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ABSTRACT

Reactions in which the steroidal 10β-methyl group, at the hydroxy or aldehyde oxidation state, was eliminated by the opening of a 5,6- or a 4,5-epoxide were investigated. In cholestane and (in part) androstan-17-one steroids, such an elimination was observed in the reactions of 19-hydroxy-5β,6β-epoxides with boron trifluoride and, under certain circumstances, in the reactions of 19-oxo-5β,6β-epoxides with base. Under comparable conditions, the isomeric 5α,6α-epoxides underwent either intramolecular or intermolecular opening of the epoxide by nucleophiles. For the acid- or base-catalyzed reactions of 19-oxo-4,5-epoxy-androstane-3,17-diones, compounds which have been postulated as intermediates in the last stage of the biosynthesis of estrogens, it was found that epoxide rearrangement or nucleophilic opening of the epoxide ring predominated, although small yields of estrone were obtained under acidic conditions. The attempts to prepare the product of a fragmentative elimination of the 10β-substituent from 19-oxo-4β,5-epoxy-5β-androstane-3,17-dione by alternate means are described.

The results of incubation experiments indicated that the aforementioned 4,5-epoxides are not intermediates in the biosynthesis of estrogens. Other intermediates which may be involved in this process were discussed.

INTRODUCTION

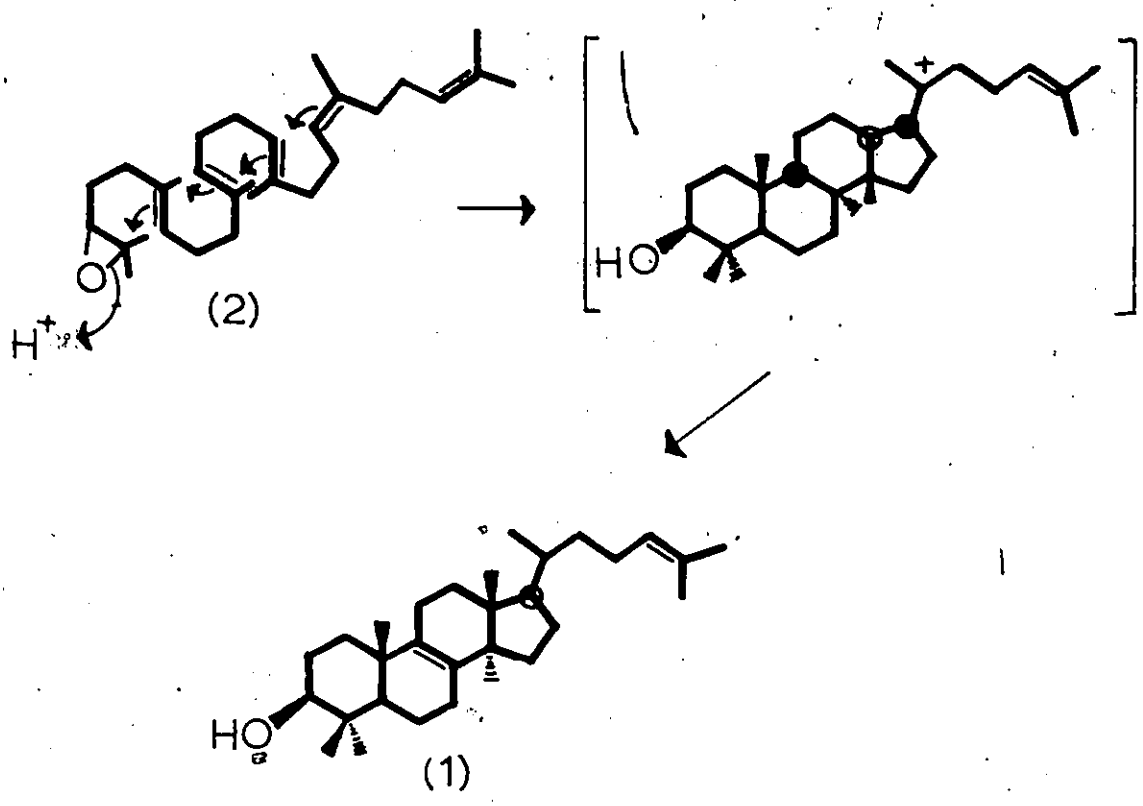
The reactivity of epoxides is attributed[1] to the strain present in the three-membered ring. This strain results from the deformation of bond angles to a point that is considerably less than the normal tetrahedral angle. Accordingly, orbitals of different hybridization and somewhat higher energy are employed to form the bonds between the ring atoms. Like cyclopropane[2], these bonds are bent with the regions of highest electron density lying outside the ring. They have a greater degree of p character and therefore there is less σ overlap. As a result, the C-O bond is weaker than its acyclic ether counterpart and this is reflected by the ease with which the ring is opened by nucleophiles in the presence of acid catalysts.

In the absence of effective nucleophiles, Lewis acids can promote heterolytic cleavage of the epoxide C-O bond and in this way initiate a variety of reactions which are characteristic of carbocations. This property of epoxides has been the subject of study by chemists and also biochemists since it has been shown to be involved in terpenoid biosynthesis. These carbocation reactions of epoxides can be arranged in three groups.

(a) Addition to Unsaturated Hydrocarbons

A carbocation generated by the opening of an epoxide can react with an unsaturated group to form a new carbocation. If this occurs intramolecularly, a cyclic

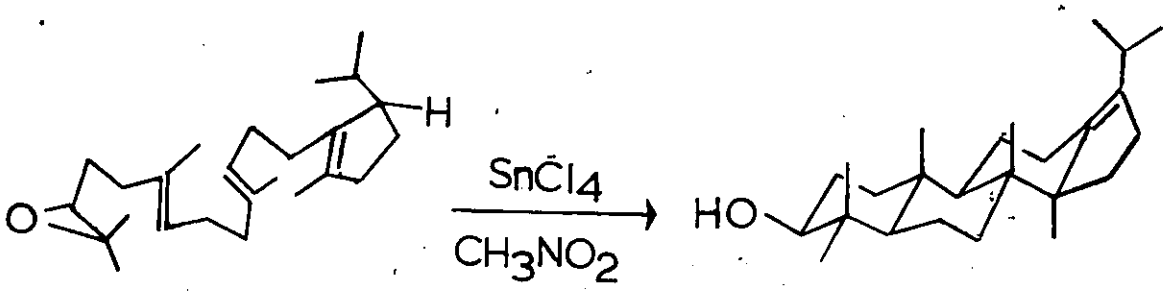
carbocation is formed. The most important example of this type of reaction is found in steroid biosynthesis and involves the formation[3] of lanosterol (1) from squalene oxide (2). Such epoxide-initiated polyene cyclizations



(2)

(1)

have been used in a number of "biomimetic" syntheses. The synthesis of the isoeuphenol system (3) by van Tamelen[4] an example of this approach.

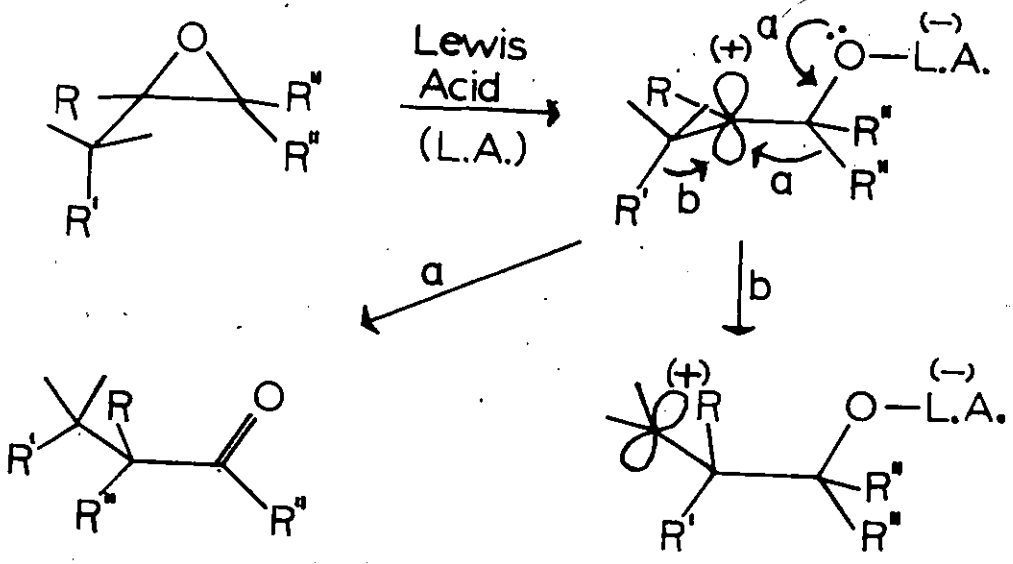


(3)

35%

(b) Rearrangement

Heterolytic opening of the epoxide can initiate a variety of carbonium ion rearrangements within the molecule. These typically take the form (SCHEME 1) of pinacol-like rearrangements (path a) or 1,2 shifts (path b). They have been widely studied in steroid chemistry[1,5] and a more detailed discussion will be given in the subsequent section.

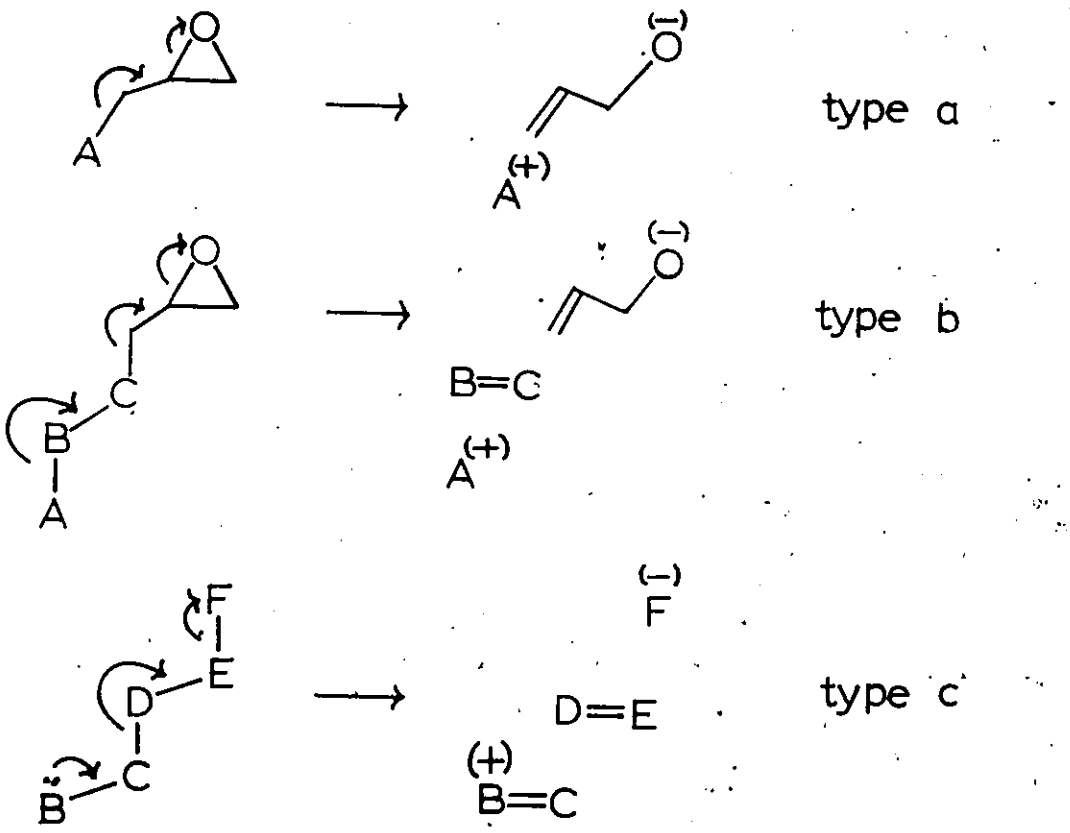


(c) Elimination

The epoxide oxygen functions as a nucleofuge in the heterolytic opening of an epoxide. If this reaction is accompanied by the loss of an electrofuge, an allylic

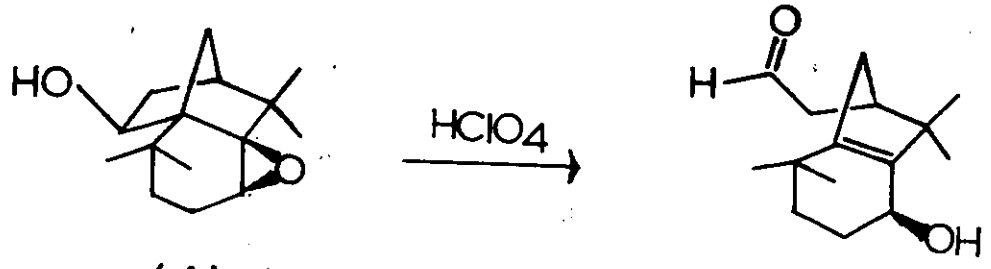
alcohol is produced. This is much like the situation encountered in 1,2 eliminations which give rise to olefins. In the latter case a wide spectrum of mechanistically different processes[6] have been demonstrated. Although the elimination reactions of epoxides have not been studied in as much detail, they would be expected to exhibit a similar diversity in their mechanisms. The reactions that will be examined in this thesis proceed in the presence of Lewis acids and would therefore involve some degree of carbocation ion character. They may be classified (SCHEME 2) according to the number of fragments that are generated in the reaction.

SCHEME 2

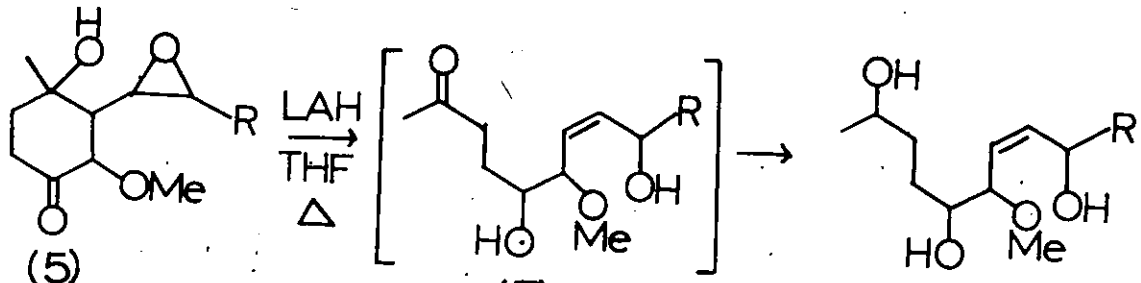


Simple cleavage (two fragments, type a) is most commonly encountered and generally involves a proton as the electrofuge. The reaction of epoxides with lithium diethylamide[7] to produce allylic alcohols is representative of this process.

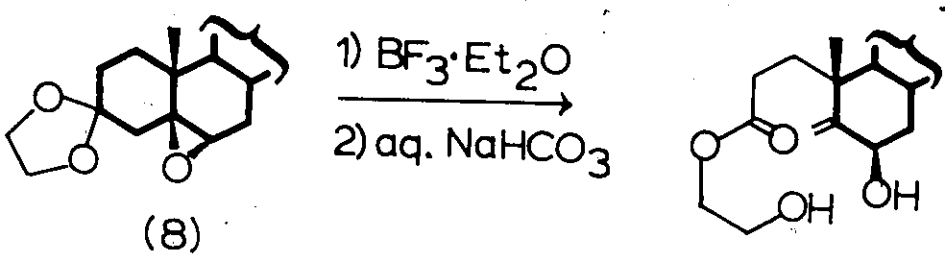
The fragmentation reactions (three fragments, type b) of epoxides may be considered to be Grob fragmentations[8] (type c). They are relatively uncommon and only a few examples have been reported. With a hydroxy group in the electrofugal fragment, the epoxides (4) and (5) undergo fragmentation to give, respectively, the aldehyde[9] (6) and the ketone[10] (7). With a ketone in the electrofugal fragment, fragmentation can occur via the ketal as with (8)[11] and (9)[12]. The epoxyacid[13] (10) undergoes a thermal decarboxylation.



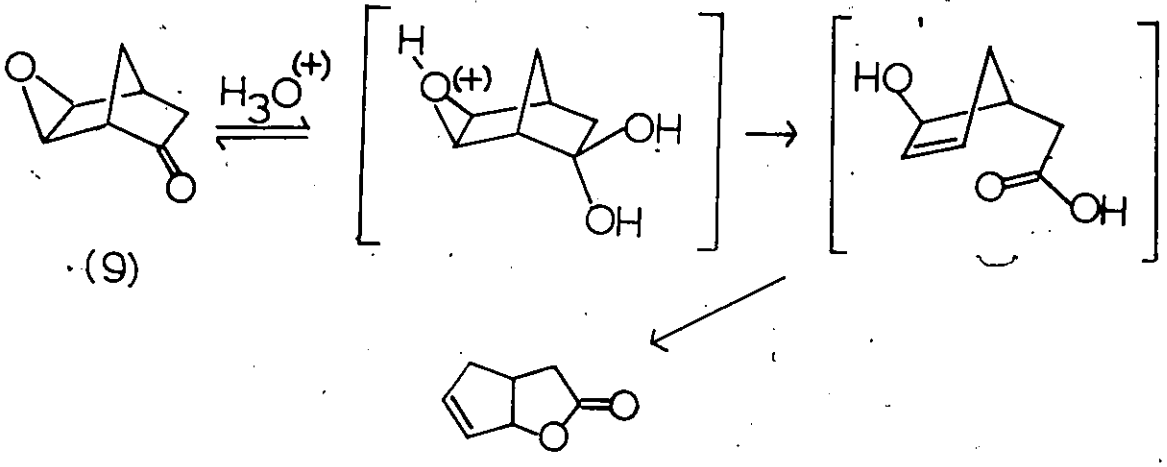
(4) (6)



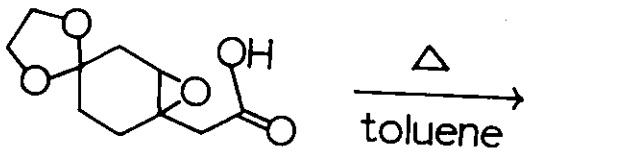
(5) (7)


1) $BF_3 \cdot Et_2O$
2) aq. $NaHCO_3$
OH
OH

(8)

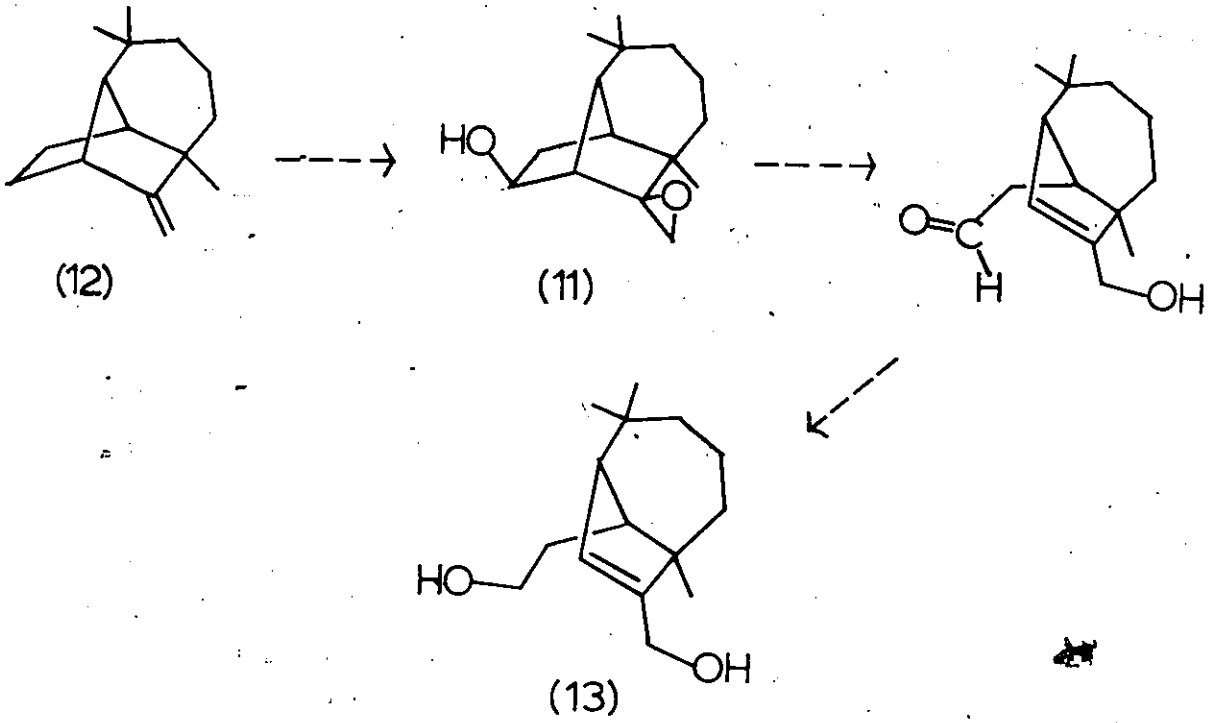

$H_3O^{(+)}$
H
O(+)
OH
OH
HO
OH

(9)

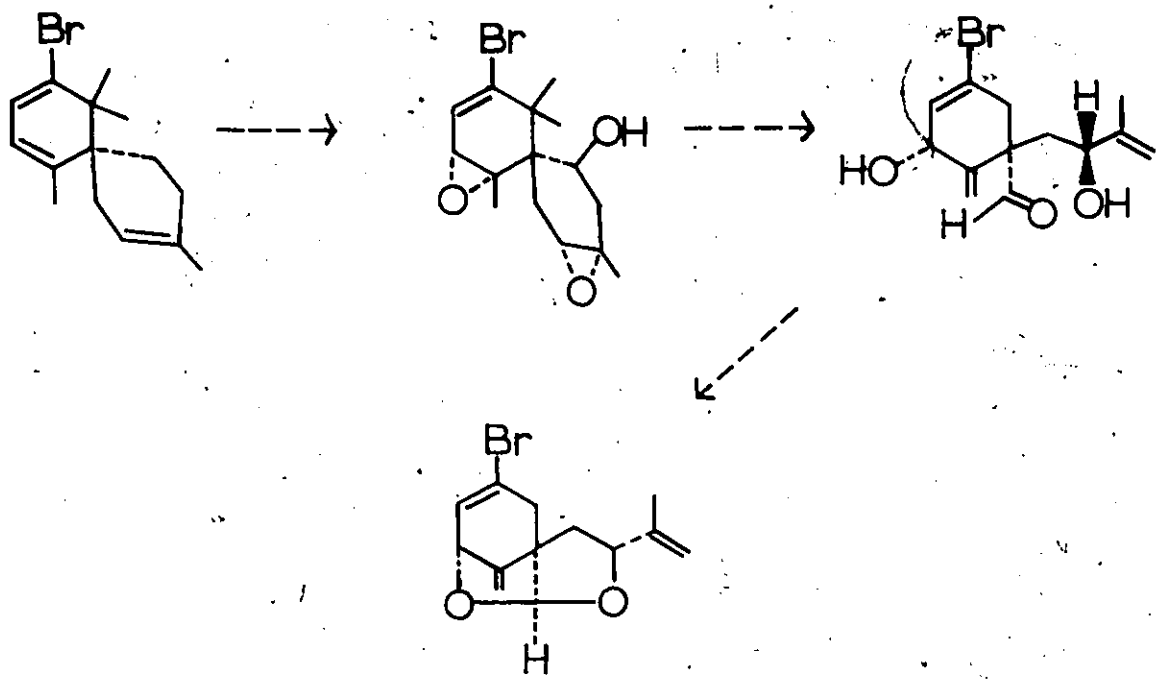

OH
△
toluene
OH
+ CO_2

(10)

The fragmentation reactions of epoxides may be of importance in terpene biosynthesis. Arigoni[14] has postulated the intermediacy of the epoxy-alcohol (11) in the conversion of (-)-longifolene (12) to (+)-secolongifolene (13). Both epoxide-initiated cleavage and fragmentation have been suggested[15] to occur in the biosynthesis of the novel secochamigrane (14).

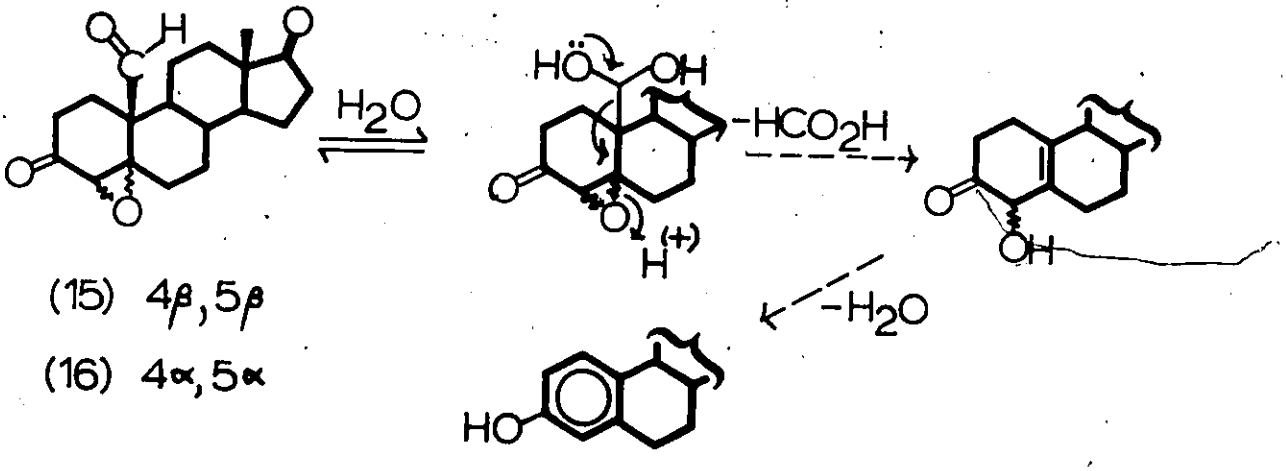


(12) (11) (13)



(14)

In this thesis, the rearrangement and fragmentation reactions of 19-substituted 4,5- and 5,6-epoxy steroids were examined. The reactions of the 4,5-epoxy-19-aldehydes (15) and (16) were of particular interest since they have been postulated[16,17] as intermediates in estrone biosynthesis.



(15) 4β,5β

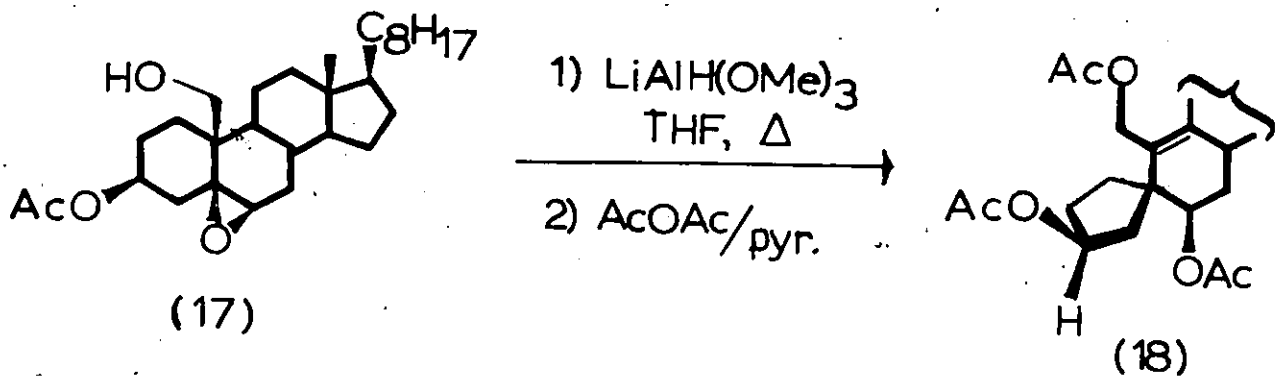
(16) 4α,5α

RESULTS AND DISCUSSION

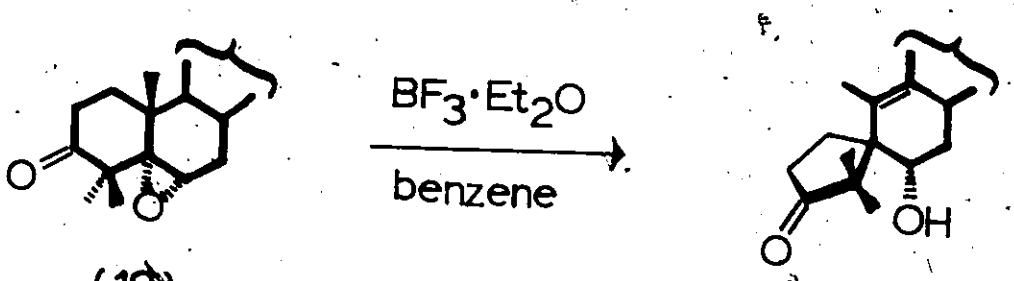
PART I

Boron Trifluoride-catalyzed Reactions of 19-Hydroxy- and 19-Acetoxy-5,6-epoxy-steroids

The work described in this portion of the thesis arose from the observation[18] that the 19-hydroxy-5β,6β-epoxide (17) rearranged upon attempted reduction to give a product for which the spiro structure (18) was suggested. This reaction was viewed as being rather novel since the contraction of the A ring to give a 1(10→5)-abeo-compound such as (18) is rarely observed in the Lewis acid-catalyzed rearrangements of 5,6-epoxy-steroids. The only reported[19] instance where this represented a major mode of rearrangement was with the 4,4-dimethyl-3-keto-steroid (19). The boron trifluoride-catalyzed reaction of (17) was therefore examined to see if this anomalous rearrangement would similarly occur with this reagent.



(17) (18)



(19)

1. Reactions with 3β-Acetoxy-19-hydroxy-5,6β-epoxy-5β-cholestane (17) and 3β-Acetoxy-19-hydroxy-5,6β-epoxy-5β-androstan-17-one (32)

The boron trifluoride-catalyzed rearrangements of 5,6-epoxy-steroids have been extensively examined[1,5,20] and some representative examples are included in TABLE 1. The common feature of these reactions is that they proceed *via* the initial heterolytic cleavage of the epoxide at the most substituted carbon, namely C-5. The ensuing bond migration can either be concerted with the opening of the epoxide ring or proceed after an open carbocation has formed. The concerted reaction occurs when the migrating group is trans periplanar with respect to the departing oxygen. If an open carbocation is involved, the only stereochemical requirement on the migrating group is that it has to be periplanar with respect to the vacant orbital of the carbocation. The transition state for a particular

TABLE 1. Boron Trifluoride-catalyzed Reactions of some 5,6-Epoxy-steroids

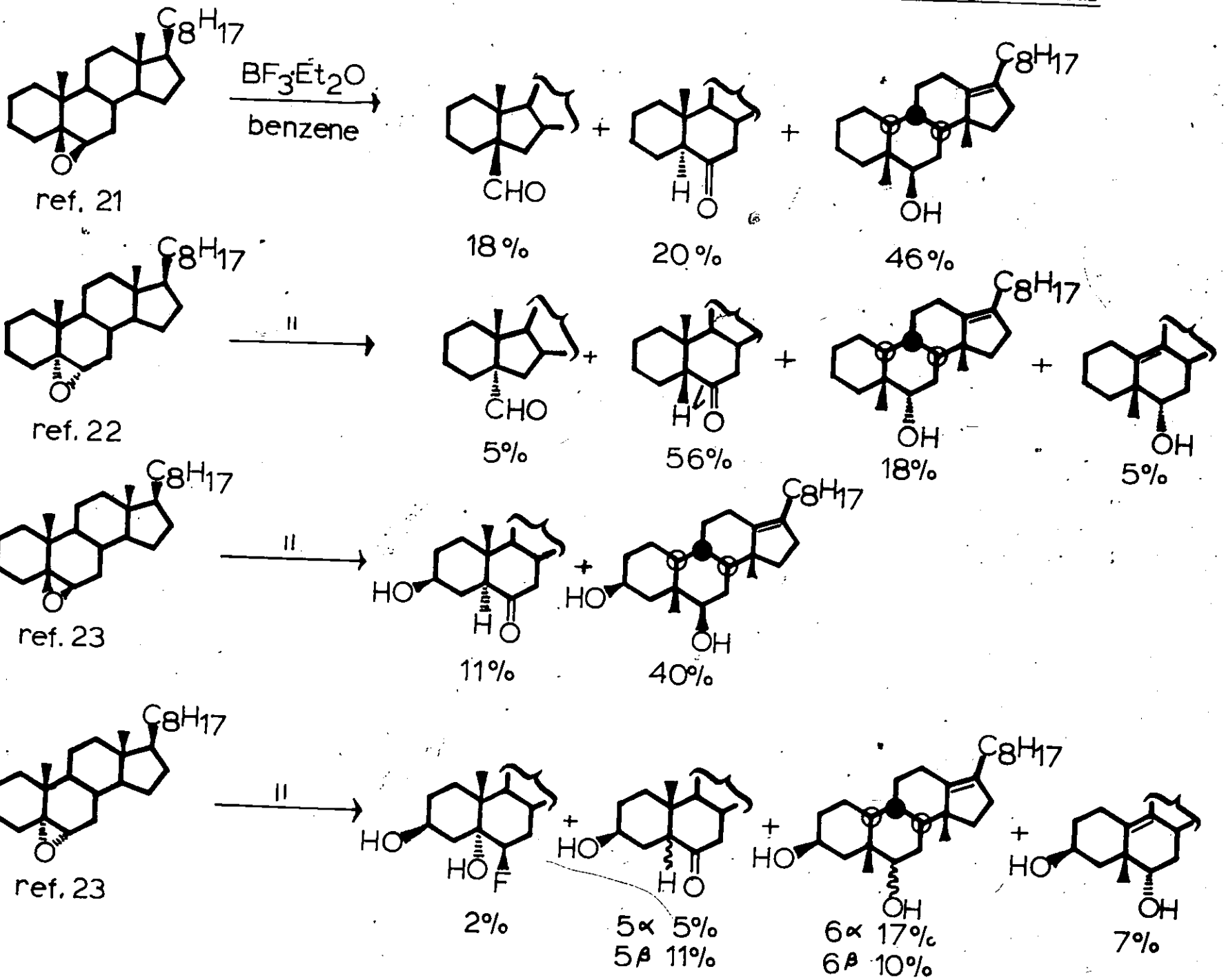
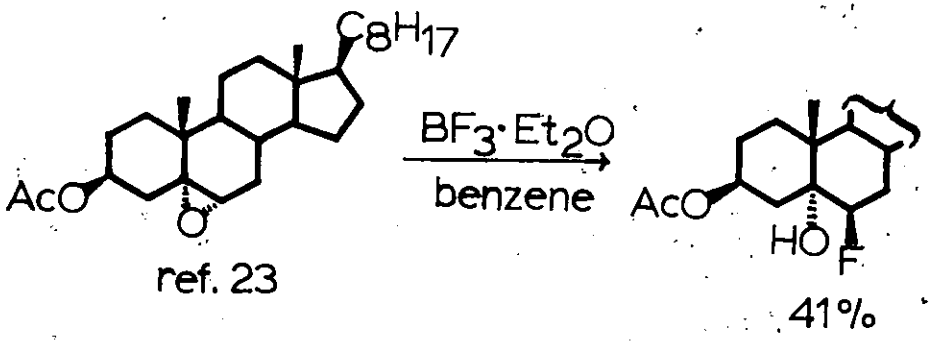
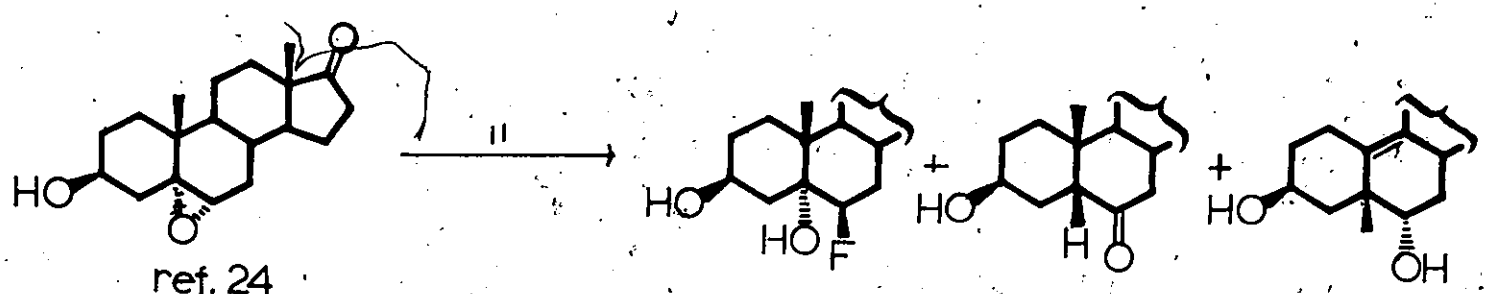


TABLE 1. Cont'd



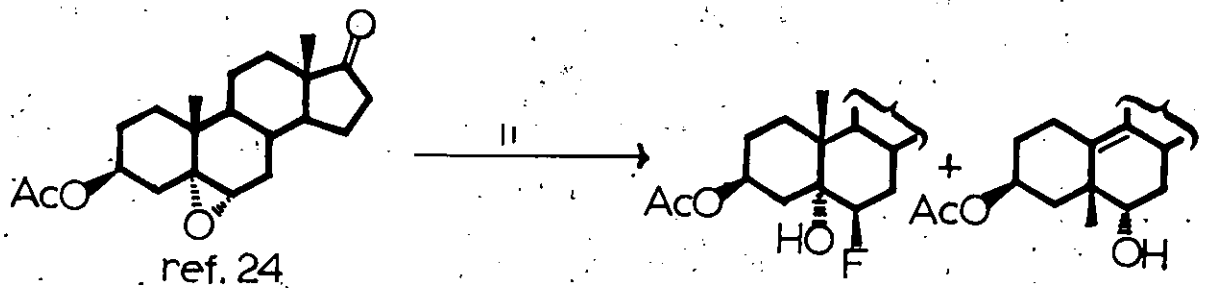
ref. 23

41%



ref. 24

25% 19% 35%

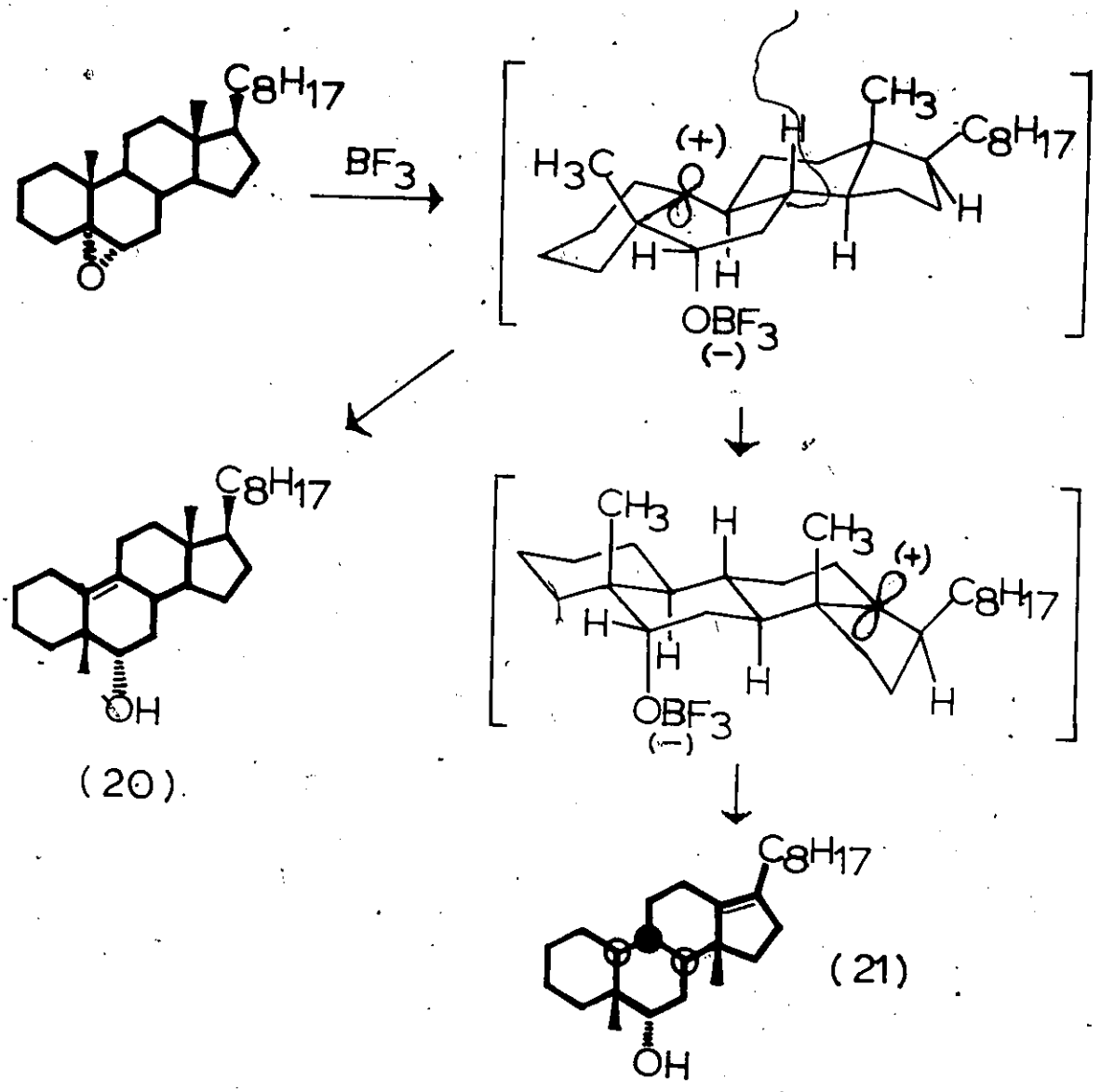


ref. 24

64% 16%

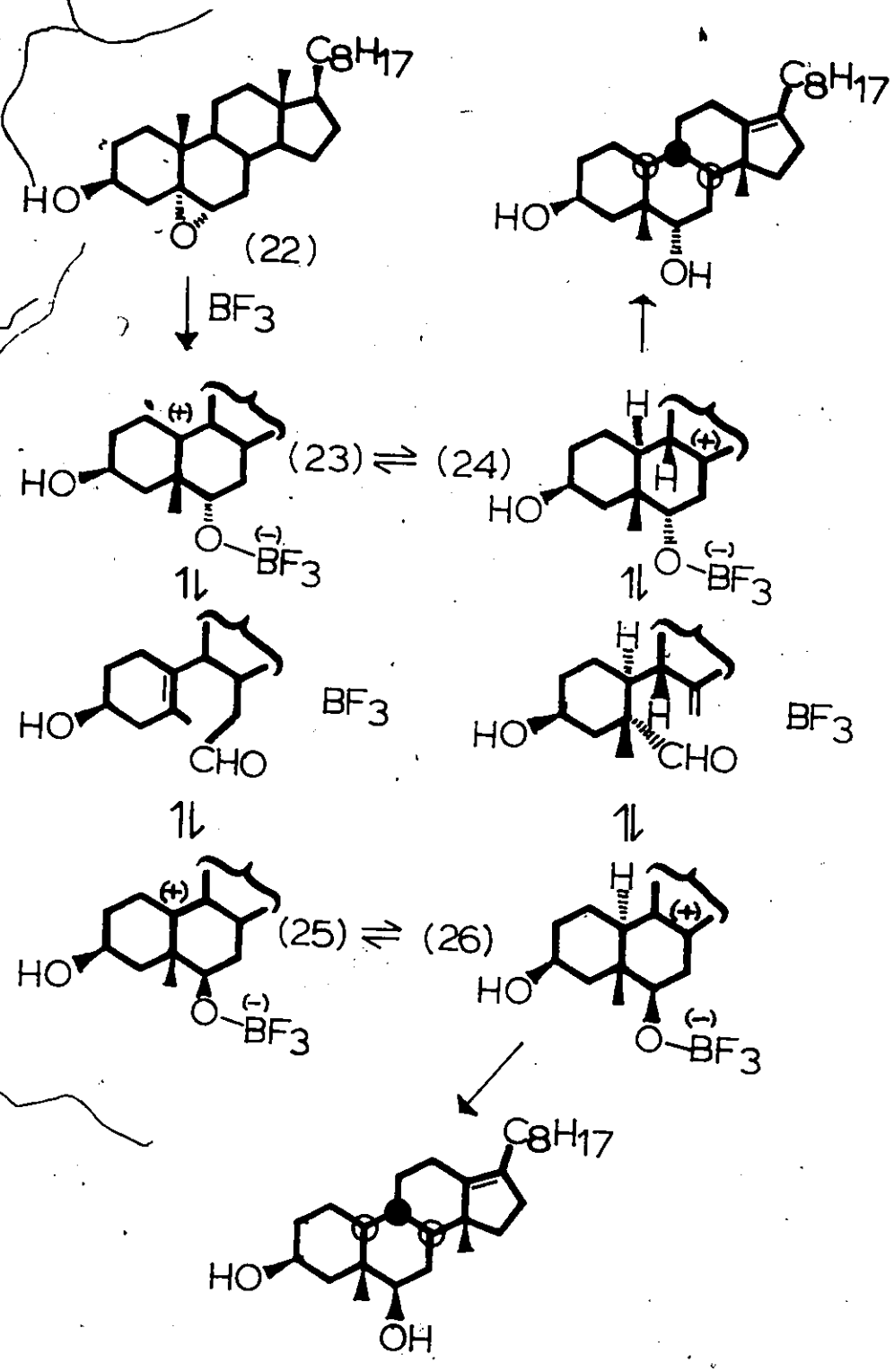
rearrangement is often considered to be product-like and therefore a reaction would be considered unfavourable if it leads to a conformation of high energy. However, it is more often the case that the energy differences between competing reactions is small and a number of different products are obtained. This can make an analysis of the responsible factors difficult since these energy differences are often within the range of subtle conformational and van der Waals effects.

It can be seen from TABLE 1 that the three major modes of rearrangement involve migration of: the C-10 methyl substituent, the 6-hydrogen atom and the C(6)-C(7) bond. The migration of the C-10 methyl group is generally the predominant mode of migration for both the 5α,6α-and 5β,6β-epoxides even though, in the latter case, the 10-methyl substituent is <u>syn</u> with respect to the epoxide group. The "Westphalen" product (eg., (20)[22]) arises if the rearrangement terminates after the initial migration of the C-10 group. Alternatively, if the rearrangement proceeds further, a series of stepwise[25] 1,2-shifts leads to "backbone" - rearranged material (eg., (21)[22]).

