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METHYLATION OF STEROIDAL C₃-KETONES -
A CONFORMATIONAL ANALYSIS

by

Hyman Stollar

A thesis submitted in partial fulfillment
of the requirements for the degree of

Master of Science

in the

Department of Chemistry

University of Ottawa

Ottawa, Canada

September, 1969



Candidate

H. Stollar

Supervisor

Professor P. Morand

77

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To My
Mother

PREFACE

The fact that conformational deformations produced by substituents in a molecule may be transmitted to remote reaction sites and can thereby influence the course of the reaction was first recognized by D.H.R. Barton in the rates of benzylidene formation in a number of 3-keto steroids, triterpenes, and decalins. The methylation of 3-keto steroids is also subject to conformational transmission effects as shown by the variation of the methylation site (at C₂ or C₄) with different remotely situated substituents. The aim of this thesis is to describe the results of methylation of 5 β -cholest-7-en-3-one (47) and to explain the course of the reaction.

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TABLE OF CONTENTS

	<u>Page No.</u>
Title Page	
Preface	1
Acknowledgments	11
Table of Contents	111
List of Tables	vi
List of Figures	vii
Abstract	viii

INTRODUCTION

Conformation and Conformational Analysis ...	1
Conformation of the Cyclohexane Molecule ...	2
Conformation of Cyclohexene and Bucourt's Rules of Dihedral Angle Changes	4
Conformation of the Steroid Nucleus	8
Conformational Transmission	9
Other Examples of Long Range Effects	14
α -Methylation of 3-Keto Steroids	19
Use of Mass Spectrometry to Analyze Methyl- ation Products	22

DISCUSSION

The Synthesis of 5 β -Cholest-7-en-3-one (47).....	24
Methylation of 5 β -Cholest-7-en-3-one (47).....	26
Mass Spectral Proof of the Structure of the Dimethyl Product	29
The Product of Monomethylation of (47)	33
Application of O.R.D. to the Structural Determination of the Methylation Products	41
Application of Bucourt's Rules in the Methyl- ation of 3-Keto Steroids	46
The Enol Acetylation of 3-Keto Steroids	51

EXPERIMENTAL

General	55
Cholesta-4,7-diene-3-one (49)	56
Catalytic Hydrogenation of Cholesta-4,7-diene- 3-one (49)	56
Methylation of 5 β -Cholest-7-en-3-one (47)	58
2 β -Methyl-5 β -Cholestan-3-one (66)	59
2 β -Methyl-5 β -Cholest-7-en-3-one Ethylene Ketal	61
2 β -Methyl-5 β -Cholestan-3-one Ethylene Ketal ...	62
2,2-Dimethyl-5 β -Cholest-7-en-3-one Ethylene Ketal	62
5 β -Cholest-7-en-3-one Ethylene Ketal	62

Page No.

Claims For Original Research	63
References	64

LIST OF TABLES

<u>Table No.</u>		<u>Page No.</u>
I.	The Direction of Change in the Dihedral Angles in Going from Cyclohexane to Cyclohexene (6).	6
II.	The Relation Between Dihedral Angle Change and Change in Steric Interactions Between Axial Substituents on the Carbon Atoms Forming the Dihedral Angle.	6
III.	Bucourt's Rules of Dihedral Angle Change Interdependences in Fused Six-membered Ring Systems (see (8) and (9)).	6
IV.	Optical Rotatory Dispersion Molecular Amplitudes, a , For Some 3-Keto Steroids.	28
V.	The Relative Abundance of the Mass Spectral Peaks Resulting from "A" and "B" Cleavage in the Ethylene Ketals of Some 3-Keto Steroids.	31
VI.	The Site of Methylation in Some 3-Keto Steroids.	47
VII.	Changes in Some of the Dihedral Angles and Steric Interactions in 5 α - (39) and 5 β -cholestan-3-one (41) as a Result of Enolate Anion Formation.	49
VIII.	The Effect of Unsaturation and of Enolate Anion Formation on Dihedral Angle Changes in Some Unsaturated 3-Keto Steroids.	52

LIST OF FIGURES

<u>Figure No.</u>		<u>Page No.</u>
I.	Some of the compounds whose rates, r , of benzylidene formation at C_2 were studied by Barton.	10
II.	The synthesis of 5β -cholest-7-en-3-one (47).	24
III.	Optical rotatory dispersion curves of 5β -cholest-7-en-3-one (47), 2,2-dimethyl- 5β -cholest-7-en-3-one (63), 2 β -methyl- 5β -cholest-7-en-3-one (62), and 2 β -methyl- 5β -cholestan-3-one (66).	27
IV.	The origin of the peaks at m/e 99, 112, and 125 in the mass spectra of the ethylene ketals of 3-keto steroids.	30
V.	The mass spectrum of the ethylene ketal of 2,2-dimethyl- 5β -cholest-7-en-3-one (63).	34
VI.	The mass spectrum of the ethylene ketal of 2 β -methyl- 5β -cholest-7-en-3-one (62).	36
VII.	The products of methylation of 5β -cholest-7-en-3-one (47) and the conversion of the monomethyl product to 2 β -methyl- 5β -cholestan-3-one (66).	38
VIII.	The mass spectrum of 2 β -methyl- 5β -cholestan-3-one (66).	39
IX.	Octant diagram for substituents at C_2 and C_4 in 5α - and 5β -3-keto steroids.	42

ABSTRACT

The synthesis of 5β -cholest-7-en-3-one (47) is described. Methylation of this compound results in 2β -methyl- 5β -cholest-7-en-3-one (62) and 2,2-dimethyl- 5β -cholest-7-en-3-one (63). The structure of (62) was proven by its conversion to the known 2β -methyl- 5β -cholestan-3-one (66). An explanation is offered for the uncharacteristic mass spectrum exhibited by the ethylene ketal of (62). The structure of (63) was proven primarily from the mass spectrum of its ethylene ketal. The optical rotatory dispersion curves of the above compounds are reported and discussed. The fact that methylation of (47) occurs at C_2 rather than C_4 is explained by invoking conformational transmission effects in the enolate anion formation step in the reaction. Use is made of Eucourt's rules of dihedral angle changes in describing the conformational transmission effects. Enol acetylation of (47) results in a large predominance of the C_2 , C_3 unsaturated enol acetate.

INTRODUCTION

Conformation and Conformational Analysis

It is both a stimulating challenge and a fascination for the organic chemist to account for the physical properties of organic compounds and to explain the manner in which chemical reactions proceed. In order to help him in these pursuits, increasingly detailed and subtle concepts have been postulated to describe the spatial arrangement of the atoms that comprise a molecule. The study of the relative positions of the atoms in a molecule is called stereochemistry and a very important aspect of stereochemistry is that of conformation.

The conformations of a molecule are the different arrangements in space of the atoms of a molecule that can arise by the rotation or twisting (but not breaking) of bonds in the molecule. Conformations may be considered as "rotational isomers".

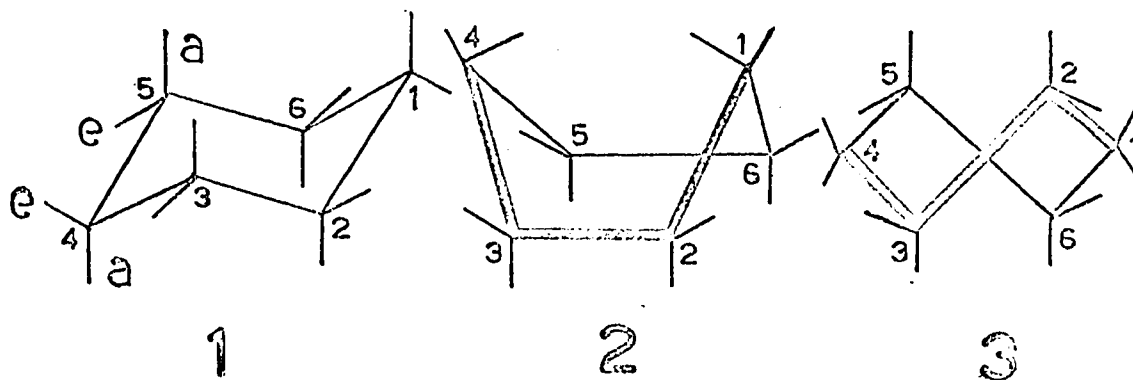
It is important to differentiate between conformation and configuration, the latter designating the stereochemistry at an asymmetric centre in the molecule. To transform one configuration of a molecule into another, it is necessary to break bonds whereas in the case of conformations, a rotation or twisting of bonds is required.

Those investigations which deal with the determin-

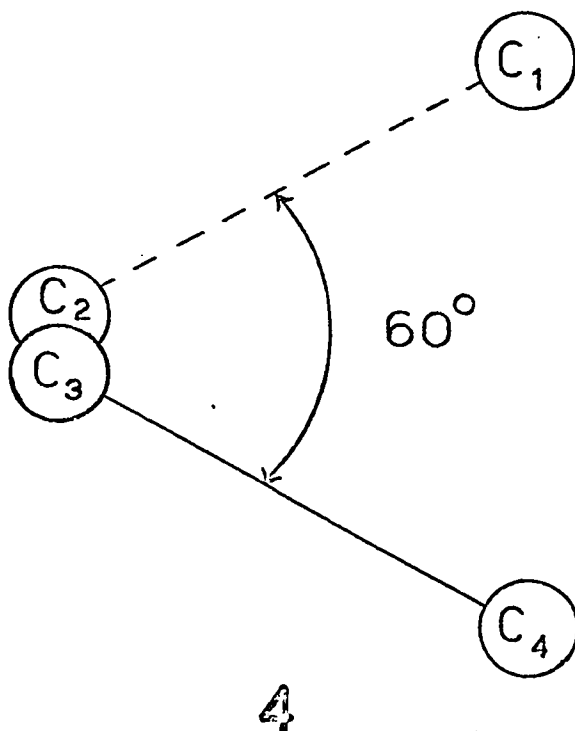
ation of the conformations of molecules and the effects that different conformations exert on the rate and direction of chemical reactions, are included in the concept of conformational analysis. The basic idea of conformational analysis is that chemical and physical properties of organic compounds are related to preferred conformations. This principle, applied to cyclohexane derivatives, was first clearly stated by Barton¹ in 1950 and was later elaborated upon² in 1953. Two books^{3,4} and a review⁵ dealing with conformational analysis have recently appeared in which the basic principles are expounded.

Conformation of the Cyclohexane Molecule

It is currently believed that the cyclohexane ring may exist in two basic forms, a rigid form commonly called the chair form (1), and a mobile one which can be easily distorted into a number of shapes, one of which resembles a boat (2), the others having a twisted conformation, e.g. (3).



In describing the conformations that result from rotation or twisting about a single bond, it is useful to consider the dihedral angles in a molecule. The dihedral angle $C_1-C_2-C_3-C_4$ in the chair form (1) of cyclohexane is shown in (4).



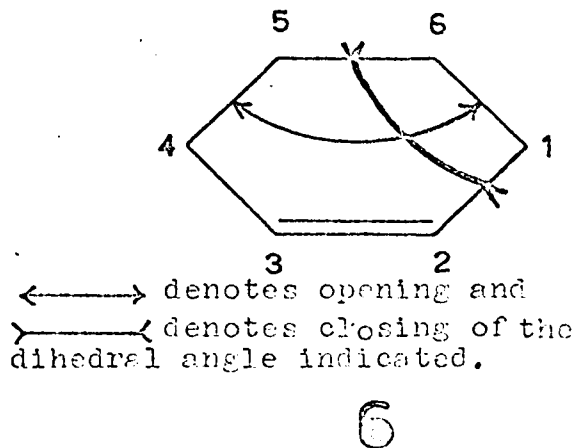
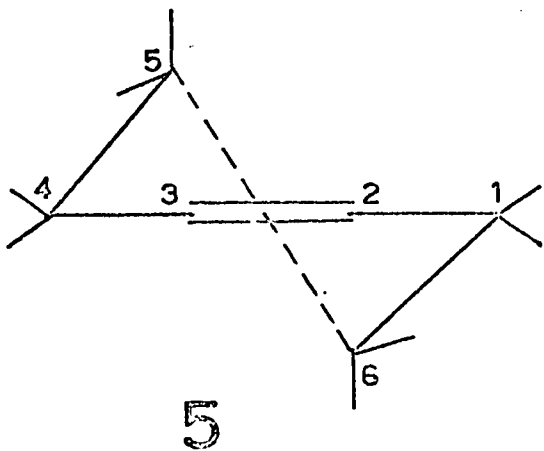
There are six equal dihedral angles of 60° each in the chair conformation of cyclohexane and steric interactions within the molecule are thereby reduced to a minimum. The boat form has two dihedral angles of 0° and four of 60° . This results in two pairs of eclipsed interactions at C_2, C_6 and C_3, C_5 respectively (see (2)) and a C_1, C_4 "bow-stern" interaction thereby making the boat form less stable than the chair form. The twist- or skew-boat

form is slightly more stable than the boat form because the highly energetic eclipsed interactions in the latter are partially relieved in the former conformation.

It can be seen from (1) that two types of carbon-hydrogen bonds exist in the chair form of cyclohexane; those which lie perpendicular to the plane of the ring, called axial (a) bonds, and those that lie essentially in the plane of the ring, designated equatorial (e) bonds. Among the non-bonded interactions in the chair form, the 1,3 - interactions between axial substituents and 1,2 - interactions between equatorial substituents are especially important.

Conformation of Cyclohexene and Eucourt's Rules of Dihedral Angle Changes

The introduction of unsaturation into the cyclohexane ring, as in cyclohexene, causes the normal chair conformation to be distorted to that of a "half-chair" (5) in which C_1 , C_2 , C_3 , and C_4 are coplanar.



By means of vectorial calculations, Bucourt^{6,7,8} studied the effects of changes in dihedral angles on the geometry of the cyclohexane ring. He found that when the dihedral angle $C_1-C_2-C_3-C_4$ (4) in cyclohexane (1) is decreased to 0° in forming cyclohexene (5), changes occur in the other dihedral angles in the ring. Thus, the "para" dihedral angle $C_4-C_5-C_6-C_1$ (6) is opened or increased to 70° , an increase of 10° above the value found in cyclohexane, while the "meta" dihedral angle $C_2-C_1-C_6-C_5$ is closed or decreased by 10° from the normal value of 60° in cyclohexane, as shown in Table I.

Changes in the dihedral angles in cyclohexane are associated with changes in the distances between axial substituents on the ring and a resultant alteration of steric interactions. Thus the axial substituents A_1, A_3 and A_2, A_4 (7) on the carbon atoms forming the dihedral angle $C_1-C_2-C_3-C_4$ approach one another when the angle is opened and move away from each other when the angle is closed. These relationships are shown in Table II. In addition, the same relations hold between changes in the dihedral angle $C_1-C_2-C_3-C_4$ and changes in steric interactions between A_5 and A_3 and A_1 , although these interaction changes are smaller than the ones described above.

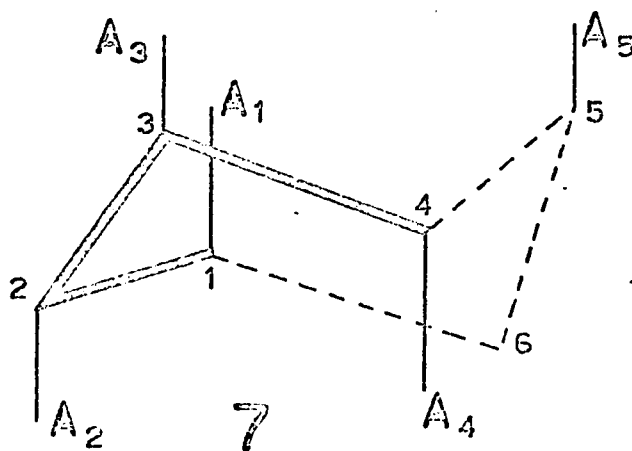


Table I The Direction of Change in the Dihedral Angles in Going from Cyclohexane to Cyclohexene (6).

Position of Dihedral Angle With Respect to the Double Bond	Change in Dihedral Angle
<u>meta</u>	closed
<u>para</u>	opened

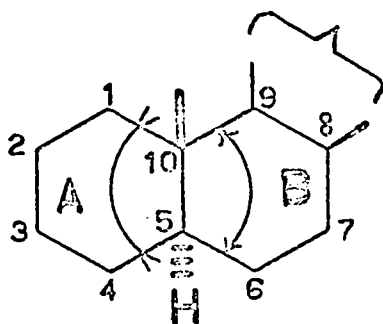
Table II The Relation Between Dihedral Angle Change and Change in Steric Interactions Between Axial Substituents on the Carbon Atoms Forming the Dihedral Angle.

Change in Dihedral Angle	Change in Steric Interactions
opened	greater
closed	smaller

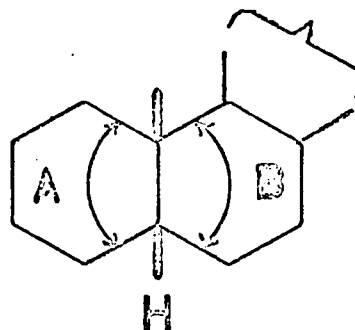
Table III Bucourt's Rules of Dihedral Angle Change Interdependences in Fused Six-membered Ring Systems (see (8) and (9)).

