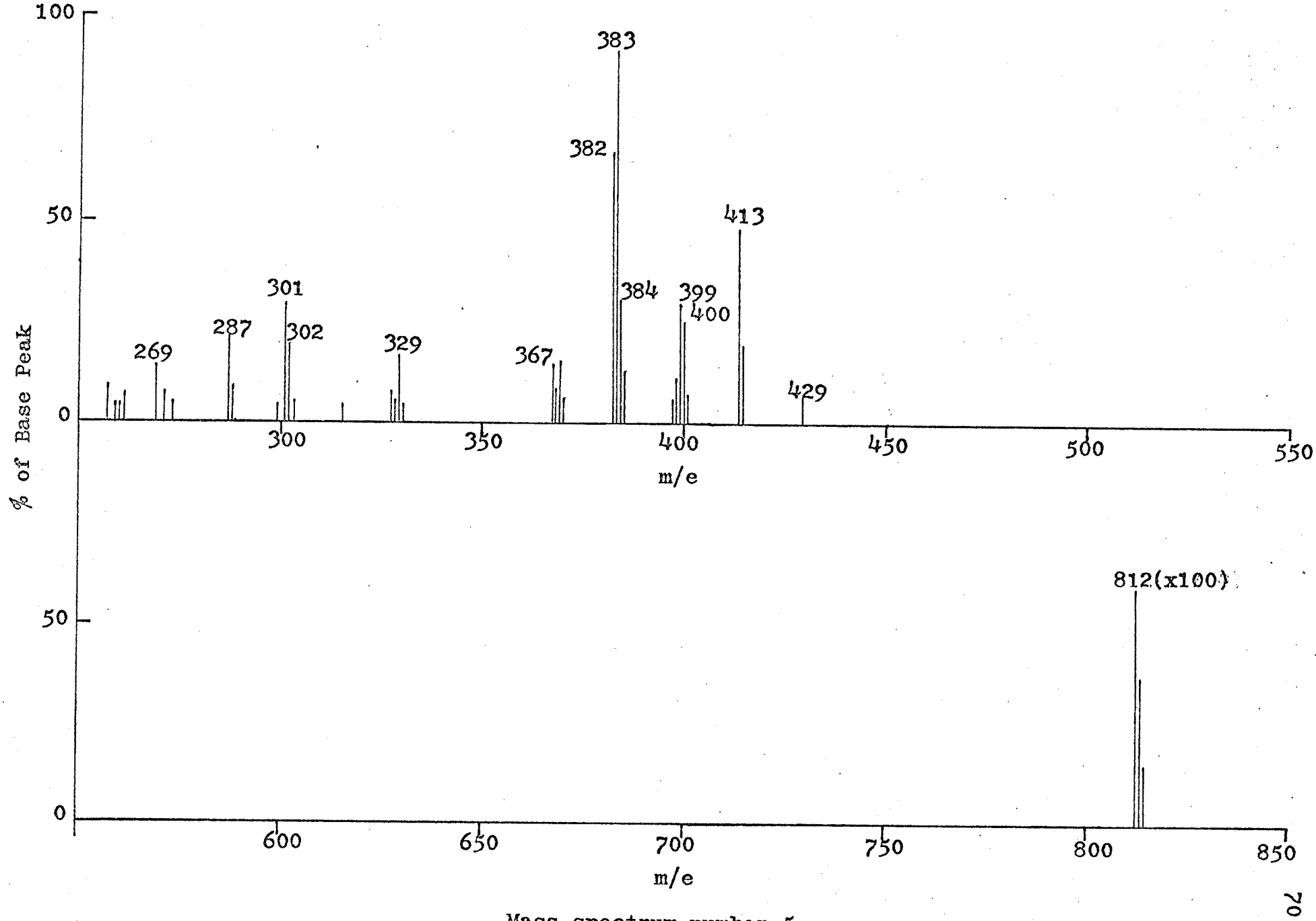


Mass spectrum number 5 (cont'd).



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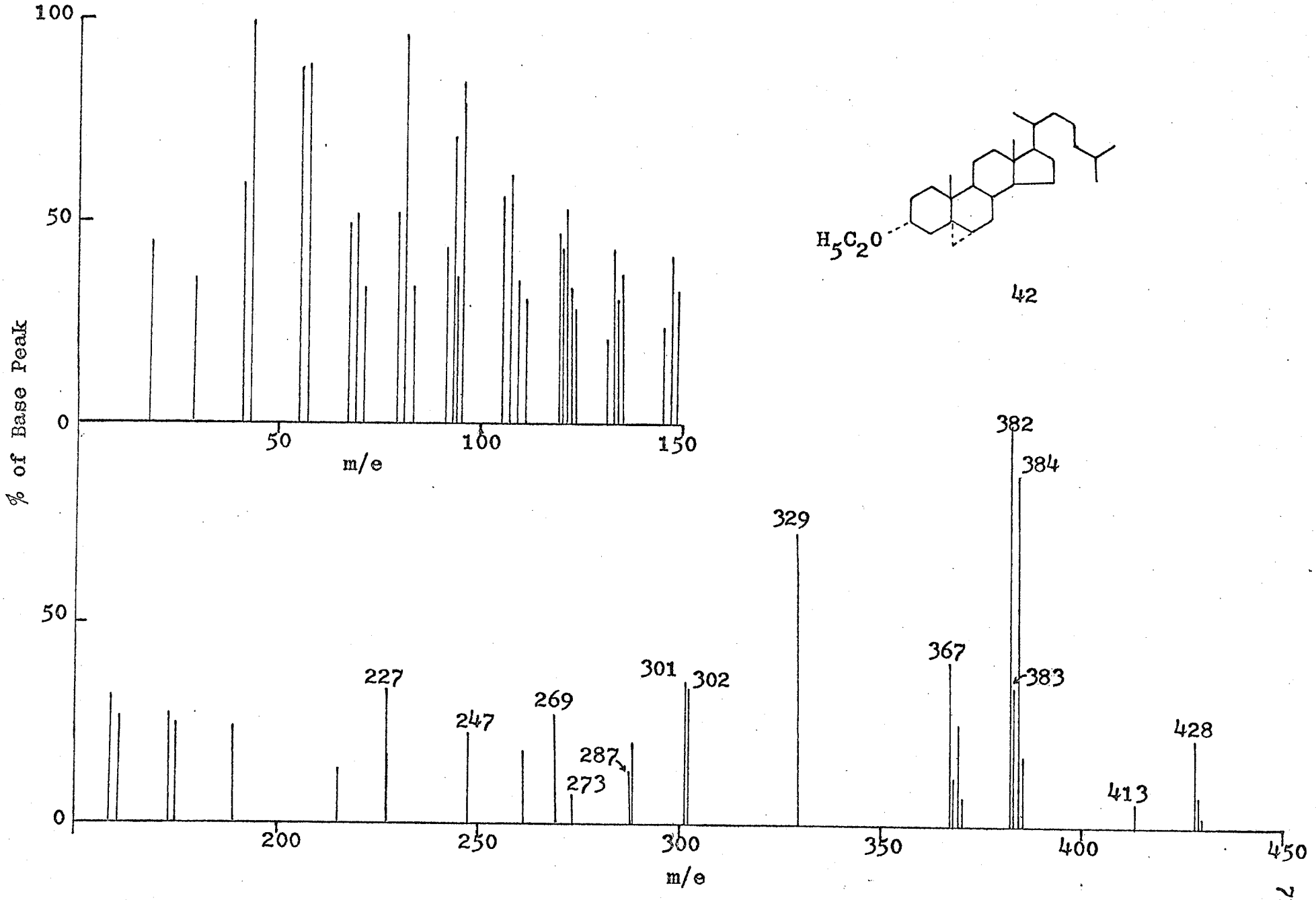