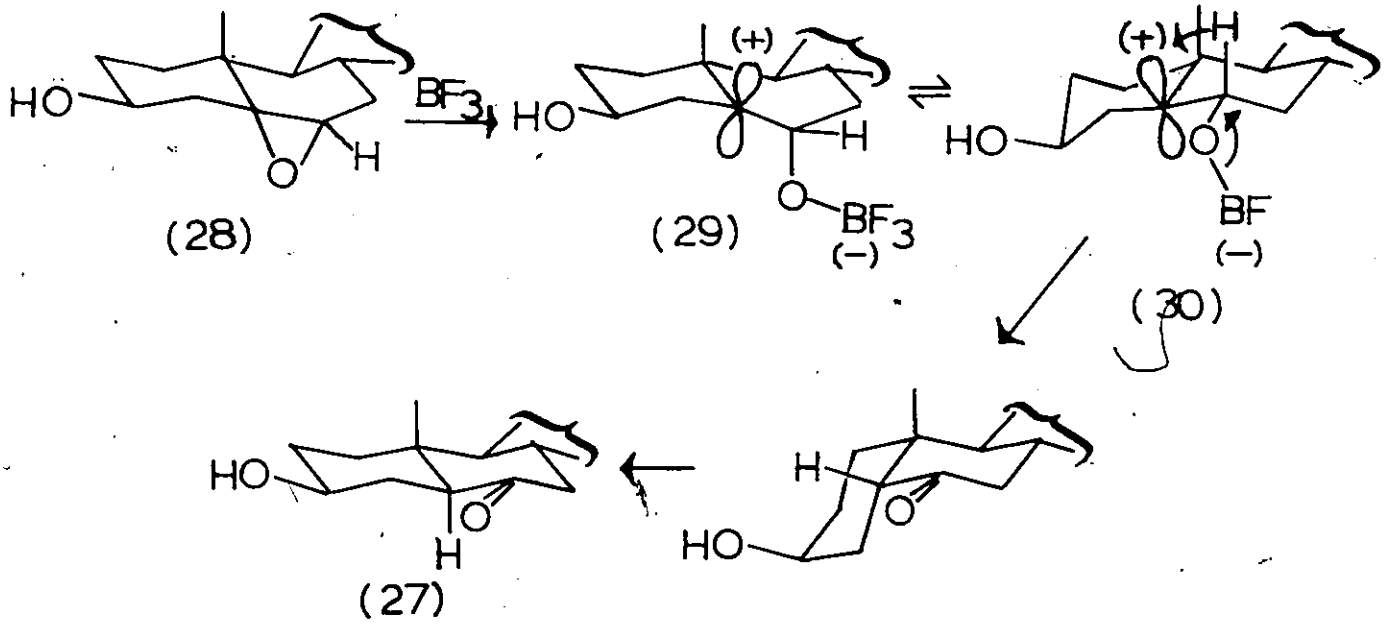


In the case of the 3β-hydroxy-5α,6α-epoxide (22), a mixture of "backbone" rearranged products were obtained[23] which were epimeric at C-6. They were thought to arise via the equilibration of the initially formed carbocations, either (23) or (24), with (25) or (26) respectively. This process would be much like a reversible

Prins reaction and is a further indication of the stepwise nature of the "backbone" rearrangement.



Migration of the groups bonded to C-6 to give B-nor-aldehydes or 6-ketones proceed stereospecifically since the 5β-6β-epoxides give material with a trans A/B ring junction and the 5α,6α-epoxides, material with a cis A/B ring junction. The 5α-ketone (27) which was obtained from the 5α,6α-epoxide (28) was simply an artifact[23] of the isolation procedure. These rearrangements most likely proceed via an open C-5 carbocation since the migrating groups are essentially orthogonal with respect to the epoxide C-O bond that is being broken. Furthermore, the

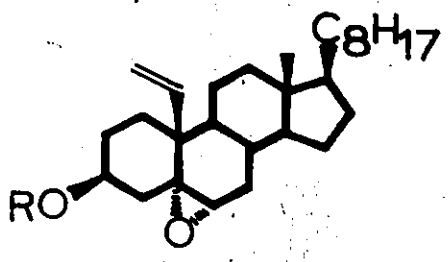


carbocation would appear to possess some degree of conformational mobility[26]. For example, the carbocation (29) which is initially formed from (28) would have the B ring

in a boat form. It would then have to convert to the chair conformer (30) before the 6β-hydrogen is suitably situated for migration.

It can also be seen from TABLE 1 that the presence of substituents at C-3 and C-17, which are inductively electron-withdrawing, bring about a decrease in the amount of rearrangement products obtained and favour fluorohydrin formation. The fluorohydrin arises from the diaxial opening of the epoxide by hydrogen fluoride[27] which is always present even if the boron trifluoride etherate has been repeatedly distilled. The electron-withdrawing substituents appear to make heterolytic cleavage of the C-O bond more difficult[28] and thereby allow nucleophilic attack by fluoride ion to compete more effectively.

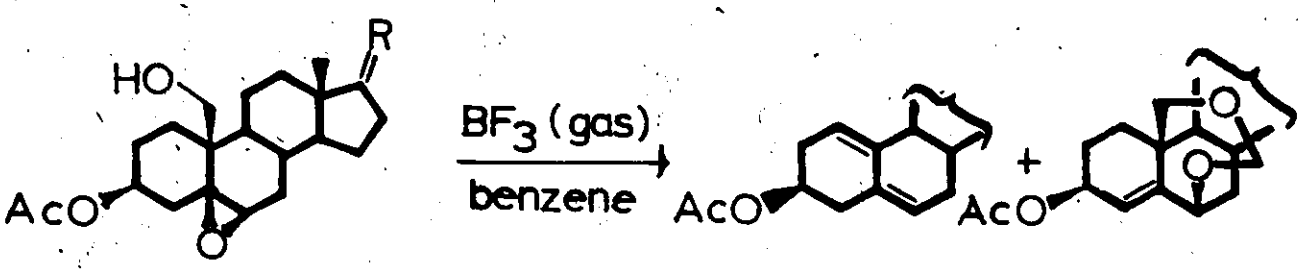
In most instances, the preferred mode of rearrangement has been found to involve the migration of the C-10 methyl group. The effects of changing the nature of the C-10 substituent has been examined but with somewhat inconclusive results. With a C-10 ethenyl group[29], which exerts an inductive electron-withdrawing effect, (31) gave a somewhat greater yield of fluorohydrin than its C-10 methyl counterpart. It was decided to examine the boron trifluoride-catalyzed reaction of the C-10 hydroxymethyl compound (17) to see whether a very different type of rearrangement might be observed (cf.p. 9).



(31)

The preliminary work[30] was conducted by M. Kalapurakal and L. Lompa-Krzymien. They found that the reactions of the 19-hydroxy-5β,6β-epoxides (17) and (32) with boron trifluoride etherate gave complicated mixtures of products. However, with boron trifluoride gas[31] and benzene as solvent, a relatively clean reaction occurred to give two major products, namely the dienes (33) and (34) and the methylenedioxy compounds (35) and (36). The dienes (33) and (34) both had similar spectral properties, those of the cholesterol analogue (34) corresponding with the data reported[32] for the same diene which had been obtained by a different route. The structure of the methylenedioxy compounds (35) and (36) was based upon spectral evidence.

These reactions were repeated and it was found that the yields of the two compounds were dependent on the way in which the boron trifluoride was introduced. The procedure which appeared to work best involved the addition of a solution of benzene that had been saturated with boron trifluoride gas to a solution of the epoxide in benzene.



(17) R=H, C_8H_{17} (33) 47% (35) 9%

(32) R=O (34) 30% (36) 16%

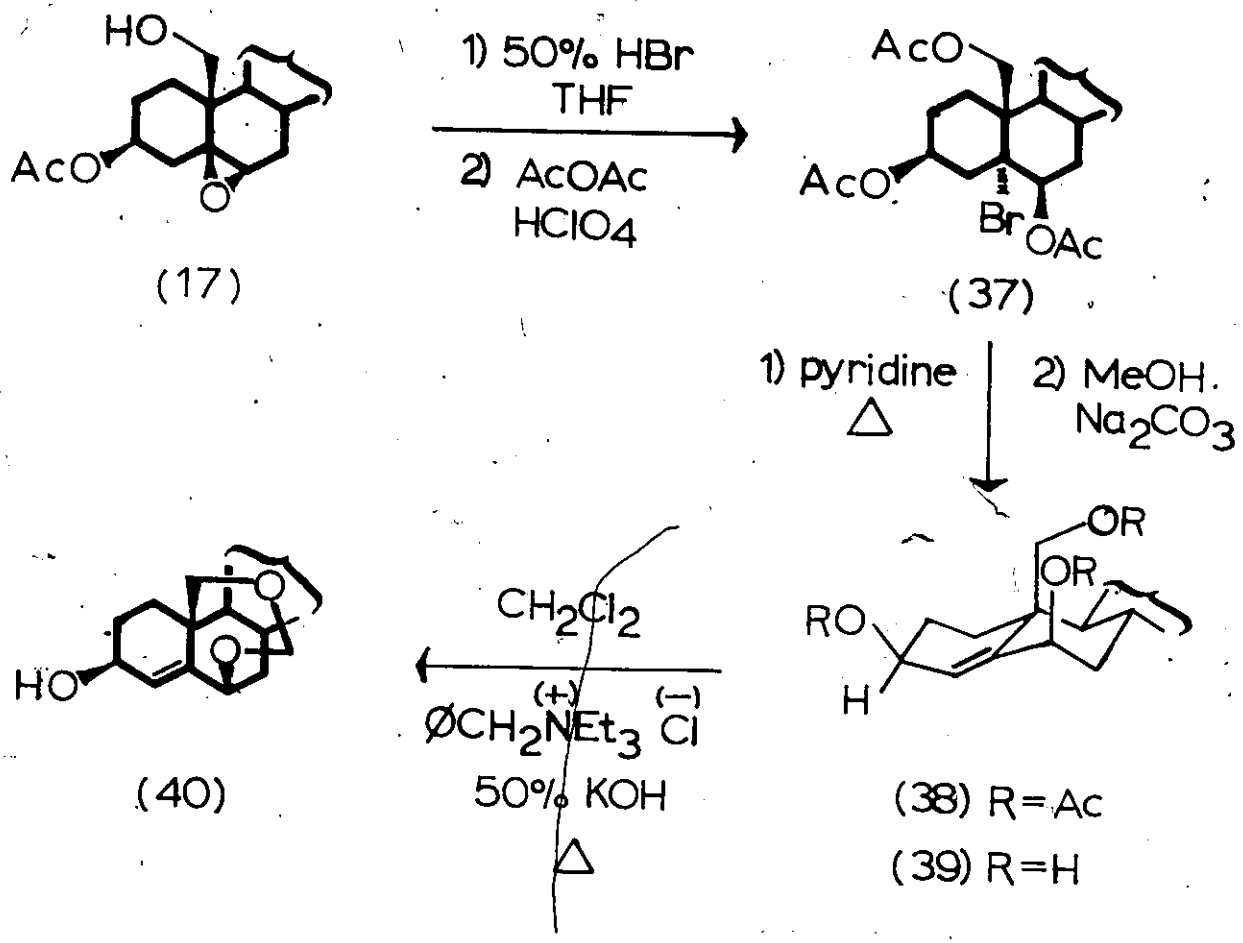
The compounds thus obtained had physical and spectral properties which were similar to those reported in the preliminary work and they also gave satisfactory analyses. The structure of the methylenedioxy compounds, (35) and (36) could be inferred by analysis of their ^1H n.m.r. spectra. For the cholesterol analogue (35), two methylene quartets were observed for the 19-methylene group (δ_A 3.99, δ_B 3.21, J_{AB} 12 Hz) and the methylene ketal (δ_A 4.98, δ_B 4.59, J_{AB} 8 Hz) as well as an apparent triplet (δ 4.43, Japp. 2 Hz) for the equatorial 6α-H, a multiplet (δ 5.25, W/2 ca. 18 Hz) for the pseudoaxial 3α-H, and a broadened singlet (δ 5.71) for the olefinic 4-H.

The structure of (35) was confirmed by the following synthesis (SCHEME 3). Trans diaxial opening of the 19-hydroxy-5β,6β-epoxide (17) with hydrobromic acid followed by acetylation with acetic anhydride-perchloric

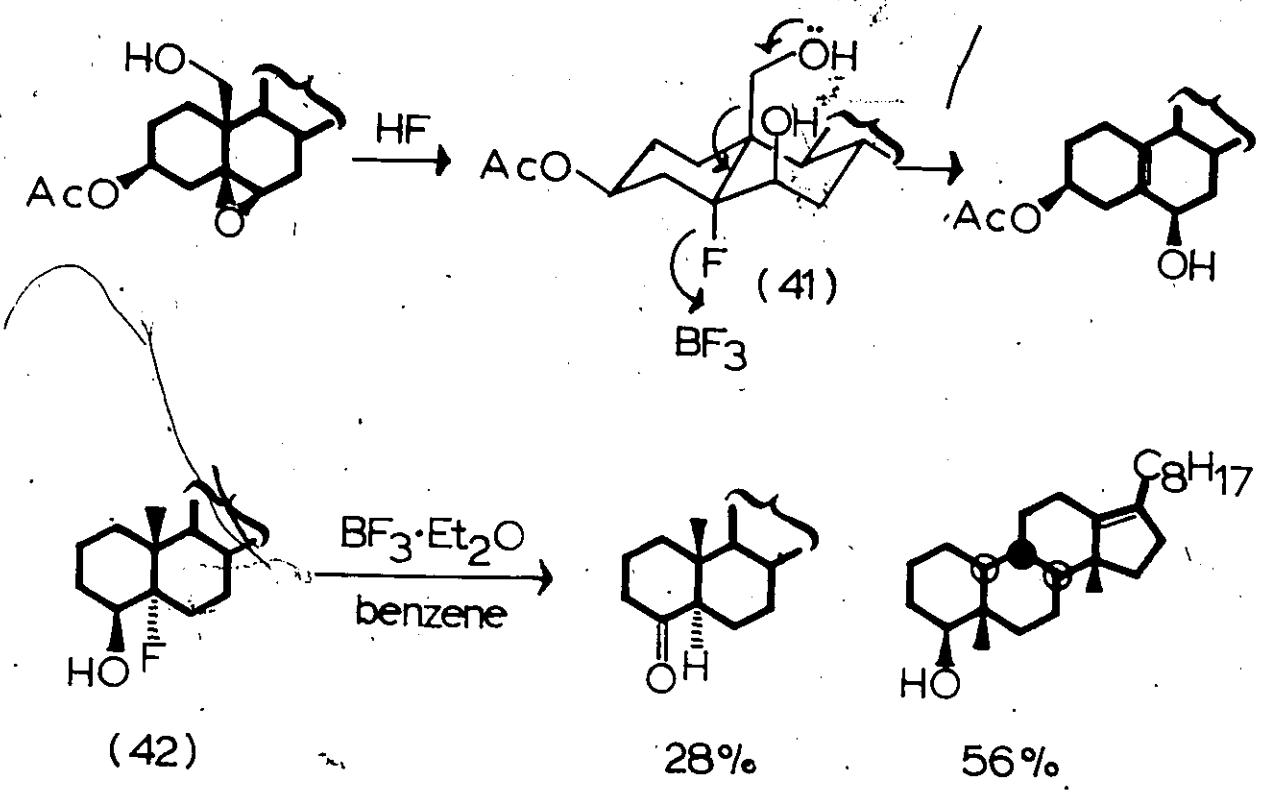
acid gave the triacetoxy-bromide (37). This was dehydrohalogenated by refluxing in pyridine to afford the Δ^4-olefin (38) which was hydrolyzed to afford the triol (39). It was noticed that the triol was not very stable in the presence of acid and, consequently, basic conditions using a phase transfer catalyst[33] were employed to prepare the methylenedioxy derivative (40). This was accomplished by allowing the triol (39) to react with methylene chloride in the presence of aqueous potassium hydroxide and benzyltriethylammonium chloride. The selective formation of the 6β,19-methylenedioxy compound (40) presumably arises via the initial formation of a 19-chloromethyl ether which would be best disposed for attack by the axial 6β-hydroxy group. Acetylation of the crude product afforded the 3β-acetate (35) which was identical with material that had been previously obtained.

The major products derived from the 5β-6β-epoxides (17) and (32) were the dienes (33) and (34) in which the 10β-hydroxymethyl group had been eliminated on epoxide opening. This was viewed as being somewhat unusual since the C-10 substituent is syn with respect to the epoxide and a Grob-type fragmentation[8], which this reaction strongly resembles, shows a strong preference for an antiperiplanar arrangement between the electrofugal and nucleofugal fragments. Accordingly, some consideration was

SCHEME 3

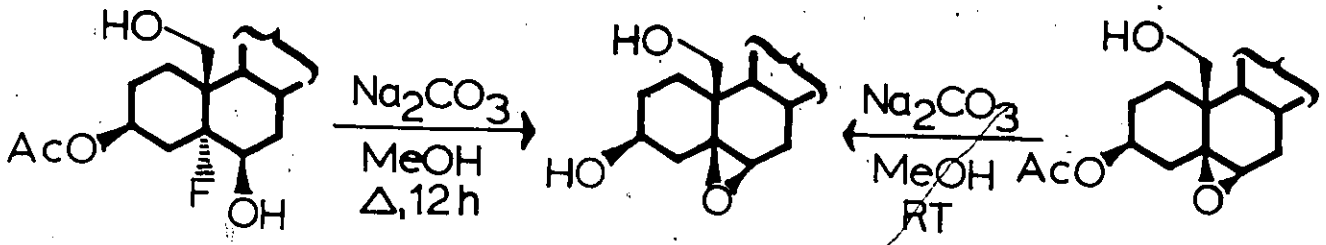


given to the possible intermediacy of the fluorohydrin (41) since it has been shown that fluorohydrins (e.g., (42)) can readily react with boron trifluoride[21] to give products identical with those obtained by the rearrangement of the epoxide.



To see if indeed a fluorohydrin is involved, this derivative (43) was prepared by treating a solution of the epoxide (17) in a mixture of benzene and ether with boron trifluoride etherate. The spectral data for (43) were somewhat ambiguous although a satisfactory elemental analysis was obtained. Its identity was confirmed by converting it to the epoxide (44) with refluxing methanolic sodium carbonate. The latter compound was identical with material prepared by the saponification of the 3β-acetate (17). When the fluorohydrin (43) was treated with boron

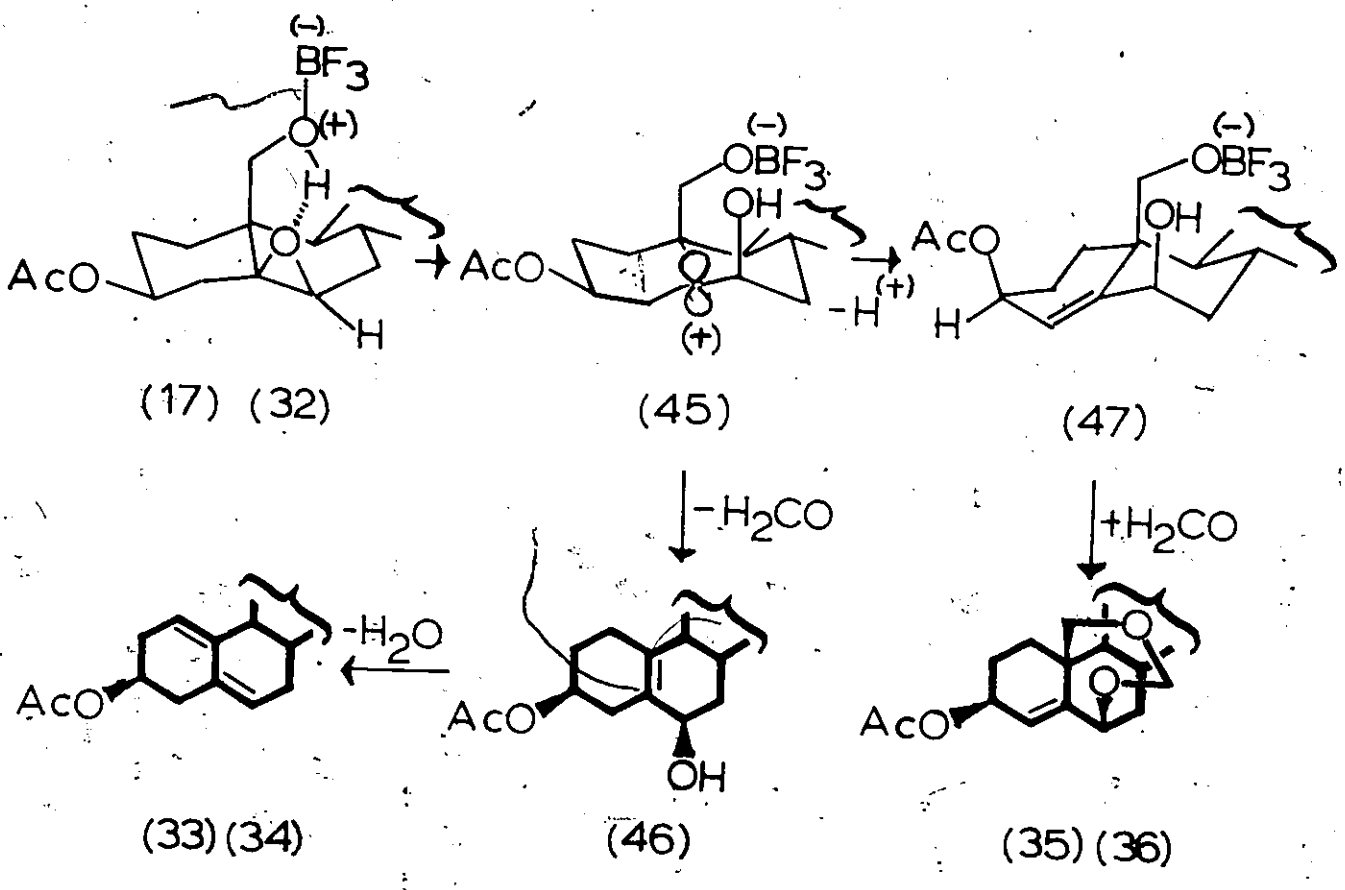
trifluoride gas in benzene, it was recovered unchanged thereby ruling out its possible intermediacy in the reaction of the epoxide (17).



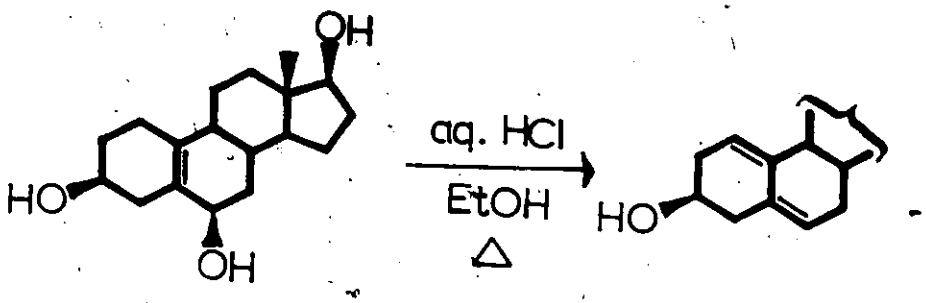
(43) (44) (17)

It would therefore appear that the products obtained from the epoxides (17) and (32) originate from the open C-5 carbocation (45) (SCHEME 4). This could arise by the direct opening of the epoxide by boron trifluoride or through protonation by a boron trifluoride complexed 19-hydroxy group. The latter course seems likely since the existence of a strong hydrogen bond between the 19-hydroxy-group and the 5β,6β-epoxide-oxygen has been demonstrated[34]. Once an open carbocation has formed, the 10β-hydroxymethyl group would be suitably placed such that fragmentation with the loss of formaldehyde could occur. The allylic alcohol (46) thus formed was not observed but would be expected to readily undergo dehydration to the

SCHEME 4



dienes (33) and (34) under the reaction conditions. This latter step has been demonstrated[35] with the $\Delta^{5(10)}$-6β-hydroxy steroid (48) which gave the 1(10),5-diene (49) upon treatment with acid. It was found[30] (t.l.c.) that the allylic alcohol (46) similarly afforded the diene (33) upon exposure to boron trifluoride.



(48) (49)

The methylenedioxy compounds (35) and (36) presumably arise through the loss of the 4β-proton from (45) (SCHEME 4). The diol (47) thus formed reacts with formaldehyde present to give (35) and (36).

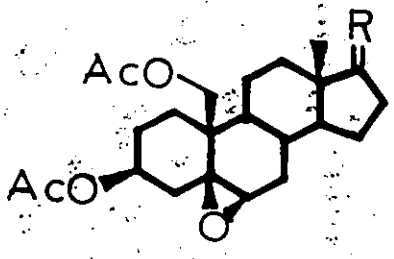
2. Reactions with 3β,19-Diacetoxy-5,6β-epoxy-5β-cholestane (51) and 3β,19-Diacetoxy-5,6β-epoxy-5β-androstan-17-one(50)

Since fragmentation was the major mode of reaction for the 19-hydroxy compounds (17) and (32) the boron trifluoride-catalyzed reactions of their 19-acetoxy analogues were examined next. It was thought that the presence of the 19-acetoxy substituent would prevent fragmentation and that rearrangement to the spiro compound (18) might occur.

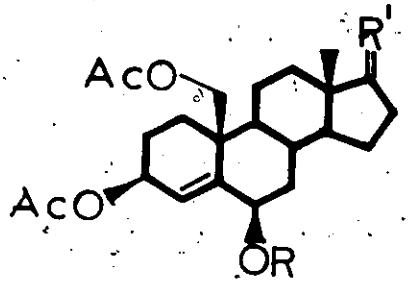
The 3β,19-diacetoxy-5,6β-epoxy-5β-androstan-17-one (50), prepared by acetylating the corresponding 19-alcohol (32), was examined first. When (50) was treated with a

saturated solution of boron trifluoride in benzene, a slow reaction ensued to give, aside from recovered starting material (19%), two products. The first compound (43%) was identified as the fluorohydrin (52) on the basis of spectral data, in particular, the mass spectrum (m/e 424, M^+) which indicated that the molecule had undergone incorporation of hydrogen fluoride. The other compound, which appeared to be the 4-olefin (55), was obtained in an impure form by column chromatography. Since the contaminating material could not be removed by crystallization, the mixture was acetylated and chromatographed to obtain pure material. This triacetate (56) had a similar ^1H n.m.r. spectrum to that of the cholesterol analogue (38) and its structure was verified by synthesizing it from (50) using the same approach ((50)→(53)→(56)) that was employed in the preparation of (38).

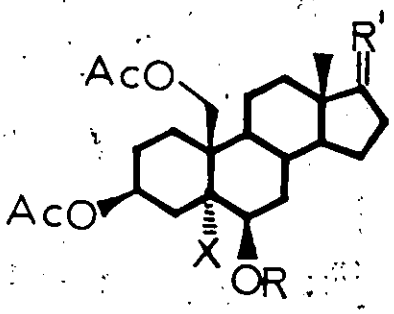
The reaction of the 3β,19-diacetoxy-5β,6β-epoxide (50) was repeated, only this time a greater quantity of boron trifluoride was used. The gas was bubbled directly into a solution of the epoxide in benzene and a much more rapid reaction occurred. This gave the fluorohydrin (52) (26%), a mixture of olefinic material which was left unidentified (although the ^1H n.m.r. did indicate the presence of the 4-olefin (55)), and a new compound (16%). The ^1H n.m.r. spectrum of the latter compound was consistent with the



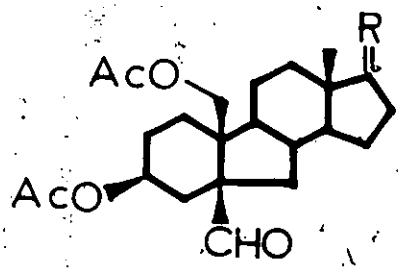
(50) R = O
(51) R = H, C_8H_{17}



(55) R = H, R' = O
(56) R = Ac, R' = O
(38) R = Ac, R' = H, C_8H_{17}



(52) X = F, R = H, R' = O
(53) X = Br, R = Ac, R' = O
(54) X = F, R = H, R' = C_8H_{17}



(57) R = O
(58) R = C_8H_{17}

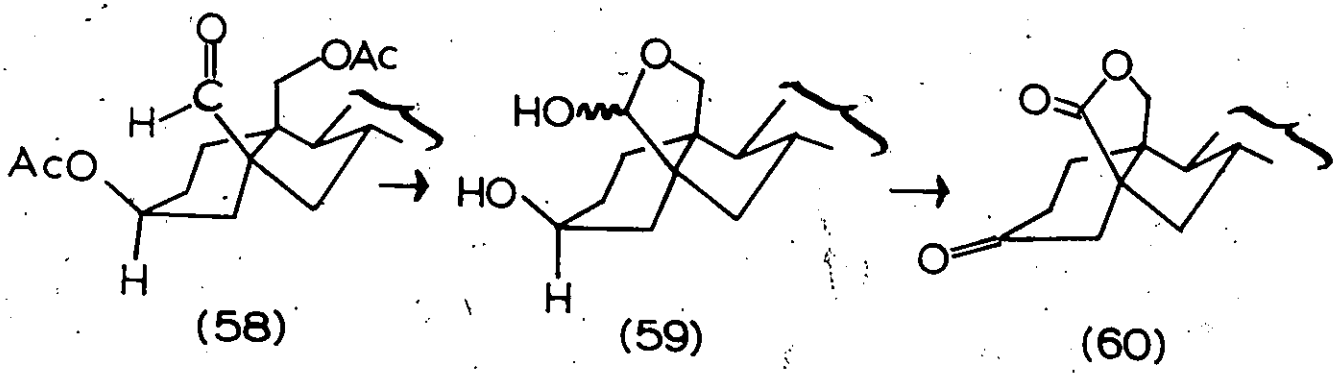
5β-formyl-B-nor structure (57) and further proof for this assignment will be presented subsequently.

Similarly, when boron trifluoride gas was bubbled into a solution of the 5β,6β-epoxy-cholestane (51), the fluorohydrin (54) (36%), the aldehyde (58) (21%) and an unidentified mixture of olefinic material were obtained.

The structure of the fluorohydrin (54) was confirmed by its conversion (refluxing methanolic sodium carbonate) to the 5β,6β-epoxide (44).

With both of the aldehydes, (57) and (58), there was some ambiguity regarding the nature of the A/B ring junction since the ^{1}H n.m.r. spectra of these compounds showed a multiplet with a half band width of ca. 15 Hz for the 3α-hydrogen. This value is somewhat larger than would normally be expected for an equatorial hydrogen although it may indicate[36] that there is some distortion of the A-ring. The following chemical transformations of (58) (SCHEME 5) were carried out to obtain an unambiguous assignment. The aldehyde (58) was hydrolyzed with methanolic sodium carbonate to give a compound which existed in the form of a lactol (59). The ^{1}H n.m.r. spectrum showed a singlet for the lactol methine proton (δ 4.96), a quartet for the 19-methylene protons (δ_A 3.80, δ_B 3.63, J_{AB} 10 Hz) and a multiplet for the 3α-H (δ_A 3.96, W/2 ca. 16 Hz). Oxidation of the lactol (59) gave the 3-keto-lactone (60) whose i.r. spectrum showed absorptions at 1769 cm^{-1} for a γ lactone and 1725 cm^{-1} for the 3-ketone, and whose ^{1}H n.m.r. spectrum showed an AB quartet (δ_A 4.29, δ_B 4.01, J_{AB} 10 Hz) for the 19-methylene protons. This would establish the cis nature of the A/B ring junction in (58) and also, by analogy, the androstan-17-one (57).

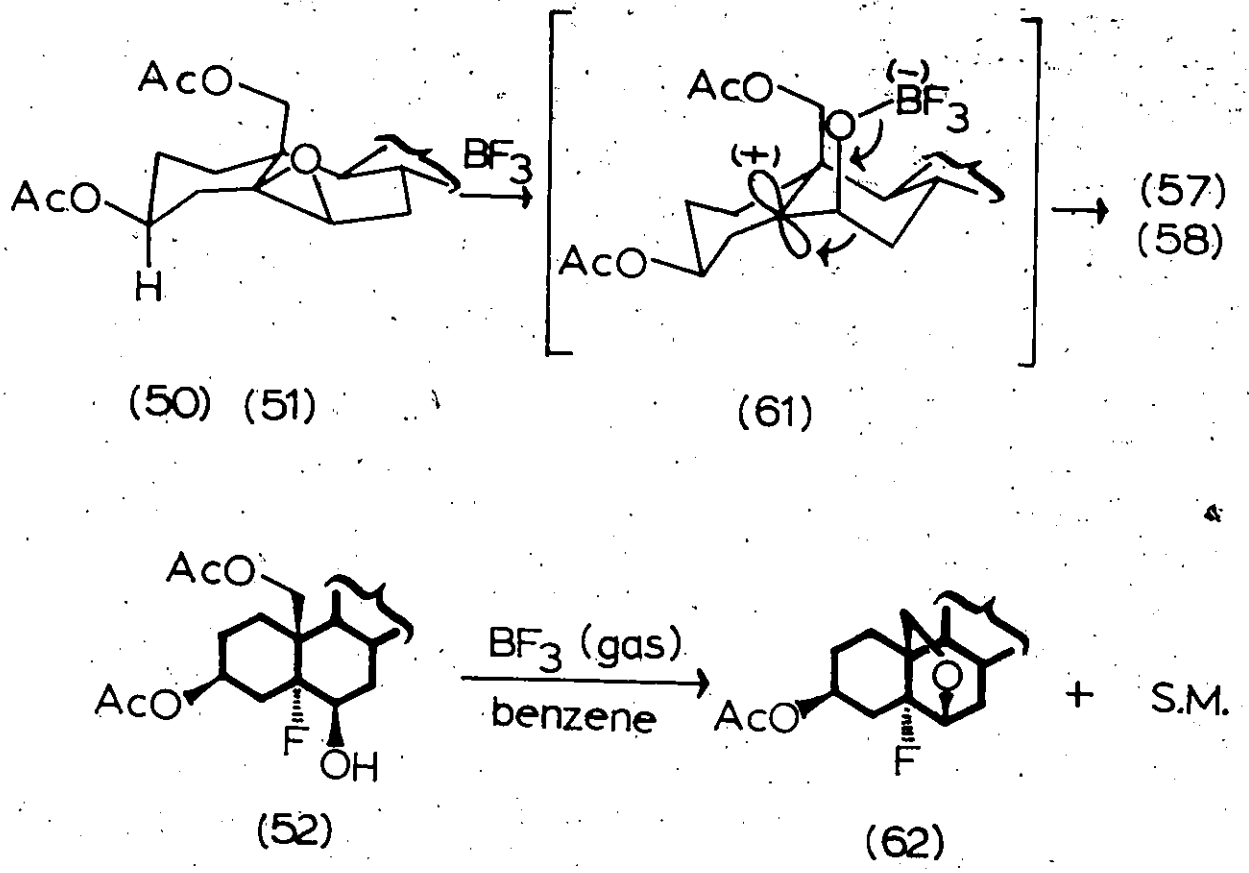
SCHEME 5



(58) (59) (60)

For the 19-acetoxy-5β,6β-epoxides, (50) and (51), it was found that the 19-acetate group prevented fragmentation involving the C-10 substituent. The inductive electron-withdrawing effect of this group was found to favour fluorohydrin formation at the expense of epoxide rearrangement. The only products of the latter process that were observed were the aldehydes (57) and (58). These would arise *via* migration of the C(6)-C(7) bond along the α-face of the initially formed C-5 carbocation (61) (SCHEME 6). The possibility that these A-*nor*-aldehydes were derived from a fluorohydrin precursor was ruled out by the observation that, when the fluorohydrin (52) was treated with boron trifluoride, only the 6β,19-oxide (62) (25%) and starting material (58%) were obtained. Evidently, the 3β- and 19-acetate groups sufficiently suppress ionization such that only the boron trifluoride-catalyzed displacement of the 19-acetate group occurs.

SCHEME 6



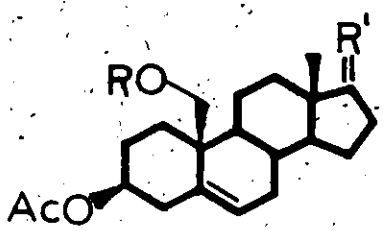
The relative yields and nature of the products which were obtained from the 3β,19-diacetoxy-5,6β-epoxy-5β-androstan-17-one (50) with the two different methods of introducing the boron trifluoride appear to reflect the fact that epoxide rearrangements can follow different paths with different reagent systems[37]. In this case, the variable appears to be the concentration of Lewis acid present. When a saturated solution of boron trifluoride in

benzene is added to a solution of the epoxide, less of the reagent is present. Under these conditions, a good portion of the boron trifluoride could be complexed with the other functional groups present. Accordingly, its overall reactivity is diminished as shown by the amount of fluorohydrin and unreacted starting material that were obtained. With the direct introduction of boron trifluoride gas, an excess of the reagent is present and this allows for the direct interaction of the epoxide with uncomplexed Lewis acid. This would appear to account for the appearance of the A-nor-aldehyde (57) under these conditions but not the former.

3. Preparation of 3β-Acetoxy-19-hydroxy-5,6α-epoxy-5α-cholestane (68) and 3β-Acetoxy-19-hydroxy-5,6α-epoxy-5α-androstan-17-one (70)

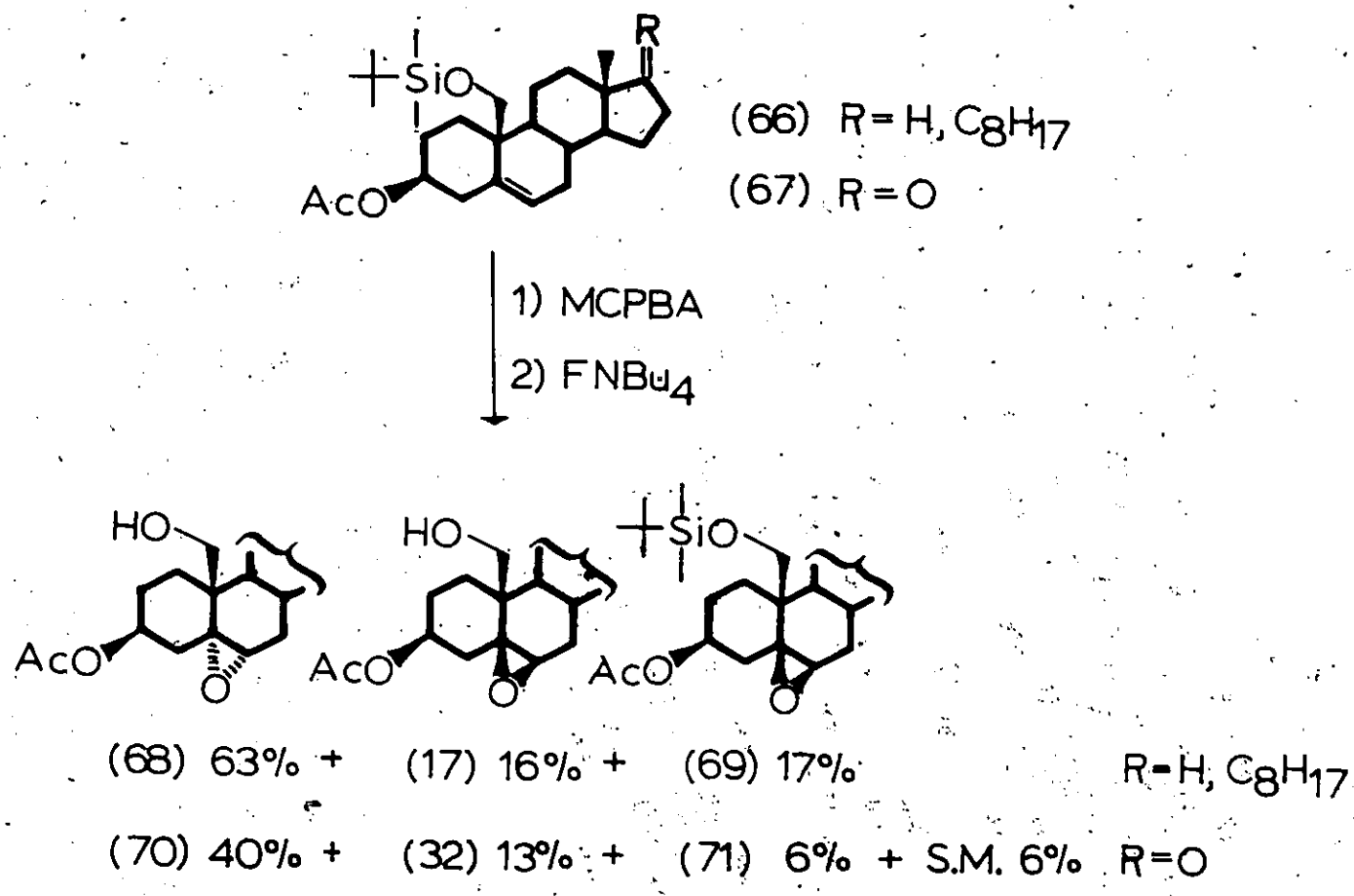
It was decided to examine the reactions of the corresponding 5α,6α-epoxides to see if the epoxide configuration was a factor. However, 19-hydroxy-5α,6α-epoxides are not that readily available owing to the directive influence exerted by the 19-hydroxy group[38] upon the course of the peracid epoxidation of the Δ^5-bond. At best, with the less stereoselective monoperphthalic acid, a 14% yield[18] of the 5α,6α-epoxide (68) was obtained from (63). When the 19-hydroxy group had been converted

to an acetate, (64) gave[18] a ca. 3:2 mixture of 5α,6α- and 5β,6β-epoxides with m-chloroperbenzoic acid. However, subsequent attempts[30] at selectively hydrolyzing the 19-acetate group were unsuccessful.



(63) R=H, R'=C_8H_{17}
(64) R=Ac, R'=C_8H_{17}
(65) R=H, R'=O

The epoxidation of the 19-t-butyldimethylsilyl ether (66) was examined since the subsequent selective removal[39] of the silyl group was a possibility. Treatment of (66) with m-chloroperbenzoic acid followed by desilylation with tetrabutylammonium fluoride afforded a ca. 2:1 mixture of 5α,6α- and 5β,6β-epoxides. The androst-5-en-17-one derivative (67) was found to behave similarly. The only unusual feature encountered was the much slower rate at which the 5β,6β-epoxides (69) and (71) underwent desilylation and this allowed for the isolation of some of this material. It was also noted that, since the reaction mixture becomes alkaline as the desilylation proceeds, transacetylation between the 3β-acetate group and the 19-hydroxy group does not appear to occur in this system.



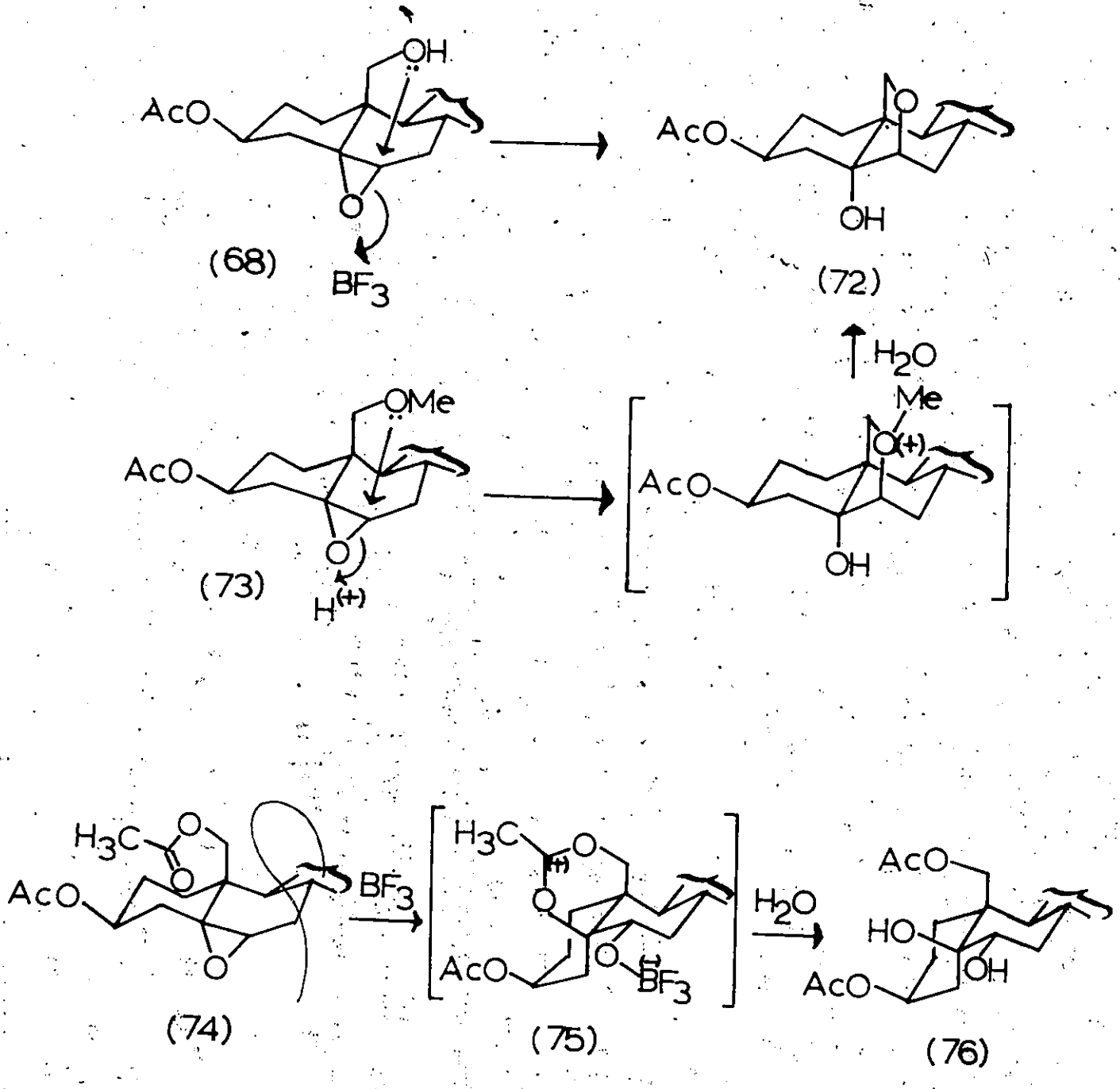
4. Reactions with 3β-Acetoxy-19-hydroxy-5,6α-epoxy-5α-cholestane (68) and 3β,19-Diacetoxy-5,6α-epoxy-5α-cholestane (74)

The reactions of the 19-hydroxy-5α,6α-epoxide (68) and its 19-acetate derivative (74) with boron trifluoride proved to be somewhat disappointing since they were both found to give products in which the 19-function participated in the opening[40] of the epoxide. The 19-hydroxy

group in (68) effected diaxial opening of the epoxide to give the 6β,19-oxide (72) in a 64% yield. This is much like the reaction[41] of the 19-methyl ether (73) with protic acids. The 19-acetate (74) cleanly gave the diequatorial alcohol (76) upon treatment with boron trifluoride. The intermediate acetoxonium ion (75) has been previously postulated[42] to account for similar results which were obtained from the protic acid catalyzed reactions of 19-acetoxy-5α,6α-epoxides.

