THE FAVORSKII RING CONTRACTION OF STEROIDAL EPOXY KETONES

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This is to certify that the

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THE FAVORSKII RING
CONTRACTION OF
STEROIDAL EPOXY KETONES

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ROBERT WATTS MOUK

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William H. Reusch
Major professor

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O-169

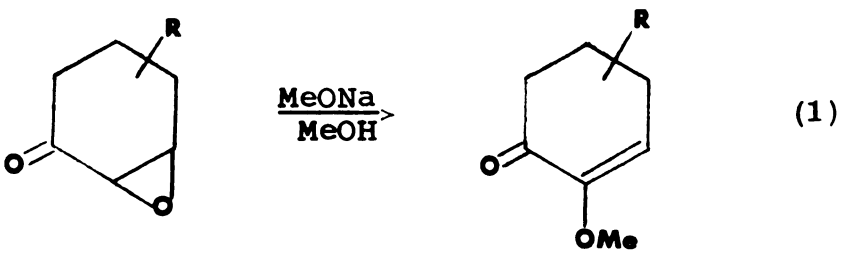
ABSTRACT

THE FAVORSKII RING CONTRACTION OF STEROIDAL EPOXY KETONES

By

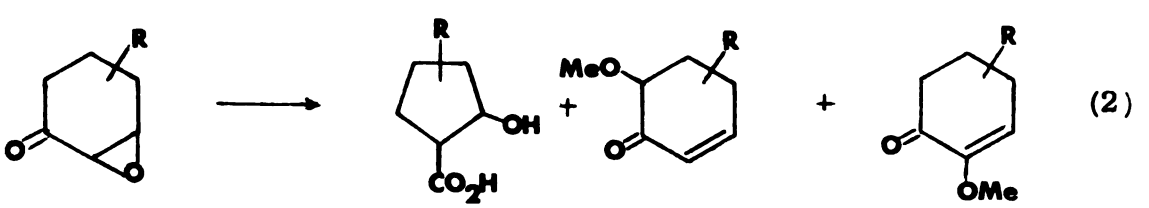
Robert W. Mouk

The reactions of α,β-epoxy ketones with nucleophilic bases may follow two courses: 1) nucleophilic substitution at the α-carbon followed by loss of water to yield an α-alkoxy enone (eq. 1), or 2) formation of a Favorskii



(1)

intermediate such as cyclopropanone or zwitterion which may then lead to ring contraction or attack on solvent (eq. 2).

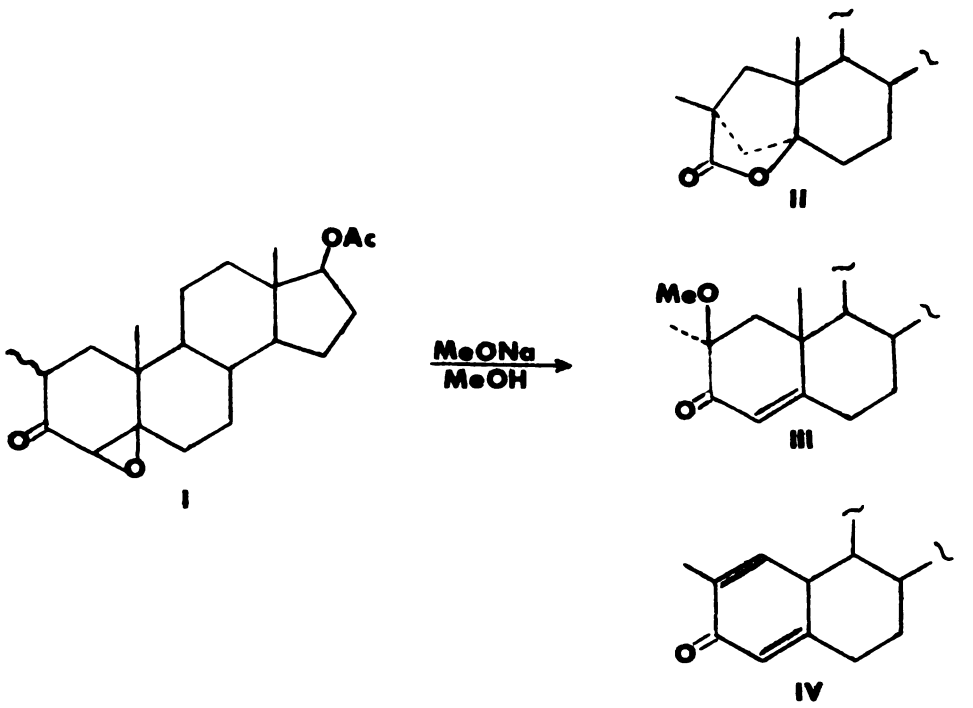


(2)

Robert W. Mouk

Studies of terpenoid epoxy ketones suggest that an α'-alkyl group facilitates ring contraction; in this investigation the steroid system was employed to minimize the conformational flexibility of the monocyclic system.

It was found that 2-methyl-4β,5β-epoxy testosterone acetate (I) is converted in 23.3% yield to the ring contracted lactone II, the α,β-unsaturated methoxy ketone III (33%) and the cross conjugated dienone IV (30%) (eq. 3)



(3)

While III is analogous to products isolated in other studies of the Favorskii rearrangement, compounds similar to IV have not been reported previously. Mechanisms involving a zwitterion intermediate are proposed to account for III and IV.

THE FAVORSKII RING CONTRACTION OF STEROIDAL EPOXY KETONES

By

Robert Watts Mouk

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To Mary Lou

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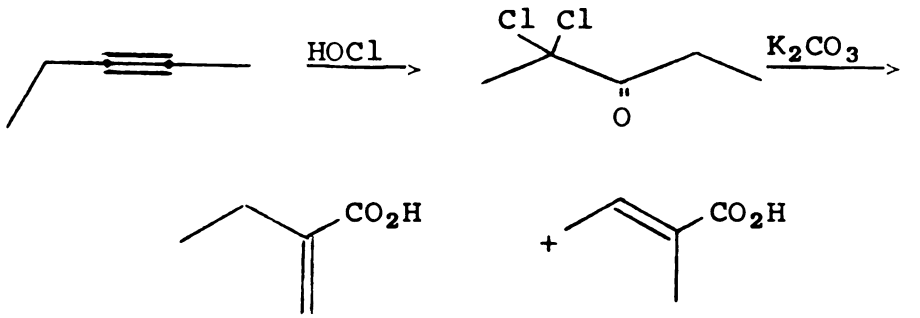
INTRODUCTION

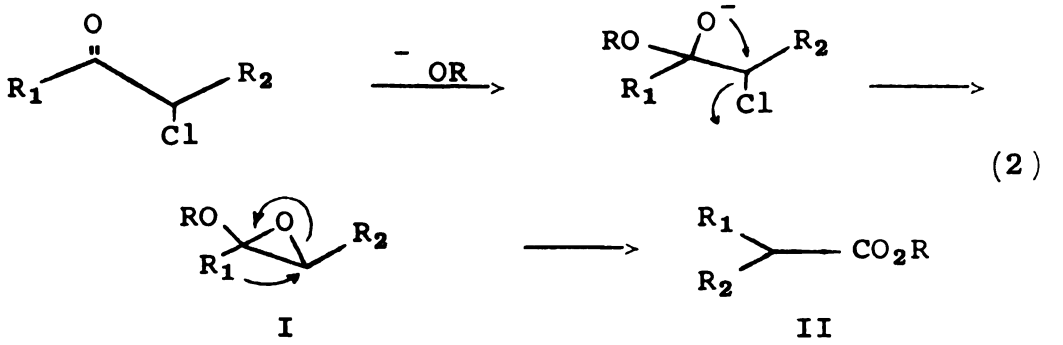
In 1894, while studying the acid catalyzed hydrolysis of acetylenes, Favorskii discovered a rearrangement of α-halo ketones[1] (shown in equation 1). In the intervening



(1)

75 years this rearrangement has been the subject of continued interest regarding its scope, mechanism and stereochemistry, and is now known as the Favorskii rearrangement. This continued interest testifies to the usefulness of the reaction as a route to contracted rings and highly substituted acids and esters.

Favorskii proposed a mechanism[2] involving formation of an epoxy ether (I) which subsequently rearranges to the ester (II).

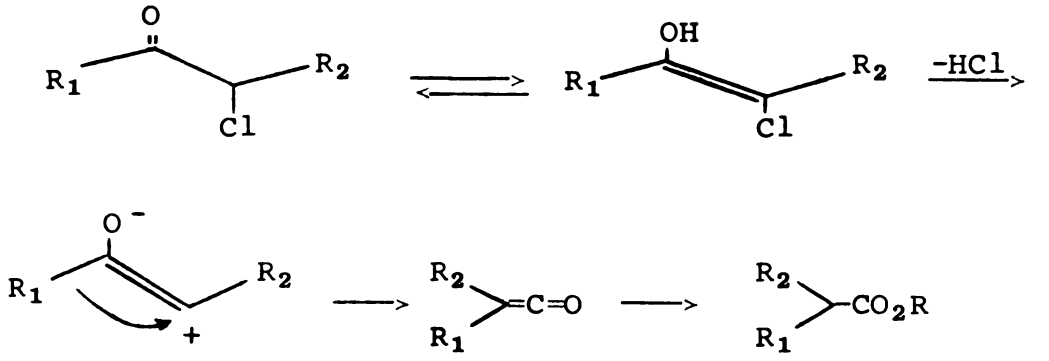


(2)

I II

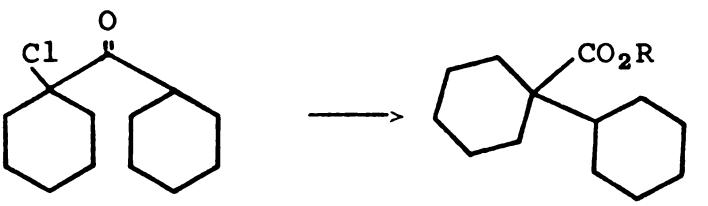
Although epoxy ethers have been isolated from reactions of α-halo ketones under Favorskii conditions, they do not generally rearrange to esters. Thus the epoxy ether is eliminated as an intermediate in this reaction.

A second mechanism (equation 3) postulated that a ketene was formed as a precursor to the ester[3]. However,



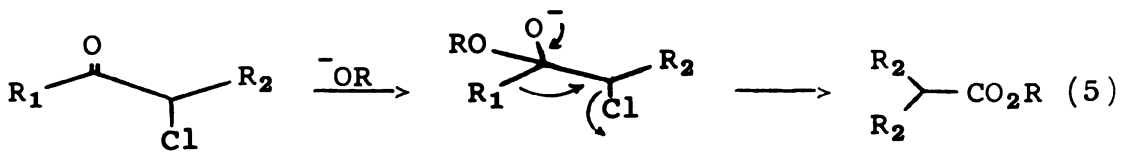
(3)

since α-halo ketones incapable of forming ketenes can undergo the Favorskii rearrangement (equation 4) this mechanism has only a limited scope.



(4)

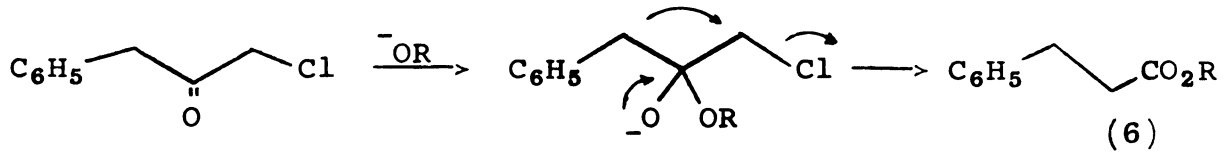
A third mechanism, one which has received considerable attention, is related to the benzilic acid rearrangement[4] and is shown in equation 5. This semibenzilic mechanism is



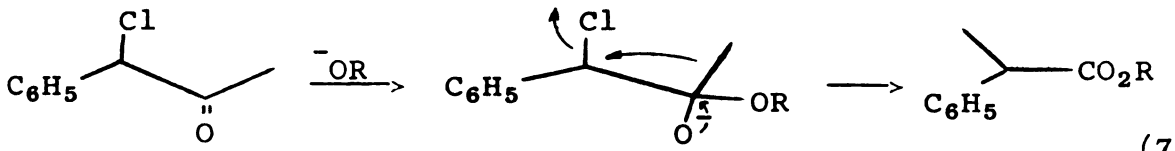
(5)

believed to operate in some cases of the Favorskii rearrangement; however, it was shown not to be generally

applicable by a study of two isomeric α-halo ketones III and V.[5] The semibenzilic mechanism demands that the α'-carbon atom* migrate; hence III and V should lead to the isomeric esters IV and VI respectively. Experimentally, both III and V yield IV, demonstrating that at some time during this reaction both halo ketones generate a common intermediate.



III IV (6)



V VI (7)

McPhee and Klingsberg suggested[5] the following mechanism (equation 8) to explain the single product; however, the necessity of placing a positive charge adjacent to a carbonyl group and the lack of any significant role for the base in their mechanism must count as serious drawbacks to to this rationalization.

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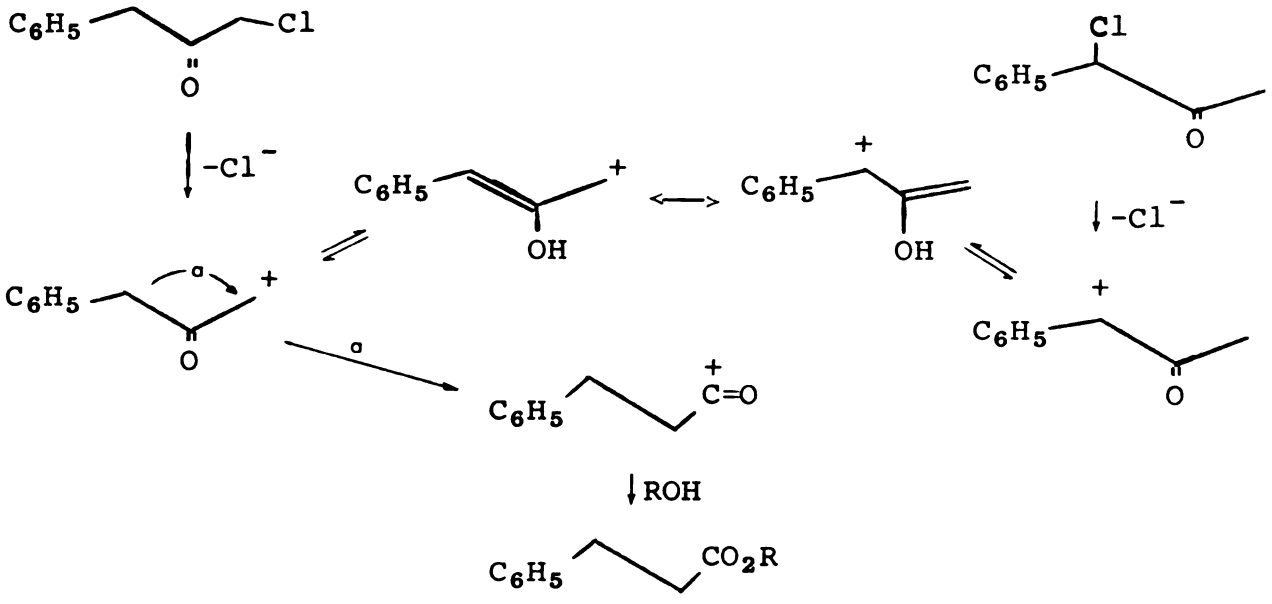
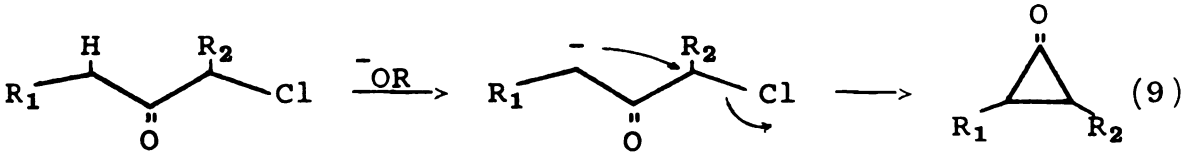
*It will be understood that the carbon atom bearing the leaving group is designated α, the other as α'.



IV

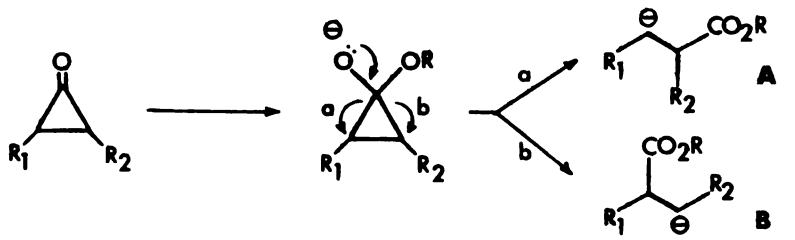
Equation 8

Cyclopropanone intermediates have also been proposed in the Favorskii rearrangement.[6,7] In this case the base acts by abstracting an acidic α'-proton followed by ejection of a chloride ion to give a cyclopropanone (equation 9). The



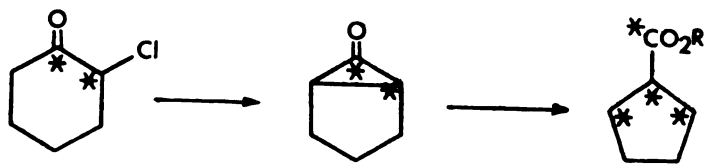
(9)

cyclopropanone is then opened by the attack of base on the carbonyl carbon atom. The relative stabilities of 10(A) and 10(B) would account for the product ratio if we assume that the more stable anion is more rapidly formed. Support for this mechanism was provided by the classic work of R. B. Loftfield[7], which showed that the Favorskii rearrangement of



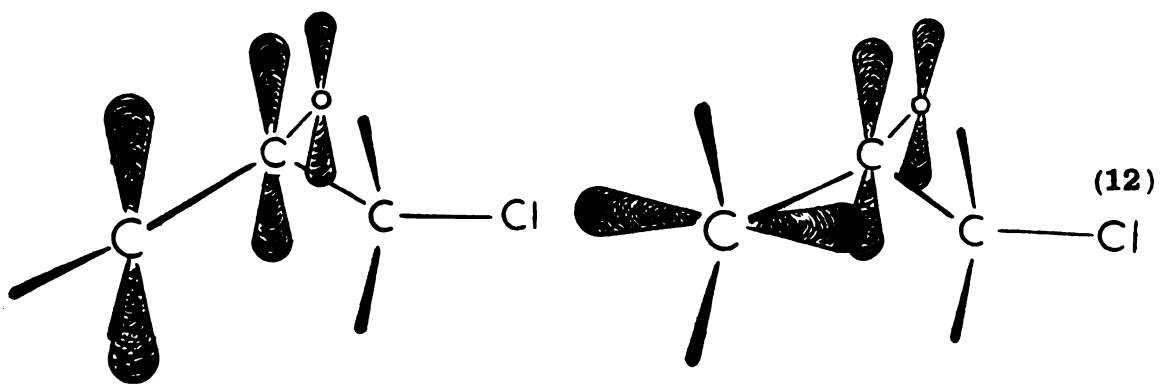
(10)

isotopically labelled 2-chlorocyclohexanone proceeded through a symmetrical intermediate (i.e., a cyclopropanone).



(11)

An objection to this mechanism was raised, however, when Anson and Newkirk[8] pointed out that the π-system of the enolate anion has an unfavorable geometry towards nucleophilic displacement of the chlorine atom on the α-carbon atom.

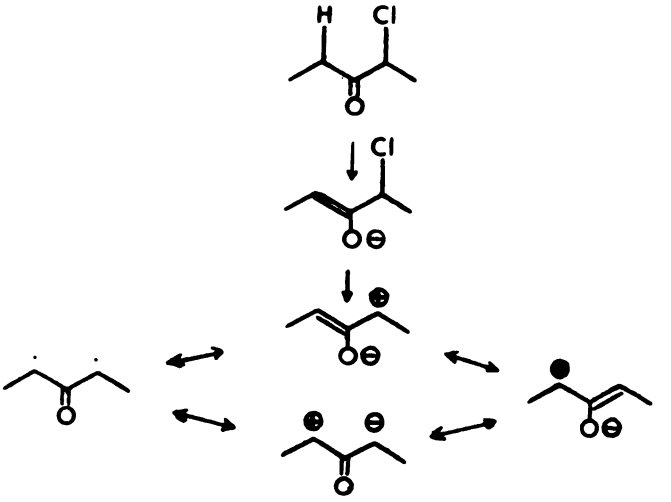


(12)

Enolate anion

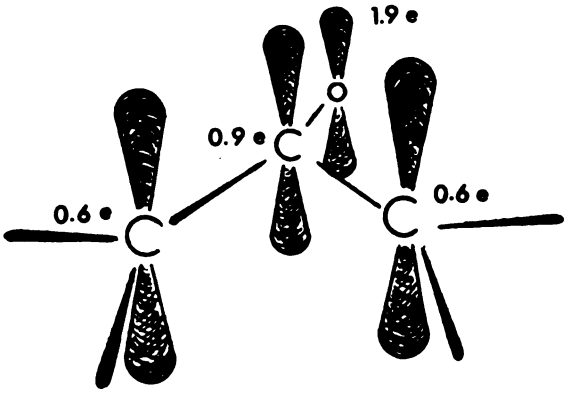
Orientation for nucleophilic displacement of chlorine

To overcome the objection to a direct S_N2 displacement, Anson and Newkirk proposed that a chloride ion is eliminated from the enolate anion system to give a zwitterion or di-radical.



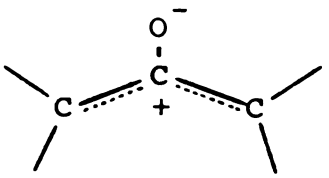
(13)

Burr and Dewar[9] have calculated that the zwitterion would be about 14 Kcal/mole more stable than the enolate anion and arrived at the following electron densities at each of the atoms.