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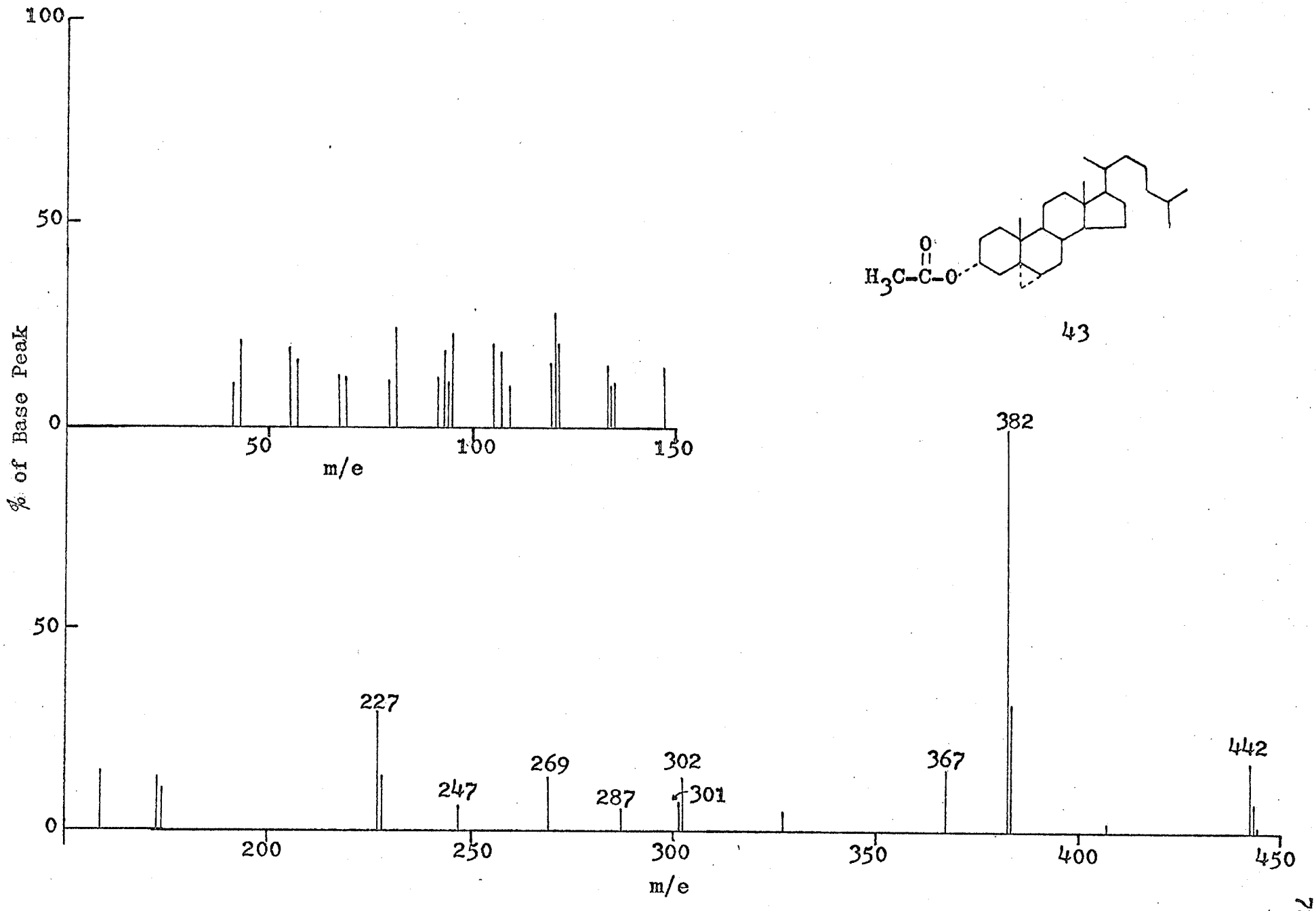