In summary, aside from those reactions involving neighbouring group participation or fragmentation, the only epoxide rearrangement that was observed was the contraction of the B-ring in the 19-acetoxy-5β,6β-epoxides (50) and (51). The other possible modes of rearrangement, especially that leading to 1(10→5)-abeo compounds, were not seen. In those instances where the boron trifluoride-catalyzed reactions were conducted with both the cholestane and androstan-17-one epoxides, it is difficult to assign the observed variation in yields to the inductive effect of the C-17 substituent since the concentration of the boron trifluoride is undoubtedly a factor and was not rigorously controlled.

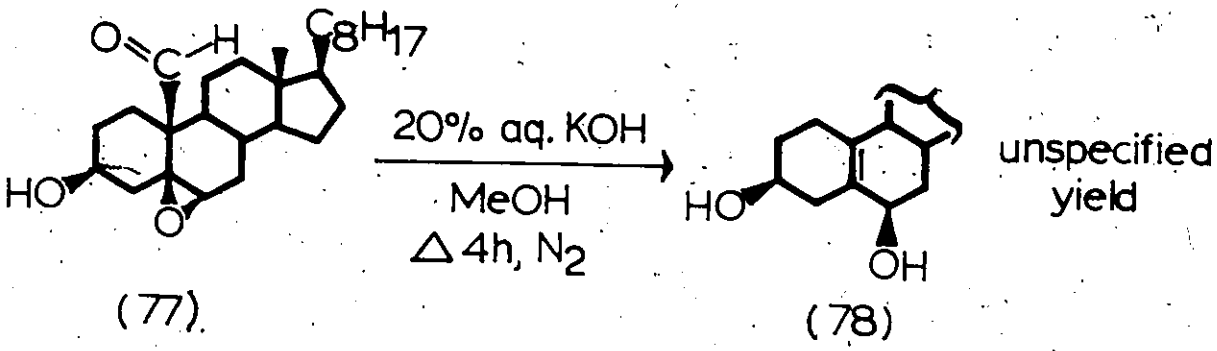
The originally described rearrangement of the 19-hydroxy-5β,6β-epoxide (17) to the spiro compound (18) was not reexamined since the fragmentative elimination of the 10-substituent was in itself an interesting reaction and suggested some further studies.


OH
AcO
O
BF3
(68)
AcO
O
OH
(72)
H2O
OMe
AcO
O
H(+)
(73)
Me
O(+)
AcO
OH
H3C
O
O
AcO
O
BF3
(74)
H3C
O(+)
O
AcO
O
BF3
(75)
H2O
AcO
HO
OH
AcO
(76)

PART II

Base-catalyzed Fragmentation of 3β-Hydroxy-5,6β-epoxy-5β-cholestan-19-al (77)

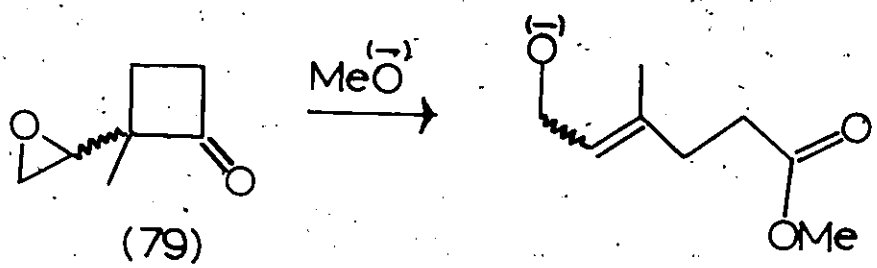
During the course of work directed at the introduction of functional groups at C-19, Barton and Akhtar[43] noted that the 19-aldehyde (77) underwent deformylation in the presence of base to give the allylic alcohol (78). This



(77) (78)

reaction is somewhat unusual since a deformylation proceeding *via* a carbanion intermediate seems unlikely in light of other base-catalyzed deformylations[44] which require electron-withdrawing groups α to the formyl group; e.g., a *retro*-Claisen reaction or the deformylation of chloral hydrate. As well, a carbocation mechanism seems unlikely since an effective Lewis acid is not present. The only other examples of base-catalyzed fragmentations of β,γ-epoxy carbonyl compounds that could

be found in the literature were those reported by Trost[45] for the cyclobutanone epoxides (79). The reactions of the latter compounds possess some interesting features which can be best understood by considering the work of Stirling.

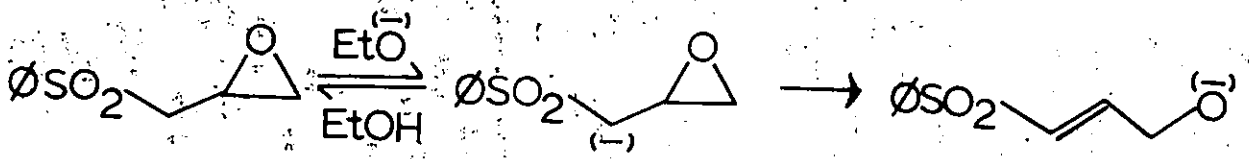


(79)

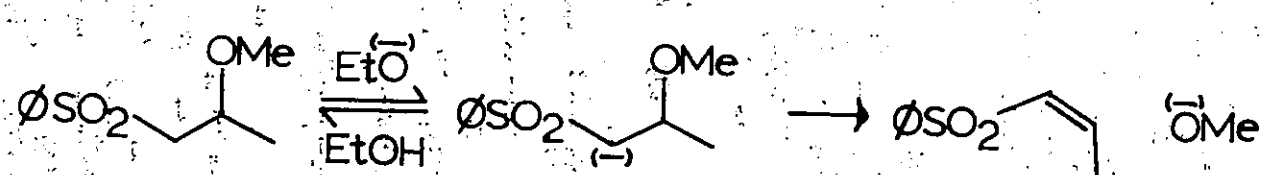
(80) (81)

Stirling[46] has classified reactions of the type (80)→(81) as nucleophilic eliminative ring fissions. For three- and four-membered rings, there is a large amount of strain energy present. If this strain energy is released in the transition state of the elimination, the activation energy will be significantly lower. As a result, large rate enhancements are found relative to what is observed in comparable acyclic systems.

For a nucleophilic eliminative ring fission involving an epoxide group, there would be approximately 27 kcal. of strain energy available. A convincing demonstration[46] of the resulting rate enhancement was shown by comparing the reaction of the sulfone epoxide (82) with that of the methyl ether (83). The epoxide (82) undergoes elimination at a rate 2×10^6 faster than that of the ether (83). For the epoxide, the rate determining step is proton abstraction which would indicate that the elimination is either concerted with deprotonation or occurs readily thereafter. In the case of the methyl ether (83), the rate determining step involves cleavage of the C-O bond in the conjugate base (84). The more rapid cleavage of the epoxide C-O bond was attributed to the release of strain energy in the elimination step.



(82)

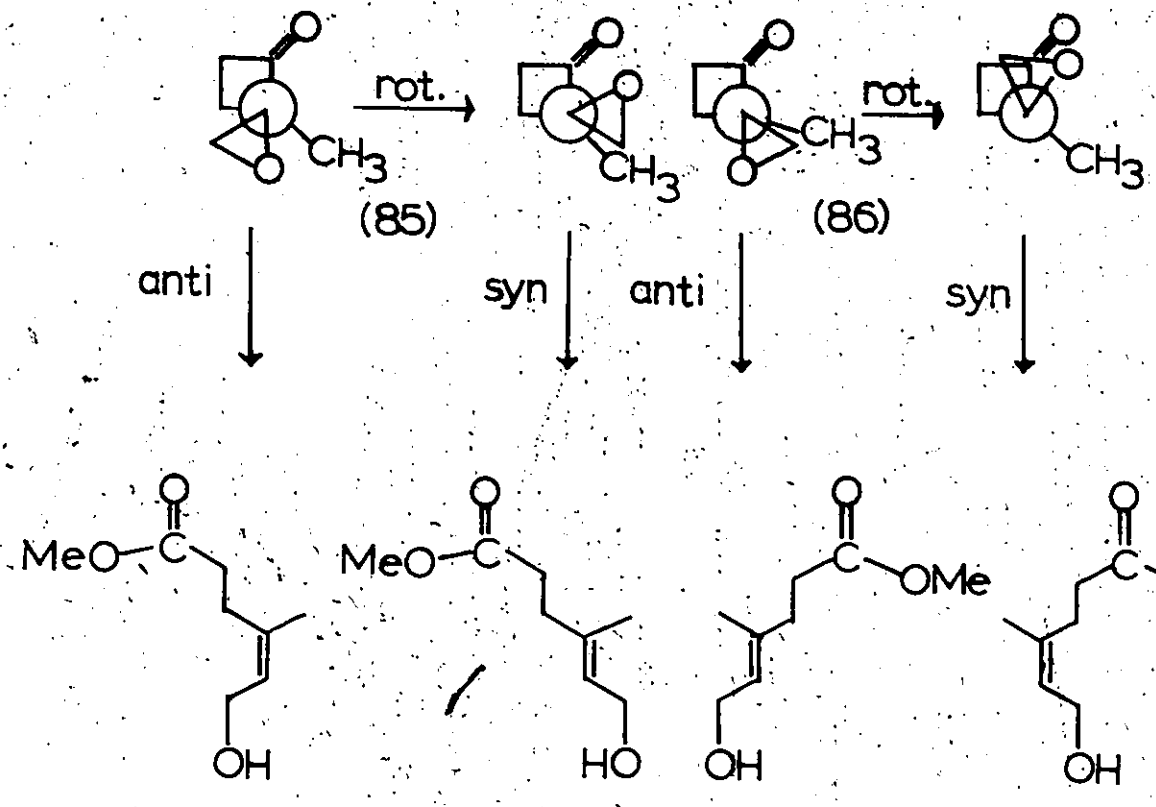


(83) (84)

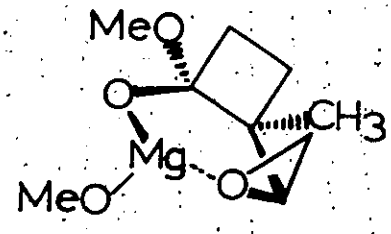
In the case of Trost's epoxycyclobutanones[45] (79) there is a total of 55 kcal. of strain energy present in both the epoxide and the cyclobutanone ring. This can significantly lower the activation energy of the base-catalyzed fragmentation reaction if a concerted mechanism is followed. In view of the ease with which the reaction occurred and the absence of side products, this was indeed thought to be the case.

The stereochemistry of the fragmentation reaction of the epoxycyclobutanones (79) was also interesting. With sodium methoxide, the diastereomeric epoxides (85) and (86) gave exclusively olefins that resulted from anti fragmentation. However, when the nature of the solvent and the base were changed to favour chelation (e.g., as in (87)), products arising from both syn and anti fragmentation were observed. The loss of stereospecificity was not thought to result from competition with a carbonium ion mechanism since epoxide solvolysis products were not observed. Instead, it was felt that both concerted anti and syn fragmentations were involved; the latter proceeding via a chelated intermediate.

For the epoxycyclobutanones (79), fragmentation occurs readily because cleavage of the electrofugal and nucleofugal fragments is assisted by the strain energy that is present in the respective rings. However, for the



NaOMe / MeOH	100%			100%		
$Mg(OMe)_2$ / MeOH	3	:	1	3	:	1
$Mg(OMe)_2$ / THF	1	:	1	1	:	1



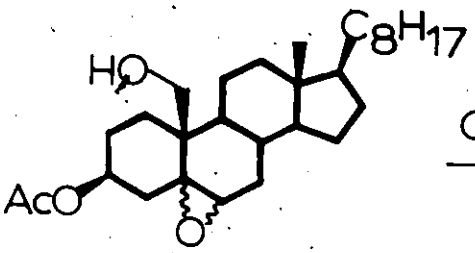
(87)

5β,6β-epoxy-aldehyde (77) there is no apparent activation for the cleavage of the electrofugal fragment. Therefore, in order to get a better idea of the factors that may be involved, the reaction of (77) was reexamined and compared with that of the isomeric 5α,6α-epoxy-aldehyde (89).

1. Preparation of 3β-Hydroxy-5,6β-epoxy-5β-cholestan-19-al (77) and 3β-Hydroxy-5,6α-epoxy-5α-cholestan-19-al (89)

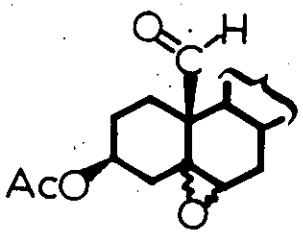
The 19 alcohols (17) and (68) were oxidized (SCHEME 7) to the 19-aldehydes (87) and (88) which were then carefully hydrolyzed to the 3β-alcohols (77) and (89). At this point, difficulty was encountered in obtaining physical constants for the known[43] 5β,6β-epoxide (77) which were consistent with those reported. The material, which was obtained after column chromatography and crystallization, invariably melted over a considerable range and exhibited a change in specific rotation with respect to time. Similarly, the ^{1}H n.m.r. spectrum (FIGURE 2) was anomalous in view of the functionality present and also changed with respect to time. These results were considered to indicate the occurrence of a slow equilibrium between the hydroxy aldehyde (77) and the hemiacetal (90). It would appear that the material obtained by crystallization from methanol existed predominantly in the form of the hydroxy aldehyde (77). The ^{1}H n.m.r. spectrum of this compound would be expected (FIGURE 1) to consist of: a multiplet (δ3.1) for the 6α-H, a broad multiplet (δ3.7) for the axial 3α-H and a singlet (δ9.73) for the aldehyde proton.

SCHEME 7



(17) 5β,6β
(68) 5α,6α

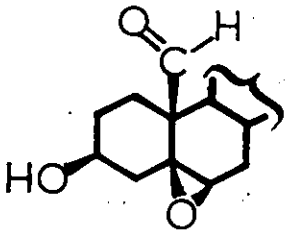
$CrO_3 \cdot pyr \cdot HCl$
NaOAc
CH_2Cl_2



(87) 5β,6β
(88) 5α,6α

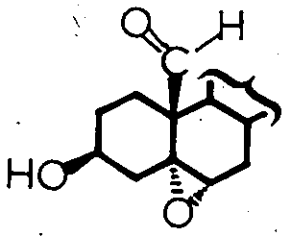
ca. 1.5 equiv. aq. NaOH

MeOH
N_2, R.T.



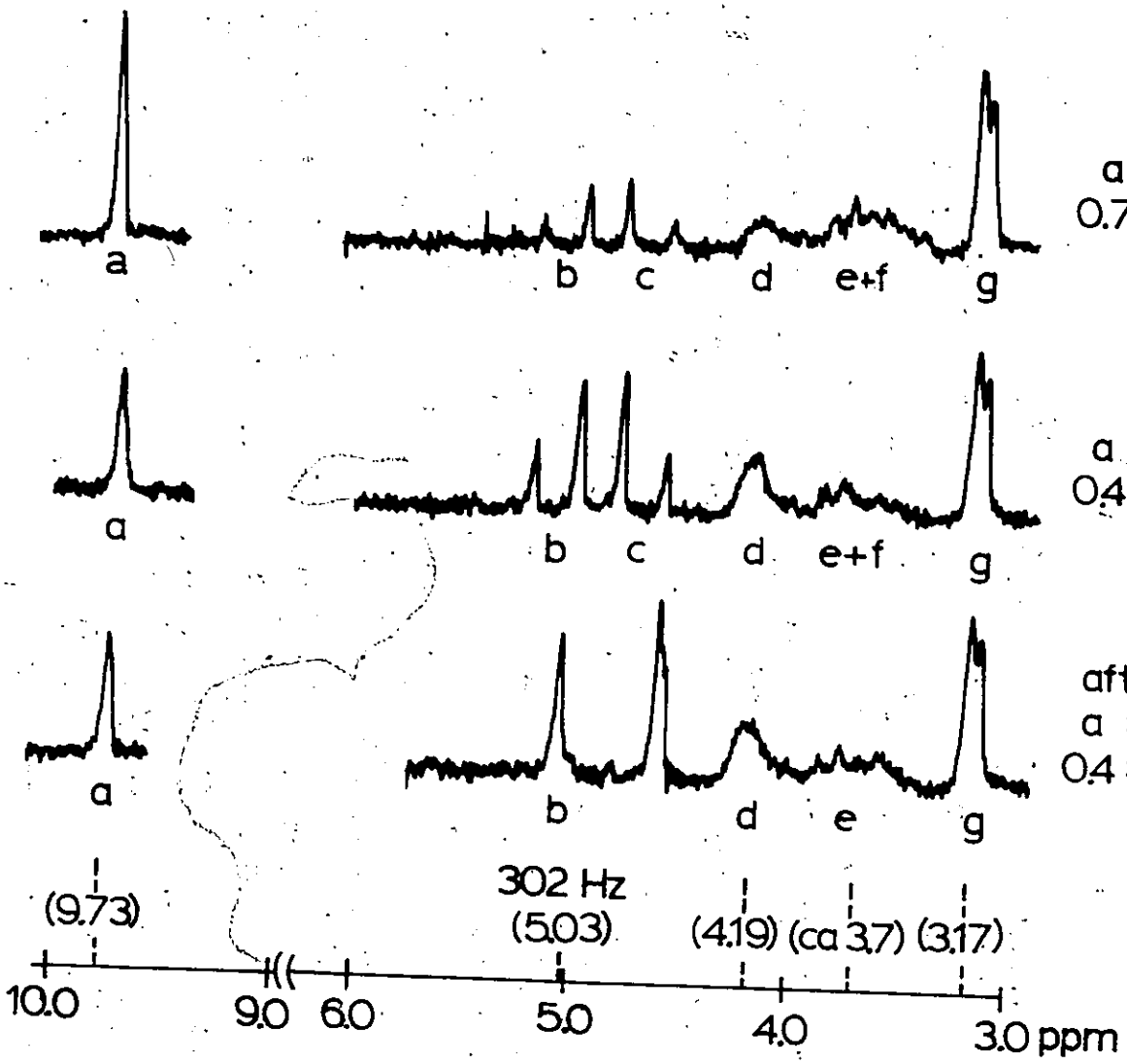
(77)
m.p. 119-132°
$[\alpha]_D$ (initial) −39°
$[\alpha]_D$ (after 24h) −18°

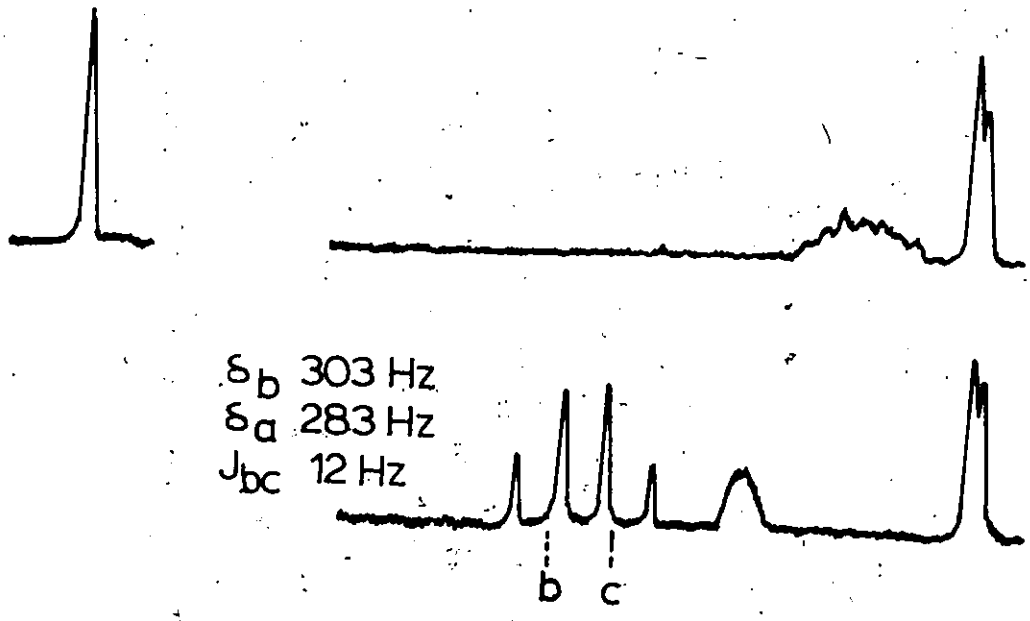
lit. (ref. 43) m.p. 138-140°
$[\alpha]_D$ −16°

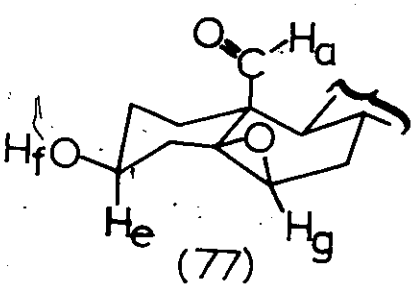


(89)
m.p. 125-137°
$[\alpha]_D$ (initial) −54°
$[\alpha]_D$ (after 24h) −46°

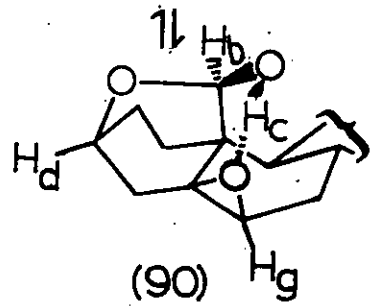
FIGURE 1. 60 Mg Hz ^{1}H N.M.R. Spectrum of 3β-Hydroxy-5,6β-epoxy-5β-cholestan-19-al (77)





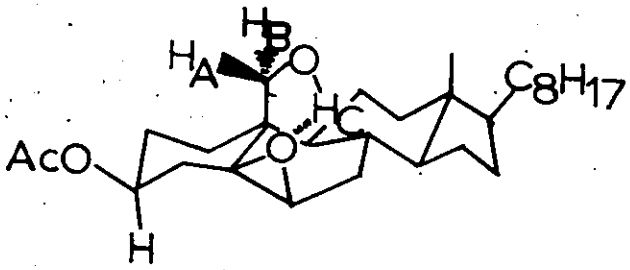


(77)



(90)

Upon being dissolved in deuterochloroform, an equilibrium is slowly established (ca. 1:1, (77):(90) after 20h) with the hemiacetal (90). The ^1H n.m.r. spectrum of the hemiacetal (90) would be expected (FIGURE 1) to consist of a multiplet (δ3.17) for the 6α-H a multiplet (δ4.19) for the pseudo-equatorial 3α-H and an AB quartet (δ_A 5.05 δ_B 4.72, J_{AB} 12 Hz) for the spin system comprised of the 19-H and the hydroxy proton. The addition of deuterium oxide caused the AB quartet to collapse to a singlet (δ5.03) for the non-exchangeable 19-H. The appearance of this AB quartet indicates the presence of a strong hydrogen bond to the epoxide oxygen similar to that observed[34] in the case of the 19-hydroxy-5β,6β-epoxide (17). Furthermore, since the magnitude of the vicinal



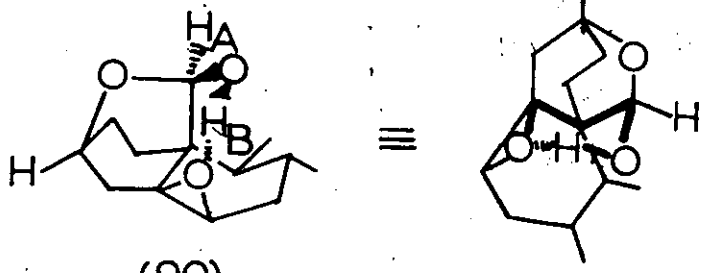
(17)

ABC Spin System ($CDCl_3$)

J_{AB} = 11.5 Hz

J_{AC} = 0.1 Hz, ø = 80°

J_{BC} = 10.5 Hz, ø = 160°



(90)

AB Spin System ($CDCl_3$)

J_{AB} = 12 Hz, ø ≃ 180°

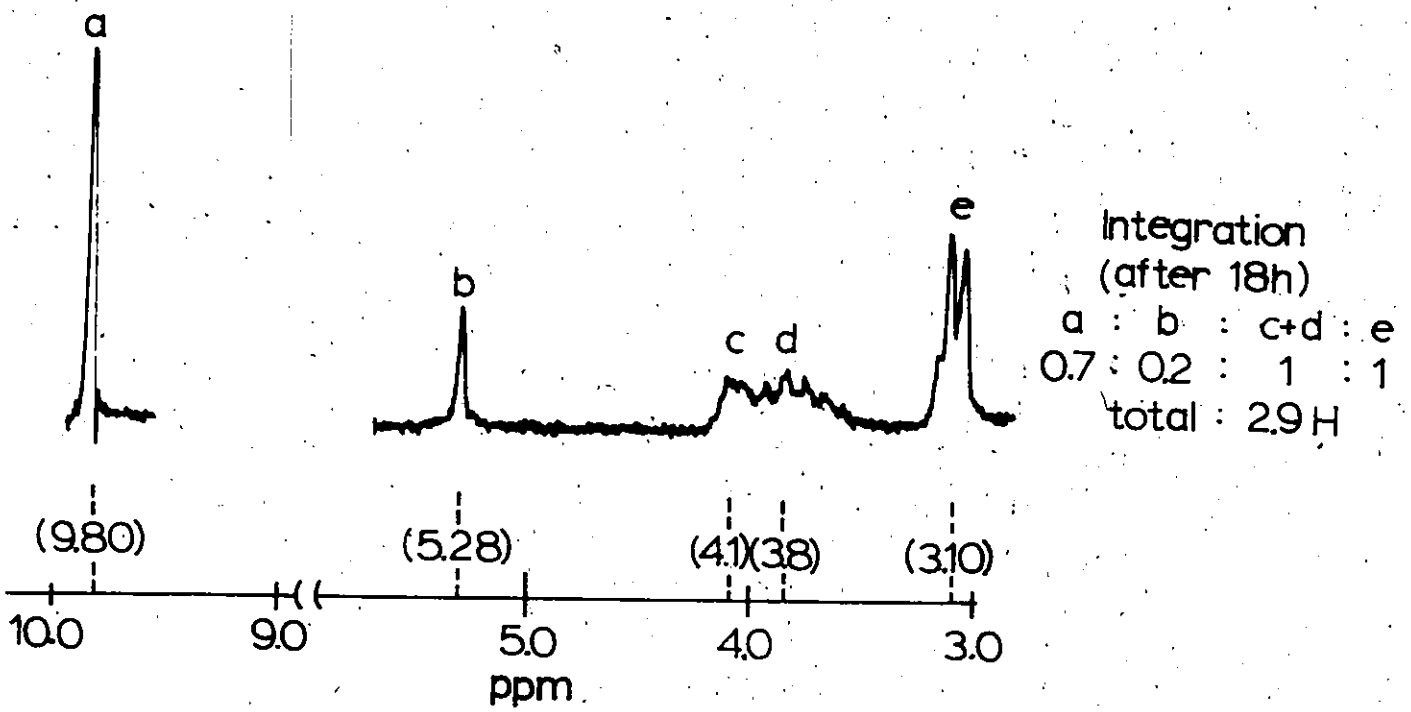
H-C-O-H coupling constant is related in a "Karplus" fashion with the dihedral angle, the observed 12 Hz coupling constant would indicate a dihedral angle of ca. 180°. This information allows for a rather interesting observation about the conformation of the hemiacetal (90); namely, that the six-membered ring, formed in part by the hydrogen bond, closely approximates the chair conformation of cyclohexane. The possible significance of this feature in the reactions of this compound will be discussed subsequently.

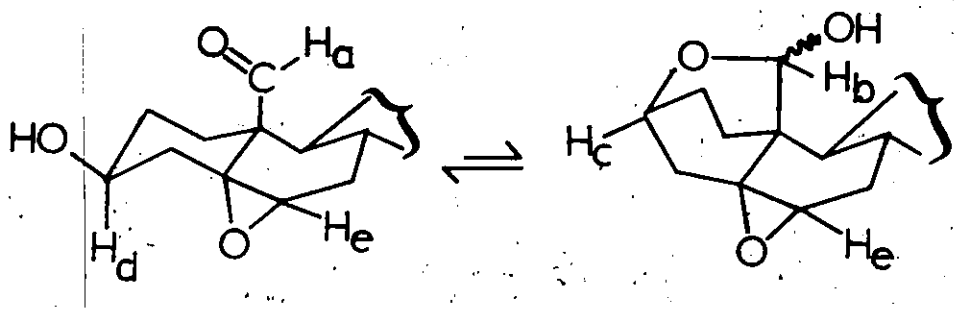
Since good analytical results were obtained for (77), as well as a reasonable explanation for the observed anomalies, no further attempt was made at obtaining material which had physical constants in agreement with those reported.

The isomeric 3β-hydroxy-5α,6α-epoxide (89) exhibited somewhat similar properties, namely a wide melting range and a specific rotation and ^1H n.m.r. spectrum which changed with respect to time. The material crystallized from methanol again consisted predominantly of the hydroxy aldehyde (89) but in solution (deuterochloroform) slowly changed until an equilibrium (ca. 4:1, (89):(91), 18h) was established (FIGURE 2). In this case, the hydroxy proton was no longer observed in the downfield region of the ^1H n.m.r. spectrum. The mass spectrum (m/e 416, M^+) was in

agreement with this structure; however, the analytical results indicated that it had been obtained as a hydrate.

FIGURE 2. 60 Mg Hz ^{1}H N.M.R. Spectrum of 3β-Hydroxy-5,6α-epoxy-5α-cholestan-19-al (89)





(89) (91)

2. Reactions of 5,6-Epoxy-19-aldehydes with Base

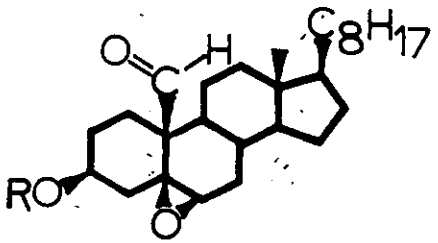
The base-catalyzed reactions of these epoxides were then examined. They were conducted at reflux temperature under a nitrogen atmosphere and their progress was monitored by t.l.c.

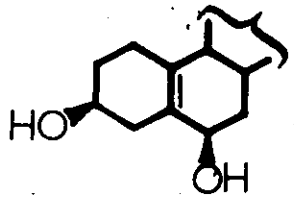
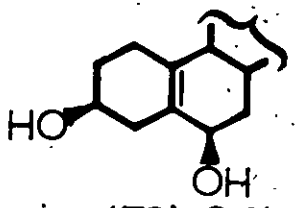
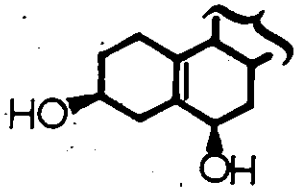
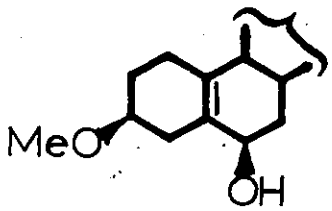
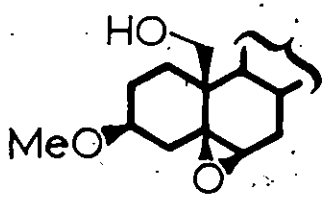
As had been reported[43], the 5β,6β-epoxide (77) was found to react in the presence of 20 per cent aqueous potassium hydroxide to give the allylic alcohol (78), although the reaction was found to be somewhat slower than suggested. The reactions of the 5β,6β-epoxide (77) were also examined with different bases and the results are included in TABLE 2.

In order to assess the importance of an intramolecular hemiacetal (e.g., (90)) in this fragmentation, the reactions of the 3β-methoxy-5β,6β-epoxide (95) were similarly examined (TABLE 2). The latter compound was prepared in an unambiguous fashion (SCHEME 8) from the t-butyldimethylsilyl ether (69).

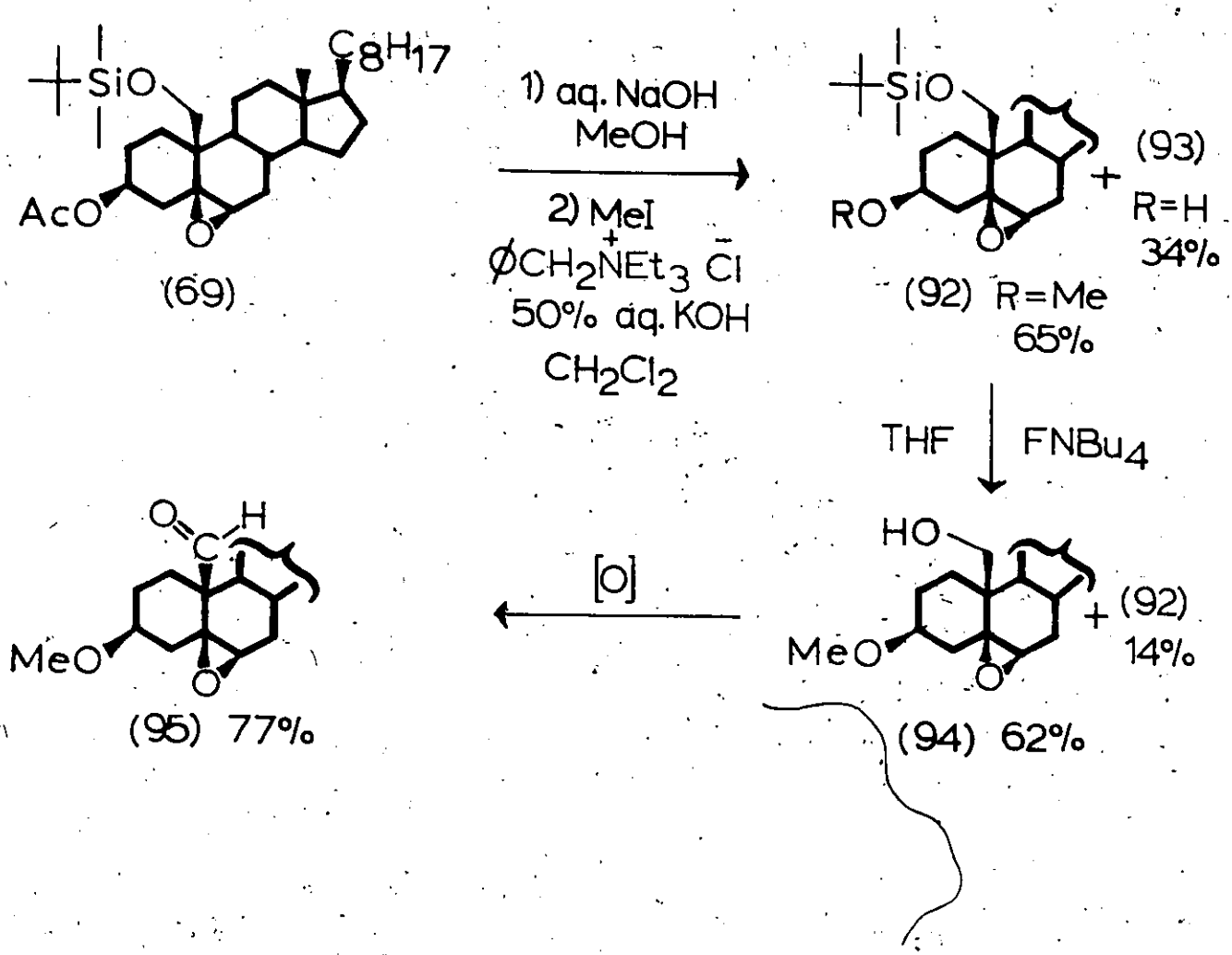
The 5α,6α-epoxide (89) was found to react rapidly in the presence of 20 percent aqueous potassium hydroxide to give a complicated mixture of products. When the reaction was repeated using a methanolic solution of potassium hydroxide, it was found to be much cleaner and the major component was isolated by column chromatography.

TABLE 2. The Base-catalyzed Fragmentation Reactions of the 5,6-Epoxy-aldehydes (77) and (95)



	20% aq. KOH MeOH △	$Mg(OMe)_2$ MeOH △	NaOMe MeOH △
(77) R=H	 36h (78) 77%	 20min (78) 91%	 142h (78) 57%
(95) R=Me	 108h (96) 49% + (95) 30%	 97h (94) 56% + (95) 35%	

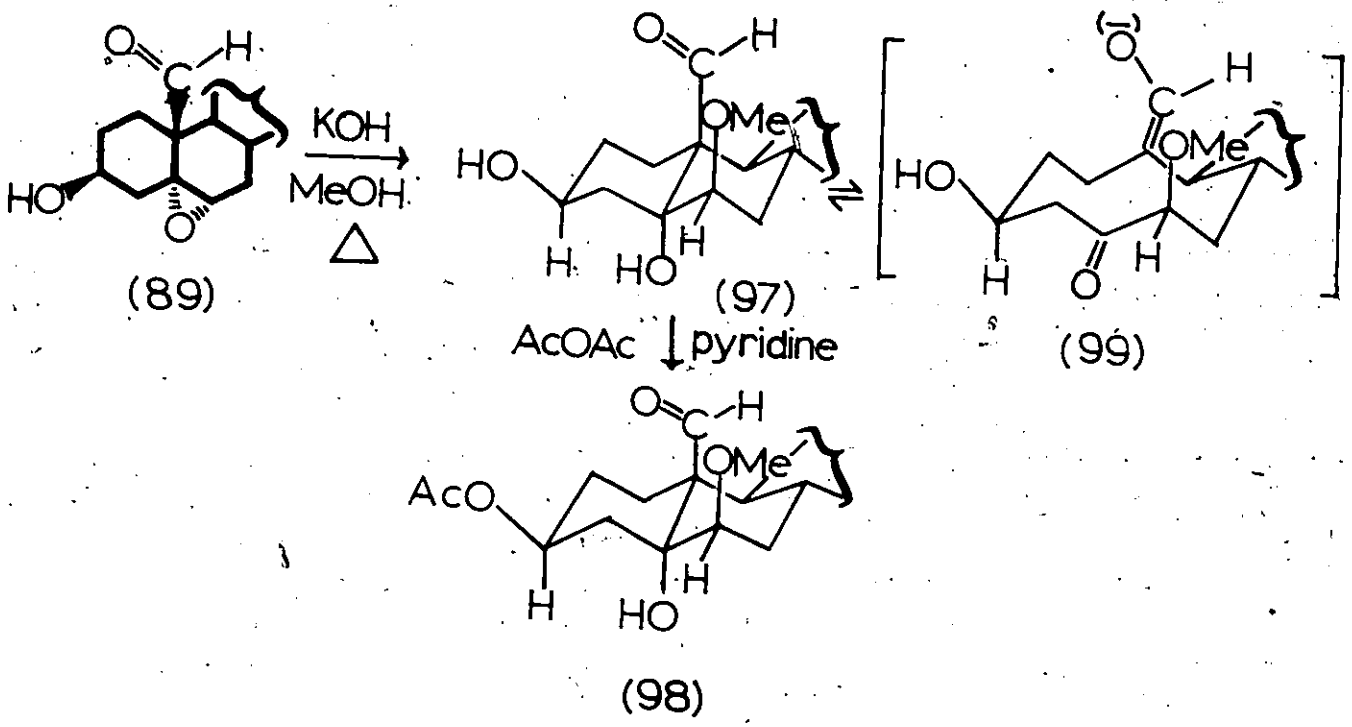
SCHEME 8



This was found to consist of one major compound accompanied by some other material which had a similar R_f value. Repeated crystallization afforded the major compound in a pure form. Its ^1H n.m.r. spectrum showed a singlet (δ3.32,3H) which indicated that methoxide had opened the epoxide ring. The two multiplets observed for the equatorial

6α-H (δ 3.15, W/2 ca. 5 Hz) and the axial 3α-H (δ 3.98, W/2 ca. 26 Hz) suggested that the compound possessed a trans A/B ring junction as in structure (97). This was confirmed by acetylating a sample of this material. The resulting monoacetate (98) showed a downfield shift for the axial 3α-H (δ 5.11, W/2 ca. 26 Hz) while the equatorial 6α-H remained essentially unchanged. This would indicate that the 5α,6α-epoxide (89) had originally undergone diaxial opening with methoxide and that the trans A/B ring junction was maintained in the major product which had been isolated. The latter feature deserved consideration since the 5-position is, in principle[47], epimerizable via the 5,10-seco-intermediate (99) which could arise via a retro-aldol reaction.

From these rather qualitative and limited observations, some insight into the features of the base-catalyzed fragmentation reaction can be obtained. First of all, the fragmentation observed with the 5β,6β-epoxide (77) would appear to be somewhat unique since the opening of the epoxide by the solvent, as was observed in the case of the 5α,6α-epoxide (89), would be expected to occur more readily. However, with the 5β,6β-epoxide (77), diaxial opening by a mucleophile would involve attack at the tertiary 5-position and as this would be unfavourable[47], the slower fragmentation process can occur.

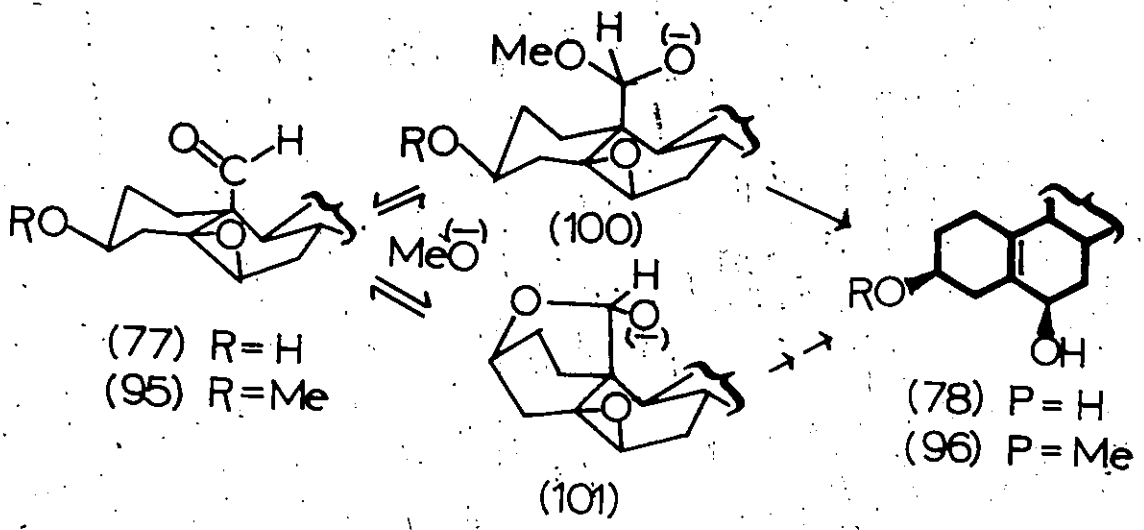


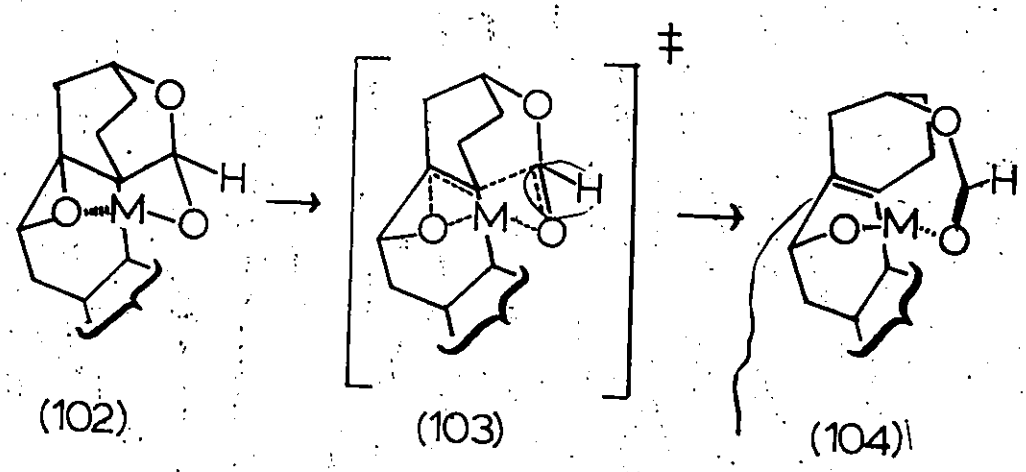
In the fragmentation of the 5β,6β-epoxides, (77) and (95), the two most important factors appear to be intramolecular hemiacetal formation (e.g., under comparable conditions the 3β-hydroxy compound (77) reacts more readily than the 3β-methoxy analogue (95)) and chelation (e.g., with approximately similar concentrations of the

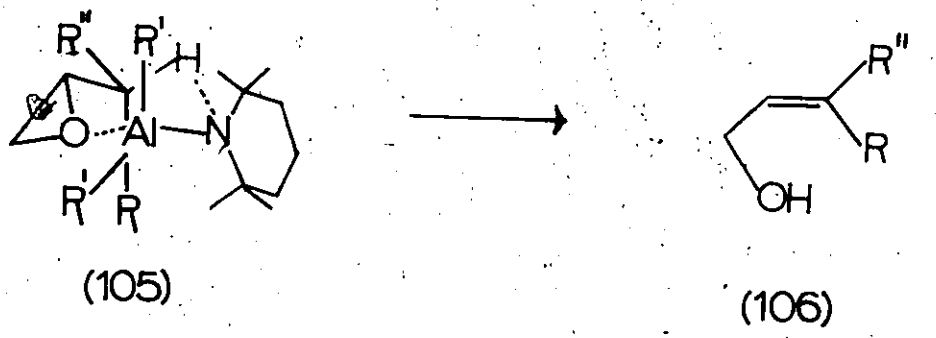
cation, magnesium methoxide is dramatically more effective in promoting the fragmentation of the 3β-hydroxy compound (77) than sodium methoxide. It is suggested that this reaction follows the mechanism shown in SCHEME 9 where an equilibrium between the aldehyde and the hemiacetal, either (100) or (101), is followed by a rate determining concerted fragmentation of the hemiacetal. The results would indicate that latter step proceeds most readily through a chelated, intramolecular, hemiacetal (102) which may resemble the previously described hydrogen-bonded hemiacetal (90). Such an intermediate would allow for a synchronous fragmentation process to occur via a pericyclic transition state (103) which would benefit from the epoxide's strain energy. This would be similar to other chair-like transition states which have been postulated for reactions that involve chelated intermediates. Two notable examples are the cleavage of epoxides by organoaluminum species[49] ((105)→(106)) and the aldol reaction[50] ((108)→(107)).