Relationship of Dihedral Angles	Direction of Change (Opening or Closing) in One Angle With Respect to Change in the Other
corresponding angles about the common bond in <u>trans</u> -fused ring systems	opposite
corresponding angles about the common bond in <u>cis</u> -fused ring systems	same

Bucourt's calculations applied to fused six-membered ring systems indicate that deformations produced in one ring may be transmitted to adjacent rings in a specific manner. In trans-fused systems, e.g. (8), if a deformation occurs in the dihedral angle about the bond common to both rings, e.g. angle $C_6-C_5-C_{10}-C_9$ in ring B, then the corresponding dihedral angle in ring A, angle $C_4-C_5-C_{10}-C_1$ undergoes a deformation of the same magnitude but of opposite direction. In cis-fused ring systems, e.g. (9), a similar relation exists except that the deformations of the dihedral angles are of the same direction as well as magnitude. These dihedral angle change interdependences are summarized in Table III and they may be readily seen using molecular models.



8

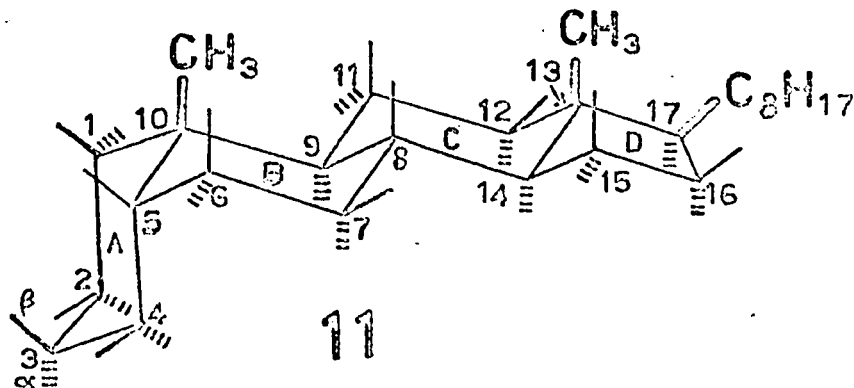
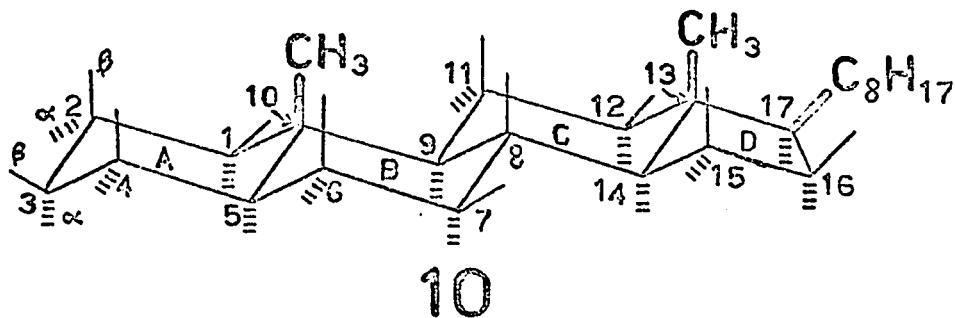


9

Conformation of the Steroid Nucleus

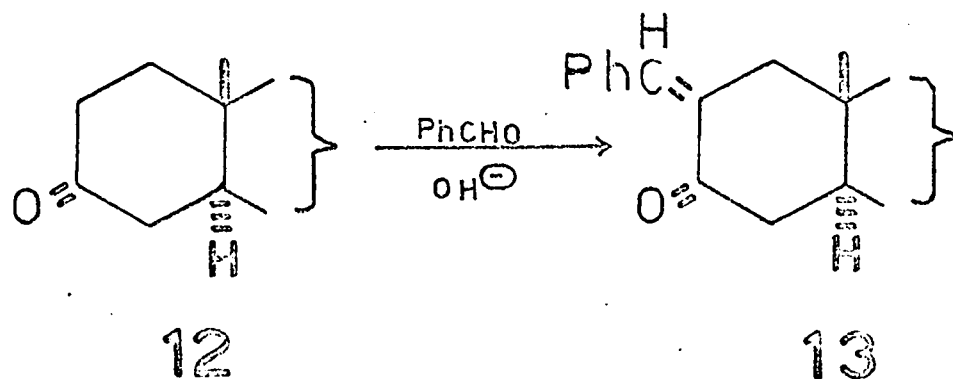
Since the chair form of cyclohexane is the most stable, it is assumed that the preferred conformation for the steroid nucleus is the one in which the three six-membered rings are all in the chair form.⁹ The steroid nucleus is therefore a rigid system and is one in which the conformation is fixed or "frozen". Occasionally, one of the rings may assume the boat form when particular substituents are present in the steroid nucleus.¹⁰

Steroid numbering is as indicated in (10) and (11) and the rings are designated by capital letters. In 5 α -cholestane (10), all the ring junctions are trans whereas in 5 β -cholestane (11), the A/B ring junction is cis while the others are trans. Substituents pointing upward (solid lines) are designated " β " and those pointing downward (dashed lines) are designated " α ".



Conformational Transmission

In a series of papers,^{11, 12, 13} Barton reported the results of studies on the base-catalyzed aldol condensation of benzaldehyde with a wide range of variously substituted 3- keto triterpenes, steroids, and decalins to give benzylidene derivatives at C₂. The reaction may be represented as follows:



He found that the rate of condensation varied quite widely and was markedly influenced by the presence of unsaturated substituents at positions in the molecules remote from the reaction site. Based on the condensation rate, r , for 5 α -lanost-8-en-3-one (14) arbitrarily set at 100, the relative rates of several of the compounds studied by Barton¹³ are shown in Figure I. It can be seen

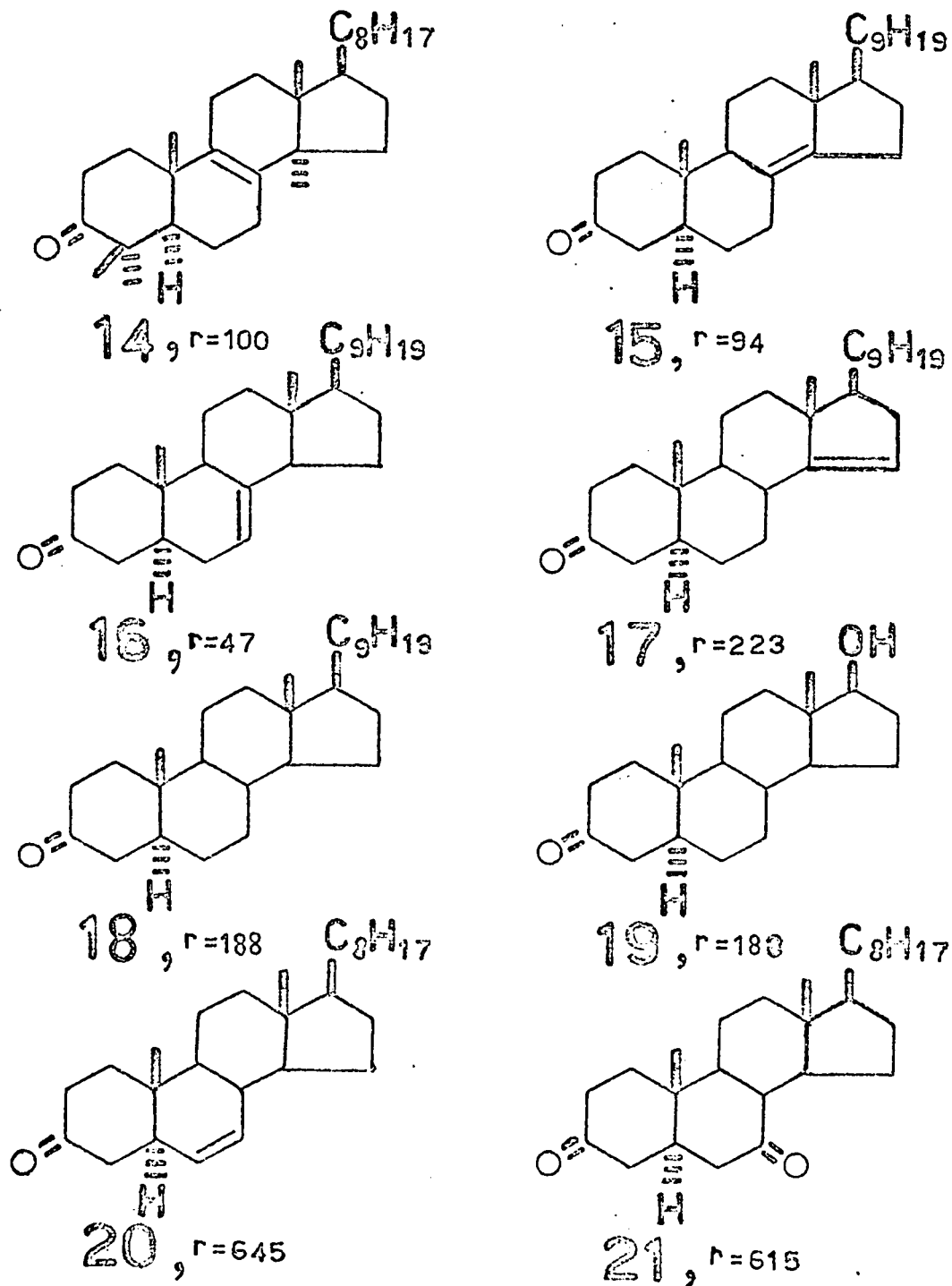


Figure I. Some of the Compounds Whose Rates, r^* , of Benzylidene Formation at C_2 were Studied by Barton.¹³

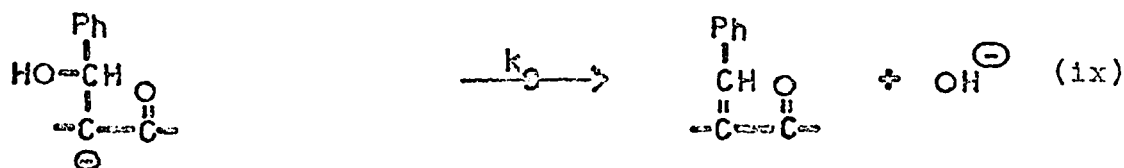
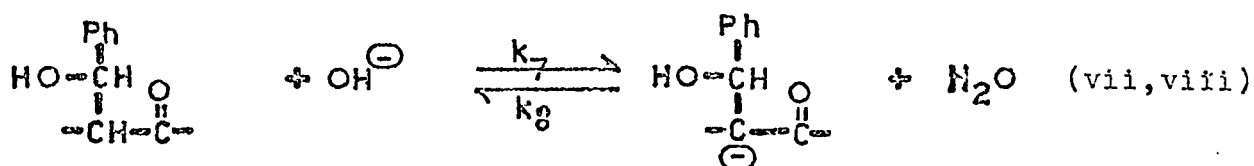
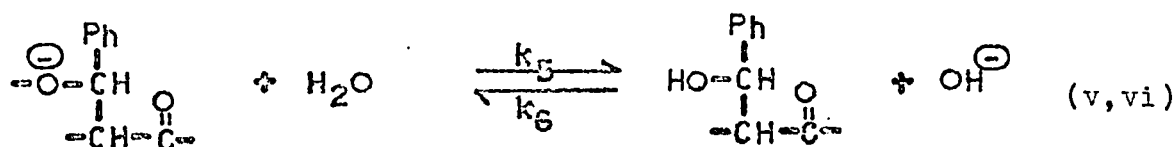
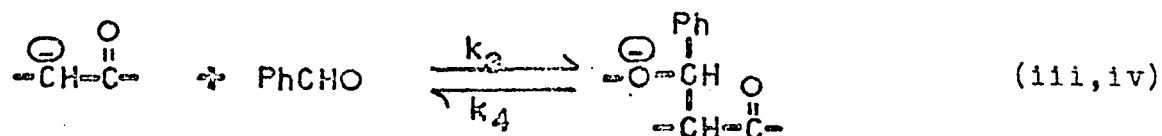
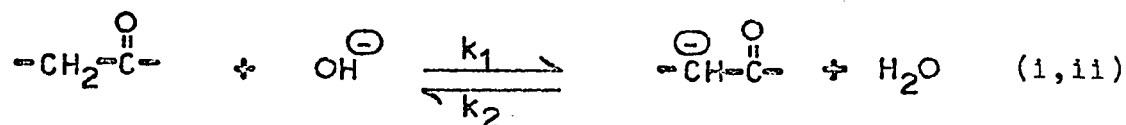
* The relative rates, r , are based on that of 5 α -lanost-8-en-3-one (14) equaling 100.

that a change in the location of the double bond from the 8,9 position to the 7,8 position in 5 α -ergost-7-en-3-one (16) caused the rate to decrease by about half to 47 while the presence of a 6,7-double bond in 5 α -cholest-6-en-3-one (20) resulted in an increase in the rate to 645, which is about fourteen times that for the compound having a 7,8-double bond (16).

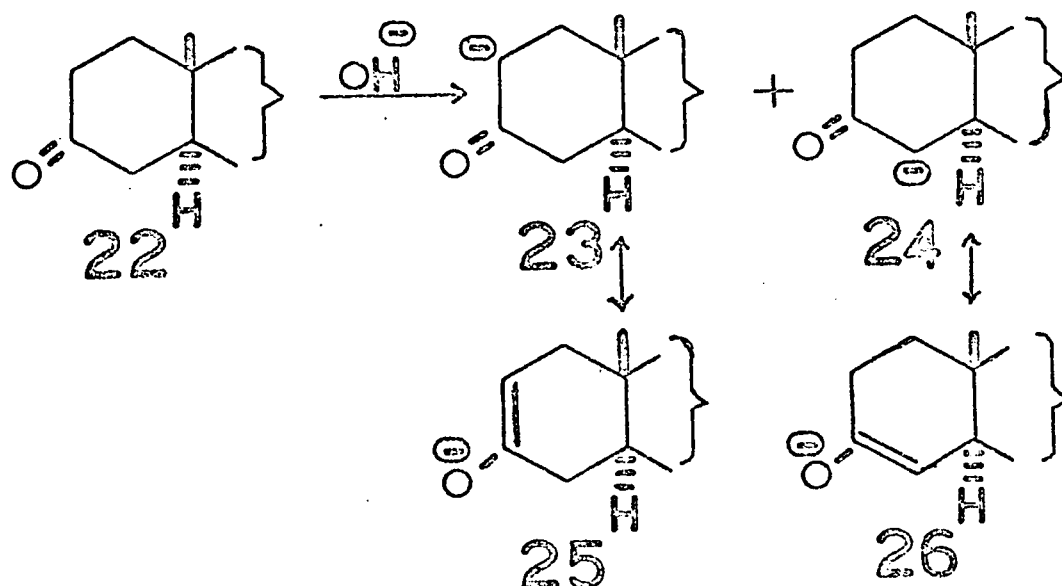
Throughout the various steroid series examined, it was found that the effect of any one substituent was consistent. For example, a 7,8-double bond always diminished the condensation rate compared with that of the analogous saturated compound, while a 6,7-double bond increased the rate.

Barton rejected the idea that the variation in the rates was caused by electrostatic or bond induction effects. He concluded that the rate differences were caused by conformational distortions in the molecule produced by unsaturated substituents, the distortions being transmitted through the molecule to the reaction site by a slight bending of dihedral angles and alterations of atomic co-ordinates, although he did not go into detail on this latter point. This effect was termed conformational transmission by Barton.

Based on the work of Noyce and Reed¹⁴ and Stiles, Wolf, and Hudson¹⁵, Barton formulated the mechanism for his base-catalyzed reaction as follows:



The first step is the formation of an enolate anion and in a 3-keto steroid such as (22) the enolization may occur in two directions, towards C₂ (23, 25) and towards C₄ (24, 26).



