REACTIONS OF STEROID EPOXIDES

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by

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CONTENTS

INTRODUCTION

The boron trifluoride catalysed rearrangements of steroid epoxides have stimulated interest in the rearrangement of the steroid nucleus. A vast literature documents these rearrangements, and although current mechanistic theories are capable of rationalising many of the products observed in the rearrangements, the success with which the products of an epoxide rearrangement can be predicted, is still limited.

The systematic investigation of epoxide rearrangements began in the fifties. Henbest and Wrigley published a paper[1] on the rearrangements of 5,6α-epoxy-5α-cholestane(1a), 5,6β-epoxy-5β-cholestane(2a), 3α-acetoxy-5,6α-epoxy-5α-cholestane(1b), and 3β-acetoxy-5,6α-epoxy-5α-cholestane (1c). They rationalised their results with the following principles:

(a) the bond from the epoxy-oxygen to the more alkylated C5-position is appreciably ionised in the transition state of the reaction, and therefore cleavage occurs preferentially towards the tertiary centre;

(b) intramolecular electron attracting groups may inhibit ionisation of the C5-O bond;

(c) reactions leading to less favourable molecular conformations are prohibited;

(d) the slower fluorohydrin formation may become significant if the inhibiting factors (b) and (c) prevent ketone formation.

Their investigation was, however, limited because many reaction products remained unidentified. When these rearrangements were re-examined by later workers, TABLE I, more refined techniques for isolating and identifying products were available. Consequently, in addition to ketones and fluorohydrins, other products including dienes, ring-contracted aldehydes, a dimeric ether, and skeletal rearrangement products were also isolated. In particular, the discovery of products arising from gross rearrangement of the steroid skeleton focussed attention on the reaction mechanism. These rearrangement products arise when heterolytic cleavage of the Lewis-acid coordinated epoxide, FIG. 1, is followed by migration of the C10-methyl to C5.

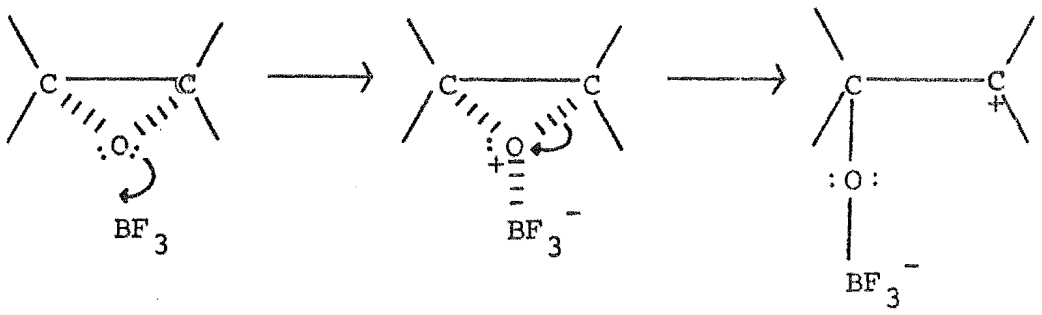
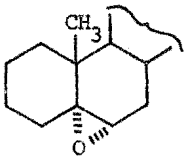
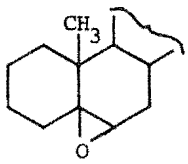
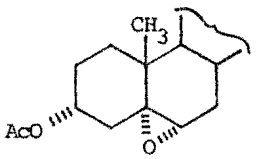
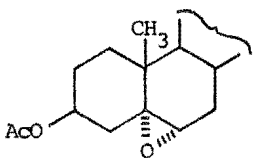


FIG. 1

A hydride shift followed by elimination of the C8β-proton gives the $\Delta^{8(9)}$-product. Two hydride shifts followed by elimination of the C14α-proton gives the $\Delta^{8(14)}$-product, and three hydride shifts followed by migration of the C13-methyl to C14, and elimination of the C17-proton gives the $\Delta^{13(17)}$-product, FIG. 2. Such rearrangements are analogous to the acid-catalysed rearrangement of friedelene(14) reported some ten years earlier[7].

TABLE I [2]

Compound	Time	Products (Henbest)		Time	Products (other workers)	
 (1a)	2min	starting material	12%	90sec[3]	3,5-diene (4)	5%
		oil	33%		β-nor-aldehyde (7a)	5%
		5β-6-one (3a)	30%		5β-6-one (3a)	56%
		oil	18%		$\Delta^{8(9)}$ (6)	5%
					$\Delta^{13(17)}$ (10a)	18%
 (2a)	4min	5α-6-one (8a)		2min[4]	3,5-& 4,6-dienes (4,5)	15%
					β-nor-aldehydes (7b)	18%
					5α-6-one (8a)	20%
					$\Delta^{13(17)}$ (10b)	46%
 (1b)	14hr	5β-6-one (3b)	61%	25sec[5]	5α-OH,6β-F (11b)	8%
		oil	18%		5β-6-one (3b)	17%
					$\Delta^{8(14)}$ (9)	27%
					$\Delta^{13(17)}$ (10c)	37%
					oil	4%
 (1c)	5min	starting material	18%	45sec[6]	dimeric-ether (12)	32%
		5α-OH,6β-F (11a)	62%			
		gum	20%		5α-OH,6β-F (11a) and gums	17%

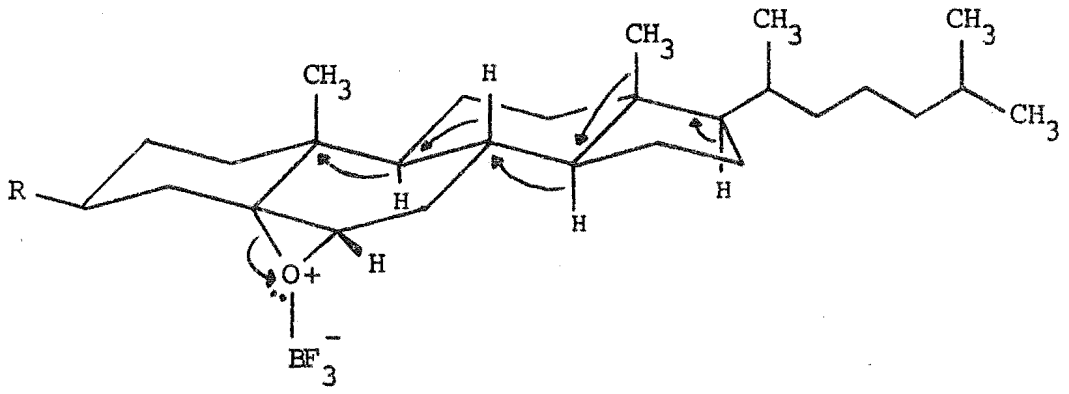


FIG. 2

The mechanism of the epoxide rearrangement reaction has been considered by some authors to be concerted[1], and by other authors to be stepwise[8]. In order that the 4,5- and 5,6-epoxysteroids rearrange via a concerted mechanism, migration of the C10-methyl to C5 must occur in concert with cleavage of the C5-O bond. For the 5,6α-epoxy-5α-cholestane(1a), the migrating C10-methyl, and the departing epoxy-oxygen are trans. For the 5β,6β-epoxide(2a), this is not the case, as the methyl migrates to the same face of the molecule as that from which the oxygen departs. Migration of the C10β-methyl can therefore not be concerted with carbon-oxygen bond cleavage. The formation of such rearrangement products from the 5β,6β-epoxide(2a) suggests that a C5-carbonium ion is an intermediate in this reaction. Thus the proposed concerted mechanism for the formation of backbone rearrangement products, at least for the β-epoxide, is untenable.

Further evidence in support of the non-concerted mechanism, involving a discrete carbonium ion intermediate, was provided by a study of the BF_3-catalysed rearrangement of several pairs of exocyclic-methylene

epoxides.

A series of steroidal exocyclic-methylene epoxides was rearranged[8] and the proportions of axial and equatorial aldehydes present in the productswere determined (see TABLE II). It was found that the aldehyde product predicted on the basis of a concerted rearrangement was not the exclusive aldehyde product, even when it was the thermodynamically more stable product. The yields of the aldehyde products formed with retention of configuration at the tertiary centre were significant and in some cases even predominated. This can only be explained by the non-concerted reaction mechanism, in which a tertiary carbonium ion forms at the ring carbon. The exocyclic-methylene group with its BF_3-coordinated oxygen can rotate about the C-C bond, and hydride migration can occur to both faces of the carbonium ion, FIG. 3.

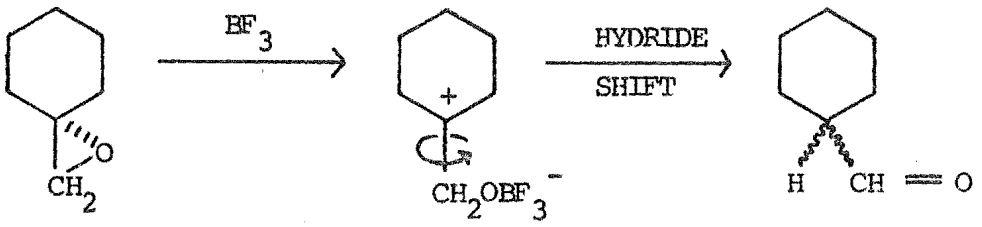


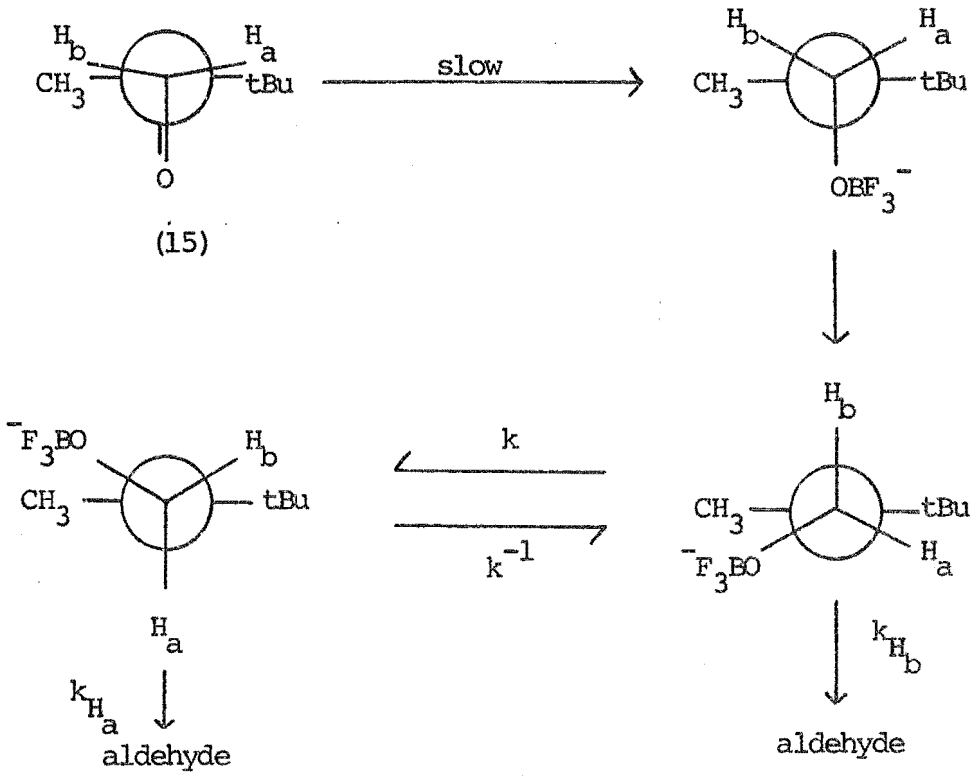
FIG. 3

An investigation[9] of the rate of hydride migration relative to the rate of rotation about the C-C bond for an unsymmetrically 1,1-disubstituted ethylene oxide(15) showed that the rate of hydride migration (k_H 1.46-1.71

TABLE II [8]

Compound	Product of concerted rearrangement	% axial CHO	% equatorial CHO
3α,3'-Epoxide	3α-(axial)CHO	26	74
3β,3'-Epoxide	3β-(equatorial)CHO	20	80
6α,6'-Epoxide	6α-(equatorial)CHO	52	48
6β,6'-Epoxide	6β-(axial)CHO	67	33
7α,7'-Epoxide	7α-(axial)CHO	95	5
7β,7'-Epoxide	7β-(equatorial)CHO	67	33
12α,12'-Epoxide	12α-(axial)CHO	72	28
12β,12'-Epoxide	12β-(equatorial)CHO	60	40

relative to k_D 1.00) was comparable to the rate of conformational rotation (k_R 1.80-1.84). The barrier to rotation is therefore comparable with the transition state barrier to hydride migration. Furthermore, by considering the possible rotational conformations of the carbonium ion intermediate it was possible to rationalise the marked preference (1.9:1) for migration of the hydrogen cis to the methyl group in epoxide (15) (see FIG. 4). Following the slow C-O cleavage it was assumed that the direction of rotation of the methylene group about the C-C bond is such that the steric interaction between the OBF_3^- and the t-butyl group is minimised (i.e. the rotation is clockwise in FIG. 4).



(15)

FIG. 4

A clockwise rotation of 60° places H_b in a favourable position to migrate to the β face of the carbonium ion. A clockwise rotation of 120° will allow H_a to migrate to the α face of the carbonium ion. Such a rotation is not favourable because of the torsional barrier involving the OBF_3^- and the t-butyl group. This model leads to an elegant rationalisation of the observed migratory preferences.

These results are relevant to rearrangements in the steroid epoxide field, if a number of assumptions are made;

a) the rate of conformational change from an initially formed C5-carbonium ion and the rate of subsequent rearrangement processes, are, at least to some extent, comparable;

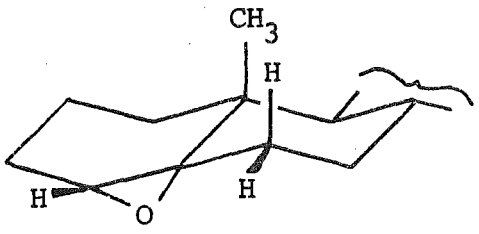
b) the feasibility of a reaction path is dependent on the ease with which the initially formed intermediate undergoes conformational adjustment to satisfy the stereochemical requirements of a subsequent rearrangement step.

This can be illustrated by considering the BF_3-catalysed rearrangements of the 4α,5α-(16a) and 4β,5β-(17a) epoxycholestanes, and the 5α,6α-(1a) and 5β,6β-(2a) epoxycholestanes[10]. In these reactions which proceed via a C5-carbonium ion, two alternative reaction paths predominate. Hydride migration may occur giving the 4- or 6-ketone, or the C10-methyl may migrate to the β-face of C5 to give the 5β-methyl-19-nor products. A less frequently observed reaction pathway involves the migration of the ring carbons C3 or C7 to C5 to give a ring-contracted aldehyde[3,4].

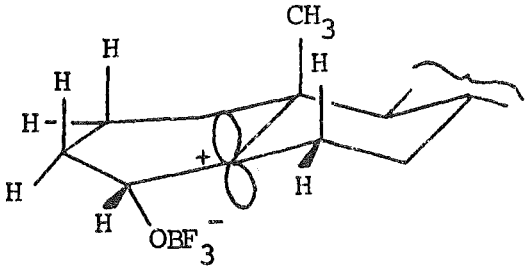
The initial conformation of the C5-carbonium ion is determined by the requirement that maximum overlap between the departing OBF_3^- and the vacant p-orbital of the developing carbonium ion, persists in the transition state for the heterolytic cleavage of the C5-O bond. This implies that the conformation of this transition state is such that the departing C-OBF_3^- is eclipsed with the vacant p-orbital of the developing C5-carbonium ion. As a consequence of the relative flexibility of ring A the

initial conformation of the 4,5-epoxycholestanes is uncertain. For the 4α,5α-epoxide(16a), the two possible conformations (a) and (e), FIG. 5, of ring A, on C5-O bond cleavage, lead to two possible conformations of the C5-carbonium ion (b) and (f) respectively. In both of these conformations, ring B is in the chair form, and the C10β-methyl is not suitably aligned with the vacant C5 p-orbital for migration to occur (observed methyl migration 11%). The conformational change required to align the C10β-methyl with the C5-carbonium ion (c) and (g) involves energetic changes in ring B in both cases. A minor conformational change (i.e. a small energy change) is required to give conformations (d) and (h) respectively, in which the C4β-hydrogen is suitably aligned for migration (observed hydride migration 76%).

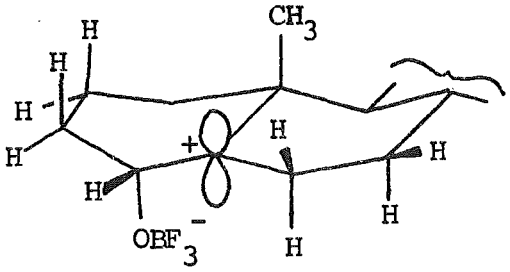
The 4β,5β-epoxide (17a) will similarly exist in one of two possible conformations (a) and (e), FIG. 6. Cleavage of the C5-O bond leads to conformations (b) and (f) respectively, of the C5-carbonium ion intermediate. In both of these conformations, ring B is in the chair form, but in contrast to the 4α,5α-epoxides, only a minor conformational adjustment is necessary for the C10β-methyl to become aligned with the vacant C5 p-orbital to give conformations (c) and (g), (observed methyl migration 37%). An alternative minor conformational change will give rise to conformations (d) and (h) in which the C4α-hydrogen can migrate (observed hydride migration c.a. 41%). For the 5β,6β-epoxide (a), FIG. 7, cleavage of the C5-O bond leads to conformation (b) in which the C10β-methyl is



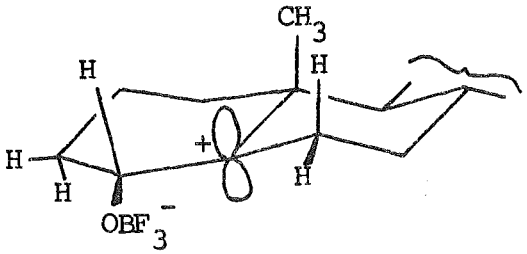
(a)



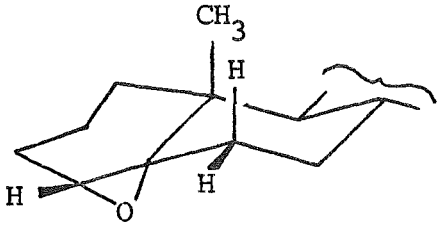
(b)



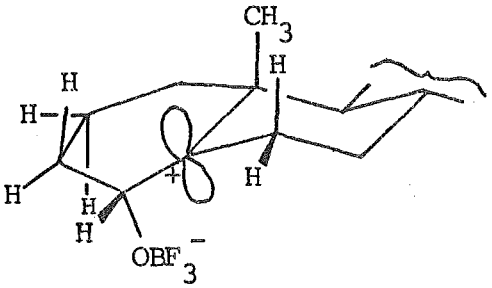
(c)



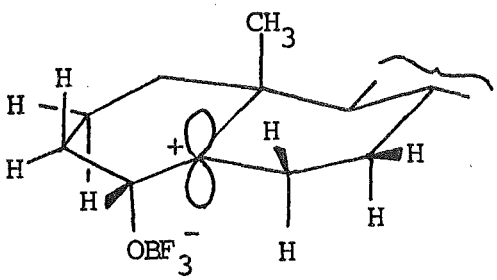
(d)



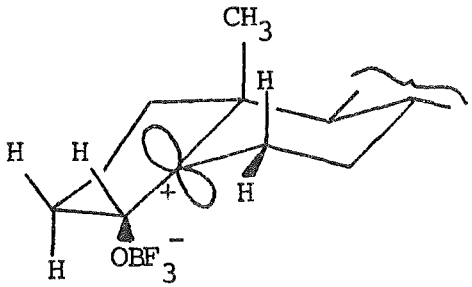
(e)



(f)

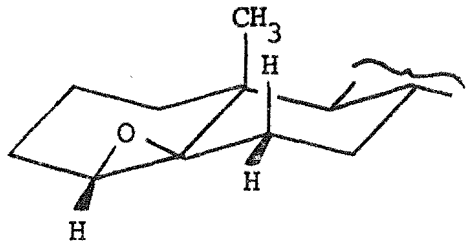


(g)



(h)

FIG. 5



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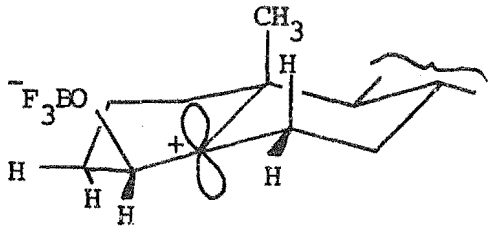

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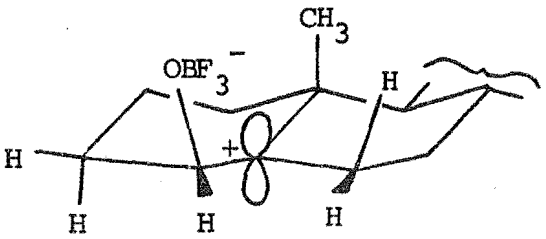

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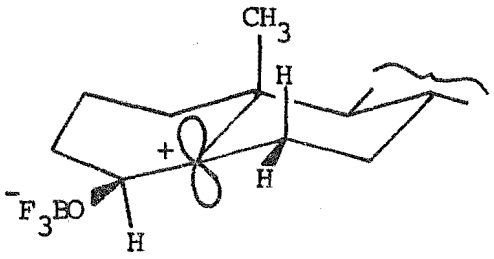

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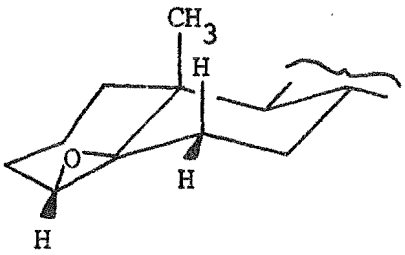

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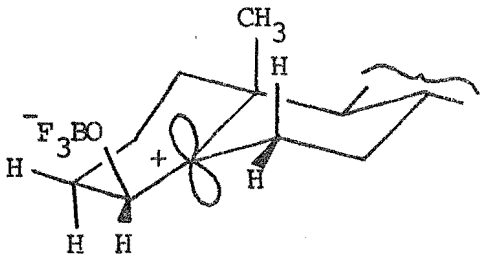

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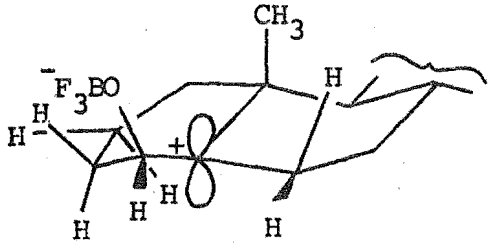
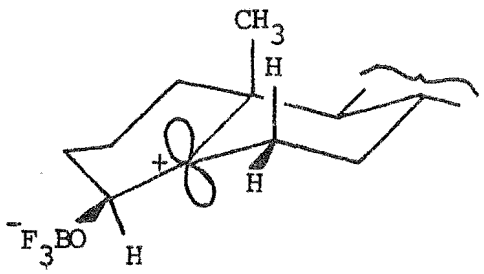
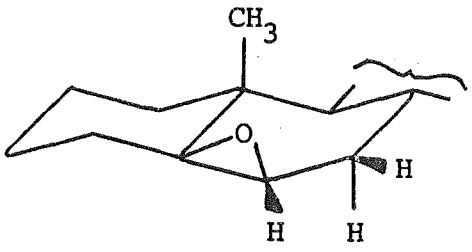


(g)

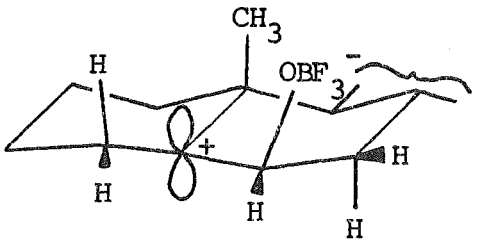


(h)

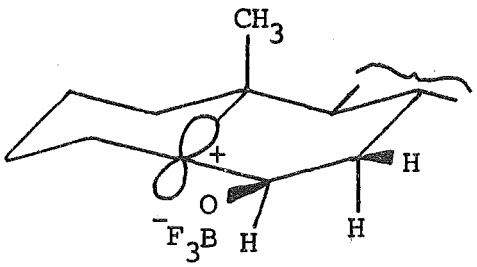
FIG. 6


CH3
O
H
H
H

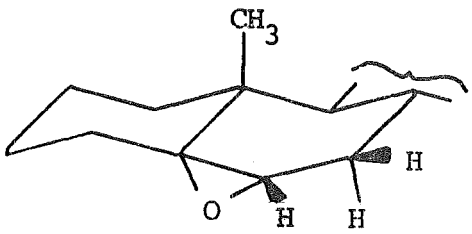
(a)


CH3
H
OBF3
+
H
H
H
H

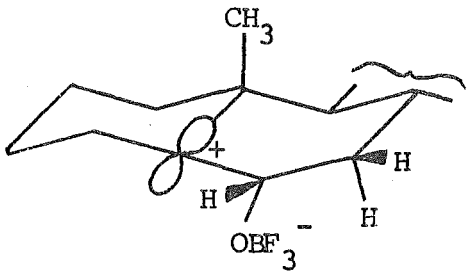
(b)


CH3
+
H
O
F3B
H
H

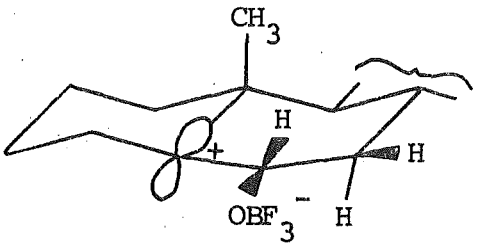
(c)


CH3
H
O
H
H

(d)


CH3
+
H
H
OBF3
H

(e)


CH3
H
+
H
OBF3
H

(f)

FIG. 7

suitably aligned for migration to C5 (observed methyl migration 46%). The carbonium ion may also undergo a conformational change to give (c) in which the C6α-hydrogen can migrate, (observed hydride migration 20%). The 5α,6α-epoxide (d), however, cleaves to form a C5-carbonium ion, the initial conformation of which has ring B in the boat form (e). In this conformation the C10β-methyl is not suitably oriented for migration to occur (20% methyl migration observed), however a conformational change to give (f) may occur, which, while not greatly affecting the relative positions of the C10β-methyl, and the C5 p-orbital, allows migration of the C6β-hydrogen to take place (50% observed).