43

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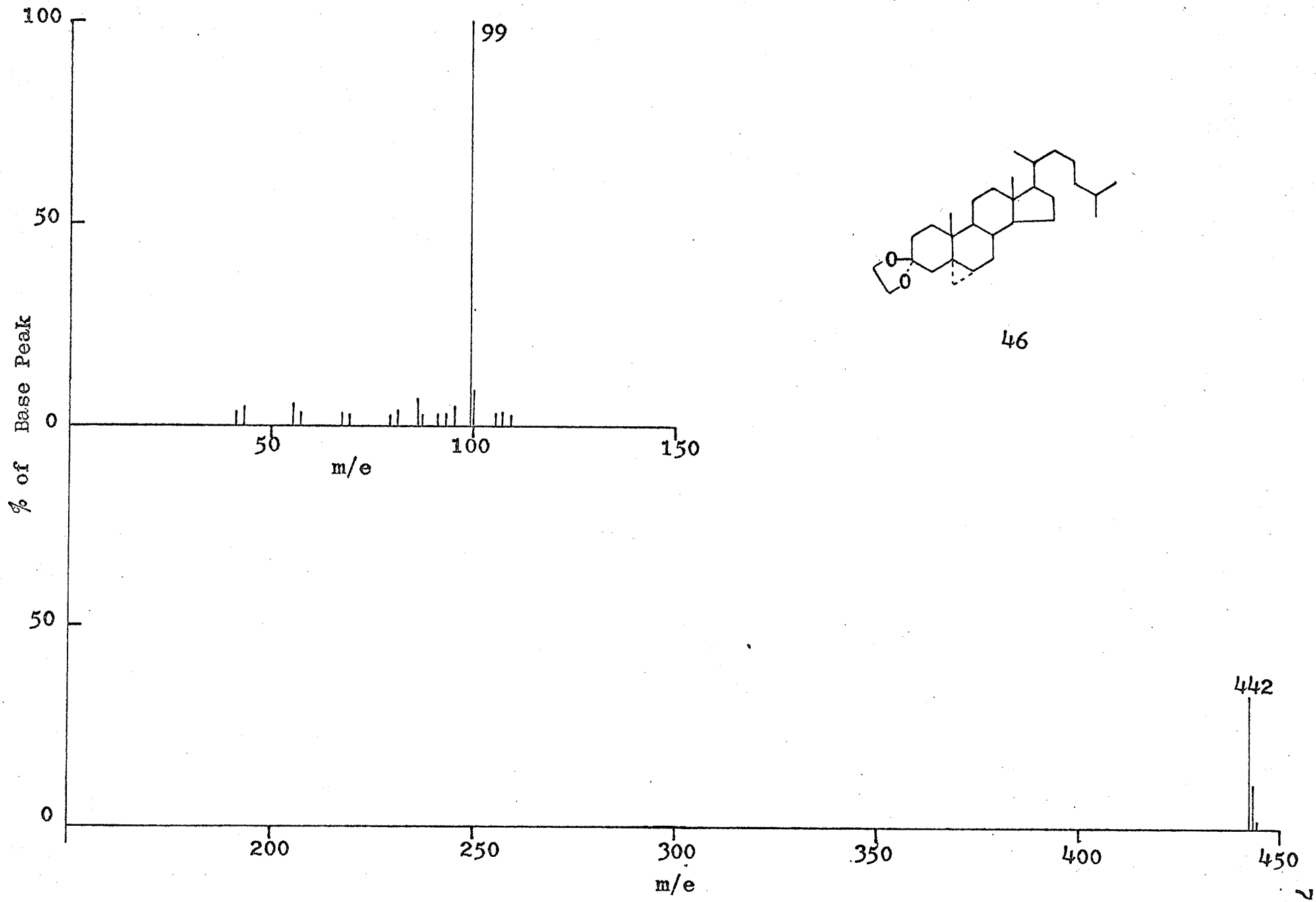
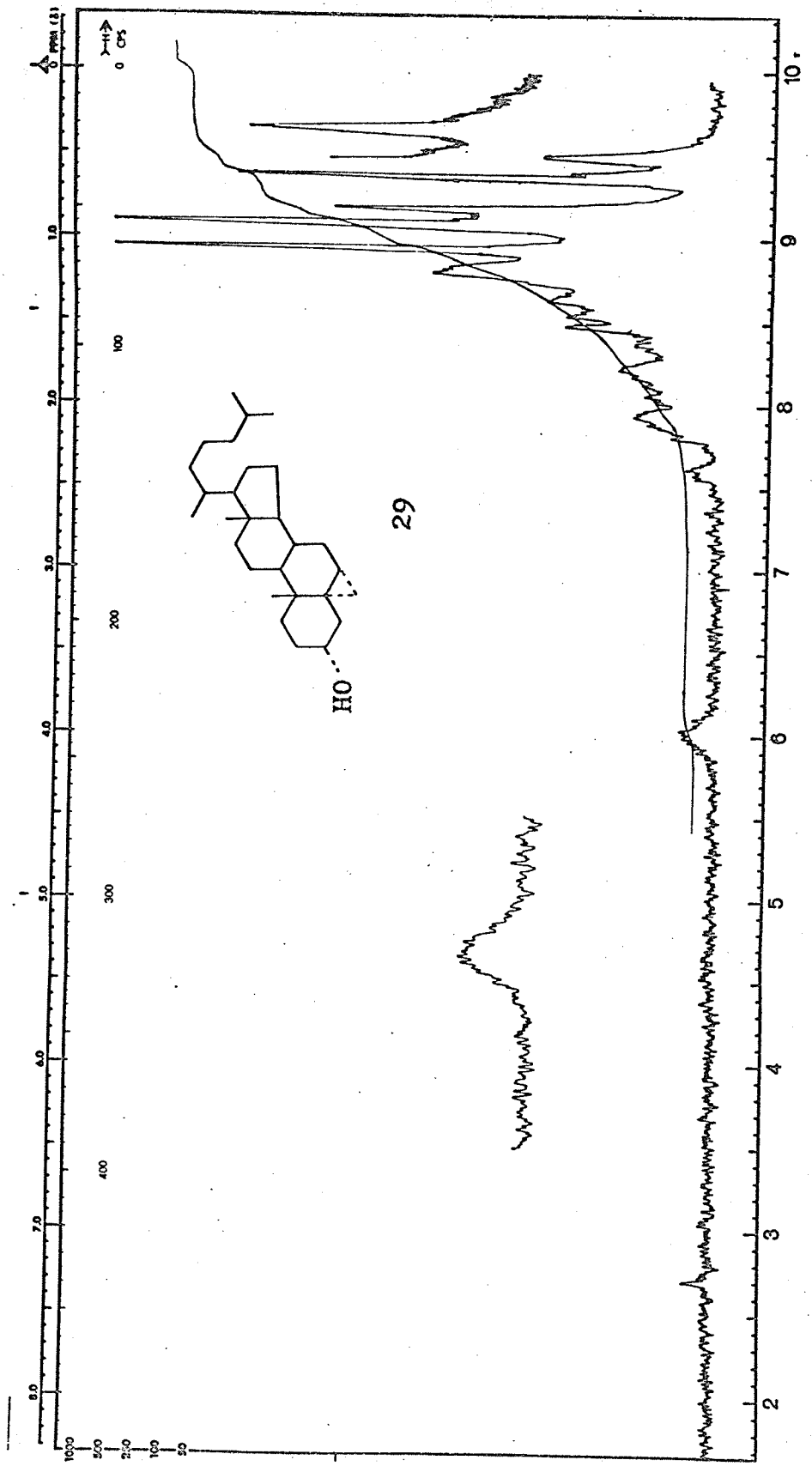
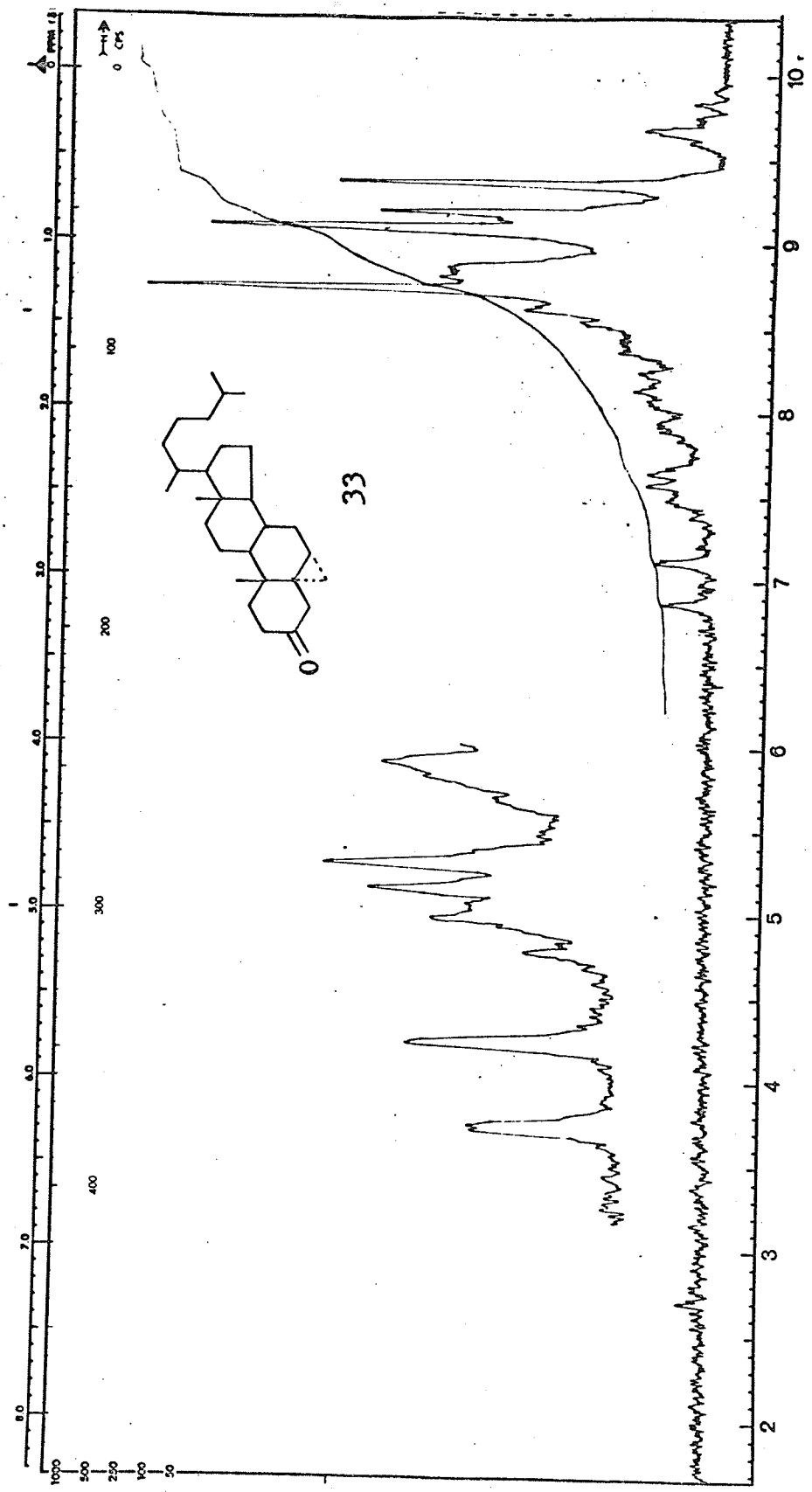