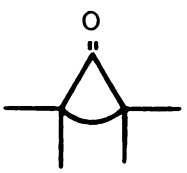
(14)

This would suggest that the best representation of the zwitterion would be:



(15)

The diradical form may also be written as a π-bond between the two α-carbon atoms (equation **16**); this π-bond,

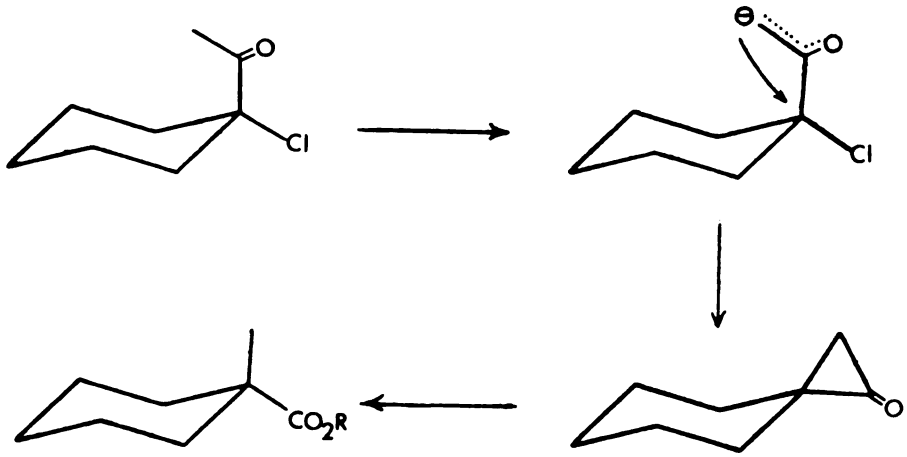


(16)

upon rotation and rehybridization, could form the σ-bond of a true cyclopropanone. Loftfield assumed[7] that the dipolar and diradical forms were merely "resonance forms contributing to the stability of the cyclopropanone intermediate", but since different molecular orbitals and atomic orientations are involved the open and closed forms must be different species.

One might anticipate that these two mechanisms could be distinguished by the stereospecificity of the Favorskii rearrangement; but it now seems unlikely that a single general mechanism will explain all examples of these rearrangements.

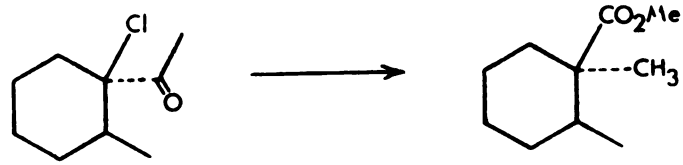
If the enolate anion displaces the chloride ion <u>via</u> S_N2 transition state there should be an inversion of configuration about the α-carbon atom, <u>e.g.</u>



(17)

In diastereomeric examples reported by Stork and Borrowitz[10] the reaction does, in fact, proceed with inversion (equations 18 and 19).

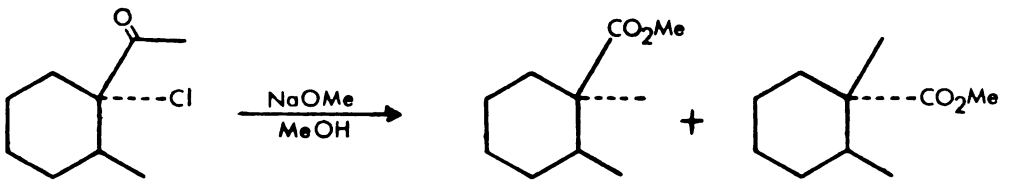
(18)



(19)

These results indicate that the cyclopropanone intermediate is being formed by direct displacement of the chlorine atom with inversion of configuration about the α'-carbon atom--the results predicted by the Loftfield mechanism. If, however, a polar solvent (i.e. methanol) is substituted for

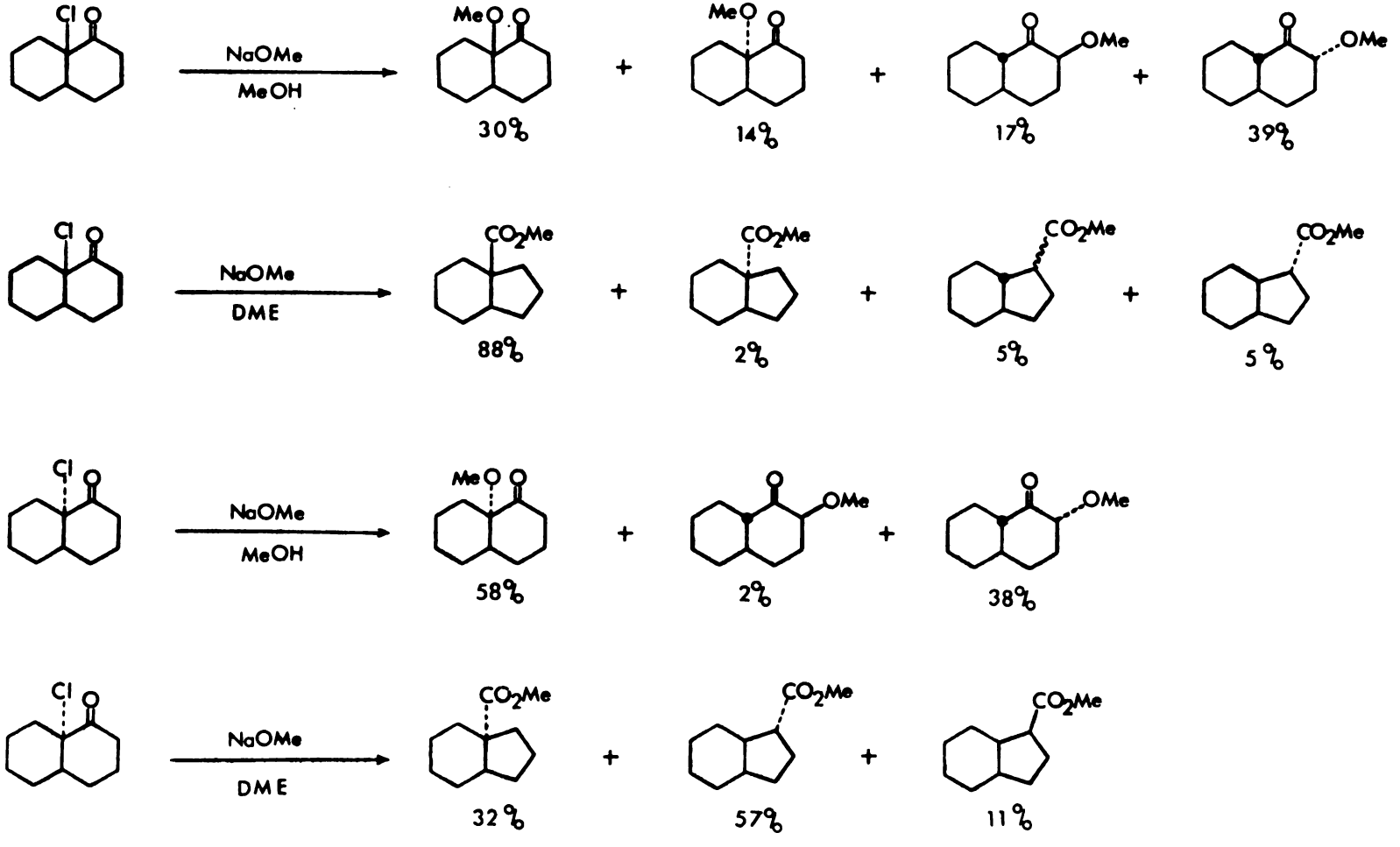
the non-polar medium used in the previous studies the reaction takes a different course.[11]



(20)

In the polar solvent the cyclopropanone apparently forms from the dipolar ion and the reaction is not stereospecific. The dipolar ion may also be attacked by base or solvent to yield an α-methoxy ketone.[12,13]

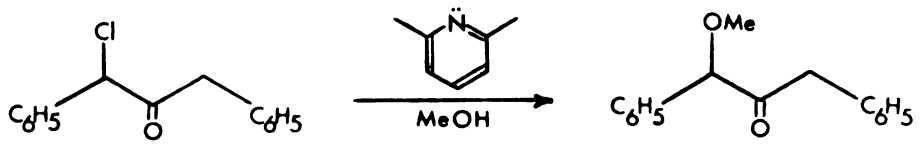
In general one finds that the Favorskii rearrangement in non-polar solvents gives stereospecific formation of esters, whereas in polar media it leads to non-stereospecific ester formation and increased α-alkoxy ketone formation. The work of House and Frank, shown in Table 1, clearly shows the effect of the solvent on the Favorskii rearrangement. In the polar solvent, methanol, the products consisted only of the various α-methoxy ketones, and no evidence of a Favorskii rearrangement could be found. However, in the non-polar solvent, dimethoxyethane (DME), the products resulted from a predominantly stereospecific Favorskii rearrangement. It is interesting to note that in the last reaction shown in Table 1 the cyclopropanone is opened to yield a tertiary rather than secondary carbanion in the majority (68%) of the products.



Solvent effects in the Favorskii rearrangement

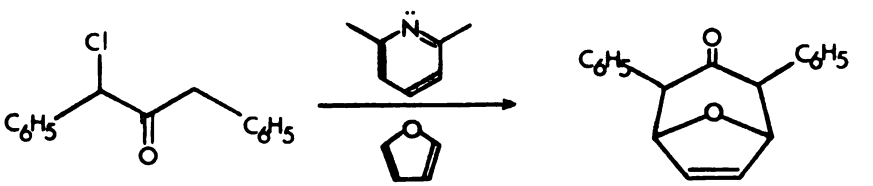
Table 1

Besides the results discussed in the preceeding paragraphs, other products tending to support one of the alternate mechanisms of cyclopropanone formation are sometimes isolated from Favorskii rearrangements. A. W. Fort[14] has shown that 1-chloro-1,3-diphenylpropanone reacts under mild conditions to yield 1-methoxy-1,3-diphenylpropanone (eq. 21).



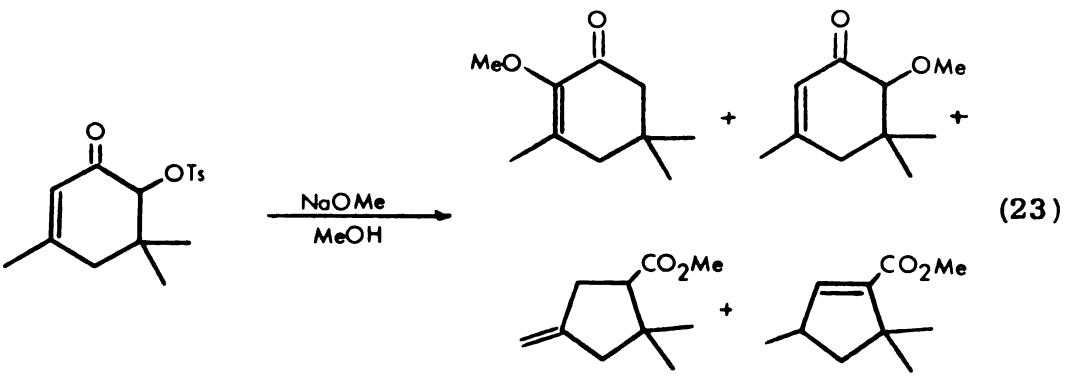
(21)

A zwitterionic intermediate was proposed, and the possibility of nucleophilic displacement of the benzylic halide by methanol or methoxide ion was ruled out by the unreactive nature of α-chloro-α-phenyl acetophenone under the same conditions. Further evidence for the zwitterionic intermediate was found[15] in the formation of a bicyclic adduct with furan under similar reaction conditions.



(22)

Fort also studied the reaction of 6-tosyloxyisophorone[16] with sodium methoxide and obtained products which indicated the intermediacy of a delocalized species:



(23)

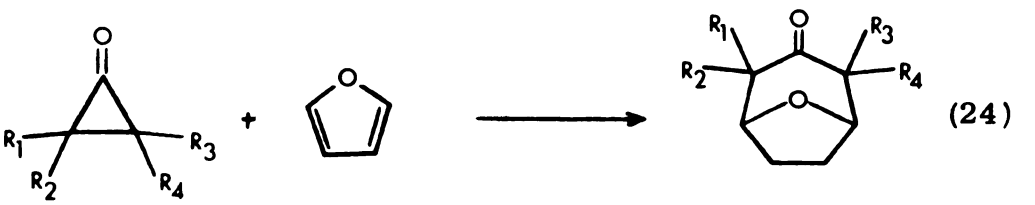
Further implications of this research will be discussed in greater detail in a later section of the introduction.

The classical test for the intermediacy of a compound in a reaction mechanism is to treat that compound under identical conditions to see whether or not it yields the expected products. Such a test of Favorskii intermediates had to wait until 1965 when Turro and Hammond succeeded in synthesizing the first cyclopropanones--tetramethylcyclopropanone and 2,2-dimethylcyclopropanone.[17,18]

Spectral data, including microwave spectroscopy, indicated that these cyclopropanones were true closed ring ketones. This being the case, it was expected that they would be very reactive molecules due to their strained ring and activated carbonyl group.

The substituted cyclopropanones studied to date can react in both the cyclic and open chain forms. For example, in equation 24, cyclopropanones react with furan to give

bicyclic adducts identical to those obtained by Fort.[17,18] Cyclopropanones also react with methanol to give hemiketals



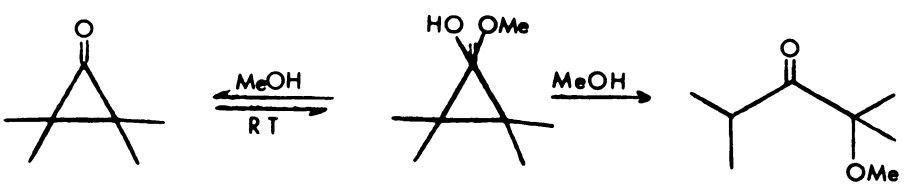
(24)

a) R_1, R_2, R_3, R_4 = CH_3

b) R_1, R_2 = CH_3 R_3, R_4 = H

c) R_1 = CH_3 R_2, R_3, R_4 = H

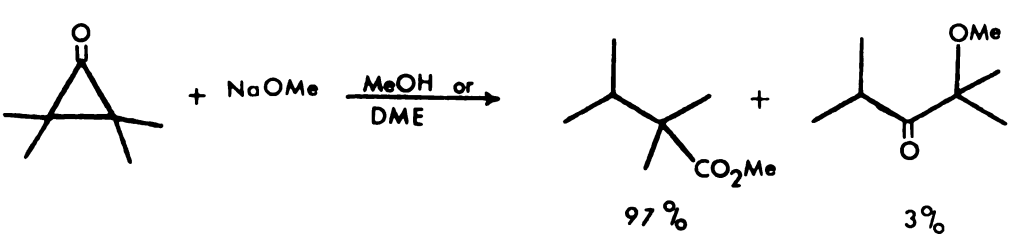
which, upon heating, are transformed into α-methoxy ketones. These reactions are consistent with the expected behavior of



(25)

the zwitterion previously postulated as an intermediate in the Favorskii rearrangement.

Reaction of cyclopropanones with alkoxide bases give esters, thus providing the first direct evidence that the Favorskii rearrangement can proceed <u>via</u> a cyclopropanone.



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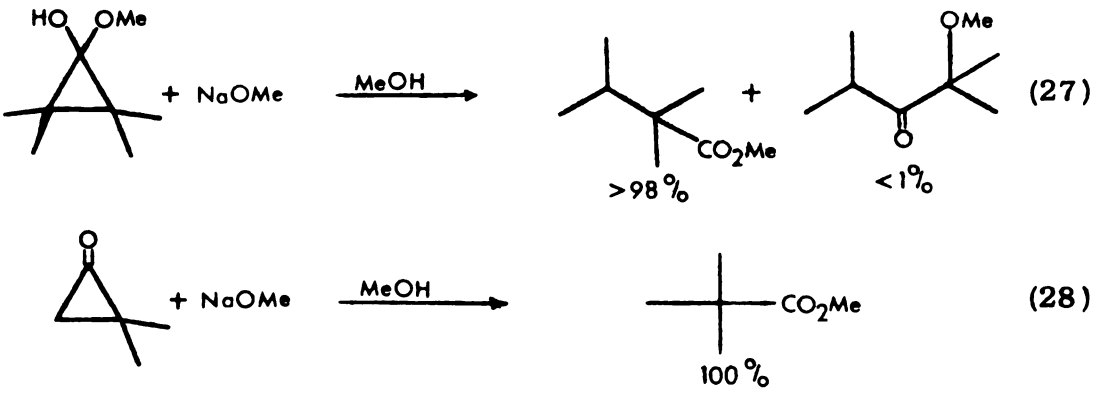
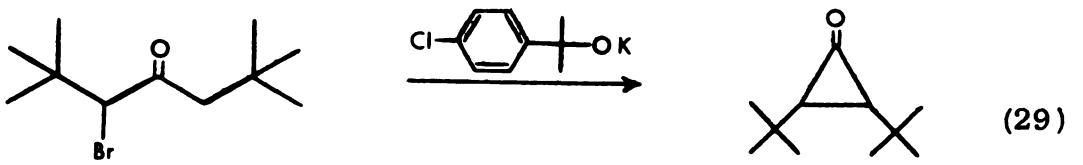
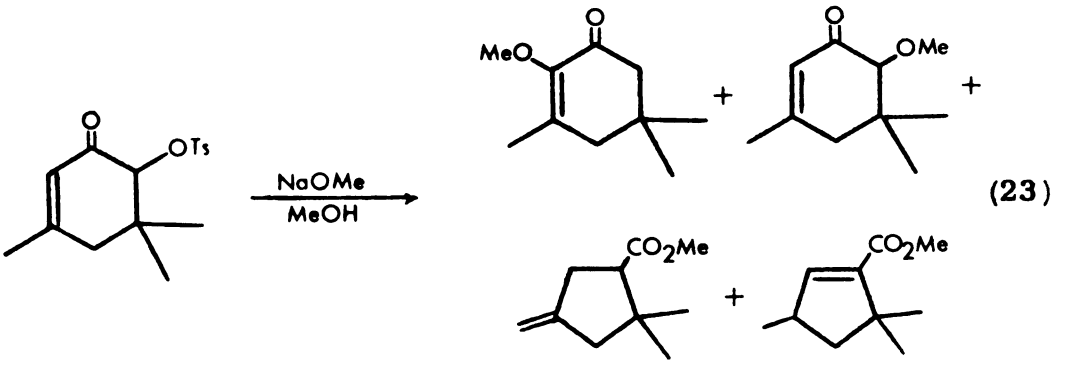


Finally, 2,3-di-t-butylcyclopropanone has been obtained from the reaction of α-bromodineopentyl ketone with a tertiary alkoxide base.[19]



The experimental evidence furnished by the reactions of cyclopropanones with alcohols and their corresponding conjugate bases suggest the following explanation of the course taken by the Favorskii rearrangement under various reaction conditions. In a polar solvent the cyclopropanone exists in equilibrium with its open form. Alkoxide ion reacts preferentially with the cyclic form to give esters, while the alcohol reacts with the open chain isomer to give α-alkoxy ketones and with the cyclic form to generate a ketone—ketal equilibrium. In non-polar solvents the ionic species is either absent or is formed slowly and in low concentrations. The only nucleophile present, alkoxide anion,

thus reacts solely with the cyclopropanone to give the corresponding ester. The stereospecificity of the Favorskii rearrangement in a non-polar medium may be the result of two factors: (a) the zwitterion does not exist in such a solvent or (b) the unsolvated alkoxide anion attacks the cyclopropanone too rapidly to permit it to equilibrate with its open form. The competition between the reactions of cyclopropanone with alkoxide and zwitterion with alcohol can be seen in the experimental data obtained by Fort for the reaction of 6-tosyloxyisophorone with sodium methoxide in methanol.[16]



(23)

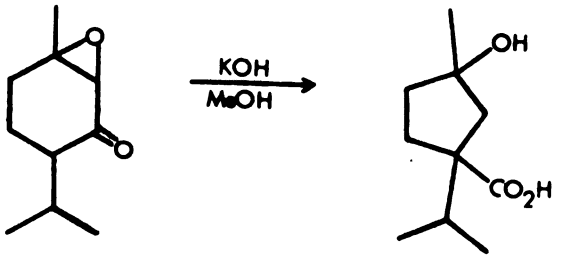
As shown in the following table, the ratio of esters to α-methoxy ketone is highly dependent upon alkoxide ion concentration. When the reaction was run with a relatively high methoxide ion concentration, roughly equal amounts of both types of products were formed. When the concentration of methoxide was lowered, the ratio of α-methoxy ketones to

esters rose to 2:1. If the solution of sodium methoxide was added to a solution of the tosylate to keep the concentration of the former very low, the esters comprised only about 2% of the product mixture.

Table 2. Reaction of 6-tosyloxyisophorone with sodium methoxide.