Barton postulated that the change in rate of benzylidene formation at C_2 caused by the introduction of an unsaturated substituent at a site remote from the A-ring in the steroid nucleus was a reflection of the ability of the unsaturated substituent to induce preferential enolization either towards C_2 or C_4 . A 7,8-double bond was assumed to cause preferential enolization towards C_4 and while it is reasonable to expect benzylidene formation at C_4 in steroids containing a 7,8-double bond, only the C_2 -isomer was detected by Barton. He explained the exclusive formation of C_2 -condensation product by supposing

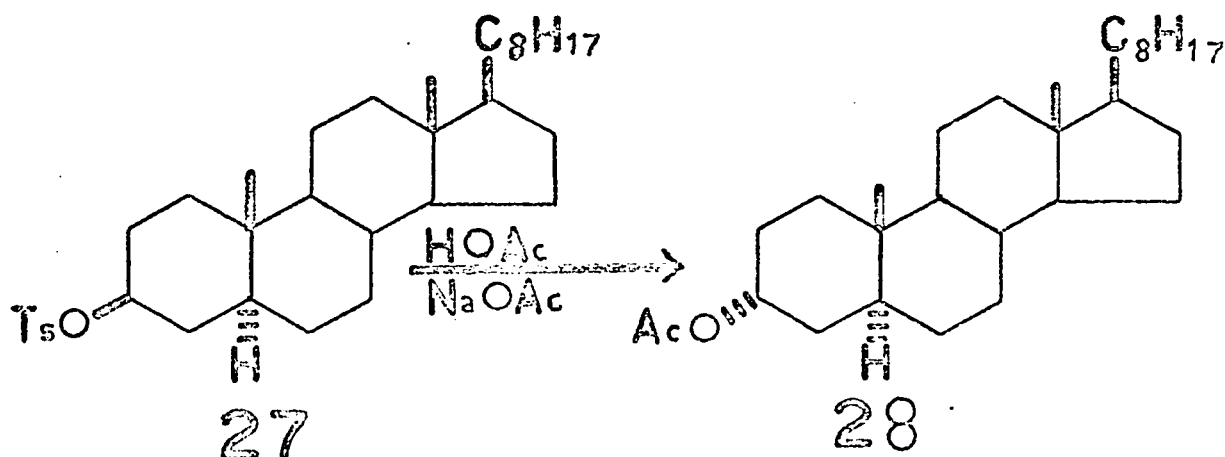
that the reverse aldol step (iv) in the above mechanism is more favourable at C_4 than at C_2 because the C_4 position is subject to extra steric hindrance by the 6-methylene group. The net rate for the formation of a 4-benzylidene derivative is, thus, very low. Barton therefore concluded that in steroids containing a 7,8-double bond preferential enolization towards C_4 is not reflected in benzylidene formation at C_4 but, rather, in a diminished rate of benzylidene formation at C_2 . On the other hand, a 6,7-double bond was assumed to induce preferential enolization towards C_2 , the required enolate anion for benzylidene formation at C_2 , and this results in an increased condensation rate in steroids containing a 6,7-double bond.

With the aid of molecular models, Robinson and Whalley¹⁶ were able to account in a semiquantitative manner for the way in which conformational deformations caused by unsaturated substituents in the steroid molecule are transmitted to the A-ring. Bucourt was also able to account for these conformational transmissions using his rules of dihedral angle changes described above, and more will be said about this later.

Other Examples of Long Range Effects

Baker and Hudec¹⁷ found a parallel between the rate of acetolysis (27, 28) of steroidal 3-tosylates containing

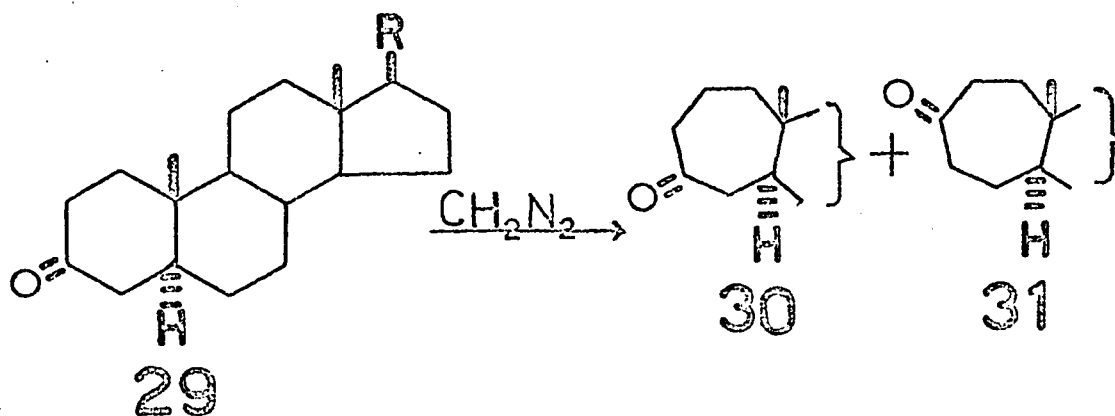
unsaturated substituents remote from the A-ring, and the rate of 2-benzylidene formation in the analogously substituted 3-keto steroids, observed by Barton. Thus,



the introduction of a 7,8-double bond into (27) lowered the acetolysis rate by about 60% whereas the presence of a 6,7-, 8,9-, or 8,14-double bond in (27) caused an increase in the rate relative to that of the compound with a 7,8-double bond, in a manner similar to that observed by Barton. The authors link the increased acetolysis rates with the presence of substituents that open the C₁-C₂-C₃-C₄ dihedral angle and the decreased rates with the presence of substituents that close this angle, although they are unable to account for the change in rate with changes in the dihedral angle.

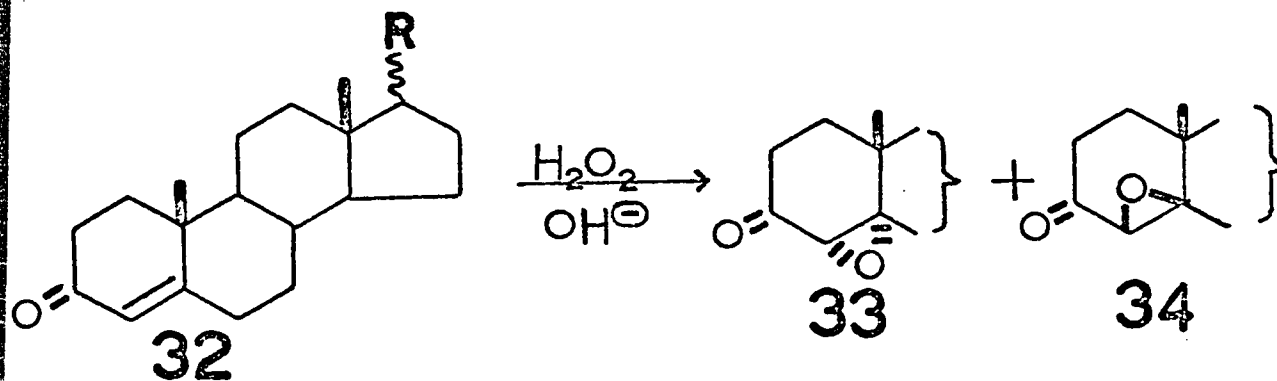
A long range effect apparently caused by different C₁₇ side chains has recently been reported. The

diazomethane homologation of 3-keto steroids may give two isomeric products as follows:



Jones and Zonder¹⁸ observed that with $\text{R}=\text{H}$, OH , or OAc , the ratio of (30):(31) was about 40:60. However, with $\text{R}=\text{C}_8\text{H}_{17}$, the ratio became 80:20. In the 5β -series the ratio was 50:50 with $\text{R}=\text{OH}$, but with $\text{R}=\text{C}_8\text{H}_{17}$, the ratio became 20:80, a reversal of the result in the 5α -series. The authors were unable to explain this long range effect in terms of polar or conformational transmission effects. It is of interest to note that Barton did not observe any effects due to different side chains.

Another example of the directive effect of C_{17} side chains has recently been reported. The epoxidation of 4,5-unsaturated 3-keto steroids (32) may result in both the α -(33) and β -(34) epoxides. Henbest and Jackson¹⁹ observed that no α -epoxide was obtained with non-polar side chains but up to 60% of α -epoxide may be obtained with polar



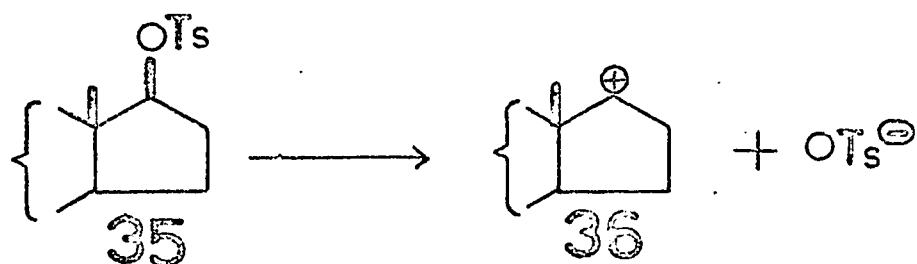
substituents. For example, with $\text{R}=\beta\text{-H}$ or $\beta\text{-C}_8\text{H}_{17}$, no (33) was obtained but a 30% yield of (33) was achieved with $\text{R}=\alpha\text{-OH}$. With $\text{R}=\beta\text{-CO}_2^-$, 60% of (33) was obtained. A similar directing effect was also noted for polar groups at C_{11} . The results were explained as being due to intramolecular electrostatic interactions by the polar substituents, which favour the formation of the α -epoxides.

Other examples of remote substituents affecting reactions occurring at the A-ring of steroids are the rate of formation and hydrolysis of thiosemicarbazones of 4,5-unsaturated 3-keto steroids²⁰ and the dissociation rate of the cyanohydrins of 3-keto steroids²¹.

Several examples of reactions occurring at the D-ring of steroids, in which the effects of remote substituents are invoked, have been reported. Mathieu, et al.²² reported a variation of the solvolysis rate of 17 β -tosylates with the degree of unsaturation in ring A.

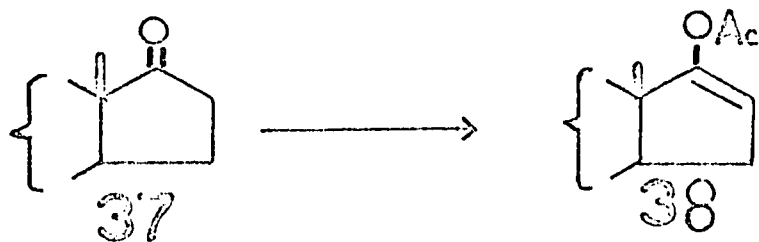
They observed that, in general, the greater the unsaturation in ring A, the smaller the rate of solvolysis of the 17 β -tosylate.

The reaction may be represented as follows:



Formation of the trigonal carbon in (36) involves overcoming a strain because the trigonal carbon causes the D-ring to become flattened. The authors suggest that additional strain resulting from unsaturation in ring A is transmitted to the D-ring by conformational transmission. The increased strain in ring D results in a reluctance to form the trigonal carbon at C₁₇ which is reflected in lower solvolysis rates.

A similar effect was noted by Fishman and Guzik²³ who obtained greatly decreased yields of enol acetates of 16- and 17-keto steroids, a reaction (38) which involves trigonal carbon formation, in compounds containing unsaturated A-rings.

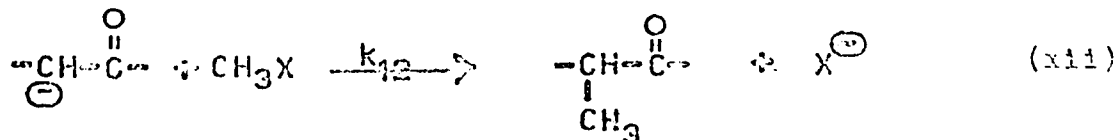
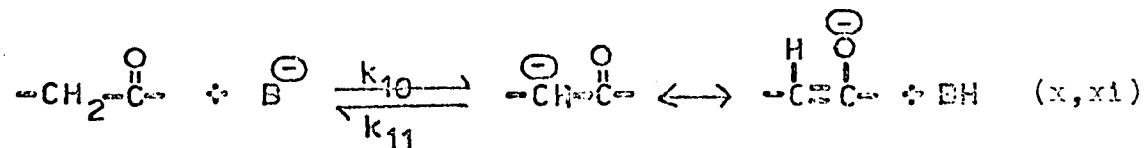


Using information obtained from x-ray crystallography, Geise, et al.²⁴ have found that the all trans steroid nucleus (10) is somewhat bent convex towards the β -side and is not flat as one might be led to believe by considering the steroid nucleus as being built up of cyclohexane building blocks. However, it is necessary to take into account interactions present in the steroid nucleus but which are not present in the cyclohexane unit. The reason proposed for the bending of the steroid nucleus is that this is the result of interactions between the axial methyl groups at C₁₀ and C₁₃ and the axial hydrogens attached to C₈ and C₁₁.

An interesting point which the authors do not make is that molecular models do not take into account the bent nature of the steroid nucleus and they are therefore fundamentally slightly inaccurate when representing steroids.

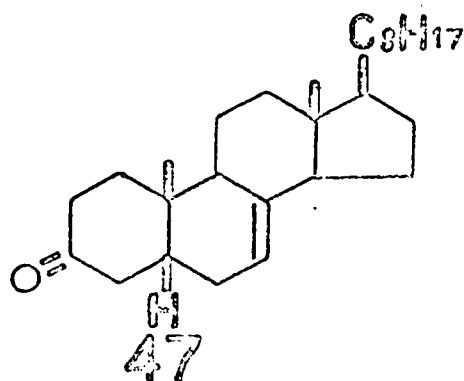
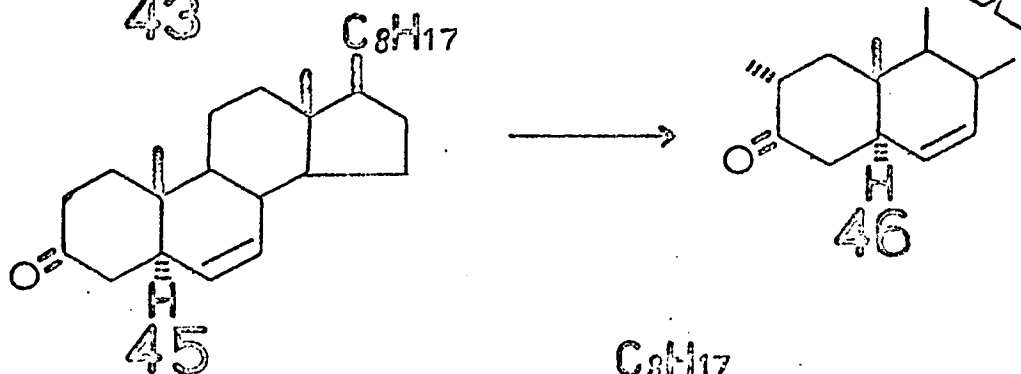
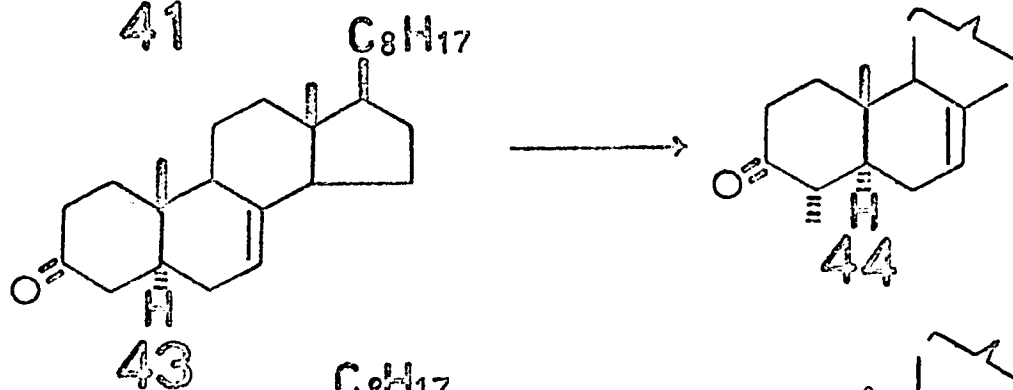
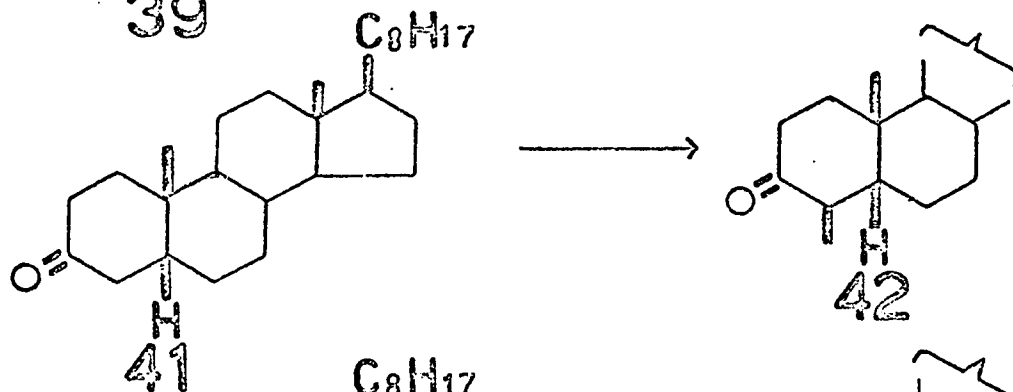
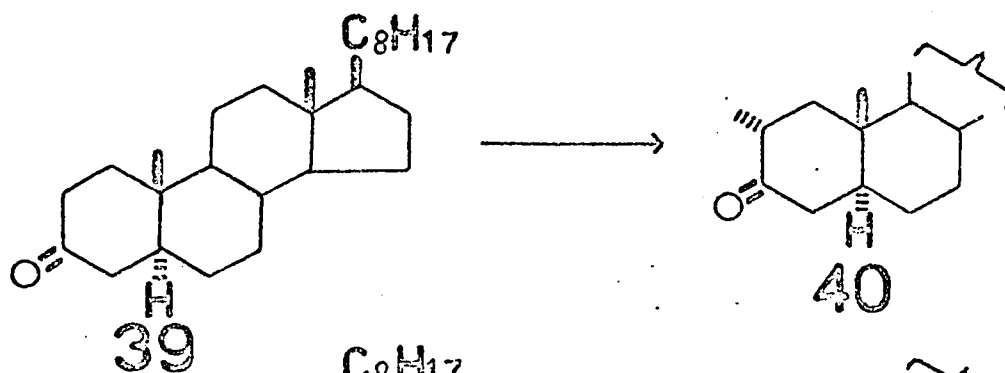
α -Methylation of 3-Keto Steroids

The mechanism^{25,26} for the base-catalyzed methylation of ketones may be represented as follows:



Since the first step in this reaction is the formation of an enolate anion, as is also the case in benzylidene formation, it may be expected that the alkylation of 3-keto steroids should be subject to similar conformational transmission effects that Barton detected in his benzaldehyde condensation reactions. This seems to be the case. For example, while the methylation of 5 α -cholestan-3-one (39) results in the 2-methyl derivative (40), 5 β -cholestan-3-one (41) gives the 4-methyl derivative (42)²⁷. The presence of a 7,8-double bond in 5 α -cholest-7-en-3-one (43) causes methylation to occur at C₄ also, resulting in compound (44)^{28,29} while in 5 α -cholest-6-en-3-one (45) the 2-methyl isomer (46) is formed¹⁰.