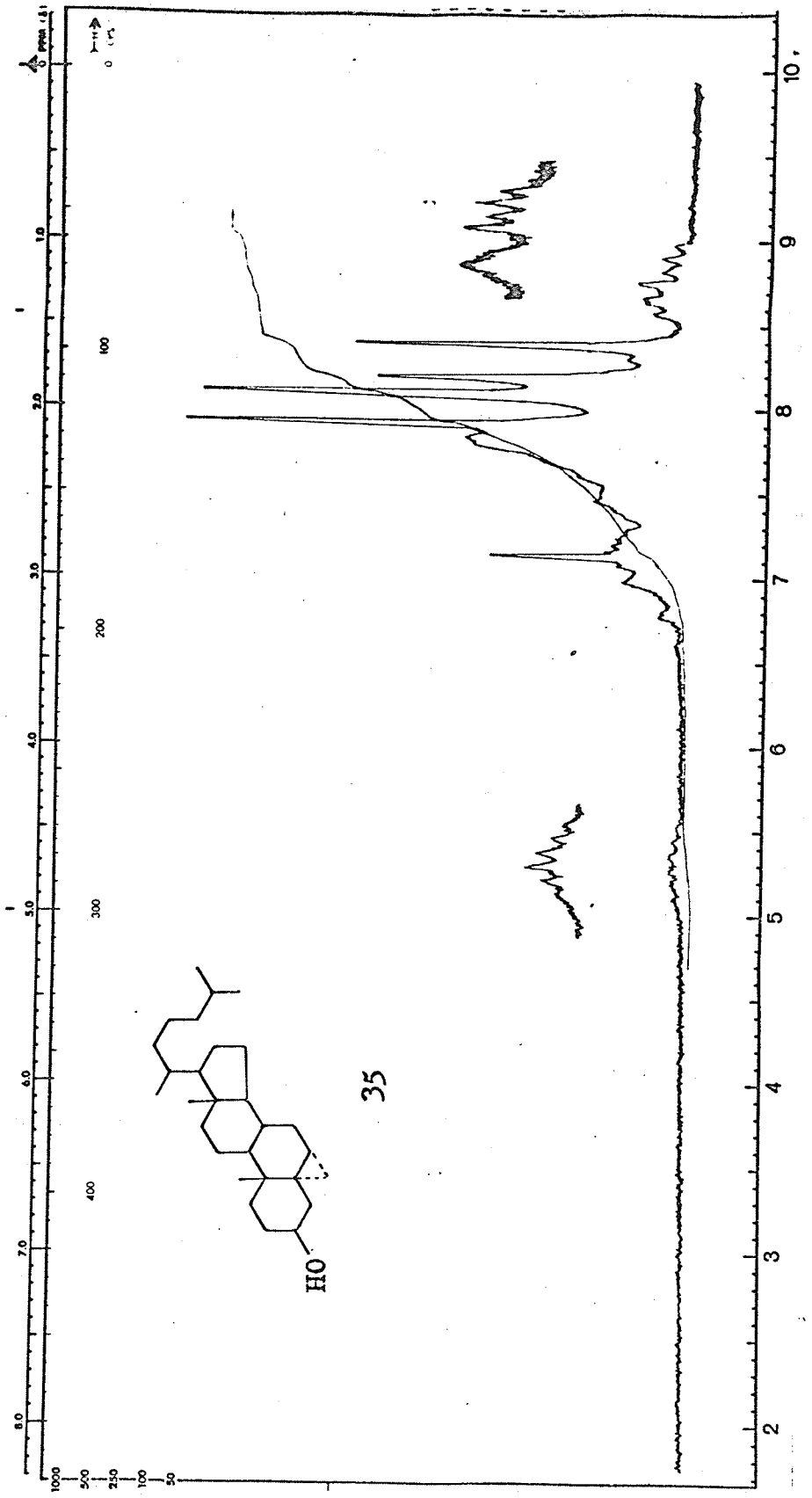
Mass spectrum number 8.



Proton magnetic resonance spectrum number 1.