[NaOMe] (M)	α-Methoxy Ketone (%)	Esters (%)
0.5	50	50
0.11	67	33
very low (inverse addition)	98	2

In the previous examples of the Favorskii rearrangement both halide and tosylate ions have served as the leaving group, and the oxygen of an epoxide may play a similar role. Treibs discovered these reactions while studying the base catalyzed oxidation of α,β-unsaturated ketones,[20,21] which he explained as the formation of an α,β-epoxy ketone followed by a Favorskii rearrangement.[22] In a separate study of several terpenoid epoxy ketones Treibs obtained the following results.[23]



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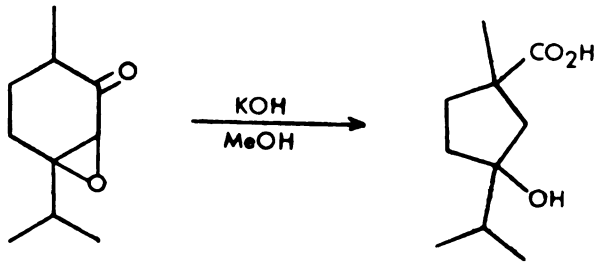

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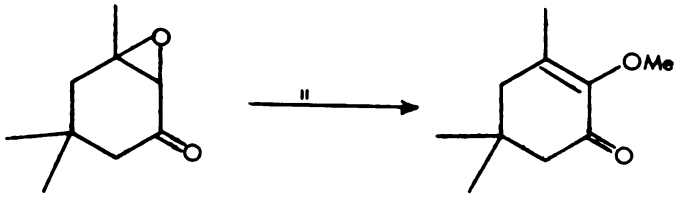
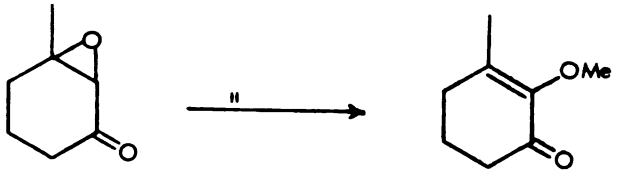


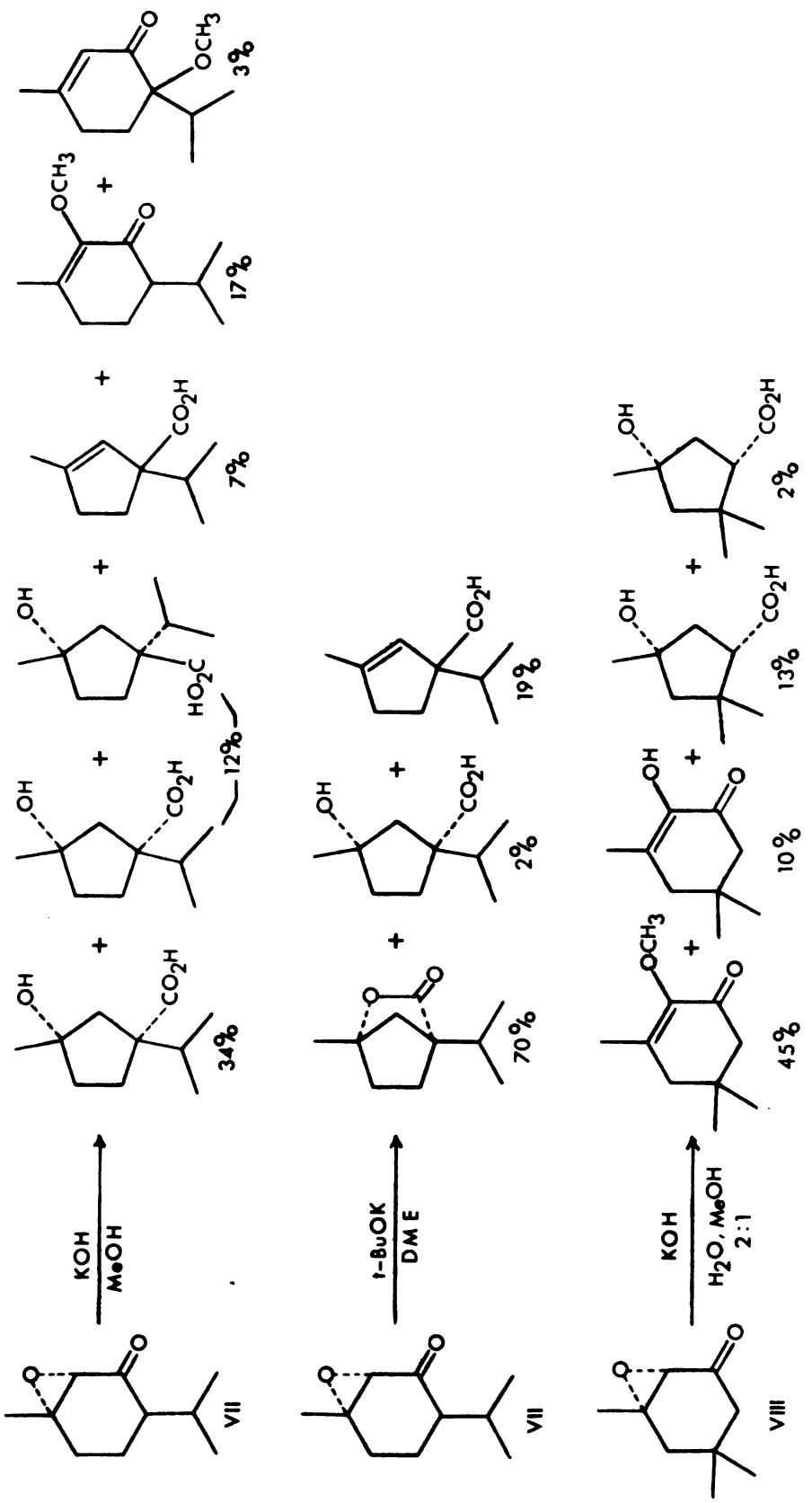
(32)



(33)

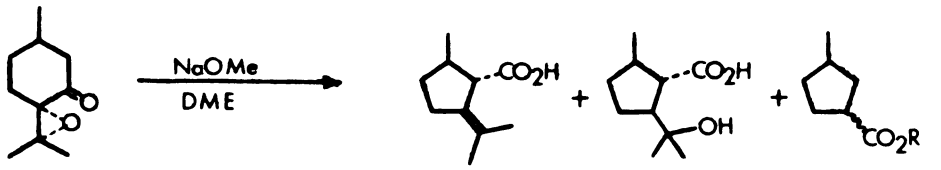
The Favorskii rearrangement of epoxy ketones is of synthetic interest because the products are difunctional in contrast to the α-halo ketone rearrangements. House and Gilmore[24] have studied the reactions of α,β-epoxy ketones with base and their findings, using piperitone oxide (VII) and isophorone oxide (VIII), support the work of Treibs (see Table 3).

Reusch and Mattison have studied the Favorskii rearrangement of the isomeric pulegone oxides.[25] In dimethoxyethane the reaction (equations 34 and 35) is stereospecific at the α carbon and has two striking aspects: the large amount of abnormal cyclopropanone ring opening (giving a tertiary carbanion) and the stereospecific protonation of this carbanion.

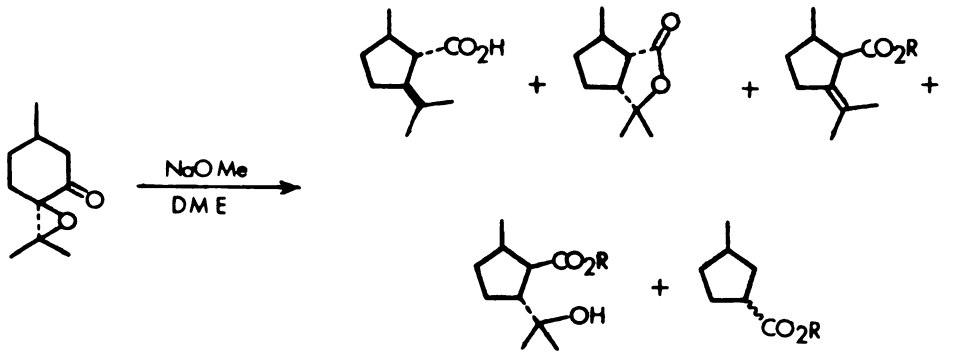


Base catalysed reactions of piperitone oxide (VII) and isophorone oxide (VIII)

Table 3

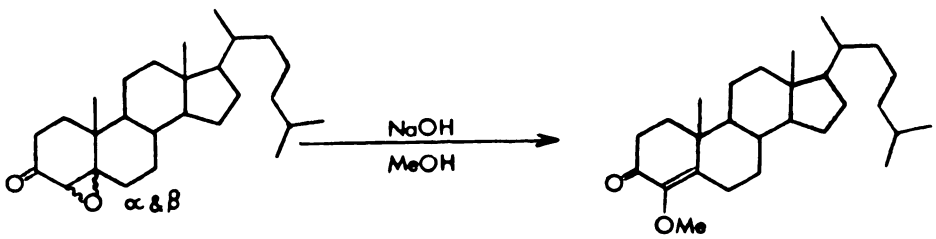


(34)

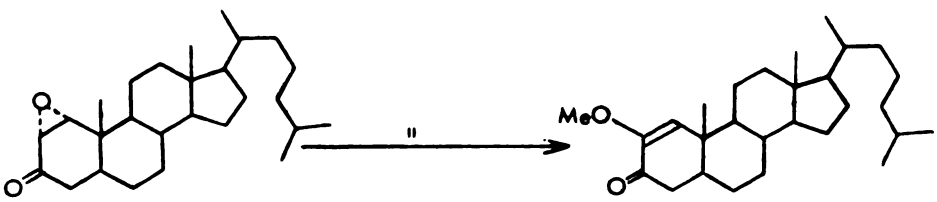


(35)

The Favorskii reaction of epoxy ketones would be of advantage in the synthesis of nor-steroids because of the availability of 4,5-epoxy-3-ketones and the previously mentioned difunctionality of the products. Reusch and LeMahieu[26] examined the reaction of epoxy cholestanones with base but obtained only the corresponding diosphenol ethers.



(36)

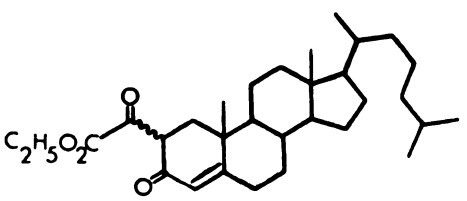


(37)

The previously described reactions of terpenoid epoxy ketones (equations 30-33) suggest that the presence of an alkyl group at the α'-position gives a marked increase of Favorskii products over nucleophilic attack. It would therefore be advantageous to study this hypothesis in a system, such as the steroids, whose rigidity will assure that any change in the reaction course upon α'-alkylation is not merely due to conformational changes in the substrate. The purpose of this research was to synthesize and study the reactions of steroidal epoxy ketones possessing such a substituent.

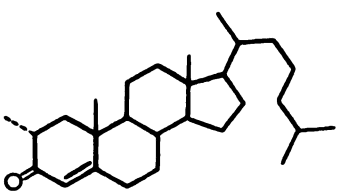
RESULTS AND DISCUSSION

The epoxidation of 2-alkyl-4-cholesten-3-ones would produce suitable epoxy ketones for this study. Since the direct alkylation of 4-cholesten-3-one results in substitution at C_4, activation of C_2 is necessary. The 2-ethoxalyl derivative of 4-cholesten-3-one (IX) was easily prepared by



IX

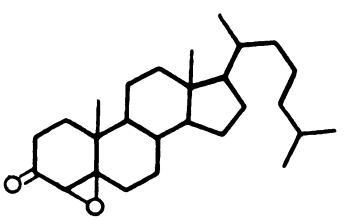
reaction with diethyloxalate, and could be alkylated by treatment with methyl iodide and potassium carbonate in acetone. The activating ethoxyoxalyl group was removed by base cleavage yielding, after chromatography and recrystallization, 2α-methyl-4-cholesten-3-one (X).



X

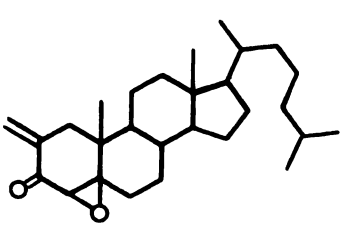
All attempts to epoxidize X with alkaline hydrogen peroxide have failed. Since the starting material is not recovered it is presumed that the epoxide is not stable in the alkaline medium. Monoperphthalic acid and m-chloroperbenzoic acid were also unsuccessful; in these cases the starting material was returned unchanged.

Since epoxidation of X did not give the desired product, an attempt to alkylate 4β,5β-epoxy cholesten-3-one (XI) which is easily prepared by the reaction of 4-cholesten-3-one with alkaline hydrogen peroxide was made.



XI

The aldol condensation of XI with formaldehyde using potassium acetate as the base gave 2-methylene-4β,5β-epoxy cholesten-3-one (XII) in 75% yield.



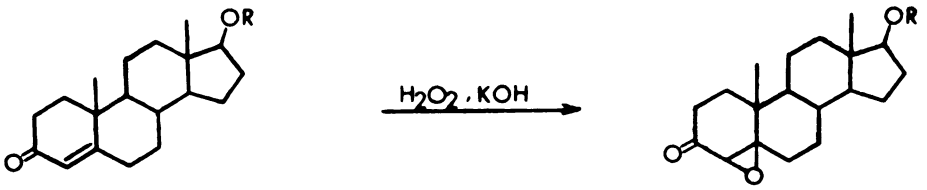
XII

Hydrogenation of XII over 10% palladium on carbon at a pressure of one atmosphere gave a glassy product. All attempts to crystallize this material proved unsuccessful.

Because of the difficulties in crystallizing the derivatives of cholestenone, another steroid system was considered. Since derivatives of testosterone tend to be higher melting and more readily crystallized than those of cholestenone and are also of potential biological interest, this seemed to be an ideal substrate. Indeed, the preparation of 4β,5β-epoxy-2ζ-methyl testosterone acetate was recently reported by I. Laos[28], and satisfied all the requirements of this project.

Testosterone acetate (XIII) was epoxidized in 2:1 methanol-methylene chloride solution as described by H. Verli et al.[29]. After acetylation with acetic anhydride in pyridine the melting point agreed well with the literature value for 4β,5β-epoxy testosterone acetate (XIV) (lit. 155-157°, obs. 156-157.5°); the infrared and nuclear magnetic resonance (nmr) spectra were also consistent with the expected compound. The material not isolated as the epoxy ketone was found to be base soluble and was not investigated further. It is presumed to be related to the dicarboxylic acid derived from 4-cholesten-3-one under these conditions.[26] No evidence for the α-epoxide was found.

Treatment of 4β,5β-epoxy testosterone acetate (XIV) for three hours in methanolic potassium hydroxide resulted only in saponification of the ester. When the crude product



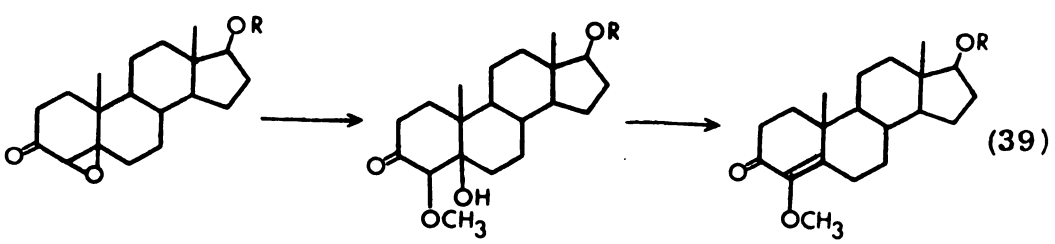
(38)

XIII XIV

was treated with acetic anhydride in pyridine and analyzed by thin layer chromatography (tlc) a single spot, identical in Rf to the starting material was observed.

More vigorous treatment of **XIV** with methanolic potassium hydroxide (24 hours under reflux) gave a reaction equivalent to that of 4β,5β-epoxy cholesten-3-one.[26] The only product which could be isolated was the corresponding enol ether **XV**; the melting point and ultraviolet spectrum agreed with the values reported for this compound by Camerino et al.[30] and the nmr spectrum (τ 6.41-S, 3H—OCH_3) and the infrared spectrum (3600 cm^{-1} — OH and 1670, 1600 cm^{-1} — α,β-unsaturated ketone) are also consistent with this structure.

The formation of **XV** probably arises from nucleophilic attack of methoxide ion on the epoxide ring as shown in the following equation. This reconfirms the failure of the

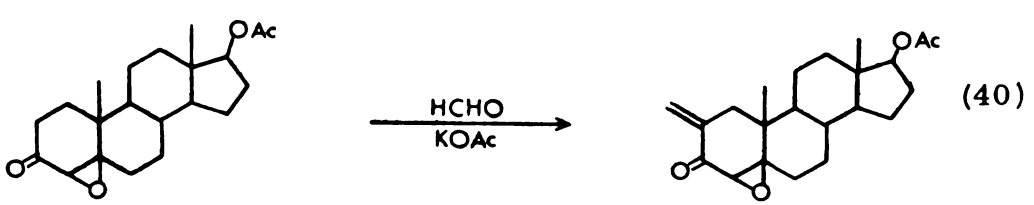


(39)

XIV XV

Favorskii rearrangement when the α'-position is unsubstituted.

The aldol condensation of either 4β,5β-epoxy testosterone or 4β,5β-epoxy testosterone acetate with formaldehyde was accomplished using the weakly basic and poorly nucleophilic acetate anion. Treatment of XIV with an ethanolic solution of formaldehyde and potassium acetate gave a mixture of two compounds, one retaining the C_{17} acetoxy group and the other having a hydroxy group at this position. Treatment with acetic anhydride in pyridine resulted in a single compound--2-methylene-4β,5β-epoxy testosterone acetate (XVI). This compound was identified by comparing its physical constants to those described in the literature: mp 227-229° (lit. 225-227°); nmr, τ 3.87 (m,1), 4.77 (m,1), 690 (s,1), 7.98



(40)

XIV XVI

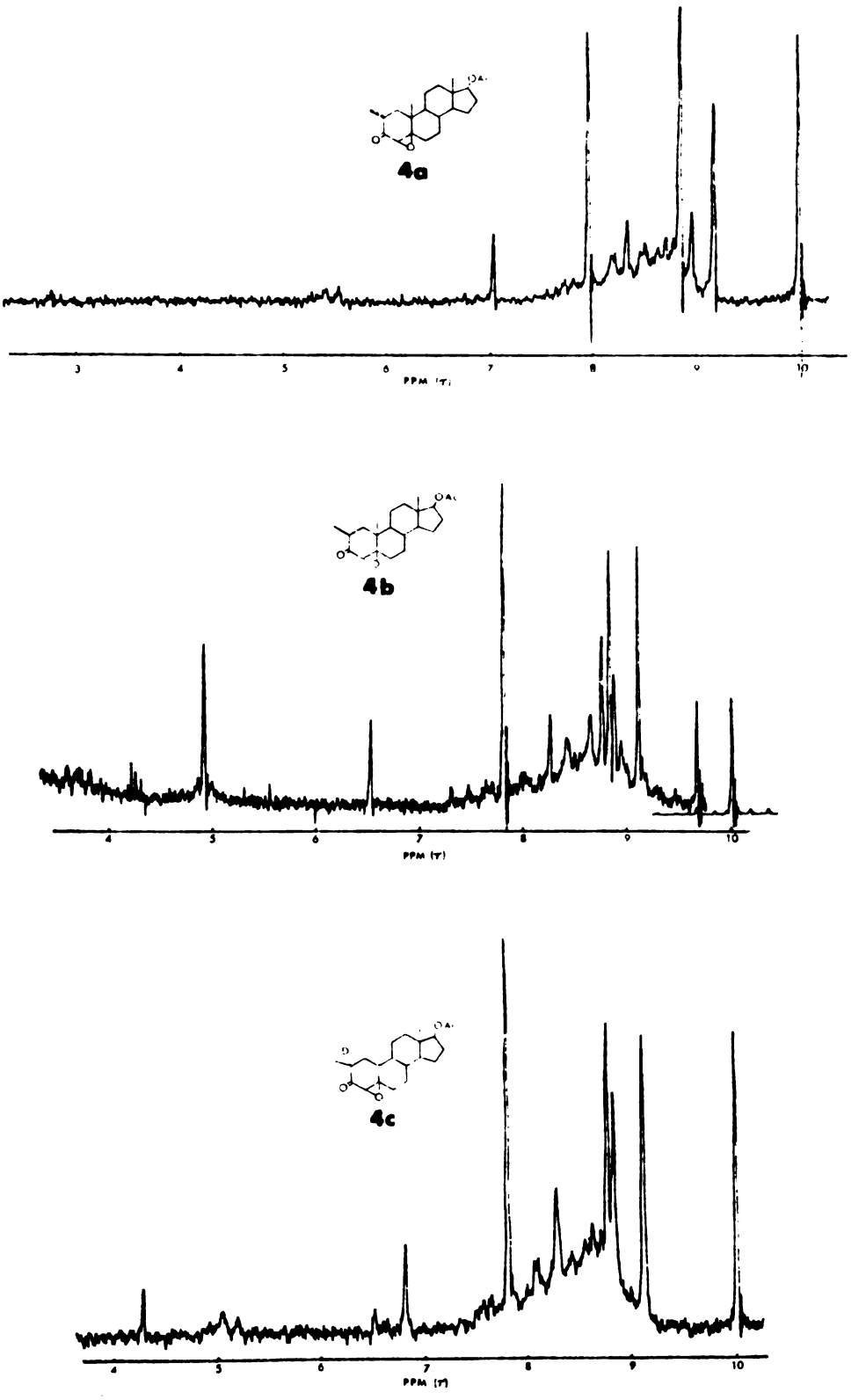
(s,3), 8.83 (s,3) and 9.20 (s,3) lit τ 3.83 (m,1), 4.77 (m,1), 6.88 (s,1), 7.97 (s,3), 8.8 (s,3) and 9.2 (s,3). The infrared spectrum contained absorption peaks due to the ester (1723 cm^{-1}) and the α,β-unsaturated ketone (1690, 1610 cm^{-1}) moieties. The band at 1610 cm^{-1} had a larger absorption than found for other unsaturated ketones in this study,

indicative of the cisoid configuration of the conjugated system.

Hydrogenation of XVI over 10% palladium on carbon proceeded rapidly to give XVII, the product previously described[28] as 4β,5β-epoxy-2ζ-methyltestosterone acetate. The melting point and nmr spectrum agreed well with the literature values: mp 208-211°, lit 211-213.5°; nmr ($CDCl_3$) τ 6.89 (s,1), 7.96 (s,3), 8.89 (s,3), 9.05 (d, 3, J = 7 Hz) and 9.19 (s,1), lit τ 6.89 (s,1), 7.96 (s,3), 8.89 (s,3), 9.05 (d,3, J = 8 Hz) and 9.19 (s,1).

Although the configuration of the C_2 methyl group was not discussed by Laos, a probably assignement can now be made based on the following observation. If XVII is dissolved in dilute methanolic potassium hydroxide at room temperature for three hours it is converted to a new compound, XVIII, which is considered to be the C_2 epimer of XVII. The infrared spectrum is basically the same as that of the precursor; however, the nmr spectrum in $CDCl_3$ (peaks at τ 7.05, 7.97, 8.88, 8.98 and 9.18) does not show a clear doublet for the C_2 methyl group (Figure 4a, next page). Integration of this spectrum indicates the relative areas under these peaks to be 1:3:4.4:1.2:3, suggesting that one of the doublet peaks due to the methyl group on C_2 has overlapped with the signal of another methyl group (C_{18}). Two tests were employed to show that this is indeed the case.

First, the spectrum of XVIII was taken in pyridine solution (Figure 4b). Aromatic solvents (most often benzene)

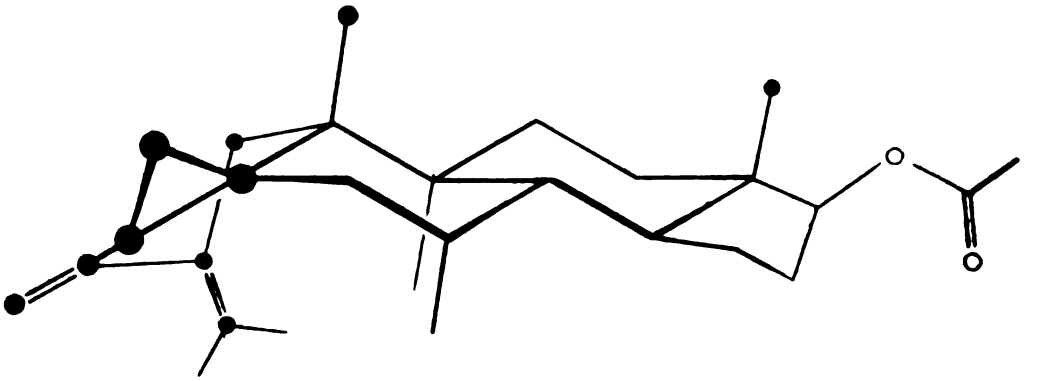


Nmr spectra of the epimeric 2-methyl-4β,5β-epoxy testosterones.

are known to shift the signals of protons near carbonyl groups due to solvation complexes between the carbonyl group and aromatic ring. The ring current of the aromatic compound produces another magnetic field in this area thereby causing changes in the chemical shifts of nearby protons. In pyridine solution the nmr spectrum of XVIII shows signals at τ 6.78 (s,1), 7.97 (s,3), 8.90 (d,3, J = 6 Hz) and 9.17 (s,3).