Whereas the benzaldehyde condensation reaction results in the exclusive formation of the 2-benzylidene product, in the methylation of 3-keto steroids both 2-methyl and 4-methyl products are formed, depending on the ketone. The difference between the two reactions may be explained by the fact that the carbon-carbon bond formation step in the benzaldehyde reaction, (iii), is reversible and the reaction can therefore equilibrate towards the more stable C₂-product even in compounds where enolization is preferentially towards C₄. In this reaction, the rate of formation of 2-benzylidene product reflects the direction of preferred enolization. In the methylation reaction, the carbon-carbon bond formation step, (xii), is irreversible and



the position of the methyl group in the product reflects the direction of preferential enolization in the reactant.

It appears that in the methylation reaction in the cholestan-3-one series two different structural features have the same effect in directing the site of methylation. The presence of either a 5β -hydrogen as in (41) or a 7,8-double bond as in (43) causes methylation to occur at C_4 whereas in the 5α saturated compound (39), methylation occurs at C_2 . It therefore was of interest to us to synthesize the compound in which both of these 4-methylation directing structural features are present, namely 5β -cholest-7-en-3-one (47), and to methylate it in order to determine whether these two structural features would exert parallel effects in such a system and cause methylation to occur at C_4 .

Use of Mass Spectrometry to Analyze Methylation Products

It has been found that very subtle structural changes may radically alter the mass spectral fragmentation patterns of steroidal ketones, ^{in an unpredictable manner,} Therefore, a correlation between cracking pattern and structure is not generally feasible³⁰. The introduction of such functional groups as dimethylamino, ethylene thioketals, and ethylene ketals, which contain hetero atoms, results in simplified spectra which are more easily interpreted. This is due to the ability of the hetero atoms to stabilize positive charge,

which results from electron bombardment in the mass spectrometer, and thereby to direct fragmentation in a predictable manner. Thus, the mass spectra of the ethylene ketals of 3-keto steroids exhibit three main peaks at m/e 99, 112, and 125^{31, 32}. The presence of methyl substituents at C₂ and C₄ alters the relative abundance of these three peaks in a characteristic manner. In this way it has been possible³² to distinguish between 2-methyl- and 4-methyl-3-keto steroids and we expected to make use of this technique in our investigation of the methylation of 5 β -cholest-7-en-3-one (47).

DISCUSSION

The Synthesis of 5 β -Cholest-7-en-3-one (47)

Synthesis of the desired compound, 5 β -cholest-7-en-one (47), was achieved in two steps from the commercially available cholesta-5,7-diene-3 β -ol (7-dehydrocholesterol, 48), as shown in Figure II. Oppenauer oxidation of the latter compound, according to the procedure of Cohen *et al.*³³, gave the known cholesta-4,7-diene-3-one (49) which was catalytically hydrogenated over palladium on charcoal following the procedure^{34,35} used for the hydrogenation of cholest-4-en-3-one (50) to 5 β -cholestan-3-one (41). Under these conditions the 7,8-double bond is not hydrogenated, however, it is prone to migrate to the 8,14-position³⁶. The desired 5 β -cholest-7-en-3-one (47) was obtained in 50% yield by chromatography of the crude

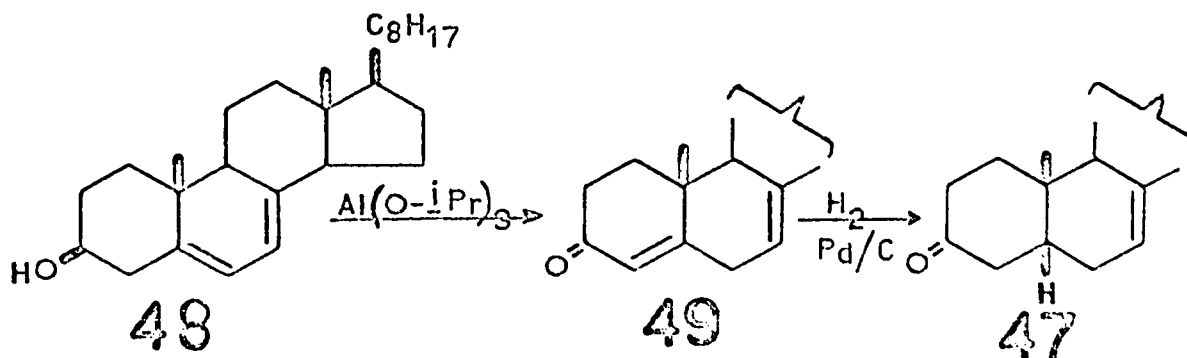
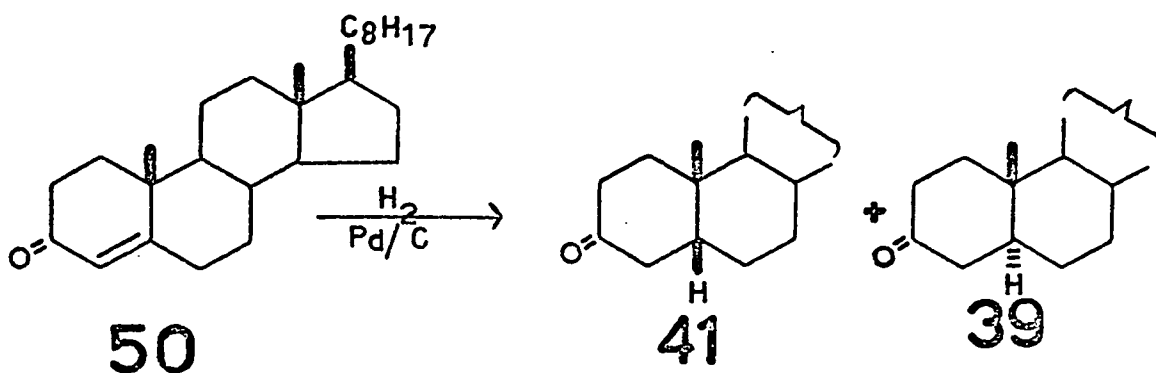


Figure II. The Synthesis of 5 β -Cholest-7-en-3-one (47).



hydrogenation product on silica gel using a large ratio of adsorbant to product (750 g/g) but even with such a large ratio, the separation was incomplete. The catalytic hydrogenation of (50) is known³⁷ to produce about a 25% yield of the 5 α -epimer (39), however, none of the corresponding 5 α -epimer (43) was isolated due to the incomplete separation.

Evidence for structure (47) was as follows. Confirmation of the molecular weight was obtained by the appearance of a parent molecular ion (p.m.i.) peak at m/e 384 in the mass spectrum. The presence of a ketone function was indicated by an infrared (i.r.) absorption at 1715 cm^{-1} as well as the fact that (47) formed an ethylene ketal. The presence of the 7,8-double bond was shown by a broad nuclear magnetic resonance (n.m.r.) peak at 5.13δ ³⁸ and the double bond was confirmed by an i.r. absorption peak at 1665 cm^{-1} . An 8,14-double bond, which might have been formed during the

hydrogenation, would show no olefin absorption in the n.m.r. spectrum since it would be tetrasubstituted. The 5 β -stereochemistry of (47) stems from the fact that its m.p. and specific rotation differed from those of the known 5 α -epimer (43). Furthermore, the optical rotatory dispersion (o.r.d.) curve of (47), Figure III, showed a negative Cotton effect as does 5 β -cholestan-3-one (41) whereas analogous 5 α -steroids, such as 5 α -ergost-7-en-3-one (16) and 5 α -cholestan-3-one (39) show strong positive Cotton effects as shown in Table IV. Indeed, the o.r.d. curve of the 5 α -epimer (43) shows a strong positive Cotton effect (see Table IV).

Methylation of 5 β -Cholest-7-en-3-one (47)

The procedure of Mazur and Sondheimer²⁹ was used for the methylation of (47). Two methylation products were isolated by chromatography on alumina, a more mobile one obtained as an oil in 24% yield and a less mobile crystalline product obtained in 53% yield, taking into account recovered starting material.

A mass spectrum of the oily product showed a p.m.i. at m/e 412 indicating a dimethyl derivative. The i.r. spectrum had a carbonyl absorption at 1700 cm^{-1} , a decrease of 15 cm^{-1} compared with that of the unmethylated compound. Mazur and Sondheimer observed²⁷ a similar lowering of the carbonyl stretching frequency

Figure III. Optical rotatory dispersion curves of 5 β -cholest-7-en-3-one (47), 2,2-dimethyl-5 β -cholest-7-en-3-one (63), 2 β -methyl-5 β -cholest-7-en-3-one (62), and 2 β -methyl-5 β -cholestan-3-one (66).

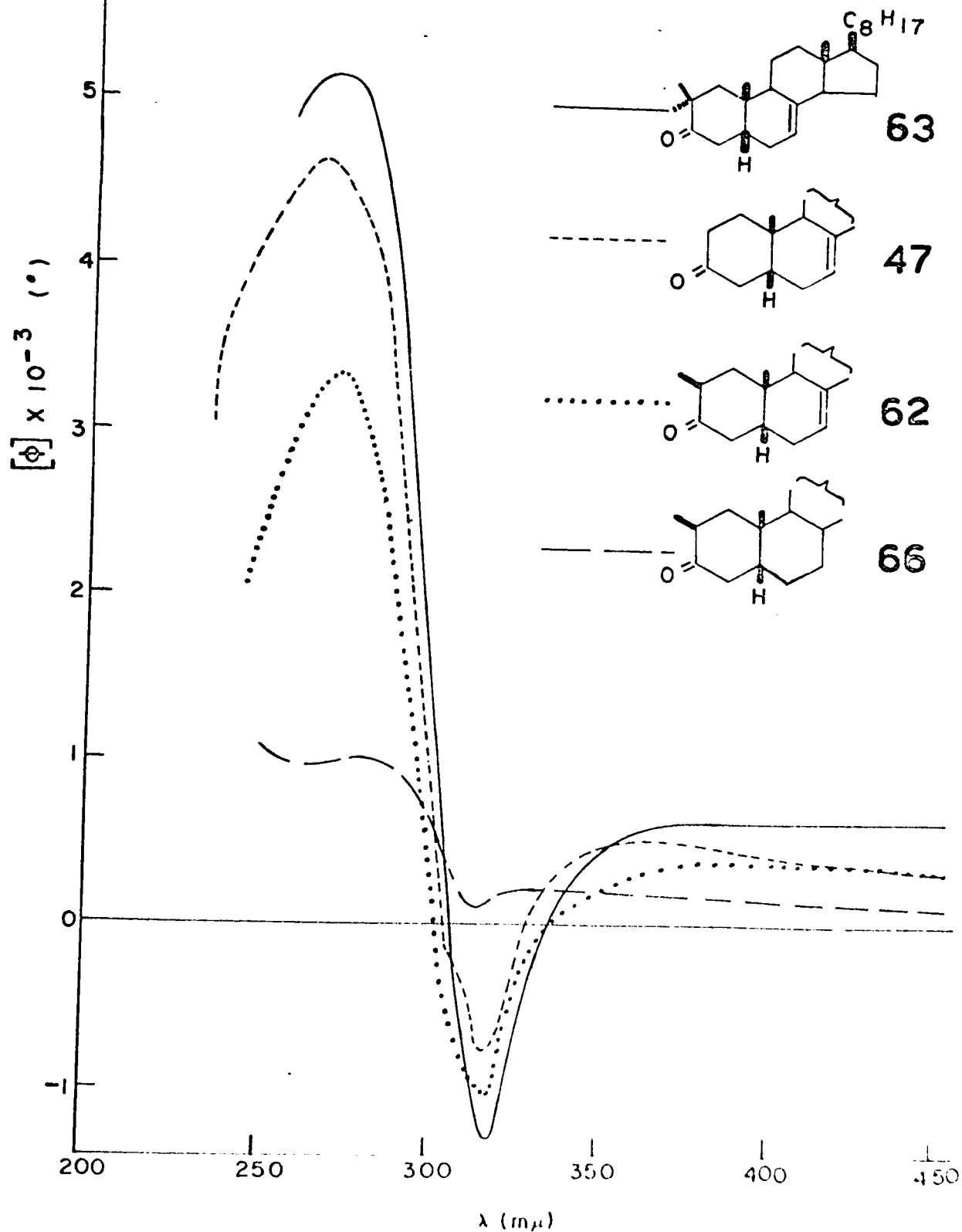


Table IV Optical Rotatory Dispersion Molecular Amplitudes, a,* For Some 3-Keto Steroids

Compound	Molecular Amplitude, <u>a</u> , (degrees)	Reference
5 β -cholest-7-en-3-one (47)	-54	
5 β -cholestan-3-one (41)	-25	41
5 α -ergost-7-en-3-one (16)	+52	42
5 α -cholestan-3-one (39)	+65	43
5 α -cholest-7-en-3-one (43)	+63	44
2 α -methyl-5 α -cholestan-3-one (40)	+63	42
2 β -methyl-5 α -cholestan-3-one (67)	+73	42
4,4-dimethyl-5 α -cholestan-3-one (61)	-11	42
4,4-dimethyl-5 β -cholestan-3-one (68)	-27	45
2,2-dimethyl-5 β -cholest-7-en-3-one (63)	-65	
2 β -methyl-5 β -cholest-7-en-3-one (62)	-44	
2 β -methyl-5 β -cholestan-3-one (66)	- 8*, -9.8 [≠]	42

* For a definition of molecular amplitude, a, see P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry", Holden-Day, San Francisco, 1965, p. 17.

** This value was obtained in this laboratory, (see Figure III).

≠ The o.r.d. curve for this compound, reported in reference 42, terminated just before the peak at 280 m μ was reached. Hence the value for a is slightly more negative than here indicated.

for C₂- and C₄- gem dimethyl derivatives in the saturated 5 α -cholestan-3-one series. The 7,8-double bond was unaffected by the methylation reaction as shown by a broad signal at 5.18 δ in the n.m.r. spectrum.