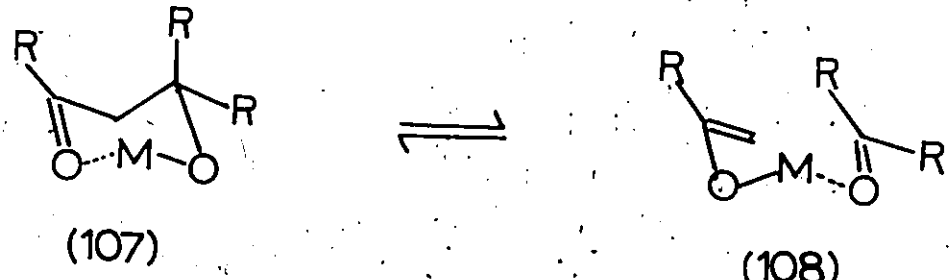
The greater reactivity associated with the intramolecular hemiacetal intermediate (101) could be attributed to the ease with which it is formed (in deuterochloroform, ca. 50% of the 3β-hydroxy-19-aldehyde (77) exists as a hemiacetal), the fact that the hemiacetal (101) already possesses the necessary geometric features of a ligand for

SCHEME 9


MeO
H
(–)
O
RO
(100)
(77) R=H
(95) R=Me
(101)
(78) P=H
(96) P=Me


M
H
‡
(102)
(103)
(104)


R''
R'
H
Al
N
O
R
OH
(105)
(106)


R
M
O
(107)
(108)

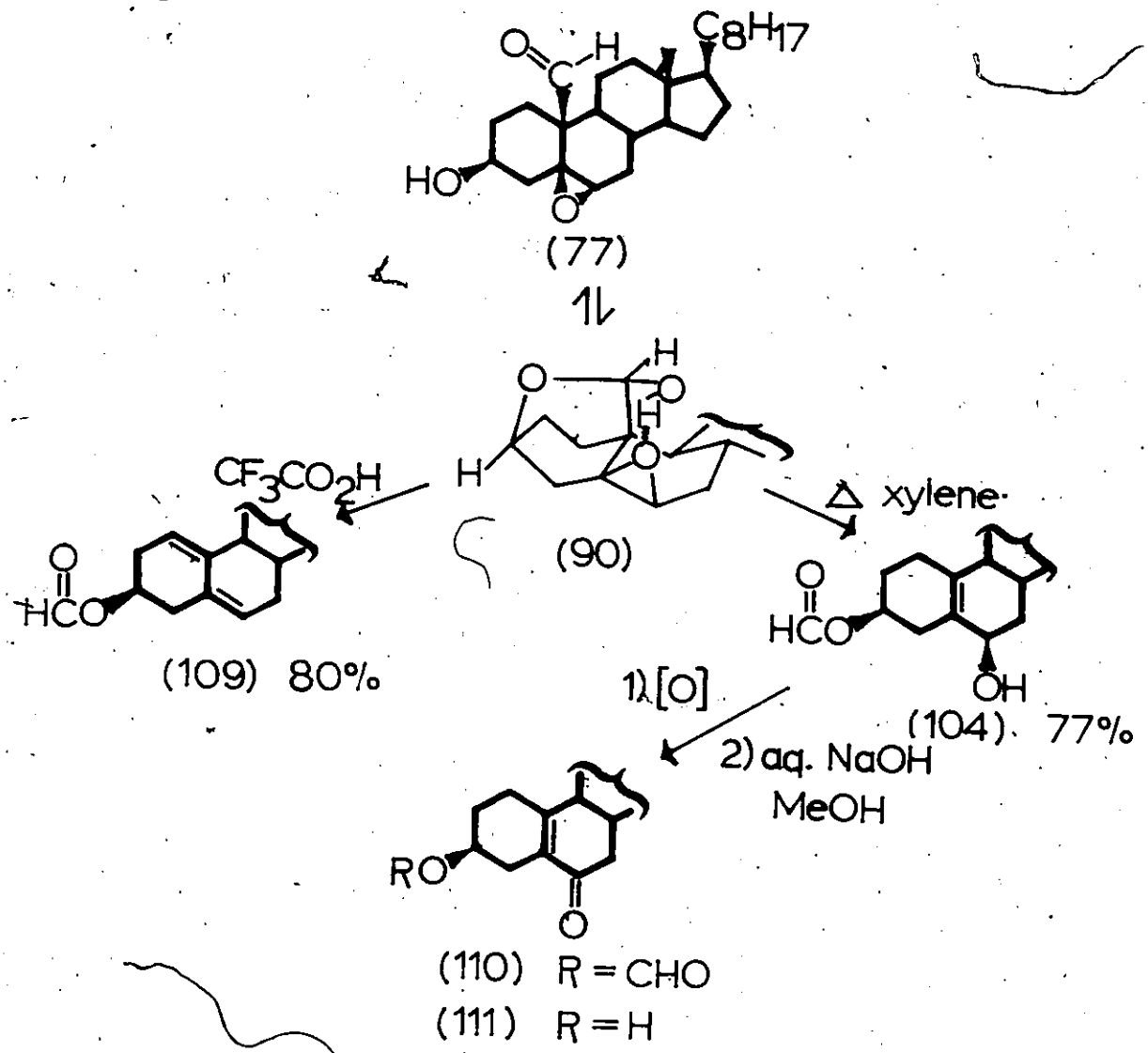
the cation, and that the chelated intermediate (102) would closely resemble that of the postulated transition state. These features may be more difficult to attain in the intermolecular version of the reaction. This would then allow for a competing reaction, such as the reduction of the 19-aldehyde group that was observed in the reaction of the 3β-methoxy compound (95) with magnesium methoxide, to occur. The latter reaction, presumably of the Meerwein-Ponndorf-Verley type, is more commonly associated with the use of aluminum alkoxides but can be effected[51], albeit less efficiently, by magnesium and sodium alkoxides.

In summary, it was found that the base-catalyzed fragmentation of 3β-hydroxy-5,6β-epoxy-5β-cholestan-19-al (77) results from a rather fortuitous combination of circumstances. The most important of these is the facile formation of an intermediate (102) which possesses a conformation that is ideal for a cation-mediated pericyclic reaction. This feature imposes a synclinal configuration between the electrofugal and nucleofugal fragments which differs from the periplanar arrangement that is normally favoured[52] in a Grob fragmentation. It is interesting to note that in this reaction ((102)→(104)) the C-O bond of the epoxide and the C-O bond in the retro-aldol reaction ((107)→(108)) share similar roles. This is much like the similarity that has often been noted[2] between the reactions of cyclopropanes and olefins.

3. Rearrangements of 3β-Hydroxy-5,6β-epoxy-5β-cholestan-19-al (77).

It was noted that if the base-catalyzed fragmentation of the 3β-hydroxy-5β,6β-epoxide (77) proceeded in an intramolecular fashion, the initial product would have been the 3β-formate (104). This compound was not observed since it would readily undergo saponification under the reaction conditions. However, it was obtained in the thermal rearrangement of the 5β,6β-epoxide (77) and this would provide direct evidence for the involvement of an intramolecular hemiacetal under these conditions. The location of the formate ester in (104) was verified by oxidizing it to the enone (110) and subsequently hydrolyzing the latter compound to obtain the known[53] 3β-alcohol (111).

Under acidic conditions, the allylic alcohol (104) was similarly formed but underwent dehydration to the diene (109) and hence was not obtained. The diene (109) had similar spectral properties, notably an absorption maximum at 239 nm, as were reported[32] for the 3β-acetoxy analogue (33).

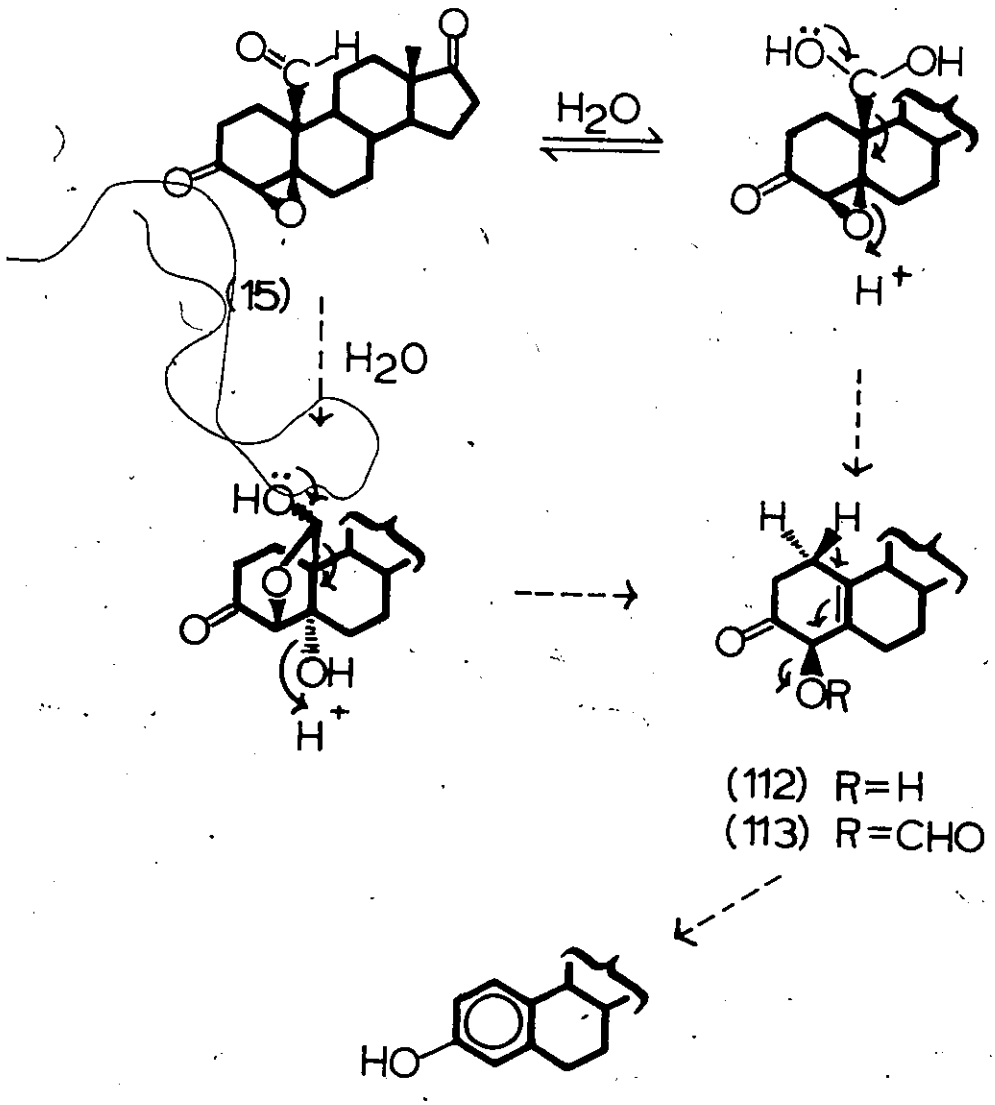

C8H17
HO
O
(77)
H
O
(90)
CF3CO2H
HCO
(109) 80%
△ xylene
HCO
OH
(104) 77%
1) [O]
2) aq. NaOH
MeOH
RO
O
(110) R = CHO
(111) R = H

PART III

Acid- and Base-catalyzed Reactions of 19-Oxo-4β,5-epoxy-5β-androstane-3,17-dione (15) and 19-Oxo-4α,5-epoxy-5α-androstane-3,17-dione (16)

The work described in the previous sections showed that the opening of a 5β,6β-epoxide could be accompanied by a fragmentation reaction in which the C-10 substituent is eliminated. This led to some speculation about the possible involvement of an epoxide in the latter stages of estrone biosynthesis. It was suggested that the 4β,5β-epoxide (15) may be the penultimate intermediate in this enzymatic process since it seemed reasonable[16,17] to expect (SCHEME 10) that (15) could undergo fragmentation to give an allylic species, either (112) or (113), which in turn underwent dehydration to give estrone (114). Further details regarding the biosynthesis of estrone as well as other mechanisms which have been put forth will be discussed subsequently (PART V). In this section, the preparation of the 4β,5β-epoxide (15) as well as the isomeric 4α,5α-epoxide (16) is described together with the results of experiments that were conducted to see if the reactions outlined in SCHEME 10 could be effected chemically.

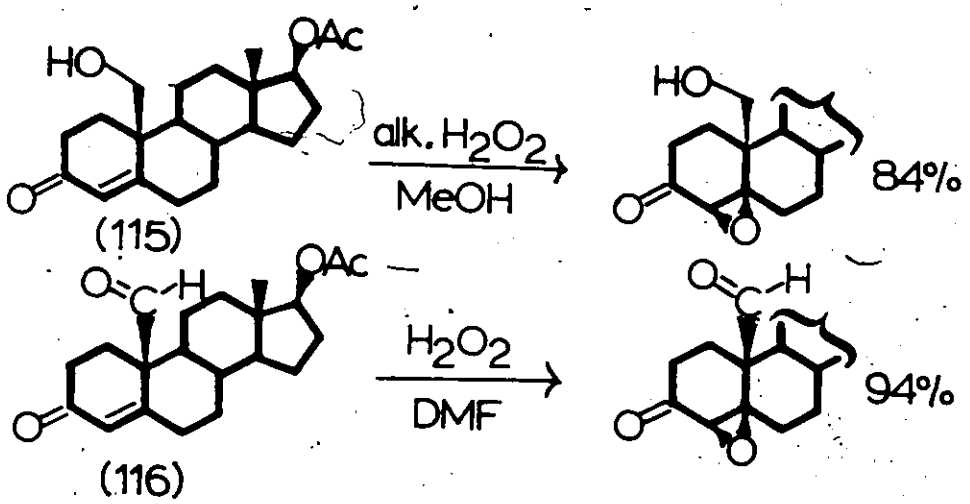
SCHEME 10



(114)

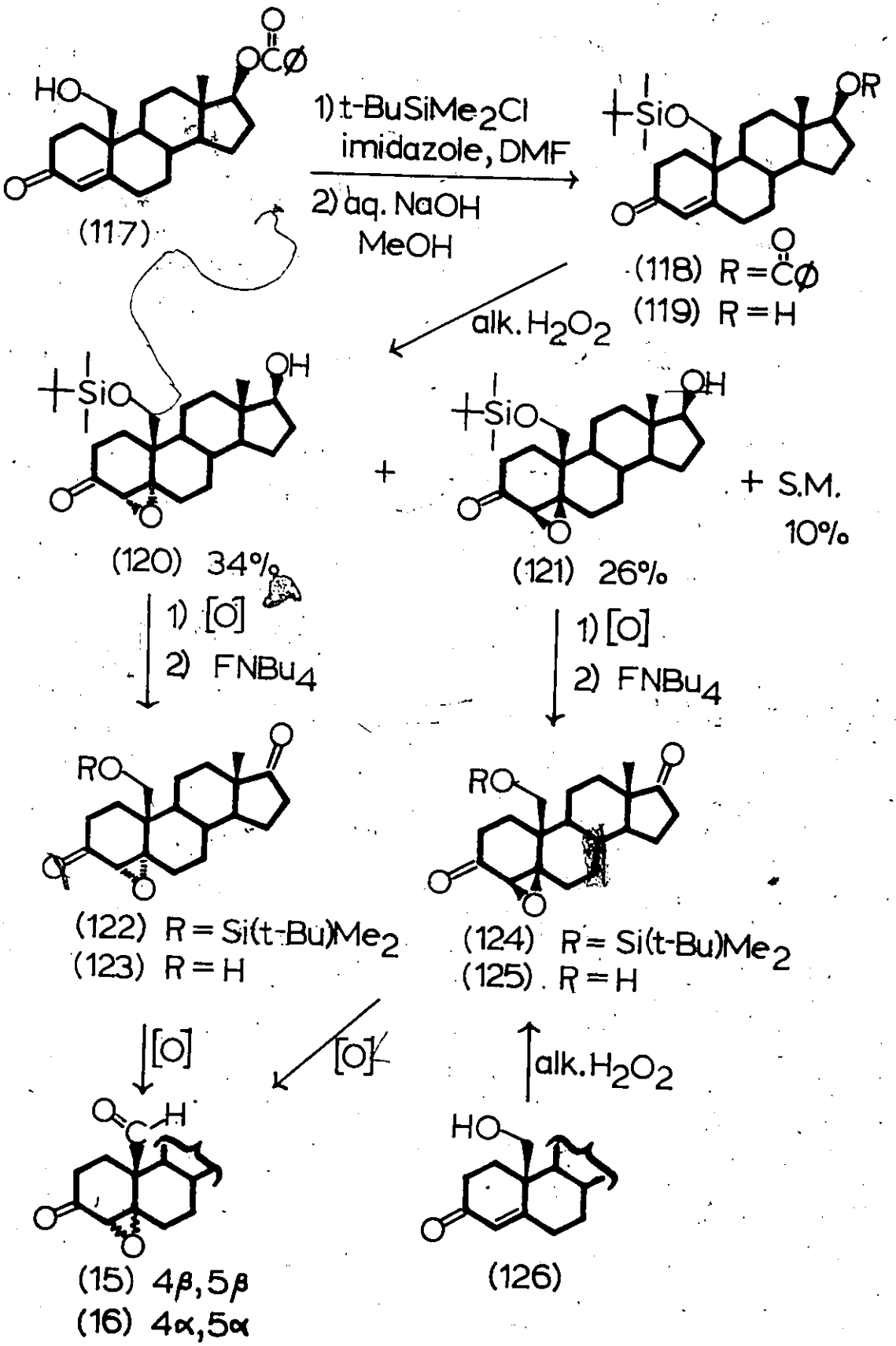
1. Preparation of 19-Oxo-4β,5-epoxy-5β-androstane-3,17-dione (15) and 19-Oxo-4α,5-epoxy-5α-androstane-3,17-dione (16)

Although the stereochemistry of the reaction of steroidal Δ^4-3-ketones with alkaline hydrogen peroxide has been shown to be influenced by substituent effects, it has generally been found that formation of the 4β,5β-epoxide will predominate. This feature has been found to extend to 19-substituted Δ^4-3-ketones, e.g., (115)[54,55] and (116)[56], which exhibit an overwhelming preference for the formation of this isomer.



In order to prepare the 19-substituted 4α,5α-epoxides which were of interest in this study, the 19-t-butyldimethylsilyl ether (119) was used (SCHEME 11). This compound was found to react relatively slowly with alkaline hydrogen

SCHEME 11


HO
OCØ
(117)
1) t-BuSiMe2Cl
imidazole, DMF
2) aq. NaOH
MeOH
OR
(118) R = CØ
(119) R = H
alk. H2O2
OH
(120) 34%
+
(121) 26%
+ S.M.
10%
1) [O]
2) FNBu4
RO
(122) R = Si(t-Bu)Me2
(123) R = H
(124) R = Si(t-Bu)Me2
(125) R = H
[O]
alk. H2O2
(15) 4β,5β
(16) 4α,5α
(126)

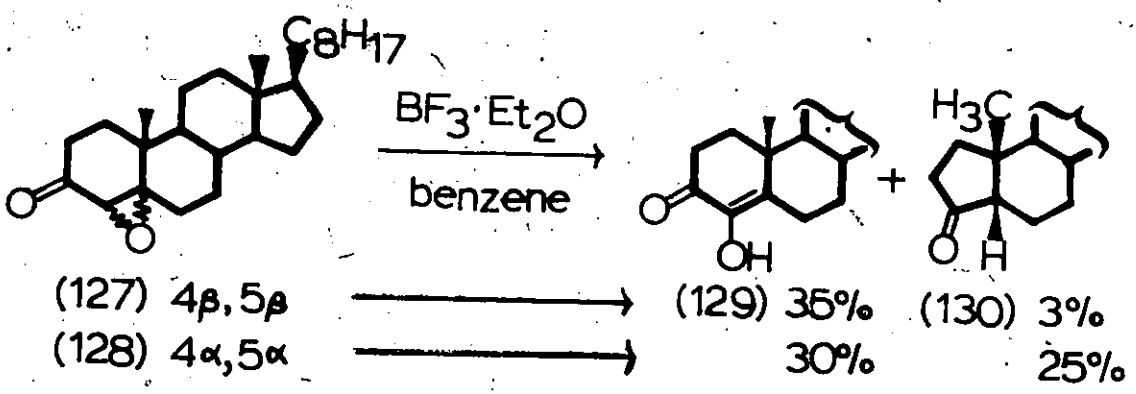
peroxide to give a 1.3:1 (4α,5α:4β,5β) mixture of epoxides. The reaction was stopped prior to completion (t.l.c.) since it was noted that, if left for longer periods of time, product decomposition became significant. The isomeric epoxides (120) and (121) were separated by column chromatography, oxidized to the 17-ketones, (122) and (124), and then desilylated to the 19-alcohols (123) and (125). The identity of (125), and hence (123), was established by the observation that the former of the two was identical with the 4β,5β-epoxide (125) which was prepared[16] by treating the 19-hydroxy-Δ^4-3-ketone (126) with alkaline hydrogen peroxide. The 19-hydroxy compounds (123) and (125) were then oxidized to give the 19-aldehydes (16) and (15).

2. Acid-catalyzed Reactions of 19-Oxo-4β,5-epoxy-5β-androstane-3,17-dione (15) and 19-Oxo-4α,5-epoxy-5α-androstane-3,17-dione (16)

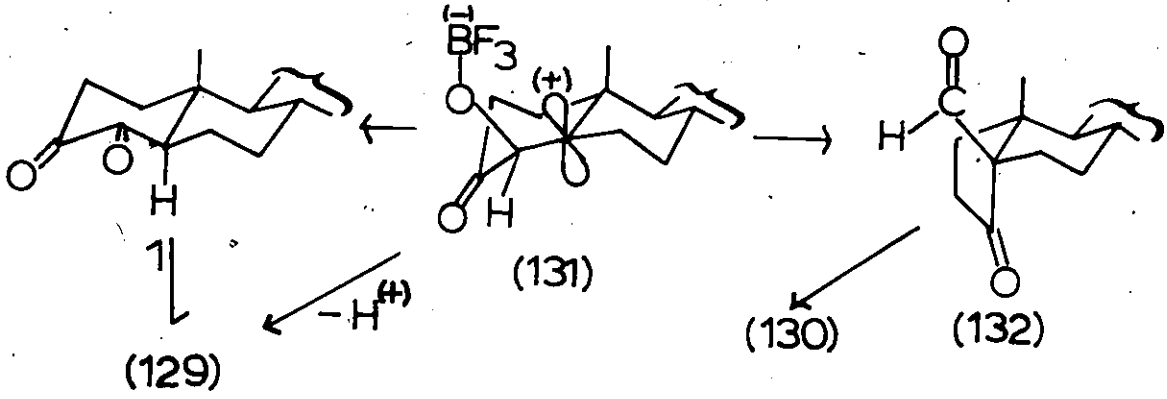
Most of the studies conducted on the acid-catalyzed reactions of 4,5-epoxy-3-ketones have been performed on steroids which have a 10β-methyl substituent. Some aspects of this work will be discussed briefly to illustrate the properties of this system.

For those reactions conducted in the absence of nucleophiles, the results obtained[56] from the boron trifluoride-catalyzed rearrangements of the 4,5-epoxy-

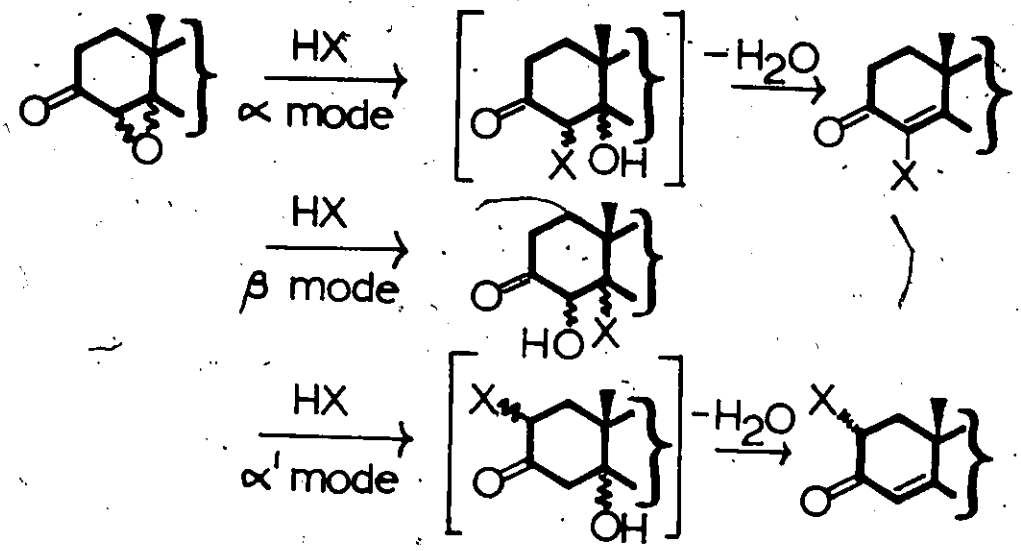
cholestan-3-ones (127) and (128) appear to be typical. With both isomers, the reaction is initiated by the cleavage of the C(5)-O bond. In the case of the 4β,5β-epoxide (127), the initially formed carbocation (131) (SCHEME 12) can undergo migration of the 4α-hydrogen atom (or its direct loss[57]) to give the diosphenol (129). Alternatively, it may undergo migration of the C(3)-C(4) bond to C-5 to give the A-nor-aldehyde (132). This latter species is not observed since it apparently undergoes a facile deformylation under the reaction conditions to give the A-nor-compound (130). A similar sequence would be involved in the reaction of the isomeric 4α,5α-epoxide (128).



SCHEME 12

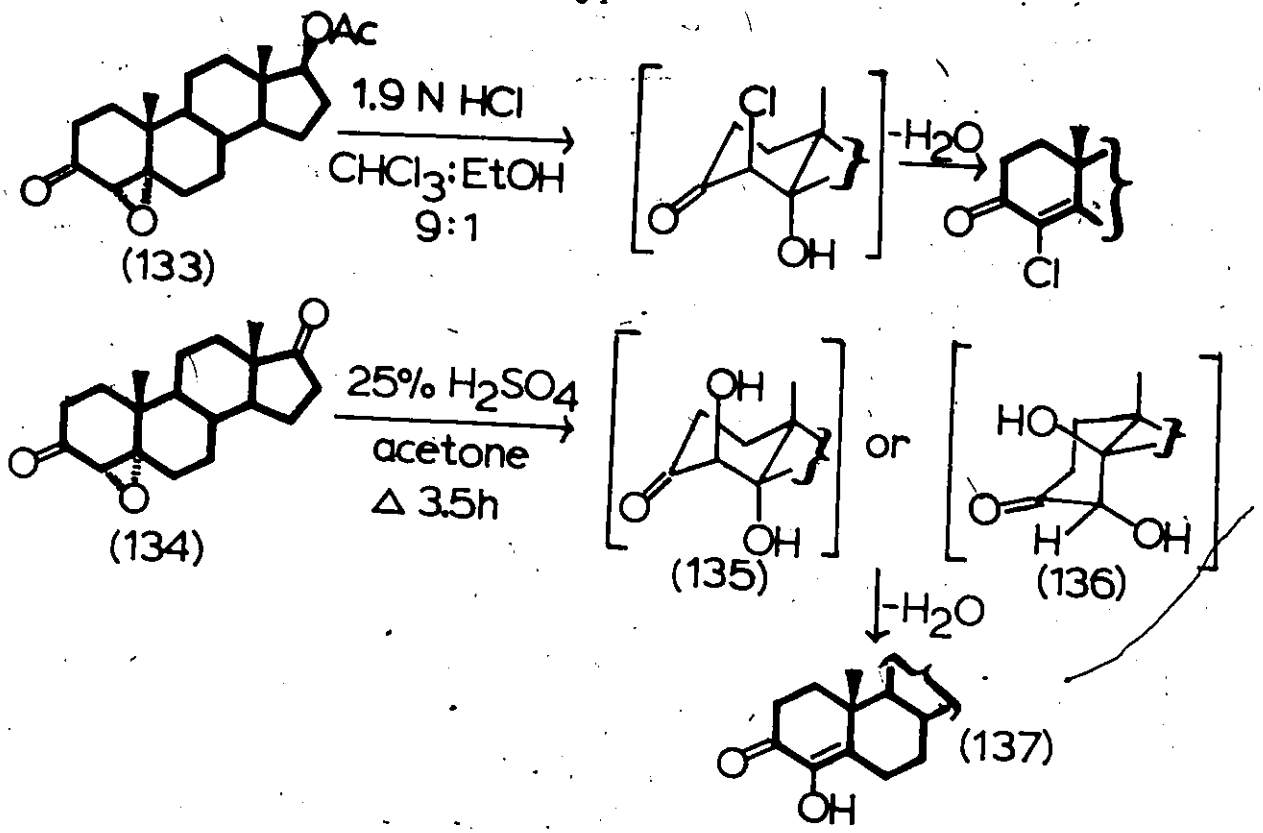


SCHEME 13

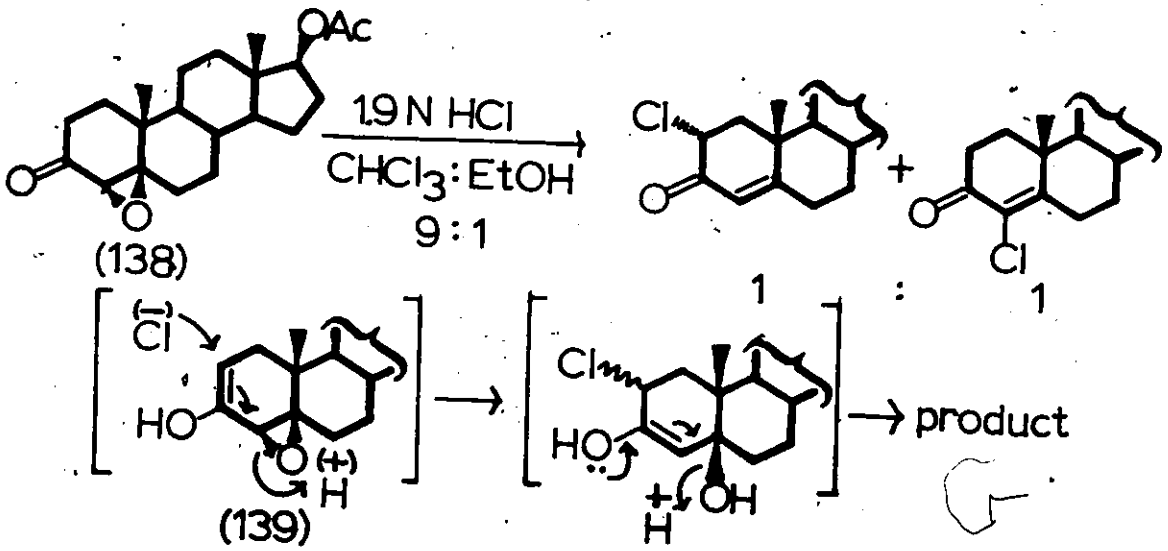


In the presence of nucleophiles, three different modes of epoxide opening have been observed[58] and these are illustrated in SCHEME 13. However, it remains difficult to understand the factors that are responsible for these differences since they seem to include not only the nature of the epoxide but also that of the solvent and the acid employed.

Generally it would appear that the 4α,5α-epoxide undergoes an α mode of ring opening as was observed[58] for (133) with aqueous hydrochloric acid. The diosphenol[59] (137), obtained from (134) with aqueous sulphuric acid, may have similarly arisen via dehydration of the initially formed diol (135) (α mode). However, in this case, the intermediacy of the diol (136) (β mode) cannot be ruled out.

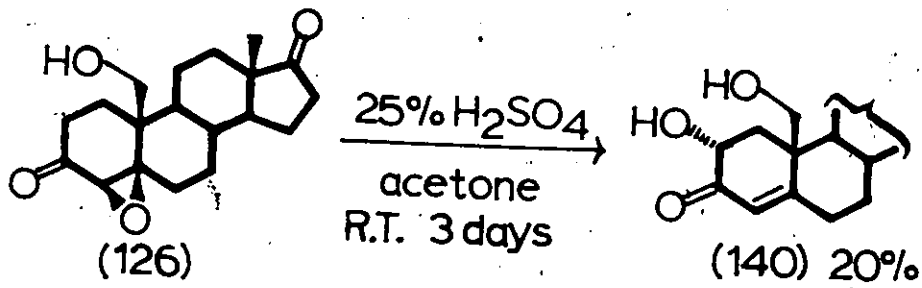


With the 4β,5β-epoxides, it appears that both α and α' modes of ring opening can occur as has been observed[58] with (138). It has been suggested[60] that the α' mode proceeds via an enol (e.g., (139)). However, the initial configuration of the 2-substituent, and hence the stereochemistry of this reaction, remain uncertain since the observed 2α configuration is more stable than the 2β and may therefore result from epimerization.



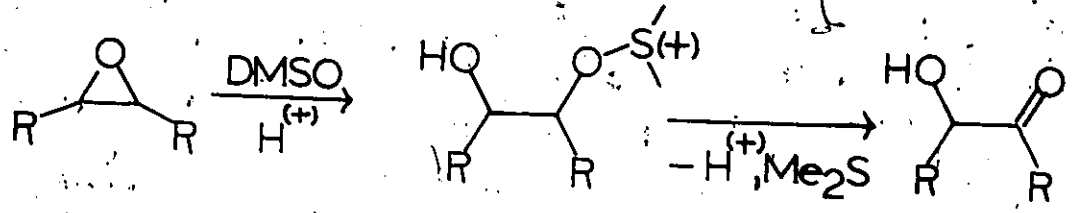
In summary, it would appear that in the absence of nucleophiles, epoxide opening to give a C-5 carbocation is preferred. However, in the presence of nucleophiles, epoxide opening occurs via attack at the positions α to the carbonyl group. This indicates that the nucleophile actively participates in the opening of the epoxide as this would appear to represent a more favourable sequence than the initial formation of a high energy C-5 carbocation intermediate which is subsequently solvated.

There are a few reports on acid-catalyzed reactions of 19-substituted 4,5-epoxy-3-ketones. With aqueous sulphuric acid[61], the 19-hydroxy-4β,5β-epoxide (126) was converted (α' mode of ring opening) to the 2α-hydroxy compound (140). The other products of this reaction were not reported.

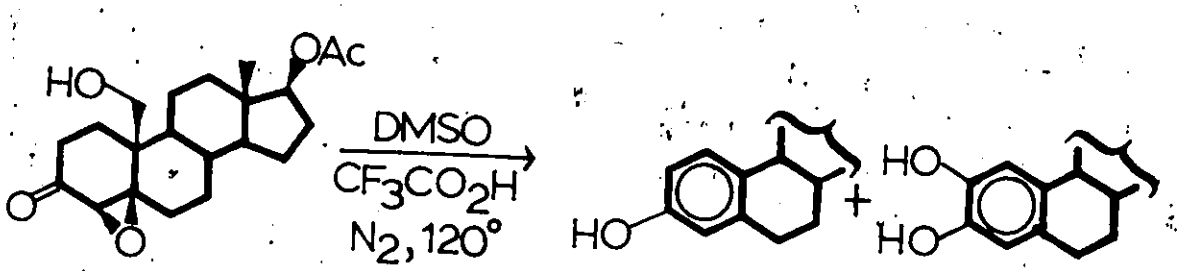


(126) (140) 20%

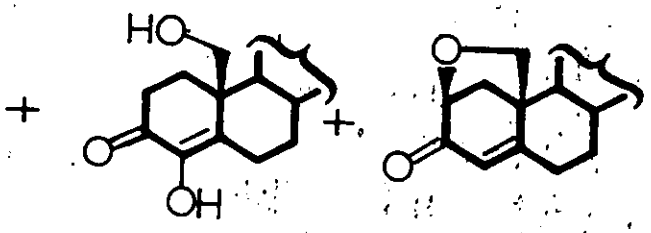
The reaction of the 19-alcohol (141) and the 19-aldehyde (142) with dimethyl sulfoxide in the presence of an acid catalyst has been described[55]. These are conditions which would normally effect[62] the conversion of an epoxide (145) to a α-hydroxy ketone (146). The major product (144),



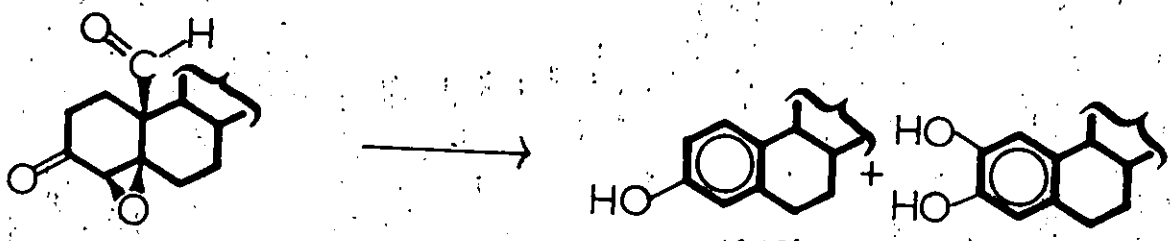
(145) (146)



(141) (143) 18% (144) 44%



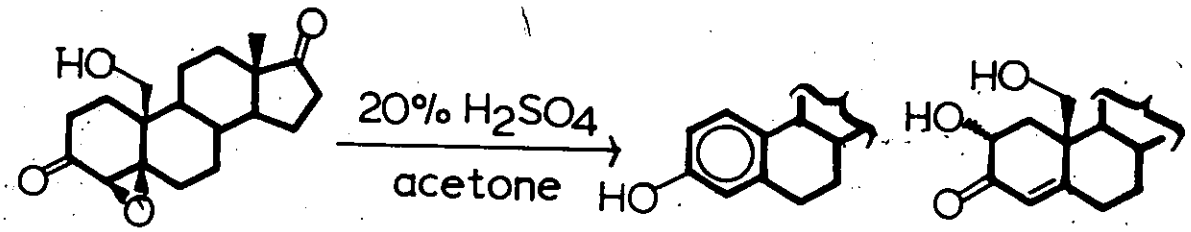
9% 14%



(142) (143) 18% (144) 33%

obtained from both (141) and (142), was suggested to arise via the initial acid-catalyzed opening (α' mode) of the epoxide by dimethyl sulfoxide. However, it can be seen that in both instances, significant amounts of 17β-acetoxy-3-hydroxy-estra-1,3,5(10)-triene (143) were also formed and this would indicate that the elimination of the C-10 substituent may occur on epoxide opening.

The acid-catalyzed reactions of the 19-substituted-4,5-epoxy-ketones were examined with attention being focused on the 19-aldehydes (15) and (16) since they were considered to be of greatest interest. However, the reaction of the 19-alcohol (126) with aqueous sulphuric acid was repeated and estrone was found to be a product.



(126) 12% (140) 23%

Preliminary studies conducted with the 19-aldehydes (15) and (16) in the presence of perchloric acid in tetrahydrofuran indicated that a number of different products were being formed whose relative yields appeared

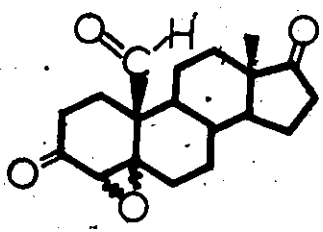
to depend upon the amount of water present. The reactions that were conducted with concentrated perchloric acid and aqueous perchloric acid (20%) are representative of the differences that were encountered and the results are presented in TABLE 3. The structural assignments were based upon the following observations.

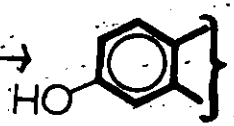
Estrone (114) was acetylated (acetic anhydride-pyridine) and the resulting 3-acetyl derivative was found to be identical (t.l.c. and ^{1}H n.m.r.) with authentic material.

The diosphenol (147) exhibited absorptions at 278 nm in the u.v. spectrum and 1670 and 1640 cm^{-1} in the i.r. spectrum which would be consistent with the structure assigned. As well, the ^{1}H n.m.r. spectrum showed singlets for the 19-aldehyde proton (δ 10.13) and the exchangeable 4-hydroxy proton (δ 6.45).

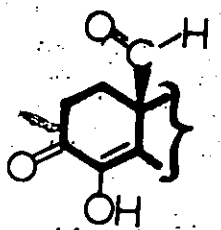
For the A-nor-19-aldehyde (148), the ^{1}H n.m.r. spectrum only showed a singlet for the 19-aldehyde proton (δ 9.78). The molecular ion (m/e 288) observed in the mass spectrum was in agreement with the analytical data ($C_{18}H_{24}O_3$) which indicated that the epoxide, (15) or (16), had, in effect, undergone a decarbonylation. The cis A/B ring junction is suggested by analogy with the A-nor-cholestan-3-one (130) which had been obtained[56] by the boron trifluoride-catalyzed reaction of the 4,5-epoxy-

TABLE 3. Acid-catalyzed Reactions of 19-Oxo-4β,5-epoxy-5β-androstane-3,17-dione (15) and 19-Oxo-4α,5-epoxy-5α-androstane-3,17-dione (16)

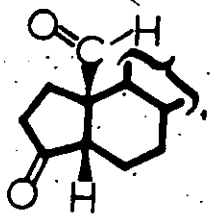




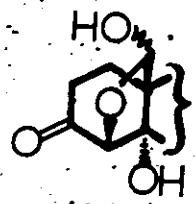
(114)



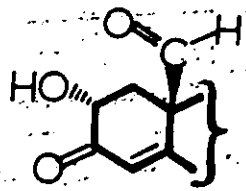
(147)



(148)



(149)



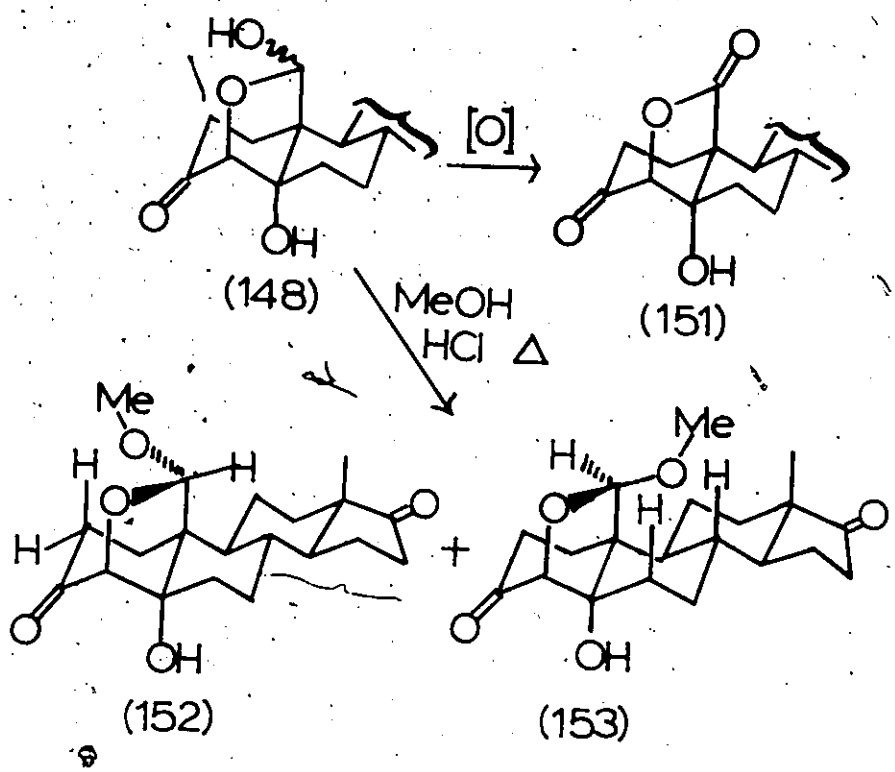
(150)

(16) 4α,5α	conc. $HClO_4$ THF	17%	29%	17%	13%	—
(15) 4β,5β	"	8%	49%	7%	17%	—
(16) 4α,5α	20% $HClO_4$ THF	13%	47%	—	17%	—
(15) 4β,5β	"	3%	—	—	82%	—
(16) 4α,5α	20% H_2SO_4 acetone	12%	47%	—	26%	—
(15) 4β,5β	"	3%	—	—	43% (60%)*	8% (15%)*

*The yields quoted in parenthises refer to those calculated (from the ^1H n.m.r.) for the fraction containing these two compounds. Some material was evidently lost when it was rechromatographed on alumina.

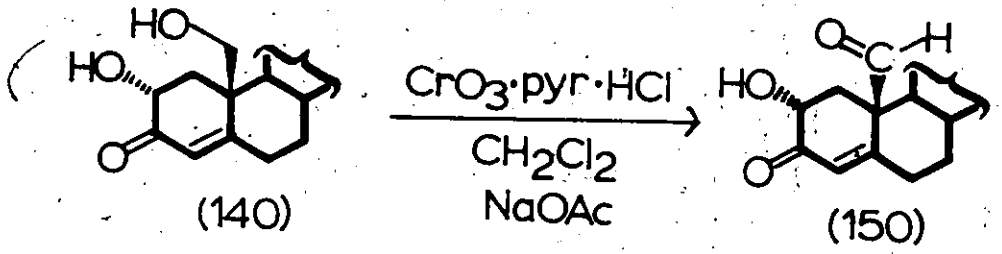
cholestan-3-ones, (127) and (128), and also the fact that 1-hydrindanones preferentially adopt[63] a cis ring junction.