So far the discussion on the development of an understanding of steroid epoxide rearrangements has been largely confined to a consideration of 4,5- and 5,6-epoxides. In order to examine the general applicability of the proposed mechanistic theories a large number of different types of epoxides have been studied. These can be divided into three main categories:

(a) tetrasubstituted epoxides;

(b) epoxides with an electron-withdrawing (-I) substituent on carbons neighbouring the epoxide ring;

(c) epoxides at different positions of the steroid skeleton, including disubstituted epoxides.

(a) Tetrasubstituted Epoxides

For the tetrasubstituted epoxides, the direction of epoxide opening is no longer explained in terms of cleavage towards the more substituted epoxy-carbon. The

preferred direction of cleavage is such that the developing OBF_3^- group can provide maximum residual solvation of the developing carbonium ion in the transition state for epoxide cleavage. This condition is fulfilled when an epoxide opens to a chair intermediate with the OBF_3^- group in an axial position, FIG. 8.

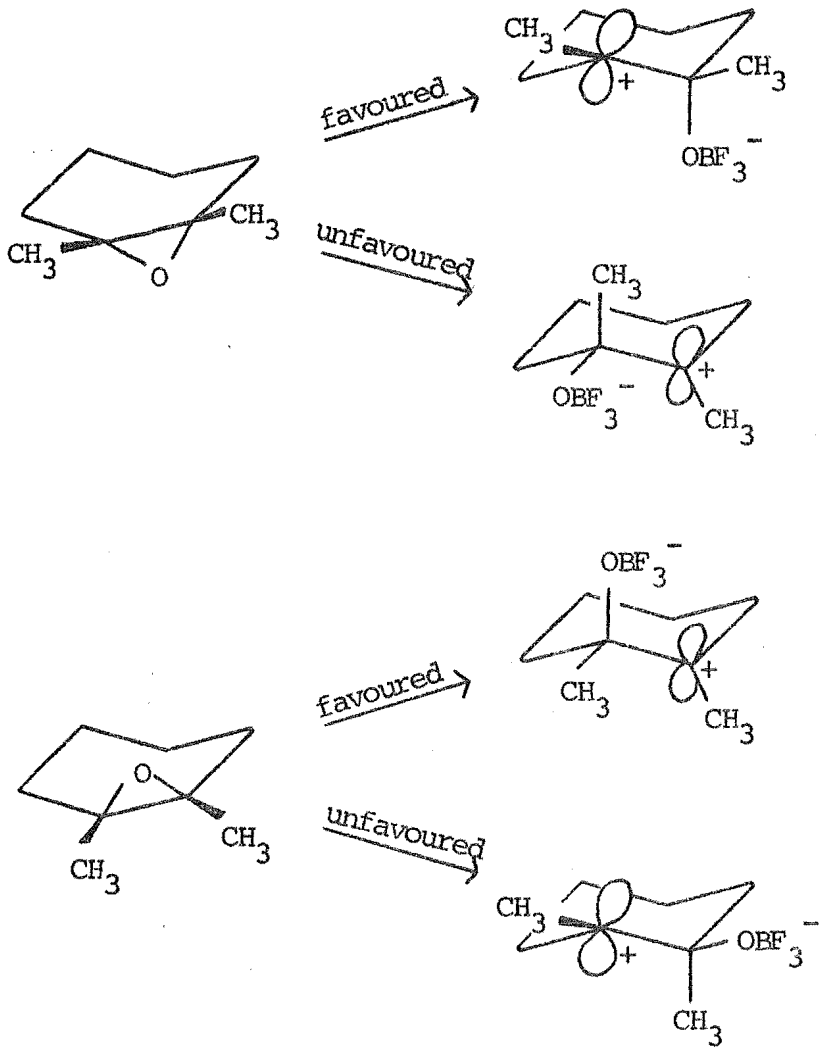


FIG. 8

The systematic study of the 4-methyl-4,5-epoxides (16b,17b)[11], and the 6-methyl-5,6-epoxides (18a,18b)[12] has shown that the major products of the BF_3-catalysed rearrangements of these epoxides are formed as a result of

a preferred direction of cleavage (see TABLE III).

TABLE III [13]

Epoxide	Product of Methyl Migration[a]	Ketones (% yield) Ring Contraction[b]	Skeletal Rearrangement[c]
4-Methylcholestane			
4α,5α-epoxide(16b)	(42[d])	-	84(ax)
4β,5β-epoxide(17b)	40(ax)	6	-
6-Methylcholestane			
5α,6α-epoxide(18a)	(30[d])	-	75(ax)
5β,6β-epoxide(18b)	16(ax)	23(ax)	-

a 5-methyl-4 or 6-ketones(19,20).

b 5-acetyl-A-nor- or 5-acetyl-B-nor-cholestanes(21,22).

c A-nor-B-homo-6-ketones or A-homo-B-nor-4a-ketones (23,24).

d Final product of thermodyanically controlled rearrangement.

(ax) product derived from axial cleavage.

(b) Epoxides with -I Substituents

The study by Henbest and Wrigley of the 3-acetoxy-5α,6α-epoxides(1b,1c), TABLE I, provoked interest in the rationalisation of the effect of a -I substituent on the course of an epoxide rearrangement. They suggested that the rearrangement of the 3α-acetoxy-5α,6α-epoxide(1b) gave the 5β-6-one(3b), whereas rearrangement of the

3β-acetoxy-5α,6α-epoxide(1c) gave the 5α-OH,6β-fluoro-derivative(11a) because:

(i) cleavage of the C5-O bond in these epoxides is hindered by an electron withdrawing (-I) 3-substituent

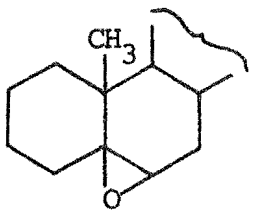
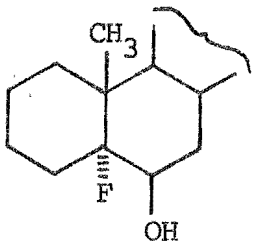
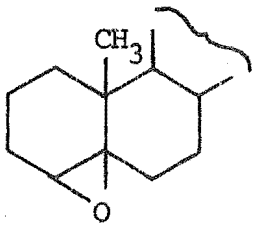
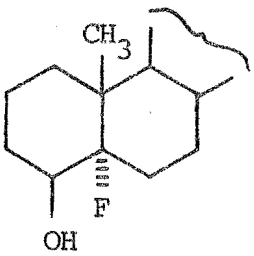
(ii) migration of the C6-hydrogen to C5 to form the 6-ketone product involves an inversion of ring A which in turn implies that the orientation of the 3-substituent also changes (i.e. axial to equatorial or vice versa).

Bowers et al.[14] set out to test this hypothesis by studying the BF_3-catalysed rearrangements of a series of 3-substituted-5α,6α-epoxides in which the symmetry of the 3-substituent was such that the group did not introduce a conformational bias during the rearrangement process. Bowers predicted that the product of the rearrangement would be a fluorohydrin arising from the C6-O cleavage because C5-O cleavage was disfavoured by the -I effect of the 3-substituent. These predictions were apparently supported by an observed yield of 44% fluorohydrin (5α-OH,6β-F(11c)) from the rearrangement of the 3-keto-5α, 6α-epoxide(1d) and 55% fluorohydrin (11d) from the rearrangement of the 3,3-ethylenedioxy-5α,6α-epoxide(1e).

An investigation[4] into the effects of varying the type of reaction solvent used in the BF_3-catalysed rearrangements of the 4β,5-epoxy-5β-cholestane(17a) and the 5,6β-epoxy-5β-cholestane(2a) showed that the nature of the reaction products depended markedly on whether the reaction solvent was benzene or ether. It was also found that the rate of product formation was greater in benzene.

For both rearrangements the yield of the corresponding fluorohydrin was significantly greater when the reaction was carried out in ether (see TABLE IV).

TABLE IV

Epoxide	Reaction Solvent		Fluorohydrin Product	
 (2a)	benzene	-		+6% fluoro compound
	ether	57%		
 (17a)	benzene	3%		
	ether	67%		

The production of higher yields of fluorohydrin in the "ether reactions" suggested the possibility of fluorohydrin intermediacy in the faster "benzene reactions". Evidence for the intermediacy of the fluorohydrins in the "benzene reaction" was obtained by reacting the respective fluorohydrins with BF_3-etherate in benzene. The products of these reactions were similar to those obtained by the rearrangement of the corresponding epoxides. It was notable that in rearrangements of the 4β,5β-epoxide(17a)

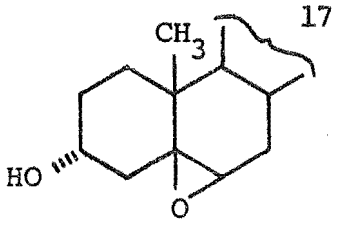
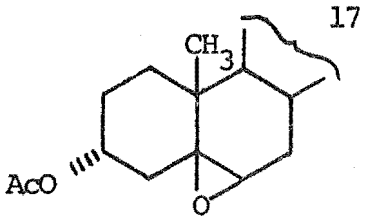
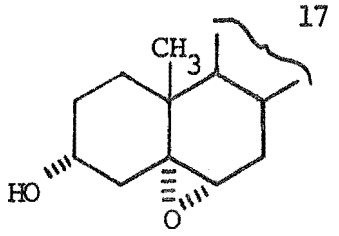
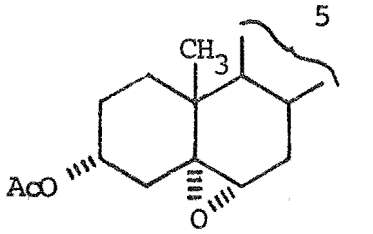
for which a benzene-ether solvent was used, admixture of 4% ether was sufficient to give the products of the "ether reaction".

In the light of the above study Coxon, Hartshorn and Sutherland[15] examined the rearrangement of the 3,3-ethylenedioxy-5α,6α-epoxide(1f) with BF_3-etherate using benzene as the reaction solvent rather than the 1:1 benzene ether solvent used by Bowers. The rearrangement products consisted of 21% fluorohydrin, 20% 6-ketone plus other products. This result was no longer consistent with the Bowers prediction, but merely reflected the observation made in the study of solvent effects[4], that subtle changes in the reaction solvent can drastically affect product ratios.

The 3,3-ethylenedioxy-5β,6β-epoxide[16](2c) was rearranged with BF_3 in benzene and reported to give 43% 6-ketone but no fluorohydrin. In this case the steric hindrance of the 3-substituent is thought to play a large part in the course of the reaction.

In addition to the initial work of Henbest, a detailed systematic study of the rearrangements of the 3α-acetoxy, and the 3α-hydroxy-5,6-epoxides was carried out[5,17] and the results of this work are summarised in TABLE V. As well as the previously observed 6-ketones and fluorohydrins, products arising from C10-methyl migration were also observed.

TABLE V

Epoxide	Reaction Solvent	Time	Products	
	benzene	35sec	starting material	7%
			3α,10α-oxido-deriv.(13b)	28%
			3α-OH-6-one(8b)	19%
			$\Delta^{13(17)}$ (10d)	36%
3α-hydroxy-5β,6β-epoxide				
	CH_2Cl_2	60sec	5α-acetoxy-3α,6β-diol(25)	88%
3α-acetoxy-5β,6β-epoxide				
	benzene	25sec	3α,10α-oxido-6α-OH(13a)	13%
			fluorohydrin(11e)	47%
			3α-OH,6-one(3c)	14%
			$\Delta^{13(17)}$ (10e) c.a.	10%
3α-hydroxy-5α,5α-epoxide				
	benzene	25sec	fluorohydrin(11b)	8%
			6-ketone(3b)	17%
			$\Delta^{13(17)}$ (10c)	37%
			$\Delta^{8(14)}$ (9)	27%
			oil	4%
3α-acetoxy-5α,6α-epoxide				

Current interpretations of these studies involve the intermediacy of a C5-carbonium ion, therefore the orientation of the 3-substituent in the product (see p.16) is no longer critical. The effect of a 3-substituent is important, however, when the relative stabilities of the various conformations of the C5-carbonium ion are being considered. In this way the orientation of the 3-substituent may influence the reaction course, but it is only one of many factors, including steric effects and solvent, which determine the final product ratio.

(c) Rearrangement of the 11,12-epoxides

A systematic study has been made of the BF_3-catalysed rearrangements of 11,12-epoxy-derivatives of titogenin acetate[18]. The rearrangement products of the 12β-methyl-11α,12α-epoxide(26) can be rationalised in terms of initial C12-carbonium ion formation, followed by migration of the C13,C14-bond to form products (27; observed yield 34%) and (28, observed yield 14%), or migration of the C9,C10-bond to form (29; observed yield 16%) and (30; observed yield 21%). The stereochemical orientation of the hydroxyl group in product (28) is anomalous; this product is thought to be formed by rupture and reclosure of ring C.

The BF_3-catalysed rearrangement of the 11α,12α-epoxy (31) and the 11β,12β-epoxy(33) derivatives represent examples of 1,2-disubstituted epoxide rearrangements. These reactions would not be likely to proceed via a discrete secondary carbonium ion intermediate but would probably tend to rearrange via a concerted mechanism. The requirement, however, that a maximum overlap between the

departing OBF_3^- group, and the developing vacant p-orbital be maintained in the transition state for heterolytic cleavage of the C-O bond is perhaps even more significant in the rearrangements of a 1,2-disubstituted epoxide.

This prediction is supported by experiment. The major products of the BF_3-catalysed rearrangements of the 11α, 12α-epoxy, and the 11β,12β-epoxy derivative are formed via a transition state with a conformation possessing maximal OBF_3^--carbon p orbital overlap. The α-epoxide cleaves towards C11 to give (32, observed yield 53%), and the β-epoxide cleaves towards C12 to give (34, observed yield 57%). The formation of the C-nor-D-homodiene (34, observed yield 40%) from the 11α,12α-epoxide, appears to be an exception.

The 11,12-epoxy steroids are the only examples of epoxides whose carbon atoms do not coincide with a skeletal ring junction, which have been subjected to systematic rearrangement studies. In this case, however, a complete explanation of the course of these rearrangements must take into account the considerable constraints imposed by the trans ring fusions of ring C to both ring B and ring D.

The purpose of the present investigation was to determine the validity of the mechanistic model of steroid epoxide rearrangements outlined above by extending the study to systems where

(i) the carbon atoms of the epoxide ring do not coincide with a skeletal ring junction;

(ii) the constraints imposed on the course of the epoxide rearrangement by the trans-ring fusions of the

steroid nucleus, are minimal;

(iii) any other functional group present is sufficiently isolated from the epoxide function to have little influence on the course of the rearrangements.

DISCUSSION

Preparation of the Ring D Epoxides

The major part of this project is concerned with the study of a series of C17-,C17a-D-homo-steroidal epoxides. The study was to be primarily concerned with the synthesis and acid-catalysed rearrangement of the unsubstituted (35,36), C17- and C17a-monomethyl(37,38, and 39) and C17, C17a-dimethyl(40), C17,C17a-epoxides of 3β-acetoxy-D-homo-5α-androstane. The carbon atoms of the epoxide ring in these compounds do not correspond with a ring junction of the steroid skeleton, but are adjacent to such a centre. The course of the rearrangement of the ring D epoxides is expected to contrast to previous work on epoxides situated in rings B and C. Rings B and C are constrained by being trans-fused to rings A and C and B and D respectively. Ring D, however, is more flexible being trans-fused only to ring C. While the above series of ring D epoxides contain a C3β-acetoxy function, it is not expected to influence the course of the rearrangement, because of its large separation from the epoxide group.

While a number of ring D epoxide studies[19] have been carried out in the normal steroid skeleton, none have been investigated in simple D-homo-systems[20]. The C1,C2-epoxides in the normal steroid would be expected to behave somewhat differently to the C17,C17a-D-homo-epoxides due to the interference of C11. Such a constraint is not present in the C17,C17a-D-homo-epoxides. Some analogy of reactions might otherwise have been expected for these two series of epoxides.

The preparative routes to the D-homo-steroids are well documented[21,22], however the D-homo products produced, in many cases, are not suitable precursors for the preparation of epoxides required in this study.

Goldberg reported[23] a synthesis involving a Tiffeneau ring enlargement on the normal 5-membered ring D steroid to give a mixture of the 17- and 17a-keto-D-homo-5α-androstanes (50a) and (49a), FIG. 9.

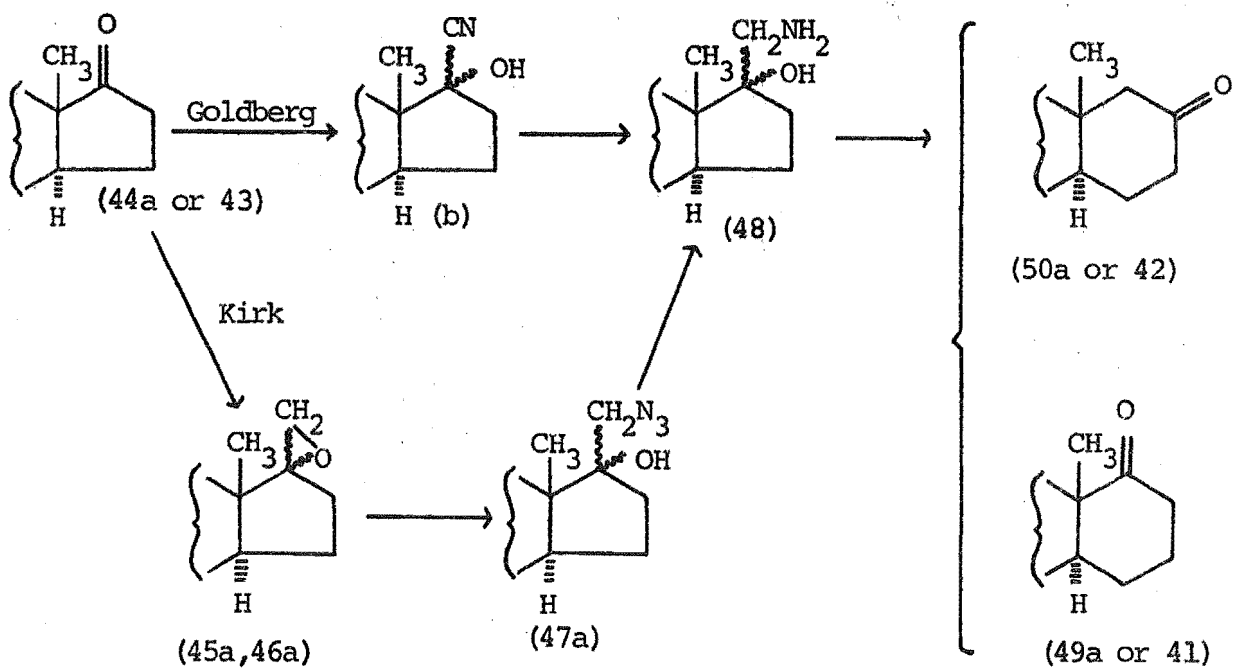


FIG. 9

A modification of this synthesis, outlined by Kirk and Wilson for the preparation of the 3β-acetoxy-D-homoandrost-5-en-17 and 17a-ones (42) and (41) from 3β-acetoxyandrost-5-en 17-one(43)[24], avoided the need to prepare the cyano-hydroxy intermediate compound (b) as required in the earlier synthesis (see FIG. 9). In the absence of the Δ^5-double

bond, however, epiandrosterone(44a) did not react to give the 17 and 17a-D-homo ketones in as high a yield as the similar reaction of 3β-acetoxyandrost-5-en-17-one(43).

Reaction of epiandrosterone with dimethyloxosulphonium methylide, prepared in situ[25], gave a mixture of two epimeric epoxides, namely 17α,20-epoxy-21-nor-5α-pregnan-3β-ol(45a), and 17β,20-epoxy-21-nor-5α-pregnan-3β-ol(46a). Only one epoxide could be isolated in a pure state from the epimeric mixture, and it was assigned the 17β,20-epoxy-configuration(46a) by a comparison of the n.m.r. spectra with that reported[26] for the analogous epoxide containing a $\Delta^{5(6)}$-double bond. The 17β-epoxide and a small sample rich in the 17α-epoxide, which had been obtained by successive recrystallisation, were acetylated.

The crude epimeric mixture of 17,20-exocyclic epoxides* was reacted with sodium azide in dimethylformamide containing boric acid[26] to give the epimeric 20-azido-21-nor-5α-pregnane-3β,17α- and 17β-diols(47a). The n.m.r. possessed a C20-methylene quartet at δ 3.67, 3.46, 3.32, 3.12 (J_{HH} 12Hz), and the infrared spectrum indicated the presence of azide (ν_{max} 2100 cm^{-1}) and hydroxyl (ν_{max} 3450 cm^{-1}) functions. Reduction of the mixture of hydroxy-azides with a solution of chromous chloride gave the corresponding mixture of epimeric hydroxy-amines(48). The successful isolation of product from this reaction was found to be critically dependent on the complete neutralisation of the solution of amine salts with a strong base, and the subsequent careful extraction of the product from a suspension with insoluble chromium salts.

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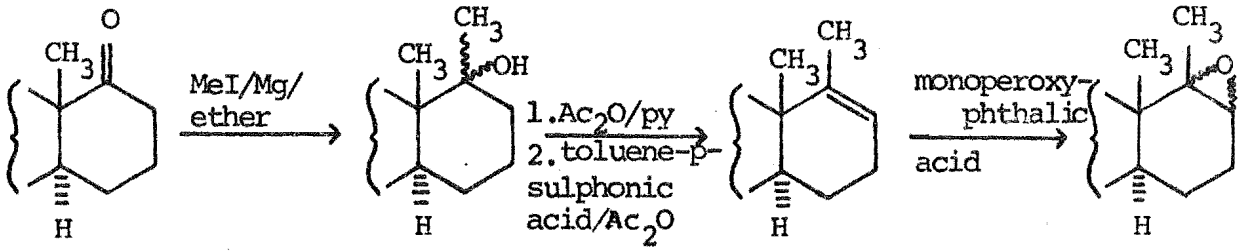
* This reaction was also carried out successfully on the 3β-acetates of the above mentioned epimeric mixture.

The crude hydroxy-amines(48) were then subjected to a Tiffeneau ring expansion reaction using sodium nitrite in aqueous acetic acid to give a mixture of 3β-hydroxy-D-homo-5α-androstan-17a-one(49a) and 3β-hydroxy-D-homo-5α-androstan-17-one(50a). Recrystallisation of the mixture of isomeric ketones gave pure 17a-ketone. Attempts to separate the ketones by column chromatography were unsuccessful.