Mass Spectral Proof of the Structure of the Dimethyl Product

It has been mentioned that the mass spectra of the ethylene ketals of 3-keto steroids show three main peaks at m/e 99, 112, and 125. The origin of these peaks are explained⁴⁶ as shown in Figure IV. A rupture of the C₃-C₄ bond in (51), the "A split", results in the m/e 99 peak (53). The "B split" in (51) results in an intermediate, (55), which can further split in three ways, α , β , and γ to give peaks at m/e 99, 112, and 125 respectively, as illustrated by the ethylene ketals of compounds (39) and (41) in Table V. The presence of a methyl group at C₂ will favour the B split since a positive charge resulting from electron bombardment will be more stable at the tertiary C₂ carbon than at the secondary C₄ carbon atom. Thus, with the ethylene ketal of 2 α -methyl-5 α -cholestan-3-one (40) the relative abundance of the peaks at m/e 112 and 125, resulting from the B split, have increased sharply with respect to those of the ethylene ketal of (39), the non-methylated compound, as shown in Table V. The A split, now indicated by the peak at m/e 113, is slightly diminished. In the case of 2,2-dimethyl

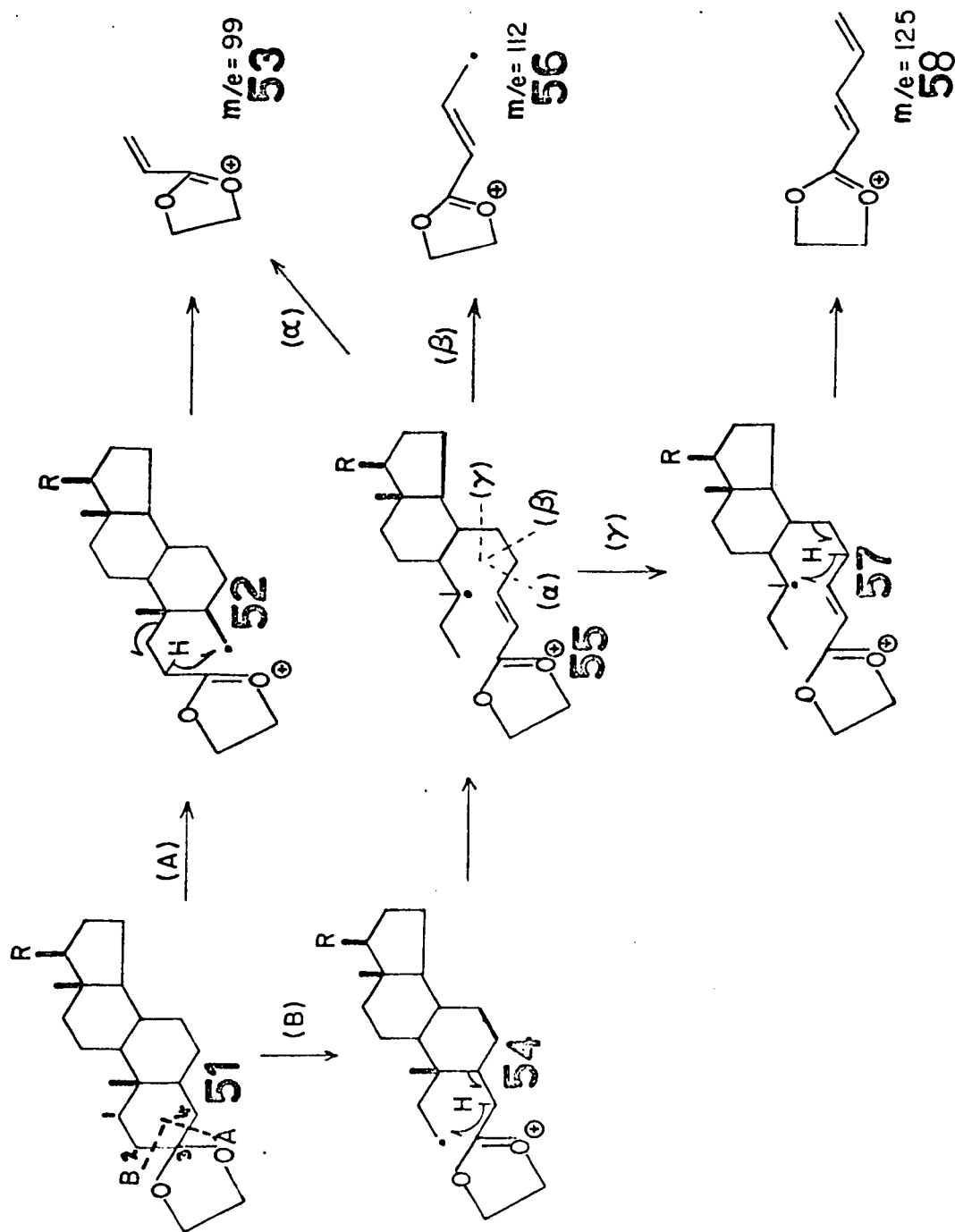
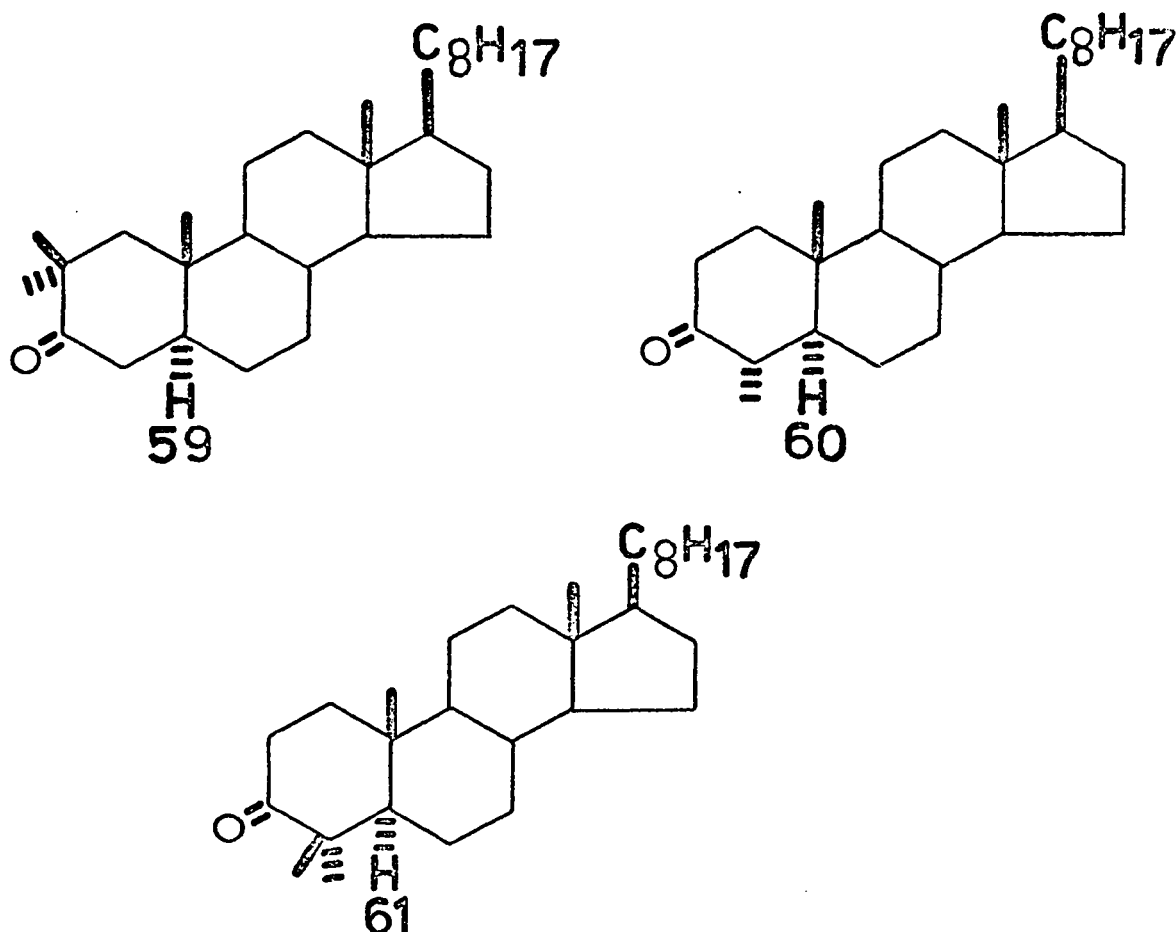


Figure IV. The origin of the peaks at m/e 99, 112, and 125 in the mass spectra of the ethylene ketals of 3-keto steroids.

Table V The Relative Abundance of the Mass Spectral Peaks Resulting from "A" and "B" Cleavage in the Ethylene Ketals of Some 3-Keto Steroids

Ethylene Ketal of	A Split		B Split					Ref.	
			α Split		β Split		γ Split		
	m/e	Rel. Abun. (%)	m/e	Relative Abundance (%)	m/e	Rel. Abun. (%)			
5α-cholesten-3-one (39)	99	100	99	included in 99 peak	112	12	125	45	32
5β-cholesten-3-one (41)	99	100	99	included in 99 peak	112	12	125	50	32
2α-methyl-5α-cholestan-3-one (40)	113	95	99	44	112	45	125	100	46
2,2-dimethyl-5α-cholestan-3-one (59)			99	12	112	37	125	100	46
4β-methyl-5α-cholestan-3-one (60)	99	100	113	—	126	—	139	1	46
4,4-dimethyl-5α-cholestan-3-one (61)	99	100							32
5β-cholest-7-en-3-one (47)	99	35	99	included in 99 peak	112	4	125	—	
2,2-dimethyl-5β-cholest-7-en-3-one (63)			99	39	112	60	125	31	
2β-methyl-5β-cholest-7-en-3-one (62)	113	22	99	11	112	11	125	—	
2β-methyl-5β-cholestan-3-one (66)	113	70	99	12	112	15	125	100	



substituted compounds such as the ethylene ketal of (59), the A split cannot occur since there is no hydrogen available at C_2 to be abstracted and therefore, the formation of a resonance stabilized conjugated dimethyl species analogous to (53) is impossible. In an analogous manner, ethylene ketals of compounds with 4-methyl substituents such as (60) preferentially undergo the A split with a resulting diminution in the relative

abundance of the B split peaks and with 4,4-dimethyl compounds such as the ethylene ketal of (61), only the A split occurs since the B split is now impossible as may be seen from the relative abundances shown in Table V.

The mass spectrum (Figure V and Table V) of the ethylene ketal of the dimethylated compound (63) obtained from methylation of (47) shows relative abundances of 60% and 31% at m/e 112 and 125 respectively and 39% at m/e 99. This information is compatible only with a 2,2-dimethyl structure. In a 2,4-dimethyl structure, peaks resulting from the B split would appear at m/e 113, 126, and 139 while the A split would show a peak at m/e 113. Such peaks are of very low intensity in the mass spectrum of the ethylene ketal of (63). In a 4,4-dimethyl structure, the B split would be suppressed and peaks at m/e 112 and 125 would be very small while the A split would be enhanced, resulting in a very strong peak at m/e 99. This is not the case with the ethylene ketal of (63). Therefore, the structure of (63) must be as formulated.

The Product of Monomethylation of (47)

It has been shown by Beton et al.⁴⁷ that in the monomethylation of 3-keto steroids, the isomer in which the methyl group is axial is formed first and that this isomer is isomerized to the thermodynamically more stable

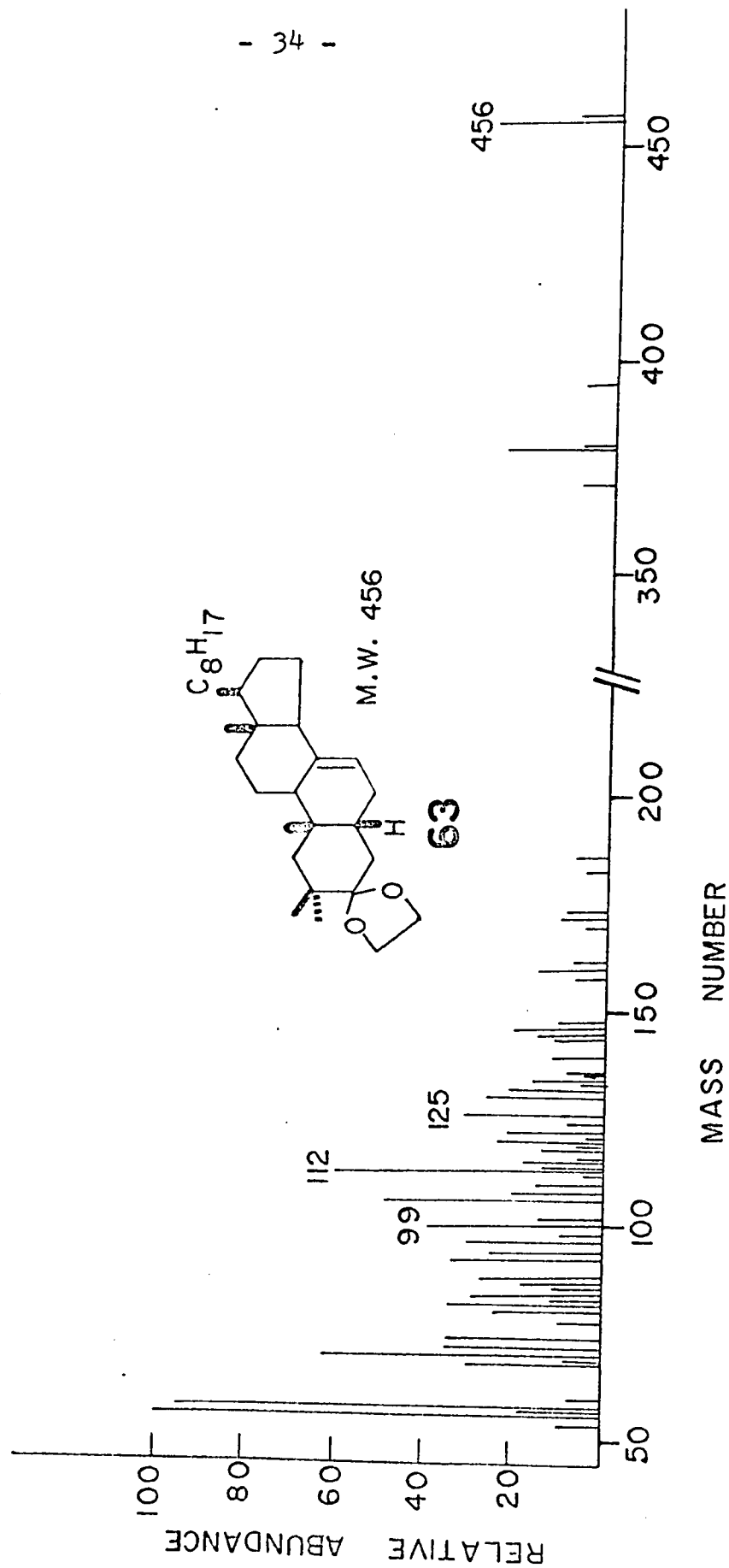


Figure V. The mass spectrum of the ethylene ketal of 2,2-dimethyl-5β-cholest-7-en-3-one (63).

equatorial isomer with potassium tert-butoxide in tert-butanol, the reaction medium used in the methylation of (47).

The mass spectrum of the crystalline product obtained from the methylation of (47) showed a p.m.i. at m/e 398 indicating a monomethyl derivative. The ketone and 7,8-double bond functions were intact as indicated by an i.r. absorption at 1710 cm^{-1} and a broad n.m.r. peak at 5.11δ respectively. Based on the work of Beton et al.⁴⁷ it is reasonable to assume that the monomethyl isomer obtained was the more stable equatorial (2 β -methyl or 4 β -methyl) one. A mass spectrum (Figure VI and Table V) of the ethylene ketal of the monomethyl product (62) showed small peaks at m/e 99, 112, and 113. The m/e 99 peak may be accounted for as arising from either an A split in a 4-substituted compound or a B split followed by an α split (Figure IV) in a 2-substituted compound. The peak at m/e 113 may be considered the result of either an A split in a 2-substituted compound or a B split followed by an α split in a 4-substituted compound. The peak at m/e 112, of relative abundance 11%, could only arise from a B split followed by a β split in a 2-substituted compound, however, the low intensity of this peak does not allow the assignment of

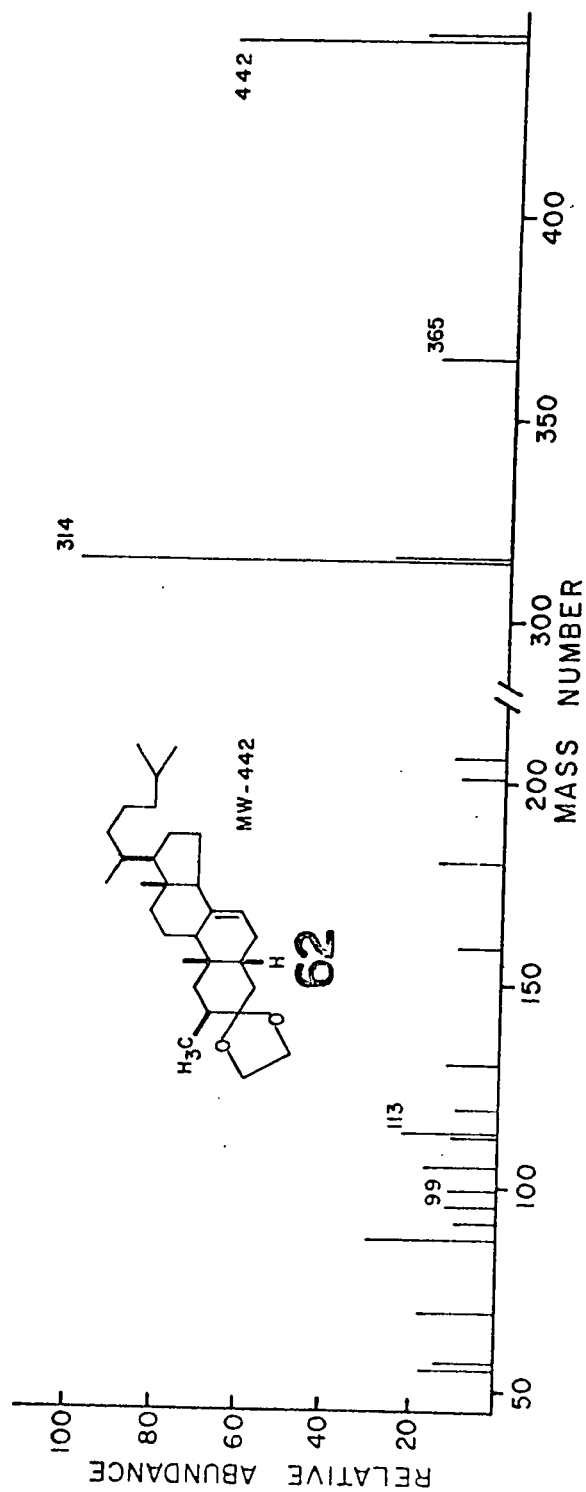


Figure VI. The mass spectrum of the ethylene ketal of 2β-methyl-5β-cholest-7-en-3-one (62)

the methyl group to the 2-position to be made with much certainty. We thus had a compound which did not undergo the usual fragmentations associated with the ethylene ketals of 2- or 4-methyl substituted 3-keto steroids. The assignment of the methyl group to the 2- or 4-position based on mass spectral data could not be made with certainty and the o.r.d. spectrum, about which more will be said later, did not resolve this problem. Since all the usual spectroscopic methods had been used without success, we therefore had to resort to a chemical proof for the structure of the monomethyl product, which is outlined in Figure VII.