The hemiacetal (149) was homogeneous on the basis of t.l.c.; however, the ^1H n.m.r. spectrum indicated that it had been obtained as a mixture of epimers. The major epimer (ca. 80%) showed singlets (acetone-d_6) at δ 2.75 for the 4α-H and δ 5.25 for the 19-H whereas the minor epimer (ca. 20%) showed singlets at δ 2.04 for the 4α-H and δ 4.90 for the 19-H. Oxidation of this mixture of epimers afforded the γ-lactone (151) which exhibited an absorption at 1790 cm^{-1} in the i.r. spectrum and showed a singlet (δ 4.07) for the 4α-hydrogen in the ^1H n.m.r. spectrum. This is consistent with an epimeric centre at C-19 for the γ-hemiacetals postulated. When the mixture of epimers was heated at reflux in methanol in the presence of a catalytic amount of hydrochloric acid, two epimeric acetals (152) and (153) were obtained and these were separated by column chromatography. It was assumed that the ratio in which these two products were formed reflected their relative thermodynamic stabilities and furthermore that the latter quantity was largely determined by the magnitude of the steric interaction between the 19-methoxy group and the axial hydrogen atoms in the A and B rings. On this basis, the 19-R



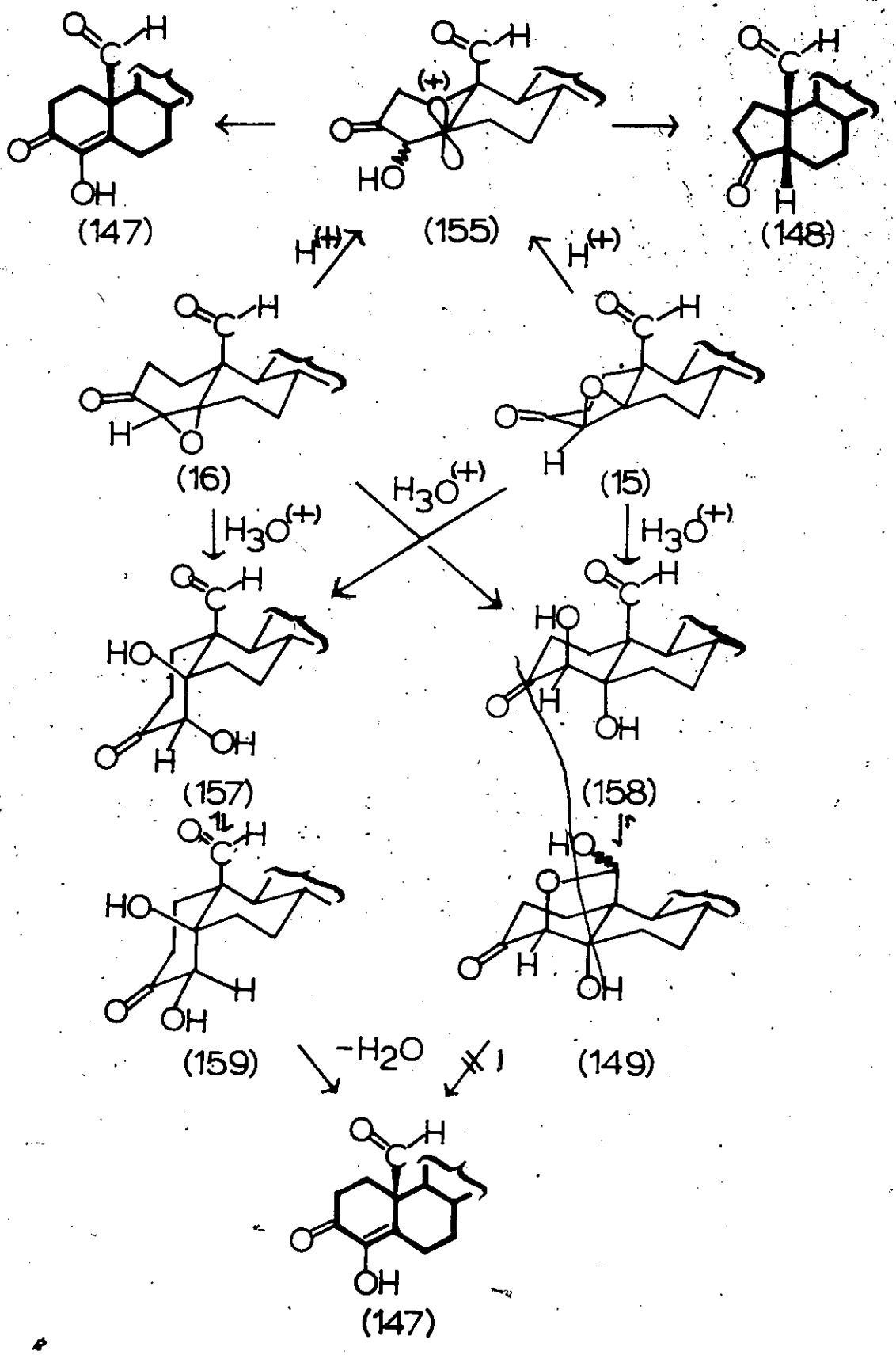
configuration was assigned to the minor isomer (153) (24%) as there would be two, approximately equal, interactions between the 19-methoxy group and the axial 8β-and 6β-hydrogen atoms. The major isomer (152) (51%) was assigned the 19-S configuration since there was only one interaction of this type (approximately equal to one of the interactions in the 19-R isomer) between the 19-methoxy group and the 2β-hydrogen atom.

The last compound that was obtained from the acid-catalyzed reactions was the 2α-hydroxy compound (150). This material exhibited spectral properties that were similar with those reported[61] although it was found that the physical properties (m.p. 217-219°, $[\alpha]_D$ +302°) differed (lit.[61], m.p. 205-209°, $[\alpha]_D$ +242°). However, the data reported were for the hydrate whereas the analytical results obtained in this work did not indicate the existence of a hydrate. Material identical with (150) was also obtained, albeit in low yield, by the selective oxidation[61] of the 2α,19-dihydroxy compound (140).



Looking at the yields obtained (TABLE 3) with aqueous perchloric acid, it can be seen that the major products are derived from the acid-catalyzed opening of the epoxide ring by water. Normally, information regarding the position of attack (α mode vs. β mode) by water is not obtainable since

SCHEME 14

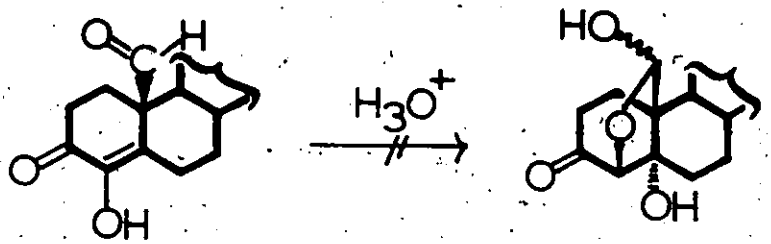


the subsequent acid-catalyzed dehydration would give the same diosphenol. However, in this case it would appear that epoxide opening to give the 4β,5α-diol (158) (SCHEME 14) results in the formation of a hemiacetal (149) which is stable under the reaction conditions. This was confirmed by the observation that the hemiacetal was recovered unchanged when subjected to the conditions of the reaction. This stability would appear to result from the fact that the hemiacetal does not allow the 4β-hydroxy group to undergo epimerization. As this would prevent the 4α-hydrogen from becoming axial, stereoelectronic requirements[64] will not allow the 3-keto group to assist in an acid-catalyzed dehydration.

The other possible product of epoxide opening, the 4α,5β diol (157), was not observed. It is suggested that (157) is formed, but readily undergoes epimerization to the 4β,5β-diol (159) and that this is followed by dehydration to give the diosphenol (147). The possibility that the diosphenol (147) was derived *via* rearrangement of the epoxide seems unlikely since the other acid-catalyzed rearrangement product, the A-*nor* compound (148), was not observed under these conditions.

This interpretation of the results obtained leads one to conclude that the β mode of epoxide opening predominates for both the epoxides. In the case of the 4β,5β-epoxide (15),

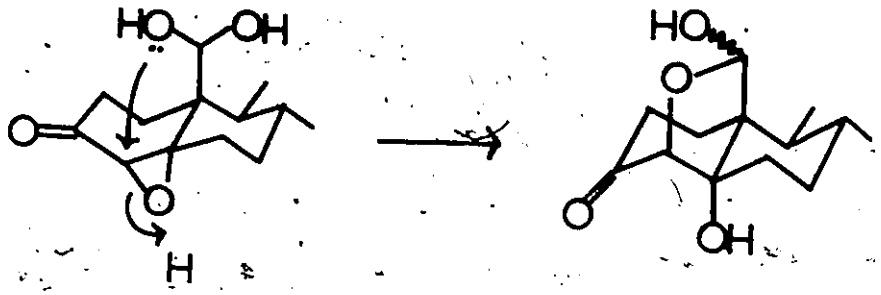
this is essentially the only mode of ring opening that is observed since the hemiacetal (149) was obtained in an 80% yield. The possibility that the hemiacetal (149) could be derived from the diosphenol (147) by hydration was ruled out by the observation that (147) was recovered



(147) (149)

unchanged when subjected to the reaction conditions. With the 4α,5α-epoxide (16) the ratio of α mode ring opening versus the β mode is ca. 1:3. In this case, the β mode predominates even though the possibility of an intramolecular version of the α mode of epoxide opening exists ((16)→(149)).

These results contrast those obtained[58] with hydrogen halides where the α and α' modes of epoxide opening were observed. However, it would be difficult to explain this difference since the nature of the solvent, the nucleophile, the acid, as well as electronic effects (i.e., the 19-aldehyde function) may be responsible.



(16) (149)

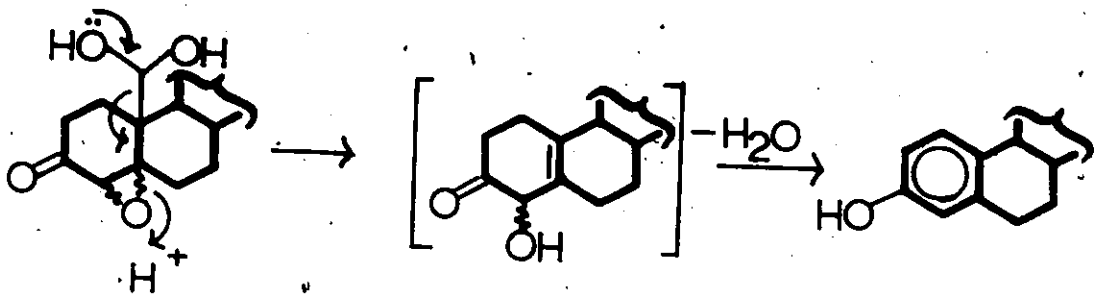
Some idea of the importance of the nature of the solvent and the acid can be seen by comparing the results just discussed with those obtained using aqueous sulphuric acid in acetone (TABLE 3). Whereas the 4β,5β-epoxide (16) was almost exclusively converted (β mode) to the hemiacetal (149) under the former conditions, with aqueous sulphuric acid a significant amount of the 2α-hydroxy compound (150) (α' mode) was obtained together with (149). This would be in agreement with previous observations[55] that the α' mode occurs more readily in the presence of a weaker acid.

When concentrated perchloric acid in tetrahydrofuran was used, epoxide rearrangement products were also observed. The A-nor-compound (148) and some portion of the diosphenol (147) would appear to be derived from the C-5 carbocation (155) (SCHEME 14). However, nucleophilic opening of the epoxide is still occurring as would be indicated by the

isolation of relatively large amounts of the hemiacetal (149) and this would suggest that some portion of the diosphenol arises *via* the dehydration of the initially formed diol (157). A greater yield of the A-*nor* compound (148) from the 4α,5α-epoxide (15) is similar to what was observed by Collins[56] with 4,5-epoxy-cholestan-3-ones.

Under the conditions examined, estrone was found to be a minor product in all of the reactions although the 4α,5α-epoxide consistently afforded a greater yield of this material. However, the origin of this compound remains unclear since most of the products obtained are stable under the reaction conditions and hence not precursors of it. It seems unlikely that the 2α-hydroxy compound (150) is the intermediate which leads to estrone since it was not observed in the reaction mixtures of the 4α,5α-epoxide (16). The possibility that the 2β-epimer of (150), a much less stable compound[61], was being formed from the 4α,5α-epoxide and subsequently reacting to give estrone also seems unlikely since there have been no reports of 4α,5α-epoxy-ketones undergoing the α' mode of ring opening. It would appear that estrone is being formed *via* some unstable intermediate, perhaps (112), which could not be isolated under these reaction conditions.

Some alternative route to (112) were examined and will be described in the subsequent section.

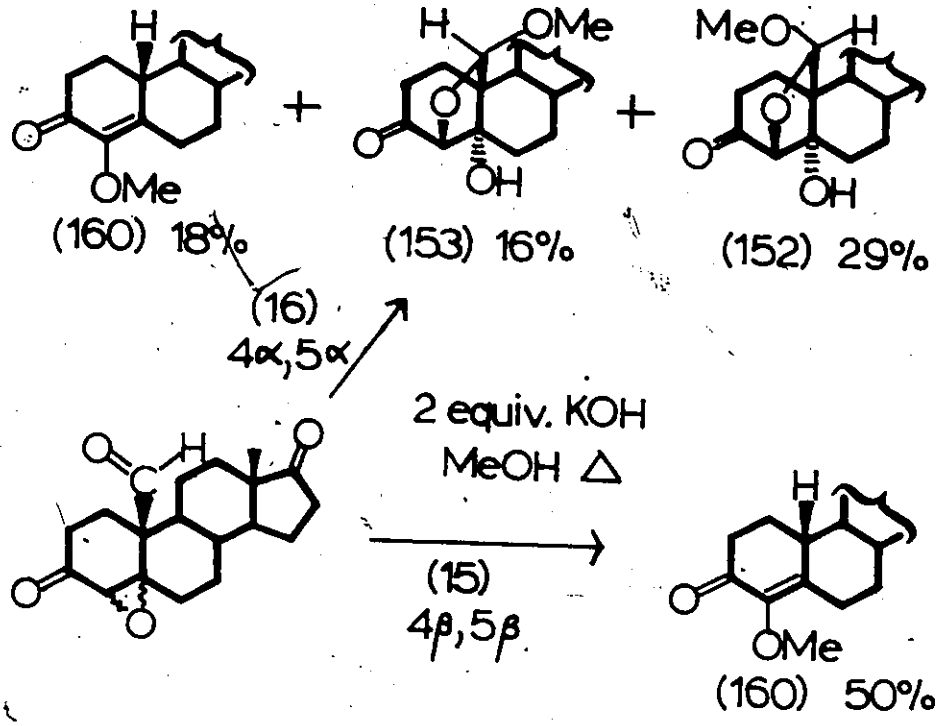


(112)

3. The Base-catalyzed Reactions of 19-Oxo-4β,5-epoxy-5β-androstane-3,17-dione (15) and 19-Oxo-4α,5-epoxy-5α-androstane-3,17-dione (16)

The epoxy-aldehydes (15) and (16) were found to react in the presence of refluxing methanolic potassium hydroxide to give relatively complicated mixtures of products. The sole product that was isolated from the reaction mixture of the 4β,5β-epoxide (15) was the 4-methoxy compound (160). The structure proposed for the latter compound was consistent with the absorptions observed in its u.v. spectrum (λ_{max} 255 nm) and its i.r. spectrum (1675 and 1610 cm^{-1}).

Three products were obtained from the 4α,5α-epoxide (16). Two of them had similar R_f values and this fact only allowed for the isolation of a portion of one of



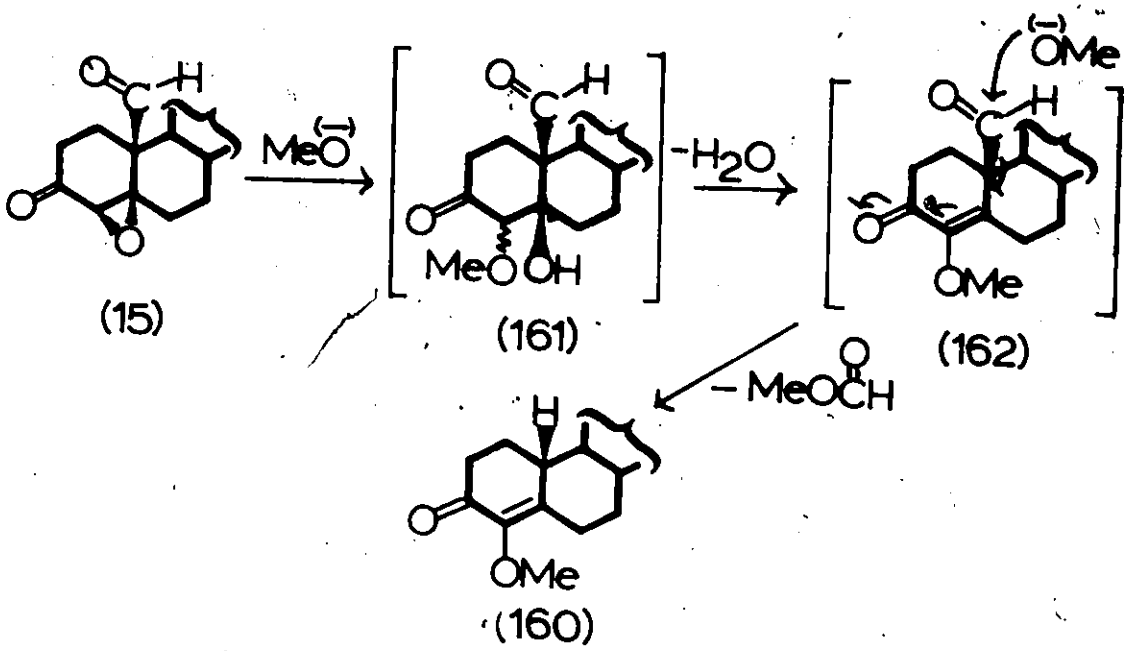
these two products in a pure form. The material thus isolated was found to be identical (t.l.c. and ^{1}H n.m.r.) with the 4-methoxy compound (160). The remainder of this mixture consisted (t.l.c. and ^{1}H n.m.r.) of the 4-methoxy compound (160) and the 19-R acetal* (153). The third product, which was isolated in a pure form, was the 19-S acetal* (152).

*The material obtained was identical (t.l.c. and ^{1}H n.m.r.) with that which had been obtained previously and for which the assignments of the configuration at C-19 were based upon thermodynamic considerations.

The results obtained indicate that the major mode in which the α,β-epoxy ketones react involve the opening of the epoxide ring by nucleophilic attack at the α position[65]. In the case of the 4β,5β-epoxide (15), the intermediate (161) thus formed (SCHEME 15) undergoes a base-catalyzed elimination of water to give the enone (162). This then undergoes a vinylogous retro-Claisen reaction to give the 4-methoxy compound (160). The latter compound is presumably formed in a similar manner from the 4α,5α-epoxide (16). However, in this case, intramolecular attack at the 4-position by the conjugate base of the hemiacetals (163) and (164) can also occur. The preference for the formation of the 19-S isomer (152) under basic conditions may result from there being less of an interaction between the 19-methoxy group and the axial hydrogens in the path leading to this isomer (SCHEME 16).

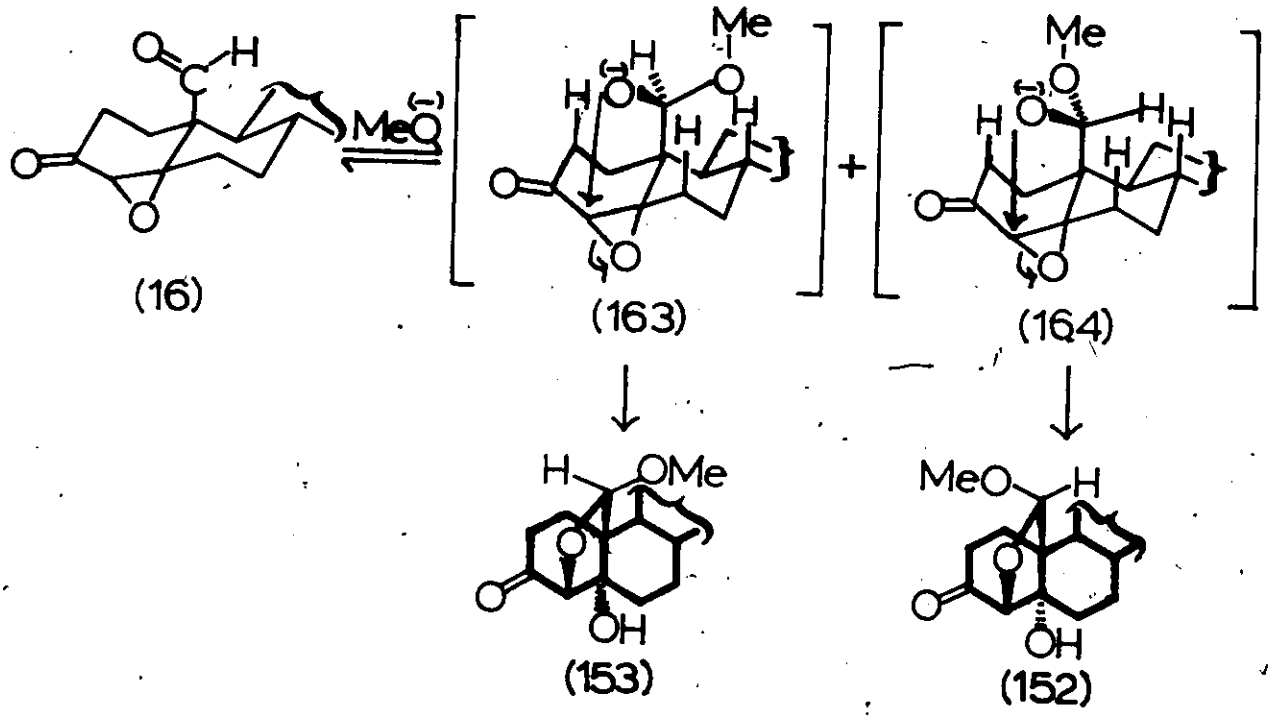
It can be seen that a base-catalyzed fragmentation as was found[43] with 3β-hydroxy-5,6β-epoxy-5β-cholestan-19-al (77), does not occur with the 4,5-epoxy-3-ketones (15) and (16).

SCHEME 15



(15) (161) (162) (160)

SCHEME 16

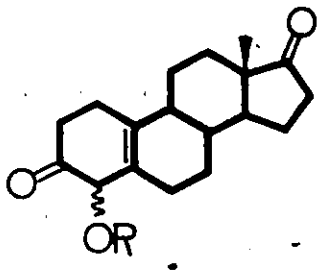


(16) (163) (164) (153) (152)

PART IV

Attempts at Preparing 4-Hydroxy-estr-5(10)-ene-3,17-dione (112)

In the preceding section, it was shown that estrone was formed, albeit in low yields, in the acid-catalyzed reactions of the 19-substituted epoxides (126), (15) and (16). In this section, the attempts at preparing the possible intermediate, the allylic alcohol (112), and some of its derivatives, (165) and (113), are described. Also included are the results of some investigations into the chemistry of the compounds that were obtained.

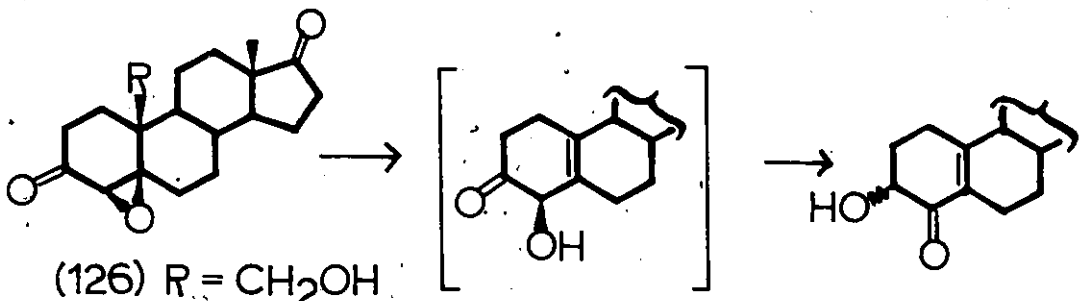


(112) R = H
(165) R = Ac
(113) R = CH(=O)

1. The Thermal Decarboxylation of 4β,5-Epoxy-5β-androstane-3,17-dion-19-oic Acid (166)

The report[13] that β,γ-epoxy-acids can be made to undergo thermal decarboxylative elimination under relatively mild conditions (refluxing toluene) suggest that a similar reaction conducted with the acid (166) may allow for the isolation of the allylic alcohol (112).

The acid (166) was prepared by Jones oxidation of the alcohol (126). It was found to be stable in refluxing toluene and xylene but, in decalin, it reacted to give two products. The minor product (9%) was estrone and the major product (79%), although tautomeric (m/e 288, M^+) with the desired allylic alcohol (112), exhibited absorptions (i.r., 1655 and 1619 cm^{-1}; u.v., 247 nm) indicative of an α,β-unsaturated ketone, namely (167). The ^1H n.m.r. showed only an apparent quartet for the 3-H, but the



(126) R = CH_2OH
(166) R = CO_2H

(112)

(167)

^{13}C n.m.r. spectrum [the more readily assignable downfield signals were: 219.92 (C-17), 182.23 and 181.58 (C-4), 159.31 and 158.26 (C-10), 129.67 (C-5), 71.91 and 71.83 (C-3)] indicated that it had been obtained as a mixture of epimers.

It is likely that the allylic alcohol (112) was initially formed but isomerized to the α,β-unsaturated ketone (167) under the reaction conditions. The estrone

formed may have arisen by the dehydration of the intermediate allylic alcohol since (167) was found to be stable to further reflux in decalin.

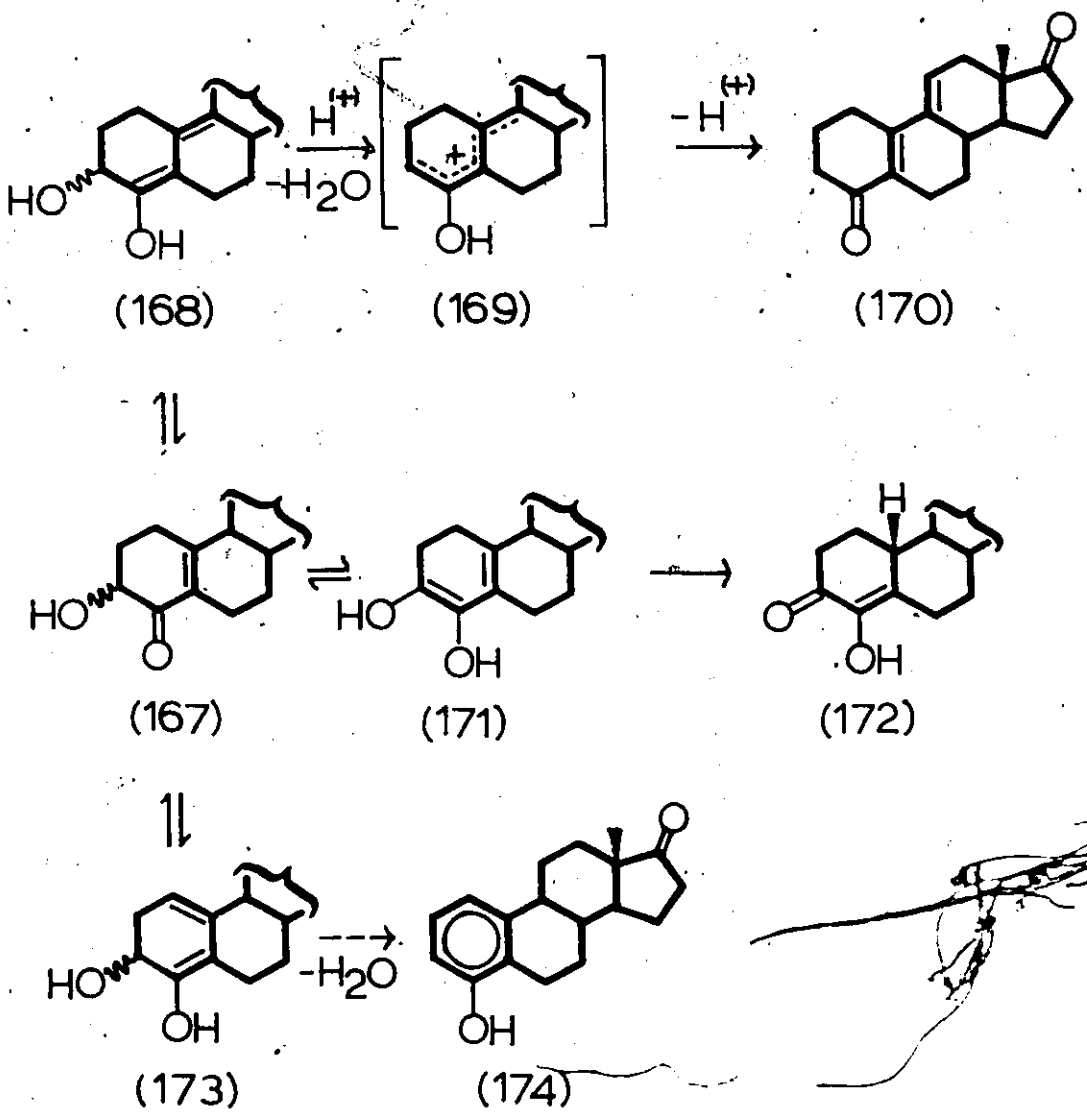
Since this 3-hydroxy-$\Delta^{5(10)}$-4-ketone system is novel in steroid chemistry, we briefly examined some of its properties. With base, (167) was found to isomerize to the diosphenol (172). This compound exhibited absorptions in the u.v. at 276 nm and in the i.r. at 1670 and 1650 cm^{-1} which would be consistent with this structure.

Under acidic conditions (70% perchloric acid-tetrahydrofuran), (167) was found to undergo dehydration to give a compound (m/e 270, M^+) whose i.r. spectrum indicated the presence of an $\alpha\beta,\gamma\delta$-unsaturated ketone (1655, 1605, 1590 cm^{-1}). Since the ^1H n.m.r. spectrum showed a single olefinic proton (δ 6.18) which was coupled with an adjacent centre, it was assigned structure (170). Although the λ_{max} (289 nm) was somewhat lower than may be expected[66] (306 nm), the chromophore is spread over three rings of the steroid and this may account for the observed deviation. The relatively large extinction coefficient (23,000) is consistent with a heteroannular diene system.

The acid- or base-catalyzed reactions of (167) would be expected to proceed via the enols (or enolates) corresponding to (168), (171) or (173) (SCHEME 17). Under basic conditions, isomerization to the diosphenol (172) proceeds

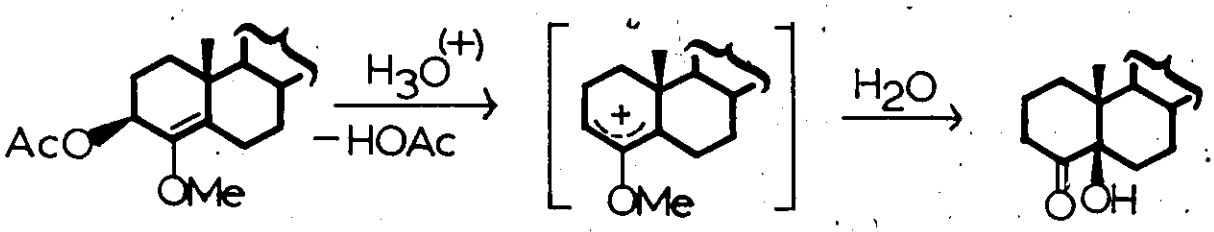
via the enolate corresponding to (171). However, under acidic conditions, it appears that the s-trans dienol (168) predominates or at least that the subsequent acid-catalyzed

SCHEME 17



dehydration [(168)→(169)→(170)] draws any possible equilibria with the other enols, (171) or (173), in this direction. This would mean that the enol (171), if formed isomerizes back to (167) more rapidly than protonation at C-10 since the diosphenol (172) was found to be stable under these reaction conditions.

The proposed dehydration sequence draws some support from the observation[67] that the enol ether (175) undergoes

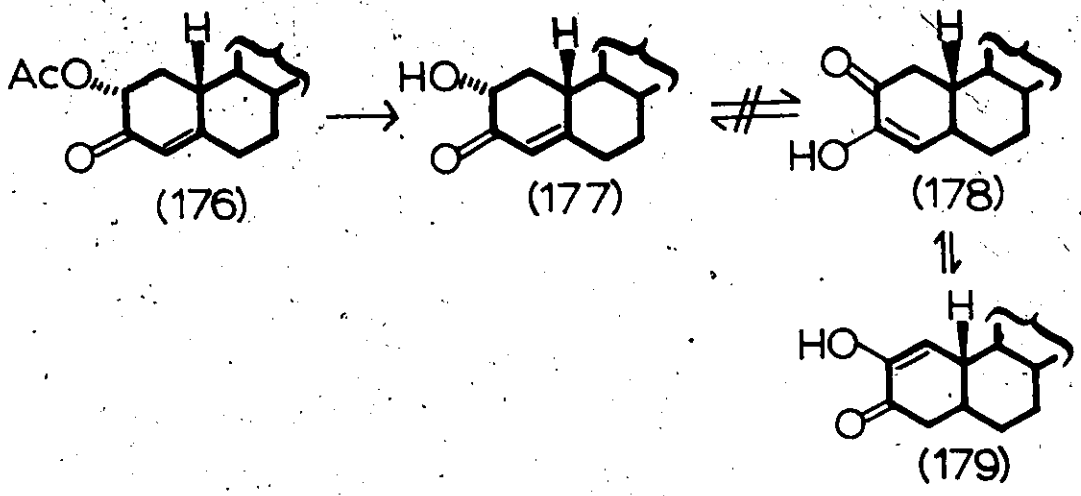


(175)

the loss of the allylic 3-substituent in preference to protonation at C-5 when treated with acid.

Unfortunately, it is not possible to make a comparison of the reactions observed for (167) with those of another system containing this arrangement of functionality since their properties have not been similarly examined. For example, the related 2α-hydroxy-Δ^4-3-ketone (177) would appear to be stable under basic conditions since it can be obtained[68] by the alkaline hydrolysis of the acetate (176). However, whether this reflects a thermodynamic preference

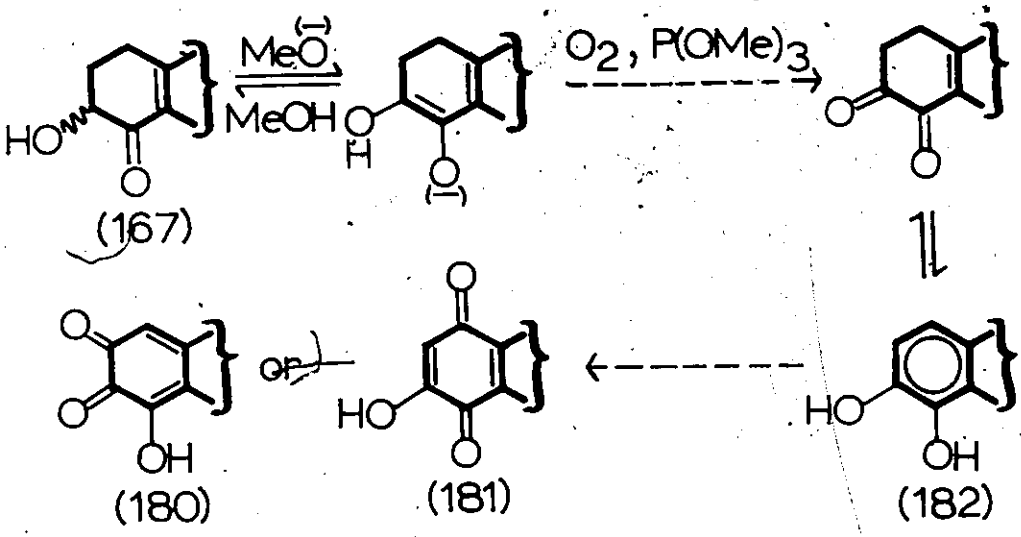
for (177) over (178) or (179) or just the fact that an equilibrium with the latter compounds was not established remains uncertain.

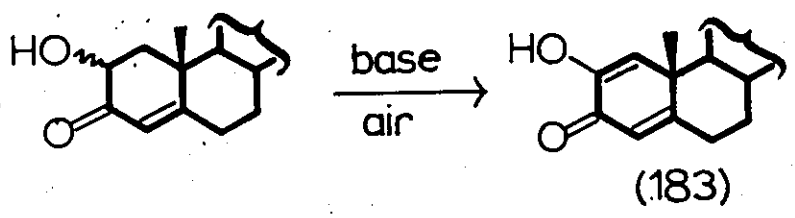


(176) (177) (178) (179)

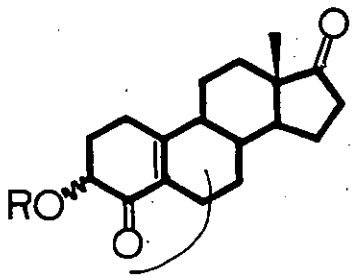
Two other features of (167) were also examined. It was noted that in the absence of a nitrogen atmosphere, an alkaline solution of (167) rapidly developed a red colouration which disappear on acidification. This was taken to indicate an air oxidation[69] and consequently the reaction of (167) in the presence of methanolic sodium methoxide and trimethyl phosphite under an oxygen atmosphere was examined. This afforded a yellow oil whose spectral data suggested that a quinone, possibly (180) or (181), had been obtained. It would seem reasonable to assume that the 4-hydroxy-estrone (182) was initially

formed since this would be analogous with the formation of the dienone[68] (183) under comparable conditions. The further oxidation of (182) would not be unexpected in view of the instability of 2-hydroxy-estrone[59] in alkaline media. However, due to a lack of starting material, this reaction was not further studied.



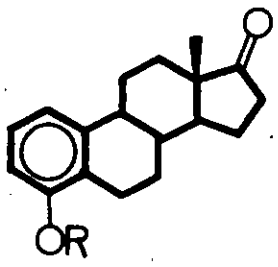


It was noted that if the s-cis dienol (173) (SCHEME 17) had undergone dehydration under acidic conditions, the 4-hydroxy isomer of estrone (174) would have been obtained. An attempt at preparing this compound by heating the 3-acetate (184) in refluxing decalin was unsuccessful since the compound proved to be stable under these conditions. However, the 3-mesylate (185) was found to undergo elimination in refluxing 2,4,6-collidine to give the somewhat obscure[70] 4-hydroxy-estra-1,3,5(10)-trien-17-one (174) which was isolated as its 4-acetate (186). The ^{13}C n.m.r. assignments of the aliphatic portion of this compound were made by comparison with those of the 3-acetyl derivative of estrone[71] (TABLE 4). The only major difference found



(184) R = Ac

(185) R = SO_2Me

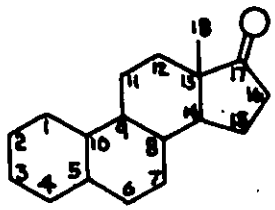


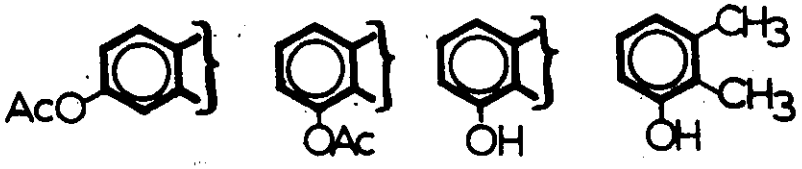
(174) R = H

(186) R = Ac

was an upfield shift of ca. 6 ppm for C-6. This shielding would be expected to arise from the ortho interaction[72] of C-6 with the C-4 substituent. The 3-acetate (186) was

TABLE 4. ^{13}C N.M.R. Chemical Shifts of 4-Hydroxy-Estra-1,3,5(10)-trien-17-one (174) and Analogues





Position	(187)[a]	(186)[b]	(174)[b]	(188)[c]	δ(186)-δ(174)
1	127.1	123.48	117.26	122.3	5.22
2	119.7	126.59	126.35	125.8	0.24
3	149.9	120.00	112.05	112.7	7.95
4	122.4	149.89	155.04	153.3	-5.15
5	138.3	129.34	123.84	122.3	5.50
6	30.0	23.87	23.93		
7	27.1	(26.36)	(26.74)		
8	38.9	38.10	38.32		
9	45.1	45.18	45.31		
10	139.0	142.54	142.09	137.6	0.45
11	26.5	(26.27)	(26.44)		
12	32.5	32.30	32.36		
13	48.2	47.94	47.98		
14	50.0	50.85	50.98		
15	22.1	21.90	21.95		
16	35.9	35.66	35.73		
17		223.12	223.13		
18	13.8	13.62	13.68		
CH_3	20.7	20.27			
$O=C$		168.87			

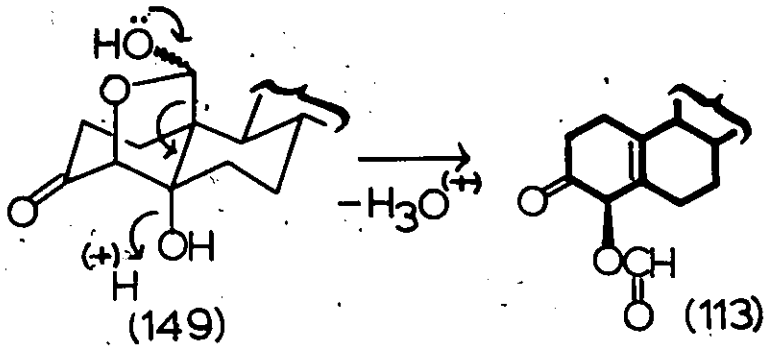
a solvent, dioxone; ref. 71
b solvent, dioxone; values in parenthesis may be interchanged
c solvent, $CDCl_3$; ref. 74; steroid numbering used

hydrolyzed to the known 4-alcohol (174). The u.v. spectrum of (174) had a λ_{max} at 275 nm (ε 1,900) which is similar to that observed[73] for 2,3-dimethyl phenol (188) (λ_{max} 276 nm, ε 1,800). The aliphatic portion of (174) exhibited similar ^{13}C n.m.r. chemical shifts as its 4-acetate derivative (186). The assignments for the aromatic carbon atoms were made by comparison with those of 2,3-dimethyl phenol[74] (188) (TABLE 4) and from the acetylation shifts[75] (downfield for the ortho and para carbons; upfield for the acetate bearing carbon).

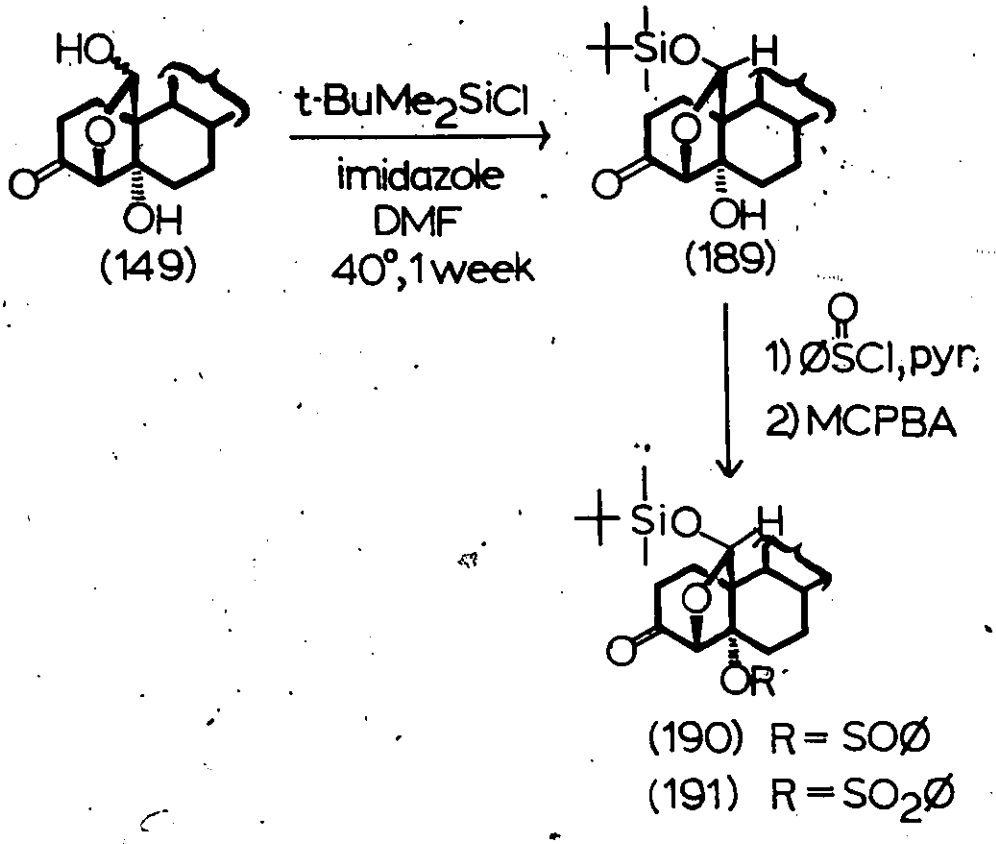
2. Attempted Fragmentation of (19R)-19-t-Butyldimethylsilyloxy-5-hydroxy-4β,19-oxido-5α-androstane-3,17-dione (191)

It was originally suggested[17] that (149) may undergo a fragmentation reaction to give the formate (113). Although this would now appear unlikely in view of the stability of (149) under acidic conditions, the reaction may occur if the 5α-hydroxy group were converted to a good leaving group such as a sulfonate ester. Furthermore, if the reaction proceeded under sufficiently mild conditions, it may be possible to isolate the formate (113).

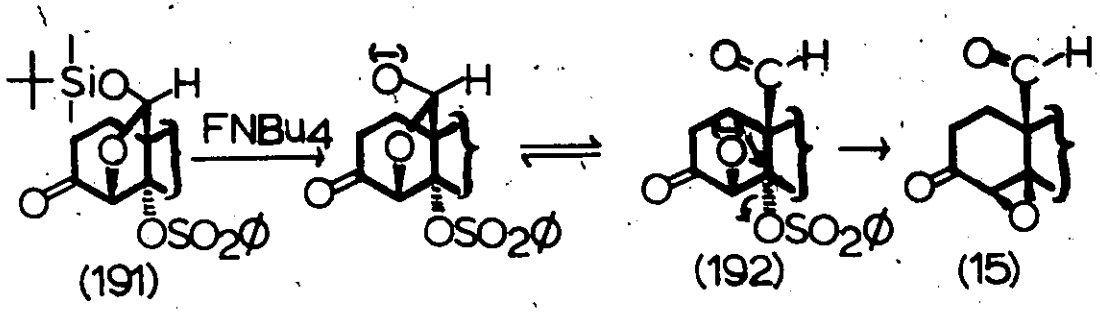
It was thought that a good substrate with which to examine the feasibility of this approach would be the sulfonate ester (191). This compound was prepared by the



following sequence of reactions. The hemiacetal (149) was converted, under somewhat forcing conditions, to the 19-t-butyldimethylsilyl ether (189). Only one of the 19-epimers (^{1}H n.m.r.) was obtained and this was presumably the 19-R diastereomer. The tertiary alcohol (189) was then allowed to react[76] with phenylsulfinyl chloride in pyridine to give the sulfinate ester (190). The ^{1}H n.m.r. spectrum of this compound, a doublet (δ 3.98 and 4.12) for the 4α-hydrogen atom and a singlet (δ 5.80) for the 19-hydrogen atom, indicated that this introduction of a new asymmetric centre had produced a mixture of diastereomers. Oxidation of (190) afforded the sulfonate ester (191) whose ^{1}H n.m.r. spectrum only showed singlets for the 4α-hydrogen atom (δ 4.35) and the 19-hydrogen atom (δ 5.70).