Acetylation of the isomeric ketones gave the corresponding 3β-acetoxy derivatives (49b,50b) which could be partially separated by chromatography on alumina. After a series of several successive columns 3β-acetoxy-D-homo-5α-androstan-17a-one(49b) was isolated in reasonable quantities, but isolation of the pure 17-ketone (50b) could not be achieved. The overall yield of 17a-ketone that could be isolated pure was c.a. 17% from epiandrosterone, but the total ketone yield was c.a. 50%. The yield of ketones is lower than that obtained in the preparation of the 3β-acetoxy-D-homoandrost-5-en-17-(42) and 17a-ones(41) from 3β-acetoxy-androst-5-en-17-one(43) (yield c.a. 80%[26]). This lower yield of ketone products together with the difficulty in separating the isomeric ketones placed constraints on the proposed investigations. It was possible to obtain sufficient quantities of 17a-ketone but no pure 17-ketone could be obtained.

The 17a-ketone(49b) was reacted with methylmagnesium iodide[27,28] to give an epimeric mixture of 17aα-methyl-D-homo-5α-androstane-3β,17aβ-diol(51a), and 17aβ-methyl-D-homo-5α-androstane-3β, 17aα-diol (52a) (see FIG. 10).



(49b) (51a,52a) (53) (37,38)

FIG. 10

This mixture of diols was converted to the corresponding mixture of 3β-monoacetates(51b,52b) which were chromatographed on alumina. Repeated chromatography gave the pure 3β-acetoxy-17aβ-methyl-17aα-alcohol(52b), but the other epimer(51b) could not be isolated in this way. Evidence for the structure of the purified isomer was provided by the presence of a third tertiary methyl resonance in the n.m.r. at δ 1.09, and the elemental analysis. The O-H stretching vibration in the infrared spectrum was split (ν_{max} 3550, 3660 cm^{-1}) due to intermolecular hydrogen-bonding. The C17a-hydroxyl was assigned the α-configuration on the grounds that the C13-methyl resonance in the n.m.r. (δ 0.85 p.p.m.) occurred upfield of the C13-methyl resonance for the epimeric isomer (δ 0.93 p.p.m.)

Dehydration of the mixed 3β-acetoxy-17a-methyl-17a-alcohols, was achieved by treating a solution of the alcohols with acetic anhydride in the presence of toluene-p-sulphonic acid[29]. The crude product was filtered through a column of alumina and recrystallised to give pure 3β-acetoxy-17a-methyl-D-homo-5α-androst-17-ene(53). The n.m.r. of this compound

indicated a vinylic C17a-methyl at δ 1.60, and an olefinic proton at δ 5.21 ($W_{h/2}$ 8 Hz) assigned to the C17-proton.

The 17a-methyl-17-ene derivative (53) was epoxidised with monoperoxyphthalic acid[28]. Chromatography of the crude product gave starting material (2%) and an unidentified compound (4%).

The third compound to be isolated was 3β-acetoxy-17β, 17aβ-epoxy-17aα-methyl-D-homo-5α-androstane(38) (15%). The structure of this compound was assigned on the basis of a one-proton signal in the n.m.r. spectra at δ 2.93 ($W_{h/2}$ 3.5 Hz) assigned to H17, the absence of an O-H stretching vibration in the infrared spectrum, and the similarity of the chemical shifts of the three angular methyl groups, with those of the subsequently isolated epimer. The elemental analysis supported the assigned formula. The assignment of the β-configuration to this epimer was made on the basis of a comparison of the two epoxide epimers and will be discussed subsequently.

The fourth compound to be isolated (9%) remains unidentified.

The final compound to be isolated was 3β-acetoxy-17α, 17aα-epoxy-17aβ-methyl-D-homo-5α-androstane(37) (65%).

The assignment of the orientation of the epoxide ring in the above epimeric epoxysteroids (37,38) is confirmed by an examination of the respective H17 n.m.r. signals. Coupling of the C17-proton to the C16-methylene was more obvious in the α-epoxide, δ 2.86 (distorted doublet; $W_{h/2}$ 5.5 Hz), than in the β-epoxide, δ 2.93 ($W_{h/2}$ 3.5 Hz). This can be rationalised in the following way. For any flexible 6-membered ring epoxide two conformations (a) and (b), FIG. 11,

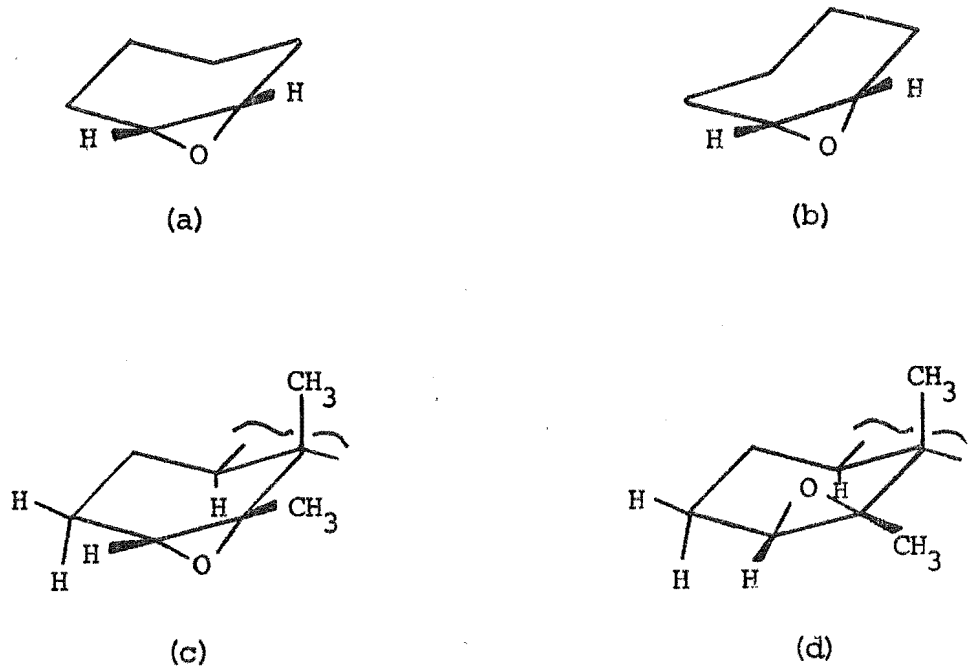
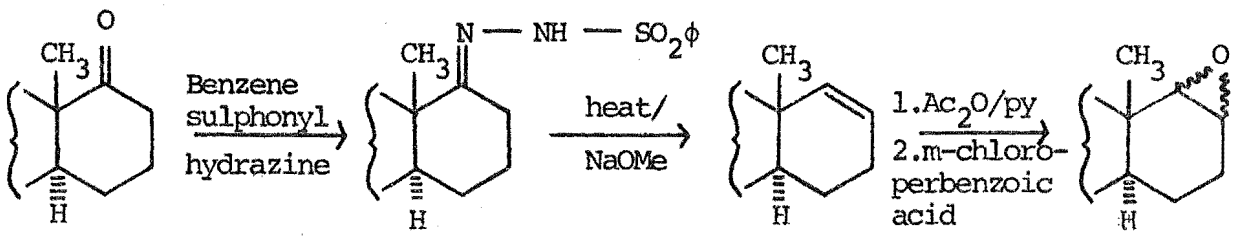


FIG. 11

of the ring are possible. However, in this instance ring D is constrained by trans-fusion with ring C and must adopt conformation (c) for the 17α,17aα-epoxide, and conformation (d) for the 17β,17aβ-epoxide. In these conformations the dihedral angles formed by the C17-proton, and the two C16-protons are c.a. 95° (H17,H16α) and c.a. 25° (H17,H16β) for the α-epoxide. The C17-proton in the β-epoxide however, approximately bisects the angle formed by H16α and H16β. A distorted doublet is predicted for the H17 signal of α-epoxide while a narrow singlet is expected for the H17 signal of the β-epoxide. These predictions are in accord with the patterns observed.

The 3β-acetoxy-17α,17aα-epoxy-(35b) and 3β-acetoxy-17β, 17aβ-epoxy-(36b) D-homo-5α-androstanes were prepared from the 17a-ketone(49b) in the following manner (see FIG. 12).



(49b) (54) (55a) (35b,36b)

FIG. 12

The 17a-ketone was converted by reaction with benzene-sulphonyl hydrazine to the benzenesulphonyl hydrazone(54). The hydrazone was pyrolysed under nitrogen at 160° in a solution of diglyme containing sodium methoxide in suspension, to give 3β-hydroxy-D-homo-5α-androst-17-ene(55a). The n.m.r. possessed a signal at δ 5.42 ($W_{h/2}$ 2 Hz) due to the C17- and C17a-olefinic protons. The olefin was then acetylated, and recrystallised to give 3β-acetoxy-D-homo-5α-androst-17-ene (55b).

Epoxidation of the acetoxy-olefin was carried out using metachloroperbenzoic acid and chromatography of the crude product gave starting olefin (c.a. 10%), followed by 3β-acetoxy-17β,17aβ-epoxy-D-homo-5α-androstane(36b) (9%). The n.m.r. of this compound showed a doublet at δ 2.71, 2.65 (J 3.5 Hz; H17a) and a broad signal at δ 3.13 ($W_{h/2}$ 7 Hz; H17). The infrared spectrum and elemental analysis were also consistent with the assigned structure. The assignment of the

β-configuration to this epimer is discussed subsequently.

The third compound to be isolated from the reaction was 3β-acetoxy-17α,17aα-epoxy-D-homo-5α-androstane(35b) (55%). The n.m.r. of this compound showed a doublet at δ 2.73,2.67 (J 4 Hz) due to H17a, and a broad peak δ 3.09 ($W_{h/2}$ 6 Hz) due to H17.

The configurations of these epoxides, were established on the basis of the stereochemistry of the fluorohydrins isolated from the rearrangement of these epoxides with BF_3-etherate, and the well-documented mode of formation of fluorohydrins in the course of an epoxide-cleaving reaction.

It was not possible to synthesise the 17,17a-epoxy-17-methyl compounds(39) by any of the attempted methods. The syntheses involved the α-methylation of 3β-acetoxy-D-homo-5α-androstan-17a-one(49b) (see FIG. 13).

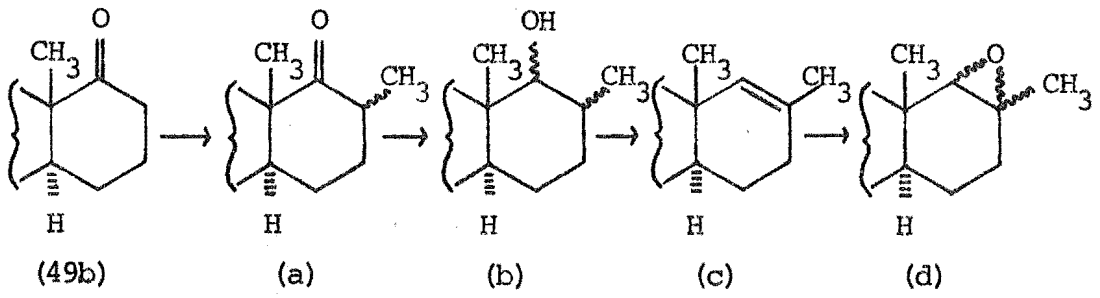


FIG. 13

This reaction was to be followed by reduction of the C17a-ketones(a) to the corresponding alcohols(b) which could then be converted by elimination of water to the

trisubstituted Δ^{17}-olefin(c). Epoxidation of the olefin would give the required epoxides(d). The α-methylation reaction was attempted using the reagents potassium-t-butoxide/methyl iodide[30] and sodium hydride/xylene/methyl iodide[31] but neither reaction was successful. The Stork modification[32] using the pyrrolidine enamine derived from the 17a-D-homo-ketone(49b) was attempted, but long reaction times under vigorous reaction conditions gave very little pyrrolidine enamine from the 17a-ketone. This could be due to the relatively hindered nature of the C17a-ketone.

The preparation of the 17,17a-dimethyl-17,17a-epoxides (40) from the available D-homo precursor would be even more difficult, as it would also involve C17-methylation, and consequently this series of epoxides was not considered further.

Rearrangements of Epoxides

In the course of the synthetic work involved in this project, a series of six epoxides were prepared. The rearrangements of these epoxides with BF_3-etherate will now be discussed.

Rearrangement of the C17,C20-epoxides(45b,46b)

Because of the difficulties in preparing large quantities of the pure isomers of these epoxides, and because of the apparent similarity in the nature of the rearrangement products as evidenced by t.l.c. the reactions were investigated in the following manner.

A mixture (c.a. 1:1) of the two epimeric exocyclic C17,C20-epoxides(45b) and (46b) was rearranged with BF_3-etherate (2 minutes at room temperature), and the products were separated by column chromatography. Two products could be isolated and identified.

The first product (9%) was shown to be 3β-acetoxy-17-methyl-18-nor-5α-androst-13(17)-ene(56). The C17-methyl signal in the n.m.r. at δ 1.59($W_{h/2}$ 4 Hz) is characteristic of a vinylic methyl group. A tetranitromethane test for a double bond was positive while the mass spectrum supported the assigned formula $C_{21}H_{32}O_2$. This product is formed by cleavage of the C17-O bond, followed by migration of the C13-methyl to C17. Elimination of formaldehyde from the steroid then gives the $\Delta^{13(17)}$-olefin, FIG. 14.

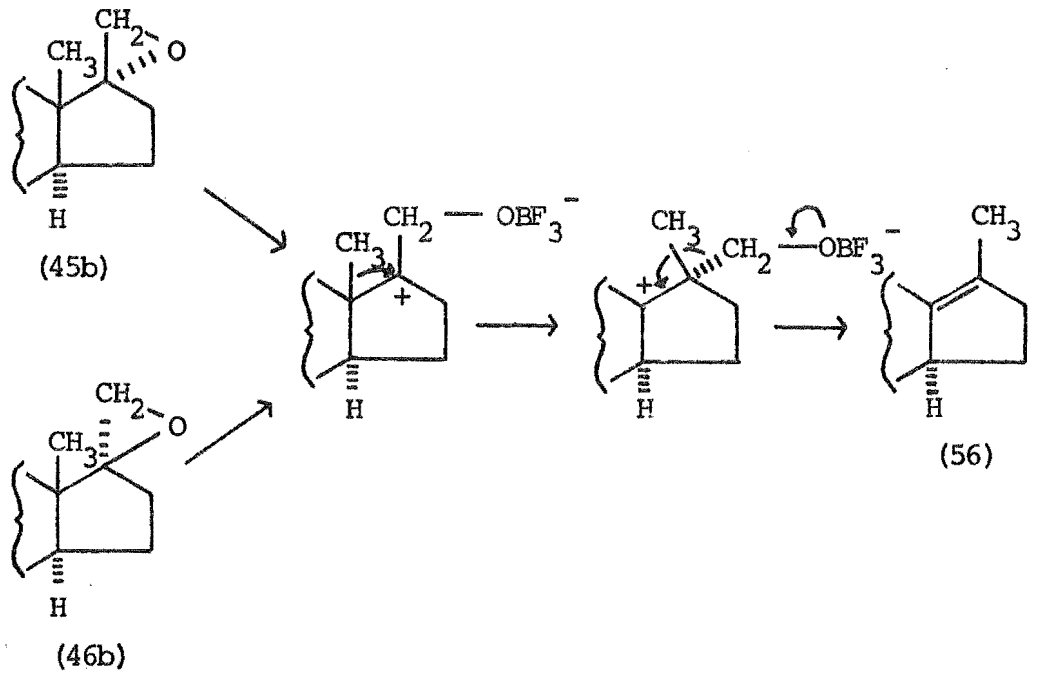


FIG. 14

This type of rearrangement, although uncommon, is not unprecedented. The rearrangement[33] of the 12α,12'-epoxy-derivative of 12-methylenetigogenin(a) , FIG. 15, gives the $\Delta^{13(17a)}$-olefin(b) in 20% yield, by a similar route.

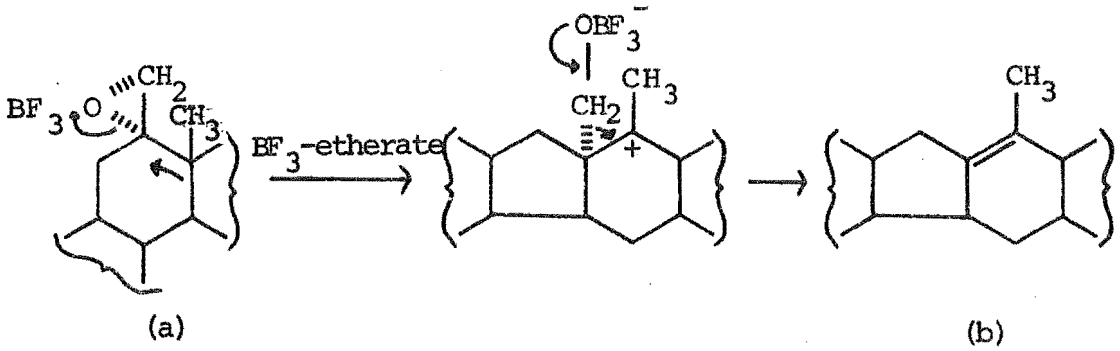
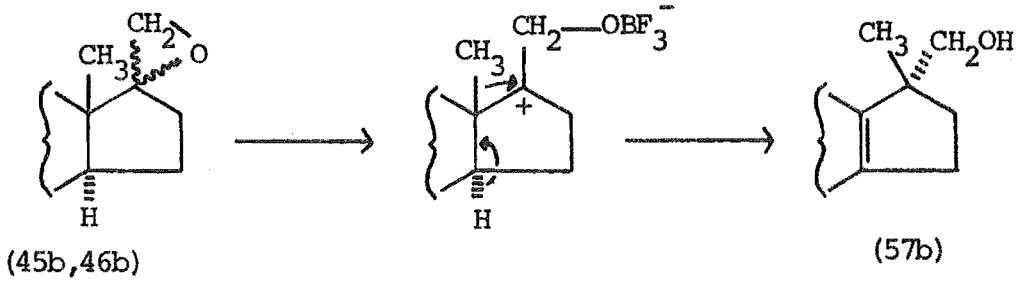


FIG. 15

The second product was identified as 3β-acetoxy-17α-hydroxymethyl-17β-methyl-18-nor-5α-androst-13-ene(57b)(37%) The compound gave a positive tetranitromethane test, the infrared spectrum possessed a hydroxyl-stretching vibration (ν_{max} 3300 cm^{-1}), and the n.m.r. resonance at δ 3.35 ($W_{h/2}$ 4 Hz) was assigned to the methylene protons α- to the hydroxyl group. The mass spectrum indicated the formula $C_{22}H_{34}O_3$. The double bond, was assigned to the $\Delta^{13(14)}$-position on the basis of the chemical shift of the C10-methyl resonance. The Zurcher values for the C10-methyl shifts caused by a $\Delta^{8(9)}$- and a $\Delta^{8(14)}$- double bond are, for the androstane series, +7.5, and -7.0 c.p.s. respectively. As no additional chemical shifts indicative of the presence of either a $\Delta^{8(9)}$- or a $\Delta^{8(14)}$- double bond were observed for the C10-methyl resonance of the above product, the double bond was assigned as $\Delta^{13(14)}$-. The

$\Delta^{8(14)}$- structure can also be excluded since ozonolysis followed by hydrolysis gave a dicarbonyl product which did not contain a 5-membered ring. This rearrangement product is formed by cleavage of the C17-O bond followed by migration of the C13-methyl and elimination of the H14-proton, FIG. 16.



(45b,46b) (57b)

FIG. 16

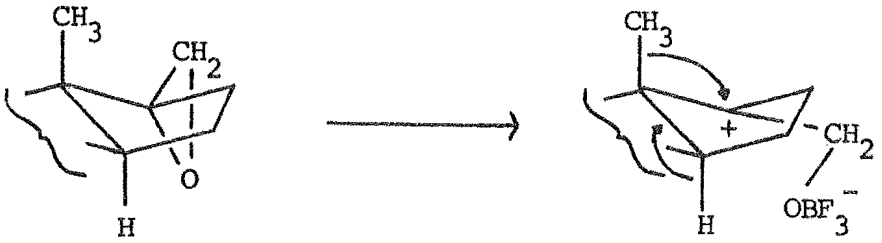
Other products present in the reaction could not be purified sufficiently to allow them to be characterised. In addition no aldehyde products were found as evidenced by the absence of aldehyde proton resonances in the n.m.r.

To establish the yields of the rearrangement products for the individual epoxides, a small pure or near-pure sample of each epoxide was isolated and rearranged. A comparison of the integrals of the C3α-proton, and the C20-methylene protons in the n.m.r. of the crude rearrangement products for each epoxide allowed an estimation of the yields of the hydroxy-olefin to be made (see TABLE VI).

TABLE VI

EPOXIDE	IDENTIFIED PRODUCTS	
	$\Delta^{13(17)}$olefin(56)	hydroxy-olefin(57b)
17α,20-epoxide(45b)	c.a. 10%	61%
17β,20-epoxide(46b)	c.a. 10%	33%

Because of the absence of a suitable peak for integration the yields of $\Delta^{13(17)}$-olefin could not be accurately obtained from the n.m.r. spectra, but were estimated to be c.a. 10% in each case. It is significant that the two epoxides rearrange to form differing amounts of the hydroxy-olefin(57b). This difference leads one to speculate as to the relative ease with which the C14-proton eliminates to form the $\Delta^{13(14)}$-olefin in the rearrangements of the epimeric epoxides. It is conceivable that the OBF_3^- group is suitably positioned during cleavage of the α-epoxide to assist in the removal of the C14-proton (see FIG. 17).



(45b) (a)

FIG. 17

Cleavage of the α-epoxide(45b) leads to the intermediate (a) in which the OBF_3^- group is placed in close proximity to the C14-proton. It is therefore possible that removal of the C14-proton in the elimination step is enhanced by the proximity of the basic OBF_3^- function. Cleavage of the β-epoxide (46b) (see FIG. 18), however, leads to intermediate (b) in which the OBF_3^- function is located on the β-face of the steroid remote from the C14-proton.

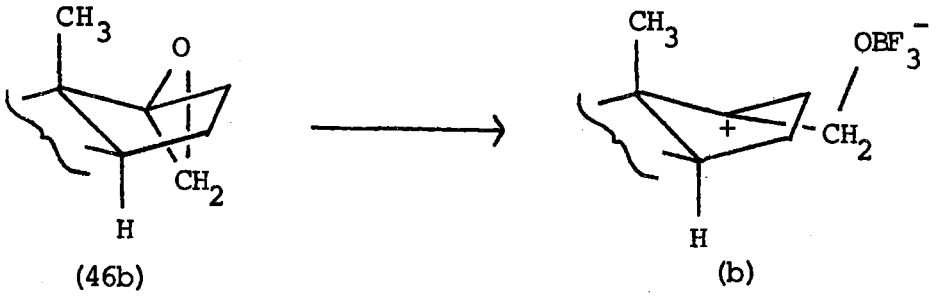


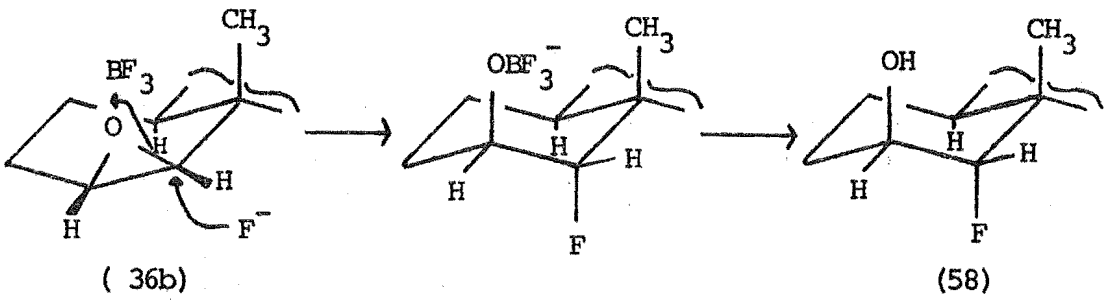
FIG. 18

In this conformation the OBF_3^- group can offer no assistance in the elimination of the C14-proton. On the basis of this argument one would expect a higher yield of hydroxy-olefin (57b) from the α-epoxide than from the β-epoxide. This prediction is in accord with experimental observations.

At the time this study was being conducted Kirk reported the rearrangement of 17β,20-epoxy-21-nor-17α-pregn-5-en-3β-ol[26]. The only product isolated was 3β-hydroxy-17α-hydroxymethyl-17β-methyl-18-norandrost-5,13(14)-ene(27.2%) analogous to the hydroxy-olefin(57a) isolated in the present study.