The monomethyl product was catalytically hydrogenated over platinum using perchloric acid catalyst according to the procedure of Fudles and Bloch⁴⁸. The mixture of saturated alcohols obtained, (64) and (65), was not separated but was oxidized with Jones' reagent to give a compound identical with 2 β -methyl-5 β -cholestan-3-one (66), previously reported in the literature.²⁷ The mass spectrum (Figure VIII and Table V) of the ethylene ketal of (66) showed an intense peak at m/e 125 and a weak one at m/e 112 both of which are compatible only with a 2-methyl structure.

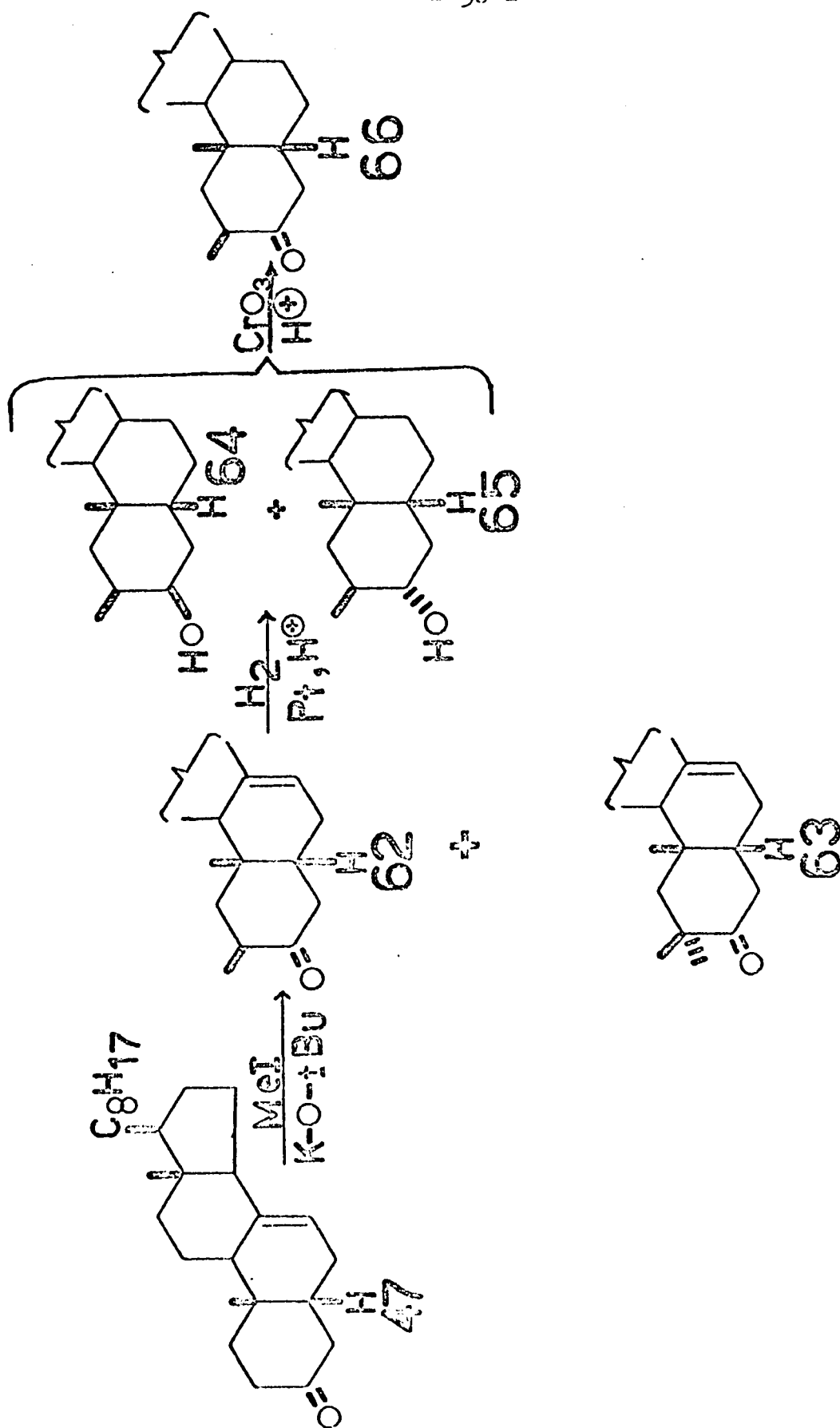


Figure VII. The products of methylation of 5β-cholest-7-en-3-one (47) and the conversion of the monomethyl product to 2β-methyl-5β-cholestan-3-one (66).

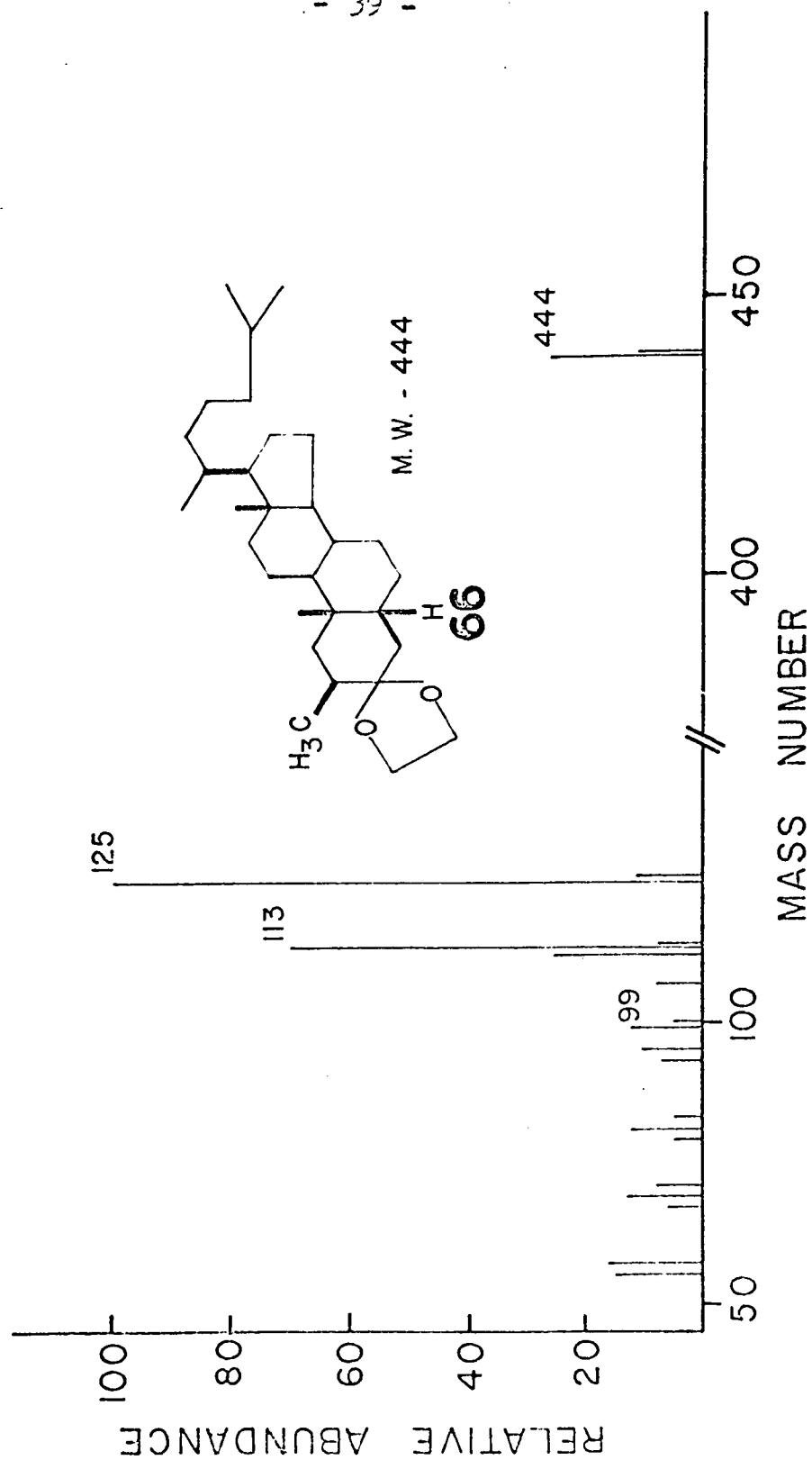


Figure VIII. The mass spectrum of 23-methyl-5 β -cholestan-3-one (66).

The anomolous fragmentation pattern observed for the ethylene ketal of (62) is most likely due to the presence of the 7,8-double bond. Among the three secondary fragmentations, α , β , or γ of the B split (Figure IV) the γ fragmentation is the most favoured in the saturated ethylene ketals. This may be seen with compounds (39), (40), (41), (59) and (66) in Table V where the relative abundances of the γ fragmentation ions are greater than those of the α or β fragmentations. Therefore any process which prevents the γ split will thereby suppress the B split since the most favoured pathway of the B split will then be blocked. The 7,8-double bond in the ethylene ketal of (62) prevents the γ split and this results in a suppressed B split. Furthermore, the 2-methyl group suppresses the A split. Thus, in the ethylene ketal of (62) both the A and B splits are suppressed and this accounts for the small peaks observed for the characteristic ions at m/e 99, 112 and 113, which makes a mass spectral interpretation of the methylation site uncertain. In the case of the ethylene ketal of the 2,2-dimethyl derivative (63) the A split is not possible, as explained previously, and therefore all of the characteristic ethylene ketal fragmentation must proceed through the B split. The presence of the peak at m/e 125 in the mass spectrum of the ethylene ketal of (63), resulting from a γ split,

may be explained by assuming that the 7,8-double bond is shifted to another position, possibly to 8,14, thereby allowing the γ split to occur. The relative abundance resulting from this γ split is half that of the β split, see Table V. Therefore the γ split is not a favourable one in this case and it occurs only because the A split is entirely suppressed.

Application of O.R.D. to the Structural Determination of the Methylation Products

The octant rule, applied to 5α -3-keto steroids⁴⁹ predicts that a bulky substituent such as methyl in the axial position at C_2 will cause the Cotton effect to become more positive and a bulky axial substituent at C_4 will make the Cotton effect more negative with respect to that of the unsubstituted ketone, as shown in the octant diagram, Figure IX. Substituents in the equatorial positions at C_2 and C_4 will have little influence on the Cotton effect. These relationships are illustrated with some examples from Table IV. While 5α -cholestan-3-one (39) has a molecular amplitude, $a = +65^\circ$, its 2 β -methyl (axial) derivative (67) has $a = +73^\circ$, an increase of 8° , whereas its 2 α -methyl (equatorial) derivative, (40), has $a = +63^\circ$, nearly the same as the unsubstituted ketone, (39).

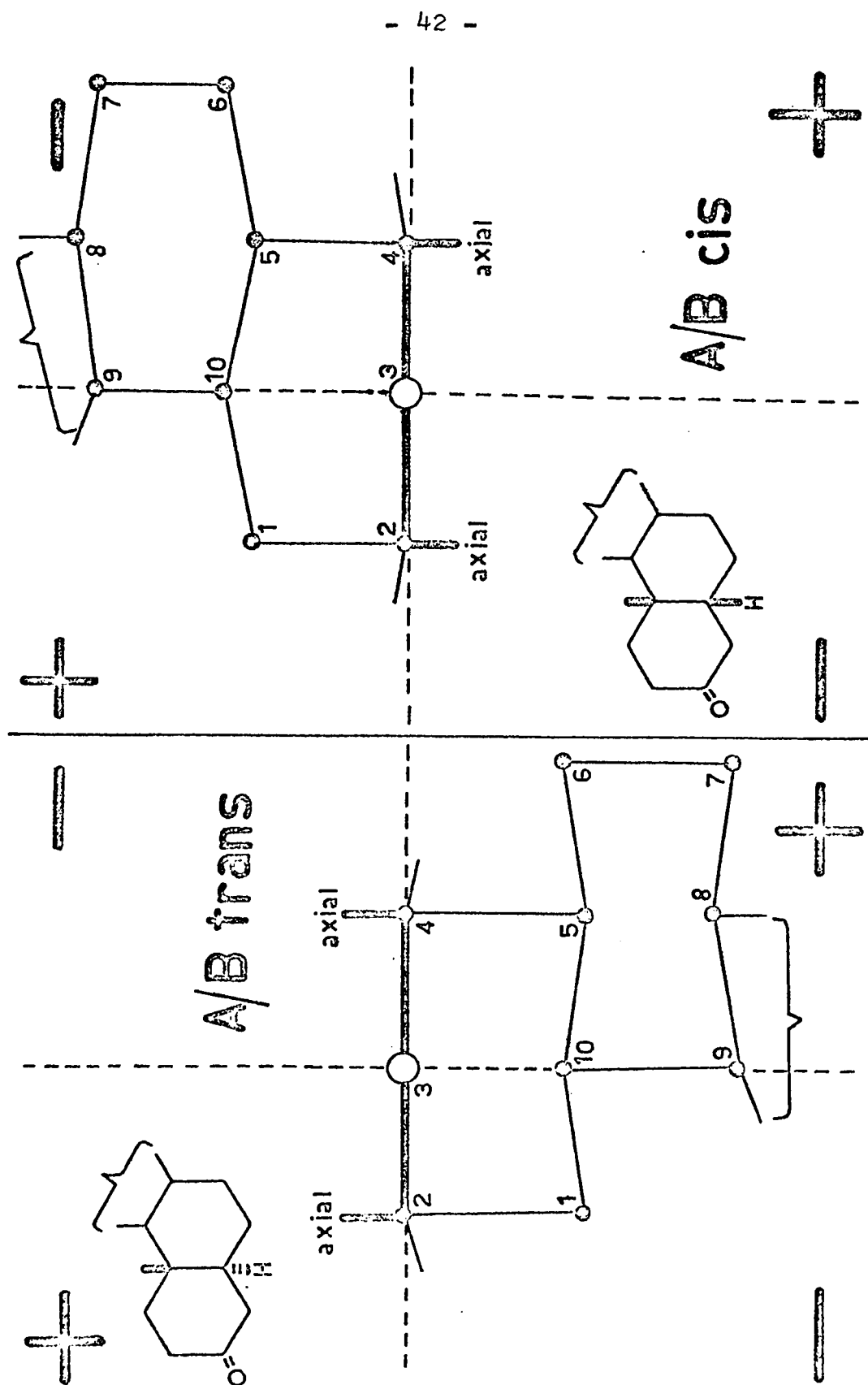
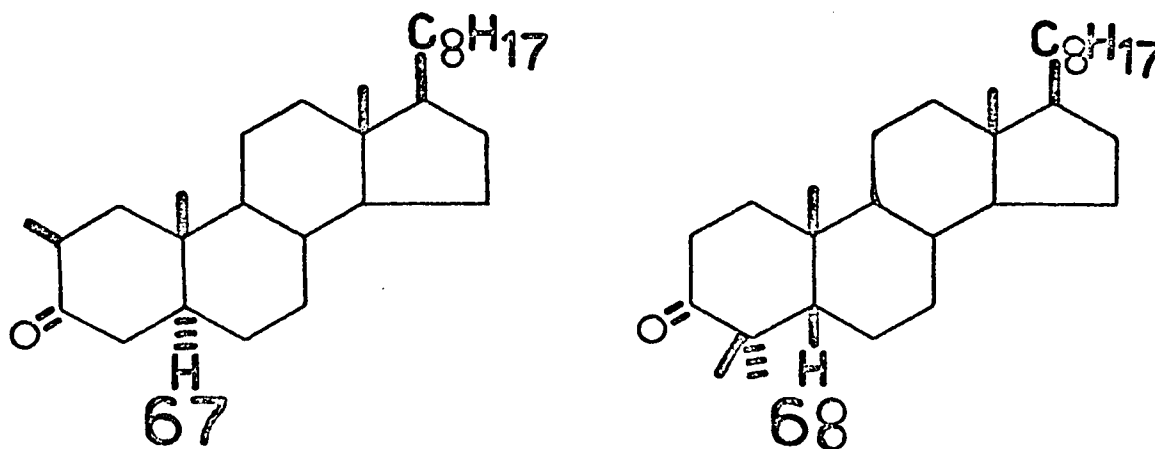


Figure IX. Octant diagram for substituents at C_2 and C_4 in 5α - and 5β -3-keto steroids.