The fragmentation of (191) was then attempted by allowing it to react with tetrabutylammonium fluoride. Unfortunately, the rapid reaction which ensued simply gave the 4β,5β-epoxy-aldehyde (15). Evidently, the hemiacetal which is initially formed is in equilibrium with the hydroxy-aldehyde (192) and the latter rapidly undergoes epoxide formation.

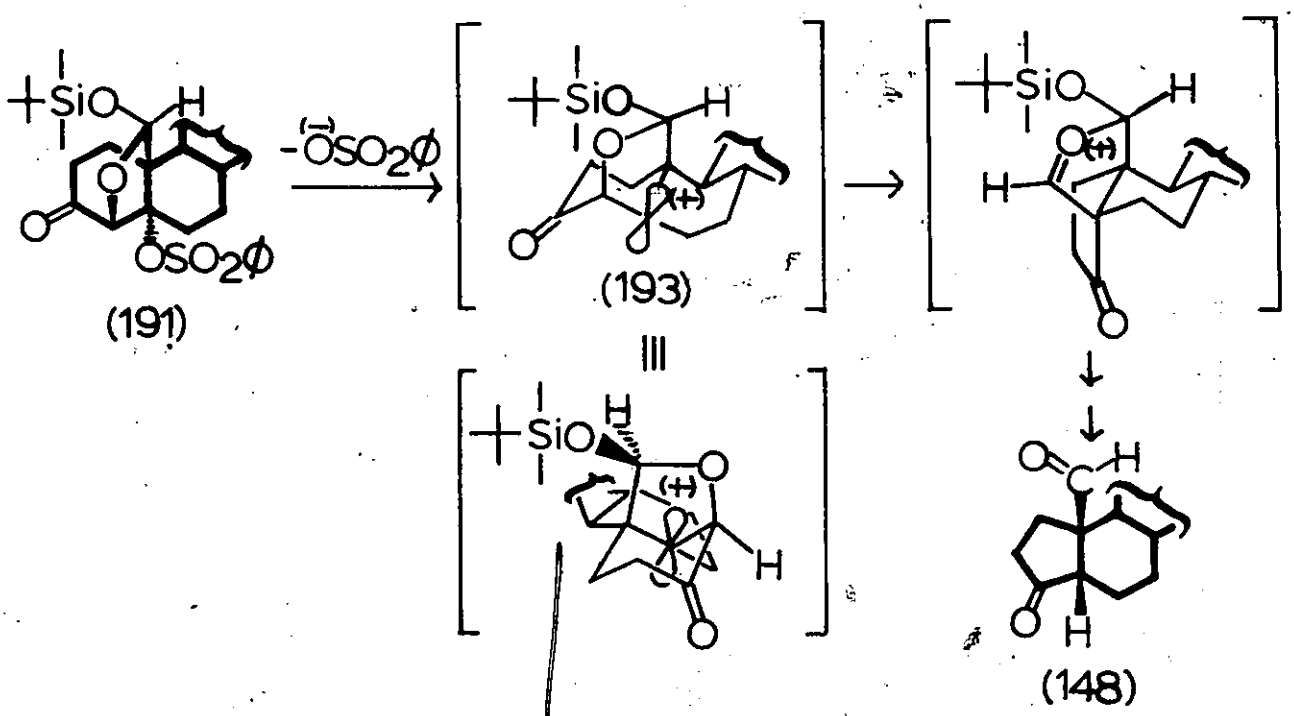


(191) (192) (15)

A fragmentation initiated by the solvolysis of the sulfonate ester (191) was then examined. It was found to react very slowly (ca. 54 h) when heated at reflux temperature in acetic acid containing sodium acetate. The major component of the reaction mixture was isolated but was found to consist (^{1}H n.m.r.) of a 6:1 mixture of the A-nor-aldehyde (148) and the 5α-alcohol (189). Since they both had the same R_f value, the mixture was treated with tetrabutylammonium fluoride to convert the silyl ether (189) to the hemiacetal (149). Chromatography allowed for the isolation of the A-nor compound (148) in a 36% yield.

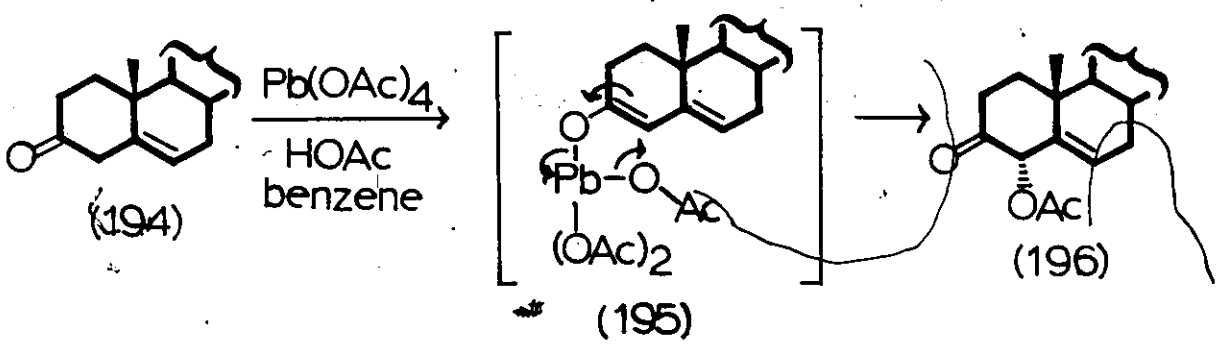
Since the epoxide (15) was not observed (t.l.c.) during the course of the reaction, its involvement can be ruled out. It would therefore appear that the ionization of the C(5)-O bond occurs prior to the loss of the silyl group. This may, in part, account for the difficulty

encountered in bringing this reaction about since the acetal bridge would impart a certain degree of rigidity to the A and B rings which would make it difficult to accommodate an sp^2 hybridized centre at C-5. However, once formed, the carbocation (193) may adopt a conformation where the B ring is boat-like and the C(3)-C(4) bond is well disposed for migration. This then leads to contraction of the A ring and ultimately to the A-nor-aldehyde (148). It is not readily apparent why cleavage of the C(19)-C(10) bond does not occur during the ionization process or after the carbocation has formed.



3. Reaction of Estr-5(10)-ene-3,17-dione (198) with Lead Tetraacetate

Fieser[77] has reported that the β,γ-unsaturated ketone (194) reacted with lead tetraacetate to give the unconjugated acetoxy compound (196). This reaction probably proceeds[78] via the lead enolate (195) which may react in an intramolecular fashion to give (196).

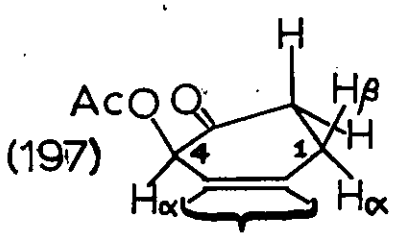


When this reaction was examined with estr-$\Delta^{5(10)}$-ene-3,17-dione (198), it was found to produce a very complicated mixture of products. However, when conducted under a nitrogen atmosphere with an excess of lead tetraacetate, it was found to be much cleaner. The attempts to isolate the major component by column chromatography were complicated by the fact that estrone, although not present (t.l.c.) in the reaction mixture after workup, eluted together with this

compound. This indicated that some compound in the reaction mixture was undergoing decomposition on the silica gel column to give estrone. The origin of the estrone was deduced by spotting the reaction mixture on a t.l.c. plate and warming it for a short period of time prior to its development with the appropriate solvent. In this way, it was found that estrone was being formed at the expense of the major component of the reaction. Those fractions of this component which were least contaminated with estrone were combined and examined.

The mass spectrum (m/e 330, M^+) of this component indicated that the substitution of an acetoxy group for a hydrogen atom had occurred and its i.r. spectrum (1730 cm^{-1}) demonstrated the absence of a conjugated ketone. The ^1H n.m.r. spectrum (FIGURE 3) showed two multiplets (δ 5.49 , 0.4 H, W/2 ca. 6 Hz and δ 5.81, 0.6 H, W/2 ca. 6 Hz). This would indicate that the acetate (199) had been obtained as a mixture of epimers at C-4 and that the hydrogen atom at this centre was undergoing long range coupling* with the hydrogen atoms at C-1 and C-2. It was

*For example, if the A ring in (199) assumed a 2β-sofa conformation[79] (197), a ca. 6 Hz half band width would not be unreasonable for the 4β-epimer from a consideration of the 5-bond H,H couplings[80] and the 4-bond H,H coupling[81].



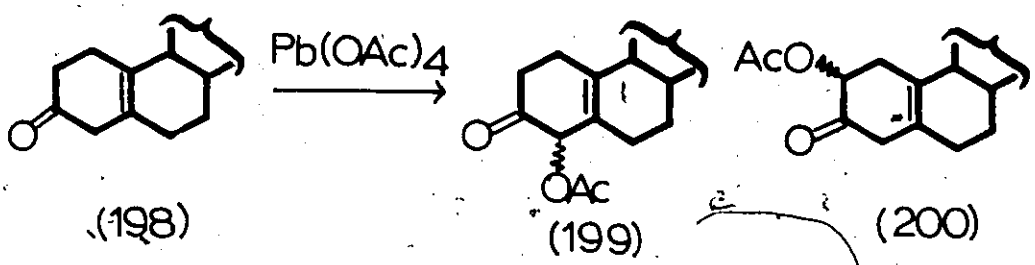
(197)

$\phi(1\beta\text{-H}) \approx 150^\circ$
$\phi(I\beta\text{-H}) \approx 270^\circ$
$\phi(4\beta\text{-H}) \approx 120^\circ$

$^5J_{1\beta\text{-H},\ 4\alpha\text{-H}} \approx 1$ Hz
$^5J_{1\alpha\text{-H},\ 4\alpha\text{-H}} \approx 4$ Hz

$^4J_{2\alpha\text{-H},\ 4\alpha\text{-H}} \approx 1$ Hz

also noted that the broad singlet (δ 2.77, ca. 2H), which was present in the starting material (FIGURE 4) and is presumably due to the C-4 hydrogen atoms, was absent in the 4-acetoxy compound (199) obtained. A C-2 substituted derivative (200), although unlikely in view of the mild conditions employed[82], would be ruled out by this observation.



The reactions of (199) under acidic and basic conditions as well as its thermal stability were examined and the results are presented in TABLE 5. These reactions were conducted with crude material which contained some estrone (t.l.c.). However, since estrone was not observed in the ^1H n.m.r. spectrum of this material, it probably represents less than 5% of the mixture. The reactions were conducted under nitrogen, monitored by t.l.c. and the estrone which was obtained was isolated and identified as its 3-acetate derivative.

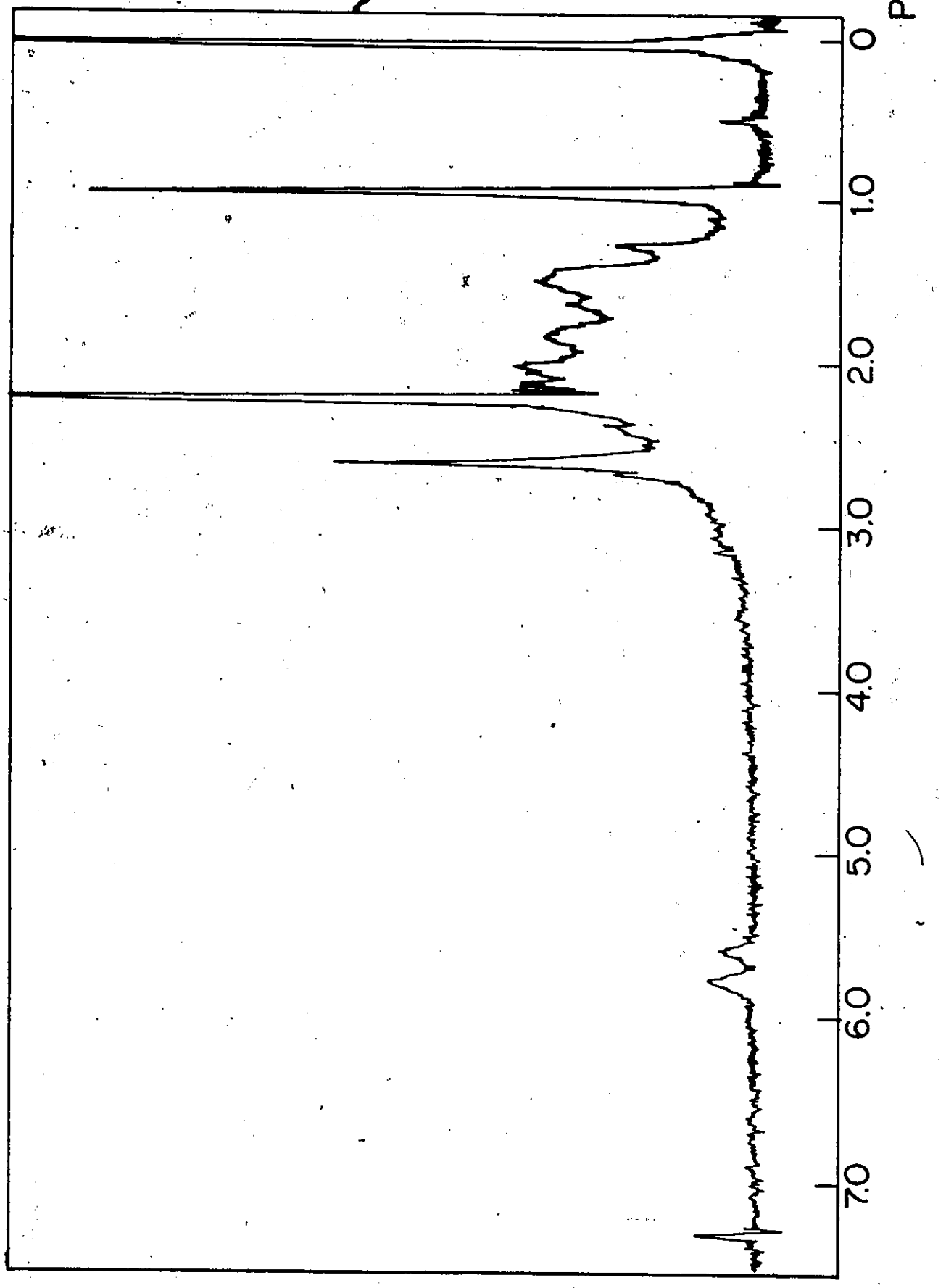


FIGURE 3. 60 Mg Hz ^{1}H N.M.R. spectrum of 4ξ-Acetoxy-estr-5(10)-ene-3,17-dione (199)

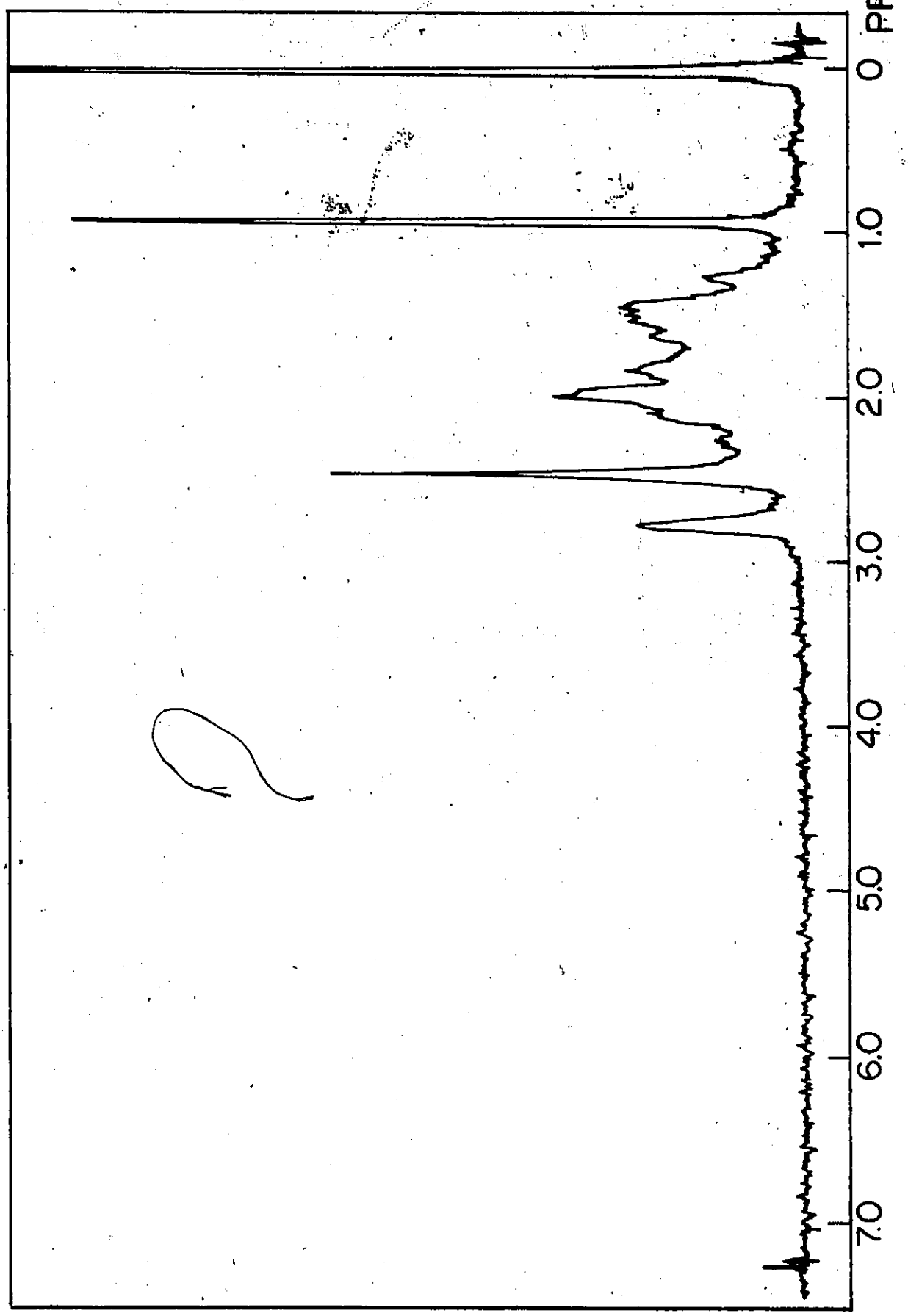
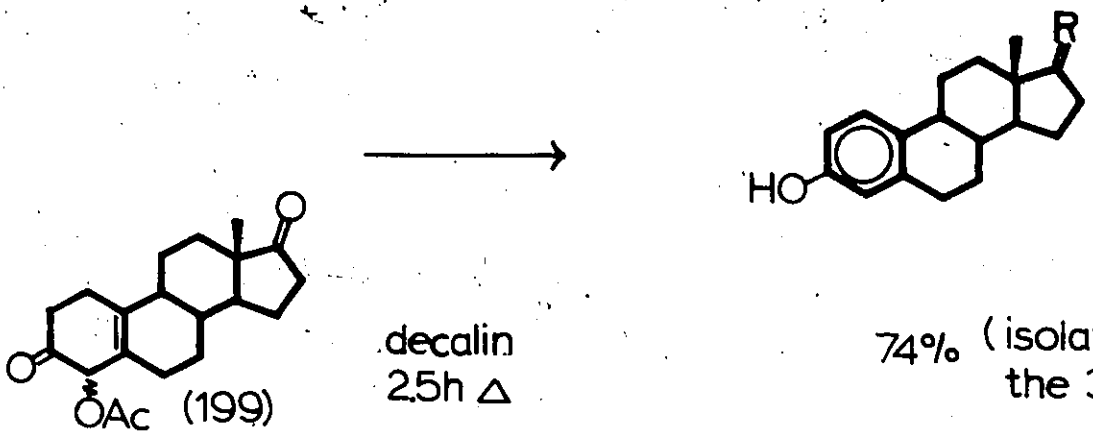


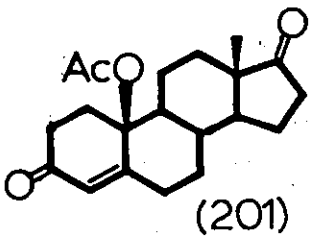
FIGURE 4, 60 Mg Hz ^{1}H N.M.R. spectrum of Estr-5(10)-ene-3,17-dione (198)

TABLE 5. Aromatization of 4ξ-Acetoxy-estr-5(10)-ene-3,17-dione (199) and Some Analogues



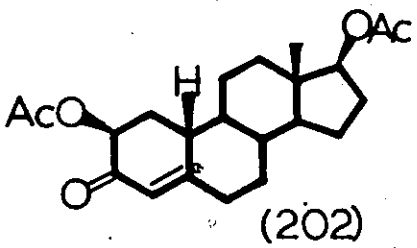
(199)

	decalin 2.5h Δ	74%	(isolated as the 3-acetate)
"	$HClO_4$ / THF 3h, R.T.	46%	"
"	NaOMe / MeOH 15min, R.T.	65%	"
"	2.1 M phosphate buffer pH 7.5, 10h, R.T.	74%	"



(201)

	$HClO_4$ / EtOH 48h, R.T.	72%	(obtained as the 3-ethyl ether, ref. 83)
"	NaOH / MeOH 3h, R.T.	98%	(ref. 83)
"	tetralin 3h, Δ	71%	(ref. 84)

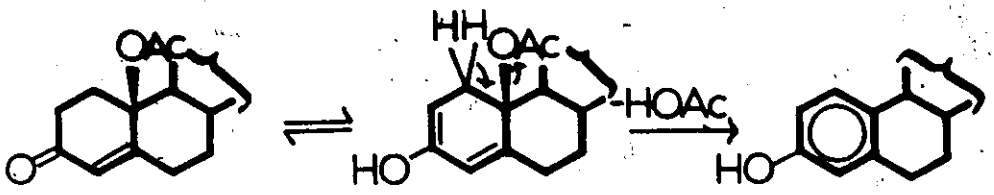


(202)

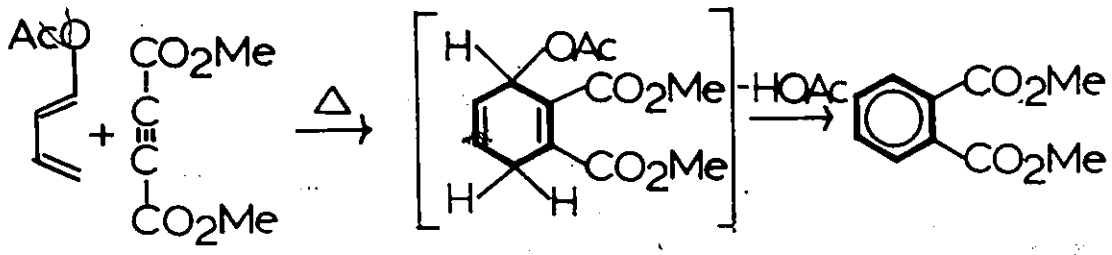
	NaOAc / HOAc 15h, Δ	80%	(ref. 68)
"	KOH / MeOH 10min, Δ	0%	(saponification of the acetate, ref. 86)

It can be seen from TABLE 5 that under all the conditions examined, the major product of the reaction was estrone. Although it was initially hoped that under sufficiently mild conditions it may be possible to saponify the 4-acetate group, it was found that aromatization occurred with a phosphate buffer at pH 7.5.

The reactions of (199) are somewhat similar to those that have been observed (TABLE 5) with the 10β-acetoxy compound (201). In the latter case, it was suggested[83] that the elimination of acetic acid occurred after (201) had undergone enolization to (203). For the 4-acetoxy compound (199) it would be reasonable to assume that the elimination proceeds <u>via</u> a similar enol, namely (205) (SCHEME 18). The thermal reaction of (199) would certainly bear a strong resemblance to the facile 1,4 elimination which occurs[85] in the initially formed Diels Alder adduct (204). However, the enol (205) would only be present in very small concentrations since it would be expected to be both thermodynamically and kinetically less favoured than the alternate enol (206). Furthermore, since (206) can rearrange to the diosphenol (207) or to the $\Delta^{5(10)}$-4-ketone (208), both of which are not estrone precursors, the elimination of acetic acid from (205) must occur at a significantly greater rate than the

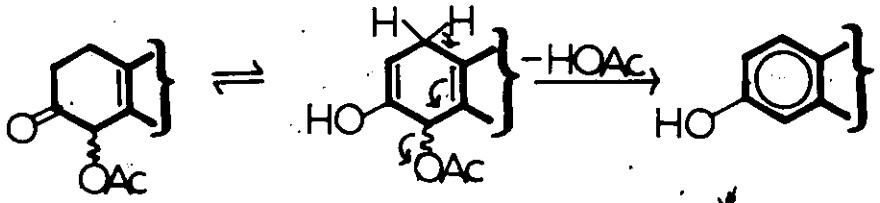


(201) (203)

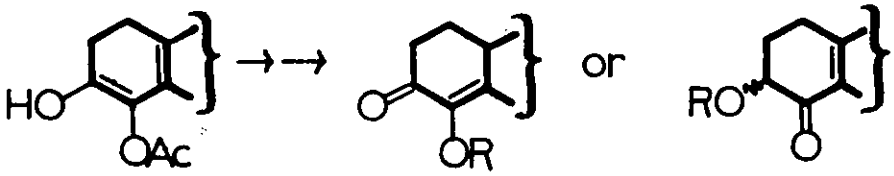


(204)

SCHEME 18



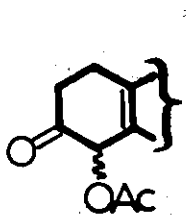
(199) (205)



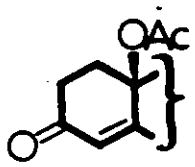
(206) (207) (208)

isomerization of (206). It is difficult to suggest a reason why this elimination should be so facile since it is undoubtedly following mechanistically different pathways depending on the reaction conditions used. However, it is noted that in those instances where the reaction may be concerted, some degree of aromatic character may already be realized in the transition state of the elimination process and this may significantly lower its activation energy.

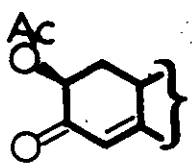
An observation can be made regarding the ease with which the base-catalyzed elimination proceeds. From the results in TABLE 5, it can be seen that (199) is more reactive than (201) whereas (202) simply undergoes saponification of the acetate group. It would be of interest to see where (209) and (210) would fit into such



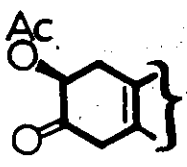
(199)



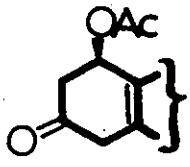
(201)



(202)



(209)



(210)

a sequence. since, as will be shown in the next section, such species may be involved in the last stages of estrone biosynthesis.

The possible intermediacy of the allylic alcohol (112) in the formation of estrone from the 4α,5α- and 4β,5β-epoxy aldehydes (15) and (16) still remains an open question. Although the allylic acetate (165) does readily undergo elimination to give estrone, the allylic alcohol (112) may possess quite different properties.

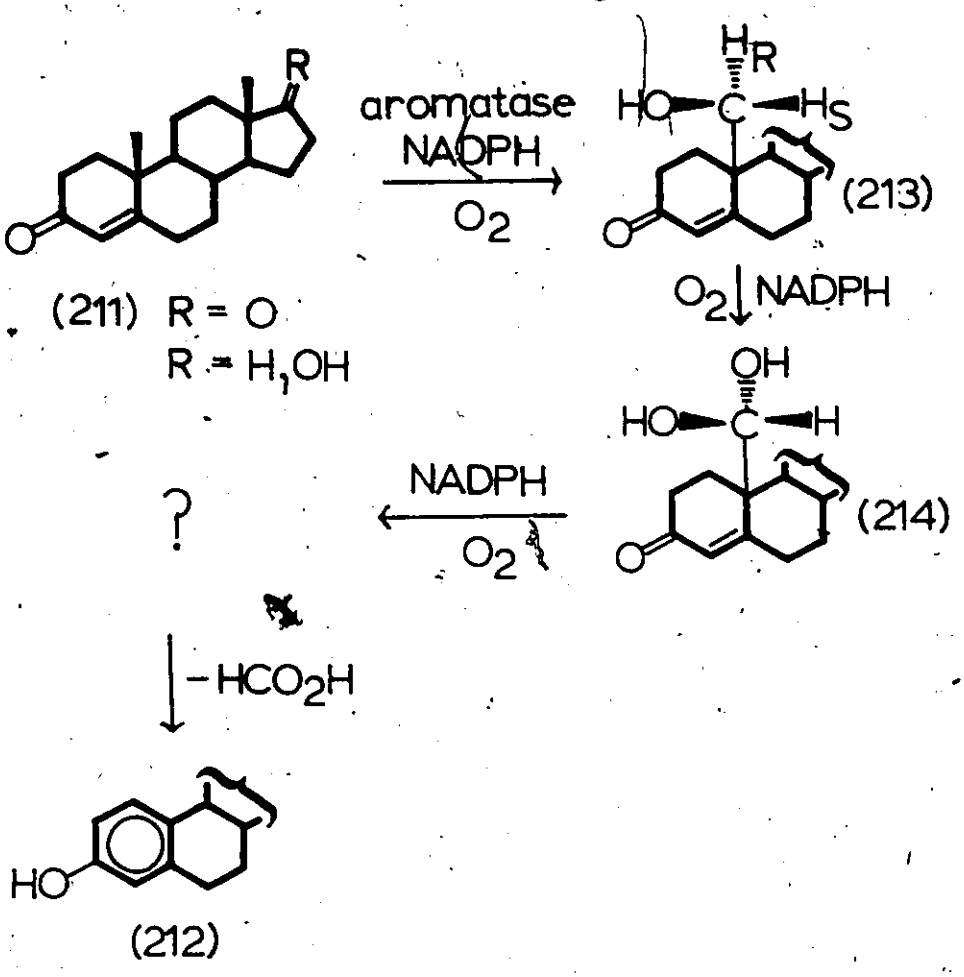
PART V

The Intermediacy of 19-Oxo-4,5-epoxy-androstane-3,17-diones in Estrone Biosynthesis

The conversion[86] of androgens (211) to estrogens (212) is effected by a complex of microsomal enzymes referred to as aromatase. This transformation has been shown to involve the loss of the C-10 methyl group as formic acid as well as the stereospecific loss of the 1β- and 2β-hydrogen atoms. The cofactors required are oxygen and NADPH in the ratio of 3 moles for each mole of estrogen produced. The latter observation indicated that the androgen undergoes 3 oxidations to produce the penultimate precursor of estrone. The first oxidation (SCHEME 19), a hydroxylation, produces the 10β-hydroxymethyl compound (213). The second oxidation involves the stereospecific replacement of the 19-pro-R hydrogen atom by a hydroxy group to give the acetal (214). The nature and site of the last oxidation remains unknown, although it has been the subject of much speculation. The different proposals which have been suggested for this step will be briefly discussed.

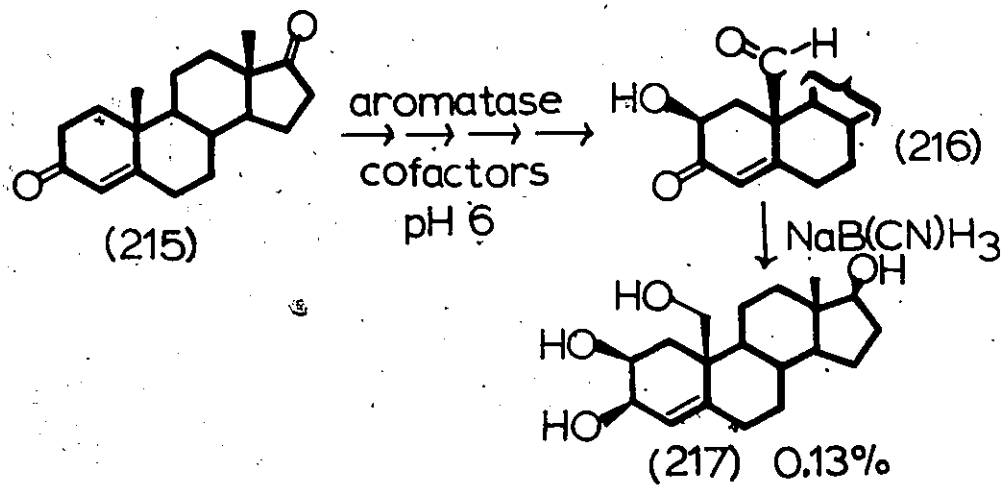
Fishman[61,86] has proposed that the last oxidation is a hydroxylation which produces the 2β-hydroxy compound (216). The latter was synthesized[61] and found to be surprisingly reactive; e.g. a solution of (216) in a phosphate buffer

SCHEME 19



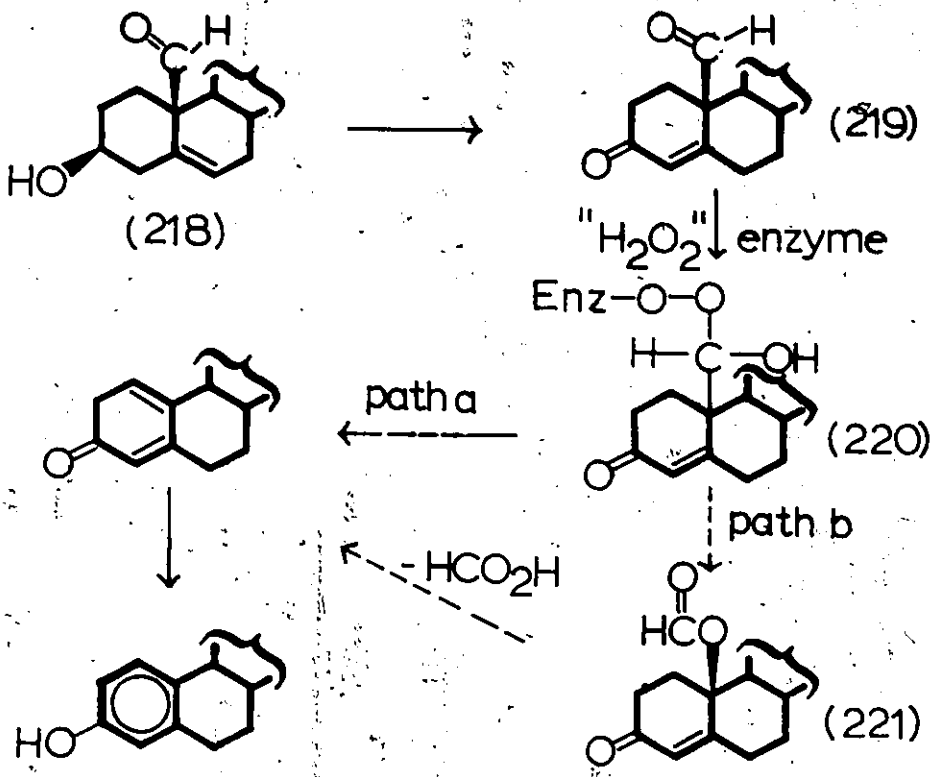
(pH 7) readily underwent aromatization ($t_{\frac{1}{2}}$ 90 sec., 37°C) to give estrone. This would indicate that if the 2β-hydroxy compound were the penultimate estrone precursor, its conversion to estrone would be nonenzymatic. Support for the formation of this intermediate was obtained by incubating[86]

labelled androst-4-ene-3,17-dione (215) with the aromatase system at a lower than optimal pH [conditions under which the 2β-hydroxy compound (216) would be more stable]. The products isolated were reduced and the labelled tetrol (217) was indeed obtained, albeit in a very low yield.



The results obtained by Akhtar[87] were taken to indicate the involvement of a peroxide. It was found that when the aldehyde (219), generated *in situ* from the 3β-hydroxy-19-aldehyde (218), was incubated with the enzyme system in the presence of oxygen containing excess $^{18}O_2$, the formic acid expelled contained excess ^{18}O. It was suggested (SCHEME 20) that a peroxide reacts with the aldehyde group to give the hypothetical intermediate (220). This species could either rearrange directly (Path a) to estrone or proceed in this direction (Path b) *via* a Baeyer-Villiger intermediate (221).

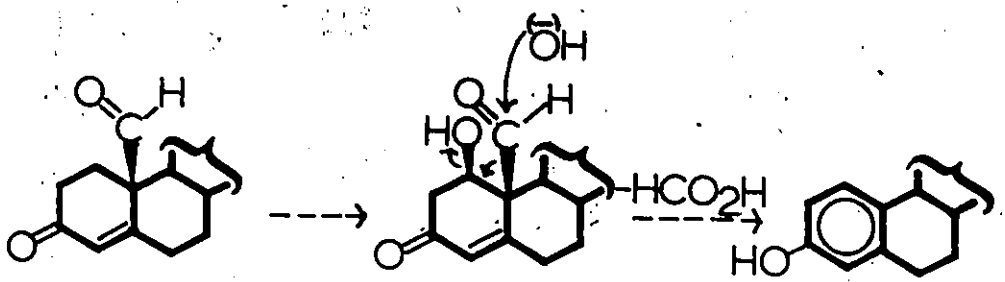
SCHEME 20



Another mechanism (SCHEME 21), involving 1β-hydroxylation to give (222), has been suggested[87] since it is the 1β-hydrogen atom which is eliminated[88] in estrone biosynthesis.

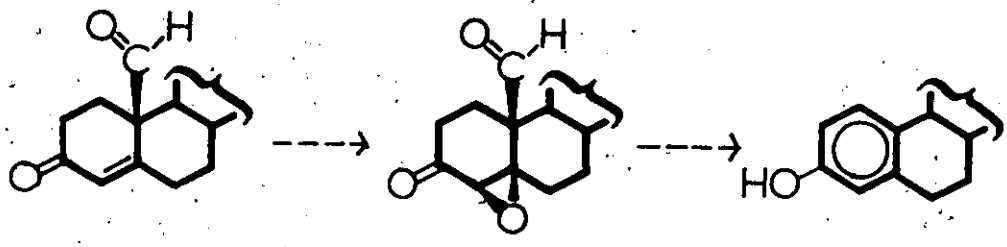
Morand et al have postulated[16,17] that the last oxidation may involve the formation of a 4β,5β-epoxide (15). The mechanism that was proposed for the conversion of (15) to

SCHEME 21

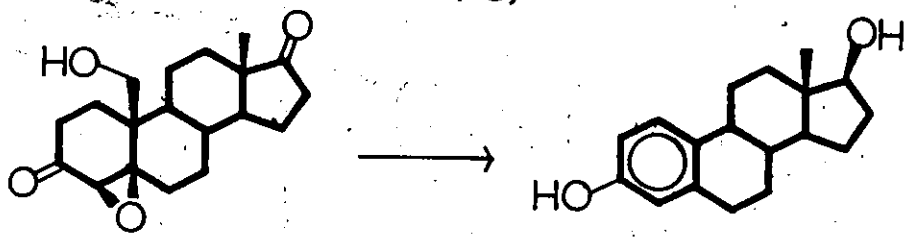


(222)

estrone was outlined previously (cf. page 58). Support for the involvement of this intermediate came from the observation[16] that the 19-hydroxy-4β,5β-epoxide (126) was converted to estradiol by the aromatase system.



(15)



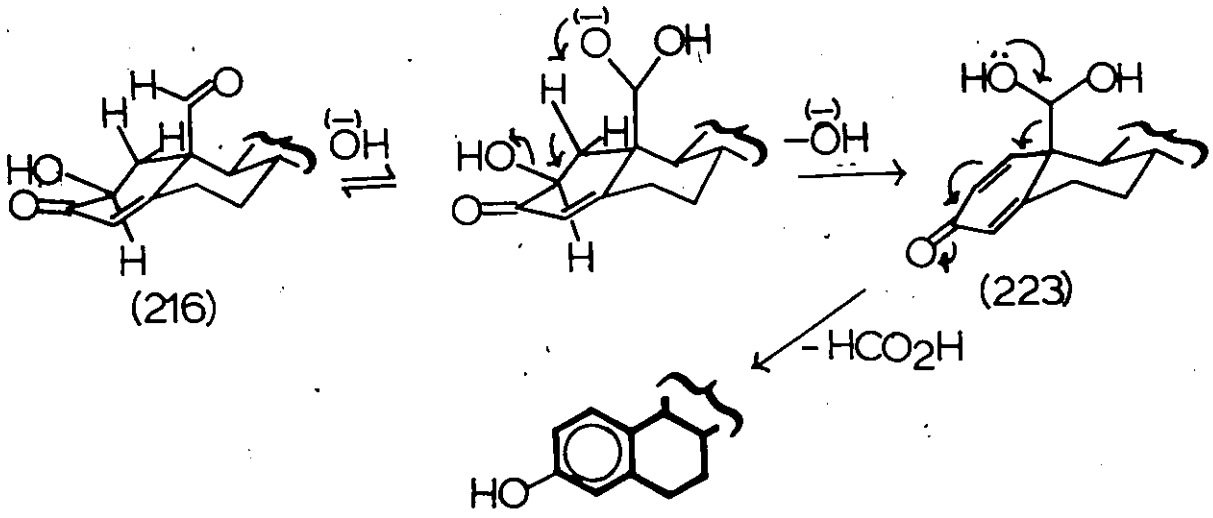
(126)

It was shown previously (Part III of this thesis) that only small yields of estrone could be obtained from the 4β,5β-epoxide (15) by chemical means. Therefore, if (15) were indeed an intermediate in estrone biosynthesis, its conversion to the latter would have to be effected enzymatically. To see if this was indeed the case, the 4β,5β-epoxide (15), as well as its 4α,5α isomer were incubated[89] with the aromatase system contained in placental microsomes. To our disappointment, it was found that neither of these compounds was converted to phenolic products. As well, for reasons unknown, it was no longer possible to obtain the relatively high yields of estradiol that had been previously observed with the 19-hydroxy-4β,5β-epoxide (126). Studies in which the incubation conditions were systematically varied did not provide a solution to this puzzling discrepancy. Therefore, on the basis of the experiments performed to date, it must be concluded that an epoxide is not an obligatory intermediate in the biosynthesis of estrogens.

Of the other mechanisms which were proposed, only that of Akhtar[87] is consistent with all of the known features of this process. The fact that the oxygen atom, introduced in the last enzymatic oxidation, is found in the C(19)-derived formate fragment would appear to rule out a 2β hydroxylation as was proposed by Fishman[86]. However, the latter mechanism involving the non-enzymatic aromatization of the 2β-hydroxy compound (212) is rather unusual and does deserve further consideration.

Fishman[61] postulated that this aromatization (SCHEME 22) involved the elimination of water from the 2β-hydroxy compound (216) to give the dienone (223) which then underwent deformylation to estrone. While it was found that (216) readily aromatized in neutral or slightly alkaline media, the isomeric 2α-hydroxy compound (150) was stable under these conditions. This difference in behaviour was attributed

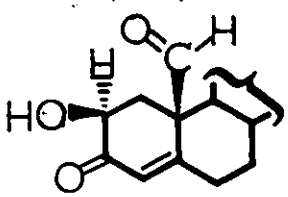
SCHEME 22



to different conformations of the A ring in these two compounds. On the basis of ^1H n.m.r. data, the 2β-hydroxy compound (216) was thought to possess a quasi-cis A/B ring

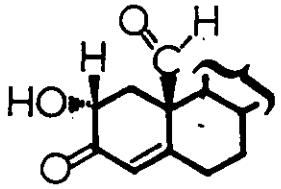
junction*. In this conformation, the 1β-hydrogen would be pseudo axial. It was suggested that this orientation of the 1β-hydrogen atom was ideally suited for a facile elimination of water since "anchimeric" assistance by the conjugate base of the hemiacetal was possible. The 2α-hydroxy compound (150) had a quasi-trans A/B ring junction* where the 1β-

*The ^{1}H n.m.r. data that were reported for (216) would be more consistent with a "half boat" conformation, e.g., (255)[59], for the A ring rather than the 2α-sofa conformation of the A ring in a compound possessing a quasi-cis A/B ring junction e.g., (224)[59]. However, for 2β-substituted 4-en-3-ones, recent work[80] has shown that there is at most only a small preference for a quasi-cis conformation and therefore it would seem that generalizations regarding the conformation in different solvent systems (i.e. extrapolating results obtained in deuterochloroform to aqueous ethanol) should be made with caution. The 2α-hydroxy compound (150) exhibited couplings that were comparable to those observed in other systems possessing a quasi-trans A/B ring junction, e.g., (226)[59].