Proton magnetic resonance spectrum number 2.



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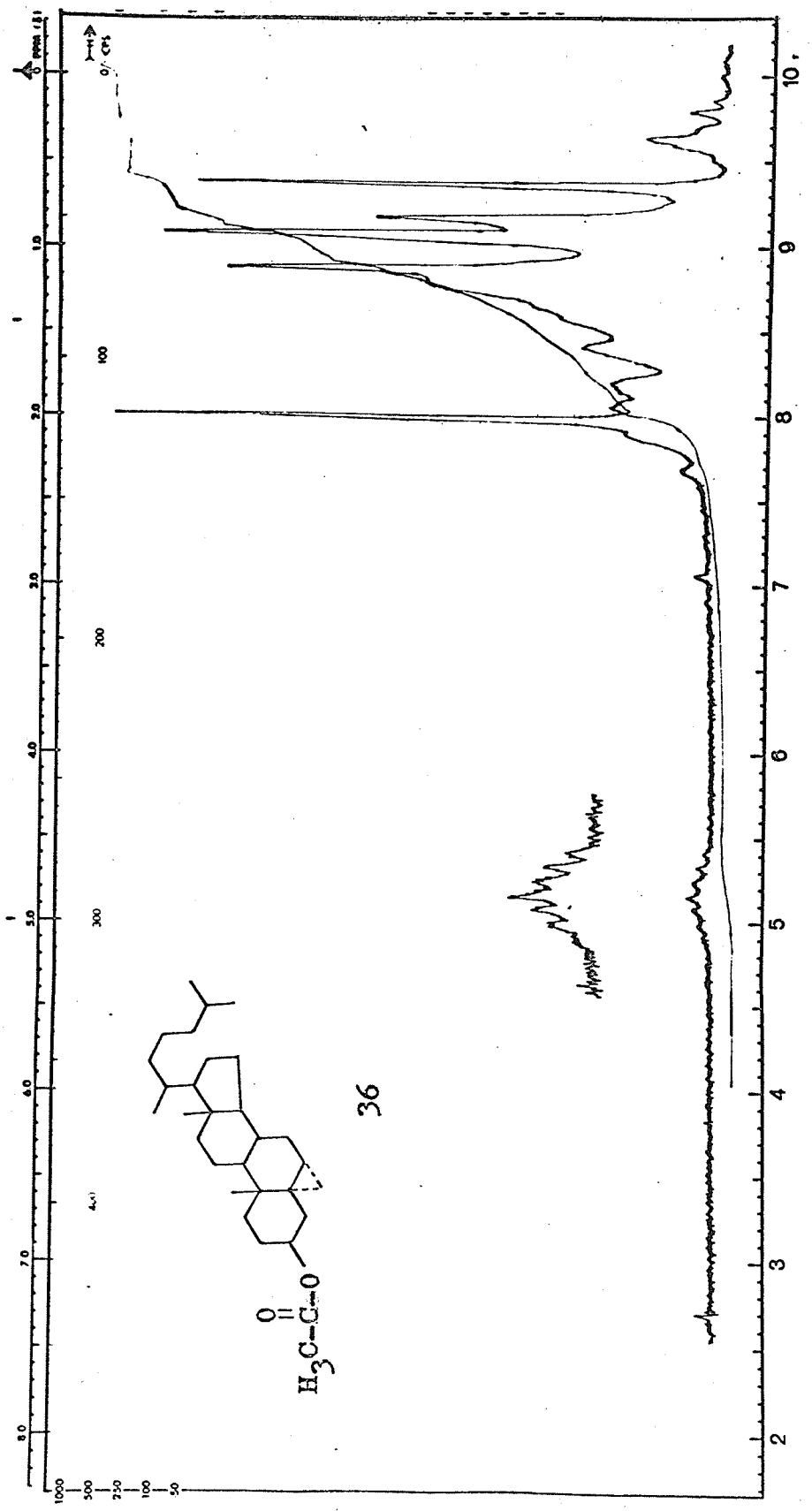

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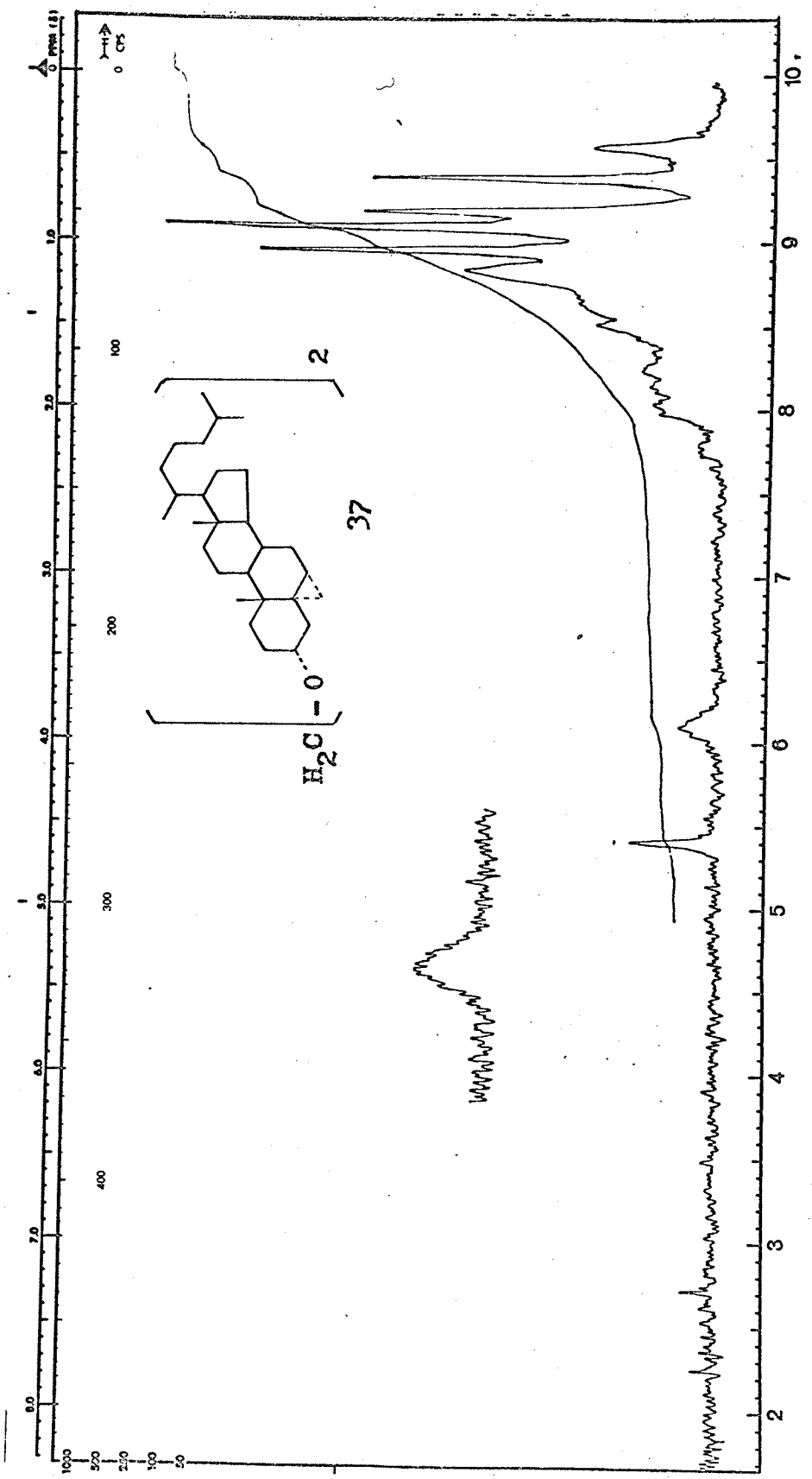