Rearrangement of the unsubstituted C17,C17a-epoxides(35b,36b)

Rearrangement of the 17β,17aβ-epoxide(36b) with BF_3-etherate (2 minutes at room temperature) followed by chromatography of the crude product on deactivated alumina gave 3β-acetoxy-17β-hydroxy-17aα-fluoro-D-homo-5α-androstane(58). The C10-methyl occurred at δ 0.08 in the n.m.r. while the C13-methyl appeared as a doublet (δ 1.02, 0.98), due to coupling with 17aα-fluorine (J_{HF} 2.5 Hz). The C17aβ-proton gave rise to a quartet at δ 4.43, 4.39, 3.68, 3.63 with coupling to F17aα (J_{HF} 45.5 Hz) and to H17α (J_{HH} 2.5 Hz), the latter coupling being demonstrated by a double-irradiation experiment. The C17α-proton appeared as a multiplet (δ 4.23, 4.18, 4.13, 4.07, 4.01, 3.97, 3.92 p.p.m. arising from H17α, F17aα coupling (J_{HF} 10 Hz) and H17α, H17aβ; H17α, H16α; and H17α, H16β coupling (J_{HH} c.a. 3.5 Hz). The C3α-proton alpha to the acetoxy-function occurred as a broad peak ($W_{h/2}$ 22 Hz) at δ 4.72. The presence of a hydroxyl group was indicated by the infrared spectrum (ν_{max} 3670 (sharp) 3470 cm^{-1} (broad)) while the formula $C_{22}H_{35}O_3F$ was consistent with the mass spectrum. Reaction of the fluorohydrin with potassium hydroxide in aqueous methanol gave an epoxide which was shown by n.m.r. to be identical to an authentic sample of 17β,17aβ-epoxy-D-homo-5α-androstan-3β-ol(36a). The fluorohydrin arises from the 17β,17aβ-epoxide by F^- attack at C17a with cleavage of the C17a-OBF_3^- bond. The OBF_3^- group is subsequently hydrolysed to give the diaxial fluorohydrin, FIG. 19.

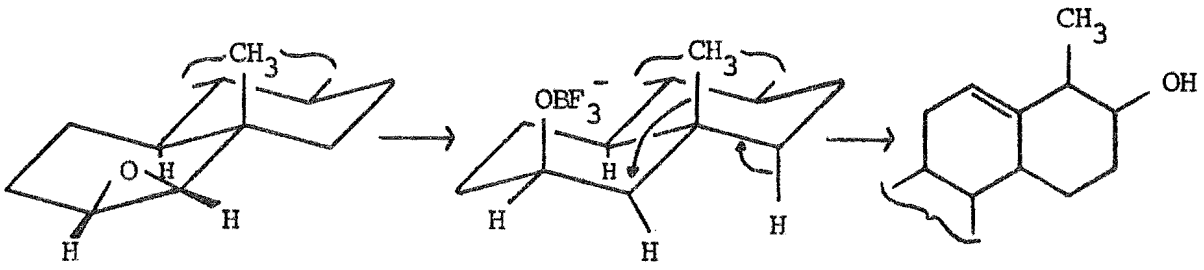


(36b) (58)

FIG. 19

A second compound (17%) isolated from the rearrangement, was assigned as 3β-acetoxy-17β-hydroxy-17aβ-methyl-18-nor-D-homo-5α-androst-12-ene(59). The n.m.r. indicated the C17aβ-methyl as a doublet at δ 1.13, 1.02, with coupling (J 7 Hz) to the C17aα-proton centred at δ 2.14. A signal characteristic of an olefinic proton at δ 5.50 ($W_{h/2}$ 11 Hz) was assigned to H12, and the signal at δ 3.87 ($W_{h/2}$ 9 Hz) was assigned to H17α. The position of the C17aα-proton was derived by a decoupling experiment. Irradiation, with a difference frequency of -64 Hz, caused the doublet C17aβ-methyl to collapse to a singlet implying that the C17aα proton was located at δ 2.14. The chemical shift of the C17aα-proton necessitates that this proton is allylic to the olefinic function, i.e. the olefinic function must lie in the Δ^{12}-position. The infrared spectrum indicated a hydroxyl function (ν_{max} 3500 cm^{-1}) and the mass spectrum was consistent with the assigned formula $C_{22}H_{34}O_3$. There appears to be no evidence for the intermediacy of the fluorohydrin(58) in

the formation of this product (59). The fluorohydrin(58) was rearranged with BF_3-etherate under conditions identical to those used in the rearrangement of epoxide(36b). After a time of 10 minutes the t.l.c. of the reaction products showed no increase in Δ^{12}-hydroxy-olefin(59) and the fluorohydrin starting material(58) appeared unchanged. The mechanism for the formation of the Δ^{12}-hydroxy-olefin product (59) in the rearrangement of the β-epoxide(36b) involves cleavage of the epoxide towards C17a, followed by migration of the C13-methyl to C17a. Elimination of H12 and hydrolysis of the OBF_3^- group gives the 17β-hydroxy-Δ^{12}-product, FIG. 20.



(36b) (59)

FIG. 20

It is again notable that retention of configuration occurs at C17a. Hence migration of the C13-methyl cannot occur in concert with C17a-O cleavage. The intermediacy of the less-favoured secondary C17a-carbonium ion is necessary for the formation of this product.

The 17α,17aα-epoxide(35b) was rearranged (2 minutes at room temperature) with BF_3-etherate, and the crude product was subjected to chromatography. The first material isolated was identified as impure 3β-acetoxy-17β-

fluoro-17aα-hydroxy-D-homo-5α-androstane(60). The yield of this product was estimated to be 40%. The C10-methyl occurred at δ 0.82 in the n.m.r. and the C13-methyl appeared as a doublet at δ 0.97, 0.90 with coupling (J 4 Hz) to the C17β - fluorine. The acetate resonance was located at δ 2.01. A quartet splitting pattern was queried for the C17aβ-proton resonance at δ 3.40 with coupling (J 9 Hz) to the C17β-fluorine, and (J 3 Hz) to the C17α-proton. The C17α-proton appeared as a doublet at δ 5.01, 4.24 with coupling (J 46 Hz) to the C17β-fluorine. The half-height widths of the doublet signals ($W_{h/2}$ 9.0 Hz; $W_{h/2}$ 8.5 Hz) are indicative of coupling of the C17α-proton to the C17aβ- and the two C16-protons. The C3α-proton occurred as a broad signal at δ 4.68 ($W_{h/2}$ 20 Hz). The infrared spectrum indicated the presence of a hydroxyl function, (ν_{max} 3650 (sharp), 3520 cm^{-1} (broad)), and the mass spectrum was consistent with the assigned formula $C_{22}H_{35}O_3F$. The impure product was acetylated with acetic anhydride-pyridine. The crude acetylation product was chromatographed on deactivated alumina, and recrystallised to give 3β-acetoxy-17aα-acetoxy-17β-fluoro-D-homo-5α-androstane(61). The n.m.r. possessed a doublet C13-methyl resonance at δ 1.05, 0.98 with coupling (J 4 Hz) to the C17β-fluorine. The two acetate resonances occurred at δ 2.02 (C3β-acetate) and δ 2.09 (C17aα-acetate), while the C17α-proton appeared as a doublet, due to coupling with the C17β-fluorine, and was partially obscured by the C3α-, and C17aβ-proton signals. The elemental analysis indicated the presence of a fluorine atom in the molecule.

Hydrolysis of the diacetate derivative with potassium hydroxide in methanol gave an epoxide which was identical with an authentic sample of 17α,17aα-epoxy-D-homo-5α-androstan-3β-ol(35a). Formation of the fluorohydrin in the above reaction involves attack by a F^- containing species at C17 (from the β-face of the steroid) and subsequent hydrolysis of the OBF_3^- function to give the diaxial fluorohydrin, FIG. 21.

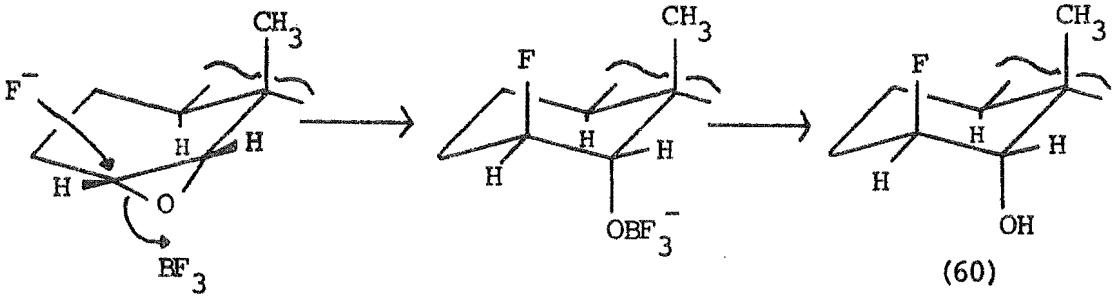


FIG. 21

Further chromatography of the crude rearrangement product gave mixtures of inseparable hydroxy-olefins. The n.m.r. and infrared spectra were consistent with the presence of hydroxyl functions (ν_{max} 3500 cm^{-1}, δ 3.45 ($W_{h/2}$ 6 Hz)), and a positive tetranitromethane test together with an absence of olefinic proton resonances in the n.m.r. indicated the presence of a tetrasubstituted double bond in these compounds.

In these studies, the formation of fluorohydrins was peculiar to the rearrangement of the unsubstituted epoxides (35b and 36b). This reaction course can be rationalised in terms of the potential intermediacy of energetically

unfavoured secondary carbonium ions in these rearrangements. Cleavage of the epoxides occurs so as to maintain maximum solvation of the developing secondary carbonium ion. The developing vacant p-orbital can be solvated not only by the departing OBF_3^- group but also by an external nucleophile (i.e. a F^- containing species). Bond formation between the solvated carbonium ion and fluorine leads to the formation of fluorohydrin. These fluorohydrin products are exclusively diaxial. When ring D is in the more stable chair conformation, maximum overlap between the departing OBF_3^- group, and the developing p-orbital is possible only when fluorohydrins are formed with diaxial stereochemistry. It is perhaps surprising that no products derived from C13-methyl migration were isolated from the rearrangement of the α-epoxide (35). Such a reaction course would have necessitated cleavage of the epoxide to give a boat conformation in order to maintain maximum overlap of the departing OBF_3^- with the developing vacant p-orbital (see FIG. 22). It is, however, possible that products derived from C13-methyl migration were produced but remained in the unresolved fractions.

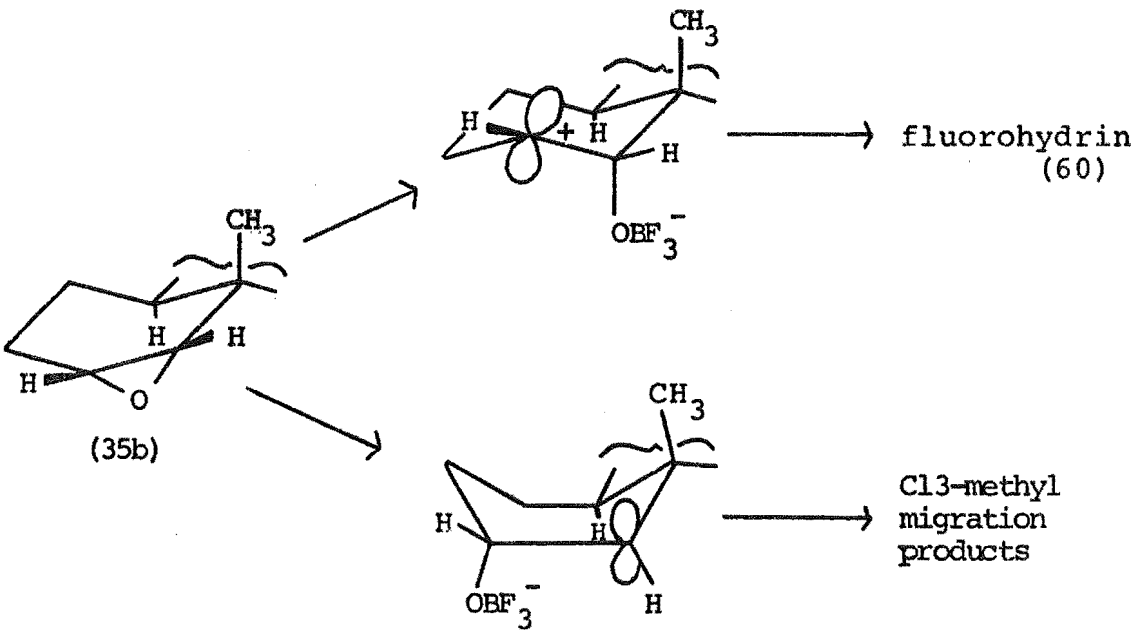


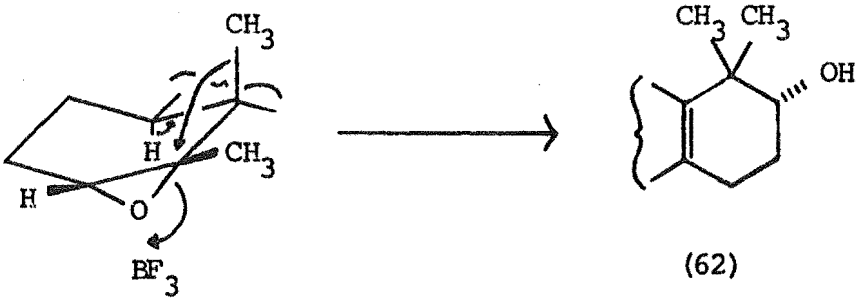
FIG. 22

Rearrangement of the C17a-methyl-C17,C17a-epoxides(37,38)

The 17aβ-methyl-17α,17aα-epoxide(37) was rearranged with BF_3-etherate (1 minute at room temperature) and the crude product was subjected to chromatography.

The major product (75%) was identified as 3β-acetoxy-17α-hydroxy-17a,17a-dimethyl-18-nor-D-homo-5α-androst-13(14)-ene(62). This compound was shown to be a secondary alcohol (ν_{max} 3450 cm^{-1}, δ 3.49 ($W_{h/2}$ 6 Hz; H7)). The double carbonyl peak in the infrared spectrum (ν_{max} 1735, 1715 cm^{-1}) reduced to a single peak (ν_{max} 1740 cm^{-1}) in the infrared spectrum of a dilute solution, indicating intermolecular hydrogen-bonding between the C17α-hydroxyl

function and the C3β-acetate. A tetrasubstituted double bond was indicated by a positive tetranitromethane test, and the absence of olefinic proton resonances in the n.m.r. The double bond was assigned to the $\Delta^{13(14)}$-position. The alternative positions for the double bond, namely $\Delta^{8(14)}$-, $\Delta^{8(9)}$-, and 9β-methy-$\Delta^{5(10)}$-, were ruled out since they necessitated an additional chemical shift of the C10-methyl resonance (δ 0.78 p.p.m. in the n.m.r. The Zürcher values for the C10-methyl shifts caused by a $\Delta^{8(9)}$- and a $\Delta^{8(14)}$- double bond are for the androstane series, +7.5, and -7.0 c.p.s. respectively. The shift in the C9-methyl signal caused by a $\Delta^{5(10)}$ -double bond, on symmetry grounds, is expected to be similar to the C10-methyl shift caused by a $\Delta^{8(9)}$-double bond. This product is envisaged as arising by cleavage of the C17a-O bond followed by migration of the C13-methyl to C17a, and elimination of the C14-hydrogen to form the $\Delta^{13(14)}$-double bond (see FIG. 23).



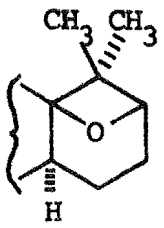
(37) (62)

FIG. 23

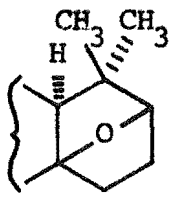
Chromium trioxide-pyridine oxidation of the product gave 3β-acetoxy-17a,17a-dimethyl-18-nor-D-homo-5α-androst-13(14)-en-17-one(63) in essentially quantitative yield. This compound showed a ketone stretching vibration in the infrared spectrum at ν 1715 cm^{-1} in addition to the acetate carbonyl stretching vibration (ν_{max} 1730 cm^{-1}). A tetranitromethane test was indicative of the presence of a double bond, while the elemental analysis supported the assigned formula $C_{23}H_{34}O_3$.

Non-polar material (14%) was also isolated from the rearrangement, but was subsequently shown to arise by reaction of the initially formed products, and was not considered further. A minor compound (7%) was isolated, but not identified. The n.m.r. and infrared spectra indicated the presence of a hydroxyl function (ν_{max} 3550 cm^{-1}, δ 3.23 ($W_{h/2}$ 7 Hz), 3.08($W_{h/2}$ 8 Hz).

The minor epoxide (38) from the epoxidation of the 17a-methyl-Δ^{17}-compound(53) was rearranged with BF_3-etherate (1 minute at room temperature) and the major components of the crude product were separated by chromatography. A cyclic ether (50%) was isolated. The n.m.r. indicated one proton α- to oxygen at δ 3.69 ($W_{h/2}$ 6.5 Hz), and the infrared spectrum showed that the compound was not an alcohol. This suggested that the compound was a cyclic ether involving an oxygen bridge between a secondary, and a tertiary carbon. It would be expected on the basis of the known preference for cleavage of the tertiary C-O bond of the epoxide, that the oxygen bridge would be between C17 and C13 or C17 and C14 (see FIG. 24).



(a)



(b)

FIG. 24

The available data, however, did not indicate conclusively which of the two possible structures (a) or (b) was correct. It is argued that the structure involving a five-membered oxido-ring, 3β-acetoxy-17a,17a-dimethyl-17β,13β-oxido-18-nor-D-homo-5α-androstane(b), would be the more likely possibility*. The larger ring strain involved in a four-membered oxido-ring would tend to disfavour this product. The cyclic ether arises <u>via</u> C17a-O cleavage of epoxide(38) to form a tertiary C17a-carbonium ion (c) (see FIG. 25). Migration of the C13-methyl to C17a results in the formation of a second tertiary carbonium ion (d) at C13. In the event that the OBF_3^- function attacks C13 <u>cis</u> to the departing methyl the four-membered oxido ring compound (a) would be formed, however, migration of H14 to C13 allows the OBF_3^- function to attack at C14(e), <u>trans</u> to the departing hydrogen to give the five-membered cyclic ether (b).

* The formation of five-membered oxido-ring compounds in the rearrangement of steroid epoxides has been previously recorded in the literature[17].

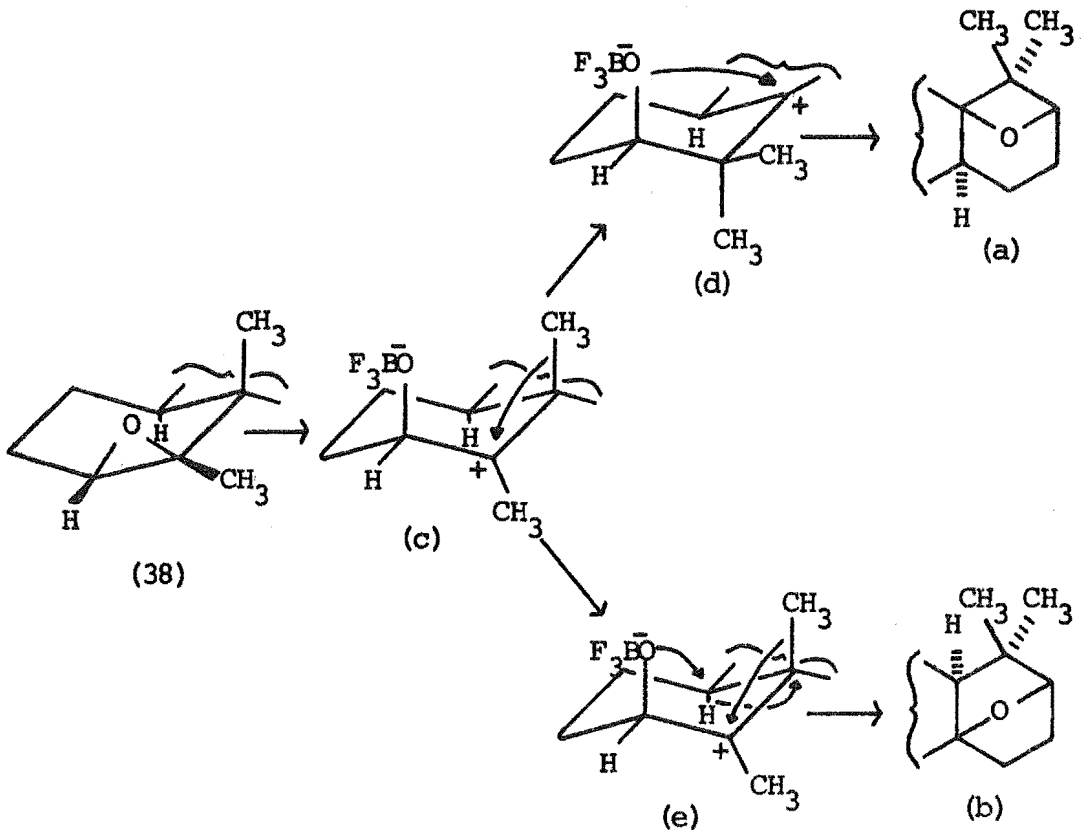


FIG. 25

It is further argued that the mechanism involving trans attack is the more feasible alternative, and hence the five-membered cyclic ether the more likely product. The mechanism cannot involve a synchronous attack of the C13-methyl at C17a with cleavage of the C17-O bond, since the methyl and the oxygen groups are in a cis relationship. The reaction must involve the intermediacy of a discrete carbonium ion at C17a. A further discrete carbonium ion at C13 would be required in order to form a four-membered oxido ring structure, but would not be necessitated in the formation of the five-membered oxido structure.

Further material (27%) was isolated from the crude rearrangement product mixture containing a predominance of a hydroxy-olefin(64). A comparison of the n.m.r. of this product with that of the 17β-hydroxy-$\Delta^{11,12}$-product(59) isolated from the rearrangement of epoxide (36b) indicated that these two products were similar (see TABLE VII).

TABLE VII

Hydroxy-olefin(64)	Hydroxy-olefin(59)	Signal
5.57 ($W_{h/2}$ 10 Hz)	5.50 ($W_{h/2}$ 11 Hz)	H12
4.68 ($W_{h/2}$ 20 Hz)	4.63 ($W_{h/2}$ 26 Hz)	H3α
3.47 ($W_{h/2}$ 10 Hz)	3.87 ($W_{h/2}$ 9 Hz)	H17α
2.01	2.01	OAc
1.12	1.13,1.02(doublet;J 7 Hz)	17a-methyl
1.03	-	17a-methyl
0.77	0.77	$(H19)_3$

The variation in the H17α- chemical shift is due to the presence of an additional C17a-methyl in the hydroxy-olefin (64). The structure of the hydroxy-olefin (64) is therefore assigned as 3β-acetoxy-17β-hydroxy-17a,17a-dimethyl-18-nor-D-homo-5α-androst-12-ene.

Finally 3β-acetoxy-17β-hydroxy-17a,17a-dimethyl-18-nor-D-homo-5α-androst-13(14)-ene(65) (19%) was isolated. The n.m.r. possessed a broad signal at δ 3.43 ($W_{h/2}$ 20 Hz), indicative of a proton α- to a hydroxyl function. The

presence of a tetrasubstituted double bond was demonstrated by a positive tetranitromethane test and the absence of olefinic proton resonance in the n.m.r. The mass spectrum supported the assigned formula $C_{23}H_{36}O_3$. The hydroxyl group was oxidised to the corresponding ketone using chromium trioxide-pyridine. The ketone derivative gave an n.m.r. which was identical to that of the ketone derived by oxidation of 3β-acetoxy-17α-hydroxy-17a,17a-dimethyl-18-nor-D-homo-5α-androst-13(14)-ene(62) indicating that the hydroxy-olefin(65) derived from the rearrangement of the 17aα-methyl-17β,17aβ-epoxide(38) was simply the C17-epimer of the hydroxy-olefin(62) derived from the rearrangement of the 17aβ-methyl-17α,17aα-epoxide(37).

The hydroxy-olefin(65) is formed in the rearrangement of the 17aα-methyl-17β,17aβ-epoxide by cleavage of the C17a-O bond to form a C17-carbonium ion intermediate, followed by migration of the C13-methyl to C17a, and elimination of the C14-proton to give the $\Delta^{13(14)}$-double bond, FIG. 26.