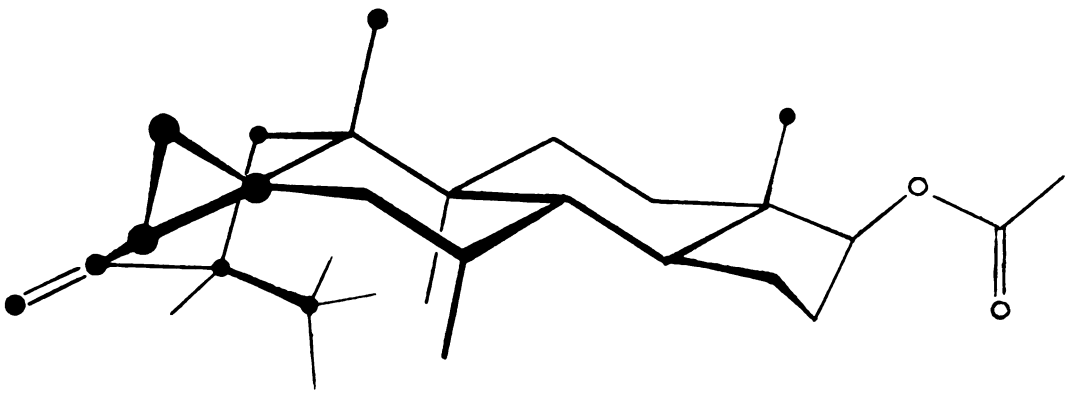
In a second test the epimerization of XVII to XVIII was carried out in a dioxane-D_2O solution with Na_2O added to provide NaOD as the base. The nmr spectrum of the deuterated XVIII in $CDCl_3$ solution (Figure 4c) shows singlet peaks at τ 7.05, 7.97, 8.88, 8.91 and 9.18 (relative areas 1:3:3:3:3). This corresponds well with the calculated position of the doublet (τ 8.92) in the nmr spectrum of XVIII in $CDCl_3$. Since the doublet assigned to the methyl group on C_2 in XVII is changed to a singlet at a different τ value upon treatment with D_2O and base and since XVII and XVII gave the same products in the Favorskii rearrangement, it appears safe to conclude that they are indeed epimers. The product (XVII) obtained from catalytic hydrogenation of XVI is assigned the 2α-methyl configuration and XVIII, the product resulting from treatment of XVII with base, is assigned the 2β-methyl configuration for the following reasons.

As shown below, the 2-methylene group in XVI is severely hindered towards reduction from the bottom of the molecule, thus XVII, the reduction product of XVI, is assigned the



XVI

2α-methyl configuration which results from hydrogenation from the top of the molecule. However, in the 5β-series

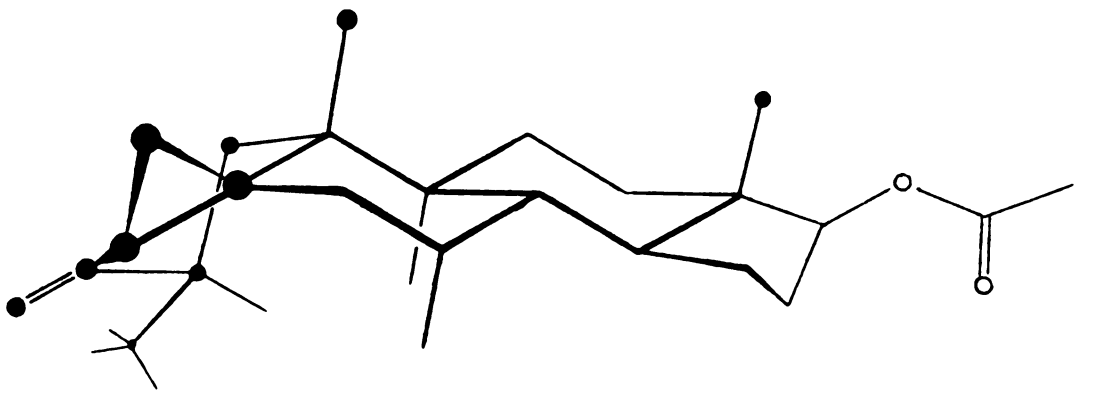


XVII

this causes the 2α-methyl group to be tucked under ring B and suffer severe interactions with the hydrogen atoms on carbons 7 and 9.

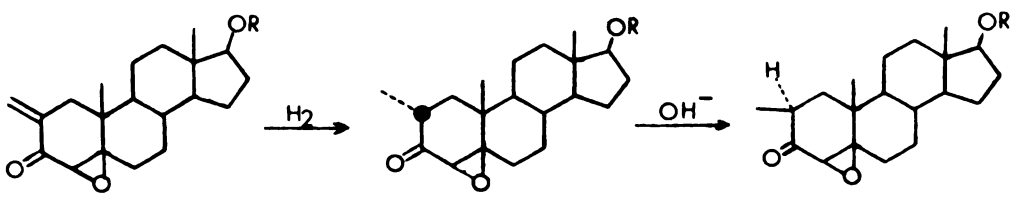
Epimerization allows the methyl group to attain the

equatorially oriented β-position. As shown in the next drawing, this relieves the steric crowding found in the previous compound.



XVIII

The overall reactions, XVI —> XVII —> XVIII, and assignments of configuration are shown in equation 41.

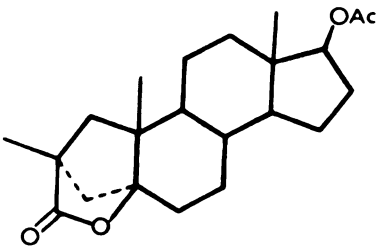


(41)

An attempt to prepare 2-ethyl-4β,5β-epoxy testosterone acetate by reaction XVII with dimethyl copper lithium was unsuccessful. House, et al. have reported excellent yields (99%) for conjugate addition to α,β-unsaturated ketones using the reagent. Reaction of $(CH_3)_2CuLi$ with XVI gave complex mistures of products, all in low yields. Presumably the epoxy ring is opened during the reaction permitting extensive degradation of the molecule. No further attempts to prepare homologs of XVII and XVIII were made and all studies of the Favorskii rearrangement were conducted with these compounds (XVII being epimerized to XVIII during the reaction).

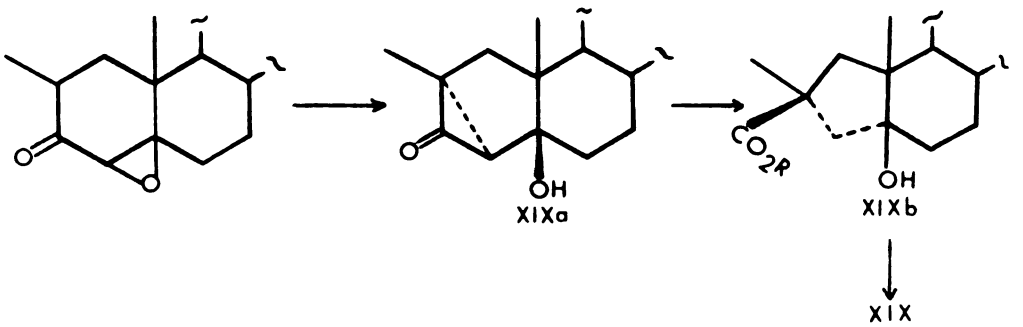
When a methanol solution of XVII or XVIII was heated under reflux with a three to four molar excess of potassium hydroxide for 2 1/2 hours, three major compounds were obtained. Extraction with concentrated base removed one of the components, the other two were neutral. The neutral material consisted of two major components and traces of other substances which were not isolated or identified.

The acidic compound (23.3%) was acetylated with acetic anhydride in pyridine and recrystallized from hexane. The infrared spectrum of this product (XIX) showed absorptions at 1770 and 1723 cm^{-1} (γ-lactone and acetate). The nmr spectrum contained singlet peaks at τ 8.02, 8.80, 9.02 and 9.21 and a broad triplet at τ 5.50 (relative areas 3:3:3:3:1). Based on this evidence and the elemental analysis structure XIX, 2α-methyl-17b-acetoxy-A-nor-5β-androstan-2β,5-carbolactone, is assigned to this product.



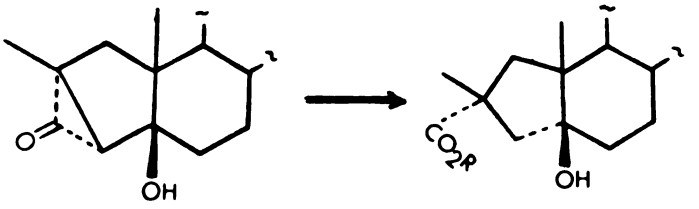
XIX

The acidic product (XIX) is probably derived from a stereospecific Favorskii rearrangement of XVIII, as shown in the following equation. The cyclopropanone intermediate



(42)

must have the structure shown as XIXa since the lactone was the only product isolated from the base soluble fraction. Since the cyclopropanone (XIXc) resulting from non-stereospecific opening of the epoxide ring would lead to the trans-hydroxy ester XIXd which could neither lactonize directly nor epimerize to a compound which could, the lack of any



XIXc XIXd

non-lactonic fraction in the base soluble material indicates that only stereospecific rearrangement occurs.

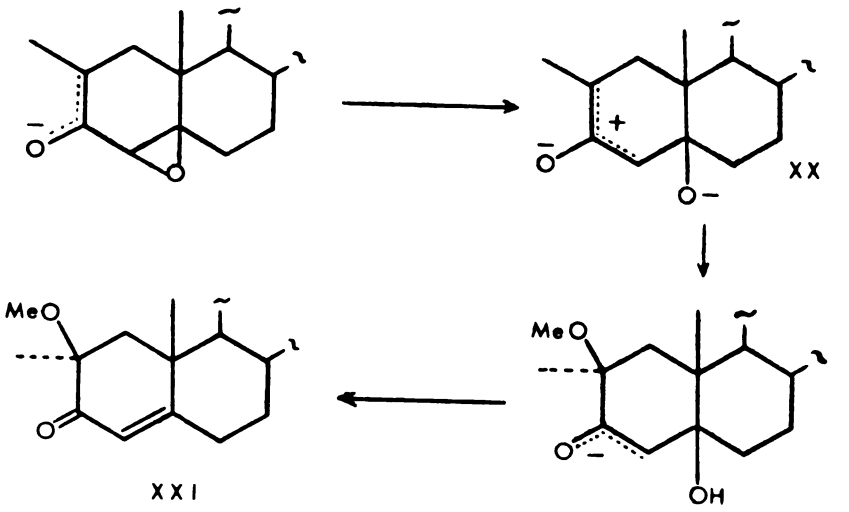
The hydroxy ester XIXb need not be formed during the reaction, as direct opening of the cyclopropanone by the epoxide oxygen could take place. This would lead to XIX directly and would prevent any abnormal opening of the cyclopropanone, since a strained β-lactone would then be formed. The γ-lactone system in XIX appears quite stable and is opened only in strong base.

The nmr spectrum of XIX can be interpreted as follows: the broad triplet at τ 5.50 (1 proton) is assigned to the 17α-proton, the three proton singlets at τ 8.02 and 9.21 are due to the acetate group and C_{18} angular methyl group respectively. The singlets at τ 8.80 and 9.02 cannot be assigned with certainty to either of the two remaining methyl groups; however, the signal at lower field seems more probable for the C_{19} angular methyl group considering the substituents in its vicinity. This permits a tentative assignment of τ8.80 to the C_{19} angular methyl group and τ 9.02 to the 2α-methyl group. The two peaks at τ 7.68 and 7.83 (see

spectrum in the appendix) integrate for one proton and are probably an AB doublet (J_{gem} = 11 Hz) due to the C_3 protons.

Acetylation of the base insoluble material and subsequent preparative thin layer chromatography (prep tlc) furnished samples of two major components. One of these (XXI), obtained in 31.5% yield as a nearly white crystalline material, showed absorptions in the infrared spectrum at 1723 cm^{-1} (acetate)., 1665 and 1620 cm^{-1} (α,β-unsaturated ketone). The nmr spectrum showed singlet absorptions at τ 4.48 (1 H), 6.98 (3 H), 8.03 (3 H), 8.70 (3 H), 8.88 (3 H) and 9.20 (3 H) and a poorly shaped triplet centered about τ 5.51 (1 H). The one-proton singlet at τ 4.48 is probably due to the C_4 proton in a 4-ene-3-one moiety and the signal at τ 6.98 is most probably due to the protons in a methoxy group. Since the 2-methyl group gives a singlet absorption at slightly lower field than normal (τ 8.70τ, the most reasonable position for the methoxy group is at C_2. These facts suggest that XXI is 2-methoxy-2-methyl-testosterone acetate.

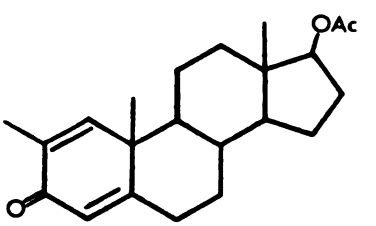
The probable configuration of the 2-methyl and 2-methoxy groups can be predicted by considering a reasonable mechanism for the formation of XXI. If the enolate anion from XVIII produces the zwitterion XX, methanol may attack the centers of positive charge. Since the bottom of the molecule is sterically hindered solvent attack should take place from the top, giving a β-configuration of the methyl ether is supported by its relatively high field nmr signal at τ 6.98.



(43)

A model of XXI shows that a freely rotating methoxyl group would be shielded by the carbonyl and double bond functions.

The second neutral product, **XXII** (30.0% yield), showed absorptions at 1730 cm^{-1} (acetate), 1670, 1645 and 1635 cm^{-1}; the last three bands are often observed in steroidal-1,4-diene-3-ones. The nmr spectrum showed singlet signals at τ 4.13 (1 H), 8.03 (3 H), 8.81 (3 H) and 9.18 (3 H), a weak three proton doublet at τ 8.20 (J = 1.5 Hz), a broad triplet at τ 5.52 (1 H) and weak, one-proton quartet at τ 3.36 (J = 1.5 Hz). These data indicate that **XXII** is 2-methyl-17β-acetoxy-1,4-androstadiene-3-one. The nmr spectrum of **XXII**



XXII

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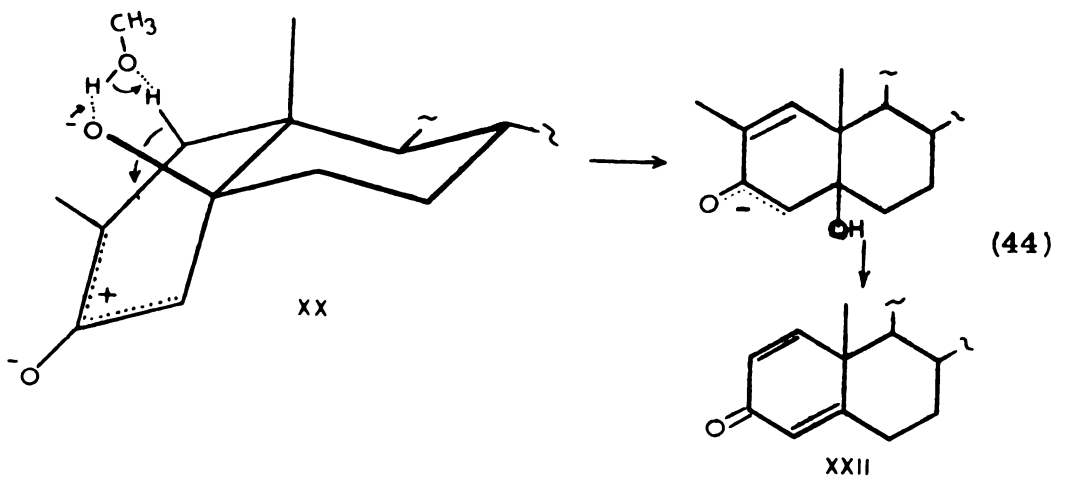
can be interpreted as follows: the singlet at τ 4.13 is assigned to the olefinic proton on C_4, and the singlets at τ 8.03, 8.81 and 9.18 are assigned to the acetate, C_{19} and C_{18} protons respectively. The small splitting constant (1.5 Hz) of the doublet at τ 8.20 is consistent with allylic coupling of the C_2-methyl protons with the olefinic proton on C_1 (τ 3.36, q, J = 1.5 Hz). The physical constants and elementary analysis of XXII agree well with the literature and calculated values.

A plausible mechanism for the formation of XXII must take into account the fact that similar cross conjugated dienones have not been isolated from the base catalyzed reactions of other α,β-epoxy ketones, and that α,β-unsaturated ketones are not common by-products of the Favorskii rearrangement of α-halo ketones. The tertiary alkoxide moiety in the zwitterionic intermediate XX can coordinate with a solvent molecule, orienting it so that the conjugate base generated by proton transfer can immediately abstract a proton from C_1. The corresponding intermediate from piperitone oxide (VII) is conformationally mobile and may not assume the necessary orientation. The rigid geometry of the steroid system apparently provides the unique arrangement necessary for this reaction.

The signals for the C_1 proton and C_2 methyl group of XXII can be seen in the nmr spectrum of the crude base insoluble products, demonstrating that it is not an artifact created during the work-up.

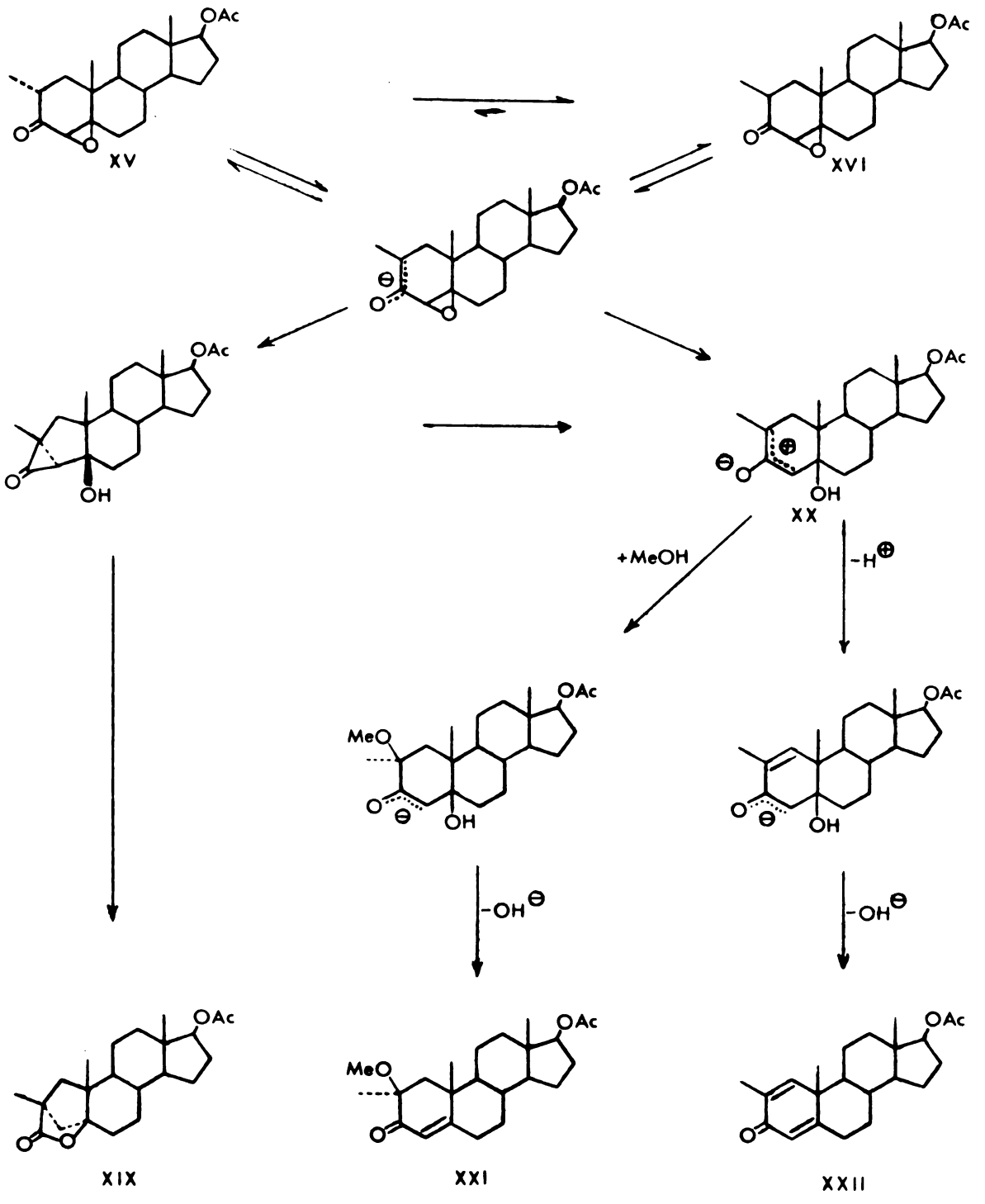


(44)

The overall reactions for XVII and XVIII are depicted in Table 4.