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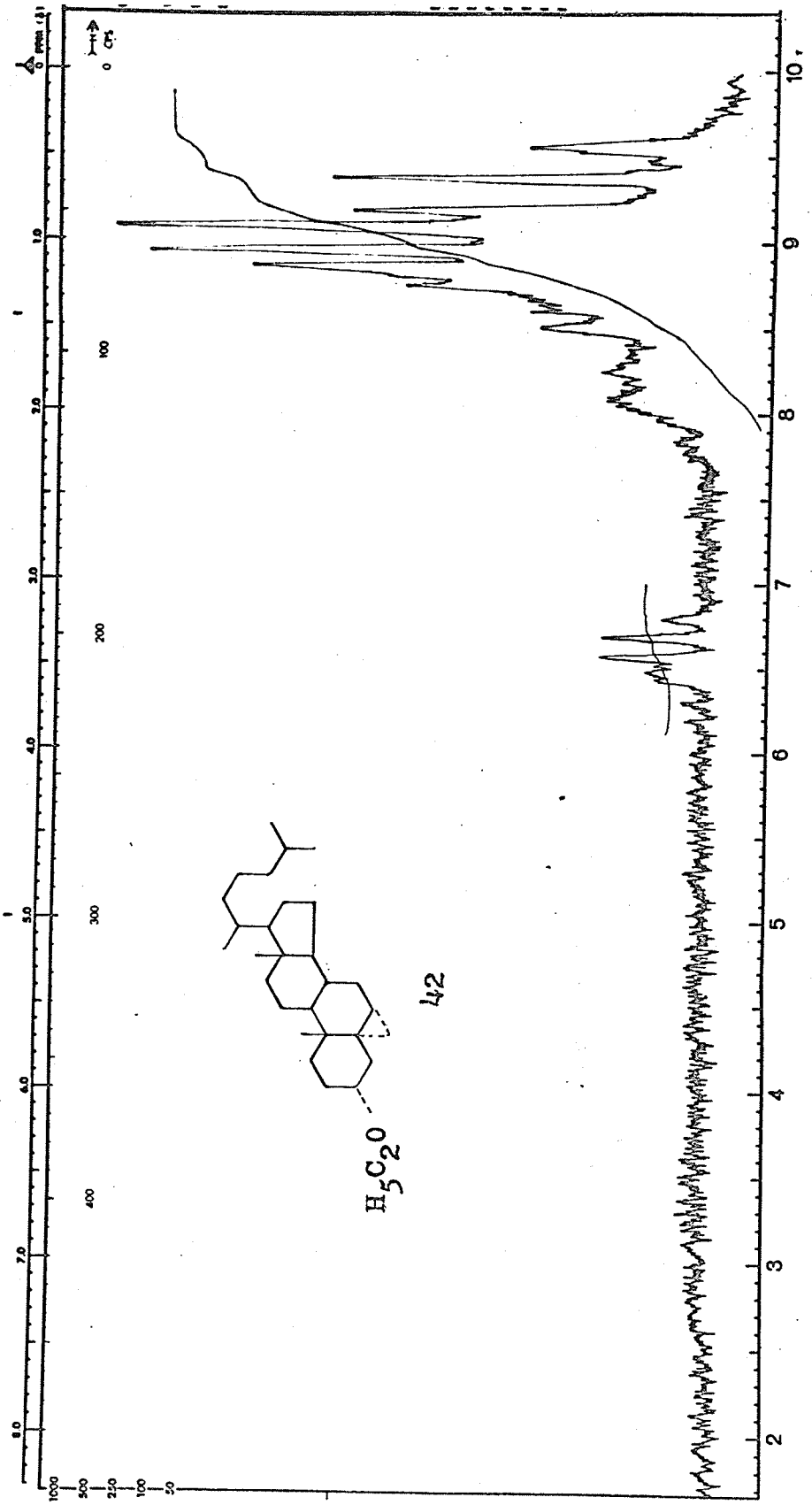

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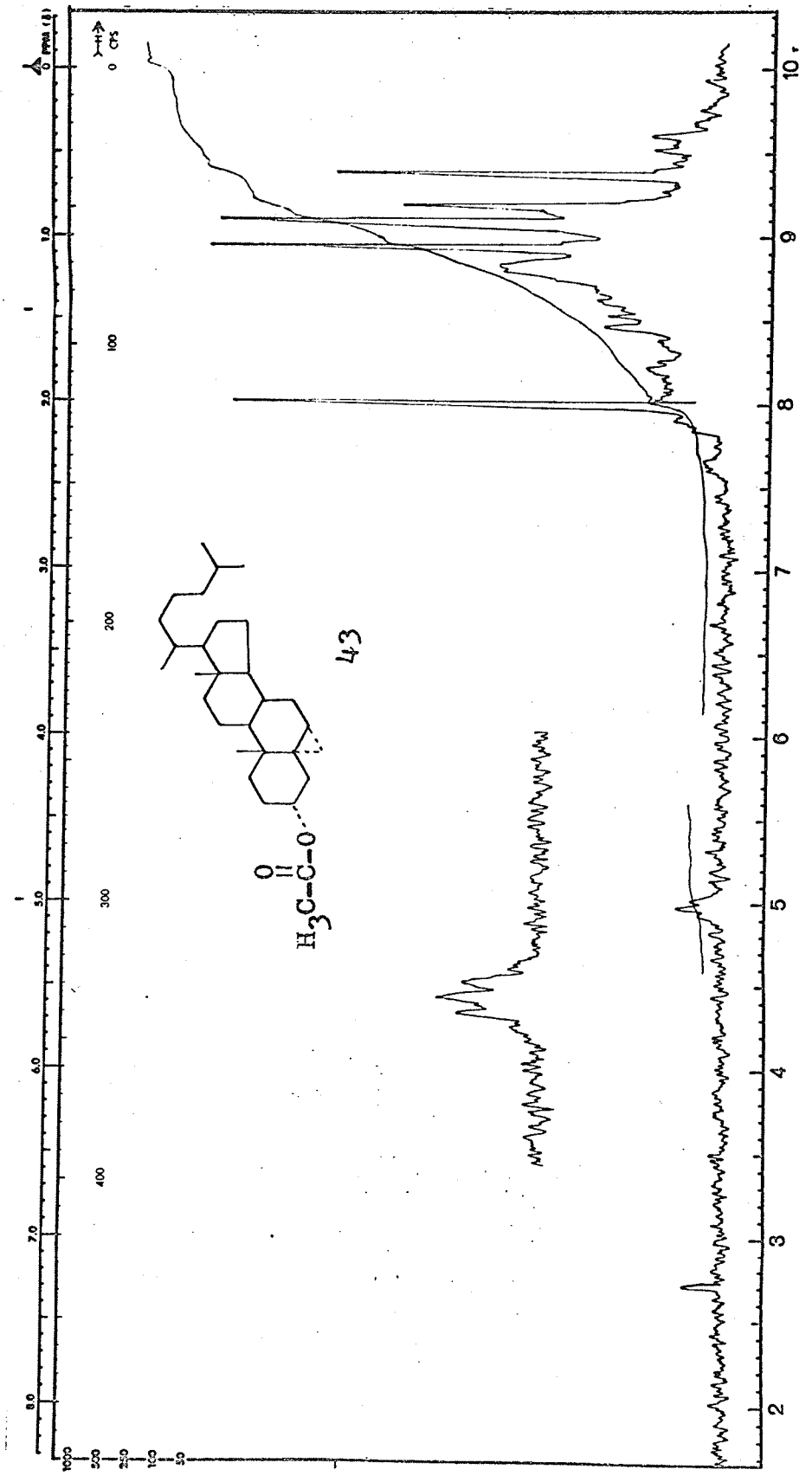