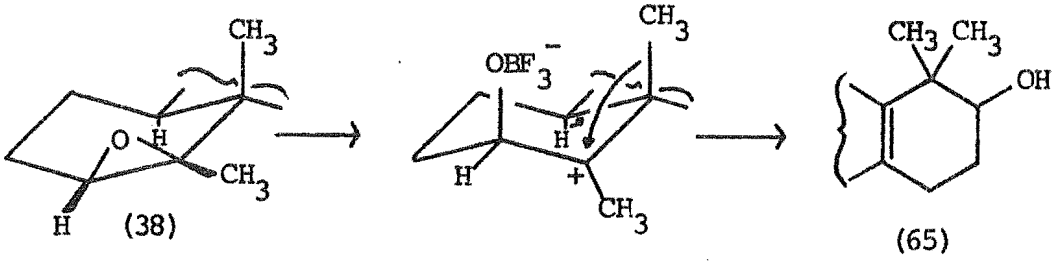
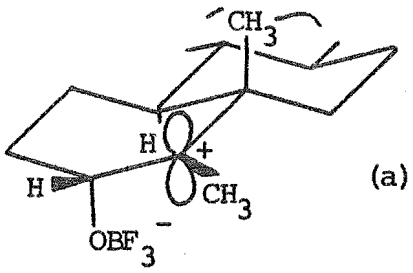


FIG. 26

It is again notable that retention of configuration occurs at C17a indicating that the reaction proceeds via a discrete C17a-carbonium ion intermediate.

The course of the rearrangements of the monomethyl-epoxides (37 and 38) is critically dependent on the stereo-chemical orientation of the reacting epoxide function. Whereas the α-epoxide(37) gives predominantly hydroxy-olefin(62), the β-epoxide(38) gives a cyclic ether in high yield and only moderate yields of hydroxy-olefin(65). In order to maintain maximum overlap between the departing OBF_3^- group, and the developing C17a-p-orbital, the α-epoxide can cleave with ring D in the boat conformation to give intermediate (a), FIG. 27.



(a)

FIG. 27

Models show that solvation of the C17a-carbonium ion by OBF_3^- in the transition state for methyl migration is stereochemically feasible; therefore a fully concerted mechanism for the formation of the hydroxy-olefin (62) from the α-epoxide cannot be excluded. It is possible that the predominance of hydroxy-olefin among the products may arise

as a consequence of the close proximity of the OBF_3^- group to the C14-proton in intermediate (a) above. In this conformation, the OBF_3^- function could assist in the removal of the C14-proton.

The β-epoxide(38), however, cleaves with ring D in the chair conformation to give the initial intermediate (a), FIG. 28.

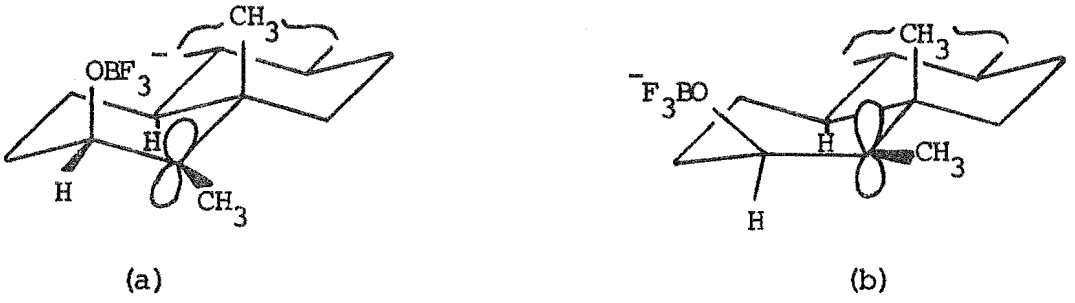


FIG. 28

A relatively minor conformational change gives (b) in which the C17a-p-orbital and the C13-methyl are aligned. In this conformation the OBF_3^- group is remote from the C14-proton and therefore cannot assist in the C14-proton removal in the formation of the $\Delta^{13(14)}$-hydroxy-olefin (65). The OBF_3^- group is however suitably positioned to form a cyclic ether by attack on the β-face of the steroid at either C13 or C14.

This study has demonstrated that where complicating features are minimal the course of an epoxide rearrangement can be rationalised in terms of the following principles.

On reaction of an epoxide with BF_3-etherate cleavage occurs towards the more highly substituted carbon of the epoxide ring. As the steroid nucleus is flexible to a degree, the epoxide cleaves in such a manner as to maintain maximum overlap between the developing vacant carbon p-orbital, and the departing OBF_3^- group. In this way the developing carbonium ion is stabilized by solvation in the transition state of the cleavage process, and the conformation of the initially formed carbonium ion is predictable. It is possible that subsequent reaction may occur without any further conformational change in the intermediate. In this case a high yield of the corresponding product (or products) is expected. In general, however, a change in the conformation of the intermediate carbonium ion is necessary in order to satisfy the stereochemical requirements of a subsequent rearrangement step and the ease of these conformational changes may determine the yields of subsequently formed products.

A prominent feature of the present studies is the ease with which the C13-methyl migrates to C17a*. With the exception of the fluorohydrins, all products isolated were formed *via* a rearrangement of this nature. It was particularly noticeable that C13-methyl migration occurred even when the departing oxy function was *cis* to the attacking methyl. This suggests that the C13-carbonium ion is significantly more stable than the C17a-carbonium ion.

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* C17 in the case of the five-membered ring D epoxides.

APPENDIX

INTRODUCTION

Extensive work has been carried out on the effects of a neighbouring substituent on the course of the BF_3-catalysed rearrangement of epoxides. In particular a study[34] was carried out concerning the effect of a conjugated olefinic function on the course of epoxide rearrangement reactions. The study showed that these reactions were generally very complex.

The present study was designed to extend this work by investigating the effect of a conjugated 3,5-cyclopropyl ring on the course of the BF_3-catalysed rearrangement of the 6,7-epoxide(73).

DISCUSSION

Preparation of the 3,5-cyclo-6,7-epoxide(73)

The synthetic work was found to be complicated due to the presence of the 3,5-cyclopropyl ring which, in some cases, drastically modified the chemistry of other functional groups. The following synthetic routes were attempted (see FIG. 29). Cholesterol(66) was converted into cholesteryl tosylate(67) using toluene-p-sulphonyl chloride in dry pyridine[35], and then the tosylate was solvolysed to give the 3,5-cyclo-6β-ol(68) using potassium acetate in aqueous acetone[35]. Oxidation of the 6β-hydroxyl function with 8N chromic acid[36] gave the 3,5-cyclocholest-6-one(69) (ν_{max} 1695 cm^{-1}).

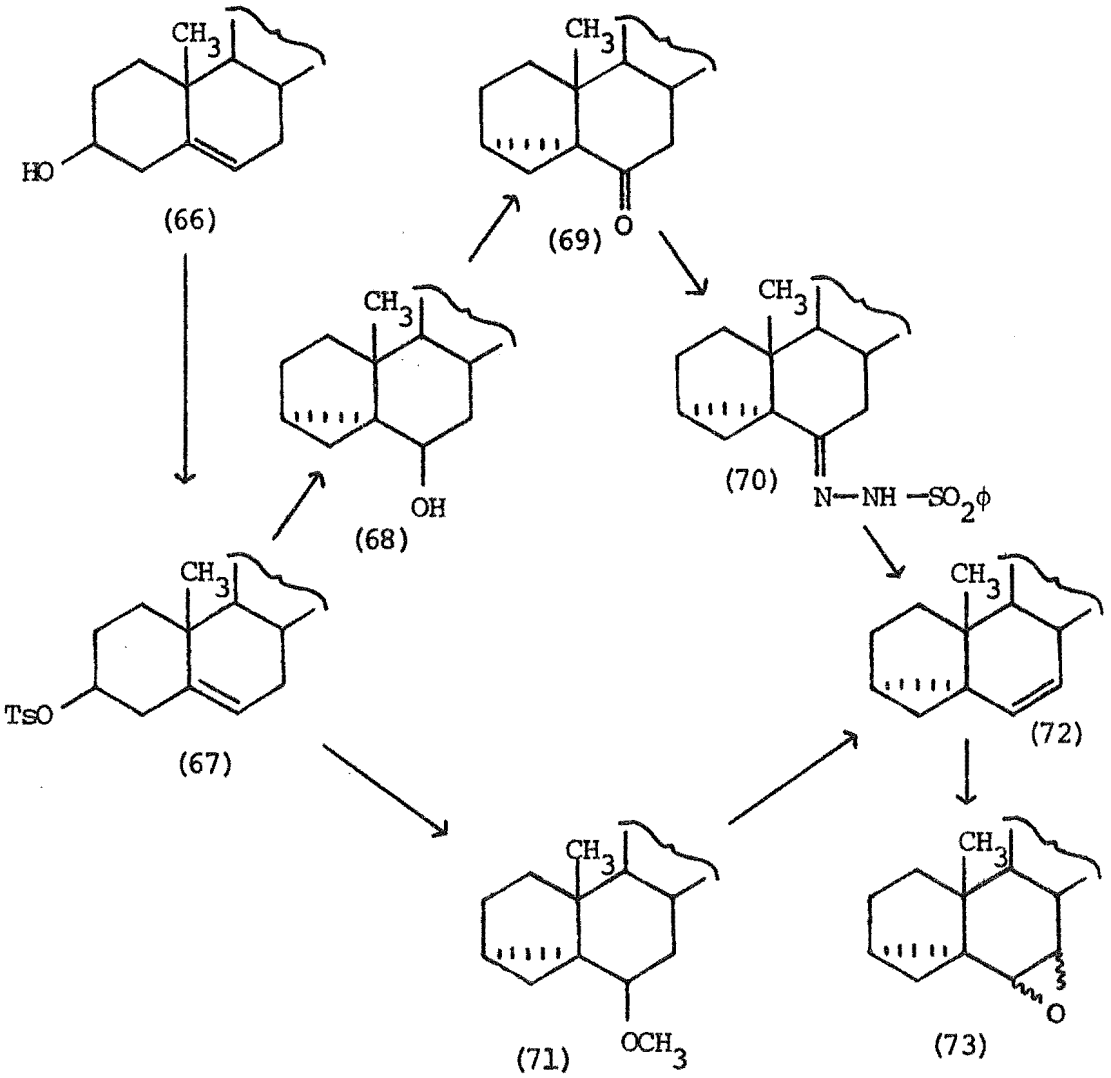

FIG. 29

Conversion of the ketone into the 6-benzenesulphonyl hydrazone(70) followed by heating with base would give the olefin(72) which could be epoxidised. The 6-benzene-sulphonyl hydrazone(70) however, could not be prepared satisfactorily. The alternative route involved the conversion of the 3β-tosylate(67) derived from cholesterol(66) into the 3,5-cyclo-6-methyl ether(71), by refluxing the tosylate with fused potassium acetate in

anhydrous methanol[37]. The 6-methoxy derivative (ν_{max} 1100 cm^{-1} (an ether), δ 2.76 ($W_{h/2}$ 3.5 Hz; C6-proton)) was then converted to the $\Delta^{6(7)}$-olefin using the method of Romeo and Villotti[38]. The product was identified as 3,5-cyclocholest-6-ene(72). The C6- and C7-protons appeared in the n.m.r. as quartet of doublets at δ 5.80, 5.77, 5.63, 5.60, 5.25, 5.22, 5.08, 5.05, with a quartet splitting of J 10 Hz and a doublet splitting by the C8-proton of J 2 Hz. The yield of 20%, however, was not anticipated as the above authors reported yields of 85% for the same reaction. Reaction of the 3,5-cyclo-6-ene derivative(72) with metachloroperbenzoic acid gave the crude epoxide(73) which was very difficult to purify. The C6- and C7-protons occurred in the n.m.r. as a quartet at δ 3.23, 3.15, 2.83, 2.77 with coupling J 4 Hz. Double irradiation experiments demonstrated the C6-, C7-proton couplings. On columns of deactivated alumina, fluorisil, and silica, the crude epoxide was unstable, giving in the first two cases mainly the corresponding diaxial 3,5-cyclo-6,7-diol(74). The n.m.r. possessed two signals due to protons alpha to hydroxyl functions; one at δ 3.75 ($W_{h/2}$ 7 Hz) was assigned to H7 while the other, a doublet at δ 3.19 and 3.14 (J 3 Hz), was assigned to H6. The doublet was decoupled by irradiating the signal due to H7. The elemental analysis supported the assigned formula.

All attempts at the purification of the crude epoxide were unsuccessful, and it was therefore necessary to rearrange the crude material.

Rearrangement of the 3,5-cyclo-6,7-epoxide(73)

The crude epoxide was rearranged (1 min at room temperature) with BF_3-etherate in benzene. The crude products were chromatographed on silica. Material was recovered which appeared as one spot on t.l.c. The infrared spectrum indicated an alcohol, and the n.m.r. possessed an olefinic proton resonance at δ 5.75 (multiplet; $W_{h/2}$ 49 Hz). The mass spectrum indicated a peak at c.a. 732 which suggests that the compound possesses a dimeric structure*. The detailed structure of this product, however, remained unsolved, due to the difficulties encountered in obtaining the pure compound. The remaining material from the chromatography of the crude rearrangement product was recovered as a series of inseparable mixtures of compounds. The unproductive nature of this latter study can be attributed to two main causes. Firstly, the epoxide was unusually sensitive to standard purification techniques, and secondly the polarities of the rearrangement products were sufficiently similar to prevent separation by chromatography. This outcome is not altogether unexpected. In previous studies of the rearrangements of epoxy-olefins[34], unstable and inseparable compounds were commonly encountered. In this project the problems were compounded by the fact that the compound being studied possessed no other polar functional groups, the presence of which might have facilitated the separation of the rearrangement products.

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* This possibility is not unprecedented in epoxide rearrangements[6].

Notwithstanding, this study has demonstrated the enhanced reactivity of an epoxide conjugated with a cyclopropane ring. The results of the study demonstrate the similarity of the overall effect of a conjugated cyclopropane ring and a conjugated olefin.

EXPERIMENTAL

Rotations were measured for $CHCl_3$ solutions. Infrared spectra were recorded on a Shimadzu IR27G spectraphotometer, ultraviolet spectra on a Shimadzu MPS-50L for cyclohexane solutions, and n.m.r. spectra on a Varian A60 or T60 spectrometer for $CDCl_3$ solutions with $CHCl_3$ and TMS as internal standards. Mass Spectra were recorded on an A.E.I. MS902 spectrometer. Aluminium used for chromatography was Spence grade H. "10% Deactivated alumina" refers to grade H to which 10% v/v of 10% acetic acid has been added. Petroleum ether refers to the fraction of b.p. 50-70°.

Trimethyloxosulphonium iodide

A mixture of methyl iodide (100 ml) and dimethylsulphoxide (48.5 ml) was left in the dark in a stoppered flask for several days. The mother liquors were decanted from the crystals and set aside again. The crystals were recrystallised from water containing sufficient sodium thiosulphate to decolourise the liberated iodine. Rapid cooling of the solution gave fine white crystals, which after drying in air were suitable for use in the preparation of dimethyloxosulphonium methylide.

Reaction of epiandrosterone(44a) with trimethyloxosulphonium methylide

Sodium hydride suspension (50% in oil; 20g) was added to dimethylformamide (600 ml) which had been dried by the azeotropic distillation of added benzene. The suspension

was stirred during the addition and slight frothing occurred. Trimethyloxosulphonium iodide (80g) was slowly added and more vigorous frothing occurred. The reaction mixture was then stirred under nitrogen for 30 minutes, during which time frothing subsided. Epiandrosterone(44a)(20g) dissolved in dimethylformamide (200 ml) was added and stirring was continued for 48 hours. The reaction mixture was poured into water and filtered. The residue was dissolved in methylene chloride, washed with water, dried over sodium sulphate, and evaporated to give a crystalline solid consisting of a mixture of 17α,20-epoxy-21-nor-5α-pregnan-3β-ol(45a) and 17β,20-epoxy-21-nor-5α-pregnan-3β-ol(46a). Successive recrystallisations of the mixture of epoxides from acetone gave 17β,20-epoxy-21-nor-5α-pregnan-3β-ol(46a)(200 mg), m.p. 167-168° (lit., 171-173°), (Found C, 78.50; H, 10.61. $C_{20}H_{32}O_2$ requires C, 78.90; H, 10.59%). ν_{max} 3500 cm^{-1}(OH). N.m.r.: δ 3.56 ($W_{h/2}$ 20 Hz; H3α), 2.93, 2.84, 2.61, 2.53 (J 5 Hz $(H20)_2$), 0.85 ($(H18)_3$), 0.80 ($(H19)_3$). Numerous recrystallisations of the original mother liquor from ether-petroleum ether gave material (191 mg) which was predominantly 17α,20-epoxy-21-nor-5α-pregnan-3β-ol(45a). N.m.r.: δ 3.57 ($W_{h/2}$ 20 Hz; H3α), 2.78, 2.70, 2.68, 2.60 (J 4.5 Hz; $(H20)_2$), 0.80 $(H19)_3$, $(H18)_3$.

Acetylation of 17β,20-epoxy-21-nor-5α-pregnan-3β-ol(46a)

A solution of 17β,20-epoxy-21-nor-5α-pregnan-3β-ol(46a) (0.188g) in dry pyridine (0.4 ml) and acetic anhydride (0.4 ml) was allowed to stand at room temperature overnight. The product was extracted with ether and washed free of pyridine

and acetic anhydride, dried over sodium sulphate and evaporated to give 17β,20-epoxy-21-nor-5α-pregnan-3β-ol acetate (46b). N.m.r.: δ 4.68 ($W_{h/2}$ 20 Hz; H3α), 2.93, 2.84, 2.62, 2.53 (J 5 Hz; $(H20)_2$), 2.0 (OAc), 0.86 ($(H18)_3$), 0.83 ($(H19)_3$).

Acetylation of 17α,20-epoxy-21-nor-5α-pregnan-3β-ol (45a) (containing some of the 17β-isomer)

17α,20-Epoxy-21-nor-5α-pregnan-3β-ol (45a) (0.191 g; impure weight) was acetylated by the above method, using dry pyridine (0.95 ml) and acetic anhydride (0.4 ml) to give 17α,20-epoxy-21-nor-5α-pregnan-3β-ol acetate (45b) (estimated isomeric purity by n.m.r. integral 79%). N.m.r.: δ 4.67 ($W_{h/2}$ 23 Hz; H3α), 2.78, 2.70, 2.67, 2.59 (J 4.5 Hz; $(H20)_2$), 2.0 (OAc), 0.83 ($(H18)_3$), 0.80 ($(H19)_3$).

Rearrangement of a mixture (c.a. 1:1) of 17α, and 17β,20-epoxy-21-nor-5α-pregnan-3β-ol acetates (45b,46b) with BF_3-etherate

The mixture of epoxides (1 g) was dissolved in sodium dry benzene (50 ml), and treated with distilled BF_3-etherate (1 ml) for 2 minutes. The reaction was quenched with water and extracted with ether. The ether extracts were washed with sodium bicarbonate solution, dried over sodium sulphate, and evaporated. The crude products were chromatographed on 10% deactivated alumina (100 g). Elution with 10% benzene in petroleum ether gave 3β-acetoxy-17-methyl-18-nor-5α-androst-13(17)-ene (56) (88 mg), m.p. 87-90°, (Found: M^+ 316.239874. $C_{21}H_{32}O_2$ requires M^+ 316.240217). N.m.r.: δ 4.70 ($W_{h/2}$ 20 Hz; H3α), 2.0 (OAc), 1.59 ($W_{h/2}$ 4 Hz; $(H20)_3$), 0.74 ($(H19)_3$).

The compound gave a positive tetranitromethane test.

Further elution with benzene-petroleum ether gave a gum which could not be further separated.

Elution with 25% ether in benzene gave 3β-acetoxy-17α-hydroxymethyl-17β-methyl-18-nor-5α-androst-13-ene(57b) (367 mg), m.p. 103-105°, (Found: M^+ 346.249765. $C_{22}H_{34}O_3$ requires M^+ 346.250781). ν_{max} 3300 cm^{-1} (OH). N.m.r.: δ 4.68 ($W_{h/2}$ 20 Hz; H3α), 3.35 ($W_{h/2}$ 4 Hz; $(H20)_2$), 2.01 (OAc), 0.97 (17β-methyl), 0.81 ($(H19)_3$).

The compound gave a positive tetranitromethane test.

Hydrolysis of 3β-acetoxy-17α-hydroxymethyl-17β-methyl-18-nor-5α-androst-13-ene(57b)

The hydroxymethyl-olefin (0.1 g) was dissolved in methanol (2.5 ml), KOH (0.8 g) was added and the reaction was allowed to stand overnight. The reaction was extracted with methylene chloride. The extracts were washed with water, dried, and evaporated to give 3β-hydroxy-17α-hydroxymethyl-17β-methyl-18-nor-5α-androst-13-ene(57a). N.m.r.: δ 3.48 (broad; H3α), 3.35 ($(H20)_2$), 0.95 (17β-methyl), 0.78 ($(H19)_3$).

Ozonolysis of 3β-hydroxy-17α-hydroxymethyl-17β-methyl-18-nor-5α-androst-13-ene(57a)

The dihydroxy-olefin (0.083 g) was dissolved in dry methanol (10 ml) and treated with ozone for 2 hours. Acetic acid (10 ml) and zinc (150 mg) were added and the reaction mixture was stirred for 2 hours. The reaction was extracted with methylene chloride. The methylene chloride extracts were washed with sodium bicarbonate solution, dried, and

evaporated. ν_{max} 3450 (OH), 1700 (CO), 1705 cm^{-1} (CO). N.m.r.: δ 3.20 ($(H20)_2$), 1.12 (17β-methyl), 0.79 ($(H19)_3$).

Rearrangement of 17β,20-epoxy-21-nor-5α-pregnan-3β-ol acetate(46b) with BF_3-etherate.

The epoxide (0.170 mg) was dissolved in sodium dry benzene (4.2 ml) and treated with a solution of distilled BF_3-etherate (0.17 ml) in sodium dry benzene (4.2 ml), for a period of 2 minutes. The reaction was then poured into water, and extracted with ether. The ether extracts were washed with sodium bicarbonate solution, and water, dried over sodium sulphate, and evaporated. N.m.r. (of the crude rearrangement product): δ 3.34 ($W_{h/2}$ 3 Hz; $(H20)_2$), 0.96 (17β-methyl), 0.80 $(H19)_3$; indicates the formation of 17α-hydroxymethyl-17β-methyl-18-nor -5α-androst-13-ene(57b) (yield based on the integral of the $(H20)_2$ signal 33%), and δ 1.59 ($(H20)_3$), 0.74 ($(H19)_3$) indicates the formation of 3β-acetoxy-17-methyl-18-nor-5α-androst-13(17)-ene(56) (c.a. 10%).

Rearrangement of 17α,20-epoxy-21-nor-5α-pregnan-3β-ol acetate(45b) (isomeric purity 79%) with BF_3-etherate

The epoxide (0.107 mg) was rearranged with BF_3-etherate using the above method. N.m.r. (of the crude rearrangement products): δ 3.34 ($W_{h/2}$ 3 Hz; $(H20)_2$), 0.96 (17β-methyl), 0.80 ($(H19)_3$), indicates the formation of 17α-hydroxymethyl-17β-methyl-18-nor -5α-androst-13-ene(57b) (yield based on the integral of the C20-protons, and corrected for the isomeric impurity of the starting epoxide 61%), and δ 1.59 ($(H20)_3$), 0.74 ($(H19)_3$) indicates the formation of 3β-acetoxy-17-methyl-18-nor-5α-androst-13(17)-ene(56) (c.a. 10%).

Preparation of 20-azido-21-nor-5α-pregnane-3β,17α-diol, and 17β-diol(47a), and their 3β-acetoxy-derivatives(47b)

A mixture of 17α, and 17β, 20-epoxy-21-nor-5α-pregnan-3β-ols(45a,46a) (20 g) was dissolved in dimethylformamide (400 ml) and sodium azide (20g) and boric acid (20g) were added. The mixture was heated under reflux for 3 hours and poured into water. The precipitated azides(47a) were washed with water and dried in air. ν_{max} 3450 (OH), 2100 cm^{-1}(N_3). N.m.r. δ 3.67, 3.46, 3.32, 3.12, (J_{HH} 12 Hz; $(H20)_2$, H3α (under quartet)), 0.88 ($(H18)_3$), 0.82 ($(H19)_3$).

The reaction can also be carried out on a mixture of 17α, and 17β,20-epoxy-21-nor-5α-pregnan-3β-ol acetates(47b) using the above reaction conditions. ν_{max} 3500 (OH), 2100 (N_3), 1720 cm^{-1} (OAc). N.m.r.: δ 4.83 ($W_{h/2}$ 20 Hz; H3α), 3.55, 3.46, 3.43, 3.32 (J c.a. 6 Hz; $(H20)_2$) 3.67, 3.46, 3.32, 3.12 (J 12 Hz; $(H20)_2$), 2.01 (OAc), 0.88 ($(H18)_3$), 0.83 ($(H19)_3$).

Preparation of Chromous Chloride

Amalgamated zinc dust was prepared by vigorously shaking zinc dust (150 g), mercuric chloride (12 g), water (150 ml) and concentrated HCl (13.5 ml) for 5 minutes, and decanting the supernatant liquid. After the addition of water (300 ml) and concentrated HCl (30 ml), chromic chloride (75 g) was added in portions with swirling in a current of carbon dioxide. The dark blue solution was kept under carbon dioxide until required.