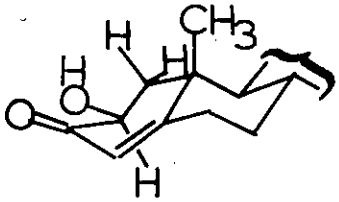
(216)

2α-H coupling
J = 6,8 Hz



(150)

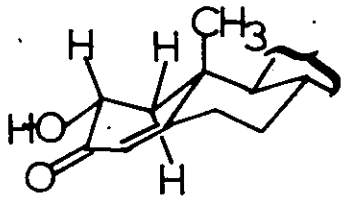
2β-H coupling
J = 6,13 Hz



(224)

quasi-cis

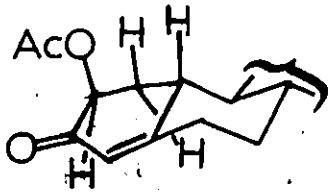
$J_{2\alpha,1\beta} = 14.4$ Hz
$J_{2\alpha,1\alpha} = 5.4$ Hz



(226)

quasi-trans

$J_{2\beta,1\alpha} = 13.6$ Hz
$J_{2\beta,1\beta} = 5.6$ Hz



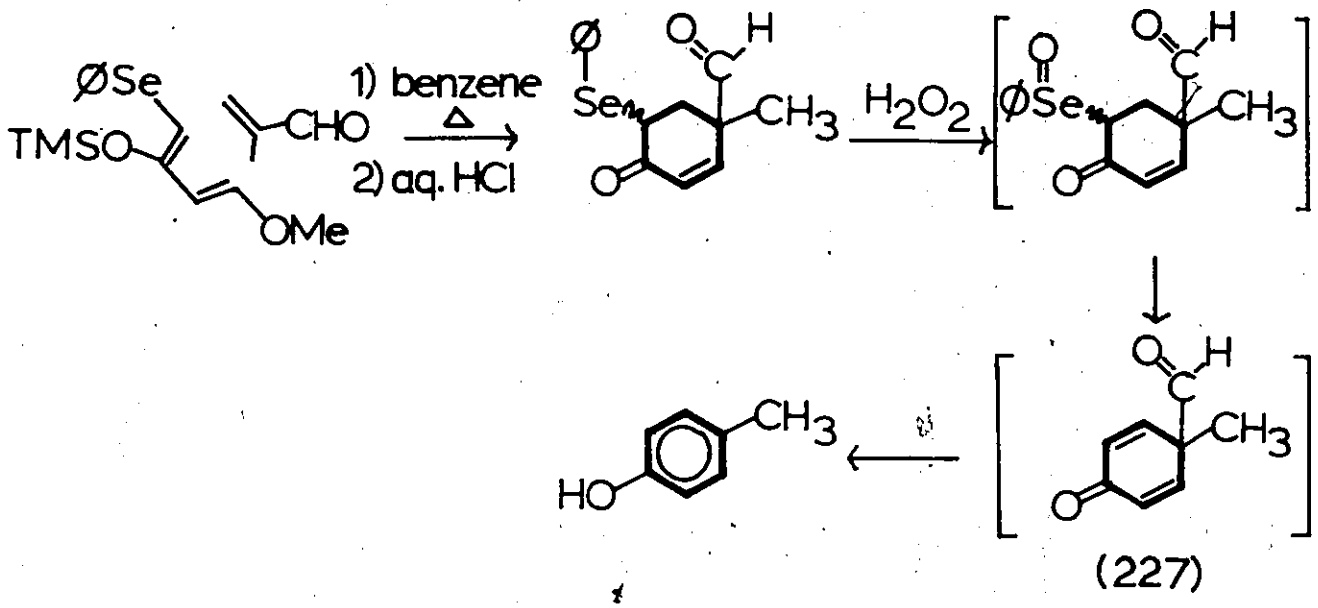
(225)

"half boat"

$J_{2\alpha,1\beta} = 7.9$ Hz
$J_{2\alpha,1\alpha} = 7.9$ Hz

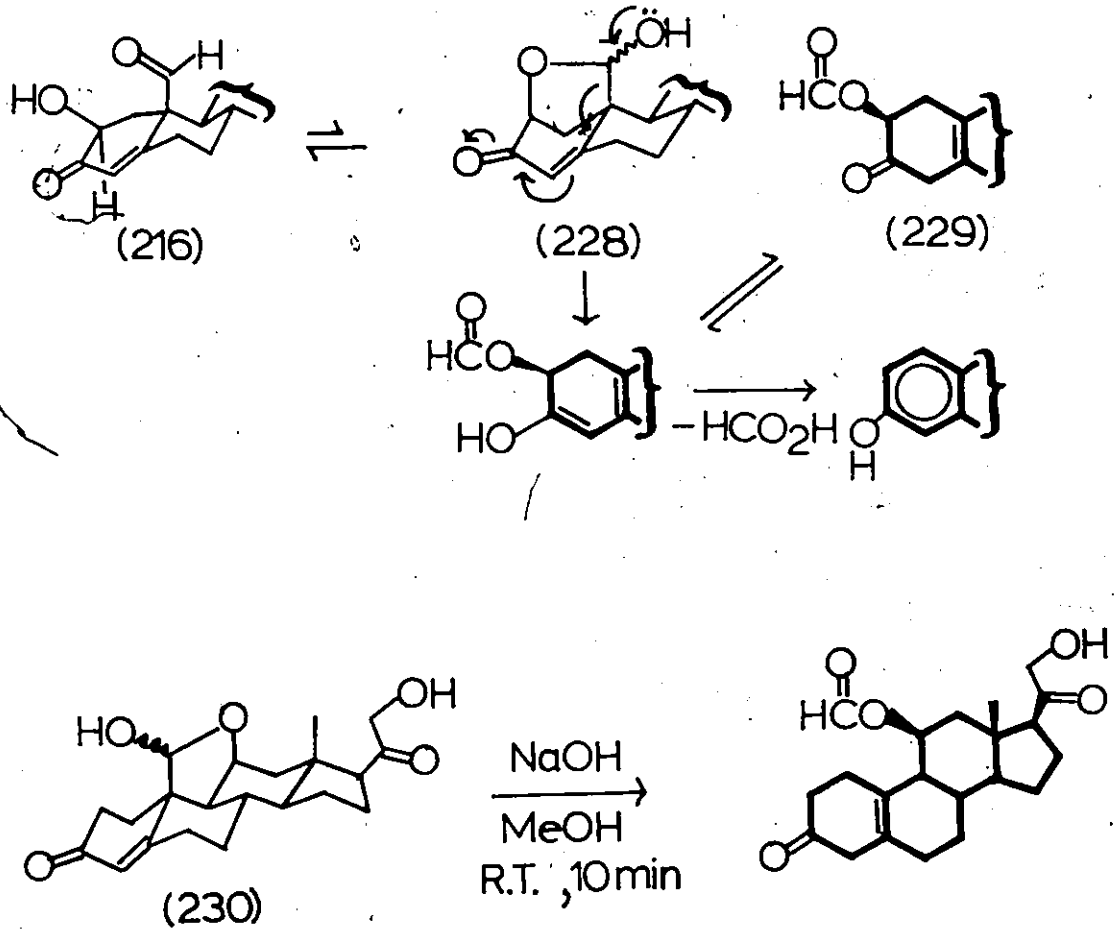
hydrogen atom would be in a pseudo equatorial position. Since this would remove the 1β-hydrogen atom from the proximity of the 10-function, "anchimeric" assistance was no longer possible and hence this compound did not ungergo the elimination of water.

This explanation is rather questionable and the reference cited, studies by Grob[91] on the intramolecular E2 reaction of γ-chloroamines, is not very supportive. Recent work by Danishefsky[92] on the attempted synthesis of the dienone (227) would indicate that a facile elimination is possible in a related system. However, in the latter case, this is not surprising since α-ketoselenoxides normally undergo elimination[93] at or below room temperature. It remains difficult to accept that the 2β-hydroxy compound (216) may possess a comparable reactivity.

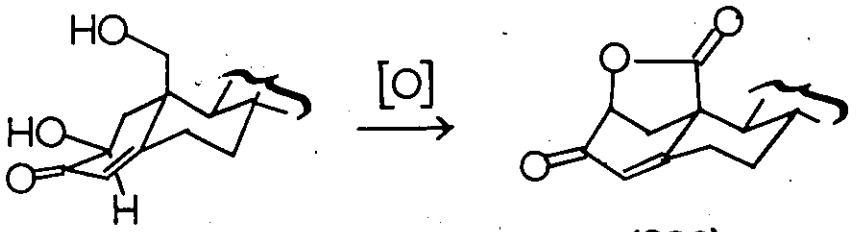


It is suggested that the differences observed in the reactivity of the 2β- and 2α-hydroxy compounds, (216) and (150), may possibly arise from the ability of 2β-isomer (216) to undergo an intramolecular deformylation (SCHEME 23) as was observed[94] with the corticosteroid (230). Although

SCHEME 23



the spectral data that were reported for (216) did not indicate the existence of the hemiacetal (228), the presence of an equilibrium with this species is suggested by the fact that oxidation of the 2β,19-diol (231) resulted in the formation of the γ-lactone (232). The



(231) (232)

2β-formate (229) which would arise via an intramolecular deformylation may be capable of undergoing a rapid elimination of formic acid as was observed previously (Part IV, Section 3) with the 4-acetoxy-Δ5(10)-en-3-one (199). In such a mechanism, the 2β-hydroxy group would be lost as formic acid and this would be consistent with the observations of Akhtar[87] regarding the fate of the last oxygen atom that was introduced. Similarly, the 1β-hydroxy compound [87](222) may be capable of undergoing an intramolecular deformylation and subsequent aromatization. If these compounds did indeed react in such a manner, it would then be difficult to distinguish between these mechanisms on the basis of the

known facts surrounding the breakdown of the last intermediate in estrone biosynthesis. However, the effect of incubating quantities of the final intermediate along with androst-4-en-3-one (215) on the yields of the 19-oxygenated intermediates, (213) and (214), may provide an answer.*

*Fishman[86] did find that the 2β-hydroxy compound (216) inhibited the production of (213) and (214).

EXPERIMENTAL

General

Melting points were determined on a Hoover Uni-melt apparatus and are uncorrected. Optical rotations are for chloroform solutions using a Perkin-Elmer 141 polarimeter. I.r. spectra were recorded on a Beckman IR-8 spectrophotometer using chloroform solutions. U.v. spectra were obtained on a Bausch and Lomb Spectronic 600 instrument. ^{1}H n.m.r. spectra were obtained on a Varian T-60 or H-100 instrument using deutorchloroform as solvent and tetramethylsylsilane as an internal standard. ^{13}C n.m.r. spectra were obtained on a Varian FT-80 instrument with ca. 0.2M solutions of the steroid in dioxane using an internal coaxially placed deuterium oxide lock. The chemical shifts are relative to the internal standard, tetramethylsilane. Mass spectra were obtained on an AEl MS9025 spectrometer. The light petroleum used was of the boiling range 30-60°. Thin layer chromatography was performed on Merck pre-coated silica gel 60 F-254 plates. Microanalyses were carried out by Galbraith Laboratories, Knoxville, Tenn., U.S.A.

For brevity, the following general procedures have been omitted from the experimental.

Workup involved pouring the reaction mixture into water, extracting with methylene chloride and washing the extracts with water. They were then dried with anhydrous sodium sulphate and the solvent removed on a rotary evaporator.

Chromatography refers to column chromatography using silica gel (Baker 60-200 mesh) where ca. 15 g of adsorbant was employed for every 100 mg of material that was being separated. The column was prepared using a mixture of ethyl acetate-hexane with which the least polar component (t.l.c.) would have a negligible R_f value. The material to be separated was introduced onto the column as a solution in methylene chloride. Elution proceeded using the original ethyl acetate-hexane mixture followed by mixtures in which the amount of ethyl acetate was increased in increments of 5%.

Two procedures were used for the oxidation of alcohols. The first procedure (Method A) involved the addition of a solution of the alcohol in dry methylene chloride to a solution of a chromium trioxide-pyridine complex[95] (6 equiv., 0.6 M, methylene chloride) and the resulting suspension was stirred for the specified period of time. Anhydrous diethyl ether was then added and the suspension was filtered through a short column of florisil (Baker 60-100 mesh). The residual semisolid was triturated with diethyl ether and the washings were also filtered through the column. The solvents were then removed under reduced pressure. The second procedure (Method B) involved the

addition of a solution of the alcohol in dry methylene chloride to a stirred suspension of pyridinium chlorochromate[96] (3 equiv.) and sodium acetate (0.6 equiv.) in dry methylene chloride. After the specified period of time, it was worked up as above.

Two procedures were also used for the boron trifluoride-catalyzed reactions of the epoxide. The first procedure (Method A) involved the addition of a solution of dry benzene (25 ml), which had been saturated with boron trifluoride gas, to a solution of the epoxide (1 g) in dry benzene (50 ml). This was stirred for 10 min. after which the reaction was stopped by the addition of an aqueous solution of sodium bicarbonate (50 ml, 5%). The organic layer was diluted with diethyl ether (75 ml) and then separated. It was washed with water, brine, and then dried (anhydrous sodium sulfate). The solvents were removed under reduced pressure. In the second procedure (Method B), boron trifluoride gas was bubbled directly into a solution of the epoxide (1 g) in dry benzene (100 ml) until a brownish gel, indicative of the epoxide-boron trifluoride complex, was formed. In those instances where such a gel was not formed, the gas was bubbled into the solution for 2 min. The reaction was stopped after 5 min. and worked up as above.

PART 1

Boron Trifluoride-catalyzed Reactions of 19-Hydroxy-and 19-Acetoxy-5,6-epoxy-steroids

1. Reactions with 3β-Acetoxy-5,6β-epoxy-5β-cholestan-19-ol (17) and 3β-Acetoxy-19-hydroxy-5,6β-epoxy-5β-androstan-17-one (32)

(i) Reaction of 3β-Acetoxy-5,6β-epoxy-5β-cholestan-19-ol (17) with Boron Trifluoride - The 5β,6β-epoxide[34] (17) (2.0 g) was treated with boron trifluoride (Method A). Chromatography afforded 3β-acetoxy-19-nor-cholesta-1(10),5-diene (33) (840 mg, 47%), m.p. 74-76°C. (prisms from methanol-ether), λ_{max} 243 nm (lit.[32], m.p. 74-75°C, λ_{max} 240 nm) (Found:C, 81.35; H, 10.85. $C_{28}H_{44}O_2$ requires C, 81.49; H, 10.73%) and 3β-acetoxy-6β,19-methylenedioxy-cholest-4-ene (35) (193 mg, 9%), m.p. 121-122°C (needles from methanol-ether); ν_{max} 1735 cm^{-1} (acetate CO); δ 2.05 (s, 3H, OAc), 3.60 (q, 2H, δ_A 3.99, δ_B 3.21, J_{AB} 12 Hz, 19-CH_2), 4.43 (t, 1H, J ca. 2Hz, 6α-H), 4.79 (q, 2H, δ_A4.98, δ_B4.59, J_{AB} 8 Hz, -OCH_2O-), 5.25 (m, 1H, W/2 ca. 18 Hz, 3α-H), and 5.71 (s, 1H, 4-H); m/e 412 (M^+-HOAc) (Found:C, 76.68; H, 10.45. $C_{30}H_{48}O_4$ requires C, 76.23; H, 10.24%).

(ii) Reaction of 3β-Acetoxy-19-hydroxy-5,6β-epoxy-5β-androstan-17-one (32) with Boron Trifluoride - The 5β,6β-epoxide[16] (32) (1.0 g) was treated with boron trifluoride (Method A). Chromatography afforded 3β-acetoxy-19-nor-androsta-1(10)-5-dien-17-one (34) (260 mg, 30%), m.p. 115°C

(prisms from benzene-ether); λ_{max} 240 nm; υ_{max} 1735 cm^{-1} (acetate CO and 17-CO); δ 0.89 (s, 3H, 18-Me), 2.02 (s, 3H, OAc), 5.01 (m, 1H, W/2 ca. 18 Hz, 3α-H), and 5.31 - 5.58 (m, 2H, 1-H and 6-H) (Found:C, 76.45; H, 8.30. $C_{20}H_{26}O_3$ requires C, 76.40; H, 8.34%) and 3β-acetoxy-6β, 19-methylenedioxy-androst-4-en-17-one (36) (143 mg, 16%, m.p. 160-161°C (prisms from methanol); υ_{max} 1740 cm^{-1} (acetate CO and 17-CO); δ 0.97 (s, 3H, 18-Me), 2.08 (s, 3H, OAc), 3.64 (q, 2H, δ_A 4.00, δ_B 3.28, J_{AB} 12 Hz, 19-CH_2), 4.50 (m, 1H, W/2 ca. 6 Hz, 6α-H), 4.81 (q, 2H, δ_A 5.00, δ_B 4.62, J_{AB} 7 Hz, -OCH_2O-), 5.12 (m, 1H, W/2 ca. 18 Hz, 3α-H), and 5.76 (s, 1H, 4-H) (Found:C, 70.70; H, 8.20. $C_{22}H_{30}O_5$ requires C, 70.56; H, 8.08%).

(iii) Synthesis of 3β-Acetoxy-6β,19-methylenedioxy-cholest-4-ene (35) - Hydrobromic acid (0.43 ml, 50%) was added to an ice-cooled solution of 3β-acetoxy-5,6β-epoxy-5β-cholestan-19-ol (17) (1.17 g) and this was stirred for 15 min. Acetic anhydride (10 ml) followed by perchloric acid (3 drops, 70%) were added and the solution was left for 1 h. Water was then added and 5-bromo-3β,6β,19-tri-acetoxy-5β-cholestane (37) (1.25 g) separated as an oily precipitate; δ2.02, 2.08, and 2.13 (9H, 3 X OAc), 4.57 (s, 2H, 19-CH_2), 5.33 (m, W/2 ca. 8 Hz, 6α-H), and 5.47 (m, W/2 ca. 24 Hz, 3α-H). The crude bromide (37) (1.25 g) was taken up in pyridine (10 ml) and the solution was heated

at reflux for 6 h. Water was added and 3β,6β,19-triacetoxycholest-4-ene (38) (870 mg, 56%) separated, m.p. 138-139°C (needles from acetone-water); υ_{max} 1730 cm^{-1} (acetate CO); δ 1.99 (s, 3H, OAc), 2.07 (s, 6H, 2 X OAc), 4.50 (q, 2H, δ_A 4.48, δ_B 4.19, J_{AB} 11 Hz, 19-CH_2), 5.23 (m, 2H, 3α-H, 6α-H) and 5.80 (d, 1H, J 2 Hz, 4-H) (Found:C, 72.55; H, 9.65. $C_{33}H_{52}O_6$ requires C, 72.76; H, 9.62%). A suspension of the triacetate (38) (750 mg) and sodium carbonate (700 mg) in methanol (50 ml) was refluxed for 7 h. Workup afforded cholest-4-ene-3β,6β,19-triol (39) (424 mg, 74%), m.p. 209-211°C (needles from ethyl acetate); m/e 400 (M^+-H_2O) (Found:C, 77.58; H, 11.10. $C_{27}H_{46}O_3$ requires C, 77.47; H, 11.08%). A solution of the triol (39) (183 mg) and benzyltriethylammonium chloride (50 mg) in methylene chloride (20 ml) was added to a solution of potassium hydroxide (15 ml, 50%) and the mixture refluxed for 2 h. Workup and chromatography afforded 6β,19-methylenedioxycholest-4-en-3β-ol (40) as an oil, δ 3.61 (q, 2H, δ_A 4.07, δ_B 3.15, J_{AB} 12 Hz, 19-CH_2), 4.23 (m, 3α-H) 4.46 (m, 6α-H), 4.79 (q, 2H, δ_A 4.93, δ_B 4.65, J_{AB} 8 Hz, $-OCH_2O-$), and 5.80 (s, 1H, 4-H) which was taken directly and acetylated (acetic anhydride-pyridine) to give the acetate (35) (53 mg, 26%), m.p. 118-120°C, mixed m.p. 118-121°C, identical (t.l.c. and ^1H n.m.r.) with that obtained previously.

(iv) Preparation of 3β-Acetoxy-5-fluoro-5α-cholestane-6β,19-diol (43) - Boron trifluoride-diethyl ether complex (2.5 ml) was added to a solution of 3β-acetoxy-5,6β-epoxy-5β-cholestan-19-ol (17) (2.5 g) in a benzene-diethyl ether mixture (250 ml, 1:1). This was left for 15 min. and worked up in the usual manner. Chromatography afforded the fluorohydrin (43) (820 mg) contaminated with a small amount of unidentified material. Repeated crystallizations from methylene chloride-light petroleum gave pure material, m.p. 148-149°C; υ_{max} 3340 (OH) and 1730 cm^{-1} (acetate CO); δ 2.02 (s, 3H, OAc), 3.55 - 4.62 (m, 3H, 19-CH_2 and 6α-H), and 5.15 (m, 1H, W/2 ca. 24 Hz, 3α-H); m/e 476* 462 (M^+-H_2O), and 420 (M^+-HOAc) (Found:C, 72.25; H, 10.49. $C_{29}H_{49}FO_4$ requires C, 72.48; H, 10.28%). The identity of the fluorohydrin (43) was confirmed by its conversion (refluxing methanolic sodium carbonate, 12 h) to 5,6β-epoxy-5β-cholestane-3β,19-diol (44), m.p. 177-178°C (ether-light petroleum); υ_{max} 3520 cm^{-1} (OH); δ 3.07 (s, 1H, 6α-H), 3.72 (m, 1H, W/2 ca. 24 Hz, 3α-H), 3.85 (q, 2H, δ_A 4.15, δ_B 3.55, J_{AB} 12 Hz, 19-CH_2); m/e 400 (M^+-H_2O). The latter material was identical with that obtained by saponification (methanol, sodium carbonate) of the 3β-acetoxy-5β,6β-epoxide (17).

*The peak at highest m/e was 476 although the fragmentation did not appear to originate from this ion. The peaks corresponding to the loss of water and acetic acid appear to be derived from the molecular ion (m/e 480) even though the latter was not observed. It is suggested that the peak at 476 originates from some recombination sequence in the mass spectrometer.

(v) Reaction of 3β-Acetoxy-5-fluoro-5α-cholestane-6β,19-diol (43) with Boron Trifluoride - The fluorohydrin (43) was treated with boron trifluoride (Method B). After work-up, analysis of the product (t.l.c. and ^{1}H n.m.r.) revealed only the presence of unreacted starting material.

2. Reactions with 3β,19-Diacetoxy-5,6β-epoxy-5β-cholestane (51) and 3β,19-Diacetoxy-5,6β-epoxy-5β-androstan-17-one (50).

(i) Preparation of 3β,19-Diacetoxy-5,6β-epoxy-5β-androstan-17-one (50) - 3β-Acetoxy-19-hydroxy-5,6β-epoxy-5β-androstan-17-one (32) was acetylated (acetic anhydride-pyridine) to give the diacetate (50), m.p. 133-134°C (prisms from light petroleum); $[\alpha]_D$ +26° (C 5.7); υ_{max} 1735 cm^{-1} (acetate CO and 17-CO); δ0.87 (s, 3H, 18-CH_3), 2.00 and 2.08 (6H, 2 x OAc), 3.07 (s, 1H, 6α-H), 4.33 (q, 2H, δ_A 4.58, δ_B 4.09, J_{AB} 12 Hz, 19-CH_2), and 4.67 (m, 1H, W/2 ca. 24 Hz, 3α-H); m/e (M^+) (Found:C, 68.35; H, 7.85. $C_{23}H_{32}O_6$ requires C, 68.29; H, 7.98%).

(ii) Reaction of 3β,19-Diacetoxy-5,6β-epoxy-5β-androstan-17-one (50) with Boron Trifluoride - The epoxide (50) (1.4 g) was reacted with boron trifluoride (Method A), but in this case the reaction was allowed to proceed for 45 min. before workup. Chromatography afforded starting material (266 mg, 19%) [identical (t.l.c. and ^{1}H n.m.r.)

with authentic material], 3β,19-diacetoxy-5-fluoro-5α-androstan-17-one (52) (633 mg, 43%); m.p. 109-111°C (prisms from ether-light petroleum); $[\alpha]_D$ +27° (C 8.1); υ_{max} 3500 (OH) and 1735 cm^{-1} (acetate CO and 17-CO); δ0.88 (s, 3H, 18-CH_3), 2.02 and 2.08 (6H, 2 x OAc), 3.72 (m, 1H, W/2 ca 8 Hz, 6α-H), 4.52 (q, 2H, δ_A 4.40, δ_B 4.64, J_{AB} 14 Hz, 19-CH_2) and 5.03 (m, 1H, W/2 ca. 22 Hz, 3α-H); m/e 424 (M^+) (Found:C, 64.85; H, 7.55. $C_{23}H_{33}FO_6$ requires C, 65.07; H, 7.84%), and a white solid (308 mg) which consisted predominantly of 3β, 19-diacetoxy-6β-hydroxy-androst-4-en-17-one (55); δ 0.91 (s, 3H, 18-CH_3), 2.08 and 2.05 (6H, 2 x OAc), 4.29 (t, 3H, J app. 3 Hz, 6α-H), 4.50 (q, 2H, δ_A 4.56, δ_B 4.44, J_{AB} 11 Hz, 19-CH_2), 5.23 (m, 1H, W/2 ca.20Hz, 3α-H), and 5.69 (d, 1H, J ca. 2 Hz, 4-H). The latter component was acetylated (acetic anhydride-pyridine) and rechromatographed to give 3β,6β,19-triacetoxy-androst-4-en-17-one (56), m.p. 132-133°C (needles from ether-light petroleum); υ_{max} 1735 cm^{-1} (acetate CO and 17-CO); δ 0.95 (s, 3H, 18-CH_3), 2.02 (s, 3H, OAc), 2.08 (s, 6H, 2 x OAc), 4.36 (q, 2H, δ_A 4.42, δ_B 4.30, J_{AB} 12 Hz, 19-CH_2), 5.20 (m, 2H, 3α- and 6α-H), 5.88 (s, 1H, 4-H), m/e 386 (M^+-HOAc) (Found:C, 67.4; H, 7.76. $C_{25}H_{34}O_7$ requires C, 67.24; H, 7.68%).

(iii) Synthesis of 3β,6β,19-Triacetoxy-androst-4-en-17-one (56) - Using the same procedure that was employed for the preparation of the cholestane analogue (38) (cf. page 122),

3β-acetoxy-19-hydroxy-5,6β-epoxy-5β-androstan-17-one (32) was converted to 5-bromo-3β,6β,19-triacetoxy-5α-androstan-17-one (53), δ 0.90 (s, 3H, 18-CH_3), 2.03, 2.10, 2.17 (9H, 3 x OAc), 4.61 (q, 2H, δ_A 4.69, δ_B 4.53, J_{AB} 13 Hz, 19-CH_2), 5.33 (m, W/2 ca. 8 Hz, 6α-H), 5.43 (m, W/2 ca. 24 Hz, 3α-H), m/e 525/527 (M^+), which was then dehydrobrominated to the 4-olefin (56). The latter compound was identical (t.l.c. and ^{1}H n.m.r.) with that which had been obtained previously.

(iv) Reaction of 3β,19-Diacetoxy-5,6β-epoxy-5β-androstan-17-one (50) with Boron Trifluoride (Method B) - The 5β,6β-epoxide (50) (250 mg) was treated with boron trifluoride (Method B). Workup followed by chromatography afforded 3β,19-diacetoxy-5-formyl-B-nor-5β-androstan-17-one (57) (41 mg, 16%) as an oil, $[\alpha]_D$ +60° (C. 20.5), υ_{max} 1735 (acetate CO, 17-CO, and -CHO); δ 0.88 (s, 3H, 18-CH_3), 2.05 (s, 6H, 2 x OAc), 4.07 (s, 2H, 19-CH_2), 5.08 (m, 1H, W/2 ca. 15 Hz, 3α-H), 9.70 (s, 1H, -CHO); m/e 404 (M^+) (Found:C, 68.34; H, 8.11. $C_{23}H_{32}O_6$ requires C, 68.27; H, 7.98%), 3β,19-diacetoxy-5-fluoro-6β-hydroxy-5β-androstan-17-one (52) (69 mg, 26%) which was identical (t.l.c. and ^{1}H n.m.r.) with that obtained previously, and a mixture (52 mg) of olefinic material. The latter was left unidentified although the ^{1}H n.m.r. spectrum of the mixture was consistent with the presence of the 4-olefin (55).

(v) Reaction of 3β,19-Diacetoxy-5,6β-epoxy-5β-cholestane (51) with Boron Trifluoride - The 5β,6β-epoxide (51) (627 mg) was treated with boron trifluoride (Method B). Chromatography afforded a mixture of olefinic material (67 mg) which was left unidentified, 3β,19-diacetoxy-5-formyl-B-nor-5β-cholestane (58) (132 mg, 21%) as an oil, υ_{max} 1730 cm^{-1} (acetate CO and -CHO); δ 0.66 (s, 3H, 18-CH_3), 2.03 (s, 6H, 2 x OAc), 4.02 (s, 2H, 19-CH_2), 5.04 (m, 1H, W/2 ca. 15 Hz, 3α-H), 9.62 (s, 1H, -CHO); m/e 502 (M^+), and 3β-19-diacetoxy-5-fluoro-5α-cholestan-6β-ol (54) (234 mg, 36%) as an oil, $[\alpha]_D$ -3° (C 12.5); υ_{max} 1735 (acetate CO); δ 0.67 (s, 3H, 18-CH_3) 2.01 and 2.06 (6H, 2 x OAc), 3.71 (m, 1H, W/2 ca. 8 Hz), 4.46 (q, 2H, δ_A 4.57, δ_B 4.34, J_{AB} 13 Hz, 19-CH_2), 5.02 (m, 1H, W/2 ca 23 Hz, 3α-H); m/e 522 (M^+) (Found:C, 71.10; H, 9.98. $C_{31}H_{51}O_5F$ requires C, 71.20; H, 9.84%). The identity of the fluorohydrin (54) was confirmed by its conversion (refluxing methanolic sodium carbonate, 12 h) to the 5β,6β-epoxide (44).

(vi) Conversion of 3β,19-Diacetoxy-5-formyl-B-nor-5β-cholestane (58) to B-nor-5β-cholestan-3-one-5β,19-carbolactone (60) - The aldehyde (58) (44 mg) was hydrolyzed (methanol, sodium carbonate). Workup and chromatography afforded the 19,5-hemiacetal of 3β,5-dihydroxy-B-nor-5β-cholestan-19-al (59) (21 mg, 57%) as a white solid, υ_{max} 3400 cm^{-1} (OH); δ 0.67 (s, 3H, 18-CH_3), 3.72 (q, 2H, δ_A 3.80,

δ_B 3.62, J_{AB} 10 Hz, 19-CH_2), 3.96 (m, 1H, W/2 ca. 16 Hz, 3α-H), 4.96 (s, 1H, -OCHRO-); m/e 400 (M^+ - 18). The lactol (59) (15 mg) was dissolved in methylene chloride (1 ml) and this solution was added to a solution of chromium trioxide-pyridine complex (1 ml, 0.02 M, methylene chloride) and left for 10 min. Workup followed by chromatography afforded the lactone (60) (7 mg, 47%), m.p. 140-141° (needles from acetone-water); υ_{max} 1769 (γ-lactone), 1725 cm^{-1} (3-CO); δ 0.67 (s, 3H, 18-CH_3), 2.64 (q, 2H, δ_A 2.81, δ_B 2.47, J_{AB} 16 Hz, 4-CH_2), 4.16 (q, 2H, δ_A 4.29, δ_B 4.01, J_{AB} 10 Hz, 19-CH_2); m/e 414 (M^+) (Found:C, 77.72; H, 10.16. $C_{27}H_{42}O_3$ requires C, 78.21; H, 10.21%).

(vii) Reaction of 3β,19-Diacetoxy-5-fluoro-6β-hydroxy-5α-androstan-17-one (52) with Boron Trifluoride - The fluorohydrin (52) (242 mg) was treated with boron trifluoride (Method B). Chromatography afforded 3β-acetoxy-5-fluoro-6β,19-oxido-5α-androstan-17-one (62) (52 mg, 25%), m.p. 186-187° (plates from acetone-water); υ_{max} 1740 cm^{-1} (acetate CO and 17-CO); δ 0.83 (s, 3H, 18-CH_3), 1.92 (s, 3H, OAc), 3.78 (s, 2H, 19-CH_2), 4.90 (m, 1H, W/2 ca. 24 Hz, 3α-H); m/e 364 (M^+) (Found:C, 69.12; H, 7.80. $C_{21}H_{29}O_4F$ requires C, 69.22; H, 8.02%), and unreacted fluorohydrin (140 mg, 58%).

3. Preparation of 3β-Acetoxy-5,6α-epoxy-5α-cholestan-19-ol (68) and 3β-Acetoxy-19-hydroxy-5,6α-epoxy-5α-androstan-17-one (70)

(i) Preparation of 3β-Acetoxy-5,6α-epoxy-5α-cholestan-19-ol (68) - A solution of 3β-acetoxy-19-hydroxy-cholest-5-ene[97] (63) (12 g) in dimethylformamide (50 ml) containing t-butyldimethylsilyl chloride (4.82 g, 1.2 equiv.) and imidazole (4.60 g, 2.5 equiv.) was stirred at room temperature for 20 h. Workup followed by chromatography afforded 3β-acetoxy-19-t-butyldimethylsilyoxy-cholest-5-ene (66) (13.87 g, 93%) as a white solid, υ_{max} 1735 cm^{-1} (acetate CO); δ ca. 0 (s, Me_2Si), 0.82 (s, t-BuSi), 1.97 (s, 3H, OAc), 3.64 (q, 2H, δ_A 3.71, δ_B 3.57, J_{AB} 11 Hz, 19-CH_2), 4.58 (m, 1H, W/2 ca. 22 Hz, 3α-H), 5.56 (m, 1H, 6-H), m/e 498 (M^+ - HOAc). The silyl ether (66) (13.64 g) was dissolved in methylene chloride (50 ml) and treated with a solution of m-chloroperbenzoic acid (5.5 g, 1.1 equiv., 85%) in methylene chloride (60 ml). After standing at room temperature for 1 h., the reaction was worked up. The crude mixture of epoxides (14.7 g) was taken up in tetrahydrofuran (15 ml) and a solution of tetrabutylammonium fluoride (47 ml, ca. 2 equiv., 1 M in tetrahydrofuran) was added. After 3 h, the reaction was worked up and the residual semisolid chromatographed. This afforded 3β-acetoxy-19-t-butyldimethylsilyloxy-5,6β-epoxy-5β-cholestane (69) (2.48 g, 17%), m.p.

97-98° (needles from acetone), υ_{max} 1730 cm^{-1} (acetate CO); δ 0.10 (s, 6H, Me_2Si), 0.92 (s, t-BuSi), 2.00 (s, 3H, OAc), 2.92 (s, 1H, 6α-H), 3.72 (s, 2H, 19-CH_2), 4.82 (m, 1H, W/2 ca. 24 Hz, 3α-H) (Found:C, 73.32; H, 10.77. $C_{35}H_{64}O_4Si$ requires C, 73.11; H, 10.87%) [a sample of this compound on treatment with tetrabutylammonium fluoride for 43 h gave material which was identical (t.l.c. and ^1H n.m.r.) with the 19-hydroxy-5β,6β-epoxide (17)], 3β-acetoxy-5,6β-epoxy-5β-cholestan-19-ol (17) (1.74 g, 16%), and 3β-acetoxy-5,6α-epoxy-5α-cholestan-19-ol (68) (6.78 g, 63%), m.p. 186-188, $[\alpha]_D$ - 47° (lit.[18], m.p. 184-186°, $[\alpha]_D$ - 57°).

(ii) Preparation of 3β-Acetoxy-19-hydroxy-5,6α-epoxy-5α-androstan-17-one (70) - Similarly, treatment of 3β-acetoxy-19-hydroxy-androst-5-en-17-one[98] (65) (2.75 g) with t-butyldimethylsilyl chloride (1.49 g, 1.2 equiv.) and imidazole (1.35 g, 2.5 equiv.) afforded the crude 19-t-butyldimethylsilyloxy derivative (67) (3.60 g) after workup. A sample which was purified had: m.p. 111-112° (needles from ethanol-water); υ_{max} 1735 cm^{-1} (acetate CO and 17-CO); δ 0.03 (s, $SiMe_2$), 0.89 (s, 12H, t-BuSi and 18-CH_3), 2.00 (s, 3H, OAc), 3.68 (q, 2H, δ_A 3.59, δ_B 3.78, J_{AB} 11 Hz, 19-CH_2), 4.62 (m, 1H, W/2 ca. 24 Hz, 3α-H), 5.58 (m, 1H, W/2 ca. 8 Hz, 6-H); m/e 400 (M^+ - HOAc). Treatment of the crude 5-olefin (67) (3.50 g) with m-chloroperbenzoic acid (1.7 g, 1.1 equiv., 85%) followed by workup afforded a mixture of

epoxides which were then allowed to react with tetrabutylammonium fluoride (17 ml, ca. 2 equiv., 1 M in tetrahydrofuran) for 40 h. Workup followed by chromatography gave: 3β-acetoxy-19-t-butyldimethylsilyloxy-5,6β-epoxy-5β-androstan-17-one (71) (220 mg, 6%) as a solid, δ ca. 0 (s, Me_2Si), 0.73 (s, 18-CH_3), 0.80 (s, t-BuSi), 1.93 (s, OAc), 2.93 (m, 1H, W/2 ca. 4 Hz, 6α-H), 3.67 (s, 2H, 19-CH_2), 4.73 (m, 1H, W/2 ca. 22 Hz, 3α-H), 3β-acetoxy-19-hydroxy-androst-5-en-17-one (65) (155 mg, 6%) (identical, t.l.c. and ^1H n.m.r. with authentic material), 3β-acetoxy-19-hydroxy-5,6β-epoxy-5β-androstan-17-one (32) (365 mg, 13%) (identical, t.l.c. and ^1H n.m.r., with authentic material), and 3β-acetoxy-19-hydroxy-5,6α-epoxy-5α-androstan-17-one (70), m.p. 204-205° (needles from methanol); υ_{max} 3500 (OH) and 1740 cm^{-1} (acetate CO and 17-CO); δ 0.85 (s, 3H, 18-CH_3); 2.00 (s, 3H, 3β-OAc), 3.07 (d, 1H, J ca. 3 Hz, 6β-H), 4.16 (s, 2H, 19-CH_2), 5.07 (m, 1H, W/2 ca. 20 Hz, 3α-H) (Found:C, 69.36; H, 8.41. $C_{21}H_{30}O_5$ requires C, 69.59; H, 8.34%).

4. Reactions with 3β-Acetoxy-5,6α-epoxy-5α-cholestan-19-ol (68) and 3β,19-Diacetoxy-5,6α-epoxy-5α-cholestane (74)

(i) Reaction of 3β-Acetoxy-5,6α-epoxy-5α-cholestan-19-ol (68) with Boron Trifluoride - The 5α,6α-epoxide (68) (190 mg) was treated with boron trifluoride (Method B). Chromatography afforded 3β-acetoxy-6β,19-oxido-5α-cholestan-5-ol (72) (122 mg, 64%), m.p. 160-161, $[\alpha]_D$ +4° (C 15.1)

(lit.[41], m.p. 162-163°, $[\alpha]_D$ +9°); δ 0.70 (s, 3H, 18-CH_3), 2.02 (s, 3H, OAc), 3.70 (m, 1H, W/2 ca. 5 Hz, 6α-H), 3.80 (s, 2H, 19-CH_2), 4.98 (m, 1H, W/2 ca. 24 Hz, 3α-H); m/e 460 (M).

(ii) Reaction of 3β-19-Diacetoxy-5,6α-epoxy-5α-cholestane (74) with Boron Trifluoride - The epoxide[18] (74) (250 mg) was treated with boron trifluoride (Method B). This afforded 3β,19-diacetoxy-5β-cholestane-5,6α-diol (76) (249 mg) as an amorphous solid (t.l.c. pure), $[\alpha]_D$ +46° (C 16.1) (lit.[99], +39°), υ_{max} 3600 (OH), 1735 cm^{-1} (acetate CO); δ 2.05 and δ 2.09 (6H, 2 x OAc), 3.95 (q, 1H, J 12 and 6 Hz, 6β-H), 4.33 (s, 2H, 19-CH_2), 5.27 (m, 1H, W/2 ca 7 Hz, 3α-H); m/e 502 (M).

PART II

Base-catalyzed Fragmentation of 3β-Hydroxy-5,6β-epoxy-5β-cholestan-19-al (77)

1. Preparation of 3β-Hydroxy-5,6β-epoxy-5β-cholestan-19-al (77) and 3β-Hydroxy-5,6α-epoxy-5α-cholestan-19-al (89).

(i) Preparation of 3β-Hydroxy-5,6β-epoxy-5β-cholestan-19-al (77) - Oxidation (Method B, 1.5 h) of 3β-acetoxy-5,6β-epoxy-5β-cholestan-19-ol (17) (1.00 g) afforded, after chromatography, 3β-acetoxy-5,6β-epoxy-5β-cholestan-19-al (87) (820 mg, 82%), m.p. 138-140° (needles from methanol) (lit.[43], 138-140°); υ_{max} 1725 cm^{-1} (acetate CO and -CHO); δ 1.95 (s, 3H, OAc), 3.15 (m, 1H, W/2 ca. 5 Hz, 6α-H), 4.73 (m, 1H, W/2 ca. 22 Hz, 3α-H), 9.77 (s, 1H, 19-H) (Found:C, 76.06; H, 10.20. $C_{29}H_{46}O_4$ requires C, 75.94; H, 10.11%). Hydrolysis of the acetate (87) (525 mg) with aqueous sodium hydroxide (2 ml, 1.0 M) in methanol (50 ml) under nitrogen at room temperature (1 h) afforded, after workup and chromatography, the epoxide (77) (442 mg, 92%), m.p. 119°-132° (fine needles from methanol); $[\alpha]_D$ (initial) -39° (C 4.5) (after 24 h, -18°) (lit.[43], m.p. 138-140°, $[\alpha]_D$ - 10°); υ_{max} 3600, 3460 (OH) and 1720 cm^{-1} (-CHO) (Found:C, 77.73; H, 10.76. $C_{27}H_{44}O_4$ requires C, 77.83; H, 10.65).

(ii) Preparation of 3β-Hydroxy-5,6α-epoxy-5α-cholestan-19-al (89) - Oxidation (Method B, 1 h) of 3β-acetoxy-5,6α-epoxy-5α-cholestan-19-ol (68) (1.00 g) afforded, after chromatography, 3β-acetoxy-5,6α-epoxy-5α-cholestan-19-al (88) (890 mg, 89%), m.p. 132-134° (needles from methanol); υ_{max} 1725 cm^{-1} (acetate CO and -CHO); δ 1.97 (s, 3H, OAc), 3.10 (app. d, 1H, J ca. 4 Hz, 6β-H), 4.90 (m, 1H, W/2 ca. 24 Hz, 3α-H), 9.82 (s, 1H, 19-H) (Found:C, 76.04; H, 10.03. $C_{29}H_{46}O_4$ requires C, 75.94; H, 10.11%). Hydrolysis of the acetate (88) (430 mg) with aqueous sodium hydroxide (1.5 ml, 1.0 m) in methanol (60 ml) under nitrogen at room temperature afforded, after workup and chromatography, the epoxide (89) (352 mg, 90%), m.p. 125-137° (plates from methanol), $[\alpha]_D$ (initial) -54° (C 5.3) (after 24 h, -46°); υ_{max} 3600, 3460 (OH) and 1720 cm^{-1} (-CHO); m/e 416 (M^+) (Found*:C, 76.59; H, 10.72. $C_{27}H_{44}O_3 \cdot \frac{1}{2}H_2O$ requires C, 76.17; H, 10.66).

2. Reactions of 5,6-Epoxy-19-aldehydes with Base

(i) Reaction of 3β-Hydroxy-5,6α-epoxy-5α-cholestan-19-al (89) with Methanolic Potassium Hydroxide - To the epoxide (89) (100 mg) in methanol (10 ml) was added a methanolic solution of potassium hydroxide (2 ml, 3.8 M) and the solution was heated at reflux for 1.5 h under nitrogen. Workup followed by chromatography gave the major component (71 mg) which was

*The results of subsequent analyses were similar, i.e., C:76.41, H:10.97; C:76.26, H:11.04; C:76.48, H:10.88%.

contaminated with some other material. Crystallization of this component from methanol afforded pure 3β,5-dihydroxy-6β-methoxy-5α-cholestan-19-al (97), m.p. 197-199°; $[\alpha]_D$ +7° (C 1.0); υ_{max} (KBr disc) 3620, 3360 (OH), and 1690*cm^{-1} (-CHO); δ 3.15 (m, 1H, W/2 ca. 5 Hz, 6α-H), 3.32 (s, 3H, -OMe), 3.98 (m, 1H, W/2 ca. 26 Hz, 3α-H), 10.2 (s, 1H, -CHO) (Found:C, 74.93; H, 10.94. $C_{28}H_{48}O_4$ requires C, 74.95; H, 10.78%). Acetylation (acetic anhydride-pyridine) of a sample of this material gave the 3β-acetate (98), 3600, 3420 (OH), 1720 cm^{-1} (acetate CO and -CHO); δ 1.97 (s, 3H, OAc) 3.13 (m, 1H, W/2 ca. 5 Hz, 6α-H), 3.30 (s, 3H, OMe) 5.11 (m, 1H, W/2 ca. 26 Hz, 3α-H), 10.2 (s, 1H, -CHO).

(ii) Preparation of 3β-Methoxy-5,6β-epoxy-5β-cholestan-19-al (95) - A solution of 3β-Acetoxy-19-t-butyldimethylsilyloxy-5,6β-epoxy-5β-cholestane (69) (1.40 g) in methanol (25 ml) containing aqueous sodium hydroxide (4.9 ml, 1.0 M) was heated at reflux for 1 h. The crude alcohol (93), which was obtained after workup, was dissolved in methylene chloride (20 ml) and an aqueous solution of potassium hydroxide (10 ml, 20%) was added. This mixture was stirred at room temperature and four additions of methyl iodide (0.23 ml, 1.5 equiv.) and benzyl triethylammonium chloride (100 mg) were made over the period of two days. Workup and chromatography afforded 19-t-

*The unusually low frequency observed for the aldehyde absorption in (97) is suggestive of either an intermolecular or an intramolecular[100] hydrogen bond to this group in the crystalline state of this compound.

butyldimethylsilyloxy-3β-methoxy-5,6β-epoxy-5β-cholestane (92) (736 mg, 65%), m.p. 87-88° (needles from acetone-water); $[\alpha]_D$ 0° (C 4.5); δ 0.07 (s, Me_2Si), 0.90 (s, t-BuSi), 2.90 (m, 1H, W/2 ca. 5 Hz, 6α-H), ca. 3.2 (m) and 3.30 (s) (4H, 3α-H and 3β-OMe), 3.70 (s, 2H, 19-CH_2) (Found:C, 74.88; H, 11.55. $C_{34}H_{62}O_3Si$ requires C, 74.66; H, 11.40%) and unreacted 19-t-butyldimethylsilyloxy-5,6β-epoxy-5β-cholestan-3β-ol (93) (440 mg, 34%), m.p. 73-76° (needles from acetone-water); $[\alpha]_D$ +2° (C 8.9); δ 0.08 (s, Me_2Si), 0.90 (s, t-BuSi), 2.93 (m, 1H, W/2 ca. 5 Hz, 6α-H), ca. 3.7 (m) and 3.72 (s) (3H, 3α-H and 19-CH_2) (Found:C, 74.44; H, 11.49. $C_{33}H_{60}O_3Si$ requires C, 74.38; H, 11.35%). To the methyl ether (92) (700 mg) in tetrahydrofuran (4 ml) was added a solution of tetrabutylammonium fluoride (2.6 ml, 1M, tetrahydrofuran). After three days, workup followed by chromatography afforded unreacted starting material (92) (98 mg, 14%) and 3β-methoxy-5,6β-epoxy-5β-cholestan-19-ol (94) (344 mg, 62%), m.p. 133-134° (needles from methanol); $[\alpha]_D$ +17° (C 1.5); υ_{max} 3500 cm^{-1} (OH); δ 3.03 (m, 1H, W/2 ca. 5 Hz, 6α-H), ca. 3.2 (m) and 3.32 (s) (4H, 3α-H and 3β-OMe), 3.87 (q, δ_A 4.17, δ_B 3.57, J_{AB} 12 Hz, 19-CH_2) (Found:C, 77.91; H, 11.02. $C_{28}H_{48}O_3$ requires C, 77.72; H, 11.18%). Oxidation (Method B, 1.5 h) of the 19-alcohol (94) (300 mg) afforded, after chromatography, the aldehyde (95) (236 mg, 77%), m.p. 102-103° (needles from methanol); $[\alpha]_D$ - 80° (C 1.8); υ_{max} 1720 cm^{-1} (-CHO); δ 2.87

(m), ca. 3.2 (m), and 3.27 (s) (5H, 6α-H, 3α-H and 3β-OMe), 9.75 (s, 1H, 19-H) (Found:C, 78.29; H, 10.89. $C_{28}H_{46}O_3$ requires C, 78.09; H, 10.77%).