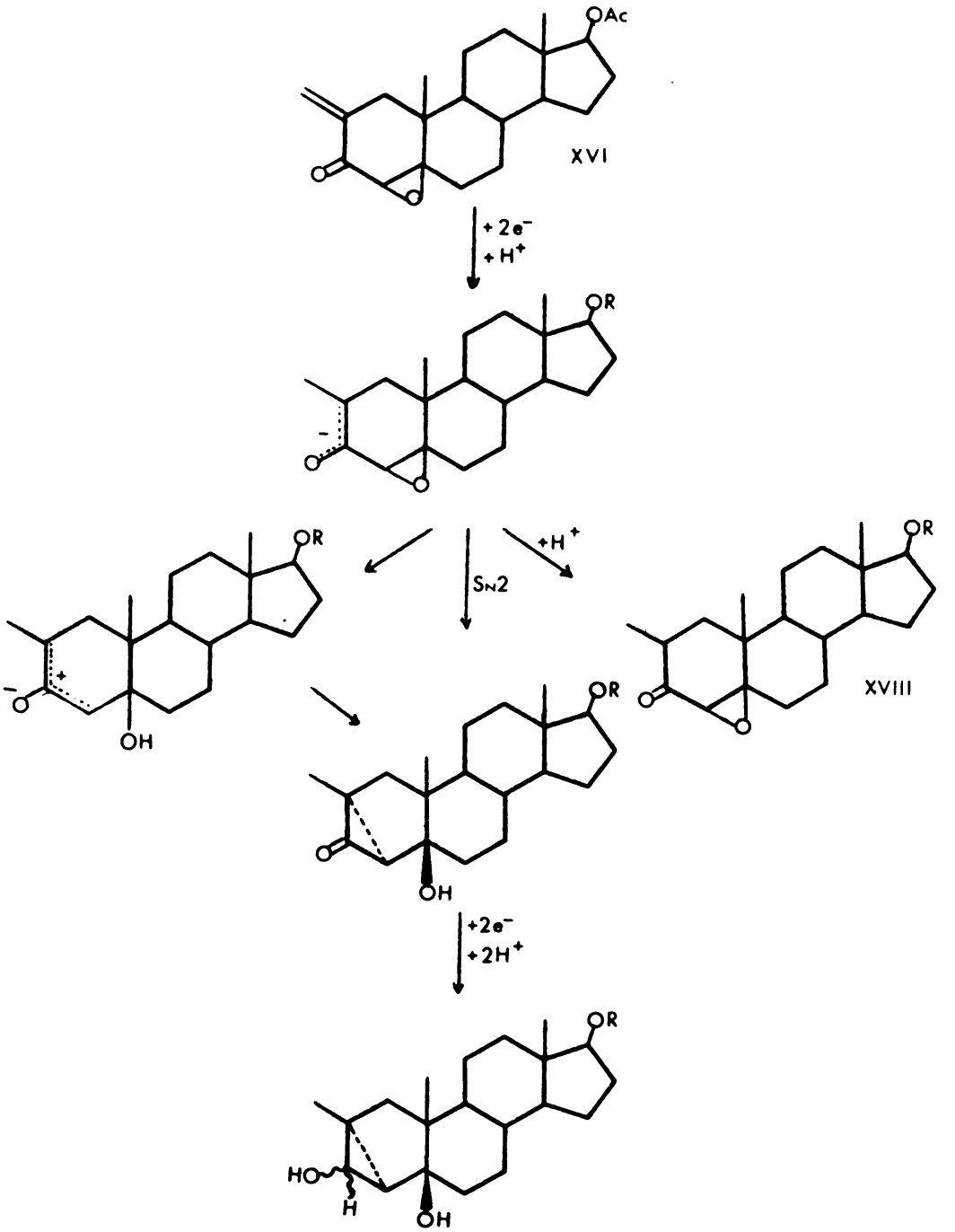
It was thought that the Birch reduction of 2-methylene-4β,5β-epoxy testosterone acetate (XVI) might be of interest to this study for three reasons: first, it offers an opportunity to study the competition between enone and epoxyketone reduction; second, reduction of the enone moiety could lead directly to 2β-methyl-4β,5β-epoxy testosterone (XVIII, as the 17-ol) thereby lending additional support to the structure assignment; and third, the intermediate enolate anion generated by enone reduction could conceivably lead to Favorskii intermediates which could be trapped as shown in Table 5.

Reduction of α,β-unsaturated ketones by alkali metals in ammonia (or amines) is known to proceed <u>via</u> an enolate anion which may be protonated or alkylated at the α-position.[32] Formation of a cyclopropanone by direct Sn2 attack or <u>via</u> a zwitterion is therefore possible. This cyclopropanone might



Base catalysed reactions of the 2-methyl-4β,5β-epoxy testosterone acetates

Table 4



Potential reactions of XVI

Table 5

then be reduced to a cyclopropanol more rapidly than it reacts in other ways.

Unfortunately, attempts to find products of this kind ended in failure. The reaction of XVI with lithium in either liquid ammonia-THF or in ethylene diamine was not clean, giving a material which could not be purified or identified. In one reaction, carried to partial completion, a trace amount of XVIII (6.4 mg as the 17-ol) was recovered along with 138 mg of XVI (from 638 mg of XVI); again the balance of the material proved untractable.

EXPERIMENTAL

General

Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer, using sodium chloride cells. Nuclear magnetic resonance spectra were taken on a Varian A-60 high resolution spectrometer; tetramethylsilane was used as an internal standard in both deutero chloroform and carbon tetrachloride solutions, the latter also contained a trace of chloroform as a second standard.

Preparative thin layer chromatography was carried out with pre-coated 2-mm layers of silica gel F-254 on 20 x 20 cm glass plates (Brinkmann Instruments Inc.).

Melting points were measured with a Koefler hot stage and are uncorrected.

Analyses were performed by Spang Microanalytical Labs, Ann Arbor, Michigan.

Saturated sodium chloride solution is referred to as brine.

Preparation of 2α-Methyl-4-cholesten-3-one (VIII)

To 8.90 g (23.1 mM) of recrystallized 4-cholesten-3-one dissolved in 100 ml of t-butyl alcohol was added 4.37 g (83 mM) of sodium methoxide powder (Fisher) and the mixture was

stirred under nitrogen for one half hour. Freshly distilled diethyl oxalate (7.0 ml, 51.8 mM) was added and stirring at room temperature was continued for four hours. The solution was acidified with dilute, ice cold sulfuric acid (approximately 1 l) and extracted twice with ether. The combined ether layers were extracted with dilute sulfuric acid, brine, and dried over magnesium sulfate. Filtration and evaporation of the ether gave 2-ethoxalyl-4-cholesten-3-one (VII) which was used immediately without further purification.

Compound VII was dissolved in 300 ml of acetone; to a 100 ml aliquot of this solution 10 g of potassium carbonate was added producing a red color. Methyl iodide (15 ml, 242 mM) was added and the mixture was heated under reflux for 24 hours. The solution was allowed to cool to room temperature, diluted with water and extracted with three portions of ether. The combined ether layers were washed with brine and dried over magnesium sulfate.

The ether was filtered, and evaporated on a rotary evaporator to give a red oily residue. This was taken up in 75 ml of methanol; powdered sodium methoxide (0.81 g) was added and the solution was heated under reflux for 8 1/2 hours. Dilution with water, acidification and extraction with ether gave a crude product which was chromatographed on alumina. The material eluted with 1:1 petroleum ether-benzene gave a light yellow solid which was recrystallized from ligroin to give 0.51 g (16.6% based on 1/3 of the starting material) of 2α-methyl-4-cholesten-3-one (VIII) as fine white

crystals: mp 121-124°; ir ($CHCl_3$) 1665 and 1620 cm^{-1} (α,β-unsaturated ketone); uv max (95% C_2H_5OH) 243 mμ.

4β,5β-Epoxy Cholestan-3-one (IX)

A solution of 4-cholesten-3-one 4.00 g, 10.4 mM in 480 ml of methanol was cooled to 2.5°. Over a 15 minute period, 24 ml of 4N sodium hydroxide and 24 ml of 30% hydogen peroxide were added to the vigorously stirred solution, which was maintained at 3-4°. Stirring was continued overnight while the solution slowly warmed to room temperature. The reaction mixture was diluted with water and extracted twice with ether; the ether was washed with water and dried ($MgSO_4$). Filtration, evaporation and recrystallization from 30-60° petroleum ether gave 1.87 g (45%) of 4β,5β-epoxy cholestan-3-one: mp 115-118° (lit 117.5-118.5°); ir 1725 cm^{-1} (carbonyl); uv max (95% C_2H_5OH) 208 mμ.

2-Methylene-4β,5β-epoxy Cholestan-3-one (X)

To a solution containing 200 ml of 95% ethanol, 50 ml or 38% formaldehyde solution and 9 g of potassium acetate (in 30 ml H_2O) was added IX (10.0 g, 24.9 mM). The mixture was heated under reflux for 5 hours and permitted to cool to room temperature. Glacial acetic acid (5 ml) was added and about one half of the solvent was removed on the rotary evaporator. The remaining liquid was poured into water and extracted with ether; the ether layers were extracted with 5% sodium bicarbonate solution, water and dried ($MgSO_4$).

The crude ether soluble material showed no evidence of a saturated ketone in the infrared spectrum.

Column chromatography over 180 g of silica gel eluted with 10% ethyl acetate in benzene gave 7.7 g (75%) of 2-methylene-4β,5β-epoxy cholestan-3-one (X).

2ζ-Methyl-4β,5β-epoxy Cholestan-3-one

A solution of (X) in 200 ml of ethyl acetate was hydrogenated at 1 atmosphere and room temperature over 0.0714 g of 10% palladium on carbon. After stirring for 17 hours, 204.5 ml of hydrogen (94% of theoretical) had been consumed. The solution was filtered to remove the catalyst and the ethyl acetate was evaporated. The remaining glassy material, pure by analytical tlc (silica gel and alumina), could not be converted to a crystalline form despite repeated attempts from petroleum ether, hexane, methyl cyclohexane, benzene, methanol, ethanol and acetonitrile.

4β,5β-Epoxy Testosterone Acetate (XI)

Testosterone acetate (Searle) (10.01 g, 30.26 mM) in 300 ml of 2:1 methanol-methylene chloride solution was cooled to -8^0 in an ice-salt bath. A total of 12 ml of 4N potassium hydroxide and 40 ml of 30% hydrogen peroxide were added in small portions to the stirred solution; the temperature was kept below -6^0. After 3 days in a refrigerator ($4-5^0$) the reaction mixture was poured into water and extracted with methylene chloride. The methylene chloride was washed

repeatedly with water and finally with ferrous chloride solution. Evaporation of the solvent gave 6.85 g of crude product consisting of both the acetate and corresponding alcohol.

The crude product was dissolved in 50 ml of pyridine and 10 ml of acetic anhydride and left to stand at room temperature overnight. The pyridine solution was poured into water and extracted with ether; the ether was washed twice with water, with dilute hydrochloric acid, sodium bicarbonate solution and saturated sodium chloride solution. Evaporation of the ether and recrystallization of the solid product from hexane gave 5.95 (57%) of 4β,5β-epoxy testosterone acetate (XII): mp 156-157.5° (lit 155-157°); ir ($CHCl_3$) 1720 cm^{-1} (carbonyl); nmr ($CDCl_3$) τ 5.40 (t,1,J = 7 Hz), 7.01 (s,1), 7.96 (s,3), 8.81 (s,3), 9.16 (s,3), 7.7-9.2 (methylene envelope).

2-Methylene-4β,5β-epoxy Testosterone Acetate (XIV)

To 4.59 g (13.3 mM) of 4β,5β-epoxy testosterone acetate dissolved in 125 ml of ethanol was added 25 ml of 37% formaldehyde solution and 4 g of potassium acetate (in 15 ml of H_2O). The solution was heated to reflux for 5 1/2 hours. After cooling, 2.4 ml of glacial acetic acid was added and about one half of the total volume of the solution was removed on the rotary evaporator (room temperature). The remaining liquid was poured into 300 ml of water and placed in the refrigerator. The crystals deposited in the beaker were

filtered and recrystallized from acetone to yield 3.72 g (10.4 mM, 77%) of 2-methylene-4β,5β-epoxy testosterone acetate: mp 227-229° (lit 225-227°); ir ($CHCl_3$) 1725 cm^{-1} (ester), 1685 and 1615 cm^{-1} (α,β-unsaturated ketone); nmr ($CDCl_3$) τ 3.89 (t,1,J = 2 Hz), 4.79 (s,1), 5.45 (t,1,J = 7 Hz), 6.90 (s,1), 7.99 (s,3), 8.83 (s,3), 9.20 (s,3) and 7.5-9.2 (methylene envelope).

2α-Methyl-4β,5β-epoxy Testosterone Acetate (XV)

Dioxane (20 ml) and 10% palladium on carbon (0.0208 g) were purged and equilibrated with hydrogen; XIV (0.2668 g, 0.744 mM) in 10 ml of dioxane was injected into the flask. Stirring for 10 minutes at 1 atmosphere and 25° resulted in the uptake of the theoretical volume of hydrogen; an additional 35 minutes produced the uptake of an additional 3%. The dioxane solution was filtered to remove the catalyst. Evaporation and recrystallization of the resulting solid from methanol gave 0.2647 g (0.734 mM, 98.7%) of XV: mp 208-210° (lit 211-213.5°); ir ($CHCl_3$) 1720 cm^{-1} (carbonyl); nmr ($CDCl_3$) τ 5.40 (t,1,J = 7 Hz), 6.98 (s,1), 7.89 (s,3), 8.80 (s,3), 9.08 (d,3,J = 4 Hz), 9.18 (s,3) and 7.7-9.2 (methylene envelope); nmr (pyridine) τ 6.63 (s,1), 7.89 (s,3), 8.82 (s,3), 9.00 (d,3,J = 4 Hz), 9.18 (s,3) and 7.8-9.2 (methylene envelope).

2β-Methyl-4β,5β-epoxy Testosterone Acetate (XVI)

A solution of 600 ml of methanol, 0.6 g of sodium hydroxide (in 3 ml H_2O) and 1.57 g (4.30 mM) of XV was left at room temperature for three hours. After about 2/3 of the solvent had been removed by the rotary evaporator (room temperature) the remaining solution was poured into water, cooled in the refrigerator and filtered. Thin layer chromatography showed only two spots--XVI and the corresponding 17-alcohol. The crystals were acetylated in the usual manner to give (from hexane) 1.46 g (4.00 mM, 93%) of 2β-methyl-4β,5β-epoxy testosterone acetate (XVI: mp 212-213°; ir ($CHCl_3$) 1720 cm^{-1} (carbonyl); nmr ($CDCl_3$) τ 5.41 (t,1, J = 7 Hz), 7.03 (s,1), 7.98 (s,3), 8.86 (s,3), 8.90 (d,3, J = 3 Hz), 9.18 (s,3) and 7.6-9.1 (methylene envelope); nmr (pyridine) τ 6.78 (s,1), 7.98 (s,3), 8.90 (d,3,J = 3 Hz), 8.91 (s,3), 9.18 (s,3) and 7.5-9.2 (methylene envelope).

2α-Deutero-2β-methyl-4β,5β-epoxy Testosterone Acetate

A solution of 0.4137 g (1.35 mM) of XV in 5 ml dioxane was added to 0.0136 g (4.38 meq) of sodium oxide in 15 ml of 20% D_2O-dioxane. After standing overnight the solution was poured into water and extracted twice with ether. The combined ether layers were washed repeatedly with water and finally with brine. Evaporation of the solvent and recrystallization from hexane gave deuterated XVI: nmr ($CDCl_3$) τ 5.41 (t,1,J = 7 Hz), 7.05 (s,1), 7.98 (s,3), 8.86 (s,3),

8.91 (s,3), 9.18 (s,3) and 7.7-9.1 (methylene envelope); nmr (pyridine) τ 6.80 (s,1), 7.98 (s,3), 8.91 (s,6), 9.18 (s,3) and 7.7-9.7 (methylene envelope).

4-Methoxy Testosterone (XIII)

4β,5β-Epoxy testosterone acetate (0.2018 g, 0.611 mM) was dissolved in 25 ml of methanol; 2.0 ml of 4N NaOH was added and the mixture was heated under reflux for 24 hours. After the solution cooled to room temperature and poured into water (75 ml) the resulting turbid suspension was placed in the refrigerator until crystalline. Filtration gave 0.1341 g of XIII. A further yield of 8.9 mg was obtained by extraction of the mother liquor and preparative tlc (0.2 mm silica gel F_{254} (Brinkmann Instruments) eluted with 20% ether in chloroform. Although other faint bands were present, only XIII could be recovered. The total yield of XIII was 0.1403 g (73.5%).

The recovered XIII was dissolved in methylene chloride-hexane and crystallized by boiling off the methylene chloride to give fine white needles of 4-methoxy testosterone (XIII): mp 219-221^0 (lit 218-220^0); ir ($CHCl_3$) 1770, 1600 cm^{-1} (α,β-unsaturated carbonyl); nmr ($CDCl_3$) τ 6.40 (s,3), 6.79 (s,3), 9.21 (s,3) and 7.5-9.1 (methylene envelope).

Favorskii Reaction of 2-Methyl-4β,5β-epoxy Testosterone Acetate

Potassium hydroxide (0.664 g, 10.2 mM) was dissolved in methanol in the reaction flask. To this was added

2β-methyl-4α,5α-epoxy testosterone acetate (XVIII) (0.937 g, 2.60 mM) and the volume was brought to 40 ml. The solution was heated under reflux for 2 1/2 hours during which time it became yellowed. After cooling to room temperature the solution was poured into 2N potassium hydroxide and extracted with ether. The ether layer was extracted twice with 1N potassium hydroxide and twice with brine.

The ether solution of neutral material was evaporated to dryness, redissolved in 10 ml of pyridine and 5 ml of acetic anhydride and placed in the hood overnight. The pyridine solution was then diluted with water and shaken with ether. The ether fraction was extracted with two more portions of water, once with cold dilute hydrochloric acid and finally with brine. Purification of the solid, ether soluble material could not be accomplished by recrystallization so preparative tlc was employed. Pre-coated 20 x 20 cm plates of 2 mm silica gel F_{254} (Brinkmann Instruments Inc.) were eluted with 5% ethyl acetate in cyclohexane. Multiple development was used to obtain the maximum separation of the components; after the plate was developed a first time it was dried and redeveloped. Under the ultraviolet lamp two intense bands were observed, accompanied by a third faint band (which was not investigated). The two major compounds were recovered from the silica gel to give 0.374 g (0.82 mM, 32%) of XXI and 0.267 g (0.78 mM, 30%) of XXII.

The alkaline extracts of the crude reaction mixture were combined and acidified to a congo red endpoint by the

slow addition of ice cold hydrochloric acid. The resulting turbid suspension was extracted with ether, dried and evaporated. After acetylation in pyridine-acetic anhydride followed by the usual work-up 0.219 g (0.616 mM, 23.3%) of XIX was obtained.

Characterization of 2α-methyl-17β-acetoxy-A-nor-5β-androstan-2β,5-carbolactone (XIX)

Mp 149-150.5°; ir ($CHCl_3$) 1770 cm^{-1} (γ-lactone) and 1723 cm^{-1} (ester); nmr (CCl_4) τ 5.50 (t,1,J = 8 Hz), 8.02 (s,3), 8.80 (s,3), 9.02 (s,3), 9.21 (s,3) and 7.8-9.2 (methylene envelope).

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.21; H, 9.02.

Characterization of 2-Methoxy-2-methyl-testosterone Acetate (XXI)

Mp 187-189°; ir ($CHCl_3$), 1723 cm^{-1} (ester) and 1665, 1620 cm^{-1} (α,β-unsaturated ketone); nmr (CCl_4), τ 4.48 (s,1), 5.51 (t,1,J = 8 Hz), 6.98 (s,1), 8.03 (s,3), 8.70 (s,3), 8.88 (s,3), 9.20 (s,3) and 7.5-9.2 (methylene envelope).

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.95; H, 9.21.

Characterization of 2-Methyl-17β-acetoxy-1,4-androstadiene-3-one (XXII)

Mp 177-178° (180-182° corr.); ir (CCl_4) 1730 cm^{-1} (ester)

and 1670, 1645, 1635 cm^{-1} (1,4-diene-3-one); nmr (CCl_4) τ 3.36 (q,1,J = 1.5 Hz), 4.13 (s,1), 5.52 (t,1,J = 7 Hz), 8.03 (s,3), 8.20 (t,3,J = 1.5 Hz), 8.81 (s,3), 9.18 (s,3) and 7.6-9.2 (methylene envelope).

Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.16; H, 8.83. Found: C, 77.18; H, 8.86.

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APPENDIX

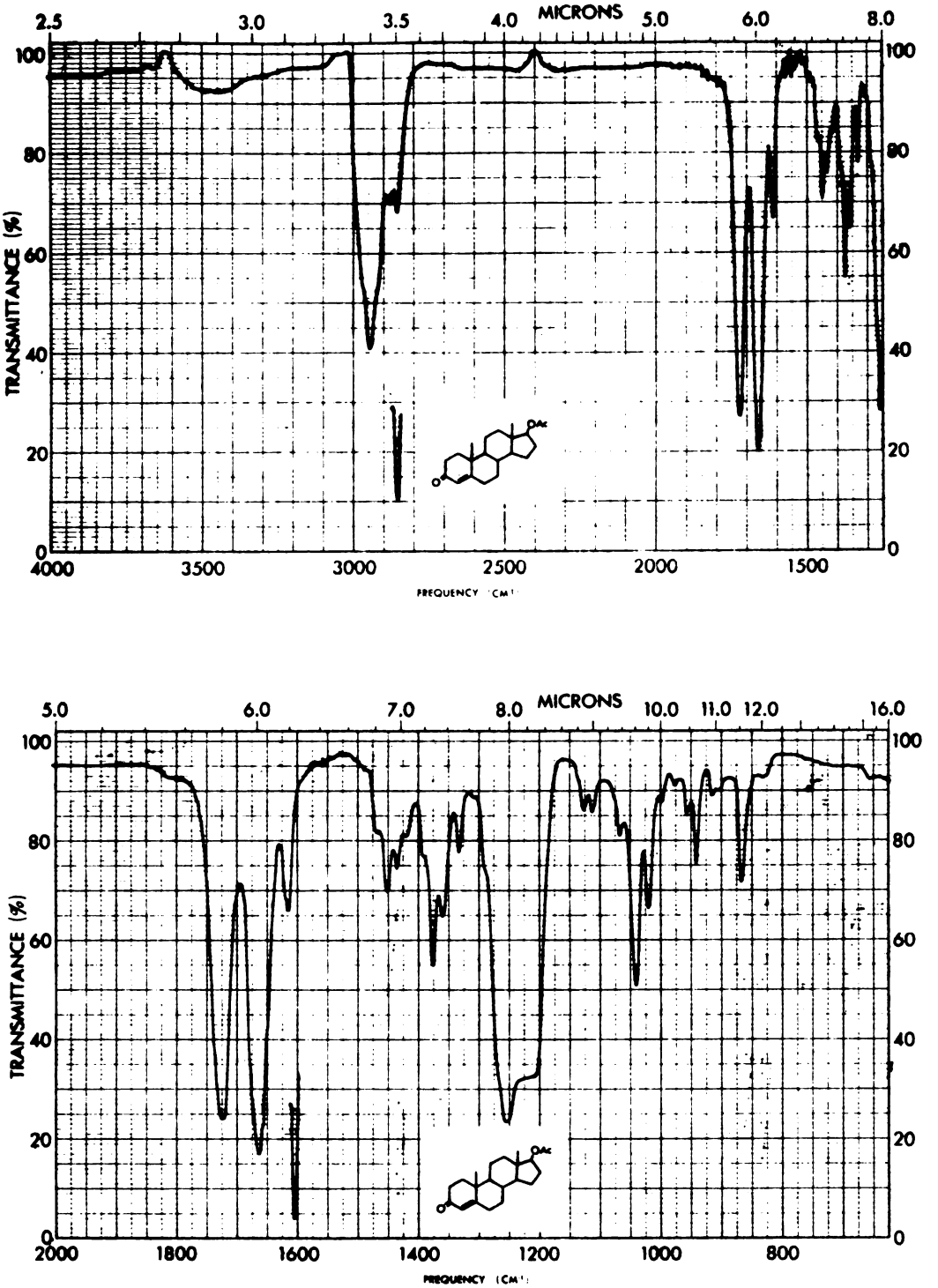

Figure 1. Infrared spectrum of testosterone acetate.