Chromous chloride reduction of the 20-azido-21-nor-5α-pregnane-3β,17-diols(47a)

The hydroxy-azides(47a) (20 g) were dissolved in acetone (400 ml) and treated with chromous chloride solution (330 ml). When the vigorous effervescence had ceased the solution was poured into water (1 ℓ) and carefully neutralised with sodium hydroxide solution. Extraction of the aqueous suspension with ether-ethyl acetate gave the hydroxy-amines(48) as a gum.

Tiffeneau ring enlargement.

The hydroxy-amines(48) (20 g) were dissolved in 50% aqueous acetic acid (400 ml) and the solution cooled in ice. Sodium nitrite (40 g) was added, the mixture was stirred for one hour, and then poured into water (2 ℓ). Extraction with ethyl acetate gave the crude ketones(49a,50a).

The above reaction sequence was repeated until a total of 90g of epiandrosterone had been converted into the crude ketones.

The combined crude products were filtered through deactivated alumina and elution with ether-benzene gave the two ketones (46g; c.a. 50% of the crude product). An attempt to separate the two hydroxy-ketones by recrystallising the mixed ketones from methanol gave only 3β-hydroxy-D-homo-5α-androstan-17a-one(49a), m.p. 196-7° (lit., 193-5°). ν_{max} 3530 (OH), 1690 cm^{-1} (CO). N.m.r.: δ 3.58 ($W_{h/2}$ 22 Hz; H3α), 1.08 ($(H18)_3$) 0.80 ($(H19)_3$). The 17-ketone could not be separated by recrystallisation.

Acetylation of the hydroxy-17a, and 17-ketones(49a,50a)

The hydroxy-ketones (46 g) were dissolved in dry pyridine (230 ml) and acetic anhydride (46 ml) was added. The reaction was allowed to stand at room temperature overnight and was then extracted with ether. The extracts were washed with water, dried, and evaporated.

Repeated chromatography (eight successive columns) of the mixed acetoxy-17a, and 17-ketones on activated alumina; eluting with 40% benzene in petroleum ether gradually gave pure 3β-acetoxy-D-homo-5α-androstan-17a-one(49b) and a mixture of the two acetoxy-ketones(49b,50b) which could not be further separated by chromatography.

The 3β-acetoxy-D-homo-5α-androstan-17a-one(49b) was recrystallised from petroleum ether-ether. (Recovery 18.4 g), m.p. 124-125° (lit., 124-125°). ν_{max} 1735 (OAc), 1695 cm^{-1} (CO). N.m.r.: δ 4.67 ($W_{h/2}$ 21 Hz; H3α), 2.00 (OAc), 1.08 ($(H18)_3$), 0.82 ($(H19)_3$).

The overall yield of 3β-acetoxy-D-homo-5α-androstan-17a-one(49b) from 90 g of epiandrosterone(44a) is c.a. 17%. N.m.r. of the mixed acetoxy-ketones showed the methyl peaks due to the acetoxy-17-ketone at δ 0.86.

Reaction of 3β-acetoxy-D-homo-5α-androstan-17a-one(49b) with methyl magnesium iodide

3β-Acetoxy-D-homo-5α-androstan-17a-one(49b) (6 g) in anhydrous ether (300 ml) was added to the Grignard reagent prepared from magnesium (6 g), methyl iodide (15.6 ml) and ether (150 ml). The reaction was refluxed for 8 hours and left overnight. Acetic acid was added with cooling, and the

reaction mixture was poured into water. The products were extracted with ethyl acetate - ether. The extracts were washed with 5% H_2SO_4, 1 m NaOH, dried, and evaporated to give a mixture of 17aα-methyl-D-homo-5α-androstane-3β,17aβ-diol(51a) and 17aβ-methyl-D-homo-5α-androstane-3β,17aα-diol(52a). (Found: M^+ 320.270799. $C_{21}H_{36}O_2$ requires M^+ 320.271516). N.m.r.: δ 3.57 ($W_{h/2}$ 20 Hz; H3α), 0.78 ($(H19)_3$); 17aα-hydroxy-17aβ-methyl isomer δ 1.09 ($(H20)_3$), 0.85 ($(H18)_3$); 17aβ-hydroxy-17aα-methyl isomer δ 1.24 ($(H20)_3$), 0.93 ($(H18)_3$).

Acetylation of the 17a-methyl-17a, 3β-diols (51a,52a)

The mixed 17a-methyl-17a,3β-diols (6 g) were dissolved in dry pyridine (30 ml). Acetic anhydride (6 ml) was added and the reaction allowed to stand at room temperature overnight. The isolated product was a mixture of 3β-acetoxy-17aα-methyl-D-homo-5α-androstan-17aβ-ol(51b) and 3β-acetoxy-17aβ-methyl-D-homo-5α-androstan-17aα-ol(52b). N.m.r.: δ 4.68 ($W_{h/2}$ 22 Hz; H3α) 2.01 (OAc), 0.80 ($(H19)_3$); 17aα-hydroxy-17aβ-methyl isomer δ 1.09 ($(H20)_3$), 0.85 ($(H18)_3$); 17aβ-hydroxy-17aα-methyl isomer δ 1.25 ($(H20)_3$), 0.93 ($(H18)_3$).

Chromatography of 1 g of the acetylation products on 40 g of 10% deactivated alumina gave, on elution with 5% ether in benzene, 3β-acetoxy-17aβ-methyl-D-homo-5α-androstan-17aα-ol(52b) (0.173 g) which was recrystallised (ether - petroleum ether), m.p. 157-157.5°, $[\alpha]_D$-35.5°. (Found: C, 75.92; H 10.62. $C_{23}H_{38}O_3$ requires C, 76.19; H, 10.56%).

ν_{max} 3550, 3600 (OH), 1750, 1730, 1715 cm^{-1} (OAc) (ν_{max} (dilute CCl_4) 1730 cm^{-1} (OAc)). N.m.r.: δ 4.67 ($W_{h/2}$ 20 Hz; H3α), 2.01 (OAc), 1.09 ($(H20)_3$), 0.85 ($(H18)_3$), 0.79 ($(H19)_3$).

The 3β-acetoxy-17aβ-hydroxy-17aα-methyl isomer(51b) could not be isolated by chromatography.

The remainder of the crude acetylation products were filtered through a 10% deactivated alumina column and the fractions containing mixed 3β-acetoxy-17a-hydroxy-17a-methyl isomers (5.4 g) were combined.

Dehydration of the mixture of 3β-acetoxy-17a-hydroxy-17a-methyl isomers(51b,52b)

The mixed 3β-acetoxy-17a-hydroxy-17a-methyl isomers (5.3 g) were dissolved in acetic acid (265 ml). Acetic anhydride (53 ml) and toluene-p-sulphonic acid (5.3 g) were added. The reaction was allowed to stand at room temperature overnight and was then extracted with ethyl acetate-ether. The extracts were washed several times with sodium bicarbonate solution, and water, dried over sodium sulphate, and evaporated. The crude product was filtered through 10% deactivated alumina to give 4.8 g of solid material. Two recrystallisations of a portion of this solid material (300 mg) gave pure 3β-acetoxy-17a-methyl-D-homo-5α-androst-17-ene(53), m.p. 129-130°, $[\alpha]_D$+52.6°. (Found: C, 79.93; H, 10.32. $C_{23}H_{36}O_2$ requires C, 80.18; H, 10.53%). ν_{max} 1735 cm^{-1} (OAc). N.m.r.: δ 5.21 ($W_{h/2}$ 8 Hz; H17), 4.71 ($W_{h/2}$ 20 Hz; H3α), 2.00 (OAc), 1.60 ($(H20)_3$), 0.92 ($(H18)_3$), 0.81 ($(H19)_3$).

The remaining solid material (4.5 g) was recrystallised once from methanol giving material (3.5 g) suitable for epoxidation.

Preparation of monoperoxyphthalic acid

Hydrogen peroxide (100 mls of 30%) was added to finely ground phthalic anhydride (60g) in ether (600 ml). After stirring for three hours, the ethereal solution was washed five times with saturated ammonium sulphate, dried twice over magnesium sulphate to give, on titration with iodine - thiosulphate reagent, a solution of peracid (c.a. 0.15 M), this standardisation being performed immediately prior to subsequent reaction.

Epoxidation of 3β-acetoxy-17a-methyl-D-homo-5α-androst-17-ene(53)

3β-Acetoxy-17a-methyl-D-homo-5α-androst-17-ene(53) (3.5 g) was treated with an excess of an ethereal solution of monoperoxyphthalic acid. The reaction was allowed to stand at $0^{o}C$ until complete as indicated by t.l.c. The reaction was extracted with ether, and the ether extracts were washed eight times with saturated sodium bicarbonate solution, dried and evaporated. The crude products were separated by repeated chromatography on 10% deactivated alumina (350 g). Elution with petroleum ether gave impure starting olefin (38 mg; 2% by t.l.c.). Further elution with petroleum ether gave an unidentified compound (75 mg; 4% by t.l.c.). (Found: M^{+} 360.266678. $C_{23}H_{36}O_3$ requires M^{+} 360.266430). ν_{max} 1740 cm^{-1} (OAc). N.m.r.: δ 4.61 ($W_{h/2}$

20 Hz; H3α), 3.18, 3.11 (1 H; J 4 Hz), 2.01 (OAc), 1.05, 0.74, 0.72 (angular methyls).

Elution with 10% benzene in petroleum ether gave 3β-acetoxy-17β,17aβ-epoxy-17aα-methyl-D-homo-5α-androstane (38) (0.398 mg; 15% by t.l.c.) which was recrystallised from methanol, m.p. 125-126.5°, $[\alpha]_D$ +24° (Found: C, 76.80; H, 10.28. $C_{23}H_{36}O_3$ requires C, 76.62; H, 10.06%). ν_{max} 1735 cm^{-1} (OAc). N.m.r.: δ 4.67 ($W_{h/2}$ 19 Hz; H3α), 2.93 ($W_{h/2}$ 3.5 Hz; H17), 2.00 (OAc), 1.18 ($(H20)_3$), 0.93 ($(H18)_3$), 0.79 ($(H19)_3$).

Further elution with 10% benzene in petroleum ether gave an unidentified compound (0.137 g; 9% by t.l.c.). (Found: M^+ 360.266678. $C_{23}H_{36}O_3$ requires 360.266430). ν_{max} 1735 cm^{-1} (OAc). N.m.r.: δ 4.68 ($W_{h/2}$ 19 Hz; H3α), 2.00 (OAc), 1.02, 0.97, 0.73 (angular methyls).

Elution with 20% benzene in petroleum ether, and recrystallisation of the solid from methanol gave 3β-acetoxy-17α,17aα-epoxy-17aβ-methyl-D-homo-5α-androstane(37) (1.96 g; 65% by t.l.c.), m.p. 158-160° (lit., 158-160°). ν_{max} 1730 cm^{-1} (OAc). N.m.r.: δ 4.69 ($W_{h/2}$ 21 Hz; H3α), 2.86 (distorted doublet; $W_{h/2}$ 5.5 Hz; H17) 2.00 (OAc), 1.19 ($(H20)_3$), 0.93 ($(H18)_3$), 0.78 ($(H19)_3$).

Rearrangement of 3β-acetoxy-17α,17aα-epoxy-17aβ-methyl-D-homo-5α-androstane(37) with BF_3-etherate

1. T.l.c. trials

The epoxide (0.005 g) was rearranged using distilled BF_3-etherate (0.005 ml) and dry solvent (0.5 ml). When benzene was used as solvent the reaction took place within

one minute to give two products on silica t.l.c. After one minute in ether the reaction gave at least four products on silica t.l.c.

2. Preparative reaction

The epoxide (0.25 g) in sodium dry benzene (25 ml) was treated with distilled BF_3-etherate (0.25 ml) for 1 minute. The reaction was poured into water and extracted with ether. The ether extracts were washed with sodium bicarbonate, dried over sodium sulphate and evaporated. The crude products were repeatedly chromatographed on 10% deactivated alumina (15 g). Elution with 20% benzene in petroleum ether gave non-polar material (31 mg; 14% by t.l.c.) which was shown by t.l.c. to be mainly due to a secondary reaction of the initially formed products. Elution with benzene gave a mixture of two products from which, on further chromatography, a sample of an unidentified compound was isolated (6 mg; 7% by t.l.c.). ν_{max} 3550 (OH), 1740 cm^{-1} (OAc). N.m.r.: δ 4.68 ($W_{h/2}$ 20 Hz; H3α), 3.23 ($W_{h/2}$ 7 Hz), 3.08 ($W_{h/2}$ 8 Hz), 2.01 (OAc), 0.98, 0.80, 0.77 (angular methyls).

Elution with 20% ether in benzene gave 3β-acetoxy-17α-hydroxy-17a,17a-dimethyl-18-nor-D-homo-5α-androst-13-ene(62) (106 mg; 75% by n.m.r.) which was recrystallised from ether-petroleum ether. m.p. 113-114°, $[\alpha]_D$ -133° (Found: C, 76.39; H, 10.00. $C_{23}H_{36}O_3$ requires C, 76.62; H, 10.06%). ν_{max} 3450 (OH), 1735, 1715 cm^{-1} (OAc) (ν_{max} (dilute CCl_4) 3500 (OH), 1740 cm^{-1} (OAc)). N.m.r.: δ 4.73 ($W_{h/2}$ 20 Hz; H3α) 3.49 ($W_{h/2}$ 6 Hz; H17), 2.02 (OAc), 1.03 (17a-methyl), 1.00 (17a-methyl), 0.78 ($(H19)_3$).

The compound gave a positive test with tetranitromethane.

Chromium trioxide - pyridine oxidation of 3β-acetoxy-17α-hydroxy-17a,17a-dimethyl-18-nor-D-homo-5α-androst-13-ene(62)

A solution of the hydroxy-olefin (200 mg) in pyridine (2 ml) was added slowly to the complex formed from chromic anhydride (250 mg) and pyridine (2.5 ml) at 0°C. After addition the reaction was left stoppered overnight at room temperature. The reaction was extracted with ether. The ether extracts were washed with water, dried and evaporated. The crude product was filtered through 10 g of 10% deactivated alumina and the pure ketone (essentially quantitative yield) was recrystallised from ether-petroleum ether to give 3β-acetoxy-17a,17a-dimethyl-18-nor-D-homo-5α-androst-13-en-17-one(63) as needles. m.p. 110-112.5°, $[\alpha]_D$ -212° (Found: C, 77.06; H, 9.41. $C_{23}H_{34}O_3$ requires C, 77.05; H, 9.56%). ν_{max} 1730 (OAc), 1715 cm^{-1} (shoulder; CO), λ_{max} 296.3 (ε 36.5; cyclohexane). N.m.r.: δ 4.67 ($W_{h/2}$ 22 Hz; H3α), 2.00 (OAc), 1.18 (17a-methyl), 1.09 (17a-methyl), 0.80 ($(H19)_3$).

The compound gave a positive test with tetranitromethane.

Rearrangement of 3β-acetoxy-17β,17aβ-epoxy-17aα-methyl-D-homo-5α-androstane(38) with BF_3-etherate

1. T.l.c. trials

The epoxide (0.005 g) was treated with distilled BF_3-etherate (0.005 ml) and a solvent (0.5 ml). Using benzene as the solvent the reaction gave, after one minute, four products, the least polar of which decreased in yield with time and was no longer evident after 20 minutes. In ether the reaction again gave four products after one minute, but

no products showed marked variation in yield with time.

2. Preparative Reaction

The epoxide (0.3 g) in sodium dry benzene (30 ml) was treated with distilled BF_3-etherate (0.3 ml) for 1 minute. The reaction was poured into water and extracted with ether. The ether extracts were washed with sodium bicarbonate, dried over sodium sulphate and evaporated. The crude products were chromatographed on 10% deactivated alumina (20 g). Elution with 20% benzene in petroleum ether gave an ether (144 mg; 50% by t.l.c.) which was recrystallised (methanol-ether), m.p. 111-112°, $[\alpha]_D$ +54° (Found: C, 76.79; H, 10.31. $C_{23}H_{36}O_3$ requires C, 76.62; H, 10.06%). ν_{max} 1735 cm^{-1} (OAc). N.m.r.: δ 4.70 ($W_{h/2}$ 21 Hz; H3α), 3.69 ($W_{h/2}$ 6.5 Hz; H17), 2.00 (OAc), 1.02 (17a-methyl), 0.92 (17a-methyl), 0.80 ($(H19)_3$).

Elution with 50% benzene in petroleum ether gave a series of fractions (61 mg; 27% by t.l.c.) which contained 67% (by n.m.r.) of 3β-acetoxy-17β-hydroxy-17a,17a-dimethyl-18-nor-D-homo-5α-androst-12-ene(64). ν_{max} 3600 (OH), 1735 cm^{-1} (OAc). N.m.r.: δ 5.57 ($W_{h/2}$ 10 Hz; H12), 4.68 ($W_{h/2}$ 20 Hz; H3α), 3.47 ($W_{h/2}$ 10 Hz; H17α), 2.01 (OAc), 1.12 (17a-methyl), 1.03 (17a-methyl), 0.77 ($(H19)_3$).

Elution with 20% ether in petroleum ether gave 3β-acetoxy-17β-hydroxy-17a,17a-dimethyl-18-nor-D-homo-5α-androst-13-ene (65) (50 mg; 19% by t.l.c. and n.m.r.) (Found: M^+ 360.266678. $C_{23}H_{36}O_3$ requires M^+ 360.266430). N.m.r.: δ 4.68 ($W_{h/2}$ 23 Hz; H3α) 3.43($W_{h/2}$ 20 Hz; H17), 2.01 (OAc), 1.03 (17a-methyl), 0.94 (17a-methyl), 0.77 ($(H19)_3$).

The compound gave a positive test with tetranitromethane.

Chromic anhydride-pyridine oxidation of 3β-acetoxy-17β-hydroxy-17a,17a-dimethyl-18-nor-D-homo-5α-androst-13-ene(65)

A solution of the hydroxy-olefin (17 mg) in pyridine (0.17 ml) was added slowly to the complex formed from chromic anhydride (21 mg) and pyridine (0.21 ml) at 0°C. After the addition the reaction was left stoppered overnight at room temperature. The reaction was extracted with ether. The ether extracts were washed with water, dried, and evaporated to give 3β-acetoxy-17a,17a-dimethyl-18-nor-D-homo-5α-androst-13-en-17-one(63). N.m.r.: δ 4.67 ($W_{h/2}$ 21 Hz; H3α), 2.03 (OAc), 1.20 (17a-methyl), 1.10 (17a-methyl), 0.80 ($(H19)_3$).

Preparation of 3β-acetoxy-D-homo-5α-androstane-17a-benzene-sulphonyl hydrazone(54)

3β-Acetoxy-D-homo-5α-androstan-17a-one(49b) (5 g) was dissolved in a minimum quantity of glacial acetic acid. Benzenesulphonyl hydrazine (10 g) was added, and the warmed reaction mixture was allowed to stand at room temperature overnight. The reaction was extracted with ether containing some ethyl acetate. The ether extracts were washed several times with saturated sodium bicarbonate and water, dried over sodium sulphate, and evaporated to give the 17a-benzenesulphonyl hydrazone(54) as an oil. N.m.r.: δ 7.97 (2H multiplet; phenyl), 7.55 (3H multiplet; phenyl), 4.64 ($W_{h/2}$ 20 Hz; H3α), 2.02 (OAc), 0.90 ($(H18)_3$), 0.80 ($(H19)_3$).

Preparation of 3β-hydroxy-D-homo-5α-androst-17-ene(55a)

To a 1.0 M suspension of sodium methoxide in diglyme (125 ml) was added the 17a-benzenesulphonyl hydrazone(54) (5 g) and the reaction was heated under N_2 at 160° until no further reaction was observed by t.l.c. (c.a. 2 hrs). The cooled reaction was extracted with ethyl acetate - ether (1:1) and the extracts were washed several times with water, dried over sodium sulphate and evaporated to give 3β-hydroxy-D-homo-5α-androst-17-ene(55a) (crude recovery 4.54 g). N.m.r.: δ 5.42 ($W_{h/2}$ 2 Hz; H17, H17a), 3.59 ($W_{h/2}$ 20 Hz; H3α), 0.86 ($(H18)_3$), 0.80 ($(H19)_3$).

Acetylation of 3β-hydroxy-D-homo-5α-androst-17-ene(55a)

3β-Acetoxy-D-homo-5α-androst-17-ene(4.54g) was dissolved in dry pyridine (23 ml), and acetic anhydride (4.5 ml) was added. The reaction was allowed to stand at room temperature overnight, and was then extracted with ether. The ether extracts were washed with water, dried over sodium sulphate and evaporated to give the crude product (4.76 g). This material was passed through 10% deactivated alumina (100 g). Elution with petroleum ether - benzene gave 3β-acetoxy-D-homo-5α-androst-17-ene(55b) which was recrystallised from methanol (yield 2.99 g), m.p. 99-100°, $[\alpha]_D$ +33° (Found: C, 79.79; H, 10.29. $C_{22}H_{34}O_2$ requires C, 79.95; H, 10.37%). ν_{max} 1735 cm^{-1} (OAc). N.m.r.: δ 5.42 ($W_{h/2}$ 2 Hz; H17, H17a), 4.68 ($W_{h/2}$ 21 Hz; H3α), 2.01 (OAc), 0.86 ($(H18)_3$), 0.83 ($(H19)_3$).

Epoxidation of 3β-acetoxy-D-homo-5α-androst-17-ene(55b)

3β-Acetoxy-D-homo-5α-androst-17-ene(2.89g) was dissolved in dry ether (300 ml) and m-chloroperbenzoic acid (4.6 g) was added. The reaction was allowed to stand at room temperature overnight, and was then extracted with ether. The ether extracts were washed eight times with saturated sodium carbonate solution, twice with water, dried over sodium sulphate and evaporated. The reaction products (3 g) were separated by successive chromatography of the crude reaction product on 10% deactivated alumina (50:1). Elution with petroleum ether gave non-polar material (0.280 g) which contained the starting olefin. Further elution with petroleum ether gave 3β-acetoxy-17β,17aβ-epoxy-D-homo-5α-androstane(36b) (0.269 g), which was recrystallised from methanol (yield of recrystallised material 0.185 g), m.p. 105-106°, $[\alpha]_D$ +15.4 (Found: C, 76.65; H, 9.89. $C_{22}H_{34}O_3$ requires C, 76.26; H, 9.89%). ν_{max} 1740 cm^{-1} (OAc). N.m.r. δ 4.63 ($W_{h/2}$ 20 Hz; H3α), 3.13 ($W_{h/2}$ 7 Hz; H17); 2.71, 2.65 (J 3.5 Hz; H17a), 2.01 (OAc), 0.94 ($(H18)_3$), 0.81 ($(H19)_3$).

Elution with 10% benzene in petroleum ether gave 3β-acetoxy 17α,17aα-epoxy-D-homo-5α-androstane(35b) (1.9 g) which was recrystallised from methanol (yield on recrystallisation: 1.58 g), m.p. 156-158°, $[\alpha]_D$ + 6.7° (Found: C, 76.19; H, 9.91. $C_{22}H_{34}O_3$ requires C, 76.26; H, 9.89%). ν_{max} 1735 cm^{-1} (OAc). N.m.r.: δ 4.66 ($W_{h/2}$ 22 Hz; H3α), 3.09 ($W_{h/2}$ 6 Hz; H17), 2.73, 2.67 (J 4 Hz; H17a), 2.00 (OAc), 0.93 ($(H18)_3$), 0.80 ($(H19)_3$).

Elution with ether gave, in addition, some unseparated polar material (0.29 g).

Rearrangement of 3β-acetoxy-17α,17aα-epoxy-D-homo-5α-androstane(35b) with BF_3-etherate

1. T.l.c. trials

The epoxide (0.3 mg) was treated with a solution (0.3 ml) of BF_3-etherate (0.1 ml) in dry solvent (10 ml). When benzene was used as the reaction solvent silica t.l.c. indicated three products after one minute. In ether the reaction again gave three products after one minute, but traces of the reacting epoxide persisted until 10 minutes.