(iii) Reactions of the 5β,6β-epoxy-19-aldehydes (77) and (95) with Base: a) 20% Aqueous Potassium Hydroxide - To a solution of the epoxide (100 mg) in methanol (10 ml) under nitrogen was added an aqueous solution of potassium hydroxide (2 ml, 20%) and the mixture was heated at reflux. This was followed by workup and column chromatography.

The 3β-hydroxy-5β,6β-epoxide (77) afforded (after 36 h of reflux) 3β,6β-dihydroxy-19-nor-cholest-5(10)-ene (78) (73 mg, 78%), m.p. 166-168° (needles from methanol); $[\alpha]_D$ +101° (C 2.2) (lit.[43], m.p. 166-168°, $[\alpha]_D$ +98°); 3.78 (m) 1H, W/2 ca. 7 Hz, 6α-H), 4.07 (m, 1H, W/2 ca. 12 Hz, 3α-H).

The 3β-methoxy-5β,6β-epoxide (95) afforded (after 108 h of reflux) unreacted starting material (30 mg, 30%) and 6β-hydroxy-3β-methoxy-19-nor-cholest-5(10)-ene (96) (46 mg, 49%), m.p. 109-111° (needles from light petroleum); $[\alpha]_D$ +103° (C 0.9); υ_{max} 3600, 3420 cm^{-1} (OH); δ 3.33 (s, 3β-OMe), ca. 3.5 (m, 3α-H), 3.78 (m, W/2 ca. 8 Hz, 6α-H) (Found:C, 80.87; H, 11.43. $C_{27}H_{46}O_2$ requires C, 80.54 H, 11.52%).

b) Sodium Methoxide - A solution of the 3β-hydroxy-5β,6β-epoxide (77) (70 mg) in methanol (7 ml) containing sodium methoxide (2 ml, 0.55 M, methanol) was heated at reflux for 142 h under nitrogen. The reaction mixture was worked up and

chromatographed. The first component was found (^{1}H n.m.r.) to consist of a mixture of starting material and an unidentified compound. The second component (37 mg, 57%) was (t.l.c. and ^{1}H n.m.r.) the allylic alcohol (78).

c) Magnesium Methoxide - To a solution of the epoxide (70 mg) in methanol (7 ml) under nitrogen was added a methanolic solution of magnesium methoxide (2 ml, 0.4 M) and the mixture was heated at reflux for the specified time. Workup involved pouring the reaction mixture into a saturated aqueous solution of ammonium chloride, extracting with methylene chloride, washing the extracts with water and then drying them with anhydrous sodium sulfate. This was followed by column chromatography.

The 3β-hydroxy-5β,6β-epoxide (77) afforded (after 20 min of reflux) the allylic alcohol (78) (59 mg, 90%) which was identical (t.l.c. and ^{1}H n.m.r.) with authentic material.

The 3β-methoxy-5β,6β-epoxide (95) afforded (after 97 h of reflux) starting material (24 mg, 35%) (t.l.c. and ^{1}H n.m.r.) and 19-hydroxy-3β-methoxy-5,6β-epoxy-5β-cholestane (94) (37 mg, 56%) (t.l.c. and ^{1}H n.m.r.).

3. Rearrangements of 3β-Hydroxy-5,6β-epoxy-5β-cholestan-19-al (77)

(i) Thermal Rearrangement - A solution of the epoxide (77) (375 mg) in xylene (10 ml) was heated at reflux for 11 h under nitrogen. Removal of the solvent followed by chromatography

afforded 3β,6β-dihydroxy-19-nor-cholest-5(10)ene 3-formate (104) (287 mg, 77%) as an oil, $[\alpha]_D$ +99° (C 4.0); υ_{max} 3605, 3440 (OH), 1715 cm^{-1} (formate CO); δ 3.80 (m, 1H, W/2 ca. 7 Hz, 6α-H), 5.20 (m, 1H, W/2 ca. 13 Hz, 3α-H), 8.00 (s, 1H, -OCHO) (Found:C, 77.66; H, 10.83. $C_{27}H_{44}O_3$ requires C, 77.83; H, 10.65%).

Hydrolysis of a sample of (104) (methanol, 1 M aqueous sodium hydroxide, 1 h) afforded the diol (78), which was identical (t.l.c. and ^1H n.m.r.) with authentic material.

Oxidation (Method B, 1.5 h) of the 3β-formate (105) (96 mg) afforded crude 3β-hydroxy-19-nor-cholest-5(10)-en-6-one 3-formate (110) as an oil, υ_{max} 1720 (-OCHO), 1660 and 1625 cm^{-1} (α,β-unsaturated ketone); δ 5.30 (m, 1H, W/2 ca. 13 Hz, 3α-H), 8.07 (s, 1H, -OCHO). This was taken up in methanol (4 ml) and treated with an aqueous solution of sodium hydroxide (1 ml, 1.0 M). After 1 h, the reaction mixture was worked up and chromatographed to give 3β-hydroxy-19-nor-cholest-5(10)-en-6-one (111) (39 mg, 43%), m.p. 145-146° (plates from methanol-water) (lit.[53], m.p. 147-148°); υ_{max} 3620 and 3460 (OH), 1660 and 1625 cm^{-1} (α,β-unsaturated ketone); δ 4.07 (m, W/2 ca. 14 Hz, 3α-H).

(ii) Acid-catalyzed Rearrangement - Trifluoroacetic acid (0.05 ml) was added to a solution of the epoxide (77) (70 mg) in dry methylene chloride (5 ml) under nitrogen. After 15 min, the reaction was stopped by the addition of

a saturated aqueous solution of sodium bicarbonate (5 ml). Workup followed by column chromatography gave 3β-hydroxy-19-nor-cholesta-1(10),5-diene 3-formate (109) (56 mg, 80%) as a solid, m.p. 67-68°, λ_{max} 239 nm (ε 15,000), υ_{max} 1720 cm^{-1} (-OCHO); δ 4.9-5.3 (m, 3H, 1-H, 3α-H, 6-H), 7.98 (s, 1H, -OCHO) (Found:C, 81.19; H, 10.74. $C_{27}H_{42}O_2$ requires C, 81.35; H, 10.62%).

PART III

Acid- and Base-catalyzed Reactions of 19-Oxo-4β,5-epoxy-5β-androstane-3,17-dione (15) and 19-Oxo-4α,5-epoxy-5α-androstane-3,17-dione (16)

1. Preparation of 19-Oxo-4β,5-epoxy-5β-androstane-3,17-dione (15) and 19-Oxo-4α,5-epoxy-5α-androstane-3,17-dione (16)

(i) Preparation of 19-t-Butyldimethylsilyloxy-17β-hydroxy-androst-4-en-3-one (119) - A solution of 17β,19-dihydroxy-androst-4-en-3-one 17-benzoate (117) (12.2 g), t-butyldimethylsilyl chloride (5.9 g, 1.2 equiv.) and imidazole (5.5 g, 2.5 equiv.) in dimethylformamide (50 ml) was left at R.T. for 24 h. Workup follwed by crystallization from acetone-water afforded 19-t-butyldimethylsilyloxy-17β-hydroxy-androst-4-en-3-one 17-benzoate (118), 13.8 g (88%), m.p. 132-133° (needles); δ 0.07 (s, Me_2Si), 0.85 (s, 9H, t-BuSi), 1.00 (s, 3H, 18-CH_3), 3.90 (s, 2H, 19-CH_2), 4.90 (m, 1H, W/2 ca 20 Hz, 17α-H), 5.70 (s, 1H, 4-H), 7.3-8.2 (m, 5H, arom.). A solution of the benzoate (118) (13.7 g) in methanol (400 ml) and aqueous sodium hydroxide (30 ml, 10%) was heated at reflux for 10 h. Workup followed by crystallization from ether-light petroleum afforded the 17-alcohol (119) (8.88 g, 81%), m.p. 139-140° (prisms), $[\alpha]_D$ +111° (C 1.6), υ_{max} 3460 (OH),

1660, 1620 cm^{-1} (α,β-unsat. ketone); δ 0.03 (s, Me_2Si), 0.80 (s, 18-CH_3), 0.83 (s, t-BuSi), 3.63 (m, 1H, 17α-H), 3.88 (s, 19-CH_2), 5.82 (s, 1H, 4-H), m/e 418 (M^+) (Found: C, 71.72; H, 10.57. $C_{25}H_{42}O_3Si$ requires C, 71.77; H, 10.11%).

(ii) Epoxidation of 19-t-Butyldimethylsilyloxy-17β-hydroxy-androst-4-en-3-one (119) - To an ice-cooled solution of the enone (119) (8.80 g) and hydrogen peroxide (60 ml, 30%) in methanol (400 ml) was added an aqueous solution of sodium hydroxide (20 ml, 10%). After 12 h, it was worked up and the residual oil chromatographed silica gel (600 g); eluting with ethyl acetate:hexane (1:19). This afforded 19-t-butyldimethylsilyloxy-17β-hydroxy-4α,5-epoxy-5α-androstan-3-one (120) (3.21 g, 34%), m.p. 84-85° (needles from ether-petroleum ether), $[\alpha]_D$ -14° (C 4.9); υ_{max} 3500 (OH), 1710 cm^{-1} (3-CO); δ ca. 0 (s, Me_2Si), 0.72 (s, 18-CH_3), 0.80 (s, t-BuSi) 3.00 (s, 1H, 4β-H), 3.72 (m, 3H, 17α-H and 19-CH_2); m/e 434 (M^+) (Found:C, 69.39; H, 10.00. $C_{25}H_{42}O_4Si$ requires C, 69.08; H, 9.74%), 19-t-butyldimethylsilyloxy-17β-hydroxy-4β,5-epoxy-5β-androstan-3-one (121) (2.50 g, 26%), m.p. 156-157° (needles from methanol), $[\alpha]_D$ +112° (C 2.1); υ_{max} 3500 (OH), 1710 cm^{-1} (3-CO); δ 0.10 (s, Me_2Si), 0.92 (s, t-BuSi), 2.85 (s, 1H, 4α-H), ca 3.7 (m, 17α-H), 3.85 (s, 19-CH_2); m/e 434 (M^+) (Found:C, 69.48; H, 10.24. $C_{25}O_{42}O_4Si$ requires C, 69.08; H, 9.84%), and starting material (119) (0.90 g, 10%).

(iii) Preparation of 19-Oxo-4α,5-epoxy-5α-androstane-3,17-dione (16) - The 17-alcohol (120) (1.61 g) was oxidized (Method A, 10 min) to afford crude 19-t-butyldimethylsilyloxy-4,5α-epoxy-5α-androstane-3,17-dione (122) (1.59 g); υ_{max} 1735 (17-CO), 1710 cm^{-1} (3-CO); δ 0.05 (s, Me_2Si), 0.87 (s, t-BuSi and 18-CH_3), 3.08 (s, 1H, 4β-H), 3.87 (s, 2H, 19-CH_2). The crude dimethylsilyl ether (122) (1.50 g) was taken up in tetrahydrofuran (5 ml) and a solution of tetrabutylammonium fluoride (5 ml, 1M, tetrahydrofuran) was added. After 4.5 h, the reaction was worked up. Chromatography afforded 19-hydroxy-4α,5-epoxy-5α-androstane-3,17-dione (123) (0.84 g, 74%), m.p. 228-230° (needles from methanol), $[\alpha]_D$ +28° (C 3.4); υ_{max} 3450 (OH), 1740 (17-CO), 1710 cm^{-1} (3-CO); δ 0.89 (s, 3H, 18-CH_3), 3.13 (s, 1H, 4β-H), 3.98 (q, 2H, δ_A 4.04, δ_B 3.90, J_{AB} 11 Hz, 19-CH_2); m/e 318 (M^+) (Found:C, 71.68; H, 8.39. $C_{19}H_{26}O_4$ requires C, 71.67; H, 8.23%). Oxidation (Method A, 15 min) of the 19-alcohol (123) (2.12 g) afforded the 19-aldehyde (16) (1.34 g, 62%), m.p. 206-208° (plates from methanol), $[\alpha]_D$ −16° (C 2.2); υ_{max} 1720 cm^{-1} (3-CO, 17-CO, 19-CO); δ 0.90 (s, 3H, 18-CH_3), 3.17 (s, 1H, 4β-H), 9.98 (s, 1H, 19-H) (Found:C, 71.59; H, 7.56. $C_{19}H_{24}O_4$ requires C, 72.12; H, 7.65%).

(iv) Preparation of 19-Oxo-4β,5-epoxy-5β-androstane-3,17-dione (15) - The 17-alcohol (121) (1.04 g) was oxidized (Method A, 10 min) to afford crude 19-t-butyldimethylsilyloxy-4β,5-epoxy-5β-androstane-3,17-dione (124) (1.00 g); υ_{max} 1735 (17-CO), 1710 cm^{-1} (3-CO); δ 0.10 (s, Me_2Si), 0.92 (s, t-BuSi and 18-CH_3), 2.90 (s, 1H, 4α-H), 3.88 (q, 2H, δ_A 3.97, δ_B 3.79, J_{AB} 10 Hz, 19-CH_2). The crude dimethylsilyl ether (124) (1.00 g) in tetrahydrofuran (4 ml) was treated with tetrabutylammonium fluoride (4.8 ml, 1 M, tetrahydrofuran) for 5 h. Workup followed by chromatography afforded 19-hydroxy-4β,5-epoxyandorstane-3,17-dione (125) (0.45 g, 59%) which was identical with authentic material. [This was prepared by adding an aqueous solution of sodium hydroxide (8 ml, 10%) to an ice-cooled solution of androst-4-ene-3,17-dion-19-ol[16] (126) (4.0 g) in methanol (120 ml) containing hydrogen peroxide (24 ml, 30%). After 2 h, the reaction was worked up. Crystallization from methanol afforded the 4β,5β-epoxide (125) (3.51 g, 83%), m.p. 200-201° (lit.[61], m.p. 201-203°).] Oxidation (Method A, 15 min) of the 19-alcohol (125) (3.48 g) afforded the 19-aldehyde (15) (3.12 g, 90%), m.p. 196-197° (prisms from methanol), $[\alpha]_D$ +222° (C 3.9), υ_{max} 1725 cm^{-1} (3-CO, 17-CO, 19-CO); δ 0.93 (s, 3H, 18-CH_3), 3.02 (s, 1H, 4α-H), 9.83 (s, 1H, 19-H) (Found:C, 71.97; H, 7.55. $C_{19}H_{24}O_4$ requires C, 72.12; H, 7.65%).

2. Acid-catalyzed Reactions of 19-Oxo-4β,5-epoxy-5β-androstane-3,17-dione (15) and 19-Oxo-4α,5-epoxy-5α-androstane-3,17-dione (16)

(i) Reaction of 19-Hydroxy-4β,5-epoxy-5β-androstane-3,17-dione (125) with Aqueous Sulphuric Acid - A solution of the 4β,5β-epoxide (125) (877 mg) in acetone (45 ml) containing concentrated sulphuric acid (0.9 ml) and water (2.7 ml) was left at room temperature for 65 h. This was diluted with water and then extracted with ethyl acetate. The extracts were washed with water and brine, dried (sodium sulfate), and then the solvents were removed. Chromatography afforded estrone (114) (92 mg, 12%) identified (t.l.c. and ^{1}H n.m.r.) as its 3-acetate and 2α,19-dihydroxy-androst-4-ene-3,17-dione (140) (206 mg, 23%), m.p. 195-197°, $[\alpha]_D$ +189° (C 3.5) (lit.[61], m.p. 201-203°, $[\alpha]_D$ +177°); υ_{max} 3500 (OH), 1740 (17-CO), 1670, 1720 cm^{-1} (α,β-unsaturated ketone); δ 0.90 (s, 3H, 18-CH_3), 4.03 (br. s, 2H, 19-CH_2), 4.66 (q, 1H, J 6 and 13 Hz, 2β-H), 5.93 (s, 1H, 4-H).

(ii) Acid-catalyzed Reactions of 19-Oxo-4β,5-epoxy-5β-androstane-3,17-dione (15) and 19-Oxo-4α,5-epoxy-5α-androstane-3,17-dione (16): a) With Concentrated Perchloric Acid - Perchloric acid (0.6 ml, 70%) was added dropwise to a cooled solution of the steroid (180 mg) in tetrahydrofuran (6 ml). The reaction was left at room

temperature for 24 h after which it was diluted with water and then extracted with ethyl acetate. The extracts were washed with water, brine, and then dried (sodium sulfate). The solvents were removed and the residual material was chromatographed.

b) With Aqueous Perchloric Acid - Perchloric acid (1.2 ml, 70%) was added dropwise to a cooled solution of the steroid (180 mg) in a mixture of tetrahydrofuran (12 ml) and water (3.6 ml). The reaction mixture was left at room temperature for 3 days after which it was worked up as above.

c) With Aqueous Sulphuric Acid - Sulphuric acid (1.2 ml, conc.) was added dropwise to a cooled solution of the steroid (180 mg) in a mixture of acetone (12 ml) and water (3.6 ml). This was left for 3 days at room temperature after which it was worked up as above.

The yields of the products obtained from the above experiments are given in TABLE 3. The properties which led to the identification of the compounds isolated were: estrone [when obtained in a yield >5%, it was identified as its 3-acetate (t.l.c. and ^{1}H n.m.r.) otherwise it was identified by t.l.c.]; 4-hydroxy-19-oxo-androst-4-en-3,17-

dione* (147), m.p. 188-189° (prisms from methylene chloride-light petroleum), $[\alpha]_D$ +320° (C 1.7), λ_{max} (methanol) 278 nm (ε 11,000); υ_{max} 3420 (OH), 1730 (17-CO), 1670, 1640 cm^{-1} (-CO-C(OH)=C); δ 0.90 (s, 3H, 18-CH_3), 6.45 (s, 1H, exchangeable), 10.13 (s, 1H, 19-H); m/e 316 (M^+) (Found:C, 72.64; H, 7.67. $C_{19}H_{24}O_4$ requires C, 72.12; H, 7.65%); 19-oxo-A-nor-5α-androstane-3,17-dione* (148), m.p. 145-147° (needles from ether-light petroleum), $[\alpha]_D$ −231° (C 2.9), υ_{max} 1735 cm^{-1} (3-CO, 17-CO and -CHO); δ 0.97 (s, 3H, 18-CH_3), 9.78 (s, 1H, 19-H); m/e 288 (M^+) (Found:C, 75.35; H, 8.63. $C_{18}H_{24}O_3$ requires C, 74.97; H, 8.39%); the 19,4-hemiacetal of 19-oxo-4β,5-dihydroxy-5α-androstane-3,17-dione** (149), m.p. 238-240° (needles from methylene chloride-light petroleum; υ_{max} (KBr disc) 3440 (OH), 1725 cm^{-1} (3-CO and 17-CO); δ (acetone-d_6) 0.90 (s, 1H, 18-CH_3), 2.75 (s) and 2.04 (s) (ca. 5:1, 1H, 4α-H), 4.90 (s) and 5.25 (s) (ca. 1:5, 1H, 19-H) (Found:C, 68.22; H, 7.94. $C_{19}H_{26}O_5$ requires C, 68.24; H, 7.84%); 2α-hydroxy-19-oxo-androst-4-ene-3,17-dione** (150), m.p. 217-219° (needles from methylene chloride-light petroleum),

*The diosphenol (147) and the A-nor-compound (148) were found to elute together on a silica gel column. The fraction containing these two compounds was rechromatoggraphed on basic alumina (activity V). The A-nor-compound (148) was eluted with methylene chloride-hexane (1:1) and the diosphenol (147) with methylene chloride.

**The hemiacetal (149) and the 2α-alcohol (150) were found to elute together on a silica gel column. The fraction containing these two components was rechromatographed on basic alumina (activity V). The 2α-alcohol (150) eluted with methylene chloride and the lactol (149) with methylene chloride:methanol (99:1).

$[\alpha]_D$ +302° (C 0.9) (lit.[61] m.p. 205-209°, $[\alpha]_D$ +242°); υ_{max} 3500 (OH), 1730 (17-CO and -CHO), 1680, 1630 cm^{-1} (α,β-unsaturated ketone); δ 0.90 (s, 3H, 18-CH_3), 4.13 (q, 1H, J 6 and 14 Hz, 2β-H), 6.02 (s, 1H, 4-H), 10.0 (s, 1H, 19-H) (Found:C, 71.81; H, 7.79. $C_{19}H_{24}O_4$ requires C, 72.12; H, 7.65%).

(iii) 5-Hydroxy-5α-androstane-3,17-dione-19,4β-carbolactone (151) - The hemiacetal (148) (80 mg) was oxidized (Method A, 10 min). Workup followed by crystallization from methylene chloride-light petroleum afforded the lactone (151) (52 mg, 65%), m.p. 264-265°, $[\alpha]_D$ +23° (C 2.4); υ_{max} 3450 (OH), 1790 (γ-lactone), 1735 (3-CO and 17-CO); δ 1.00 (s, 3H, 18-CH_3), 4.07 (s, 1H, 4α-H) (Found:C, 68.46; H, 7.41. $C_{19}H_{24}O_5$ requires C, 68.65; H, 7.28%).

(iv) Formation of the Mixed 19-Acetals of the 19,4-Hemiacetal of 19-Oxo-4β,5-dihydroxy-5α-androstane-3,17-dione (148) - A solution of (148) (190 mg) in methanol (10 ml) containing concentrated hydrochloric acid (3 drops) was heated at reflux for 11 h. The solution was poured into water and extracted with methylene chloride. The extracts were washed with a saturated aqueous solution of sodium bicarbonate, water, and then dried (sodium sulfate). Chromatography afforded (19R)-5-hydroxy-19-methoxy-4β,19-oxido-5α-androstane-3,17-dione (153)

(48 mg, 24%), m.p. 254-257° (decomp.) (needles from methylene chloride-light petroleum), $[\alpha]_D$ - 2° (C 2.5); υ_{max} 3420 (OH), 1730 cm^{-1} (3-CO and 17-CO); δ 0.90 (s, 3H, 18-CH_3), 3.43 (s, 3H, 19-OMe), 3.75 (s, 1H, 4α-H), 4.92 (s, 1H, 19-H) (Found:C, 69.07; H, 8.15. $C_{20}H_{28}O_5$ requires C, 68.94; H, 8.10%) and the (19S)-isomer (152) (102 mg, 51%), m.p. 252-255° (decomp.) (needles from methylene chloride-light petroleum), $[\alpha]_D$ +104° (C 2.8); υ_{max} 3440 (OH), 1725 cm^{-1} (3-CO and 17-CO); δ 0.88 (s, 3H, 18-CH_3), 3.50 (s, 3H, 19-OMe), 3.63 (s, 1H, 4α-H), 5.27 (s, 1H, 19-H) (Found:C, 69.10; H, 8.25. $C_{20}H_{28}O_5$ requires C, 68.94; H, 8.10%.

(v) Oxidation of 2α,19-Dihydroxy-androst-4-ene-3, 17-dione (140) - A solution of the diol (140) (145 mg) in dry methylene chloride (10 ml) was added to a suspension of pyridinium chlorochromate (296 mg, 3 equiv.) and sodium acetate (22 mg, 0.6 mg) in methylene chloride (3 ml) and the mixture was stirred for 1 h. It was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate, water, brine, and then dried (sodium sulfate). Removal of the solvents followed by chromatography afforded the 19-aldehyde (150) (20 mg, 14%) which was identical (t.l.c., i.r. and ^1H n.m.r.) with material previously obtained, and starting material (14 mg, 10%).

3. Base-catalyzed Reactions of 19-Oxo-4β,5-epoxy-5β-androstane-3,17-dione (15) and 19-Oxo-4α,5-epoxy-5α-androstane-3,17-dione (16)

(i) Reactions of the Epoxides (15) and (16) with Methanolic Potassium Hydroxide - To a solution of the epoxide (200 mg) in methanol (30 ml) under nitrogen was added a methanolic solution of potassium hydroxide (4.5 ml, 0.28 M, 2 equiv.). The mixture was heated at reflux for the specified period of time after which it was worked up and chromatographed.

The 4α,5α-epoxide (16) (12 h of reflux) afforded 4-methoxy-estr-4-ene-3,17-dione (160) (24 mg, 13%), m.p. 154-156° (needles from methylene chloride-light petroleum), $[\alpha]_D$ +124° (C 6.0), λ_{max} (methanol) 255 nm (ε14,000); ν_{max} 1735 (17-CO), 1675, 1610 cm^{-1} (-CO-C(OMe)=C-); δ 0.93 (s, 3H, 18-CH_3), 3.60 (s, 3H, 4-OMe) (Found:C, 75.09; H, 8.56. $C_{19}H_{26}O_3$ requires C, 75.46; H, 8.64%), a mixture (42 mg) whose ^1H n.m.r. spectrum was consistent with a 1:3 mixture of the 4-methoxy compound (160) (5%) and the (19R)-acetal (153) (16%), and lastly, the (19S)-acetal (152) (63 mg, 29%) which was identical (t.l.c. and ^1H n.m.r.) with material obtained previously.

The 4β,5β-epoxide (16) (43 h of reflux) afforded the 4-methoxy compound (160) (95 mg, 50%).

PART IV

Attempts at Preparing 4-Hydroxy-estr-5(10)-ene-3,17-dione (112)

1. The Thermal Decarboxylation of 4β,5-Epoxy-5β-androstan-3,17-dion-19-oic Acid (166)

(i) Preparation of 4β,5-Epoxy-5β-androstane-3,17-dion-19-oic Acid (166) - To a cooled solution (ca. 5°) of the 19-alcohol (126) (500 mg) in acetone (50 ml) was added a solution of Jones reagent (1.75 ml). After 4 h, methanol (2 ml) was added, and after an additional 15 min, the solution was diluted with water (50 ml). It was extracted with ether and the extracts washed with water, brine, and then dried (sodium sulfate). Removal of the solvents followed by crystallization from ether-light petroleum afforded the acid (116) (541 mg, 79%), m.p. 184-186° (decomp.), $[\alpha]_D$ +189° (C 8.9); υ_{max} 3100 (OH), 1720 cm^{-1} (3-CO, 17-CO and 19-CO_2H); δ 0.97 (s, 3H, 18-CH_3) 3.08 (s, 1H, 4α-H); m/e 322 (M^+) (Found:C, 68.56; H, 7.31. $C_{19}H_{24}O_5$ requires C, 68.65; H, 7.28%).

(ii) Decarboxylation of the Acid (166) - A suspension of the acid (166) (800 mg) in decalin (100 ml) was heated at reflux under nitrogen for 2.5 h. After cooling, the solvent was removed under reduced pressure. The residual semisolid was chromatographed to afford estrone (58 mg, 9%) (a sample converted to the 3-acetate was identical (t.l.c. and ^1H n.m.r.) with authentic material) and 3ξ-hydroxy-estr-5(10)-ene-4,17-dione (167) (541 mg, 79%), m.p.

159-161°, λ_{max} (methanol) 247 nm (ε 11,200); ν_{max} 3460 (OH), 1735 (17-CO), 1655 and 1619 cm^{-1} (α,β-unsaturated ketone); δ 0.92 (s, 3H, 18-CH_3), 4.09 (app. q, 1H, J 5 and 13 Hz); m/e 288 (M^+) (Found:C, 74.78; H, 8.43. $C_{18}H_{24}O_3$ requires C, 74.97; H, 8.39%).

(iii) Isomerization of (167) with Base - A solution of (167) (60 mg) in a methanolic solution of sodium methoxide (3 ml, 0.55 M) was heated at reflux for 2 h under nitrogen. The solution was then acidified with aqueous hydrochloric acid (5%) and diluted with water. This was extracted with with the ethyl acetate and the extracts were washed with water, brine, and then dried (sodium sulfate). Chromatography afforded 4-hydroxy-estr-4-ene-3,17-dione (172) (42 mg, 70%), m.p. 200-202° (prisms from acetone), $[\alpha]_D$ +120° (C 4.9), λ_{max} (methanol) 276 nm (ε 11,000); υ_{max} 3460 (OH), 1740 (17-CO), 1670 and 1650 cm^{-1} (-CO-C(OH)=CR_2); m/e 288 (M^+) (Found:C, 75.03; H, 8.36. $C_{18}H_{24}O_3$ requires C, 74.97; H, 8.39%).

(iv) Acid-catalyzed Dehydration of (167) - A solution of (167) (33 mg) in tetrahydrofuran containing perchloric acid (0.5 ml, 70%) was allowed to stand for 3 days under nitrogen. Workup followed by chromatography afforded estra-5(10),9(11)-diene-4,17-dione (170) (18 mg, 60%), m.p. 130-132°, $[\alpha]_D$ +412° (C 1.5), λ_{max} (methanol) 289 nm

(ε 23,000); υ_{max} 1740 (17-CO), 1655, 1605, 1590 cm^{-1} (αβ,γδ-unsaturated ketone); δ 0.92 (s, 3H, 18-CH_3), 6.18 (m, 1H, W/2 ca. 6 Hz, 11-H); m/e 270 (M^+) (Found:C, 79.79; H, 8.29. $C_{18}H_{22}O_2$ requires C, 79.96; H, 8.20%).

Similar treatment of the diosphenol (172) (30 mg) afforded after workup and chromatography, unreacted starting material (25 mg).

(v) Oxidation of (167) - A solution of (167) (60 mg) and trimethylphosphite (55 mg, ca. 2 equiv.) in methanolic sodium methoxide (3 ml, 0.55M) was stirred at room temperature under an oxygen atmosphere. After 3 h, the deep burgundy coloured solution was acidified with acetic acid whereupon it turned a pale yellow colour. Workup followed by chromatography (eluents contained a trace of acetic acid since the material was strongly adsorbed onto the silica gel) affording an oil, possibly (180) or (181), (18 mg); υ_{max} 3405 (OH), 1730 (17-CO), 1650 and 1600 cm^{-1}; δ 0.92 (s, 3H, 18-CH_3), 5.95 (s, 1H); m/e 300, 282.

(vi) Conversion of (167) to 4-Hydroxy-estra-1,3,5(10)-trien-17-one (174) a) Attempted Elimination of Acetic Acid from 3ξ-Acetoxy-estra-5(10)-ene-4,17-dione (184) - A solution of (167) (100 mg) in a mixture of acetic anhydride (1 ml) and pyridine (2 ml) was left at room temperature for 12 h. The solvents were removed at reduced pressure to

leave the acetate (184) as an oil; υ_{max} 1740 (acetate CO and 17-CO), 1680, 1625 cm^{-1} (α,β-unsaturated ketone); δ 0.90 (s, 3H, 18-CH_3), 2.13 (s, 3H, OAc), 5.23 (m, 1H, 3-H). The oil was dissolved in decalin (3 ml) and heated at reflux for 24 h. T.l.c. analysis of the reaction mixture only indicated the presence of unreacted starting material.

b) Elimination of Methanesulfonic Acid from 3ξ-Hydroxy-estra-5(10)-ene-4,17-dione 3-Methanesulfonate (185) - To a cooled solution (ca. 5°) of (167) (100 mg) in pyridine (3 ml) was added methanesulfonyl chloride (0.1 ml). After 2 h, the solution was poured into water and extracted with methylene chloride. The extracts were washed with aqueous hydrochloric acid (5%), aqueous sodium bicarbonate (5%), water and were then dried (sodium sulfate). Removal of the solvent afforded the crude mesylate (185) as an oil; υ_{max} 1740 (17-CO), 1690, 1625 (α,β-unsaturated ketone), 1180 cm^{-1} (-OSO_2Me); δ 0.90 (s, 3H, 18-CH_3), 3.23 (s, 3H, -OSO_2Me), 5.00 (m, 1H, 3-H). The oil was taken up in 2,4,6-collidine (3 ml) and heated at reflux for 20 h. After cooling, it was poured into an aqueous solution of hydrochloric acid (5%) and this was extracted with ethyl acetate. The extracts were washed with aqueous hydrochloric acid (5%), aqueous sodium bicarbonate (5%), water, brine and were then dried (sodium sulfate). After the solvent was removed, the crude material was acetylated (acetic anhydride-pyridine)

and chromatographed. This afforded 4-acetoxy-extra-1,3,5(10)-trien-17-one (186) (65 mg, 60%), m.p. 173-174° (needles from ethanol-water), $[\alpha]_D$ +145° (C 3.5): ν_{max} 1740 (acetate CO and 17-CO), 1610, 1580 cm^{-1} (arom.); δ (acetone-d_6) 0.87 (s, 3H, 18-CH_3), 2.24 (s, 3H, OAc), 6.7-7.2 (higher order multiplet, 3H, arom.); m/e 312 (M^+) (Found:C, 76.99; H, 7.87. $C_{20}H_{24}O_3$ requires C, 76.89; H, 7.74%).

Hydrolysis [methanol, aqueous sodium hydroxide (10%), reflux (4h)] of the 4-acetate (186) afforded 4-hydroxy-estra-1,3,5(10)-trien-17-one (174) in an essentially quantitative yield, m.p. 269-271° (needles from methanol), (lit.[70a], 270-275°), $[\alpha]_D$ +152° (C 1.1), λ_{max} (dioxane) 275 nm (ε 1,900).

2. Attempted Fragmentation of (19R)-19-t-Butyldimethylsilyloxy-5-hydroxy-4β,19-oxido-5α-androstane-3,17-dione (191)

(i) Preparation of (19R)-19-t-Butyldimethylsilyloxy-5-hydroxy-4β,19-oxido-5α-androstan-3,17-dione (191) - A solution of the hemiacetal (149) (350 mg) in dimethylformamide (5 ml) containing t-butyldimethylsilyl chloride (760 mg) and imidazole (716 mg) was maintained at 40° for 1 week. Workup followed by chromatography afforded the silyl ether (189) (305 mg, 65%), m.p. 233-235° (needles from methylene chloride-light petroleum), $[\alpha]_D$ +125°

(C 1.9); ν_{max} 3440 (OH), 1725 cm^{-1} (3-CO and 17-CO); δ 0.17 (s, 6H, Me_2Si), 0.90 (s, 18-CH_3), 0.93 (s, t-BuSi), 3.57 (s, 1H, 4α-H), 5.73 (s, 1H, 19-H) (Found:C, 66.88; H, 8.85. $C_{25}H_{40}O_5Si$ requires C, 66.91; H, 8.99%) and unreacted starting material (48 mg, 14%). The silyl ether (189) (139 mg) was added to an ice-cooled solution of benzenesulfinyl chloride* (75 mg) in pyridine (2 ml). This was allowed to come to room temperature and after 1 h it was poured into water. The mixture was extracted with methylene chloride and the extracts were washed with aqueous sodium bicarbonate (5%), water and then dried (sodium sulfate). Removal of the solvents under high vacuum afforded the crude sulfinate ester (190) as an oil; ν_{max} 1725 (3-CO and 17-CO), 1130 cm^{-1}(-OSOφ); δ 0.15 (s, 6H, Me_2Si), 0.90 (s, t-BuSi and 18-CH_3), 3.98 and 4.12 (d, 1H, 4α-H), 5.80 (s, 1H, 19-H), 7.4-7.9 (m, 5H, arom.). The oil was taken up in methylene chloride (5 ml) and the solution was cooled in an ice bath. To this was added a solution of m-chloroperbenzoic acid (69 mg, 85%) in methylene chloride (4 ml) and the resultant mixture was allowed to come to room temperature. After 5 h, the reaction was worked up. Chromatography afforded the sulfonate ester (191) (148 mg, 81%), m.p. 200-201° (prisms from ether-light

*This was freshly prepared by the reaction[101] of diphenyldisulfide with chlorine gas in the presence of acetic anhydride.

petroleum), ν_{max} 1730 (17-CO and 3-CO), 1360 cm^{-1} (-OSOϕ); δ 0.15 (s, 6H, Me_2Si), 0.90 (s, 12H, t-BuSi and 18-CH_3), 4.35 (s, 1H, 4α-H), 5.70 (s, 1H, 19-H), 7.6-8.1 (m, 5H, arom.) (Found:C, 63.19; H, 7.33. $C_{31}H_{44}O_7SiS$ requires C, 63.23; H, 7.53%).

(ii) Desilylation of (191) - To a solution of the silyl ether (191) (44 mg) in tetrahydrofuran (2 ml) was added a solution of tetrabutylammonium fluoride (0.15 ml, 1M, tetrahydrofuran). After 10 min, the reaction was worked up. Chromatography afforded the 4β,5β-epoxide (15) (18 mg, 76%).

(iii) Solvolysis of (191) - A solution of the silyl ether (191) (137 mg) in a solution of sodium acetate (3 ml, 0.1M, acetic acid) was heated at reflux under nitrogen for 54 h. It was then diluted with water and extracted with methylene chloride. The extracts were washed with a saturated aqueous solution of sodium bicarbonate, water and then dried (sodium sulfate). Removal of the solvent followed by chromatography allowed for the isolation of a solid (58 mg) which consisted (^1H n.m.r.) of a 6:1 mixture of the A-nor compound (148) and the silyl ether (189). The mixture was taken up in tetrahydrofuran (2 ml) and a solution of tetrabutylammonium fluoride (0.10 ml, 1M, tetrahydrofuran) was added. The solution was left under

nitrogen for 4 h after which it was worked up. Chromatography afforded the A-nor compound (148) (26 mg, 36%), identical (t.l.c., i.r., ^{1}H n.m.r.) with authentic material.

3. Reaction of Estr-5(10)-ene-3,17-dione (198) with Lead Tetraacetate

(i) Preparation of 4ξ-Acetoxy-estr-5(10)-ene-3,17-dione (199) - Lead tetraacetate (10 g, 90%, 5.5 equiv.) was added to a solution of estr-5(10)-ene-3,17-dione (198) (1.0 g) in a mixture of benzene (10 ml) and acetic acid (10 ml) under nitrogen. The mixture was stirred at room temperature for 72 h after which it was poured into an ice-cooled aqueous solution of sodium thiosulfate (100 ml, 20%). This mixture was extracted with ether and the extracts were washed with aqueous sodium bicarbonate (5%), water, brine and then dried (sodium sulfate). After the solvents were removed, the residual oil was chromatographed to afford the crude acetate (199) (300 mg, ca. 25%) as an oil which was contaminated with some estrone (t.l.c.). This mixture had the following spectral properties: ν_{max} 1730 cm^{-1} (3-CO, 17-CO and acetate CO); δ 0.92 and 0.90 (3H, 18-CH_3), 2.20 (s, 3H, OAc), 5.49 (m, ca. 0.4H, W/2 ca. 6 Hz, 4-H), 5.81 (m, ca. 0.6H, W/2 ca. 6 Hz, 4-H); m/e 330 (M^+), 288 (M^+-CH_2CO), 270 (M^+-HOAc).

(ii) Aromatization Reactions of 4ξ-Acetoxy-estr-5(10)-ene-3,17-dione (199) a) Thermal Reaction - A solution of the acetate (199) (50 mg) in decalin (5 ml) was heated at reflux for 2.5 h under nitrogen. The solvent was then removed under high vacuum and the residual semisolid was acetylated (acetic anhydride-pyridine). Chromatography afforded the 3-acetyl derivative of estrone (35 mg, 74%).

b) With Acid - To a solution of the acetate (199) (130 mg) in tetrahydrofuran (5 ml) was added a solution of concentrated perchloric acid (0.5 ml, 70%). After 3 h the reaction was diluted with water and extracted with ethyl acetate. The extracts were washed with a saturated aqueous solution of sodium bicarbonate, water, brine and were then dried (sodium sulfate). Removal of the solvents left a semisolid which was acetylated (acetic anhydride-pyridine). Chromatography afforded the 3-acetyl derivative of estrone (56 mg, 46%).

c) With Base - A solution of the acetate (199) (50 mg) in methanol (3 ml) was added to a methanolic solution of sodium methoxide (2 ml, 0.55M) under nitrogen. After 15 min, the reaction was neutralized with aqueous hydrochloric acid (5%). It was diluted with water and extracted with ethyl acetate. The extracts were washed with water, brine and were then dried (sodium sulfate). After removal of the solvents, the crude material was acetylated (acetic anhydride-pyridine). Chromatography afforded the 3-acetyl derivative of estrone (31 mg, 65%).

d) With a Phosphate Buffer - To a solution of the acetate (199) 60 mg) in a mixture of ethanol (4 ml) and water (4 ml) under nitrogen was added an aqueous solution of a phosphate buffer* (2 ml, 2.1M, pH ca. 7.5). The resulting two phase mixture was stirred at room temperature for 10 h after which it was diluted with water. This was then extracted with ethyl acetate and the extracts were washed with water, brine and dried (sodium sulfate). The solvents were removed and the residual semisolid was acetylated (acetic anhydride-pyridine). Chromatography afforded the 3-acetyl derivative of estrone (42 mg, 74%).

*This was prepared[102] by adding an aqueous solution of sodium hydroxide (50 ml, 5.0M) to an aqueous solution of potassium dihydrogen phosphate (40.9 ml, 5.0M) and diluting the mixture to 100 ml with water.

CLAIMS TO ORIGINAL RESEARCH

1. The boron trifluoride-catalyzed reactions of 19-hydroxy- and 19-acetoxy-5,6-epoxy-steroids were examined.

2. The base-catalyzed reactions of 19-oxo-5,6-epoxy-cholestanes were investigated and an explanation for the novel fragmentative elimination observed with the 3β-hydroxy-19-oxo-5β,6β-epoxide was suggested.

3. The 19-oxo-4,5-epoxy-androstane-3,17-diones were prepared and their acid- and base-catalyzed reactions were examined.

4. The thermal decarboxylation of 4β,5-epoxy-5β-androstane-3,17-dion-19-oic acid is described together with the chemical transformations of the derived product.

5. The ^{13}C n.m.r. assignments for 4-hydroxy- and 4-acetoxy-estra-1,3,5(10)-trien-17-one were made

6. The solvolysis of (19 R)-19-t-butyldimethylsilyloxy-5-hydroxy-4β,19-oxido-5α-androstan-3,17-dione 5-benzene-sulfonate was examined.

7. The reaction of lead tetraacetate with estr-5(10)-ene-3,17-dione was investigated together with the aromatization reactions of the derived product.

8. The following new compounds were prepared and characterized (including elemental analyses):

   1) 3β-acetoxy-6β,19-methelenedioxy-cholest-4-ene*
   2) 3β-acetoxy-19-nor-androsta-1(10)-5-dien-17-one*
   3) 3β-acetoxy-6β,19-methylenedioxy-androst-4-en-17-one*
   4) 3β,6β,19-triacetoxycholest-4-ene
   5) cholest-4-ene-3β,6β,19-triol
   6) 3β-acetoxy-5-fluoro-5α-cholestane-6β,19-diol
   7) 3β,19-diacetoxy-5,6β-epoxy-5β-androstan-17-one
   8) 3β,19-diacetoxy-5-fluoro-5α-androstan-17-one
   9) 3β,6β,19-triacetoxyandrost-4-en-17-one
   10) 3β,19-diacetoxy-5-formyl-B-nor-5β-androstan-17-one

*Previously prepared[30] but only identified by spectral methods.

11) B-nor-5β-cholestan-3-one-5β,19-carbolactone

12) 3β-acetoxy-5-fluoro-6β,19-oxido-5α-androstan-17-one

13) 3β-acetoxy-19-t-butyldimethylsilyloxy-5,6β-epoxy-5β-cholestane

14) 3β-acetoxy-19-hydroxy-5,6α-epoxy-5α-androstan-17-one

15) 3β-acetoxy-5,6α-epoxy-5α-cholestan-19-al

16) 3β-hydroxy-5,6α-epoxy-5α-cholestan-19-al

17) 3β,5-dihydroxy-6β-methoxy-5α-cholestan-19-al

18) 19-t-butyldimethylsilyloxy-3β-methoxy-5,6β-epoxy-5β-cholestane

19) 19-t-butyldimethylsilyloxy-5,6β-epoxy-5β-cholestan-3β-ol

20) 3β-methoxy-5,6β-epoxy-5β-cholestan-19-ol

21) 3β-methoxy-5,6β-epoxy-5β-cholestan-19-al

22) 6β-hydroxy-3β-methoxy-19-nor-cholest-5(10)-ene

23) 3β,6β-dihydroxy-19-nor-cholest-5(10)-ene 3-formate

24) 3β-hydroxy-19-nor-cholesta-1(10),5-diene 3-formate

25) 19-t-butyldimethylsilyloxy-17-hydroxy-androst-4-en-3-one

26) 19-t-butyldimethylsilyloxy-17β-hydroxy-4α,5-epoxy-5α-androstan-3-one

27) 19-t-butyldimethylsilyloxy-17β-hydroxy-4β,5-epoxy-5β-androstan-3-one

28) 19-hydroxy-4α,5-epoxy-5α-androstane-3,17-dione

29) 19-oxo-4α,5-epoxy-5α-androstane-3,17-dione

30) 19-oxo-4β,5-epoxy-5β-androstane-3,17-dione

31) 3α-hydroxy-19-oxo-androst-4-ene-3,17-dione*

32) 19-oxo-A-nor-5α-androstane-3,17-dione

33) 19,4-hemiacetal of 19-oxo-4β,5-dihydroxy-5α-androstane-3,17-dione

34) 5-hydroxy-5α-androstane-3,17-dione-19,4β-carbolactone

35) (19 R)-5-hydroxy-19-methoxy-4β,19-oxido-5α-androstane-3,17-dione

36) (19 S)-5-hydroxy-19-methoxy-4β,19-oxido-5α-androstane-3,17-dione

*Previously obtained[61] as a hydrate.

37) 4-methoxy-estr-4-ene-3,17-dione

38) 4β,5-epoxy-5β-androstane-3,17-dion-19-oic acid

39) 3ξ-hydroxy-estr-5(10)-ene-4,17-dione

40) 4-hydroxy-estr-4-ene-3,17-dione

41) estra-5(10),9(11)-diene-3,17-dione

42) 4-acetoxy-estra-1,3,5(10)trien-17-one

43) (19 R)-19-t-butyldimethylsilyloxy-5-hydroxy-4β,19-oxido-5α-androstan-3,17-dione

44) (19 R)-19-t-butyldimethylsilyloxy-5-hydroxy-4β,19-oxido-5α-androstan-3,17-dione 5-benzenesulfonate

LIST OF PUBLICATIONS FROM THE THESIS

H. Mastalerz and P. Morand, J.C.S. Perkin I, in press.

H. Mastalerz and P. Morand, J. Org. Chem., accepted for publication with minor revision.

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