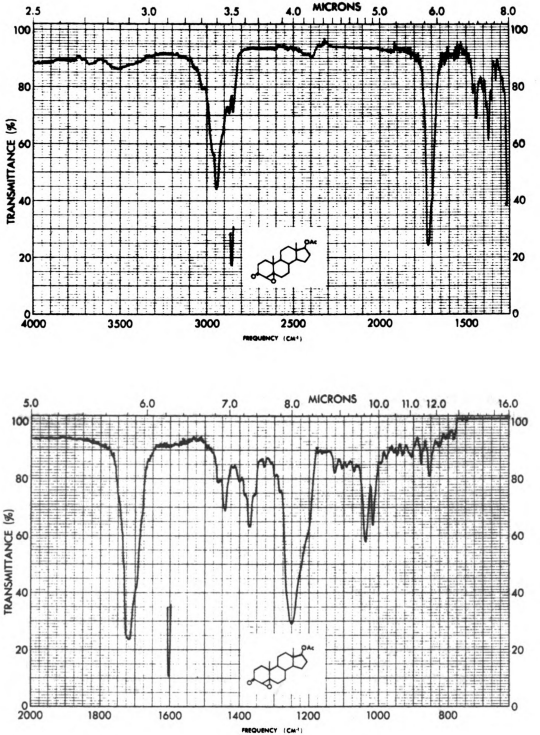

Figure 2. Infared spectrum of 4β,5β-epoxy testosterone acetate.

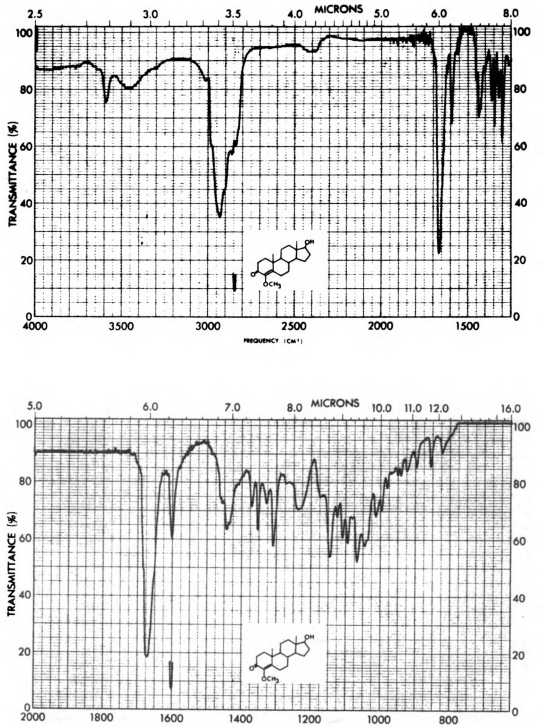

Figure 3. Infrared spectrum of 4-methoxy testosterone.

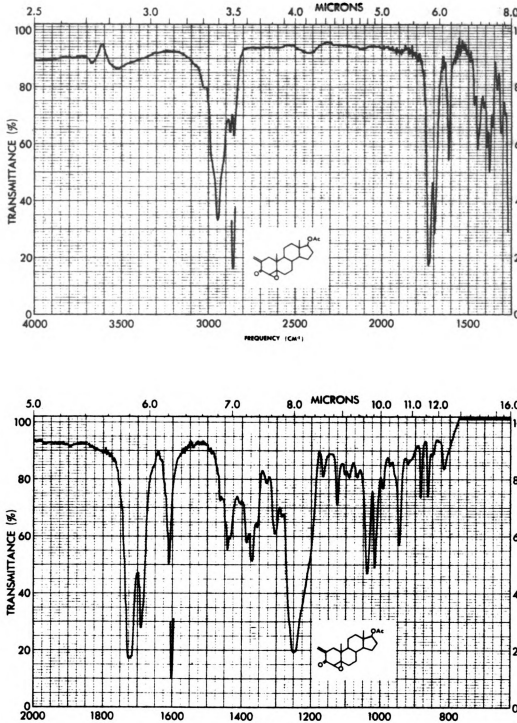

Figure 4. Infrared spectrum of 2-methylene-4β,5β-epoxy testosterone acetate.

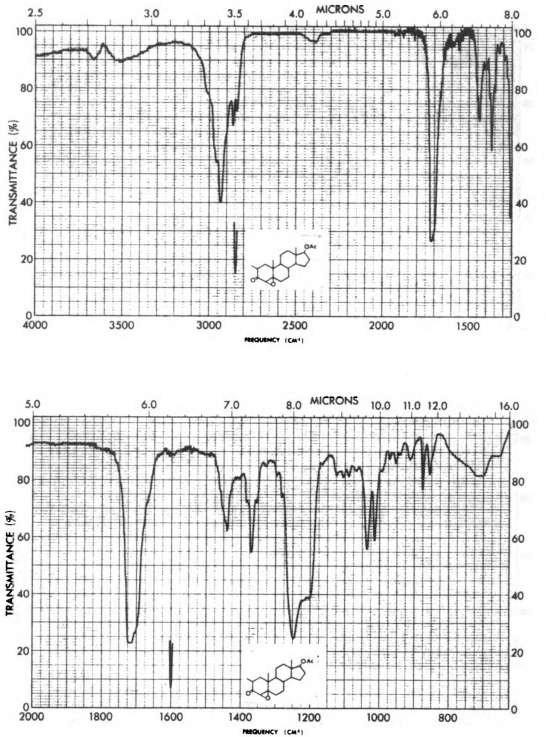

Figure 5. Infrared spectrum of 2α-methyl-4β,5β-epoxy testosterone acetate.

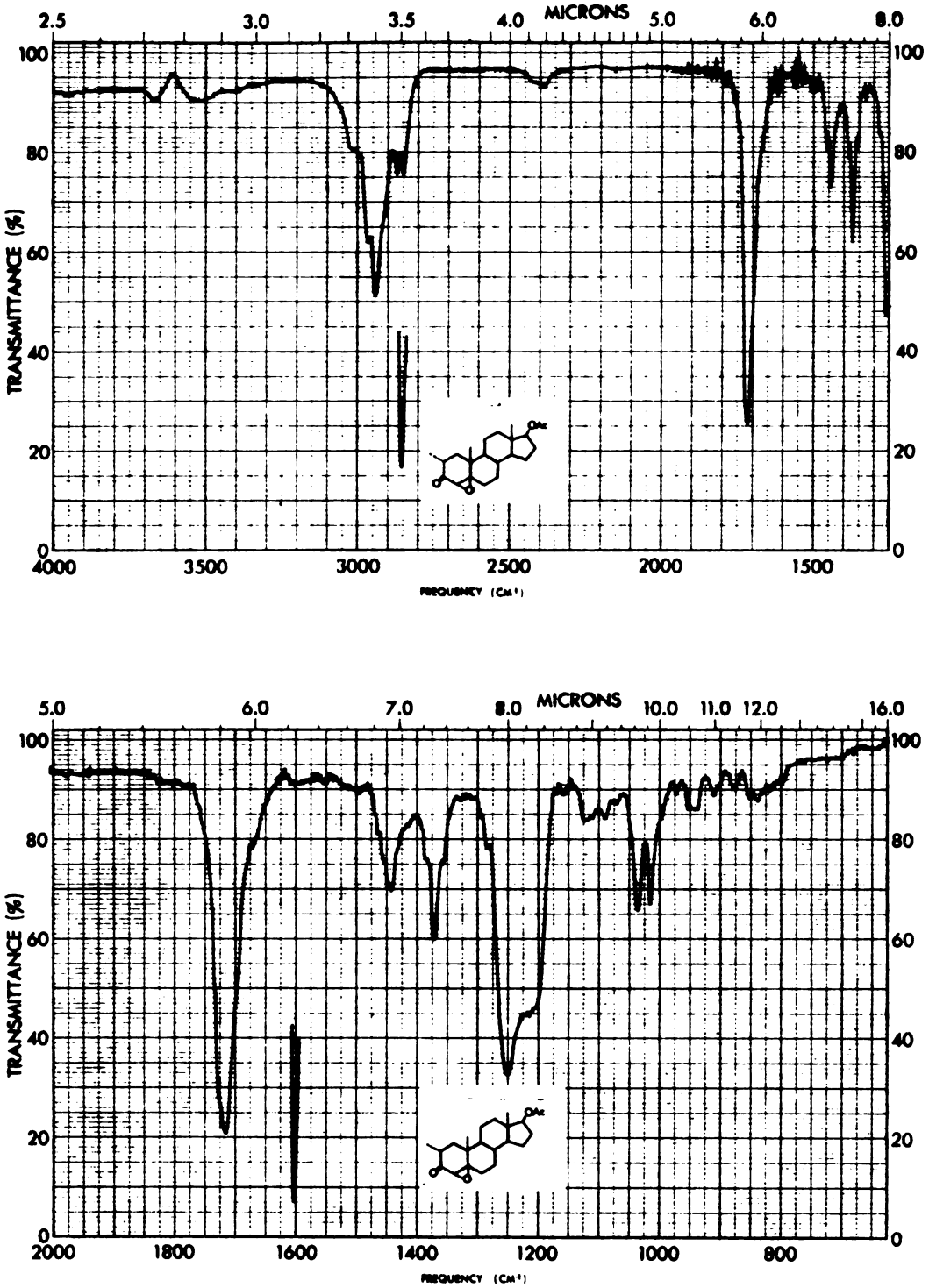

Figure 6. Infrared spectrum of 2β-methyl-4β,5β-epoxy testosterone acetate.

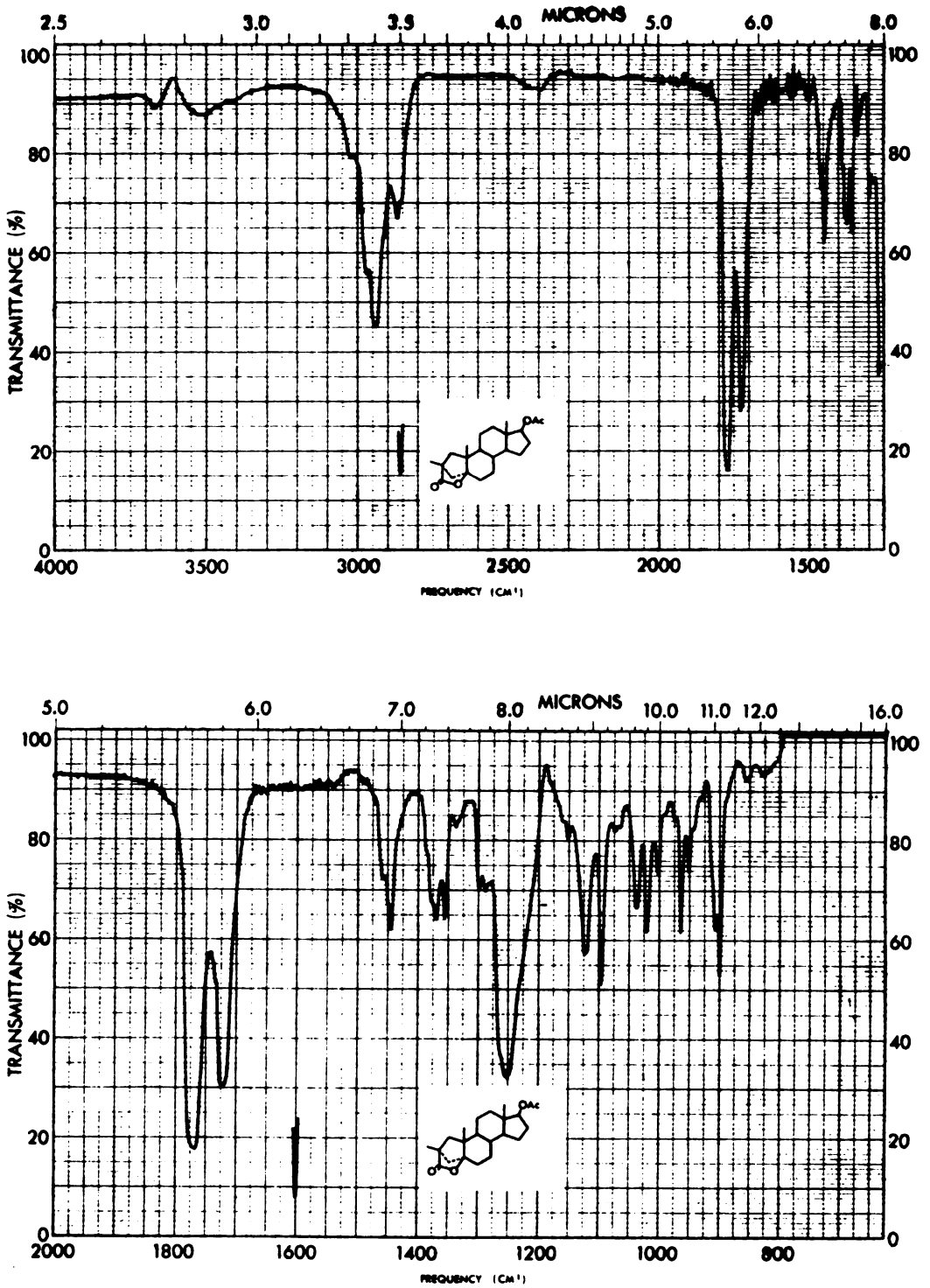

Figure 7. Infrared spectrum of 2α-methyl-17β-acetoxy-A-nor-5β-androstan-2β,5-carbolactone.

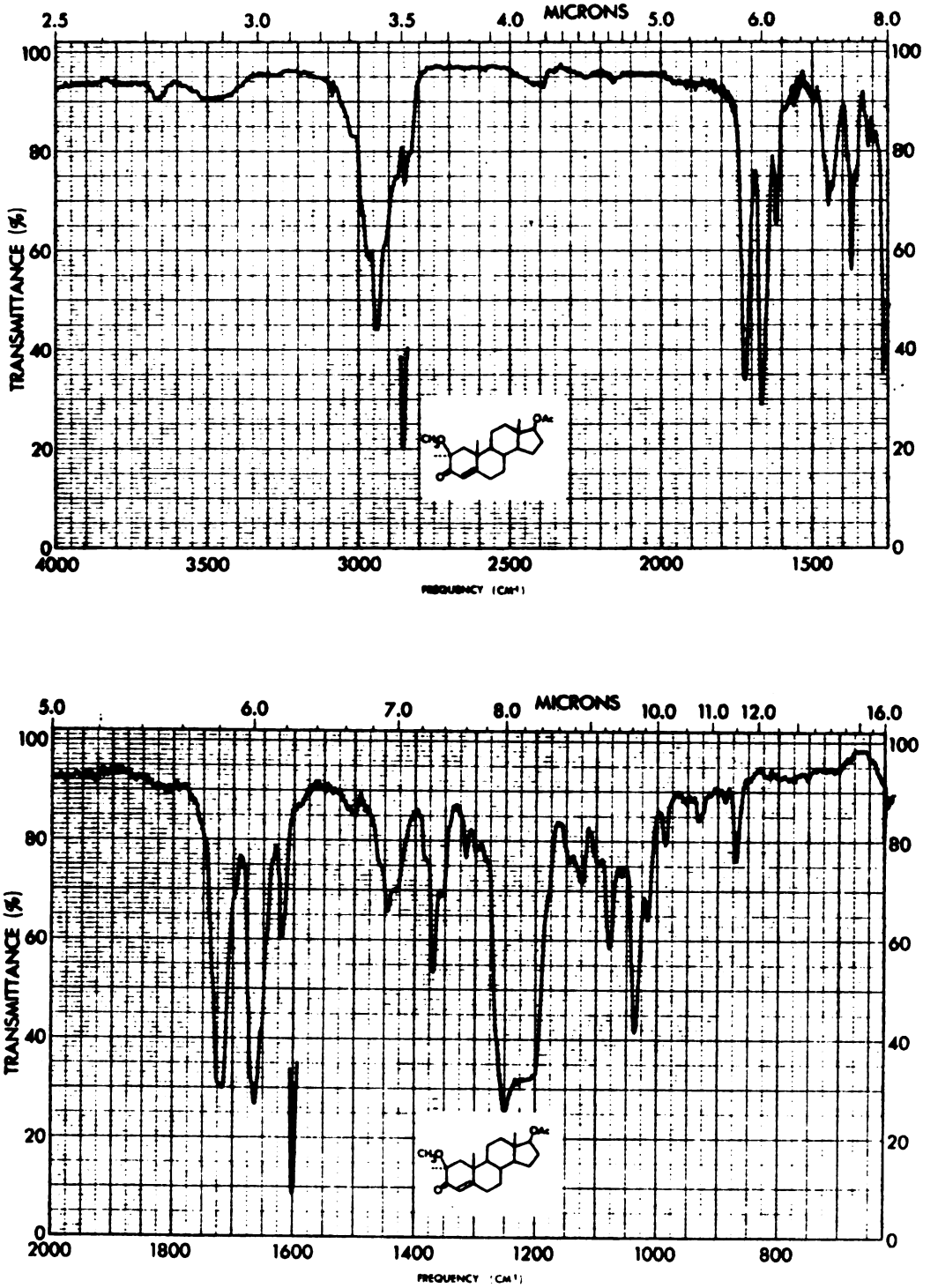

Figure 8. Infrared spectrum of 2-methoxy-2-methyl testosterone acetate

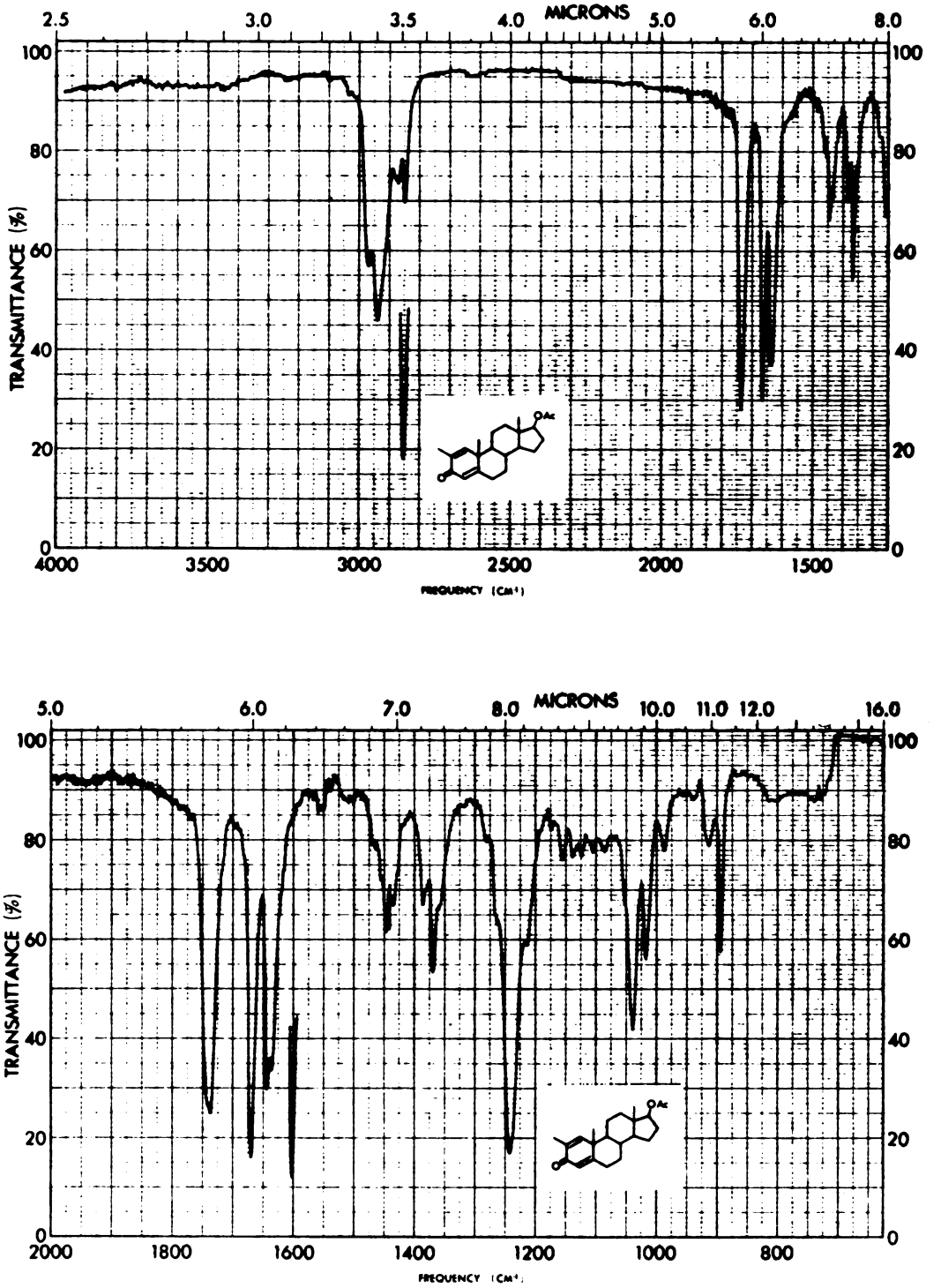

Figure 9. Infrared spectrum of 2-methyl-17β-acetoxy-1,4-androstadiene-3-one.