2. Preparative Reaction

The epoxide (0.5 g) was dissolved in sodium dry benzene (50 ml) and distilled BF_3-etherate (0.5 ml) was added. After 2 min. the reaction was poured into water, and extracted with ether. The ether extracts were washed with saturated sodium bicarbonate, and water, dried over sodium sulphate and evaporated. The crude product was chromatographed on 10% deactivated alumina (100 g). Elution with 50% benzene in petroleum ether gave mixed non-polar material (0.012 g). Elution with 10% petroleum ether in benzene gave an impure fraction (79 mg) which contained predominantly 3β-acetoxy-17β-fluoro-17aα-hydroxy-D-homo-5α-androstane(60). (Found M^+-60 306.235952. $C_{22}H_{35}O_3F$ requires M^+-60 306.235880). ν_{max} 3650 (sharp), 3520 cm^{-1} (broad) (OH). N.m.r.: δ 4.68 ($W_{h/2}$ 20 Hz; H3α), 5.01, 4.24 ($W_{h/2}$ 9.0 Hz; $W_{h/2}$ 8.5 Hz; J 46 Hz; H17), 3.40 (query a quartet; J_{HF} 9 Hz; J_{HH} 3 Hz; H17aβ), 2.01 (OAc), 0.97, 0.90 (J 4 Hz; $(H18)_3$), 0.82 ($(H19)_3$).

Further chromatography of the residual material gave a series of fractions containing predominantly an inseparable mixture (t.l.c.) of hydroxy-olefins. ν_{max} 3500 cm^{-1} (OH). N.m.r.: δ 4.76 ($W_{h/2}$ 22 Hz; H3α), 3.45 ($W_{h/2}$ 6 Hz; proton α to OH), 2.01 (OAc).

The mixed hydroxy-olefins gave a positive test with tetranitromethane.

A yield of 40% 3β-acetoxy-17β-fluoro-17aα-hydroxy-D-homo-5α-androstane(60) was calculated from the integral of the n.m.r. of the crude rearrangement product.

Acetylation of crude 3β-acetoxy-17β-fluoro-17aα-hydroxy-D-homo-5α-androstane(60)

3β-Acetoxy-17β-fluoro-17aα-hydroxy-D-homo-5α-androstane (0.383 g crude) isolated from the rearrangement products of 3β-acetoxy-17α,17aα-epoxy-D-homo-5α-androstane(35b) (0.5 g) was dissolved in dry pyridine (2 ml). Acetic anhydride (0.4 ml) was added and the reaction was allowed to stand at room temperature overnight. The reaction was extracted with ether; the ether extracts were washed with water, dried and evaporated. The crude acetylation product was chromatographed on 10% deactivated alumina (40 g). Elution with 20% benzene in petroleum ether gave material (0.057 g) which recrystallised from methanol to give 3β-acetoxy-17aα-acetoxy-17β-fluoro-D-homo-5α-androstane(61) (29 mg), m.p. 167-168.5°, $[\alpha]_D$ +31° (Found: C, 71.15; H, 9.09; F, 5.45. $C_{24}H_{37}O_4F$ requires C, 70.56; H, 9.13; F, 4.65%). ν_{max} 1740 cm^{-1} (OAc). N.m.r.: δ 4.67 (broad with downfield shoulder; H3α,H17aβ,H17α(½H)), 4.14 ($W_{h/2}$ 7.5 Hz; H17α(½H)),

2.09 (17aα-OAc), 2.02 (3β-OAc), 1.05, 0.98 J_{HF} 4 Hz; $(H18)_3$), 0.82 ($(H19)_3$).

Hydrolysis of 3β-acetoxy-17aα-acetoxy-17β-fluoro-D-homo-5α-androstane(61)

The diacetoxy-fluorohydrin (0.013 g) was treated with a solution (0.65 ml) of KOH (0.67 g) in methanol (10 ml), and allowed to stand overnight. The reaction was then extracted with ether. The ether extracts were washed with water, dried over sodium sulphate and evaporated. T.l.c. indicated essentially one product. N.m.r.: δ 3.63 ($W_{h/2}$ 26 Hz, H3α), 3.11 ($W_{h/2}$ 8 Hz; H17), 2.75, 2.68 (J 4 Hz; H17a), 0.93 ($(H18)_3$), 0.78 ($(H19)_3$).

Hydrolysis of 3β-acetoxy-17α,17aα-epoxy-D-homo-5α-androstane (35b)

The epoxide (0.030 g) was hydrolysed with KOH-methanol as above. The t.l.c. (essentially one product (35a)) was identical to the t.l.c. of hydrolysed diacetoxy-fluorohydrin. N.m.r. (of the hydrolysed epoxide): δ 3.63 ($W_{h/2}$ 25 Hz; H3α), 3.11 ($W_{h/2}$ 8.5 Hz; H17), 2.75, 2.68 (J 4 Hz; H17a), 0.93 ($(H18)_3$), 0.78 ($(H19)_3$).

Rearrangement of 3β-acetoxy-17β,17aβ-epoxy-D-homo-5α-androstane (36b) with BF_3-etherate

1. T.l.c. trials

The epoxide (0.3 mg) was treated with a solution (0.3 ml) of BF_3-etherate (0.1 ml) in dry solvent (10 ml). Using benzene as the reaction solvent at least three products were indicated by silica t.l.c. after 2 minutes. The least polar

product appeared to increase in yield with time even though the starting epoxide persisted for less than two minutes. In ether the reaction was slower. Three polar products were evident on silica t.l.c. after one minute, together with the starting epoxide which persisted for at least one hour.

2. Preparative reaction

The epoxide (0.138 g) was dissolved in sodium dry benzene (13.8 ml) and distilled BF_3-etherate (0.14 ml) was added. After two minutes the reaction was poured into water and extracted with ether. The ether extracts were washed with sodium bicarbonate solution and water, dried over sodium sulphate and evaporated. The crude product mixture was chromatographed on 10% deactivated alumina (15 g). Elution with petroleum ether containing increasing amounts (up to 30%) of benzene gave a series of unidentified mixed fractions (21 mg; 14%).

Elution with 50% benzene in petroleum ether gave (7 mg; 17% by t.l.c.) of material identified as 3β-acetoxy-17β-hydroxy-17aβ-methyl-18-nor-D-homo-5α-androst-12-ene(59). (Found: M^+ 346.251623. $C_{22}H_{34}O_3$ requires 346.250781). ν_{max} 3500 (OH), 1735 cm^{-1} (OAc). N.m.r.: δ 5.50 ($W_{h/2}$ 11 Hz; H12), 4.63 ($W_{h/2}$ 26 Hz; H3α), 3.87 ($W_{h/2}$ 9 Hz; H17α), 2.01 (OAc),1.13, 1.02 (J 7 Hz; decoupled by irradiating a signal c.a. 64 Hz downfield; 17aβ-methyl 0.77 ($(H19)_3$).

Elution with benzene gave a solid (14 mg; 26% by t.l.c.) identified as 3β-acetoxy-17β-hydroxy-17aα-fluoro-D-homo-5α-androstane(58). (Found: $M^+ - 60$ 306.235952. $C_{22}H_{35}O_3F$ requires $M^+ - 60$ 306.235880). ν_{max} 3670 (sharp), 3470 (broad) (OH), 1735 cm^{-1} (OAc). N.m.r.: δ 4.72 ($W_{h/2}$ 22 Hz; H3α),

4.23, 4.18, 4.13, 4.07, 4.01, 3.97, 3.92 (multiplet; J_{HF} 10 Hz; J_{HH} c.a. 3.5 Hz; H17α), 4.43, 4.39, 3.68, 3.63 (J_{HF} 45.5 Hz; J_{HH} 2.5 Hz; doublet at δ 4.43, 4.39 decoupled by irradiating a signal 16 Hz upfield; doublet at δ 3.68, 3.63 decoupled by irradiating a signal 19 Hz downfield; H17aβ), 2.0 (OAc), 1.02, 0.98 (J 2.5 Hz; $(H18)_3$), 0.08 ($(H19)_3$).

Further elution with benzene followed by 20% ether in benzene gave a series of fractions containing mixtures of hydroxy compounds (62 mg; 42%). N.m.r.: δ 4.65 ($W_{h/2}$ 20 Hz; H3α), 3.65 (broad; proton α to OH), 2.00 (OAc). These compounds could not be isolated separately.

Hydrolysis of 3β-acetoxy-17β-hydroxy-17aα-fluoro-D-homo-5α-androstane(58)

The fluorohydrin (11 mg) was treated with 0.55 ml of a solution of KOH (0.423 g) in methanol (10 ml) and the reaction mixture was refluxed overnight (refluxing was found to be necessary for the reaction to proceed). The reaction mixture was extracted with ether; the ether extracts were washed with water, dried over sodium sulphate and evaporated. T.l.c. showed a predominance of a single product. N.m.r.: δ 3.60 ($W_{h/2}$ 23 Hz; H3α), 3.15 ($W_{h/2}$ 8 Hz; H17), 2.73, 2.67 (J 4 Hz; H17a), 0.95 ($(H18)_3$), 0.80 ($(H19)_3$).

Hydrolysis of 3β-acetoxy-17β,17aβ-epoxy-D-homo-5α-androstane (36b)

The epoxide (17 mg) was treated with KOH-methanol as above. The t.l.c. of the product (36a) was identical to the t.l.c. of the hydrolysed fluorohydrin. N.m.r. (of the hydrolysed epoxide): δ 3.58 ($W_{h/2}$ 23 Hz; H3α), 3.15 ($W_{h/2}$ 8 Hz; H17), 2.72, 2.65 (J 4 Hz; H17a), 0.93 ($(H18)_3$), 0.78 ($(H19)_3$

Rearrangement of the fluorohydrin(58) with BF_3-etherate

An attempt was made to rearrange the fluorohydrin(58) with BF_3-etherate under the conditions used to rearrange the β-epoxide(36b). The reaction mixture was subjected to silica t.l.c. at intervals of time. After 10 minutes the fluorohydrin appeared unchanged.

Attempted synthesis of the 17,17a-epoxy-17-methyl series by way of 3β-acetoxy-D-homo-5α-androstan-17a-one(49b)

1. α-Methylation of 3β-acetoxy-D-homo-5α-androstan-17a-one(49b)

a) Using potassium-t-butoxide and methyl iodide.

A solution of potassium (1 g) in sodium distilled t-butanol (25 ml) was added to a boiling solution of the ketone (1 g) in sodium dry benzene (25 ml) and t-butanol (12.5 ml). Methyl iodide (7.5 ml) in sodium dry benzene (25 ml) was added and the reaction mixture was refluxed for one hour. The cold reaction was quenched with ice, and the products extracted with ether-ethyl acetate. The n.m.r. and t.l.c. gave no indication of a methylated product. The only observed reaction was a partial hydrolysis of the 3β-acetoxy function.

b) Using sodium hydride, xylene and methyl iodide.

A solution of 3β-acetoxy-D-homo-5α-androstan-17a-one (0.3 g) in xylene (7.7 ml) was dried by azeotropic distillation. The solution was cooled and 50% sodium hydride dispersion (100 mg) and t-butyl alcohol (1 drop) were added.

The reaction was refluxed under N_2 for 50 minutes. The yellow suspension was cooled and methyl iodide (4.4 ml), dried by shaking with $CaCl_2$, was added and the suspension refluxed overnight. Water was added, and the reaction was extracted with ethyl acetate-ether. The extracts were washed with water, dried over sodium sulphate, and evaporated. T.l.c. showed a complex mixture of products which were not considered further.

2. The Stork Synthesis (α-methylation of the pyrrolidine enamine of 3β-acetoxy-D-homo-5α-androstan-17a-one(49b))

Preparation of the pyrrolidine enamine

The ketone (100 mg) was dissolved in benzene (2 ml) and pyrrolidine (1 ml) was added. The reaction was refluxed, using a Dean-Stark moisture trap to remove excess water. After 48 hours reflux, the t.l.c. of the reaction showed a predominance of the starting ketone. Toluene-p-sulphonic acid, and further quantities of pyrrolidine were added, but the starting ketone still predominated in the t.l.c. of the reaction, even after a period of reflux in excess of four days.

As a consequence of the failure to prepare the pyrrolidine enamine the Stork synthesis was not considered further.

Preparation of cholesteryl tosylate(67)

Cholesterol(66) (58 g) was dissolved in dry pyridine (100 ml), and toluene-p-sulphonyl chloride (58 g) was added. The reaction was allowed to stand at room temperature for 24 hours, and was then extracted with chloroform. The chloro-

form extracts were washed with saturated sodium chloride solution, dried over magnesium sulphate, filtered through deactivated alumina (250 g), and evaporated. The crude product was crystallised from acetone (300 ml) to give cholesteryl tosylate(67) (75 g), m.p. 132-133° (lit., 131.7-132.6°). N.m.r.: δ 7.89, 7.75, 7.40, 7.28 (phenyl), 5.31 ($W_{h/2}$ 9 Hz; H6), 4.29 ($W_{h/2}$ 20 Hz; H3α), 2.44 (aromatic methyl), 0.97 ($(H19)_3$), 0.91, 0.82 (side chain methyls), 0.66 ($(H18)_3$).

Preparation of 3,5-cyclocholestan-6β-ol(68)

Cholesteryl tosylate(67) (70 g), dry potassium acetate (66.7 g), acetone (1065 ml), and water (266 ml) were refluxed together for 15 hours. Benzene (300 ml) was added, and the solvents were removed by distillation. The residual oil (50 g) was chromatographed on 5% deactivated alumina (800 g). Elution with petroleum ether gave a solid which was recrystallised from acetone to give 3,5-cyclocholestan-6β-ol (68) (32 g), m.p. 63-65° (lit., 66.7-67.9°). ν_{max} 3450 cm^{-1} (OH). N.m.r.: δ 3.24 ($W_{h/2}$ 4.5 Hz; H6), 1.06 ($(H19)_3$), 0.91, 0.82 (side chain methyls), 0.73 ($(H18)_3$), 0.62-0.14 (multiplet; cyclopropyl).

Preparation of 3,5-cyclocholestan-6-one(69)

8N Chromic acid (7.5 ml) was added dropwise to a stirred, ice cold solution of 3,5-cyclocholestan-6β-ol(68) (10 g) in acetone (120 ml) until a permanent brown colour remained. Sodium metabisulphite was added and the acetone was removed by distillation. The reaction was then extracted with ether, and the ether extracts were washed with water,

dried over sodium sulphate, and evaporated. The crude products (10 g) were chromatographed on 5% deactivated alumina (250 g). Elution with petroleum ether followed by 10% benzene in petroleum ether gave a solid (8.0 g) which was recrystallised from methanol to give 3,5-cyclocholestan-6-one(69) (6.1 g), m.p. 96.5-97° (lit., 96-97°). ν_{max} 1695 cm^{-1} (CO). N.m.r.: δ 1.01 ($(H19)_3$), 0.92, 0.82 (side chain methyls), 0.72 ($(H18)_3$).

Attempted preparation of the benzenesulphonyl hydrazone(70)

a) Benzenesulphonyl hydrazine (47 mg) was dissolved in ethanol and sodium acetate (71 mg) and acetic acid (0.04 ml) were added. The mixture was warmed and 3,5-cyclocholestan-6-one(69) (0.1 g) was added. After 5 hours at room temperature the reaction was extracted with ether, and the ether extracts were washed with water, and sodium carbonate solution, dried over sodium sulphate and evaporated. The n.m.r. of the product indicated a predominance of starting material.

b) A similar result was obtained even after refluxing the reaction mixture for 1½ hours.

c) By adding a drop of concentrated sulphuric acid to the reaction where methanol was used instead of ethanol a partial reaction did take place. This reaction, however, could not be made to proceed in sufficient quantities to be of practical use in the proposed synthesis.

Preparation of the 3,5-cyclocholestane-6-methyl ether(71)

A solution of cholesteryl tosylate(67) (50 g) and fused potassium acetate (50 g) in anhydrous methanol (2,300 ml) was refluxed for 8 hours. After most of the solvent had been removed, water and ether were added. The aqueous layer was

extracted twice more with ether and the combined ether extracts were washed with water, sodium bicarbonate solution and again with water. On drying the ether extracts with sodium sulphate, and removing the ether, the product mixture (35 g) was isolated and chromatographed on activated alumina (1200 g). Elution with petroleum ether gave 3,5-cyclocholestane-6-methyl ether(71) (30.2 g). ν_{max} 1100 cm^{-1} (ether). N.m.r. δ 3.31 (6-methoxy), 2.76 ($W_{h/2}$ 3.5 Hz; H6), 1.02 ($(H19)_3$), 0.91, 0.82 (side chain methyls, 0.72 ($(H18)_3$), downfield of 0.23 (multiplet; cyclopropyl).

Preparation of 3,5-cyclocholest-6-ene(72)

3,5-Cyclocholestane-6-methyl ether(71) (30.2 g) was dissolved in sodium dry hexane (242 ml) and added to a suspension of Brockmann no. 1 activated alumina (905 g) in dry hexane (302 ml). The mixture was shaken thoroughly and then left to stand at room temperature for one week. The steroidal products were recovered by washing the alumina with several volumes of ether containing 10% methanol. The washings were combined and evaporated, and the crude products (26.2 g) were chromatographed on activated alumina (1300 g). Elution with petroleum ether gave a solid (6.0 g) which, when recrystallised twice gave 3,5-cyclocholest-6-ene(72), m.p. 71-72° (lit., 73°). N.m.r.: δ 5.80, 5.77, 5.63, 5.60, 5.25, 5.22, 5.08, 5.05 (quartet, J 10 Hz; doublets J 2 Hz; H6, H7), 0.90 (side chain methyls; $(H19)_3$), 0.82 (side chain methyls), 0.72 ($(H18)_3$). The remaining reaction product consisted of a mixture of polar compounds (c.a. 20 g) which were not considered further.

Reaction of 3,5-cyclocholest-6-ene(72) with metachloroperbenzoic acid

This reaction was found to be very sensitive to changes in reaction and workup conditions. As a result of a series of trial reactions, in which the amount of peracid, the reaction time, and the workup conditions, were varied, the following set of conditions was found to be satisfactory in the preparation of 3,5-cyclo-6,7-epoxycholestane(73).

3,5-Cyclocholest-6-ene(72) (1 g) was dissolved in sodium dry ether (100 ml), and metachloroperbenzoic acid (1.41 g) was added. The reaction was left for 1 hour, and then extracted with ether. The ether extracts were washed with 10% sodium hydroxide solution, and water (three times), dried over sodium sulphate, and evaporated to give crude 3,5-cyclo-6,7-epoxycholestane(73). (Found: M^+ 384.338751. $C_{27}H_{44}O$ requires M^+ 384.339199). N.m.r.: δ 3.23, 3.15, 2.83, 2.77, (J 4 Hz, doublet at 3.23, 3.15 decoupled by a signal 23 Hz upfield, doublet at 2.83, 2.77 decoupled by a signal 23 Hz downfield; H6, H7). Attempts were made to further purify the epoxide by chromatography.

(i) The crude epoxide (1 g) was chromatographed on 10% deactivated alumina (100 g). Elution with ether gave 0.305 g of material which was purified by further chromatography to give 3,5-cyclocholest-6,7-diol(74) (0.214 g). ν_{max} 3440 cm^{-1} (OH). (Found: C, 80.15; H,11.66. $C_{27}H_{46}O_2$ requires C, 80.53; H, 11.51%). N.m.r.: δ 3.75 ($W_{h/2}$ 7 Hz; H7), 3.19, 3.14 (J 3 Hz; doublet decoupled by irradiating a signal 35 Hz downfield; H6), 0.90, 0.81 (side chain methyls), 1.03 ($(H19)_3$), 0.72 ($(H18)_3$), 0.07-0.62 (multiplet; cyclopropyl protons).

(ii) Chromatography on florisil also gave 6,7-diol.

(iii) Silica t.l.c. of the epoxidation reaction mixture showed at least nine products and hence the epoxide was presumed unstable to silica.

(iv) The epoxide appeared to be stable to cellulose chromatography but no increase in purity was achieved.

Attempts to purify the crude product by recrystallisation from (i) acetone, (ii) acetone-water, (iii) petroleum ether, (iv) methanol-pyridine, were also unsuccessful.

In that all attempts to further purify the crude epoxide were unsuccessful, subsequent rearrangements were performed on the crude epoxide.

Rearrangement of 3,5-cyclo-6,7-epoxycholestane(73) with BF_3-etherate

The epoxide (500 mg) was dissolved in sodium dry benzene (12.5 ml) and distilled BF_3-etherate (0.5 ml) in sodium dry benzene (12.5 ml) was added. After one minute the reaction was quenched with water, and extracted with ether. The ether extracts were washed with water (four times), dried over sodium sulphate, and evaporated. The crude products were chromatographed on silica (50 g). Elution with pentane gave an unidentified material (0.174 g) which appeared as one spot on silica t.l.c. (Found: M^+ c.a. 732). ν_{max} 3450 cm^{-1} (OH), λ_{max} 241 nm (ε 9,800). N.m.r.: δ 5.75 (multiplet; $W_{h/2}$ 49 Hz; olefinic protons), 0.83, 0.91 (angular and side chain methyls). Remaining products were recovered from the column as inseparable mixtures.

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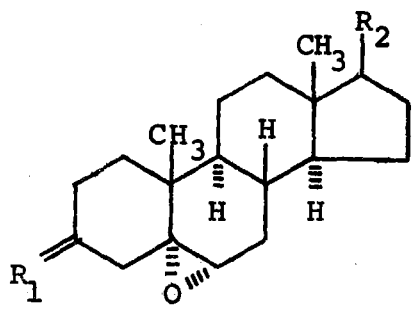
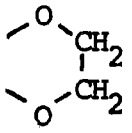
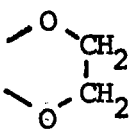
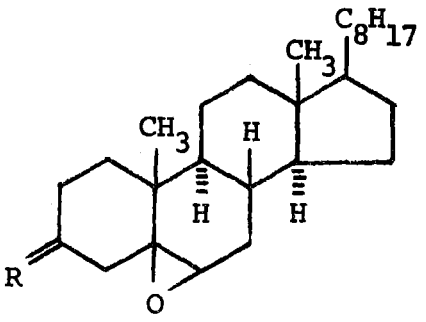
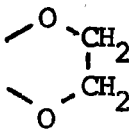
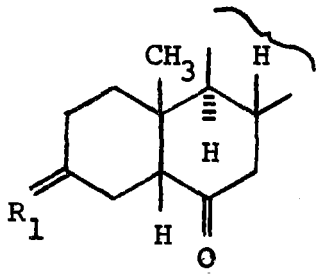
Structural Formulae



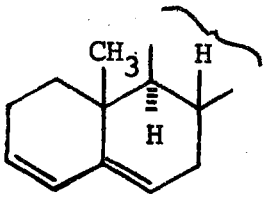
(1) (a) R_1 = α-H,β-H ; R_2 = C_8H_{17}
(b) R_1 = α-OAc,β-H; R_2 = C_8H_{17}
(c) R_1 = α-H,β-OAc; R_2 = C_8H_{17}
(d) R_1 = O ; R_2 = $COCH_3$
(e) R_1 =  ; R_2 = $COCH_3$
(f) R_1 =  ; R_2 = C_8H_{17}



(2) (a) R = α-H,β-H
(b) R = α-OAc,β-H
(c) R = 



(3) (a) R = α-H,β-H
(b) R = α-OAc,β-H
(c) R = α-OH,β-H



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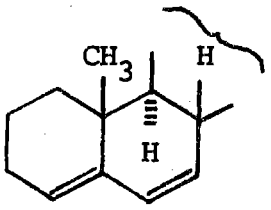

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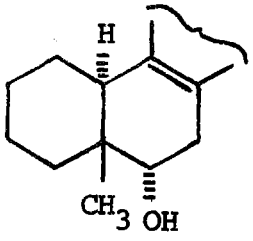

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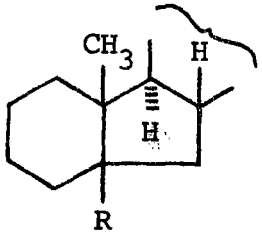
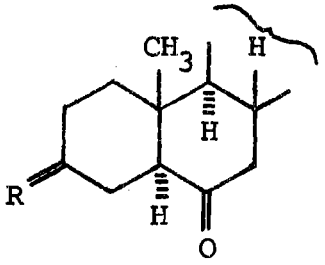
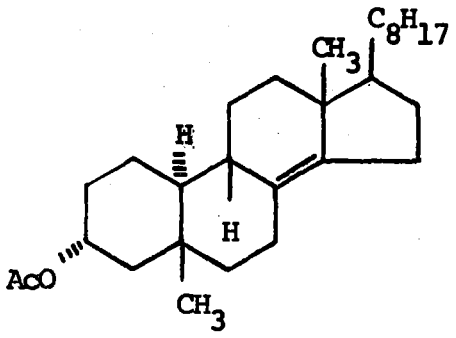