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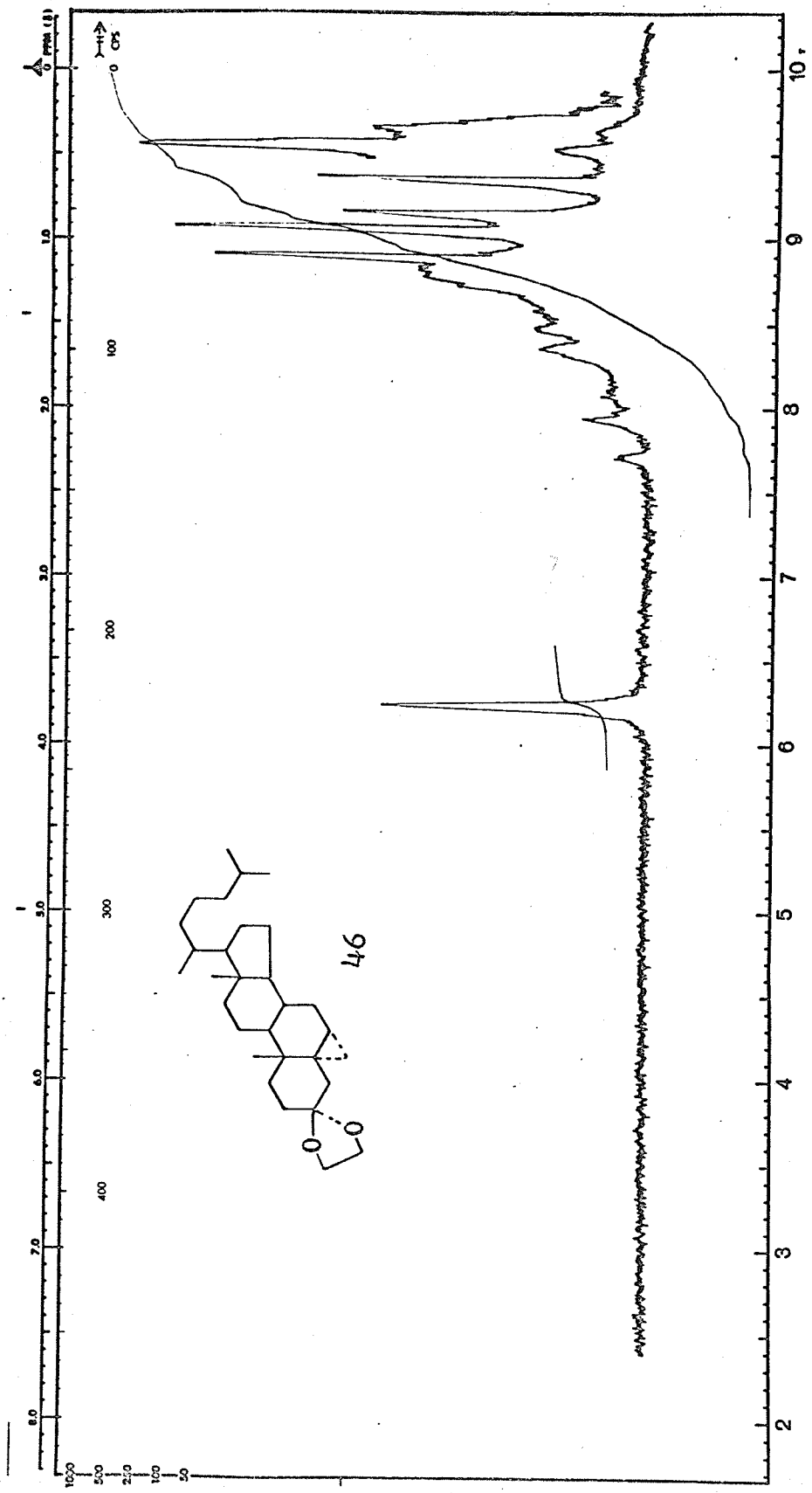
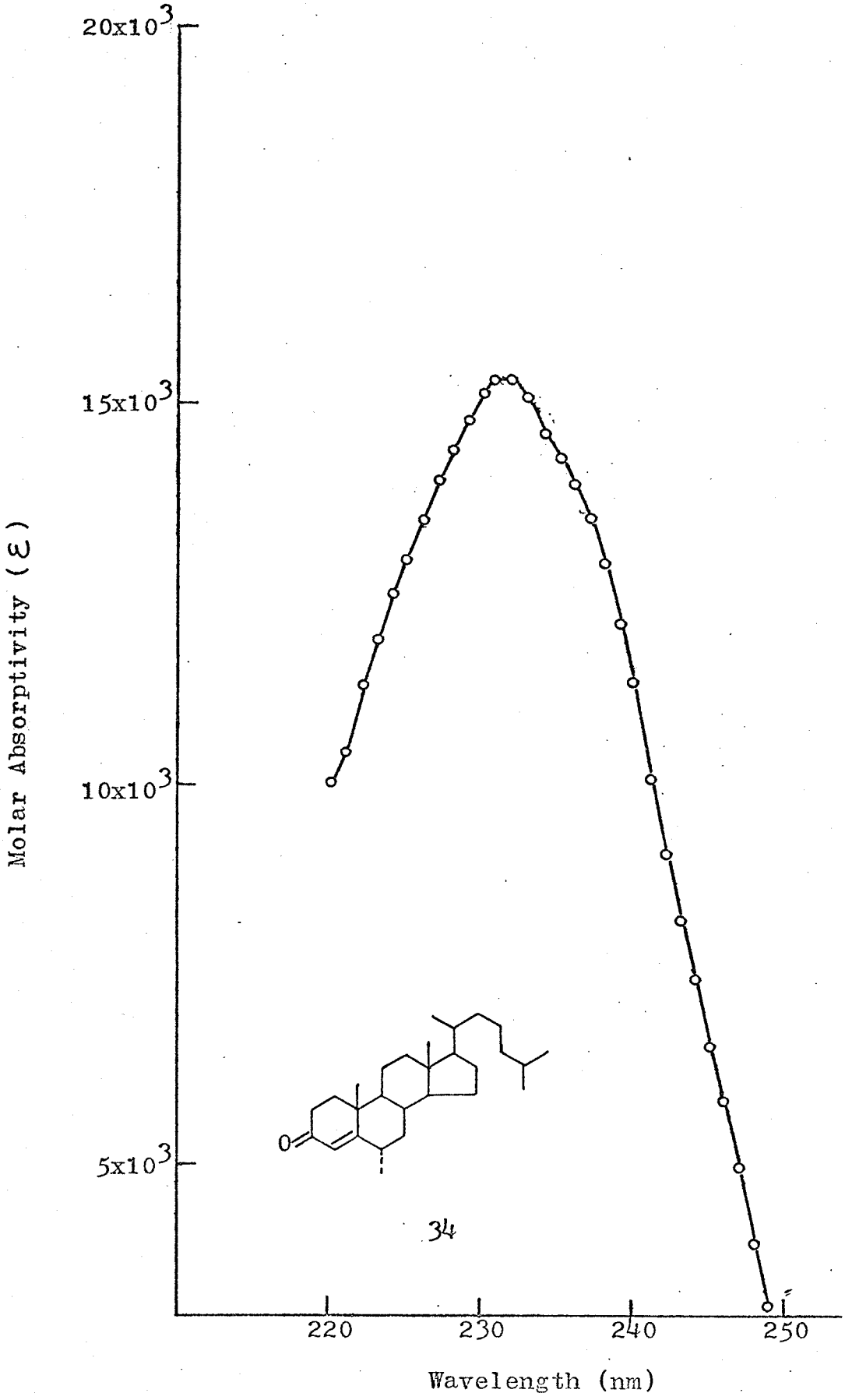
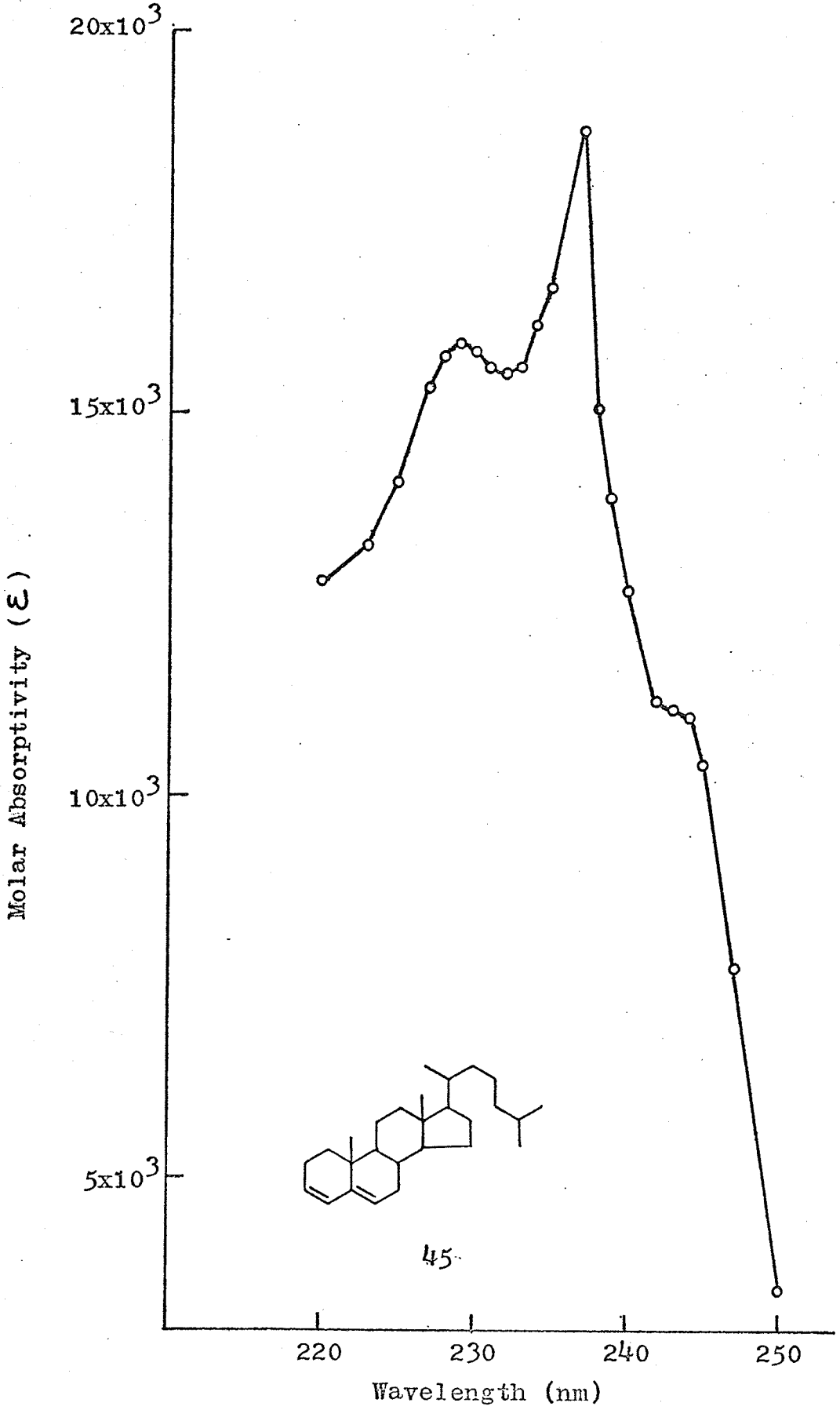


Proton magnetic resonance spectrum number 8.



Ultraviolet spectrum number 1.



Ultraviolet spectrum number 2.

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