4,4-Dimethyl-5 α -cholestan-3-one (61), however, containing an axial 4 β -methyl group, has $a = -11^\circ$, a significantly large negative difference resulting in a change of the sign of the Cotton effect compared with the unsubstituted compound.



Whereas in 5 α -steroids the 2 β - and 4 β -positions are axial and the α -positions are equatorial, in 5 β -steroids the reverse is true and the 2 α - and 4 α -positions are now axial. This causes a reversal of the octant rule predictions for axial substituents in these positions, as shown in Figure IX. Thus in 5 β -3-keto steroids a bulky axial substituent at C₂ will cause the Cotton effect to become more negative and such a substituent at C₄ will make the Cotton effect more positive with respect to that of the unsubstituted ketone.

Few 5 β -3-keto steroids having axial substituents at C₂ or C₄ have been reported so that these predictions have not yet been thoroughly tested. One such example is 4,4-dimethyl-5 β -cholestan-3-one (68) which has $\underline{a} = -27^\circ$, a value nearly the same as that of the unsubstituted analogue (41) with $\underline{a} = -25^\circ$ (Table IV) whereas the octant rule would predict a more positive value. The fact that the octant rule did not apply here was attributed⁴⁴ to a flattened A-ring in which the methyl groups at C₄ are equivalent with respect to the ketone group.

The o.r.d. spectrum of 2,2-dimethyl-5 β -cholest-7-en-3-one (63), Figure III, has a molecular amplitude 11 $^\circ$ more negative than the value (Table IV) for the unmethylated compound (47). This is consistent with the octant rule prediction that the axial methyl group at C₂ in (63) would exert a negative influence on the Cotton effect (see Figure IX). With the monomethyl product (62), however, the o.r.d. spectrum, Figure III, has a molecular amplitude which is 10 $^\circ$ more positive than the value (Table IV) for the unsubstituted compound (47). This is inconsistent with the octant rule which predicts little change in molecular amplitude due to the equatorial 2 β -methyl group in (62). A similar inconsistency was

observed in the o.r.d. spectrum, Figure III, of the analogous saturated compound, (66), whose molecular amplitude value of -8° , which has previously been reported⁴² as slightly less than -9.8° , is 17° more positive than the value (Table IV) for the unsubstituted compound, (41).

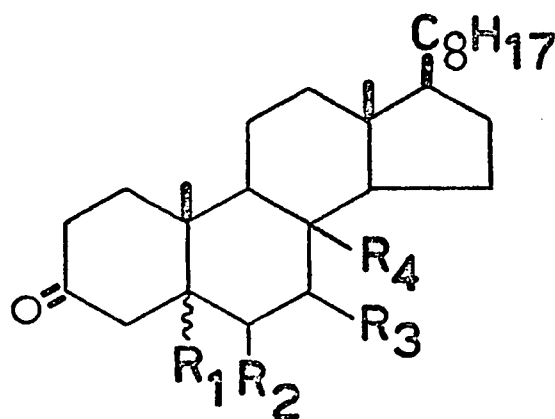
Some examples have been reported of 5 α -3-keto steroids containing axial substituents at C₂ in which it was suggested that ring A exists in a boat conformation^{10,50} or a flattened conformation intermediate between the chair and boat forms⁵¹. These conclusions were arrived at, in part, from the o.r.d. curves of these compounds which differed from the octant rule predictions assuming a chair conformation. The non-chair conformation for ring A was attributed to large steric interactions inherent in a normal chair conformation between axial substituents at C₂ and the axial C₁₀ methyl group. In the case of compounds (62) and (66), such interactions are very small because of the bent nature of the A/B cis steroid molecule (cf. C₂ in (10) and (11)). It is therefore unlikely that the inconsistencies with the octant rule predictions observed for the o.r.d. curves of (62) and (66) are due to major conformational distortions of the normal chair form of the A-ring but, rather, are due to more subtle conformational changes in the molecules.

Application of Bucourt's Rules in the Methylation of
3-Keto Steroids

In Table VI it may be seen that while methylation of 5 α -cholestan-3-one (39) results in 2-methyl derivatives, the analogous compounds containing either a 5 β -hydrogen, (41), or a 7,8-double bond, (43), form the 4-methyl derivatives. With a 6,7-double bond in the analogous 5 α -compound, (45), methylation occurs at C₂. We have now shown that methylation of the analogous compound containing both a 5 β -hydrogen and a 7,8-double bond, (47), results in 2-methyl derivatives. It is therefore apparent that changes occurring in the B-ring have a great influence on the site of methylation of 3-keto steroids and that the type of A/B-ring junction is also an important factor in the reaction. These two factors support Barton's idea¹³ that conformational deformations produced by unsaturation in the B-ring of steroids are transmitted across the A/B-ring junction and influence reactions occurring in the A-ring. The methylation of 3-keto steroids may therefore serve as a useful means of studying conformational transmission effects.

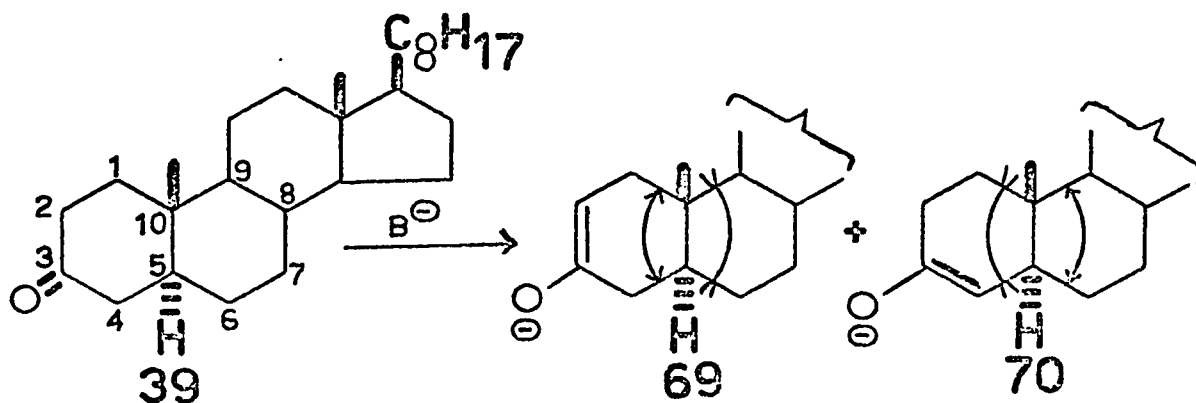
The results of the methylation reactions in the various ketones mentioned above may be explained by using Bucourt's rules of dihedral angle changes, which are summarized in Tables I, II, and III. In the case

Table VI The Site of Methylation in Some 3-Keto Steroids



Compound	R ₁	R ₂	R ₃	R ₄	Site of Methylation	Reference
5 α -cholestan-3-one (39)	5 α -H	H	H	H	2	27
5 β -cholestan-3-one (41)	5 β -H	H	H	H	4	27
5 α -cholest-7-en-3-one (43)	5 α -H	H	Double Bond		4	28,29
5 α -cholest-6-en-3-one (45)	5 α -H	Double Bond		H	2	10
5 β -cholest-7-en-3-one (47)	5 β -H	H	Double Bond		2	

of 5 α -cholestan-3-one (39), formation of the 2,3-double bond in the enolate anion, (69), causes the para



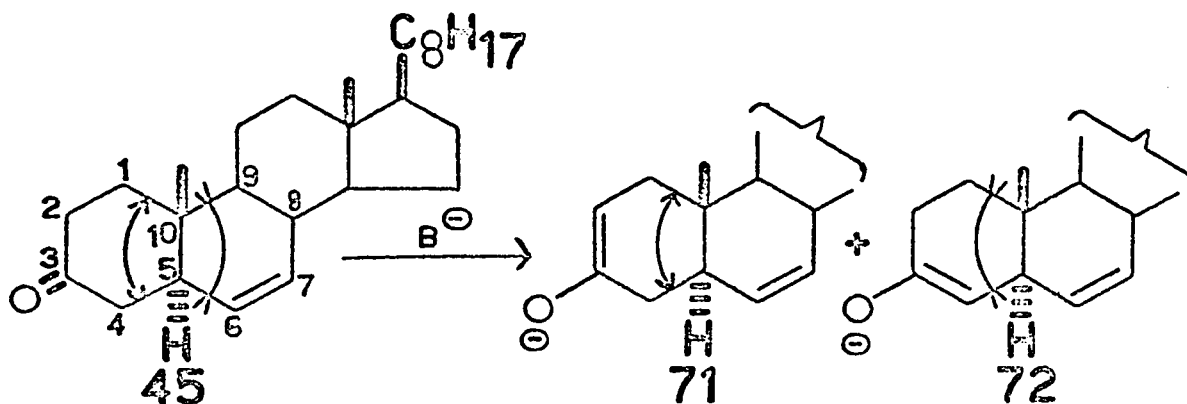
dihedral angle $C_4-C_5-C_{10}-C_1$, to open and since the rings are trans fused, the dihedral angle $C_6-C_5-C_{10}-C_9$ is closed. Closure of the latter dihedral angle causes the distance to increase between the axial methyl group at C_{10} and the axial hydrogens at C_6 and C_8 , thereby decreasing the steric interactions between these groups. Formation of the 3,4-double bond in (70) causes the meta dihedral angle $C_4-C_5-C_{10}-C_1$ to close and angle $C_6-C_5-C_{10}-C_9$ to open with a resultant increase in the C_{10} , C_6 and C_{10} , C_8 axial substituent interactions. Therefore formation of the 2,3-enolate anion (69) is favoured over (70) and methylation occurs at C_2 . Similar considerations in the case of 5 β -cholestan-3-one (41), shown in Table VII, indicate the formation of

Table VII Changes in Some of the Dihedral Angles and Steric Interactions in 5 α -(39) and 5 β -cholestan-3-one (41) as a Result of Enolate Anion Formation

Compound	Form of Enolate Anion	Change in Angle C ₄ -C ₅ -C ₁₀ -C ₁	Change in Angle C ₆ -C ₅ -C ₁₀ -C ₉	Change in Interactions Between C ₁₀ Me and C ₆ and C ₈ Axial Hydrogens	Enolate Preferably Formed	Methylation Site
5 α -cholestan-3-one (39)	C ₂ , C ₃	opened	closed	decreased	C ₂ , C ₃	C ₂
	C ₃ , C ₄	closed	opened	increased		
5 β -cholestan-3-one (41)	C ₂ , C ₃	opened	opened	increased	C ₃ , C ₄	C ₄
	C ₃ , C ₄	closed	closed	decreased		

the 3,4-enolate anion is favoured here and this accounts for the fact that methylation of (41) takes place at C_4 .

Let us now consider the ring B unsaturated steroids. The presence of the 6,7-double bond in 5 α -cholest-6-en-3-one (45) causes the meta dihedral angle $C_6-C_5-C_{10}-C_9$ to close with respect to that of the saturated compound. Closure of this dihedral angle causes the dihedral angle $C_4-C_5-C_{10}-C_1$ to open since the rings are trans fused. Formation of the 2,3-enolate anion (71) would result in



an opening of the para dihedral angle $C_4-C_5-C_{10}-C_1$ which would be compatible with the effect on this angle exerted by the 6,7-double bond, whereas formation of the 3,4-enolate anion (72) would close the meta angle $C_4-C_5-C_{10}-C_1$ which would be incompatible with the effect of the 6,7-double bond on this angle. Therefore, (45) preferentially forms an enolate anion with a 2,3-double bond (71) and methylation occurs at C_2 .

Similar considerations, outlined in Table VIII, for 5 α -cholest-7-en-3-one (43) and the compound studied in this report, 5 β -cholest-7-en-3-one (47), may account for the site of methylation in these compounds. The difference in the methylation sites in these two compounds may be attributed to the different manner in which deformations in the B-ring are transmitted to ring A in A/B trans and A/B cis steroids.

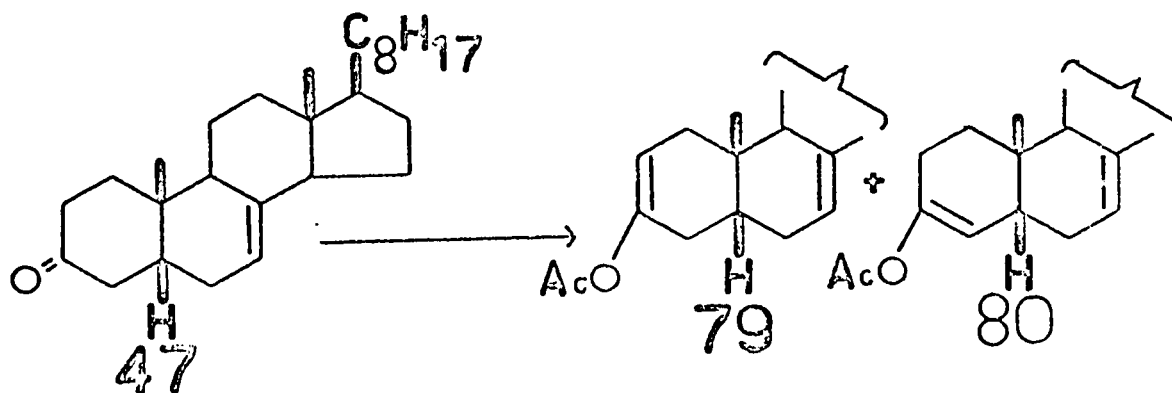
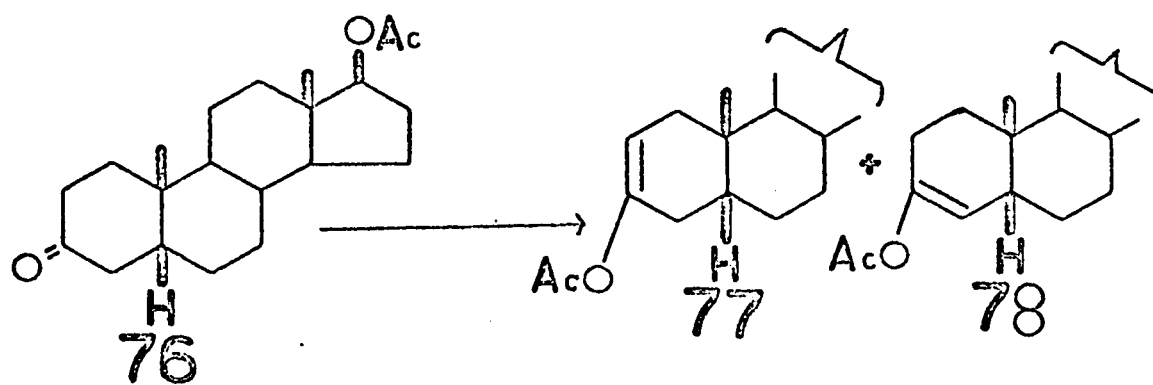
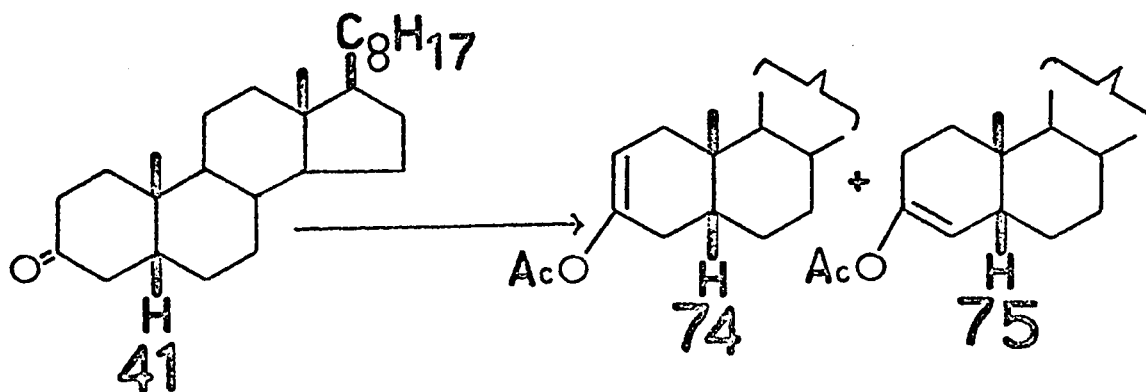
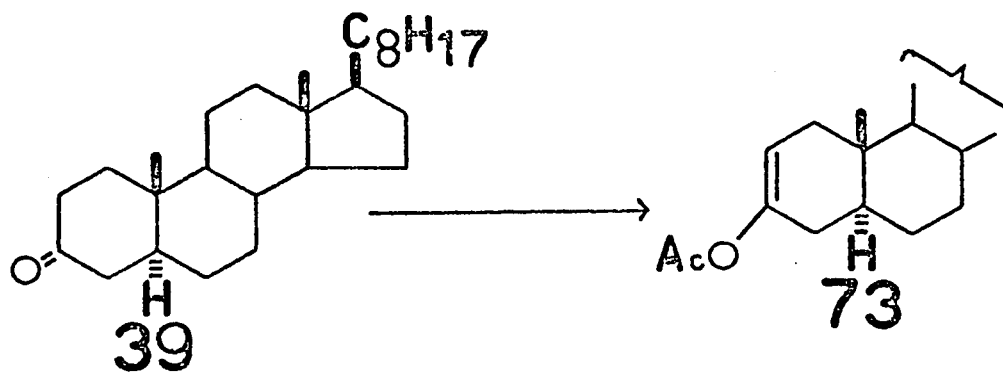
Thus the use of Bucourt's rules of dihedral angle changes can account for the course of methylation in the steroidal C₃-ketones mentioned above.