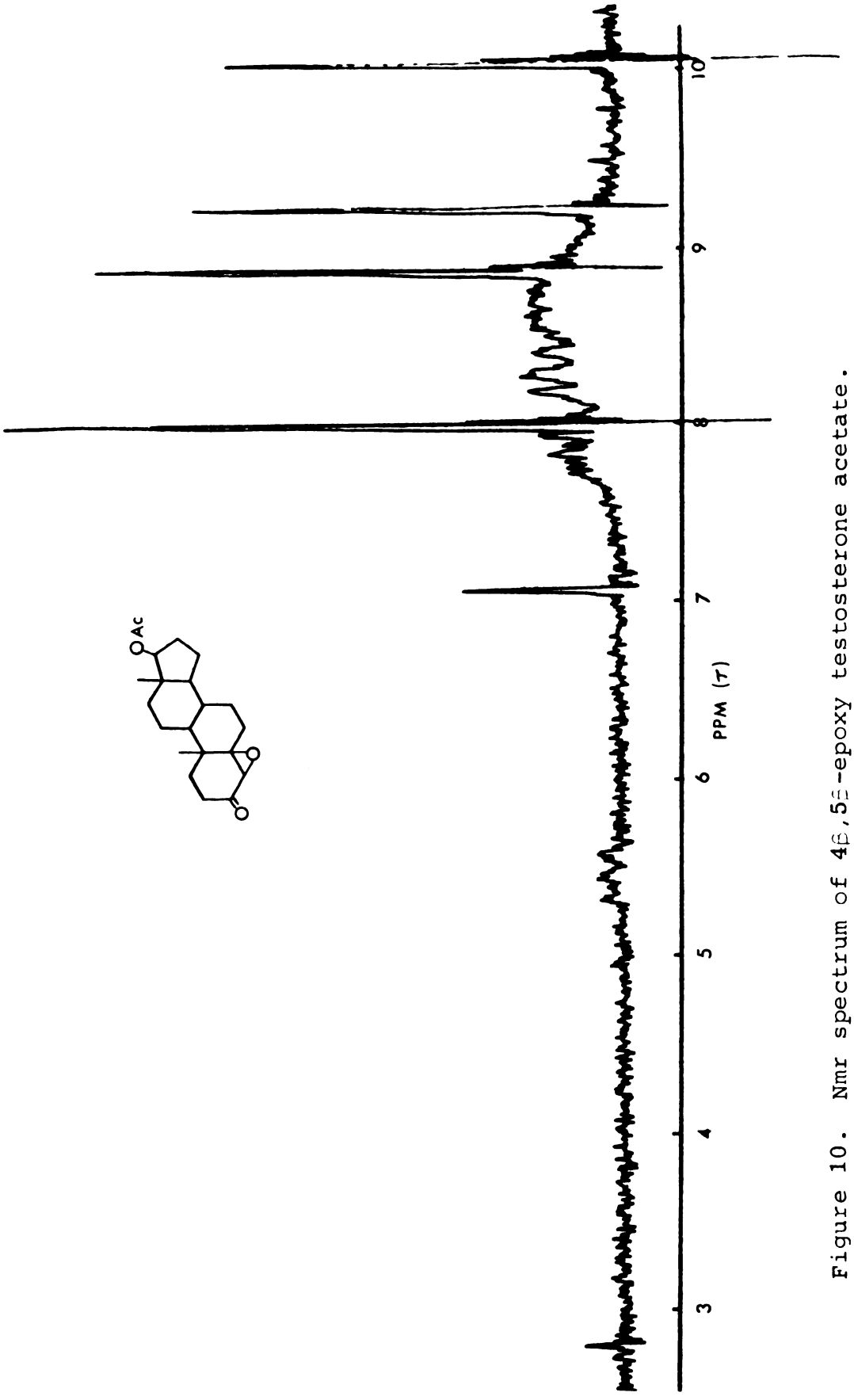

Figure 10. Nmr spectrum of 4β,5ξ-epoxy testosterone acetate.

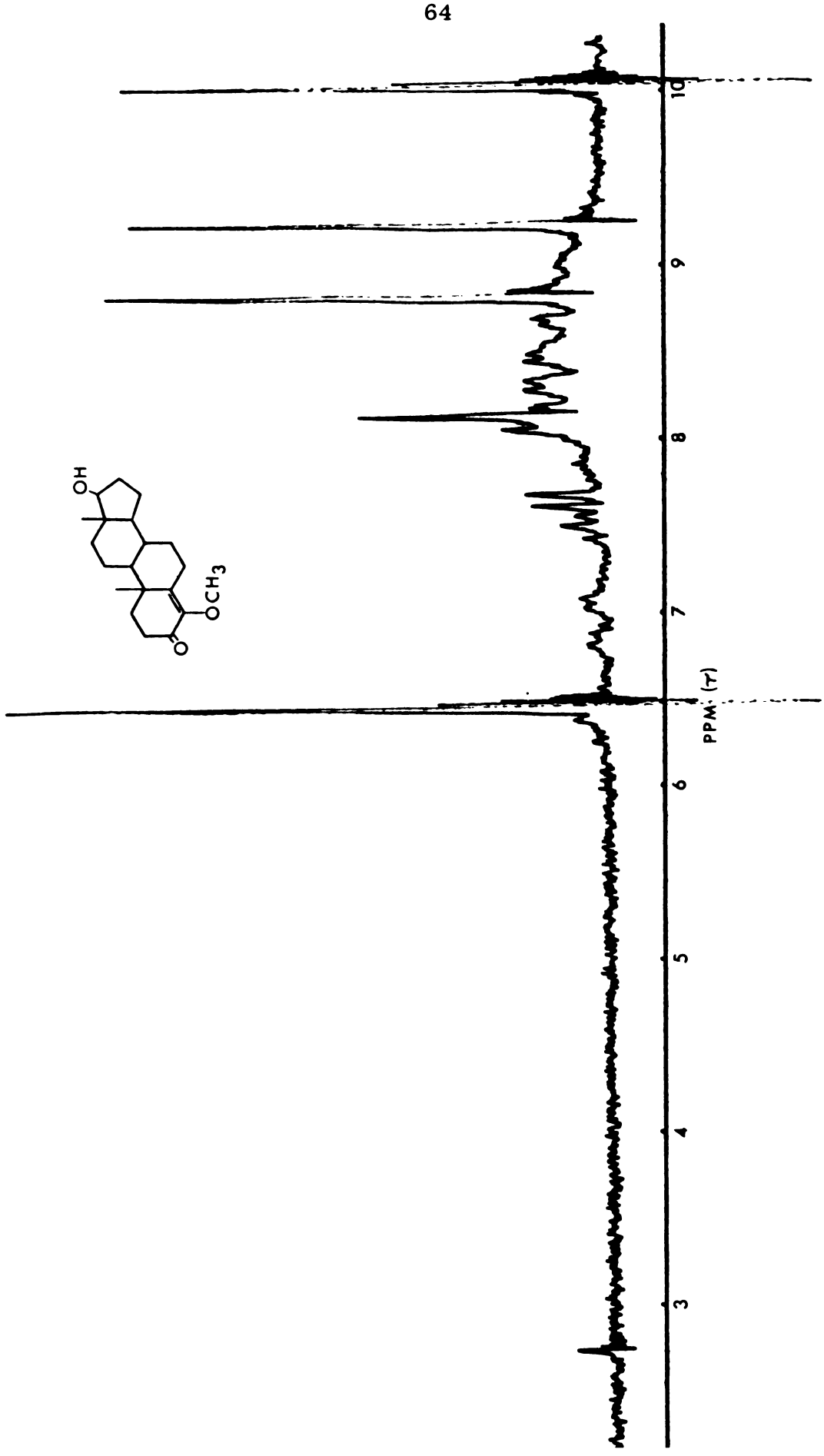

Figure 11. Nmr spectrum of 4-methoxy testosterone.

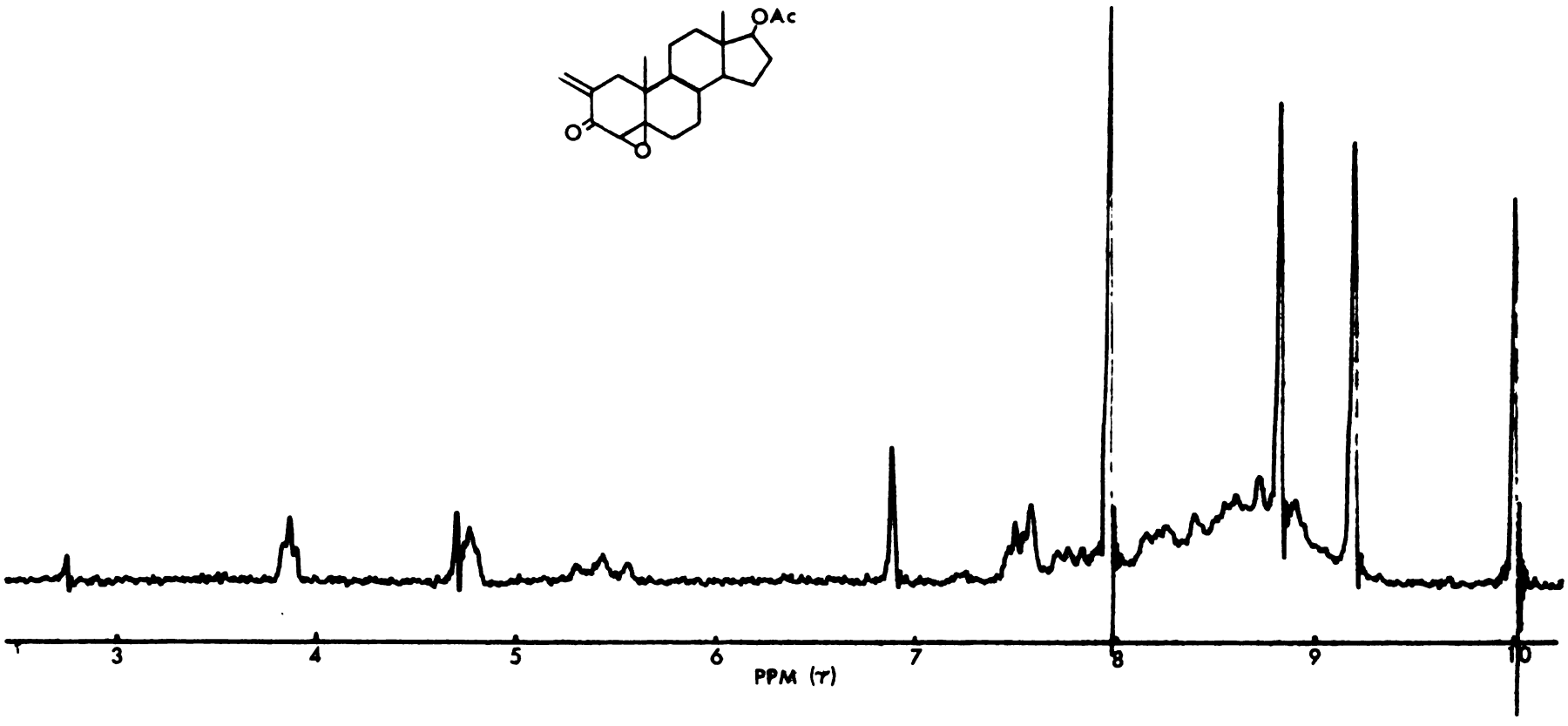

Figure 12. Nmr spectrum of 2-methylene-4β,5β-epoxy testosterone acetate.

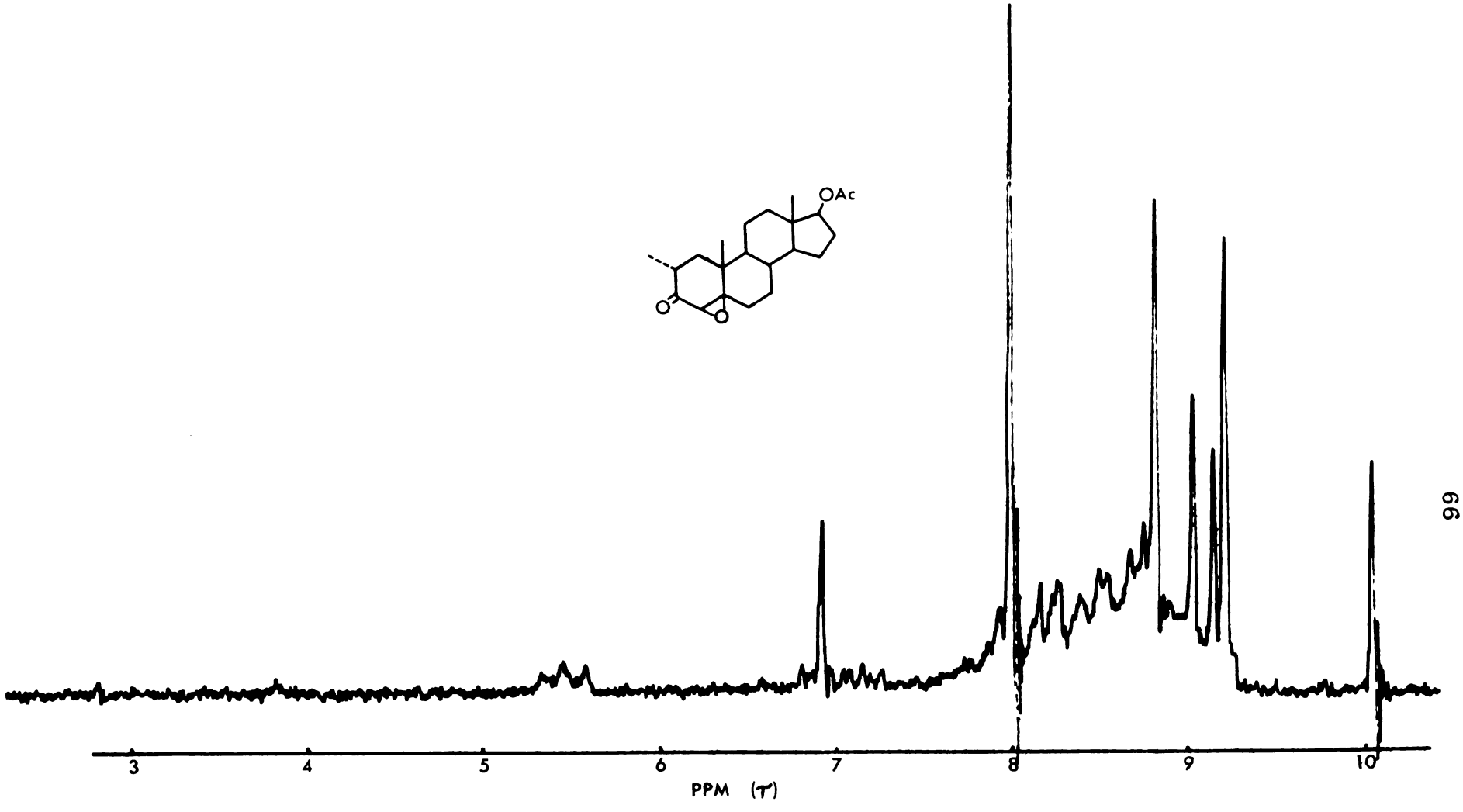

Figure 13. Nmr spectrum of 2α-methyl-4β,5β-epoxy testosterone acetate ($CDCl_3$).

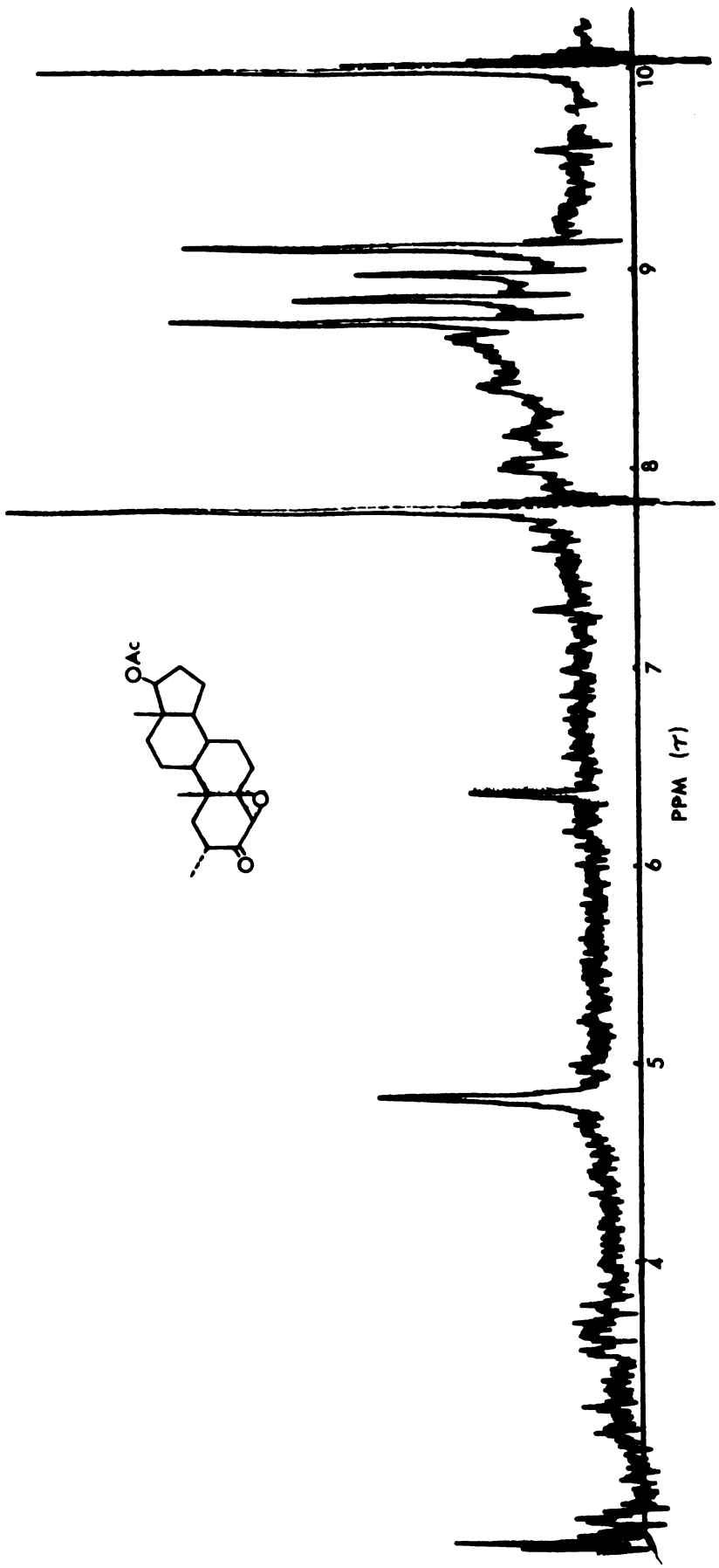

Figure 14. Nmr spectrum of 2α-methyl-4β,5β-epoxy testosterone acetate (pyridine).

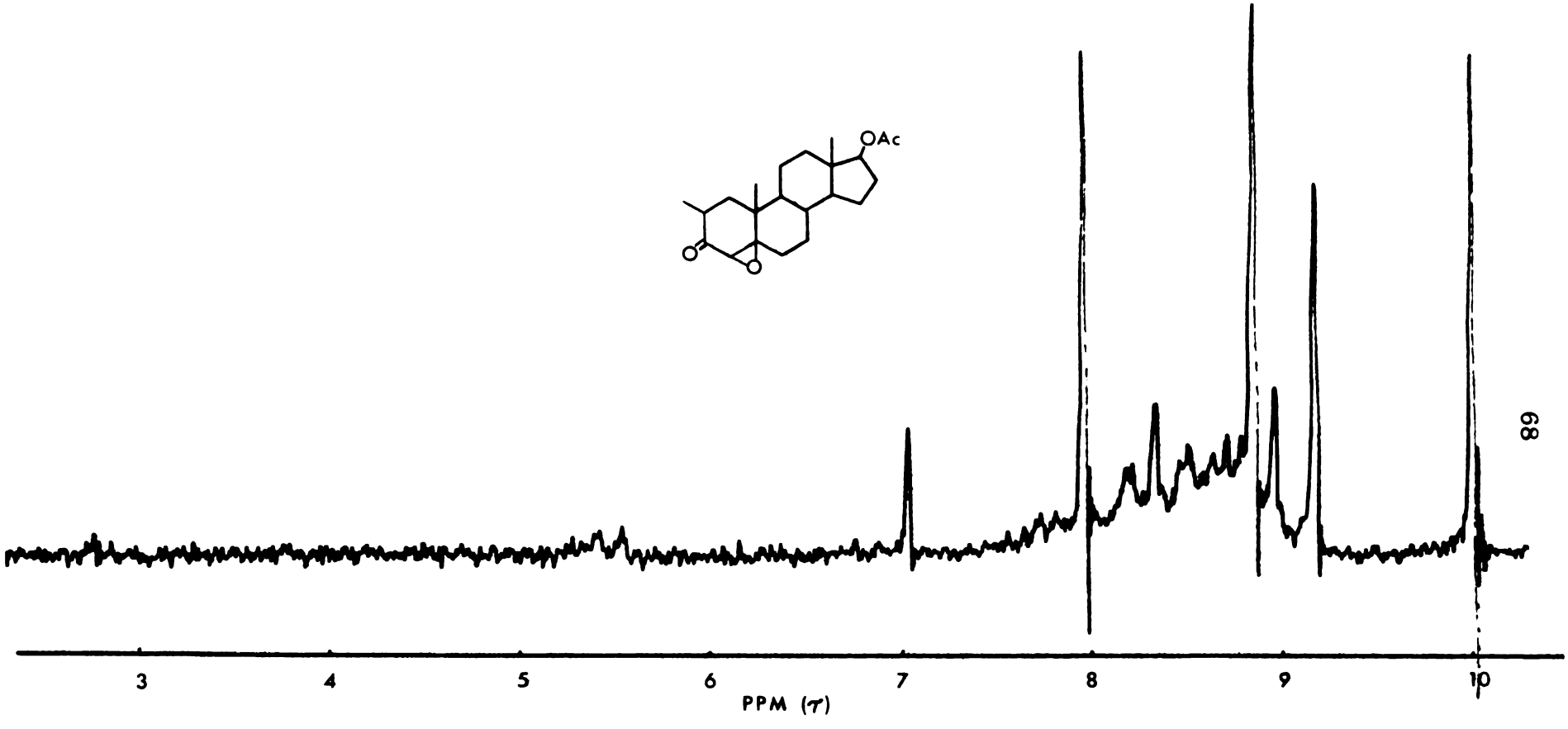

Figure 15. Nmr spectrum of 2β-methyl-4β,5β-epoxy testosterone acetate ($CDCl_3$).