(7) (a) R = α-CHO
(b) R = β-CHO



(8) (a) R = α-H,β-H
(b) R = α-OH,β-H



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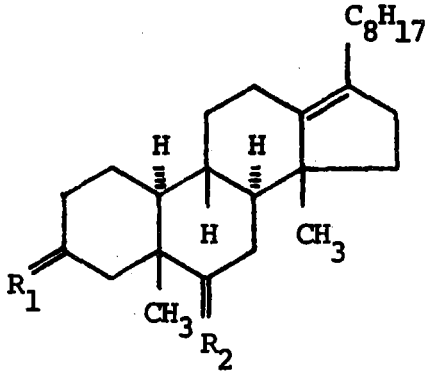
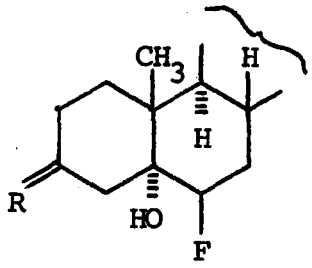


(10) (a) R_1 = α-H,β-H ; R_2 = α-OH,β-H
(b) R_1 = α-H,β-H ; R_2 = α-H,β-OH
(c) R_1 = α-OAc,β-H; R_2 = α-OH,β-H
(d) R_1 = α-OH,β-H; R_2 = α-H,β-OH
(e) R_1 = α-OH,β-H; R_2 = α-OH,β-H



(11) (a) R = α-H,β-OAc
(b) R = α-OAc,β-H
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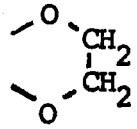
(d) R = 
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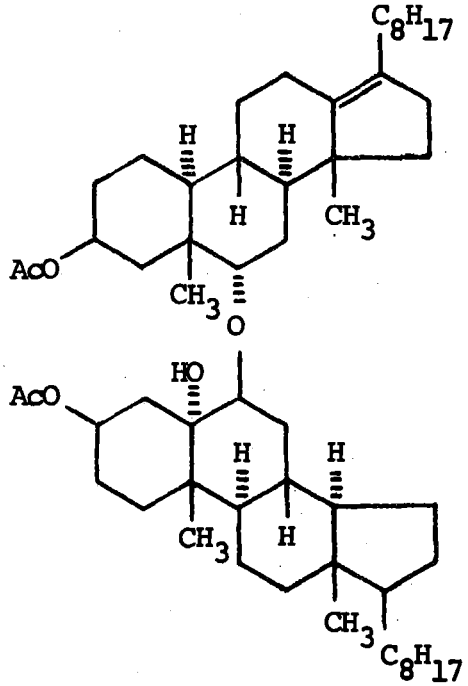

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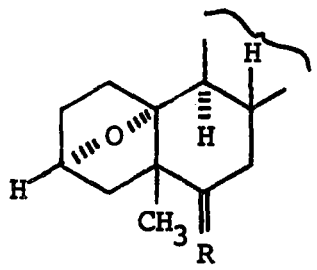

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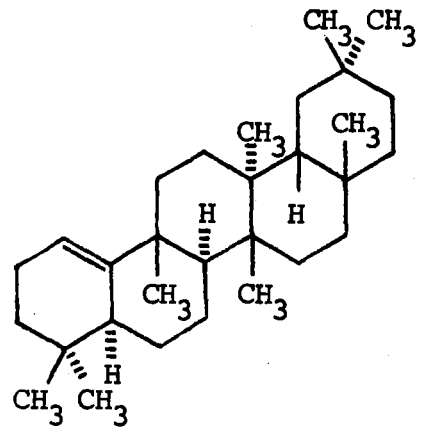

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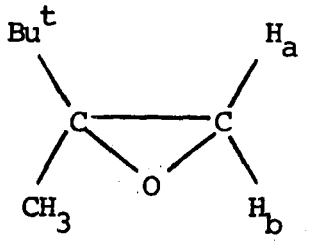

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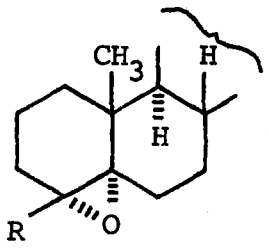
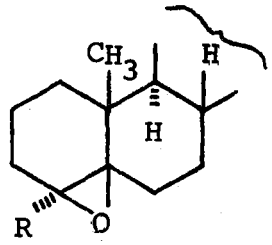


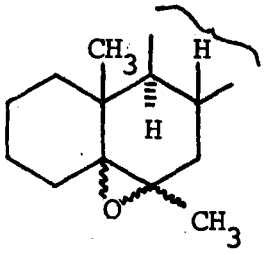
(16)(a) R = H

(b) R = CH_3



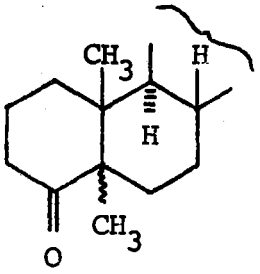
(17) (a) R = H

(b) R = CH_3



(18) (a) α-epoxide, 6β-methyl

(b) β-epoxide, 6α-methyl



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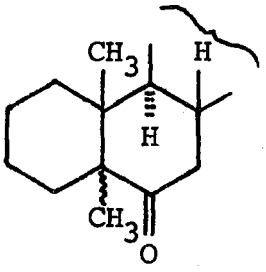

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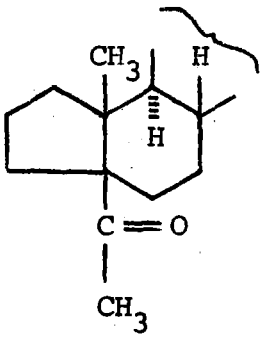

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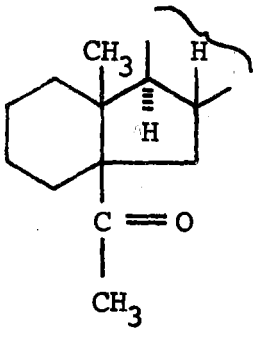

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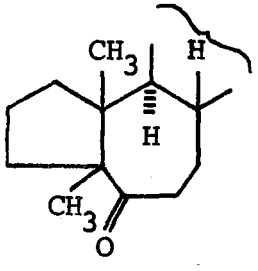

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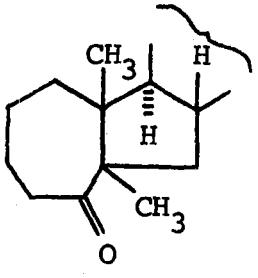

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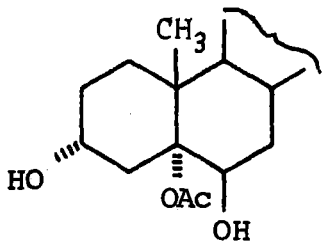

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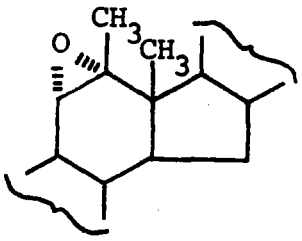

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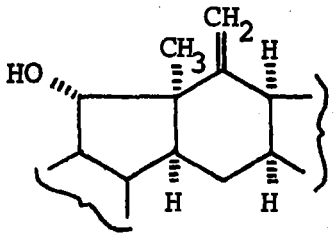

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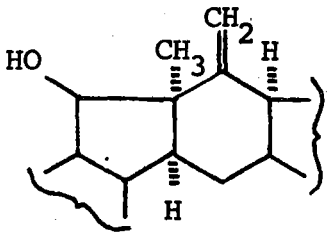

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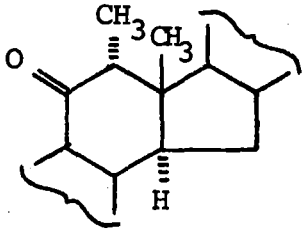

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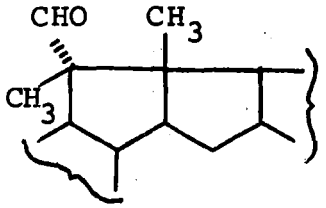

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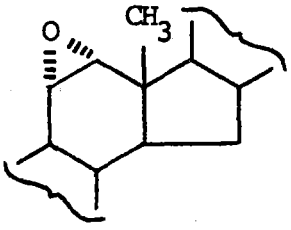

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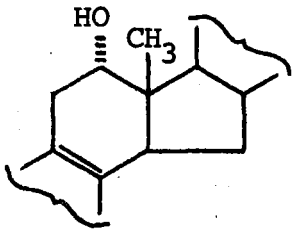

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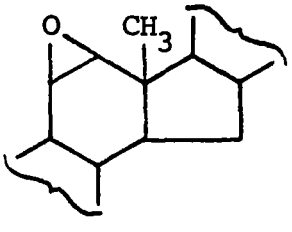

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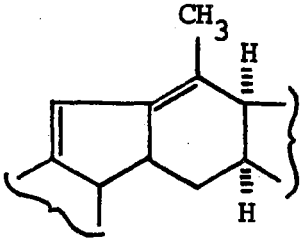

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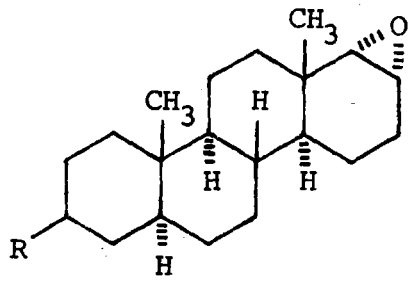
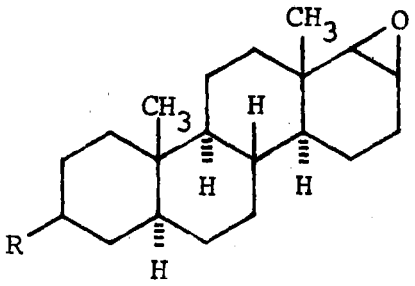


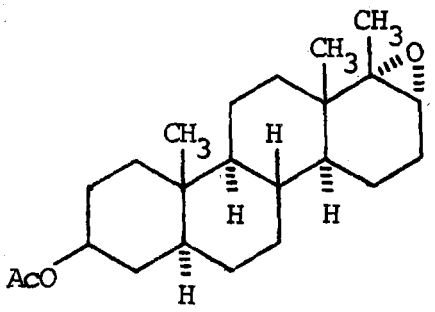
(35) (a) R = OH

(b) R = OAc



(36) (a) R = OH

(b) R = OAc



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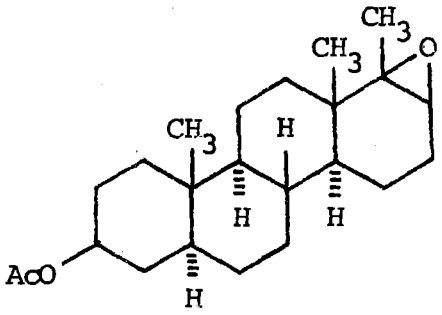

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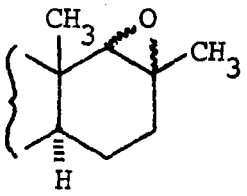

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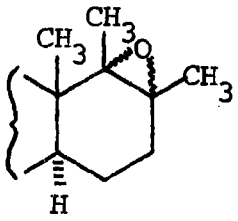

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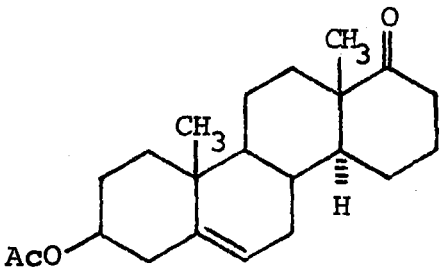

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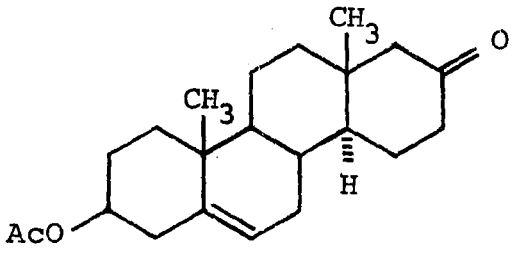

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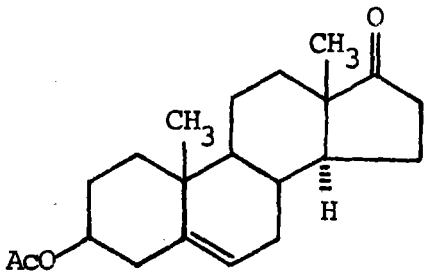

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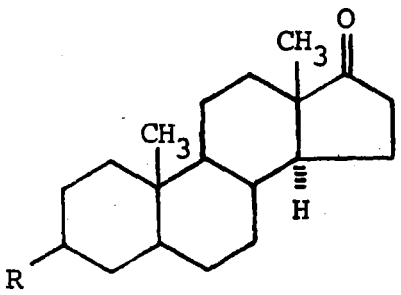
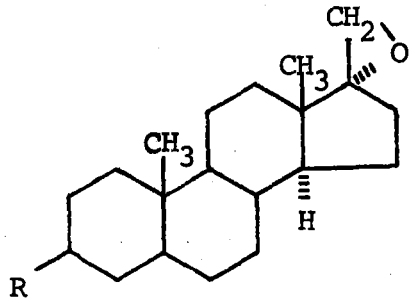


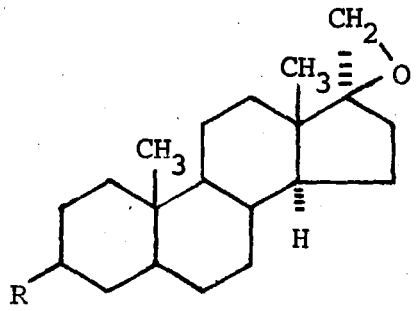
(44) (a) R = OH

(b) R = OAc



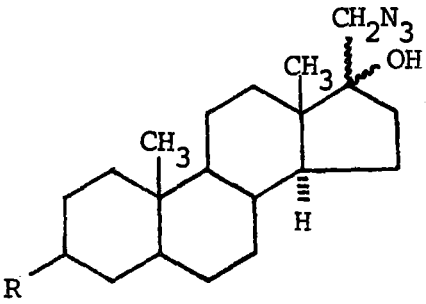
(45) (a) R = OH

(b) R = OAc



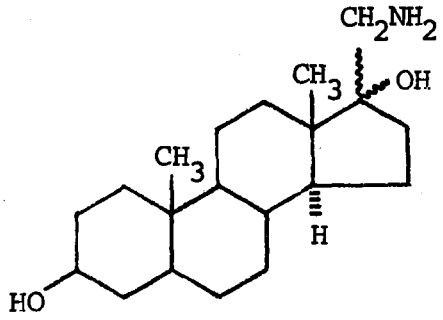
(46) (a) R = OH

(b) R = OAc



(47) (a) R = OH

(b) R = OAc



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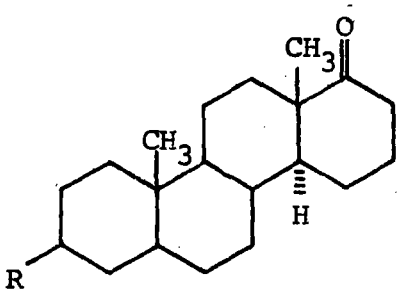
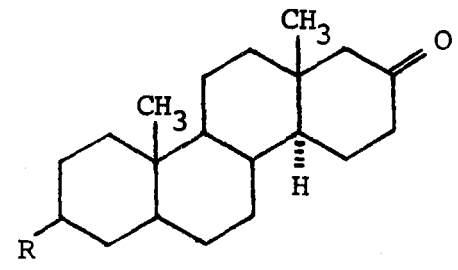


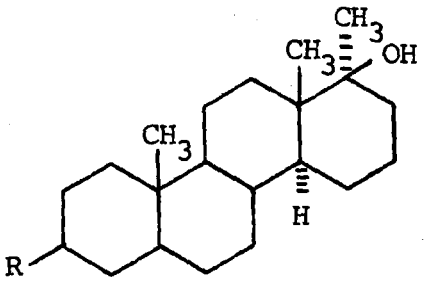
(49) (a) R = OH

(b) R = OAc



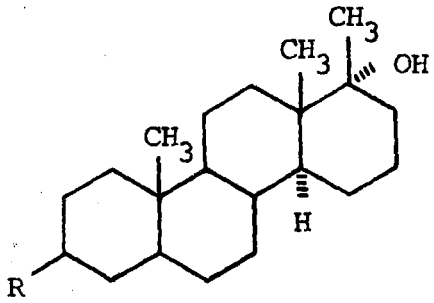
(50) (a) R = OH

(b) R = OAc



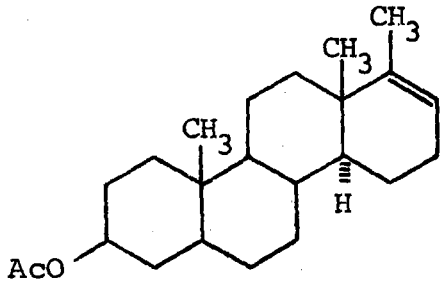
(51) (a) R = OH

(b) R = OAC



(52) (a) R = OH

(b) R = OAc



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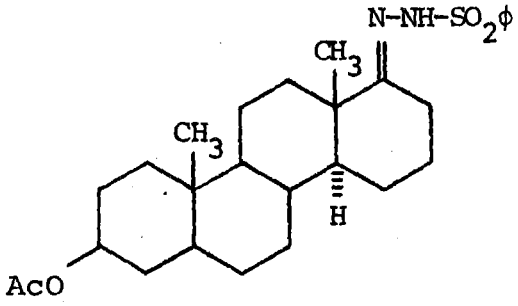

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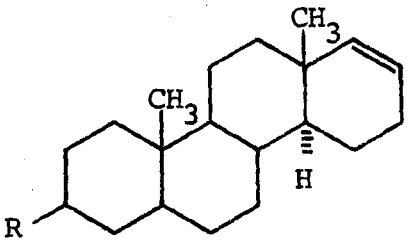
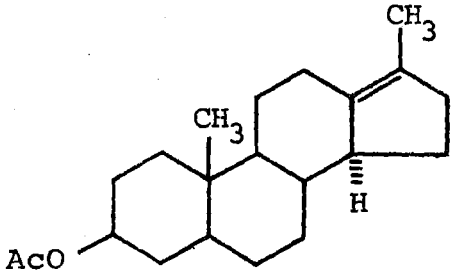


(55) (a) R = OH

(b) R = OAc



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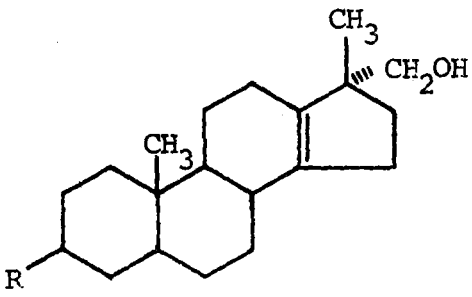
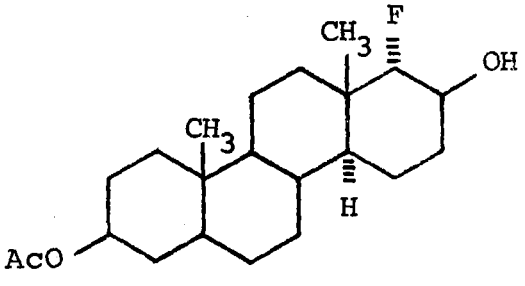


(57) (a) R = OH

(b) R = OAc



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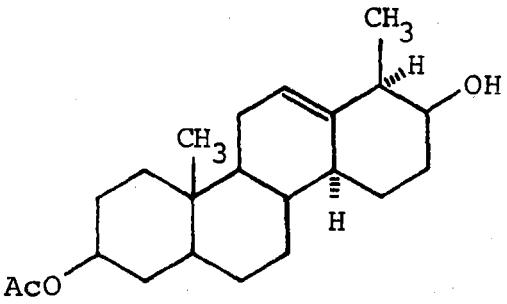

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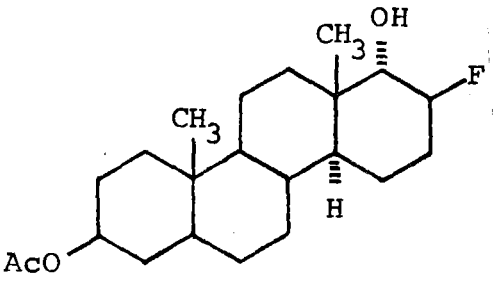

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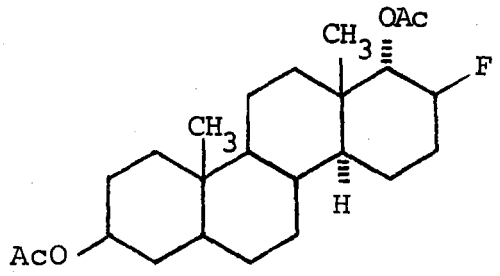

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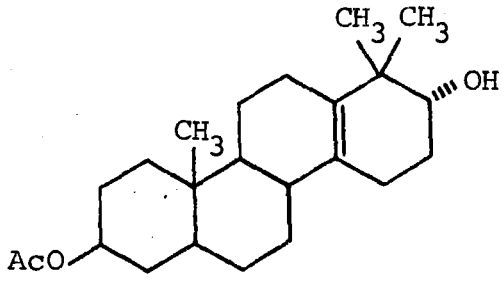

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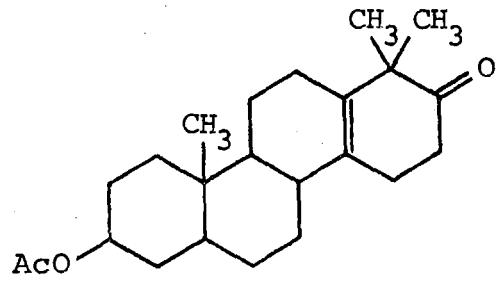

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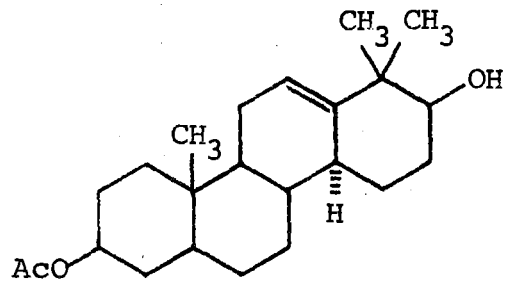

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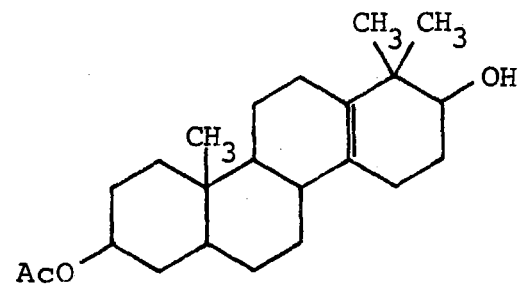

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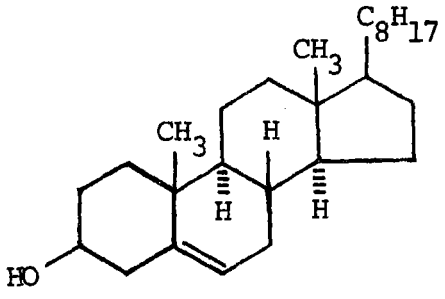

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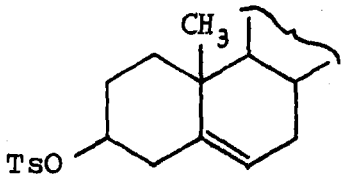

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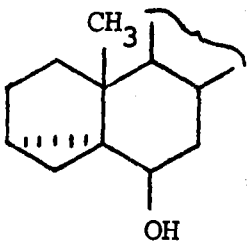

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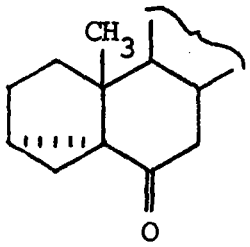

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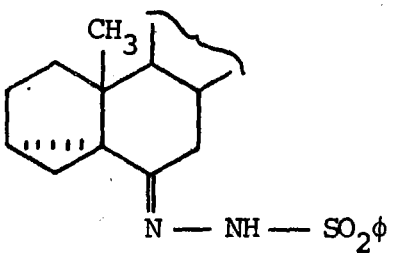

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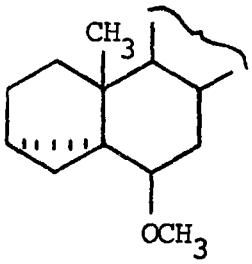

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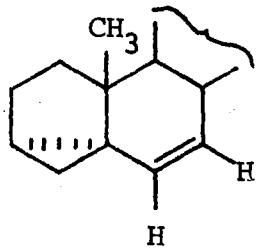

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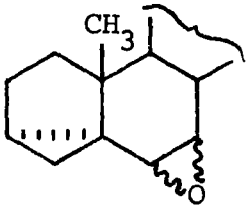
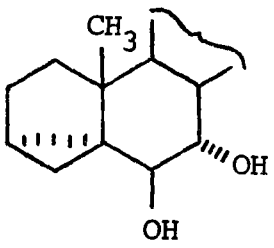


(73)



(74)