The Enol Acetylation of 3-Keto Steroids

It has been shown⁵² that the perchloric acid catalyzed acetic anhydride enol acetylation is thermodynamically controlled whereas the sulphuric acid catalyzed isopropenyl acetate enol acetylation is kinetically controlled. Dauben et al.⁵³ found that the isopropenyl acetate enol acetylation of 5 α -cholestan-3-one (39) resulted in the 2,3-unsaturated enol acetate (73) while 5 β -cholestan-3-one (41) gave the 3,4-unsaturated enol acetate (75). Using gas chromatography to analyze products, Favre and Baczynskyj⁵⁴ repeated the latter reaction and they detected both the 3,4-(75) and 2,3-(74) enol acetates in the ratio of about 71:29. Using the same analytical

Table VIII The Effect of Unsaturation and of Enolate Anion Formation on Dihedral Angle Changes in Some Unsaturation 3-Keto Steroids.

Compound	Effect of Unsaturation on Dihedral Angle		Effect on Angle C ₄ -C ₅ -C ₁₀ -C ₁ of a 2,3-Enolate anion		Enolate Preferably Formed	Methylation Site
	C ₆ -C ₅ -C ₁₀ -C ₉	C ₄ -C ₅ -C ₁₀ -C ₁				
5 α -cholest-6-en-3-one (45)	to close	to open	to open	to close	C ₂ , C ₃	C ₂
5 α -cholest-7-en-3-one (43)	to open	to close	to open	to close	C ₃ , C ₄	C ₄
5 β -cholest-7-en-3-one (47)	to open	to open	to open	to close	C ₂ , C ₃	C ₂



techniques, Liston⁵⁵ observed that the perchloric acid catalyzed acetic anhydride enol acetylation of 17 β -acetoxy-5 β -androstan-3-one (76) resulted in 94% of the 3,4-unsaturated enol acetate (78) and 6% of the 2,3-unsaturated isomer (77). With isopropenyl acetate and sulphuric acid, the ratio of (78) to (77) was 71:29. A sample of 5 β -cholest-7-en-3-one (47) was submitted to Dr. A.J. Liston, who prepared the enol acetates (79) and (80) under the conditions of thermodynamic and kinetic control described above. Under kinetic control, the ratio of (79) to (80) obtained was 87.5:12.5 while the thermodynamically controlled reaction resulted in 90.5:9.5 as the ratio of (79) to (80)⁵⁶. These results show that the preferred direction of acid catalyzed enol acetylation (towards C₂ or C₄) in 3-keto steroids is the same as that for enolate anion formation in alkaline medium, as reflected in the site of methylation of steroidal C₃-ketones.

EXPERIMENTAL

General

Melting points were taken on a Thomas-Hoover Uni-melt apparatus and are uncorrected. Infrared (i.r.) spectra were recorded on Beckman IR-8 or Beckman IR-20 instruments in chloroform solution, unless otherwise indicated. Nuclear magnetic resonance (n.m.r.) spectra were taken on Varian T-60 or HA-100 spectrometers in chloroform-d with tetramethylsilane as internal standard. Mass spectra were determined on a Hitachi Perkin-Elmer R.M.U. 6D mass spectrometer at an ionization potential of 70 e.V. Optical rotatory dispersion (o.r.d.) curves were obtained in dioxane solution on a Durrum-Jasco Model ORD/UV-5 spectropolarimeter. Optical rotations were measured at room temperature (23°) in chloroform solution on a Perkin-Elmer 141 photoelectric polar^aimeter. In recording o.r.d. data and optical rotations, the concentrations are expressed in g/100 ml. of solution. Microanalyses were determined in the Microanalytical Laboratory of Dr. A. Bernhardt, Elbach uber Engelskirchen, West Germany. Ultraviolet (u.v.) spectra were recorded on a Perkin-Elmer 202 recording spectrophotometer. SilicaR (200-300 mesh) and neutral alumina (Woelm) were used as ^dabsorbants for column chromatography. Silica gel G

(according to Stahl) was used as ^dabsorbant for thin layer chromatography (t.l.c.) and sulphuric acid was used as spraying agent. Petroleum ether boiling in the range 30-60° was used. Reactions were followed by t.l.c. and, in column chromatography, an L.K.B.- 3400 automatic fraction collector was used and fractions with similar t.l.c. flow rates were combined, unless otherwise specified.

Cholesta-4,7-diene-3-one (49) .-

This compound was prepared by Oppenauer oxidation of cholesta-5,7-diene-3 β -ol (48)* according to the procedure of Cohen, et al. ^{33¹²} with the following modifications; four times the amount of silica gel was used for chromatography and benzene was used as eluant instead of hexane. Yield, 60%, m.p. 87-89°; u.v. max (hexane), 230 m μ (ϵ 15,200). Lit. ^{33¹²} m.p. 87-89°; u.v. max (hexane), 230 m μ (ϵ 17,400).

Catalytic Hydrogenation of Cholesta-4,7-diene-3-one (49).

To a solution of 2.00 g (5.24 mM) of cholesta-4,7-diene-3-one (49) in 100 ml of anhydrous ether was added 200 mg. of finely powdered 10% Pd on charcoal. The

* This compound was purchased from Nutritional Biochemical Corporation.

resulting slurry was hydrogenated for 2.5 hr. at atmospheric pressure and room temperature with constant agitation. The slurry was then filtered through a pad of celite on a sintered glass funnel and the filtrate was evaporated to dryness leaving a residue of 2.03 g. of colourless oil. This was chromatographed on a column containing 1.5 kg. of SilicaR and petroleum ether was used as eluant. The first materials eluted were solids with m.p.'s between 80° and 86° which were combined to give 1.0 g. Recrystallization from methanol gave 778 mg. of 5 β -cholest-7-en-3-one (47), m.p. 86-87°. Concentration of mother liquors gave an additional 72 mg., m.p. 85-87°, total yield, 42.5%. Recrystallization of one of the early fractions three times from methanol gave an analytical sample, m.p. 87-88°; $[\alpha]_D +65.4^\circ$ (c, 0.57); i.r. (Nujol), 1715 (ketone), 1665 (double bond) cm^{-1} ; n.m.r. δ 5.13 (s, 7-H); o.r.d. (c, 0.24) $[\phi]_{450} +325^\circ$, $[\phi]_{370} +520^\circ$, $[\phi]_{316} -781^\circ$, $[\phi]_{265} +4620^\circ$, $[\phi]_{235} +3050^\circ$, $a -54^\circ$; mass spectrum, m/e (relative intensity) 384(100), 351(55), 313(37), 119(38), 105(74).

Anal. Calcd. for $\text{C}_{27}\text{H}_{44}\text{O}$; C, 84.31; H, 11.53%.
Found: C, 84.41; H, 11.52.

Reported⁴⁰ for 5 α -cholest-7-en-3-one (43), m.p. 146-148°; $[\alpha]_D +24.7^\circ$. Subsequent fractions were

partially crystalline oils showing one spot on t.l.c. corresponding to that of 5 β -cholest-7-en-3-one (47). These were combined (850 mg) and rechromatographed to obtain more of compound (47).

Methylation of 5 β -Cholest-7-en-3-one (47).

A solution of 137 mg of potassium metal (3.5 mM) in 9 ml. of t-butanol was added to a boiling solution of 889 mg (2.31 mM) of 5 β -cholest-7-en-3-one (47). The solution was refluxed for one minute and a solution of 0.8 ml. of MeI (excess) in 4 ml. of benzene was added and refluxing was continued for an additional 35 minutes. After cooling the reaction vessel, water was added and the resulting mixture was extracted with three ether portions. The combined ethereal extract was dried (anhydrous Na₂SO₄) and the solvent was evaporated giving 965 mg. of yellow oil. Chromatography on a column containing 1 kg of alumina (grade III) using petroleum ether as eluant gave four products. The first was 52 mg. of a colourless oil assumed to be tri- or tetramethylated species but was not characterized. The second was 162 mg. (17%) of 2,2-dimethyl-5 β -cholest-7-en-3-one (63) obtained as a colourless oil which showed one spot on t.l.c. Attempts at crystallizing this product from different solvents were unsuccessful. The oily product showed

$[\alpha]_D +20.5^\circ$ (c, 1.12); i.r. 1700 (ketone) cm^{-1} ; n.m.r. δ 5.18 (s, 7-H); o.r.d. (c, 0.36) $[\phi]_{450} +630^\circ$, $[\phi]_{317} -1320^\circ$, $[\phi]_{270} +5140^\circ$, $[\phi]_{256} +4900^\circ$, $\epsilon -65^\circ$; mass spectrum, m/e (relative intensity) 412(37), 379(59), 105(100), 91(65). A correct analysis was obtained on the crystalline ethylene ketal of this compound. The third product was 344 mg. (37%) of 2 β -methyl-5 β -cholest-7-en-3-one (62) which, after recrystallization from hexane, had m.p. 128-130 $^\circ$. A second recrystallization from hexane gave the analytical sample m.p. 131-132 $^\circ$; $[\alpha]_D +42.6^\circ$ (c, 0.83); i.r. (Nujol) 1710 (ketone), 1665 sh (double bond) cm^{-1} ; n.m.r. δ 5.11 (s, 1, 7-H); o.r.d. (c, 0.38), $[\phi]_{450} +335^\circ$, $[\phi]_{317} -1040^\circ$, $[\phi]_{272} +3350^\circ$, $[\phi]_{245} +2050^\circ$, $\epsilon -43.9^\circ$; mass spectrum, m/e (relative intensity) 398(100), 365(79), 314(95), 136(30), 105(40).

Anal. Calcd. for $\text{C}_{28}\text{H}_{46}\text{O}$; C, 84.33; H, 11.62.
Found: C, 84.58; H, 11.68.

Finally, 270 mg. (30%) of unchanged 5 β -cholest-7-en-3-one (47) was eluted, m.p. 85-87 $^\circ$ after recrystallization from methanol.

2 β -Methyl-5 β -Cholestan-3-one (66).

To a solution of 211 mg. (0.53 mM) of 2 β -methyl-5 β -cholest-7-en-3-one (62) in 10 ml of glacial acetic acid plus 2 ml of ethyl acetate was added one drop of 70% aqueous perchloric acid and 100 mg of PtO_2 .⁴⁸

This mixture was hydrogenated for 48 hr at atmospheric pressure and room temperature with constant magnetic stirring. A second batch of 100 mg of PtO_2 was then added and hydrogenation was continued for an additional 72 hr. After filtering the mixture and evaporating the solvent under reduced pressure, 255 mg of a yellow oil was obtained which was refluxed for 0.5 hr in 20 ml of a 15% methanolic KOH solution. The methanolic solution was diluted with water and extracted with three ether portions. Drying (anhydrous Na_2SO_4) and evaporation of the combined ethereal extracts gave 234 mg of yellow oily residue whose n.m.r. spectrum showed lack of olefinic absorption. Chromatography using a column containing 200 g of SilicaR and benzene as eluant gave 34 mg of oily material which was not characterized, and 157 mg of more polar material which, on recrystallization from methanol/ether, had m.p. 60-70°. The product was assumed to be a mixture of the alcohols (64) and (65). The mixture of alcohols was oxidized with 15 drops of Jones' reagent⁵⁷ in 20 ml of acetone for 0.5 hr. Methanol was then added to destroy excess reagent and the oxidized product was isolated with ether in the usual way to give 143 mg of 23-methyl-53-cholestan-3-one (66) as a partially crystalline oil. Filtration through charcoal in ethereal solution followed by crystallization from ether/methanol gave 40 mg of

product m.p. 111-112°; $[\alpha]_D +26.2^\circ$ (c, 1.1); o.r.d. (c, 0.21) $[\phi]_{450} +97^\circ$, $[\phi]_{325} +216^\circ$, $[\phi]_{313} +151^\circ$, $[\phi]_{280} +1010^\circ$, $[\phi]_{263} +970^\circ$, $[\phi]_{250} +1080^\circ$, $a -8^\circ$. Lit.²⁷ m.p. 111-112°; $[\alpha]_D +30^\circ$. Lit.⁴² a , slightly less than -9.8° . $\wedge$ 4 β -Methyl-5 β -cholestan-3-one has m.p. 58-59°; $[\alpha]_D +34^\circ$ 27.⁶

Concentration of mother liquors gave an additional 46 mg of product m.p. 109-110°. Total yield, 41%.

2 β -Methyl-5 β -Cholest-7-en-3-one Ethylene Ketal

A solution of 113 mg (0.29 mM) of 2 β -methyl-5 β -cholest-7-en-3-one (62) in 25 ml of benzene containing 0.2 ml of ethylene glycol (excess) and 8 mg of *p*-toluene sulphuric acid was refluxed for 6 hr in a 50 ml one-necked flask fitted with a Soxhlet extraction apparatus containing a thimble of calcium carbide⁵⁸. Water formed during the reaction was thus continuously removed as acetylene gas. The reaction solution was then poured into a mixture of ether and 5% aqueous NaHCO₃ in a separatory funnel. The ether layer was washed with water, dried (anhydrous Na₂SO₄), and evaporated to dryness to give 128 mg of ketal. Three recrystallizations from ether/methanol containing a trace of pyridine gave the analytical sample m.p. 118-119°; $[\alpha]_D +65^\circ$ (c, 1.37); i.r. 1080 (ether) cm⁻¹; n.m.r. δ 3.97 (s, 4, -O-CH₂CH₂-O-), 5.10 δ (s, 1, 7-H); mass spectrum, m/e (relative intensity)

442(66), 365(18), 314(100), 113(22), 87(30).

Anal. Calcd. for $C_{30}H_{50}O_2$; C, 81.39; H, 11.39.

Found: C, 81.23; H, 10.81.

The following ketals were similarly prepared:

23-Methyl-53-Cholestan-3-one Ethylene Ketal

m.p. $104-105^{\circ}$; $[\alpha]_D +27.2^{\circ}$ (c, 1.03); i.r. 1080 (ether) cm^{-1} ; n.m.r. δ 3.95 (s, 4, $-O-CH_2CH_2-O-$); mass spectrum, m/e (relative intensity) 444(26), 125(100), 113(70), 99(12).

Anal. Calcd. for $C_{30}H_{52}O_2$; C, 81.02; H, 11.79.

Found: C, 80.70; H, 11.69.

22-Dimethyl-53-Cholest-7-en-3-one Ethylene Ketal

m.p. $103-104^{\circ}$; $[\alpha]_D +43.4^{\circ}$ (c, 1.03); i.r. 1070 (ether) cm^{-1} ; n.m.r. δ 3.93 (s, 4, $-O-CH_2CH_2-O-$), 5.10 (s, 1, 7-H); mass spectrum m/e (relative intensity) 456(27), 379(24), 125(31), 112(60), 99(39), 55(100).

Anal. Calcd. for $C_{31}H_{52}O_2$; C, 81.52; H, 11.48.

Found: C, 81.44; H, 11.49.

53-Cholest-7-en-3-one Ethylene Ketal

m.p. $46-48^{\circ}$; $[\alpha]_D +50.4^{\circ}$ (c, 1.8); i.r. 1670 (double bond), 1105 (ether) cm^{-1} ; n.m.r. δ 3.93 (s, 4, $-O-CH_2CH_2-O-$), 5.13 (s, 1, 7-H); mass spectrum m/e (relative intensity) 428(18), 314(24), 105(20), 99(35), 73(111). A satisfactory C and H analysis was not obtained for this compound which appeared as one spot on t.l.c.

CLAIMS FOR ORIGINAL RESEARCH

1. The methylation of 5β -cholest-7-en-3-one (47) has been shown to occur at the C_2 position despite the fact that in 5β -cholestan-3-one (41) and 5α -cholest-7-en-3-one (43) methylation occurs at C_4 .
2. The normal mass spectral fragmentation pattern associated with the ethylene ketals of 2-methyl substituted 3-keto steroids has been shown to be absent in the case of the ethylene ketal of 2β -methyl- 5β -cholest-7-en-3-one (62). An explanation for this has been postulated which assumes that the rupture of the C_2, C_3 bond, which results in the normal fragmentation pattern, is suppressed here because of the presence of the 7,8-double bond.
3. The following new compounds were prepared and characterized:
 - (a) 5β -cholest-7-en-3-one (47)
 - (b) 2β -methyl- 5β -cholest-7-en-3-one (62)
 - (c) 2,2-dimethyl- 5β -cholest-7-en-3-one (63)
 - (d) 5β -cholest-7-en-3-one ethylene ketal
 - (e) 2β -methyl- 5β -cholestan-3-one ethylene ketal
 - (f) 2β -methyl- 5β -cholest-7-en-3-one ethylene ketal
 - (g) 2,2-dimethyl- 5β -cholest-7-en-3-one ethylene ketal.

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