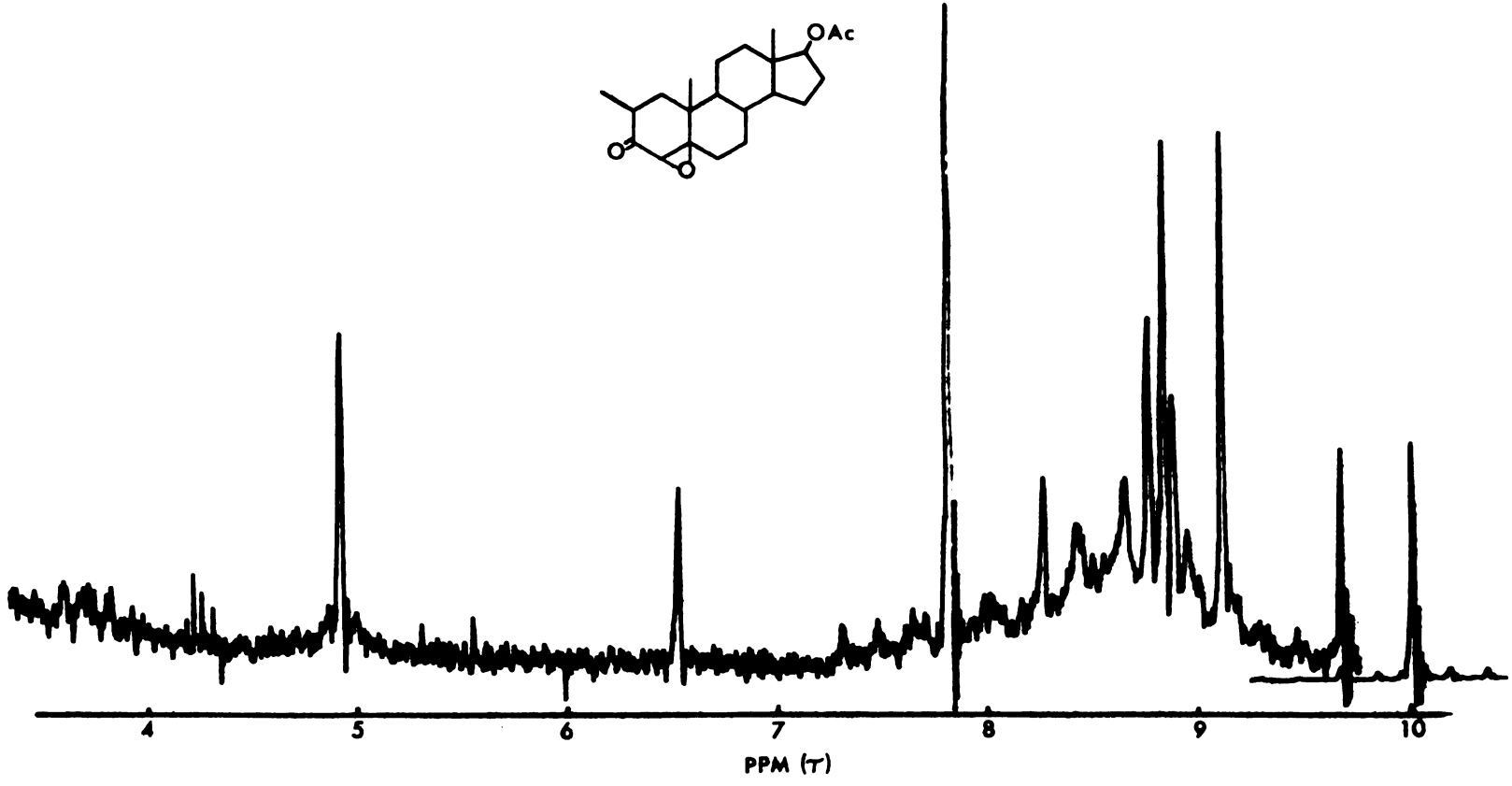

Figure 16. Nmr spectrum of 2β-methyl-4β,5β-epoxy testosterone acetate (pyridine).

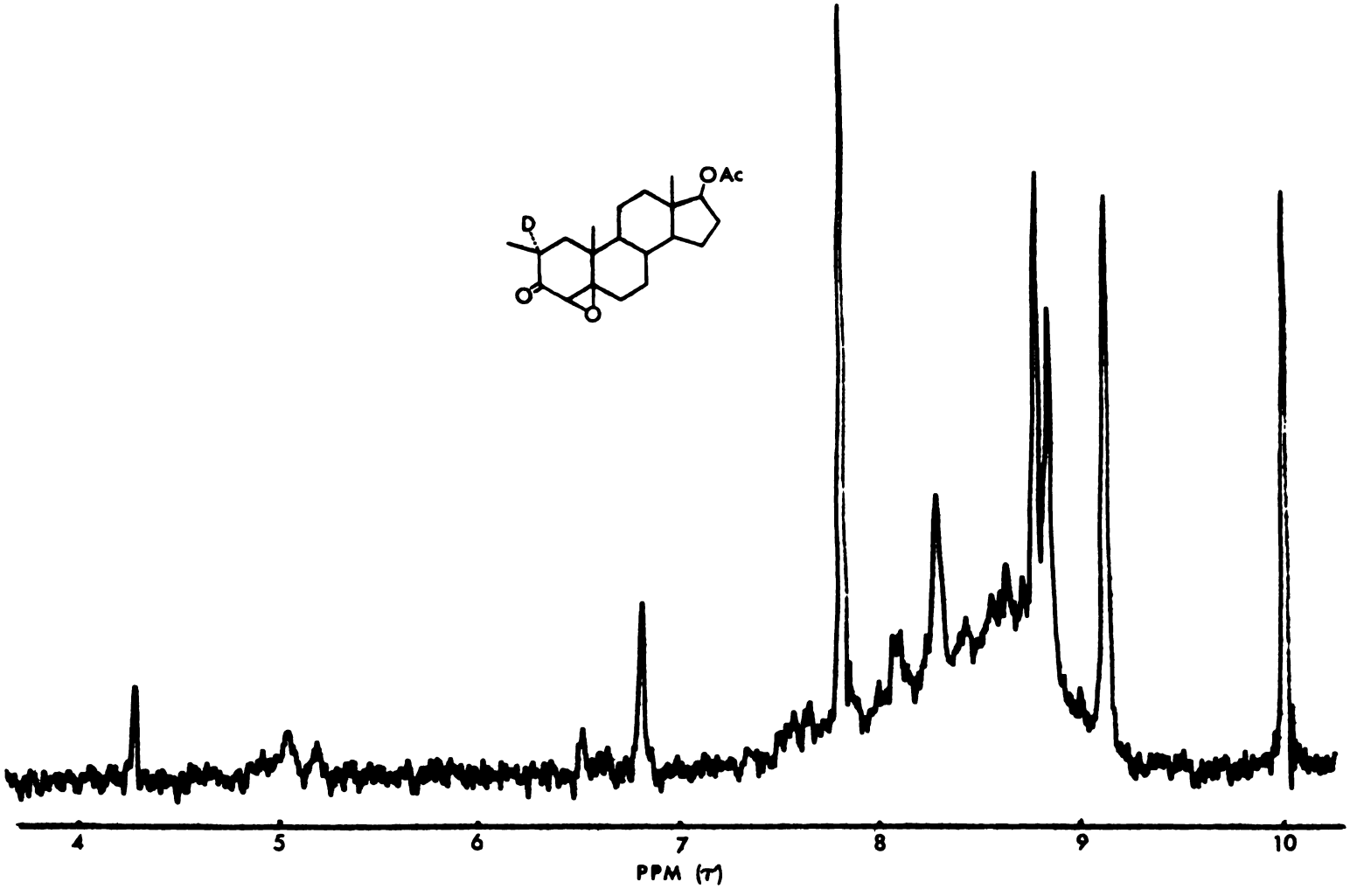

Figure 17. Nmr spectrum of 2α-deutero-2β-methyl-4β,5β-epoxy testosterone acetate ($CDCl_3$).

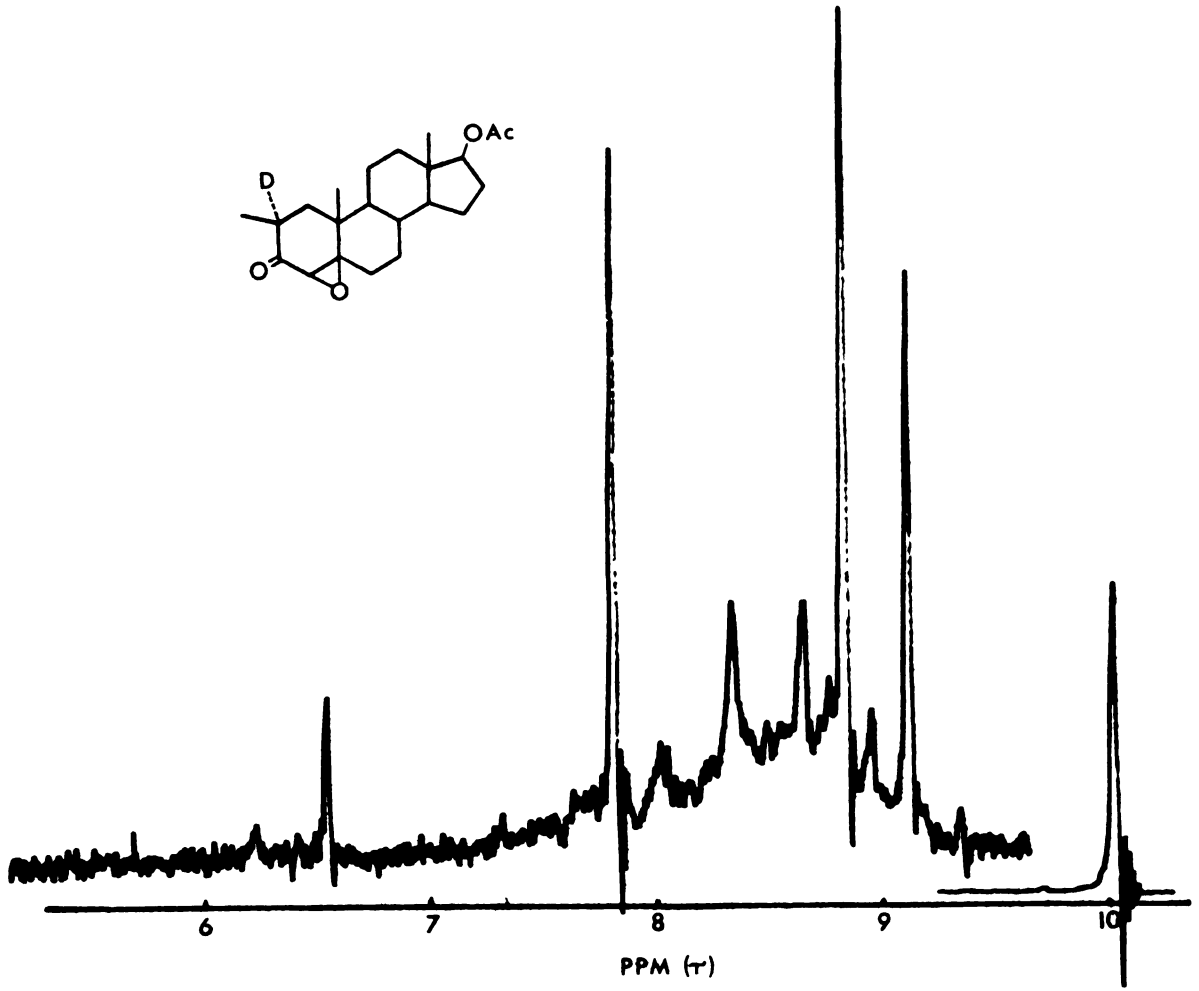

Figure 18. Nmr spectrum of 2α-deutero-2β-methyl-4β,5β-epoxy testosterone acetate (pyridine).

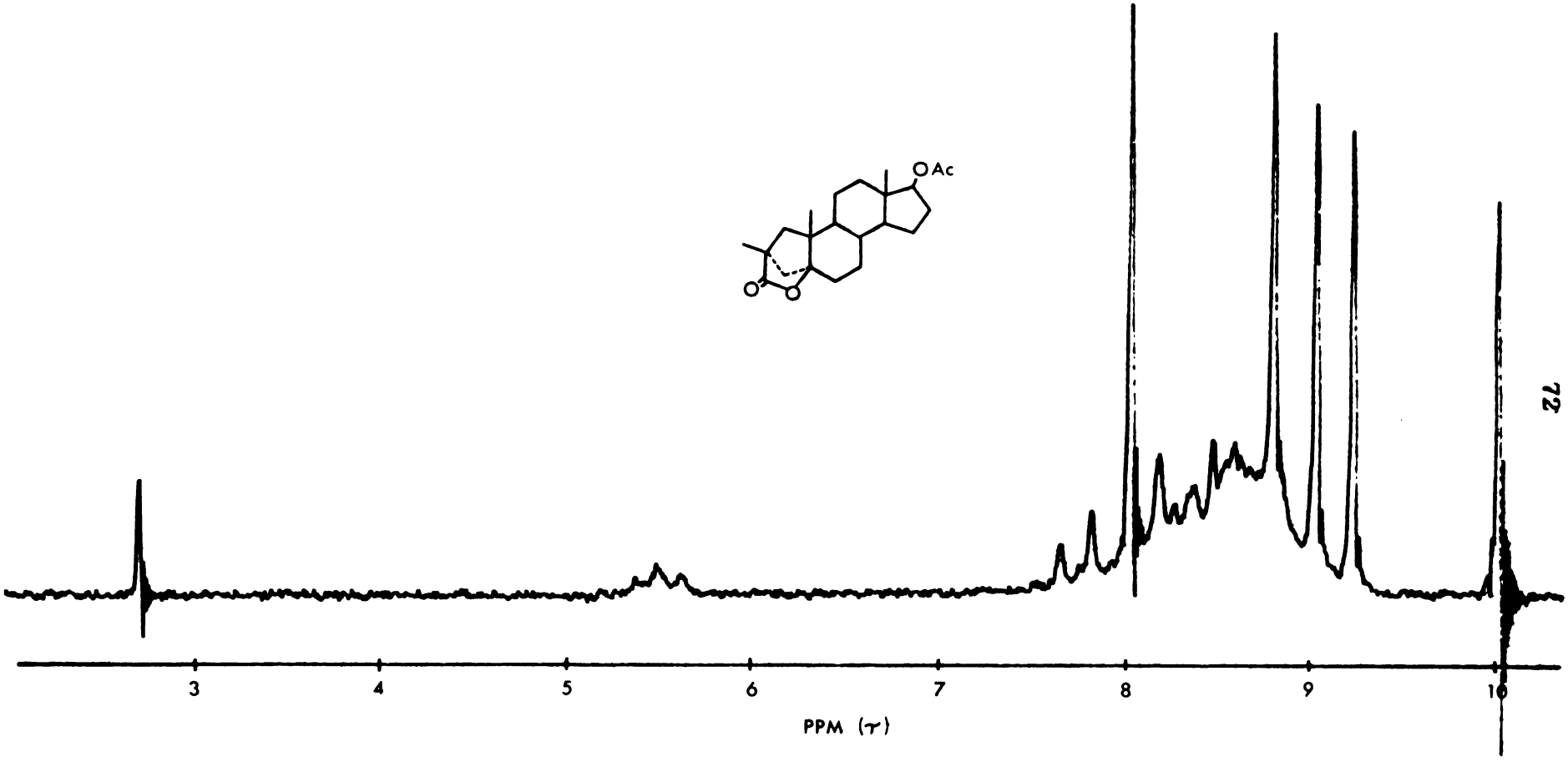

Figure 19. Nmr spectrum of 2α-methyl-17β-acetoxy-A-nor-5β-androstan-2β,5-carbolactone.

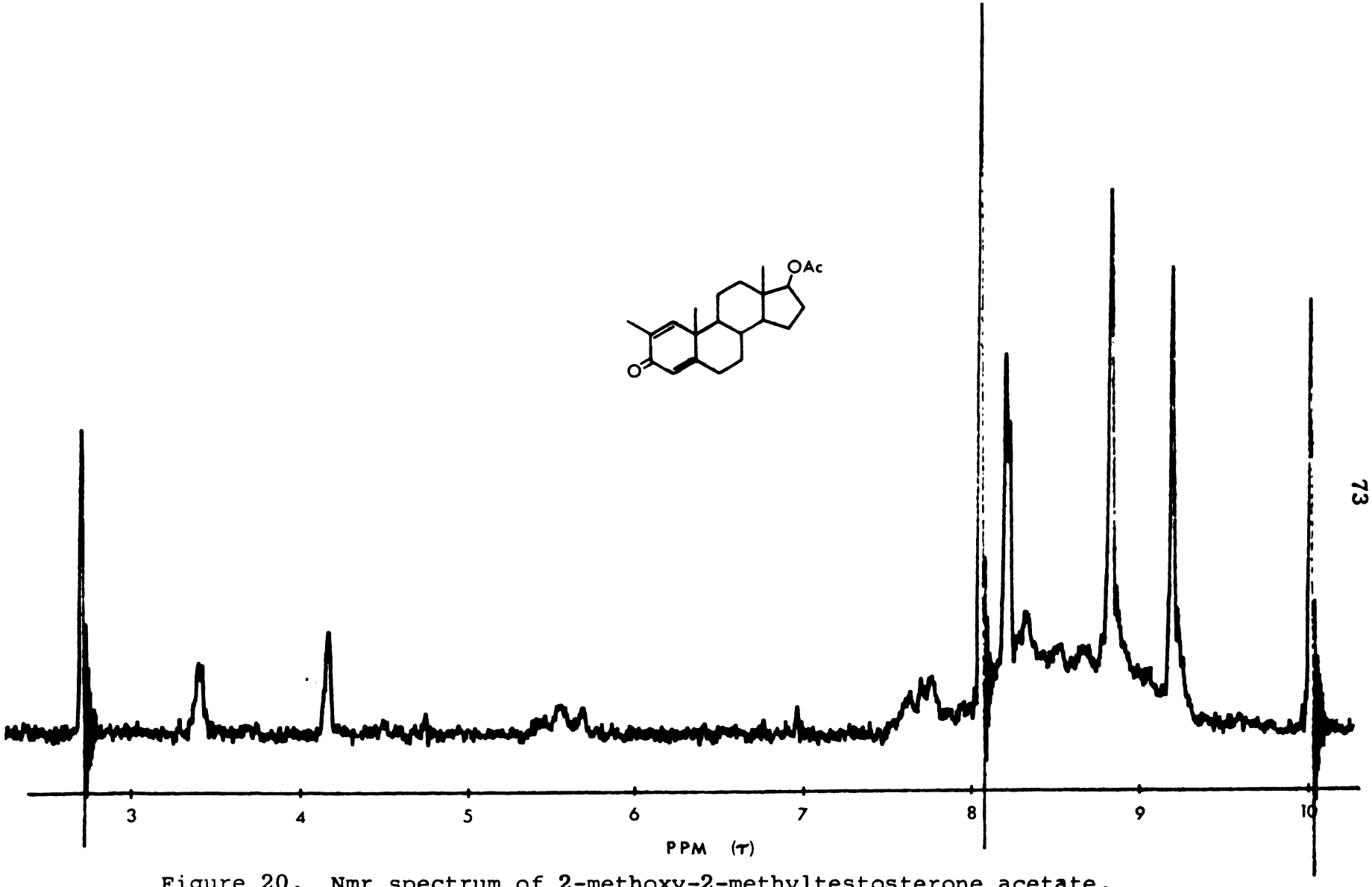

Figure 20. Nmr spectrum of 2-methoxy-2-methyltestosterone acetate.

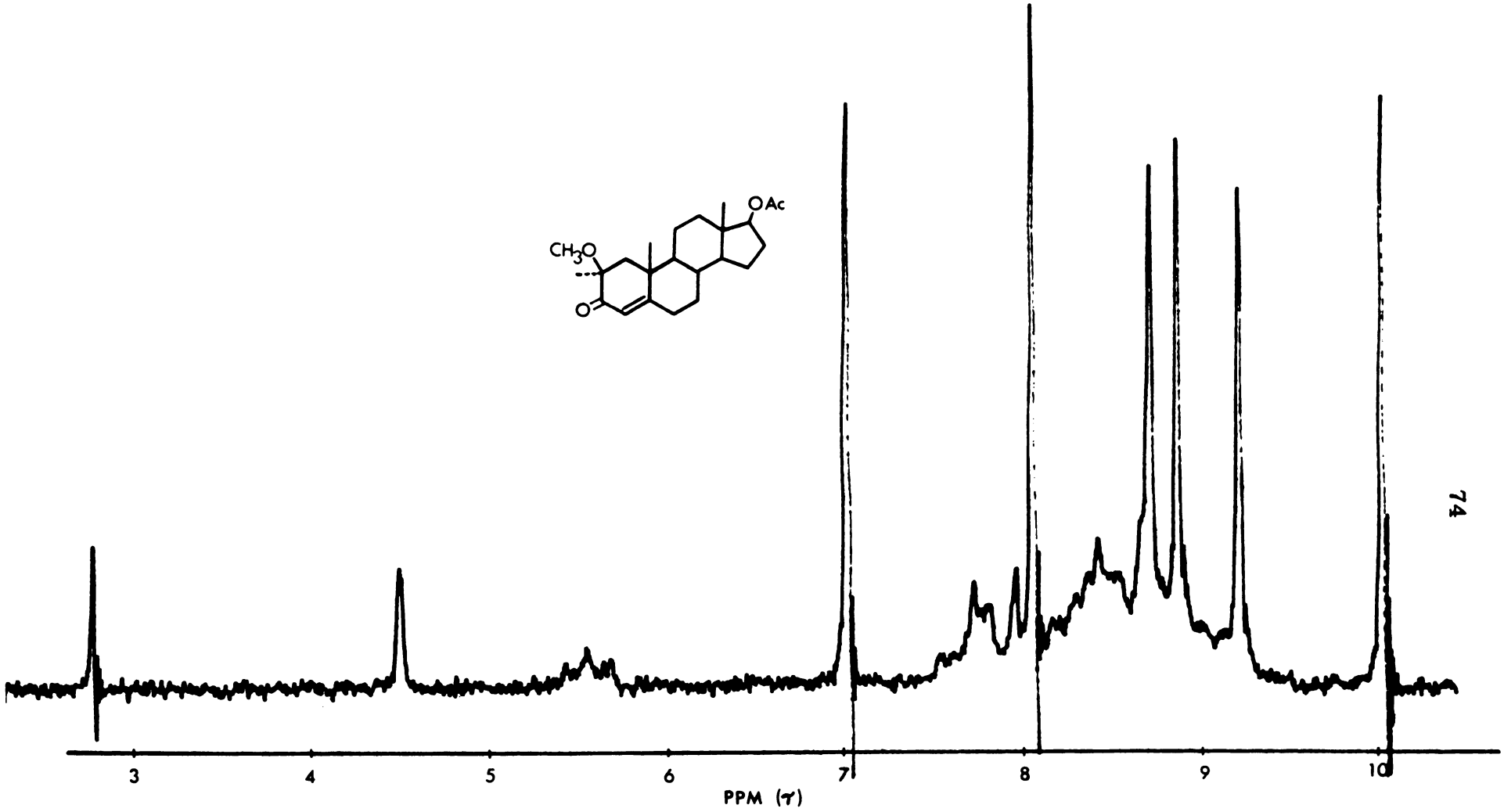

Figure 21. Nmr spectrum of 2-methyl-17β-acetoxy-1,4-androstadiene-3-one.